# Novel anticoagulants in atrial fibrillation: focused update

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## Background

More than a half of the patients with atrial fibrillation (AF) are not adequately anti-coagulated, even though in prevention of ischemic stroke in this patient-population, there is strong evidence in favor of oral anticoagulant (OAC) therapy.
Most frequent factors causing this problem are: non-adherence to the Guidelines as well as limitations such as difficulties in the maintenance of INR within therapeutic range, necessity of monitoring and numerous interactions with food or other medications.
Although characterised as investigational agents, in the Guidelines for AF from 2010 (1), the new oral anticoagulants (NOAC) have ultimately been considered as preferable to Vitamin K antagonists (VKA).
Indeed in the interim period, three randomised trials (RE-LY, ROCKET AF, ARISTOTLE) (2,3,4) were finished, showing excellent results in favor of the NOAC.
New oral anticoagulants simplify greatly the anticoagulation regime: fixed daily dosage, wide therapeutic window, no need of monitoring and no food interaction.

## 1 - 2012 ESC Guidelines

1. In patients with CHA2DS2 -VASc **score≥2**
   Oral anticoagulant therapy is recommended (unless contraindicated) with:
   Dose adjusted VKA (INR 2-3); or
   A direct thrombin inhibitor (dabigatran); or
   An oral factor Xa inhibitor (eg. rivaroxaban, apixaban*)(Class I, Level of evidence A).
2. In patients with CHA2DS2 -VASc **score = 1**
   Oral anticoagulant therapy should be considered, based on an assessment of the risk for the bleeding complications and patient preferences with:
   A dose adjusted VKA (INR 2-3); or
   A direct thrombin inhibitor (dabigatran); or
   An oral factor Xa inhibitor (eg. rivaroxaban, apixaban*)(Class IIa, Level of evidence A). *Apixaban still waiting for approval.
3. In patients with CHA2DS2 -VASc **score of 0,** no antithrombotic therapy is recommended

It is important to know that when OAK is recommended, one of the NOAK should be considered instead of vitamin K antagonist for most patients with AF (Class IIa, LAvel of evidence A) (5).
For a look at improving Stroke risk assessment in atrial fibrillation, see previous journal here, stroke and thromboembolism risk stratification in chronic atrial fibrillation, see previous journal here.

## 2 - Risk of bleeding

When we decide to treat AF-patients with anticoagulant therapy, our utmost care is given to diminishing the risk of bleeding complications. In this regard, the new oral anticoagulants have shown much greater results than VKA. All new oral anticoagulants (rivaroxaban, apixaban, dabigatran) are safer than VKA, in regards to intracranial bleeding, where apixaban, and dabigatran (lower dose 110mg b.i.d.) are again safer than VKA in all major bleedings (Table 1).

Table 1: Major bleeding and Intra-cranial bleeding – ROCKET AF, RE-LY, ARISTOTLE

| | ROCKET AF | | RE-LY | | | | ARISTOTLE | |
|---|---|---|---|---|---|---|---|---|
| **Major bleeding** | Rivaroxaban | Warfarin | Dabigatran 110 | Warfarin | Dabigatran 150 | Warfarin | Apixaban | Warfarin |
| | Event rate | | Event rate | | Event rate | | Event rate | |
| | 3.6 | 3.4 | 2.71 | 3.76 | 3.13 | 3.76 | 2.13 | 3.09 |
| | *HR 1.04(0.90-1.20)* | | *HR 0.80(0.69-0.93)* | | *HR 0.93(0.81-1.07)* | | *HR 0.69(0.60-0.80)* | |
| | *p- value 0.58* | | *p- value 0.03* | | *p- value 0.31* | | *p- value <0.01* | |
| **Intra-cranial bleeding** | Rivaroxaban | Warfarin | Dabigatran 110 | Warfarin | Dabigatran 150 | Warfarin | Apixaban | Warfarin |
| | Event rate | | Event rate | | Event rate | | Event rate | |
| | 0.5 | 0.7 | 0.23 | 0.74 | 0.30 | 0.74 | 0.33 | 0.80 |
| | *HR 0.67(0.47-0.93)* | | *HR 0.31(0.20-0.47)* | | *HR 0.40 (0.27-0.60)* | | *HR 0.42(0.30-0.58)* | |
| | *p- value 0.02* | | *p- value <0.01* | | *p- value <0.01* | | *p- value <0.01* | |

Event rates are per 100 patients- years, based on first event in the safety population during treatment

## 3 - European heart rhythm association practical guide on the use of NOAC in patients with non-valvular AF

A writing group gave us this document as a guide how to use NOAC optimally, effectively and safely in clinical practice, based on available evidence. There are recommendations how to start and follow up the therapy with NOAC, how to measure the anticoagulant effect of NOAC, drug interactions and pharmacokinetics, how to deal with dosing errors, management of bleeding complications, planned surgical interventions and also switching between anticoagulant regimens.
The NOAC can immediately be initiated at the point where INR is lower than 2.0. If the INR is in the range of 2.0-2.5, NOAC should be started next day. For INR >2,5 the actual INR value and the half-life of the used VKA should be considered to estimate the time span when INR will drop below 2.5, and in that point measure INR again.
Switching from NOAC to VKA, need to have in consideration slow onset of action of VKA. NOAC and VKA should be administered concomitantly until INR reaches the minimal acceptable value of 2.0. A loading dose in not recommended for acenocumarol and warfarin, but is appropriate  with phenoprocoumon.
NOAC can be started once the intravenous unfractionated heparin (UFH) is discontinued, or when the next dose of LMWH would have been foreseen. The parenteral anticoagulant (UFH, LMWH) can be initiated when the next dose of the NAOC is due (6).

## 4 - Aspirin

The 2010 Guidelines for the management of AF, recommended Aspirin or oral anticoagulants (OAC) in patients with CHA2DS2 -VASc score = 1, but preferably OAC, where Aspirin or without antithrombotic therapy in patients with CHA2DS2 -VASc score = 0.
The use of Aspirin lowers the relative risk of ischemic stroke in AF-patients by 22%, whereas the OAC does it by 68%, which makes aspirin very insufficient.
The results of AVERROES (7) and BAFTA (8) trials show that Aspirin's safety profile is not good at all. Aspirin use increases the risk of intracranial bleeding above and beyond OAC. It is time to abandon the perception that Aspirin is safer alternative to OAC. Use of Aspirin as a monotherapy should be limited to the few patients who refuse any form of OAC and cannot tolerate aspirin-clopidogrel combination therapy due to excessive bleeding risk.

## 5 - Other guidelines

Focused 2012 Update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines (9) also prefer the new oral anticoagulants versus warfarin. In comparison, AHA/ASA Guidelines published in August 2012 (10), indicate that the NOAC are safer in respect to intracranial hemorrhage, yet equal to warfarin (provided INR in therapeutic range) in ischemic stroke prevention in AF.
For a look at symptomatic drug-resistant AF, look at previous journal here. Surgical management of lone AF, look at previous journal here, a review of recommendations for CRT in AF, look at a previous journal here, and for information on a live streaming event on how to manage NOACS click here.

## Conclusion

It seems that NOAC are preferable agents for stroke prevention in patients with non-valvular atrial fibrillation. Data indicators have yet to show which of the NOAC has better safety or efficacy profile.
It is crucial to remember that NOAC patients' compliance is even greater than with VKA, because if a patient skips few doses of the medicine than he/she practically remains non-anticoagulated.
Never forget that in patients with renal impairment dose adjustment may be necessary, whilst in end-stage renal failure warfarin still remains the only option.
The combination of NOAC with antiplatelet agents has yet to be researched.