

Cochrane corner: vitamin K for improved anticoagulation control in patients receiving warfarin

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There has been a substantial increase in the use of oral anticoagulants, notably in the ageing population. This is primarily driven by the use of warfarin in people with atrial fibrillation (AF) in order to reduce the risks of thromboembolic events such as stroke.¹ In elderly patients with AF, warfarin use has been shown to reduce the relative risk of stroke by >50% compared with aspirin alone.² Warfarin is also used to treat patients with deep vein thrombosis, mechanical heart valve replacement, cardioversion, cardiomyopathy and antiphospholipid syndrome.¹

The clinical benefits of warfarin must also be balanced with potential risks. Over-dosage can cause major haemorrhage while under-anticoagulation may lead to thrombosis. As a result of these risks, warfarin therapy is monitored regularly using the international normalised ratio (INR) to prevent under-anticoagulation or over-anticoagulation. For example, a target INR of 2.0–3.0 is recommended for the prevention of thromboembolic events in AF and an INR of 3.0–4.0 for mitral valve replacement.¹

Maintaining individuals within the narrow target ranges for INR can, however, prove challenging in routine clinical practice. The percentage of time in target range (TTR) for INR is an important marker of control, with a clear association between a low TTR and adverse events. In recent guidance on the management of anticoagulation in AF (CG180), the National Institute for Health and Care Excellence (UK) has suggested reassessing patients with poor INR control when TTR is <65%.¹

Several factors can affect INR variability, most notably dietary-related and drug–drug interactions. Medications (such as macrolide and other antibiotics, non-steroidal anti-inflammatory drugs, lipid-modifying agents and amiodarone) and certain foods that are rich in vitamin K (such as Brussels sprouts and broccoli) can interfere with the INR and over-anticoagulation or under-anticoagulation can result. Interactions with diet can occur because warfarin acts as a vitamin K antagonist (VKA) preventing the recycling of vitamin K that is otherwise needed in the hepatic synthesis of factors II, VII, IX and X, all of which are involved in the clotting cascade. Since there is little storage of vitamin K in the body, the production of vitamin K-dependent clotting factors and proteins is highly dependent on dietary vitamin K. A brief period of reduced intake of vitamin K can cause increased warfarin sensitivity, while an increased intake of vitamin K-containing foods can reduce anticoagulation; both these effects can last for several days.³

Patients with unstable control of anticoagulation have a consistently and significantly lower intake of vitamin K than their stable counterparts matched for age, sex and indication for warfarin.⁴ Patients who were allocated to an 80% reduction in vitamin K intake increased their INR by almost 30% 7 days after the intervention. These findings have led to observational

studies of low-dose vitamin K, which demonstrate a significantly higher number of INRs in range as well as the time in range for those patients receiving the intervention.⁵ However, the mechanism by which a low-dose, steady-state, dietary vitamin K supplements can improve INR control is poorly understood.³

In light of the emerging evidence of a possible benefit of low-dose vitamin K, we conducted a Cochrane systematic review to assess the effects of concomitant supplementation of low-dose oral vitamin K for anticoagulation control in patients being initiated on or taking a maintenance dose of warfarin.³ We included randomised controlled trials (RCTs) of participants on warfarin in primary care or hospital settings taking concomitant oral vitamin K compared with placebo or no treatment.

We obtained a total of 4031 references after executing the search strategy of which we included two RCTs, involving 100 participants. One study reported a significant improvement in the mean time in therapeutic range for 35 participants randomised to 150 µg vitamin K daily for 6 months versus a matched placebo. The authors of this study reported that the mean time in therapeutic range (%) was 59±20 before the study and 87±14 after the intervention period (difference 28±20, $p<0.01$). For the placebo group, the mean time in therapeutic range (%) was 63±18 in the six months before commencement of the study and 78±17 at the end of the study (difference 15±20, $p<0.01$). The same study also reported that the median number of warfarin dosage changes was significantly lower in the group receiving vitamin K supplementation compared with the placebo group. The other study was published in abstract form only and included 30 patients randomised to either 175 µg vitamin K once daily or placebo for a duration of 6 months. The primary outcome of the study was anticoagulation stability, defined as a reduction in the number of dose modifications during follow-up, and the published abstract reported no overall benefit for vitamin K.

Neither of the included studies reported evidence of any adverse events or mortality associated with vitamin K supplementation. Neither study reported any data relating to our secondary outcomes of interest (see table 1).

Limitations of the evidence

The main limitation of the evidence base is that we only found two included studies, further compounded by the fact only one of these was published in abstract form only. Correspondence with the author of the latter study confirmed that the study remained unpublished in full. Therefore, we interpreted our results with caution as they were largely based on only one full published trial of 70 participants. Furthermore, we were unable to assess the risk of bias in the full, unpublished study and found the risk of bias to be unclear in a number of domains ('random sequence generation', 'allocation concealment' and 'other bias') when assessing the full included study. We were also unable to construct a funnel plot to examine the risk of publication bias and felt that the abstract may not have been available in full as a result of it not demonstrating an overall benefit. Neither study reported data relating to our secondary

outcomes either. We also found no consistency in the doses of vitamin K being tested (150 µg/day in one study and 175 µg/day in another).³ The limitations of our review, such as observing low-quality evidence, are also mirrored in a broader review that examined the impact of low-dose vitamin K on other VKAs, such as phenprocoumon and acenocoumarol.⁶ Future updates of our review will consider included these drugs as well.

Clinical implications

Despite the above limitations, our review highlighted a trend towards a positive benefit of low-dose vitamin K but was limited by the publication of relatively small studies with heterogeneous doses of vitamin K being tested.³ Nevertheless, identifying an effective, safe and cost-effective intervention that improves INR control may be an advantageous additional option to consider in patients with poor control before switching to a direct oral anticoagulant. These include direct thrombin and factor Xa inhibitors that have been shown to be non-inferior to warfarin in comparator trials but may be limited by the lack of an antidote and expense. Therefore, we concluded that a larger, higher quality trial was needed to examine whether low-dose vitamin K improves INR control in those starting or already taking warfarin. Such a study would ideally focus on identifying the correct dose needed to achieve a benefit while minimising the risks of harms. If proven, low-dose vitamin K could be an effective, low-cost and safe method for improving INR control in patients taking warfarin.

Footnotes

Contributors KRM drafted the manuscript. DN and CH contributed substantially to further revisions of the manuscript, and all authors approved the final version.

Disclaimer The views expressed are those of the author(s) and not necessarily those of the National Health Service, the National Institute for Health Research or the Department of Health.

Competing interests KRM is an NIHR-funded clinical lecturer in general practice, UK.

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Table 1
PICO summary

Population	Adults who are >18 years old and are on warfarin irrespective of the indication for treatment (eg, valve replacement, AF)
Intervention(s))	<p>We included two types of intervention in this review</p> <p><i>Intervention 1:</i> oral vitamin K (of various doses), which has been added to the loading dose of warfarin. These participants were followed for the duration of the intervention, which is the first five days after initiation of warfarin</p> <p><i>Intervention 2:</i> oral vitamin K (of various doses), which has been added to the maintenance dose of warfarin. This is a lifelong intervention</p>
Control	These interventions were compared with either control or placebo groups
Outcome(s)	<p><i>Primary outcomes</i></p> <ul style="list-style-type: none"> • Time taken to the first INR in range (intervention one) • Mean time of therapeutic range (TTRs) (intervention one) • Mean time in therapeutic range (intervention two) • Thromboembolic events included stroke, arterial embolism, symptomatic DVT or pulmonary embolism (both interventions) • Major haemorrhage • Mortality (both interventions) <p><i>Secondary outcomes</i></p> <ul style="list-style-type: none"> • Proportion of supratherapeutic INRs and subtherapeutic INRs (both interventions) • Minor haemorrhage (all other haemorrhagic conditions that are not included in the criteria for major haemorrhage as stated in the primary outcome) (both interventions) • Rescue medication needed (eg, additional dose of vitamin K) (both interventions) • Cost-effectiveness (both interventions) • Quality of life (both interventions)

- AF, atrial fibrillation; DVT, deep vein thrombosis; INRs, international normalised ratios; TTR, time in target range.