Stroke Treatment Academic Industry Roundtable (STAIR) Recommendations for New Oral Anticoagulants

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The Stroke Treatment Academic Industry Roundtable (STAIR) meetings bring together academic physicians, industry representatives, and regulators to discuss ways to enhance the development stroke therapies. This report is based on expert opinion distilled from discussions and workshops at the STAIR VIII meeting held on March 10 and 11, 2013, in Washington, DC.

While the acronym NOAC is frequently used to designate the class of novel (or new) oral anticoagulants, the first drug described by this rubric (ximelagatran) appeared in the clinical literature a decade ago. The NOACs are no longer new or novel but what distinguishes them from Vitamin K antagonists (VKAs) is that they directly interact with their coagulation protein target. We propose "direct oral anticoagulant" (DOAC) as a more useful and durable term, describing the direct inhibition of thrombin or Factor Xa. DOACs are the long-awaited alternatives to oral anticoagulation with vitamin K antagonists, the standard of care for almost 60 years, but VKAs are fraught with complicated dosing, requirement for regular monitoring and dose adjustments, drug interactions and substantial risk of intracranial bleeding. Clinical experience with DOACs is rapidly accumulating as an increasing number of NVAF patients have been treated with these agents. Recent analysis from the FDA's Mini-Sentinel database revealed lower incidence of gastrointestinal hemorrhage (1.6/100,000 days at risk vs.3.5/100,000 days at risk) and intracranial hemorrhage (0.8 /100,000 days at risk vs. 2.4/100,000 days at risk) with dabigatran as compared to warfarin. [1]

Previous iterations of the guidelines have generally advocated anticoagulation with VKAs for atrial fibrillation patients at moderate to high risk of stroke. Several stroke risk stratification schemes have been proposed for atrial fibrillation patients. The $CHADS_2$ is the most widely promulgated. VKAs have been recommended for atrial fibrillation patients with a $CHADS_2$ score of ≥ 2 (corresponding to absolute stroke rates of about 1-3%/year if not anticoagulated), while either aspirin or VKAs were recommended for those with $CHADS_2$ scores of 1 (corresponding to absolute stroke rates of about 1-3% ~~%~~/year), depending on patient preference and bleeding risks.[2] Recently, the $CHA2DS_2VASC$ stroke risk stratification scheme has been proposed as a refinement of the $CHADS_2$ scheme that further stratifies low-risk atrial fibrillation patients (e.g. $CHADS_2$ score of 1) into those with higher vs. lower stroke risks.[3] Additional stroke risk stratification schemes for atrial fibrillation patients have been proposed.[4, 5] Female sex is included as a predictor in the more recent stroke stratification schemes because it has been a consistent independent predictor of stroke in atrial fibrillation patients.[6] Should the threshold of absolute stroke risk that warrants anticoagulation with DOACs be lower? DOACs are associated with a reduced risk of intracranial bleeding, the most devastating complication of anticoagulation in elderly patients with atrial fibrillation, compared with warfarin.[7] Thus, the question warrants careful consideration in future

guidelines and more recent updates reflect a greater acceptance of the newer agents. .[8-11]

Guidelines have evolved during the past 4 years from recommending DOACs as alternatives to anticoagulation of non-valvular atrial fibrillation (NVAF) with oral VKAs to generally favoring use of DOACs over VKAs for most patients based on evidence that DOACs offer comparable protection against ischemic stroke with reduced risks of intracranial (and particularly intracerebral) hemorrhage. Clinical trials of oral direct thrombin (dabigatran) and Factor Xa inhibitors (rivaroxaban, apixaban) suggest that all three currently approved agents are at least as efficacious as dose-adjusted warfarin, with similar major bleeding profiles. An indirect comparison of the new anticoagulants based on existing trial data indicated that in patients with moderate or high stroke risk, dabigatran 150 mg, rivaroxaban 20 mg and apixaban 5 mg resulted in statistically similar or lower rates of stroke and systemic embolism. Of the three, dabigatran 150 mg had the lowest risk of stroke and apixaban had the lowest risk of major hemorrhage.[12] These comparisons should be interpreted with caution as dabigatran, apixaban and rivaroxaban have not been compared head-to-head.

All of the DOACs undergo partial renal metabolism, ranging from roughly 80% for dabigatran to 25% for apixaban. Eligibility for DOAC use and DOAC dosing is influenced by renal function, and periodic monitoring of renal function is recommended for NVAF patients receiving DOACs. In the phase III randomized trials that defined the benefits and risks of DOACs in NVAF patients, renal function was assessed based on serum creatinine levels using the antiquated Cockcroft-Gault equation to calculate the estimated creatinine clearance.[13, 14] Estimated glomerular filtration rate (eGFR) using the MDRD or, more recently, the CKD-EPI formulas have largely replaced estimated creatinine clearance.[15] While generally similar in defining renal function, eGFR and estimated creatinine clearance are not identical.[16] It would be valuable to have the data from the phase III trials and future management guidelines expressed in terms of the eGFR. Most laboratories supply only the eGFR and clinicians generally assume that the eGFR and eCrCl can be used interchangeably.

The absence of an antidote to immediately reverse the anticoagulant effects of the DOACs in case of bleeding has been raised as a concern. It is sensible to consider this issue separately for intracranial vs. extracranial bleeding. In most cases, it is unlikely that reversal of VKA anticoagulation can be done quickly enough to improve the outcome of intracerebral hemorrhage. While agents to reverse the effects of VKA-based anticoagulation such as vitamin K_1 or prothrombin complex concentrate (Kcentra) are available, it has never been convincingly demonstrated that their use improves neurological outcome, and surveys have demonstrated that reversal of anticoagulant effect is uncommon within 12 hours of hemorrhage onset. In the RE-LY trial, case-fatality rates associated with intracranial bleeding were similar for patients assigned warfarin vs. dabigatran. .[4, 17] Extracranial bleeding rates are about equivalent with the DOACs vs. warfarin in atrial fibrillation patients (and higher for gastrointestinal bleeding with dabigatran 150 mg and rivaroxaban 20 mg).). The relevant concern about absence of a reversal agent concerns extracranial hemorrhage even though far less likely to result in death or permanent disability than intracranial bleeding.[7] Ongoing pharma-sponsored research is actively pursuing safe reversal agents.

There are several unresolved issues surrounding the management of DOACs after stroke, such as:
(i) When to start DOACs in the setting of acute ischemic stroke due to NVAF,?
(ii) How to manage DOAC failures?
(iii) What is the best approach to assessing intravenous tPA eligibility in acute stroke?
Combination aspirin-DOAC therapy is not recommended given the uncertain benefit, and the established increased risk of bleeding. There have been case reports of IV tPA treatment in patients prescribed a DOAC. Practice varies widely, but many centers only treat patients who have not ingested a DOAC within 48 hours and, in the case of dabigatran, have either a normal or mildly prolonged aPTT. Currently, there are limited data available to address these issues, and all areready for clinical trials.

Specific coagulation assays for DOACs are commercially available, although not routinely performed at most hospital laboratories. Anticipating the growing use of DOACs, hospitals should consider offering the HemoClot test (for dabigatran) and factor Xa assay (for apixaban and rivaroxaban). Although there is no justification for dose adjustment based on biological activity, there are four common clinical situations in which a factor Xa assay or HemoClot test could be used:
1. In a patient known to be taking a DOAC who presents with an acute ischemic stroke and is eligible for intravenous tPA. In this case, results of the assay would need to be available within a few minutes in order to be of use,
2. In an acutely bleeding patient receiving a DOAC to determine whether prothrombin complex concentrate should be used,
3. In a patient receiving a DOAC who requires surgery to determine the optimal timing of the surgery, and
4. To assess adherence in patients taking a DOAC.

Most importantly, more research is needed to optimize the utility of DOACs in stroke prevention. These are summarized in **Table 1**.

Table 1: Research Priorities involving DOACs and Stroke Prevention

High-priority

- Convert RCT data and management recommendations based on estimated creatinine clearance to estimated GFR.
- Clinical trials assessing safe time to initiation of DOACs after acute stroke regarding secondary hemorrhagic transformation.
- Studies defining the safety of i.v. tPA, endovascular thrombectomy in acute stroke patients receiving DOACs.
- DOAC vs. antiplatelet therapy in cryptogenic strokes / embolic strokes of undetermined source.

Other potential research:

- Clinical trials of DOAC vs. warfarin or aspirin in atrial fibrillation patients with end-stage renal disease.
- DOAC vs. antiplatelets for secondary prevention in patients with intracranial atherosclerotic stenosis.
- DOAC vs. best comparator for secondary prevention in patients with aortic arch atheroma as a potential embolic source.

- Utility of brain MRI in selecting patients for DOAC therapy
- DOAC vs. closure vs. alternative antithrombotic therapies for cryptogenic stroke associated with patent foramen ovale.
- DOAC vs. aspirin in patients with low ejection fraction or hypokinetic wall segments with relatively preserved LV function on echocardiogram
- DOAC vs. warfarin or antiplatelet therapy in acute arterial dissection.

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