

# A 10-mg nomogram was more effective than a 5-mg nomogram for warfarin induction in outpatient venous thromboembolism

Kovacs MJ, Rodger M, Anderson DR, et al. Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism. A randomized, double-blind, controlled trial. *Ann Intern Med.* 2003;138:714-9.

## QUESTION

In outpatients with acute venous thromboembolism (VTE), is warfarin induction with a 10-mg nomogram more effective than with a 5-mg nomogram?

## DESIGN

Randomized (allocation concealed\*), blinded (clinicians, patients, and outcome assessors)\* controlled trial with 90-day follow-up.

## SETTING

4 Canadian academic centers.

## PATIENTS

201 patients who were  $\geq 18$  years of age (mean age 55 y, 56% men) and had objectively confirmed acute VTE (deep venous thrombosis or pulmonary embolism). Exclusion criteria were a baseline international normalized ratio (INR)  $> 1.4$ , platelet count  $< 50 \times 10^9$  cells/mL, need for hospitalization, use of oral anticoagulant therapy in the previous 2 weeks, or high risk for major bleeding. 90-day follow-up was complete.

## INTERVENTION

Patients were allocated to warfarin induction with either a 10-mg ( $n = 104$ ) or a 5-mg warfarin nomogram ( $n = 97$ ). Treatment began with full-dose subcutaneous low-molecular-weight heparin (LMWH) (dalteparin or tinzaparin) and continued daily

for 5 days until the INR reached therapeutic levels ( $> 1.9$ ).

## MAIN OUTCOME MEASURES

Time to a therapeutic INR. Secondary outcomes included proportion of patients with INRs of 2.0 to 3.0 on the fifth day, recurrent VTE, major bleeding, and mortality.

## MAIN RESULTS

Analysis was by intention to treat. Patients in the 10-mg–nomogram group had a shorter mean time to a therapeutic INR and were more likely to have a therapeutic INR at day 5 than were patients in the 5-mg–nomogram

group (Table). The groups did not differ for rates of VTE, major bleeding, or death (Table).

## CONCLUSION

In outpatients with venous thromboembolism, a warfarin nomogram using 10-mg loading doses was more effective than a warfarin nomogram using 5-mg loading doses.

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\*See Glossary.

## 5-mg vs 10-mg loading dose of warfarin for a warfarin nomogram in venous thromboembolism†

Outcomes	Loading dose		Mean difference (95% CI)	
	10-mg	5-mg	RBI (CI)	NNT (CI)
Time to therapeutic INR $> 1.9$	4.2 d	5.6 d	1.4 d (1.1 to 1.7)	
Patients with therapeutic INR at 5 d	83%	46%	78% (43 to 128)	3 (3 to 5)
			RRI (CI)	NNH
Venous thromboembolism at 90 d	2.9%	0%	$\infty$	Not significant
			RRR (CI)	NNT
Major bleeding at 28 d	0.96%	1.0%	6.7% (–786 to 90)	Not significant
Death at 90 d	0%	1.0%	100% (–256 to 100)	Not significant

†INR = international normalized ratio. Other abbreviations defined in Glossary; mean difference, RBI, RRR, RRI, NNT, NNH, and CI calculated from data in article.

## COMMENTARY

VTE is a common and potentially fatal disease that annually affects 2 persons per 1000 (1, 2). Although advances in diagnostics and treatment have been made, much more work is needed to lessen the burden of this chronic disease. Recent work has focused on determining the optimal duration (3) and intensity of therapy (4) to prevent recurrent disease. Efforts to improve the ease and efficiency of management and patient convenience without sacrificing safety would be further advances. Newer therapies, such as LMWH, have shifted treatment of acute VTE to the outpatient setting where maximizing the efficiency and safety of warfarin loading could reduce the time needed to achieve a therapeutic INR. This could potentially be translated into cost savings if the overlap of heparin and warfarin therapies and the frequency of INR testing were minimized.

Kovacs and colleagues' study attempted to maximize the efficiency of warfarin loading. As the authors rightly conclude, patients who require inpatient treatment are clinically different, and this nomogram may not be appropriate for them or other patients who require a lower loading dose. The trial's main strength was the 90-day follow-up, although the

study was not powered to detect significant differences in the outcomes of recurrent VTE, major bleeding, or death. Thus, firm conclusions about the safety of the 10-mg nomogram cannot be made.

The 10-mg nomogram resulted in a therapeutic INR in less time and with fewer INR measurements. A formal cost analysis would have added significantly to the authors' findings. Nonetheless, Kovacs and colleagues should be applauded for conducting high-quality work to define "best practices" in the treatment and management of acute VTE.

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## References

- Anderson FA Jr, Wheeler HB, Goldberg RJ, et al. *Arch Intern Med.* 1991;151:933-8.
- Silverstein MD, Heit JA, Mohr DN, et al. *Arch Intern Med.* 1998;158:585-93.
- Schulman S, Rhedin AS, Lindmarker P, et al. *N Engl J Med.* 1995;332:1661-5.
- Ridker PM, Goldhaber SZ, Danielson E, et al. *N Engl J Med.* 2003;348:1425-34.