Randomised Dabigatran Etexilate Dose Finding Study In Patients With Acute Coronary Syndromes Post Index Event With Additional Risk Factors For Cardiovascular Complications Also Receiving Aspirin and Clopidogrel

RE-DEEM

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Disclosure

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Randomised Dabigatran Etexilate Dose Finding Study In Patients With Acute Coronary Syndromes Post Index Event With Additional Risk Factors For Cardiovascular Complications Also Receiving Aspirin And Clopidogrel (RE-DEEM)

Financial disclosure:

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Background

- After acute coronary syndromes patients continue to have recurrent ischemic events despite revascularization and dual antiplatelet therapy
- Oral anticoagulation is superior to aspirin alone following acute coronary syndromes, however warfarin is rarely used
- Novel oral anticoagulants offer an opportunity to reduce recurrent ischemic events beyond dual antiplatelet therapy but also pose a risk of bleeding, as shown in previous phase II studies with inhibitors of factors IIa and Xa

Dabigatran etexilate
an oral direct thrombin inhibitor

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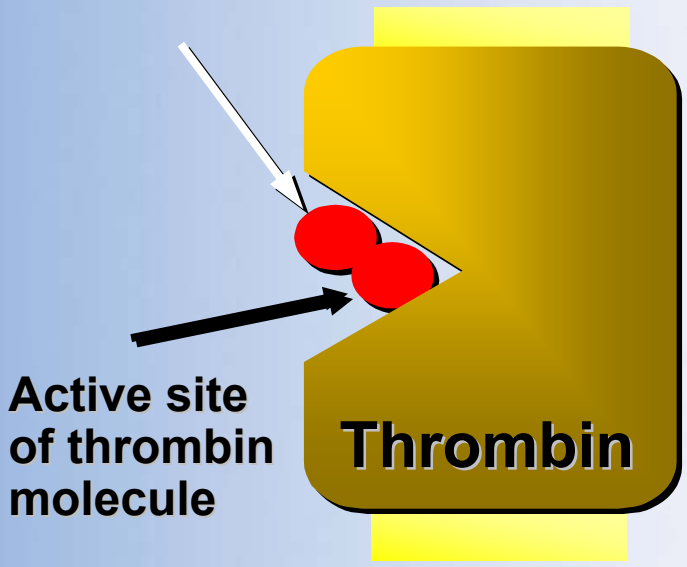
Dabigatran



- Rapid oral absorption & biotransformation of prodrug to active drug
- Bioavailability 6.5%
- Rapid onset, T½ ~ 14-17 h
- Mainly renal excretion (80%)
- Low potential for food/drug interactions, not a CYP 450 substrate, inhibitor or inducer
- No coagulation monitoring required
- Efficacy and safety comparable to LMW heparin for prevention of VTE after orthopedic surgery
- Better efficacy and safety than warfarin for stroke prevention in atrial fibrillation (RE-LY)

Objectives

Compare treatment with 4 different dose regimens of dabigatran versus placebo for 6 months in patients on dual antiplatelet treatment after acute coronary syndrome concerning

- major & clinical relevant minor bleeding events (primary outcome)

- levels of coagulation activity, i.e. D-dimer (secondary)

- composite of cardiovascular death, non-fatal MI and non-hemorrhagic stroke (secondary)

Phase II RE-DEEM Overview

Randomised, double blind, placebo controlled, dose escalation study

ST elevation or non-ST elevation ACS with
≥ 1 additional risk factor for CV complications,
on aspirin & clopidogrel at randomisation

Randomisation within 14 days

Placebo b.d N=373	Dabigatran 50 mg b.d N=372	Dabigatran 75 mg b.d N=371	Dabigatran 110 mg b.d N=411	Dabigatran 150 mg b.d N=351

Study treatment for 6 months

Dose adjustments: Patients with moderate renal impairment (GFR 30-50 ml/min) randomised to 75, 110 or 150 mg were analysed as part of that dose group but were treated with the next lower dose.

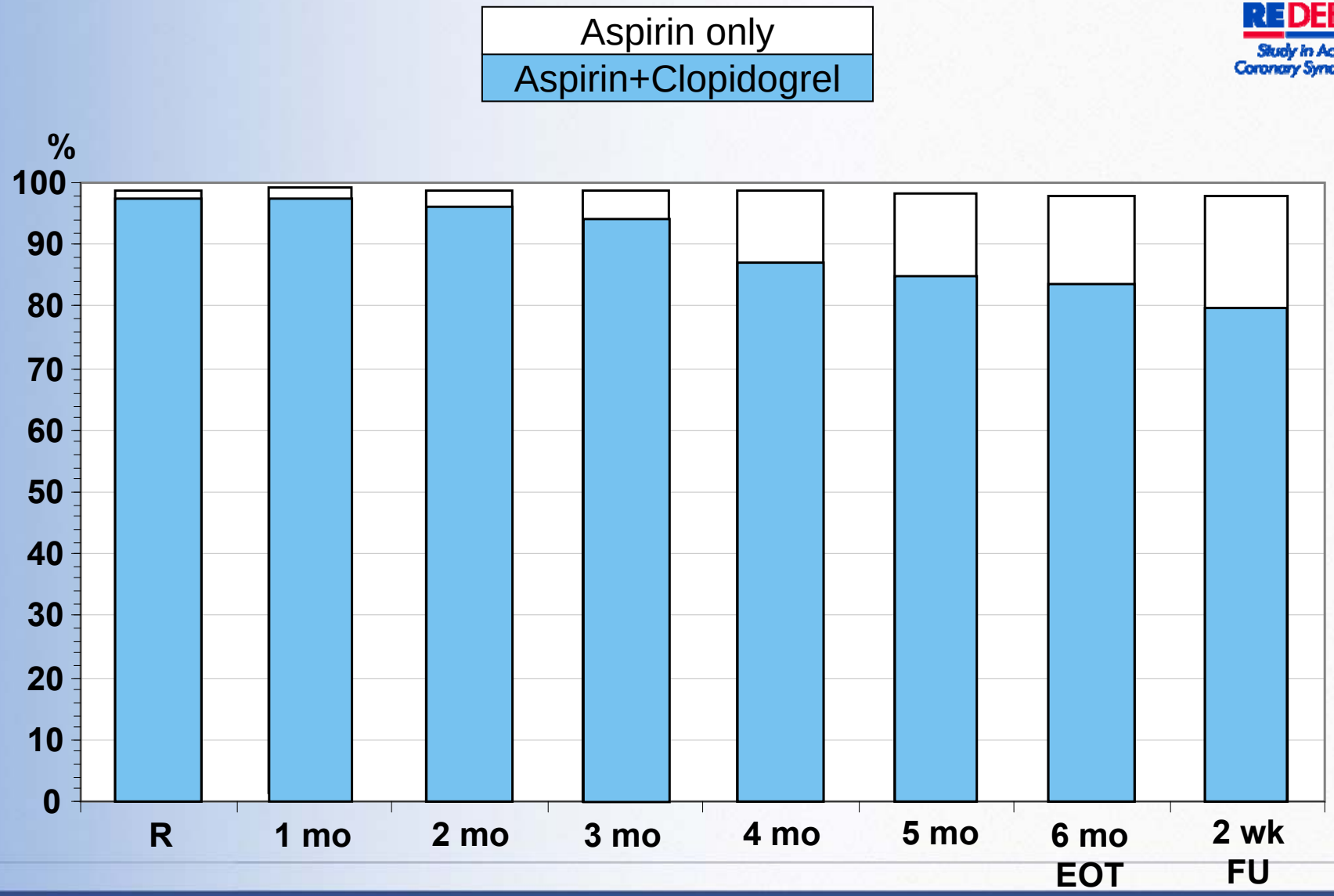
Baseline characteristics

Number of patients	1878	STEMI / NSTEMI	60 / 40 %
Age (mean)	61.8 years	PCI at index event	54 %
Gender (males)	76 %	Days to randomisation (mean)	7.4 days

Risk factors for cardiovascular complications:

Age ≥ 65 years	44 %	Left bundle branch block	3 %
Diabetes mellitus	31 %	Congestive Heart Failure	12 %
Previous MI	29 %	GFR 30-60 ml/min	9 %
Peripheral artery disease	6 %	No revascularisation for index event	31 %

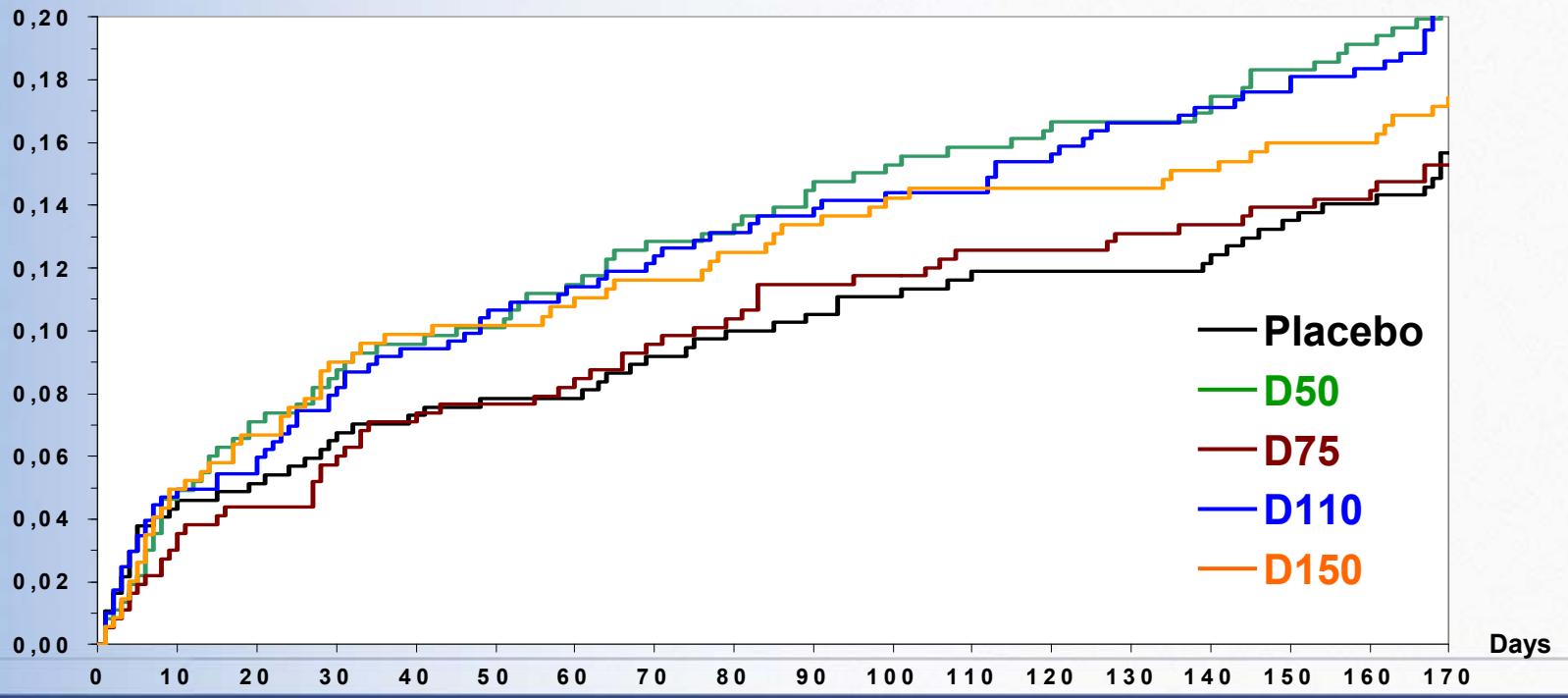
Concomitant antiplatelet medication



R=Randomisation, EOT=End of treatment, FU=Follow-up

Study drug discontinuation

	Placebo	D 50	D 75	D 110	D 150
No of pts	373	372	371	411	351
Serious adverse events	9 %	9 %	8 %	9 %	6 %
Discontinued study treatment	14 %	20 %	16 %	19 %	18 %
- due to AE	8 %	9 %	8 %	12 %	10 %



Primary outcome - definition

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Major bleeding (ISTH)*

- Fatal bleed

and/or

- Symptomatic bleeding in a critical area or organ,

and/or

- Bleeding causing a fall in hemoglobin level of ≥ 20 g/L, or leading to transfusion of ≥ 2 units of whole blood or red cells

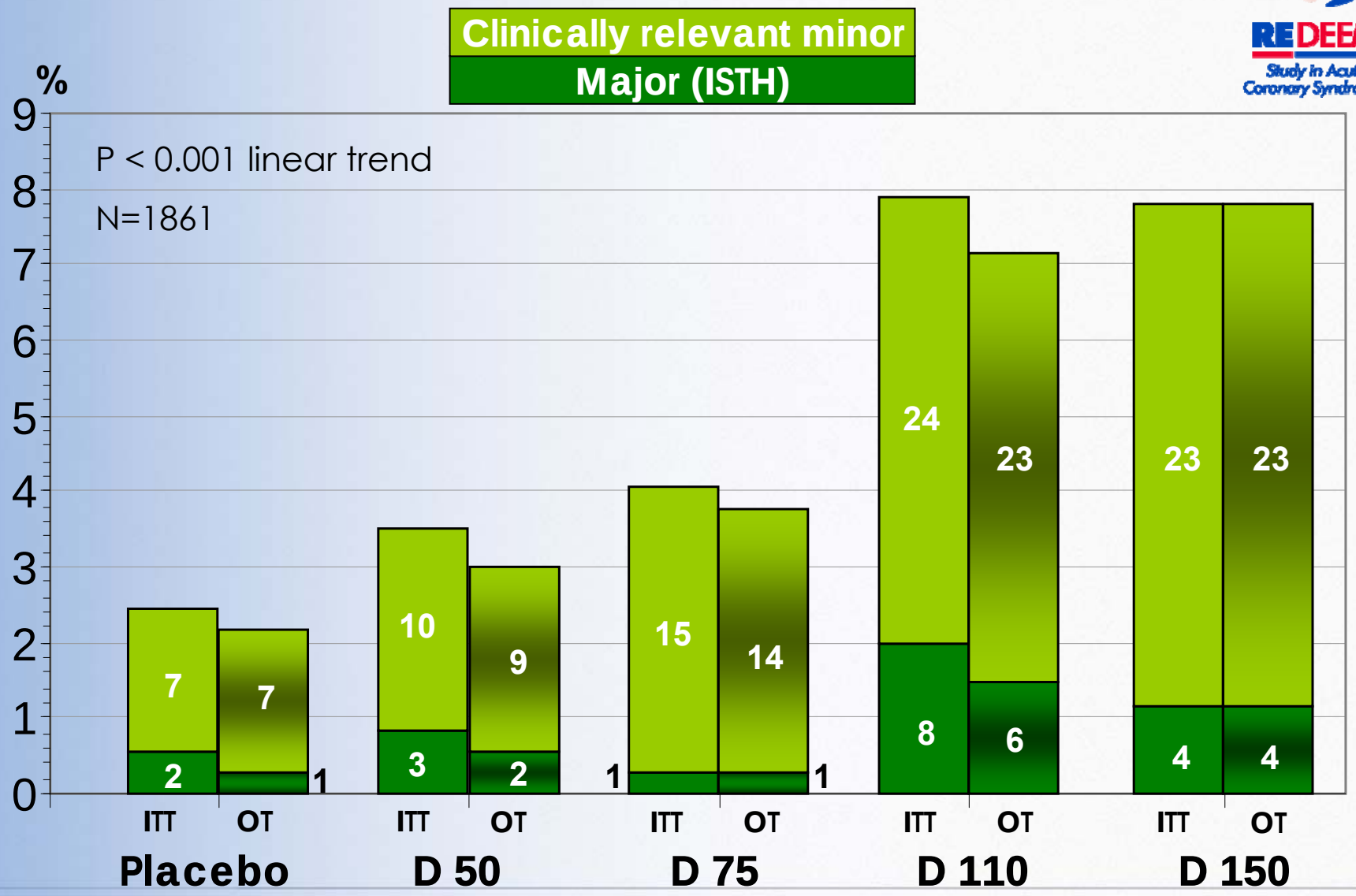
Clinically relevant minor bleeding

- A clinically overt bleed that does not meet the criteria for major bleed but prompts a clinical response,

  i.e hospital admission for bleeding, medical or surgical treatment, or a change in antithrombotic therapy including study drug

*International Society of Thrombosis and Haemostasis

Primary outcome - bleeding



ITT = Intention to treat; OT = On treatment (within 3 days before the event)

Primary outcome – Major and clinically relevant minor bleeding

Time to first event

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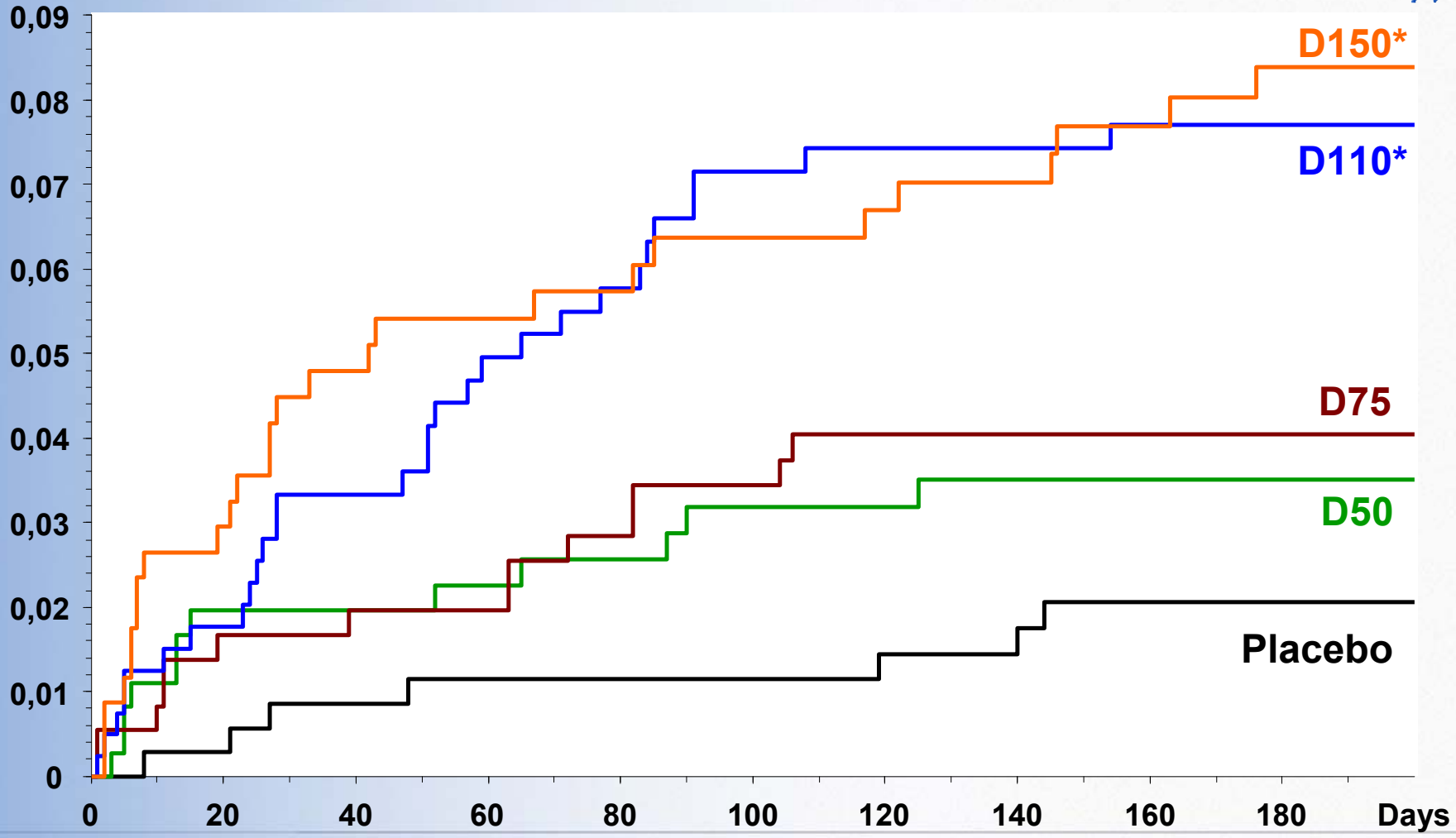

*p < 0.01 log rank test vs placebo N=1861

Major bleeding comparisons

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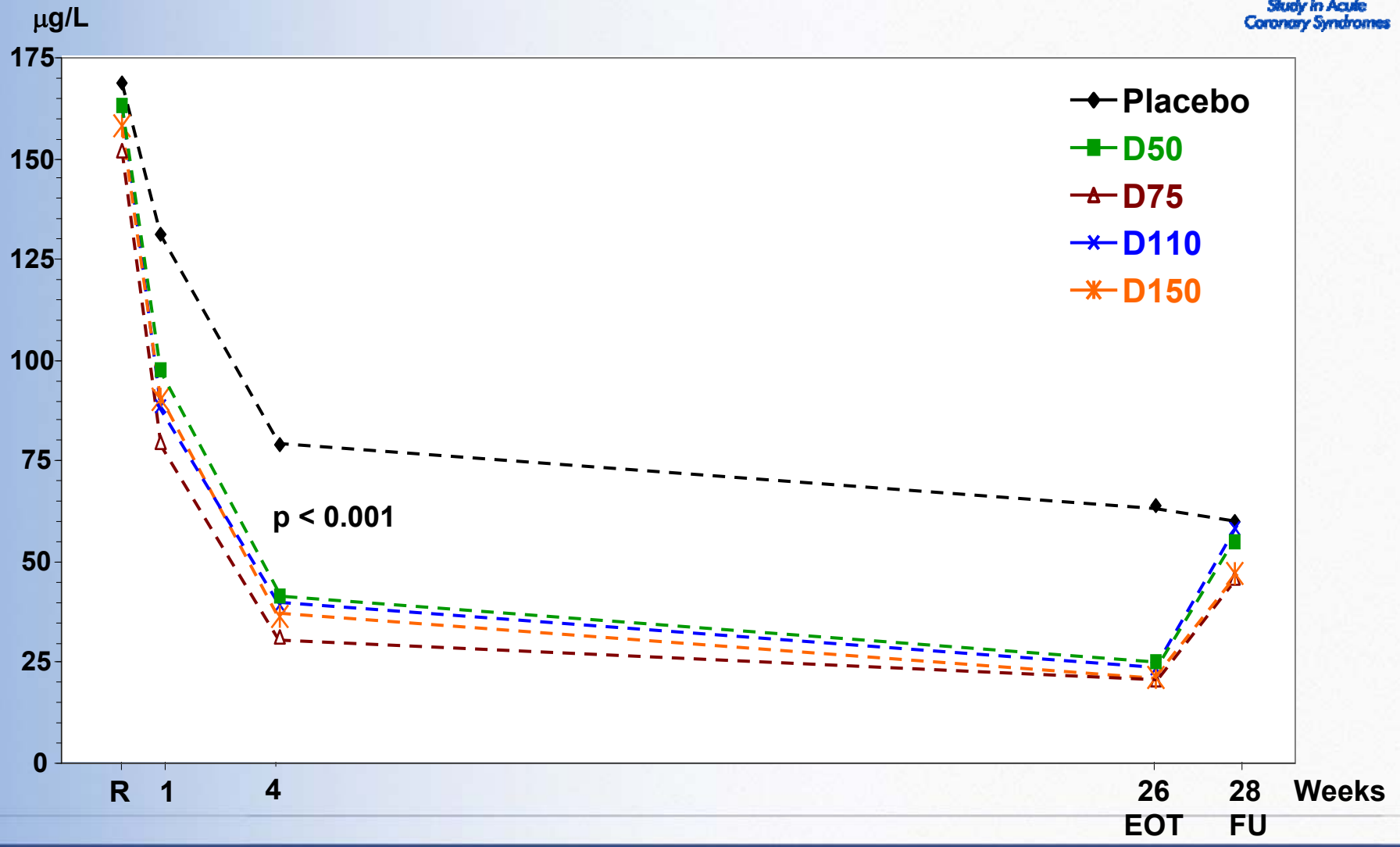
	Placebo N=371	D 50 N=369	D 75 N=368	D 110 N=406	D 150 N=347
ISTH Major	**0.5 %**	**0.8 %**	**0.3 %**	**2.0 %**	**1.2 %**
TIMI Major	**0.3 %**	**0.3 %**	**0**	**1.2 %**	**0.3 %**
GUSTO Severe	**0.3 %**	**0.3 %**	**0**	**0.5 %**	**0**

D-dimer – secondary outcome (medians)



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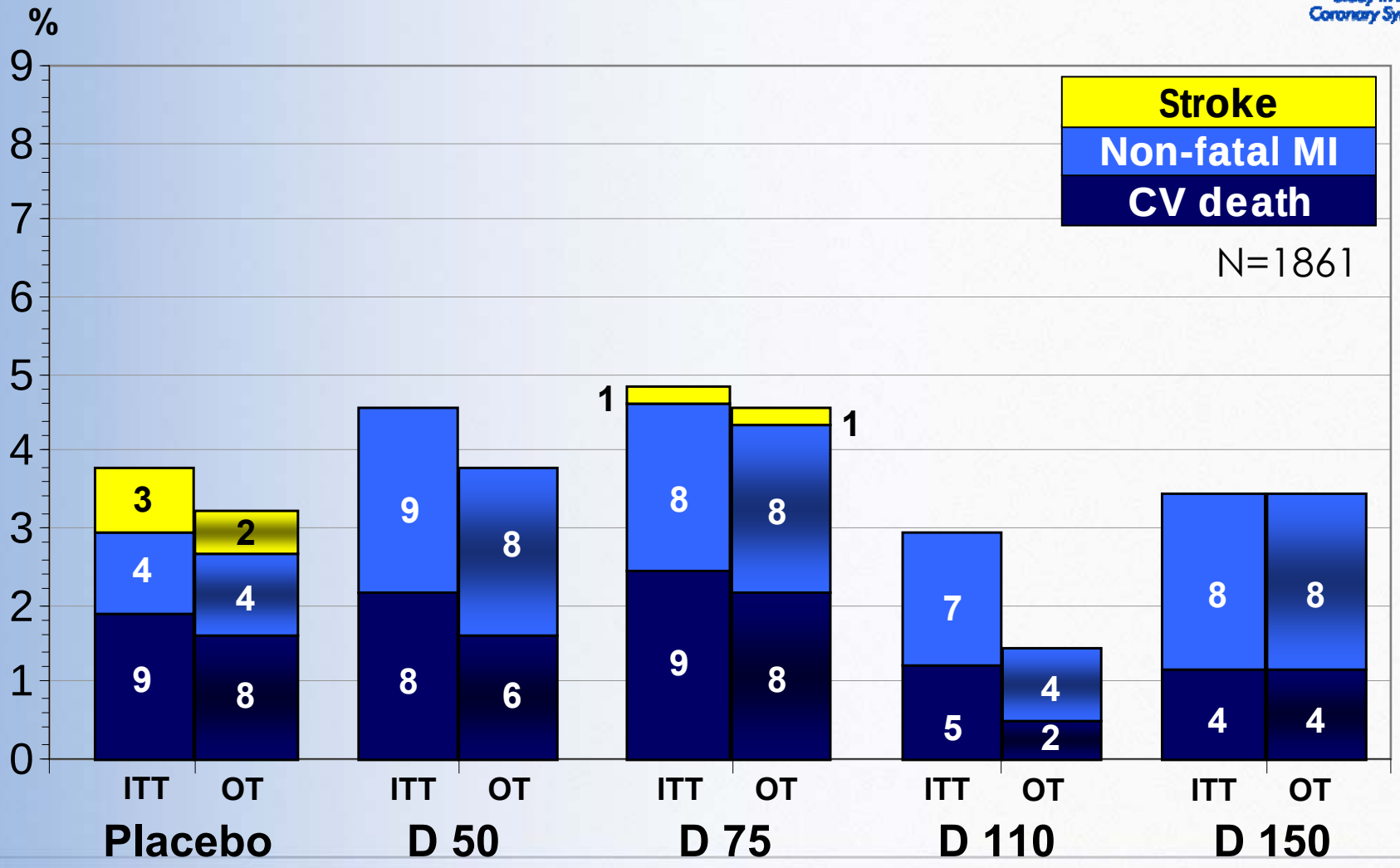
Clinical endpoint – secondary outcome

composite of CV death, non fatal MI, stroke



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Conclusions

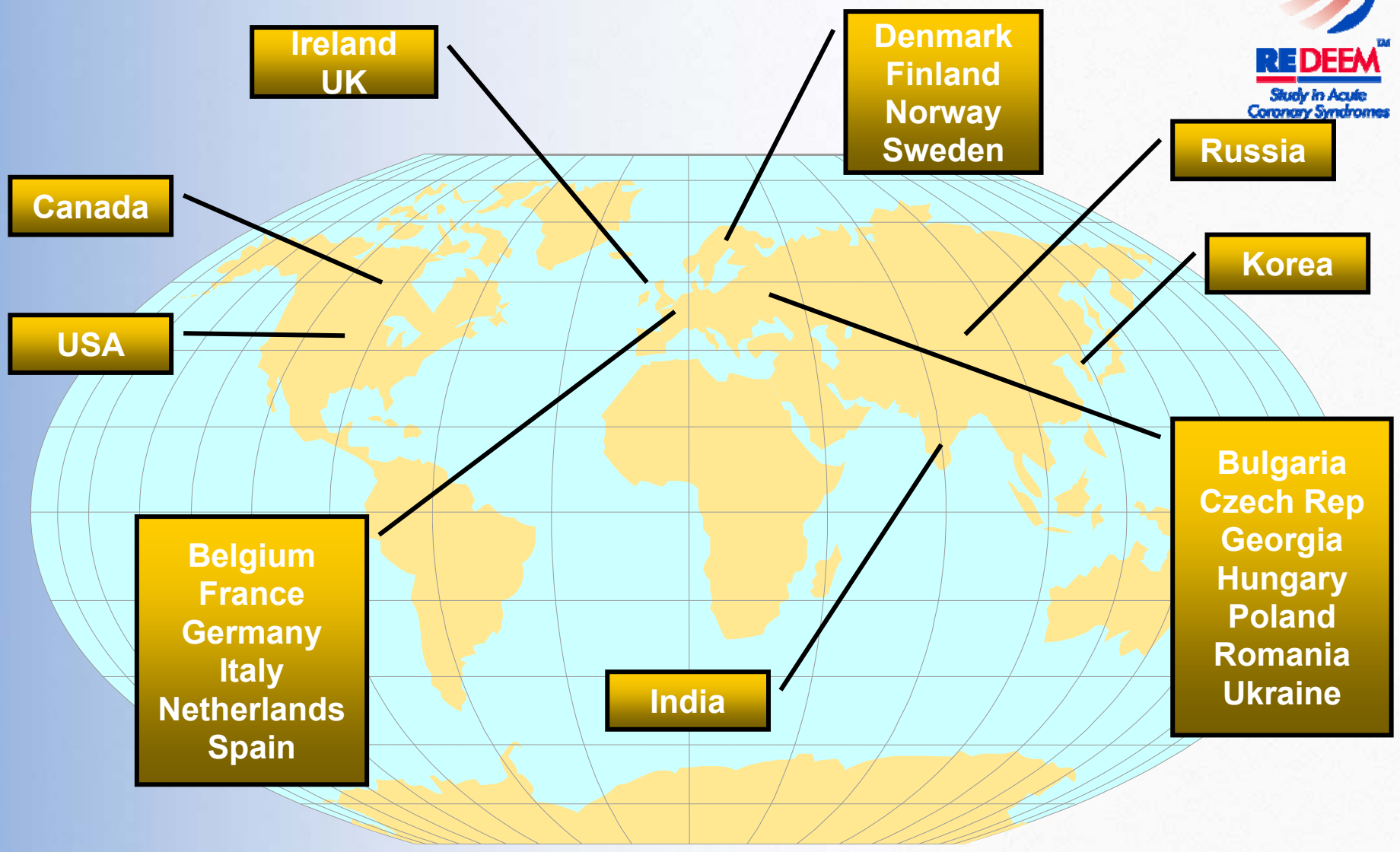
Dabigatran in addition to aspirin and clopidogrel after an acute coronary syndrome is associated with a

- low overall bleeding rate, with
  - dose dependent increase in the composite of major (ISTH) and clinically relevant minor bleeding
  - < 1% absolute increase in major/severe bleeds (ISTH, TIMI, GUSTO) with dabigatran 110 - 150 mg b.d.
- significant reduction in coagulation activity (D-dimer) without dose relationship
- low number of clinical endpoints in all treatment arms
- good tolerability with all four doses

Implications

- Dabigatran up to 150 mg b.d. on top of dual antiplatelet therapy can be used with modestly increased bleeding risk
  - This is of relevance for atrial fibrillation patients after acute coronary syndromes and stenting
- RE-DEEM supports the rationale for evaluation of the 110 and 150 mg dabigatran doses on clinical outcome in acute coronary syndrome patients in a larger adequately powered study

Thank You!



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First patient in March 14, 2008; Last patient out October 2, 2009