Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: http://www.tandfonline.com/loi/icmo20

Evaluating adherence to non-vitamin-K antagonist oral anticoagulants in post-approval observational studies of patients with atrial fibrillation

Tatjana S. Potpara, Giuseppe Boriani & Gregory Y.H. Lip

To cite this article: Tatjana S. Potpara, Giuseppe Boriani & Gregory Y.H. Lip (2017): Evaluating adherence to non-vitamin-K antagonist oral anticoagulants in post-approval observational studies of patients with atrial fibrillation, Current Medical Research and Opinion, DOI: 10.1080/03007995.2017.1313210

To link to this article: http://dx.doi.org/10.1080/03007995.2017.1313210

Published online: 11 Apr 2017.

CURRENT MEDICAL RESEARCH AND OPINION, 2017
http://dx.doi.org/10.1080/03007995.2017.1313210
Article FT-0115.R1/1313210

Taylor & Francis
Taylor & Francis Group

EDITORIAL

Evaluating adherence to non-vitamin-K antagonist oral anticoagulants in post-approval observational studies of patients with atrial fibrillation

The landmark randomized clinical trials (RCTs) of non-vitamin-K antagonist oral anticoagulants (NOACs, i.e. dabigatran, rivaroxaban, apixaban and edoxaban) for stroke prevention in patients with non-valvular atrial fibrillation (AF) – that is, AF without prosthetic mechanical heart valves or significant (rheumatic) mitral valve stenosis – have clearly established their efficacy and safety relative to dose-adjusted warfarin[1]. The most impressive finding in all NOAC treatment arms of the landmark RCTs was a significant reduction in hemorrhagic stroke and intracranial bleeding in comparison to warfarin[2]. In a meta-analysis of the phase III trials, the risk ratio (RR) for hemorrhagic stroke was 0.49, 95% confidence interval (CI) 0.38–0.64; and the RR for intracranial bleeding was 0.48, 95% CI 0.39–0.59 (both $p < .0001$) with NOACs relative to warfarin[1].

Following their approval, NOACs have rapidly changed the landscape of AF-related stroke prevention in clinical practice[3] and are increasingly used in AF patients with variable stroke and bleeding risk profiles, sometimes rather different (e.g. very old patients, those with recent major bleeding, advanced chronic kidney disease, active malignancy, etc.) from those included in the strictly defined study populations in the pivotal RCTs that are carefully followed up at regular protocol-based intervals. In addition, clinicians may sometimes choose NOAC dosing regimens that were not well studied in the RCTs[4]. Notwithstanding their limitations, well conducted post-approval large observational studies are of key importance to provide data (so called "real-world" data, RWD) on the effectiveness and safety of NOACs used outside the RCTs, in a routine clinical setting[5]. Indeed, the RWD on the comparative effectiveness and safety of NOACs for the prevention of AF-related stroke published thus far has broadly confirmed the results of the respective RCTs[6–10].

Compared with warfarin, NOACs are not only safer (in terms of intracranial bleeding or major life-threatening/fatal bleeding risk, both in the RCTs and "real-world" observational studies), but are viewed as more convenient for long-term use than vitamin K antagonists (VKAs), due to their predictable, dose-related anticoagulant effect enabling fixed dosing without the need for routine laboratory monitoring of the anticoagulation intensity[11,12]. In addition, NOACs have a fast onset and offset of action – the full anticoagulant effect is reached 2–3 hours after oral ingestion of the NOAC dose, thereafter gradually decreasing until the trough plasma level of the particular NOAC is reached (the exact timing of anticoagulant effect cessation is also dependent on renal function, particularly with dabigatran). Thus, NOACs may be more convenient than VKAs when short interruptions of oral anticoagulant therapy are needed (e.g. in case of major surgery)[11].

However, the downside of these pharmacological properties is that NOACs are less forgiving of dose omissions than VKAs – skipping just a dose or two of a NOAC may transiently expose the patient to increased risk of stroke[13]. Persistence with treatment (that is, the time interval from initiation to discontinuation of treatment) and adherence to medication (that is, taking the drug as prescribed) are crucial for effective long-term therapy in general, including treatment with NOACs for thromboprophylaxis in AF[14]. Suboptimal adherence to either VKAs or NOACs is potentially harmful for AF patients, since poor adherence may result in increased risks of stroke and bleeding[15].

Assessment of adherence and/or persistence to medication is challenging, and many direct or indirect methods have been developed to address the issue[16]. Nevertheless, the pivotal RCTs of NOACs for stroke prevention in AF reported only the rates of permanent drug discontinuation (20.7% and 21.2% for dabigatran 110 mg dose and 150 mg dose, respectively; 25.3% for rivaroxaban; 17.9% for apixaban; and 33.0% and 34.4% for edoxaban 30 mg dose and 60 mg dose, respectively), which were similar to the warfarin or aspirin discontinuation rates in the RCT setting in a recent meta-analysis of persistence with antithrombotic therapies for stroke prevention in AF[17].

Overall, "real-world" observational studies utilizing different methodologies and various data sources report highly variable NOAC persistence and adherence rates, ranging from 38% in a retrospective analysis of administrative claims-based dataset[18] to almost 100% in a cohort of AF patients managed in an anticoagulation clinic[19]. Prospective observational studies may artificially inflate persistence and adherence to investigated treatment by virtue of written informed consent the participants are required to provide and regular pre-planned follow-up, which may increase the awareness and thus the adherence of participants to the investigated therapy[5].

Retrospective "real-world" observational studies using large, administrative claims-based datasets commonly define persistence as the proportion of patients who do not discontinue therapy, and adherence as the number and proportion of days (PDC) covered by the drug of interest, as derived from the re-fill data and days of supply provided in the pharmacy claims[14]. A PDC of $\geq$80% is generally considered to be an indicator of good adherence. Overall, available RWD consistently shows better adherence of AF patients to NOACs

compared with VKAs and lower adherence to dabigatran compared with rivaroxaban or apixaban (e.g. 67.2% versus 72.7% or 69.5%, respectively)[14]. However, the follow-up in most of the studies was up to 1 year, and adherence to medication is inversely related to follow-up duration, declining with time[14]. Hence, the adherence to NOACs in the retrospective "real-world" observational studies may be overestimated.

In the elegant study published in this issue of *Current Medical Research and Opinion*, Coleman *et al.* addressed two important methodological considerations regarding the estimation of adherence in retrospective administrative claims-based observational studies of NOACs used for stroke prevention in AF[21]. Using data from two large US commercial insurance databases (the IMS Health Real World Data [IMS RWD] Adjudicated Claims and Truven Health MarketScan Research databases) and a retrospective cohort design, Coleman *et al.* created four different study populations of patients with non-valvular AF to test two research hypotheses in each of the two insurance datasets.

First, the authors hypothesized that the difference in follow-up duration between rivaroxaban and apixaban users would affect the comparative adherence estimates for the two NOACs. In the study population with unbalanced follow-up (SP-I), which included patients with $\geq$1 dispensings of rivaroxaban or apixaban at any time after the approval of rivaroxaban, mean follow-up was significantly longer among patients taking rivaroxaban than in those on apixaban, in both insurance databases (both $p < .0001$). This is not surprising, given the 13 month difference in the US approval of rivaroxaban (November 2011) and apixaban (December 2012). The unadjusted analysis of SP-I showed significantly worse adherence to rivaroxaban (44.7% in the IMS RWD Adjudicated Claims and 48.7% in the Truven Health database) compared with apixaban (57.1% and 61.1%, respectively), both $p < .05$.

In the study population adjusted for unbalanced follow-up and baseline confounders using propensity score matching (i.e. SP-II), the difference remained statistically significant but substantially narrowed down from 12.4 percentage points in both databases to 2.2 percentage points in the IMS RWD and 4.3 percentage points in the Truven Health database, thus showing how different follow-up duration influenced the adherence estimates for rivaroxaban and apixaban.

Indeed, PDC (a measure of adherence) is calculated as the total number of days of supply divided by the follow-up duration, thus expressing the inverse relationship between follow-up duration and adherence. With a fixed total number of days of supply, adherence would always look much better if evaluated over a shorter follow-up, but may turn into a poor adherence when evaluated over a longer follow-up period. Coleman *et al.*[20] nicely show that comparisons of adherence rates among medications marketed for different time periods without accounting for the imbalance in the total available follow-up would yield biased results in favor of the drug which last entered the market.

Second, the authors hypothesized that the study population selection criteria (that is, restriction to chronic medication users as opposed to the inclusion of single-time medication users and non-chronic users) would affect the medication adherence estimates. Using SP-II as the source, the authors created another two study populations: SP-III, which included all patients who had at least two dispensings of rivaroxaban or apixaban, and SP-IV, which included only chronic users (defined using the Pharmacy Quality Alliance criteria of at least two dispensings at least 6 months apart, with more than 60 days of supply).

In SP-III, there was no statistically significant difference in adherence rates for rivaroxaban and apixaban, either in the IMS RWD dataset (64.2% for rivaroxaban and 64.0% for apixaban) or in the Truven Health dataset (69.1% and 69.6%, respectively). However, in the SP-IV dataset of chronic users only, the adherence to rivaroxaban in both databases (79.6% and 81.9%, respectively) was significantly better compared with adherence to apixaban (74.6% and 77.9%, respectively), both $p < .05$. These findings were confirmed in a sensitivity analysis using a PDC of $\geq$90% as an indicator of good adherence, instead of the commonly used 80% cut-off.

Why is focusing on chronic users important? Administrative claims data allows for identification of patients who fill their prescriptions, but cannot establish the consumption of medication. Whilst with a single dispensing we cannot be sure that a patient took even a single pill, the occurrence of two or more dispensed prescriptions in the same patient at least suggest some intention to adhere to treatment, and the use of the 6 month span criterion should better identify true chronic users. This would eliminate AF patients such as, for example, those at a lower risk of stroke who were prescribed NOACs based on the physician's decision but are not truly convinced that they should take the medication, those taking NOACs before or shortly after cardioversion, etc. Indeed, the study of Coleman *et al.* shows how the inclusion of non-chronic medication users in the analysis may result in underestimation of adherence rates in all treatment groups.

Nonetheless, caution is still needed when interpreting such large retrospective administrative datasets analyses, even if an extensive adjustment for numerous variables has been performed. These datasets may not capture various factors which can influence medication adherence (such as, for example, patient education level, characteristics of a particular healthcare setting, the context of oral anticoagulation prescription, reasons for treatment discontinuation, socioeconomic or cultural factors, etc.), and adjustment can only be made for observable variables that have been collected in the particular dataset.

A recent report showed that substantial resources and time are utilized to improve thromboprophylaxis in AF[21]. Whilst more research is needed to inform adequate strategies to increase adherence of AF patients to oral anticoagulant therapy, the study of Coleman *et al.* adds important messages pertinent to the methodology of retrospective assessment of adherence to NOACs in the "real-world" administrative datasets providing large AF cohorts and valuable insights into thromboprophylaxis in AF in routine clinical practice.

Transparency

Declaration of funding

This editorial was not funded.

Declaration of financial/other relationships

TS.P., G.B., and G.Y.H.L. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

CMRO peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

1. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-62
2. Potpara TS, Lip GY. Oral anticoagulant therapy in atrial fibrillation patients at high stroke and bleeding risk. Prog Cardiovasc Dis 2015;58:177-94
3. Hsu JC, Akao M, Abe M, et al. International Collaborative Partnership for the Study of Atrial Fibrillation (INTERAF): rationale, design, and initial descriptives. J Am Heart Assoc 2016;5
4. Nielsen PB, Skjoth F, Sogaard M, et al. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ 2017;356:j510. doi: 10.1136/bmj.j510
5. Potpara TS, Lip GY. Postapproval observational studies of non-vitamin K antagonist oral anticoagulants in atrial fibrillation. JAMA 2017;317:1115-1116
6. Lip GY, Keshishian A, Kamble S, et al. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. Thromb Haemost 2016;116:975-986
7. Potpara TS. Dabigatran in "real-world" clinical practice for stroke prevention in patients with non-valvular atrial fibrillation. Thromb Haemost 2015;114:1093-8
8. Staerk L, Fosbol EL, Lip GY, et al. Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study. Eur Heart J 2016Oct 14. pii:ehw496. [Epub ahead of print]
9. Beyer-Westendorf J, Camm AJ, Coleman CI, Tamayo S. Rivaroxaban real-world evidence: validating safety and effectiveness in clinical practice. Thromb Haemost 2016;116:S13-23
10. Bai Y, Deng H, Shantsila A, Lip GY. Rivaroxaban versus dabigatran or warfarin in real-world studies of stroke prevention in atrial fibrillation: systematic review and meta-analysis. Stroke 2017;48:970-976
11. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace 2015;17:1467-507
12. Schulman S. New oral anticoagulant agents – general features and outcomes in subsets of patients. Thromb Haemost 2014;111:575-82
13. Hohnloser SH, Eikelboom JW. The hazards of interrupting anticoagulation therapy in atrial fibrillation. Eur Heart J 2012;33:1864-6
14. Raparelli V, Proietti M, Cangemi R, et al. Adherence to oral anticoagulant therapy in patients with atrial fibrillation. Focus on non-vitamin K antagonist oral anticoagulants. Thromb Haemost 2017;117:209-218
15. Yao X, Abraham NS, Alexander GC, et al. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. J Am Heart Assoc 2016;5:pii: e003074
16. Wang Y, Kong MC, Ko Y. Comparison of three medication adherence measures in patients taking warfarin. J Thromb Thrombolysis 2013;36:416-21
17. Chatterjee S, Sardar P, Giri JS, et al. Treatment discontinuations with new oral agents for long-term anticoagulation: insights from a meta-analysis of 18 randomized trials including 101,801 patients. Mayo Clin Proc 2014;89:896-907
18. Coleman CI, Tangirala M, Evers T. Medication adherence to rivaroxaban and dabigatran for stroke prevention in patients with non-valvular atrial fibrillation in the United States. Int J Cardiol 2016;212:171-3
19. Schulman S, Shortt B, Robinson M, Eikelboom JW. Adherence to anticoagulant treatment with dabigatran in a real-world setting. J Thromb Haemost 2013;11:1295-9
20. Coleman C, Yuan Z, Schein J, et al. Importance of balancing follow-up time and impact of oral-anticoagulant users' selection when evaluating medication adherence in atrial fibrillation patients treated with rivaroxaban and apixaban. Curr Med Res Opin 2017; DOI: 10.1080/03007995.2017.1297932
21. Potpara TS, Pison L, Larsen TB, et al. How are patients with atrial fibrillation approached and informed about their risk profile and available therapies in Europe? Results of the European Heart Rhythm Association Survey. Europace 2015;17:468-72

Tatjana S. Potpara
School of Medicine, Belgrade University, Belgrade, Serbia
Cardiology Clinic, Clinical Centre of Serbia, Belgrade, Serbia
tatjana.potpara@mfub.bg.ac.rs; tanjapotpara@gmail.com

Giuseppe Boriani
Cardiology Division, Department of Diagnostics, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy

Gregory Y.H. Lip
School of Medicine, Belgrade University, Belgrade, Serbia
University of Birmingham Institute of Cardiovascular Science, City Hospital, Birmingham, United Kingdom
Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Received 23 February 2017; revised 13 March 2017; accepted 23 March 2017