



Universiteit
Leiden
The Netherlands

Course of the international normalized ratio in response to oral vitamin K1 in patients overanticoagulated with phenprocoumon

Rosendaal, F.R.

Citation

Rosendaal, F. R. (1999). Course of the international normalized ratio in response to oral vitamin K1 in patients overanticoagulated with phenprocoumon, 241-245. Retrieved from <https://hdl.handle.net/1887/1671>

Version: Not Applicable (or Unknown)

License:

Downloaded from: <https://hdl.handle.net/1887/1671>

Note: To cite this publication please use the final published version (if applicable).

Course of the International Normalized Ratio in response to oral vitamin K₁ in patients overanticoagulated with phenprocoumon

F. J. A. PENNING-VAN BEEST,¹ F. R. ROSENDAAL,² D. E. GROBBEE,³ E. VAN MEEGEN⁴ AND B. H. CH. STRICKER^{1,5}

¹Pharmaco-epidemiology Unit, Departments of Internal Medicine II and Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam, ²Haemostasis and Thrombosis Research Centre, Department of Clinical Epidemiology, Leiden University Medical Centre, ³Julius Centre for Patient Oriented Research, Utrecht University Medical School, ⁴Red Cross Anticoagulant Clinic, The Hague, and ⁵Drug Safety Unit, Inspectorate for Health Care, Rijswijk, The Netherlands

Received 29 June 1998; accepted for publication 12 November 1998

Summary. Oral vitamin K₁ is used for the treatment of excessive anticoagulation. Detailed information on changes in the International Normalized Ratio (INR) in response to vitamin K₁ is not available. We therefore measured the INR for the first 7 d following the oral intake of 1–5 mg of vitamin K₁ in 24 patients routinely treated with phenprocoumon who had an INR ≥ 6.0 at presentation. On the first 2 d after administration of vitamin K₁, the mean INR decreased by 40% and 23% respectively. After day 2, the day-to-day proportional change in the mean INR depended on the dose of vitamin K₁ and varied from a decrease of 12% to an

increase of 21%. On day 7 the mean INR was higher than on day 2 in three out of five treatment groups. Between day 2 and day 7, in general, 32% of the patients had an INR value within the target zone, 25% had an INR value ≥ 6.0 and 8% had an INR value < 2.0 . These findings suggest that our routine treatment of overanticoagulation in patients on phenprocoumon should be intensified to improve its efficacy.

Keywords: overanticoagulation, coumarin anticoagulants, vitamin K₁, International Normalized Ratio, efficacy.

Oral anticoagulants have a narrow therapeutic index (Rosendaal, 1996). The optimal therapeutic range of oral anticoagulant therapy, as recommended by the Federation of Dutch Thrombosis Centres, lies between 2.5 and 3.5 International Normalized Ratio (INR) or between 3.0 and 4.0 INR (Cannegieter *et al*, 1995; The SPIRIT Study Group, 1997), depending on the indication for treatment. When the INR is > 6.0 the risk of bleeding, the most common adverse reaction to oral anticoagulants, sharply increases (Cannegieter *et al*, 1995). Therefore such an excess anticoagulant effect should be treated promptly and adequately.

In the absence of life-threatening haemorrhagic complications, the usual way to achieve a reduction in anticoagulant effect is to discontinue the drug for 2 or more days and, depending on the intensity of the INR value,

administer 1–10 mg of vitamin K₁ orally (Federatie van Nederlandse Trombosediensten, 1987). Detailed information on changes in the International Normalized Ratio in response to vitamin K₁ is not available since INR values are usually not measured daily, but only after a week. The literature provides limited information: two studies have been performed on the response of the INR to oral vitamin K₁ (Weibert *et al*, 1997; Pengo *et al*, 1993). In one (Weibert *et al*, 1997) the INR was measured twice: 1 or 2 d after administration of vitamin K₁ and 4–7 d after warfarin therapy was resumed. In the other study (Pengo *et al*, 1993) the INR value was determined after 1, 2 and 9 d. These studies both focused on efficacy and expressed the results in the number of patients with an INR below or above 5.0. No data were given on changes in INR over time. Harrell & Kline (1995) reported on five patients in whom oral vitamin K₁ was used to treat overanticoagulation. After 1 or 2 d the INR had decreased by 58% to 89%.

To obtain detailed insight into the course of the INR after oral administration of vitamin K₁ and to test the efficacy of

Correspondence: Dr B. H. Ch. Stricker, Pharmaco-epidemiology Unit, Room L448, Department of Internal Medicine II, Erasmus University Medical School, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands.

our routine treatment of overanticoagulation, we determined the INR value over 7 consecutive days in patients on phenprocoumon who had an INR >6.0 at presentation.

SUBJECTS AND METHODS

Patients treated with phenprocoumon (Marcoumar®) by the regional Red Cross anticoagulant clinic The Hague who were prescribed oral vitamin K₁ because of an INR value ≥ 6.0 between 9 June 1997 and 27 June 1997, were asked to participate in this prospective study. Patients treated with vitamin K₁ because of a subsequent medical intervention or whose prothrombin time had to be checked within 7 d were excluded.

On day 0 patients suspended phenprocoumon therapy and took an oral dose of vitamin K₁ (Konaktion® Cremophor EL-based drop solution 20 mg/ml). This dose was determined by the INR value and the target zone of anticoagulation, according to an algorithm employed at the anticoagulant clinic (Table I). Because of individual factors, the algorithm could be deviated from. The required number of drops were taken with about half a cup of water. The day at which the patient restarted phenprocoumon, as well as the adjustment of the dosage, depended on the patient's individual circumstances: standard practice was to restart phenprocoumon on day 2 and to lower the dosage by about 15%.

Table I. Algorithm for the administration of vitamin K₁ in patients on phenprocoumon.

INR value	Target zone of anticoagulation	
	2.0–3.5 INR	2.5–4.0 INR
6.0–7.9	Optional	Optional
8.0–8.9	2 mg	1 mg
9.0–11.9	3 mg	2 mg
12.0–14.9	5 mg	4 mg

On the next 7 d after taking vitamin K₁, day 1 to day 7, venous blood samples were collected in 3.2% sodium citrate Vacutainer tubes. The patients were visited at home between 8.00 and 12.30 a.m. Within 5 h after collection the blood samples were centrifuged at 3000 rpm for 10 min and plasma was frozen at -20°C . Prothrombin times were measured after the 1-week follow-up in order not to affect treatment. All measurements were done at the same time on an automatic coagulation analyser (Electra 1600C). The thromboplastin used was a human recombinant tissue factor (Ortho® RecombiPlasTin) with an international sensitivity index of 1.05 (batch RTF-159).

To confirm the assumption of no effect of freezing on the prothrombin time measurement, two blood samples were taken on day 7. Of one of these samples plasma was frozen and the prothrombin time was measured afterwards. Of the other sample the prothrombin time was measured directly. The mean difference in the INR value between both samples

was -0.1 , 95% CI $[-0.5; 0.3]$, indicating that freezing did not affect prothrombin time measurement.

To control for other factors that may affect the INR, patients were asked about their health and changes in co-medication and alcohol intake during the study period. In addition, the intake of vitamin K₁ and phenprocoumon were verified by questionnaire.

The course of the INR is described in terms of the proportional change in the mean INR between 2 consecutive days. Baseline INR and dose of vitamin K₁ are highly correlated: more vitamin K₁ is prescribed when the INR is higher (Table I). Therefore we also analysed patients separately according to the dose of vitamin K₁ (1, 2, 3, 4 or 5 mg), starting from the patients being compliant. To test the efficacy of the routine treatment of overanticoagulation, the frequency of INR values ≥ 6.0 , INR values within the target zone (2.0–3.5 INR or 2.5–4.0 INR) and INR values <2.0 was calculated.

RESULTS

The number of patients treated with vitamin K₁ and fulfilling the inclusion criteria in the 3-week study period was 41. Of the 34 patients we were able to contact, 24 (71%) were willing to participate, 10 men and 14 women. One patient was lost to follow-up after day 2. The mean age of the patients was 70 years (range 42–87 years). They had been using phenprocoumon for 3 d to 19 years, with a median duration of use of 2 years and 4 months. Indications for anticoagulant

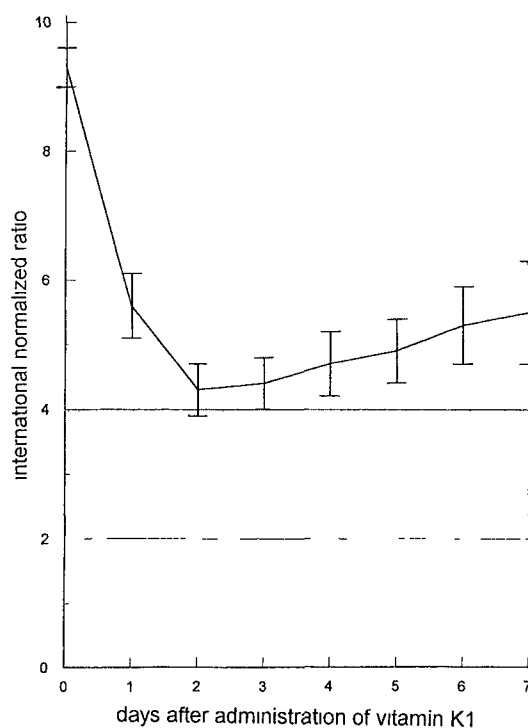


Fig 1. Course of the INR (mean $\pm$ SE) during the first week after administration of vitamin K₁ in patients overanticoagulated with phenprocoumon. The grey area indicates the target zone.

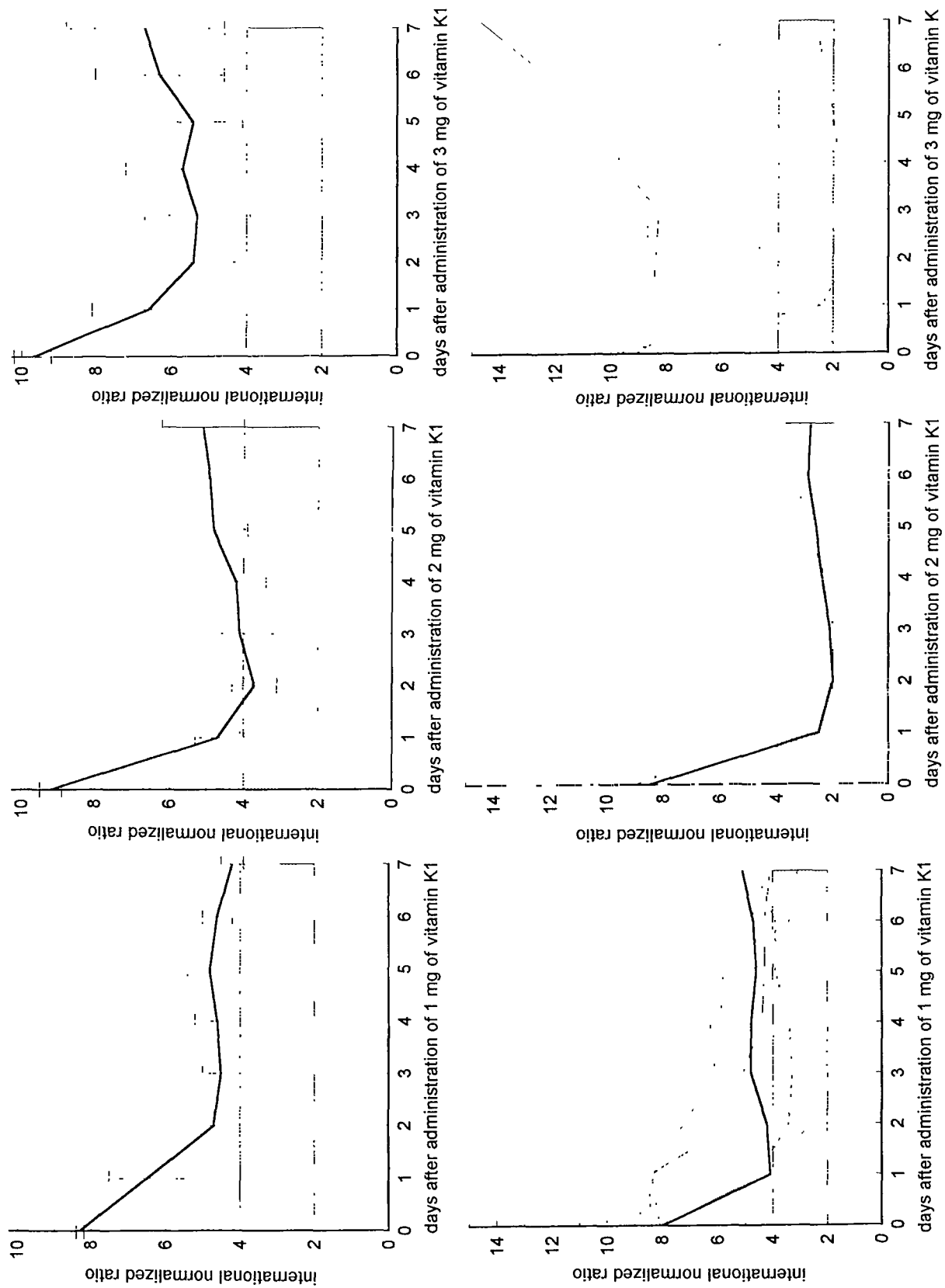


Fig 2. Course of the INR during the first week after administration of 1, 2 and 3 mg of vitamin K₁ in patients overanticoagulated with phenprocoumon (six, six and five patients respectively). The upper panel shows the mean INR $\pm$ SE. The bottom panel shows the course of the INR for the individual patients. The grey area indicates the target zone.

therapy were: cardiac disease (13 patients), cerebrovascular thromboembolism (four patients), peripheral arterial disease (three patients), venous embolism (two patients) and prophylactic venous treatment (two patients). The INR at presentation ranged from 7.3 to 14.2, with a mean of 9.3. The mean dose of vitamin K₁ prescribed was 2.7 mg (range 1–5 mg). In 17/24 patients the dose of vitamin K₁ was according to the algorithm; seven patients were prescribed a higher dose.

Fig 1 shows the course of the INR (mean $\pm$ SE) during the first week following administration of vitamin K₁ for all patients combined. On the first 2 d after administration of vitamin K₁, the INR decreased. On day 0, the mean INR was 9.3 ± 0.3 . On day 1 and day 2, the mean values were 5.6 ± 0.5 and 4.3 ± 0.4 respectively. The proportional decrease in the mean INR was 40% on day 1 and 23% on day 2. After day 2, the mean INR did not decrease further, but slightly increased instead. The day-to-day proportional increase ranged from 2% to 8%. On day 7, the mean INR was 5.5 ± 0.8 , 28% higher than the mean value on day 2. Remarkably, the mean INR did not reach the target zone on any of the 7 d.

The pattern of a decrease in the INR during the first 2 d following the intake of vitamin K₁, was observed for all doses of vitamin K₁ (Fig 2, upper panel) and for each of the patients (Fig 2, bottom panel). The extent of the response to oral vitamin K₁ varied greatly between patients: the range in INR values on day 0 was much smaller compared to the range on day 1 and day 2. In a few patients the INR did not decrease immediately but only after 1 d.

The course of the INR after day 2 was not consistent. The day-to-day proportional change in the mean INR depended on the dose of vitamin K₁ and varied from a decrease of 12% to an increase of 21%. On day 7, the mean INR was lower than on day 2 in the 1 mg and the 5 mg group and was higher than on day 2 in the 2, 3 and 4 mg group.

In addition to determining the effect of vitamin K₁ administration on the time-course of the INR, we also looked at its effectiveness in reducing the excess anticoagulant effect to lower and safer levels, preferably in the target zone. Of 24 patients with an INR ≥ 6.0 on day 0 who received 1–5 mg of vitamin K₁, eight (33%) still had an INR ≥ 6.0 on day 1, five (21%) on day 2, 3 and 4, seven (29%) on day 5 and day 6 and six (25%) on day 7. This concerned 12 individual patients, five of whom had an INR ≥ 6.0 on at least 5 d. All patients had taken <5 mg of vitamin K₁.

The number of patients with an INR value within the target zone was five (21%) on day 1, eight (33%) on day 2 and day 6, seven (29%) on day 3, day 4 and day 7, and nine (38%) on day 5. 12 different patients were involved; in three of them the INR was in the target zone for only 1 or 2 d.

An INR value <2.0 occurred in two patients (8%) on day 2, 3 and 4.

DISCUSSION

To obtain detailed insight into the course of the INR after oral administration of vitamin K₁ in doses of 1–5 mg, we measured the INR value for 7 consecutive days in patients

on phenprocoumon with an INR ≥ 6.0 at presentation. The first 2 d after administration of vitamin K₁ the mean INR decreased; afterwards it slightly increased again. On all days the mean INR was above the target zone. After a week 25% of the patients were still overanticoagulated (INR ≥ 6.0), only 29% had an INR within the target zone and none were underanticoagulated.

The routine treatment of overanticoagulation employed at the anticoagulant clinic has not been tested extensively before and is an empirical one. Therefore one aim of this study was to test its efficacy. Starting from a duration of effect of oral vitamin K₁ of 2 d, as discussed below, the efficacy of the treatment can be judged on the INR value between day 2 and day 7. Overall, just 32% of the patients had an INR value within the target zone, 25% had an INR value ≥ 6.0 and consequently were at increased risk of bleeding. An INR value <2.0 , and so an increased risk of thromboembolism, only occurred on day 2, 3 and 4 in two patients (8%). These figures indicate that the treatment is not sufficiently intense and an adjustment is recommended. Increasing the dosage of vitamin K₁ is one possibility. Another option would be to administer an additional small dose of vitamin K₁ on day 1 or day 2.

Although this study was only performed at the anticoagulant clinic of The Hague, the conclusion regarding the efficacy of the treatment of overanticoagulation in patients on phenprocoumon may also apply to many of the other anticoagulant clinics. Most clinics prescribe comparable doses of vitamin K₁, and some even lower doses.

This study was performed in a setting of routine medical care. As a consequence, in six patients, three of whom had just started oral anticoagulant therapy, the standard practice of restarting phenprocoumon on day 2 and lowering the dosage by about 15% was deviated from. However, the course of the INR in these patients was comparable with that observed in the patients in whom the standard practice was applied.

The greatest effect of vitamin K₁ was seen in the first 2 d. Considering the half-life of vitamin K₁ of approximately 1.5–3 h (Park *et al*, 1984a, b), a duration of effect of 2 d is plausible.

The extent of the response to oral vitamin K₁ varied greatly between patients. A difference in the degree of overanticoagulation is a plausible explanation. However, serum levels of phenprocoumon were not determined. The difference between the dose of phenprocoumon at presentation and the dose in a stable condition at a later time, as a proxy of the degree of overanticoagulation, was available for only a limited number of patients. We did not find a relationship between the dose of vitamin K₁ and the proportional decrease in INR between day 0 and day 2. Sex and age also were not related to this decrease.

Other factors that may affect the INR were not substantially present and cannot have had an appreciable effect on the results.

Our study was restricted to patients on phenprocoumon, since at the anticoagulant clinic of The Hague vitamin K₁ is only incidentally prescribed to patients on acenocoumarol, namely when the INR is >15.0 . Because of a difference in half-life between oral anticoagulants, the course of the INR

in response to oral vitamin K₁ would be different for other anticoagulants. This aspect should be taken into account when comparing our study with those of Weibert *et al* (1997), Pengo *et al* (1993) and Harrell & Kline (1995) which were performed in patients on warfarin. The former two studies both focused on efficacy and gave no data on changes in INR over time. In the study of Pengo *et al* (1993) nearly all patients had an INR <5.0 on days 1, 2 and 9. The INR at presentation, however, was much lower than in our study. Weibert *et al* (1997) found that 1 or 2 d after administration of vitamin K₁, 73% of the INR values fell within the target zone, 10% exceeded 5.0 and 17% was <2.0. 4–7 d after warfarin therapy was resumed these percentages were 83%, 1% and 16% respectively. So, compared to our study, fewer patients had an INR above the target zone, but more patients had an INR below this zone. A higher dosage of vitamin K₁ in proportion to the INR at presentation by Weibert *et al* (1997) is a plausible explanation.

In a report on five patients by Harrell & Kline (1995) the INR had decreased by 58% to 89% after 1 or 2 d. In our study the maximum decrease in INR on an individual patient level was 77% on day 1 and 43% on day 2.

In conclusion, in this study among 24 patients on phenprocoumon with an INR ≥ 6.0 , the INR decreased during the first 2 d after administration of 1–5 mg of oral vitamin K₁, but slightly increased again afterwards. Only one third of the patients had an INR value within the target zone between day 2 and day 7. To improve its efficacy, the routine treatment of overanticoagulation in patients on phenprocoumon should be intensified.

REFERENCES

- Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJM, Vandenbroucke JP & Briet E (1995) Optimal oral anticoagulant therapy in patients with mechanical heart valves. *New England Journal of Medicine* 333: 11–17.
- Federatie van Nederlandse Trombosediensten (1987) Vademecum voor poliklinische behandeling met orale anticoagulantia's. Gravenhage.
- Harrell CC & Kline SS (1995) Oral vitamin K₁: an option to reduce warfarin's activity. *Annals of Pharmacotherapy* 29: 1228–1232.
- Park BK, Scott AK, Wilson AC, Haynes BP & Breckenridge AM (1984a) Plasma disposition of vitamin K₁ in relation to anticoagulant poisoning. *British Journal of Clinical Pharmacology* 18: 655–662.
- Park BK, Wilson AC, Kaatz G & Ohnhaus EE (1984b) Enzyme induction by phenobarbitone and vitamin K₁ disposition in man. *British Journal of Clinical Pharmacology* 18: 94–97.
- Pengo V, Banzato A, Garelli E, Zasso A & Biasiolo A (1993) Reversal of excessive effect of regular anticoagulation: low oral dose of phytonadione (vitamin K₁) compared with warfarin discontinuation. *Blood Coagulation and Fibrinolysis* 4: 739–741.
- Rosendaal FR (1996) The Scylla and Charybdis of oral anticoagulant treatment. *New England Journal of Medicine* 335: 587–589.
- The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) Study Group (1997) A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. *Annals of Neurology* 42: 857–865.
- Weibert RT, Thele D, Kayser SR & Rapaport SI (1997) Correction of excessive anticoagulation with low-dose oral vitamin K₁. *Annals of Internal Medicine* 125: 959–962.