Meeting Impression

Latest Frontiers in Anticoagulation Therapy, *Live CME webcast*, January 12, 2018 – Amsterdam, The Netherlands

LATEST FRONTIERS IN ANTICOAGULATION THERAPY

In this live webcast, prof. John Eikelboom (McMaster University, Hamilton, Ontario, Canada) summarized recent clinical evidence on non-vitamin K antagonist anticoagulants / direct oral anticoagulants (NOACs or DOACs) in patients with both atrial fibrillation (AF) and venous thromboembolism (VTE). The webcast was moderated by prof. Saskia Middeldorp (Academic Medical Center, Amsterdam, The Netherlands) and dr. Hanna Pohjantähti-Maaroos (Kuopio University Hospital, Finland).

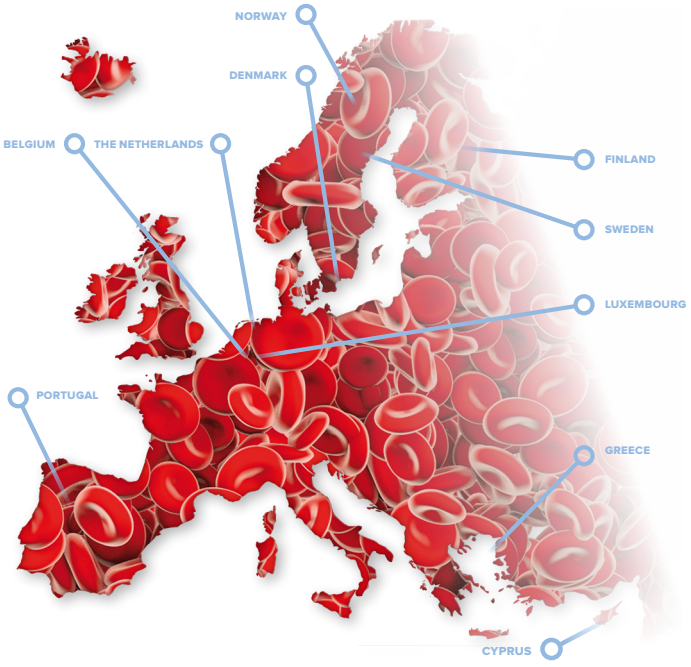
The panel discussed the clinical guidance based on these novel insights and provided an expert perspective on how to use these agents in the most optimal way.

TOPICS

Anticoagulation 2017:
The key lessons and implications from recent clinical trials

Practical guidance on NOACs and safety:
How to deal with challenging situations in AF

Appropriate use of NOACs:
What is state of the art for 2018?



Anticoagulation 2017: The key lessons and implications from recent clinical trials

Prof. Eikelboom discussed data from four recent trials with NOACs in various patient groups. He started by presenting two clinical trials on the use of the NOAC dabigatran in AF patients undergoing ablation / after PCI (RE-CIRCUIT and RE-DUAL PCI). Anticoagulant therapy is important around the time of ablation as patients are at risk of stroke. In the past, if a patient was treated with a NOAC prior to ablation, treatment would have to be interrupted and then either bridged with heparin or switched to warfarin, as these have been used in an uninterrupted fashion during ablation. However, switching to warfarin is cumbersome for patients and physicians, and starting and stopping is not only inconvenient, but more importantly, it is also associated with risk of periprocedural bleeding.

RE-CIRCUIT: Uninterrupted dabigatran versus warfarin in patients undergoing catheter ablation of AF

RE-CIRCUIT[1] was a study in approximately 700 patients undergoing ablation for AF. The goal of this study was to determine the safety and efficacy of dabigatran (150 mg bid) given in an uninterrupted way, compared with uninterrupted warfarin, in patients undergoing ablation. Patients who were randomized to uninterrupted dabigatran had a 5.3% absolute reduction in major bleeding (95% CI: -8.4 to -2.2, P=0.0009) as compared with those on warfarin and a relative reduction in major bleeding of 77.2%, with no difference in thromboembolic events.
As a result of this trial, the 2017 expert consensus statement on catheter and surgical ablation of AF adopted catheter ablation of AF as a Class IA indication for uninterrupted dabigatran.

RE-DUAL PCI: Dual antithrombotic therapy with dabigatran after PCI in patients with AF

The second study, RE-DUAL PCI[2], was conducted in patients with AF who underwent PCI with stenting. The RE-DUAL PCI study compared 2 doses of dabigatran

(110 mg bid / 150 mg bid) combined with a P2Y12 inhibitor to triple therapy with warfarin, P2Y12 inhibitor and ASA in the control arm.
The results showed a substantial reduction in bleeding with dual therapy with dabigatran and a P2Y12 inhibitor, particularly intracranial bleeding (HR: 0.30 (95% CI: 0.08–1.07, P=0.064); HR: 0.12 (95% CI:0.02–0.98, P=0.047), for dabigatran 110 mg or 150 mg bid, respectively), but no difference with respect to the incidence of a composite efficacy end point of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularization between treatment arms.

It is expected that the results of RE-CIRCUIT and RE-DUAL PCI will most probably change clinical practice and that NOACs will become the first line combination therapy post PCI

During the discussion, the question was raised whether the results of RE-DUAL PCI apply to patients on hemodialysis. This is not the case, as the NOACs in general and dabigatran in particular are at least partly renally cleared and should not be used in end-stage kidney disease. For clinicians it is important when reading a publication to not only look at inclusion and exclusion criteria, but also at the baseline characteristics of the population, to be sure whether the data can be generalized to a specific patient group.
Although warfarin is not eliminated renally, it should also be used with great precaution in end-stage kidney disease because of the high bleeding rate.

Overall, in both the RE-CIRCUIT and RE-DUAL PCI study, dabigatran demonstrated to be effective and safer than warfarin in patients with AF. As a result, it is expected that these data will most probably change clinical practice and that NOACs will become the first line combination therapy post PCI.

COMPASS: Rivaroxaban with or without aspirin for cardiovascular among patients with stable atherosclerotic vascular disease

Patients with stable coronary or peripheral artery disease show a substantial residual risk despite long-term treatment. The COMPASS trial[3,4] addressed this residual risk by evaluating low-dose rivaroxaban with or without aspirin for cardiovascular prevention. The study included 27,395 patients in three arms: 1) the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily; 2) rivaroxaban 5 mg twice daily, and 3) the control arm aspirin 100 mg once daily. The two rivaroxaban doses were selected based on the results of the ATLAS ACS 2–TIMI 51 study[5].
The combination of low-dose rivaroxaban and aspirin significantly reduced the risk of the primary outcome of CV death, stroke, and myocardial infarction by 24%, compared with aspirin (95% CI: 0.66-0.86, P<0.0001). Rivaroxaban alone, as compared with aspirin alone, produced an intermediate result, a 10% risk reduction, which was not statistically significant (95% CI: 0.79-1.03, P=0.12).
In addition to the primary outcome, there were several additional outcomes. With the combination of rivaroxaban and aspirin, there was a reduction in major adverse limb events (MALE). This was reduced by 47% (95% CI: 0.35-0.80, P=0.002) and likewise amputations were reduced by 52% (95% CI: 0.26-0.89, P=0.02).
There was a price to be paid in terms of bleeding: a 70% increase in major bleeding (95% CI 1.40-2.05, P<0.0001).
How should the benefits and the risks of treatment be weighed? The ultimate measure of net benefit is mortality. In COMPASS there was an 18% reduction in mortality (95% CI: 0.71-0.96, P=0.01).

When looking at the prespecified net clinical benefit outcome, which included a decrease in ischemic events and an increase of most serious bleeding events, there was a reduction of about 20% in the net clinical benefit outcome, using a combination of rivaroxaban and aspirin, compared with aspirin alone. This was paralleled by a similar magnitude reduction in mortality, which is in the end the best measure of net benefit.

Giving low-dose rivaroxaban plus aspirin is the first long-term antithrombotic therapy that shows a mortality reduction since aspirin, clopidogrel or clopidogrel and aspirin, ticagrelor and aspirin, warfarin and aspirin or warfarin alone. The combination of 24% reduction in the risk of the primary outcome of CV death, stroke, and myocardial infarction, a reduction in the complications of stroke and amputation, and the mortality benefit will be attractive for clinical practice. Translating these findings to practice can be done by starting with the higher risk population, and then moving to intermediate risk. In the lowest risk population there may be no need to use the combination of low-dose rivaroxaban and aspirin.

Hokusai VTE-Cancer: LMWH/edoxaban versus dalteparin for VTE associated with cancer

When patients with cancer and VTE are treated with heparin followed by warfarin, there is a very high recurrence rate of VTE of up to 10 to 20% per year. We know this group is difficult to manage.
In the CLOT trial[6], patients treated with dalteparin had a substantial reduction in recurrent thrombotic events as compared with those treated with warfarin. This led to the adoption of dalteparin as the standard of care in these patients. Because of the quite high number of drop-outs after 3 to 6 months, a simpler treatment that is as effective and safe would be a major advance.
The Hokusai VTE cancer study[7] compared edoxaban-

based therapy (60 mg once daily) with a lead-in of 5 days of LMWH, with a control group that received dalteparin given in the CLOT regimen (200 IU/kg ➔ 150 IU/kg). Patients were followed up to 1 year. The primary outcome was a composite of thrombotic and bleeding events. The two treatments were essentially the same in terms of this primary outcome.
Recurrent VTE occurred in 7.9% in the edoxaban group and in 11.3% in the dalteparin group (difference in risk, −3.4 percentage points). Major bleeding occurred in 36 patients (6.9%) in the edoxaban group and in 21 patients (4.0%) in the dalteparin group (difference in risk, 2.9 percentage points; 95% CI: 0.1 to 5.6).
There was a 3.4% lower rate of VTE (95% CI: −7.0 to 0.2) and a 2.9% higher risk of bleeding (95% CI: 0.1-5.6) in this study, but overall edoxaban was noninferior to dalteparin. This will probably lead to the adoption of edoxaban-based therapy as an attractive alternative to the current standard of care for the treatment of VTE.

In the discussion, prof. Eikelboom answered to the question whether this trial would change his practice, that in the vast majority of people with cancer and thrombosis he would use edoxaban. He was also reassured by the fact that there were no fatal pulmonary embolisms, and no fatal bleeds in the edoxaban group, and the investigators very carefully looked at the severity of bleeding. In fact, the slight excess of bleeds with edoxaban was confined to less severe bleeds.

In the Hokusai VTE cancer trial, there was a slight excess in gastro-intestinal (GI) bleeding, which seemed to be confined to those with GI cancers. In the Select-D trial[8] with rivaroxaban in the same type of patients, it was decided not to include any GI cancers because of the fear of increased bleeding. It is unfortunate that these patients were not included, as more data is needed. Several other studies are ongoing in this area that will hopefully shed more light on this topic.

Practical guidance on NOACs and safety: How to deal with challenging situations in AF

All clinicians are familiar with dealing with emergencies in patients on anticoagulants, and bleeding remains the number one concern for clinicians. Now there is good news, because with the recent studies of reversal therapy for dabigatran, there is the ability to instantaneously, completely, and permanently reverse anticoagulation, which is a great progress in anticoagulation. A simple drug can now be given to stop anticoagulation, with no monitoring, which is an advantage.

There are several principles in bleeding management:
- Hold drug(s)
- Local measures to control bleeding
- Resuscitation (i.v. access, fluid administration, blood product transfusion)
- General hemostatic measures
- Percutaneous and/or surgical intervention to stop bleeding

Despite these types of measures, there are patients on anticoagulants in whom the bleeding cannot be controlled. In patients on a NOAC the good news is that these agents have a short half-life, so they wear off rapidly.

For dabigatran, there is now the ability to instantaneously, completely, and permanently reverse anticoagulation

NOAC-specific approaches for bleeding management are to determine the presence, concentration and expected duration of the drug, limit drug absorption, and remove, bypass or reverse the drug.

Indications for specific reversal are bleedings that are life-threatening (e.g., intracranial), occur in a critical organ (e.g., pericardial, retroperitoneal), are ongoing (despite measures to control bleeding) or have an expected long delay in spontaneous restoration of normal hemostasis (over-anticoagulation, renal failure).

NOAC reversal agents[9]:

	Idarucizumab	Andexanet alfa
Structure	Humanized Fab fragment	Human rXa variant
Target	Dabigatran	FXa inhibitors
Binding	Non-competitive High affinity	Competitive
Phase 2 results	Rapid complete sustained reversal	Rapid complete reversal during infusion
Phase 3 trial	Completed (RE-VERSE AD)	Ongoing (ANNEXA)

The RE-VERSE AD trial[10,11] was a cohort study that included 503 people with life-threatening bleeding (group A) and subjects requiring emergency surgery (group B).
The primary endpoint of RE-VERSE AD was reversal of the anticoagulant effect of dabigatran within four hours as measured by diluted thrombin time (dTT) and ecarin

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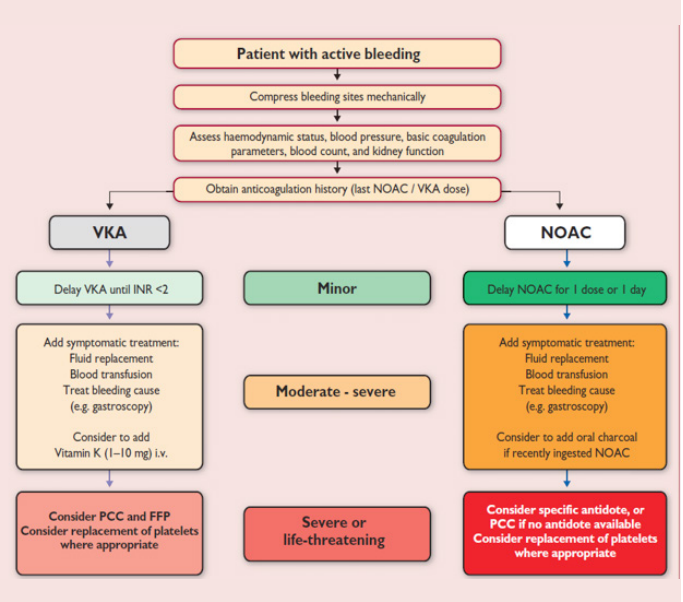
clotting time (ECT), and was observed in 100% of patients. Reversal became evident immediately after administration of idarucizumab and was maintained for 24 hours in most patients. Reversal was independent of age, sex, kidney function or dabigatran concentration at baseline. A single 5 g dose of idarucizumab was sufficient in 98% of patients. The effects were consistent both in patients requiring urgent surgery or intervention, and in patients presenting with uncontrollable or life-threatening bleeding.
Time to cessation of a GI bleeding was 3.5 hours; of non-GI, non-intracranial hemorrhage this was 4.5 hours. For group B, in more than 90% of people there was no excess in bleedings, and thromboembolic event rates were low at 30 and 90 days (4.4% at 30 days; 6.3% at 90 days).

The use of andexanet alfa in patients with acute major bleeding following a factor Xa inhibitor to reverse anti-factor Xa activity is being evaluated in the ongoing ANNEXA-4 trial[12,13], a cohort study restricted to patients with major bleeding within 18 hours after having received direct (apixaban, rivaroxaban, edoxaban) or indirect (enoxaparin) factor Xa inhibitors. Interim results of this study included 67 patients with a mean age of 77 years[12]. All patients first received andexanet alfa as a bolus (15-30 min), then 2 hours of infusion. Dosing of andexanet alfa was based on the timing and dose of the factor Xa inhibitor the patient had received.
Changes in measures of anti-factor Xa activity were evaluated and clinical hemostatic efficacy was assessed during a 12-hour period. All the patients were subsequently followed for 30 days. Andexanet alfa substantially reduced anti-factor Xa activity in patients with acute major bleeding associated with factor Xa inhibitors, with effective hemostasis occurring in 79%. The reversal was incomplete and not sustained when the infusion was stopped.
The overall rate of thromboembolism was 12% at day 30, which is higher than with idarucizumab.
Andexanet alfa is currently under review for regulatory approval, whereas idarucizumab is now widely available in Europe. The ESC guidelines have already adopted the recommendation for the use of idarucizumab in people with life-threatening bleeding who were treated with dabigatran[14].



Management of active bleeding in patients receiving anticoagulation.

In the discussion, the question was asked how bleeding risk can be reduced. Prof. Eikelboom emphasized that it is important to monitor blood pressure, avoid concomitant use of aspirin and NSAIDs, and switch to a NOAC when a patient is on warfarin or another VKA and has poor INR control.
In patients with a history of GI bleeding, a proton pump inhibitor (PPI) could be started prophylactically, although that has not yet been proven.

While most clinicians believe it is important to have antidotes in case of bleeding, most patients who need an antidote are those undergoing an emergency surgery.

Appropriate use of NOACs: What is the state of the art for 2018?

Current state of the art choice of anticoagulant includes different indications varying from VTE prevention, VTE cancer to AF. There are some issues to consider, mainly convenience and safety. For AF, for example, there is a clear efficacy advantage as compared with VKA, particularly with dabigatran 150 mg and also with apixaban. With respect to safety, fewer intracranial hemorrhages translate into a favorable profile for mortality. An additional advantage of using a NOAC over warfarin is that NOACs do not require monthly monitoring of INR.

The arrival of NOACs has been a considerable development in anticoagulation therapy with important advances for patients

VKAs are still needed in some cases, for example, in patients with moderate to severe mitral stenosis and in patients with mechanical heart valves, warfarin is the drug of choice. There will always be groups that will not be able to take NOACs.

There are some points to consider in NOAC management[15]. Although NOACs are simple to use, they do still confer a risk of bleeding and it needs to be checked that patients are on the right dose, because there is a tendency to under-dose and patients themselves sometimes skip a dose. It is furthermore important to monitor renal function and prevent undesirable drug-drug interactions. With respect to follow-up, prof. Eikelboom strongly advocated to see every patient on a NOAC at least once a year and more often in case of renal impairment. Working environment (academic or not, hospital or not) and local healthcare system may determine how to organize this follow-up.

After that, treatment adherence and persistence are the biggest challenge for clinicians. Early careful patient education, engaging the patient and careful follow-up are crucial in this respect. Patients need to know why they are taking the medication and the importance of treatment adherence, they need to know the risks, and the importance of persisting despite the risk. Patients need to be informed about the different treatment options.

Prof. Eikelboom concluded the session by saying that the arrival of NOACs has been a considerable development in anticoagulation therapy with important advances for patients. Now supplemented by a reversal agent for dabigatran, it has completed the full circle of coagulation control, which is an incredible advance for patients.

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