New Advances in Anticoagulation

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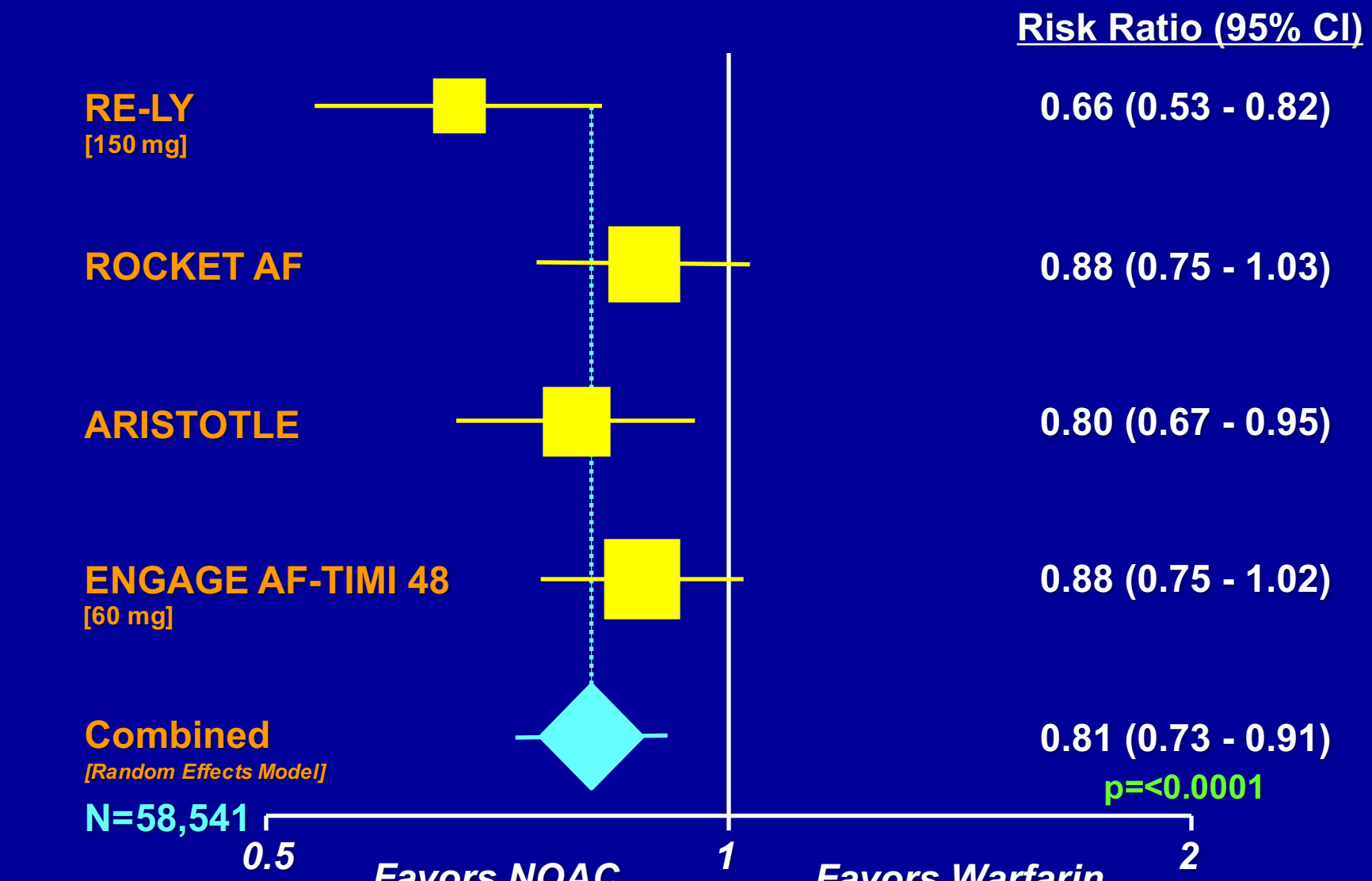
Disclosures for Freek W. A. Verheugt

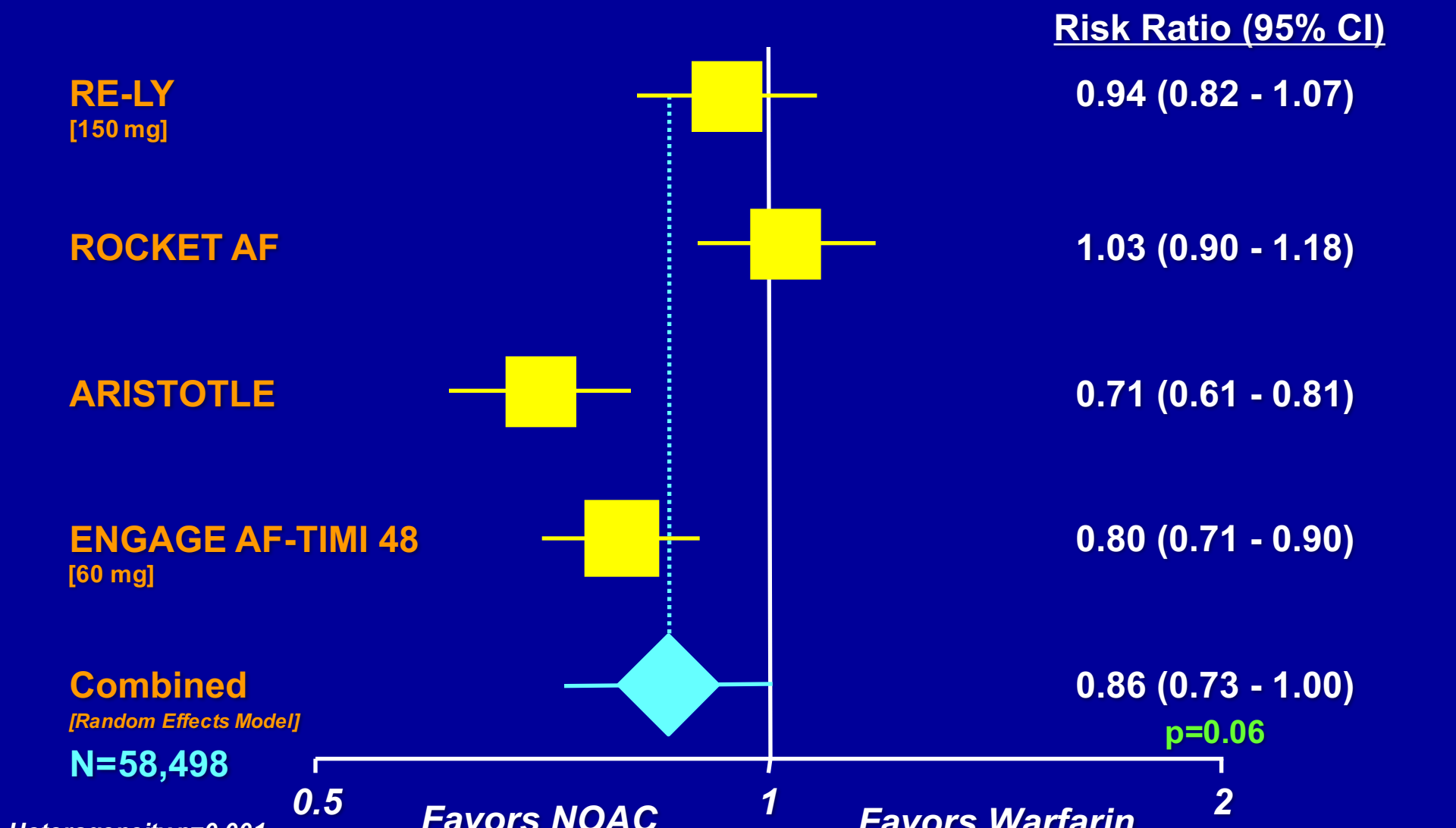
Research support/ principal investigator	Bayer HealthCare, Boehringer Ingelheim, Eli Lilly and Roche
Consultant	Bayer Healthcare, Eli Lilly, Daiichi-Sankyo, and Merck
Speakers' bureau	none
Honoraria	Bayer Healthcare, Eli Lilly, Daiichi-Sankyo and Merck
Scientific advisory board	AstraZeneca

All NOACS: Stroke or SEE



Ruff CT. Lancet 2014;383:955-962

All NOACS: Major Bleeding



Ruff CT. Lancet 2014;383:955-962

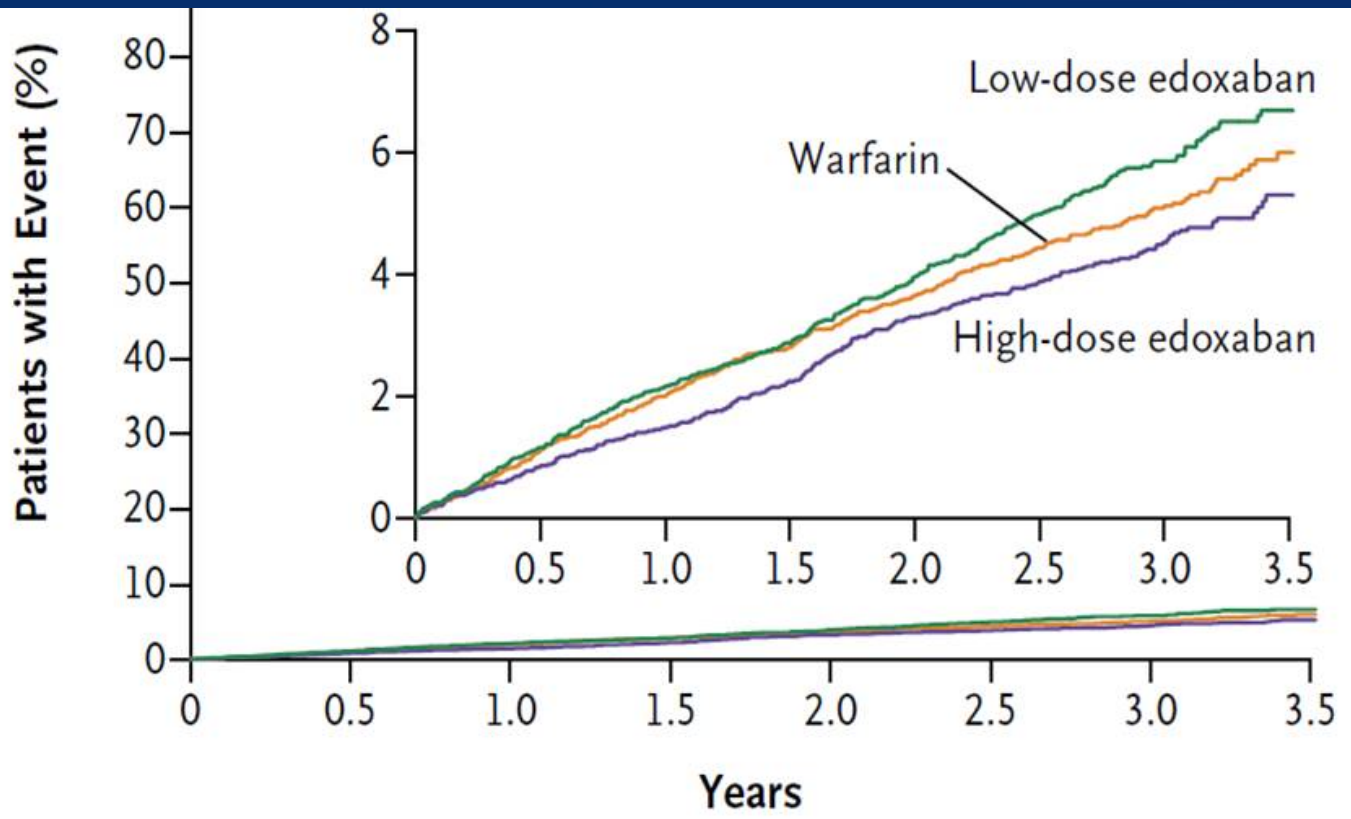
The 4 SPAF Trials with NOACs

	RE-LY	ROCKET-AF*	ARISTOTLE	ENGAGE-AF*
n	18,113	14,264	18,201	21,150
drug	dabigatran	rivaroxaban	apixaban	edoxaban
class	a-IIa	a-Xa	a-Xa	a-Xa
design	open	d-blind	d-blind	d-blind
dosing	bid	qd	bid	qd
2 doses	yes	no	no	yes
median f/u (m)	24	23	22	34
w/ of consent	2.3%	8.7%	1.1%	0.9%
median TTR	64%**	58%	66%	68%

* $CHADS_2 \geq 2$ only

* * mean TTR

STROKE OR SYSTEMIC EMBOLISM



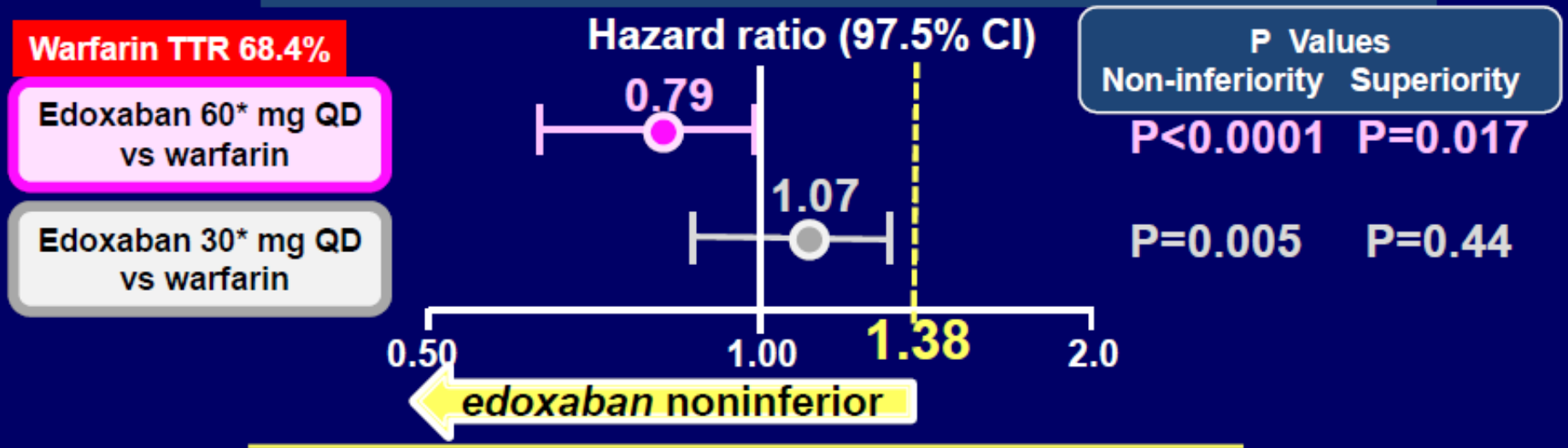
No. at Risk								
Warfarin	7036	6798	6615	6406	6225	4593	2333	536
High-dose edoxaban	7035	6816	6650	6480	6283	4659	2401	551
Low-dose edoxaban	7034	6815	6631	6461	6277	4608	2358	534

ENGAGE AF TIMI-48. N Engl J Med 2013:369:2093-2104

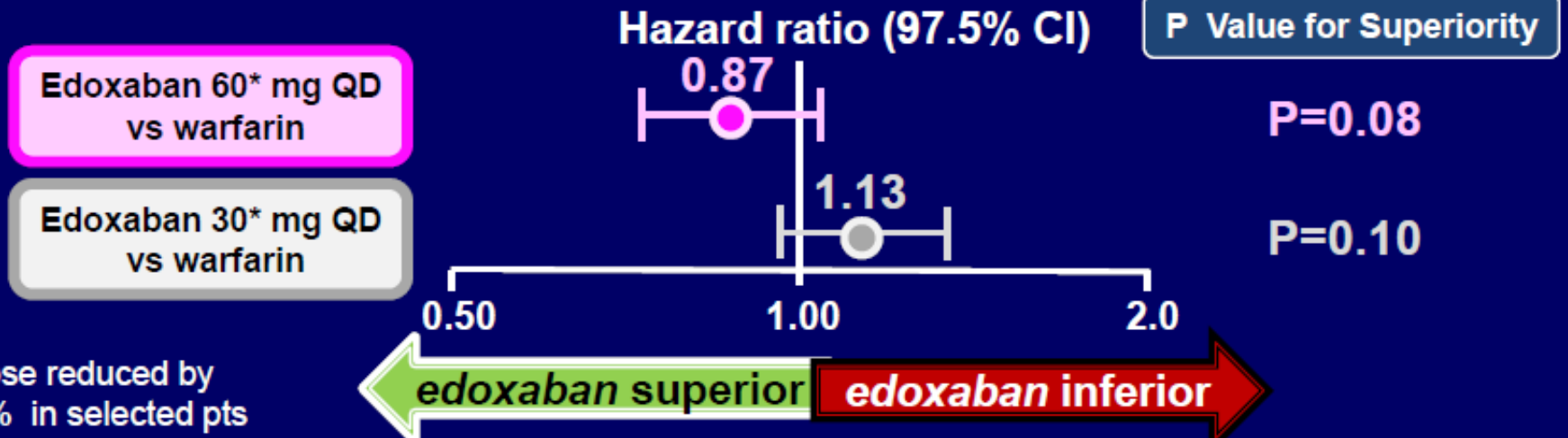
Primary Endpoint: Stroke / SEE
(2.8 years median f/u)

Engage AF TIMI 48

Noninferiority Analysis (mITT, On Treatment)

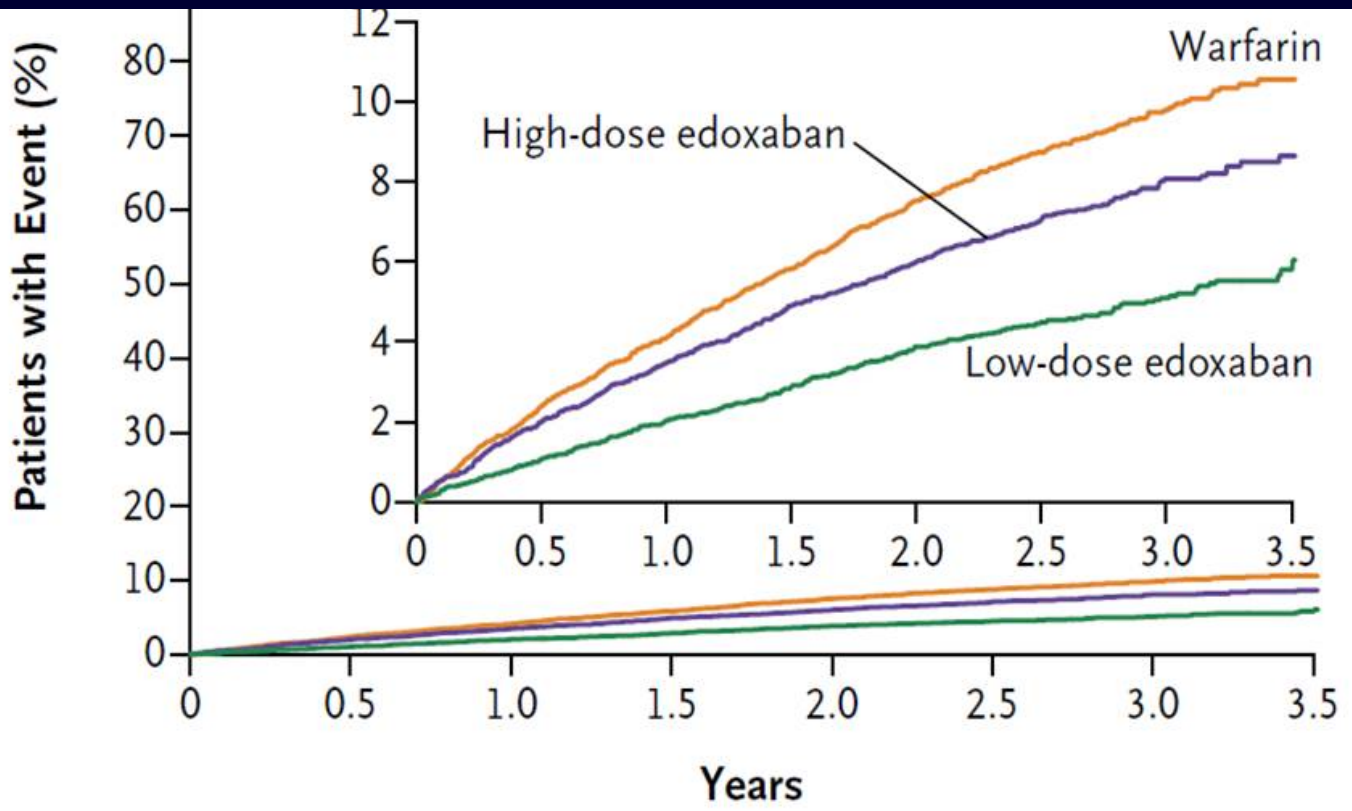


Superiority Analysis (ITT, Overall)



*Dose reduced by 50% in selected pts

Major Bleeding

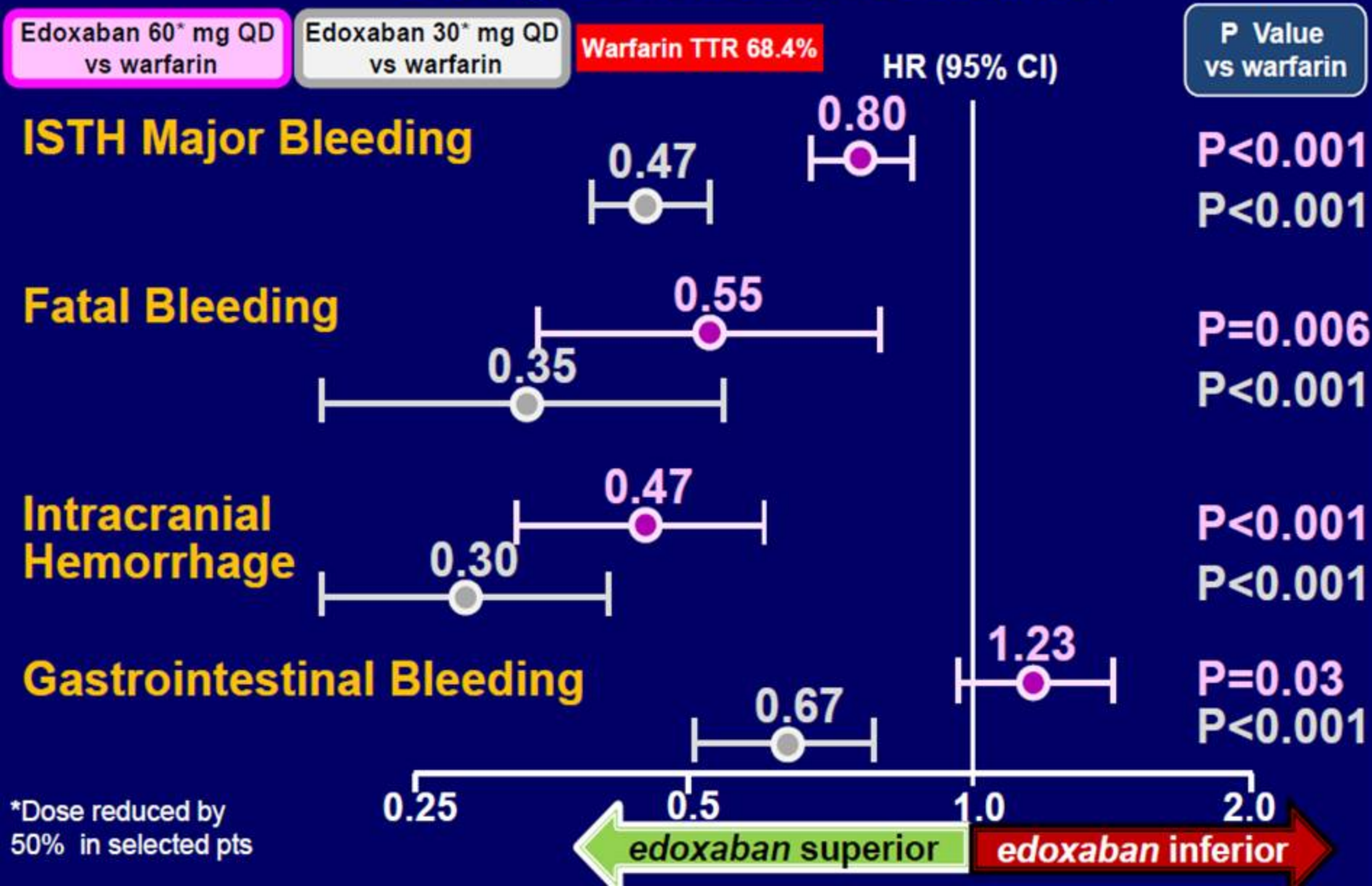


No. at Risk								
Warfarin	7012	6116	5630	5278	4941	3446	1687	370
High-dose edoxaban	7012	6039	5594	5232	4910	3471	1706	345
Low-dose edoxaban	7002	6218	5791	5437	5110	3635	1793	386

Main Safety Results

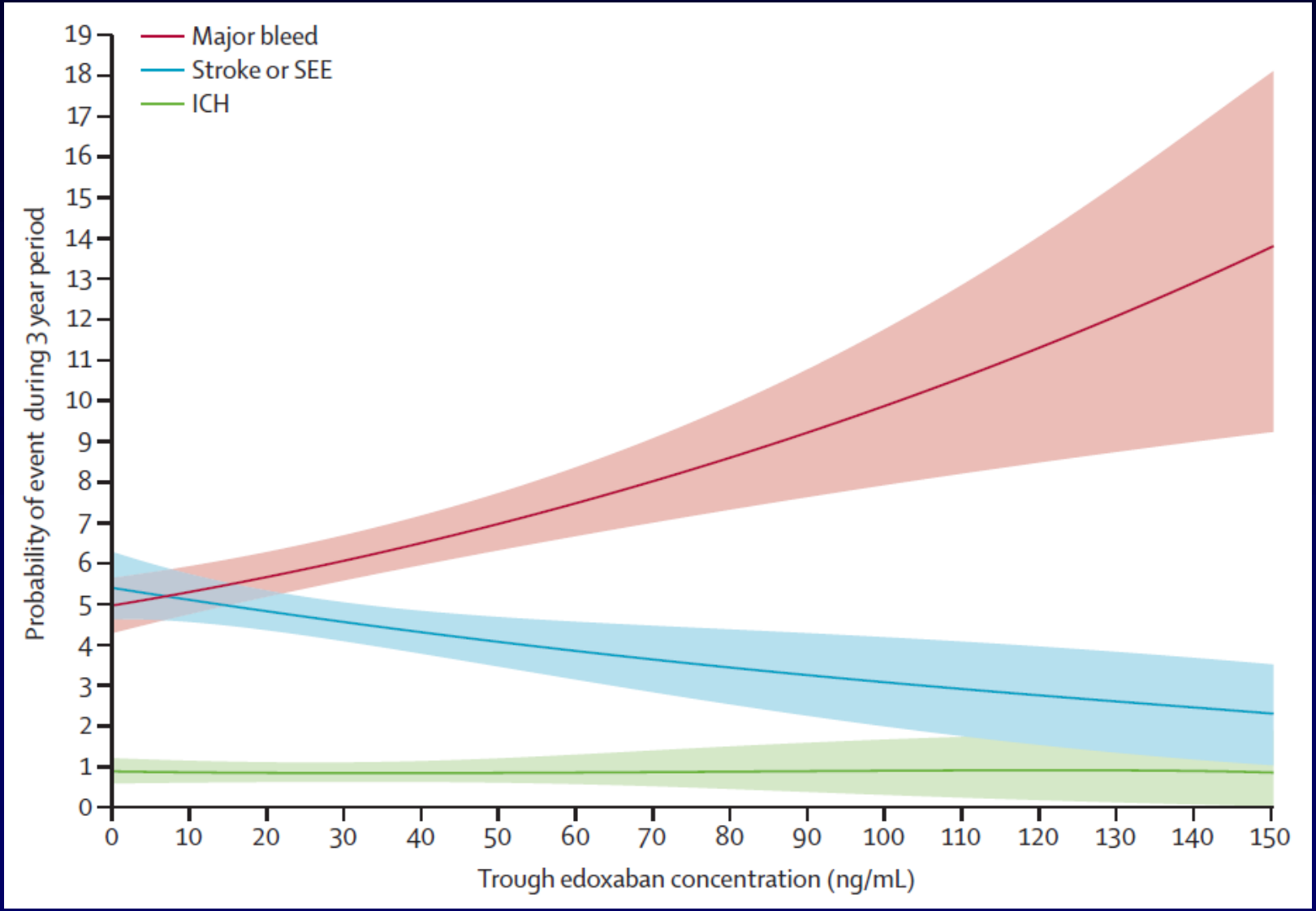
- Safety Cohort on Treatment -

Engage AF TIMI 48

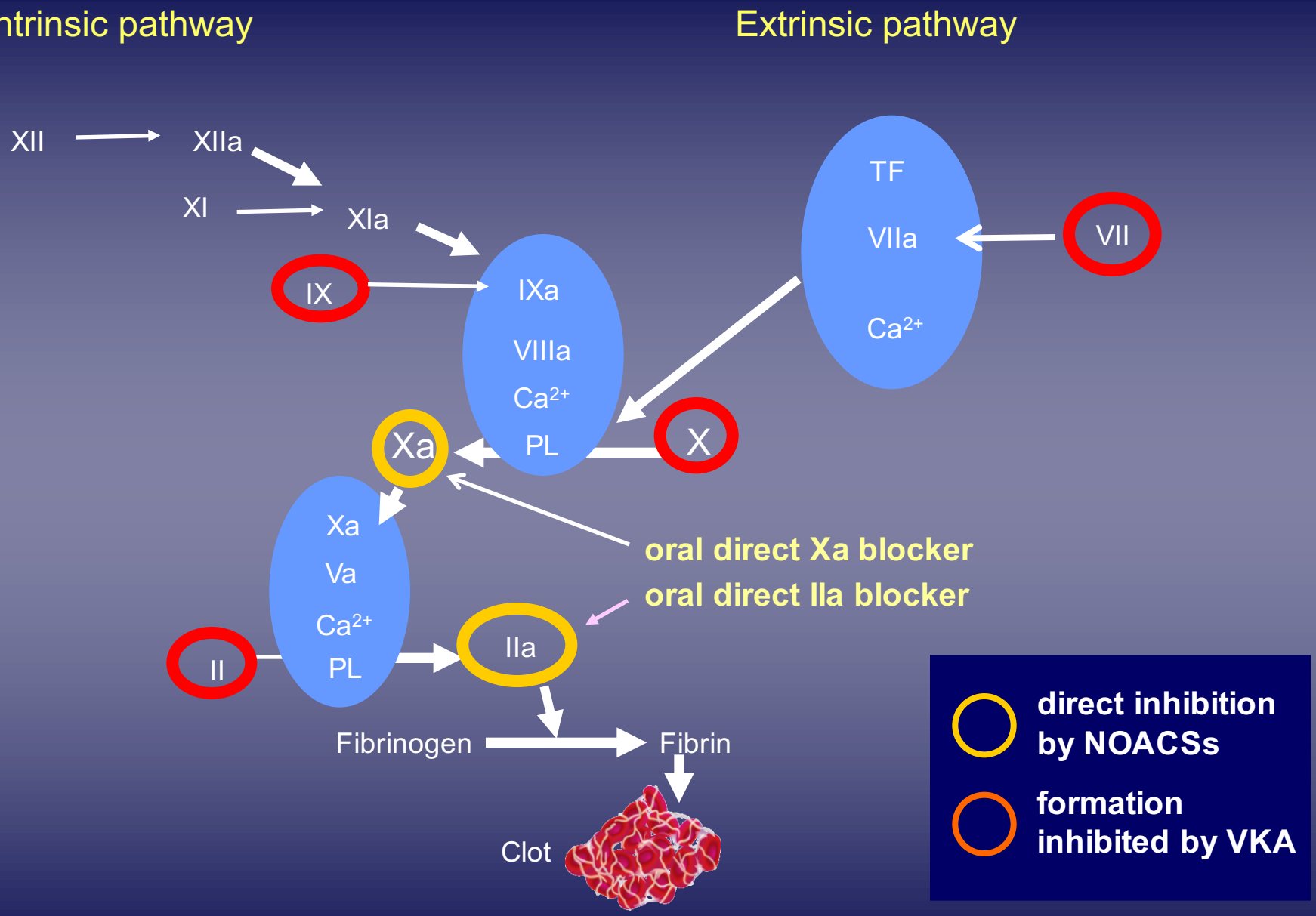


*Dose reduced by 50% in selected pts

Edoxaban blood levels and events in ENGAGE



Ruff CT. Lancet 2015;385:2288-2295



Adapted from *Brouwer MA, Verheugt FWA. Circulation 2002;105:1270-1274*

Novel antithrombotic agents 3

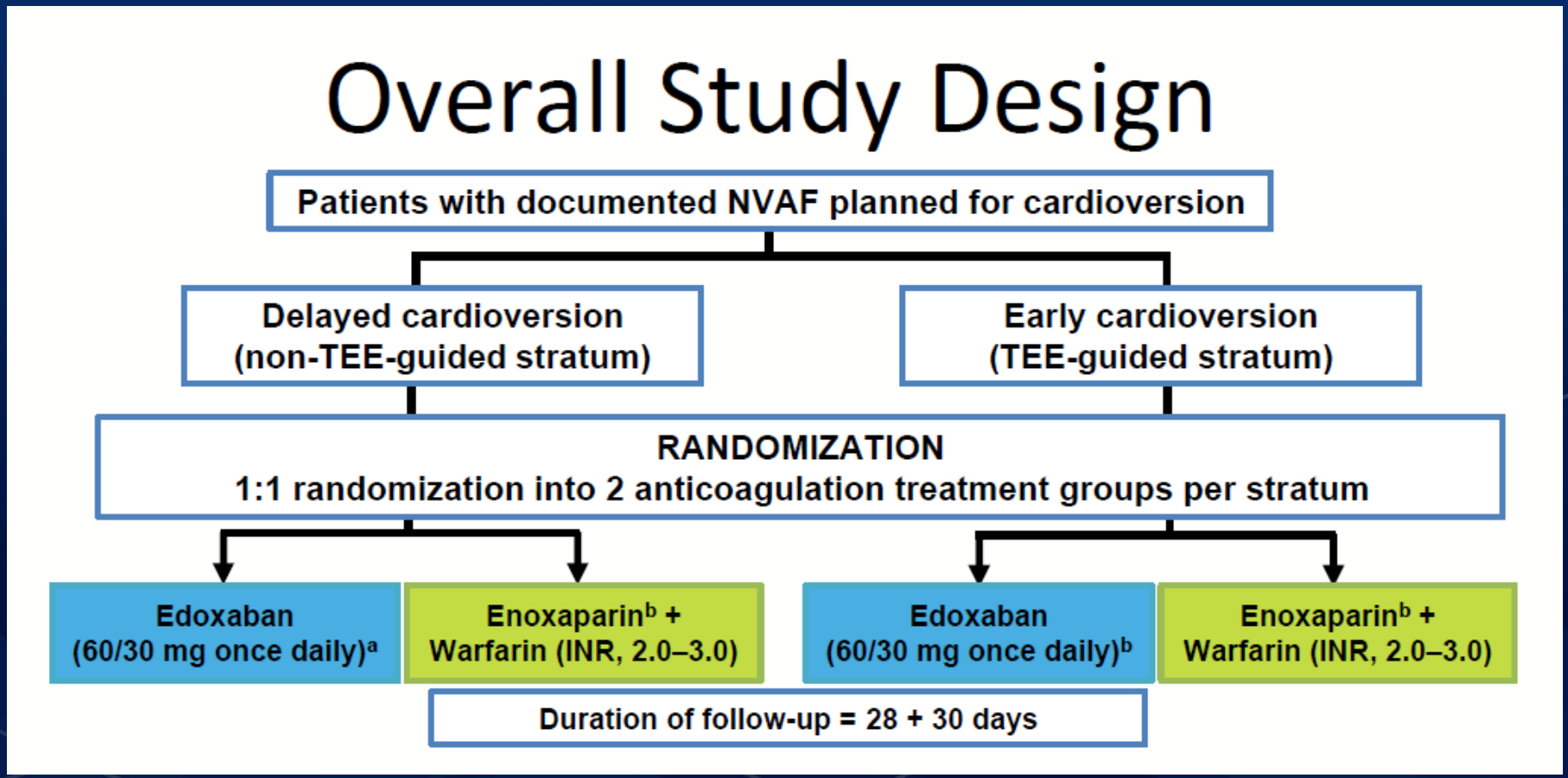
Oral anticoagulants for stroke prevention in atrial fibrillation: current status, special situations, and unmet needs

Freek W A Verheugt, Christopher B Granger

In patients with non-valvular atrial fibrillation, oral anticoagulation with vitamin K antagonists reduces the risk of stroke by more than 60%. But vitamin K antagonists have limitations, including causing serious bleeding such as intracranial haemorrhage and the need for anticoagulation monitoring. In part related to these limitations, they are used in only about half of patients who should be treated according to guideline recommendations. In the past decade, oral agents have been developed that directly block the activity of thrombin (factor IIa), as well as drugs that directly inhibit activated factor X (Xa), which is the first protein in the final common pathway to the activation of thrombin. These novel non-vitamin K antagonist oral anticoagulants (NOACs) have been shown to be at least as good as warfarin for stroke prevention in atrial fibrillation and they have proved to have better safety profiles. Their net advantage is underscored by significantly lower all-cause mortality compared with warfarin in large clinical trials. Because of these features and their ease of use, they are recommended for stroke prevention in atrial fibrillation. They have also a fast onset and offset of action, but they currently lack specific antidotes. This paper addresses the role of anticoagulation for stroke prevention in atrial fibrillation in the era of NOACs, with a focus on special situations including management in the event of bleeding and around the time of procedures including cardioversion, catheter ablation, and device implantation. Also their use in patients with concomitant coronary artery disease, with advanced age, with chronic kidney disease, or with valvular heart disease will be discussed as well as the interaction of NOACs with other cardiac medication, and switching between anticoagulants.

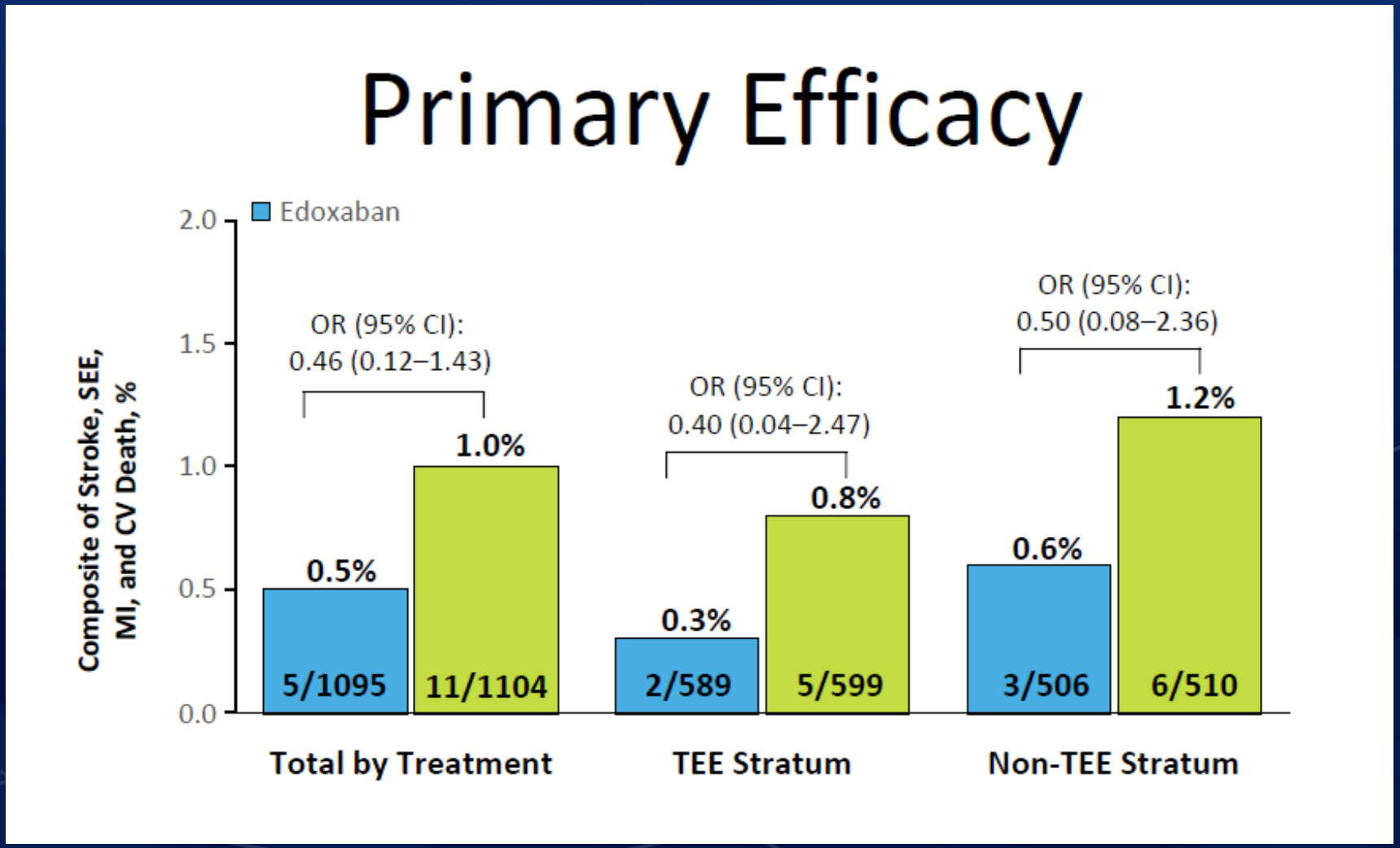
Cardioversion

ENSURE-AF



Lancet 2016;388:1995-2003

ENSURE-AF

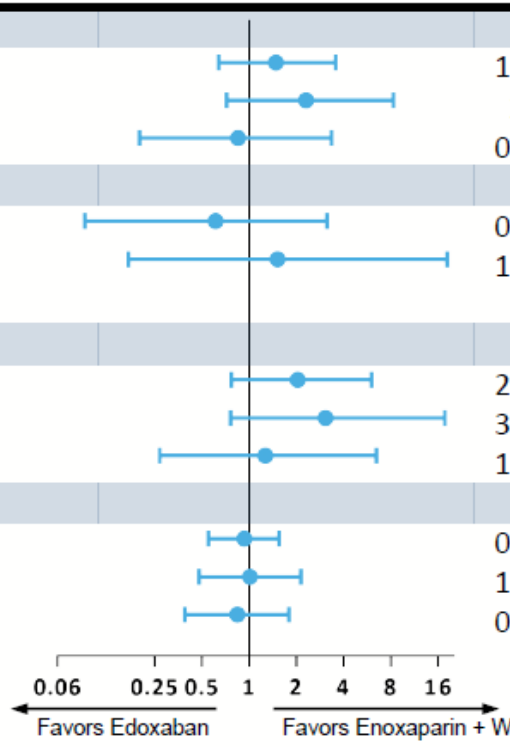


Lancet 2016;388:1995-2003

ENSURE-AF

Adjudicated Safety Outcome

	Event Rate, % (n/N)		Edoxaban vs Enoxaparin + Warfarin	
	Edoxaban	Enoxaparin + Warfarin		OR (95% CI)
First Major or CRNM Bleeding				
Total by Treatment	1.5 (16/1067)	1.0 (11/1082)		1.48 (0.64–3.55)
TEE Stratum	1.9 (11/570)	0.9 (5/577)		2.3 (0.72–8.31)
Non-TEE Stratum	1.0 (5/497)	1.2 (6/505)		0.85 (0.20–3.35)
Major Bleeding				
Total by Treatment	0.3 (3/1067)	0.5 (5/1082)		0.61 (0.09–3.13)
TEE Stratum	0.5 (3/570)	0.3 (2/577)		1.52 (0.17–18.27)
Non-TEE Stratum	0	0.6 (3/505)		NC
CRNM Bleeding				
Total by Treatment	1.3 (14/1067)	0.6 (7/1082)		2.04 (0.77–6.00)
TEE Stratum	1.6 (9/570)	0.5 (3/577)		3.07 (0.76–17.70)
Non-TEE Stratum	1.0 (5/497)	0.8 (4/505)		1.27 (0.27–6.45)
Any Bleeding				
Total by Treatment	3.0 (32/1067)	3.2 (35/1082)		0.93 (0.55–1.55)
TEE Stratum	3.0 (17/570)	2.9 (17/577)		1.01 (0.48–2.13)
Non-TEE Stratum	3.0 (15/497)	3.6 (18/505)		0.84 (0.39–1.79)

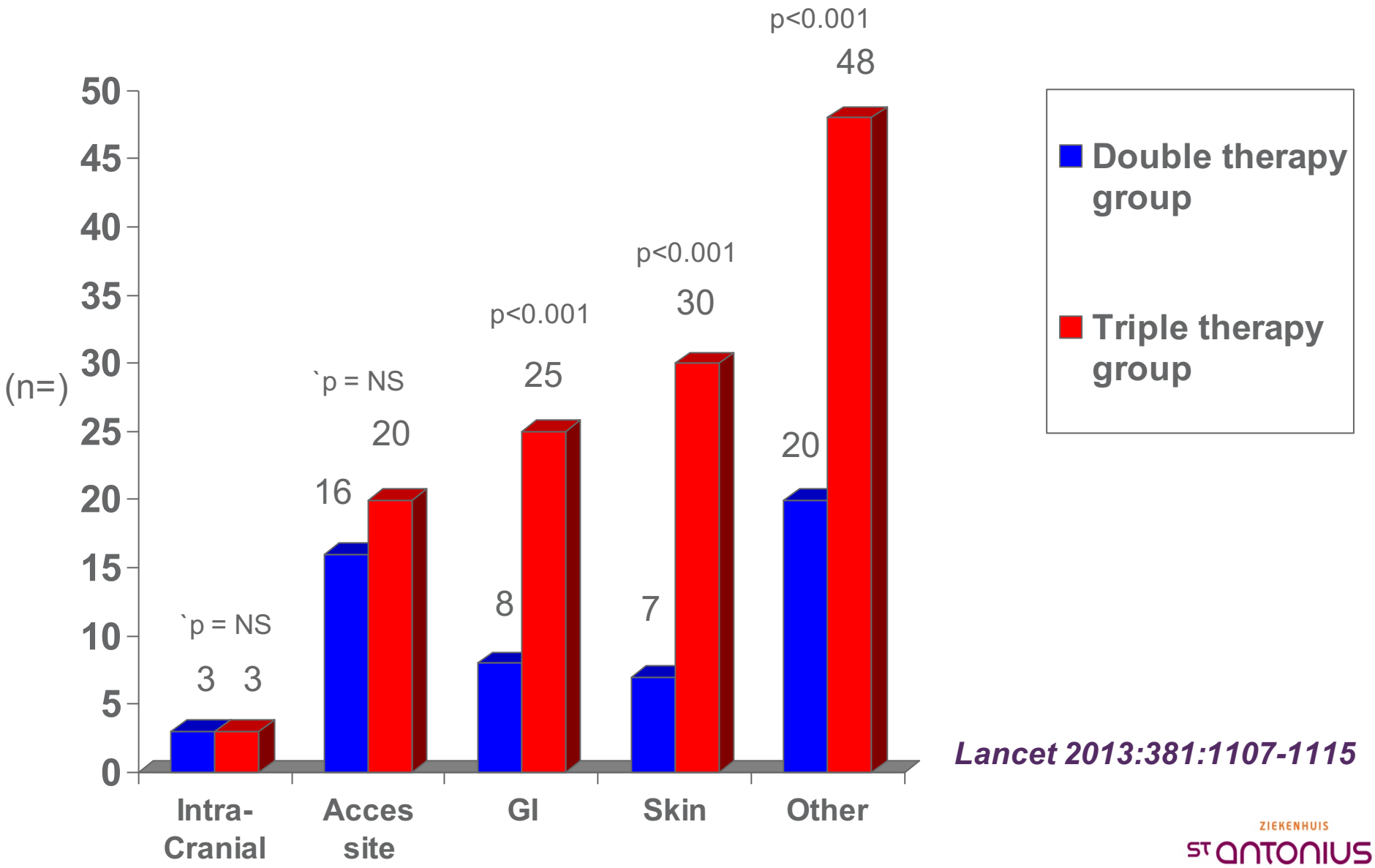


[a] In the safety population assessed during the on-treatment period
CI = confidence interval; CRNM = clinically relevant nonmajor; NC = not calculated; OR = odds ratio;

Lancet 2016;388:1995-2003

PCI

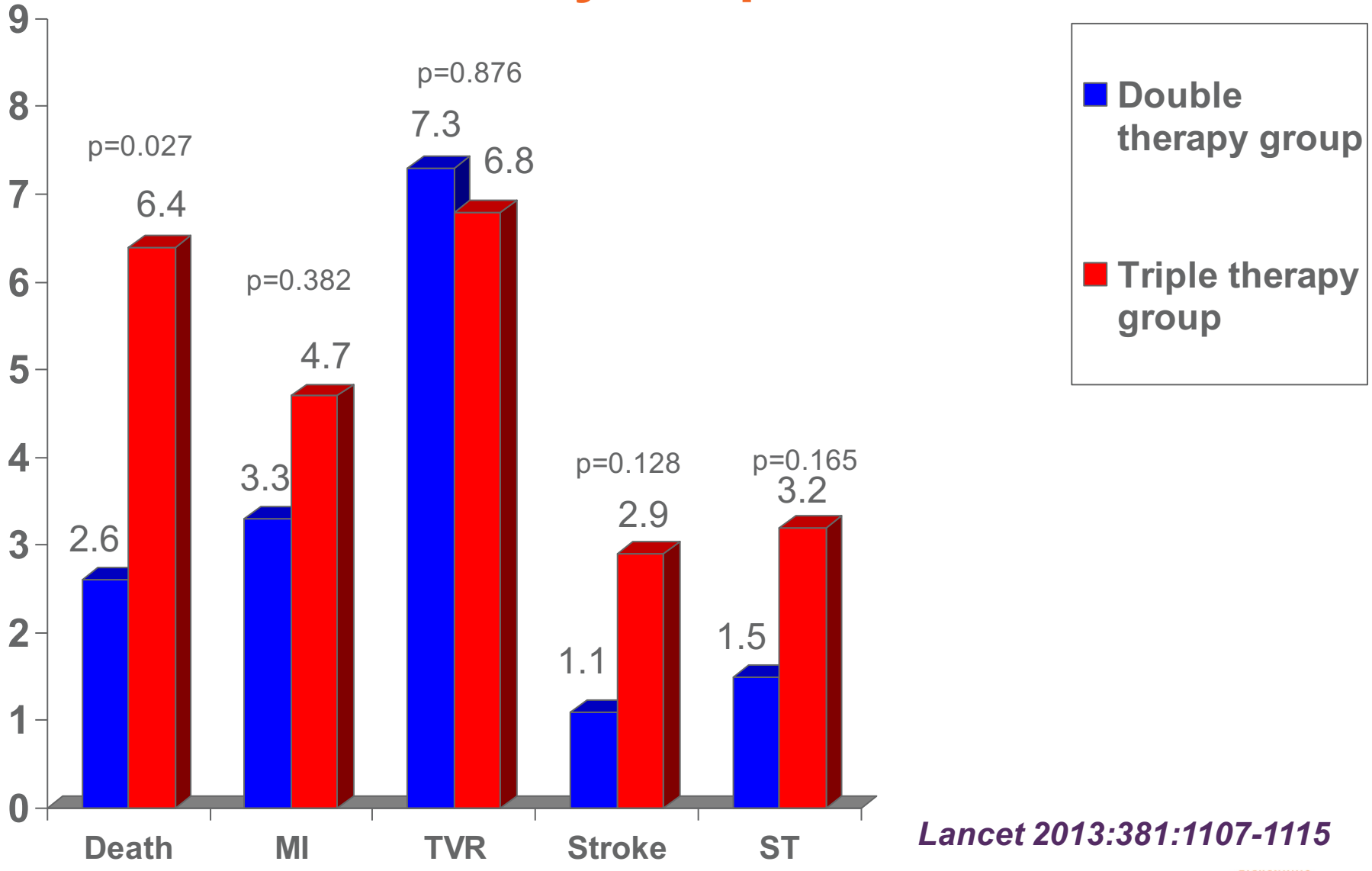
Locations of TIMI bleeding: Worst bleeding per patient



Lancet 2013:381:1107-1115

Lancet 2013:381:1107-1115

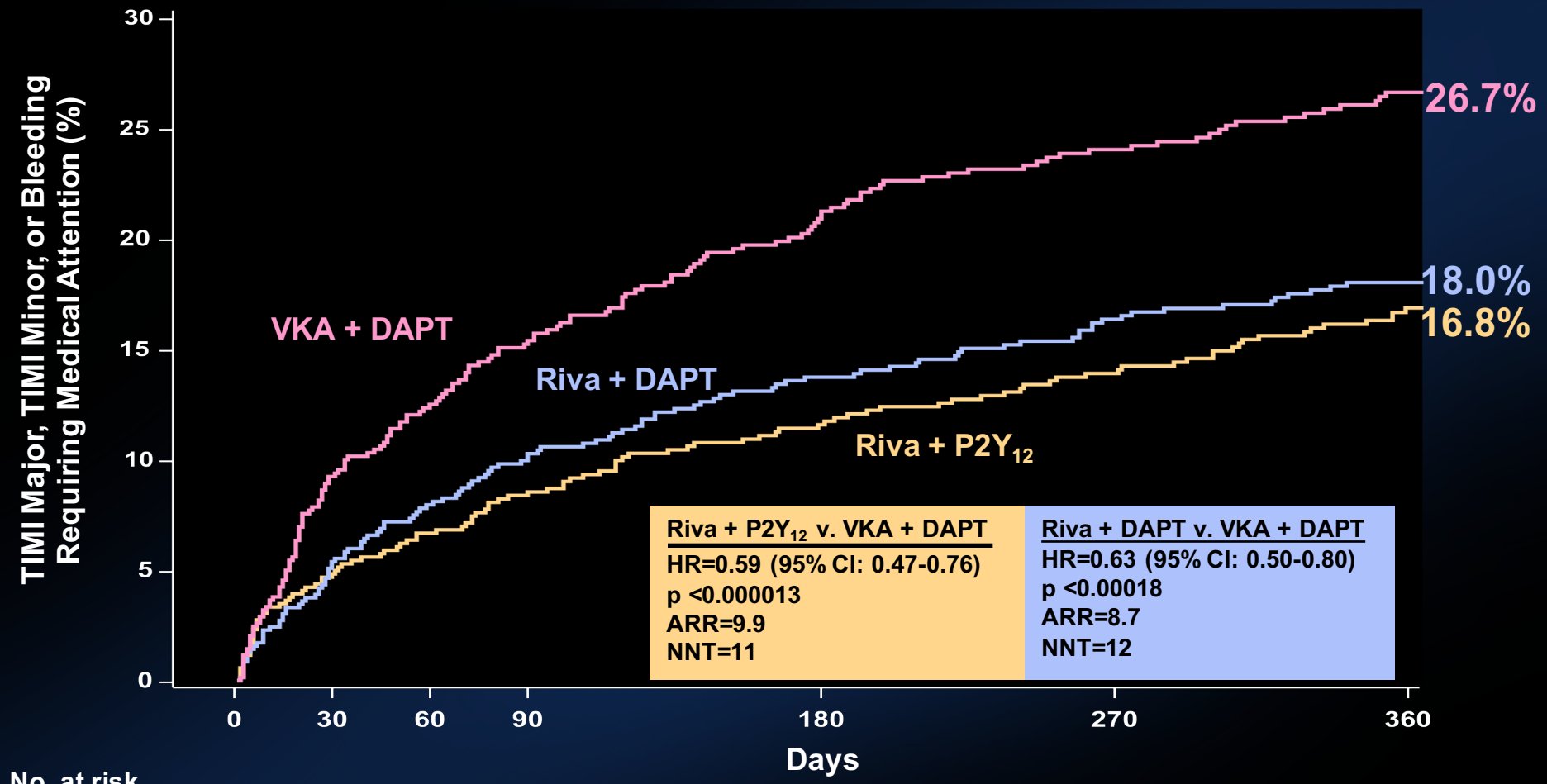
Secondary Endpoint



Lancet 2013:381:1107-1115

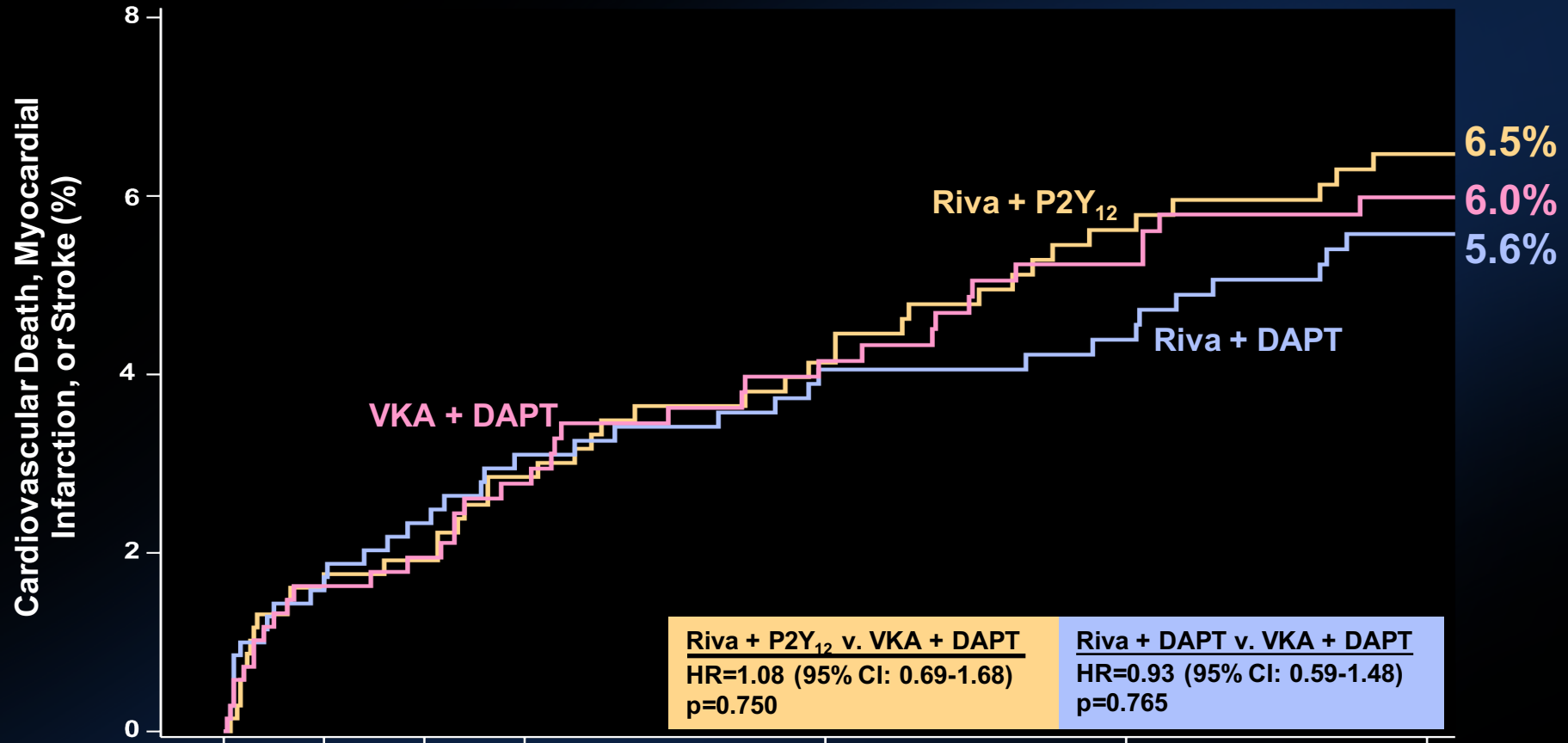
MI=any myocardial infarction; TVR= target vessel revascularisation (PCI + CABG); ST= stent thrombosis

Kaplan-Meier Estimates of First Occurrence of Clinically Significant Bleeding Events



N Engl J Med 2016;375:2432-2434

Kaplan-Meier Estimates of First Occurrence of CV Death, MI or Stroke

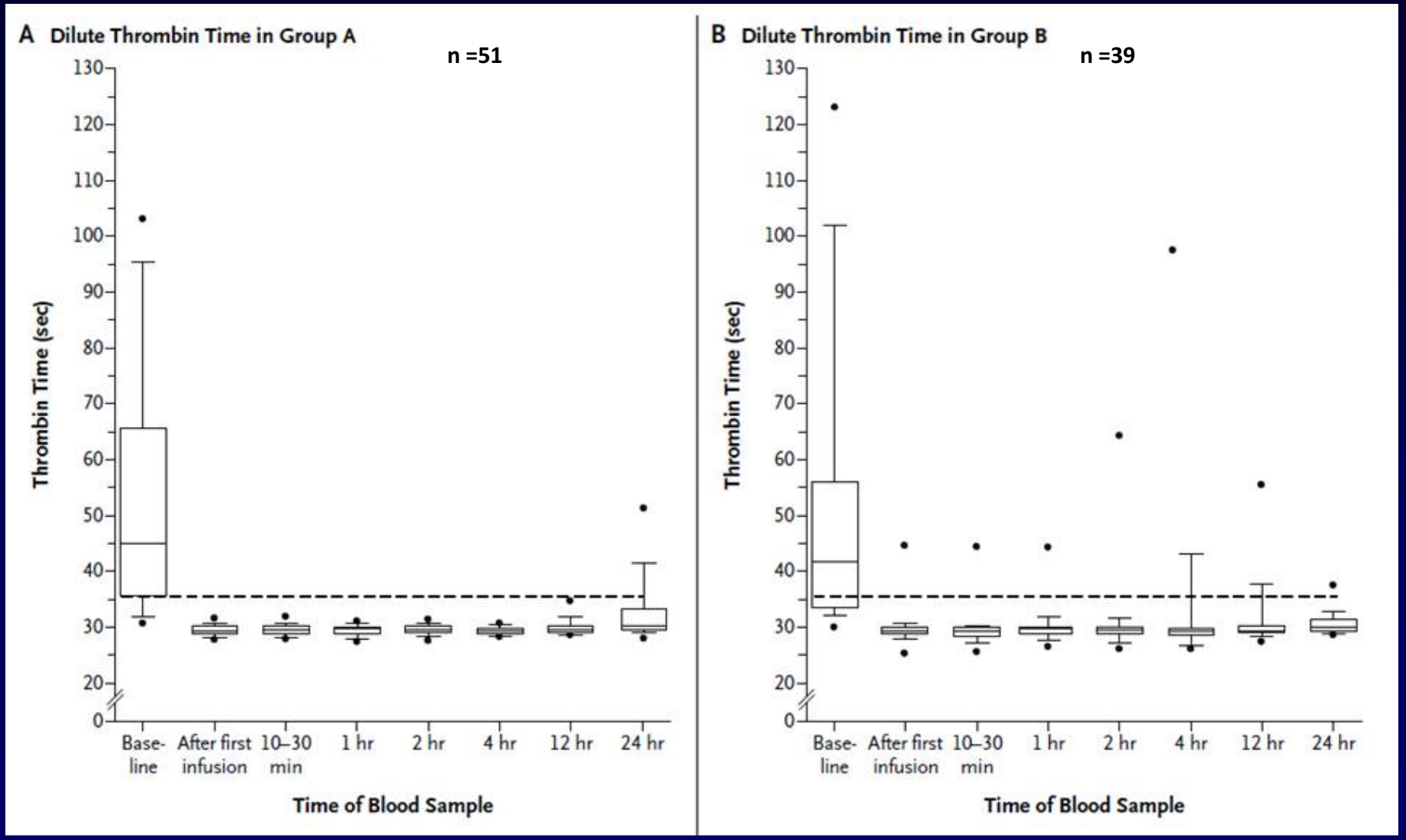


No. at risk							
Riva + P2Y12	694	648	633	621	590	562	430
Riva + DAPT	704	662	640	628	596	570	457
VKA + DAPT	695	635	607	579	543	514	408

N Engl J Med 2016;375:2432-2434

Antidotes

Pharmacodynamics of Idarucizumab in REVERSE-AD



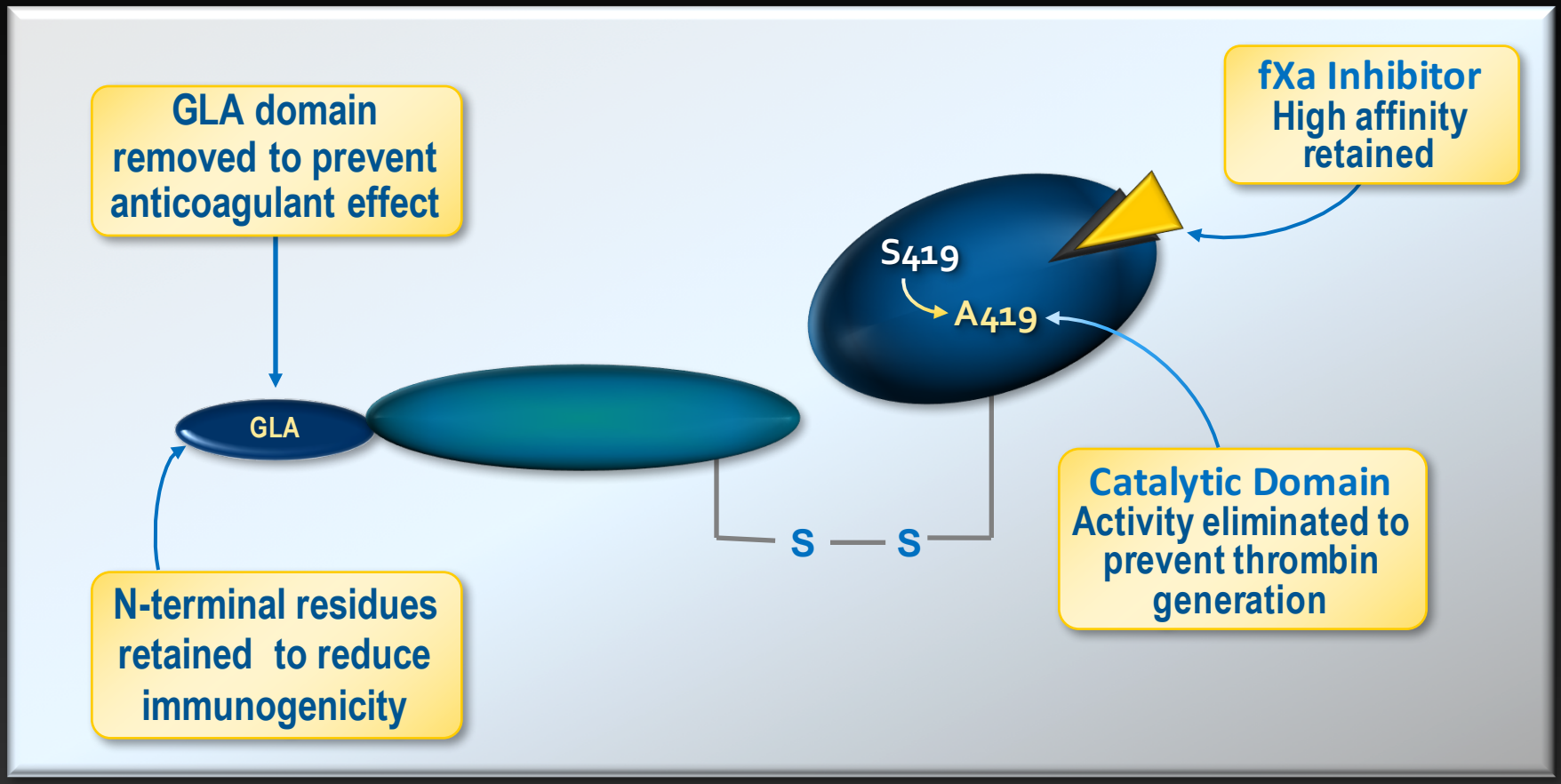
N Engl J Med 2015;373:511-520

olvg

Onze Lieve Vrouwe Gasthuis, Amsterdam

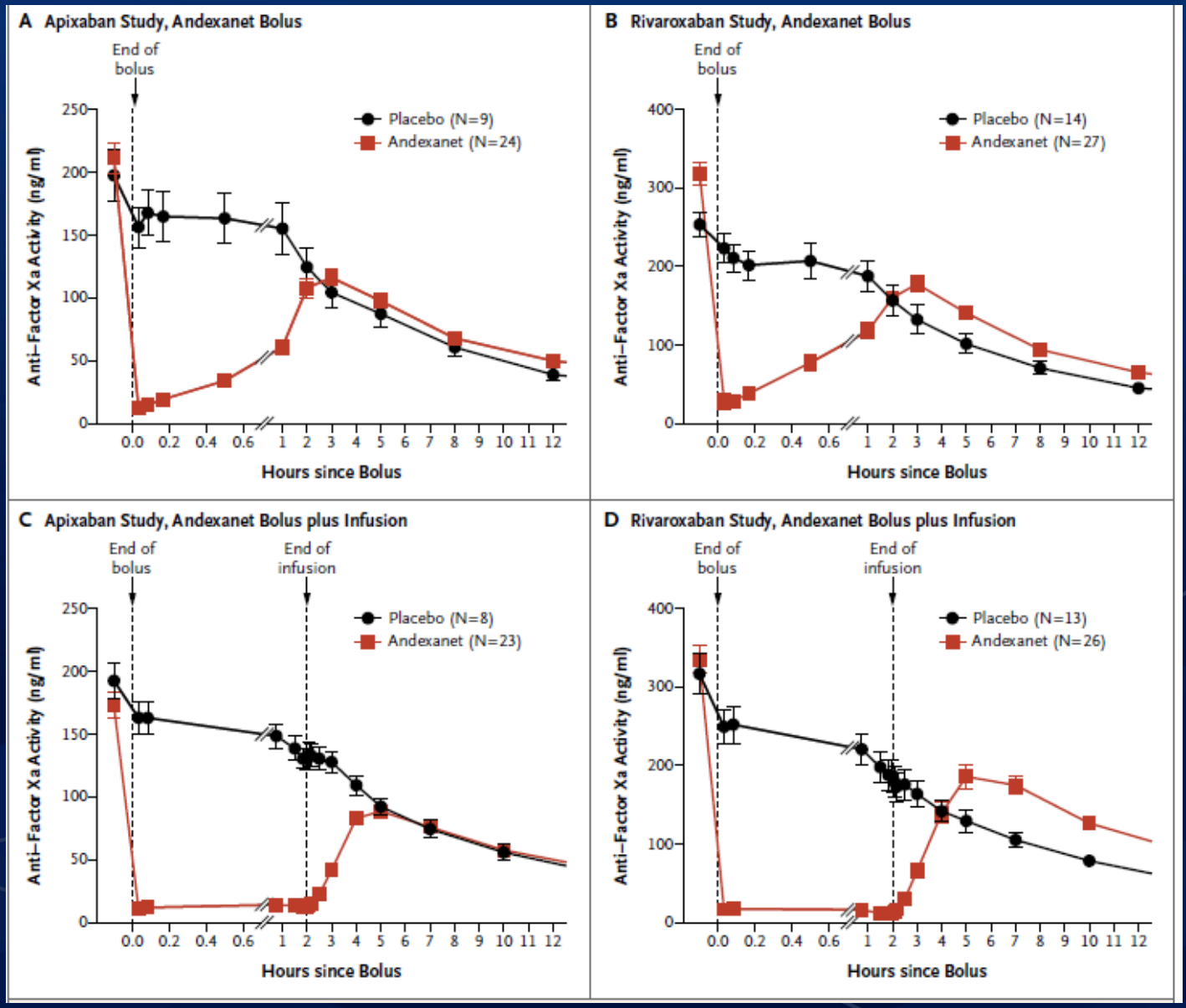
Andexanet Alfa: Recombinant, Modified Version of Human Factor Xa

- Acts as a fXa decoy and retains high affinity for all direct inhibitors of fXa
- Retains high affinity for ATIII-dependent fXa inhibitors (LMWH, fondaparinux)



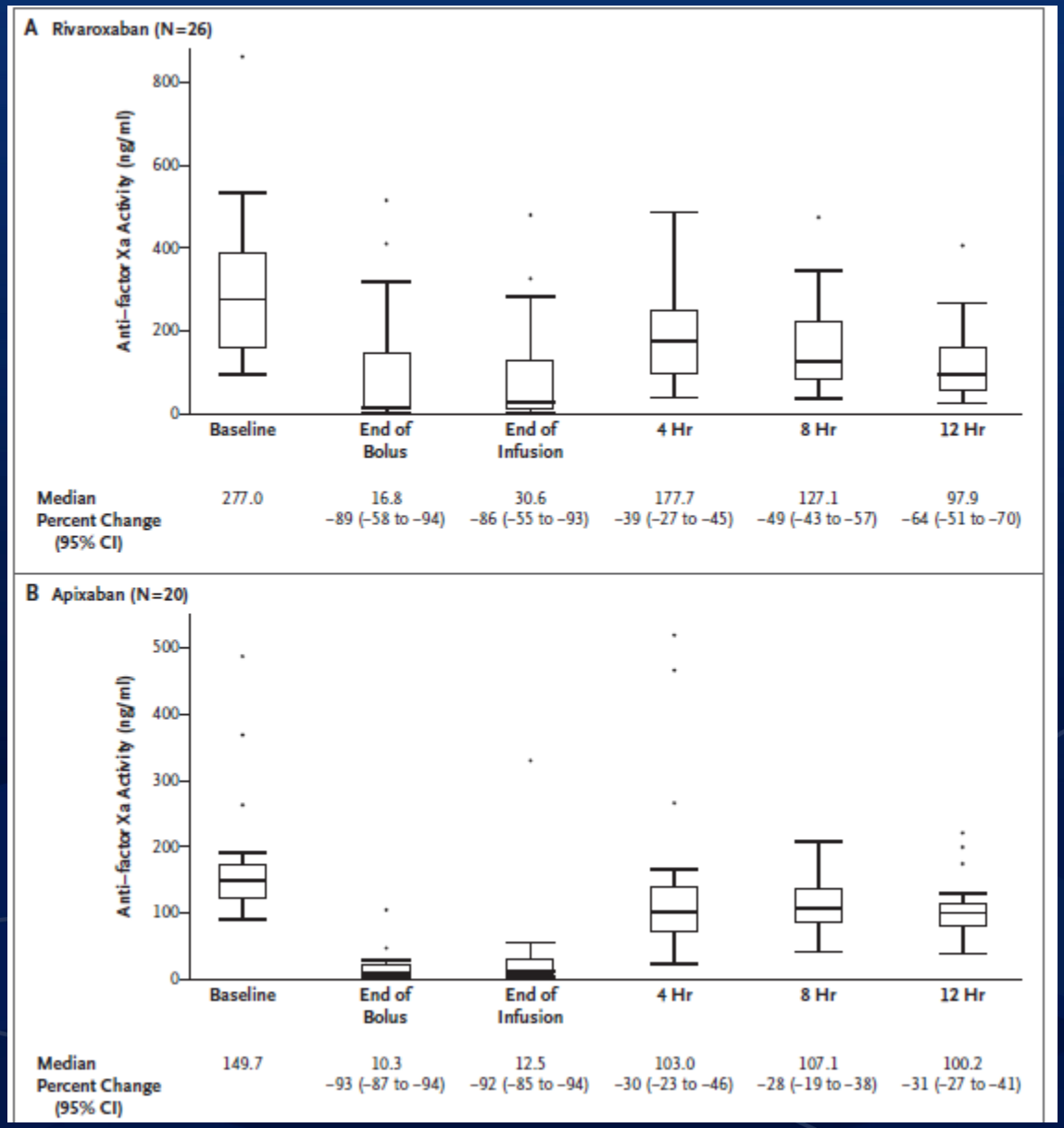
Lu G. Nat Med 2013;19:446-451

Andexanet Alfa in Oral anti-Xa Reversal



ANNEXA. N Engl J Med 2015;373:2413-2424

Andexanet Alfa in Bleeding on Oral anti-Xa



ANNEXA-IV. N Engl J Med 2016;375:1131-1141

New Advances in Anticoagulation

Conclusions

- NOACs are more effective and safer than VKA in SPAF
- In particular, 60 mg edoxaban once-daily with patient-specific dose-reduction to 30 mg is more effective and safer than well-managed warfarin (median TTR 68%) for SPAF
- NOACs are also effective and safe under special circumstances: in cardioversion and PCI. Furthermore, there are antidotes available in case of bleeding and urgent surgery