Clinical trials of antithrombotics for venous thrombosis in secondary prevention - 2

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1 antiagregant

Trial	Treatments	Patients	Trials design and methods
aspirin vs placebo			
ASPIRE , 2012 n=411/411 follow-up: 37.2 months median	aspirin, at a dose of 100 mg daily, for up to 4 years versus placebo	patients who had completed initial anticoagulant therapy after a first episode of unprovoked venous thromboembolism	
WARFASA , 2012 n=205/197 follow-up:	aspirin, 100 mg daily for 2 years versus placebo	patients with first-ever unprovoked venous thromboembolism who had completed 6 to 18 months of oral anticoagulant treatment	

References

ASPIRE, 2012:

Brighton TA, Eikelboom JW, Mann K, Mister R, Gallus A, Ockelford P, Gibbs H, Hague W, Xavier D, Diaz R, Kirby A, Simes J Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med 2012;367:1979-87 [23121403] 10.1056/NEJMoa1210384

WARFASA, 2012:

Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, Silingardi M, Bianchi M, Moia M, Ageno W, Vandelli MR, Grandone E, Prandoni P Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med 2012;366:1959-67 [22621626] 10.1056/NEJMoa1114238

2 direct anti-IIa

Trial	Treatments	Patients	Trials design and methods
dabigatran vs placebo			
RESONATE , 2013 n=681/662 follow-up:	dabigatran at a dose of 150 mg twice daily versus placebo	-	
ximelagatran vs placebo			
THRIVE 3 , 2003 n=612/611 follow-up:	ximelagatran (24 mg) versus placebo	patients with venous thromboembolism who had undergone six months of anticoagulant therapy	
dabigatran vs warfarin			

continued...

Trial	Treatments	Patients	Trials design and methods
REMEDY , 2013 n=1430/1426 follow-up:	-	-	

References

RESONATE, 2013:

Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, Kvamme AM, Friedman J, Mismetti P, Goldhaber SZ Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013;368:709-18 [23425163] 10.1056/NEJMoa1113697

THRIVE 3, 2003:

Schulman S, Whlander K, Lundstrm T, Clason SB, Eriksson H Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med 2003;349:1713-21 [14585939] 10.1056/NEJMoa030104

REMEDY, 2013:

Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, Kvamme AM, Friedman J, Mismetti P, Goldhaber SZ Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013 Feb 21;368:709-18 [23425163]

3 direct anti-Xa

Trial	Treatments	Patients	Trials design and methods
rivaroxaban 10mg vs aspirin			
EINSTEIN CHOICE (10mg) , 2017 [NCT02064439] n=1127/1131 follow-up:	Rivaroxaban 10 mg once daily for 12 months versus ASA (Acetylsalicylic Acid) 100 mg once daily for 12 months	Patients with confirmed symptomatic DVT (Deep Vein Thrombosis) or PE (Pulmonary embolism) who completed 6 or 12 months of treatment of anticoagulation	
apixaban 2.5mg vs placebo			
AMPLIFY EXT 2.5mg , 2013 n=842/829 follow-up:	apixaban (2.5 mg and 5 mg, twice daily) versus placebo	patients with venous thromboembolism who had completed 6 to 12 months of anticoagulation therapy	
apixaban 5mg vs placebo			
AMPLIFY EXT 5mg , 2013 n=815/829 follow-up:	apixaban (2.5 mg and 5 mg, twice daily) versus placebo	patients with venous thromboembolism who had completed 6 to 12 months of anticoagulation therapy	
rivaroxaban 20mg vs placebo			
EISNTEIN EXT , 2010 n=602/595 follow-up:	rivaroxaban alone (20 mg once daily)for an additional 6 or 12 months versus placebo	patients who had completed 6 to 12 months of treatment for venous thromboembolism	
rivaroxaban 20mg vs aspirin			

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Trial	Treatments	Patients	Trials design and methods
EINSTEIN CHOICE (20mg) , 2017 [NCT02064439] n=1107/1131 follow-up:	Rivaroxaban 20 mg once daily for 12 months versus ASA (Acetylsalicylic Acid) 100 mg once daily for 12 months	Patients with confirmed symptomatic DVT (Deep Vein Thrombosis) or PE (Pulmonary embolism) who completed 6 or 12 months of treatment of anticoagulation	

References

EINSTEIN CHOICE (10mg), 2017:

Weitz JI, Lensing AWA, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, Freitas MCS, Holberg Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism. N. Engl. J. Med. 2017; 376:1211-1222 [28316279] 10.1056/NEJMoa1700518

AMPLIFY EXT 2.5mg, 2013:

Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699-708 [23216615] 10.1056/NEJMoa1207541

AMPLIFY EXT 5mg, 2013:

Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699-708 [23216615] 10.1056/NEJMoa1207541

EISNTEIN EXT, 2010:

Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agnelli G, Bounameaux H, Cohen A, Davidson BL, Piovella F, Schellong S Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-510 [21128814] 10.1056/NEJMoa1007903

EINSTEIN CHOICE (20mg), 2017:

Weitz JI, Lensing AWA, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, Freitas MCS, Holberg Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism. N. Engl. J. Med. 2017; 376:1211-1222 [28316279] 10.1056/NEJMoa1700518

4 idraparinux

Trial	Treatments	Patients	Trials design and methods
idraparinux vs placebo			
Van Gogh , 2007 [NCT00071279] n=594/621 follow-up:	once-weekly injections of 2.5 mg of idraparinux for 6 months without monitoring versus placebo	patients who had completed 6 months of prophylaxis with idraparinux or a vitamin K antagonist and in whom extended anticoagulation was warranted	Parallel groups double-blind

References

Van Gogh, 2007:

Buller HR, Cohen AT, Davidson B, Decousus H, Gallus AS, Gent M, Pillion G, Piovella F, Prins MH, Raskob GE Extended prophylaxis of venous thromboembolism with idraparinux. N Engl J Med 2007;357:1105-12 [17855671] 10.1056/NEJMoa067703

5 VKA

Trial	Treatments	Patients	Trials design and methods
VKA vs control			
AUREC FVII , 2009 n=17/17 follow-up: 37 months mean	continue VKA for additional 24 months versus discontinuation	patients with first spontaneous VTE and FVIII levels >230 IU/dl after 6 montsh of VKA	
DACUS (Siragusa) , 2008 [NCT00438230] n=88/92 follow-up:	anticoagulants for 9 additional months versus no treatment	with a first episode of deep vein thrombosis, treated with OAT for 3 months and with Residual vein thrombosis	
DURAC II , 1997 n=116/111 follow-up: 4 years	anticoagulant therapy continued indefinitely versus six months of oral anticoagulant therapy	patients who had had a second episode of venous thromboembolism	
PROLONG (Palarati) , 2006 [NCT00264277] n=105/122 follow-up: 1.4 years	resume treatment versus discontinue treatment	patients with a first unprovoked proximal deep-vein thrombosis or pulmonary embolism who had received a vitamin K antagonist for at least 3 months and with abnormal D-dimer testing 1 month after the discontinuation of anticoagulation	
WODIT DVT , 2001 n=134/133 follow-up: at least two years	continuation for nine additional months versus discontinuation	Patients with a first episode of idiopathic proximal deep venous thrombosis who had completed three months of oral anticoagulant therapy	
WODIT PE , 2003 n=165/161 follow-up:	-	patients after a first episode of pulmonary embolismwho had had 3 months of oral anticoagulant therapy without experiencing recurrence or bleeding	
DDOAT2006 *ongoing* [NCT00895505] n=300 follow-up: 24 months	Extension of OAT versus discontinuation	-	
warfarin vs control			
Vitotec , 2009 n=27/25 follow-up:	continuation of warfarin for another 6 months versus discontinuation of warfarin	patients with idiopathic DVT After 6 months of standard therapy (heparin/LMWH, warfarin with target INR 2-3) and persistent echogenic masses of over 20% of venous diameter	
warfarin vs low intensity warfarin			
ELATE , 2003 n=369/369 follow-up: 2.4 years mean	continue warfarin therapy with a target international normalized ratio (INR) of 2.0 to 3.0 versus target INR of 1.5 to 1.9 (low intensity)	patients who had completed three or more months of warfarin therapy for unprovoked venous thromboembolism	Parallel groups open-label
low-intensity warfarin vs placebo			

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Trial	Treatments	Patients	Trials design and methods
PREVENT , 2003 n=255/253 follow-up: 2.1 years mean	low-intensity warfarin (target INR, 1.5 to 2.0) versus placebo	Patients with idiopathic venous thromboembolism who had received full-dose anticoagulation	double-blind
VKA vs placebo			
PADIS-PE (Couturaud) , 2015 [NCT00740883] n=184/187 follow-up:	additional 18-month treatment with warfarin versus placebo	patients who had experienced a first episode of symptomatic unprovoked pulmonary embolism (ie, with no major risk factor for thrombosis) and had been treated initially for 6 uninterrupted months with a vitamin K antagonist	double-blind
warfarin vs placebo			
LAFIT , 1999 n=79/83 follow-up: 10 months	warfarin for a further 24 months versus placebo	patients who had completed 3 months of anticoagulant therapy for a first episode of idiopathic venous thromboembolism	double-blind
Levine , 1995 n=109/105 follow-up:	continue warfarin (targeted International Normalized Ratio 2.0 to 3.0) for a further eight weeks versus placebo	Patients with venographically confirmed acute proximal DVT who had received four weeks of warfarin after initial heparin and whose four week IPG was normal	

References

AUREC FVII, 2009:

Eischer L, Gartner V, Schulman S, Kyrle PA, Eichinger S 6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII. Ann Hematol 2009;88:485-90 [18931845] 10.1007/s00277-008-0626-1

DACUS (Siragusa), 2008:

Siragusa S, Malato A, Anastasio R, Cigna V, Milio G, Amato C, Bellisi M, Attanzio MT, Cormaci O, Pellegrino M, Dolce A, Casuccio A, Bajardi G, Mariani G Residual vein thrombosis to establish duration of anticoagulation after a first episode of deep vein thrombosis: the Duration of Anticoagulation based on Compression UltraSonography (DACUS) study. Blood 2008;112:511-5 [18497320] 10.1182/blood-2008-01-131656

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Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, Moia M, Guazzaloca G, Bertoldi A, Tomasi C, Scannapieco G, Ageno W Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med 2001;345:165-9 [11463010] 10.1056/NEJM200107193450302

WODIT PE, 2003:

Agnelli G, Prandoni P, Becattini C, Silingardi M, Taliani MR, Miccio M, Imberti D, Poggio R, Ageno W, Pogliani E, Porro F, Zonzin P Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med 2003;139:19-25 [12834314]

DDOAT2006, :

Vitotec, 2009:

Vtovec M, Goln L, Roztocil K, Linhart A The development of persistent thrombotic masses in patients with deep venous thrombosis randomized to long-term anticoagulation treatment. Vasa 2009;38:238-44 [19736635] 10.1024/0301-1526.38.3.238

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Kearon C, Ginsberg JS, Kovacs MJ, Anderson DR, Wells P, Julian JA, MacKinnon B, Weitz JI, Crowther MA, Dolan S, Turpie AG, Geerts W, Solymoss S, van Nguyen P, Demers C, Kahn SR, Kassis J, Rodger M, Hambleton J, Gent M Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med 2003;349:631-9 [12917299] 10.1056/NEJMoa035422

PREVENT, 2003:

Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, Cushman M, Moll S, Kessler CM, Elliott CG, Paulson R, Wong T, Bauer KA, Schwartz BA, Miletich JP, Bounameaux H, Glynn RJ Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med 2003;348:1425-34 [12601075] 10.1056/NEJMoa035029

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Couturaud F, Sanchez O, Pernod G, Mismetti P, Jego P, Duhamel E, Provost K, dit Sollier CB, Presles E, Castellant P, Parent F, Salaun PY, Bressollette L, Nonent M, Lorillon P, Girard P, Lacut K, Gugan M, Bosson JL, Laporte S, Leroyer C, Dcousus H, Meyer Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial. JAMA 2015;314:31-40 [26151264] 10.1001/jama.2015.7046

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6 About TrialResults-center.org

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