Welcome to this review of the ESC Annual Congress that was held in Rome earlier this year.

I attended a number of interesting sessions at the Congress, with a particular focus on NVAF. I’ve highlighted the latest ESC guidelines for AF that were presented, and have summarised the major changes. The guidelines and some of the presentations have subsequently appeared in major journals so where possible I have included the link to the published article. Otherwise abstracts and presentations can be reached via the ESC365 application on the ESC website (http://congress365.escardio.org/).

I hope you enjoy this conference review and find it useful in your clinical practice.

Kind Regards,

Associate Professor John Amerena
john.amerena@researchreview.com.au

New guidelines for the management of AF
Presenter: Paulus Kirchhof (Birmingham, England)

Summary and comment: The ESC has released new guidelines for the management of NVAF and these were presented at the conference. There were two updates that have the potential to impact on clinical practice as they differ from current recommendations.

Firstly, the definition of NVAF has been clarified (at least from a European perspective). Current US guidelines classify AF in the context of mitral valve repair and bioprosthetic valves as “valvular”, despite these valve conditions not requiring anticoagulation in their own right, and recommend a VKA be used for stroke prevention in these situations. The previous iteration of the ESC guidelines was not so definitive, and the latest update states that in their opinion, “valvular” AF is only that which is associated with moderate to severe mitral valve stenosis and metallic prosthetic valves, and that in these conditions stroke prevention should be with a VKA. They have also recommended that if the valvular heart disease does not require anticoagulation in its own right (valve repair or bioprosthetic valve, tricuspid valve regurgitation, mitral regurgitation or aortic stenosis/insufficiency), then a VKA or NOAC can be used for stroke prevention. This liberalisation of the definition of valvular versus nonvalvular AF will make things clearer and extend the patient population eligible for NOAC therapy.

Secondly, there has been a relaxation in the CHADSVA Sc threshold for initiation of anticoagulation in females. The first version of the CHADSVA Sc score suggested that anticoagulation be considered in men and women if the score was 1 (apart from gender alone) and was recommended if the score was ≥2. It has become clear in subsequent studies that gender is a relatively weak risk factor for stroke, so that the latest ESC guidelines for women recommend a more liberal threshold, in that anticoagulation should be considered if the CHADSVA Sc score is 2 and recommended if it is ≥3. The recommendations for men have not changed and it will be interesting to see if this relaxation of the threshold for women will be implemented in clinical practice in Australia.

Reference: 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016, published online 27 Aug

Abstract

Independent commentary by Associate Professor John Amerena. Associate Professor John Amerena trained in Melbourne before spending four years in the United States at the University of Michigan. Over that period, he worked in the fields of hypertension and hyperlipidaemia, before returning to Australia where he is now a Cardiologist at Barwon Health. He currently has a joint appointment in the Department of Clinical and Biomedical Sciences at the University of Melbourne and the Department of Epidemiology and Preventive Medicine at Monash University. He is Director of the Geelong Cardiology Research Unit, which is currently involved in many phase II–III clinical trials. While still actively researching in hypertension, his focus has changed to research in antithrombotic/antiplatelet therapies, particularly in the context of acute coronary syndromes and atrial fibrillation. Heart failure is also a major interest, and he is also Director of the Heart Failure Programme at Barwon Health. He is well published in these areas, as well as in many other areas of cardiovascular medicine.
Andexanet alfa for reversal of Factor Xa inhibitors in patients with acute major bleeding (ANNEXA-4 study)

Presenter: Stuart Connolly (Hamilton, Canada)

Summary: The efficacy of andexanet was evaluated in 67 patients who developed acute major bleeding within 18 hours after receiving a factor Xa inhibitor. Andexanet was administered as a bolus followed by a 2-hour infusion. The mean time from emergency department presentation to the administration of the andexanet bolus was 4.6 hours. After the bolus dose, anti-factor Xa activity decreased by a median 89% in rivaroxaban recipients and 93% in apixaban recipients. Levels remained similar during the 2-hour infusion. Twelve hours after the andexanet infusion, clinical haemostasis was considered to be excellent or good in 79% of patients. Thrombotic events occurred in 18% of patients during the 30-day follow-up.

Comment: The lack of a reversal agent for the NOACs has always been of concern in the patient who is bleeding or who needs urgent surgery whilst taking these medications. Idarucizumab (a monoclonal antibody) is available to reverse dabigatran, and now andexanet (a decoy factor Xa molecule) has been shown to reverse the anticoagulant effect of apixaban and rivaroxaban in patients who have significant bleeding while on these agents. In this preliminary report presented at the ESC, bleeding was reduced after a bolus then infusion, but haemostasis in patients who required urgent surgery was not evaluated. Andexanet should also be able to reverse edoxaban and low molecular weight heparin, but this data has not been presented yet. Production issues may delay the drug becoming available in Australia for several years, but hopefully this will be overcome in the near future.


Screening for AF to prevent stroke

Presenter: Ben Freedman (Sydney, Australia)

Summary and comment: This presentation from Australia looked at the feasibility of screening for AF in the community using a smart phone application to produce single lead rhythm strip. It found that AF was detected in 1.5% of the general population, and that this had not been recognised previously. Given that the prognosis of patients with incidental AF is as bad as or worse than those with recognised AF, it is important that these patients be picked up, evaluated for stroke risk and treated appropriately. This technology is affordable, available and can be widely used in clinical practice but has not been proven to reduce stroke rates or be cost effective yet, but this is likely to be the case and is being studied.

Session: Atrial Fibrillation; ESC Congress 2016

Risk scores for patients with nonvalvular AF

Presenter: Keith Fox (Netty Bridge, Scotland)

Summary and comment: The CHADS2-VASc score is the risk score that is most frequently used globally to predict stroke risk in NVAF and has largely replaced the CHADS score. These scores are good at predicting patients at high risk of stroke but not so good at identifying the truly low risk patient, although the CHADS2-VASc score is significantly better than CHADS in this regard. New scores have been developed, and in this case the GARFIELD-AF score has been derived from data from the GARFIELD study of 40,000 patients enrolled with recently detected AF. The C-statistics for this score are better than the CHADS2-VASc score for prediction of all-cause mortality, stroke and bleeding and thus it could be an alternative to CHADS2-VASc once external validation studies have been completed.

Session: Risk profiles for patients with atrial fibrillation and the quality of stroke prevention: results from the GARFIELD-AF registry; ESC Congress 2016

Vitamin K antagonist control for patients with nonvalvular atrial fibrillation in Eastern and Southeastern Asia: an analysis of event rates from GARFIELD-AF

Presenter: Shinya Goto (Isehara, Japan)

Summary: This analysis of data from the GARFIELD-AF registry determined the optimal INR range in patients from Eastern and Southeastern Asia who were taking a vitamin K antagonist for newly diagnosed NVAF. 1370 patients on the GARFIELD-AF registry were from Eastern and Southeastern Asia and had ≥3 INR values taken during 1-year of follow-up. Mean age was 67.7 years, mean CHADS2-VASc score was 3.1 and mean HAS-BLED score was 1.4. The lowest rates of stroke/systemic embolism and major bleeding were observed at an INR level of 1.6–2.0.

Comment: We know that patients from Asia have increased risk of intracerebral haemorrhage (ICH) on warfarin compared with Caucasian populations. The reasons for this are not clear, but because of this concern many Asian physicians aim for a target INR of 1.6–2.0 in their patients with NVAF on warfarin, and have been criticised for doing so by their non-Asian colleagues. This analysis from the GARFIELD study suggests that this may be a reasonable approach in Asian patients, in that the optimal INR range in warfarin-treated Asian patients with newly diagnosed AF was 1.6–2.0 as this was associated with the lowest rates of stroke and bleeding. The availability of NOACs in Asia will largely overcome this consideration as all of them have been shown to be more effective and safer than warfarin in preventing stroke and bleeding in Asian patients despite the time in therapeutic range (TTR) in the studies being lower in Asia than in other parts of the world.

Reference: Eur Heart J 2016;37(Suppl):1007-8

ENSURE-AF study: edoxaban for cardioversion of atrial fibrillation

Presenter: Andreas Goette (Paderborn, Germany)

Summary and comment: Anticoagulation around the time of direct cardioversion (DCR) is essential to prevent thromboembolic stroke and it is recommended that patients are therapeutically anticoagulated for at least 3 weeks before and 4 weeks after DCR, with ongoing therapy depending on the CHADS2-VASc score. In all the large NOAC trials patients underwent DCR and there was no apparent difference in efficacy and safety between warfarin and the new agents when used in this context, but these were unrandomised data. The randomised X-VERT study with rivaroxaban and now the ENSURE-AF study with edoxaban showed that there was no difference in stroke rates or bleeding compared with warfarin when used for anticoagulation in DCR but did allow more timely reversion due to more certainty about duration of anticoagulation. There is an ongoing study with apixaban in this area, and it is likely that these new agents will be seen as alternatives to warfarin for this indication.

Session: Hot Line preventive strategies 2; ESC Congress 2016

Heart failure and atrial fibrillation: which comes first?

Presenter: John Cleland (London, England)

Summary and comment: This interesting presentation by John Cleland explored the relationship between AF and heart failure (HF), and specifically addressed if there were differences in outcomes depending on whether AF occurred before or after HF was present. AF and HF often co-segregate, and it appears that if AF occurs first and is followed by HF, survival is better than if AF is a consequence of HF, irrespective of whether the HF is due to preserved or reduced ejection fraction. Presumably initial AF with secondary HF is more amenable to treatment with a potential improvement in left ventricular (LV) function, whereas HF with secondary AF is a reflection of a rise in intracardiac pressures associated with LV dysfunction due to intrinsic myocardial disease. Restoration of sinus rhythm with direct cardioversion or drugs in patients with HF and secondary AF has not improved outcomes, but there is some evidence that ablation to restore sinus rhythm can improve LV function.

Session: Atrial fibrillation in clinical practice; ESC Congress 2016
Confidence from Evidence and Real World Experience

*Xarelto has evidence for its efficacy and safety profile for eligible patients from RCTs and real world studies in SPAF\textsuperscript{1-3} and PE/DVT.\textsuperscript{4,5}

Xarelto is the world's most prescribed NOAC,\textsuperscript{6} with over 23 million patients treated across multiple indications.\textsuperscript{7,8}

RCT=randomised controlled trial; SPAF=stroke prevention in atrial fibrillation; PE=pulmonary embolism; DVT=deep vein thrombosis; NOAC=non-vitamin K antagonist oral anticoagulant.

Calculation based on IMS Health MIDAS, Database: Monthly Sales June 2016.
Summary: This real-world study compared the risk of a first major bleeding event among NVAF patients newly initiated on warfarin compared with those newly initiated on apixaban, dabigatran, or rivaroxaban. Data were retrieved from commercial and Medicare supplemental databases. Patients who initiated warfarin (n=15,461; 34.08%) were older and had higher baseline mean CHA2DS2-VASc score and higher Charlson Comorbidity Index scores followed by apixaban (n=7,438; 16.40%), rivaroxaban (n=17,801; 39.24%), and dabigatran (n=4,661; 10.28%). Analysis of propensity score-matched patients showed that patients newly initiated on apixaban or dabigatran had a significantly lower risk of major bleeding than those newly initiated on warfarin (hazard ratios 0.57 and 0.73, respectively), but the risk in patients newly initiated on rivaroxaban was similar to that in warfarin recipients.

Comment: Postmarketing surveillance of the safety of new drugs when released for use in large populations is essential to detect rare side effects but also to reassure physicians that the results seen in the highly supervised clinical trial environment are translatable to real world practice. This report from Lip et al. derived from MarketScan data in the US shows that the bleeding rates of the NOACs compared with warfarin seen in ReLy, ROCKET-AF and Aristotle are similar to those seen in clinical practice, with dabigatran and apixaban having lower rates of bleeding compared to warfarin, and rivaroxaban a similar rate.

Reference: Eur Heart J 2016;37(Suppl.):493

Summary: This report evaluated the long-term efficacy of a Watchman left atrial appendage (LAA) occlusion device in patients with NVAF who were at high risk for stroke. 329 patients with NVAF and contraindications to the use of oral anticoagulants received a Watchman implant between 2010 and 2016. The implant was successful in 96% of patients. Periprocedural complications occurred in 5 patients (1.5%). All patients were treated with aspirin and clopidogrel for 6 weeks post procedure, then only with aspirin thereafter. During a mean follow-up period of 376 days, only 3 patients had an ischaemic stroke, 3 had a major bleed and 3 developed a device-related thrombus that resolved after prolonged warfarin therapy.

Comment: Stroke prevention by occlusion of the LAA with the Watchman device has been shown to be similar to warfarin in patients with NVAF who are eligible for anticoagulation in randomised trials but this has never been formally tested in patients who have contraindications to any form of anticoagulation (e.g., intracerebral haemorrhage, or incessant irreversible gastrointestinal tract or joint bleeding). In many centres, these patients who cannot be anticoagulated have LAA occlusion devices implanted, and there are several registries looking at outcome and safety, as it is unlikely that a randomised controlled trial will ever be conducted in this population. This report of the Israeli experience of LAA occlusion in this population is reassuring, and when other registry data become available I suspect LAA occlusion will become the preferred procedure to prevent strokes in this high-risk population.

Reference: Eur Heart J 2016;37(Suppl.):511