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The New Novel Oral Anticoagulants (NOACs) In Patients With Atrial Fibrillation: Dogma, Dilemmas, And Decisions On Dosing

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With the advent of the new novel oral anticoagulants (NOACs) and specifically, their role in patients with atrial fibrillation (AF), the epitaph for warfarin is being written. Leaving aside AF patients with mechanical prosthetic valves or rheumatic mitral stenosis, for whom these agents are not indicated, there hardly seems a role for warfarin in this population any more. In the aftermath of RE-LY (dabigatran vs warfarin),[1] ROCKET AF (rivaroxaban vs warfarin),[2] ARISTOTLE (apixaban vs warfarin),[3] and ENGAGE AF (edoxaban vs warfarin),[4] the reports of these pivotal trials taken individually along with the data from multiple meta-analyses examining them together[5-13] clearly show that better clinical outcomes are obtained with these new agents. All reduce stroke and systemic embolism at least as well as warfarin; all are superior in reducing hemorrhagic stroke and intracerebral bleeds than warfarin; some are superior to warfarin in reducing all strokes and systemic emboli; and dabigatran is superior at specifically reducing ischemic stroke. Simultaneously, the NOACs (several or all) have reduced mortality versus warfarin and have reduced major and fatal bleeding versus warfarin.[1-13] Gastrointestinal bleeding appears higher with the NOACs than warfarin (with the exception of apixaban in the ARISTOTLE trial) but still with lower fatality. None of the NOACs require anticoagulant blood test monitoring (in contrast to warfarin) and all have fewer drug interactions than warfarin. While rivaroxaban requires significant food intake at the time the dose is taken, none of the NOACs has the multiple food interactions that can plague warfarin users and warfarin dosing. Additionally, as regards dosing, the options with the NOACs are limited, and infrequently change over time, which contrasts dramatically with the picture seen with warfarin. Finally, while the medication cost itself of any of the NOACs is higher than that of generic warfarin, multiple cost-effectiveness analyses[14,15] have shown that when global costs are considered, including factors associated with laboratory testing, care-related costs of strokes, systemic emboli, bleeding, and the like, the NOACs are or may be preferable. And, in my practice, the higher costs of the NOACs can be lessened by obtaining them through discounted pharmacy sources (such as at COSTCO) and can be offset by purchasing other routine items in discount outlets (again, such as COSTCO) where the significant cost savings on other products purchased can offset higher medication co-pays.

That having been said, the use of the NOACs in patients with AF [specifically "non-valvular AF", the somewhat misleading term that has been used in their indication statements*] does require some important dosing considerations that can pose and has posed confusion for some practitioners and may result in harm to patients if not followed appropriately. To some extent the dosing regimens are dogmatic: they are clearly stated in the package insert of each of the so-far FDA approved agents – dabigatran, rivaroxaban, and apixaban. However, to some extent, clinical acumen, experience, and judgment are necessary to maximize the benefit of these agents for our patients. For some, the Federal Food and Drug Administration (FDA) has tied our hands unnecessarily.**

* "Non-valvular AF is a term used primarily to reflect the exclusions utilized in the pivotal trials of AF patients that compared the NOACs with warfarin. In general, the exclusions included mechanical prosthetic heart valves (for which the issue of thrombus formation is more complex regarding site, mechanism, and anticoagulant dosing), rheumatic valve disease – primarily mitral stenosis (as such patients were excluded from the old warfarin-placebo trials on which the expected warfarin efficacy rates and statistical boundaries used in the pivotal AF trials versus the NOACs were based), and patients whose valve disease was so hemodynamically advanced that intervention was likely in the near future (such that it would be unlikely for them to complete the pivotal trial).

** Note also, in the material below, that only drug interactions that affect dosing/pharmacokinetics are discussed. Pharmacodynamic interactions that may increase bleeding risk, such as co-administered

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antiplatelet agents, nonsteroidal anti-inflammatory drugs, and the like are not discussed as they apply equally to each of the agents considered and regardless of the dose used.

Dabigatran

Dabigatran is available in the U.S. for AF (not yet indicated for venous thrombosis or pulmonary embolism) in doses of 150 mg bid and 75 mg bid.[16] It may be taken with or without food; however, in my experience, the likelihood of gastrointestinal symptoms, which are the most common side effect encountered with dabigatran, are less if it is taken with food. The 150 mg bid approval was based upon its data in RE-LY.[1] The 75 mg bid dose approval was based upon pharmacokinetic modeling such that for patients whose creatinine clearance (CrCl) is 15-30 cc/min, this dose would provide serum concentrations in the same range as the higher dose in patients with better renal function. Both doses are contraindicated in patients with a CrCl <15 cc/min. Accordingly, CrCl needs to be assessed prior to starting dabigatran and periodically during its use as clinically appropriate.

Elsewhere in much of the world, a dose of 110 mg bid is available. This dose, too, was based upon its data from RE-LY[1] where it was non-inferior to warfarin in reducing stroke and systemic embolism while simultaneously proving superior as regards its bleeding profile. Reasons given for its lack of availability in the U.S.[17,18] have included the concern that the 150 mg bid was not only superior to warfarin but it was also superior to the 110 mg bid dose and that release of the latter might deprive patients of the superior dose if physicians failed to dose-escalate most patients. It is not apparent to me why a dosing algorithm such as is used for dofetilide could not have been utilized. That is, mandate starting with the 150 mg bid dose unless specific clinical conditions were present or were to develop, in which case down-titration would be indicated.

Drug interactions with dabigatran essentially only relate to potent P-glycoprotein (P-gp) inducers [such as rifampin or St. John's wart] (which can reduce dabigatran levels) and inhibitors [such as ketoconazole or dronedarone] (which can raise dabigatran levels). For patients with moderate renal impairment (CrCl 30-50 mL/min), the package insert[16] says to consider reducing the dose of dabigatran to 75 mg twice daily when dronedarone or systemic ketoconazole is coadministered with dabigatran. For patients with severe renal impairment (CrCl 15-30 mL/min), avoid concomitant use of dabigatran and P-gp inhibitors. However, what should a clinician do if the patient has mild renal impairment, such as a CrCl of 50-70 cc/min and is taking a mild-moderate P-gp inhibitor, such as amiodarone, or others? Clinical judgment might suggest (and clinical practice outside the U.S. would support) the use of the 110 mg bid dose were it available in the U.S. Some physicians in the U.S. have tried to mimic this total daily dose by using 75 mg tid or by alternating 75 mg and 150 mg doses bid under such circumstances.[19,20] It is my sincere hope that the FDA will reconsider their prior adverse determination regarding the 110 mg bid dose, which I believe was wrong, such that our patients will be the better for it. In this regard, the FDA certainly could do so utilizing pharmacokinetic modeling in the same manner as they used to approve the 75 mg bid dose. If only they would. Notably, the 110 mg bid dose was not approved by the FDA despite non-inferior efficacy versus warfarin plus less bleeding while rivaroxaban (see below) was approved with both similar efficacy and bleeding (non-inferiority) versus warfarin.

Rivaroxaban

Rivaroxaban is available in the U.S. for AF as well as for venous thrombosis and pulmonary embolism.[21] Importantly, and notably, the doses used are not the same for AF as for its other indications.[21] For AF, the dose is 20 mg taken with the evening meal for CrCl >50 cc/min, and 15 mg taken with the evening meal for CrCl 15-50 cc/min. These doses are taken directly from the doses used in ROCKET AF[2] (although in ROCKET AF, the minimum CrCl allowed for enrollment in the trial was 30 cc/min). Like dabigatran, rivaroxaban is contraindicated for CrCl <15 cc/min. In contrast, for the treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE), the dose is 15 mg bid taken with food for the first 21 days followed by 20 mg taken once a day with food (but not specifically with the evening meal). For the prevention of DVT in medically ill patients, the dose is 20 mg taken once a day with food; for prevention of DVT/PE after knee or hip surgery, the dose is 10 mg once a day for 12 days (knee) or 10 mg once a day for 35 days (hip). CrCl is not used to guide dosing for these non-AF, shorter-term indications.

Rivaroxaban, like dabigatran, interacts with P-gp inducers and inhibitors. However, rivaroxaban is less dependent upon renal function for its elimination than dabigatran (for which 80% of dabigatran's elimination is renal) as rivaroxaban is also hepatically metabolized (by the cytochrome P450 system). Consequently, it is only in the presence of strong inhibitors or inducers of both P-gp and CYP3A4 (dual inhibitors or inducers) that important interactions occur with rivaroxaban.[21] Concomitant use of rivaroxaban and strong dual inhibitors or inducers should be avoided. Strong dual inhibitors include many antifungal and antiviral agents while strong inducers include phenytoin, rifampin, St. John's wart, and carbamazepine. Rivaroxaban should be used in the presence of mild to moderate dual inhibitors if clinically justifiable. These include amiodarone, dronedarone, quinidine, ranolazine, verapamil, and many non-cardiac drugs.[21] However, this list is far shorter than the list of agents that interact with warfarin. Whether the use of 15 mg rather than 20 mg daily would be appropriate if a mild-moderate dual inhibitor was co-administered has not been studied and is not noted in the package insert. Similarly, the package insert does not discuss why the dose must be taken with the evening meal for AF, but with any meal for the non-AF indications. While these dosing differences reflect the dosing regimens used in the specific pivotal trials that led to the specific indications approved, a rationale for maintaining the differences in clinical practice should be provided, in my opinion, if there is a sound clinical/physiological rationale. Moreover, it should be simple enough to do a pharmacokinetic study of giving the drug with a substantial breakfast versus the evening meal to determine if the different dosing-meal patterns should be continued. However, I have not seen any public mention of such a study.

Apixaban

Apixaban is available in the U.S. for AF (not yet indicated for venous thrombosis or pulmonary embolism) in doses of 5 mg bid and 2.5 mg bid.[22] The approval of these doses was based upon their use and results in ARISTOTLE.[3] 5 mg bid is the dose for most patients. 2.5 mg bid should be used if any two of the following three conditions are present: age 80 years or above, body weight 60 kg or less, or serum creatinine 1.5 mg/dl or higher. Apixaban is less dependent upon renal clearance (only about 27% of the drug is renally cleared) than is dabigatran or rivaroxaban; hence, its dosing is

not adjusted solely based upon CrCl. Very recently, an update to the package insert [22] notes that for patients on dialysis, the 5 mg bid dose is to be used unless one or the other of the age and weight factors is present. However, as most of apixaban's clearance is hepatic, the 2.5 mg bid dose should also be used if the patient is taking a strong dual P-gp and CYP3A4 inhibitor.[22] For patients already taking the 2.5 mg bid dose, strong dual inhibitors should be avoided. In contrast to rivaroxaban, apixaban can be taken with or without food. As with rivaroxaban, co-administration of apixaban and strong dual inducers should be avoided.

Edoxaban

Edoxaban is not yet FDA approved for use, so, no package insert or other specific guidelines are yet available. However, based upon its results in ENGAGE AF,[4] it seems likely that we will see this agent become available as well. Edoxaban's renal clearance is 35-50%, so renal function will likely be a consideration in its dosing regimen. In ENGAGE AF,[4] doses of 30 mg and 60 mg daily were compared to warfarin. The dose was lowered by 50% if the CrCl was 30-50 cc/min, if the patient's weight was 60 kg or less, or if the patient was taking a potent dual inhibitor (which, for this trial, included dronedarone, quinidine, or verapamil). CrCl < 30 cc/min was an exclusion in ENGAGE AF. Note, that whether a specific agent has been termed a strong versus moderate dual inhibitor has varied among the trials of the different factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) and in their package inserts.[16,21,22] In ENGAGE AF[4] if the dual inhibitor was stopped, apixaban's dose was re-increased, but if the former two factors were present, the dose was not changed during the trial. Given the observation that the clinically approved doses of dabigatran, rivaroxaban, and apixaban were based upon observations in their pivotal trials, it would seem to follow that these considerations will also hold true if/when edoxaban is approved. As for the specific edoxaban doses we might expect to see: In ENGAGE AF[4] both doses of edoxaban were non-inferior to warfarin for reducing stroke and systemic embolism; however, neither dose was superior by intention-to-treat [ITT] analysis while the 30 mg/d dose actually had a numerically higher incidence of these thromboembolic endpoints (hazard ratio 1.13 by ITT analysis). Both doses were associated with less major bleeding than warfarin. In the ITT analysis, the primary event rate was lower with edoxaban 60 mg/d than with edoxaban 30 mg/d ($p<0.001$); this difference was driven by a 29% relative reduction in ischemic stroke (236 vs 333 events) which more than offset a higher incidence of hemorrhagic stroke (49 vs 30 events); although hemorrhagic strokes had more severe sequelae. The overall stroke rare was: 1.69%/yr with warfarin, 1.49%/yr with 60 mg/d edoxaban (HzR 0.88, $p=0.11$), 1.91%/yr with 30 mg/d edoxaban (HzR 1.13, $p=0.12$). The hemorrhagic stroke rate was: 0.47%/yr with warfarin, 0.26%/yr with 60 mg/d edoxaban (HzR 0.54, $p<0.001$), 0.16%/yr with 30 mg/d edoxaban (HzR 0.33, $p<0.001$). The ischemic stroke rate was: 1.25%/yr with warfarin, 1.25% with 60 mg/d of edoxaban (HzR 1.0, $p=0.97$), 1.77%/yr with 30 mg/d edoxaban (HzR 1.41, $p<0.001$). In light of these numbers, as well as the FDA's approach with dabigatran it is possible, if not likely, that only the 60 mg dose will be approved, unless pharmacokinetic studies are utilized to determine the ultimately approved doses as was the case with dabigatran. Finally, given the interaction of this agent, too, with dual P-gp/CYP3A4 inhibitors and inducers, their co-administration will also likely play a role in dosing recommendations.

Final Thoughts

In light of the above, I have difficulty in my own mind justifying the initiation of warfarin rather than a NOAC in a patient with "non-valvular" AF and risk-markers for stroke/systemic embolism. The NOACs have better efficacy/safety profile,; are more convenient for patients and physicians alike, and have fewer drug and dietary interactions. Nonetheless, when the NOACs are employed, especially in the setting of different doses for different indications, different doses for different concomitant clinical characteristics or disorders, or different doses with specific metabolic inhibitors/inducers, careful attention is/will be required to ensure that the efficacy and safety profiles established in their pivotal clinical trials will remain the same in the wider world of clinical practice. Hence, clinical acumen and judgment is necessary with these agents beyond their package insert dosing dictates.

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