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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

Ph Gabriel Steg*, J Wouter Jukema, Gregory YH Lip, Shamir R Mehta, Ronny W Renfurm, Christopher B Granger, on behalf of the Ruby-1 investigators

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Ph. Gabriel Steg - Disclosures

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Enrique Gurfinkel (1957–2011)

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Acute Coronary Syndromes

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

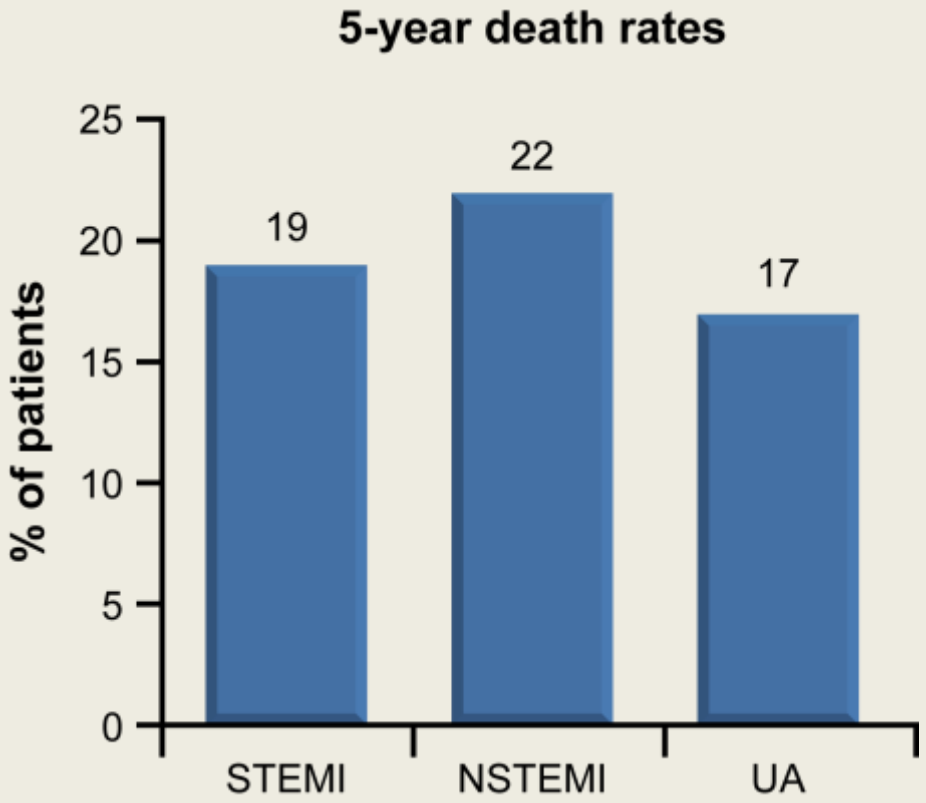
- Guidelines from the European Society of Cardiology[2,3] and the American College of Cardiology/American Heart Association[4–6] recommend continuation of dual antiplatelet therapy (acetylsalicylic acid and clopidogrel) for up to 1 year after an ACS event

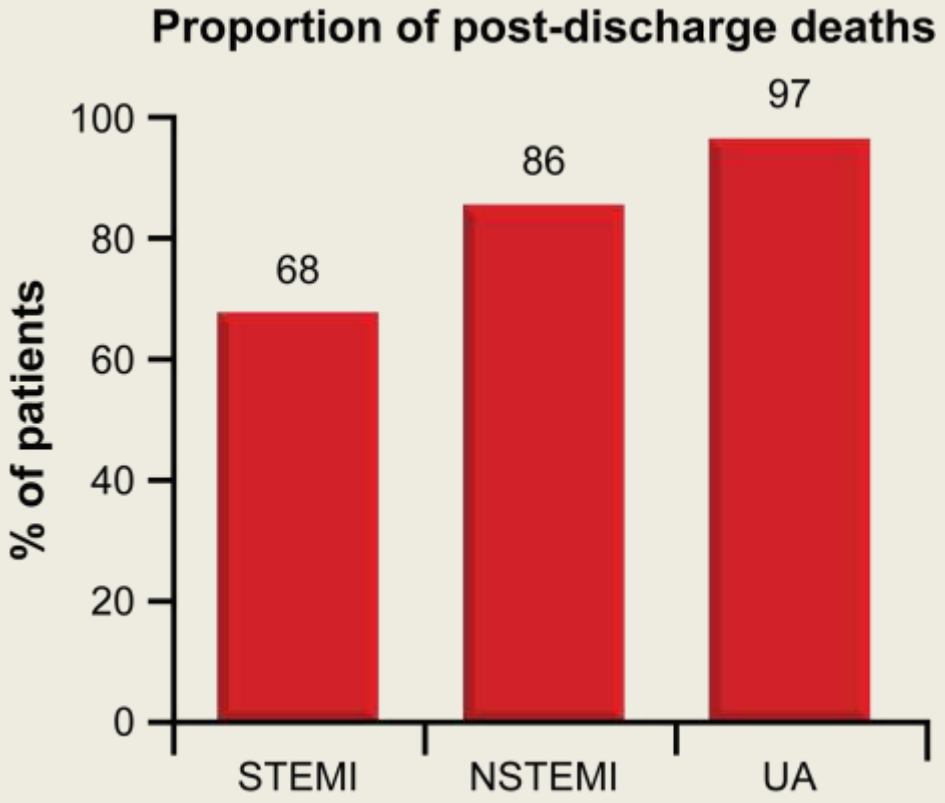
- Despite potent dual antiplatelet therapy, the recurrence of ischaemic events after an ACS event remains high, up to 9.1% at 6 months[7] and mortality up to 22% at 5 years [8].

[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]Fox KA et al. eur Heart J 2010;31:2755-64

Long-term event rates post ACS

The UK–Belgian GRACE experience

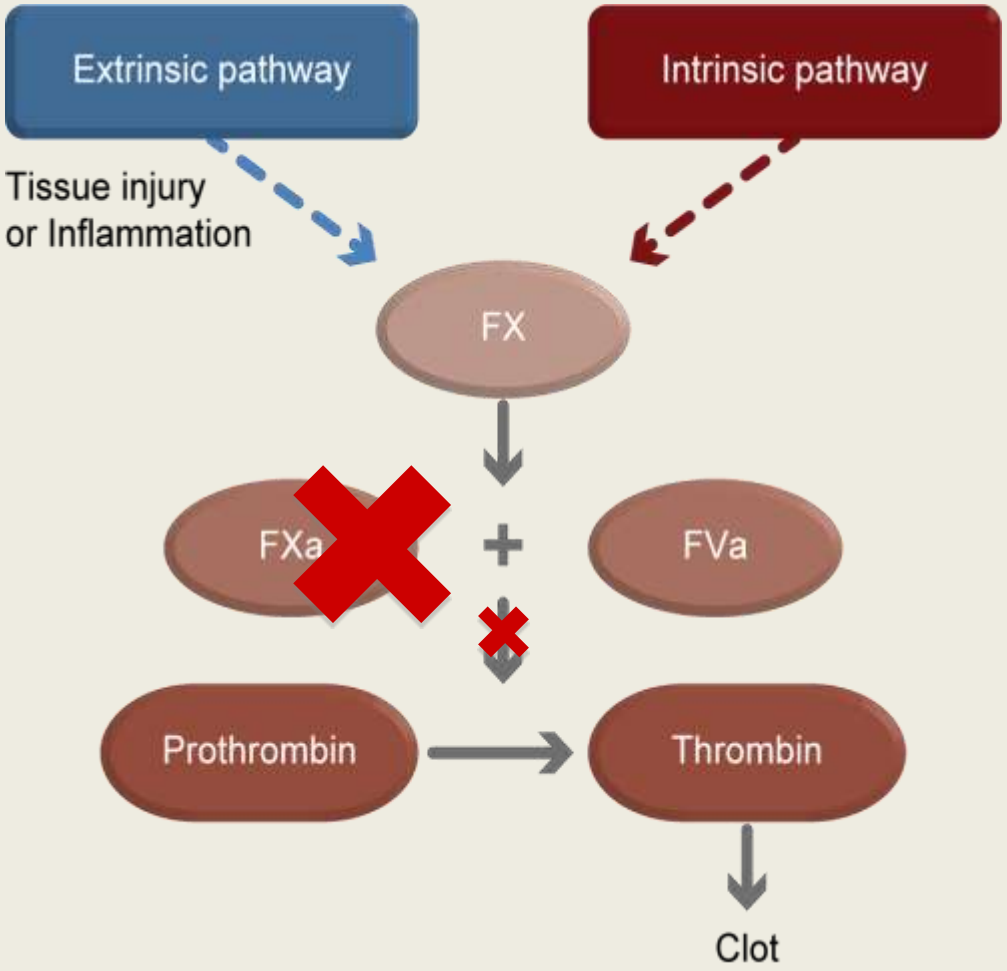




European Heart Journal

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

Darexaban



- **Darexaban (Astellas Pharma) is a novel, direct FXa inhibitor** :
  - Rapid onset of action
  - Terminal ½ life: 14-18 h
  - Predictable PK profile
    (unaffected by renal/hepatic impairment)
  - Minimal food interactions
  - No drug-drug interactions
- Darexaban is effective for the treatment of VTE
- Its efficacy in stroke prevention in AF is being explored

PK=pharmacokinetics; DDI=drug–drug interaction; VTE=venous thromboembolism; AF=atrial fibrillation

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Study Objective and Endpoints

RUBY-1 was a prospective, randomized, double-blind, multicentre, multiple-dose, placebo-controlled, parallel-group study (26 weeks) in patients with recent ACS

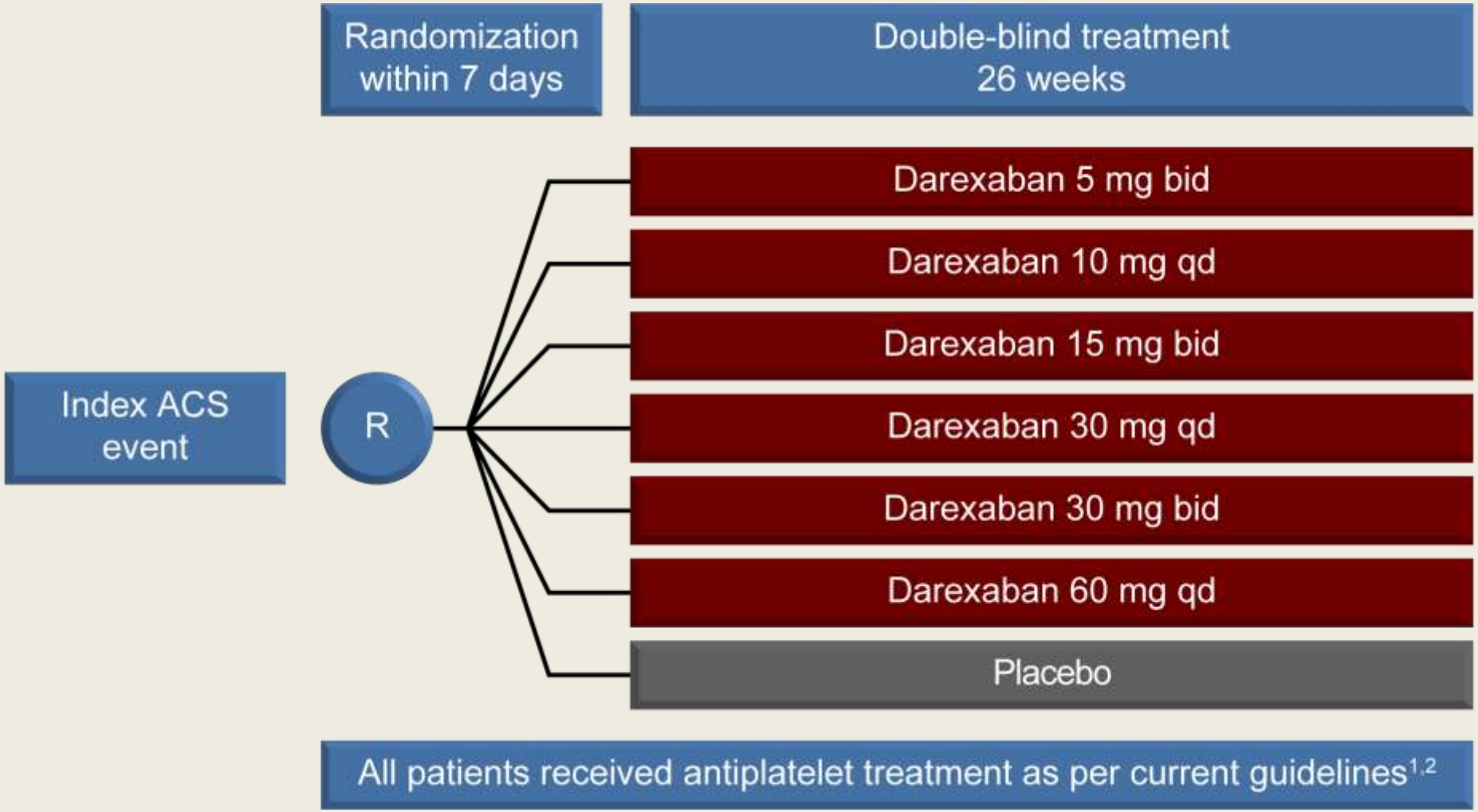
- The **primary objective** was to evaluate the safety and tolerability of different doses and dose regimens of darexaban on top of standard treatment (ASA with or without clopidogrel) in the secondary prevention of ischaemic vascular events in patients with recent ACS

- 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 :
    - 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

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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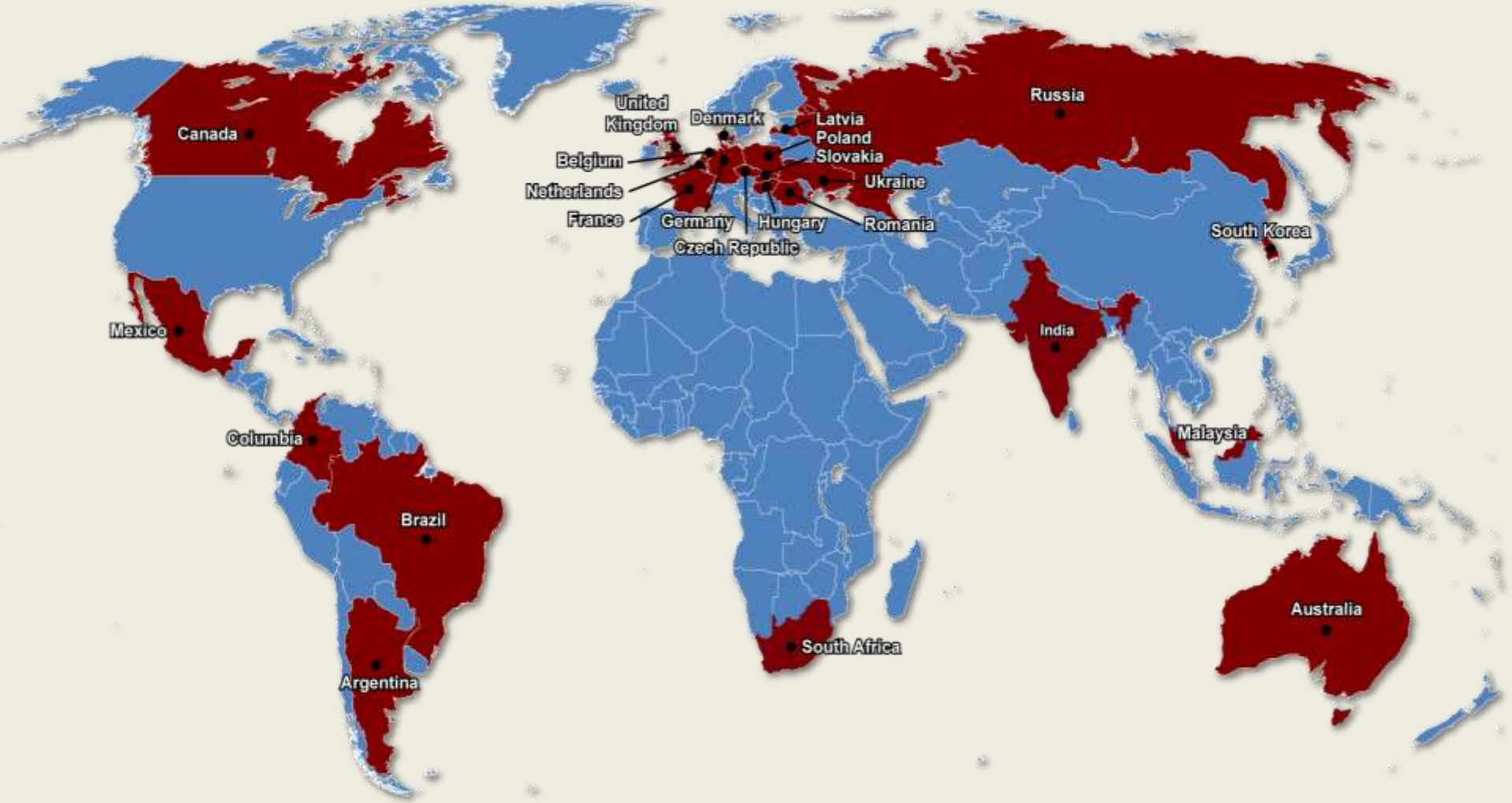
Participating Countries



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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
- There was no adjustment for multiple comparisons

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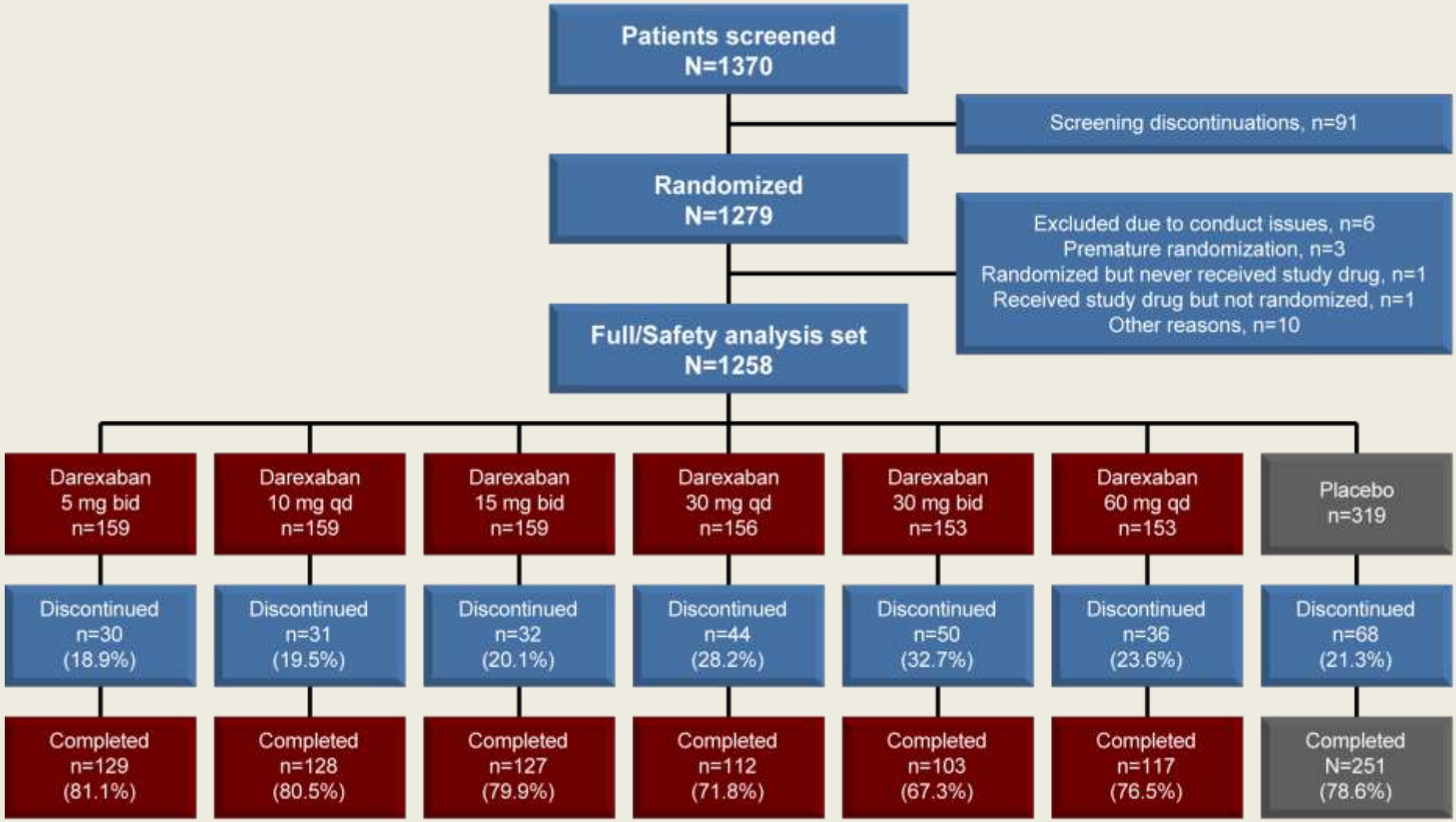
Subject Disposition



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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 (10.9%)
  - Withdrawal of consent − 62 patients (4.9%)
  - Lost to follow-up − 8 patients (0.6%)
- **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
- **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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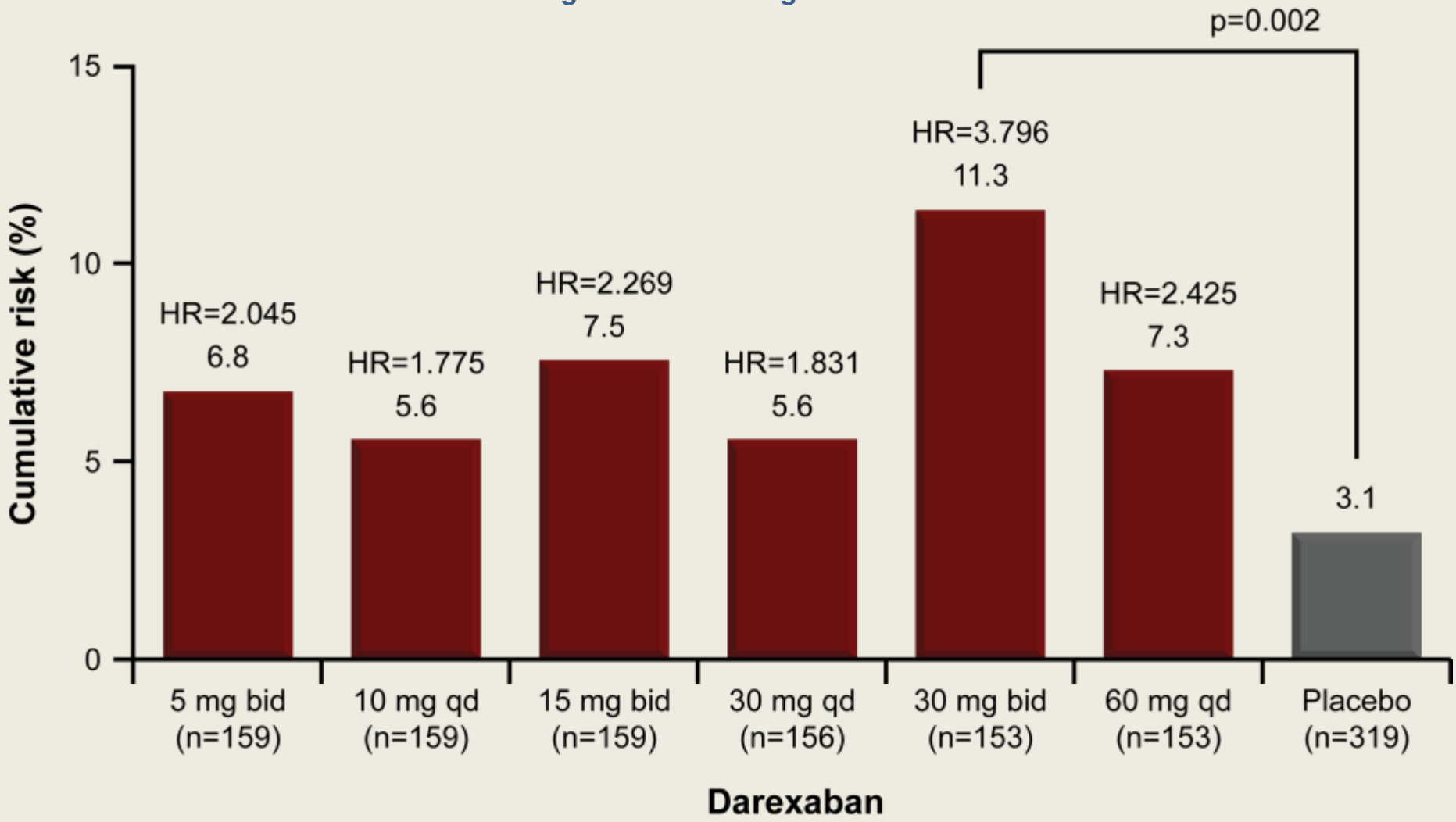
Primary Safety Endpoint: Major and CRNM Bleeding at 6 months

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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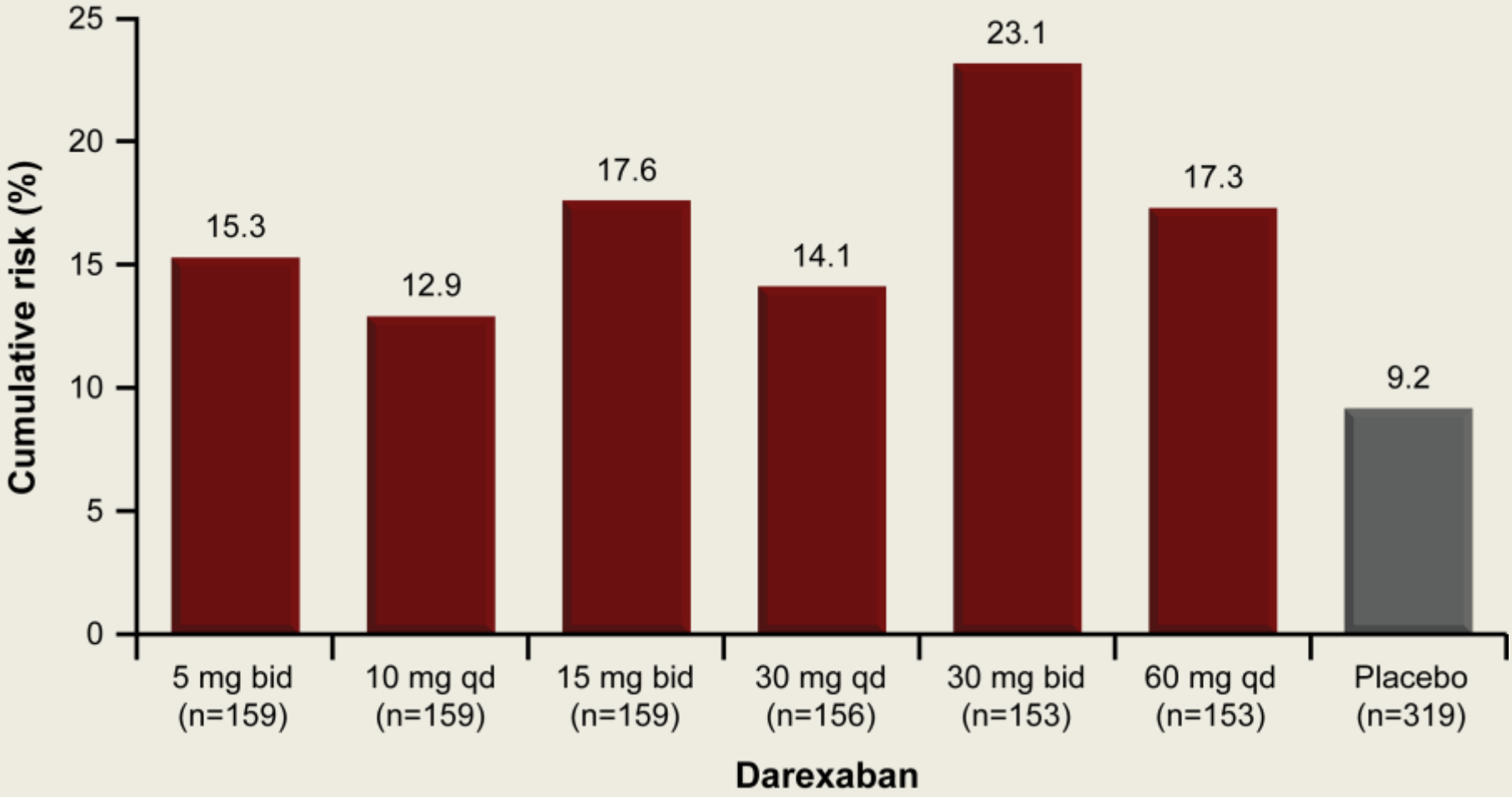
Cumulative Risk of Any Bleeding Events at 6 Months



Data based on Kaplan–Meier analysis

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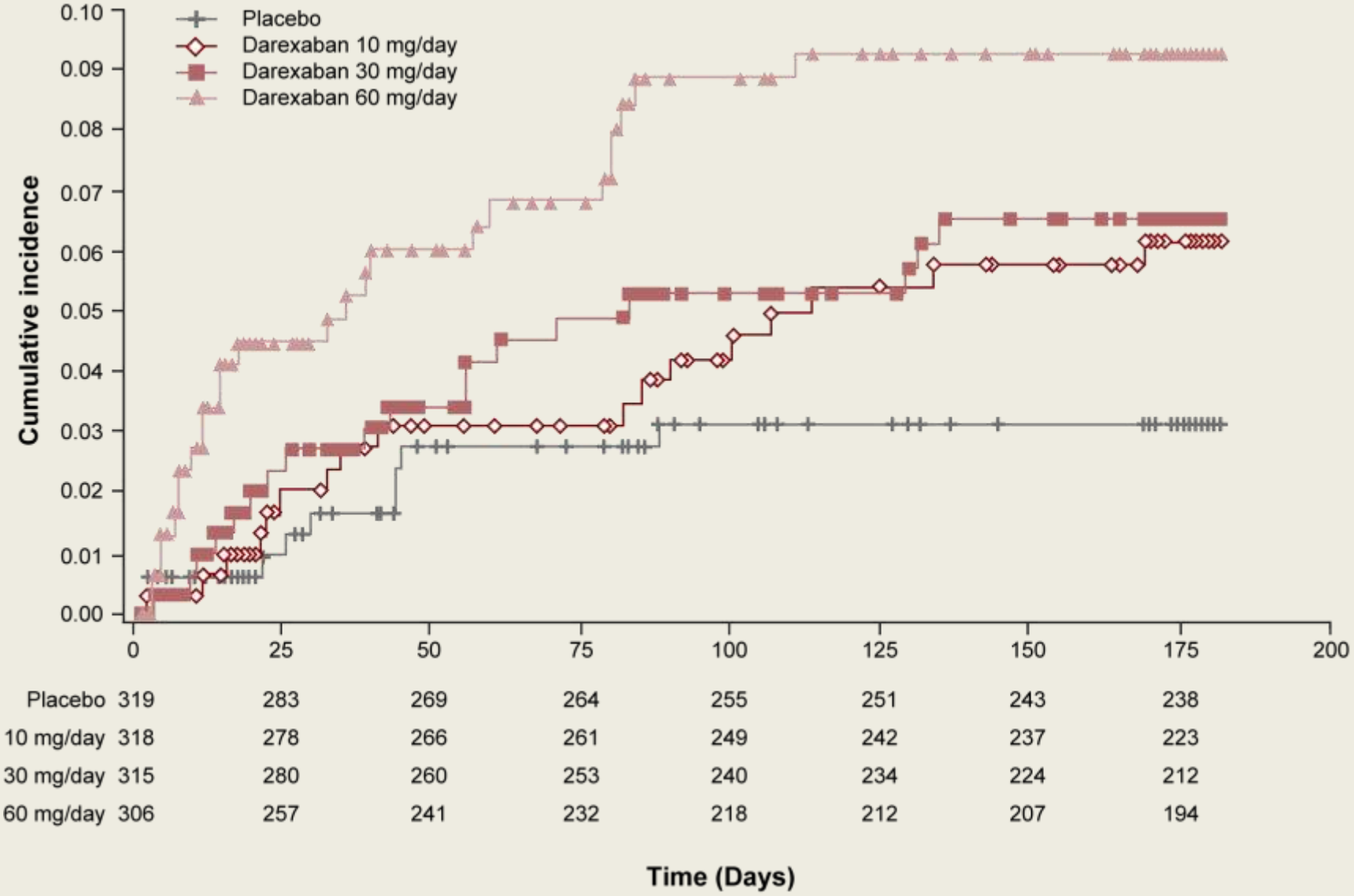
Cumulative Risk of Major and CRNM Bleeding for Darexaban Total Daily Doses at 6 Months



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

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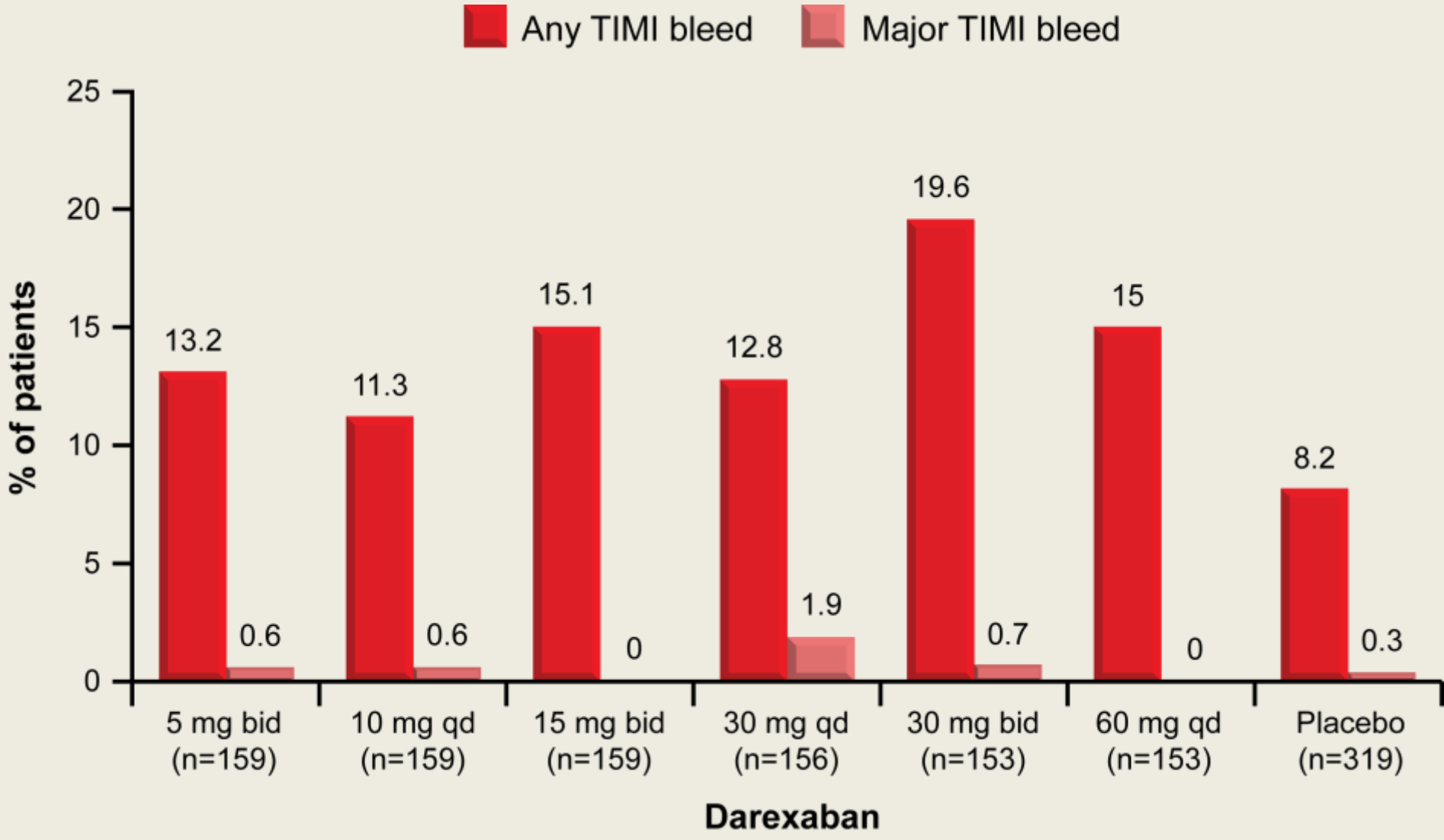
TIMI Bleeding Rates at 6 Months



All data are n (%)

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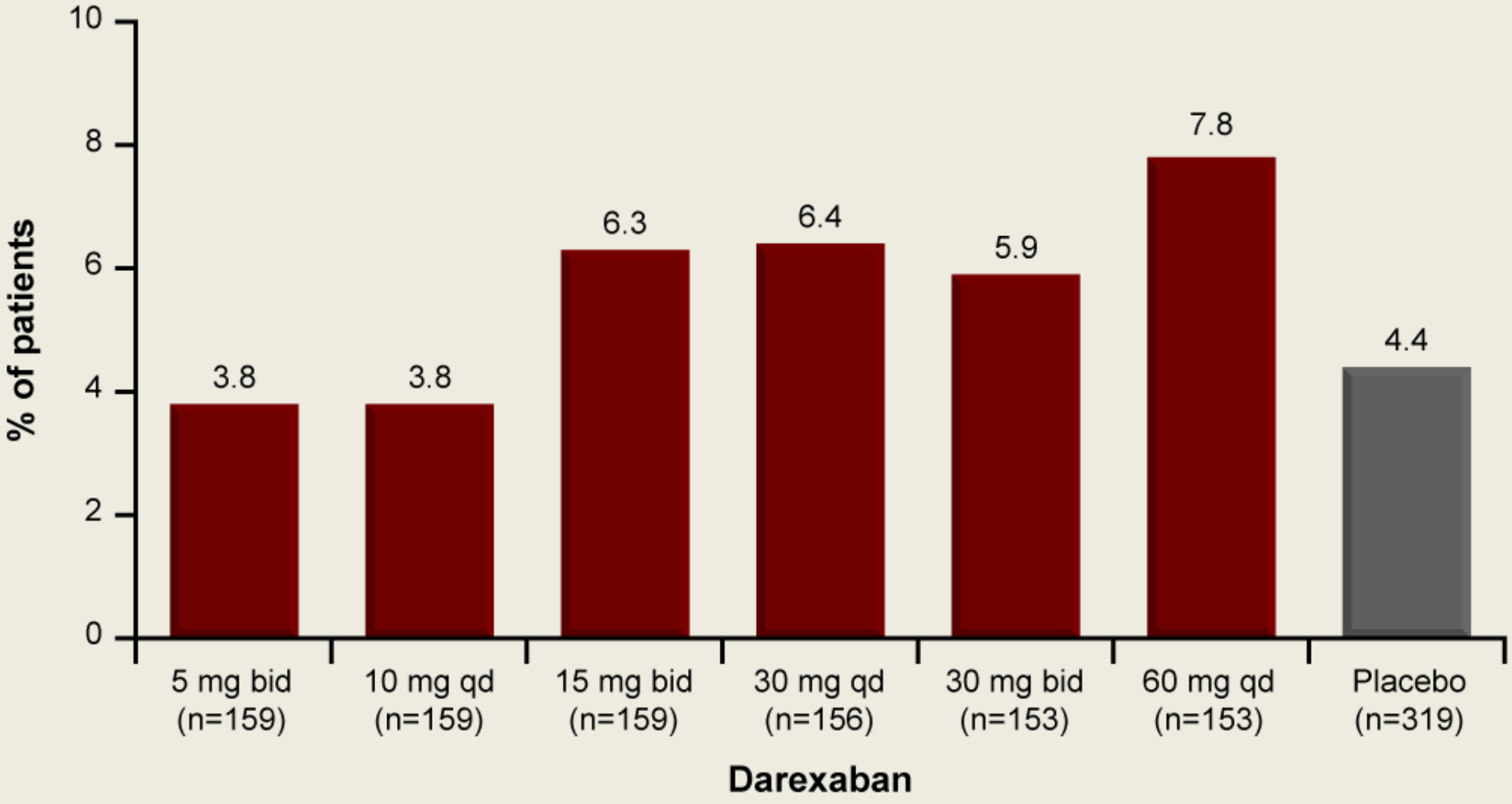
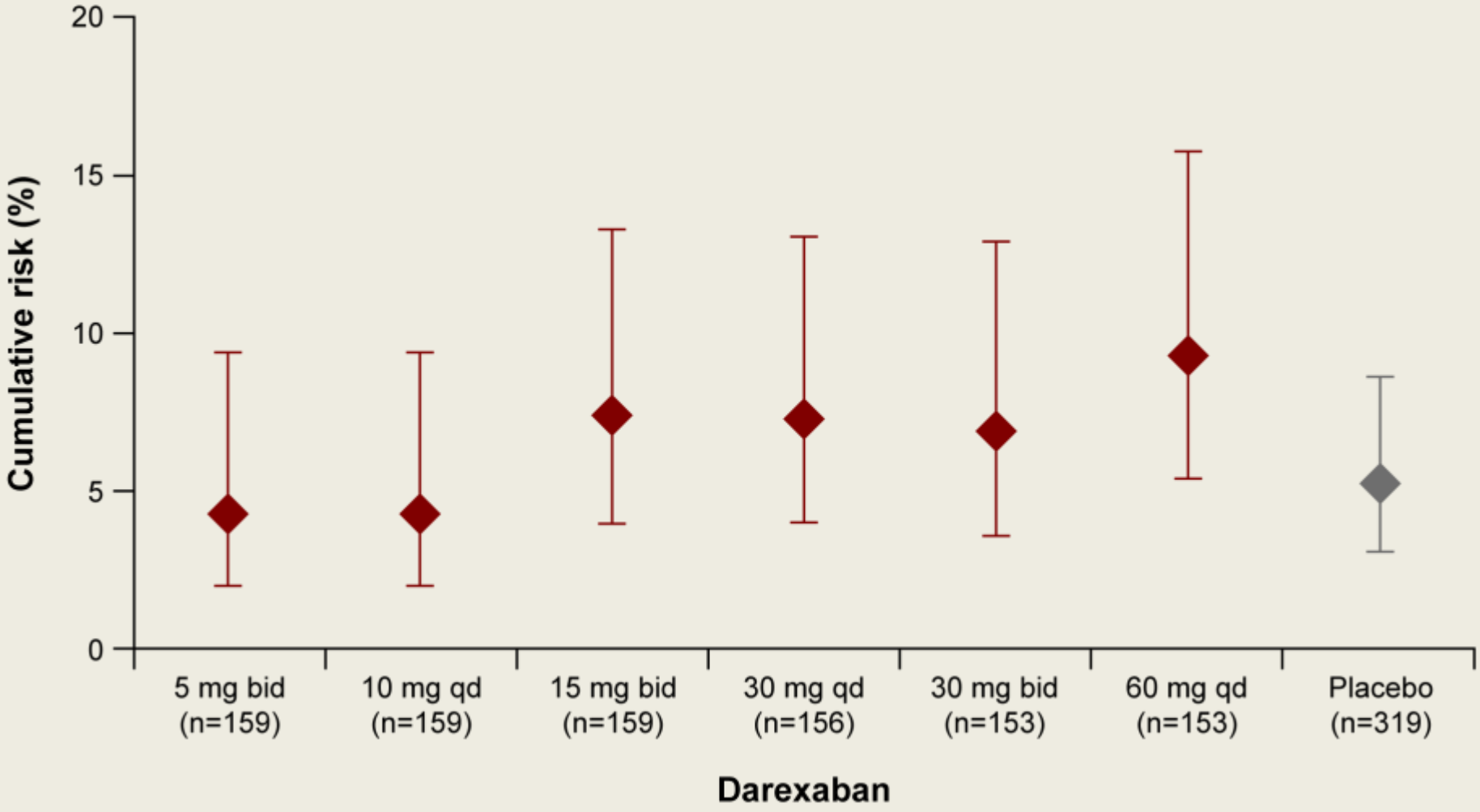
Main Secondary Endpoint: Composite Efficacy Outcome at 6 Months



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

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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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

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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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Acknowledgements

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- **Editorial assistance**: FV Gambling (Medicus International, UK)
- **Study execution and monitoring**: ICON plc (UK)
- **Study sponsorship**: Astellas, (Netherlands)

Darexaban Global Clinical Development Program

Clinical Programme: 9520 subjects

Phase 1 clin pharm studies	953 (831 received Darexaban)
Phase 2/3 studies	8567 (6473 received Darexaban)

Total exposure Darexaban = 7304 subjects

NVAF

- **OPAL-1** (Asia/Japan)
- **OPAL-2** (EU/Japan))

ACS

- **RUBY-1**

VTE prevention

- **PEARL-1 PEARL-2 & PEARL-3 (TKR)**
- **ONYX-1, ONYX-2, ONYX-3 & ONYX-4 (THR)**