VIEWPOINT

Postapproval Observational Studies of Non–Vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation

Tatjana S. Potpara, MD, PhD, FESC
School of Medicine, Belgrade University, Belgrade, Serbia; and Cardiology Clinic, Clinical Centre of Serbia, Belgrade, Serbia.

Gregory Y. H. Lip, MD
School of Medicine, Belgrade University, Belgrade, Serbia; and University of Birmingham Institute of Cardiovascular Science, City Hospital, Birmingham, United Kingdom.

Related article
page 1151

Corresponding Author: Gregory Y. H. Lip, MD, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Dudley Road, Birmingham B18 7QH, United Kingdom (g.y.h.lip@bham.ac.uk).

The pivotal randomized clinical trials (RCTs) of non–vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in atrial fibrillation (AF) established the efficacy and safety of these drugs for patients with AF without mechanical prosthetic heart valves or significant (rheumatic) mitral valve stenosis.[1] A clinical trial setting with strict inclusion and exclusion criteria was needed to obtain high-quality scientific evidence on the effects of NOACs compared with standard care (ie, warfarin), but these results in highly selected trial cohorts may not be fully applicable to a diversity of patients or clinical circumstances encountered in daily practice.

Postapproval observational NOAC studies have therefore been conducted to validate the RCT results in populations of patients with AF in the clinical setting. Well-conducted postmarketing observational studies evaluating the clinical effectiveness and safety of NOACs in daily practice complement the RCTs and provide additional information about the use of NOACs among high-risk patients such as those who are very old or have substantial comorbid illness. These studies sometimes may involve NOAC dosages that have not been well-studied in the respective RCTs; the use of different, broader treatment regimens; various patterns of drug selection or dose selection; longer follow-up; and variation in adherence and persistence with therapies. Importantly, postmarketing observational studies may reveal potential safety signals not detected in the RCTs.

Observational data from clinical practice settings can be obtained from various sources, all of which have certain advantages and limitations.

First, professional society–conducted registries (eg, the EuroObservational Research Programme [EORP] Long-term AF registry; the National Cardiovascular Data Registry Practice Innovation and Clinical Excellence [NCDR PINNACLE] registry) or industry-funded registries (eg, the Global Anticoagulant Registry in the Field [GARFIELD]; the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation [ORBIT-AF]) provide prospective data with predefined end points and rigorous data collection (particularly in the industry-sponsored registries). However, patients may be recruited from preselected health care settings (eg, cardiology practices), and the requirement for patient informed consent may create a selective population, whereas regular prespecified follow-up may influence adherence to treatment. The definition of end points in registries may differ from those used in RCTs, and an independent adjudication of outcome events may be absent. There is also the possibility of missing data, and a proportion of patients may be lost to further follow-up.

Second, nationwide administrative registry–based or administrative claims–based data sets from health care or insurance systems enable rapid collection of large AF cohorts with information about medical visits and prescriptions and no specific inclusion or exclusion criteria apart from the beneficiary status, thus minimizing the selection bias. However, these are mostly retrospective analyses with possible differences in outcomes definition when compared with RCTs (or variable coding of end point events in the insurance claims, which may affect the end point event rates). There is also a possibility of coding errors, missing data, lack of clinically relevant data due to unmeasured variables (eg, the International Normalized Ratio), or concomitant over-the-counter drug use that usually cannot be captured in such data sources.

Following drug approval, a large number of administrative data set–based studies of dabigatran[2] and an increasing number of studies including rivaroxaban and apixaban have been published.[3-7] To reduce the "healthy oral anticoagulant (OAC) user" bias, almost all studies included only patients with AF who were newly prescribed OACs.[4] To decrease baseline differences between treatment groups, the studies used various methods including multivariable adjustment, propensity weighing, or propensity score matching. Although propensity score matching is ordinarily preferable, it may not be feasible in smaller data sets because the necessary matching process usually would result in substantial reduction in numbers of patients in each treatment group. Follow-up in observational studies has ranged from 90 days to 2 years.

All published observational studies have addressed the safety of NOACs in relation to major bleeding (intracranial, gastrointestinal, or other major bleeding as defined in each study) and reported the following: (1) remarkably consistent major bleeding rates with apixaban ranging from 2.29% to 2.38% per 100 patient-years[3-5] (in the ARISTOTLE trial[1] the major bleeding rate with apixaban was 2.13%); (2) variable major bleeding rates with dabigatran (2.04%-3.60% per 100 patient-years)[3,5] with lower rates for 150-mg twice-daily dose than with the 110-mg or 75-mg dose[3-5] (in the RE-LY trial,[1] the major bleeding rate was 3.11% with dabigatran, 150 mg, and 2.17% with dabigatran, 110 mg), and (3) highly variable major bleeding rates with rivaroxaban (2.90%-6.00% per 100 patient-years,[3-5,8] and 3.60% in the ROCKET-AF trial[1]), with the highest rate for rivaroxaban, 15 mg once daily.

Overall, all 3 NOACs were safer than or as safe as warfarin in terms of major bleeding risk, with rates of warfarin-associated major bleeding ranging from 3.58% to 4.46% per 100 patient-years in the studies comparing apixaban and warfarin,[3,5] from 3.03% to 4.80% in the studies

comparing dabigatran and warfarin,[4,5] and from 3.40% to 5.09% in the studies comparing rivaroxaban to warfarin.[5,9] In pair-wise comparisons among NOACs, major bleeding rates were the lowest with apixaban, intermediate with dabigatran, and highest with rivaroxaban. All 3 NOACs were safer than warfarin in terms of intracranial bleeding (0.22%-0.49% vs 0.32%-1.06%),[3,4,6] although the rates of gastrointestinal bleeding were higher with rivaroxaban than with warfarin, (3.26% vs 2.53%) and similar among apixaban, dabigatran, and warfarin users.[4,7]

The effectiveness of NOACs has not been investigated in all observational studies, but the use of apixaban or rivaroxaban (both the 20-mg and 15-mg dose) was associated with lower rate of stroke or systemic embolism than warfarin (1.33% vs 1.55% for apixaban[4]; 2.89% vs 3.25% for 20 mg of rivaroxaban[3]; and 4.60% vs 3.90% for 15 mg of rivaroxaban[8]). When reported, the use of apixaban or dabigatran was associated with lower all-cause mortality than use of warfarin (5.01% vs 7.41% and 4.62% vs 7.41%, respectively),[3] and rivaroxaban use was associated with similar or higher all-cause mortality compared with warfarin (7.02% vs 7.41% to 25.7% vs 8.8%).[3,8]

Available data from clinical settings reveal broadly consistent OAC prescribing patterns across the observational studies. In general, warfarin is commonly prescribed to older patients and those with greater comorbidities (as evident via the Deyo-Charlson Comorbidity Score), both of which have less favorable stroke risk profiles (as assessed using the CHA_2DS_2-VASc score) compared with NOACs users. Among NOACs, dabigatran, 150 mg twice daily, was more commonly prescribed for younger healthier patients with AF, whereas the other 2 NOACs were more often prescribed to older patients with more comorbid illness (rivaroxaban) or those at increased risk of bleeding (apixaban). Concomitant aspirin use is more frequent with warfarin than among NOAC users.

Lower doses of NOACs may seem attractive due to apparently greater safety. Use of lower doses of dabigatran or edoxaban in RCTs was associated with better safety but at the expense of some reduction in efficacy. Overall, lower NOAC doses were more often used in daily practice than reported in the pivotal RCTs,[1] but in clinical studies, both stroke and bleeding rates were higher with lower NOAC doses than with standard doses. This could be attributed to less favorable risk profiles among patients who received lower NOAC doses, but some unjustified underdosing also seems very likely, resulting in lower net clinical benefit with reduced NOAC doses compared with standard NOAC doses in clinical studies.[8]

Observational studies consistently show better adherence to NOACs compared with warfarin (particularly among AF patients with ≥2 stroke risk factors), but study-specific rates of adherence are highly variable and generally lower with dabigatran (67.2%) than with rivaroxaban (72.7%) or apixaban (69.5%).[10] While prospective registry-based studies using clinical data with structured follow-up may increase adherence, retrospective claims-based data are likely overestimating medication adherence, to some extent, for several reasons. First, follow-up was 12 months or less in most of these studies, and both OAC adherence and persistence progressively decline over time. Second, claims-based studies use the proportion of days covered by a NOAC of at least 80% as a measure of good adherence and define persistence as percentage of patients who do not discontinue treatment. However, these data are derived from refill dates and days of supply and cannot reliably distinguish between temporary interruption and permanent discontinuation, determine whether the patient has actually been taking the medication, or identify reasons for nonadherence.

Importantly, observational clinical data cannot establish a cause-effect relationship between medication prescription and outcomes but only an association between the studied variables and should not be regarded as direct comparisons between NOACs. The size of study cohort, follow-up duration, NOAC prescribing patterns (eg, standard doses only), type of analysis (eg, claims-based retrospective analysis), end point definition(s), and method used to adjust for baseline differences (eg, propensity score matching) should be taken into account when interpreting reports based on observational clinical data.

Notwithstanding the limitations of these observational data from clinical practice settings and appropriately acknowledging their role with respect to RCTs as the criterion standard for exploring new therapies, available observational data about NOAC use for stroke prevention in AF broadly confirm results of the pivotal NOAC RCTs and show that NOACs are viable alternatives to warfarin in routine clinical practice. The decision to select a NOAC or a more traditional medicine such as warfarin should involve a discussion with patients reviewing the risks and benefits of both approaches.

ARTICLE INFORMATION

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