Unanswered Questions during the live event :

1. When to start anti coagulation in patient after hemorrhagic stroke?
2. Would you prescribe a DOAC to a patient where you suspect the INR variation on warf is due to bad adherence?
3. In end stage renal disease GFR < 20 which NOAC is best to use? Which is the best OAC to give if we have renal failure?
4. How about NOAC actions in Pregnancy and lactating mother? Can we give NACO in pregnant women?
5. I think we need much more trails from different countries to get accurate data.
6. What NOAC can be used as long acting function...is there any?
7. Does Noac produces rebound phenomenon when stopped?
8. If the risk of bleeding is mostly related to c-through as has been shown with dabigatran and edoxaban do you think that OD is safer aproach?
9. If OD regiment increases the effectiveness of antihypertensive medication do you think the same applies to DOAC (regarding clinical outcomes)
10. In some country existing important difficulty-like price NOACs bad compliance(adherence) small time for pts education high % pts on waefarin and acenocumarol...-that is the big problem!
11. Low compliance-adherence=contraindication for NOAC therapy?
12. What is current options for the monitoring of anticoagulation intensity of NOAC?
13. Dabigatran 2x150 mg vs 2x110 mg and risk of GI bleeding compared with Xa f.inhibitors?
14. Is it any valvular disease contraindications for noac ? Example mild lesion
15. Do you think it is possible to prescribe NOAC to young male patient (46 year0 with ASD (patent foramen ovale with aneurism of interatrial septum) with pulmonary hypertension of 1 stage-(45 mmHg-pressures in PA)?
16. Please comment about betrixaban
17. How to manage patients who have stroke while on NOAC?
18. How manage NOAC in acute coronary syndrome? and which place of rivaroxaban in this indication?

Replies from the Faculty Members :

1. **When to start anti coagulation in patient after hemorrhagic stroke?**

Trial-based guidelines regarding NOACs in intracerebral haemorrhage are missing. By analogy to the use of VKAs, administration of NOACs may be restarted 4-8 weeks after intracerebral haemorrhage if cardioembolic risk is high and the risk of new intracerebral haemorrhage is estimated to be low. For patients with low cardioembolic risk and high bleeding risk, the indication for oral anticoagulation should be reconsidered. In practice, however, the same factors that are predictive for embolic stroke (age, hypertension, previous stroke, and others) are also predictive for haemorrhages. We should not forget that according to the labelling of VKAs and also of the NOACs, a history of a spontaneous intracerebral bleed constitutes a contraindication against anticoagulation, unless the cause of the intracerebral bleed has been reversed. This is especially true after an intracerebral bleeding in a patient with amyloid angiopathy.

It will always be a very difficult individual decision making whether to reconstitute anticoagulation of any type in patients who have experienced an anticoagulation related intracerebral haemorrhage. This is also true for extracerebral, intracranial haemorrhages such as subdural or epidural haemorrhages, both spontaneous or traumatic. Non-pharmacological prevention strategies such as ablation or occlusion of the atrial appendage should be considered as potential (and likely only partial) substitutes for the contra-indicated resumption of long-term anticoagulation.(1-3)

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2. **Would you prescribe a DOAC to a patient where you suspect the INR variation on warf is due to bad adherence?**

Some patients are reluctant to initiate warfarin or discontinue warfarin treatment due to the high burden associated with warfarin treatment (INR measurements and associated dose adjustments). Variations in INR measures may also constitute a negative feedback to the patient who may be reluctant to persist with warfarin treatment. So, if the problem of adherence is related to treatment non initiation or non-persistence due to the burdens associated to warfarin, switching to a NOAC may solve the problem.

3. In end stage renal disease GFR < 30 ml/min? Which is the best OAC to give if we have renal failure

Chronic kidney disease (CKD) is an important risk factor for both stroke and bleeding in anticoagulated patients with AF.(4-9) Each of the NOACs is eliminated via the kidneys to some degree: 80% for dabigatran, 50% for edoxaban, 33% for rivaroxaban, and 27% for apixaban. This results in substantially different plasma concentrations across the spectrum of creatinine clearance. For example, the area under the plasma concentration curve for dabigatran is 3.2 times greater in a patient with a creatinine clearance of 30 ml/min than in a patient with a clearance of 80 ml/min (US Dabigatran FDA Package Insert: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022512s000lbl.pdf). This relationship between NOAC plasma concentration and kidney function underlies the advice to reduce the doses of each of the NOACs in patients with CKD, as shown in Table 2 (see also the EHRA practical guide).(10)

With the dose reductions (based at least in part on renal function) that were part of the protocols in three of the four warfarin-comparator trials, the results were consistent for patients with creatinine clearance of 30–49 ml/min.(6-8) These findings provide confidence that NOACs can be safe and effective, compared with warfarin, for patients with moderate renal impairment. The AVERROES trial found that the benefit of apixaban compared with aspirin was similar in patients with and without stage III CKD.(5) In the ARISTOTLE trial, the major bleeding rate in patients with moderate renal impairment was lower with apixaban than with warfarin.(8) By contrast, major bleeding was similar with dabigatran (both doses) and warfarin in the RE-LY trial(7) and with rivaroxaban 20 mg daily and warfarin(11)

There are no clinical outcome data regarding the use of NOACs for patients with creatinine clearance (calculated by the Cockroft–Gault equation) of <30 ml/min. This includes patients on haemodialysis,(12) for whom warfarin provides uncertain benefit.(13) Until trial outcome data are available, warfarin is the preferred anticoagulant for these patient subgroups.(12) The FDA has approved apixaban for patients on haemodialysis without safety data from this population.

The FDA review of the ENGAGE AF trial raised a question of efficacy among patients with high normal creatinine clearance (>95 ml/min), and resulting lower plasma concentration of drug: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM421613.pdf). There was a statistically lower treatment effect (interaction p=0.002) for prevention of ischaemic stroke with edoxaban compared with warfarin for patients with creatinine clearance >95 ml/min, and a higher stroke rate with edoxaban in this subgroup.

Whether this was due to under-dosing of edoxaban, particular effectiveness of warfarin in this subgroup, or a combination of factors is not known.

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On the other hand, if the variations in INR are the result of suboptimal day to day implementation of the dosing regimen, switching to a NOAC may not resolve the problem. It is recommended to build a strong habit of medication taking before switching such a patient to a NOAC.

4. How about NOAC actions in Pregnancy and lactating mother? Can we give NOAC in pregnant women?

NOACs are contraindicated in pregnancy and lactating mothers

5. **I think we need much more trails from different countries to get accurate data.**

Agree. AEGEAN is the first clinical trial investigating the impact of an intervention on adherence to apixaban. More research in the field of adherence to NOACs is urgently needed.

6. **What NOAC can be used as long acting function..is there any?**

NOACs have half-lives ranging between 9 and 14 hours. If we assume that the action of NOACs on the anticoagulation process is closely related their pharmacokinetics, one can conclude that their duration of action is relatively short.

7. **Do NOACs produce rebound phenomenon when stopped?**

No rebound phenomenon observed in normal subjects or patients

8. **If the risk of bleeding is mostly related to c-through as has been shown with dabigatran and edoxaban do you think that OD is safer aproach?**

There is NO solid evidence that the risk of bleeding would be associated to c-through. This myth is derived from spurious analysis, ignoring key confounding variables, and should not be considered in the choice between NOACs.

9. **If OD regiment increases the effectiveness of antihypertensive medication do you think the same applies to DOAC (regarding clinical outcomes)**

In practice, hypertension remains a poorly managed condition despite the wide availability of OD treatments. High prevalence of nonadherence to OD antihypertensive medications remains a problem of striking magnitude. One should thus expect that the same applies to NOACs in medical practice.

10. **In some country existing inortant difficulty-like price NOACs bad compliance(adherence) smal time for pts education high % pts on waefarin and acenocumarol...-that is the big problem!**

Cost of medication is certainly a barrier to medication adherence. Affordability of NOACs treatment should be a priority in health budgets

11. **Low compliance-adherence=contraindication for NOAC therapy?**

NOACs have predictable and fast onset/offset action on the anti-coagulation process. While those properties constitute major advantages in the daily management of oral anticoagulation, the fast offset of NOACs requires precise implementation of the dosing regimen to guarantee continuity of drug action.

On the other hand, warfarin has a longer duration of action and is thus more forgetful for single missed doses. However, warfarin action is affected by many other factors like food and drug interaction that make the process and anti-coagulation unpredictable in some patients.

12. What are current options for the monitoring of anticoagulation intensity of NOACs?

There is no need to monitor NOACs. Dose adaptation might be necessary depending on age (>75 years), kidney function (CrCl < 50 ml/min), body weight (< 50 kg) or concomitant medication (dual antiplatelet therapy). In an emergency situation the activity dabigatran is measured nby the aPTT or TT, the activity of apixaban, edoxaban or rivaroxaban by anti-Xa activity.

13. Dabigatran 2x150 mg vs 2x110 mg and risk of GI bleeding compared with Xa-inhibitors?

There are no direct comparisons. Compared to warfarin 2 x 150 mg dabigatran, 1 x 20 mg rivaroxaban and 2 x 60 mg edoxaban increase the risk of GI bleeding. Dabigatran 2 x 110 mg has the same GI bleeding risk as warfarin. Apixaban has a reduced riks of GI bleeds.

14.. How to manage patients who have stroke while on NOAC?

Patients with acute stroke requiring thrombolysis or thrombectomy

Anticoagulants, including NOACs, present special challenges for the emergency management of ischaemic stroke. Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) within 4.5 hours after symptom onset is currently the only licensed medical therapy for stroke. As per licence, anticoagulation is a contraindication to thrombolysis because it can increase the risk of intracerebral haemorrhage.

In a recent series, almost 10% of acute ischaemic stroke patients were taking vitamin K antagonists (VKAs) at the time of the event.(14) However, up to 20% of patients with acute stroke are unable to convey information about anticoagulation status when presenting in the emergency room. Rapid assessment of coagulation status at presentation is necessary to guide a decision for or against thrombolysis. For those taking a VKA, this can be done quickly by using a point-of-care device to measure the International Normalized Ratio (INR).(15) Beyond the qualitative determination of whether a patient is anticoagulated, the threshold intensity at which thrombolysis can safely be used is uncertain.(16) Data from two large observational registries in the USA and Europe suggest that thrombolysis does not increase the risk of intracerebral haemorrhagic complications in patients on VKA when the INR is $\leq$1.7.(17, 18)

In randomized trials of anticoagulation, the annual risk of ischaemic stroke among patients with AF ranged from 1–2% for primary to 2–3% for secondary stroke prevention.(19) Experience with patients taking VKA suggests that low levels or an absence of anticoagulation with NOACs might allow thrombolysis with rtPA. Extrapolation of intracerebral haemorrhagic risk may not be appropriate, and safety thresholds for the NOACs have not been established. An observational study in 78 patients on NOACs undergoing systemic thrombolysis and or thrombectomy showed no increased bleeding risk.(20) During long-term therapy, the risk of spontaneous intracerebral haemorrhage in patients treated with NOACs was consistently about half that during VKA therapy, and pharmacodynamic differences may contribute to this difference in rates of intracranial haemorrhage (ICH).(19) In preclinical experiments, haemorrhagic transformation of brain infarcts after thrombolysis is elevated in rodents exposed to VKA but not in those given NOACs when compared with animals that were not anticoagulated.(21, 22)

Management of ischaemic stroke in patients treated with NOACs must balance efficacy against safety concerns.(23-25) Currently, no emergency point-of-care test is available to test quantitatively for the anticoagulant effect of any of the NOACs. For dabigatran, the activated partial thromboplastin time can be used as a qualitative screening test. Diluted thrombin time or the ecarin clotting-time assays allow quantitative assessment of anticoagulation intensity corresponding to dabigatran plasma levels. For rivaroxaban, apixaban, and edoxaban, substance-specific Factor Xa assays are needed. The EHRA recommendations have defined levels of anticoagulant effect that are deemed to be safe for intravenous thrombolysis, but confirmation of safety is needed.(25) In view of the relatively short half-life of NOACs in patients with normal renal clearance, another approach is to consider thrombolysis only when more than 2–4 half-lives have elapsed since NOAC dosing. Interventional mechanical thrombectomy is strongly recommended in anticoagulated patients with proximal intracranial vessel occlusion.(25) Finally, the advent of specific reversal agents for NOACs, without prothrombotic side effects, may in the future allow rapid termination of the anticoagulant effect before starting thrombolysis. Whether this approach is safe and feasible needs to be determined. Evidence from large prospective registries is needed to evaluate this important management issue.

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