NUEVOS ANTIAGREGANTES EN SCA

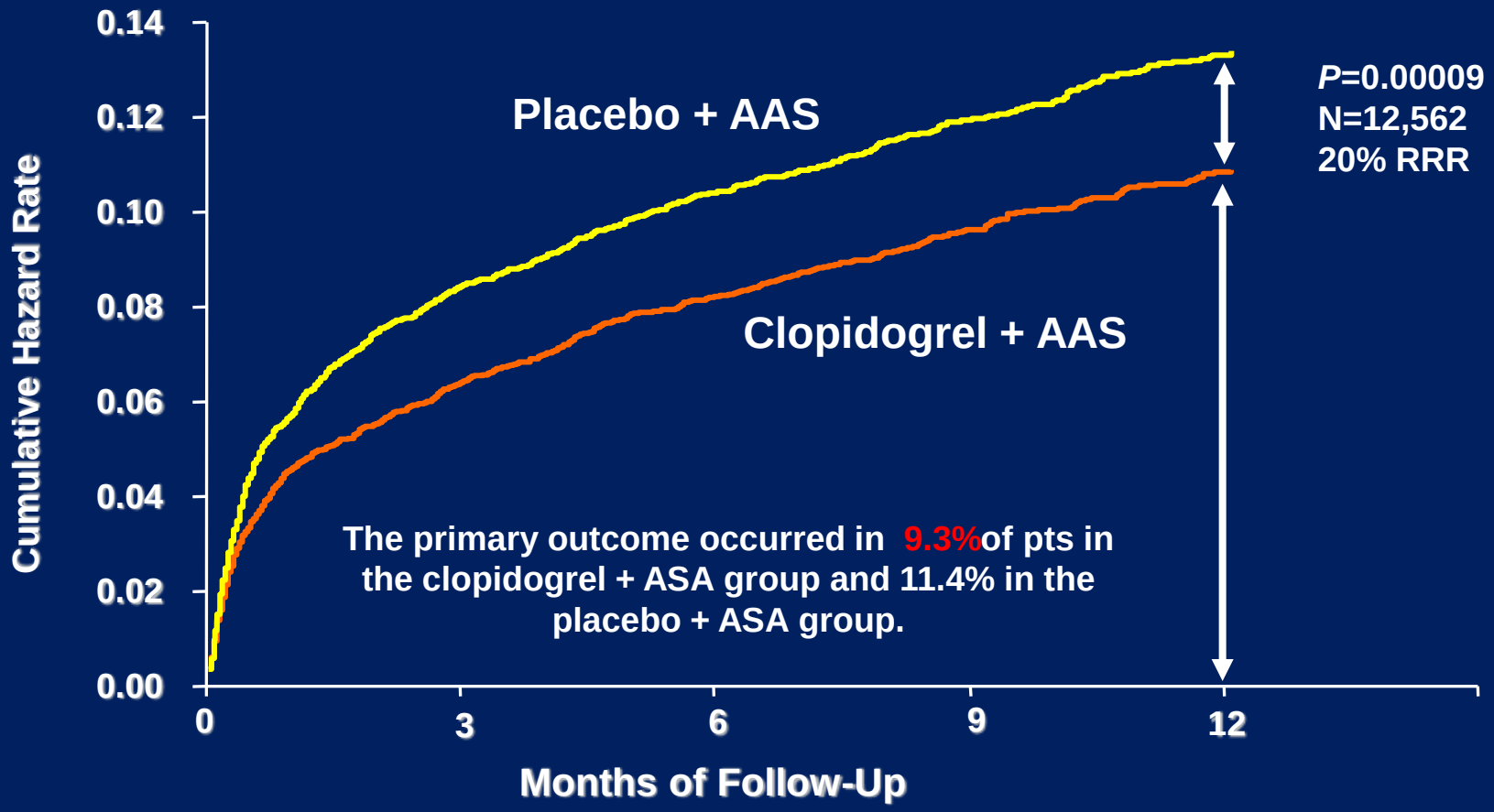
Dra. Inmaculada Roldán Rabadán

Junio 2012

SOCIEDAD ESPAÑOLA DE Cardiología

CURE

INTRODUCCION



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

INTRODUCCION

Mortalidad post SCA. Registro GRACE

Table 2 Total cohort ($n = 3721$) distribution of death from index and up to 5 years post-index hospitalization by index ACS diagnosis

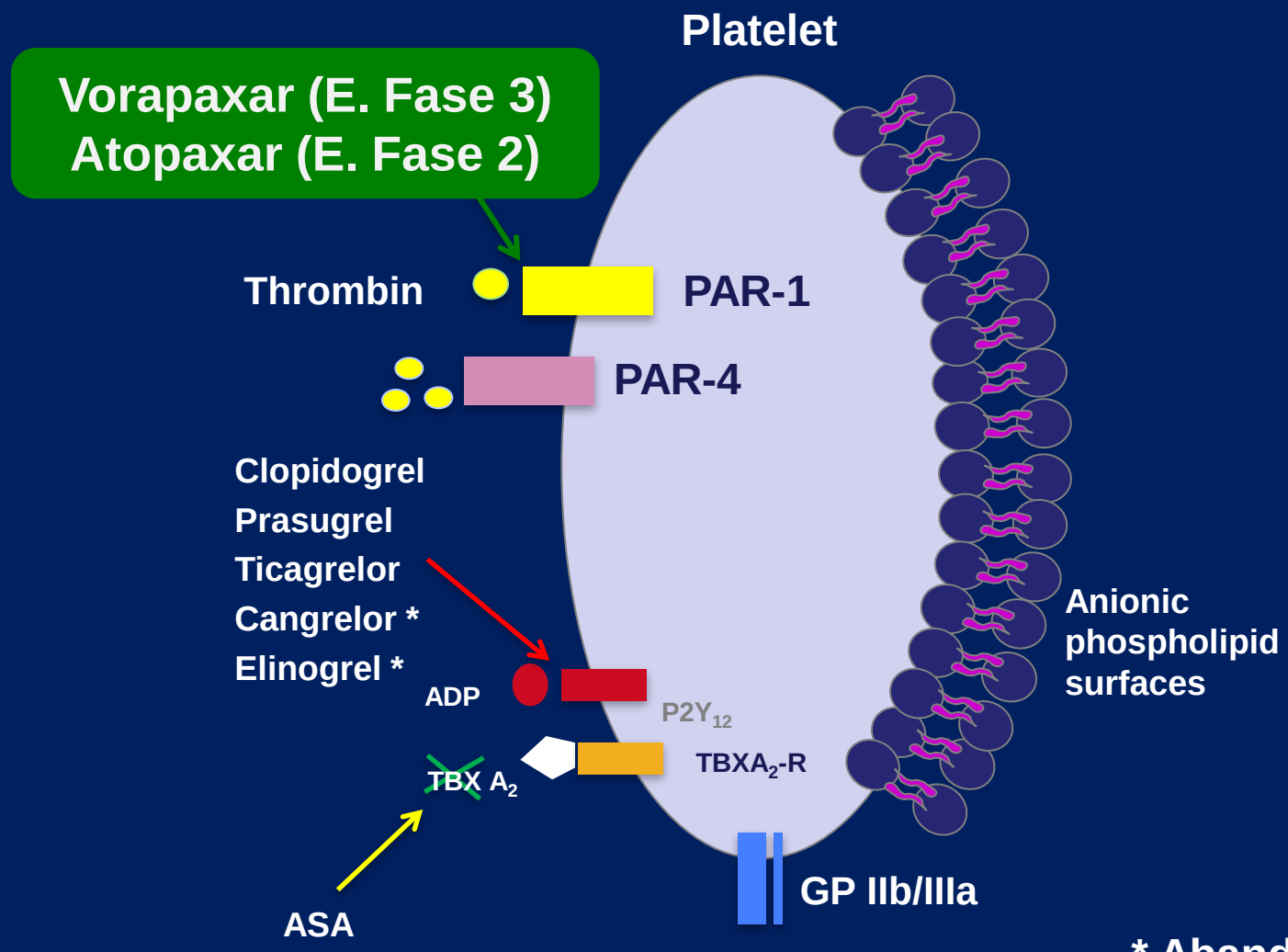
Total $n = 3721$	5 Year total no. deaths, $n = 736$ (20%)	Index death, $n = 129$ (3%)	Index cardiovascular death, $n = 114$ (3%)	Post-discharge death, $n = 607$ (16%)	Post-discharge cardiovascular death, $n = 368$ (10%)
STEMI (1403)	269 (19%)	88 (6%)	78 (6%)	184 (13%)	103 (7%)
Non-STEMI (1170)	262 (22%)	36 (3%)	28 (2%)	226(19%)	137 (13%)
UA (850)	149 (18%)	4 (1%)	6 (1%)	145 (17%)	84 (10%)
Other cardiac (135)	30 (22%)	3 (2%)	3 (2%)	27 (20%)	19 (14%)
Non-cardiac (163)	27 (17%)	3 (2%)	2 (1%)	25 (15%)	15 (9%)

Fox KA et al. E Heart J 2010; 31: 2755-64.

INTRODUCCION

1. **Recurrencia de episodios trombóticos.**
   - * Insuficiente inhibición plaquetar:
     ¿A. más potentes?, ¿triple terapia?, ¿ACO además?
   - * Abandono tratamiento.
   - * No correcta prevención secundaria.
2. **Muerte cardiovascular no trombótica.**
   - * ICC, arritmia severa etc…
3. **Muerte de causa no cardiovascular.**
   - * Cáncer, neumonía, etc…

LUGAR DE INHIBICION PLAQUETAR



* Abandono desarrollo

Modificada de Chackalamannil S. J Med Chem 2006.

VORAPAXAR

Primer inhibidor oral y selectivo del receptor plaquetar de la trombina, PAR-1.

- **Metabolismo y farmacocinética:**

- **Principalmente hepático vía CYP 3A4. No depende de AclCr.**
- **No requiere activación metabólica.**
- **Comienzo de acción rápido (inhibición plaquetar en 60 m).**
- **Vida media larga: ~126–269 hrs. 1 dosis/día.**
- **No interfiere con la generación de fibrina.**
- **No alarga el tiempo de sangría ni el TP/TTPA**

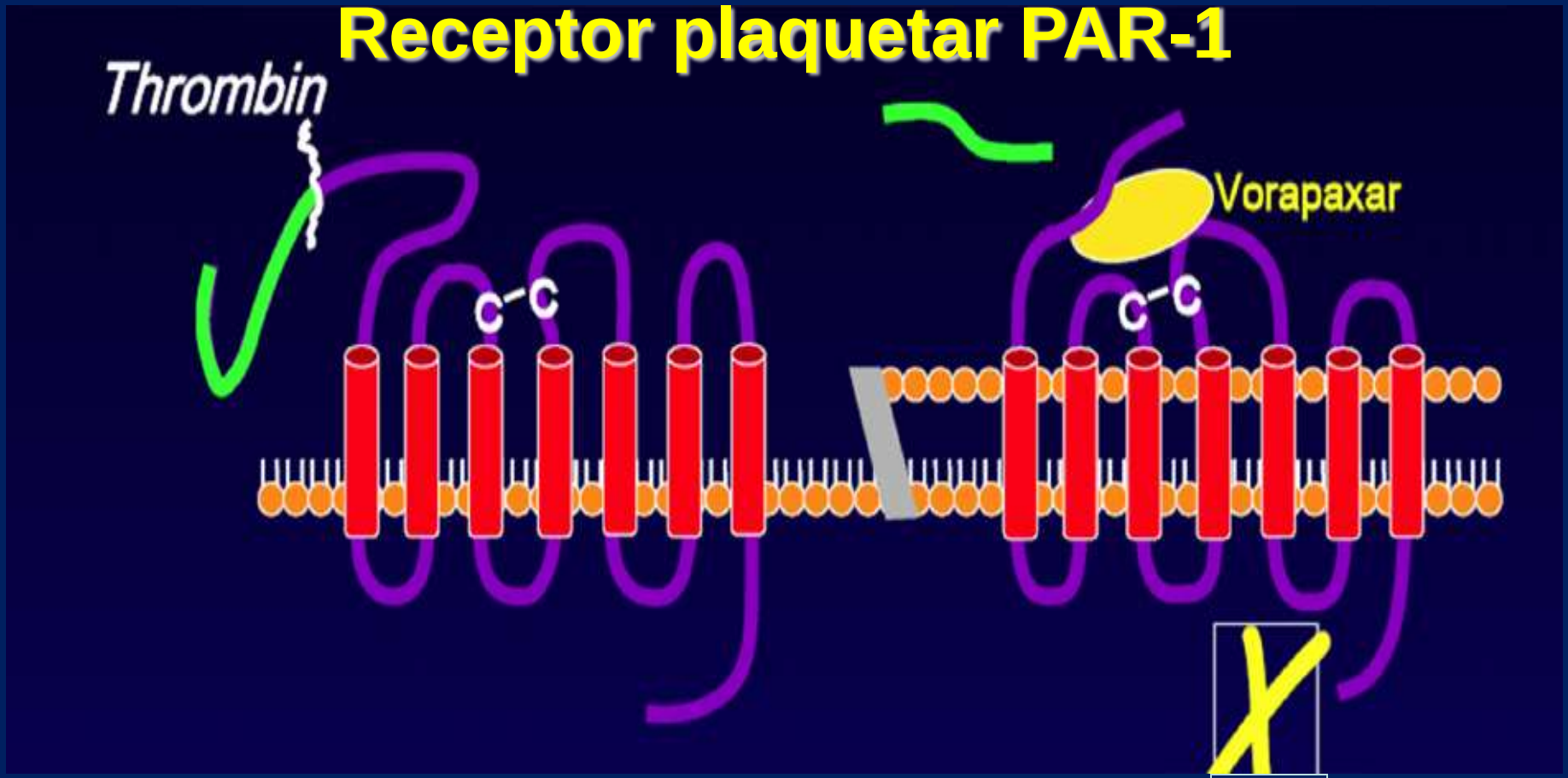
- **Estudios previos (TRA-PCI):**

- **No incremento de sangrados y tendencia a menos eventos trombóticos.**

- **Estudios en Fase III: TRA-CER (SCASEST) y TRA 2º P- TIMI 50.**

Oestreich J. Curr Opin Investig Drugs 2009; 10: 988-96.
Husted S. Eur Heart J 2007; 9: D20-D27.

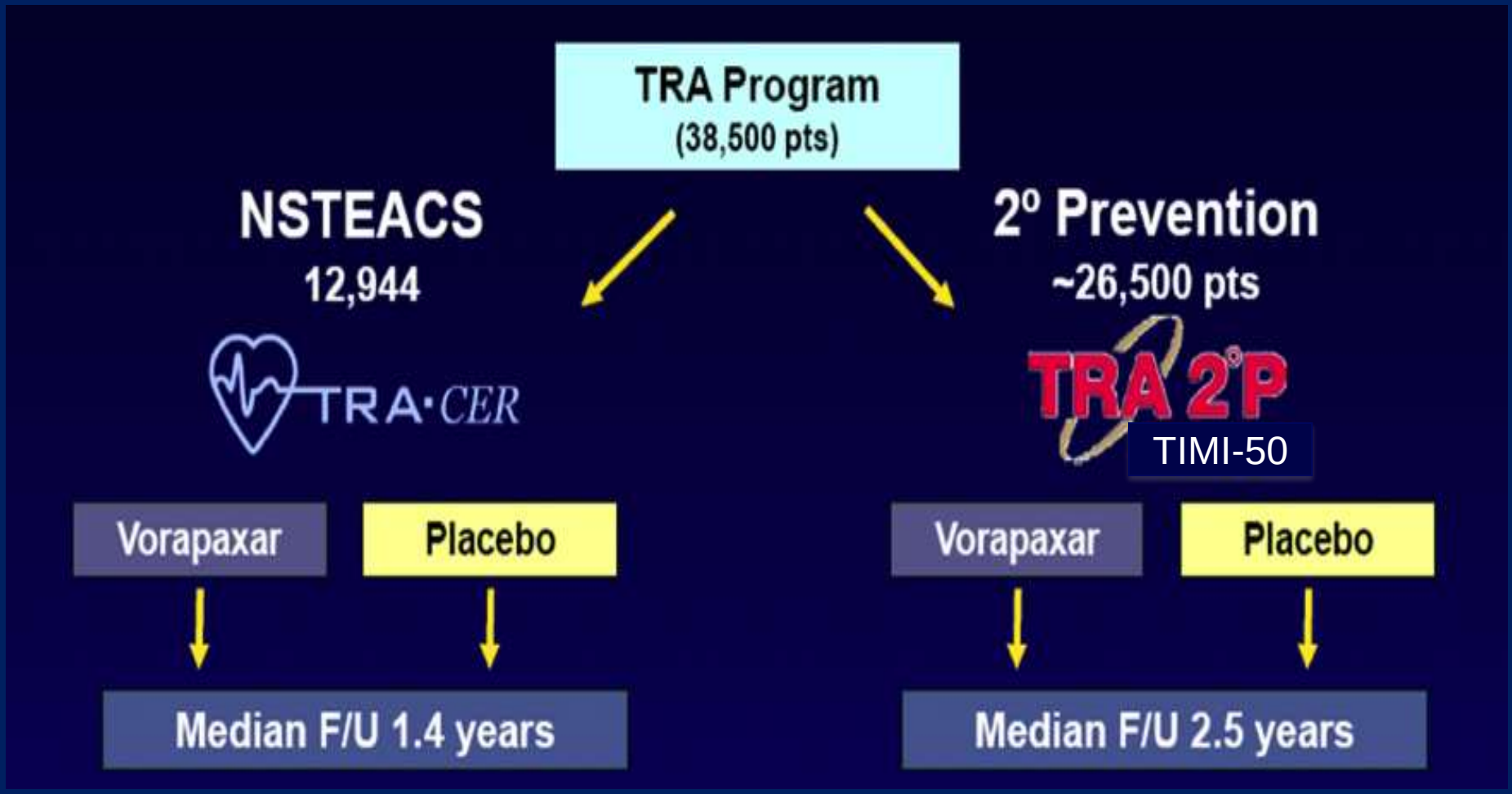
Inhibidores PAR-1



Cambio de forma
Activación
Agregación

Modificada de Vu TH et al. Cell 1991; 64: 1057-66.

Programa TRA. Estudios Fase 3 vorapaxar



Inhibidores PAR-1

TRA·CER

NSTE ACS

Key inclusion criteria
- Within 24 hrs of symptoms
- ↑biomarkers or ECG changes
- 1 other high-risk feature

1:1
Randomized
Double-blind

Placebo

Vorapaxar

Loading: 40 mg
Maintenance: 2.5 mg daily

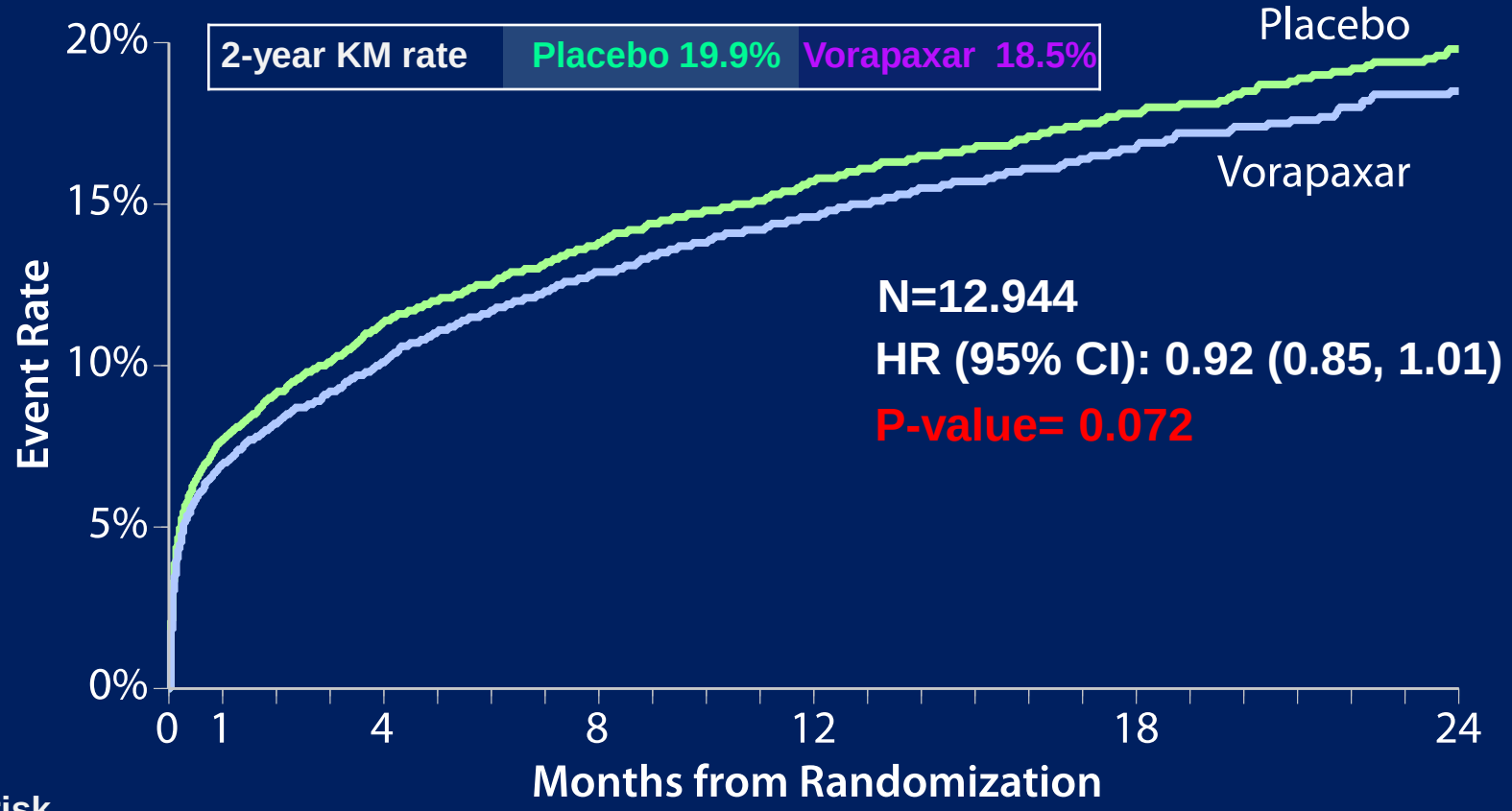
El 8 de Enero de 2011 se paró el estudio en fase seguimiento

Follow-up: 1, 4, 8, 12 months, then every 6 months
Standard of care based on practice guidelines

Efficacy Endpoints
Primary: CV death, MI, stroke, hospitalization for ischemia, urgent revascularization
Key Secondary: CV death, MI, stroke
Bleeding Endpoints: GUSTO moderate or severe and clinically significant TIMI bleeding

Primary Endpoint

CV Death, MI, Stroke, Hospitalization for Ischemia, Urgent Revascularization

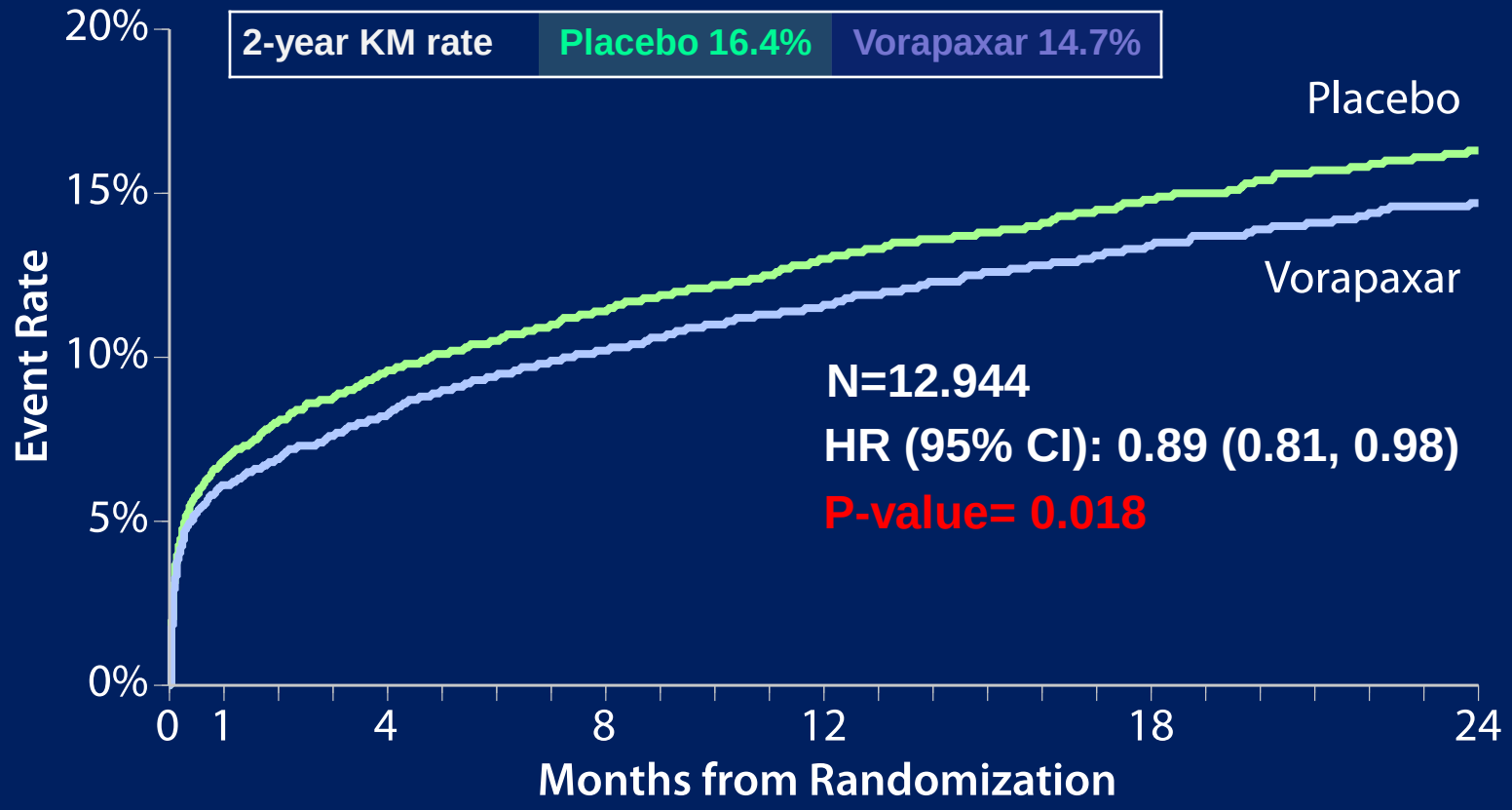


No. at risk							
Placebo	6471	5844	5468	5121	3794	2291	795
Vorapaxar	6473	5897	5570	5199	3881	2318	832

P Tricoci et al. N Engl J Med 2011.

Key Secondary Endpoint

CV Death, MI, Stroke



No. at risk							
Placebo	6471	5895	5575	5263	3922	2383	830
Vorapaxar	6473	5949	5684	5356	4023	2427	868

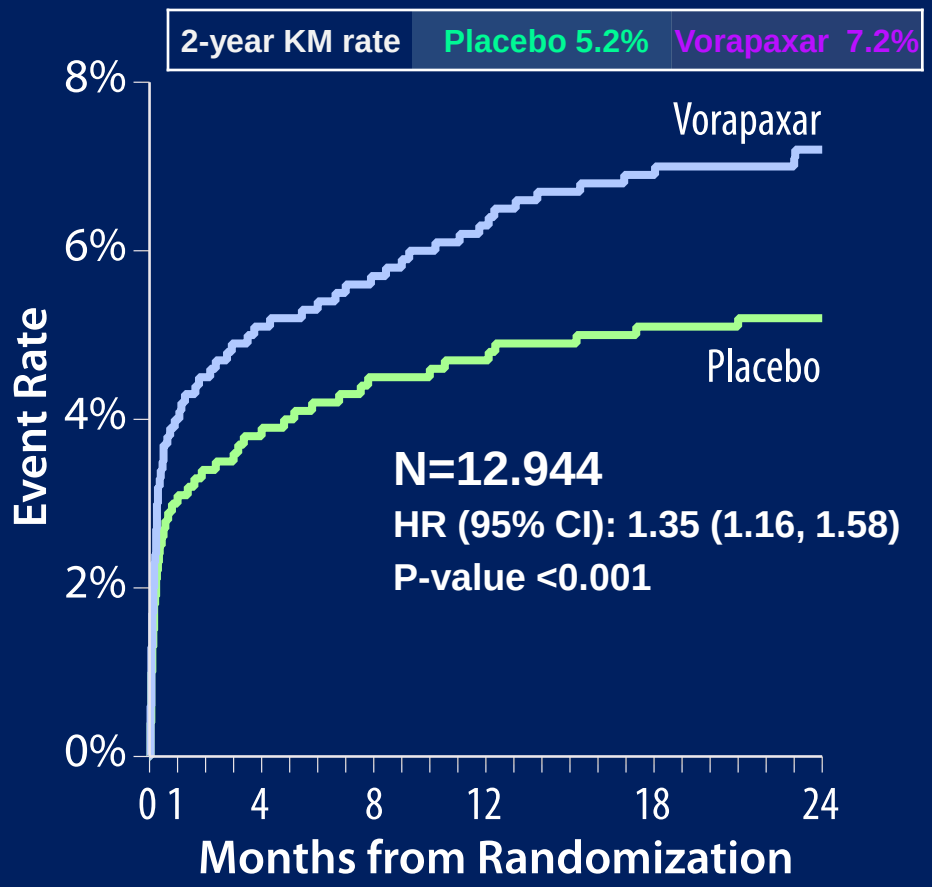
P Tricoci et al. N Engl J Med 2011.

Selected Efficacy Outcomes

	Placebo (N=6471) 2-yr KM rate (%)	Vorapaxar (N=6473) 2-yr KM rate (%)	HR (95% CI)	P-value
Primary endpoint	19.9	18.5	0.92 (0.85–1.01)	0.072
CV death	3.8	3.8	1.00 (0.83–1.22)	0.96
MI	***12.5***	***11.1***	***0.88 (0.79–0.98)***	***0.021***
Stroke	2.1	1.9	0.93 (0.70–1.23)	0.61
Hospitalization for ischemia	1.5	1.6	1.14 (0.83–1.58)	0.42
Urgent revascularization	3.5	3.8	1.07 (0.88–1.31)	0.49
Stent Thrombosis	1.5	1.7	1.12 (0.78–1.62)	0.54
All-cause mortality	6.1	6.5	1.05 (0.90–1.23)	0.52

P Tricoci et al. N Engl J Med 2011.

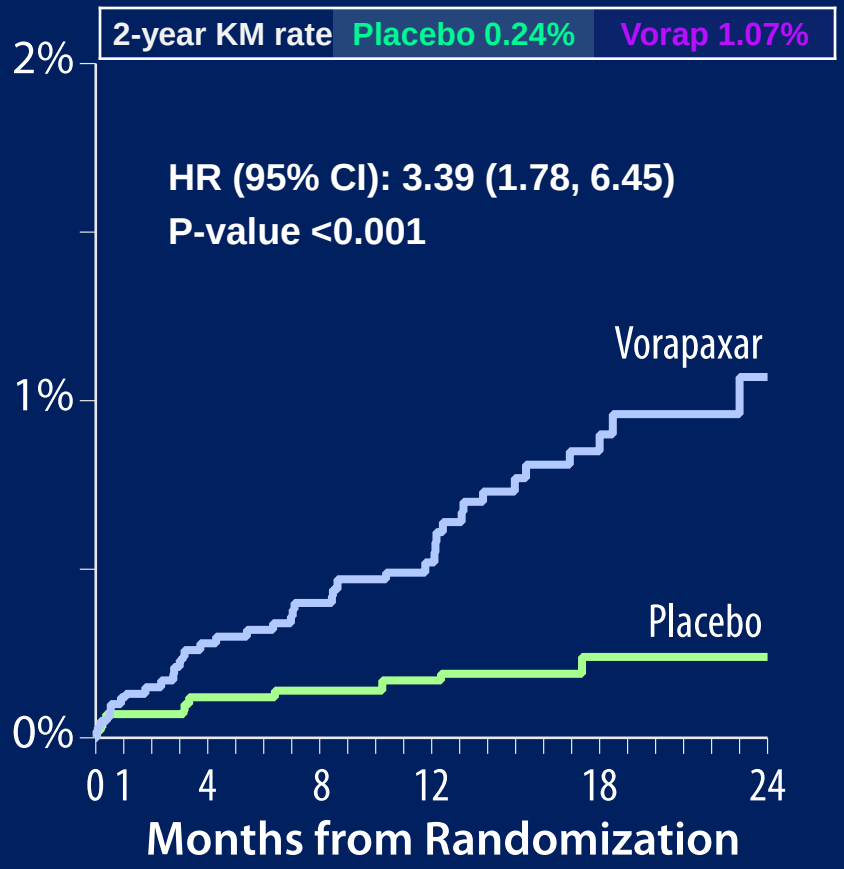
Bleeding outcomes: GUSTO Moderate/Severe



No. at risk

6441	5536	5137	4674	3393	1972	650
6446	5529	5108	4598	3278	1883	625

ICH



No. at risk

6441	5673	5281	4823	3511	2038	678
6446	5694	5272	4760	3411	1965	657

P Tricoci et al. N Engl J Med 2011.

CONCLUSIONES

Vorapaxar con AAS y Clopidogrel en SCASEST:

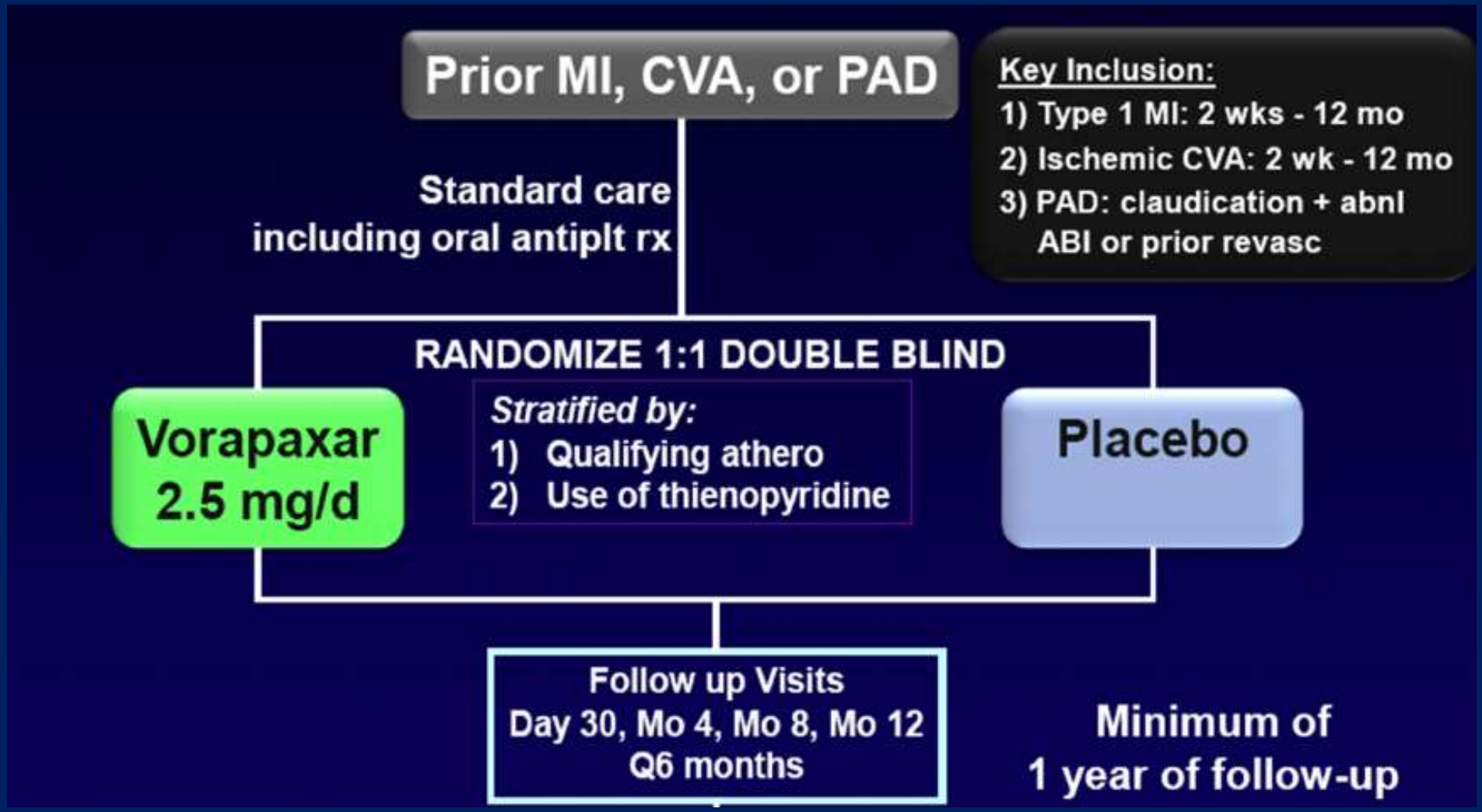
1.- No disminuye el objetivo primario de eficacia.

2.- Reduce el objetivo secundario de Muerte CV/ IM/ ICTUS.

3.-Aumenta significativamente el sangrado, incluyendo hemorragia mayor e intracraneal.

P Tricoci et al. N Engl J Med 2011.

Diseño de TRA 2º P- TIMI 50



D. Morrow et al. ACC 2012, Chicago.

Objetivos de eficacia y seguridad

Efficacy: hierarchical testing

1. Cardiovascular (CV) death, MI, or stroke
2. CV death, MI, stroke, or urgent coronary revascularization
3. CV death or MI

Bleeding endpoints of primary interest:

- GUSTO moderate or severe bleeding
- TIMI Clinically Significant Bleeding:
  TIMI major, TIMI minor, or bleeding requiring medical attention (medical/surgical rx, lab eval)

D. Morrow et al. ACC 2012, Chicago.

TRA•2P TIMI-50

January, 2011, the DSMB announced that based on its ongoing review of safety:

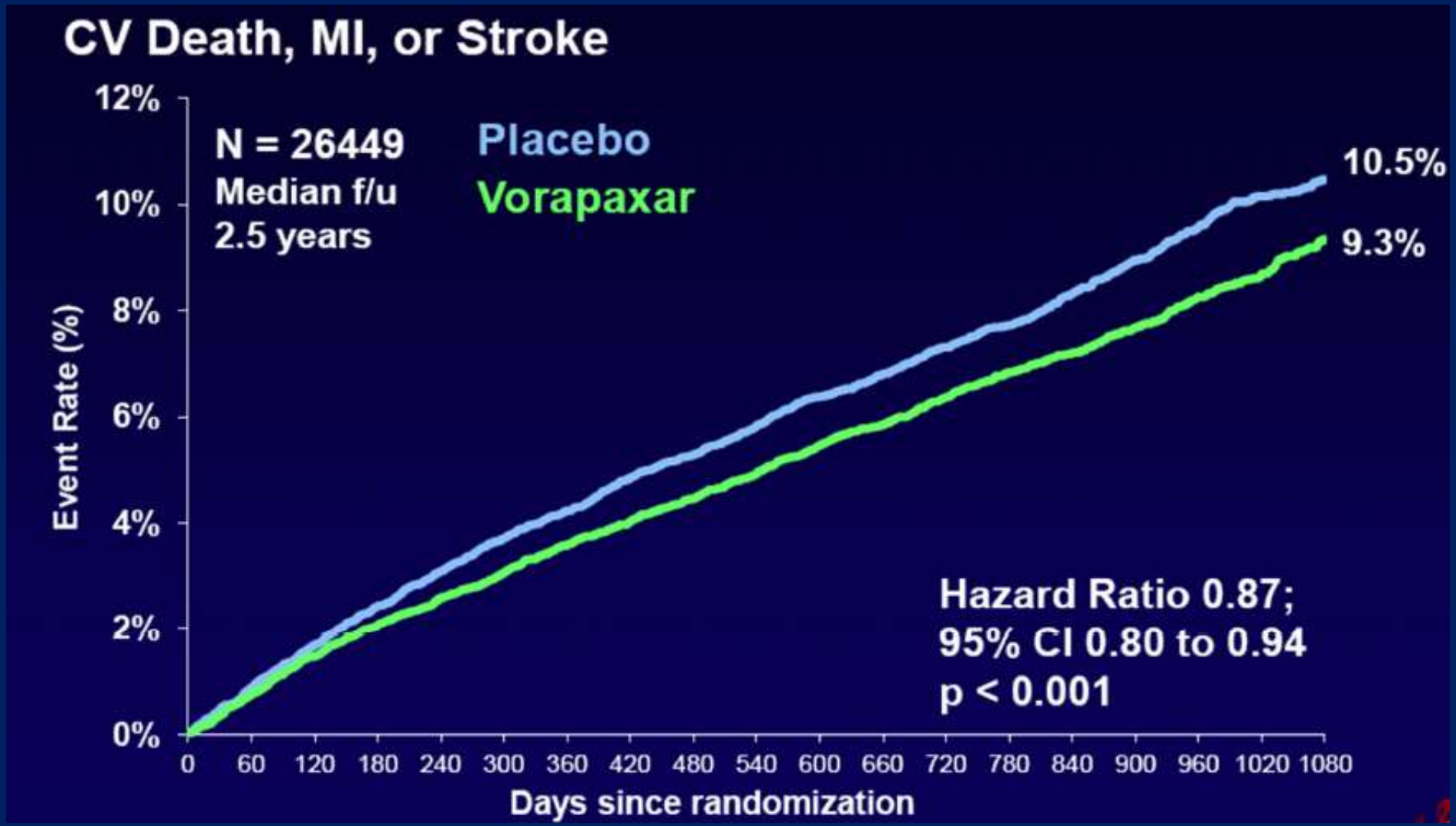
- ↑ ICH with vorapaxar in pts w/ a prior stroke
  ➔ D/C all pts with a prior stroke
- Trial should continue in pts without a hx of stroke

Analyses

- 1st line analysis in *all* patients, including stroke
- 2nd line analysis (*new*): pts w/out prior stroke
- Special interest in patients who qualified w/ MI

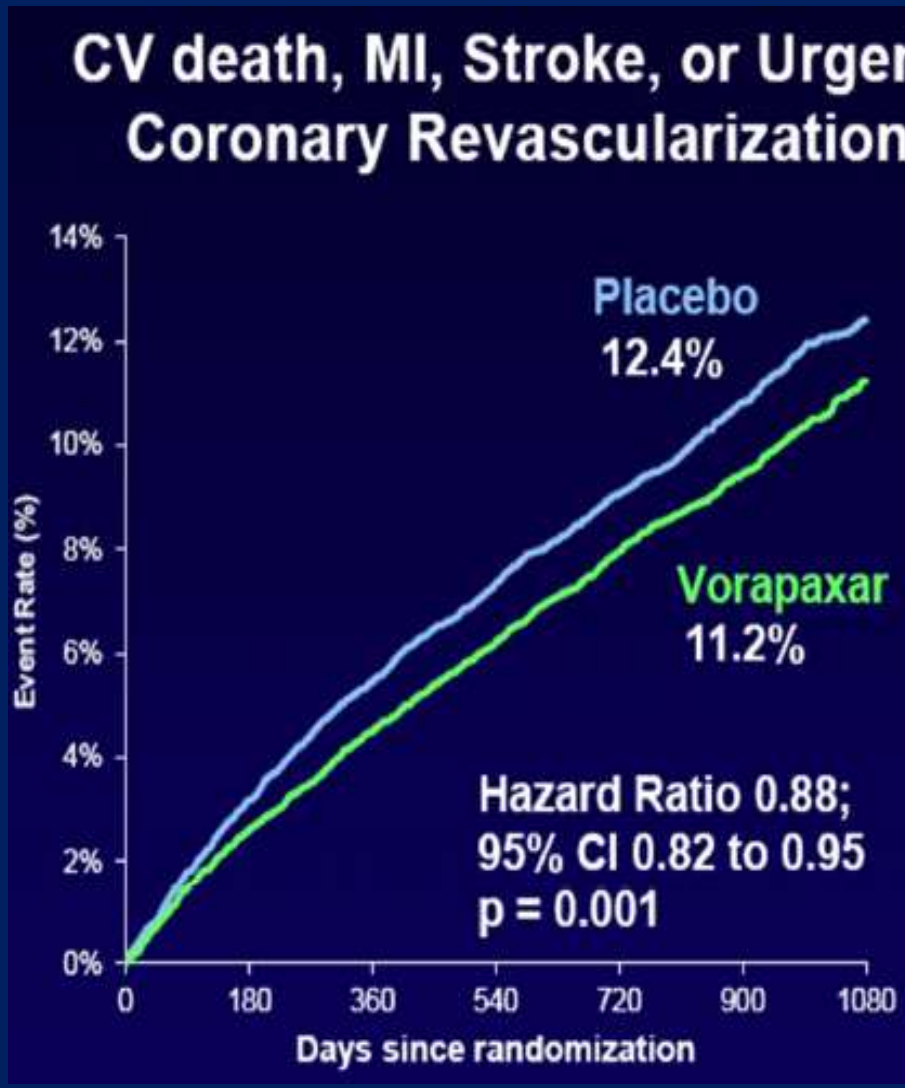
D. Morrow et al. ACC 2012, Chicago

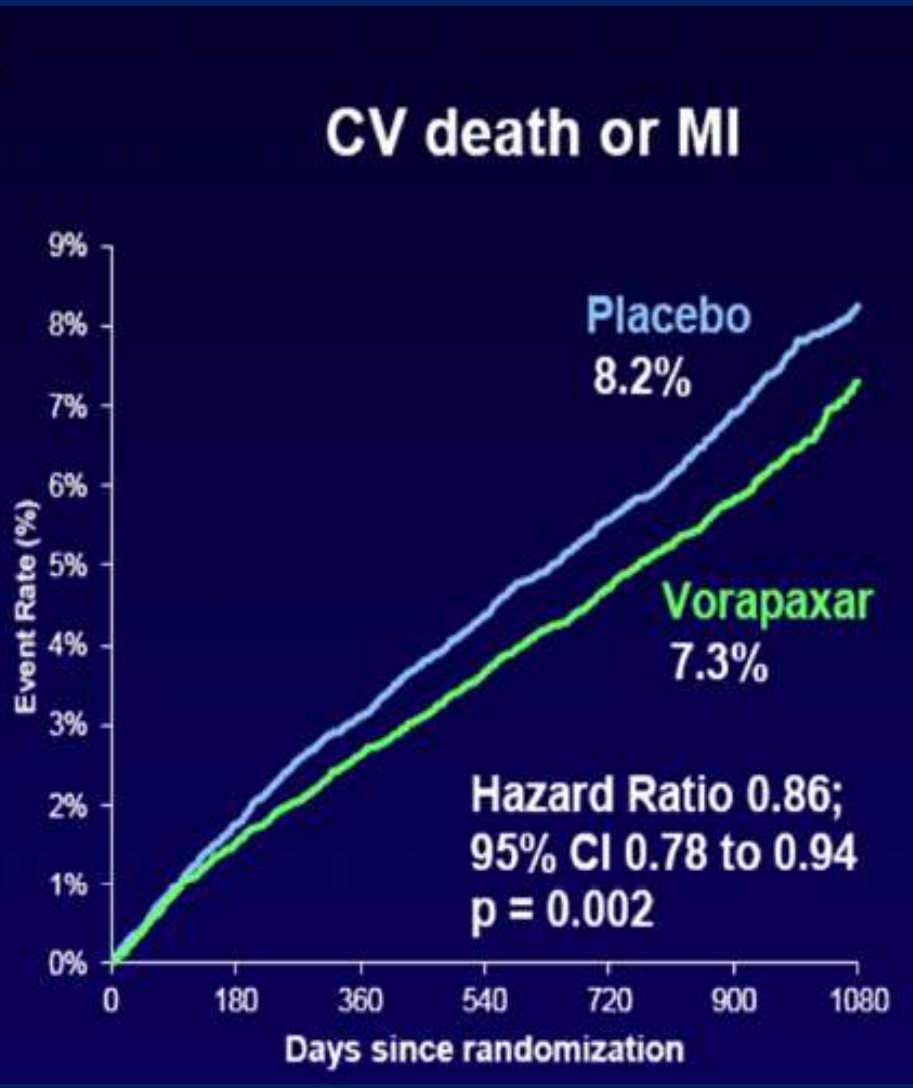
Objetivo primario de eficacia



D. Morrow et al. ACC 2012, Chicago.

Objetivos secundarios de eficacia





D. Morrow et al. ACC 2012, Chicago.

Objetivos de eficacia: población total

n=26.449

3-*yr* KM rate (%)	Placebo (N = 13224)	Vorapaxar (N = 13225)	HR	*p-value*
CV death, MI, stroke	10.5	9.3	0.87	*<0.001*
CV death	3.0	2.7	0.89	*0.15*
MI	6.1	5.2	0.83	*0.001*
Any Stroke	2.8	2.8	0.97	*0.73*
Ischemic stroke	2.6	2.2	0.85	*0.059*
Urgent coronary revascularization	2.6	2.5	0.88	*0.11*
CVD, MI, Stroke, UCR, vascular hosp.	14.7	13.1	0.87	*<0.001*
All-cause mortality	5.3	5.0	0.95	*0.41*

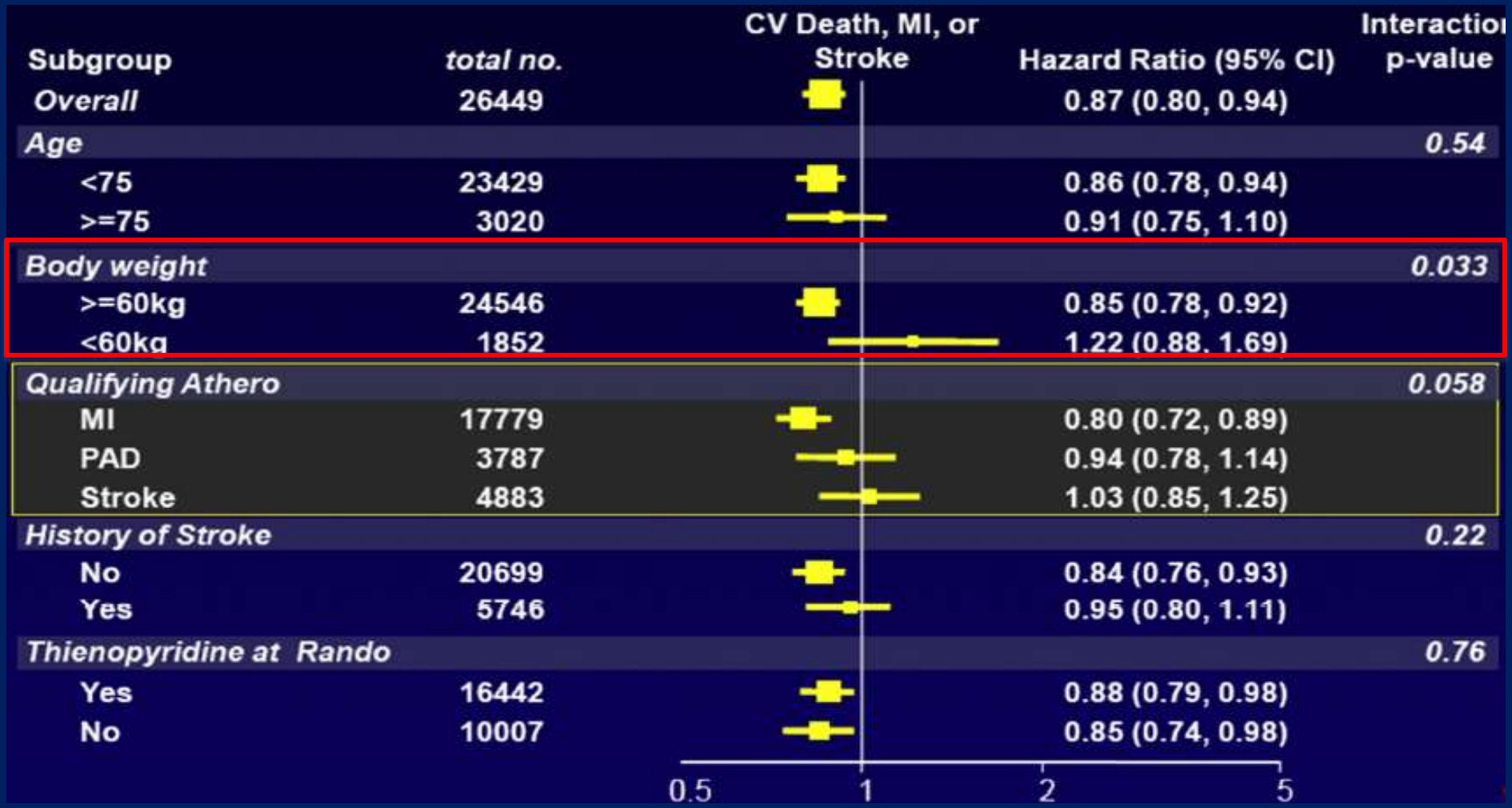
D. Morrow et al. ACC 2012, Chicago.

Objetivos de eficacia: no Ictus previo

3-*yr* KM rate (%)	Placebo (N = 10344)	Vorapaxar (N = 10335)	HR	*p-value*
CV death, MI, stroke	9.6	8.3	0.84	*<0.001*
CV death	2.8	2.5	0.87	*0.13*
MI	6.4	5.5	0.84	*0.004*
Any Stroke	1.7	1.5	0.82	*0.11*
Ischemic stroke	1.5	1.1	0.72	*0.013*
CVD, MI, Stroke, urg coronary revasc.	11.8	10.6	0.86	*<0.001*
CV death or MI	8.4	7.4	0.85	*0.002*
CVD, MI, Stroke, UCR, vascular hosp.	14.0	12.3	0.86	*<0.001*

D. Morrow et al. ACC 2012, Chicago.

Objetivo primario: principales subgrupos



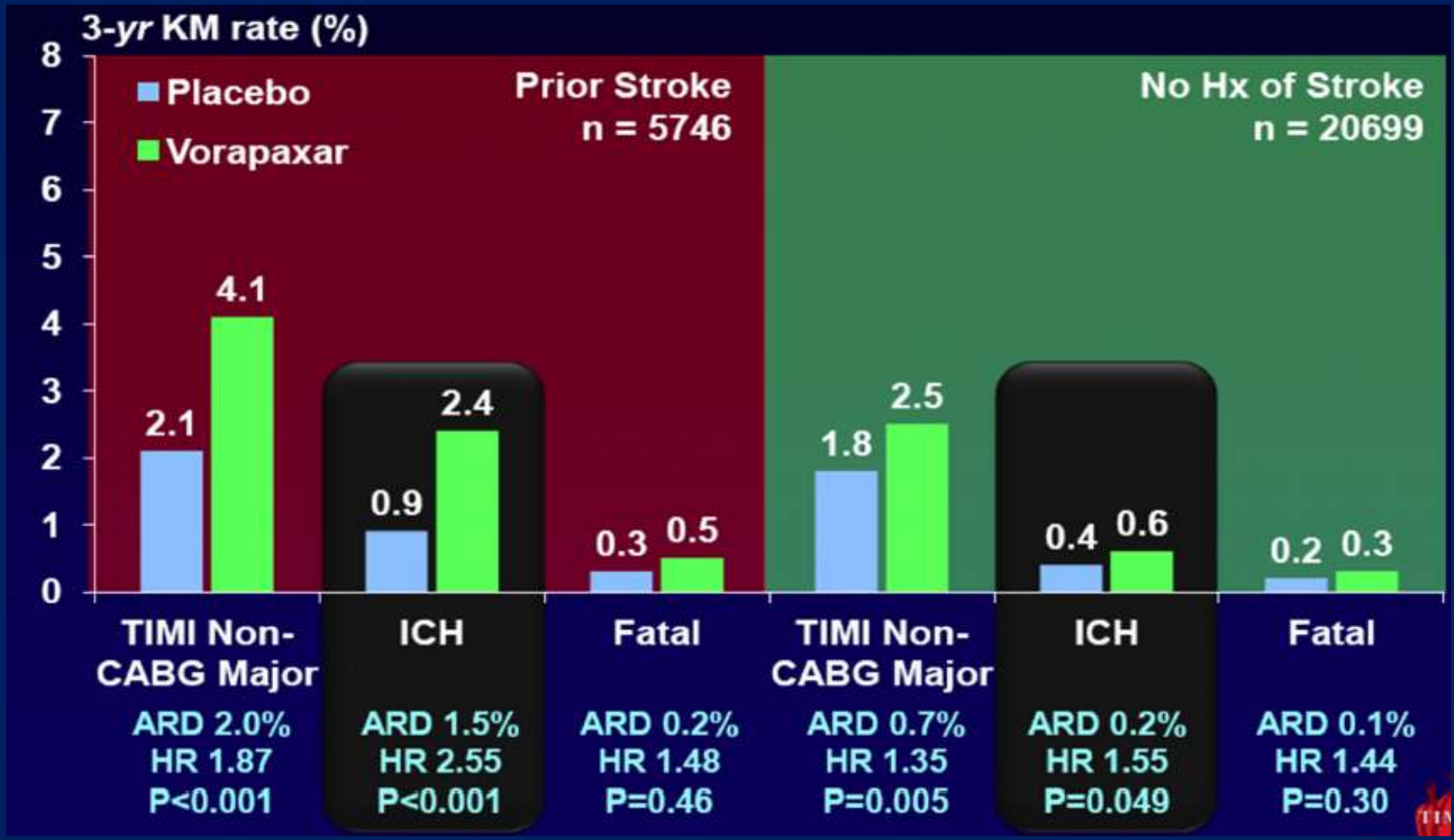
D. Morrow et al. ACC 2012, Chicago.

Objetivo primario de seguridad

3-*yr* KM rate (%)	Placebo (N = 13166)	Vorapaxar (N = 13186)	HR	*p-value*
GUSTO Moderate or Severe	2.5	4.2	1.66	*<0.001*
TIMI Clinically Significant	11.1	15.8	1.46	*<0.001*
TIMI Non-CABG Major	1.8	2.8	1.46	*<0.001*
Intracranial	0.5	1.0	1.94	*<0.001*
Fatal	0.2	0.3	1.46	*0.19*

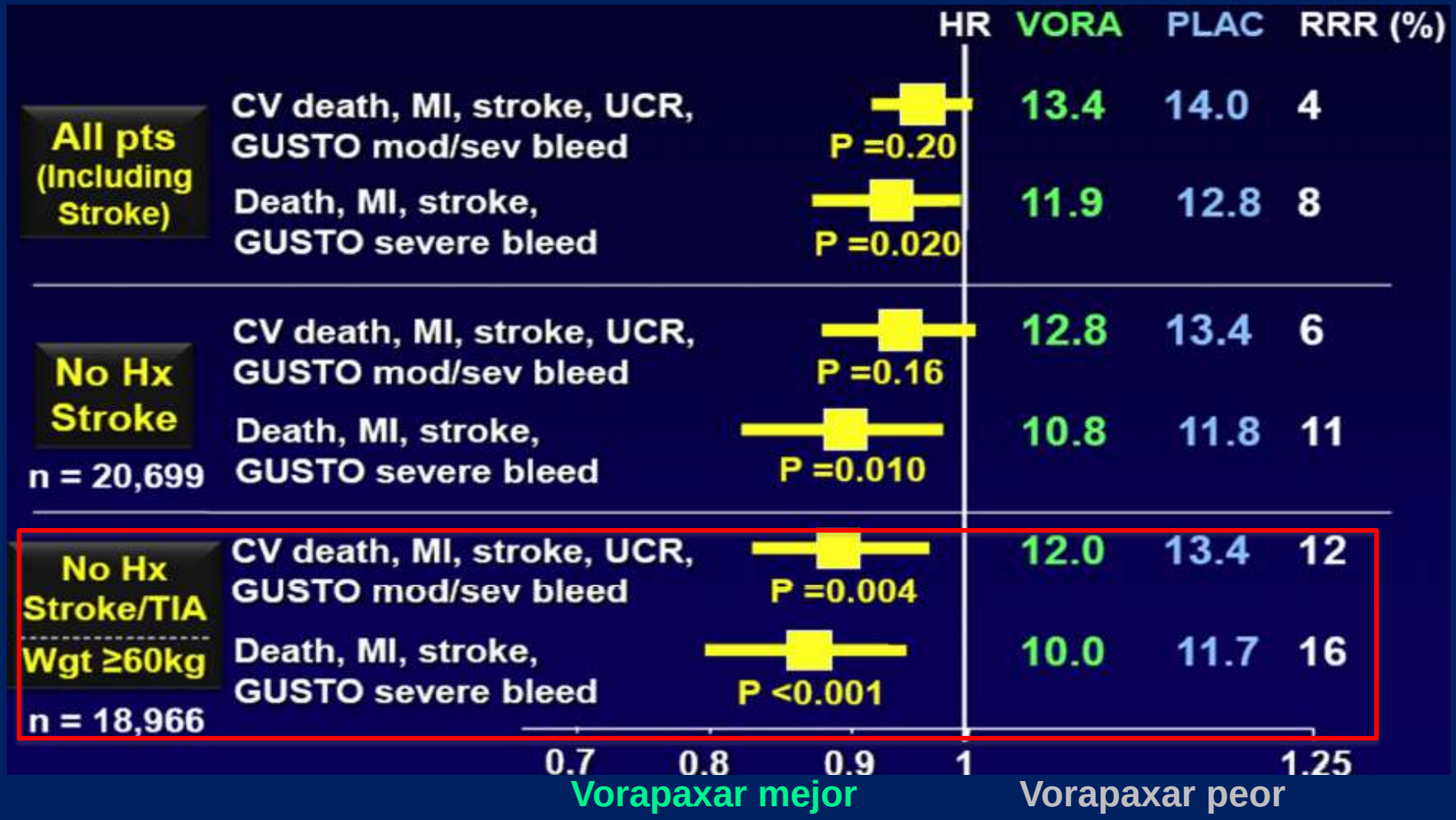
D. Morrow et al. ACC 2012, Chicago.

Objetivo primario de seguridad



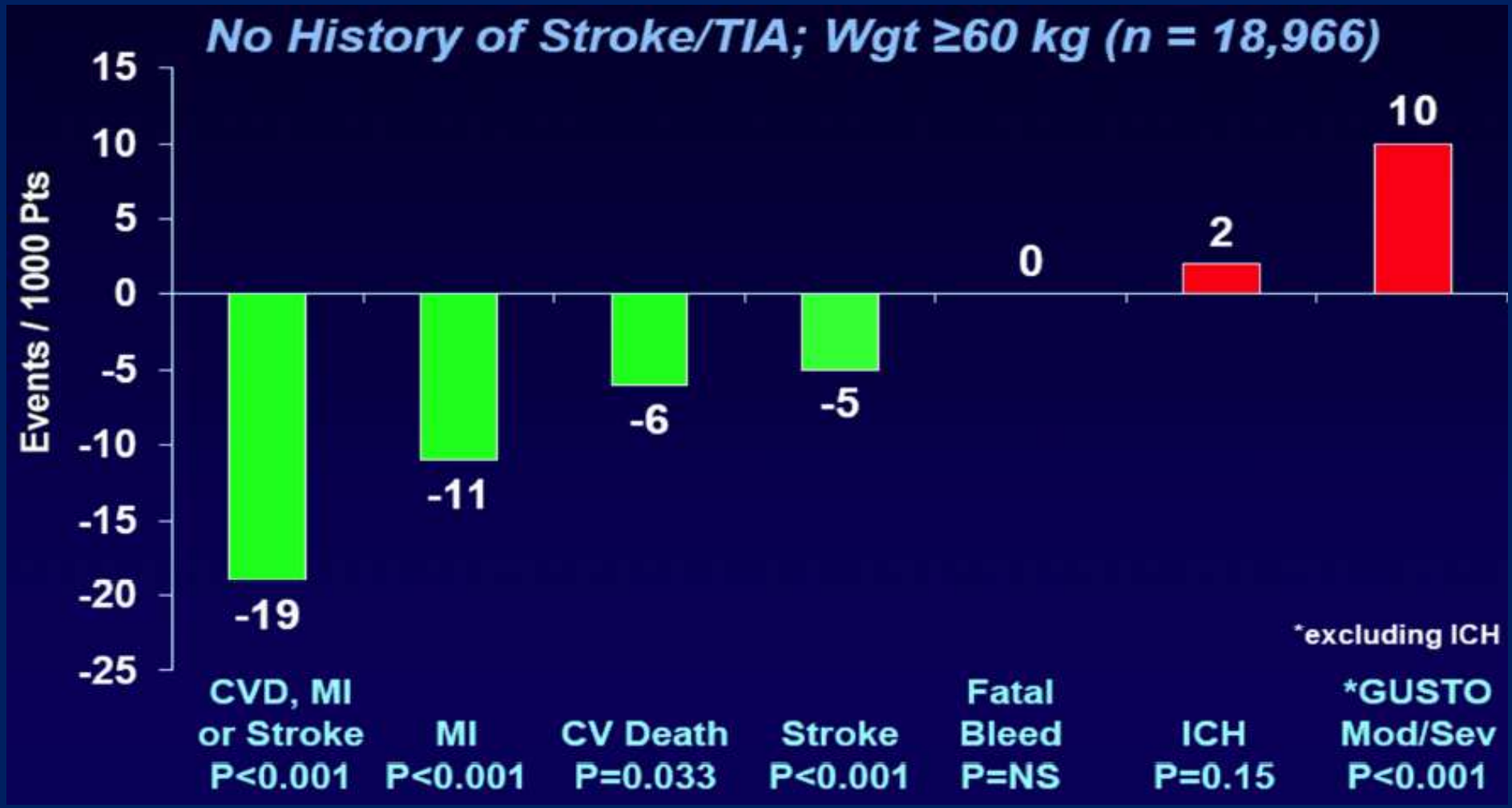
D. Morrow et al. ACC 2012, Chicago.

Beneficio clínico neto



D. Morrow et al. ACC 2012, Chicago.

Por cada 1.000 p con vorapaxar



D. Morrow et al. ACC 2012, Chicago.

Conclusiones

Vorapaxar con AAS y Clopidogrel en pacientes estables con aterotrombosis:

1.- Disminuye la muerte/IM/ICTUS.

2.- Incrementa hemorragias mode-severa, incluyendo HIC.

3.- Efectivo en prevención 2ª en IM previo. Beneficio dudoso en EAP. Riesgo inaceptable Ictus previo.

D. Morrow et al. ACC 2012, Chicago.