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The New Blood Thinners in Atrial Fibrillation, Did They Keep Their Promise a Decade Later? And What About my Risky Older Patient?

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Abstract:

A decade after the Randomized Controlled Studies (as RCT's) on Direct Oral Anticoagulants as DOAC's, or as called by other names as:

• NOAC's (as novel oral anticoagulants or non- vitamin K dependent oral anticoagulants) or

• TSOAC (as target specific oral anticoagulants), have been published what have we learned?

According to the metanalyses of those RCT's (comparison to warfarin \ VKA and not a direct comparison) all of the DOAC's are either superior to warfarin (dabigatran 150 mg bid, apixaban) or noninferior (rivaroxaban, edoxaban, dabigatran 110 mg bid) in the reduction of stroke.

An unexpected but very important finding was that all are associated with a significant reduction (around 50% RRR) in intracranial hemorrhage compared to adjusted dose of warfarin.

Another important outcome was their safety, being either noninferior to warfarin with respect to major bleeds (dabigatran 150 mg bid and rivaroxaban) or result even in a significant reduction in major bleeding (dabigatran only at 110 mg bid, edoxaban, and apixaban full dose).

Adding to the data demonstrating their efficacy and safety in those large-scale trials, the additional benefits of novel oral anticoagulants (NOACs) are their simplicity of use compared to warfarin:

• as routine monitoring of anticoagulant effect is not required,

• no bridging with heparin or LMH needed before invasive procedures because of their pharmacokinetics and metabolism,

• And there are no relevant food and few drug-anticoagulant pharmacokinetic interactions.

Of all the factors that are associated with increased risk of stroke in the presence of AF, old age is the most potent risk factor.

The risk of stroke is doubled in patients aged 65-75 years compared to younger individuals, but they also have usually increased bleeding risk.

According to the RCT's metanalysis, relying on indirect comparisons, it seemed that Apixaban conferred a balanced safety vs efficacy, in aged patients, more than other DOAC's and the same in those with renal impairment or GI bleeding tendency.

Of course, those are exploratory findings, especially if taking into consideration that the ROCKET study with Rivaroxaban, enrolled patients with more comorbidities and at a higher embolic risk.

Can the long–term efficacy and safety benefits of NOAC`s over warfarin be expanded to the real-life scenario?

No head to head comparison was ever made in between the drugs of the DOAC family and probably never will be done, but a lot of matched comparisons from large data base (national health\claims large data and different registries), reassured those findings, and also being less robust then the RCT's, at least reflects real life daily practice. According to some well-matched some national studies:

• As presented by the Danish registries, we may suggest meanwhile that

• All NOAC's are generally safe and effective alternatives to warfarin in a clinical care setting.

• For ischemic stroke, weighted analysis suggests no significant differences between the NOAC's and warfarin.

• The risks for death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran, compared with warfarin, or as presented by Noseworthy PA, et al., in Chest. 2016 Dec;150(6):1302-1312 from the Mayo Clinic,

• Those findings were largely consistent with indirect comparison studies that tended to demonstrate similar efficacy between the NOACs,

• But suggest lower major bleeding risk with apixaban compared with dabigatran and rivaroxaban.

• Their data suggested that apixaban may have the most favorable safety profile of the three medications.

• For some patients and clinicians, the higher bleeding risk may dissuade them from using rivaroxaban, but for others, the advantage of once-daily administration with rivaroxaban may be worth the increase in bleeding risk.

• Subgroup analyses showed a consistent benefit across the range of baseline risk strata, suggesting that apixaban may yield a lower risk of major bleeding in the majority of the patients

Or even as stated by Gregory Y.H. Lip, MD. in Stroke; 2018; 49:98- 106, according to a review summarizing a meta-analysis of 16 real-world studies:

• Use of apixaban in real-life is associated with an overall similar effectiveness in reducing stroke and any thromboembolic events when compared with warfarin and as effective as dabigatran and rivaroxaban.

• Under currently available real-world studies evidence, apixaban could possibly represent the best alternative for OAC therapy, balancing effectiveness and safety for many patients with AF.

We have learned that is very important to stick to the guidelines and give the right dosage to the right patient otherwise we lose efficacy and even safety, if less or more than the required dosage, dictated by the RCT's:

• Most patients treated with NOACs for stroke prevention in AF received doses according to FDA-approved PI.

• However, a significant minority did not receive such doses, and • Off-label doses were associated with increased risk for adverse event.

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That was most obvious when giving apixaban, as its safety profile was preferred in those with comorbidities, also giving a reduced dose (which is 50% the normal), without indications for reduced dosage.

We also have to get rid of underestimating thromboembolic and overestimating bleeding risk as citing Savarese G, et al.in Heart 2018;0:1–8:

• Physicians perceived a 10% absolute risk of major bleeding in patients with AF receiving OAC whereas the true estimate has been shown to be 1%.

• Other studies showed that physicians were less likely to prescribe OAC for 1 year after that one of their patients experienced a major bleeding episode under OAC therapy and felt responsible for that,

• whereas those who had one of their patients suffering from a stroke due to lack of OAC therapy felt less responsible for this outcome and did not change their OAC prescription strategy.

We have to always keep in our minds when giving preventive stroke treatment in AF, that The risk of ischaemic stroke "without" OAC exceeds the risk of intracranial bleeding "with" OAC in those fitting the CHA2DS2-VASc indication.

It is also very important to avoid as much as possible predisposing factors to increased bleeding tendency, especially treating hypertension to target, avoid concomitant usage of NSAIDS, and unneeded antiplatelets, and investigate endoscopically GI bleeding, as anticoagulants do not cause the bleeding but only facilitate it, if an underlying concealed pathology exists.

As mostly citated sentences are:

"it is easier to prevent bleeding than to treat bleeding" and
" an ounce of prevention is worth a pound of cure".

Fig. DOAC's

In summary the DOAC's represent a breakthrough for many, who were not treated or undertreated due to fear, cumbersome and inflexible but important anticoagulant treatment (VKA) which were shown to reduce by 2\3's the embolic risk of AF, with a drug that emerged as to kill rats, especially a drug almost doubling the risk of intracranial bleeds compared to the DOAC's.