Clinical trials of antithrombotics for pulmonary embolism in all type of patients

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1 anticoagulant

Trial	Treatments	Patients	Trials design and methods
anticoagulant vs no anticoagulant			
BARRIT , 1960 n=16/19 follow-up:	heparin IV 10000 UI every 6 hours for 6 doses, nicoumalone ajusted for prothrombin time between 2-3x control versus no anticoagulant	patients with pulmonary embolism	Parallel groups open

References

BARRIT, 1960:

BARRITT DW, JORDAN SC Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet 1960 Jun 18;1:1309-12 [13797091]

2 direct anti-Xa

Trial	Treatments	Patients	Trials design and methods
apixaban 2.5mg vs discontinuation			
AMPLIFY-EXT 2.5mg , 2012 [NCT00633893] n=842/829 follow-up: 12 mo	Extended Treatment with apixaban 2.5 mg twice daily 12 months versus placebo	patients who have completed their intended treatment for deep vein thrombosis or pulmonary embolism	Parallel groups double blind
apixaban 5mg vs discontinuation			
AMPLIFY-EXT 5mg , 2012 [NCT00633893] n=815/829 follow-up: 12 mo	Extended Treatment with apixaban 5 mg twice daily 12 months versus placebo	patients who have completed their intended treatment for deep vein thrombosis or pulmonary embolism	double blind
apixaban (without LMWH) vs LMWH/VKA			
AMPLIFY , 2013 [NCT00643201] n=2691/2704 follow-up: 6 mo	apixaban 10 mg twice daily for 7 days then 5 mg, twice daily, 6 months versus conventional therapy: enoxaparin 1mg/kg twice daily until INR>=2 then warfarin for an INR between 2-4, once daikly, 6 months	patients with deep vein thrombosis or pulmonary embolism	Parallel groups double blind
rivaroxaban (without LMWH) vs LMWH/VKA			

continued...

Trial	Treatments	Patients	Trials design and methods
Einstein-PE Evaluation , 2012 [NCT00439777] n=2419/2413 follow-up: 9.8 months	rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) for 3, 6, or 12 months versus standard therapy with enoxaparin followed by an adjusted-dose vitamin K antagonist	patients who had acute symptomatic pulmonary embolism with or without deep-vein thrombosis	Parallel groups open 38 countries

References

AMPLIFY-EXT 2.5mg, 2012:

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 2012 Dec 8;: [23216615] 10.1056/NEJMoa1207541

AMPLIFY-EXT 5mg, 2012:

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 2012 Dec 8;: [23216615] 10.1056/NEJMoa1207541

AMPLIFY, 2013:

Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013 Aug 29;369:799-808 [23808982] 10.1056/NEJMoa1302507

Einstein-PE Evaluation, 2012:

Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism. N Engl J Med 2012 Mar 26;: [22449293] 10.1056/NEJMoa1113572

3 low molecular weight heparin

Trial	Treatments	Patients	Trials design and methods
Certoparin vs unfractionated heparin			
Certoparin-Study Group sub group , 1998 n=39/41 follow-up: 6 mo	Certoparin, 8000 IU twice daily, 14 days versus Unfractioned heparin: bolus 5000 IU, infusion 20 IU/kg per hour	Symptomatic PE	Parallel groups open
Dalteparin vs unfractionated heparin			
Kuijer , 1995 n=32/35 follow-up: 3 mo	Dalteparin, 120 IU/kg twice daily, 5 days versus Unfractioned heparin: bolus 5000 IU, infusion 1250 IU/h	Symptomatic PE	Parallel groups open
Meyer , 1995 n=29/31 follow-up: 3 mo	Dalteparin, 120 IU/kg twice daily, 10 days versus Unfractioned heparin: no bolus, infusion 500 IU/kg per day	Symptomatic PE	Parallel groups open
Enoxaparin vs unfractionated heparin			

continued...

Trial	Treatments	Patients	Trials design and methods
PREPIC , 1998 n=41/54 follow-up: 2 y	Enoxaparin, 1 mg/kg twice daily, 8-12 days versus Unfractioned heparin: bolus 5000 IU, infusion 500 IU/kg per day	patients with proximal deep-vein thrombosis who were at risk for pulmonary embolism	Factorial plan open
Merli sub group , 2001 n=199/88 follow-up: 3 mo	Enoxaparin, 1mg/kg twice daily or 1.5 mg/kg once daily, 5 days versus Unfractioned heparin: according nomogram at local institution	patients with confirmed pulmonary embolism	Parallel groups open 16 countries
Nadroparin vs unfractionated heparin			
European multicentre study , 1991 n=61/47 follow-up: 3 mo	Nadroparin, 47506650 antifactor Xa IU twice daily, 10 days versus Unfractioned heparin: no bolus, infusion, 20 IU/kg per hour	Symptomatic proximal DVT	Parallel groups open (blind assessment) Europe
Prandoni sub-group , 1992 n=45/46 follow-up: 6 mo	Nadroparin, 47506650 antifactor Xa IU twice daily, 10 days versus Unfractioned heparin: bolus 100 IU/kg, infusion 35 000 IU/d	Symptomatic proximal DVT	Parallel groups open
Thery , 1992 n=35/33 follow-up: 14 d	Nadroparin, 76 IU/kg twice daily, 14 days versus Unfractioned heparin: bolus 50 IU/kg, infusion 600 IU/kg per day	patients with submassive pulmonary embolism	Parallel groups open
Reviparin vs unfractionated heparin			
COLOMBUS sub group , 1997 n=138/133 follow-up: 3 mo	Reviparin, 35006300 IU twice daily, 5 days versus Unfractioned heparin: bolus 5000 IU, infusion 1250 IU/h	patients with symptomatic DVT and associated pulmonary embolism	Parallel groups open
Tinzaparin vs unfractionated heparin			
ACTSG (Hull) sub-group , 1992 n=97/103 follow-up: 3mo	Tinzaparin, 175 IU/kg once daily, 6 days versus Unfractioned heparin: bolus 5000 IU, infusion 29 76040 320 IU/d	patients with objectively documented PE and underlying proximal deep vein thrombosi	Parallel groups double blind US, Canada
THESEE , 1997 n=301/307 follow-up: 3 mo	Tinzaparin, 175 IU/kg once daily, 5 days versus Unfractioned heparin: bolus 50 IU/kg, infusion 500 IU/kg per day	patients with symptomatic pulmonary embolism	Parallel groups open
Campbell , 1998 n=6/10 follow-up: 3 mo	Tinzaparin, 175 IU/kg once daily, 5 days versus Unfractioned heparin: bolus 5000 IU, infusion 1400 IU/h	Symptomatic PE	Parallel groups open

References

Certoparin-Study Group sub group, 1998:

Kirchmaier CM, Wolf H, Schfer H, Ehlers B, Breddin HK Efficacy of a low molecular weight heparin administered intravenously or subcutaneously in comparison with intravenous unfractionated heparin in the treatment of deep venous thrombosis. Certoparin-Study Group. Int Angiol 1998;17:135-45 [9821025]

Kuijer, 1995:

Kuijer PM, Gallus AS, Cade JE, Buller HR./jpeg Randomized comparison of LMWH versus standard heparin in the initial treatment of pulmonary embolism [Abstract].ocumen Thromb Haemost. 995;73:974

Meyer, 1995:

Meyer G, Brenot F, Pacouret G, Simonneau G, Gillet Juvin K, Charbonnier B, Sors H Subcutaneous low-molecular-weight heparin fragmin versus intravenous unfractionated heparin in the treatment of acute non massive pulmonary embolism: an open randomized pilot study. Thromb Haemost 1995;74:1432-5 [8772215]

PREPIC, 1998:

Decousus H, Leizorovicz A, Parent F, Page Y, Tardy B, Girard P, Laporte S, Faivre R, Charbonnier B, Barral FG, Huet Y, Simonneau G A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prvention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. N Engl J Med 1998;338:409-15 [9459643]

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European multicentre study, 1991:

A randomised trial of subcutaneous low molecular weight heparin (CY 216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis. A collaborative European multicentre study. Thromb Haemost 1991;65:251-6 [1646490]

Prandoni sub-group, 1992:

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Thery, 1992:

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COLOMBUS sub group, 1997:

Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. The Columbus Investigators. N Engl J Med 1997;337:657-62 [9280815]

ACTSG (Hull) sub-group, 1992:

Hull RD, Raskob GE, Pineo GF, Green D, Trowbridge AA, Elliott CG, Lerner RG, Hall J, Sparling T, Brettell HR Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. N Engl J Med 1992;326:975-82 [1545850]

Hull RD, Raskob GE, Brant RF, Pineo GF, Elliott G, Stein PD, Gottschalk A, Valentine KA, Mah AF Low-molecular-weight heparin vs heparin in the treatment of patients with pulmonary embolism. American-Canadian Thrombosis Study Group. Arch Intern Med 2000;160:229-36 [10647762]

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Simonneau G, Sors H, Charbonnier B, Page Y, Laaban JP, Azarian R, Laurent M, Hirsch JL, Ferrari E, Bosson JL, Mottier D, Beau B A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THESEE Study Group. Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire. N Engl J Med 1997;337:663-9 [9278462]

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Campbell IA, Yeoh J, Medlicott S.p, imag Duration of hospital stay in patients with pulmonary venous thromboembolism: a randomised comparison of unfractionated heparin versus low molecular weight heparin [Abstract] Thorax. 1998;53: 254

4 outpatient treatment

Trial	Treatments	Patients	Trials design and methods
outpatient treatment vs inpatient treatment			
OTPE (Aujesky) , 2011 [NCT00425542] n=171/168 follow-up: 90 days	initial outpatient treatment with subcutaneous enoxaparin (5 days) followed by oral anticoagulation (90 days). versus inpatient treatment with subcutaneous enoxaparin (5 days) followed by oral anticoagulation (90 days)	patients with acute, symptomatic pulmonary embolism and a low risk of death (pulmonary embolism severity index risk classes I or II)	Parallel groups open-label Switzerland, France, Belgium, and the USA
Otero , 2010 [NCT00214929] n=72/60 follow-up: 3 months	early discharge versus standard hospitalization	low-risk patients with acute symptomatic PE	Parallel groups open-label Spain

References

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Aujesky D, Roy PM, Verschuren F, Righini M, Osterwalder J, Egloff M, Renaud B, Verhamme P, Stone RA, Legall C, Sanchez O, Pugh NA, N'gako A, Cornuz J, Hugli O, Beer HJ, Perrier A, Fine MJ, Yealy DM Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. Lancet 2011;378:41-8 [21703676] 10.1016/S0140-6736(11)60824-6

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Otero R, Uresandi F, Jimnez D, Cabezudo MA, Oribe M, Nauffal D, Conget F, Rodrguez C, Cayuela A Home treatment in pulmonary embolism. Thromb Res 2010;126:e1-5 [19853892] 10.1016/j.thromres.2009.09.026

5 reversible longlasting indirect inhibitor of activated factor X

Trial	Treatments	Patients	Trials design and methods
idrabiotaparinux vs warfarin			
CASSIOPEA , 2012 [NCT00345618] n=1599/1603 follow-up: 99 days	subcutaneous idrabiotaparinux (starting dose 30 mg) after 5-10 days' enoxaparin 10 mg/kg twice daily for at least 3 months or 6 months dependent on clinical presentation versus adjusted-dose warfarin (target INR 2-3) after 5-10 days' enoxaparin 10 mg/kg twice daily	adults with objectively documented acute symptomatic pulmonary embolism	Parallel groups double-blind 37 countries

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CASSIOPEA, 2012:

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pulmonary embolism: a randomised, double-blind, double-dummy, non-inferiority trial. Lancet 2012;379:123-9 [22130488] 10.1016/S0140-6736(11)61505-5

6 synthetic oligosaccharide

Trial	Treatments	Patients	Trials design and methods
fondaparinux vs heparin			
MATISSE PE , 2003 n=1103/1110 follow-up: 3 mo	fondaparinux subcutaneously once daily versus continuous intravenous infusion of unfractionated heparin	patients with acute symptomatic pulmonary embolism	Parallel groups open
idraparinux (without heparin) vs heparin/VKA			
VanGogh PE , 2007 [NCT00062803] n=1095/1120 follow-up: 3 mo (6 mo)	subcutaneous idraparinux (2.5 mg once weekly) versus heparin followed by an adjusted-dose vitamin K antagonist	patients with pulmonary embolism	Parallel groups open

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Bller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, Prins MH, Raskob G, van den Berg-Segers AE, Cariou R, Leeuwenkamp O, Lensing AW Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med 2003 Oct 30;349:1695-702 [14585937]

VanGogh PE, 2007:

7 About TrialResults-center.org

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