Gaps in Monitoring During Oral Anticoagulation

Insights Into Care Transitions, Monitoring Barriers, and Medication Nonadherence

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Background: Among patients receiving oral anticoagulation, a gap of > 56 days between international normalized ratio tests suggests loss to follow-up that could lead to poor anticoagulation control and serious adverse events.

Methods: We studied long-term oral anticoagulation care for 56,490 patients aged 65 years and older at 100 sites of care in the Veterans Health Administration. We used the rate of gaps in monitoring per patient-year to predict percentage time in therapeutic range (TTR) at the 100 sites.

Results: Many patients (45%) had at least one gap in monitoring during an average of 1.6 years of observation; 5% had two or more gaps per year. The median gap duration was 74 days (interquartile range, 62-107). The average TTR for patients with two or more gaps per year was 10 percentage points lower than for patients without gaps ($P < .001$). Patient-level predictors of gaps included nonwhite race, area poverty, greater distance from care, dementia, and major depression. Site-level gaps per patient-year varied from 0.19 to 1.78; each one-unit increase was associated with a 9.2 percentage point decrease in site-level TTR ($P < .001$).

Conclusions: Site-level gap rates varied widely within an integrated care system. Sites with more gaps per patient-year had worse anticoagulation control. Strategies to address and reduce gaps in monitoring may improve anticoagulation control.

CHEST 2013; 143(3):751-757

Abbreviations: ACC = anticoagulation clinic; INR = international normalized ratio; IQR = interquartile range; TTR = time in therapeutic range; VA = Veterans Health Administration

Like any anticoagulant, warfarin is hazardous; correct use is imperative to avoid thromboembolic or hemorrhagic complications. The narrow therapeutic window and variable dose response of warfarin mandate frequent monitoring of the international normalized ratio (INR) to ensure that the patient remains

within the therapeutic range. During our study period, prominent guidelines recommended INR testing at least every 28 days¹ or every 42 days,² although the latest American College of Chest Physicians guidelines allow an interval of up to 90 days for selected patients with extremely stable control.³ The Anticoagulation Forum states that "A tracking system (e.g. an electronic

Manuscript received May 1, 2012; revision accepted August 17, 2012.

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Funding/Support: This project was supported by a grant from the Veterans Affairs Health Services Research and Development Service [IIR-10-374]. Dr Rose is supported by a Career Development Award from the Veterans Affairs Health Services Research and Development Service [CDA-2-08-017].

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database) should be implemented to minimize the possibility that a patient on anticoagulation therapy could be lost to follow-up, even for a brief period.”⁴

Despite our sense that preventing gaps in INR monitoring is important, relatively little is known about gaps, including how often they occur and their relationship to anticoagulation control. However, our previous work has suggested that sites with excellent anticoagulation control have systems in place to minimize gaps, whereas sites with poor control do not.⁵ This raises the possibility that intervening to help sites develop such systems could improve anticoagulation control and outcomes for patients.

We, therefore, used a large database of patients receiving warfarin from the Veterans Health Administration (VA) to examine the prevalence of gaps in INR monitoring and their patient-level and site-level correlates. We sought to answer the following questions: (1) How frequent are gaps in INR monitoring among patients receiving long-term warfarin therapy? (2) How do gaps impact patient-level anticoagulation control, as measured by time in therapeutic range (TTR)? (3) What patient-level characteristics predict gaps in monitoring? (4) Do sites of care differ in the rate of gaps per patient-year? (5) Does the rate of gaps predict site-level anticoagulation control? The overarching goal of our study was to examine the suitability of the site-level rate of gaps in INR monitoring as a performance measure in anticoagulation care and a target for quality improvement efforts.

MATERIALS AND METHODS

Data

The database for this study also been described elsewhere.^{6,7} The Veterans Affairs Study to Improve Anticoagulation (VARIA) included all patients receiving oral anticoagulation from the VA between October 1, 2006, and September 30, 2008, as described later. The study was approved by the institutional review board of the Bedford VA Medical Center (Protocol Number: Rose 0001).

Patients

We included all patients aged 65 years and older who received warfarin from the VA during the 2-year study period. We limited this study to patients aged 65 years and older because of the availability of Medicare data. We excluded patients enrolled in Medicare Advantage during any part of the study period (15,905 or 22%), because Medicare use data for such patients are incomplete. The combined VA and Medicare database ensured essentially complete capture of all INR testing for these patients.⁸ Although we were aware of all dates when the INR was tested (which allowed us to measure gaps in monitoring), we had access to INR results only in the VA data, and all TTR calculations came from this source.

We excluded patients whose primary indication to receive warfarin was valvular heart disease. Many such patients have a target INR range of 2.5 to 3.5, rather than the more standard 2 to 3, and because we could not identify which patients had the higher target range, we could not calculate TTR.

Laboratory Values and Calculation of Percentage TTR

We calculated TTR using Rosendaal’s method,⁹ which uses linear interpolation to assign an INR value to each day between successive observed INR values. Gaps of >56 days between INR values were not interpolated. After interpolation, the percentage of time during which the interpolated INR values lay between 2.0 and 3.0 (from 0% to 100%) was calculated.⁹

We excluded INR tests measured during hospitalizations, because hospitalized patients may receive temporary parenteral anticoagulation or no anticoagulation. For this study, we also excluded INR data from each patient’s first 6 months of therapy with warfarin (the “inception period”), when treatment may have differed from that received by experienced warfarin patients.

Sites of Care

We included 100 VA sites of care, each of which has a specialized anticoagulation clinic (ACC) run by clinical pharmacists.¹⁰ By policy, all patients whose anticoagulation is managed in the VA are treated by specialized ACCs.¹⁰ Most patients visited only one site of care; for the remainder (3% of patients), we partitioned their data by site.

Risk-Adjustment Model

We have previously described our risk-adjustment model for TTR.^{6,7} We considered many variables that might have affected TTR, including demographics, area-level poverty, driving distance to care, physical health conditions, mental health conditions, number of medications, and number of hospitalizations. We used a simple, rather than a hierarchical, approach to derive our risk-adjustment model, because the exact *P* values were not important in this context, and the point estimates were unchanged regardless of the approach taken. Table 1 lists the variables that compose the risk-adjustment model for TTR. We calculated risk-adjusted TTR as follows. First, we calculated each patient’s observed TTR and applied the risk-adjustment model to calculate the expected TTR. Second, an observed minus expected score was calculated for each patient; we also computed the mean observed, expected, and observed minus expected score for each site of care. Therefore, site-level risk-adjusted TTR was based on the mean observed TTR and the mean expected TTR at each site.

Rate of Gaps in Monitoring

We defined a gap in monitoring as any period >56 days between two successive INR tests. This interval was chosen because a gap of 56 days is traditionally understood to indicate a lack of monitoring, and a period across which TTR is not interpolated.⁹ We considered both VA and Medicare INR values when calculating gaps; that is, any outpatient INR test in either system caused the clock to be reset, and the patient was given another 56 days to obtain the next INR. However, in INR tests obtained during an inpatient stay, we did not reset the clock for calculating gaps. We calculated gaps per year for each patient, as well as gaps per patient-year for each site of care.

We also conducted sensitivity analyses, exploring what our findings would have been had we counted only gaps that did not contain a hospital stay. Applying this alternative definition of “gap” reduced the calculated rate of gaps for some patients, but otherwise the results obtained were quite similar to those presented here.

Possession of Warfarin

We characterized warfarin possession during gaps to better understand their context. We considered patients to be in possession

Table 1—Baseline Characteristics of Study Sample

Variable	Study Sample (N = 56,490)
Female sex	808 (1.4)
Age, ^a median (IQR), y	77 (72-81)
Race/ethnicity	
Non-Hispanic white	50,601 (89.6)
Non-Hispanic black	3,550 (6.3)
Hispanic	1,594 (2.8)
Asian	212 (0.4)
Native American	217 (0.4)
Other	106 (0.2)
Unknown/missing	201 (0.4)
Poverty in zip code of residence, median (IQR), %	10.4 (6.4-15.4)
Distance from nearest VA facility, median (IQR), km	12.5 (5.8-27.0)
Primary indication for warfarin ^b	
Atrial fibrillation	40,173 (71.1)
VTE	12,277 (21.7)
All others combined	4,040 (7.2)
Physical comorbid conditions	
Cancer (newly diagnosed)	4,056 (7.2)
Chronic kidney disease	8,845 (15.7)
Chronic liver disease	413 (0.7)
Chronic lung disease	17,261 (30.6)
Diabetes	21,947 (38.9)
Epilepsy	1,248 (2.2)
Heart failure	18,988 (33.6)
Hyperlipidemia	42,726 (75.6)
Hypertension	48,964 (86.7)
Mental comorbid conditions	
Alcohol abuse	3,075 (5.4)
Bipolar disorder	665 (1.2)
Dementia	3,938 (7.0)
Major depression	9,177 (16.2)
Substance abuse (nonalcohol)	749 (1.3)
Medications, median (IQR), No.	8 (6-11)
Hospitalized at least once	13,810 (24.4)
Anticoagulation control	
Time in range, mean (SD), %	63.1 (21.5)
Follow-up, mean (SD), patient-y	1.6 (0.5)

Data are presented as No. (%) unless indicated otherwise. IQR = interquartile range; VA = Veterans Health Administration.

^aThis study included only patients aged 65 years and older.

^bPatients whose main indication to receive anticoagulation therapy was valvular heart disease or a prosthetic heart valve were excluded from the study.

of warfarin for the number of days in their most recently filled VA prescription. However, patients are often instructed to take one-half a pill on some days and they may sometimes have extra pills left over from previous prescriptions. We, therefore, also examined warfarin possession during gaps after allowing a 30-day grace period following each prescription.

Statistical Analyses

We examined the baseline characteristics of patients in our database. We calculated unadjusted and risk-adjusted TTR for individual patients and sites of care. We calculated each patient's gaps per year and each site's rate of gaps per patient-year. We examined patient-level predictors of any gaps in monitoring vs none, using logistic regression via generalized estimating equations to account for correlated outcomes by site of care. Finally, we

examined the relationship between gaps and anticoagulation control at the patient and the site level. The patient-level analysis used a linear regression via generalized estimating equations to account for correlated outcomes by site of care; the site-level analysis used analysis of variance with a Tukey post hoc test. All analyses were conducted using SAS, version 9.2 (SAS Institute Inc).

RESULTS

Patient-Level Analysis

Our database contained 56,490 patients aged 65 years and older who had used warfarin for > 6 months and were not enrolled in Medicare Advantage. Patient characteristics are described in Table 1. The sample was 99% men, with a median age of 77 years. Most patients (71%) were anticoagulated for atrial fibrillation, 22% for VTE, and 7% for other indications. The population had a substantial burden of comorbidity, including both physical and mental health conditions, as well as substance abuse.

Many patients (45%) had at least one gap in monitoring. There were 44,430 gaps in total, representing 4,482,100 days without monitoring. A total of 13.8% of follow-up time in our database consisted of gaps in monitoring. By definition, the duration of a gap was at least 56 days, and the median duration was 74 days (interquartile range [IQR], 62-107). Many gaps (29%) contained a hospital admission (either to a VA or a non-VA facility); another 5% were preceded by a hospital discharge within 30 days. Patients were frequently in possession of warfarin during gaps. Even without considering a grace period, patients possessed warfarin during at least part of 50% of gap episodes. When allowing for a 30-day grace period, patients possessed warfarin during at least part of 68% of gap episodes and were in possession for the entire episode 50% of the time.

Patients with more gaps per year recorded lower TTR (Table 2). For example, among the 5% of patients with the highest rate of gaps (two or more per year),

Table 2—Patient-Level Relationship Between Gaps in Monitoring and Anticoagulation Control (N = 56,490)

Gaps Per Patient-y	% of Patients	Mean TTR, Unadjusted	Mean TTR, Risk Adjusted ^a
0	55	65.6	+1.9
> 0-1	22	63.4 ^b	+0.9 ^b
> 1-2	18	58.2 ^b	−3.7 ^b
> 2	5	53.6 ^b	−8.1 ^b

Data are presented as %. Analysis was conducted via generalized estimating equations and accounts for correlated outcomes by site of care. Gaps in monitoring are 56-d gaps between successive international normalized ratio tests per year of follow-up. TTR = time in therapeutic range (0%-100%; higher is better).

^aRisk-adjusted TTR is expressed in percentage above or below the expected value based on the risk-adjustment model.

^bDiffers from the reference category (group with zero gaps), $P < .001$.

risk-adjusted TTR was 10% lower than among patients with no gaps ($P < .001$). Patient-level predictors of having any gaps (vs none) included nonwhite race, living in a high-poverty zip code, living farther from the nearest VA facility, dementia, and major depression (Table 3).

Site-Level Analysis

The median site treated 502 patients who qualified for our study cohort (IQR, 307-709). Site mean TTR ranged from 45% to 74%, and risk-adjusted site TTR ranged from 19 percentage points below to 13 above expected. Sites varied widely regarding the number of gaps per patient-year, from a low of 0.19 to a high of

1.78 (Fig 1). For each additional gap per patient-year at a site, the unadjusted TTR was 10.2% lower and the risk-adjusted TTR was 9.2% lower (both $P < .001$). We divided the 100 sites into tertiles according to the number of gaps per patient-year (Table 4). The tertile with the most frequent gaps had considerably worse anticoagulation control than did the other tertiles, both unadjusted and risk adjusted.

DISCUSSION

In this study, we found that prolonged gaps in INR monitoring are common (45% of patients had at least one gap) and are associated with worse anticoagulation

Table 3—Patient-Level Predictors of Any Gaps in Monitoring (vs No Gaps) During Warfarin Therapy

Variable	No. (%)	Unadjusted Effect, OR (95% CI)	Adjusted Effect, OR (95% CI)
Female sex	808 (1.4)	1.10 (0.97-1.25)	1.07 (0.95-1.22)
Age group			
65-69 y	9,452 (16.7)	1.11 (1.04-1.17) ^a	1.07 (1.01-1.13) ^b
70-74 y	13,146 (23.3)	1.04 (0.99-1.10)	1.02 (0.97-1.07)
≥ 75 y	33,892 (60.0)	...	...
Race/ethnicity			
Non-Hispanic white	50,601 (89.6)	...	...
Non-Hispanic black	3,550 (6.3)	1.32 (1.20-1.47) ^a	1.26 (1.15-1.39) ^a
Hispanic	1,594 (2.8)	1.42 (1.21-1.67) ^a	1.31 (1.14-1.50) ^a
Asian	212 (0.4)	1.29 (0.87-1.91)	1.33 (0.89-2.00)
Native American	217 (0.4)	1.37 (1.04-1.81) ^b	1.32 (1.01-1.73) ^b
Other/unknown	316 (0.6)	0.80 (0.63-1.01)	0.88 (0.69-1.10)
Poverty in zip code of residence by quintile			
Wealthiest (0.0%-5.9%)	11,978 (21.2)	...	...
Wealthy (5.9%-9.0%)	11,511 (20.4)	1.03 (0.93-1.14)	1.03 (0.93-1.14)
Moderate (9.0%-12.6%)	11,500 (20.4)	1.08 (0.97-1.21)	1.07 (0.96-1.19)
Poor (12.6%-17.8%)	11,299 (20.0)	1.13 (0.98-1.29)	1.12 (0.97-1.28)
Poorest (17.8%-100.0%)	10,202 (18.1)	1.31 (1.12-1.53) ^a	1.24 (1.06-1.45) ^b
Driving distance from nearest VA facility by quintile			
Nearest (0-5 km)	11,649 (20.6)	...	...
Near (5-10 km)	11,014 (19.5)	1.03 (0.95-1.12)	1.06 (0.98-1.14)
Moderate (10-17 km)	11,015 (19.5)	1.10 (1.01-1.20) ^b	1.16 (1.07-1.27) ^a
Far (17-33 km)	11,219 (19.9)	1.10 (1.01-1.20) ^b	1.16 (1.06-1.27) ^b
Farthest (> 33 km)	11,593 (20.5)	1.22 (1.07-1.38) ^b	1.25 (1.10-1.41) ^a
Primary indication for warfarin ^c			
Atrial fibrillation	40,173 (71.1)	...	...
VTE	12,277 (21.7)	1.11 (1.06-1.17) ^a	1.06 (1.02-1.12) ^b
All others combined	4,040 (7.2)	0.93 (0.85-1.01)	0.91 (0.84-0.99) ^b
Mental comorbid conditions			
Alcohol abuse	3,075 (5.4)	1.19 (1.11-1.29) ^a	1.09 (1.01-1.18) ^b
Anxiety	4,462 (7.9)	1.19 (1.12-1.27) ^a	1.06 (0.99-1.14)
Bipolar disorder	665 (1.2)	1.32 (1.14-1.53) ^a	1.11 (0.94-1.30)
Dementia	3,938 (7.0)	1.35 (1.25-1.46) ^a	1.28 (1.19-1.39) ^a
Major depression	9,177 (16.2)	1.34 (1.28-1.41) ^a	1.28 (1.22-1.35) ^a
PTSD	2,218 (3.9)	1.13 (1.02-1.25) ^b	0.97 (0.87-1.08)
Schizophrenia	349 (0.6)	1.23 (1.01-1.49) ^b	1.00 (0.82-1.22)
Substance abuse (nonalcohol)	749 (1.3)	1.47 (1.25-1.72) ^a	1.25 (1.06-1.48) ^b

Analysis was conducted via generalized estimating equations and accounts for correlated outcomes by site of care. A gap is defined as a period of ≥ 56 d without an international normalized ratio test; 45% of patients had at least one gap during the 2-y study (n = 56,490). PTSD = posttraumatic stress disorder. See Table 1 for expansion of other abbreviations.

^a $P < .001$

^b $P < .05$.

^cPatients whose main indication to receive anticoagulation therapy was valvular heart disease or a prosthetic heart valve were excluded from the study.

FIGURE 1. Relationship between site-level mean gaps per patient-year and site-level risk-adjusted anticoagulation control ($n = 100$ sites). Larger dots represent sites with more patients. The correlation between the site-level gap rate and risk-adjusted TTR was $r = -0.56$ (95% CI, -0.68 to -0.41 ; $P < .001$). TTR = time in therapeutic range.

control. One-quarter of gaps were 107 days or longer. In addition, our data suggested that patients ran out of medication during approximately 50% of gaps, even after allowing for a 30-day grace period. Important patient-level predictors of gaps included poverty, driving distance, dementia, depression, and nonwhite race.

As a marker of adherence to anticoagulant therapy, the concept of a “gap” used in this study was likely to considerably underestimate the impact of nonadherence on the effectiveness of anticoagulant therapy. TTR was not calculated during gaps, because the INR was not measured. We also did not include an assessment of frank discontinuations of therapy; we considered a patient as having a gap only if he or she eventually resumed regular monitoring. Finally, this study focused only on patients who had already used warfarin for at least 6 months and had, thus, shown some ability to persist with therapy and monitoring.

We found that sites in the VA, an integrated system of care, varied almost 10-fold in gaps per patient-year. Sites with more gaps recorded poorer anticoagulation control; for each additional gap per patient-year, risk-adjusted TTR was 9.2% lower. In a parallel qualitative study, we observed that the best ACCs in the VA (ie, those with the highest TTR) had effective systems in place to minimize gaps in monitoring, in marked contrast to the ACCs with the lowest TTR.⁵ In that study, we observed several effective strategies to improve patient tracking and reduce loss to follow-up, although software-driven solutions seemed most effective.⁵ Taken together, these two studies suggest that strategies to minimize gaps in monitoring may be important for sites seeking to improve anticoagulation control.

The present study illustrates an important point, namely that warfarin is not a monolithic therapy whose benefits are realized equally by all patients who receive it. On the contrary, our results reinforce the contention that the quality of management at the site level is a key determinant of anticoagulation control and thus net patient benefit from therapy.¹¹⁻¹⁷ The implication for pulmonologists who treat patients with VTE is that placing a patient on warfarin is not enough; it is also important to consider who will be managing the patient’s anticoagulation and how well they will do it. Referring one’s patients to a high-performance ACC, or working to improve the performance of one’s local ACC, can have an important impact on patient outcomes.¹⁵ Our results also suggest that working to reduce the rate of gaps at the site level may improve patient outcomes. Accordingly, our group is beginning an ambitious quality improvement project whose goal is to achieve benchmark levels of anticoagulation control in the New England Region of the VA. We hope to achieve this goal in large part by measuring and improving site-level processes of care, including the rate of gaps in monitoring.

Our study has important strengths, including the large size of the database and the representation of 100 sites of care within the nation’s largest integrated health-care system. We also used a linked VA-Medicare database that could completely capture all INR tests.

Table 4—Site-Level Gaps in Monitoring per Patient-y as a Predictor of Site-Level Anticoagulation Control ($N = 100$ Sites)

Site-Level Rate of Gaps	No. Sites	Range of Gaps Per Patient-y	Unadjusted TTR, %	Adjusted TTR ^a
Lowest	33	0.19-0.40	64.8	+1.32
Middle	33	0.41-0.62	63.4	+0.62
Highest	34	0.63-1.78	59.7	-2.82
<i>P</i> value (ANOVA)	...	...	< .001	< .001

Gaps in monitoring are 56-d gaps between successive international normalized ratio tests per year of follow-up. All pairwise comparisons were statistically significant by Tukey post hoc test, except for those between “Lowest” and “Middle.” ANOVA = analysis of variance. See Table 2 for expansion of other abbreviations.

^aRisk-adjusted TTR is expressed in percentage above or below the expected value based on the risk-adjustment model.

Thus, we are confident that patients truly did not have INR testing during periods that we call “gaps.”

Our study also has limitations. First, we examined an intermediate outcome of care (anticoagulation control) and not definitive outcomes (such as stroke, VTE, and major hemorrhage). However, there is ample evidence linking TTR to definitive outcomes at the patient and the site level.^{11,13,15-17} Second, we were unable to determine the causes of the gaps in monitoring that we observed. One possible contributor to gaps could have been challenging patients. However, our use of risk-adjusted TTR should have accounted for such patient-level factors. Third, although our linked VA-Medicare database provided considerable detail about the care patients received, 17% of INR values in our database were Medicare values, and these could not be used for calculating TTR. Finally, the patients were veterans, mostly men, and all were aged 65 years and older, possibly impacting generalizability to other populations. However, 13.8% of time in our database consisted of gaps, compared with 18% in a large cohort of patients from Kaiser Permanente of Northern California.¹⁸ This suggests that our VA patients were in many ways typical rather than exceptional.

CONCLUSIONS

In conclusion, we found that gaps in monitoring predict worse anticoagulation control both at the patient and at the site level. Sites vary widely in gap rates, presumably because some have better systems to minimize loss to follow-up among patients receiving anticoagulation. Sites and systems of care seeking to improve anticoagulation control should focus on implementing systems to minimize gaps in monitoring.

ACKNOWLEDGMENTS

Author contributions: Dr Rose is the guarantor of the entire manuscript.

Dr Rose: contributed to the concept and design of the study, analysis and interpretation of the data, drafting of the manuscript, obtaining of funding, study supervision, and critical revision of the manuscript for important intellectual content.

Dr Miller: contributed to the analysis and interpretation of the data and critical revision of the manuscript for important intellectual content.

Dr Ozonoff: contributed to the analysis and interpretation of the data, statistical supervision, and critical revision of the manuscript for important intellectual content.

Dr Berlowitz: contributed to the analysis and interpretation of the data, obtaining of funding, study supervision, and critical revision of the manuscript for important intellectual content.

Dr Ash: contributed to the analysis and interpretation of the data and critical revision of the manuscript for important intellectual content.

Ms Zhao: contributed to the analysis and interpretation of the data, statistical analysis, and critical revision of the manuscript for important intellectual content.

Mr Reisman: contributed to the analysis and interpretation of the data, statistical analysis, and critical revision of the manuscript for important intellectual content.

Dr Hylek: contributed to the analysis and interpretation of the data, study supervision, and critical revision of the manuscript for important intellectual content.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Hylek has served on advisory boards for Bayer; Boehringer Ingelheim GmbH; Bristol-Myers Squibb; Daiichi Sankyo, Inc; Johnson & Johnson; Merck & Co; and Pfizer, Inc. Drs Rose, Miller, Ozonoff, Berlowitz, and Ash; Ms Zhao; and Mr Reisman have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsor had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, and approval of the manuscript. The opinions expressed in this manuscript do not necessarily represent the official views of the Department of Veterans Affairs.

REFERENCES

1. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G; American College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest*. 2008;133(suppl 6):160S-198S.
2. Fuster V, Rydén LE, Cannom DS, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114(7):e257-e354.
3. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl):e152S-e184S.
4. Garcia DA, Witt DM, Hylek E, et al; Anticoagulation Forum. Delivery of optimized anticoagulant therapy: consensus statement from the Anticoagulation Forum. *Ann Pharmacother*. 2008;42(7):979-988.
5. Rose AJ, Petrakis BA, Callahan P, et al. Organizational characteristics of high- and low-performing anticoagulation clinics in the veterans health administration. *Health Serv Res*. 2012;47(4):1541-1560.
6. Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JJ, Berlowitz DR. Patient characteristics associated with oral anticoagulation control: results of the Veterans Affairs Study to Improve Anticoagulation (VARIA). *J Thromb Haemost*. 2010;8(10):2182-2191.
7. Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JJ, Berlowitz DR. 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(1):22-29.
8. Fleming C, Fisher ES, Chang CH, Bubolz TA, Malenka DJ. Studying outcomes and hospital utilization in the elderly. The

- advantages of a merged data base for Medicare and Veterans Affairs hospitals. *Med Care*. 1992;30(5):377-391.
9. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost*. 1993;69(3):236-239.
 10. Veterans Health Administration. VHA Directive 2010-020. Anticoagulation Therapy Management. http://www.va.gov/vhapublications/viewpublication.asp?pub_ID=2234. Accessed January 9, 2012.
 11. Connolly SJ, Pogue J, Eikelboom J, et al; ACTIVE W Investigators. 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(20):2029-2037.
 12. Rose AJ, Berlowitz DR, Frayne SM, Hylek EM. Measuring quality of oral anticoagulation care: extending quality measurement to a new field. *Jt Comm J Qual Patient Saf*. 2009;35(3):146-155.
 13. van Leeuwen Y, Rosendaal FR, Cannegieter SC. Prediction of hemorrhagic and thrombotic events in patients with mechanical heart valve prostheses treated with oral anticoagulants. *J Thromb Haemost*. 2008;6(3):451-456.
 14. van Walraven C, Oake N, Wells PS, Forster AJ. Burden of potentially avoidable anticoagulant-associated hemorrhagic and thromboembolic events in the elderly. *Chest*. 2007;131(5):1508-1515.
 15. Veeger NJ, Piersma-Wichers M, Tijssen JG, Hillege HL, van der Meer J. Individual time within target range in patients treated with vitamin K antagonists: main determinant of quality of anticoagulation and predictor of clinical outcome. A retrospective study of 2300 consecutive patients with venous thromboembolism. *Br J Haematol*. 2005;128(4):513-519.
 16. Wallentin L, Yusuf S, Ezekowitz MD, et al; RE-LY investigators. 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(9745):975-983.
 17. 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(3):239-245.
 18. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA*. 2003;290(20):2685-2692.