Patient self-management of warfarin therapy

Pragmatic feasibility study in Canadian primary care

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Abstract

Objective To investigate the effectiveness of patient self-management (PSM) of anticoagulation using warfarin in a typical primary care site in Canada and to determine the feasibility of conducting a future large-scale trial in this setting.

Design An 8-month pragmatic open-label randomized crossover trial.

Setting A typical Canadian primary care practice in British Columbia.

Intervention Patients were randomized to PSM or physician management for 4 months, after which allocation was reversed. The PSM group members were instructed to monitor their serum international normalized ratio (INR) at community laboratories and to adjust their warfarin doses independently using provided nomograms. Education on warfarin dose adjustment was limited to a single 15-minute office visit.

Main outcome measures The primary outcome was the proportion of INR values in the therapeutic range among participants. Feasibility outcomes included proportion of eligible patients consenting, patients' preference of management strategy, patients' satisfaction, and visits or phone communication with physicians regarding dose adjustment. Safety outcomes included bleeding or thromboembolic events.

Results Eleven patients completed the trial, contributing 99 patient-months of monitoring and providing 122 INR measures. The mean proportion of INR values in therapeutic range among subjects in the PSM and physician-management groups was 82% and 80%, respectively ($P = .82$). The improvement in patient satisfaction with PSM was not significant. Ten of the 11 patients preferred PSM to physician management and elected to continue with this strategy after study completion ($P = .001$). No calls or visits were made to the physician regarding dose adjustment during the PSM period. There were no episodes of major bleeding or thromboembolic events.

Conclusion Patient self-management was not demonstrated to be superior to standard care, but was easily implemented and was the method preferred by patients. Our feasibility outcomes justify a larger trial and suggest that subject recruitment and protocol adherence would not pose barriers for such a study.

Trial registration number NCT00925028 (ClinicalTrials.gov).

EDITOR'S KEY POINTS

- Maintenance of a therapeutic international normalized ratio (INR) in patients has proven to be difficult, with patients spending an average of only 57% to 66% of the time within the therapeutic range. Patient self-management (PSM) is a concept in which patients obtain their INR values directly and adjust their warfarin doses independently.
- Data from randomized controlled trials (RCTs) examining PSM have consistently shown an increased proportion of INR values in the therapeutic range; decreased rates of thromboembolic events and major hemorrhage; and, in one study, a mortality benefit. Further, it has been shown that patients are more satisfied with PSM strategies, that PSM is cost-effective, and that PSM is superior to both usual care and care from tertiary anticoagulation clinics. Despite this, PSM has not been adopted in routine primary care in Canada, possibly because of its reliance on expensive personal coagulation analyzers and tertiary hospital-based education programs.
- The primary objective was to determine whether a PSM strategy implemented in a typical Canadian family practice clinic could reliably and consistently maintain therapeutic INR values; results showed that a simple PSM strategy in a typical primary care practice with no additional resources is feasible and was preferred by patients.

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Autogestion par le patient du traitement à la warfarine

Étude de faisabilité pragmatique en contexte de soins primaires au Canada

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Résumé

Objectif Vérifier l'efficacité de l'autogestion par le patient (AGP) du traitement par l'anticoagulant warfarine dans une clinique soins primaires typique du Canada et établir la faisabilité d'un essai éventuel à grande échelle dans ce contexte.

Type d'étude Un essai pragmatique randomisé croisé sans insu de 8 mois.

Contexte Une clinique de soins primaires typique du Canada située en Colombie-Britannique.

Intervention Les patients ont été répartis au hasard entre l'AGP et la gestion par un médecin pour une durée de 4 mois, après quoi la répartition a été inversée. On a demandé aux membres du groupe AGP de faire mesurer leur RIN par des laboratoires communautaires et d'ajuster eux-mêmes leur dose de warfarine à l'aide des nomogrammes fournis. Une seule visite de 15 minutes au bureau suffisait pour apprendre à ajuster les doses.

Principaux paramètres à l'étude Le principal paramètre était la proportion de valeurs d'INR des patients situées dans la fourchette thérapeutique. Les paramètres de faisabilité comprenaient la proportion des patients admissibles qui acceptaient, la stratégie préférée des patients, leur satisfaction et les visites ou appels téléphoniques aux médecins pour ajustement des doses. Les paramètres de sécurité incluaient les hémorragies et les accidents thromboemboliques.

Résultats Onze patients ont complété l'essai, pour un total de 99 mois-patients de monitorage et 122 mesures de RIN. La proportion des valeurs de RIN dans la fourchette thérapeutique était en moyenne de 82 % dans le groupe AGP et de 80 % dans le groupe géré par un médecin (P = ,82). L'utilisation de l'AGP n'apportait pas une amélioration significative de la satisfaction des patients. Dix des 11 patients ont préféré l'AGP plutôt que la gestion par un médecin et ont choisi de continuer avec cette stratégie à la fin de l'étude (P = ,001). Il n'y a pas eu d'appel ou de visite au médecin pour ajustement des doses au cours de l'AGP. On n'a pas enregistré d'hémorragies importantes ni d'accidents thromboemboliques.

Conclusion Même si l'autogestion par le patient ne s'est pas révélée supérieure au traitement standard, elle a été facile à mettre en pratique et c'était la méthode préférée des patients. Nos indices de faisabilité justifient un essai plus étendu et laissent croire que le recrutement de volontaires et l'adhésion au protocole ne feront pas obstacle à une telle étude.

Numéro d'enregistrement de l'étude NCT00925028 (ClinicalTrials.gov).

Cet article a fait l'objet d'une révision par des pairs.
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POINTS DE REPÈRE DU RÉDACTEUR

- Il s'avère difficile de maintenir un rapport international normalisé (RIN) chez les patients, qui ne passent en moyenne que 57 à 66 % du temps à l'intérieur de la fourchette thérapeutique. L'autogestion par le patient (AGP) est un concept selon lequel les patients reçoivent leurs valeurs d'INR directement et ajustent eux-mêmes leur dose de warfarine.

- Les données d'essais cliniques randomisés (ECR) portant sur l'AGP ont régulièrement montré une augmentation de la proportion de valeurs de RIN dans la fourchette thérapeutique, des taux plus faibles d'accidents thromboemboliques et d'hémorragies importantes et, dans une étude, une moindre mortalité. On a aussi constaté que les patients sont plus satisfaits avec les stratégies d'AGP, que l'AGP est économique et qu'elle est supérieure à la gestion habituelle et à celle des cliniques tertiaires d'anticoagulation. Malgré ces avantages, l'AGP n'a pas été adoptée dans les soins primaires habituels au Canada, peut-être parce qu'elle exige des analyseurs personnels dispendieux et des programmes de formation dispensés dans les hôpitaux de soins tertiaires.

- L'objectif premier était de déterminer si une stratégie d'AGP mise à l'essai dans une clinique de médecine familiale canadienne typique pouvait maintenir de façon fiable et régulière des valeurs thérapeutiques de RIN; les résultats ont montré qu'une stratégie simple d'AGP dans une clinique de soins primaires sans ressources additionnelles est faisable et que les patients l'ont préférée.

Oral vitamin K antagonists such as warfarin are frequently prescribed because of their ease of administration and proven benefit for a variety of conditions (eg, atrial fibrillation, mechanical heart valves, or venous thromboembolism). Since the introduction of warfarin into routine clinical practice, maintenance of a therapeutic international normalized ratio (INR) in patients has proven to be difficult, with patients spending an average of only 57% to 66% of the time within the therapeutic range.[1]

Patient self-management (PSM) is a concept in which patients obtain their INR values directly and adjust their warfarin doses independently. Data from randomized controlled trials (RCTs) examining PSM have consistently shown an increased proportion of INR values in therapeutic range,[2-7] decreased rates of thromboembolic events and substantial hemorrhages,[2,8] and in one study a mortality benefit.[9] Further, it has been shown that patients are more satisfied with PSM strategies,[2,10] that PSM is cost-effective,[11] and that PSM is superior to both usual care[3,5] and care from tertiary anticoagulation clinics.[6,7] A recent systematic review found that the average time in the therapeutic range for PSM was 72% compared with 50% in community settings.[1] Guidelines from the American College of Chest Physicians state that "in patients who are suitably selected and trained, PST [patient self-testing] or PSM is an effective alternative treatment model. We suggest that such therapeutic management be implemented where suitable."[12]

In consideration of implementing PSM strategies in Canada, there are several points to examine. First, all RCTs examining PSM involved extensive training, with nurse clinicians or specialized physicians at tertiary care centres to educate participants in the fundamentals of warfarin therapy and adjustment regimens and offered patient support. These resources are simply unavailable to Canadian family physicians. Second, electronic INR testing devices were provided to all patients, which would cost each patient approximately $1000 with the additional cost of testing strips. Third, benefit from PSM implementation in a typical Canadian setting could be substantial. A Canadian study designed to examine a more pragmatic method of PSM is clearly necessary.

In light of this, we conducted a practical open-label randomized crossover trial using a PSM strategy that incorporated outpatient laboratory monitoring (rather than point-of-care devices) and PSM education limited to 1 office visit. The primary objective was to determine whether a PSM strategy implemented in a typical Canadian family practice clinic could reliably and consistently maintain therapeutic INR values. We also sought to determine patient preference for treatment strategy and to evaluate the feasibility of conducting a large-scale RCT of similar design.

METHODS

Study design and population

The study was approved by the Ethics Committee at the University of British Columbia in Vancouver, and informed written consent was obtained from all participants. Patients were recruited from a private family practice in British Columbia. All patients receiving warfarin therapy were considered for participation. Inclusion criteria included age older than 18 years, warfarin therapy that preceded the study for more than 3 months and that would be expected to continue for the duration of the study, previous record of compliance with medication, and competence judged by demonstrated ability to use drug-adjustment nomograms (**Table 1**). Patients were excluded on the basis of severe psychiatric disease, serious language barrier, poor visual acuity, or the primary care physician's judgment that the patient would be a poor candidate for the study.

Table 1. "SHEET E" dose-adjustment nomogram for daily 4-mg dose of warfarin (4 pink-coloured pills*)

INR RANGE	DOSE ADJUSTMENT	FOLLOW-UP
Below 1.5	Take an extra 5 mg (1 peach-coloured pill*) today AND switch to SHEET G (5 mg/d) tomorrow	1 wk
1.5-1.9	Switch to SHEET F (4.5 mg/d)	1 wk
2.0-3.0	No change	2 wk
3.1-3.9	No change; if still above 3 at follow-up, switch to SHEET D (3.5 mg/d)	1 wk
4.0-5.0	Do not take tomorrow's dose; switch to SHEET D (3.5 mg/d)	2-5 d
Above 5	Contact doctor's office	

INR—international normalized ratio.
*Warfarin was prescribed to patients in the form of 5-mg (peach-coloured) and 1-mg (pink-coloured) tablets.

An open-label crossover design was used and participants were randomly assigned to 2 groups using computerized random selection. Group A was assigned to PSM and Group B to physician anticoagulation management (usual care); later, the treatment strategies were reversed. The duration of each stage (PSM and usual care) was 4.5 months (126 days).

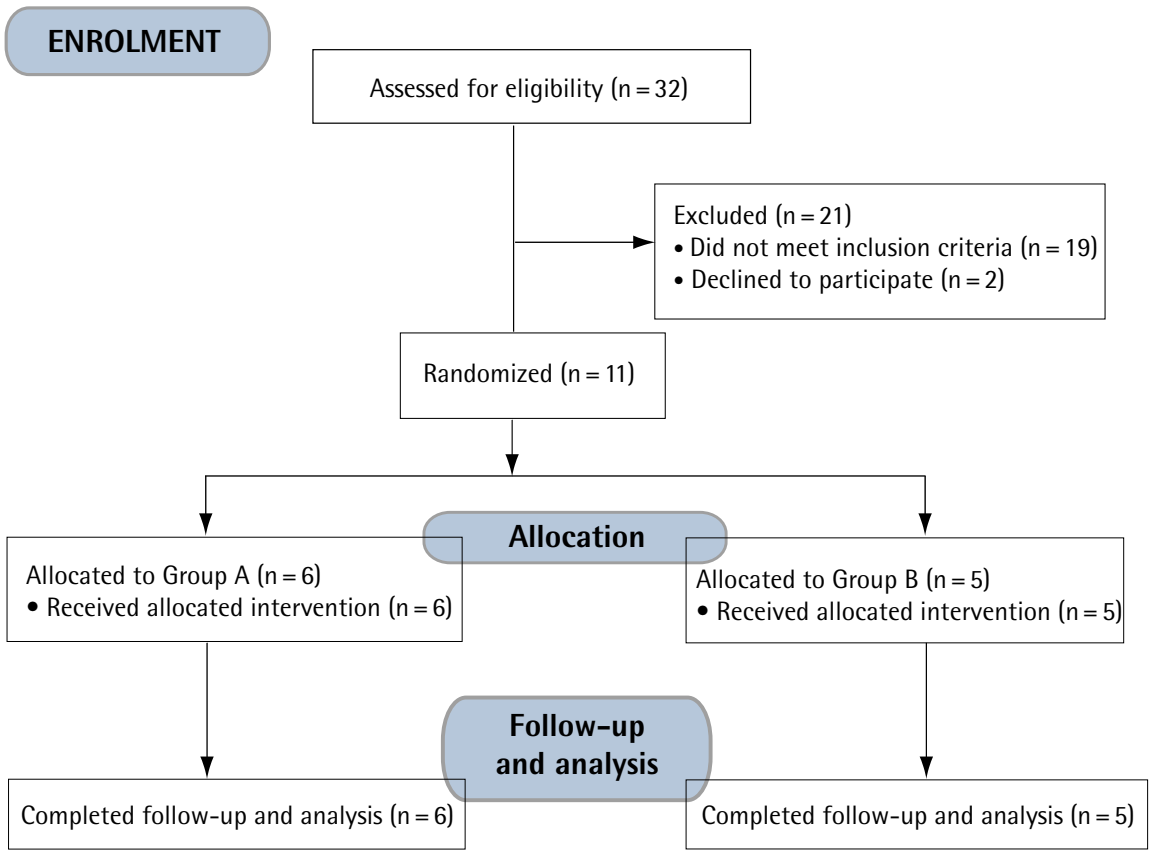
Patient education and scheduled office visits

A total of 3 scheduled office visits of 15 minutes' duration took place, with 1 visit allocated for patient education. During the first visit, the consent form and the trial were discussed. The second visit was used to determine the patient's willingness to participate and, if randomized to Group A, to educate the patient briefly on the fundamentals of anticoagulation therapy and to explain the strategy of PSM. The study commenced the day of the second office visit. A third office visit took place mid-study, at which time patients in Group B were educated in PSM methods and patients in Group A relinquished their PSM materials.

Patient self-management

All bloodwork was done at community laboratories, which were unaware of treatment assignments. Arrangements were made for patients in the PSM group to receive their INR results either by mail or in person. A PSM binder given to each patient included a simple instruction page, a progress chart, and warfarin dose-adjustment nomograms for 5 different doses (**Figure 1**[13]). Nomograms instructed patients which dose to switch to if necessary and when to retest their blood. The investigators did not contact PSM participants to ensure they were changing doses properly or at the correct times. Warfarin was prescribed to patients in the form of 5-mg (peach-coloured) and 1-mg (pink-coloured) tablets. Patients were instructed to contact the office by phone or in person any time they were having difficulty with the PSM or if their INR value exceeded 5.

Figure 1. CONSORT[13] flow diagram



CONSORT—Consolidated Standards of Reporting Trials.

Outcomes

The primary outcome for effectiveness was the proportion of INR values in the therapeutic range for each management strategy. The number of days in the therapeutic range was also determined. Feasibility end points included determination of the proportion of eligible patients consenting, the preferred management strategy of individual patients at the end of the study, a treatment-related satisfaction survey measuring 5 categories of quality of life, and additional office visits and phone calls pertaining to anticoagulation. Categories in the survey included medical treatment satisfaction, self-efficacy, general psychological distress, daily hassles, and strained social network; the survey was completed by all participants immediately before and after the PSM phase. This survey has been used in similar studies and has been validated.[2] Safety end points included hemorrhagic or thromboembolic complications. Major and minor hemorrhages were defined by the bleeding severity index described by Landefeld et al.[14] If it became necessary for patients to suspend their warfarin therapy temporarily during the study, the duration of time was recorded and INR value recording recommenced 1 week after restarting therapy.

Statistical analysis

Outcomes were analyzed according to intention-to-treat principles and were conducted using SAS (Statistical Analysis System), version 9.2. The primary effectiveness outcome was the proportion of individual INR values within target range for each subject according to treatment group. To calculate the proportion of time within target range, initial and final INR results were carried forward and backward to days 0 and 126, respectively, and linear interpolation was used. Comparisons were made using the paired *t* test for both the proportion of INR results within range and when comparing time spent within the therapeutic INR range. These methods have been used in similar trials previously.[2,4,7,8,10] For the secondary outcome of patient satisfaction, the differences between preintervention and postintervention scores on 32 individual items and on 5 derived categories were compared using paired *t* tests. A sign test was also used to assess whether the number of items showing increased postintervention satisfaction exceeded the number expected by chance. This feasibility study was designed to be conducted at a single site over the course of 9 months; therefore, no formal sample size calculation was performed because all eligible consenting patients were to be included.

RESULTS

Thirty-two patients were identified, and 13 who fulfilled the inclusion and exclusion criteria were invited to participate. Eleven patients agreed to participate and were enrolled (85%). The mean age of participants was 73 years, and 64% of participants had no education beyond high school (**Table 2**). The study observed 99 patient-months of monitoring and recorded 122 INR measures (**Table 3**). When comparing the mean proportion of INR values in the therapeutic range among the 2 groups, there was a non-significant difference of 2.2% (95% confidence interval 19.1 to 23.6) favouring PSM (*P*=.82), with values for PSM and usual care of 82.4% and 80.2%, respectively. A non-significant difference was also found comparing the number of days in therapeutic range per patient using PSM and usual care (*P*=.76), with results of 82.2% and 79.7%, respectively (**Figure 2**).

Table 2. Participant characteristics

PARTICIPANT CHARACTERISTICS	GROUP A (N = 6)	GROUP B (N = 5)	TOTAL (N = 11)
Mean age, y	67.7	77.8	72.3
Sex, male:female	4:2	4:1	8:3
Indications for anticoagulation, n			
• Atrial fibrillation	2	3	5
• Venous thromboembolism	3	2	5
• Prosthetic heart valve	1	1	2
Target INR range, n			
• 2.0-3.0	5	4	9
• 2.5-3.5	1	1	2
Highest level of education, n			
• Did not complete high school	1	3	4
• High school	2	1	3
• Attended college or trade school	1	1	2
• Attended university	2	0	2

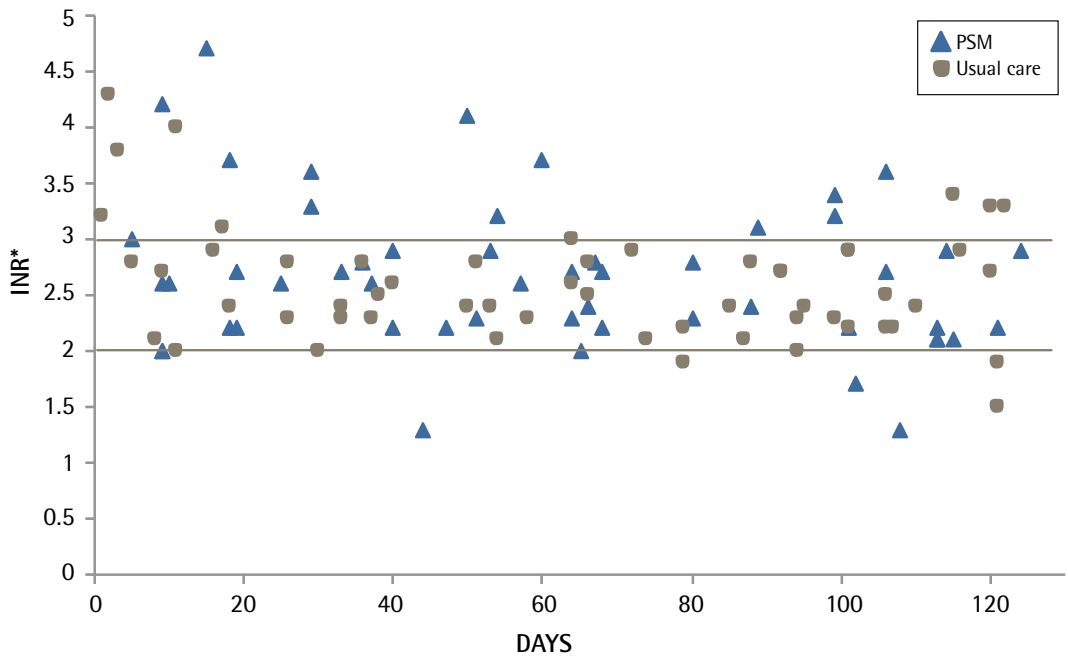
INR—international normalized ratio.

Table 3. Results

TREATMENT MEASURES	PSM	USUAL CARE	*P* VALUE
INR values in range,* n	52.0	43.0	.82
• Mean proportion of values, %	82.4	80.2	
• Total values	64.0	58.0	
Days in therapeutic range†	1176.0	1071.0	.76
• Proportion of days in range, %	82.2	79.7	
• Total days	1386.0	1344.0	
• Omitted days	42.0	0	

INR—international normalized ratio, PSM—patient self-management.
*Out of a recorded 122 INR measures.
†Out of 99 patient-months.

Figure 2. Scatter data plot of INR values among patients in the PSM and usual care groups



INR—international normalized ratio, PSM—patient self-management.
*Therapeutic target range 2.0 to 3.0.

Patient preference for warfarin management strategy was identified at the final office visit on the last day of the study. Ten participants (91%) identified preference for PSM and were invited to continue with this strategy. One participant (9%) elected to continue with physician management ($P=.001$). There were no statistical differences in any of the categories of the quality-of-life survey when comparing PSM with usual care.

No additional office visits or phone support were required to assist patients in PSM. There were no thromboembolic complications, suggesting good protocol adherence and comfort. One episode of self-limited bleeding, defined as minor, occurred in 1 patient during the PSM phase. During the PSM phase, 2 patients suspended warfarin therapy for a total of 35 patient-days (1% of the total patient-days) to undergo procedures.

DISCUSSION

Warfarin therapy has been shown to decrease the risk of complications in thrombogenic conditions, although control of this drug in the therapeutic range is a serious challenge. Patient self-management has proven to be an effective strategy, but typical implementation methods are not feasible in Canadian primary care practices. In our study we have shown that a simple PSM strategy in a typical primary care practice with no additional resources is feasible and was preferred by patients; however, we cannot conclude its superiority or noninferiority to standard care with respect to INR control. This study justifies a large trial of similar design and has demonstrated the feasibility of conducting such a trial in a community-based setting as measured by high consent, established preference by patients, and minimal need for primary care physicians' involvement during the study.

In this study the proportion of days in the therapeutic range for PSM and usual care were 82.2% and 79.7%, respectively. These proportions are higher than either PSM in large clinical trials (72%)[1] or usual care in primary care clinics (50%).[1] A 6-month quality assessment of randomly selected patients taking warfarin in the study clinic (conducted before this study) showed that 80% of days were within the target INR (unpublished data). This suggests that management of the usual care group was not influenced by the study.

There were 2 significant differences between our study and large RCTs examining PSM. First, patient education occurred during a single 15-minute office visit rather than several extensive training sessions at a tertiary care centre, which were standard in other RCTs.[2,4,6-8,10,15] We believe that our simple instructional

method was adequate, as there were no requests for assistance with PSM despite a strong emphasis during the study that patients were to call or visit the office in the event of any confusion. The mean age of the patient population in this study was similar to published values for populations receiving warfarin therapy,[16] and the level of education was likely not above average for this age group (**Table 1**).

Second, INR values were obtained through community laboratory testing rather than point-of-care devices. Patients received their results either in person or through the mail. Some difficulty was experienced in dealing with the public hospital laboratory, as mailings to patients were in a few instances delayed or not sent, requiring study investigators to contact laboratory management. This was in contrast to the local private laboratory in which there were no administrative errors. Patients' unimpeded access to their INR results would be critical in any future applications of this management strategy.

We found no statistical difference in general patient satisfaction between the PSM and the usual care groups. This is in contrast to 2 previous studies using the same survey. One study reported statistical improvement in all 5 categories[10] and a second in 4 categories.[2] Our study was likely underpowered to detect these differences.

This study is subject to several limitations. First is a lack of external validity, as only 1 practice was used in patient recruitment. This is more likely to affect the usual care group in which physician variability in INR-based warfarin dosing is to be expected, rather than the PSM group, which used a standard dosing algorithm. Second, the inclusion and exclusion criteria involved considerable subjectivity; however, this is typical in similar research and more robust criteria do not currently exist. This study was not designed to determine the criteria for PSM patient selection. Physicians wishing to implement a PSM strategy should monitor use before allowing patient independence to ensure only appropriate patients are selected. Finally, our relatively small sample size limited our ability to determine possible statistical significance. The use of a crossover design, however, was a substantial strength of this small trial, as it was able to control for differences between groups because subjects acted as their own controls.

Conclusion

We attempted to assess the feasibility and effectiveness of implementing a PSM strategy for patients using warfarin therapy in a real-world Canadian primary care setting, using community laboratories and comparatively little training. We have found that, for appropriately selected patients, this strategy is effective in maintaining therapeutic INR values and is the strategy patients find most desirable. This study established the feasibility of implementing a fully powered study to assess the effectiveness of a simple and pragmatic PSM intervention in Canadian primary care. The results of this study demonstrated neither superiority nor noninferiority of PSM compared with usual care, although it was not powered to detect such a difference.

Dr Grunau is a resident in the Department of Family Medicine and the Department of Emergency Medicine at the University of British Columbia (UBC) in Vancouver. **Dr Wiens** is Pharmacotherapeutic Specialist at Chilliwack General Hospital in British Columbia and is a research fellow in the School of Population and Public Health at UBC. **Dr Harder** is Clinical Assistant Professor in the Department of Family Medicine at UBC.

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Contributors

Dr Grunau contributed to the study conception and literature review, design, ethics proposal, and intervention implementation, and was the primary manuscript author. **Dr Wiens** contributed to the study design, statistical analysis, and manuscript revisions. **Dr Harder** contributed to the study conception, implementation, and manuscript review.

Competing interests

None declared

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