

# Vitamin K lowered the international normalised ratio into the therapeutic range in patients receiving warfarin

Crowther MA, Julian J, McCarty D, et al. *Treatment of warfarin-associated coagulopathy with oral vitamin K: a randomised controlled trial. Lancet* 2000 Nov 4;356:1551-3.

**QUESTION:** In patients who are receiving warfarin and have an international normalised ratio (INR) value between 4.5 and 10.0, does low dose vitamin K lower the INR better than placebo?

## Design

Randomised (allocation concealed\*), blinded (patients, clinicians, and outcome assessors)†, \* placebo controlled trial with 3 months of follow up.

## Setting

5 thromboembolism services at teaching hospitals in London and Hamilton, Ontario, Canada.

## Patients

92 patients (mean age 65 y, 53% women) who were receiving warfarin and had an INR value between 4.5 and 10.0. Exclusion criteria were INR determined >12 hours before screening, life expectancy <10 days, need for immediate normalisation of INR, severe liver disease, major bleeding in the previous month, allergy to vitamin K, bleeding diathesis or thrombolytic treatment within 48 hours of screening, inability to take oral medications, platelet count <50 × 10<sup>9</sup>/l, or geographic inaccessibility. 89 patients (97%) completed the trial and were analysed.

## Intervention

Patients were allocated to 1 mg of oral vitamin K (Abbott Laboratories, Montreal, Quebec, Canada) (n = 46) or to placebo (n = 46).

## Main outcome measures

Proportion of patients with an INR value between 1.8 and 3.2 the day after the intervention. Patients were assessed for thrombotic and haemorrhagic events at 1 and 3 months after enrolment.

## Main results

More patients who received vitamin K than patients who received placebo had INR values between 1.8 and 3.2 the day after the intervention (p = 0.001) (table). No vitamin K group patients and 4 placebo group patients (9%) had an increase in INR values the day after treatment (p = 0.056). An INR value of <1.8 occurred in 7 vitamin K group patients (16%) and no placebo group patients (p = 0.012). After the second day after treatment, the INR values were similar in the 2 groups. At 3 months, fewer patients receiving vitamin K had bleeding episodes than patients receiving placebo (4% v 17%, p < 0.05).

## Conclusion

In patients who are receiving warfarin and have an international normalised ratio (INR) value between 4.5 and 10.0, low dose vitamin K lowered the INR to between 1.8 and 3.2 the day after administration.

\*See glossary.

†Information provided by author.

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*Vitamin K v placebo for lowering the international normalized ratio (INR) to the therapeutic range 1 day after the intervention‡*

Outcome	Vitamin K	Placebo	RBI (95% CI)	NNT (CI)
INR value between 1.8 and 3.2	56%	20%	272% (49 to 421)	3 (2 to 7)

‡Abbreviations defined in glossary; RBI, NNT, and CI calculated from data in article.

## COMMENTARY

In the US, more than 1 million people each year receive anticoagulation treatment to treat or prevent various thromboembolic complications. Of those receiving such treatment, the INR values will be >3.9 approximately 8% to 9% of the time.<sup>1</sup> The risk for substantial bleeding increases progressively with every 1 point increment of INR above 4.0.<sup>2</sup> For patients with serious bleeding, transfusion with fresh frozen plasma or prothrombin concentrate is the appropriate intervention. In asymptomatic patients, reduction of the INR can be achieved passively by withholding treatment or actively by giving vitamin K. Is active treatment more safe and effective than passive withholding? A recent review of the literature identified the need for large, well designed, randomised controlled trials to answer this question.<sup>3</sup>

A previous prospective cohort study by Crowther *et al* suggested that 1 mg of oral vitamin K was safe and effective in reversing anticoagulation for most patients within 16 hours of treatment.<sup>4</sup> The current study by Crowther *et al* provides additional insight into optimal treatment. Oral vitamin K in asymptomatic patients without an overt bleeding risk produces a clinically important increase in the proportion of target range INR values. For unclear reasons, the intervention group had fewer bleeding episodes during the 3 month follow up period. Active oral treatment appears to be safe and effective, but it is also unclear whether additional benefit and equivalent safety exist using intravenous or subcutaneous vitamin K administration.

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- 2 van der Meer FJ, Rosendaal FR, Vandenbroucke JP, *et al*. Bleeding complications in oral anticoagulant therapy. An analysis of risk factors. *Arch Intern Med* 1993;153:1557-62.
- 3 Taylor CT, Chester EA, Byrd DC, *et al*. Vitamin K to reverse excessive anticoagulation: a review of the literature. *Pharmacotherapy* 1999;19:1415-25.
- 4 Crowther MA, Donovan D, Harrison L, *et al*. Low-dose oral vitamin K reliably reverses over-anticoagulation due to warfarin. *Thromb Haemost* 1998;79:1116-8.