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Extended International Normalized Ratio Testing Intervals for Warfarin-treated Patients

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Running Head: Extended INR Testing for Stable Warfarin Patients

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

Keywords

Anticoagulation

Atrial Fibrillation

Quality Improvement

Venous Thromboembolism

Warfarin

Abstract

Background

A prior single center randomized trial suggested that patients with stable INR values could safely receive INR testing as infrequently as every 12 weeks.

Objective

To test the implementation success of an extended INR testing interval for stable warfarin patients in a practice-based, multi-center collaborative of anticoagulation clinics.

Methods

At six anticoagulation clinics, patients were identified as being eligible for extended INR testing based on 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 890/3362 (26.5%) warfarin-treated patients. Overall, the use of extended INR testing in eligible patients increased from 41.8% in 2014/Q1 to 69.3% in 2016/Q4. The number of subsequent out-of-range next INR values were similar between eligible patients who did and did not receive an extended INR testing interval (27.3% vs. 28.4%, respectively). The number of major bleeding events were not different between the two groups, but rates of clinically relevant non-major bleeding (0.02/100-patient-years vs. 0.09/100-patient-years) and emergency department visits (0.07/100-patient-years vs. 0.19/100-patient-years) were lower for eligible patients with extended vs. 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.

Background

Due to 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 on chronic warfarin therapy to ensure safe and effective levels of anticoagulant therapy within a narrow target range.[1] While many patients have difficulty maintaining consistent in-range INR values, some patients are remarkably consistent and rarely require warfarin dose adjustment.[2]

Following an observational study demonstrating safety of INR testing intervals up to 14 weeks, a single-center randomized trial demonstrated safety and feasibility of an every 12-week vs. an every 4-week INR testing interval for stable warfarin patients in 2011.[3, 4] Based on this single-center trial, the American College of Chest Physicians (ACCP) 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 (MAQI²) 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 their 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

Michigan Anticoagulation Quality Improvement Initiative (MAQI²)
MAQI² 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 newly initiating warfarin for any indication are enrolled at each site and all clinical interactions with the anticoagulation clinic or health care system, including laboratory values, are manually abstracted from the medical chart and entered into the MAQI² database by trained data abstractors. Abstracted data undergoes random audits by the coordinating center team. Each of the centers participate in a number of quality improvement efforts, but all clinical care is provided by the anticoagulation staff (nurses and pharmacists) independent of the MAQI² research team. Data collection, research, and quality improvement efforts have been approved by the IRB 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 their own guidelines to determine which patients were deemed stable and eligible for an extended INR testing interval (Table 1). Similarly, each clinic established the maximum INR testing interval at which eligible patients could be recommended, usually extending from a prior maximum of 4 weeks to a new maximum of 6 or 8 weeks (specific to each clinic). Utilization rates of the extended INR testing interval (based on assessment of nurse or pharmacists 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 percent of next INRs that were out of range or extremely out of range, bleeding events, thromboembolic events, and emergency department 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 use self-testing of the INR, had a left ventricular assist device placed, had evidence of chronic renal insufficiency documented in the medical chart problem list, or the patient had previously expressed refusal to any recommended extended INR testing intervals. At one site (Site 2), patients were further excluded if they had any history of bleeding, were taking foods with high vitamin K content to help with warfarin dosing, or had the 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 6 weeks) at each participating center, assessed quarterly. Secondary outcomes included the number of in-range vs. 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 by the ISTH criteria, and thromboembolic event rates that occurred 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) are 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 access the association between INR testing interval extending and clinical variables including age, gender, HAS-BLED score and indications.[10] To test the difference in number of out-of-range INR and extreme INR values between patients who did and did not receive extended INR testing interval, a chi-square test was used. A generalized linear model was developed to

analyze the difference in rate of adverse events including major bleeding, CRNM bleeding and emergency department 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 the individual site protocol (Table 1). Of those, 770 (86.5%) patients had their INR testing interval extended at least once. In total, 2479/4094 (60.6%) eligible patient interactions were recommended for an extended INR testing interval. Eligible patients who received at least one extended INR testing interval had no significant difference on warfarin anticoagulation indications, gender, and bleeding risk as compared to patients who never received an extended INR testing interval despite being eligible (Table 2).

The overall percentage of eligible patients who received an extended INR testing interval increased from 41.8% in the first quarter of 2014 (2014/Q1) to 69.3% in 2016/Q4 (p<0.0001 for trend; Figure). Significant heterogeneity exists between centers with regards to the rate of extended INR interval testing utilization (Figure S1).

The median length of time between INR draws was 42 (interquartile range 42-55) days for patients who received an extended INR testing interval. The median length of time between INR draws was 28 (interquartile range 21-29) days for patients who were eligible for an extended INR testing interval, but were not offered one (p<0.0001).

The number 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 receive an extended INR testing interval (Table 3). The number of extreme

follow up INR values (INR ≤1.5 or INR ≥4) were also similar between the two groups. Among patients who scheduled their next INR in 5-7 weeks, the percent of next INR values that were out-of-range trended lower than patients who scheduled their next INR in 8 or more weeks (504/1910 [26.4%] vs. 173/569 [30.4%], respectively, p=0.06). The percent of next INR values that were in the extreme range were also lower for the 5-7 week group than the 8+ week group (105/1910 [5.5%] vs. 53/569 [9.3%], respectively, p=0.001).

The number of major and CRNM bleeding events were small, but numerically similar between eligible patients who did and did not get 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 more than 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 for patients who did and did not get an extended INR testing interval. However, out of range INR values may be more frequent with patients who go 8 or more weeks between INR tests as compared to patients with shorter testing intervals. Lastly, the overall number of clinical adverse events were low, with lower rates of CRNM bleeding events and emergency department visits between the two groups. Perhaps contrary to common assumptions, the percentage of patients with a CRNM bleeding event was higher in the cohort of patients who did not get an extended INR testing interval as compared to the patients who did get their INR testing interval extended.

In the randomized trial on which this intervention was based, Schulman and colleagues 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 lead 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 were implemented in our clinics. By shortening the required time 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 at which patients can have their INR checked. 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 suggests that for many patients, a 5-8 week period may produce better outcomes than longer intervals, at least in regards to the next INR value.

As this represents practice-based implementation, significant heterogeneity exists between each site (Figure). 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 5 centers at a monthly anticoagulation staff meeting. This presentation included data about the frequency of extended INR testing interval utilization and the safety outcomes from those sites. Many of the nursing and pharmacist staff expressed their concern 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 over 45% of eligible patients at that center receiving an extended INR testing interval by 2014/Q4.

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 work load. 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 through this implementation effort. In other recent work, we measured a median of 2.9 minutes (IQR 1.8-5.8 minutes) for anticoagulation staff to manage an in-range INR value.[12] By avoiding these INR tests, the available time can quickly add up for anticoagulation staff to spend with patients at greater need of their services.

Our study has a number of important strengths. First, it represents the first published data exploring 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 and subsequent successes with implementing randomized clinical evidence into an everyday practice among diverse set of anticoagulation clinics. Still, 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 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 draw firm conclusions 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. Lastly, 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 "gut sense" from an anticoagulation nurse or pharmacist about the safety of extending the INR testing interval for a given patient at a given time. However, as this manuscript is meant 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 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. While 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. Efforts to understand the remaining barriers to more complete implementation and adoption of this evidence base remain to be explored.

Addendum: G. D. Barnes and X. Kong had full access to all of the data in the study, 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.

Disclosures and Conflicts of Interest:

G. D. Barnes reports grants from Blue Cross Blue Shield of Michigan, during the conduct of the study; grants and personal fees from Pfizer/BMS, and personal fees from Janssen and Portola, outside the submitted work.
E. Kline-Rogers reports personal fees from Janssen and AC Forum Board of Directors, outside the submitted work.

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Table 1 – Clinic-specific Guidelines for Extended INR Testing Intervals

	Clinic 1	Clinic 2	Clinic 3	Clinic 4	Clinic 5	Clinic 6
Maximum INR Testing Interval	6 weeks	6 weeks	8 weeks	6 weeks	6 weeks	6 weeks
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 on vitamin K foods, no Antiphospholipid syndrome.				

INR – international normalized ratio

Table 2 – Demographics – Stable Patients who Did and Did Not Receive Extended INR Testing

	Stable Patients who Received Extended INR Testing (n=770; 86.5%)	Stable Patients who did not Receive Extended INR Testing (n=120; 13.5%)
Mean Age (as of Jan 2014)	69.4±13.4	67.8±14.9
% Male	431 (56.1)	64 (53.3)
Median HAS-BLED Score (IQR)	2 (1-3)	2 (1-3)
Indication		
- 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)	

Among all patients with at least one INR value that qualified for extended INR testing, a comparison 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. INR – international normalized ratio, IQR – interquartile range

Table 3 – Outcomes With and Without Extended 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	
Median (IQR) Length of INR Testing Interval (days)	42 (42-55)	28 (21-29)	
Next INR Value Out-of-range (%)	677 (27.3%)	458 (28.4%)	0.46
Next INR Value Extreme (%)	158 (6.4%)	124 (7.7%)	0.11
Major Bleeding	5 (0.02/patient-year)	1 (0.01/patient-year)	
CRNM Bleeding	6 (0.02/patient-year)	10 (0.09/patient-year)	
Emergency	23 (0.07/patient-	21 (0.19/patient-	

Department Visits	year)	year)	
Thromboembolic Events	0	0	

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

Figure – 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
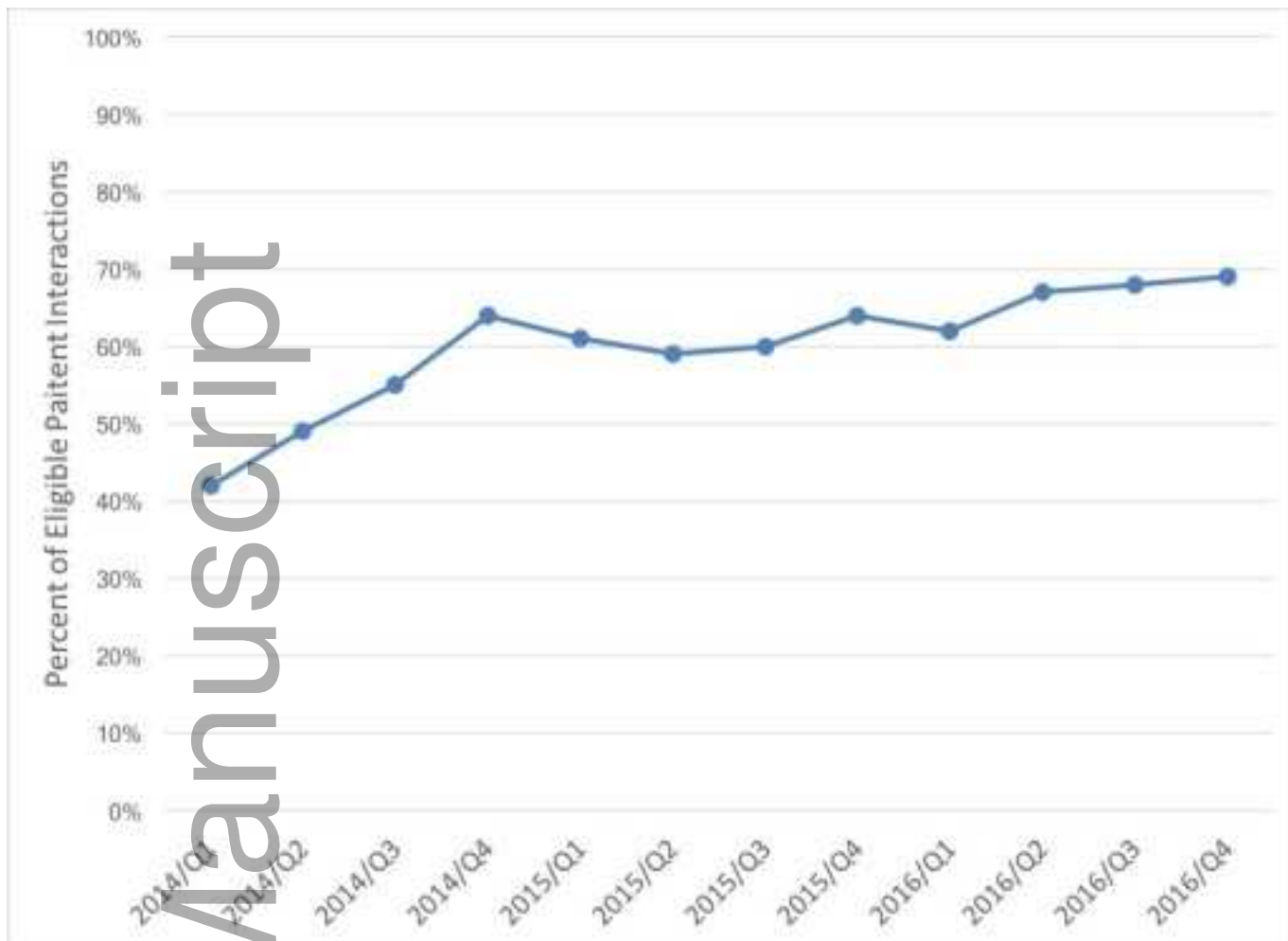
Supplementary Figure
Figure – Rate of Extended INR Testing in Eligible Patients by Center, 2014-2016

Percent of eligible patient INR values where an extended testing interval was recommended. Percentages are shown quarterly for the entire cohort and each individual health center. INR – international normalized ratio

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