Stroke Prevention and Treatment: New Insights into NOACs and Reversal

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A B S T R A C T

Non-vitamin-K oral anticoagulants (NOACs) have become the standard of care in stroke prevention for individuals with atrial fibrillation (AF). This symposium provided insight into NOACs for primary and secondary stroke prevention based on data from randomized controlled trials, subgroup and post-hoc analyses, and real world studies. The symposium also explored the conundrum of treating patients on a NOAC who have experienced an acute stroke, and highlighted idarucizumab—an antidote specific to dabigatran—that has been incorporated into medical guidelines. NOACs are also being investigated for the secondary prevention of embolic stroke of undetermined source (ESUS). Recent and ongoing trials in this area were discussed.

Key words: acute stroke, atrial fibrillation, NOAC, reversal agent, ESUS

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INTRODUCTION

The symposium, *Stroke Prevention and Treatment: New Insights into NOACs and Reversal* was held during the 4th European Stroke Organization Conference in May 2018 in Gothenburg. This symposium presented new insights into non-vitamin-K oral anticoagulants (NOACs) and reversal agents in acute stroke management, with a focus on implementing evidence-based medicine and best practices. The symposium also examined clinical data on the secondary prevention of stroke in individuals with atrial fibrillation (AF), including the effect of using lower doses of NOACs. The symposium also provided an update on embolic stroke of undetermined source (ESUS), an emerging stroke classification.

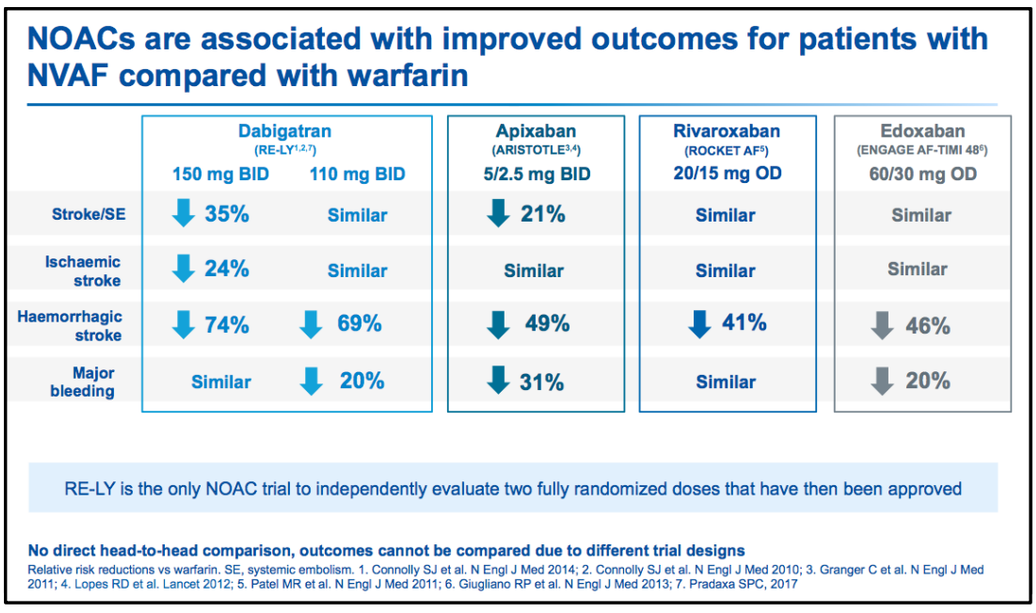
STROKE PREVENTION IN AF: HOW CAN WE OPTIMIZE ANTICOAGULATION?

Not only is AF associated with a five-fold increase in the risk of stroke[1], but also, AF-related strokes are more likely to be disabling or fatal compared to non-AF-related strokes. [2,3] As a result, stroke prevention is a cornerstone of management of individuals with AF. Unfortunately, many individuals are only diagnosed with AF after having an index stroke. Although oral anticoagulation (OAC) drugs significantly reduce stroke risk, any anticoagulant introduces the risk of bleeding. With warfarin, the challenge is often achieving the appropriate dose to provide optimal stroke protection and to minimize bleeding events. Until the development of NOACs, this represented a large unmet clinical need.

Randomized controlled trials (RCTs) have shown all commercially available NOACs to be non-inferior to warfarin in stroke prevention. Dabigatran 150 mg and apixaban (pooled cohort) were superior to warfarin in the reduction of stroke and systemic embolism (SE).[4,5] However, only dabigatran 150 mg was superior to warfarin in the reduction of ischemic stroke.[4] With regard to bleeding, all NOACs were associated with a significant reduction in hemorrhagic stroke compared with warfarin.[4-5,17-18]

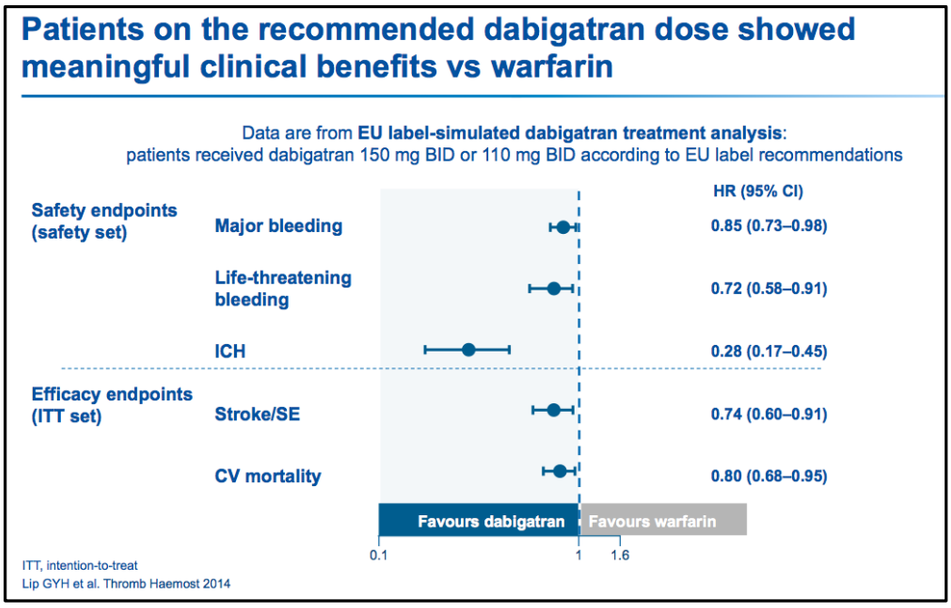
Randomized **E**valuation of **L**ong-term therap**Y** (RE-LY) was the only NOAC trial to randomize two different doses of the investigational drug. In other NOAC trials, lower doses of the investigational drugs could be given to patients with certain baseline characteristics (e.g., age or body weight), however, the studies were not designed to provide statistical assessment of the relative safety and effectiveness of the lower doses. Since there have not been head-to-head RCTs using NOACs, outcomes cannot be directly compared owing to different trial designs (Figure 1).

Figure 1. Outcomes Associated with NOACs



Over- or underdosing are both concerns for any anticoagulation regimen. Investigators of RE-LY randomly assigned patients with AF and a risk for stroke to receive, in a double-blind fashion, fixed doses of dabigatran (150 mg BID or 110 mg).[4] A post-hoc analysis showed that using the indicated dose of dabigatran resulted in a significant reduction in stroke/SE and cardiovascular (CV) death compared to individuals well controlled on warfarin (Figure 2). The EU label-simulated dabigatran cohort also had significantly fewer major bleeding events, including intracranial hemorrhage (ICH).[6]

Figure 2. Clinical Benefits of Recommended Dabigatran Doses

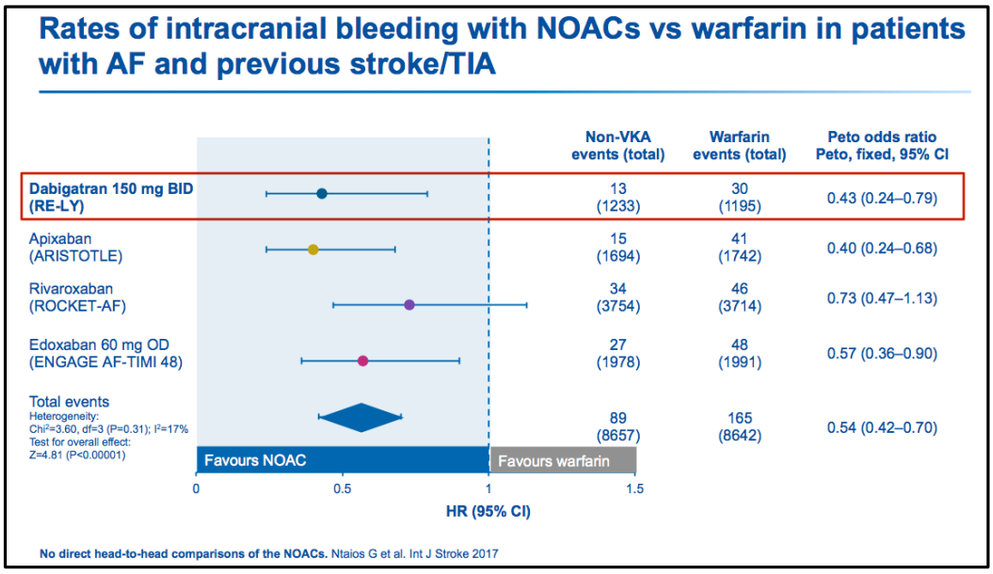


In 2016, the European Society of Cardiology (ESC) guidelines, which were endorsed by the European Stroke Organization (ESO), elevated NOACs to first-line therapy for secondary prevention, over warfarin and aspirin for patients with AF and a previous stroke (Class IB recommendation). Professor Danilo Toni of Sapienza University in Rome commented that he has not prescribed warfarin for stroke patients with AF since the availability of the NOACs. The only exceptions have been individuals with clear contraindications for NOACs.

Stroke or transient ischemic attack (TIA) increases the risk of a recurrent event by nearly two-fold in patients with AF. Therefore, it is critical to optimize OAC for secondary prevention. Another analysis of RE-LY evaluated outcomes of patients with a previous stroke or TIA. Both doses of dabigatran were non-inferior to warfarin in secondary stroke prevention. The relative risk (RR) of stroke/SE for dabigatran 150 mg was 0.75 (95% CI 0.52–1.08) compared to warfarin; the RR for dabigatran 110 mg was 0.84 (95% CI 0.58–1.20).[7]

NOACs are also safer than warfarin in the setting of secondary prevention. A systematic review and meta-analysis of patients with previous stroke or TIA enrolled in a NOAC RCT demonstrated that, in aggregate, NOACs reduced the relative risk of ICH by 46.1% compared to warfarin, with dabigatran 150 mg and apixaban having the largest relative risk reduction (Figure 3).[8]

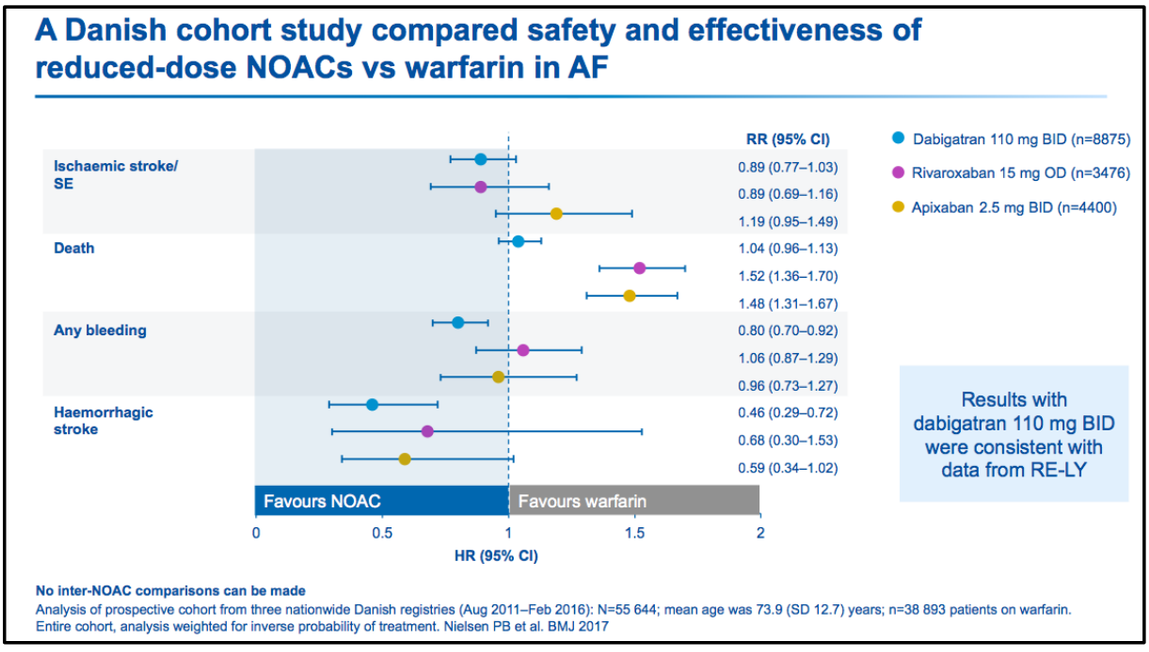
Figure 3. ICH Rates with NOACs vs Warfarin in Patients with AF and Previous Stroke/TIA



Real-world evidence (RWE) provides insights into varied settings and patient characteristics encountered in every day clinical practice. RWE also can provide confirmation of the safety and efficacy of a new therapy in a broader patient population. With regard to dabigatran's better ICH profile compared with warfarin, Professor Toni presented information from 17 real world studies published in 2014-2017, each of which met the following criteria: ≥3,000 patients enrolled, adjusted comparison available (e.g. propensity score matching), and a calculated hazard ratio (HR) for major bleeding provided. All studies (N>550,000) showed that dabigatran was associated with a lower or similar risk of major bleeding to warfarin, confirming the RE-LY results.

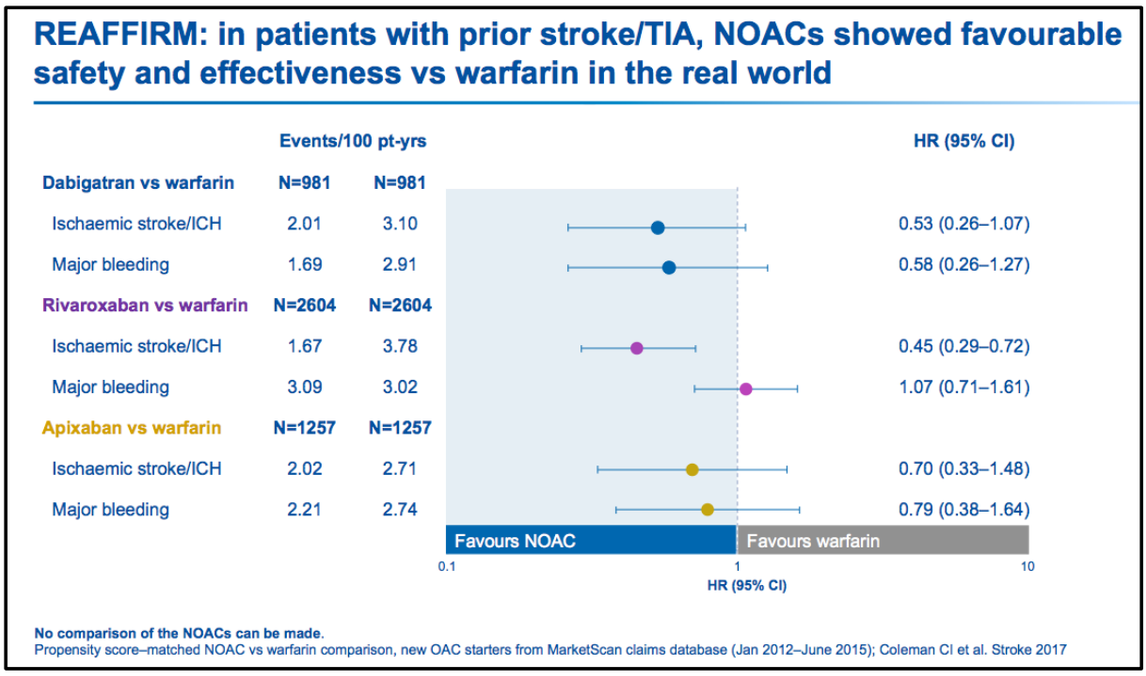
A Danish cohort study evaluated the safety and effectiveness of reduced doses of dabigatran, rivaroxaban, and apixaban compared to warfarin in patients with AF (Figure 4). Taken from three Danish registries in August 2011-February 2016, there were 55,644 patients taking a reduced-dose NOAC and 38,893 individuals prescribed warfarin. Dabigatran 110 mg had results consistent with that observed in RE-LY with a RR of 0.89 for ischemic stroke/SE, 0.80 for any bleeding, and 0.46 for haemorrhagic stroke. The RR for mortality was 1.04. Comparatively, low doses of rivaroxaban and apixaban were associated an increased RR for mortality of 1.52 and 1.48, respectively.[9] This may reflect overuse of the lower doses of NOACs, as some clinicians may believe that a lower dose would reduce the risk of ICH or haemorrhage in general. However, using lower doses could increase the risk of ischemic stroke or death. This underscores the importance of using a lower-dose NOAC that has been appropriately evaluated in an RCT.

Figure 4. Safety and Effectiveness of Reduced-Dose NOACs vs Warfarin in AF



There is scant RWE of the safety and efficacy of NOACs for secondary stroke prevention. In a Danish cohort study of OAC-naïve patients with a history of stroke/TIA (N=3,264), both doses of dabigatran had similar or lower rates of stroke or TIA compared to warfarin, confirming the earlier-mentioned sub-group analysis of RE-LY.[10] In the United States (US), the investigators of the REAFFIRM study used records from a claims database to compare outcomes for OAC-naïve patients taking dabigatran, rivaroxaban, or apixaban for secondary prevention (Figure 5). A propensity score was used to match these individuals with those taking warfarin. The results were generally consistent with the effect of NOACs on the risk of stroke/ICH or major bleeding compared with warfarin. This analysis should not be viewed as direct comparison of the NOACs, as the three subsets of patients had differing baseline characteristics.

Figure 5. Comparative Outcomes for OAC-Naïve Patients Taking NOACs



The initial two years of follow-up data for patients enrolled in the prospective GLORIA AF registry, which is the largest registry of patients taking dabigatran, have recently been reported. The risk of ischemic or haemorrhagic stroke was 0.65 per 100 patient years (PY), similar to that recorded in RE-LY. The event rate for life-threatening bleeds was 0.46 per 100 PY, with major bleeding of 0.97 per 100 PY. Approximately 11.5% of the cohort had previous stroke/TIA.[12]

STROKE TREATMENT: CAN DABIGATRAN REVERSAL IMPROVE OUTCOMES?

Stroke neurologists have a key role in managing stroke patients with AF in terms of prescribing the appropriate OAC at the appropriate dose for patients who need secondary prevention, as well as managing patients taking a NOAC who may have an ischemic stroke. To this end, according to an interactive symposium poll, approximately 85% of attendees consider the availability of a reversal agent when selecting an OAC for secondary stroke prevention. At this time, dabigatran is the only NOAC with a specific reversal agent available in the EU, which may facilitate stroke treatment (e.g., thrombolysis) and enable clinicians to optimize outcomes. In May 2018, the US Food and Drug Administration approved andexanet alfa as a reversal agent for patients treated with rivaroxaban or apixaban. Andexanet alfa is still under review by the European Medicines Agency.

Idarucizumab, a humanized monoclonal antigen-binding fragment (Fab), is a specific reversal agent for dabigatran. Its binding affinity with dabigatran is approximately 350 times higher than dabigatran's binding of thrombin and it has a rapid onset of action. Idarucizumab does not have any intrinsic procoagulant or anticoagulant effect, and it does not reverse other NOACs or heparin. A ready-to-use package of idarucizumab includes two vials of 2.5g and must be refrigerated at 2-8°C. The shelf life is approximately three years. A total dose of 5g of idarucizumab is administered either as a bolus injection or rapid infusion.[13] Anticoagulation can be restarted after 24 hours, and heparin can be initiated at any time.

The **REVERS**al Effects of idarucizumab on **A**ctive **D**abigatran (RE-VERSE AD) studied the ability of idarucizumab to reverse dabigatran in two patient cohorts. Group A (N=293) consisted of individuals with uncontrolled bleeding; group B (N=193) was composed of patients needing an urgent procedure. (Idarucizumab is the only reversal agent that has been studied in these two patient populations.) The primary endpoint was the maximum reversal of dabigatran anticoagulation within four hours of idarucizumab administration as confirmed by diluted thrombin time (dTT) or ecarin clotting time (ECT). One hundred percent reversal was achieved in almost all patients.[14] Idarucizumab has been approved for reversal of dabigatran in patients with life-threatening or uncontrolled bleeding and for use prior to emergency surgery/urgent procedures, such as stroke thrombolysis; there are no contraindications for fibrinolytic treatments. Guidelines from the European Heart Rhythm Association (EHRA) indicate that patients taking a NOAC who have had a clinically relevant acute ischemic stroke should be considered for thrombolysis, unless contraindicated, and notes that idarucizumab is the only reversal agent available in the EU.[15] Idarucizumab is available in over 8,500 hospitals.[16]

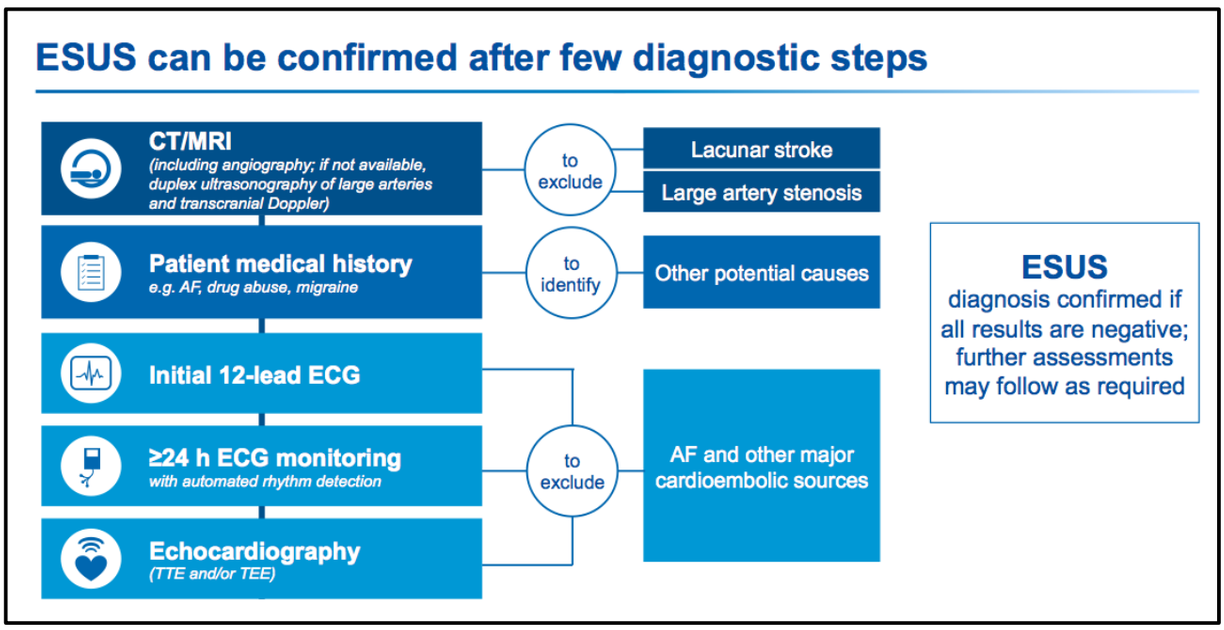
Neurologists also need to be prepared for managing ICH in patients taking a NOAC. In the NOAC RCTs, the incidence of ICH was 0.23 per 100 PYs to 0.50 per 100 PYs, lower than that recorded in the warfarin arms of the trials.[9,10,17,18] Despite NOACs' lower ICH event rates, there is no difference in 90-day mortality rates or haematoma expansion between the NOACs and warfarin. Prothrombin complex concentrate (PCC) has been used in patients taking warfarin or a NOAC who experience an ICH. Even with the use of PCC, mortality rates remain high.[19] In addition, PCC may not abate hematoma growth if the patient is taking a NOAC targeting the Factor Xa pathway.[20]

In the RE-VERSE AD trial, 98 patients had ICH. Idarucizumab completely reversed the effects of dabigatran in 100% of evaluable individuals based on dTT and more than 90% of evaluable patients based on ECT. Reversal happened within minutes for most patients and after administration of a single vial of idarucizumab. The 30-day mortality rate was 16.4%.[14] Comparatively, patients in RE-LY who had an ICH had mortality rates of 35% (150 mg dose) and 41% (110 mg dose). Use of idarucizumab has been incorporated into EHRA guidelines for patients on dabigatran experiencing a life-threatening bleed.[15]

EMBOLIC STROKE OF UNDETERMINED SOURCE (ESUS): CONCEPTS AND CURRENT TREATMENT OPTIONS

ESUS, which was introduced as a clinical concept in 2014, strives to improve categorization of strokes that have traditionally been deemed cryptogenic (Figure 6).[22] ESUS may arise from various factors, such as embolism originating in the mitral or aortic valves or in the setting of cancer-related thrombosis. ESUS is confirmed by excluding common sources of ischaemic stroke, such as such as cardioembolic, lacunar, and occlusive large atherosclerosis.

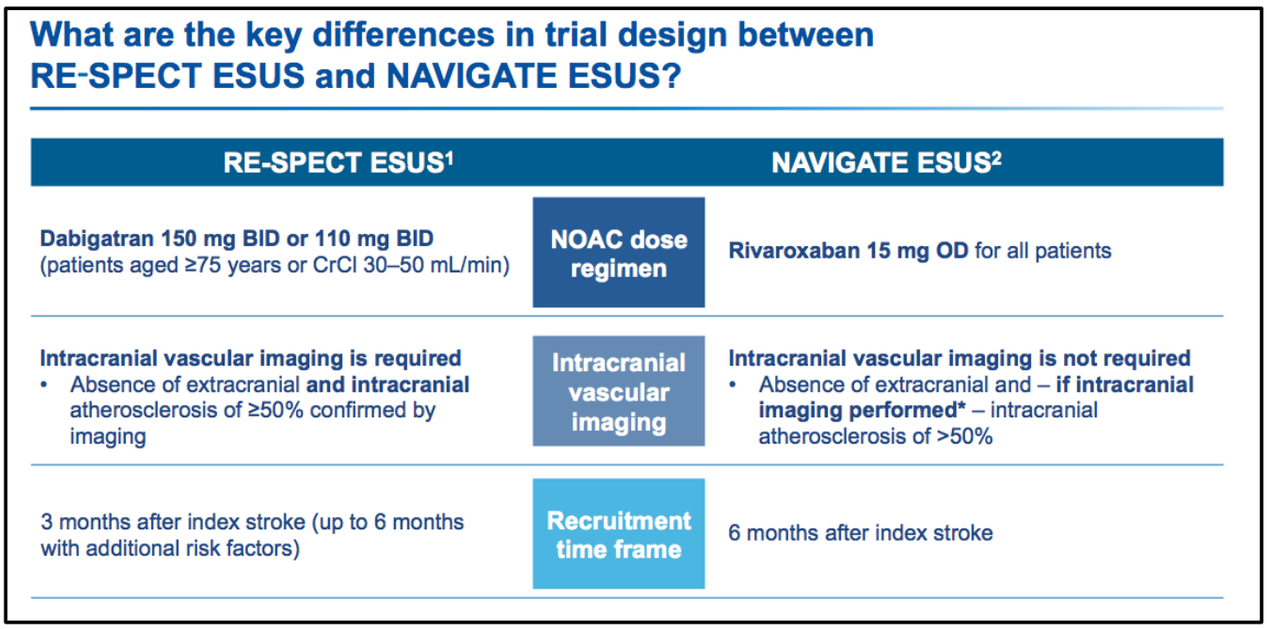
Figure 6. Diagnostic Steps to Confirm ESUS



The recurrence rate of ESUS is high, similar to that of cardioembolic strokes. In most countries, the current standard of care is aspirin. RCTs are being conducted to assess whether NOACs are effective in the secondary prevention of ESUS. NAVIGATE ESUS, a double-blind trial comparing rivaroxaban to aspirin in patients with ESUS, was terminated early owing to increased bleeding in the rivaroxaban arm without the benefit of lower risk of stroke/SE.[23]

The RE-SPECT ESUS trial, which is evaluating dabigatran to aspirin in 5,390 patients, is still ongoing. Patients aged ≥75 years or CrCl 30-50 mL/min receive dabigatran 110 mg BID; all other patients randomized to dabigatran take the standard dose (150 mg BID). Compared with NAVIGATE ESUS, RE-SPECT ESUS uses a dosing concept as proven to be effective and safe in stroke prevention in AF, with a standard dose of 150 mg BID and the lower dose of dabigatran for patients with high bleeding risk (Figure 7). NAVIGATE-ESUS used a fixed dose (15 mg) for all patients randomized to the treatment arm, which corresponds to the lower dose for stroke prevention in AF, which is approved only for patients with creatinine clearance <50 ml/min. ARCADIA, an intermediate-size double-blind RCT comparing apixaban with aspirin, recently began enrolling patients with cryptogenic stroke and is expected to be completed in 2022.[24]

Figure 7. Differences in Trial Design: RE-SPECT ESUS and NAVIGATE ESUS



CONCLUSION

NOACs have changed the standard of care for stroke prevention in AF. However, patients taking a NOAC may experience an ischemic stroke or ICH, and stroke neurologists play an important role in the management of these patients. Dabigatran is currently the only NOAC with a specific antidote (idarucizumab), which is endorsed by EHRA guidelines for reversal in acute ischemic stroke and life-threatening bleeding. Guidelines have also elevated NOACs to first-line therapy in the secondary prevention of AF-related stroke. Since recurrence rates are high following an initial stroke, choosing an effective and safe OAC is paramount. Dabigatran is the only NOAC to demonstrate superiority to warfarin in the reduction of ischemic stroke and has two doses that have been properly evaluated in clinical trials. Dabigatran's safety has also been established in randomized trials such as RE-LY and has been confirmed in real-world studies. It remains to be seen whether NOACs will improve outcomes in the secondary prevention of ESUS.

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