Amongst 1 149 delegates, I attended this EBAC CME accredited meeting as a guest of Bayer Pharma along with 3 other South African colleagues. The event was sponsored through an unrestricted grant from Bayer. The Steering Committee comprised of Dr the Lord Ajay Kakkar (London), Dr Jean-Pierre Bassand (Brescanson), Dr Henri Bounnameaux (Geneva), Dr Sylvia Haas (Munich) and Dr Freek Verheught (Amsterdam) who were assisted by a faculty of 18 experts drawn from Europe and the USA.

The presentations centred around the management of anticoagulation in three patient groups: those with atrial fibrillation (AF), those following an acute coronary syndrome (ACS) and those with venous thrombo-embolism (VTE) with special emphasis upon the appropriate use of the direct oral anti-coagulants (DOACs). The DOACs comprise both the direct thrombin inhibitor (DTI) dabigatran and to date at least 3 oral anti-Factor Xa antagonists (anti-Xa) viz. rivaroxaban, apixaban and edoxaban. Edoxaban is not yet commercially available whereas apixaban is to be released shortly in South Africa. Randomised controlled trials with these agents have evaluated >200 000 patients. It has been shown that the new agents have a comparable or improved efficacy to vitamin K antagonists (eg. warfarin) with an improved safety profile, are convenient to use and are cost-effective. The trials have also illustrated that there are unmet clinical needs, a need for risk assessment and clinical outcomes which might be improved even further.

For simplicity, I shall first deal with general considerations surrounding the use of a DOAC and then with each of the 3 treatment indications in turn, rather than in the sequence in which the presentations were delivered.

**General considerations**

Drug interactions with DOACs, though fewer than with warfarin, must be kept in mind. The main concerns relate to the anti-arrhythmic drugs frequently used in AF, especially verapamil and amiodarone (Heidbuchel H et al, European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace, 2013; 15: 625-51). Naproxen increases apixaban’s blood level by 50%.

DOACs must not be used in patients with mechanical prosthetic valves or in moderate / severe mitral stenosis. Their use in other valvular disease and with bioprosthesis valves is acceptable.

When transitioning from warfarin to a DOAC wait until the INR falls <2.0.

The absence of a reversal agent is not a contraindication to DOAC. The incidence of bleeding and the outcomes of bleeding are similar to those of warfarin. Adexanet alfa is a universal reversal agent for FXa agents which is under development. The antibody fragment idarucizumab is being developed as an immediately acting antidote for dabigatran.
Aripazine is another anticoagulant reversal agent that is being researched. It is reported to have a wide spectrum of effect which includes all NOACs, argatroban, heparin and fondaparinux.

It may be useful to estimate the anticoagulant activity of a DOAC in situations of overdose, questionable compliance, urgent intervention, extremes of body weight, children and in patients with impaired kidney function. The dose administration to sampling time is critical to the interpretation of the anti-FXa test. In the rare instances where it is necessary to establish the effect of a DOAC, the following tests may be used:

<table>
<thead>
<tr>
<th>DOAC Combination</th>
<th>Test 1</th>
<th>Test 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran or rivaroxaban</td>
<td>Prothrombin time</td>
<td>If normal, assume little effect</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Hemoclot</td>
<td>Quantitative measure of effect</td>
</tr>
<tr>
<td>Rivaroxaban or apixaban</td>
<td>Anti-FXa</td>
<td>Quantitative measure of effect: Use reagent for the specific drug</td>
</tr>
</tbody>
</table>

When treating bleeding, follow the protocol proposed by Heidbuchel et al. Do not attempt reversal of DOACs unless bleeding is severe and life-threatening. Four factor concentrates and / or NovoSeven should be withheld from non-critical cases of bleeding because they increase the risk of stroke. Consider consulting a haematologist in these instances. Four factor PCC reverses rivaroxaban completely but has no effect on dabigatran.

Prospective studies are needed to validate the safety of cardioversion when the patient is treated with a DOAC. Cardioversion should be delayed until the patient has been on treatment for 30 days. There is little information regarding the management of the patient on a DOAC who has new-onset AF.

Avoid agents that could cause a gastro-intestinal (GI) bleeding. Reconsider the concomitant use of aspirin in patients with coronary artery disease. The prophylactic role of proton pump inhibitors is uncertain as 50% of the GI bleeding encountered originates in the lower tract.

A study from Dresden has shown no benefit from heparin bridging with more bleeding in those getting heparin (Eur Heart J). The duration of withdrawal of NOAC before surgery depends on the existing bleeding risk. The drug (half-life, clearance), patient (renal function, conmeds) and procedure (bleeding risk, thrombosis risk) all have to be considered. Withhold the DOAC before minor surgical procedures for 24 hours, for 2-3 days if the bleeding risk is higher, and for 4 days if there is chronic kidney injury.

Carefully consider when to restart DOAC after a surgical procedure. Recall that NOACs, unlike warfarin, have a rapid onset of effect so that full anticoagulation is achieved on the first day of treatment.

DOACs have been shown to be cost-effective in a number of studies.

Cost remains the biggest barrier to DOAC use.

*Non-valvular atrial fibrillation (NVAF)*
By non-valvular atrial fibrillation is understood that the patient does not have moderate or severe mitral stenosis nor an implanted mechanical heart valve prosthesis.

It may be difficult to detect AF in a patient presenting with a stroke. There is a pronounced benefit of prolonged monitoring to detect AF following a cryptogenic stroke. AF detection is increased 5-fold with an implantable REVEAL device. One unreported study (CRYSTAL AF, Bernstein RA) found a higher incidence of AF after 1 year of monitoring compared to 6 months, and at 3 years compared to 1 year with AF detected in fully 30% by that time. NT-proBNP is an excellent marker for the risk of AF and predicting the likelihood of stroke. It adds additional prognostic evidence to CHA\textsubscript{2}DS\textsubscript{2}-VaSC score (Hijazi, ARISTOTLE trial). In the as yet unvalidated BEST score the risk of stroke, in decreasing order of importance, was determined by prior stroke/TIA, NT-proBNP, hs-troponin T, and age. Granger suggested using these biomarkers as a tie-breaker in dubious cases when deciding upon the need for anticoagulation. In the trials, DOACs were as effective as warfarin in patients who had had a stroke previously. Risk factor control in AF patients after a stroke should receive attention. A substudy of the ARISTOTLE trial found that the risk of stroke was 50% higher in patients whose BP was not controlled.

Warfarin reduces stroke >60% and mortality by 26% yet only 50% of patients currently receive appropriate treatment. It is estimated that appropriate warfarin treatment would reduce the worldwide stroke incidence by 2 million per year. In comparison to warfarin, DOACs reduce stroke as much as warfarin, reduce the rate of intracranial haemorrhage (ICH) encountered with warfarin by 50% and reduce mortality by a further 10%. An FDA study has confirms these results. The European and US guidelines for anticoagulant treatment in AF are now very similar regarding the recommendations for DOAC use. The newest US guidelines recommend a DOAC if “unable to maintain a stable INR” on warfarin.

The GARFIELD multinational registry of AF patients reveals an average age 69 years with a third >75 years. 80% have HT. Their average CHADS-VaSC score was 3.2. The inappropriate use of anticoagulation is noteworthy with both over-treatment in low risk patients and under-treatment in 10-15% of high risk cases. Only 50% of warfarin-treated patients have adequate INR control. Comparing good INR control to poor control reveals increased rates of stroke, major bleeding and mortality in the latter. Patients with poor control do worse that those not taking warfarin. Reassuringly, the data from the most recent (third) GARFIELD cohort does show some improvement in the treatment pattern.

The CHA\textsubscript{2}DS\textsubscript{2}-VaSC score is generally used to select the right treatment for the AF patient. Nonetheless, patients with AF are heterogenous. A CHA\textsubscript{2}DS\textsubscript{2}-VaSC score of 1 makes anticoagulation optional and requires careful decision making. Other factors such as the left atrial size and the NT proBNP may be considered in borderline cases. Although aspirin alone is ineffective in preventing stroke and systemic embolism in AF, dual anti-platelet therapy with aspirin and clopidogrel may be considered in patients unable to take anticoagulant/s if the CHA\textsubscript{2}DS\textsubscript{2}-VaSC score is >2. A Swedish study has shown that there is benefit from warfarin treatment even in a group with a low stroke risk and a high bleeding risk. Although DOACs offer reductions in both stroke and mortality their use is associated with a 25% increase in GI bleeding, 50% of which occurs in the lower GI tract. DOACs are indicated in a variety of circumstances which may involve patient preference, patients who are naïve to
anticoagulant treatment, patients with an unstable INR, or even patients on stable VKA therapy. GARFIELD has demonstrated a 300% increase in DOAC use between Cohorts 1 and 2. In trying to choose between the DOACs, network analyses show less bleeding with apixaban, less stroke with dabigatran and more myocardial infarction with dabigatran, thus a preceding history of any of these conditions may influence the choice of agent. In a multinational survey, once daily therapy was preferred by 80% of patients.

Left atrial appendage occlusion seems to be effective in preventing stroke in patients at high risk of bleeding and may offer an alternative to patients unable to take any anticoagulant.

Managing an ischaemic stroke in the patient on a VKA or DOAC presents a significant problem. Thrombolysis should not be given to patients on warfarin if the INR is >1.5. The timing of thrombolysis in patients on a DOAC should be governed by the time the last dose was taken. Catheter intervention may be a useful alternative in these settings.

Trials are being planned to evaluate dabigatran (RESPECT ESUS) and rivaroxaban in cryptogenic stroke.

**Anticoagulation in ACS**

It is important to recognize that plaque rupture or erosion is neither singular nor rare. 9% of fatal road traffic accident victims are found to have an incidental plaque disruption with twice this incidence in patients with diabetes or hypertension. Most of these lesions repair themselves.

From the GRACE registry, the 5 year mortality is around 20% after any form of ACS (whether unstable angina, non-ST segment elevation myocardial infarction or ST segment elevation myocardial infarction). 67% of these deaths occur after hospital discharge (Nat Clin Pract Cardiovasc Med 2008 5 580-9). The incidence of recurrent events is also significant – 50% of ACS patients will require readmission for unstable angina. Half of these episodes will be due to new lesions. Both environmental and genetic factors play a role in disease progression after ACS. Merlini has shown that thrombin generation amplifies the thrombotic risk for up to 6 months post-ACS. Genetics also impact upon the occurrence of first and recurrent ACS – 9q21 is one of the loci implicated. Currently research is directed towards the early detection of “vulnerable plaque.” Sodium fluoride PET-CT imaging can identify localized upregulation of inflammation in the coronary tree (Dweck, J Am Coll Cardiol, 2012).

A meta-analysis of warfarin given after myocardial infarction indicated that a benefit derived from anticoagulation (Rothberg, Ann Int Med 2005; 143: 241-50). ATLAS ACS, which compared the effect of rivaroxaban 2.5 mg bd in combination with aspirin and clopidogrel to aspirin and clopidogrel alone, showed reductions in the composite endpoint, all-cause mortality and stent thrombosis. There was an increase in bleeding but there was no increase in fatal bleeding with the low dose. These findings were not reproduced by the APPRAISE-2 study in which full dose apixaban was employed. The APPRAISE-2 results looked better when stroke or TIA patients were excluded. Stent thrombosis was reduced in the trial. Though the comparison is of dubious value, a cross trial comparison between PLATO (ticagrelor) and ATLAS ACS shows very similar outcomes.
Patients with STEMI and NSTEMI may be suitable for aspirin, clopidogrel and rivaroxaban treatment after their presentation. However the balance between the ongoing ischaemic risk and the bleeding risk should always be considered first. It is considered inappropriate to treat these patients with the third generation P2Y12 inhibitors (prasugrel or ticagrelor) in combination with a DOAC as the bleeding risk is anticipated to be prohibitive. It is currently recommended to continue rivaroxaban for 1 year post-MI, though the Kaplan-Meyer curves of ATLAS ACS seem still to be separating at that time point.

In patients with ACS requiring anticoagulation for AF, it is pertinent to reduce their exposure to “triple therapy” with aspirin, clopidogrel and warfarin to a minimum. When triple therapy is no longer needed it would be reasonable to first discontinue aspirin in keeping with the findings of the WOEST trial. However, the WOEST results require confirmation in a larger study before they may be regarded as generally applicable. There is no proven role for 3rd generation P2Y12 anticoagulants in triple therapy.

**Venous thromboembolism**

30% of individuals with venous thromboembolism (VTE) will suffer a recurrence. Although the incidence of recurrence is less after provoked deep venous thrombosis (DVT), both provoked and unprovoked DVT have significant recurrence rates. Recurrences are associated with a 47% mortality rate. Although persistent hypercoagulability may be due to anti-phospholipid syndrome, Factor V Leiden, prothrombin mutation and unknown familial factors, there is no difference in recurrence rates between thrombophilic and non-thrombophilic groups. An interaction between innate and environmental factors influences risk. The updated Vienna risk score for recurrence includes gender, location of first DVT and the current D-dimer. The RESONATE study showed a 92% reduction in recurrence with dabigatran after 6 months of standard anticoagulation. However, recurrences occurred once dabigatran was discontinued, tracking the same rate as the placebo-treated group. It is recommended that anticoagulation should be continued despite the absence of residual evidence of pulmonary embolism (PE) on scan.

Current streamlined treatment recommendations allow for upfront rivaroxaban / apixaban or initial parenteral anticoagulation followed by dabigatran / edoxaban after some days. DOACs are effective in patients with extensive clot, in the aged, in frail patients, in patients with cancer and those with a stable INR (less major bleeding). The duration of anticoagulant treatment should be adapted according to the assessed risk of bleeding; the higher the risk the shorter should be the duration of anticoagulation. DOACs may facilitate the decision to prolong therapy because of their better efficacy-safety profiles.

DOACs offer the possibility of home-based treatment. The majority of PE patients may be treated with oral therapy at home or given early discharge. The PESI score may assist in stratifying patients suitable for home treatment. Updated pulmonary thromboembolism guidelines are expected to be released at ESC 2014.
Routine testing for PE in proximal DVT is not recommended. 60% of patients will have a defect and a positive finding will not alter treatment. Most patients should not be tested for thrombophilia.

There is no indication for DOACs in pregnancy. These agents are small molecules which will cross the placenta and anticoagulate the foetus. The conventional approach remains the use of low molecular weight heparin. Oral warfarin should not be used.