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On-treatment follow-up in real-world studies of direct oral anticoagulants in atrial fibrillation: Association with treatment effects

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ABSTRACT

Background: Numerous observational studies support the safety and effectiveness of the direct oral anticoagulants (DOAC) for stroke prevention in atrial fibrillation (AF), but these data are often limited to short duration of follow-up. We aimed to assess the length of on-treatment follow-up in the accumulated real-world evidence and the relationship between follow-up duration and estimates of DOAC effectiveness and safety.

Methods: We searched the literature for observational studies reporting comparative effectiveness and safety outcomes of DOACs versus warfarin. In random-effects *meta*-analyses, we assessed associations of specific DOACs vs warfarin for stroke/systematic embolism (SE) and major bleeding. In *meta*-regression analyses, we assessed the correlation between the reported on-treatment follow-up with the effect sizes for stroke/SE and major bleeding outcomes.

Results: In 45 eligible observational studies, the average on-treatment follow-up was <1 year for all DOACs. In *meta*-analyses, all DOACs showed significantly lower risks of stroke/SE, but only dabigatran and apixaban showed lower risks for major bleeding compared to warfarin. There was no correlation between follow-up duration and magnitude of stroke/SE reduction for any of the DOACs. Longer follow-up correlated with greater major bleeding reduction for dabigatran ($p = 0.006$) and rivaroxaban ($p = 0.033$) as compared to warfarin, but it correlated with smaller major bleeding reduction for apixaban ($p = 0.004$).

Conclusions: The numerous studies of DOAC effectiveness and safety in the routine AF practice pertain to short treatment follow-up. Study follow-up correlates significantly with DOAC-specific vs warfarin associations for major bleeding.

1. Introduction

The direct oral anticoagulants (DOACs) including dabigatran, apixaban, rivaroxaban, and edoxaban are now recommended as first-line treatment for patients with atrial fibrillation (AF) who are at risk of stroke [1,2]. DOACs and warfarin are generally prescribed with the intent of being lifelong treatments for the prevention of stroke. The pivotal trials that led to the approval of DOACs had on average approximately 2–3 years of on-treatment follow-up [3–6]. However, data from observational studies often rely on even shorter follow up reflecting the challenges of real-world use of pharmacological interventions and making any extrapolated estimations of long-term comparative effectiveness unreliable. Thus, despite the increasing availability of real-world data, there may be a mismatch between the accumulated evidence and the perceived certainty of the comparative safety and effectiveness for long-term use of these agents. In this empirical assessment of the DOAC AF literature, we sought to assess the length of on-treatment follow-up in the accumulated real-world evidence and the relationship between follow-up duration and safety and effectiveness association estimates in DOAC vs warfarin comparisons.

2. Methods

We searched the MEDLINE database from October 2010 to June 2020 for observational studies comparing at least one DOAC versus warfarin for patients with AF. The search terms included ("Non-Vitamin K Antagonist Oral Anticoagulant" or "novel oral anticoagulant" or "direct oral anticoagulant" or "dabigatran" OR "apixaban" OR

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"rivaroxaban" OR "edoxaban") AND "atrial fibrillation." The results were then screened based on the title and abstract for preliminary inclusion. Studies were further included if they reported hazard ratios for each DOAC for stroke (ischemic or hemorrhagic) or systemic embolism (SE), and for major bleeding. If multiple studies used the same cohort with the same inclusion criteria, we selected the study with the longer follow-up duration for inclusion in order to avoid redundancy.

From each eligible study, we documented basic study information, and the reported mean or median follow-up on treatment in each of the DOAC and warfarin groups (until treatment end or censoring per each study's definition). If a study reported follow-up as patient-years rather than mean/median follow-up, mean follow up (days) was calculated by multiplying patient-years by 365 and dividing by the number of patients in the analysis. We also documented the hazard ratios (HR) and 95% confidence intervals (CI) for the associations of DOAC vs warfarin corresponding to that period of follow-up for each outcome of interest. When unadjusted and adjusted estimates were available, we included the most adjusted estimates.

We report descriptive characteristics of the eligible studies and summary statistics of average follow-up stratified per DOAC vs warfarin comparison and per outcome. Further, we performed random-effects *meta*-analysis with the Hartung-Knapp-Sidik-Jonkman method for each DOAC-warfarin comparison for stroke/SE and major bleeding [7]. In *meta*-regression analyses we examined the association between the per-study follow-up period and the effect size of effectiveness (stroke/SE) and safety (major bleeding) associations specific to each DOAC vs warfarin comparison. Edoxaban was not included in the *meta*-analyses due to the limited number of studies reporting bleeding or stroke outcomes.

3. Results

Out of 4,595 search items that we screened, a total of 45 observational studies were included comprising 454 comparisons unique to specific DOACs vs warfarin and outcomes (n = 161 for dabigatran, n = 150 for rivaroxaban, n = 117 for apixaban, n = 26 for edoxaban). Of these, 72 comparisons included stroke/SE and 81 comparisons included major bleeding which were the outcomes of interest in the *meta*-analyses in this study.

The mean total population per study was 68,873 (IQR 20,473–80,337). For any outcome, the range of reported on-treatment mean/median follow-up was 25 to 823 days. For any outcome, the median of the reported mean or median follow-up was 327 days (IQR 210–396 days) in the dabigatran vs warfarin comparisons; 331 days (IQR 178–432 days) in the rivaroxaban vs warfarin comparisons; 274 days (IQR 196–392 days) in the apixaban vs warfarin comparisons; and 321 days (IQR 256–438 days) in the edoxaban vs warfarin comparisons.

Specifically for stroke/SE, the median of the reported mean or median follow-up was 297 days (IQR 186–358 days) in the dabigatran vs warfarin comparisons; 310 days (IQR 176–415 days) in the rivaroxaban vs warfarin comparisons; 264 days (IQR 161–345 days) in the apixaban vs warfarin comparisons; and 321 days (IQR 256–438 days) in the edoxaban vs warfarin comparisons. For major bleeding, the median of the reported mean or median follow-up was 307 days (IQR 180–393 days) in the dabigatran vs warfarin comparisons; 310 days (IQR 167–415 days) in the rivaroxaban vs warfarin comparisons; 262 days (IQR 159–332 days) in the apixaban vs warfarin comparisons; and 321 days (IQR 256–438 days) in the edoxaban vs warfarin comparisons.

In random-effects *meta*-analyses, dabigatran and apixaban demonstrated statistically significantly lower risks for both stroke/SE and major bleeding compared to warfarin. In the *meta*-analyses for rivaroxaban, there was a statistically significant reduction for stroke/SE compared to warfarin, but there was no difference for major bleeding. There was significant heterogeneity ($I^2 > 50\%$) in all pairwise comparisons for both stroke/SE and major bleeding. Detailed *meta*-analysis results are shown in Table 1.

Table 1
Results of Random-Effects Meta-Analysis of DOAC vs Warfarin Comparisons for Stroke/Systemic Embolism and Major Bleeding.

	N patients DOAC	N patients warfarin	HR (95% CI)	p-value	I^2 (95% CI) (%)
Stroke/systemic embolism					
Dabigatran	412,366	696,334	0.82 (0.76–0.89)	<0.001	64 (44–77)
Rivaroxaban	555,791	774,558	0.80 (0.74–0.86)	<0.001	74 (62–82)
Apixaban	360,055	614,653	0.72 (0.63–0.83)	<0.001	82 (74–88)
Major bleeding					
Dabigatran	445,408	878,584	0.75 (0.69–0.82)	<0.001	86 (81–90)
Rivaroxaban	597,286	934,442	0.96 (0.90–1.03)	0.2558	87 (82–90)
Apixaban	371,822	768,876	0.62 (0.58–0.68)	<0.001	83 (76–80)

Abbreviations: HR, hazard ratio: CI, confidence interval.
$I^2 > 50\%$ indicates significant heterogeneity.
The number of patients shown refers to the total number of patients included across all studies in each specific *meta*-analysis.

In *meta*-regression analyses, longer follow-up duration correlated with a larger magnitude of association for the reduction of major bleeding with dabigatran (p = 0.006) and rivaroxaban (p = 0.033) as compared to warfarin. In contrast, for apixaban, longer follow-up duration correlated with smaller effect size for the reduction of major bleeding compared to warfarin (p = 0.004). None of the DOACs demonstrated a statistically significant relationship between follow-up duration and stroke/SE associations (Fig. 1).

4. Discussion

We demonstrate that the reported on-treatment follow-up varied widely, but it was generally short (mean < 1 year) in all observational comparative effectiveness studies examining DOACs and warfarin for the prevention of stroke in AF. As has been previously demonstrated [8], DOACs were overall associated with more favorable safety and effectiveness compared to warfarin in combined analyses of all included studies. Also, the estimated safety of dabigatran and rivaroxaban (bleeding risk) seemed to improve relative to warfarin in studies that included longer follow-up. Conversely, studies with shorter follow-up tended to report a larger effect size for the superiority of apixaban over warfarin in reducing the risk of major bleeding. We did not detect any correlation between the reported on-treatment follow-up and the magnitude of association estimates for reduction in the risk thromboembolism with any of the DOACs.

The DOACs represent a major breakthrough in the care of AF in the last decade. Their safety and effectiveness profile coupled with convenience of use have brought them to the forefront of the stroke prevention armamentarium for the large number of AF patients worldwide. A strong evidence base has been generated by well-conducted large RCTs but also numerous observational studies in general populations and specific subgroups. The general consistency in treatment effects between the RCTs and the observational DOAC literature has further increased confidence in these agents [9]. In the current study we did not intend to perform another systematic review of DOAC safety and effectiveness as numerous such studies, often redundant, already exist in the literature [10,11]. Our report adds new insights by demonstrating that there is a mismatch in the studied length of follow-up between the pivotal RCTs and the real-world studies. The reported associations of comparative effectiveness and safety are derived from only a few months of on-treatment follow-up in the real-world experience. Considering that OAC is intended as long-term treatment in AF, this raises questions regarding DOAC non-adherence in routine practice and long-term

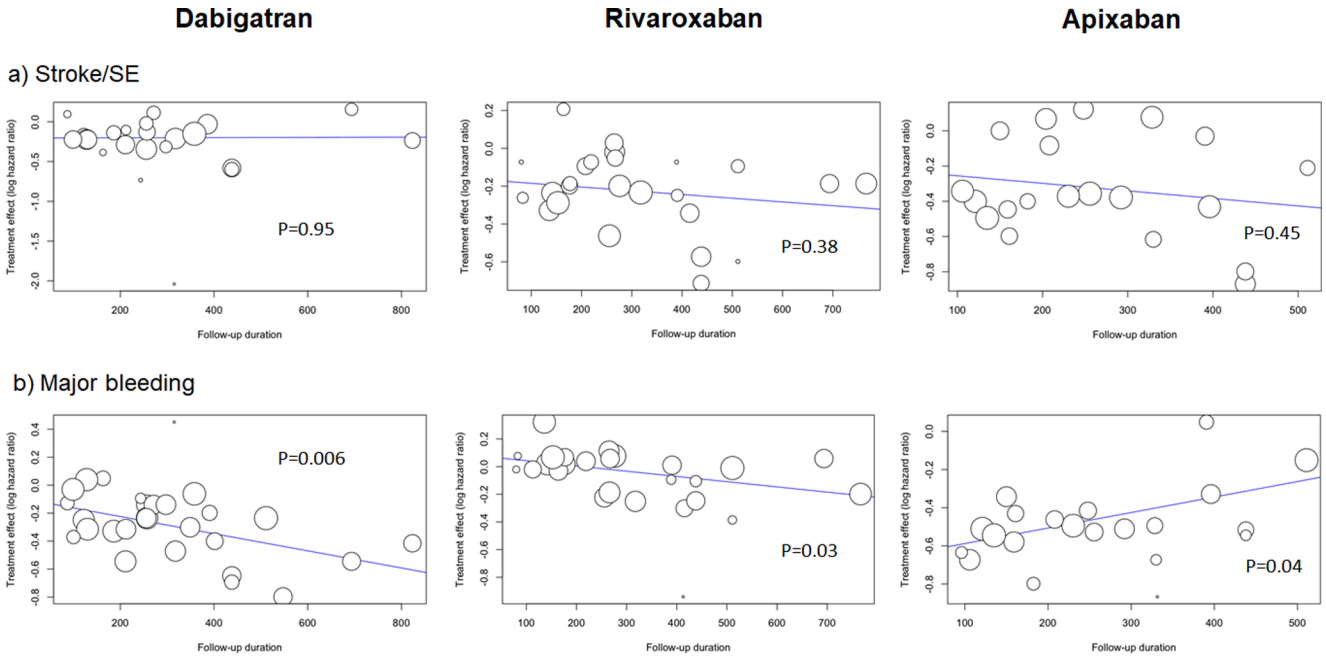

Fig. 1. Correlation of the Duration of Follow-up with the Effect Size of the Associations for Stroke/Systemic Embolism and Major Bleeding.

treatment outcomes. We have previously shown that adherence is poor with OAC in general and only modestly improved with the DOACs [12]. Long-term uninterrupted or minimally interrupted OAC may be further complicated by polypharmacy and complex comorbidities that amplify the bleeding risk. In one notable example, in a nationwide sample of patients with dialysis-dependent end-stage kidney disease and AF, the average duration of continuous apixaban therapy was just over 3 months with approximately 6 of 10 patients having an expired prescription or >30-day gap between prescription refills in the first year of therapy [13].

The relationship between on-treatment follow-up duration and the effect size of an intervention is an important factor to consider in the interpretation of such real-world data. Our study provides reassurance that the efficacy of DOACs compared to warfarin in preventing stroke was not dependent on the duration of follow-up. Associations for stroke reduction for all DOACs might be consistent regardless of reported on-treatment follow-up. However, the observation that dabigatran and rivaroxaban have further reduced rates of bleeding outcomes compared to warfarin when studied for a longer time period is interesting. This suggests that dabigatran and rivaroxaban might be safer than initially reported when followed for longer periods of time. This improved safety would be important to consider when selecting an OAC agent for patients who might suffer more from bleeding complications. Conversely, the safety advantage with apixaban appears to decrease as the duration of study increases. Apixaban was approved approximately 3 years after dabigatran and rivaroxaban were approved. Since apixaban is newer, there are fewer long-term observational studies and cumulative on-treatment follow-up compared to dabigatran and rivaroxaban which may introduce some bias. Further studies are warranted to better understand the mechanisms that underlie these differences within the DOACs. It should also be noted that we did not examine longitudinal comparative effectiveness and safety across various subgroups defined by patient characteristics as this was beyond the scope of this study. Prior literature suggests that results of DOAC comparisons are largely consistent across patient subgroups, with some exceptions largely related to advanced kidney disease subgroups [14].

5. Conclusions

This empirical assessment demonstrates that the large amount of accumulated evidence from the use of DOACs for stroke prevention in routine practice pertains to short follow-up that may be unable to accurately inform long-term outcomes. While follow-up duration within the studied range does not appear to correlate with comparative effectiveness (stroke/SE) estimates, there were significant correlations between follow-up duration and comparative effects on major bleeding that may inform patient counseling and the research agenda of DOAC therapy in AF.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] C.T. January, L.S. Wann, H. Calkins, L.Y. Chen, J.E. Cigarroa, J.C. Cleveland, P. T. Ellinor, M.D. Ezekowitz, M.E. Field, K.L. Furie, P.A. Heidenreich, K.T. Murray, J. B. Shea, C.M. Tracy, C.W. Yancy, 2019 AHA/ACC/HRS Focused Update of the 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 Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons, Circulation. 140 (2) (2019).

[2] G. Hindricks, T. Potpara, N. Dagres, E. Arbelo, J.J. Bax, C. Blomstrom-Lundqvist, et al., 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC, Eur Heart J. 42 (2021) 373–498.

[3] C.B. Granger, J.H. Alexander, J.J.V. McMurray, R.D. Lopes, E.M. Hylek, M. Hanna, H.R. Al-Khalidi, J. Ansell, D. Atar, A. Avezum, M.C. Bahit, R. Diaz, J.D. Easton, J. A. Ezekowitz, G. Flaker, D. Garcia, M. Geraldes, B.J. Gersh, S. Golitsyn, S. Goto, A. G. Hermosillo, S.H. Hohnloser, J. Horowitz, P. Mohan, P. Jansky, B.S. Lewis, J. L. Lopez-Sendon, P. Pais, A. Parkhomenko, F.W.A. Verheugt, J. Zhu, L. Wallentin,

Apixaban versus warfarin in patients with atrial fibrillation, N Engl J Med. 365 (11) (2011) 981–992.
[4] S.J. Connolly, M.D. Ezekowitz, S. Yusuf, J. Eikelboom, J. Oldgren, A. Parekh, J. Pogue, P.A. Reilly, E. Themeles, J. Varrone, S. Wang, M. Alings, D. Xavier, J. Zhu, R. Diaz, B.S. Lewis, H. Darius, H.-C. Diener, C.D. Joyner, L. Wallentin, Dabigatran versus Warfarin in Patients with Atrial Fibrillation, New Engl J Med. 361 (12) (2009) 1139–1151.
[5] R.P. Giugliano, C.T. Ruff, E. Braunwald, S.A. Murphy, S.D. Wiviott, J.L. Halperin, A.L. Waldo, M.D. Ezekowitz, J.I. Weitz, J. Špinar, W. Ruzyllo, M. Ruda, Y. Koretsune, J. Betcher, M. Shi, L.T. Grip, S.P. Patel, I. Patel, J.J. Hanyok, M. Mercuri, E.M. Antman, Edoxaban versus Warfarin in Patients with Atrial Fibrillation, New Engl J Med. 369 (22) (2013) 2093–2104.
[6] M.R. Patel, K.W. Mahaffey, J. Garg, G. Pan, D.E. Singer, W. Hacke, G. Breithardt, J. L. Halperin, G.J. Hankey, J.P. Piccini, R.C. Becker, C.C. Nessel, J.F. Paolini, S. D. Berkowitz, K.A.A. Fox, R.M. Califf, Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation, New Engl J Med. 365 (10) (2011) 883–891.
[7] C. Rover, G. Knapp, T. Friede, Hartung-Knapp-Sidik-Jonkman approach and its modification for random-effects meta-analysis with few studies, BMC Med Res Methodol. 15 (2015) 99.
[8] Lopez-Lopez JA, Sterne JAC, Thom HHZ, Higgins JPT, Hingorani AD, Okoli GN, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. Bmj. 2017;359: j5058.
[9] K.C. Siontis, S. Checkole, X. Yao, B.J. Gersh, P.A. Noseworthy, Do Observational Studies Agree With Randomized Trials?: Evaluation of Oral Anticoagulants in Atrial Fibrillation, J Am Coll Cardiol. 75 (5) (2020) 562–563.
[10] I. Doundoulakis, C. Antza, F. Apostolidou-Kiouti, E. Akrivos, H. Karvounis, V. Kotsis, A.-B. Haidich, G. Giannakoulas, Overview of Systematic Reviews of Non-Vitamin K Oral Anticoagulants in Atrial Fibrillation, Circ Cardiovasc Qual Outcomes. 11 (12) (2018), e004769.
[11] K.C. Siontis, J.P.A. Ioannidis, Replication, Duplication, and Waste in a Quarter Million Systematic Reviews and Meta-Analyses, Circ Cardiovasc Qual Outcomes. 11 (2018), e005212.
[12] X. Yao, N.S. Abraham, G.C. Alexander, W. Crown, V.M. Montori, L. R. Sangaralingham, B.J. Gersh, N.D. Shah, P.A. Noseworthy, Effect of Adherence to Oral Anticoagulants on Risk of Stroke and Major Bleeding Among Patients With Atrial Fibrillation, J Am Heart Assoc. 5 (2) (2016).
[13] K.C. Siontis, X. Zhang, A. Eckard, N. Bhave, D.E. Schaubel, K. He, A. Tilea, A. G. Stack, R. Balkrishnan, X. Yao, P.A. Noseworthy, N.D. Shah, R. Saran, B. K. Nallamothu, Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States, Circulation. 138 (15) (2018) 1519–1529.
[14] X. Yao, J.W. Inselman, J.S. Ross, R. Izem, D.J. Graham, D.B. Martin, A. M. Thompson, M. Ross Southworth, K.C. Siontis, C.G. Ngufor, K.A. Nath, N. R. Desai, B.K. Nallamothu, R. Saran, N.D. Shah, P.A. Noseworthy, Comparative Effectiveness and Safety of Oral Anticoagulants Across Kidney Function in Patients With Atrial Fibrillation, Circ Cardiovasc Qual Outcomes. 13 (10) (2020), e006515.