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RUBY-1
At the heart of ACS patient care

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Ruby-1
Safety, Tolerability and Efficacy of Darexaban (YM150) in Patients with Acute Coronary Syndrome: a Phase II Study

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Gregory YH Lip, Shamir R Mehta, Ronny W Renfurm, Christopher B Granger, on behalf of the Ruby-1 investigators

ClinicalTrials.gov Identifier: NCT00994292

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

GROUPE HOSPITALIER BICHAT-CLAUDE BERNARD

Ph. Gabriel Steg - Disclosures

- **Research grant**: Servier
- **Speaking or consulting**: Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi-Sankyo-Lilly, GSK, Medtronic, Merck, Otsuka, Pfizer, Roche, sanofi-aventis, Servier, The Medicines Company
- **Stockholding**: Aterovax

The RUBY-1 trial was supported and funded by ASTELLAS Pharma, Leiderdorp, The Netherlands

Enrique Gurfinkel (1957–2011)

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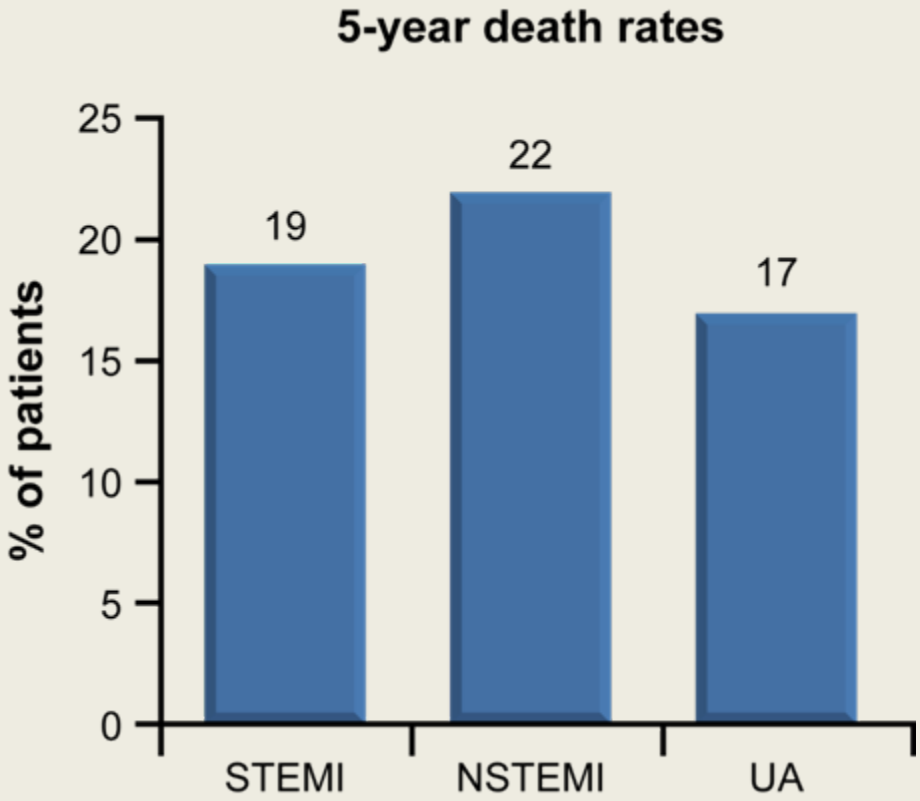
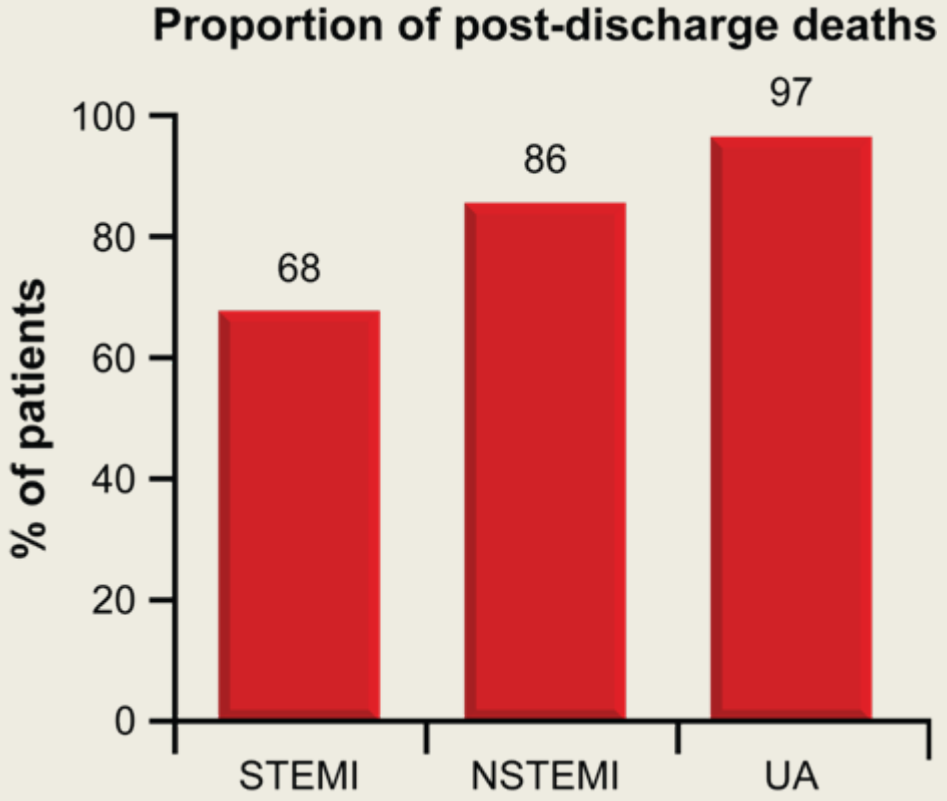
Long-term event rates post ACS

The UK–Belgian GRACE experience





European Heart Journal

Fox KAA, et al. *Eur Heart J* 2010;**31**:2755–2764

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Acute Coronary Syndrome and Oral Anticoagulation

- The management of acute coronary syndrome (ACS) has improved considerably over the past decades, leading to a substantial decline in morbidity and mortality[1]

- Guidelines from the European Society of Cardiology[2,3] and the American College of Cardiology/American Heart Association[4–6] recommend continuation of dual antiplatelet therapy (acetylsalicylic acid and clopidogrel) for up to 1 year after an ACS event

- Despite potent dual antiplatelet therapy, the recurrence of ischaemic events after an ACS event remains high, up to 9.1% at 6 months[7]

- Great interest has been directed towards new oral anticoagulants, such as direct thrombin inhibitors and factor Xa inhibitors[8,9]

[1]Fox KA, et al. *JAMA* 2007;**297**:1892–1900
[2]Van de Werf F, et al. *Eur Heart J* 2008;**29**:2909–2945
[3]Bassand JP, et al. *Eur Heart J* 2007;**28**:1598–1660
[4]Antman EM, et al. *J Am Coll Cardiol* 2004;**44**:E1–E211
[5]Anderson JL, et al. *J Am Coll Cardiol* 2007;**50**:e1–e157
[6] Anderson JL, et al. *Circulation* 2011;1**23**:e426–e579
[7]Fox KA, et al. *BMJ* 2006;**33**:1091
[8]Garcia D, et al. *Blood* 2010;**115**: 5–20
[9]Turpie AGG. *Eur Heart J* 2007; **29**:155–165

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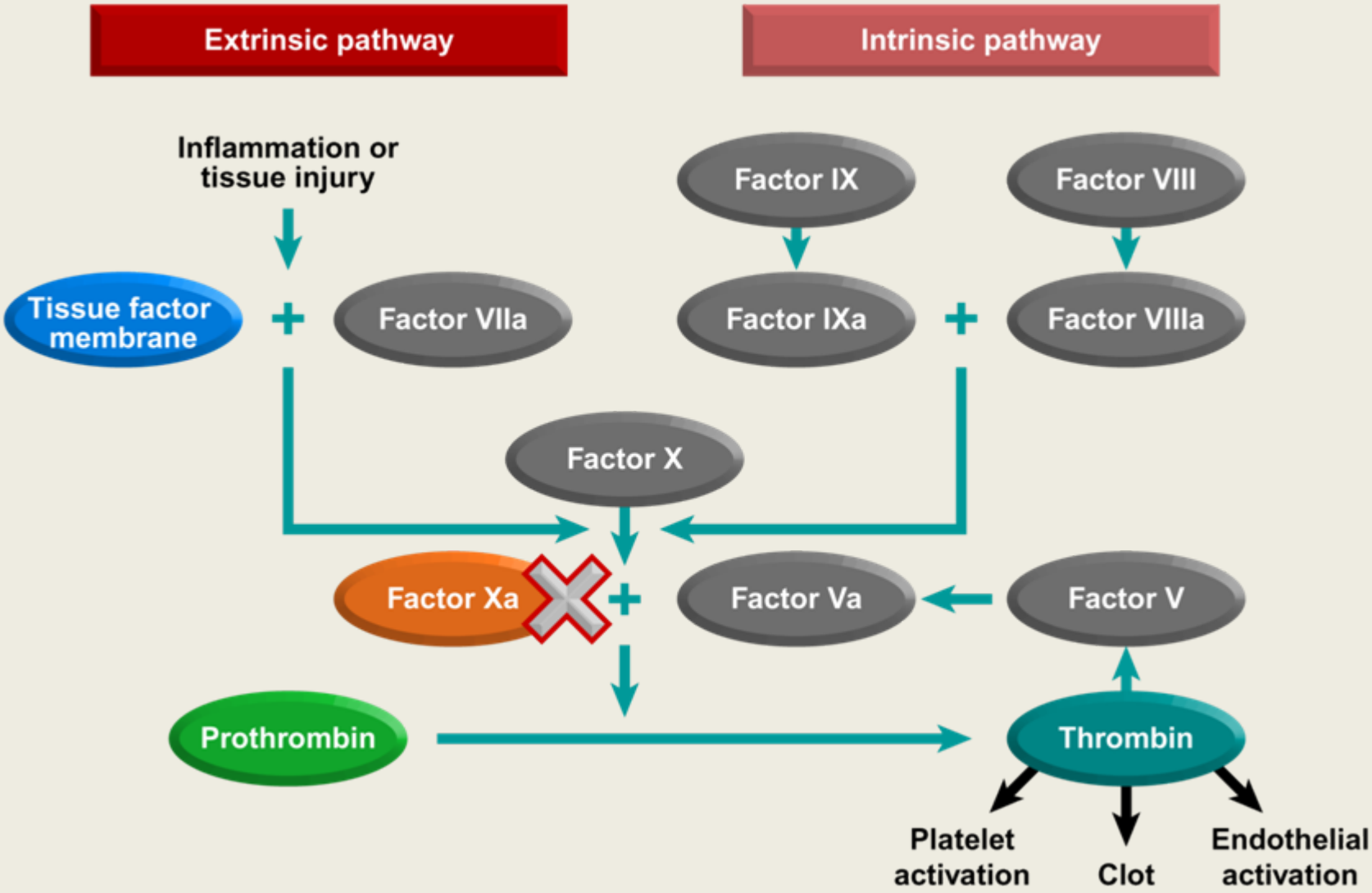
Darexaban: Direct Factor Xa Inhibitor



Turpie AG. *Arterioscler Thromb Vasc Biol* 2007;**27**:1238–1247

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Profile of Darexaban (YM150)

Darexaban is a **direct factor Xa inhibitor** with[1–7]:

- Rapid absorption
- Rapid and almost complete conversion to darexaban glucuronide by UGTs, as potent as darexaban, the main active moiety
- Peak concentration occurs at 1–1.5 hours post-dose
- Terminal half-life is 14−18 hours
- Balanced excretion routes (renal/faecal: 50/50%)
- Strong PK/PD relationship, unaffected by renal and hepatic impairment
- No DDIs with CYP3A4/P-glycoprotein inhibitors and inducers
- No clinically relevant DDIs with ASA, ASA + clopidogrel, or naproxen
- Minimal food interaction

[1]Iwatsuki Y, et al. *Blood (ASH Annual Meeting Abstracts)* 2006;108:Abstract 911;
[2]Kaku S, et al. *Blood (ASH Annual Meeting Abstracts)* 2007;110:Abstract 3153;
[3]Saitoh M, et al. *Blood (ASH Annual Meeting Abstracts)* 2007;110:Abstract 3155;
[4]Groenendaal D, et al. *Blood (ASH Annual Meeting Abstracts)* 2010; 116:Abstract 3323;
[5]Groenendaal D, et al. Poster P-TU-163; ISTH 2011, July 23–28, 2011, Kyoto, Japan;
[6]Heeringa M, et al. Poster P-TU-164; ISTH 2011, July 23–28, 2011, Kyoto, Japan;
[7] Shiraga T, et al. *Drug Metab Rev* 2011;43:S1

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Study Objective and Endpoints

- The primary objective was to evaluate the safety and tolerability of different doses and dose regimens of darexaban on top of standard treatment (ASA with or without clopidogrel) in the secondary prevention of ischaemic vascular events in patients with recent ACS

- The primary endpoint was the incidence of major and/or CRNM bleeding events, during the 6 months of double-blind treatment (defined using a modified ISTH definition[1])

- Secondary endpoints included the following:
    - Major bleeding events according to the TIMI bleeding definition[2]
    - Composite of all cause mortality, non-fatal myocardial infarction, non-fatal stroke and severe recurrent ischaemia

1. Schulman S, et al. *J Thromb Haemost* 2005;**3**:692–694
2. Cannon CP, et al. *J Am Coll Cardiol* 2001;**38**:2114–2130

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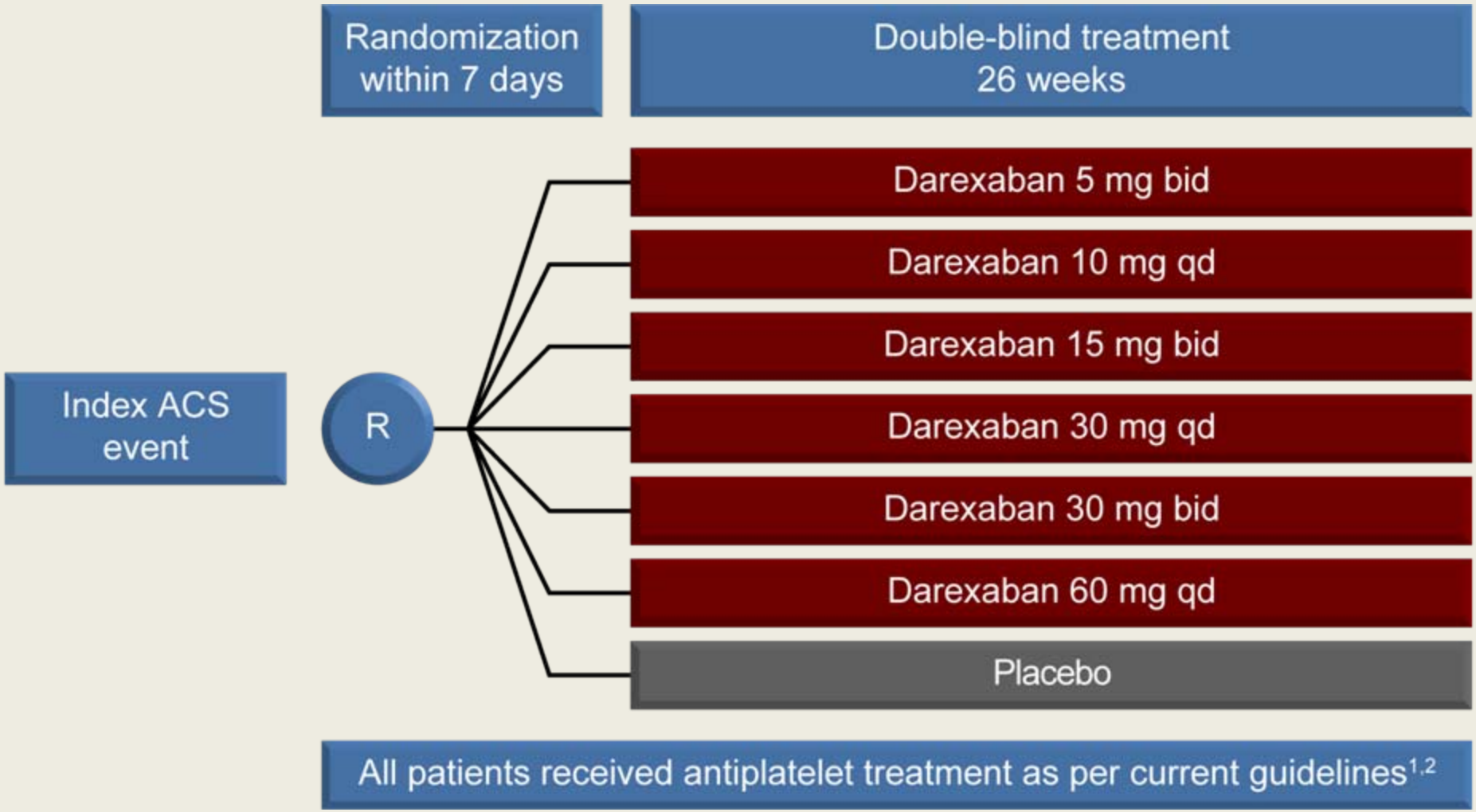
Study Design

- Prospective, randomized, double-blind, multicentre, multiple-dose, placebo-controlled, parallel-group study (26 weeks) in patients presenting with ACS

- Once stabilized, eligible patients were randomized to one of seven parallel study treatment groups

- Six dose groups of darexaban and one placebo control group were evaluated

Study Flow



ASA was used at a dose of 75–325 mg daily, as per local practice. The lower dose range of ASA (75–81 mg/day) was recommended, or clopidogrel 75 mg/day if ASA was contraindicated or not tolerated, or a combination of ASA 75–325 mg and clopidogrel 75 mg daily

R=randomization

1. Bassand JP, et al. *Eur Heart J* 2007;**28**:1598–1660
2. Anderson JL, et al. *J Am Coll Cardiol* 2007;**50**: e1–e157

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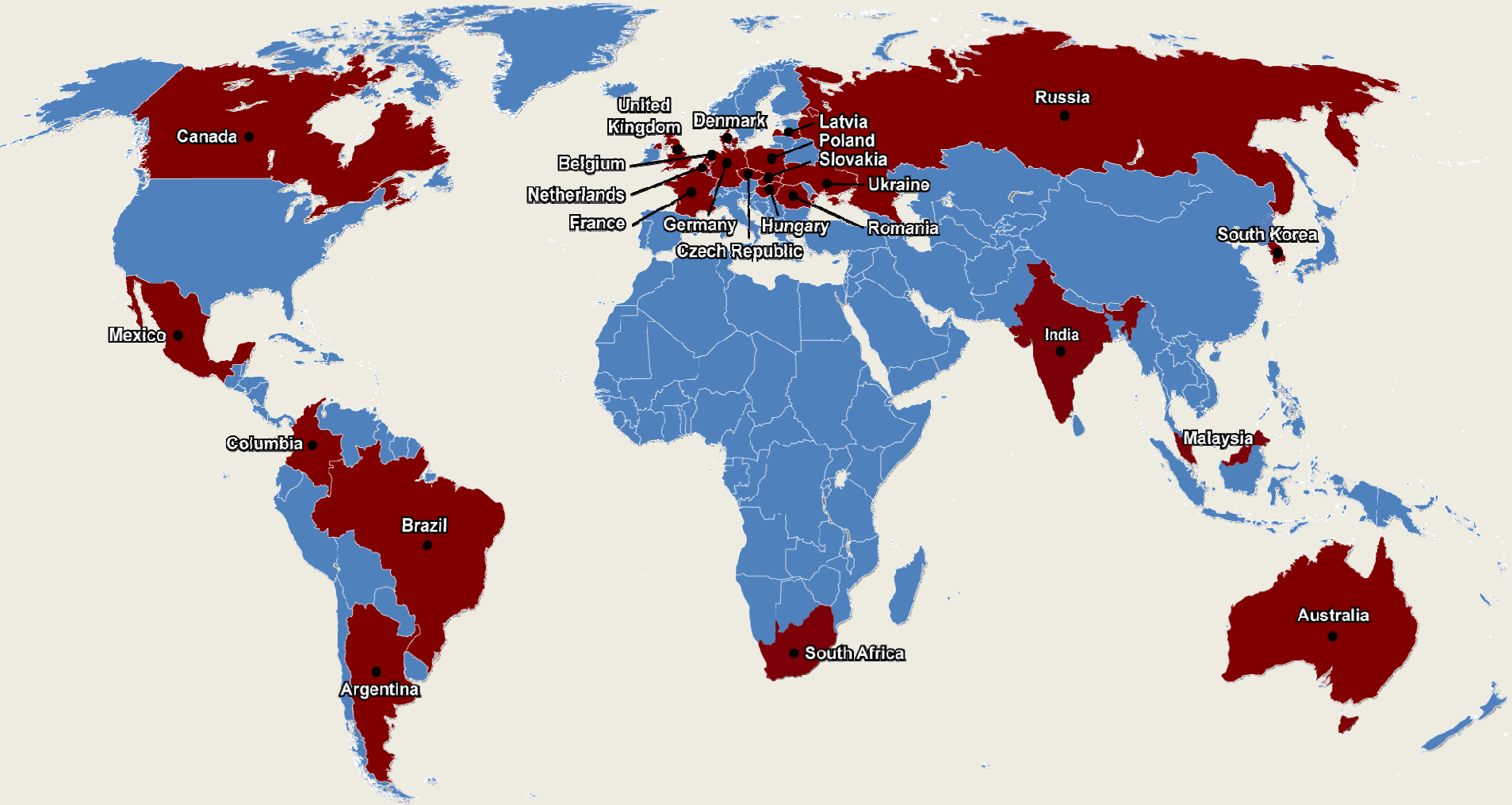
Participating Countries



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Inclusion and Exclusion Criteria

Key inclusion criteria

- Age ≥18 years old
- Diagnosis of STE-ACS or NSTE-ACS* as index event
- Elevated cardiac biomarkers (Troponin T or I, or CK-MB)
- Clinically stable and receiving current standard oral antiplatelet therapy
- Able to be randomized within 7 days after presentation

Key exclusion criteria

- Need for ongoing anticoagulant therapy, thrombolytics, glycoprotein IIb/IIIa antagonists or other antiplatelet drugs
- Patient scheduled for invasive procedures with potential for bleeding within 60 days
- Active bleeding or high risk of bleeding during the study
- Recent stroke or TIA less than 12 months prior to index event
- Persistent SBP of ≥160 mmHg and/or DBP of ≥100 mmHg at baseline
- Hepatic insufficiency or ALT >2.0x the ULN or total bilirubin >1.5x the ULN
- Renal creatinine clearance <60 mL/min

* For patients with NSTE-ACS, at least one additional risk factor for ischaemic events had to be present

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Statistical Analysis

- A sample size of 1264 randomized subjects allowed 91% power to detect a linear trend in the incidence of CRNM and major bleeding versus daily dose, using a two-sided test with 95% confidence level
- The primary analysis was performed based upon the modified intention-to-treat dataset (all randomized patients who took at least one dose of study drug)
- Primary and secondary variables were analysed while patients were on study treatment and 1 day after discontinuation of treatment
- Cumulative risk and 95% CIs at 30 days and 6 months were calculated using Kaplan–Meier estimates
- These variables were also inferentially analysed using a Cox regression model, using treatment group and antiplatelet therapy as fixed effects
- There was no adjustment for multiple comparisons

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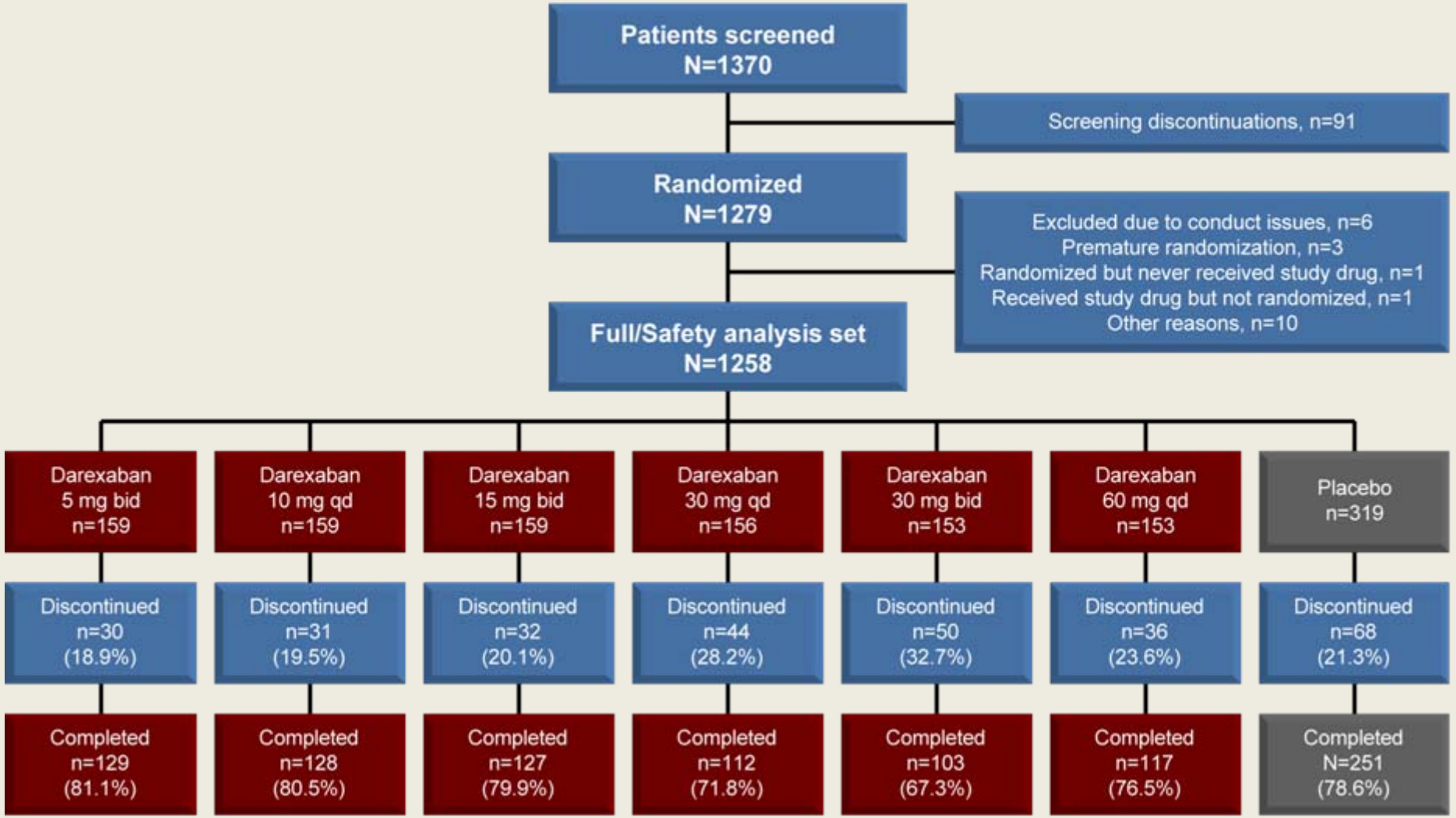
Subject Disposition



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Baseline Characteristics (I)

	Darexaban (n=939)	Placebo (n=319)
Male, n (%)	759 (80.8)	242 (75.9)
Mean age, years	56.6	57.5
Primary diagnosis for index event, n (%)		
STEMI	674 (71.8)	220 (69.0)
NSTEMI	265 (28.2)	99 (31.0)
Use of PCI for index event	703 (74.9)	235 (73.7)
Standard antiplatelet therapy, n (%)		
With clopidogrel	906 (96.5)	309 (96.9)
Without clopidogrel	33 (3.5)	10 (3.1)
Time from index event for first dose (mean days)	4.1	4.0
GRACE risk score at presentation (evaluated population)	132.8	132.8

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Baseline Characteristics (II)

	Darexaban (n=939)	Placebo (n=319)
Hypertension, n (%)	566 (60.3)	194 (60.8)
Dyslipidaemia, n (%)	474 (50.5)	153 (47.9)
Type 2, diabetes mellitus, n (%)	217 (23.5)	60 (18.8)
Hx of prior CHF, n (%)	22 (2.3)	8 (2.5)
Hx of stroke/TIA, n (%)	31 (3.3)	6 (1.6)
Hx of prior MI, n (%)	105 (11.2)	45 (14.1)
Hx of CABG, n (%)	25 (2.7)	6 (1.9)
Hx of PCI, n (%)	10 (6.3)	25 (7.8)
Peripheral arterial disease	32 (3.4)	13 (4.0)

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Baseline Characteristics (III)

	Darexaban (n=939)	Placebo (n=319)
Premature permanent study discontinuation	223 (19.0)	68 (21.3)
Concomitant medications, n (%)		
Beta-blockers	859 (91.5)	293 (91.8)
ACE-inhibitors	731 (77.8)	248 (77.7)
Angiotensin receptor blockers	124 (13.2)	43 (13.5)
Statins	897 (95.5)	304 (95.3)
Fibrates	25 (2.7)	10 (3.1)
PPIs	336 (35.8)	99 (31.0)

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Study Discontinuations, Treatment Exposure and Compliance

- 291 patients (23.1%) discontinued treatment early
  - Adverse events – 137 patients (47.1%)
  - Withdrawal of consent – 62 patients (21.3%)
  - Lost to follow-up – 8 patients (9.3%)

- Overall mean exposure to study drug was 21.3 weeks
  - Mean exposure was 19.7–22.0 weeks in the darexaban groups
  - Mean exposure was 21.9 weeks in the placebo group

- Overall mean compliance to study drugs was 97.9%
  - Mean compliance was 95.9–99.3% in the darexaban groups
  - Mean compliance was 98.3% in the placebo group

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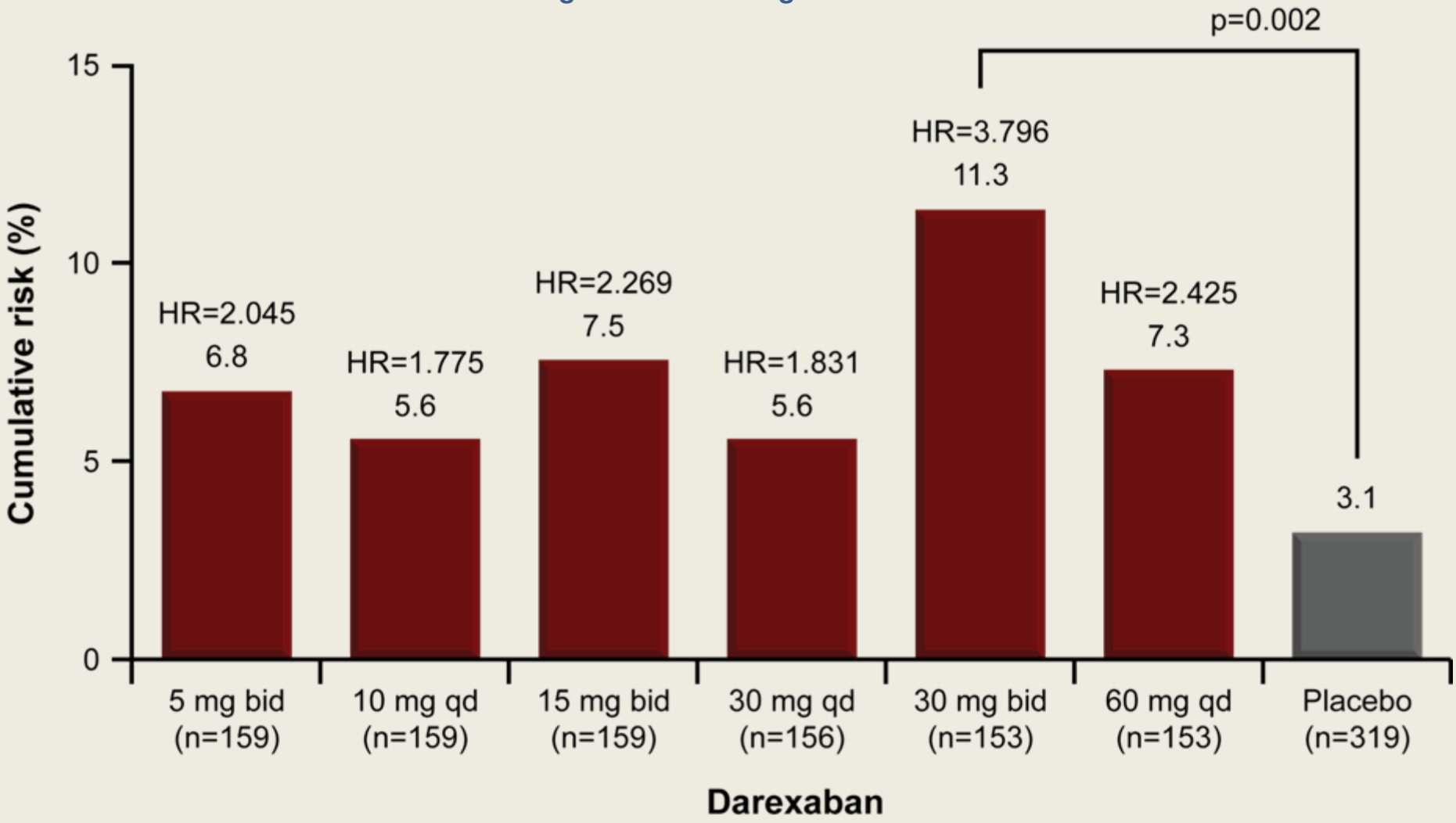
Primary Safety Endpoint: Major and CRNM Bleeding at 6 months

Using placebo as reference, there was a dose-response relationship (p=0.009) for increased bleeding with increasing darexaban dose



Kaplan–Meier analysis of cumulative risk of major and CRNM bleeding events

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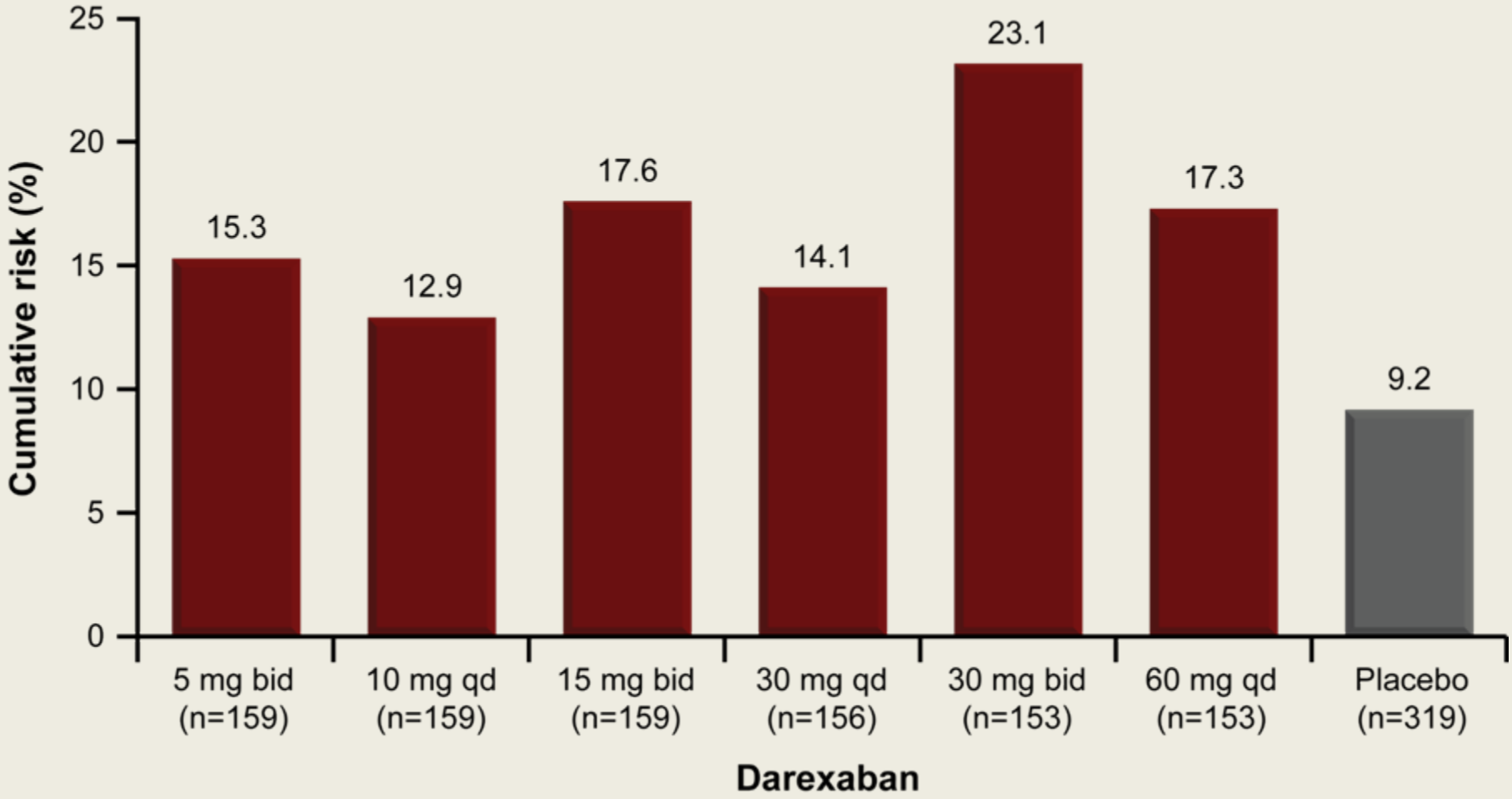
Cumulative Risk of Any Bleeding Events at 6 Months



Data based on Kaplan–Meier analysis

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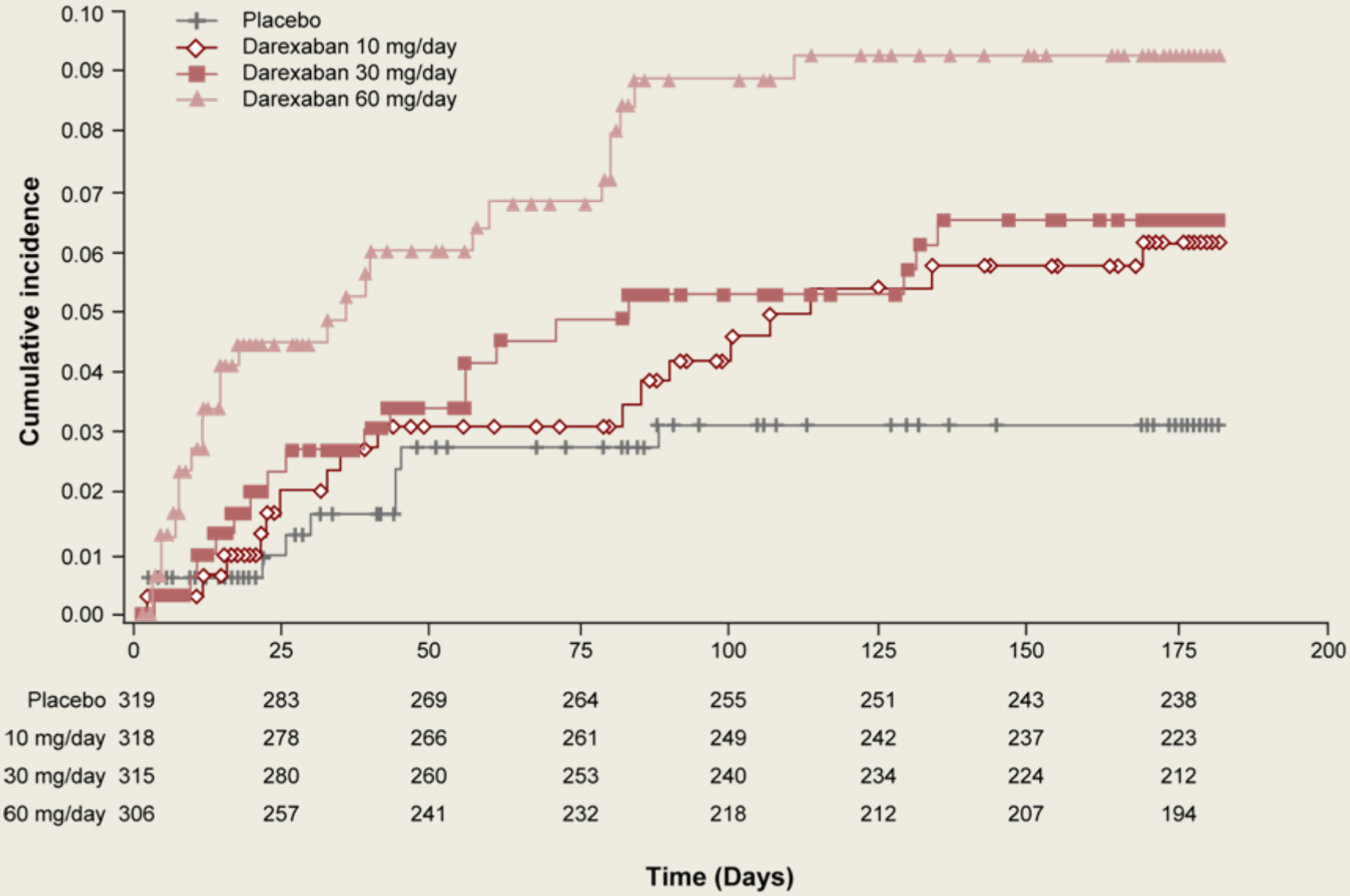
Cumulative Risk of Major and CRNM Bleeding for Darexaban Total Daily Doses at 6 Months



Cumulative incidences are calculated using Kaplan–Meier estimates and presented as relative to 1 (e.g. 0.06 represents 6%)

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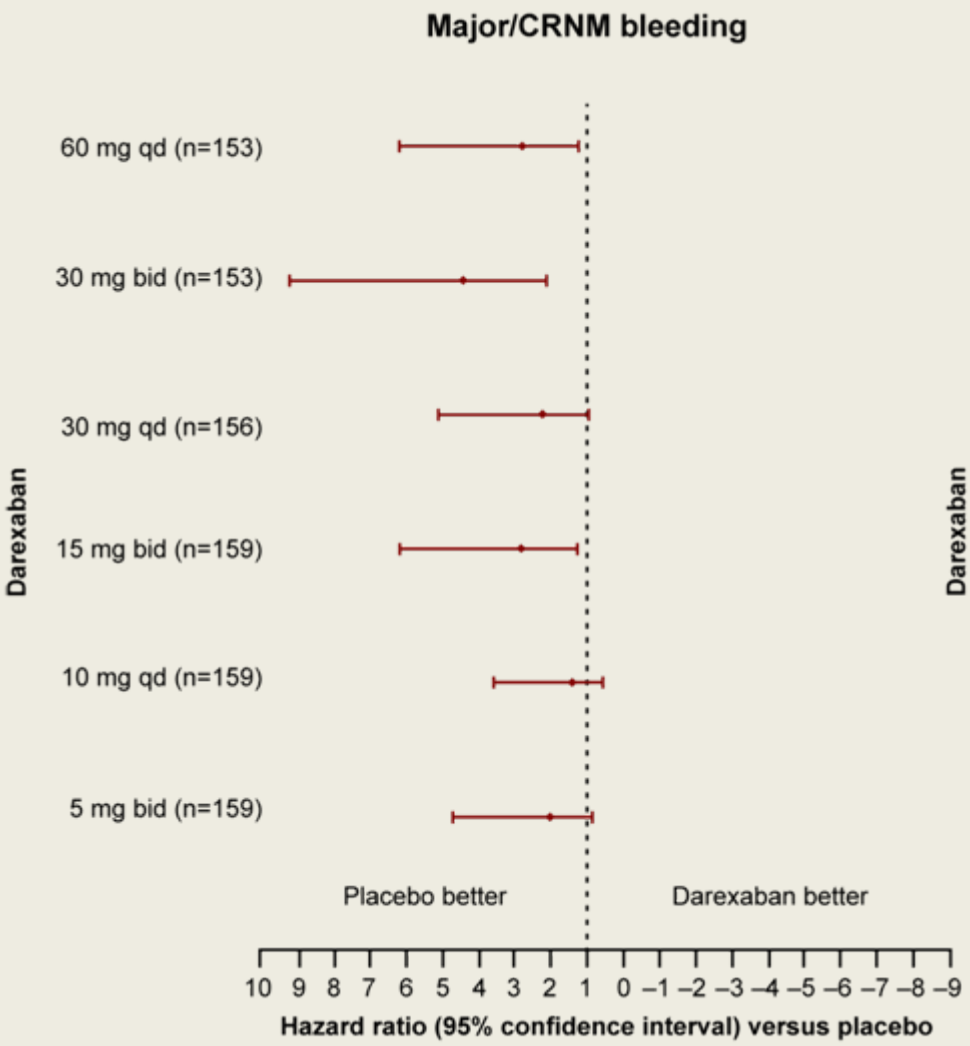
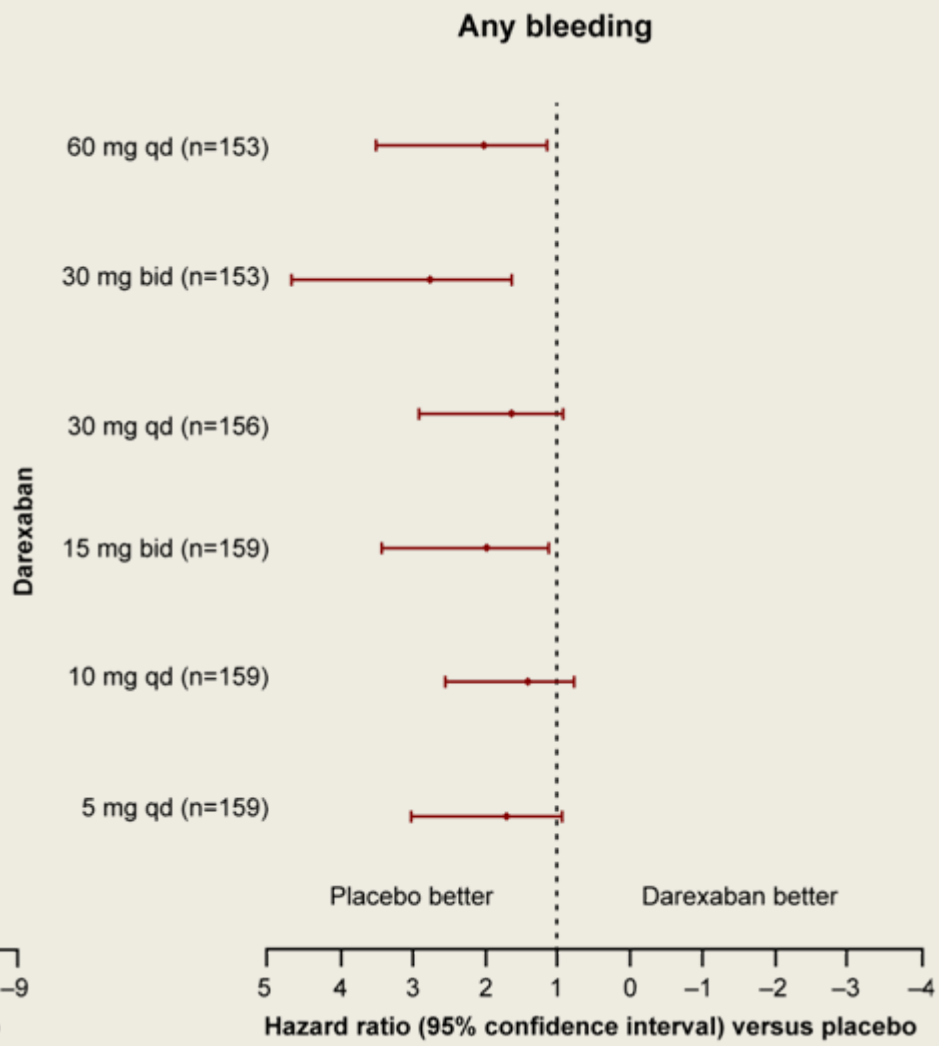
Cumulative Risk of Major and CRNM Bleeding and Any Bleeding Events at 6 Months





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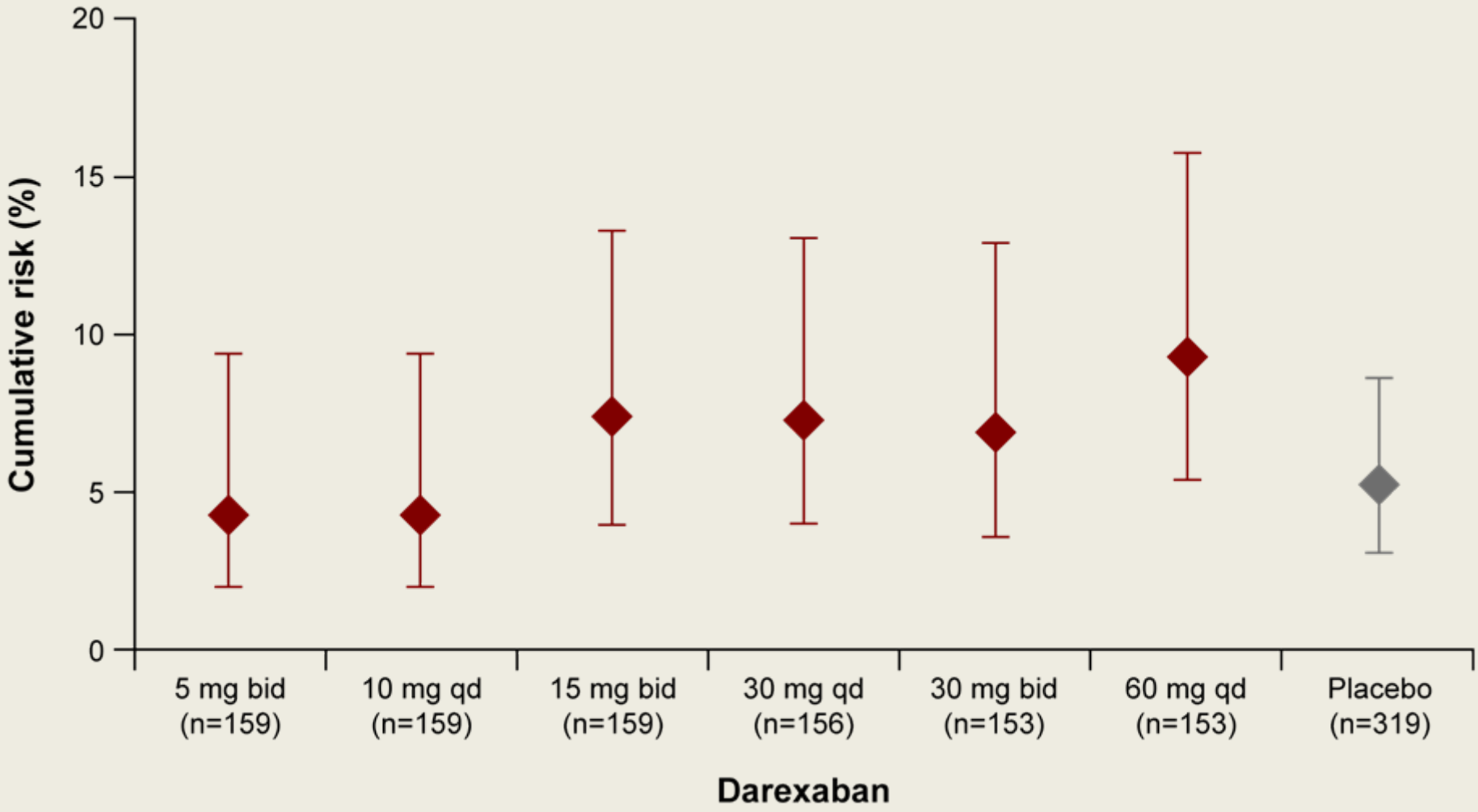
Main Secondary Endpoint: Cumulative Risk of Composite Efficacy Outcome at 6 Months



Kaplan–Meier analysis of cumulative risk of all cause mortality, non-fatal myocardial infarction, non-fatal stroke and severe recurrent ischaemia

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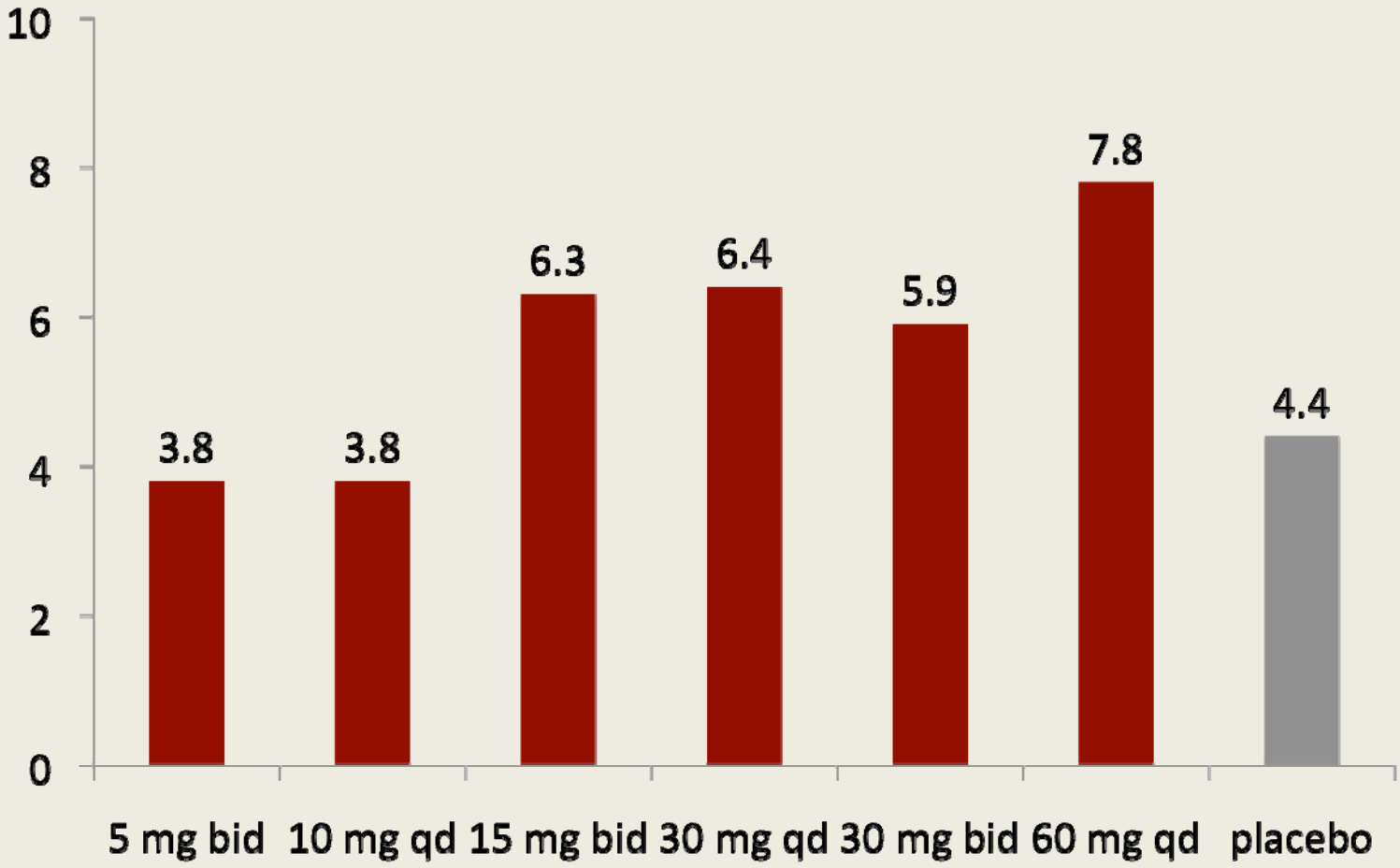
Main Secondary Endpoint: Composite Efficacy Outcome at 6 Months



Crude risk of all cause mortality, non-fatal myocardial infarction, non-fatal stroke and severe recurrent ischaemia

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Adverse Events

	Darexaban						Placebo
	5 mg bid (n=159)	10 mg qd (n=159)	15 mg bid (n=159)	30 mg qd (n=156)	30 mg bid (n=153)	60 mg qd (n=153)	(n=319)
All AEs, N (%)	100 (62.9)	102 (64.2)	100 (62.9)	96 (61.5)	101 (66.0)	99 (64.7)	181 (56.7)
Most common AEs, N (%)*							
Hypertension	13 (8.2)	9 (5.7)	6 (3.8)	6 (3.8)	9 (5.9)	8 (5.2)	16 (5.0)
Cough	7 (4.4)	11 (6.9)	5 (3.1)	6 (3.8)	6 (3.9)	3 (2.0)	11 (3.4)
Angina pectoris	7 (4.4)	5 (3.1)	4 (2.5)	4 (2.6)	4 (2.6)	9 (5.9)	9 (2.8)
Epistaxis	5 (3.1)	2 (1.3)	5 (3.1)	7 (4.5)	10 (6.5)	6 (3.9)	5 (1.6)
Chest pain	3 (1.9)	5 (3.1)	7 (4.4)	4 (2.6)	6 (3.9)	9 (5.9)	4 (1.3)
Non-cardiac chest pain	5 (3.1)	7 (4.4)	4 (2.5)	4 (2.6)	3 (2.0)	4 (2.6)	7 (2.2)
Increased blood creatinine	4 (2.5)	4 (2.5)	4 (2.5)	4 (2.6)	4 (2.6)	3 (2.0)	6 (1.9)
Haematoma	2 (1.3)	4 (2.5)	5 (3.1)	2 (1.3)	2 (1.3)	4 (2.6)	9 (2.8)
Serious AEs, N (%)	13 (8.2)	22 (13.8)	28 (17.6)	26 (16.7)	26 (17.0)	26 (17.0)	40 (12.5)
Study drug related	3 (1.9)	6 (3.8)	5 (3.1)	3 (1.9)	4 (2.6)	4 (2.6)	3 (0.9)

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Laboratory Assessments

	Darexaban						Placebo
	5 mg bid (n=159)	10 mg qd (n=159)	15 mg bid (n=159)	30 mg qd (n=156)	30 mg bid (n=153)	60 mg qd (n=153)	(n=319)
ALT or AST >3x ULN	5/143 (3.5)	4/149 (2.7)	2/148 (1.4)	1/138 (0.7)	2/139 (1.4)	2/137 (1.5)	7/290 (2.4)
ALT or AST >5x ULN	2/149 (1.3)	2/155 (1.3)	0 (0.0)	0 (0.0)	1/146 (0.0)	1/144 (0.7)	2/302 (0.7)
Total bilirubin >2x ULN	1/150 (0.7)	1/151 (0.7)	0 (0.0)	1/147 (0.7)	2/141 (1.4)	1/141 (0.7)	0 (0.0)
Total bilirubin >3x ULN	0 (0.0)	1/151 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

All data are n (%)

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Conclusions

- 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 bid
- 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
- Darexaban was well tolerated, with no signs of liver toxicity
  - ALT, AST and bilirubin levels were similar between placebo and all doses of darexaban
- Investigating the potential role of low-dose darexaban in preventing major cardiac events after ACS requires a large Phase III trial

Darexaban Global Clinical Development Program

NVAF

- **OPAL-1** (Asia/Japan) (presented ESC 2010)
- **OPAL-2** (EU/Japan/Asia)

ACS

- **RUBY-1** (EU/Asia) N=1278 (completed)
- Double-blind, placebo-controlled, Phase IIb dose ranging study

VTE prevention

- **PEARL-1 and -2** (completed)
  - Phase IIa and b in TKR
  - Results to be published Q3/4 2011
- **ONYX-1 and -2** (completed and published)
- **ONYX-3** (US/EU): (completed)
  - Phase IIb, double-blind, enoxaparin-controlled, dose-ranging in THR
  - Data presented at ISTH 2011

Published online today at http://eurheartj.oxfordjournals.org/

European Heart Journal
doi:10.1093/eurheartj/ehr334

FASTTRACK
ESC HOT LINE

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

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Received 20 July 2011; revised 3 August 2011; accepted 5 August 2011

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Acknowledgements

- **Executive Steering Committee:** Ph G Steg (Chair; France), CB Granger (USA), JW Jukema (Netherlands), GYH Lip (UK), S Mehta (Canada), RW Renfurm (non-voting; Astellas, Netherlands)
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- **Editorial assistance**: FV Gambling (Medicus International, UK)
- **Study execution and monitoring**: ICON plc (UK)
- **Study sponsorship**: Astellas, (Netherlands)