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ORIGINAL ARTICLE

Extended International Normalized Ratio testing intervals for warfarin-treated patients

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Essentials

- Warfarin typically requires International Normalized Ratio (INR) testing at least every 4 weeks.
- We implemented extended INR testing for stable warfarin patients in six anticoagulation clinics.
- Use of extended INR testing increased from 41.8% to 69.3% over the 3 year study.
- Use of extended INR testing appeared safe and effective.

Summary. *Background:* A previous single-center randomized trial suggested that patients with stable International Normalized Ratio (INR) values could safely receive INR testing as infrequently as every 12 weeks. *Objective:* To test the success of implementation of an extended INR testing interval for stable warfarin patients in a practice-based, multicenter collaborative of anticoagulation clinics. *Methods:* At six anticoagulation clinics, patients were identified as being eligible for extended INR testing on the basis of prior INR value stability and minimal warfarin dose changes between 2014 and 2016. We assessed the frequency with which anticoagulation clinic providers recommended an extended INR testing interval (> 5 weeks) to eligible patients. We also explored safety outcomes for eligible patients, including next INR values, bleeding events, and emergency department visits. *Results:* At least one eligible period for extended INR testing was identified in 890 of 3362 (26.5%) warfarin-treated patients. Overall, the use of extended INR testing in eligible patients increased from 41.8% in the first quarter of 2014 to 69.3% in the fourth quarter of 2016. The number of subsequent out-of-range next INR values were similar between eligible patients who did and did not have an extended INR testing interval (27.3% versus 28.4%, respectively). The numbers of major bleeding events were not different between the two groups, but rates of clinically relevant non-major bleeding (0.02 per 100 patient-years versus 0.09 per 100 patient-years) and emergency department visits (0.07 per 100 patient-years versus 0.19 per 100 patient-years) were lower for eligible patients with extended INR testing intervals than for those with non-extended INR testing intervals. *Conclusions:* Extended INR testing for stable warfarin patients can be successfully and safely implemented in diverse, practice-based anticoagulation clinic settings.

Keywords: anticoagulation; atrial fibrillation; quality improvement; venous thromboembolism; warfarin.

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Background

Because of complex pharmacokinetic properties and multiple drug–drug and drug–food interactions, warfarin dosing is complex and requires frequent blood test monitoring in most patients. The International Normalized Ratio (INR) is customarily checked at least every 4 weeks in patients receiving chronic warfarin therapy, to ensure safe and effective levels of anticoagulant therapy within a narrow target range [1]. Whereas many patients have difficulty in maintaining consistent in-range INR values, some patients have remarkably consistent in-range INR values, and rarely require warfarin dose adjustment [2].

Following an observational study demonstrating the safety of INR testing intervals up to 14 weeks, a single-

center randomized trial demonstrated the safety and feasibility of an every 12-week versus an every 4-week INR testing interval for stable warfarin patients in 2011 [3,4]. On the basis of this single-center trial, the American College of Chest Physicians provided a Grade 2B recommendation in favor of an every 12-week INR testing interval over an every 4-week INR testing interval for stable warfarin patients [5]. However, practice-based adoption has not been reported outside of a clinical trial setting [6].

In 2014, six participating anticoagulation centers in the Michigan Anticoagulation Quality Improvement Initiative ($MAQI^2$) collaborative modified INR testing interval protocols to allow extended intervals for stable warfarin patients. Given the diversity of each clinic's patient population and structure, each clinic established its own definition of 'stable' warfarin patients and the maximum allowable INR testing interval. We explored the rate of extended INR testing interval utilization at each of these six anticoagulation services and the associated clinical outcomes.

Methods

$MAQI^2$

The $MAQI^2$ is a collaborative of six anticoagulation clinics sponsored by Blue Cross-Blue Shield of Michigan/Blue Care Network to improve the quality of anticoagulation care in the state of Michigan [7]. A sample of patients who have started receiving warfarin for any indication are enrolled at each site, and all clinical interactions with the anticoagulation clinic or healthcare system, including laboratory values, are manually abstracted from the medical chart and entered into the $MAQI^2$ database by trained data abstractors. The abstracted data undergo random audits by the coordinating center team. Each of the centers participates in a number of quality improvement efforts, but all clinical care is provided by the anticoagulation staff (nurses and pharmacists) independently of the $MAQI^2$ research team. Data collection, research and quality improvement efforts have been approved by the Institutional Review Boards at the coordinating center (University of Michigan) and all participating sites.

Extended INR testing interval quality improvement effort

In 2014, a collaborative-wide quality improvement effort was initiated to allow for extended INR testing intervals for stable warfarin-treated patients. After review by the medical directors and clinic staff, each anticoagulation clinic established its own guidelines to determine which patients were deemed to be stable and eligible for an extended INR testing interval (Table 1). Similarly, each clinic established the maximum INR testing interval that could be recommended for eligible patients, usually extending from a previous maximum of 4 weeks to a new maximum of 6 weeks or 8 weeks (specific to each clinic). Utilization rates of the extended INR testing interval (based on the assessment of nurse-recommended or pharmacist-recommended next INR test date) were provided to each center's nurse or pharmacist and physician leaders on a quarterly basis, with details about any patient who was eligible but not offered an extended INR testing interval. Clinically important outcomes, such as the percentage of next INRs that were out of range or

Table 1 Clinic-specific guidelines for extended International Normalized Ratio (INR) testing intervals

	Clinic 1	Clinic 2	Clinic 3	Clinic 4	Clinic 5	Clinic 6
Maximum INR testing interval (weeks)	6	6	8	6	6	6
Inclusion criteria	No weekly dose change for ≥ 12 weeks and INR strictly in range for ≥ 12 weeks	No weekly dose change ≥ 12 weeks and INR strictly in range ≥ 12 weeks	No weekly dose change for ≥ 6 months and INR strictly in range for ≥ 6 months	No weekly dose change for ≥ 6 months and INR in ± 0.1 of range for ≥ 6 months	INR strictly in range for ≥ 10 weeks	No weekly dose change for ≥ 4 months and INR in ± 0.1 of range for ≥ 4 months
Exclusion	(a) Self INR testing (b) Left ventricular assist device (c) Chronic renal insufficiency (d) Patient permanently refused					
Additional exclusion criteria		No history of bleeding, not eating vitamin K-rich foods, no antiphospholipid syndrome				

INR, international normalized ratio.

extremely out of range, bleeding events, thromboembolic events, and emergency department (ED) visits, were reviewed quarterly with the anticoagulation clinic leadership teams.

Patient selection and outcomes

For this analysis, eligible patients with active warfarin prescriptions in 2014–2016 who met their individual center's definition of a stable warfarin patient (Table 1) were included. Patients were excluded if they regularly self-tested the INR, had a left ventricular assist device in place, had evidence of chronic renal insufficiency documented in the medical chart problem list, or had previously refused any recommended extended INR testing intervals. At one site (Site 2), patients were also excluded if they had any history of bleeding, were eating foods with a high vitamin K content to help with warfarin dosing, or had antiphospholipid antibody syndrome. Similarly, patients who experienced an adverse clinical event (e.g. ED visit or bleeding event), underwent any medication change, temporarily stopped warfarin therapy (e.g. for a surgical procedure), developed a new comorbidity or were undergoing chemotherapy during an otherwise stable period were not included in the analysis, as most of the anticoagulation clinics would not have offered an extended INR testing interval in these situations.

The primary outcome was the percentage of eligible patients who were scheduled for an extended INR testing interval (> 5 weeks; average of 6 weeks) at each participating center, assessed quarterly. Secondary outcomes included the number of in-range versus out-of-range follow-up INR values, the number of extremely out-of-range follow-up INR values (≤ 1.5 or ≥ 4.0), major and clinically relevant non-major (CRNM) bleeding as defined according to the ISTH criteria, and thromboembolic event rates during the INR testing interval for eligible patients who did and did not receive an extended INR testing interval [8,9]. All clinical events (bleeding and thromboembolic) were chart-abstracted by the trained abstractors and randomly audited by the MAQI^2 coordinating center to ensure accuracy.

Statistical analysis

A chi-square test was used to assess the association between an extended INR testing interval and clinical variables, including age, gender, HAS-BLED score, and indications [10]. To test the difference in the numbers of out-of-range INR and extreme INR values between patients who did and did not have an extended INR testing interval, a chi-square test was used. A generalized linear model was developed to analyze the differences in rates of adverse events, including major bleeding, CRNM bleeding, and ED visits, in relationship to a standard or extended INR testing interval.

Results

Of the 3362 warfarin-treated patients managed by the six participating MAQI^2 centers between January 2014 and December 2016, 890 (26.5%) had at least one period of stable INRs and warfarin dosing that qualified for extended INR testing intervals according to the individual site protocol (Table 1). Of these, 770 (86.5%) patients had their INR testing interval extended at least once. In total, 2479 of 4094 (60.6%) eligible patient interactions were recommended for an extended INR testing interval. Eligible patients who had at least one extended INR testing interval had no significant differences in warfarin anticoagulation indications, gender or bleeding risk from patients who never had an extended INR testing interval despite being eligible (Table 2).

The overall percentage of eligible patients who had an extended INR testing interval increased from 41.8% in the first quarter of 2014 to 69.3% in the fourth quarter of 2016 ($P < 0.0001$ for trend; Fig. 1). There was significant heterogeneity between centers with regard to the rate of extended INR interval testing utilization (Fig. S1).

The median length of time between INR draws was 42 days (interquartile range [IQR] 42–55 days) for patients who had an extended INR testing interval. The median length of time between INR draws was 28 days (IQR 21–29 days) for patients who were eligible for an extended INR testing interval, but were not offered one ($P < 0.0001$).

The numbers of subsequent out-of-range follow-up INR values (first INR after the extended testing interval) were similar between eligible patients who did and did not have an extended INR testing interval (Table 3). The numbers of extreme follow-up INR values (INR ≤ 1.5 or INR ≥ 4)

Table 2 Demographics – stable patients who did and did not have extended International Normalized Ratio (INR) testing

	Stable patients who had extended INR testing (n = 770; 86.5%)	Stable patients who did not have extended INR testing (n = 120; 13.5%)
Mean age as of January 2014 (years)	69.4 ± 13.4	67.8 ± 14.9
Male gender, no. (%)	431 (56.1)	64 (53.3)
Median HAS-BLED score (IQR)	2 (1–3)	2 (1–3)
Indication, no. (%)		
Atrial fibrillation	467 (60.7)	68 (56.7)
Venous thromboembolism	206 (26.8)	38 (31.7)
Valve replacement	37 (4.8)	7 (5.8)
Other	59 (7.7)	9 (7.5)

IQR, interquartile range. Among all patients with at least one INR value that qualified for extended INR testing, a comparison was made between those patients who were recommended for extended INR testing intervals at least once and those patients who were never recommended for extended INR testing.

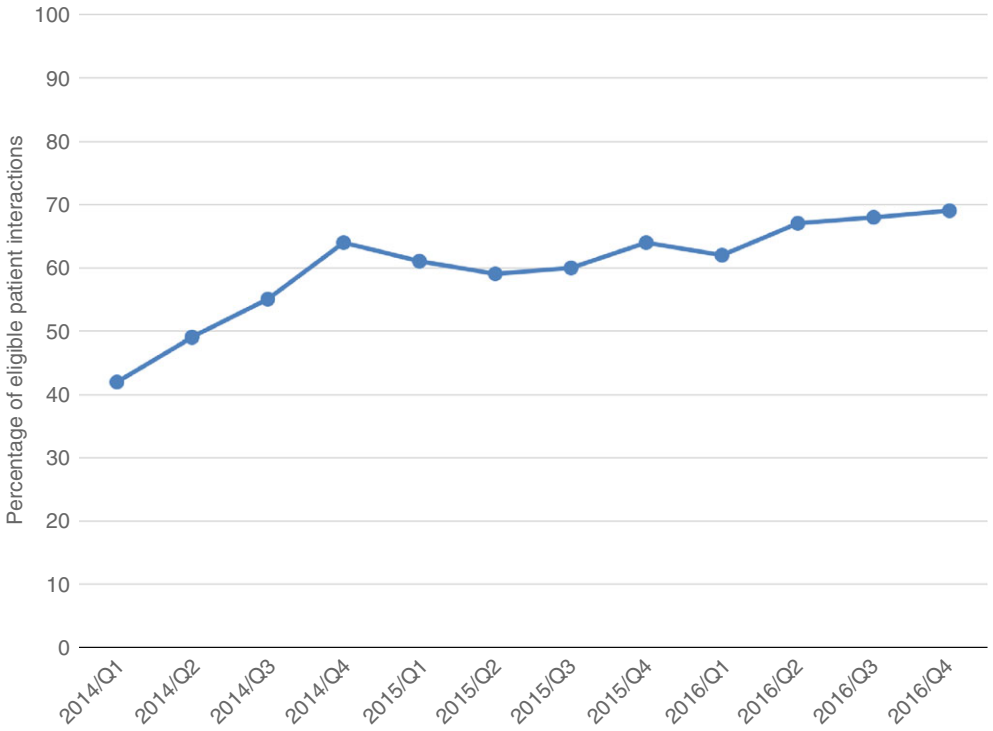

Fig. 1. Rate of extended INR testing in eligible patients, 2014–2016. Percent of eligible patient INR values where an extended testing interval was recommended. Percentages are shown quarterly for the entire cohort. INR, international normalized ratio.[Color figure can be viewed at wileyonlinelibrary.com]

Table 3 Outcomes with and without extended International Normalized Ratio (INR) testing intervals

	Extended INR testing interval (n = 2479)	No extended INR testing interval (n = 1615)	P-value
Total follow-up time (days)	118 368	39 609	
Length of INR testing interval (days), median (IQR)	42 (42–55)	28 (21–29)	
Next INR value out-of-range, no. (%)	677 (27.3)	458 (28.4)	0.46
Next INR value extreme, no. (%)	158 (6.4)	124 (7.7)	0.11
Major bleeding (no.)	5 (0.02 per patient-year)	1 (0.01 per patient-year)	
CRNM bleeding (no.)	6 (0.02 per patient-year)	10 (0.09 per patient-year)	
Emergency department visits (no.)	23 (0.07 per patient-year)	21 (0.19 per patient-year)	
Thromboembolic events (no.)	0	0	

CRNM, clinically relevant non-major; IQR, interquartile range. Comparison of outcomes for patients was based on an individual patient INR value eligible for an extended follow-up interval on the basis of whether the next INR was scheduled at a normal time (< 5 weeks) or an extended time (≥ 5 weeks). Extreme values were defined as INR ≤ 1.5 or INR ≥ 4.0. P-values are for number of events for out-of-range and extreme INR values.

were also similar between the two groups. Among patients who scheduled their next INR in 5–7 weeks, the percentage of next INR values that were out of range was lower than in patients who scheduled their next INR in ≥ 8 weeks (504/1910 [26.4%] versus 173/569 [30.4%], respectively, P = 0.06). The percentage of next INR values that were in the extreme range was also lower for the 5–7-week group than for the ≥ 8-week group (105/1910 [5.5%] versus 53/569 [9.3%], respectively, P = 0.001).

The numbers of major and CRNM bleeding events were small, but numerically similar between eligible patients who did and did not have extended INR testing intervals (Table 3). There were no documented thromboembolic events in either group.

Discussion

We have demonstrated the ability to safely and effectively implement a policy allowing for extended INR testing intervals in stable warfarin patients across six diverse anticoagulation clinics. Implementation increased during the study period to include > 85% of eligible patients

being offered at least one extended INR testing interval. Most importantly, there were no significant differences in out-of-range and extreme follow-up INR values between patients who did and did not have an extended INR testing interval. However, out-of-range INR values may be more frequent in patients who go ≥8 weeks between INR tests than in patients with shorter testing intervals. Finally, the overall numbers of clinical adverse events were low, with lower rates of CRNM bleeding events and ED visits in the two groups. Perhaps in contrast to common assumptions, the percentage of patients with a CRNM bleeding event was higher in the cohort of patients who did not have an extended INR testing interval than in the cohort of patients who had their INR testing interval extended.

In the randomized trial on which this intervention was based, Schulman *et al*. randomized 250 patients with 6 months of stable warfarin dosing to a standard 4-week INR testing interval or an extended 12-week testing interval [3]. With more than twice the number of patients as the Schulman study, we were able to demonstrate similar safety and efficacy, albeit with a shorter amount of time between the INR tests in the extended group. Each of our anticoagulation clinics elected to use a shorter period for the extended INR testing interval (6–8 weeks). Two primary factors led to this decision. First, very few patients across the six anticoagulation clinics would have qualified as stable if the 6-month stable warfarin dose requirement that was used in the randomized trial had been implemented in our clinics. By shortening the required time for patients to be deemed stable, we were able to include many more patients. However, that decision made most of the clinic staff and physician directors feel that a full 12 weeks between INR tests would not be appropriate. Therefore, each clinic decided to begin with a 6–8-week maximum interval. After reviewing the safety data, many of these clinics have begun to extend the INR testing interval to 8–10 weeks since 2015, with continued safety monitoring. Our data suggest that, for many patients, a 5–8-week period may produce better outcomes than longer intervals, at least with regard to the next INR value.

As this represents practice-based implementation, there was significant heterogeneity between sites (Fig. 1). One site in particular (clinic 3) had stable low rates of extended INR testing utilization during the first few quarters. In April 2014, the research team presented the ongoing data from the other five centers at a monthly anticoagulation staff meeting. This presentation included data on the frequency of extended INR testing interval utilization and the safety outcomes from those sites. Many of the nursing and pharmacist staff expressed their concerns about the safety and lack of willingness to trust a single randomized trial in their patient population before the presentation [11]. However, after the presentation, implementation of this intervention improved, with > 45% of eligible patients at that center having an extended INR testing interval by the fourth quarter of 2014.

In addition to reducing the burden of frequent blood draws on patients, implementing an extended INR testing interval may also help to reduce overall healthcare costs and reduce anticoagulation clinic workload. Using a payment cost of $5.37 per INR test, we estimate that the six participating anticoagulation clinics saved more than $400 000 over a 4-year time period because of this implementation effort. In other recent work, we measured a median of 2.9 min (IQR 1.8–5.8 min) for anticoagulation staff to manage an in-range INR value [12]. With avoidance of these INR tests, the available time for anticoagulation staff to spend with patients at greater need of their services can quickly add up.

Our study has a number of important strengths. First, it provides the first published data on the implementation, safety and efficacy of an extended INR testing interval for stable warfarin patients following the single randomized trial published in 2011. Second, it demonstrates the unique challenges of and subsequent successes with the implementation of randomized clinical evidence in everyday practice among a diverse set of anticoagulation clinics. However, certain limitations must be acknowledged. First, our protocols for determining warfarin stability and the maximal INR testing interval were somewhat individualized for each center, and differed from those of the randomized trial on which they are based. However, this represents the practice-based implementation and dissemination of randomized trials. Second, our sample size and number of hard clinical events (e.g. major bleeding and thromboembolic events) were too small to allow firm conclusions to be drawn about the association between an extended INR testing interval and these risks. However, the intermediate outcomes of out-of-range and extreme follow-up INR values are very reassuring. Finally, as this analysis represents observational data, we cannot account for potential bias in the patients who did and did not receive an extended INR testing interval. This includes the instincts of an anticoagulation nurse or pharmacist regarding the safety of extending the INR testing interval for a given patient at a given time. However, as this article is intended to describe the implementation reach and effectiveness of known clinical evidence, these biases highlight the challenges that nurses, pharmacists, clinicians and patients must encounter when trying to implement the randomized trial evidence base. It also highlights the potential success and impact that such a policy can have for stable warfarin-treated patients.

In conclusion, we have demonstrated a successful ongoing implementation effort to extend the INR testing interval for stable warfarin patients. Although further progress remains to be made, over half of all eligible patients are recommended for INR testing no more frequently than every 6 weeks, reducing the burden of

frequent blood draws. Further efforts are needed to understand the remaining barriers to more complete implementation and adoption of this evidence base.

Addendum

G. D. Barnes and X. Kong had full access to all of the data in the study, and take responsibility for the integrity of the data, and the accuracy of the data analysis. G. D. Barnes performed the literature search and wrote the manuscript. X. Kong performed data analysis. D. Cole, B. Haymart, E. Kline-Rogers, S. Almany, M. Dahu, M. Ekola, S. Kaatz, J. Kozlowski, and J. B. Froehlich performed crucial appraisal and critically reviewed the manuscript. All authors interpreted the data.

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Disclosure of Conflict of Interests

G. D. Barnes reports receiving grants from Blue Cross-Blue Shield of Michigan during the conduct of the study, and grants and personal fees from Pfizer/BMS, and personal fees from Janssen and Portola, outside the submitted work. E. Kline-Rogers reports receiving personal fees from Janssen and AC Forum Board of Directors, outside the submitted work. S. Almany reports receiving personal fees from Biostarventures, Ablative Solutions, Trice, Corindus, and Foldax, outside the submitted work. S. Kaatz reports receiving grants from Blue Cross-Blue Shield of Michigan/Blue Care Network during the conduct of the study, and grants and personal fees from Janssen, and personal fees from Boehringer-Ingelheim, Bristol Myer Squibb, Pfizer, Daiichi Sankyo, CSL Behring, Portola, and Roche, outside the submitted work. J. B. Froehlich reports receiving grants from Blue Cross-Blue Shield of Michigan during the conduct of the study, and grants and personal fees from Pfizer, personal fees from Merck, Janssen, and Aralez, outside the submitted work; also, the Blue Cross-Blue Shield Foundation of Michigan has supported the quality improvement registry project in anticoagulation state-wide. The other authors state that they have no conflict of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig. S1. Rate of extended INR testing in eligible patients by center, 2014–2016.

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