Comparison of Outcomes Using 2 Delivery Models of Anticoagulation Care

Anthony G. Staresinic, PharmD; Christine A. Sorkness, PharmD; Brian M. Goodman, PhD; Denise Walbrandt Pigarelli, PharmD

Background: Studies demonstrate the effectiveness of anticoagulation management service (AMS) in providing antithrombotic therapy for eligible patients. We sought to extend this concept by determining whether an interim telephone model (IT) is comparable to our current AMS model at achieving optimal therapeutic outcomes.

Methods: The 36-month trial (24-month study plus 12-month extension) enrolled 192 eligible patients receiving long-term warfarin therapy at a Veterans Affairs hospital. Consenting participants were randomly assigned to either our current face-to-face clinic model (AMS), or our IT model. The primary outcome was the percentage of time individuals' international normalized ratios (INRs) were maintained within their target INR range (2.0-3.0 or 2.5-3.5). Secondary outcomes included the number of adverse events (eg, thromboembolism or hemorrhage) experienced during the study.

Results: We found no statistically significant difference between the 2 groups in the percentage of time maintained within INR target range overall (55.1% for AMS; 57.8% for IT; \( P = .28 \)) nor over the course of the study. There were no statistically significant differences in the rate of thromboembolic or serious bleeding events between IT and AMS participants. Nevertheless, we did note differences related to intensity of anticoagulation. The IT group receiving treatment at a higher intensity (INR, 2.5-3.5) experienced greater anticoagulation control (\( P = .04 \)) and fewer complications than the AMS group. The IT participants, however, reported a significantly higher rate of minor bleeding events, experienced mainly by those at an INR range of 2.0 to 3.0.

Conclusion: Our IT model is a viable modification of our AMS model for the management of patients undergoing chronic anticoagulant therapy.

Arch Intern Med. 2006;166:997-1002

The medical literature contains evidence of the efficacy of anticoagulant therapy to prevent venous and arterial thrombosis.\(^1,2\) Despite this, some health care providers are reluctant to prescribe anticoagulant drugs, particularly for elderly patients. Fear of hemorrhagic complications, a perceived lack of anticoagulant efficacy, or difficulties in patient management result in the underuse of drugs such as warfarin.\(^3,4\) Without appropriate anticoagulant treatment, patients may experience preventable thromboembolic events. Striking a balance between reducing the risks of thrombosis and attendant bleeding complications represents the goal of anticoagulant management. Currently, achievement of desired anticoagulation outcomes includes keeping patients' international normalized ratios (INRs) within their target therapeutic range, which is determined primarily by disease indication.\(^1,2\)

Maintaining INRs within this target range is complicated by several factors, including drug interactions, diet, and medication adherence; frequent clinical and laboratory monitoring, warfarin dose adjustment, patient education, and encouragement are necessary.\(^3\) The risks of both thrombosis and hemorrhage are diminished for those receiving high-quality and systematic management.\(^5\)

With the complexities of anticoagulation therapy, the absence of an established system of communication between providers and patients can lead to an increased risk of poor outcomes.\(^5\) In the United States, most patients requiring anticoagulation receive treatment from their primary care provider or a specialist, often without the benefit of such a coordinated system.\(^5\) Increasingly however, health care organizations are developing models of systematic care designed to achieve high-quality patient management. One version of this service model, anticoagulation man-

Author Affiliations: Pharmacy Practice Division, University of Wisconsin School of Pharmacy (Drs Staresinic, Sorkness, Goodman, and Pigarelli), and William S. Middleton Veterans Affairs Hospital (Drs Sorkness and Pigarelli), Madison, Wis. Dr Staresinic is now with Navitus Health Solutions, Madison, Wis.
agement service (AMS), most commonly employs allied health professionals (eg, pharmacists) in collaboration with a medical director to deliver and manage care. Although somewhat limited, available evidence indicates that AMS is associated with substantial decreases in major bleeding complications, fewer deaths, and improvements in patient outcomes. The American College of Chest Physicians (ACCP) suggests that such dedicated clinics lead to improved anticoagulation control, although the extent of improvement and the impact on health care costs need additional clarification.

Growing patient enrollment in anticoagulation clinics challenges personnel to find new approaches to increase efficiency of service delivery, while maintaining safe and high-quality patient management. Data from the Medicare patient database for 1995 indicated a potential patient pool of 2.5 million for anticoagulation therapy at an estimated cost of greater than $12 billion. Different methods for delivering AMS—face-to-face clinic visits, telephone follow-up, and self-management—have not been compared in a rigorous controlled manner to determine equivalency.

In this randomized prospective study, we examined whether patients receiving care via an interim telephone model differed in the amount of time their INR values were within their INR target range compared with patients receiving care via the usual AMS clinic protocol.

**METHODS**

**ELIGIBLE PARTICIPANTS**

The anticoagulation clinic of the William S. Middleton Memorial Veterans Affairs (VA) Hospital, established in 1979, is located in Madison, Wis. Patients are referred to this service by their primary care provider for management of their anticoagulation therapy. In the screening phase of the study, patients were assessed for eligibility at a routine anticoagulation clinic visit by clinic personnel. Study inclusion criteria included age 18 years or older, a requirement for indefinite warfarin therapy, completion of at least 3 months of warfarin therapy before the screening visit, and telephone availability. Individuals were ineligible if they declined or were unable to provide written informed consent, planned absences from the state, planned interruptions of warfarin therapy within 2 weeks of study enrollment, did not have a suitable caregiver for participants requiring assistance for cognitive or physical deficiencies, or were enrolled in other VA-Madison investigational protocols. Individuals discontinued study participation if they withdrew written informed consent, were unavailable by telephone, lost VA-Madison care benefits, did not adhere to study protocols, or transferred care to another medical facility. The University of Wisconsin Hospital and Clinics human subjects committee and the VA research committee approved the study.

**TREATMENT**

Following screening during a routine clinic visit, eligible patients were invited to participate in a 24-month study; staff obtained informed written consent at that time. We recorded participant characteristics (age and sex) and medical history (indication for warfarin and comorbidities). We classified the potential impact of comorbid disease and age on outcomes using the method of Charlson et al. Participants were assigned points for both age (if ≥50 years old) and comorbidity using a weighted scale to yield the Charlson Comorbidity Index (CCI). The CCI score reflected the likelihood of the participant’s death from the combined risk of age and disease during study enrollment. Participants also reported their current alcohol intake and aspirin use.

Measurements of INR obtained at the initial visit served as the baseline measurement for the study. Trained study staff evaluated each individual’s ability to read and comprehend study progress forms by asking questions designed to gauge participant understanding; staff also reviewed any general knowledge deficiencies, self-management strategies, and emergency care procedures. On completion of these tasks, participants were randomized to either the interim telephone (IT) or the usual (AMS) model.

Regardless of group assignment, each participant’s INR and clinical status were evaluated every 4 weeks. The anticoagulation regimen was adjusted, if necessary, and INR reevaluated as needed until the INR was back within the INR target range. We used participant self-reports as the primary means of monitoring warfarin adherence. Individuals were also encouraged to report all adverse events, hospitalizations, health care provider visits, and telephone triage calls occurring over the previous period. Individuals assigned to the AMS group received usual clinic care (face-to-face clinic visits), which included review of medical status and medication changes, evaluation of signs and symptoms of bleeding or thromboembolism, focused physical examination, verification of warfarin regimen, query of adherence, review of INR value, and determination of subsequent warfarin regimen. Conversely, IT participants completed a written self-assessment form asking many of the same questions (symptoms of bleeding or thromboembolism, medication adherence and availability, use of alcohol and other medications, and urgent care or hospitalization). After submitting the form to the clinic nurse, those without report of problems were allowed to leave the clinic. Individuals experiencing difficulties (eg, bleeding events or angina) were required to consult with a clinic practitioner in person. Clinic staff later reviewed the self-assessment form and contacted IT participants by telephone within 24 hours to follow up on INR results. At 3-month intervals, all IT participants had a routine face-to-face clinic visit as described for AMS participants.

Near completion of the 24-month study, we obtained permission from the VA research committee and the human subjects committee of the University of Wisconsin to continue the protocol for an additional 12 months. Because of favorable participant acceptance, we sought an extension to gather longer-term data concerning safety and effectiveness of the IT model of care. On reaching the end of the 24-month study, participants were invited to participate in the 12-month extension period, those agreeing maintained their original randomization assignment.

**PARTICIPANT OUTCOMES**

We used the percentage of time in therapeutic range (TTR) as the primary study outcome. Secondary outcomes included event rates of hemorrhage, thromboembolism, urgent care visits, and hospitalizations. We classified hemorrhagic and thromboembolic events (TEs) as minor, serious, life threatening, or fatal using the criteria of Fihn et al. 11

**LABORATORY ANALYSIS**

Blood samples were collected using venipuncture and INRs determined using Innovin thromboplastin (Dade International Inc, Deerfield, Ill) with an international sensitivity index of 1.03 for the entire 36-month study period.
natural extension of the pioneering work of Rosendaal et al.13 We strictly defined the INR target range (eg, 2.0-3.0 vs 2.5-3.3). Measurements outside of the strict INR target range were considered as such. We did so to avoid introducing a statistical bias toward artificially inflated measures of time spent within the target range. In addition, we excluded INR measurements asssociated with 10 participants who were enrolled for less than 6 months. These participants accounted for few measurements; moreover, many of the values were statistical outliers. Direct numerical time integration is more sensitive to inclusion of these aberrant values, which led us to exclude them. We included data from these 10 participants in all other outcome analyses.

Event rates were calculated for bleeding events and health care utilization as the total number of events divided by the total number of study patient-years (comparable to how the time percentages were calculated) for each randomized treatment group and also for each of their respective INR target range subgroups. For convenience, the event rates, which typically are much less than 1, are presented in the tabulated results as events per 100 patient-years. Differences in event rates between randomized treatment group and INR target range subgroup were tested for statistical significance by converting these rates into relative risk measures and using the relative risk 2-proportion test.14

PARTICIPANT CHARACTERISTICS

Approximately 500 patients received care at the anticoagulation clinic in the year prior to the study. We screened 391 of these, and 192 met study inclusion criteria and agreed to participate (Figure 1). Of those, 143 (74.5%) completed the 24-month study; 136 (70 in AMS and 66 in IT) agreed to continue with the 12-month extension. After randomization, relevant participant characteristics were not significantly different between the 2 treatment groups (Table 1). Most patients seen at our hospital were older white men with substantial comorbid disease, as indicated by CCI, and our study population reflected this. We estimated the combined impact of age and comorbid disease on the survival rate of the study participants indicated by CCI, and our study population reflected this.

Table 1. Baseline Study Participant Demographic and Clinical Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AMS (n = 94)</th>
<th>IT (n = 98)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.2 ± 10.1</td>
<td>70.4 ± 8.1</td>
<td>.10</td>
</tr>
<tr>
<td></td>
<td>(43.5-83.6)</td>
<td>(48.3-82.3)</td>
<td></td>
</tr>
<tr>
<td>Male sex, %</td>
<td>97</td>
<td>98</td>
<td>.62</td>
</tr>
<tr>
<td>Duration of clinic enrollment, y</td>
<td>4.92 ± 4.39</td>
<td>4.32 ± 4.07</td>
<td>.32</td>
</tr>
<tr>
<td></td>
<td>(0.3-17.8)</td>
<td>(0.3-20.0)</td>
<td></td>
</tr>
<tr>
<td>Warfarin dose, mg/vk</td>
<td>34.6 ± 14.7</td>
<td>33.0 ± 13.4</td>
<td>.42</td>
</tr>
<tr>
<td></td>
<td>(11.0-87.5)</td>
<td>(7.0-60.5)</td>
<td></td>
</tr>
<tr>
<td>Owns answering machine, %</td>
<td>56.4</td>
<td>63.3</td>
<td>.33</td>
</tr>
<tr>
<td>Self-reported alcohol consumption, %</td>
<td>50.0</td>
<td>41.8</td>
<td>.26</td>
</tr>
<tr>
<td>Concurrent ASA use, %</td>
<td>26.6</td>
<td>35.7</td>
<td>.17</td>
</tr>
<tr>
<td>Primary indication for warfarin, %</td>
<td>91</td>
<td>91</td>
<td>.91</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>35 (37)</td>
<td>44 (45)</td>
<td>.28</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>12 (13)</td>
<td>11 (11)</td>
<td>.74</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>9 (10)</td>
<td>10 (10)</td>
<td>.88</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>6 (6)</td>
<td>6 (6)</td>
<td>.94</td>
</tr>
<tr>
<td>Prosthetic valve replacement</td>
<td>19 (20)</td>
<td>17 (17)</td>
<td>.61</td>
</tr>
<tr>
<td>Other</td>
<td>13 (14)</td>
<td>10 (10)</td>
<td>.44</td>
</tr>
<tr>
<td>CCI</td>
<td>4.52 ± 2.04</td>
<td>4.74 ± 1.74</td>
<td>.41</td>
</tr>
<tr>
<td></td>
<td>(0-10)</td>
<td>(2-9)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AMS, anticoagulation management service; ASA, acetylsalicylic acid; CCI, Charlson Comorbidity Index10; IT, interim telephone service.

*Unless otherwise indicated, data are reported as mean ± SD (range).

Figure 1. Study participant disposition. Inclusion and exclusion criteria are as described in the “Methods” section. VA indicates Veterans Affairs.

STATISTICAL ANALYSIS

Primary and secondary outcome measures were compared across randomized treatment groups (AMS and IT) and then across their respective INR target range subgroups (2.0-3.0 and 2.5-3.5). Differences between continuous variable means were tested for statistical significance using analysis of variance. Differences between the main effects of categorical variable odds ratios were tested for statistical significance using logistic regressions. All statistical analyses were performed using procedures from the statistical software application SPSS, version 12.0.0 (SPSS Inc, Chicago, Ill). We considered significance level probabilities of P≤.05 to be statistically significant.

The primary outcome measures of anticoagulation control of overall mean INR and percentages of time above, within, and below each participant’s respective target INR range were calculated from a direct numerical time integration of each participant’s irregularly spaced series of recorded INR values.12 The application of more rigorous time series analysis techniques is a natural extension of the pioneering work of Rosendaal et al.13 Numerical time integration produces conservative unbiased estimates for time ensemble statistics.12 We calculated TTR using INR measurements recorded at 4-week intervals as well as any interim INR values obtained during warfarin dosage adjustments. We strictly defined the INR target range (eg, 2.0-3.0 vs 1.8-3.3). Measurements outside of the strict INR target range were considered as such. We did so to avoid introducing a statistical bias toward artificially inflated measures of time spent within the target range. In addition, we excluded INR measurements associated with 10 participants who were enrolled for less than 6 months. These participants accounted for few measurements;
The average INR measured over the entire course of the study was the same for both AMS and IT groups (Table 2). Furthermore, intensity of anticoagulation did not affect this metric. We chose TTR as the primary clinical outcome based on the strong relationship between TTR and the rate of adverse events.1 There was no statistically significant difference when comparing TTR between the AMS and IT groups, with the exception of those IT participants in the 2.5 to 3.5 INR target range (Table 2). Individuals in the AMS group averaged 25.1 days between encounters, whereas those in the IT group averaged 25.2 days.

We performed a time-series analysis to evaluate the change in TTR over the course of the study. There were no statistical differences in TTR between the AMS and IT participants, when comparing the groups as a whole. For those in the 2.0 to 3.0 INR range, TTR did not differ significantly. However, we did see a trend towards greater control in the IT group, with the exception of those participating in the 2.5 to 3.5 INR target range exhibited greater control than their AMS counterparts, although these differences were only statistically significant during 2 time periods. The average INR INR, 2.0-3.0 (n = 22).

### Table 2. Comparison of INR-Related Outcomes Between AMS and IT Study Groups*

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>AMS Group</th>
<th>IT Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n = 94)</td>
<td>INR, 2.0-3.0 (n = 72)</td>
</tr>
<tr>
<td>INR†</td>
<td>2.6 ± 0.35</td>
<td>2.5 ± 0.27</td>
</tr>
<tr>
<td>Time below INR target, %†</td>
<td>24.2 ± 36.0</td>
<td>22.0 ± 34.6</td>
</tr>
<tr>
<td>Time within INR target, %†</td>
<td>55.1 ± 39.1</td>
<td>59.3 ± 38.8</td>
</tr>
<tr>
<td>Time above INR target, %†</td>
<td>17.6 ± 11.3</td>
<td>15.1 ± 9.7</td>
</tr>
</tbody>
</table>

Participants with INR >6.0:

<table>
<thead>
<tr>
<th></th>
<th>No events</th>
<th>1 Event</th>
<th>2 Events</th>
<th>3 Events</th>
<th>4 Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMS Group</td>
<td>76 (81)</td>
<td>14 (15)</td>
<td>3 (3)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>IT Group</td>
<td>63 (88)</td>
<td>7 (9)</td>
<td>2 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>13 (86)</td>
<td>7 (9)</td>
<td>1 (5)</td>
<td>0</td>
<td>1 (0)</td>
</tr>
</tbody>
</table>

*For total, AMS vs IT groups.
‡For total (INR, 2.0-3.0), AMS vs IT group.
§For total (INR, 2.5-3.5), AMS vs IT group.

Abbreviations: AMS, anticoagulation management service; INR, international normalized ratio; IT, interim telephone.

†Participants enrolled in the study for less than 6 months (AMS group, n = 90; IT group, n = 92) were excluded from these analyses.
‡For total (INR, 2.0-3.0) (INR, 2.5-3.5), AMS vs IT group.
§For total, AMS vs IT groups.

### INR MANAGEMENT

The average INR INR, 2.0-3.0 (n = 22).

![Figure 2](https://jamanetwork.com/10000/image)
Overall, participants experienced a low rate of TEs during the study. Events tended to be more common among AMS participants, particularly in the INR target of 2.5 to 3.5, than in IT participants, but the difference did not reach statistical significance (Table 4). Although all TEs were serious,11 none was fatal. Participants’ INR values measured nearest these events were generally within target INR range (data not shown).

Individuals reported the occurrence of minor and serious bleeding events in fewer than 3% of total participant encounters. Overall, there were statistically significant differences in the rates between AMS and IT participants (Table 4). For events characterized as serious, IT participants in the INR 2.0 to 3.0 range noted a statistically greater number of events. Conversely, AMS participants with an INR target of 2.5 to 3.5 reported more serious bleeding events than individuals in the IT group. The rates of all-cause hospitalizations and utilization of health care resources followed a similar pattern, with IT participants in the INR 2.0 to 3.0 range requiring greater resources, whereas AMS participants with an INR target of 2.5 to 3.5 reported more utilization (Table 4).

This study demonstrates that modifications to our AMS model can maintain high-quality patient management while potentially improving efficiency in the delivery of care. Both our current AMS model and our IT model achieved clinically similar TTR percentages (55.1% and 57.8%, respectively). In addition, both groups experienced rare and similar rates of TE and bleeding complications.

Previous studies have suggested clinical and economic advantages of the AMS model over routine medical care delivered by primary health care providers.16-9 Our VA hospital has used the AMS model in the anticoagulation clinic for over 25 years. Given this, we undertook this prospective randomized study to examine modifications that might improve the efficiency (ie, decrease clinician patient load) of our AMS. The study incorporated limited patient self-management with telephone lo-
low-up of clinic appointments. Recently, a retrospective study of a telephone-based AMS managed by clinical pharmacists associated with a health maintenance organization noted a lower risk of anticoagulation-related complications and improved INR control. This study differs from ours in that the pharmacists are at a remote location and do not evaluate the patients face-to-face in the clinic; rather, they manage patient care mainly by telephone and mail. Yet this study confirms our observation that rigorous telephone follow-up can be associated with high-quality patient management.

Although both our AMS and IT groups as a whole demonstrated comparable outcomes, we did note some differences related to intensity of anticoagulation. Those participants undergoing treatment at a higher intensity experienced greater anticoagulation control and fewer complications in the IT group than in the AMS group. However, IT participants reported a greater number of minor bleeding events at the lower intensity of anticoagulation. At present, we cannot explain these observations.

We acknowledge certain features of our study that may limit application of results to all patients undergoing anticoagulation therapy. First, we included only those patients with a long-term need for anticoagulation who were stable on warfarin therapy for at least 3 months. We were interested in examining long-term anticoagulation control, which excluded patients with a temporary requirement for warfarin. Second, although our IT group did incorporate some aspects of self-management, they nonetheless consulted briefly with nursing staff at every encounter and a pharmacist every 3 months. Thus, our IT model differs substantially from others in which those providing telephone consultation never meet with patients. In our model, participants were likely more familiar with clinicians delivering the telephone consult because they met face-to-face at regular intervals.

Participants in the IT group demonstrated anticoagulation control at least equivalent to those in the AMS group. Furthermore, this control was sustainable over the long term. We believe that the fastidious telephone contact following each clinic visit played a critical role in achieving these results. Moreover, involving patients in limited self-assessment of warfarin treatment may have led to greater empowerment and self-responsibility for their own health outcomes. Improving the efficiency of anticoagulation therapy while maintaining safety and optimal clinical outcomes is critical as a greater number of patients are referred for these services.

Accepted for Publication: November 29, 2005.
Correspondence: Christine A. Sorkness, PharmD, University of Wisconsin School of Pharmacy, 777 Highland Ave, Madison, WI 53705 (sorkness@wisc.edu).
Financial Disclosure: None.
Previous Presentation: Preliminary results of this study were presented at the Pharmacy Invitational Conference on Antithrombotic Therapy; December 2003; New Orleans, La.

Acknowledgment: We thank the anticoagulation clinic staff of the William S. Middleton Memorial VA Hospital and the study participants. In addition, Kasi Krause, PharmD, and Eileen Murphy, PharmD, assisted in data entry and management. Peggy Hatfield, PhD, assisted in preparation of the manuscript.

REFERENCES