Safety of the DOAC's … and the novel antiplatelet agents

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Topics

- Are the DOAC's safe?
- Reversibility
- Monitoring
- Choice and duration of anticoagulation
- Dealing with new antiplatelet agents

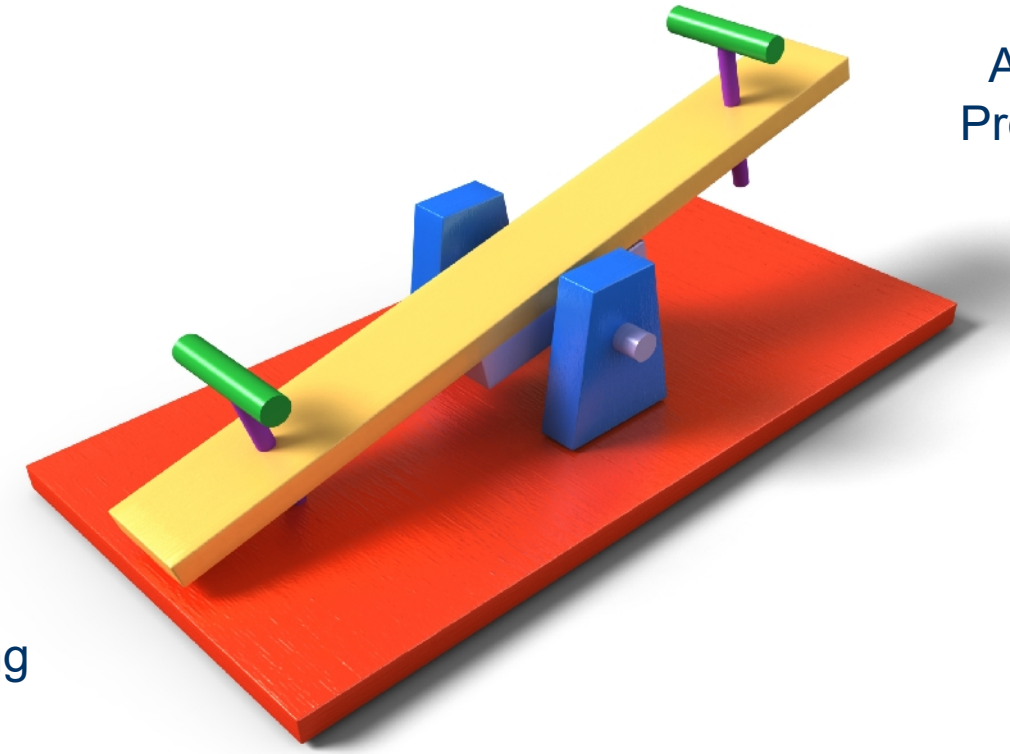
Let's assume …

That for

- DVT therapy, and
- Non-valvular atrial fibrillation

that the DOAC's are at least non-inferior to LMWH / VKA alternative

The Risk See-Saw in choice of anti-coagulant



Availability of Proven antidote

Lower bleeding Risk

Thromboprophylaxis in Medical Patients

- MAGELLAN[1]
  - Thromboprophylaxis in medically ill patients
  - Randomised, double blinded
    - Rivaroxaban (35+/-4 days) v clexane (10+/-4 days)
    - Non-inferiority assessment at 10 days
    - Superiority assessment at 35 days
  - Efficacy:
    - Non-inferior at 10 days: 78 v 82 events
    - Superior at 35 days: 131 v 175 events (p=0.02)
  - Safety

1 **Cohen AT et al. N Engl J Med 2013;368:513-523**

Safety Outcomes.

Table 4. Safety Outcomes.*

Outcome	Rivaroxaban (N=3997)	Enoxaparin–Placebo (N=4001)	Relative Risk (95% CI)	P Value
	no. (%)			
Clinically relevant bleeding: principal safety outcome at day 10	111 (2.8)	49 (1.2)	2.3 (1.63–3.17)	<0.001
Any major bleeding	24 (0.6)	11 (0.3)	2.2 (1.07–4.45)	0.03
Major bleeding leading to fall in hemoglobin of ≥2 g/dl	17 (0.4)	7 (0.2)	—	—
Major bleeding leading to transfusion of ≥2 units of blood	15 (0.4)	5 (0.1)	—	—
Major bleeding at a critical site	5 (0.1)	1 (<0.1)	—	—
Fatal major bleeding	5 (0.1)	1 (<0.1)	—	—
Clinically relevant bleeding: principal safety outcome at day 35	164 (4.1)	67 (1.7)	2.5 (1.85– 3.25)	<0.001
Any major bleeding	43 (1.1)	15 (0.4)	2.9 (1.60–5.15)	<0.001
Major bleeding leading to fall in hemoglobin of ≥2 g/dl	31 (0.8)	10 (0.2)	—	—
Major bleeding leading to transfusion of ≥2 units of blood	24 (0.6)	8 (0.2)	—	—
Major bleeding at a critical site	9 (0.2)	4 (0.1)	—	—
Fatal major bleeding	7 (0.2)	1 (<0.1)	—	—
Other safety outcomes				
Any cardiovascular event during treatment†	51 (1.3)	49 (1.2)	—	—
Any adverse event during treatment, excluding bleeding	2616 (65.4)	2607 (65.2)	—	—
Any serious adverse event during treatment, excluding bleeding	616 (15.4)	569 (14.2)	—	—

* Two-sided 95% confidence intervals for weighted relative risks were calculated with the use of asymptotic methods, with weights based on sample sizes per stratum of geographic region. The P values were calculated on the basis of the normal approximation. Outcomes for which relative risks and P values are not shown are those for which the analyses were not prespecified.

† Included are events of cardiovascular death, ischemic stroke, acute myocardial infarction, and acute stroke of unknown type.

Cohen AT et al. N Engl J Med 2013;368:513-523.

The NEW ENGLAND JOURNAL of MEDICINE

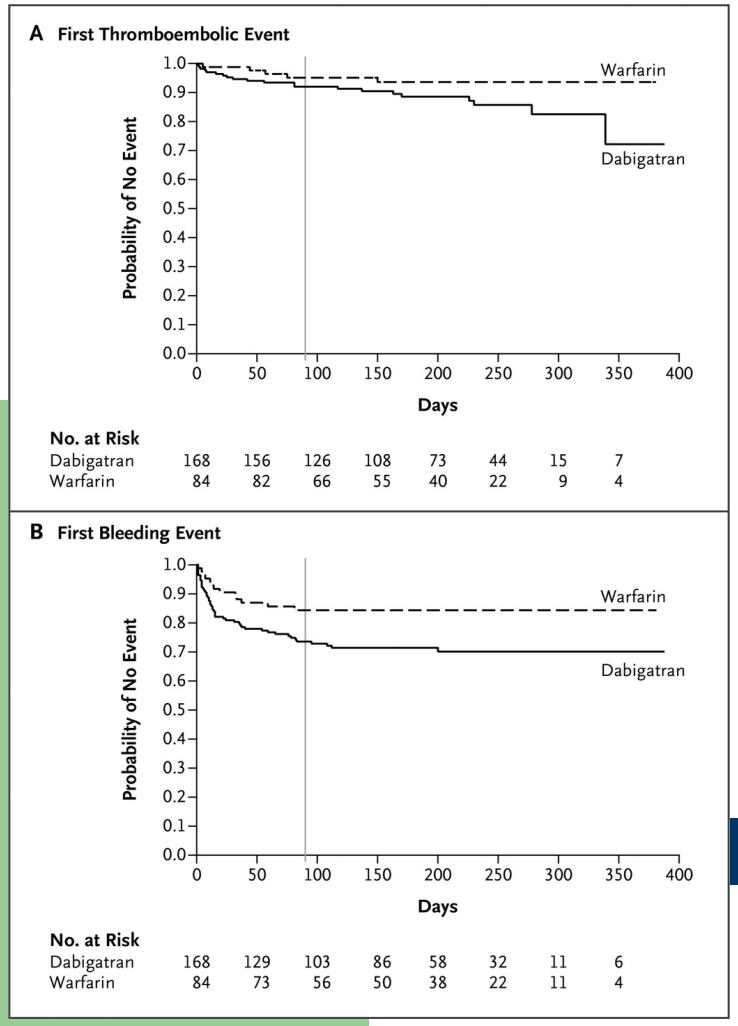
Re-ALIGN STUDY

- Prospective, randomised, open-label Phase II
- 2 populations:
  - Undergoing bileaflet mechanical mitral or aortic valve replacement
  - Undergone mitral valve replacement 3 months ago.
- Dabigatran (adjusted dose based on trough levels) *versus* warfarin (INR 2.0-3.0)
- 12 week study duration

- Early study termination

Eikelboom JW et al. N Engl J Med 2013;369:1206-1214.

Kaplan–Meier Analysis of Event-free Survival.



p=0.24

p=0.01

Eikelboom JW et al. N Engl J Med 2013;369:1206-1214.

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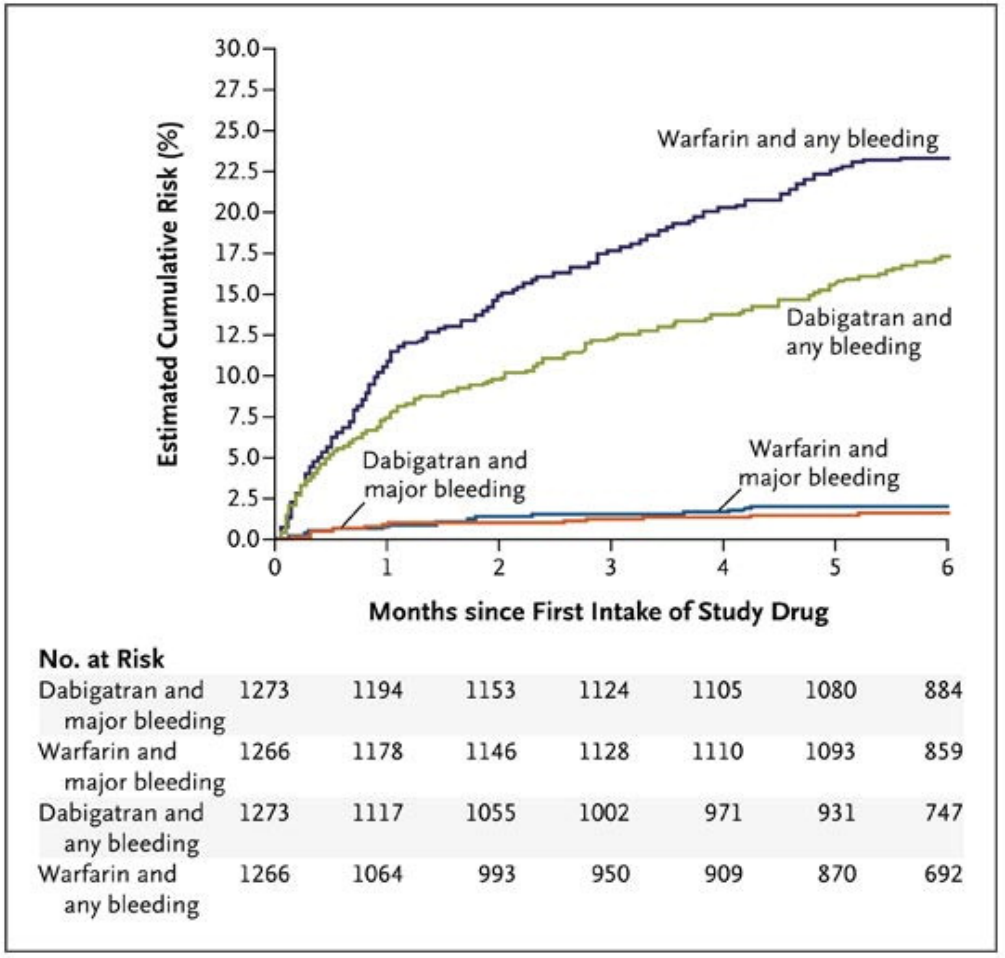
Bleeding Definitions

- Major bleeding
  - Drop in Hb of 20g/L
  - 2U PRBC transfusion
  - Intracranial
  - Retroperitoneal
  - Death
- Clinically significant non-major
  - Medical intervention
  - Unscheduled physician review
  - Study interruption / discontinuation
  - Pain, or effect on activities

Cumulative Risks of a First Event of Major Bleeding and of Any Bleeding among Patients Randomly Assigned to Dabigatran or Warfarin.



No. at Risk							
Dabigatran and major bleeding	1273	1194	1153	1124	1105	1080	884
Warfarin and major bleeding	1266	1178	1146	1128	1110	1093	859
Dabigatran and any bleeding	1273	1117	1055	1002	971	931	747
Warfarin and any bleeding	1266	1064	993	950	909	870	692

Schulman S et al. N Engl J Med 2009;361:2342-2352.

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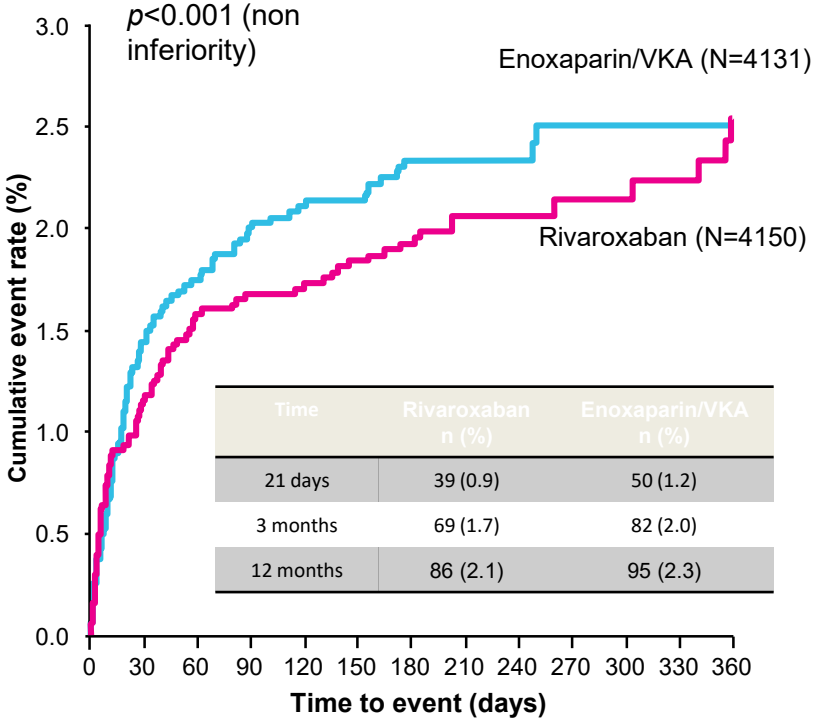
Similar Efficacy with less Major Bleeding Risk

Recurrent VTE[1]

HR=0.89
95% CI 0.66–1.19
p<0.001 (non inferiority)



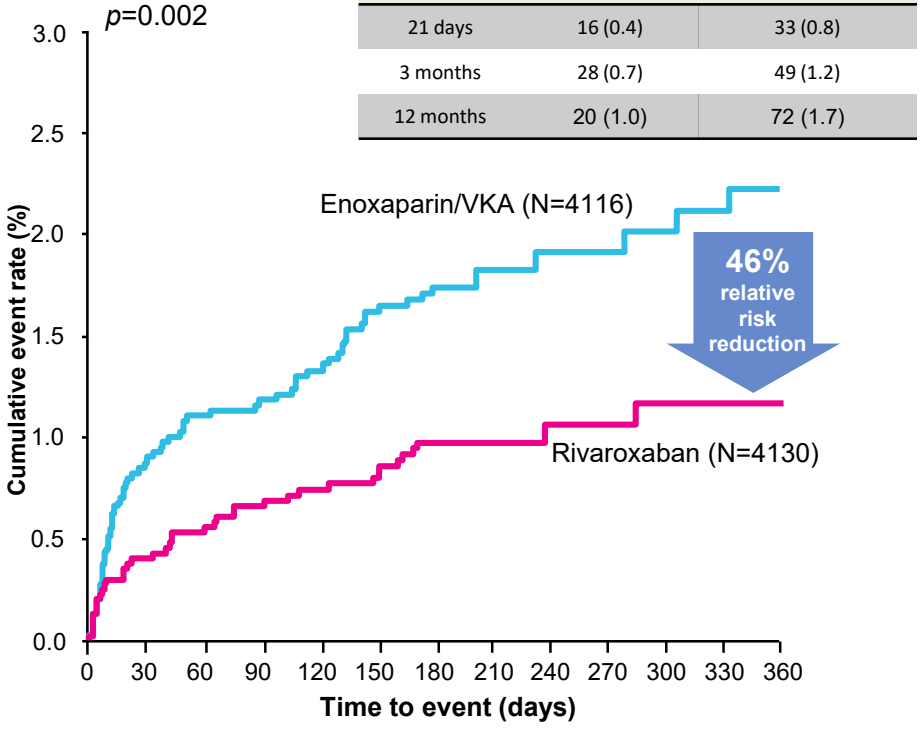
Time	Rivaroxaban n (%)	Enoxaparin/VKA n (%)
21 days	39 (0.9)	50 (1.2)
3 months	69 (1.7)	82 (2.0)
12 months	86 (2.1)	95 (2.3)

Number of patients at risk													
Rivaroxaban	4150	4018	3969	3924	3604	3579	3283	1237	1163	1148	1102	1034	938
Enox/VKA	4131	3932	3876	3826	3523	3504	3236	1215	1149	1109	1071	1019	939

Major Bleeding[2]

HR=0.54
95% CI 0.37–0.79
p=0.002

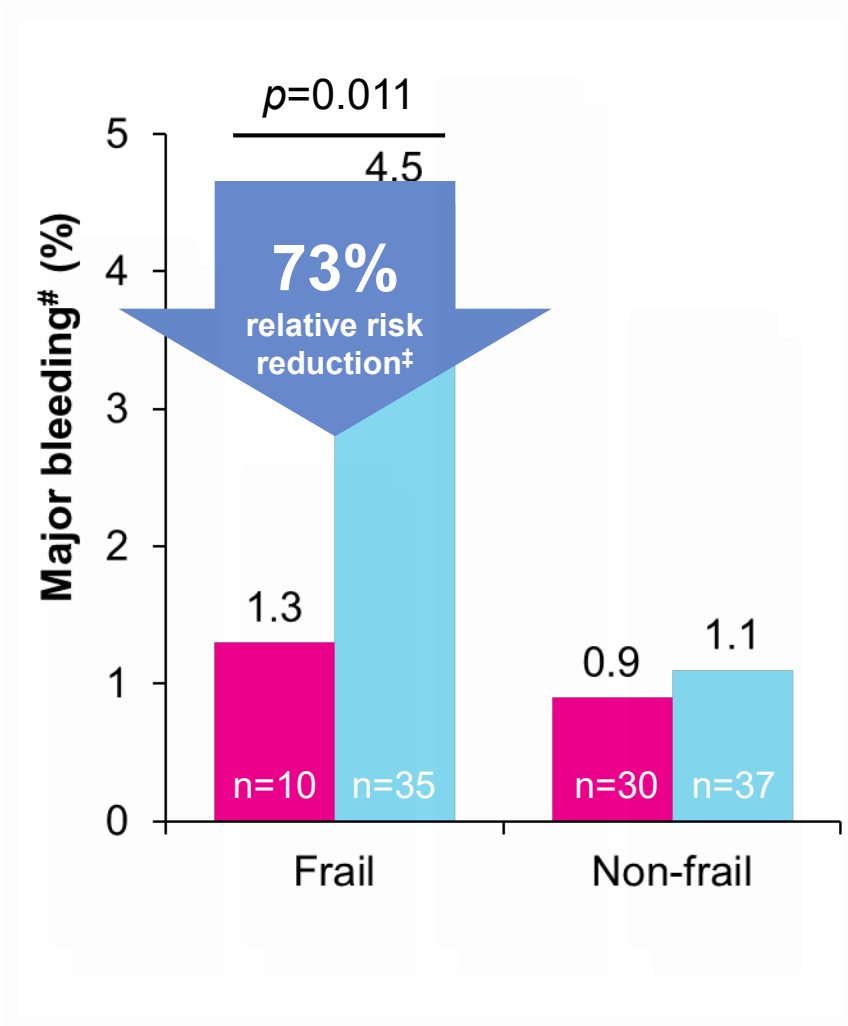
Time	Rivaroxaban n (%)	Enoxaparin/VKA n (%)
21 days	16 (0.4)	33 (0.8)
3 months	28 (0.7)	49 (1.2)
12 months	20 (1.0)	72 (1.7)

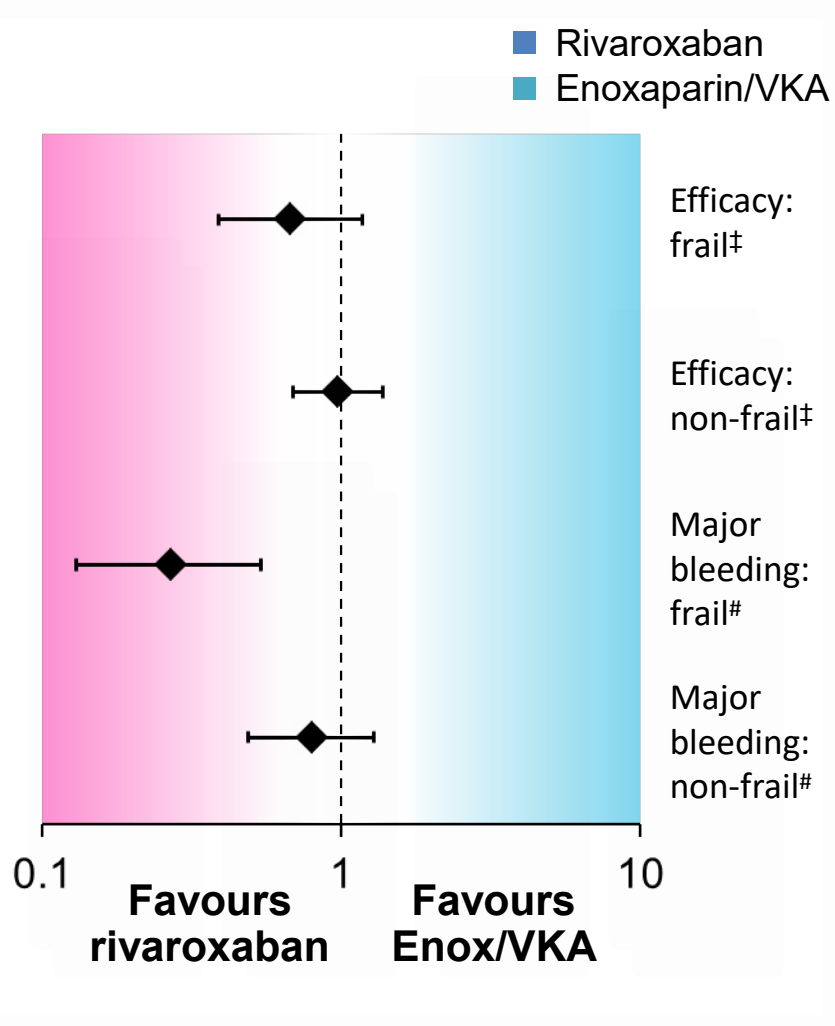


Number of patients at risk													
Rivaroxaban	4130	3921	3862	3611	3479	3433	2074	1135	1095	1025	969	947	499
Enox/VKA	4116	3868	3784	3525	3394	3348	1835	1109	1065	990	950	916	409

[1]Recurrent VTE measured in the ITT population; [2]Major bleeding measured from the safety population as a secondary outcome measure
Prins *et al*, 2013

Effective treatment of Frail* VTE patients with a significantly reduced incidence of major bleeding

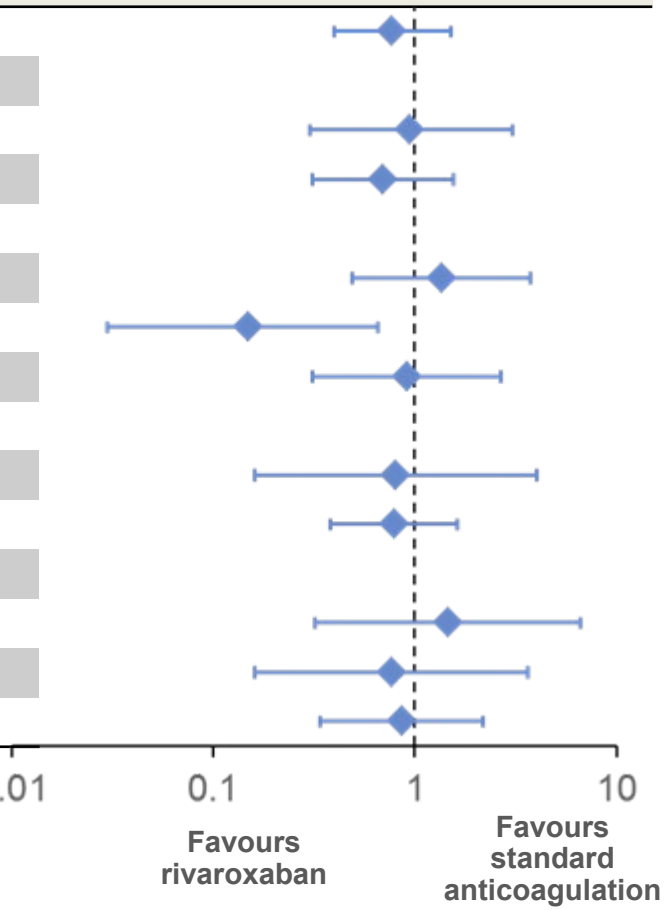




*One or more of: >75 years old, CrCl <50 ml/min, low body weight (≤50 kg); #safety population (N=8246); frail patients (n=1567);
‡ITT population (N=8281); frail patients (n=1573)
Prins MH *et al*. *Thromb J* 2013

Treatment-Emergent Major Bleeding Across Subgroups

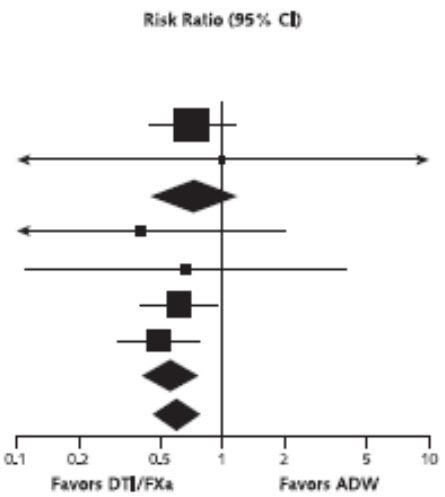
	Rivaroxaban		Standard anticoagulation		HR (95% CI)
	n/N	(%)	n/N	(%)	
All patients	19/2505	(0.8)	43/2010	(2.1)	
Age					
<60 years	8/1286	(0.6)	11/785	(1.4)	
≥60 years	11/1219	(0.9)	32/1225	(2.6)	
Weight					
≤70 kg	7/522	(1.3)	14/495	(2.8)	
>70–<90 kg	3/843	(0.4)	14/663	(2.1)	
≥90 kg	6/599	(1.0)	12/482	(2.5)	
Active cancer at baseline					
Yes	2/144	(1.4)	13/338	(3.8)	
No	17/2361	(0.7)	30/1672	(1.8)	
First available CrCl					
<50 ml/min	3/98	(3.1)	9/194	(4.6)	
≥50–<80 ml/min	3/410	(0.7)	10/366	(2.7)	
≥80 ml/min	12/1047	(1.1)	16/757	(2.1)	



Note: some demographic parameters have data missing
Propensity score-adjusted population

Pooled Data – Fatal Bleeding

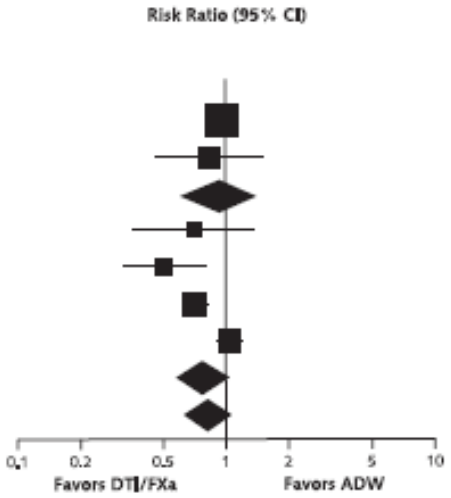
Study, Year (Reference)	Events/Total, n/N DTI/FXa	Warfarin	Risk Ratio	Lower Limit	Upper Limit
Fatal bleeding					
Connolly et al, 2009 (32)	28/6075	39/6022	0.71	0.44	1.15
Schulman et al, 2009 (35)	1/1273	1/1266	0.99	0.06	15.88
DTI			0.72	0.45	1.16
Bauersachs et al, 2010 (36)	2/1731	5/1718	0.40	0.08	2.04
Büller et al, 2012 (16)	2/2412	3/2405	0.66	0.11	3.97
Granger et al, 2011 (33)	34/9088	55/9052	0.62	0.40	0.94
Patel et al, 2011 (34)	27/7111	55/7125	0.49	0.31	0.78
FXa			0.55	0.41	0.75
Total			0.60	0.46	0.77



Adam S, Ann Intern Med 2012; 157: 796

Pooled Data – Major Bleeding

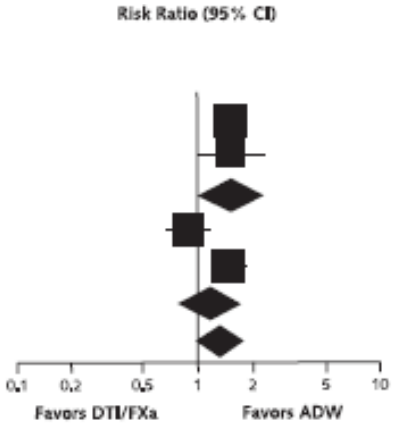
Study, Year (Reference)	Events/Total, *n/N*		Risk Ratio	Lower Limit	Upper Limit
	DTI/FXa	Warfarin			
Major bleeding					
Connolly et al, 2009 (32)	399/6076	421/6022	0.94	0.82	1.07
Schulman et al, 2009 (35)	20/1273	24/1266	0.83	0.46	1.49
DTI			0.90	0.60	1.37
Bauersachs et al, 2010 (36)	14/1731	20/1718	0.69	0.35	1.37
Büller et al, 2012 (16)	26/2412	52/2405	0.50	0.31	0.80
Granger et al, 2011 (33)	327/9088	462/9052	0.70	0.61	0.81
Patel et al, 2011 (34)	395/7111	386/7125	1.03	0.89	1.18
FXa			0.75	0.56	1.00
Total			0.80	0.63	1.01



Adam S, Ann Intern Med 2012; 157: 796

Pooled Data – GIT Bleeding

Study, Year (Reference)	Events/Total, *n/N*		Risk Ratio	Lower Limit	Upper Limit
	DTI/FXa	Warfarin			
Gastrointestinal bleeding					
Connolly et al, 2009 (32)	223/6076	148/6022	1.49	1.22	1.83
Schulman et al, 2009 (35)	53/1273	35/1266	1.51	0.99	2.29
DTI			1.50	0.99	2.28
Granger et al, 2011 (33)	105/9088	119/9052	0.88	0.68	1.14
Patel et al, 2011 (34)	224/7111	154/7125	1.46	1.19	1.78
FXa			1.14	0.77	1.70
Total			1.30	0.97	1.73



Adam S, Ann Intern Med 2012; 157: 796

Is outcome after bleeding different?

Resource utilization for major bleeds inthe RE-LY study	Dabigatran N=741	Warfarin N=421	P-value
Major bleeds transfused with red cells, n (%)	439 (59)	210 (50)	0.0013
Major bleeds transfused with plasma, n (%)	147 (20)	127 (30)	<0.0001
Major bleeds treated with vitamin K, n (%)	70 (9)	115 (27)	<0.0001
Mean length of stay in intensive care, days (SD)	1.9	3.2	0.03
Bleeds requiring invasive procedure, n (%)	79 (9)	59 (14)	0.09

Majeed et al 2012 ASH: Abstract 19

Is outcome after bleeding different?

Outcomes based on event reports from 5 phase III trials	Dabigatran N=696	Warfarin N=425	P-value
30-day mortality after the 1st major bleed, n/N (%)	57/627 (9.1)	53/407 (13.0)	0.044
Efficacy of management of bleed: good/moderate/poor			
Overall	67%/24%/9%	57%/29%/14%	0.09
With hemostatic agents (plasma, factors, vitamin K)	59%/26%/14%	58%/30%/12%	0.61
With vitamin K alone	53%/42%/5%	59%/38%/3%	0.64

Majeed et al 2012 ASH: Abstract 19

Outcome of bleeding – post-hoc analysis of ROCKET-AF

Table 6 Outcomes post-major bleed

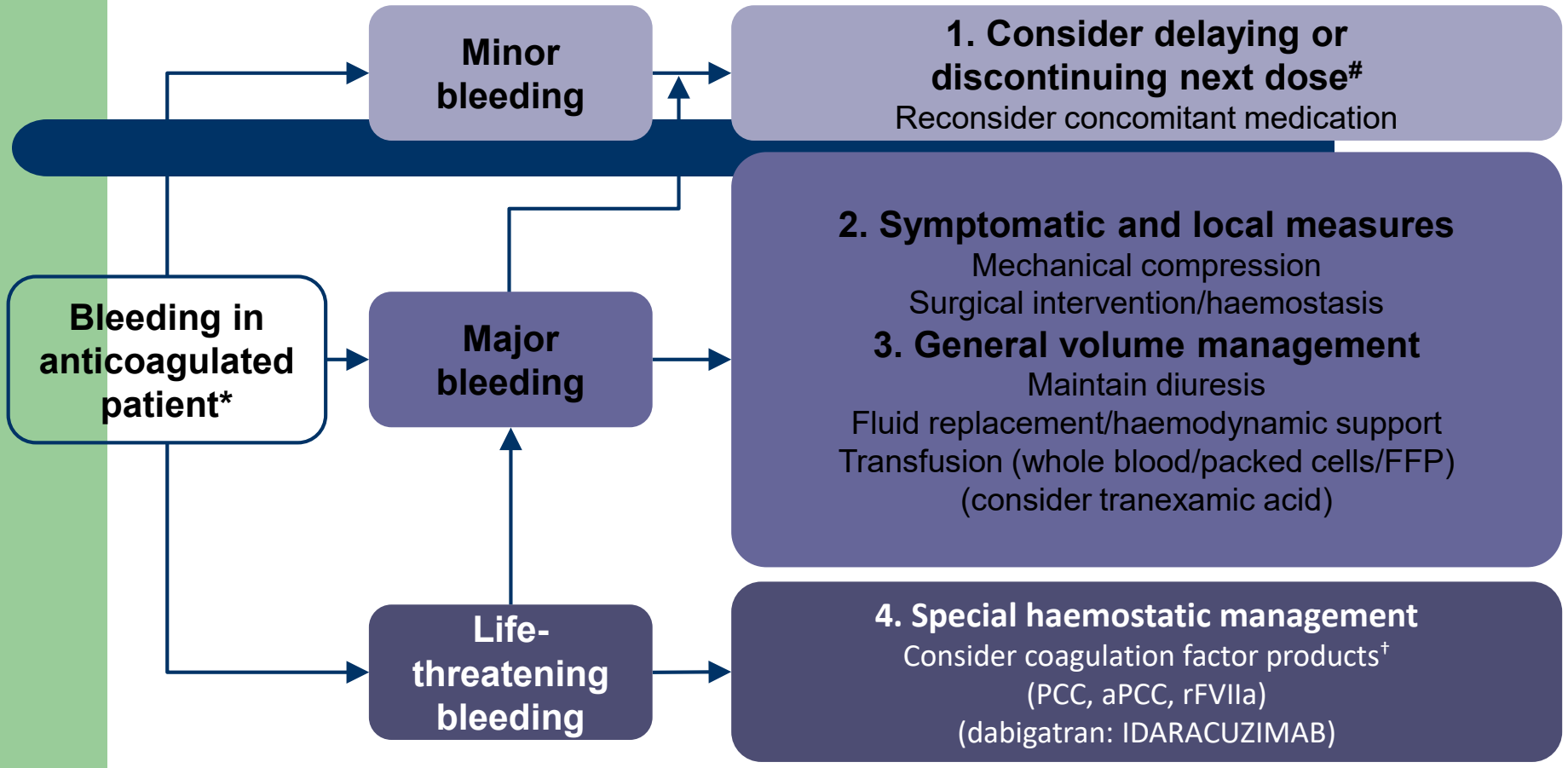
Outcome[a]	Rivaroxaban (n = 431)	Warfarin (n = 409)	HR (95% CI)[b]	Treatment × major bleed interaction, P-value[c]
Stroke or systemic embolism[d]	20 (4.7%)	22 (5.4%)		
Time to stroke or SE, median (range), days	64 (16–249)	15 (1–71)		
Post-major bleed			0.888 (0.420, 1.876)	0.5135
Pre/no major bleed			1.102 (0.715, 1698)	
Composite of all stroke, non-CNS embolism, MI/UA, and all-cause death	104 (24.8%)	120 (29.9%)		
Time to composite of all stroke, non-CNS embolism, MI/UA, and all-cause death, median (range), days	58 (8–248)	11 (2–82)		
Post-major bleed			0.758 (0.530, 1.082)	0.0975
Pre/no major bleed			0.970 (0.768, 1.225)	
All-cause death	86 (20.4%)	105 (26.1%)		
Time to all-cause death, median (range), days	60 (8–246)	7 (2–88)		
Post-major bleed			0.688 (0.455, 1.042)	0.1098
Pre-/no major bleed			0.905 (0.686, 1.194)	
MI/UA	11 (2.6%)	7 (1.7%)		
Time to MI/UA, median (range), days	282 (9–485)	14 (3–26)		
Post-major bleed			1.848 (0.572, 5.971)	0.5597
Pre/no major bleed			1.374 (0.707, 2.670)	

Piccini et al (2014) European Heart Journal 35(28): 1873-1880

When it all goes wrong …

WHO YOU GONNA CALL?

Bleeding management protocols are currently in place



*Assessment of bleeding should also include location; #temporary or permanent discontinuation should always balance the risk of bleeding against the increased risk of thromboembolic events occasioned by the discontinuation

†The clinical efficacy of coagulation factor products in active bleeding has not been established for novel oral anticoagulant agents

Heidbuchel *et al,* 2013; Makris *et al,* 2012; Peacock *et al,* 2012

ASH 2008

Potential of Activated Prothrombin Complex Concentrate and Activated Factor VII to Reverse the Anticoagulant Effects of Rivaroxaban in Primates

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Introduction

- Rivaroxaban is a novel, oral, once-daily anticoagulant that directly inhibits Factor Xa. It has been approved in Canada and the European Union for the prevention of venous thromboembolism after elective hip and knee replacement surgery
- Bleeding is a potential side-effect of all anticoagulant therapies, including rivaroxaban[1]
  - Standard strategies to control bleeding consist of delaying the next dose or discontinuation, mechanical compression, surgical intervention, fluid replacement and hemodynamic support, or blood product or component transfusion
- Both activated prothrombin complex concentrate (APCC; FEIBA® [Baxter HealthCare Corp., Westlake Village, CA, USA]) and recombinant human activated Factor VII (rFVIIa; NovoSeven® [Novo Nordisk, Copenhagen, Denmark]) have demonstrated hemostatic effects in rat models of high-dose rivaroxaban (higher than would be administered in clinical practice)[2,3]

Objective

- Because bleeding emergencies (defined as life-threatening bleeding events) may occur in patients receiving rivaroxaban, we determined whether APCC and rFVIIa could attenuate the antihemostatic effects of rivaroxaban in non-human primates if standard

Methods

- Juvenile male baboons (8.5–11.6 kg, N=11) were used to investigate the pharmacokinetic and pharmacodynamic profile of high-dose rivaroxaban (0.6 mg/kg intravenous bolus followed by a continuous infusion of rivaroxaban 0.6 mg/kg for 60 minutes)
- Baboons received either 50 U/kg APCC (2 U/kg/min, n=7) or 210 µg/kg bolus rFVIIa (n=7) 30 minutes after the start of rivaroxaban administration
- The hemostatic effects of APCC and rFVIIa after administration of high-dose rivaroxaban were assessed by measurement of prothrombin time (PT), bleeding time (BT), and plasma thrombin–antithrombin complex (TAT) levels

Results

Effect of High-Dose Rivaroxaban on Hemostasis

- Steady-state conditions were obtained after 15 minutes of continuous infusion of high-dose rivaroxaban, and were maintained until the end of infusion (after 60 minutes)
- At steady state, PT increased 3.16- to 3.58-fold times baseline, and BT increased 2.19- to 3.01-fold times baseline ($p<0.001$ for both)
- No adverse events, except the occasional rebleeding of BT wounds, were observed

Effect of APCC on Hemostasis

- In the APCC group, BT increased 2.02-fold±0.56 times baseline, and PT increased 3.04±0.26 times baseline 30 minutes after the infusion of high-dose rivaroxaban (Table 1; Figure 1)
- On completion of APCC infusion, BT returned to baseline (1.02-fold±0.33 times baseline) before increasing again to 1.65-fold±0.94 times baseline

Table 1. The effect of APCC and rFVIIa on BT, PT, and TAT concentration in baboons anticoagulated with high-dose rivaroxaban (n=7 each)

Time	BT (x-fold change from baseline)	PT (x-fold change from baseline)	TAT concentration (µg/l)
APCC			
Baseline	1.00	1.00	3.51±0.08
30 minutes after rivaroxaban	2.02±0.56*	3.04±0.26*	3.01±1.37
At the end of APCC infusion	1.02±0.33	2.20±0.29*	10.35±1.41*
20 minutes after the end of APCC infusion	1.65±0.94	2.28±0.29*	ND
rFVIIa			
Baseline	1.00	1.00	7.35±4.17
30 minutes after rivaroxaban	2.54±0.79*	3.17±0.42*	2.95±0.79
5 minutes after rFVIIa	1.68±0.80	2.38±0.41*	2.58±0.52
30 minutes after rFVIIa	1.96±1.26	2.48±0.49*	4.00±1.12

*$p<0.05$ (paired t-test) compared with pretreatment baseline. Values are given as mean ± standard deviation. APCC, activated prothrombin complex concentrate; BT, bleeding time; ND, no data; PT prothrombin time; rFVIIa, recombinant activated Factor VII; TAT, thrombin-antithrombin complex.

- A sustained reduction of PT was seen after APCC infusion; 2.20-fold±0.29 times baseline at the end of infusion, and 2.28-fold±0.29 times baseline 20 minutes later (Table 1; Figure 1B)
- TAT levels increased from baseline after APCC administration despite the high concentration of rivaroxaban in circulation ($p<0.001$; Table 1)

Effect of rFVIIa on Hemostasis

- In the rFVIIa group, high-dose rivaroxaban prolonged BT to 2.54-fold±0.79 ($p<0.019$) times baseline 30 minutes after the infusion (Table 1; Figure 2A)
- After an infusion of rFVIIa, BT was partially shortened (34%), and PT was reduced (Table 1; Figure 2)
- Circulating TAT levels did not change significantly after

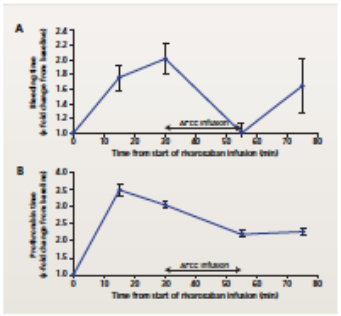

Figure 1. Effect of activated prothrombin complex concentrate (APCC) infusion (50 U/kg over 25 minutes) in baboons (n=7) anticoagulated with high-dose rivaroxaban. (A) Bleeding time; (B) prothrombin time. Values are shown as mean ± standard error of the mean.

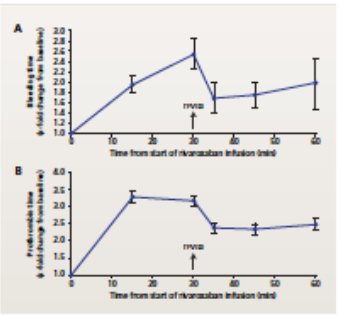

Figure 2. Effect of recombinant activated Factor VII (rFVIIa) injection (210 µg/kg at 30 minutes) in baboons (n=7) anticoagulated with high-dose rivaroxaban. (A) Bleeding time; (B) prothrombin time. Values are shown as mean ± standard error of the mean.

Conclusions

- Administration of APCC or rFVIIa rapidly reversed the effect of high-dose rivaroxaban on markers of hemostasis impairment in baboons
- The effect of rFVIIa on BT was continuous, in contrast to that of APCC
- APCC and rFVIIa may provide potential hemostatic antidotes during bleeding emergencies in patients receiving rivaroxaban
- Whether APCC and rFVIIa could achieve reversal of rivaroxaban anticoagulation without increasing the risk of thrombus formation remains to be established

References and Disclosures

1. Schulman S *et al. Chest* 2008;133:257S–298S.
2. Perzborn E. *Pathophysiol Haemost Thromb* 2008;36:A40.

this study was supported by bayer healthcare ag and johnson & johnson pharmaceutical research & development, l.l.c. andras gruber, ulla m marzec, and stephen r hanson receive research funding from bayer healthcare. ulf buetehorn and elisabeth perzborn are employed by bayer healthcare ag. the data contained within this poster do not support or recommend the use of rivaroxaban in any countries in which it is not approved.

Conclusions

- Administration of APCC or rFVIIa rapidly reversed the effect of high-dose rivaroxaban on markers of hemostasis impairment in baboons
- The effect of rFVIIa on BT was continuous, in contrast to that of APCC
- APCC and rFVIIa may provide potential hemostatic antidotes during bleeding emergencies in patients receiving rivaroxaban
- Whether APCC and rFVIIa could achieve reversal of rivaroxaban anticoagulation without increasing the risk of thrombus formation remains to be established

1094 Prothrombin Complex Concentrate Reverses the Anticoagulant Effect of Rivaroxaban In Healthy Volunteers

Oral and Poster AbstractsPoster Session: Antithrombotic Therapy: Poster ISaturday, December 4, 2010, 5:30 PM-7:30 PMHall A3/A4 (Orange County Convention Center) Poster Board I-74

Elise S Eerenberg, MD*, Meertien K Sijpkens, BSc*, Pieter W Kamphuisen, MD*, Joost CM Meijers, PhD and Marcel Levi, MD*Vascular Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands

In a randomized, double-blind, placebo-controlled trial, **twelve healthy male** subjects received Rivaroxaban 20mg twice daily for two and a half days. One group (n=6) was then randomized to receive a single bolus of 50 IU/kg PCC (Co-fact ®, Sanquin, the Netherlands) while the other group (n=6) was given a similar volume of saline.

RESULTS:
The prothrombin time (PT) was significantly prolonged by Rivaroxaban (15.8 sec ± 1.3 versus 12.3 ± 0.7 at baseline; $p < 0.001$).
Immediately after the infusion of PCC, the PT normalised almost completely (12.8 ± 1.0; $p < 0.001$), which was sustained for 24 hours. Saline did not reverse the PT prolongation (16.2 ± 0.8; $p = 0.4$).
Furthermore, Rivaroxaban inhibited the endogenous thrombin potential (ETP) (51% ± 22, baseline 92 ± 22; $p = 0.002$), with normalisation after administration of PCC (114 ± 26; $p < 0.001$), but not after saline (41 ± 6; $p = 0.2$).

CONCLUSIONS: This study provides the first data that Prothrombin Complex Concentrate reverses the anticoagulant effect of Rivaroxaban in humans and may serve as an antidote for the new oral factor Xa inhibitors.

1094 Prothrombin Complex Concentrate Reverses the Anticoagulant Effect of Rivaroxaban In Healthy Volunteers

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Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate : A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects
Elise S. Eerenberg, Pieter W. Kamphuisen, Meertien K. Sijpkens, Joost C. Meijers, Harry R. Buller and Marcel Levi

Circulation. 2011;124:1573-1579; originally published online September 6, 2011;

Idarucizumab

- Monoclonal antibody fragment that binds ***DABIGATRAN***
- Binds in high-affinity 1:1 molar ratio
- Binds to dabigatran 350 times more avidly than thrombin
- Given as 2 x 2.5g 50mL boluses, no greater than 15 mins apart
- Most larger hospitals are developing protocols

Idarucizumab

Table 1. Clinical Characteristics of the Patients.*

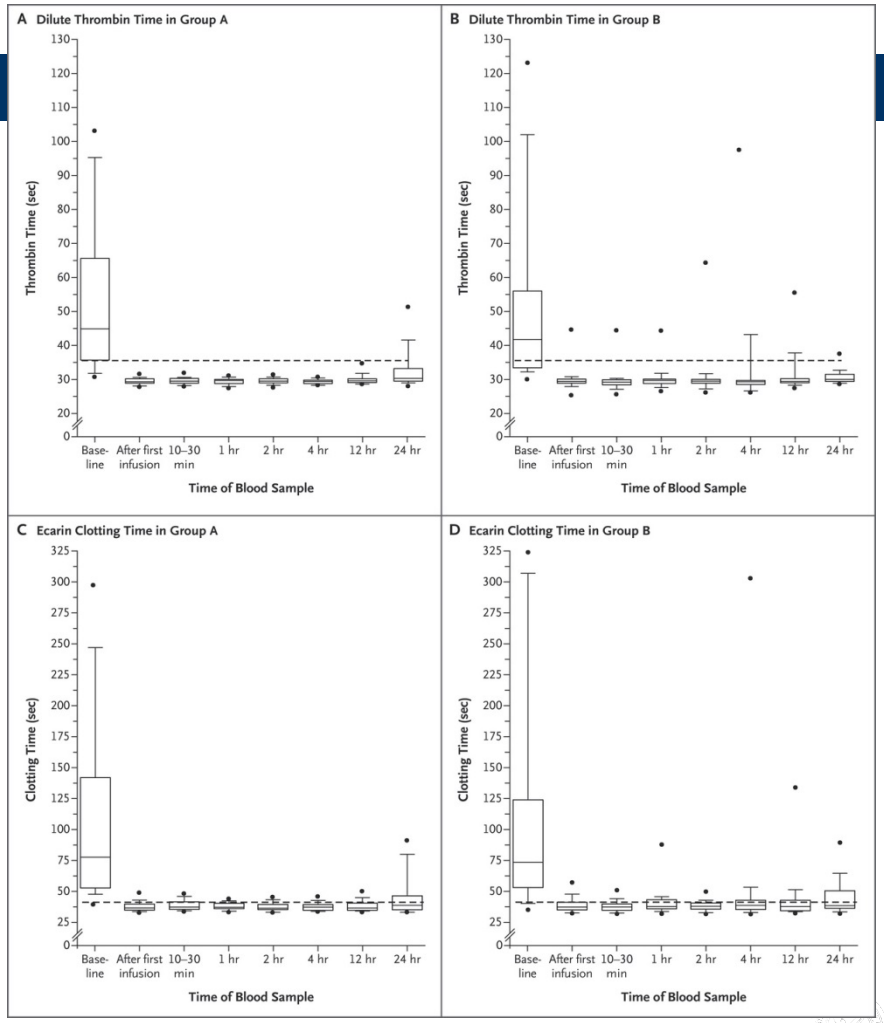
Characteristic	Group A (N=51)	Group B (N=39)	Total (N=90)
Age — yr			
Median	77.0	76.0	76.5
Range	48–93	56–93	48–93
Male sex — no. (%)	32 (63)	18 (46)	50 (56)
Race or ethnic group — no. (%)†			
Asian	5 (10)	1 (3)	6 (7)
Hawaiian or Pacific Islander	3 (6)	3 (8)	6 (7)
White	43 (84)	35 (90)	78 (87)
Weight — kg			
Median	70.5	73.0	71.9
Range	42.4–127.5	49.5–116.0	42.4–127.5
Creatinine clearance‡			
Value — ml/min			
Mean	59±33	65±36	62±35
Median	54	60	58
Range	16–187	11–171	11–187
Distribution — no. (%)			
<30 ml/min	5 (10)	7 (18)	12 (13)
30 to <50 ml/min	14 (27)	6 (15)	20 (22)
50 to <80 ml/min	16 (31)	11 (28)	27 (30)
≥80 ml/min	6 (12)	9 (23)	15 (17)
Missing data	10 (20)	6 (15)	16 (18)
Dose of dabigatran — no. (%)			
150 mg twice daily	14 (27)	15 (38)	29 (32)
110 mg twice daily	34 (67)	24 (62)	58 (64)
75 mg twice daily	1 (2)	0	1 (1)
Other	2 (4)	0	2 (2)
Indication for dabigatran — no. (%)			
Atrial fibrillation	47 (92)	39 (100)	86 (96)
Venous thromboembolism	1 (2)	0	1 (1)
Other	3 (6)	0	3 (3)
Time since last intake of dabigatran			
Median — hr	15.2	16.6	15.4
Distribution — no. (%)			
<12 hr	17 (33)	15 (38)	32 (36)
12 to <24 hr	21 (41)	10 (26)	31 (34)
24 to <48 hr	12 (24)	10 (26)	22 (24)
≥48 hr	1 (2)	4 (10)	5 (6)
Elevated dilute thrombin time at baseline — no. (%)	40 (78)	28 (72)	68 (76)
Elevated ecarin clotting time at baseline — no. (%)	47 (92)	34 (87)	81 (90)
Type of bleeding — no. (%)§			
Intracranial	18 (35)	—	18 (20)
Trauma-related	9 (18)	—	9 (10)
Gastrointestinal	20 (39)	—	20 (22)
Other	11 (22)	—	11 (12)

* Plus–minus values are means ±SD. Group A included patients who had serious bleeding. Group B included patients who required urgent surgery or intervention.
† Race or ethnic group was self-reported.
‡ Creatinine clearance was estimated by the Cockroft–Gault equation.
§ Patients may have had more than one type of bleeding.

Pollack CV Jr et al. N Engl J Med 2015;373:511-520.

Idarucizumab

Time Course of the Dilute Thrombin Time and Ecarin Clotting Time before and after Administration.

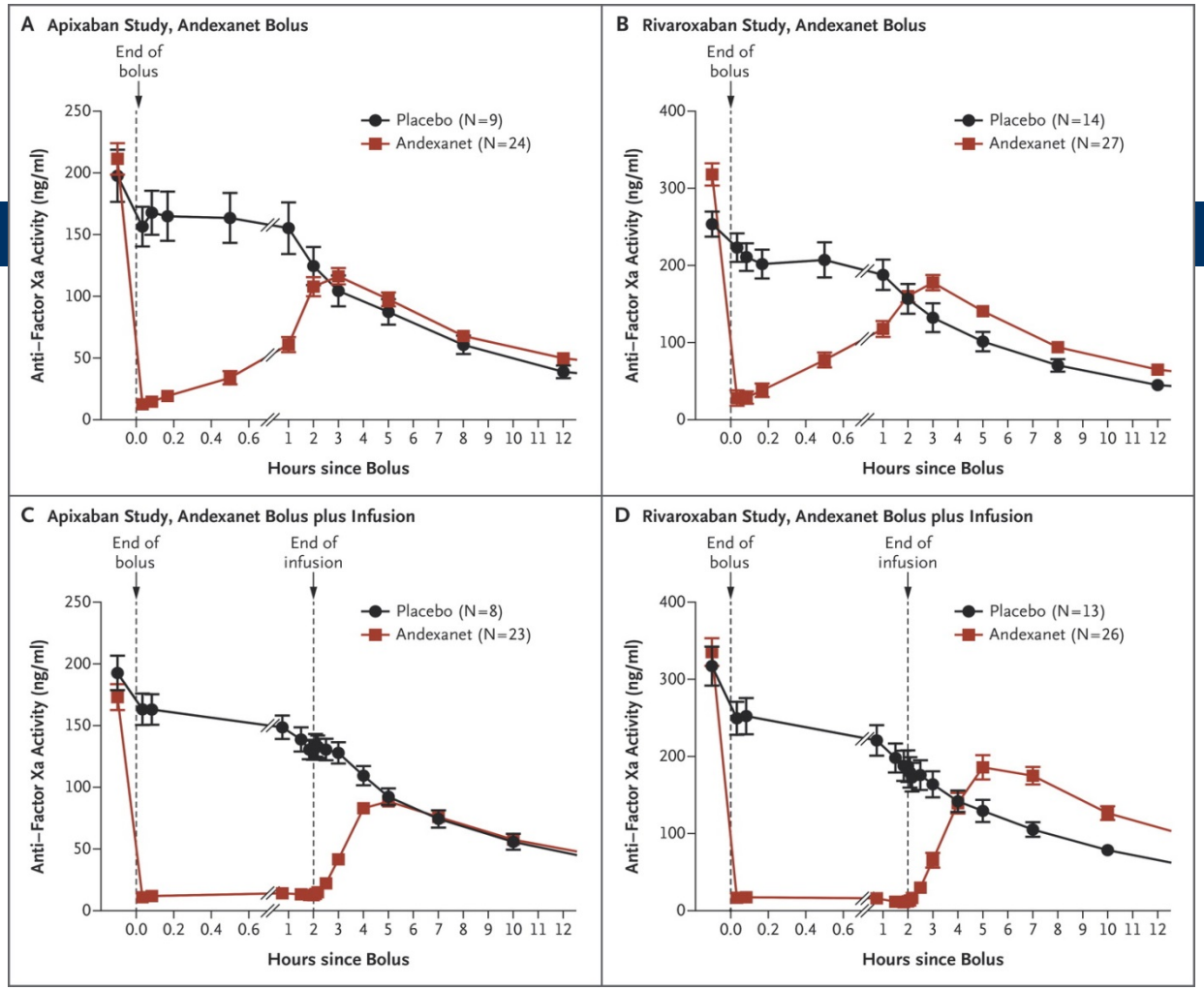


Pollack CV Jr et al. N Engl J Med 2015;373:511-520.

Andexanet Alpha

- Recombinant modified human factor Xa decoy protein
- Binds in high-affinity 1:1 molar ratio
- Catalytically inactive
- Now FDA approved

Andexanet Alpha



Siegal DM et al. N Engl J Med 2015;373:2413-2424.

Monitoring the NOACS

- Not routinely required
- Selected populations e.g. renal impairment, elderly, low body weight
- In situations of clinical bleeding or peri-operatively

Therapeutic Dabigatran (Pradaxa)

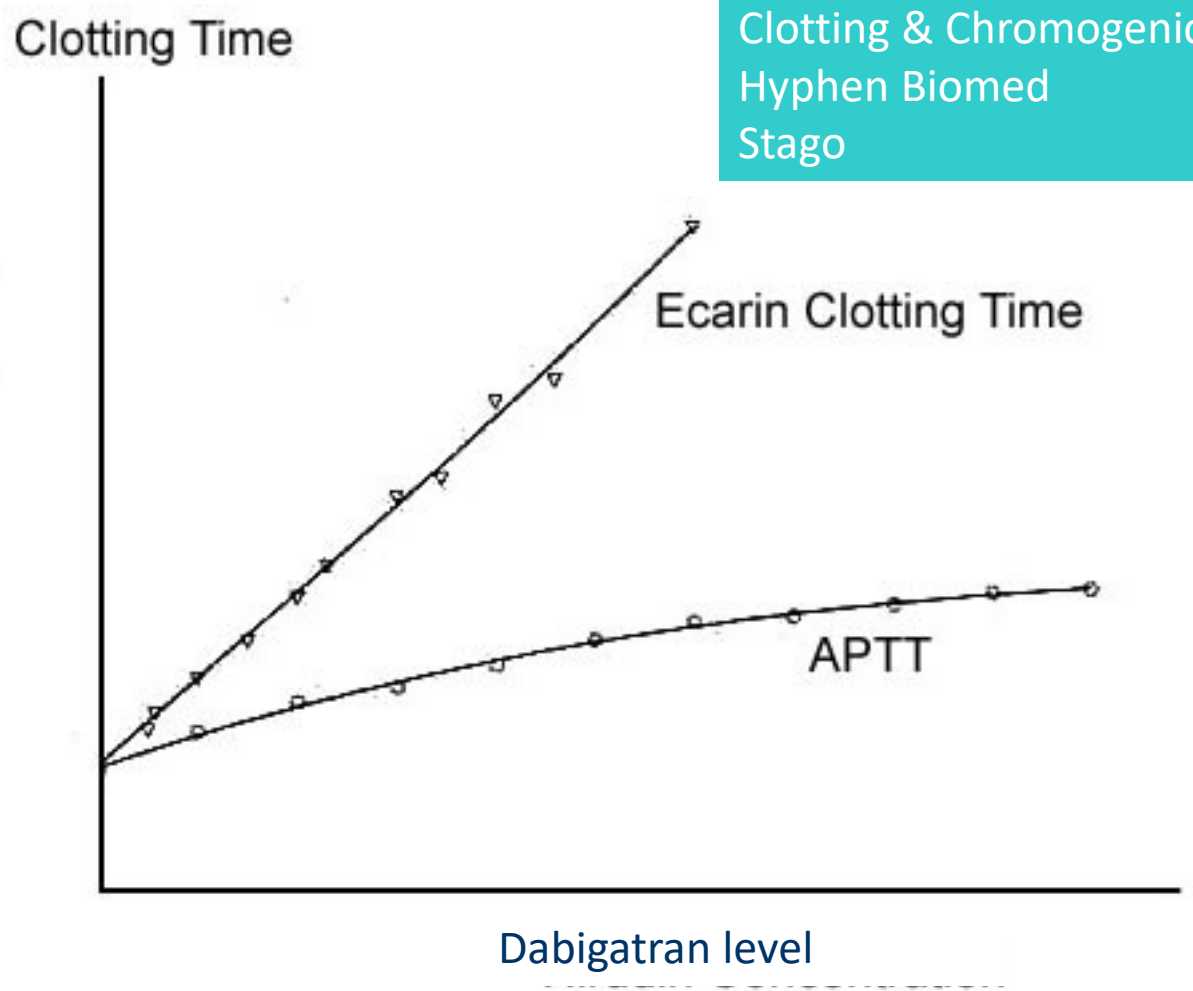
GENERAL COAGULATION — Specimen: Blood ddcd+F

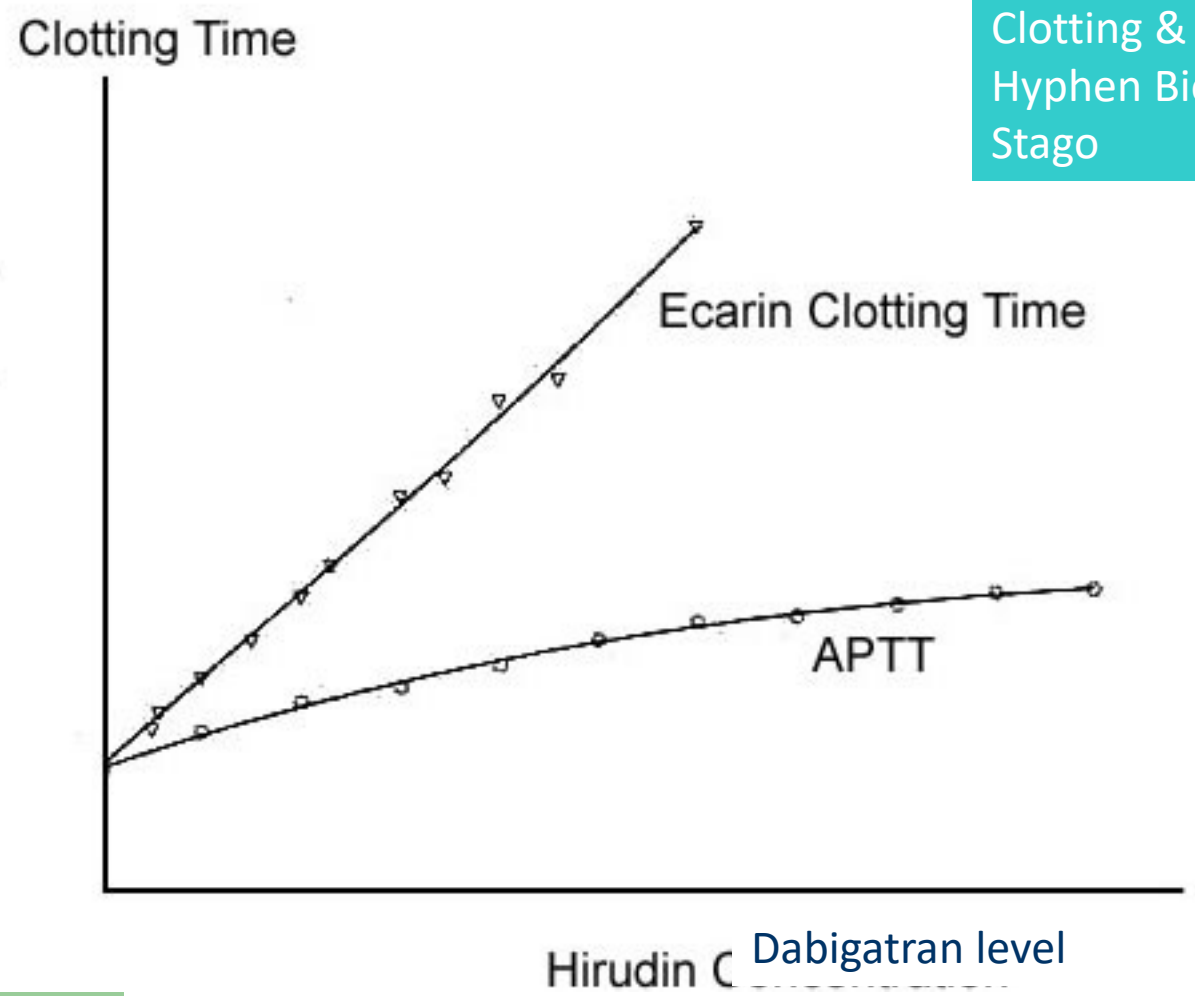
INR	1.3 H	Platelets	170
Prothrombin Time	14 H		
APTT	56 H		
Thrombin Time	> 80 H		
Thrombin Time (P)	>80 H		
Fib (derived)	8.0 H		

Comment: Use shift-insert to view reference ranges. 59 years

Result phoned. Staff advises patient on Dabigatran.

Clotting & Chromogenic
Hyphen Biomed
Stago





Clotting & Chromogenic
Hyphen Biomed
Stago

Echis Carinatus

Therapeutic Rivaroxaban (Xarelto)

GENERAL COAGULATION		Specimen: Blood	*+F*+IPd+IP
INR	1.2	Platelets	218
Prothrombin Time	12		
APTT	43 H		
Thrombin Time	15		
Fib (derived)	2.9		

Comment: Use shift-insert to view reference ranges. 22 years

Rivaroxaban

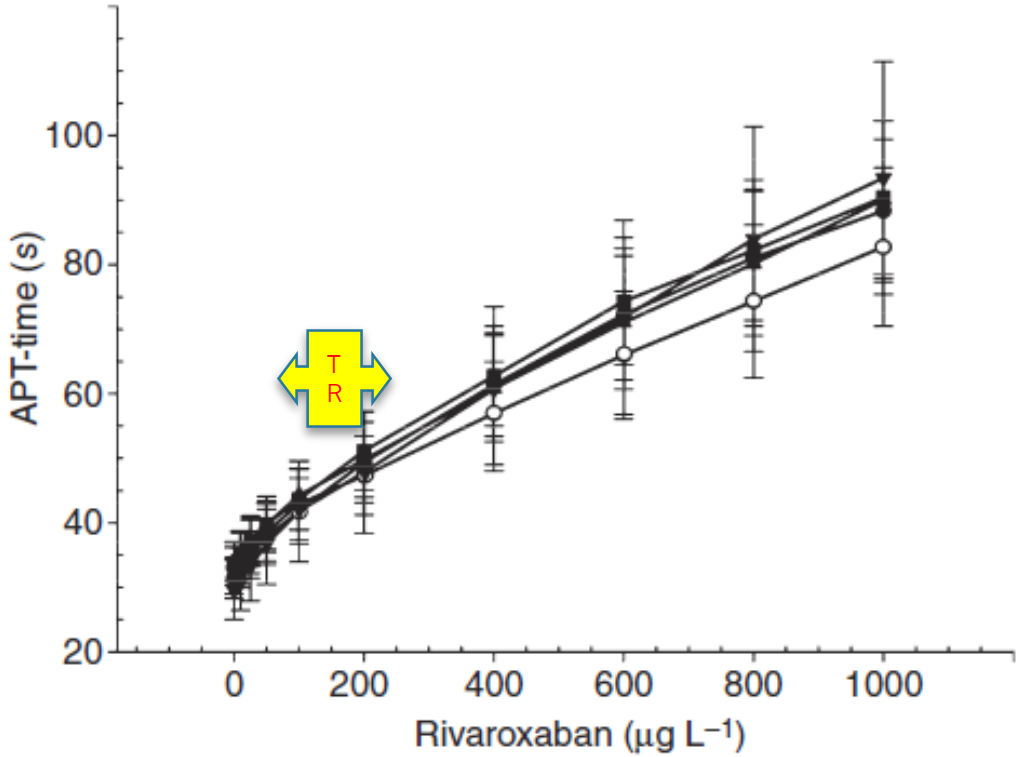


Fig. 1. Effect of rivaroxban on the APTT. The obtained APTT using five different reagents was plotted against the rivaroxaban concentration in plasma. Triniclot aPTT HS (○), Actin FSL (●), PTT-Automate (■), APTT-SP (▲) and DG-APTT (▼). Results are the mean of 10 different healthy donors ± SD.

Monitoring of Xa inhibitors

- Xa inhibitors may be monitored using anti Xa assay
  - i.e. similar to LMWH's
- However, the standard curve for EACH drug will be different, and will require individual laboratory calibration

2016 ACCP / Chest Guidelines

- Updated recommendations around DOAC's
- Substantially altered recommendation for unprovoked DVT / PE's

Kearon Chest. (2016);149(2):315-352

Choice of anticoagulation:

- 2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest **dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy** (all Grade 2B).

Each option is distinctive …

	Dabigatran	Rivaroxaban	Apixaban
Type	Direct Thrombin	Anti Xa	Anti Xa
Half-life	12-14 hrs	9-13 hrs	8-15 hrs
Bioavailability	7%	80%	66%
Elimination	80%	66% (half inactive)	27%
Dosing Interval	bd	Daily (after bd)	bd
Protein Binding	35%	>95%	87%

DVT / PE after surgery

- 5. In patients with a proximal DVT of the leg or PE provoked by surgery, **we recommend treatment with anticoagulation for 3 months** over
  - (i) treatment of a shorter period (Grade 1B),
  - (ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B), or
  - (iii) extended therapy (no scheduled stop date) (Grade 1B).

DVT / PE triggered by transient risk factor

- 6. In patients with a proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor, **we recommend treatment with anticoagulation for 3 months** over
  - (i) treatment of a shorter period (Grade 1B) and
  - (ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B).

- We **suggest treatment with anticoagulation for 3 months over extended therapy**
  - if there is a low or moderate bleeding risk (Grade 2B)
  - if there is a high risk of bleeding (Grade 1B).

Unprovoked DVT / PE

- 9. In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a
  - (i) low or moderate bleeding risk (see text), **we suggest extended anticoagulant therapy** (no scheduled stop date) over 3 months of therapy (Grade 2B), and
  - (ii) high bleeding risk (see text), we **recommend 3 months of anticoagulant therapy over extended therapy** (no scheduled stop date) (Grade 1B).

- *Remarks*:
  - Patient sex and D-dimer level measured a month after stopping anticoagulant therapy may influence the decision to stop or extend anticoagulant therapy (see text).
  - In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

ACCP Recommendations for duration of Rx in non-cancer associated thrombosis

- Transient (reversible) risk factor -> 3 months
- Unprovoked -> indefinite therapy
  - Consider shorter duration in low-risk bleeding

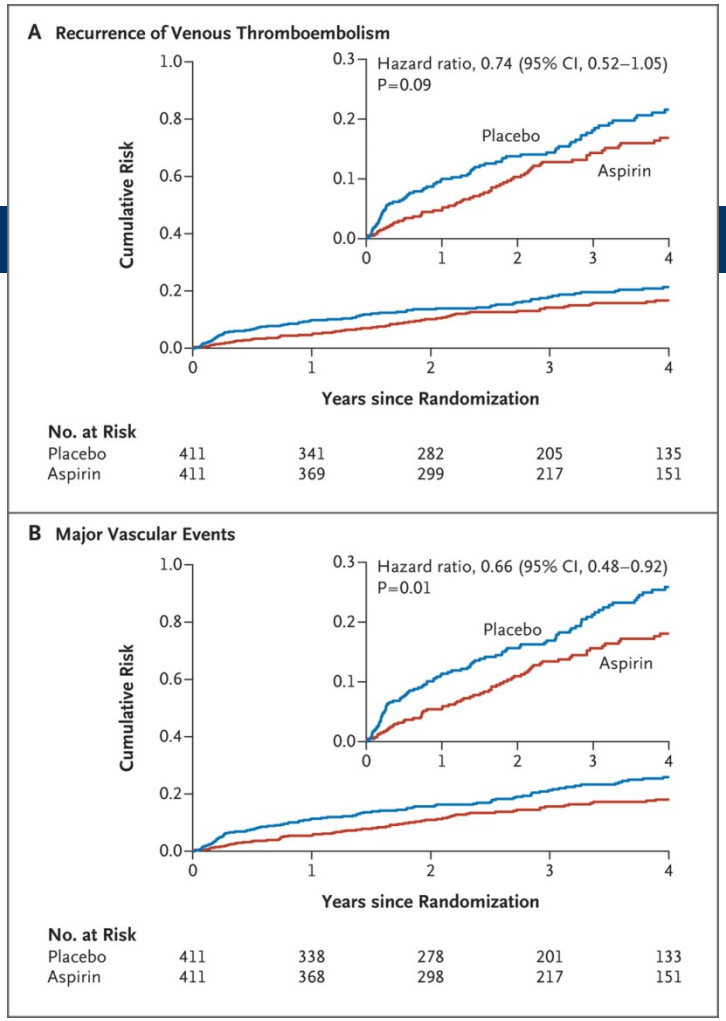
Updated ACCP Guidelines: Cancer Associated Thrombosis

- Choice
  - LMWH as initial choice (over all oral anticoagulants) (Grade 2C)
- Duration
  - Extended anticoagulation beyond 3 months
    - Low bleeding risk (Grade IB)
    - High bleeding risk (Grade 2B)

Kearon *Chest.* (2016);149(2):315-352

Is there a benefit to extended secondary prophylaxis?

Risks of First Recurrent Venous Thromboembolism and Major Vascular Events.



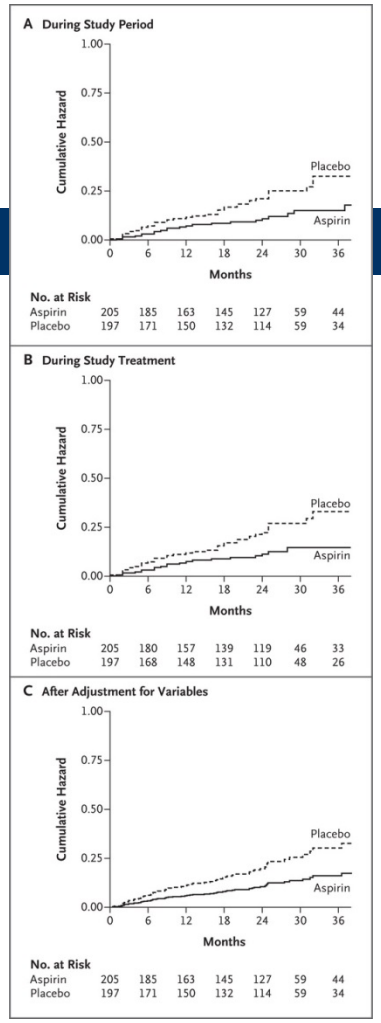
Aspirin v placebo
- Up to 4 years of Rx

Aspirin arm: 4.8% / year
Placebo arm: 6.5% / year

No signif increase in risk of bleeding

Brighton TA et al. N Engl J Med 2012;367:1979-1987.

Risk of Recurrence of Venous Thromboembolism in Patients Randomly Assigned to Aspirin or Placebo.



Aspirin v placebo
- 2 years of Rx

Aspirin arm: 6.6% / year
Placebo arm: 11.2% / year

No signif increase in risk of bleeding

Becattini C et al. N Engl J Med 2012;366:1959-1967.

EINSTEIN CHOICE

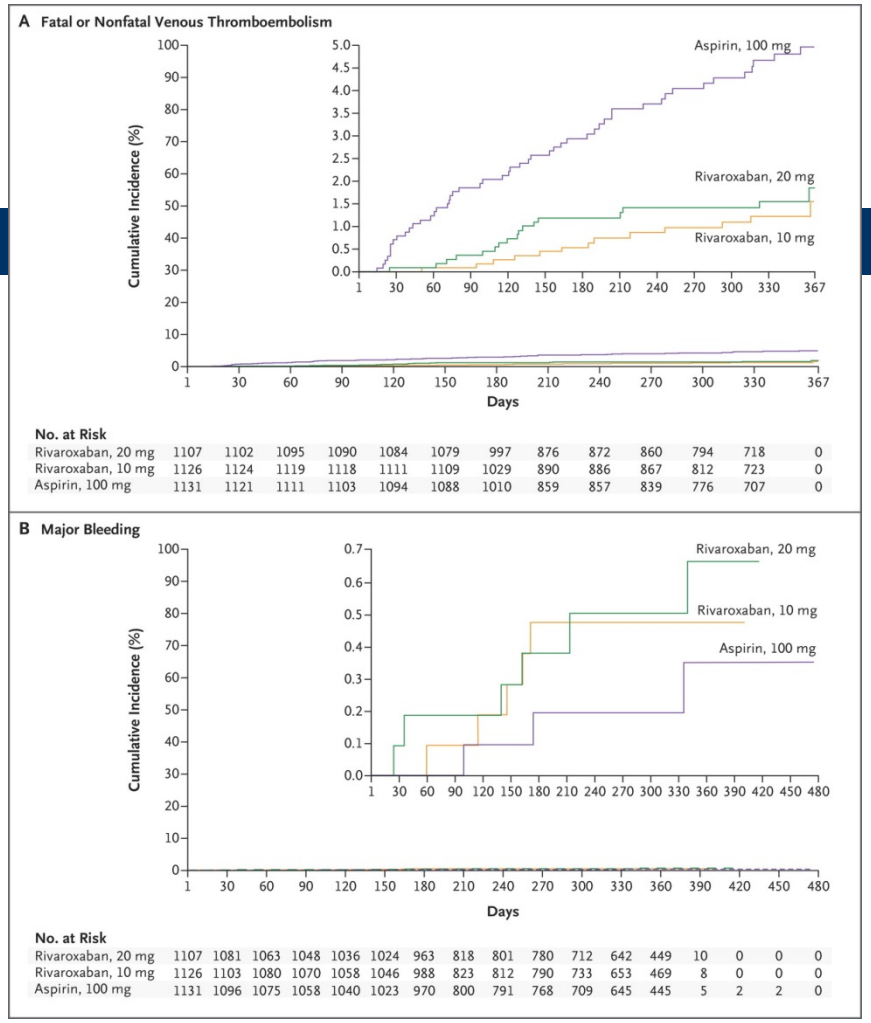
- n= 3365 patients
- Equipoise around need for ongoing therapy

- Randomised to:
  - Rivaroxaban 20mg daily
  - Rivaroxaban 10mg daily
  - Aspirin 100mg

- 1º endpoint: composite of symptomatic, recurrent fatal or non-fatal DVT or PE, and unexplained death where PE could not be excluded

Weitz JI et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1700518

Kaplan–Meier Rates of Recurrent Fatal or Nonfatal Venous Thromboembolism and Major Bleeding.

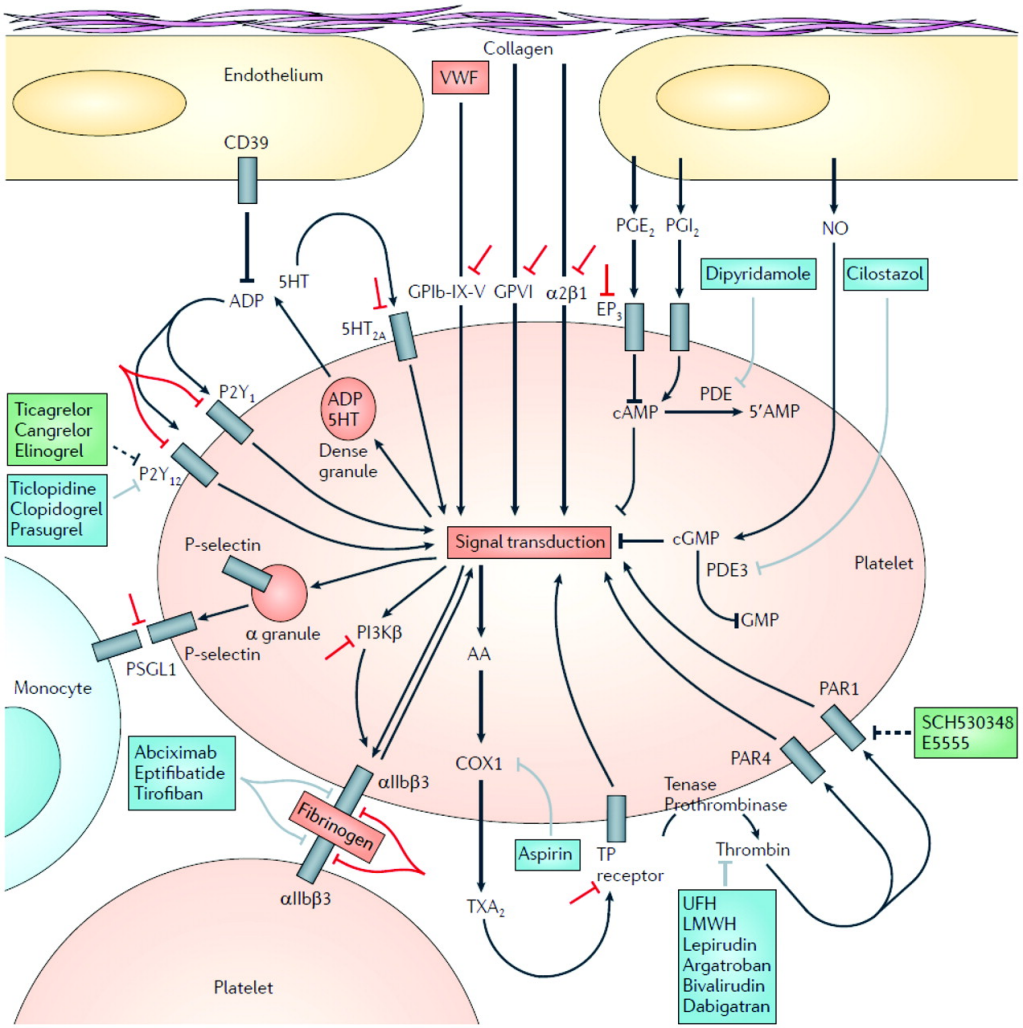


Weitz JI et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1700518

Incidence of outcomes

- Median of 351 days f/up
- 1o Endpoint
  - Rivaroxaban 20mg 1.5%
  - Rivaroxaban 10mg 1.2%
  - Aspirin 4.4%
- Major or clinically relevant bleeding
  - Rivaroxaban 20mg 3.3%
  - Rivaroxaban 10mg 2.4%
  - Aspirin 2.0%

Platelet function and molecular targets of antiplatelet agents.



Michelson A D Hematology 2011;2011:62-69

Novel Anti-Platelet Agents

- Prasugrel (Effient)
- Clopidogrel (Plavix; Iscover etc)
- Ticagrelor (Brilinta)

Prasugrel

- Thienopyridine (like clopidogrel)
  - Prodrug
  - Irreversible binding to P2Y12
  - More rapid onset of action
  - More predictable metabolism
    - Esterase dependent
    - Less influence of CYP450 e.g. CYP 2C19, 2C9

Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

Stephen D. Wiviott, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D., Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D., Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesmeyer, M.D., Govinda Weerakkody, Ph.D., C. Michael Gibson, M.D., and Elliott M. Antman, M.D., for the TRITON–TIMI 38 Investigators*

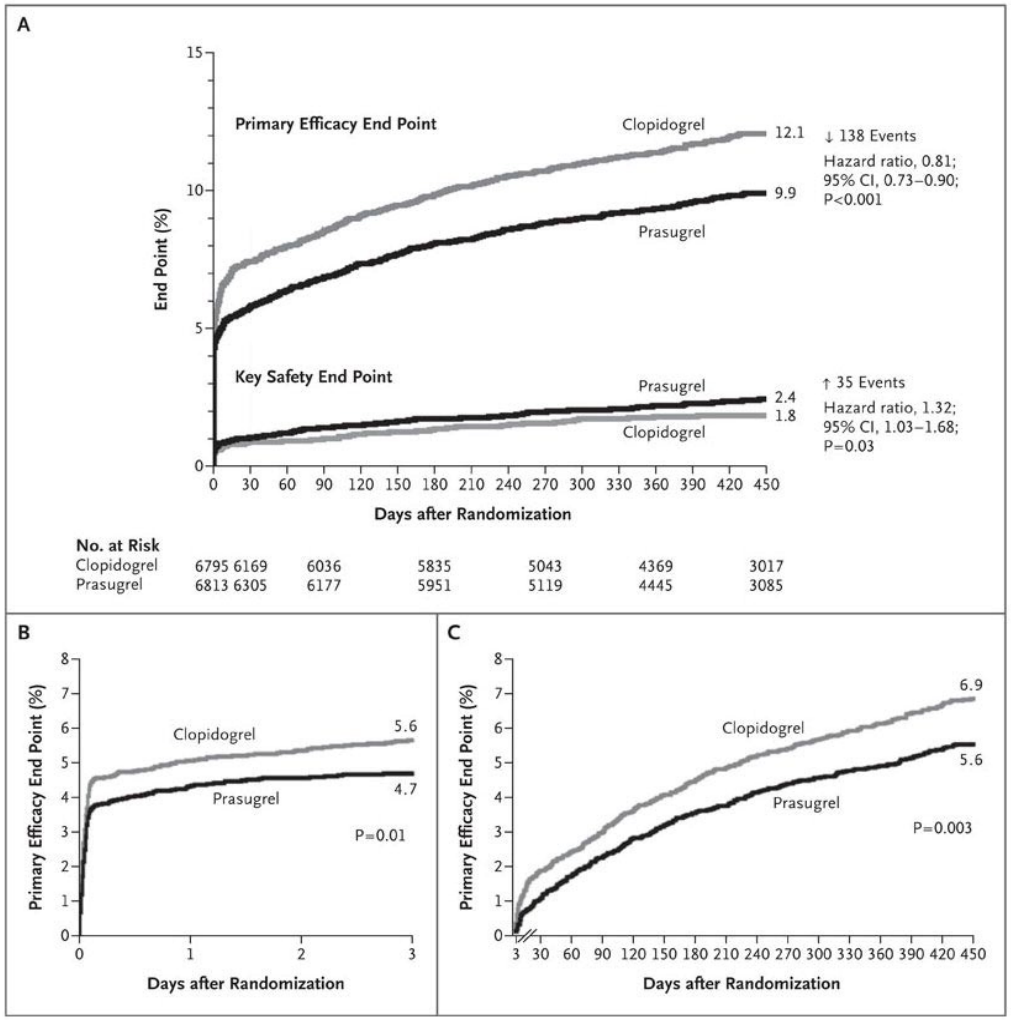
TRITON-TIMI

- Randomised trial
- Clopidogrel load (300mg) + 75mg ongoing *versus* Prasugrel load (60mg) + 10mg ongoing
- 6-15 months planned treatment duration

- n=608

Wiviott SD et al. N Engl J Med 2007;357:2001-2015.

Cumulative Kaplan–Meier Estimates of the Rates of Key Study End Points during the Follow-up Period.



Wiviott SD et al. N Engl J Med 2007;357:2001-2015.

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Thrombolysis in Myocardial Infarction (TIMI) Bleeding End Points in the Overall Cohort at 15 Months.

Table 3. Thrombolysis in Myocardial Infarction (TIMI) Bleeding End Points in the Overall Cohort at 15 Months.*

End Point	Prasugrel (N=6741)	Clopidogrel (N=6716)	Hazard Ratio for Prasugrel (95% CI)	P Value
	no. of patients (%)			
Non–CABG-related TIMI major bleeding (key safety end point)	146 (2.4)	111 (1.8)	1.32 (1.03–1.68)	0.03
Related to instrumentation	45 (0.7)	38 (0.6)	1.18 (0.77–1.82)	0.45
Spontaneous	92 (1.6)	61 (1.1)	1.51 (1.09–2.08)	0.01
Related to trauma	9 (0.2)	12 (0.2)	0.75 (0.32–1.78)	0.51
Life-threatening†	85 (1.4)	56 (0.9)	1.52 (1.08–2.13)	0.01
Related to instrumentation	28 (0.5)	18 (0.3)	1.55 (0.86–2.81)	0.14
Spontaneous	50 (0.9)	28 (0.5)	1.78 (1.12–2.83)	0.01
Related to trauma	7 (0.1)	10 (0.2)	0.70 (0.27–1.84)	0.47
Fatal‡	21 (0.4)	5 (0.1)	4.19 (1.58–11.11)	0.002
Nonfatal	64 (1.1)	51 (0.9)	1.25 (0.87–1.81)	0.23
Intracranial	19 (0.3)	17 (0.3)	1.12 (0.58–2.15)	0.74
Major or minor TIMI bleeding	303 (5.0)	231 (3.8)	1.31 (1.11–1.56)	0.002
Bleeding requiring transfusion§	244 (4.0)	182 (3.0)	1.34 (1.11–1.63)	<0.001
CABG-related TIMI major bleeding¶	24 (13.4)	6 (3.2)	4.73 (1.90–11.82)	<0.001

* The data shown are for patients who received at least one dose of the study drug and for end points occurring within 7 days after the study drug was discontinued or occurring within a longer period if the end point was believed by the local investigator to be related to the use of the study drug. Percentages are Kaplan–Meier estimates of the rate of the end point at 15 months. Patients could have had more than one type of end point. CABG denotes coronary-artery bypass grafting.

† The most frequent sites of life-threatening bleeding were gastrointestinal sites, intracranial sites, the puncture site, and retroperitoneal sites.

‡ One patient in the clopidogrel group had a fatal gastrointestinal hemorrhage while receiving the study medication, but hemoglobin testing was not performed and, therefore, the criteria for TIMI major bleeding (including life-threatening and fatal bleeding) could not be applied and the data do not appear in this table.

§ Transfusion was defined as any transfusion of whole blood or packed red cells.

¶ For major bleeding related to CABG, the total number of patients were all patients who had received at least one dose of prasugrel or clopidogrel before undergoing CABG: 179 and 189, respectively. The ratio is the odds ratio, rather than the hazard ratio, and was evaluated with the use of the Cochran–Mantel–Haenszel test.

Wiviott SD et al. N Engl J Med 2007;357:2001-2015.

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Ticagrelor

- Cyclopentyl-triazolo-pyrimidine
- Does not require metabolism to be active, but metabolites are active
  - More predictable effects

- Reversible inhibitor
- Rapid onset, but slow offset
- CYP P450 substrate

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

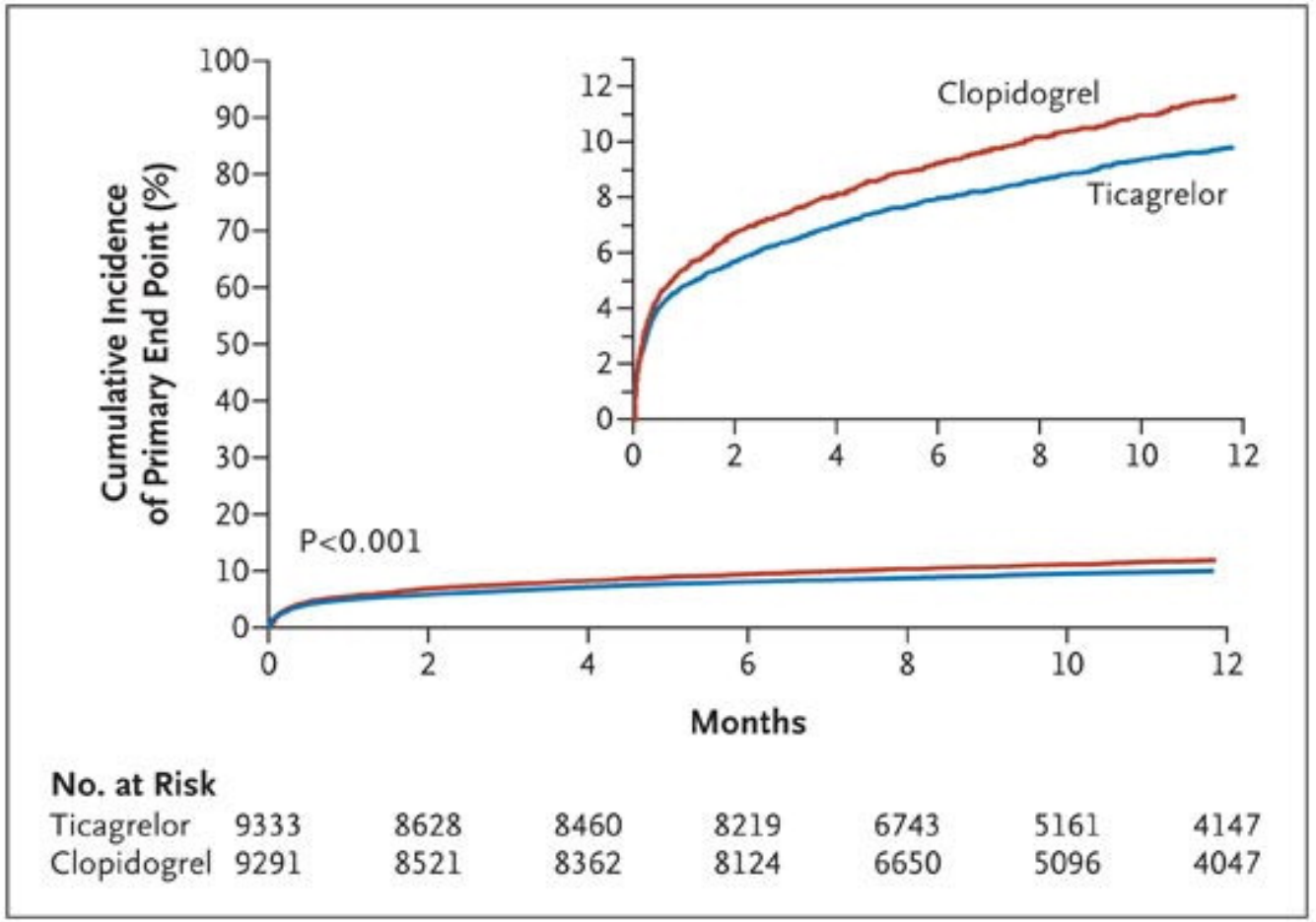
Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D., for the PLATO Investigators*

PLATO

- Randomised, double blind, double-dummy trial
- Clopidogrel load (300mg) + 75mg ongoing *versus* ticagrelor load (180mg) + 90mg bd ongoing
- 12 months planned treatment duration

Wallentin NEJM 2009; 361: 1045

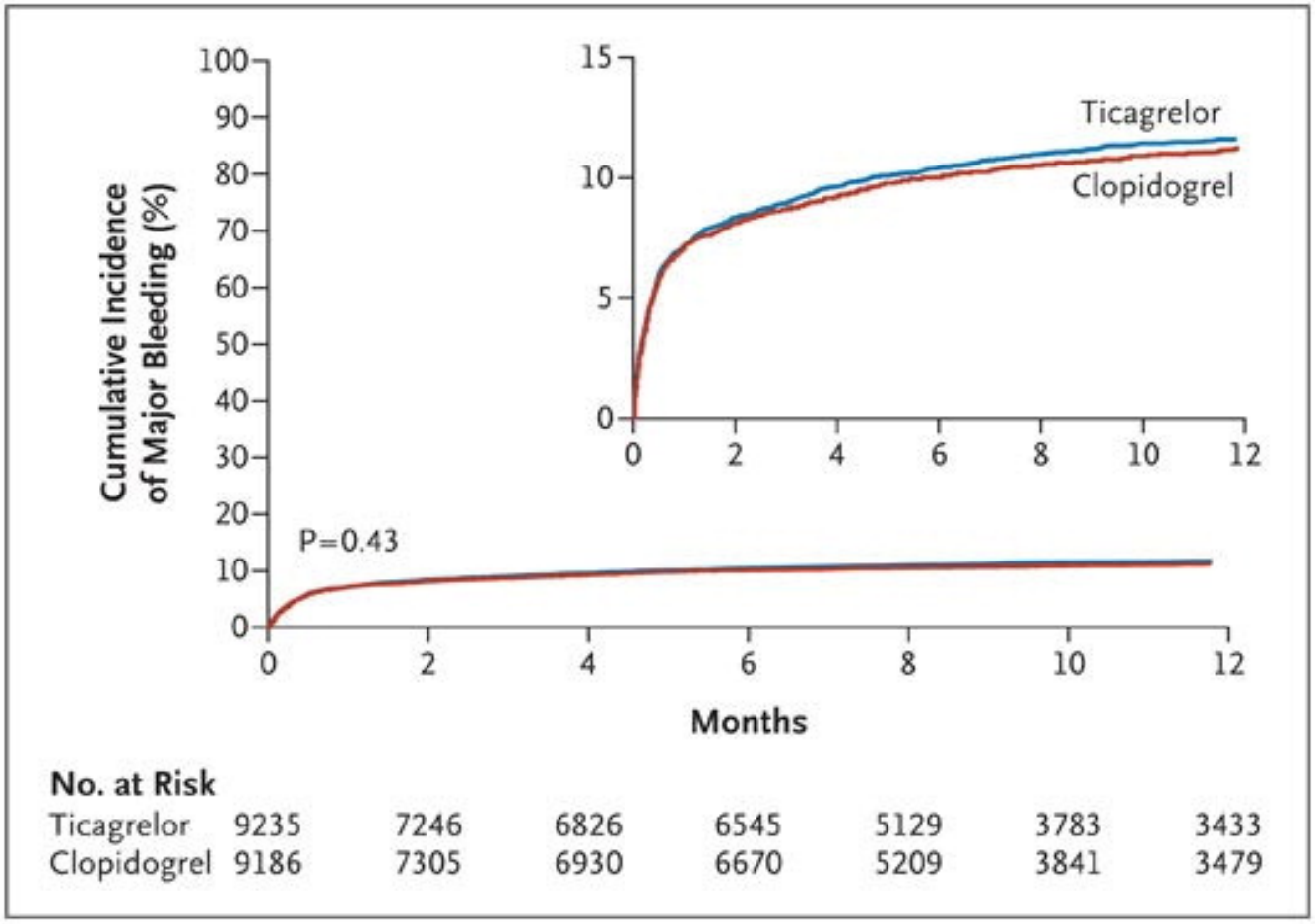
Cumulative Kaplan–Meier Estimates of the Time to the First Adjudicated Occurrence of the Primary Efficacy End Point.



Wallentin L et al. N Engl J Med 2009;361:1045-1057.

The NEW ENGLAND JOURNAL of MEDICINE

Cumulative Kaplan–Meier Estimates of the Time to the First Major Bleeding End Point, According to the Study Criteria.



Wallentin L et al. N Engl J Med 2009;361:1045-1057.

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Bleeding with Novel Antiplatelet Drugs

- Clopidogrel / Prasugrel
  - Desmopressin / DDAVP
    - 17 health volunteers
    - Improvements in platelet aggregomtery
  - Platelets
    - Theoretical
      - short half-life of agents

Leihthauser *Clin Hemorheol Microcirc* 2008; 39: 293

Bleeding with Novel Antiplatelet Drugs

- Ticagrelor
  - Problematic due to slow off-set
    -> persistent activity despite reversibility
  - Not dialyzable
  - Evidence of *in vitro* of improvement in platelet aggregation with addition of normal platelets[1,2]
    - probably proceed with desmopressin / platelet transfusions
    - efficacy predicted to be less than with prasugrel
  - Supportive cares / transfusion support

1 Nylander et al, ACC-13 1300-190
2 Hobel et el, Clinical Therapeutics, 35 (8): E10-E11

Surgical Procedures

- Cessation only necessary if bleeding risk high

- Dabigatran ~ 24 hrs prior
- Rivaroxaban ~ 48 hrs prior

- Antiplatelet agents ~ 7-10 days prior