Triple Antiplatelet Therapy: Lights and Shadows

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CCRC

Presenter Disclosure Information

Gaetano M. De Ferrari

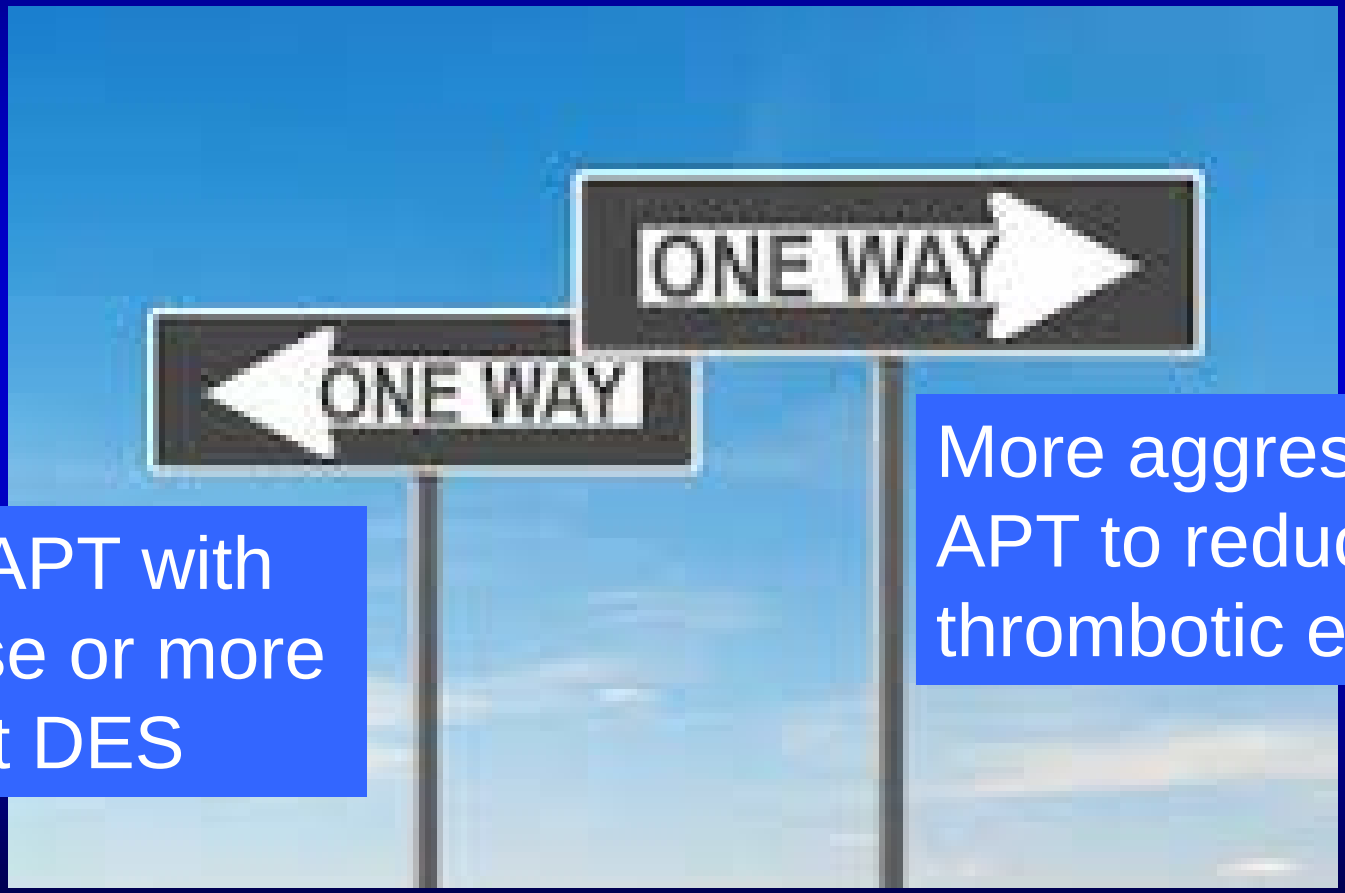
The following relationships exist :

MSD: Steering Committee, Advisory Board, Invited Speaker

Amgen: Advisory Board, Invited Speaker

Boston Scientific: Steering Committee, Advisory Board

More or Less APT ?



Less APT with the use or more recent DES

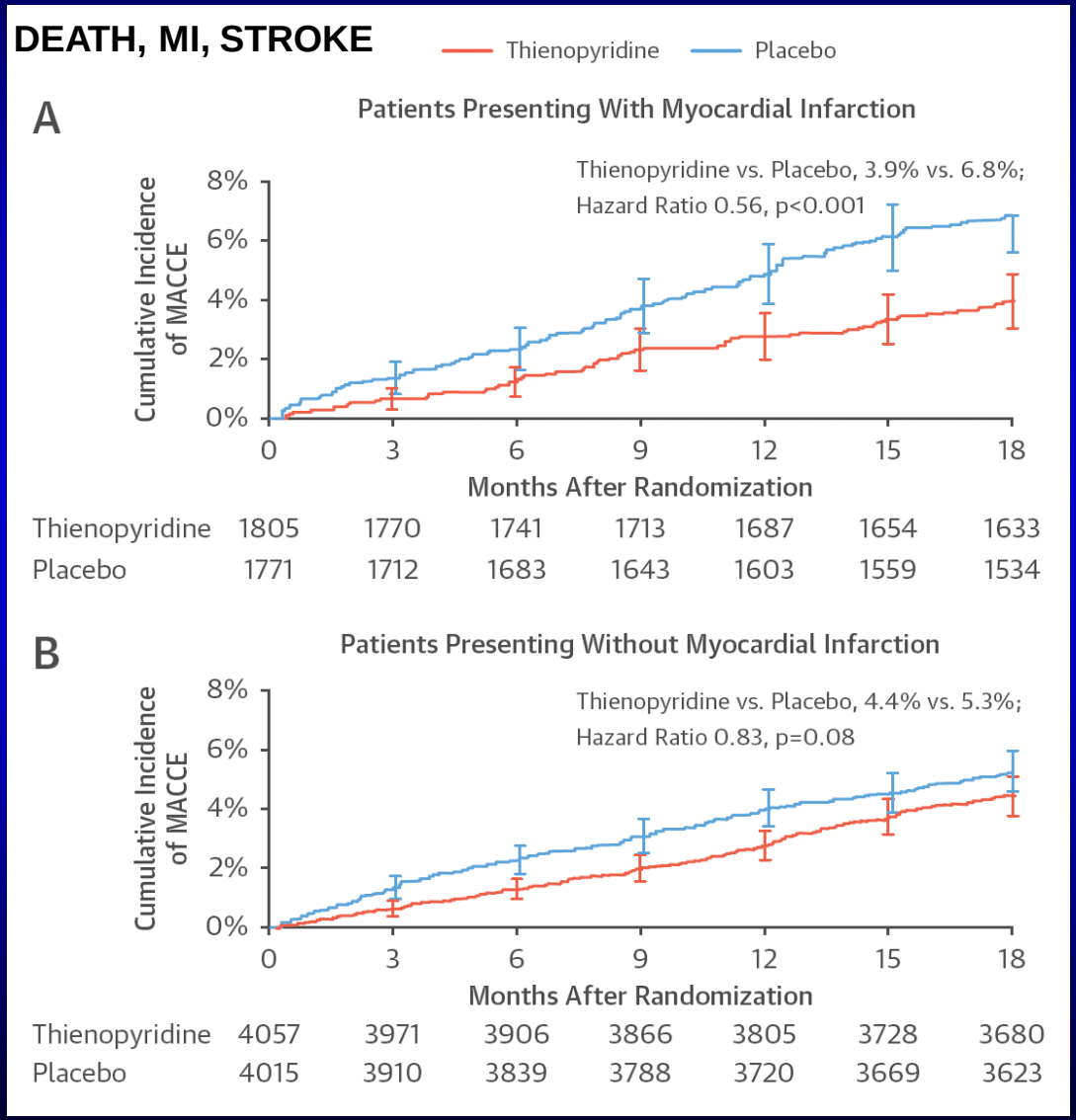
More aggressive APT to reduce thrombotic events

MACE in the DAPT Trial Based on Presentation with MI

P for interaction=0.03

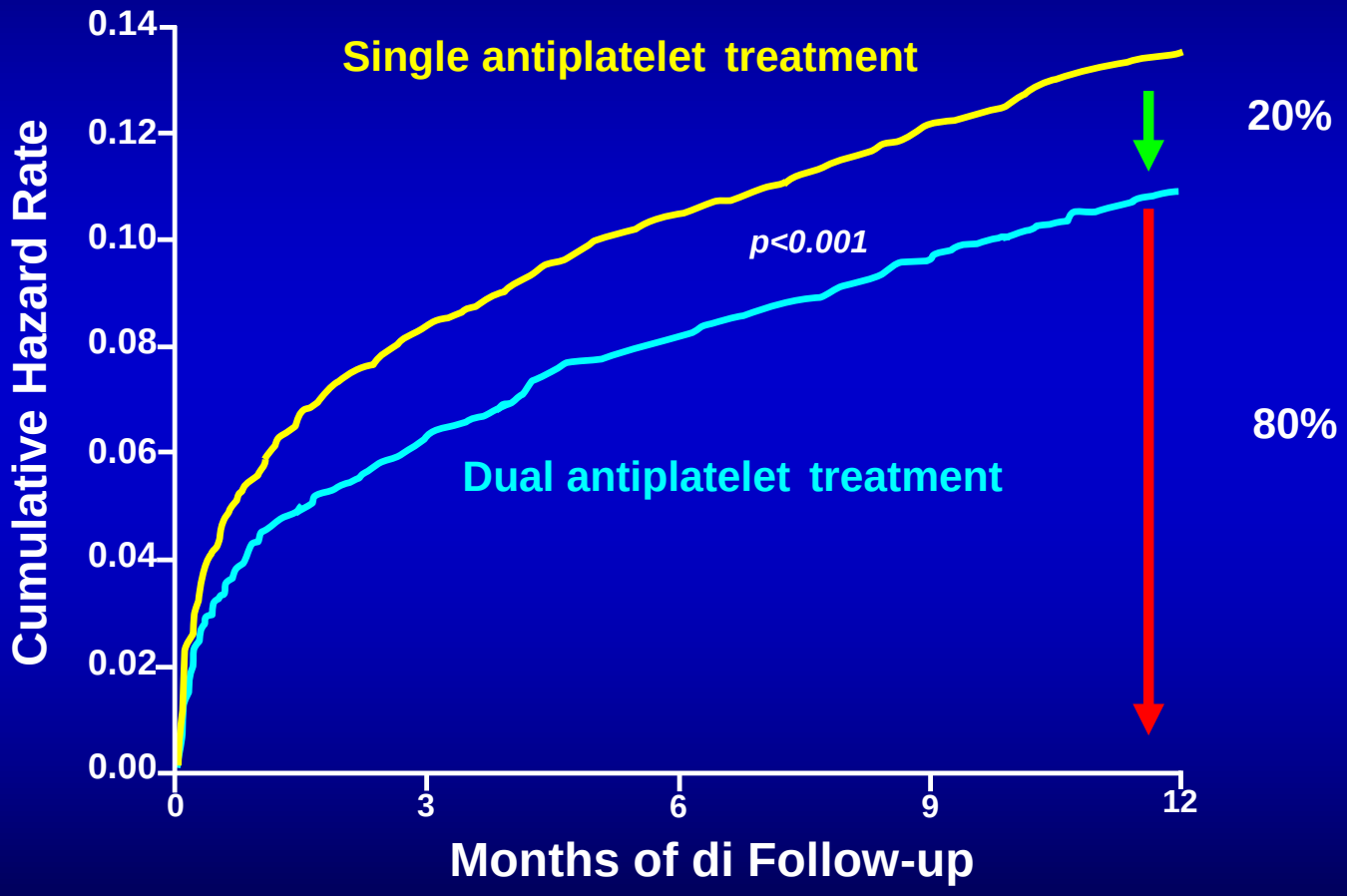
N= 3.576

N= 8.072



Yeh RW, et al. J Am Coll Cardiol 2015;65:2211-21

Mortality + MACE During DAPT for ACS

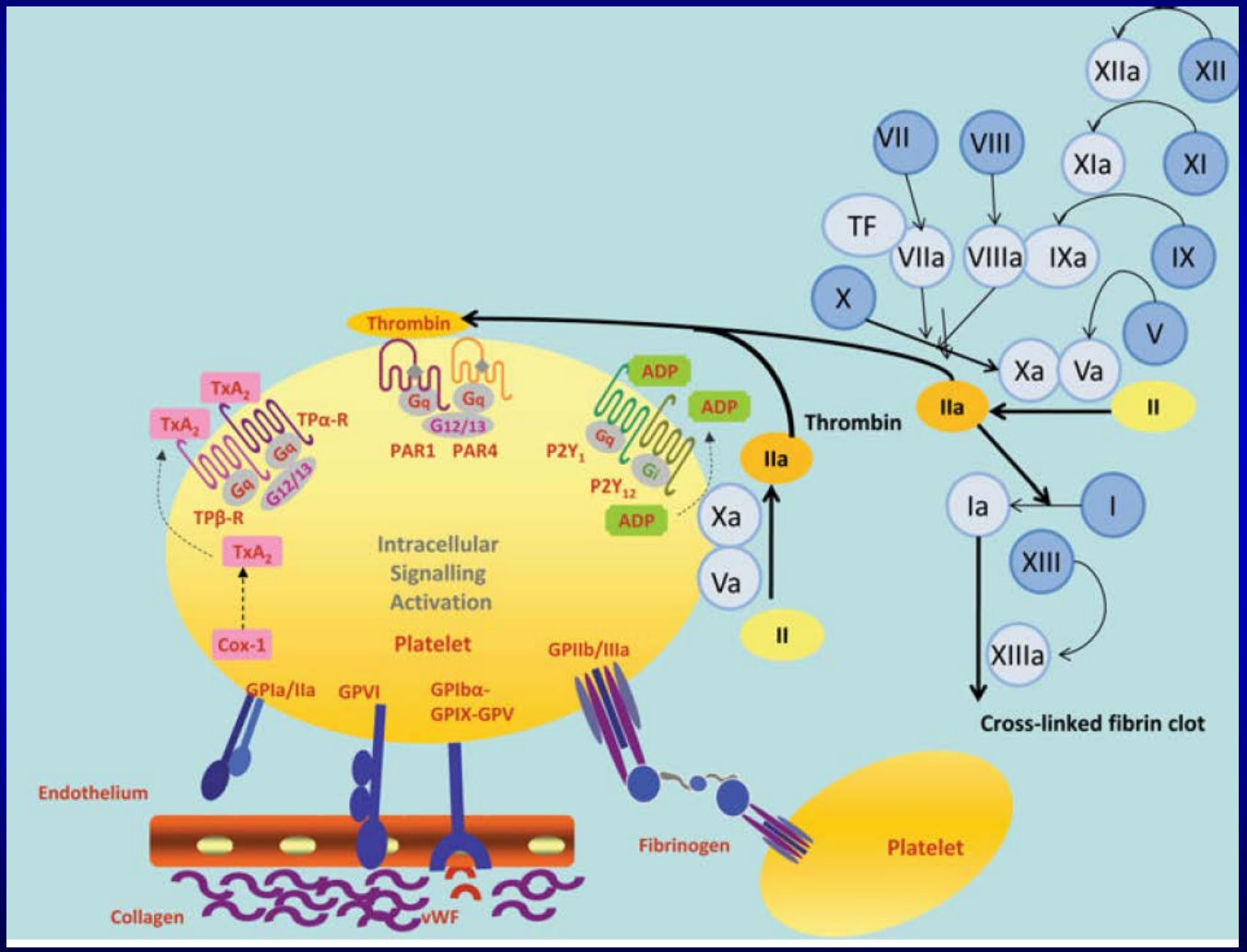


Modified from Yusuf S, et al. N Engl J Med 2001;345:494-502

Among subjects with a recent ACS, how do we recognise high risk patients ?

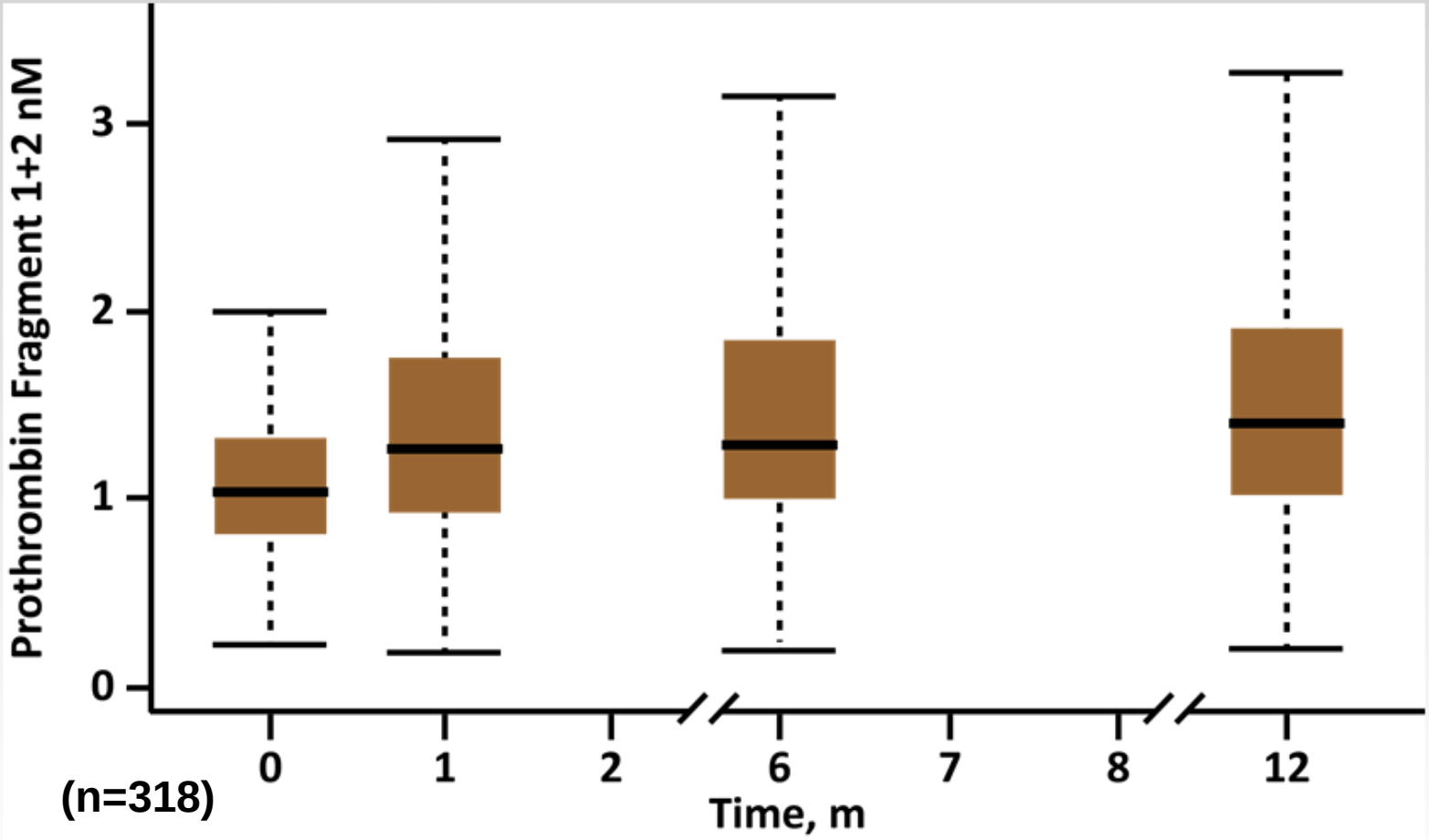
- High Risk Scores
- Diabetics
- PAD
- Multivessel, extensive CAD
- LM or proximal LAD stents
- CABG
- Patients with index event on APT
- Smokers
- Non revascularised (part nSTE ACS)

The Platelet Activation Pathways and the Coagulation Cascade



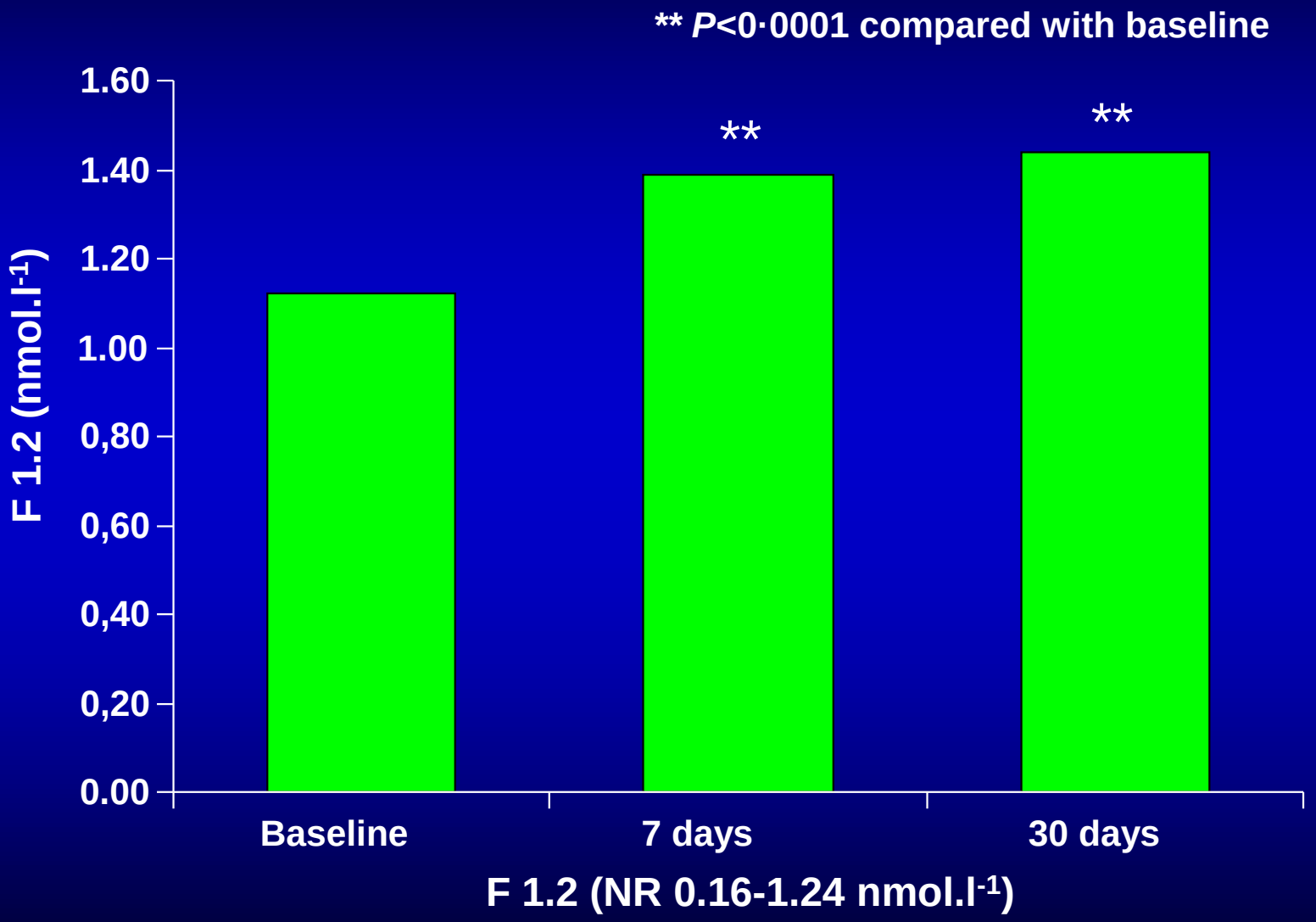
Angiolillo DJ and Ferreiro JL. Am J Cardiovasc Drugs 2013;13:233-50

Thrombin Generation Persists Long After ACS

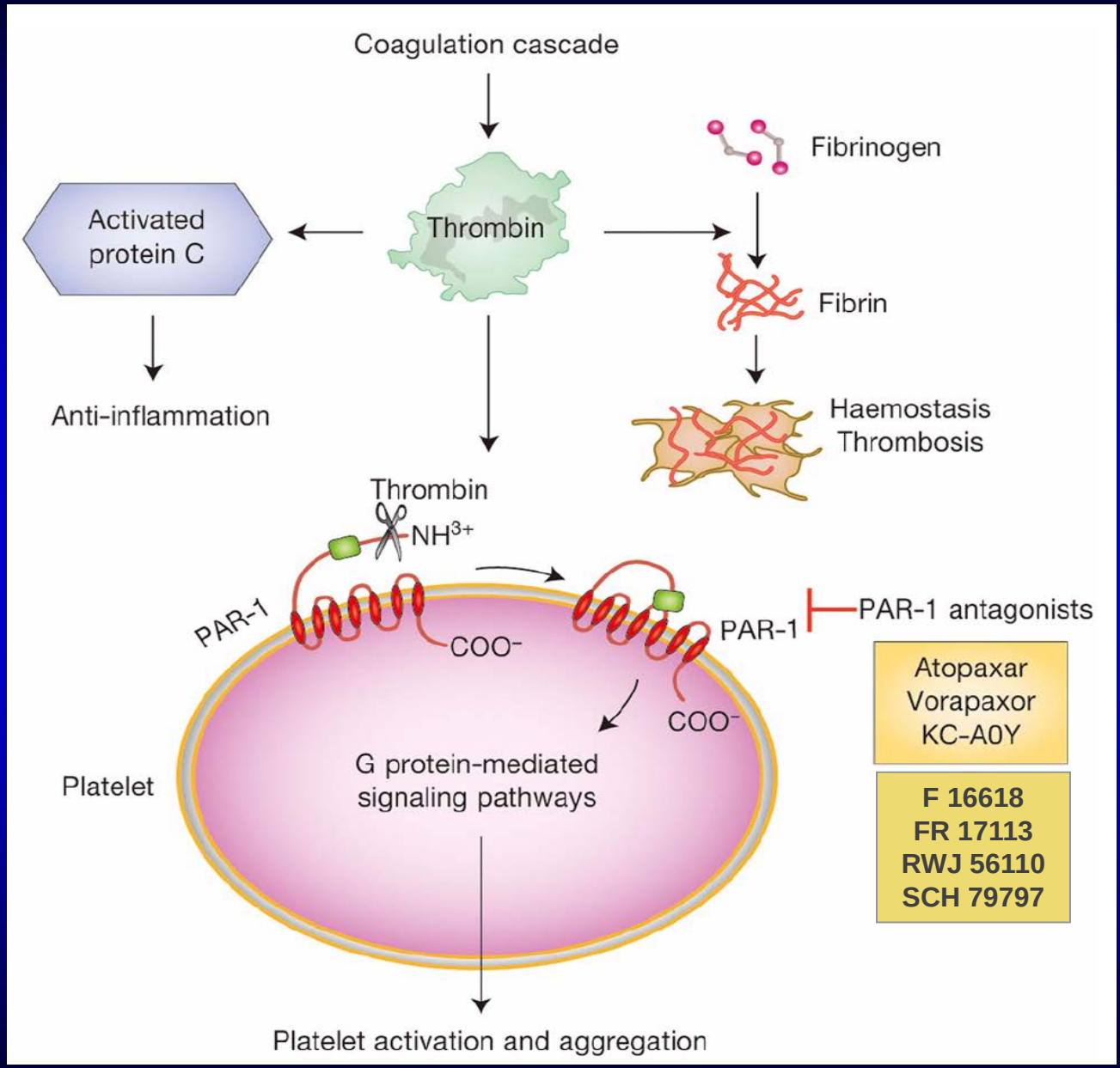


Ardissino et al. Blood 2003;102:2731-5

Thrombin Generation is not Prevented by DAPT



Eikelboom JW, et al. Eur Heart J, 2002;23:1771-1779



Modified from Lee S. Arch Pharm Res 2011:34;515-7

TRA-2P Trial Design

Morrow et al. N Engl J Med 2012
ClinicalTrials.gov NCT00526474

Prior MI, CVA, or PAD
N=26,449

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

Standard care including oral antiplt rx

RANDOMIZE 1:1 DOUBLE BLIND

Stratified by:
1) Qualifying Disease State
2) Use of thienopyridine

Vorapaxar 2.5 mg/d

Placebo

Median F/U
30 Months

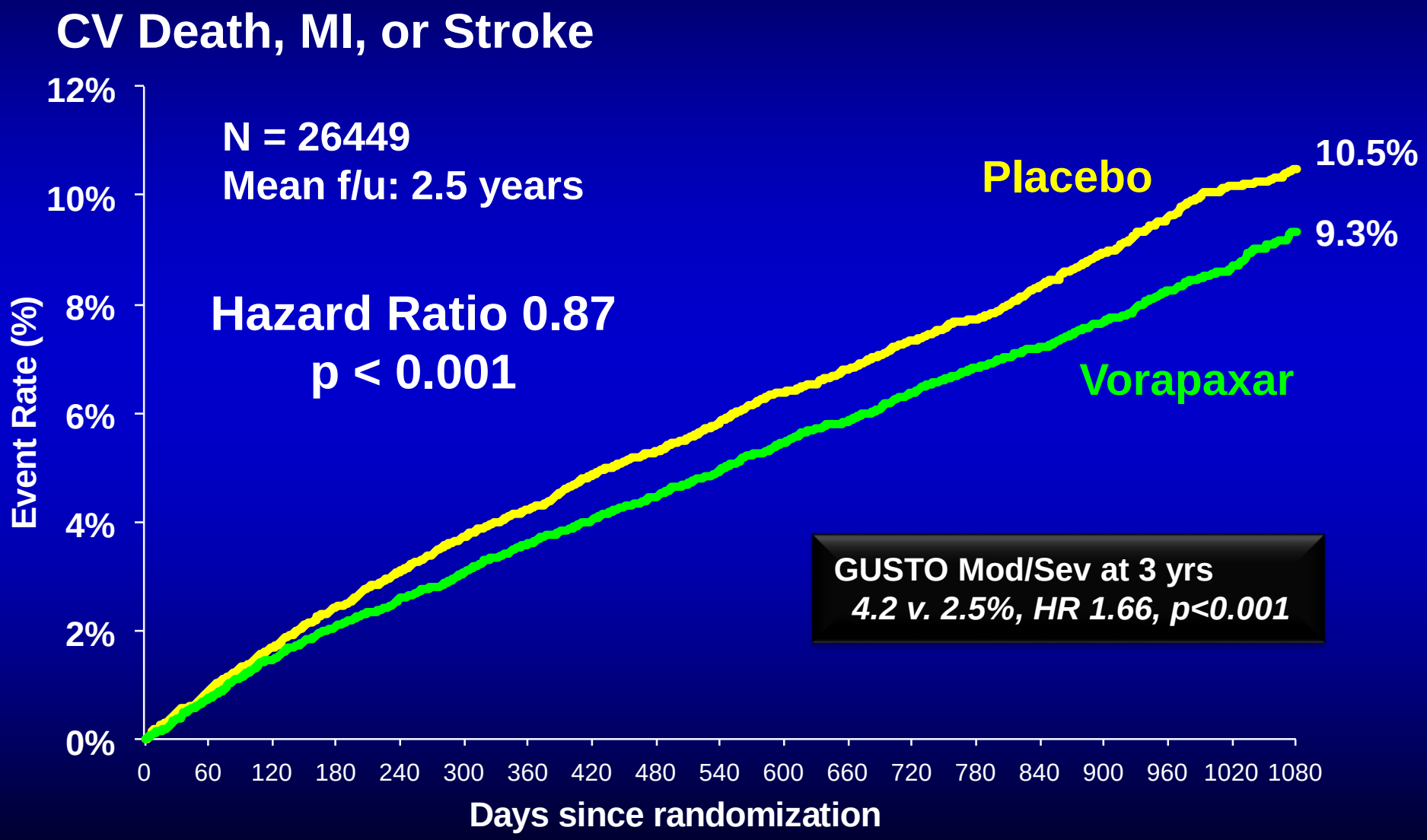
Follow up Visits
Day 30, Mo 4, Mo 8, Mo 12
Q6 months

Final Visit

Primary Efficacy Analysis:
1.CVD/MI/Stroke
2.CVD/MI/Stroke/Urgent Coronary Revasc

Principal Safety EP:
•GUSTO Mod/Sev bleeding

TRA-2P Primary Endpoint



Morrow DA, et al. N Engl J Med 2012;366:1404-13

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•GUSTO Mod/Sev bleeding

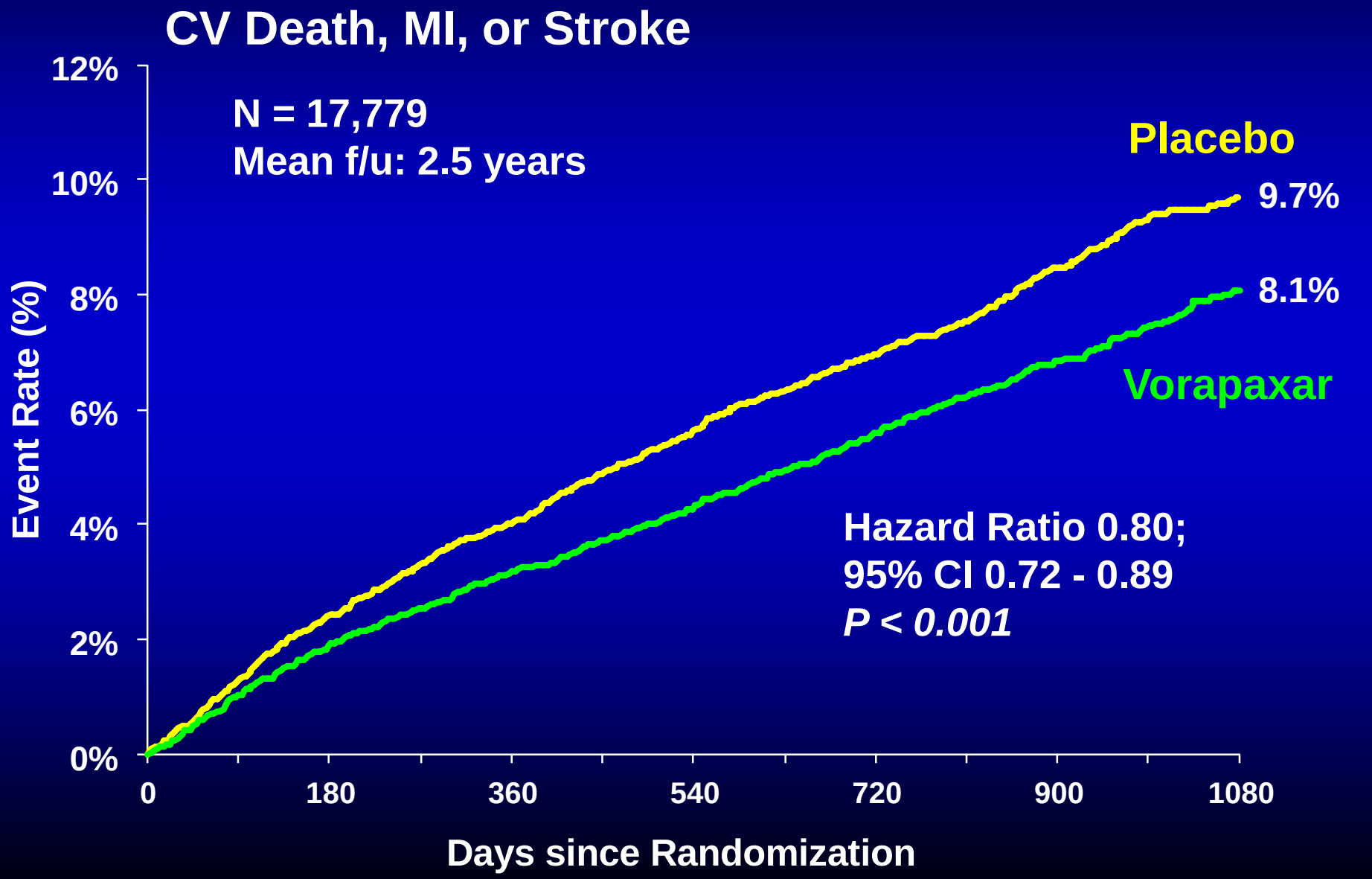
Baseline Characteristics

Prior MI Cohort

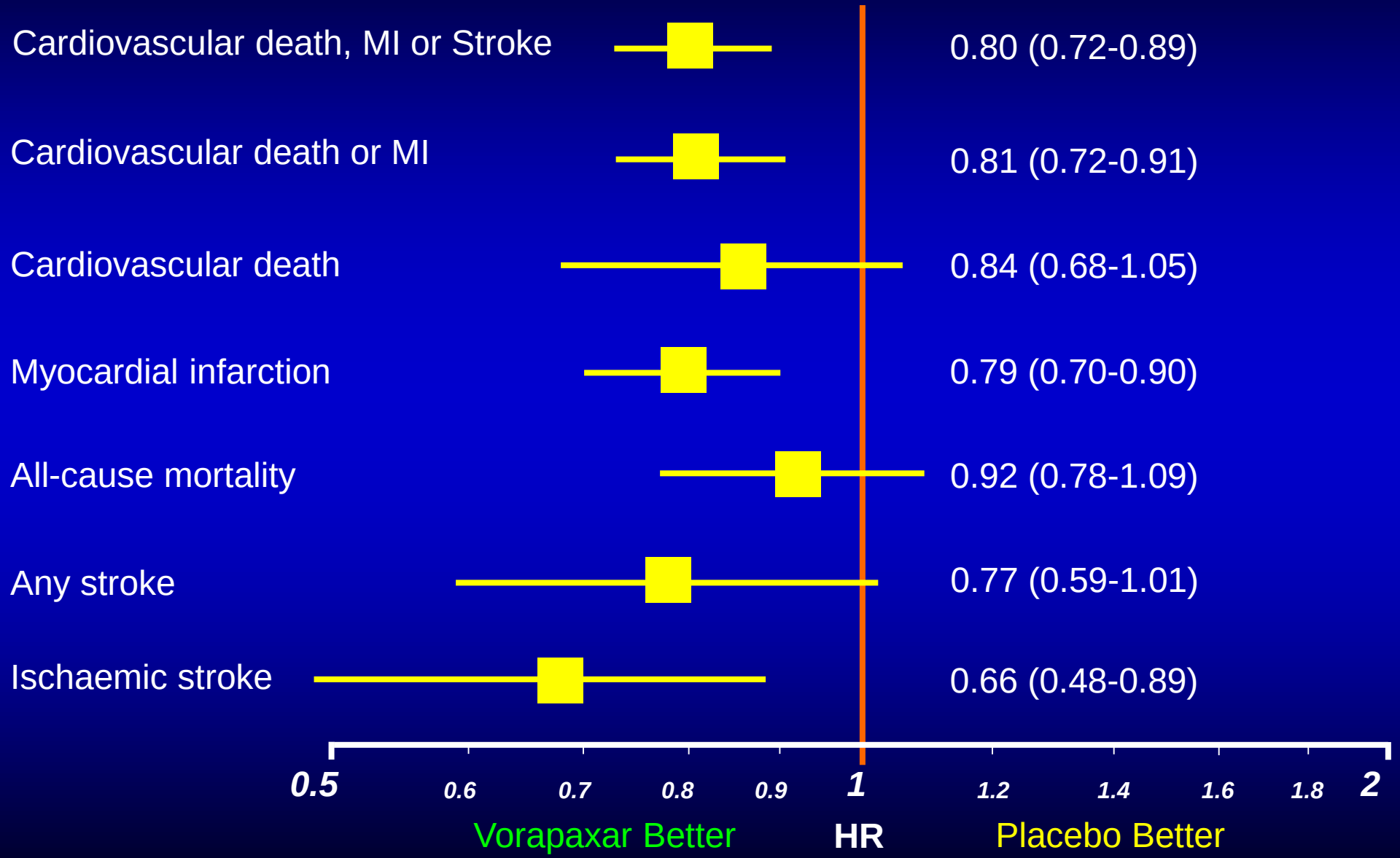
	Prior MI Cohort N=17,779
Demographics	
Age, median (IQR)	59 (51-66)
Age >=75 years (%)	8
Female (%)	21
Clinical Characteristics	
Diabetes mellitus (%)	22
Hypertension (%)	63
Hyperlipidemia (%)	85
Current smoker (%)	20
Prior coronary revasc (%)	86
Any cerebrovascular event (%)	5
Baseline Medical Therapy	
Aspirin (%)	98
Thienopyridine (%)	78
Lipid-lowering therapy (%)	96

No differences between treatment groups

Primary Efficacy Evaluation



Efficacy Endpoints at 3 Years in the MI Population



From Scirica BM, et al. Lancet 2012;380:1317-24

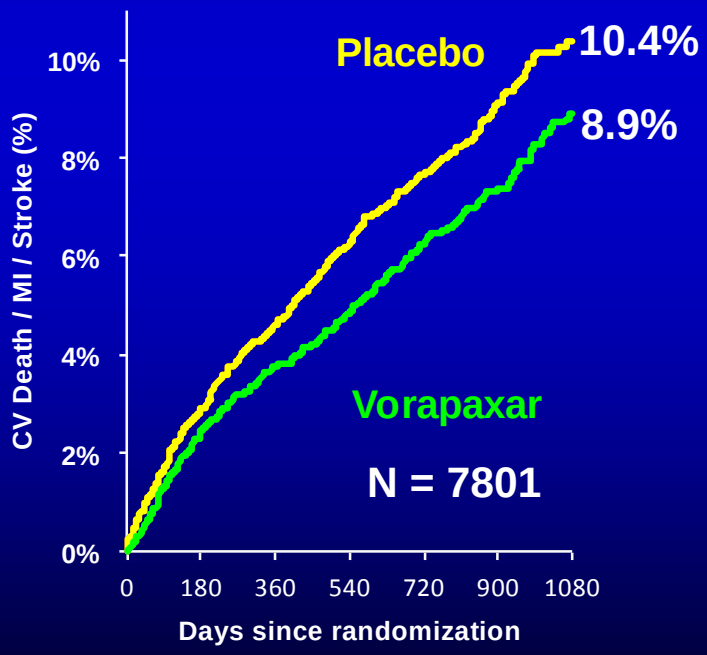
Efficacy by Time from Qual MI

Prior MI Cohort

Time from qualifying MI to Randomizations

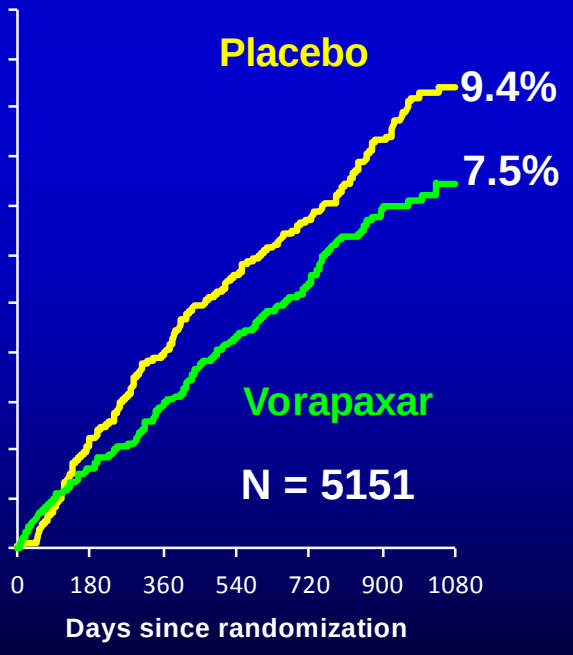
< 3 months

HR 0.82
p = 0.011



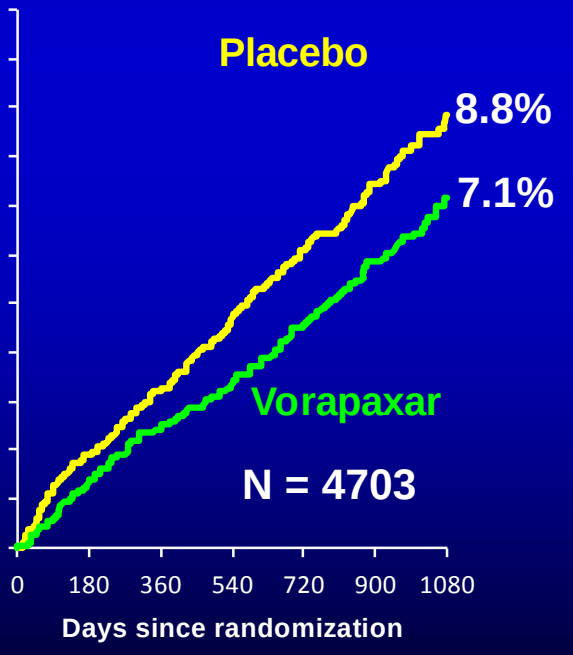
3 to 6 months

HR 0.79
p = 0.023



>6 months

HR 0.78
p = 0.026

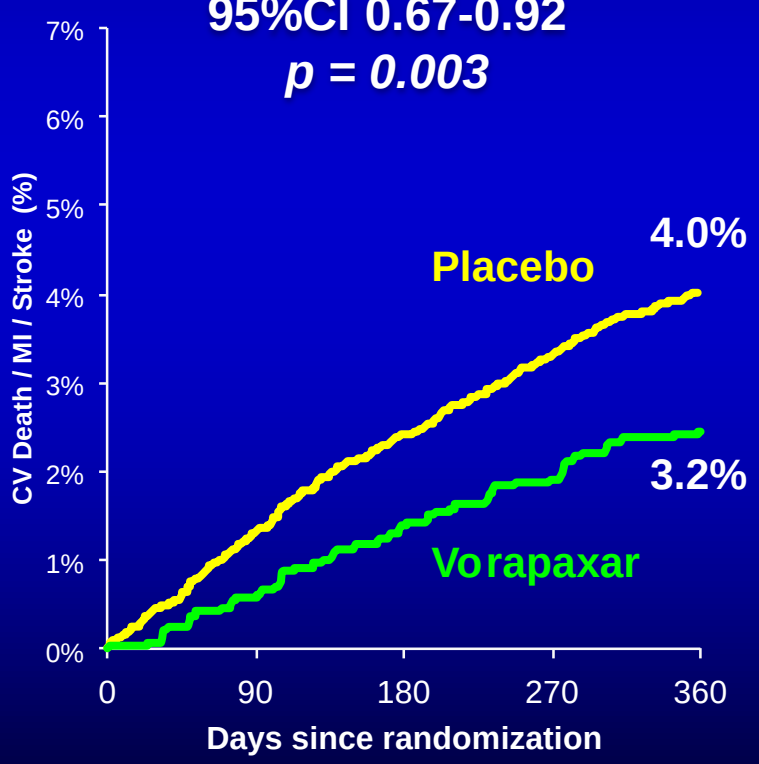


Efficacy Early and Late

Prior MI Cohort

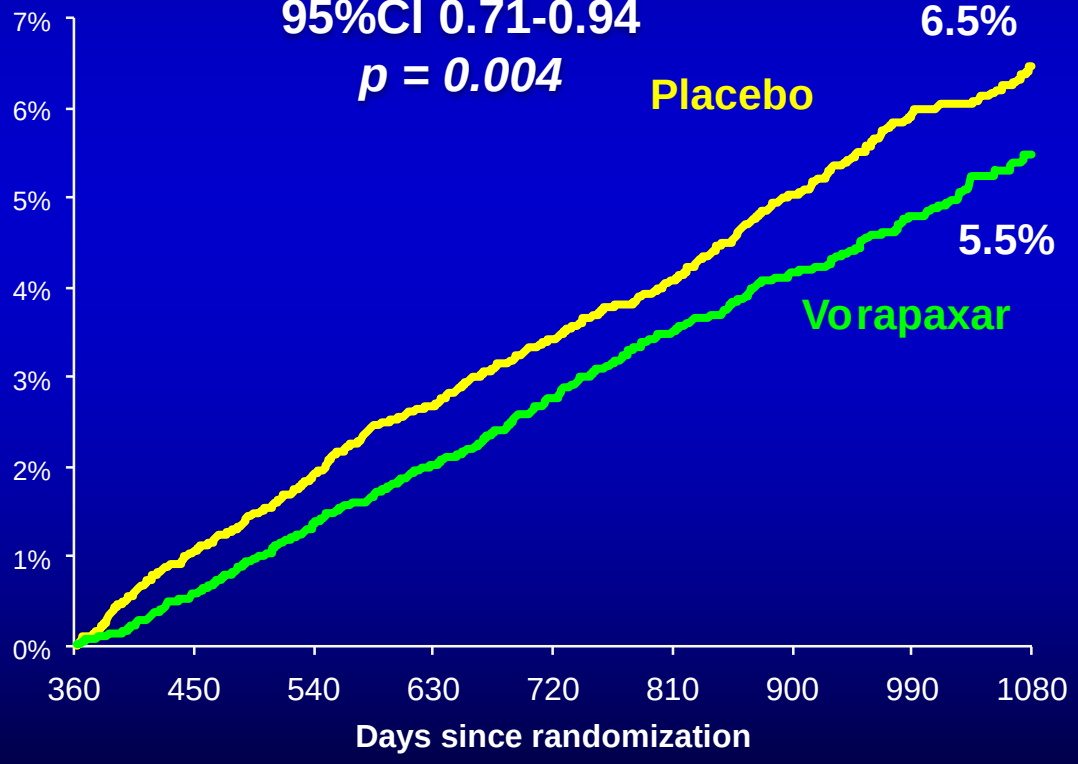
Days 0 to 360

HR 0.79
95%CI 0.67-0.92
p = 0.003



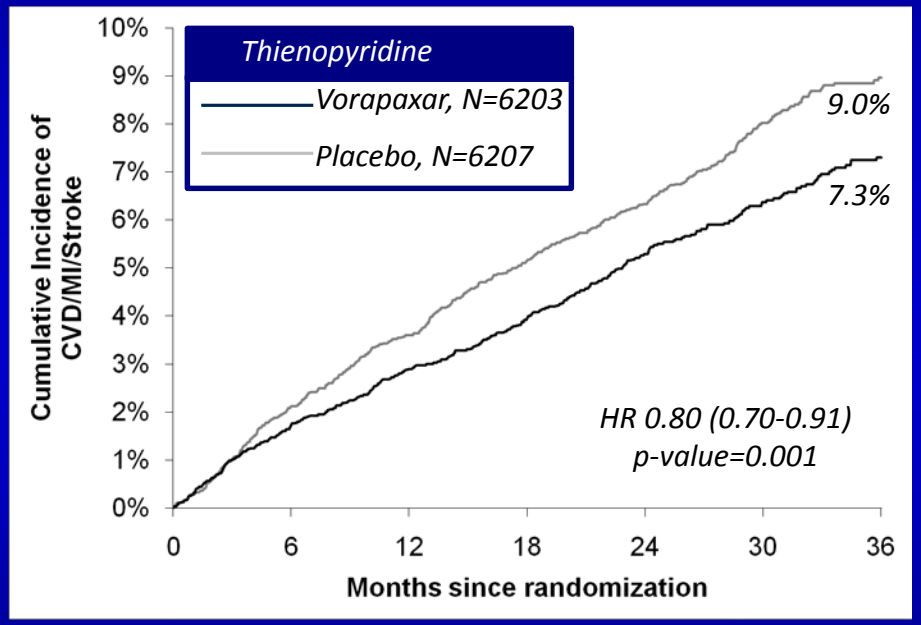
Day 360 to 1080

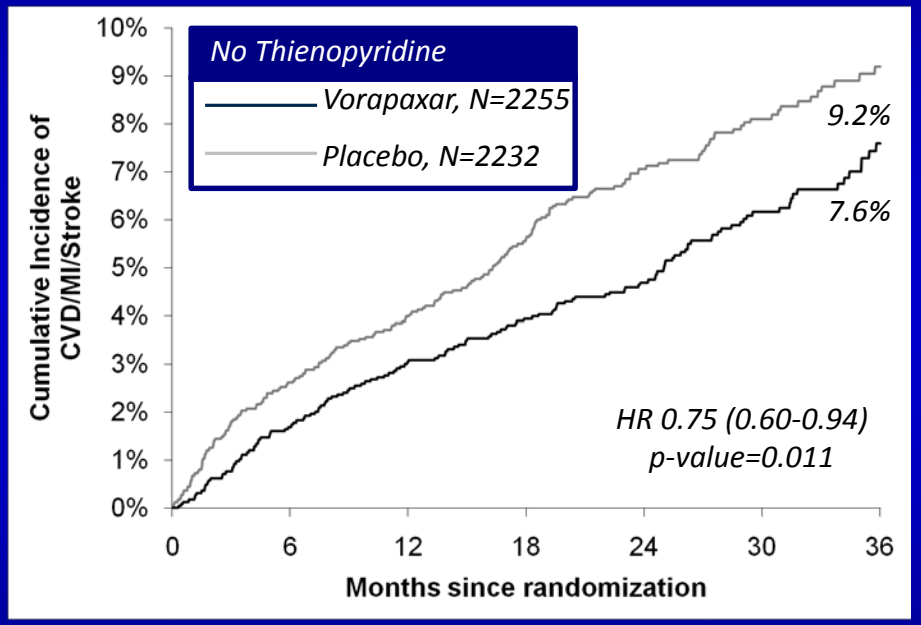
HR 0.82
95%CI 0.71-0.94
p = 0.004



Primary Efficacy By Planned TP Use

MI Without History of TIA or Stroke





p-interaction = 0.67

- **Significant reduction in primary efficacy endpoint (~20-25%)**
- **No modification by thienopyridine treatment**

Bohula EA et al. Circulation 2015

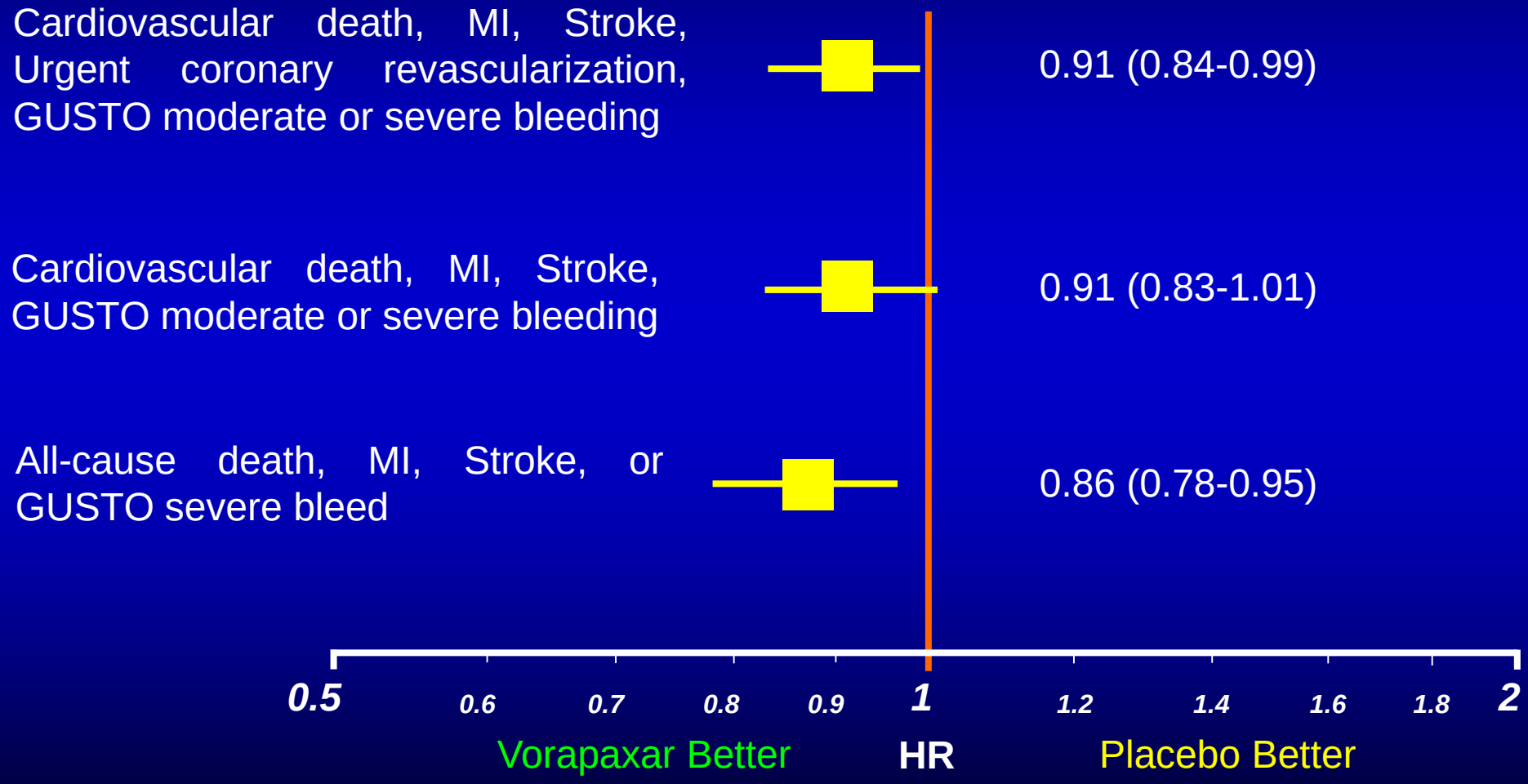
doi: 10.1161/CIRCULATIONAHA.114.015042

Safety Endpoints at 3 Years

	Vorapaxar group	Placebo group	Hazard ratio (95% CI)	p value
Safety endpoints*				
GUSTO moderate or severe bleeding	241 (3·4%)	151 (2·1%)	1·61 (1·31–1·97)	<0·0001
TIMI clinically significant bleeding	1159 (15·1%)	801 (10·4%)	1·49 (1·36–1·63)	<0·0001
GUSTO severe bleeding	86 (1·2%)	71 (1·0%)	1·22 (0·89–1·67)	0·22
GUSTO moderate bleeding	161 (2·2%)	85 (1·2%)	1·91 (1·47–2·48)	<0·0001
GUSTO mild bleeding	2047 (25·4%)	1432 (18.1%)	1.51 (1·41–1·62)	<0·0001
TIMI non-coronary artery bypass graft, major bleeding	156 (2·2%)	121 (1·6%)	1·29 (1·02–1·64)	0·033
TIMI minor bleeding	108 (1·5%)	44 (0·6%)	2·47 (1·74–3·51)	<0·0001
TIMI non-coronary artery bypass graft, major or minor bleeding	258 (3·6%)	162 (2·2%)	1·60 (1·32–1·95)	<0·0001
Fatal bleeding	14 (0·2%)	9 (0·1%)	1·56 (0·67–3·60)	0·30
Intracranial haemorrhage	43 (0·6%)	28 (0·4%)	1·54 (0·96–2·48)	0·076

Scirica BM, et al. Lancet 2012;380:1317-24

Net Clinical Outcome in All MI Patients



From Scirica BM, et al. Lancet 2012;380:1317-24

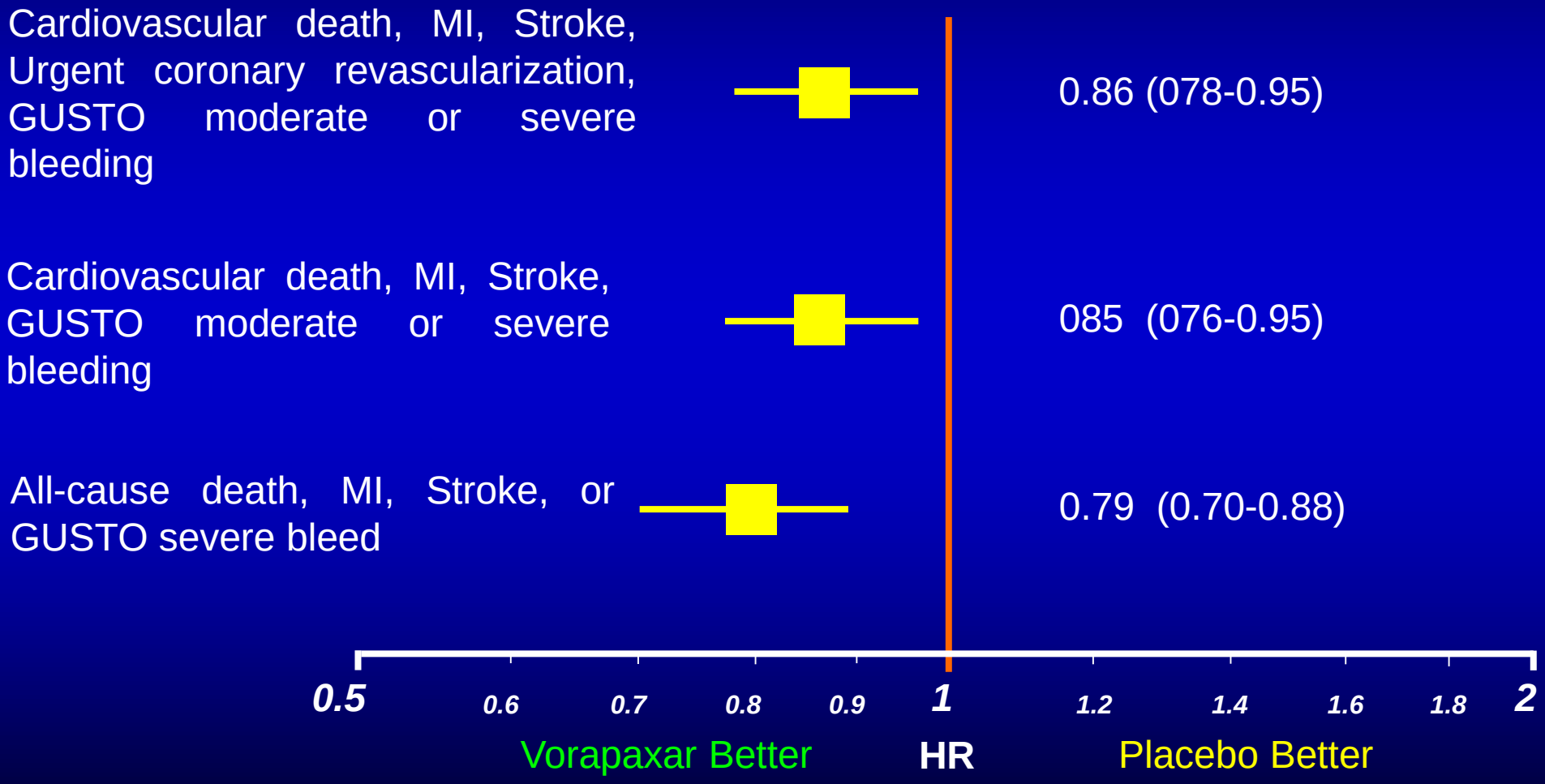
Can we further improve the Net Clinical Benefit ?

Net Clinical Benefit of Vorapaxar in TRA-2P: Analysis of the Low Bleeding Risk Cohort

- Based on prior studies[1], we applied previously established criteria to identify patients with a low risk of bleeding who have potential for improved net clinical outcomes with potent antiplatelet Rx:
  - No hx of stroke/TIA
  - Weight ≥60 kg
  - Age <75 yr
  - -14,909 patients (84% of prior MI cohort)

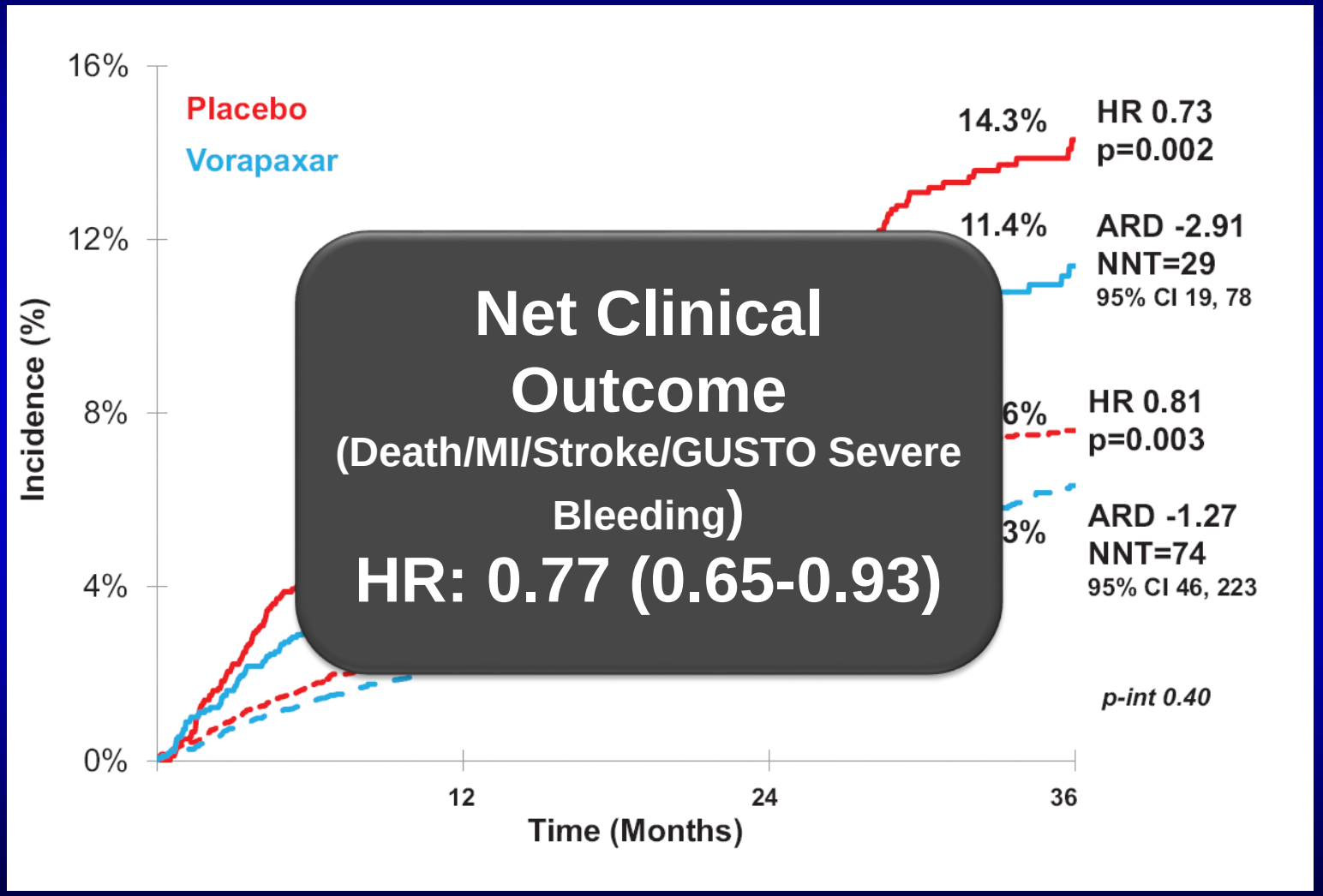
[1] *Wiviott SD, et al. NEJM 2007*

Net Clinical Outcome in Low Bleeding Risk Cohort



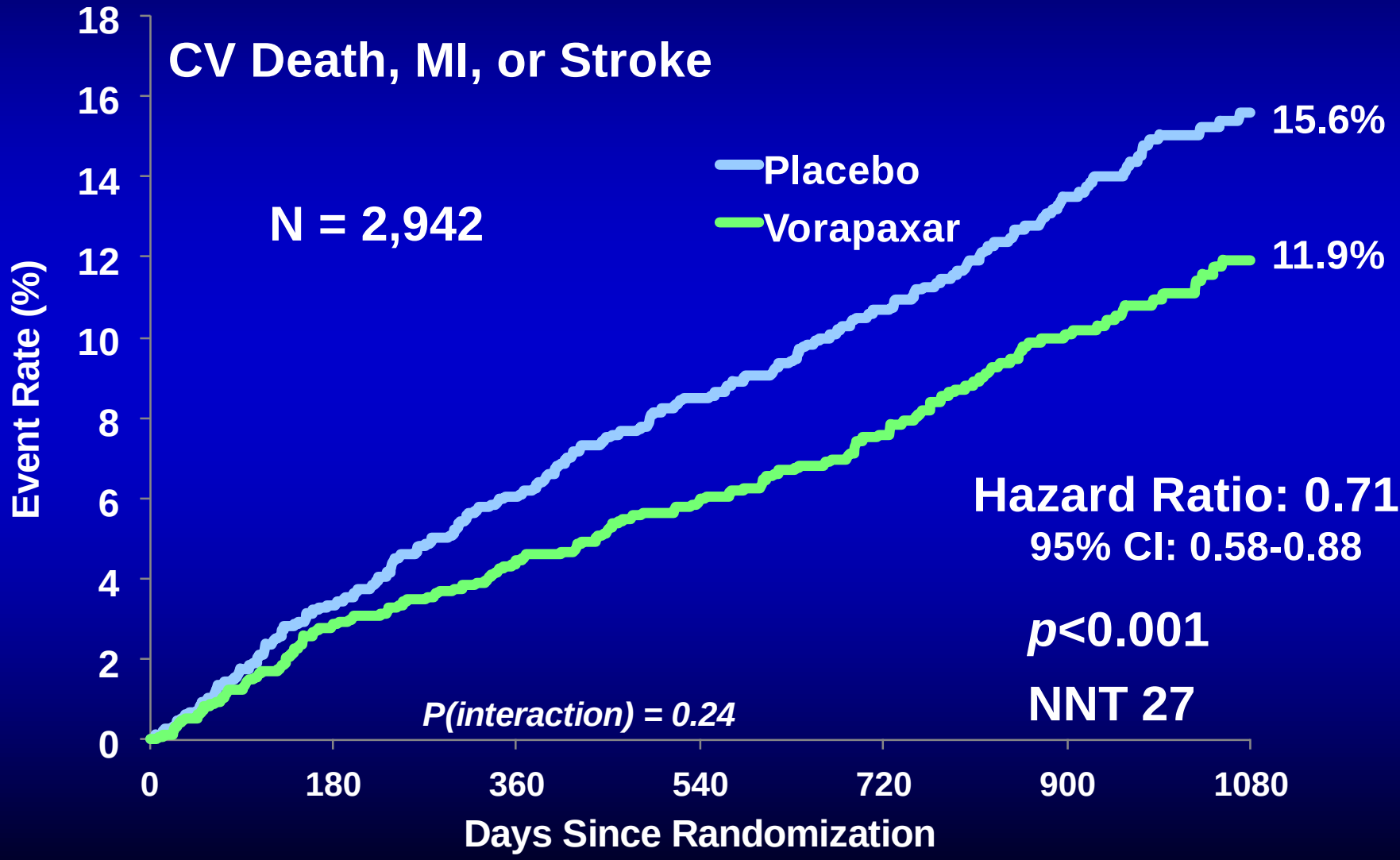
Modified from Supplementary Appendix. Scirica BM, et al. Lancet 2012;380:1317-24

Efficacy of Vorapaxar in Patients w/ Prior MI Based on Diabetes History



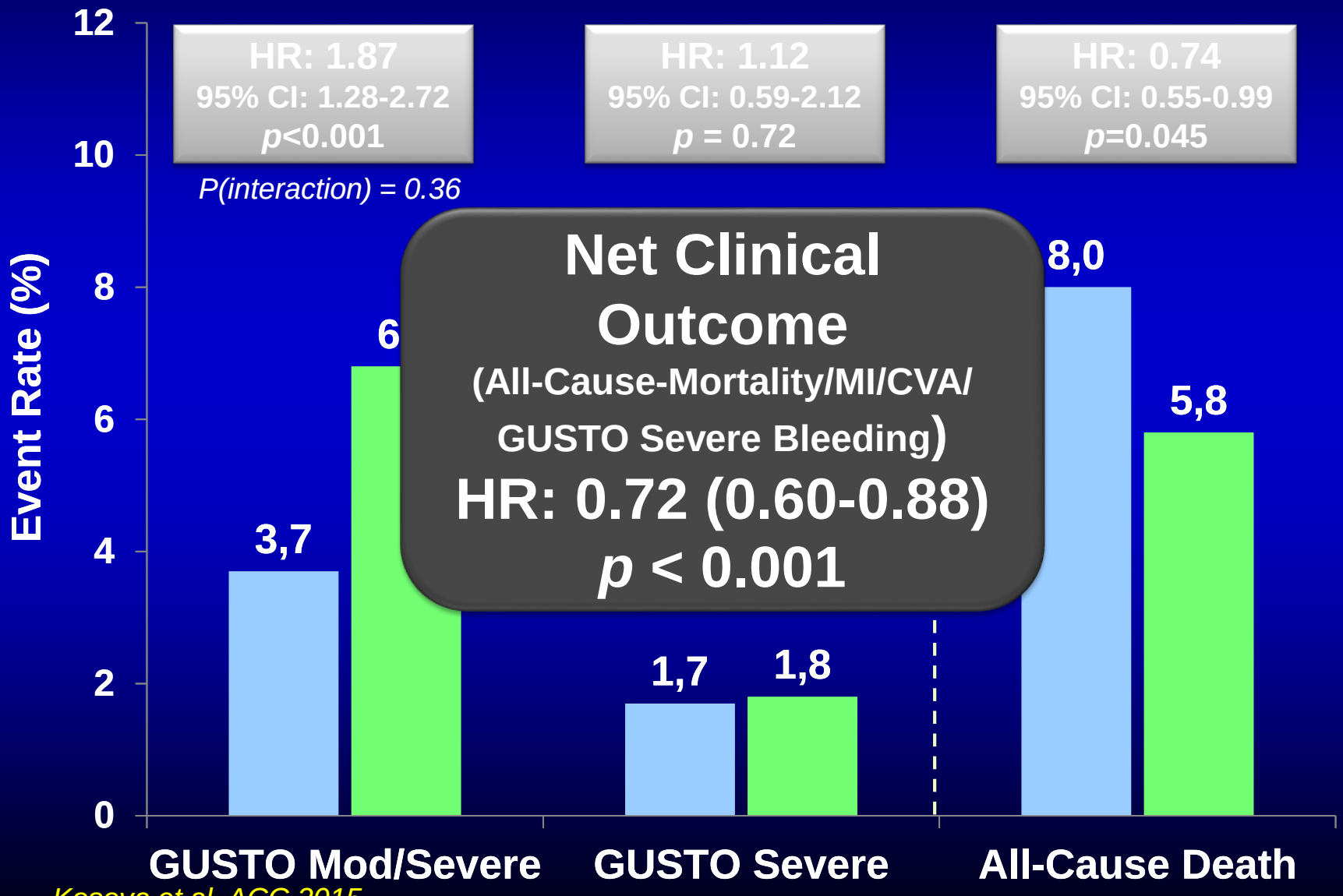
Cavender et al. Circulation 2015

Efficacy of Vorapaxar in Patients with Prior CABG



Kosova et al. ACC 2015

Safety Endpoints in the Prior CABG Population



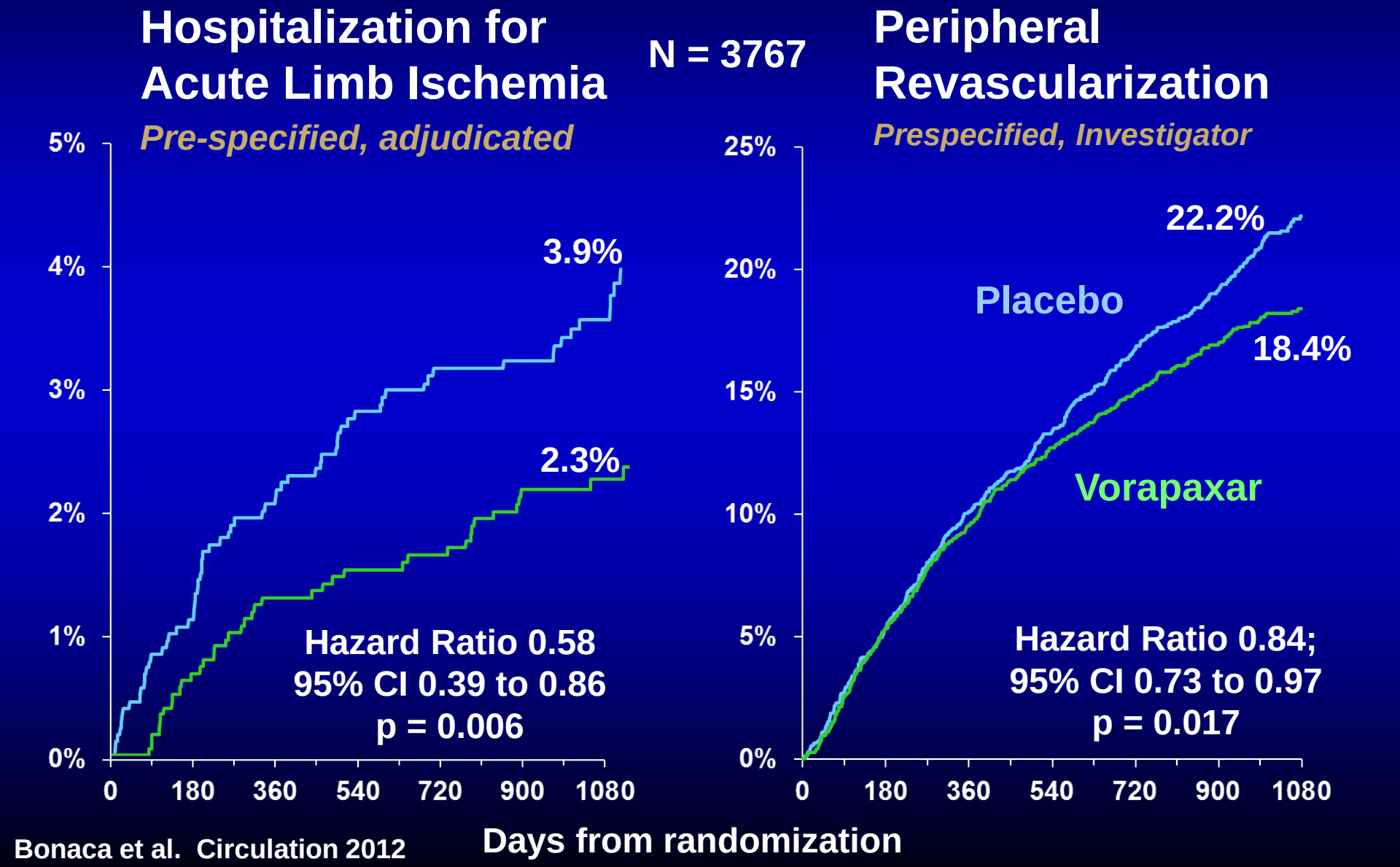
Kosova et al. ACC 2015

Take Home Messages

- Thrombin plays a pivotal role in platelet aggregation
- The addition of the PAR-1 Receptors Antagonist Vorapaxar reduces MACE in patients with a previous MI at the expense of an increase in bleeding
- The net clinical benefit can be improved by careful patient selection.

- **Discussion slides**

Vorapaxar and Limb Vascular Efficacy

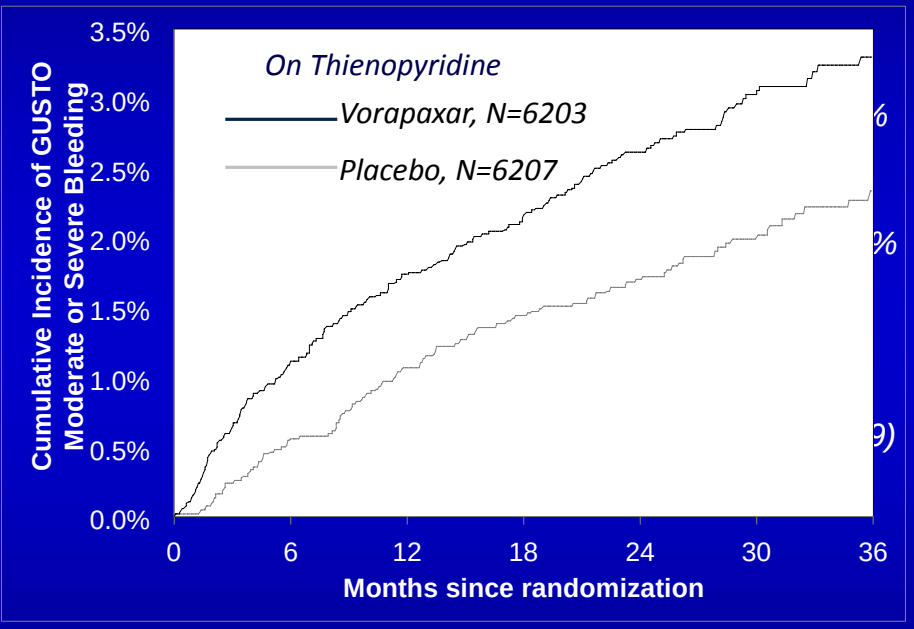


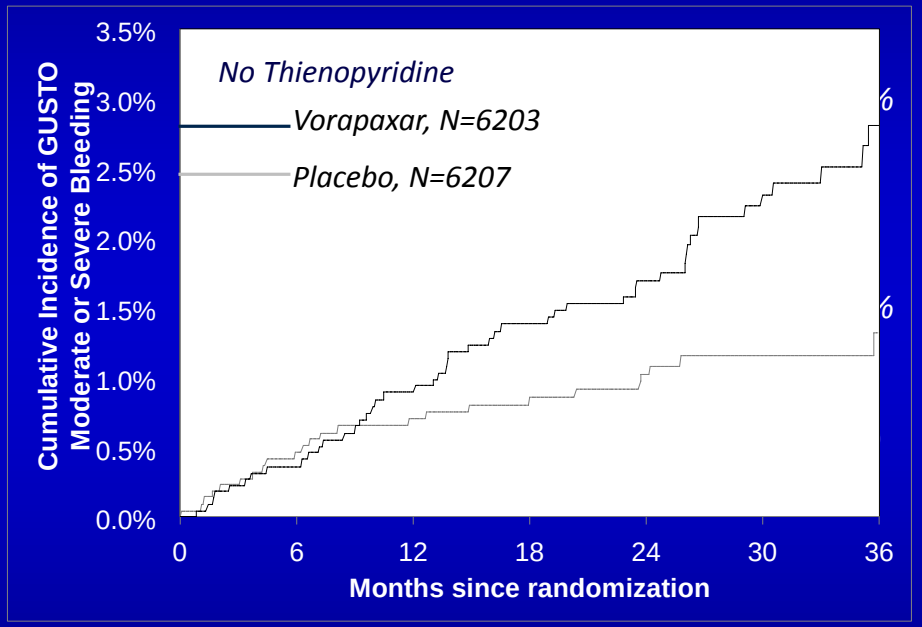
Bonaca et al. Circulation 2012

Primary Safety By Planned TP Use

MI Without History of TIA or Stroke

Overall HR ~1.6





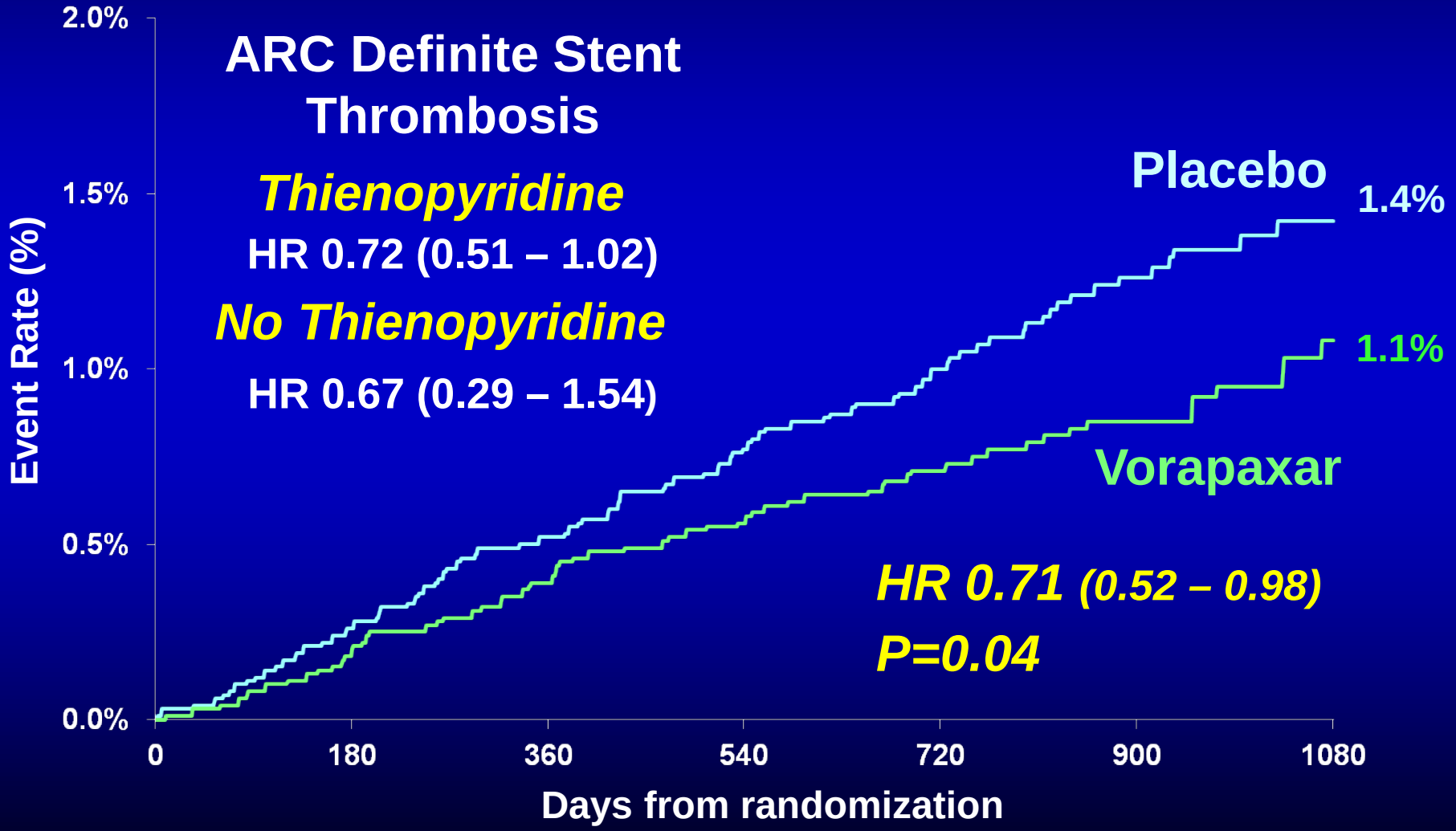
p-interaction = 0.37

- Significantly more GUSTO moderate or severe bleeding events
- No modification by thienopyridine treatment

Bohula EA et al. Circulation 2015

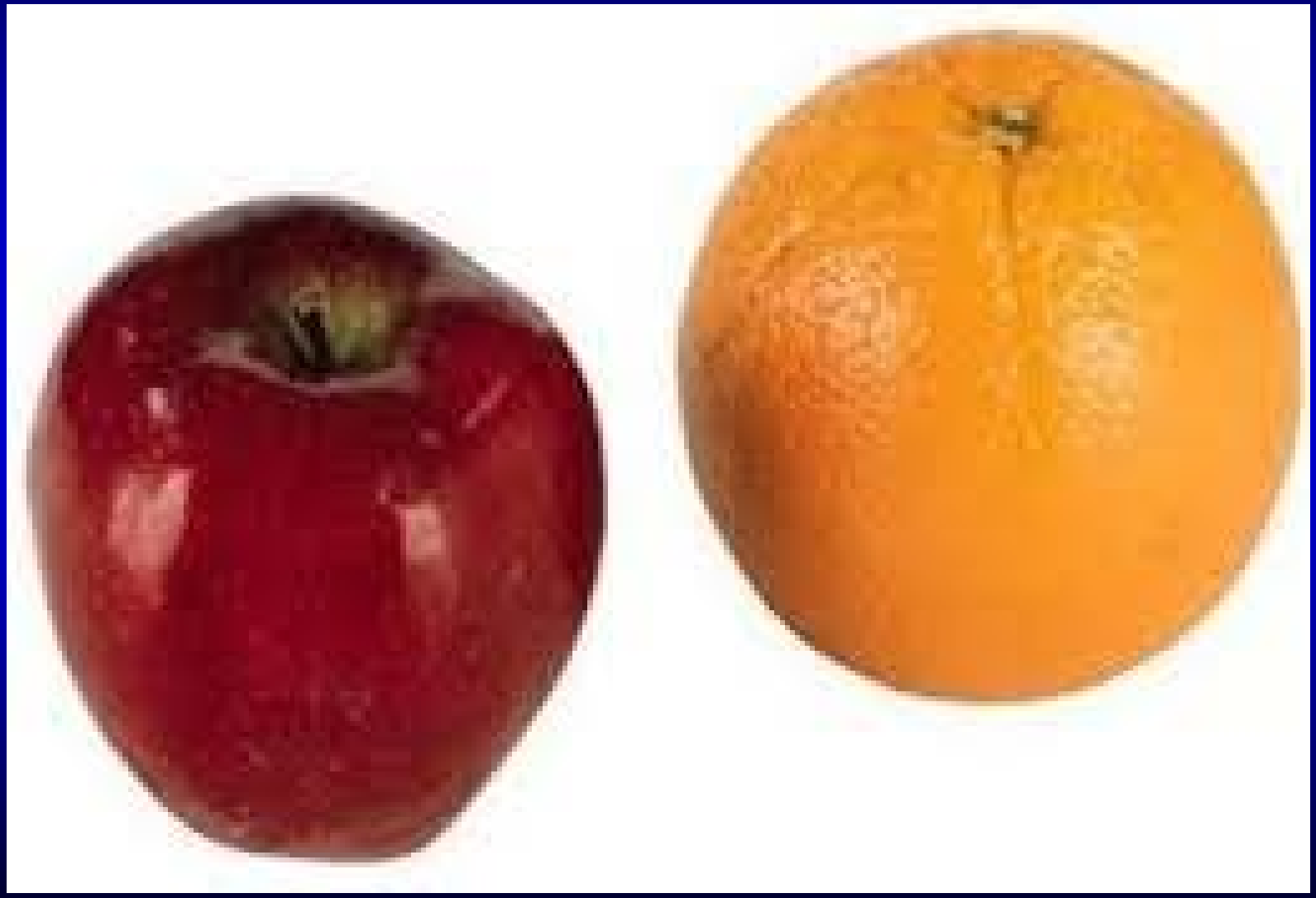
doi: 10.1161/CIRCULATIONAHA.114.015042

Stent Thrombosis by Randomized Treatment

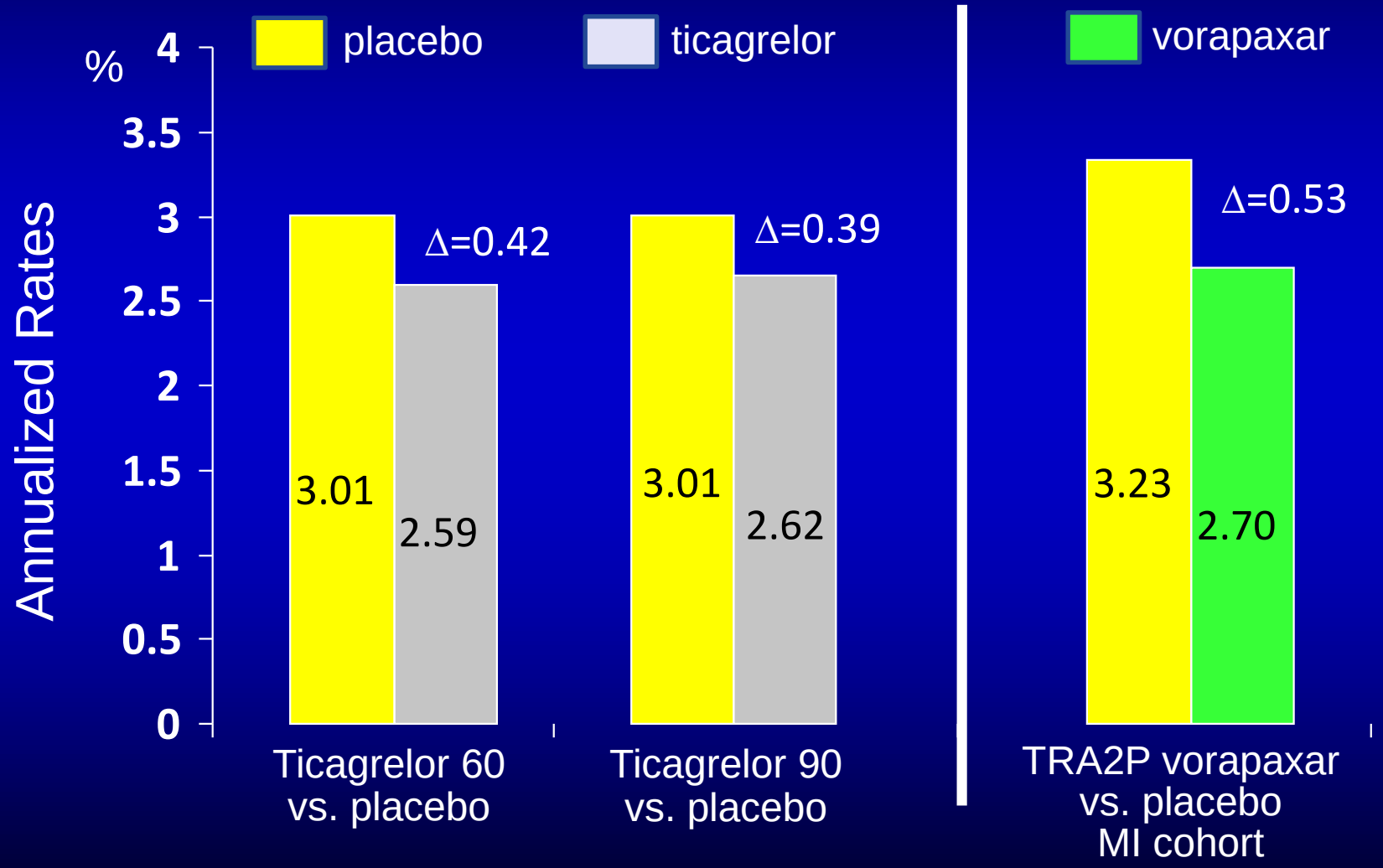


Bonaca et al. JACC 2014

Be aware: we are now starting an inappropriate activity



Aggressive Treatment and CV Death/MI/Stroke

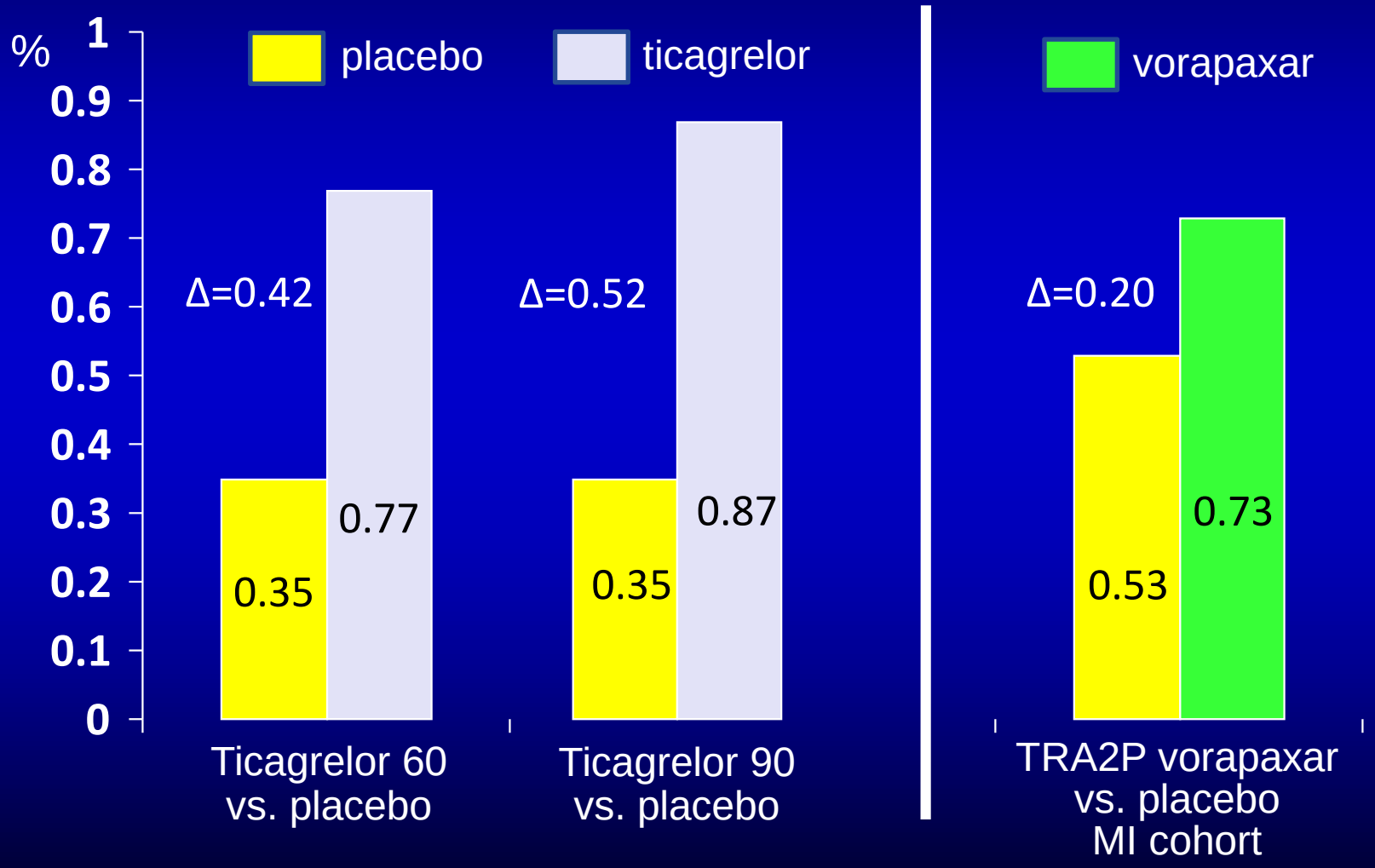


Bonaca et al. N Engl J Med 2015

Scirica et al. Lancet 2013

Aggressive Treatment and Bleeding

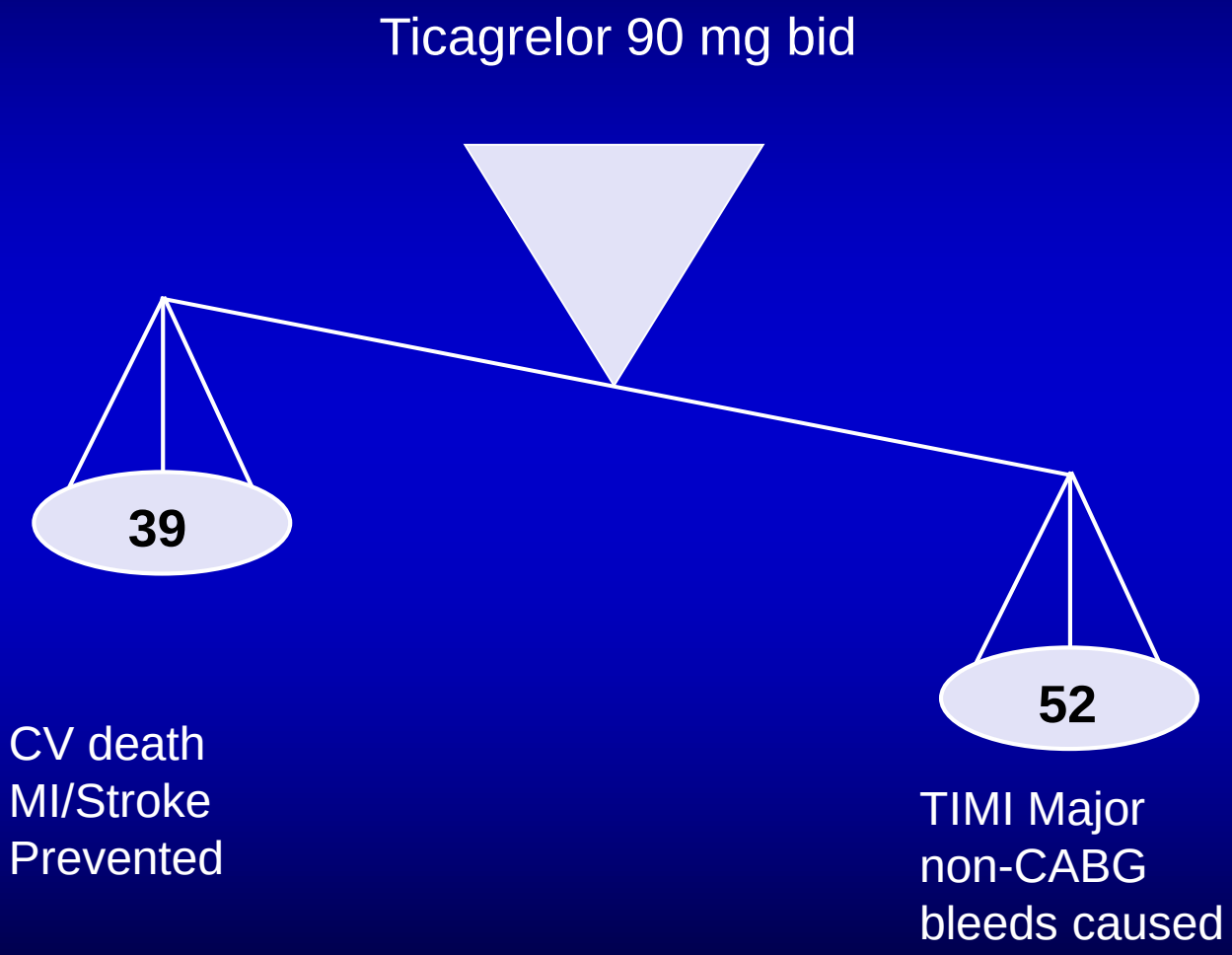
Annualized Rates of TIMI non-CABG major bleeds



Bonaca et al. N Engl J Med 2015

Scirica et al. Lancet 2013

Effect of Treatment for 10000 Pt. Years vs Placebo



Bonaca et al. N Engl J Med 2015

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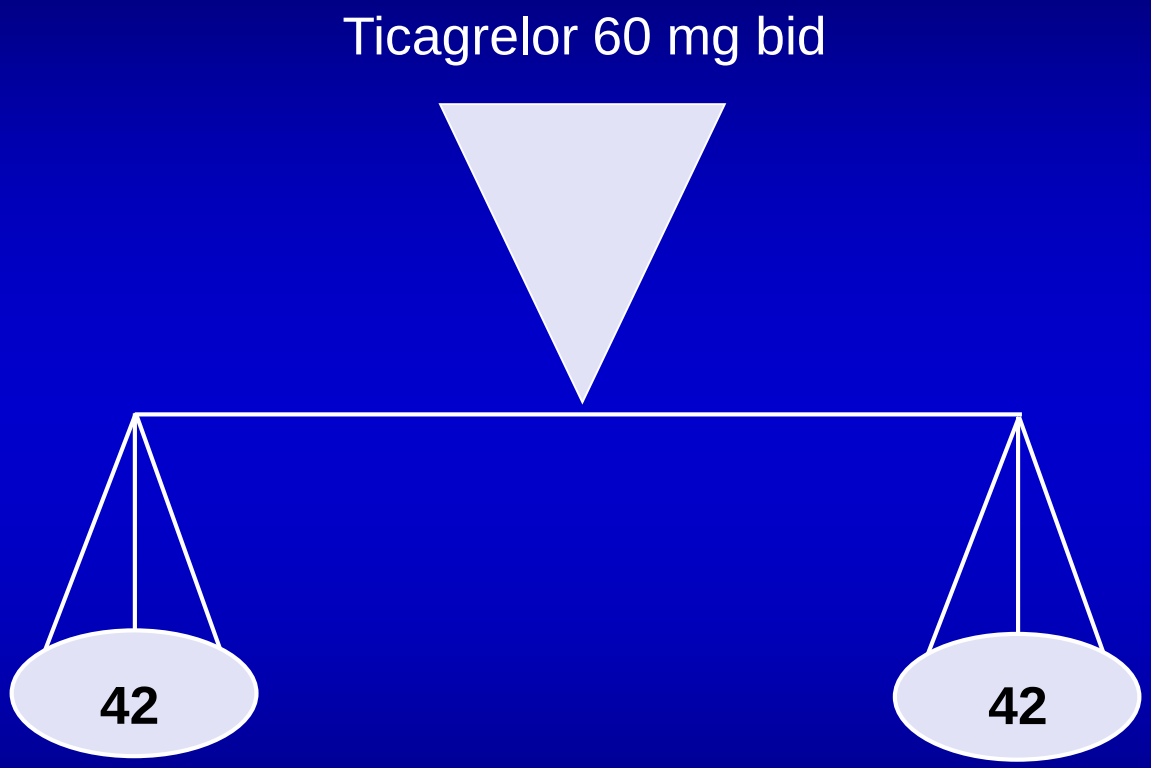

Bonaca et al. N Engl J Med 2015

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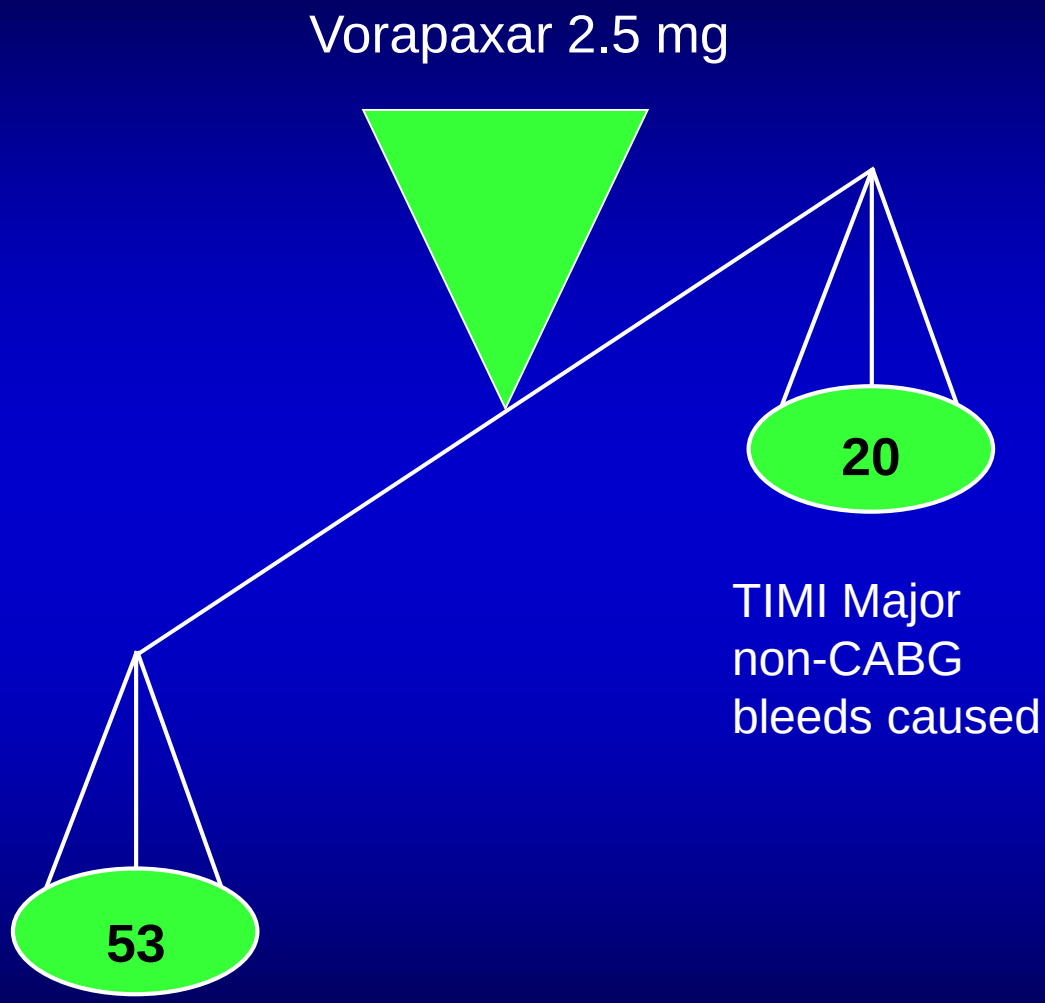
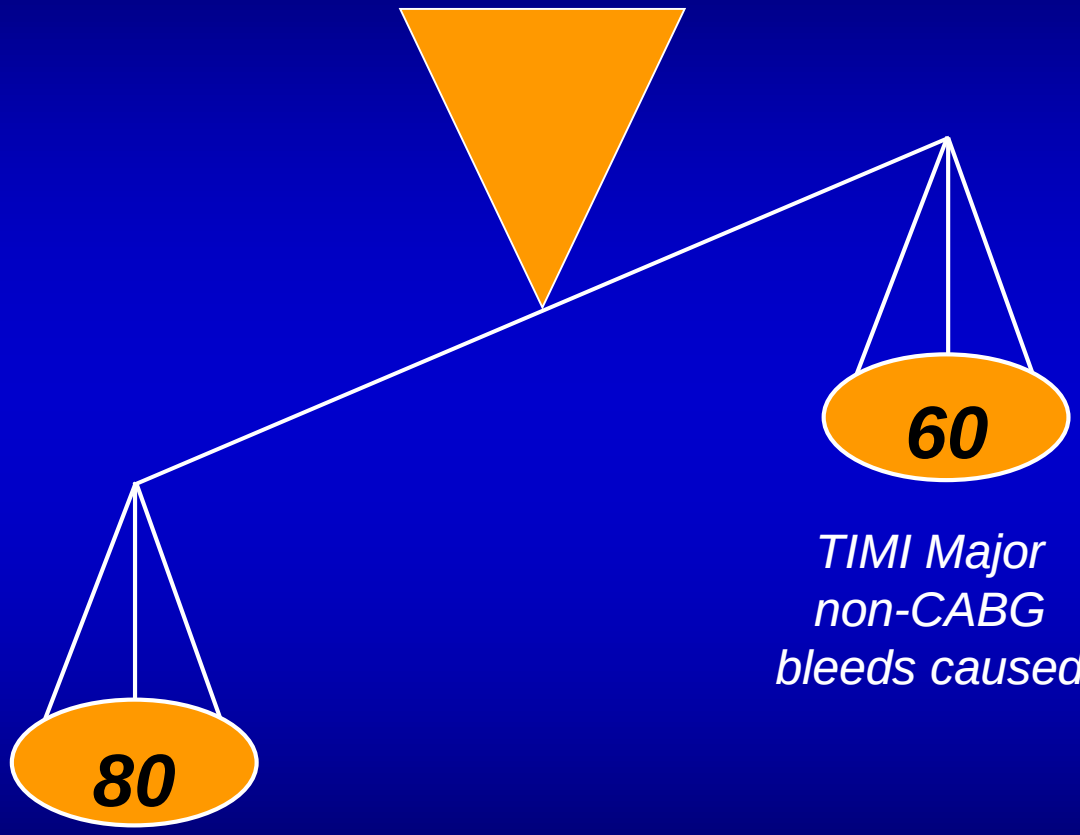


Scirica et al. Lancet 2013

Effect of Treatment for 10000 Pt. Years vs Placebo

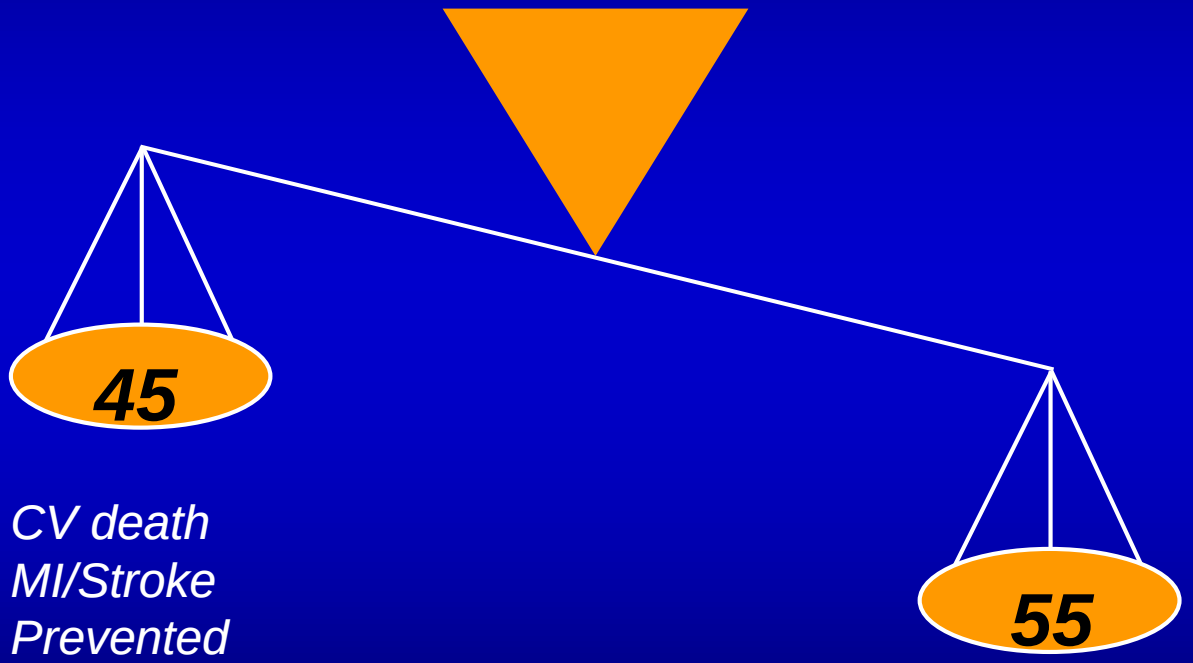
Rivaroxaban 2.5 mg bid (overall pop.)



Mega et al. NEJM 2012

Effect of Treatment for 10000 Pt. Years vs Placebo

Rivaroxaban 2.5 mg bid (STEMI pop.)



CV death
MI/Stroke
Prevented

TIMI Major
non-CABG
bleeds caused

Mega et al. NEJM 2012

DAPT-MI; TRA 2°P-TIMI50; PEGASUS
Clinical characteristics in the three trials

	DAPT-MI n=3.371	PEGASUS n=21.162	TRA 2°P-TIMI50 n=17.779
Age (median)	58	65	59
Female	22%	24%	21%
Weight (Kg)	90	82	N.A.
Diabetes	21%	32%	22%
Hypertension	58%	77%	62%
STEMI	47%	53%	52%
PAD	3%	5%	9%
CKD	3%	23%	11%
Prior PCI	100%	83%	83%
Multivessel CAD	NA	59%	NA
PriorStroke/TIA	2%	Excluded	5%
F-up duration (months)	18	33 (median)	30 (median)

PEGASUS and TRA2P Results Comparison

Item	TRA2°P (PLP)	PEGASUS T60 arm
Population	Hx stroke excluded MI 2 wks-12mo prior	Hx stroke excluded MI 1-3 yrs prior
% Female / Smoker	20 / 20	24 / 17
% Diabetic / PAD	21 / 5.0	32 / 5.4
Age (yr)	59±10	65±8
Background Rx	ASA ± clopidogrel	ASA
3yr KM% MACE	7.4 vs. 9.0 (HR .78, p<.001)	7.8 vs. 9.0 (HR .84, p=.004)
3yr KM% CV Death	1.9 vs. 2.2 (HR .82, ns)	2.9 vs. 3.4 (HR .83, ns)
3yr KM% All Death	3.4 vs. 3.7 (HR .91, ns)	4.7 vs. 5.2 (HR .89, ns)
3yr KM% TIMI maj	2.2 vs. 1.8 (HR 1.2, ns)	2.3 vs. 1.1 (HR 2.3, p<.001)
Gout (%)	1.4 vs. 1.2 (HR N/C)	2.0 vs. 1.5 (HR 1.5, p=.01)
Dyspnea (%)	4.1 vs. 4.3 (HR N/C)	15.8 vs. 6.4 (HR 2.7, p<.001)
…leading to D/C	N=8 vs. N=6	297 (4.3%) vs 51 (0.7%) p<.001

N/C = not calculated

Prolonged Antiplatelet Therapy and Bleeding