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GARFIELD-AF Report: A wakeup call to Asia

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The findings have important implications for Asia because the prevalence of atrial fibrillation (AF) is growing across the region. It is the most common sustained arrhythmia, causing a 2-fold increase in mortality and a 5-fold increase in stroke.

Non-vitamin K antagonists oral anticoagulants or NOACs are often prescribed at lower than recommended doses in many Asian countries but a late breaking report from the European Society of Cardiology Congress (ESC 2018) indicates the practice may be putting patients at risk.

The global scope of the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) - the largest multinational prospective registry in patients with newly diagnosed atrial fibrillation (AF) has provided an opportunity to evaluate whether the actual dosing of NOACs in real-life conforms to the approved dosing regimen (based on country-specific guidelines for each NOAC for stroke prevention).

The findings have important implications for Asia because the prevalence of atrial fibrillation (AF) is growing across the region. It is the most common sustained arrhythmia, causing a 2-fold increase in mortality and a 5-fold increase in stroke. The Asian population is rapidly aging, and in 2050, the estimated population with AF will reach 72 million, of whom 2.9 million may suffer from AF-associated stroke. Therefore, stroke prevention in AF is an urgent issue in Asia.

The new analysis, one of several from GARFIELD-AF presented at a Late-Breaking Science “Registry 2” session, revealed the detrimental effects of non-recommended NOAC dosing. In a Rapid Fire session at ESC Congress 2018, Professor A. John Camm, St George’s, University of London reported that although a large number of the 10,417 patients studied received the correct dose of NOAC, almost 26% of patients received non-recommended low-dose NOAC. For these patients, all-cause mortality increased by 51% over the first year of follow-up (adjusted HR: 1.51% [95% CI 1.16-1.96]), compared with patients who received the recommended dose of NOAC for stroke prevention.

Dosing above the recommended dose was relatively rare (3.6%, overall), and largely confined to cases where dose-modification was not heeded for moderate-to-severe chronic kidney disease. Although all NOACs marketed have a specific dosing algorithm for renal-impaired patients. Rivaroxaban is the only NOAC with a prospectively researched dose for patients with reduced kidney function and poor creatinine clearance. The lower 15mg dose recommendation was added to the rivaroxaban dosing guidelines after the pivotal ROCKET AF phase 3 trial, demonstrating its safety and efficacy for patients with moderate-to-severe chronic kidney disease, defined in the ROCKET-AF trial as a creatinine clearance below 50

(CrCl15–49 mL/minute).

NOACs are recommended as first-line anticoagulants in the prevention of AF-associated stroke in the latest international guidelines for the management of AF. While they offer a new standard of care in preventing AF-related strokes, major bleeding in NOACs is a consideration of doctors. Unfounded concerns that higher doses of NOACs resulted in increased risk of bleeding led to some doctors in Asia prescribing lower doses than recommended, or not prescribing any type of NOACs. However several studies have demonstrated that it is the patient's characteristics which drive the bleeding risk more than the dose of an oral anticoagulant. No distinct difference between the higher and lower doses was seen in clinical trials, rather it is the $CHADS_2$ score or CHA_2DS_2-VASc scores that primarily drive the bleeding risk; the higher they are the greater the risk of bleeding regardless of NOAC dose. The late breaking report from ESC 2018 demonstrated that underdosing not only does not reduce the risk of bleeding, but does significantly increased risk of stroke and death. This reaffirms the results of previous studies. In one such study published in the Journal of the American College of Cardiology, patients treated with an inappropriately low dose of a NOAC exhibited a 4.8 times higher risk of stroke, but with no statistically significant difference in major bleeding.

Benefits of anticoagulant therapies for AF patients far outweigh the risks

The new analysis of GARFIELD also reassures physicians that the benefits of anticoagulant therapies for AF patients far outweigh the risks. It confirmed that NOACs are superior to vitamin-K antagonists (VKAs) such as warfarin in reducing 2-year mortality in higher risk patients (CHA_2DS_2-VASc score ?2). In the study of 19,134 patients, there were 19% fewer deaths in patients initiated on NOACs than VKAs at the time of diagnosis of AF. In this group of high risk patients, there were 17% fewer deaths and 27% fewer strokes/systemic emboli in those with anticoagulant therapy than in those without.

Asia however lags behind the rest of the world when it comes to prescribing anticoagulant therapies and particularly NOACs. Prescription rates are slowly improving but figures from the GARFIELD-AF Registry, show that still only 20 % of Asian patients are being prescribed NOACs. 60% of patients still receive either the VKAs (with or without antiplatelet therapy) or antiplatelet therapy like Aspirin alone, while 20% receive no treatment.

The positive benefit risk profile of NOACs in Asian patients was specifically highlighted recently in the XANAP study, which was published this July in the Journal of Arrhythmia. XANAP highlights low bleeding rate (1.5% per year) and low stroke rate (1.7% per year) in AF patients treated with the NOAC rivaroxaban, and confirms rivaroxaban's safety and efficacy for stroke prevention in Asian patients with AF. XANAP is the first and largest prospective study to date in Asia investigating the use of rivaroxaban in a broad patient population.The new Garfield AF analysis, together the studies like XANAP, may encourage more doctors in Asia to prescribe NOACs.