Ali Massumi Cardiac Arrhythmia Symposium

Clinical Challenges of Using Novel Oral Anticoagulants

for Stroke Prevention in Patients with Atrial Fibrillation

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Atrial fibrillation (AF) is the most prevalent arrhythmia, and patients with AF have an increased risk of stroke. According to the CHA_2DS_2-VASc scoring system, stroke risk is greater when these patients are older than 65 years; are female; have systolic heart failure, diabetes mellitus, hypertension, peripheral vascular disease, or a recent myocardial infarction; or have a history of stroke or transient ischemic attack.[1] Oral anticoagulants are the mainstay therapy for stroke prevention in AF patients. Drugs called new oral anticoagulants (NOACs) are often prescribed for this purpose and are as effective as warfarin. Currently, 4 NOACs are approved by the U.S. Food and Drug Administration: dabigatran (a direct thrombin inhibitor), rivaroxaban, apixaban, and edoxaban (a direct factor Xa inhibitor). Only dabigatran has a reversal agent. In comparison with warfarin, NOACs have fewer interactions with foods and medications, and routine bloodwork is not required to evaluate patients' anticoagulation levels when they take these drugs.[1-3]

When NOACs are prescribed instead of warfarin, considerations include patients' renal and liver function, and possible drug interactions. A management challenge is to formulate an appropriate plan for NOAC use before noncardiac surgery, with answers to the following questions: should we hold NOACs? When should they be stopped? Do we need to bridge the patient with heparin? When should we restart the NOACs?

Other factors to consider are the risk of bleeding associated with the procedure, the patient's individual risk of stroke and bleeding, and the type of NOAC to use.[2] Bridging is not typically recommended for NOACs.[2] For example, in a patient with persistent AF who is taking apixaban, has a CHA_2DS_2-VASc score of 3, has normal renal function, and is to undergo transurethral resection of the prostate (associated with a high risk of bleeding), apixaban should be stopped 48 hours preoperatively, without heparin bridging; it can be restarted as soon as the surgeon determines that doing so is safe.

Cytochrome P450 subgroup CYP3A4 is important in the metabolism of NOACs,[4] P-glycoprotein in their absorption, and renal function in their excretion. Medications that induce or inhibit the functions of CYP3A4 or P-glycoprotein can affect the bioavailability of NOACs and increase the risk of bleeding or thromboembolism.[4] One such, an over-the-counter supplement, is St. John's wort. Typically taken as therapy for psychological depression, this herb induces P-glycoprotein and can thus decrease the bioavailability of dabigatran.

Therapy with NOACs is limited in patients with valvular heart disease. However, current data suggest that NOACs can decrease stroke risk in patients with nonvalvular AF.[1] This condition is defined as AF in the absence of rheumatic mitral valve stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.[1] For instance, in a patient with AF and severe mitral stenosis, the anticoagulant of choice is warfarin. Conversely, in a patient with AF and severe aortic stenosis, a NOAC may be considered.

Concomitant oral anticoagulation and dual antiplatelet therapy (DAPT) (aspirin and an adenosine diphosphate inhibitor)—known as triple therapy—greatly increases a patient's bleeding risk; however, NOACs can be used. The expert recommendation is to keep the duration of triple therapy as short as possible in patients who have acute coronary syndrome and AF. It is essential to accurately evaluate the

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patient's risk of bleeding, thrombosis, or recurrent acute coronary syndrome during triple therapy. Clopidogrel is the adenosine diphosphate inhibitor of choice; conversely, ticagrelor and prasugrel should be avoided.[3,5] In DAPT plus warfarin, the target international normalized ratio is 2 to 2.5. In DAPT plus a NOAC, the NOAC prescription should be the lowest dose studied in the relevant clinical trial.[3,5] Proton-pump inhibitors are recommended for patients with a risk or history of gastrointestinal bleeding, and their use is encouraged in all patients who are prescribed triple therapy.[3,5] For example, in a patient with acute myocardial infarction, persistent AF, and no history of bleeding, the recommended combination would be aspirin, clopidogrel, and either a NOAC (apixaban, 2.5 mg twice daily) or warfarin.

To maintain the clinical benefits and minimize the adverse effects of NOACs, clinicians must consider the pharmacologic characteristics of the particular drug, the patient's risk of bleeding, the correct drug combination with antiplatelet therapy, and potential interactions between the NOAC and the patient's other medications. In addition, all patients should be counseled about the potential side effects before they start taking NOACs.

References

1. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society [published erratum appears in J Am Coll Cardiol 2014; 64(21):2305-7]. J Am Coll Cardiol 2014;64(21):e1-76.
2. Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL Jr, Ortel TL, Saxonhouse SJ, Spinler SA. 2017 ACC Expert Consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: a report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol 2017;69(7): 871-98.
3. Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, Ten Berg JM, et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). Eur Heart J 2014;35(45):3155-79.
4. Di Minno A, Frigerio B, Spadarella G, Ravani A, Sansaro D, Amato M, et al. Old and new oral anticoagulants: food, herbal medicines and drug interactions. Blood Rev 2017;31(4):193-203.
5. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39(3):213-60.