STABLE Results: Warfarin Home Monitoring Achieves Excellent INR Control

Grace DeSantis, PhD; Jackie Hogan-Schlientz, RN, BSN; Gary Liska, BS; Shari Kipp, BS; Ramarion Sallee; Mark Wurster, MD; Kenneth Kupfer, PhD; and Jack Ansell, MD

Objectives: Point-of-care, home international normalized ratio (INR) monitoring (patient self-testing, or PST) provides an opportunity to optimize warfarin therapy as demonstrated in randomized trials. This study sought to determine the quality of warfarin therapy as determined by time in therapeutic INR range (TTR) in patients who perform home monitoring outside of a clinical trial setting.

Study Design: Retrospective analysis.

Methods: The data base of an independent diagnostic testing facility was retrospectively queried over a 2.5-year period (January 2008-June 2011) and patient TTR was analyzed based on frequency of testing, age, gender, indication for therapy, duration of therapy, and critical value occurrence.

Results: A total of 29,457 patients with multiple indications for warfarin therapy comprised the database. The mean TTR for the entire group was 69.7%, with weekly testers achieving a TTR of 74% versus 68.9% for variable testers (testing every 2-4 weeks) (*P* <.0001). In all categories analyzed (age, indication for anticoagulation, and referral site volume), weekly testers performed significantly better than variable testers. Older individuals had a higher TTR than younger patients. Weekly testers experienced significantly fewer critical values (INR <1.5 or >5.0) than did variable testers.

Conclusions: Point-of-care patient self-testing at home achieves high-quality warfarin therapy outside of clinical trials and compares favorably with the results achieved in randomized trials or in anticoagulation clinic settings.

Am J Manag Care. 2014;20(3):202-209

For author information and disclosures, see end of text.

Approximately 4 million people in the United States receive oral anticoagulation therapy with the vitamin K antagonist (VKA) warfarin,[1] and require frequent international normalized ratio (INR) monitoring to maintain time in the therapeutic range.[2] There are several models of warfarin management designed to maintain the patients' INR within these desired parameters.[3] These include usual care (UC), which means an individual physician manages multiple patients without formal systematic monitoring policies or procedures to focus on dose management; anticoagulation clinic care (AC), which means dose management is overseen by a healthcare provider (usually a nurse or pharmacist) under physician leadership with systematic policies and procedures in place; and patient self-testing (PST) or patient self-management (PSM), which means patients perform their own INR test at home with a portable point-of-care (POC) instrument and receive dose instructions from a healthcare provider (PST) or manage their own dose (PSM). Under UC or AC, test frequency may be irregular, and is often determined by a patient's ability to travel to a lab or clinic to obtain the INR test result, rather than INR testing frequency depending on the pharmacology and metabolism of warfarin.[4]

Clinical evidence has demonstrated that more frequent testing improves warfarin safety and reduces risks for thromboembolic and major bleeding events.[5] The advent of POC INR devices and home monitoring has facilitated more frequent testing, provided greater consistency in testing reagents and instrumentation, and increased patient empowerment. Since 2004, the American College of Chest Physicians (ACCP) has recommended PST as a means of warfarin dose management, and according to the 2012 ACCP guidelines,[6] "for patients who are motivated and can demonstrate competency, PSM is recommended over UC (Grade 2B)." This recommendation is based on the results of numerous clinical trials of PST/PSM compared with both UC and AC care. Recently, Heneghan, et al, and Bloomfield, et al, have performed independent meta-analyses of a number of clinical trials documenting the benefit of PST or PSM.[7,8] Depending on how the analyses are done, each investigative group has shown greater efficacy of PST/PSM with a reduction in thromboembolism risk and/or major bleeding risk. However, there is little evidence to date, outside of randomized clinical trials (RCTs), to assess outcomes for patients who perform PST or PSM.[9] We evaluated the qual-

ity of PST anticoagulation management as reflected by time in therapeutic INR range (TTR) in a large cross-section of real world (non-study) patients from the United States enrolled in a home monitoring program and sought to determine whether INR testing frequency had an impact on TTR.

METHODS

Data Source

Alere Inc, an independent diagnostic testing facility (IDTF), has a database that includes anticoagulation patient data starting in 1993 and PST data starting in 1998. It includes data from over 68,000 PSTs (>3.1 million INR results) who were referred from a variety of settings ranging from office practices (cardiology, internal medicine, family practice, hematology, oncology) to large organized clinics, and enrolled in a comprehensive PST support service.

Prescribing physicians generally select PST candidates based on whether the patient is able, willing, and reliable enough to measure their INR on a POC instrument at home.[10,11] Then, physicians complete prescription forms for patient submission to the IDTF. Patients are then individually trained. Standardized protocols developed by Alere, based on human factors, support training retention and positive testing behaviors.[12] All patients in this analysis were trained by experienced healthcare professionals, and immediate follow-up was provided, as needed. Following physician instructions for data and adherence management, Alere helped each patient to initiate PST, become adherent to testing, and remain adherent to therapy. Clinicians were notified of all INR results, and if patients were nonadherent.

Study Design

This Self-Testing Analysis Based on Long-term Evaluation (STABLE) is a retrospective cohort analysis of data from real-world PST assessing 2 groups: variable and weekly testing cohorts. A query was developed to collect data on all patients who were trained on or after January 1, 2008, and who completed at least 6 months of PST before June 30, 2011 (**Figure 1**). This window of observation was selected to capture a large cross-section of patients who qualified for PST before and after the Centers for Medicare & Medicaid Services (CMS) expanded Medicare coverage to more indications.

Selection Criteria

To eliminate potential bias as a result of individual differences in learning aptitude and time to mastery, we excluded the first 3 months of PST results after the training date, con-

Take-Away Points

Real-world retrospective analysis of over 29,000 patients performing International Normalized Ratio (INR) home monitoring for warfarin therapy shows excellent time in therapeutic range.

■ This study documents the ability of patients to monitor their own warfarin therapy outside of a clinical trial setting.

■ The high rate of time in therapeutic range and limited extreme INR values indicates the potential for this model of therapy to reduce adverse events with warfarin therapy.

■ This model of therapy has the potential to improve quality of life for patients on warfarin therapy, to reduce physician work, and ultimately lead to an increase in treatment of patients who are not currently being treated.

sidering this to be the initiation period,[13] thus offering at least 3 months of PST data to evaluate. In addition, we excluded patients with results greater than 56 days between tests (DBT) as per the Rosendaal methodology,[14] patients with INR target range widths other than 1.0 (to comply with ACCP guideline ranges that are all 1.0 INR in width [eg, 2.0-3.0, 2.5-3.5]) and patients younger than 18 years (to maintain focus of this analysis on adults).

The PST prescription form requires the physician to direct the test frequency (TF), with selections that accommodate ACCP Guidelines for weekly, or options for 1 to 4 times per month (variable). Since not all patients adhere to their prescribed TF, the actual TF for each patient was established and reported. The definition adopted for this study was based on the THINRS trial that defined weekly testing as 5 to 9 days between tests (7 ± 2 DBT).[13] The definition of monthly testing varies in the literature. THINRS defined monthly clinic testing as 21 to 49 DBT (35 ± 14 DBT), but patients showed a very low adherence rate of only 52% in that study. STABLE adopted a tighter range of 24 to 38 DBT (31 ± 7 DBT).

Patient adherence to PST was used to establish study cohorts. We defined patients who reported 10 out of 12 weekly tests (83.3%) for at least a 3-month period after the initial 3-month initiation period as those who represented strong adherence. We also applied the same 83.3% adherence rate to the other TF categories for each patient over the duration of time the patient performed PST. Patients within any fixed TF who failed to meet this threshold were recategorized to the variable TF (1-4 tests/month). In summary, 4 nominal TF categories for all included patients were assigned based on the adherence model: weekly (83.3% of tests with 5-9 DBT), twice per month (83.3% of tests with 10-17 DBT), monthly (83.3% of tests with 24-38 DBT), and variable (less than 83.3% of tests in any one of the previously defined categories).

Study Measures

The TTR determined by the Rosendaal method[14] was used as the primary surrogate end point for clinical outcomes. A stratified analysis was also performed, separating patients into

■ **Figure 1.** Selection Criteria
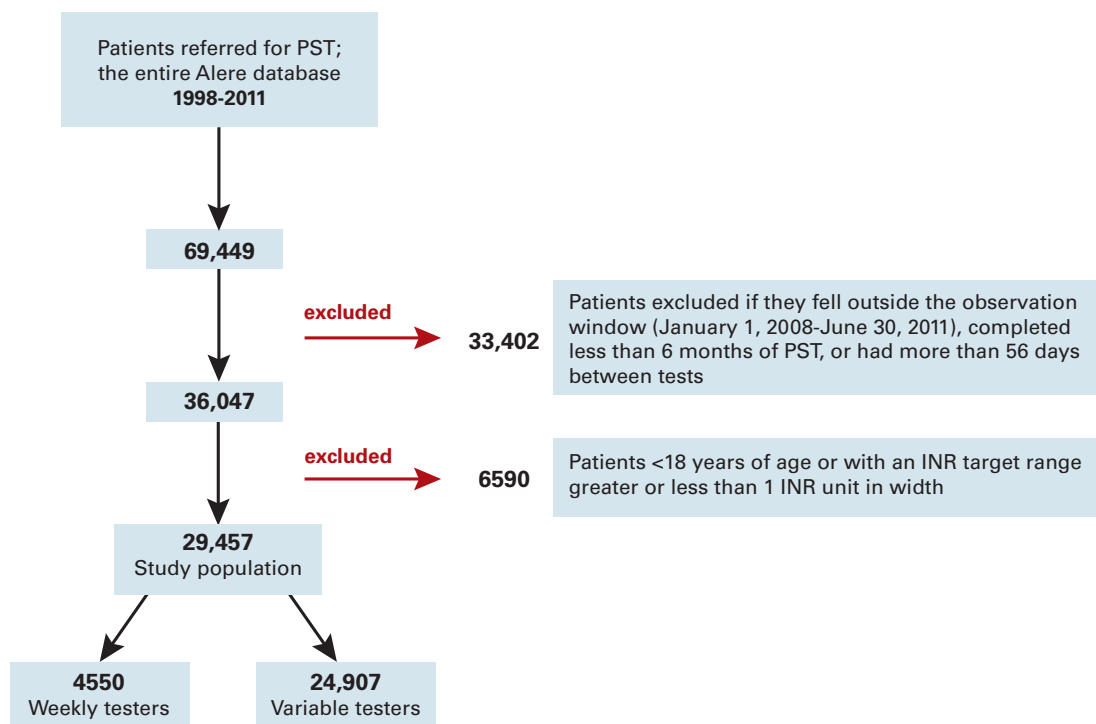
INR indicates international normalized ratio; PST, patient self-testing.

2 groups: low TTR and high TTR. The incidence of critical INR values (INR <1.5 or INR >5.0)[15] in each group was computed as the secondary surrogate end point. These surrogate end points were categorized by actual testing frequencies. Four primary patient characteristics were evaluated: age, primary indication for warfarin, gender, and duration of PST.

Statistical Analysis

The mean TTR for each subject was calculated based on all INR test results within the observation period. The distribution of mean TTR over all subjects (and within groups of subjects) was characterized by the mean and the standard deviation (SD). The distribution of mean TTRs between subject groups was compared via the Wilcoxon rank sum test. Mean TTR was also treated as a dichotomous variable (low-mean TTR <60% vs high-mean TTR ≥60%). The odds ratio (OR) was used to characterize the strength of association between dichotomous variables. The significance of association between categorical variables was assessed via the χ^2 test. The correlation of an ordinal variable (eg, referral clinic size) with mean TTR was characterized by the Spearman correlation coefficient. The incidence of critical values (per unit time) was characterized by Kaplan-Meier cumulative probability curves and by Cox proportional hazard regression of the time between critical values (multiple critical values

within each observation period were included; intervals containing no critical values were considered censored observations; repeat test results within a single day were excluded). Statistical analysis was conducted in MATLAB version 7.5 (MathWorks, Natick, Massachusetts).

Role of the Funding Source

The study was designed by clinical quality assurance and research and development teams from Alere Inc, in collaboration with outside experts in the field. All funding was provided by Alere, which conducted the query and data analysis. To maintain the privacy of all patients' identifiable health information, and following Health Insurance Portability and Accountability Act privacy rules, only de-identified patient data were evaluated, and institutional review board approval was granted (Western IRB).

RESULTS

PST Patient Population Characteristics

A total of 29,457 patients met the criteria described in the query (Figure 1), and ranged in age from 18 to 105 years at the time they started PST, with a mean age of 70.5 years (Table). Of all the patients, 80% were at least 65 years or older, 56.0% were male, and atrial fibrillation (AF) was the

■ Table. Mean and Standard Deviation of the Distribution of Mean Therapeutic Range (Units of Percent) for All Patients Also Broken Out by Demographics and by Test Frequency (with *P* value for the comparison of weekly vs variable)

| Group | All TF | | | Variable (non-weekly) TF | | | Weekly TF | | | Weekly Versus Variable |
	N	Mean TTR (%)	SD	N	Mean TTR (%)	SD	N	Mean TTR (%)	SD	P
All	29,457	69.7	18.6	24,907	68.9	19.1	4550	74.0	15.1	<.0001
Gender										
M	16,492	72.2	18.4	13,888	71.4	18.9	2604	76.1	15.0	
Age										
18-45 y	1105	63.1	22.7	1017	62.6	23.1	88	69.8	16.8	.0060
46-64 y	4780	67.0	20.0	4222	66.3	20.4	558	72.4	16.0	<.0001
65-74 y	12,398	71.5	18.0	10,250	70.7	18.5	2148	75.4	14.9	<.0001
75-79 y	5246	70.8	17.4	4344	70.1	17.9	902	73.9	14.5	<.0001
80-84 y	3661	68.9	17.8	3102	68.1	18.3	559	73.1	14.0	<.0001
85-105 y	2267	67.6	18.6	1972	67.3	18.9	295	69.9	16.6	.0285
Primary indication										
AF and MHV	1466	66.2	18.4	1215	65.0	18.5	251	71.7	16.9	<.0001
AF, no MHV	19,754	71.2	17.8	16,615	70.5	18.3	3139	74.7	14.6	<.0001
DVT	932	66.6	20.7	827	65.8	21.1	105	72.9	16.9	.0018
MHV, no AF	3844	65.8	19.7	3194	64.7	20.3	650	71.0	15.7	<.0001
Other	3461	67.8	20.0	3056	66.9	20.3	405	74.8	15.7	<.0001
No. referrals per site[a]										
<10	6301	67.5	20.4	5606	66.8	20.7	695	73.6	16.4	<.0001
11 to 50	6739	68.9	18.7	5642	68.1	19.1	1097	73.3	15.6	<.0001
51 to 100	4468	71.0	17.9	3664	70.2	18.4	804	74.4	14.7	<.0001
100+	11,593	70.9	17.6	9704	70.3	18.0	1889	74.5	14.3	<.0001
No data	356	67.1	21.2	291	66.2	21.9	65	71.4	17.2	.1033

AF indicates atrial fibrillation; DVT, deep vein thrombosis; MHV, mechanical heart valve; SD, standard deviation; TF, test frequency; TTR, therapeutic range.
[a]Each numerical grouping represents the number of patients referred per site (eg, 6301 patients were referred from sites, each of which referred <10 patients; 11,593 patients came from sites, each of which referred >100 patients).

primary diagnosis for anticoagulation. Patient follow-up ranged from 3 to 38 months with weekly and variable testers having an average of 17.2 and 14.5 months of follow-up data available, respectively. All patients were considered to have performed self-testing and not self-management because the prescription form does not indicate whether caregiver support is needed or whether PSM was to be followed.

Many physician specialties prescribed PST (cardiology, internal medicine, family practice, general practice, hematology, and oncology) for patients representing all major indications for warfarin (data not shown). Referral sites are categorized as to whether they referred only a few patients per site for PST training (<10 per site) to many patients per site (>100 per site) for PST. Weekly testing was performed by 15.4% of the patients.

PST Patient Population Performance

The overall mean TTR was 69.7% (standard deviation [SD] 18.6) for all 29,457 patients (Table). The majority of patients fell within 2 of our previously defined TF categories: variable (n = 24,480; 83.1%) and weekly (n = 4550; 15.4%). The remaining 1.4% (n = 427) tested at a fixed TF of 2 tests per month (n = 320) or 1 test per month (n = 107). Due to the very small sample size for the 1-test-per-month and 2-tests-per-month TF patients, we merged those patient populations with the large variable TF group to create a variable/non-weekly group (n = 24,907; 904,687 INR results). The mean TTR for this group was 68.9% (SD 19.1). Weekly testing, the single most commonly observed fixed TF (n = 4550; 333,068 INR results), provided a significantly higher mean TTR of 74.0% (SD 15.1). These patients were at least 83.3% adherent to

■ Figure 2. Time in Therapeutic Range (%) by Age Group
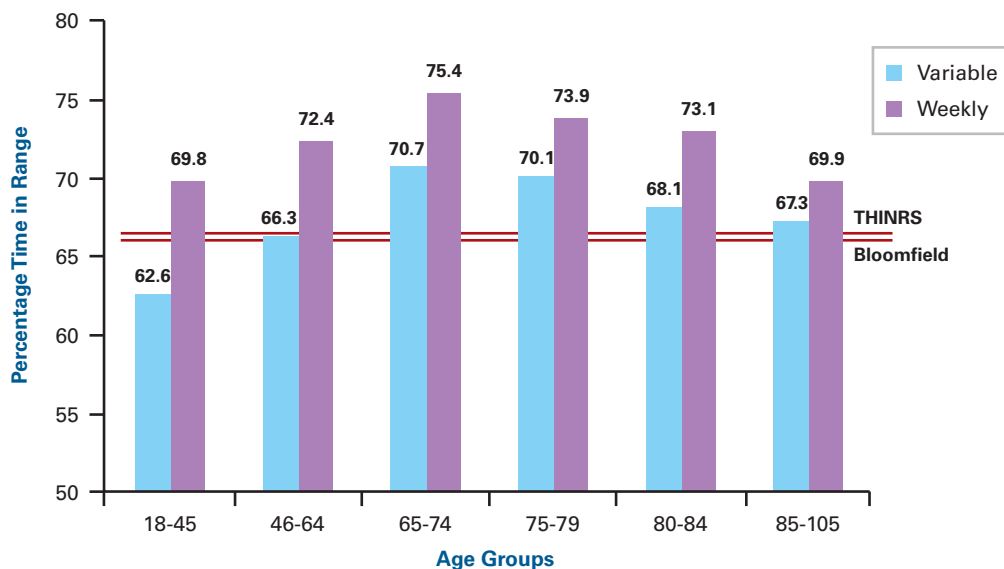
THINRS[13] and Bloomfield[8] represent the mean TTR from the 2 studies.

weekly testing by definition. The Table also shows the TTR for subjects comparing variable versus weekly, and broken out by demographic and baseline characteristics. Significantly higher mean TTR in weekly TF compared with variable TF groups was sustained across all patient demographics. A positive correlation was also found between the TTR and the number of patients referred per site; patients who came from practices that referred a larger number of patients showed higher mean TTR with smaller standard deviations.

Performance by Age

Patients aged 65 to 74 years (71.5% TTR, SD 18.0; all TF) had higher TTR than the younger population of 46 to 64 years (67.0%, SD 20.0; all TF) (Table). Patients older than 75 years also achieved relatively high TTR (75-79 years: 70.8%, SD 17.4; 80-84 years: 68.9%, SD 17.8; all TF). **Figure 2** illustrates a summary of TTR achieved by age in this study, with TTR from published controlled trials such as THINRS (TTR = 66.2% weekly PST) and Bloomfield's 22-study meta-analysis (TTR = 66.1%) shown as warfarin control comparators.

### Critical Value Incidence Analysis

A total of 49.8% of patients from the entire data set had one or more critical values (INR <1.5, or INR >5.0) during the observation period. The Kaplan-Meier curves (**Figure 3**) characterize the frequency of critical values (FCV) in months based on whether patients had a high (mean TTR ≥60%) or low (mean TTR <60%) TTR, and whether patients were weekly or variable testers. Mean FCV is the total exposure (patient months of observation) divi-

ded by the total number of critical values. Patients with low TTR had a dramatically increased incidence of critical values (higher mean FCV) when compared with patients with high TTR (lower mean FCV). Patients with low TTR experienced a critical value every 4.46 months, while patients with high TTR only experienced a critical value every 18.7 months, indicating a hazard ratio (HR) of 3.16 with 95% confidence interval (CI) of 1.89 to 2.22 from Cox regression. Variable/non-weekly testers had a significantly higher probability of being in the low TTR group when compared with weekly testers (29.8% vs 17.1%, OR = 2.05, 95% CI, 1.89-2.22). When Cox regression model is adjusted for test frequency, the HR of high versus low TTR strengthens (HR = 3.20, 95% CI, 3.14-3.27) and the HR of weekly versus variable test frequency is relatively weak (HR = 1.15, 95% CI, 1.12-1.17). The Cox regression model shows that when both TTR and test frequency are considered independent variables, weekly testers have a higher probability of detecting a critical value and thus are able to respond appropriately to return to the therapeutic range.
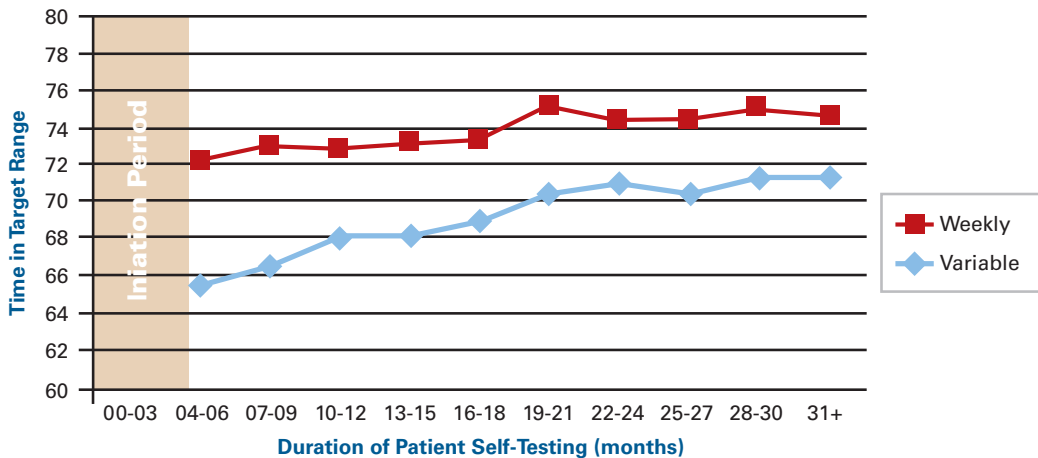
Duration Analysis

We performed a duration analysis to evaluate how patients perform over time. Patients in the weekly TF category achieved greater than 72% TTR in their first 3 months postinitiation, and maintained or improved TTR over time (**Figure 4**). The TTR for weekly testers exceeded the TTR for variable TF patients for each 3-month period throughout the study. Patients in the variable TF began at a lower TTR of 65.5% and steadily increased their overall TTR over time.

■ **Figure 3.** Kaplan-Meier Curves Showing Cumulative Probability of a Critical Value in High Versus Low TTR Groups and Weekly Versus Variable Testers
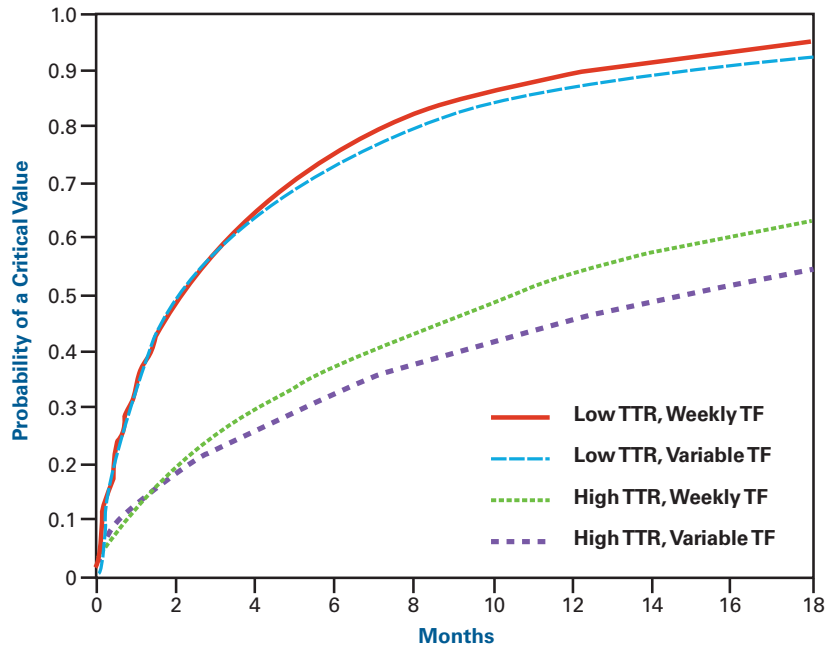
Weekly testers had a greater probability of being in the high TTR group (defined as TTR >60%).

■ **Figure 4.** Time in Therapeutic Range (%) According to Duration of Patient Self-Testing (PST)

However, it took the variable TF group 20 months longer to achieve TTR greater than 70%, while never achieving the level of control attained by weekly testers.

DISCUSSION

STABLE is the largest observational retrospective analysis published to date, characterizing 29,457 real-world warfarin patients who self-test, and evaluating their performance over a 42-month observation window. This study is the first to show that patients perform well with self-testing as an adjunct to warfarin therapy outside of clinical trial settings. The analysis confirmed that in the United States, a wide variety of patients successfully perform PST and sustain high surrogate end points of high TTR with low incidence of critical INR values over time.

The overall mean TTR was high (69.7%), exceeding the TTR of published RCTs[16] and meta-analyses,[7,8] as well

Figure 5. Comparison of Alere Real-World STABLE Time in Therapeutic Range Versus Recent Large Controlled Trials or Meta-analyses
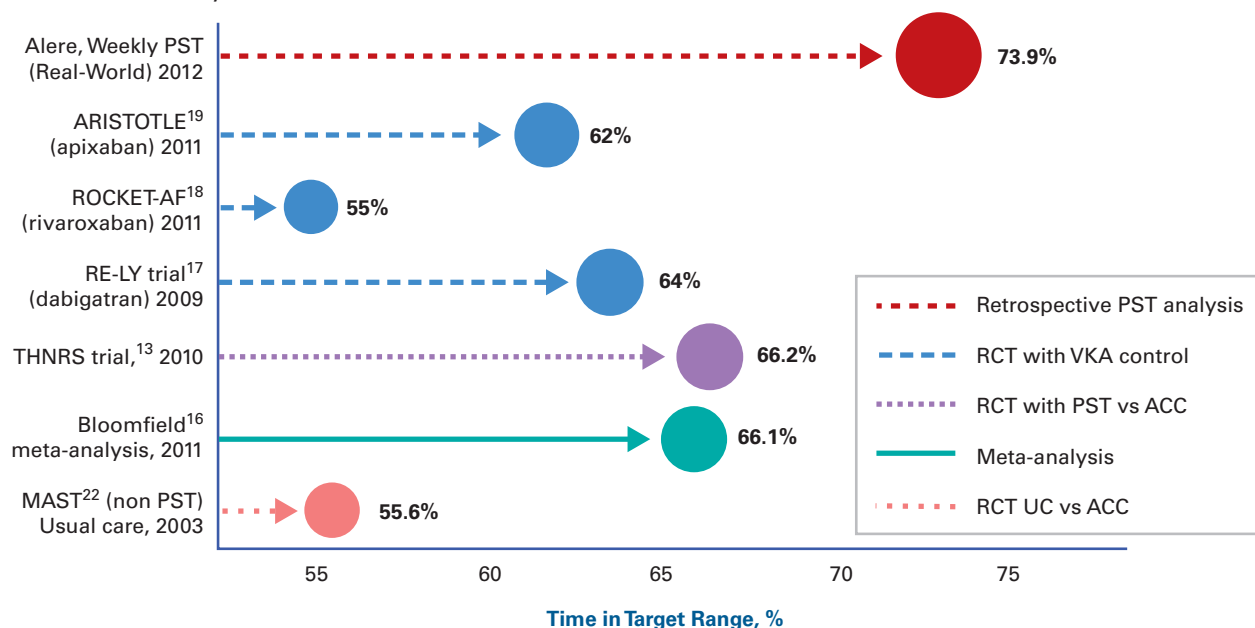
ACC indicates anticoagulation clinic; PST, patient self-testing; RCT, randomized controlled trial; UC, usual care; VKA, vitamin K antagonist.

as warfarin control comparators in studies of new target-specific oral anticoagulants (**Figure 5**).[17-19] Even the lowest performing TF category of variable testers in this analysis performed better than the best TTR among warfarin-treated patients in randomized trials of the new target-specific oral anticoagulants. Studies have shown a strong correlation between the TTR as well as the distance of a result from the therapeutic range and the occurrence of adverse events.[20] It is therefore important to see that critical values, a quality measure of control and risk, used by an increasing number of clinicians, showed a significant difference between the 2 major test frequencies evaluated. Patients with a higher TTR ($\geq$60%) had a lower probability of having a critical value compared with those with a lower TTR (<60%) (mean FCV 18.7 months per critical value for TTR $\geq$60% vs 4.46 months for those with TTR <60%), and weekly testers were less likely to be in the low TTR group (17.1% vs 29.8%; OR = 2.05). The data also showed that weekly testers achieved and maintained a high TTR earlier than non-weekly or variable testers. This triple benefit of early control, high TTR, and occurrence of low critical value suggests that INR testing conducted on a structured weekly and non-variable schedule promotes a higher degree of better clinical outcomes than variable testing schedules based on these surrogate outcome indicators. A weekly TF may represent a challenge to clinicians who are accustomed to and trained on counseling and titrating at traditional

monthly intervals, but POC monitoring at home makes this option easily available and manageable for both physicians and patients.

The elderly are often considered to be at higher risk of bleeding during warfarin therapy[3] and fewer than half of those patients who would benefit from warfarin actually receive it. Given that an increasing number of elderly patients could benefit from warfarin, it is significant that in this STABLE analysis, patients 75 years and older performed well, with a mean TTR above 73% for weekly testers.

Limitations and Strengths

Strengths of this retrospective analysis include a large study population of nearly 30,000 real-world patients of all ages, indications for warfarin, and care settings over a 38-month period. There are limitations of this analysis, however. Patients referred for PST may represent a select population of patients who are reliable, adherent, and already stable on warfarin therapy, although in many of the large RCTs, large cohorts of patients were also warfarin experienced. Time in therapeutic range is also time-dependent from the start of therapy[21] and the elimination of the first 3 months of start-up time eliminates initial non-therapeutic INRs. In 4 non-POC randomized trials where the first 3 months were eliminated, TTR was measured between 65% and 80%.[21] These results, therefore, indicate that non-study patients can achieve a therapeutic

quality that is at least as good as well-designed prospective randomized trials. Furthermore, only patients who successfully achieved competency and completed at least 6 months of PST were included, but it has previously been documented that 80% of patients are able to achieve success in PST performance.[13] Finally, Alere, the study sponsor, provided patient support in the form of education and patient reminders.

CONCLUSIONS

This retrospective analysis offers the first insights into surrogate outcomes for patients on warfarin who were managed via home PST with the support of a health management service in a real-world setting. With close to 30,000 patients, there was a categorical benefit for all, with an overall mean TTR of 69.7%, higher than that observed for PST in RCT. Weekly testing proved to be the optimal frequency for achieving the greatest TTR. Across several analyses (age, gender, diagnosis), TTR for weekly testers exceeded TTR of those with non-weekly and variable TFs, suggesting that regimented weekly testing enables improved TTR, while less regimented variable testing results in smaller improvement. By maintaining high TTR, weekly testing represents the greatest opportunity to minimize the risk of critical value INRs, because critical value incidence rises dramatically when TTR is low.

REFERENCES

1. Nutescu E, Bathija S, Sharp L, Gerber BS, Schumock GT, Fitzgibbon ML. Anticoagulation patient self-monitoring in the United States: considerations for clinical practice adoption. *Pharmacotherapy.* 2011;31 (12):1161-1174.

2. Centers for Medicare & Medicaid Services. Decision memo for prothrombin time (INR) monitor for home anticoagulation management (CAG-00087C, 2001; CAG-00087R, 2008). [memorandum]. Baltimore, MD.

3. Ansell J, Hirsh J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: ACCP Evidence-Based Clinical Practice Guidelines. *Chest.* 2008;133(6 suppl):160S-198S.

4. Rose A, Berlowitz D, Ash A, Ozonoff A, Hylek EM, Goldhaber-Fiebert JD. The business case for quality improvement: oral anticoagulation for atrial fibrillation. *Circ Cardiovasc Qual Outcomes.* 2011;4(4):416-424.

5. Samsa GP, Matchar DB. Relationship between test frequency and outcomes of anticoagulation: a literature review and commentary with implications for the design of randomized trials of patient self-management. *J Thromb Thrombolysis.* 2000;9(3):283-292.

6. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy. *Chest.* 2012;141(2 suppl):e152S-e184S.

7. Heneghan C, Ward A, Perera R, et al. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual data. *Lancet.* 2012;379(9813):322-334.

8. Bloomfield HE, Krause A, Greer N, et al. Meta-analysis: effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. *Ann Intern Med.* 2011;154(7):472-482.

9. Gardiner C, Longair I, Pescott M, et al. Self-monitoring of oral anticoagulation: does it work outside trial conditions? *J Clin Pathol.* 2009; 62(2):168-171.

10. Oral anticoagulation patient self-testing: consensus guidelines for practical implementation. *Managed Care.* 2008; 17(10, suppl 9):1-8.

11. Ansell J, Jacobson A, Levy J, Voller H, Hasenkam JM. Guidelines for implementation of patient self-testing and patient self-management of oral anticoagulation: international consensus guidelines prepared by international self-monitoring association for oral anticoagulation. *Int J Cardiol.* 2005;99(1):37-45.

12. Association for the Advancement of Medical Instrumentation. Standard HE75: Human factors engineering—design of medical devices. Arlington, VA: 2009.

13. Matchar DB, Jacobson A, Dolor R, et al. Effect of home testing of international normalized ratio on clinical events. *N Eng J Med.* 2010; 363(17):1608-1620.

14. Rosendaal R, Cannegieter S, van der Meer F, van der Meer F, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost.* 1993;69(3):236-239.

15. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schunemann JH. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: ACCP Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 suppl):7S-47S.

16. Wan Y, Heneghan C, Perera R, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circ Cardiovasc Qual Outcomes.* 2008;1(2):84-91.

17. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361(12): 1139-1151.

18. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365(10):883-891.

19. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(10): 981-992.

20. Hylek E, Skates S, Sheehan M, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with non-rheumatic atrial fibrillation. *N Eng J Med.* 1996;335(8):540-546.

21. Erkens PMG, ten Cate H, Buller HR, Prins MH. Benchmark for time in therapeutic range in venous thromboembolism: a systematic review and meta-analysis. *PLoS One.* 2012;7(9):e42269.

22. Matchar DB. Do anticoagulation management services improve care? implications of the managing anticoagulation services trial. *Card Electrophysiol Rev.* 2003;7(4):379-381. ∎