

Clinical trials of antithrombotics for atrial fibrillation in primary prevention of thromboembolic events

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1 anticoagulant

Trial	Treatments	Patients	Trials design and methods
warfarin low dose vs control			
BAATAF (warfarin vs no treatment) , 1990 [NCT00000517] n=212/208 follow-up: 2.2 years	warfarin low dose (target INR:1.5-2.7) versus no placebo.people received no treatment but could choose to take aspirin.	non rheumatic AF	Parallel groups Open
warfarin standard dose vs control			
AFASAK (warfarin standard dose vs control) , 1989 n=335/336 follow-up: 2 years	warfarin standard dose(target INR:2.8-4.2) versus control	chronic non rheumatic AF	Parallel groups Open Denmark
SPAF (warfarin standard dose) , 1991 n=210/211 follow-up: 1.3 years	warfarin standard dose(target INR:2.0-4.5) versus control	-	Parallel groups Open USA
warfarin low dose vs placebo			
SPINAF (warfarin vs placebo) , 1992 n=260/265 follow-up: 1.75 years	warfarin low dose(target INR 1.4-2.8) versus placebo	men ,with chronic nonrheumatic atrial fibrillation	Parallel groups Double blind usa
warfarin standard dose vs placebo			
CAFA , 1991 n=187/191 follow-up: 15.2 months	warfarin standard dose (target INR 2-3) versus placebo	non rheumatic atrial fibrillation	Parallel groups Double blind canada
coumadin low dose vs coumadin standard dose			
PATAF (coumadin low dose vs coumadin standard dose) , 1999 n=122/131 follow-up: 2.7 years	coumarin low dose(target INR 1.1-1.6) versus coumarin standard dose(target INR 2.5-3.5)	non rheumatic AF,recruited in general practice,with no established indication for anticoagulation.	Parallel groups Simple aveugle Netherlands
tecarfarin vs warfarin standard dose			
EmbraceAC <i>ongoing</i> n=NA follow-up:	tecarfarin versus warfarin	AF, implanted prosthetic heart valves, and a history of venous thromboembolic disease	

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Trial	Treatments	Patients	Trials design and methods
warfarin low dose vs warfarin standard dose			
AFASAK II (warfarin low dose vs warfarin standard dose) , 1998 n=167/170 follow-up: 3.5 years	warfarin fixed low dose (1.25 mg/d) versus warfarin standard dose(target INR 2-3)	chronic non valvular atrial fibrillation	Parallel groups Open Denmark
MWNAF , 1998 n=150/153 follow-up: 14.5 months	warfarin low dose (1.25mg/d) versus warfarin standard dose(target INR 2.0-3.0)	Patients over 60 with non rheumatic atrial fibrillation	Parallel groups Open Italy

References

BAATAF (warfarin vs no treatment), 1990:

The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators N Engl J Med. 1990 Nov 29;323(22):1505-11 [2233931]

AFASAK (warfarin standard dose vs control), 1989:

Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. Lancet 1989 Jan 28;1:175-9 [2563096]

SPAF (warfarin standard dose), 1991:

Stroke Prevention in Atrial Fibrillation Study. Final results Circulation. 1991 Aug;84(2):527-39. [1860198]

SPINAF (warfarin vs placebo), 1992:

Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornick CC, Krause-Steinrauf H, Kurtzke JF, Nazarian SM, Radford MJ Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. N Engl J Med 1992 Nov 12;327:1406-12 [1406859]

CAFA, 1991:

Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. J Am Coll Cardiol 1991 Aug;18:349-55 [1856403]

PATAF (coumadin low dose vs coumadin standard dose), 1999:

Hellemons BS, Langenberg M, Lodder J, Vermeer F, Schouten HJ, Lemmens T, van Ree JW, Knottnerus JA Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomised controlled trial comparing two intensities of coumarin with aspirin. BMJ 1999 Oct 9;319:958-64 [10514159]

EmbraceAC, :

AFASAK II (warfarin low dose vs warfarin standard dose), 1998:

Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, Boysen G Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. Arch Intern Med 1998 Jul 27;158:1513-21 [9679792]

MWNAF, 1998:

Pengo V, Zasso A, Barbero F, Banzato A, Nante G, Parissenti L, John N, Noventa F, Dalla Volta S Effectiveness of fixed minidose warfarin in the prevention of thromboembolism and vascular death in nonrheumatic atrial fibrillation. Am J Cardiol 1998 Aug 15;82:433-7 [9723629]

2 anticoagulants + antiplatelet agents

Trial	Treatments	Patients	Trials design and methods
warfarin low dose + aspirin vs control			
SAFT(warfarin low dose + aspirin vs no treatment) , 2003 n=334/334 follow-up: 33 months	warfarin low dose (1.25 mg/d) + aspirin 75 mg/d versus no treatment	Low-medium risk patients with non valvular atrial fibrillation.	Parallel groups Open Sweden
triflusal+coumadin medium dose vs coumadin standard dose			
NASPEAF (triflusal + coumadin medium dose vs coumadin standard dose) , 2004 n=235/237 follow-up: 2.76 years	Triflusal 600 mg/d + coumadin medium dose (target INR 1.25-2) versus coumadin standard dose(target INR 2-3)	Non valvular atrial fibrillation. Intermediate risk patients.	Parallel groups Open Spain
triflusal+coumadin medium dose vs triflusal			
NASPEAF (triflusal+coumadin medium dose vs triflusal) , 2004 n=235/242 follow-up: 2.76 years	Triflusal 600 mg/d + coumadin medium dose (target INR 1.25-2) versus Triflusal 600 mg/d	Non valvular atrial fibrillation. Intermediate risk patients	Parallel groups Open Spain
warfarin + aspirin vs warfarin standard dose			
AFASAK II (warfarin low dose+aspirin vs warfarin standard dose) , 1998 n=171/170 follow-up: 3.5 years	warfarin fixed low dose(1.25mg/d) + aspirin(300mg/d) versus warfarin standard dose(target INR 2.0-3.0)	chronic non valvular atrial fibrillation	Parallel groups Open Denmark
SPAF III , 1996 n=521/523 follow-up: 1.1 years	warfarin low dose(target INR 1.2-1.5)+ aspirin 325 mg/d versus warfarin standard dose(target INR 2.0-3.0)	non rheumatic atrial fibrillation,patients with at least one additional thromboembolic risk factor(high risk patients)	Parallel groups Open USA,Canada

References

SAFT(warfarin low dose + aspirin vs no treatment), 2003:

Edvardsson N, Juul-Moller S, Omblus R, Pehrsson K Effects of low-dose warfarin and aspirin versus no treatment on stroke in a medium-risk patient population with atrial fibrillation. J Intern Med 2003 Jul;254:95-101 [12823646]

Edvardsson N, Juul-Moller S, Omblus R, Pehrsson K Effects of low-dose warfarin and aspirin versus no treatment on stroke in a medium-risk patient population with atrial fibrillation. J Intern Med 2003 Jul;254:95-101 [12823646]

NASPEAF (triflusal + coumadin medium dose vs coumadin standard dose), 2004:

Perez-Gomez F, Alegria E, Berjon J, Iriarte JA, Zumalde J, Salvador A, Mataix L Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study. J Am Coll Cardiol 2004 Oct 19;44:1557-66 [15489085]

NASPEAF (triflusal+coumadin medium dose vs triflusal), 2004:

Perez-Gomez F, Alegria E, Berjon J, Iriarte JA, Zumalde J, Salvador A, Mataix L Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study. J Am Coll Cardiol 2004 Oct 19;44:1557-66 [15489085]

AFASAK II (warfarin low dose+aspirin vs warfarin standard dose), 1998:

Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, Boysen G Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. Arch Intern Med 1998 Jul 27;158:1513-21 [9679792]

SPAF III, 1996:

Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. Lancet. 1996 Sep 7;348(9028):633-8. [8782752]

3 oral direct thrombin inhibitor

Trial	Treatments	Patients	Trials design and methods
AZD0837 vs aspirin			
phase 2 AZD0837 unpublished [NCT00623779] n=NA follow-up:	AZD0837 versus aspirin	patients with atrial fibrillation, who are appropriate for but unable or unwilling to take Vitamin-K antagonist(VKA) therapy	Parallel groups open
AZD0837 vs warfarin standard dose			
Lip (phase 2 AZD0837) , 2009 unpublished [NCT00684307] n=636/318 follow-up: 3 or 9 months	AZD0837 for 3-9 months versus dose-adjusted Vitamin-K antagonists (VKA) (aiming for an international normalized ratio (INR) 2.0 to 3.0)	patients with non-valvular atrial fibrillation (AF) with one or more additional risk factors for stroke	Parallel groups double blind
dabigatran vs warfarin standard dose			
phase 2 dabigatran unpublished [NCT01136408] n=NA follow-up:	Dabigatran 110, 220, 300 mg twice daily versus warfarin	patients with non-valvular atrial fibrillation (paroxysmal, persistent or permanent)	Parallel groups open Japan
dabigatran 110mg vs warfarin standard dose			
RE-LY (110mg) , 2009 [NCT00262600] n=6015/6022 follow-up: 2 y (median)	dabigatran 110 mg twice a day versus warfarin adjusted dose to a 2-3 INR	Patients With Non-Valvular Atrial Fibrillation	Parallel groups open (blind assessment) 44 countries
dabigatran 150mg vs warfarin standard dose			
PETRO (150mg) , 2007 n=166/70 follow-up: 12 weeks	dabigatran 150 mg twice daily (alone or combined with 81- or 325-mg aspirin) versus warfarin administered to achieve an international normalized ratio of 2 to 3 for	patients with AF at high risk for thromboembolic events	Factorial plan double blind Denmark, The netherlands, Sweden, US
RE-LY (150mg) , 2009 [NCT00262600] n=6076/6022 follow-up: 2 y (median)	dabigatran 150 mg twice a day versus warfarin adjusted-dose to a 2.0 to 3.0 INR	Patients With Non-Valvular Atrial Fibrillation	Parallel groups open (blind assessment) 44 countries
ximelagatran vs warfarin standard dose			

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Trial	Treatments	Patients	Trials design and methods
SPORTIF V , 2005 n=1960/1962 follow-up: 20 months	ximelegatran 36 mg twice daily versus warfarin standard dose(target INR 2-3)	One or more stroke risk factor in addition to atrial fibrillation.High risk patients with non valvular atrial fibrillation.	Parallel groups Double blind north america
SPORTIF II (ximelegatran vs warfarin standard dose) , 2002 n=187/67 follow-up: 16 weeks	ximelegatran 20,40,60 mg twice daily versus warfarin standard dose(target INR 2-3)	Medium to high risk patients with chronic non valvular atrial fibrillation.	Parallel groups Open Europe ,USA
SPORTIF III , 2003 n=1704/1703 follow-up: 17.4 months	ximelegatran 36 mg twice daily versus warfarin standard dose (target INR 2-3)	One or more stroke risk factor in addition to AF.High risk patients with non valvular atrial fibrillation.	Parallel groups Open europe,asia,australasia

References

phase 2 AZD0837, 0:

Lip (phase 2 AZD0837), 2009:

Lip GY, Rasmussen LH, Olsson SB, Jensen EC, Persson AL, Eriksson U, Whlander KF Oral direct thrombin inhibitor AZD0837 for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: a randomized dose-guiding, safety, and tolerability study of four doses of AZD0837 vs. vitamin K antagonists. Eur Heart J 2009;30:2897-907 [19690349] 10.1093/eurheartj/ehp318

phase 2 dabigatran, 0:

RE-LY (110mg), 2009:

PETRO (150mg), 2007:

RE-LY (150mg), 2009:

SPORTIF V, 2005:

SPORTIF II (ximelegatran vs warfarin standard dose), 2002:

SPORTIF III, 2003:

4 oral factor Xa inhibitors

Trial	Treatments	Patients	Trials design and methods
edoxaban low dose vs warfarin standard dose			
ENGAGE-AF TIMI 48 Low dose , 2013 [NCT00781391] n=7034/7036 follow-up: 2.8 years	edoxaban xxx once daily versus warfarin (INR 2-3)	AF patients (CHADS2 >=2)	double blind 46 countries
apixaban vs aspirin			

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Trial	Treatments	Patients	Trials design and methods
AVERROES , 2011 [NCT00496769] n=2808/2791 follow-up: maximum 21 months	apixaban 5 mg (or 2.5 mg) twice daily versus aspirin 81-324 md daily	patients with atrial fibrillation who have failed or are unsuitable for vitamin K antagonist treatment	Parallel groups double blind 36 countries
apixaban vs warfarin standard dose			
ARISTOTLE , 2011 [NCT00412984] n=9120/9081 follow-up: 1.8 yrs (median)	apixaban 5mg twice daily versus warfarin adjusted for an INR between 2 and 3	subjects with atrial fibrillation and risk factors for stroke	Parallel groups double blind 39 countries
phase 2 apixaban unpublished [NCT00787150] n=222 follow-up: 12 weeks	apixaban 5 or 2.5 mg twice daily versus warfarin	patient with non valvular AF	Parallel groups double blind
edoxaban vs warfarin standard dose			
Weitz (edoxaban phase 2) unpublished [NCT00504556] n=1146 follow-up: 3 months	Four Fixed Dose Regimens of edoxaban (DU-176b) versus warfarin	Subjects With Non- Valvular Atrial Fibrillation	Parallel groups double-blind USA, Europe, South and central america,
phase 2 edoxaban unpublished [NCT00806624] n=NA follow-up:	edoxaban (DU-176b) versus warfarin	male and female subjects aged 18 to 80 years, inclusive, with non-valvular AF and a CHADS2 Score of at least 1	Parallel groups double-blind China
edoxaban high dose vs warfarin standard dose			
ENGAGE-AF TIMI 48 High dose , 2013 [NCT00781391] n=7035/7036 follow-up: 2.8 years	edoxaban 60mg once daily versus warfarin (INR 2-3)	AF patients (CHADS2 \geq 2)	Parallel groups double blind 46 countries
rivaroxaban vs warfarin standard dose			
ROCKET-AF , 2010 [NCT00403767] n=7131/7133 follow-up: median 1.94 y	Rivaroxaban 20mg p.o. once daily versus Warfarin p.o. once daily titrated to a target INR of 2.5 (range 2.0 to 3.0, inclusive)	Subjects With Non-Valvular Atrial Fibrillation	Parallel groups double blind 45 countries
ROCKET J ongoing [NCT00494871] n=NA follow-up:	Rivaroxaban versus warfarin	-	parallel groups double-blind Japan
YM150 vs warfarin standard dose			
phase 2 YM150 unpublished [NCT00448214] n=NA follow-up:	YM150 ASTELLAS versus warfarin	subjects with non-valvular atrial fibrillation	Parallel groups open Australia

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Trial	Treatments	Patients	Trials design and methods
OPAL-2 <i>ongoing</i> [NCT00938730] n=NA follow-up:	YM150 versus warfarin	subjects with non-valvular atrial fibrillation	double-blind Australia

References

ENGAGE-AF TIMI 48 Low dose, 2013:

AVERROES, 2011:

ARISTOTLE, 2011:

phase 2 apixaban, 0:

Weitz (edoxaban phase 2), 0:

phase 2 edoxaban, 0:

ENGAGE-AF TIMI 48 High dose, 2013:

ROCKET-AF, 2010:

ROCKET J, :

phase 2 YM150, 0:

OPAL-2, :

5 platelet aggregation inhibitors

Trial	Treatments	Patients	Trials design and methods
aspirin vs control			
Japanese AF Trial , 2006 n=426/445 follow-up:	aspirin at 150 to 200 mg per day versus no antiplatelet or anticoagulant therapy	patients with nonvalvular atrial fibrillation	
LASAF(aspirin vs no treatment) , 1999 n=NA follow-up:	aspirin:125mg/day(group A1);125mg on alternate days(group A2) versus no control treatment(group C)	-	Open
aspirin vs placebo			
AFASAK (aspirin vs placebo) , 1989 n=336/336 follow-up: 2 years	aspirin 75 mg/d versus placebo	patients with chronic non-rheumatic atrial fibrillation	Parallel groups Double aveugle Denmark
SPAF (aspirin , warfarin eligible arm) , 1991 n=206/211 follow-up: 1.3 years	aspirin 325mg/d versus placebo	nonrheumatic atrial fibrillation,warfarin eligible patients	Parallel groups Double blind USA

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Trial	Treatments	Patients	Trials design and methods
SPAF (aspirin,warfarin ineligible arm) , 1991 n=346/357 follow-up: 1.3 years	aspirin 325mg/d versus placebo	nonrheumatic atrial fibrillation, warfarin ineligible patients	Parallel groups Double blind USA
aspirin + clopidogrel vs anticoagulant			
ACTIVE W , 2006 [NCT00243178] n=3335/3371 follow-up: 1.28 y (median)	clopidogrel (75 mg per day) plus aspirin (75100 mg per day) versus oral anticoagulation therapy (target international normalised ratio of 2030)	Patients with atrial fibrillation plus one or more risk factor for stroke	Parallel groups open
aspirin + clopidogrel vs aspirin			
ACTIVE A , 2009 [NCT00249873] n=3772/3782 follow-up: 3.7 y	clopidogrel 75 mg daily + aspirin 75-100 mg daily versus aspirin 75-100 mg daily alone	Patients with AF and at least one risk factor for stroke and who are not candidates for warfarin therapy	Parallel groups double blind
aspirin vs coumadin low dose			
PATAF (vs coumadin low dose) , 1999 n=319/279 follow-up: 2.7 years	aspirin 300mg/d versus coumarin low dose(target INR 1.1-1.6)	non rheumatic AF,recruited in general practice,with no established indication for anticoagulation.	Parallel groups Simple aveugle Netherlands
aspirin vs coumadin standard dose			
PATAF (vs coumadin standard dose) , 1999 n=141/131 follow-up: 2.7 years	aspirin 150mg/d versus coumarin standard dose(target INR 2.5-3.5)	non rheumatic AF,recruited in general practice,with no established indication for anticoagulation.	Parallel groups Simple aveugle Netherlands
trifusaf vs coumadin standard dose			
NASPEAF (trifusaf vs coumadin standard dose) , 2004 n=242/237 follow-up: 2.76 years	Trifusaf 600 mg/d versus coumadin standard dose(target INR 2-3)	Non valvular atrial fibrillation. Intermediate risk patients.	Parallel groups Open Spain
aspirin vs warfarin low dose			
AFASAK II (aspirin vs warfarin low dose) , 1998 n=169/167 follow-up: 3.5 years	aspirin 300 mg/d versus warfarin low dose (1.25mg/d)	chronic non valvular atrial fibrillation	Parallel groups Open Denmark
aspirin vs warfarin standard dose			
AFASAK (aspirin vs warfarin standard dose) , 1989 n=336/335 follow-up: 2 years	aspirin (low dose 75 mg) versus warfarin standard dose(target INR 2.8-4.2)	chronic non rheumatic AF	Parallel groups Open Denmark

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Trial	Treatments	Patients	Trials design and methods
AFASAK II (aspirin vs warfarin standard dose) , 1998 n=169/170 follow-up: 3.5 years	aspirin 300 mg/d versus warfarin standard dose(target INR 2-3)	chronic non valvular atrial fibrillation	Parallel groups Open Denmark
SPAF II (aspirin vs warfarin standard dose, age<75) , 1994 n=357/358 follow-up: 3.1 years	aspirin 325 mg/d versus warfarin standard dose(target INR 2.0-4.5)	non rheumatic atrial fibrillation,medium to high risk patients. Patients aged 75 and less.	Parallel groups Open USA
SPAF II (aspirin vs warfarin standard dose, age>75) , 1994 n=188/197 follow-up: 2.0 years	aspirin 325 mg/d versus warfarin standard dose (target INR 2.0-4.5)	Non rheumatic atrial fibrillation,medium to high risk patients.Patients aged more than 75.	Parallel groups Open USA
BAFTA (aspirin vs warfarin standard dose) <i>ongoing</i> n=NA follow-up:	aspirin (75 mg/d) versus warfarin standard dose (target INR:2-3)	elderly people, primary care setting	Parallel groups Open England

References

Japanese AF Trial, 2006:

LASAF(aspirin vs no treatment), 1999:

AFASAK (aspirin vs placebo), 1989:

SPAF (aspirin , warfarin eligible arm), 1991:

SPAF (aspirin,warfarin ineligible arm), 1991:

ACTIVE W, 2006:

ACTIVE A, 2009:

PATAF (vs coumadin low dose), 1999:

PATAF (vs coumadin standard dose), 1999:

NASPEAF (triflusal vs coumadin standard dose)), 2004:

AFASAK II (aspirin vs warfarin low dose), 1998:

AFASAK (aspirin vs warfarin standard dose), 1989:

AFASAK II (aspirin vs warfarin standard dose), 1998:

SPAF II (aspirin vs warfarin standard dose, age<75), 1994:

SPAF II (aspirin vs warfarin standard dose, age>75), 1994:

BAFTA (aspirin vs warfarin standard dose), 0:

6 synthetic oligosaccharide

Trial	Treatments	Patients	Trials design and methods
idraparinux vs warfarin standard dose			

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Trial	Treatments	Patients	Trials design and methods
AMADEUS , 2008 [NCT00070655] n=2283/2293 follow-up: 10.7 months	subcutaneous idraparinux 25 mg weekly versus adjusted-dose vitamin K antagonists (target of an international normalised ratio of 23)	patients with atrial fi brillation at risk for thromboembolism	Parallel groups open
idraparinux BOREALIS-AF <i>ongoing</i> [NCT00580216] n=NA follow-up:	idraparinuxonce-weekly subcutaneous injection versus warfarin oral INR adjusted-dose	-	Parallel groups double blind

References

AMADEUS, 2008:
idraparinux BOREALIS-AF, 0:

7 About TrialResults-center.org

TrialResults-center is an innovative knowledge database that collects the results of RCTs and provides dynamic interactive systematic reviews and meta-analysis in the field of all major heart and vessels diseases.

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