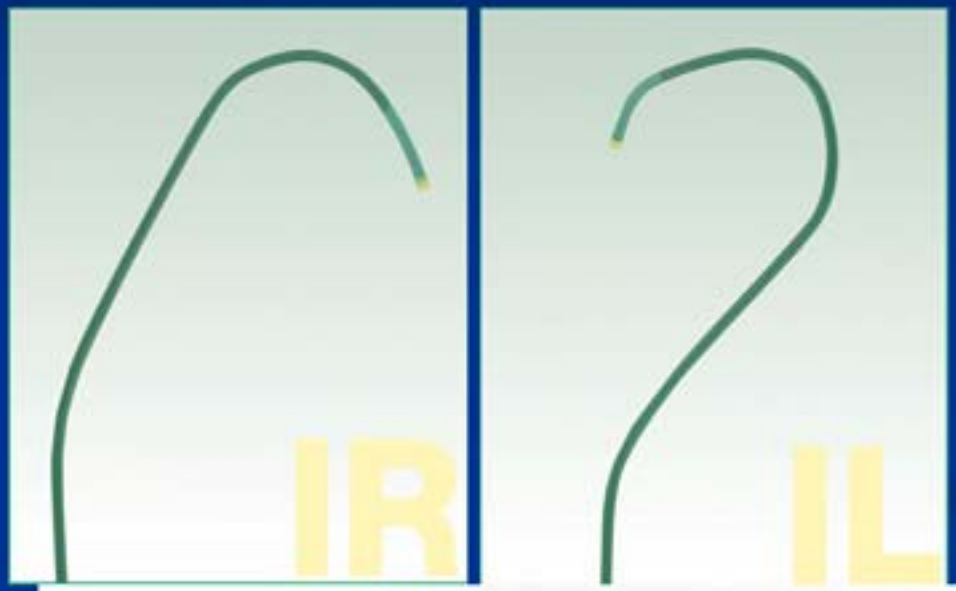
Medical Treatment for Patients with Post-Myocardial Infarction -Importance of angiotensin receptor blocker-

Yuji Ikari, MD, PhD, FACC
Professor, Department of Cardiology
Tokai University School of Medicine

IKARI guide catheter for transradial intervention (TRI)



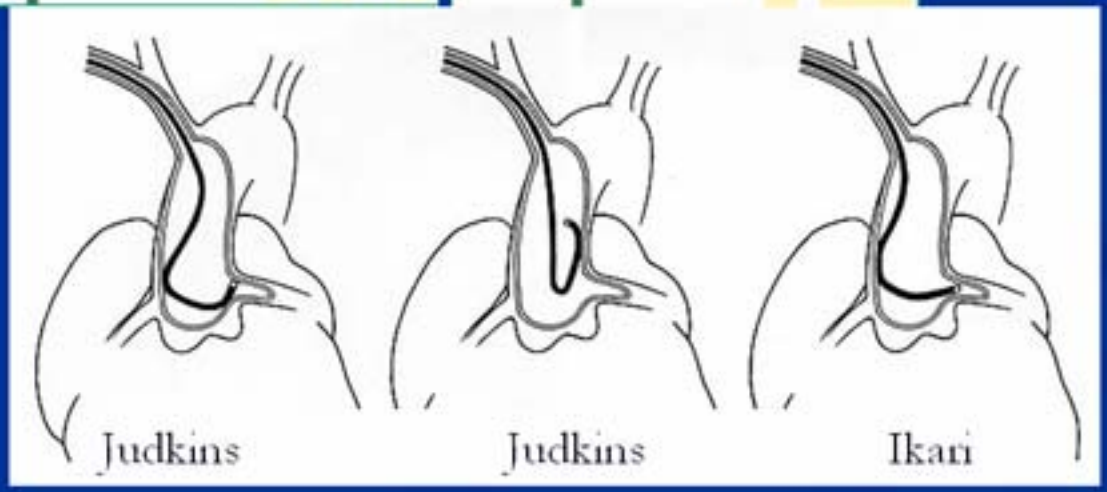
Invention in 1996

Patent is approved in

US (1999)

Europe (2001)

Japan (2005).



Acute Myocardial Infarction

- Number 1 cause of death in western countries
- Number 2 cause of death in Japan

Reduction of mortality rate in patients with AMI is important

Treatment of AMI

- Revascularization
  - Thrombolysis
  - Percutaneous coronary intervention (PCI)
- Medical treatment following revascularization therapy

Thromobolysis or PCI ?

PCI is better

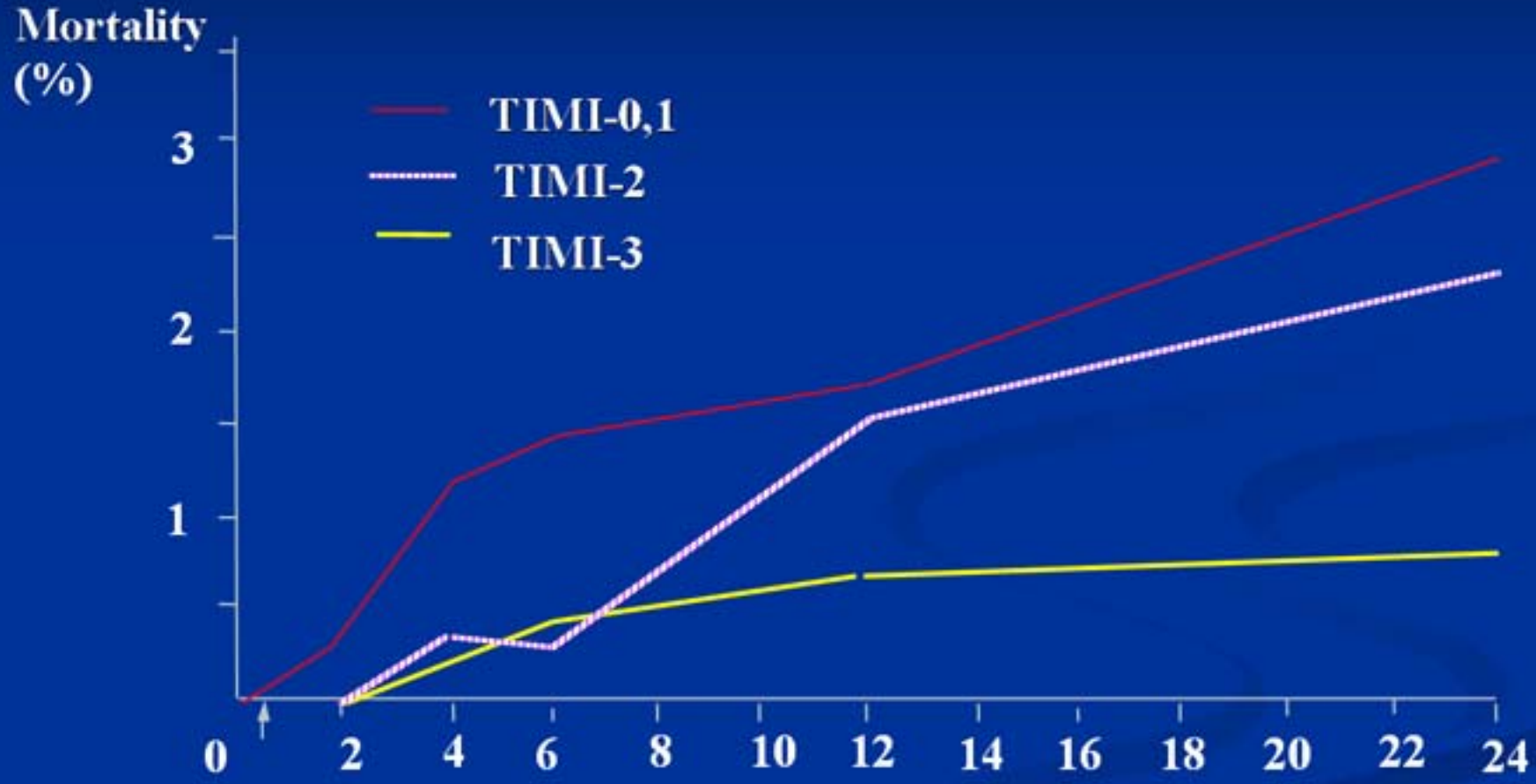
PCI is better

- Meta analysis showed (Circulation 1995; 91:476);
  - 34% risk reduction in mortality at 30 days: 6.5% vs. 4.4%, (OR 0.66:95%CI 0.46-0.94)
  - 40% risk reduction in mortality and repeat MI
  - 90% risk reduction in cerebral bleeding
- PAMI study showed (J Am Coll Cardiol 1999;33:412)
  - PCI is better in mortality, recurrence of ischemia, repeat intervention and repeat admission

But still we need more,

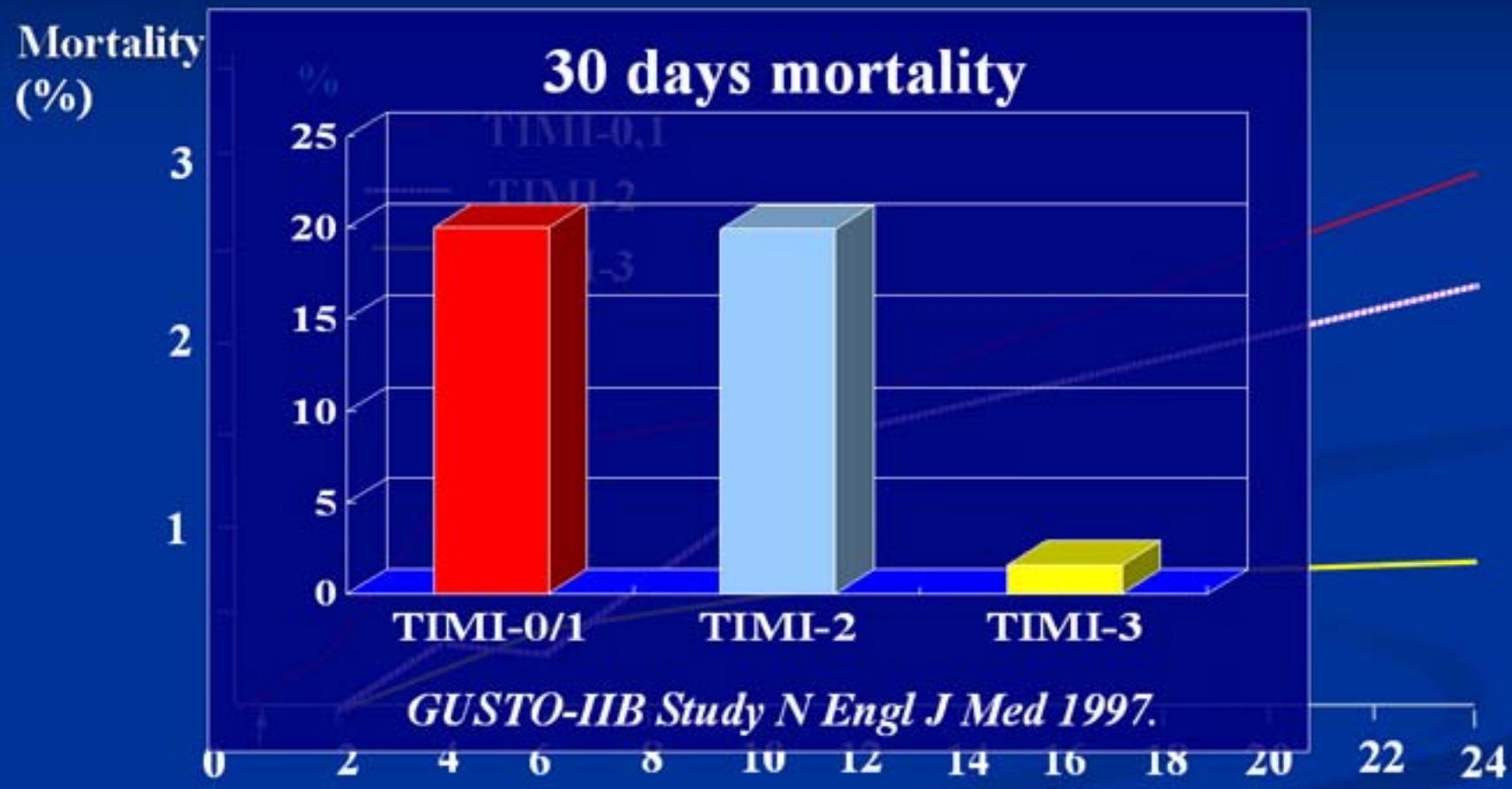
- Because mortality rate of patients with AMI is still high.

TIMI flow grade and prognosis



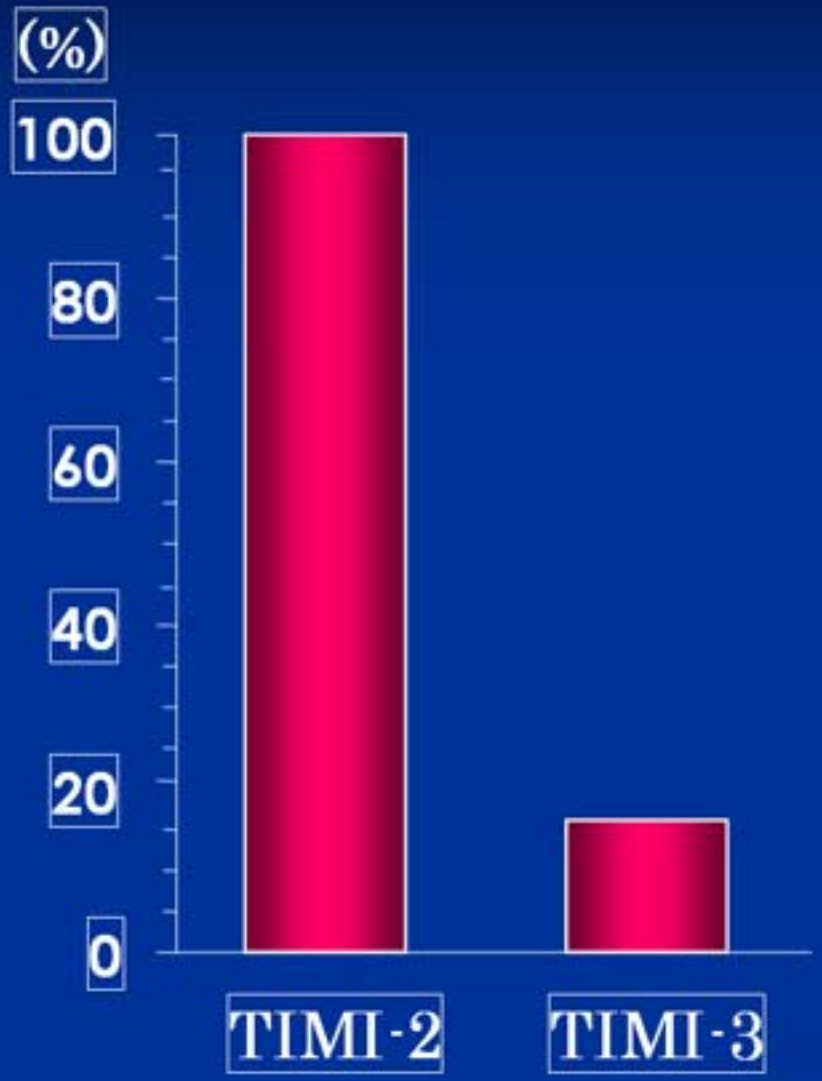
GUSTO Circulation 1994;90:2658-2665

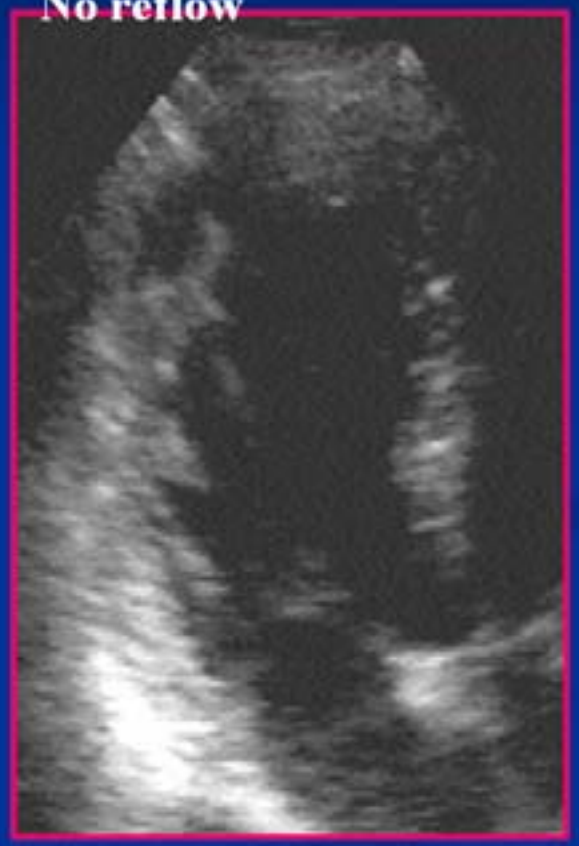
TIMI flow grade and prognosis



GUSTO Circulation 1994;90:2658-2665

TIMI Grade and No Reflow

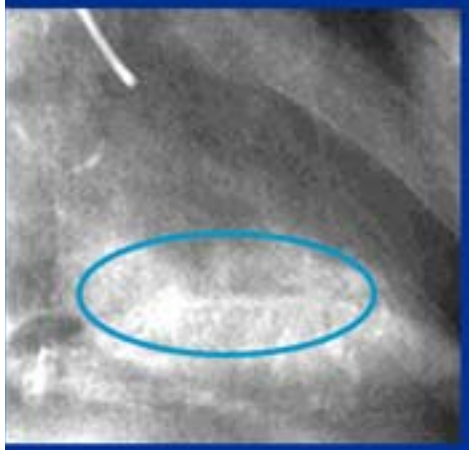
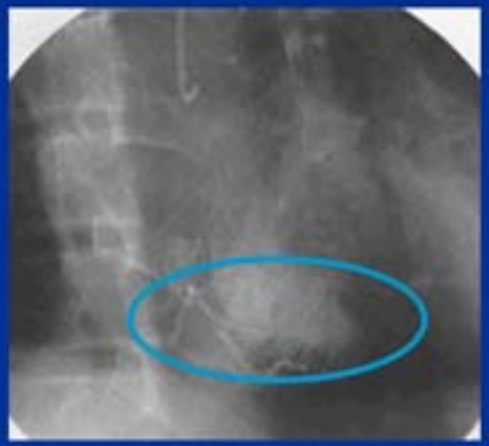
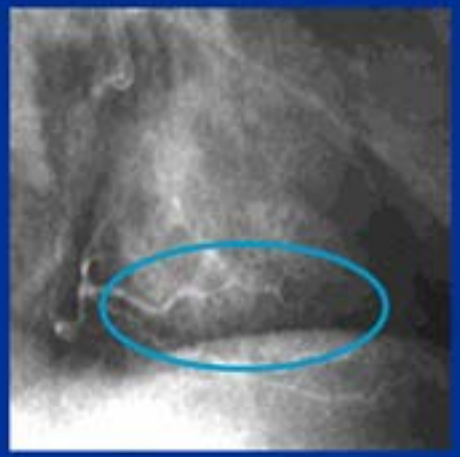
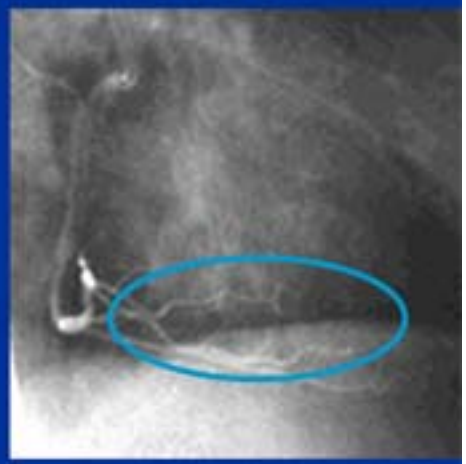




Ito H et al.,: Circulation, 93: 1993-1999, 1996

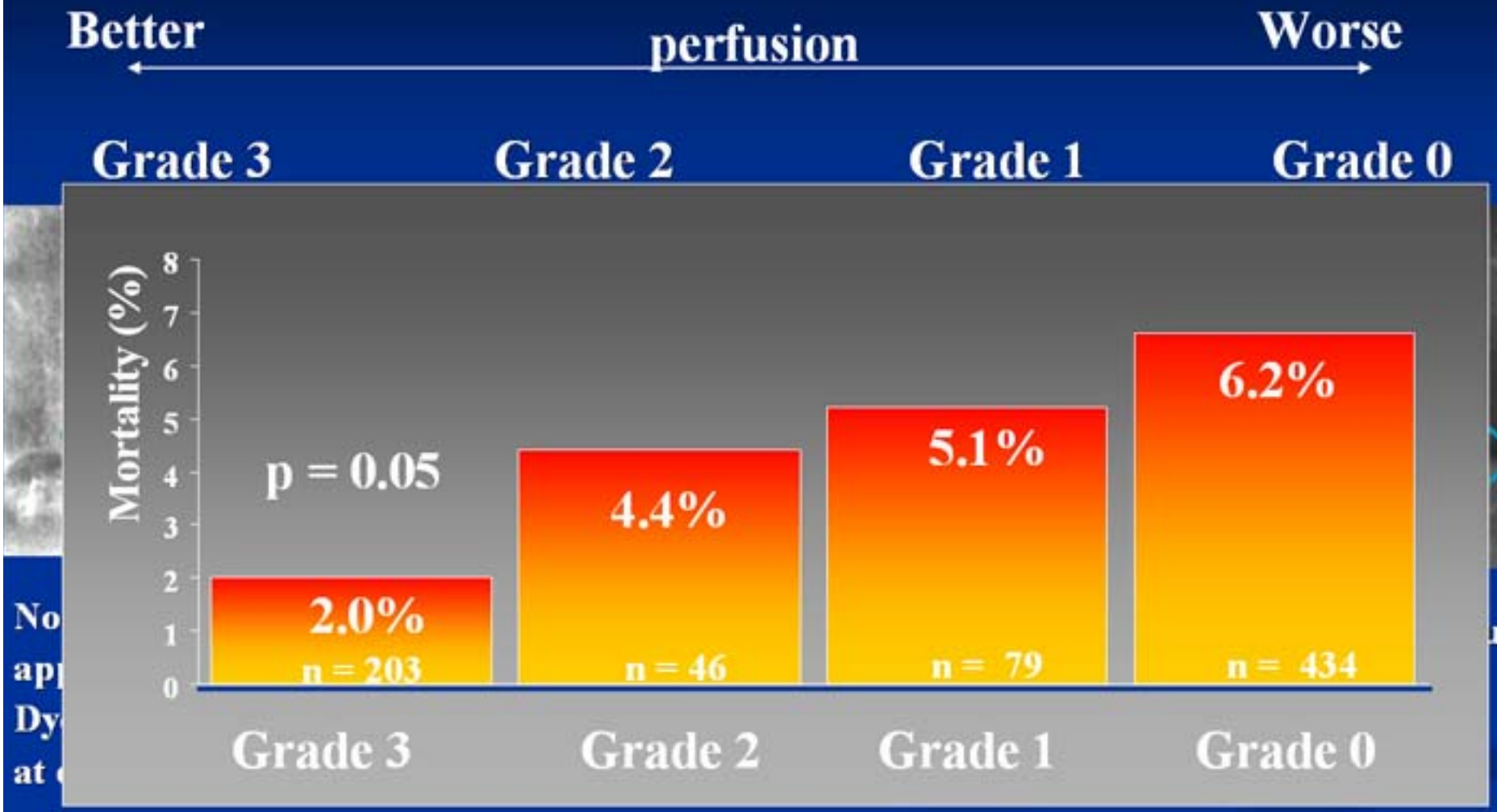
TIMI Perfusion (TMP) Grade

Better perfusion Worse

Grade 3	Grade 2	Grade 1	Grade 0
			
Normal ground glass appearance of blush Dye mildly persistent at end of washout	Dye strongly persistent at end of washout Gone by next injection	Stain present Blush persists on next injection	No or minimal blush

Gibson et al, Circulation 2000

TIMI Perfusion (TMP) Grade



Gibson et al, Circulation 2000

Distal Protection for AMI

- In EMERALD study, percusruge guardwire did not result in improved microvascular flow.
- In other studies, the data are sometimes positve and sometimes negative.

CARDIOCORE

VAMPIRE STUDY

VAcuuM asPIration thrombus REmoval

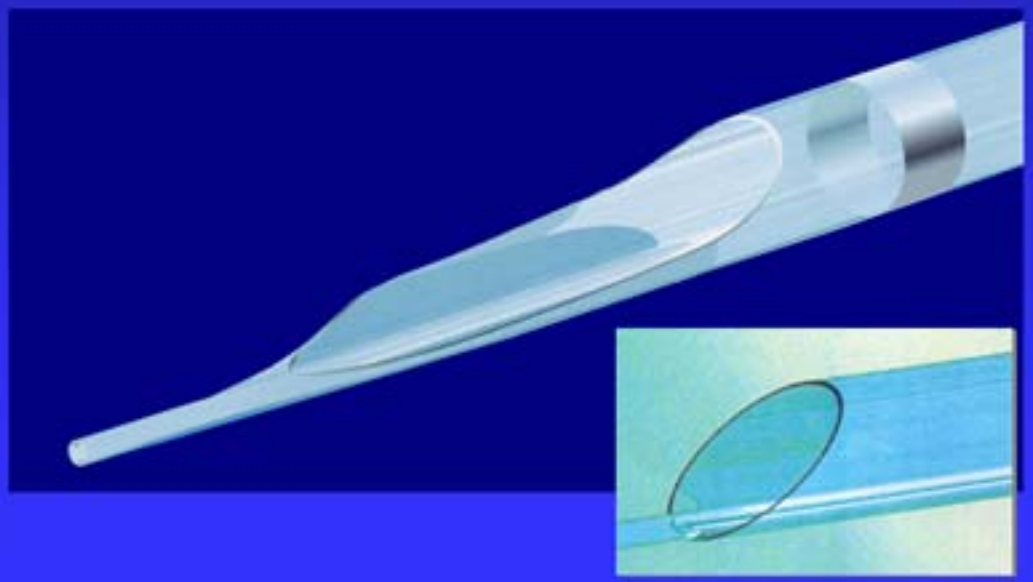
Interim Report of 362 cases

CARDIOCORE

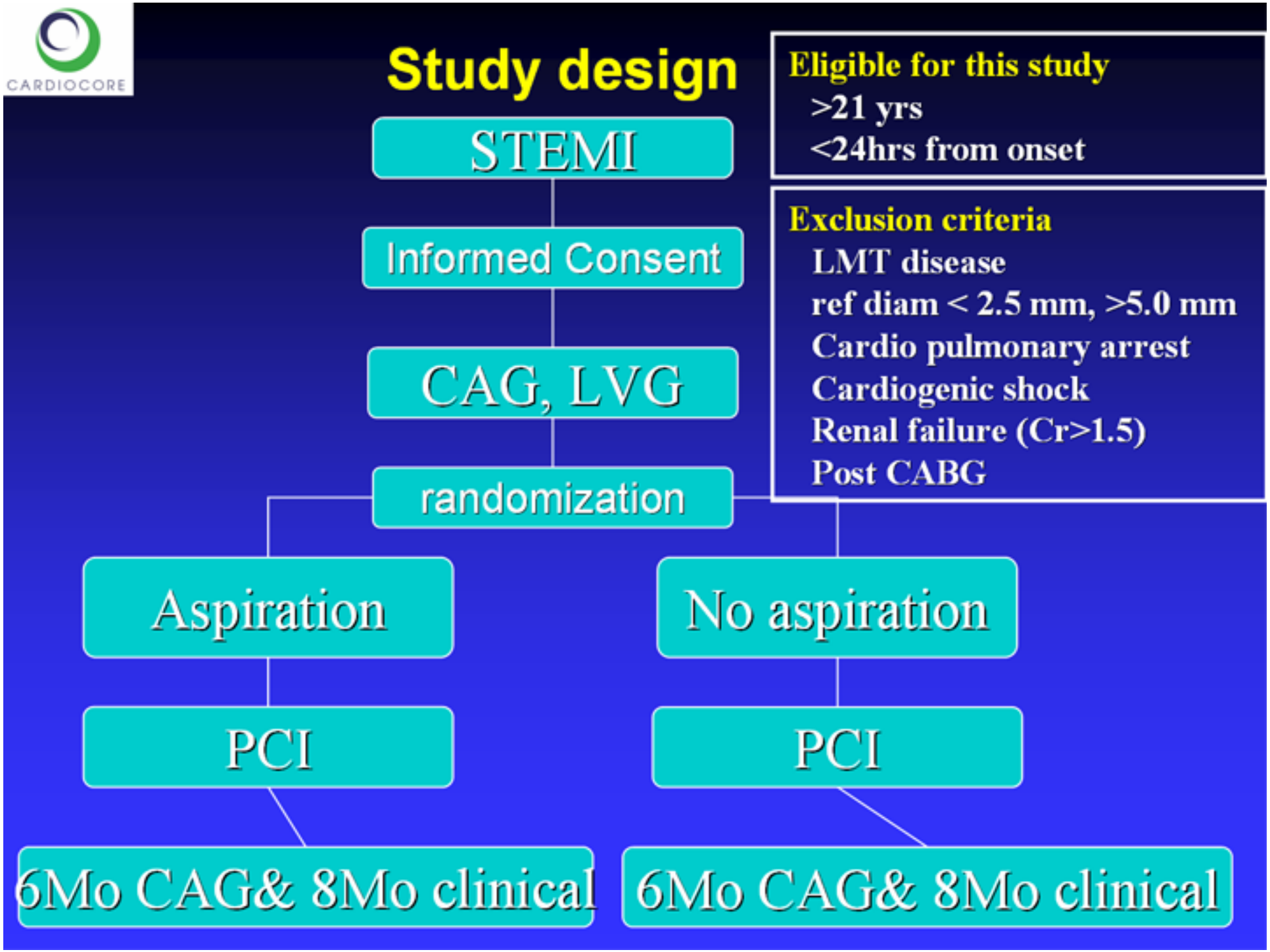
TVAC

(Transluminal Vascular Aspiration Catheter), Nipro, Japan

- Simple tube type aspiration catheter
- Distal tip looks like a beak of duckbill. It has a wider area compared to others.



Sakurada M, Ikari Y and Isshiki T. Catheter Cardiovasc Interv. 2004 Nov;63(3):299-306.


CARDIOCORE
Study design
STEMI
Informed Consent
CAG, LVG
randomization
Aspiration
PCI
6Mo CAG& 8Mo clinical
No aspiration
PCI
6Mo CAG& 8Mo clinical
Eligible for this study
>21 yrs
<24hrs from onset
Exclusion criteria
LMT disease
ref diam < 2.5 mm, >5.0 mm
Cardio pulmonary arrest
Cardiogenic shock
Renal failure (Cr>1.5)
Post CABG

Angiographic results (n=326)

Post-procedural Blush Score

CARDIOCORE

Distal Protection in AMI

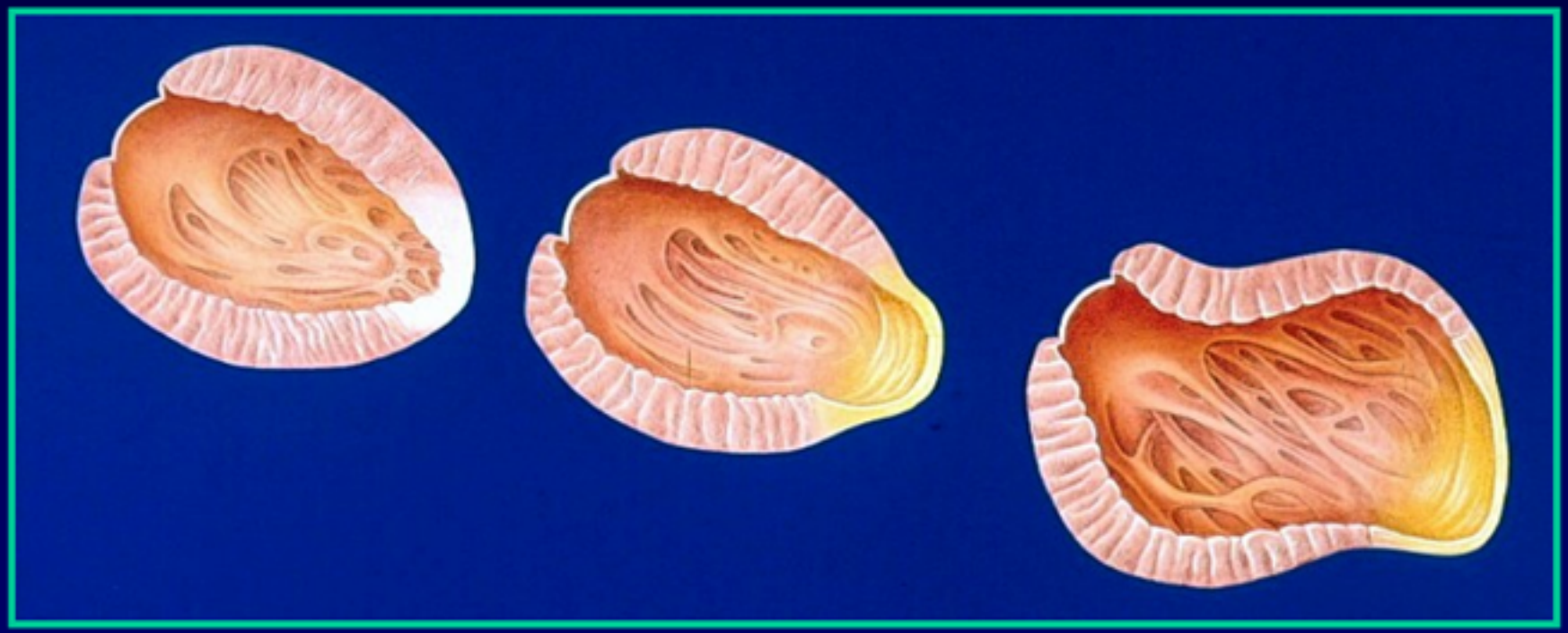
- Despite of failure in EMERALD study, an aspiration tube instead of primary balloon may improve microcirculation.
- Final results of the VAMPIRE study will be shown in autumn this year.

Left Ventricular Remodeling Following Myocardial Infarction

Acute Infarction (hours)

Infarct Expansion (hours to days)

Global Remodeling (days to months)



ACEI is known to prevent remodeling and to improve mortalit

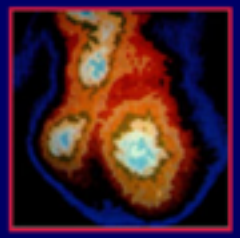
ACE Inhibitor MI Mortality Trials

VALIANT

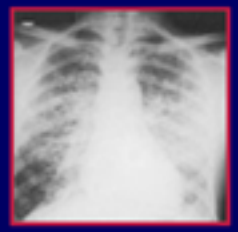
Broad (short term)
CONSENSUS II
GISSI-3
ISIS-4
Chinese-Cap

Selective (higher risk, long term)	
SAVE	(EF $\leq$ 40%)
AIRE	(clinical HF)
SMILE	(anterior MI, no lytic)
TRACE	(wall motion score, EF $\leq$ 35%)

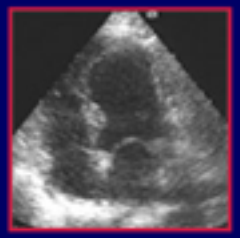
AHA guideline class I : ACE inhibitor for acute myocardial infarction



SAVE
Radionuclide
EF ≤ 40%

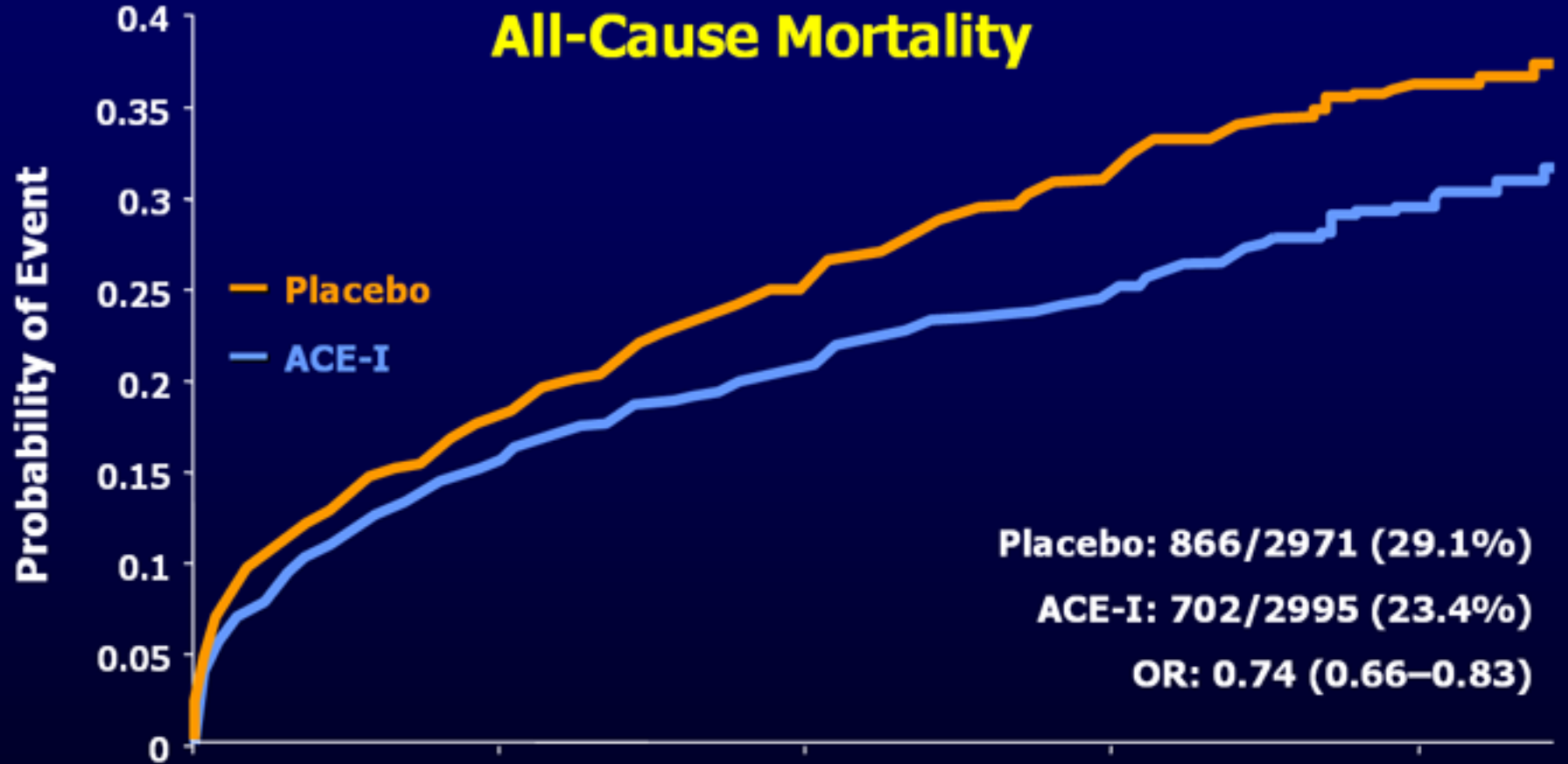


AIRE
Clinical and/or
radiographic
signs of HF



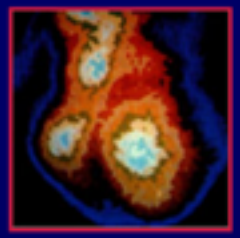
TRACE
Echocardiographic
EF ≤ 35%

All-Cause Mortality

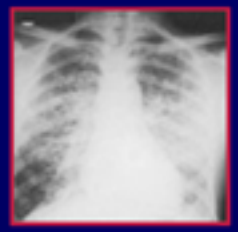


Years	0	1	2	3	4
ACE-I	2995	2250	1617	892	223
Placebo	2971	2184	1521	853	138

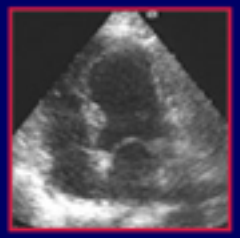
Flather MD, et al. *Lancet*. 2000;355:1575–1581



SAVE
Radionuclide
EF ≤ 40%

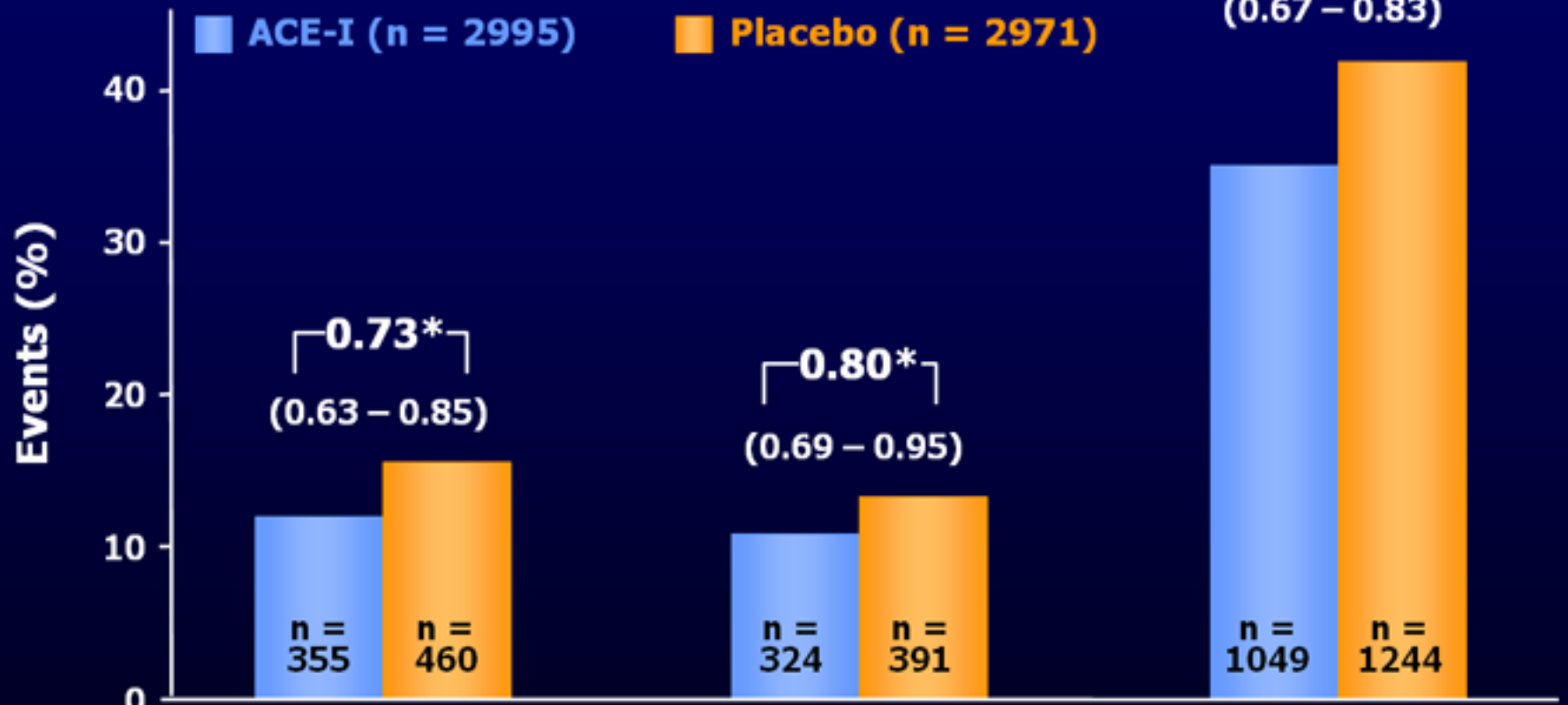


AIRE
Clinical and/or
radiographic
signs of HF



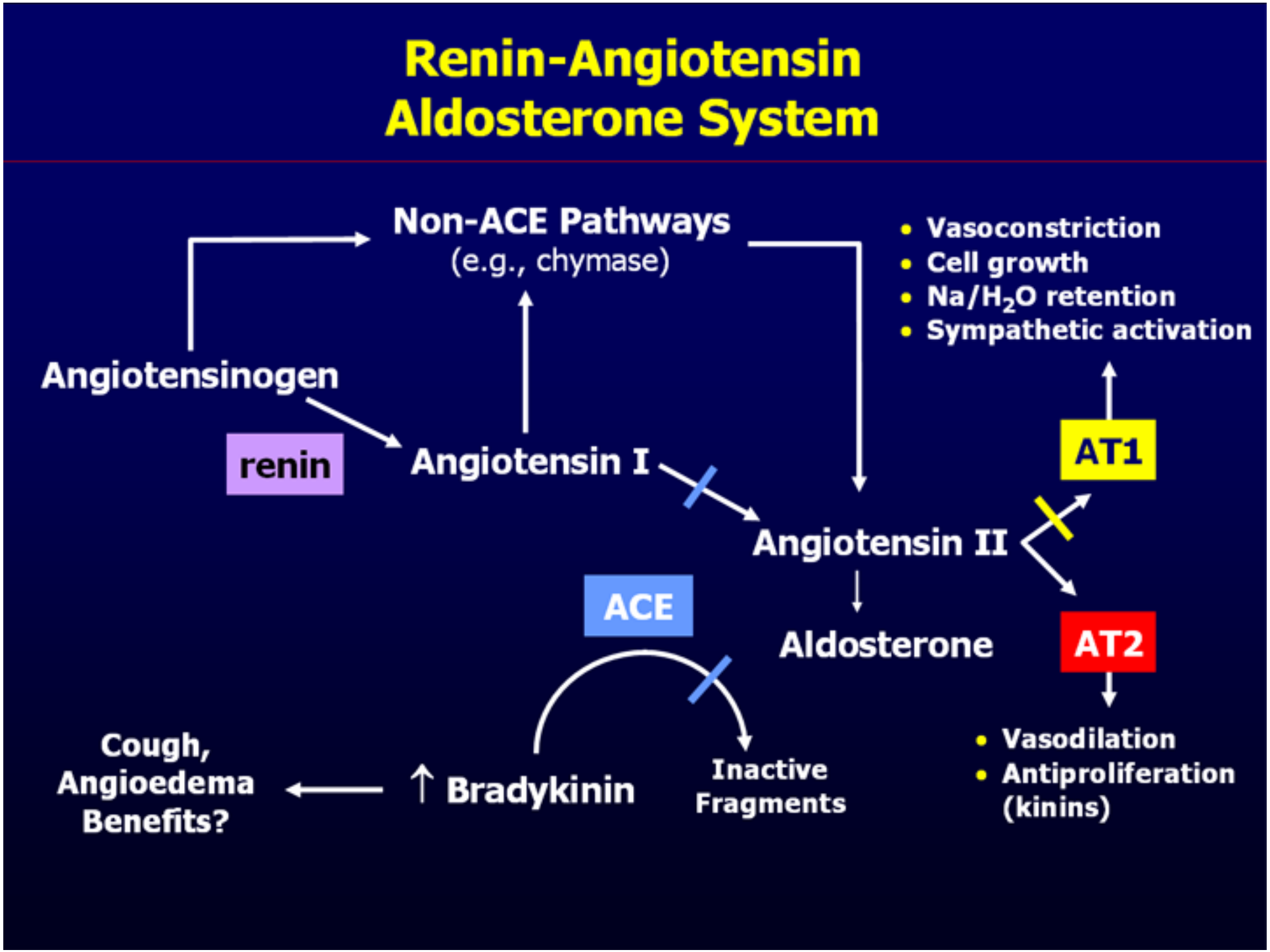
TRACE
Echocardiographic
EF ≤ 35%

Death and Major CV Events



*odds ratio (95% CI)

Flather MD, et al. *Lancet*. 2000;355:1575–1581


Renin-Angiotensin Aldosterone System
Non-ACE Pathways
(e.g., chymase)
Angiotensinogen
renin
Angiotensin I
ACE
Angiotensin II
Aldosterone
AT1
AT2
• Vasoconstriction
• Cell growth
• Na/H2O retention
• Sympathetic activation
• Vasodilation
• Antiproliferation (kinins)
Bradykinin
Inactive Fragments
Cough, Angioedema Benefits?

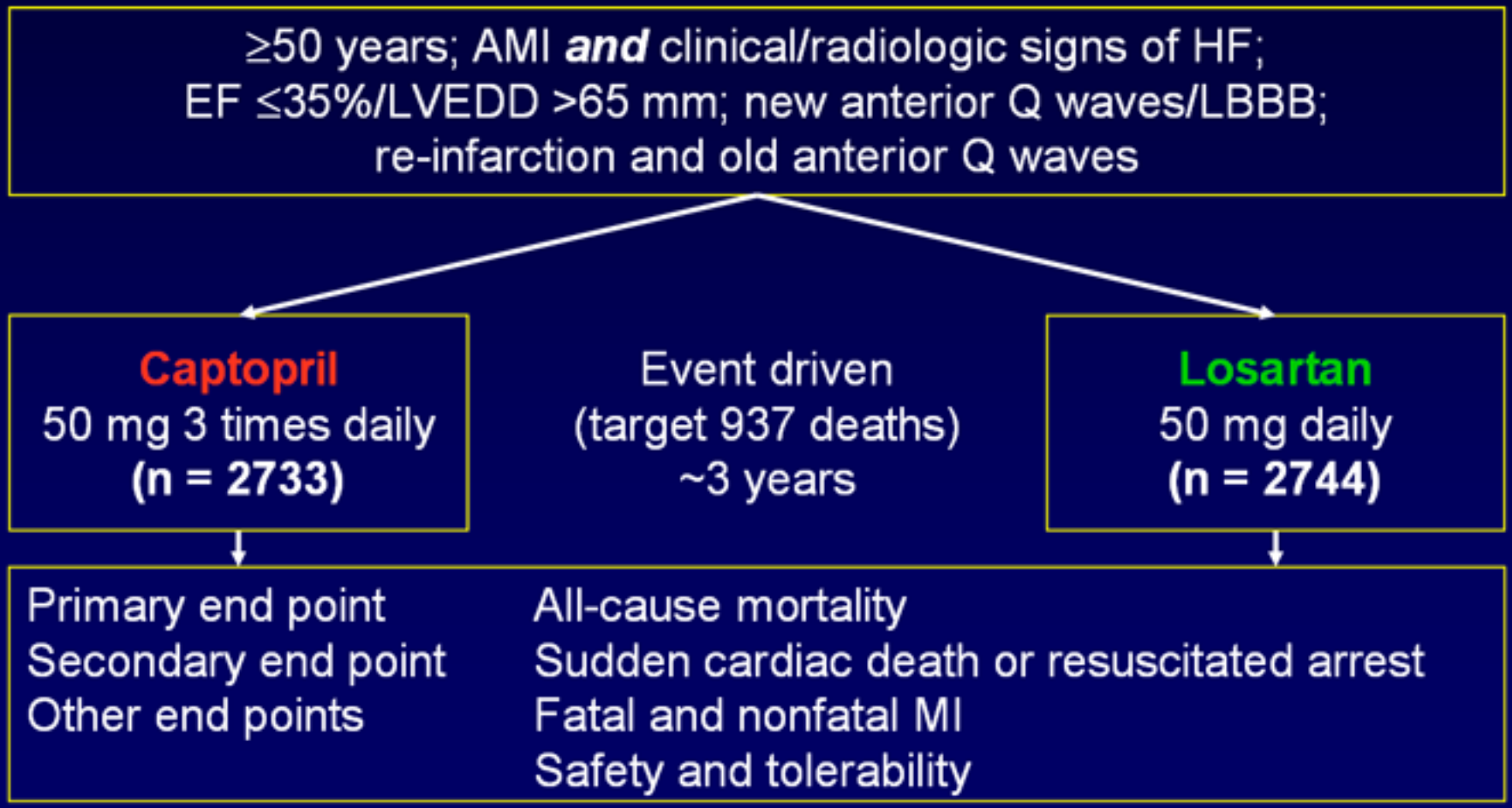
Clinical studies in ARB

VALIANT

	Losartan	Valsartan	Irbesartan	Candesartan	Telmisartan
Hypertension	LIFE* (9193)	VALUE (15,314)	—	SCOPE (4000) TROPHY (1000)	ON-TARGET (23,400) TRANSCEND (5000)
Heart failure	ELITE Ⅱ * (3152)	Val-HeFT* (5010)	I-PRESERVE (3000)	CHARM * (7000)	—
MI	OPTIMAAL* (5000)	VALIANT (14,500)	—	—	—
Type 2 DM	RENAAL* (1513)	ABCD-2V (620)	IDNT* (1715) IRMA Ⅱ * (590)	—	—
Glucose intolerance	—	NAVIGATOR (7500)	—	—	—
Total number	18,858	43,000	5300	12,000	28,400

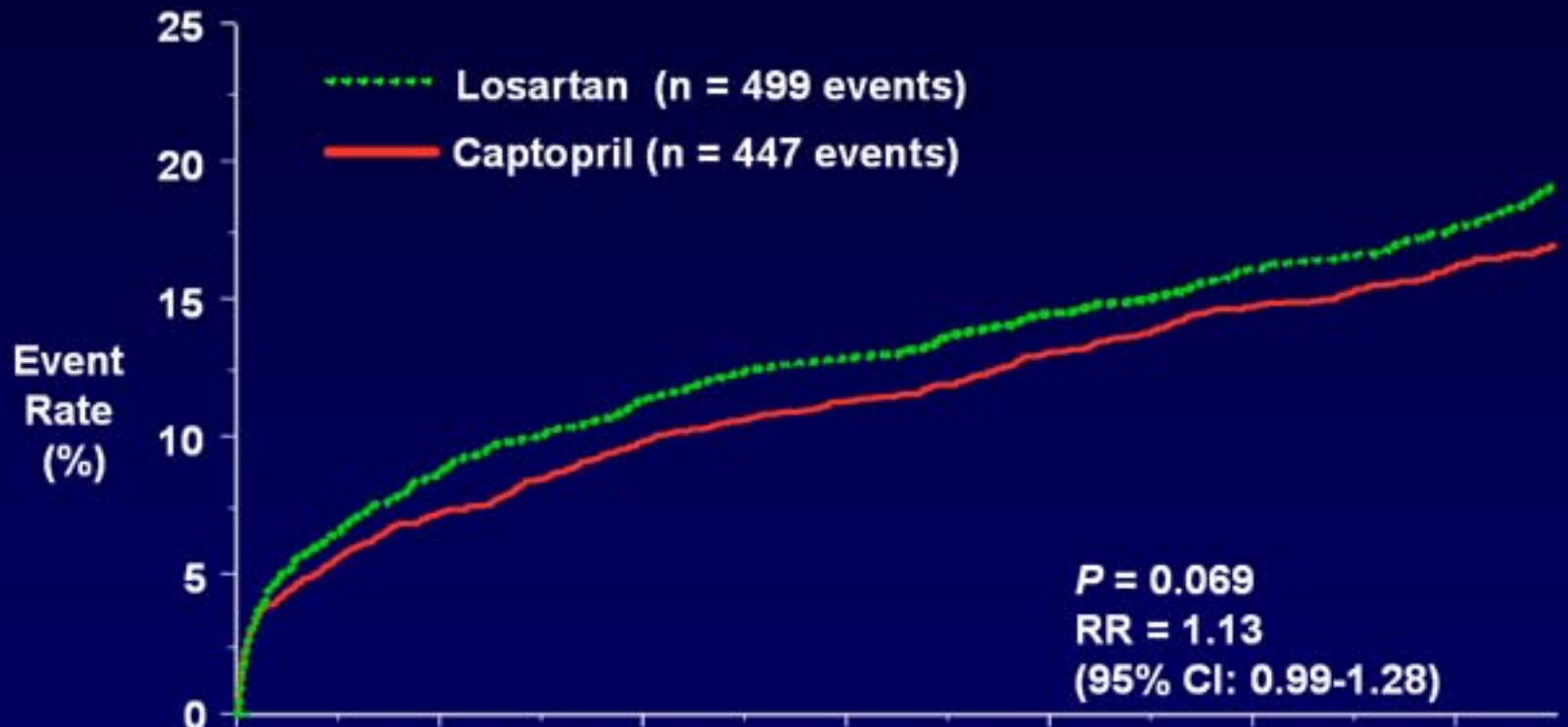
OPTIMAAL Study Design

Captopril vs Losartan After Acute MI



Dickstein K et al. *Lancet*. 2002;360:752-760.

OPTIMAAL: All-Cause Mortality



Losartan (n)	2744	2504	2432	2390	2344	2301	1285
Captopril (n)	2733	2534	2463	2423	2374	2329	1309

Dickstein K et al. *Lancet*. 2002;360:752-760.

VALIANT

VALsartan In Acute myocardial iNfarcTion

Marc A. Pfeffer, M.D., Ph.D. (Chair), John J.V. McMurray, M.D. (Co-Chair), Eric J. Velazquez, M.D., Jean-Lucien Rouleau, M.D., Lars Køber, M.D., Aldo P. Maggioni, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., Frans Van de Werf, M.D., Ph.D., Harvey D. White, D.Sc., Jeffrey D. Leimberger, Ph.D., Marc Henis, M.D., Susan Edwards, M.S., Steven Zelenkofske, D.O., Mary Ann Sellers, M.S.N., and Robert M. Califf, M.D., for the VALIANT Investigators

Other Steering Committee Members:
P. Aylward, P. Armstrong, S. Barvik, Y. Belenkov, A. Dalby, R. Diaz, H. Drexler, G. Ertl, G. Francis, J. Hampton, A. Harsanyi, J. Kvasnicka, V. Mareev, J. Marin-Neto, J. Murin, M. Myers, R. Nordlander, G. Opolski, J. Soler-Soler, J. Spac, T. Stefenelli, D. Sugrue, W. Van Gilst, S. Varshavsky, D. Weaver, F. Zannad.

Dr. Pfeffer is named as a coinventor on a patent awarded to the Brigham and Women's Hospital regarding the use of inhibitors of the renin-angiotensin system in selected survivors of myocardial infarction; there is a licensing agreement between Novartis Pharmaceuticals and the Brigham and Women's Hospital, which is not linked to sales.

Supported by a grant from Novartis Pharmaceuticals

Aims

VALIANT

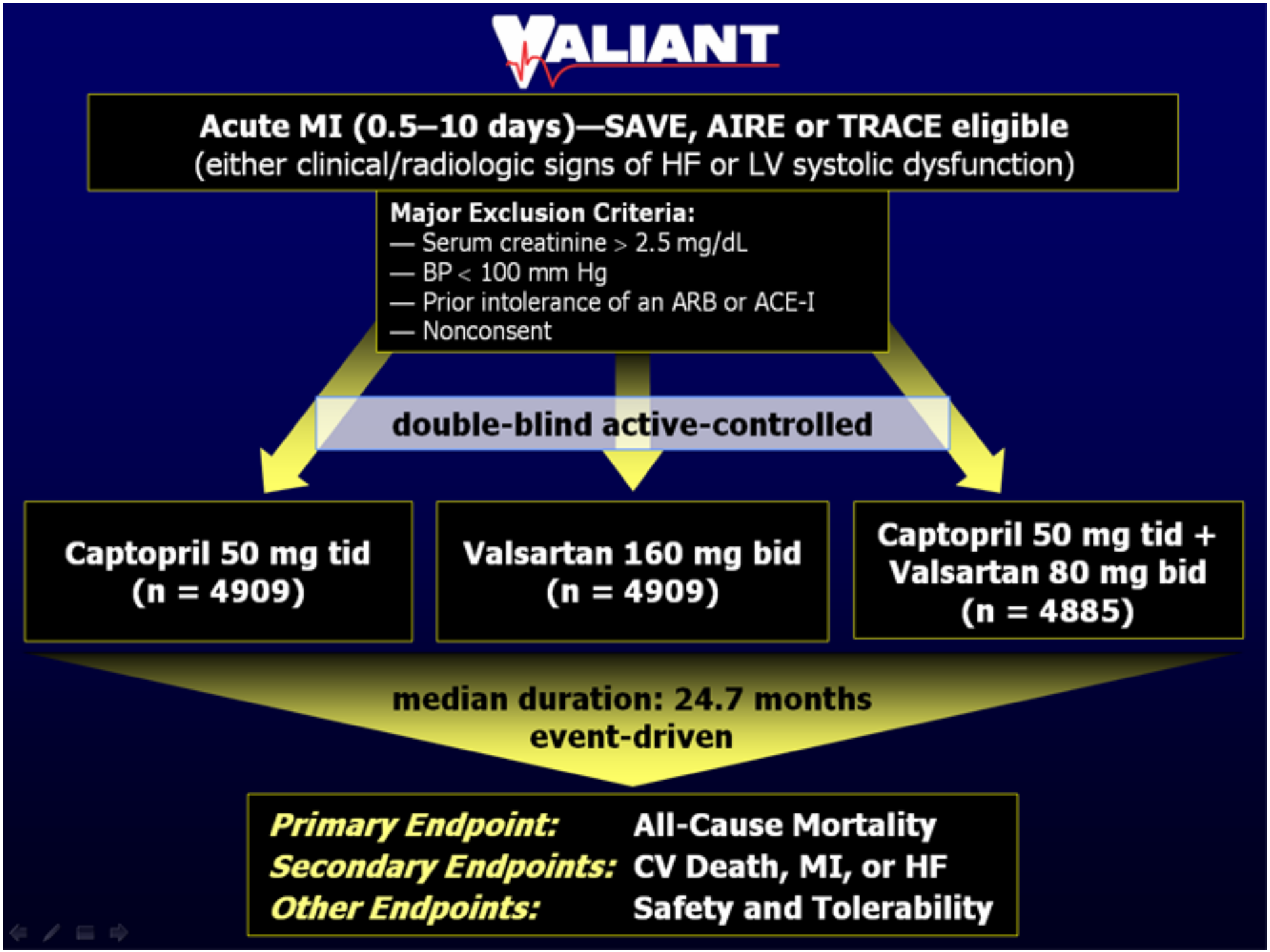
VALIANT was designed as a mortality trial in high-risk MI patients (SAVE, AIRE, TRACE) who derived particular benefits from an ACE inhibitor.

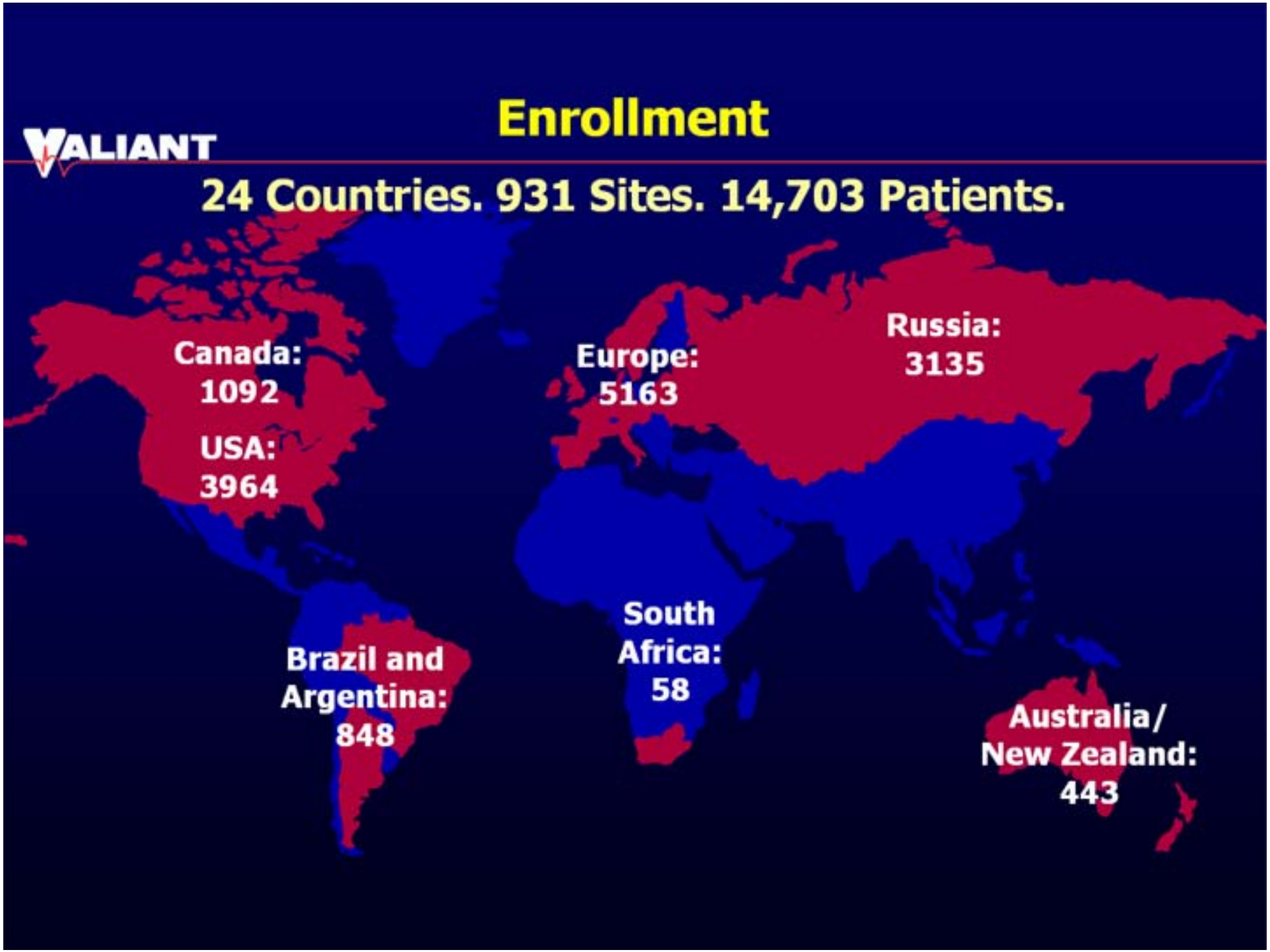
To determine whether:

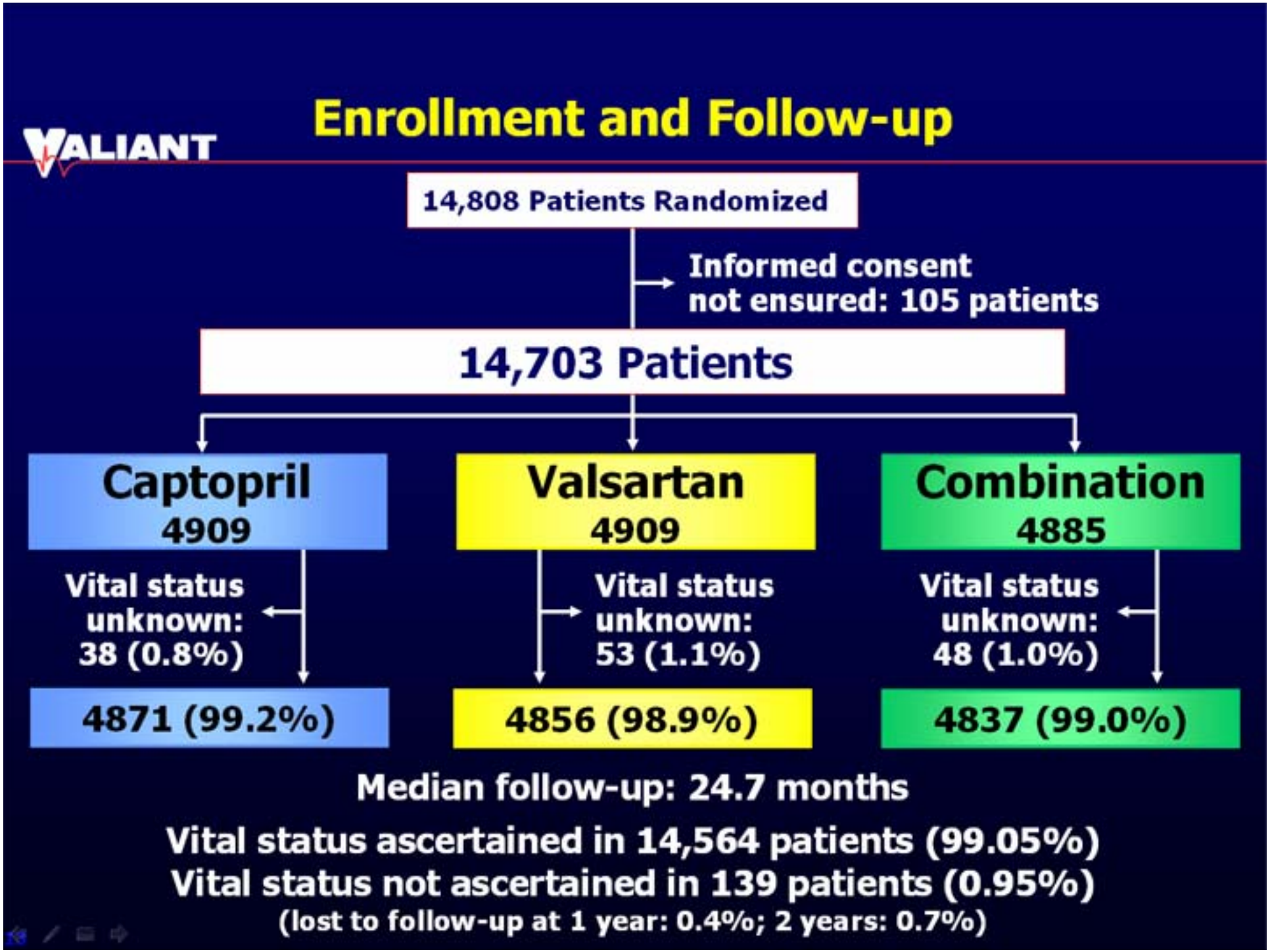
- **the ARB valsartan was superior to captopril in improving survival**

and with equal statistical power

- **the addition of the ARB valsartan to captopril was superior to the proven dose of captopril in improving survival**
- **If valsartan was not superior to captopril, a non-inferiority analysis was prespecified to determine whether valsartan could be considered "as effective as" captopril**


VALIANT
Acute MI (0.5–10 days)—SAVE, AIRE or TRACE eligible
(either clinical/radiologic signs of HF or LV systolic dysfunction)
Major Exclusion Criteria:
— Serum creatinine > 2.5 mg/dL
— BP < 100 mm Hg
— Prior intolerance of an ARB or ACE-I
— Nonconsent
double-blind active-controlled
Captopril 50 mg tid (n = 4909)
Valsartan 160 mg bid (n = 4909)
Captopril 50 mg tid + Valsartan 80 mg bid (n = 4885)
median duration: 24.7 months
event-driven
Primary Endpoint: All-Cause Mortality
Secondary Endpoints: CV Death, MI, or HF
Other Endpoints: Safety and Tolerability


VALIANT
Enrollment
24 Countries. 931 Sites. 14,703 Patients.
Canada:
1092
USA:
3964
Europe:
5163
Russia:
3135
Brazil and
Argentina:
848
South
Africa:
58
Australia/
New Zealand:
443


VALIANT
Enrollment and Follow-up
14,808 Patients Randomized
Informed consent not ensured: 105 patients
14,703 Patients
Captopril 4909
Valsartan 4909
Combination 4885
Vital status unknown: 38 (0.8%)
Vital status unknown: 53 (1.1%)
Vital status unknown: 48 (1.0%)
4871 (99.2%)
4856 (98.9%)
4837 (99.0%)
Median follow-up: 24.7 months
Vital status ascertained in 14,564 patients (99.05%)
Vital status not ascertained in 139 patients (0.95%)
(lost to follow-up at 1 year: 0.4%; 2 years: 0.7%)

Baseline Characteristics

VALIANT

Mean age (years)		64.8
Women (%)		31.1
Mean BP (mm Hg)		123/72
Killip class (%)	I	28.0
	II	48.3
	III	17.3
	IV	6.4
Mean LVEF* (%)		35.3
Creatinine		1.1 mg/dL 98 μ mol/L
Time to randomization (d)		4.9

Thrombolytic therapy (%)	35.2
Primary PCI (%)	14.8
Other PCI after MI, prior to randomization (%)	19.8
Qualifying MI site (%)	
Anterior	59.4
Inferior	34.4
Qualifying MI type (%)	
Q wave	66.6
Non Q wave	31.9

*data on LVEF were available for 11,338 patients

Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349:1893–1906

Baseline Characteristics

VALIANT

Medical History (%):	
Diabetes mellitus	23.1
Hypertension	55.2
Smoking	31.7
Prior:	
Myocardial infarction	27.9
Heart failure	14.8
Stroke	6.1
CABG	7.0
PCI	7.3

Baseline Medications (%):	
ACE inhibitor*	39.6
ARB*	1.2
Beta-blocker	70.4
Aspirin	91.3
Other antiplatelet	24.8
Potassium-sparing diuretic	9.0
Other diuretic	50.3
Statin	34.1

*stopped prior to randomization

Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349:1893–1906

Baseline Characteristics

VALIANT

Characteristic	Valsartan (n = 4909)	Valsartan + Captopril (n = 4885)	Captopril (n = 4909)
Age (yr)	65.0 ± 11.8	64.6 ± 11.9	64.9 ± 11.8
Race			
Caucasian	4604 (93.8%)	4553 (93.2%)	4591 (93.5%)
Black	125 (2.5%)	137 (2.8%)	145 (3.0%)
Asian	44 (0.9%)	53 (1.1%)	44 (0.9%)
Other	136 (2.8%)	142 (2.9%)	129 (2.6%)
Females	1544 (31.5%)	1490 (30.5%)	1536 (31.3%)
Blood pressure (mm Hg)			
Systolic	122.7 ± 16.8	122.5 ± 17.1	122.8 ± 17.0
Diastolic	72.3 ± 11.3	72.3 ± 11.4	72.4 ± 11.2
Heart rate (beats/min)	76.2 ± 13.0	76.2 ± 12.7	76.2 ± 12.8

Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349:1893–1906

Baseline Characteristics

VALIANT

Characteristic	Valsartan (n = 4909)	Valsartan + Captopril (n = 4885)	Captopril (n = 4909)
BMI (kg/m^2) (median) (25th, 75th percentile)	**27.34 (24.69, 30.47)**	**27.24 (24.62, 30.35)**	**27.14 (24.54, 30.22)**
LVEF* (%)	**35.3 ± 10.4**	**35.3 ± 10.3**	**35.3 ± 10.4**
Killip class			
I	**1294 (26.5%)**	**1381 (28.4%)**	**1424 (29.1%)**
II	**2401 (49.2%)**	**2329 (47.9%)**	**2346 (48.0%)**
III	**874 (17.9%)**	**842 (17.3%)**	**813 (16.6%)**
IV	**313 (6.4%)**	**312 (6.4%)**	**306 (6.3%)**
Days from MI to randomization	**4.8**	**4.9**	**4.9**
Serum creatinine (mg/dL)	**1.1 ± 0.3**	**1.1 ± 0.3**	**1.1 ± 0.4**

*measured in 11,338 (77.1%) of the patients

Baseline Characteristics

VALIANT

Characteristic	Valsartan n = 4909	Combination n = 4885	Captopril n = 4909
Qualifying MI site (%)			
Anterior	58.7	60.3	59.3
Inferior	34.1	34.4	34.7
Qualifying MI type (%)			
Q wave	65.8	66.4	67.5
Non Q wave	32.5	32.2	31.1
Thrombolytic therapy (%)	35.5	35.0	35.0
Primary PCI (%)	14.9	14.9	14.6
Other PCI after MI, prior to randomization (%)	20.6	19.4	19.5

Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349:1893–1906

Medical History

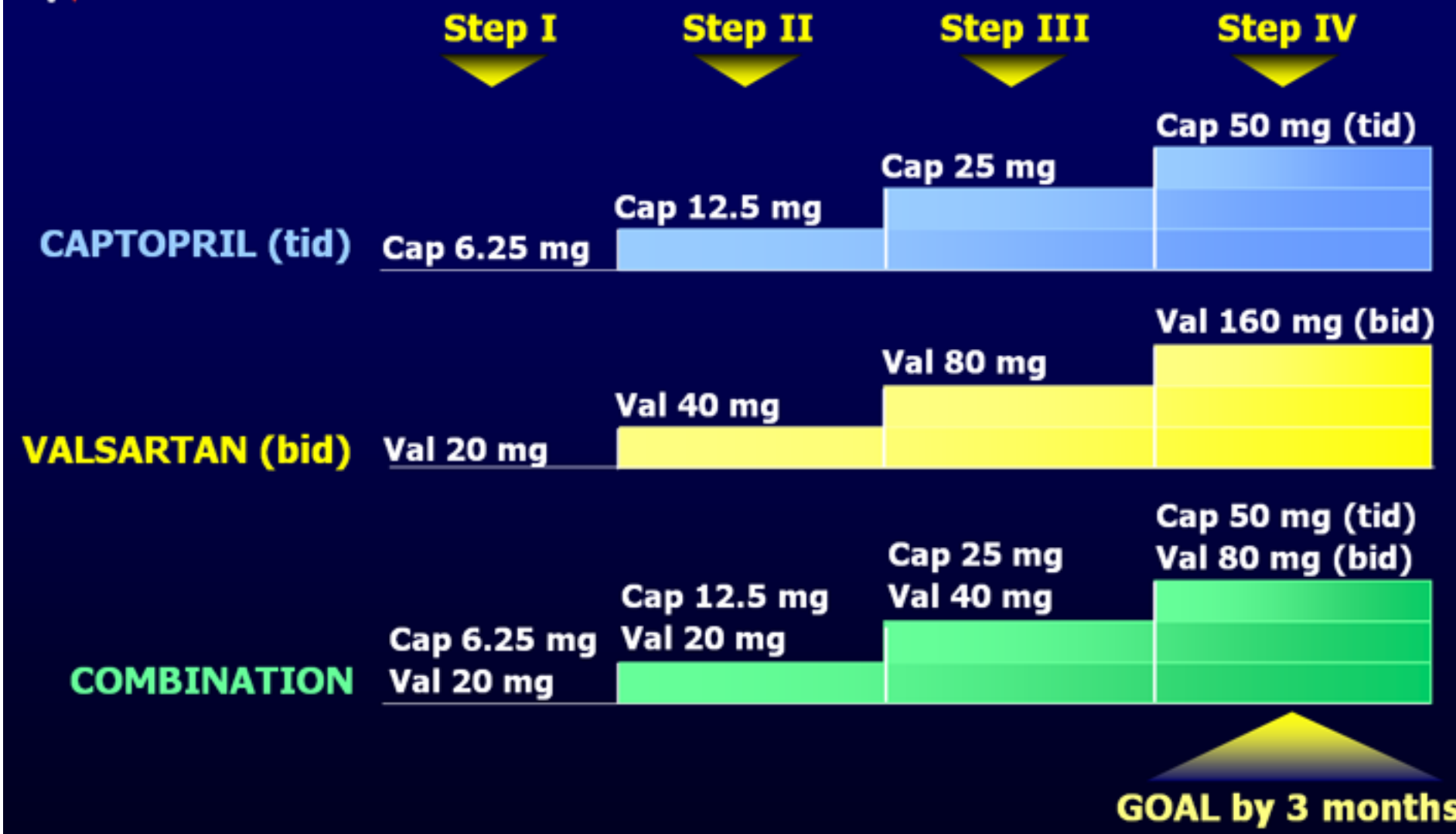
VALIANT

History of…	Valsartan (n = 4909)	Valsartan + Captopril (n = 4885)	Captopril (n = 4909)
MI	1395 (28.4%)	1376 (28.2%)	1333 (27.2%)
Hypertension	2732 (55.7%)	2700 (55.3%)	2690 (54.8%)
Diabetes mellitus	1134 (23.1%)	1146 (23.5%)	1120 (22.8%)
Heart failure	759 (15.5%)	701 (14.4%)	714 (14.5%)
Stroke	292 (5.9%)	305 (6.2%)	298 (6.1%)
Smoking	1556 (31.7%)	1546 (31.7%)	1562 (31.9%)
Prior CABG	355 (7.2%)	327 (6.7%)	344 (7.0%)
Prior PCI	376 (7.7%)	337 (6.9%)	354 (7.2%)

Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349:1893–1906

Study Drug Dose Titration

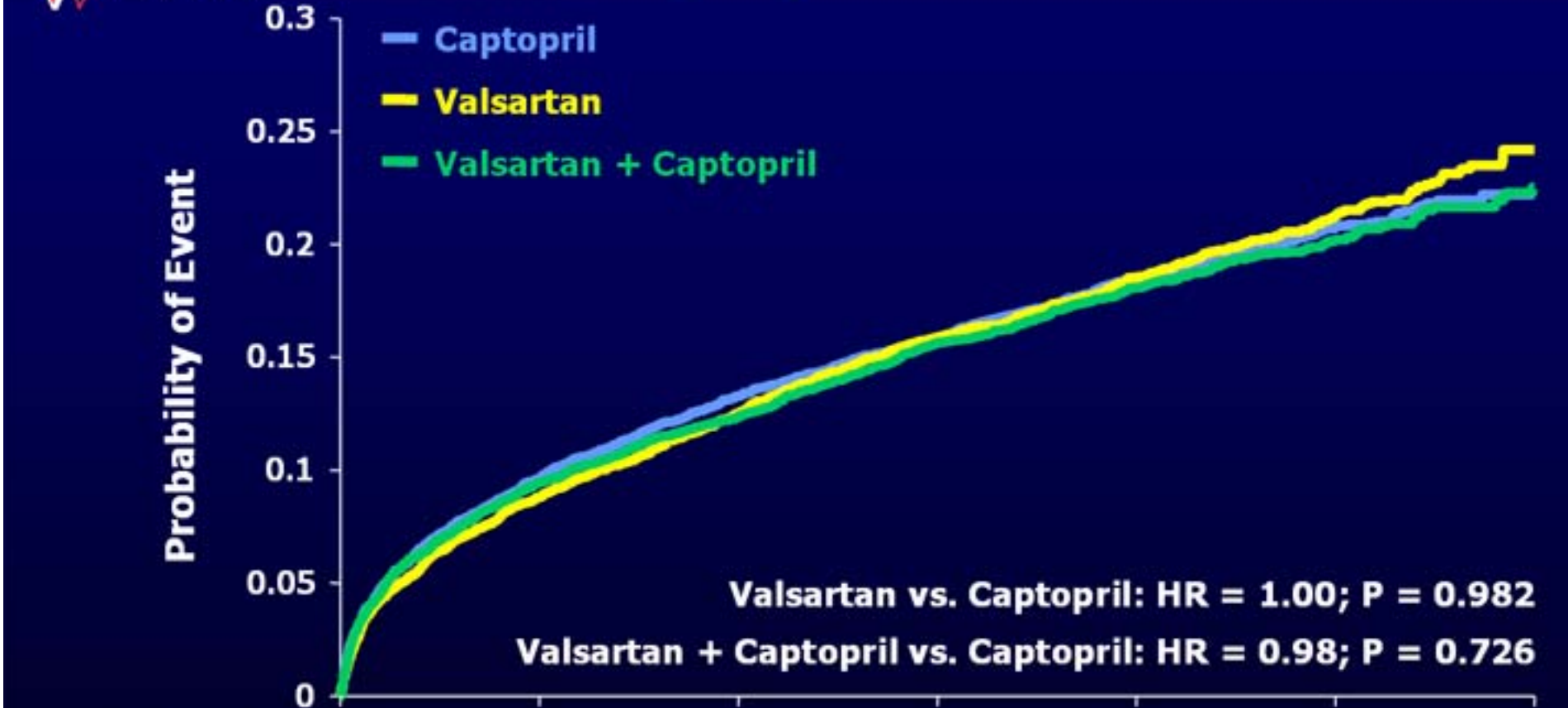
VALIANT



Am Heart J. 2000;140:727–734.

Mortality by Treatment

VALIANT

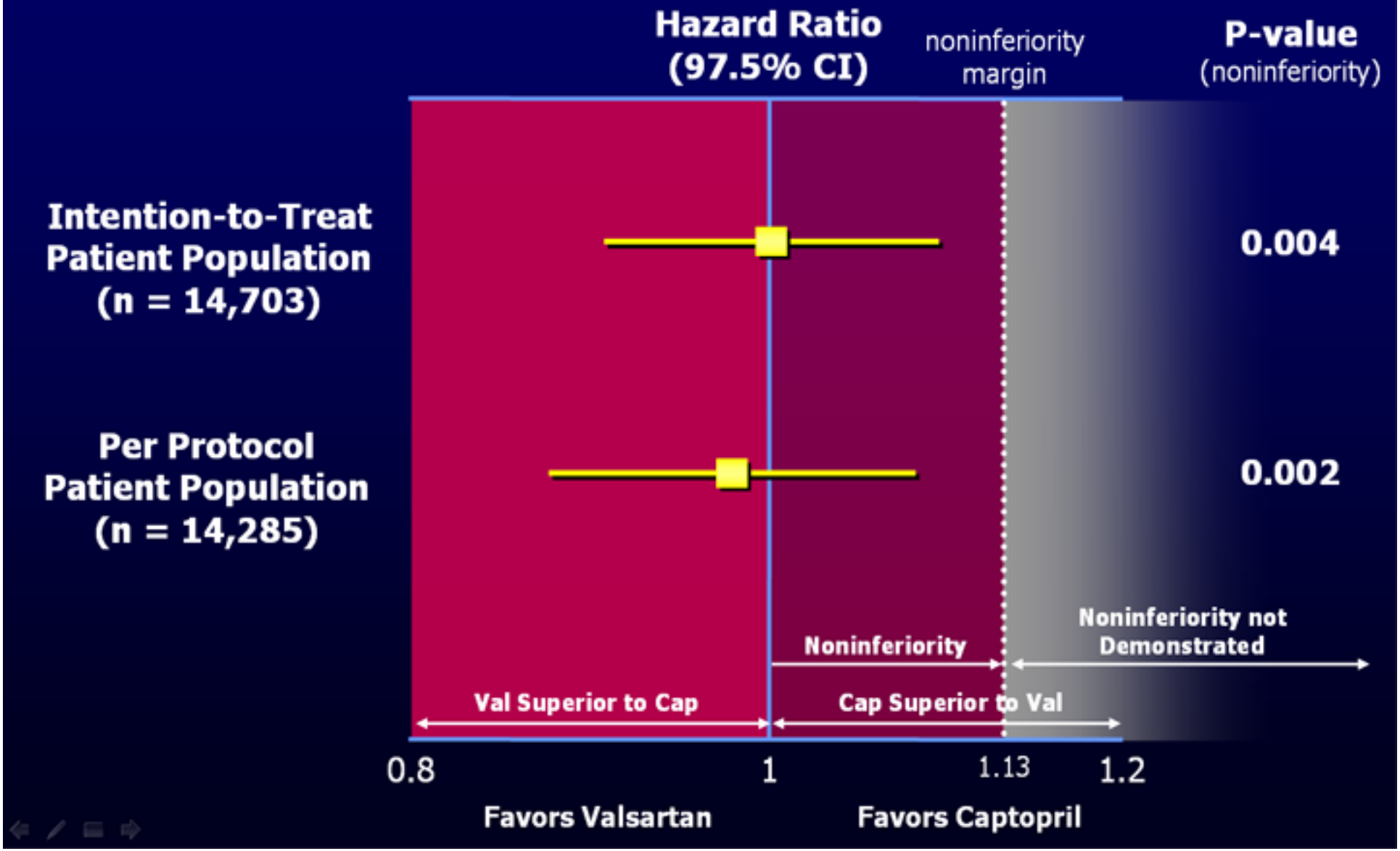


Months	0	6	12	18	24	30	36
Captopril	4909	4428	4241	4018	2635	1432	364
Valsartan	4909	4464	4272	4007	2648	1437	357
Valsartan + Cap	4885	4414	4265	3994	2648	1435	382

Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349

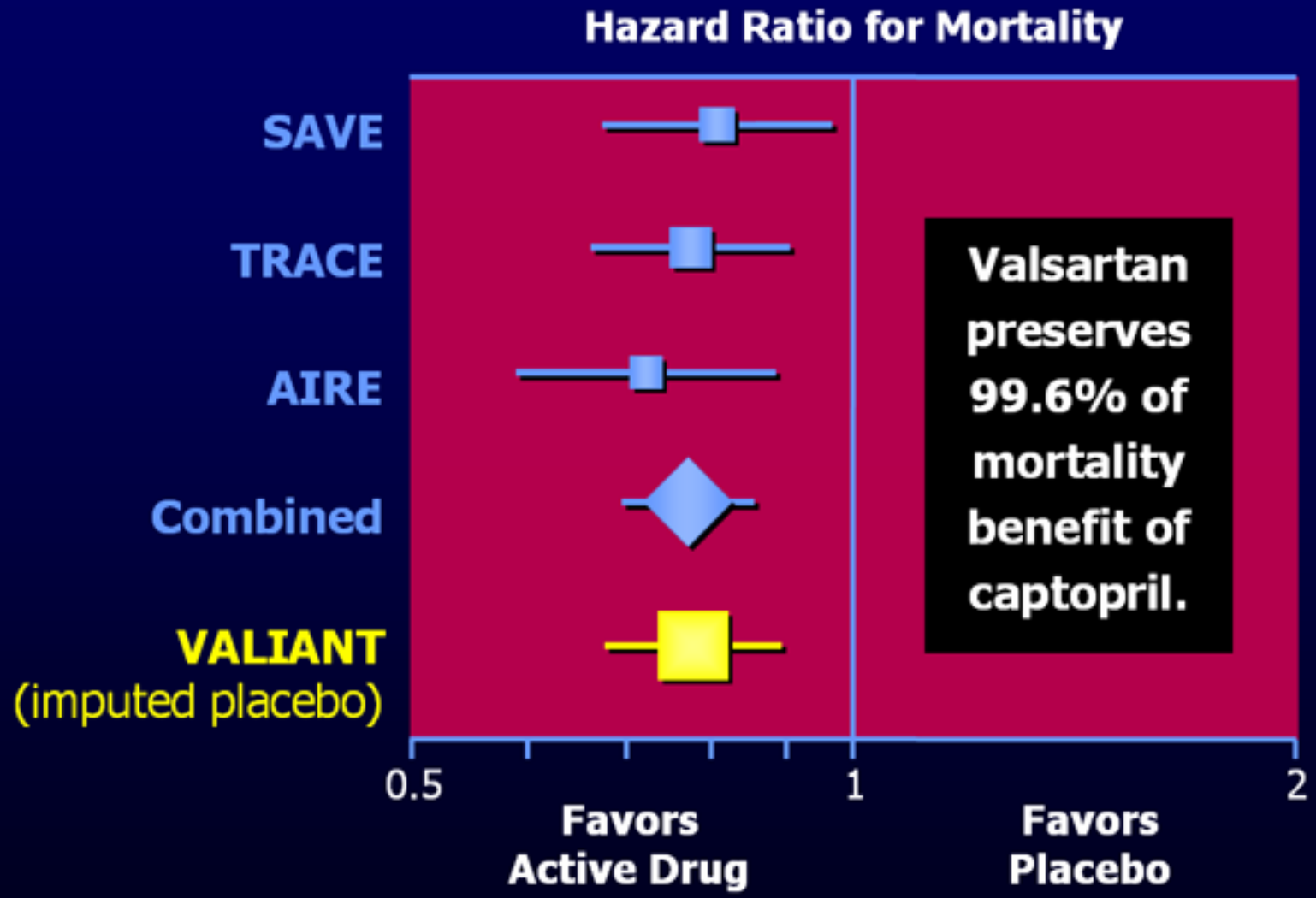
All-Cause Mortality: Non-Inferiority Analyses

VALIANT



Mortality in SAVE, TRACE, AIRE, and VALIANT

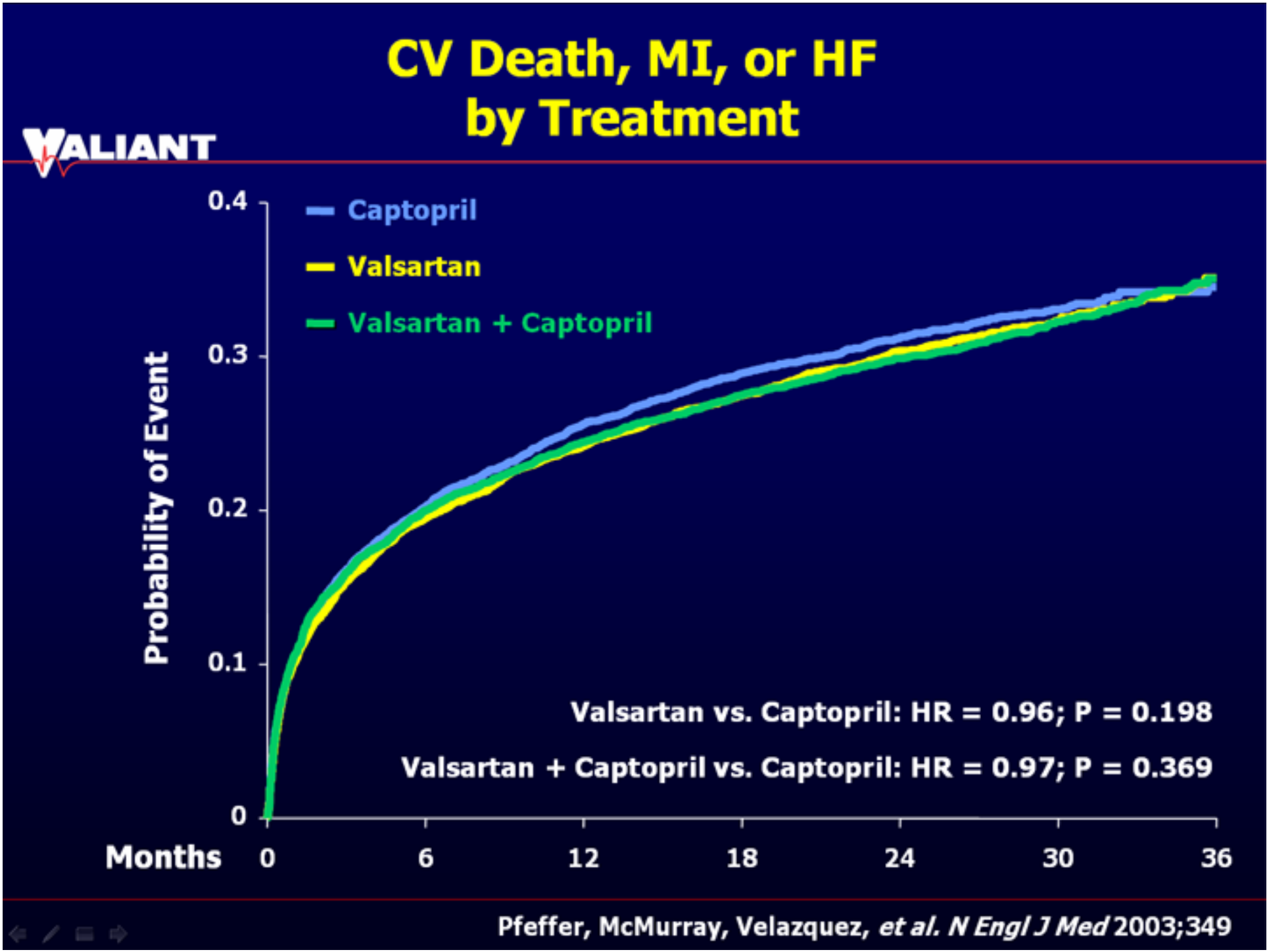
VALIANT



Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349

CV Death, MI, or HF by Treatment

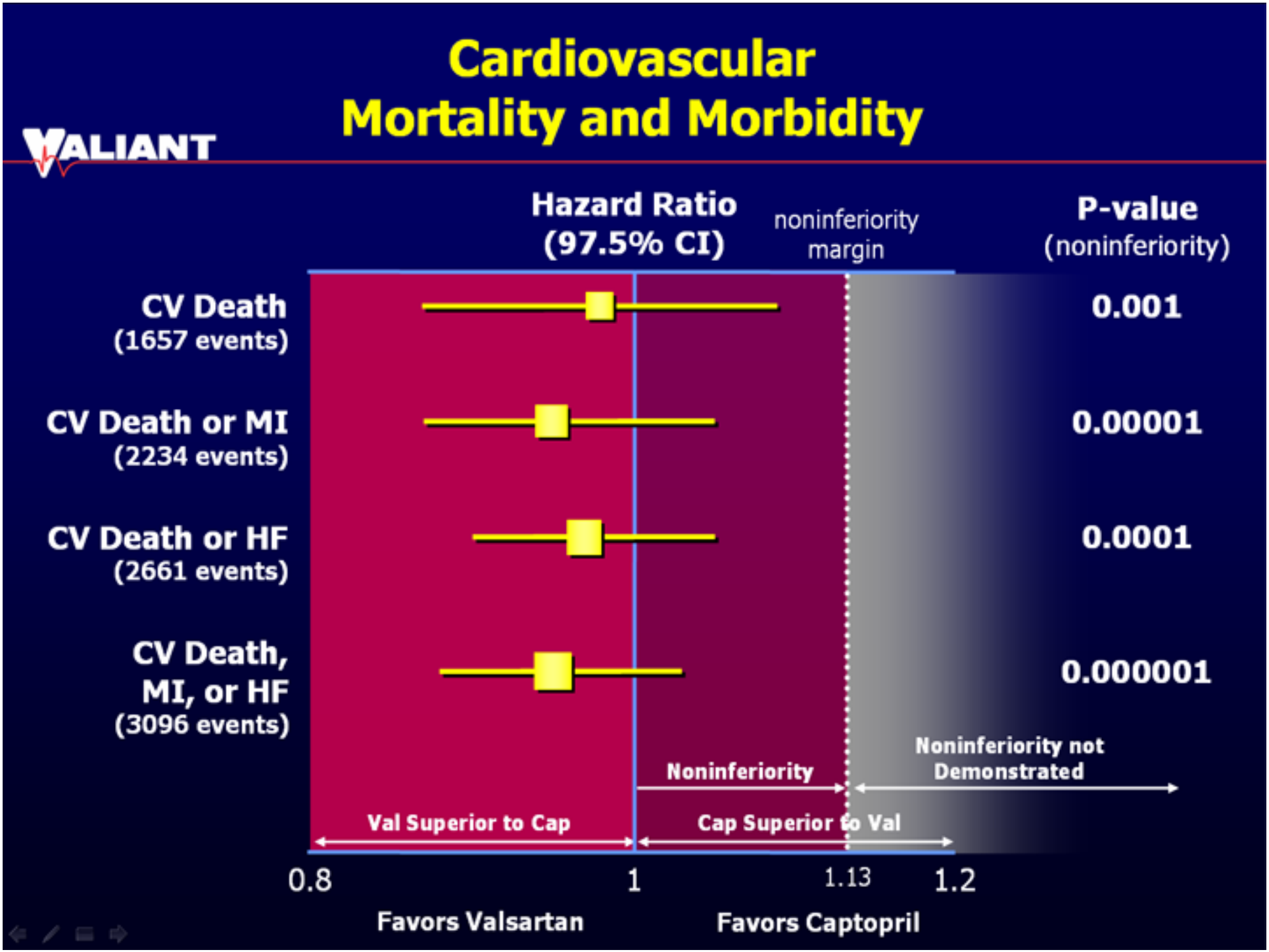
VALIANT



Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349

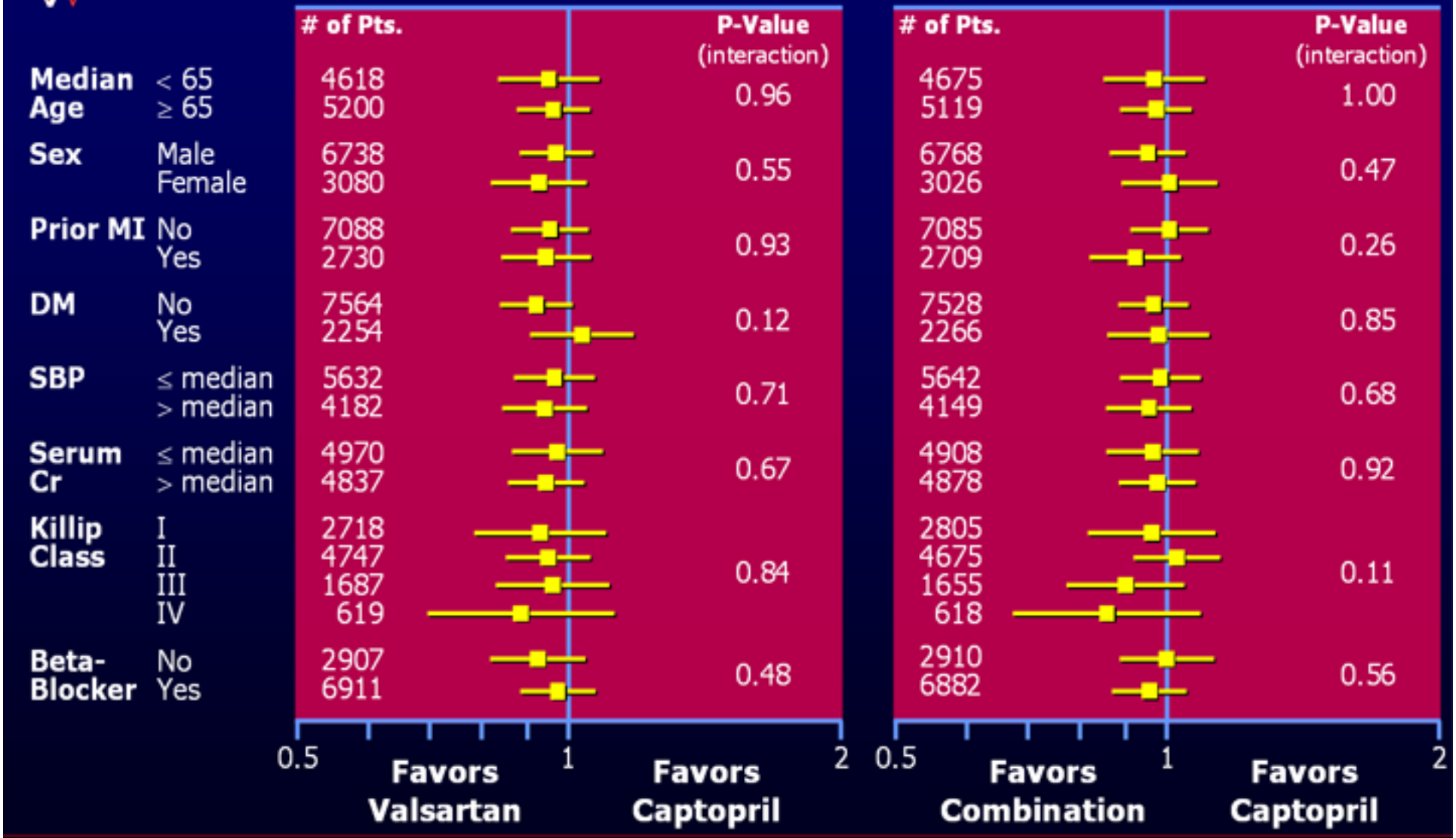
Cardiovascular Mortality and Morbidity

VALIANT



Hazard Ratios (95% CI) for CV Death, MI, or HF

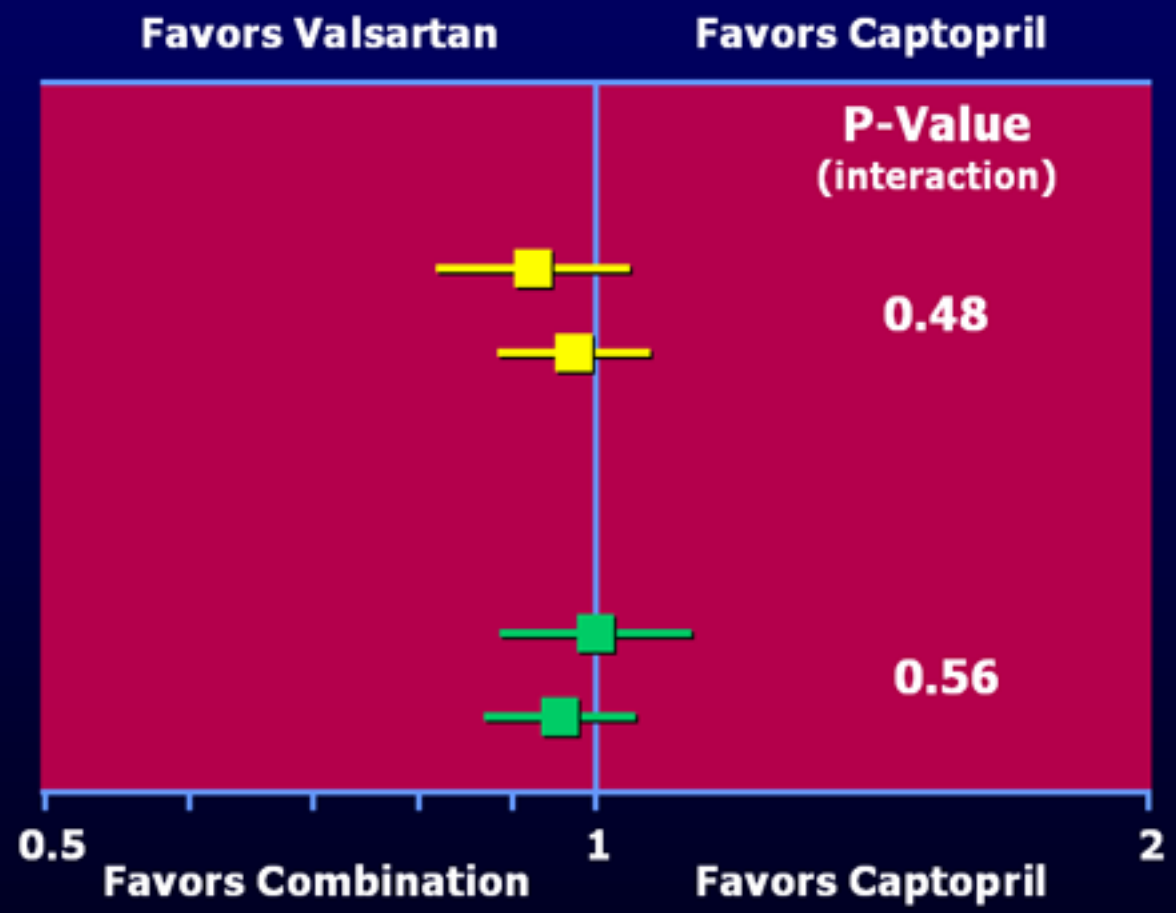
VALIANT



Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349:1893–1906

Hazard Ratios (95% CI) for CV Death, MI, or HF

VALIANT



Valsartan vs. Captopril:

No Beta-Blocker (n = 2907)

Beta-Blocker (n = 6911)

Combination vs. Captopril:

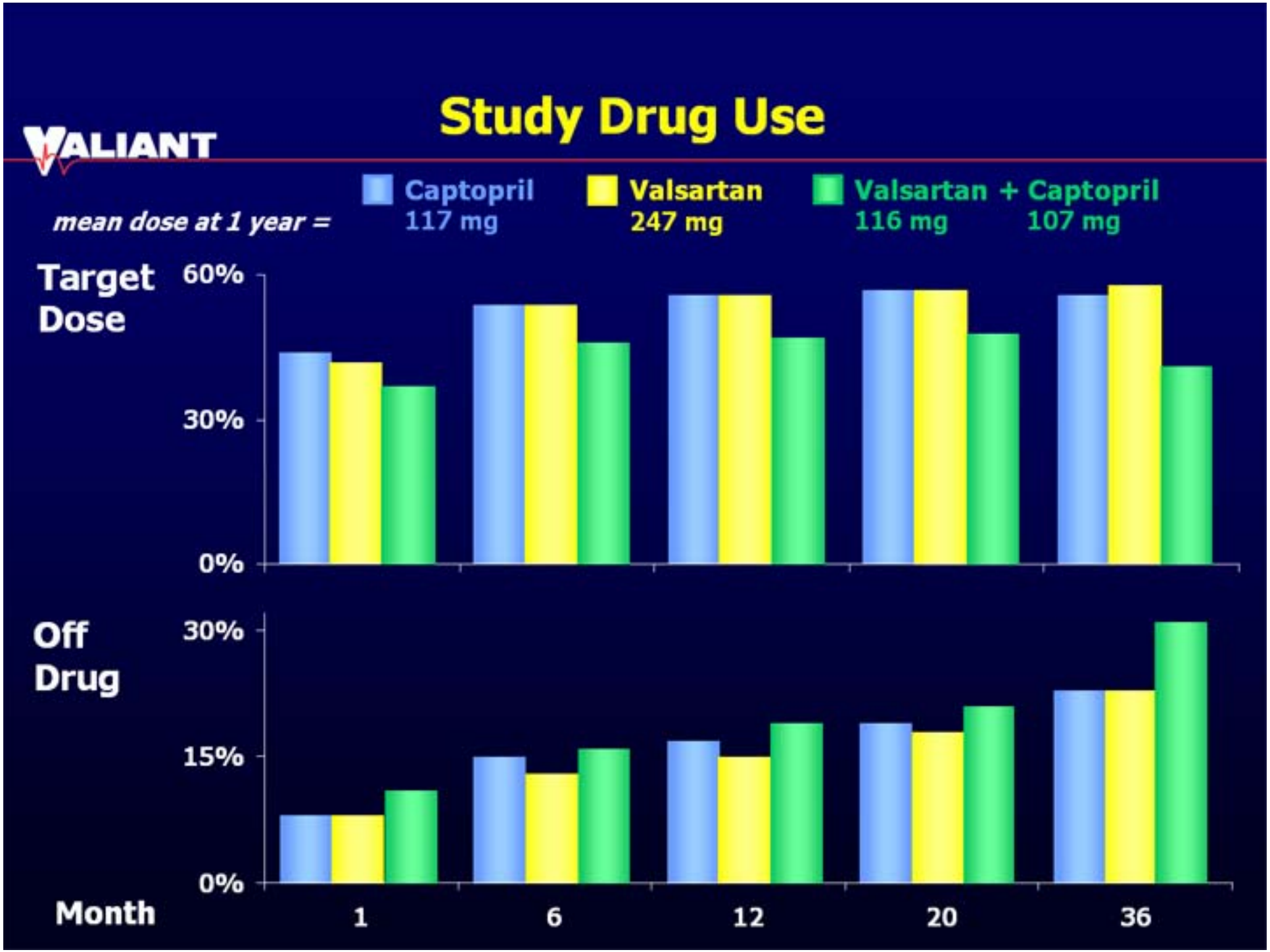
No Beta-Blocker (n = 2910)

Beta-Blocker (n = 6882)

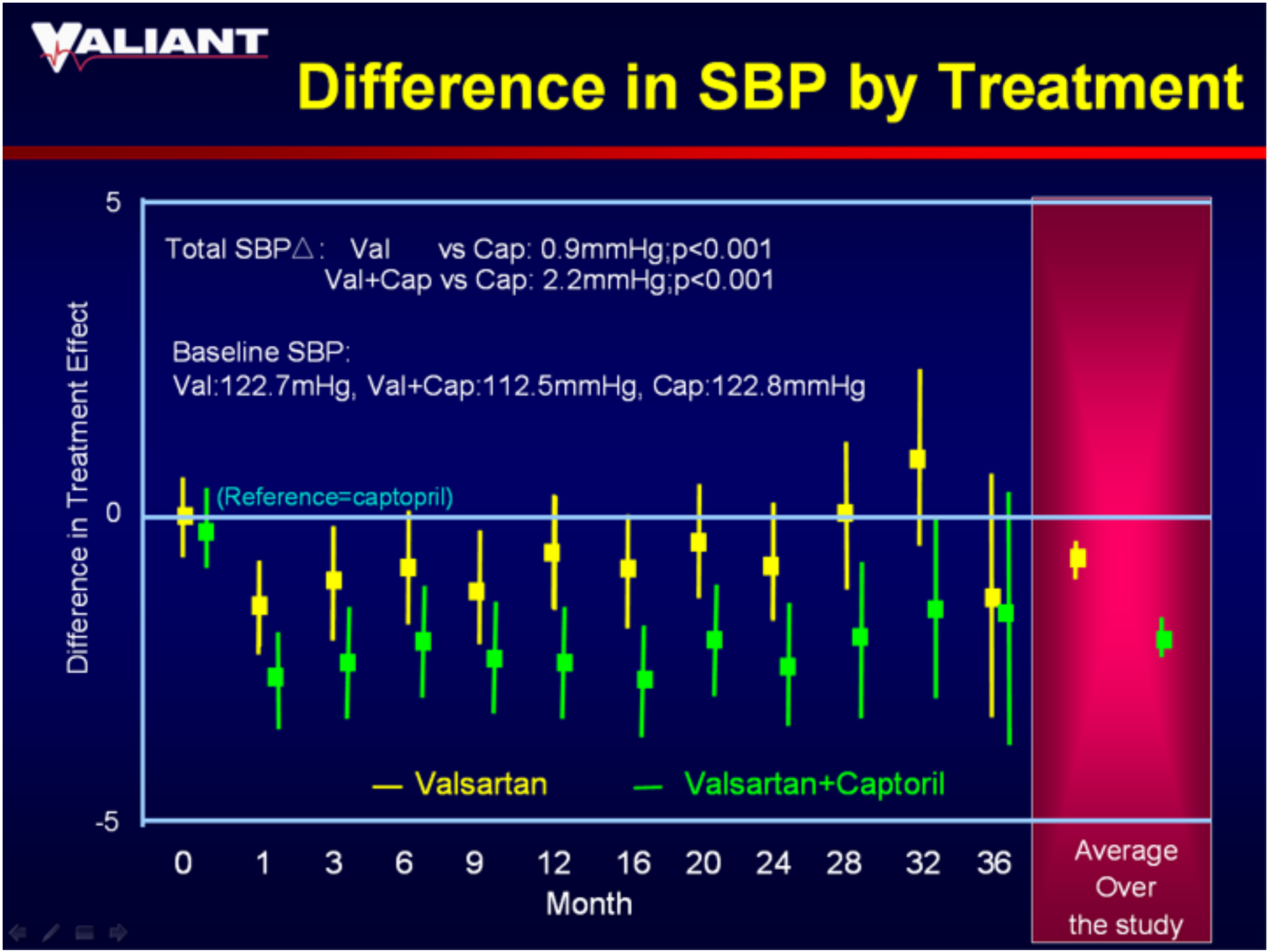
Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349:1893–1906

Study Drug Use

VALIANT

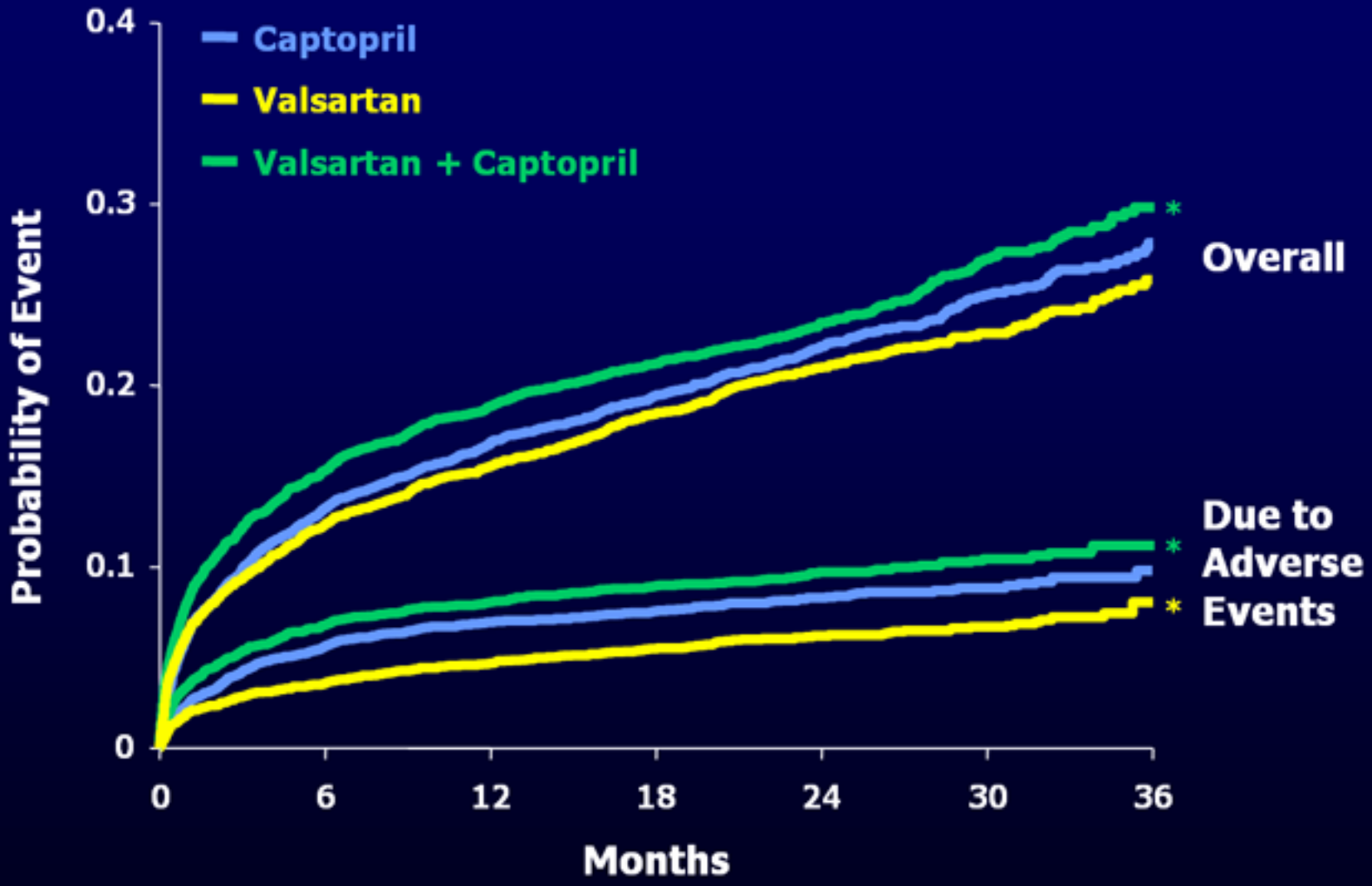


Difference in SBP by Treatment



Study Drug Discontinuation

VALIANT



*P < 0.05 vs Captopril

Adverse Events Leading to Study Drug Discontinuation

	captopril n=4879	valsartan n=4885	valsartan+captopril n=4879
Hypotension	41(0.8)	70(1.4)*	90(1.9)*
Renal causes	40(0.8)	53(1.1)	61(1.3)*
Hyperkalemia	4(0.1)	7(0.1)	12(0.2)
Cough	122(2.5)	30(0.6)*	101(2.1)
Rash	39(0.8)	17(0.3)*	34(0.7)
Taste disturbance	21(0.4)	9(0.2)*	16(0.3)
Angioedema	13(0.3)	9(0.2)	12(0.2)
Any adverse event	375(7.7)	282(5.8)*	438(9.0)*
Any reason	1055(21.6)	1001(20.5)*	1139(23.4)*

*p<0.05 vs captopril

Pfeffer MA et al :NEJM 349:1893 2003

Conclusion of VALIANT study

In patients with MI complicated by heart failure, left ventricular dysfunction or both:

- **Valsartan is as effective as a proven dose of captopril in reducing the risk of:**
  - —Death
  - —CV death or nonfatal MI or heart failure admission
- **Combining valsartan with a proven dose of captopril produced no further reduction in mortality—and more adverse drug events.**

Implications:

In these patients, valsartan is a clinically effective alternative to an ACE inhibitor.

VALIANT vs OPTIMAAL

- ARB (Valsartan) is not inferior to ACEI in Valiant study. However, ARB (Losartan) was inferior to ACEI in OPTIMAAL study.
- ACE-I is the same captopril 150mg
- Valsartan 320 mg vs Losartan 50 mg
- Drug itself or dose?

Question

- In studies for patients with heart failure (CHARM, Val-HEFT), the combination between ACEI and ARB was more effective than the single drug. Why the additional effect was negative in VALIANT?

Difference between VALIANT and CHARM, Val-HeFT

- **Disease: AMI or heart failure**
- **Protocol: In Valiant, ACEI and ARB started simultaneously. However, in CHARM and Val-HeFT, ARB was added for patients who had already had ACEI.**
- **Dose of ACEI (captopril)**
  - —Val-HEFT 80 mg
  - —CHARM-Added 83 mg
  - —VALIANT : 107 mg

Lessons from the VALIANT study

- Valsartan is the only ARB that is prove in a multicenter randomized trial to be effective for post-MI patients.
- ACE-I or Valsartan should be started for AMI with heart failure or low LV systolic function possibly within one day.

Class 1 Drugs for STEMI patients AHA/ACC guide line 2004

- Beta blocker (level of evidence A)
- Nitroglycerin within first 48 hours for persistent ischemia, CHF, or HT (level B)
- ACEI (level A)
- ARB (Valsartan) for patients with intolerance of ACEI (level B)
- Aldosterone blockade (level A)
- Aspirin (level A)
- Heparin for high risk patients for emboli (level C)

Conclusion

- Revascularization therapy either PCI or thrombolysis is important for AMI
- Medical treatment is also important for post MI patients as listed in the AHA/ACC guideline
- Valsartan is the only proven ARB in a prospective randomized study for patients with AMI and should be considered in case of intolerance to ACEI