

Anticoagulation management by community pharmacists in New Zealand: an evaluation of a collaborative model in primary care

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Keywords

anticoagulants; community pharmacy services; primary health care; quality of health care; warfarin

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Abstract

Objectives Despite the introduction of new oral anticoagulants, vitamin K antagonists remain the mainstay of the prevention and treatment of thromboembolism. The advent of affordable point-of-care testing presents an opportunity for community pharmacists to provide anticoagulation management services, better utilizing their training, reducing the workload on medical practices and improving accessibility and convenience for patients. This study aimed to determine the effectiveness of anticoagulation management by community pharmacists.

Methods All patients enrolled in a pilot programme for a community pharmacy anticoagulation management service using point-of-care international normalized ratio testing and computer-assisted dose adjustment were included in a follow-up study, including before–after comparison. Outcomes included time in therapeutic range (TTR), time above and below range, number and proportion of results outside efficacy and safety thresholds, and a comparison of care led by pharmacists and care led by a primary-care general practitioner (GP).

Key findings A total of 693 patients were enrolled, predominantly males over 65 years of age with atrial fibrillation. The mean TTR was 78.6% (95% CI 49.3% to 100%). A subgroup analysis ($n = 221$) showed an increase in mean TTR from 61.8% under GP-led care to 78.5% under pharmacist-led care ($P < 0.001$), reflecting a reduction in the time above and, in particular, below the range. The mean TTR by pharmacy ranged from 71.4% to 84.1%. The median number of tests per month was not statistically different between GP- and pharmacist-led care.

Conclusions Community-pharmacist-led anticoagulation care utilizing point-of-care testing and computerized decision support is safe and effective, resulting in significant improvements in TTR. Our results support wider adoption of this model of collaborative care.

Introduction

Despite the recent introduction of new oral anticoagulants, warfarin remains a mainstay of the prevention and treatment of thromboembolism. In order to maximize the benefits and minimize the risks of warfarin treatment, regular monitoring of the international normalized ratio (INR) is necessary to ensure the patient remains in a safe but effective therapeutic range. The burdens that this places on both patients and health professionals are well known.

In New Zealand, warfarin treatment is typically managed by primary-care physicians, known as general practitioners

(GPs). Patients collect a laboratory form from their GP and attend a blood collection centre; the sample is sent to a centralized laboratory service, and the result is sent to the physician electronically. The physician later retrieves and reviews the result in the absence of the patient – and therefore of much of the context of common causes of INR variability – and makes required dose adjustments; the result and revised instructions are then communicated to the patient, usually over the telephone by the practice nurse or receptionist. The process is fragmented, inefficient in terms of workflow, and

inconvenient for the patient and the health-care practitioners involved. Furthermore, it is associated with suboptimal anticoagulation; in New Zealand and elsewhere, this model of care typically delivers a time in therapeutic range (TTR) of less than 60%.^[1–3] There is good evidence that at this level of control warfarin offers no benefit over antiplatelet therapy in atrial fibrillation.^[4]

Dedicated anticoagulation management services (AMSs) aim to provide a systematic and coordinated model of care and are particularly well established in the UK, Canada and the USA. Examples exist in New Zealand, but they are not widespread. There is consistent evidence showing that AMSs, including pharmacist-led services, achieve better outcomes when compared with 'usual care' management in terms of both increased TTR and reduced incidence of haemorrhage or thromboembolism.^[5–9]

The role of pharmacists in secondary-care AMSs, particularly in North America, is well documented.^[9–14] Unfortunately, these services are often based in secondary-care facilities, thereby creating a barrier to access and reducing convenience for patients in the community. The potential benefits of community-based AMSs involving pharmacists include improved access to testing, greater convenience for patients, a reduction of the burden on primary-care practices and an improvement in anticoagulation control when compared with usual care. There are some published reports of community-based AMSs involving pharmacists, but these typically describe pilot or small studies. They include hospital outreach services,^[15] pharmacist-led primary-care clinics^[16–19] and community pharmacy services.^[20–23] In most cases the INR was measured at a centralized laboratory, but some services used point-of-care testing to enable pharmacists to perform INR testing and implement immediate dose adjustments.^[15,18–20]

This study evaluates the quality of anticoagulation control in a new programme of care, the Community Pharmacy Anticoagulation Management Service (CPAMS), piloted in New Zealand between November 2010 and July 2011.

Methods

Fifteen community pharmacies across New Zealand were selected to participate in the project, representing a range of urban, suburban and rural populations and a variety of sociodemographic and ethnicity profiles. Pharmacists participating in the CPAMS service underwent a structured training and accreditation programme run by the Pharmaceutical Society of New Zealand. Patients were referred to CPAMS by their GP. As part of the enrolment process, the patient's three most recent INR results were supplied to the pharmacist and were entered into the decision-support system. Authority to perform testing, review results and implement dose adjustments was delegated to the

pharmacist by the patient's GP. The GP retained overall responsibility for patient management and could intervene at any time, but a collaborative care protocol was developed whereby the pharmacist acted autonomously, sending INR results and dose changes electronically to the patient's electronic health record, and discussed management decisions with the GP where there were safety concerns, for example if the INR was above 5.0 or if the patient reported significant bleeding.

Patients enrolled in the service had their INR tested at the pharmacy using a point-of-care testing device (CoaguChek XS Plus, supplied by Roche Diagnostics New Zealand, Auckland, New Zealand) and a capillary blood sample. The results were made available immediately, and dose adjustments were made by the pharmacist with the aid of an online decision-support system that incorporates a dosing algorithm (INR Online, www.inronline.net); pharmacists were able to override dosing recommendations provided by the decision-support system at their own discretion. A record was made if the patient reported any bleeding or bruising or had been admitted to hospital since the previous test. As part of the authority delegation arrangements, all patients were initially tested once a week, regardless of their previous test frequency. If patients' subsequent results were stable, the interval between tests was gradually extended to a maximum of 4 weeks.

All patients were eligible for inclusion except those with antiphospholipid syndrome (INR results obtained from point-of-care testing devices can be unreliable in these patients) and those undergoing treatment for neoplasm.

Patient recruitment into the CPAMS took place from November 2010 to January 2011. All patients enrolled in the service were included in the programme evaluation. Patients were informed about the nature of the pilot study and gave their consent to their data being used for the purposes of evaluation as part of the clinical consent process. Patients were followed up from the time of enrolment until the programme evaluation ended on 31 July 2011 or until they left the service, whichever came earlier. Pharmacies were paid a fee for the initial training and set-up of the service and a fee for each patient visit to cover the cost of time and consumables.

Data extraction and management

Data on each patient's age, gender, pharmacy and GP, indication for warfarin treatment, INR target, test results, test dates, adverse events, and hospitalizations were extracted from the decision-support system. Reasons for patients withdrawing from the service were obtained either from the database or directly from pharmacists.

Information on hospitalization and bleeding events was extracted from the decision-support system. Each event was

reviewed and allocated to one of three categories: hospitalization related to warfarin treatment; hospitalization potentially related to warfarin treatment; hospitalization unrelated to warfarin treatment. Bleeding events were categorized as major or minor. Major bleeding was defined as bleeding requiring hospitalization or blood transfusion. In the absence of a separate code for thromboembolic events, these were identified by manual review of the patient record.

To enable a meaningful comparison of INR control during GP-led care and pharmacist-led care, pre-pharmacy INR data was obtained from GPs to allow a paired before–after comparison. Patient consent was requested to allow collection of a further 6 months of INR results and enable the calculation of TTR under GP-led care. For those patients who gave consent, results were requested either from the primary-care practice or from the laboratory service. Results provided by the laboratory service were marked with the identity of the original requester; any data relating to INR during hospitalizations were excluded from the calculation of usual-care TTR, as these were not considered to represent primary-care warfarin management.

Data analysis

The TTR was calculated for each patient based on each patient's target INR, as recorded in the decision-support system. In line with standard practice, the patient's therapeutic range was defined as the target INR \pm 0.5 units. Each patient's TTR was calculated as the cumulative number of days in range divided by the total number of days, using the linear interpolation method described by Rosendaal *et al.*^[24] The period analysed was that from the first recorded pharmacy test to the last. The mean TTR, the mean time below range (TBR) and the mean time above range (TAR) were calculated at an individual-patient level prior to aggregation into appropriate groups to allow additional analysis to be performed, for example, comparing the mean TTR achieved at each pharmacy. The proportions of tests showing INRs more than 1.0 unit below target, INRs below 2.0, above 5.0 and INRs above 8.0 were calculated (these values being outside the British Committee for Standards in Haematology^[25] safety indicator thresholds), as were the numbers of patients with one or more tests with these values. The frequency of testing, the interval between tests and the difference between planned and actual test dates were calculated.

A descriptive analysis of the number, incidence and nature of adverse events and hospitalizations was undertaken.

The analyses described above were repeated for the subgroup of patients for whom pre- and post-enrolment data were available. Paired comparisons of the proportions of TTR, TBR and TAR were made.

Ethical approval

This study was approved by the New Zealand Multi-region Ethics Committee in December 2010 (MEC/10/10/105).

Results

Forty-one community pharmacists were accredited to provide warfarin management. A total of 693 patients, under the care of 115 GPs from 52 practices, were enrolled in the service. A median 47 patients were enrolled at each pharmacy (range 26 to 75). Some pharmacies recruited patients from a single primary-care practice; others recruited from multiple practices. The median number of patients per practice was 4 (range 1 to 64). Two hundred and twenty-one patients gave consent to their historical community laboratory data being used for the paired comparison between GP- and pharmacist-led care.

Of the 693 patients enrolled, 106 patients left the pharmacist-led service before the end of the follow-up period; of these 22 were excluded from analysis because they had insufficient test results recorded in the database (a minimum of two results was required to allow calculation of TTR). The remaining 671 patients were included in the analysis, with median duration of follow-up of 197 days (interquartile range 168 to 219).

Table 1 shows the gender, age and indication for warfarin treatment for patients included in the analysis. Patients were predominantly male (62.4%), aged 65 or over (70.6%), and receiving warfarin for prevention of ischaemic stroke complicating atrial fibrillation (73.8%).

The reasons for patients' withdrawal from the service are shown in Table 2.

The mean TTR for patients in the pharmacist-led service was 78.6% (95% confidence interval 49.3% to 100%). The mean TBR was 10.4% (95% confidence interval 0.0% to 32.5%), and the mean TAR was 11.0% (95% confidence interval 0.0% to 28.7%). Small increases in mean TTR were observed when results were analysed for patients who completed 16 and 26 weeks in the pharmacist-led service – to 79.4% and 80.3%, respectively ($P < 0.001$).

All pharmacies achieved a mean TTR of over 60%. The mean TTR by pharmacy ranged from 71.4% to 84.1%. The difference in TTR between sites was statistically significant but was not adjusted for patient demographic variables or prior TTR.

Figure 1 shows the distribution of INR test results (as opposed to TTR) for patients enrolled in the CPAMS service; 55.6% of tests were between 2.0 and 3.0, with a very small proportion of tests greater than 5.0, and fewer greater than or equal to 8.0.

The median interval between tests for patients in the pharmacist-led service was 10 days (interquartile range 8 to

Table 1 Patient demographics and clinical characteristics

	Number of patients (n = 671)	Percentage of patients
Gender		
Male	419	62.4%
Female	252	37.6%
Age		
Median (range)	72 (13 to 97)	
Age group		
75+	276	41.1%
65–74	198	29.5%
55–64	115	17.1%
45–54	48	7.2%
35–44	25	3.7%
25–34	5	0.7%
15–24	3	0.4%
0–14	1	0.1%
Indication		
Atrial fibrillation	495	73.8%
Mechanical heart valve	58	8.6%
Deep vein thrombosis	40	6.0%
Pulmonary embolus	24	3.6%
Transient ischaemic attack	8	1.2%
Mural thrombus	4	0.6%
Myocardial infarction	4	0.6%
Tissue heart valve	4	0.6%
Other	34	5.1%
Total	671	100%

Table 2 Reasons for withdrawal from the pharmacist-led service

Reason	Number of patients
Warfarin discontinued	37
Treatment changed to dabigatran	17
Returned to GP-led care [†]	24
Moved away or changed GP	11
Died	13
Unspecified	4
Total	106

[†]To enable home testing (5); clinical reasons (6); blood tests in addition to international normalized ratio required (1); patient preference (7); non-compliance with pharmacist-led service (5).

21 days), which approximates to 3.0 tests per month. The median interval between tests rose from 8 days during the first 3 months of enrolment to 15 days for months 4 to 6. Over the study period, the majority of tests (83.1%) were performed on or before the due date.

Overall, 11.5% of dose recommendations were overridden by the pharmacist. Adjustment of the dose recommendations was significantly more common where the dose was below the therapeutic range (17.1%) than when it was in (10.1%) or above (10.3%) the range ($P < 0.001$).

There were 436 episodes of bleeding or bruising recorded. Seven events were categorized as major, requiring

hospitalization or blood transfusion. One event, a cerebral haemorrhage, resulted in the death of the patient. Three thromboembolic events were recorded, all of which resulted in hospitalization. There were 192 hospital visits recorded, the majority for outpatient appointments rather than for inpatient stays or visits to accident and emergency departments. The majority (91%) of hospitalizations were considered to be unrelated to warfarin treatment (Table 3).

Two hundred and twenty-one patients were included in the comparison between GP- and pharmacist-led care. The subgroup represented patients from 10 of the 15 pharmacies and 19 of the 52 primary-care practices. The median duration of follow up was 178 days (interquartile range 161 to 189 days) for GP-led care and 208 days (interquartile range 175 to 225 days) for pharmacist-led care.

Figure 2 illustrates the distribution of individual patient TTR between the usual-care (GP) group and the pharmacy-care (CPAMS) groups. Comparison of the data for GP- and pharmacist-led care showed a statistically significantly higher TTR ($P < 0.001$, related-samples Wilcoxon signed-rank) and lower TBR ($P < 0.001$, related-samples Wilcoxon signed-rank) for pharmacist-led care, with no difference in TAR ($P = 0.804$, related-samples Wilcoxon signed-rank).

Table 4 shows the comparison of GP- and pharmacist-led care in terms of INR results falling outside efficacy and safety thresholds often used as measures of quality assurance for anticoagulation programmes. The pattern of results is broadly similar, except for the proportion of test results more than 1.0 below target, but this difference was not statistically significant.

The median interval between tests for patients was 11 days (interquartile range 7 to 20) under GP-led care and 9 days (interquartile range 7 to 20) for pharmacist-led care, a non-significant difference ($P = 0.831$, independent-samples median test). Correspondingly, the median number of tests per patient per month was not found to be significantly different for pharmacist-led care (3.4 tests) compared with GP-led care (2.8 tests).

Discussion

This study evaluated the safety and efficacy of community-pharmacy-led anticoagulation management facilitated by point-of-care testing and computerized decision support. The mean TTR for patients enrolled in the study was 78.6%. All of the pharmacies achieved mean TTRs in excess of 60%. Comparison of post-enrolment data for the pharmacist-led service with pre-enrolment data and with data for GP-led care from previous studies showed that pharmacist-led care was more effective than GP-led care in increasing TTR for patients undergoing warfarin therapy. For those patients for whom both pre- and post-enrolment data were available, there was a statistically significant increase in the mean TTR

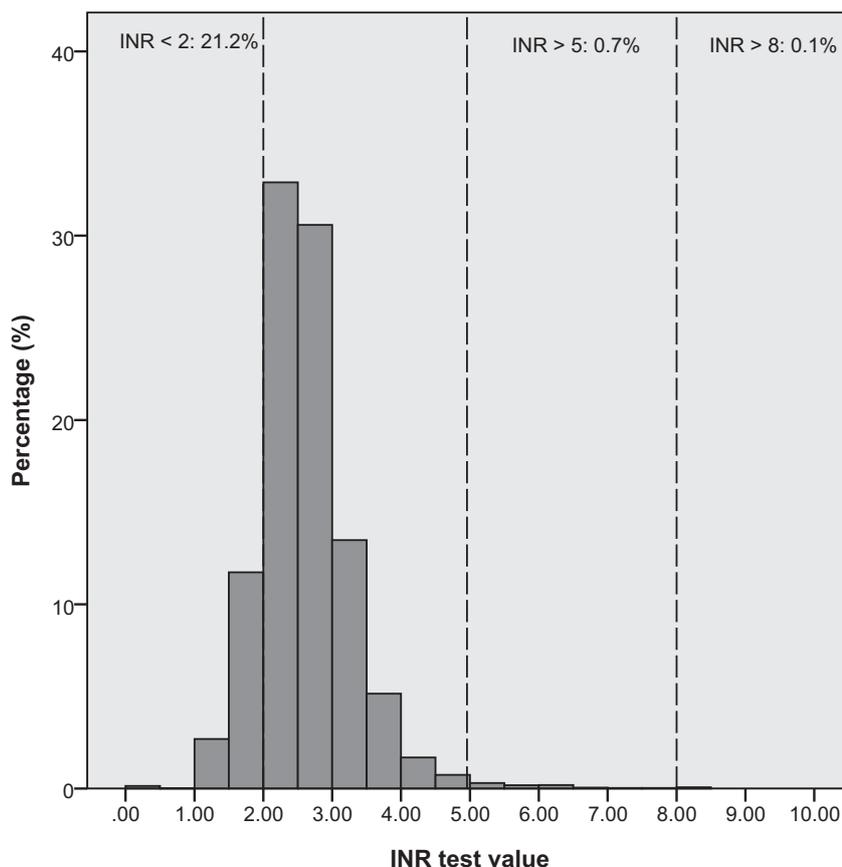


Figure 1 Distribution of international normalized ratio values ($n = 9265$) in 671 patients under Community Pharmacy Anticoagulation Management Service (CPAMS). Mean 2.56 ± 0.698 .

Table 3 Adverse events and hospitalizations

	Number	Incidence per 100 patient years of follow-up
Adverse events		
Minor bleeding	429	125.0
Major bleeding	7	2.0
Thromboembolism	3	0.9
Hospitalizations		
Related to warfarin treatment	10	2.9
Potentially related to warfarin treatment	8	2.3
Unrelated to warfarin treatment	174	50.7
Total	192	56.0

from 61.8% under GP-led care to 78.5% under pharmacist-led care, an absolute increase of 16.7%.

There are a number of limitations to be considered when interpreting our findings. We report the outcomes of a naturalistic study rather than an experimental study; neither

pharmacies nor patients were randomized, leading to the risk of selection bias in both cases and potentially limiting the generalizability of our findings with regard to whether the service should be universally implemented. The pharmacies chosen already had well-established relationships with their local GPs and may have been more clinically oriented practices than average. Not all of the patients and GPs who were invited to participate consented; however, the criteria for patient inclusion were deliberately broad and allowed for the referral of patients with persistently unstable INRs and complex multiple pathology.

An important limitation, unavoidable given the nature of the programme, was the relatively small sample size. This limited the ability of our study to measure clinical outcomes directly. The programme is currently being extended to other pharmacies in New Zealand, and an important part of the ongoing monitoring will be collection of clinical outcome data. At the time of publication, the programme has been extended to 125 pharmacies nationwide as part of a central-government-administered contract. This contract is supported by a training and accreditation programme run by the

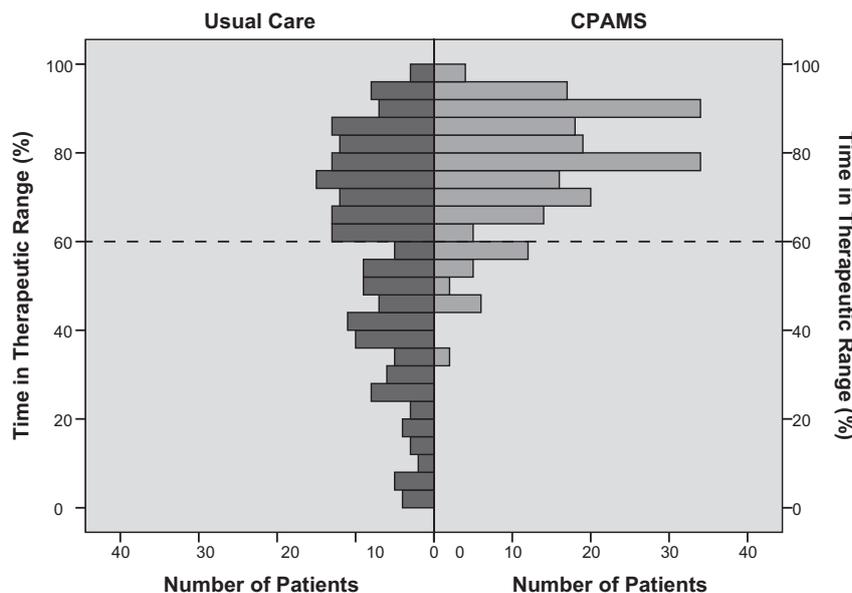


Figure 2 Distribution of time in therapeutic range under usual care and Community Pharmacy Anticoagulation Management Service (CPAMS) in before–after comparison for a subgroup of patients ($n = 221$).

Table 4 INRs outside efficacy and safety thresholds

	GP-led care (221 patients, 2752 tests)			Pharmacist-led care (221 patients, 3584 tests)		
	INR more than 1.0 unit below target [†]	INR above 5.0	INR 8.0 or above [‡]	INR more than 1.0 unit below target [†]	INR above 5.0	INR 8.0 or above [‡]
Number of test results	220	26	8	130	33	2
Percentage of test results	8.0%	0.9%	0.3%	3.6%	0.9%	0.1%
Number of patients with one or more test results in band stated	84	14	4	66	20	1
Percentage of patients with one or more test results in band stated	38.0%	6.3%	1.8%	29.9%	9.0%	0.5%

[†]This column may include test results from patients recently started or restarted on warfarin whose INRs had not yet reached the therapeutic range. [‡]The measure ≥ 8.0 , rather than >8.0 as recommended in the guidelines of the British Committee for Standards in Haematology,^[30] was used because the CoaguChek XS device has a maximum INR reading of 8.0. INR, international normalized ratio.

Pharmaceutical Society of New Zealand. The service is funded by an initial payment to assist with setting up the service, including the purchase of point-of-care testing equipment, and a fixed monthly management fee per patient enrolled in the service.

One of the strengths of this evaluation was that we obtained pre-enrolment INR data for one-third of patients enrolled. This enabled a paired comparison, with each patient acting as his or her own control. These patients may not have been representative of warfarin patients as a whole, but we were able to demonstrate an improvement in anticoagulation control under pharmacist-led care for this subgroup.

The mean TTR of 78.6% achieved by the pharmacist-led service in this study is significantly higher than the 63%

reported in a meta-analysis of data from specialist anticoagulant clinics in the United States.^[2] However, the performance achieved in the CPAMS pilot is similar to the mean TTRs recently reported from a pharmacist-led, primary-care-practice-based clinic in Canada (73%) and from a national registry in Sweden (76.2%), where oral anticoagulation is managed by specialist centres.^[16,26]

There is some evidence from the literature to support the hypothesis that higher TTRs may be associated with more frequent testing.^[27] The pharmacist-led service required all patients to be tested once a week on enrolment, regardless of their previous test frequency. If patients' subsequent results were stable, the interval between tests was gradually extended to a maximum of 4 weeks. The median number of tests per

month was found to be higher for patients under pharmacist-led care (3.4 tests) than under GP-led care (2.8 tests). However, the difference is not statistically significant and is unlikely to explain the increase in TTR achieved by the pharmacist-led service. Recent guidelines from the American College of Chest Physicians recommend that for patients with stable INRs, the test interval may be extended up to 12 weeks.^[28] It is reasonable to postulate that improved control in the intervention group, as demonstrated by a higher TTR, may facilitate less frequent testing.

TTR is an established measure of the quality of anticoagulation control that has been demonstrated to have a significant inverse relationship with adverse outcomes, including major haemorrhage and thromboembolic rates. Wan *et al.* concluded that as little as a 7% improvement in TTR reduced the rate of major haemorrhage by 1 event per 100 patient years, and a 12% improvement in TTR reduced the thromboembolic rate by 1 event per 100 patient years.^[29] It could therefore be expected that the increase in TTR achieved for patients in the pharmacist-led service would lead to a decrease in adverse events. However, it has been noted that not all of the variability in the risk of adverse outcomes can be accounted for by differences in TTR alone and that INR variability may be an important predictor of outcomes.^[30,31] While TTR is not the only measure that should be considered when assessing the quality of anticoagulation control, it does provide a readily measurable and reliable intermediate measure at both individual-patient and practice levels.

A potential problem with intensive efforts to increase the TTR could be an associated increase in TAR as a result of patients being dosed more aggressively. This could result in a higher risk of bleeding. However, comparison of the mean time in and above the therapeutic range for GP- and pharmacist-led care shows that the pharmacist-led service achieved an increase in TTR without increasing the mean TAR.

Implications of the findings

The project was carried out as part of an initiative to better utilize the health workforce in New Zealand, particularly with regard to reducing the burden on GPs. The results presented here indicate that a community pharmacist-led service for warfarin management can provide an effective alternative to the usual GP-led model of care in terms of TTR achieved. Analysis of the acceptability of the new service to participants found that it was well accepted by an overwhelming majority of patients and practitioners alike, with widespread support for its continuation and expansion, which is happening.^[32]

The pharmacist-led service was designed as a collaborative arrangement between patient, pharmacist and primary-care

practice. It reduces the complexity of care by the incorporation of blood sampling, testing and dose adjustment into one consultation involving a single health professional. However, CPAMS also has the potential to fragment care unintentionally if the pharmacist operates independently of rather than collaboratively with the GP; successful implementation relies on close professional relationships, good communication and the full support of the GPs involved.

There is good evidence to support the use of decision-support aids, including computerized systems, when determining anticoagulation dose.^[33] At the time of publication it is unclear what proportion of New Zealand general practices use anticoagulation-dosing algorithms to manage patients' treatment. GPs could introduce point-of-care INR testing and decision-support software in order to improve anticoagulation control; however, this would not achieve the aim of reducing the burden on primary-care practitioners through better use of the health workforce. For some patients, self-monitoring of INR with a portable testing device and support from a health professional as necessary may be the optimum model of care, this view being supported by a recent meta-analysis^[34]; however, this is not cost-effective from a government payer perspective, and only a small percentage of patients are likely to be willing and able to undertake it.^[35]

Conclusion

A new model of care in which community pharmacists provided anticoagulant management facilitated by point-of-care testing resulted in better outcomes as measured by TTR. This study supports the wider adoption of this model of collaborative care in New Zealand. The wider adoption of this model will provide the opportunity for the evaluation of clinical outcomes as well as quality markers.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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Authors' contributions

JS and JH conceived the study. JS, JH and JEH were involved in study design and study coordination. JH undertook the data analysis, and JS, JH and JEH were responsible for

interpretation. JH was responsible for database management. All authors were involved in the preparation of the manuscript. JS and JH are the guarantors.

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