D-Fine study: results

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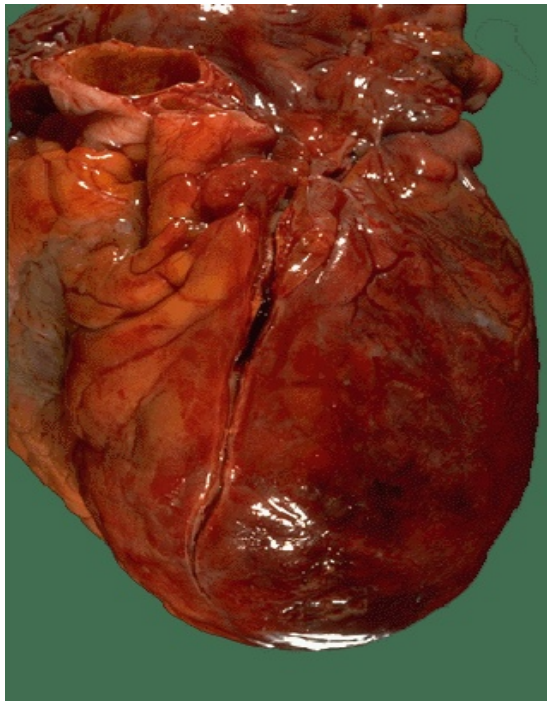
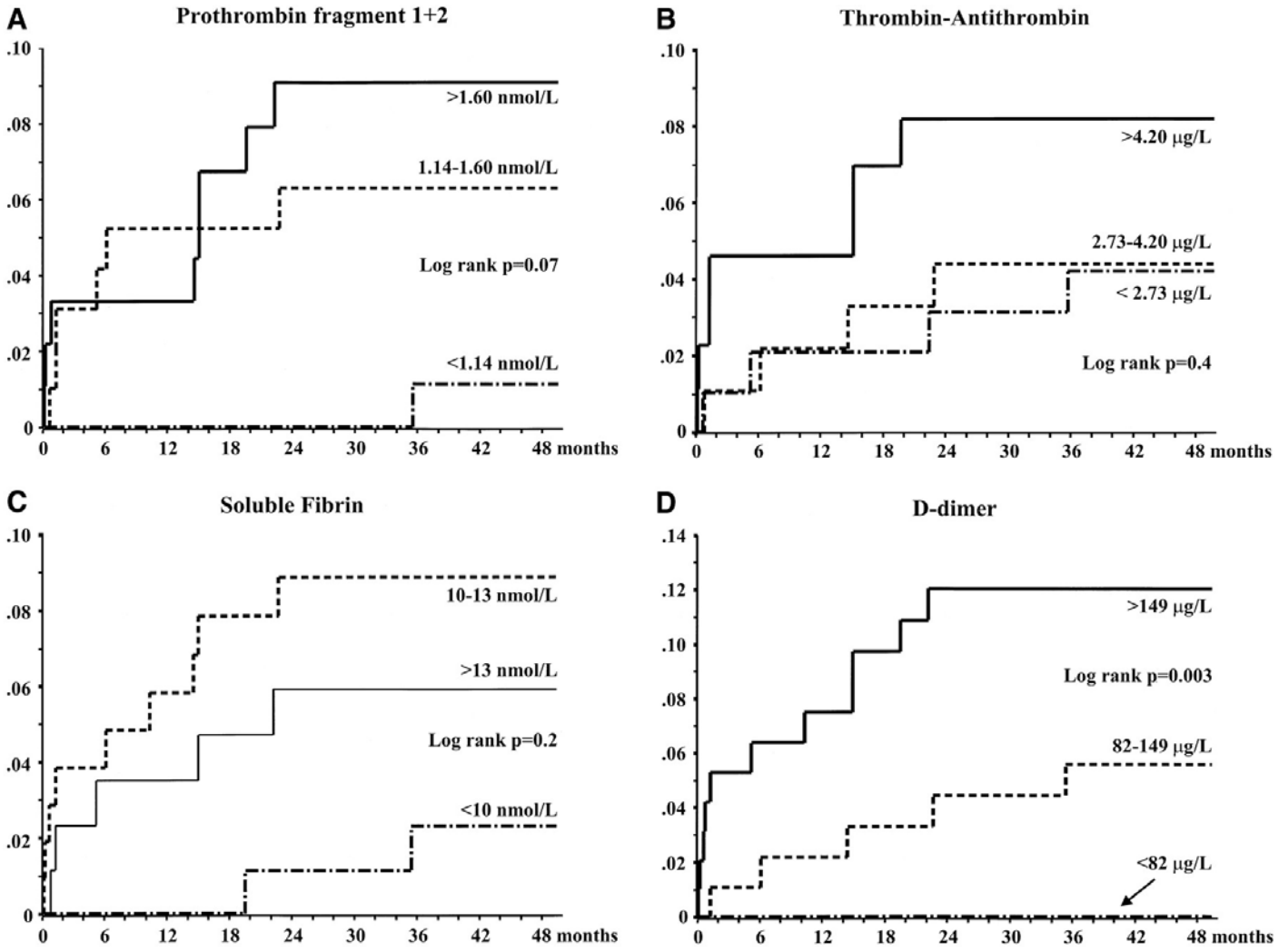
Treatment acute coronary syndrome/ unstable angina pectoris

- PCI/stent
- During PCI thrombus formation may occur
- Burst of thrombin occurs during PCI
  - Enhanced platelet aggregation
  - Enhanced fibrin formation
- During PCI: block thrombin generation

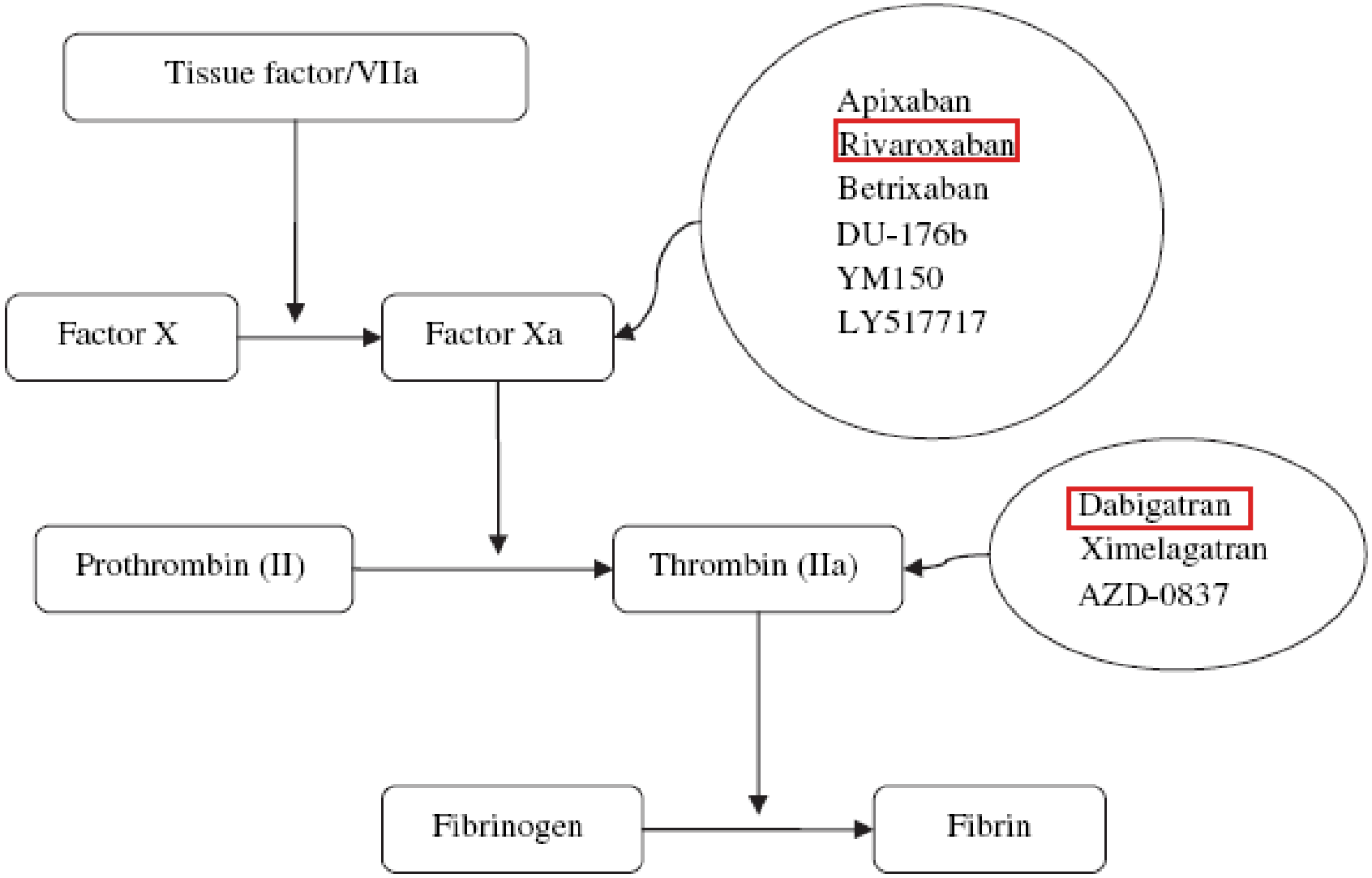


Probability of death during long-term follow-up



Oldgren J et al. ATVB 2001;21:1059-1064

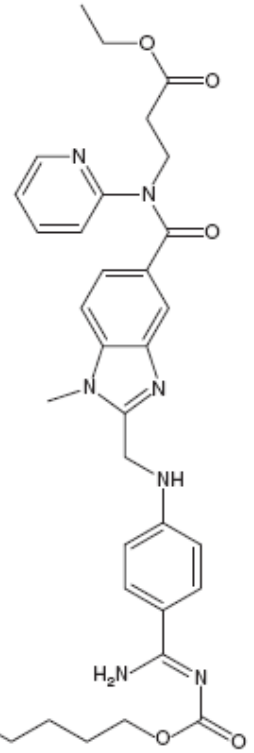
New anticoagulant drugs



Dabigatran Etexilate

- Oral drug
- Small molecule, reversible, direct trombin inhibitor
- Half-life 14-17 hour
- No laboratory control

Box 1. Drug summary.

Drug name (generic)	Dabigatran etexilate
Phase	II – III
Indication	Atrial fibrillation
Pharmacology description/ mechanism of action	Direct thrombin inhibitor
Route of administration	Oral
Chemical structure	
Pivotal trial(s)	PETRO RE-LY

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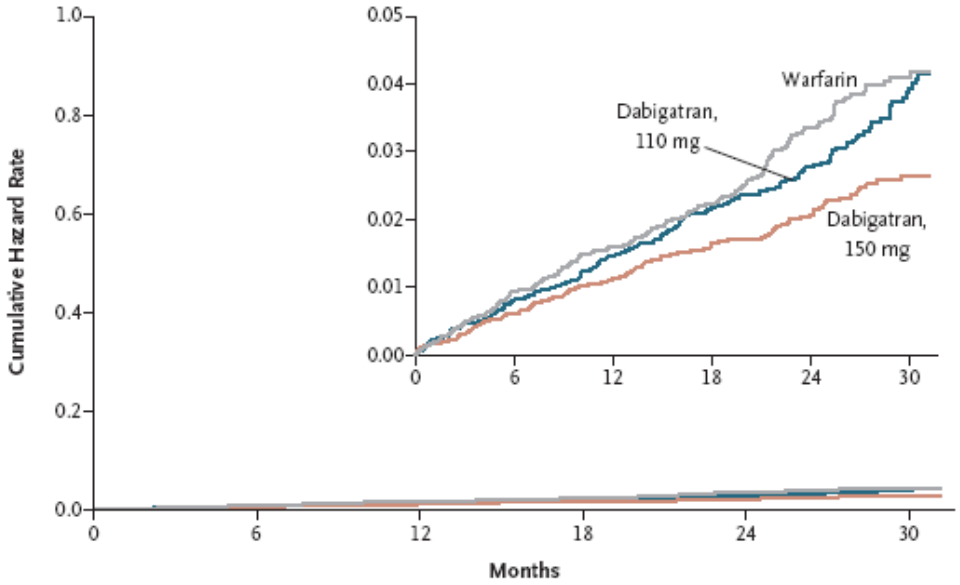
Erasmus MC

Dabigatran versus Warfarin in Patients with Atrial Fibrillation



Dabigatran more effective than VKA for prevention stroke.

D-Fine study

- Randomized, open-label study of dabigatran etexilate in elective percutaneous coronary intervention (PCI)
- Phase II, exploratory study, initially single-centre but later a multi-centre trial
- Low to medium risk patients with coronary arteriy disease
- Dabigatran etexilate (110 or 150 mg 3 dosis twice daily) compared with standard unfractionated heparin (70 IU per kilogram of body weight with subsequent boluses targeted to achieve an activated clotting time (ACT) of 250 to 300)

Vranckx P et al. A randomised study of dabigatran in elective percutaneous coronary intervention in stable coronary artery disease patients. EuroIntervention. 2013 Jan 22;8(9):1052-60.

Primary endpoint

- **Anticoagulant effect** was determined based on the number of patients who needed rescue anticoagulant therapy and/or had clinical signs of catheter related thrombosis during the PCI procedure (until removal of the guiding catheter and the patient has left the catheterization suite).

Secondary endpoint

- The number of patients who experienced
  - Catheter related thrombi which required rescue anticoagulant therapy
  - Abrupt vessel closure, new thrombus with reduced flow, or no-reflow
  - Catheter related thrombi who resulted not in clinical complications including guide-catheter (wire) thrombosis
- Coagulation parameters (measured before and after study drug administration)
  - APTT
  - ACT
  - PT/INR
  - TT (5U and 10U)
  - Fibrinogen
  - F1+2
  - TAT complexes

Table 1. Baseline characteristics of each treatment group.

	Dabigatran 110 mg (n=22)	Dabigatran 150 mg (n=21)	Dabigatran 110 or 150 mg (n=43)	Heparin (n=10)
Age (yr), mean	65.5	63.0	64.3	67.0
Male sex (%)	63.6	71.4	67.4	70.0
BMI (kg/m²), mean (SD)	27.8 (3.5)	27.4 (3.9)	27.6 (3.6)	29.6 (4.4)
BSA (m²), mean (SD)	2.0 (0.2)	2.0 (0.2)	2.0 (0.2)	2.0 (0.2)
Previous MI (%)	22.7	23.8	23.3	10.0
Previous PCI (%)	36.4	33.3	34.9	60.0
Previous CABG (%)	4.5	14.3	9.3	10.0
Hypertension	63.6	71.4	67.4	70.0
Diabetes mellitus	18.2	23.8	20.9	20.0
Current smoker (%)	9.1	9.5	9.3	0.0
Creatinine clearance Class ml per minute per 1.73 m² of BSA				
≥30 and <50 ml	3	0	3	0
≥50 and <80 ml	2	4	6	3
≥80 ml	14	17	31	7
Unknown	3	0	3	0
Silent ischaemia, n (%)	1 (4.5)	0 (0.0)	1 (2.3)	0 (0.0)
Stable angina (%)	21 (95.5)	21 (100.0)	42 (97.7)	10 (100.0)

Categorical variables are presented in absolute values and percent n (%) Non-ST-ACS: non-ST-segment elevation acute coronary syndrome was defined as: unstable angina class I-III according to Braunwald classification with or without elevation of troponin I. Stable angina was defined according to the classification of the Canadian Cardiovascular Society. BMI: body mass index; BSA: body surface area; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; CABG: coronary artery bypass grafting

Clinical outcome

Table 3. The need for rescue medication and/or clinical signs of catheter-related thrombosis during the PCI procedure.

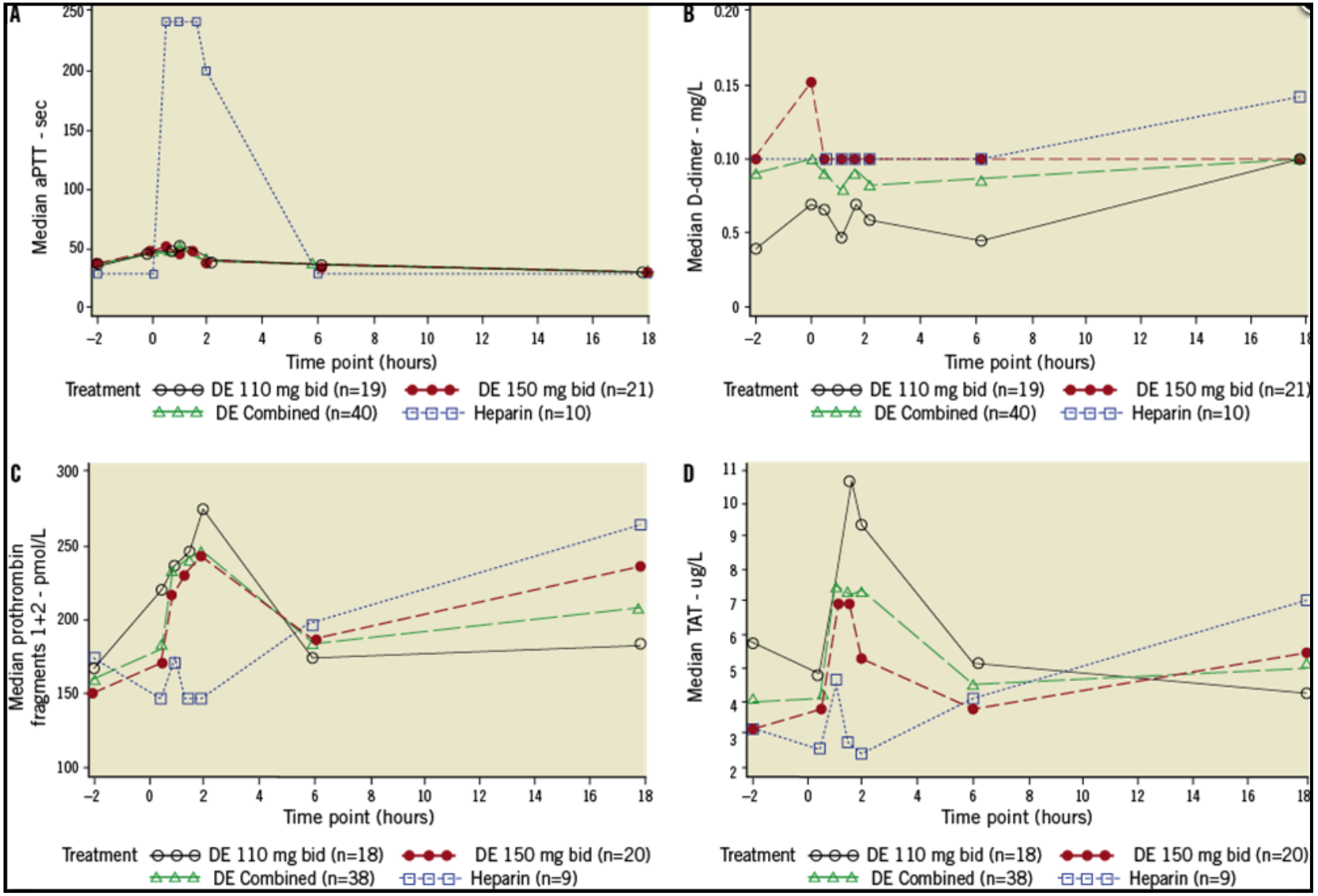
	Dabigatran 110 mg n (%)	Dabigatran 150 mg n (%)	Dabigatran 110 or 150 mg n (%)	Heparin n (%)
Total number of patients in analysis set	19 (100)	21 (100)	40 (100)	10 (100)
Bailout AC therapy and/or catheter-related thrombosis during the procedure*	2 (11)	3 (14)	5 (13)	1 (10)
Odds ratio (95% CI) vs. heparin	1.00 (0.08, 12.76)	1.50 (0.13, 16.82)	1.25 (0.13, 12.25)	
Bailout antithrombotic therapy				
UFH	0	3 (14)	3 (8)	0
GP IIb/IIIa inhibitor	1 (5)	2 (10)	3 (8)	1 (10)
Abrupt vessel closure, new thrombus with reduced flow, or no-reflow	2 (11)	1 (5)	3 (8)	0
Myocardial infarction				
Periprocedural	2 (11)	3 (14)	5 (13)	0
Procedural	1 (5)	3 (14)	4 (11)	0

AC: anticoagulation; UFH: unfractionated heparin; *Until removal of the guiding catheter and the patient left the catheterisation laboratory; GP IIb/IIIa inhibitor=abciximab

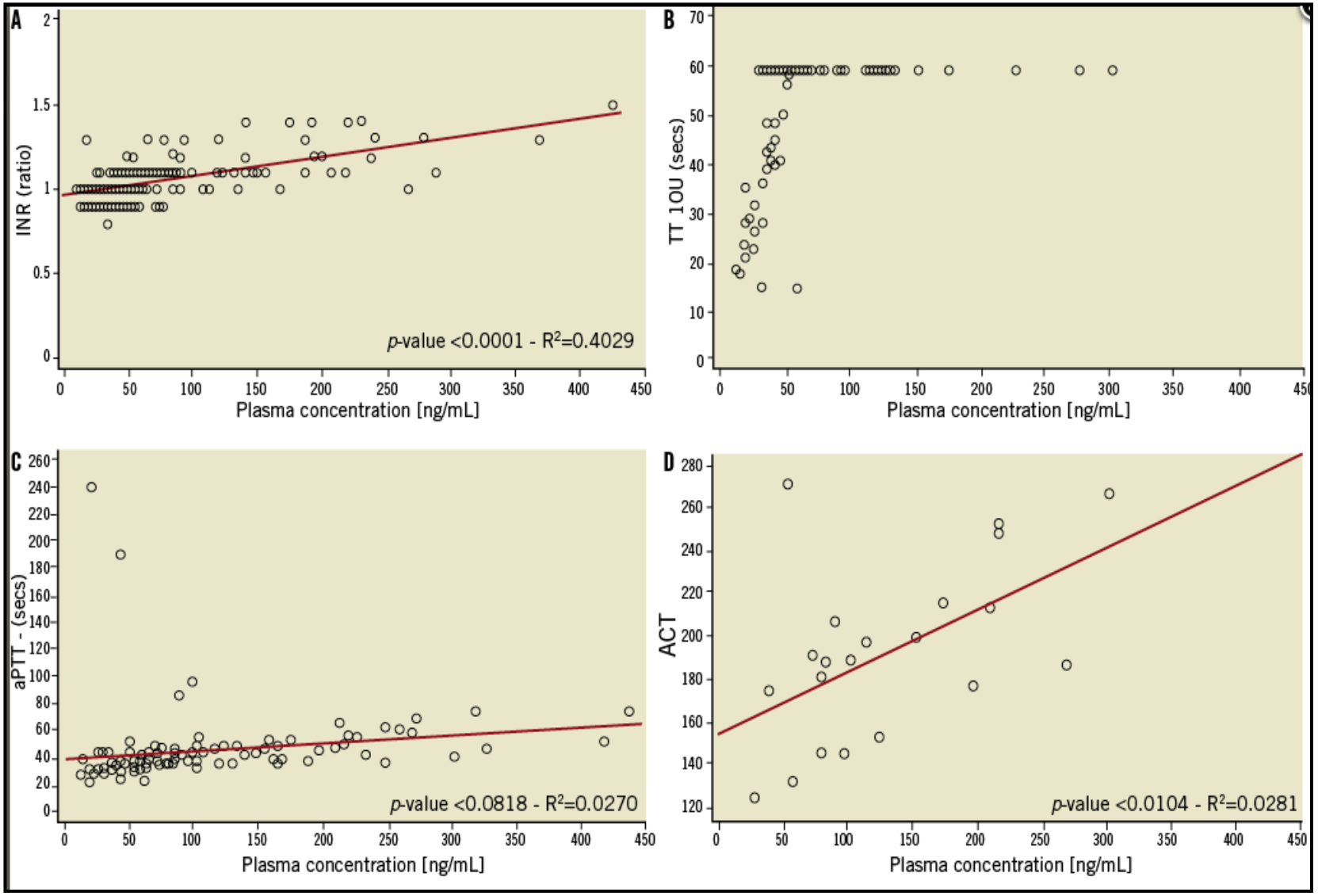
Results: Primary endpoint

- The primary endpoint (rescue medication and/or clinical signs of catheter related thrombus during the PCI) occurred in 5 patients in the dabitatran treatment group and in 1 patient in the UFH group. In the per protocol analysis 1 patient in the dabigatran group was left out of the analysis compared to the FAS. No significant differences were seen.

Results of markers of coagulation related to the index PCI

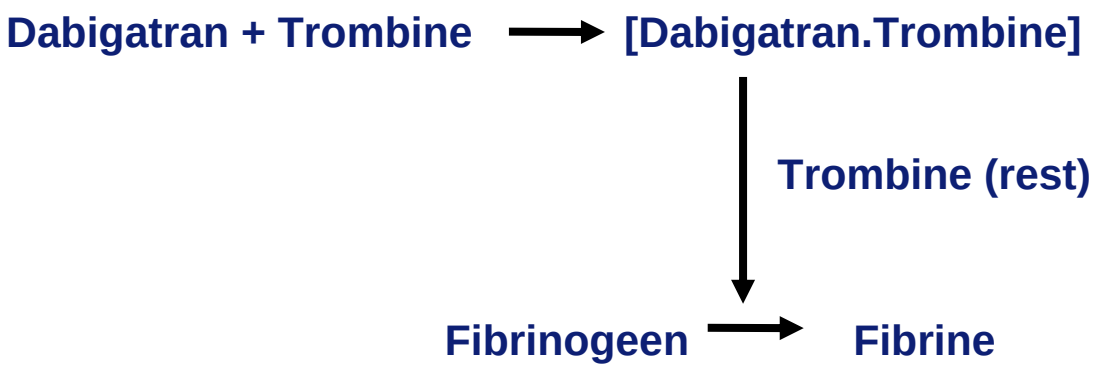


Relationship between dabigatran plasma concentrations and INR, TT 10U, aPTT and ACT

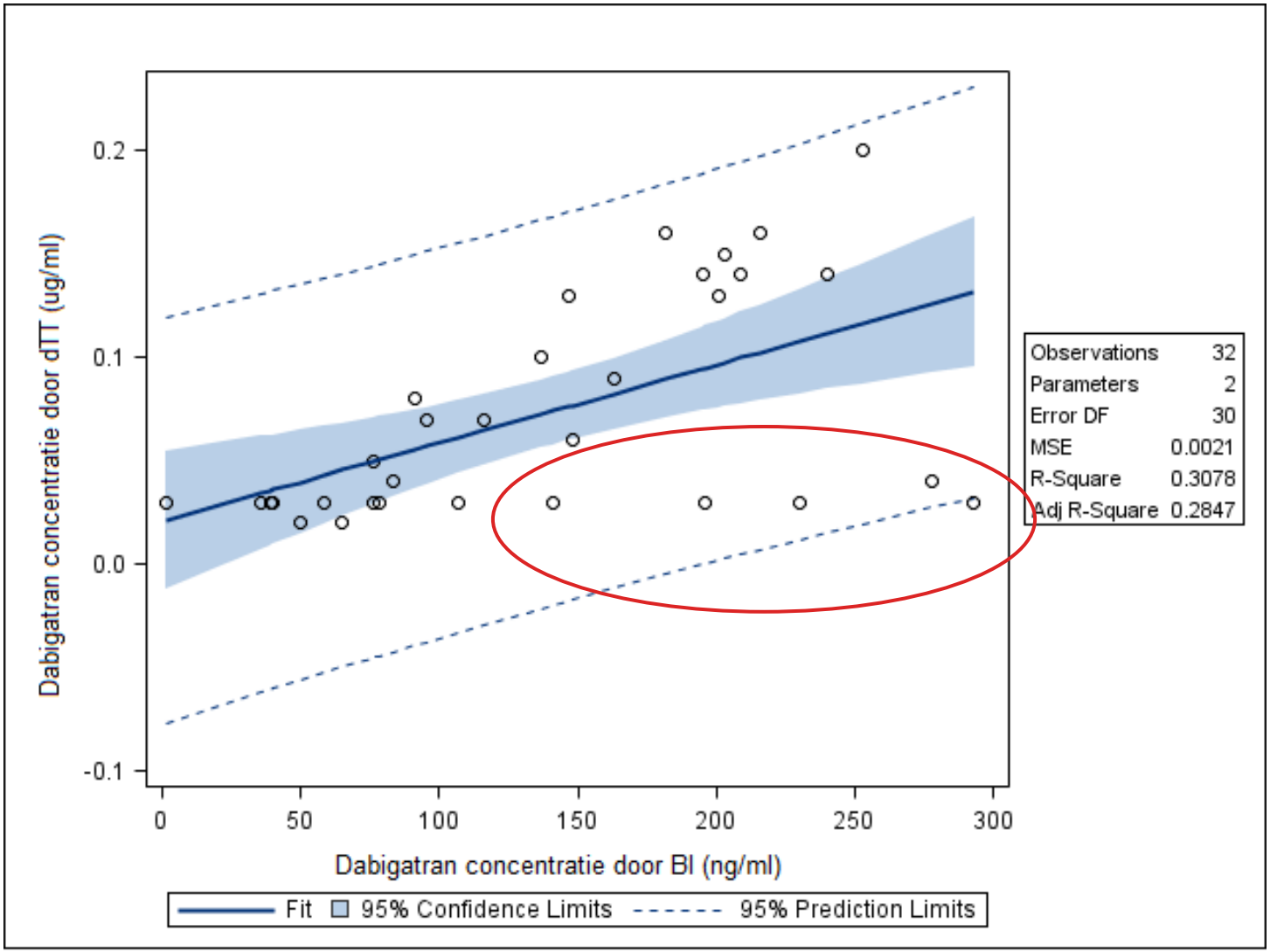


PT: Tromborel S, APTT: Triniclot

dTT (Hemoclot, Nodia)



Relationship between dabigatran concentration and dTT



Conclusions lab studies

- Increase of F 1+2 and TAT complexes in patients treated with dabigatran, no increase in UFH treated patients
- Is this related to the occurrence of Ischemic events ??
- How is the course of coagulation activation markers in patients with and without events?

Overall conclusions

- This trial demonstrated that dabigatran was comparabel to the standard treatment of UFH for the primary endpoint. However, this study was too small to provide conclusive statistical inference. No statistically significant treatment differences were seen for any of the pre-specified secondary clinical endpoints.
- With respect to the coagulation parameters, known differences in measurements between heparin and dabigatran were confirmed. Only one bleeding event took place and this was a puncture site bleed