Quality of anticoagulation with warfarin in patients with nonvalvular atrial fibrillation in the community setting

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Abstract

Background: The benefit of oral anticoagulation therapy with warfarin for stroke prevention in atrial fibrillation (AF) is directly dependent on the quality of anticoagulation (QoA), which in the US is provided predominantly in the community setting. With the emergence of new oral anticoagulation agents, the current QoA needs to be assessed.

Objectives: The purpose of our study is to define the QoA with warfarin in patients with nonvalvular AF who are managed exclusively in community practices, and to compare the quality in the community setting with the quality demonstrated in the recent large randomized control trials. In addition, this study will assess the differences in the QoA based on cardiology vs primary care practices.

Methods: This is a retrospective, observational, multi-center study of 392 patients with AF in the community who were initiated on anticoagulation with warfarin for stroke prevention. International Normalized Ratio (INR) values were collected over a one-year period and the QoA was expressed as time in therapeutic range (TTR) calculated by the linear interpolation method.

Results: One hundred patients from cardiology practices and 292 patients from primary care were studied. During the one-year period, the overall mean TTR was 56.7%. The TTR in the primary care vs cardiology practices was 55.3% vs. 60.8% (p=0.02). Both practices had similar percent of time below therapeutic range, 29.8% vs. 29.2%. However, the primary care practice patients were above the therapeutic range 15% of the time vs. 10% in cardiology (p<0.001). There were one death secondary to intracranial bleed and one major bleed in the primary care group. There were no strokes during the study period in either group.

Conclusion: The QoA with warfarin, as assessed by TTR, in the current community setting remains suboptimal, and there has been little to no improvement in current clinical practices. TTR should be considered when assessing the recent comparative studies evaluating novel pharmacologic agents to warfarin for the treatment of AF.

Subject Areas: Arrhythmias, preventive cardiology, anticoagulation, thromboembolism, cardiovascular disease risk factors.

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Keywords: Anticoagulants; Warfarin; VKA; INR; Atrial fibrillation; Stroke prevention and time in therapeutic range

Introduction

Atrial fibrillation (AF) affects approximately 2.3 million adults with a prevalence exceeding 10% among those aged 75 years and older.1,2 AF increases the risk for ischemic stroke nearly 5-fold3 and accounts for approximately 15% of...
all strokes nationally. Furthermore, stroke in AF patients is associated with greater morbidity, mortality, and costlier hospital stays than in stroke patients without AF, independent of age.

Randomized controlled trials (RCTs) have demonstrated that dose-adjusted warfarin reduces the risk of an ischemic stroke by up to 68% compared with no therapy. Despite its proven efficacy in stroke prevention, warfarin remains underused secondary to the following challenges: narrow therapeutic range, highly variable interpatient response, numerous drug and food interactions, requirement for serial laboratory monitoring, and risks related to nonadherence. In addition to under-prescribing warfarin, a wide variation in percentage of time in therapeutic range (TTR), 29%–75%, has been reported.

Insufficient anticoagulation therapy can increase the risk of ischemic stroke and excessive anticoagulation can increase the risk of bleeding events, including intracranial hemorrhage. The post hoc analysis of TTR values in ACTIVE-W suggested that with a TTR below 58%, oral anticoagulation (OAC) showed little, if any, benefit over antiplatelet therapy for prevention of vascular events. Suboptimal TTR values, defined as <58%, can prompt interventions, such as increasing patient education, referral to anticoagulation specialty services, and now have the choice of alternative oral anticoagulant agents.

Although some providers have specialized anticoagulation clinics dedicated exclusively to the management of warfarin dosing, in the United States, OAC is managed predominantly by internists and family physicians. We undertook the study to define the current quality of anticoagulation with warfarin in patients with nonvalvular AF in a community practice and to identify if differences exist between the quality of anticoagulation when managed in a cardiology practice versus the primary care practice setting.

Statistical analysis

Demographic and clinically relevant medical history data were recorded for each patient. Continuous data were reported as mean±standard deviation and were compared using Student’s t-test. Categorical data were reported as n (%) and were compared using the Chi-squared test.

The primary endpoint of this study was the TTR. The primary objective of this study was to observe whether the overall mean TTR was less than 58%. One-sample Students’ t tests were conducted to evaluate this primary objective. The secondary objective was to compare the distribution of TTR values between primary care patients and cardiology patients. This was done by performing a two-sample Students’ t test comparing the mean TTR of the primary care patients to the mean TTR of the cardiology patients.

Results

We enrolled 100 patients at 10 cardiology practices and 292 patients at 30 primary care practices. The demographics are listed in Table 1. The mean age of the population was 73 years with the majority being Caucasian. Most subjects had hypertension. There were more patients with prior MI in
the cardiology practices, 23% vs. 13% (p=0.02). The overall mean CHADS2 score (Cardiac Failure, Hypertension, Age, Diabetes, Stroke) was 2.1.22

Both groups had approximately equal frequency of INR testing with an average of 18.1 INR tests per patient in cardiology vs. 18.0 in primary care over the preceding year [Table 2]. The mean patient INR values within a one-year period in the cardiology practice were 2.33 vs. 2.44 in the primary care practice (p=0.006). Overall, the mean TTR in cardiology was 60.8% vs. 55.3% in primary care (p=0.02). Both practices had similar percent of time below the therapeutic range, 29.2% vs. 29.8% [Table 3]. However, the cardiology practice patients were above the therapeutic range 10% of the time vs. 15% in the primary care practices (p<0.001).

Patients were maintained on warfarin therapy 95.4% of the time [Table 2]. A total of 18 patients (4.6 %) stopped warfarin therapy, 3 (3%) in cardiology and 15 (5.1%) in primary care. Therapy was most commonly stopped in order to add antplatelet therapy. There were 2 deaths in the primary care cohort, one secondary to intracranial hemorrhage and one secondary to MI. There were no strokes during the study period in either group. The INR was 8.3 at the time of the intracranial bleed. One major gastrointestinal bleed was reported in the primary care practice.

Discussion

The primary finding of this study is that patients with nonvalvular atrial fibrillation treated with warfarin were in the therapeutic INR range approximately half the time, 56.7%. Cios et al.23 and Baker et al.24 found similar results in their meta-analyses of all published randomized trials and cohort studies in the US. In evaluating the quality of management of warfarin in AF patients in both anticoagulation clinics and community practices, the overall mean time in therapeutic INR was 57% and 55%, in their respective studies. When evaluating settings, both studies found that community management resulted in 11%–13% less time in the therapeutic range (p<0.001) compared to

Table 1
Demographics.

<table>
<thead>
<tr>
<th>Race/Other</th>
<th>Cardiology Practice (N=100)</th>
<th>Primary Care Practice (N=292)</th>
<th>Total (N=392)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian or White</td>
<td>90 (90.0%)</td>
<td>252 (86.3%)</td>
<td>342 (87.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Native American or Alaska Native</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Asian (Oriental)</td>
<td>1 (1.0%)</td>
<td>3 (1.0%)</td>
<td>4 (1.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Asian (Other)</td>
<td>13 (1.0%)</td>
<td>2 (0.7%)</td>
<td>3 (0.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Black</td>
<td>3 (3.0%)</td>
<td>23 (7.9%)</td>
<td>26 (6.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hispanic (Latino)</td>
<td>5 (5.0%)</td>
<td>11 (3.8%)</td>
<td>16 (4.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Medical History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>82 (82.0%)</td>
<td>244 (83.6%)</td>
<td>326 (83.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>28 (28.0%)</td>
<td>80 (27.4%)</td>
<td>108 (27.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart Failure or Left Ventricular Dysfunction</td>
<td>31 (31.0%)</td>
<td>85 (29.1%)</td>
<td>116 (29.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke / Transient Attack</td>
<td>13 (13.0%)</td>
<td>41 (14.0%)</td>
<td>54 (13.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>23 (23.0%)</td>
<td>38 (13.0%)</td>
<td>61 (15.6%)</td>
<td>0.017</td>
</tr>
<tr>
<td>Mean CHADS2 score</td>
<td>2.2</td>
<td>2.1</td>
<td>2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>101.7</td>
<td>101.6</td>
<td>101.6</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine Clearance (ml/min)</td>
<td>75.9</td>
<td>73.5</td>
<td>74.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

* NS=nonsignificant p-value>0.05; N=number of patients.

Table 2
Warfarin therapy.

<table>
<thead>
<tr>
<th>Practice</th>
<th>Cardiology Practice (N=100)</th>
<th>Primary Care Practice (N=292)</th>
<th>Total (N=392)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean INR During 1 Year Period</td>
<td>2.33</td>
<td>2.44</td>
<td>2.41</td>
<td></td>
</tr>
<tr>
<td>Mean Total Weekly Starting Dose of Warfarin (mg)</td>
<td>26.8</td>
<td>31.2</td>
<td>30.0</td>
<td></td>
</tr>
<tr>
<td>Mean Total Weekly Ending Dose of Warfarin (mg)</td>
<td>31.5</td>
<td>32.4</td>
<td>32.2</td>
<td></td>
</tr>
<tr>
<td>Warfarin Therapy Permanently Stopped Prior to or at End of Chart Review Period</td>
<td>2/3 (66.7%)</td>
<td>5/18 (27.8%)</td>
<td>7/21 (33.3%)</td>
<td></td>
</tr>
</tbody>
</table>

* Counts and denominators for the primary reason that warfarin therapy was permanently stopped include both the number of subjects that permanently stopped and those where it was unknown.

Table 3
Time Therapeutic Range (TTR).

<table>
<thead>
<tr>
<th>Practice</th>
<th>Cardiology Practice (N=100)</th>
<th>Primary Care Practice (N=292)</th>
<th>Total (N=392)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR</td>
<td>60.8</td>
<td>55.3</td>
<td>56.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Percent Below Therapeutic Range</td>
<td>29.2</td>
<td>29.8</td>
<td>29.6</td>
<td>NS</td>
</tr>
<tr>
<td>Percent Above Therapeutic Range</td>
<td>10.0</td>
<td>15.0</td>
<td>13.7</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* NS=nonsignificant p-value>0.05.
anticoagulation clinics. The relevance of these findings is highlighted by Connolly et al., who concluded that a TTR < 58% provides no benefit over dual antiplatelet therapy in prevention of vascular events. Several reports indicate an association between low TTR (< 60%) and increased rates of both vascular events and major hemorrhage in patients on OAC. It has been estimated that a 10% increase in time outside the therapeutic range is associated with a 29% increased risk of mortality, a 10% increased risk of ischemic stroke and a 12% increased risk of all thromboembolic phenomena. In contrast, TTR in RCTs and anticoagulation clinics seems to be higher (64%–87%) than in ordinary practices. However, in the recently completed ROCK-ET AF trial the mean TTR was only 55%. Some RCTs probably achieve better INR control because they use stricter protocols, employ more scrutiny of trial subjects which could improve compliance, and can include non-representative patient groups, compared to ‘real-life’ settings.

The study also identified that there is a difference between primary and cardiology practices in maintaining TTR, with cardiology practices having a significant higher TTR at 60.8% versus 55.3% for primary care. Although the difference may seem small, cardiology practices crossed the identified threshold of 58% that has been previously identified as being required to provide a benefit from oral anticoagulation therapy. The difference was almost entirely due to more time spent above the therapeutic range in the primary care practices, possibly increasing their bleeding risks.

The explanation for the better anticoagulation control among the cardiology practices compared to primary care practices can not be answered from this study, however, previous studies have found similar results. Nieuwlaat et al., found that cardiology practices utilized anticoagulation algorithms more frequently than primary care practices (61% vs 29%). In contrast, primary care practices tend to manage warfarin based mostly on personal experience. In one study, use of simple warfarin dosing algorithms has been shown to increase overall TTR by 11%.

Several methods to improve anticoagulation management have been studied. Dolan et al., found that studies employing frequent monitoring and those using highly organized anticoagulant services reported a greater mean time in the target INR range. Improving education and knowledge about the risks and benefits of OAC therapy improve the safety and efficacy. Despite such efforts, however, it is disappointing to observe that anticoagulation control has only marginally improved over the last 20 years from 62.2% (1987 to 1997) to 65% (1998 to 2005) internationally, and from 51% (1998–2002) to 57% (2003–2008) in the U.S. Recent studies suggest that a pharmacogenomics-guided dosing algorithm can accurately predict warfarin dosage and might reduce adverse effects. Clinical studies utilizing this algorithm are currently in progress.

One potential alternative is the availability of new oral anticoagulants. The first of the new oral anticoagulants approved by the FDA was dabigatran, a direct thrombin inhibitor. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study, the incidence of stroke and systemic embolism was 35% lower in patients treated with 150 mg dose of dabigatran than in those treated with warfarin with a similar rate of major bleeding. The mean TTR of 64% in the warfarin group is similar to that in most other prospective randomized trials. The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF), recently published showed that rivaroxaban is noninferior to dose-adjusted warfarin. One of the criticisms of the study is that the mean TTR was only 55%, yet based on the results of our study, this seems to be a more accurate reflection of the patients in the ‘real world’ community setting. Most recently, the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial showed that the use of apixaban as compared to warfarin significantly reduces the risk of stroke or systemic embolism by 21%, major bleeding by 31%, and death by 11% in the trial. The mean TTR was 62%, a target, which we have found has been difficult to achieve in the community setting. The lower mean TTR levels found in the actual community setting as compared to the two randomized control trials RELY and ARISTOTLE, may suggest a potentially even greater therapeutic benefit with these novel anticoagulants as compared to warfarin.

Despite their impressive advantages, currently illustrated in randomized controlled trials, their long-term efficacy and safety still require evaluation in the ‘real-world’ clinical practice. Several issues remain concerning the new oral anticoagulants. There is no test to assess the effect or therapeutic range. There is no antidote in cases of bleeding or when acute surgical intervention is necessary. It has not been clearly established how anticoagulant bridging should be done before surgery. Forgetting more than one dose may put the patient at a prothrombotic risk. Caution is advised in case of renal failure. Furthermore, the new anticoagulant drugs are more costly and may not be cost effective in moderate-risk patients unless INR control was poor.

Limitations

Retrospective, observational cohort studies may provide a more accurate assessment of real-life patient management since the positive effect of prospective follow-up on INR control may influence management decisions and outcome. Although the retrospective design can be a strength, the data abstracted from medical records on which they are based are limited by the accuracy of completeness of documentation. In addition, this is a relatively small study of a mostly Caucasian population. The INR values of patients who are acutely ill (calculated for other reasons other than OAC monitoring), are likely to be less therapeutic. Finally, it has been demonstrated that the degree of deviation outside the target range correlates with the degree of both bleeding and thromboembolism. This study did not assess the rates of complications with the degree of deviation outside the therapeutic window.

Conclusion

Although the efficacy of warfarin to prevent stroke in patients with non-valvular atrial fibrillation has been well
established, its use remains problematic. The quality of anticoagulation with warfarin, in the current community setting remains inadequate. The clinical relevance of the statistically significant higher TTR in cardiology practices than in primary care practices is not clear but the results for both types of practices indicate the need for improved INR control for prevention of thromboembolism. It is possible that additional patient education, specialty clinics, the wider use of algorithms, and newer agents may improve patient outcomes. Furthermore, low TTR in the community setting becomes more relevant with the emergence of oral anticoagulants, which may potentially have a greater beneficial impact.

Disclosures

We have the following interest. This study was funded by Boehringer Ingelheim Pharmaceuticals, Inc. There are no patents, products in development or marketed products to declare. All the authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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References


