Six months *versus* two years of oral anticoagulation after a first episode of unprovoked deep-vein thrombosis. The PADIS-DVT randomized clinical trial

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**Members of the Prolongation d'un traitement par antivitamine K pendant dix-huit mois versus placebo au décours d'un premier épisode de thrombose veineuse profonde Idiopathique traité six mois (PADIS-DVT) Study Group are listed in the Online Appendix.*

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Six months versus two years of oral anticoagulation after a first episode of unprovoked deep vein thrombosis. The PADIS-DVT randomized, clinical trial

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Online supplemental content

List of elements

Inclusion and exclusion criteria

Inclusion criteria

- Patients having experienced a first episode of symptomatic idiopathic proximal deep vein thrombosis who had been initially treated during 6 months (5.5 to 7 months) with a vitamin K antagonist with a target international normalized ratio (INR) ranging from 2 to 3.

Exclusion criteria

- Age < 18 years,
- Allergy to warfarin,
- Refusal or incapacity to give written informed consent to participate in the study,
- Isolated pulmonary embolism or distal deep-vein thrombosis,
- Proximal deep vein thrombosis provoked by a major reversible risk factor (including surgery with locoregional or general anesthesia lasting more 30 minutes, trauma with or without lower limb immobilization in a plaster cast, and bed-rest for more than 72 hours within the three months prior to diagnosis,
- Documented recurrent venous thromboembolism while on a vitamin K antagonist in the therapeutic range or anticoagulant-related bleeding during the first 6 months of anticoagulation,
- Known major thrombophilia (protein C or S or antithrombin deficiency, antiphospholipid antibodies, homozygous factor V Leiden),
- Previous documented pulmonary embolism or proximal deep-vein thrombosis,
- Indication for treatment with a vitamin K antagonist for reasons other than venous thromboembolism (e.g. atrial fibrillation, mechanical heart valve, etc.),
- Patients in whom ongoing antiplatelet therapy could be stopped during treatment with a vitamin K antagonist for the index pulmonary embolism but in whom antiplatelet therapy was to be restarted after the end of the treatment period,
- Ongoing pregnancy or pregnancy planned within 18 months from randomization,
- Childbearing age without effective contraceptive measures,
- Major surgery planned within less than 18 months from randomization,
- Active cancer or cancer resolved within less than two years prior to diagnosis,
- High risk of bleeding (e.g. active gastric ulcer, recent hemorrhagic stroke) or other contraindication to vitamin K antagonist therapy,
- Platelet count below 100 x 10^9/L,
- Life expectancy less than 18 months (e.g. patients with an end-stage chronic disease).

ACCP bleeding risk score

The ACCP (American College of Chest Physicians) bleeding risk score was proposed as a risk stratification tool for situations in which the risk of bleeding may be substantial, such as extended-duration anticoagulation treatment.[1] The risk depends on the number of patient risk factors for bleeding, and is categorized as low (no risk factor), moderate (one risk factor) and high (≥2 risk factors). Risk factors include age >65 years, age >75 years, previous bleeding, cancer, metastatic cancer, renal failure, liver failure, thrombocytopenia, previous stroke, diabetes, anemia, antiplatelet therapy, poor anticoagulant control, co-morbidity and reduced functional capacity, recent surgery, frequent falls, and alcohol abuse.

Outcome definitions

All outcomes were adjudicated by an independent central Critical Events Committee, the members of which were unaware of treatment group assignment. This committee had full access to any relevant medical reports and images from objective tests to adjudicate suspected events notified by investigators or detected during routine site monitoring.

The primary outcome was the composite of symptomatic recurrent venous thromboembolism (including non-fatal symptomatic pulmonary embolism or proximal deep-vein thrombosis or fatal venous thromboembolism)

and non-fatal or fatal major bleeding occurring during the 18-month treatment period. If a bleed and a recurrence occurred in the same patient, only the first event was included in the analysis. This composite outcome and its components were also assessed during the entire study period (i.e. up to 42 months).
Symptomatic recurrent pulmonary embolism was diagnosed on the basis of a clinical suspicion of pulmonary embolism associated with:

- a new segmental or larger perfusion defect with normal ventilation on ventilation/perfusion lung scanning; or a new intraluminal filling defect in a segmental or more proximal pulmonary artery;
- or an intraluminal filling defect in a segmental or more proximal pulmonary artery, in an area where perfusion was normal on ventilation/perfusion lung scanning performed at the time of initial diagnosis of pulmonary embolism;
- or a constant intraluminal filling defect or sudden cut-off of a pulmonary artery >2.5 mm in diameter on pulmonary angiography, in an area where perfusion was normal on ventilation/perfusion lung scanning performed at the initial diagnosis of pulmonary embolism;
- or in cases of non-conclusive ventilation/perfusion lung scan, spiral computerized tomography angiography or pulmonary angiography, or lower-limb ultrasonography showing new non-compressibility of a proximal vein;
- or documented pulmonary embolism on autopsy;
- or sudden death for which no other cause could be identified (recurrent pulmonary embolism could not be ruled out by the Critical Events Committee). [2,3]

Symptomatic recurrent deep-vein thrombosis was diagnosed on the basis of a clinical suspicion of venous thrombosis associated with non-compressibility of a segment of a proximal vein that was fully compressible at the time of diagnosis of initial proximal deep vein thrombosis or at the at the time of inclusion in the study (if the segment was not fully compressible at diagnosis of initial acute DVT). This definition was applied in case of ispilateral and in contralateral recurrent DVT.”.[4]

Recurrent venous thromboembolism was defined as fatal in cases of death caused by recurrent venous thromboembolism diagnosed according to the above criteria .[2,3]

Bleeding was considered as major if it was fatal, involved a critical organ (intra-cerebral, medullar, retroperitoneal, pericardial, or non-traumatic intra-articular), or was overt and associated with a fall in hemoglobin level of 2 g/dL or more, or required transfusion of at least two units of packed red cells.[5]

The secondary outcome was death unrelated to pulmonary embolism or major bleeding during the 18-month treatment period and 42-month entire study period.

Imaging procedures used to diagnose recurrent venous thromboembolism

Compression ultrasonography of the lower limbs

At the time of deep-vein thrombosis diagnosis, bilateral compression ultrasonography was performed in B-mode, using probes 3.5-7.5 MHz, exploring veins from the inferior vena cava to the tibial and fibular veins in the longitudinal and then transversal plans. Failure to fully collapse the vein was the main criterion for vein thrombosis, whether or not this was associated with an endovenous echogenic image suggestive of the presence of a thrombus. Deep-vein thrombosis was classified as proximal if it was located at the level of the popliteal trifurcation or above. Neither impedance plethysmography nor venography was used to diagnose deep-vein thrombosis recurrence in this study.
Bilateral compression ultrasonography was also performed in all included patients at the time of inclusion (i.e. after the initial six months of anticoagulation): residual deep-vein thrombosis was defined by the presence of a persistent incompete compressibility of a proximal deep vein that was initially non-compressible in one or the two lower limbs.

Ventilation/perfusion lung scanning

Perfusion scintigraphy was performed by intravenous injection of ^{99m}Technetium macroaggregated human albumin, and aerosols of ^{81m}Krypton or ^{99m}Technetium were used for ventilation scintigraphy, both in the supine position. Six views were obtained and results were interpreted according to the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria.[6]

Spiral computerized tomography angiography

100-140 mL of a radiocontrast (>200 mg/mL concentration) were injected through a 18-20 G brachial venous catheter at a rate of 4-5 mL/s. Slices (one per second) were acquired with 3 mm collimation at 2 mm intervals (pitch 1.5 to 2) allowing imaging acquisition of the entire pulmonary arterial system through a single apnea after a deep breath intake.

Laboratory assays

Thrombophilia testing was performed for all the patients from centralized frozen blood samples taken at day 0, excepted protein C, protein S and lupus anticoagulant which were measured from frozen plasmas taken at 1 and 19 months in order to obtain results in the absence of anticoagulation (at 1 month in the placebo group and 19 months in the warfarin group). The following assays were performed:
- *Factor V Leiden* was identified as described by Bertina *et al.* and the *G20210A prothrombin gene variant* as described by Poort *et al*.; positive results were classified as heterozygous or homozygous for the mutation.[7,8]
- *Factor VIII* assay was achieved with a one stage functional clotting assay using specific factor VIII depleted plasma and STA CK Prest (STAGO, Asnière, France). A level above the 90th percentile was considered elevated.
- *Antithrombin* assay (Normal range: 66%-124%) was carried out with a colorimetric anti IIa assay using STA Stachrom AT III kit (STAGO, Asnière, France).
- *Protein C* (Normal range: 54%-166%) and *Protein S* (Normal range: 54%-103%) assays were performed with chronometric methods using respectively STA Staclot Protein C and Protein S kits (STAGO, Asnière, France).
- The presence of *Lupus anticoagulant (LA)* was identified using with at least two LA assays: a dilute Russell viper venom test (dRVVT) (Staclot dRVV Screen and Confirm [STAGO, Asnière, France]), dRVVT being considered positive when the dRVVT screen/dRVVT confirm ratio was >1.2, and a mixing study using LA–sensitive activated partial thromboplastin time reagent PTT (PTT-LA, STAGO, Asnière, France). If either of the assays was abnormal and the confirmatory test provided confirmatory evidence of the test results, patients were considered to have a lupus anticoagulant.[6]
- The presence of an *anticardiolipin antibody*, either IgG or IgM, was determined using an ELISA (Diagnostica Stago, Asnières, France). An anticardiolipin antibody was considered present if either the IgG or IgM antibody titer was more the 99th percentile.[9]
- *D-dimer* levels were measured using quantitative high sensitivity VIDAS D-dimer test (bioMérieux).

eTable 1. Number (%) of attending patients per follow-up visit[a]

Visit, no. (%)	Warfarin (N=50)	Placebo (N=54)	Total (N=104)
Inclusion	50 (100.0)	54 (100.0)	104 (100.0)
3 months	50 (100.0)	54 (100.0)	104 (100.0)
6 months	50 (100.0)	53 (98.1)	103 (99.0)
12 months	50 (100.0)	52 (96.3)	102 (98.1)
18 months	50 (100.0)	52 (96.3)	102 (98.1)
24 months	50 (100.0)	51 (94.4)	101 (97.1)
30 months	49 (98.0)	50 (92.6)	99 (95.2)
36 months	49 (98.0)	50 (92.6)	99 (95.2)
42 months	49 (98.0)	51 (94.4)	100 (96.2)

[a]During December 2016, every effort was made to ensure that patients completed visits at 42, 36 and 30 months. The last 4 patients included, for whom the 42-month follow-up was planned between January 2017 and March 2017, had their 42-month visit brought forward during the last week of December 2016. In addition, all patients who had yet to complete the entire 42-month follow-up period by December 31 th 2016 were contacted by phone during the last week of December 2016 to enquire whether they had experienced recurrent venous thromboembolism or major bleeding, and to check that they were still alive.

eTable 2. INR metrics in the two study groups

Percentage of time spent with INR in a given range		Warfarin (N=50) True INR	Placebo (N=54) Sham INR
INR between 2.0 and 3.0			
	Mean±SD	70.3±13.9	75.9±16.9
	Median (Q1-Q3)	69.6 (63.5-81.0)	75.7 (69.3-88.0)
INR <2.0			
	Mean±SD	19.1±12.5	14.6±17.3
	Median (Q1-Q3)	18.0 (10.6-27.1)	11.1 (3.1-18.3)
INR >3.0			
	Mean±SD	10.6±8.0	9.6±10.4
	Median (Q1-Q3)	9.3 (5.4-13.9)	7.8 (0.0-13.2)
Delay between INR measurements, days			
	Mean±SD	19.8±5.4	20.5±6.8
	Range	9.8-29.4	4.0-31.8

Q1-Q3: interquartile range

eTable 3. Baseline thrombophilia of study participants according to randomized assignment

	Warfarin (N=50)	Placebo (N=52)
Thrombophilia , no. (%)*		
Minor thrombophilia – no. (%)	8 (16.0)	8 (15.4)
Heterozygous Factor V Leiden	7 (14.0)	8 (15.7)**
Heterozygous G20210A prothrombin gene variant	1 (2.0)	3 (5.9)**
Elevated factor VIII (90th percentile)	0 (0.0)	1 (1.9)
Major thrombophilia – no. (%)	9 (18.0)	14 (26.9)
Homozygous Factor V Leiden	0 (0.0)	0 (0.0)**
Heterozygous Factor V Leiden and Heterozygous G20210A prothrombin gene variant	0 (0.0)	1 (2.0)**
Antithrombin deficiency	2 (4.0)	1 (1.9)
Protein C deficiency	0 (0.0)	0 (0.0)
Protein S deficiency	2 (4.0)	3 (5.8)
Anticardiolipin antibodies (99th percentile)	2 (4.0)	0 (0.0)
Lupus anticoagulant	6 (12.0)	10 (19.2)

*Thrombophilia testing was performed for all the patients from centralized frozen blood samples taken at day 0, except for protein C, protein S and lupus anticoagulant which were measured from frozen plasmas taken at 1 and 19 months in order to obtain results in the absence of anticoagulation (at 1 month in the placebo group and 19 months in the warfarin group).

** Test results were available for 51 patients

There was no statistically significant difference between the two groups for any type of thrombophilia

eTable 4. Description of major bleeding events according to MedDRA Preferred Terms[a]

Treatment group	Inclusion date	Date of occurrence	Time from randomization (months)	Description	Cause	Issue (resolution)	On warfarin or not
Warfarin	14 Sept 2011	08 May 2014	968 days	Hospitalization for rectorragia with a fall in hemoglobin level ≥2gr/dL	Related to diverticulosis	Resolved without sequelae	fluindione

[a]MedDRA – Medical Dictionary for Regulatory Activities. The MedDRA preferred terms differ in some cases from the terms used in the reports sent by the investigators to the sponsor but seem to be more accurate, as in seven cases, investigators only described the location as “other”. The MedDRA version 17.1 was used in this study.

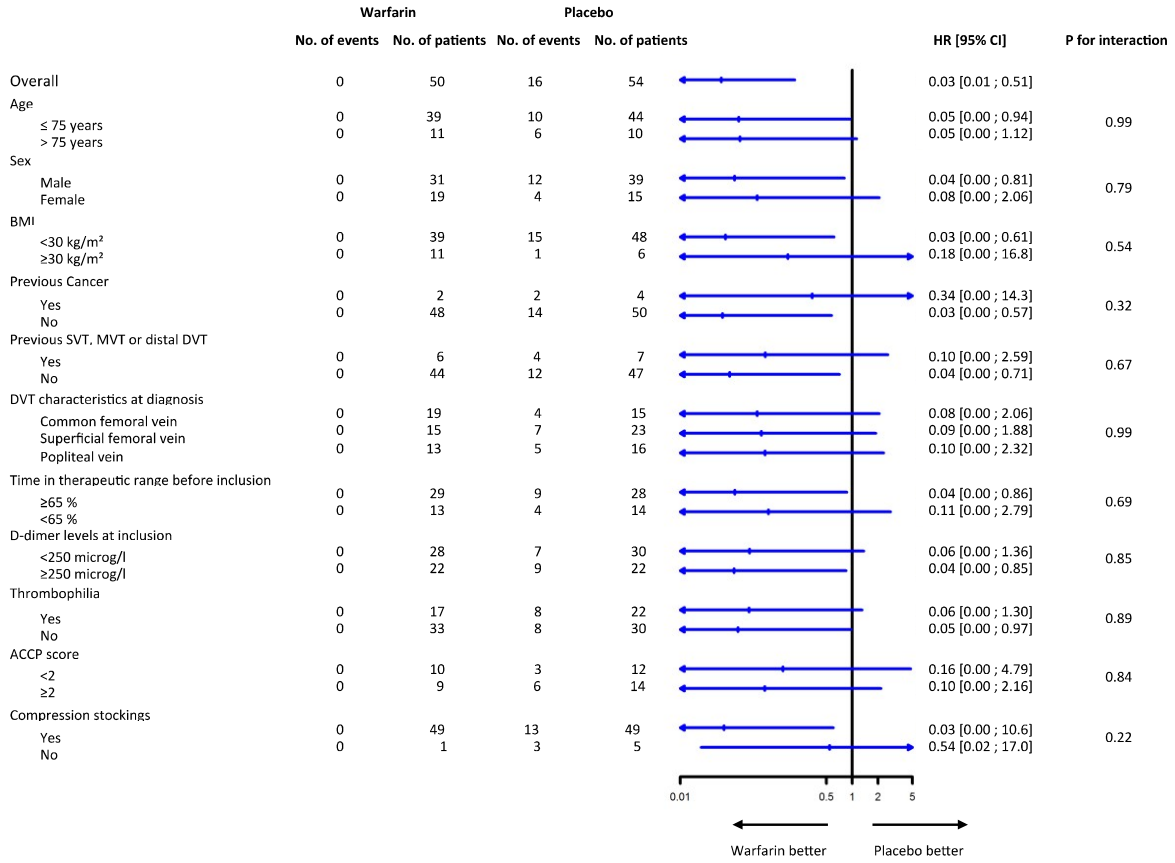
eTable 5. Causes of death

	Warfarin N=1	Placebo N=3
Recurrent pulmonary embolism[a]	0	0
Major bleeding	0	0
Sudden death[a]	0	1
End-of-life rectal cancer with major deterioration of general state	0	1
Mesenteric infarction	0	1
Aspiration pneumonia	1	0

[a]All episodes were unexplained sudden deaths considered to reflect fatal pulmonary embolism by the Critical Events Committee.

eFigure 1A: Rates of the primary outcome* in pre-specified subgroups

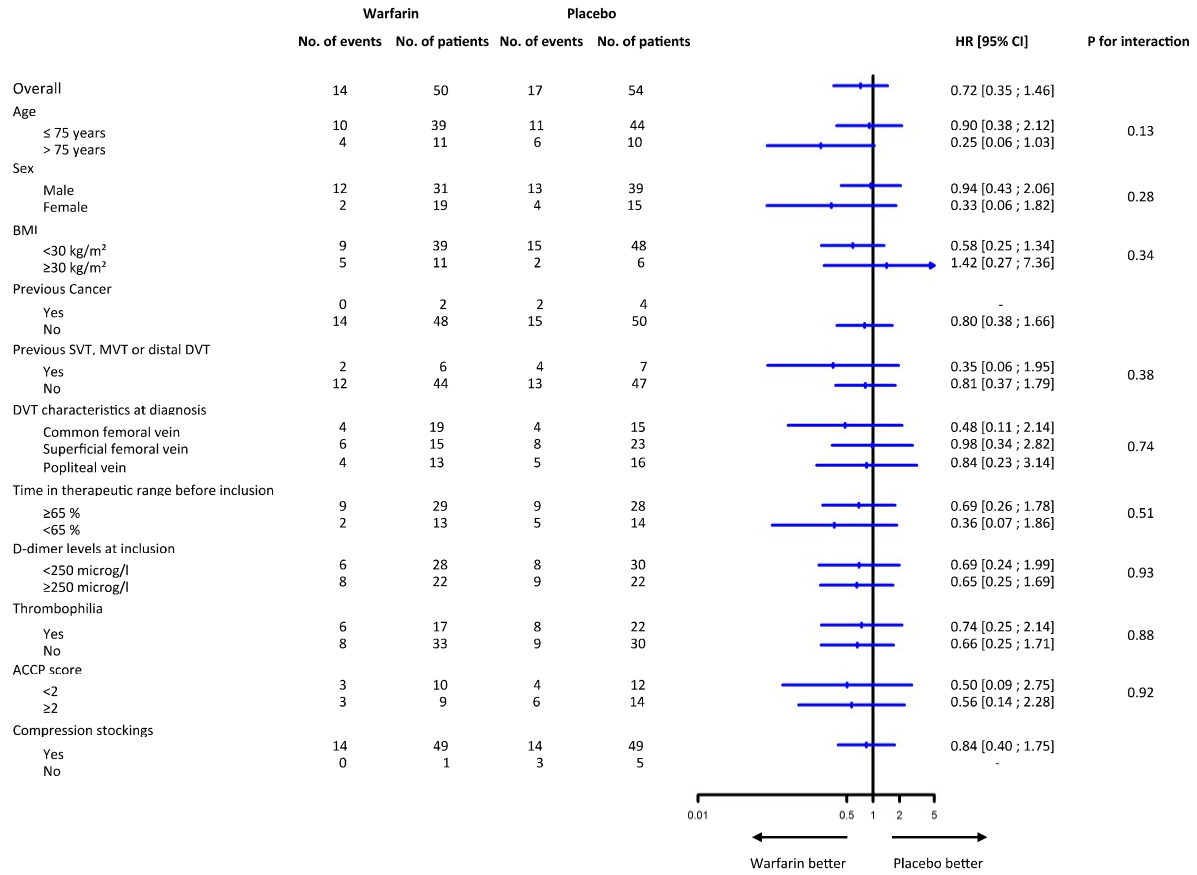
(study treatment period)



BMI: body mass index. PE: pulmonary embolism. DVT: deep vein thrombosis. SVT: superficial vein thrombosis. MVT: muscular vein thrombosis. ACCP: American College of Chest Physicians; this score was calculated at the time of the statistical analysis, using baseline patient characteristics.

*The primary outcome was the composite of symptomatic recurrent venous thromboembolism (including non-fatal symptomatic pulmonary embolism or proximal deep-vein thrombosis or fatal venous thromboembolism) and non-fatal or fatal major bleeding occurring during the 18-month treatment period.

eFigure 1B. Rates of the composite outcome* in pre-specified subgroups (entire study period)



BMI: body mass index. PE: pulmonary embolism. DVT: deep vein thrombosis. SVT: superficial vein thrombosis. MVT: muscular vein thrombosis. ACCP: American College of Chest Physicians; this score was calculated at the time of the statistical analysis, using baseline patient characteristics.
*The composite outcome included symptomatic recurrent venous thromboembolism (i.e. non-fatal symptomatic pulmonary embolism or proximal deep-vein thrombosis or fatal venous thromboembolism) and non-fatal or fatal major bleeding.

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