

The community pharmacy-based anticoagulation management service achieves a consistently high standard of anticoagulant care

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ABSTRACT

AIM: To ensure that the Community Pharmacy-Based Anticoagulation Management Service (CPAMS) in New Zealand has continued to deliver a high standard of anticoagulant care as the service has grown to provide warfarin supervision to over 4,000 patients.

METHODS: A clinical audit of patients managed through CPAMS over two years from 1 January, 2013. Anticoagulant control was assessed by measuring the time in therapeutic range (TTR), proportion of high and low INR results and incidence of reported bleeds. Compliance with the service was evaluated by monitoring the frequency of testing and the interval between tests.

RESULTS: There has been only a modest change in the TTR from 76.4% to 74% during the audit period, despite the growth in patient numbers from 850 to 4,350. There was no change in the proportion of INR results above 4.0. Bleeding was reported in less than 4% of visits and 82% of bleeds were minor. 75% of patients attended for INR testing on the expected date, and only 3.3% were more than 2 weeks overdue. The interval between tests remained constant at approximately 19 days.

CONCLUSION: CPAMS provides safe reliable anticoagulant care with a consistently high level of anticoagulant control.

In New Zealand approximately 35,000 people regularly take warfarin and more than 80% have their treatment supervised by their own general practitioners. There is no standardised procedure for warfarin management, with no regular audit process or national reporting. The level of anticoagulant control achieved by general practitioners is unknown, but an audit in 2004 of a large cohort of patients managed through primary care showed that the INR was maintained within the therapeutic range only 55% of the time.¹ International guidelines recommend the time in the therapeutic range (TTR) should be greater than 60%.² In 2010, a proposal was put to Health Workforce New Zealand to pilot an alternative method of warfarin management supervised by pharmacists using near-pa-

tient-testing and decision support software (DSS). The aim was to reduce the general practitioners' workload by making use of other skilled health professionals and to see if this type of service could achieve a safe level of anticoagulant control.

The pilot study included 690 patients managed through 15 pharmacies over 9 months. It achieved a high level of anticoagulant control with the INR maintained in the therapeutic range at 78.6% of the time³. The study also received positive feedback from the patients, pharmacists and general practitioners involved.⁴ On the basis of these findings, a service funded by the Ministry of Health was introduced into approved pharmacies from late 2012.

Over the last 2½ years, the service has grown steadily, is now available in

140 pharmacies and provides warfarin supervision for over 4,500 patients. One potential risk of expanding the service is that the level of anticoagulant control could fall. It is recognised that the outcome of pilot studies and clinical trials is not always maintained when the service is extended into more general use. In the Community Pharmacy Based Anticoagulation Management Service (CPAMS) pilot, the pharmacists involved were highly motivated, had a well-established relationship with their local general practitioners and were able to provide close supervision with appropriate collaboration with medical staff during the trial period; such close monitoring may not be possible in all pharmacies long-term. There was also potential for patient selection bias, as patients were referred at the discretion of the local general practitioners. Although the entry criteria for patients were wide and allowed for unstable patients to be included, there was the possibility that the more complex cases were not referred as this service was new and seen by some as experimental.

The aim of our audit was to see if the CPAMS service has continued to provide a high level of anticoagulant control as it has grown and to ensure that it maintains appropriate INR testing frequency and good adherence to testing on time.

Methods

Data for the audit were collected from the decision support software database (INR Online Ltd, Palmerston North, New Zealand). All patients on warfarin between 1 January, 2013 and 31 December, 2014, managed through CPAMS were included in the audit. To enable accurate calculation of TTR, the INR results from 1 November 2011 to 28 February 2015 were collected for the audit patients. The following data were recorded for each patient: date of birth; gender; reason for anticoagulant therapy; and length of treatment. The following data were collected each time an INR test was performed: date of the test; the INR result; the DSS recommended dose; the given dose; the DSS recommended date of the next test; and the pharmacists selected date of next test. At each test the patient was

asked about missed medication, changes to medication, episodes of bleeding since the previous test and hospital admissions; this was recorded on the computer system. Since April 2014, the user has been able to record the severity of the bleed as minor (gum bleeding, spotting from the nose, minor bruising), moderate (blood in the bowel motions, haematuria, bruising >4cm) or major (bleeding requiring attention in hospital, intracranial bleeding, major gastro-intestinal bleed, major urinary tract bleed or any bleed requiring a blood transfusion). The service was supported with close collaboration between the pharmacist and the referring doctor. A mechanism was in place at each pharmacy to ensure that results outside the INR range 1.5 to 4.0 could be discussed with a supervising doctor at the patient's own general practice.

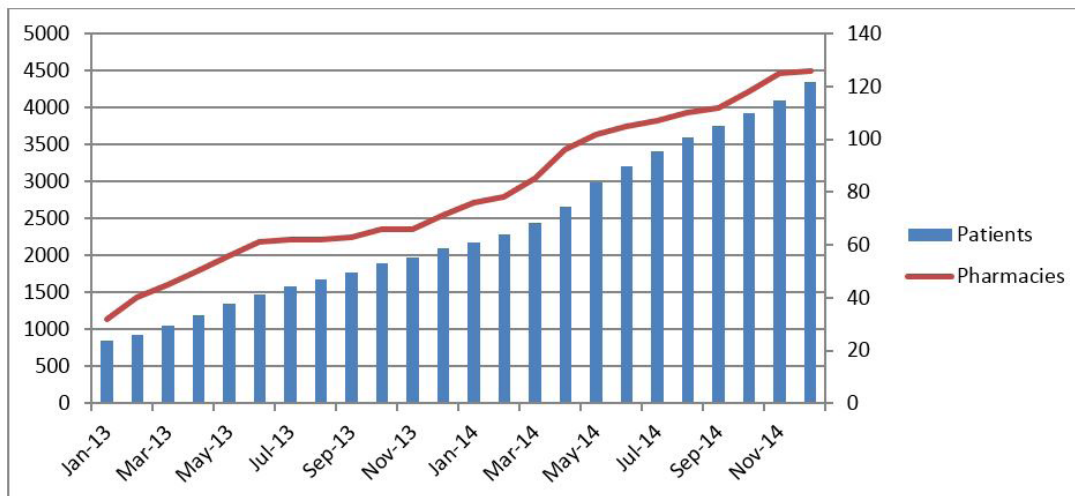
Assessment of anticoagulant control

Time in therapeutic range (TTR) was calculated using the method of Rosendaal,⁵ which uses linear interpolation between successive INR values; the time in days above, within and below the therapeutic range was calculated for the total population for each month by calculating the sum of all results up to each time point. The TTR was also calculated for each patient using all their available INR results from November 2011 to February 2015.

The proportion of INR results between 4.0 to 4.5, 4.5 to 5.0, 5.0 to 5.5, 5.5 to 6.0 and above 6.0, and the proportion of INR result at 1.5 or lower were calculated each month, based on INR tests performed in that month. The number of episodes of bleeding reported by the patients was calculated each month and reported as a percentage of the total number of tests performed each month. From April, 2014, the severity of the bleed was also recorded.

Test intervals and adherence to testing

At each INR test the interval since the previous test was recorded and the mean interval calculated each month. Adherence to testing was calculated by measuring the difference between the recommended test date and the actual test date and recorded as on time, 1 to 3 days late, 3 to 7 days late, 7 to 14 days or more than 14 days late.

Figure 1: Growth of patient numbers and pharmacies providing the service.**Table 1:** Diagnostic groups.

Diagnosis	Female	Male	Total	Percent	Mean age (yrs)
Atrial fibrillation	1,515	2,178	3,693	63.00%	71.8
Deep vein thrombosis	247	319	566	9.60%	60
Mechanical heart valve	242	448	690	11.70%	59.2
Pulmonary embolus	226	218	444	7.60%	61.5
Other	179	294	473	8.10%	62.6
Total	2,409	3,457	5,866	100.00%	67.65

Statistical analysis

The assessment of trends for each parameter was measured using the Mann-Kendall test; $p < 0.05$ was regarded as a significant trend. The comparison of the incidence of bleeding at various TTR ranges was calculated using chi-squared. The comparison of the mean time between intervals at various TTR ranges was evaluated using t-test. $p < 0.05$ was regarded as significant.

Results

A total of 5,866 patients on warfarin have been managed through CPAMS during the audit period. The number of patients actively on treatment has grown steadily over the 2-year audit period, from 850 (January 2013) to 4,350 patients (December 2014). By December 2014, the service was provided in 126 pharmacies (Figure 1).

Demographics

The reason patients were taking warfarin is shown in Table 1. The most common indi-

cations for treatment were atrial fibrillation (63%), venous thromboembolic disease (DVT & PE) (17.2%) and mechanical heart valves (11.7%); 59% of patients were male.

The median age for males was 69.7 years (mean 67.3 years) and for females 71.6 years (mean 68 years). The mean age was higher in patients with atrial fibrillation than the other patient groups.

Assessment of stability of control

To assess the stability of control we measured the time in the therapeutic range, proportion of tests above 4.0 and below 1.5 and the incidence of reported bleeds each month.

Time in the therapeutic range: At the start of the audit period, 32 pharmacies were providing the service to 853 patients. The TTR for this population was 76.4% based on 17,000 INR results. As the size of the patient population increased there was

Figure 2: The time above, within and below the therapeutic range each month.

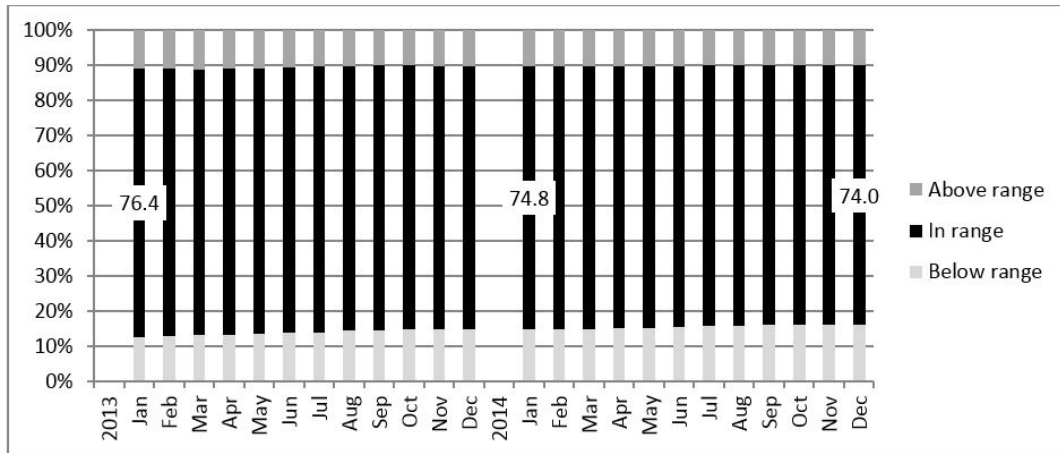


Figure 3: Patients were grouped by deciles based on their TTR. The figure shows the number of patients in each group at the end of the audit period.

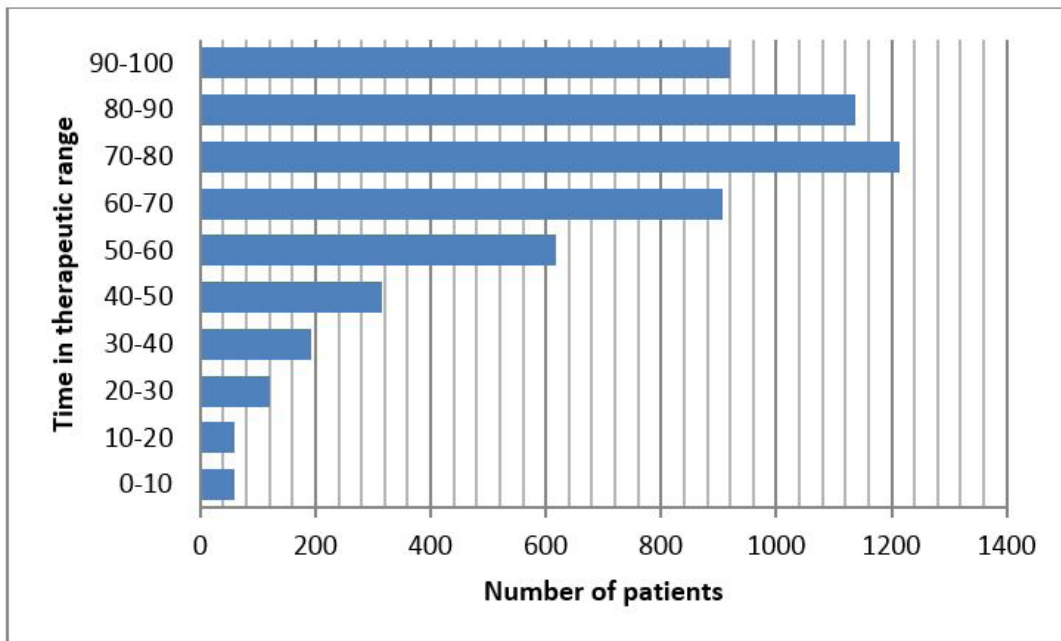


Figure 4: Percentage of tests with an INR above 4.0 each month.

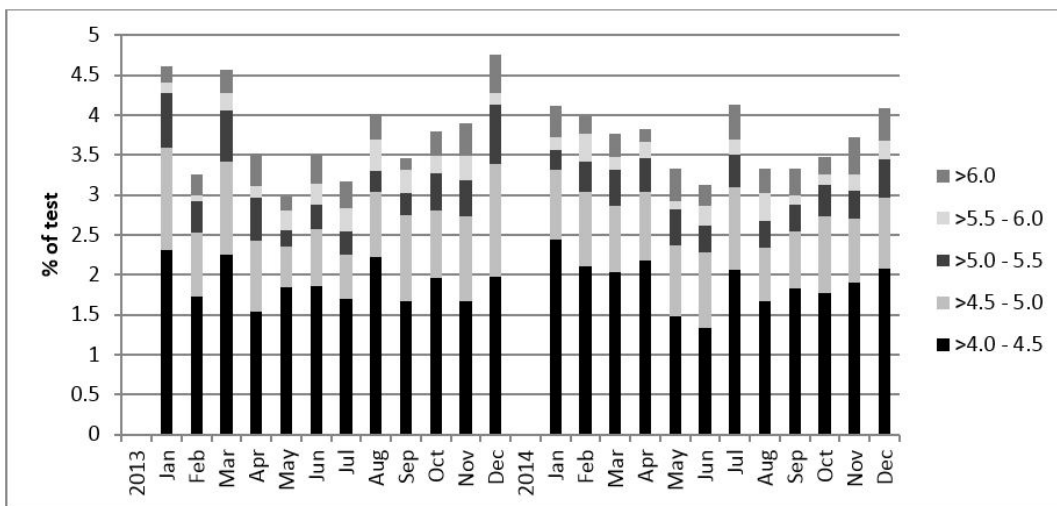


Figure 5: Percentage of tests with an INR of 1.5 or less each month.

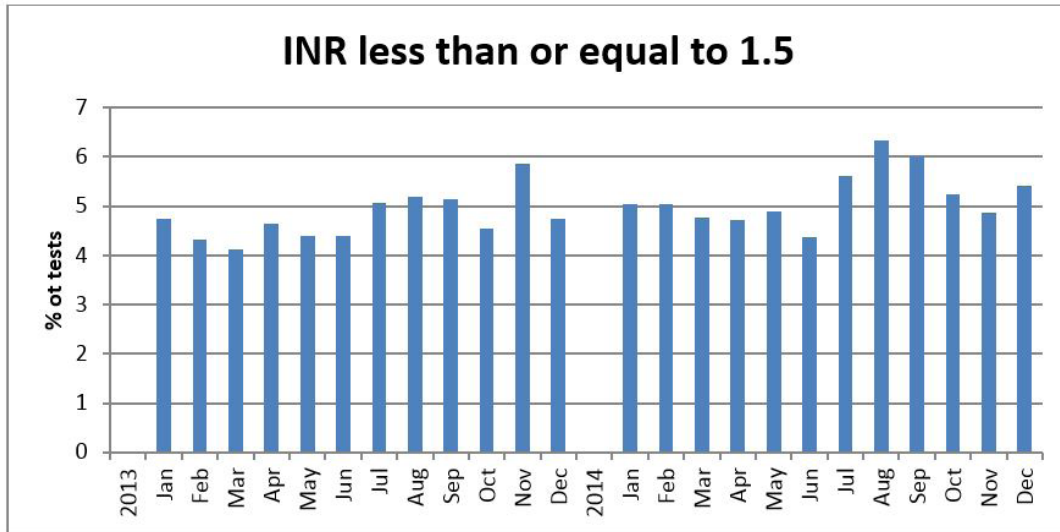


Figure 6: Proportion of tests where the patient reported bleeding since the previous test.

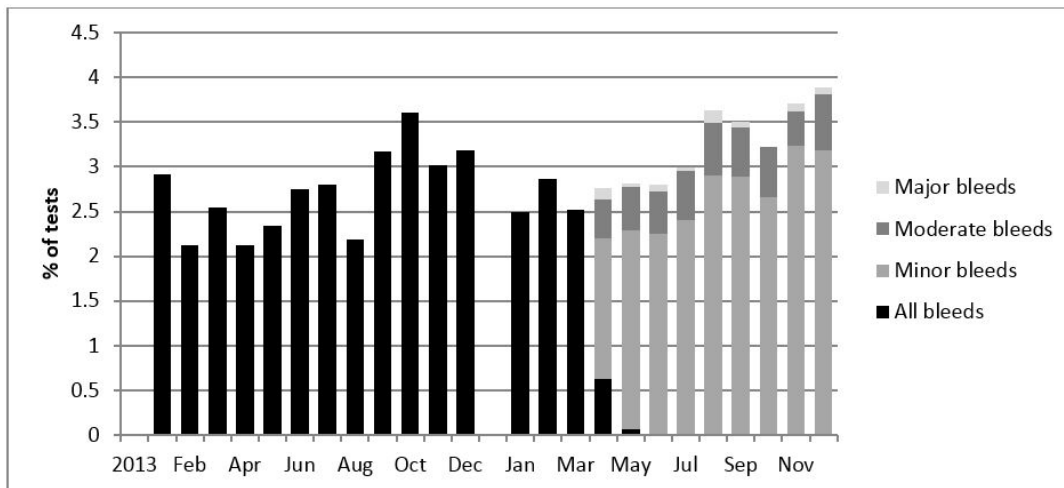


Figure 7: Relationship between the time in range (patients grouped in deciles based on TTR) and the reported incidence of bleeding. Bleeding rate falls significantly between TTR 50% and 100%; P<0.001.

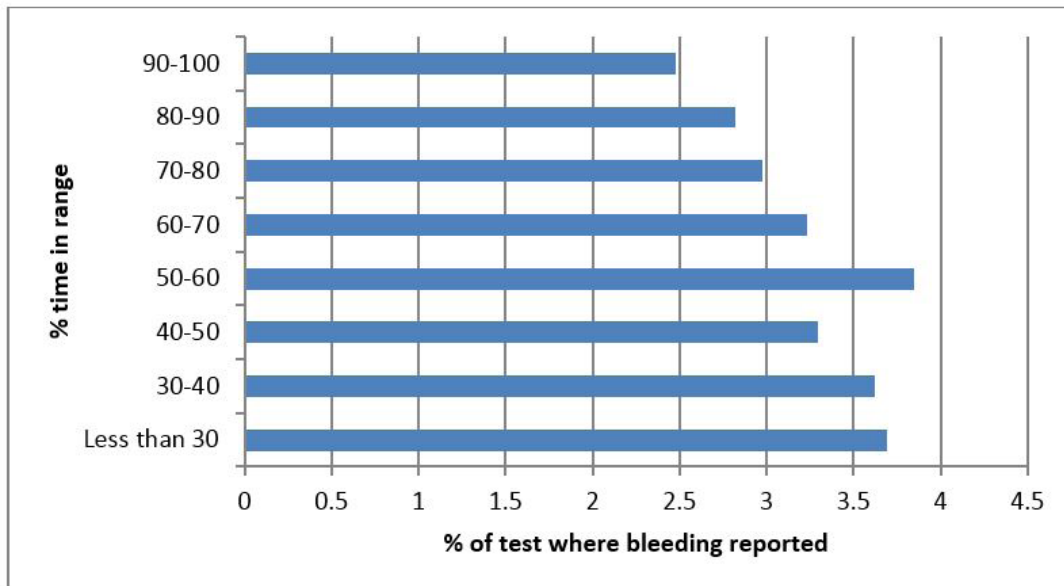


Figure 8: Mean interval between INR tests + 1 SD.

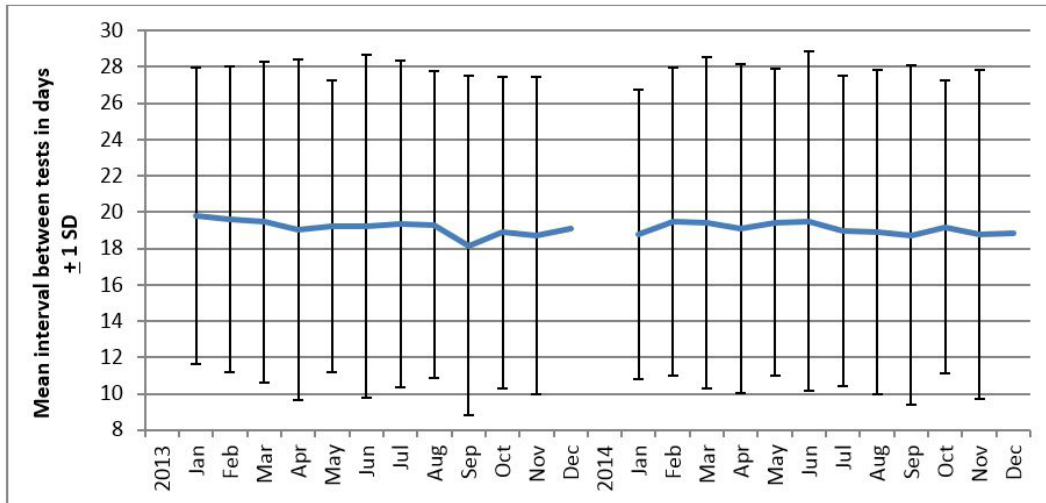


Figure 9: Relationship between time in range (patients grouped in deciles based on TTR) and mean test interval (+ SEM).

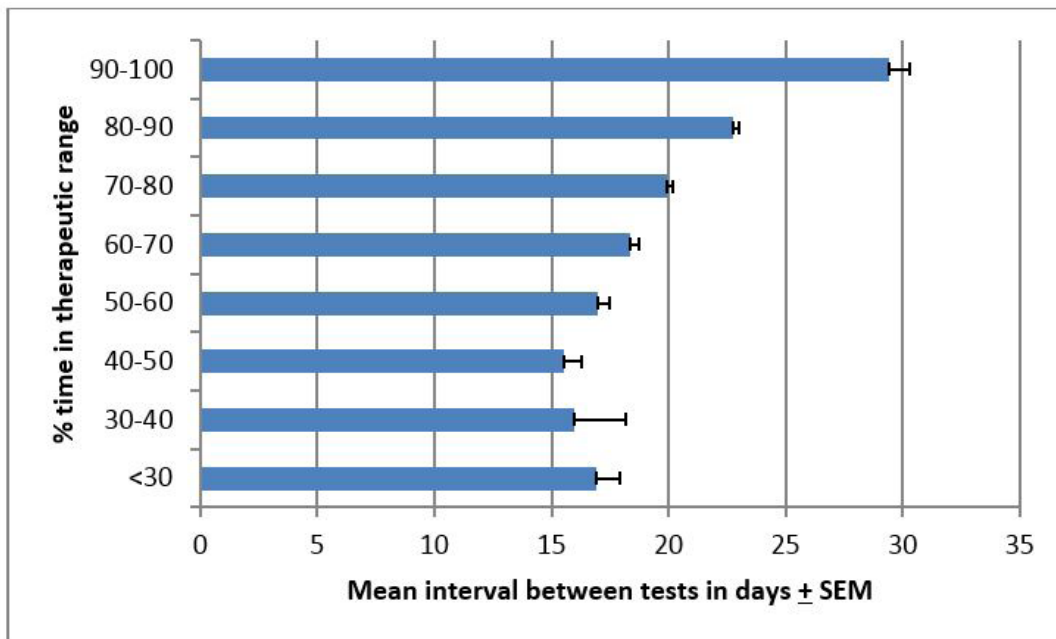
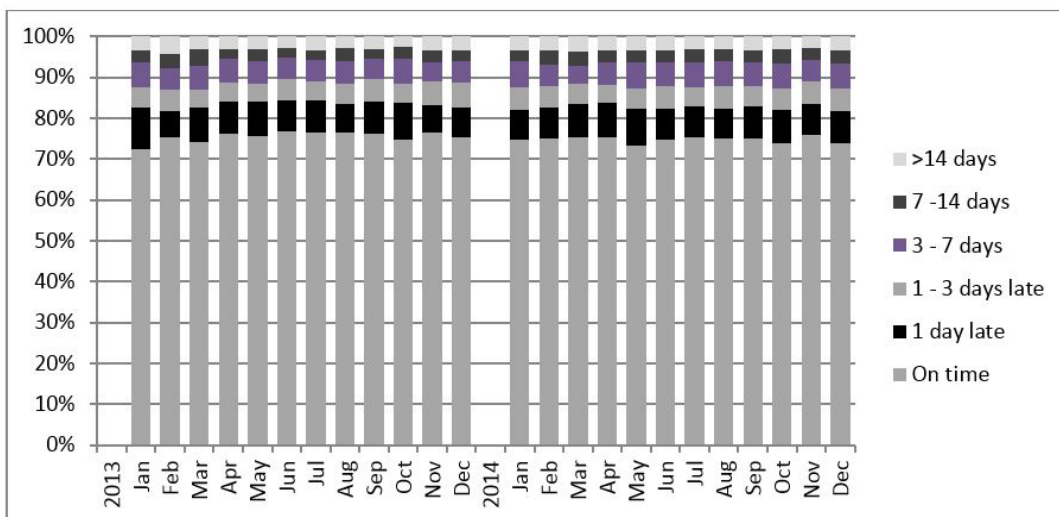


Figure 10: Proportion of tests performed on the expected test date or later than the expected date.



a fall in the TTR to 74.8% (45,000 results) at 12 months and 74% (124,000 results) at 24 months (significant decreasing trend, $p < 0.05$). The change in the TTR was largely due to an increase in the proportion of time below the therapeutic range, which increased from 12.6% to 16% ($p < 0.05$). The proportion of time above the therapeutic range remained around 10% for the whole audit period (Figure 2).

The time in range was calculated for each patient at the end of the audit period. The distribution of results is shown in Figure 3; 75.4% of patients had a TTR greater than 60%.

Proportion of INR results outside the therapeutic range: Between 3% and 4.7% of INR results had a value of >4.0 each month. This did not change significantly over the audit period (no significant trend, Mann-Kendall test) (Figure 4). Between 4.1% and 6.3% of INR tests were less than or equal to 1.5 (Figure 5). The results show a significant positive trend.

Proportion of bleeds reported by the patient at each visit: The patient was asked about bleeding events since the previous test at each visit. The user could not proceed with the INR test until this had been answered on the computer system. The software was changed in April 2014 to allow the user to record the severity of the bleed. The proportion of tests where bleeding was reported, ranged from 2.1% to 4.9% each month. The trend was not uniform, with more bleeds reported during the months September to December. There is no significant trend during the first 15 months (only bleeding reported). The rate of reporting was higher after the pharmacists were able to report the bleed severity; 82.3% of bleeds are minor, 15.6% moderate and 2.1% major (Figure 6). Figure 7 shows the relationship between anticoagulant control and the incidence of bleeding calculated at the end of the audit period.

Assessment of stability of testing frequency and adherence to testing

Test interval: The mean interval between each test was calculated each month. This remained constant at approximately 19 days throughout the audit (Figure 8). The interval increased significantly as the INR

control improved, with a mean of 23 days for patients with a TTR of 80 to 90% and 29 days with a TTR of 90 to 100% (Figure 9).

Adherence: Adherence to testing was assessed by monitoring the proportion of patients who attended for testing on the expected test date and the proportion who were late for testing. 75% of tests were performed on the expected date, a further 7.8% were only one day late. A total of 93.8% of tests were performed within a week of the expected test date and only 3.3% were more than 2 weeks late. Adherence remained stable throughout the audit period (Figure 10).

Discussion

The main finding of our audit is that community pharmacy-based anticoagulant service consistently delivers high quality anticoagulant care with the time in therapeutic range above 74%. This is in spite of the fact that the patient population has grown approximately five-fold during the audit period (Figure 1), and that the service is now supervised by more than 250 trained pharmacists. Our results also show that the frequency of testing remained remarkably constant, and patient adherence to testing is consistently high. However along with this growth, there has been a trend showing a modest fall in anticoagulant control, with the TTR dropping from 76.4% to 74% over two years.

The TTR is the most widely used measure of anticoagulant control, with several studies showing a correlation between the time in range and the incidence of both bleeding and thrombosis. A TTR around 75%, as achieved by the CPAMS programme, would be expected to achieve good clinical outcomes with a low incidence of warfarin complications. Two large clinical trials^{6,7} showed that patients on warfarin with good control (INR within range 75% of the time) had an annual mortality of 1.69% and major bleeding events of 1.58%, whereas the poorly controlled patients (INR within the therapeutic range $<60\%$ of the time) had an annual mortality of 4.2% and major bleeding of 3.85%. A TTR of 74% is significantly higher than the results from a meta-analysis of anticoagulant clinics in the USA (TTR 63%)⁸ and well above the level of control reported in this country

(TTR 55%)¹. Our results are similar to those achieved by a pharmacy-based service in Canada (TTR 73%)⁹.

Although the TTR is a useful measure of the quality of anticoagulant management, there is some evidence that the variability of INR results is also linked to adverse events.¹⁰ There is no standardised method of recording variability,¹¹ but monitoring the proportion of INR results at the extremes of measurement can give an indirect assessment. Over the audit period we found no significant change in the proportion of INR results above 4.0 (Figure 4) and only a slight increase in INRs below 1.5. Although the trend reached statistical significance, the proportion of low INR results reported each month only increased by about 1 % over the whole audit period (Figure 5).

The most direct measure of the complications of warfarin is the incidence of bleeding. In our audit we have tried to capture this by asking the patients about bleeds since their previous test. This has some limitations as it is dependent on the pharmacists asking the question and recording the answer on the computer system, however the software is designed to ensure that a question about bleeding must be answered before the INR test can be performed. During the first 15 months of the audit the software only allowed the user to record the presence of bleeding without giving details of the severity; during this period, the number of tests where bleeding was reported fluctuated from 2% to 3.5% each month with no overall trend. For the last 8 months, pharmacists were able to add details of severity and a slightly higher rate of bleeding was reported. It is difficult to know if this increase is clinically significant, as the different criteria for reporting may have influenced the pharmacists' decision to report a bleed. Anecdotally, pharmacists reported that not all minor bleeds were reported prior to the change. Of note, the rate of reported bleeds in our study correlates with the TTR supporting the hypothesis that there is a relationship between anticoagulant control and bleeding complications (Figure 7).

The gradual fall in the TTR over time could be due to a number of factors, including changes in the patient popu-

lation, varied experience of the supervising pharmacists, and varied adherence to the decision support software. It is likely that the proportion of more complex cases has increased as the service has expanded. Patients were referred to the service at the discretion of their doctor, and in some practices only stable patients were submitted initially; only when the doctors were comfortable with the service were the more complex cases referred. The level of control fell most during the first 12 months of the audit, and stabilised during the second year—suggesting that control had reached a more steady state (Figure 2)

Another concern with an expanded service and a more diverse group of patients is that it could become less efficient, with patients requiring more frequent testing and worse adherence to the expected test dates. However, our results show that the interval between tests remains remarkably stable with mean interval of approximately 19 days with a similar distribution of results (Figure 8). The consistent test interval is, in part, due to the use of DSS as this recommends a test date at each visit and the pharmacists followed this 70% of the time. There is no recognised standard test frequency for warfarin management. International guidelines advise that testing every 4 to 6 weeks is appropriate for stable patients, but more frequent testing is necessary for those with less stable control. Studies have shown that more frequent testing improves control,^{12,13} however the benefit of frequent testing has to be balanced against the practicality of delivering a manageable service. We believe that a mean test interval around 20 days has been appropriate for our service, with the testing interval extended to around 4 weeks for well-controlled patients (Figure 9).

Another consistent finding is the adherence to testing, with 75% of patients attending for their INR tests on the expected date and only 3.3% more than 2 weeks overdue. The robust recall system which identifies patients overdue for testing and delivers automated e-mail reminders to the patients contributes to the high adherence rate.

The use of DSS for warfarin dosing, test dates and reminders has helped to maintain the consistent service but several other factors are likely to contribute to

the success of the programme. One key component is the streamlined process which enables patients to have an INR test, see their previous results, have a consultation with their pharmacist and get immediate treatment advice in a single visit. The feed-back from patients is that this has made their warfarin management

a simpler process and they feel more involved with their care. In conclusion, our results confirm that a community pharmacy-based anticoagulant service can deliver a safe and reliable service and further expansion would be appropriate to offer the same level of care to a larger number of patients on warfarin.

Competing interests:

Paul Harper reports he is a share holder and director of INR Online Ltd, a patient management system to assist in Anticoagulation Management. Dale Griffiths reports some funding from Health Workforce New Zealand during the conduct of the study and personal fees from Pharmaceutical Society of New Zealand, as a member of the Society's National Executive, outside the submitted work. Joe Mr. Harper reports he is a shareholder and director of INR Online Limited, a patient management system to assist in Anticoagulation Management.

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