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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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Aims To establish the safety, tolerability and most promising regimen of darexaban (YM150), a novel, oral, direct factor Xa inhibitor, for prevention of ischaemic events in acute coronary syndrome (ACS).

Methods In a 26-week, multi-centre, double-blind, randomized, parallel-group study, 1279 patients with recent high-risk non-ST-segment or ST-segment elevation ACS received one of six darexaban regimens: 5 mg b.i.d., 10 mg o.d., 15 mg b.i.d., 30 mg o.d., 30 mg b.i.d., or 60 mg o.d. or placebo, on top of dual antiplatelet treatment. Primary outcome was incidence of major or clinically relevant non-major bleeding events. The main efficacy outcome was a composite of death, stroke, myocardial infarction, systemic thromboembolism, and severe recurrent ischaemia.

Results Bleeding rates were numerically higher in all darexaban arms vs. placebo (pooled HR: 2.275; 95% CI: 1.13–4.60, $P = 0.022$). Using placebo as reference (bleeding rate 3.1%), there was a dose–response relationship ($P = 0.009$) for increased bleeding with increasing darexaban dose (6.2, 6.5, and 9.3% for 10, 30, and 60 mg daily, respectively), which was statistically significant for 30 mg b.i.d. ($P = 0.002$). There was no decrease (indeed a numerical increase in the 30 and 60 mg dose arms) in efficacy event rates with darexaban, but the study was underpowered for efficacy. Darexaban showed good tolerability without signs of liver toxicity.

Conclusions Darexaban when added to dual antiplatelet therapy after ACS produces an expected dose-related two- to four-fold increase in bleeding, with no other safety concerns but no signal of efficacy. Establishing the potential of low-dose darexaban in preventing major cardiac events after ACS requires a large phase III trial.
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Keywords Anticoagulant • Acute coronary syndrome • Secondary prevention • Darexaban

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† A complete list of RUBY-1 investigators is attached in Appendix 1.

Introduction

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 (ESC)[2,3] and the American College of Cardiology/American Heart Association (ACC/AHA)[4–6] recommend the continuation of dual antiplatelet therapy [acetylsalicylic acid (ASA) and clopidogrel] for up to 1 year after an ACS event.

Despite this, the recurrence of ischaemic events after an ACS event remains high, up to 9.1% at 6 months,[7] generating interest for improved antithrombotic therapy in addition to the current standard of antiplatelet therapy. Since thrombin plays a pivotal role in the formation and consolidation of thrombi in ACS, there has been interest in thrombin inhibitors, particularly as oral forms have become available. Conventional oral anticoagulation with vitamin K antagonists (VKAs), while effective at preventing ischaemic events,[8] is fraught with problems related to the narrow therapeutic range of these agents, the need for careful monitoring, the frequent interactions with drugs and food, and the delay in onset and offset of action.[9–12] Use of chronic triple antithrombotic therapy with ASA, thienopyridines, and VKAs beyond the acute phase is associated with a high risk of bleeding.[13,14] In this context, more selective oral anticoagulants, direct thrombin inhibitors such as dabigatran[15] or factor Xa (FXa) inhibitors such as apixaban[16] and rivaroxaban,[17] have generated interest.

Darexaban (YM150) and its major metabolite darexaban glucuronide (YM-222714) are direct inhibitors of FXa. Darexaban is rapidly absorbed from the gut and almost completely converted into darexaban glucuronide which reaches maximum plasma levels at 1–1.5 h post-dose and has a terminal half-life of 14–18 h. Darexaban glucuronide is the main active moiety driving the antithrombotic effect and demonstrates a predictable pharmacokinetic (PK)/pharmacodynamic (PD) profile. Darexaban has minimal interaction with food[18] and importantly no drug–drug interactions with CYP3A4/P-glycoprotein inhibitors and inducers.[19] Darexaban shows no PK or PD interaction with ASA and clopidogrel, although the skin bleeding time increases as expected.[20] In addition, no interaction was observed with naproxen.[20] The drug is excreted equally through the kidneys and faeces.[21] Since direct FXa inhibitors are small molecules that bind to and inhibit FXa, independent of other proteins, they are thought to bind to both clot-bound and free FXa.[22] The potential benefit of darexaban has been shown in venous thromboembolic disease,[23,24] and has recently been explored in the prevention of stroke in subjects with non-valvular atrial fibrillation in a phase II study (Clinical Trials.gov identifier: NCT00938730).[25–27] RUBY-1 (150-CL-201 ClinicalTrials.gov identifier: NCT00994292) is a phase II trial aimed at exploring the potential role of darexaban in patients with recent ACS, as well as defining a dose range in this indication.

Methods

Study objectives

The primary objective of this study was the evaluation of the safety and tolerability of different doses and dose regimens of darexaban on top of standard treatment with ASA with or without clopidogrel, for the secondary prevention of ischaemic vascular events in patients with recent ACS. The secondary objectives were the evaluation of the efficacy of different doses and dose regimens of darexaban on top of standard dual antiplatelet treatment in the secondary prevention of ischaemic vascular events in patients with recent ACS, as well as helping to define the suitable population for further development (i.e. phase III).

Study population

Male or female patients with a diagnosis of non-ST-segment elevation (NSTE)-ACS and high-risk features, or ST-segment elevation (STE)-ACS were eligible for randomization. Acute coronary syndrome was defined according to accepted international guidelines.[3,5] If eligible, patients were randomized as early as possible after clinical stabilization, as long as this occurred within 7 days of presentation of the index event. In total, 1264 patients with NSTE-ACS or STE-ACS as the index event were planned for randomization. The complete inclusion and exclusion criteria are detailed in Appendix 2.

Study design and treatments

RUBY-1 was a prospective, randomized, double-blind, multi-centre, multiple-dose, placebo-controlled, parallel-group trial in subjects presenting with ACS. Following presentation with the index ACS event, patients were managed according to local standards of care, which could include primary percutaneous coronary intervention (PCI), thrombolysis, or medical management. All subjects were to receive antiplatelet treatment as per current guidelines.[3,5] Acetylsalicylic acid was used at a dose of 75–325 mg daily, as per local practice. The lower dose range of ASA (i.e. 75–81 mg daily) was recommended, or clopidogrel 75 mg daily if ASA was contraindicated or not tolerated, or a combination of ASA 75–325 mg and clopidogrel 75 mg daily (a maintenance dose of clopidogrel of up to 150 mg was allowed up to 7 days after the index event).

Subjects were screened for eligibility following presentation with ACS. Once stabilized, eligible subjects were randomized, via an interactive voice response system, in a double-blind manner, to one of seven parallel study treatment groups within 7 days of presentation with the index event. The study drug was administered for a total duration of 26 weeks, in addition to standard antiplatelet treatment. Six dose groups of darexaban and one placebo control group were evaluated. Randomization was stratified by country and clopidogrel use. The allocation ratio was 1:1:1:1:1:1:2 to the following groups: darexaban 5 mg b.i.d., darexaban 10 mg o.d., darexaban 15 mg b.i.d., darexaban 30 mg o.d., darexaban 30 mg b.i.d., and darexaban 60 mg o.d., or placebo. The selection of this dose range was based on previous experience in healthy volunteers (in whom doses of up to 320 mg for 14 days were well tolerated), as well as on prior experience in venous thromboembolism prophylaxis,[23,24] where doses of up to 120 mg daily have been studied and were safe and effective; prior experience in a phase II trial of stroke prevention in atrial fibrillation[28] where darexaban was safe; and an indirect comparison with rivaroxaban suggesting that darexaban 60 mg resulted in approximately the same FXa inhibition as rivaroxaban 10 mg.[18] In addition, two drug–drug interaction studies suggested no clinically relevant interaction with ASA with or without clopidogrel.[20] Given that most ACS patients would be on dual antiplatelet therapy, it appeared prudent to explore the lower end of the dose range in order to study the drug at doses that may minimize the bleeding caused by superimposition of oral anticoagulation, which is why a daily dose of 10 mg was selected as the starting point. Other antithrombotic drugs given for the initial management of the index event during the acute phase had to be

discontinued before initiation of study treatment. Other medical treatments, such as beta-blockers and angiotensin II inhibitors, were given as per local practice and guidelines. The study was approved by the Institutional Review Boards/Ethical Review Committees for each participating hospital. All patients provided written informed consent prior to randomization.

Outcome measures

Primary outcomes

The primary outcome was the incidence of major and clinically relevant non-major (CRNM) bleeding events, according to a modified version of the International Society on Thrombosis and Haemostasis (ISTH) definition,[29] during the 6 months of the study. All overt bleeding events were adjudicated by the independent adjudication committee (IAC) as either major, CRNM, or minor bleeding events. Bleeds were also adjudicated according to the thrombolysis in myocardial infarction (TIMI) bleeding definition.[30] Definitions of bleeding events are detailed in Appendix 3.

Secondary outcomes

Secondary outcomes included TIMI major bleeding events, and, as the main secondary outcome, the composite of all-cause mortality, non-fatal myocardial infarction (MI), non-fatal stroke, and severe recurrent ischaemia. Severe recurrent ischaemia was defined as worsening anginal symptoms lasting at least 10 min and associated with at least two of the following: dynamic $\geq$0.1 mV ST depression or elevation, hospitalization, or unplanned cardiac catheterization with evidence of significant coronary stenosis. Stent thromboses were also analysed after adjudication as per the academic research consortium criteria.[31]

Sample size

Assuming an incidence of major and CRNM bleeding events at 6 months of 3% for placebo and 4, 7, and 9% for darexaban 10, 30, and 60 mg per day, respectively, a sample size of 1264 randomized subjects allowed a 91% power to detect a linear trend in the mentioned incidence vs. daily dose, using a two-sided test with 95% confidence level.

Statistical analysis

The primary analysis was performed based upon the modified intention-to-treat data set, defined as all randomized subjects 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 the discontinuation of treatment. Cumulative risk and 95% confidence intervals (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 the treatment group and antiplatelet therapy as fixed effects. There was no adjustment for multiple comparisons. The data analysis was generated using SAS software (version 9.1.3; SAS Institute, Inc., Cary, NC, USA).

Results

Patient disposition

From September 2009 to July 2010, 1279 subjects were enrolled from 152 centres in 24 countries in Europe, the Americas, South Africa, and Asia. The patient disposition is highlighted in *Figure 1*. Overall, 1258 patients were included in the modified-intention-to-treat data set. Patient demographics and clinical characteristics for the overall study cohort is summarized in *Table 1*. The patient demographics and clinical characteristics for all treatment groups are summarized in Appendix 4. The majority of patients were enrolled in Eastern European countries. Overall, the treatment groups appeared comparable clinically, with a median age of 56 years old (inter-quartile range: 50–64 years old), the majority of patients enrolled following ST-elevation MI (71.1%) and 74.6% had PCI for treatment of the index event. The average risk, measured by the GRACE (Global Registry of Acute Coronary

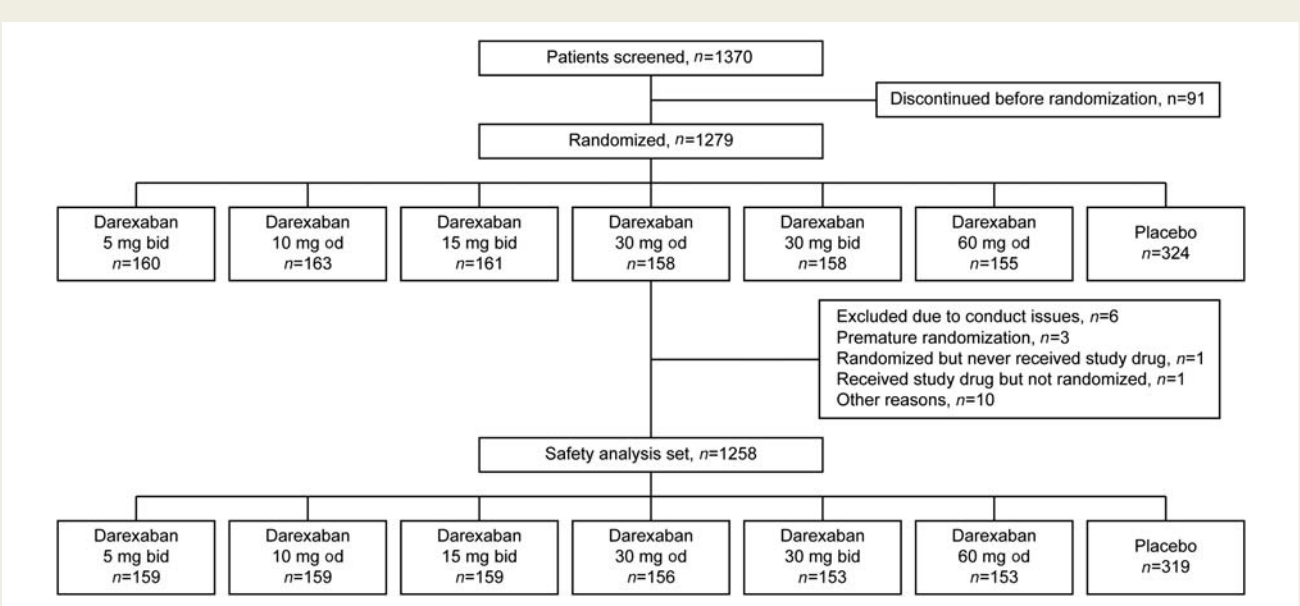

Figure 1 Study flow. b.i.d., twice daily; o.d., once daily.

Table 1 Clinical characteristics of the patients (overall study cohort)

	Grand total
n	1258
Age, mean (SD)	56.9 (10.40)
Female, %	20.4
Ethnicity, *n* (%)	
Caucasian	991 (78.8)
Black/African American	8 (0.6)
Asian	220 (17.5)
Other	39 (3.1)
Smoker, *n* (%)	
Former	297 (23.6)
Current	531 (42.2)
Never	430 (34.2)
Hypertension, *n* (%)	760 (60.4)
Dyslipidaemia, *n* (%)	627 (49.8)
Diabetes mellitus Type 2, *n* (%)	277 (22.0)
Primary diagnosis for index event, *n* (%)	
STEMI	894 (71.1)
NSTEMI	364 (28.9)
Use of PCI for index event	938 (74.6)
GRACE risk score at presentation (evaluated population)	132.8 ($n = 1243$)
Hx of prior CHF, *n* (%)	30 (2.4)
Hx of stroke/TIA, *n* (%)	37 (2.9)
Hx of prior MI, *n* (%)	150 (11.9)
Hx of CABG, *n* (%)	31 (2.4)
Hx of PCI, *n* (%)	111 (8.8)
Peripheral arterial disease, *n* (%)	45 (3.6)

SD, standard deviation; STEMI, ST-segment elevation; NSTEMI, non-ST-segment; PCI, percutaneous coronary intervention; GRACE, Global Registry of Acute Coronary Events; Hx, history; CHF, chronic heart failure; TIA, transient ischaemic attack; MI, myocardial infarction; CABG, coronary artery bypass graft.

Events) score[32] at presentation was similar at baseline across the various groups, indicating that baseline risks of in-hospital and 6-month death were comparable across the groups. Since 97% of patients were in the ASA and clopidogrel strata, results are reported together for patients on ASA only and dual antiplatelet therapy. Permanent discontinuation rates were 21.3% for placebo and 23.7% for darexaban.

Bleeding

The primary safety outcome of major and/or CRNM bleeds while on study treatment (including 1 day after treatment discontinuation) is shown in *Table 2* and *Figure 2A* and *B*. This primary analysis shows that the bleeding rate was numerically higher in all darexaban treatment arms than in the placebo arm, with hazard ratios (HRs) ranging from 1.8 to 3.8. Starting with placebo as reference (bleeding rate 3.1%), there was a dose–response relationship ($P = 0.009$, for trend analysed using the Cox regression model) 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 ($n = 318$), 30 ($n = 315$), and 60 mg ($n = 306$) darexaban, respectively (*Figure 2B*). This increase was statistically significant for the darexaban 30 mg b.i.d. dose ($P = 0.002$).

The rates of bleeding were similar for patients receiving b.i.d. ($n = 471$) vs. o.d. ($n = 468$) dosing with darexaban (8.4 vs. 6.1%, respectively, $P = 0.310$). Pooling together all dose arms of darexaban (in a *post hoc* analysis), the primary endpoint was more frequent with darexaban than with placebo (HR: 2.275; CI: 1.13–4.60; $P = 0.022$).

Additional information regarding other bleeding events is included in *Table 2*, reporting each component of the primary safety outcome, and the additional outcomes of minor bleeding, any bleeding, and bleeding categorized according to the TIMI scheme. There were no cases of fatal bleeding or intracranial haemorrhage in any group. All bleeding events (*Figure 2A*) followed a pattern similar to that of the primary safety outcome.

Bleeding rates analysed for the entire duration of follow-up (including the 4-week observation period following treatment completion or premature permanent discontinuation) were similar to results observed during the period on treatment (data not shown).

The overall number of subjects with adverse events (AEs; which included bleeding and efficacy outcomes) was similar across the darexaban arms and, consistent with the higher bleeding rates previously described, was slightly higher than with placebo. In addition, AEs leading to discontinuation of the study drug were higher in the darexaban 30 mg o.d., 30 mg b.i.d., and 60 mg o.d. arms. The percentage of subjects with alanine transaminase (ALT) or aspartate transaminase (AST) >3 or $>5\times$ the upper limit of normal (ULN) was similar across all treatment arms (*Table 3*). The percentage of subjects with total bilirubin $>2\times$ ULN ranged from 0% with placebo and darexaban 15 mg b.i.d. to 1.4% with darexaban 30 mg b.i.d., with no clear pattern across darexaban doses. Two subjects, both receiving darexaban, had concurrent elevations, one of whom had total bilirubin $>3\times$ ULN. Additionally, there was no difference in creatinine elevations between groups (data not shown).

Efficacy

The composite of all-cause mortality, non-fatal MI, non-fatal stroke, and severe recurrent ischaemia at 6 months was the main secondary outcome (*Table 4*) Event rates at 6 months showed no decrease with darexaban compared with placebo. Although this study was not powered for efficacy, the cumulative incidence of this composite efficacy outcome was numerically higher in the darexaban 30 and 60 mg daily dose arms compared with placebo. At these doses, the increase appeared largely driven by severe recurrent ischaemia. The composite efficacy outcome was infrequent with the lowest doses of darexaban (10 mg daily arms), and numerically lower than placebo. Other secondary efficacy outcomes are overviewed in Table 4: event rates were low and similar between dose groups. Definite or probable stent

Table 2 Safety outcomes

Placebo KM rate (*n*/*N*)	Total daily darexaban dose	Once daily dosing			Twice daily dosing		
		KM rate (*n*/*N*)	HR (95% CI) vs. placebo	*P*-value	KM rate (*n*/*N*)	HR (95% CI) vs. placebo	*P*-value
Primary safety endpoint—Kaplan–Meier analysis of the cumulative risk of major and clinically relevant non-major bleeding events							
3.1% (9/319)							
	10 mg	5.6% (8/159)	1.775 (0.68, 4.60)	0.238	6.8% (9/159)	2.045 (0.81, 5.15)	0.129
	30 mg	5.6% (8/156)	1.831 (0.71, 4.75)	0.213	7.5% (10/159)	2.269 (0.92, 5.59)	0.075
	60 mg	7.3% (10/153)	2.425 (0.98, 5.97)	0.054	11.3% (15/153)	3.796 (1.66, 8.68)	0.002
	Darexaban, 5 mg b.i.d. (*n* = 159)	**Darexaban, 10 mg o.d. (*n* = 159)**	**Darexaban, 15 mg b.i.d. (*n* = 159)**	**Darexaban, 30 mg o.d. (*n* = 156)**	**Darexaban, 30 mg b.i.d. (*n* = 153)**	**Darexaban, 60 mg o.d. (*n* = 153)**	**Placebo (*n* = 319)**
Absolute event rates for individual categories of bleeding events							
Major and CRNM	9 (5.7)	8 (5.0)	10 (6.3)	8 (5.1)	15 (9.8)	10 (6.5)	9 (2.8)
Major	1 (0.6)	1 (0.6)	2 (1.3)	3 (1.9)	3 (2.0)	0 (0.0)	1 (0.3)
CRNM	8 (5.0)	7 (4.4)	8 (5.0)	5 (3.2)	13 (8.5)	10 (6.5)	8 (2.5)
Minor	13 (8.2)	12 (7.5)	16 (10.1)	12 (7.7)	17 (11.1)	16 (10.5)	18 (5.6)
Any	21 (13.2)	18 (11.3)	24 (15.1)	20 (12.8)	30 (19.6)	23 (15.0)	26 (8.2)
TIMI bleeding events							
Major	1 (0.6)	1 (0.6)	0 (0.0)	3 (1.9)	1 (0.7)	0 (0.0)	1 (0.3)
Minor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Requiring medical attention	8 (5.0)	6 (3.8)	9 (5.7)	5 (3.2)	13 (8.5)	10 (6.5)	6 (1.9)
Insignificant	13 (8.2)	13 (8.2)	16 (10.1)	14 (9.0)	19 (12.4)	16 (10.5)	20 (6.3)
Any	21 (13.2)	18 (11.3)	24 (15.1)	20 (12.8)	30 (19.6)	23 (15.0)	26 (8.2)

All data are *n* (%); KM, Kaplan–Meier; HR, hazard ratio; CI, confidence interval, b.i.d., twice daily; o.d, once daily; CRNM, clinically relevant non-major; TIMI, thrombolysis in myocardial infarction.

thromboses (as per ARC criteria) occurred in 1.1% (8/703) of patients receiving darexaban and 0.4% (1/319) of patients receiving placebo.

Discussion

This phase II dose-ranging study showed that the frequency of major or CRNM bleeding events during 6 months of double-blind treatment (on top of dual antiplatelet therapy) after ACS was two- to four-fold higher (HRs ranging from 1.8 to 3.8) with the various doses of darexaban than with placebo. There was an increase in bleeding rates with increasing increments in the total daily dose. As with most phase II dose-ranging trials of antithrombotic drugs, RUBY-1 was underpowered to study efficacy. There was no signal for efficacy. There was no significant difference in the composite of non-fatal MI, non-fatal stroke, severe recurrent ischaemia, and death due to any cause during 6 months of double-blind treatment. The incidence of these events was numerically higher than placebo at the higher dose range, and numerically lower at the lower end of the dose range. However, the CIs around these point estimates were wide. Liver safety, as measured by ALT, AST, and bilirubin levels, appeared similar between placebo and the various doses of darexaban.

Classic trials of VKAs added to single antiplatelet therapy with ASA have demonstrated superior efficacy compared with antiplatelet therapy alone in secondary prevention after ACS,[33,34] although this was achieved at the expense of an increased risk of major bleeding.[8,34] However, VKAs have a narrow therapeutic margin, a slow onset and offset of action, and numerous food and drug interactions, and, therefore, require careful monitoring. New oral anticoagulants targeting thrombin or factor X have been designed to overcome these problems, and darexaban is particularly attractive in this setting given its predictable PK properties[18] and minimal potential for drug–drug interactions.[19,20] Indeed, there is evidence from several phase II studies[15–17,35] that adding an oral anticoagulant to antiplatelet therapy in patients with recent ACS may have some efficacy in the prevention of ischaemic events and death compared with antiplatelet therapy alone, and this concept has led to several phase III trials.[36,37]

However, even with novel anticoagulants that have a broader therapeutic margin than VKAs, the selection of dose is critical for

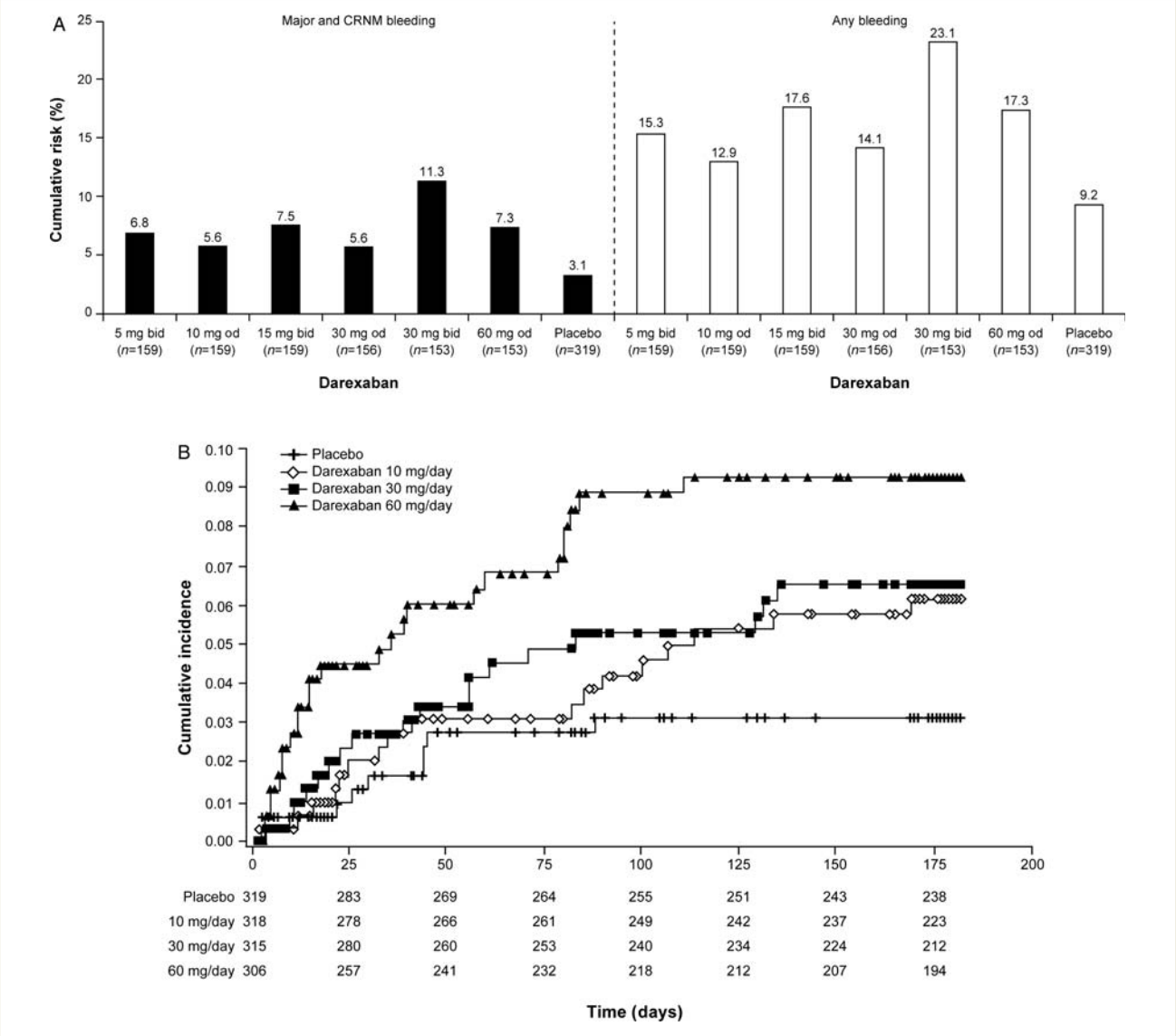

Figure 2 (*A*) Kaplan–Meier analysis of the cumulative risk of major and clinically relevant non-major bleeding (black bars), and any bleeding events (white bars) at 6 months (safety analysis set). (*B*) Kaplan–Meier analysis of the cumulative risk of the primary safety endpoint of major and clinically relevant non-major bleeding events for the three total daily doses of darexaban (10, 30, and 60 mg). Cumulative incidences are calculated using Kaplan–Meier estimates and presented as relative to 1 (e.g. 0.06 represents 6%). CRNM, clinically relevant non-major; b.i.d., twice daily; o.d., once daily.

secondary prevention after ACS, because in this setting (in which most patients have received coronary stents) dual antiplatelet therapy is part of the standard of care and is recommended by guidelines.[2,3,5] Indeed, in the present study, 95% of patients were on dual antiplatelet therapy, contrasting with prior studies with VKAs, which were performed before the era of dual antiplatelet therapy after ACS. Therefore, adding an anticoagulant would result in long-term triple antithrombotic therapy, which may result in unacceptable bleeding, and indicates that this strategy would need to show a tangible efficacy benefit, with a reduction in cardiovascular death, MI, and stroke, to offset any bleeding hazard. In fact, a large phase III trial of apixaban in this setting was recently stopped due to increased bleeding which was not offset by increased efficacy,[37] and development of another FXa inhibitor in ACS was halted after a phase II study.[38] Another phase III trial with rivaroxaban after ACS[36] is ongoing and is expected to be reported on later this year. This trial will be key in understanding whether the concept of adding an oral anticoagulant to standard of care dual antiplatelet therapy in order to prevent recurrent events after ACS is valid or whether in the current environment of potent antiplatelet therapy, this can only result in increased bleeding without compensatory reductions in thrombotic/ischaemic endpoints.

Darexaban has been previously studied in human volunteers[18–20] and in patients with venous thromboembolism or atrial fibrillation for the prevention of stroke.[23–28] It provides reliable inhibition of FXa and shows no unexpected safety concerns. Given

Table 3 **Overview of adverse events, including liver-related clinical laboratory abnormalities during the treatment period**

	Darexaban, 5 mg b.i.d. (*n* = 159)	Darexaban, 10 mg o.d. (*n* = 159)	Darexaban, 15 mg b.i.d. (*n* = 159)	Darexaban, 30 mg o.d. (*n* = 156)	Darexaban 30 mg b.i.d. (*n* = 153)	Darexaban 60 mg o.d. (*n* = 153)	Darexaban, all (*n* = 939)	Placebo (*n* = 319)
Adverse events (%)	100 (62.9)	102 (64.2)	100 (62.9)	96 (61.5)	101 (66.0)	99 (64.7)	598 (63.7)	181 (56.7)
AEs leading to discontinuation (%)	16 (10.1)	25 (15.7)	21 (13.2)	27 (17.3)	29 (19.0)	25 (16.3)	95 (10.1)	31 (9.7)
ALT or AST >3× 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)	16/854 (1.9)	7/290 (2.4)
ALT or AST >5× ULN	2/149 (1.3)	2/155 (1.3)	0 (0.0)	0 (0.0)	1/146 (0.7)	1/144 (0.7)	6/909 (0.7)	2/302 (0.7)
Total bilirubin >2× ULN	1/150 (0.7)	1/151 (0.7)	0 (0.0)	1/147 (0.7)	2/141 (1.4)	1/141 (0.7)	6/889 (0.7)	0 (0.0)
Total bilirubin >3× ULN	0 (0.0)	1/151 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1/931 (0.1)	0 (0.0)

All data are *n* (%); b.i.d., twice daily; o.d., once daily; AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; ULN, upper limit of normal.

Table 4 **Efficacy outcomes**

	Darexaban, 5 mg b.i.d. ($n = 159$)	Darexaban, 10 mg o.d. ($n = 159$)	Darexaban, 15 mg b.i.d. ($n = 159$)	Darexaban, 30 mg o.d. ($n = 156$)	Darexaban, 30 mg b.i.d. ($n = 153$)	Darexaban, 60 mg o.d. ($n = 153$)	Darexaban, all ($n = 939$)	Placebo ($n = 319$)
Kaplan–Meier analysis of cumulative risk of composite of all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, and severe recurrent ischaemia								
Cumulative risk	4.3	4.3	7.4	7.3	6.9	9.3	6.5	5.2
95% CI	2.0–9.4	2.0–9.4	4.0–13.3	4.0–13.1	3.6–12.9	5.4–15.8	5.0–8.5	3.1–8.6
Absolute frequencies and proportions of secondary efficacy endpoints at 6 months								
Non-fatal MI, non-fatal stroke, severe recurrent ischaemia and all deaths, *n* (%)	6 (3.8)	6 (3.8)	10 (6.3)	10 (6.4)	9 (5.9)	12 (7.8)	53 (5.6)	14 (4.4)
Non-fatal MI, non-fatal stroke, and all deaths *n* (%)	4 (2.5)	5 (3.1)	4 (2.5)	5 (3.2)	5 (3.3)	4 (2.6)	27 (2.9)	7 (2.2)
Deaths, *n* (%)	0 (0.0)	2 (1.3)	0 (0.0)	3 (1.9)	1 (0.7)	1 (0.7)	7 (0.7)	2 (0.6)
MI, *n* (%)	4 (2.5)	4 (2.5)	4 (2.5)	5 (3.2)	4 (2.6)	4 (2.6)	25 (2.7)	6 (1.9)
Severe recurrent ischaemia, *n* (%)	2 (1.3)	1 (0.6)	6 (3.8)	5 (3.2)	4 (2.6)	8 (5.2)	26 (2.8)	7 (2.2)
Stroke, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TIA, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	2 (0.2)	0 (0.0)
STE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

In each row, only the first event is counted, however, patients may be counted in more than one row. All data are *n* (%) unless otherwise stated; b.i.d., twice daily; o.d., once daily; CI, confidence interval; MI, myocardial infarction; TIA, transient ischaemic attack; STE, systemic thromboembolic event.

the concerns regarding bleeding associated with long-term triple oral antithrombotic therapy, the observation in RUBY-1 that bleeding increases with dose suggests that a phase III trial of darexaban after ACS should use doses at the lower end of the dose range (e.g. 10 mg daily). The lower doses of darexaban are expected to result in an increased risk of bleeding, as shown in this study, but may provide sufficient FXa inhibition to result in an efficacy benefit. Prior studies with other FXa antagonists have previously shown that they may have a flat dose–response, as seen in a phase II dose-ranging trial of fondaparinux after ACS,[39] in which the lowest doses appeared to be associated with the lowest rates of bleeding but no benefit in increasing the dose in terms of efficacy. There was no efficacy signal in RUBY-1, even though the trial was underpowered for efficacy. Given the failure of FXa inhibition to add benefit to dual antiplatelet therapy after ACS in the APPRAISE-2 trial, the validity of the concept of combining dual antiplatelet therapy with anticoagulant therapy after ACS remains at best uncertain. The likelihood of the success of a phase III trial with darexaban will need to be placed in the context of the results of ongoing trials like ATLAS ACS-2.[17,36]

As with any clinical trial, results from this study should be interpreted with consideration of the potential limitations. This study had limited power to detect differences in efficacy between the various dose groups and placebo, as is clear from the wide CIs of the point estimates of the event rates. However, efficacy results from phase II studies in this setting have been documented as unreliable, with encouraging phase II results not confirmed in phase III[16,37] and apparently neutral phase II studies being followed by resounding efficacy in properly powered phase III trials.[40–42] This study does, however, provide clear information and guidance regarding the tolerability of darexaban, in terms of bleeding, when added as a third antithrombotic agent to treatment with ASA and clopidogrel, as well as the fact that the relative risks of bleeding are consistent regardless of the severity and bleeding scale used. Another limitation of this study is that it is only relevant to treatment when added on top of ASA and clopidogrel. The safety of darexaban when combined with more potent P2Y12 antagonists such as prasugrel[43] or ticagrelor[42] is unknown. Given the superiority of these agents over clopidogrel after ACS, the potential clinical efficacy benefit of adding darexaban to dual antiplatelet therapy may be reduced and the bleeding risk increased when ASA is combined with either of these new agents. Generalizability of results is always an important consideration in trials, and even though the majority of patients were enrolled in Eastern Europe, our study has broad geographical representation with enrolment in 24 countries over four continents, including India and South Africa. In addition, the trial enrolled a relatively young and low-risk patient population, with a predominance of STEMI. The bleeding rates observed may not necessarily be representative of bleeding rates, which might be expected in a less selected, older patient population, with more comorbidities. The trial has pooled together STE-ACS and NSTE-ACS, which may have introduced further heterogeneity, although current recommendations for secondary prevention with antithrombotics are identical for both conditions,[2–5] and many prior trials of antithrombotics in this setting have done so.[15–17,35–37,42,43]

Conclusion

Darexaban, when added to dual antiplatelet therapy after ACS (including patients who have undergone PCI), produces an expected dose-related two- to four-fold increase in bleeding. While the trial was underpowered to study efficacy, there was no reduction in the composite efficacy outcome, which was numerically higher than placebo at the higher dose range and numerically lower at the lower dose range. Establishing the potential of low-dose darexaban in preventing major cardiac events after ACS would require a large phase III trial to test whether it might achieve clinical efficacy on top of dual antiplatelet therapy without an unacceptable increase in the risk of bleeding.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Appendix 1

RUBY-1

Executive Steering Committee: Ph Gabriel Steg (Chair), Christopher B Granger, J Wouter Jukema, Gregory YHK Lip, Shamir Mehta, Ronny W Renfurm (non-voting).

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Appendix 2: Complete inclusion and exclusion criteria

Inclusion criteria—all needed to be fulfilled for a patient to be eligible for the study
18 years of age or older
Diagnosis of STE-ACS or NSTE-ACS as index event
Elevated cardiac biomarkers (Troponin T or I, or CK-MB) >2× ULN for CK-MB or >ULN for Troponin
For subjects with a diagnosis of NSTE-ACS, at least one of the following additional risk factors for ischaemic events had to be present:
ST deviation on ECG at any time between presentation and randomization
Age 65 years of age or older
Previous ACS <12 months prior to randomization
Multi-vessel coronary artery disease
Ischaemic stroke or TIA at least 12 months prior to randomization
Type 2 diabetes mellitus
Peripheral arterial disease
Clinically stable (defined as discontinuation of parenteral antithrombotics and not likely to require reinstitution of parenteral antithrombotics at the time of randomization) and receiving current standard oral antiplatelet therapy
Able to be randomized within 7 days after presentation. Subjects should be randomized as soon as possible after discontinuation of parenteral antithrombotics
Has provided Institutional Review Board-/Independent Ethics Committee-approved written informed consent and privacy language as per national regulations or informed consent has been obtained from the legally authorized representative prior to any study-related procedures
Main exclusion criteria
Need for ongoing therapy with parenteral or oral anticoagulants, thrombolytics, glycoprotein IIb/IIIa antagonists, or other antiplatelet drugs
Patient planned for myocardial revascularization or any other invasive procedure with increased risk for bleeding (i.e. elective surgical procedures) within 60 days
Active bleeding or, in the opinion of the investigator, high risk of bleeding during the study
Recent stroke or TIA <12 months prior to index event
Bleeding diathesis or any other condition or laboratory abnormality with increased tendency for bleeding (e.g. platelet count <100 000/μL)
Female of childbearing potential who refuses to use a medically acceptable form of contraception throughout the study
Female who is pregnant or lactating
Persistent SBP of 160 mmHg or higher and/or DBP of 100 mmHg or higher at baseline with or without medication
Hepatic insufficiency or ALT >2.0 times the ULN or total bilirubin >1.5 times the ULN
Renal creatinine clearance of <60 mL/min (Cockcroft–Gault equation)
Any concurrent illness which may interfere with treatment or evaluation of safety or completion of this study
Participation in another clinical trial within 30 days
Participation in any darexaban clinical trials
Known allergy to the study drug or any of its components

STE-ACS, ST segment elevation ACS; ACS, acute coronary syndrome; NSTE-ACS, non-ST segment elevation ACS; CK, creatine kinase; ULN, upper limit of normal; ECG, electrocardiogram; TIA, transient ischaemic attack; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine transaminase.

Appendix 3: Definitions of bleeding events

Type of bleeding	Definition
Major bleeding	Fatal bleeding, clinically overt bleeding associated with a decrease in the haemoglobin level of >2 g/dL (1.24 mmol/L) compared with the pre-bleeding level, clinically overt bleeding leading to transfusion of two or more units of whole blood or packed cells, and symptomatic bleeding in a critical area or organ, such as retroperitoneal, intracranial, intraocular, intra-spinal, intra-articular, pericardial, or intramuscular bleeding with compartment syndrome
CRNM bleeding	Any bleeding event considered as clinically relevant by the IAC that did not meet the criteria of a major bleeding event, e.g. any bleeding event that required medical attention or any bleeding requiring discontinuation of blinded study drug treatment
All other bleeding events	Those events not fulfilling the criteria of major or CRNM bleeding events. In addition, transfusions and the reasons behind them were tracked, and for each bleeding episode, an adjusted decrease in haemoglobin was computed by adding the number of units of packed red blood cells transfused to the decrease in haemoglobin

CRNM, clinically relevant non-major; IAC, independent adjudication committee.

Appendix 4: Clinical characteristics of the patients

Variable	Darexaban, 5 mg b.i.d.	Darexaban, 10 mg o.d.	Darexaban, 15 mg b.i.d.	Darexaban, 30 mg o.d.	Darexaban, 30 mg b.i.d.	Darexaban, 60 mg o.d.	Placebo
n	159	159	159	156	153	153	319
Age, mean (SD)	57.4 (10.43)	57.1 (10.35)	56.3 (9.58)	56.1 (10.05)	57.2 (11.53)	55.7 (10.39)	57.5 (10.44)
Female, %	20.8	21.4	18.2	16.0	21.6	17.0	24.1
Ethnicity, *n* (%)							
Caucasian	124 (78.0)	123 (77.4)	124 (78.0)	126 (80.8)	117 (76.5)	120 (78.4)	257 (80.6)
Black/African American	2 (1.3)	4 (2.5)	1 (0.6)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Asian	27 (17.0)	28 (17.6)	30 (18.9)	26 (16.7)	28 (18.3)	27 (17.6)	54 (16.9)
Other	6 (3.8)	4 (2.5)	4 (2.5)	4 (2.6)	7 (4.6)	6 (3.9)	8 (2.5)
Enrolment region, *n* (%)							
Europe	108 (67.9)	108 (67.9)	108 (67.9)	108 (69.2)	104 (68.0)	105 (68.6)	219 (68.7)
North America	9 (5.7)	7 (4.4)	7 (4.4)	8 (5.1)	7 (4.6)	7 (4.6)	15 (4.7)
Central/South America	11 (6.9)	13 (8.2)	11 (6.9)	10 (6.4)	12 (7.8)	11 (7.2)	24 (7.5)
Asia/Pacific/South Africa	31 (19.5)	31 (19.5)	33 (20.8)	30 (19.2)	30 (19.6)	30 (19.6)	61 (19.1)
Smoker, *n* (%)							
Former	42 (26.4)	34 (21.4)	31 (19.5)	33 (21.2)	33 (21.6)	41 (26.8)	83 (26.0)
Current	69 (43.4)	65 (40.9)	68 (42.8)	63 (40.4)	62 (40.5)	64 (41.8)	140 (43.9)
Never	48 (30.2)	60 (37.7)	60 (37.7)	60 (38.5)	58 (37.9)	48 (31.4)	96 (30.1)
Hypertension, *n* (%)	90 (56.6)	99 (62.3)	95 (59.7)	91 (58.3)	95 (62.1)	96 (62.7)	194 (60.8)
Dyslipidaemia, *n* (%)	77 (48.4)	74 (46.5)	77 (48.4)	89 (57.1)	76 (49.7)	81 (52.9)	153 (48.0)
Diabetes mellitus Type 2, *n* (%)	39 (24.5)	37 (23.3)	37 (23.3)	43 (27.6)	34 (22.2)	27 (17.6)	60 (18.8)

Continued

Appendix 4: (*Continued*)

Variable	Darexaban, 5 mg b.i.d.	Darexaban, 10 mg o.d.	Darexaban, 15 mg b.i.d.	Darexaban, 30 mg o.d.	Darexaban, 30 mg b.i.d.	Darexaban, 60 mg o.d.	Placebo
Primary diagnosis for index event, *n* (%)							
STEMI	111 (69.8)	121 (76.1)	119 (74.8)	106 (67.9)	108 (70.6)	109 (71.2)	220 (69.0)
NSTEMI	48 (30.2)	38 (23.9)	40 (25.2)	50 (32.1)	45 (29.4)	44 (28.8)	99 (31.0)
Use of PCI for index event	122 (76.7)	116 (73.0)	119 (74.8)	115 (73.7)	118 (77.1)	113 (73.9)	235 (73.7)
Standard antiplatelet therapy, *n* (%)							
With clopidogrel	154 (96.9)	152 (95.6)	152 (95.6)	152 (97.4)	148 (96.7)	148 (96.7)	309 (96.9)
Without clopidogrel	5 (3.1)	7 (4.4)	7 (4.4)	4 (2.6)	5 (3.3)	5 (3.3)	10 (3.1)
Time from index event to first dose (mean days)	4.1	4.0	4.3	3.8	4.1	4.2	4
GRACE risk score at presentation (evaluated population)	132.6 ($n = 158$)	134.7 ($n = 156$)	135.1 ($n = 156$)	130.6 ($n = 154$)	132.3 ($n = 152$)	131.2 ($n = 153$)	132.8 ($n = 314$)
Hx of prior CHF, *n* (%)	4 (2.5)	3 (1.9)	6 (3.8)	2 (1.3)	3 (2.0)	4 (2.6)	8 (2.5)
Hx of stroke/TIA, *n* (%)	3 (1.9)	4 (2.5)	4 (2.5)	8 (5.1)	6 (3.9)	6 (3.9)	6 (1.9)
Hx of prior MI, *n* (%)	19 (11.9)	9 (5.7)	17 (10.7)	24 (15.4)	18 (11.8)	18 (11.8)	45 (14.1)
Hx of CABG, *n* (%)	8 (5.0)	3 (1.9)	1 (0.6)	5 (3.2)	3 (2.0)	5 (3.3)	6 (1.9)
Hx of PCI, *n* (%)	10 (6.3)	8 (5.0)	13 (8.2)	13 (8.3)	22 (14.4)	20 (13.1)	25 (7.8)
Peripheral arterial disease, *n* (%)	9 (5.7)	4 (2.5)	6 (3.8)	5 (3.2)	4 (2.6)	4 (2.6)	13 (4.0)
Premature permanent study drug discontinuation, *n* (%)	30 (18.9)	31 (19.5)	32 (20.1)	44 (28.2)	50 (32.7)	36 (23.5)	68 (21.3)
Duration of drug exposure, median weeks (Q1, Q3)	26.0 (23.9, 26.1)	26.0 (24.3, 26.1)	26.0 (19.6, 26.1)	26.0 (20.6, 26.1)	25.7 (11.6, 26.1)	26.0 (17.7, 26.1)	26.0 (25.0, 26.1)
Concomitant medications, *n* (%)							
Beta-blockers	146 (91.8)	147 (92.4)	149 (93.7)	145 (92.9)	139 (90.8)	133 (86.9)	293 (91.8)
ACE-inhibitors	128 (80.5)	126 (79.2)	121 (76.1)	117 (75.0)	123 (80.4)	116 (75.8)	248 (77.7)
Angiotensin receptor blockers	17 (11.0)	23 (14.5)	25 (15.7)	17 (10.9)	19 (12.4)	23 (15.0)	43 (13.5)
Statins	150 (94.3)	154 (96.9)	156 (98.1)	146 (93.6)	146 (95.4)	145 (94.8)	304 (95.3)
Fibrates	4 (2.5)	6 (3.8)	3 (1.9)	5 (3.2)	2 (1.3)	5 (3.3)	10 (3.1)
PPIs	50 (31.4)	49 (30.8)	47 (29.6)	67 (42.9)	63 (41.2)	60 (39.2)	99 (31.0)

Variable	Darexaban, b.i.d.	Darexaban, o.d.	Darexaban, 10 mg doses	Darexaban, 30 mg doses	Darexaban, 60 mg doses	Darexaban, total	Grand total
n	471	468	318	315	306	939	1258
Age, mean (SD)	57.0 (10.52)	56.3 (10.26)	57.2 (10.37)	56.2 (9.80)	56.5 (10.98)	56.6 (10.39)	56.9 (10.4)
Female, %	20.2	18.2	21.1	17.1	19.3	19.2	20.4
Ethnicity, *n* (%)							
Caucasian	365 (77.5)	369 (78.8)	247 (77.7)	250 (79.4)	237 (77.5)	734 (78.2)	991 (78.8)
Black/African American	4 (0.8)	4 (0.9)	6 (1.9)	1 (0.3)	1 (0.3)	8 (0.9)	8 (0.6)

Continued

Appendix 4: (*Continued*)

Variable	Darexaban, b.i.d.	Darexaban, o.d.	Darexaban, 10 mg doses	Darexaban, 30 mg doses	Darexaban, 60 mg doses	Darexaban, total	Grand total
Asian	85 (18.0)	81 (17.3)	55 (17.3)	56 (17.8)	55 (18.0)	166 (17.7)	220 (17.5)
Other	17 (3.6)	14 (3.0)	10 (3.1)	8 (2.5)	13 (4.2)	31 (3.3)	39 (3.1)
Enrolment region, *n* (%)							
Europe	320 (67.9)	321 (68.6)	216 (67.9)	216 (68.6)	209 (68.3)	641 (68.3)	860 (68.4)
North America	23 (4.9)	22 (4.7)	16 (5.0)	15 (4.8)	14 (4.6)	45 (4.8)	60 (4.8)
Central/South America	34 (7.2)	34 (7.3)	24 (7.5)	21 (6.7)	23 (7.5)	68 (7.2)	92 (7.3)
Asia/Pacific/South Africa	94 (20.0)	91 (19.4)	62 (19.5)	63 (20.0)	60 (19.6)	185 (19.7)	246 (19.6)
Smoker, *n* (%)							
Former	106 (22.5)	108 (23.1)	76 (23.9)	64 (20.3)	74 (24.2)	214 (22.8)	297 (23.6)
Current	199 (42.3)	192 (41.0)	134 (42.1)	131 (41.6)	126 (41.2)	391 (41.6)	531 (42.2)
Never	166 (35.2)	168 (35.9)	108 (34.0)	120 (38.1)	106 (34.6)	334 (35.6)	430 (34.2)
Hypertension, *n* (%)	280 (59.4)	286 (61.1)	189 (59.4)	186 (59.0)	191 (62.4)	566 (60.3)	760 (60.4)
Dyslipidaemia, *n* (%)	230 (48.8)	244 (52.1)	151 (47.5)	166 (52.7)	157 (51.3)	474 (50.5)	627 (49.8)
Diabetes mellitus Type 2, *n* (%)	110 (23.4)	107 (22.9)	76 (23.9)	80 (25.4)	61 (19.9)	217 (23.1)	277 (22.0)
Primary diagnosis for index event, *n* (%)							
STEMI	338 (71.8)	336 (71.8)	232 (73.0)	225 (71.4)	217 (70.9)	674 (71.8)	894 (71.1)
NSTEMI	133 (28.2)	132 (28.2)	86 (27.0)	90 (28.6)	89 (29.1)	265 (28.2)	364 (28.9)
Use of PCI for index event, *n* (%)	359 (76.2)	344 (73.5)	238 (74.8)	234 (74.3)	231 (75.5)	703 (74.9)	938 (74.6)
Standard antiplatelet therapy, *n* (%)							
With clopidogrel	454 (96.4)	452 (96.6)	306 (96.2)	304 (96.5)	296 (96.7)	906 (96.5)	1215 (96.6)
Without clopidogrel	17 (3.6)	16 (3.4)	12 (3.8)	11 (3.5)	10 (3.3)	33 (3.5)	43 (3.4)
Time from index event to first dose (mean days)	4.2	4.0	4.1	4.1	4.1	4.1	4.1
GRACE risk score at presentation (evaluated population)	133.3 ($n = 466$)	132.2 ($n = 463$)	133.6 ($n = 314$)	132.9 ($n = 310$)	131.8 ($n = 305$)	132.8 ($n = 929$)	132.8 ($n = 1243$)
Hx of prior CHF, *n* (%)	13 (2.8)	9 (1.9)	7 (2.2)	8 (2.5)	7 (2.3)	22 (2.3)	30 (2.4)
Hx of stroke/TIA, *n* (%)	13 (2.8)	18 (3.8)	7 (2.2)	12 (3.8)	12 (3.9)	31 (3.3)	37 (2.9)
Hx of prior MI, *n* (%)	54 (11.5)	51 (10.9)	28 (8.8)	41 (13.0)	36 (11.8)	105 (11.2)	150 (11.9)
Hx of CABG, *n* (%)	12 (2.5)	13 (2.8)	11 (3.5)	6 (1.9)	8 (2.6)	25 (2.7)	31 (2.5)
Hx of PCI, *n* (%)	45 (9.6)	41 (8.8)	18 (5.7)	26 (8.3)	42 (13.7)	86 (9.2)	111 (8.8)
Peripheral arterial disease, *n* (%)	19 (4.0)	13 (2.8)	13 (4.1)	11 (3.5)	8 (2.6)	32 (3.4)	45 (3.6)
Premature permanent study drug discontinuation, *n* (%)	112 (23.8)	111 (23.7)	61 (19.2)	76 (24.1)	86 (28.1)	223 (23.7)	291 (23.1)
Duration of drug exposure, median weeks (Q1,Q3)	26.0 (19.1, 26.1)	26.0 (21.9, 26.1)	26.0 (24.1, 26.1)	26.0 (19.6, 26.1)	26.0 (13.1, 26.1)	26.0 (20.0, 26.1)	26.0 (22.0, 26.1)

Continued

Appendix 4: (*Continued*)

Variable	Darexaban, b.i.d.	Darexaban, o.d.	Darexaban, 10 mg doses	Darexaban, 30 mg doses	Darexaban, 60 mg doses	Darexaban, total	Grand total
Concomitant medications, *n* (%)							
Beta-blockers	434 (92.1)	425 (90.8)	293 (92.1)	294 (93.3)	272 (88.9)	859 (91.5)	1152 (91.6)
ACE-inhibitors	372 (79.0)	359 (76.7)	254 (79.9)	238 (75.6)	239 (78.1)	731 (77.8)	979 (77.8)
Angiotensin receptor blockers	61 (13.0)	63 (13.5)	40 (12.6)	42 (13.3)	42 (13.7)	124 (13.2)	167 (13.3)
Statins	452 (96.0)	445 (95.1)	304 (95.6)	302 (95.9)	291 (95.1)	897 (95.5)	1201 (95.5)
Fibrates	9 (1.9)	16 (3.4)	10 (3.1)	8 (2.5)	7 (2.3)	25 (2.7)	35 (2.8)
PPIs	160 (34.0)	176 (37.6)	99 (31.1)	114 (36.2)	123 (40.2)	336 (35.8)	435 (34.6)

SD, standard deviation; STEMI, ST-segment elevation; NSTEMI, non-ST-segment; PCI, percutaneous coronary intervention; GRACE, Global Registry of Acute Coronary Events; Hx, history; CHF, chronic heart failure; TIA, transient ischaemic attack; MI, myocardial infarction; CABG, coronary artery bypass graft; PPI, proton pump inhibitor; Q, quartile; ACE, angiotensin-converting enzyme.

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