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THE EFFICACY AND SAFETY OF THE NOVEL ANTICOAGULANTS IN ELDERLY ADULTS

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Abstract

Atrial fibrillation is a common arrhythmia in older patients that predisposes them to cardioembolic strokes. The novel anticoagulants, dabigatran, apixaban, and rivaroxaban have been shown in trials to be non-inferior or superior to warfarin in reducing embolic strokes. These novel anticoagulants have been approved in Canada and are attractive alternatives to warfarin. However, there are concerns around prescribing the novel anticoagulants due to the lack of a reversal agent and limited experience with their use. Apixaban may be the best choice in the older patient population with multiple co-morbidities, although dose reduction may be indicated, and there is a lack of head to head trials between the three novel anticoagulants. The novel anticoagulants should not be used when patients have severe renal impairment (CrCl < 30 mL/min). There are also higher costs associated with these agents, lack of long-term effectiveness data and little data is available regarding drug interactions.

Résumé

La fibrillation auriculaire est une arythmie fréquente chez les personnes âgées, avec un risque associé d'AVC cardio-emboliques. Les nouveaux anticoagulants (NOAC), dabigatran, apixaban et rivaroxaban, ont démontré dans plus d'une étude leur non-infériorité, voire même une supériorité face à la warfarine pour diminuer le risque d'AVC embolique. Ces NOAC ont été approuvés au Canada et sont des alternatives attrayantes à la warfarine à prime abord. Néanmoins, l'expérience limitée dans leur utilisation ainsi que la crainte associée au fait qu'il soit impossible de renverser leur effet en cas de saignement a limité leur utilisation clinique. L'apixaban pourrait être le meilleur choix chez les personnes âgées présentant plusieurs comorbidités, bien qu'il faille diminuer la posologie dans certains cas. Cependant, aucune étude comparative n'ait été effectuée entre les 3 NOAC. De plus, ces NOAC ne devraient pas être utilisés en cas d'insuffisance rénale sévère (CrCl < 30 mL/min). Ces médicaments sont également associés à un coût plus élevé et, pour l'instant, nous manquons de données sur leur efficacité à long terme et peu de données sont disponibles sur les interactions médicamenteuses possibles.

Case Study

An 87-year-old woman with nonvalvular atrial fibrillation (AF), who was on warfarin for stroke prevention, asks you about switching to one of the novel anticoagulants, as she has heard that you do not require regular blood work. Her other comorbidities include stage 3 chronic kidney disease with an estimated glomerular filtration rate (GFR) of 40 millilitres per minute (mL/min), hypertension, and type 2 diabetes mellitus. How safe and efficacious are the novel anticoagulants that are approved in Canada for nonvalvular AF (Figure 1) in an older adult population with multiple comorbidities?

Introduction

Atrial fibrillation (AF), a common arrhythmia in older patients, predisposes them to cardioembolic strokes.[1] Warfarin therapy is known to significantly reduce the risk of cardioembolic strokes in all ages (8.8% per annum in controls vs. 3.4% per annum with warfarin).[2] Older patients with AF are at the highest risk of stroke; however, studies consistently report the underuse of anticoagulation in this

Anticoagulant Therapy
for atrial fibrillation patients

Warfarin therapy is known to significantly reduce the risk of cardioembolic strokes in all ages. The new novel anticoagulants, dabigatran (a direct thrombin inhibitor) and apixaban and rivaroxaban (both direct factor Xa inhibitors), have been shown in trials to be non-inferior or superior to warfarin in reducing embolic strokes.

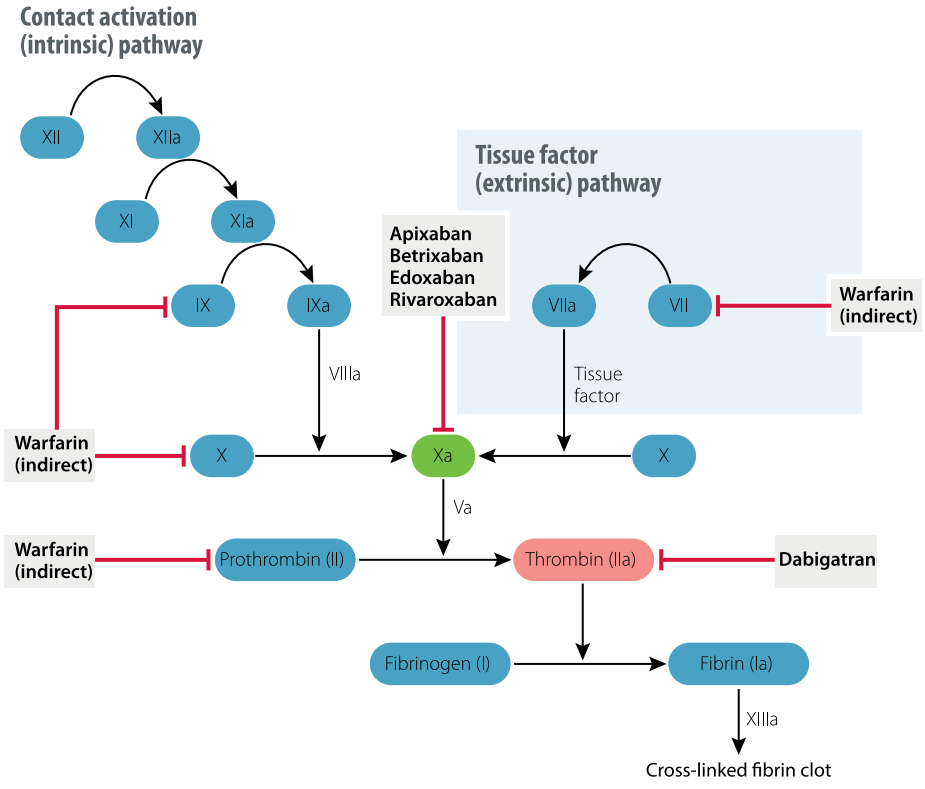

Figure 1. Nonvalvular atrial fibrillation.

patient population.[3] The most commonly cited reasons for not prescribing anticoagulation are high risk of falls, cognitive impairment, poor patient adherence, and fear of bleeding.[3,4] The only absolute contraindications to warfarin therapy in older adults that have been cited are bleeding diathesis, platelet count less than 50 × 103 μL, untreated or poorly controlled hypertension (consistently >160/90 mm Hg), and noncompliance with medication or international normalized ratio (INR) monitoring.[5] Those at average risk of stroke from AF (5% per year) and who are on anticoagulants such as warfarin must fall around 300 times per year for the risks of anticoagulant therapy to outweigh its benefit.[6]

Older patients are often prescribed aspirin instead of warfarin on the presumption that it is a safer alternative. The efficacy of warfarin (INR 2–3) over aspirin 75 milligrams (mg) daily for stroke prevention in those aged greater than 75 years has been clearly shown (relative risk [RR]= 0.48) with no difference in major bleeding rates between the two agents.[7] Warfarin has also been shown to be effective across all CHADS (congestive heart failure, hypertension, age, diabetes, and previous stroke) 2 score, with the exception of those with no clinical risk factors for increased risk of stroke.[7]

The new novel anticoagulants, dabigatran (a direct thrombin inhibitor) as well as apixaban and rivaroxaban (both direct factor Xa inhibitors), have been shown in trials to be non-inferior or superior to warfarin in reducing embolic strokes.[8–10] These novel anticoagulants have been approved in Canada and are attractive alternatives to warfarin, as monitoring is not required, these agents have less food and drug interactions, and are fixed doses. However, there are concerns around prescribing the novel anticoagulants because of the lack of a reversal

agent and limited experience with their use. In our review, we looked at the data surrounding the novel anticoagulants approved in Canada for AF in "frail" individuals over the age of 65 years. We looked specifically at the efficacy of these agents in preventing stroke and at their adverse effects.

Search Strategy

A Medline search was performed in March 2013 using a variety of keywords for the novel anticoagulants approved in Canada and several different terms for efficacy and safety outcomes. The term "frail" was not included as a main search term because an initial search that included the term returned only a limited number of citations. The inclusion criteria were (1) English language; (2) human studies; (3) randomized control trials (RCTs), meta-analyses or systematic reviews; (4) patients age >65 years included in the study; (5) comorbidities of subjects listed; (6) the anticoagulants apixaban, dabigatran, rivaroxaban and their respective trade name studied; (7) indication for trial, which was prevention of stroke or transient ischemic attack (TIA) in nonvalvular AF; and (8) comparison treatment with warfarin, aspirin, placebo, or another anticoagulant. Exclusion criteria were (1) non–English-language studies; (2) anticoagulants used for indications other than AF; (3) studies that were not an RCT, meta-analysis, or systematic review; (4) studies for which only the abstract was available.

Our search resulted in 53 abstracts being reviewed, and of these articles, 21 met inclusion and exclusion criteria. Four large RCTs with appropriate subgroup analyses were included.[8-11] One retrospective audit was included as it looked at bleeding episodes in a frail older adult population.[12] The 2012 Update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines was also included. http://www.onlinecjc.ca/article/S0828-282X(12)00046-3/abstract

Dabigatran

The results of the Dabigatran versus Warfarin in Patients with Atrial Fibrillation (RE-LY) trial[8] revealed that both doses of dabigatran (110 mg and 150 mg) were non-inferior to warfarin, and the 150-mg dose was superior to warfarin for the primary endpoint of stroke or systemic embolism.[8] The associated number needed to treat (NNT) is 167 per year.[8] This was also true in a subgroup analysis looking at secondary prevention of strokes and the quality of INR control in various centres.[12,13]

In those aged 75 years or greater, the risk of intracranial bleeding was lower with both doses of dabigatran (0.37% per year for 110-mg dosing, and 0.41% per year for 150-mg dosing) compared with warfarin (1% per year).[14] Those with intracranial hemorrhage were, on average, older (p <0.001), had a history of stroke or TIA (p <0.001), more often took aspirin during follow-up (p <0.001), less often had heart failure (p = 0.02), and had, on average, lower estimated creatinine clearances (p <0.001).[15] Only age (relative risk [RR] = 1.06 per year; p = 0.002) was independently predictive of intracranial hemorrhage among patients assigned to dabigatran.[15] Mortality associated with intracranial hemorrhage was similar between the three treatment arms (36% warfarin, 35% dabigatran 150 mg, 41% dabigatran 110 mg) despite the absence of a proven treatment to emergently reverse the antithrombotic effect of dabigatran.[15] A history of falls before study entry was not significantly predictive of subdural hematomas.[15] The rate of subdural hematomas was significantly lower with dabigatran 110 mg compared with warfarin (0.08% per year and 0.31% per year, respectively; RR = 0.27; p <0.001).[14] Fatal subdural bleeding occurred in 10 patients assigned to warfarin versus 5 patients and 2 patients to dabigatran 150 mg and 110 mg, respectively (p <0.05 for dabigatran 110 mg compared with warfarin).[15] The rate of major bleeding was significantly less with the 110-mg dose of dabigatran, with no difference found with the 150-mg dose compared with warfarin, irrespective of INR control in the centres.[8,13] The rate of major gastrointestinal bleeding with dabigatran at the 150-mg dose was significantly higher than with warfarin (number needed to harm [NNH] = 204 per year).[8] Local effects of dabigatran on diseased mucosa was thought to account for the relative increase in lower gastrointestinal bleeding seen with dabigatran compared with warfarin in older patients.[14] The only other adverse effect that was significantly more common with dabigatran than with warfarin was dyspepsia (NNH 33/yr [110 mg] and 66/yr [150mg]).[8]

The rate of myocardial infarction was higher with both doses of dabigatran, but the results did not reach statistical significance.[8] The RE-LY trial was not designed to detect a difference in myocardial infarction between treatments, and a subsequent further analysis found that there was no evidence that dabigatran treatment was associated with excess in any of these events.[16]

Apixaban

The results of the Apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE) trial[9] showed that in patients with AF and at least one additional risk factor for stroke, the use of apixaban significantly reduced the risk of stroke or systemic embolism by 21% (NNT = 167/1.8 yr), major bleeding by 31% (NNT = 67/1.8 yr), and death by 11% (NNT = 132/1.8 yr) compared with warfarin.[9] The predominant effect on stroke prevention was on hemorrhagic stroke.[9] For those age 75 years or greater, the numbers of events per year for stroke and systemic embolism were 1.6% with apixaban and 2.2% with warfarin.[9] There was no significant (p >0.10) statistical interaction with age and the primary outcome or major bleeding.[9] Similarly, in the AVERROES (Apixaban Versus Acetylsalicylic acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Unsuitable for

Vitamin K Antagonist Treatment) trial, they found a significant reduction in the event rate of stroke or systemic embolism with apixaban, as compared with aspirin for those age 75 or greater (2.0%/yr and 6.1%/yr, respectively).[17]

However, the efficacy of apixaban among patients with chronic kidney disease has not been proven. Among 3017 participants with estimated creatinine clearance of 25 to 50 mL/min per 1.73 m^2 (89% between 31 and 50 mL/min per 1.73 m^2), stroke rates were higher overall, and the efficacy of apixaban relative to warfarin in this subgroup was not statistically different.[9,18]

With respect to the outcome of major bleeding in the ARISTOTLE trial, a greater reduction was seen in bleeding among patients who did not have diabetes ($p = 0.003$ for interaction) and among patients with moderate or severe renal impairment ($p = 0.03$ for interaction).[9] For those age 75 years or greater, major bleeding events occurred less in the apixaban group (3.3%/yr), versus warfarin (5.2%/yr).[9] In the AVERROES trial, the rate of a bleeding event was 3.8%/yr with aspirin and 4.5%/yr with apixaban (hazard ratio [HR] = 1.18; 95% confidence interval [CI] 0.92–1.51).[19] Among those age 75 years or greater, similar event rates of major bleeding were seen for apixaban 2.6%/yr versus aspirin 2.2%/yr.[17] The only statistically significant independent predictors of major and clinically relevant nonmajor bleeding shared between those assigned to aspirin and apixaban were the use of nonstudy aspirin greater than 50% of the time ($p = 0.02$ for both treatments) and a history of daily or occasional nosebleeds ($p = 0.01$ and $p = 0.02$, respectively).[19]

The advantages of apixaban compared with warfarin, in terms of stroke or systemic embolism, major bleeding, and mortality, were similar across patients, irrespective of their risk for stroke and bleeding assessed by CHADS2, CHA2DS2VASc, and HAS-BLED scores.[20] (HAS-BLED website: http://www.ncbi.nlm.nih.gov/pubmed/20299623). The reduction in intracranial bleeding with apixaban tended to be greater in patients with the highest HAS-BLED score (≥3) (HR = 0.22; CI 0.10–0.48; for interaction for all HAS-BLED score, $p = 0.0604$), although the ARISTOTLE trial was not designed or powered to detect interactions between the study-drug and risk-score subgroups and the risk scores were not developed in those taking apixaban.[20]

The additional benefits found in both the AVERROES and ARISTOTLE trials were that apixaban, compared with warfarin, was associated with a reduction in the rate of gastrointestinal bleeding and fewer patients receiving apixaban had myocardial infarction compared with those receiving either warfarin or aspirin.[9,17]

Rivaroxaban

In the Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET-AF) trial[10], there was an increased risk of baseline stroke among the participants in comparison with the RE-LY and ARISTOTLE trials.[8-10] Rivaroxaban was found to be non-inferior to warfarin for the primary endpoint of stroke or systemic embolism.[10] This remained the case for those age 75 years or greater (rivaroxaban 4.06% per year versus warfarin 5% per year, $p = 0.313$).[10] Major and clinically relevant nonmajor bleeding occurred in 14.9% per year in those taking rivaroxaban and 14.5% per year in those taking warfarin (HR 1.03; $p = 0.44$).[10] Rates of major bleeding were similar between the two treatments (rivaroxaban 3.6% versus warfarin 3.4%, $p = 0.58$).[10] Decreases in hemoglobin levels (2 grams per decilitre [g/dL] or more) and transfusions were more common among patients in the rivaroxaban group, whereas fatal bleeding and bleeding at critical anatomical sites were less frequent.[10] Rates of intracranial hemorrhage were significantly lower in the rivaroxaban group than in the warfarin group (0.5% versus 0.7% per year, respectively; HR 0.67; $p = 0.02$),[10] whereas major bleeding from a gastrointestinal site was more common in the rivaroxaban group (3.2% versus 2.2%, $p<0.001$).[10] For those age 75 years or greater, the rates of major and nonmajor clinically relevant bleeding did not differ between treatments (rivaroxaban 25.78% versus warfarin 23.43%; HR 1.12; $p = 0.118$).[10]

In a subgroup analysis looking at subjects with moderate renal insufficiency (creatinine clearance [CrCl] 30–49 mL/min at baseline, 20.7% of the trial cohort), in which the dose of rivaroxaban was reduced from 20 to 15 mg daily, the adverse event rates were similar between those randomized to rivaroxaban and to warfarin.[21]

In another subgroup analysis looking at the efficacy and safety of rivaroxaban compared with warfarin for secondary prevention of stroke or TIA, there was no evidence of a difference between the two agents.[22]

Indirect Comparison of the Three Novel Anticoagulants

In subgroups of patients with CHADS2 scores 3 or greater, which ensured fairer and less confounded comparisons among rivaroxaban, apixaban, and dabigatran, both dabigatran 150 mg and apixaban reduced the risk of stroke and embolism by about 20% compared with rivaroxaban, without reaching statistical significance.[23] In the same subgroup, the risk of major hemorrhage was again lowest for apixaban (2.9 event rate per 100 person-years) compared with both other drugs (rivaroxaban 3.64 event rate per 100 person-years, dabigatran 150 mg dosing 4.86 event rate per 100 person-years); however, compared with dabigatran 110 mg, there was no difference (3.80 event rate per 100 person-years).[23] The dabigatran data presented in the analysis were from the intention-to-treat analysis presented in the U.S. Food and Drug Administration (FDA) Advisory Committee briefing documents, as on-treatment analysis was not reported for the subgroups within the RE-LY trial.[23]

Apixaban showed significantly less myocardial infarction versus dabigatran (150 mg) (HR = 0.39; 95% CI, 0.16–0.95).[24] Apixaban was superior to dabigatran 110 mg for primary prevention of disabling or fatal stroke (HR = 0.59; 95% CI, 0.36–0.97), whereas it was associated with more stroke compared with the 150-mg dose of dabigatran (HR = 1.45; 95% CI, 1.01–2.08) and with less major bleeding (HR = 0.75; 95% CI, 0.60–0.94), gastrointestinal bleeding (HR = 0.61; 95% CI, 0.42–0.89), and other location bleeding (HR = 0.74; 95% CI, 0.58–0.94).[24]

Summary

The RE-LY, ARISTOTLE, and ROCKET-AF trials all showed the non-inferiority of their respective agents compared with warfarin for the primary endpoint of stroke or systemic embolism.[8-10] Patients were, however, only followed up for 1.8 to 2 years,[8-10] and these agents have only been used in clinical practice for the last couple of years. Long-term efficacy safety data in a real world practice are not available. A retrospective audit of bleeding episodes involving 44 patients taking dabigatran, who presented to a New Zealand hospital over a 2-month period, showed that the mean age of those presenting with bleeds was 78 years, whereas 66% were over the age of 80 years.[12] Of these bleeds, 12 were considered major bleeds.[12] The key factors contributing to the major bleeds were prescriber error, with failure to allow the INR ratio to fall below 2.0 prior to initiating dabigatran; impaired renal function, in which dabigatran was used in severe renal impairment (CrCl <30 mL/min); patient age; and complications arising from lack of a reversal agent.[12] This study reminds us to be cautious in extrapolating trial data to patient populations not readily studied. It also demonstrates the importance of monitoring creatinine clearance while patients are on these agents. It is recommended that the glomerular filtration rate (GFR) be monitored every 6 months.[25] The use of the novel anticoagulants should be reconsidered in those at risk of frequent episodes of acute kidney injury.[26]

Each trial also used reduced dosing in certain patient populations (see Table 1). Apixaban 2.5 mg twice daily was prescribed to patients with two or more of the following criteria: age 80 years or greater, body weight of 60 kg or greater, and serum creatinine 133 millimoles per litre (μmol/L) or greater.[9] Dabigatran at 110 mg twice daily was prescribed to patients who were 80 years or older, or 75 to 79 years of age with 1 or more bleeding risk factors, for example, those with active peptic ulcer, those on antiplatelets or on P-glycoprotein inhibitors (see product monograph), or those with creatinine clearance of 30 to 45 mL/min with 1 or more bleeding risk factor (see product monograph).[26] Rivaroxaban 15 mg daily was used if creatine clearance was between 30 and 49 mL/min.[10] All three are contraindicated in severe renal impairment (CrCl, <30 mL/min).[8-10]

Although the results of the indirect comparison between the three novel anticoagulants suggests similar efficacy and less risk of bleed with apixaban compared with the other agents in older adults with chronic diseases, these trials can only be interpreted as hypothesis generating. Until head-to-head trials are performed, no final conclusion can be drawn.

The lack of a reversal agent will likely remain a concern until one is found. Despite this, it has been shown that fatal bleeding can be reduced with rivaroxaban and mortality rates improved with apixaban, which suggests that even with a reversal agent for warfarin, outcomes from major bleeds are likely no different or improved. What has not been considered, however, is delay in emergency surgeries for patients who are on the novel agents. This may be an important clinical consideration and potentially should be taken into account in a frail older adult population with higher incidences of hip fractures and ischemic bowel, for example.

The agent of choice for patients with concomitant AF and coronary artery disease still remains to be elucidated through randomized trials. The Focused 2012 Update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines now recommend either warfarin or one of the new anticoagulants, although this guideline is based on extrapolated data.[25]

Important long-term safety data associated with possible drug

Key Points

1. *Novel anticoagulants are an option for the treatment of nonvalvular atrial fibrillation. Apixaban may be the best choice in the older patient population with multiple comorbidities, although dose reduction may be indicated. (Table 1)*
2. *Do not use these agents when patients have severe renal impairment (CrCl, <30 mL/min).*
3. *Patients require regular follow-up of their creatinine clearance, with a suggested interval of 6 months, while on novel anticoagulants. Dose reduction may be indicated in those with low body weight.*
4. *There is currently no reversal agent for the anticoagulant effects.*
5. *Higher costs are associated with novel anticoagulants.*
6. *There is a lack of long-term effectiveness data.*
7. *Little data is available regarding drug interactions.*
8. *When prescribing, one needs to consider other outcomes such as possible delay in emergency surgery and tendency to experience future declines in creatine clearance.*
9. *If switching from warfarin, do not start these agents until the INR is below 2.0.*

Table 1. Criteria for Dose Reduction

Medication	Criteria for Dose Reduction	Reduced dose
Apixaban* 5 mg twice daily	Two or more of the following:	2.5 mg twice daily
	≥80 years	
	Body weight of ≤60 kg	
	Serum creatinine ≥133 μmol/L	
Dabigatran* 150 mg twice daily	≥80 years	110 mg twice daily
	or 75–79 years of age with ≥1 bleeding risk factor	
	Or creatinine clearance (CrCl) 30–45 mL/min with ≥1 bleeding risk factor	
Rivaroxaban* 20 mg twice daily	CrCl between 30 and 49 mL/min	15 mg daily
All three are contraindicated in severe renal impairment (CrCl, <30 mL/min).		

interactions are still lacking. Strong inhibitors of both CYP 3A4 and P−glycoprotein are contraindicated with all three new agents (e.g., azoles such as fluconazole or ketoconazole), and caution is to be exercised in the use of weaker inhibitors such as amiodarone and inducers such as phenytoin and rifampin.[26, 28, 29]

As a final note, cost is significantly different between the use of warfarin therapy and INR monitoring and the use of the novel anticoagulants. This difference ranges between $60 and $100 per month above the cost of warfarin.[25]

Conclusion of the Case

The patient remained on warfarin after understanding the risks and benefits of each therapy. Her decision was primarily based on the lack of a reversal agent, the cost of the novel anticoagulants, and the fact that she had been doing well on warfarin therapy to this point. Alternatively, one of the novel anticoagulants could be considered as they are indicated. Apixaban may be the best choice given its efficacy, reduced risk of bleeds, and improvement in mortality. A reduced dose would be indicated given the patient's degree of renal failure and her age. Another consideration is that a novel anticoagulant may not be covered by her provincial health care drug plan because of her history of therapeutic INRs.

There are no conflicts of interest either author has to declare.

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