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Abstract:

A decade a er 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 speci c 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 nding was that all are associated with a signi cant 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 signi cant reduction in major bleeding (dabigatran only at 110 mg bid, edoxaban, and apixaban full dose).

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

• as routine monitoring of anticoagulant e e(l)-3nc.stqit seemed that Apixaban conferred a balanced safety vs e cacy, 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 ndings, 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 e cacy and safety bene ts 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 di erent registries), reassured those ndings, and also being less robust then the RCT's, at least re ects 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 e ective alternatives to warfarin in a clinical care setting.

• For ischemic stroke, weighted analysis suggests no signi cant di erences between the NOAC's and warfarin.

at was most obvious when giving apixaban, as its safety pro le 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 a er 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 su ering 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 e risk of ischaemic stroke “without” OAC exceeds the risk of intracranial bleeding “with” OAC in those tting 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 in exible 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.