Effect of Temporary Interruption of Warfarin Due to an Intervention on Downstream Time in Therapeutic Range in Patients With Atrial Fibrillation (from ORBIT AF)

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The aim of this study was to quantify time in therapeutic range (TTR) before and after a temporary interruption of warfarin due to an intervention in the Outcomes Registry for Better Informed Treatment of atrial fibrillation (AF). AF patients on warfarin who had a temporary interruption followed by resumption were identified. A nonparametric method for estimating survival functions for interval censored data was used to examine the first therapeutic International Normalized Ratio (INR) after interruption. TTR was compared using Wilcoxon signed rank test. Cox proportional hazards model was used to investigate the association between TTR in the first 3 months after interruption and subsequent outcomes at 3 to 9 months. Of 9,749 AF patients, 71% were on warfarin. Over a median (IQR) follow-up of 2.6 (1.8 to 3.1) y, 33% of patients had a total of 3,022 temporary interruptions. The first therapeutic INR was recorded within 1 week in 35.0% (95% confidence interval 32.6% to 37.4%), 2 weeks in 54.6% (52.2% to 57.0%), 30 days in 70.0% (67.9% to 72.1%) and 90 days in 91.3% (90.0% to 92.5%) of patients. Compared with pre-interruption, TTR 3 months after interruption was significantly lower (61.1% [36.6% to 85.0%] vs 67.6% [50.0% to 81.3%], p <0.0001). A 10 unit increment in the TTR in the first 3 months after interruption was associated with a lower risk of major bleeding [Hazard ratio 0.91 (0.85 to 0.97), p = 0.005]. This association was noted in patients who received bridging anticoagulation, but not in those who did not. In conclusion, temporary interruption of warfarin is common, and nearly half of these patients had subtherapeutic INR after 2 weeks. Lower TTR in the first 3 months after interruption was associated with higher incidence of major bleeding in patients who received bridging anticoagulation. **(Am J Cardiol 2020;132:66−71)**

Warfarin anticoagulation remains a common therapeutic option for patients with atrial fibrillation (AF), despite the emergence of direct oral anticoagulation (OAC) agents in recent years. Temporary interruption of OAC is often required prior to procedures in patients with AF.[1] However, resumption of warfarin OAC after medication interruption for a procedure may predispose patients to an extended period of risk as they may remain subtherapeutic in serum levels based on measurement of International Normalized Ratio (INR). The objective of this study was to describe the frequency of interruption of warfarin OAC and to quantify the time required to reach therapeutic range (TTR) in a

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Manuscript received April 2, 2020; revised manuscript received and accepted July 3, 2020.

Funding: This work was supported by the ORBIT AF Registry which is sponsored by Janssen Scientific Affairs, LLC, Titusville, NJ.

See page 70 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2020.07.006

large national cohort of AF patients. In addition, the rate of adverse outcomes after warfarin interruption for a procedure was compared with the period pre-intervention.

Methods

The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) is a registry of a nationally representative sample of outpatients with electrocardiographically confirmed AF enrolled at 176 sites in the USA from June 2010 to August 2011. The study design and cohort are described in detail elsewhere.[2] Temporary interruption of OAC was defined as reported interruption related to an invasive procedure prior to a follow-up visit with subsequent resumption of the same OAC at the time of that visit. Interruptions for reasons other than a procedural intervention were not included. All study subjects provided written informed consent. The study was designed and conducted by the Duke Clinical Research Institute. The study was approved by the Duke Institutional Review Board and local institutional review boards at participating sites.

The outcomes of interest were (1) all-cause mortality, (2) stroke/transient ischemic attack (TIA)/noncentral nervous system systemic embolism, (3) major bleeding, and (4) composite of cardiovascular death, myocardial infarction, major bleeding or stroke/TIA/non- central nervous system systemic embolism. Major bleeding was defined per the International Society on Thrombosis and Haemostasis criteria.[3] Cardiovascular death included heart failure, sudden cardiac death, stroke related, MI related, or other type of cardiovascular death.

Categorical variables are presented as frequencies and percentages and differences between the groups were assessed by the Chi-Square test. Continuous variables are presented as median (Q1 to Q3) and differences between the groups were assessed by the Wilcoxon Rank Sum Test. A nonparametric method for estimating survival functions for interval censored data was used to examine first therapeutic INR after temporary interruption. Therapeutic INR was defined as INR 2.0 to 3.0. The Rosendaal method of linear interpolation was used between each pair of measured INR values. Gaps between INRs >8 weeks were excluded. TTR was calculated as the percentage of days with INR between 2 and 3, subtherapeutic as the percentage of days with INR <2 and supra-therapeutic as the percentage of days with INR >3. The median (Q1, Q3) of the percentage TTR, subtherapeutic and supra-therapeutic across all patients were generated. These estimands were also generated before and after temporary interruption and comparisons in the 2 time periods tested using the Wilcoxon signed rank test. TTR prior to interruption was calculated from enrollment till the time of interruption. Events rates per 100 patient years are presented. The first interruption was considered the interruption of interest for those who had multiple interruptions. The procedure date for the interruption is time 0. Events occurring on the same day of the interruption were included. A landmark analysis of the association between outcome events occurring between 3 and 9 months post temporary interruption and the TTR in the first 3 months after interruption was performed. Both the unadjusted and adjusted hazard ratio with corresponding 95% confidence intervals are presented. Multivariable Cox proportional hazard models were used to adjust for age, history of hypertension, diabetes, heart failure, stroke/TIA, vascular disease, and female sex. History of heart failure, history of stroke/TIA, and history of vascular disease was assessed from baseline to 3 months post interruption. For the major bleeding and composite endpoints, history of major bleeding from baseline to 3 months post interruption was added for adjustment. Robust standard errors were used to account for within site clustering. All continuous variables that were nonlinear with respect to the outcome were fit with linear splines. There was no missing data on the adjustment variables. All statistical analyses were performed using SAS Version 9.4 software (SAS Institute). All hypothesis tests were 2-sided, with $p < 0.05$ considered statistically significant.

Results

The registry enrolled 10,137 patients of whom 9,749 patients with at least 1 follow-up visit were included. Of these, 6,567 patients were on warfarin. Only patients on warfarin at enrollment were included in this analysis. Permanent discontinuation of warfarin occurred in 223 patients. The final population for this analysis consisted of 2,166 patients on warfarin who had at least 1 temporary interruption of warfarin. Baseline characteristics of those who had a temporary interruption of warfarin are compared with those without temporary interruption in Table 1.

Overall, the 2,166 patients on warfarin had a total of 3,022 temporary interruptions with >1 interruption in 636 (29.4%) patients. Median (range) number of temporary interruptions per patient was 1 (1 to 2). Patients who did not have a date for the interruption (n = 17) or INR data after interruption (n = 63) were excluded from the TTR analysis. Warfarin was interrupted for cardiac catheterization (n = 289, 9.6%), cardiac surgery (n = 113, 3.7%), cardiac device implantation (n = 256, 8.5%), catheter ablation (n = 122, 4.0%), noncardiac surgery (n = 838, 27.7%), endoscopic procedure (n = 569, 18.8%), a dental procedure (n = 256, 8.5%), and otherwise unspecified (n = 772, 25.5%). Bridging anticoagulation was used in 756 (25.0%) patients on warfarin. The use of bridging anticoagulation and its association with outcomes in ORBIT-AF have been previously described by Steinberg et al.[1]

The frequency of INR measurement was greater in the short-term after warfarin interruption compared with before. Mean (SD) number of days between INR testing before the interruption was 27.3 (21.5) days. This was reduced to 19.2 (10.8) days the first 3 months after procedural interruption, 22.9 (14.1) days the first 6 months and 26.3 (22.8) days the first 12 months after the temporary interruption. At 14 days after interruption, 54.6% (95% CI, 52.2% to 57.0%) of patients had an INR within TTR. This percentage increased to 70.0% (67.9% to 72.1%) at 30 days, 86.5% (85.0% to 88.0%) at 60 days and 91.3% (90.0% to 92.5%) at 90 days. The TTR in the first 3, 6, and 12 months after warfarin interruption was lower than that prior to the interruption, driven primarily by an increase in subtherapeutic INR values (Table 2). Next, the TTR within 3 and 6 months after interruption was compared with the TTR 3 and 6 months immediately prior to interruption with

Table 1
Baseline characteristics of anticoagulated AF patients stratified by occurrence of temporary interruption of Warfarin

Variable	Overall N = 6567	No TI N = 4401	TI N = 2166	p Value
Age (year)*	76.0 (68.0, 82.0)	76.0 (68.0, 82.0)	75.0 (68.0, 81.0)	0.0013
Men	3,781 (57.6%)	2,502 (56.9%)	1,279 (59.0%)	0.0902
White	5,872 (89.4%)	3,888 (88.3%)	1,984 (91.6%)	0.0008
Black	312 (4.8%)	226 (5.1%)	86 (4.0%)	
Hispanic	286 (4.4%)	213 (4.8%)	73 (3.4%)	
Other	90 (1.4%)	69 (1.6%)	21 (1.0%)	
Missing	7 (0.1%)	5 (0.1%)	2 (0.1%)	
Hypertension	5,572 (84.8%)	3,693 (83.9%)	1,879 (86.7%)	0.0026
Hyperlipidemia	4,850 (73.9%)	3,161 (71.8%)	1,689 (78.0%)	<0.0001
Diabetes mellitus	1,991 (30.3%)	1,281 (29.1%)	710 (32.8%)	0.0023
Smoker	3,190 (48.6%)	2,023 (46.0%)	1,167 (53.9%)	<0.0001
Prior coronary artery disease	2,418 (36.8%)	1,541 (35.0%)	877 (40.5%)	<0.0001
Heart failure	2,267 (34.5%)	1,442 (32.8%)	825 (38.1%)	<0.0001
Peripheral vascular disease	902 (13.7%)	550 (12.5%)	352 (16.3%)	<0.0001
Stroke/TIA	1,090 (16.6%)	732 (16.6%)	358 (16.5%)	0.9149
Hemorrhagic stroke	40 (0.6%)	27 (0.6%)	13 (0.6%)	0.9497
Chronic kidney disease	2,302 (35.1%)	1,503 (34.2%)	799 (36.9%)	0.4768
CHA_2DS_2VASc score*	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	0.0010
Atria score*	3.0 (1.0, 4.0)	3.0 (1.0, 4.0)	3.0 (1.0, 4.0)	0.0071
CHA2DS2VASc score				
Low: 0	79 (1.2%)	61 (1.4%)	18 (0.8%)	<0.0001
Medium: 1	342 (5.2%)	266 (6.0%)	76 (3.5%)	
High: 2+	6,146 (93.6%)	4,074 (92.6%)	2,072 (95.7%)	
Atria score				
Low: 0-3	4,362 (66.4%)	2,986 (67.8%)	1,376 (63.5%)	0.0015
Medium: 4	728 (11.1%)	454 (10.3%)	274 (12.7%)	
High: 5+	1,477 (22.5%)	961 (21.8%)	516 (23.8%)	
Aspirin	2,352 (35.8%)	1,536 (34.9%)	816 (37.7%)	0.0276
Any antiplatelet therapy	2,523 (38.4%)	1,640 (37.3%)	883 (40.8%)	0.0061

* Median (interquartile range)

Table 2
Comparison of time in therapeutic range (median and interquartile range) before and after temporary interruption (TI) of warfarin

Variable	Prior to TI	After TI	
3 months			
Percentage time in therapeutic range	67.6 (50.0-81.3)	61.1 (36.6-85.0)	<0.0001
Percentage time sub-therapeutic INR	15.9 (4.3-31.5)	17.3 (0.0-44.3)	<0.0001
Percentage time supra-therapeutic INR	8.8 (0.0-20.2)	0.0 (0.0-19.5)	0.0007
6 months			
Percentage time in therapeutic range	67.6 (49.7-81.3)	63.4 (44.1-82.1)	0.0016
Percentage time sub-therapeutic INR	15.9 (4.1-31.6)	18.2 (3.6-38.3)	<0.0001
Percentage time supra-therapeutic INR	8.6 (0.0-20.3)	5.7 (0.0-21.4)	0.0212
12 months			
Percentage time in therapeutic range	67.5 (49.5-81.3)	65.3 (48.7-80.5)	0.0401
Percentage time sub-therapeutic INR	15.7 (3.9-31.8)	17.7 (5.9-33.8)	0.0019
Percentage time supra-therapeutic INR	8.5 (0.0-20.3)	8.4 (0.0-20.5)	0.5723

similar findings (supplemental Table). The analysis was then repeated excluding the INR values between the date of interruption and the subsequent first therapeutic INR. In this analysis, TTR was slightly higher after the temporary interruption compared with before interruption at 6 months (71.4% [51.2% to 91.4%] vs 68.2% [50.8% to 81.5%], p <0.0001) and 12 months (69.8% [54.1% to 84.7%] vs 67.8% [50.0% to 81.4%], p <0.0001).

The outcomes within 30 days, 3 months, and 6 months of temporary interruption of warfarin are presented in Table 3. The association between TTR in the first 3 months after interruption of warfarin and subsequent outcomes are presented in Table 4. In multivariable analysis, increasing

Table 3
Outcome after temporary interruption of warfarin

Outcome post temporary interruption (Events/ 100 patient years)	30 days	3 months	6 months
Death	1 (0.57)	7 (2.03)	39 (3.89)
Major bleed	75 (44.36)	82 (24.63)	120 (12.50)
Stroke/non-CNS embolism or TIA	14 (8.05)	16 (4.67)	26 (2.61)
Composite of CV death, major bleeding, stroke/TIA or MI	97 (57.85)	108 (32.76)	167 (17.61)

Table 4
Association between time in therapeutic range (TTR) within 3 months after interruption and subsequent outcomes 3 to 9 months after interruption

Outcome	Unadjusted HR* (95% CI)	P-value	Adjusted HR*,† (95% CI)	p value
Death	0.95 (0.88-1.02)	0.1730	0.95 (0.87-1.03)	0.2101
Major bleeding	0.90 (0.84-0.96)	0.0011	0.91 (0.85-0.97)	0.0051
Stroke or non-CNS embolism/TIA	0.98 (0.85-1.13)	0.7777	0.99 (0.85-1.15)	0.8817
Composite end point‡	0.92 (0.87-0.99)	0.0172	0.93 (0.87-1.00)	0.0504

* Per 10 unit increment in TTR.
† Cox proportional hazards model adjusted for age, history of hypertension, history of diabetes, history of heart failure, history of stroke/TIA, history of vascular disease and female sex. For the major bleeding and composite endpoints, history of major bleeding was included for adjustment.
‡ Composite endpoint includes: Cardiovascular death, major bleeding, stroke/TIA or MI.

Table 5
Association between time in therapeutic range (TTR) within 3 months after interruption and subsequent outcomes 3 to 9 months after interruption stratified by whether bridging anticoagulation was used.

Outcome	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	p value
Patients with bridging anticoagulation				
Death	0.94 (0.81-1.09)	0.4232	0.95 (0.81-1.12)	0.5509
Major bleeding	0.83 (0.74-0.93)	0.0010	0.84 (0.73-0.97)	0.0147
Stroke or non-CNS embolism/TIA	0.94 (0.68-1.31)	0.7233	1.04 (0.73-1.47)	0.8356
Composite	0.90 (0.80-1.00)	0.0509	0.92 (0.81-1.03)	0.1518
Patients without bridging anticoagulation				
Death	0.97 (0.88-1.08)	0.6073	0.97 (0.88-1.08)	0.6012
Major bleeding	0.93 (0.85-1.02)	0.1090	0.94 (0.86-1.02)	0.1450
Stroke or non-CNS embolism/TIA	0.96 (0.84-1.09)	0.5395	0.97 (0.84-1.12)	0.6409
Composite	0.94 (0.87-1.01)	0.0891	0.95 (0.88-1.02)	0.1379

TTR was associated with a lower risk of major bleeding and the composite end point of cardiovascular death, stroke/TIA, MI, and major bleeding. There was no association between TTR and the occurrence of death and stroke/TIA. The multivariable analysis was then repeated with the cohort stratified by bridging anticoagulation (Table 5). Increasing TTR was associated with lower risk of major bleeding in the group that received bridging anticoagulation, but not in those who were not bridged.

Discussion

In a large representative sample of AF patients, temporary interruption of warfarin for procedures occurred in approximately 30% of the cohort. These findings are comparable to that of 2 large randomized controlled trials of OAC in AF that reported temporary interruption for procedures in one-third of participants.[4,5] Nearly half of these patients had subtherapeutic INR 2 weeks after the first day of interruption. The time in TTR was significantly lower for the 3 month period after the interruption compared with prior to the interruption, driven predominantly by subtherapeutic INRs. Low TTR in the first 3 months after temporary interruption was associated with higher incidence of major bleeding and the composite cardiovascular endpoint at 3 to 9 months after interruption. Further subgroup analysis showed that the association between low TTR and major bleeding was noted only in those who received bridging anticoagulation.

The efficacy and safety of warfarin anticoagulation depends on the ability to maintain the INR in a narrow therapeutic window of 2 to 3.[6] Lower TTR has been shown to correlate with a higher risk of thromboembolism.[7–9] Due to its slow onset of anticoagulant activity, there is often a delay of several days before therapeutic anticoagulation is achieved after reinitiating warfarin. In the ORBIT-AF cohort, nearly half of patients continued to have a sub-therapeutic INR level at 2 weeks after the first day of warfarin interruption. This was reduced to 30% at 30 days and the majority had a therapeutic INR at 3 months after the interruption. Corresponding to the prolonged time taken to achieve therapeutic INR, patients with an interruption had lower TTR at 3 and 6 months after the interruption compared with prior to the interruption. However, TTR returned to pre-interruption levels once the first therapeutic INR was achieved, indicating that the impact of the interruption on the TTR was temporary. These findings emphasize the importance of close monitoring of INR in the first few weeks after warfarin is restarted to minimize the time when patients remain inadequately anticoagulated after a procedure.

Patients with lower TTR in the first 3 months after procedural interruption of warfarin had a higher risk of the composite end point and major bleeding. Bridging anticoagulation was used in one-fourth of the cohort, and lower TTR was associated with risk of major bleeding in these patients, but not in those who were not bridged. Multiple recent studies, including data from ORBIT-AF, have shown a correlation between bridging anticoagulation and increased risk of major bleeding.[1,10] This practice is no longer routinely recommended for the majority of AF patients.[11] However, if bridging is necessary, close attention to achieving therapeutic INR in a timely fashion may

lead to a higher TTR and lower risk of bleeding as evidenced in this analysis. This is likely due to a truncated period of heparin bridging in these patients. Another potential explanation for the observed increased risk of major bleeding is an underlying propensity to bleeding that may have resulted in the interruption of OAC in the first place. Thus patients at high risk of bleeding due to a procedure or underlying bleeding diathesis may have had their warfarin withheld for a longer period of time, leading to a lower TTR. In addition, the performance of procedures may also predispose to bleeding complications.

Although this study presents valuable real-world experience with warfarin interruption in a large AF cohort, it is subject to the limitations of an observational study design. The outcomes findings represent associations that may be impacted by confounding. The use of bridging anticoagulation, dosing of warfarin upon resumption and the frequency of INR monitoring were not standardized and left to the discretion of the treating physician. TTR calculated from periodic INR measurements using linear interpolation may not accurately reflect the fluctuations in INR that may occur on a daily basis. Lastly, we only reviewed interruptions associated with procedures, which are unlikely to reflect findings among patients with interruptions for other reasons. The ORBIT-AF registry included only a small number of patients on direct oral anticoagulants. Hence comparison between interruption of warfarin and direct oral anticoagulants was not possible.

In conclusion, temporary interruption of warfarin in AF is common and is associated with a period of subtherapeutic anticoagulation after resumption of the drug. Lower TTR after interruption was associated with higher risk of major bleeding in patients who received bridging anticoagulation. Although bridging anticoagulation should generally be avoided during warfarin interruption, the rapid achievement of therapeutic INR is a reasonable goal to reduce bleeding risk in those who require bridging.

Disclosures

Madhavan: Research grant from Bristol Myers Squibb and Pfizer. D Simon: None. JP Piccini: ARCA biopharma, Boston Scientific, GE Healthcare, and Johnson & Johnson/Janssen Scientific Affairs and consultancies to Forest Laboratories, Janssen Scientific Affairs, Pfizer/BMS, Spectranetics, and Medtronic. JE Ansell: Consultant activities and honoraria from: Bristol Myers Squibb, Pfizer, Daiichi Sankyo, Berhenger Ingelheim, Janssen, Instrumentation Laboratories, Perosphere Inc, Equity interest: Perosphere, Inc. GC Fonarow: consultant to Janssen. EM Hylek: honoraria, modest: Boehringer-Ingelheim, Bayer, and consultant/advisory board, modest: Daiichi Sankyo, Ortho-McNeil-Janssen, Johnson & Johnson, Boehringer-Ingelheim, Bristol-Myers Squibb. PR Kowey: Consultant J&J, Daiich-Sankyo, BMS, BI. KW Mahaffey: financial disclosures can be viewed at http://med.stanford.edu/profiles/kenneth-mahaffey. L Thomas: Participation in research with Novartis, Boston Scientific, Gilead Sciences, Inc, Janssen Scientific. ED Peterson: Research support from Eli Lilly & Company and Janssen. BJ Gersh: Modest DSMB/Advisory Board support from Medtronic, Baxter Healthcare Corporation, InspireMD, Cardiovascular Research Foundation, PPD Development, LP, Boston Scientific, and St. Jude.

Authors Contribution

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Acknowledgments

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.07.006.

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