Long-term and short-term oral anticoagulation therapies were equivalent for venous thromboembolism

Pinede L, Ninet J, Duhaut P, et al., for the Investigators of the "Durée Optimale du Traitement AntiVitamines K" (DOTAVK) Study. **Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis.** Circulation. 2001 May 22; 103:2453-60.

QUESTION

In patients with proximal deep venous thrombosis (PDVT) or pulmonary embolism, or both, or isolated calf deep venous thrombosis (CDVT), is long-term treatment better than short-term treatment with oral anticoagulants for preventing recurrences and bleeding complications?

DESIGN

Randomized (allocation concealed*), unblinded,* controlled trial with 15-month follow-up.

SETTING

France.

PATIENTS

736 patients (mean age 59 y, 53% women) who had symptomatic PDVT or pulmonary embolism, or both, or symptomatic CDVT confirmed by objective diagnostic tests. Exclusion criteria included pregnancy, breastfeeding, vena cava filter implantation, surgical thrombectomy, free-floating thrombus in the inferior vena cava, active cancer or malignant hematologic disease, or a previous venous thromboembolism. 97% of patients completed the study.

INTERVENTION

375 patients (270 with PDVT or pulmonary embolism, or both, and 105 with CDVT) were allocated to short-term (3 mo for PDVT–pulmonary embolism, 6 wk for CDVT) oral anticoagulant therapy, and 361 patients (269 with PDVT or pulmonary embolism, or both, and 92 with CDVT) were allocated to long-term (6 mo for PDVT–pulmonary embolism, 12 wk for CDVT) treatment with oral anticoagulants. Fluindione was used for oral anticoagulation with dose adjustments to maintain an international normalized ratio of 2.0 to 3.0.

MAIN OUTCOME MEASURES

Incidence of recurrent venous thromboembolism and hemorrhage (major, minor, or fatal).

MAIN RESULT

Intention-to-treat analyses showed that the treatment groups did not differ for incidence rates of recurrent venous thromboembolism and hemorrhage (Table).

CONCLUSIONS

In patients with proximal deep venous thrombosis or pulmonary embolism, or both, 6 months is equivalent to 3 months of therapy with anticoagulants for preventing recurrences and bleeding complications. Similarly, in patients with calf deep venous thrombosis, 6 weeks is equivalent to 12 weeks of therapy with oral anticoagulants.

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*See Glossary.

Long-term vs short-term treatment with oral anticoagulants for venous thromboembolism†

Outcomes at 15 mo	Long-term (12 wk)	Short-term (6 wk)	RRI (95% CI)	NNH
CDVT				
Recurrence	3%	2%	71% (–65 to 743)	Not significant
Hemorrhage (major, minor, or fatal)	21%	12%	66% (–12 to 216)	Not significant
Major hemorrhage	3%	1%	242% (–50 to 2269)	Not significant
	Long-term (6 mo)	**Short-term (3 mo)**		
PDVT/PE				
Recurrence	9%	8%	10% (–37 to 92)	Not significant
Hemorrhage (major, minor, or fatal)	17%	16%	7% (–26 to 57)	Not significant
			RRR (CI)	**NNT**
Major hemorrhage	2%	3%	60% (–45 to 363)	Not significant

†CDVT = calf deep venous thrombosis; PDVT/PE = proximal deep venous thrombosis or pulmonary embolism, or both. Other abbreviations defined in Glossary; RRI, RRR, NNH, NNT, and CI calculated from data in article.

COMMENTARY

5 previous, well-designed, randomized trials have compared different durations of anticoagulation for venous thromboembolism (VTE) (1–5). 3 of these studies tested whether the duration of anticoagulation could be reduced from 3 (1, 3) or 6 months (2) to only 4 or 6 weeks in patients who, for the most part, had a first episode of VTE and did not have cancer. All 3 studies found that shortening the duration of therapy resulted in about a 2-fold increase in the rate of recurrent VTE after anticoagulants were stopped, without being associated with a convincing reduction in the rate of bleeding. These studies also found that the risk for recurrent VTE was about 4 times higher for "unprovoked" or "idiopathic" VTE than for thrombosis that was provoked by a transient risk factor, such as recent surgery.

The other 2 trials evaluated an extended duration of anticoagulant therapy in 2 groups of patients with VTE who were thought to have a high risk for recurrence: those with a second episode of VTE (4) and those with a first unprovoked episode of VTE (5). Both studies found that extending oral anticoagulant therapy (international normalized ratio of 2.0 to 3.0) was effective for preventing recurrent VTE; however, long-term use was associated with a substantial risk for bleeding. Schulman and colleagues (4) concluded that after a second episode of thrombosis the risk for recurrent VTE after completing 6 months of treatment (about 6% per year) was not high enough to routinely recommend extended therapy. Our group found that after a first episode of unprovoked thrombosis, the risk for recurrent VTE after completing 3 months of treatment was higher than expected (about 25% during the first year), which justified treatment for longer than

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3 months and 1 year of oral anticoagulant therapy were equivalent for idiopathic proximal deep venous thrombosis

Agnelli G, Prandoni P, Santamaria MG, et al., and the Warfarin Optimal Duration Italian Trial Investigators. **Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis.** N Engl J Med. 2001 Jul 19;345:165-9.

QUESTION

In patients who have had a first episode of idiopathic proximal deep venous thrombosis, what is the long-term effectiveness of extending to 1 year the initial 3-month course of oral anticoagulant therapy?

DESIGN

Randomized (unclear allocation concealment*), unblinded,* controlled trial with ≥ 2-year follow-up.

SETTING

10 study centers in Italy.

PATIENTS

267 patients (mean age 67 y, 58% men) who had a first episode of symptomatic idiopathic proximal deep venous thrombosis confirmed by compression ultrasonography or venography and had completed 3 uninterrupted months of oral anticoagulant therapy without a recurrence of thromboembolism or bleeding. Exclusion criteria included anticoagulant therapy for reasons other than venous thromboembolism, major psychiatric disorders, life expectancy < 2 years, and inability to return for follow-up. 90% of patients completed the study.

INTERVENTION

After 3 months of therapy with warfarin (97% of patients) or acenocoumarol, 133 patients were allocated to discontinue (3-mo treatment group) and 133 patients to continue (1-y treatment group) oral anticoagulant therapy for 9 additional months. The dose of the oral anticoagulant was adjusted to maintain an international normalized ratio of 2.0 to 3.0.

MAIN OUTCOME MEASURES

The primary outcome was recurrent deep venous thrombosis. Secondary outcomes were major bleeding and all-cause mortality.

MAIN RESULTS

At ≥ 2 years, intention-to-treat analyses showed that the groups did not differ for incidence rates of recurrent deep venous thrombosis, major bleeding, and all-cause mortality (Table). The study had an 80% power to detect a 50% reduction in the risk for recurrence at the 5% level of significance.

CONCLUSION

In patients who had a first episode of idiopathic proximal deep venous thrombosis, 3 months was equivalent to 1 year of oral anticoagulant therapy in preventing recurrences at ≥ 2 years.

Source of funding: Not stated.

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*See Glossary.

1-year vs 3-month treatment with oral anticoagulants for proximal deep venous thrombosis†

Outcomes at ≥ 2 y	1-y treatment	3-mo treatment	RRR (95% CI)	NNT
Recurrence	16%	16%	1% (–72 to 43)	Not significant
All-cause mortality	5%	5%	1% (–165 to 63)	Not significant
			RRI (CI)	NNH
Major bleeding	3%	2%	99% (–57 to 817)	Not significant

†Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.

COMMENTARY *(continued from page 10)*

3 months; however, we could not say how much longer than 3 months was required (5).

In a mix of patients with provoked and unprovoked VTE, Pinede and colleagues found the risk for recurrent VTE to be similar after completing 3 and 6 months of treatment. In patients with a first episode of unprovoked deep venous thrombosis, Agnelli and colleagues found a similar risk for recurrent VTE after completing 3 months and 12 months of treatment. In the latter study, this risk was only about 5% per year, much lower than the 25% observed after 3 months of therapy in a similarly defined patient population (5).

A consistent finding across studies is that 3 months of anticoagulant therapy is adequate for patients with VTE that has been provoked by a major transient risk factor. The subsequent risk for recurrence is low (< 5% per year). However, uncertainty exists whether the risk for recurrence after an unprovoked VTE is as low after 3 months of treatment as it is after 6 months. Although the 2 new studies strongly suggest that 3 months of therapy achieves as low a subsequent risk for recurrent VTE as 6 or 12 months of treatment, neither study had the power to establish this definitively. On the basis (mostly) of the results of our own study (5), which is representative of our patient population, I will continue to recommend a minimum of 6 months of anticoagulant therapy for a first unprovoked episode of VTE, provided patients do not have a high risk for bleeding. Current evidence suggests that patients with unprovoked VTE who have been treated for 6 months or longer have a risk for recurrent VTE of about 10% during the year after anticoagulant therapy is stopped. Therefore, once patients have successfully completed 6 months of treatment, I encourage them to remain on long-term therapy provided they have a low risk for bleeding and do not find treatment a burden.

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