Is home warfarin self-management effective? Results of the Randomised Self-Management of Anticoagulation Research Trial

The Warfarin SMART Investigators

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Abstract

Aims

The Warfarin Self-Management Anticoagulation Research Trial (Warfarin SMART) was designed to determine whether patients self-managing warfarin (PSM) using the CoaguChek device and a dosing algorithm developed for the trial could keep the INR (International Normalised Ratio) test in target range at least as often as patients managed by usual care by the family doctor or hospital clinic.

Methods and Results

310 patients were randomly assigned to PSM or usual care. The PSM group was trained to perform home INR testing and warfarin dosing using a validated ColourChart algorithm. The primary endpoint was the proportion of times over 12 months that a monthly, blinded "outcome INR test", measured in a central laboratory, was outside the patients' target therapeutic range.

The rate of out-of-range outcome INRs was lower in PSM, and non-inferior to the usual care group (PSM: 36% vs. usual care: 41%, $P<0.0001$ for non-inferiority; $P=0.08$ for superiority in closed-loop testing). The deviations from the patients' midpoint of target INR range ($P=0.02$) and number of extreme INRs ($P=0.03$) were significantly less in the PSM group than the usual-care group. There was no significant difference between groups in rates of bleeding or thrombotic adverse events.

Conclusion

Patient self-management performed at least as well as usual care in maintaining the INR within the target range, without any safety concerns. This treatment modality for the long-term use of warfarin has the potential to change current local and international practice.

Keywords: warfarin, patient self-management, INR, adverse events

Introduction

Observational and experimental studies of patients on oral anticoagulation therapy show annual fatal bleeding rates of up to 4.8% and major nonfatal bleeding rates of 2.4% to 8.1%. [1] Although newer oral anticoagulant direct thrombin inhibitor agents are available, their high cost and uncertain safety profile will limit their use in the short-term. [2, 3]

Careful control of warfarin is critical to prevent bleeding and thromboembolic complications. There is evidence that the number of complications increases in parallel with the time patients spend outside target therapeutic International Normalised Ratio (INR) range. [4, 5] Extreme INRs increase the risk of adverse events. [6] In one study, the risk of bleeding at an INR over 7 was 40 times the risk at an INR in the low therapeutic range (2–2.9) and 20 times the risk at an INR in the high therapeutic range (3–4.4). [6] Higher variability of the INR in patients with mechanical heart valves is associated with shorter survival. [7]

Patient self-management (PSM) of warfarin may improve anticoagulation control and thereby reduce adverse events through convenient, frequent INR testing. The CoaguChek coagulometer, a self-testing device, has been shown to be accurate and reliable in experimental and clinical studies. [8, 9]

PSM varies in scope from calling an anticoagulation clinic to confirm a dose, to total independent management by the patient after one or more teaching sessions. Dosing algorithms have occasionally been used in trials of PSM where INR has been stabilised already, with good results. [10, 11] Evidence from European trials seems to support PSM as a method to improve anticoagulation management outcomes, but many randomised studies to date have been biased or small.

This large study with an unbiased design with regard to evaluation of outcome INRs investigated whether PSM is non-inferior or superior to usual warfarin management. PSM using the CoaguChek device and a dosing algorithm was compared to usual care by determining the proportion of blinded outcome INRs in the target range. The hypothesis test was that the proportion of out-of-range INRs in the PSM group would be 6% less than in the usual care group.

Methods

Study design

The study used a randomised controlled trial design to compare 1. standard management of warfarin control (usual care) using local laboratory testing and dose scheduling by a general practitioner, cardiologist or coagulation clinic with 2. use of an INR home self-testing device combined with dosing scheduled via a validated home individualised algorithm (PSM). Study staff and trial patients were blinded to assessment of the primary outcome.

Patient population

Cardiology and cardiac surgery patients from South-Western and Central Sydney areas (Liverpool, Royal Prince Alfred, and Strathfield Private Hospitals) in Australia were screened and recruited between January 1, 2004 and July 3, 2008 with follow-up until July 3, 2009. Patients were receiving warfarin for at least 3 months for either atrial fibrillation or for one or more mechanical heart valves. Patients needed to have a stable INR within the therapeutic range for the 2 weeks before enrolment, without maintenance dose adjustments above 2 mg per day, so that an individual algorithm could be developed. Patients were required to be at least 18 years of age, able to be contacted by telephone, and assessed by study staff as having adequate English-language skills, including reading ability. Patients were excluded if they had a known

coagulation disorder, underlying liver disease, a condition limiting their ability to comply with the study routine such as drug or alcohol addiction, a visual deficit, or tremor or tactile dysfunction; or if they failed a mini-mental state evaluation (score <8 out of 10). They were also excluded if they were unable to comply with monthly laboratory INR tests with blood transportable to the central study laboratory.

All patients gave written informed consent. The study protocol was approved by local and national ethics committees and was undertaken in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (ACTRN12606000019505).

Study intervention and randomisation

All patients received a 60-minute training session in the therapeutic use of warfarin. Eligible patients were randomly allocated to ongoing usual care or PSM for 12 months using a central phone-based randomisation system at the NHMRC Clinical Trials Centre. The randomisation method was minimisation, with stratification for age (≤65, >65), sex, duration of prior warfarin therapy (3-6 months, >6 months), current midpoint of INR range (<2.5, 2.5–2.9, >3.0), indication for warfarin (chronic atrial fibrillation, a mechanical heart valve, 2 or more mechanical heart valves) and type of management (general practitioner, cardiologist, clinic) before enrolment into the study.

Study coordinators notified patients of their study group allocation as blinding was not possible. Patients allocated to the PSM group received two additional training sessions (60 and 45 minutes) on 1. use of the device (CoaguChek S or XS, Roche Diagnostics) including internal liquid quality control tests for the CoaguChek S device, and 2. use of the self-dosing algorithm (a colour-coded INR warfarin-dosing algorithm, Figure 1).

The algorithm was validated against records of patients by ensuring dose changes using the algorithm were negligible compared to typically prescribed doses.

The algorithm was unique for each target INR and warfarin dose range and used dose adjustments that ranged from 10% to 50% of the maintenance dose (i.e. from 0.5 mg for a 5 mg dose to 1 mg for a 2 mg dose) to ensure patients maintained their INR range. The time to the next INR measurement was also recommended in the algorithm based on INR deviation from the target range. PSM patients checked their INR at least once a week, and more frequently if required by the algorithm. Patients were instructed to call the study nurse to discuss maintenance dose adjustment if the INR was less than 1.6 greater than 4.5, or out-of-range for more than 4 tests.

The usual-care group was also given instructions on how to complete a black-and-white chart similar to the ColourChart to record their clinical INR test results but without the algorithm instructions: they documented the date of each INR test, the result, and the dose they were instructed to take. This process was intended to match levels of involvement in individual data tracking in the two groups as far as possible.

Study outcomes

For 12 months, all patients had monthly outcome INRs measured at a central accredited laboratory (Davies, Campbell, de Lambert, now Symbion Pathology). All general practitioners, patients and investigators were blinded to the outcome INR results, which were sent to the unblinded statistician at the NHMRC Clinical Trials Centre. The only exception to this was that the trial staff were notified when the outcome INR readings were in the extreme high range (over 4.5), so that patients and their general practitioners could be notified of a potential safety issue (this occurred in 12/3114 (0.4%) of outcome INR tests).

For each patient, the proportion of out-of-range INRs was calculated and treatment groups were compared (primary endpoint). Secondary endpoints included: 1. the number of times outcome INR results occurred in extreme ranges (≥4.5, <1.5); and 2. rates of serious adverse events related to bleeding or thrombosis.. Subsidiary (tertiary) endpoints were: 1. the average deviation from the middle of each individual's INR target range; 2. the mean outcome INR, by treatment group allocation; and 3. time to the first INR reading in an extreme range.

Serious adverse events were classified as embolism, thrombosis, moderate bleeding (requiring medical evaluation or treatment, minor and nuisance bleeding excluded), severe, life threatening, or fatal bleeding, and other events, and were adjudicated by a blinded assessor as to nature and cause (MA). Outcome INR results and serious adverse events were monitored by an Independent Safety and Data Monitoring Committee (ISDMC).

Statistical analysis

The study was designed to detect a 10% difference between assigned groups in the proportion of INR readings outside the therapeutic range. A sample size of 310 patients was expected to offer at least 80% power, with a two-sided alpha, with 95% confidence, to detect such a difference, allowing for up to 10% drop-ins to PSM in some form, and up to 10% dropouts from PSM. The investigators considered it reasonable to miss a 20% effect because of the number of smaller studies and the high number of patients that would have been required to obtain 90% power. During the study, the blinded Steering Committee determined that a non-inferior outcome for PSM would be meaningful owing to the convenience afforded by home testing, provided that the PSM strategy proved safe. Consequently, the planned study analysis was modified to a closed testing procedure, first of non-inferiority with a pre specified

margin of 6% in rate of out-of-range values followed by superiority testing if non-inferiority was satisfied. The margin of 6% was empirically based on the maximum plausible risk of detriment that would not outweigh the added convenience of home testing and dosing with PSM.

The primary test for comparison was the two-sample *t* test. The primary endpoint data was normally distributed along with the other continuous endpoints and thus parametric tests could be used.

A secondary analysis used generalised estimating equations, with a compound symmetric correlation structure and a logistic link, to account for the repeated measures for each patient. Statistical inferences were drawn for a two-sided *P* value of less than 5%. All analyses were unadjusted and based on the intention-to-treat principle.

Results

Screening and baseline characteristics

Of 1722 subjects screened for the trial, 310 were eligible and consented to be randomised (Figure 2). The treatment groups were generally well-balanced with respect to baseline and anticoagulation characteristics, including the span of the prescribed INR range (Table 1). Compliance with trial participation was generally good, with only 11 (7%) subjects allocated to PSM withdrawing during the treatment period and 24 (15%) allocated to usual care withdrawing from monthly provision of central-outcome blood samples at some time during the 12-month follow-up period. Patients who withdrew from the PSM group were managed by their usual practitioner. One subject was lost to follow-up (usual care group). The mean number of outcome INRs captured was 10.1 out of a possible 12. All patients were analysed for the primary outcome.

The mean number of blinded outcome INRs obtained, the mean value of the blinded outcome INRs, and the mean warfarin dose taken did not appear to differ between groups (Table 2). The primary endpoint, the proportion of out-of-range INRs, was non-significantly lower for the PSM-allocated group (40.7% usual care versus 35.5% PSM), just failing to reach significance for superiority (P=0.08), but being highly significant for non-inferiority, with the one-sided 95% confidence interval being much greater than –6% (at +5.2%, P<0.001).

Self-managed patients also had significantly fewer extreme INR readings (P=0.03) and a smaller average deviation over all readings from the centre of their individual target INR ranges than the usual-care patients (difference = 0.04; 95% CI, 0.01–0.09, P=0.02). No significant differences were seen between treatment groups for the proportion of subjects with at least one reading in an extreme range at any time. There is evidence that the time to the first extreme reading was 46% longer among those allocated to the PSM group (95% CI, 20%–103%, P=0.05; Figure 3).

There was no difference in the rate of serious adverse events (Table 3). Irrespective of treatment allocation, there were more than twice as many bleeding as thrombotic events. The only death, of a patient with pulmonary hypertension and severe cardiac dysfunction who died from recurrent intracerebral haemorrhage, was arbitrated by the ISDMC to be due to warfarin therapy (but not in the extreme range) and not related to the study protocol.

Discussion

Summary of findings

Frequent INR testing combined with a warfarin management algorithm for self-management is as good as usual care, and superior to usual care in some aspects of warfarin control. The primary study analysis, comparing proportion of out-of-range

INR readings, showed non-inferiority of PSM. PSM was also associated with significantly less variability of readings and fewer extreme readings (≥4.5 or <1.5), both of which are of major clinical importance in relation to risk of bleeding or thrombotic complications.

Potential mechanisms for PSM benefit

PSM may offer better control by more frequent testing, allowing earlier adjustment of warfarin dose when the INR deviates from the therapeutic range. In usual care, general practitioners may increase the time interval between INR checks for the patient's convenience. Educating patients about the dosing algorithm, and daily use of the algorithm, may improve motivation and compliance with testing and dose adjustment, improving the quality of anticoagulation control in PSM.

Possible study limitations explained

The eligibility criteria were designed to be minimally restrictive. There was no requirement as to education level or age. No patient was excluded based on the mini-mental exam. Almost 40% of patients were aged over 65 years, and 25% were over 70 years, indicating a balance of young and old patients who were able to use the test device and dosing self-management algorithm.

A single laboratory network was used to ensure consistency of quality control procedures for outcome INR measurement. Of the 1722 screened patients, 356 (20.7%) were ineligible because they lived too far from a pathology laboratory thereby limiting the trial to patients in the city areas. In real practice rural patients could self-manage warfarin. Self management would facilitate in-range INRs compared to usual care in rural areas because testing and general practitioner management (usual care) are likely to be less accessible in rural than urban areas.

Inability to understand English (10.3%) was an exclusion criteria but this group of patients could have been included in real practice provided an English-speaking family member was available for education.

Of all patients screened for the study, 27.4% declined to participate, largely because of a preference for usual care and the difficulty in attending the single laboratory for outcome INRs. Only a small proportion of screened patients were ineligible based on inclusion and exclusion criteria (21.8%). The two major reasons for withdrawal were difficulty in attending for the outcome INR test (9 of 35 withdrawals; 25.7%) and a request by the patient to withdraw (8 of 35 withdrawals; 22.9%).

There was potential risk of bias because of inability to blind the investigators or patients to the treatment. The patients in the PSM treatment group may have felt privileged and more motivated than the usual care group to maintain the INR in the target range. If present, it is likely that this effect is small because of GP control of dosing in the patient population. Patient education about the warfarin dosing algorithm may have improved the outcome in the PSM group. However, the usual-care group also learned and used a black-and-white chart similar to the ColourChart which may have improved their performance slightly.

Greater INR variability may result from usual care patients managed mostly by general practitioners rather than anticoagulation clinic specialists.[12] Here, INR results were determined by a central laboratory blinded to treatment, which eliminated bias in terms of the outcome INR.

INR measurement device and primary endpoint

In a study comparing the CoaguChek S and XS with plasma INR testing, the device had good correlation with lab measurement (r^2 of 0.9). [13] Correlation decreased at

high INR levels and laboratory testing was recommended. All INR methods (lab and point of care testing), however, may provide variable INR results for the same sample.[14] The CoaguChek S and XS differ in the way the instrument measures the prothrombin time. The CoaguChek S uses a photometric principle where the CoaguChek XS uses an electrochemical detection system. The XS replaced the S in January 2007 after a voluntary recall of the S test strips by Roche Diagnostics. This was to avoid a <0.001% chance of a potential test strip defect that may cause falsely elevated test results**.**

Measurement bias of any INR method is dependent on the way each particular method is standardised and traceable to higher-level standards. For the CoaguChek, each lot of test strips is calibrated to a reference lot that is traceable to the WHO International Reference Preparations. The International Sensitivity Index (ISI) for the system has been confirmed as 1.0.

Time in therapeutic range (TTR) can be determined in different ways, so comparisons between studies may be difficult**.** TTR is commonly estimated by using proportion of out-of-range INRs. Since clinical outcome studies have not compared one methodology with another and correlated their results with adverse events, no one method can be recommended over the other.[15, 16] The proportion of out of range INRs reported in other studies is 21% to 51%, the results of this study being consistent with those studies.[17–21]

Significance and strengths of this study

This study is of interest in Asian-Pacific and North American regions where self testing and self management are not as widespread as in Europe. Valve companies issue self measurement devices to patients who have had mechanical valve

replacement. Patients self test INR and possibly even self manage, as is widely done in Germany.

This study is the largest randomised trial with an unbiased design of outcome measurement demonstrating PSM to be as good as usual care in terms of anticoagulation control and the proportion of INRs in the target range. It was designed to avoid the inherent bias in evaluating differing numbers of INR tests between groups. In many studies, the PSM group have undergone more frequent testing than those receiving usual care. The proportion of INR readings falling out of range may then be a lower percentage of the total number of tests, even when the instances of out-of-range episodes are identical (Figure 4).

The other strengths of this study are the medium-term follow-up of one year and the intention-to-treat method of analysis. Furthermore, assessment of potentially haemorrhagic and thromboembolic events was restricted to blinded assessors. The high capture rate of serious adverse events in both groups may have been due to use of the Australian Medicare (Health Insurance Commission) database and diagnosis related group (DRG) designation from admitting hospitals rather than reliance on reporting by patients.

Consistency with other studies

Of the 11 randomised trials included in the recent Cochrane review of warfarin self-management, only three used central blinded outcome INR tests, and all were smaller than our study. [17] Two (*n*=50, *n*=100) were unable to show a difference in outcome INR measurements with PSM. [18, 19] The third, a well-designed, unbiased but smaller trial (*n*=179), showed a higher proportion of INRs in target range for PSM than usual care. [22] The present, larger study adds weight to that study by proving non-inferiority of PSM.

Limitations of other large studies on out-of-range INRs

The Early Self-Controlled Anticoagulation Trial (ESCAT) series of studies on PSM, were large and showed that PSM was associated with a greater time within the therapeutic INR range, and a decreased rate of thromboembolism and bleeding events [23]. However, these studies have been criticised [12] because there was more frequent testing in the PSM group, and follow-up studies included additional patients and a different primary endpoint (long-term survival) [24].

A large, randomised trial of PSM, by Menéndez-Jándula et al.[23], showed improved time in range but was limited by testing up to 6 times as frequently in the PSM group. Another large (*n*=617) randomised controlled trial was unable to show a difference in time in range between PSM and conventional management. [24]

Two large meta-analyses of time in therapeutic INR range favoured PSM or patient self-testing, but again did not analyse equivalent numbers of INR measurements in each group, thereby potentially introducing bias.[12, 25]

Significance of randomised trials and meta-analyses with serious adverse events as an outcome measure

Because of the paucity of high-quality, randomised trials, PSM has not been shown to reduce serious adverse events other than in a selected population of elderly patients. [26] This positive result may have been due to the high rate of haemorrhage in those over 70 years of age. [27]

Another recent randomised study of PST [28] was unable to show a difference in clinical outcomes despite a large number of patients (n=2922). Perhaps, addition of PSM may have improved the clinical outcomes in that trial.

A large meta-analysis of individual patient data (6417 patients) from randomised trials included a heterogeneous group of trials of PST only and trials of PSM. [29] A

pre-specified subgroup analysis showed a reduction in events in the PSM group but the self-testing individuals were not significantly different from the control group. This adds evidence to the positive impact of PSM on adverse events.

A meta-analysis of 22 randomised trials with PST or PSM, 5 of which were considered high quality, showed an improvement in thromboembolic complications and death. [30] In another meta-analysis of 10 randomised trials of PSM, there was a reduction in death and major complications when PSM was used. [25] Only 2 of the trials were considered to be high quality and the positive effect of PSM on risk of death was not evident in these two trials. The effect of PSM, therefore, needs to be clearly delineated from PST alone when designing meta-analyses and randomised trials about the clinical outcomes of warfarin therapy.

Conclusions

The Warfarin SMART study, the largest of its kind with an unbiased design of outcome INR measurement, was powered to determine whether home PSM offers comparable or better INR and warfarin management than usual care. PSM performed at least as well as usual care in maintaining INR within target range, with significantly fewer extreme readings and smaller INR variability. This was achieved safely and has the potential to change current practice. This study supports the positive, smaller, well designed randomised trial by Sawiki[12], several meta-analyses with surrogate markers for adverse events, and meta-analyses showing reduction in adverse events with PSM. A large, definitive randomised trial of PSM is required to determine the effect on clinical outcomes.

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Study personnel

RD, ACK, VG, KM, and CH designed and conducted the study and composed the manuscript, VG and KM analysed the data, and RD, ACK, VG, CH and KM interpreted the results. All authors had access to the data, commented on drafts and approved the final version for submission. These authors take responsibilitiy for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Legends

Figure 1

Sample algorithm for a patient using the ColourChart

Figure 2

Flow chart for SMART study

Figure 3

Proportion of patients over time with at least one INR reading in an extreme range (high ≥4.5; low <1.5). Log-rank *P*=0.05.

Figure 4

More frequent testing of the INR can lead to higher proportion of tests being out of range despite the same number of INR spikes out of range.

Table 1: Baseline characteristics

	Usual care (*n*=157)	Self-management (*n*=153)
Male	111 (71%)	103 (67%)
Age at randomisation (years)	60.1 (11.5)	59.3 (13.1)
Age >65 years	58 (37%)	59 (39%)
Height (cm)	173.8 (10.6)	172.6 (9.6)
Weight (kg)	83.4 (19.6)	80.3 (18.3)
Caucasian	147 (94%)	138 (90%)
Education at secondary level or higher	156 (99%)	149 (97%)
English primary language	145 (92%)	141 (92%)
Full-time or part-time employment	75 (48%)	74 (48%)
Current or exsmoker	73 (46%)	69 (45%)
Consumes alcohol	128 (82%)	122 (80%)
NYHA class II or higher	18 (11%)	18 (12%)
Diabetes	19 (12%)	36 (24%)
Hypertension	75 (48%)	71 (46%)
Previous cerebral vascular accident	17 (11%)	10 (7%)
Previous transient ischaemic attack	9 (6%)	16 (10%)

	Usual care (*n*=157)	Self-management (*n*=153)
Warfarin for valve(s) ± atrial fibrillation	111 (71%)	110 (72%)
Chronic atrial fibrillation	64 (41%)	66 (43%)
Mechanical heart valves		
0	46 (29%)	44 (29%)
1	101 (64%)	99 (65%)
2+	10 (6%)	10 (7%)
Years since surgery	4.0 (5.8)	3.4 (4.3)
Prestudy management		
By general practitioner	152 (97%)	147 (96%)
By laboratory or clinic	4 (3%)	6 (4%)
By cardiologist	1 (1%)	0 (0%)
Prior time on warfarin >6 months	116 (74%)	110 (72%)
Midpoint of target INR range		
< 2.5	4 (3%)	3 (2%)
2.5– 2.9	56 (36%)	48 (31%)
≥3.0	97 (62%)	102 (67%)
Width of target INR range	0.9 (0.2)	0.9 (0.2)
INR range		
Upper limit	3.3 (0.3)	3.3 (0.3)

	Usual care (*n*=157)	Self-management (*n*=153)
Midpoint	2.87 (0.27)	2.85 (0.29)
Lower limit	2.4 (0.3)	2.4 (0.3)

All statistics are means (SD) or *n* (%)

Table 2: Main results

Outcomes	Usual care (n=157)	Self-management (n=153)	P
Treatment			
INRs per patient, mean (SD)	9.7 (3.0)	10.4 (2.2)	—*
Warfarin dose (mg), mean (SD)	5.2 (2.1)	5.8 (2.4)	—*
Primary endpoint			
INRs out of target range,% (SD)	40.7% (24.0%)	35.5% (26.0%)	Noninferiority <0.001 Superiority 0.08
Secondary endpoint†			
Total INR readings in extreme range (≥4.5 or <1.5), *n* (%)**	20 (1.4%)	10 (0.6%)	0.03
Other endpoints			
Deviation from target midrange (IU), mean (SD)	0.48 (0.17)	0.44 (0.18)	0.02
Mean outcome INR (IU), mean (SD)	2.6 (0.4)	2.6 (0.3)	—*
At least one INR in extreme range, %	11.8%	6.7%	0.132
INRs above target INR range (%), mean (SD)	7.5% (11.8%)	7.4% (12.3%)	0.92
INRs below target INR range (%), mean (SD)	33.2% (25.8%)	28.2% (25.6%)	0.10

* Not calculated.

† Adverse events was another secondary endpoint (table 3)

** As a percent of all blinded outcome INR readings

Table 3: Serious adverse events

	Usual care		Self-management	
Event	**Events**	**Patients**	**Events**	**Patients**
Bleeding	17	16	15	15*
Embolism or thrombosis	7	7	3	3

* 1 patient with recurrent intracranial haemorrhages and chronic heart failure died of multi-organ failure after surgery.