J Thromb Thrombolysis (2006) 21: 191–198
DOI 10.1007/s11239-006-4968-z

Monitoring anticoagulation in atrial fibrillation

Chaitanya Sarawate · Mirko V. Sikirica · Vincent J. Willey · Michael F. Bullano · Ole Hauch

Abstract *Background*: Randomized control trials and observational studies show high-quality warfarin therapy leads to safe and effective stroke prophylaxis. In usual community practice, patient, physician and health care system factors are barriers to optimal anticoagulation. We examined the predictive relationship between inpatient and outpatient INR values in chronic non-valvular atrial fibrillation (AF) patients hospitalized for ischemic stroke (S), bleed (B) and control events (C) in usual community practice.

Methods: This nested case-control analysis identified AF patients hospitalized for S, B and C using medical and pharmacy claims spanning 4.5 years ('98–'03) and validating diagnosis with chart abstraction. AF was defined as 2 medical claims for AF $\geq$ 42 days apart with a related prescription claim for warfarin. INRs from both outpatient and inpatient settings were used to yield a continuous history of coagulation status. Time-in-therapeutic-range (TTR) was calculated by Rosendaal's linear interpolation method. Correlation of inpatient and prognostic utility of last outpatient INRs was tested with S or B hospitalizations using univariate and multivariate logistic regression.

Results: Overall, 614 hospitalizations (means: age 73.9, $CHADS_2 = 3.24$; 52% male) included S ($n = 98$), B ($n = 101$) and C ($n = 415$) events. Average TTR was 28.6% (49.4% at INR <2.0, 21.9% at INR >3.0). First INR on admission (INR <2.0 or >3.0) was associated with S and B hospitalizations (OR-adjusted [95%CI], 1.68 [1.04–2.73] and 1.72 [1.02–2.90]), respectively. Last outpatient INR <2.0 was not associated with S (OR-adjusted [95%CI], 1.12 [0.77–1.81]), and INR >3.0 was not associated with B (OR-adjusted [95%CI], 1.25 [0.67–2.32]). Last outpatient INR measurement occurred at 28, 22 and 24 days (median; S, B & C, respectively) before hospitalization.

Conclusion: Patients were observed within therapeutic range less than 30% of their time on warfarin. While inpatient INRs were clearly associated with both ischemic stroke and bleed events, last outpatient INR before event was not predictive.

Keywords Atrial fibrillation · Monitoring · Retrospective · Administrative claims

Introduction

Chronic non-valvular atrial fibrillation (AF) is a major, independent risk factor for thromboembolic stroke, and is the cause of approximately 15–20% of all strokes [1]. If left untreated, the incidence of ischemic stroke is approximately 5% per year [2]. Stroke is associated with a high cost [3], serious long-term disability and a high mortality rate [1].

Clinical trials show that preventing thromboembolism with oral anticoagulant agents, such as warfarin, significantly reduces the rate of stroke to 1.4% and lowers the death rate by 33% [2]. Numerous other randomized trials have established warfarin to be efficacious in reducing risk of ischemic stroke and other systemic thromboembolism, while maintaining relatively low rates of major adverse bleeding events including intracranial hemorrhage [2,4–7]. The American College of Chest Physicians (ACCP) recommends a range for the target

C. Sarawate (✉) · M. V. Sikirica · V. J. Willey · M. F. Bullano
HealthCore, 800 Delaware Ave. 5th Floor, Wilmington, DE, 19801
e-mail: csarawate@healthcore.com
Tel: 302-230-2130 office
Fax: 302-230-2020

O. Hauch
AstraZeneca, LP, 1800 Concord Pike, Wilmington, DE, 19850

level of anticoagulation therapy for vitamin K antagonists to be an international normalized ratio (INR) of 2.0–3.0 [2]. Patients who are maintained in this range achieve optimal anticoagulation while minimizing adverse events [2]. At the same time, effective thromboembolism prophylaxis includes the risk of major bleeding events and the numerous complications of managing warfarin therapy when patients stray from the optimal INR range. For example, the risk of hemorrhage increases significantly with INR levels greater than 4.0, especially in patients older than 75 years [8].

Outside of clinical trials, however, preventing thromboembolism is highly dependent on patient, physician, and healthcare system factors which are barriers to optimal anticoagulation [9]. Previous studies have attempted to provide evidence whether randomized trials can be translated into usual community clinical practice. However, observational studies appear to be contradictory in their assessments of how well clinical trials translate into usual community practice for anticoagulation of patients with AF [10–16]. Accordingly, a review of community practice management of patients with atrial fibrillation showed that target anticoagulation levels are achieved less than half of the time [17], possibly due to challenges in the usual community practice. In the usual community setting there are many challenges that may cause INR measurements to be out of the optimal 2.0–3.0 range, and events continue to occur. Thus, it is essential to examine those patients who did experience events in terms of their outpatient and inpatient INR history.

The purpose of this study was: (1) to characterize and describe a commercially-insured cohort of chronic non-valvular atrial fibrillation patients, treated with warfarin, who had thromboembolic or hemorrhagic adverse events requiring hospitalizations; (2) to examine the quality of INR control while on warfarin therapy; and (3) to determining the prognostic utility of INR monitoring in anticipating future thromboembolic and hemorrhagic events.

Methods

Study population

We conducted a nested case-control study for the overall time-period from October 1, 1998 to March 31, 2003 using a database from a single health plan located in the Southeastern United States and containing approximately 4 million covered lives. The database contains medical and pharmacy administrative claims and outpatient laboratory results which were supplemented with medical chart abstraction.

To be eligible for inclusion, patients must have fulfilled several criteria. First, patients must have had two medical claims for the ICD-9 diagnosis code 427.31 (Atrial Fibrillation). In order to ensure a population of *chronic* AF, the medical diagnostic codes must have occurred at least six weeks apart and at some point between the date range from January 1, 1999 to December 31, 2002. The date of the first medical claim for AF within this date range was called the *index date*. Second, patients must have had a prescription for warfarin filled within 3 months after the index date. Third, patients must have maintained health plan enrollment for a minimum of three months before and after the index date.

Patients were excluded if they had a medical claim for AF or a pharmacy claim for warfarin, in the three months preceding the index date, in order to ensure a naïve patient sample; or if they were less than 18 years old at the index date. All patients with medical claims indicating valvular or rheumatic etiology prior to index date were also excluded. During the chart abstraction phase, charts indicating valvular origin of AF were excluded from the study.

Identification of hospitalizations

Patients were followed longitudinally after the index diagnosis and to the end of benefit eligibility or to the end of the study period (i.e. March 31, 2003), whichever occurred first. Hospitalizations occurring during this study period were identified based on diagnosis codes for stroke, diagnosis codes for major hemorrhage or any other diagnosis codes (i.e. non-stroke, non-bleed), which are referred to as "control" hospitalizations. Additionally, warfarin had to be prescribed within 120 days prior to the subsequent event (or a minimum 1 INR value during the study period). Records were divided into three groups: (1) ischemic strokes and TIAs; (2) bleeding events requiring hospitalization; and (3) hospitalizations for other reasons (control) based on UB-92 codes; *Current Procedure Terminology, Fourth Edition* codes; and ICD-9 codes. Based on sample size calculation, we estimated that 600 total charts would be sufficient to fulfill study objectives. All hospitalization events identified from claims data were narrowed to a subset of patients with events occurring in high-volume hospitals. High-volume hospitals were identified to increase efficiency of chart abstraction.

Chart abstraction

In order to confirm the hospitalization diagnosis, obtain patient demographic information, inpatient laboratory results and inpatient prescription information, a convenience random sample of patients' hospital medical records was abstracted. A chart abstraction instrument was developed to collect the hospitalization diagnosis, related demographics and past medical history. Using the chart abstraction document, diagnoses of stroke/bleed were confirmed and Patients documenting valvular or rheumatic etiology were excluded.

All chart reviewers were trained on the study's design, the instrument, and procedures for completing the chart review in order to ensure consistency of the data collection process. Each patient medical record was abstracted by one abstractor. Abstractors were blinded to patient assignment and were trained to examine and check for the presence/absence of key terms in the provider progress notes section. Paper forms were used to perform medical chart abstractions. Data was key-punched and verified by a separate person for each individual response. The study protocol was reviewed by a central institutional review board which approved a Waiver Authorization Request for the study pursuant to the HIPAA Privacy Rule.

Warfarin exposure and INR intensity

INR monitoring was used as a proxy for length of overall warfarin therapy. Rosendaal's linear interpolation method [18] was applied to calculate the time spent at different INR levels for the entire duration between first INR value and last INR value prior to hospitalization. An INR value was considered to hold true for a maximum of 28 days pre- and post-INR evaluation date. If the duration between two consecutive INR values was less than 56 days, the duration was equally distributed between the two INR values. The time beyond 28 days of an INR value was considered to be of "unknown" INR intensity.

Statistics

Data analysis was conducted to determine descriptive statistics including mean (SD) and median values for continuous data, and relative frequencies for categorical data for this commercially insured cohort of AF patients. Whenever appropriate, outcome variables were assessed using parametric and nonparametric tests. The $CHADS_2$ [19] score index measures stroke risk by assigning 1 point to congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus, and 2 points to patients with a history of stroke or transient ischemic attack. The percentage of time that patients spent at different INR intensities was estimated and tested across stroke, bleed and control events. In addition, INR values obtained upon admission were tested for association with all inpatient events, while INR values obtained before the event were tested for their prognostic utility in predicting events. Further analysis included a stratification of the outpatient INR values before the inpatient event to determine the point at which the INR value becomes predictive of the stroke or bleeding event.

Logistic regression was performed to determine possible associations between inpatient and outpatient INR values and occurrence of stroke or bleed events. It was also performed to evaluate the predictive ability of outpatient INR values at variable time intervals in the pre-event period. Statistical significance was defined *a priori* as $P < 0.05$. The statistical analysis program STATA v8.2 (StataCorp LP, College Station, TX) was used to perform all the analyses.

Results

Population identification and characteristics

The final cohort of patients utilized in this analysis consisted of 470 chronic non-valvular atrial fibrillation patients accounting for 631 hospitalizations overall, divided into the three groups: stroke, bleed, and control based on chart confirmation. (Fig. 1) Seventeen hospitalizations, with both a confirmed stroke and bleed during the hospitalization were excluded from analysis.

Patient characteristics during hospitalization are presented in Table 1. The overall cohort had 304 (48.2%) events that occurred in females. Mean (SD) age was 73.9 (9.6) overall, 76.6 (8.2) in the stroke group, 76.1 in the bleed group, and 72.5 (10.2) in the control group. Overall, 323 events occurred in patients (51.2%) who were older than 75 years of age, while 158 (25%) were older than 80 years of age. The mean age (SD) in the control cohort, 72.5 (10.2), was significantly different from the stroke (76.6 ± 8.2, $p < 0.001$) and bleed (76.1 ± 7.8, $p = 0.0013$) cohorts.

Risk factors for stroke are also presented in Table 1. The average $CHADS_2$ score for all events was 1.9 (1.3), with mean (SD) $CHADS_2$ scores 2.5 (1.3), 1.9 (1.2), and 1.7 (1.3) for the stroke, bleed and control groups, respectively. The $CHADS_2$ score for the stroke and control groups was

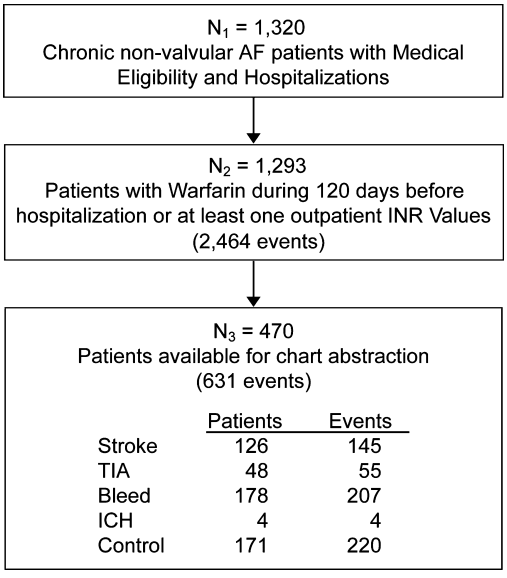

Fig. 1 atrial fibrillation cohort selection

Table 1 Hospitalization characteristics summary

Characteristics	Stroke ($n = 98$)	Bleed ($n = 101$)	Control ($n = 415$)
Mean Age ± SD [median]	76.6 ± 8.2 [78]**	76.1 ± 7.8 [76]*	72.5 ± 10.2 [74]
Range	49–95	48–95	33–95
Male (%)	47 (48.0)	54 (53.5)	221 (53.3)
Race			
Caucasian	70 (71.4)	77 (76.2)	318 (76.6)
African American	5 (5.1)	4 (4.0)	12 (2.9)
Other	4 (4.1)	8 (7.9)	21 (5.1)
Not Reported	19 (19.4)	12 (11.9)	64 (15.4)
Smoking Status (%)		*	
Active or Previous	33 (33.7)	24 (23.8)	167 (40.2)
Non-Smoker	48 (49.0)	58 (57.4)	185 (44.6)
Not Reported	17 (17.3)	19 (18.8)	63 (15.2)
Body Mass Index			
Mean ± SD [median]	26.1 ± 6.1 [25.6]	29.5 ± 22.3 [25.9]	28.5 ± 14.0 [26.6]
Risk Factors for Stroke			
$CHADS_2$ Score ± SD [median]	2.5 ± 1.3 [2]**	1.9 ± 1.2 [2]	1.7 ± 1.3 [2]
Prior Ischemic stroke (%)	40 (40.8)**	11 (10.9)	60 (14.4)
Systemic Embolism (%)	2 (2.0)	7 (6.9)	27 (6.5)
CHF (%)	16 (16.3)	27 (26.7)	94 (22.7)
Prior MI (%)	10 (10.2)	12 (11.9)	48 (11.6)
CHD (%)	36 (36.7)	36 (35.6)	153 (36.9)
Hypertension (%)	70 (71.4)*	57 (56.4)	230 (55.4)
Diabetes (%)	19 (19.4)	20 (19.8)	87 (21.0)
Age ≥ 75 (%)	61 (62.2)*	61 (60.4)*	192 (46.3)

*denotes significance compared with control group at $p < 0.05$ level.
**denotes significance compared with control group at $p < 0.001$ level.

significantly different at $p < 0.001$. Several risk factors, including prior ischemic strokes ($p < 0.001$), hypertension ($p < 0.05$) and proportion of patients older than 75 years ($p = 0.002$) were significantly different in the stroke group versus the control group.

Time in Therapeutic Range (TTR)

The time in range for the overall population was 41.8% at INR less than 2.0, 25.4% at in between 2.0 and 3.0, 20.7% at INR greater than 3.0 and 12.1% of the time which was unknown. The percentage of TTR for the individual three cohorts is presented in Fig. 2. We tested the percentage of time spent at various INR intensities for significant differences between the stroke and bleed groups versus the control. Once these data were analyzed among the three cohorts, no significant differences for TTR between any of them were found. The patients with bleed events spent an average of 25.2% of their time above INR of 3.0, while the stroke cohort had 53.9% of their time under INR of 2.0. The control group spent 28.8% of time between INR 2.0–3.0. Also, there was no statistical significance between any of the three cohorts in terms of time spent at various INR intensities outside of the 2.0–3.0 therapeutic range.

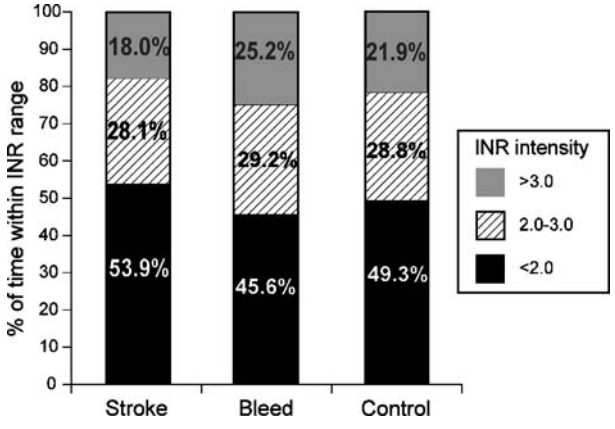

Fig. 2 Time in therapeutic range (extrapolated time)

Correlation between INR monitoring for inpatient and outpatient events

In trying to establish the prognostic utility of inpatient and outpatient INR values, several sub-analyses were conducted. Primarily, the mean number of days from the last outpatient INR until the event was calculated for the three cohorts. Median days from the last outpatient INR until the hospital admission date were 27.5, 21.5, and 24.0 for the stroke, bleed and control groups respectively. Stroke or bleed groups did not produce statistically significant difference from the

Table 2 Association between time of INR value and negative outcome

(Last Outpatient Value vs. First Inpatient Value)

	Last Outpatient INR Values		First Inpatient INR Values	
Event Type	Odds Ratio (95% CI)	*p*-value	Odds Ratio (95% CI)	*p*-value
Stroke				
<2.0	1.20 (0.77–1.88)	0.414	1.68 (1.05–2.67)	0.029
<2.0 (adjusted)*	1.21 (0.75–1.94)	0.431	1.71 (1.07–2.72)	0.024
Bleed				
>3.0	1.15 (0.64–2.08)	0.642	1.90 (1.14–3.18)	0.014
>3.0 (adjusted)**	1.25 (0.67–2.30)	0.483	1.74 (1.03–2.93)	0.038

*Adjusted for age, sex, $CHADS_2$ score, CHF, hypertension.

**Adjusted for age, sex, $CHADS_2$ score, smoking, coagulation defect.

control group. Subsequently, inpatient and outpatient INR values were tested for their association and prognostic utility, respectively.

Inpatient association

Inpatient associations are shown in Table 2 for the first INR value on admission. Patients with first inpatient INR values less than 2.0 had a 68% greater unadjusted and adjusted likelihood of stroke events. In addition, patients with inpatient INR values greater than 3.0 had a 90% and 72% greater unadjusted and adjusted likelihood, respectively, of bleed events.

Outpatient prognostic utility

The outpatient INR values closest in time proximity, but before the stroke or bleed event, were not associated with either event, as shown in Table 2. The patients with last outpatient INR values lower than 2.0 did not have a greater likelihood of having stroke events upon admission, when compared with control hospitalizations on both an unadjusted and adjusted basis. Similarly, there was a lack of an association between the last outpatient INR above 3.0 and bleed events when evaluated on both an unadjusted and adjusted basis.

Sub-analysis of outpatient INR time

In order to determine the time point at which outpatient INR values became predictive of the hospitalization event outpatient days (at which INRs were measured) were stratified. The total time period in days at which an INR value was taken was stratified by quartiles (75^{th}, 50^{th}, 25^{th}). In other words, if a theoretical patient had 100 INR measurements, one on each day before an admission with the first measurement being the most proximal to the admission, then the 25^{th}, 50^{th} and 75^{th} measurement were considered to see if they were associated with the event. These quartiles are presented in Fig. 3. The outpatient INR values lower than 2.0 were not associated with stroke events at any time-point before the hospitalization. Conversely, for outpatient INR values higher than 3.0 a trend was apparent. We also stratified this same time period by week-long increments. Patients had significantly greater likelihood of bleeding at three weeks by 119% (95%CI, 1.08–4.47), at two weeks by 174% (95%CI, 1.17–6.40) and at ten days by 232% (95%CI, 1.21–9.06) when their INR value at that time was greater than 3.0. There was no significant association observed at the one week stratum for bleed events.

Discussion

This nested case-control study of AF patients used one large Southeastern US managed care plan and identified a

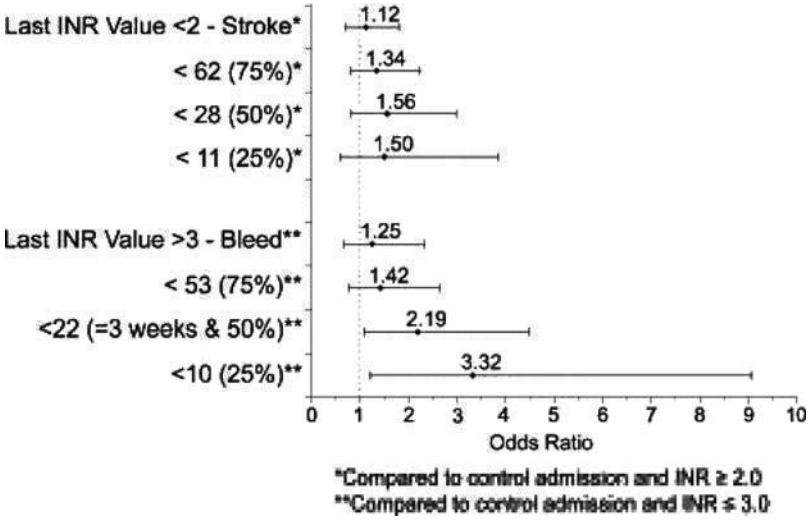

Fig. 3 Adjusted odds of adverse events stratified by days from last outpatient INR measurement

randomized subset of 631 medical records. These were used to characterize and describe the quality of outpatient INR monitoring in those patients that experienced thromboembolic or hemorrhagic events. Outpatient TTR and predictive associations between outpatient versus inpatient INR values and stroke and bleed hospitalizations were estimated.

Basic demographic characteristics for the overall cohort indicate that this population was probably clinically severe and therefore more difficult to manage. For instance, the average age was 73.9, in the stroke group about 40% of patients had prior ischemic stroke, greater than 25% had a $CHADS_2$ score of $\geq$3, including 10% with $CHADS_2$ score of $\geq$4. Considering their age and related co-morbidities, these patients were more difficult to treat and had higher risk for recurrent events, since $CHADS_2$ score of 4, 5 and 6 correspond with adjusted stroke rates of 8.5, 12.5 and 18.2 [19,20].

One important finding was that of the relative percentage of time where patient's INR ranged was correlated to the reason for hospitalization, even though it was not statistically significant. For example, patients in the Stroke group spent the highest percentage (53.9%) of the time below INR 2.0, relative to the Control and Bleed groups. Eventually, this resulted in hospitalizations for strokes. In addition, this cohort showed that stroke patients spent an average of 71.9%, bleed patients spent 70.8%, and control patients spent 71.2% of their time outside of the confirmed 2.0–3.0 therapeutic range. There are many possible factors resulting in the population spending extensive period of time outside of therapeutic range [21].

Some of the common challenges associated with warfarin therapy in the usual community setting may cause INR measurements to be out of the optimal 2.0–3.0 range. Some of the barriers include: (1) a narrow therapeutic window; (2) considerable variability in dose response among subjects; (3) numerous drug-drug and drug-food interactions; (4) laboratory control that is difficult to standardize; and (5) problems with dosing as a result of patient non-adherence and miscommunication between the patient and physician [21]. Accordingly, a review of community practice management of patients with atrial fibrillation showed that target anticoagulation levels are achieved less than half of the time [22,23], possibly due to these challenges in usual community practice. While frequent INR monitoring can help to ensure that patients are maintained in the optimal INR range, it is not always achieved [21].

When results from this study are compared to those observed in prior observational studies, it is evident the patients in our study spend a higher proportion of time outside of the target INR intensity across all cohorts. Although, prior observational studies reporting higher TTR were conducted in specialized anti-coagulation clinics that may have substantially different care patterns, patient characteristics, and health provider motivations as compared to the "real world" community setting as represented in this study cohort. For example, in a previous study evaluating quality of anticoagulation, while patients with access to an anti-coagulation clinic spent 60.3% of TTR, patients without access to anticoagulation clinic spent only 35.6%–46.9% TTR (comparable to the TTR observed in this study) [17]. In addition, our study included warfarin naïve patients while some of the previous studies included a cross-section of warfarin naïve and long-term warfarin users. It is well known during initial period of treatment (i.e. prior to stabilization of a patient on warfarin), patients can potentially remain outside of therapeutic range. Finally, INR measurements recorded at 'out-of-network' locations were not available in our laboratory database. Although, it is difficult to quantify both number of patients or measurements missed, we believe the impact may have been minimal. In an earlier study in a similar commercially insured population, approximately 6% of the laboratory measurements were missed on account of out-of-network providers [27].

Upon examining the relationships between inpatient versus outpatient INR values, a clear and significant association was found between inpatient INR values less than 2.0 and stroke events. The same clear association was found as well for INR values greater than 3.0 and bleed events (1.90 and 1.72 adjusted). These results support previous work which also found a correlation of bleed or stroke diagnosis with admission INR [25].

This association did not exist for outpatient INR values. When the outpatient INR values were stratified by weeks, a significant association was found for only outpatient INR values collected between three weeks to ten days before the event, and only with regard to bleeding events. In addition, outpatient INR values were not associated even though there was enough power to detect the difference. This was likely because the mean time from the last outpatient INR value until the hospitalization was more than six weeks for all three cohorts, and more than eight weeks in the stroke cohort (stroke = 59.1, bleed = 51.6, control = 47.0). Published literature suggests that patients who are receiving warfarin therapy, should be monitored no less than every 4 weeks, and more frequently in patients who exhibit an unstable dose response [21].

Our results did not collect event rates and do not dispute the absolute efficacy or safety of warfarin in preventing stroke in AF patients as proven in controlled trials. However the implications of controlled trial results for the "real world" clinical practice are not as clear as those presented in randomized trials. Due to small proportions of enrollment of screened patients, relatively few elderly patients and use of extremely cautious and frequent monitoring of anticoagulation intensity [2,24,26] the results observed in the controlled clinical trials may not be replicated in "real world" community setting unless there is improved monitoring.

In the clinical practice setting, perhaps the most recent and best designed study in the United States was conducted by Go et al., the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. The community-based cohort of 13,559 ambulatory adults with non-valvular AF was followed up for anticoagulation therapy and clinical outcomes. The study showed significant effectiveness and relative safety of oral anticoagulation in patients with AF treated in this setting, with the caveat that high levels of INR monitoring were possible due to specialized pharmacists or nurses in anticoagulation clinics in approximately 80% of the patients [27]. Good clinical management is possible, although the results in the ATRIA study may not be applicable to other care settings [15]. Further, even in studies with more general clinical settings, and a population more similar to this one in terms of age and stroke risk factors, anticoagulation services may not be totally effective [28].

This study has several limitations. The retrospective design allows for association to be made only between variables of interest and outcomes. As well, during subset analysis the lack of sample size lead to wide CI reducing our capability to make precise inferences. Misclassification or coding errors in administrative claims data have been well documented [29]. This issue is most critical for the seventeen events that were coded with both non-valvular AF and bleeding event. Since this data set included only events that were abstracted, the proportion of patients that had access to or lacked anticoagulation management services is not known. It is fair to suggest that this patient population represented the general clinical setting and thus shared some similarities with the Managing Anticoagulation Services Trial (MAST) [28]. The MAST demonstrated that when anticoagulation services were available, they successfully managed anticoagulation in AF patients, although the average improvement in time in target range showed only modest benefits [9,28]. This lack of effect was attributed to local challenges that need to be overcome before the service can be assured to have long-term success [9]. Since this patient population was predominantly Caucasian, the results may not be generalized to African American, Hispanic, Native American or other groups.

Conclusion

The results from this analysis show that AF patients taking warfarin who had hospitalizations for strokes, bleeds or other reasons, spent more than 70% of time outside of the therapeutic range. There was a correlation between the inpatient INR at the time of event and adverse outcome. The outpatient INR values greater than 3.0 and collected between 10 days up to three weeks prior, also appear to be predictive of bleed hospitalizations. However, any single outpatient INR appears not to predict individual patients at risk for adverse thromboembolic outcomes for outpatient INR values less than 2.0. There remains great potential to improve the quality of care delivered, which potentially could decrease the incidence of stroke and bleeding episodes, and thus improve outcomes in patients with AF.

Acknowledgments The authors wish to thank J. Matthew Groesbeck for his help in the preparation of this manuscript. This study was funded by a grant from AstraZeneca, LP. The authors have no conflict of interest outside this financial support to disclose.

References

1. American Heart Association (2004) Heart Disease and Stroke Statistics—2004 Update. AHA 2–50
2. Singer DE, Albers GW, Dalen JE, et al. (2004) Antithrombotic therapy in atrial fibrillation: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 126:429S–456S
3. Diringer MN, Edwards DF, Mattson DT, et al. (1999) Predictors of acute hospital costs for treatment of ischemic stroke in an academic center. Stroke 30:724–728
4. (1990) The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. N Engl J Med 323:1505–1511
5. (1993) Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. Lancet 342:1255–1262
6. (1996) Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. Lancet 348:633–638
7. Ezekowitz MD, Bridgers SL, James KE, et al. (1992) Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. N Engl J Med 327:1406–1412
8. Levine MN, Raskob G, Beyth RJ, Kearon C, Schulman S (2004) Hemorrhagic complications of anticoagulant treatment: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 126:287S–310S
9. Matchar DB (2003) Do anticoagulation management services improve care? Implications of the Managing Anticoagulation Services Trial. Card Electrophysiol Rev 7:379–381
10. Aronow WS, Ahn C, Kronzon I, Gutstein H (1999) Incidence of new thromboembolic stroke in persons 62 years and older with chronic atrial fibrillation treated with warfarin versus aspirin. J Am Geriatr Soc 47:366–368
11. Caro JJ, Flegel KM, Orejuela ME, et al. (1999) Anticoagulant prophylaxis against stroke in atrial fibrillation: effectiveness in actual practice. CMAJ 161:493–497
12. Evans A, Perez I, Yu G, Kalra L (2001) Should stroke subtype influence anticoagulation decisions to prevent recurrence in stroke patients with atrial fibrillation? Stroke 32:2828–2832
13. Evans A, Kalra L (2001) Are the results of randomized controlled trials on anticoagulation in patients with atrial fibrillation generalizable to clinical practice? Arch Intern Med 161:1443–1447
14. Gage BF, Boechler M, Doggette AL, et al. (2000) Adverse outcomes and predictors of underuse of antithrombotic therapy in medicare beneficiaries with chronic atrial fibrillation. Stroke 31:822–827
15. Go AS (2004) Efficacy of anticoagulation for stroke prevention and risk stratification in atrial fibrillation: translating trials into clinical practice. Am J Manag Care 10:S58–S65

16. Kalra L, Yu G, Perez I, Lakhani A, Donaldson N (2000) Prospective cohort study to determine if trial efficacy of anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness. BMJ 320:1236–1239
17. Samsa GP, Matchar DB, Goldstein LB, et al. (2000) Quality of anticoagulation management among patients with atrial fibrillation: results of a review of medical records from 2 communities. Arch Intern Med 160:967–973
18. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E (1993) A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 69:236–239
19. Gage BF, Waterman AD, Shannon W, et al. (2001) Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 285:2864–2870
20. Bushnell CD, Matchar DB (2004) Pharmacoeconomics of atrial fibrillation and stroke prevention. Am J Manag Care 10:S66–S71
21. Ansell J, Hirsh J, Poller L, et al. (2004) The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 126:204S–233S
22. Casey M, Hanley K (2001) A measurement of the efficacy of anticoagulation monitoring in a general practice based setting. Ir Med J 94:245–246
23. Willey VJ, Bullano MF, Hauch O, et al. (2004) Management patterns and outcomes of patients with venous thromboembolism in the usual community practice setting. Clin Ther 26:1149–1159
24. (1991) Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation study: final results. Circulation 84:527–539
25. Hylek EM, Go AS, Chang Y, et al. (2003) Effect of Intensity of Oral Anticoagulation on Stroke Severity and Mortality in Atrial Fibrillation. NEngl J Med 349:1019–1026
26. (1994) Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 154:1449–1457
27. Go AS, Hylek EM, Chang Y, et al. (2003) Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? JAMA 290:2685–2692
28. Matchar DB, Samsa GP, Cohen SJ, Oddone EZ, Jurgelski AE (2002) Improving the quality of anticoagulation of patients with atrial fibrillation in managed care organizations: results of the managing anticoagulation services trial. Am J Med 113:42–51
29. Armstrong EP, Manuchehri F (1997) Ambulatory care databases for managed care organizations. Am J Health Syst Pharm 54:1973–1983