Benefit of Extended Anticoagulation After Unprovoked PE Lost After Treatment Discontinuation

Written by Lynne Lederman

Patients with a first episode of unprovoked pulmonary embolism (PE) have a high risk of recurrence after the discontinuation of anticoagulation. Extending anticoagulation beyond the initial 3 to 6 months significantly reduces the risk of recurrent venous thromboembolism (VTE) but increases the risk of bleeding. Most studies assessing extended treatment have not followed patients after treatment discontinuation [AMPLIFY-EXT Investigators. *N Engl J Med*. 2013; Kearon C et al. *Chest*. 2012; Kearon C et al. *N Engl J Med*. 1999; Einstein Investigators. *N Engl J Med*. 2010; Agnelli G et al. *N Engl J Med*. 2004; Ridker PM et al. *N Engl J Med*. 2003].

Francis Couturaud, MD, PhD, Brest University Hospital, Brest, France, reported on the Extended Duration of Oral Anticoagulant Therapy After a First Episode of Idiopathic Pulmonary Embolism randomized controlled trial [PADIS-PE; NCT00740883].

The primary objective was to assess the superiority of 18 additional months of warfarin vs placebo on the risk of recurrent VTE or major bleeding in patients with a first episode of unprovoked PE following 6 uninterrupted months of treatment. The secondary objective was to investigate if this superiority was maintained during a follow-up of 2 years after discontinuing anticoagulation.

The primary outcome was a composite of recurrent VTE or major bleeding during the 18-month treatment period. Secondary outcomes included a composite of recurrent VTE or major bleeding over 42 months, recurrent VTE, major bleeding, and deaths unrelated to the composite end point during the treatment period and the entire study period.

After a first unprovoked PE, patients were treated with a vitamin K antagonist for 6 months and then were randomly assigned to warfarin or placebo. Outcomes were assessed at the end of the 18-month treatment period and at the end of the 24-month follow-up period.

Of the 374 patients in the study, 184 were assigned to warfarin and 187 to placebo (3 withdrew consent and refused to be included in analyses). Patient characteristics were well balanced between the treatment groups, with the exception of more women in warfarin group (58% vs 45%; $P = .01$). PE at diagnosis was associated with a proximal deep vein thrombosis in 31% in both groups.

For the primary outcome, during the 18-month treatment period, warfarin significantly reduced composite ($P = .0004$) and recurrent VTE ($P < .0001$), with no difference for major bleeding. At 42 months, there was no significant difference between groups in recurrent VTE ($P = .10$) or major bleeding ($P = .71$) or for secondary outcomes ($P = .19$). The outcomes are summarized in Table 1.

Table 1. Study Outcomes at 18 and 42 Months

	Warfarin, no. (%) (n = 184)	Placebo, no. (%) (n = 187)	HR (95% CI)	*P* Value
18-mo treatment period				
Primary outcome, composite	6 (3.3)	25 (13.5)	0.23 (0.09 to 0.55)	.0004
Secondary outcomes				
Recurrent VTE	3 (1.7)	25 (13.5)	0.11 (0.03 to 0.37)	< .0001
Major bleeding	4 (2.2)	1 (0.5)	4.07 (0.45 to 36.38)	.18
42-mo study period				
Secondary outcomes				
Composite	33 (20.8)	42 (24.0)	0.74 (0.47 to 1.17)	.19
Recurrent VTE	28 (17.9)	39 (22.1)	0.67 (0.41 to 1.08)	.10
Major bleeding	6 (3.5)	5 (3.0)	1.12 (0.38 to 4.10)	.71
Other outcomes				
Recurrent VTE in the absence of provoking risk factor	25	33	N/A	N/A
Proximal DVT without PE	7	8	N/A	N/A
Fatal PE	4	0	N/A	N/A
Nonfatal PE	17	31	N/A	N/A
Death unrelated to composite	8	6	N/A	N/A

DVT, deep vein thrombosis; N/A, not applicable; PE, pulmonary embolism; VTE, venous thromboembolism.

After a first episode of symptomatic unprovoked PE initially treated for 6 months, extending anticoagulation for 18 addition months was associated with a relative risk reduction of 77% for recurrent VTE or major bleeding. This benefit was lost during 2-year follow-up after discontinuing anticoagulation. Additional investigation is necessary to identify subgroups of patients at lower risk of thrombotic events who may not need indefinite anticoagulation.