

Self-Managed Anticoagulation: Results From a Two-Year Prospective Randomized Trial With Heart Valve Patients

Pushpinder Sidhu, FRCSI, and Hugh O. O'Kane, FRCS

Department of Cardiac Surgery, Royal Hospitals Trust, Belfast, Northern Ireland

Background. This study was conducted to assess the ability of patients receiving heart valve replacements to practice self-managed anticoagulation using a portable coagulometer.

Methods. We carried out a prospective, randomized trial, comparing self-managed anticoagulation with conventional management. Patients practicing self-managed anticoagulation (51 patients) did so at home, measuring their international normalized ratio and then deciding on their dosage of warfarin, while conventionally controlled patients (n = 49) attended hospital clinics or were managed by their family physicians.

Results. We successfully trained 41 of 44 patients who agreed to self-manage their anticoagulant therapy; 34 of

the 41 managed their own anticoagulation at home for 2 years. Their control, assessed by a number of tests in range (67.6% versus 58.0%) and time in therapeutic range (76.5% versus 63.8%), was significantly better than that for the group managed conventionally ($p < 0.0001$). There was no significant difference in mortality or morbidity between the two groups.

Conclusions. Self-managed anticoagulation is a reliable, easily learned method of controlling anticoagulation, and it is suitable for approximately two thirds of patients, with excellent results.

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Anticoagulant-related complications after heart valve replacement are major contributors to mortality and morbidity [1]. Determination of the prothrombin time expressed as the international normalized ratio (INR) using a laboratory coagulometer and a standardized thromboplastin is currently the gold standard method for anticoagulation monitoring. Many approaches to improving control of anticoagulation have been tried with some success, including computer-assisted dosing [2], more frequent testing [3], management by specialist clinics [4], and management by general practitioners [5, 6].

More recently, easy to use portable coagulometers that perform an INR on a single drop of capillary blood have become available. Early experience with self-managed anticoagulation (SMA) indicates that selected patients can control their own anticoagulation using such a portable coagulometer as the CoaguChek (Roche Diagnostics, Lewes, UK) with excellent results [7-9].

Our aim with this study was to conduct a prospective, randomized controlled trial to assess the ability of our patients to control their anticoagulation with the CoaguChek.

Material and Methods

The CoaguChek is a portable coagulometer that uses a test strip containing a reaction chamber coated with iron oxide particles and thromboplastin derived from rabbit brain. A drop of capillary blood (10 to 25 μ L) obtained from a finger prick is applied to the strip, which is in an electromagnetic field. As the blood clots, the iron oxide particles, previously agitated by the electromagnetic field, stop moving, and this lack of movement is detected by reflectance photometry. Each box of test strips is supplied with a coded chip providing calibration data for the coagulometer. The manufacturer provides a liquid quality control.

Patients

We enrolled the first 100 patients who consented to enter the study from those who had previously had heart valve operations between 1994 and 1997 by one surgeon (H.O.K.) and were on life-long anticoagulation therapy with warfarin (231 patients). Exclusion criteria were kept to a minimum, ie, all patients older than 85 years were excluded, as were those with visual difficulties. These 100 patients were then randomized using a simple random number generator program to allocate the 100 patients into two groups:

Group 1 consisted of 51 patients (mean age, 61.0 years; range, 32 to 85 years). The male:female ratio was 27:24. They had 35 aortic valve replacements, 15 mitral valve replacements, and one double valve replacement. All prosthetic valves were St. Jude Medical except 1 patient

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Address reprint requests to Mr O'Kane, Department of Cardiac Surgery, Royal Hospitals Trust, Grosvenor Rd, Belfast BT12 6BA, Northern Ireland; e-mail: hugh@doctors.org.uk.

Table 1. Protocol Used by Patients to Adjust Dose of Warfarin^a

INR Value Obtained	Action Taken by Patient
< 1.5	Contact doctor for advice
1.5-1.9	Increase dose of warfarin by 1 mg daily
2.0-2.5	Same dose of warfarin
2.6-4.0	Decrease dose of warfarin by 1 mg daily
> 4.0	Contact doctor for advice

^a If the patient fluctuated between ranges very often, the dose increment was changed to 0.5 mg daily rather than 1 mg.

INR = international normalized ratio.

who had a repair of a paraprosthetic leak of a Bjork Shiley mitral prosthesis and 1 patient who previously had an Edwards Duromedics mitral valve and returned for an aortic valve replacement. These patients were offered training in SMA, and those who accepted were trained in two 3-hour sessions. Training group size varied from 2 to 5 patients, and during training patients were given basic facts about blood clotting, how to recognize the side effects of over- and under-anticoagulation, and how drugs, diet, alcohol, and infection may alter coagulation. They were also supervised through 10 international normalized ratio (INR) determinations using the Coaguchek, and also through a quality control test. Patients received basic education about hand hygiene while performing tests, to reduce risk of infection. Theoretical knowledge was assessed using a simple examination of 10 questions requiring one- or two-word answers. Successful patients were asked to perform INR testing once a week. They were encouraged to perform more frequent INR measurements if they were commenced on new medication, consumed more than usual amounts of alcohol, had unstable INRs, or had an infection. The therapeutic range for their INR was 2.0 to 3.0, with aortic valve replacements advised to stay between 2.0 and 2.5 and mitral valve replacements and double valve replacements 2.5 and 3.0. They adjusted their anticoagulant dosage according to a simple protocol (Table 1). Patients were also taught the importance of seeking medical advice if their INR was too high (> 4.0) or too low (< 1.5) and also if they had any bleeding or thromboembolic events. A doctor from our unit was available to answer calls from patients. Routine review by a physician was not arranged.

Group 2 consisted of 49 patients (mean age, 60.8 years; range, 26 to 81 years). Male:female ratio was 19:30. They had 24 aortic valve replacements, 22 mitral valve replacements, and 3 double valve replacements. These patients were left with their usual anticoagulant management by their family physician, or at a hospital anticoagulant clinic. Although we did not control the therapeutic range, we recommended the same ranges for all patients on discharge.

Ethical approval for this study was obtained from the local hospital ethics committee. We obtained informed consent from all patients.

Data Collection

Group 1 patients (SMA) recorded the results of their INR measurements in a standard book issued by the Health Authority. These were then mailed to us at 3- to 4-month intervals as requested, and the data reviewed by one of us (P.S.). General practitioners and anticoagulation clinics used the same books for group 2 patients, and these were collected at similar intervals and reviewed by one author (P.S.). In addition, data on morbidity (ie, hemorrhage or thromboembolic phenomena) as defined by the guidelines of The Society of Thoracic Surgeons [10] was collected by postal questionnaire. We ensured complete follow-up by telephone contact with each patient and by contacting the patient's general practitioner if required. Autopsy records were obtained in relevant cases.

Statistical Analysis

An IBM PC-compatible desktop computer was used for data analysis. We used the Statistica software package (StatSoft Inc, 1998; STATISTICA for Windows, Tulsa, OK).

For group comparisons, we used Fisher's exact test for small sample numbers and the χ^2 test for larger groups. To calculate time in therapeutic range for each group, we used the method described by Rosendaal and associates [11]. This method, assuming a linear relationship between two consecutive INR values, calculates the time in days at various INR values in-between and thus is an estimate of the time in therapeutic range.

Results

Of the 51 patients who were randomized to group 1 (SMA group), 7 patients declined training. The reasons stated were distance from training center ($n = 4$), lack of confidence in ability to manage warfarin dosing ($n = 2$), and lack of confidence in ability to perform finger-prick sampling of blood ($n = 1$).

The remaining patients ($n = 44$) attended all the required training sessions. Of these patients, 3 were considered unsuitable for SMA as they either had difficulty with blood sampling or with managing their own warfarin dosing. Thus, 41 (80%) of the original 51 patients commenced SMA. Three of these patients initially required the help of a caregiver (in all cases a relative), but later managed independently.

In group 1, at the end of 3 months, 6 of the 41 patients had abandoned SMA in favor of conventional management: 3 had difficulty obtaining blood samples, 2 preferred general practitioner management, and 1 had technical problems with the instrument. Of the remaining 35 patients (69%), 1 patient successfully practiced SMA for a year and then returned to her general practitioner when she had difficulty obtaining strips from us. The other 34 patients continued to practice SMA for 2 years. This yields a total follow-up of 67 patient-years. During this period, they have performed 3,136 tests, of which 67.6% were in the therapeutic range (INR, 2.0 to 3.0). Mean INR for the group was 2.5.

In group 2, follow-up was obtained for 48 of the 49

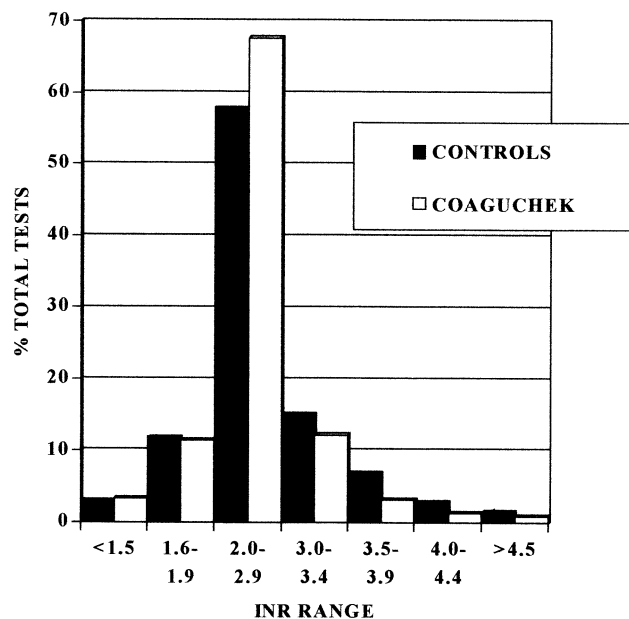


Fig 1. Distribution of tests (expressed as percentage of total number of tests) for patients practicing self-managed anticoagulation (COAGUCHEK, n = 35) and for patients undergoing conventional testing (CONTROLS, n = 49). (INR = international normalized ratio.)

patients for the period of the trial. One patient, a 70-year-old woman (mitral valve replacement previously), died within the first 3 months of the trial; no INR data were available for this period. The other 48 patients had 1,060 tests performed during the trial period, of which 58% were in the therapeutic range ($p < 0.0001$ when compared with group 1). The total follow-up period was 85.1 patient-years. Mean INR over the period was 2.6. The distribution of the number of tests versus INR for groups 1 and 2 is shown in Figure 1.

Frequency of Testing

The frequency of testing for group 1 (SMA) was calculated at 3, 6, 12, and 24 months and was 1.35, 1.06, 0.96, and 0.90 tests/wk, respectively, demonstrating a fall in testing frequency during the trial period (Table 2). The testing frequency for group 2 was 0.24 tests/wk and did not vary during the study period.

Table 2. Frequency of Tests Performed by Group 1 Patients^a

Interval From Start of Study	Frequency of Testing (tests/wk)
3 months	1.35
6 months	1.06
12 months	0.96
24 months	0.90

^a Patients in group 1 practiced self-managed anticoagulation (n = 35 for first year and 34 for second year). The frequency of tests performed by group 2 did not vary.

Table 3. Comparison of Time in Therapeutic Range^a

INR Range	Controls (%)	Coaguchek (%)
1.5-1.9	9.4	10.0
2.0-2.4	34.0	43.0
2.5-2.9	29.8	33.5
3.0-3.4	17.2	9.5
3.5-3.9	5.85	2.3

^a Time in therapeutic range was expressed as percentage of total time in study. The therapeutic range was taken to be INR 2-3 and thus equals the sum of rows 2 and 3.

INR = international normalized ratio.

Time in Therapeutic Range

Group 1 patients (SMA) were in therapeutic range 76.5% of the time compared with the patients in group 2 (conventional management, 63.8%, $p < 0.0001$; Table 3).

Furthermore the group 1 patients were in the 3.5 to 3.9 INR range for only 2.3% of the time compared with 5.9% for the group 2 patients

Complications of Anticoagulant Therapy

In the 35 patients in group 1 who have practiced SMA, nine minor thromboembolic events and two minor bleeding events have occurred. Among the 6 patients who switched to conventional monitoring in the first 3 months, one has suffered a major gastrointestinal bleed, requiring hospital admission and transfusion, and another patient has suffered a major thromboembolic stroke. There has been no mortality in this group.

Among group 2 (conventional monitoring), 1 patient died of a valve thrombosis, confirmed at autopsy (INR, 1.2 at time of death). Three patients have died of cardiac (nonvalve-related) events. Autopsies were not performed. The difference in mortality (4 in group 2 versus 0 in group 1, $p = 0.15$) was not significant statistically.

In this group, 10 minor thromboembolic events have occurred along with two minor bleeding events.

Comment

Most patients in our study were able to learn SMA, and we successfully trained 41 of 44 (93%) patients who attempted SMA. Of the 3 patients (6.8%) deemed unsuitable for SMA, 1 could not grasp the concept of self-dosing and the other 2 could not consistently measure their INR. It is interesting that one of the latter patients who had difficulty measuring her INR was a non-insulin-dependent diabetic who practiced home monitoring of her blood glucose levels. She had difficulty obtaining the 25 μ L of blood required for the Coaguchek at the time of her training. Three other patients, who opted out of the trial, also had difficulty obtaining the required amount of blood. Newer test strips have since been developed that require 10 μ L of blood, closer to the volume required for blood glucose monitoring. Had these newer test strips been available during the training period of our trial, more patients may have been successful at performing the INR measurement.

We did not preselect our patients for this trial, and after reviewing the data on the 9 patients who did not continue with SMA, we were unable to identify any characteristics, such as age or educational background, that would aid preselection. Cromheecke and colleagues [12] reported that 1 of 50 patients (2%) in their study was unable to continue with SMA. Our dropout rate is higher (20%), possibly because our unselected patient cohort is much older (mean age, 60.8 years versus 42 years).

After 2 years, 34 of the original 51 patients (67%) were successfully practicing SMA. Not all patients will be suitable for this method, and indeed some may not wish to pursue self-management. However, we believe that all interested patients should be offered training until criteria that can predict which patients will be successful at self-management are established.

Although our results show that patients practicing SMA achieved better control compared with conventional management, we were unable to demonstrate a significant reduction in anticoagulant-related complications. However, other authors have confirmed that better control results in a reduction of anticoagulant related complications [13, 14].

In addressing the question of testing frequency, we advised our patients to undertake one test per week. In our study, patients performed 0.90 tests per week during the 2-year study period, and this is similar to the results obtained by Cromheecke and coworkers [12], who reported a test rate of one per 8.6 days (0.81/wk). After the first few months we were pleased to note that the testing frequency did not exceed that recommended by us. An increased testing frequency has obvious major implications for the cost of such a system. We do, however, have some concern that patients were performing fewer than 1 test per week as this suggests that there may be an element of complacency on the part of our patients, and we believe that the success of SMA depends on consistent, regular, and frequent testing.

A quality assurance system is required to ensure that instrument failure or drift does not result in erroneous results, leading to inappropriate dosages. The internal quality controls provided by the manufacturer are difficult to use. Although we instructed our patients to carry out a quality control test with every new box of test strips that they used and also if they obtained widely variant INR measurements, our experience is that they do not comply. Therefore we intend to carry out annual external quality control comparisons with a laboratory INR for future participants in our SMA program [15].

Self-managed anticoagulation will be expensive to introduce. However, during this 2-year study period, the cost of the portable coagulometer has halved. We envision these costs coming down further in a manner similar to the cost of glucometers, which have fallen to less than a fifth of their introductory costs 15 years ago. Further savings should result from a fall in anticoagulant-related complications and consequent hospital costs. This is illustrated in a recent study [16], which assessed cost-effectiveness using a Markov model and hypothetical groups and then factoring in all costs, including patient-

related costs. This study predicted a potential saving with SMA. The weakness of their method lies in it being a theoretical method yet to be tested in clinical practice. Additional savings would result from reduced visits to physicians for monitoring purposes.

Other benefits obtained by patients practicing SMA are harder to quantify. They report greater personal convenience, more confidence in their therapy, and the ability to travel widely with less fear of deviation from therapeutic range while away from home.

With increasing indications for warfarin therapy such as atrial fibrillation [17, 18], there will inevitably be an increased workload for the health services. Self-managed anticoagulation may reduce this if some patients could independently monitor and manage their own anticoagulation, with only minimal input from health professionals.

We thank Roche Diagnostics (Lewes, Surrey, UK; formerly Boehringer Mannheim) for providing the CoaguChek coagulometers and test strips used in this study.

Copies of our training schedule and written tests for patients are available upon request.

References

1. Ibrahim M, O'Kane H, Cleland J, Gladstone D, Sarsam M, Patterson C. The St. Jude Medical prosthesis. A thirteen-year experience. *J Thorac Cardiovasc Surg* 1994;108:221-30.
2. Fitzmaurice DA, Hobbs FD, Murray ET, Bradley CP, Holder R. Evaluation of computerized decision support for oral anticoagulation management based in primary care. *Br J Gen Pract* 1996;46:533-5.
3. Horstkotte D, Piper C, Wiemer M. Optimal frequency of patient monitoring and intensity of oral anticoagulation therapy in valvular heart disease. *J Thromb Thrombolysis* 1998;5(Suppl 1):19-24.
4. Ansell JE. Anticoagulation management clinics for the outpatient control of oral anticoagulants. *Curr Opin Pulm Med* 1998;4:215-9.
5. Pell JP, McIver B, Stuart P, Malone DN, Alcock J. Comparison of anticoagulant control among patients attending general practice and a hospital anticoagulant clinic. *Br J Gen Pract* 1993;43:152-4.
6. Good J. The monitoring of prothrombin time ratios in general practice—a model for chronic disease care? *Ir Med J* 1991;84:126-7.
7. Ansell J, Holden A, Knapic N. Patient self-management of oral anticoagulation guided by capillary (fingerstick) whole blood prothrombin times. *Arch Intern Med* 1989;149:2509-11.
8. White RH, McCurdy SA, von Marensdorff H, Woodruff DE Jr, Leftgoff L. Home prothrombin time monitoring after the initiation of warfarin therapy. A randomized, prospective study. *Ann Intern Med* 1989;111:730-7.
9. Hasenkam JM, Kimose HH, Knudsen L, et al. Self management of oral anticoagulant therapy after heart valve replacement. *Eur J Cardiothorac Surg* 1997;11:935-42.
10. Edmunds LH Jr, Clark RE, Cohn LH, Grunkemeier GL, Miller DC, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity of The American Association for Thoracic Surgery and The Society of Thoracic Surgeons. *J Thorac Cardiovasc Surg* 1996;112:708-11.
11. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A

- method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993;69:236-9.
12. Cromheecke ME, Levi M, Colly LP, et al. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison. *Lancet* 2000;356:97-102.
 13. Bernardo A. [Optimizing long-term anticoagulation by patient self-management?]. *Z Kardiol* 1998;87(Suppl 4):75-81.
 14. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs [see comments]. *Arch Intern Med* 1998;158:1641-7.
 15. Preston FE. Quality control and oral anticoagulation. *Thromb Haemost* 1995;74:515-20.
 16. Lafata JE, Martin SA, Kaatz S, Ward RE. The cost-effectiveness of different management strategies for patients on chronic warfarin therapy. *J Gen Intern Med* 2000;15:31-7.
 17. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation. *Stroke Prevention in Atrial Fibrillation III* randomised clinical trial. *Lancet* 1996;348:633-8.
 18. Cleland JG, Cowburn PJ, Falk RH. Should all patients with atrial fibrillation receive warfarin? Evidence from randomized clinical trials *Eur Heart J* 1996;17:674-81.

INVITED COMMENTARY

This study confirms the findings of several other trials which have shown a benefit from self-managed anticoagulation in comparison to conventional management, in terms of a greater number of International Normalized Ratio (INR) values within the chosen target range. The importance of good quality anticoagulation control cannot be over-emphasised, as it has been shown that poor control, with a high percentage of INRs outside the target range, is a major independent risk factor for reduced long-term survival after valve replacement. Not only should self-managed anticoagulation facilitate this tighter control and thereby possibly enhance survival but patients should enjoy an improved quality of life with less reliance on hospital-based systems and greater freedom to travel.

Although there were more INR values in the target range and a greater estimated time within this range in the self-managed anticoagulation group, the authors were unable to demonstrate any associated reduction in thromboembolic and bleeding events in comparison to conventional anticoagulation, despite a higher ratio of aortics to mitrals in the self-managed group which should have favored this group. There may be several explanations for this:

1. This was a small study with relatively short follow-up.
2. Many events labelled as 'thromboembolic' in all valve series occur as the result of pathogenetic mechanisms not directly related to the prosthesis and uninfluenced by anticoagulation.

3. The target INR ranges were lower than those recommended for prosthetic valves, particularly in the mitral position, and the thromboembolic rate was high in both groups, 13.4% per year in the self-managed group and 11.7% per year in the conventional management group.
4. Data on adverse events were collected by postal questionnaire. This methodology is less accurate than direct patient interview and may overestimate the true number of thromboembolic events if ill-defined neurological symptoms are incorrectly ascribed to transient ischemic attacks (TIAs). A large number of "false" events in both groups could then blunt the discriminatory power of the comparison.

Further randomized trials of self-managed anticoagulation versus conventional management are required, beginning at the time of surgery and with larger numbers, longer follow-up, and more detailed stratification of patients according to their risk factors. Nevertheless, it is already apparent from this and other studies that there are many advantages of self-managed anticoagulation and it is likely that eventually this method of anticoagulation control will become almost as commonplace as the self-management of insulin dosage by diabetics.

Eric G. Butchart, FRCS

*Department of Cardiothoracic Surgery
University Hospital
Cardiff CF14 4XW, Wales, United Kingdom*