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

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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 patient's 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%, $P < 0.001$ for non-inferiority; $P = 0.08$ for superiority in closed-loop testing). The deviations from the patient's 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.

1. Introduction

Observational and experimental studies of patients on oral anticoagulation therapy show annual fatal bleeding rates of up to 4.8% and major non-fatal 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 in which 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

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proportion of blinded outcome INRs in the target range. The hypothesis tested was that the proportion of out-of-range INRs in the PSM group would be 6% less than in the usual care group.

2. Methods

2.1. 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.

2.2. 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).

2.3. Study intervention and randomisation

All patients received a 60-min 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 min) 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, Fig. 1).

The algorithm was validated against records of patients by ensuring that 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 that 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.

2.4. 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).

2.5. 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 prespecified 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.

3. Results

3.1. Screening and baseline characteristics

Of 1722 subjects screened for the trial, 310 were eligible and consented to be randomised (Fig. 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%, $P = 0.05$; Fig. 3).

There was no difference in the rate of serious adverse events (Table 3). Irrespective of treatment allocation, there were more than