

Aggregate analysis of published reports as summarized in “ProThrombin Time Self-Testing (PST) in Anticoagulation Management” – Technical Report to Centers for Medicare and Medicaid Services (CMS) by Patient Self-Testing Coalition, July 2000

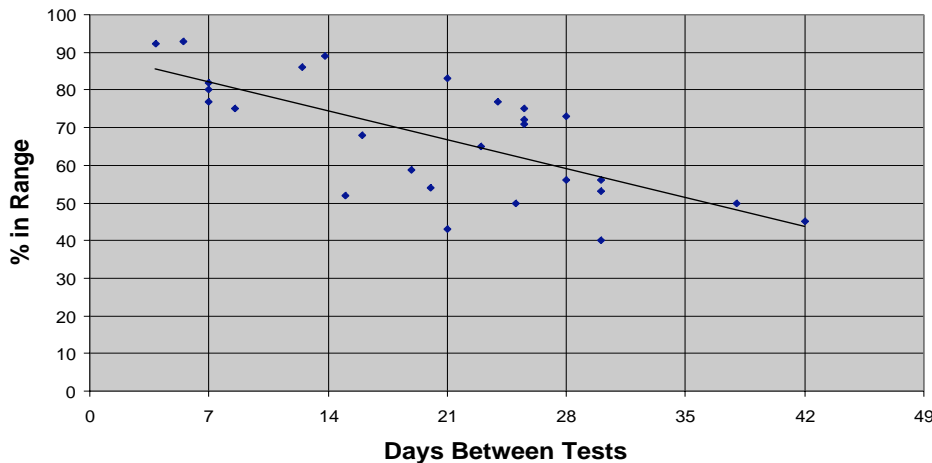
In an April 2000 review of the relationship between test frequency and outcomes in anticoagulation (including analysis of 15 studies that addressed this question), Samsa and Matchar noted that:

. . . a strong relationship between TTR [time in target range] and event rates is consistent not only with the pharmacokinetics of warfarin . . . and consensus statements, but has also been observed across a large number of studies with different patient populations, different target ranges, and different scales for measuring intensity of anticoagulation. . . . we recommend using TTR as the primary outcome, while also recording clinical events among the secondary outcome.¹

Test intervals. Increased frequency of testing has consistently been shown to increase time in range, as noted by Samsa and Matchar as well as many others, and as demonstrated in Figures 1 and 2. The summary of 25 treatment groups from 18 studies in Figure 1 shows that as time between tests *decreases*, time in range *increases*. Testing roughly every 28 days keeps test results in range 40-70% of the time. Testing at least weekly achieves approximately 80% time in range. The target ranges used in the studies in Figure 1 varied widely, and some were broad compared to present consensus ranges (2.5-3.5 for prosthetic valves, 2.0-3.0 for most other indications). Staying within ranges as broad as 2.0 to 4.5 is considerably easier than staying in narrower ones, so that frequency of testing has become even more important as target ranges have narrowed to comply with the evolving consensus. Figure 2 summarizes only those study groups that had relatively narrow ranges (maximum of 1.5 INR units, e.g., 2.0-3.5).

In these studies, testing approximately once a month kept INRs in the target range about 40-55% of

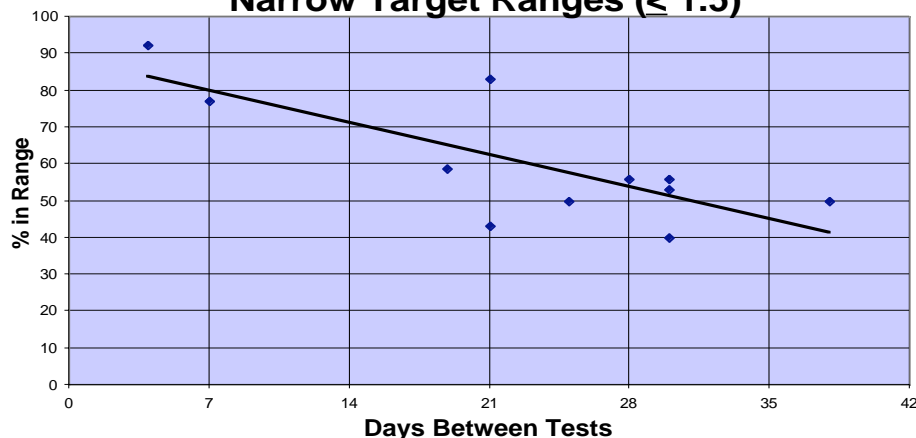
Figure 1
Test Interval vs. % in Range
All Target Ranges



the time, which is inadequate for good control. It is also far below some of the time-in-range percentages achieved with monthly testing and broader ranges, reinforcing the idea that as the target range narrows, testing frequency must increase. The one trial that employed weekly testing achieved 77% time in a 2.0-3.0 range.ⁱⁱ A study of valve patients who self-tested every three days showed 92.4% time in range with a very narrow range of 3.5-4.0.ⁱⁱⁱ

A complete listing of the studies included in Figures 1 and 2 is in Appendix 1.

Figure 2
Test Interval vs. % in Range
Narrow Target Ranges (< 1.5)



Alan Jacobson, M.D., Chief of Anticoagulation Services for the Loma Linda VA Medical Center, emphasized the importance of frequent testing in testimony before an FDA advisory panel in 1997.

Traditionally. . .we have done testing on a monthly basis, but there is no medical basis for that frequency of testing. It has kind of been a historical tradition that has evolved as a compromise between the patients. . .and the providers. . . One of the advantages of increased frequency of testing is [that] you now have more data points and can have better clinical decision making capabilities.^{iv}

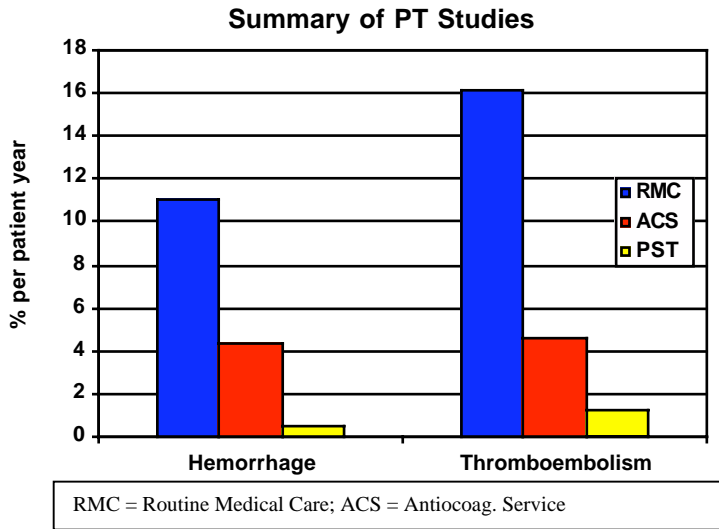
Methods of monitoring. Monitoring has traditionally involved periodic patient visits for laboratory tests and follow-up calls for dosage adjustments by the physician within a few days of the blood draw. Two other approaches to PT testing are now available. With the second, the patient goes to the point of care—a physician’s office or anticoagulation clinic—for PT testing with a portable device that reports test results immediately, thus eliminating the wait and the need for telephone follow-up. Since a fingerstick blood sample can be used, venipuncture also is eliminated.

The third approach is prothrombin time self-testing (PST). With PST, patients are trained in use of a portable monitor so that they can do PT monitoring at home (or wherever they may be) and report the results to the physician. The CoaguChek™ System from Roche Diagnostics, the AvoSure™ from Avocet Medical, Inc., and the ProTime® from ITC are FDA-cleared for PST.

Experience with self-testing in both Europe and the United States indicates that about 50% of all warfarin patients are capable of self-testing. Criteria for patient selection have been developed to insure that only patients capable of achieving reliable results are included in PST programs. All the studies included training programs and observation of patient technique by trained professionals before PST results were used in management of therapy.

The health outcome (time in therapeutic range) is superior to that obtained with routine care or ACS. Results of a number of short- and long-term studies of PST are summarized in Table 1. While the studies vary in size, duration, target INR ranges, and other variables, they have consistently demonstrated significantly increased time in range and decreased adverse events with PST as compared to either routine care or anticoagulation services. Figure 3 illustrates the differences in adverse events among the three approaches to monitoring.

Figure 3
Adverse Events in Different Management Schemes



narrow target range (3.5-4.0) and reported percentage of tests in range for several different testing intervals (see Table 1 for details). Time in range steadily increased from 48% to 92% as testing frequency rose from 4 weeks to 2 days.

A large, randomized, controlled study of valve patients in Europe has also obtained superior results with PST. In the Early Self Controlled Anticoagulation Trial (ESCAT), patients were randomized to routine care or PST. The PST group (n=250), testing weekly, was in the therapeutic range 70% of the time after three years of follow-up, compared with 42% for the routine care group (n=162), which tested about 1.5 times a month.^v

A study reported in abstract form by Beyth and Landefeld of 325 elderly patients randomized to either routine care or an intervention that included education and self-testing showed a 52.5% reduction in adverse events in the PST group after six months (1.2% incidence of major hemorrhage in self-testers).^{vi} This is the largest randomized PST trial in the U.S. to date, and the results appear to be consistent with the other studies that also included a substantial patient education component.

Many other PST studies are underway or completed in the U.S. and other countries, although not all have been published. Investigators from the Netherlands, Austria, and Israel reported their experience with PST at the 1999 Congress of the International Society on Thrombosis and Haemostasis. According to the summary by Ansell, all reported highly positive results.^{vii}

Many patients prefer home monitoring. Studies have consistently reported very high levels of patient satisfaction and a preference for home testing. Patients have reported an overwhelming preference for fingerstick sampling and PST. In the 1993 study by Anderson et al,^{viii} all of the patients who expressed a preference (38 of 40) wanted to continue with self-testing after the trial, and 97% reported that using the monitor gave them a greater sense of control and involvement with management of their illness. Hasenkam et al^{ix} and Sunderj^x found that all their PST patients also wanted to continue self-testing. White et al reported that “most” patients wanted to continue PST after the initial eight-week study.^{xi} Sawicki found that patients who self-tested and self-managed reported greater treatment satisfaction.^{xii} In Germany, where structured training and insurance reimbursement have made PST routine, approximately 40,000 patients are involved in self-testing and self-management, and 600 training centers are training thousands of patients per month.^{xiii}

These studies strongly support the thesis (demonstrated in Figures 1 and 2 above) that increased frequency of testing by well-trained patients at home is the best way to increase time in range. In the Roche 510(k) study group, where patients tested approximately every 4 days, more than 96% of tests were within the target range, and 21 of 37 patients, or 57%, were in the target range 100% of the time. The PST studies that compared PST to the other models *all* reported more frequent testing with PST, and *all* showed increased time in range and a lower adverse event rate. Horstkotte’s studyⁱⁱⁱ of 150 valve patients randomized to PST or routine care is especially instructive because he used a very

Table 1
Summary of Prothrombin Time Self-Testing Studies

Study/ Publication Date	Sample Size (Patient Yrs.)	Type of Study/ Population Studied	Frequenc y of PT Testing	Target Range/ % Tests in Range	Incidence of Adverse Events (% per/patient year unless otherwise stated)
Ansell J et al, 1995 Long-term patient self- management of oral anticoagulation. Arch Intern Med 155:2185-9.	40 (172)	Retrospective cohort study of 20 patients compared w/ 20 matched controls. Various indications.	ACS/avg 16 days PST/avg 13.8 days	Target unknown ACS: 68% PST: 88.6%	ACS: 1 thromboembolic event PST: 2 major bleeds (1.1%), 1 thromboembolic event (0.6%)
Bernardo A et al, 1995 Self-monitoring of oral anticoagulant therapy: first experience. Deutsch Arzteblatt 92:A442-44.	92 (118) PST 317 (412) RMC	Non-randomized, retrospective comparison of German valve patients treated by routine care (RMC) or home test (PST)	PST/week ly RMC/not given	INR 2.5-4.5 PST 83.1%	PST: 3.38% minor bleeds 3.38% total AE RMC: 3.89% minor bleeds .49% severe bleeds 1.95% thromboembolism 6.07% total AE
Bernardo A et al, 1996 Long-term experience with patient self-management of oral anticoagulation. Ann Hematol 72 (Supp. I):A62	351 (834)	Patients (91% valve) followed for up to 8.5 yrs while self-testing and self-managing	weekly	INR 2.5-4.5 82% 2.4% above 15.6% below	Minor bleeds: 7.7% Other bleeds:1.2% Transient thromboemb: 0.5%
Hasenkam JM et al, 1997 Self-management of oral anticoagulant therapy after heart valve replacement. Europ J Cardiothorac Surg 11:935-42.	21 PST 20 RMC	Prospective study of 21 valve patients age 19- 70, and retrospective study of 20 matched controls	Daily for 6 weeks, then weekly	INR 2.0-3.0 PST: 77% RMC: 53%	PST: No major events RMC: N/A
Horstkotte D, 1996 Improvement of prognosis by home PT estimation in patients w/ lifelong AC therapy. Meeting abstract.	150 (221)	150 valve patients randomized to home testing (PST) or routine medical care (RMC)	RMC/Freq unknown PST/every 3-4 days	INR 3.5-4.0 PST: 43.2% RMC: 22.3% INR "corridor" 3.0- 4.5 PST: 92.4% RMC: 58.8%	PST 4.49% RMC 10.88%
Horstkotte D et al 1998 Optimal frequency of patient monitoring and intensity of oral anticoagulation therapy in valvular heart disease. J Thromb Thrombolysis 1998;5:S19-24. (Long-term follow-up of study above)	150 (221)	150 valve patients randomized to home testing (PST) or routine medical care (RMC)	RMC/19 days PST/4 days (average)	INR 3.5-4.0 By test frequency: PST/2 days 92% PST/4 days 90% PST 8 days 67% RMC/2 wks 60% RMC/4 wks 48%	PST: Bleeds 4.5% Thromboembolic events 0.9% RMC: Bleeds 10.9% Thromboembolic events 8.6%

Table 1, continued

Study/ Publication Date	Sample Size (Patient Yrs.)	Type of Study/ Population Studied	Frequency of PT Testing	Target Range/ % Tests in Range	Incidence of Adverse Events (% per /patient year unless otherwise stated)
Korfer R, Kortke H,1998. ESCAT (Early self controlled anticoagulation trial). In: Krian A et al. Advancing the technology of bileaflet mechanical heart valves. Darmstadt: Steinkopft-Verlag, 1998:12-22.	412 (1236)	Prospective, randomized, controlled study of German valve patients randomized to PST or RMC	PST 4x/mo. RMC 1.5x/mo.	Target: 2.5-4.5 After 3-year follow-up: 250 PST pts: 70% 162 RMC pts: 42%	N/A
Kulinna W et al, 1999. The effect of self-monitoring the INR on quality of anticoagulation and quality of life. Sem Thrombos Hemostas 1999;25: 123-26.	100	Prospective 6-month cohort study of German patients with various diagnoses	Not stated (approx. 3 x a month)	Target: 2.5-4.5 or 2.0-4.0 % in range: 79.6% Month 1 85.6% Month 6	N/A
Morsdorf S et al, 1999. Training of patients for self-management of oral anticoagulant therapy: standards, patient suitability, and clinical aspects. Sem Thrombos Hemostas 1999;25;109-15.	50	Prospective study of German patients who took part in a standardized PST/PSM training course	Not stated	Targets unknown 88% of tests within ± 0.3 of lab- measured values	Unknown – no LT follow-up after training
Sawicki PT, 1999 A structured teaching and self-management program for patients receiving oral anticoagulation: a randomized controlled trial. JAMA;281:145-50.	179	Prospective study of patients on lifelong anticoagulation randomized to PST/PSM or RMC	PST 1-2x/wk RMC 2x/mo	Varying targets (some After 6 months: PST: 53% RMC: 43%)	N/A
Sunderj R, et al, 1999 Outpatient self-management of warfarin therapy: a pilot study. Pharmacotherapy 1999;19:787-93.	10	Open prospective study (3-month pilot). Stable, mentally competent patients w/ no AE history (8 of 10 on PST/PSM).	Weekly	Target 2.0-3.0 or 2.5-3.5 PST: 76.5% mean	None
White RH et al, 1989 Home prothrombin monitoring after the initiation of warfarin therapy. Ann Intern Med 111:730-7.	46	Randomized prospective cohort study. Warfarin outpatients randomized to PST or ACS care	ACS: weekly PST: 2x a week	Various targets PST: 93% ACS: 75%	

APPENDIX 1

These studies were used to produce the graphs in Figures 1 and 2:

Ansell JE, Patel N, Ostrovsky D, et al. Long-term patient self-management of oral anticoagulation. *Arch Intern Med* 1995;155:2185-9.

Bernardo A. Experience with patient self-management of oral anticoagulation. *J Thromb Thrombolysis* 1996;2:321-25.

Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *New Engl J Med* 1990;323:1505-11.

Cannegieter SC, Rosendaal FR, Wintzen AR, et al. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med* 1995;333:11-17.

Connolly SJ, Laupacis AL, Gent AM, et al. Canadian Atrial Fibrillation (CAFA) Study. *J Am Coll Cardiol* 1991;18:349-55.

Cortelazzo S, Finazzi G, Viero P, et al. Thrombotic and hemorrhagic complications in patients with mechanical heart valve prosthesis attending an anticoagulation clinic. *Thromb Haemost* 1993;69:316-20.

European Atrial Fibrillation Trial Study Group. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. *N Engl J Med* 1995;333:5-10.

Ezekowitz MD, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation [SPINAF Study]. *N Engl J Med* 1992;327:1406-12.

Gottlieb LK, Salem-Schatz S. Anticoagulation in atrial fibrillation: does efficacy in clinical trials translate into effectiveness in practice? *Arch Intern Med* 1994;154:1945-53.

Hasenkam JM, Kimose HH, Knudsen L, Gronnesby H, et al. Self management of oral anticoagulant therapy after heart valve replacement. *Eur J Cardiothorac Surg* 1997;11:935-42.

Horstkotte D. Improvement of prognosis by home PT estimation in patients with lifelong anticoagulation therapy. Meeting abstract, 1997.

Korfer R, Kortke H. ESCAT (Early self controlled anticoagulation trial). First results of a randomised, prospective study of controlling the effect of oral anticoagulant therapy by means of a home prothrombin monitor (CoaguChek Plus) following mechanical heart valve replacement with Medtronic, Hall, Carbomedics or St. Jude Medical). Brief report, 1997.

Peterson P, Boysen G, Godtfredsen J, et al [for the AFASAK group]. Placebo-controlled, randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. *Lancet* 1989;1:175-79.

Seabrook GR, Karp D, Schmitt DD, et al. An outpatient anticoagulation protocol managed by a vascular nurse-clinician. *Am J Surg* 1990;160:501-5.

Stroke Prevention in Atrial Fibrillation Investigators: Stroke Prevention in Atrial Fibrillation Study: final results. *Circulation* 1991;84:527-39.

Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for the prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet* 1994;343:687-91.

van der Meer FJ, Van Den Broucke JP, et al. Bleeding complications in oral anticoagulant therapy: an analysis of risk factors. *Arch Intern Med* 1993;153:1557-62.

White RH, McCurdy SA, von Marensdorff H, Woodruff DE, Leftgoff, L. Home prothrombin time monitoring after the initiation of warfarin therapy: a randomized, prospective study. *Ann Intern Med* 1989;111:730-37.

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- ⁱ 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;9:283-92.
- ⁱⁱ Hasenkam JM, Knudsen L, Kimose HH, et al. Practicability of patient self-testing of oral anticoagulant therapy by the international normalized ratio (INR) using a portable whole blood monitor: a pilot investigation. *Thromb Res* 1997;85:77-82.
- ⁱⁱⁱ Horstkotte D. Improvement of prognosis by home PT estimation in patients with lifelong anticoagulation therapy. Meeting abstract, 1997.
- ^{iv} Jacobson A. Testimony before the Hematology and Pathology Devices Panel of the Medical Devices Advisory Committee, U.S. Food and Drug Administration, September 5, 1997.
- ^v Korfer R, Kortke H. ESCAT (Early self controlled anticoagulation trial). In: Krian A et al. *Advancing the technology of bileaflet mechanical heart valves*. Darmstadt: Steinkopft-Verlag, 1998:12-22.
- ^{vi} Beyth RJ, Landefeld CS. Prevention of major bleeding in older patients treated with warfarin: results of a randomized trial [abstract]. *J Gen Intern Med* 1997;12:66.
- ^{vii} Ansell J. An international perspective on advances in the management of oral anticoagulation. Proceedings of the XVII Congress of the International Society on Thromb and Haemostasis, 1999.
<http://www.medscape.com/MEDSCAPE/CNO/1999/ISTH/ISTH-08.html>
- ^{viii} Anderson DR, Harrison L, Hirsh L. Evaluation of a portable prothrombin time monitor for home use by patients requiring long-term oral anticoagulation therapy. *Arch Intern Med* 1993;153:1441-48.
- ^{ix} Hasenkam JM, Kimose HH, Knudsen L, Gronnesby H, et al. Self management of oral anticoagulant therapy after heart valve replacement. *Eur J Cardiothorac Surg* 1997;11:935-42.
- ^x Sunderj R, Campbell L, Shalansky K, et al. Outpatient self-management of warfarin therapy: a pilot study. *Pharmacotherapy* 1999;19:787-93.
- ^{xi} White RH, McCurdy SA, von Marensdorff H, Woodruff DE, Leftgoff, L. Home prothrombin time monitoring after the initiation of warfarin therapy: a randomized, prospective study. *Ann Intern Med* 1989;111:730-37.
- ^{xii} Sawicki PT. A structured teaching and self-management program for patients receiving oral anticoagulation: a randomized controlled trial. *JAMA* 1999;281:145-50.
- ^{xiii} Taborski W, Muller-Berghaus G. State-of-the-art patient self-management for control of oral anticoagulation. *Semin Thromb Hemostas* 1999;25:43-47.



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