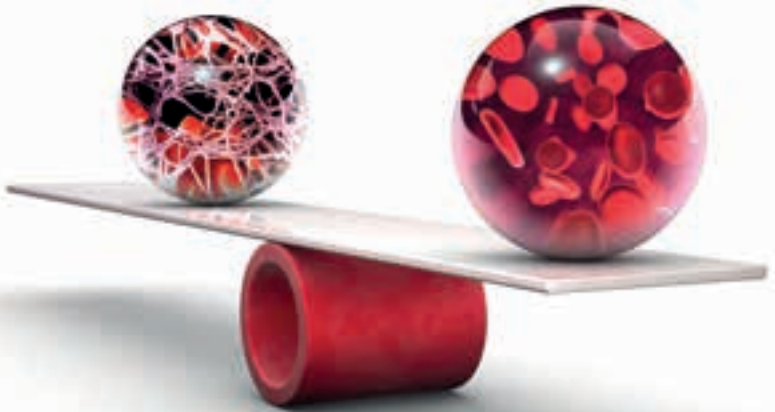


2014

Anticoagulants



A Guide through Acronyms and Major Clinical Trials

4th edition

Daiichi Sankyo Europe GmbH

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and
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Bibliographic information of the German National Library

The "Deutsche Nationalbibliothek" lists this publication in the "Deutsche Nationalbibliografie"; detailed bibliographic data are available at <http://dnb.d-nb.de>

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Fourth edition 2014

ISBN 978-3-928485-57-9

**Published by Daiichi Sankyo Europe GmbH
Zielstattstraße 48, 81379 Munich, Germany**

Layout and text prepared by Verlag Perfusion GmbH



Verlag Perfusion GmbH
Storchenweg 20
90617 Puschendorf, Germany
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fax +49-9101-990 11 19
e-mail: info@verlag-perfusion.de

Editor-in-chief: Brigitte Söllner, Erlangen, Germany
Typesetting: Rolf Wolle, HGS5, Fürth, Germany

Printed in Germany 2014 by Druckerei C. H. Beck, Nördlingen

Introduction

Since the first discovery of heparin in 1916 by second year medical student Jay McLean and his Professor of Pharmacology, William Henry Howell, it took 20 years for the introduction of heparin to be used in clinical practice in 1936 and its clinical use is still widespread around the world. Since then it has taken decades for a further significant improvement of parenteral anticoagulants. As an example, the discovery of LMWH in 1976 and the first clinical trials during the early 1980s.

The discovery of dicoumarol as the cause of the “sweet clover disease”, a hemorrhagic disease of cattle that have been fed with spoiled sweet clover, resulted in the description of the first oral anticoagulant in 1941 (Butt HR, Allen EU, Mayo Clin Proc 1941;16:388).

Despite the introduction of parenteral and oral anticoagulants in routine clinical practice, thromboembolic diseases remain a major cause of mortality and morbidity.

Currently four novel oral anticoagulants (OACs) are either launched or in phase III of clinical development to compete with vitamin K antagonists and parenteral anticoagulants:

- the direct oral thrombin inhibitor dabigatran*
- the direct oral factor Xa inhibitors rivaroxaban*, apixaban* and edoxaban**

In addition, a parenteral direct factor Xa inhibitor, otamixaban is developed for acute coronary syndrome.

Around 200,000 patients were involved in dozens of phase III clinical trials with different novel OACs just within a few years. These studies resulted in a vast amount of new data and acronyms.

This guide is focused on providing summaries of phase III clinical trials (both completed and concurrent of the novel OACs) as well as offering an overview of the indications under investigation by the different drugs.

Where available, the phase II data of novel OACs in acute coronary syndrome and in atrial fibrillation, is included.

In addition, as a reminiscence to the plethora of clinical studies that have been conducted with other anticoagulants (i.e. vitamin K antagonists, unfractionated heparin and low molecular weight heparins), for each indication area covered in this book, a few selected examples of major or relevant trials with these drugs are summarized. Obviously the selection of these studies is far from being complete and can only be arbitrary.

Within the guide, antiplatelets are noted as active comparators to OACs, however this guide focuses specifically on OAC and therefore antiplatelets are not referred to in any detail.

* = launched

** = in clinical development, no market authorization in Europe yet; launched in Japan

The trials are sorted alphabetically by their acronyms, where no acronyms are available, the name of the first author is referenced. All acronyms and first author names are supplemented by the year of the publication.

An overview of the substances covered in this book is given in table 1 and a detailed list of studies covered is included on the next pages. A complete list of single substances and can be found in the registry at the end of this book.

Class of anticoagulants	Substances
Vitamin K antagonists	Acenocoumarol Dicoumarol Fluindione Warfarin
Indirect parenteral factor Xa/IIa inhibitors <ul style="list-style-type: none"> • Heparin • Low-molecular-weight heparin (LMWH) • Synthetic pentasaccharides 	Unfractionated heparin (UFH) Dalteparin Enoxaparin Nadroparin Reviparin Tinzaparin Fondaparinux Idraparinux Idrabioparinux
Direct factor Xa inhibitors <ul style="list-style-type: none"> • Oral • Parenteral 	Apixaban Betrixaban Edoxaban Darexaban Rivaroxaban Otamixaban
Direct oral thrombin (IIa) inhibitors	Dabigatran Ximelagatran (withdrawn)

Table 1 Anticoagulants covered in this book.

We hope that you find this guide useful as a first overview on this rapidly changing treatment area with novel oral anticoagulants.

With our compliments,
Daiichi Sankyo Europe GmbH

Content

ACTIVE A	1
ACTIVE W	3
ADOPT	5
ADVANCE-1	7
ADVANCE-2	9
ADVANCE-3	11
AFASAK	13
AFASAK II	15
AMADEUS	17
American-Canadian Thrombosis Study	19
AMPLIFY	21
AMPLIFY-EXT	23
APPRAISE-1	25
APPRAISE-2	27
APRICOT-2	29
ARISTOTLE	31
ASPECT-2	33
ATLAS ACS-TIMI 46	35
ATLAS ACS 2-TIMI 51	37
AVERROES	40
BAATAF	42
BAFTA	44
BARRITT	46
BASU	48
BOREALIS-AF	50
BRANDJES	51
CAFA	53
CARS	55
CASSIOPEA	57
CHAMP	60
COAG	62
COLUMBUS	64
COMPASS	66
DAPPAR-AF	67
DURAC II	68
EAFT	70
Edoxaban Study 018	73
EINSTEIN-DVT	75
EINSTEIN-Extension	77
EINSTEIN-PE	79
EINSTEIN pooled analysis	81
ENGAGE AF-TIMI 48	84
ENOXAPARIN Clinical Trial Group (1)	87
ENOXAPARIN Clinical Trial Group (2)	89
ENOXAPARIN Clinical Trial Group (3)	91
ENTIRE-TIMI 23	93
ESSENCE	96
ESTEEM	98
EU-PACT	100
EXPLORE-Xa	102
ExTRACT-TIMI 25	104
FFAACS	106
FIDO Investigators	108
FRAXIS	110
FRIC	112

FRISC-II	115
GALILEI Investigators	117
GALLUS	119
Hokusai-VTE	121
HULL	123
INTERACT (long-term follow-up)	125
ISIS Pilot	127
J-ROCKET AF	130
LAFIT	132
LEVINE (1)	134
LEVINE (2)	136
MAGELLAN	138
MATISSE-DVT	140
MATISSE-PE	142
MEDENOX	144
MONREAL	146
OASIS Pilot	148
OASIS-2 (substudy)	150
OASIS-5 (PCI substudy)	152
OASIS-6	154
PATAF	156
PENTAMAKS	158
PENTATHLON	160
PENTHIFRA	162
PETRO	164
PIONEER AF-PCI	166
PLANES	168
POWERS	170
PRANDONI	172
PREVENT	174
PROTECT-AF	176
RASCHKE	178
RE-ALIGN	180
RECORD1	182
RECORD2	184
RECORD3	186
RECORD4	188
RE-COVER I	190
RE-COVER II	192
RE-DEEM	194
RE-LY	196
RELY-ABLE	198
RE-MEDY	200
RE-MOBILIZE	202
RE-MODEL	204
RE-NOVATE	206
RE-NOVATE II	208
RE-SONATE	210
RISC	212
ROCKET AF	214
RUBY-1	217
SACRE	220
SEPIA-ACS1 TIMI 42	222
SPAF	225
SPAF II	227
SPAF III	229
SPINAF	231

SPORTIF III	233
SPORTIF V	235
STARS E-III.	237
STARS J-V	239
SVT	241
SYNERGY	242
TAO.	244
TASMAN Study Group	247
THÉSÉE	249
TIMI 11B.	251
VAN GOGH	253
VAN GOGH Extension	256
VENTURE-AF	258
WARCEF	259
WARIS II	261
WODIT DVT.	263
WODIT PE.	265
WOEST.	267
XAMOS	269
X-PLOREX	272
X-Vert.	274
Index of anticoagulants	276

Abbreviations

ACS	acute coronary syndrome
aPTT	activated partial thromboplastin time
AF	atrial fibrillation
ASA	acetylsalicylic acid
CABG	coronary artery bypass graft
CAD	coronary artery disease
CHADS ₂	score for estimating the risk of stroke in patients with atrial fibrillation (C = congestive heart failure, H = hypertension, A = Age, D = diabetes mellitus, S ₂ = prior stroke or TIA)
CNS	central nervous system
CV	cardiovascular
DVT	deep-vein thrombosis
EF	ejection fraction
INR	international normalized ratio
ISTH	International Society of Thrombosis and Hemostasis
ITT	intention to treat
IU	international unit
i.v.	intravenous
LMWH	low-molecular-weight heparin
MD	medical doctor
MI	myocardial infarction
NSTEMI	non-ST-elevated myocardial infarction
PCI	percutaneous coronary intervention
PE	pulmonary embolism
p.o.	per os
PTCA	percutaneous transluminal coronary angioplasty
RR	relative risk
RRR	relative risk reduction
s.c.	subcutaneous
STEMI	ST-elevation myocardial infarction
TIA	transient ischemic attack
UA	unstable angina
UFH	unfractionated heparin
VKA	vitamin K antagonist
vs.	versus
VTE	venous thromboembolism

ACTIVE A

The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events A (2009)

Condition

Stroke prevention in patients with AF

Objective

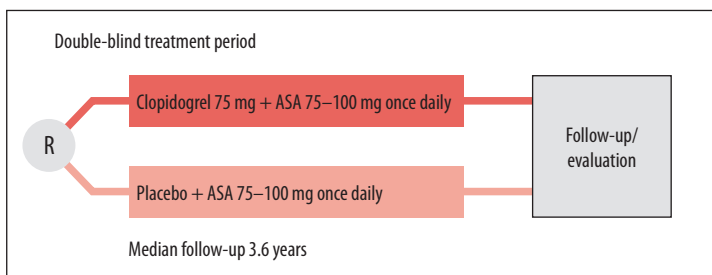
To evaluate, if addition of clopidogrel to ASA would reduce the risk of vascular events in patients with AF

Trial design

Randomized, double-blind placebo-controlled study

Active treatment: clopidogrel 75 mg plus ASA 75–100 mg once daily (n=3772)

Control treatment: matching placebo plus ASA 75–100 mg once daily (n=3782)



Endpoints

Primary efficacy endpoint: composite of stroke, myocardial infarction, non-CNS systemic embolism or death from vascular causes

Secondary efficacy endpoints: stroke, all individual components of the primary outcome; primary outcome and major hemorrhage

Primary safety endpoint: major bleeding

Secondary safety endpoints: minor bleeding, any bleeding

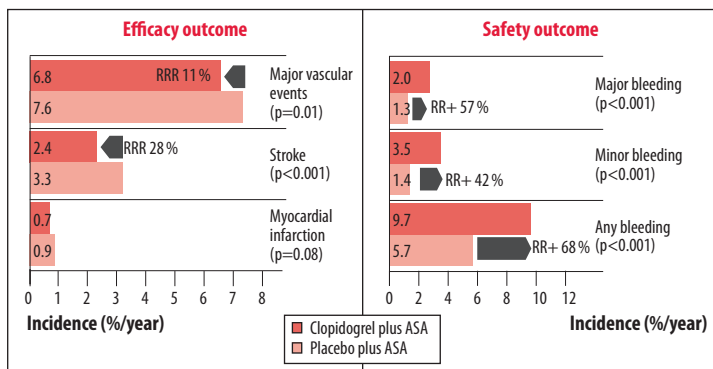
Trial participants

7554 patients (mean age 71 years) with AF who had an increased risk of stroke and for whom vitamin K-antagonist therapy was contraindicated

Results

Efficacy outcome: After a median follow-up of 3.6 years, major vascular events had occurred in 832 of 3772 patients receiving clopidogrel (6.8% per year) and in 924 of 3782 patients receiving placebo (7.6% per year). The difference was primarily due to a reduction in the rate of stroke with clopidogrel. Stroke occurred in 296 patients receiving clopidogrel (2.4% per year) and 408 patients receiving placebo (3.3% per year)

Safety outcome: Major bleeding occurred in 251 patients receiving clopidogrel (2.0% per year) and in 162 patients receiving placebo (1.3% per year)



Summary

Efficacy: The addition of clopidogrel to ASA reduced the risk of major vascular events. This reduction was primarily due to a significant reduction in the risk of stroke

Safety: The patients treated with clopidogrel plus ASA had a significant increase in the risk of major and minor hemorrhage. With the combination of major vascular events (the primary outcome) and major hemorrhage, there was no significant difference between the overall event rate with ASA plus clopidogrel and the rate with ASA alone (968 vs. 996 events; p=0.54)

Reference

Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer MA, Chrolavicius S, Yusuf S for the ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;360:2066-2078

Corresponding author

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ACTIVE W

The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events W (2006)

Condition

Prevention of vascular events in patients with AF and increased risk for stroke

Objective

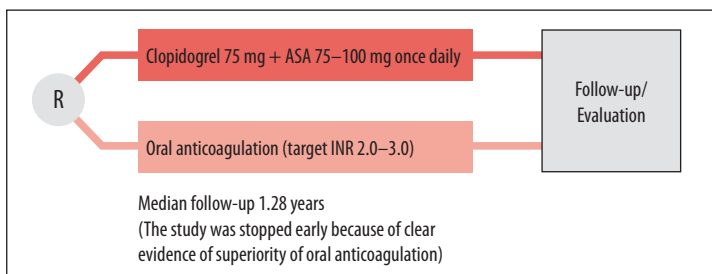
To establish that clopidogrel plus ASA is non-inferior to standard oral anticoagulation therapy for prevention of vascular events in patients with AF

Trial design

Randomized, open trial

Active treatment: clopidogrel 75 mg plus ASA 75–100 mg once daily (n=3335)

Control treatment: oral anticoagulation (INR 2.0–3.0) (n=3371)



Endpoints

Primary endpoint: composite of stroke, non-CNS systemic embolus, myocardial infarction, and vascular death

Secondary endpoints: stroke, stroke severity, total mortality, major and minor hemorrhages, net benefit

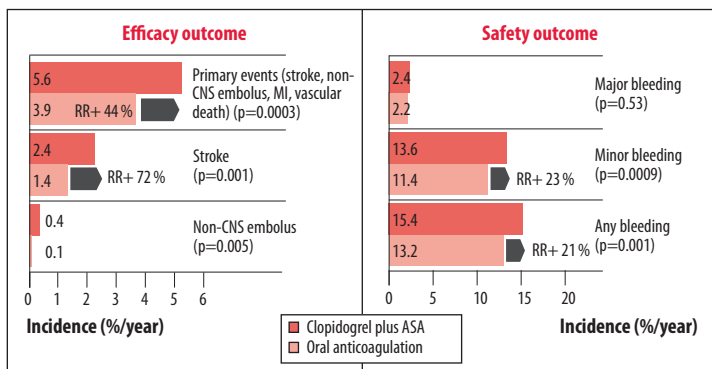
Trial participants

6706 patients (mean age 70 years) with a documented history of permanent, persistent, or at least 2 episodes of paroxysmal atrial fibrillation and at least one additional risk factor for stroke

Results

Efficacy outcome: The study was stopped early because of clear evidence of superiority of oral anticoagulation. In the intent-to-treat population, 165 primary events occurred in the group with oral anticoagulation (annual risk 3.9%) compared to 234 in the clopidogrel/ASA group (annual risk 5.6%). The increase in relative risk for clopidogrel/ASA was 44%. Patients already receiving oral anticoagulation therapy at study entry had a greater reduction in vascular events than patients starting with oral anticoagulation treatment at study entry

Safety outcome: Rates of major hemorrhage were similar in the two groups (annual rate 2.4% with clopidogrel/ASA and 2.2% with oral anticoagulation). Significantly more minor bleeds occurred with clopidogrel/ASA than with oral anticoagulation. Patients already receiving oral anticoagulation therapy at study entry had a significantly lower risk of major bleeding than patients starting with oral anticoagulation treatment at study entry



Summary

Efficacy outcome: Oral anticoagulation therapy was superior to clopidogrel/ASA for prevention of vascular events in AF patients with high risk for stroke, especially in patients already taking oral anticoagulation therapy at study entry

Safety outcome: Rates of major bleedings were comparable between groups. The net benefit (primary outcome event plus major hemorrhage) favored oral anticoagulation therapy ($p < 0.0001$)

Reference

Connolly S, Yusuf S, Camm J, Chrolavicius S, Commerford P, Flather M, Hart RG, Hohnloser S, Joyner C, Pfeffer M, Pogue J, for the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;367:1903-1912

Corresponding author

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ADOPT

Apixaban for the prevention of thrombosis-related events in patients with acute medical illness (2011)

Condition

Prevention of VTE in patients hospitalized for acute medical illness

Objective

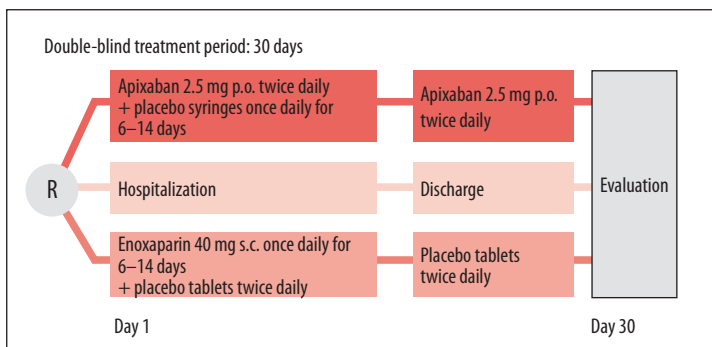
To evaluate the safety and efficacy of apixaban versus enoxaparin for prophylaxis of VTE in acutely ill medical patients during and following hospitalization

Trial design

Randomized, double-blind phase III study

Active treatment: while hospitalized: apixaban 2.5 mg p.o. twice daily plus placebo (syringes, s.c.) once daily for 6–14 days; after hospital discharge: apixaban 2.5 mg p.o. twice daily up to 30 days (= duration of double-blind treatment)

Control treatment: enoxaparin 40 mg s.c. once daily for 6–14 days plus placebo (tablets, p.o.) twice daily; after hospital discharge: placebo (tablets, p.o.) twice daily up to 30 days (= duration of double-blind treatment)



Endpoints

Primary efficacy endpoint: 30-day composite of VTE-related death and fatal or non-fatal PE, symptomatic DVT, or asymptomatic proximal-leg DVT

Secondary efficacy endpoints: Additional secondary efficacy outcomes included the composite of total VTE and VTE-related death occurring from the time of randomization to the time the blinded parenteral therapy was discontinued (the parenteral-treatment period), all cause death during the 30-day treatment period and during the entire 90-day study period

Safety endpoints: major bleeding, clinically relevant non-major bleeding and all bleeding reported by investigators

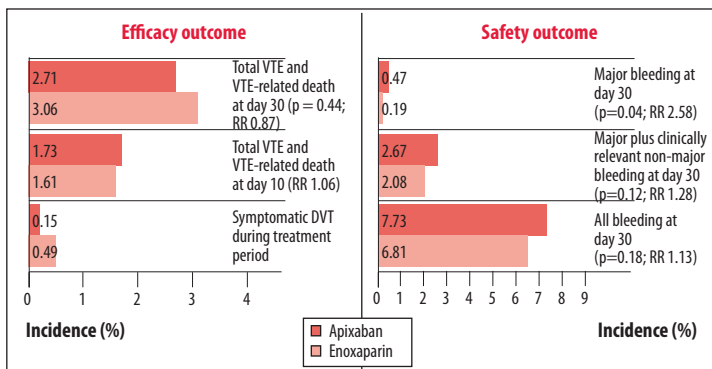
Trial participants

6528 patients ≥ 40 years, hospitalized for congestive heart failure, acute respiratory failure, infection (without septic shock), acute rheumatic disorder, or inflammatory bowel disease, who had an expected hospital stay of at least 3 days and were severely restricted in their mobility. 4495 patients could be evaluated for the primary efficacy outcome at day 30, 2211 in the apixaban group and 2284 in the enoxaparin group

Results

Efficacy outcome: The primary efficacy outcome, the composite of VTE and death related to VTE, evaluated at day 30, occurred in 2.71% of the patients randomly assigned to receive extended prophylaxis with apixaban (60 of the 2211 patients in the primary efficacy data set) and in 3.06% of those assigned to receive short-term prophylaxis with enoxaparin (70 of 2284 patients) (relative risk with apixaban 0.87; $p=0.44$). After the parenteral-treatment period (analysis on day 10), the primary efficacy outcome occurred in 1.73% of patients in the apixaban group (43 of 2485 patients) and in 1.61% in the enoxaparin group (40 of 2488 patients) (relative risk 1.06). The rate of symptomatic DVT was lower among patients with apixaban than among those who received enoxaparin (0.15% vs. 0.49%), but this difference did not reach significance. There was no significant difference in the rate of death between the apixaban and the enoxaparin treated group (4.1% in each group, 131 and 133 patients, respectively)

Safety outcome: By day 30, major bleeding was two and a half times more likely in the apixaban group, occurring in 0.47% of patients (15 of the 3184 patients who received at least one dose of apixaban), compared with 0.19% of those in the enoxaparin group (6 of the 3217 patients who received at least one dose of enoxaparin) (relative risk with apixaban 2.58; $p=0.04$). Major plus clinically relevant non-major bleeding occurred in 2.67% of the patients with apixaban and in 2.08% of those treated with enoxaparin (relative risk 1.28; $p=0.12$). The rates of total bleeding events in the apixaban and enoxaparin groups were 7.73% and 6.81%, respectively ($p=0.18$).



Summary

Efficacy: Prolonging prophylaxis for venous thromboembolism in medically ill patients with a 30-day course of the oral anticoagulant apixaban was not superior to a shorter six- to 14-day course of subcutaneous enoxaparin

Safety: Apixaban was associated with significantly more major bleeding events than was enoxaparin

Reference

Goldhaber SZ, Leizorovicz A, Kakkar AK, Haas SK, Merli G, Knabb RM, Weitz JI, for the ADOPT Trial Investigators. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med* 2011;365:2167-2177

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ADVANCE-1

Apixaban Dose Orally Vs. ANtiCoagulation with Enoxaparin 1 (2009)

Condition

Prophylaxis for VTE after total knee arthroplasty

Objective

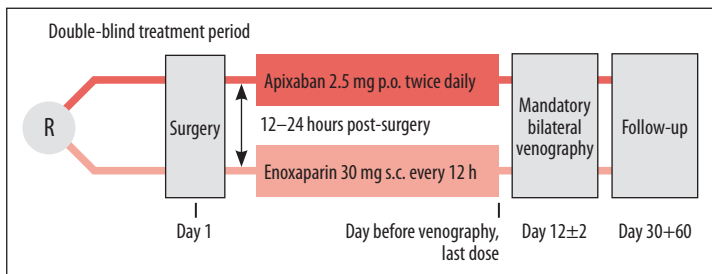
To prove non-inferiority of apixaban compared to enoxaparin in the prevention of venous thromboembolism after total knee replacement

Trial design

Randomized, double-blind phase III study

Active treatment: apixaban 2.5 mg p.o. twice daily, starting 12–24 hours after surgery, continued for 10–14 days; placebo injections as in control treatment (n=1599)

Control treatment: enoxaparin 30 mg s.c. every 12 hours, starting 12–24 hours after surgery, continued for 10–14 days; placebo tablets as in active treatment (n=1596)



Endpoints

Primary efficacy endpoint: composite of asymptomatic and symptomatic DVT, non-fatal PE, and death from any cause during treatment

Secondary efficacy endpoints: composite of major thromboembolism (the composite of adjudicated proximal DVT, non-fatal PE and VTE-related death) and death from any cause during treatment; symptomatic thromboembolism (the composite of adjudicated symptomatic DVT and non-fatal or fatal PE) during treatment

Primary safety endpoint: composite incidence of major bleeding and clinically relevant non-major bleeding during treatment and within 2 days after the last dose

Secondary safety endpoints: elevated aminotransferase or bilirubin levels and arterial thromboembolic events (myocardial infarction, acute ischemic stroke, or other systemic thromboembolism) occurring during treatment and the 60-day follow-up

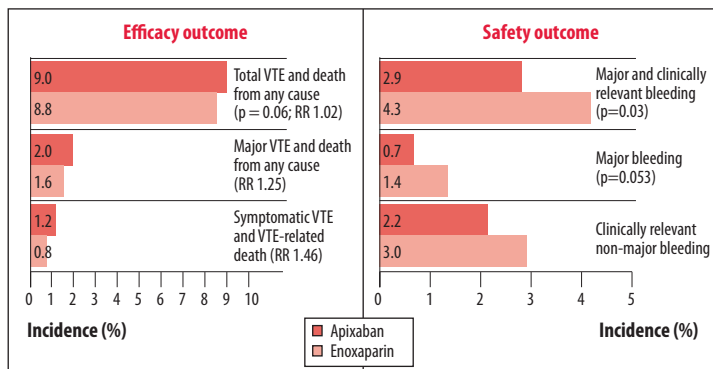
Trial participants

3195 patients scheduled for elective total knee replacement

Results

Efficacy outcome: In the population with evaluable efficacy outcome (n=2287), the primary efficacy endpoint (all VTE and death from any cause) occurred in 104 of 1157 patients (9.0%) given apixaban and in 100 of 1130 patients (8.8%) given enoxaparin (relative risk 1.02; p=0.06 for non-inferiority; difference in risk 0.11%)

Safety outcome: In the safety population (n=3184) major bleeding and clinically relevant non-major bleeding occurred in 46 of 1596 patients (2.9%) receiving apixaban and in 68 of 1588 patients (4.3%) receiving enoxaparin (p=0.03). Major bleeding occurred in 11 (0.7%) patients in the apixaban group and in 22 (1.4%) in the enoxaparin group (p=0.053). The incidence of serious adverse events was similar in the two groups: 8.5% with apixaban and 8.6% with enoxaparin



Summary

Efficacy: Apixaban was similarly effective in preventing VTE after total knee arthroplasty. The prespecified statistical criteria for the non-inferiority of oral apixaban as compared with twice-daily administration of enoxaparin were not met for the primary efficacy outcome (composite of any VTE plus death from any cause during treatment)

Safety: Apixaban was superior to enoxaparin for major and clinically relevant bleeding episodes

Reference

Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med* 2009;361:594-604

Corresponding author

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ADVANCE-2

Apixaban Dose Orally Vs. ANtiCoagulation with Enoxaparin 2 (2010)

Condition

Prophylaxis for VTE after total knee arthroplasty

Objective

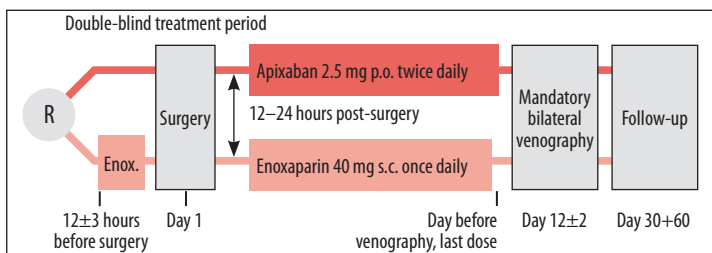
To prove non-inferiority of apixaban compared to enoxaparin in the prevention of venous thromboembolism after total knee replacement

Trial design

Randomized, double-blind phase III study

Active treatment: apixaban 2.5 mg p.o. twice daily, starting 12–24 hours after wound closure, continued for 10–14 days; placebo injections as in control treatment (n=1528)

Control treatment: enoxaparin 40 mg s.c., first dose 12±3 hours preoperatively and then once daily starting 12–24 hours after surgery, continued for 10–14 days; placebo tablets as in active treatment (n=1529)



Endpoints

Primary efficacy endpoint: composite of asymptomatic and symptomatic DVT, non-fatal PE, or death from any cause during treatment period

Secondary efficacy endpoints: during treatment phase: major VTE (composite of symptomatic DVT, non-fatal PE and VTE-related death); during follow-up: symptomatic DVT, the composite of PE and VTE-related death, and all-cause death

Primary safety endpoint: bleeding reported during treatment, assessed for discrete predefined categories of severity (major, clinically relevant non-major, minor, and the composite of major and clinically relevant non-major bleeding according to ISTH criteria)

Secondary safety endpoints: elevated aminotransferase or bilirubin levels, thrombocytopenia and arterial thromboembolic events (myocardial infarction, acute ischemic stroke, or other systemic thromboembolism) occurring during treatment and follow-up

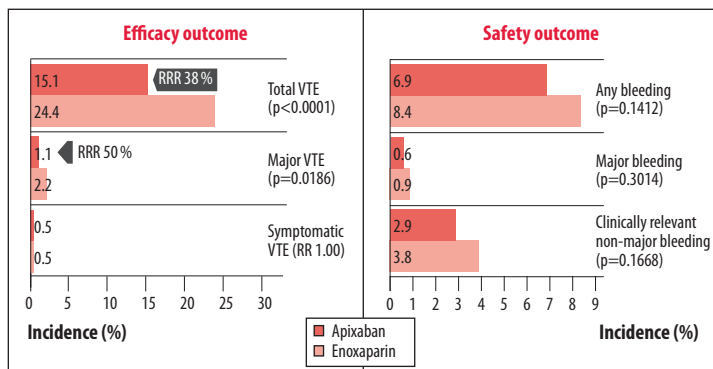
Trial participants

3057 patients scheduled for elective total knee replacement

Results

Efficacy outcome: In the population with evaluable efficacy outcome (n=1973), the primary efficacy endpoint (total VTE events) occurred in 147 of 976 patients (15.1%) given apixaban and in 243 of 997 patients (24.4%) given enoxaparin (absolute risk reduction 9.3%, relative risk reduction 38%; p<0.001). Major VTE were registered in 1.1% of the patients treated with apixaban and in 2.2% treated with enoxaparin

Safety outcome: In the safety population (all patients receiving at least one dose of the study medication; n=3009) major bleeding and clinically relevant non-major bleeding occurred in 53 of 1501 patients (3.5%) receiving apixaban and in 72 of 1508 patients (4.8%) receiving enoxaparin (p=0.0881). Major bleeding occurred in 9 patients in the apixaban group (0.6%) and 14 patients in the enoxaparin group (0.9%). The incidence of drug-related adverse events was 14% in both groups



Summary

Efficacy: Oral apixaban (2.5 mg twice daily) was superior to subcutaneous enoxaparin (40 mg once daily) for prevention of total VTE and major VTE

Safety: The incidence of major bleeding events was low and comparable between both groups. There was no difference in clinically relevant non-major bleeding and adverse events

Reference

Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P and the ADVANCE-2 investigators. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet* 2010;375:807-15

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ADVANCE-3

Apixaban Dose Orally Vs. ANtiCoagulation with Enoxaparin 3 (2010)

Condition

Prophylaxis for VTE after hip replacement

Objective

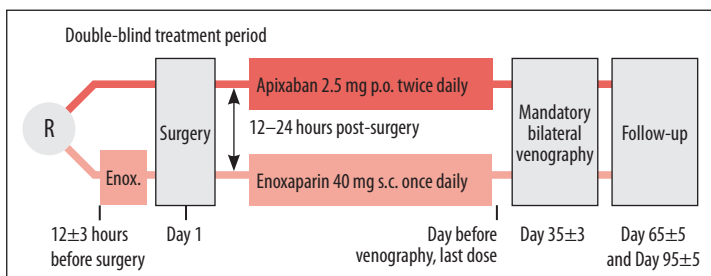
Evaluate the safety and efficacy of apixaban versus enoxaparin after total hip replacement

Trial design

Randomized, double-blind phase III study

Active treatment: apixaban 2.5 mg p.o. twice daily, starting 12–24 hours after wound closure, continued for 35 days; placebo injections as in control treatment (n=2708)

Control treatment: enoxaparin 40 mg s.c., first dose 12±3 hours preoperatively and then every 24 hours starting 12–24 hours after wound closure, continued for 35 days; placebo tablets as in active treatment (n=2699)



Endpoints

Primary efficacy endpoint: composite of asymptomatic and symptomatic DVT, non-fatal PE, and all-cause death during treatment period

Secondary efficacy endpoint: major VTE (composite of proximal DVT, non-fatal PE, and VTE-related death during treatment period)

Primary safety endpoint: bleeding during treatment period or until 2 days after last study medication, assessed for discrete predefined categories of severity (major, clinically relevant non-major, minor, and the composite of major and clinically relevant non-major bleeding according to ISTH criteria)

Secondary safety endpoints: elevated aminotransferase or bilirubin levels, thrombocytopenia and arterial thromboembolic events (myocardial infarction, acute ischemic stroke, or other systemic thromboembolism) occurring during treatment and follow-up

Trial participants

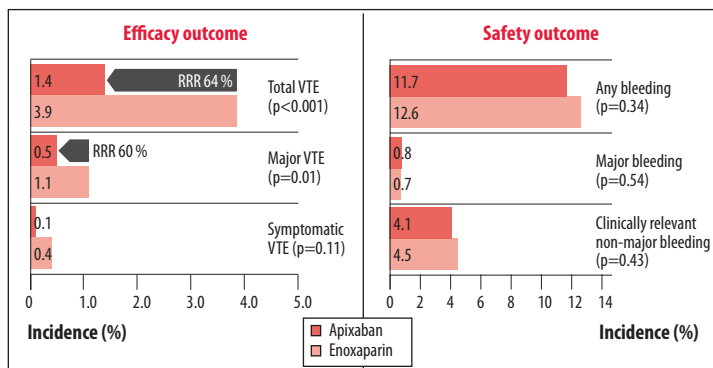
5407 patients scheduled for total hip replacement

Results

Efficacy outcome: In the population with evaluable efficacy outcome (n=3866), the primary efficacy endpoint occurred in 27 of 1949 patients (1.4%) given apixaban and in 74 of 1917 patients (3.9%) given enoxaparin (absolute risk reduction 2.5%, relative risk reduction 64%; p<0.001 for non-inferiority and superiority). Major VTE were registered in 0.5% of the patients treated with apixaban and in 1.1% treated with enoxaparin (p<0.001 for non-inferiority and <0.01 for superiority). Symptomatic VTE or death related

to VTE during the 60-day follow-up period occurred in none of 2598 patients in the apixaban group and in 6 of 2577 patients (0.2%) in the enoxaparin group

Safety outcome: In the safety population (n=3009), major bleeding and clinically relevant non-major bleeding occurred in 129 of 2673 patients (4.8%) receiving apixaban and in 134 of 2659 patients (5.0%) receiving enoxaparin (p=0.72). Major bleeding occurred in 22 patients in the apixaban group (0.8%) and 18 patients in the enoxaparin group (0.7%). The incidence of drug-related adverse events was similar in both groups



Summary

Efficacy: Oral apixaban (2.5 mg twice daily) was superior to subcutaneous enoxaparin (40 mg once daily) for prevention of all VTE, all-cause death, and major VTE in patients after total hip replacement

Safety: The incidence of major or clinically relevant non-major bleeding was similar in both groups

Reference

Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM for the ADVANCE-3 investigators. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med* 2010;363:2487-2498

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AFASAK

Copenhagen **A**trial Fibrillation, **A**spirin and **A**nticoagulation (1989)

Condition

Prevention of VTE in chronic non-rheumatic AF

Objective

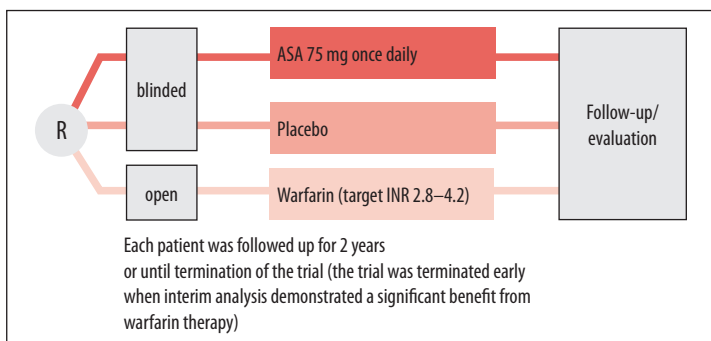
To compare the efficacy of ASA and warfarin in preventing thromboembolic complications in chronic AF

Trial design

Randomized, open (warfarin), double-blind (ASA) placebo-controlled phase III study

Active treatment: ASA 75 mg once daily (n=336)

Control treatment: warfarin standard dose (target INR 2.8–4.2) (n=335), placebo (n=336)



Endpoints

Primary endpoint: thromboembolic complication (stroke, transient cerebral ischemic attack, or embolic complications to the viscera and extremities)

Secondary endpoint: death

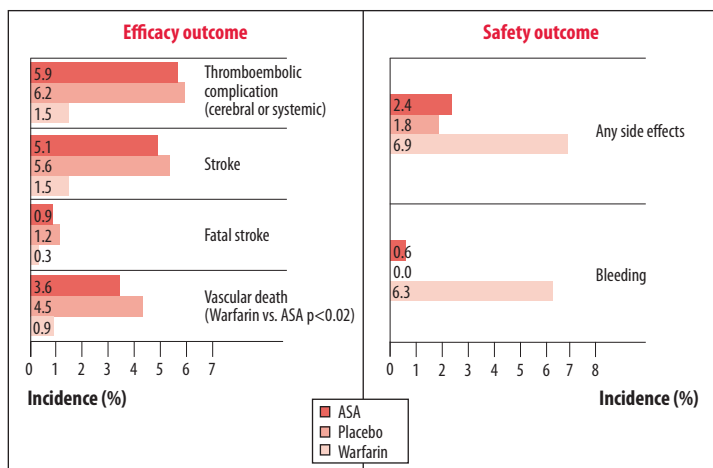
Trial participants

1007 patients aged ≥ 18 years (mean age 74.2 years), with ECG-verified chronic non-rheumatic AF

Results

Efficacy outcome: The incidence of thromboembolic complications (stroke, TIA, or embolic complications) on treatment was significantly lower in the warfarin group (5 of 335 patients, 2.0%/year) than in the ASA group (20 of 336 patients; 5.5%/year) or the placebo group (21 of 336 patients, 5.5%/year; relative risk reduction for warfarin vs. placebo 71%). There were 3 vascular deaths in the warfarin group (0.9%), 12 in the ASA group (3.6%), and 15 in the placebo group (4.5%). The trial was terminated early when interim analysis demonstrated a significant benefit from warfarin therapy

Safety outcome: Bleeding complications were more common in the warfarin group (21/335 patients) than in the ASA (2/336 patients) or placebo group (0)



Summary

Efficacy: The incidence of thromboembolic complications and vascular mortality was significantly lower in the warfarin group than in the ASA and placebo groups, which did not differ significantly

Safety: There were more bleeding episodes with warfarin than with ASA

Reference

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;1:175-179

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AFASAK II

Copenhagen **A**trial Fibrillation, **A**spirin and **A**nticoagulation II (1997)

Condition

Prevention of VTE in chronic non-valvular AF

Objective

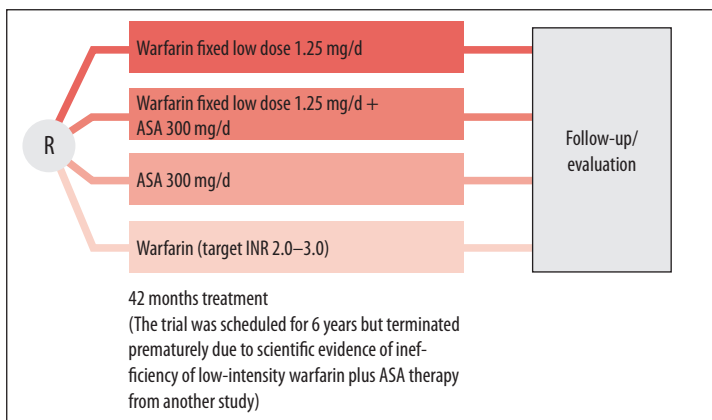
To investigate the antithrombotic effects of a fixed minidose warfarin alone or in combination with ASA, of conventional dose-adjusted warfarin and of ASA alone in patients with chronic non-valvular AF

Trial design

Randomized, controlled phase III study with parallel groups

Active treatment: warfarin fixed low dose 1.25 mg/d (n=167)

Control treatment: warfarin fixed low dose 1.25 mg/d + ASA 300 mg once daily (n=171) or ASA 300 mg once daily (n=169) or dose-adjusted warfarin to target INR 2.0–3.0 (n=170)



Endpoints

Primary endpoint: stroke (ischemic or hemorrhagic) or a systemic thromboembolic event

Secondary endpoint: transient ischemic attack, acute myocardial infarction, and death

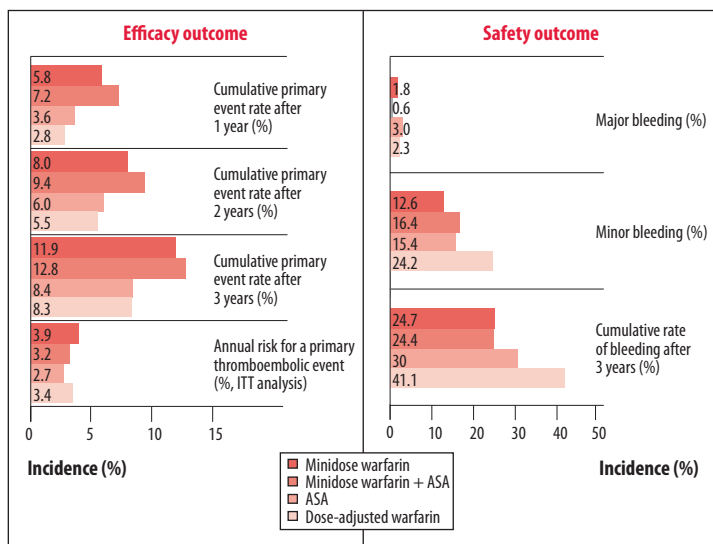
Trial participants

677 patients (mean age 74 years), with chronic non-rheumatic AF, documented twice using electrocardiography (ECG), with an interval of at least 1 month

Results

Efficacy outcome: 39 primary thromboembolic events occurred in patients receiving treatment: 12 with minidose warfarin, 12 with warfarin plus ASA, 8 with ASA, and 7 with adjusted dose warfarin. The cumulative primary event rate after 1 year was 5.8% in patients receiving minidose warfarin, 7.2% with warfarin plus ASA, 3.6% with ASA alone, and 2.8% with adjusted-dose warfarin; differences between groups were not significant ($p=0.67$). After 3 years of treatment, there was no difference between the groups

Safety outcome: On treatment, 47 patients had a secondary adverse event: 12 with minidose warfarin, 8 with warfarin plus ASA, 13 with ASA, and 14 with dose-adjusted warfarin. The cumulative mortality after 3 years was 3.9% in patients receiving minidose warfarin, 5.9% with warfarin plus ASA, 13.4% with ASA alone, and 10.3% with dose-adjusted warfarin ($p=0.27$). The cumulative rate of any bleeding was significantly higher in patients receiving dose-adjusted warfarin than in other groups ($p=0.003$).



Summary

Efficacy: There was no significant difference in the frequency of stroke, systemic thromboembolic events, myocardial infarction, TIA, or death between the groups. Although the difference was not significant, dose-adjusted warfarin seemed superior to minidose warfarin and to warfarin plus ASA after 1 year of treatment

Safety: Major bleeding events were rare in all groups. The higher rate of bleeding with dose-adjusted warfarin was ascribed only to a higher rate of minor bleeding

Reference

Gulløv 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;158:1513-1521

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AMADEUS

Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation (2008)

Condition

Prevention of stroke and systemic embolic events in patients with AF

Objective

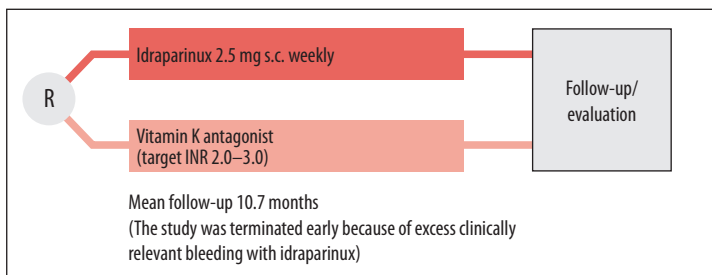
To compare the efficacy and safety of idraparinux with conventional anticoagulation with a vitamin K antagonist in the prevention of thromboembolic events

Trial design

Randomized, open-label non-inferiority phase III trial

Active treatment: idraparinux 2.5 mg s.c. weekly (n=2283)

Control treatment: vitamin K antagonists (warfarin or acenocoumarol) (INR 2.0–3.0) (n=2293)



Endpoints

Primary efficacy endpoint: cumulative incidence of all strokes and systemic embolism

Secondary endpoints: ischemic stroke, non-ischemic stroke (hemorrhagic and undefined), systemic embolic events, cardiovascular death, myocardial infarction, and VTE

Primary safety endpoint: clinically relevant bleeding (major bleeding and clinically relevant non-major bleeding)

Trial participants

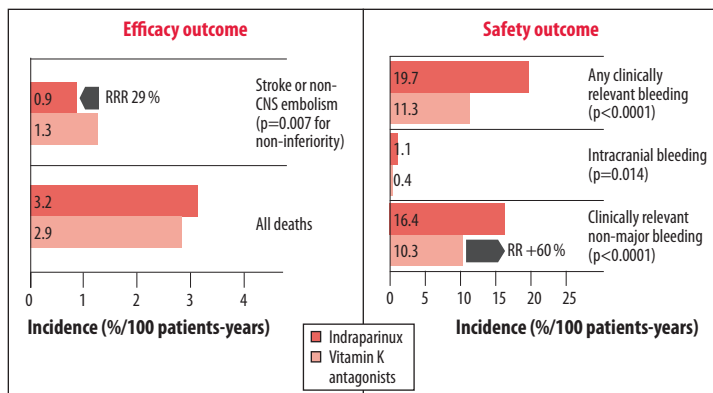
4576 patients (mean age 72 years) with non-valvular AF and at least one additional risk factor for stroke

Results

Primary outcome: The trial was stopped after a mean follow-up period of 10.7 months because of excess clinically relevant bleeding with idraparinux. At that time, the primary efficacy endpoint had occurred in 18 of the 2283 patients given idraparinux (0.9% per 100 patient-years) and in 27 of 2293 patients given vitamin K antagonists (1.3% per 100 patient-years) satisfying the non-inferiority criterion. 62 patients in the idraparinux group (3.2% per 100 patient-years) and 61 in the vitamin K antagonist group (2.9% per 100 patient-years) died during follow-up

Safety outcome: Clinically relevant bleeding occurred in 346 patients given idraparinux (19.7% per 100 patient-years) and in 226 patients given a vitamin K antagonist (11.3% per 100 patient-years). Intracranial bleeding was more frequent in the idraparinux group (n=21, 1.1% per 100 patient-years)

compared to the vitamin K antagonists group (n=9; 0.4% per 100 patient-years). Elderly patients and those with renal impairment were at greater risk of such complications



Summary

Efficacy: Long-term treatment with idraparinux was non-inferior to anti-coagulation with a vitamin K antagonist in terms of preventing stroke and systemic embolic events

Safety: Treatment with idraparinux caused significantly more clinically relevant bleeding events than conventional treatment with a vitamin K antagonist

Reference

Bousser MG, Bouthier J, Buller HR, Cohen AT, Crijns H, Davidson BL, Halperin J, Hankey G, Levy S, Pengo V, Prandoni, Prins PMH, Tomkowski W, Thorp-Pedersen C, Wyse DG; the AMADEUS investigators (steering and writing committee). Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. *Lancet* 2008;371:315-321

Corresponding author

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American-Canadian Thrombosis Study

Subcutaneous low-molecular-weight heparin vs. standard heparin in the treatment of proximal DVT (1996)

Condition

Initial treatment of acute proximal DVT

Objective

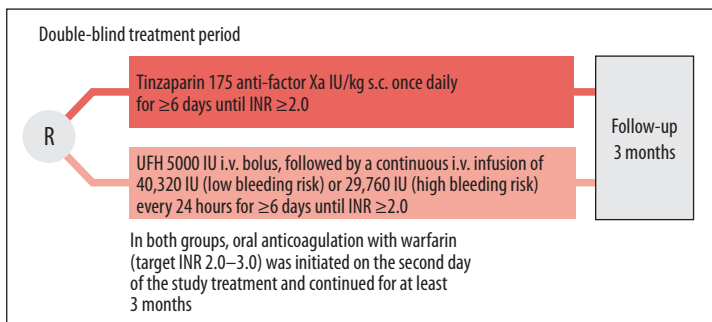
To compare the efficacy and safety of a single subcutaneous injection of fixed-dose low-molecular-weight heparin per day with those of continuous intravenous standard heparin for the initial treatment of proximal DVT

Trial design

Randomized, double-blind, placebo-controlled study

Active treatment: Tinzaparin 175 anti-factor Xa IU/kg s.c. once daily for 6 days, provided INR was ≥ 2.0 ; intravenous UFH placebo (n=213)

Control treatment: UFH 5000 IU i.v. bolus, followed by continuous infusion of 40,320 IU every 24 hours for patients without the designated risk factors for bleeding, and 29,760 IU every 24 hours for patients who had one or more designated risk factors, to target an aPTT of 1.5–2.5 times the control value of 30 s, for 6 days, provided INR was ≥ 2.0 ; subcutaneous tinzaparin placebo (n=219)



Endpoints

Primary efficacy endpoint: symptomatic recurrent VTE during 3-month follow-up

Primary safety endpoints: major and minor bleeding

Trial participants

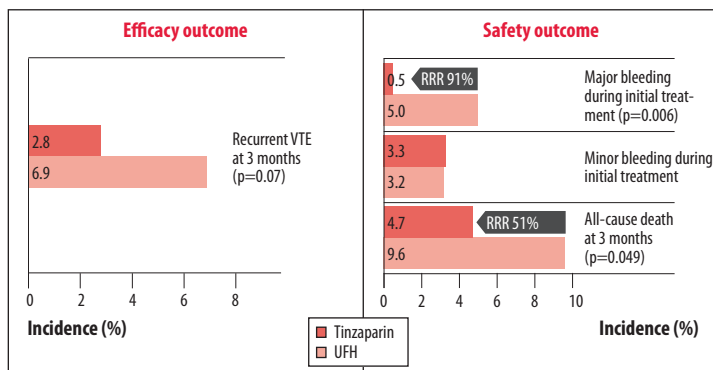
432 consecutive symptomatic patients (≥ 18 years of age) with acute proximal DVT documented by venography

Results

Efficacy outcome: 6 of the 213 patients assigned to tinzaparin (2.8%) and 15 of the 219 patients receiving standard heparin (6.9%) had new episodes of symptomatic VTE. Time-to-event analysis by the log-rank test showed a significant difference in the frequency of VTE ($p=0.049$)

Safety outcome: In the tinzaparin group, there were significantly fewer major bleeding complications during initial therapy than in the UFH group (0.5% vs. 5.0%, relative risk reduction 91%). This benefit was lost during long-term therapy. Minor hemorrhages occurred in 7 patients given tinzaparin (3.3%) and in 7 patients given UFH (3.2%). The UFH group had a higher over-

all mortality: 9.6% (21/219) patients receiving UFH died, as compared with 4.7% (10/213) patients assigned to tinzaparin (relative risk reduction 51%)



Summary

Efficacy: Treatment of proximal DVT with fixed-dose subcutaneous tinzaparin was as least as effective as continuous intravenous treatment with standard heparin but more convenient to administer

Safety: During initial treatment, rates of major bleeding were higher in patients receiving UFH

Reference

Hull RD, Raskob GE, Pineo GF, Green D, Trowbridge AA, Elliott CG, Lerner RG, Hall J, Sparling T, Brettell HR, Norton J, Carter CJ, George R, Merli G, Ward J, Mayo W, Rosenblom D, Brant R. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med* 1992;326:975-982

Corresponding author

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AMPLIFY

Apixaban after the initial Management of PuLmonary embollism and deep vein thrombosis with First-line therapY (2013)

Condition

Treatment of acute DVT and PE

Objective

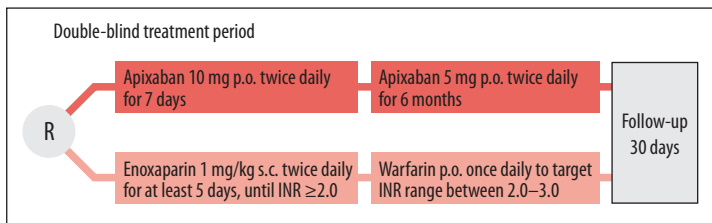
To evaluate the safety and efficacy of apixaban in preventing VTE recurrence or death in patients with DVT or PE (with and without DVT) versus the standard treatment (enoxaparin followed by warfarin)

Trial design

Randomized, double-blind phase III study

Active treatment: apixaban 10 mg p.o. twice daily for one week and 5 mg p.o. twice daily for 6 months thereafter; placebo injections as in control treatment (n=2691)

Control treatment: enoxaparin 1 mg/kg s.c. twice daily, for at least 5 days, until INR ≥ 2.0 ; then warfarin once daily (INR 2.0–3.0) for 6 months; placebo tablets as in active treatment (n=2704)



Endpoints

Primary efficacy endpoint: incidence of the composite of recurrent symptomatic VTE or death related to VTE

Secondary efficacy endpoints: The predefined secondary efficacy outcomes included each component of the primary efficacy outcome, as well as death from cardiovascular causes and death from any cause. An additional predefined secondary outcome was the composite of symptomatic recurrent VTE with death from cardiovascular causes, with death from any cause, or with death related to VTE plus major bleeding

Primary safety endpoint: major bleeding

Secondary safety endpoint: composite of major bleeding and clinically relevant non-major bleeding

Trial participants

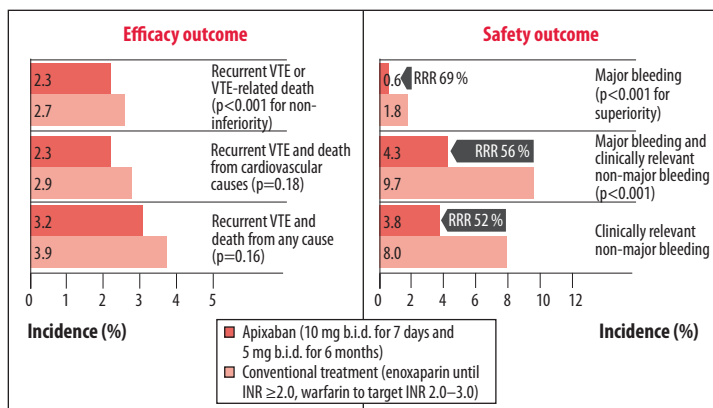
5395 patients ≥ 18 years of age with objectively confirmed, symptomatic proximal deep-vein thrombosis or pulmonary embolism (with or without deep-vein thrombosis). 5244 patients were included in the efficacy analysis and 5365 patients were included in the safety analysis

Results

Efficacy outcome: The primary efficacy endpoint of recurrent VTE or death related to VTE occurred in 59 of 2609 patients (2.3%) in the apixaban group and in 71 of 2635 (2.7%) in the conventional-therapy group ($p < 0.001$ for non-inferiority; relative risk reduction 16%). The efficacy of apixaban in the patients with pulmonary embolism was similar to that in the patients with

deep-vein thrombosis (primary efficacy outcome in 2.3% vs. 2.6% with conventional therapy and in 2.2% vs. 2.7% with conventional therapy, respectively)

Safety outcome: Major bleeding was observed in 0.6% (15 of 2676) of patients who received apixaban and in 1.8% (49 of 2689) of those who received conventional therapy ($p < 0.001$ for superiority; relative risk reduction 69%). The composite outcome of major bleeding and clinically relevant non-major bleeding occurred in 4.3% of the patients in the apixaban group, as compared with 9.7% of those in the conventional-therapy group ($p < 0.001$; relative risk reduction 56%). Rates of other adverse events were similar in the two groups



Summary

Efficacy: For the treatment of acute VTE, a fixed-dose regimen of apixaban alone was non-inferior to conventional treatment consisting of enoxaparin followed by warfarin

Safety: Treatment with apixaban was associated with significantly less major and clinically relevant non-major bleeding

Reference

Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369:799-808

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AMPLIFY-EXT

Apixaban after the initial Management of PuLmonary embolism and deep vein thrombosis with First-line therapY-EXTended treatment (2013)

Condition

Long-term VTE-prophylaxis after treatment of acute DVT and PE

Objective

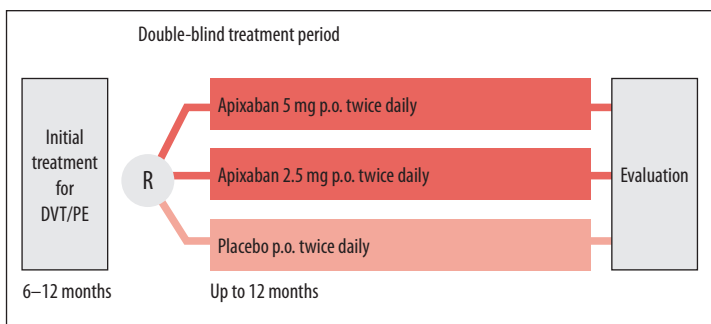
To evaluate the safety and efficacy of 2 different apixaban doses versus placebo during extended treatment following initial treatment of DVT or PE for 6–12 months

Trial design

Randomized, double-blind phase III study

Active treatment: apixaban 5 mg (n=840) or 2.5 mg (n=813) p.o. twice daily for up to 12 months

Control treatment: placebo twice daily for up to 12 months (n=829)



Endpoints

Primary efficacy endpoint: composite of VTE recurrence (fatal and non-fatal PE and DVT) or death from any cause

Primary safety endpoint: major bleeding

Secondary safety endpoint: composite of major or clinically relevant non-major bleeding

Trial participants

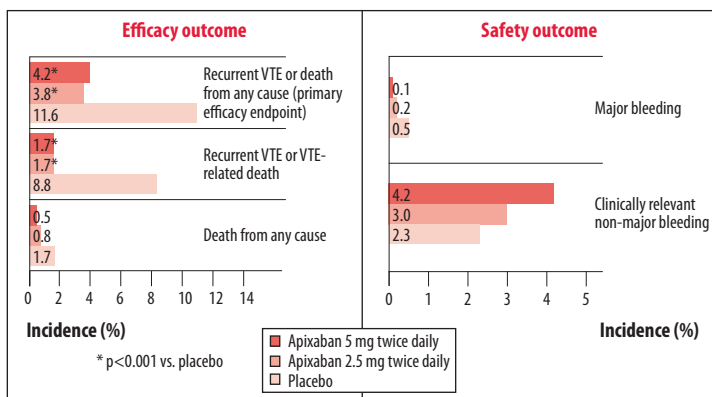
2486 patients with acute DVT or PE ≥ 18 years of age, who had completed 6–12 months of prior anticoagulant treatment (standard anticoagulant therapy or treatment with apixaban or enoxaparin and warfarin as participants in the AMPLIFY trial) with no symptomatic recurrence. 2482 patients were included in the intention-to-treat analyses

Results

Efficacy outcome: Symptomatic recurrent VTE or death from VTE occurred in 14 of the 840 patients (1.7%) treated with 2.5 mg of apixaban and in 14 of the 813 patients (1.7%) given 5 mg of apixaban as compared with 73 of the 829 patients (8.8%) who were receiving placebo. 52 patients were lost to follow-up (13 in the 2.5-mg apixaban group, 20 in the 5-mg apixaban group, and 19 in the placebo group). They were classified as having had a primary outcome event. Therefore 3.8% (32 of 840 patients) with 2.5 mg of apixaban, 4.2% (34 of 814) with 5 mg of apixaban and 11.6% (32 of 840) with placebo reached the primary efficacy endpoint. The rate of death from any cause was

1.7% in the placebo group, as compared with 0.8% in the 2.5-mg apixaban group and 0.5% in the 5-mg apixaban group

Safety outcome: Major bleeding was observed in 0.2% in the 2.5-mg apixaban group, in 0.1% in the 5-mg apixaban group, and in 0.5% in the placebo group. The rates of clinically relevant non-major bleeding were, 3.0% with 2.5 mg of apixaban, 4.2% with 5 mg of apixaban, and 2.3% with placebo



Summary

Efficacy: Extended anticoagulation with apixaban at either a treatment dose (5 mg) or a thromboprophylactic dose (2.5 mg) resulted in a large and significant reduction in the risk of recurrent fatal or non-fatal VTE

Safety: Both of the regimens of apixaban were safe. The rates of major bleeding in the apixaban groups were low and similar to those in the placebo group

Reference

Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Ras-kob GE, Weitz JI for the AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med* 2013;368:699-708

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APPRAISE-1

APIxaban for PRevention of Acute Ischemic and Safety Events 1 (2009)

Condition

Prevention of acute ischemic events in patients with ACS

Objectives

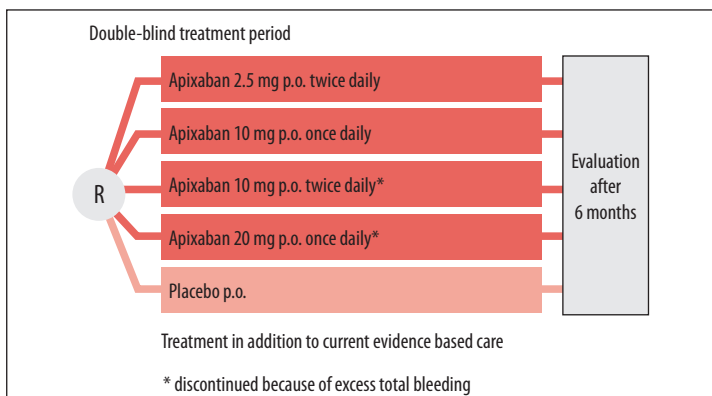
- (1) To evaluate the effect on bleeding of 4 doses of apixaban vs. placebo given over 26 weeks in patients with a recent ACS receiving current evidence based care (ASA \leq 165 mg/d in all patients, clopidogrel per MD discretion)
- (2) To determine the optimal dose of apixaban for further investigation

Trial design

Randomized, double-blind phase II study

Active treatment: apixaban 2.5 mg twice daily (n=317) or apixaban 10 mg once daily (n=318) or apixaban 10 mg twice daily (n=248) or apixaban 20 mg once daily (n=221) in addition to mono or dual antiplatelet therapy

Control treatment: placebo in addition to mono or dual antiplatelet therapy (n=611)



Endpoints

Primary endpoint (safety): major and/or clinically relevant non-major bleeding according to the ISTH definitions

Secondary endpoint (efficacy): composite of cardiovascular death, myocardial infarction, severe recurrent ischemia, or ischemic stroke

Trial participants

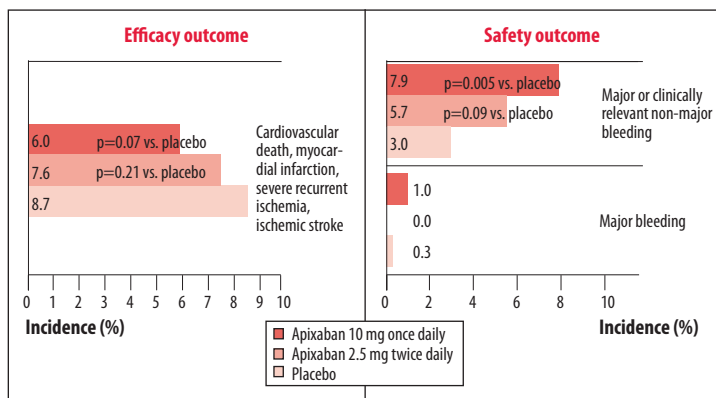
1715 patients between 18 and 90 years of age with a recent (<7 days) ST-elevation or non-ST-elevation ACS; clinically stable, receiving evidence based care, with \geq 1 additional risk factor for recurrent ischemic events and not scheduled for an invasive procedure

Results

Primary endpoint (safety): At the recommendation of the data monitoring committee, the two higher-dose apixaban arms (10 mg twice daily and 20 mg once daily) were discontinued because of excess total bleeding. 1229 patients (315 apixaban 2.5 mg twice daily, 315 apixaban 10 mg once daily, 599 placebo) were included in the safety analysis. 5.7% of patients receiving apixaban 2.5 mg twice daily, 7.9% in the apixaban 10 mg once daily arm

and 3.0% in the placebo group experienced an increase in major or clinically relevant non-major bleeding. When bleeding was stratified by clopidogrel status, the study drug was still associated with increased bleeding. Patients taking clopidogrel: 7.0% bleeding for apixaban 2.5 mg twice daily (n=230), 9.1% for apixaban 10 mg once daily (n=241), 3.1% for placebo (n=453); no clopidogrel: 2.4% bleeding for apixaban 2.5 mg twice daily (n=85), 4.1% for apixaban 10 mg once daily (n=74), and 2.7% for placebo (n=146)

Secondary endpoint (efficacy): 1246 patients (317 apixaban 2.5 mg twice daily, 318 apixaban 10 mg once daily, 611 placebo) were included in the efficacy analysis. There were no significant differences in the incidence of the efficacy endpoint of cardiovascular death, myocardial infarction, severe recurrent ischemia or ischemic stroke between the apixaban 2.5 mg twice daily group (7.6%), the apixaban 10 mg once daily group (6.0%), and the placebo group (8.7%). The reduction in ischemic events was less evident in patients taking ASA plus clopidogrel than in those taking ASA alone



Summary

Safety: Apixaban treatment was associated with a dose dependent increase in major or clinically relevant non-major bleeding

Efficacy: There was a trend in reduction of clinically important ischemic events (statistically non-significant)

Dosage range: A total daily dose of between 5 and 10 mg apixaban appears safe and effective in ACS patients

Reference

APPRAISE Steering Committee and Investigators. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome. Results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. *Circulation* 2009;119:2877-2885

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APPRAISE-2

APixaban for PRevention of Acute ISchemic Events 2 (2010)

Condition

Prevention of cardiovascular events after ACS

Objective

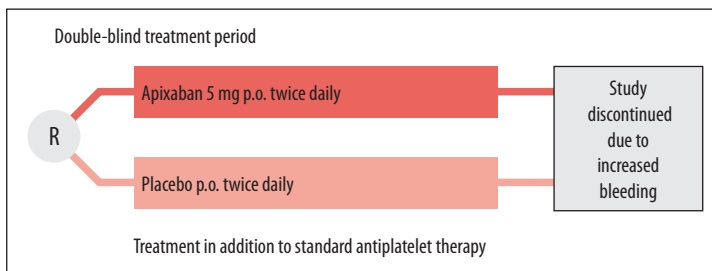
Determine if apixaban is superior to placebo for preventing cardiovascular death, non-fatal myocardial infarction or ischemic stroke in post-ACS patients

Trial design

Randomized, double-blind phase III study

Active treatment: apixaban 5 mg p.o. twice daily in addition to mono or dual antiplatelet therapy (either ASA or ASA plus clopidogrel). This dose was considered to be safe according to the results of the preceding APPRAISE-1 study

Control treatment: placebo in addition to mono or dual antiplatelet therapy



Endpoints

Primary efficacy endpoint: composite of cardiovascular death, myocardial infarction, or ischemic stroke

Primary safety endpoint: major bleeding, according to the Thrombolysis in Myocardial Infarction (TIMI) definition

Secondary endpoints: ischemic or hemorrhagic stroke, unstable angina, stent thrombosis, minor bleeding, fatal bleeding

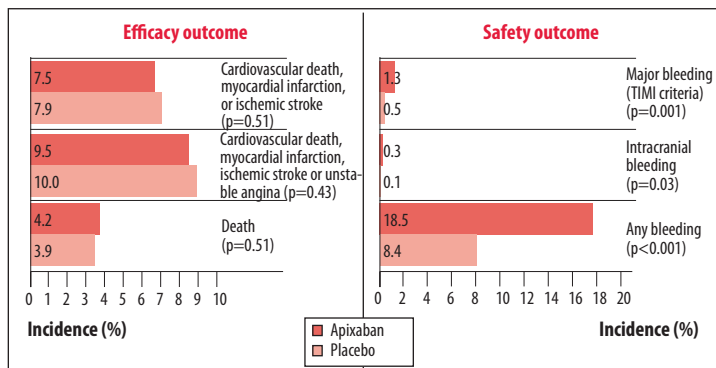
Trial participants

The study was designed to include approximately 10,800 patients ≥ 18 years with an acute coronary syndrome (myocardial infarction, with or without ST-segment elevation, or unstable angina) within the previous 7 days and with symptoms of myocardial ischemia and at least two additional risk factors for recurrent ischemic events (e.g. diabetes mellitus, PAD, age > 65 years). After recruitment of 7392 patients the trial was terminated prematurely because of an increase in major bleeding events with apixaban, which was not offset by clinically meaningful reductions in ischemic events

Results

Efficacy outcome: With a median follow-up of 241 days, the primary outcome occurred in 279 of the 3705 patients (7.5%) assigned to apixaban (13.2 events per 100 patient-years) and in 293 of the 3687 patients (7.9%) assigned to placebo (14.0 events per 100 patient-years) (hazard ratio with apixaban 0.95; $p=0.51$).

Safety outcome: In the on-treatment analysis, the primary safety outcome of major bleeding occurred in 46 of the 3673 patients (1.3%) who received at least one dose of apixaban (2.4 events per 100 patient-years) and in 18 of the 3642 patients (0.5%) who received at least one dose of placebo (0.9 events per 100 patient-years) (hazard ratio with apixaban 2.59; $p=0.001$). Among the patients receiving apixaban, as compared with those receiving placebo, there were more events of fatal bleeding (5 vs. 0), intracranial bleeding (12 vs. 3), ISTH major or clinically relevant non-major bleeding (117 vs. 45), and total bleeding (679 vs. 305)



Summary

The addition of the oral factor Xa inhibitor apixaban to standard antiplatelet therapy (ASA or ASA plus clopidogrel) in high-risk patients after an acute coronary syndrome resulted in a significant increase in bleeding events, including increases in events of fatal and intracranial bleeding, without a significant reduction in recurrent ischemic events

Reference

Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, Bhatt DL, Goodman S, Verheugt FW, Flather M, Huber K, Liaw D, Husted SE, Lopez-Sendon J, De Caterina R, Jansky P, Darius H, Vinereanu D, Cornel JH, Cools F, Atar D, Leiva-Pons JL, Keltai M, Ogawa H, Pais P, Parkhomenko A, Ruzyllo W, Diaz R, White H, Ruda M, Geraldes M, Lawrence J, Harrington RA, Wallentin L, for the APPRAISE-2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med* 2011;365:699-708

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APRICOT-2

Antithrombotics in the **P**revention of **R**eoocclusion In **CO**ronary Thrombolysis Trial (2002)

Condition

Prevention of reocclusion and recurrent ischemic events after fibrinolysis for STEMI

Objective

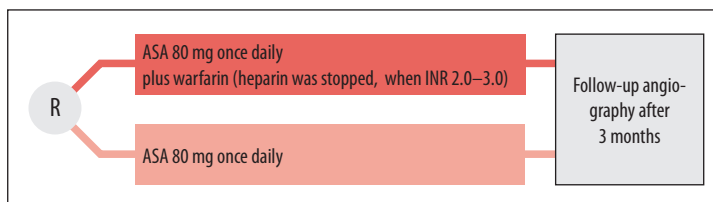
To assess the impact of a prolonged anticoagulation regimen as adjunctive to ASA in the prevention of reocclusion and recurrent ischemic events after fibrinolysis

Trial design

Randomized, open study

Active treatment: ASA 80 mg once daily plus moderate-intensity warfarin, including continued heparinization until a target INR of 2.0–3.0 (n=157)

Control treatment: ASA 80 mg once daily (standard heparinization was discontinued after 48 hours) (n=151)



Endpoints

Primary efficacy endpoint: reocclusion of the infarct-related artery at angiographic follow-up, defined as TIMI grade 2 flow or less

Secondary efficacy endpoint: event-free survival (a clinical course without death, reinfarction or revascularization)

Primary safety endpoint: TIMI major and minor bleeding

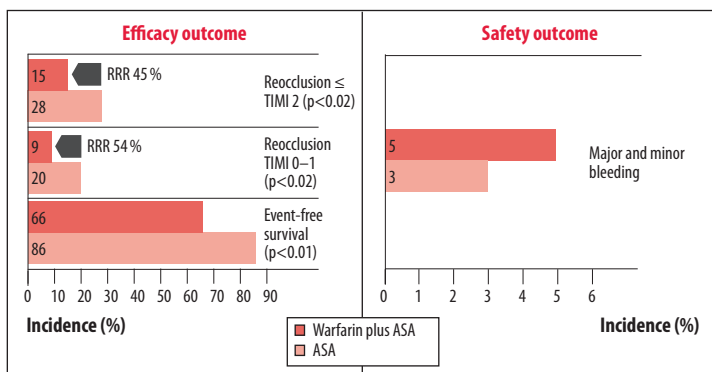
Trial participants

308 patients ≤75 years receiving ASA and i.v. heparin, who had a patent infarct-related artery (TIMI grade 3 flow) 48 hours after fibrinolytic therapy of STEMI

Results

Efficacy outcome: Reocclusion was observed in 19 of 123 patients (15%) receiving ASA and warfarin compared with 36 of 128 patients (28%) receiving ASA alone (relative risk reduction 45%). This was mainly due to a reduced incidence of TIMI grade 0–1 flow: 11 of 123 patients (9%) with ASA vs. 25 of 128 patients (20%) with ASA plus warfarin (relative risk reduction 54%). The event-free survival rate was significantly higher with combined treatment (86% vs. 66%)

Safety outcome: TIMI major and minor bleeding complications occurred in 7 patients (5%) in the combination treatment group (2 major, 5 minor) and in 4 (3%) in the ASA alone group (2 major, 2 minor). No cerebral bleeding was reported in either group



Summary

Efficacy: After successful fibrinolysis, a 3-month-regimen of moderate-intensity warfarin as adjunctive to ASA markedly reduced the reocclusion and recurrent events compared to ASA alone

Safety: Bleeding complications occurred infrequently; there was no significant difference between the two groups

Reference

Brouwer MA, van den Bergh PJ, Aengevaeren WRM, Veen G, Luijten HE, Hertzberger DP, van Boven AJ, Vromans RP, Uijen GJH, Verheugt FWA. Aspirin plus coumarin versus aspirin alone in the prevention of reocclusion after fibrinolysis for acute myocardial infarction. Results of the Antithrombotics in the Prevention of Reocclusion In COronary Thrombolysis (APRICOT)-2 Trial. *Circulation* 2002;106:659-665

Corresponding author

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ARISTOTLE

Apixaban for Reduction In STroke and Other ThromboemboLic Events in atrial fibrillation trial (2011)

Condition

Prevention of ischemic or hemorrhagic stroke in AF

Objective

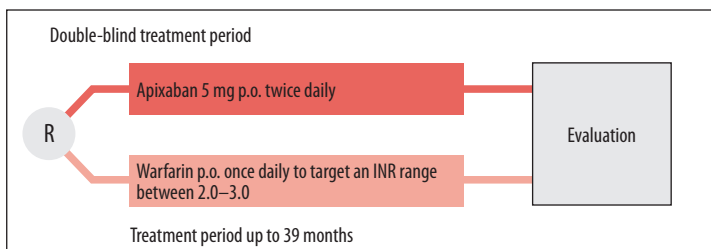
To evaluate the safety and efficacy of apixaban compared to warfarin in preventing stroke and systemic embolism in patients with AF

Trial design

Randomized, double-blind phase III study

Active treatment: apixaban 5 mg p.o. twice daily for up to 39 months (minimum 12 months) (n=9120). Lower dose of apixaban (2.5 mg twice daily) was used in patients meeting two or more of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, serum creatinine level ≥ 1.5 mg/deciliter

Control treatment: warfarin (INR 2.0–3.0) for up to 39 months (n=9081)



Endpoints

Primary efficacy endpoint: confirmed stroke (ischemic, hemorrhagic, or of uncertain type) or systemic embolism

Secondary efficacy endpoints: death from any cause, rate of myocardial infarction

Primary safety endpoint: major bleeding, defined according to the ISTH criteria

Secondary safety endpoints: composite of major bleeding and clinically relevant non-major bleeding, any bleeding, other adverse events, and liver-function abnormalities

Trial participants

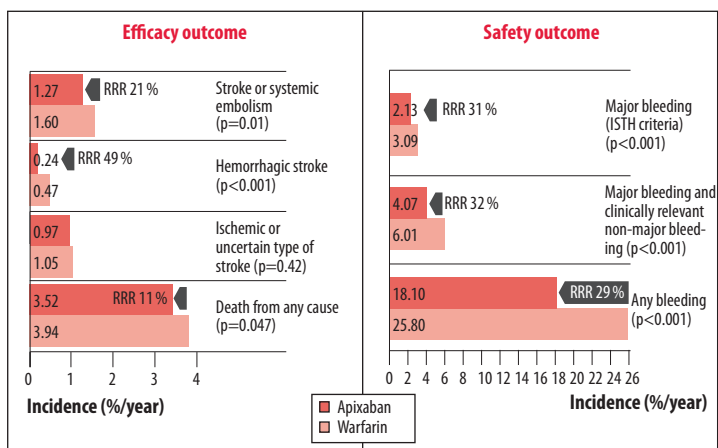
18,201 patients ≥ 18 years with AF and at least one additional risk factor for stroke

Results

Efficacy outcome: The median duration of follow-up was 1.8 years. The primary outcome of stroke or systemic embolism occurred in 212 of 9120 patients in the apixaban group (1.27% per year) as compared with 265 of 9081 patients in the warfarin group (1.60% per year) (RRR 21%; $p=0.01$). The rate of hemorrhagic stroke was 49% lower in patients assigned to apixaban than in those receiving warfarin (0.24 vs. 0.47% per year; $p<0.001$), and the rate of ischemic or uncertain type of stroke was 0.97% vs. 1.05%, but the difference was statistically not significant ($p=0.42$). Death from any cause occurred in 603 patients in the apixaban group and in 669 patients in the warfarin group (3.52 vs. 3.94% per year, RRR 11%; $p=0.047$). The rate of myocardial infarction

was lower in the apixaban group than in the warfarin group, but the difference was not significant (0.53 vs. 0.61% per year; $p=0.37$)

Safety outcome: Major bleeding, as defined according to ISTH criteria, was recorded in 327 patients on apixaban (2.13% per year), as compared with 462 patients on warfarin (3.09% per year) (RRR 31%; $p<0.001$). The secondary safety outcome measure (composite of major bleeding and clinically relevant non-major bleeding) occurred in 613 patients receiving apixaban and in 877 patients receiving warfarin (4.07 vs. 6.01% per year; RRR 32%; $p<0.001$). The rate of intracranial hemorrhage was 0.33% per year in the apixaban group and 0.80% per year in the warfarin group (RRR 68%, $p<0.001$), and the rate of any bleeding was 18.10% per year in the apixaban group and 25.80% per year in the warfarin group (RRR 29%; $p<0.001$). A reduced dose of apixaban (2.5 mg twice daily) was administered in 4.7% of the patients in the apixaban group



Summary

In patients with atrial fibrillation and at least one additional risk factor for stroke, the direct oral factor Xa inhibitor apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality: Apixaban reduced the risk of stroke or systemic embolism by 21%, major bleeding by 31%, and death of any cause by 11%

References

Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L, for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in the patients with atrial fibrillation. *N Engl J Med* 2011;365:981-992

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ASPECT-2

Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (2002)

Condition

Prevention of reocclusion and recurrent ischemic events after acute coronary syndromes

Objective

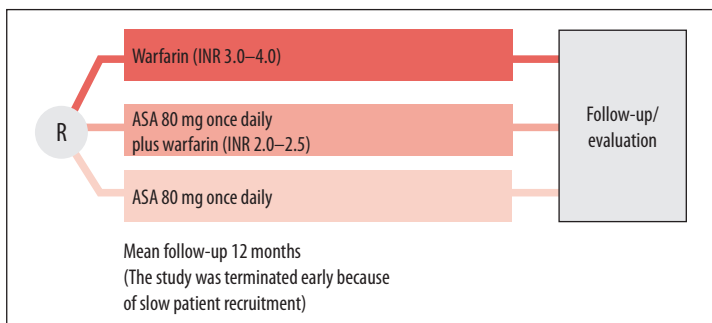
To assess the effect of high-intensity anticoagulation and ASA plus moderate-intensity anticoagulation, compared to ASA alone in patients with an acute coronary event

Trial design

Randomized, controlled open-label study

Active treatment: warfarin (INR 3.0–4.0) (n=330), or low-dose ASA (80 mg once daily) plus warfarin (INR 2.0–2.5) (n=333)

Control treatment: ASA 80 mg once daily (n=336)



Endpoints

Primary efficacy endpoint: composite of death, myocardial infarction, or stroke

Secondary efficacy endpoint: death from all causes (vascular death, myocardial infarction, unstable angina, cardiac interventions, and stroke)

Safety endpoints: major and minor bleeding

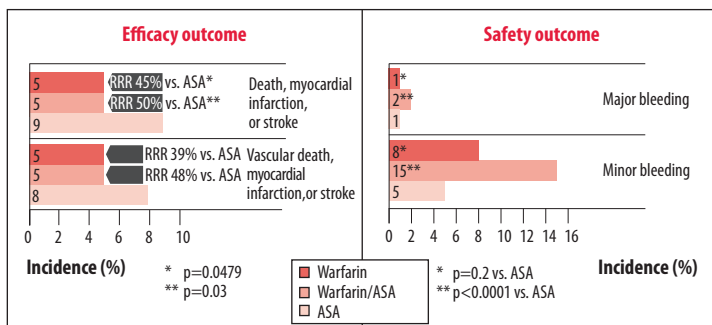
Trial participants

999 patients (mean age 61 years) admitted with acute myocardial infarction or unstable angina within the preceding 8 weeks

Results

Efficacy outcome: The primary endpoint was reached in 31 of 336 patients (9%) on ASA, in 17 of 325 patients (5%) on warfarin, and in 16 of 332 patients (5%) on ASA plus warfarin

Safety outcome: Major bleeding was recorded in 3 patients (1%) on ASA, 3 patients (1%) on warfarin, and 7 patients (2%) on ASA plus warfarin. The frequency of minor bleeding was 5%, 8% and 15%, respectively



Summary

Efficacy: In patients recently admitted with acute coronary syndromes, treatment with high-intensity warfarin or ASA plus moderate-intensity warfarin was more effective than ASA alone in the reduction of recurrent cardiovascular events and death

Safety: Treatment with ASA plus warfarin was associated with an insignificant two-fold increase in major bleeding and a significant three-fold increase in minor bleeding

Reference

Van Es RF, Jonker JJC, Verheugt FWA, Deckers JW, Grobbee DE, for the ASPECT-2 Research Group. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. *Lancet* 2002;360:109-113

Corresponding author

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ATLAS ACS-TIMI 46

Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects with Acute Coronary Syndrome – Thrombolysis in Myocardial Infarction 46 Trial (2009)

Condition

Antithrombotic therapy in patients with recent ACS

Objective

Primary goal: to assess the safety and efficacy of rivaroxaban in patients after an ACS and to select the most favorable dose and dosing regimen for a phase III trial

Secondary goal: to explore efficacy of rivaroxaban at tolerable doses

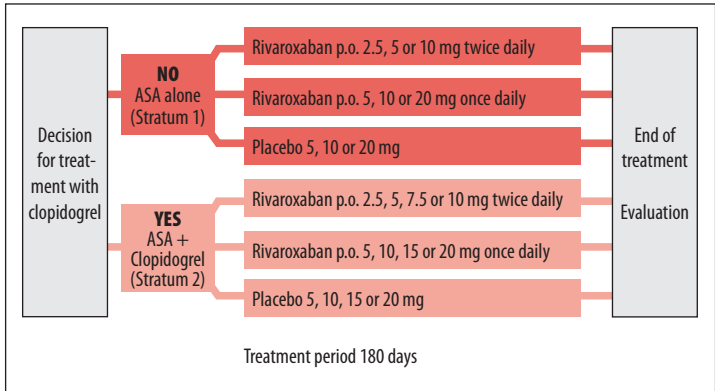
Trial design

Phase II dose ranging study

Active treatment:

- Stratum 1 (patients receiving ASA alone; n=761): rivaroxaban in doses of 5, 10 and 20 mg p.o. once daily (n=254), or 2.5, 5 and 10 mg twice daily (n=254) for 6 months
- Stratum 2 (patients receiving ASA plus clopidogrel; n=2730): rivaroxaban in doses of 5, 10, 15 and 20 mg p.o. once daily (n=912), or 2.5, 5, 7.5 and 10 mg twice daily (n=911) for 6 months

Control treatment: placebo for 6 months (stratum 1: n=253, stratum 2: n=907)



Endpoints

Primary safety endpoint: clinically significant bleeding (major, minor bleeding and bleeding requiring medical attention)

Secondary safety endpoints: adverse events, abnormal laboratory parameters

Primary efficacy endpoint: composite of death, myocardial infarction, stroke or severe recurring ischemia requiring revascularization

Secondary efficacy endpoint: composite of death, myocardial infarction, stroke

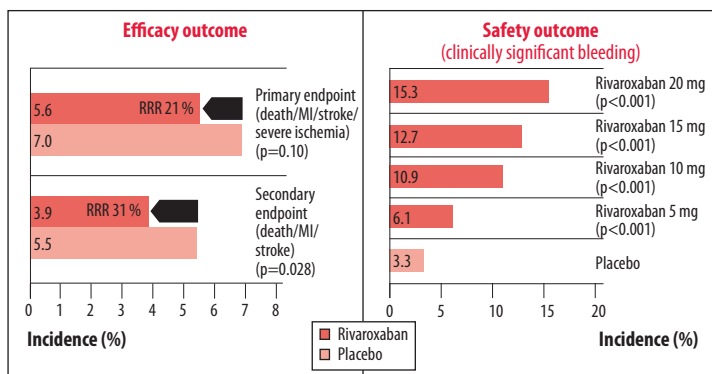
Trial participants

3491 patients with recent ACS in stabilized condition, 1–7 days post index event

Results

Safety outcome: Clinically significant bleeding up to 6 months occurred in 6.1% of the patients receiving a total daily dose of 5 mg rivaroxaban, 10.9% receiving 10 mg, 12.7% receiving 15 mg and 15.3% receiving 20 mg, compared to 3.3% in the placebo group. Bleeding events were more frequent in stratum 2. There were no significant differences in liver function abnormalities

Efficacy outcome: The primary efficacy endpoint occurred in 5.6% of all patients given rivaroxaban (n=2331) and in 7.0% of all patients given placebo (n=1160). The secondary efficacy endpoint occurred in 3.9% of the rivaroxaban and in 5.5% of the placebo patients



Summary

Safety:

- Most bleeding was bleeding requiring medical attention
- Increased bleeding rates were observed with higher doses of rivaroxaban
- Twice daily dosing appeared slightly safer
- No evidence of drug induced liver injury

Efficacy:

- Rivaroxaban numerically reduced the risk of death, myocardial infarction, stroke or severe recurrent ischemia (primary endpoint)
- Rivaroxaban significantly reduced the risk of death, myocardial infarction or stroke (secondary endpoint)
- Twice daily dosing appeared slightly more efficacious

Dosage: Two low doses, 2.5 mg twice daily and 5 mg once daily, have been selected for the phase III trial

Reference

Mega JL, Braunwald E, Mohanavelu S, Burton P, Poulter R, Misselwitz F, Hricak V, Barnathan ES, Bordes P, Witkowski A, Markov V, Oppenheimer L, Gibson CM; ATLAS ACS-TIMI 46 Study Group. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. *Lancet* 2009;374:29-38

Corresponding author

TIMI Study Group, Boston, MA, USA. jmega@partners.org

ATLAS ACS 2-TIMI 51

Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects with Acute Coronary Syndrome 2 – Thrombolysis in Myocardial Infarction 51 Trial (2011)

Condition

Prevention of ACS in patients who are treated with ASA and a thienopyridine, given at their physician's discretion

Objective

To investigate, if rivaroxaban, when added to standard care, is safe and reduces the risk of the composite of cardiovascular death, myocardial infarction, or stroke in patients with ACS compared to placebo

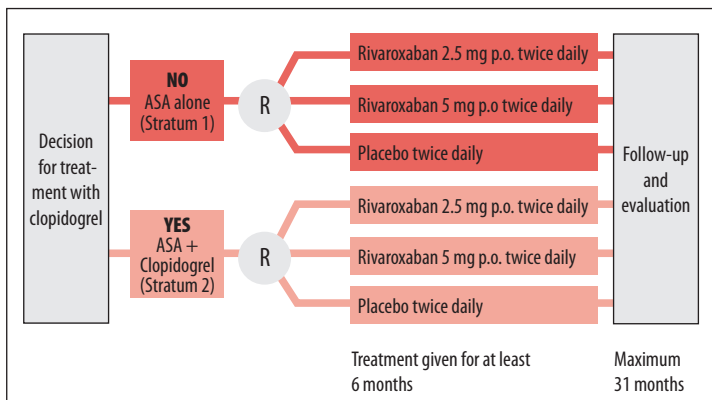
Trial design

Randomized placebo-controlled event-driven phase III study, comparing two doses of rivaroxaban with placebo in a 1:1:1 fashion

Active treatment:

- Stratum 1 (patients receiving ASA alone): rivaroxaban 2.5 or 5 mg p.o. twice daily for at least 6 months
- Stratum 2 (patients receiving ASA plus clopidogrel): rivaroxaban 2.5 or 5 mg p.o. twice daily for at least 6 months

Control treatment: stratum 1 and stratum 2: placebo for at least 6 months



Endpoints

Primary efficacy endpoint: composite of death from cardiovascular causes, myocardial infarction, or stroke (ischemic, hemorrhagic, or stroke of uncertain cause)

Secondary efficacy endpoint: death from any cause, myocardial infarction, or stroke

Primary safety endpoint: TIMI major bleeding events not associated with CABG surgery

Secondary safety endpoints: other bleeding events, serious adverse events

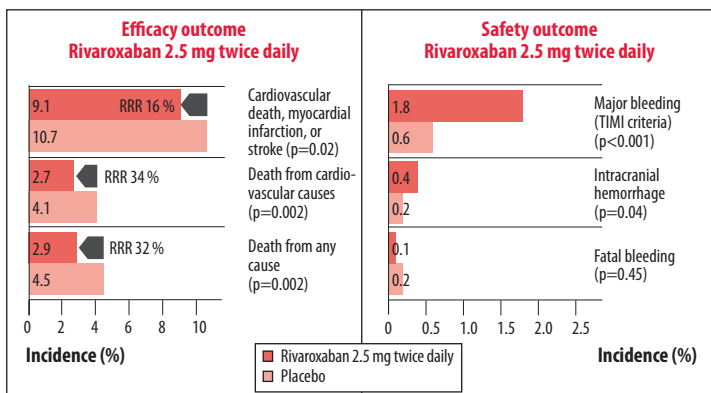
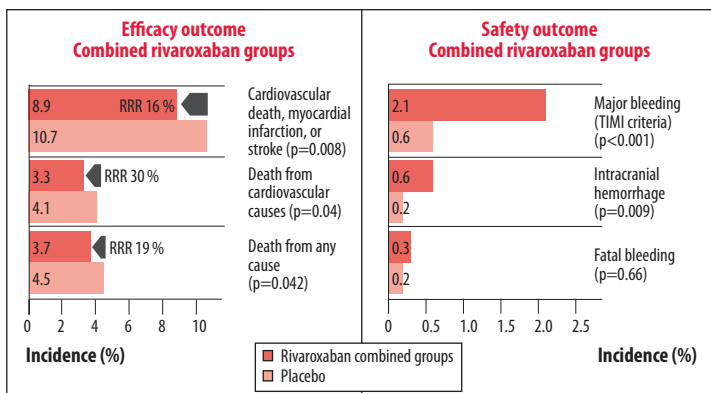
Trial participants

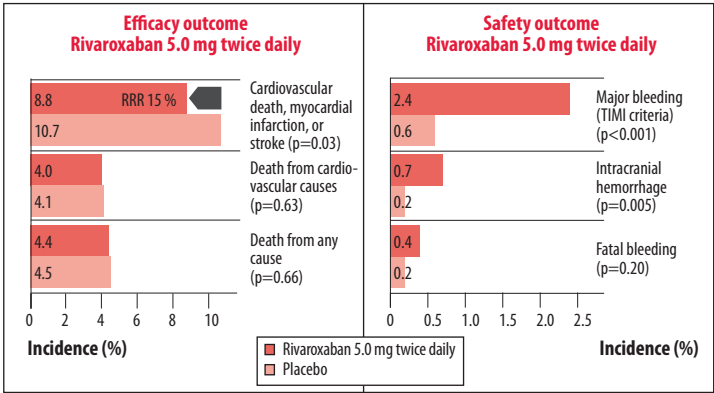
15,526 patients ≥18 years of age with recent ACS in stabilized condition were included 1–7 days post index event. 5174 of the patients were randomly assigned to receive the 2.5-mg dose of rivaroxaban, 5176 to receive the 5-mg dose of rivaroxaban, and 5176 to receive placebo

Results

Efficacy outcome: The primary efficacy endpoint occurred in 8.9% of all patients treated with rivaroxaban (n=10,229) and in 10.7% of all patients assigned to receive placebo (n=5113) (RRR 16% for the combined rivaroxaban groups; $p=0.008$). Each of the doses reduced the risk of cardiovascular death, myocardial infarction, or stroke, as compared with placebo, with rates in patients receiving the 2.5-mg dose of 9.1% vs. 10.7% (RRR 16%; $p=0.02$) and rates in patients receiving the 5-mg dose of 8.8% vs. 10.7% (RRR 15%; $p=0.03$). The twice-daily 2.5-mg dose of rivaroxaban reduced the rates of death from cardiovascular causes (2.7% vs. 4.1%, $p=0.002$) and from any cause (2.9% vs. 4.5%, $p=0.002$). This survival benefit was not seen with the twice-daily 5-mg dose

Safety outcome: Rivaroxaban increased the rates of major bleeding not related to CABG (2.1% vs. 0.6%; $p<0.001$) and intracranial hemorrhage (0.6% vs. 0.2%, $p=0.009$), without a significant increase in fatal bleeding (0.3% vs. 0.2%, $p=0.66$), a finding that was also significant for the 2.5-mg and 5-mg doses of rivaroxaban ($p<0.001$ for both comparisons). The twice-daily 2.5-mg dose resulted in fewer fatal bleeding events than the twice-daily 5-mg dose (0.1% vs. 0.4%, $p=0.04$). The rates of adverse events that were not related to bleeding were similar in the rivaroxaban and placebo groups





Summary

Efficacy outcome: Added to standard medical treatment, both doses of the oral factor Xa inhibitor rivaroxaban reduced the risk of the composite end point of death from cardiovascular causes, myocardial infarction, or stroke in patients with a recent acute coronary syndrome, as compared with placebo

Safety outcome: The overall results showed a threefold increase in major bleeding and intracranial hemorrhage but no significant increase in fatal bleeding with rivaroxaban. The 2.5-mg twice-daily dose had the better benefit/risk balance, due to a lower bleeding risk than the 5-mg twice-daily dose

References

(1) Gibson CM, Mega JL, Burton P, Goto, S, Verheugt F, Bode C, Plotnikov A, Sun X, Cook-Bruns N, Braunwald E. Rationale and design of the anti-Xa therapy to lower cardiovascular events in addition to standard therapy in subjects with acute coronary syndrome –Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2-TIMI 51) trial: a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of rivaroxaban in subjects with acute coronary syndrome. *Am Heart J* 2011;161:815-821

(2) Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM, for the ATLAS ACS 2-TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;366:9-19

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AVERROES

Apixaban **VER**sus acetylsalicylic acid [ASA] to prevent **StRO**ke in atrial fibrillation **PatiEntS** who have failed or are unsuitable for vitamin K antagonist treatment (2011)

Condition

Prevention of ischemic or hemorrhagic stroke in AF

Objective

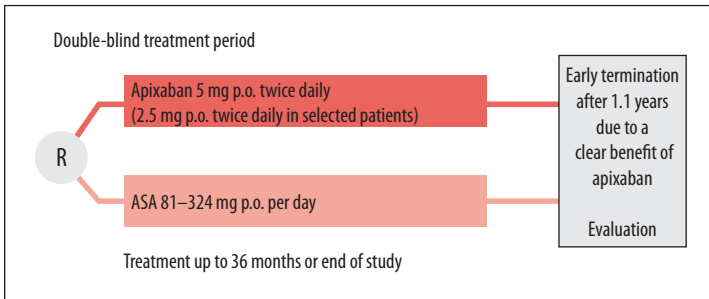
To evaluate the safety and efficacy of apixaban versus acetylsalicylic acid (ASA) in preventing strokes in subjects with AF and at least one additional stroke risk factor, who are not suitable for vitamin K antagonist treatment

Trial design

Randomized, double-blind phase III study

Active treatment: apixaban 5 mg p.o. twice daily for up to 36 months or end of study (n=2808)

Control treatment: ASA (81–324 mg once daily) for up to 36 months or end of study (n=2791)



Endpoints

Primary efficacy endpoint: time (days) from first dose of study drug to first occurrence of unrefuted ischemic stroke, hemorrhagic stroke or systemic embolism

Primary safety endpoint: occurrence of major bleeding

Other outcome measures: occurrence of myocardial infarction, death from vascular causes, and death from any cause, as well as of composites of major vascular events

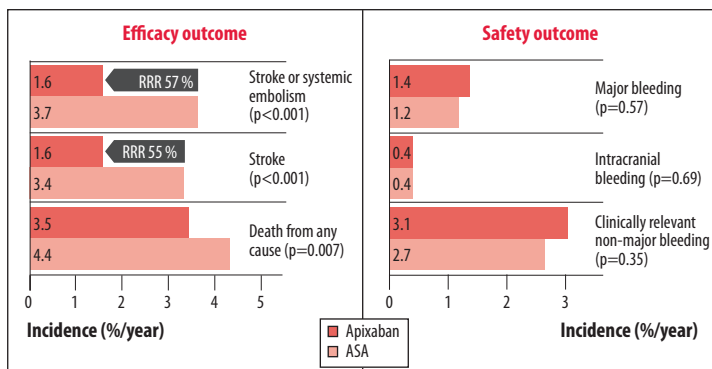
Trial participants

5599 patients ≥ 50 years of age with atrial fibrillation and increased risk for stroke (presence of at least one risk factor), who are not suitable for vitamin K antagonist therapy

Results

Efficacy outcome: The data and safety monitoring board recommended early termination of the study because of a clear treatment benefit in favor of apixaban for the primary outcome that exceeded 4 SD. After a mean duration of follow-up of 1.1 years there were 51 primary outcome events (1.6% per year) in patients assigned to apixaban (n=2808) and 113 (3.7% per year) in patients assigned to ASA (n=2791) (absolute risk reduction with apixaban 2.1%, relative risk reduction 55%; $p < 0.001$)

Safety outcome: There were 44 major bleeding events (1.4% per year) among patients taking apixaban and 39 (1.2% per year) among those taking ASA ($p=0.57$). Significantly fewer patients in the apixaban group than in the ASA group had a serious adverse event (22% vs. 27%, $p<0.001$)



Summary

Efficacy: Oral apixaban was superior to aspirin in preventing

- Stroke or systemic embolism
- Stroke, systemic embolism or death
- Stroke, systemic embolism, myocardial infarction, death from vascular cause, or major bleeding event
- Stroke
- Systemic embolism
- Hospitalization for cardiovascular cause

Safety:

- No difference in major, intracranial, clinically relevant non-major and minor bleeding
- Significantly less severe adverse events in the apixaban group

Reference

Connolly SJ, Eikelboom J, Campbell Joyner BS, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Mieghem W, Lip GYH, Kim JH, Lanus-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, O'Donnell M, Lawrence J, Lewis G, Afzal R, Yusuf S, for the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;364:806-817

Corresponding author

Dr. Stuart J. Connolly, Population Health Research Institute, 237 Barton St. E., Hamilton, ON L8L 2X2, Canada, e-mail: stuart.connolly@phri.ca

BAATAF

Boston Area Anticoagulation Trial for Atrial Fibrillation (1990)

Condition

Prevention of stroke in chronic non-valvular AF

Objective

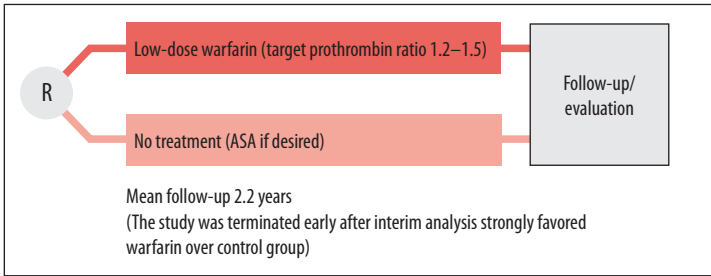
To assess the efficacy of low-dose warfarin for primary stroke prevention in patients with AF

Trial design

Randomized, unblinded, controlled phase III study

Active treatment: low-dose warfarin (target range for the prothrombin-time ratio: 1.2–1.5 times the control; estimated INR equivalent 1.5–2.7) (n=212)

Control treatment: no treatment (n=208); ASA allowed, but not in the warfarin group



Endpoints

Primary endpoint: ischemic stroke

Secondary endpoint: systemic emboli, major and minor bleeding, death

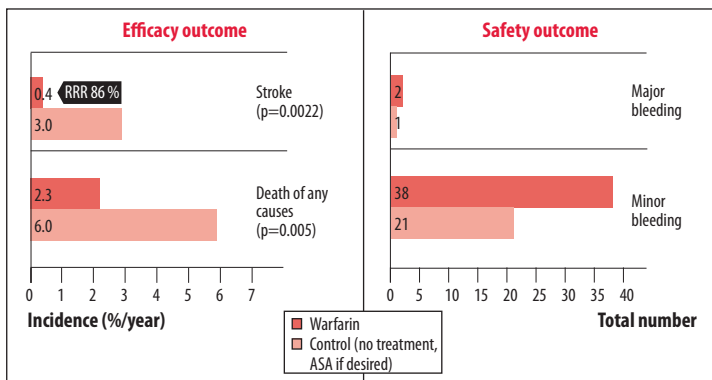
Trial participants

420 patients (mean age 68 years), with chronic, sustained or intermittent non-valvular AF with no evidence of mitral stenosis on two-dimensional echocardiography

Results

Efficacy outcome: There were 2 ischemic strokes with warfarin (487 patient-years of observation; incidence 0.5% per year) as compared with 13 ischemic strokes in the control group (435 patient-years; incidence 3.0% per year) which corresponds to an 86% reduction in risk of stroke in the warfarin group. The overall death rate was markedly lower in the patients receiving warfarin than in the controls (2.2% vs. 6.0%)

Safety outcome: Major bleeding occurred in 2 patients of the warfarin group and in 1 patient of the control group. The rate of minor hemorrhage was higher with warfarin than in the controls (38 vs. 21 patients). The frequency of bleeding events that led to hospitalization or transfusion was essentially the same in both groups



Summary

Efficacy: Low-dose warfarin is highly effective in preventing stroke in patients with AF. The risk reduction as compared to untreated controls (ASA allowed) was 86%

Safety: With careful monitoring the long-term low-dose warfarin therapy is safe. The total mortality rate was lower as compared to the control group

Reference

The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with non-rheumatic atrial fibrillation. *N Engl J Med* 1990;323:1505-1511

Corresponding author

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BAFTA

Birmingham Atrial Fibrillation Treatment of the Aged (2007)

Condition

Prevention of stroke in elderly patients with AF

Objective

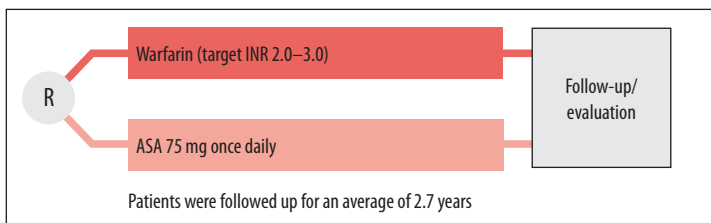
To assess whether warfarin reduces the risk of major stroke, arterial embolism, or other intracranial hemorrhage compared with ASA in patients aged ≥ 75 years

Trial design

Randomized, controlled phase III study

Active treatment: warfarin to target INR 2.0–3.0 (n=488)

Control treatment: ASA 75 mg once daily (n=485)



Endpoints

Primary endpoint: composite of fatal or disabling stroke (ischemic or hemorrhagic), intracranial hemorrhage, and clinically significant arterial embolism

Secondary endpoints: composite of all major hemorrhages (intracranial and fatal bleeding, or one that resulted in the need for transfusion or surgery), all-cause mortality, other vascular mortality, or non-vascular deaths

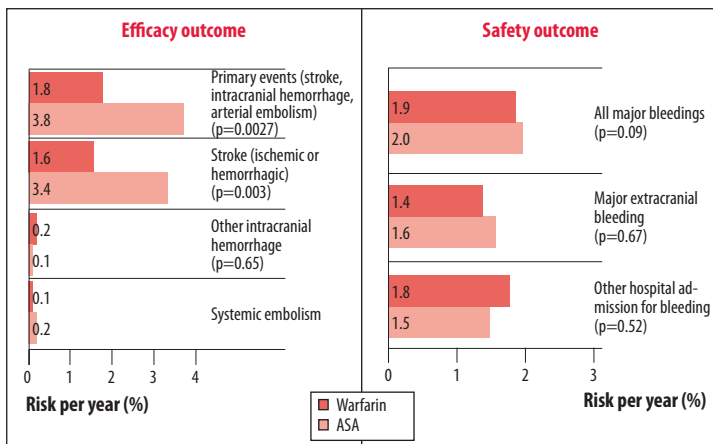
Trial participants

973 patients aged ≥ 75 years (mean age 81.5 ± 4.2 years) with AF, recruited from primary-care settings

Results

Efficacy outcome: There were 24 primary events (21 strokes, 2 other intracranial hemorrhages, and 1 systemic embolus) in patients assigned to warfarin and 48 primary events (44 strokes, 1 other intracranial hemorrhage, and 3 systemic emboli) in those assigned to ASA. The corresponding yearly risk was 1.8% vs. 3.8%. No differences were seen in secondary outcomes, including all-cause mortality, other vascular mortality, and non-vascular deaths

Safety outcome: The yearly risk of extracranial hemorrhage was 1.4% with warfarin and 1.6% with ASA. There was no difference between the composite of all major hemorrhages. Risks of bleeding rose by similar amounts with age in both groups



Summary

Efficacy: Anticoagulation with warfarin was superior to ASA for primary stroke prevention in elderly patients with AF. Warfarin was as effective in people aged ≥ 85 years as it was in younger people. There were no differences in vascular events, all-cause mortality, other vascular mortality, and non-vascular deaths between the groups

Safety: No difference was seen in the risk for hemorrhage between the groups. Even in the highest age groups there was no increased bleeding risk with age

Reference

Mant J, Hobbs FDR, Fletcher K, Roalfe A, Fitzmaurice D, Lip GYH, Murray E, on behalf of the BAFTA investigators and the Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007;370:493-503

Corresponding author

Jonathan Mant, MD, Primary Care Clinical Sciences Building, University of Birmingham, Birmingham B15 2TT, UK, e-mail: j.w.mant@bham.ac.uk

BARRITT

Anticoagulant drugs in the treatment of pulmonary embolism (1960)

Condition

Treatment of PE and prophylaxis for recurrence

Objective

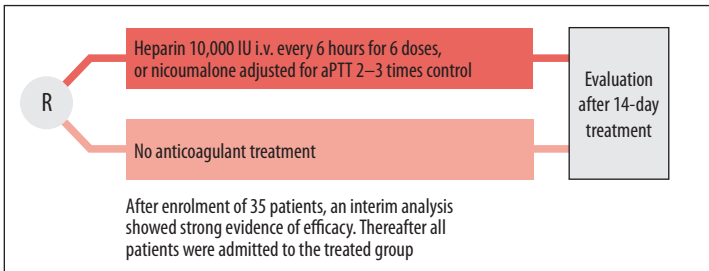
To measure the effect of anticoagulant treatment in patients with PE, both on the course of the first embolism and on the risk of further attacks

Trial design

Open study with parallel groups; a non protected interim analysis was performed after the first 35 cases

Active treatment: heparin 10,000 IU i.v. every 6 hours for 6 doses without laboratory control, or nicoumalone (= acenocoumarol) 16 mg, followed at 12-hourly intervals by 8, 8, and 4 mg adjusted for prothrombin time between 2–3 times control (n=16 before interim analysis + 38 after interim analysis)

Control treatment: no anticoagulant treatment (n=19 before and after interim analysis)



Endpoints

Primary efficacy endpoint: death from PE

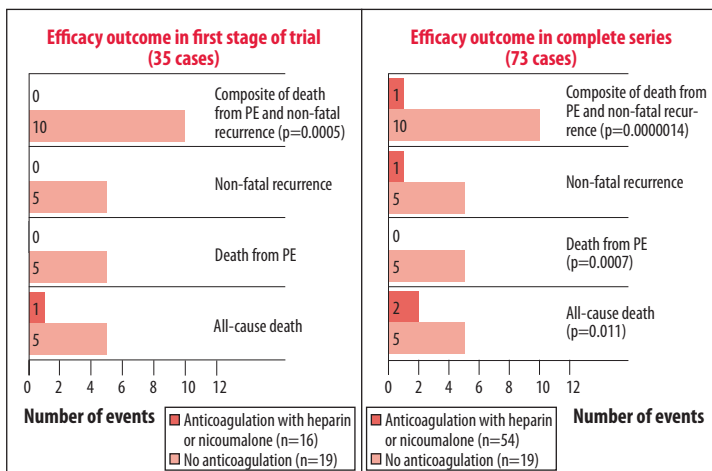
Secondary endpoints: non-fatal recurrence, other deaths

Trial participants

73 patients with PE (documented acute right heart failure or pulmonary infarction or both) and no contraindication to anticoagulant therapy

Results

Efficacy outcome: After enrollment of 35 patients, an interim analysis showed that the difference in the 2 groups was unlikely to be due to chance. Of the 19 untreated patients 5 had died from PE and 5 others had non-fatal recurrences of PE, as compared with no death from PE and no recurrence in the treated group (p=0.0005). Thereafter all patients were admitted to the treated group. At the end of the study, in the treated group no patient has died from PE, and only 1 patient had a non-fatal recurrence. The 2 deaths in the treated group were due to other causes than PE



Summary

In patients with PE, treatment with heparin or nicoumalone significantly reduced the risk of mortality. The likelihood of recurrent embolism was also diminished significantly

Reference

Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. *Lancet* 1960;1:1309-1312

Corresponding author

D. W. Barritt, MD, Departments of Medicine and Cardiology, United Bristol Hospitals, Bristol, England

BASU

Monitoring heparin treatment with the activated partial thromboplastin time (1972)

Condition

Treatment of VTE with heparin

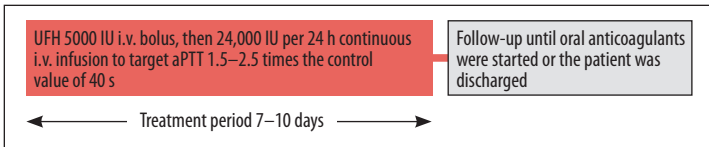
Objective

To seek a relation between the aPTT and recurrent VTE or bleeding during heparin treatment

Trial design

Prospective, open study

Active treatment: All patients (n=234) received an initial i.v. bolus of 5000 IU heparin, followed by a maintenance dose of 24,000 IU per 24 h given by continuous i.v. infusion and adjusted to keep the aPTT between 1.5 and 2.5 times the control level of 40 s all times. All patients were treated for 7–10 days



Endpoints

Primary endpoints in patients treated for venous embolism: recurrent symptomatic VTE and bleeding during heparin treatment

Primary endpoints in patients treated for other reasons: bleeding events

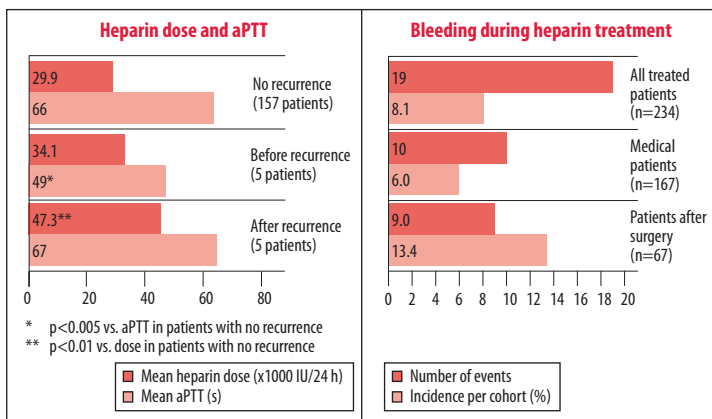
Trial participants

A total of 234 patients entered the study. 162 of these patients (mean age 54 years) were treated for venous thrombotic disease and the remaining 72 patients (mean age 57 years) for myocardial infarction or arterial thromboembolism, or to prevent venous thrombosis. 67 patients were treated after surgery

Results

Efficacy outcome: Only 5 of 162 patients (3%) developed a recurrence of VTE. These patients received a mean dose of 34,100 IU heparin per 24 h before recurrence and had a mean aPTT of 49 s. This amount compared with a mean dose of 29,900 IU and a mean aPTT of 66 s in the 157 patients without recurrence ($p < 0.005$ for aPTT). After recurrence, patients were treated with 47,300 IU heparin per 24 h ($p < 0.01$ vs. dose in patients without recurrence) and reached a mean aPTT of 67 s – a value similar to that of patients without recurrence. Further analysis showed that the time spent with an aPTT < 50 s provided the best discrimination between patients with and those without recurrence

Safety outcome: Bleeding occurred in 19 of all 234 heparin treated patients: in 9 of 67 postoperative patients (13.4%) and in 10 of 167 medical patients (6.0%). Their mean heparin dose and aPTT were similar to those of patients without bleeding complications



Summary

Efficacy: The results of the study suggest that patients with VTE should be given enough heparin to prolong the aPTT >1.5 times the control level, irrespective of the amount of heparin required to obtain that result

Safety: Even with an aPTT of 1.5–2.5, bleeding complications can not be avoided, especially in postoperative patients

Reference

Basu D, Gallus A, Hirsh J, Cade J. A prospective study of the value of monitoring heparin treatment with the activated partial thromboplastin time. *N Engl J Med* 1972;287:324-327

Corresponding author

Dilip Basu, MD, St. Joseph's Hospital, Hamilton, Ontario, Canada

BOREALIS-AF

Evaluation of weekly subcutaneous biotinylated idrabiotaparinux versus oral adjusted-dose warfarin to prevent stroke and systemic thromboembolic events in patients with atrial fibrillation (2011)

Condition

Prevention of stroke and systemic thromboembolic events in patients with AF

Objective

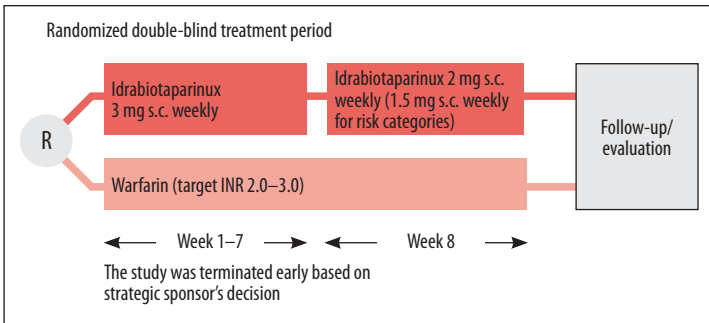
To compare the efficacy and safety of idrabiotaparinux with adjusted-dose warfarin in the prevention of stroke and systemic thromboembolic events in patients with AF

Trial design

Randomized, double-blind, assessor-blind, non-inferiority phase III trial

Active treatment: idrabiotaparinux 3 mg s.c. weekly for 7 weeks followed by 2 mg weekly or 1.5 mg for risk categories

Control treatment: warfarin (INR 2.0–3.0)



Endpoints

Primary efficacy endpoint: composite of all strokes or non-CNS systemic embolic events

Secondary endpoints: separate components of the primary study outcome; composite of stroke, non-CNS systemic embolic events, major bleeding, and death

Trial participants

Approximately 9600 patients with non-valvular AF indicating for long-term vitamin-K antagonist therapy based on the presence of previous ischemic stroke, transient ischemic attack or systemic embolism and/or at least two additional risk factors

Results

The trial was stopped early due to sponsor's decision not driven by any safety concern. There are no results available

Reference

ClinicalTrials.gov (NCT00580216)

BRANDJES

Acenocoumarol and heparin compared with acenocoumarol alone in VTE treatment (1992)

Condition

Initial treatment of proximal DVT

Objective

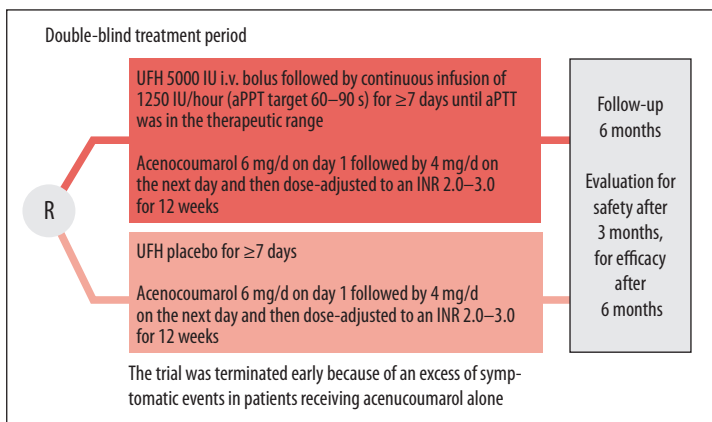
To compare the safety and efficacy of continuous i.v. heparin plus acenocoumarol with that of acenocoumarol alone in the initial treatment of proximal DVT

Trial design

Randomized, placebo-controlled, double-blind study

Active treatment: UFH 5000 IU i.v. bolus followed by continuous infusion of 1250 IU/hour (aPTT target 60–90 s) for at least 7 days until the aPTT was in the therapeutic range plus acenocoumarol 6 mg p.o. once daily on the first day followed by 4 mg p.o. once daily on the next day and then dose-adjusted to an INR 2.0–3.0 for 12 weeks (n=60)

Control treatment: UFH placebo plus acenocoumarol (same dosing as above) (n=60)



Endpoints

Primary efficacy endpoint: composite of documented symptomatic extension of VTE, symptomatic PE or VTE recurrence during a 6-months follow-up

Secondary efficacy endpoint: asymptomatic extension of VTE (calculated at the end of the first week)

Primary safety endpoint: major and minor bleeding during the first 3 months

Trial participants

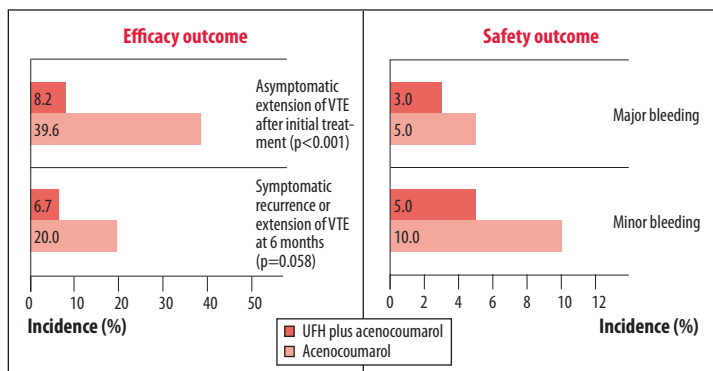
120 consecutive patients between 18 and 85 years of age with documented acute proximal venous thrombosis

Results

Efficacy outcome: During the 6-months study period, 4 of 60 patients (6.7%) receiving the combined strategy and 12 of 60 patients (20.0%) on acenocoumarol alone experienced a symptomatic extension or recurrence of VTE.

In the combination therapy group, 4 of 49 evaluable patients (8.2%) had asymptomatic worsening of VTE, as compared with 21 of 53 patients (39.6%) in the monotherapy group

Safety outcome: Major bleeding occurred in 2 patients (3%) in the combined treatment group compared to 3 patients (5%) in the monotherapy group



Summary

Efficacy: A combined treatment with UFH and an oral anticoagulant is superior to an anticoagulant monotherapy in preventing VTE extension or recurrence in patients with acute proximal DVT

Safety: Major bleeding complications were infrequent during anticoagulant treatment and comparable in both groups

Reference

Brandjes DPM, Heijboer H, Büller HR, De Rijk M, Jagt H, Ten Kate JW. Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal vein thrombosis. *New Engl J Med* 1992;327:1485-1489

Corresponding author

Dees P.M. Brandjes, MD, Department of Medicine, Slotervaart Ziekenhuis, Louwesweg 6, 1066 EC Amsterdam, the Netherlands

CAFA

Canadian Atrial Fibrillation Anticoagulation study (1991)

Condition

Prevention of stroke and systemic embolism in patients with non-valvular AF

Objective

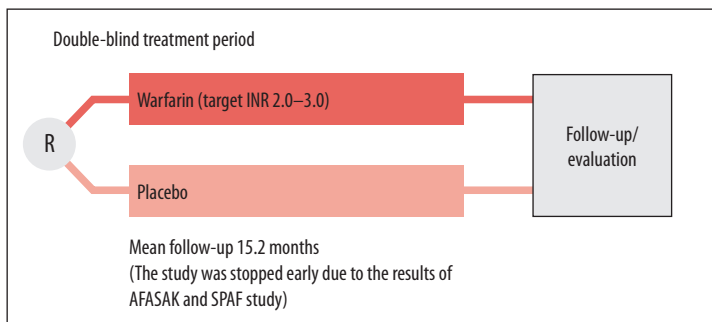
To assess the potential of warfarin to reduce systemic thromboembolism and its inherent risk of hemorrhage in patients with AF

Trial design

Randomized double-blind, placebo-controlled study

Active treatment: warfarin (INR 2.0–3.0) (n=187)

Control treatment: placebo (n=191)



Endpoints

Primary endpoint: composite of non-lacunar stroke, non-CNS systemic embolism, and fatal or intracranial hemorrhage

Secondary endpoints: TIA, lacunar infarction, major bleeding, minor bleeding, and death

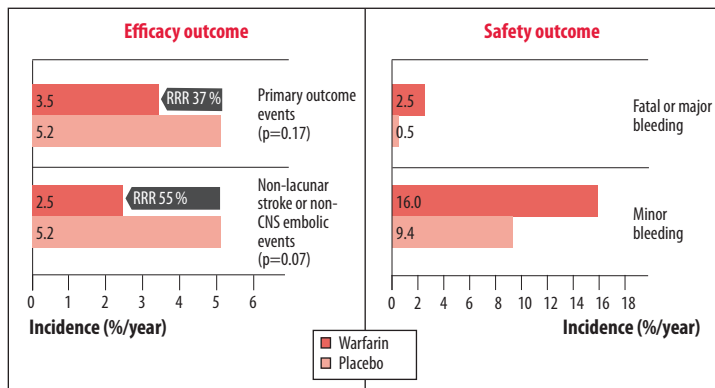
Trial participants

378 patients (planned 630) with AF; mean age 67.7 years

Results

Efficacy outcome: Primary outcome events occurred in 7 of 187 patients receiving warfarin and in 11 of 191 patients receiving placebo corresponding to an annual rate of 3.5% and 5.2%, respectively (relative risk reduction 37%). The annual rate of the event cluster non-lacunar stroke or non-CNS embolic events was 2.5% with warfarin and 5.2% with placebo, the resulting relative risk reduction 55%. Recruitment and follow-up were stopped early because two other similar studies had shown a decrease in the rate of stroke among patients treated with warfarin.

Safety outcome: Fatal or major bleeding occurred in 5 patients receiving warfarin and one patient receiving placebo. The corresponding annual rates were 2.5% in warfarin-treated and 0.5% in placebo-treated patients. Minor bleeding occurred in 16% of patients receiving warfarin and 9.4% receiving placebo



Summary

Efficacy: In AF-patients, anticoagulation with warfarin was superior to placebo in reducing non-lacunar stroke and non-CNS embolism

Safety: Major and minor bleedings were more common in the warfarin group

Reference

Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol* 1991;18:349-355

Corresponding author

Stuart J. Connolly, MD, Population Health Research Institute, McMaster University, 237 Barton Street East, Hamilton, ON L8L 2X2, Canada, e-mail: stuart.connolly@phri.ca

CARS

Coumadin Aspirin Reinfarction Study (1997)

Condition

Reduction of cardiovascular events following acute myocardial infarction

Objective

To investigate, whether a combination of low-dose warfarin and low-dose ASA would give superior results to standard ASA monotherapy without excessive bleeding risk

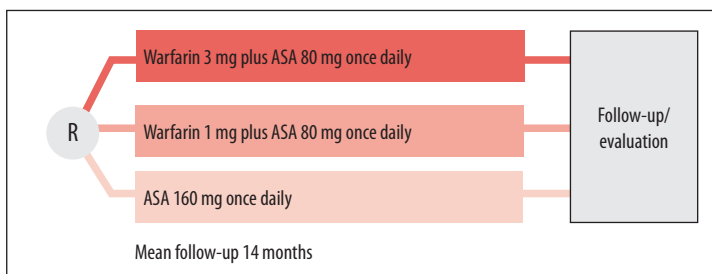
Trial design

Randomized, double-blind controlled study

Active treatment:

- warfarin 3 mg plus ASA 80 mg once daily (n=3382)
- warfarin 1 mg plus ASA 80 mg once daily (n=2028)

Control treatment: ASA 160 mg once daily (n=3393)



Endpoints

Primary efficacy endpoints: non-fatal myocardial reinfarction, non-fatal ischemic stroke and cardiovascular death

Secondary efficacy endpoints: all-cause mortality, silent myocardial infarction, unstable angina requiring admission to hospital, TIA and systemic (non-CNS) embolization

Primary safety endpoint: major hemorrhagic events

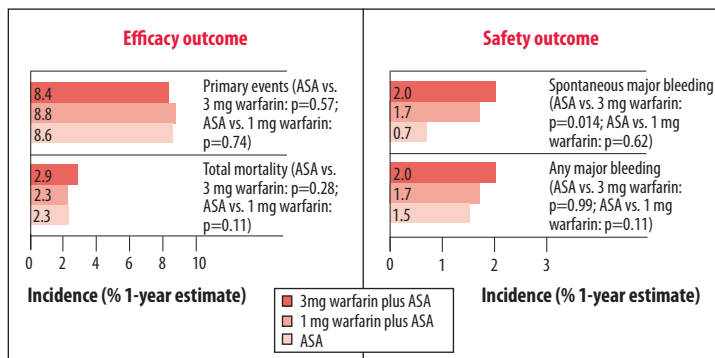
Trial participants

8803 patients between 21 and 85 years, enrolled 3–21 days after a recent myocardial infarction

Results

Primary outcome: A primary event occurred in 295 of 3382 patients (8.4% 1-year life-table estimate) in the 3 mg warfarin group, 237 of 2028 patients (estimate 8.8%) in the 1 mg warfarin group and in 308 of 3393 patients (estimate 8.6%) in the ASA monotherapy group

Safety outcome: For major (not procedure related) hemorrhage, 1-year life-table estimates were 1.4% for the 3 mg warfarin group (n=52), 1.0% in the 1 mg warfarin group (n=26) and 0.7% in the ASS monotherapy group (n=30)



Summary

Efficacy: In patients with recent myocardial infarction, low, fixed-dose warfarin (1 mg or 3 mg) combined with low-dose ASA (80 mg) does not provide a greater risk reduction of myocardial reinfarction, stroke and cardiovascular death than 160 mg ASA monotherapy

Safety: Spontaneous major hemorrhage (not procedure-related) occurred more frequently in the 3 mg warfarin/ASA group compared to ASA alone. There was no significant difference between 1 mg warfarin/ASA and ASA alone, and also among all groups concerning any major hemorrhage

Reference

Fuster V, Califf RM, Chesebro JH, Cohen M, Comp PC, Gheorghide M, Hall J, Halperin J, Khan S, Kopecky S, Langer A, Molk B, Moss A, O'Connor CM, O'Gara PT, Raskob E, Sutton J. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. *Lancet* 1997;350:389-396

Corresponding author

Valentin Fuster, MD, Mount Sinai Hospital, Box 1030, 1 Gustave Levy Place, New York, NY 10029, USA

CASSIOPEA

Clinical study Assessing SSR126517E Injections Once-weekly in Pulmonary Embolism therapeutic Approach (2010)

Condition

Treatment of acute pulmonary embolism (PE)

Objective

To assess the non-inferiority of idrabiotaparinux to warfarin in patients with acute symptomatic PE

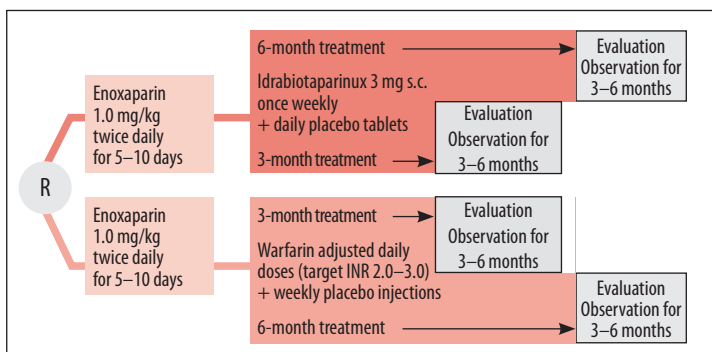
Trial design

Randomized, double-blind, double-dummy, non-inferiority phase III study

Active treatment: enoxaparin 1.0 mg/kg s.c. twice daily for 5–10 days followed by subcutaneous idrabiotaparinux 3.0 mg once weekly and placebo tablets (n=1599)

Control treatment: enoxaparin 1.0 mg/kg s.c. twice daily for 5–10 days followed by adjusted-dose warfarin (target INR 2.0–3.0) plus weekly placebo injections (n=1603)

Both regimens lasted 3 months or 6 months dependent on clinical presentation. 79% of the patients continued study therapy for 6 months (n=1269 in the enoxaparin-idrabiotaparinux group and n=1267 in the enoxaparin-warfarin group)



Endpoints

Primary efficacy endpoint: symptomatic recurrent VTE, defined as either recurrent PE or DVT within 99 days of randomization

Secondary efficacy endpoint: symptomatic recurrent VTE within 190 days in patients assigned to receive treatment for 6 months

Primary safety endpoint: clinically relevant bleeding (major or non-major) and death from all causes

Trial participants

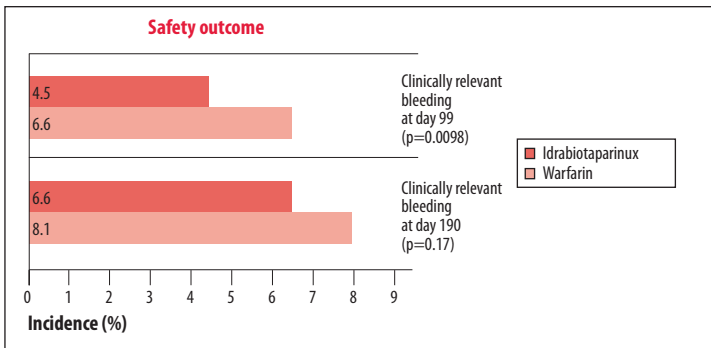
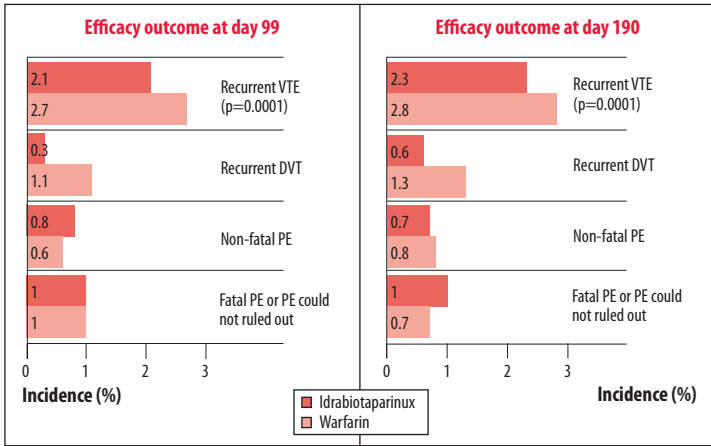
3202 patients aged 18–96 years with objectively confirmed, symptomatic, acute PE

Results

Efficacy outcome: At day 99, 2.1% (34 of 1599) patients randomly allocated to receive enoxaparin-idrabiotaparinux and 2.7% (43 of 1603) patients given enoxaparin-warfarin had recurrent venous thromboembolic events (p=0.0001 for non-inferiority). Incidence of recurrent VTE also did not dif-

fer significantly between treatment groups at day 190 for patients assigned to receive 6 months' treatment: 2.3% with enoxaparin-idrabioparinix vs. 2.8% with enoxaparin-warfarin ($p=0.0001$ for non-inferiority). However, the protective effect of idrabioparinix remained present for additional 6 months after treatment cessation, whereas there was an almost immediate and constant increase over time of recurrent VTE after cessation of warfarin. During follow-up after planned end of study drug intake (i.e., 99 days or 190 days), there were only 9 recurrences in patients originally assigned to receive idrabioparinix and 47 in those assigned to receive warfarin in one year

Safety outcome: By day 99, more patients had clinically relevant bleeding in the enoxaparin-warfarin group (4,5%) than in the enoxaparin-idrabioparinix group (6,6%) ($p=0.0098$ for superiority). However, this difference did not persist to 190 days in patients assigned to receive 6 months' treatment (6,6% vs. 8,1%; $p=0.17$ for superiority)



Summary

Efficacy: In patients with symptomatic acute pulmonary embolism treated with enoxaparin for 5–10 days, once weekly subcutaneous idrabioparinix was as effective as adjusted daily doses of warfarin for long-term treatment and prevention of VTE. The indirect factor Xa inhibitor showed a protective effect up to 12 months

Safety: Idrabiotaparinux was associated with less frequent bleeding than was treatment with warfarin

Reference

Büller HR, Gallus AS, Pillion G, Prins MH, Raskob GE, for the CASSIOPEA Investigators. Enoxaparin followed by once-weekly idrabiotaparinux versus enoxaparin plus warfarin for patients with acute symptomatic pulmonary embolism: a randomised, double-blind, double-dummy, non-inferiority trial. *Lancet* 2012;379:123-129

Corresponding author

Prof. Harry R. Buller, Department of Vascular Medicine, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, Netherlands, e-mail: h.r.buller@amc.uva.nl

CHAMP

Combination Hemotherapy And Mortality Prevention (2002)

Condition

Secondary prevention of vascular events and death after acute myocardial infarction

Objective

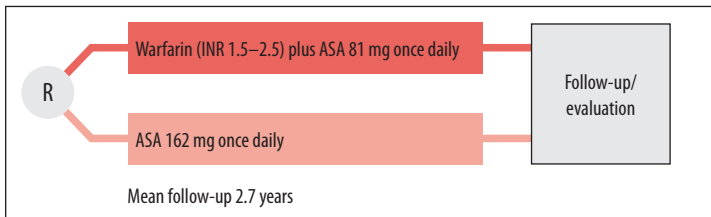
To investigate, whether ASA and warfarin, when combined in moderate doses, would be more effective than ASA alone in reducing all-cause mortality following acute myocardial infarction

Trial design

Randomized, open-label study

Active treatment: warfarin (INR 1.5–2.5) plus ASA 81 mg once daily (n=2522)

Control treatment: ASA 162 mg once daily (n=2537)



Endpoints

Primary efficacy endpoint: all-cause mortality

Secondary efficacy endpoints: recurrent myocardial infarction, stroke, vascular mortality, composite of recurrent myocardial infarction, or stroke

Primary safety endpoint: major hemorrhagic events

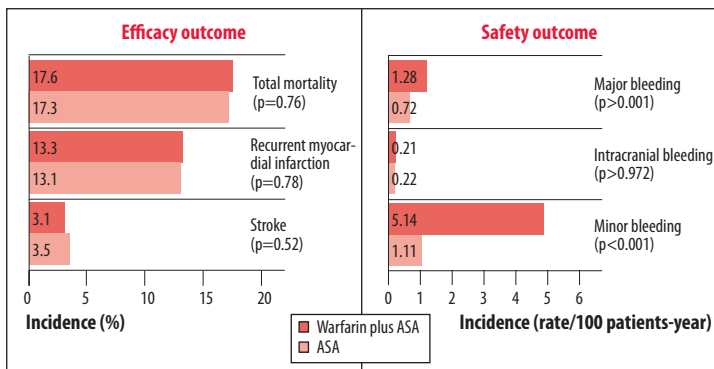
Trial participants

5059 patients (mean age 64 years) who sustained an acute myocardial infarction within the preceding 14 days

Results

Efficacy outcome: During the mean follow-up of 2.7 years, 438 of 2537 patients (17.3%) assigned to ASA and 444 of the 2522 patients (17.6%) assigned to warfarin plus ASA died. Recurrent myocardial infarction occurred in 333 patients (13.1%) given ASA and in 336 patients (13.3%) given the combination therapy. Stroke occurred in 89 patients (3.5%) receiving ASA and in 79 patients (3.1%) receiving warfarin plus ASA

Safety outcome: Major bleeding was observed in 50 patients treated with ASA and in 87 patients treated with the combination (1.28 vs. 0.72 events per 100 person years). 77 patients on ASA and 349 on the combination therapy suffered from minor bleedings (1.11 vs. 5.14 events per 100 person years)



Summary

Efficacy: In post-myocardial infarction patients, moderate-dose warfarin (INR 1.5–2.5) combined with low-dose ASA was not superior to ASA monotherapy in reducing all-cause mortality and cardiovascular events

Safety: Major and minor bleeding occurred more frequently in the combination therapy group than in the ASA group

Reference

Fiore LD, Ezekowitz MD, Brophy MT, Lu D, Sacco J, Peduzzi P, for the Combination Hemotherapy and Mortality Prevention (CHAMP) study group. Department of Veterans Affairs Cooperative Studies Program clinical trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: Primary results of the CHAMP study. *Circulation* 2002;105:557-563

Corresponding author

Louis Fiore, MD, Department of Veterans Affairs Cooperative Studies Program Coordinating Center, VA Boston Healthcare System, 150 S Huntington Ave, Boston, MA 02130, e-mail: louis.fiore@med.va.gov

COAG

Clarification of Optimal Anticoagulation through Genetics (2013)

Condition

Initiating anticoagulation with warfarin

Objective

Observational studies have identified two genes, CYP2C9 and VKORC1, that are associated with variation in warfarin maintenance doses. The aim of this trial was to test the hypothesis that initiating warfarin therapy at a genotype-guided maintenance dose for the first 5 days, as compared with initiating warfarin at a clinically predicted maintenance dose, improves anticoagulation control

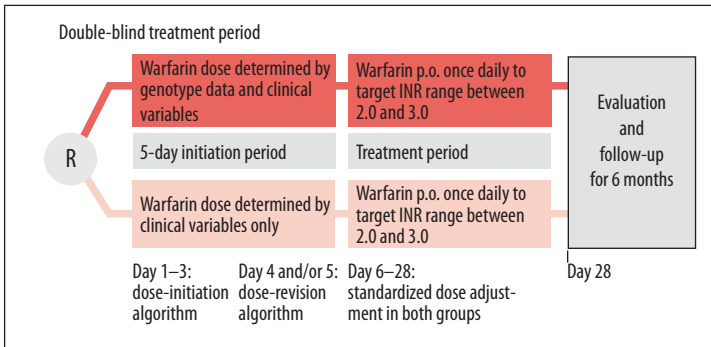
Trial design

Randomized, double-blind, controlled study using two different strategies to choose the initial warfarin dose

Active treatment: During the first 5 days of anticoagulation the patients received warfarin at the maintenance dose predicted by prespecified algorithms that included both clinical variables and genotype data for CYP2C9*2, CYP2C9*3, and VKORC1 (n=514)

Control treatment: In the 5-day initiation period patients were treated with warfarin doses determined according to a dosing algorithm that included only clinical variables such as age, race, body size, smoking status, and use of certain cardiovascular medications (n=501)

For each dosing strategy, a dose-initiation algorithm was used during the first 3 days of therapy, and a dose-revision algorithm was used on day 4, 5, or both. After the 5-day initiation period, the dose was adjusted during the first 4 weeks of therapy, starting with the doses predicted by the algorithms and making the same relative adjustments on the basis of the INR in the two study groups. The clinicians were informed of the relative dose change at each INR measurement but not of the actual dose of warfarin. All patients were to be followed for a total of 6 months



Endpoints

Primary outcome: percentage of time in therapeutic range (INR=2.0–3.0) from day 4 or 5 through day 28 of warfarin therapy in the entire study population and in the subgroup with ≥ 1.0 mg/day difference in warfarin dose as determined by genotype- or clinical-only dosing

Secondary outcome: composite of any INR value ≥ 4 , major bleeding, or thromboembolism in the first 4 weeks, time to the first therapeutic INR, adverse events

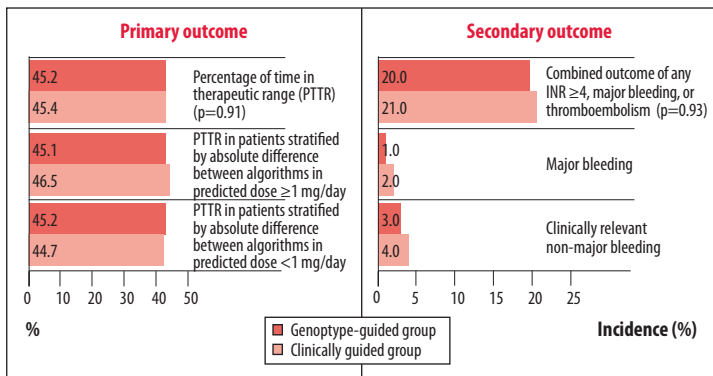
Trial participants

1015 patients ≥ 18 years of age with a clinical condition requiring anticoagulation with warfarin were enrolled. Genotype data were available in the genotype-guided group for 45% of the patients before the first warfarin dose, for 94% before the second warfarin dose, and for 99% before the application of the dose-revision algorithm on day 4 or 5

Results

Primary outcome: At 4 weeks, the mean percentage of time in the therapeutic range (PTTR) was 45.2% in the genotype-guided group and 45.4% in the clinically guided group. The between group-difference was not significant ($p=0.91$). No benefit of genotype-guided dosing of warfarin was observed, either overall or among patients with a predicted dose difference between the genotype-guided algorithm and the clinically guided algorithm of at least 1 mg per day. Among African Americans, the PTTR was 35.2% for the genotype-guided group and 43.5% in the clinically guided group ($p=0.01$)

Secondary outcome: The rates of the combined outcome of any INR ≥ 4 , major bleeding, or thromboembolism did not differ significantly according to dosing strategy ($p=0.93$)



Summary

Genotype-guided dosing of warfarin did not improve anticoagulation control during the first 4 weeks of therapy

Reference

Kimmel SE, French B, Kasner SE, Johnson JA, Anderson JL, Gage BF, Rosenberg YD, Eby CS, Madigan RA, McBane RB, Abdel-Rahman SZ, Stevens SM, Yale S, Mohler ER 3rd, Fang MC, Shah V, Horenstein RB, Limdi NA, Muldowney JA 3rd, Gujral J, Delafontaine P, Desnick RJ, Ortel TL, Billett HH, Pendleton RC, Geller NL, Halperin JL, Goldhaber SZ, Caldwell MD, Califf RM, Ellenberg JH; COAG Investigators. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med* 2013;369:2283-2293

Corresponding author

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COLUMBUS

Low-molecular-weight heparin in the treatment of patients with venous thromboembolism (1997)

Condition

Initial treatment of symptomatic VTE

Objective

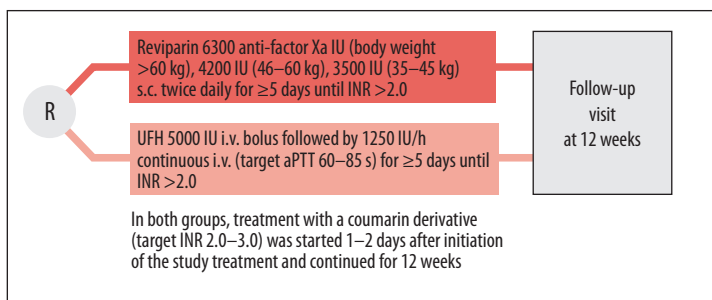
To evaluate the efficacy and safety of fixed-dose reviparin compared with adjusted-dose UFH in unselected patients with confirmed DVT, with or without associated PE

Trial design

Randomized, open study with parallel groups

Active treatment: reviparin 6300 anti-factor Xa IU (body weight >60 kg), 4200 IU (46–60 kg), 3500 IU (35–45 kg) s.c. twice daily for at least 5 days and until the concomitant treatment with a coumarin derivative resulted in an INR >2.0 (n=510)

Control treatment: UFH 5000 IU i.v. bolus followed by 1250 IU/h continuous i.v. infusion (target aPTT 60–85 s) for at least 5 days and until the use of a coumarin derivative induced an INR >2.0 (n=511)



Endpoints

Primary efficacy endpoint: 12-weeks incidence of symptomatic recurrent VTE complications (DVT and PE)

Primary safety endpoints: major bleeding within 12 weeks of randomization, mortality

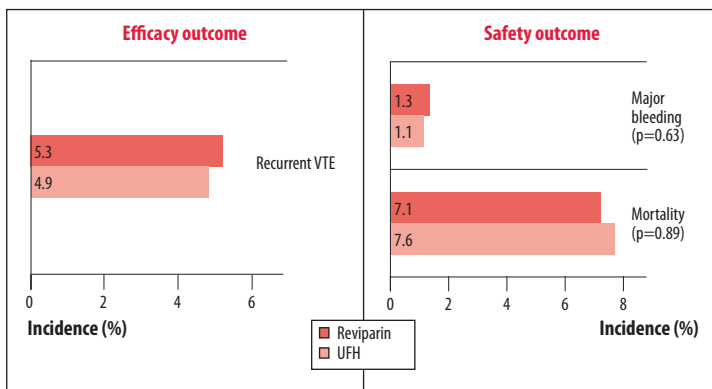
Trial participants

1021 consecutive patients with acute symptomatic DVT, PE or both and who required antithrombotic therapy

Results

Efficacy outcome: At 12 weeks, the incidence of recurrent VTE events was 5.3% in the reviparin group and 4.9% in the UFH group. The absolute difference of 0.4% indicated equivalence between the 2 treatments. Most episodes of recurrent VTE occurred in the first 14 days and the risk of recurrence decreased over time

Safety outcome: 16 patients assigned to reviparin (3.1%) and 12 patients assigned to UFH (2.3%) had episodes of major bleeding. 12-week mortality rates were 7.1% in the reviparin group and 7.6% in the UFH group



Summary

Efficacy: Fixed-dose reviparin and adjusted-dose UFH are equivalent in the treatment of unselected patients with confirmed DVT, with or without associated PE

Safety: The incidence of major bleeding was similar with reviparin and UFH

Reference

The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med* 1997;337:657-662

Corresponding author

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COMPASS

Cardiovascular **OutcoMes** for **People** using **Anticoagulation StrategieS** (2013, ongoing)

Condition

Prevention of heart attacks, stroke or cardiovascular death in patients with coronary or peripheral artery disease

Objective

To evaluate whether treatment with rivaroxaban and ASA or rivaroxaban alone is better than ASA alone in prevention of major cardiac events in patients with CAD or PAD

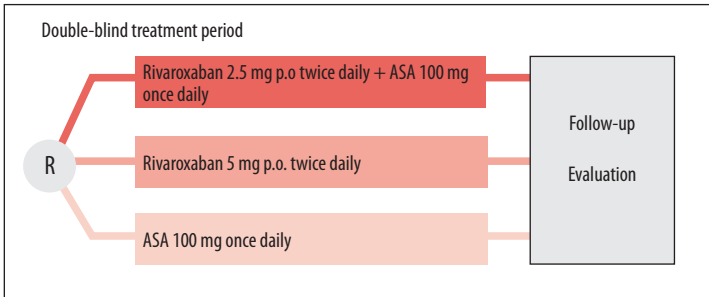
Trial design

Randomized placebo-controlled phase III study, event driven, expected duration 3–4 years

Active treatment:

- Stratum 1: rivaroxaban 2.5 mg p.o. twice daily plus ASA 100 mg once daily
- Stratum 2: rivaroxaban 5 mg p.o. twice daily plus ASA placebo

Control treatment: ASA 100 mg once daily plus rivaroxaban placebo



Endpoints

Primary efficacy endpoint: composite of cardiovascular death, myocardial infarction and stroke

Primary safety endpoint: major bleeding

Secondary outcome measures: composite of myocardial infarction, stroke, cardiovascular death, venous thromboembolism and cardiovascular hospitalization, all-cause mortality

Trial participants

~20,000 patients ≥ 18 years with documented atherosclerosis related to CAD or PAD plus one of the following inclusion criteria:

- age ≥ 65 years
- age < 65 years plus documented atherosclerosis in at least two vascular beds or at least 2 additional risk factors

References

ClinicalTrials.gov (NCT01776424)

Corresponding author

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DAPPAR-AF

Dabigatran for Peri-Procedure Anticoagulation During Radiofrequency Ablation of Atrial Fibrillation (2013, ongoing)

Condition

Radiofrequency ablation of atrial fibrillation

Objective

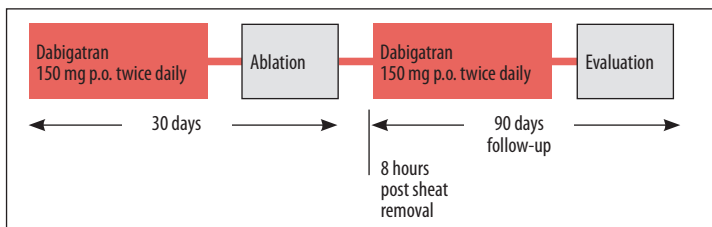
To evaluate the efficacy and safety of dabigatran in peri-procedural anticoagulation during ablation of atrial fibrillation

Trial design

Prospective, open-label phase IV study

Active treatment: dabigatran 150 mg twice daily (110 mg twice daily in high-risk groups for bleeding and patients >80 years) for at least 30 days prior to the ablation procedure and for 90 days post ablation. Dabigatran will be initiated 8 hours post sheath removal and continued twice daily during the 3 month follow-up

Control treatment: historical data using other OAC methods for pulmonary vein ablation



Endpoints

Primary outcome measures: incidence of peri-procedural major bleeding complications

Trial participants

~ 200 patients, aged ≥18 years, undergoing first-time catheter ablation for paroxysmal or persistent symptomatic AF. At least one episode of AF must have been documented by ECG, Holter, loop recorder, telemetry, or trans-telephonic monitoring within 24 months of entry in the trial

References

ClinicalTrials.gov (NCT01468155)

Corresponding author

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DURAC II

DURation of AntiCoagulation II (1997)

Condition

Long-term prophylaxis after a second episode of VTE

Objective

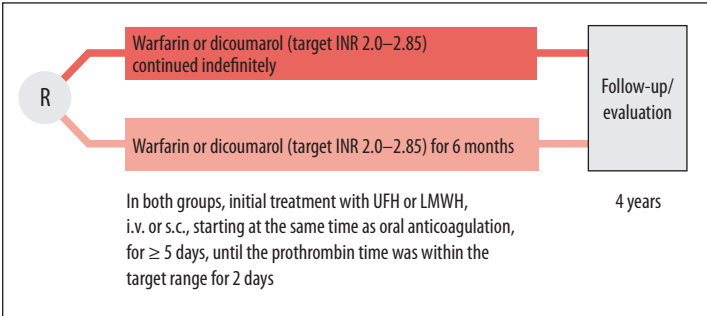
To compare 6 months of oral anticoagulant therapy after a second occurrence of DVT or PE to the same therapy continued indefinitely

Trial design

Randomized, open study with parallel groups

Active treatment: warfarin or dicoumarol, to target INR 2.0–2.85, continued indefinitely (follow-up period 4 years) (n=116)

Control treatment: warfarin or dicoumarol, to target INR 2.0–2.85, for 6 months (n=111)



Endpoints

Primary efficacy endpoint: recurrent thromboembolism during 4 years of follow-up

Primary safety endpoints: major hemorrhagic complications and death during the 4-year period

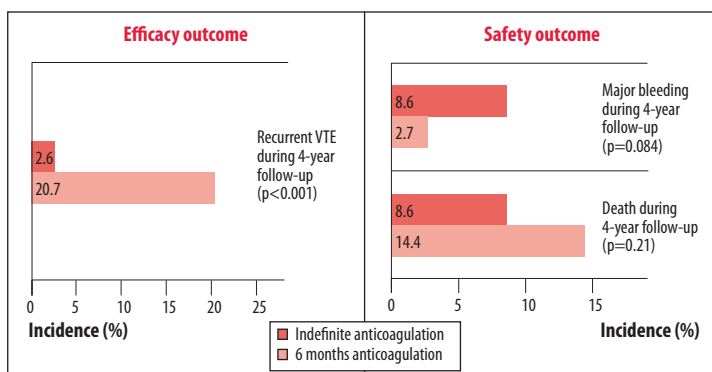
Trial participants

227 consecutive patients at least 15 years of age who had a second episode of VTE (acute PE or DVT in the leg, the iliac veins, or both)

Results

Efficacy outcome: The primary endpoint of recurrent thromboembolic events during 4 years occurred in 23 of 116 patients (20.7%) who received 6-month oral anticoagulant therapy and in 3 of 111 patients (2.6%) who received indefinite anticoagulant therapy; the difference was statistically significant ($p < 0.001$)

Safety outcome: The incidence of major bleeding was 2.7% (3/116) in the 6-month group and 8.6% (10/111) in the group assigned to indefinite anticoagulation. 16 patients (14.4%) with 6-months treatment and 10 patients (8.6%) receiving therapy indefinitely died. No cases of fatal pulmonary embolism could be confirmed



Summary

Efficacy: Prophylactic oral anticoagulation that was continued for an indefinite period after a second episode of VTE was associated with a significantly lower rate of recurrence during 4 years of follow-up than oral anticoagulant treatment for 6 months

Safety: There was a trend toward more major hemorrhages in the group assigned to indefinite anticoagulation

Reference

Schulman S, Granqvist S, Holmström M, Carlsson A, Lindmarker P, Nicol P, Eklund SG, Nordlander S, Lärfars G, Leijd B, Linder O, Loogna E, and the Duration of Anticoagulation Trial Study Group. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. *N Engl J Med* 1997;336:393-398

Corresponding author

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EAF^T

European Atrial Fibrillation Trial (1993)

Condition

Secondary prevention of thromboembolic events in patients with non-rheumatic AF after TIA or minor stroke

Objective

To assess the preventive benefit of standard oral anticoagulation vs. ASA in patients with non-rheumatic AF after TIA or minor stroke

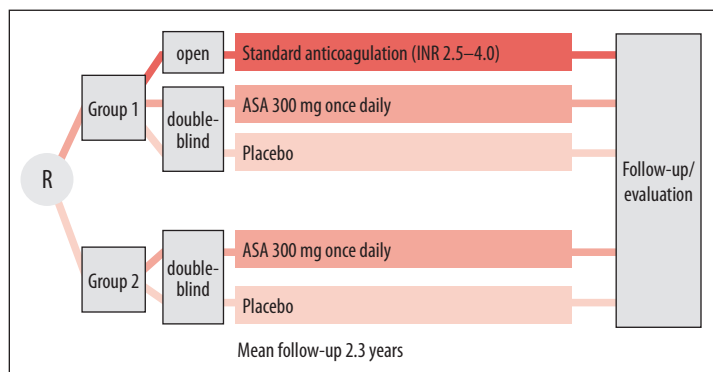
Trial design

Randomized, open (oral anticoagulation), double-blind (ASA), placebo-controlled non-inferiority phase III trial

Active treatment: oral standard anticoagulation (target INR 2.5–4.0; the choice of anticoagulant type was free but most physicians chose coumarin derivatives); ASA 300 mg once daily

- Group 1: patients eligible for anticoagulation (n=669) were randomly assigned to receive either open-label oral anticoagulants (n=225) or double-blind treatment with ASA 300 mg once daily (n=230) or placebo (n=214)
- Group 2: patients ineligible for anticoagulation (n=338) were randomized to double-blind treatment with ASA 300 mg (n=174) or matching placebo (n=164)

Control treatment: placebo



Endpoints

Primary endpoint: death from vascular disease, any stroke, myocardial infarction, or systemic embolism

Secondary endpoints: death from all causes, all strokes (fatal or non-fatal), and major thromboembolic events (vascular death, major stroke, major systemic embolism, or myocardial infarction)

Trial participants

1007 patients ≥ 25 years (mean age 71 years) with recent TIA or minor ischemic stroke and non-rheumatic AF

Results

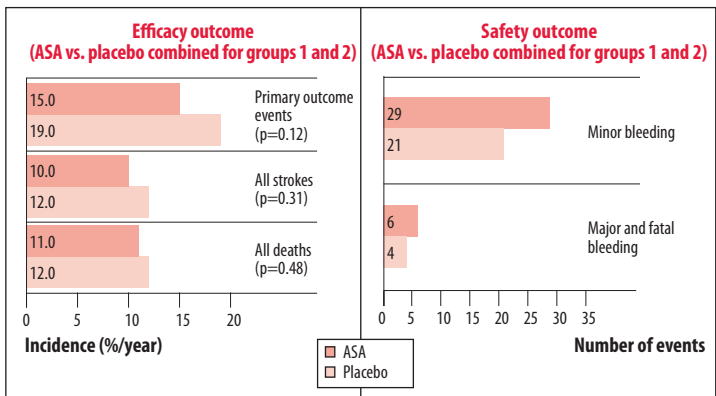
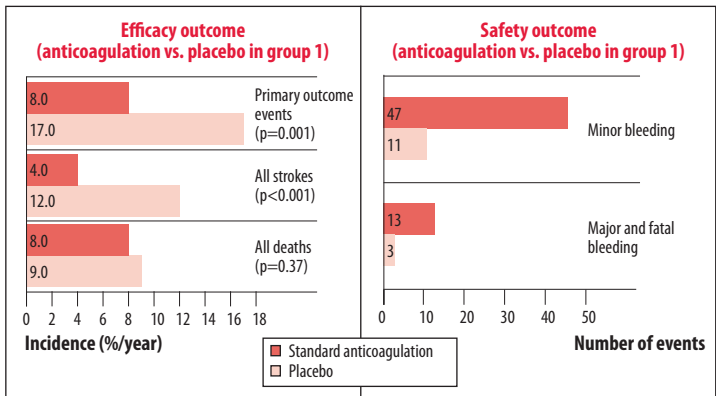
Primary outcome:

- Anticoagulation vs. placebo (group 1): In the intention-to-treat analysis, the annual rate of outcome events was 8% in patients assigned to antico-

agulants vs. 17% in placebo-treated patients. Anticoagulation reduced the risk of stroke of any type from 12% to 4% per year and the risk of subsequent major disabling or fatal stroke by 62% ($p=0.012$). No significant benefit of oral anticoagulants was found on mortality, vascular death alone, or major thromboembolic events

- Anticoagulation vs. ASA (group 1): Oral anticoagulation was more effective than ASA in preventing the occurrence of a primary outcome event ($p=0.008$), largely because of reducing the risk for all strokes significantly ($p<0.001$)
- ASA vs. placebo (group 1 and 2): All patients assigned to ASA had a lower risk for primary outcome events (15% vs. 19% per year) and of stroke alone (10% vs. 12% per year) than those on placebo

Safety outcome: The incidence of major bleeding events was low, both on anticoagulation (2.8% per year) and on aspirin (0.9% per year) or placebo (0.7% per year). Significantly more bleeding complications occurred with anticoagulation than with ASA or placebo ($p<0.001$). No intracranial bleeds were found in patients assigned to anticoagulation



Summary

Efficacy: Anticoagulant treatment almost halved the risk of vascular complications in patients with non-rheumatic AF and a recent TIA or minor stroke. The risk of recurrent stroke decreased by two-third. In patients with a contraindication, ASA alone is a safe, though significantly less effective alternative

Safety: The incidence of major bleeding events was low both on anticoagulation and on ASA

Reference

(EAF) European Atrial Fibrillation Trial Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993;342:1255-1262

Corresponding author

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Edoxaban Study 018

A study to assess the safety of a potential new drug in comparison to the standard practice of dosing with warfarin for non-valvular atrial fibrillation (2011)

Condition

Stroke prevention in patients with non-valvular AF

Objective

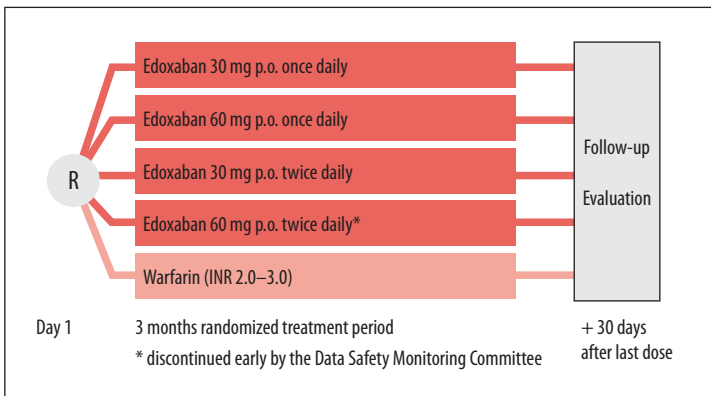
To evaluate the safety of 4 fixed-dose regimens of edoxaban versus warfarin in patients with atrial fibrillation (CHADS₂ score ≥ 2)

Trial design

Randomized phase II dose-finding study (double-blind for edoxaban, open label for warfarin); treatment period 3 months

Active treatment: edoxaban 30 or 60 mg p.o. once daily or twice daily (n=235, n=244, n=234, n=180, respectively)

Control treatment: warfarin (INR 2.0–3.0) (n=250)



Endpoints

Primary outcome measure: occurrence of major and/or clinically relevant non-major bleeding, elevated hepatic enzymes and/or bilirubin

Secondary outcome measure: composite of stroke, systemic embolic events, myocardial infarction, cardiovascular death and hospitalization for any cardiac condition; edoxaban pharmacokinetic and -dynamic markers, adverse events

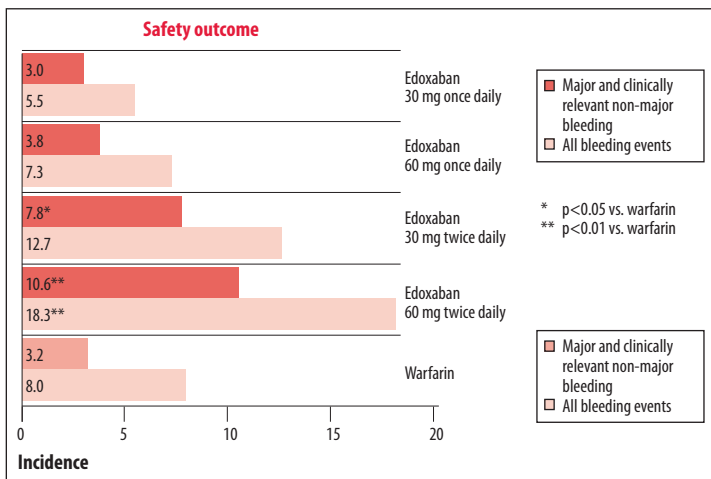
Trial participants

1146 patients between 18 and 85 years with persistent non-valvular AF and risk of stroke

Results

Primary outcome results: Major and clinically relevant non-major bleeding occurred in 7 of 235 patients (3.0%) receiving 30 mg edoxaban once daily, 11 of 234 patients (3.8%) receiving 60 mg edoxaban once daily, 19 of 244 patients (7.8%) receiving 30 mg edoxaban twice daily and 19 of 180 patients (10.6%) receiving 60 mg edoxaban twice daily. In the warfarin group, major and clinically relevant non-major bleeding was observed in 8 of 250 patients (3.2%). Also the incidence of all bleeding showed a dose-related increase.

The incidence of other adverse events (increased liver enzymes, bilirubin) was similar in all edoxaban groups and in the warfarin group



Summary

Safety:

- The 60 mg twice daily dose regimen was prematurely discontinued because of an excess of bleedings
- Major and clinically relevant non-major bleeding occurred significantly more often in patients receiving 30 and 60 mg edoxaban twice daily compared to warfarin
- 60 mg edoxaban once daily: bleeding similar to warfarin
- 30 mg edoxaban once daily: major and clinically relevant non-major bleeds similar to warfarin, rate of all bleeding numerically lower than with warfarin
- Rates of liver enzyme and bilirubin elevation similar in all arms; no signals of significant concern
- The dose regimens with 30 mg and 60 mg edoxaban once daily were safe and well tolerated

Reference

Weitz JL, Connolly SJ, Patel I, Salazar D, Rohatagi S, Mendell J, Kastrissios H, Jin J, Kunitada S. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. *Thromb Haemost* 2010;104:633-641

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EINSTEIN-DVT

Oral, direct Factor Xa inhibitor rivaroxaban in patients with acute symptomatic deep vein thrombosis or pulmonary embolism (2010)

Condition

Treatment of acute symptomatic DVT

Objective

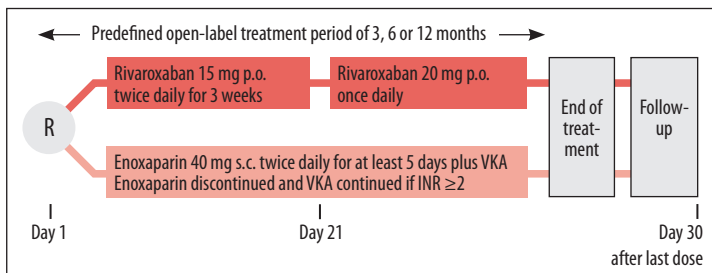
To compare rivaroxaban to enoxaparin/vitamin K antagonist (VKA) in the treatment of patients with acute symptomatic DVT

Trial design

Randomized, open-label phase III non-inferiority study

Active treatment: rivaroxaban 15 mg p.o. twice daily for 3 weeks followed by rivaroxaban 20 mg once daily for 3, 6 or 12 months (n=1731)

Control treatment: enoxaparin 40 mg s.c. twice daily for at least 5 days in combination with VKA; enoxaparin discontinued, if INR ≥ 2 , VKA continued for 3, 6 or 12 months (n=1718)



Endpoints

Primary efficacy endpoint: symptomatic recurrent VTE – the composite of recurrent DVT or fatal or non-fatal PE

Secondary efficacy endpoint: all-cause mortality, vascular events (acute coronary syndrome, ischemic stroke, transient ischemic attack, or systemic embolism), and net clinical benefit (defined as the composite of the primary efficacy outcome or major bleeding), net clinical benefit (defined as the composite of the primary efficacy outcome or major bleeding)

Primary safety endpoint: major and clinically relevant non-major bleeding

Secondary safety endpoint: adverse events

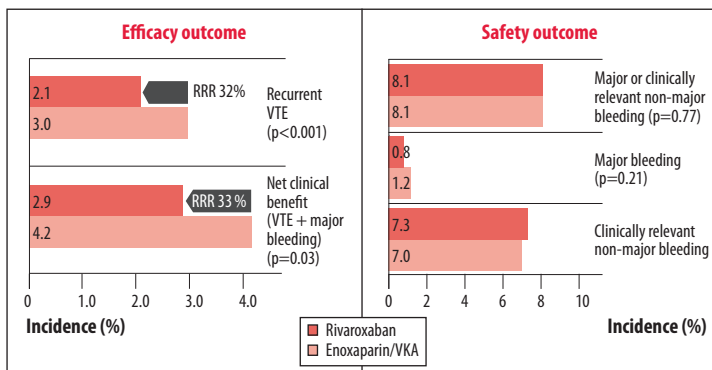
Trial participants

3449 patients with objectively confirmed acute symptomatic DVT and without symptomatic PE

Results

Efficacy outcome: In the intent-to-treat population the primary efficacy endpoint occurred in 36 of 1731 patients (2.1%) given rivaroxaban and in 51 of 1718 patients (3.0%) given enoxaparin/VKA. The outcome of net clinical benefit occurred in 51 (2.9%) of the patients who received rivaroxaban and in 73 (4.2%) of the patients who received enoxaparin/VKA

Safety outcome: In the safety population, the primary safety endpoint occurred in 139 of 1718 patients of the patients given rivaroxaban (8.1%) and 138 of 1711 patients given enoxaparin/VKA (8.1%). The incidence of major bleeding was similar in the 2 groups: 0.8% and 1.2%, respectively



Summary

Efficacy: Rivaroxaban was as effective as standard therapy with enoxaparin/VKA for the treatment of acute DVT

Safety: There was no difference in the incidence of major and clinically relevant non-major bleeding in both treatment groups

Reference

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 for the EINSTEIN investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *New Engl J Med* 2010;363(26):2499-2510

Corresponding author

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EINSTEIN-Extension

Once-daily oral rivaroxaban versus placebo in the long-term prevention of recurrent symptomatic venous thromboembolism (2010)

Condition

Extended thromboprophylaxis after completing a 6 or 12 months treatment of acute DVT or PE

Objective

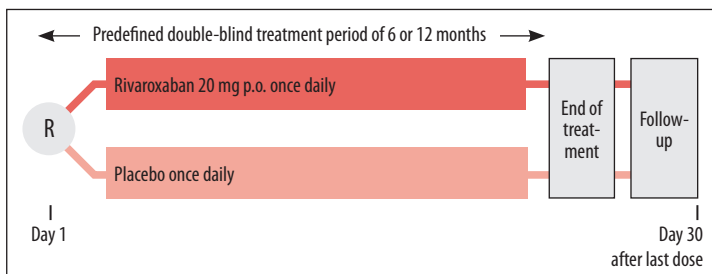
To evaluate the efficacy and safety of once-daily rivaroxaban for the secondary prevention of recurrent VTE versus placebo

Trial design

Randomized, placebo-controlled phase III superiority study

Active treatment: rivaroxaban 20 mg once daily for 6 or 12 months (n=602)

Control treatment: placebo once daily (n=594)



Endpoints

Primary efficacy endpoint: symptomatic recurrent VTE – the composite of recurrent DVT or fatal or non-fatal PE

Secondary efficacy endpoint: all-cause mortality, vascular events (acute coronary syndrome, ischemic stroke, transient ischemic attack, or systemic embolism), and net clinical benefit (defined as the composite of the primary efficacy outcome or major bleeding), net clinical benefit (defined as the composite of the primary efficacy outcome or major bleeding)

Primary safety endpoint: major bleeding

Secondary safety endpoint: adverse events, abnormal laboratory findings

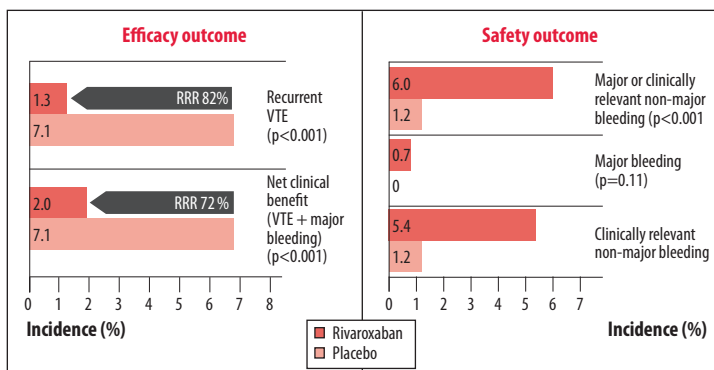
Trial participants

1197 patients who have previously completed 6 or 12 months of treatment for an acute episode of VTE

Results

Efficacy outcome: In the intent-to-treat population the primary efficacy endpoint occurred in 8 of 602 patients (1.3%) given rivaroxaban and in 42 of 594 patients (7.1%) given placebo. The outcome of net clinical benefit occurred in 12 (2.0%) of the patients who received rivaroxaban and in 42 (7.1%) of the patients who received placebo

Safety outcome: In the safety population major bleeding occurred in 4 of 598 patients given rivaroxaban (0.7%) and in none of the 590 placebo patients. Clinically relevant non-major bleeding was noted in 32 (5.4%) of the rivaroxaban and in 7 (1.2%) of the placebo recipients, respectively. No patients were observed to have an ALT rise above 3x ULN combined with a total bilirubin above 2x ULN



Summary

Efficacy: Extended treatment with rivaroxaban was superior to placebo in preventing symptomatic recurrent VTE. A prespecified indicator of net clinical benefit (symptomatic recurrent VTE plus major bleeding) favored rivaroxaban

Safety: The incidence of major bleeding was similar in both groups. However, the rate of clinically relevant non-major bleeding was higher in the patients assigned to rivaroxaban

Reference

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 for the EINSTEIN investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *New Engl J Med* 2010;363(26):2499-2510

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EINSTEIN-PE

Oral, direct Factor Xa inhibitor rivaroxaban in patients with acute symptomatic deep vein thrombosis or pulmonary embolism (2012)

Condition

Treatment of acute symptomatic PE

Objective

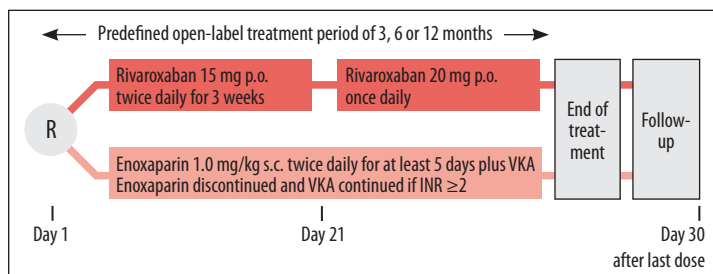
To compare rivaroxaban to standard anticoagulant therapy with enoxaparin and vitamin K antagonist (VKA) in the treatment of patients with acute symptomatic PE

Trial design

Randomized, open-label phase III non-inferiority study

Active treatment: rivaroxaban 15 mg p.o. twice daily for 3 weeks followed by rivaroxaban 20 mg once daily for 3, 6 or 12 months (n=2419)

Control treatment: enoxaparin 1.0 mg/kg s.c. twice daily for at least 5 days in combination with VKA; enoxaparin discontinued, if INR ≥ 2 , VKA continued for 3, 6 or 12 months (n=2413)



Endpoints

Primary efficacy endpoint: symptomatic recurrent VTE (defined as the composite of recurrent DVT or fatal or non-fatal PE)

Primary safety endpoint: composite of major and clinically relevant non-major bleeding

Secondary outcomes: major bleeding, all-cause mortality, vascular events (acute coronary syndrome, ischemic stroke, transient ischemic attack, or systemic embolism), and net clinical benefit (defined as the composite of the primary efficacy outcome and major bleeding)

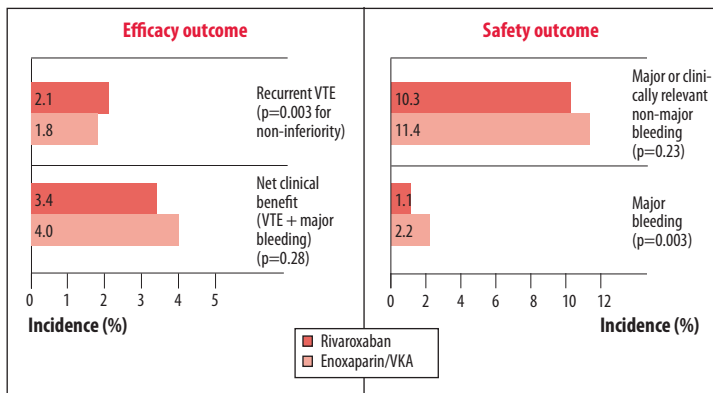
Trial participants

4832 patients with acute symptomatic PE with or without symptomatic DVT

Results

Efficacy outcome: 50 patients (2.1%) in the rivaroxaban group and 44 patients (1.8%) in the standard-therapy group experienced a symptomatic recurrent VTE (primary efficacy endpoint). The outcome of a net clinical benefit occurred in 83 patients (3.4%) treated with rivaroxaban and 96 patients (4.0%) in the standard-therapy group

Safety outcome: The primary safety endpoint, a first major and clinically relevant non-major bleeding episode, was observed in 10.3% of patients in the rivaroxaban group and 11.4% of those in the standard-therapy group. Major bleeding occurred in 1.1% and 2.2% of patients respectively



Summary

Efficacy: The fixed dose regimen of rivaroxaban is at least as effective for the initial and long-term treatment of PE as the standard therapy with enoxaparin followed by a VKA

Safety: The bleeding rates were similar in the two study groups, with fewer major bleeding events in the rivaroxaban group

Reference

The EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366:1287-1297

Corresponding author

Harry R. Büller, MD, Department of Vascular Medicine, Academic Medical Center, F4-275, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands, h.r.buller@amc.uva.nl

EINSTEIN pooled analysis

Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies (2013)

Condition

Treatment of acute symptomatic VTE

Objective

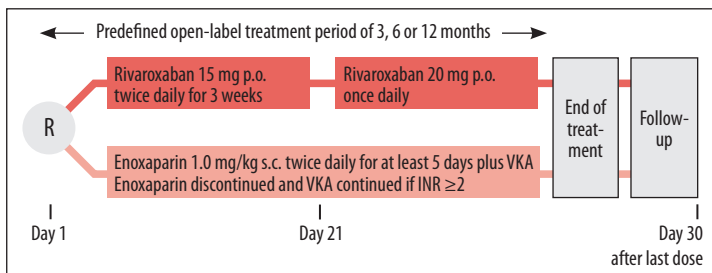
To provide more precise estimates of efficacy and safety of rivaroxaban vs. standard treatment in patients with VTE, focusing key clinical subgroups in which VKA therapy is associated with an increase in complications, such as in patients who are elderly or renally impaired, and in those with cancer or previous VTE

Trial design

Prespecified pooled analysis of the EINSTEIN-DVT and EINSTEIN-PE randomized phase III studies

Active treatment: rivaroxaban 15 mg p.o. twice daily for 3 weeks followed by rivaroxaban 20 mg once daily for 3, 6 or 12 months, as determined locally (n=4151)

Control treatment: enoxaparin 1.0 mg/kg s.c. twice daily for at least 5 days in combination with either warfarin or acenocoumarol (INR 2.0–3.0); enoxaparin discontinued if INR ≥ 2 , VKA continued for 3, 6 or 12 months, as determined locally (n=4131)



Endpoints

Primary efficacy endpoint: symptomatic recurrent VTE (defined as the composite of recurrent DVT or fatal or non-fatal PE)

Primary safety endpoint: composite of major and clinically relevant non-major bleeding

Secondary outcomes: major bleeding, net clinical benefit (defined as the composite of the primary efficacy outcome and major bleeding)

Trial participants

8282 patients with symptomatic DVT and/or PE. Efficacy and safety outcomes were separately analyzed in key prespecified subgroups of patients, i.e. fragile patients (>75 years, calculated creatinine clearance <50 ml/min, or body weight ≤ 50 kg; n=1573), those with cancer (n=597), patients with a previous VTE (n=1610), and patients presenting with a clot burden (limited: n=1614, intermediate: n=3754, extensive: n=2691)

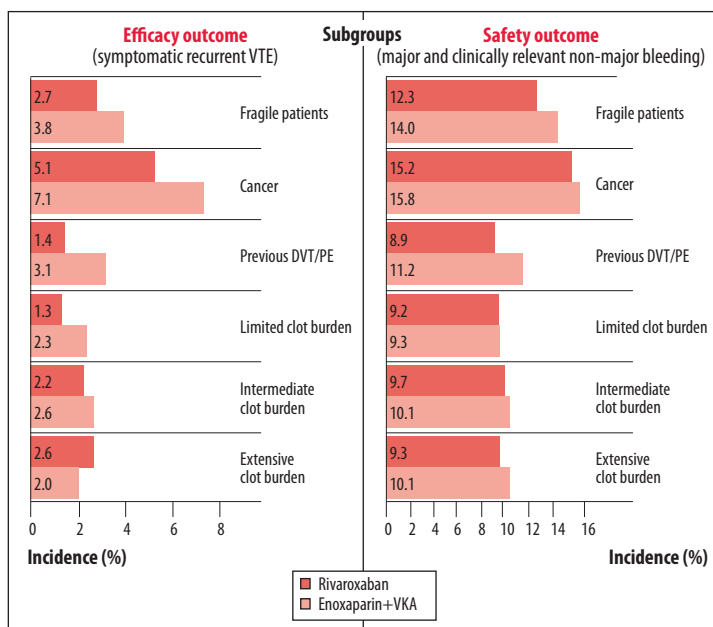
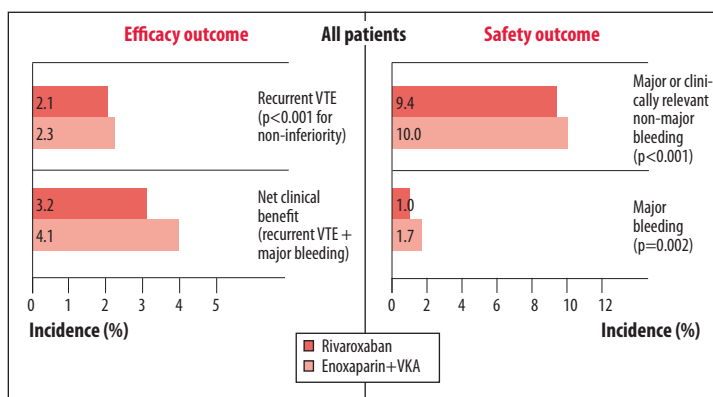
Results

Efficacy outcome: 86 patients (2.1%) treated with rivaroxaban and 95 patients (2.3%) receiving the standard therapy experienced a symptomatic re-

current VTE (primary efficacy outcome; HR 0.89, $p < 0.001$ for non-inferiority). The corresponding rates for the prespecified subgroups are shown in the diagram below

Safety outcome: The primary safety endpoint, a first major or clinically relevant non-major bleeding episode, was observed in 9.4% of patients in the rivaroxaban group and 10.0% of those in the standard-therapy group (HR 0.93). For the corresponding rates for the prespecified subgroups see the diagram below

Major bleeding occurred in 1.0% of all patients treated with rivaroxaban vs. 1.7% of patients given standard therapy (HR 0.54). The composite of recurrent VTE and major bleeding (net clinical benefit) was significantly improved in patients treated with rivaroxaban, occurring in 3.2% of patients in the rivaroxaban group as compared with 4.1% in the standard-therapy group (HR 0.77)



Summary

Efficacy: The fixed-dose regimen of oral rivaroxaban is at least as effective for the treatment of acute symptomatic VTE as the standard therapy with subcutaneous enoxaparin and INR-titrated VKA

Safety: The bleeding rates were similar in the two study groups, with significantly fewer major bleeding events in the rivaroxaban group

Efficacy and safety results were consistent amongst key patient subgroups. Particularly in those patients in whom VKA therapy is associated with an increase in complications, use of rivaroxaban resulted in an important safety advantage

Reference

Prins MH, Lensing AW, Bauersachs R, van Bellen B, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, Raskob GE, Berkowitz SD, Wells PS; EINSTEIN Investigators. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J* 2013;11:21; doi: 10.1186/1477-9560-11-21

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ENGAGE AF-TIMI 48

Effective anticoagulation with factor XA next Generation in Atrial Fibrillation (2013)

Condition

Prevention of stroke and systemic embolism in patients with AF

Objective

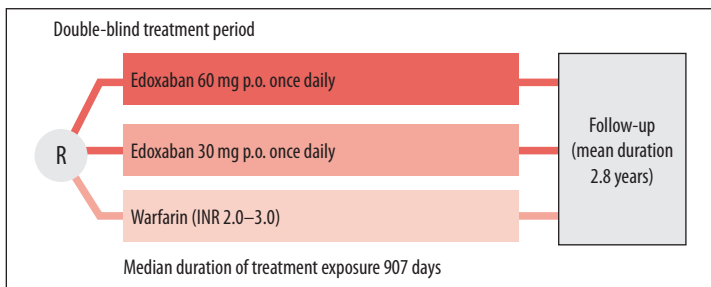
To determine if two once-daily regimens (60 mg high-dose strategy and 30 mg low-dose strategy) of edoxaban were non-inferior to warfarin with respect to the composite primary efficacy endpoint of stroke (ischemic or hemorrhagic) and systemic embolic events in patients with non-valvular atrial fibrillation

Trial design

Randomized, double-blind, double-dummy phase III non-inferiority study; median duration of treatment exposure 907 days, mean duration of follow-up 1022 days (2.8 years)

Active treatment: edoxaban 60 mg (n=7035) or 30 mg (n=7034) p.o. once daily. The dose was halved if any of the following characteristics were present: estimated creatinine clearance of 30–50 ml/min, body weight of ≤ 60 kg, concomitant use of potent P-glycoprotein inhibitors

Control treatment: warfarin (INR 2.0–3.0; n=7036) once daily



Endpoints

Primary efficacy endpoint: stroke (ischemic or hemorrhagic) or systemic embolic event during treatment

Primary safety endpoint: major bleeding during treatment

Secondary composite endpoints:

- stroke, systemic embolic event, or death from cardiovascular causes (including bleeding)
- major adverse cardiac event (myocardial infarction, stroke, systemic embolic event, or death due to cardiovascular causes or bleeding)
- stroke, systemic embolic event, or death from any cause

Other composite endpoints (net clinical outcome):

- stroke, systemic embolic event, major bleeding, or death
- disabling stroke, life-threatening bleeding, or death
- stroke, systemic embolic event, life-threatening bleeding, or death

Trial participants

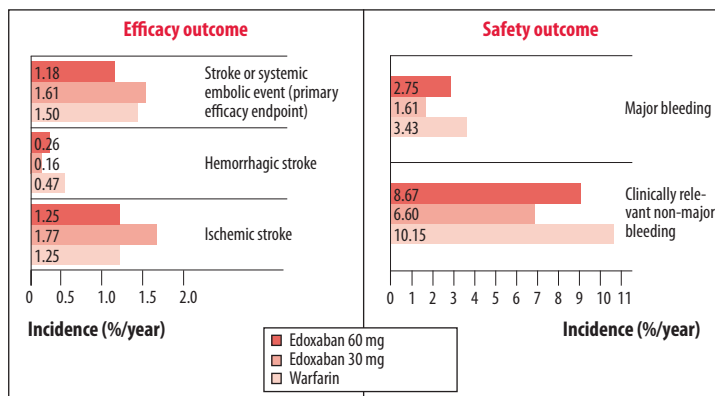
21,105 patients ≥ 21 years (mean age 72 years) with AF within the prior 12 months and with moderate to-high-risk atrial fibrillation (CHADS₂ risk score ≥ 2)

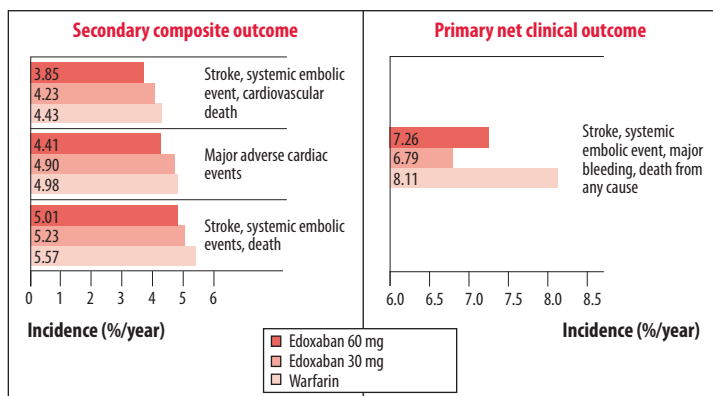
Results

Efficacy outcome: During the treatment period, the primary endpoint (stroke or systemic embolic event) occurred in 232 patients in the warfarin group (representing a rate of 1.50% per year), as compared with 182 patients in the high-dose edoxaban group (1.18% per year; hazard ratio vs. warfarin, 0.79; $p < 0.001$ for non-inferiority) and 253 patients in the low-dose edoxaban group (1.61% per year; hazard ratio vs. warfarin, 1.07; $p = 0.005$ for non-inferiority). In the intention-to-treat analysis (data from the overall study period), there was a trend favoring high-dose edoxaban versus warfarin (1.57% vs. 1.80%; hazard ratio 0.87; $p = 0.08$) and an unfavorable trend with low-dose edoxaban versus warfarin (2.04% vs. 1.80%; hazard ratio 1.13; $p = 0.10$). The annualized rate of hemorrhagic stroke was 0.47% in the warfarin group, as compared with 0.26% with high-dose edoxaban ($p < 0.001$) and 0.16% with low-dose edoxaban ($p < 0.001$). The rate of ischemic stroke was 1.25% with warfarin as compared with 1.25% with high-dose edoxaban ($p = 0.97$) and 1.77% with low-dose edoxaban ($p < 0.001$).

Safety outcome: The annualized rate of major bleeding was 3.43% with warfarin versus 2.75% with high-dose edoxaban (hazard ratio 0.80; $p < 0.001$) and 1.61% with low-dose edoxaban (hazard ratio 0.47; $p < 0.001$).

Composite outcomes: The rates of all three prespecified secondary composite outcomes were significantly lower with high-dose edoxaban than with warfarin; there were no significant differences between low-dose edoxaban and warfarin in the rates of those outcomes. The annualized rate of the primary net clinical outcome (composite of stroke, systemic embolic event, major bleeding, or death from any cause) was significantly lower with both edoxaban regimens than with warfarin: 8.11% with warfarin, as compared with 7.26% with high-dose edoxaban (hazard ratio 0.89; $p = 0.003$) and 6.79% with low dose-edoxaban (hazard ratio 0.83; $p < 0.001$).





Summary

Efficacy outcome: Both once-daily regimens of edoxaban were non-inferior to warfarin with respect to the prevention of stroke or systemic embolism; the high-dose edoxaban regimen tended to be more effective than warfarin

Safety outcome: As compared with warfarin, edoxaban was associated with consistently lower, dose-related rates of major bleeding, intracranial bleeding, and life-threatening bleeding. The single exception was gastrointestinal bleeding, which occurred more frequently with high-dose edoxaban but less frequently with low-dose edoxaban than it did with warfarin

Composite outcomes: The rates of net clinical outcomes (composites of cardiovascular events, death from any cause, or bleeding) were significantly lower with both edoxaban regimens than with warfarin

Reference

Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093-2104

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ENOXAPARIN Clinical Trial Group (1)

Enoxaparin vs. unfractionated heparin for the prevention of deep venous thrombosis after hip replacement (1994)

Condition

Prophylaxis for DVT after total hip replacement

Objective

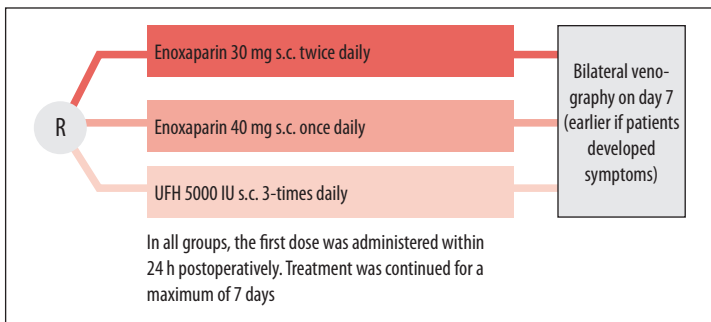
To compare the efficacy and safety of two dosages of enoxaparin vs. standard heparin for DVT prophylaxis after elective hip surgery

Trial design

Randomized, open-label study with parallel groups

Active treatment: enoxaparin 30 mg s.c. twice daily (n=195) or enoxaparin 40 mg s.c. once daily (n=205), starting within 24 hours after surgery and continued for 7 days

Control treatment: UFH 5000 IU s.c. every 8 hours, starting within 24 hours after surgery and continued for 7 days (n=210)



Endpoints

Primary efficacy endpoint: DVT

Primary safety endpoints: major and minor bleeding

Secondary safety endpoints: need for transfusion, hemoglobin level

Trial participants

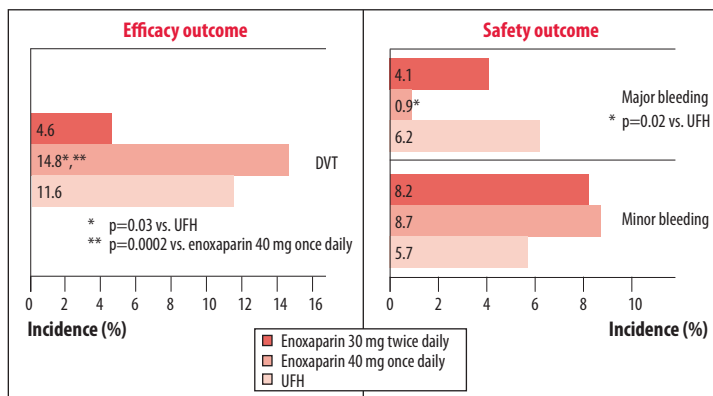
610 consecutive patients (mean age 65 years) scheduled for elective total hip replacement; 604 patients were included in the intent-to-treat analysis

Results

Efficacy outcome: In the intent-to-treat population (n=604), DVT occurred in 9 of 194 patients (4.6%) assigned to 30 mg enoxaparin twice daily, 30 of 203 patients (14.8%) assigned to 40 mg enoxaparin once daily, and 24 of 207 patients treated with UFH (11.6%). The rate of DVT was significantly lower in the group that received 30 mg of enoxaparin every 12 hours than in the group that received UFH ($p=0.03$) and in the group that received 40 mg of enoxaparin once daily ($p=0.0002$). The rate was not significantly different between the 40 mg enoxaparin group and the UFH group ($p=0.24$)

Safety outcome: Major bleeding occurred in 6 patients (4.1%) managed with 30 mg enoxaparin twice daily, 3 patients (0.9%) receiving 40 mg enoxaparin once daily, and 13 patients (6.2%) in the UFH group. The difference between the 40 mg enoxaparin group and the UFH group was statistically significant ($p=0.02$). The rates of minor bleeding episodes were 8.2%, 8.7%,

and 5.7% in the patients given 30 mg enoxaparin twice daily, 40 mg enoxaparin once daily, and UFH, respectively



Summary

Efficacy: In patients undergoing elective hip replacement, treatment with enoxaparin, administered postoperatively in a dosage of 30 mg twice daily, is more effective than UFH

Safety: The rate of major bleeding episodes was not significantly different between the patients assigned to 30 mg of enoxaparin twice daily and the patients receiving UFH

Reference

Colwell CW Jr, Spiro TE, Trowbridge AA, Morris BA, Kwaan HC, Blaha JD, Comerota AJ, Skoutakis VA, for the Enoxaparin Clinical Trial Group. Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement. A clinical trial comparing efficacy and safety. *J Bone Joint Surg* 1994;76:3-14

Corresponding author

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ENOXAPARIN Clinical Trial Group (2)

Enoxaparin vs. warfarin for the prevention of venous thromboembolism after primary total knee arthroplasty (2001)

Condition

Prophylaxis for VTE after unilateral total knee replacement

Objective

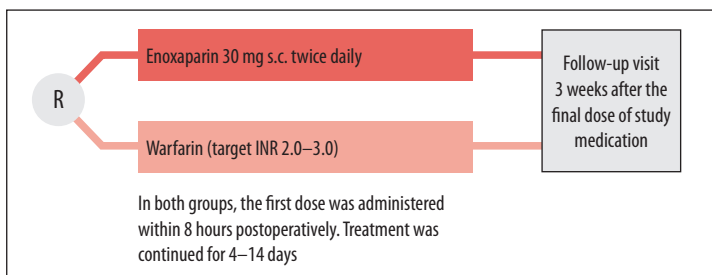
To compare the efficacy and safety of fixed-dose enoxaparin with that of adjusted-dose warfarin in the prevention of VTE in patients undergoing total knee arthroplasty

Trial design

Prospective, randomized, open-label study with parallel groups

Active treatment: enoxaparin 30 mg s.c. twice daily starting within 8 hours after surgery and continued for 4–14 days (n=173)

Control treatment: warfarin 7.5 mg within 8 hours after wound closure, followed by adjusted daily doses to maintain an INR of 2.0–3.0 for 4–14 days (n=176)



Endpoints

Primary efficacy endpoint: DVT and PE during the postoperative period

Primary safety endpoints: major and minor bleeding

Trial participants

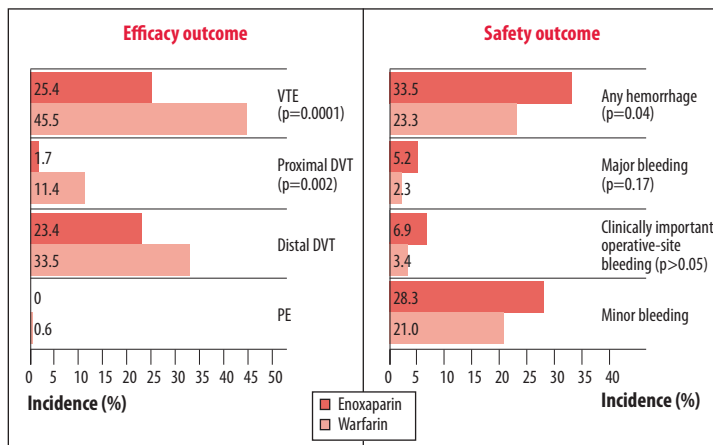
349 consecutive patients (38–89 years of age) undergoing a primary unilateral total knee arthroplasty

Results

Efficacy outcome: In the all-treated-patients population (n=349), 80 of the 176 patients assigned to warfarin (45.5%) and 44 of the 173 patients assigned to enoxaparin (25.4%) had episodes of VTE; the difference between both groups was significant. The enoxaparin-treated patients also had a significantly lower incidence of proximal DVT (1.7% vs. 11.4%). Distal DVT occurred in 23.7% in the enoxaparin group and in 33.5% of the warfarin group. One patient treated with warfarin developed PE, as compared with none patient given enoxaparin

Safety outcome: Major bleeding occurred in 4 patients (2.3%) assigned to warfarin and in 9 patients (5.2%) assigned to enoxaparin. The incidence of clinically important operative-site hemorrhage was 3.4% and 6.9%, respectively. Minor bleeding events occurred in 21.0% of the warfarin-treated patients, as compared with 28.3% of the patients given enoxaparin. The rate of

overall bleeding complications was significantly lower in the warfarin group than in the enoxaparin group (23.3% vs. 33.5%)



Summary

Efficacy: In patients undergoing total knee arthroplasty, fixed-dose enoxaparin significantly reduced the incidence of VTE compared with that associated with adjusted-dose warfarin

Safety: Patients treated with enoxaparin had a significantly higher rate of overall bleeding complications, but there was no significant difference between groups with regard to occurrence of major hemorrhage

Reference

Fitzgerald RH Jr, Spiro TE, Trowbridge AA, Gardiner GA Jr, Whitsett TL, O’Connell MB, Ohar JA, Young TR, for the Enoxaparin Clinical Trial Group. Prevention of venous thromboembolic disease following primary total knee arthroplasty. A randomized, multicenter, open-label, parallel-group comparison of enoxaparin and warfarin. *J Bone Joint Surg* 2001;83-A:900-906

Corresponding author

R.H. Fitzgerald Jr., MD, Department of Orthopedic Surgery, Silverstein Pavilion, Hospital of the University of Pennsylvania, 3400 Spruce Street, Second Floor, Philadelphia, PA 19104

ENOXAPARIN Clinical Trial Group (3)

Enoxaparin once or twice daily vs. intravenous unfractionated heparin for VTE treatment (2001)

Condition

Treatment of acute VTE

Objective

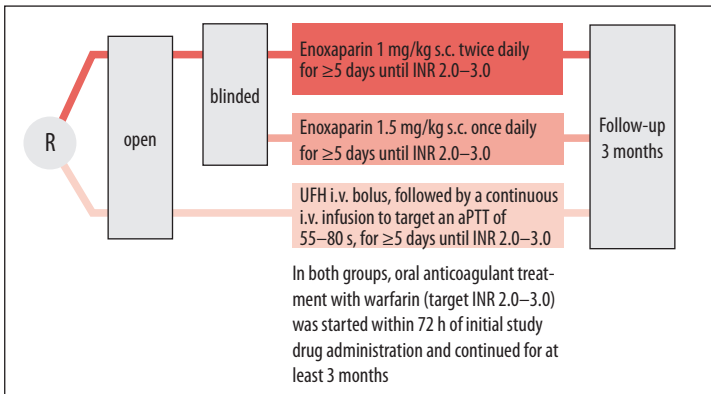
To determine whether subcutaneous enoxaparin administered once or twice daily is as effective as continuously infused unfractionated heparin in acute symptomatic VTE

Trial design

Randomized, partially blinded (dosing of enoxaparin) equivalence study with parallel groups

Active treatment: enoxaparin 1 mg/kg s.c. twice daily (n= 312) or 1.5 mg/kg once daily (n= 298) for ≥ 5 days and until the concomitant oral anticoagulant therapy resulted in an INR 2.0–3.0

Control treatment: UFH, initial i.v. bolus followed by continuous infusion to target an aPTT of 55–80 s, for ≥ 5 days until INR 2.0–3.0 (n=290)



Endpoints

Primary efficacy endpoint: symptomatic recurrent DVT or PE during 3-month follow-up

Primary safety endpoints: major and minor bleeding, any adverse safety events

Secondary endpoints: subgroup analyses according to demographic and physical characteristics, risk factors for and location of VTE

Trial participants

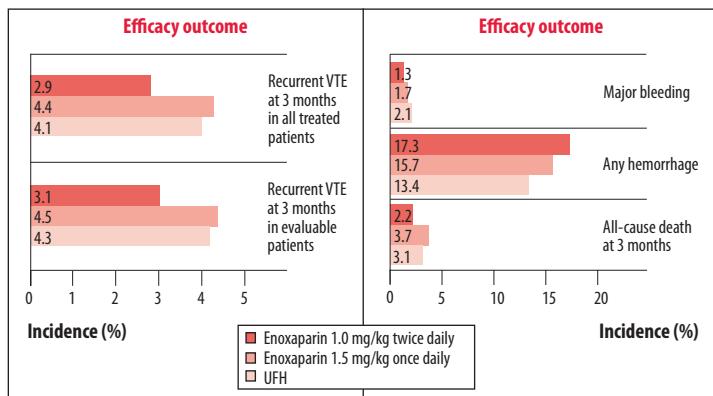
900 patients (mean age 60.7 years) with symptomatic lower-extremity DVT, including 287 (32%) with confirmed PE; of these 900 patients, 740 were evaluable

Results

Efficacy outcome: Among all treated patients (n=900), VTE recurred in 12 of 290 (4.1%) patients in the UHF group, 9 of 312 (2.9%) in the twice-daily enoxaparin group, and 13 of 298 patients (4.4%) in the once-daily enoxaparin group. Both enoxaparin treatments met preestablished criteria for efficacy.

cy equivalent to that of UFH. The findings for the evaluable patients (n=740) also met the protocol-specified definition for treatment equivalence. Patients with cancer and symptomatic pulmonary embolism were more likely to develop recurrence regardless of treatment group

Safety outcome: Major hemorrhage occurred in 6 of 290 (2.1%) patients assigned to UFH, 4 of 312 (1.3%) patients receiving twice-daily enoxaparin, and 5 of 298 patients (1.7%) receiving once-daily enoxaparin. 9 patients in the UFH group (3.1%), 7 in the twice-daily enoxaparin group (2.2%), and 11 in the once-daily enoxaparin group (3.7%) died during 3-month follow-up. The incidence of thrombocytopenia was similar in the 3 treatment groups



Summary

Efficacy: Enoxaparin administered subcutaneously once or twice daily was as effective as UFH in preventing recurrence of venous thromboembolic disease. The protocol-specified definition of equivalence was achieved by both enoxaparin regimens for all treated patients and evaluable patients

Safety: The treatment groups did not differ significantly in safety profile

Reference

Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, Eldor A, Elias D, Grigg A, Musset D, Rodgers GM, Trowbridge AA, Yusen RD, Zawilska K, for the Enoxaparin Clinical Trial Group. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med* 2001;134:191-202

Corresponding author

Theodore E. Spiro, MD, Aventis Pharma SA, Cardiovascular Therapeutic Area, 20 Avenue Raymond Aron, 92165 Antony Cedex, France, e-mail: theodore.spiro@aventis.com

ENTIRE-TIMI 23

ENoxaparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as REperfusion strategy – Thrombolysis in Myocardial Infarction 23 (2002)

Condition

Prophylaxis for reocclusion after acute myocardial infarction with ST-elevation (STEMI)

Objective

To evaluate enoxaparin as adjunctive antithrombin therapy with various forms of pharmacological reperfusion in patients with STEMI

Trial design

Randomized, open-label, phase II study

Patients were randomized either to full-dose tenecteplase (TNK, 0.53 mg/kg; standard reperfusion) or half-dose TNK (0.27 mg/kg) plus abciximab (combination therapy), and then further randomized into two corresponding regimens of unfractionated heparin (UFA) or varying regimens of enoxaparin with and without an initial intravenous bolus:

- Standard reperfusion (n=242):

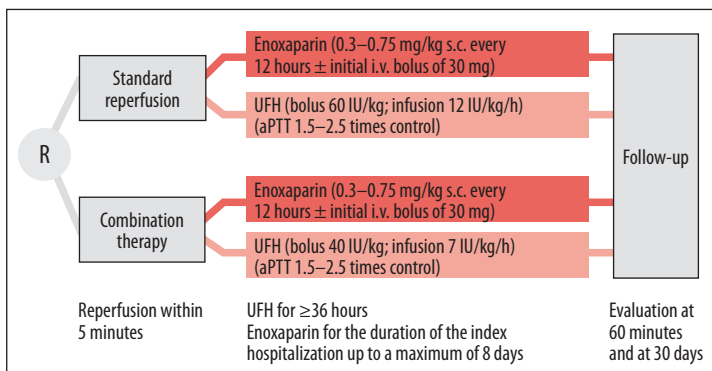
Active treatment: enoxaparin (1.0 mg/kg s.c. every 12 hours ± initial 30 mg i.v. bolus) (n=160)

Control treatment: UFH (bolus 60 IU/kg; infusion 12 IU/kg/h) (n=82)

- Combination therapy (n=241):

Active treatment: enoxaparin (0.3–0.75 mg/kg s.c. every 12 hours ± initial i.v. bolus of 30 mg) (n=164)

Control treatment: UFH (bolus 40 IU/kg; infusion 7 IU/kg/h) (n=77)



Endpoints

Primary efficacy endpoint: TIMI 3 flow at 60 minutes in the infarct related artery

Secondary efficacy endpoints: all-cause mortality, recurrent myocardial infarction

Primary safety endpoint: TIMI major hemorrhage at 30 days

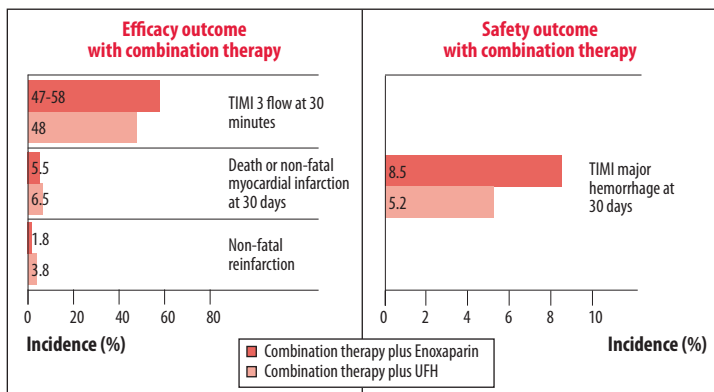
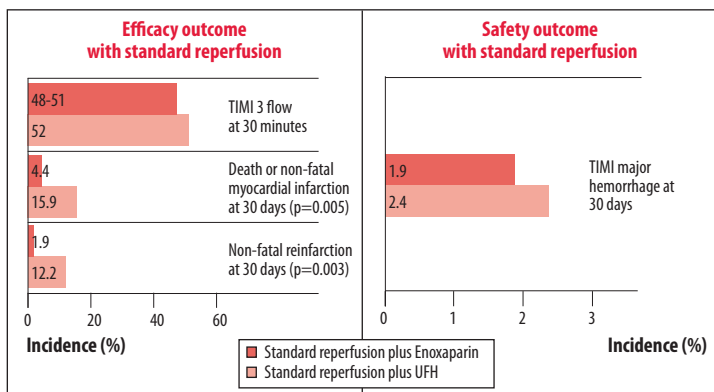
Trial participants

438 patients with STEMI presenting <6 hours from symptom onset

Results

Efficacy outcome: With standard reperfusion, the rate of TIMI 3 flow at 60 minutes was 52% with UFH and 48–51% with enoxaparin. Using combination therapy, the rate of TIMI 3 flow was 48% with UFH and 47–58% with enoxaparin. Among all UFH patients, the rate of TIMI 3 flow was 50% and among enoxaparin patients it was 51%. Through 30 days, the composite endpoint of death and/or recurrent myocardial infarction occurred in the standard reperfusion group in 15.9% of patients with UFH and in 4.4% with enoxaparin. In the combination therapy group, the rates were 6.5% with UFH and 5.5% with enoxaparin. The pooled rate among all UFH patients was 11.3% and 4.9% among enoxaparin patients ($p=0.01$)

Safety outcome: Among patients receiving standard reperfusion, the rate of major hemorrhage with UFH was 2.4% and 1.9% with enoxaparin (pooled data for all enoxaparin groups). The rates of major hemorrhage were higher with combination therapy: 5.2% with UFH and 8.5% with enoxaparin



Summary

Efficacy: Enoxaparin is a more effective adjunctive antithrombin therapy than UFH used either with full-dose TNK or the combination of half-dose TNK and abciximab

Safety: There was no increased risk of major bleeding with enoxaparin compared with UFH when standard reperfusion is used

Reference

Antman EA, Louwerenburg HW, Baars HF, Wesdorp JCL, Hamer B, Bassand J-P, Bigonzi F, Pisapia G, Gibson CM, Heidbuchel H, Braunwald E, Van de Werf F, for the ENTIRE-TIMI 23 Investigators. Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction. Results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 trial. *Circulation* 2002;105:1642-1649

Corresponding author

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ESSENCE

Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (1997)

Condition

Treatment of unstable coronary artery disease

Objective

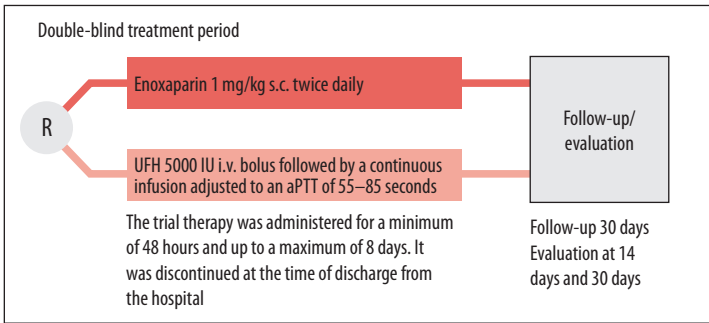
To evaluate the efficacy of enoxaparin vs. UFH, plus ASA, in patients with unstable angina or non-Q-wave infarction

Trial design

Randomized, double-blind, placebo-controlled study

Active treatment: enoxaparin 1 mg/kg s.c. twice daily; UFH placebo (n=1607)

Control treatment: UFH i.v. bolus of 5000 IU followed by a continuous infusion to target an aPTT of 55–85 seconds; enoxaparin placebo (n=1564)



Endpoints

Primary efficacy endpoint: composite of death, myocardial infarction (or reinfarction), or recurrent angina at 14 days of follow-up

Secondary efficacy endpoints: triple composite endpoint at 48 hours and at 30 days; composite of death or myocardial infarction at 48 hours, 14 days, and 30 days

Safety endpoint: major and minor hemorrhage

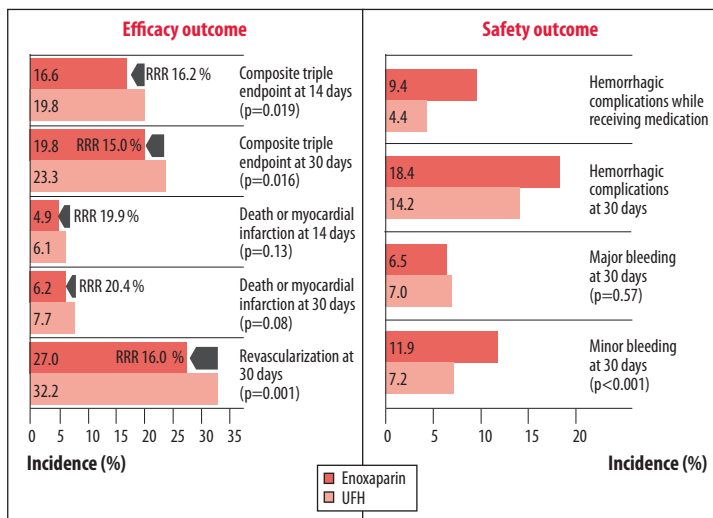
Trial participants

3171 patients (mean age 63.5 years) with recent onset of angina at rest lasting at least 10 minutes or non-Q-wave myocardial infarction

Results

Efficacy outcome: The incidence of the composite triple endpoint (death, myocardial infarction, or recurrent angina) was significantly lower in the enoxaparin group than in the UFH group at 14 days (16.6% vs. 19.8%, relative risk reduction 16.2%) and at 30 days (19.8% vs. 23.3%, relative risk reduction 15.0%). The secondary composite endpoint of death or myocardial infarction was reached at 14 days in 4.9% of the enoxaparin treated patients as compared with 6.1% of the UFH treated patients (relative risk reduction 19.9%) and at 30 days in 6.2% of the enoxaparin group vs. 7.7% of the UFH group (relative risk reduction 20.4%). The need for revascularization at 30 days was significantly lower in the enoxaparin group than in the UFH group (27.0% vs. 32.2%; relative risk reduction 16.0%)

Safety outcome: Hemorrhagic complications occurred more frequently in patients treated with enoxaparin than among those treated with UFH: 9.4% vs. 4.4% while patients were receiving the study medication and 18.4% vs. 14.2% 30 days after randomization



Summary

Efficacy: Antithrombotic treatment with enoxaparin was significantly more effective than UFH in preventing death, myocardial infarction, or recurrent angina in patients with unstable angina or non-Q-wave infarction. The benefit at 14 days was sustained through 30 days of follow-up

Safety: There was a significant increase in minor bleeding with enoxaparin but not in serious hemorrhagic complications

Reference

Cohen M, Demers C, Gurfinkel EP, Turpie AG, Fromell GJ, Goodman S, Langer A, Califf RM, Fox KA, Premmureur J, Bigonzi F, for the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med* 1997;337:447-452

Corresponding author

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ESTEEM

Efficacy and Safety of the oral direct Thrombin inhibitor ximelagatran in patients with recent Myocardial damage (2003)

Condition

Secondary prophylaxis after acute myocardial infarction

Objective

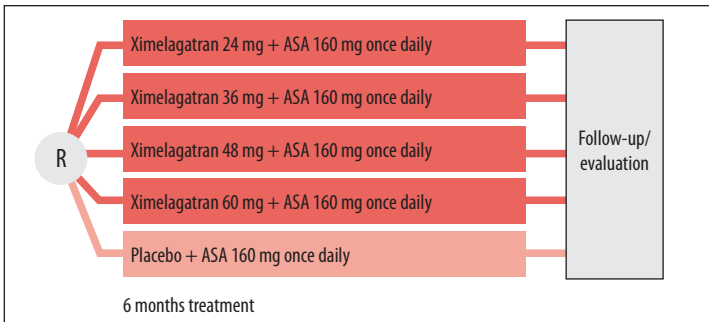
To compare the efficacy and safety of 4 doses of ximelagatran with placebo for prevention of death, non-fatal myocardial infarction, and severe recurrent ischemia after a recent myocardial infarction

Trial design

Randomized, double-blind, placebo-controlled study

Active treatment: ximelagatran 24, 36, 48, or 60 mg plus ASA 160 mg once daily (n=307, 303, 311, 324, respectively)

Control treatment: placebo plus ASA 160 mg once daily (n=638)



Endpoints

Primary efficacy endpoint: composite of all-cause death, non-fatal myocardial infarction, and severe recurrent ischemia

Secondary efficacy endpoints: composite of cardiovascular death, non-fatal myocardial infarction, ischemic stroke, severe recurrent ischemia; composite of death or non-fatal myocardial infarction

Safety endpoints: major and minor bleeding, adverse events

Trial participants

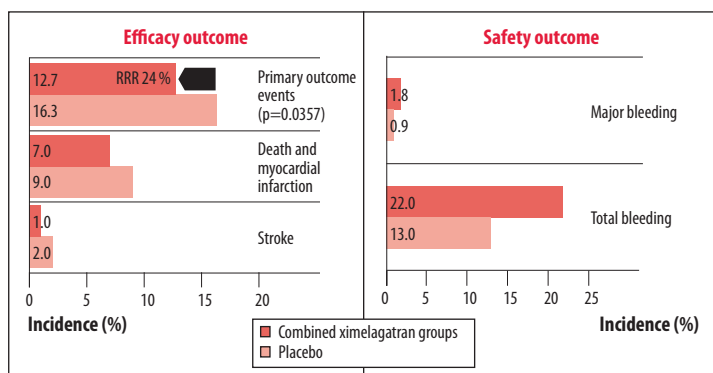
1883 patients admitted for acute myocardial infarction (66% STEMI) within the preceding 14 days

Results

Efficacy outcome: As no difference in effects was found for the 4 ximelagatran doses, the various ximelagatran dose groups were pooled. Ximelagatran significantly reduced the risk for the primary endpoint compared with placebo from 16.3% (102 of 638 patients) to 12.7% (154 of 1245 patients), equating to a risk reduction of 24%. Ximelagatran was more effective for the secondary endpoints: Death and myocardial infarction occurred in 82 of 1245 patients (7%) in the combined ximelagatran groups compared to 55 of 638 patients (9%) with placebo. Patients on ximelagatran had fewer strokes (11 of 1254) than those in the placebo group (13 of 638)

Safety outcome: Major bleeding events were rare, they occurred in 23 of 1245 (1.8%) in the combined ximelagatran groups and in 6 of 638 (0.9%)

in the placebo group. Total bleeding (major and minor) was higher in the ximelagatran groups (22% vs. 13%). Elevated liver enzymes were seen in 6.5% of patients at the lowest ximelagatran dose, 24 mg, and in 12.2–13.0% of patients at the higher doses, but these were not associated with clinical complications



Summary

Efficacy: Ximelagatran and ASA provided significant additional benefits compared to ASA alone in prevention of major cardiovascular events in patients following acute myocardial infarction

Safety: Treatment with ximelagatran plus ASA resulted in a doubling of bleeding complications and a fourfold excess of liver enzyme elevations, compared to ASA alone

Reference

Wallentin L, Wilcox RG, Weaver WD, Emanuelsson H, Goodvin A, Nyström P, Bylock A, for the ESTEEM investigators. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial. *Lancet* 2003;362:789-797

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EU-PACT

EUropean Pharmacogenetics of AntiCoagulant Therapy – Warfarin (2013)

Condition

Initiating anticoagulation with warfarin in patients with atrial fibrillation or venous thromboembolism

Objective

Polymorphisms in two genes, CYP2C9 and VKORC1, account for a large portion of the inter-individual variability in warfarin dose requirements. To date, several pharmacogenetic guided dosing algorithms for warfarin have been developed. The aim of this trial was to compare the effect of genotype-guided dosing with that of standard dosing on anticoagulation control in patients requiring warfarin for AF or VTE

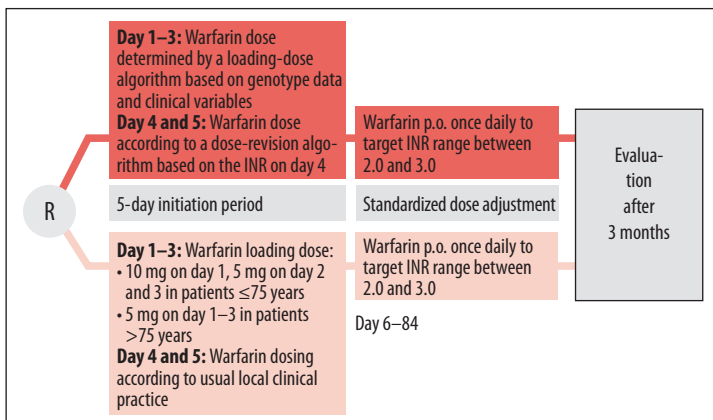
Trial design

Randomized two-armed, single-blind, controlled trial using two different strategies to choose the initial warfarin dose for the first 5 days of anticoagulation

Active treatment: Patients assigned to the genotype-guided dosing group (n=227) received warfarin doses according to algorithms that included genotyping for CYP2C9*2, CYP2C9*3, and VKORC1 in addition to clinical variables. For days 1 through 3, the warfarin doses were determined on the basis of a predefined loading-dose algorithm. For days 4 and 5 a dose-revision algorithm was used, that was based on the INR value on day 4

Control treatment: Patients in the standard-dosing group (n=228) received a 3-day loading-dose regimen. Patients ≤ 75 years of age received 10 mg of warfarin on day 1, 5 mg on day 2, and 5 mg on day 3, whereas patients > 75 years received 5 mg per day on days 1 through 3. The doses on days 4 and 5 were determined according to usual local clinical practice

After the 5-day initiation period, the treatment in both groups was managed according to routine clinical practice. All patients were followed for 3 months



Endpoints

Primary outcome: percentage of time in therapeutic range (INR=2.0–3.0) during the first 12 weeks after the initiation of warfarin therapy

Secondary outcome: incidence of INR ≥ 4.0 , percentage of time with an INR ≥ 4.0 , percentage of time with an INR < 2.0 , time to reach a therapeutic INR, time to

reach a stable warfarin dose, major and minor bleeding events, thromboembolic events, sensitivity to warfarin, resistance to warfarin, number of warfarin dose adjustments, clinical usefulness of the rapid point-of-care genotyping test

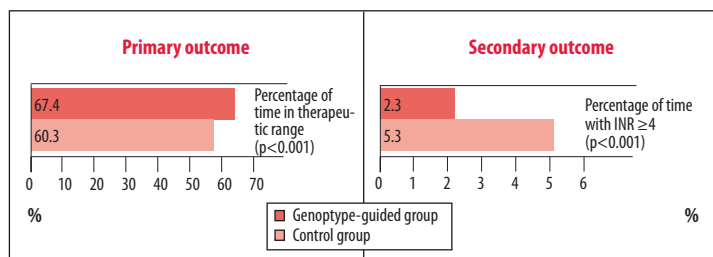
Trial participants

455 patients ≥ 18 years (mean age 67.3 years) suffering from atrial fibrillation or venous thromboembolism and requiring anticoagulation with warfarin with a target INR of 2.0–3.0

Results

Primary outcome: Primary analysis was conducted only in the 427 patients who had at least 13 days of INR data (211 in the genotyped-guided group and 216 in the control group). The percentage of time with an INR of 2.0–3.0 was 67.4% in the genotype-guided group as compared with 60.3% in the control group ($p < 0.001$). The difference in mean INR between the two groups was greatest near the start of the trial and became less pronounced during the 3-month follow-up period (54.6% vs. 45.7% in week 1–4, 73.9% vs. 63.5% in week 5–8, and 74.5% vs. 72.9% in week 9–12)

Secondary outcome: In the genotype-guided group, the incidence of excessive anticoagulation (INR ≥ 4.0) was significantly lower as in the standard dosing group ($p < 0.001$). The median time to reach a therapeutic INR was 21 days in the genotype-guided group as compared with 29 days in the control group ($p < 0.001$). 82.0% of the patients in the genotype-guided group reached a stable dose by 3 months, as compared with 70.4% in the control group. There were no significant differences in the other secondary outcomes (e.g. time spent $< \text{INR } 2.0$: 20% vs. 21.9%, bleeding events: 37.0% vs. 38.0%)



Summary

Genotype-guided dosing of warfarin for days 1–5 was superior to standard dosing for achieving and maintaining therapeutic INR levels in patients with AF or VTE requiring anticoagulation. There was also a significant reduction in suprathreshold INRs with genotype-based dosing

Reference

Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, Kesteven P, Christersson C, Wahlström B, Stafberg C, Zhang JE, Leathart JB, Kohnke H, Maitland-van der Zee AH, Williamson PR, Daly AK, Avery P, Kamali F, Wadelius M; EU-PACT Group. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med* 2013;369:2294-2303

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EXPLORE-Xa

Phase II study of the safety, tolerability and pilot efficacy of oral factor Xa inhibitor betrixaban compared with warfarin (2013)

Condition

Prevention of stroke in patients with AF

Objective

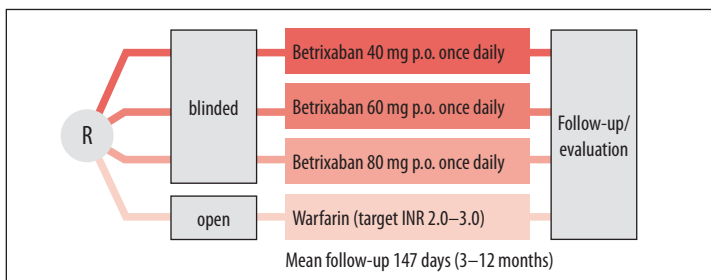
To assess the safety and tolerability of betrixaban at 3 different doses compared with dose-adjusted warfarin in patients with AF at risk of stroke

Trial design

Phase IIb, randomized, dose finding study; open-label for randomization to warfarin vs. betrixaban, blinded for the 3 doses of betrixaban

Active treatment: betrixaban at doses of 40 mg (n=127), 60 mg (n=127) and 80 mg (n=127) given orally once daily for at least 3 months

Control treatment: dose-adjusted warfarin (INR 2.0–3.0) (n=127)



Endpoints

Primary endpoint: occurrence of major or clinically relevant non-major bleeding

Secondary endpoints: any bleeding, occurrence of death, stroke, myocardial infarction, and systemic embolism

Trial participants

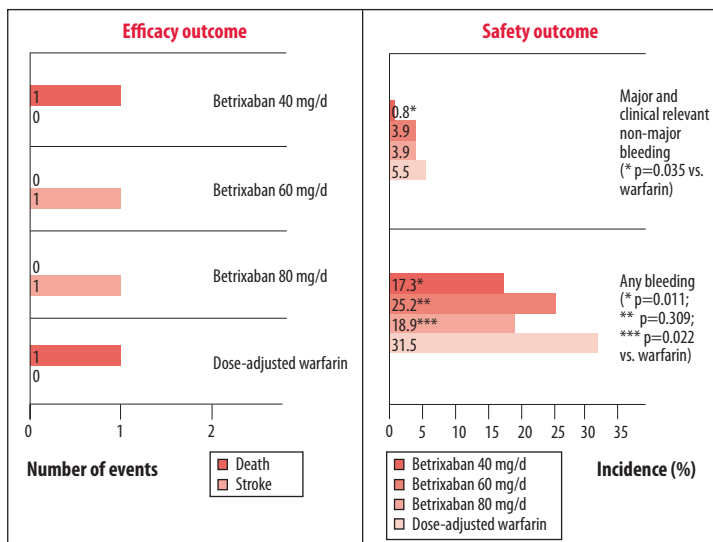
508 patients (mean age 73 years) with documented AF and at least one additional risk factor for stroke

Results

Efficacy outcome: The numbers of strokes and deaths were within the range expected for warfarin: one ischemic stroke each in the betrixaban 60 mg and 80 mg groups, and one vascular death each in the betrixaban 40 mg and warfarin groups. There were no myocardial infarctions, systemic embolic events, or pulmonary embolism in any of the 4 dosing groups

Safety outcome: Patients receiving 40 mg betrixaban once daily had significantly less major and clinically relevant non-major bleedings than patients receiving warfarin (incidence 0.8% vs. 5.5%; HR 0.14). The risk of major and clinically relevant non-major bleeding for the 60 mg and 80 mg doses of betrixaban was similar to warfarin (3.9% in both groups). The incidence of any bleeding was significantly lower as compared with warfarin (31.5%) for patients taking betrixaban 40 mg (17.3%) and 80 mg (18.9%); but not for those taking betrixaban 60 mg (25.2%)

Betrixaban was as well tolerated as warfarin with similar rates of serious adverse events (9.4, 9.4, 8.7, 9.4% on betrixaban 40, 60, 80 mg, and warfarin, respectively)



Summary

Oral betrixaban at doses of 40–80 mg per day was well tolerated in AF patients at risk for stroke. The rates of major or clinically relevant non-major bleeding were numerically lower with all 3 doses of betrixaban compared with well-managed warfarin; and betrixaban 40 mg daily has a statistically significant lower rate than with warfarin

References

- (1) Late-breaking clinical trials session at the American College of Cardiology (ACC) 59th Annual Scientific Session in Atlanta, March 15, 2010
- (2) Connolly SJ, Eikelboom J, Dorian P, Hohnloser SH, Gretler DD, Sinha U, Ezekowitz MD. Betrixaban compared with warfarin in patients with atrial fibrillation: results of a phase 2, randomized, dose-ranging study (Explore-Xa). *Eur Heart J* 2013;34:1498-505

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EXTRACT-TIMI 25

Enoxaparin and Thrombolysis Reperfusion for Acute myocardial infarction Treatment – Thrombolysis In Myocardial Infarction 25 (2006)

Condition

Prevention of reocclusion after successful fibrinolysis in patients with ST-elevation myocardial infarction (STEMI)

Objective

To compare enoxaparin and unfractionated heparin as adjunctive therapy for fibrinolysis in patients with STEMI

Trial design

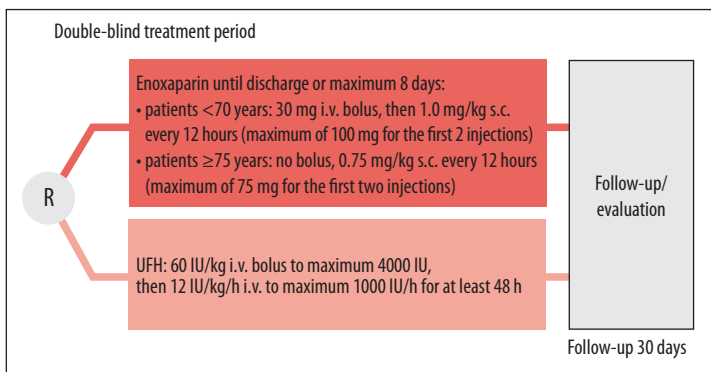
Randomized double-blind, parallel-group study with double-dummy design

Active treatment: enoxaparin, dosing according to the patients age:

- patients <70 years: 30 mg i.v. bolus, then 1.0 mg/kg s.c. every 12 hours (maximum of 100 mg for the first two injections)
- patients ≥75 years: no bolus, 0.75 mg/kg s.c. every 12 hours (maximum of 75 mg for the first two injections)

until discharge or maximum 8 days; matching placebo (n=10,256)

Control treatment: weight-based UFH: 60 IU/kg i.v. bolus to maximum 4000 IU, then 12 IU/kg/h i.v. to maximum 1000 IU/h for at least 48 hours; matching placebo (n=10,223)



Endpoints

Primary endpoint: composite of death from any cause or non-fatal recurrent myocardial infarction in the first 30 days after randomization

Secondary endpoints: (1) composite of death, non-fatal reinfarction, or recurrent myocardial ischemia leading to urgent revascularization in the first 30 days; (2) composite of death, non-fatal reinfarction, or non-fatal intracranial hemorrhage (net clinical benefit)

Trial participants

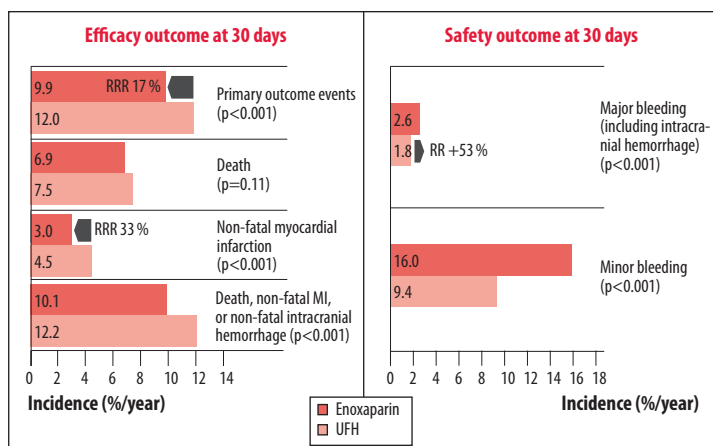
20,506 patients with STEMI infarction who were scheduled to undergo fibrinolysis with streptokinase, tenecteplase, alteplase, or reteplase

Results

Efficacy outcome: At 30 days primary outcome events (death or non-fatal myocardial infarction) had occurred in 12.0% of patients in the UFH group and in 9% of those treated with enoxaparin (relative risk reduction 17%). The

mortality rate was 7.5% in the UFH group, as compared to 6.9% in the enoxaparin group. Enoxaparin significantly reduced the rate of recurrent non-fatal myocardial infarction (3.0% vs. 4.5% with UFH; relative risk reduction 33%) and the incidence of the main secondary end point of death, non-fatal myocardial infarction, or urgent revascularization (11.7% vs. 14.5%). The composite of death, non-fatal reinfarction, or non-fatal intracranial hemorrhage (a measure of net clinical benefit) occurred in 12.2% of patients given UFH and in 10.1% of those given enoxaparin

Safety outcome: The rates of major bleeding (including intracranial hemorrhage) at 30 days were 1.4% in the UFH group and 2.1% in the enoxaparin group (increase in relative risk 53%). Minor bleeding occurred in 1.8% and 2.6%, respectively



Summary

Efficacy: In patients receiving fibrinolysis for STEMI, treatment with enoxaparin throughout the index hospitalization was superior to treatment with UFH for 48 hours in preventing reocclusion

Safety: Treatment with enoxaparin was associated with a significant increase in major bleedings

Reference

Antman EM, Morrow DA, McCabe CH, Murphy SA, Ruda M, Sadowski Z, Budaj A, López-Sendón JL, Guneri S, Jiang F, White HD, Fox KAA, Braunwald E, for the ExTRACT-TIMI 25 Investigators. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 2006;354(15):1477-1488

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FFAACS

Fluindione, Fibrillation Auriculaire, Aspirine et Contraste Spontané (2001)

Condition

Prevention of thromboembolic events in high-risk patients with AF

Objective

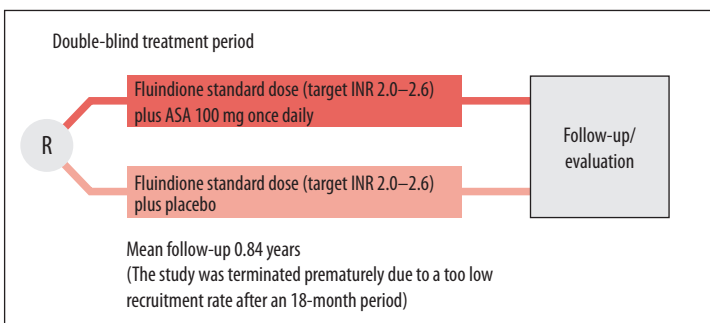
To assess whether a combination of the anticoagulant fluindione and low-dose ASA provides better protection against thromboembolic events compared to fluindione alone

Trial design

Randomized, double-blind, placebo-controlled phase III trial

Active treatment: fluindione standard dose (target INR 2.0–2.6) plus ASA 100 mg once daily (ASA group) (n=76)

Control treatment: fluindione standard dose (target INR 2.0–2.6) plus placebo (n=81)



Endpoints

Primary endpoint: composite of stroke (ischemic or hemorrhagic), myocardial infarction, systemic arterial emboli, or vascular death

Secondary endpoint: hemorrhagic complications

Trial participants

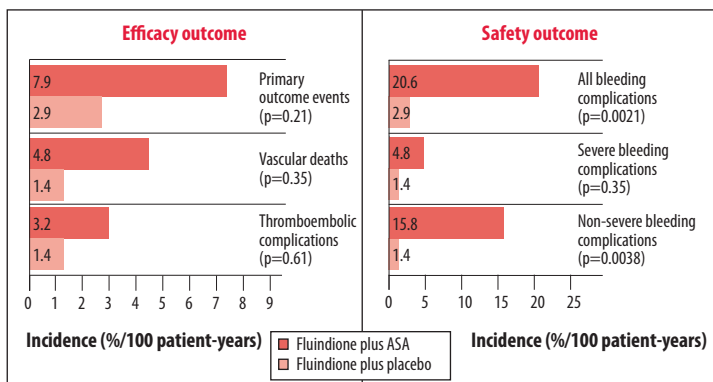
157 patients (mean age 74 years) with non-valvular AF and a previous thromboembolic event, or aged >65 years with hypertension, a recent episode of heart failure, or left ventricular dysfunction

Results

Primary outcome: For the primary endpoint no statistical difference was seen between the groups (incidence 2.9% vs. 7.9% per 100 patient-years). Non-fatal thromboembolic events occurred in 2 patients receiving fluindione plus ASA and in 1 patient receiving fluindione plus placebo. 6 patients in each group died, none of them from a thromboembolic complication

Safety outcome: Death from severe bleeding complications occurred in 2 patients treated with fluindione plus ASA and in 1 patient receiving fluindione plus placebo. Non-fatal hemorrhagic complications were significantly more frequent in patients with fluindione plus ASA (n=10; 13.1%) than in patients with fluindione plus placebo (n=1; 1.2%)

The trial was prematurely stopped because the slower than expected inclusion rate would have necessitated a longer trial duration incompatible with the financial resources allocated to the study



Summary

Efficacy: The incidence of primary endpoint events was not statistically different between the groups. The effect on thromboembolism could not be accurately assessed in this study due to the limited number of ischemic events.

Safety: Hemorrhagic complications were significantly more frequent in the fluidione plus ASA group. So far the combination of fluidione plus ASA cannot be recommended in high-risk patients with AF.

Reference

Lechat P, Lardoux H, Mallet A, Sanchez P, Derumeaux G, Lecompte T, Maillard L, Mas JL, Mentre F, Pousset F, Lacomblez L, Pisica G, Solbes-Latourette S, Raynaud P, Chaumet-Riffaud P. Anticoagulant (fluidione)-aspirin combination in patients with high-risk atrial fibrillation. A randomized trial (Fluidione, Fibrillation Auriculaire, Aspirin et Contraste Spontane; FFAACS). *Cerebrovasc Dis* 2001;12:245-252

Corresponding author

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FIDO Investigators

Fixed-dose, weight-adjusted, subcutaneous unfractionated heparin vs. low-molecular-weight heparin for acute treatment of VTE (2006)

Condition

Treatment of acute DVT and PE

Objective

To determine if fixed-dose, weight-adjusted, subcutaneous UFH is as effective and safe as subcutaneous LMWH for the treatment of acute VTE

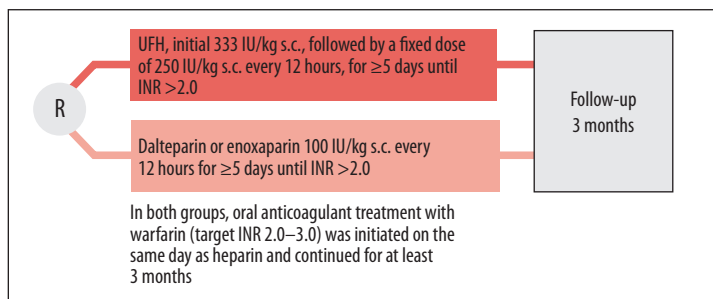
Trial design

Randomized, open-label, non-inferiority study with parallel groups

Active treatment: UFH, initial 333 IU/kg s.c., followed by a fixed dose of 250 IU/kg s.c. every 12 hours, without subsequent use of coagulation tests to modify those doses, for at least 5 days and until INR >2.0 (n=345)

Control treatment: dalteparin or enoxaparin 100 IU/kg s.c. every 12 hours for at least 5 days and until INR >2.0 (n=352)

Both treatments could be administered out of hospital and both were overlapped with 3 months of warfarin therapy



Endpoints

Primary efficacy endpoint: recurrent VTE during 3-month follow-up

Primary safety endpoints: major bleeding within 10 days of randomization

Secondary endpoints: hospital stay

Trial participants

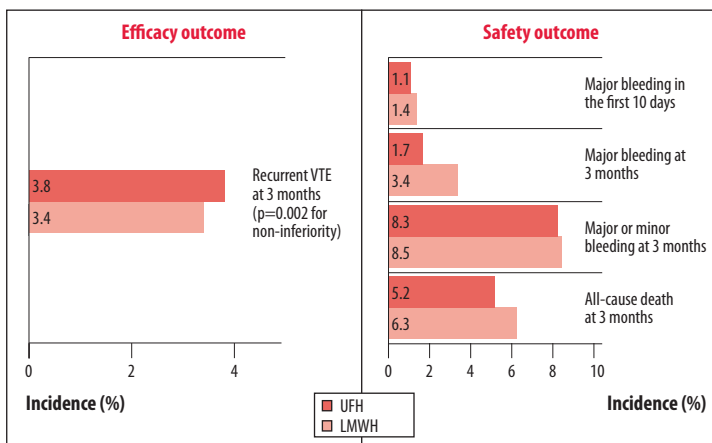
708 patients (mean age 60 years) with newly diagnosed symptomatic or asymptomatic DVT of the legs or symptomatic PE. Of the randomized patients, 11 were subsequently excluded from the analysis of efficacy and 8 from the analysis of safety

Results

Efficacy outcome: During the 3-month follow-up, recurrent VTE occurred in 13 of 345 patients (3.8%) in the UFH group as compared with 12 of 352 patients (3.4%) in the LMWH group. 2 patients in the UFH group and 4 patients with LMWH had PE, the remaining episodes were DVT

Safety outcome: Major bleeding complications occurred during the first 10 days in 4 of 348 patients given UFH (1.1%) and 5 of 352 patients in the LMWH group (1.4%). At 3 months, the rates were 1.7% and 3.4%, respectively. 18 patients (5.2%) assigned to UFH and 22 patients (6.3%) assigned to LMWH died

Hospital stay: Treatment was administered entirely out of hospital in 72% of the UFH group and 68% of the LMWH group



Summary

Efficacy: Fixed-dose, unmonitored, subcutaneous UFH is as effective as fixed-dose, unmonitored, subcutaneous dalteparin or enoxaparin in patients with acute VTE and is suitable for treatment at home

Safety: Total bleeding, which included major and minor bleeding, was not significantly different between both groups

Reference

Kearon C, Ginsberg JS, Julian JA, Douketis J, Solymoss S, Ockelford P, Jackson S, Turpie AG, MacKinnon B, Hirsh J, Gent M, for the Fixed-Dose Heparin (FIDO) Investigators. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. *J Am Med Ass* 2006;296:395-342

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FRAXIS

FRAXiparine in Ischemic Syndrome (1999)

Condition

Treatment of unstable angina or non-Q wave myocardial infarction

Objective

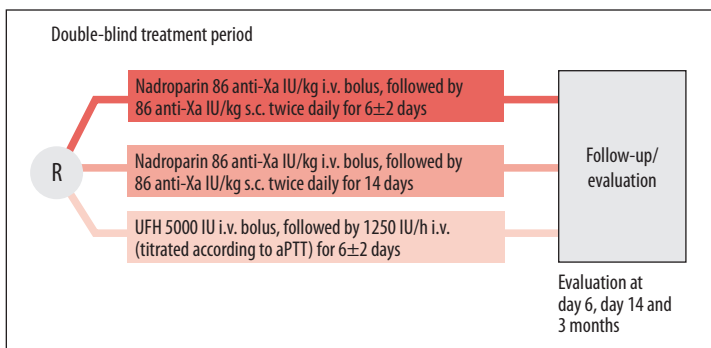
To assess the benefit of nadroparin compared with UFH in patients with unstable angina or non-Q wave myocardial infarction and to determine whether a prolonged nadroparin regimen would offer additional clinical benefit

Trial design

Prospective, randomized, double-blind study with parallel groups

Active treatment: nadroparin 86 anti-Xa IU/kg i.v. bolus, followed by 86 anti-Xa IU/kg s.c. twice daily for 6 ± 2 days (n=1666) or for 14 days; UFH placebo (n=1151)

Control treatment: UFH 5000 IU i.v. bolus, followed by an infusion of 1250 IU/h (titrated according to aPTT) for 6 ± 2 days; nadroparin placebo (n=1151)



Endpoints

Primary efficacy endpoint: composite of cardiac death, myocardial infarction, refractory angina, or recurrence of unstable angina at day 14

Secondary efficacy endpoint: combined efficacy outcome at 6 days and 3 months; occurrence of individual outcomes (cardiac death, death from any cause, myocardial infarction, refractory angina, recurrent angina, emergency or planned PTCA or CABG); composite of all-cause death and myocardial infarction, at day 6, day 14 and month 3

Safety endpoint: major hemorrhage, severe thrombocytopenia and other serious adverse events at days 6 and 14

Trial participants

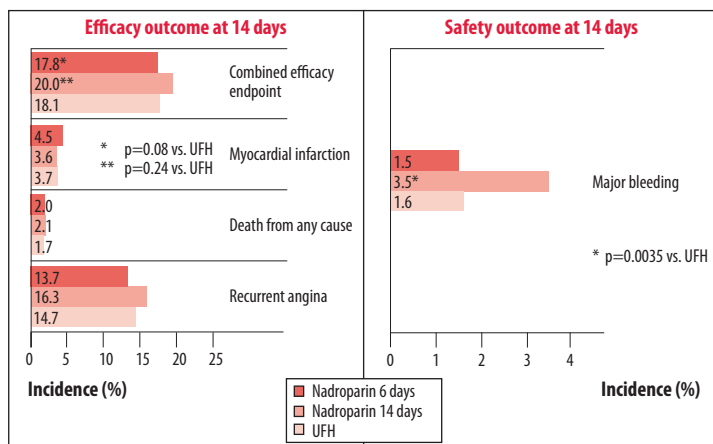
3468 patients (mean age 64 years) admitted with characteristic anginal pain within the 48 hours prior to inclusion or non-Q wave myocardial infarction, defined as ST-segment depression

Results

Efficacy outcome: The intention-to-treat population included 3457 patients. At day 14, the primary composite endpoint occurred in 207 of 1151 patients (18.1%) in the UFH group, 207 of 166 patients (17.8%) treated 6 days with nadroparin and in 230 of 1151 patients (20.0%) treated 14 days with nadroparin. The differences between the groups were not statistically

significant. Furthermore, there were no significant intergroup differences regarding any of the secondary efficacy outcomes at day 14. At 3 months, a 4% absolute increase in the occurrence of the combined efficacy outcome was observed in the nadroparin 14 group compared with the UFH group, mainly due to an excess of recurrent angina ($p=0.03$)

Safety outcome: At 14 days, there was an increased risk of major hemorrhages in the nadroparin 14 group: 3.5% compared with 1.6% in the UFH group 1.5% in the nadroparin 6 group



Summary

Efficacy: The short-term treatment with nadroparin was as effective as the treatment with UFH. Prolonged nadroparin treatment provides no additional clinical benefit

Safety: Prolonged nadroparin treatment was associated with an increase of major bleeding events

Reference

FRAX.I.S. Study Group. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q wave myocardial infarction: FRAX.I.S. (FRAXiparine in Ischaemic Syndrome). *Eur Heart J* 1999;20:1553-1562

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FRIC

FRagmin In unstable Coronary artery disease study (1997)

Condition

Treatment of unstable coronary artery disease

Objective

To compare the efficacy and safety of dalteparin and UFH in the acute treatment of unstable angina or non-Q-wave myocardial infarction

Trial design

Randomized, parallel-group study with 2 phases: days 1–6 open; days 6–45: double-blind, placebo-controlled

- Phase 1 (days 1–6):

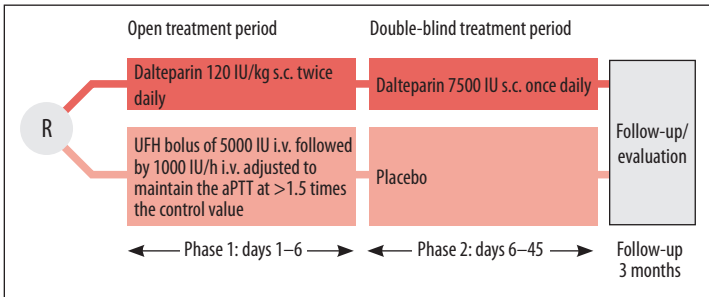
Active treatment: dalteparin 120 IU/kg s.c. twice daily (n=751)

Control treatment: UFH bolus of 5000 IU i.v. followed by 1000 IU/h i.v. adjusted to maintain the aPTT at >1.5 times the control value (n=731)

- Phase 2 (days 6–45):

Active treatment: dalteparin 7500 IU s.c. once daily (n=567)

Control treatment: matched placebo (n=565)



Endpoints

Primary efficacy endpoint: composite of death, myocardial infarction, and recurrence of angina during the double-blinded phase (days 6–45)

Secondary efficacy endpoints: composite of death, myocardial infarction, and recurrence of angina occurring in the acute phase of the study; revascularization by PTCA or CABG during either phase of the study

Safety endpoints: major and minor bleeding, thrombocytopenia, and allergic reactions

Trial participants

1482 patients (mean age 65 years) with unstable angina or non-Q-wave myocardial infarction, admitted within 72 hours of last episode of chest pain and ECG evidence of ongoing ischemia; 1132 patients entered the double-blind phase

Results

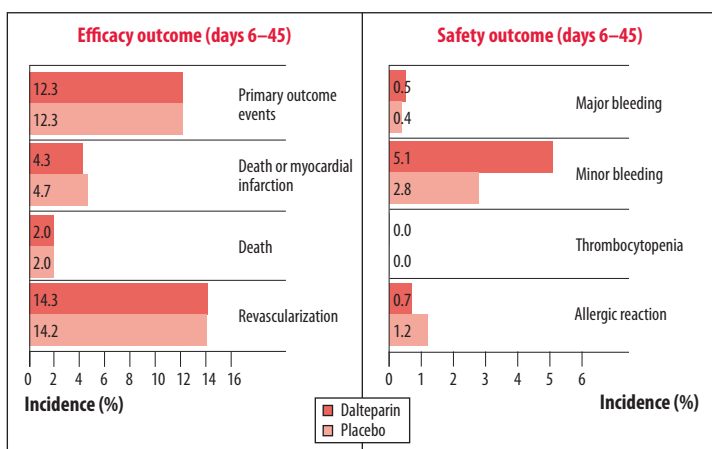
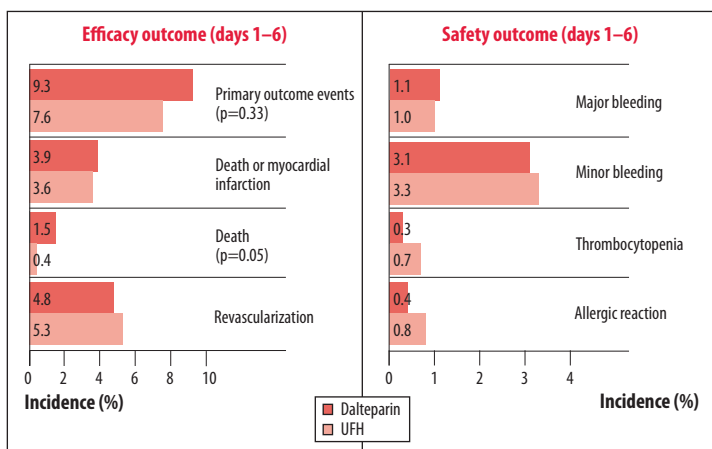
Efficacy outcome:

- Phase 1: During the acute treatment phase, no significant difference in the combined outcome was observed between dalteparin (55 of 731 patients, 9.3%) and UFH (69 of 751 patients, 7.6%). The corresponding rates of the

composite endpoint of death or myocardial infarction were 3.6% and 3.9%. Revascularization procedures were undertaken in 4.8% of dalteparin-treated patients and in 5.3% of UFH-treated patients

- Phase 2: The rate of the combined outcome over days 6–5 was 12.3% in both treatment groups. The composite endpoint of death or myocardial infarction occurred in 4.3% of patients assigned to dalteparin compared with 4.7% of patients given placebo. Revascularization procedures were undertaken in 14.3% of dalteparin-treated patients and in 14.2% of the placebo group

Safety outcome: The rates of major bleeding events were comparable throughout the study (phase 1: 1.1% with dalteparin and 1.0% with UFH; phase 2: 0.5% with dalteparin and 0.4% with placebo. In phase 2, minor bleedings occurred more frequently in the dalteparin-treated patients (5.1% vs. 2.8% in the placebo group)



Summary

Efficacy: The frequency of the combined clinical outcome of death, myocardial infarction, and recurrence of angina was similar in both treatment groups. This suggested that body weight-adjusted low-molecular-weight

heparins as dalteparin administered subcutaneously twice daily can be used as an alternative to intravenous UFH in the acute treatment of unstable coronary heart disease

Safety: In both groups, bleeding events were rare throughout the study

Reference

Klein W, Buchwald A, Hillis SE, Monrad S, Sanz G, Turpie AG, van der Meer J, Olaisson E, Undeland S, Ludwig K. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC). *Circulation* 1997;96:61-68

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FRISC-II

Fast Revascularization during InStability in Coronary artery disease - II (1999, 2006)

Condition

Treatment of unstable coronary artery disease

Objective

To compare an early invasive with a non-invasive primarily medical strategy in patients with unstable coronary artery disease in addition to optimum background antithrombotic medication

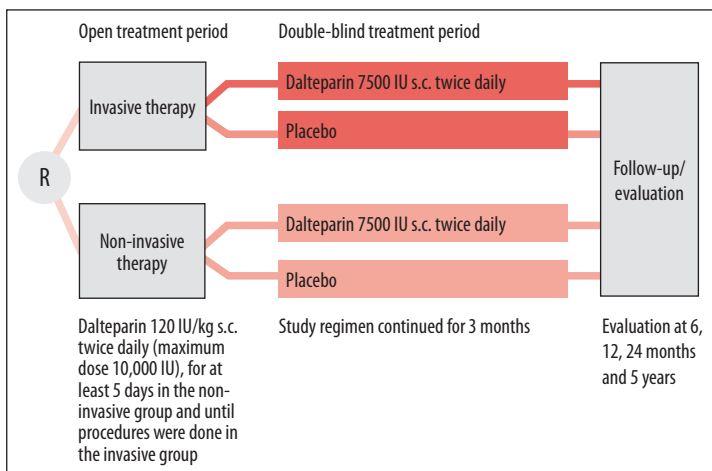
Trial design

Prospective, randomized, open (invasive/non-invasive approach) and double-blind, placebo-controlled (prolonged dalteparin) study with parallel groups:

- invasive treatment plus dalteparin (n=611)
- invasive treatment plus placebo (n=611)
- non-invasive treatment plus dalteparin (n=621)
- non-invasive treatment plus placebo (n=614)

Active treatment: early invasive strategy (coronary angiography and, if appropriate, revascularization, within 7 days from admission); dalteparin 7500 IU s.c. twice daily (n=1222)

Control treatment: dalteparin 7500 IU s.c. twice daily; placebo (n=1235)



Endpoints

Primary efficacy endpoint: composite of death, myocardial infarction, or both at 6 months and 5 years

Secondary efficacy endpoints: death, myocardial infarction, late revascularization, readmissions to hospital, and cardiac symptoms at 6, 12, and 24 months

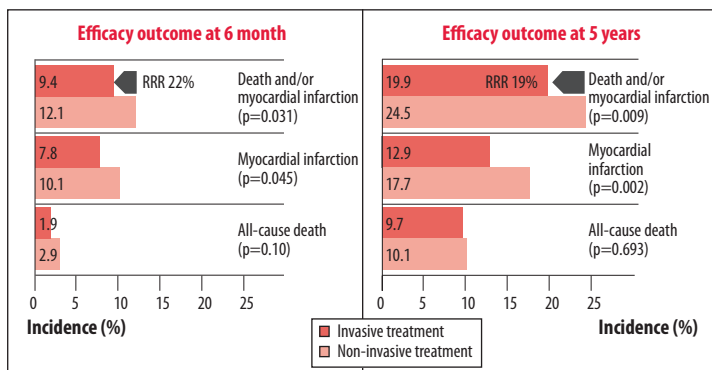
Trial participants

2457 patients (median age 66 years, 70% men) admitted with symptoms of myocardial ischemia or non-ST-elevation myocardial infarction with the last episode of chest pain within 48 hours before start of treatment

Results

Efficacy outcome at 6 months: After 6 months, the composite endpoint of death or myocardial infarction had occurred in 9.4% of the invasive treated patients compared with 12.1% in the non-invasive treated group (relative risk reduction 22%). The rate of myocardial infarction was significantly lower in the invasive group (7.8% vs. 10.1%) and the mortality was non-significantly lower (1.9% vs. 2.9%) in the invasive group. Symptoms of angina and re-admission were halved by the invasive strategy. Results were independent of the randomized dalteparin treatments

Efficacy outcome at 5 years: At 5 years, the differences remained between the groups: Death and/or myocardial infarction were less frequent in the invasive than in the non-invasive group (19.9% vs. 24.5%; relative risk reduction 19%). 5-year mortality was 9.7% in the invasive group compared with 10.1% in the non-invasive group. Rates of myocardial infarction were 12.9% and 17.7%, respectively



Summary

The 5-year outcome indicates sustained benefit of an early invasive strategy compared with a non-invasive approach in patients with non-ST-elevation acute coronary syndromes at moderate to high risk. The benefit of the invasive strategy was confined to male patients, non-smokers, and patients with two or more risk indicators

References

- (1) FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC-II prospective randomised multicentre study. *Lancet* 1999;354:708-15
- (2) Lagerqvist B, Husted S, Kontny F, Stähle E, Swahn E, Wallentin L. 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. *Lancet* 2006;368:998-1004

Corresponding author

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GALILEI Investigators

Adjusted-dose unfractionated heparin vs. fixed-dose low-molecular-weight heparin in the initial treatment of VTE (2004)

Condition

Treatment of acute symptomatic VTE, including recurrent VTE and PE

Objective

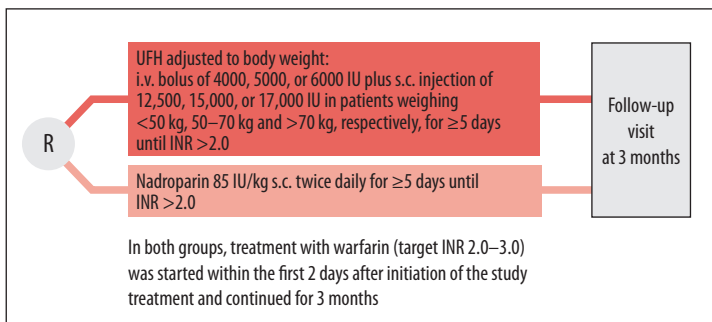
To determine whether the subcutaneous administration of UFH with the use of aPTT-adjusted doses according to a weight-based algorithm is effective and safe as fixed-dose nadroparin for the initial treatment of patients with VTE

Trial design

Randomized, open trial with parallel groups

Active treatment: UFH i.v. bolus followed by s.c. injection in doses adjusted to body weight (targeted aPTT range 50–90 s): 4000 IU i.v. plus 12,500 IU s.c. in patients weighing <50 kg; 5000 IU plus 15,000 IU, in patients weighing 50–70 kg; and 6000 IU plus 17,500 IU in patients weighing >70 kg. UFH was administered for ≥ 5 days and until the concomitant treatment with warfarin resulted in an INR > 2.0 (n=360)

Control treatment: nadroparin 85 IU/kg s.c. twice daily for ≥ 5 days until INR > 2.0 (n=360)



Endpoints

Primary efficacy endpoint: recurrent VTE during the initial treatment period and 3-month follow-up

Primary safety endpoints: major bleeding during the initial treatment period and death during 3-month follow-up

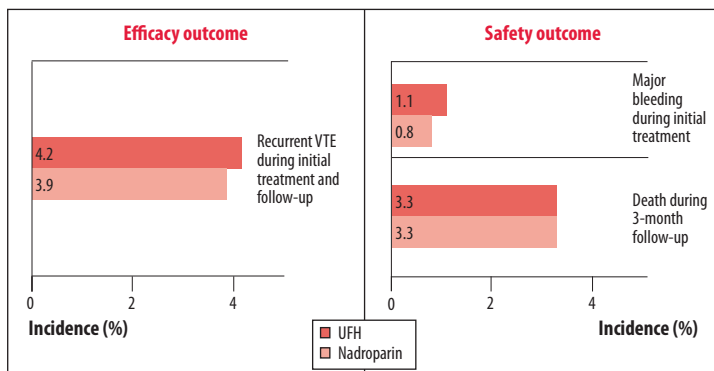
Trial participants

720 consecutive patients with acute symptomatic VTE, including 119 non-critically ill patients with PE and 102 with recurrent VTE

Results

Efficacy outcome: Among the 360 patients assigned to UFH, 15 (4.2%) had recurrent VTE, as compared with 14 (3.9%) of the 360 patients assigned to nadroparin. Recurrent VTE were similarly distributed throughout the study period. In the UFH group, 5 episodes occurred in the initial 2 weeks, 4 in the following month, and 6 in the remaining 6 weeks; the corresponding figures in the nadroparin group were 4, 5, and 5, respectively

Safety outcome: Major bleeding during initial treatment period occurred in 1.1% (4/360) of the patients treated with UFH, which was fatal in 1 patient. Among the 360 patients in the nadroparin group, 3 (0.8%) developed a major bleeding. During the 3 months of follow-up 12 patients in each group died (3.3%)



Summary

Efficacy: Treatment with subcutaneous UFH with dose adjusted by aPTT by means of a weight-based algorithm is as effective and safe as fixed-dose (adjusted only for body weight) nadroparin for the initial treatment of patients with VTE, including those with PE and recurrent VTE

Safety: The incidence of major bleeding was similar with UFH and nadroparin. Overall mortality was the same in each group

Reference

Galilei Investigators. Subcutaneous adjusted-dose unfractionated heparin vs fixed-dose low-molecular-weight heparin in the initial treatment of venous thromboembolism. *Arch Intern Med* 2004;164:1077-1083

Corresponding author

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GALLUS

Early start of warfarin in VTE treatment (1986)

Condition

Treatment of clinically submassive DVT or PE

Objective

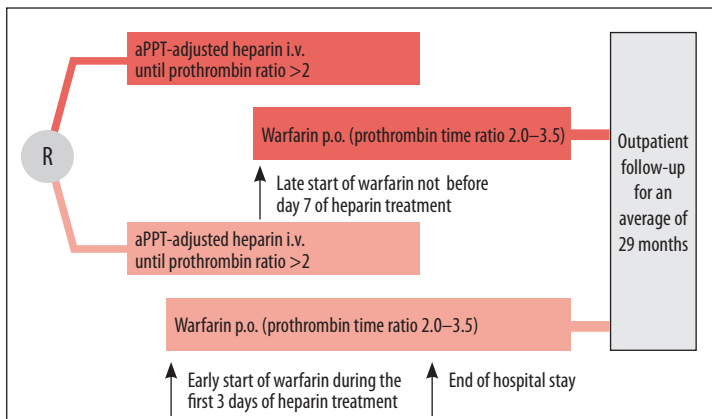
To define the most appropriate initial treatment schedule with heparin followed by warfarin

Trial design

Randomized, open study with parallel groups

Active treatment: warfarin 10 mg followed by adjusted dosing (prothrombin time ratio 2.0–3.5), starting not before 7 days of initial i.v. aPTT-adjusted (50–60 s) heparin treatment (n=127)

Control treatment: warfarin 10 mg followed by adjusted dosing (prothrombin time ratio 2.0–3.5), starting within 3 days of initial i.v. aPTT-adjusted (50–60 s) heparin treatment (n=139)



Endpoints

Primary efficacy endpoint: confirmed, probable, or possible, clinically apparent recurrent VTE during hospital stay

Secondary efficacy endpoints: symptomless I^{125} -fibrinogen uptake proximal to the level of initially documented VT and symptomless new perfusion lung scan defects

Safety endpoints: major and minor bleeding episodes during hospital stay

Trial participants

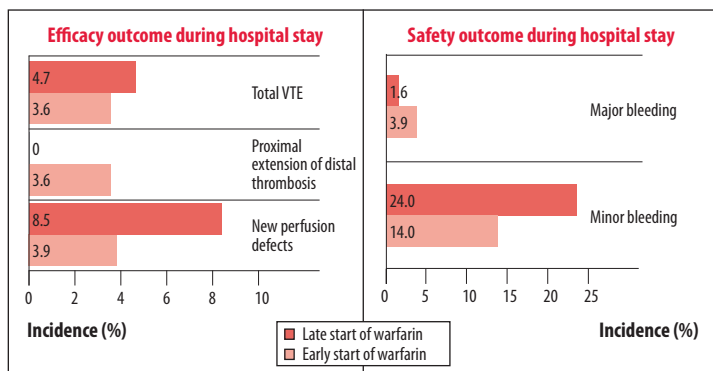
318 patients with confirmed VTE entered the study, 266 patients completed the trial

Results

Efficacy outcome: During the hospital stay, recurrent VTE developed in 6 of 127 patients (4.7%) with late and in 11 of 139 patients (3.6%) with early start of warfarin treatment. On routine I^{125} -fibrinogen leg scanning of patients presenting with distal thrombosis (n=55), symptomless proximal extension was found in 1 of 27 patients (3.6%) of the late start warfarin group compared to none of 28 patients in the early start warfarin group. Symptom-

less new perfusion defects in repeat lung scans were found in 8.5% of 118 patients in the late start and 3.9% of 128 patients in the early start warfarin group. During the follow-up of 29 months on average, mortality and symptomatic recurrence rates were similar in both groups

Safety outcome: During the hospital stay, major bleeding occurred in 2 patients in the late start warfarin (1.6%) and in 3 patients (3.9%) in the early start warfarin group. Minor bleeding episodes were observed in 31 (24%) vs. 19 (14%) in the late respectively early start warfarin group



Summary

Efficacy: The frequency of symptomatic VTE recurrence during hospital stay was comparable in both groups

Safety: The incidence of major and minor bleeding was similar in both groups

Reference

Gallus A, Jackaman J, Tillett J, Mills W, Wycherley A. Safety and efficacy of warfarin started early after submassive venous thrombosis or pulmonary embolism. *Lancet* 1986;2(8519):1293-1296

Corresponding author

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Hokusai-VTE

Edoxaban for the long-term treatment of venous thromboembolism (2013)

Condition

Acute treatment and secondary prevention of symptomatic VTE

Objective

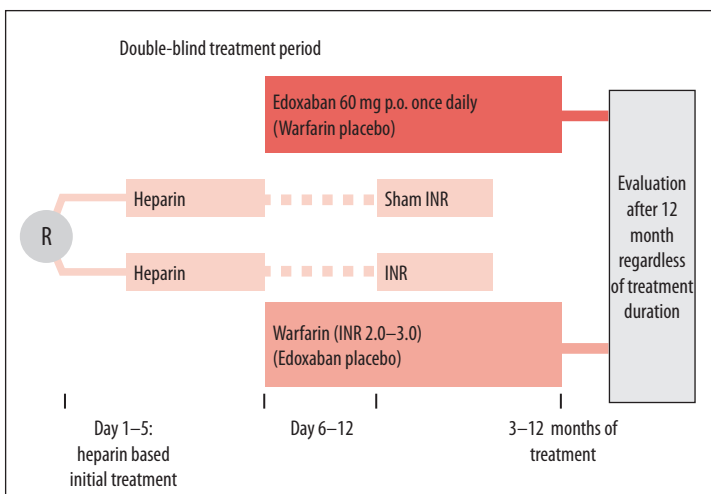
Evaluation of efficacy and safety of heparin followed by edoxaban versus heparin overlapping with warfarin in patients with DVT and/or PE

Trial design

Randomized, double-blind phase III non-inferiority study

Active treatment: heparin (LMW heparin s.c. 1 mg/kg twice daily or 1.5 mg/kg once daily; unfractionated heparin: 5,000 IU bolus i.v., 1,300 IU/h continuous infusion, minimum of 5 days and maximum of about 12 days treatment) plus edoxaban 60 mg p.o. once daily (30 mg once daily for patients with creatinine clearance of 30–50 ml/min or a body weight of 60 kg or less or in patients who were receiving concomitant treatment with potent P glycoprotein inhibitors) for 3–12 months (n=4118)

Control treatment: heparin as in active treatment plus warfarin (INR 2.0–3.0) (n=4122)



Endpoints

Primary efficacy endpoint: composite of DVT, non-fatal PE and fatal PE during 12 months, regardless of treatment duration

Secondary efficacy endpoint: composite outcome of symptomatic recurrent DVT, non-fatal recurrent PE and all-cause mortality during 12 months

Principal safety endpoint: major and clinically relevant non-major bleeding during 12 months

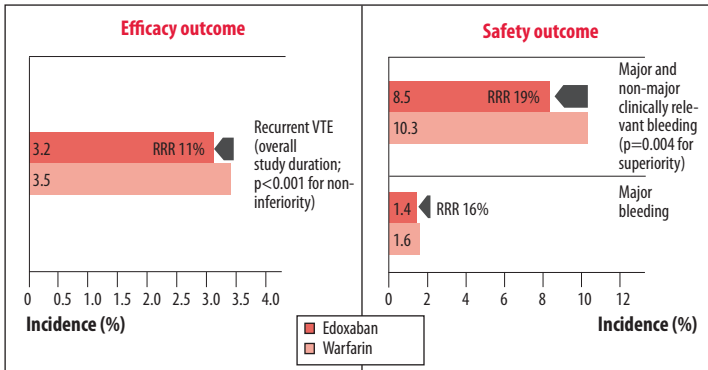
Trial participants

8292 patients >18 years with confirmed DVT and/or symptomatic PE

Results

Efficacy outcome: A recurrence of venous thromboembolism during the overall study period occurred in 130 of 4118 patients (3.2%) in the edoxaban group and in 146 of 4122 patients (3.5%) in the warfarin group. Among patients who qualified for the 30-mg dose of edoxaban, recurrent venous thromboembolism occurred in 22 of 733 patients (3.0%) receiving edoxaban, as compared with 30 of the 719 patients (4.2%) receiving warfarin

Safety outcome: Clinically relevant bleeding (major or non-major) occurred in 349 of 4118 patients (8.5%) in the edoxaban group and in 423 of 4122 patients (10.3%) in the warfarin group. Major bleeding occurred in 56 patients (1.4%) in the edoxaban group and 66 patients (1.6%) in the warfarin group. Among patients who qualified for the 30-mg dose of edoxaban, clinically relevant bleeding occurred in 58 of 733 patients (7.9%) who received edoxaban, and in 92 of the 719 patients (12.8%) who received warfarin



Summary

Edoxaban administered once daily after initial treatment with heparin was non-inferior to high-quality standard therapy and caused significantly less bleeding in a broad spectrum of patients with venous thromboembolism, including those with severe pulmonary embolism

Reference

The Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;369:1406-1415

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HULL

10-day versus 5-day course of heparin in VTE treatment (1990)

Condition

Treatment of proximal DVT

Objective

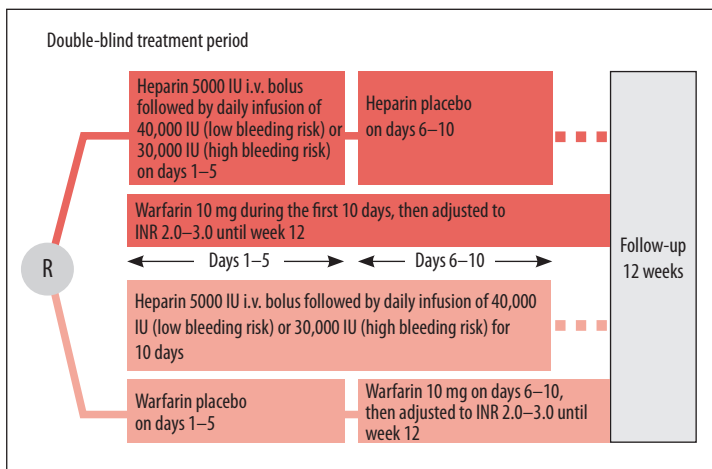
To compare safety and efficacy of a short course heparin with the traditional longer course treatment

Trial design

Randomized, double-blind study

Active treatment: heparin, i.v. bolus of 5000 IU followed by continuous infusion of 40,000 IU (patients with low bleeding risk) or 30,000 IU (patients with high bleeding risk) per 24 hours over 5 days plus warfarin for 12 weeks started on the first day (10 mg during the first 10 days, then adjusted to INR 2.0–3.0) (n=99)

Control treatment: heparin (same dosing as above) given over 10 days plus warfarin for 12 weeks started on the fifth day (10 mg during the first 5 days, then adjusted to INR 2.0–3.0) (n=100)



Endpoints

Primary efficacy endpoint: new documented symptomatic VTE during 3-month follow-up

Primary safety endpoints: major and minor bleeding complications during initial heparin treatment

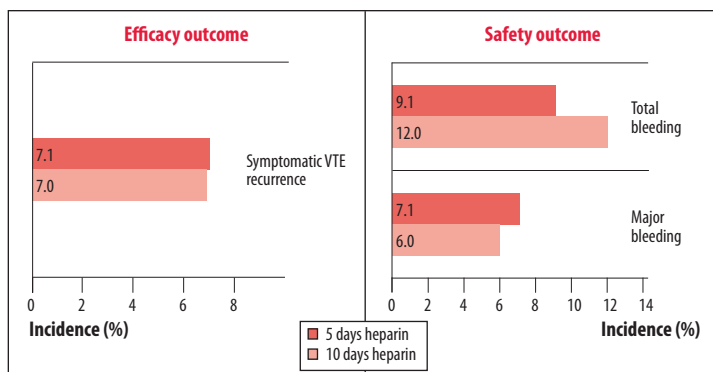
Trial participants

199 patients with acute proximal DVT documented by venography

Results

Efficacy outcome: 7 of 99 patients (7.1%) receiving the short course of heparin experienced a symptomatic VTE during the initial phase and the 3-month follow-up period compared to 7 of 100 patients (7.0%) receiving the standard long course

Safety outcome: Hemorrhagic complications occurred in 9 of 99 patients (9.1%) during short-term and in 12 of 100 (12.0%) during long-term heparin treatment. 7 (7.1%) vs. 6 (6.0%) of these complications were major bleeding



Summary

Efficacy: A 5-day course of heparin is as effective as a 10-day course in preventing symptomatic VTE recurrence in patients with acute proximal DVT

Safety: There was a trend towards less bleeding complications in the short-term heparin group

Reference

Hull RD, Raskob GE, Rosenbloom D, Panju AA, Brill-Edwards P, Ginsberg JS, Hirsh J, Martin GJ, Green D. Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis. *N Engl J Med* 1990;322:1260-1264

Corresponding author

Russell D. Hull, MD, University of Calgary, Department of Medicine, Foothills Hospital, 3330 Hospital Dr., N.W., Calgary, AB T2N 4N1, Canada

INTERACT (long-term follow-up)

INTEGRilin and Enoxaparin Randomized assessment of Acute Coronary syndrome Treatment trial (long-term follow-up) (2006)

Condition

Treatment of high-risk non-ST-segment elevation acute coronary syndromes

Objective

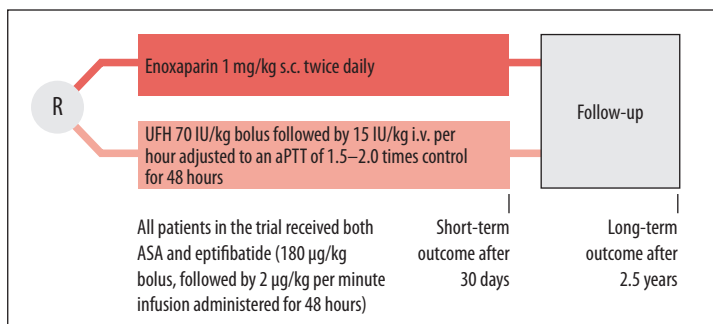
To determine whether the short-term benefits of enoxaparin compared with UFH observed in high-risk patients with non-ST-segment elevation acute coronary syndromes receiving ASA and eptifibatid are maintained over a prolonged period of follow-up

Trial design

Randomized, open-label trial with parallel groups

Active treatment: enoxaparin 1 mg/kg s.c. twice daily (n=325)

Control treatment: UFH 70 IU/kg bolus followed by 15 IU/kg i.v. per hour adjusted to an aPTT of 1.5–2.0 times control for 48 hours (n=314)



Endpoints

Primary efficacy endpoint: composite of death or non-fatal myocardial infarction

Secondary efficacy endpoints: occurrence of cardiac catheterization, coronary revascularization, and readmission to hospital for either unstable angina or congestive heart failure

Safety endpoint: non-CABG major bleeding

Trial participants

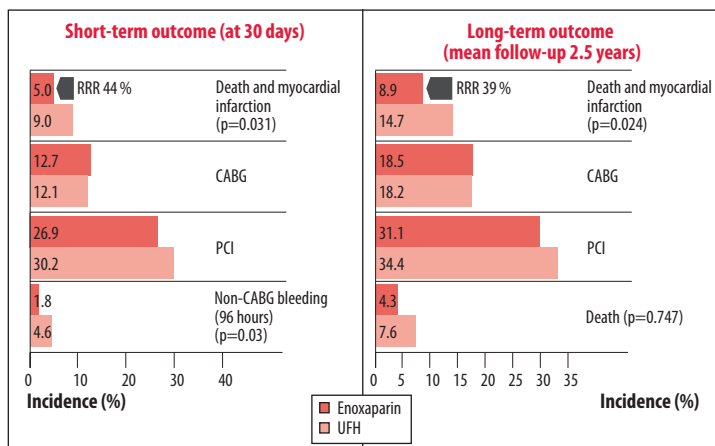
639 patients of the total population of 746 subjects in the INTERACT trial were followed up. This trial randomized 746 patients with ischemic symptoms at rest within the past 24 hours, ST-segment deviation, and/or elevated serum biomarkers to receive either enoxaparin or UFH for a 30-days follow-up period. The results of this trial are summarized as “short-term outcome”

Results

Short-term outcome: In the population of 746 patients, the incidence of death or myocardial infarction at 30 days was 44% lower in the enoxaparin-treated group compared with the UFH-treated group (5% vs. 9%). Non-CABG major bleeding was lower in the enoxaparin compared to the UFH group (1.8% vs. 4.6%)

Long-term outcome: The early benefit of enoxaparin at 30 days was maintained during longer-term follow-up. At a mean follow-up of 2.5 years, pa-

tients receiving enoxaparin had a significantly lower rate of death or myocardial infarction compared with those who received UFH (8.9% vs. 14.7%, relative risk reduction 39%). There was no difference in the frequency of cardiac catheterization in the groups receiving either enoxaparin or UFH. 38 patients died, 14 of 325 (4.3%) in the enoxaparin group and 25 of 314 (7.6%) in the UFH group



Summary

Efficacy: In high-risk patients with non-ST-elevation acute coronary syndromes receiving concomitant ASA and eptifibatide, the early outcome benefit of enoxaparin over UFH is sustained with a 39% relative risk reduction in death or myocardial infarction over a prolonged follow-up period of 2.5 years

Safety: When cardiac catheterization is not performed in the first 24–48 hours the use of enoxaparin is associated with less serious bleeding

Reference

Fitchett DH, Langer A, Armstrong PW, Tan M, Mendelsohn A, Goodman SG, for the INTERACT Trial Long-Term Follow-Up Investigators. Randomized evaluation of the efficacy of enoxaparin versus unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes receiving the glycoprotein IIb/IIIa inhibitor eptifibatide. Long-term results of the Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT) trial. *Am Heart J* 2006;151:373-379

Corresponding author

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ISIS Pilot

International Studies of Infarct Survival (1987)

Condition

Suspected myocardial infarction within 24 hours of symptom onset

Objective

To investigate the efficacy and safety of streptokinase in the acute phase and heparin as well as ASA thereafter

Trial design

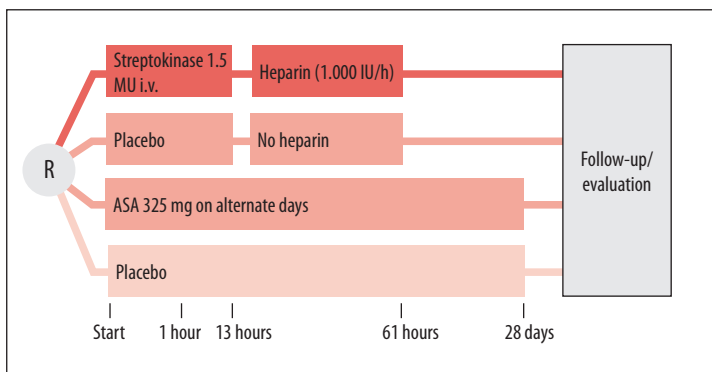
Randomized, placebo-controlled, double-blind study with 2x2x2 factorial design

Active treatment:

- Comparison 1: streptokinase 1.5 MU i.v. over 1 hour (n=413)
- Comparison 2: ASA 325 mg on alternate days for 28 days starting immediately (n=313)
- Comparison 3: heparin 1000 IU/h i.v. for 48 hours starting 12 hours after the end of streptokinase infusion (n=314)

Control treatment:

- Comparison 1: placebo infusion over 1 hour (n=206)
- Comparison 2: placebo tablets for 28 days (n=306)
- Comparison 3: no heparin (n=305)



Endpoints

Efficacy endpoints: non-fatal myocardial reinfarction in hospital, death in hospital, death after discharge, stroke

Safety endpoints: bleeding requiring transfusion, minor bleeding, other adverse events (hypotension, tachycardia, allergic reaction, nausea)

Trial participants

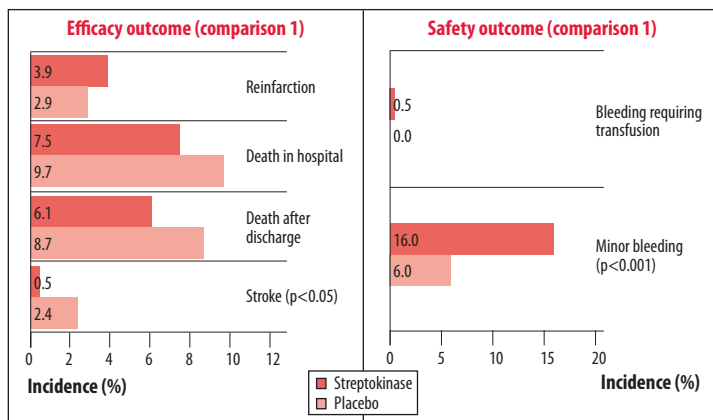
619 patients with suspected myocardial infarction (mean age 60 years) up to 24 hours after symptom onset

Results

Comparison 1 (streptokinase vs. placebo):

Efficacy: Non-fatal reinfarction occurred in 16 of 413 patients (3.9%) randomized to streptokinase and in 6 of 206 patients (2.9%) randomized to placebo. 31 patients (7.5%) receiving streptokinase died in hospital compared to 20 placebo patients (9.7%). After discharge, death occurred in 25 (6.1%)

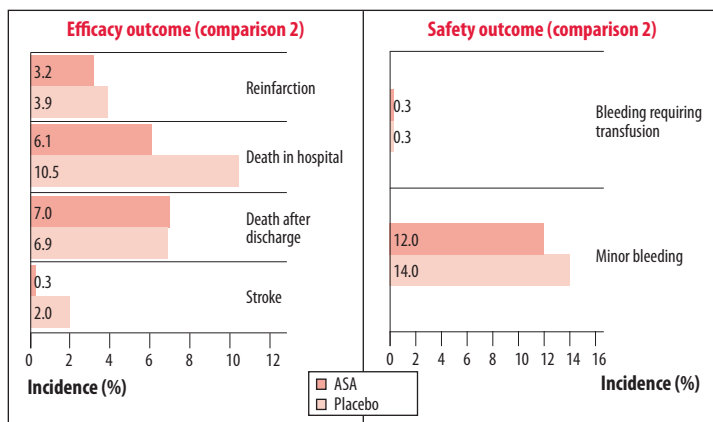
vs. 18 (8.7%) of the patients. After streptokinase, 2 patients (0.5%) experienced a stroke compared to 5 patients (2.4%) in the placebo group
Safety: 16% of the patients receiving streptokinase suffered minor bleeding events compared to 6% of the placebo patients. There were no significant differences in bleeding requiring transfusion between groups. Other adverse events, especially hypotension and nausea occurred more frequently in the streptokinase group



Comparison 2 (ASA vs. placebo):

Efficacy: Non-fatal reinfarctions occurred in 10 of 313 patients (3.2%) given ASA compared to 12 of 306 patients (3.9%) given placebo. In hospital deaths were registered in 19 (6.1%) vs. 32 patients (10.5%), and deaths after discharge in 22 (7.0%) vs. 21 patients (6.9%) receiving ASA respectively placebo. 1 patient (0.3%) in the ASA group compared to 6 patients in the placebo group (2.0%) suffered a stroke

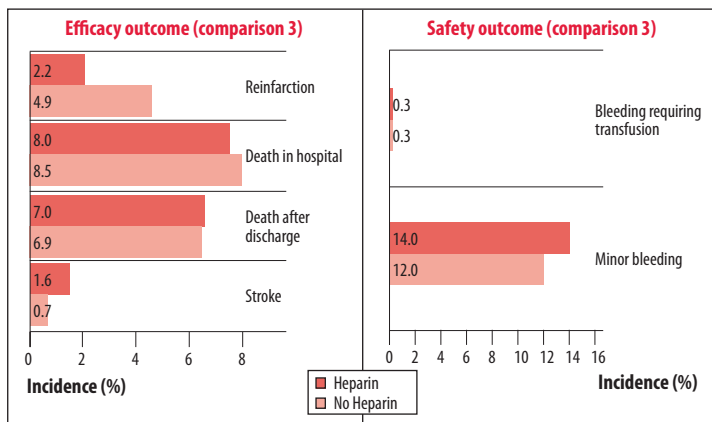
Safety: There was no significant increase in bruising or minor bleeding in the ASA group as well as in other adverse events compared to placebo



Comparison 3 (heparin vs. no heparin):

Efficacy: 7 of the 314 patients (2.2%) randomized to heparin vs. 15 of the 305 control patients (4.9%) suffered a non-fatal reinfarction in hospital. 25 patients (8.0%) in the heparin group vs. 26 control patients (8.5%) died in hospital, and 22 (7.0%) vs. 21 (6.9%) after discharge. In the heparin group, 5 patients (1.6%) experienced a stroke compared to 2 patients (0.7%) in the control group

Safety: Bruising and bleeding occurred in 14% of the patients given heparin and in 12% of the control patient. There was no difference in bleeding requiring transfusion between groups



Summary

Comparison 1 (streptokinase vs. placebo): High-dose streptokinase infusion was associated with a non-significant increase in reinfarction rate and decrease in mortality during hospital stay and thereafter, as well as a significant reduction in stroke incidence. Streptokinase induced a significant increase in minor bleeding

Comparison 2 (ASA vs. placebo): ASA was associated with a non-significant decrease in non-fatal reinfarctions, deaths after discharge and strokes, as well as a significant reduction in hospital mortality. There were no significant differences in bleeding between ASA and placebo

Comparison 3 (heparin vs. no heparin): Heparin was associated with a non-significant decrease in reinfarction and a trend towards more strokes. There were no differences in hospital deaths and mortality after discharge. In the heparin group, a non-significant trend towards more bruising and minor bleeding was observed

Reference

Collins R, Conway M, Alexopoulos D, Yusuf S, Sleight P, Brooks N, Bowes R, Marshall A, Harding S, Maskell G, Sanderson J, Mittra B, Hunt D, Tibbutt D, Sterry H, Jackson D, Scrimgeour A, Lim L, Appleby P, Parish S, Peto R. Randomized factorial trial of high-dose intravenous streptokinase, of oral aspirin and of intravenous heparin in acute myocardial infarction. *Eur Heart J* 1987;8:634-642

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J-ROCKET AF

Japanese Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonist for prevention of stroke and Embolism Trial in Atrial Fibrillation (2012)

Condition

Prevention of VTE in Japanese patients with non-valvular AF and increased risk for stroke

Objective

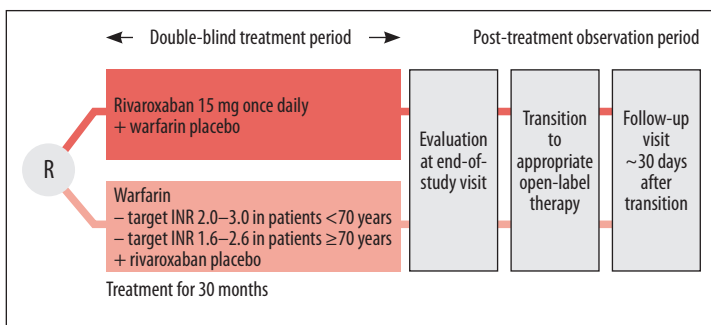
To compare the safety of a Japan-specific rivaroxaban dose with warfarin administered according to Japanese guidelines in Japanese patients with AF

Trial design

Randomized, double-blind, double-dummy phase III study

Active treatment: rivaroxaban 15 mg once daily plus warfarin placebo for 30 months (n=639)

Control treatment: warfarin dose-adjusted to a target INR of 2.0–3.0 in patients aged <70 years, or a reduced INR of 1.6–2.6 in patients aged ≥70 years (according to Japanese guidelines), plus rivaroxaban placebo for 30 months (n=639)



Endpoints

Primary efficacy endpoint: composite of adjudicated all-cause stroke (ischemic or hemorrhagic) and non-CNS systemic embolism

Secondary efficacy endpoints: composite of stroke, systemic embolism, and vascular death and composite of stroke, systemic embolism, vascular death, and MI

Primary safety endpoint: composite of major and non-major clinically relevant bleeding

Trial participants

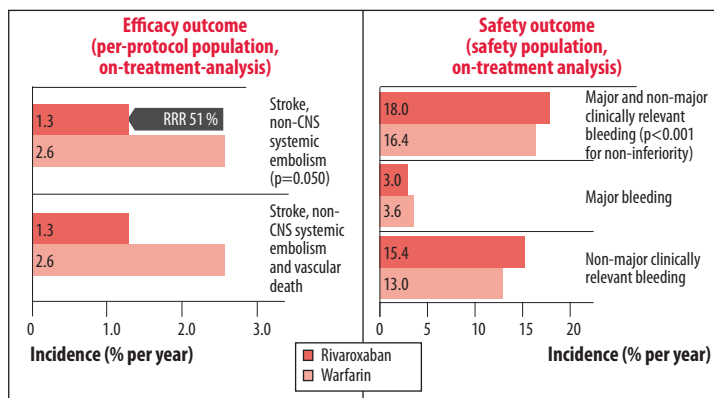
1280 Japanese patients aged ≥20 years (mean age 71.1 years) with non-valvular AF, documented electrocardiographically ≤30 days before randomization, and with ≥2 risk factors for thromboembolism. The safety population (n=1278, 639 in each group) included all patients who received ≥1 dose of study drug. 1274 patients without major protocol violations were included in the per-protocol population (637 in each group)

Results

Efficacy outcome: In the per-protocol population, while on treatment, stroke or non-CNS systemic embolism occurred at a rate of 1.3% per year in

the rivaroxaban arm, compared with 2.6% per year in the warfarin arm (RRR 51%; $p=0.050$). All-cause stroke occurred at a lower rate in patients treated with rivaroxaban than with warfarin (10/637 patients vs. 21/637 patients; HR 0.46), as did primary ischemic stroke (7/637 patients vs. 17/637 patients; HR 0.40). Primary hemorrhagic stroke occurrence was similar in both treatment arms (3/637 Patients vs. 4/637 patients; HR 0.73). The numbers of MI, vascular death, and all-cause mortality were also low in both treatment groups.

Safety outcome: The composite of major bleeding and non-major clinically relevant bleeding events, evaluated in the safety population (on-treatment analysis), occurred in 138 patients in the rivaroxaban group (18.0% per year) compared with 124 patients in the warfarin group (16.4% per year) (HR 1.11; p for non-inferiority <0.001). The observed rate of major bleeding events was 3.0% per year in the rivaroxaban group compared with 3.6% per year in the warfarin group (HR 0.85). Non-major clinically relevant bleeding event rates were 15.4% per year in rivaroxaban-treated patients compared with 13.0% per year in warfarin-treated patients (HR 1.20)



Summary

Safety: The oral direct factor XA inhibitor rivaroxaban was non-inferior to warfarin dose-adjusted according to Japanese guideline recommendations with respect to the primary safety outcome of major plus non-major clinically relevant bleeding. Although no significant differences in overall bleeding rates were observed, rivaroxaban use was associated with a non-significant lower major bleeding rate and a slightly higher non-major clinically relevant bleeding rate than treatment with warfarin

Efficacy: Compared with warfarin therapy, there was a strong trend towards reduction in stroke and non-CNS systemic embolism with rivaroxaban. The findings of J-ROCKET AF support bridging of the broader safety and efficacy data from the larger, global ROCKET AF study to Japanese patients with AF

Reference

Hori M, Matsumoto M, Tanahashi N, Momomura SI, Uchiyama S, Goto S, Izumi T, Koretsune Y, Kajikawa M, Kato M, Ueda H, Iwamoto K, Tajiri M, on behalf of the J-ROCKET AF study investigators. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation. *Circ J* 2012 Jun 5. [Epub ahead of print]

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LAFIT

Long-term Anticoagulation for a First episode of Idiopathic venous Thromboembolism (1999)

Condition

Long-term prevention of recurrent idiopathic VTE

Objective

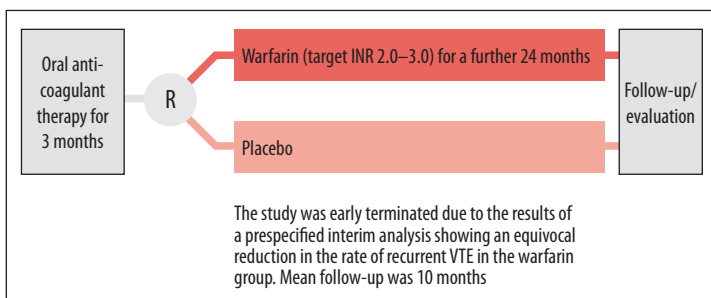
To determine the effects of extending a 3-month course of oral anticoagulant therapy for a further 24 months on the rates of recurrent symptomatic VTE and bleeding in patients with a first episode of idiopathic VTE

Trial design

Randomized, double-blind study

Active treatment: continuation of warfarin therapy (target INR 2.0–3.0) for a further 24 months (n=79)

Control treatment: placebo (n=83)



Endpoints

Primary efficacy endpoint: symptomatic, objectively confirmed recurrence of VTE

Primary safety endpoints: major and minor bleeding, all-cause death

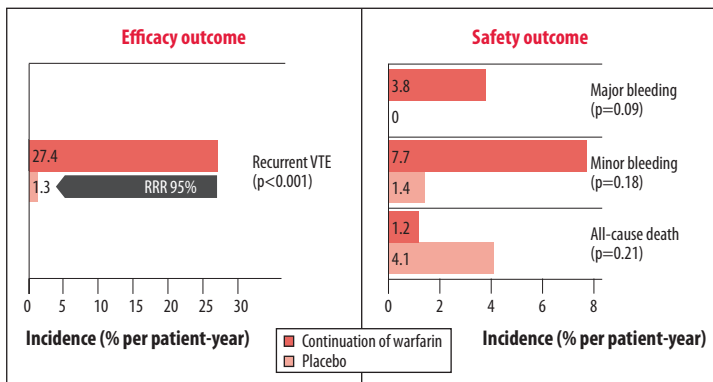
Trial participants

162 consecutive patients (mean age 59 years) with a first episode of idiopathic VTE who had completed 3 uninterrupted months of oral anticoagulant treatment after an initial course of treatment with UFH or LMWH

Results

Efficacy outcome: Of the 79 patients assigned to continue warfarin, one had a confirmed episode of recurrent VTE (1.3% per patient-year), as compared with 17 of 83 patients given placebo (27.4% per patient-year). This resulted in a relative risk reduction of 95%. All episodes of recurrent VTE were idiopathic

Safety outcome: Major bleeding occurred in 3 patients assigned to warfarin (3.8% per patient-year) and no such episodes among those receiving placebo. Minor bleeding occurred in 7.7% and 1.4% per patient-years, respectively. One patient in the warfarin group and 3 patients in the placebo group died during the study (1.2% vs. 4.1% per patient-year)



Summary

Efficacy: The clinical benefit achieved during the additional 24 months of oral anticoagulant therapy was significant. Therefore patients with a first episode of idiopathic VTE should be treated with anticoagulants for longer than 3 months

Safety: Extended warfarin therapy was associated with a risk of major bleeding of about 3% per year

Reference

Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, Turpie AG, Green D, Ginsberg JS, Wells P, MacKinnon B, Julian JA. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999;340:901-907

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LEVINE (1)

Comparing activated thromboplastin time with heparin assay in patients requiring large doses of heparin (1994)

Condition

Treatment of patients with acute VTE who require large daily doses of intravenous heparin

Objective

To compare the monitoring of heparin therapy either by anti-factor Xa levels or by the aPTT in patients requiring 35,000 IU or more of intravenous heparin for the treatment of acute VTE

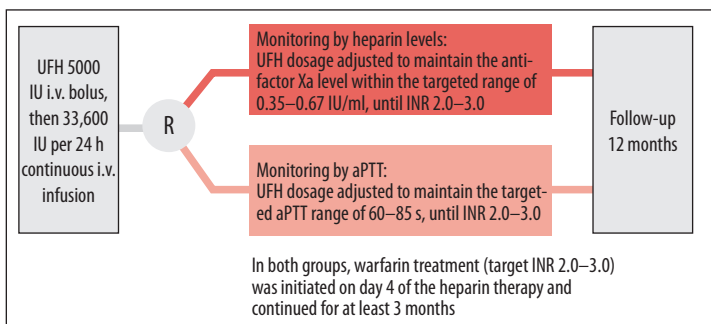
Trial design

Randomized, controlled study with parallel groups

Active treatment: All patients (n=131) received an initial i.v. heparin bolus of 5000 IU followed by an infusion at a starting dose of 33,600 IU per 24 h (20,000 IU in 500 ml of 2/3 : 1/3 dextrose-saline infusion at 35 ml/h). The aPTT was measured 6 hours after the initiation of therapy, and the dosage was adjusted according to a standard nomogram. The following day, patients who required the equivalent of 35,000 IU of heparin or more were eligible for randomization to one of the 2 methods of monitoring the heparin therapy

- Monitoring by heparin level: Heparin dosage was adjusted to maintain the anti-factor Xa level within the targeted range of 0.35–0.67 IU/ml (n=65)
- Monitoring by aPTT: Heparin dosage was adjusted to maintain the targeted aPTT range of 60–85 s (n=66)

Both ranges were equivalent to a heparin level of 0.2–0.4 IU/ml by protamine titration



Endpoints

Primary endpoints: recurrent venous thrombosis, PE, and bleeding

Secondary endpoints: heparin dosage, aPTT and anti-factor Xa levels

Trial participants

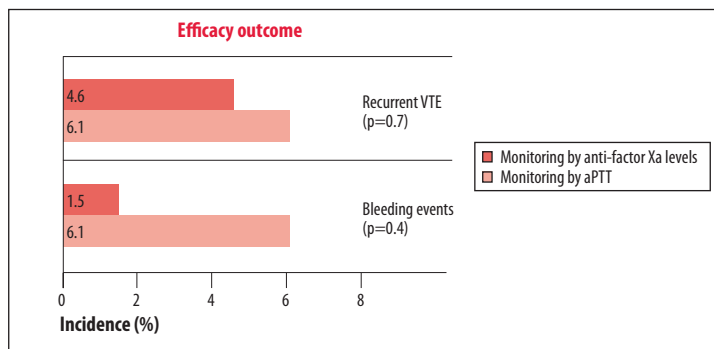
131 patients with acute DVT, PE, or axillary vein thrombosis who required 35,000 IU or more of intravenous heparin by continuous infusion during the previous 24 hours

Results

Primary outcome: 3 of 65 patients (4.6%) in the anti-factor Xa group experienced recurrent VTE compared with 4 of 66 (6.1%) patients in the aPTT

group. Bleeding events occurred in one patient (1.5%) in the anti-factor Xa group and in 4 patients (6.1%) in the aPTT group

Secondary endpoints: During the first 4 days, the patients in the aPTT group required a significantly greater amount of heparin ($p < 0.001$). The daily mean aPTT was subtherapeutic in patients in the anti-factor Xa group, and it was within the therapeutic range in the aPTT group. The daily mean anti-factor Xa levels for both groups were within the therapeutic range



Summary

The incidence of recurrent VTE was similar in both treatment groups, and there was a non-significant trend for lower bleeding in patients monitored by anti-factor Xa levels. These findings indicate that in patients who are resistant by the aPTT assay, dosage escalation can be avoided without compromising efficacy, by performing a heparin assay and not increasing the dose if the heparin level is in the therapeutic range

Reference

Levine MN, Hirsh J, Gent M, Turpie AG, Cruickshank M, Weitz J, Anderson D, Johnson M. A randomized trial comparing activated thromboplastin time with heparin assay in patients with acute venous thromboembolism requiring large daily doses of heparin. *Arch Intern Med* 1994;154:49-56

Corresponding author

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LEVINE (2)

Treatment of proximal DVT with low-molecular-weight heparin at home vs. standard heparin in hospital (1996)

Condition

Treatment of acute proximal DVT in outpatients

Objective

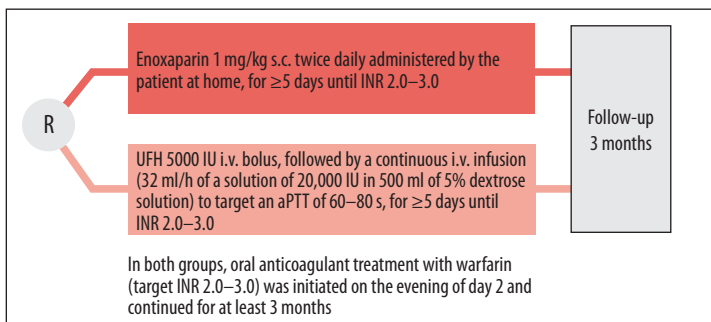
To compare the efficacy and safety of fixed-dose subcutaneous low-molecular-weight heparin given at home with those of adjusted-dose intravenous standard heparin given in the hospital in patients with proximal DVT

Trial design

Randomized, open study with parallel groups

Active treatment: enoxaparin 1 mg/kg s.c. twice daily administered by the patient at home (hospitalized patients were allowed to be discharged early) for ≥ 5 days and until the concomitant oral anticoagulant therapy resulted in an INR 2.0–3.0 (n=247)

Control treatment: UFH 5000 IU i.v. bolus, followed by continuous infusion of 20,000 IU in 500 ml of a 5% dextrose solution, with 32 ml administered per hour to target an aPTT of 60–80 s, for ≥ 5 days until INR 2.0–3.0. The patients were treated in hospital (n=253)



Endpoints

Primary efficacy endpoint: symptomatic recurrent VTE during 3-month follow-up

Primary safety endpoints: major and minor bleeding during the period of administration of study medication or within 48 hours after its discontinuation

Secondary endpoint: hospital stay

Trial participants

500 consecutive symptomatic outpatients with acute proximal DVT proven on venography or duplex scan but with no signs of PE

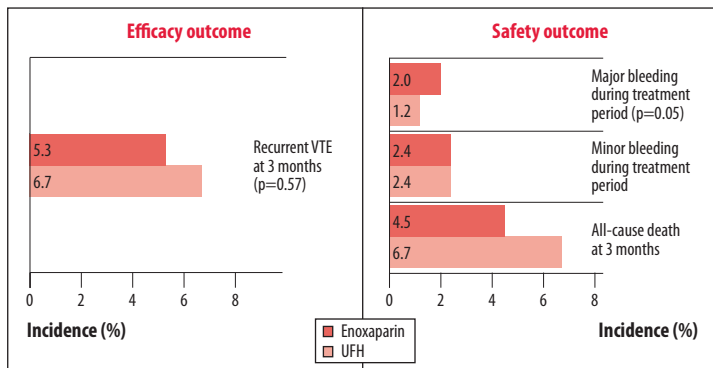
Results

Efficacy outcome: During the 3-month follow-up, 13 of the 247 patients assigned to enoxaparin (5.3%) and 17 of the 253 patients receiving standard heparin (6.7%) had symptomatic recurrent VTE. 2 patients in the UFH group had PE, and both died

Safety outcome: Major bleeding complications occurred during the period of study-drug administration or the subsequent 48 hours in 5 patients given

enoxaparin (2.0%) as compared with 3 patients given UFH (1.2%). 2 of the 5 episodes of bleeding in the enoxaparin group were fatal. Minor bleeding was observed in 2.4% of the patients in both groups

Hospital stay: Of the 247 patients assigned to enoxaparin, 120 were never admitted to the hospital, and the remaining 127 patients spent an average of 2.2 days in the hospital after randomization. The average hospital stay for all patients in this group was 1.1 days, as compared with 6.5 days for the patients receiving standard heparin



Summary

Efficacy: Treatment of proximal DVT with enoxaparin at home was least as effective as treatment with standard heparin in hospital, with a non-significant trend in favor of enoxaparin

Safety: Rates of major bleeding were low and similar in both treatment groups

Reference

Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, Ginsberg J, Turpie AG, Demers C, Kovacs M, Geerts W, Kassis J, Desjardins L, Cusson J, Cruickshank M, Powers P, Brien W, Haley S, Willan A. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med* 1996;334:677-681

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MAGELLAN

Multicenter, randomized, parallel Group Efficacy and safety study for the prevention of VTE in hospitalized medically ill patients comparing rivaroxaban with enoxaparin (2011)

Condition

Prophylaxis for VTE in hospitalized acutely medically ill patients

Objective

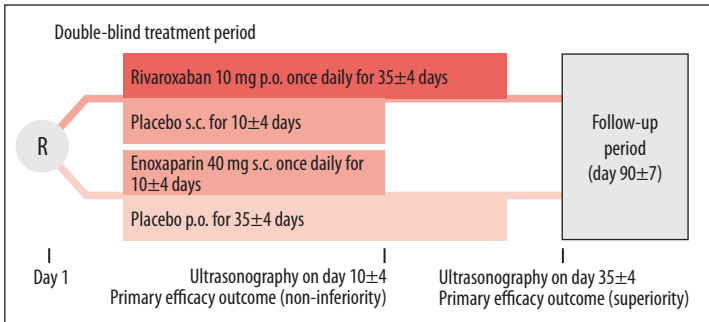
To prove non-inferiority of standard-duration (~10 days) anticoagulation with rivaroxaban compared to enoxaparin and to prove superiority of extended-duration (~35 days) rivaroxaban compared to standard-duration enoxaparin in the prevention of VTE in acutely medically ill patients

Trial design

Randomized, double-blind phase III study

Active treatment: rivaroxaban 10 mg p.o. once daily for 35±4 days; placebo injections as in control treatment (n=4050)

Control treatment: enoxaparin 40 mg s.c. once daily for 10±4 days; placebo tablets as in active treatment (n=4051)



Endpoints

Primary efficacy endpoint: composite of asymptomatic and symptomatic DVT, non-fatal PE, and VTE-related death at day 10 and 35

Secondary efficacy endpoint: composite of asymptomatic proximal DVT, symptomatic DV, symptomatic non-fatal PE and all-cause mortality at day 10 and 35

Primary safety endpoint: composite of major bleeding and clinically relevant non-major bleeding during treatment and within 2 days after the last dose

Secondary safety endpoints: treatment-emergent adverse events and abnormal laboratory parameters

Trial participants

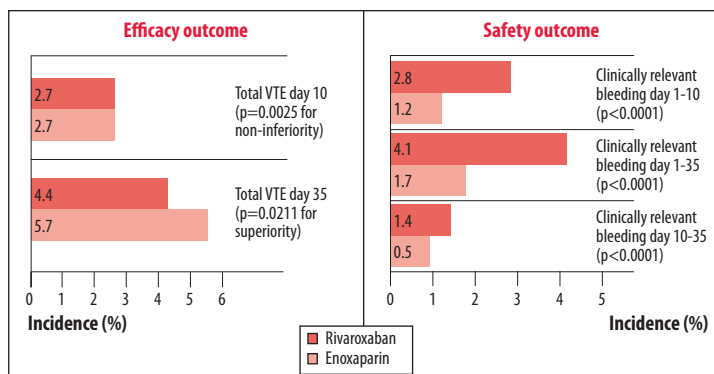
8101 patients ≥40 years hospitalized and immobilized for acute medical illness

Results

Efficacy outcome: In the population with evaluable efficacy outcome the primary efficacy endpoint at day 10 occurred in 78 of 2939 patients (2.7%) given rivaroxaban and in 82 of 2993 patients (2.7%) given enoxaparin. At day

35 it occurred in 131 of 2967 patients (4.4%) receiving rivaroxaban and in 175 of 3057 patients (5.7%) receiving enoxaparin/placebo

Safety outcome: In the safety population major bleeding and clinically relevant non-major bleeding up to day 10 occurred in 111 of 3997 patients (2.8%) receiving rivaroxaban and in 49 of 4001 patients (1.2%) receiving enoxaparin. Up to day 35 the primary safety endpoint occurred in 164 (4.1%) patients in the rivaroxaban group and in 67 (1.7%) in the enoxaparin group. The incidence of other adverse events (cardiac events) and abnormal laboratory parameters (liver function) was similar in the 2 groups



Summary

Efficacy: Rivaroxaban was non-inferior to enoxaparin in reducing the risk of VTE at day 10. Extended thromboprophylaxis with rivaroxaban was superior to enoxaparin followed by placebo in reducing the risk of VTE at day 35

Safety: Overall bleeding rates were low, but significantly higher in the rivaroxaban arm across the entire study period. Rates of other adverse events were similar in both arms

References

- (1) Cohen AT, Spiro TE, Büller HR, Haskell L, Hu D, Hull R, Mebazaa A, Merli G, Schellong S, Spyropoulos A, Tapson V. Extended-duration rivaroxaban thromboprophylaxis in acutely ill medical patients: MAGELLAN study protocol. *J Thromb Thrombolysis* 2011;4:407-416
- (2) Bayer press release. In the prevention of VTE in acutely ill patients, rivaroxaban compares favorably with enoxaparin but does not show a consistent net clinical benefit. April 5, 2011

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MATISSE-DVT

Mondial Assessment of Thromboembolism treatment Initiated by Synthetic pentasaccharide with Symptomatic Endpoints – Deep Vein Thrombosis (2004)

Condition

Initial treatment of symptomatic DVT

Objective

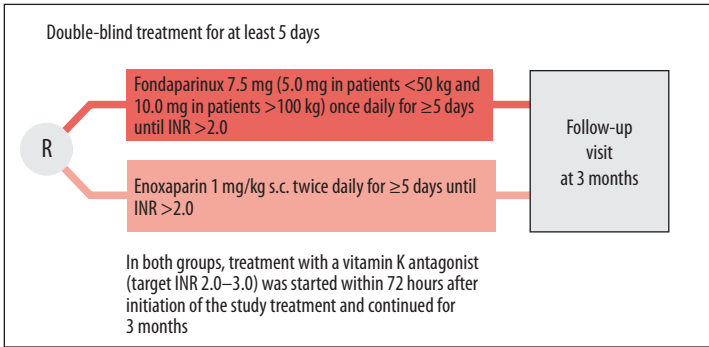
To evaluate the efficacy and safety of fondaparinux compared with enoxaparin in the initial treatment of symptomatic DVT

Trial design

Randomized, double-blind placebo-controlled study

Active treatment: fondaparinux 7.5 mg (5.0 mg in patients weighing <50 kg and 10.0 mg in patients weighing >100 kg) s.c. once daily for at least 5 days and until the use of vitamin K antagonists resulted in an INR >2.0; enoxaparin placebo (n=1098)

Control treatment: enoxaparin 1 mg/kg s.c. twice daily for at least 5 days and until vitamin K antagonists induced an INR >2.0; fondaparinux placebo (n=1107)



Endpoints

Primary efficacy endpoint: 3-month incidence of symptomatic recurrent VTE complications (DVT and PE)

Primary safety endpoints: major bleeding during the initial treatment period and 3-months mortality

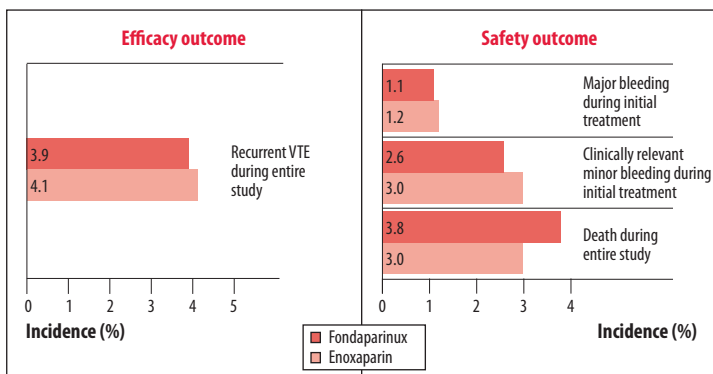
Trial participants

2205 patients (mean age 61 years) with acute symptomatic DVT and who required antithrombotic therapy

Results

Efficacy outcome: The composite primary endpoint of recurrent thromboembolic events at 3 months occurred in 43 of the 1098 patients receiving fondaparinux (3.9%) and in 45 of the 1107 patients assigned to enoxaparin (4.1%)

Safety outcome: The incidence of major bleeding during initial treatment was 1.1% in the fondaparinux group and in 1.2% in the enoxaparin group. At 3 months, 3.8% of the patients given fondaparinux and 3.0% of the patients given enoxaparin had died



Summary

Efficacy: Once-daily administration of fondaparinux was not inferior to twice daily administration of enoxaparin for initially treating symptomatic DVT

Safety: The incidence of major bleeding was similar with fondaparinux and enoxaparin

Reference

Büller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovello F, Prins MH, Raskob G, Segers AE, Cariou R, Leeuwenkamp O, Lensing AW, for the Matisse Investigators. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med* 2004;140:867-873

Corresponding author

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MATISSE-PE

Mondial Assessment of Thromboembolism treatment Initiated by Synthetic pentasaccharide with Symptomatic Endpoints – Pulmonary Embolism (2003)

Condition

Treatment of acute symptomatic pulmonary embolism (PE)

Objective

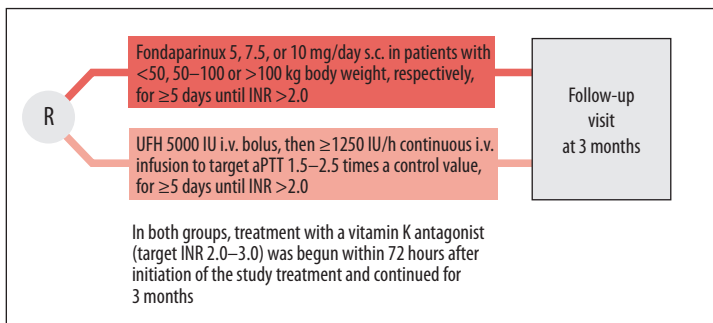
To determine whether fixed-dose fondaparinux is at least as effective as adjusted-dose UFH for the initial treatment of symptomatic PE

Trial design

Randomized, open trial with parallel groups

Active treatment: fondaparinux 5.0, 7.5, or 10.0 mg s.c. once daily in patients weighing <50, 50–100, or >100 kg, respectively, given for at least 5 days and until the use of vitamin K antagonists resulted in an INR >2.0 (n=1103)

Control treatment: UFH 5000 IU i.v. bolus, then ≥ 1250 IU/h continuous i.v. infusion to target aPTT 1.5–2.5 times a control value, for ≥ 5 days until INR >2.0 (n=1110)



Endpoints

Primary efficacy endpoint: 3-month incidence of the composite of symptomatic, recurrent PE (non-fatal or fatal) and new or recurrent DVT

Primary safety endpoints: major bleeding during the initial treatment period and death during the 3-month study period

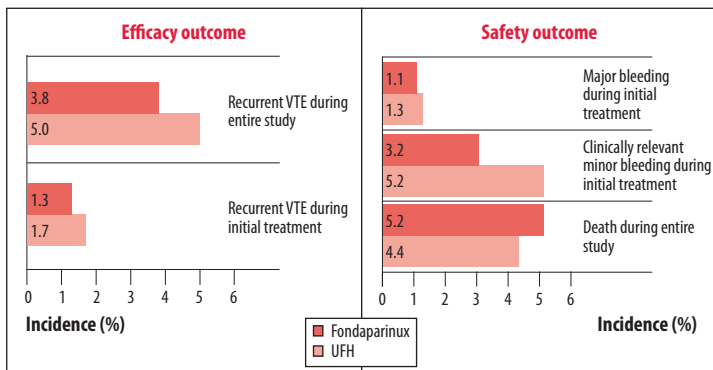
Trial participants

2213 patients (mean age 62.5 years) with acute symptomatic PE and who required antithrombotic therapy

Results

Efficacy outcome: The composite primary endpoint of recurrent thromboembolic events occurred in 42 of the 1103 patients assigned to fondaparinux (3.8%) and in 56 of the 1110 patients receiving UFH (5.0%)

Safety outcome: Major bleeding during initial treatment occurred in 1.3% of the patients in the fondaparinux group and in 1.1% of the UFH group. Mortality rates at 3 months were similar in the 2 groups (5.2% with fondaparinux vs. 4.4% with UFH)



Summary

Efficacy: Once-daily unmonitored subcutaneous administration of fondaparinux is at least as effective as adjusted-dose intravenous administration of UFH in the initial treatment of hemodynamically stable patients with PE

Safety: The incidence of major bleeding was similar with fondaparinux and UFH

Reference

Büller 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;349:1695-1702

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MEDENOX

Prophylaxis in MEDical patients with ENOXaparin (1999)

Condition

Prophylaxis for VTE in acutely ill medical patients

Objective

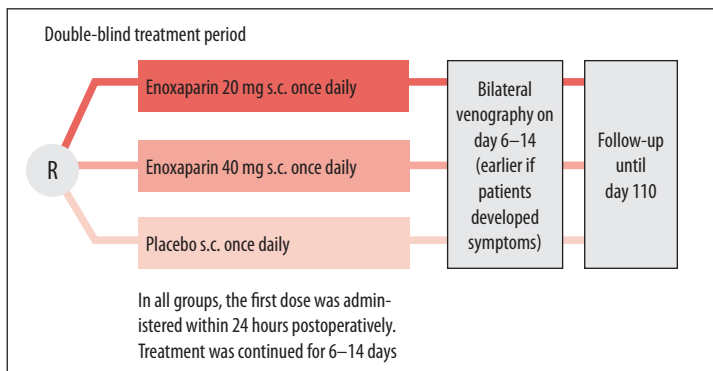
To evaluate the efficacy and safety of 2 dosage regimens of enoxaparin for the prevention of VTE in medical patients immobilized with severe illness

Trial design

Randomized, double-blind, placebo-controlled study

Active treatment: enoxaparin 20 mg (n=364) or 40 mg (n=367) s.c. once daily for 6–14 days

Control treatment: placebo s.c. once daily for 6–14 days (n=371)



Endpoints

Primary efficacy endpoint: DVT, PE, or both between days 1 and 14

Secondary efficacy endpoint: VTE between days 1 and 110

Safety endpoints: major and minor bleeding between days 1 and 14, overall mortality between days 1 and 110, and thrombocytopenia

Trial participants

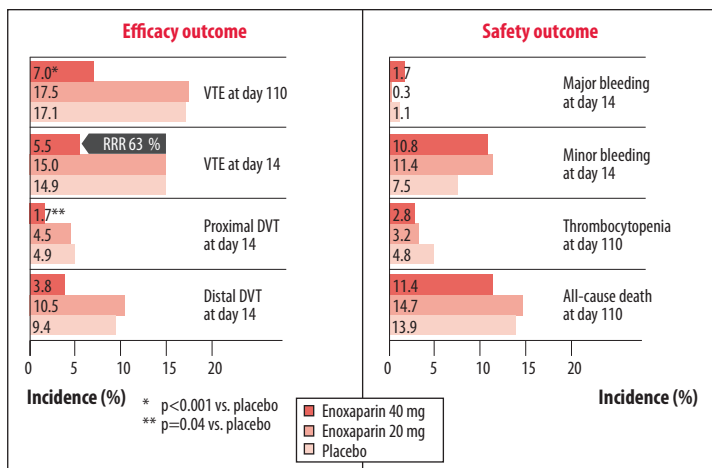
1102 general medical patients (mean age 73 years) whose projected stay in the hospital was at least 6 days, and who were immobilized for <3 days for acute medical disorders (heart failure NYHA class III or IV, respiratory failure, acute infection, rheumatic disorder, or active episode of inflammatory bowel disease); most of the patients had ≥ 2 risk factors for VTE

Results

Efficacy outcome: 866 patients were included in the analysis. The incidence of VTE by day 14 was 15.0% (43 of 287) in patients receiving enoxaparin 20 mg, 5.5% (16 of 291) in those receiving enoxaparin 40 mg, and 14.9% (43 of 288) in those assigned to placebo. The difference observed between enoxaparin 40 mg and placebo was statistically significant ($p < 0.001$; relative risk reduction 63%). The incidence of any DVT or of proximal or distal DVT was significantly lower among patients in the 40-mg group than among those given placebo; the risk reduction for proximal DVT was 65%. The benefit observed with enoxaparin was maintained during the 3-months follow-up period. By 110 days, the incidence of VTE was 17.5%, 7.0%, and 17.1%,

respectively ($p < 0.001$ for enoxaparin 40 mg vs. placebo). There were no significant differences in primary outcome between the 20-mg group and the placebo group

Safety outcome: 1073 patients were included in the analysis of safety. During the treatment period, major hemorrhage occurred in 1 of 351 patients assigned to enoxaparin 20 mg (0.3%), 6 of 360 patients receiving enoxaparin 40 mg (1.7%), and 4 of 362 patients of the placebo group (1.1%). The rates for minor bleeding complications were 11.4%, 10.8%, and 7.5%, respectively. The incidence of thrombocytopenia was not different between treatment groups. At 110 days, 142 patients had died: 50 in the placebo group (13.9%), 51 in the 20-mg group (14.7%), and 41 in the 40-mg group (11.4%)



Summary

Efficacy: Enoxaparin 40 mg reduced significantly the risk of VTE in acutely ill medical patients during hospitalization. This benefit was maintained during 3-month follow-up

Safety: Bleeding complications and other adverse events did not significantly differ between the placebo group and either enoxaparin group

References

Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, Leizorovicz A, Nguyen H, Olsson CG, Turpie AG, Weisslinger N. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med* 1999;341:793–800

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MONREAL

Low-molecular-weight heparin vs. conventional low-dose heparin for the prevention of venous thromboembolism in patients with hip fracture (1989)

Condition

Prophylaxis for thromboembolic complications in patients admitted for surgery because of hip fracture

Objective

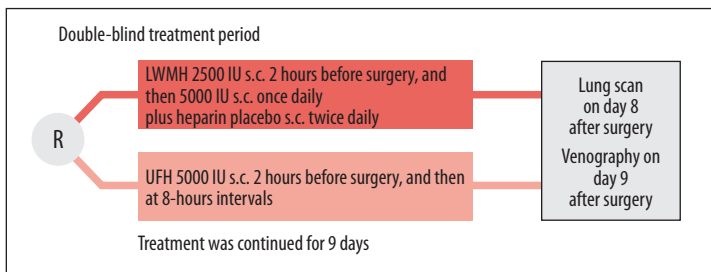
To compare the efficacy of a LMWH with that of standard low-dose heparin in the prevention of VTE in patients with hip fracture

Trial design

Prospective, randomized, double-blind study

Active treatment: LMWH (2165 LMWH, Kabi Vitrum AG) 2500 IU s.c. 2 hours before surgery, thereafter 5000 IU s.c. once daily for 9 days; heparin placebo s.c. twice daily (n=46)

Control treatment: UFH 5000 IU s.c. 2 hours before surgery, thereafter at 8-hours intervals for 9 days (n=44)



Endpoints

Primary efficacy endpoint: DVT and PE during the postoperative period

Primary safety endpoints: bleeding, red cell transfusion requirement, hematocrit level

Trial participants

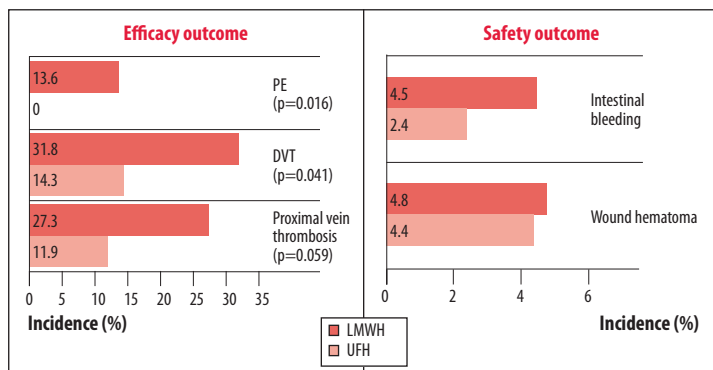
90 consecutive patients (>40 years of age) who were admitted because of hip fracture and were operated on the day of fracture; 86 patients were evaluable

Results

Efficacy outcome: 6 of 44 patients (13.6%) of the LMWH group developed postoperative PE, but none of the 42 patients in the UFH group; the difference was statistically significant. Indeterminate lung scans were detected in 8 patients (18.2%) assigned to LMWH and 6 patients (13.6%) given UFH. DVT occurred in significantly more patients given LMWH than in UFH-treated patients (31.8% vs. 14.3%). The rates for proximal vein thrombosis were 27.3% and 11.9%, respectively

Safety outcome: Intestinal bleeding complications occurred in 2 patients (4.5%) receiving LMWH and in 1 patient (2.4%) assigned to UFH. 2 patients in each group developed a wound hematoma (4.4% and 4.8%, respectively). Red cell transfusion requirements were larger in the LMWH group (40 units) than in the UFH group (20 units). The hematocrit levels on day 4 after surgery

were similar in both groups. 2 patients in the LMWH group and 3 in the UFH group died (4.5% vs. 7.1%)



Summary

Efficacy: In patients undergoing surgery because of hip fracture, low-dose standard heparin was more effective in preventing postoperative PE and DVT than a single daily injection of LMWH, in the dosage used

Safety: No significant difference was observed between both treatment groups in terms of bleeding, fall in postoperative hemoglobin, and the frequency of wound hematoma

Reference

Monreal M, Lafoz E, Navarro A, Granero X, Caja V, Caceres E, Salvador R, Ruiz J. A prospective double-blind trial of a low molecular weight heparin once daily compared with conventional low-dose heparin three times daily to prevent pulmonary embolism and venous thrombosis in patients with hip fracture. *J Trauma* 1989;29:873-875

Corresponding author

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OASIS Pilot

Organization to Assess Strategies for Ischemic Syndromes pilot study (1998)

Condition

Treatment of unstable angina or myocardial infarction without ST elevation (NSTEMI) after 3 days of intravenous antithrombotic therapy

Objective

To investigate the efficacy and safety of low-intensity warfarin and then, in a second trial phase, the effects of moderate-intensity warfarin in patients with unstable angina or NSTEMI

Trial design

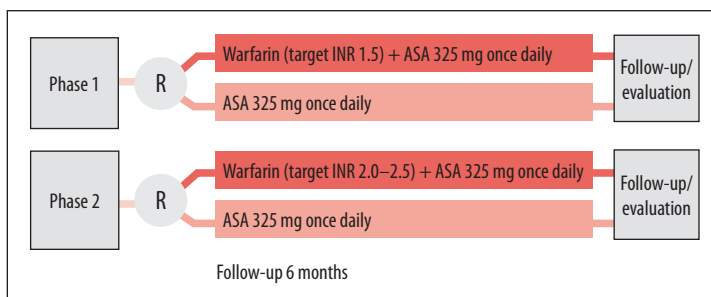
Randomized, controlled open-label study

Active treatment:

- Phase 1: warfarin (target INR 1.5) and ASA (325 mg once daily in 87% of patients) (n=155)
- Phase 2: warfarin (target INR 2.0 – 2.5) and ASA (325 mg once daily in 85% of patients) (n=98)

Control treatment:

- Phase 1: standard therapy (ASA 325 mg once daily in 87% of patients) (n=154)
- Phase 2: standard therapy (ASA 325 mg once daily in 85% of patients) (n=99)



Endpoints

Primary efficacy endpoint: combined endpoint of cardiovascular death, new myocardial infarction or refractory angina

Secondary efficacy endpoints: combined endpoint of CV death, new myocardial infarction, refractory angina or severe angina; rehospitalization with unstable angina

Safety endpoints: stroke, major and minor bleeding

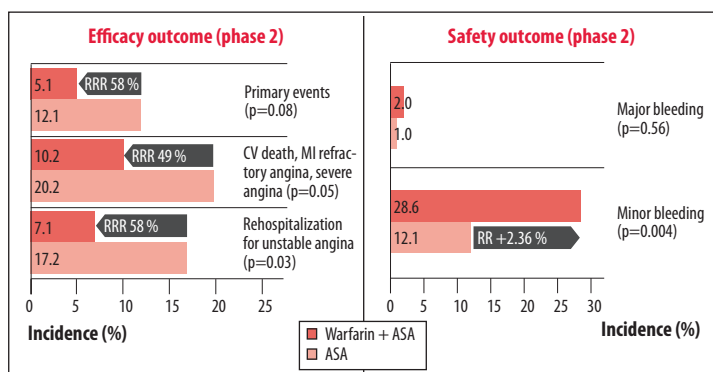
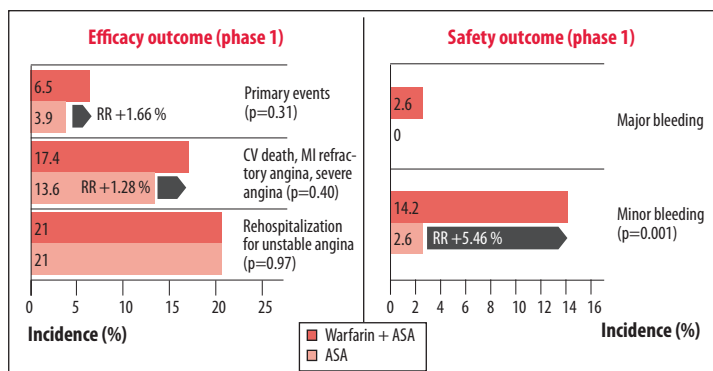
Trial participants

309 (phase 1) and 197 (phase 2) patients with unstable angina or NSTEMI after 3 days of intravenous antithrombotic therapy

Results

Primary outcome: In phase 1 of the study, the primary outcome occurred in 10 of 155 patients (6.5%) receiving warfarin and ASA and in 6 of 154 (3.9%) receiving ASA alone (relative risk +1.66 %). In phase 2, 5 of 98 patients assigned to warfarin and ASA (5.1%) and 12 of 99 patients assigned to ASA (12.1%) experienced a primary event (relative risk reduction 58%)

Safety outcome: In phase 1, the risk of major bleeding was 2.6% (n=4) in patients given warfarin + ASA compared to 0% in ASA patients. In phase 2, 2 patients assigned to warfarin + ASA (2.0%) experienced a major bleeding complication compared to 1 patient (1.0%) assigned to ASA



Summary

Efficacy: In phase 1 with the low-intensity therapy there were no benefits of warfarin compared to standard therapy. In phase 2 with higher dosage of warfarin the combination of warfarin and ASA strongly reduced the rate of acute ischemic syndromes when compared to ASA alone

Safety: In both phases of this study there were higher rates of bleeding complications in patients receiving warfarin + ASA when compared to ASA alone

Reference

Anand SS, Yusuf S, Pogue J, Weitz JI, Flather M. Long-term oral anticoagulant therapy in patients with unstable angina or suspected non-Q-wave myocardial infarction: Organization to Assess Strategies for Ischemic Syndromes (OASIS) pilot study results. *Circulation* 1998;98:1064-1070

Corresponding author

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OASIS-2 (substudy)

Organization to Assess Strategies for Ischemic Syndromes – 2 (2001)

Condition

Anticoagulation in unstable angina

Objective

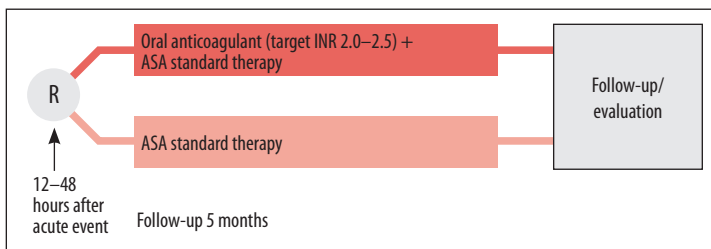
To evaluate whether oral anticoagulant therapy given for 5 months was superior to standard therapy in patients with unstable angina receiving ASA

Trial design

Randomized, controlled, double-blind study

Active treatment: oral anticoagulant therapy (loading dose of 10 mg followed by 3 mg once daily for 2 days, then target INR 2.5) in addition to ASA for 5 months (n=1848)

Control treatment: standard therapy with ASA alone for 5 months (n=1864)



Endpoints

Primary efficacy endpoint: composite of cardiovascular death, myocardial infarction, or stroke

Secondary efficacy endpoints: composite of cardiovascular death, myocardial infarction, stroke and readmission to the hospital for unstable angina

Safety endpoints: major and minor bleeding

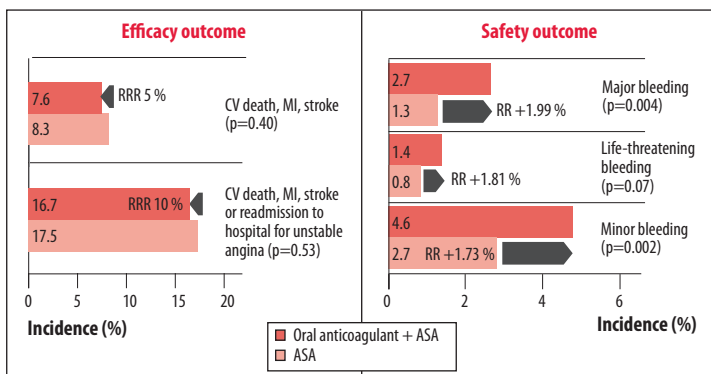
Trial participants

3,712 patients eligible for the main OASIS-2 trial, which compared a 3-day regimen of hirudin vs. heparin, who could be randomized within 12 hours of symptom onset

Results

Primary outcome: A primary endpoint occurred in 140 of 1848 patients (7.6%) randomized to oral anticoagulants compared to 155 patients (8.3%) in the control group (relative risk reduction 10%). 308 patients (16.7%) experienced the secondary outcome in the oral anticoagulant group compared to 327 patients (17.5%) in the control group (relative risk reduction 5%)

Safety outcome: Major bleeding occurred in 49 patients (2.7%) in the oral anticoagulant group compared to 25 control patients (1.3%). Life-threatening bleedings accounted for about half of these events



Summary

Efficacy: In the group receiving oral anticoagulants, a small, non-significant reduction in the risk of the primary (cardiovascular death, myocardial infarction, stroke) and secondary (cardiovascular death, myocardial infarction, stroke, readmission to hospital for unstable angina) efficacy outcomes was observed

Safety: There was an excess of major and minor bleeding with oral anticoagulants

Reference

Yusuf S, Pogue J, Anand S for the OASIS Investigators. Effects of long-term, moderate-intensity oral anticoagulation in addition to aspirin in unstable angina. *J Am Coll Cardiol* 2001;37:475-484

Corresponding author

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OASIS-5 (PCI substudy)

Organization to Assess Strategies for Ischemic Syndromes – 5 (2007)

Condition

Prevention of recurrent events in patients who underwent early percutaneous coronary intervention (PCI)

Objective

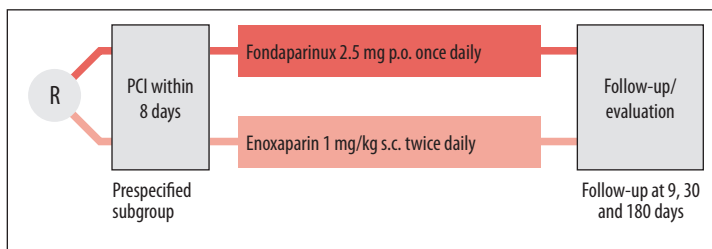
To compare the efficacy and safety of fondaparinux and enoxaparin in patients enrolled in the OASIS-5 trial who underwent PCI during the study treatment period

Trial design

Prespecified subgroup analysis of a randomized, controlled, double-blind study

Active treatment: fondaparinux 2.5 mg p.o. once daily; for PCI fondaparinux 2,5 mg i.v. was given additionally, if PCI was >6 hours from last dose or patients received no GPIIb/IIIa-antagonists. If both was the case, the patients received additionally fondaparinux 5 mg i.v. for the procedure (n=3105)

Control treatment: enoxaparin 1 mg/kg s.c. twice daily (dose reduced to 1 mg/kg once daily in patients with creatinine clearance <30 ml/min); no additional anticoagulant was given, if PCI was <6 hours, and additional i.v. UFH was given, if PCI was >6 hours from last s.c. dose (n=3072)



Endpoints

Primary efficacy endpoint: composite of death, myocardial infarction or stroke at days 9, 30, and 180

Primary safety endpoint: major bleeding

Trial participants

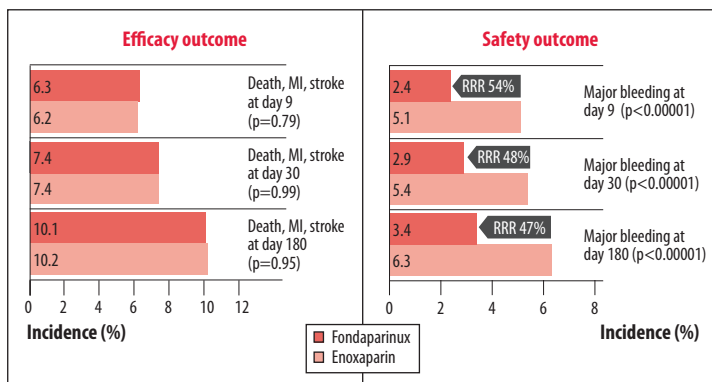
6,238 patients with acute coronary syndromes (mean age 65 years) eligible for the main OASIS-5 trial, who underwent PCI within 8 days after the acute event

Results

Primary efficacy outcome: In the fondaparinux group, 197 of 3105 patients (6.3%) experienced death, myocardial infarction or stroke by day 9, compared with 190 of 3072 patients (6.2%) in the enoxaparin group. By day 30, a primary efficacy endpoint had occurred in 7.4% of the patients in either group, by day 180 in 10.1% of the patients given fondaparinux and in 10.2% of the patients given enoxaparin

Safety outcome: By day 9 major bleeding had occurred in 73 patients (2.4%) in the fondaparinux group compared to 155 patients (5.1%) of the patients in the enoxaparin group. By day 30, major bleeding had occurred in 88

(2.9%) vs. 166 (5.4%), by day 180 in 104 (3.4%) vs. 190 (6.3%) of the patients receiving fondaparinux respectively enoxaparin



Summary

Efficacy: Upstream fondaparinux compared with upstream enoxaparin had comparable impact on the primary efficacy endpoint (death, myocardial infarction or stroke) at day 9, 30, and 180

Safety: Fondaparinux substantially reduced major bleeding, resulting in a superior net clinical benefit

Reference

Mehta SR, Granger CB, Eikelboom JW, Bassand JP, Wallentin L, Faxon DP, Peters RJG, Budaj A, Afzal R, Chrolavicius S, Fox KA, Yusuf S. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2007;50:1742-1751

Corresponding author

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OASIS-6

Organization to Assess Strategies for Ischemic Syndromes – 6 (2006)

Condition

Prevention of reinfarction and death in patients with ST-segment elevation myocardial infarction (STEMI)

Objective

To investigate the effect of fondaparinux in patients with STEMI when compared to usual care

Trial design

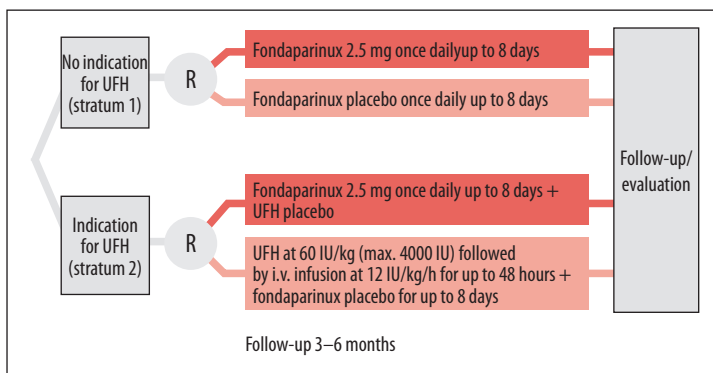
Randomized, controlled, double-blind study; randomization was stratified by indication for the use of UFH: patients with no indication for UFH were enrolled in stratum 1, patients with indication for UFH in stratum 2

Active treatment (n=6036):

- Stratum 1: fondaparinux 2.5 mg s.c. once daily up to 8 days (n=2823)
- Stratum 2: fondaparinux 2.5 mg s.c. once daily up to 8 days plus UFH placebo (3213)

Control treatment (n=6056):

- Stratum 1: fondaparinux placebo (n=2835)
- Stratum 2: UFH bolus injection of 60 IU/kg followed by an infusion of 12 IU/kg per hour for 24 to 48 hours plus fondaparinux placebo for up to 8 days (n=3221)



Endpoints

Primary efficacy endpoint: death or reinfarction at 30 days

Secondary efficacy endpoints: death or reinfarction at 9 days and at study end; all deaths, reinfarction, stroke

Safety endpoints: major bleeding

Trial participants

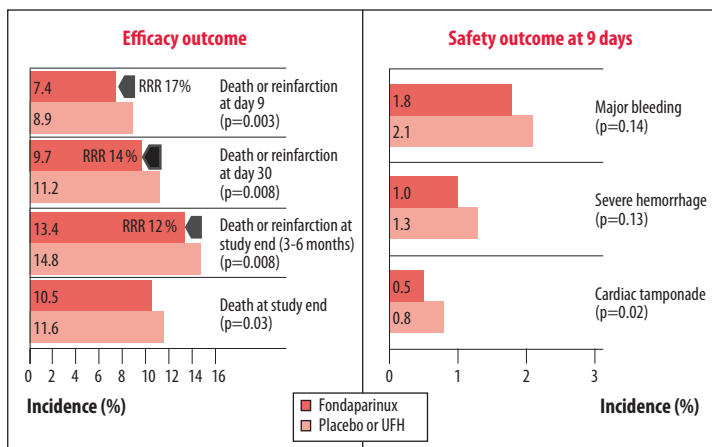
12,092 patients (mean age 61 years) with acute STEMI

Results

Primary outcome: The primary composite outcome of death or reinfarction was significantly reduced in the fondaparinux group compared to the placebo/UFH group at 9 days (7.4% vs. 8.9%), at 30 days (9.7% vs. 11.2%) and at the end of the study (3–6 months) (13.4% vs. 14.8%). The relative risk reduc-

tion was 17% at 9 days, 14% at day 30, and 12% at study end. Consistent reductions in both death and reinfarction were observed with fondaparinux at each of the 3 time points, with the reduction in deaths being statistically significant throughout

Safety outcome: At 9 days, the risk of major bleeding was 1.8% (107/6036) in patients given fondaparinux compared to 2.1% (130/6056) in patients treated with placebo or heparin. There was a tendency to fewer severe bleeds (79 for placebo/UFH vs. 61 for fondaparinux), with significantly fewer cardiac tamponade (48 vs. 28; $p=0.02$) with fondaparinux at 9 days



Summary

Efficacy: Fondaparinux was superior to UFH in preventing death or reinfarction at 30 days and at 3 or 6 months

Safety: There was a non-significant trend towards fewer severe hemorrhages with fondaparinux compared to both control groups

Reference

Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, Budaj A, Peters RJ, Bassand JP, Wallentin L, Joyner C, Fox KA; OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *J Am Med Ass* 2006;295:1519-1530

Corresponding author

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PATAF

Prevention of Arterial Thromboembolism in Non-valvular Atrial Fibrillation trial (1999)

Condition

Prevention of arterial thromboembolism in low risk patients with AF

Objective

To investigate the effectiveness of ASA and warfarin in preventing thromboembolic events in patients with non-rheumatic AF in general practice

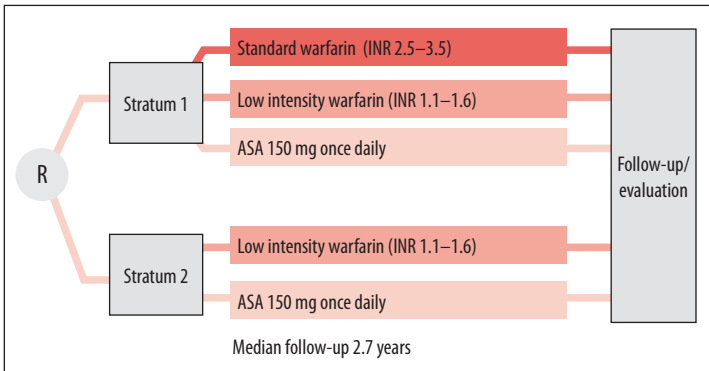
Trial design

Randomized, controlled trial

Active treatment:

- Stratum 1 (394 patients eligible for standard anticoagulation): standard warfarin (INR 2.5–3.5; n=131) vs. very low intensity warfarin (INR 1.1–1.6; n=122)
- Stratum 2 (335 patients ineligible for standard anticoagulation): low intensity warfarin (INR 1.1–1.6; n=157)

Control treatment: ASA 150 mg once daily (stratum 1: n=141; stratum 2: n=178)



Endpoints

Primary endpoint: stroke, systemic arterial embolism, major hemorrhage, vascular death

Secondary endpoints: non-fatal myocardial infarction, retinal infarction, TIA, minor bleeding, non-vascular death

Trial participants

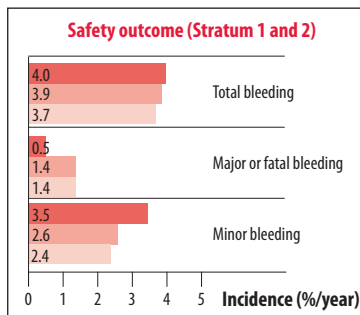
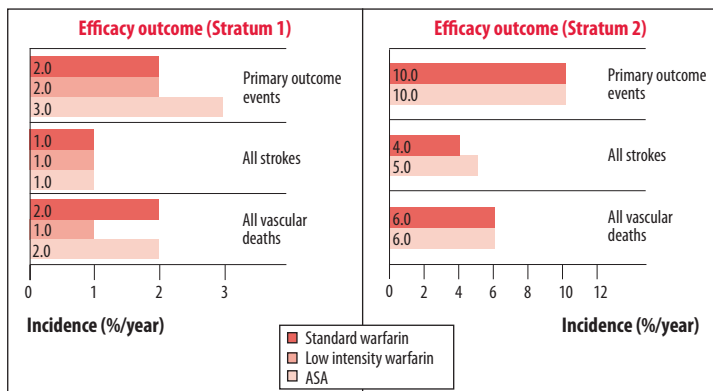
729 patients aged >60 years with AF and no established indication for warfarin, recruited in general practice

Results

Primary outcome: Mean follow-up was 2.7 years with a total of 1939 patient-years. In total 108 primary events occurred: 30 in stratum 1 and 78 in stratum 2. 10 events in stratum 1 occurred in the standard warfarin group (2% per year), 8 in the low intensity warfarin group (2% per year) and 12 in the ASA group (3% per year). 37 events in stratum 2 occurred in the low intensity warfarin group (10% per year) and 41 in the ASA group (10% per year). The average total annual event rate was 5.5%. Compared with ASA,

the hazard ratio was 0.91 for low intensity warfarin (both strata) and 0.78 for standard warfarin (stratum 1)

Safety outcome: The total annual bleeding rate was 3.9%: 1.2% for major or fatal bleeding (n=23) and 2.7% for minor bleeding (n=52). 17 of the major bleeds occurred in stratum 2, with 10 in the ASA group. Between treatment groups no significant difference in risk of bleeding was found



Summary

Efficacy: In a general practice population (without established indications for warfarin) neither low intensity nor standard warfarin treatment is better than ASA in preventing stroke, systemic arterial embolism, major hemorrhage or vascular death

Safety: There were no significant differences between groups in bleeding incidence

Reference

Hellemons BSP, Langenberg M, Lodder J, Vermeer F, Schouten HJA, 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. *Br Med J* 1999;319:958-964

Corresponding author

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PENTAMAKS

PENTAsaccharide in MAjor Knee Surgery study (2001)

Condition

Prophylaxis for VTE after elective major knee surgery

Objective

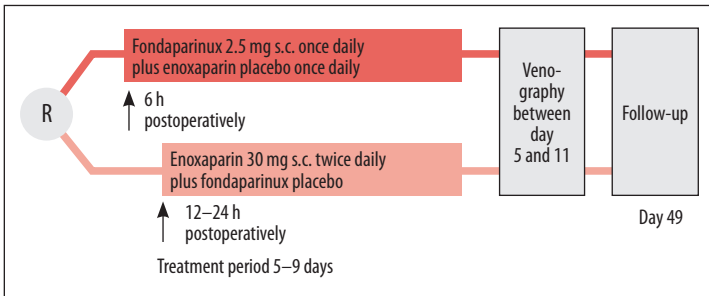
To compare the efficacy and safety of fondaparinux and enoxaparin for VTE prophylaxis after elective major knee surgery

Trial design

Randomized, double-blind, study with parallel groups

Active treatment: fondaparinux 2.5 mg s.c. once daily, initiated 6±2 hours postoperatively, second dose given ≥12 hours after the first, treatment for 5–9 days; enoxaparin placebo (n=517)

Control treatment: enoxaparin 30 mg s.c. twice daily, first dose given 12–24 hours after surgery, for 5–9 days; fondaparinux placebo (n=517)



Endpoints

Primary efficacy endpoint: DVT and PE up to day 11 after surgery

Secondary efficacy endpoints: total, proximal, or distal DVT or symptomatic VTE up to day 11 and symptomatic VTE up to day 49

Primary safety endpoint: major bleeding

Secondary safety endpoints: minor bleeding, death, blood transfusion requirement, thrombocytopenia

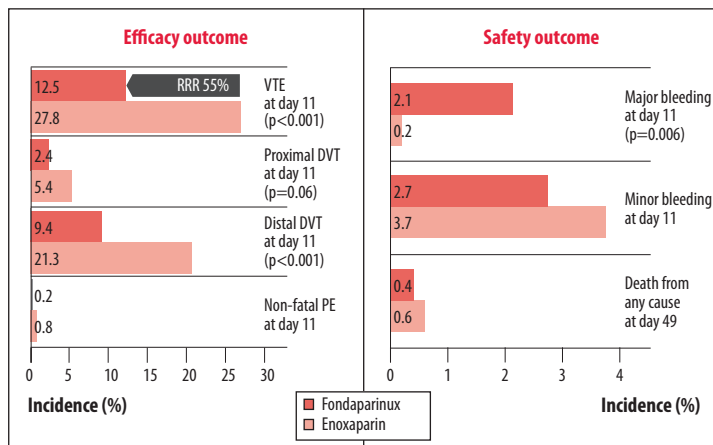
Trial participants

1049 patients (mean age 67.5 years) scheduled to undergo major knee surgery (resection of the distal end of the femur or proximal end of the tibia or revision of at least one component of a previously implanted total-knee prosthesis)

Results

Efficacy outcome: 724 patients were included in the primary efficacy analysis. At day 11, the incidence of VTE was 12.5% in the fondaparinux group (101 of 363 patients) and 27.8% in the enoxaparin group (45 of 361 patients). The resulting relative risk reduction was 55% ($p < 0.001$). Proximal DVT occurred in 2.4% of patients assigned to fondaparinux and 5.4% of patients treated with enoxaparin (relative risk reduction 55%, $p < 0.001$). Non-fatal PE developed in 1 patient receiving fondaparinux (0.2%) and 4 patients given enoxaparin (0.8%). By day 49, the incidence of symptomatic VTE did not differ significantly between both groups (1.0% in the fondaparinux group vs. 1.9% in the enoxaparin group)

Safety outcome: At day 11, the primary safety outcome of major bleeding had occurred significantly more frequently in the fondaparinux-treated patients: 2.1% (11 of 517 patients) vs. 0.2% (1 of 517 patients) in the enoxaparin group. But there were no significant differences in the incidence of bleeding leading to death or reoperation or occurring in a critical organ. The rates for minor bleeding, transfusion requirements and other adverse events did not differ significantly between groups. At the end of follow-up, 2 patients treated with fondaparinux (0.4%) and 3 treated with enoxaparin (0.6%) had died



Summary

Efficacy: Fondaparinux was superior to enoxaparin in preventing VTE after elective major knee surgery

Safety: Major bleeding was significantly more frequent in patients treated with fondaparinux, but there were no significant differences between both groups in the incidence of fatal bleeding, bleeding in critical organs or bleeding leading to reoperation

Reference

Bauer KA, Eriksson BI, Lassen MR, Turpie AGG, for the Steering Committee of the Pentasaccharide in Major Knee Surgery Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl J Med* 2001;345:1305-1310

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PENTATHLON

PENTAsaccharide in Total Hip replacement, or LOw-molecular-weight hepariN (2002)

Condition

Prophylaxis for VTE after elective hip-replacement surgery

Objective

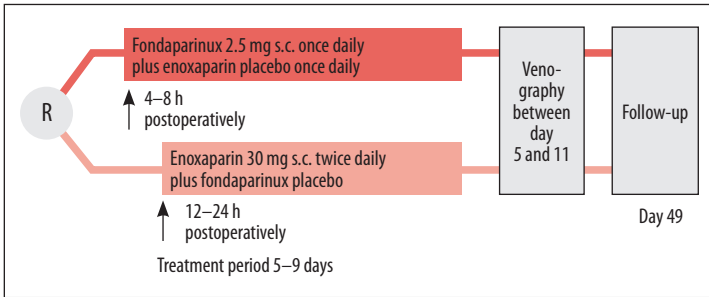
To compare the efficacy and safety of fondaparinux and enoxaparin for VTE prophylaxis after elective total hip replacement

Trial design

Randomized, double-blind study with parallel groups

Active treatment: fondaparinux 2.5 mg s.c. once daily, initiated 4–8 hours postoperatively, for 5–9 days; enoxaparin placebo (n=1138)

Control treatment: enoxaparin 30 mg s.c. twice daily, first dose given 12–24 hours after surgery, for 5–9 days; fondaparinux placebo (n=1137)



Endpoints

Primary efficacy endpoint: DVT and PE up to day 11 after surgery

Secondary efficacy endpoints: total, proximal, or distal DVT or symptomatic VTE up to day 11 and symptomatic VTE up to day 49

Primary safety endpoint: major bleeding

Secondary safety endpoints: minor bleeding, death, blood transfusion requirement, thrombocytopenia

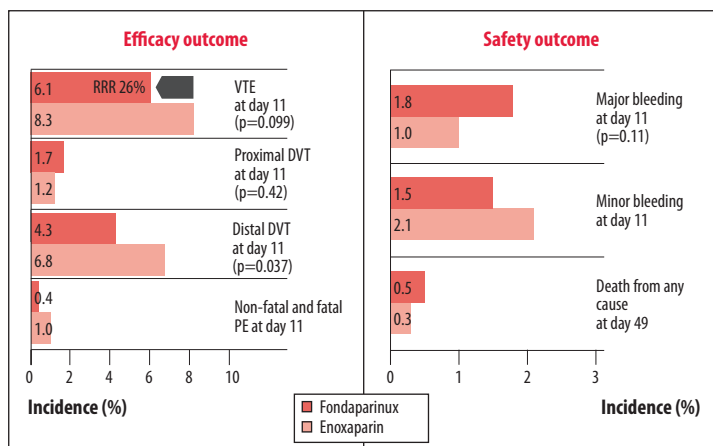
Trial participants

2275 patients (mean age 67 years) undergoing a first elective total hip replacement or a revision of at least one component of a previously implanted total hip prosthesis

Results

Efficacy outcome: 1584 patients were included in the primary efficacy analysis. The primary efficacy outcome of VTE up to day 11 occurred in 48 of 787 patients (6.1%) receiving fondaparinux and in 66 of 797 patients (8.3%) receiving enoxaparin (relative risk reduction 26%, but the difference was not significant; $p=0.099$). The incidence of proximal DVT was nearly the same in both groups, 1.7% with fondaparinux and 1.2% with enoxaparin. Distal DVT developed in 4.3% of patients assigned to fondaparinux and 6.8% of patients treated with enoxaparin (relative risk reduction 37%, $p=0.037$). Non-fatal and fatal PE was recorded in 5 patients receiving fondaparinux (0.4%) and 1 patient given enoxaparin (0.1%). By day 49, more patients on fondaparinux had symptomatic VTE than those on enoxaparin (2.6% vs. 1.2%; $p=0.013$)

Safety outcome: At day 11, the primary safety outcome of major bleeding had occurred in 20 of 1128 (1.8%) fondaparinux-treated patients and in 11 of 1129 (1.0%) patients in the enoxaparin group. The rates for minor bleeding, transfusion requirements and other adverse events did not differ significantly between groups. At the end of follow-up, 6 patients given fondaparinux (0.5%) and 3 patients given enoxaparin (0.3%) had died



Summary

Efficacy: Fondaparinux was not significantly more effective than enoxaparin in reducing risk of VTE after elective total hip replacement. However, the 26% reduction in risk recorded for fondaparinux was clinically important

Safety: The two groups did not differ in the incidence of clinically relevant bleeding and all-cause death

Reference

Turpie AGG, Bauer KA, Eriksson BI, Lassen MR, for the PENTATHLON 2000 Study Steering Committee. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. *Lancet* 2002;359:1721-1726

Corresponding author

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PENTHIFRA

PENTasaccharide in Hip-FRActure surgery study (2001)

Condition

Prophylaxis for VTE after surgery for hip fracture

Objective

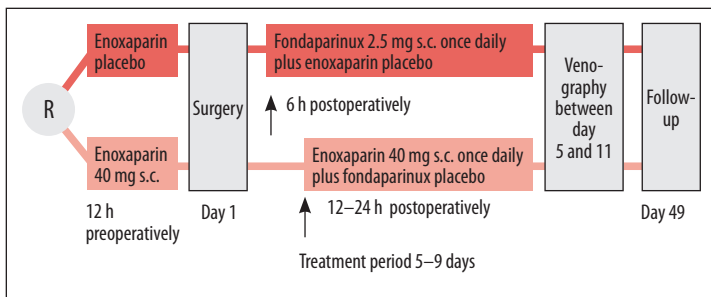
To compare the efficacy and safety of fondaparinux and enoxaparin for VTE prophylaxis after surgery for fractured hip

Trial design

Randomized, double-blind study with parallel groups

Active treatment: fondaparinux 2.5 mg s.c. once daily, initiated 6±2 hours postoperatively, second dose given ≥12 hours after the first, treatment for 5–9 days; enoxaparin placebo (n=842)

Control treatment: enoxaparin 40 mg s.c. once daily, first dose given 12±2 hours preoperatively, second dose 12–24 hours after surgery, for 5–9 days; fondaparinux placebo (n=831)



Endpoints

Primary efficacy endpoint: DVT and PE up to day 11 after surgery

Secondary efficacy endpoints: total, proximal, or distal DVT or symptomatic VTE up to day 11 and symptomatic VTE up to day 49

Primary safety endpoint: major bleeding

Secondary safety endpoints: minor bleeding, death, blood transfusion requirement, thrombocytopenia

Trial participants

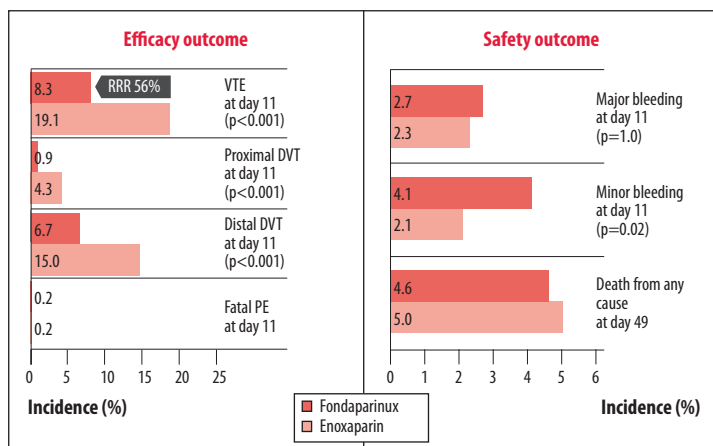
1711 patients (mean age 77 years) scheduled to undergo surgery for fracture of the upper third of the femur within 48 hours of admission

Results

Efficacy outcome: 1250 patients were included in the primary efficacy analysis. At day 11, the incidence of VTE was 8.3% in the fondaparinux group (52 of 626 patients) and 19.1% in the enoxaparin group (119 of 624 patients). The resulting relative risk reduction was 56% ($p<0.001$). Proximal DVT occurred in 0.9% of patients assigned to fondaparinux and 4.3% of patients treated with enoxaparin (relative risk reduction 79%, $p<0.001$). The rate of fatal PE was 0.2% in both groups. By day 49, the incidence of symptomatic VTE was similar in the fondaparinux group (2.0%) and the enoxaparin group (1.5%)

Safety outcome: By day 11, major bleeding had occurred in 18 of 831 patients (2.7%) treated with fondaparinux and 19 of 842 patients (2.3%) receiv-

ing enoxaparin. The incidence for minor bleeding was 4.1% and 2.1%, respectively. Transfusion requirements and other adverse events did not differ significantly between groups. At the end of follow-up, 38 patients treated with fondaparinux (4.6%) and 42 treated with enoxaparin (5%) had died



Summary

Efficacy: In patients undergoing surgery for hip fracture, fondaparinux was superior to enoxaparin in preventing VTE

Safety: There were no significant differences between both groups in the incidence of clinically relevant bleeding or death

Reference

Eriksson BI, Bauer KA, Lassen MR, Turpie AGG, for the Steering Committee of the Pentasaccharide in Hip-Fracture Surgery Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. *N Engl J Med* 2001;345:1298-1304

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PETRO

Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with non-valvular atrial fibrillation (2007)

Condition

Non-valvular AF

Objective

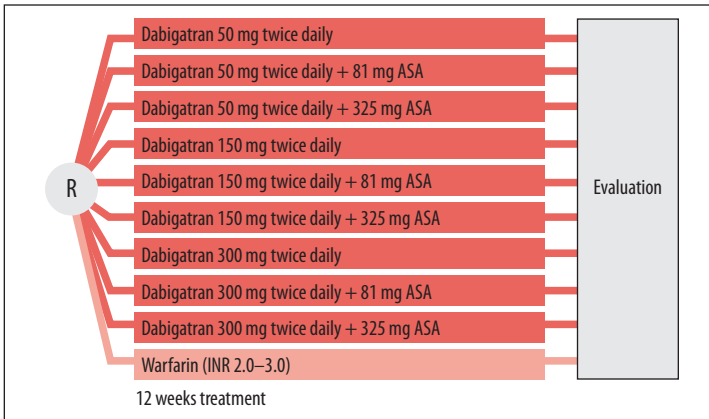
To determine the safety and efficacy of dabigatran with or without concomitant treatment with ASA in patients with AF when compared to warfarin

Trial design

Randomized, parallel group, double-blind (for dabigatran), open-label (for ASA and warfarin), phase II study

Active treatment: dabigatran 50 mg (n=107), 150 mg (n=169) or 300 mg (n=169) p.o. twice daily in combination with no ASA, 81 mg or 325 mg ASA once daily, for 12 weeks

Control treatment: warfarin (INR 2.0–3.0) (n=70)



Endpoints

Primary endpoint: incidence of bleeding events

Secondary endpoints: change from baseline in plasma concentrations of D-dimer; a composite clinical endpoint of any thromboembolic or cardiac event, other major adverse cardiac events and all-cause mortality; the incidence of all adverse events

Trial participants

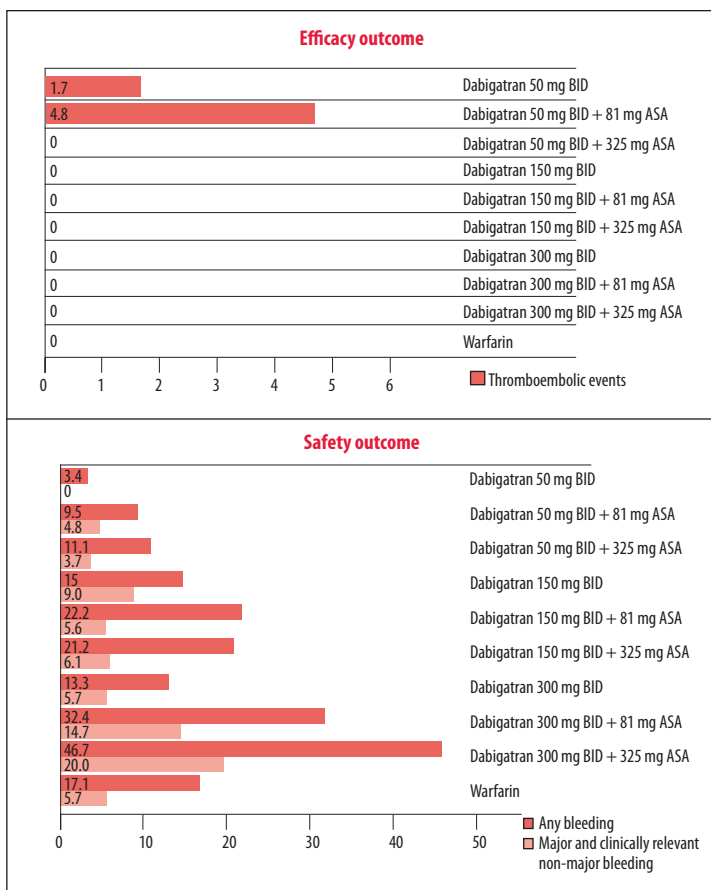
502 patients with non-valvular atrial fibrillation with/without CAD + ≥ 1 risk factor for CV complications (hypertension requiring medical treatment, diabetes mellitus [type 1 or 2], symptomatic heart failure or left ventricular dysfunction [EF <40%], previous stroke or TIA, or age >75 years)

Results

Primary outcome: The rate of major or clinically relevant non-major bleeding events increased with the dose of dabigatran

Secondary outcomes: After 12 weeks treatment the change of D-Dimer value compared to baseline was +10 in patients given 50 mg dabigatran twice daily, +2 in patients given 150 mg dabigatran twice daily, ± 0 in patients given 300 mg twice daily and -1 in patients given warfarin. With in-

creasing dose of dabigatran adverse events leading to treatment discontinuation were more frequent (4.8% in 50 mg dabigatran twice daily, 5.3% in 150 mg dabigatran twice daily, and 8.9% in 300 mg dabigatran twice daily) and did not occur in patients given warfarin



Summary

Efficacy: All thromboembolic events occurred in patients treated with low dose of dabigatran

Safety: With increasing dose of dabigatran bleeding events and adverse events leading to treatment discontinuation were more frequent

Reference

Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K, Pedersen KE, Lionetti DA, Stangier J, Wallentin L. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with non-valvular atrial fibrillation (PETRO Study). *Am J Cardiol* 2007;100:1419-426

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PIONEER AF-PCI

Study exploring two strategies of rivaroxaban and one of oral vitamin K antagonists in patients with atrial fibrillation who undergo percutaneous coronary intervention (2013, ongoing)

Condition

Non-valvular AF requiring anticoagulation for stroke prevention and overlapping acute coronary syndrome requiring stenting and dual antiplatelet therapy

Objective

The primary purpose of this study is to evaluate the safety of two different rivaroxaban treatment strategies and one vitamin K antagonist treatment strategy utilizing various combinations of dual antiplatelet therapy or low-dose aspirin or clopidogrel (or prasugrel or ticagrelor) in patients with paroxysmal, persistent, or permanent non-valvular AF who undergo PCI with stent placement

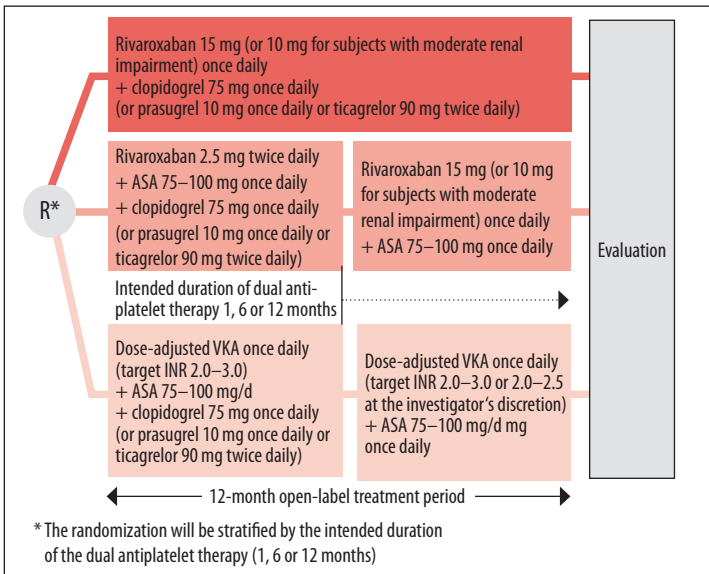
Trial design

Randomized, controlled phase IIIb clinical study with a 12-month open-label treatment phase

Active treatment:

- **double antithrombotic therapy:** rivaroxaban 15 mg (or 10 mg for subjects with moderate renal impairment) once daily plus a P2Y12 inhibitor (such as clopidogrel 75 mg once daily or prasugrel 10 mg once daily or ticagrelor 90 mg twice daily) for 12 months (n= ~700)
- **triple antithrombotic therapy:** rivaroxaban 2.5 mg p.o. twice daily plus dual antiplatelet therapy with aspirin (ASA) 75–100 mg once daily and a P2Y12 inhibitor (such as clopidogrel 75 mg once daily or prasugrel 10 mg once daily or ticagrelor 90 mg twice daily) followed by rivaroxaban 15 mg (or 10 mg for subjects with moderate renal impairment) once daily plus ASA 75–100 mg/d for 12 months (n= ~700)

Control treatment: text see next page



Control treatment:

- **triple antithrombotic therapy:** dose-adjusted vitamin K antagonist (VKA) once daily (target INR 2.0–3.0) plus dual antiplatelet therapy with ASA 75–100 mg/d and a P2Y12 inhibitor (such as clopidogrel 75 mg once daily or prasugrel 10 mg once daily or ticagrelor 90 mg twice daily) followed by dose-adjusted VKA once daily (target INR 2.0–3.0 or 2.0–2.5 at the investigator's discretion) plus ASA 75–100 mg/d for 12 months (n= ~700)

Endpoints

Primary outcome measure: number of participants with clinically significant bleeding (composite of major bleeding, minor bleeding, and bleeding requiring medical attention)

Secondary outcome measures:

- number of participants with clinically significant bleeding events
- number of participants with adverse cardiovascular events (cardiovascular death, myocardial infarction, stroke, stent thrombosis)
- number of participants with other adverse events
- composite of clinically significant bleeding and adverse cardiovascular events

Trial participants

The study will enroll approximately 2100 patients with atrial fibrillation requiring anticoagulant therapy for stroke prevention and who have undergone a percutaneous coronary intervention procedure with stent placement and therefore requiring dual antiplatelet therapy

Reference

ClinicalTrials.gov (NCT01830543)

Corresponding author

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PLANES

Enoxaparin vs. unfractionated heparin in patients undergoing total hip replacement (1988)

Condition

Prophylaxis for VTE after total hip replacement

Objective

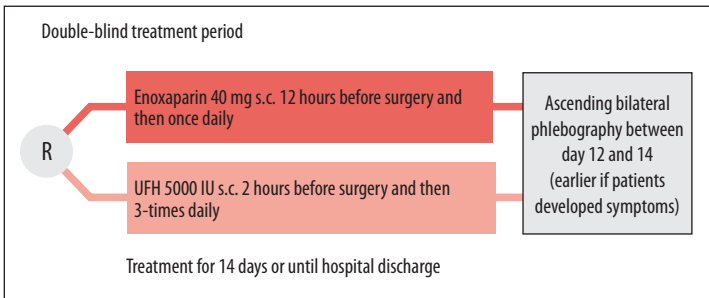
To compare the efficacy and safety of enoxaparin and standard heparin for VTE prophylaxis after elective hip surgery

Trial design

Randomized, double-blind, placebo-controlled study

Active treatment: enoxaparin 40 mg s.c. 12 hours before surgery and then once daily for 14 days or until hospital discharge; UFH placebo (n=124)

Control treatment: UFH 5000 IU s.c. 2 hours before surgery and then 8 hourly for 14 days or until hospital discharge; enoxaparin placebo (n=113)



Endpoints

Primary efficacy endpoint: venous thrombosis

Primary safety endpoints: major and minor bleeding

Secondary endpoints: number of units of blood transfused during and after surgery, hemoglobin level

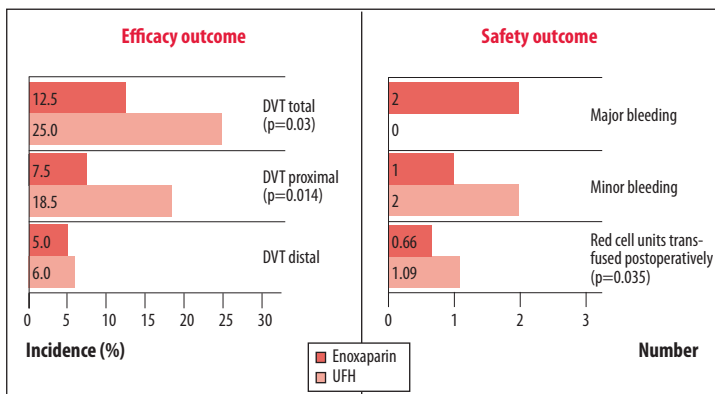
Trial participants

237 consecutive patients aged ≥ 45 years, scheduled for elective total hip replacement

Results

Efficacy outcome: The efficacy analysis was based on 120 patients assigned to enoxaparin and 108 patients assigned to UFH. In the enoxaparin group, DVT was detected in 15 patients (12.5%), as compared with 27 patients (25%) in the UFH group. Proximal DVT occurred in 7.5% and 18.5%, respectively. The differences between groups were statistically significant ($p=0.03$ and $p=0.014$, respectively)

Safety outcome: The safety analysis was performed in 124 patients assigned to enoxaparin and 112 patients assigned to UFH. Major bleeding occurred in 2 patients treated with enoxaparin, minor bleeding developed in 1 patient given enoxaparin and in 2 patients given UFH. Patients in the enoxaparin group required fewer red blood cell transfusions after surgery (0.66 vs. 1.09 units) and had significantly higher hemoglobin levels on postoperative day 3 and 4 (12.524 vs. 11.993 g/100 ml; $p=0.039$)



Summary

Efficacy: In patients undergoing elective hip replacement who have a high risk for both thrombosis and bleeding, treatment with once daily enoxaparin resulted in a significantly lower incidence of total and proximal DVT than treatment with 3-times daily UFH

Safety: The rates of bleeding were low in both groups and were not statistically different. In patients receiving UFH, the red cell transfusion requirements and the fall in hemoglobin were significantly greater, as compared with patients assigned to enoxaparin

Reference

Planes A, Vochelle N, Mazas F, Mansat C, Zucman J, Landais A, Pascariello JC, Weill D, Butel J. Prevention of postoperative venous thrombosis: a randomized trial comparing unfractionated heparin with low molecular weight heparin in patients undergoing total hip replacement. *Thromb Haemost* 1988;60:407-410

Corresponding author

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POWERS

Warfarin vs. ASA for the prevention of venous thromboembolism in patients undergoing surgery for fractured hip (1989)

Condition

Prophylaxis for VTE in patients admitted for surgery because of hip fracture

Objective

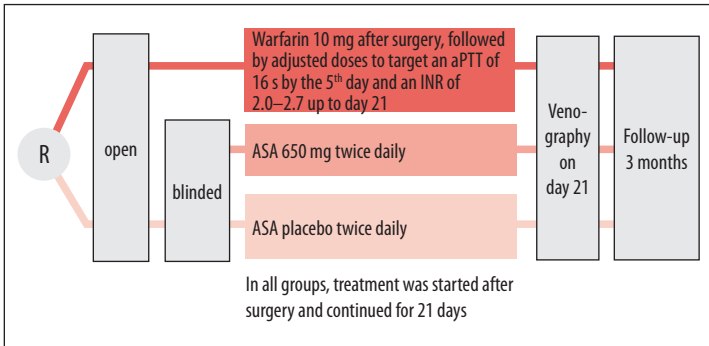
To compare the efficacy and safety of warfarin and ASA for VTE prophylaxis after surgery for fractured hip

Trial design

Randomized, double-blinded (ASA), placebo-controlled study

Active treatment: warfarin 10 mg as soon as possible after surgery, followed by adjusted daily doses to achieve an aPTT of 16 s by the 5th postoperative day and to maintain an aPTT of 16–18 s (INR 2.0–2.7) up to day 21 after surgery or discharge from hospital (n=65)

Control treatment: ASA 650 mg (n=66) or ASA placebo (n=63) twice daily for 21 days or until hospital discharge



Endpoints

Primary efficacy endpoint: DVT and PE during the postoperative period

Primary safety endpoints: major and minor bleeding

Secondary endpoints: blood transfusion requirement, death

Trial participants

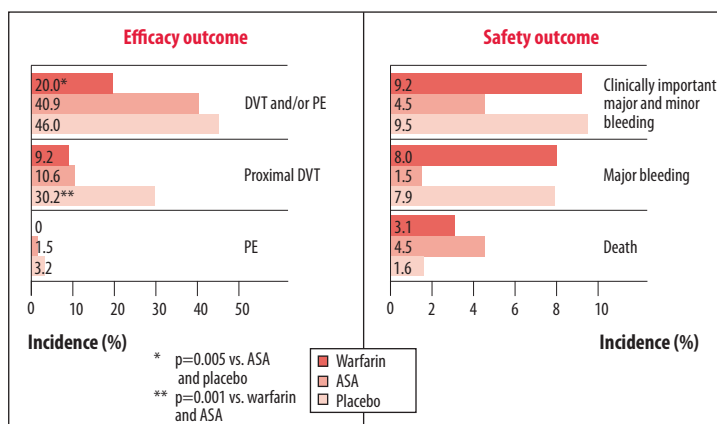
194 consecutive patients (aged 30–91 years) admitted for surgical treatment of hip fracture

Results

Efficacy outcome: DVT and/or PE was detected in 13 of 65 patients (20.0%) in the warfarin group, 27 of 66 patients (40.9%) in the ASA group, and 29 of 63 patients (46.0%) in the placebo group. The difference between warfarin and ASA was statistically significant ($p=0.005$). Proximal DVT occurred in 9.2% of the warfarin-treated patients, 10.6% of the patients given ASA and 30.2% in the patients assigned to placebo. The differences between the placebo group and either the warfarin or ASA group were statistically significant ($p=0.001$). One patient receiving ASA and 2 patients receiving placebo developed PE (1.5% and 3.2% respectively)

Safety outcome: Major bleeding occurred in 5 patients in each of the warfarin and placebo groups and in 1 patient given ASA (8.0%, 7.9%, and 1.5%,

respectively); none of these bleeding episodes was fatal. Clinical important major and minor hemorrhage was observed in 6 patients (9.2%) treated with warfarin, 3 patients (4.5%) given ASA, and 6 patients (9.5%) in the placebo group. The number of patients who needed blood transfusions was similar across treatment groups. 6 patients died during the 21-day treatment period: 2 in the warfarin group, 3 in the ASA group and 1 on the placebo group



Summary

Efficacy: In patients undergoing surgery for hip fracture, less intensive warfarin was significantly much more effective than ASA or placebo in preventing VTE, and there was little difference between ASA and placebo

Safety: In patients treated with warfarin, there was no increase in bleeding complications, as compared with the ASA and placebo groups

Reference

Powers PJ, Gent M, Jay RM, Julian DH, Turpie AG, Levine M, Hirsh J. A randomized trial of less intense postoperative warfarin or aspirin therapy in the prevention of venous thromboembolism after surgery for fractured hip. Arch Intern Med 1989;149:771-774

Corresponding author

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PRANDONI

Low-molecular-weight heparin compared with standard heparin in proximal DVT (1992)

Condition

Initial treatment of acute proximal DVT in outpatients

Objective

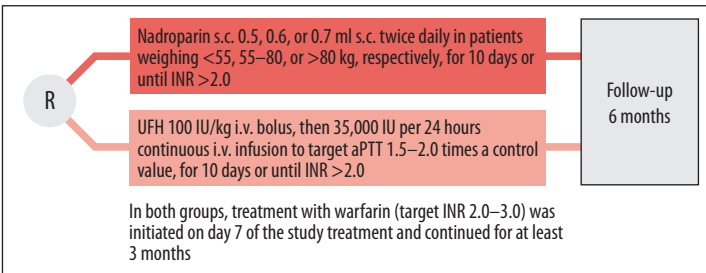
To compare the efficacy and safety of adjusted-dose intravenous standard heparin with those of fixed-dose subcutaneous low-molecular-weight heparin in the initial treatment of proximal DVT

Trial design

Randomized, open study with parallel groups

Active treatment: nadroparin adjusted for the patient's weight: 0.5, 0.6, or 0.7 ml s.c. twice daily in patients weighing <55, 55–80, or >80 kg, respectively (1.0 ml contains 25,400 anti factor Xa IU), given for 10 days, or longer if the INR was <2.0 (n=85)

Control treatment: UFH 100 IU/kg i.v. bolus, then 35,000 IU per 24 hours continuous i.v. infusion to target aPTT 1.5–2.0 times a control value, for 10 days or until INR >2.0 (n=85)



Endpoints

Primary efficacy endpoints: recurrent symptomatic DVT (including symptomatic extension), and symptomatic PE during 6-month follow-up

Secondary efficacy endpoints: change in the extent of venous thrombosis between the day 10 and day 0 venograms; change in the number of segmental defects on the day 10 and day 0 perfusion lung scans

Primary safety endpoints: major bleeding during or within 48 hours of the end of heparin treatment

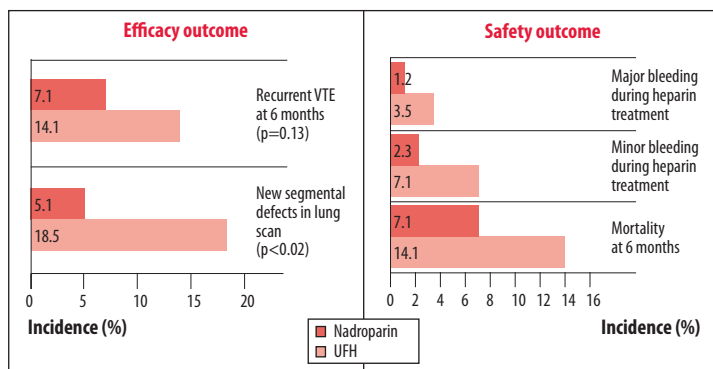
Trial participants

170 consecutive symptomatic outpatients with venographically proven proximal DVT but no signs of PE

Results

Efficacy outcome: During the 6-month follow-up, symptomatic recurrent VTE developed in 6 of the 85 patients assigned to nadroparin (7.1%) and in 12 of the 85 patients receiving standard heparin (14.1%). In the nadroparin group, there was a significantly lower rate of new segmental defects on lung scans compared with the standard-heparin group (5% vs. 19%; $p < 0.02$). The changes in the extend of VTE on venography showed a significant difference in favor of nadroparin treatment ($p = 0.017$)

Safety outcome: Major bleeding occurred during or within 48 hours of heparin treatment in 3 (3.5%) patients in the UFH group and in 1 (1.2%) patient in the nadroparin group. The frequency of minor bleeding was 7.1% and 2.3%, respectively. 12 (14.1%) patients in the standard-heparin group and 6 (7.1%) patients in the nadroparin group died during the 6-months study period



Summary

Efficacy: Nadroparin was least as effective as standard heparin in the prevention of recurrent VTE. The greater efficacy of LMWH than of UFH is supported by the significantly lower rate of symptomless extension of thromboembolic disease found on posttreatment venograms and lung scans

Safety: Clinically important bleeding was infrequent in both treatment groups

Reference

Prandoni P, Lensing AW, Büller HR, Carta M, Cogo A, Vigo M, Casara D, Ruol A, ten Cate JW. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. *Lancet* 1992;339:441-445

Corresponding author

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PREVENT

PREVENTion of recurrent venous thromboembolism (2003)

Condition

Long-term prevention of recurrent idiopathic VTE

Objective

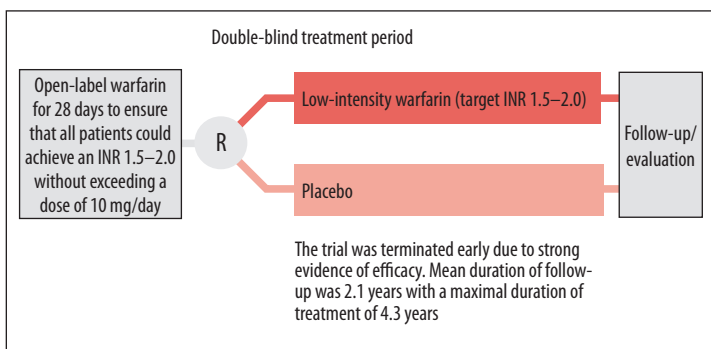
To test the hypothesis that long-term, low-intensity warfarin therapy is an effective and safe method of reducing the risk of recurrent VTE in patients with a previous episode of idiopathic VTE

Trial design

Randomized, double-blind, placebo-controlled study with a 28-day open-label run-in phase

Active treatment: low-intensity warfarin (target INR 1.5–2.0) (n=255)

Control treatment: placebo (n=253)



Endpoints

Primary efficacy endpoint: composite of recurrent VTE, major hemorrhage, and death from any cause

Secondary endpoints: minor bleeding, stroke (hemorrhagic and thromboembolic)

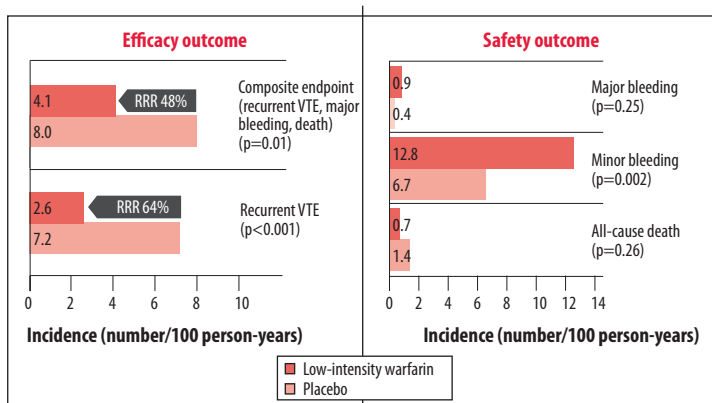
Trial participants

508 patients (≥ 30 years, mean age 53 years) with idiopathic VTE who had completed 3 uninterrupted months of oral anticoagulant treatment with full-dose warfarin

Results

Efficacy outcome: Low-intensity warfarin was associated with a 48% reduction in the composite end point of recurrent venous thromboembolism, major hemorrhage, or death (4.1 vs. 8.0/100 person-years). Recurrent VTE occurred in 37 of 253 patients assigned to placebo (7.2/100 person-years), as compared with 14 of 255 patients assigned to low-intensity warfarin (2.6/100 person-years); the relative risk reduction was 64%

Safety outcome: Major hemorrhage occurred in 2 patients assigned to placebo (0.4/100 person-years) and 5 assigned to low-intensity warfarin (0.9/100 person-years). A total of 34 patients in the placebo group and 60 patients in the warfarin group reported minor bleeding or bruising. 8 patients given placebo and 4 patients given low-intensity warfarin died



Summary

Efficacy: Long-term, low-intensity warfarin therapy given with a target INR of 1.5–2.0 resulted in a large and significant reduction in the risk of recurrent VTE

Safety: The benefit of warfarin treatment was achieved with little evidence of any increase in the risk of major hemorrhage or stroke

Reference

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, for the PREVENT Investigators. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med* 2003;348:1425-1434

Corresponding author

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PROTECT-AF

Watchman left atrial appendage system for embolic **PROTECTION** in patients with **AF** (2009)

Condition

Prevention of stroke and systemic embolic events in patients with AF

Objective

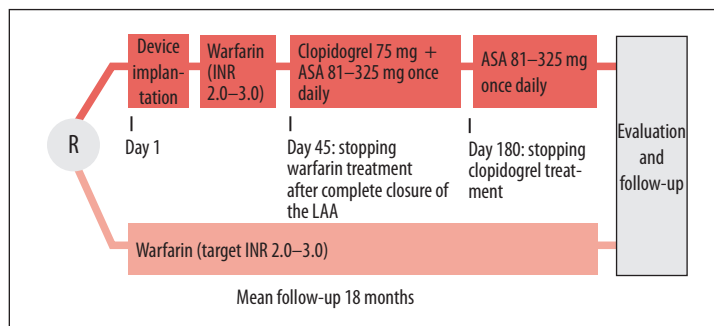
To evaluate, if the percutaneous closure of the left atrial appendage (LAA) with the Watchman device in patients with AF is non-inferior to oral anticoagulation with warfarin

Trial design

Prospective randomized controlled trial

Active treatment: percutaneous closure of LAA with the Watchman device (a self-expanding nickel titanium frame structure with fixation barbs and a permeable polyester fabric cover, implanted via a trans-septal approach; diameter 21–33 mm) and subsequent discontinuation of warfarin after complete closure of the LAA. After stopping warfarin treatment, once daily clopidogrel (75 mg) plus ASA (81–325 mg) until completion of the 6-month follow-up visit, thereafter ASA alone continued indefinitely (n=463)

Control treatment: warfarin (INR 2.0–3.0) (n=244)



Endpoints

Primary efficacy endpoint: composite of stroke (ischemic and hemorrhagic), cardiovascular or unexplained death, and systemic embolism

Primary safety endpoint: composite of major bleeding, pericardial effusion, and device embolization

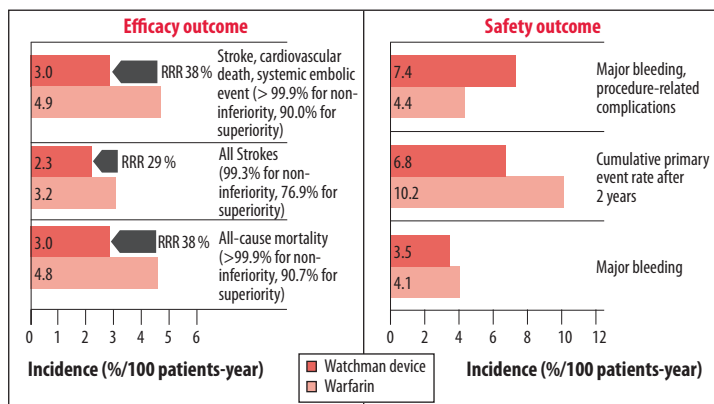
Trial participants

707 adult patients (mean age 72 years) with non-valvular AF and at least one additional risk factor for stroke

Results

Efficacy outcome: After a follow-up of 1065 patient-years, in the intent-to-treat population the primary efficacy event rate was 3.0 per 100 patient-years in the intervention group and 4.9 per 100 patient-years in the control group. The probability of non-inferiority of the intervention was >99.9%. In patients with a successful intervention, who discontinued warfarin (n=389), the primary endpoint rate was 1.9 per 100 patient-years compared with 4.6 per 100 patient-years in control patients who received warfarin (n=241)

Safety outcome: The primary safety endpoint occurred at a higher rate in the intervention group than in the control group (relative risk 1.69). In the intervention group, the majority of events occurred on the day of the procedure, in contrast to the control group, in which most events occurred later. At 2 years after randomization, the cumulative primary safety event rate was 10.2% for the intervention group and 6.8% for the control group. In the successfully treated patients, the primary safety event rate was lower in the intervention group than in the control group (relative risk reduction 65%)



Summary

Efficacy: Closing of the LAA was non-inferior to warfarin therapy in the primary efficacy endpoint of all strokes, cardiovascular death and systemic embolic events

Safety: There was a higher rate of primary safety events in the intervention group as compared to the control group. The events in the intervention group were mainly a result of periprocedural complications

Reference

Holmes D, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P, for the PROTECT investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;374:534-542

Corresponding author

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RASCHKE

Weight-based heparin dosing nomogram compared with a "standard care" nomogram (1993)

Condition

Venous or arterial thromboembolism or unstable angina

Objective

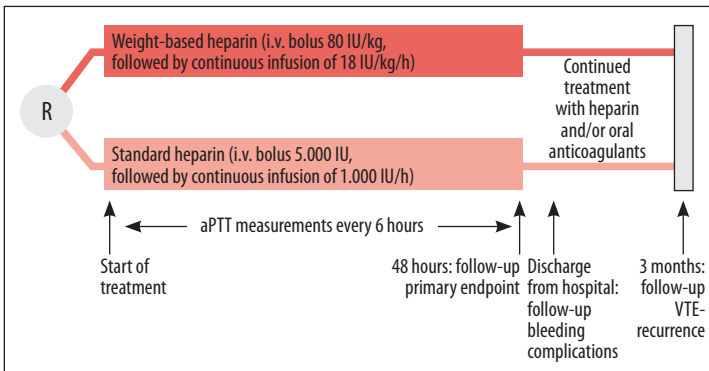
To determine, whether a weight-based approach achieves therapeutic anticoagulation with heparin more rapidly than a standard approach

Trial design

Randomized, controlled study with parallel groups

Active treatment: weight-based heparin (i.v. bolus of 80 IU/kg, followed by continuous infusion of 18 IU/kg/hour for at least 48 hours, in which no oral anticoagulant was administered (n=62)

Control treatment: standard heparin regimen (i.v. bolus of 5.000 IU, followed by continuous infusion of 1.000 IU/hour for at least 48 hours, in which no oral anticoagulant was administered (n=53)



Endpoints

Primary endpoints: time to exceed the therapeutic threshold (aPTT 1.5 times the control) and time to achieve the therapeutic range (aPTT 1.5–2.3 times the control); documented symptomatic extension of VTE, symptomatic PE or VTE recurrence during a 6-months follow-up

Secondary endpoints: major and minor hemorrhages during hospital stay, thromboembolic recurrences at 3 months in VTE-patients

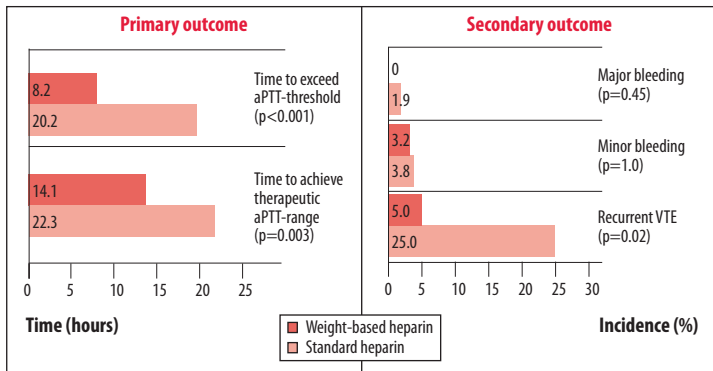
Trial participants

115 patients with DVT or PE (n=85), unstable angina (n=26) and acute peripheral arterial ischemia (n=2)

Results

Primary outcome: The mean time required to exceed the therapeutic threshold was 8.2 hours in the weight-based group and 20.2 hours in the standard-care group. 60 of 62 patients (97%) in the weight-based group exceeded the therapeutic threshold within 24 hours, compared to 37 of 48 patients (77%) in the standard care group (p<0.002). The mean time before an aPTT value within the therapeutic range was reached, was 14.1 hours in the weight-based group and 22.3 hours in the standard care group

Secondary outcomes: Major bleeding occurred in 0 of 63 patients in the weight-based group and in 1 of 52 patients in the standard group. Minor bleeding complications were observed in 2 patients in each group. 8 of 32 VTE-patients (25%) had recurrent VTE compared to 2 of 41 patients (5%) in the standard care group



Summary

Primary outcome: The weight-based heparin strategy achieved both primary outcomes (aPTT exceeding the therapeutic threshold and aPTT within the therapeutic range) significantly more rapidly as compared with the standard approach

Secondary outcomes: Recurrent thromboembolism was more frequent in the standard care group. The incidence of bleeding complications was comparable in both groups

Reference

Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. *Ann Intern Med* 1993;119:874-881

Corresponding author

Robert A. Raschke, MD, Department of Medicine, Good Samaritan Regional Medical Center, 1111 E. McDowell Road, Phoenix, AZ 85006

RE-ALIGN

Randomized, phase II study to Evaluate the sAfety and pharmacokinetics of oral dabIGatran etexilate in patients after heart valve replacemeNt (2013)

Condition

Heart valve replacement

Objective

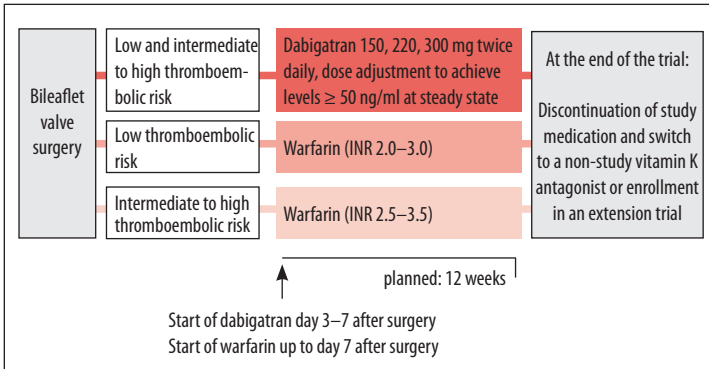
To identify doses of dabigatran that are expected to be safe and effective for the prevention of thromboembolic complications in patients with a bileaflet mechanical heart valve

Trial design

Prospective randomized phase II dose-validation study with open-label design and blinded endpoint adjudication

Active treatment: dabigatran for 12 weeks with a starting dose of 150, 220 or 300 mg twice daily (n=168). The initial doses based on the estimated creatinine clearance and were adjusted to obtain a trough plasma level ≥ 50 ng/ml at steady state. If a patient receiving 150 mg twice a day had a plasma level of < 50 ng/ml, the dose was up-titrated to 220 mg twice a day. Similarly, the 220 mg dose was up-titrated to 300 mg. Patients with a plasma level of < 50 ng/ml despite receiving 300 mg twice a day were switched to receive non-study vitamin K antagonist or be withdrawn from the study treatment

Control treatment: warfarin for 12 weeks to maintain an INR level 2.0–3.0 in patients at low thromboembolic risk and 2.5–3.5 in patients at intermediate to high thromboembolic risk (n=84)



Endpoints

Primary outcome: trough plasma level of dabigatran, as determined on high-performance liquid chromatography-tandem mass spectrometry

Secondary outcome: stroke, systemic embolism, transient ischemic attack, valve thrombosis, bleeding, venous thromboembolism, myocardial infarction, and death

Trial participants

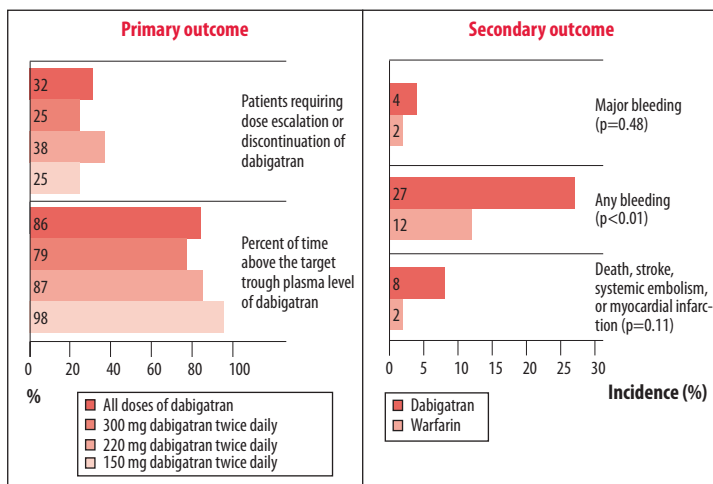
252 patients aged ≥ 18 years and ≤ 75 years, either undergoing implantation of a mechanical bileaflet valve (aortic or mitral or both) during the current hospital stay or having undergone implantation of a mitral bileaflet valve > 3 months before randomization. A total of 74 patients (29%) were deemed to be at low risk for thromboembolic complications, and 178 patients (71%) were deemed to be at intermediate or high risk

Results

The trial was terminated prematurely after the enrollment of 252 patients because of an excess of thromboembolic and bleeding events among patients in the dabigatran group. All participating patients discontinued the assigned study drug and were switched to a non-study vitamin K antagonist

Primary outcome: The initial dose of dabigatran was 150 mg twice daily in 15% of patients, 220 mg twice daily in 54%, and 300 mg twice daily in 31%. The dose was increased in 39 of 162 patients (24%), and discontinuation of dabigatran therapy was required in 13 patients (8%) who had a trough plasma level <50 ng/ml despite treatment with dabigatran at a dose of 300 mg twice daily. The targeted plasma level of 50 ng/ml was reached for an average of 86% of the time

Secondary outcome: In the dabigatran group, ischemic or unspecified stroke occurred in 9 patients (5%) and myocardial infarction occurred in 3 patients (2%), whereas there were no cases of stroke or myocardial infarction in the warfarin group. Major bleeding was seen in 7 patients (4%) and 2 patients (2%), respectively; and bleeding of any type occurred in 45 patients (27%) and 10 patients (12%), respectively (HR 2.45; $p=0.01$). All patients with major bleeding had pericardial bleeding



Summary

Dabigatran is not appropriate as an alternative to warfarin for the prevention of thromboembolic complications in patients who require anticoagulation after the implantation of a prosthetic heart valve. The use of dabigatran was associated with increased rates of thromboembolic and bleeding complications, thus showing no benefit and an excess risk

References

Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, Blatchford J, Devenny K, Friedman J, Guiver K, Harper R, Khder Y, Lobmeyer MT, Maas H, Voigt JU, Simoons ML, Van de Werf F; RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013;369:1206-1214

Corresponding author

Frans Van de Werf, MD, University Hospitals Leuven, Department of Cardiovascular Medicine, Herestraat 49, B-3000 Leuven, Belgium, e-mail: frans.vandewerf@med.kuleuven.be

RECORD1

Regulation of Coagulation in ORthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism 1 (2008)

Condition

Prophylaxis for VTE after total hip replacement

Objective

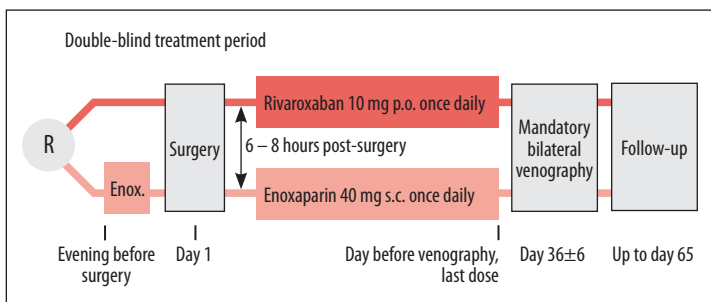
To compare the efficacy and safety of rivaroxaban with those of enoxaparin for extended thromboprophylaxis in patients undergoing total hip arthroplasty

Trial design

Randomized, double-blind phase 3 study

Active treatment: rivaroxaban 10 mg p.o. once daily, starting 6–8 hours after wound closure, through day 35 after surgery, plus placebo injections as in control treatment (n=2266)

Control treatment: enoxaparin 40 mg s.c. once daily, initiated 12 hours before surgery and restarted 6–8 hours after wound closure, administered for 35 days, plus placebo tablets as in active treatment (n=2275)



Endpoints

Primary efficacy endpoint: composite of DVT, non-fatal PE, or death from any cause up to 36±6 days

Secondary efficacy endpoints: major VTE (proximal DVT, non-fatal PE, or death from VTE), DVT (any, proximal, distal), symptomatic VTE during treatment and follow-up, and death during the follow-up period

Primary safety endpoint: major bleeding

Secondary safety endpoints: any on-treatment bleeding, non-major bleeding, hemorrhagic wound complications, adverse events, and death

Trial participants

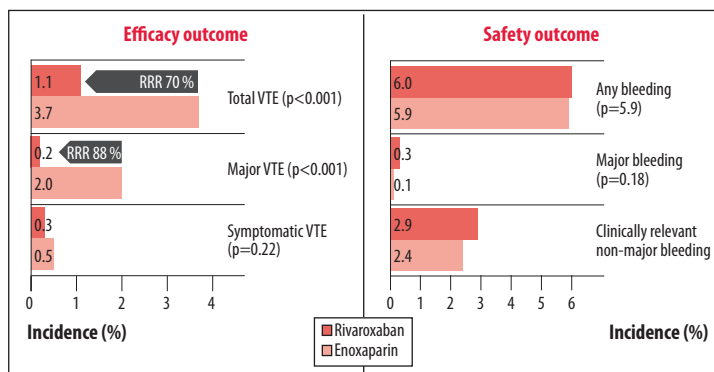
4541 patients ≥18 years scheduled for elective total hip replacement

Results

Efficacy outcome: In the modified ITT population (n=3153), the primary efficacy endpoint (total VTE) occurred in 18 of 1595 patients (1.1%) in the rivaroxaban group and in 58 of 1558 patients (3.7%) in the enoxaparin group (absolute risk reduction 2.6%, relative risk reduction 70%)

Safety outcome: The superior efficacy of rivaroxaban was not associated with any significant increases in the incidence of major bleeding or any other bleeding events. Major bleeding occurred in 6 of 2209 patients (0.3%) in the rivaroxaban group and in 2 of 2224 patients (0.1%) in the enoxaparin

group. The number of adverse events was similar for rivaroxaban (65.8%) and enoxaparin (66.1%)



Summary

Efficacy: Oral rivaroxaban was superior to subcutaneous enoxaparin for prevention of venous thromboembolic events

Safety: The rates of all bleeding events, hemorrhagic wound complications, and adverse events were similar in both groups

Reference

Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, Bandel TJ, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008;358:2765-2775

Corresponding author

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RECORD2

REGulation of Coagulation in ORthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism 2 Study in Patients Undergoing Elective Total Hip Replacement (2008)

Condition

Prophylaxis for VTE after total hip replacement

Objective

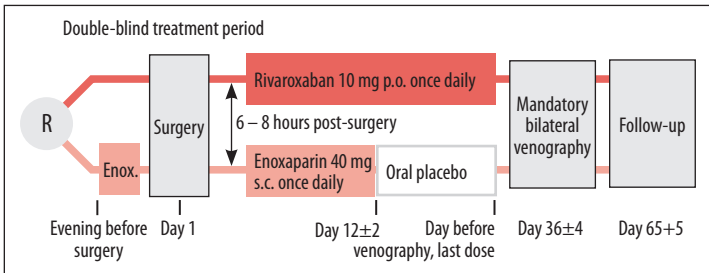
To compare the use of rivaroxaban for extended thromboprophylaxis with short-term thromboprophylaxis with enoxaparin in patients undergoing total hip arthroplasty

Trial design

Randomized, double-blind phase 3 study

Active treatment: rivaroxaban 10 mg p.o. once daily, beginning 6–8 hours after wound closure, for 31–39 days, plus placebo injection for 10–14 days (n=1252)

Control treatment: enoxaparin 40 mg s.c. once daily, initiated 12 hours before surgery and restarted 6–8 hours after wound closure, for 10–14 days, plus placebo tablet for 31–39 days (n=1257)



Endpoints

Primary efficacy endpoint: composite of any DVT, non-fatal PE, and all-cause mortality up to day 36±6

Secondary efficacy endpoints: major VTE (proximal DVT, non-fatal PE, and VTE-related death), DVT (any, proximal, distal), symptomatic VTE during treatment and follow-up, and death during the follow-up period

Primary safety endpoint: major bleeding (beginning after the first blinded dose up to 2 days after the last dose)

Secondary safety endpoints: any on-treatment bleeding, non-major bleeding, hemorrhagic wound complications, adverse events, and death

Trial participants

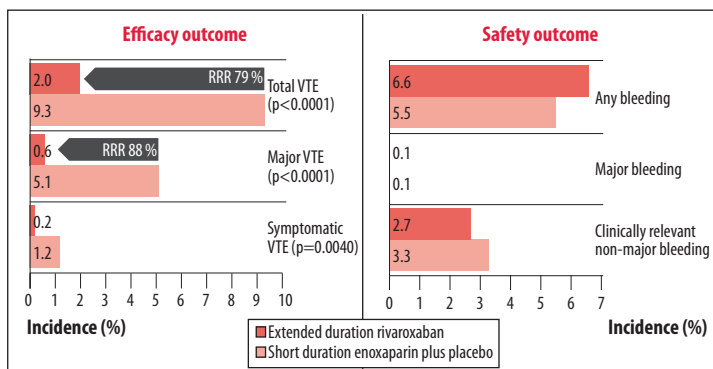
2509 patients ≥18 years scheduled for elective total hip replacement

Results

Efficacy outcome: In the modified ITT population (n=1733), the primary efficacy endpoint occurred in 17 of 864 patients (2.0%) in the rivaroxaban group and in 81 of 869 patients (9.3%) in the enoxaparin group (absolute risk reduction 7.3%, relative risk reduction 79%)

Safety outcome: The incidence of any on-treatment bleeding was similar in both groups: 81 events in 1228 patients (6.6%) in the rivaroxaban safety population vs. 68 events in 1229 patients (5.5%) in the enoxaparin safety

population ($p=0.25$). Major bleeding occurred in one patient in each group ($<0.1\%$). Both treatments were associated with a similar number of adverse events (rivaroxaban 62.5% vs. enoxaparin 65.7%)



Summary

Efficacy: Extended thromboprophylaxis with rivaroxaban was significantly more effective than short-term enoxaparin for the prevention of VTE in patients undergoing total hip arthroplasty

Safety: The rates of major and clinically relevant non-major bleeding were low and much the same in both groups

Reference

Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, Sogliani AG, Pap AF, Misselwitz F, Haas S for the RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008;372:31-39

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RECORD3

Regulation of Coagulation in ORthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism 3 (2008)

Condition

Prophylaxis for VTE after total knee arthroplasty

Objective

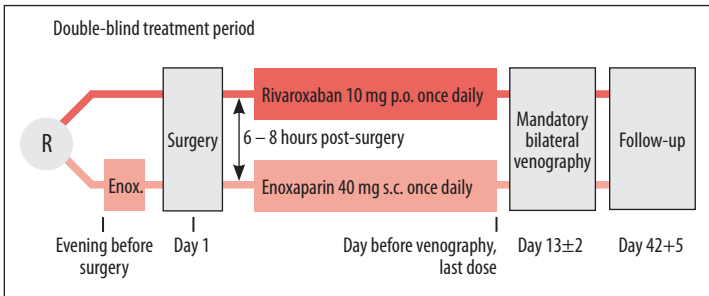
To compare the efficacy and safety of rivaroxaban with those of enoxaparin for the prevention of venous thromboembolism after elective total knee replacement

Trial design

Randomized, double-blind phase III study

Active treatment: rivaroxaban 10 mg p.o. once daily, beginning 6–8 hours after surgery and continued for 10–14 days; placebo injections as in control treatment (n=1254)

Control treatment: enoxaparin 40 mg s.c. once daily, initiated 12 hours before surgery and restarted 6–8 hours after wound closure, administered for at least 10 days and up to day 14; placebo tablets as in active treatment (n=1277)



Endpoints

Primary efficacy endpoint: composite of any DVT, non-fatal PE, and all-cause mortality within 13–17 days after surgery

Secondary efficacy endpoints: major VTE (proximal DVT, non-fatal PE, or VTE-related death), DVT (any, proximal, distal), symptomatic VTE during treatment and follow-up, and death during the follow-up period

Primary safety endpoint: major bleeding occurring between intake of the first dose of study drug and 2 days after the last dose

Secondary safety endpoints: any on-treatment bleeding, non-major bleeding, hemorrhagic wound complications, other adverse events, and death

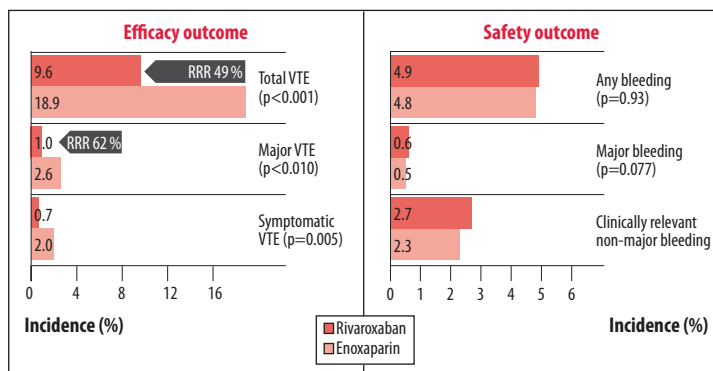
Trial participants

2531 patients ≥ 18 years scheduled for elective total knee replacement

Results

Efficacy outcome: In the modified ITT population (n=1702), the primary efficacy endpoint (total VTE) occurred in 79 of 824 patients (9.6%) who received rivaroxaban and in 166 of 878 (18.9%) who received enoxaparin (absolute risk reduction 9.2%, relative risk reduction 49%). There were no pulmonary emboli or deaths in the rivaroxaban group; in the enoxaparin group, 4 patients had a pulmonary embolus and an additional 2 patients died

Safety outcome: In the safety population (n=2459), major bleeding occurred in 7 of 1220 patients (0.6%) who received rivaroxaban and in 6 of 1239 patients (0.5%) who received enoxaparin. The incidences of drug-related adverse events were similar in the two groups: 12.0% with rivaroxaban and 13.0% with enoxaparin



Summary

Efficacy: Oral rivaroxaban was superior to subcutaneous enoxaparin for thromboprophylaxis after total knee arthroplasty

Safety: Both groups showed similar rates of all bleeding events, hemorrhagic wound complications, and adverse events

Reference

Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, Missetwitz F, Turpie AGG for the RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008;358:2776-2786

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RECORD4

REgulation of **Co**agulation in major **Orthopedic** Surgery reducing the **R**isk of **Deep Venous Thrombosis** and **Pulmonary Embolism** 4 (2009)

Condition

Prophylaxis for VTE after total knee arthroplasty

Objective

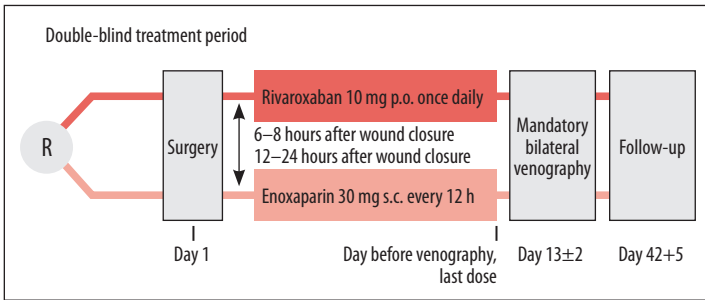
To compare the efficacy and safety of rivaroxaban with those of enoxaparin for the prevention of venous thromboembolism after elective total knee replacement

Trial design

Randomized, double-blind phase III study

Active treatment: rivaroxaban 10 mg p.o. once daily (every 22–26 h), beginning 6–8 hours after wound closure and continued for 10–14 days; placebo injections as in control treatment (n=1584)

Control treatment: enoxaparin 30 mg s.c. every 10–14 hours, starting 12–24 hours after wound closure, administered for at least 10 days and up to day 14; placebo tablets as in active treatment (n=1564)



Endpoints

Primary efficacy endpoint: composite of any DVT, non-fatal PE, and all-cause mortality within 13–17 days after surgery

Secondary efficacy endpoints: major VTE (proximal DVT, non-fatal PE, or VTE-related death), DVT (any, proximal, distal), symptomatic VTE during treatment and follow-up, and death during the follow-up period

Primary safety endpoint: major bleeding occurring between intake of the first dose of study drug and 2 days after the last dose

Secondary safety endpoints: any on-treatment bleeding, non-major bleeding, hemorrhagic wound complications, other adverse events, and death

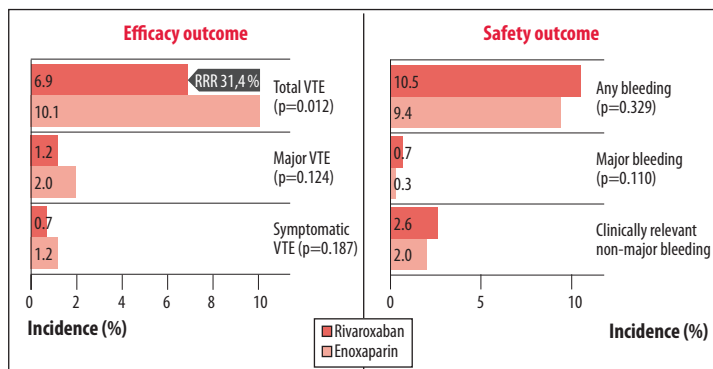
Trial participants

3148 patients ≥ 18 years scheduled for elective total knee replacement

Results

Efficacy outcome: In the modified ITT population (n=1924), the primary efficacy endpoint (total VTE) occurred in 67 of 965 patients (6.9%) given rivaroxaban and in 97 of 959 patients (10.1%) given enoxaparin (absolute risk reduction 3.2%, relative risk reduction 31%). On-treatment in the rivaroxaban group there were 2 deaths and 4 patients had a pulmonary embolus; in the enoxaparin group, 3 patients died and pulmonary embolism occurred in 8 patients

Safety outcome: In the safety population (n=3034), major bleeding occurred in 10 of 1526 patients (0.7%) receiving rivaroxaban and in 4 of 1508 patients (0.3%) receiving enoxaparin. The incidences of drug-related adverse events were similar in the two groups: 20.3% with rivaroxaban and 19.6% with enoxaparin



Summary

Efficacy: Oral rivaroxaban was significantly superior to subcutaneous enoxaparin for thromboprophylaxis after total knee arthroplasty

Safety: Although there were more major, major plus clinically relevant non-major, and any bleeding events with rivaroxaban, the differences compared with enoxaparin were not statistically significant

Reference

Turpie AGG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, Cushner FD, Lotke PA, Berkowitz SD, Bandel TJ, Benson A, Misselwitz F, Fisher WD for the RECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. The Lancet 2009;373:1673-1680

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RE-COVER I

Dabigatran versus warfarin in the treatment of acute venous thromboembolism I (2009)

Condition

Treatment of acute VTE

Objective

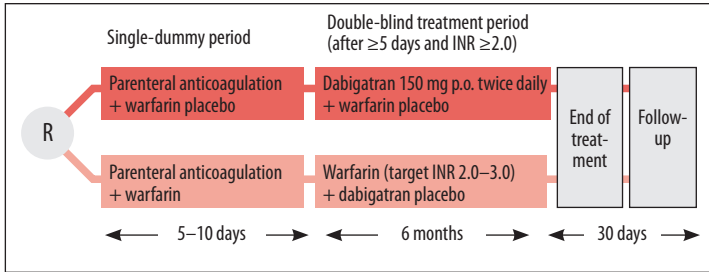
To compare the efficacy and safety of dabigatran vs. warfarin in the treatment of acute VTE

Trial design

Randomized, double-blind phase III non-inferiority study

Active treatment: dabigatran 150 mg p.o. twice daily for 6 months plus warfarin placebo after an initial treatment with a parenteral anticoagulant (low molecular weight or unfractionated heparin) plus warfarin placebo (sham INR) for at least 5 days (n=1274)

Control treatment: dose-adjusted warfarin (INR 2.0–3.0) for 6 months, starting after randomization, plus dabigatran placebo, starting after at least 5 days parenteral anticoagulation (n=1265)



Endpoints

Primary efficacy endpoint: 6-month incidence of recurrent symptomatic, objectively confirmed VTE and related deaths

Secondary efficacy endpoints: symptomatic VTE, symptomatic non-fatal PE, VTE-related death, all deaths

Safety endpoints: bleeding events, acute coronary syndromes, other adverse events, and liver function parameters

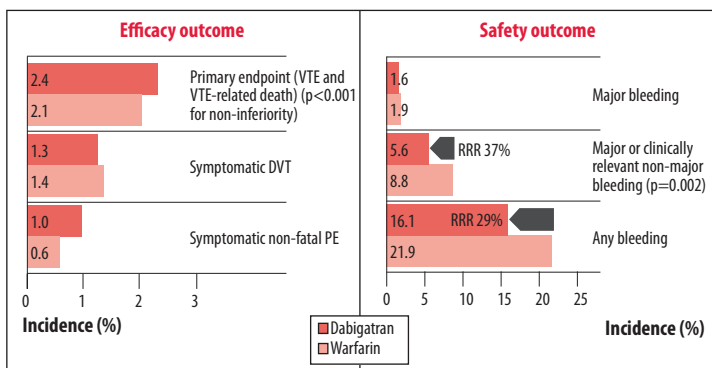
Trial participants

2539 patients (mean age 55 years) with acute venous thromboembolism

Results

Efficacy outcome: The primary endpoint (symptomatic VTE and VTE-related deaths) occurred in 30 of 1274 patients (2.4%) given 150 mg dabigatran twice daily and in 27 of 1265 patients (2.1%) given warfarin during the study period

Safety outcome: Major bleeding occurred in 20 of 1274 patients (1.6%) receiving 150 mg dabigatran twice daily and in 24 of 1265 patients (1.9%) receiving warfarin. A total of 71 patients in the dabigatran group (5.6%), as compared with 111 in the warfarin group (8.8%), had major or clinically relevant non-major bleeding (relative risk reduction 37%, $p=0.002$). The numbers of deaths, acute coronary syndromes, and abnormal liver-function tests were similar in both groups



Summary

Efficacy: Dabigatran was non-inferior to warfarin in the prevention of recurrent or fatal VTE in patients with acute VTE

Safety: In the dabigatran group, the rate of major or clinically relevant non-major bleeding events was significantly lower as in the warfarin group. The difference in major bleeding was not significant

Reference

Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361:2342-2352

Corresponding author

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RE-COVER II

Dabigatran versus warfarin in the treatment of acute venous thromboembolism II (2013)

Condition

Treatment of acute VTE

Objective

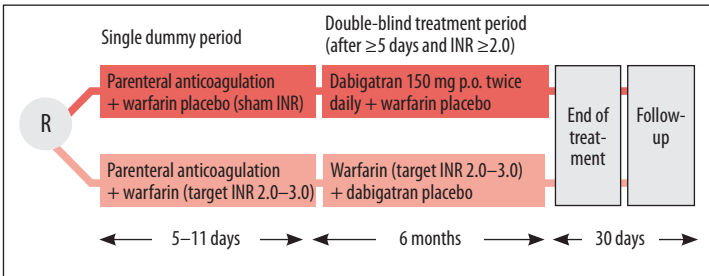
To compare the efficacy and safety of dabigatran vs. warfarin in the treatment of acute VTE and to confirm the results of RE-COVER I

Trial design

Randomized, double-blind, double-dummy phase III non-inferiority study (same design as RE-COVER I, duplicate trials)

Active treatment: dabigatran 150 mg p.o. twice daily for 6 months plus warfarin placebo after an initial treatment with a parenteral anticoagulant (low molecular weight or unfractionated heparin) plus warfarin placebo (sham INR) for at least 5 days and until the sham INR had been ≥ 2.0 for 2 consecutive measurements (n=1279)

Control treatment: dose-adjusted warfarin (INR 2.0–3.0) for 6 months, starting after randomization, plus dabigatran placebo, starting after at least 5 days parenteral anticoagulation and until the INR had been ≥ 2.0 for 2 consecutive measurements (n=1289)



Endpoints

Primary efficacy endpoint: 6-month incidence of recurrent symptomatic VTE and deaths related to VTE

Secondary efficacy endpoints: symptomatic VTE, symptomatic non-fatal PE, VTE-related death, all deaths

Safety endpoints: bleeding events, acute coronary syndromes, other adverse events, and liver function parameters

Trial participants

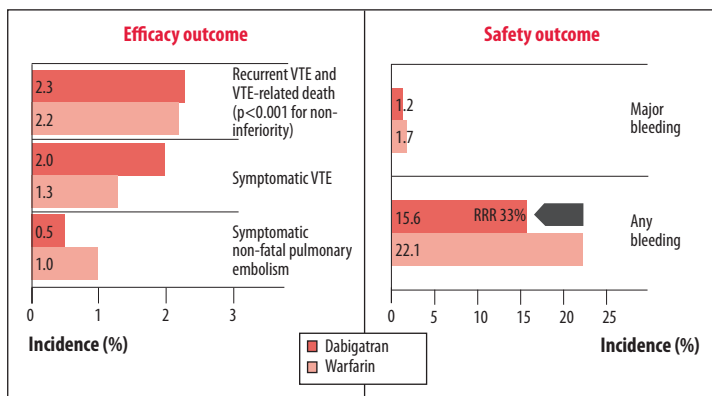
2568 patients ≥ 18 years with acute VT

Results

Efficacy outcome: At 6 months, of 1279 patients randomized to dabigatran, 30 (2.3%) had recurrent fatal or non-fatal VTE compared with 28 (2.2%) of 1289 patients randomized to warfarin (hazard ratio for dabigatran 1.08; $p < 0.001$ for non-inferiority)

Safety outcome: Major bleeding events occurred in 15 patients (1.2%) treated with dabigatran and 22 patients (1.7%) receiving warfarin (hazard ratio 0.69). Rates of any bleeding favored dabigatran, with 200 bleeding events in the dabigatran group (15.6%) and 285 bleeding events in the warfarin group

(22.1%) (hazard ratio 0.67). The frequency of reported ACS events was less than 1% in the trial, with more cases in the dabigatran treatment group (4 vs. 2; difference not statistically significant). There were 25 deaths in each treatment arm, and serious adverse events were similar in both groups



Summary

The results of the trial confirm that the direct thrombin inhibitor dabigatran has similar effects on VTE recurrence and a lower risk of bleeding compared with well-controlled warfarin for the treatment of acute VTE. Pooled analysis of this study RE-COVER II and the RE-COVER trial gave hazard ratios for recurrent VTE of 1.09, for major bleeding of 0.73, and for any bleeding of 0.70

Reference

Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, Christiansen AV, Friedman J, Le Maulf F, Peter N, Kearon C; RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation* 2014;129:764-772; published online December 16, 2013; doi: 10.1161/CIRCULATIONAHA.113.004450

Corresponding author

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RE-DEEM

Dabigatran versus placebo in patients with acute coronary syndromes on dual antiplatelet therapy (2011)

Condition

Secondary prevention in ACS

Objective

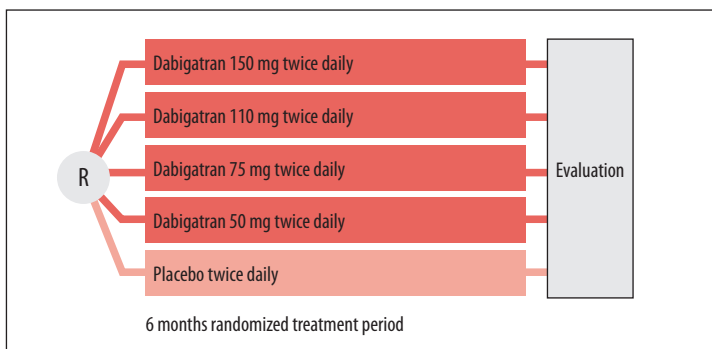
Evaluation of 4 different dose regimens of dabigatran compared to placebo regarding efficacy and safety in patients with ACS on dual antiplatelet therapy

Trial design

Randomized, double-blind phase II study, dose-escalation trial

Active treatment: dabigatran 50 mg (n=369), 75 mg (n=368), 110 mg (n=406) or 150 mg (n=347) p.o. twice daily, for 6 months

Control treatment: placebo for 6 months (n=371)



Endpoints

Primary endpoint: major or clinically relevant non-major bleeding events

Secondary endpoints: clinical chemistry levels of coagulation activity, composite of cardiovascular death, non-fatal myocardial infarction and non-hemorrhagic stroke

Trial participants

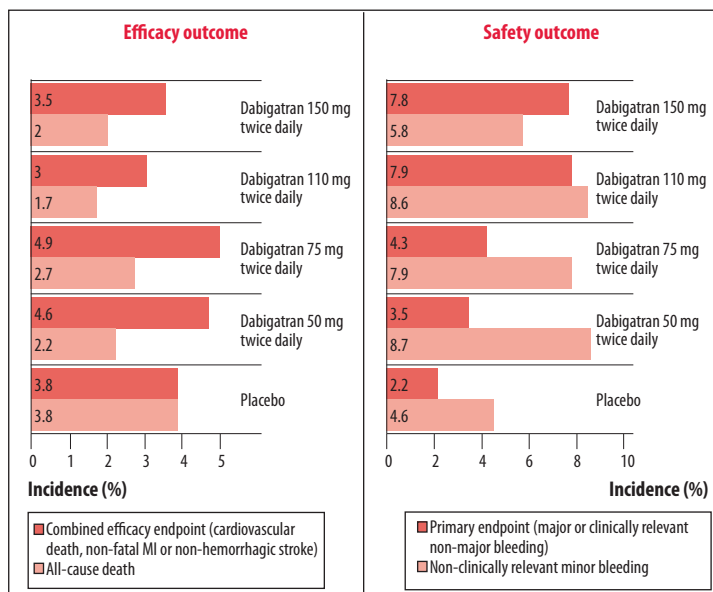
1861 patients (mean age 61 years), hospitalized with non-ST (40%) or ST-segment (60%) elevation myocardial infarction within the last 14 days and ≥ 1 risk factor for cardiovascular complications, receiving dual antiplatelet treatment (ASA and clopidogrel or another thienopyridine)

Results

Primary outcome: The primary endpoint (major or clinically relevant non-major bleeding events) occurred in 27 of 347 patients (7.8%) given 150 mg dabigatran twice daily, in 32 of 406 patients (7.9%) given 110 mg dabigatran twice daily, in 16 of 368 patients (4.3%) given 75 mg dabigatran twice daily, in 13 of 369 patients (3.5%) given 50 mg dabigatran twice daily, and in 8 of 371 patients (2.2%) given placebo during the study period

Secondary outcomes: D-Dimer-levels in patients were significantly lower during treatment with dabigatran when compared to placebo. In patients treated with higher doses of dabigatran the rate of the combined efficacy endpoint of cardiovascular death, non-fatal myocardial infarction and non-

hemorrhagic stroke was lower (110 mg: 3.0%; 150 mg: 3.5%) than in patients with lower doses of dabigatran (50 mg: 4.6%; 75 mg: 4.9%)



Summary

Efficacy: There were higher rates of cardiovascular death, non-fatal myocardial infarction or non-hemorrhagic stroke in lower doses of dabigatran when compared to higher doses

Safety: Addition of dabigatran in patients on dual antiplatelet therapy was associated with a dose-dependent increase of major or clinically relevant minor bleedings

Reference

Oldgren J, Budaj A, Granger C, Khder Y, Roberts J, Siegbahn A, Tijssen J G P, Van de Werf F, Wallentin L, for the RE-DEEM Investigators. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. *Eur Heart J* 2011, May 7, epub ahead of print

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RE-LY

Randomized Evaluation of Long-term anticoagulant therapy (2009)

Condition

Anticoagulation in AF

Objective

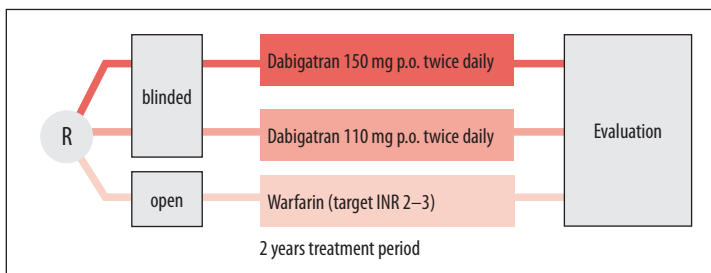
To compare the efficacy and safety of two dose regimens of dabigatran vs. warfarin in patients with non-valvular AF

Trial design

Randomized, partially blinded (warfarin: open; dabigatran: closed) phase III study, non-inferiority trial

Active treatment: dabigatran 110 mg (n=6015) or 150 mg (n=6076) p.o. twice daily, for 2 years, in a blinded fashion

Control treatment: warfarin (INR 2.0–3.0); for 2 years, in an unblinded fashion (n=6022)



Endpoints

Primary efficacy endpoint: composite of stroke or systemic embolism

Primary safety endpoint: major bleeding

Secondary endpoints: stroke, systemic embolism and death

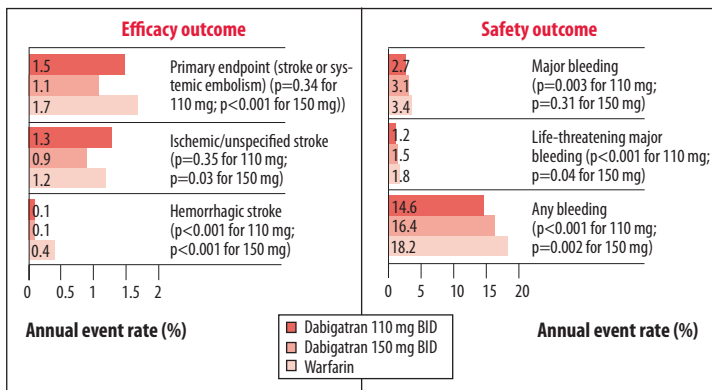
Trial participants

18,113 patients (mean age 71 years), with AF documented within 6 months before screening and ≥ 1 risk factor (previous stroke or TIA, LVEF $<40\%$, NYHA \geq II or higher heart failure symptoms)

Results

Efficacy outcome: The primary endpoint (stroke or systemic embolism) showed an annual event rate of 1.5% in patients given 110 mg dabigatran twice daily, of 1.1% in patients given 150 mg dabigatran twice daily and of 1.7% in patients given warfarin

Safety outcome: The annual event rate of major bleeding was 2.7% in patients receiving 110 mg dabigatran twice daily, 3.1% in patients receiving 150 mg dabigatran twice daily and 3.4% in patients receiving warfarin. The only adverse event occurring significantly more often in patients receiving dabigatran when compared to warfarin was dyspepsia (110 mg dabigatran: 11.8%, 150 mg dabigatran: 11.3%, and warfarin: 5.8%)



Summary

Efficacy: Both dabigatran dosage regimens showed lower rates of stroke or systemic embolism when compared to warfarin, only reaching statistical significance in 150 mg dabigatran twice daily. Compared to warfarin a significantly lower annual event rate of hemorrhagic strokes occurred in both dabigatran dosage regimens

Safety: Both doses of dabigatran markedly reduced intra-cerebral, life-threatening and total bleeding compared to warfarin. Dabigatran had no major toxicity, but did increase dyspepsia and gastrointestinal bleeding

Reference

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener H-C, Joyner C D, Wallentin L, and the RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-1151

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RELY-ABLE

Long-term multicenter extension of dabigatran treatment in patients with atrial fibrillation who completed the RE-LY trial (2013)

Condition

Atrial fibrillation requiring long-term anticoagulation

Objective

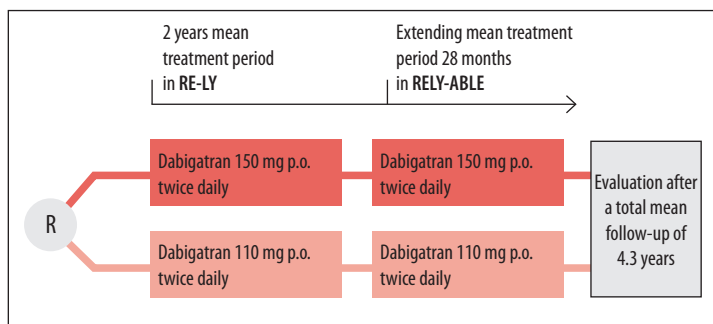
To evaluate the long-term safety of dabigatran 150 mg twice daily vs. 110 mg twice daily in patients with non-valvular AF

Trial design

Randomized, phase III safety study; extension of the RE-LY trial (Randomized Evaluation of Long-term anticoagulant therapy), enrolled patients continued to receive the double-blind dabigatran dose received in RE-LY

Active treatment: dabigatran 150 mg p.o. twice daily, for up to 28 months (n=2914)

Control treatment: dabigatran 110 mg p.o. twice daily, for up to 28 months (n=2937)



Endpoints

Primary endpoint (safety): major bleeding

Secondary endpoints (efficacy): stroke (ischemic or hemorrhagic), systemic embolism, pulmonary embolism, myocardial infarction, deep vein thrombosis, death, net clinical benefit (defined as a composite of the following events: stroke, systemic embolism, pulmonary embolism, acute myocardial infarction, death, or major bleeding)

Trial participants

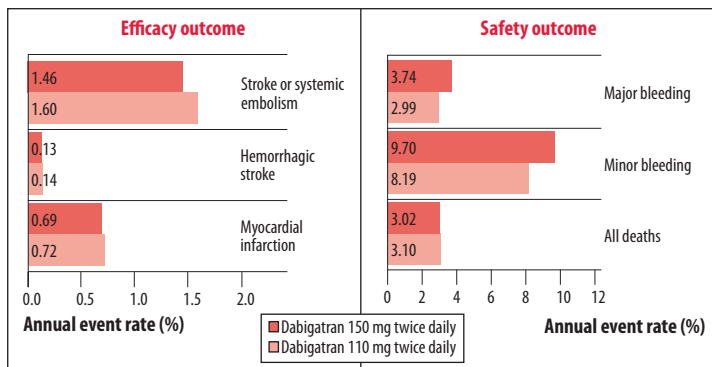
5851 patients ≥ 18 years with atrial fibrillation after participation in the RE-LY trial with randomization to dabigatran further requiring long-term anticoagulation

Results

Safety outcome: Major bleeding (primary endpoint) occurred at rates of 3.74% per year with dabigatran 150 mg twice daily and 2.99%/y with 110 mg twice daily. Mortality rates were similar for the 2 dabigatran doses: 3.10% and 3.02%/y for 110 mg and 150 mg, respectively

Efficacy outcome: The annual rates of stroke or systemic embolism were 1.46% and 1.60% on dabigatran 150 mg and 110 mg, respectively. The rates of hemorrhagic stroke were similar in the 2 treatment arms and were very low at 0.13%/y with dabigatran 150 mg and 0.14%/y with dabigatran

110 mg. Annual rates of myocardial infarction were also low and similar between the 2 groups at 0.69% vs. 0.72%. The results for the composite of all major ischemic, hemorrhagic, and fatal events (7.36% vs. 6.89%/y) indicate that the 2 doses achieve similar net clinical effects



Summary

During 2.3 years of continued treatment with dabigatran after the RE-LY trial, there was no significant difference in stroke or mortality with dabigatran 150 mg vs. 110 mg twice daily, but there was a higher rate of major and minor bleeding with higher dabigatran dose

Reference

Connolly SJ, Wallentin L, Ezekowitz MD, Eikelboom J, Oldgren J, Reilly PA, Brueckmann M, Pogue J, Alings M, Amerena JV, Avezum A, Baumgartner I, Budaj AJ, Chen JH, Dans AL, Darius H, Di Pasquale G, Ferreira J, Flaker GC, Flather MD, Franzosi MG, Golitsyn SP, Halon DA, Heidbuchel H, Hohnloser SH, Huber K, Jansky P, Kamensky G, Keltai M, Kim SS, Lau CP, Le Heuzey JY, Lewis BS, Liu L, Nanas J, Omar R, Pais P, Pedersen KE, Piegas LS, Raev D, Smith PJ, Talajic M, Tan RS, Tanomsup S, Toivonen L, Vinereanu D, Xavier D, Zhu J, Wang SQ, Duffy CO, Themeles E, Yusuf S. The long-term multicenter observational study of dabigatran treatment in patients with atrial fibrillation (RELY-ABLE) study. *Circulation* 2013;128:237-243

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RE-MEDY

A randomized, multicenter, double-blind, active controlled study to investigate the efficacy and safety of dabigatran etexilate, 150 mg b.i.d. administered orally (capsules) for 18 months, compared to warfarin tablets (target INR) for the secondary prevention of venous thromboembolism (2011)

Condition

Secondary prevention of VTE after 3–6 months successful treatment for acute symptomatic DVT or PE

Objective

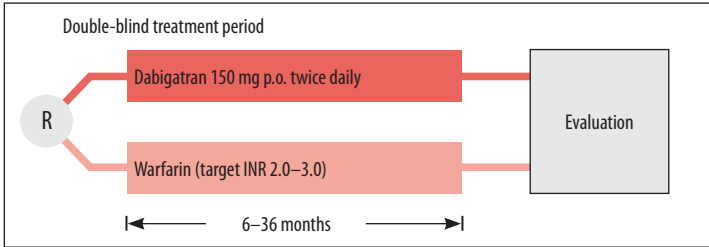
To evaluate the efficacy and safety of dabigatran compared to warfarin for the secondary prevention of VTE

Trial design

Randomized, double-blind non-inferiority phase III study

Active treatment: dabigatran 150 mg p.o. twice daily for 6–36 months and warfarin placebo (n=1430)

Control treatment: warfarin (INR 2.0–3.0) for 6–36 months and dabigatran placebo (n=1426)



Endpoints

Primary efficacy endpoint: composite of recurrent symptomatic VTE and deaths related to VTE during the treatment period

Secondary efficacy endpoints: composite of recurrent symptomatic VTE and all deaths, symptomatic DVT, symptomatic PE, deaths related to VTE and all deaths

Safety endpoint: bleeding events, acute coronary syndromes and other adverse events

Trial participants

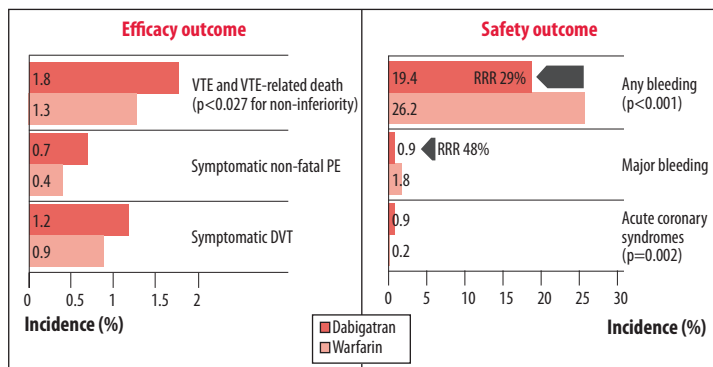
2856 patients who had initially received 3–12 months of anticoagulant therapy for acute symptomatic DVT or PE

Results

Efficacy outcome: The primary efficacy endpoint, the composite of recurrent VTE and VTE-related deaths, occurred in 26 (1.8%) of 1430 patients treated with dabigatran and in 18 (1.3%) of 1426 patients treated with warfarin (hazard ratio 1.44; $p=0.027$ for non-inferiority). The rate of symptomatic DVT was higher with dabigatran (1.2% vs. 0.9%), as well as the rate of symptomatic non-fatal PE (0.7% vs. 0.4%)

Safety outcome: There were 13 major bleeding events (0.9%) in the dabigatran group and 25 (1.8%) in the warfarin group (relative risk reduction 48%; $p=0.058$). Any bleeding occurred in 277 patients (19%) on treatment with dabigatran and in 373 patients (26%) on warfarin (relative risk reduc-

tion 29%; $p < 0.001$). Acute coronary syndromes were observed in 13 patients (0.9%) on treatment with dabigatran and in 3 patients (0.2%) on warfarin ($p = 0.02$). 17 patients in the dabigatran group and 19 patients in the warfarin group have died. Other adverse events were also similar with the two treatments



Summary

Efficacy outcome: Dabigatran was as effective as well-controlled warfarin in the extended treatment of VTE and secondary prevention of symptomatic VTE

Safety outcome: Treatment with the direct thrombin inhibitor was associated with a reduced risk for bleeding but an increased incidence of acute coronary events

References

- (1) ClinicalTrials.gov (NCT00329238)
- (2) Schulman S, Eriksson H, Goldhaber SZ, Kakkar AKL, Kearon C, Kvamme AM, Mismetti P, Schellong S, Schnee J. Dabigatran or warfarin for extended maintenance therapy of venous thromboembolism. ISTH 2011; July 28. Journal of Thrombosis and Haemostasis 2011;9 (Suppl 2):731; Abstract O-TH-033

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RE-MOBILIZE

Oral thrombin inhibitor dabigatran etexilate versus North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty (2009)

Condition

Prophylaxis for VTE after total knee replacement

Objective

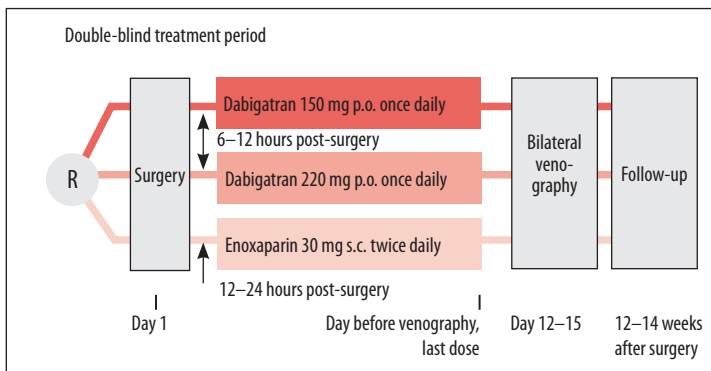
To compare the efficacy and safety of dabigatran and enoxaparin in the prevention of venous thromboembolism after total knee replacement

Trial design

Randomized, double-blind non-inferiority phase III study

Active treatment: dabigatran 150 mg (n=871) or 220 mg (n=857) p.o. once daily, starting 6–12 hours after surgery with half dose on the first day, for 12–15 days; placebo injections as in control treatment

Control treatment: enoxaparin 30 mg s.c. twice daily, starting 12–24 hours after surgery, for 12–15 days; placebo tablets as in active treatment (n=868)



Endpoints

Primary efficacy endpoint: composite of total VTE events (symptomatic or venographic DVT and/or symptomatic PE) and all-cause mortality during treatment

Secondary efficacy endpoints: composite of major VTE (proximal DVT, PE, and VTE-related mortality); proximal DVT; incidence of total VTE and all-cause mortality during follow-up

Primary safety endpoint: major bleeding

Secondary safety endpoints: clinically relevant non-major bleeding and minor bleeding

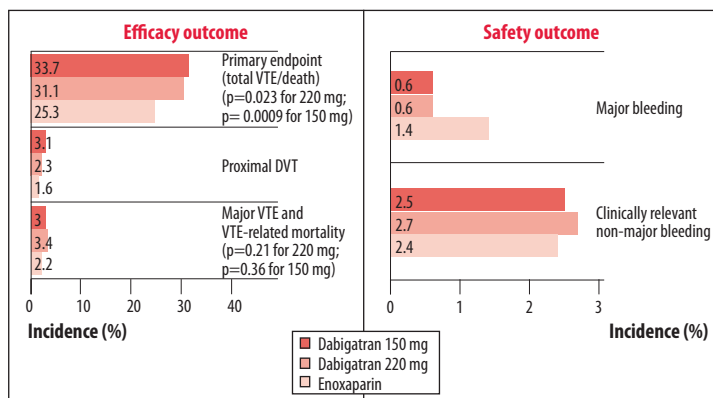
Trial participants

2615 patients (mean age 66 years), scheduled for elective total knee replacement

Results

Efficacy outcome: In patients with evaluable efficacy outcome (n=1896), the primary endpoint (all VTE and all-cause mortality) occurred in 219 of 649 patients (33.7%) given 150 mg dabigatran, in 188 of 604 patients (31.1%) given 220 mg dabigatran and in 163 of 643 patients (25.3%) given enoxaparin

Safety outcome: In the study population of 2596 patients major bleeding occurred in 5 of 871 patients (0.6%) receiving 150 mg dabigatran, in 5 of 857 patients (0.6%) receiving 220 mg dabigatran and in 12 of 868 patients (1.4%) receiving enoxaparin. During the treatment period comparable rates of clinically relevant non-major bleeding events in the three groups were observed



Summary

Efficacy: Both dabigatran dosage regimens failed to show statistical non-inferiority to enoxaparin, as the combined incidence of VTE and death was slightly higher in patients treated with dabigatran

Safety: In patients receiving enoxaparin, major bleeding events were more frequent. The rate of clinically relevant non-major bleeding events was comparable in all three study groups

Reference

Ginsberg JS, Davidson BL, Comp PC, Francis CW, Friedman RJ, Huo MH, Lieberman JR, Muntz JE, Raskob GE, Clements ML, Hantel S, Schnee JM, Caprini JA for the RE-MOBILIZE Writing Committee. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty* 2009;24:1-9

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RE-MODEL

Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement (2007)

Condition

Prophylaxis for VTE after total knee replacement

Objective

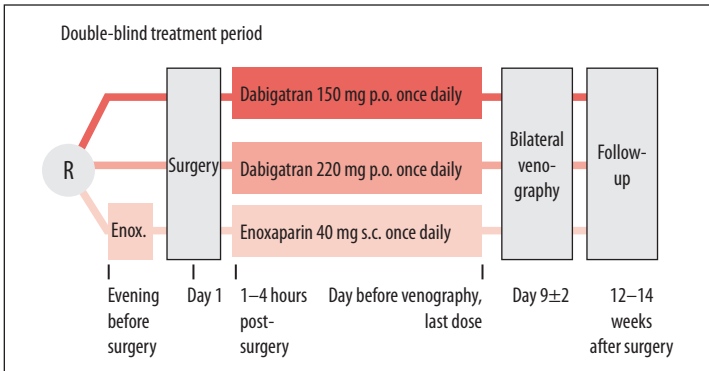
To prove non-inferiority of dabigatran compared to enoxaparin in the prevention of venous thromboembolism after total knee replacement

Trial design

Randomized, double-blind phase III study

Active treatment: dabigatran 150 mg (n=703) or 220 mg (n=679) p.o. once daily, starting 1–4 hours after surgery with half dose on the first day, for 6–10 days; placebo injections as in control treatment

Control treatment: enoxaparin 40 mg s.c. once daily, starting in the evening before surgery for 6–10 days; placebo tablets as in active treatment (n=694)



Endpoints

Primary efficacy endpoint: composite of total VTE and death from any cause during treatment

Secondary efficacy endpoints: composite of major VTE (proximal DVT and PE) and VTE-related mortality, proximal DVT, the incidence of total VTE and all-cause mortality during follow-up

Primary safety endpoint: major bleeding

Secondary safety endpoints: bleeding events during study treatment; hepatic enzyme abnormalities and suspected cardiovascular events during study treatment and follow-up

Trial participants

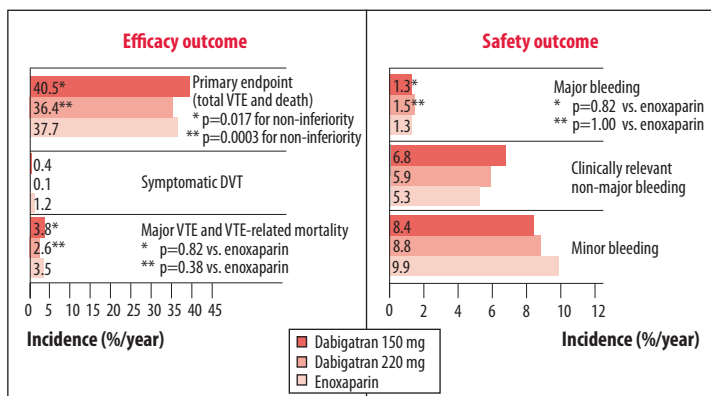
2101 patients (mean age 68 years), scheduled for elective total knee replacement

Results

Efficacy outcome: In patients with evaluable efficacy outcome (n=1541), the primary efficacy endpoint (all DVT, symptomatic PE and death from any cause) occurred in 213 of 526 patients (40.5%) given 150 mg dabigatran, in 183 of 503 patients (36.4%) given 220 mg dabigatran and in 193 of 512 patients (37.7%) given enoxaparin. Both doses of dabigatran were non-inferior

to enoxaparin ($p=0.017$ for 150 mg, $p=0.0003$ for 220 mg). The secondary outcome of major VTE and VTE-related mortality occurred in 2.6% and 3.8% of the dabigatran 220-mg and 150-mg groups, as compared with 3.5% of the enoxaparin group

Safety outcome: In the study population of 2076 patients major bleeding occurred in 9 of 703 patients (1.3%) receiving 150 mg dabigatran, in 10 of 679 patients (1.5%) receiving 220 mg dabigatran and in 9 of 694 patients (1.3%) receiving enoxaparin. None of the major bleeding events was fatal. Clinically relevant non-major bleeding developed in 6.8%, 5.9%, and 5.3% of the patients receiving 150 mg dabigatran, 220 mg dabigatran, and enoxaparin, respectively. The incidences for minor bleeding were 8.4%, 8.8%, and 9.9%



Summary

Efficacy: Oral administration of dabigatran was non-inferior to subcutaneous enoxaparin for the combined endpoint of DVT, symptomatic PE and death

Safety: The rate of minor and major bleeding was comparable in all 3 study groups

Reference

Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Kälebo P, Christiansen AV, Hantel S, Hettiarachchi R, Schnee J, Büller HR; RE-MODEL Study Group. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007;5:2178-2185

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RE-NOVATE

Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement (2007)

Condition

Prophylaxis for VTE after total hip replacement

Objective

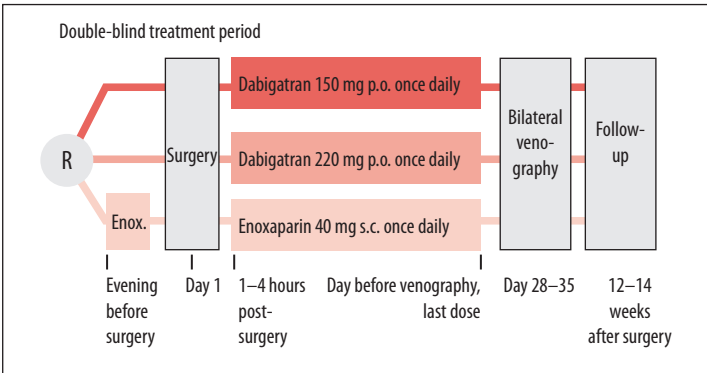
To compare the efficacy and safety of dabigatran and enoxaparin in the prevention of VTE after total hip replacement

Trial design

Randomized, double-blind phase III study with non-inferiority design

Active treatment: dabigatran 150 mg (n=1174) or 220 mg (n=1157) p.o. once daily, starting 1–4 hours after surgery with half dose on the first day, for 28–35 days; placebo injections as in control treatment

Control treatment: enoxaparin 40 mg s.c. once daily, starting in the evening before surgery, for 28–35 days; placebo tablets as in active treatment (n=1162)



Endpoints

Primary efficacy endpoint: composite of total VTE and all-cause mortality during treatment

Secondary efficacy endpoints: all-cause mortality, symptomatic DVT, distal DVT, composite of fatal/non-fatal DVT and PE during follow-up

Primary safety endpoint: major bleeding

Secondary safety endpoints: composite of major and clinically relevant non-major bleeding events, other bleeding events during treatment, liver enzyme elevation and acute coronary events

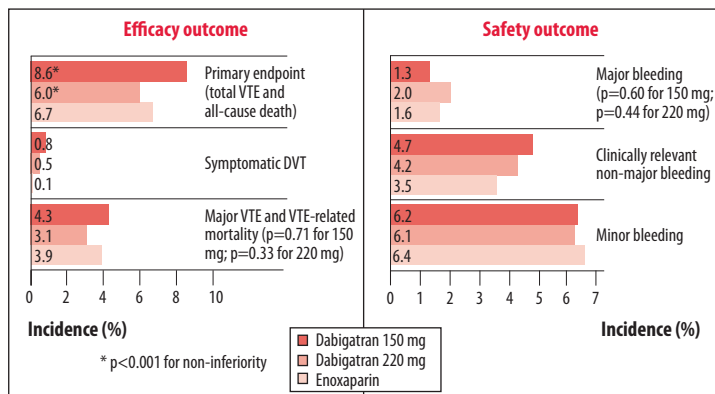
Trial participants

3494 patients (mean age 64 years), scheduled for elective total hip replacement

Results

Efficacy outcome: In patients with evaluable efficacy outcome (n=2651), the primary efficacy endpoint (all VTE and death from any cause) occurred in 75 of 874 patients (8.6%) given 150 mg dabigatran, in 53 of 880 patients (6.0%) given 220 mg dabigatran and in 60 of 897 patients (6.7%) given enoxaparin

Safety outcome: In the patient population for safety analysis of 3463 patients, major bleeding occurred in 15 of 1163 patients (1.3%) receiving 150 mg dabigatran, in 23 of 1146 patients (2.0%) receiving 220 mg dabigatran and in 18 of 1154 patients (1.6%) receiving enoxaparin. Minor bleeding developed in 6.2% of patients on 150 mg dabigatran, 6.1% on 220 mg dabigatran and in 6.2% receiving enoxaparin. Adverse events leading to treatment discontinuation occurred in 8%, 6% and 6% for 150 mg dabigatran, 220 mg dabigatran, and enoxaparin, respectively



Summary

Efficacy: Oral dabigatran showed statistical non-inferiority to subcutaneous enoxaparin for VTE and all-cause death. There was no significant difference between dabigatran and enoxaparin for major VTE and VTE-related death

Safety: The rates of minor and major bleeding were comparable in all 3 study groups

Reference

Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Prins MH, Hettiarachchi R, Hantel S, Schnee J, Büller HR; RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007;370:949-956

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RE-NOVATE II

Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (2011)

Condition

Prophylaxis for VTE after total hip arthroplasty

Objective

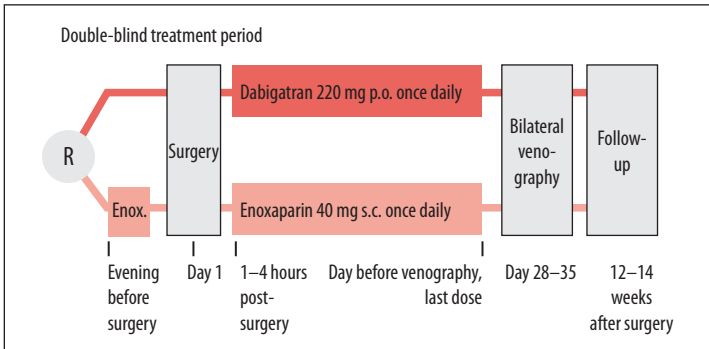
To compare the efficacy and safety of dabigatran and enoxaparin in the prevention of VTE after total hip arthroplasty

Trial design

Randomized, double-blind phase III study with non-inferiority design

Active treatment: dabigatran 220 mg p.o. once daily, starting 1–4 hours after surgery with half dose on the first day, for 28–35 days; placebo injections as in control treatment (n=1010)

Control treatment: enoxaparin 40 mg s.c. once daily, starting in the evening before surgery, for 28–35 days; placebo tablets as in active treatment (n=1003)



Endpoints

Primary efficacy endpoint: composite of total VTE and all cause mortality during the treatment period

Secondary efficacy endpoints: major VTE and VTE-related mortality

Safety endpoints: major bleeding events, clinically relevant bleeding events, any bleeding events

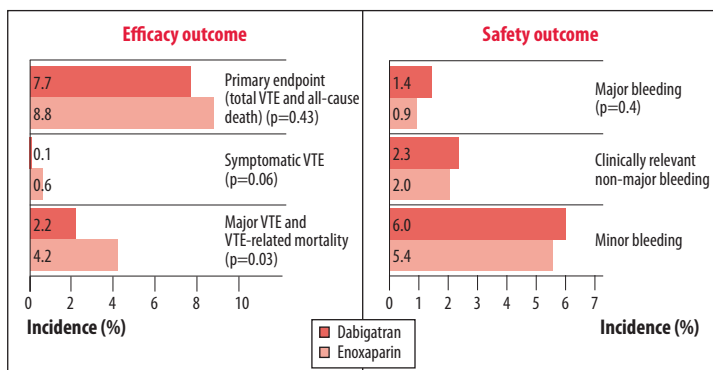
Trial participants

2055 patients aged ≥ 18 years, scheduled for elective total hip arthroplasty

Results

Efficacy outcome: In patients with evaluable efficacy outcome (n=1577), the primary efficacy endpoint (all VTE and death from any cause) occurred in 61 of 792 patients (7.7%) given dabigatran and in 69 of 785 patients (8.8%) given enoxaparin

Safety outcome: In the patient population for safety analysis of 2013 patients major bleeding occurred in 14 of 1010 patients (1.4%) receiving dabigatran and in 9 of 1003 patients (0.9%) receiving enoxaparin. Minor bleeding developed in 6.0% of the patients assigned to dabigatran and in 5.4% of the patients treated with enoxaparin. Adverse events leading to treatment discontinuation occurred in 5.9% and 5.2% for dabigatran and enoxaparin



Summary

Efficacy: Extended prophylaxis with dabigatran was as effective as prophylaxis with enoxaparin in reducing the risk of VTE after total hip arthroplasty, and superior to enoxaparin in reducing the risk of major VTE

Safety: The risk of bleeding and safety profiles were similar in both study groups

Reference

Eriksson BE, Dahl OE, Huo MH, Kurth AA, Hantel S, Hermansson K, Schnee JM, Friedman RJ; RE-NOVATE II Study Group. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II). *Thromb Haemost* 2011;105:721-729

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RE-SONATE

Twice-daily oral direct thrombin inhibitor dabigatran etexilate in the long-term prevention of recurrent symptomatic VTE (2011)

Condition

Secondary prevention of VTE after 6–16 months successful treatment for acute symptomatic DVT or PE

Objective

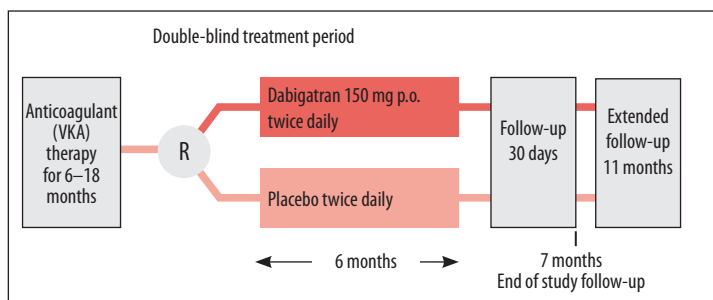
To evaluate if dabigatran is effective and safe compared to placebo in the extended treatment after symptomatic proximal DVT or PE

Trial design

Randomized, double-blind phase III study

Active treatment: dabigatran 150 mg p.o. twice daily for 6 months (n=681)

Control treatment: placebo tablets twice daily for 6 months (n=662)



Endpoints

Primary efficacy endpoint: recurrent symptomatic VTE (DVT, fatal/non-fatal PE) and related deaths at the end of the planned treatment period

Primary safety endpoint: major bleeding and clinically relevant non-major bleeding

Secondary endpoints: clinically relevant bleeding events, deaths and cardiovascular events

Trial participants

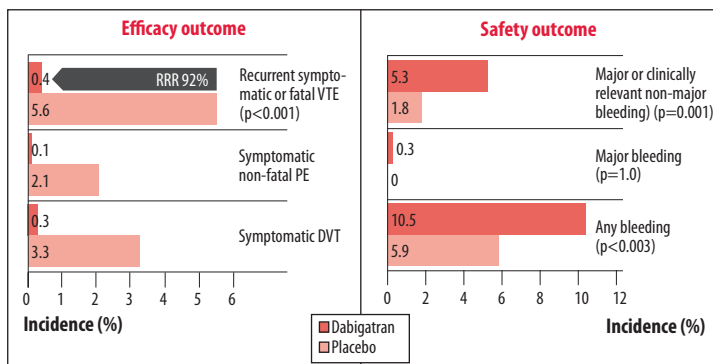
1343 patients with confirmed symptomatic PE or proximal DVT of the leg(s) who have been treated for 6–18 months with therapeutic dosages (INR 2–3) of an oral vitamin K antagonist

Results

Efficacy outcome: Recurrent VTE occurred in 3 (0.4%) of 681 patients treated with dabigatran and 37 (5.6%) of 662 patients treated with placebo (hazard ratio 0.08; $p < 0.001$). The rates of symptomatic DVT in the dabigatran and placebo group were 0.3% and 3.3%, respectively. One patient (0.1%) assigned to dabigatran compared with 14 (2.1%) patients in the placebo arm had a symptomatic non-fatal PE

Safety outcome: Clinically relevant bleeding was observed in 36 patients (5.3%) in the dabigatran group and in 12 patients (1.8%) on placebo (hazard ratio 2.9; $p = 0.001$). The rates of major bleeding were 0.3% on Dabigatran and 0% on placebo ($p = 1.0$). Any bleeding occurred in 10.5% of the patients receiving dabigatran compared to 5.9% of the patients in the placebo arm ($p < 0.003$). Cardiovascular events occurred in 3 patients (0.4%) assigned to

dabigatran and in 2 patients (0.4%) on placebo. There was no difference in acute coronary syndrome events between groups



Summary

Efficacy outcome: Extended treatment with the direct thrombin inhibitor dabigatran significantly reduced the rate of recurrent VTE

Safety outcome: On treatment with dabigatran, the frequency of any bleeding events was about two times greater than with placebo; the rate of major bleeding was low

References

- (1) Schulman S, Baanstra D, Eriksson H, Goldhaber S, Kakkar A, Kearon C, Mismetti P, Schellong S, Schnee J and the RE-SONATE Study Group Thrombosis Service. Dabigatran vs. placebo for extended maintenance therapy of venous thromboembolism. ISTH 2011; July 25. Journal of Thrombosis and Haemostasis 2011;9 (Suppl 2):22; Abstract O-MO-037
- (2) Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, Kvamme AM, Friedman J, Mismetti P, Goldhaber SZ; RE-MEDY Trial Investigators; RE-SONATE Trial Investigators. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013;368:709-718

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RISC

Research on InStability in Coronary Artery Disease (1990)

Condition

Treatment of unstable coronary artery disease

Objective

To examine if low-dose ASA (75 mg/day) for up to 1 year and/or heparin during the initial 5 days have any effect on the incidence of myocardial infarction and mortality in men after an episode of unstable coronary artery disease

Trial design

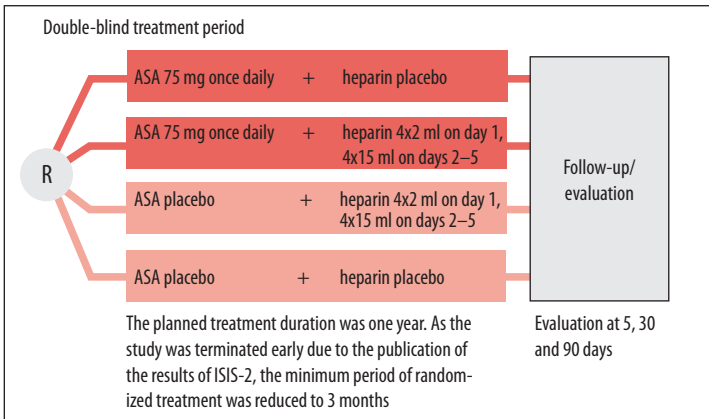
Prospective, randomized, double-blind placebo-controlled study

Active treatment: ASA 75 mg once daily up to 1 year; heparin 5000 IU/ml, injected 6-hourly (2 ml) during the first 24 hours followed by 15 ml 6-hourly for 4 days

Control treatment: oral and i.v. placebo

2x2 factorial design:

- ASA + heparin placebo (n=189)
- ASA + heparin (n=210)
- ASA placebo + heparin (n=198)
- ASA placebo + heparin placebo (n=199)



Endpoints

Primary efficacy endpoint: myocardial infarction and death

Secondary efficacy endpoint: revascularization

Safety endpoints: hemorrhagic and other adverse events

Trial participants

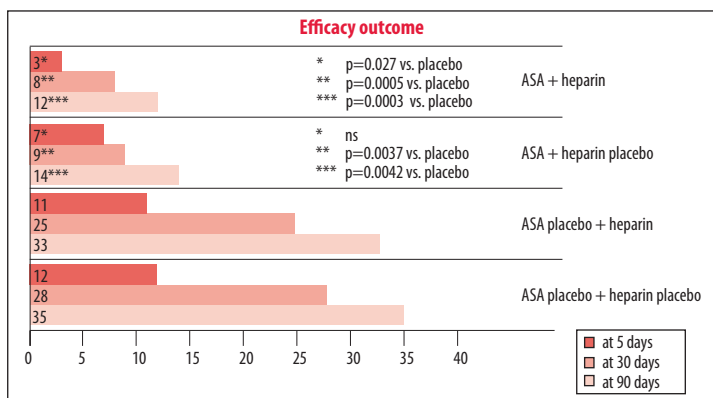
796 patients (only male, aged >70 years, mean age 58 years) with unstable coronary artery disease (defined as non-Q wave myocardial infarction or increasing angina within last 4 weeks)

Results

Efficacy outcome: At 5 days and thereafter, low-dose ASA given alone or with heparin reduced the rate of myocardial infarction and death by 57–69% compared with heparin alone and placebo treatment. The highest risk re-

duction was seen in the patients treated with ASA plus heparin. Treatment with heparin alone did not alter the event rates. In the ASA + placebo group occurred fewer cases of revascularization than in the oral placebo group: 0.8% vs. 2.8% after 1 month, 2.5% vs. 5.3% after 3 months

Safety outcome: Hemorrhages due to ASA were rare and minor, but more frequent than with placebo



Summary

Efficacy: Treatment with ASA 75 mg daily reduces the risk of myocardial infarction by 50% at 3 months after an episode of unstable coronary artery disease in men. The combination of ASA and heparin may be more effective during the initial hospital period

Safety: There was no increased risk of severe bleeding

Reference

The RISC Group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. *Lancet* 1990;326:827-830

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ROCKET AF

Rivaroxaban – Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonist for prevention of stroke and Embolism Trial in Atrial Fibrillation (2010)

Condition

Prevention of VTE in patients with AF

Objective

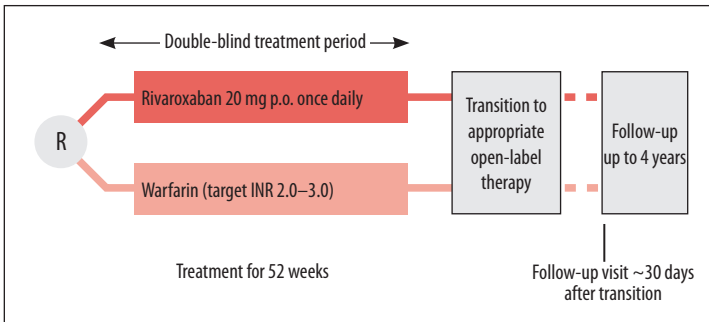
To establish the non-inferiority of rivaroxaban compared with warfarin in patients with non-valvular AF who have a history of stroke or at least 2 additional independent risk factors for future stroke (heart failure, hypertension, age ≥ 75 years, diabetes mellitus)

Trial design

Prospective, randomized, double-blind, double-dummy phase III study with parallel groups

Active treatment: rivaroxaban 20 mg p.o. once daily plus warfarin placebo (n=7131)

Control treatment: warfarin once daily titrated to a target INR of 2.0–3.0 plus rivaroxaban placebo (n=7133)



Patients

14,264 patients (mean age 73 years) with non-valvular AF documented on ≥ 2 episodes, with 55% having had a prior TIA or stroke and $\geq 90\%$ having hypertension. In addition, 87% of the patients had a CHADS₂ score of 3 or higher

Endpoints

Primary efficacy endpoint: composite of all-cause stroke and non-CNS systemic embolism

Primary safety endpoint: composite of major and clinically relevant non-major bleeding events

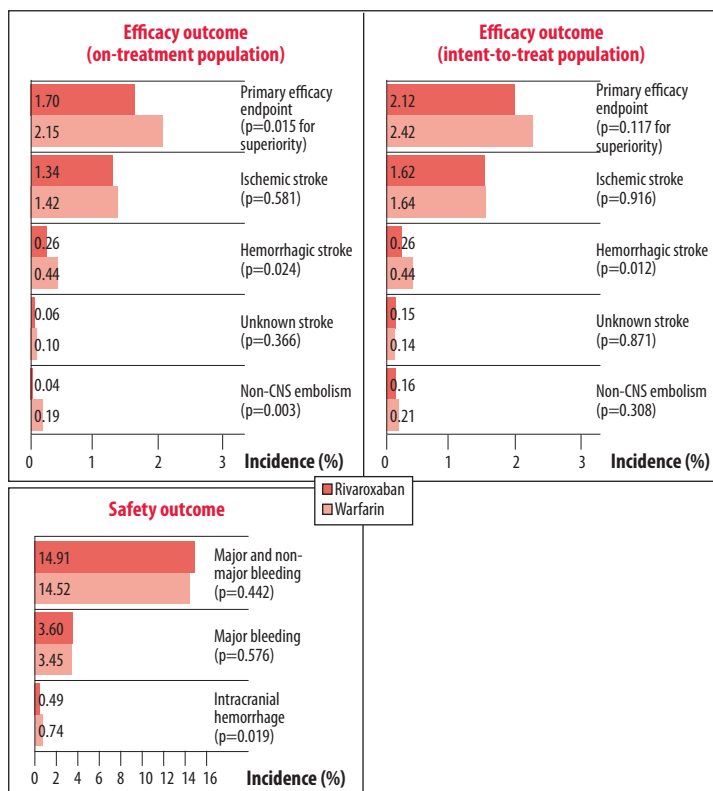
Secondary efficacy endpoints: all-cause death, vascular death, and myocardial infarction

Results

Efficacy outcome: Overall, rivaroxaban was non-inferior to warfarin in terms of the primary end point (event rate 1.71 vs. 2.16; $p < 0.001$), and superior to warfarin when investigators analyzed the risk of stroke and non-CNS embolism in patients who remained on treatment over the course of the 40-month trial (event rate 1.70 vs. 2.15; $p = 0.015$). Rivaroxaban was not superior to war-

farin in the stricter intent-to-treat analysis (event rate 2.12 vs. 2.42; $p=0.117$)

Safety outcome: On the principal safety measure of major and non-major clinically relevant bleeding events, rivaroxaban was similar compared with warfarin (14.91% vs. 14.52%, $p=0.442$). Rates of major bleeding were also comparable between rivaroxaban and warfarin (3.60% vs. 3.45%, $p=0.576$). Patients treated with rivaroxaban had fewer intracranial hemorrhages (0.49% vs. 0.74%, $p=0.019$), fewer critical organ bleeds (0.82% vs. 1.18%, $p=0.007$) and lower bleeding-related deaths (0.24% vs. 0.48%, $p=0.003$) than those on warfarin



Summary

Efficacy: Overall, rivaroxaban was non-inferior to warfarin in terms of the primary endpoint (composite of stroke and non-CNS embolism), and was superior to warfarin in patients who remained on treatment over the course of the 40-month trial. In the stricter intent-to-treat analysis, rivaroxaban was non-inferior to warfarin, but did not achieve superiority

Safety outcome: The rates of major and non-major clinically relevant bleeding were comparable in both groups, with less fatal bleeding and intracranial hemorrhage observed among patients treated with rivaroxaban

References

(1) The Executive Steering Committee, on behalf of the ROCKET AF Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial

in atrial fibrillation: rationale and design of the ROCKET AF study. Am Heart J 2010;159:340-347.e1

(2) Mahaffey KW on behalf of the ROCKET AF Study Investigators. American Heart Association Scientific Sessions 2010; Late Breaking Clinical Trials, Nov 15th 2010

(3) ClinicalTrials.gov (NCT00403767)

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RUBY-1

Study evaluating safety, tolerability and efficacy of darexaban in subjects with acute coronary syndromes (2011)

Condition

Secondary prevention of ischemic events in acute coronary syndrome (ACS)

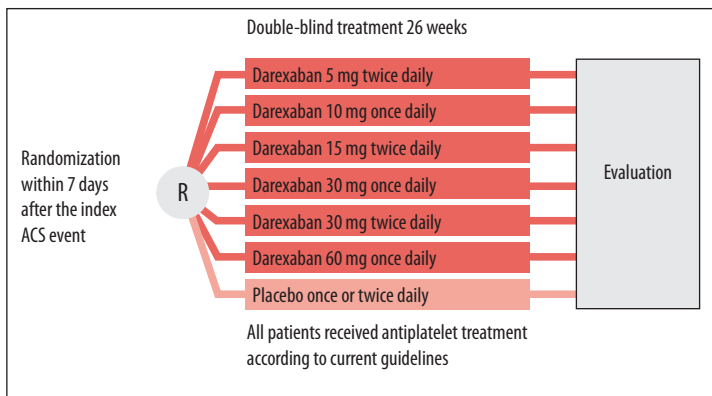
Objective

To evaluate the safety and tolerability of different doses and dose regimens of darexaban on top of standard treatment with ASA with or without clopidogrel for secondary prevention of ischemic vascular events in patients with recent ACS

Trial design

Randomized, double-blind, placebo-controlled, dose-ranging phase II study
Active treatment: six different darexaban regimens: 5 mg twice daily (n=159), 10 mg once daily (n=159), 15 mg twice daily (n=159), 30 mg once daily (n=156), 30 mg twice daily (n=153), 60 mg once daily (n=153) on top of antiplatelet treatment with ASA and/or clopidogrel, for 26 weeks

Control treatment: placebo tablets once or twice daily on top of antiplatelet treatment with ASA and/or clopidogrel (n=319)



Endpoints

Primary safety endpoint: incidence of major and clinically relevant non-major bleeding events (according to a modified ISTH definition) during the 6 months of double-blind treatment

Secondary safety endpoint: TIMI major bleeding events

Primary efficacy endpoint: composite of all-cause mortality, non-fatal myocardial infarction (MI), non-fatal stroke, and severe recurrent ischemia

Trial participants

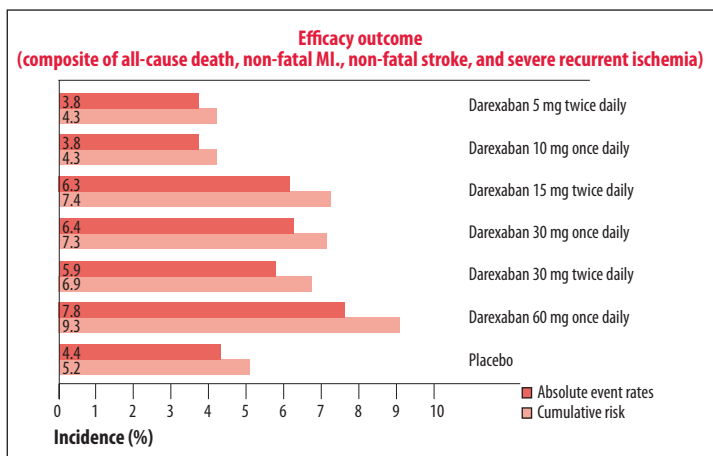
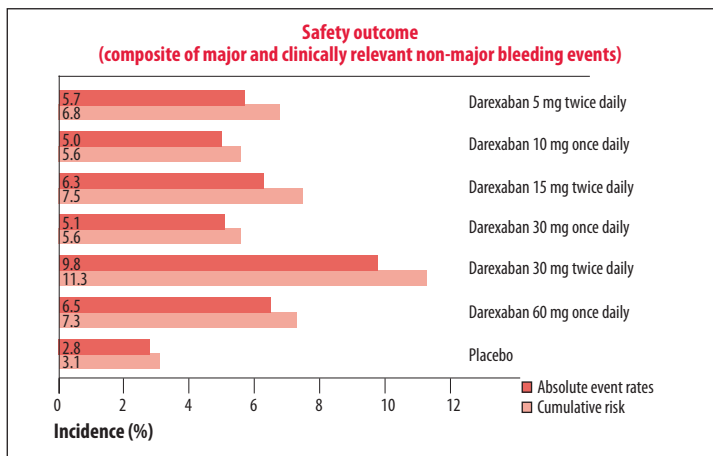
1258 patients with recent high-risk non-ST-segment or ST-segment elevation ACS

Results

Safety outcome: The primary outcome of the study (major or clinically relevant non-major bleeding events) was numerically higher in all darexaban arms than in the placebo group, with hazard ratios ranging from 1.8 to 3.8. (pooled hazard ratio 2.275; p=0.022). Using placebo as reference (with a bleeding rate of 3.1%), there was a dose-response relationship for increased

bleeding rates with increasing darexaban dose, since the cumulative incidence of bleeding was 6.2, 6.5, and 9.3% for patients receiving total daily doses of 10, 30, and 60 mg darexaban, respectively. This increase was statistically significant for the 30 mg twice daily dose ($p=0.002$). The rates of bleeding were similar for patients receiving twice daily vs. once daily dosing with darexaban (8.4 vs. 6.1%, respectively, $p=0.310$). There were no other significant drug-related safety concerns associated with darexaban

Efficacy outcome: At 6 months, there was no decrease in rates of efficacy outcome (composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, and severe recurrent ischemia) with darexaban versus placebo. The cumulative incidence of this composite efficacy outcome was numerically higher in the darexaban 30 and 60 mg daily dose arms compared with placebo, and numerically lower with the lowest dose (10 mg daily)



Summary

Safety outcome: Darexaban, when added to dual antiplatelet therapy after ACS, produces an expected, dose-related 2- to 4-fold increase in bleeding:
 – Bleeding rates were numerically higher in all darexaban arms versus placebo

– There was a dose-response relationship for increased bleeding with increasing darexaban dose, which was statistically significant for darexaban 30 mg twice daily

Darexaban was well tolerated, with no signs of liver toxicity

Efficacy outcome: There was no decrease in efficacy event rates with darexaban. However, as with most phase II dose-ranging trials of antithrombotic drugs, this study was underpowered for efficacy

Reference

Steg PG, Mehta SR, Jukema JW, Lip GY, Gibson CM, Kovar F, Kala P, Garcia-Hernandez A, Renfurm RW, Granger CB, on behalf of the RUBY-1 Investigators. RUBY-1: a randomized, double-blind, placebo-controlled trial of the safety and tolerability of the novel oral factor Xa inhibitor darexaban (YM150) following acute coronary syndrome. *Eur Heart J* 2011;32:2541-2554

Corresponding author

Prof. Philippe Gabriel Steg, INSERM U-698 'Recherche Clinique en Athérombose', Université Paris VII-Denis Diderot, Centre Hospitalier Bichat-Claude Bernard, 46 rue Henri Huchard, 75877 Paris Cedex 18, France, e-mail: gabriel.steg@bch.aphp.fr

SACRE

Study comparing oral anticoagulants with reviparin (2002)

Condition

Extended prophylaxis for VTE after total hip replacement

Objective

To evaluate the efficacy and safety of fixed-dose reviparin compared with adjusted-dose acenocoumarol for extended out-of-hospital VTE prophylaxis after elective hip surgery

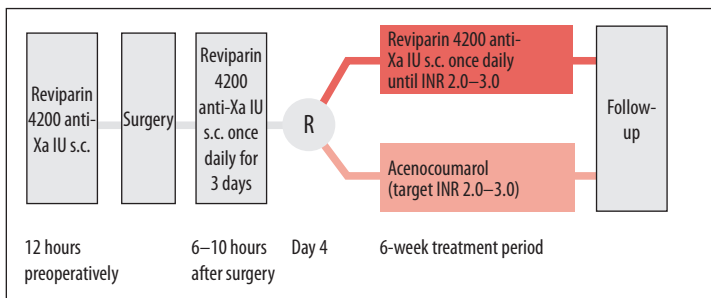
Trial design

Randomized study with parallel groups

All patients (n=1289) received reviparin, 4200 anti-Xa IU s.c. as an initial dose 12 hours preoperatively and 6–10 hours after surgery 4200 anti-Xa IU s.c. once daily for 3±1 days until randomization

Active treatment: reviparin 4200 anti-Xa IU s.c. once daily (n=644)

Control treatment: acenocoumarol (target INR 2.0–3.0) once daily for 6 weeks (n=645)



Endpoints

Primary efficacy endpoint: cumulative failure rate of symptomatic VTE, major bleeding, and death

Secondary endpoints: symptomatic VTE, bleeding complications, mortality

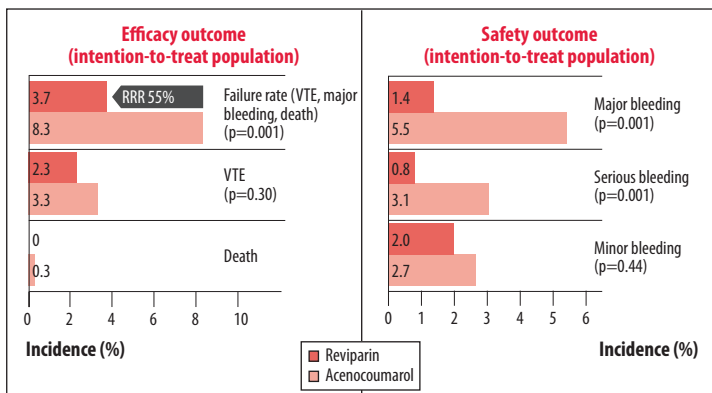
Trial participants

1289 patients aged ≥18 years, scheduled for elective total hip replacement

Results

Efficacy outcome: In the intent-to-treat population (n=1279), the cumulative failure rate was 3.7% (24 of 643 patients) in the reviparin group compared with 8.3% (53 of 636 patients) in the acenocoumarol group (relative risk reduction 55%). Symptomatic thromboembolic events occurred in 2.3% (15/643) patients vs. 3.3% (23/636) patients receiving reviparin or oral anticoagulants, respectively. 2 patients assigned to acenocoumarol died (0.3% vs. 0%)

Safety outcome: Major bleeding occurred in 1.4% (9/643) patients assigned to reviparin and in 5.5% (35/646) assigned to acenocoumarol. The incidence of clinically serious bleeding was also much less frequent in patients receiving reviparin (0.8% vs. 3.1%). 13 patients (2.0%) in the reviparin group developed minor bleeding, as compared with 17 patients (2.7%) in the acenocoumarol group



Summary

Efficacy: In patients undergoing elective hip replacement who received extended out-of-hospital prophylaxis, fixed-dose reviparin resulted in a significantly higher benefit-risk ratio as adjusted-dose acenocoumarol

Safety: The incidence of major bleeding complications was significantly lower with reviparin, as compared with acenocoumarol

Reference

Samama CM, Vray M, Barré J, Fiessinger JN, Rosencher N, Lecompte T, Potron G, Basile J, Hull R, Desmichels D, for the SACRE Study Investigators. Extended venous thromboembolism prophylaxis after total hip replacement: a comparison of low-molecular-weight heparin with oral anticoagulant. *Arch Intern Med* 2002;162:2191-2196

Corresponding author

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SEPIA-ACS1 TIMI 42

Study Program to Evaluate the Prevention of Ischemia with direct Anti-Xa inhibition in Acute Coronary Syndromes 1 (2009)

Condition

Prophylaxis for ischemic events in patients with non-ST-elevation acute coronary syndromes

Objective

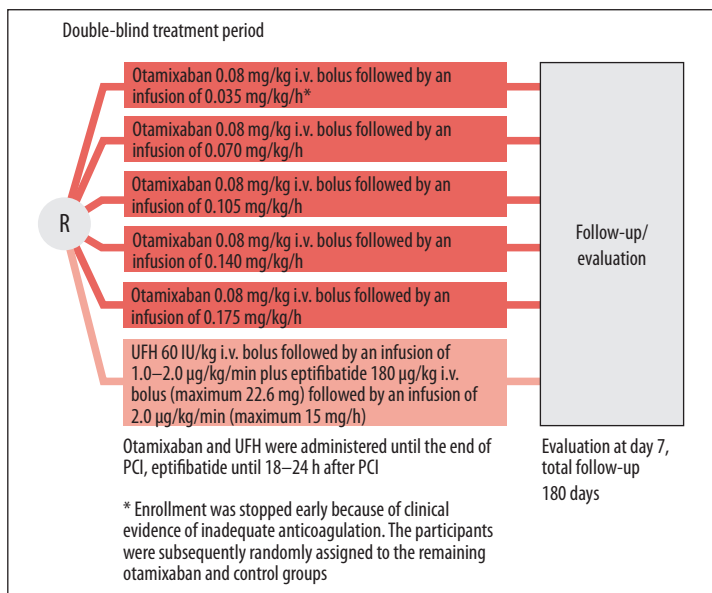
To assess the efficacy and safety of different doses of otamixaban compared with UFH plus eptifibatide in patients with high-risk non-ST-elevation acute coronary syndromes and to identify the optimum dose range for further assessment

Trial design

Randomized, double-blind, triple-dummy, dose-ranging phase II study

Active treatment: otamixaban 0.08 mg/kg i.v. bolus followed by an infusion of 0.035 mg/kg/h (n=125), 0.070 mg/kg/h (n=676), 0.105 mg/kg/h (n=662), 0.140 mg/kg/h (n=658), or 0.175 mg/kg/h; matching placebo (n=671)

Control treatment: UFH 60 IU/kg i.v. bolus followed by an infusion of 1.0–2.0 µg/kg/min plus eptifibatide 180 µg/kg i.v. bolus (maximum 22.6 mg) followed by an infusion of 2.0 µg/kg/min (maximum 15 mg/h); matching placebo (n=449)



Endpoints

Primary efficacy endpoint: composite of all-cause death, new myocardial infarction, severe recurrent ischemia requiring urgent revascularization and in-hospital bailout use of glycoprotein GPIIb/IIIa inhibitor up to 7 days

Secondary efficacy endpoints: individual components of the composite endpoint, composite endpoint up to 180 days

Primary safety endpoint: composite of TIMI major or minor bleeding up to 7 days

Secondary safety endpoints: TIMI major bleeding, TIMI minor bleeding, stroke

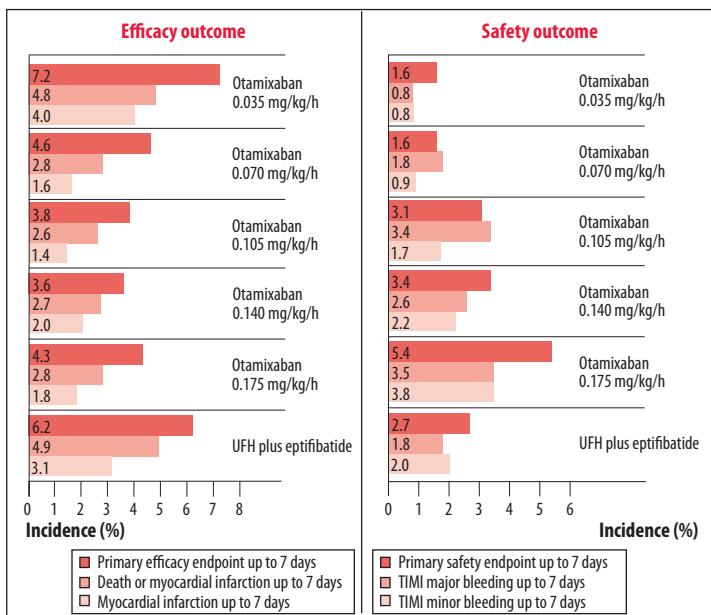
Trial participants

3241 patients aged ≥ 18 years with non-ST-elevation acute coronary syndromes at rest of at least 10 minutes duration within 24 hours of randomization who were planned to be treated with an invasive strategy (PCI)

Results

Efficacy outcome: In the 5 otamixaban groups, the primary efficacy endpoint occurred in 7.2% (9 of 125 patients) with 0.035 mg/kg/h, 4.6% (31/676) with 0.070 mg/kg/h, 3.8% (25/662) with 0.105 mg/kg/h, 3.6% (24/658) with 0.140 mg/kg/h, and 4.3% (29/671) with 0.175 mg/kg/h. In the control group, the rate was 6.2% (28/449). There was no statistically significant trend in the rate of the primary efficacy endpoint across the otamixaban groups ($p=0.34$). At intermediate doses (0.105 and 0.140 mg/kg/h), treatment with otamixaban resulted in about 40% reductions vs. the control group. These differences were driven by reductions of 45% or more in death or myocardial infarction compared to UFH plus eptifibatide (2.6% and 2.7% vs. 4.9%)

Safety outcome: The rates of the primary safety endpoint in the 5 otamixaban groups showed a significant dose response ($p=0.0001$ for trend): TIMI major and minor bleedings occurred in 1.6% (2/122) with 0.035 mg/kg/h, 1.6% (11/669) with 0.070 mg/kg/h, 3.1% (20/651) with 0.105 mg/kg/h, 3.4% (22/651) with 0.140 mg/kg/h, and 5.4% (36/664) with 0.175 mg/kg/h. In the control group, the rate was 2.7% (12/448). The difference between the highest otamixaban dose (5.4%) and the controls (2.7%) was statistically significant ($p=0.0273$)



Summary

Efficacy: Otamixaban infusions of 0.100–0.140 mg/kg/h were associated with a 40% reduction in death or ischemic complications compared with UFH plus eptifibatide

Safety: Otamixaban infusions of 0.100–0.140 mg/kg/h had a safety profile similar to UFH plus eptifibatide. In summary, otamixaban 0.100–0.140 mg/kg/h seems to be the most reasonable choice for future studies

Reference

Sabatine MS, Antman EM, Widimsky P, Ebrahim IO, Kiss RG, Saaiman A, Polasek R, Contant CF, McCabe CH, Braunwald E. Otamixaban for the treatment of patients with non-ST-elevation acute coronary syndromes (SEPIA-ACS1 TIMI 42): a randomised, double-blind, active-controlled, phase 2 trial. *Lancet* 2009;374:787-795

Corresponding author

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SPAF

Stroke Prevention in Atrial Fibrillation (1991)

Condition

Prevention of stroke and systemic embolism in patients with AF

Objective

To investigate the efficacy and safety of warfarin and ASA in the prevention of stroke and systemic embolism

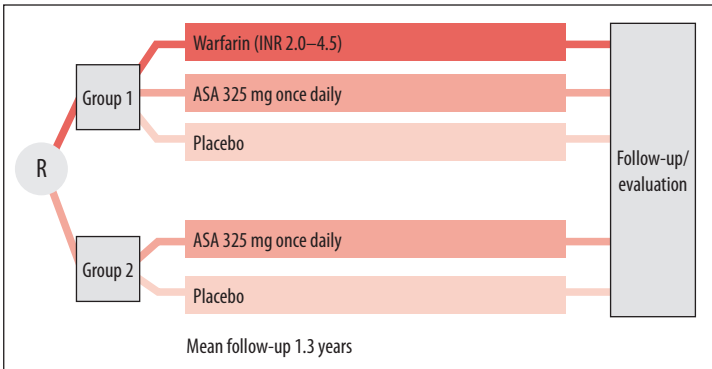
Trial design

Randomized, placebo-controlled trial

Active treatment:

- Group 1 (627 patients eligible for oral anticoagulation): warfarin (INR 2.0–4.5) (n=210) or ASA (325 mg once daily)
- Group 2 (703 patients ineligible for oral anticoagulation): ASA (n=346) or placebo (n=357)

Control treatment: placebo (group 1: n=211, group 2: n=357)



Endpoints

Primary efficacy endpoint: ischemic stroke or systemic embolism

Secondary efficacy endpoints: death, myocardial infarction, TIA, or unstable angina pectoris requiring hospital admission

Primary safety endpoint: major hemorrhagic events

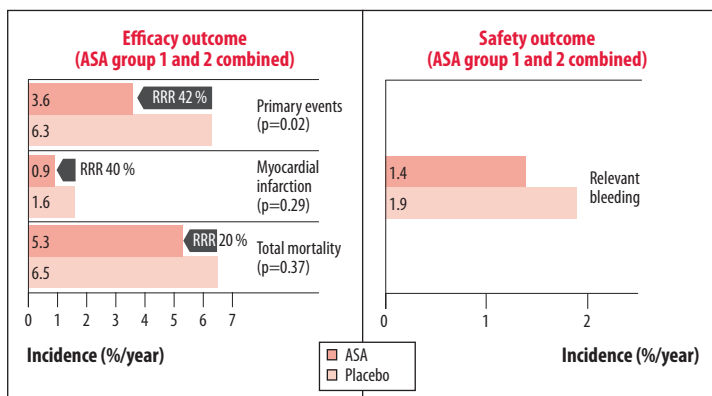
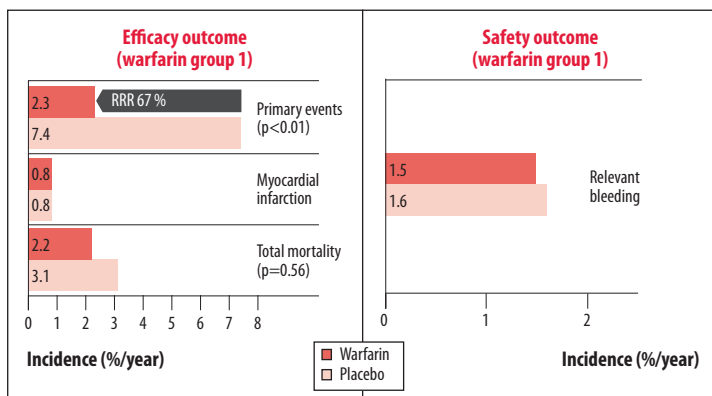
Trial participants

1330 inpatients and outpatients with constant or intermittent AF

Results

Primary outcome: Mean follow-up was 1.3 years. In group 1, a primary event occurred in 6 of 210 patients (2.3% per year) receiving warfarin and in 18 of 211 (7.4% per year) placebo patients (relative risk reduction 67%). In group 2, 26 of 552 patients assigned to ASA (3.6% per year) and 46 of 568 patients assigned to placebo (6.3% per year) experienced a primary event (relative risk reduction 42%)

Safety outcome: In group 1, the risk of relevant bleeding was 1.5% (n=4) in patients given warfarin compared to 1.6% (n=4) in placebo patients. In group 2, 10 patients assigned to ASA (1.4%) experienced a relevant bleeding complication compared to 14 patients (1.9%) assigned to placebo



Summary

Efficacy: Warfarin and ASA are both effective in reducing ischemic stroke and systemic embolism in patients with AF. Too few events occurred in warfarin-eligible patients to directly assess the relative benefit of ASA compared with warfarin

Safety: There were no significant differences in bleeding events between groups

Reference

Cohen BA, Feldman G, Flaker GC, Hart RG, McAnulty JH, McBride R. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation* 1991;84:527-539

Corresponding author

Ruth McBride, Statistics and Epidemiology Research Corporation, 1107 NE 45th Street, Suite 520, Seattle, WA 98105

SPAF II

Stroke Prevention in Atrial Fibrillation II study (1994)

Condition

Prevention of stroke and systemic embolism in patients with AF

Objective

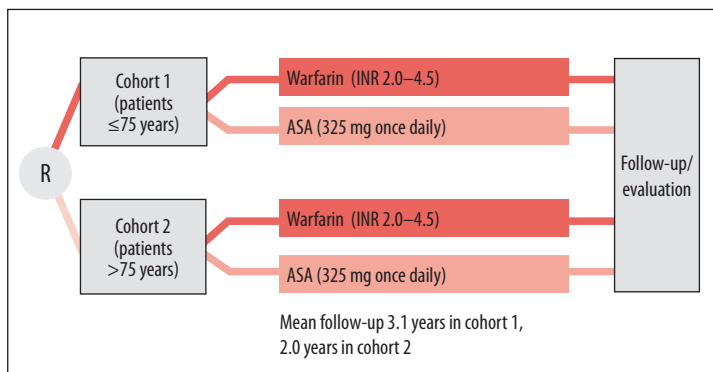
To compare the efficacy and safety of warfarin with ASA in the prevention of stroke and systemic embolism in two age-cohorts

Trial design

Two parallel randomized controlled trials

Active treatment: warfarin (INR 2.0–4.5)

Control treatment: ASA (325 mg once daily)



Endpoints

Primary efficacy endpoint: ischemic stroke or systemic embolism

Secondary efficacy endpoints: TIA, myocardial infarction, strokes with residual deficits, death

Primary safety endpoints: major hemorrhagic events, intracranial hemorrhage

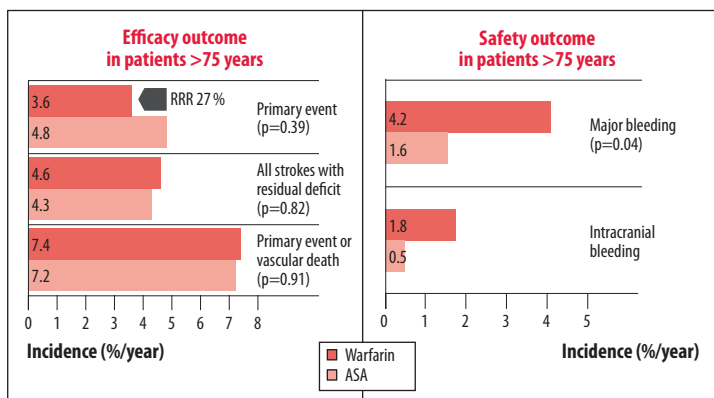
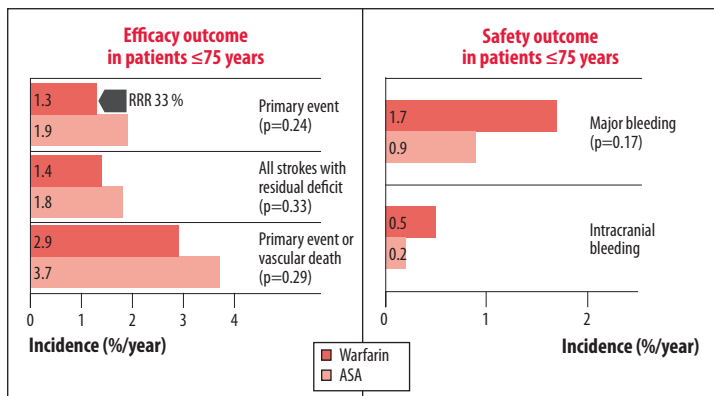
Trial participants

715 patients with AF aged 75 years or younger and 385 patients older than 75 years

Results

Efficacy outcome: In the younger patients, primary events occurred in 14 of 358 patients (1.3% per year) given warfarin and 21 of 357 patients (1.9% per year) given ASA (relative risk reduction 33%). In the older patient cohort, primary events were observed in 14 of 197 patients (3.6% per year) receiving warfarin and in 18 of 188 patients (4.8% per year) receiving ASA (relative risk reduction 27%)

Safety outcome: In the younger patient group rates of major hemorrhage were 1.7% per year with warfarin and 0.9% per year with ASA. For older patients, the rates were 4.2% (warfarin) and 1.6% per year (ASA). In older patients assigned to warfarin, the annual rate of intracranial hemorrhage was 1.8% (71% fatal, 29% with residual deficit) compared to 0.5% in younger patients assigned to warfarin



Summary

Efficacy: Warfarin may be more effective than ASA in reducing ischemic stroke and systemic embolism in younger and older patients with AF. In older patients, the rate of stroke was substantial, irrespective of which agent was given

Safety: The risk of major bleeding and intracranial bleeding among anticoagulated patients ≤75 years was lower than in the older cohort (p=0.008, and p=0.05, respectively)

Reference

Halperin JL, Hart RG, Kronmal RA, McBride R, Pearce LA, Sherman DG. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet* 1994;343:687-691

Corresponding author

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SPAF III

Stroke Prevention in Atrial Fibrillation III study (1996)

Condition

Prevention of stroke and systemic embolism in high-risk patients with AF

Objective

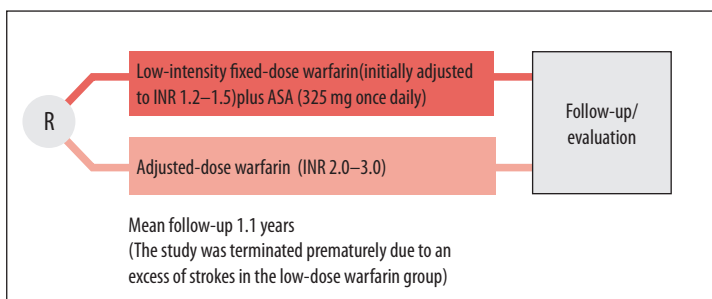
To compare the efficacy and safety of a low-intensity fixed-dose warfarin/ASA combination with adjusted-dose warfarin in the prevention of stroke and systemic embolism

Trial design

Randomized, controlled, open-label study

Active treatment: low-intensity fixed-dose warfarin (initially adjusted to INR 1.2–1.5) combined with ASA (325 mg once daily) (n=521)

Control treatment: adjusted-dose warfarin (INR 2.0–3.0) (n=523)



Endpoints

Primary efficacy endpoint: ischemic stroke or systemic embolism

Secondary efficacy endpoints: TIA, disabling/fatal strokes, myocardial infarction, death

Primary safety endpoints: major hemorrhage, intracranial hemorrhage

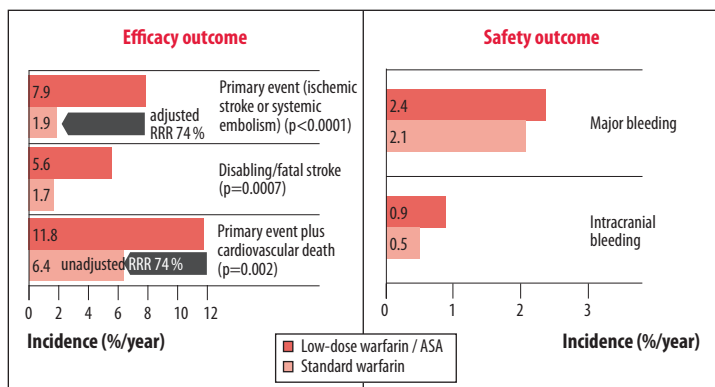
Trial participants

1044 patients (mean age 72 years) with AF and at least one thromboembolic risk factor

Results

Efficacy outcome: At the time of an interim analysis after a mean follow-up of 1.1 years a primary event had occurred in 44 of 521 patients (7.9% per year) receiving low-dose warfarin plus ASA compared to 11 of 523 patients (1.9% per year) receiving adjusted standard-dose warfarin (absolute risk reduction 6.0% per year and relative risk reduction 74% by adjusted-dose warfarin). The study was stopped due to the excess of strokes in the low-dose warfarin group

Safety outcome: Major hemorrhage occurred in 13 of 521 patients receiving low-dose warfarin plus ASA (2.4% per year) and in 12 of 523 patients receiving adjusted-dose warfarin (2.1% per year). Also the rates of intracranial bleeding were similar in both treatment groups



Summary

Efficacy: In high-risk AF-patients, low-intensity, fixed-dose warfarin plus ASA was inferior to adjusted standard-dose warfarin in reducing

- ischemic stroke and systemic embolism
- disabling stroke
- ischemic stroke, systemic embolism and vascular death

Safety: The rates of major and intracranial bleeding were similar in both groups

Reference

Blackshear L, Halperin JL, Hart RG, Laupacis A, McAnulty JH, McBride R. 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;348:633-638

Corresponding author

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SPINAF

Stroke Prevention In Non-rheumatic Atrial Fibrillation (1992)

Condition

Prevention of stroke in patients with non-rheumatic AF

Objective

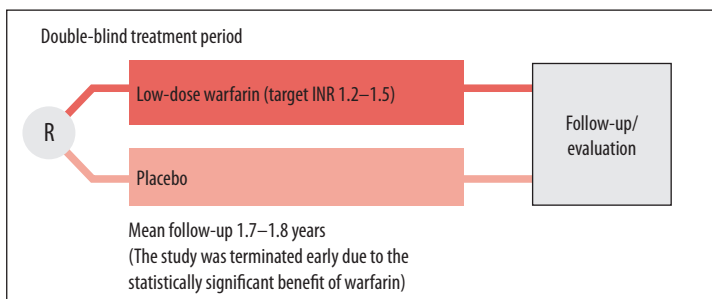
To investigate whether low-intensity anticoagulation with warfarin would reduce the risk of stroke associated with non-rheumatic AF

Trial design

Randomized, double-blind, placebo-controlled phase III trial

Active treatment: low-dose warfarin (INR 1.2–1.5) (n=260 with no history of infarction; n=21 with previous stroke)

Control treatment: placebo (n=265 with no history of infarction; n=25 with previous stroke)



Endpoints

Primary endpoint: cerebral infarction

Secondary endpoints: cerebral hemorrhage and death

Trial participants

571 men (mean age 67 years) with chronic non-rheumatic AF, divided in 2 groups:

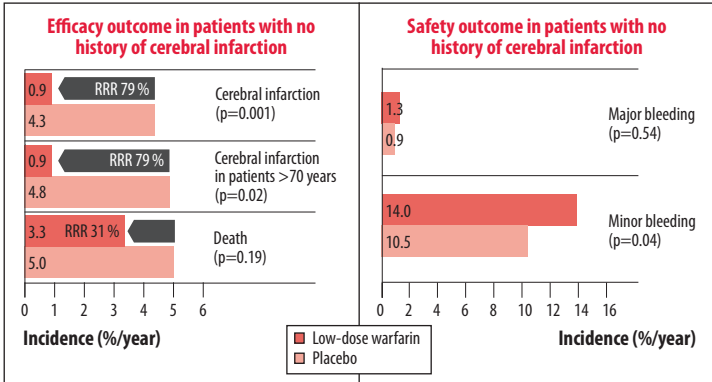
- 525 patients with no history of stroke
- 46 patients with previously cerebral infarction

Results

Efficacy outcome: In patients with no history of stroke receiving warfarin, cerebral infarction occurred in 0.9% per year compared to 4.3% per year for the placebo group (relative risk reduction with warfarin 79%). A special benefit of warfarin was observed in patients aged >70 years (n=288). In this subgroup, the annual event rate was 0.9% with warfarin vs. 4.8% with placebo (relative risk reduction with warfarin 79%). Cerebral infarction was more common among patients with a history of stroke: 6.1% per year in the warfarin group compared to 9.3% per year in the placebo group (relative risk reduction with warfarin 40%). The only non-fatal cerebral hemorrhage occurred in a patient assigned to warfarin. Of the 525 patients without a previous cerebral infarction, 15 in the warfarin group and 22 in the placebo group died (3.3% vs. 5.0% per year, relative risk reduction with warfarin 31%)

Safety outcome: In patients with no history of cerebral infarction, major bleeding events were slightly more common in the warfarin group (1.3%

vs. 0.9% per year). The incidence of minor hemorrhages was 14.0% per year with warfarin and 10.5% per year with placebo



Summary

Efficacy: Low-intensity anticoagulation with warfarin reduces the incidence of cerebral infarction among patients with AF. This benefit extended to patients >70 years of age

Safety: With warfarin, there was no excess risk of major bleeding. Both major and minor hemorrhages were slightly more common in the warfarin group

Reference

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;327:1406-1412

Corresponding author

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SPORTIF III

Stroke Prevention using an **ORaI** Thrombin Inhibitor in atrial **Fibrillation III** (2003)

Condition

Stroke prevention in non-valvular AF

Objective

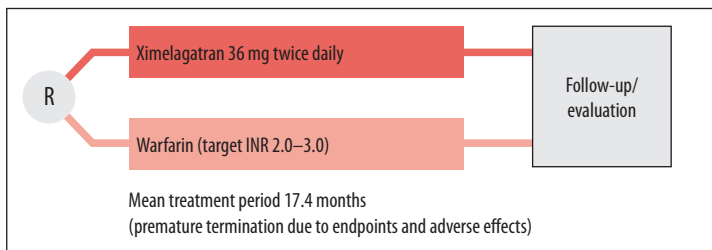
To establish whether ximelagatran is non-inferior to warfarin in the prevention of stroke and systemic embolism in AF

Trial design

Randomized, open parallel group phase III study; non-inferiority trial; the primary analysis was only by intent to treat

Active treatment: ximelagatran 36 mg twice daily (n=1704)

Control treatment: warfarin (INR 2.0–3.0) (n=1703)



Endpoints

Primary efficacy endpoint: all strokes (ischemic or hemorrhagic) and systemic embolic events

Secondary efficacy endpoints: all-cause death, cardiovascular death, fatal stroke, thromboembolic event; thromboembolic event, ischemic stroke or systemic embolism; ischemic stroke, myocardial infarction (fatal and non-fatal), hemorrhagic stroke

Primary safety endpoint: composite incidence of major and minor bleeding

Secondary safety endpoints: major bleeding, minor bleeding, adverse events

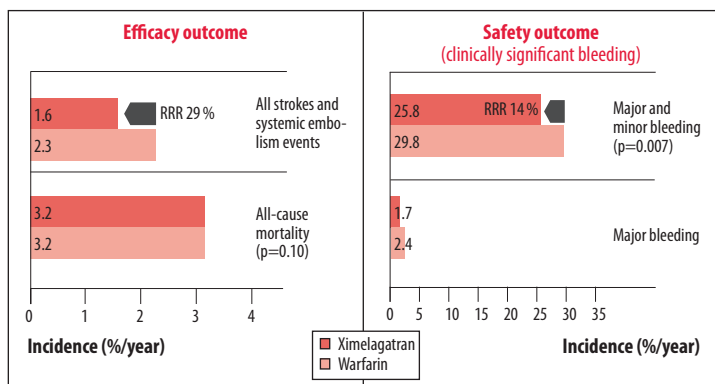
Trial participants

3407 patients (mean age 70 years) with non-valvular AF and one or more stroke risk factors

Results

Efficacy outcome: In the intent-to-treat population, primary events occurred in 40 of 1704 patients (1.6% per year) in the ximelagatran group and in 56 of 1703 patients (2.3% per year) in the warfarin group (absolute risk reduction 0.7%, relative risk reduction 29%). Rates of disabling or fatal stroke, mortality, and major bleeding were similar between groups. All-cause mortality was 3.2% per year in both groups

Safety outcome: The incidence of combined minor and major bleeding was 25.8% per year with ximelagatran compared to 29.8% with warfarin (relative risk reduction 14%). Adverse events occurred in 8% of the ximelagatran patients and in 4% of the warfarin patients. This difference was due to elevations of liver enzyme levels occurring more commonly with ximelagatran



Summary

Efficacy: In high-risk patients with atrial fibrillation, fixed-dose oral ximelagatran was at least as effective as well-controlled warfarin for prevention of stroke and systemic embolic events

Safety: Ximelagatran was associated with more adverse events than warfarin, especially liver enzyme elevations. The study was prematurely terminated due to efficacy and safety endpoints

Reference

Olsson SB for the SPORTIV III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet* 2003;362:1691-1698

Corresponding author

Prof. S. Bertil Olsson, Department of Cardiology, University Hospital, Lund SE-221 85, Sweden, e-mail: bertil.olsson@kard.lu.se

SPORTIF V

Stroke Prevention using an **ORal Thrombin Inhibitor** in atrial **Fibrillation V** (2005)

Condition

Prevention of VTE in non-valvular AF

Objective

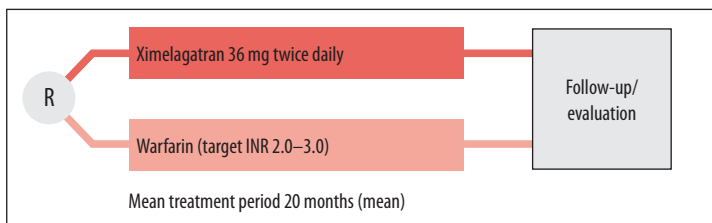
To compare the efficacy of ximelagatran with warfarin for the prevention of stroke and systemic embolism

Trial design

Randomized, double-blind phase III study, non-inferiority design

Active treatment: ximelagatran 36 mg twice daily (n=1960)

Control treatment: warfarin (INR 2.0–3.0) (n=1962)



Endpoints

Primary endpoint: all strokes (ischemic or hemorrhagic) and systemic embolic events

Secondary endpoints: composite of stroke, systemic embolic events, death, myocardial infarction; composite of ischemic stroke, TIA, systemic embolic events; major bleeding; major and minor bleeding; adverse events

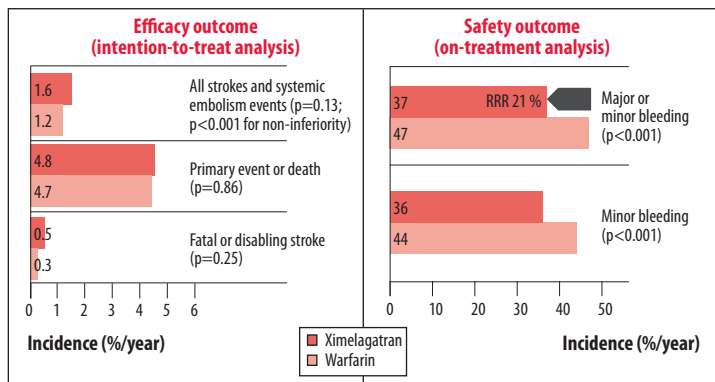
Trial participants

3922 patients with non-valvular AF and additional stroke risk factors

Results

Efficacy outcome: In the intent-to-treat population, primary events occurred in 51 of 1960 patients (1.6%) in the ximelagatran group and in 37 of 1962 patients (1.2%) in the warfarin group (absolute difference 0.45%; $p < 0.001$ for the predefined non-inferiority hypothesis). The primary event or death occurred in 153 patients given ximelagatran (4.8%) and 151 patients given warfarin (4.7%)

Safety outcome: In the on-treatment population, major and minor bleeding occurred in 737 patients (37%) with ximelagatran compared to 903 patients (47%) with warfarin (relative risk reduction 21%). Almost all events were minor bleedings. There was no significant difference in major bleedings. Elevations of serum ALT levels above 3x ULN were observed in 6% of the patients treated with ximelagatran compared to 0.8% of the patients receiving warfarin



Summary

Efficacy: In high-risk patients with atrial fibrillation, fixed-dose oral ximelagatran was non-inferior to warfarin

- in the prevention of stroke and SEE
- in the prevention of stroke, SEE and death

Safety: Compared to warfarin ximelagatran was associated with a

- lower total bleeding rate
- lower minor bleeding rate
- comparable rate of major bleeding
- higher incidence of liver enzyme elevations requiring further consideration

Reference

Albers GW, Diener HC, Frison L, Grind M, Nevinson M, Partridge S, Halperin JL, Horrow J, Olsson SB, Petersen P, Vahanian A for the SPORTIV V investigators. Ximelagatran vs warfarin for stroke prevention in patients with non-valvular atrial fibrillation: a randomized trial. *J Am Med Ass* 2005;293:690-698

Corresponding author

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STARS E-III

Studying Thrombosis After Replacement Surgery E-III (2010)

Condition

Prophylaxis for VTE after total knee arthroplasty

Objective

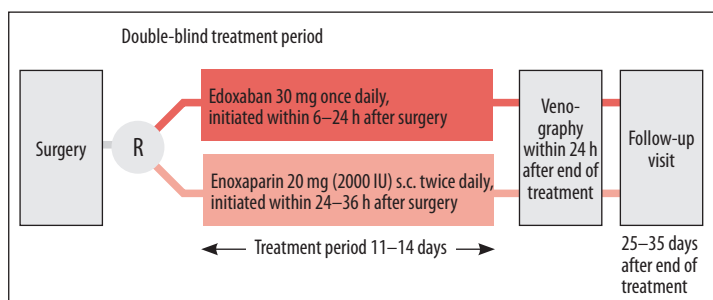
To evaluate the efficacy and safety of edoxaban compared with enoxaparin in Japanese patients undergoing elective total knee replacement

Trial design

Randomized, double-blind, double dummy phase III trial

Active treatment: edoxaban 30 mg once daily, initiated within 6–24 hours after surgery; enoxaparin placebo (n=360)

Control treatment: enoxaparin 20 mg (2000 IU) s.c. twice daily, initiated within 24–36 hours after surgery; edoxaban placebo (n=356)



Endpoints

Primary efficacy endpoint: composite of symptomatic PE, symptomatic and asymptomatic DVT

Primary safety endpoints: composite of major bleeding and clinically relevant minor bleeding

Secondary safety endpoints: adverse events

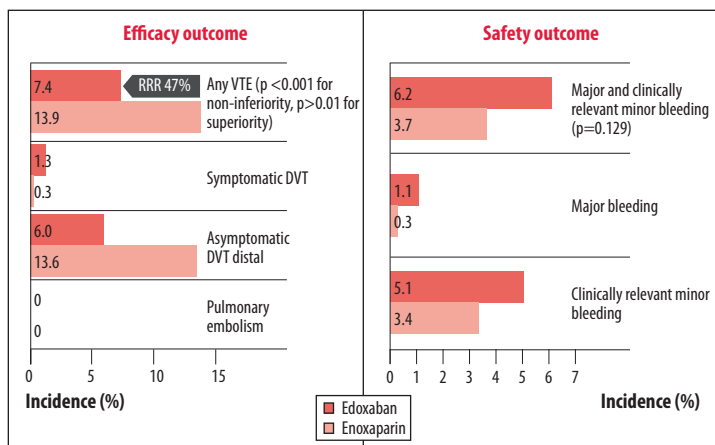
Trial participants

716 patients (20–84 years, mean age 72 years) undergoing elective unilateral total knee arthroplasty

Results

Efficacy outcome: There were no PE events observed in either treatment group. Symptomatic and asymptomatic DVT occurred in 22 of 299 (7.4%) of patients receiving edoxaban compared with 41 of 295 (13.9%) patients receiving enoxaparin (relative risk reduction 47%). No patient died and there were no cases of intracranial hemorrhage in either treatment group

Safety outcome: The incidences of major and clinically relevant minor bleeding were 6.2% with edoxaban vs. 3.7% with enoxaparin. The rate of liver function test abnormalities with edoxaban was lower than with enoxaparin (ALT or AST $\geq 3 \times$ ULN in 1.4% with edoxaban and 9.5% with enoxaparin)



Summary

Efficacy: Edoxaban was superior to enoxaparin in preventing VTE in patients undergoing total hip arthroplasty

Safety: Incidence of major and clinically relevant minor bleeding was similar with edoxaban and enoxaparin

References

- (1) Fuji T, Wang CJ, Fujita S, Tachibana S, Kawai Y, Koretsune Y, Yamashita T, Nakamura M. Edoxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty: the STARS E-III Trial. Oral presentation at the International Congress on Thrombosis 2010 (ICT), 6–9 July 2010, Milan, Italy
- (2) ClinicalTrials.gov (NCT01181102)

Corresponding author

Takeshi Fuji, MD, Department of Orthopedic Surgery, Osaka Koseinenkin Hospital, Osaka, Japan, e-mail: fuji-th@umin.ac.jp

STARS J-V

Studying Thrombosis After Replacement Surgery J-V (2010)

Condition

Prophylaxis for VTE after total hip arthroplasty

Objective

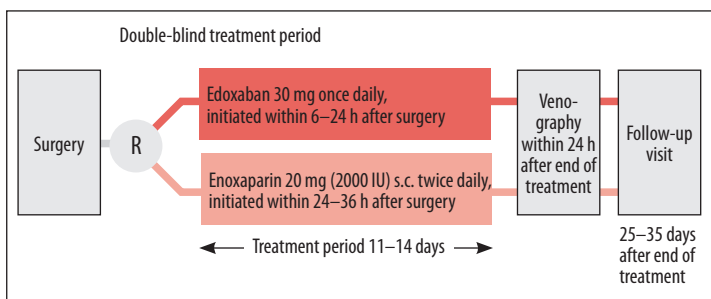
To evaluate the efficacy and safety of edoxaban compared with enoxaparin in Japanese patients undergoing elective total hip replacement

Trial design

Randomized, double-blind, double dummy phase III trial

Active treatment: edoxaban 30 mg once daily, initiated within 6–24 hours after surgery; enoxaparin placebo (n=303)

Control treatment: enoxaparin 20 mg (2000 IU) s.c. twice daily, initiated within 24–36 hours after surgery; edoxaban placebo (n=301)



Endpoints

Primary efficacy endpoint: composite of symptomatic PE, symptomatic and asymptomatic DVT

Primary safety endpoints: composite of major bleeding and clinically relevant minor bleeding

Secondary safety endpoints: adverse events

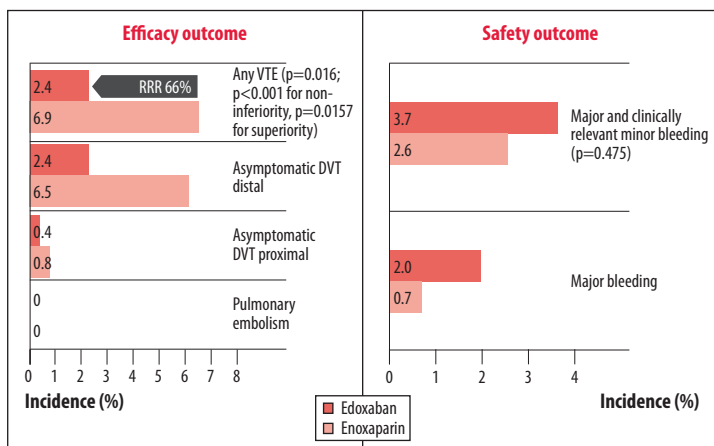
Trial participants

610 patients (20–84 years, mean age 62.8 years) undergoing elective unilateral total hip arthroplasty

Results

Efficacy outcome: The primary efficacy outcome occurred in 6 of 255 (2.4%) patients receiving edoxaban and 17 of 248 (6.9%) patients receiving enoxaparin (relative risk reduction=65.7%). The thromboembolic events were all asymptomatic DVT. No symptomatic DVT or PE was observed in both treatment groups. There were no cases of intracranial hemorrhage or death in either treatment group

Safety outcome: The incidence of major and clinically relevant minor bleeding events was 2.6% (8/303) vs. 3.7% (11/301) in the edoxaban and enoxaparin groups, respectively. Major bleeding occurred in 0.7% of the edoxaban group and 2.0% of the enoxaparin group. Elevations $\geq 3x$ ULN of serum aminotransferase levels occurred in 2.6% of patients taking edoxaban compared with 10% of those taking enoxaparin



Summary

Efficacy: Edoxaban was superior to enoxaparin in preventing VTE following total hip arthroplasty

Safety: Incidence of major and clinically relevant minor bleeding was similar with edoxaban and enoxaparin

References

- (1) Fuji T, Fujita S, Tachibana S, Kawai Y, Koretsune Y, Yamashita T, Nakamura M. et al. Efficacy and safety of edoxaban versus enoxaparin for the prevention of venous thromboembolism following total hip arthroplasty: STARS J-V trial. Poster presentation at the 52nd Annual Meeting of the American Society of Hematology, December 4–7 2010, Orlando, Florida
- (2) ClinicalTrials.gov (NCT01181167)

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SVT

Superficial vein thrombosis (SVT) treated with rivaroxaban versus fondaparinux (2013, ongoing)

Condition

Treatment of superficial vein thrombosis (SVT)

Objective

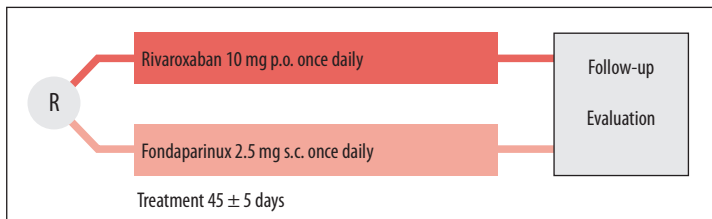
To evaluate the efficacy and safety of rivaroxaban versus fondaparinux in the treatment of SVT

Trial design

Randomized, open-label phase III study

Active treatment: rivaroxaban 10 mg p.o. once daily for 45 (\pm 5) days

Control treatment: fondaparinux 2.5 mg s.c. once daily for 45 (\pm 5) days



Endpoints

Primary efficacy endpoint: major bleeding and death from any cause after 90 (\pm 10) days

Secondary outcome measures: major bleeding, death from any cause, major VTE, surgery for SVT, clinically relevant non-major, minor and any bleeding after 90 (\pm 10) days

Trial participants

~506 patients \geq 18 years with acute symptomatic supragenaal superficial vein thrombosis of the leg and at least one major risk factor for VTE (e.g. age > 65 years, history of DVT/PE/SVT, SVT of a non-varicose vein)

References

ClinicalTrials.gov (NCT01499953)

SYNERGY

Superior Yield of the New strategy of Enoxaparin, Revascularization and GIIYcprotein IIb/IIIa inhibitors (2005)

Condition

Prophylaxis for ischemic events in high-risk patients with non-ST-elevation acute coronary syndromes

Objective

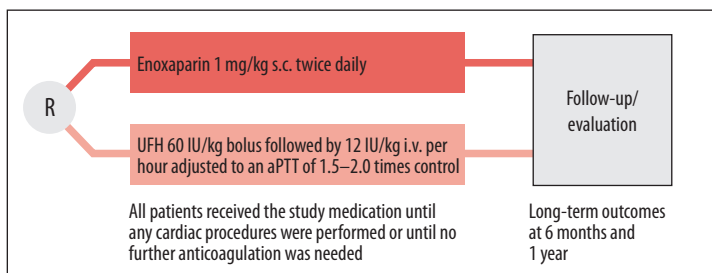
To compare the long-term effects of enoxaparin and UFH in patients with high-risk non-ST-elevation acute coronary syndromes and to evaluate the continued risk in this cohort throughout 6-months and 1-year follow-up after completion of the overall trial

Trial design

Randomized, open study with parallel groups

Active treatment: enoxaparin 1 mg/kg s.c. twice daily (n=4993)

Control treatment: UFH 60 IU/kg i.v. bolus (maximum 5000 IU) followed by an infusion of 12 IU/kg/h with a target aPTT of 1.5–2.0 times the institutional ULN or 50–70 seconds (n=4985)



Endpoints

Efficacy endpoints at 6 months: composite of death or non-fatal myocardial infarction; need for rehospitalization, rate of revascularization procedures

Efficacy endpoint at 1 year: all-cause death

Trial participants

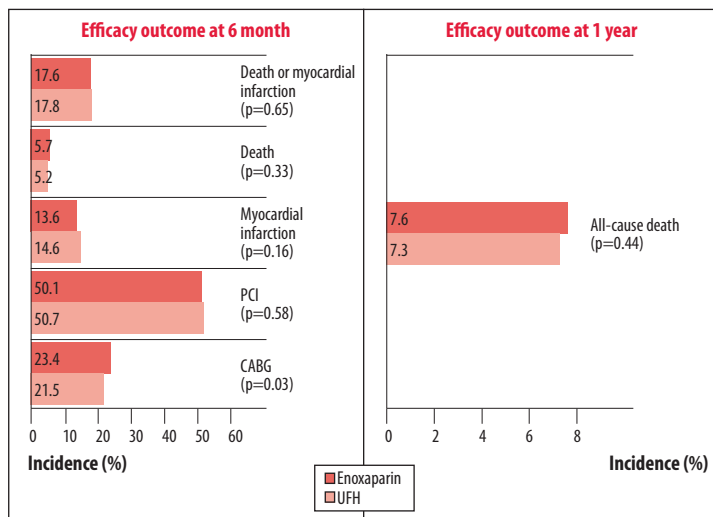
9978 patients (mean age 68 years) with non-ST-elevation acute coronary syndromes at rest of at least 10 minutes duration within 24 hours of randomization and with two of the following high-risk features: age ≥ 60 years, ST-segment changes, abnormal cardiac markers. Of these patients followed up 30 days in the first part of the SYNERGY trial, 6-month and 1-year follow-up data were available for 9957 and 9608 patients, respectively

Results

Efficacy outcome at 6 months: The composite endpoint of death or myocardial infarction occurred in 872 of 4993 patients (17.6%) receiving enoxaparin and in 884 of 4985 patients (17.8%) receiving UFH. 282 (5.7%) patients in the enoxaparin group and 259 (5.2%) died within 180 days. Rehospitalization occurred in 858 patients assigned to enoxaparin (17.9%) and in 911 receiving UFH. Revascularization procedures were performed in 73.5% of patients given enoxaparin and in 72.2% given UFH. Stroke was infrequent during 6-month follow-up and occurred in only 148 (1.5%) of all patients,

without difference between treatment groups (1.5% for enoxaparin vs. 1.6% for UFH)

Efficacy outcome at 1 year: One-year all-cause death rates were similar in the 2 treatment groups: 7.6% (380/4974) for enoxaparin vs. 7.3% (359/4948) for UFH



Summary

The rates of overall mortality and composite of death and non-fatal myocardial infarction were similar between treatment groups, showing that enoxaparin was at least as effective as UFH. Despite aggressive coronary revascularization and high use of evidence-based therapies, patients remained at high risk for recurrent cardiovascular ischemic complications

Reference

Mahaffey KW, Cohen M, Garg J, Antman E, Kleiman NS, Goodman SG, Berdan LG, Reist CJ, Langer A, White HD, Aylward PE, Col JJ, Ferguson JJ 3rd, Califf RM. High-risk patients with acute coronary syndromes treated with low-molecular-weight or unfractionated heparin: outcomes at 6 months and 1 year in the SYNERGY trial. *J Am Med Ass* 2005;294:2594-2600

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TAO

Treatment of Acute coronary syndrome with Otamixaban (2013)

Condition

Treatment of acute coronary syndrome

Objective

To compare the clinical efficacy and safety of otamixaban with that of unfractionated heparin (UFH) plus downstream eptifibatide in patients with non-ST-segment elevation acute coronary syndromes (NSTEMI-ACS) undergoing early invasive strategy

Trial design

Randomized, double-blind, triple-dummy, placebo-controlled phase III study with 2 phases:

Phase 1: from randomization until the end of PCI (or, if no PCI, up to day 4 or hospital discharge, whichever came first):

Active treatment:

- Arm 1: otamixaban – dose 1: i.v. bolus of 0.080 mg/kg followed by continuous infusion of 0.100 mg/kg per hour; UFH matching placebo (n = 2657)
- Arm 2: otamixaban – dose 2: i.v. bolus of 0.080 mg/kg followed by continuous infusion of 0.140 mg/kg per hour; UFH matching placebo (n = 5106)

Control treatment:

- Arm 3: UFH i.v. bolus of 60 IU/kg (maximum 4000 IU) followed by continuous infusion of 12 IU/kg per hour (maximum 1000 IU/h) to maintain an activated partial thromboplastin time at 1.5–2.0 times the control group; at the time of PCI, additional UFH boluses could be administered if the activated clotting time was not in the 200- to 250-seconds range; otamixaban matching placebo (n = 5466)

Phase 2: from PCI (downstream use) until 18–24 hours post PCI or hospital discharge:

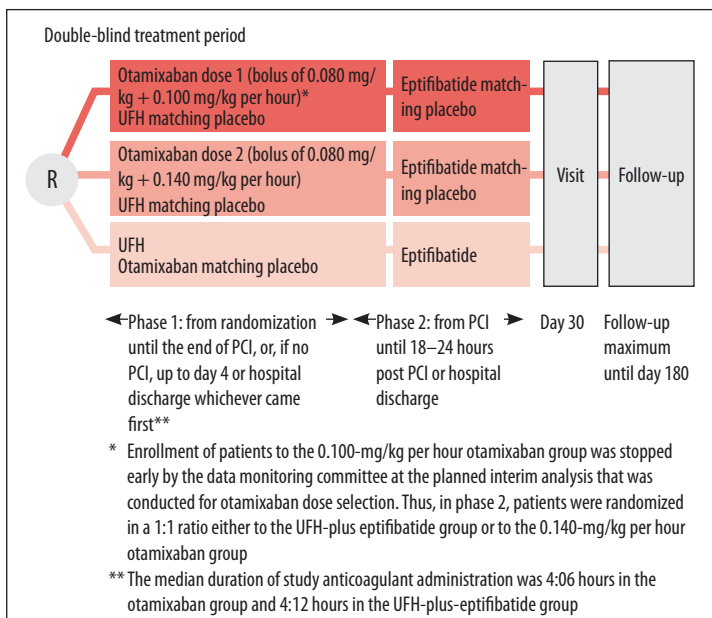
Active treatment:

- Arm 1: eptifibatide matching placebo
- Arm 2: eptifibatide matching placebo

Control treatment:

- Arm 3: eptifibatide i.v. bolus of 180 µg/kg immediately before PCI, followed by a continuous infusion of 2.0 µg/kg per minute, and a second 180-µg/kg bolus 10 minutes later (for patients with a creatinine clearance <50 ml/min, the infusion rate was reduced to 1 µg/kg per minute); otamixaban matching placebo

An interim analysis, to be performed after at least 1969 patients had been randomized in each group and had completed a 7-day follow-up allowed the data monitoring committee to choose the optimal otamixaban-dose group to continue until study end



Endpoints

Primary efficacy endpoint: composite of all-cause death and new myocardial infarction from randomization to day 7

Secondary efficacy endpoints: primary efficacy outcome up to day 30; composite of all-cause death, new myocardial infarction, and any stroke (days 1–7); rehospitalization or prolongation of hospitalization due to a new episode of myocardial ischemia/myocardial infarction (days 1–30); all-cause death (days 1–7); procedural thrombotic complications during the index PCI

Primary safety endpoints: composite of TIMI major and minor bleeding (days 1–7)

Secondary safety endpoints: CABG-related and non-CABG-related bleedings

Trial participants

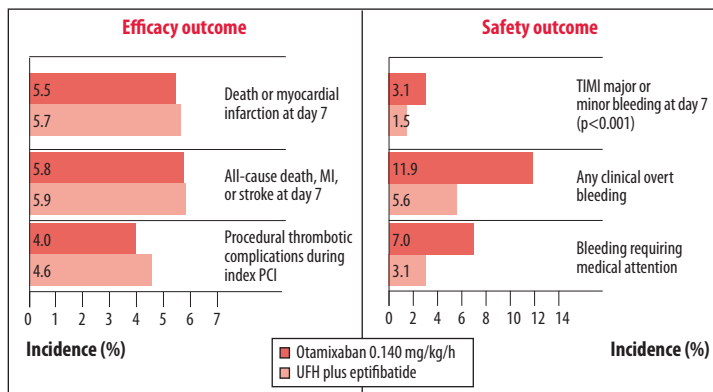
13229 patients with non-ST-segment elevation acute coronary syndrome with ischemic symptoms at rest ≥ 10 minutes within 24 hours of randomization, scheduled to undergo a coronary angiography (followed, when indicated, by PCI) to be performed within 36 hours of randomization and at the latest on day 3. Angiography was performed in 13125 patients (99.2%) and led to PCI in 8656 patients (65.4%) and to CABG surgery in 682 patients (5.2%)

Results

Efficacy outcome: The primary outcome of death or myocardial infarction through day 7 occurred in 5.5% of the patients treated with otamixaban 0.140 mg/kg per hour vs. 5.7% of the patients treated with UFH plus eptifibatide (RR 0.99). In the lower-dose otamixaban group, discontinued by the data monitoring committee, the rate of the primary outcome at day 7 was 6.3%. Otamixaban 0.140 mg/kg per hour did not significantly reduce the risk of any of the components of the secondary efficacy outcomes. The rate of thrombotic procedural complications was 4.0% in patients treated with otamixaban vs. 4.6% in those receiving UFH plus eptifibatide (RR 0.88), in

particular, the rates of stent thrombosis were 1.3% vs. 1.6% and the rates of catheter or guidewire thrombus were less than 0.1% vs. 0.3%. Analysis of the primary outcome by 30 days confirmed the absence of a reduction with otamixaban

Safety outcome: Patients in the otamixaban group had an increased rate of the primary safety outcome of TIMI major or minor bleeding at day 7 compared with patients in the combination of UFH-plus-eptifibatid group (3.1% vs. 1.5%; RR 2.13). There were marked increases in CABG-related and non-CABG-related bleedings with otamixaban (0.8% vs. 0.4% and 0.9% vs. 0.4%, respectively)



Summary

Efficacy: Otamixaban did not reduce ischemic events compared with UFH plus eptifibatid in patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS) and a planned invasive strategy

Safety: The risk of major or minor bleeding was approximately doubled with otamixaban

Reference

Steg PG, Mehta SR, Pollack CV Jr, Bode C, Cohen M, French WJ, Hoekstra J, Rao SV, Ruzyllo W, Ruiz-Nodar JM, Sabaté M, Widimsky P, Kiss RG, Navarro Estrada JL, Hod H, Kerkar P, Guneri S, Sezer M, Ruda M, Nicolau JC, Cavallini C, Ebrahim I, Petrov I, Kim JH, Jeong MH, Ramos Lopez GA, Laanmets P, Kovar F, Gaudin C, Fanouillere KC, Minini P, Hoffman EB, Moryusef A, Wiviott SD, Sabatine MS; TAO Investigators. Anticoagulation with otamixaban and ischemic events in non-ST-segment elevation acute coronary syndromes: the TAO randomized clinical trial. *J Am Med Ass* 2013;310:1145-1455

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Philippe Gabriel Steg, MD, Université Paris-Diderot, Département Hospitalo-Universitaire FIRE, Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, 46 Rue Henri Huchard, 75018 Paris, France, e-mail: gabriel.steg@bch.aphp.fr

TASMAN Study Group

Treatment of proximal DVT with low-molecular-weight heparin at home vs. standard heparin in hospital (1996)

Condition

Treatment of acute proximal DVT in outpatients

Objective

To compare the efficacy and safety of adjusted-dose intravenous standard heparin given in hospital with those of fixed-dose subcutaneous low-molecular-weight heparin given at home in patients with proximal DVT and to confirm through quality-of-life assessments that home treatment had no adverse effects on patients' well-being

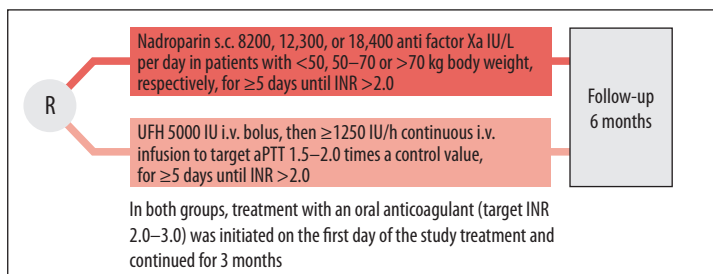
Trial design

Randomized, open study with parallel groups

Active treatment: nadroparin s.c. twice daily adjusted for the patient's weight: 8200, 12,300, or 18,400 anti factor Xa IU/L per day in patients weighing <50, 50–70, or >70 kg, respectively, given for at least 5 days and until the concomitant oral anticoagulant therapy resulted in an INR >2.0. As soon as appropriate, patients were allowed to be treated at home (n=202)

Control treatment: UFH 5000 IU i.v. bolus, then ≥ 1250 IU/h continuous i.v. infusion to target aPTT 1.5–2.0 times a control value, for ≥ 5 days until INR >2.0. The patients were treated in hospital (n=198)

Quality-of-life assessment: Patients completed disease-specific questionnaires before randomization, after initial treatment, and 12 and 24 weeks after randomization



Endpoints

Primary efficacy endpoint: recurrent VTE during 6-month follow-up

Secondary endpoints: major bleeding during the first 3 months; quality of life

Trial participants

400 consecutive symptomatic outpatients with documented acute proximal DVT but no signs of PE

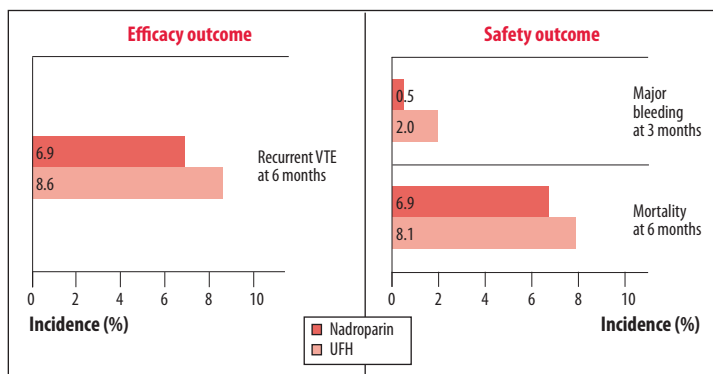
Results

Efficacy outcome: 17 of the 198 patients receiving standard heparin (8.6%) and 14 of the 202 patients assigned to nadroparin (6.9%) had recurrent VTE during the 6-month follow-up

Safety outcome: At 3 months, major bleeding occurred in 4 patients in the UFH group (2.0%) and in 1 patient in the nadroparin group (0.5%). 16 (8.1%) patients in the standard-heparin group and 14 (6.9%) patients in the nad-

roparin group died during the 6-months study period. No patient died during the initial treatment

Quality of life: Quality of life improved in both groups. Physical activity and social functioning were better in the patients assigned to nadroparin. Among the patients in that group, 36% were never admitted to the hospital at all, and 40% were discharged early. This treatment was associated with a mean reduction in hospital days of 67%



Summary

Efficacy: Nadroparin was least as effective as standard heparin but permits approximately 75% of patients with proximal DVT to be treated as outpatients or discharged early from the hospital

Safety: Rates of major bleeding were both low and similar in the two treatment groups

Quality of life: Home treatment with nadroparin improved physical and mental well-being more than in-hospital treatment with standard heparin

Reference

Koopman MM, Prandoni P, Piovella F, Ockelford PA, Brandjes DP, van der Meer J, Gallus AS, Simonneau G, Chesterman CH, Prins MH, Bossuyt PMM, de Haes H, van den Belt AGM, Sagnard L, D'Azemar P, Büller HR, for the Tasman Study Group. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. *N Engl J Med* 1996;334:682-687

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THÉSÉE

Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie pulmonaire (1997)

Condition

Initial treatment of acute symptomatic PE

Objective

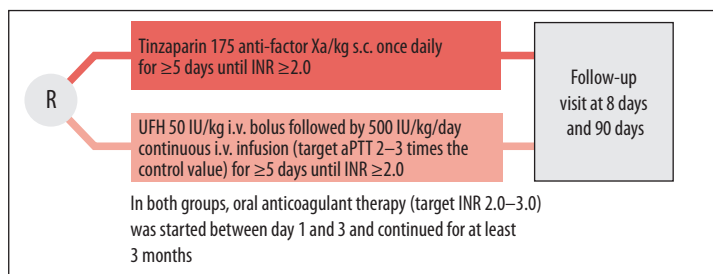
To compare the efficacy and safety of fixed-dose tinzaparin compared with adjusted-dose UFH in patients with acute symptomatic PE

Trial design

Randomized, open study with parallel groups

Active treatment: tinzaparin 175 anti-factor Xa/kg s.c. once daily for at least 5 days and until the concomitant oral anticoagulant therapy resulted in an INR ≥ 2 (n=304)

Control treatment: UFH 50 IU/kg i.v. bolus followed by 500 IU/kg/day continuous i.v. infusion (target aPTT 2–3 times the control value) for at least 5 days and until the oral anticoagulant therapy induced an INR ≥ 2.0 (n=308)



Endpoints

Primary endpoint: composite of recurrent thromboembolism, major bleeding, and death within the first 8 days and at day 90

Secondary endpoint: change from day 1 to day 8 in the extent of scintigraphically detectable pulmonary vascular obstruction

Trial participants

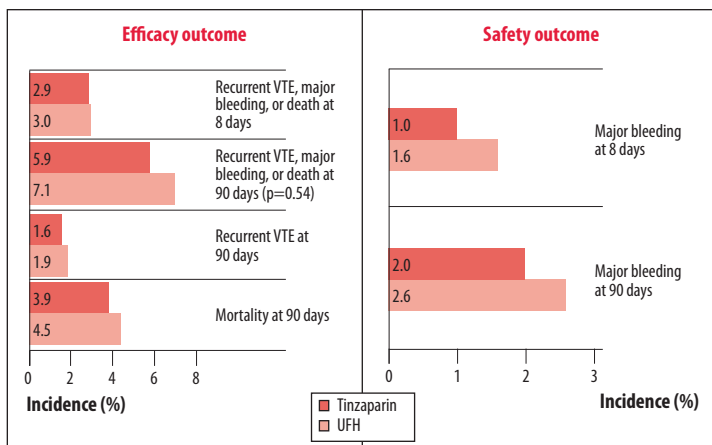
612 consecutive patients (mean age 67 years) with documented acute symptomatic PE who did not require thrombolytic therapy or embolectomy

Results

Efficacy outcome: At 8 days, the incidence of the primary endpoint (death, symptomatic recurrent thromboembolism or major bleeding) was similar in the tinzaparin and UFH group (3.0% vs. 2.9%). By day 90, this incidence was slightly, but not significantly, lower in patients assigned to tinzaparin than in patients assigned to UFH (5.9% vs. 7.1%). From day 1 to day 8, 4 of 304 patients (1.3%) receiving tinzaparin died, as compared with 3 of 308 patients (1.0%) receiving UFH. The mortality rates at 3 months were 3.9% and 4.5%, respectively. At day 8, the absolute decrease in pulmonary vascular obstruction was $18.4 \pm 13.5\%$ in 258 patients assigned to tinzaparin and $19.0 \pm 13.9\%$ in 260 patients assigned to UFH

Safety outcome: At day 8, 1.0% in the tinzaparin group and 1.6% in the UFH group had episodes of major bleeding. By 3 months the incidences were 2.0% and 2.6%, respectively. During the initial treatment, minor bleeding

was noted in 17 patients receiving tinzaparin and 8 patients receiving UFH (p=0.10)



Summary

Efficacy: Treatment of confirmed PE with fixed-dose tinzaparin was as effective as treatment with adjusted-dose UFH

Safety: The incidence of major bleeding was similar with tinzaparin and UFH throughout the study

Reference

Simonneau G, Sors H, Charbonnier B, Page Y, Laaban J-P, Azarian R, Laurent M, Hirsch J-L, Ferrari E, Bosson J-L, Mottier D, Beau B, for the THÉSÉE Study Group. A comparison of low-molecular weight heparin with unfractionated heparin for acute pulmonary embolism. *N Engl J Med* 1997;337:663-669

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TIMI 11B

Thrombolysis In Myocardial Infarction (1999)

Condition

Treatment of unstable angina or non-Q-wave myocardial infarction

Objective

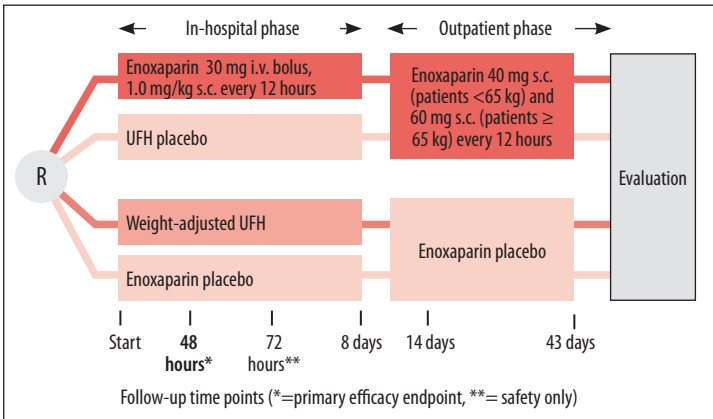
To determine whether treatment with enoxaparin is superior to UFH for preventing events in the acute phase, and whether there is a potential benefit for enoxaparin administration for an additional 35 days after hospital discharge

Trial design

Randomized, double-blind placebo-controlled study

Active treatment: enoxaparin during the acute phase (initial 30 mg i.v. bolus followed by 1.0 mg/kg s.c. every 12 hours) and outpatient phase (40 mg s.c. for patients weighing <65 kg and 60 mg s.c. for those weighing ≥65 kg every 12 hours) plus UFH-matching placebo; ASA 100–325 mg once daily for the entire follow-up (n=1953)

Control treatment: weight-adjusted UFH i.v. for ≥3 days and enoxaparin-matching placebo followed by placebo s.c.; ASA 100–325 mg once daily for the entire follow-up (n=1957)



Endpoints

Primary efficacy endpoint: composite of death, myocardial infarction, or urgent revascularization

Primary safety endpoint: major hemorrhage

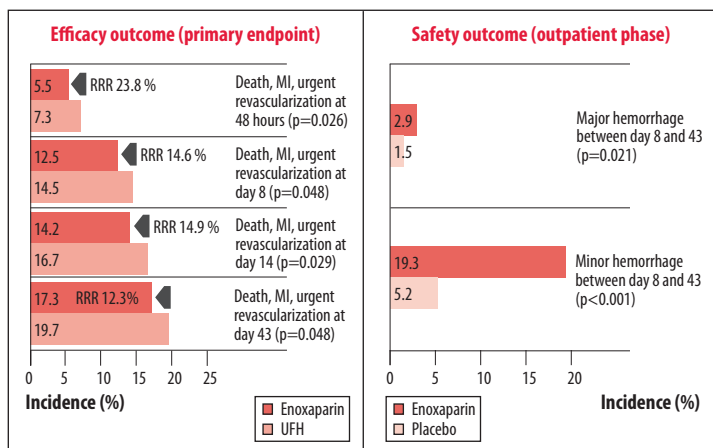
Trial participants

3910 patients with unstable angina or non-Q-wave myocardial infarction of any age who suffered an acute myocardial infarction within the preceding 14 days

Results

Efficacy outcome: By 48 hours, in 108 of 1953 patients (5.5%) and in 142 of 1957 patients (7.3%) receiving UFH, a primary event had occurred. At 8 days, the incidence of the primary end point was 12.4% in the enoxaparin group and 14.5% in the UFH group. At 14 days, the incidence was 14.2% vs. 16.7%, and by 43 days 17.3% vs. 19.7%

Safety outcome: During the first 72 hours major hemorrhage occurred in 16 of 1938 patients given enoxaparin (0.8%) and in 14 of 1936 patients given UFH (0.7%), as well as during the entire hospitalization phase in 29 patients (1.5%) given enoxaparin and 19 patients (1.0%) given UFH. Minor hemorrhage occurred in 99 (5.1%) vs. 45 (2.3%) of the enoxaparin vs. the UFH patients during the first 72 hours and in 176 (9.1%) vs. 48 (2.5%) patients during the entire hospitalization phase. During the outpatient phase, 34 of 1179 patients in the enoxaparin group (2.9%) and 18 of 1185 patients in the placebo group (1.5%) suffered a major hemorrhage, and 227 (19.3%) vs. 62 (5.2%) a minor hemorrhage



Summary

Efficacy: Enoxaparin is superior to UFH in reducing the composite endpoint of death, myocardial infarction, and urgent revascularization during the acute management of unstable angina or non-Q-wave-infarction. In the outpatient phase the curves for the primary event rate remained parallel to each other, which suggests that there was no further relative treatment benefit of an additional 35 days of enoxaparin therapy

Safety: During the first 72 hours and throughout the initial hospitalization, there was no significant difference in the rate of major hemorrhage in the 2 treatment groups. There was a significantly higher rate of major hemorrhage during the outpatient phase in the enoxaparin group. At all time points, the rate of minor hemorrhage was significantly higher in the enoxaparin group

Reference

Antman EM, McCabe CH, Gurfinkel EP, Turpie AGG, Bernink PJL, Salein D, Bayes de Luna A, Fox K, Lablanche J-M, Radley D, Premmreur J, Braunwald E, for the TIMI 11B Investigators. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction – Results of the Thrombolysis In Myocardial Infarction (TIMI) 11B. *Circulation* 1999;100:1593-1601

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VAN GOGH

Idraparinus versus standard therapy for venous thromboembolic disease (2007)

Condition

Treatment of DVT and acute PE

Objective

To demonstrate that idraparinus is at least as effective and safe as standard therapy (low molecular weight heparin or heparin, followed by an adjusted-dose vitamin K antagonist) in the treatment of patients with DVT or PE

Trial design

Two separate, randomized, open-label, non-inferiority phase III trials with parallel groups

■ DVT Study

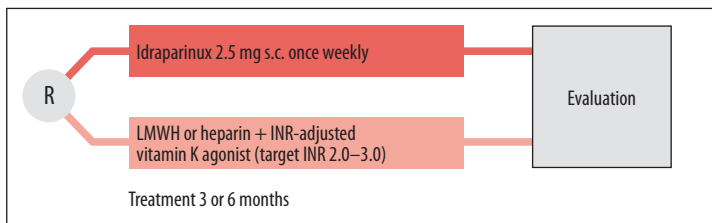
Active treatment: idraparinus 2.5 mg s.c. once weekly for either 3 or 6 months (n=321 in the 3-month stratum; n=1131 in the 6-month stratum)

Control treatment: tinzaparin, enoxaparin, or i.v. heparin adjusted for an activated partial-thromboplastin time of 1.5–2.5, followed by adjusted-dose warfarin or acenocoumarol (target INR 2.0–3.0) for either 3 or 6 months (n=316 in the 3-month stratum; n=1136 in the 6-month stratum)

■ PE Study

Active treatment: idraparinus 2.5 mg s.c. once weekly for either 3 or 6 months (n=102 in the 3-month stratum; n=103 in the 6-month stratum)

Control treatment: standard therapy as in the DVT study (n=993 in the 3-month stratum; n=1017 in the 6-month stratum)



Endpoints

Primary efficacy endpoint: incidence of symptomatic recurrent VTE (non-fatal or fatal)

Primary safety endpoints: clinically relevant bleeding (major or non-major) and death from all causes

Trial participants

DVT Study: 2904 patients aged ≥ 18 years (mean 58 years) with acute symptomatic VTE (lower-extremity symptoms)

PE Study: 2215 patients aged ≥ 18 years (mean 62 years) with acute symptomatic VTE (chest symptoms)

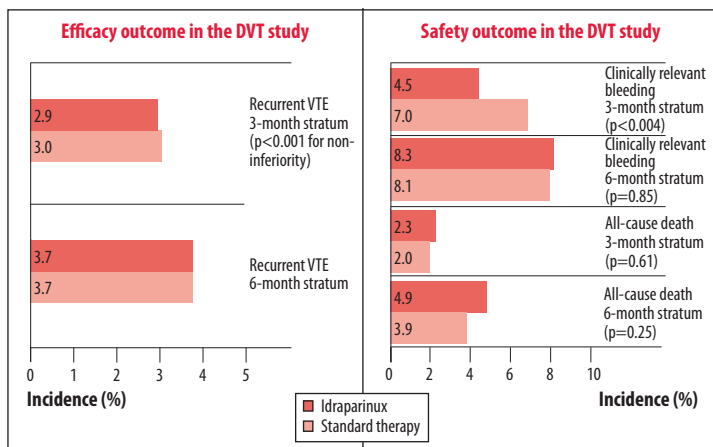
Results

■ DVT Study

Efficacy outcome: At 3 months, the incidence of recurrent VTE was 2.9% in the idraparinus group as compared with 3.0% in the standard-therapy

group (odds ratio 0.98; $p < 0.001$ for non-inferiority). The rates in the 6-month stratum were similar in both groups (3.7% and 3.7%, respectively)

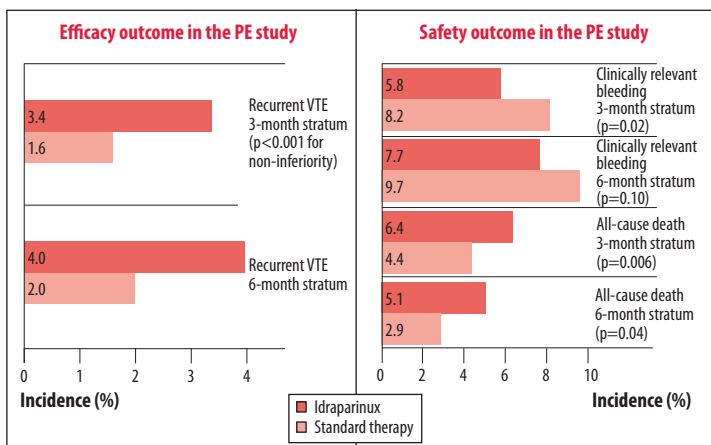
Safety outcome: At 3 months, clinically relevant bleeding had occurred in 4.5% of the patients treated with idraparinux and 7.0% in the standard-therapy group ($p = 0.004$). In the 6-month stratum, the incidence was 8.3% in the idraparinux arm and 8.1% in patients receiving standard therapy ($p = 0.85$). The corresponding rates of major bleeding were 0.8% and 1.2%, respectively, at 3 months ($p = 0.35$) and 1.9% and 1.5% at 6 months ($p = 0.50$). At 3 months, the mortality was 2.3% in the idraparinux group and 2.0% in the standard-therapy group ($p = 0.61$). In the 6-month stratum the mortality rates were 4.9% and 3.9%, respectively ($p = 0.25$)



■ PE Study

Efficacy outcome: In the 3-month stratum, the incidence of recurrent VTE was 3.4% in patients treated with idraparinux and 1.6% in patients assigned to standard therapy (odds ratio 2.14; $p = 0.59$ for non-inferiority). The corresponding rates in the 6-month stratum were 4.0% and 2.0%, respectively

Safety outcome: The incidence of clinically relevant bleeding at 3 months was 5.8% in the idraparinux group and 8.2% in the standard-therapy group. These rates in the 6-month stratum were 7.7% and 9.7%, respectively. The corresponding rates of major bleeding were 1.1% and 2.1% at 3 months and 1.4% and 2.8% at 6 months. At 3 months, the rate of all-cause death was 5.1% in the idraparinux group and 2.9% in the standard-therapy group ($p = 0.006$). In the 6-month stratum the mortality rates were 6.4% and 4.4%, respectively ($p = 0.04$)



Summary

Efficacy: In patients with DVT, the efficacy of once-weekly subcutaneous idraparinux in preventing subsequent thromboembolic events was similar to that of standard therapy with heparin plus vitamin K antagonist. In contrast, in patients with PE, the efficacy of idraparinux was inferior to that of standard therapy

Safety: Bleeding rates in the idraparinux groups were similar to or lower than those in the standard-therapy groups. However, there was an excess of early fatal and non-fatal recurrences of PE. In patients with PE, the idraparinux treatment was associated with an increase in total mortality

Reference

The van Gogh Investigators; Büller HR, Cohen AT, Davidson B, Decousus H, Gallus AS, Gent M, Pillion G, Piovella F, Prins MH, Raskob GE. Idraparinux versus standard therapy for venous thromboembolic disease. *N Engl J Med* 2007;357:1094-1104

Corresponding author

Prof. Harry R. Büller, Department of Vascular Medicine, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, Netherlands, e-mail: h.r.buller@amc.uva.nl

VAN GOGH Extension

Extended prophylaxis of venous thromboembolism with idraparinux (2007)

Condition

Extended prophylaxis of VTE after 6 months anticoagulation

Objective

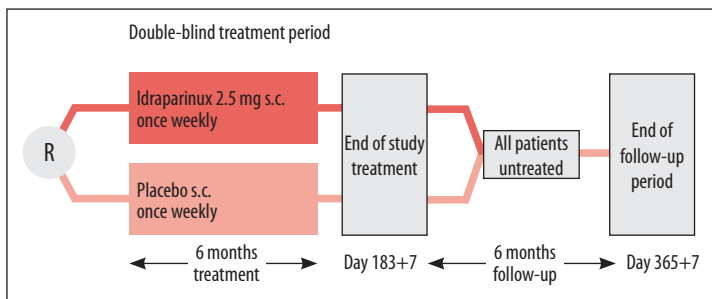
To evaluate the efficacy and safety of a 6-month extension of VTE prophylaxis with idraparinux in patients who had initially received 6 months of prophylaxis with an anticoagulant

Trial design

Randomized, placebo-controlled, double-blind phase III study

Active treatment: idraparinux 2.5 mg s.c. once weekly for 6 months (n=594)

Control treatment: placebo s.c. once weekly for 6 months (n=621)



Endpoints

Primary efficacy endpoint: incidence of symptomatic recurrent VTE (non-fatal or fatal)

Primary safety endpoint: major bleeding

Secondary safety endpoint: clinically relevant bleeding, death from any cause

Trial participants

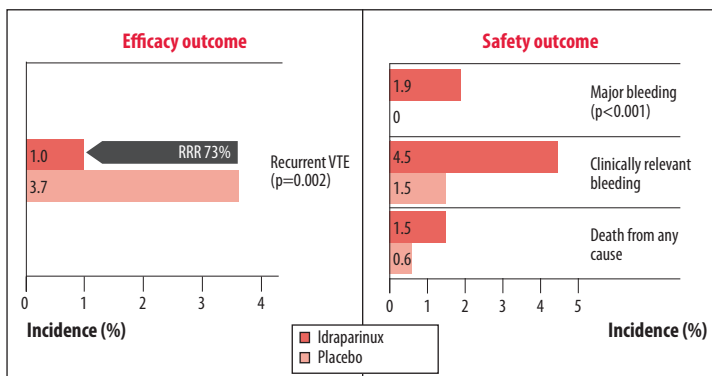
1215 patients (age ≥ 18 years) with confirmed, symptomatic DVT or PE who had been treated for 6 months with acenocoumarol or warfarin (either in previous VAN GOGH studies or outside these studies)

Results

Efficacy outcome: During the 6 months of randomly assigned treatment, 6 of 594 patients in the idraparinux group (1.0%) and 23 of 621 patients in the placebo group (3.7%) had recurrent VTE (relative risk reduction 73%; $p=0.002$). In the placebo group, a higher VTE incidence was observed in patients who had received a vitamin K antagonist before randomization than in those who had received idraparinux (5.9% vs. 0.7%; $p=0.004$)

Safety outcome: Major bleeding occurred in 11 of 594 patients in the idraparinux group (1.9%) and in none of the 621 patients in the placebo group ($p<0.001$). Three bleeding episodes in the idraparinux group were fatal intracranial hemorrhages. The incidence of major bleeding was higher in patients who had received idraparinux before randomization than in those who had received a vitamin K antagonist (3.1% vs. 0.9%; $p=0.06$). The rate for clinically relevant bleeding was 4.5% in the idraparinux arm compared

to 1.5% in the placebo group. The mortality was lower in the placebo group (0.6 vs. 1.5%)



Summary

During the 6-month extension of thromboprophylaxis, the factor X inhibitor idraparinux was effective in preventing recurrent thromboembolism but was associated with an increased risk of a major hemorrhage

Reference

The van Gogh Investigators; Büller 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;357:1105-1112

Corresponding author

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VENTURE-AF

A study exploring two treatment strategies in patients with atrial fibrillation who undergo catheter ablation therapy (2013, ongoing)

Condition

Prevention of cardiovascular events in patients undergoing catheter ablation therapy for atrial fibrillation

Objective

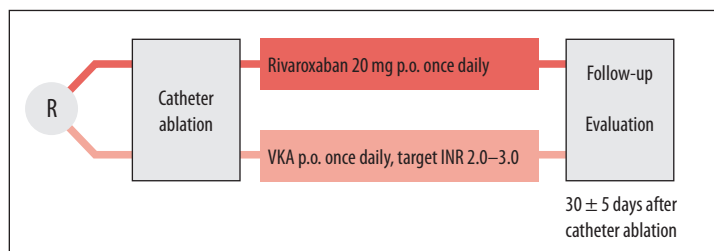
To assess the safety of uninterrupted rivaroxaban vs. usual care in patients undergoing catheter ablation therapy for non-valvular AF

Trial design

Prospective, randomized, open-label, active-controlled phase III study

Active treatment: rivaroxaban 20 mg p.o. once daily

Control treatment: uninterrupted vitamin K antagonist (VKA), dose-adjusted to achieve a target international normalized ratio (INR) of 2.0–3.0



Endpoints

Primary efficacy endpoint: incidence of post-procedure major bleeding during the first 30 ± 5 days after the catheter ablation procedure

Secondary outcome measures: event rate of myocardial infarction, ischemic stroke, non-central nervous system systemic embolism and vascular death

Trial participants

~250 patients ≥ 18 years with a history of paroxysmal or persistent non-valvular AF who are scheduled to undergo their first elective catheter ablation procedure

References

ClinicalTrials.gov (NCT01729871)

WARCEF

Warfarin versus Aspirin Reduced Cardiac Ejection Fraction study (2012)

Condition

Prevention of vascular events in patients with heart failure and sinus rhythm

Objective

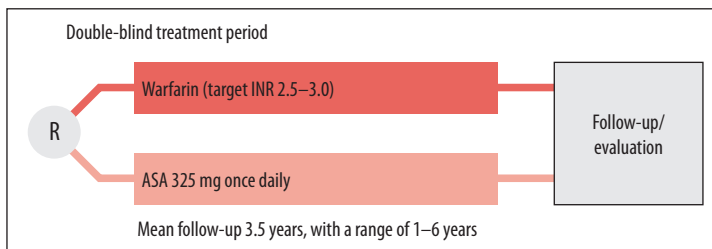
To compare the efficacy of warfarin and ASA in preventing death, ischemic stroke, and intracerebral hemorrhage in patients with heart failure (LVEF $\leq 35\%$) and sinus rhythm

Trial design

Randomized, double-blind, phase III trial

Active treatment: warfarin (INR 2.5–3.0) plus placebo (n=1142)

Control treatment: ASA 325 mg once daily plus placebo (n=1163)



Trial participants

2305 patients >18 years with a left ventricular ejection fraction (LVEF) $\leq 35\%$ or a wall motion index ≤ 1.2 , who do not have atrial fibrillation or mechanical cardiac valves. Patients must be treated with a betablocker, an ACE inhibitor (or angiotensin-receptor blocker), or hydralazine and nitrates

Endpoints

Primary efficacy endpoint: time to the first event in a composite end point of ischemic stroke, intracerebral hemorrhage, or death from any cause

Primary safety endpoint: composite of death, ischemic stroke, intracerebral hemorrhage, or intracranial hemorrhage

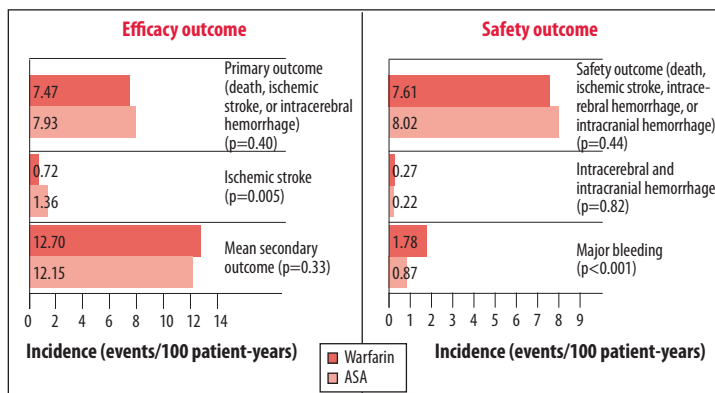
Secondary outcomes: death, ischemic stroke, intracerebral hemorrhage, myocardial infarction, or hospitalization for heart failure

Results

Efficacy outcome: As compared with ASA, warfarin did not significantly reduce the rate of the primary outcome (7.47 events per 100 patient-years in the warfarin group and 7.93 in the ASA group). Throughout the follow-up period, warfarin was associated with a significant reduction in the rate of ischemic stroke (0.72 vs. 1.36 events per 100 patient-years). With respect to the main secondary outcome (first event in the composite of death, ischemic stroke, intracerebral hemorrhage, myocardial infarction, or hospitalization for heart failure), there was no significant difference between the warfarin and ASA groups (12.70 vs. 12.15 events per 100 patient-years)

Safety outcome: The overall safety outcome did not differ significantly between the two treatment groups. But the rate of major hemorrhage was

significantly higher with warfarin than with ASA (1.78 vs. 0.87 events per 100 patient-years)



Summary

Efficacy: There was no significant overall difference between warfarin and ASA with respect to the primary outcome of death, ischemic stroke, or intracerebral hemorrhage. However, warfarin was associated with a significant reduction in the risk of ischemic stroke

Safety: The benefit of warfarin in reducing the risk of ischemic stroke was offset by a significant increase in the rate of major bleeding

Reference

Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, Ammon SE, Graham S, Sacco RL, Mann DL, Mohr JP, Massie BM, Labovitz AJ, Anker SD, Lok DJ, Ponikowski P, Estol CJ, Lip GY, Di Tullio MR, Sanford AR, Mejia V, Gabriel AP, del Valle ML, Buchsbaum R for the WARCEF Investigators. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med* 2012;366:1859-1869

Corresponding author

Shunichi Homma, MD, Columbia University Medical Center, PH 3-342, 622 West 168th St., New York, NY 10032, sh23@columbia.edu

WARIS II

Warfarin-Aspirin Reinfarction Study II (2002)

Condition

Secondary prevention of myocardial infarction

Objective

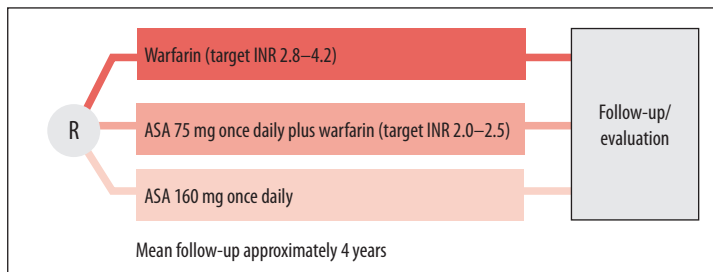
To compare the efficacy and safety of warfarin, ASA or both after myocardial infarction

Trial design

Randomized, open-label study

Active treatment: warfarin (INR 2.8–4.2) (n=1216), or ASA 75 mg daily combined with warfarin (INR 2.0–2.5) (n=1208)

Control treatment: ASA 160 mg daily (n=1206)



Endpoints

Primary efficacy endpoint: composite of death, non-fatal reinfarction, or thromboembolic stroke, whichever came first

Secondary efficacy endpoints: number of therapeutic interventions (percutaneous coronary intervention, coronary-artery bypass grafting)

Primary safety endpoint: major bleeding events

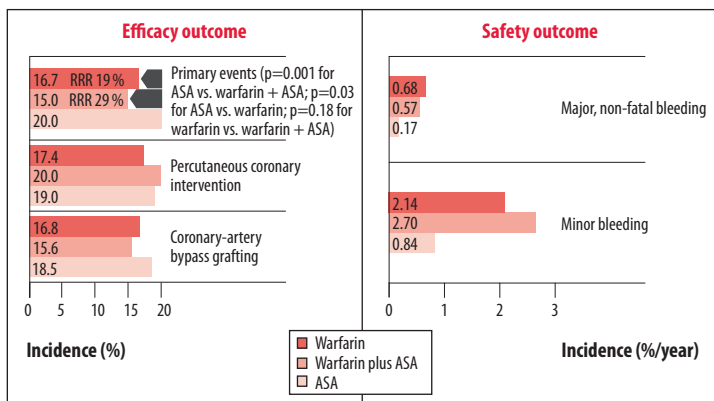
Trial participants

3630 patients, younger than 75 years (mean age 60 years), hospitalized for acute myocardial infarction

Results

Efficacy outcome: A primary outcome event occurred in 203 of 1216 of patients (16.7%) receiving warfarin alone, in 241 of 1206 patients (20.0%) receiving ASA, and in 181 of 1208 (15.0%) of patients receiving both. As compared with ASA alone, the risk reduction in the warfarin plus ASA group was 29% and in the warfarin alone group it was 19%. Between the two groups receiving warfarin the difference was not significant. The total number of therapeutic interventions was 1300: 224 with ASA, 204 with warfarin, and 188 in the combined-therapy group for coronary-artery bypass grafting and 230, 212, and 242, respectively, for percutaneous coronary intervention

Safety outcome: The rates of major, non-fatal bleeding were 0.17% per treatment-year in patients receiving ASA, 0.68% in the group receiving warfarin, and 0.57% in the combined-therapy group. The incidence of minor bleeding episodes was 0.84%, 2.14% and 2.70% per year, respectively



Summary

Efficacy: As compared with ASA alone, therapy with moderate-intensity warfarin combined with ASA and high-intensity warfarin alone resulted in a reduced risk of reinfarction and ischemic stroke

Safety: There were approximately four times as many major bleeding episodes in the two groups receiving warfarin than in the group receiving ASA alone

Reference

Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002;347:969-974

Corresponding author

Mette Hurlen, MD, Medical Department, Ullevål University Hospital, N-0407 Oslo, Norway

WODIT DVT

Warfarin Optimal Duration Italian Trial in patients with Deep Vein Thrombosis (2001)

Condition

Long-term prevention of recurrent idiopathic DVT

Objective

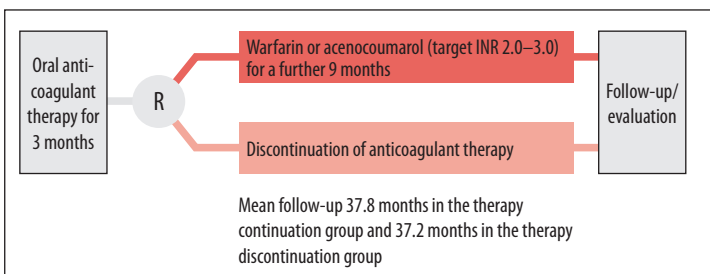
To evaluate the long-term clinical benefit of extending a 3-month course of oral anticoagulant therapy to 1 year in patients with a first episode of idiopathic proximal DVT

Trial design

Randomized, open study with parallel groups

Active treatment: continuation of warfarin or acenocoumarol (target INR 2.0–3.0) for a further 9 months (n=134)

Control treatment: discontinuation of anticoagulant therapy (n=133)



Endpoints

Primary efficacy endpoint: symptomatic, objectively confirmed recurrence of VTE during at least 2 years of follow-up

Primary safety endpoints: major bleeding, all-cause death

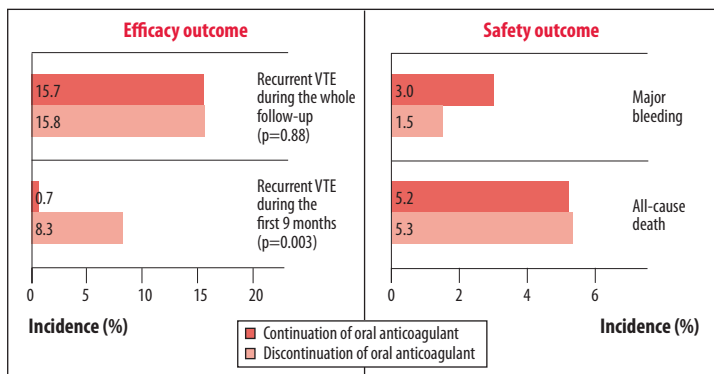
Trial participants

267 patients, aged 15–85 years, with a first episode of idiopathic proximal DVT who had completed 3 uninterrupted months of oral anticoagulant therapy without a recurrence or bleeding

Results

Efficacy outcome: In the intention-to-treat analysis, 21 of the 134 patients assigned to continue therapy (15.7%) and 21 of the 133 patients assigned to discontinue therapy (15.8%) had recurrent VTE. All episodes of recurrent VTE were idiopathic, and none were fatal. The average time to recurrence was 16.0 months from randomization in the patients assigned to continue therapy and 11.2 months from randomization in those assigned to discontinue therapy. The risk of recurrence during the first 9 months of follow-up was lower among the patients assigned to continue therapy (1 patient, 1.2% per patient-year) than in those assigned to discontinue therapy (11 patients, 12.3% per patient-year). After 9 months the corresponding rates were 5.1% and 5.0% per patient-year

Safety outcome: Major bleeding occurred in 3.0% of patients in the continuation group and in 1.5% in the discontinuation group. 5.2% and 5.3% of the patients died



Summary

Efficacy: The clinical benefit achieved during the additional 9 months of oral anticoagulant therapy was not maintained after the discontinuation of therapy. Therefore recurrences of idiopathic DVT could be prevented only by continuous anticoagulation of indefinite duration

Safety: The incidence of adverse events (major bleeding, all-cause death) was similar in both groups

Reference

Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, Moia M, Guazzaloca G, Bertoldi A, Tomasi C, Scannapieco G, Ageno W, and the Warfarin Optimal Duration Italian Trial Investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. *N Engl J Med* 2001;345:165-169

Corresponding author

Prof. Giancarlo Agnelli, MD, Sezione di Medicina Interna e Cardiovascolare, Dipartimento di Medicina Interna, Università di Perugia, Via Enrico dal Pozzo, 06123 Perugia, Italy, e-mail: agnellig@unipg.it.

WODIT PE

Warfarin Optimal Duration Italian Trial in patients with Pulmonary Embolism (2003)

Condition

Long-term prevention of recurrent VTE after a first episode of PE

Objective

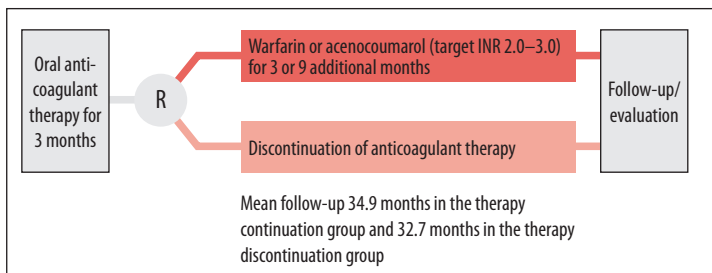
To evaluate the long-term clinical benefit of extending a 3-month course of oral anticoagulant therapy to 6 months in patients with a first episode of PE associated with temporary risk factors or to 1 year in patients with idiopathic PE

Trial design

Randomized, open study with parallel groups

Active treatment: continuation of warfarin or acenocoumarol (target INR 2.0–3.0) for 3 or 9 additional months in patients with a first episode of PE and transient risk factors (n=75) or for 9 additional months in patients with idiopathic PE (n=90)

Control treatment: discontinuation of anticoagulant therapy (patients with PE and transient risk factors, n=70; patients with idiopathic PE, n=91)



Endpoints

Primary efficacy endpoint: recurrence of symptomatic, objectively confirmed VTE after the initial 3 months of anticoagulation

Primary safety endpoints: cumulative incidence of adverse outcome events (recurrence of VTE, death, or major bleeding)

Trial participants

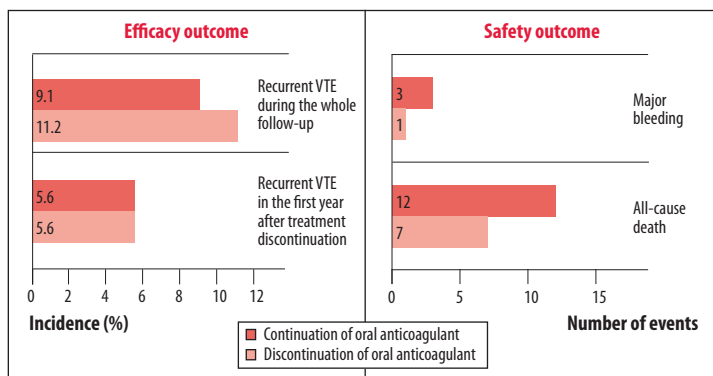
326 patients, aged 15–85 years, with a first episode of symptomatic, confirmed PE who had completed 3 uninterrupted months of oral anticoagulant therapy without a recurrence or bleeding. Patients were categorized as having idiopathic PE or PE associated with transient risk factors (e.g. recent trauma, surgery, prolonged immobilization)

Results

Efficacy outcome: Recurrent VTE occurred in 9.1% (15/165) of patients in the continuation group and in 11.2% (18/161) of patients in the discontinuation group. In patients with idiopathic PE, the incidence of recurrence was 12.2% in the continuation group and 12.1% in the discontinuation group. In patients with PE associated with transient risk factors, the rates were 5.3% and 10.0%, respectively. All but one of the recurrences occurred after anticoagulant treatment was discontinued. After treatment discontinuation, the incidence of recurrence was 5.6% in both treatment groups during the first

year and 3.9% and 3.5% during the second year in patients assigned to continue and discontinue treatment, respectively.

Safety outcome: The cumulative incidence of VTE recurrence, death, or major bleeding was 16.5% in patients in the continuation group and 14.9% in patients in the discontinuation group. Major bleeding occurred in 3 patients assigned to continue anticoagulation and in one patient assigned to discontinue anticoagulation. The mortality rates were 7.5% and 4.2%, respectively



Summary

Efficacy: The clinical benefit during the 3 or 9 additional months of anticoagulation was not maintained after treatment was discontinued. Therefore patients with PE are potential candidates for indefinite oral anticoagulant therapy

Safety: During extended anticoagulation, the incidence of major bleeding was low

Reference

Agnelli G, Prandoni P, Becattini C, Silingardi M, Taliani MR, Miccio M, Imberti D, Poggio R, Ageno W, Pogliani E, Porro F, Zonzin P, for the Warfarin Optimal Duration Italian Trial Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. *Ann Intern Med* 2003;139:19-25

Corresponding author

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WOEST

What is the **O**ptimal antiplatelet & anticoagulant therapy in patients with oral anticoagulation and coronary sten**T**ing? (2013)

Condition

Prevention of thrombotic complications with antiplatelet therapy after percutaneous coronary intervention (PCI) in patients taking oral anticoagulants

Objective

To evaluate the safety and efficacy of clopidogrel alone compared with clopidogrel plus ASA in patients receiving oral anticoagulants and undergoing PCI

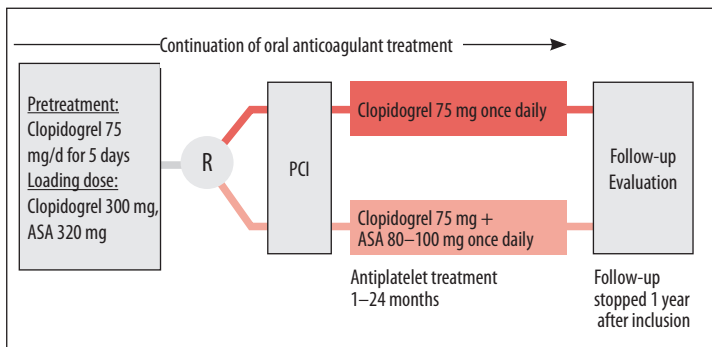
Trial design

Randomized, open-label, controlled phase IV study

All patients were pretreated with a maintenance dose of 75 mg clopidogrel per day for at least 5 days, a loading dose of 300 mg at least 24 h before PCI, or a loading dose of 600 mg at least 4 h before PCI, and a 320 mg loading dose of ASA. During the intervention, oral anticoagulants were continued with a target INR of 2.0

Active treatment: clopidogrel 75 mg once daily ("double therapy"; n=284)

Control treatment: clopidogrel 75 mg once daily plus ASA 80–100 mg once daily ("triple therapy"; n=289)



Endpoints

Primary efficacy endpoint: combined end point of minor, moderate or major bleeding complications during the initial hospitalization & one year follow-up

Secondary efficacy endpoints: combined event of death, myocardial infarction, stroke, systemic embolization & target vessel revascularization, and the individual components of the composite primary and secondary endpoints

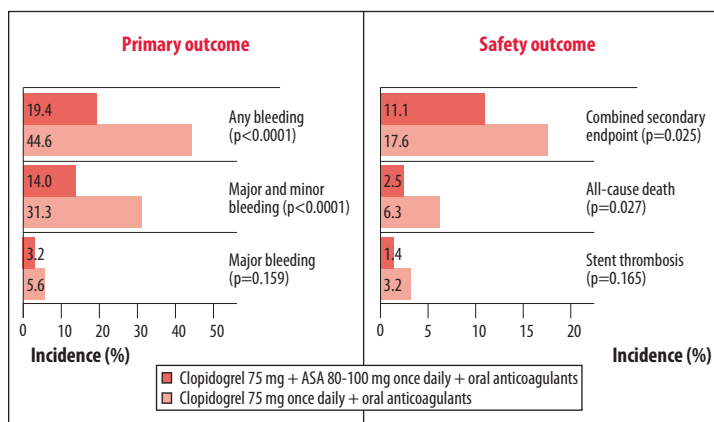
Trial participants

573 patients (mean age 70.3 years) were enrolled; 1-year data were available for 279 patients assigned to double therapy and 284 assigned to triple therapy. Inclusion criteria were a long-term indication for oral anticoagulation treatment, a severe coronary lesion with indication for PCI, and 18–80 years of age

Results

Primary outcome: At 1-year follow-up, any bleeding had occurred in 54 patients (19.4%) in the double-therapy group and in 126 patients (44.4%) in the triple-therapy group. 9 patients (3.2%) assigned to clopidogrel alone had major bleeding events, compared with 16 patients (5.6%) treated with clopidogrel + ASA. The incidence of major and minor bleeding events was significantly higher in the triple-therapy group (31.3% vs. 14.0%)

Secondary outcome: The combined secondary endpoint of death, myocardial infarction, stroke, target-vessel revascularization, and stent thrombosis was reported in 31 patients (11.1%) in the double-therapy group and in 50 (17.6%) in the triple-therapy group. At 1 year, 7 patients (2.5%) treated with clopidogrel and 18 patients (6.3%) given clopidogrel + ASA had died from any cause. The rates for the other individual components of the secondary endpoint did not differ significantly between both groups



Summary

Efficacy and safety: In patients taking oral anticoagulants and undergoing percutaneous coronary intervention, treatment with clopidogrel and oral anticoagulants was associated with a significantly lower risk of bleeding complications than triple therapy including ASA. There was no evidence of increased thrombotic risk without the use of ASA

Reference

Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermaans AA, Vis MM, Tijssen JG, van, t Hof AW, ten Berg JM for the WOEST study investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;381:1107-1115

Corresponding author

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XAMOS

XArelto in the prophylaxis of postsurgical VTE after elective **M**ajor **O**rthopaedic Surgery of hip or knee (2013)

Condition

Prophylaxis of VTE in patients undergoing major orthopaedic surgery of the hip or knee (predominantly elective arthroplasty)

Objective

To compare the safety and effectiveness of rivaroxaban after elective major orthopaedic surgery with other pharmacological thromboprophylaxis in everyday clinical practice

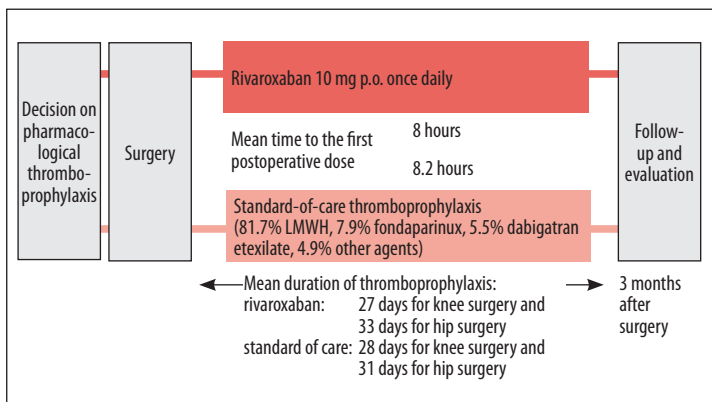
Trial design

Non-interventional, open-label, controlled cohort study

Active treatment: rivaroxaban 10 mg p.o. once-daily, starting 6–10 hours post surgery (n=8778)

Control treatment: standard-of-care thromboprophylaxis including low-molecular-weight heparins (LMWH), unfractionated heparins (UFH), fondaparinux, dabigatran etexilate, acetylsalicylic acid and vitamin K antagonists (n=8635)

The type, duration and dose of pharmacological agents were determined by the attending physician before patients entered the study



Endpoints

Primary outcome: bleeding events, symptomatic thromboembolic events (DVT, PE), uncommon adverse events (incidence rate between 0.1% and 1%), all-cause mortality

Secondary outcome: health care resource use, treatment convenience, patient compliance, use in special patient populations, such as renal impairment

Trial participants

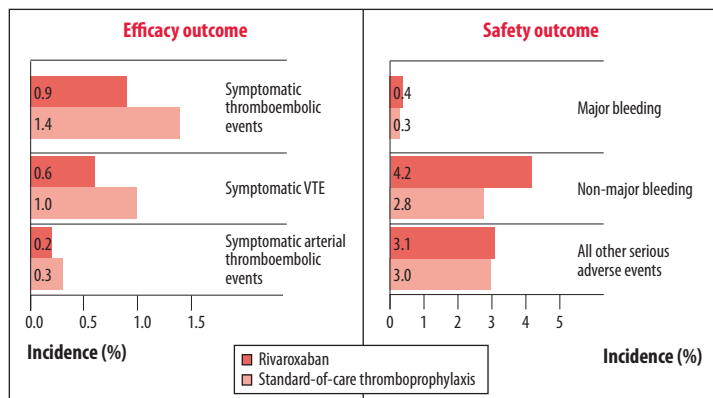
17413 patients, aged 18 years or older, who were to undergo hip or knee replacement surgery (or hip fracture surgery where rivaroxaban is indicated) and in whom a decision on pharmacological thromboprophylaxis had already been made

Results

Efficacy outcome: In the safety population (17413 patients), symptomatic thromboembolic events (arterial and venous) occurred in 78 of 8778 patients (0.9%) in the rivaroxaban group compared with 117 of 8635 patients (1.4%) in the standard-of-care group (OR 0.65). Patients receiving rivaroxaban had a significantly lower incidence of symptomatic VTE (0.6% vs. 1.0%) and a numerically lower incidence of arterial thromboembolic events (0.2% vs. 0.3%)

Safety outcome: Major bleeding events occurred in 0.4% of the patients treated with rivaroxaban and in 0.3% of patients given the standard-of-care thromboprophylaxis (OR 1.19). The rates of non-major bleeding were 4.2% and 2.8%, respectively. In both treatment arms similar incidences of other serious adverse events were observed. All-cause mortality was ~0.1% in both groups

During the period from hospital discharge until treatment completion, more patients in the standard-of-care group required support from general practitioners (10.3% vs. 8.7%) and nurse home visits (6.9% vs. 2.6%). Patients receiving rivaroxaban reported a higher degree of satisfaction in terms of treatment tolerability and convenience, compared with those receiving standard-of-care therapy



Summary

Efficacy: In unselected patients undergoing hip or knee surgery in routine practice, rivaroxaban was associated with a significantly lower incidence of symptomatic thromboembolic events than the current standard-of-care thromboprophylaxis

Safety: Rates of any bleeding events were increased with rivaroxaban, but major bleeding was similar between the treatment arms

References

- (1) Turpie AG, Schmidt AC, Kreutz R, Lassen MR, Jamal W, Mantovani L, Haas S. Rationale and design of XAMOS: non-interventional study of rivaroxaban for prophylaxis of venous thromboembolism after major hip and knee surgery. *Vasc Health Risk Manag* 2012;8:363-370
- (2) Turpie AG, Haas S, Kreutz R, Mantovani LG, Pattanayak CW, Holberg G, Jamal W, Schmidt A, van Eickels M, Lassen MR. A non-interventional comparison of rivaroxaban with standard of care for thromboprophylaxis after major orthopaedic surgery in 17,701 patients with propensity score adjustment. *Thromb Haemost* 2014;111:94-102; doi: 10.1160/TH13-08-0666. Epub 2013 Oct 24

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X-PLORER

Exploring the efficacy and safety of rivaroxaban to support elective percutaneous coronary intervention (2013, ongoing)

Condition

Prevention of heart attacks, stroke or cardiovascular death in patients with coronary or peripheral artery disease

Objective

To explore whether rivaroxaban, as compared to unfractionated heparin (UFH), on the background of standard dual antiplatelet therapy, can effectively suppress thrombosis and related adverse ischemic events, upon balloon inflation and stent expansion, during elective PCI, without increasing bleeding

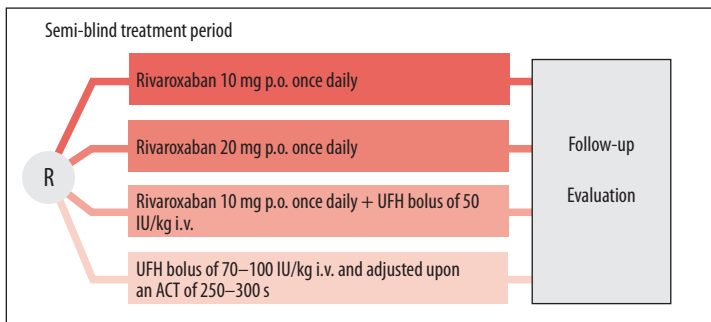
Trial design

Prospective, randomized, heparin-controlled dose-finding trial, semi-blinded design: no blinding for randomization either to rivaroxaban (one of the 3 arms) or the control (UFH) group. However, all will be blinded for the treatment dose of rivaroxaban (either 10 mg or 20 mg); the 10 mg rivaroxaban plus 50 IU UFH arm will not be blinded

Active treatment:

- Stratum 1: rivaroxaban 10 mg p.o. single dose
- Stratum 2: rivaroxaban 20 mg p.o. single dose
- Stratum 3: rivaroxaban 10 mg p.o. single dose followed by a bolus of 50 IU/kg UFH

Control treatment: UFH: 70–100 IU/kg bolus i.v. and adjusted upon activated coagulation time (ACT) of 250–300 seconds



Endpoints

Primary efficacy endpoints: percentage of subjects who

- require bail-out anticoagulant therapy in the context of an ischemic coronary event
- experience an angiographic flow limiting thrombotic event
- experience thrombus formation on the PCI equipment
- experience a myocardial infarction due to PCI

Secondary outcome measures: bleeding, composite of clinical ischemic events (all-cause death, non-fatal myocardial infarction, non-fatal stroke and target lesion revascularization)

Trial participants

106 patients ≥ 18 years with symptomatic coronary artery disease due to undergo an elective (non-emergent) PCI on one or two lesions in the native coronary vessel(s); cardiac standard troponin at baseline has to be within the normal limits

References

ClinicalTrials.gov (NCT01442792)

X-VeRT

Explore the efficacy and safety of once-daily oral rivaroxaban for the prevention of cardiovascular events in subjects with non-valvular atrial fibrillation scheduled for cardioversion (2013, ongoing)

Condition

Prevention of cardiovascular events in patients with non-valvular atrial fibrillation scheduled for cardioversion

Objective

To explore whether rivaroxaban, as compared to vitamin K antagonists (VKA), can effectively prevent cardiovascular events in patients with non-valvular AF undergoing cardioversion

Trial design

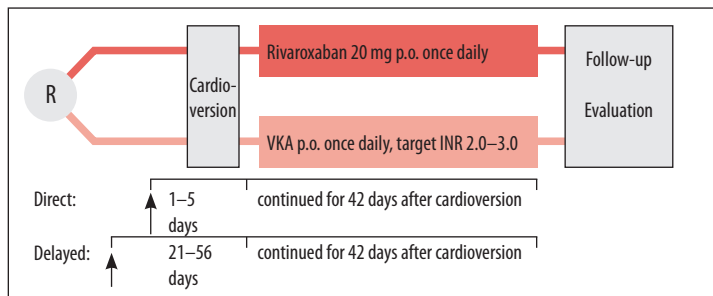
Prospective, randomized, open-label, parallel-group, active-controlled phase III study

Active treatment: rivaroxaban 20 mg p.o. once daily, 15 mg once daily in patients with moderate renal impairment

Control treatment: VKA orally once daily, titrated to a target international normalized ratio (INR) of 2.0–3.0. The VKA type (eg, warfarin, acenocoumarol, phenprocoumon, fluindione, etc) will be assigned by the investigator according to local treatment standards

Duration of anticoagulant treatment depends on strategy:

- Direct cardioversion strategy if sufficient anticoagulation is proven during the last 21 days prior to randomization: rivaroxaban/VKA for 1–5 days before cardioversion and continued for 42 days after the cardioversion
- Delayed cardioversion strategy if sufficient anticoagulation is not proven during the last 21 days prior to randomization: rivaroxaban/VKA for at least 21 (+4) to a maximum of 56 (+4) days prior to planned cardioversion and continued for 42 days after the cardioversion



Endpoints

Primary efficacy endpoint: composite of stroke, transient ischemic attack, non-central nervous system systemic embolism, myocardial infarction and cardiovascular death

Primary safety endpoint: major bleedings

Secondary outcome measures: number of strokes, transient ischemic attacks, non-central nervous system systemic embolisms, myocardial infarctions, cardiovascular deaths, all-cause mortality, major and non-major bleeding events

Trial participants

~1,500 patients ≥ 18 years with hemodynamically stable non-valvular atrial fibrillation longer than 48 hours or of unknown duration, scheduled for cardioversion (electrical or pharmacological)

References

ClinicalTrials.gov (NCT01674647)

Index of anticoagulants

(given as active treatment in clinical studies covered in this book)

A

Acenocoumarol

- DVT treatment and secondary prevention 51
- PE treatment and secondary prevention 46

Apixaban

- ACS treatment and secondary prevention 25, 27
- Long-term prevention of VTE recurrence 23
- Stroke prevention in AF 31, 40
- VTE prophylaxis after hip replacement 11
- VTE prophylaxis after knee arthroplasty 7, 9
- VTE prophylaxis in acute medical illness 5
- VTE treatment and secondary prevention 21

ASA (acetylsalicylic acid)

- ACS treatment and secondary prevention 29, 33, 55, 60, 127
- Stroke prevention in AF 1, 3, 13, 15, 70, 166
- Treatment of unstable CAD 212
- VTE prophylaxis after PCI 166

B

Betrixaban

- Stroke prevention in AF 102

C

Clopidogrel

- Stroke prevention in AF 1, 166
- Prevention of vascular events in AF 3
- VTE prophylaxis after PCI 166, 267

D

Dabigatran

- ACS treatment and secondary prevention 194
- Long-term prevention of VTE recurrence 200, 210
- Stroke prevention after radiofrequency ablation of AF 67
- Stroke prevention in AF 164, 196, 198
- VTE prophylaxis after heart valve replacement 180
- VTE prophylaxis after hip replacement 206, 208
- VTE prophylaxis after knee arthroplasty 202, 204
- VTE treatment and secondary prevention 190, 192

Dalteparin

- Treatment of unstable CAD 112, 115

Darexaban

- ACS treatment and secondary prevention 217

Dicoumarol

- Long-term prophylaxis after recurrent VTE 68

E

Edoxaban

- Stroke prevention in AF 73, 84
- VTE prophylaxis after hip replacement 239
- VTE prophylaxis after knee arthroplasty 237
- VTE treatment and secondary prevention 121

Enoxaparin

- ACS treatment and secondary prevention 125, 242
- DVT treatment and secondary prevention 136
- Prevention of reocclusion after STEMI 93, 104
- Treatment of CAD 96, 251
- VTE prophylaxis after hip replacement 87, 168
- VTE prophylaxis after knee arthroplasty 89
- VTE prophylaxis in acute medical illness 144
- VTE treatment and secondary prevention 91

F

Fluindione

- Stroke prevention in AF 106

Fondaparinux

- DVT treatment and secondary prevention 140
- PCI treatment and secondary prevention 152
- PE treatment and secondary prevention 142
- Prevention of reocclusion after STEMI 154
- VTE prophylaxis after hip replacement 160
- VTE prophylaxis after knee surgery 158
- VTE prophylaxis after surgery for hip fracture 162

I

Idrabiotaparinux

- PE treatment and secondary prevention 57
- Stroke prevention in AF 50

Idraparinux

- Extended VTE prophylaxis 256
- DVT treatment and secondary prevention 253
- PE treatment and secondary prevention 253
- Stroke prevention in AF 17

N

Nadroparin

- DVT treatment and secondary prevention 172, 247
- Treatment of unstable CAD 110

O

Otamixaban

- ACS treatment and secondary prevention 222, 244

R

Reviparin

- VTE prophylaxis after hip replacement 220
- VTE treatment and secondary prevention 64

Rivaroxaban

- ACS treatment and secondary prevention 35, 37
- DVT treatment and secondary prevention 75
- Long-term prevention of VTE recurrence 77
- PE treatment and secondary prevention 79
- Prevention of cardiac events in patients with CAD or PAD 66
- Stroke prevention after catheter ablation of AF 258
- Stroke prevention in AF 130, 166, 214

- SVT treatment 241
- VTE prophylaxis after hip replacement 182, 184, 269
- VTE prophylaxis after knee arthroplasty 186, 188, 269
- VTE prophylaxis after PCI 166, 272
- VTE prophylaxis in acute medical illness 138
- VTE prophylaxis in AF patients scheduled for cardioversion 274
- VTE treatment and secondary prevention 81

S

Streptokinase

- Treatment of acute MI 127

T

Tinzaparin

- DVT treatment and secondary prevention 19
- PE treatment and secondary prevention 249

U

UFH (unfractionated heparin)

- ACS treatment and secondary prevention 125
- DVT treatment and secondary prevention 51, 123
- PE treatment and secondary prevention 46
- Prevention of reocclusion after fibrinolysis for STEMI 29
- Target aPTT for VTE treatment 48
- Treatment of unstable CAD 212
- VTE treatment and secondary prevention 108, 117, 134, 178

W

Warfarin

- ACS treatment and secondary prevention 33
 - Genotype-guided dosing 62, 100
 - Long-term prevention of recurrent idiopathic DVT 263
 - Long-term prevention of recurrent idiopathic VTE 132
 - Long-term prevention of recurrent PE 265
 - Long-term prophylaxis after recurrent VTE 68
 - MI treatment and secondary prevention 55, 60, 261
 - Prevention of reocclusion after fibrinolysis in STEMI 29
 - Stroke prevention in AF 15, 42, 44, 53, 70, 156, 225, 227, 229, 231
 - Treatment of heart failure 259
 - Treatment of unstable CAD 148, 150
 - VTE prophylaxis after surgery for hip fracture 170
 - VTE treatment and secondary prevention 119, 174
- ### Watchman device
- Stroke prevention in AF 176

X

Ximelagatran

- MI treatment and secondary prevention 98
- Stroke prevention in AF 233, 235

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