PAR receptor as a target for antiplatelet therapy: Focus on Vorapaxar

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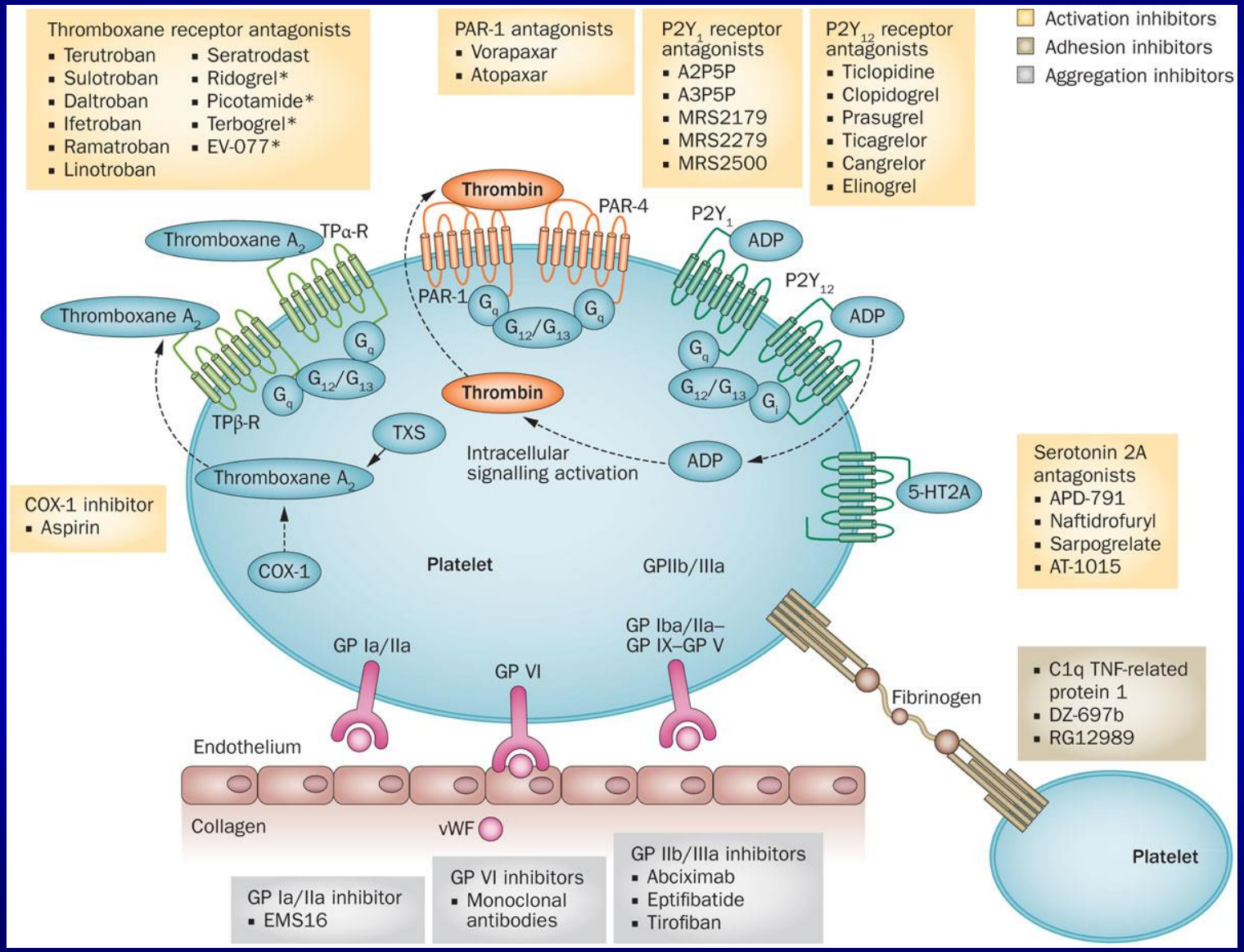
Disclosures:

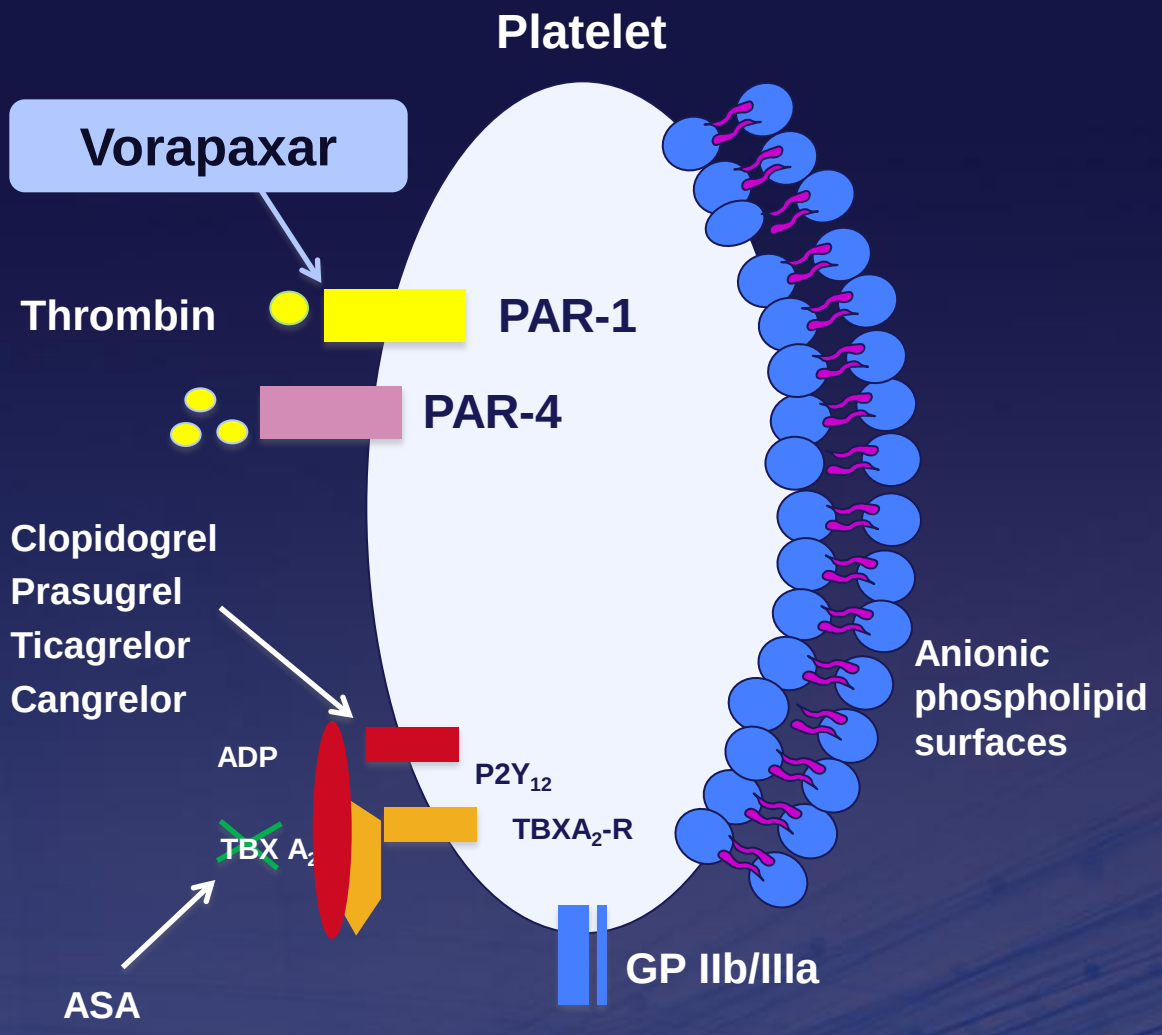
- **Ownership: Heart*Drug*™ Research, LLC**
- **Grants: Pfizer, Sanofi-BMS, Novartis, Lundbeck, Boehringer Ingelheim, Eli Lilly, AtheroGenics, Guilford, J&J, Bayer, Merck, Fibrex, Cardax, Eisai, Abbott, Brain Pool Program (Ministry of Science & Technology, Korea)**
- **Consulting: FDA, Pfizer, Sanofi-BMS, McNeil, NPS Pharma, Bayer, Eisai, mutual funds, hedge funds**
- **Speaking Bureau: Pfizer, Sanofi-BMS**
- **Patents: British Technology Group, Novartis, Boehringer Ingelheim, Eli Lilly, Pfizer, AtheroGenics, Eisai, PAR receptors and statins**
- **Unlabeled/Unapproved use: none**

Science is there, but what is missing?



Franchi, F. D. J. *Nat. Rev. Cardiol.* 2014

Vorapaxar: Mechanism of action



- Vorapaxar:
  - First-in-class
  - Oral PAR-1 inhibitor
- Metabolism:
  - Primarily hepatic via CYP 3A4
  - Terminal half-life: ~126–269 hrs
- Prior phase 2 trials:
  - No increase in bleeding and fewer MIs

Chackalamannil S, J Med Chem, 2006

Vorapaxar Program

Evaluation of Efficacy and Safety in Acute and Chronic Atherothrombosis

Vorapaxar Program
(~38,500 pts)

NSTEACS
12,944 pts

T·R·A- CER

2º Prevention
26,499 pts

TRA 2°P TIMI 50

Vorapaxar | **Placebo** | **Vorapaxar** | **Placebo**

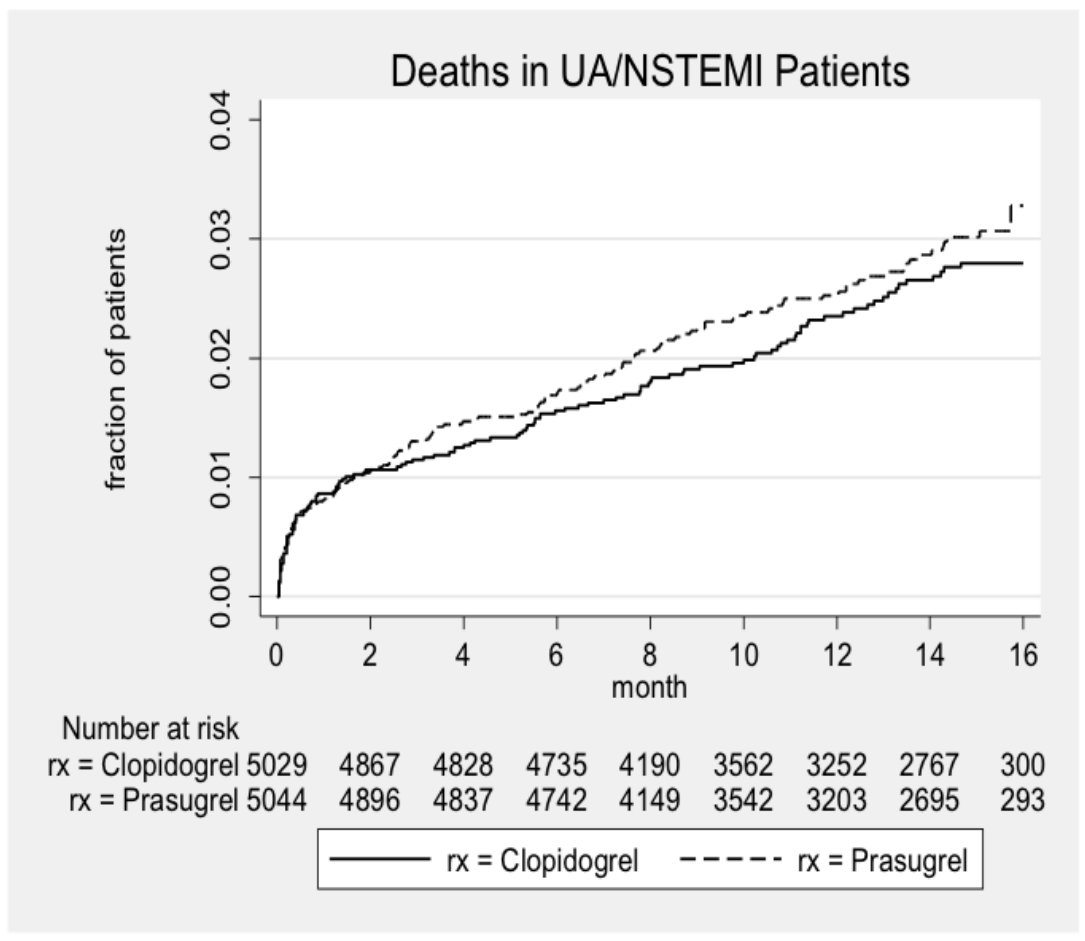
F/U: 30 days, 4,8,12 months, and 6 months thereafter

F/U 1 yr minimum

1º EP: Composite of CV death, MI, Stroke, urgent revascularization and Recurrent Ischemia w/ Rehosp

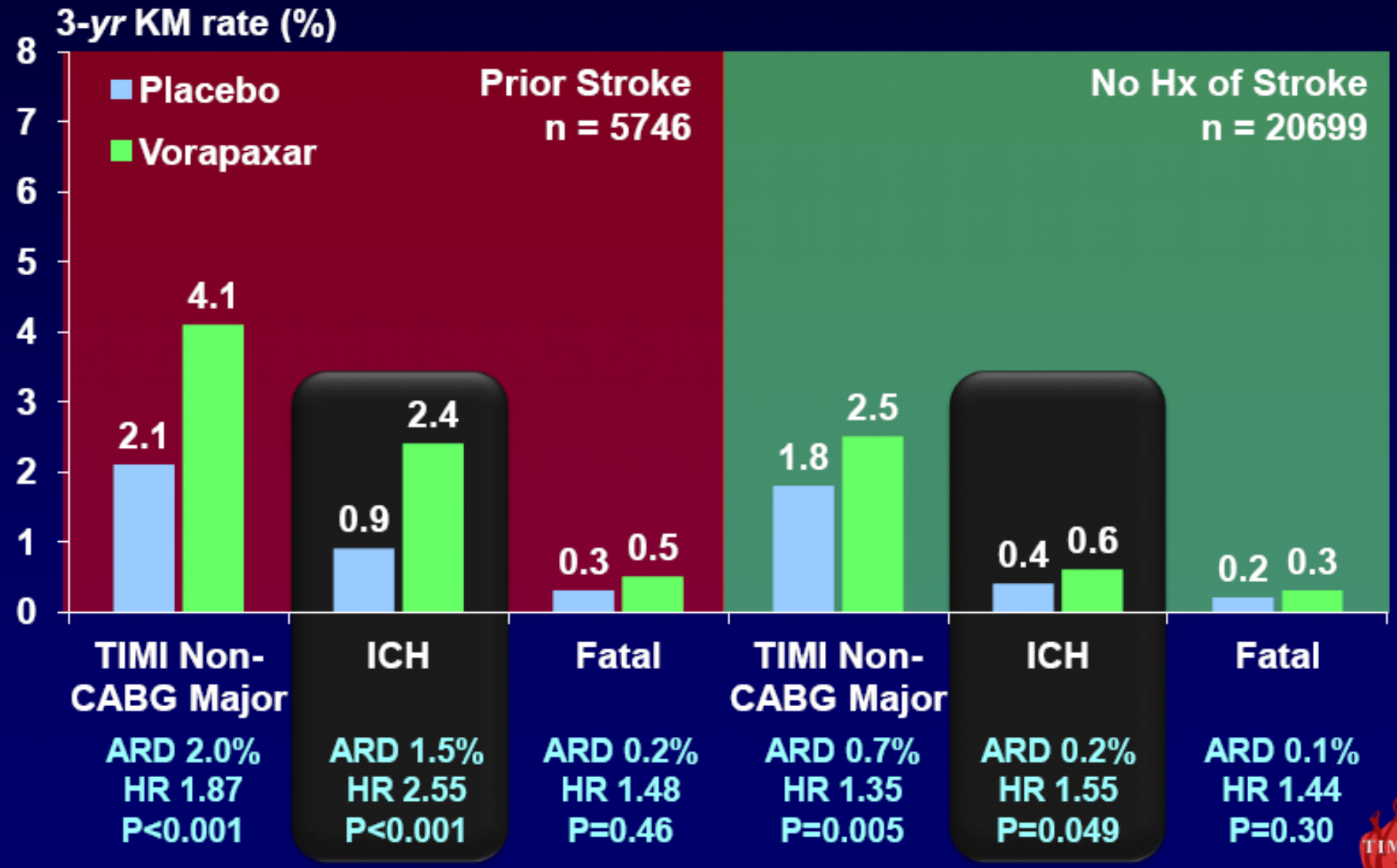
1º EP: Composite of CV death, MI, Stroke, and urgent revascularization

Redesigning TRACER after TRITON?



Serebruany, Int J Cardiol, 2015; FDA Prasugrel Review, 2009

Major Bleeding Endpoints

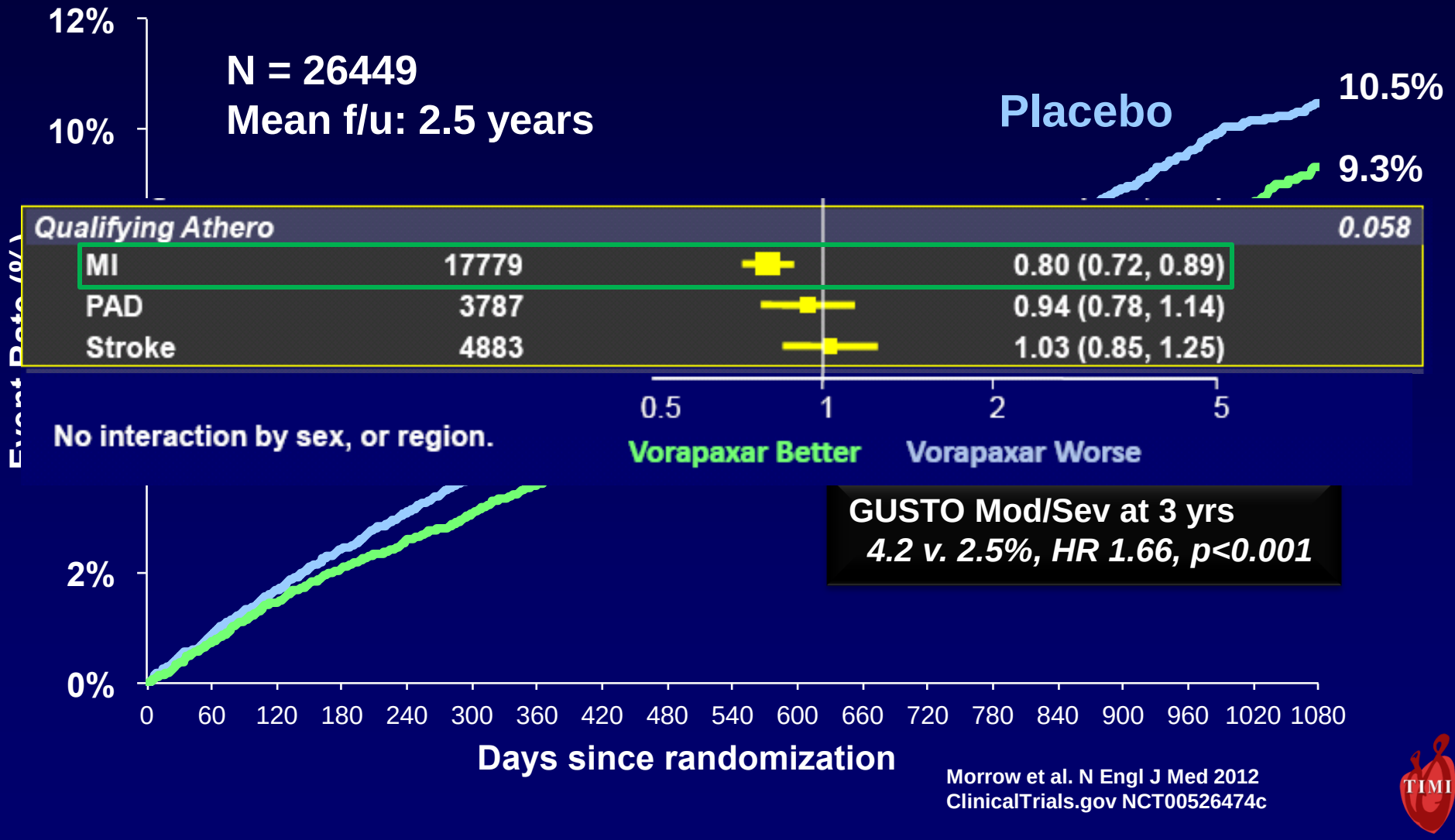


Morrow et al. ACC 2012, Chicago, March 24, 2012

Background – 1° Efficacy Evaluation

Overall Population (N=26449)

CV Death, MI, or Stroke



Morrow et al. N Engl J Med 2012
ClinicalTrials.gov NCT00526474c

MI Cohort

Primary Efficacy Evaluation

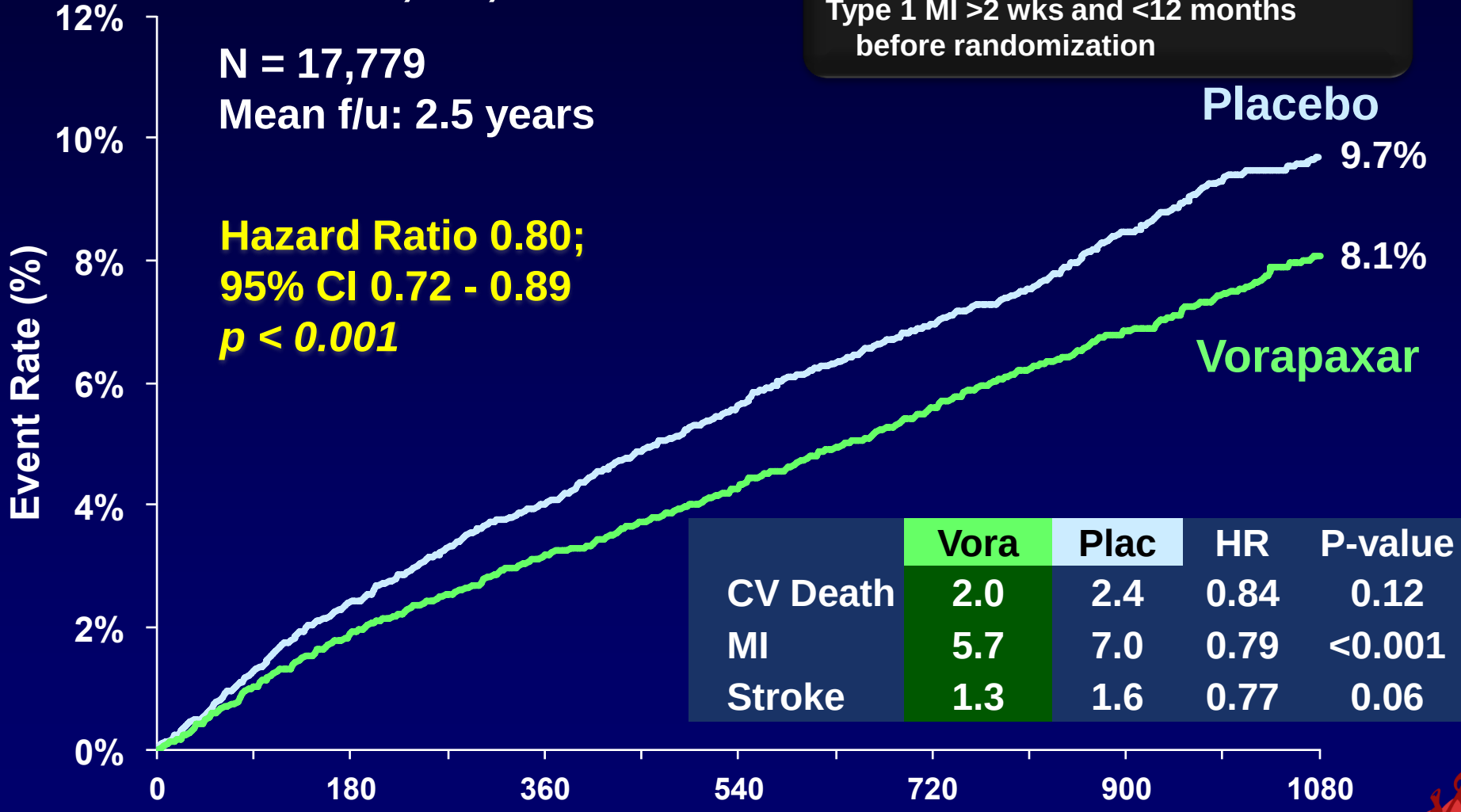
Prior MI Cohort (N=17,779)

CV Death, MI, or Stroke

Prior MI Inclusion:
Type 1 MI >2 wks and <12 months before randomization

N = 17,779
Mean f/u: 2.5 years

Hazard Ratio 0.80;
95% CI 0.72 - 0.89
p < 0.001



	Vora	Plac	HR	P-value
CV Death	2.0	2.4	0.84	0.12
MI	5.7	7.0	0.79	<0.001
Stroke	1.3	1.6	0.77	0.06

Scirica et al. Lancet 2012
ClinicalTrials.gov NCT00526474c

TIMI

MI Cohort

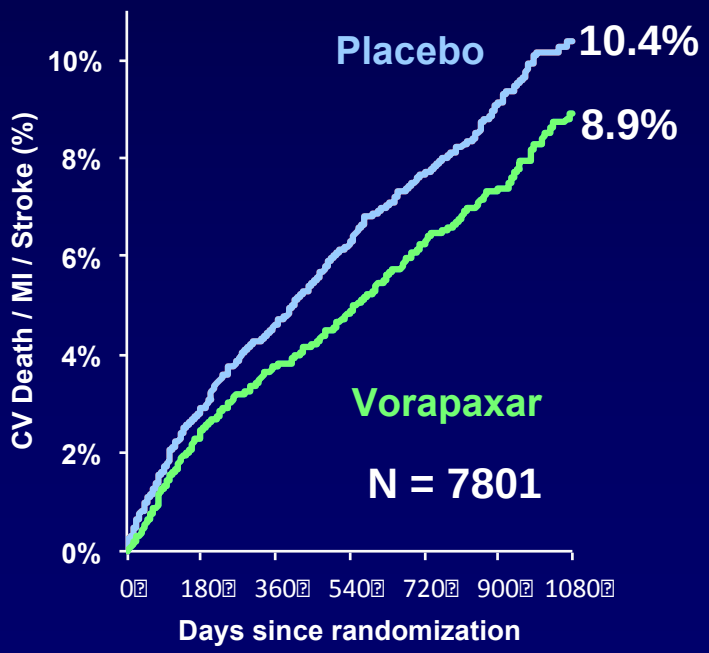
Efficacy by Time from Qual MI

Prior MI Cohort

Time from qualifying MI to Randomizations

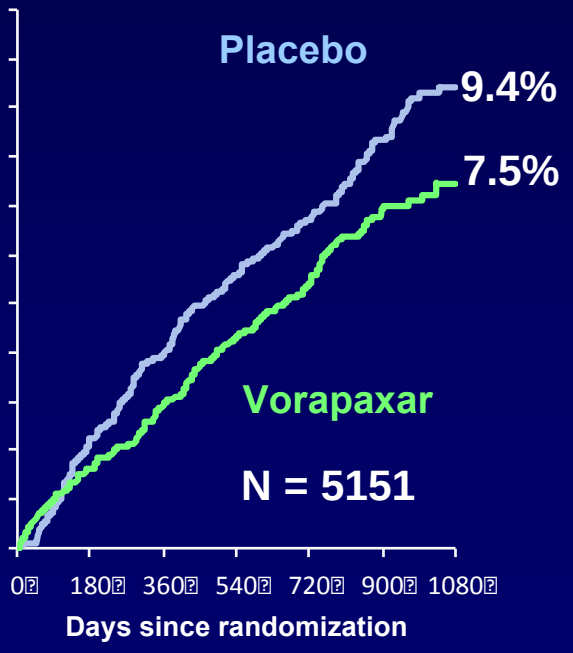
< 3 months

HR 0.82
p = 0.011



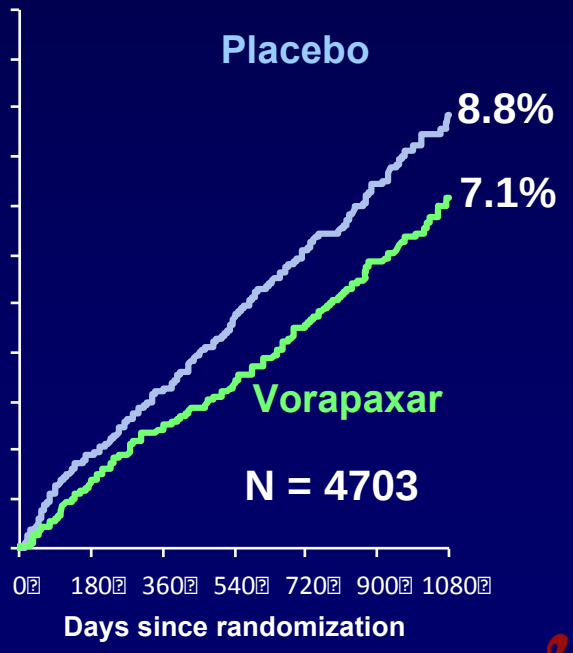
3 to 6 months

HR 0.79
p = 0.023



>6 months

HR 0.78
p = 0.026



Scirica et al. Lancet 2012
ClinicalTrials.gov NCT00526474c

TIMI

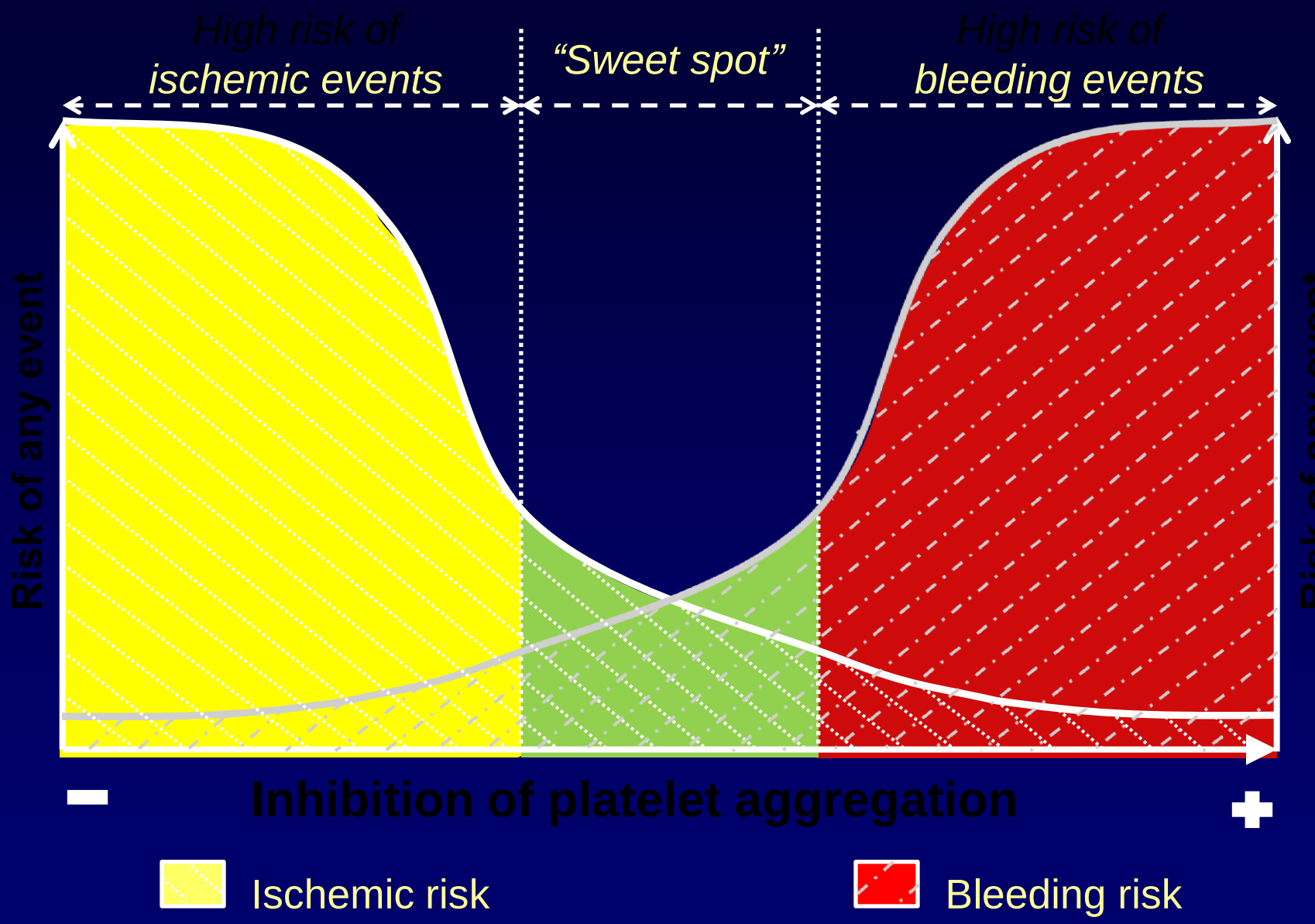
GUSTO Moderate/Severe Bleeding and Primary Efficacy Endpoint Rates by Indication Subgroup and Thienopyridine Use in TRA2P

sub group	thieno-pyridine	N		primary endpoint		GUSTO mod/sev	
		placebo	vorapaxar	placebo	vorapaxar	placebo	vorapaxar
MI	yes	6,207	6,203	10.6%	8.9%	2.1%	3.0%
	no	2,232	2,256	9.6%	8.1%	1.3%	2.2%
stroke*	yes	945	959	15.0%	17.9%	3.6%	5.4%
	no	2,189	2,184	9.5%	8.9%	2.2%	3.9%
PAD	yes	527	515	14.6%	13.4%	6.5%	9.5%
	no	1,124	1,108	11.6%	10.0%	3.8%	5.0%

*includes MI and PAD strata patients with a prior history of stroke/TIA

FDA Secondary Vorapaxar Review, 2014

Balancing Safety and Efficacy



Ferreiro & Angiolillo. Thromb Haemost 2010

Primary Endpoint Rates in Patients with and without GUSTO Moderate/Severe Bleeding Events in TRA2P

	GUSTO moderate/severe bleed	
	no	yes
placebo	10.1%	37% (of 317)
vorapaxar	8.5%	40% (of 476)

FDA Secondary Vorapaxar Review, 2014

Primary Endpoint Rates by Weight < or ≥ 60 kg and Treatment in TRA2P

	N	placebo	vorapaxar
< 60 kg	1,852	8.4%	10.6%
≥ 60 kg	24,587	11.0%	9.6%

FDA Secondary Vorapaxar Review, 2014

Primary Endpoint Rates by Weight < or ≥ 60 kg and Treatment in TRACER

	N	placebo	vorapaxar
< 60 kg	1,046	18.2%	19.3%
≥ 60 kg	11,898	16.9%	15.6%

FDA Secondary Vorapaxar Review, 2014

Primary Endpoint Rates by eGFR < or ≥ 60 mL/min/1.73m^2 and Treatment in TRA2P

	N	placebo	vorapaxar
≥60	17,313	9.7%	7.9%
<60	2,859	17.0%	15.6%

FDA Secondary Vorapaxar Review, 2014

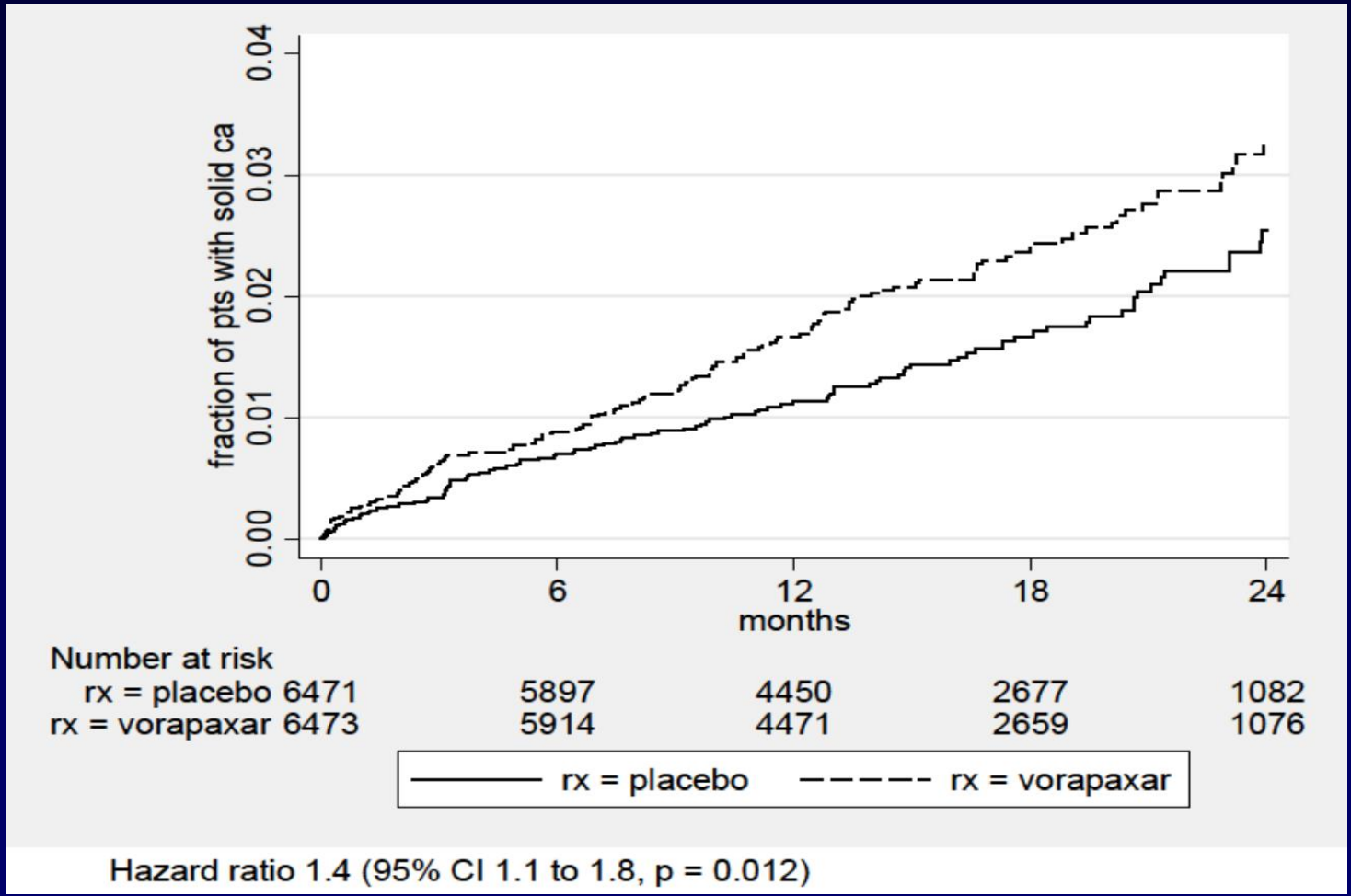
CABG: Missed Opportunity

	placebo	vorapaxar
Number of CABGs	953	935
GUSTO moderate/severe bleed	17.0%	21.1%
TIMI minor/major bleed	8.5%	11.1%
TIMI major bleed	8.1%	11.0%
Intracranial hemorrhage	0.0%	0.3%
Primary endpoint*	8.3%	5.9%
Deaths	3.9%	1.7%

*Excluding 85 placebo and 92 vorapaxar patients with primary endpoints prior to CABG

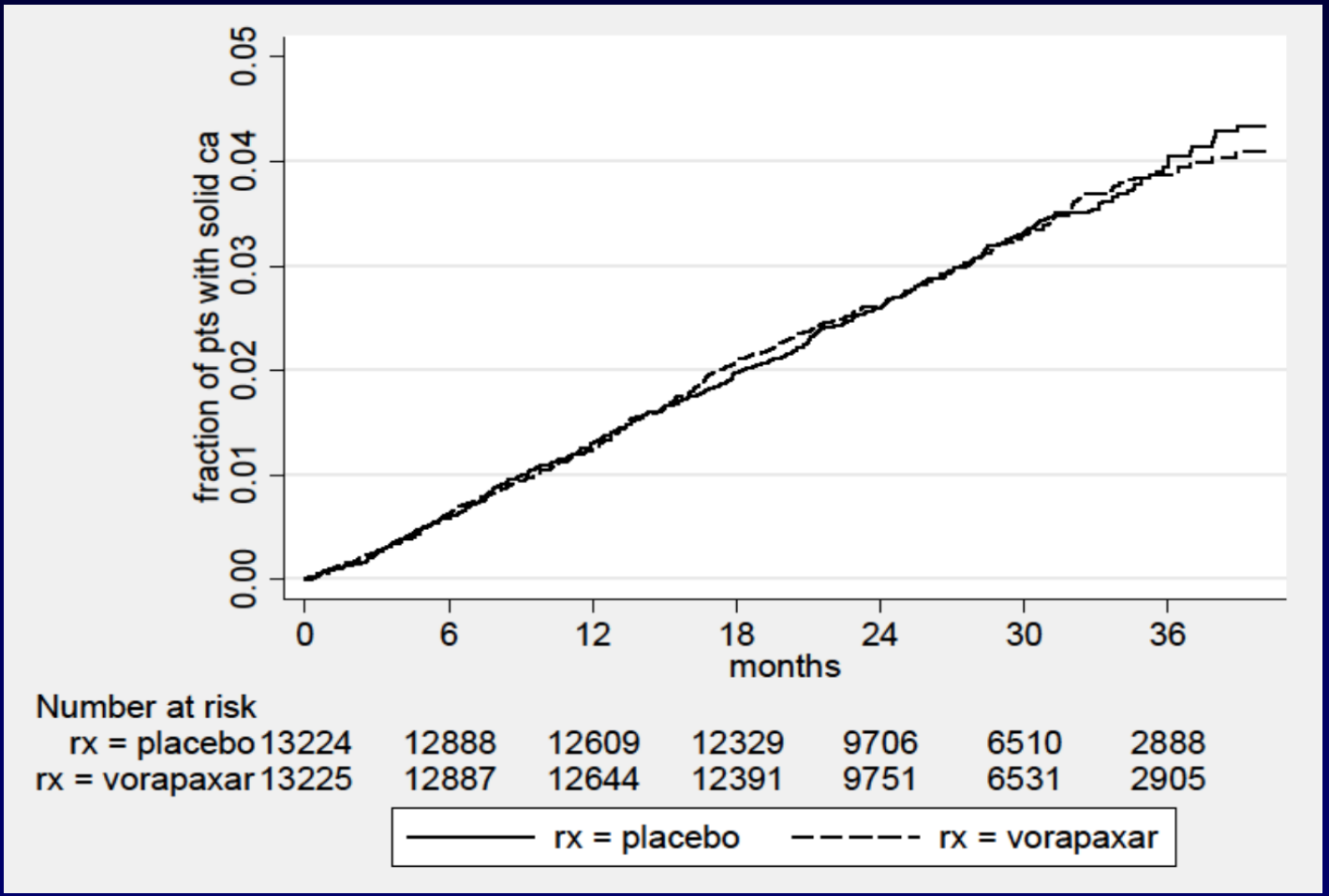
FDA Secondary Vorapaxar Review, 2014

Times to First Solid Cancer Events by Arm in TRACER



FDA Secondary Vorapaxar Review, 2014

Times to First Solid Cancer Events by Arm in TRA2P



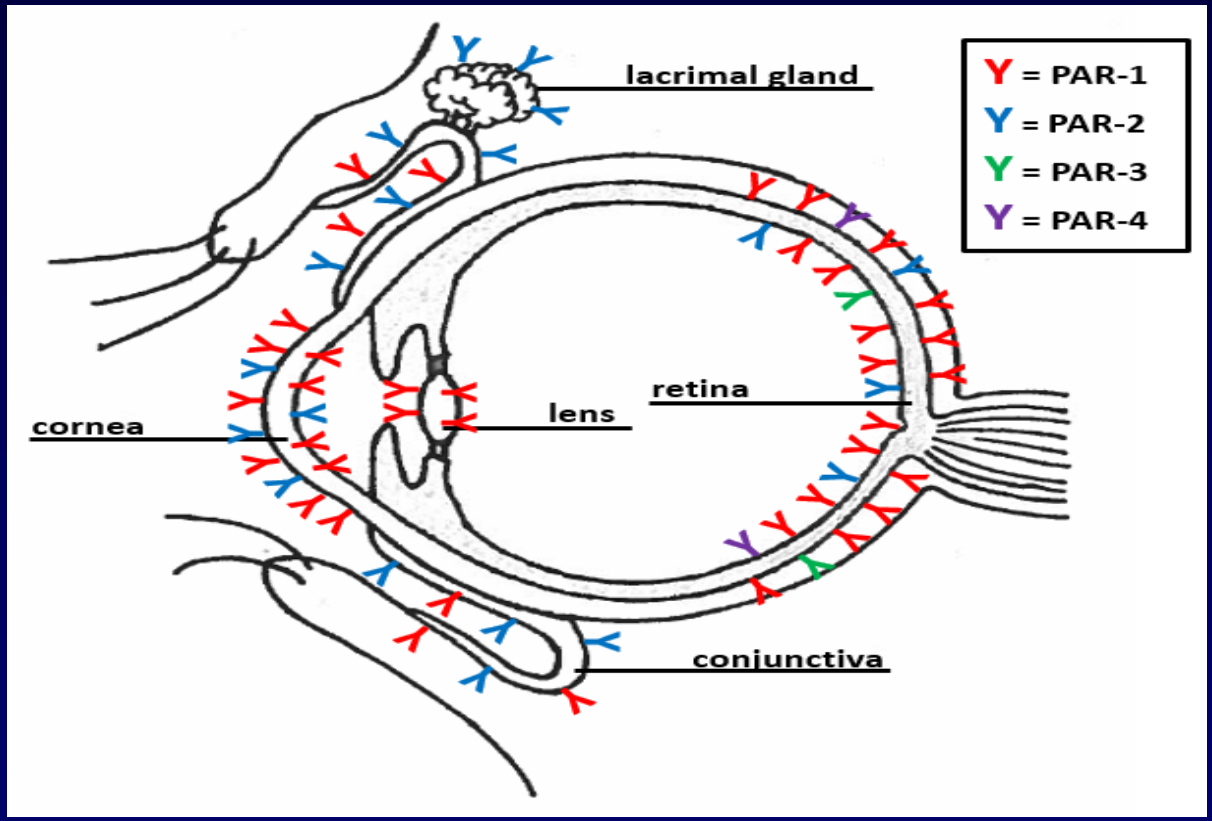
FDA Secondary Vorapaxar Review, 2014

Follow-up Rates in Patients with and without GUSTO Moderate/Severe Bleeding Events in TRA2P

	GUSTO moderate/severe bleed	
	no	yes
placebo	96.4%	97.8%
vorapaxar	96.6%	95.6%

FDA Secondary Vorapaxar Review, 2014

Diplopia after Vorapaxar



Serebruany, et al, Thromb Haemost; 2015

Vorapaxar: Strategy

Strategy	Year	Outcome
Developing PAR-1 antagonist	2004	Unclear
Initial investment	2007	Failure
PAD Indication	2012	Success
Better Efficacy/Safety	2012	Potential Success
Sponsor commitment	2014	Failure

Impressions:

- **Despite obvious advantages in patients undergoing heart surgery, and renal impairment, vorapaxar clinical utilization (if any) is woefully low.**
- **Broad FDA approved indication is still not sufficient for success**
- **Top problem – lack of shareholders control in trial design and marketing**