STUDY PROTOCOL

Effectiveness of a Nursing Intervention Module on Adherence, Knowledge, Quality of Life, and Complications Among Patients Receiving Anticoagulation therapy—a Randomized Controlled Trial Protocol

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Background: Cardiovascular diseases are one of the major causes of mortality at the global level. They account for approximately 17.9 million deaths per year. Warfarin and acenocoumarol are the commonly used oral anticoagulants to treat and prevent thromboembolic disorders in patients with cardiovascular diseases. In India, approximately 2–2.5 million patients with rheumatic heart disease are receiving oral anticoagulation therapy. Additionally, this therapy is provided for stroke prevention in the case of atrial fibrillation and the treatment of valvular heart disease, stroke, and deep vein thrombosis. As the therapeutic range of these drugs is narrow and is affected by many factors, their use is challenging. This study aims to evaluate the effectiveness of a nursing intervention module in terms of adherence to therapy, knowledge, quality of life, and complications among patients receiving oral anticoagulation therapy. Furthermore, this study will address factors that affect adherence and the risk for bleeding by using a randomized controlled trial design.

Methods: This single-blind, single-center, randomized controlled trial will focus on adherence to oral anticoagulation therapy. A total of 320 patients who are on oral anticoagulation therapy will be randomized into blocks and allocated to either the intervention or standard care group. The intervention will comprise the use of a nursing intervention module that includes a booklet, log sheet, and decision aid on oral anticoagulation therapy adherence. Outcome measures, that is, knowledge regarding oral anticoagulation therapy, adherence, complications, and quality of life, will be assessed at the baseline and during follow-ups.

Discussion: Patient safety can be best achieved through patients' adherence to medication dose and monitoring of blood test values. Thromboembolic and bleeding complications are likely to occur when either the patient does not adhere to the treatment or the therapeutic range of the international normalized ratio is not maintained. This study will assess the nonadherence behavior and the effectiveness of a nursing intervention module toward adherence behavior.

Trial Registration: This research project is registered under the Clinical Trial Registry of India (CTRI/2019/06/019610).

Keywords: nonadherence, warfarin, efficacy, awareness, well-being

Background

Cardiovascular diseases (CVDs) are the major cause of deaths globally every year. As per the 2019 census, approximately 17.9 million people have died from CVDs alone at the global level, which accounts for 32% of deaths worldwide.[1] Patients

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with CVDs receive oral anticoagulation therapy for conditions such as cardiac thromboembolism, severe left ventricular dysfunction, mechanical heart valves, and bioprosthetic heart valves.[2,3] Oral anticoagulants such as warfarin and acenocoumarol (coumarin) are used to manage these conditions clinically. Many new direct oral anticoagulants have been developed, but they are not widely used in India owing to high costs, lack of specific laboratory monitoring tests, unavailability of specific antidotes, and serious bleeding in patients with renal impairment.[4] As the therapeutic ranges of warfarin and acenocoumarol are narrow and affected by many factors such as diet–drug and drug–drug interactions, their use is challenging.[5]

In a study from Saudi Arabia, only 31.8% (95/298) of the enrolled patients were reported to adhere to the therapy. Treatment satisfaction was the only predictor of adherence (p = 0.009), and improved international normalized ratio (INR) control was significantly associated with adherence (p = 0.023) and satisfaction (p = 0.038).[6] Regarding knowledge and adherence to oral anticoagulation therapy, as per a study conducted in Belgium consisting of 57 patients with mechanical heart valves, most patients poorly understood the effects of alcohol and vitamins on oral anticoagulants as well as the symptoms relevant to over anticoagulation.[7]

A study conducted in the United States to evaluate patient adherence compared patient self-reports through electronic medication event monitoring at Pennsylvania-based anticoagulation clinics. Approximately 145 participants were recruited for the study, and the mean percent days of nonadherence was 21.8%.[8] A study from Saudi Arabia reported that approximately 53.6% of the 192 patients on oral anticoagulation therapy had poor adherence, and no association was observed between therapy adherence and INR control.[9] A study conducted in Sudan on oral anticoagulation therapy demonstrated that only approximately 5.4% of the people complied with the therapy.[10]

Several studies have reported that participants have average or poor knowledge regarding oral anticoagulation therapy. A report from Singapore highlighted patients' knowledge deficits regarding oral anticoagulation treatment and their relation with adherence and INR.[11] A study conducted in New Delhi, India, demonstrated that 50% of the patients had suboptimal knowledge and interventions are needed for knowledge improvement.[12]

Oral anticoagulants are useful in many clinical conditions; however, they may occasionally cause adverse effects. When either the patient is not adherent to the treatment or the therapeutic range of INR is not maintained within limits, thromboembolic and bleeding complications are likely to occur.[13] Caution must be exercised when a patient has known risk factors for bleeding. These complications may be severe and may overshadow the benefits of warfarin therapy.[12] Researchers from Canada reported that 28 bleeding complications are related to supratherapeutic levels of INR and 4 thromboembolic events are related to subtherapeutic levels of complications.[14] Another study from the USA reported that 12 of 306 patients had adverse events related to the subtherapeutic and supratherapeutic levels of INR.[15]

Oral anticoagulation therapy also affects several domains of quality of life (QoL) such as mobility, usual activities, self-care, pain or discomfort, and anxiety or depression.[16] These domains must be focused on to improve patients' QoL. The QoL perception of a person is influenced by oral anticoagulation therapy. This therapy induces changes in patients with definite risks such as bleeding complications.[17] A report from Pakistan suggested that nonclinical factors rather than health-related factors affected the QoL scores.[18] Another report from Saudi Arabia concluded that the strong adherence to warfarin therapy may improve physical health of patients.[19]

Studies have reported that educational interventions improve patients' knowledge of oral anticoagulation therapy and hence lead to improved adherence to the treatment. A report from the United Kingdom states that educational interventions improve patients' knowledge regarding the acceptable INR range as well as the factors that affect INR levels.[20] A narrative review from Australia suggested that educational interventions substantially improve INR control, reduce adverse events, and increase patient knowledge. Further research is needed in the area of patient-focused interventions, including patients with inadequate health literacy, culturally and linguistically diverse backgrounds, and patient caregivers.[21] Improving patients' compliance to warfarin therapy is a major challenge to health care professionals. Health education along with continuous patient motivation is necessary to ensure adherence. Educational interventions significantly improve adherence to warfarin and are essential for safe treatment.[22]

Knowledge of and adherence to oral anticoagulation therapy are poor, which negatively affect patients' QoL. Good adherence to treatment, appropriate medication dosage, and regular monitoring for INR are mandatory to safely manage patients with warfarin therapy. Thus, educating and motivating patients by using a nursing intervention module (NIM) comprising an information booklet, a maintenance log sheet, and an adherence decision aid on oral anticoagulation therapy

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may help improve patients' knowledge and adherence. Thus, there may be a reduction in complications such as thromboembolic and bleeding events. All these factors may help ensure a good QoL among patients on long-term anticoagulation therapy.

Methods

The protocol for this clinical trial is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines/methodology (http://www.spirit-statement.org/wp-content/uploads/2013/01/SPIRIT-Checklist-download-8Jan13.pdf).

Aim

This study will assess knowledge, adherence, factors affecting adherence, complications, QoL, and bleeding risk among patients receiving oral anticoagulants. Furthermore, this study intends to determine the association between knowledge, QoL, and adherence and evaluate the effectiveness of the NIM in terms of knowledge, QoL, adherence, and complications among patients receiving oral anticoagulants.

Study Design

A randomized controlled trial design will be adopted, and the research will be conducted at a selected tertiary care center in Karnataka, India. Adults on oral anticoagulation therapy will be recruited according to eligibility criteria, and patients will be allocated to either the control group or the intervention group based on the block randomization method.

Patient and Recruitment

Adults on oral anticoagulation therapy visiting cardiology and cardiothoracic units of the selected hospital will be screened for eligibility and will be recruited for this study. Information will be provided to patients regarding the study by using a patient information sheet, which includes the purpose and requirement of the study, benefits, risks involved, and compensation. A duly signed informed consent will be obtained from the patients. A block randomization technique will be used to allocate the participants to either the control group or the intervention group. In total, 32 blocks will be made, with the block size being 10, that is, 16 patients in each group. By using the computer-generated sequence numbers, the sequence will be generated. Sequentially numbered opaque sealed envelopes (SNOSEs) will be used to conceal the allocation. Figure 1 presents a consort flowchart depicting the enrolment, randomization, allocation, and follow-up of patients.

Inclusion Criteria

The inclusion criteria of this study are as follows: age $\geq$ 21 years; receiving oral anticoagulation therapy for a minimum duration of 1 year with a minimum of five INR readings in the past 1 year; and having the ability to understand and speak Kannada or English language.

Exclusion Criteria

The exclusion criteria of the study are as follows: receiving oral anticoagulation therapy for <1 year, maintaining time in therapeutic range (TTR) of $\geq$60%, having cognitive impairment, unwillingness to participate, having a terminal illness, and undergoing pregnancy.

Sample Size

The sample size was calculated based on the formula for comparison of the proportion. The comparison of the proportion of nonadherence between the control and intervention groups with 80% power and a 5% significance level was used. The sample size was determined using the Hosmer–Lemeshow test and EzR software.[23] The sample size needed is 138 in each group. A preliminary study conducted in a local setting indicated that the proportion of nonadherence is 80%. After the intervention, investigators expect a minimal clinically significant difference of 15% between the two groups. With a 10% dropout rate, the sample size needed is 153 in each group; however, investigators have decided to include 160 participants in each group.
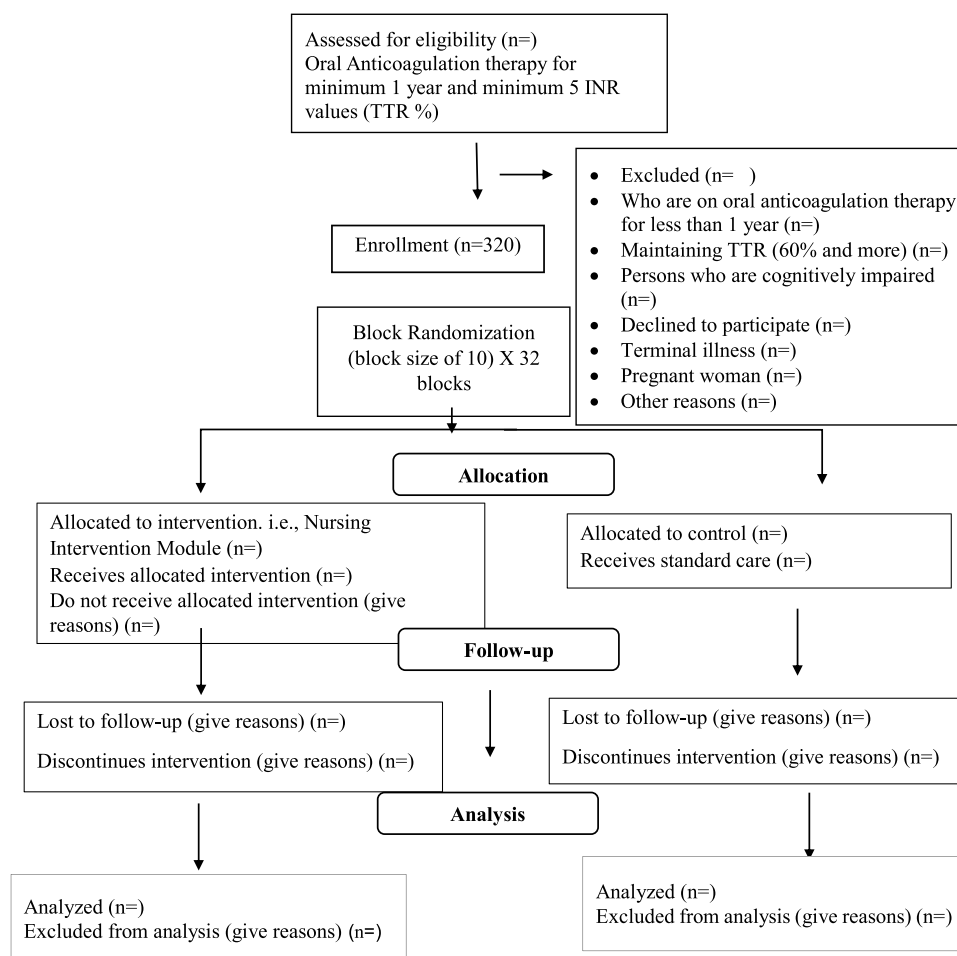
Figure 1 Consort flow sheet depicting the randomized controlled trial.

Randomization and Blinding

The block randomization method will be used to allocate the patients to the control and experimental groups. A block size of 10 will be used, with a total of 32 blocks. The sequence will be generated using computer-generated sequence numbers, which will be handled by the researcher. SNOSE will be used to conceal the allocation. The data collecting personnel will allocate the participants to either the control group or the intervention group based on the sequence number provided by the researcher. Participants will be blinded regarding their allocation group. The researcher will also be in charge of solving any problems or addressing any concerns that arise during the study. Intention-to-treat analysis will be used in case of dropouts. Outcome assessors and data analysts will be blinded to the study as they will not be coming in contact with the study participants.

Intervention Protocol

Control Group

A baseline assessment will be performed for knowledge, adherence, factors affecting adherence, complications, bleeding risk, and QoL. The control group will receive the standard treatment, that is, information and advice from the treating physician. Follow-up will be conducted at 2-month intervals for up to 10 months as patients will be reporting to the hospital once in 2 months. The standard care, that is, regular checkups, blood investigations, and medication prescriptions will be provided as established in the cardiac and cardiothoracic outpatient departments.

Intervention Group

A baseline assessment will be performed for knowledge, adherence, factors affecting adherence, complications, bleeding risk, and QoL. The NIM will be administered to the participants in the intervention group. The information booklet on oral anticoagulation therapy will be explained to them, which includes indications for the therapy, medication intake, medication interactions, laboratory monitoring, activity, diet, side effects, pregnancy, procedures, safety precautions, and self-care. An anticoagulation maintenance log sheet will be provided, wherein the details of the therapy, INR target range, prothrombin time (PT)/INR values, and dates for follow-up visits will be mentioned. Anticoagulation therapy adherence decision aids will be provided to all the patients in the intervention group as they all belong to the nonadherence group as per inclusion and exclusion criteria. The specific reason for nonadherence behavior and the patient's ability to make the right decision will be explored. Patients will be supported to make an informed and effective decision through one-to-one teaching and counseling, which may lead to adherence behavior. The effectiveness of the intervention will be measured after the final follow-up.

Outcome Assessment, Variables, and Measurement Instruments

The baseline and final assessment data of all the participants in both the groups will be analyzed by researchers for objective evaluation. Patients on oral anticoagulation therapy visiting cardiac and cardiothoracic surgery outpatient departments will be enrolled in the study. At the baseline visit, informed consent will be obtained after explaining the participant information sheet. They will be allocated either to the control group or the intervention group by using the block randomization technique. Baseline assessment will be performed for knowledge, adherence, factors affecting adherence, complications, bleeding risk, and QoL. The NIM will be administered to the intervention group, whereas the control group will receive the standard treatment, that is, information and advice, from the treating physician. In the follow-up periods, that is, in the second month, patients' knowledge, adherence, and complications will be assessed. In the fourth, sixth, and eighth months, an assessment will be conducted for patients' adherence and complications. In the 10th month, patients' adherence, complications, and QoL will be assessed. The follow-ups will be conducted in the cardiac and cardiothoracic outpatient departments. Blood for PT/INR will be collected at every visit as a part of their regular follow-up to monitor the dose. Blood for hemoglobin and serum creatinine (to calculate the glomerular filtration rate) will be collected as a part of Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) tool use to check for bleeding risk.[24] At the closure of the study, the intervention, that is, NIM, will be administered to all the control group participants as well. Two nursing staff will be trained during the second year of the project to continue the work in the anticoagulation clinic. More staff will be trained based on the need. The principal investigator and research assistant will provide the intervention. The mode of delivery will be face-to-face interaction, and it will be provided individually. The booklet will be provided, a log sheet will be maintained, and therapy adherence decision aid will be used for each patient individually. The interventions will be provided only once, that is, at the baseline for 45 min. It will be reinforced during subsequent follow-ups once in 2 months for a total of five follow-ups. The schematic diagram explains the research design in detail (Figure 2).

The independent variable is NIM, which refers to an interventional package developed by the investigator for the patients receiving anticoagulation therapy who are visiting cardiology and cardiothoracic surgery units. This module comprises an information booklet, a maintenance log sheet, and an adherence decision aid for oral anticoagulation therapy.

The dependent variables are as follows:

Knowledge: It refers to a person's awareness regarding the anticoagulant drug they are consuming; its mode of action, indications, and contraindications; drug–drug interactions; side effects; diet–drug interactions; safety precautions to be taken; follow-up; and INR maintenance.

Adherence: It refers to the degree to which a person is compliant with the recommendations of the treating physician in terms of oral anticoagulation therapy[25] and is measured using the adherence scale and INR measurements in terms of TTR%. The expected target range for TTR% is 2.0–3.0 for all conditions except mitral valve replacement (2.5–3.5) across time. A person is considered to be adherent if the INR fraction is in the target range of ≥60%. It is measured using the following formula:

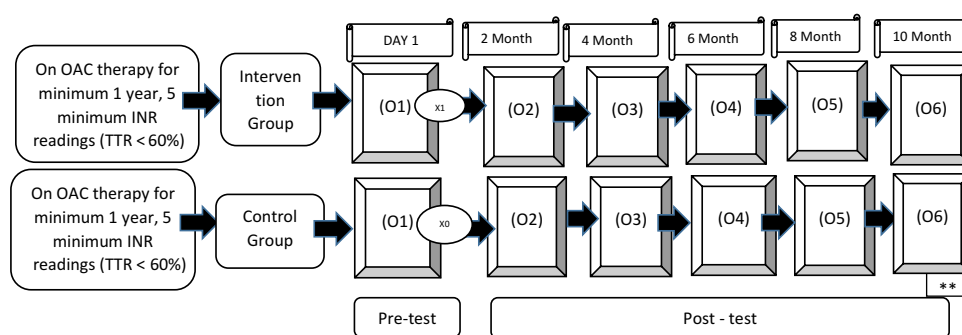**Figure 2** Schematic representation of research design.
Notes: O: Assessment. O1: Assessment for knowledge, adherence, factors affecting adherence, complications, the risk for bleeding, quality of life. X1: Implementation of Nursing Intervention module (NIM). X0: Receives standard care. O2: Assessment for knowledge, adherence, complications. O3, O4, O5: Assessment for adherence, complications. O6: Assessment for adherence, complications, quality of life. **: Intervention for the control group.

Number of tests in range/Total number of tests × 100 = TTR%.[26]

Complications: Complications refer to any problems caused by nonmaintenance of the therapeutic INR, that is, any sort of bleeding and thromboembolic complications as measured using the complication checklist.

QoL: QoL refers to the patients' overall health when they are on oral anticoagulants as measured using Ferrans and Powers Quality of Life Index Cardiac Version-IV.[27]

Description of the Instrument

The instrument consists of the following six tools:

Tool 1: Part A: Demographic Variables; Part B: Clinical Variables

Tool 2: Knowledge questionnaire on oral anticoagulation therapy (Anticoagulation Knowledge Questionnaire)

Tool 3: Tool to assess adherence to oral anticoagulation therapy (Modified Manipal Scale for Cardiac Drug Compliance and INR measurements in terms of TTR %)

Tool 4: Tool to assess factors affecting adherence (Tool on Adherence Barrier)

Tool 5: Tool to assess complications (Complication Checklist)

Tool 6: Tool to assess the risk of bleeding (ATRIA bleeding scores)

Tool 7: Tool to measure the QoL of persons receiving oral anticoagulation therapy (Ferrans and Powers Quality of Life Index Cardiac Version-IV).

The tools and intervention module will be submitted to experts from the fields of cardiology, cardiothoracic surgery, and cardiovascular nursing to establish their content validity. To assess the reliability of the tools, it will be administered to 20 patients. The split-half method will be used to assess the knowledge questionnaire's reliability. The Kudar–Richardson formula will be used to assess the adherence tool's reliability. Cronbach's alpha will be used to assess the reliability of the tools used for evaluating the barriers to anticoagulation therapy and QoL. The test–retest method will be used to assess the reliability of the complication checklist and ATRIA tool. After the reliability establishment, the pretesting of the tools will be performed by providing them to five patients to assess for any difficulty in understanding the tools. To determine the feasibility of the study, a pilot study will be conducted among 40 patients, that is, 20 each in the control and experimental groups.

Statistical Analysis

Data analysis will be performed through inferential and descriptive statistics by using the IBM SPSS statistics 20.0 version. To describe the characteristics of the population, frequency and percentage calculations will be performed. To determine the effectiveness of the NIM in terms of adherence among participants of the control group compared with the intervention group, logistic regression will be performed. To compare the knowledge level between and within the groups, repeated measures analysis of variance will be used. The complication rates and bleeding risk will be compared using frequency and percentage. QoL between the control and experimental groups will be compared through the

calculation of the mean and standard deviation. The Pearson correlation coefficient will be used to determine the correlation between knowledge, adherence, complications, and QoL in the control and experimental group participants. Intention-to-treat analysis will be performed in case of loss to follow-up.

Discussion

Vitamin K antagonists are commonly used; however, their use is challenging owing to drug and diet interactions and a narrow therapeutic range. Patient safety can be achieved through good adherence, but studies have indicated that a small percentage of people are adherent to the therapy.[28] Knowledge deficit exists in the area of oral anticoagulation therapy and INR monitoring among patients.[29] The rate of intracranial bleeding ranges from 0.1% to 0.9% per year, and the rate of major extracranial hemorrhage ranges from 0.4% to 2% per year.[30] Oral anticoagulation therapy negatively affects the QoL domains.[31] Educational interventions improve adherence to anticoagulant therapy.[32] The expected outcome of NIM is good adherence to oral anticoagulation therapy. Furthermore, it may minimize the complications of bleeding and thromboembolism and improve the QoL of persons receiving oral anticoagulants.

Provision of knowledge based on need is crucial so that patients realize the importance of adherence to the therapy. Factors affecting adherence are varied and individual. Through the analysis of individual factors responsible for nonadherent behaviors by using a decision aid, researchers may be able to identify individual reasons for nonadherence and develop strategies that can be implemented on a one-to-one basis. We intend to start a nurse-led oral anticoagulation clinic, if feasible.

Limitations

Although this study may provide guidelines to improve patient adherence to oral anticoagulation therapy, it has some limitations. This study will be conducted in a single center. Hence, generalization of the findings to a larger group may not be possible. Participants may not turn up for the follow-up, maintain a proper follow-up schedule, or agree to undergo repeated PT/INR testing, which may need a lot of motivation. Patients on direct oral anticoagulants will not be included in this study, and hence, the generalizability of the findings to these patients will not be feasible.

Conclusion

This study may contribute to improving knowledge regarding oral anticoagulation therapy. This study will attempt to address knowledge gaps regarding oral anticoagulation therapy, such as adherence to the therapy, factors contributing to nonadherence to the therapy, people at high risk of bleeding with the therapy, and QoL of the patients who are on this therapy. An anticoagulation clinic may help people become receptive to therapy instructions and motivate them to adhere to the therapy.

Abbreviations

CVD, cardiovascular disease; NIM, nursing intervention module; PT, prothrombin time; INR, international normalized ratio; QoL, quality of life; SNOSE, sequentially numbered opaque sealed envelopes; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; TTR, time in the therapeutic range; ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation.

Ethics Approval and Consent to Participate

The presented study protocol received approval from the Kasturba Medical College and Kasturba Hospital Institutional Ethics Committee, Manipal, India, on March 12, 2019 (IEC 170/2019). Participants will only be included in the study if they provide written informed consent beforehand. This trial will be conducted according to the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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