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Improved anticoagulant control in patients using home international normalized ratio testing and decision support provided through the internet

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Key words
anticoagulant monitoring, warfarin, decision support, internet, telemedicine.

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Abstract

Aim: To compare anticoagulant control using self-testing and decision support provided via the internet with standard laboratory testing.

Methods: A prospective comparative study of 41 patients on long-term warfarin. All patients were monitored using a laboratory-based service for at least 12 months prior to changing to self-testing using a portable testing device and online decision support. The level of anticoagulant control was assessed using the time the international normalized ratio (INR) was within the therapeutic range (TTR), the proportion of INR results in range and the interval between tests. This was a non-inferiority study.

Results: There was no statistically significant difference between the two methods of anticoagulant control with a trend in favour of self-testing; the mean TTR was 72% vs 81%. However, a small cohort of patients with poor control (TTR 38%) during laboratory testing achieved a significant improvement (TTR 71%) using self-testing. The INR was above the therapeutic range for a similar time in both groups but below the range for a significantly shorter period during self-testing suggesting a lower risk of complication in this group.

Conclusion: Self-testing with online computer decision support achieved anticoagulant control at least as good as laboratory management. Additional benefits of a home-based service make this an attractive option for selected patients.

Introduction

It is well established that oral anticoagulants significantly reduce the risk of systemic emboli in patients with atrial fibrillation[1] and mechanical heart valves, and prevents further thromboses in patients with venous thromboembolic disease. It has been estimated that approximately 1% of the population could benefit from anticoagulant therapy based on the incidence of atrial fibrillation[2,3]. A significant number of patients is deemed unsuitable for anticoagulation for sound clinical reasons, but some patients are denied treatment because of difficulties with access to appropriate monitoring[4]. In New Zealand, patients in remote areas may have to travel considerable distances for blood tests and could benefit from the convenience of home monitoring.

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There is no consistent method for monitoring anticoagulants in New Zealand. It is largely managed by general practitioners, but in some cities there are laboratory or hospital-based services with dosing provided by hospital doctors. The level of control is difficult to assess as audit of these services is complex and carried out infrequently. An audit in Auckland[5] showed that control by general practitioners achieved a mean time in the therapeutic range (TTR) of only 58%, which is considered suboptimal as international guidelines recommend that the TTR should be greater than 60%.

The availability of home testing devices has removed some of the problems associated with anticoagulant management and has led to an increased interest in patient self-testing and patient self-management. Patient self-testing is where a patient measures his or her own international normalized ratio (INR) with dose adjustment by a physician; patients' self-management is where the patient is responsible for both the INR measurement and dose adjustment. Several studies have shown that the quality of anticoagulant control achieved by patients is as

good as or better than control attained using conventional management.[6] Although patient self-management is an attractive option for some patients it is likely that only a relatively small number will feel comfortable taking on full control of their treatment; in one clinical trial using self-management only 13% of eligible patients agreed to participate.[7] Patient self-testing may be easier for more patients, but has the disadvantage that a supervising doctor has to be contacted for advice, which can be time-consuming and cumbersome. In order to overcome these problems we have developed an internet-based warfarin management system that allows patients to carry out self-testing at home and enter their INR results into a secure website and receive immediate dosing advice. If the result is outside a specified range the result is automatically sent for review by a doctor. The website is designed with several safeguards to minimize the risk of complications.

We carried out a prospective study in which the quality of warfarin control achieved using patient self-testing and the internet-based management system was compared with control achieved using conventional laboratory-based management.

Patients and methods

Patients on long-term warfarin attending the laboratory at Palmerston North Hospital, New Zealand were invited to participate. The patients were self-selected and could be included if they had been on anticoagulant therapy for more than 12 months, were willing to perform their own INR blood test using the CoaguChek XS (Roche Diagnostics NZ, Auckland, NZ) and had access to the internet. The study was approved by the central ethics committee in New Zealand and all patients provided written informed consent.

Methods

This was a comparative study comparing retrospective data from patients using laboratory-based anticoagulant management with prospective data from the same patients using self-testing and internet-based decision support. During the 12 months before the study, all patients had INR tests performed at their local laboratory and anticoagulant control managed by medical staff in the laboratory or by their own general practitioner. Dosing information and INR results were collected for all patients during the 12 months before the study.

Each patient was provided with a CoaguChek XS monitor (Roche Diagnostics NZ Ltd). The testing devices and test-strips were provided free by Roche Diagnostic for the trial period. The patients were taught how to perform an INR test using a finger prick blood sample. The patients used an online decision support package (INR Online Ltd, Palmerston North, NZ) to assist with dose recommendations. Each patient had access to a secure website protected by username and password. Access was free for the trial period.

There were three steps to the self-testing procedure. First, the INR was performed on the CoaguChek XS. Second, the patient logged-on to a secure website and answered questions about compliance, bleeding complications and changes to concomitant medication since their previous test. This information was recorded and was accessible to the reviewing doctor. Finally, the patient entered the INR result and received an immediate dose recommendation and date for the next test. The patient also received an email with the same information and a dosing calendar that could be printed to assist with compliance. If the INR was outside the recommended therapeutic range, the result was automatically flagged for review by a doctor. Following review the patient received a second email with details of any further dose adjustment.

Sample size

This is a non-inferiority study. The hypothesis is that anticoagulant control using self-management is at least as good as standard laboratory monitoring.

In the audit of general practitioner warfarin management in the community performed by the principal investigator, 58% of INR measurements were within the therapeutic range (sample size 9000 INR measurements). It is assumed that anticoagulant control using near-patient testing is as good as standard if the percentage of INR measurements within the therapeutic range differs by less than 5% of our previous study. We conclude that computerized monitoring is non-inferior if the calculated one-sided *P*-value is less than 0.05. With a test power of 0.8, a sample size of 750 INR measurements is sufficient to reject the null hypothesis. Each patient will perform an INR every 1 to 2 weeks for 12 months using self-testing. Therefore, each patient will perform approximately 40 tests during the self-testing period of the study. A total of approximately 50 patients would provide sufficient results.

Data analysis

The time within the therapeutic range was calculated by assuming a linear change in INR between tests using the method described by Rosendaal *et al*.[8]

The following data were recorded for each patient: (i) The percentage of time the INR results were above, below

Table 1 Comparison of anticoagulant control between laboratory management and self-testing using internet-based decision support

	Laboratory management	Self-testing and computer support	*P*-value
Mean % days in range ($n = 41$)	72.4	81.3	0.16
Mean % days in range in patients with >60% of TTR before change (Good control prior) ($n = 32$)	83.0	82.5	NS
Mean % days in range in patients with <60% of TTR before change (Poor control prior) ($n = 9$)	38.8	71.1	0.01
Mean % days below therapeutic range	20.3	10.9	<0.005
Mean % days above therapeutic range	6.3	9.0	NS
%INR results within the therapeutic range	63	70	
Average interval between tests	19.6 days	10 days	<0.005
No. patients with >60% of time in range	32	37	
% tests with INR >4.0	2.17	2.66	
% tests with INR >5.0	0.57	0	

INR, international normalized ratio; NS, not significant; TTR, time in the therapeutic range.

and within the therapeutic range; (ii) the percentage of INR results above, below and within the therapeutic range; (iii) the percentage of INR results above 4.0 and above 5.0; and (iv) the mean interval between test.

Patients were defined as having 'good control' if their INR results were within the therapeutic range for >60% of the time (based on BCSH Guidelines[9]).

Statistical method

The Wilcoxon signed-rank test was used to test for difference between paired data as the results showed a non-normal distribution. A *P*-value of <0.05 was considered statistically significant.

Results

A total of 46 patients was entered into the study, five patients withdrew early and were not included in the assessment; three had difficulties performing self-testing (two before entering any results and one after three INR tests); one died in a road traffic accident; and one stopped warfarin after the diagnosis of pancreatic cancer. The results of 41 patients were included in the analysis.

The time in range

The TTR was calculated from the sum of all patient results. During the 12 months of laboratory testing before the study, the TTR was 72.4% (based on 14 847 patient days), which improved during the self-testing period to 79.6% (based on 10 786 patient days). In several patients control was unstable during the first month of self-testing. If data during this period were excluded, control improved even further to 81.3% of the time in range (Table 1).

Patients had results below the therapeutic range for a significantly longer time during the laboratory testing period than during self-testing (mean 20.3% vs 10.8%; $P < 0.005$). There was no significant difference in the time above the therapeutic range between the two groups; 6.3% with laboratory testing and 9% with self-testing ($P = 0.095$). The highest INR recorded during laboratory testing was 7.0 with four INR results above 5.0. In the self-testing group the highest INR was 5.6 with three results above 5.0. When the unstable results during the first month of self-testing were excluded there were no INR measurements above 5.0 in the self-testing group.

INR results in range

The INR results in range were calculated using a composite of all INR results. During the laboratory testing there were 876 INR results recorded; 63% of INR results were in range, 25% were below range and 11% over range. During self-testing, control improved with 70% of INR results in range, 15% below and 14% above based on 1120 INR results (Table 1).

Individual results

The composite results give an overall assessment of control, but do not truly reflect the changes for individual patients. During the 12 months of laboratory testing we calculated the time in range for each patient. This gave a wide scatter of results from 19.9% of time in range to 100% with a median of 78.5%. This allowed us to divide the patients into two groups based on anticoagulant control. We categorized patients as having 'good' control if the TTR was greater than or equal to 60% and 'poor' control if the TTR was less than 60%.

During the period of laboratory testing, 32 patients had good control and nine patients had poor control. The

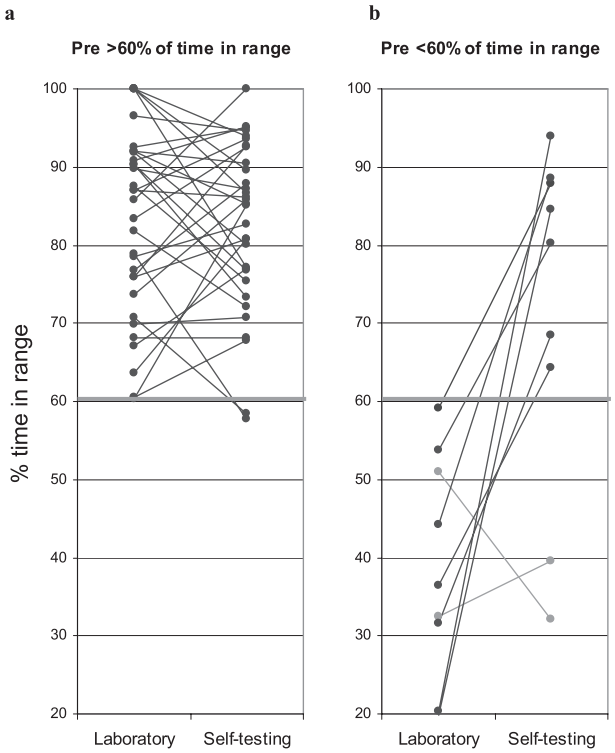

Figure 1 Anticoagulant control measured by % days in range during the period of laboratory testing and self-testing with internet-based support. (a) Patients with 'good' control during laboratory testing. (b) Patients with 'poor' control during laboratory testing.

patients with 'good' control had a mean TTR of 83%, which was virtually unchanged during self-testing with a mean TTR of 82.5%; however, the patients with 'poor' control using laboratory testing showed a significant improvement in mean TTR from 38.8% to 71.1%, with seven patients achieving a TTR of >60% (Fig. 1).

Discussion

This study uses an internet-based automated decision support system giving patients the advantage of full anticoagulant management from home. The patients performed self-testing using the CoaguChek XS testing device, entered their INR results through a webpage and received immediate treatment advice. Remote medical review of results was provided for INR results outside the therapeutic range and any further dose changes were conveyed to the patient by email.

Our results show that this method of anticoagulant control was at least as good as conventional laboratory testing maintaining the INR within the therapeutic range for 80% of the time. The study was designed as a non-inferiority study and was not intended to show a significant difference between methods; however, there is a trend in favour of the self-testing model. Interestingly, the level of anticoagulant control in our patients during the period of laboratory testing was higher than we expected with a mean time in range of 72%, which is considerably better than the level of control reported in our earlier audit where patients maintained a time in range of only 58%.[5] The reason for the good control in this group may be related to the patient selection. Those choosing to participate in the study are likely to be well motivated with some understanding of warfarin control and more likely to be compliant.

Although the mean values show no statistically significant benefit, the self-testing model does show a significant improvement in control for a selected group of patients, namely those with poor control using the conventional laboratory-based service. In our series nine patients had poor control during the 12 months before self-testing with a mean time in range of only 38%. The reason for poor control is uncertain, but in some cases testing was infrequent. During self-testing, control improved in this group of patients with the mean time in range increasing significantly to 71% with seven cases achieving a time in range of greater than 60% (Fig. 1). Although this is only a small number of patients, improving control in this group has a major clinical benefit as patients with TTR <45% have a high risk of complications.[10]

The close control of warfarin is important to minimize both haemorrhagic and thrombotic complications. Our study was not powered to detect a significant difference in the incidence of complications, but an assessment of risk is possible using the TTR and the level of INR control as surrogate markers. The TTR is directly related to the risk of both bleeding and embolic complications.[10] A retrospective study showed that an improvement in TTR by 7% reduced major haemorrhage by 1 event per 100 patient years, and a 12% increase in TTR reduced thromboembolic complications by a similar amount.[11] Our results suggest that self-testing may reduce the risk of thrombotic complications as the INR was below the therapeutic range for a significantly shorter time (10.9% of the time) than during laboratory testing (20.3% of the time). The reason for the difference between the computerized dosing and clinician dosing is uncertain, but may be explained by doctors tending to be cautious when increasing the warfarin dose. A similar difference has been reported in a study comparing clinician and computer dosing, which showed comparable results at a low therapeutic range but at a higher range the computer achieved better control as doctors tended to under dose.[12]

The risk of bleeding can also be assessed using a surrogate as there is a strong association between an

elevated INR and bleeding with the incidence rising rapidly when the INR exceeds 5.0. In our series there was no significant difference in the number of INR measurements above 5.0 between the two groups with no episodes of serious bleeding requiring admission or transfusion. There were only three INR measurements above 5.0 in the self-testing group.

Our results are in line with two other studies showing improved control for patients performing self-testing with clinical support provided through the internet. These both showed a similar level of improvement with the TTR increasing from 63% to 74.3%[13] in one study and from 58.6% to 74%[14] in the other. Several other studies of self-testing or self-management of warfarin have also shown improved control. A meta-analysis of 13 publications showed that patient self-testing had a lower risk of bleeding and thrombosis, and in several series achieved a better time in the therapeutic range than conventional testing.[6] There are several suggested reasons for the improved control, including better compliance, consistent dosing using an automated algorithm and an automated recall system; however, more frequent testing is probably the major factor.[6,15] One study showed that it is possible to achieve a TTR of 90% with self-testing every 4 days and 76% with weekly testing; however, control fell to only 48% when tested every 24 days.[16] In our series the mean interval between tests was significantly shorter while patients were self-testing (10 days) than during the period of laboratory control (19.6 days)

In addition to the measured improved control, an automated internet-based service provides a number of advantages for both clinicians and patients. A general practice-based service can be inefficient and time-consuming. There is often no established system for dosing, record keeping, patient recall or audit, where as these problems are easily managed by a computer system. An online service also has the advantage that the doctor does not need to purchase expensive software for the management of a small number of cases and can access the service from anywhere.

There are also considerable benefits for the patient. The process is more convenient as there is no need to attend a blood collecting room or laboratory for a blood test, which may require time-off work, lengthy travel and difficulties with parking. The home-based system allows patients to test anywhere at any time, which is particularly beneficial for patients who travel overseas. The system also offers consistent dosing, a printable dosing calendar and automated email reminders to assist with safety and compliance. Cost benefit analysis of this type of service has been assessed. In a Canadian study the set-up costs for self-testing including training were higher than laboratory testing at approximately C$1500; however, the ongoing costs for monitoring were similar, with self-testing patients performing weekly tests and usual care patients testing every month. In New Zealand the set-up costs are approximately NZ$1000 with ongoing costs around $15/month including internet supervision. In the Canadian model the benefits achieved by improved control off-set the increased cost. The cost-effectiveness of self-managed long-term anticoagulation therapy over physician-managed care was C$14 129 per quality-adjusted life year gained over 5 years,[17] implying this is a cost-effective intervention. In New Zealand there is no public funding or insurance cover for this type of service.

Conclusion

A consumer survey was sent to all participants who completed the study. All respondents expressed a preference for home-based testing over the conventional laboratory management. We have shown that patient self-testing using an internet-based service achieves good anticoagulant control for the majority of patients. The added convenience makes this method of management an attractive option for selected motivated individuals.

References

1 Segal JB, McNamara RL, Miller MR, Kim N, Goodman SN, Powe NR *et al*. Prevention of thromboembolism in atrial fibrillation. A meta-analysis of trials of anticoagulants and antiplatelet drugs. *J Gen Intern Med* 2000; **15**: 56–67.

2 Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP *et al*. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006; **114**: 119–25.

3 Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV *et al*. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation. *JAMA* 2001; **285**: 2370–5.

4 Beyth RJ, Antani MR, Covinsky KE, Miller DG, Chren MM, Quinn LM *et al*. Why isn't warfarin prescribed to patients with nonrheumatic atrial fibrillation? *J Gen Intern Med* 1996; **11**: 721–8.

5 Young L, Ockelford P, Harper P. Audit of community-based anticoagulant monitoring in patients with thromboembolic disease: is frequent testing necessary? *Intern Med J* 2004; **34**: 639–41.

6 Heneghan C, Alonso-Coello P, Garcia-Alamino JM, Perera R, Meats E, Glasziou P. Self-monitoring of oral anticoagulation: a systematic review and

meta-analysis. *Lancet* 2006; **367**: 404–11.
7 Gardiner C, Williams K, Mackie IJ, Machin SJ, Cohen H. Review. Patient self-testing is a reliable and acceptable alternative to laboratory INR monitoring. *Br J Haematol* 2005; **128**: 242–7.
8 Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët EA. Method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993; **69**: 236–9.
9 Baglin TP, Keeling DM, Watson HG. Guidelines on oral anticoagulation (warfarin): third edition – 2005 update; British Committee for Standards in Haematology. *Br J Haematol* 2006; **132**: 277–85.
10 Veeger NJ, Piersma-Wichers M, Tijssen JG, Hillege HL, van der Meer J. Individual time within target range in patients treated with vitamin K antagonists: main determinant of quality of anticoagulation and predictor of clinical outcome. A retrospective study of 2300 consecutive patients with venous thromboembolism. *Br J Haematol* 2005; **128**: 513–19.
11 Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P *et al*. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation a systematic review. *Circ Cardiovasc Qual Outcomes* 2008; **1**: 84–91.
12 Poller L, Wright D, Rowlands M. Prospective comparative study of computer programs used for management of warfarin. *J Clin Pathol* 1993; **46**: 299–303.
13 O'Shea SI, Arcasoy MO, Samsa G, Cumming SE, Thames EH, Surwit RS *et al*. Direct-to-patient expert system and home INR monitoring improves control of oral anticoagulation. *J Thromb Thrombolyisis* 2008; **26**: 14–21.
14 Ryan F, Byrne S, O'Shea S. Randomized controlled trial of supervised patient self-testing of warfarin therapy using an internet-based expert system. *J Thromb Haemostas* 2009; **7**: 1284–90.
15 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.
16 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.
17 Regier DA, Sunderji R, Lynd LD, Gin K, Marra CA. Cost-effectiveness of self-managed versus physician-managed oral anticoagulation therapy. *Can Med Assoc J* 2006; **174**: 1847–52.

Prothrombin complex concentrates used alone in urgent reversal of warfarin anticoagulation

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Abstract

Background: Prothrombinex-VF (a three-factor prothrombin complex concentrate) contains little factor VII. Therefore, the Warfarin Reversal Consensus Guidelines from 2004 published by The Australasian Society of Haemostasis and Thrombosis recommend that it be administered with fresh frozen plasma to reverse warfarin anticoagulation.
Aim: To evaluate the efficacy and safety of Prothrombinex-VF used alone in warfarin reversal.
Methods: Adult patients requiring urgent reversal of warfarin anticoagulation were defined as having achieved complete (target international normalized ratio (INR) <1.4) or partial reversal (target INR 1.4–2.0) of their anticoagulation. Prothrombinex-VF was given at doses of between 25 and 50 IU/kg based on the intent of reversal and an INR was obtained 30 min post infusion.
Results: A total of 50 patients (mean age 72 years, range 32–85 years) was included. The median initial INR in the complete reversal arm ($n = 35$) was 3.5 (range 1.7–20) with 91% achieving the target INR (mean 1.1, range 0.9–1.4). In the partial reversal arm ($n = 15$) the mean initial INR was 5.6 (range 2.5–12) with 93% achieving the target INR (mean 1.6, range 1.4–2.2). There were no adverse effects attributed to Prothrombinex-VF.
Conclusions: Prothrombinex-VF is very effective and safe when used alone to reverse warfarin anticoagulation. The supplementary use of fresh frozen plasma in these patients is not required. A review of the current Warfarin Reversal Consensus Guidelines is needed.