Impact of Co-morbidities and Patient Characteristics on International Normalized Ratio Control Over Time in Patients With Nonvalvular Atrial Fibrillation☆

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This study determined the association between co-morbidities, including heart failure (HF) and time in therapeutic range (TTR), in patients with nonvalvular atrial fibrillation. Longitudinal patient-level anticoagulation management records collected from 2006 to 2010 were analyzed. Adult patients with nonvalvular atrial fibrillation who used warfarin for a 12-month period with no gap of >60 days between visits were identified. TTR <55% was defined as "lower" TTR. $CHADS_2$ score of ≥2 was defined as "higher" $CHADS_2$. Logistic regression analyses were conducted to determine the association between co-morbidities and TTR. A total of 23,425 patients met the study criteria. The mean age ± SD was 74.8 ± 9.7 years, with 84.8% aged ≥65 years. The most common co-morbidities were hypertension (41.7%), diabetes (24.1%), HF (11.7%), and previous stroke (11.1%). The mean TTR ± SD was 67.3 ± 14.4%, with 18.6% of patients in the lower TTR range. In multivariate analyses using age, gender, hypertension, diabetes, stroke, and region as covariates, HF (adjusted odds ratio [OR] 1.41, 95% confidence interval [CI] 1.28 to 1.56; p <0.001), diabetes (OR 1.28, 95% CI 1.19 to 1.38; p <0.001), and previous stroke (OR 1.15, 95% CI 1.04 to 1.27; p <0.001) were associated with lower TTR. In a second set of multivariate analyses using gender and region as covariates, a higher $CHADS_2$ score was associated with lower TTR (OR 1.11, 95% CI 1.04 to 1.18; p <0.001). In conclusion, HF was associated with the greatest likelihood of a lower TTR, followed by diabetes, then stroke. Anticoagulation control may be more challenging for patients with these conditions. **(Am J Cardiol 2013;112:509−512)**

Until recently, vitamin K antagonists such as warfarin were the only efficacious oral anticoagulants available for the prevention of embolic events in patients with nonvalvular atrial fibrillation (NVAF) at high risk of stroke.[1,2] For most patients on long-term warfarin therapy, an international normalized ratio (INR) of 2.0 to 3.0 is the recommended range for prevention of stroke and systemic embolism[3]; this level of anticoagulation has been shown to translate to improved outcomes in patients with NVAF.[4,5] Time spent in therapeutic range (TTR), a measure used to describe the quality of INR control in clinical practice, also correlates with improved patient outcomes.[6,7] Thus, characterizing TTR and the variables that can influence it, may be helpful in identifying challenges to optimal anticoagulation and improving anticoagulation strategies. The present analysis sought to determine the association among co-morbidities, patient characteristics, and TTR in patients with NVAF whose INR was managed by anticoagulation clinics in the United States.

Methods

This study used longitudinal patient-level anticoagulation management records collected from 2006 to 2010 by the decision support software CoagClinic (Standing Stone, Inc., Westport, Connecticut). This software is used by a large number of institutions (mostly hospital-based) in 49 states. As of December 2010, this system contained data on ∼400,000 patients; this is the largest database of patients receiving anticoagulation therapy.

Because the data were intended to be used for clinical purposes, the International Classification of Diseases 9th Revision, Clinical Modification codes used for medical claims were not included. Therefore, all the data fields were converted into International Classification of Diseases 9th Revision, Clinical Modification format to extract co-morbidity information.

Adult patients with NVAF who used warfarin for ≥1 year with no gap of >60 days between anticoagulation clinic visits

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See page 512 for disclosure information.

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Table 1
Patient demographic and baseline characteristics

Characteristic	Total, n = 23,425 (%)
Age (yrs)	
18 to <65	3,572 (15.3)
65 to <75	6,432 (27.5)
≥75	13,421 (57.3)
Women	10,864 (46.4)
Men	12,556 (53.6)
$CHADS_2$ score	
0	3,890 (16.6)
1	8,736 (37.3)
2	6,403 (27.3)
3	2,841 (12.1)
4	1,154 (4.9)
5	346 (1.5)
6	55 (0.2)
Co-morbidities	
Heart failure	2,733 (11.7)
Hypertension	9,765 (41.7)
Diabetes mellitus	5,636 (24.1)
Previous stroke	2,593 (11.1)
United States region	
Northeast	6,447 (27.5)
Midwest	6,673 (28.5)
West	4,385 (18.7)
South	4,965 (21.2)

Table 2
Impact of demographics and co-morbidities on likelihood of lower time in therapeutic range

Characteristic	OR (95% CI)	p
Age ≥75 (vs <75) (yrs)	0.94 (0.88−1.01)	NS
Men (vs women)	0.78 (0.73−0.83)	<0.001
United States region		
Northeast	1.00 (Referent)	—
West	1.39 (1.26−1.54)	<0.001
South	1.38 (1.26−1.52)	<0.001
Midwest	1.04 (0.95−1.14)	NS
Co-morbidities (vs not present)		
Heart failure	1.41 (1.28−1.56)	<0.001
Diabetes	1.28 (1.19−1.38)	<0.001
Previous stroke	1.15 (1.04−1.27)	0.0075
Hypertension	0.86 (0.80−0.93)	<0.001

CI = confidence interval; OR = odds ratio.

were identified; this criterion is in alignment with standard clinical practice, in which regular weekly, bimonthly, or monthly visits are recommended. Subjects with valvular atrial fibrillation were excluded. TTR was calculated according to the Rosendaal method, which uses linear interpolation to assign an INR value to each day between successive observed INR values.[8] This approach, which assumes that INR is gradually increasing or decreasing between measurements, will produce a percentage of days when the INR measurements are within a prespecified range. TTR was calculated for interpolated INR values within the recommended therapeutic range of 2.0 to 3.0.

Two sets of independent logistic regression analyses were conducted. The first set was conducted to determine the association between TTR and co-morbidities, including

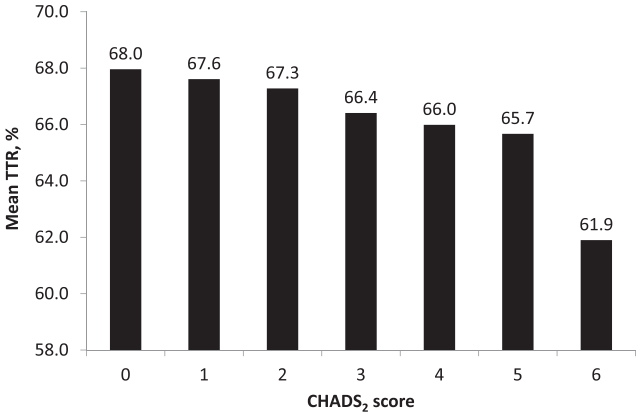

Figure 1. The relation between TTR and $CHADS_2$ score (0 to 6).

Table 3
Impact of $CHADS_2$ score on likelihood of lower time in therapeutic range

Characteristic	OR (95% CI)	p
$CHADS_2$ score ≥2 (vs <2)	1.11 (1.04−1.18)	0.003
Men (vs women)	0.80 (0.75−0.85)	<0.001
United States region		
Northeast	1.00 (Referent)	—
West	1.43 (1.29−1.58)	<0.001
South	1.39 (1.27−1.53)	<0.001
Midwest	1.06 (0.96−1.16)	NS

CI = confidence interval; OR = odds ratio.

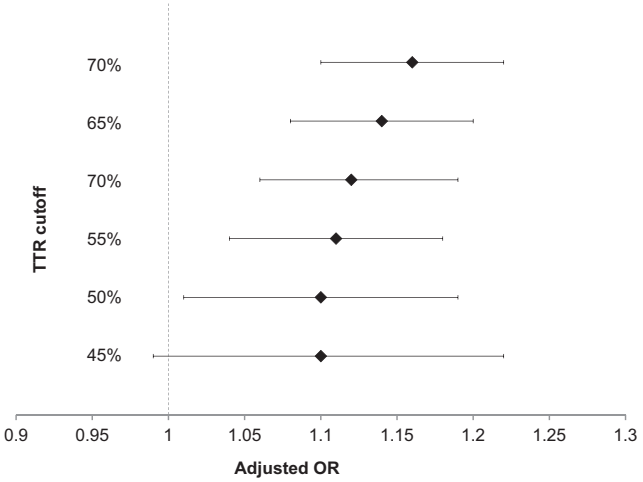

Figure 2. Sensitivity analysis of the relation between $CHADS_2$ score and TTR cut-off point used to define lower range. Analyses were performed for 6 different TTR cut-off points: 45%, 50%, 55%, 60%, 65%, and 70%. These cut-off points defined high and low TTR values. Adjusted odds ratios (ORs) >1 indicate that a $CHADS_2$ score ≥2 was associated with lower TTR. The adjusted ORs are statistically significant when the 95% confidence intervals (CIs) exclude 1.

heart failure (HF), hypertension, diabetes, and previous stroke. "Lower" TTR was defined as <55%. The second set was conducted to determine the association between TTR and $CHADS_2$ score—a cumulative point-based scoring system. We used $CHADS_2$ scoring rather than CHA_2DS_2-VASc, as it is more widely used in the United States despite CHA_2DS_2-VASc being more inclusive in Europe, and it is stipulated as the primary approach for stratifying stroke risk

in patients with NVAF in the most current American College of Chest Physicians guidelines.[9]

The $CHADS_2$ system assigns 1 point for each of the following: presence of HF, presence of hypertension, age $\geq$75 years, and presence of diabetes. Two points are assigned for a history of stroke or a transient ischemic attack. In the present study, a "higher" $CHADS_2$ score was defined as $\geq$2.

Sensitivity analyses were conducted using TTR cut-off points at 45%, 50%, 55%, 60%, 65%, and 70% to determine the impact of different definitions of low and high TTR on the relation between $CHADS_2$ scores and TTR.

Results

A total of 23,425 patients met the study criteria. Patients had a mean age of 74.8 $\pm$ 9.7 years, with 84.8% aged $\geq$65 years. More than 1/2 (53.9%) of patients had a $CHADS_2$ score <2. Patient demographics are listed in Table 1.

The most common co-morbidities were hypertension, diabetes, HF, and previous stroke. The mean TTR $\pm$ SD was 67.3 $\pm$ 14.4%, with 18.6% of patients in the lower TTR range. Using age, gender, hypertension, diabetes, stroke, and region as covariates, multivariate analysis (Table 2) revealed that increased risk for having a lower TTR was significantly and independently associated with HF, diabetes, and previous stroke. Patients in the Western and Southern regions of the United States were significantly more likely to have lower TTR values than those in the Northeast region (Table 2). Male patients had a lower likelihood of having a lower TTR (Table 2); conversely, female patients were at an increased risk for having lower TTR values. Neither older age ($\geq$75 years) nor location in the Midwest (as compared with the Northeast) was independently associated with the likelihood of lower TTR in this analysis.

A negative correlation between $CHADS_2$ scores and TTR is shown in Figure 1; the highest $CHADS_2$ score, 6, was associated with the lowest TTR. In the second multivariate analysis using gender and region as covariates (Table 3), a higher $CHADS_2$ score, defined as $\geq$2, was significantly associated with a lower TTR. As in the first multivariate analysis, patients in the Western and Southern regions of the United States were significantly more likely to have lower TTR values than those in the Northeast region (Table 3). Male patients also continued to have a lower likelihood of having a lower TTR compared with female patients (Table 3).

Sensitivity analyses on the impact of different definitions of low and high TTR on the relation between $CHADS_2$ scores and TTR found the results of our analysis to be consistent. Depending on the TTR cut-off points used to define lower TTR, estimates of the odds ratio of higher $CHADS_2$ associated with lower TTR ranged from 1.1 to 1.16 (Figure 2).

Discussion

Although TTR is routinely assessed, there is a lack of a consensus on an acceptable TTR. For the purpose of our analysis, the cut-off point for TTR was defined as 55% in alignment with the meta-analysis by Baker et al.[7] By this definition, approximately 19% of patients included in the analysis were found to have a lower TTR. Patients with a higher $CHADS_2$ score and co-morbidities—specifically, diabetes, stroke, and HF—were more likely to have a lower TTR. We may hypothesize that a lower TTR found in patients with co-morbidities, such as diabetes, could be associated with concomitant chronic kidney disease, which is known to reduce anticoagulation stability.[10]

This analysis supports observations from previous research.[6,11–16] In a retrospective cross-sectional study of patients with atrial fibrillation in Israel treated with warfarin for $\geq$6 months, HF and female gender were significant predictors of low TTR, defined as TTR <60%.[11] Moreover, diabetes and stroke were also significantly associated with lower TTR. Interestingly, patients with excellent anticoagulation control (defined as TTR >75%) were less likely to have these co-morbidities. Substantial co-morbidities (39% had diabetes and 31% had HF) were also found in patients with low TTR in 100 United States Veteran Affairs sites; patients from these sites, adjusted for the lowest predicted TTR, had several-fold higher rates of co-morbidities compared with patients from sites with the highest predicted TTR.[17]

Conflicting results exist regarding age and its association with anticoagulation control. The Cardiovascular Research Network WAVE (Warfarin for AF or VTE) analysis found that age >50 years was a predictor of not having a low TTR, and the retrospective study in Israel found older age to be associated with a lower TTR,[11,18] whereas our study found no age association. We hypothesize that the lack of age association in our study is a consequence of stricter adherence to the anticoagulation regimen among older compared with younger patients, as a result of their greater experience in taking medicines. Younger patients also tend to perceive themselves as healthier and thus may be less likely to adhere to their medication regimen. To further quantify our findings of no age association, we recomputed the primary logistic regression model with age as a continuous variable instead of a dichotomized variable. The odds ratios of the co-morbidities did not change, and no statistical or clinical significance was found between TTR and increasing age. The use of the secondary model was thus omitted from the final analyses. Given the high prevalence of co-morbidities in patients with NVAF, their potential association with lower TTR is of note. In this study, HF was associated with the greatest likelihood of a lower TTR, followed by diabetes, then previous stroke. Anticoagulation control may be more challenging for patients with these co-morbidities; therefore, strategies should be undertaken by the clinician to improve TTR in these patients. Because the patients in our study attended anticoagulation clinics regularly and received specialized care, we believe that lower TTR was not a consequence of a lack of strict INR control. We therefore hypothesize that for such complex patients, adjusting the anticoagulation regimen, for example by implementing novel oral anticoagulant agents, might improve the quality of anticoagulation care.

The limitations of our study include its retrospective observational nature and potentially incomplete data records, which may fail to report preexisting co-morbidities or may not be generalized to patients managed in settings other than

anticoagulation clinics. In this analysis, any misclassification would most likely reflect unreported co-morbidities, that is a patient with a co-morbidity being classified as not having one. Underreporting would bias our odds ratio findings toward the null hypothesis; thus, our findings may be more conservative than the true value. Other factors that may contribute to lower TTR, such as adherence to prescribed anticoagulant regimens, were not evaluated, because the information was not included in the database.

In summary, common co-morbidities that accompany NVAF are associated with lower TTR. HF is associated with the greatest likelihood of a lower TTR, followed by diabetes, then previous stroke. Anticoagulation control may be more challenging for patients with these conditions. As a result, clinicians should pay special attention to patients with NVAF who have co-morbid conditions.

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Disclosures

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