Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: Results from ORBIT-AF registry

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Background Time in therapeutic range (TTR) of international normalized ratio (INR) of 2.0 to 3.0 is important for the safety and effectiveness of warfarin anticoagulation. There are few data on TTR among patients with atrial fibrillation (AF) in community-based clinical practice.

Methods Using the US Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), we examined TTR (using a modified Rosendaal method) among 5,210 patients with AF on warfarin and treated at 155 sites. Patients were grouped into quartiles based on TTR data. Multivariable logistic regression modeling with generalized estimating equations was used to determine patient and provider factors associated with the lowest (worst) TTR.

Results Overall, 59% of the measured INR values were between 2.0 and 3.0, with an overall mean and median TTR of 65% ± 20% and 68% (interquartile range [IQR] 53%-79%). The median times below and above the therapeutic range were 17% (IQR 8%-29%) and 10% (IQR 3%-19%), respectively. Patients with renal dysfunction, advanced heart failure, frailty, prior valve surgery, and higher risk for bleeding (ATRIA score) or stroke (CHA_2DS_2-VASc score) had significantly lower TTR ($P < .0001$ for all). Patients treated at anticoagulation clinics had only slightly higher median TTR (69%) than those not (66%) ($P < .0001$).

Conclusions Among patients with AF in US clinical practices, TTR on warfarin is suboptimal, and those at highest predicted risks for stroke and bleeding were least likely to be in therapeutic range. (Am Heart J 2015;170:141-148.e1.)

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, and hospitalizations because of AF are increasing.[1] Patients with AF have a 5- to 7-fold greater risk of stroke than the general population.[2-4] Oral anticoagulants can effectively decrease the stroke rate by more than two thirds; however, this therapy also puts patients at increased risk for bleeding and intracranial hemorrhage.[5-7]

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0002-8703

http://dx.doi.org/10.1016/j.ahj.2015.03.017

The clinical benefit and risks of warfarin are associated with the proportion of time that international normalized ratio (INR) values are between 2 and 3, meaning the time in therapeutic range (TTR).[8] To date, only a few multicenter studies have examined patients' TTR in clinical practice in the United States. These studies, however, had limited sample size,[9] failed to explore patient-level clinical data,[10] or were not generalizable to the overall population.[11]

The objective of this analysis is to describe patient-level TTR within the nation's largest community-based AF clinical registry. The detailed clinical data on the patients in this study provide insight into characteristics of patients associated with low TTR, who may be predicted to be candidates for alternatives to non–vitamin K oral anticoagulants (NOAC).

Methods

Study population

The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) is a US national prospective registry of AF.[12] Enrolling providers include primary

care physicians', cardiologists', and electrophysiologists' clinics. Eligible patients are at least 18 years of age with nonreversible AF that has been documented on an electrocardiogram. Patients were excluded if they had a life expectancy of <6 months or were not capable of at least 2 years of follow-up.

Sites entered data from the medical record into a web-based case report form at baseline and every 6 months over longitudinal follow-up. Patient demographics, medical history, AF history, AF symptoms, AF treatment strategy, vital signs, laboratory data, imaging data, incident procedures, and adverse events were collected. The Duke Clinical Research Institute was responsible for study design and data management.

There were 10,132 consecutive patients from 176 clinic sites enrolled in ORBIT-AF from June 2010 through August 2011. Patients were excluded from this analysis if they were not on warfarin at baseline (n = 2,918) or did not have documented INR data at follow-up (n = 1,201). This analysis is intended to evaluate patients on long-term warfarin therapy, so patients with <5 INR values were excluded (n = 803). The final study population included 5,210 patients, who were enrolled at 155 sites.

Time in therapeutic range calculation

A modified Rosendaal method of linear interpolation was used between each pair of measured INR values.[13] Daily INR values were imputed between each measured INR. No extrapolation was performed before the baseline visit at the time of registry enrollment or after the end of follow-up. For patients with time between any 2 measurements of ≥60 days (4.8% of the intervals between 2 INR measurements), this time span was excluded from the TTR calculation. A sensitivity analysis calculated the overall TTR without excluding any time spans. The TTR was calculated as the proportion of days with INR values between 2 and 3. An INR value of <2.0 was defined as subtherapeutic, and an INR value >3.0 was defined as supratherapeutic.

Statistical methods

Patients were stratified into quartiles based on TTR. Baseline characteristics were determined for the overall population and by quartile. Categorical variables were defined as frequencies and percentages, and differences between the groups were assessed by the χ^2 test. Continuous variables were characterized by median (interquartile range [IQR]), and differences between the groups were determined by the Kruskal-Wallis test.

Patients in the lowest TTR quartile were considered to be poor responders to warfarin. A multivariable logistic regression model with generalized estimating equations was constructed for the outcome of poor responders (quartile 1) versus non–poor responders (quartiles 2-4), using clinical and demographic characteristics (online Appendix).

All continuous variables were evaluated for nonlinearity with the outcome, and variables that did not meet the linear relationship criteria ($P < .05$) were accounted for using linear splines. Missing data were 4% for level of education, 6% for chronic kidney disease (CKD), 9% for hemoglobin level, and <1% for all remaining covariates. Missing data on the covariates were imputed using multiple imputation. Backward selection with an inclusion criterion of 0.05 was performed on the first imputed data set to obtain a set of factors that were independently associated with poor responders. For each imputed data set, a model with the significant covariates was fit using a logistic generalized estimating equations method with exchangeable working correlation matrix to account for intrasite clustering. Patients at the same site are more likely to have similar responses relative to patients at other sites (ie, within-center correlation for responses).[14] The results from each model were then combined. All analyses were performed using SAS software (version 9.3, SAS Institute, Cary, NC). The ORBIT-AF registry is sponsored by Janssen Scientific Affairs, LLC, Raritan, NJ. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Results

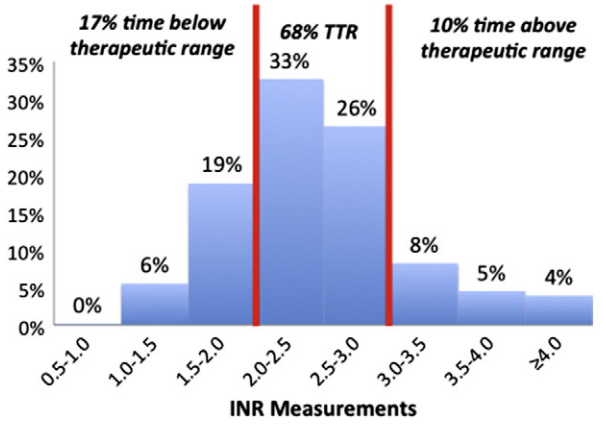
Baseline characteristics

Among the 5,210 patients with AF included in this analysis, there were 119,842 INR measurements over a median of 18 months (IQR 12-23 months) of follow-up. The median number of INR draws per patient was 20 (IQR 12-30). Among all measured INR values, the median INR value was 2.3 (IQR 2.0-2.8), and 59% of all measured INR values were in the therapeutic range, whereas 25% of all INR values were <2.0, and 17% were >3.0. The mean and median patient-level TTRs were 65% ± 20% and 68% (IQR 53%-79%), respectively (Figure 1). The median times that individual patients spent below and above the therapeutic range were 17% (IQR 8%-29%) and 10% (IQR 3%-19%), respectively.

The frequency of INR checks was associated with INR results. Specifically, the mean number of days between INR measurements was 21 to 24 days for patients with INR values within the therapeutic range (ie, 2.0-3.0), whereas patients with subtherapeutic or supratherapeutic values had their INR tested more frequently (Figure 2). The median number of INR draws per month was also higher among the quartile of patients with the highest TTR: 0.86 INR draws per month (IQR 0.72-1.08) for quartile 4, 0.78 (IQR 0.64-0.99) for quartile 3, 0.75 (IQR 0.56-0.98) for quartile 2, and 0.72 (IQR 0.51-1.00) for quartile 1 ($P < .0001$).

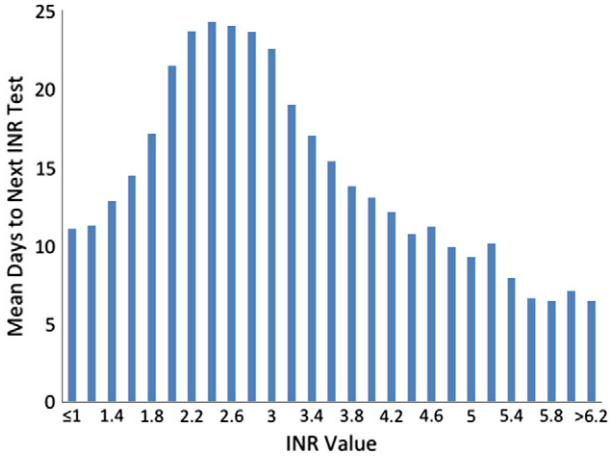
The patients within the lowest quartile TTR (ie, TTR ≤53) were more often female, nonwhite, and had less college education than those with higher TTRs. Patients with comorbidities, including diabetes, CKD, and heart failure, were also less likely to have high TTR (Table).

Figure 1



Distribution of INR measurements with median TTR and median time above/below therapeutic range displayed.

Figure 2



Mean number of days until subsequent INR check based on INR values.

Poor warfarin response

A multivariable model was designed to identify factors associated with individual patients being in the lowest quartile of TTR (Figure 3). Advanced heart failure, frailty, and prior valve surgery were some of the factors with the highest odds ratios for association with low TTR. Warfarin management by an anticoagulation clinic and diagnosis of AF <1 year from ORBIT-AF enrollment were both associated with lower odds of having low TTR.

Patient-level TTR also varied as a function of CHA_2DS_2-VASc scores (Figure 4, *A*). There were 268 patients with CHA_2DS_2-VASc scores of 0 or 1, who were on long-term warfarin, and these patients had a TTR of 70% (IQR 58%-82%). Most patients in the analysis (n = 2,860) had a CHA_2DS_2-VASc score of 2 to 4, and these patients had a median TTR of 69% (IQR 55%-80%). Patients with a high CHA_2DS_2-VASc score of ≥5 had a statistically significant lower median TTR of 65% (IQR 51%-77%), relative to patients with a CHA_2DS_2-VASc score of 0 or 1 ($P < .001$).

Variations by ATRIA score yielded similar findings (Figure 4, *B*). Patients with a high ATRIA score of ≥5 (n = 893) had a statistically significant lower median TTR of 65% (IQR 50%-77%), compared with patients with an ATRIA score of 0 to 3 (median TTR 68% [IQR 54%-80%], $P < .001$).

The multivariable model demonstrated that decreasing creatinine clearance <60 mg/dL was associated with a patient having a TTR in the lowest quartile (odds ratio 1.08 per 5 mg/dL decrease [95% CI 1.05-1.11, $P < .001$]). Patients with stage 3, 4, and 5 chronic kidney disease (CKD) had significantly lower TTR relative to patients with stage 1 or 2 CKD (Figure 4, *C*). Patients with stage 4 CKD had statistically lower TTR than patients with stage 3 CKD (63% vs 66%, $P = .011$), and the same relationship was true for stage 5 versus stage 3 CKD (47% vs 66%, $P < .001$).

Site level variation

There was significant variation in median TTR by site (online Appendix) with an overall median site TTR of 67% (IQR 61%-71%). There were nearly 3% of sites with a median TTR of 50% to 55%, compared with 2% of sites with median TTR ≥80%. Warfarin patients followed at anticoagulation clinics had higher median TTR (69%, IQR 55%-80%) than those patients not followed at anticoagulation clinics (66%, IQR 51%-78%) ($P < .0001$). There was minimal geographic variation of TTR with median TTR values of 68% (IQR 55%-79%) for the Midwest, 68% (IQR 53%-80%) for the Northeast, 67% (IQR 52%-78%) for the South, and 67% (IQR 53%-79%) for the West ($P = .12$).

Sensitivity analysis of TTR

A sensitivity analysis was performed for the exclusion of interpolated INR values between 2 measured INRs that were at least 60 days apart, which represented 4.8% of the intervals between 2 INR measurements. This was done by including all interpolated INR values between the first and last measured INR for all patients with at least 5 measured INR values. This methodology yielded an identical median TTR of 68%. The IQR of 52% to 80% was nearly the same as the IQR from the main analysis (53%-79%).

Discussion

Overall, we found that only 59% of all INR values drawn on patients with AF on warfarin were in a therapeutic range (INR 2-3), resulting in a median patient-level TTR of 68%. Time in therapeutic range varied across the patient population, and of concern, we found that patients with the highest risk of bleeding and stroke had paradoxically

Table. Patient characteristics

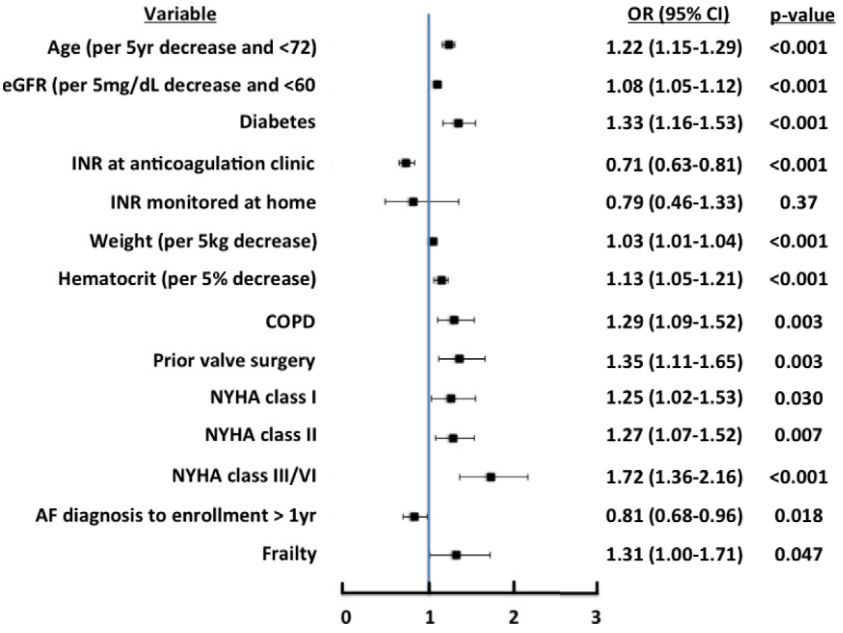
Variable	Overall, N = 5,210	Quartile 1 (TTR 0%-53%), N = 1,131	Quartile 2 (TTR 54%-67%), N = 1,267	Quartile 3 (TTR 68%-79%), N = 1,353	Quartile 4 (TTR 80%-100%), N = 1,259	*P*
Demographics						
Age, mean (SD)	75 (10)	74 (11)	75 (10)	75 (9)	75 (9)	.51
Female sex	2,218 (43%)	595 (45%)	579 (46%)	570 (42%)	474 (38%)	<.001
White race	4,714 (90%)	1,166 (88%)	1,146 (90%)	1,234 (91%)	1,168 (93%)	.003
College education	1,552 (30%)	336 (25%)	376 (30%)	423 (31%)	417 (33%)	<.001
Insurance status						<.001
Medicare	3,666 (70%)	902 (68%)	904 (71%)	975 (72%)	885 (70%)	
Medicaid	216 (4%)	87 (7%)	57 (5%)	40 (3%)	32 (3%)	
Private	1,096 (21%)	289 (22%)	248 (20%)	278 (21%)	281 (22%)	
Past medical history						
Anemia	975 (19%)	296 (22%)	255 (20%)	217 (16%)	207 (16%)	<.001
Frailty	276 (5%)	99 (7%)	82 (6%)	55 (4%)	40 (3%)	<.001
Chronic obstructive pulmonary disease	868 (17%)	279 (21%)	234 (18%)	198 (15%)	157 (12%)	<.001
Hypertension	4,475 (86%)	1,162 (87%)	1,084 (86%)	1,162 (86%)	1,067 (85%)	.30
Diabetes	1,587 (30%)	486 (37%)	409 (32%)	355 (26%)	337 (27%)	<.001
Chronic kidney disease	1,898 (36%)	548 (41%)	469 (37%)	488 (36%)	393 (31%)	<.001
Prior gastrointestinal bleed	424 (8%)	133 (10%)	97 (8%)	106 (8%)	88 (7%)	.031
Obstructive sleep apnea	980 (19%)	274 (21%)	260 (21%)	248 (18%)	198 (16%)	.004
Peripheral vascular disease	737 (14%)	219 (16%)	189 (15%)	190 (14%)	139 (11%)	<.001
Prior cerebrovascular event	915 (18%)	251 (19%)	232 (18%)	229 (17%)	203 (16%)	.24
Heart failure	1,866 (36%)	582 (44%)	466 (37%)	462 (34%)	356 (28%)	<.001
Risk stratification						
$CHADS_2$ score, mean (SD)	2.4 (1.2)	2.6 (1.3)	2.5 (1.3)	2.4 (1.2)	2.3 (1.2)	<.001
CHA_2DS_2-VASc score, mean (SD)	4.1 (1.6)	4.3 (1.7)	4.2 (1.7)	4.1 (1.6)	3.9 (1.6)	<.001
ATRIA bleeding score, mean (SD)	2.8 (1.9)	3.0 (2.0)	2.9 (1.9)	2.8 (1.9)	2.7 (1.8)	<.001
Site characteristics						
Anticoagulation clinic	2,545 (49%)	577 (43%)	624 (49%)	685 (51%)	659 (52%)	<.001

the lowest TTRs. Finally, sites performing their warfarin management through anticoagulation clinics had only slightly higher TTR than those managed in regular clinics.

The TTR value has been shown to be associated with clinical outcomes. This was first demonstrated in observational data from the Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and V trials, in which patients were divided into TTR tertiles of <60%, 60%-75%, and >75%, and the analysis found that patients in the lowest tertile had higher rates of mortality, major bleeding, and stroke relative to the highest tertile.[15] The Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W) trial evaluated the association of center TTR and outcomes.[8] The median center TTR in ACTIVE W was 65%, and warfarin administration reduced vascular events compared with the combination of aspirin and clopidogrel when center TTR was >65%. Population modeling based on the data from ACTIVE W determined that a TTR <58% would not generate a net clinical benefit. These findings are consistent with a secondary analysis from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY trial) that showed that dabigatran had the greatest advantage over warfarin in prevention of stroke and systemic embolism among patients at centers with the lowest TTR.[16] However, the effects of rivaroxaban and apixaban were similar across a range of center TTRs.[17,18]

Historical US data identified lower therapeutic rates of warfarin in clinical practice than in clinical trials with only 50% of INR values being therapeutic in clinical practice in the early 1990s.[19] A more contemporary study of 392 patients with AF in the United States identified a mean TTR of 57% with warfarin management by a mix of primary care and specialists.[9] This finding was consistent with a mean TTR of 58% among 100 Veterans Affairs clinics[11] as well as a large, recently published analysis of data from Quest Diagnostics that identified a mean TTR of 54% among nearly 140,000 patients in the United States.[10] The median TTR value in our study was the same as was seen in the clinical trial that compared edoxaban with warfarin in AF patients (median TTR 68%), and the edoxaban trial had the highest TTR of the NOAC trials.[20] The higher TTR in our analysis relative to what was reported by Dlott et al[10] could be caused by several factors. The INR target for patients is not known in our analysis or the Quest study, and lower INR targets in the Quest analysis could have resulted in subtherapeutic values 31% of the time versus 17% in our analysis. Our registry patients may have been more ambulatory, less sick, more adherent to medications, and better able to follow-up with frequent INR monitoring, which could

Figure 3



eGFR = estimated glomerular filtration rate by MDRD. COPD = chronic obstructive pulmonary disease

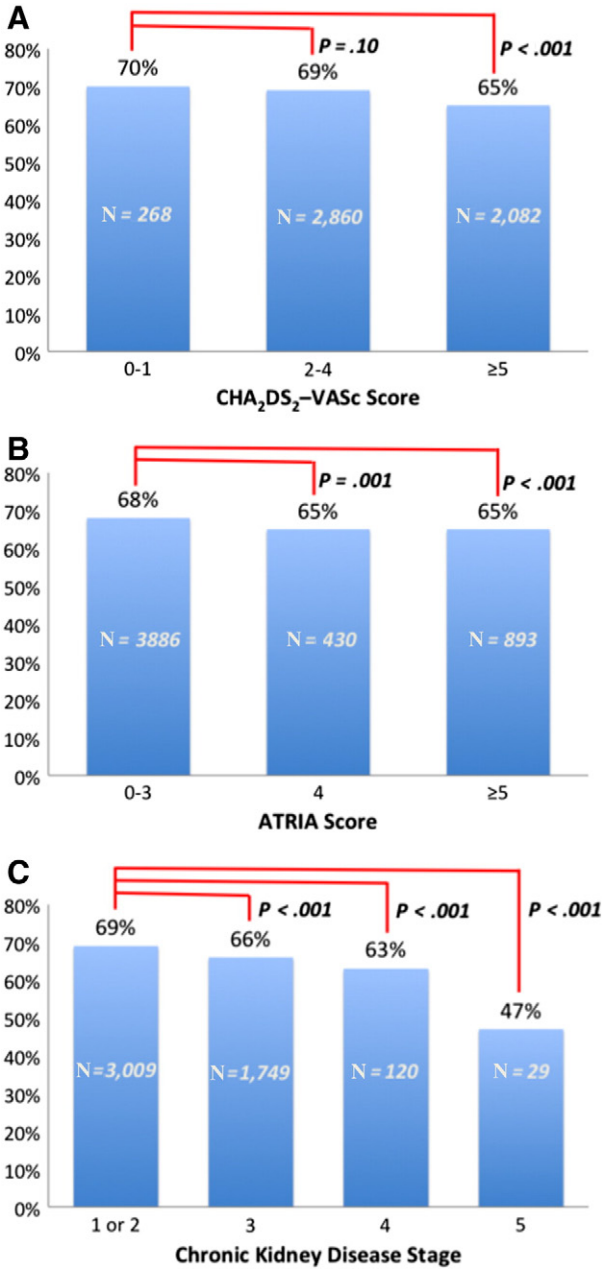
Factors associated with TTR in the lowest quartile (≤53%).

explain the higher TTR in the ORBIT-AF population. In addition, Dlott et al noted that most providers in their data were low-volume providers, and higher volume providers, which may represent anticoagulation clinics, had higher mean TTR values. One key difference between our data and the Quest data is that the types of clinics are more clearly defined in ORBIT-AF, and nearly half of the patients in ORBIT-AF were followed by anticoagulation clinics, which could also explain the difference in TTR values between the 2 studies.

Patients with lower TTR derive less benefit from warfarin, so it would be valuable to be able to identify patients at risk for low TTR at the time of OAC initiation. Unlike ORBIT-AF, the study by Dlott et al did not have access to detailed clinical data but did find that younger age, female sex, and lower income were independently associated with low TTR.[10] Similarly, we identified younger age as a risk factor for low TTR. Our findings also identified multiple comorbidities such as frailty, heart failure, CKD or lower estimated glomerular filtration rate, chronic obstructive pulmonary disease, and diabetes as risk factors for low TTR. Diabetes and heart failure have previously been shown to be associated with subtherapeutic INR values in the Anticoagulation Consortium to Improve Outcomes Nationally (ACTION) study.[21] The SAME-TT_2R_2 score has been developed and validated as a tool to predict TTR.[22,23] A higher score is associated with a lower TTR. Female sex, race, and smoking status are components of the SAME-TT_2R_2 score , and these factors were not associated with being in the lowest quartile of TTR in our model. Both the SAME-TT_2R_2 score and our model identified multiple comorbidities as being associated with lower TTR, and both stroke risk by CHA_2DS_2-VASc and bleeding risk by ATRIA are driven by comorbid conditions. It may be the comorbid disease states themselves that result in the finding seen in this manuscript that patients at higher risk for stroke or bleeding have lower TTR. This observation was not described in previous TTR analyses, and it emphasizes the importance of close follow-up for warfarin patients at increased risk for stroke or bleeding. Decision support tools for warfarin dosing may represent a future opportunity to further increase TTR,[24] whereas a pharmacogenetic warfarin algorithm has been studied in a US randomized trial with no short-term improvement in TTR over a clinical algorithm.[25]

Our analysis did show that INR management by an anticoagulation clinic was protective against low TTR with an odds ratio of 0.71 (95% CI 0.63-0.81), whereas TTR in anticoagulation clinics was slightly higher than that of non-anticoagulation clinics (69% vs 66%). Anticoagulation clinics may be serving a self-selected group of patients. The increased use and homogeneity of anticoagulation clinics in Europe[26] may, at least in part,

Figure 4



A, TTR by CHA_2DS_2-VASc score. **B**, TTR by ATRIA score. **C**, TTR by stage of chronic kidney disease.

explain the higher TTR values of 68% in Germany,[27] 76% in Sweden,[28] and 83% in Denmark.[24] Patients with multiple factors associated with low TTR may not be ideal candidates for warfarin therapy, and these patients should be considered for a NOAC.

Limitations

This analysis has several important limitations. There were 1,201 patients excluded because INR data were not available, and it is possible that this group of patients would have affected the results had their data been available. The target INR range for patients was not known. Although the standard goal is 2.0 to 3.0, it is possible that some physicians may have set a lower goal of 1.5 to 2.5 in patients with higher risk of bleeding. The study describes variations in INR and TTR, but there are no associated outcomes that may allow for determinations of the clinical impact of TTR variation. Periods of >60 days between 2 INR measurements were excluded from the TTR calculation, but the reasons for gaps between INR measurements are not known. Despite this, a sensitivity analysis demonstrated that the inclusion of these gaps in the TTR calculation did not meaningfully change the results. Residual measured and unmeasured confounding may have influenced these findings. We were unable to account for medication nonadherence as a risk factor for low TTR. If patients have a low TTR because of nonadherence with warfarin, they may be at greater risk of adverse events with shorter-acting NOACs. Finally, ORBIT-AF investigators may not be representative of all US providers, which may limit the generalizability of these findings.

In US clinical practices, warfarin patients are in the therapeutic range about two thirds of the time. Patients at highest risk for stroke and bleeding were least likely to be in the therapeutic range. Finally, there was variation in TTR between sites, with anticoagulation clinics having the highest overall TTR.

Acknowledgements

None.

Disclosures

D.N.H., L.T., R.G.B., and A.S.G. report no disclosures. S.D.P. reports modest educational grant support from Astra Zeneca and modest advisory board to Janssen Pharmaceuticals. G.C.F. reports modest consultant/advisory board support from Janssen Pharmaceuticals. P.R.K. reports modest consultant/advisory board support from Boehringer Ingelheim, Bristol-Myers Squibb, Johnson & Johnson, Portola, Merck, Sanofi, and Daiichi Sankyo. P.C. reports significant employment with Johnson & Johnson. D.E.S. reports significant consulting fees from Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Johnson & Johnson, Pfizer, and CSL Behring; significant research grant from Johnson & Johnson. J.A. reports modest consultant/advisory board: Boehringer Ingelheim, Alere, Bristol-Myers Squibb, Pfizer, Janssen, and Daiichi. B.G. reports modest Data and Safety Monitoring Board/advisory board support from Medtronic, Baxter Healthcare Corporation, InspireMD, Cardiovascular Research

Foundation, PPD Development, LP, Boston Scientific, and St. Jude. K.W.M. financial disclosures before August 1, 2013, can be viewed at https://www.dcri.org/about-us/conflict-of-interest/Mahaffey-COI_2011-2013.pdf; disclosures after August 1, 2013, can be viewed at http://med.stanford.edu/profiles/kenneth_mahaffey. E.M.H. reports modest honoraria from Boehringer Ingelheim and Bayer and modest consultant/advisory board from Daiichi Sankyo, Ortho-McNeil-Janssen, Johnson & Johnson, Boehringer Ingelheim, Bristol-Myers Squibb, Roche, and Pfizer. J.P.P. reports significant research grant support from Johnson & Johnson/Janssen Pharmaceuticals; significant other research support from Bayer HealthCare Pharmaceuticals Inc (formerly Berlex Labs), Boston Scientific Corporation, Johnson & Johnson Pharmaceutical Research & Development; modest Consultant/Advisory Board support from Forest Laboratories, Inc and Medtronic, Inc; and significant Consultant/Advisory Board support from Johnson & Johnson/Janssen Pharmaceuticals. E.D.P. reports significant research grant support from Eli Lilly & Company, Janssen Pharmaceuticals, Inc, and the American Heart Association; modest consultant/advisory board support from Boehringer Ingelheim, Bristol-Myers Squibb, Janssen Pharmaceuticals, Inc, Pfizer, and Genentech Inc.

References

1. Patel NJ, Deshmukh A, Pant S, et al. Contemporary trends of hospitalization for atrial fibrillation in the United States, 2000 through 2010: implications for healthcare planning. Circulation 2014;129:2371-9.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly: the Framingham Study. Arch Intern Med 1987;147:1561.
3. Wolf PA, Dawber TR, Thomas Jr HE, et al. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke. Neurology 1978;28:973-977.
4. Flegel K, Shipley M, Rose G. Risk of stroke in non-rheumatic atrial fibrillation. Lancet 1987;329:526-9.
5. Wilke T, Groth A, Mueller S, et al. Oral anticoagulation use by patients with atrial fibrillation in Germany. Adherence to guidelines, causes of anticoagulation under-use and its clinical outcomes, based on claims-data of 183,448 patients. Thromb Haemost 2012;107:1053-65.
6. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. Ann Intern Med 1994;120:897-902.
7. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003;349:1019-26.
8. Connolly SJ, Pogue J, Eikelboom J, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation 2008;118:2029-37.
9. Han SY, Palmeri ST, Broderick SH, et al. Quality of anticoagulation with warfarin in patients with nonvalvular atrial fibrillation in the community setting. J Electrocardiol 2013;46:45-50.
10. Dlott JS, George RA, Huang X, et al. National assessment of warfarin anticoagulation therapy for stroke prevention in atrial fibrillation. Circulation 2014;129:1407-14.
11. Rose AJ, Hylek EM, Ozonoff A, et al. Risk-adjusted percent time in therapeutic range as a quality indicator for outpatient oral anticoagulation: results of the Veterans Affairs Study to Improve Anticoagulation (VARIA). Circ Cardiovasc Qual Outcomes 2011;4:22-9.
12. Piccini JP, Fraulo ES, Ansell JE, et al. Outcomes registry for better informed treatment of atrial fibrillation: rationale and design of ORBIT-AF. Am Heart J 2011;162:606-12.
13. Rosendaal FR, Cannegieter SC, van der Meer FJ, et al. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69:236-9.
14. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986;42:121-30.
15. White HD, Gruber M, Feyzi J, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. Arch Intern Med 2007;167:239-45.
16. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet 2010;376:975-83.
17. Wallentin L, Lopes RD, Hanna M, et al. Apixaban for Reduction in S and Other Thromboembolic Events in Atrial Fibrillation I. Efficacy and safety of apixaban compared with warfarin at different levels of predicted international normalized ratio control for stroke prevention in atrial fibrillation. Circulation 2013;127:2166-76.
18. Piccini JP, Hellkamp AS, Lokhnygina Y, et al. Relationship between time in therapeutic range and comparative treatment effect of rivaroxaban and warfarin: results from the ROCKET AF trial. J Am Heart Assoc 2014;3:e000521.
19. Gottlieb LK, Salem-Schatz S. Anticoagulation in atrial fibrillation. Does efficacy in clinical trials translate into effectiveness in practice? Arch Intern Med 1994;154:1945-53.
20. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-104.
21. Rose AJ, Ozonoff A, Grant RW, et al. Epidemiology of subtherapeutic anticoagulation in the United States. Circ Cardiovasc Qual Outcomes 2009;2:591-7.
22. Gallego P, Roldan V, Marin F, et al. SAMe-TT2R2 score, time in therapeutic range, and outcomes in anticoagulated patients with atrial fibrillation. Am J Med 2014;127:1083-8.
23. Poli D, Antonucci E, Testa S, et al. A prospective validation of the SAME-TT2R 2 score: how to identify atrial fibrillation patients who will have good anticoagulation control on warfarin. Intern Emerg Med 2014;9:443-7.
24. Nielsen PB, Lundbye-Christensen S, Rasmussen LH, et al. Improvement of anticoagulant treatment using a dynamic decision support algorithm: a Danish Cohort study. Thromb Res 2014;133:375-9.
25. Kimmel SE, French B, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. N Engl J Med 2013;369:2283-93.
26. Ansell J, Hollowell J, Pengo V, et al. Descriptive analysis of the process and quality of oral anticoagulation management in real-life practice in patients with chronic non-valvular atrial fibrillation: the

international study of anticoagulation management (ISAM). J Thromb Thrombolysis 2007;23:83-91.
27. Mueller S, Pfannkuche M, Breithardt G, et al. The quality of oral anticoagulation in general practice in patients with atrial fibrillation. Eur J Intern Med 2014;25:247-54.
28. Wieloch M, Sjalander A, Frykman V, et al. Anticoagulation control in Sweden: reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA. Eur Heart J 2011;32: 2282-2289.

Appendix. Site variation in TTR