Closing the Gaps in the Continuum of Care for Patients with Acute Coronary Syndromes: Implications for Optimal Antiplatelet Use

Supported by an educational grant from AstraZeneca

Opening Remarks

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- During the panel discussion, please use the Question Cards located on each table.
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Antiplatelet Agents Across the ACS Spectrum

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Disclosures for Dr. Bhatt

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This presentation discusses off-label and/or investigational uses of various drugs and devices.

ARS QUESTION 1

A 73-year-old female comes in with a NSTEMI and receives a DES to the proximal left circumflex artery. In addition to aspirin, which antiplatelet agent would you discharge her on?

A. Clopidogrel

B. Prasugrel

C. Ticagrelor

ARS QUESTION 2

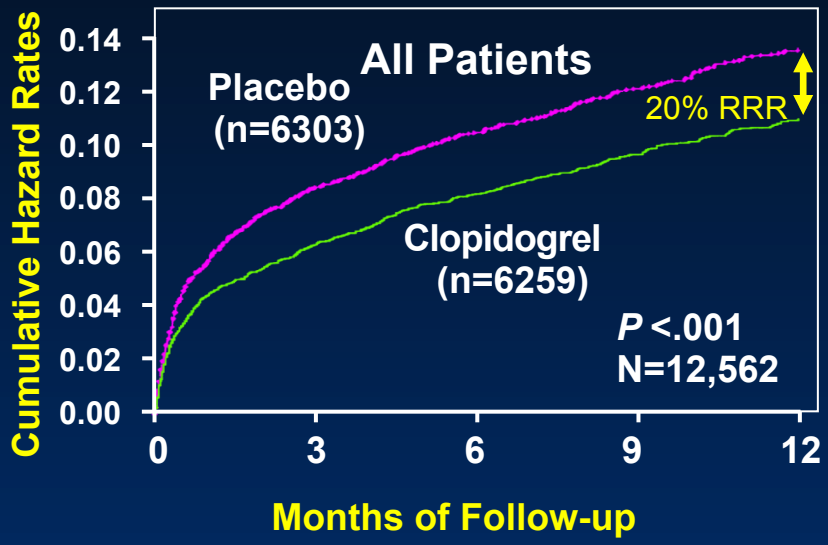
A 78-year-old male comes in with a NSTEMI and is found to have diffuse three vessel disease. Medical management is elected. In addition to aspirin, which antiplatelet agent would you discharge him on?

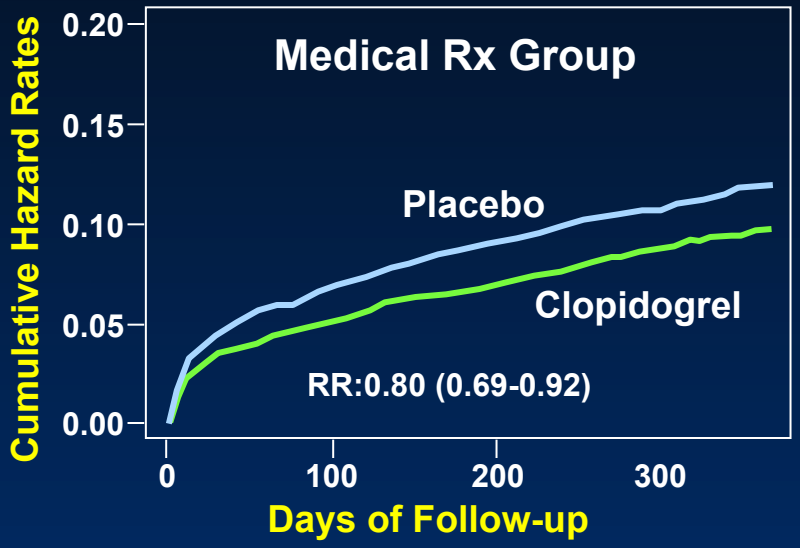
A. Clopidogrel

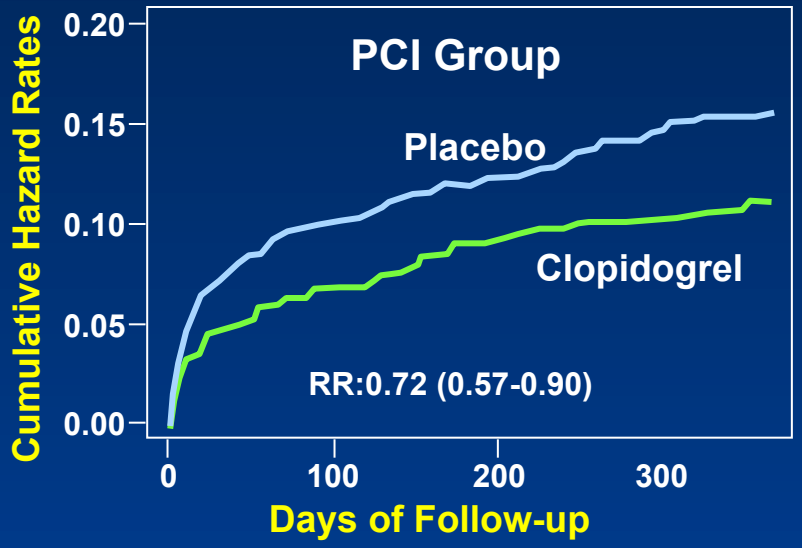
B. Prasugrel

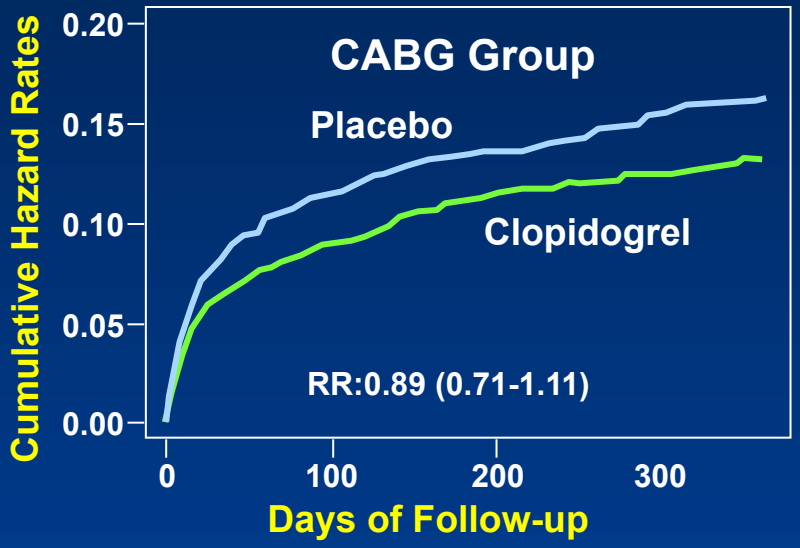
C. Ticagrelor

CURE: Primary Outcome by Management Strategy



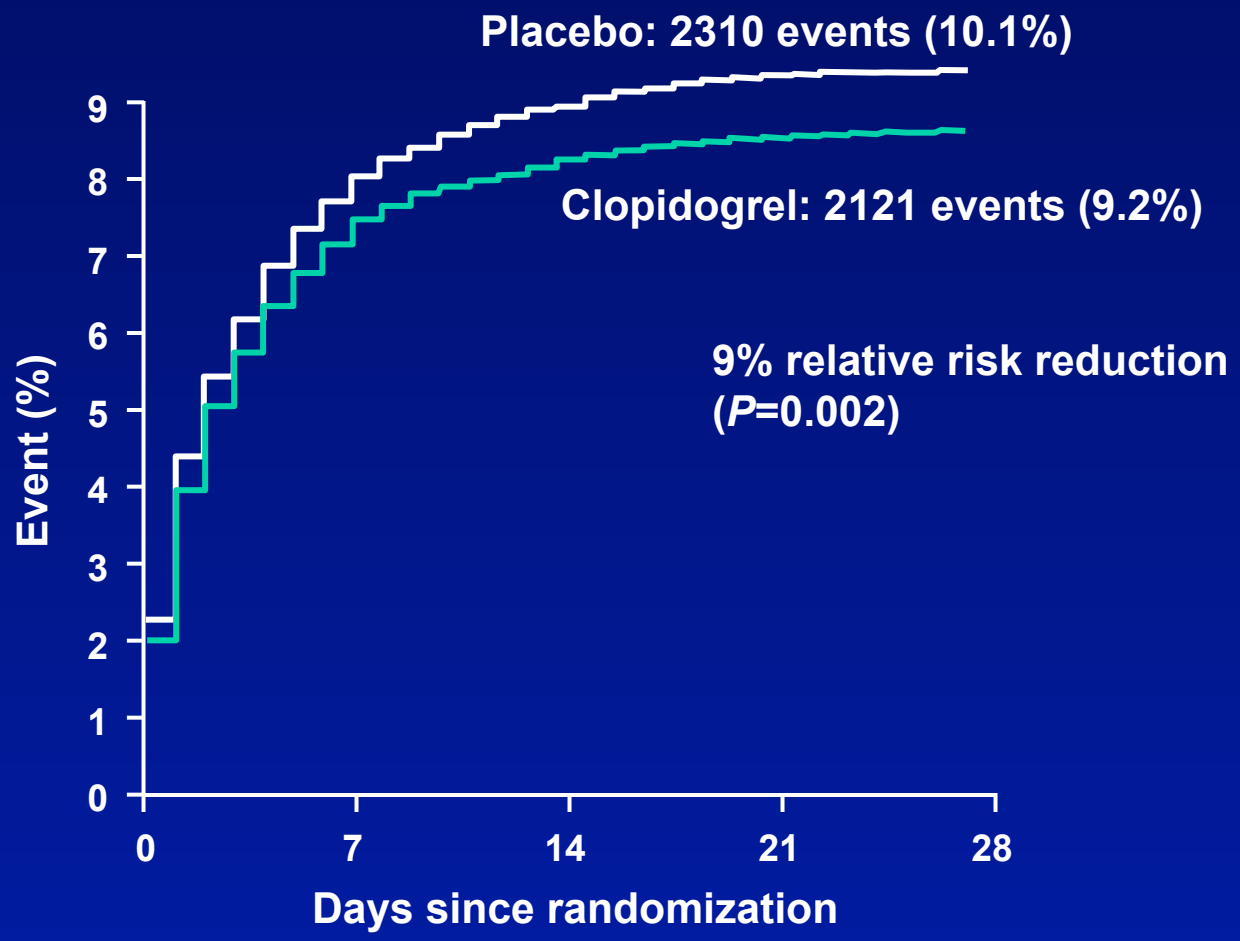






Yusuf et al. N Engl J Med. 2001;345:494-502.
Fox et al. Circulation. 2004;110:1202-08.

COMMIT: Incidence of Death, Re-MI, or Stroke at 28 Days



COMMIT Collaborative Group. Lancet. 2005;366:1607.

CURRENT-OASIS 7: Clopidogrel Results

Patients with UA/NSTEMI or STEMI planned for early invasive strategy
(ie, intended for PCI as early as possible within 72 hours)

Randomize

Clopidogrel Standard-dose Group
Clopidogrel 300 mg (+ placebo) day 1 followed by 75 mg (+ placebo) from days 2 to 7; 75 mg from days 8 to 30

Clopidogrel High-dose Group
Clopidogrel 600 mg LD day 1 followed by 150 mg from days 2 to 7; 75 mg from days 8 to 30

	Standard	Double	HR (95% CI)	*P*-value
CV death/MI/Stroke				
Overall (N=25,086)	4.4	4.2	0.94 (0.83-1.06)	0.30
PCI (n=17,263)	4.5	3.9	0.86 (0.74-0.99)	0.039
No PCI (n=7823)	4.3	4.9	1.14 (0.92-1.40)	0.23

LD = loading dose.

CURRENT-OASIS 7 Investigators et al. N Engl J Med. 2010;363:930-42.
Mehta et al. Lancet. 2010;376:1233-43.

CURRENT-OASIS 7: Clopidogrel Std vs Double Dose
Bleeding Outcome in PCI Population

Outcome	Clopidogrel Standard N= 8703	Clopidogrel Double N=8560	Hazard Ratio	95% CI	P
TIMI Major[1]	0.7	1.0	1.36	0.97-1.90	0.07
CURRENT Major[2]	1.1	1.6	1.41	1.09-1.83	0.009
CURRENT Severe[3]	0.8	1.1	1.34	0.99-1.82	0.06
Fatal	0.2	0.07	0.46	0.18-1.22	0.12
ICH	0.05	0.04	0.77	0.17-3.43	0.73
RBC transfusion ≥ 2U	0.9	1.3	1.42	1.06-1.91	0.02
CABG-related Major	0.07	0.1	1.70	0.62-4.69	0.30

[1]ICH, Hb drop ≥ 5 g/dL (each unit of RBC transfusion counts as 1 g/dL drop) or fatal
[2]Severe bleed + disabling or intraocular or requiring transfusion of 2-3 units
[3]Fatal or ↓Hb ≥ 5 g/dL, sig hypotension + inotropes/surgery, ICH or transfusion of ≥ 4 units

Mehta et al. Lancet. 2010;376:1233-43.

TRÎTON TIMI-38

Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA ↓ **N= 13,600**

Double-blind

CLOPIDOGREL 300 mg LD/ 75 mg MD	**PRASUGREL** 60 mg LD/ 10 mg MD

Median duration of therapy - 12 months

1º endpoint: CV death, MI, Stroke

2º endpoints: CV death, MI, Stroke, Rehosp-Rec Isch
CV death, MI, UTVR
Stent Thrombosis (ARC definite/prob.)

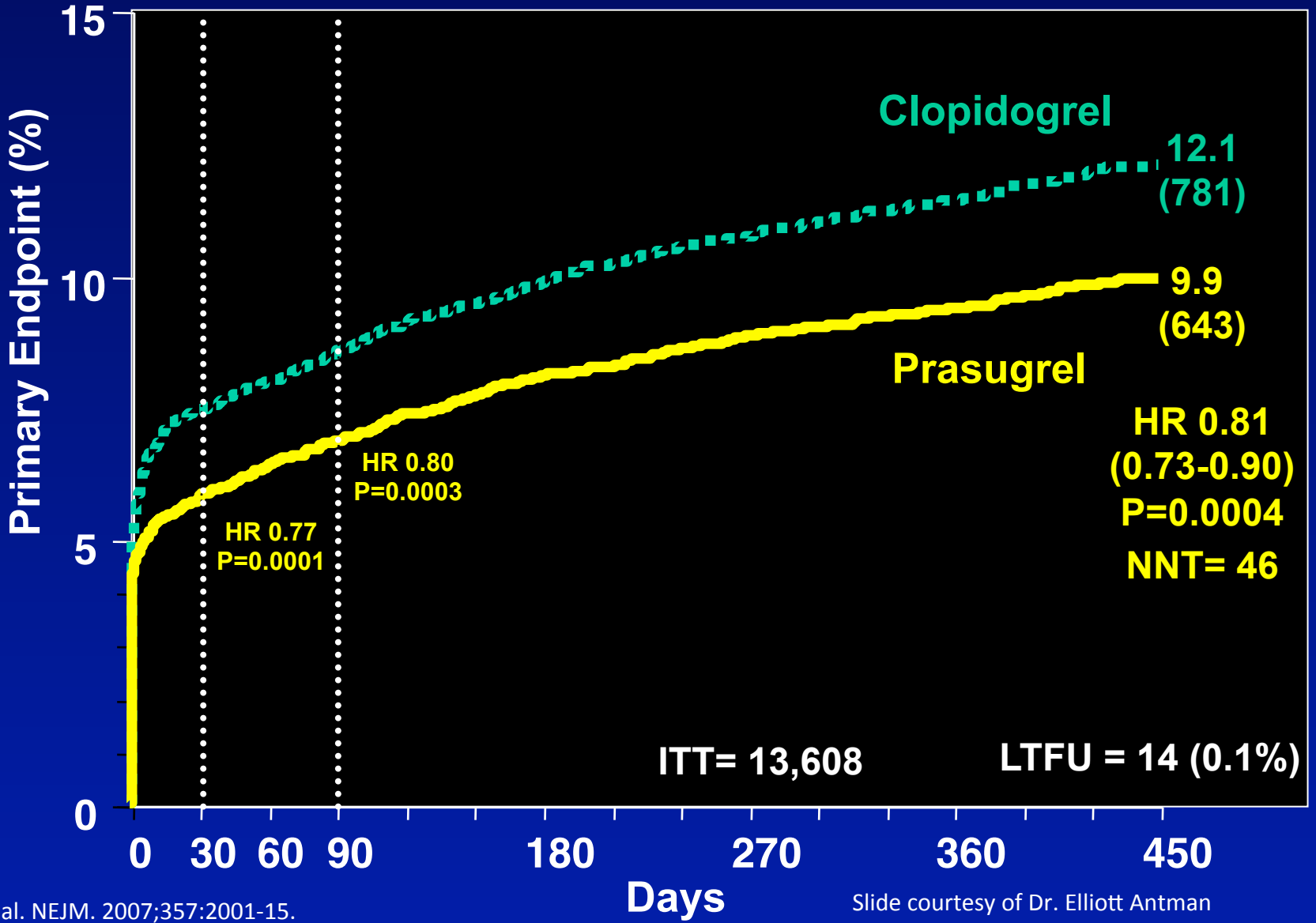
Safety endpoints: TIMI major bleeds, Life-threatening bleeds

Key Substudies: Pharmacokinetic, Genomic

Wiviott et al. Am Heart J. 2006;152:627-35.

TRITON – TIMI 38

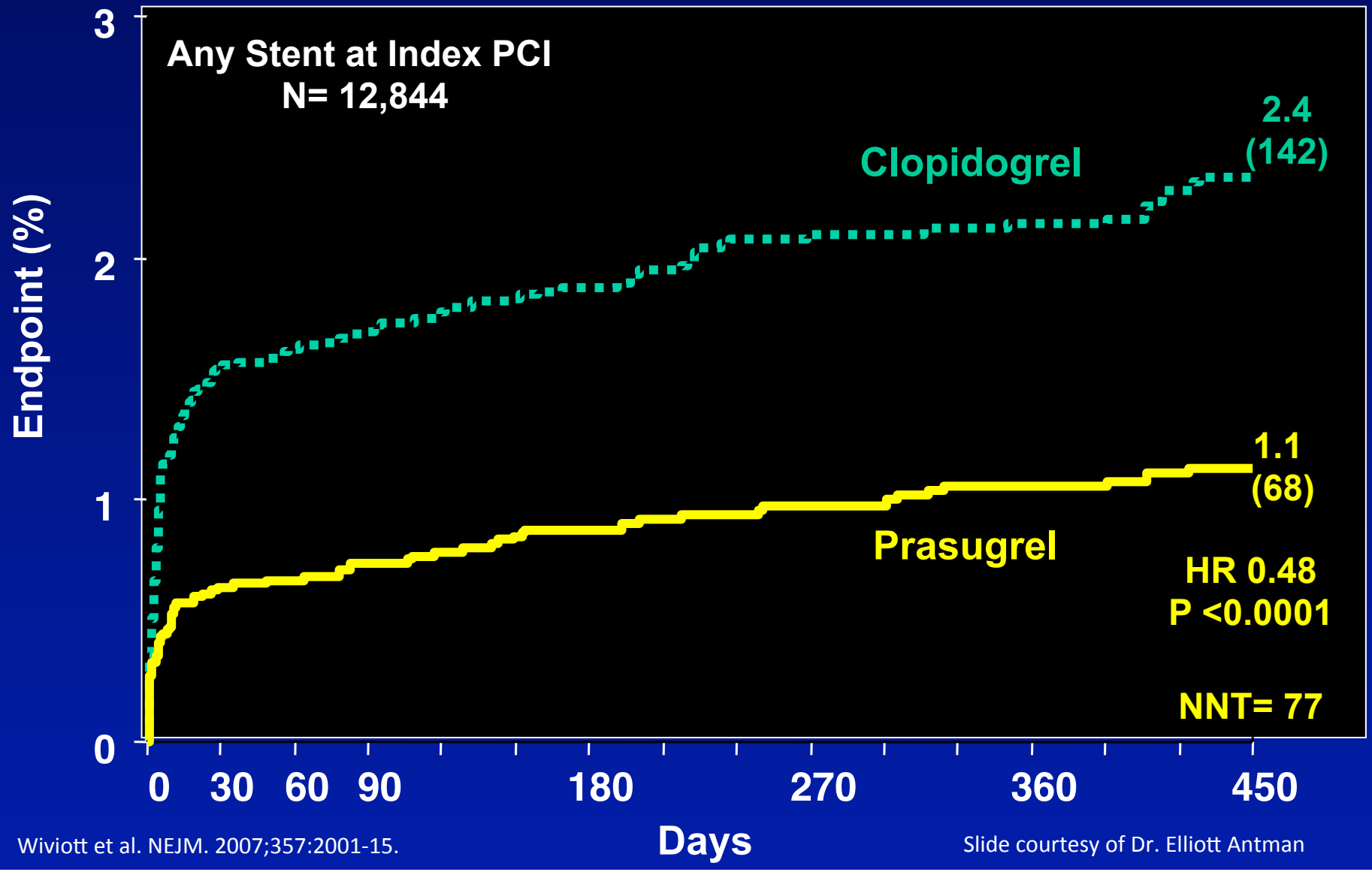
CV Death, MI, Stroke



Wiviott et al. NEJM. 2007;357:2001-15.

Slide courtesy of Dr. Elliott Antman

TRITON-TIMI 38: Stent Thrombosis (ARC Definite + Probable)



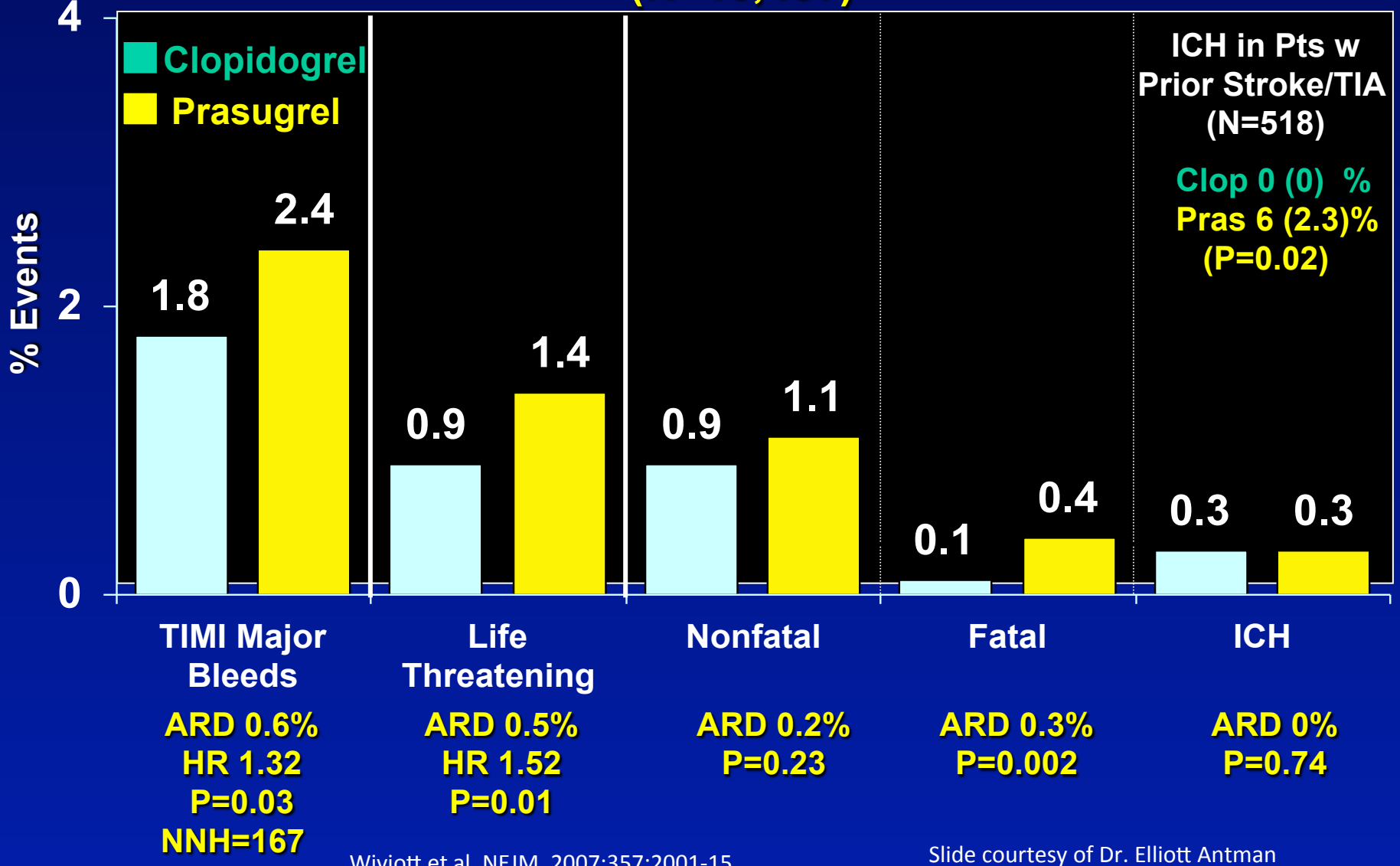
Wiviott et al. NEJM. 2007;357:2001-15.

Slide courtesy of Dr. Elliott Antman

TRITON-TIMI 38: Bleeding Events

Safety Cohort

(N=13,457)



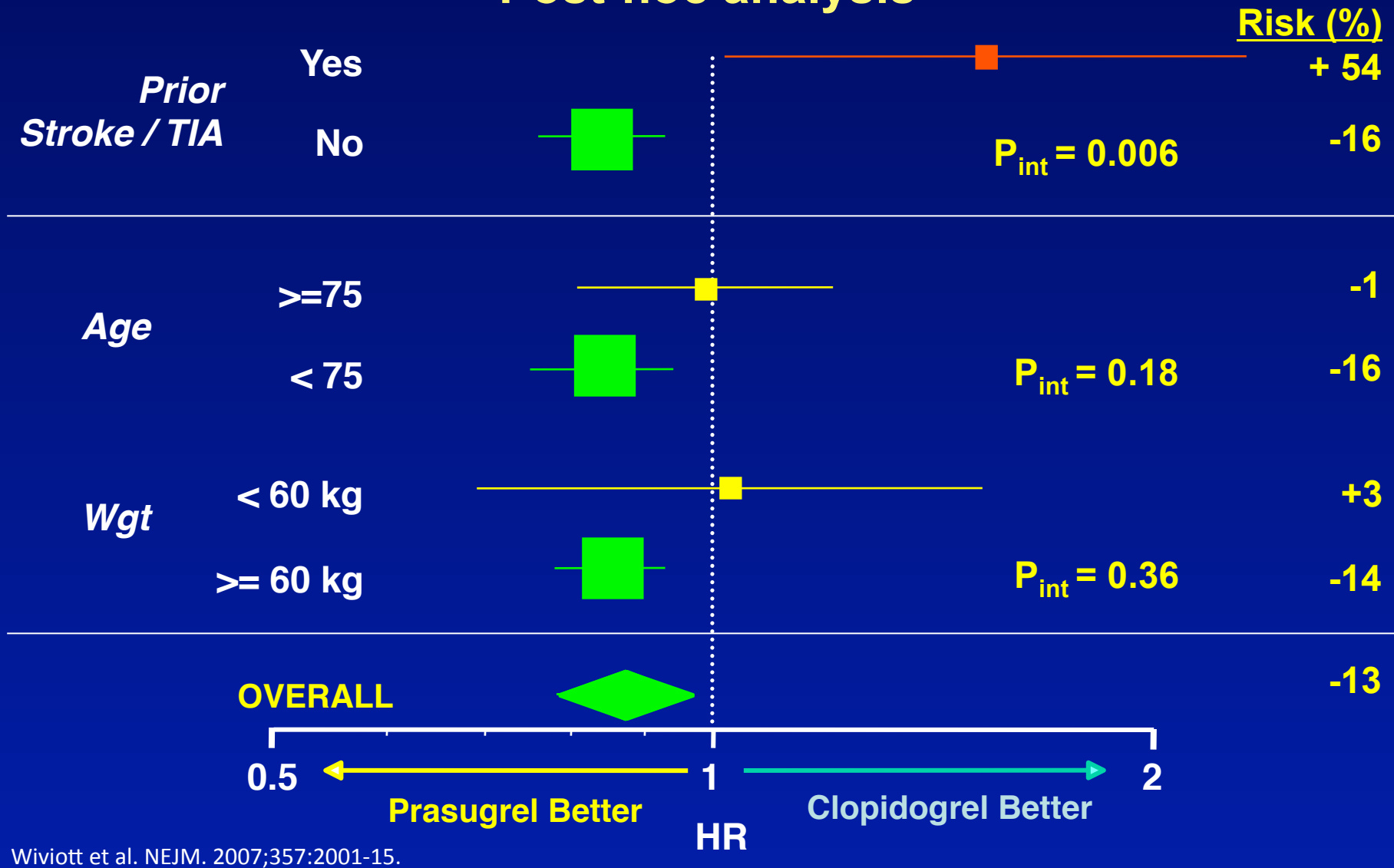
Wiviott et al. NEJM. 2007;357:2001-15.

Slide courtesy of Dr. Elliott Antman

TRITON TIMI-38: Net Clinical Benefit

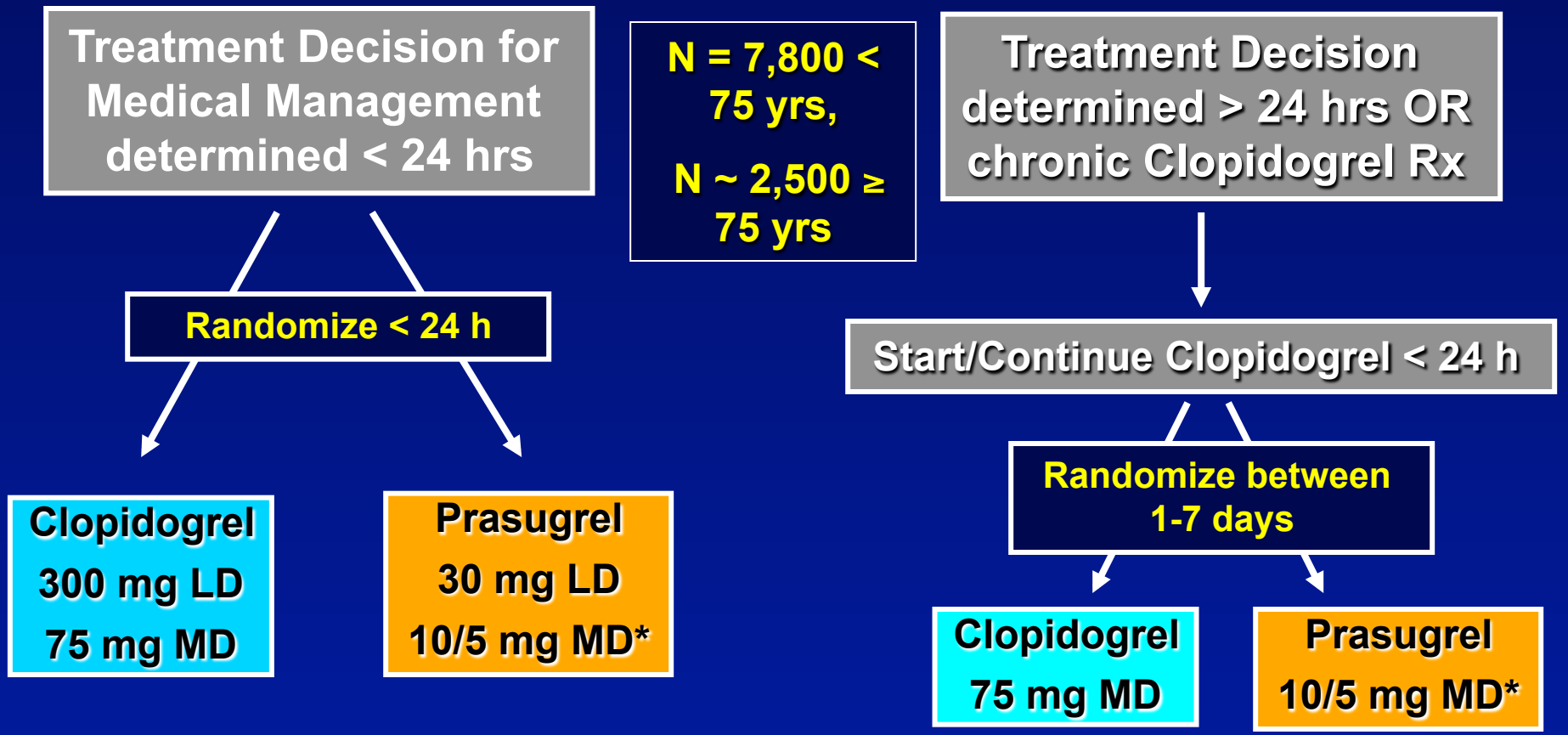
Bleeding Risk Subgroups

Post-hoc analysis



Wiviott et al. NEJM. 2007;357:2001-15.

TRILOGY-ACS



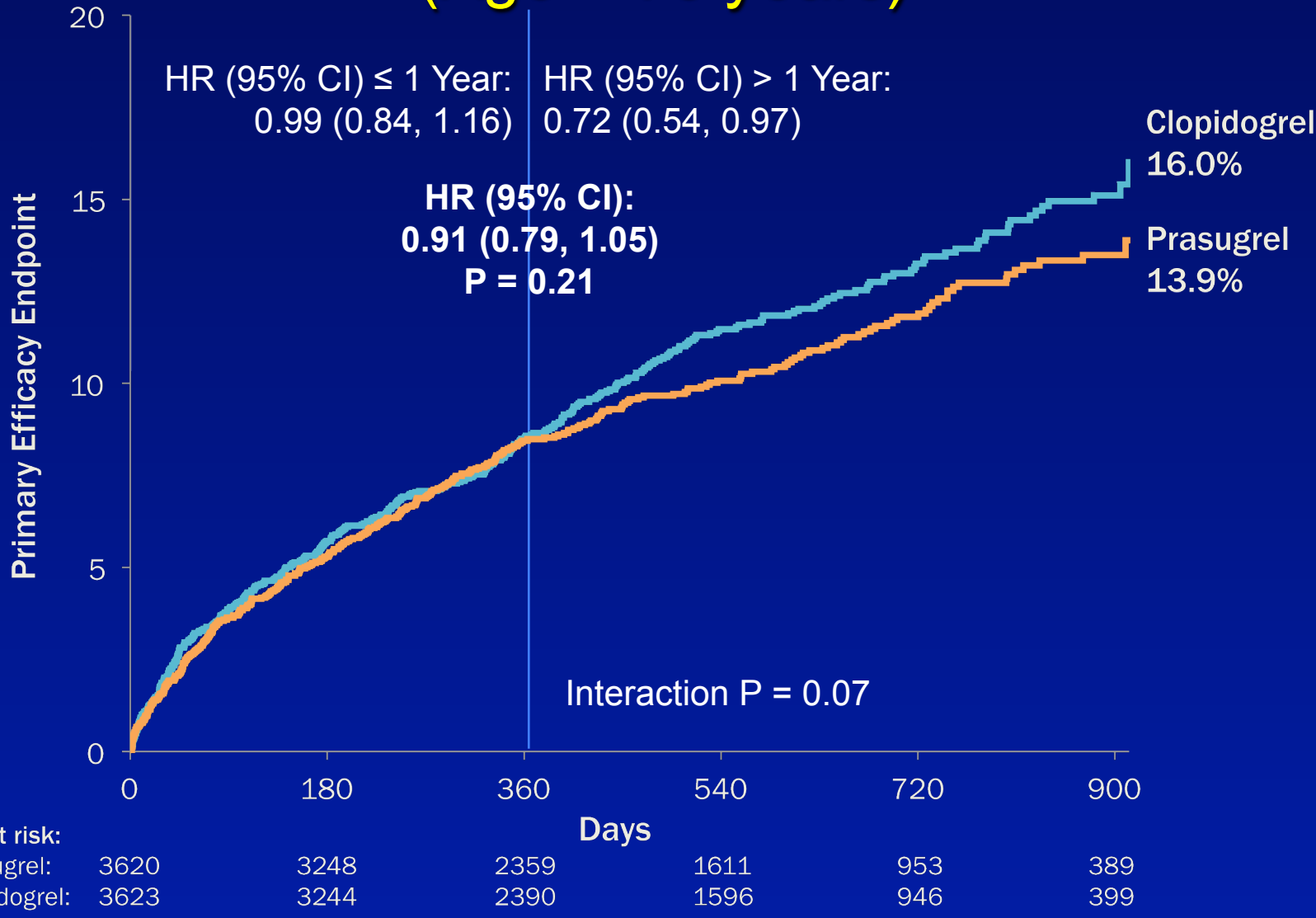
* 5 mg MD of prasugrel for age ≥ 75 yrs or weight < 60 kg

Median duration of treatment ~ 18 months

Slide courtesy of Drs. Ohman and Roe.

Roe et al. N Engl J Med 2012;367:1297-1309.

TRILOGY-ACS: Primary Endpoint to 30 Months (Age < 75 years)



No. at risk:						
Prasugrel:	3620	3248	2359	1611	953	389
Clopidogrel:	3623	3244	2390	1596	946	399

Roe et al. N Engl J Med 2012;367:1297-1309.

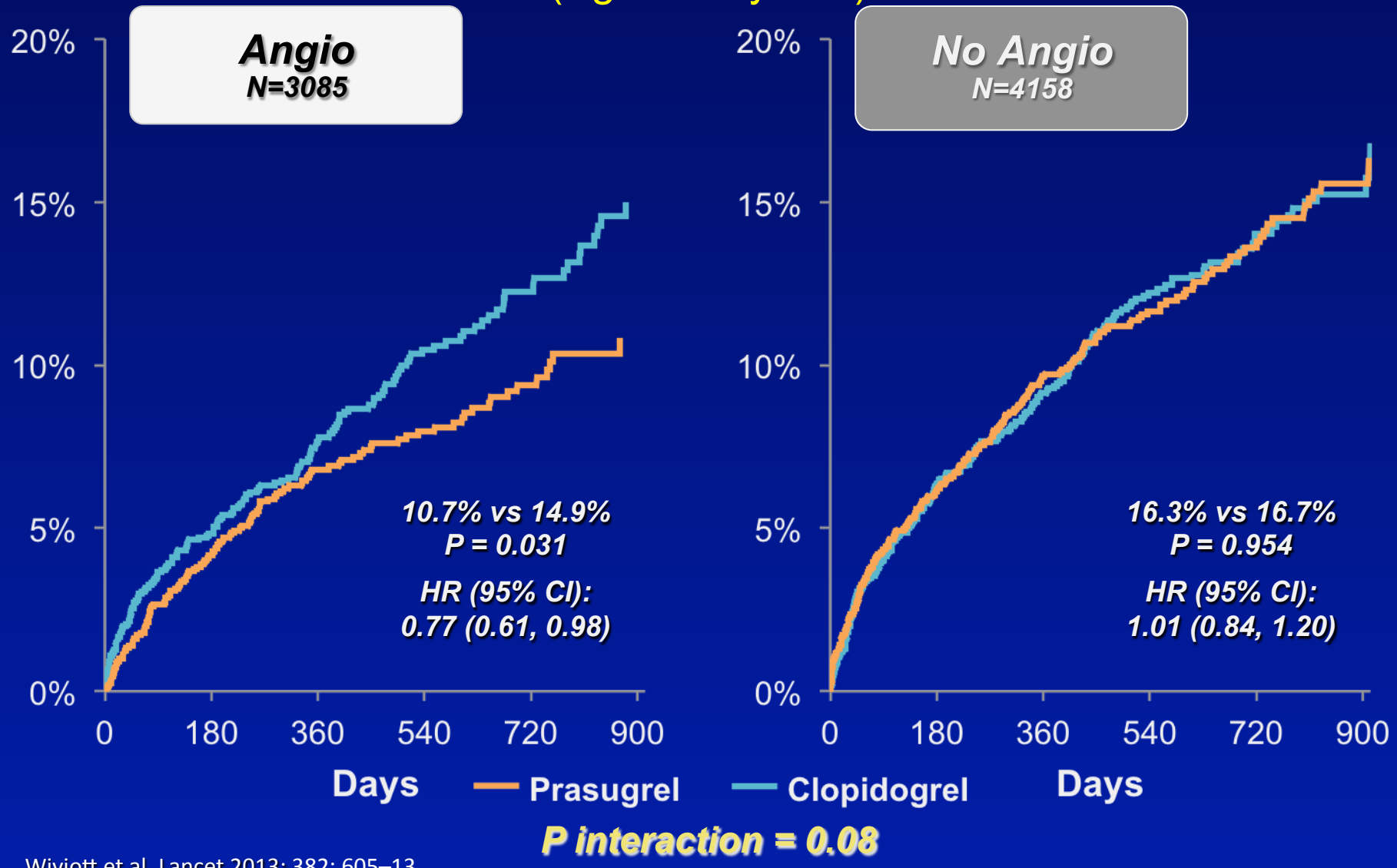
Prasugrel versus clopidogrel for patients with unstable angina or non-ST-segment elevation myocardial infarction with or without angiography: a secondary, prespecified analysis of the TRILOGY ACS trial

Stephen D Wiviott, Harvey D White, E Magnus Ohman, Keith A A Fox, Paul W Armstrong, Dorairaj Prabhakaran, Gail Hafley, Yuliya Lokhnygina, William E Boden, Christian Hamm, Peter Clemmensen, Jose C Nicolau, Alberto Menozzi, Witold Ruzyllo, Petr Widimsky, Ali Oto, Jose Leiva-Pons, Gregory Pavlides, Kenneth J Winters, Matthew T Roe, Deepak L Bhatt

Wiviott et al. Lancet 2013; 382: 605–13.

TRILOGY-ACS: Primary Efficacy Endpoint to 30 Months

(Age < 75 years)



Wiviott et al. Lancet 2013; 382: 605–13.

PLATO Study Design

NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)

Clopidogrel
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

Ticagrelor
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

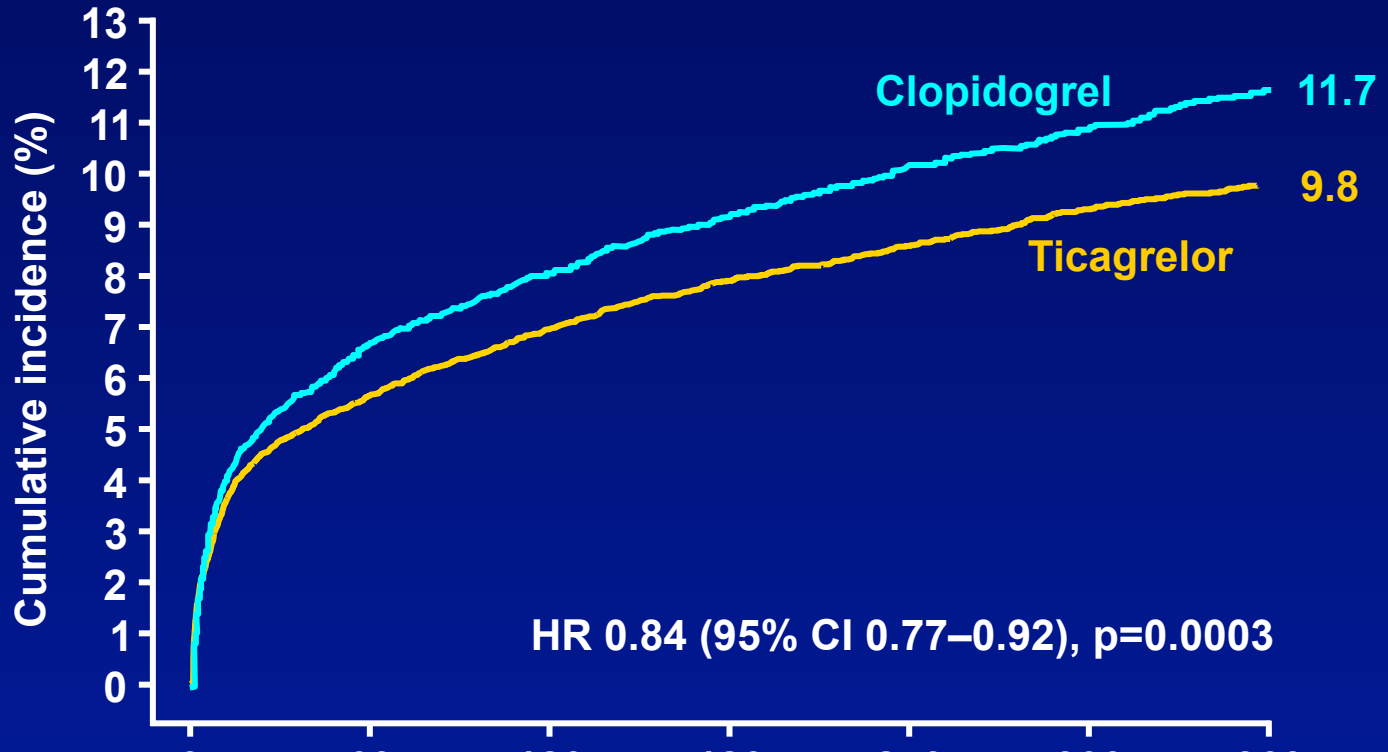
6–12-month exposure

Primary endpoint: CV death + MI + Stroke
Primary safety endpoint: Total major bleeding

Wallentin et al. N Engl J Med. 2009;361:1045-57.

Study Chairs: Drs. Harrington and Wallentin

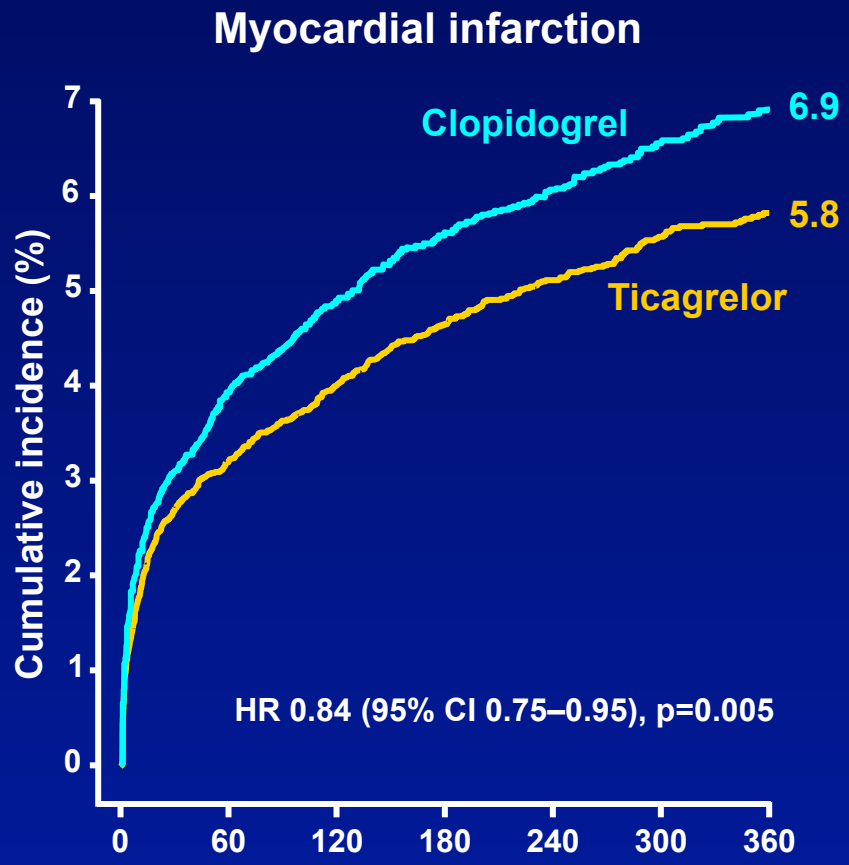
PLATO: CV Death, MI, or Stroke

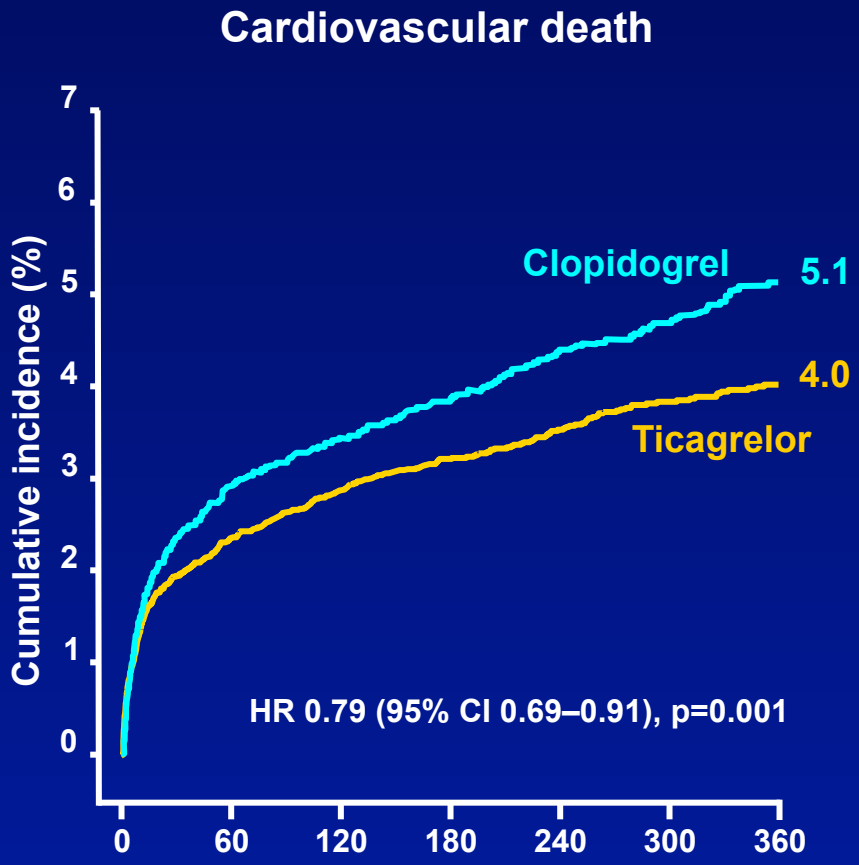


No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

Wallentin et al. N Engl J Med. 2009;361:1045-57.

PLATO: Secondary Efficacy Endpoints



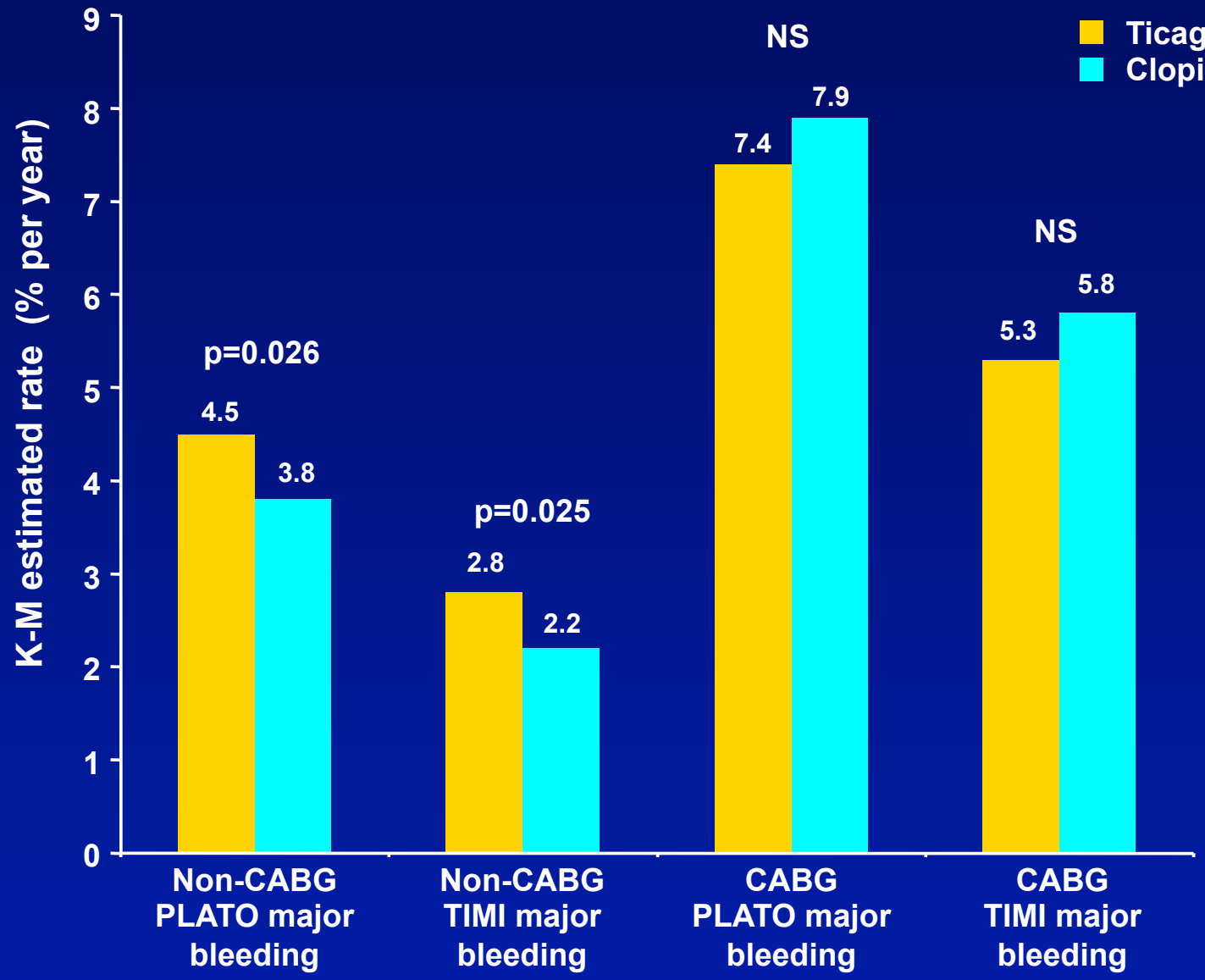


No. at risk							
Ticagrelor	9,333	8,678	8,520	8,279	6,796	5,210	4,191
Clopidogrel	9,291	8,560	8,405	8,177	6,703	5,136	4,109

9,333	8,294	8,822	8,626	7119	5,482	4,419
9,291	8,865	8,780	8,589	7079	5,441	4,364

Wallentin et al. N Engl J Med. 2009;361:1045-57.

Major Bleeding: Non-CABG vs CABG



Wallentin et al. N Engl J Med. 2009;361:1045-57.

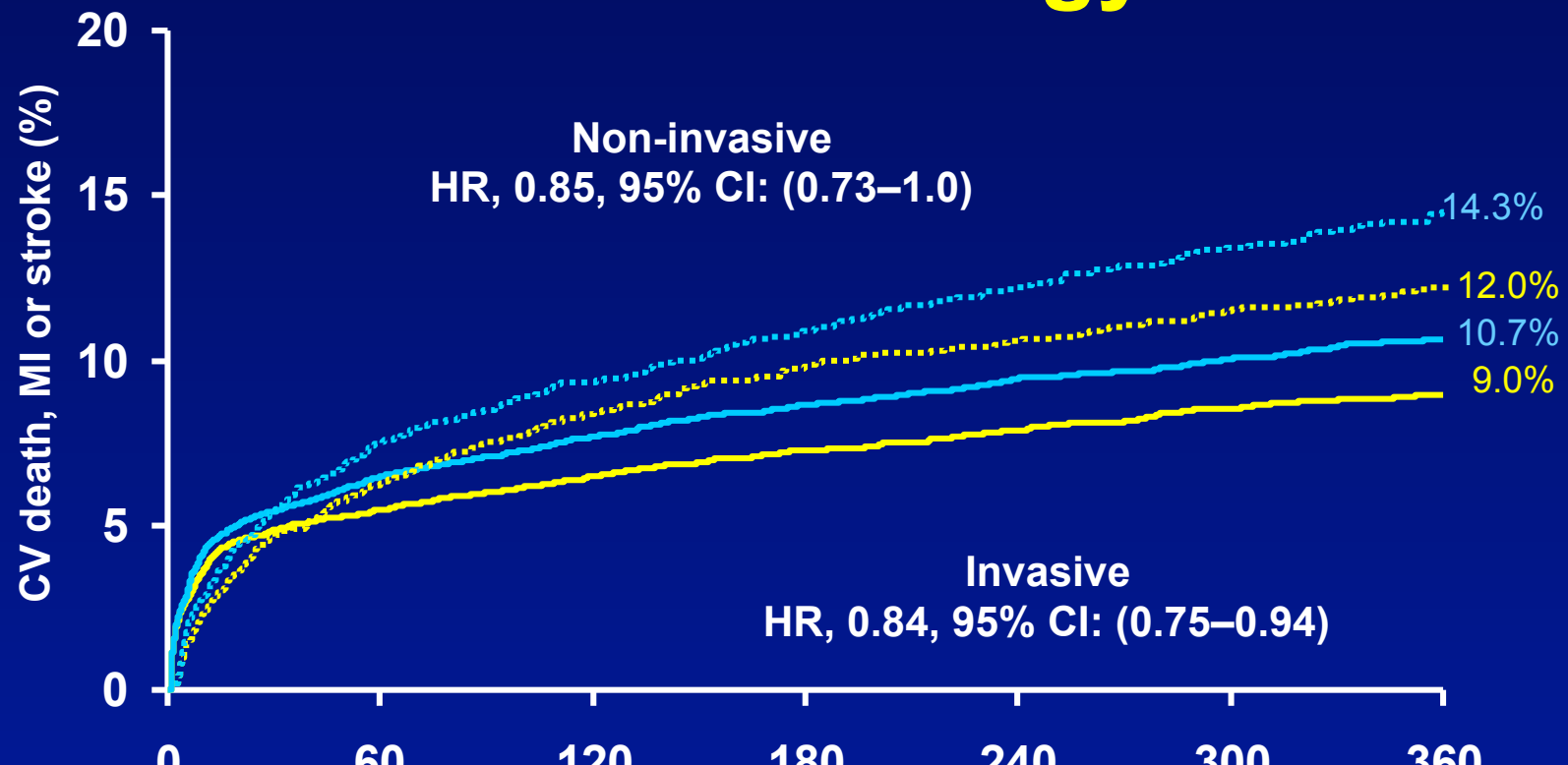
PLATO: Major Bleeding, Holter Monitoring, and Other Related Events

Bleeding	Ticagrelor (n=9235)	Clopidogrel (n=9186)	*P*-value
Total Major — PLATO criteria, %	11.6	11.2	0.43
Total Major — TIMI criteria , %	7.9	7.7	0.57
Non-CABG Major — PLATO criteria, %	4.5	3.8	0.026
Non-CABG Major — TIMI criteria , %	2.8	2.2	0.025
Holter Monitoring at First Week	**Ticagrelor (n=1451)**	**Clopidogrel (n=1415)**	***P*-value**
Ventricular pauses ≥3 seconds, %	5.8	3.6	0.01
Ventricular pauses ≥5 seconds, %	2.0	1.2	0.10
All Patients	**Ticagrelor (n=9235)**	**Clopidogrel (n=9186)**	***P*-value***
Dyspnea, %			
Any	13.8	7.8	<0.001
With discontinuation of study treatment	0.9	0.1	<0.001
Bradycardia-related Event, %			***P*-value**
Syncope	1.1	0.8	0.08
Bradycardia	4.4	4.0	0.21

****P*-values were calculated using Fischer's exact test**

Wallentin et al. N Engl J Med. 2009;361:1045-57.

PLATO: Stratification by Invasive vs Conservative Strategy

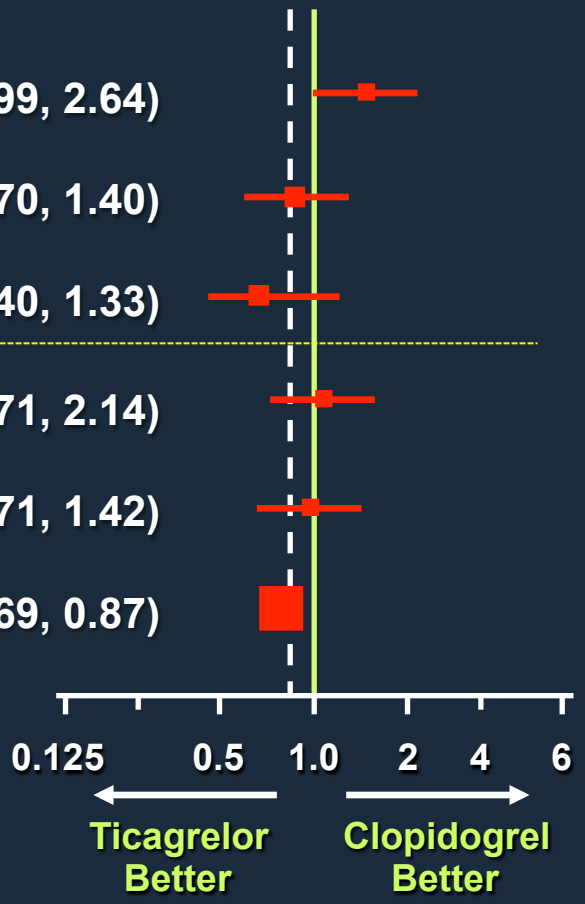


Number at risk							
Invasive							
Ticagrelor	6732	6236	6134	5972	4889	3735	3048
Clopidogrel	6676	6129	6034	5881	4815	3680	2965
Non-invasive							
Ticagrelor	2601	2392	2326	2247	1854	1426	1099
Clopidogrel	2615	2392	2328	2243	1835	1416	1109

James et al. BMJ 2011;342:d3527

PLATO: Treatment Effects in Relation to ASA Maintenance Dose in US and Non-US

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
US	≥300	324	40	352	27	1.62 (0.99, 2.64)
	>100-<300	22	2	16	2	0.99 (0.70, 1.40)
	≤100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	≥300	140	28	140	23	1.23 (0.71, 2.14)
	>100-<300	503	62	511	63	1.00 (0.71, 1.42)
	≤100	7449	546	7443	699	0.78 (0.69, 0.87)



N, number of patients; E, number of events

Mahaffey et al. Circulation. 2011;124:544-54.

Summary

- Clopidogrel superior to placebo across ACS (in addition to ASA)
- Prasugrel superior to clopidogrel in ACS undergoing PCI
- Prasugrel not superior to clopidogrel in med management of ACS
- Ticagrelor superior to clopidogrel across the full spectrum of ACS

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Thank You!

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Upstream therapy in ACS: does timing of antiplatelet therapy matter ?

Ph. Gabriel Steg

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French Alliance for Cardiovascular Clinical Trials
and Imperial College, Royal Brompton Hospital, London, UK

PG. Steg – Disclosures

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- **Stockholder:** Aterovax
- **Steering committee member for:**
  - The TRITON/TIMI 38 trial with prasugrel
  - The PLATO trial with ticagrelor
  - The CURRENT/OASIS 7 trial with clopidogrel

« Upstream therapy »: What Does it Mean?

- **Pre-hospital treatment**

  In systems and countries where drug treatment can be started upstream of the hospital (does not necessarily require physicians)

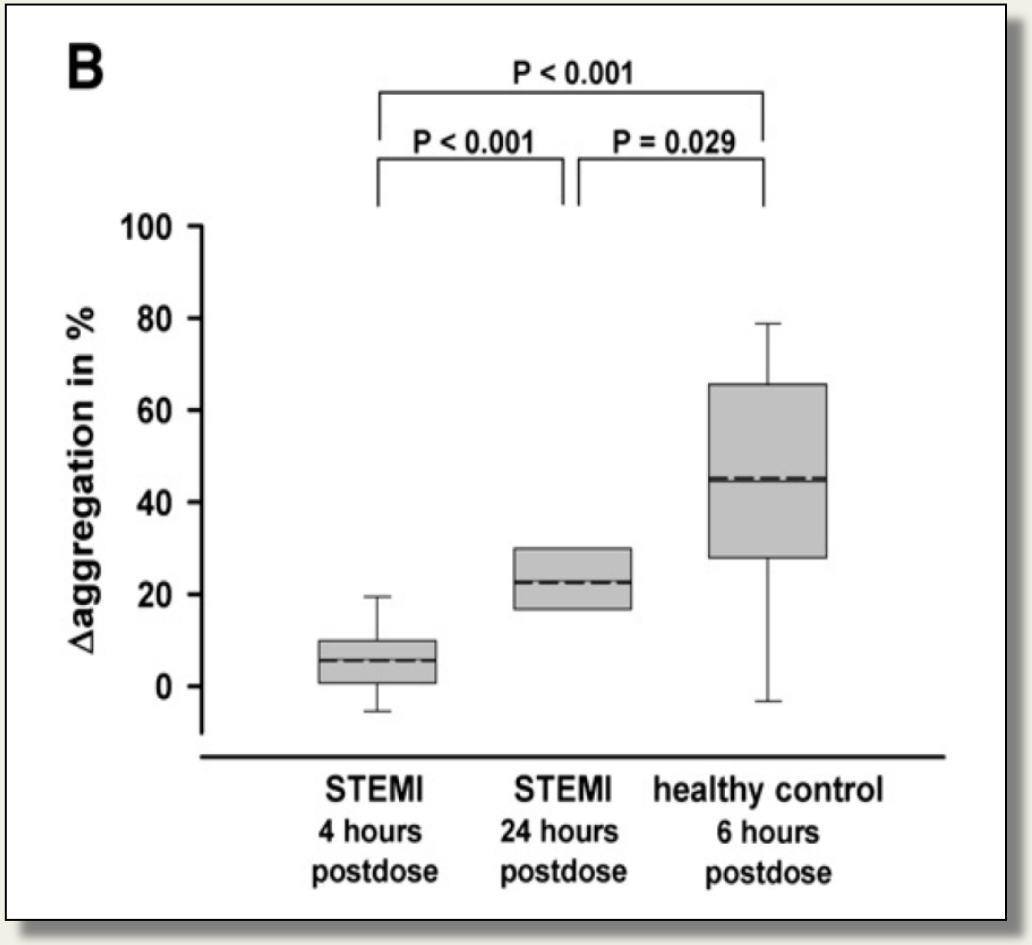
Or

- **Treatment upstream of coronary angiography**

Pre-hospital Treatment with Oral Antiplatelet Agents (vs in-hospital)

- **STEMI**
  - Diagnosis is often clear from clinical and ECG findings
  - Risk of urgent surgery is low
  - Oral antiplatelet therapy requires several hours to reach efficacy

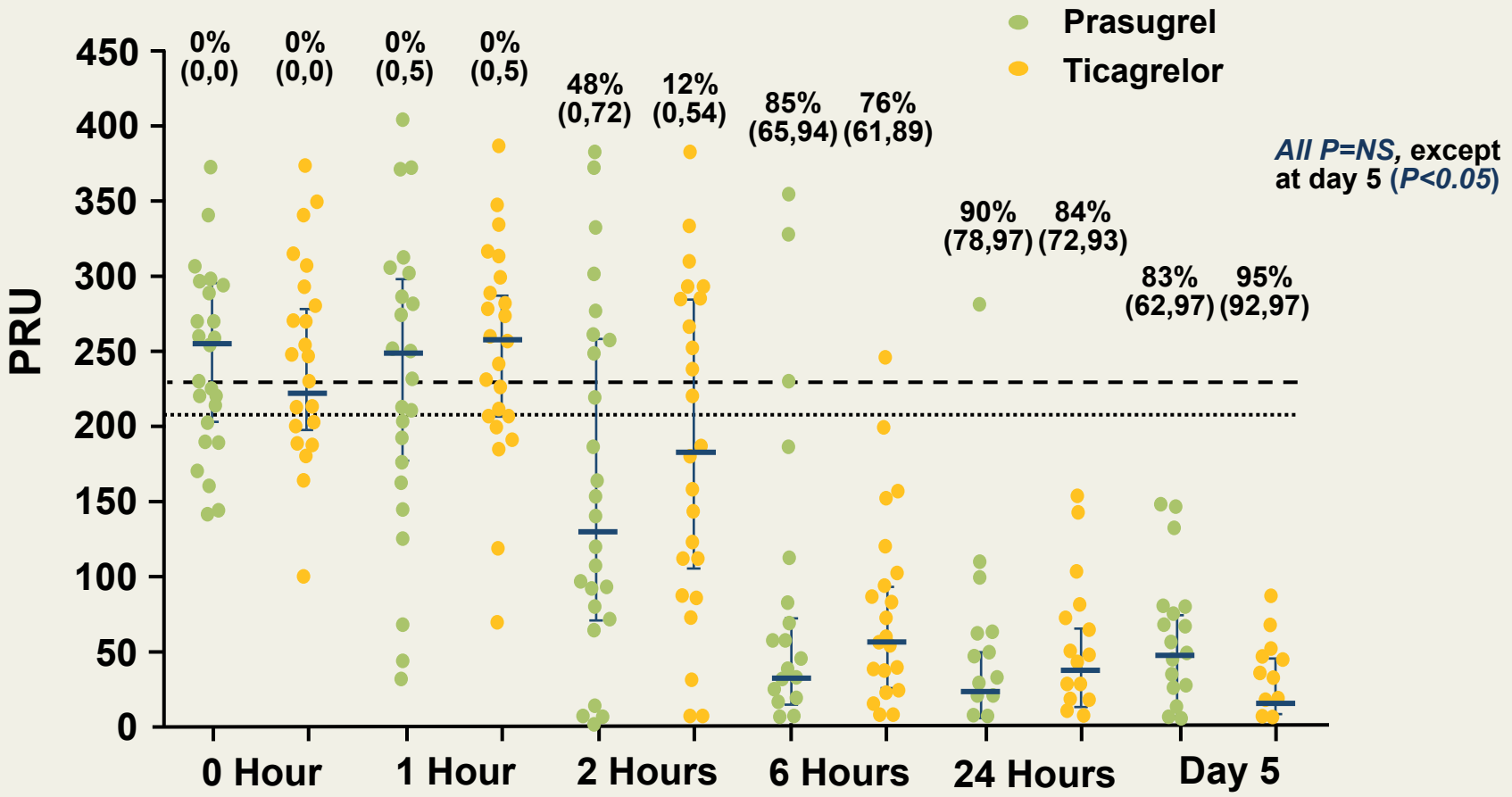
Bioavailability of Clopidogrel is Markedly Reduced in STEMI Patients



Heestermans et al. ***Thrombosis Research*** 2008; 122: 776−781

Ticagrelor and Prasugrel PD in STEMI

Verify Now P2Y12 at 0, 1, 2, 6, 24 hrs, and 5 days post randomisation in 55 STEMI pts (standard dosing). % inhibited:



Alexopoulos D et al. ***Circ Cardiovasc Interv***. 2012;5:797−804

Pre-hospital Treatment with Oral Antiplatelet Agents (vs in-hospital)

STEMI

- Diagnosis is often clear from clinical and ECG findings
- Risk of urgent surgery is low
- Oral antiplatelet therapy requires several hours to reach efficacy

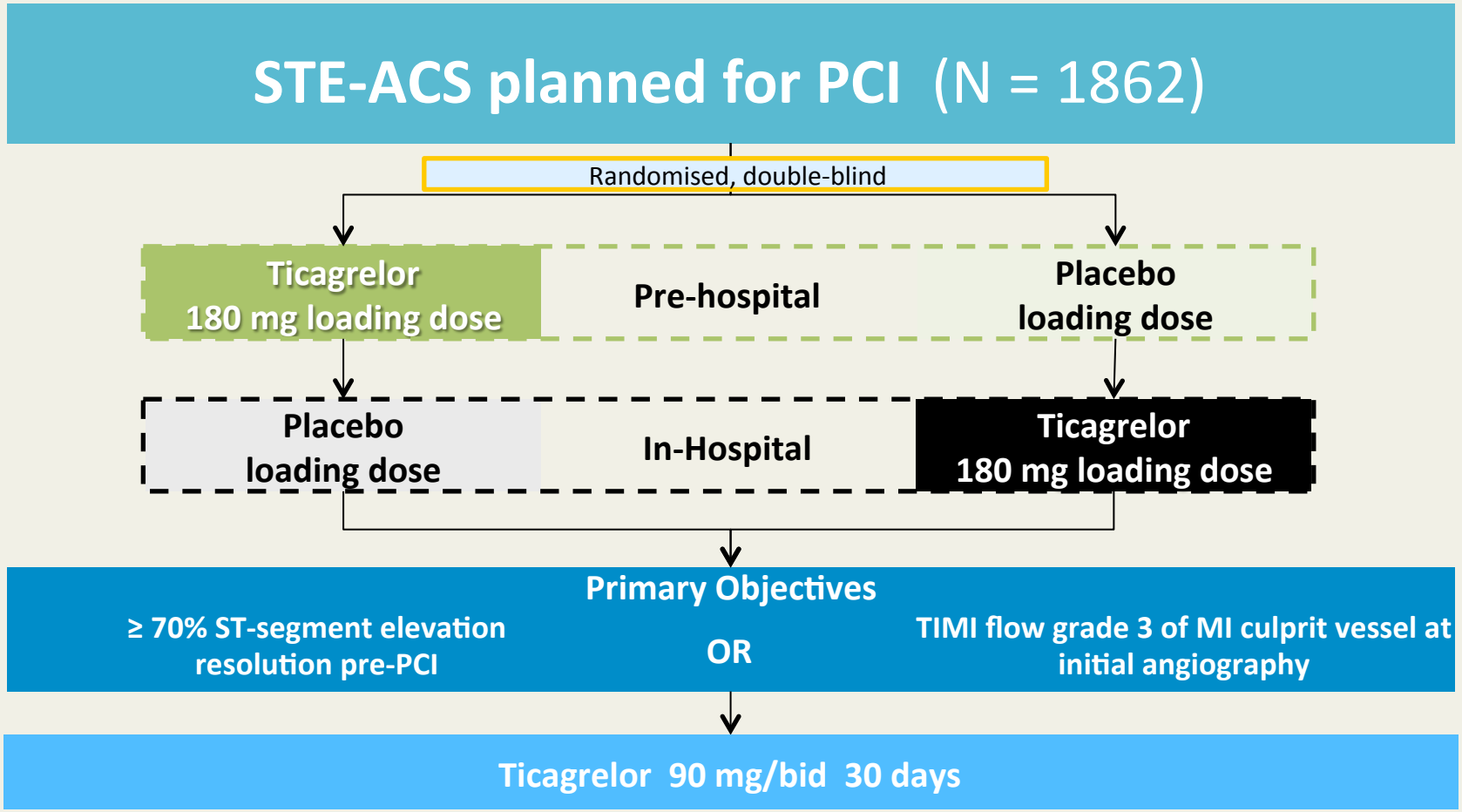
→ **The earlier, the better?**

However, no trial demonstration until the ATLANTIC trial

ATLANTIC Study Design

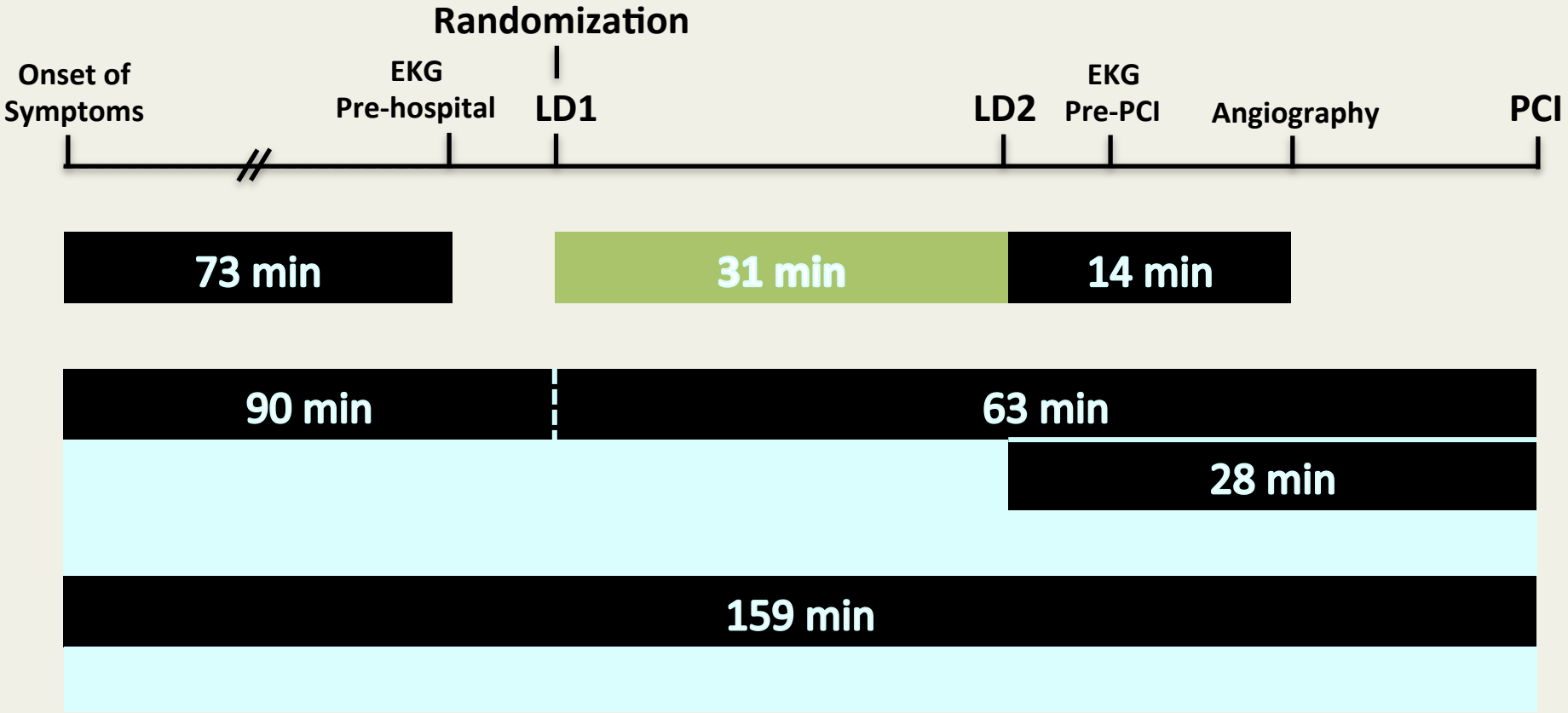
- Male and female patients aged 18 years and over
- With documented evidence of **STEMI**
- Planned for **angioplasty (PCI)**

- **onset of ischaemic symptoms within 6 h** before randomization
- **initially managed by ambulance physician/personnel in pre-hospital settings**; also concerning patients not pre-treated for STEMI in **emergency rooms of non-PCI hospitals**

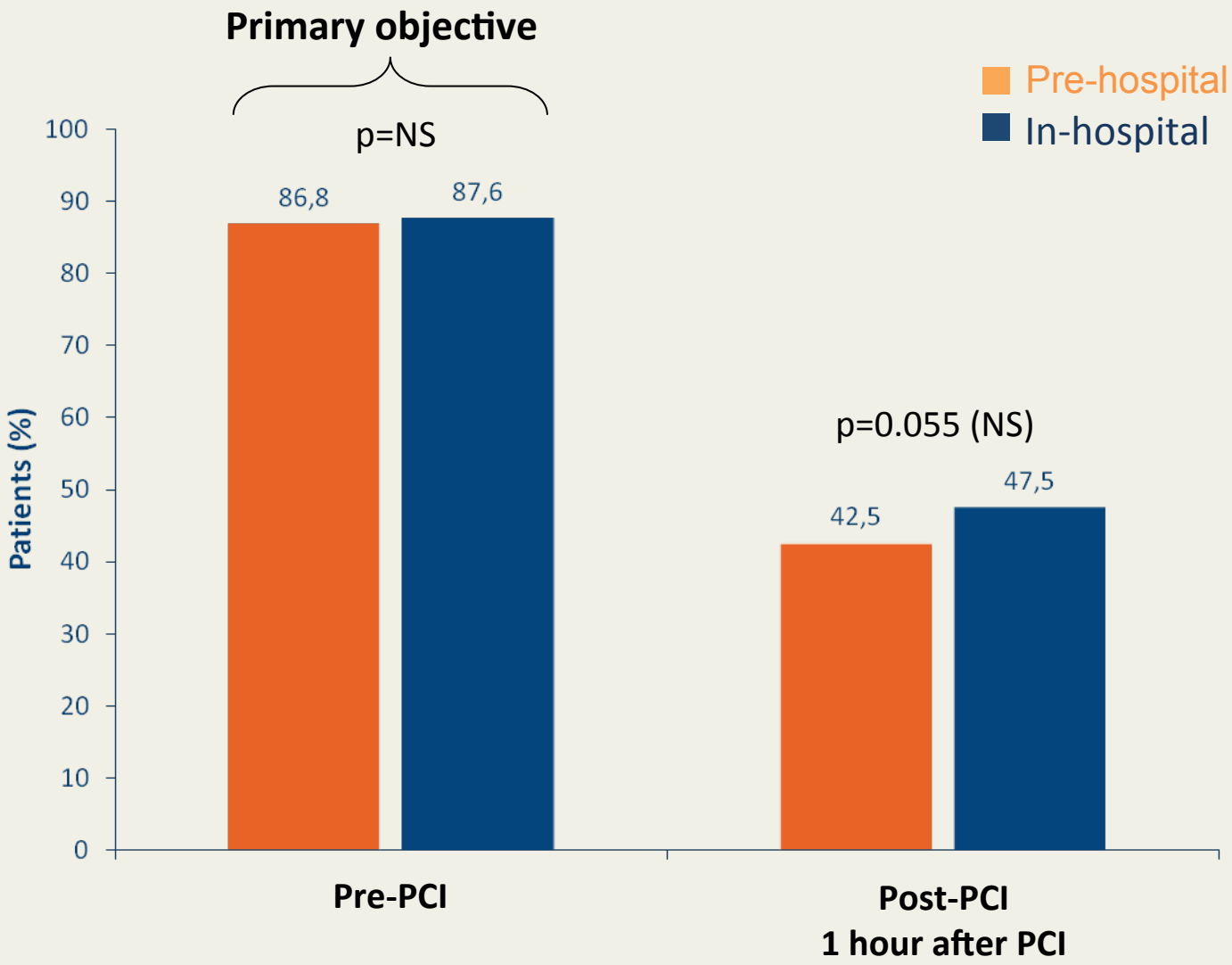


Montalescot G et al. *Am Heart J*. 2013;165:515–522.

Median times to pre- and in-hospital steps



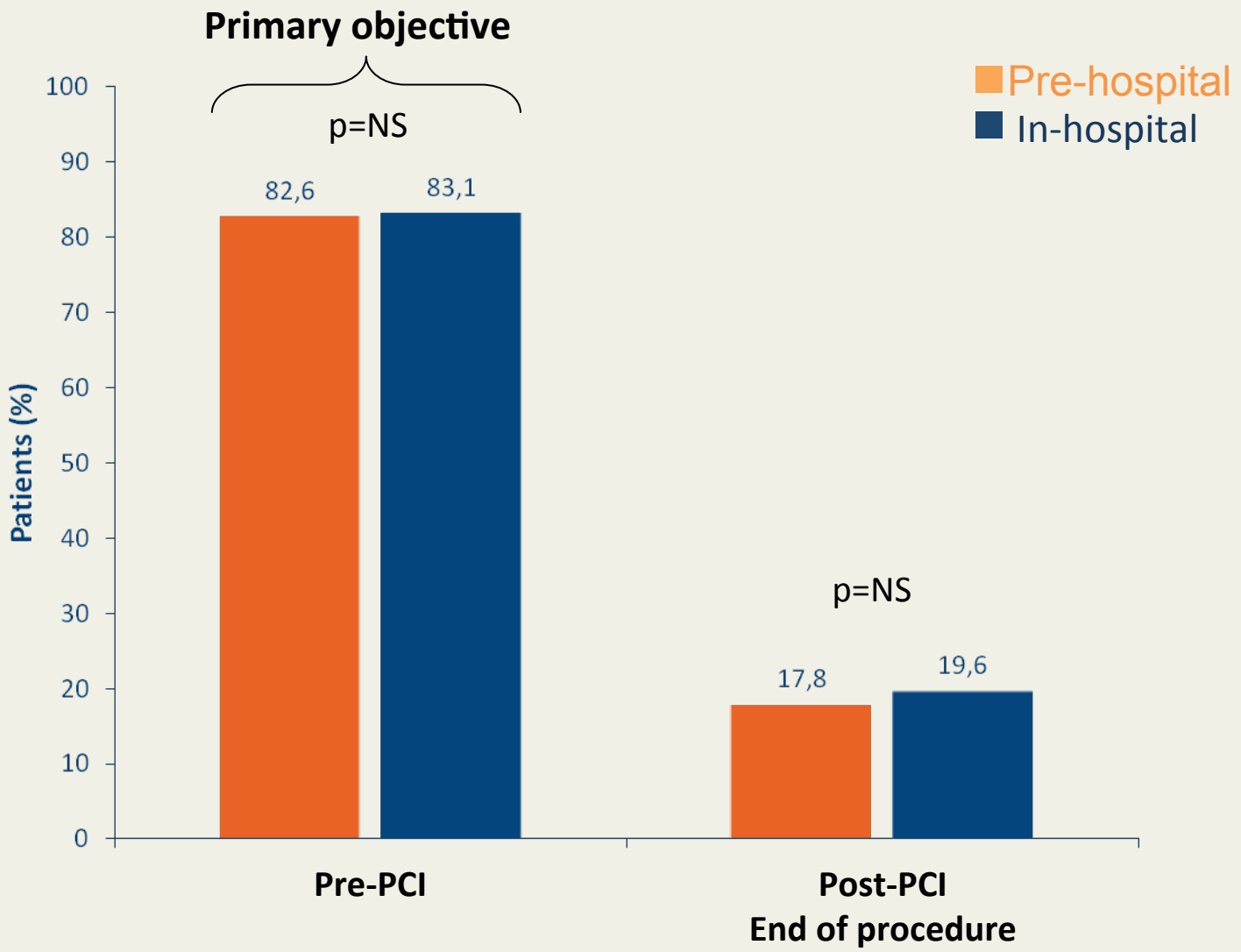
Co-primary efficacy endpoints (mITT)
Absence of ST-segment elevation ≥70%



- Pre-PCI†
  - Pre-hospital n=774
  - In-hospital n=824
- Post-PCI‡
  - Pre-hospital n=713
  - In-hospital n=743

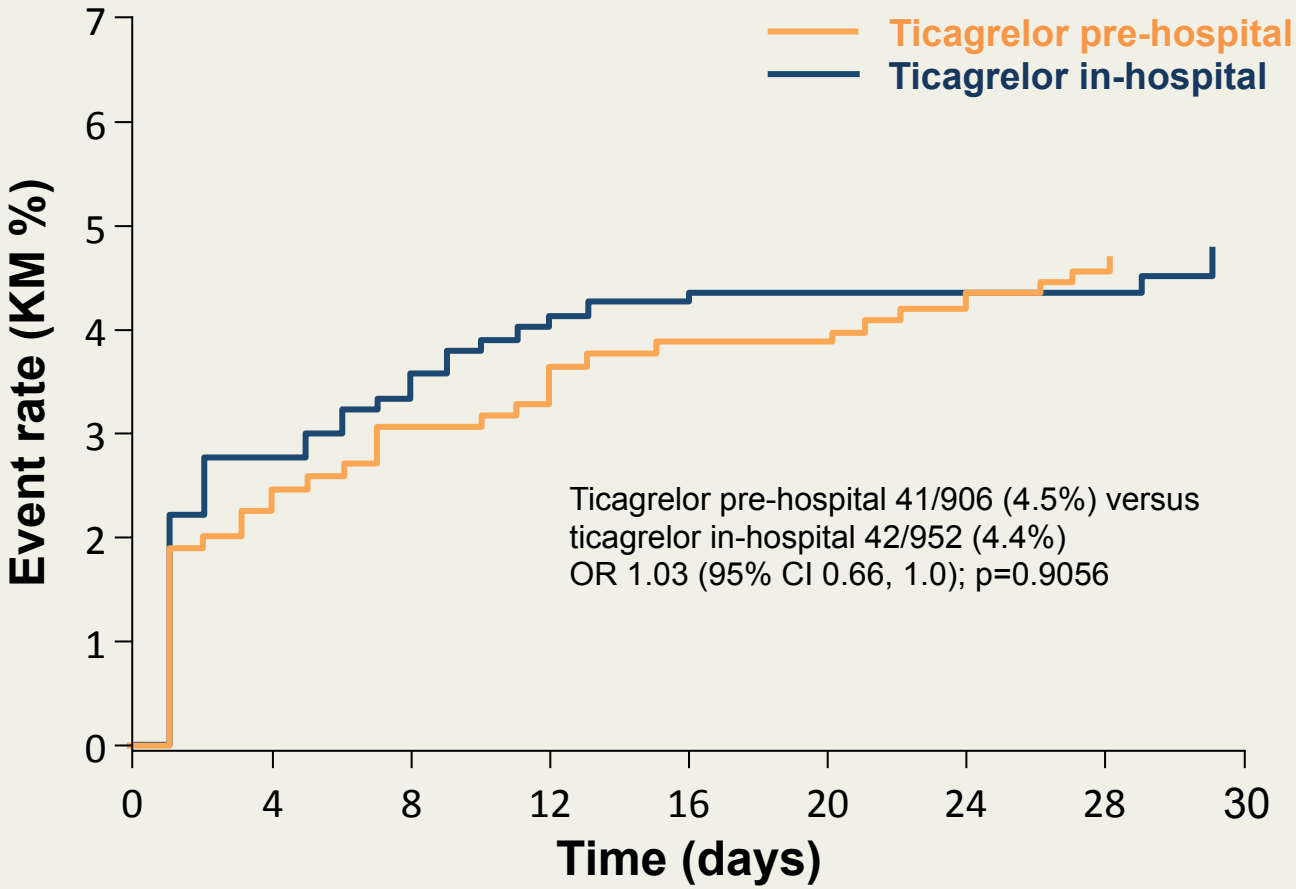
Co-primary efficacy endpoints (mITT)

Absence of TIMI flow grade 3 in infarct-related artery



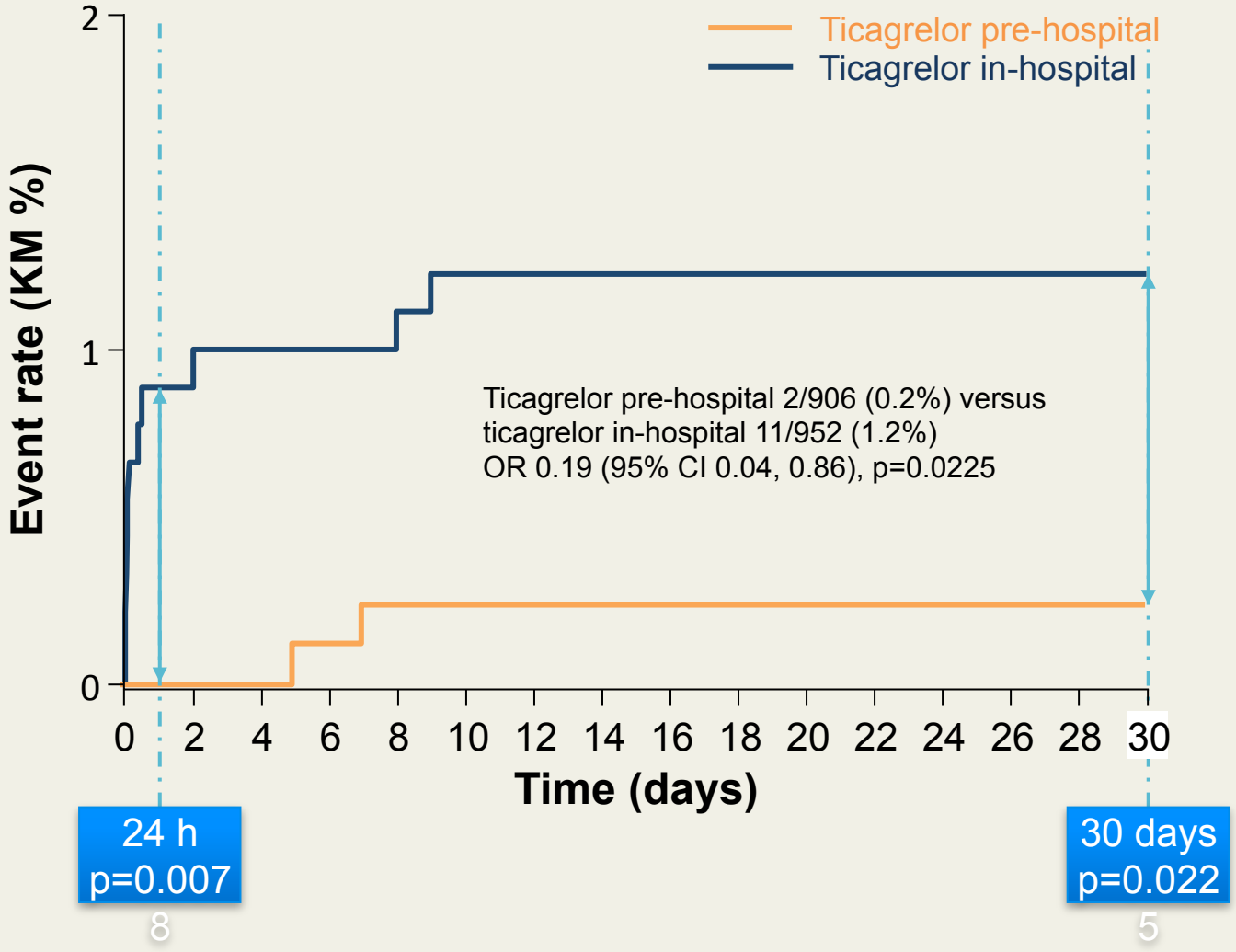
- Pre-PCI†
  - Pre-hospital n=824
  - In-hospital n=856
- Post-PCI‡
  - Pre-hospital n=760
  - In-hospital n=784

Major adverse CV events up to 30 days: Kaplan–Meier curves



Major adverse CV events: death, myocardial infarction, stroke or urgent revascularisation

Definite acute stent thrombosis up to 30 days: Kaplan–Meier curves



Clinical endpoints at 30 days

Values are %	Ticagrelor pre-hosp (n=906)	Ticagrelor in-hosp (n=952)	Odds ratio (95% CI)	p-value
Death (all-cause)	3.3	2.0	1.68 (0.94, 3.01)	0.08
MI	0.8	1.1	0.73 (0.28, 1.94)	0.53
Stroke	0.4	0.2	2.11 (0.39, 11.53)	0.39
TIA	0	0.1		Not estimable
Urgent coronary revascularization	0.6	0.8	0.66 (0.21, 2.01)	0.46
Bail-out GP IIb/IIIa inhibitors	8.6	10.5	0.80 (0.59, 1.10)	0.17

Pre-hospital Treatment with Oral Antiplatelet Agents (vs in-hospital)

In Non-STE-ACS

- Diagnosis is often very uncertain in the pre-hospital setting and includes ACS and other diagnoses
- Management pathways are highly variable and some patients may require urgent surgery
- Angiography and PCI will often be delayed by several hours or even days (and therefore delaying treatment start by an hour is unlikely to affect outcomes)

→ **Starting therapy when diagnosis is confirmed makes sense**

Starting Oral Antiplatelet Therapy Before Angiography in NSTE-ACS

Rationale:

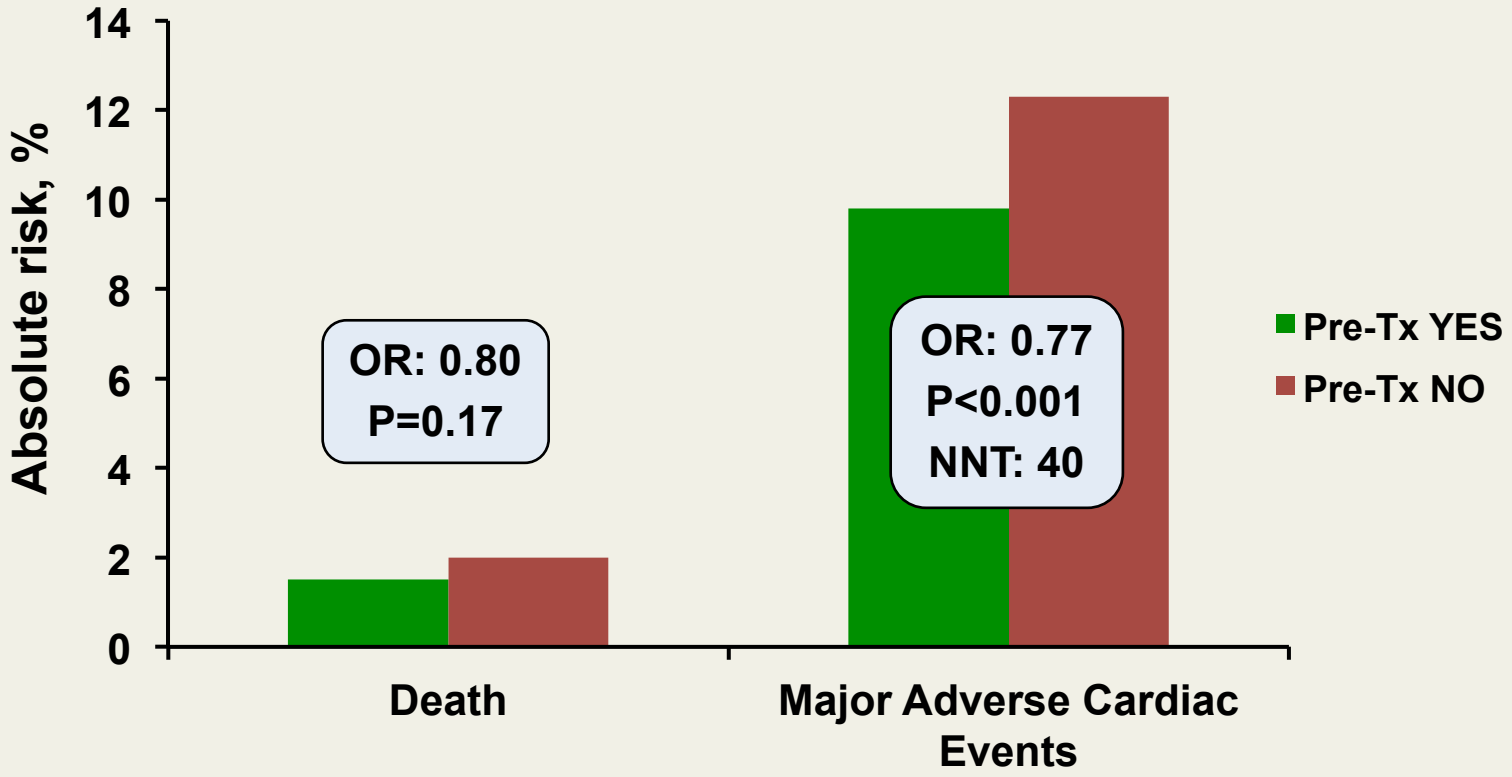
- Allowing time to full efficacy prior to performing PCI for those pts who will require stenting
- Providing antithrombotic protection against death/MI at the time of greatest thrombotic risk: which is early after symptom onset…
- Delay from diagnosis to angiography may range from few hours to… several days

Caveats:

- In non ST-ACS, diagnostic uncertainty is frequent: 15% of patients may end up with a non-ACS diagnosis, 30% of patients will not undergo PCI
- 5 to 12% of patients will require surgery and if $P2Y_{12}$ inhibitors have been given, the risk of bleeding is increased and requires waiting

Clopidogrel and Pre-treatment in PCI: A Meta-analysis

8608 patients out of 7 RCTs undergoing PCI, including NSTEACS, STEMI, and elective PCI

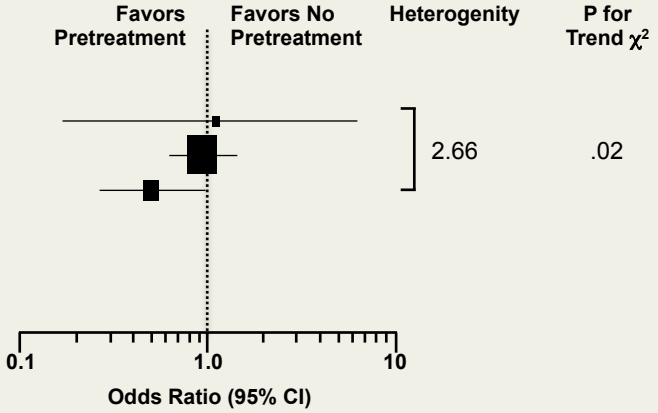


Bellemain-Appaix A, et al. ***JAMA***. 2012;308:2507−16

Upstream therapy with Clopidogrel in ACS vs Elective PCI

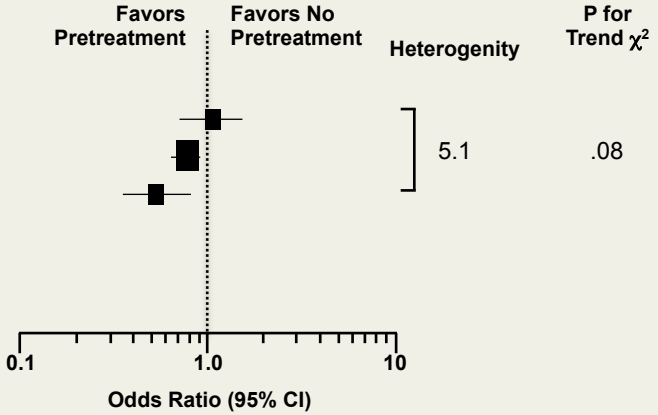
All-cause Mortality

Presenting feature	No. of Patients: Pretreatment	No. of Patients: No Pretreatment	OR (95% CI)
Elective PCI	820	816	1.12 (0.17-7.27)
NSTE ACS	2366	2408	0.93 (0.63-1.36)
STEMI	1097	1101	0.50 (0.26-0.96)



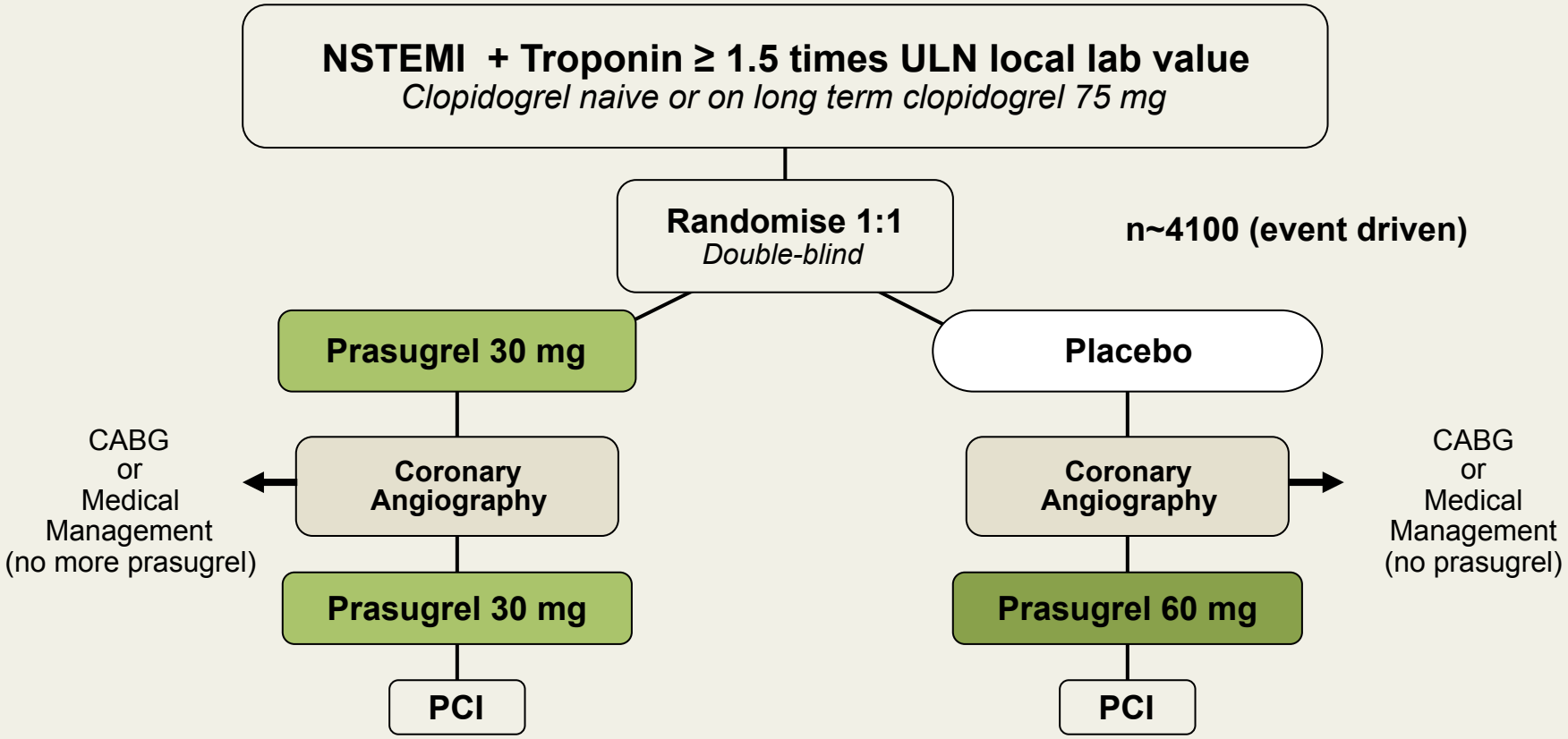
Major Coronary Event

Presenting feature	No. of Patients: Pretreatment	No. of Patients: No Pretreatment	OR (95% CI)
Elective PCI	820	816	1.05 (0.70-1.57)
NSTE ACS	2366	2408	0.78 (0.66-0.91)
STEMI	1097	1101	0.54 (0.36-0.81)



Bellemain-Appaix A, et al. ***JAMA***. 2012;308:2507−16

ACCOAST Design



Prasugrel 10 mg or 5 mg (based on weight and age) for 30 days

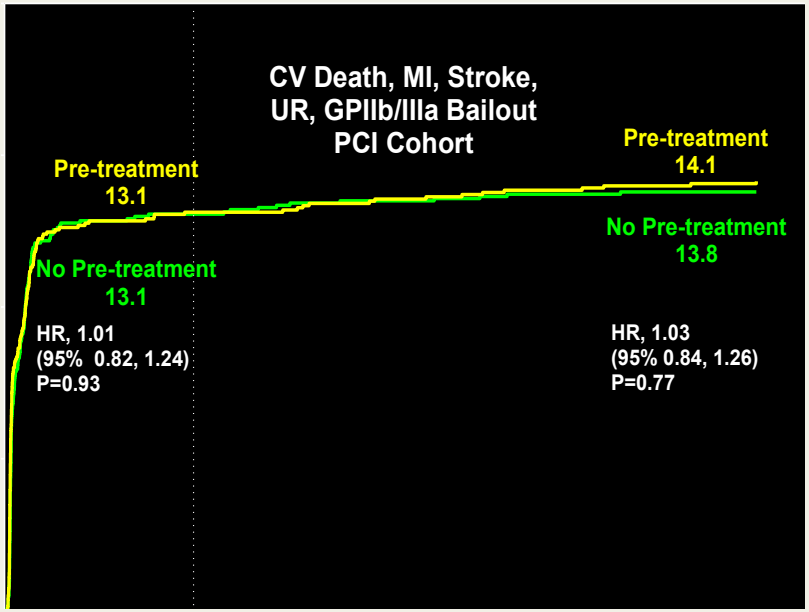
<u>1°Endpoint:</u> CV Death, MI, Stroke, Urg Revasc, GP IIb/IIIa bailout, at 7 days

Montalescot G et al. ***Am Heart J*** 2011;161:650−656

The ACCOAST Trial: Lack of Benefit but Real Harm of Prasugrel Upstream Compared to Downstream Loading

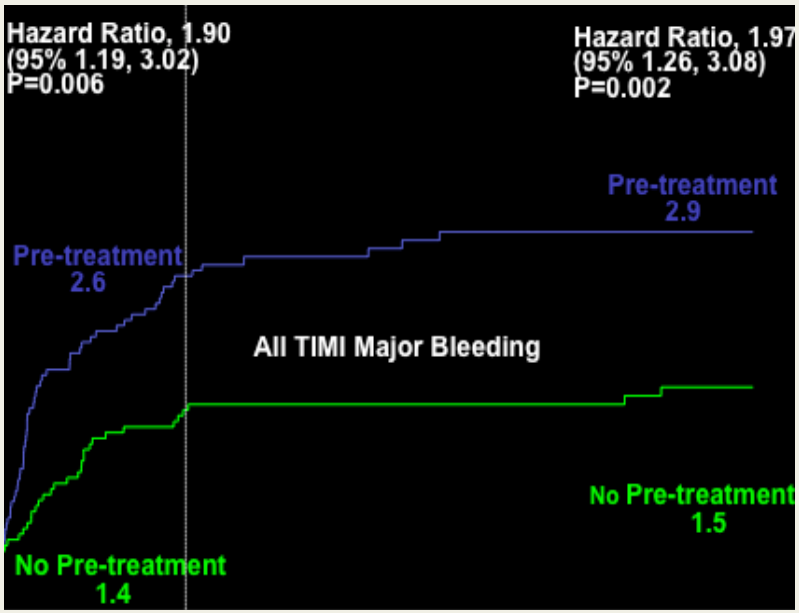
Primary efficacy endpoint

CV Death, MI, Stroke, Urg Revasc, GP IIb/IIIa bailout



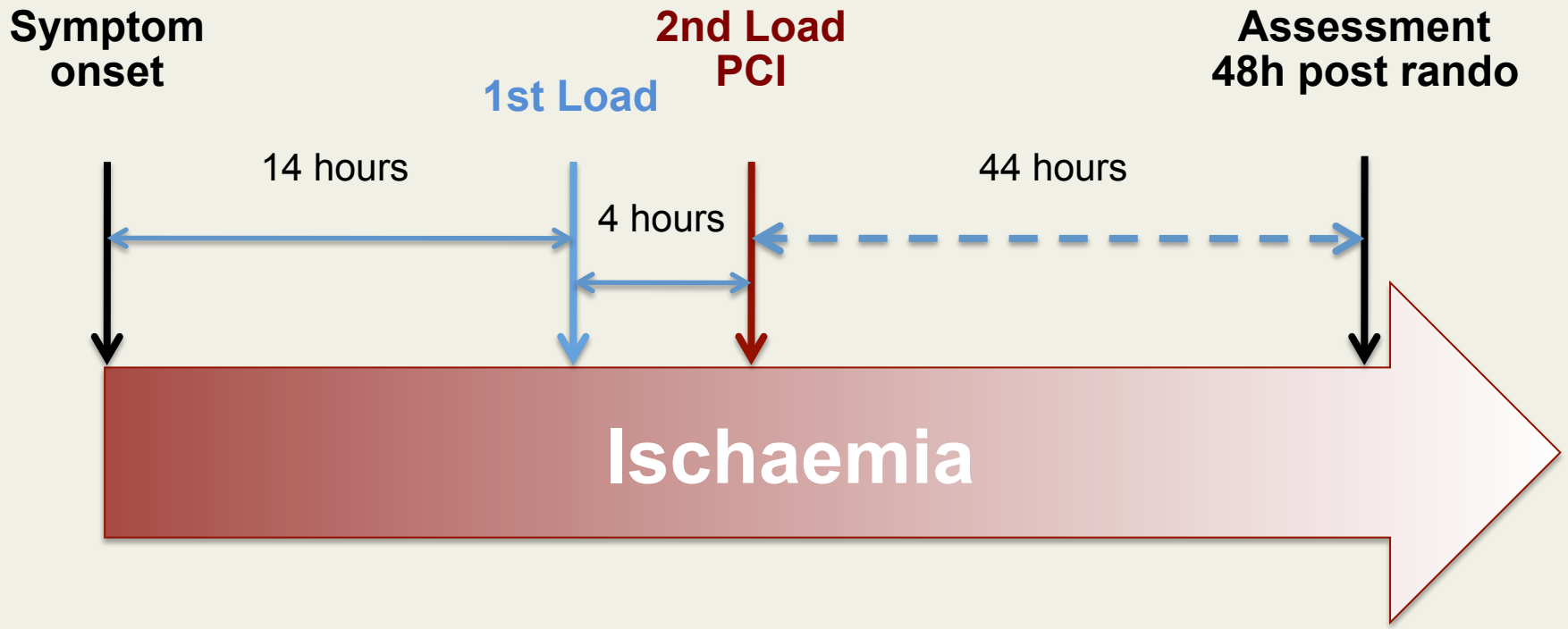
Primary safety endpoint

TIMI major bleeding



Montalescot G et al. ***N Engl J Med*** 2013

Timelines in ACCOAST

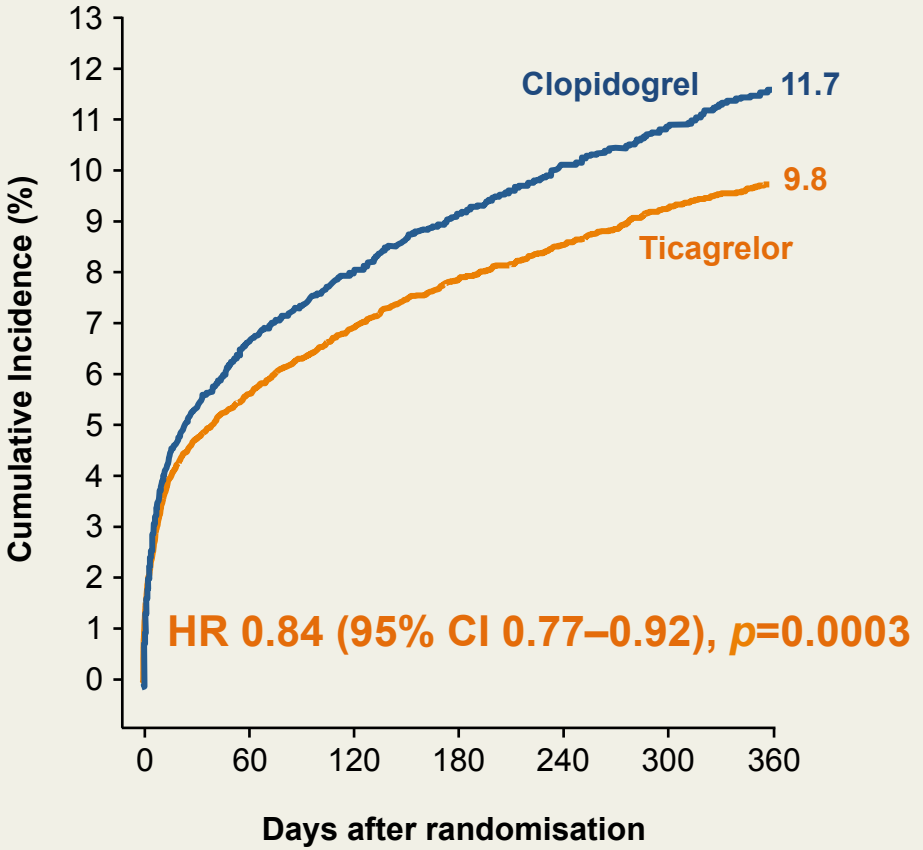


Short delay between 1st and 2nd load:

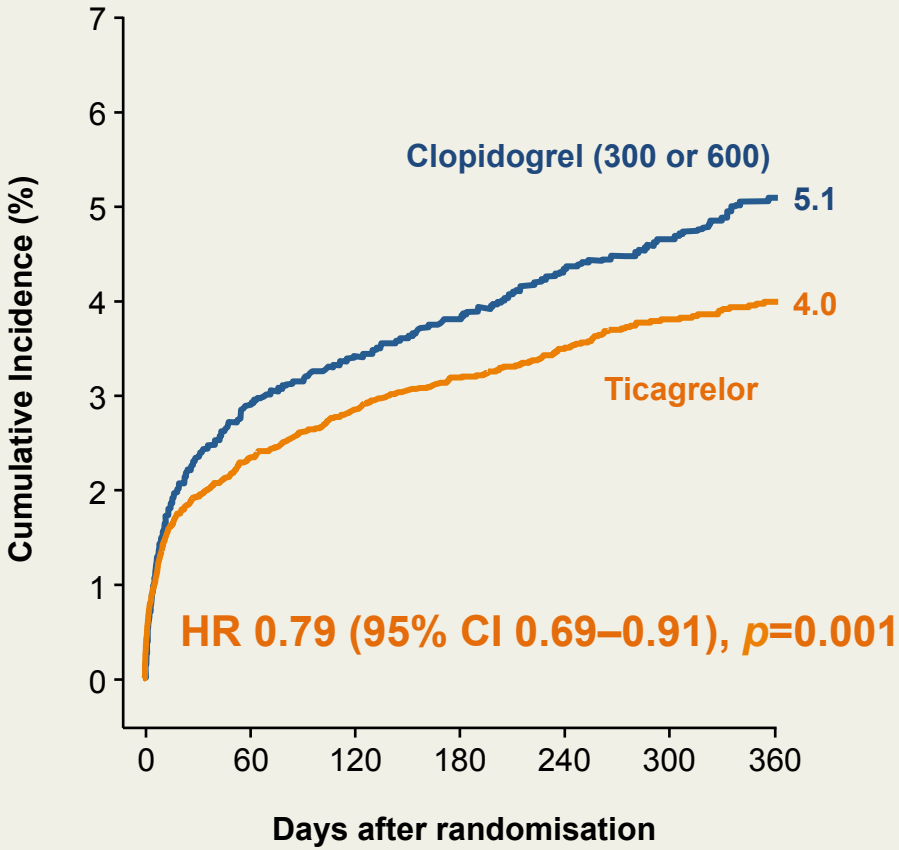
- minimises contrast between study arms
- impairs ascertainment of periprocedural MIs, which are undistinguishable from index MI

PLATO: ticagrelor vs clopidogrel in ACS

Primary endpoint time to CV death, MI or stroke



Cardiovascular death over time



Wallentin et al ***NEJM*** 2009

Upstream Therapy in ACS

- **Pre-hospital treatment with OAP therapy seems logical in STEMI patients going on to Primary PCI**
- **Pre-hospital treatment of non-STE-ACS patients is probably not wise**
- **In hospital « upstream therapy» before angiography**
  - Probably does not matter for patients going on rapidly to angiography and PCI
  - But may be useful if patients will wait for angiography or if clopidogrel is used (given its slow onset of action)
  - Had no demonstrated benefits with prasugrel if patients go to the cath lab rapidly (4h) in ACCOAST
  - Was an effective strategy with ticagrelor in PLATO

Thank you!

STANFORD MEDICINE

Closing the Gaps in the Continuum of Care for Patients with Acute Coronary Syndromes: Implications for Optimal Antiplatelet Use

High Risk Patients with ACS: What Are the Concerns

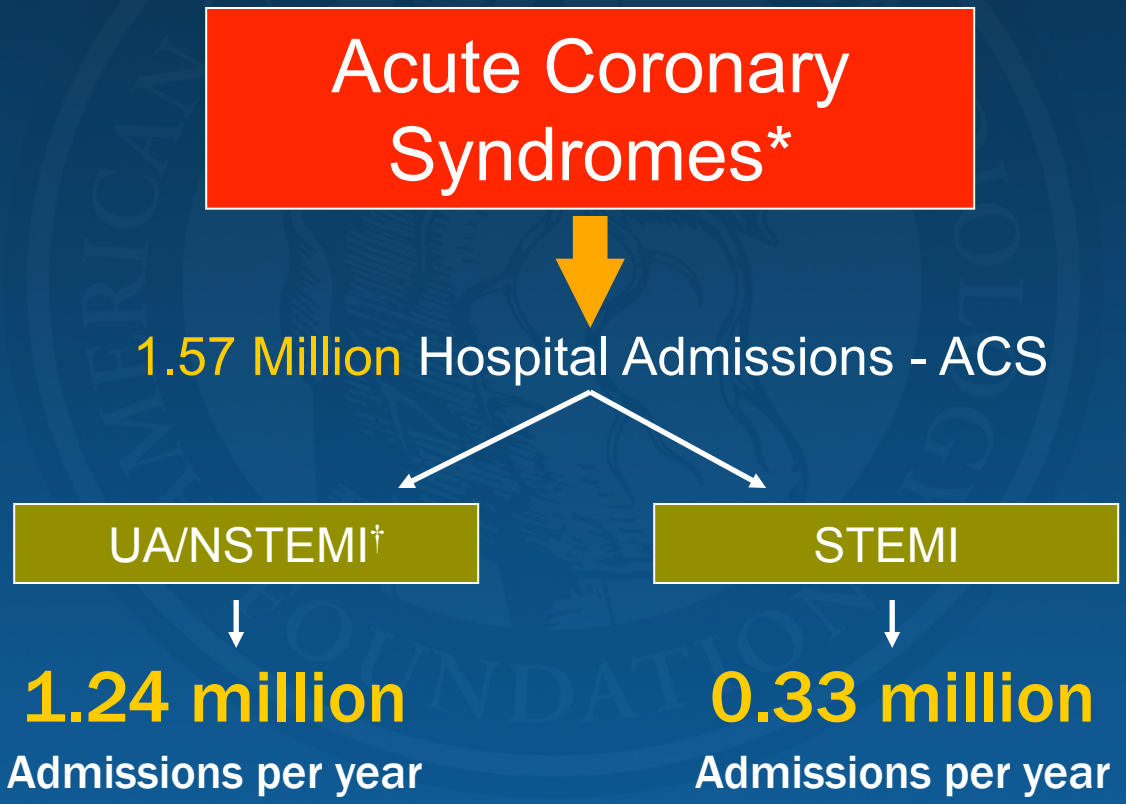
Robert A. Harrington MD, FACC, FAHA, FESC
Arthur L. Bloomfield Professor of Medicine
Chair, Department of Medicine
Stanford University

High Risk ACS: What Are the Concerns

Stanford MEDICINE

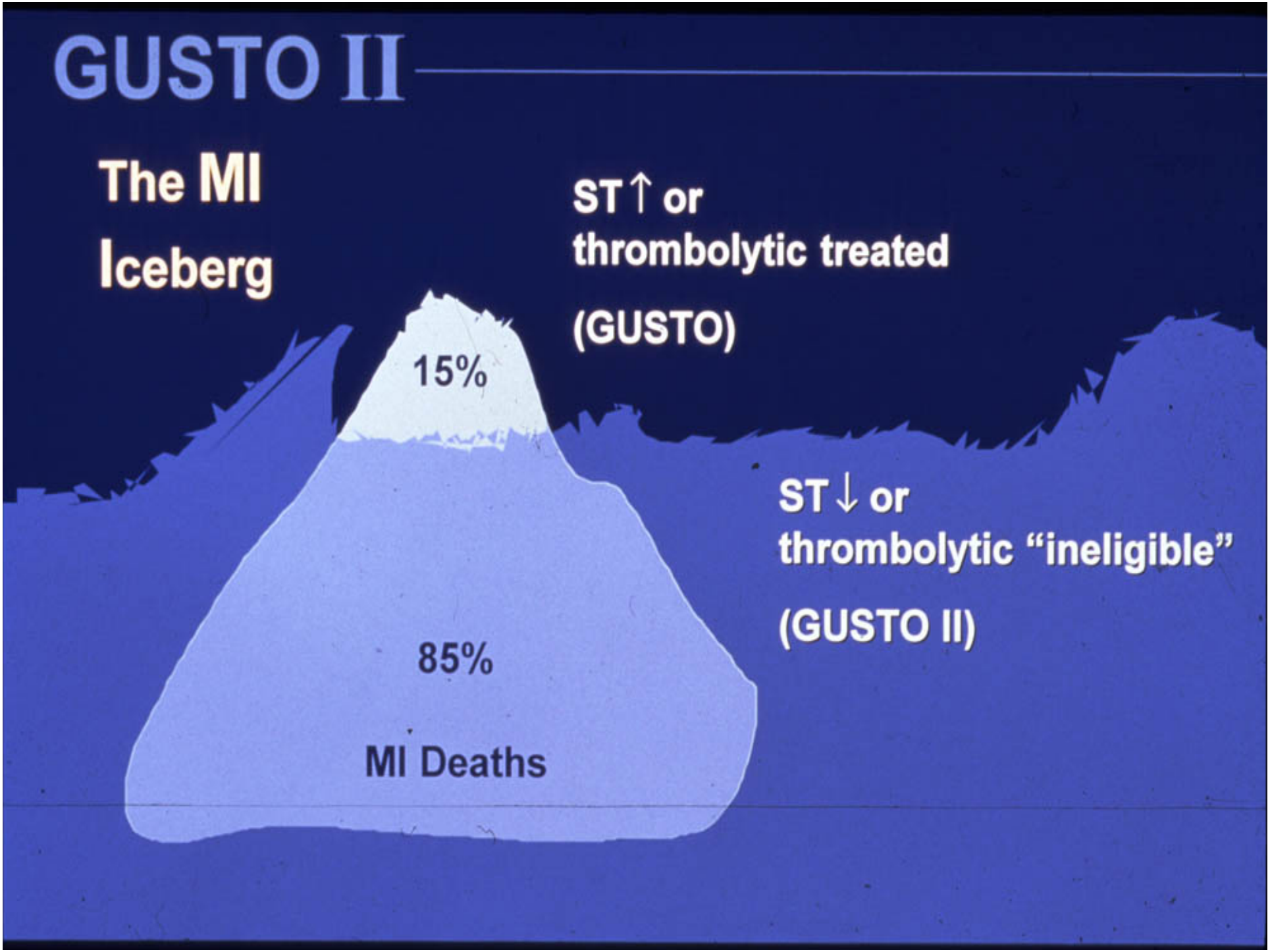
- Initial assessment of acute chest pain
  - Based on 12-lead ECG (STE versus NSTE)
  - Cardiac biomarkers (information from CKMB and troponin)
- Evolution of risk scores
  - For prognosis
  - For therapeutic decision making
- Moving from acute to long term care
- General concepts of antithrombotic therapy use
  - Balancing ischemia and bleeding
- What's next?
  - Adherence
  - Lipids
  - inflammation

US ACS Hospitalizations



*Primary and secondary diagnoses. †About 0.57 million NSTEMI and 0.67 million UA.
Heart Disease and Stroke Statistics – 2007 Update. Circulation 2007; 115:69–171.

GUSTO II


The MI Iceberg
ST↑ or thrombolytic treated
(GUSTO)
15%
ST↓ or thrombolytic "ineligible"
(GUSTO II)
85%
MI Deaths

First UA Guidelines

Diagnosing and Managing Unstable Angina

Eugene Braunwald, MD (Panel Chair); Robert H. Jones, MD; Daniel B. Mark, MD; Jay Brown, MD; Leslie Brown, MPH, JD; Melvin D. Cheitlin, MD; Craig A. Concannon, MD; Marie Cowan, PhD, RN; Conan Edwards, PhD; Valentin Fuster, MD, PhD; Lee Goldman, MD; Lee A. Green, MD, MPH; Cindy L. Grines, MD; Bruce W. Lytle, MD; Kathleen M. McCauley, PhD, RN, CS; Alvin I. Mushlin, MD, ScM; Gregory C. Rose, MD; Earl E. Smith III, MD; Julie A. Swain, MD; Eric J. Topol, MD; and James T. Willerson, MD

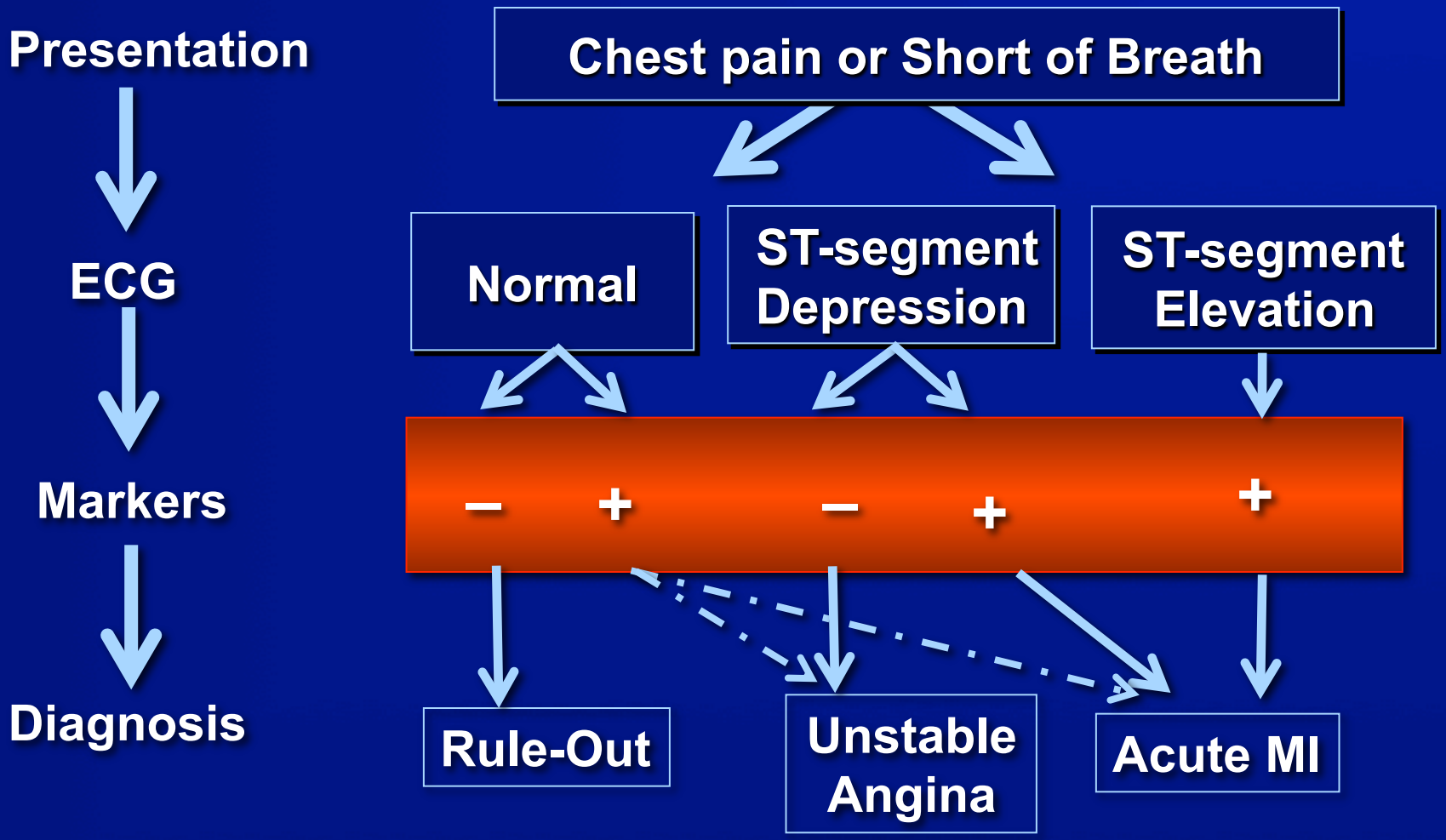
Abstract This *Quick Reference Guide for Clinicians* contains recommendations on the care of patients with unstable angina based on a combination of evidence obtained through extensive literature reviews and consensus among members of an expert panel. Principal conclusions include the following. (1) Many patients suspected of having unstable angina can be discharged home after adequate initial evaluation. (2) Further outpatient evaluation may be scheduled for up to 72 hours after initial presentation for patients with clinical symptoms of unstable angina judged at initial evaluation to be at low risk for complications. (3) Patients with acute ischemic heart disease judged to be at intermediate or high risk of complications should be hospitalized for careful monitoring of their clinical course. (4) Intravenous thrombolytic therapy should not be administered to patients without evidence of ST segment elevation and acute myocardial infarction. (5) Assessment of prognosis by noninvasive testing often aids selection of appropriate therapy. (6) Coronary angiography is appropriate for patients judged to be at high risk for cardiac complications or death based on their clinical course or results of noninvasive testing. (7) Coronary artery bypass surgery should be recommended for almost all patients with left main disease and many patients with three-vessel disease, especially those with left ventricular dysfunction. (8) The discharge care plan should include continued monitoring of symptoms; appropriate drug therapy, including aspirin; risk-factor modification; and counseling. (***Circulation*****. 1994;90:613-622.)**

Assessing Risk in UA

TABLE 5. Short-term Risk of Death or Nonfatal Myocardial Infarction in Patients With Symptoms Suggesting Unstable Angina

High Risk	Intermediate Risk	Low Risk
At least one of the following features must be present	No high-risk feature but must have any of the following	No high- or intermediate-risk feature but may have any of the following
Prolonged ongoing (>20 min) rest pain	Rest angina now resolved but not low likelihood of CAD	Increased angina frequency, severity, or duration
Pulmonary edema	Rest angina (>20 min or relieved with rest or nitroglycerin)	Angina provoked at a lower threshold
Angina with new or worsening mitral regurgitation murmurs	Angina with dynamic T-wave changes	New-onset angina within 2 weeks to 2 months
Rest angina with dynamic ST changes ≥1 mm	Nocturnal angina	Normal or unchanged ECG
Angina with S_3 or rales	New-onset CCSC III or IV angina in past 2 weeks but not low likelihood of CAD	
Angina with hypotension	Q waves or ST depression ≥1 mm in multiple leads	
	Age >65 years	

Time Dependent Emergency Evaluation of ACS



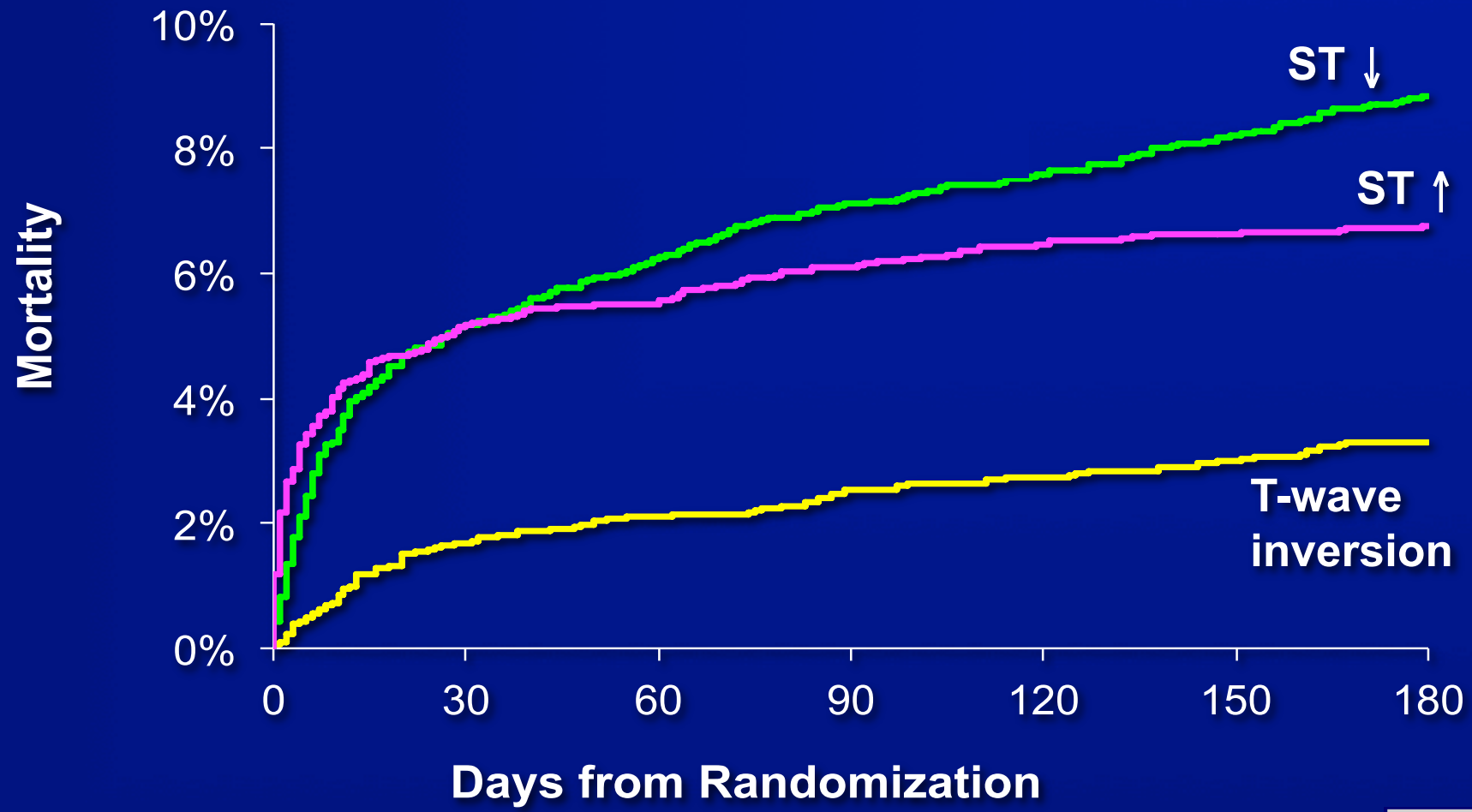
Braunwald E,2002 http://www.acc.org/clinical/guidelines/unstable/unstable

Baseline Characteristics STEMI vs. NSTEMI

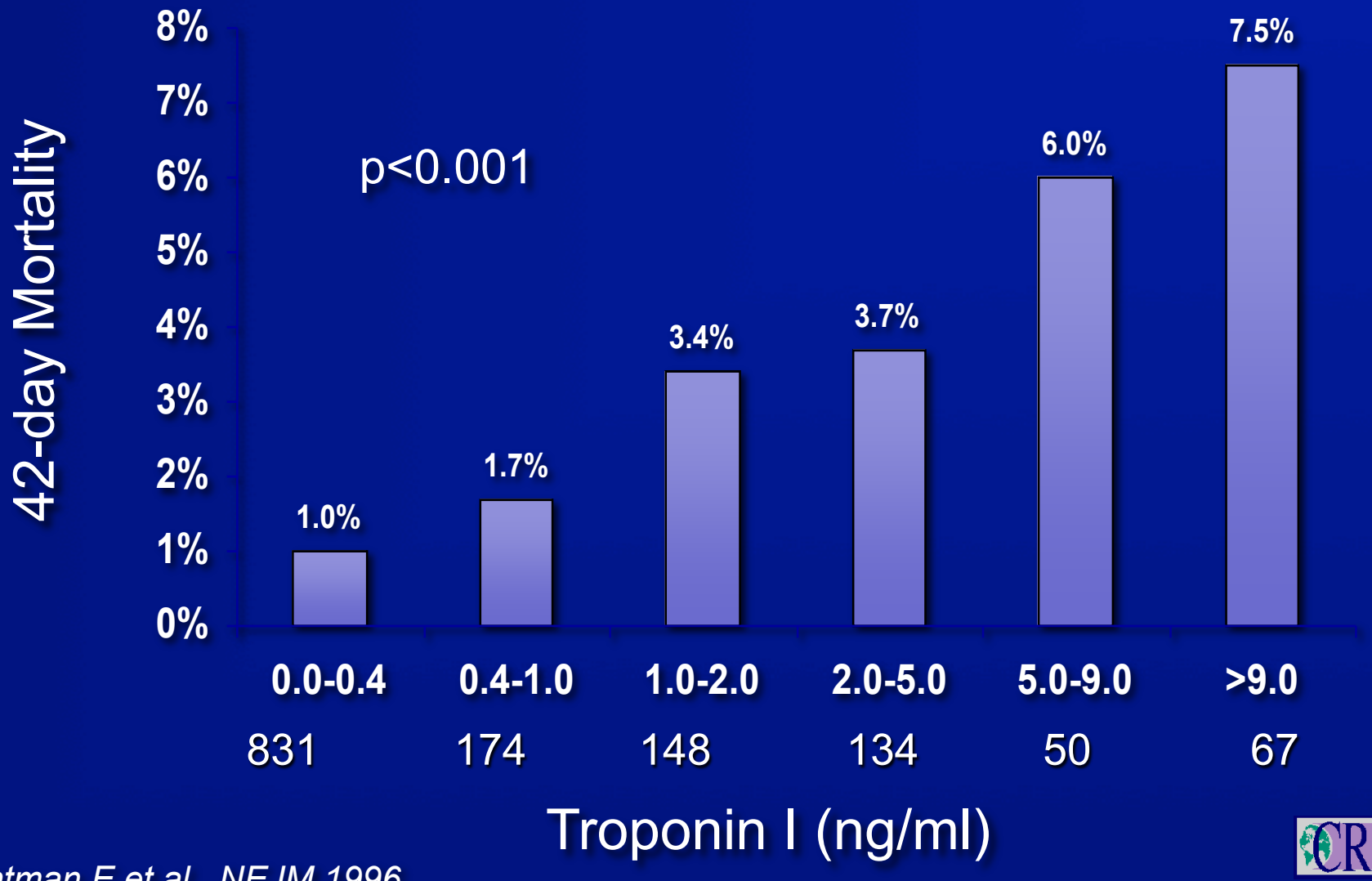
Variable	STEMI (n= 56,761)	NSTEMI (n= 88,407)
Mean age (yrs)	62	67
Female sex	30%	39%
Diabetes mellitus	25%	39%
Prior MI	19%	30%
Prior HF	5%	17%
Prior PCI	20%	28%
Prior CABG	7%	18%
Prior stroke	5%	10%

ACTION Registry-GWTG DATA: January 01, 2012 - December 31, 2012

ACS without Persistent ST Elevation:
Initial ECG ST Status and Risk: GUSTO II



Mortality by Quantitative Troponin I: TIMI-IIIB



-Antman E et al. NEJM 1996

Combining ECG Findings and Cardiac Markers

Mortality by ECG and TnT Status in GUSTO-IIa

	N	Total	TnT >0.1 ng/ml	TnT ≤0.1 ng/ml
ST Elevation	435	7.4%	13.0%	4.7%
ST Depression	88	8.0%	11.6%	4.4%
ECG Confounders*	69	11.6%	15.4%	6.7%
T-wave inversion	133	1.2%	4.1%	0

*LBBB, LVH, Paced

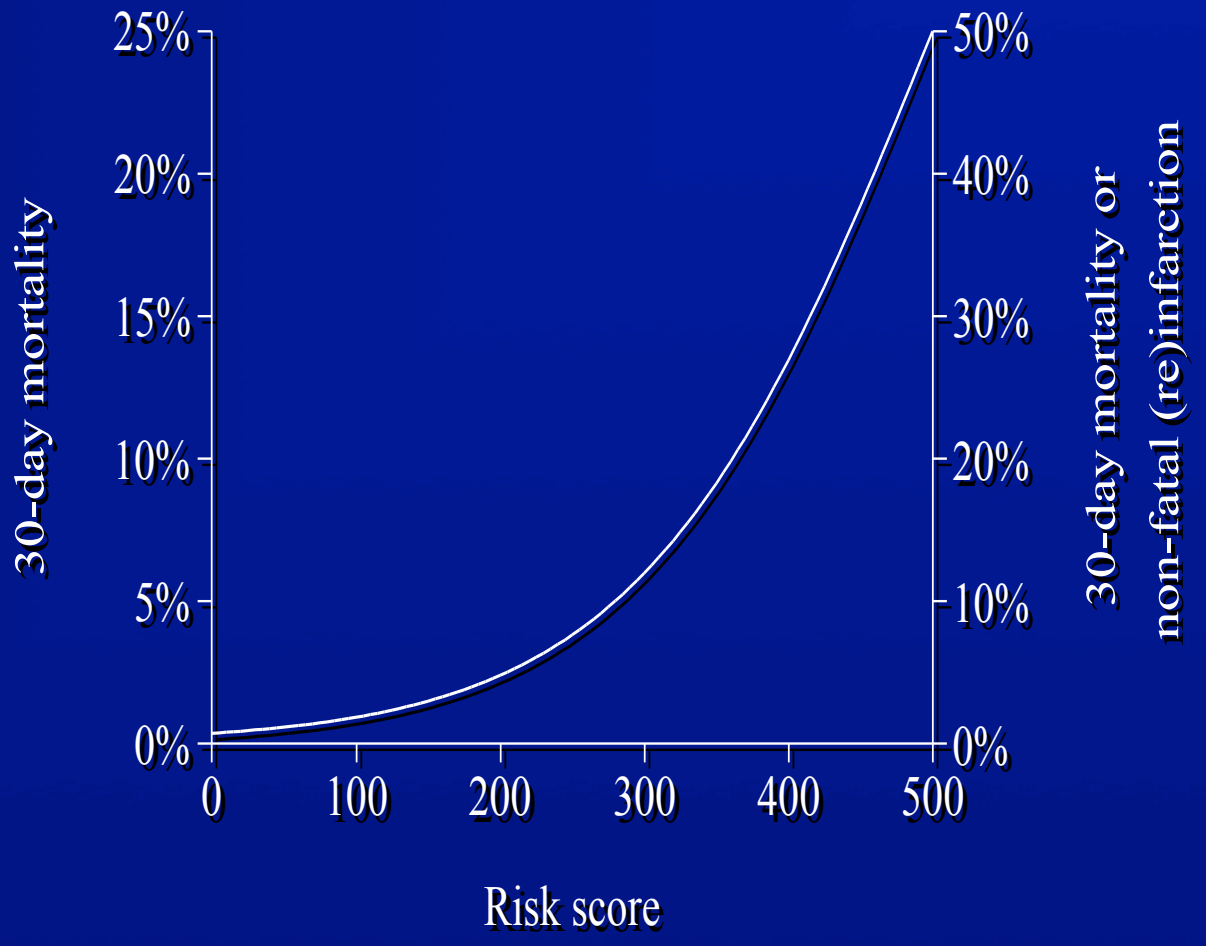
Ohman, NEJM , 1997

Predicting Risk in ACS without Persistent ST↑

Creating a 30-Day Risk Score

Pre-Randomization Variables

- Age
- Gender (male)
- Prior angina (CCS Class)
- Heart rate
- Systolic BP
- Rales
- ST depression



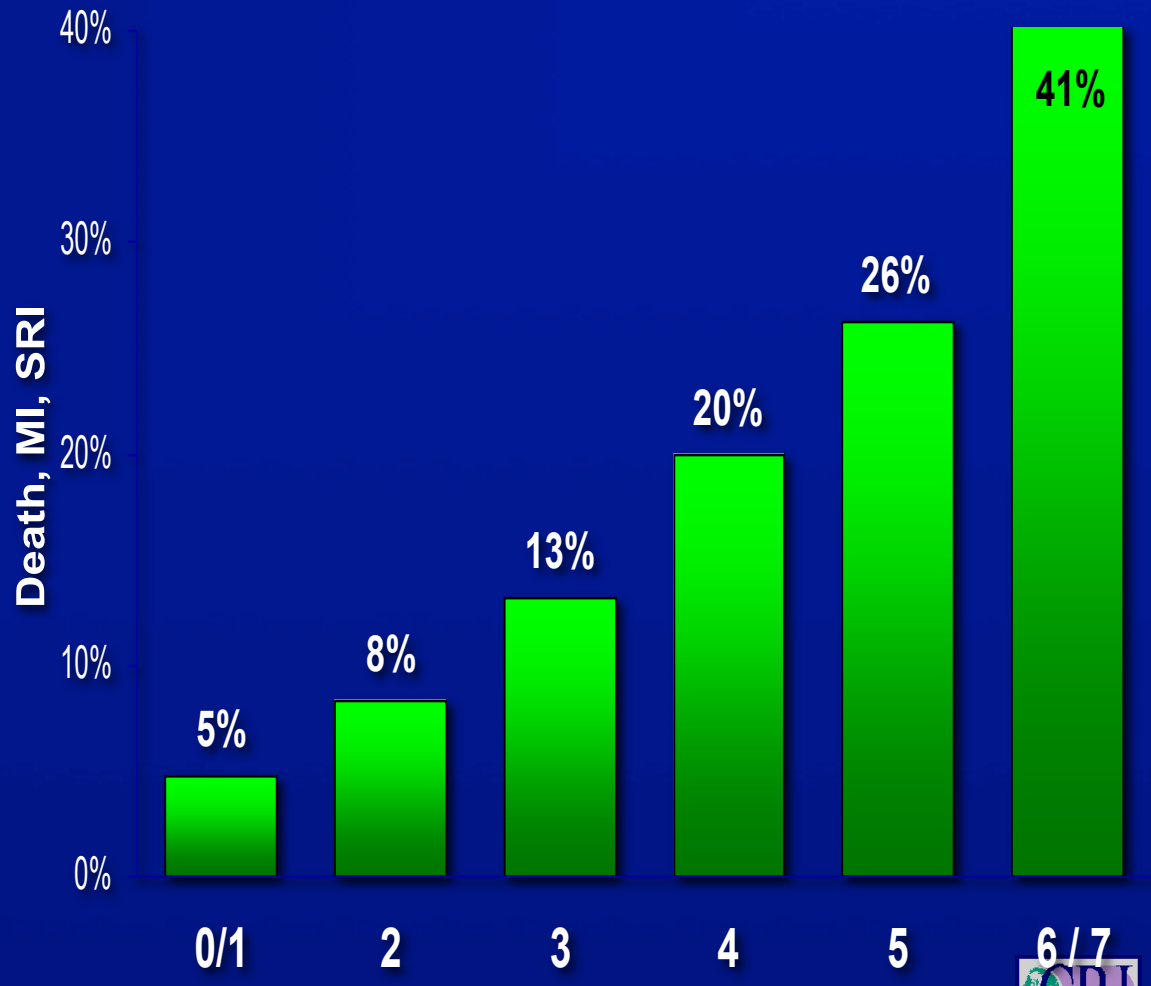
-Boersma E et al. Circulation 2000;101:2557

TIMI Risk Score for UA/Non ST↑MI

From ESSENCE/TIMI 11B

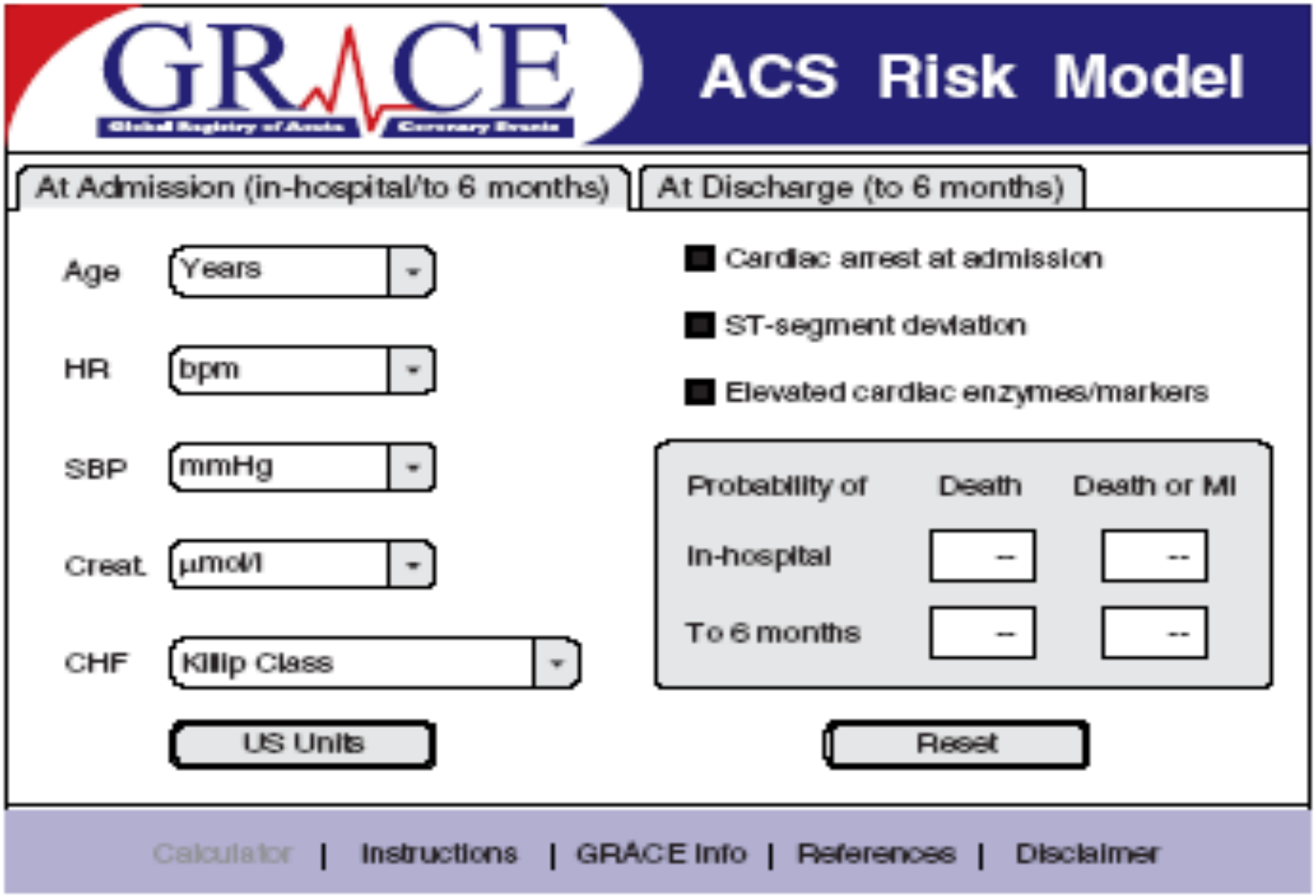
Variables

- Age ≥ 65
- ≥ 3 risk factors
- Prior coronary stenosis ≥ 50%
- ST deviation
- 2 anginal events in 24 hr
- ASA in prior 7d
- Elevated cardiac markers

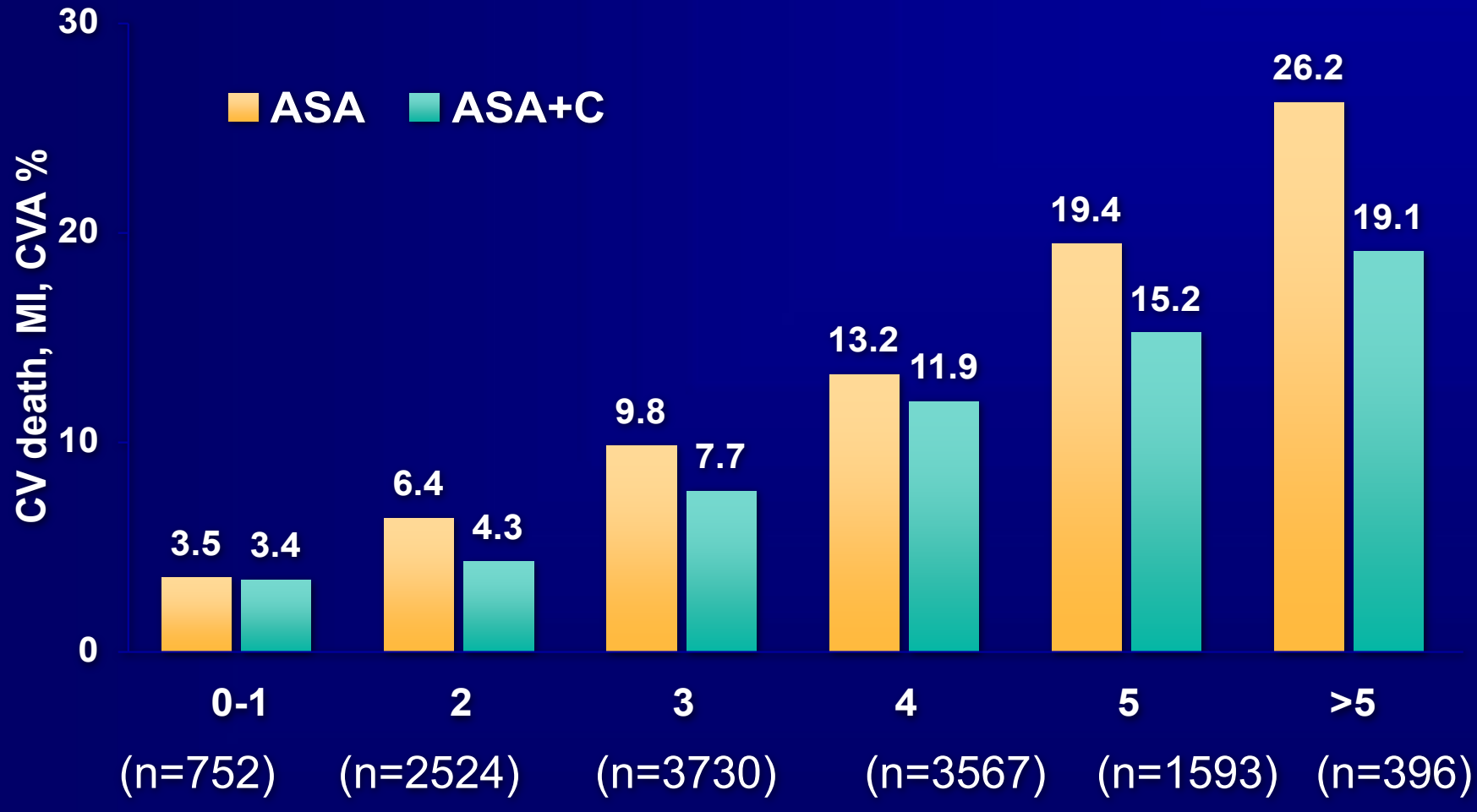


—*Antman E et al. JAMA 2000;284*

GRACE ACS Risk Model



Clopidogrel and ASA in ACS:
Benefit by Risk Groups in CURE (Outcome vs. TIMI Score)

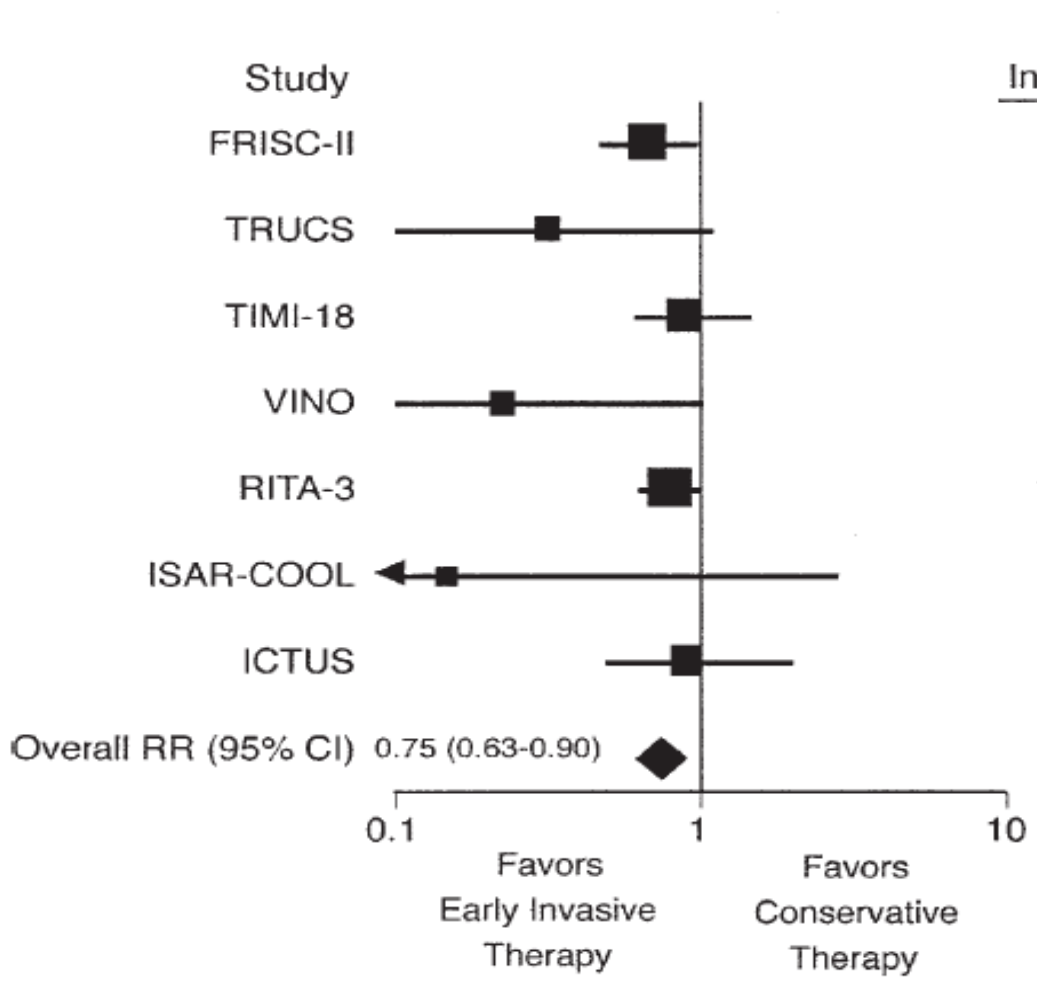


DUKE UNIVERSITY MEDICAL CENTER

—Budaj A, et al. Circ 106:1622;2002

Duke Clinical Research Institute

Invasive versus Conservative Rx in NSTE ACS

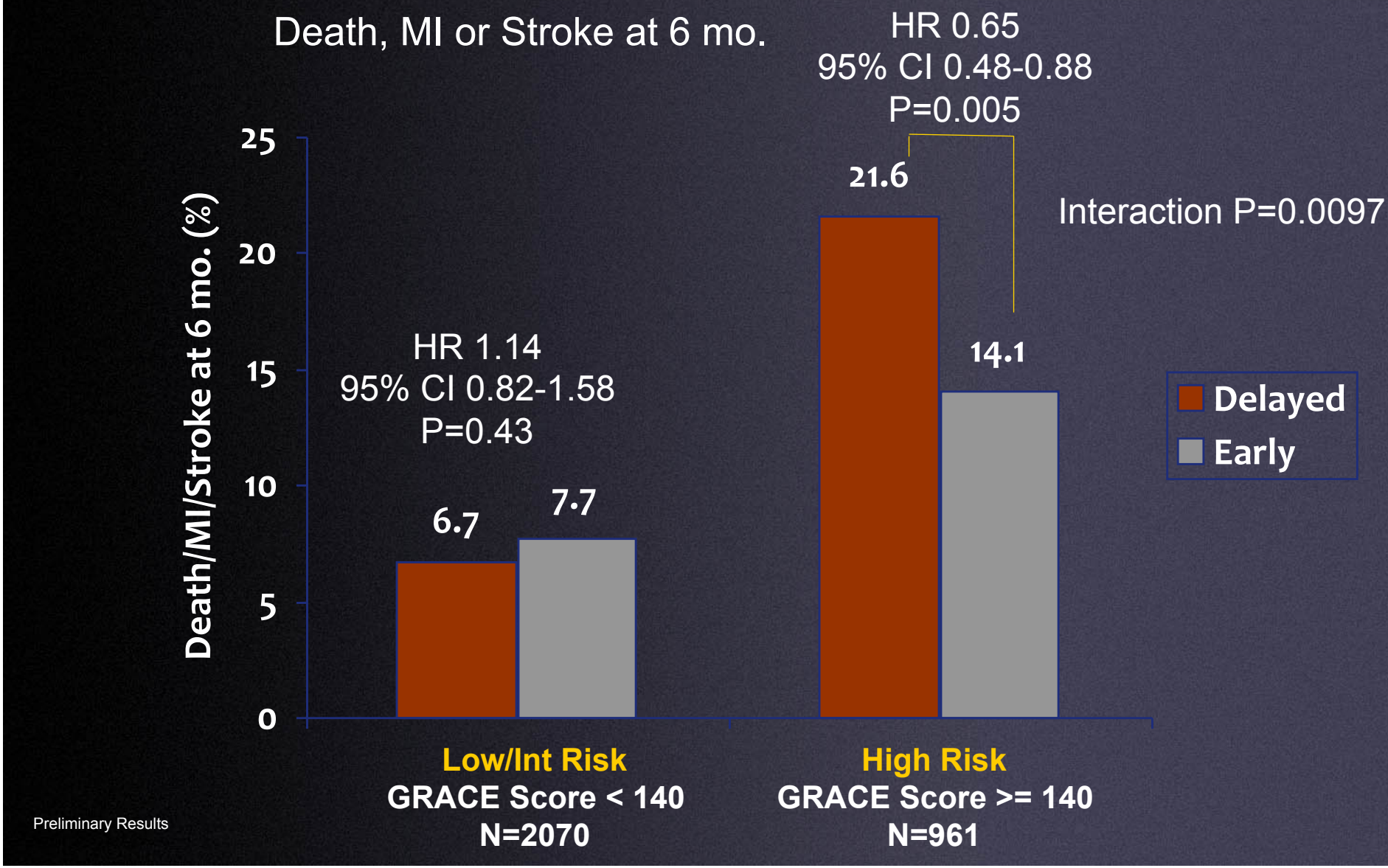


Study	Deaths, n		Follow-up, Months
	Invasive	Conservative	
FRISC-II	45	67	24
TRUCS	3	9	12
TIMI-18	37	39	6
VINO	2	9	6
RITA-3	102	132	60
ISAR-COOL	0	3	1
ICTUS	15	15	12

-Bavry AA, et al. JACC 48;2006

Figure 1. Relative risk of all-cause mortality for early invasive therapy compared with conservative therapy at a mean follow-up of 2 years. The

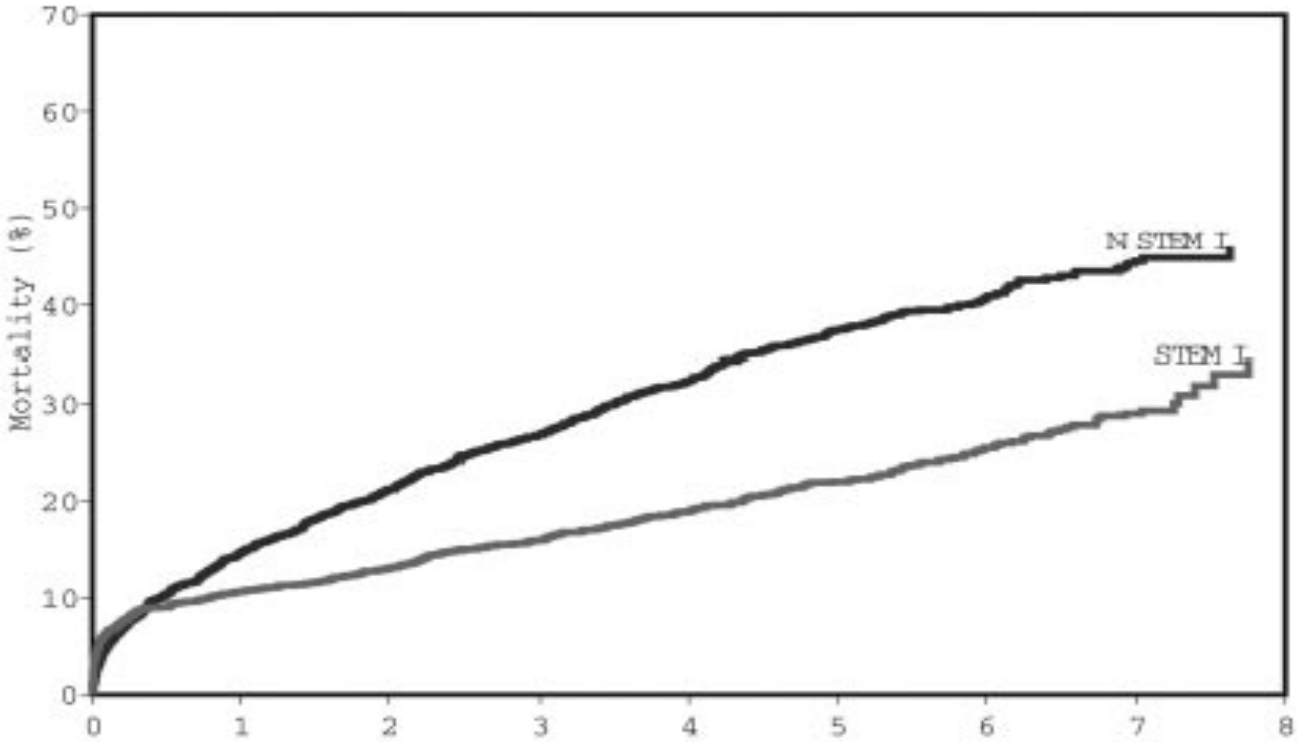
GRACE Risk Score: Primary Outcome



Preliminary Results

Long-term Mortality: NSTE MI versus STE MI

Duke Databank Experience

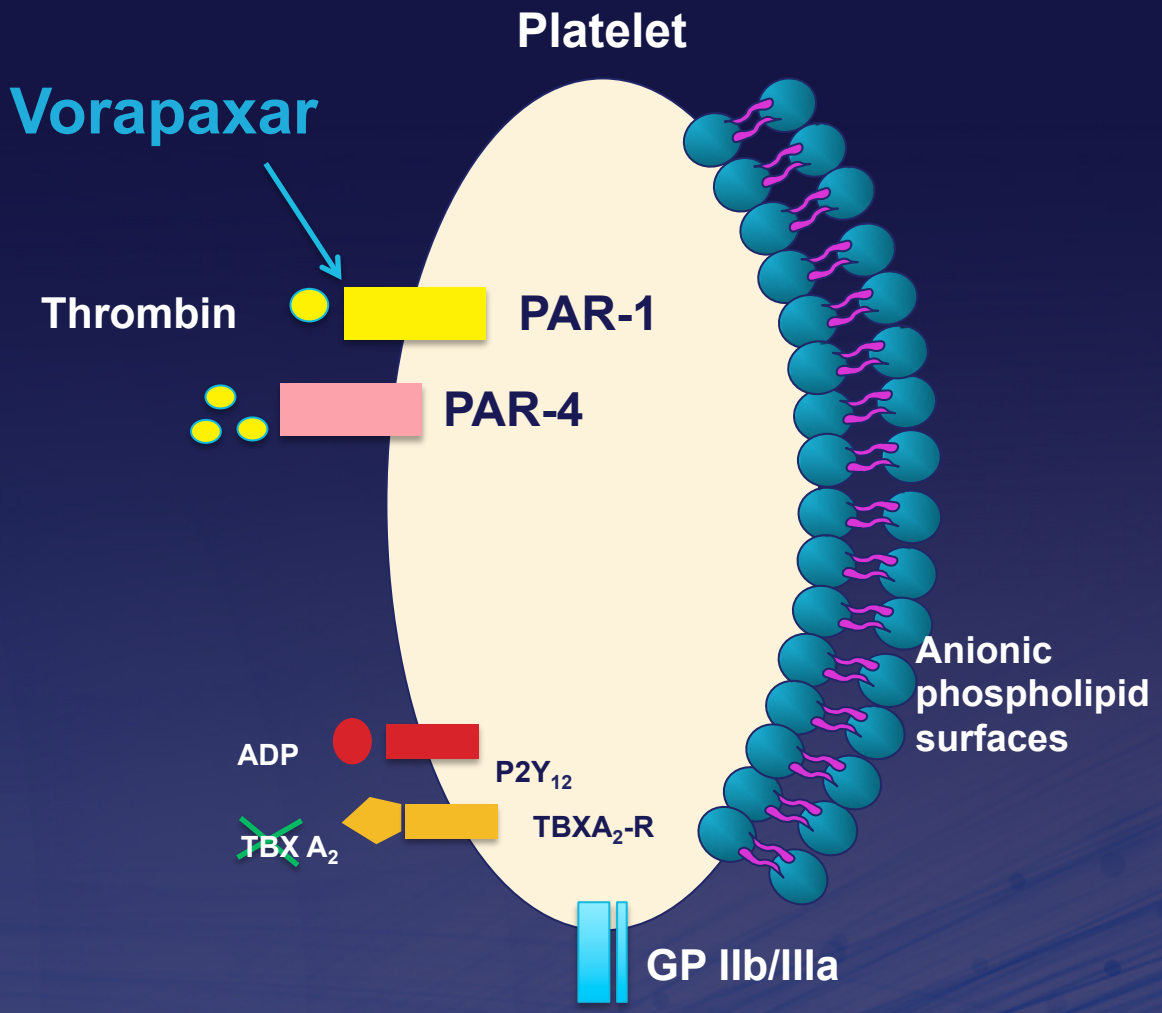


No.atrisk

STEM I	1951	1751	1628	1418	1143	878	576	289	35
N STEM I	2399	2024	1771	1437	1093	769	451	208	32

-Chan MY, et al. Circulation 119; 2009

Background



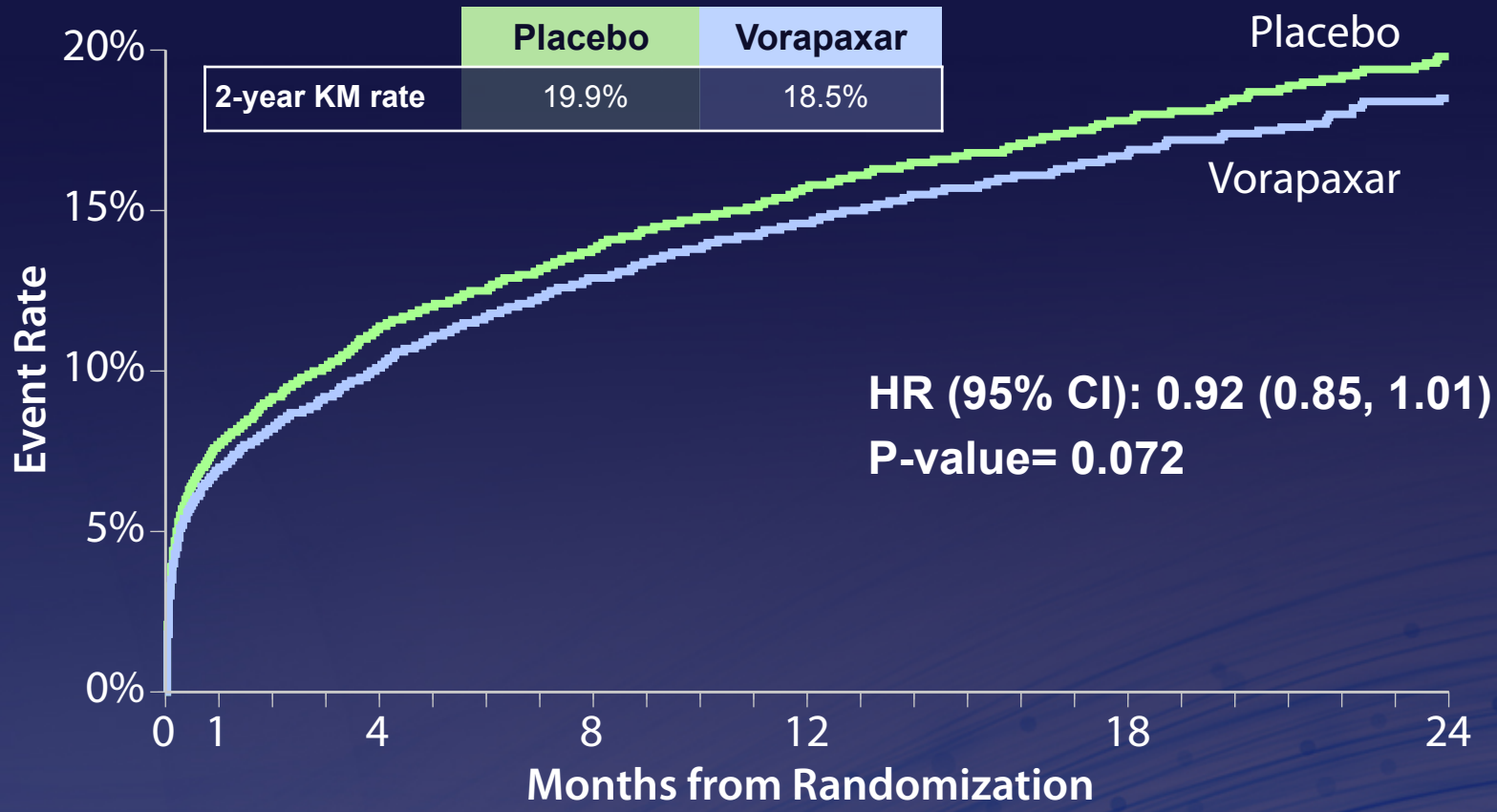
- Vorapaxar:
  - First-in-class
  - Oral PAR-1 inhibitor
- Metabolism:
  - Primarily hepatic via CYP 3A4
  - Terminal half-life: ~126–269 hr
- PK-PD
  - Exposure to vorapaxar is dose-proportional with predictable PD
- Prior ACS and elective PCI trials with no increase in bleeding and fewer MIs

Chackalamannil S, J Med Chem, 2006

Primary Endpoint

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

TRA·CER

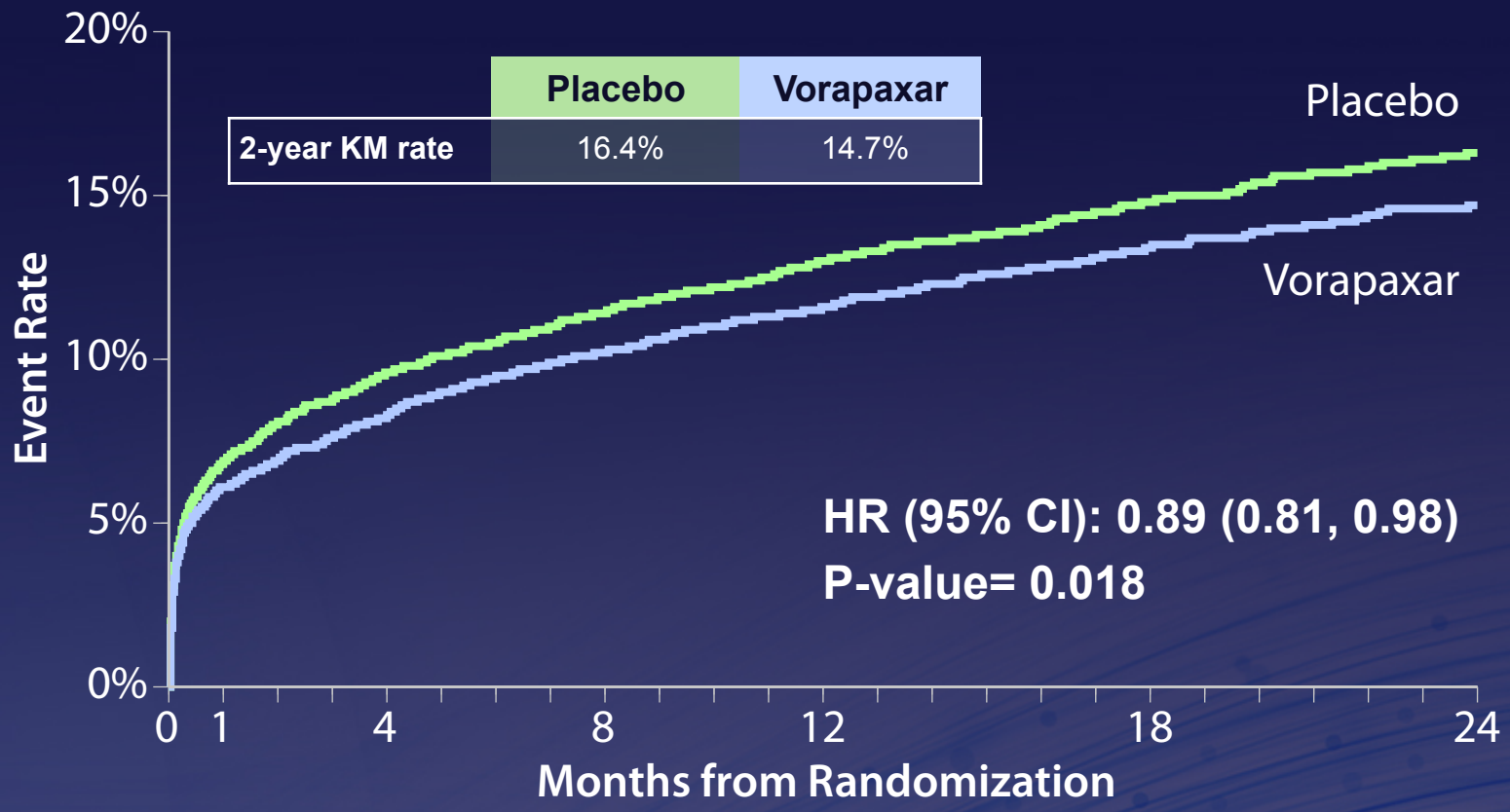


No. at risk							
Placebo	6471	5844	5468	5121	3794	2291	795
Vorapaxar	6473	5897	5570	5199	3881	2318	832

Key Secondary Endpoint

CV Death, MI, Stroke

TRA·CER



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

Duke Clinical Research Institute

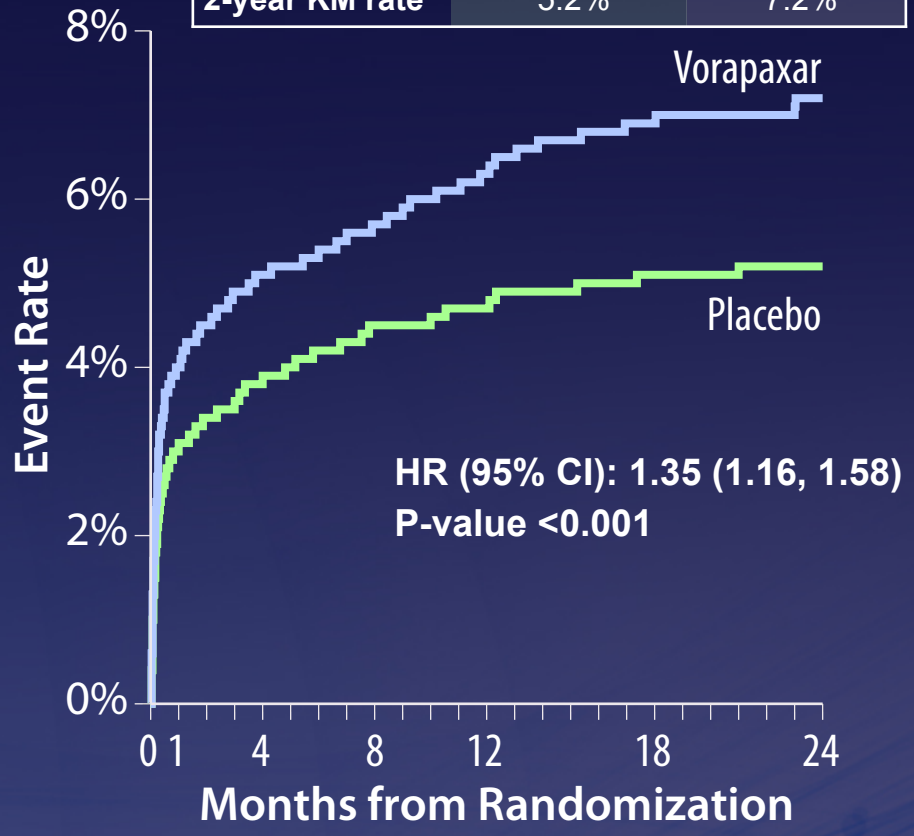
Tricoci NEJM 2011

Bleeding Outcomes

TRA·CER

GUSTO Moderate/Severe

	Placebo	Vorapaxar
2-year KM rate	5.2%	7.2%

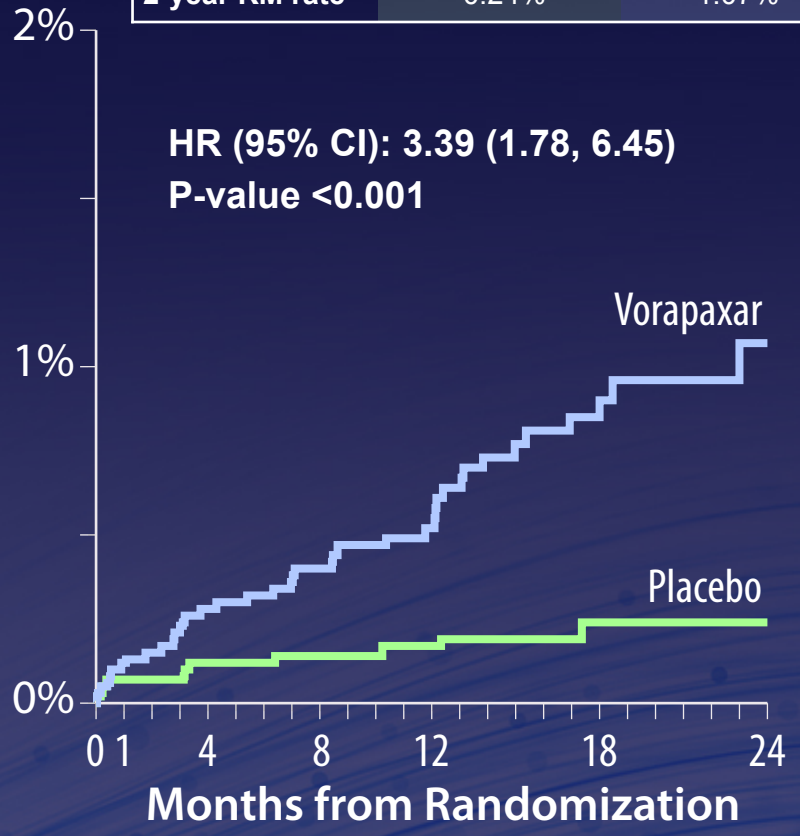


No. at risk

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

ICH

	Placebo	Vorapaxar
2-year KM rate	0.24%	1.07%



No. at risk

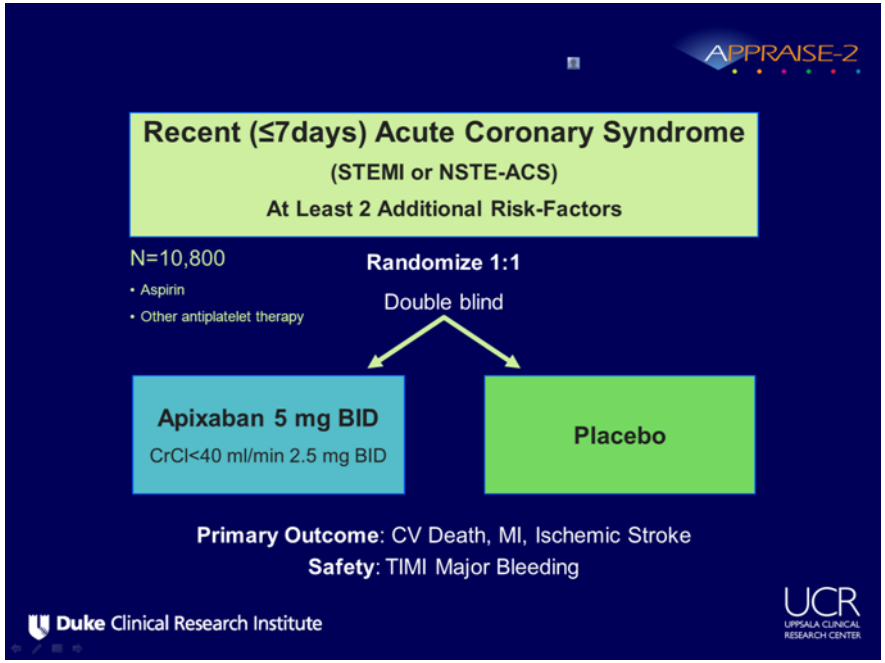
6441	5673	5281	4823	3511	2038	678
6446	5694	5272	4760	3411	1965	657

Duke Clinical Research Institute

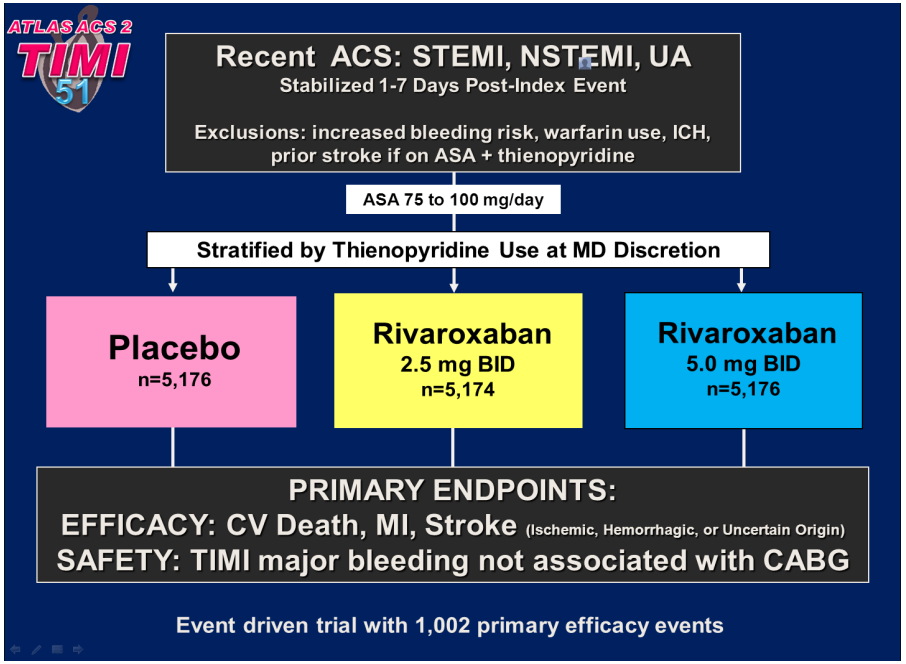
Tricoci NEJM 2011

Adding OAC Rx to Antiplatelet Rx Longterm Post ACS

APPRAISE-2



ATLAS ACS-2



European Heart Journal (2012) **33**, 2510–2512
doi:10.1093/eurheartj/ehs015

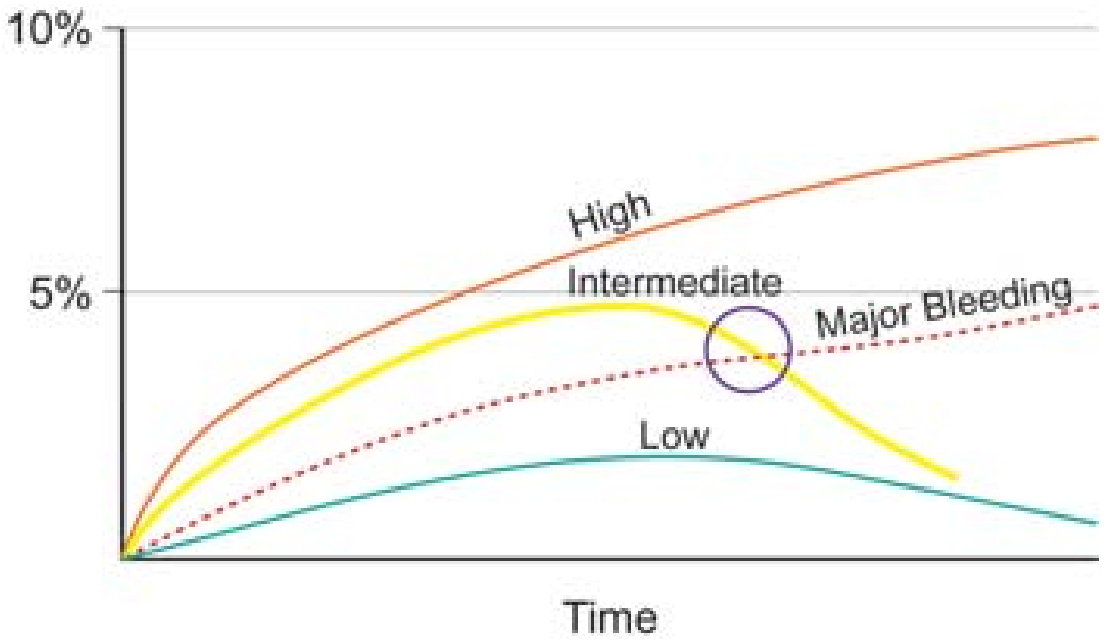
EDITORIAL COMMENT

Road mapping ATLAS ACS 2: are we there yet?

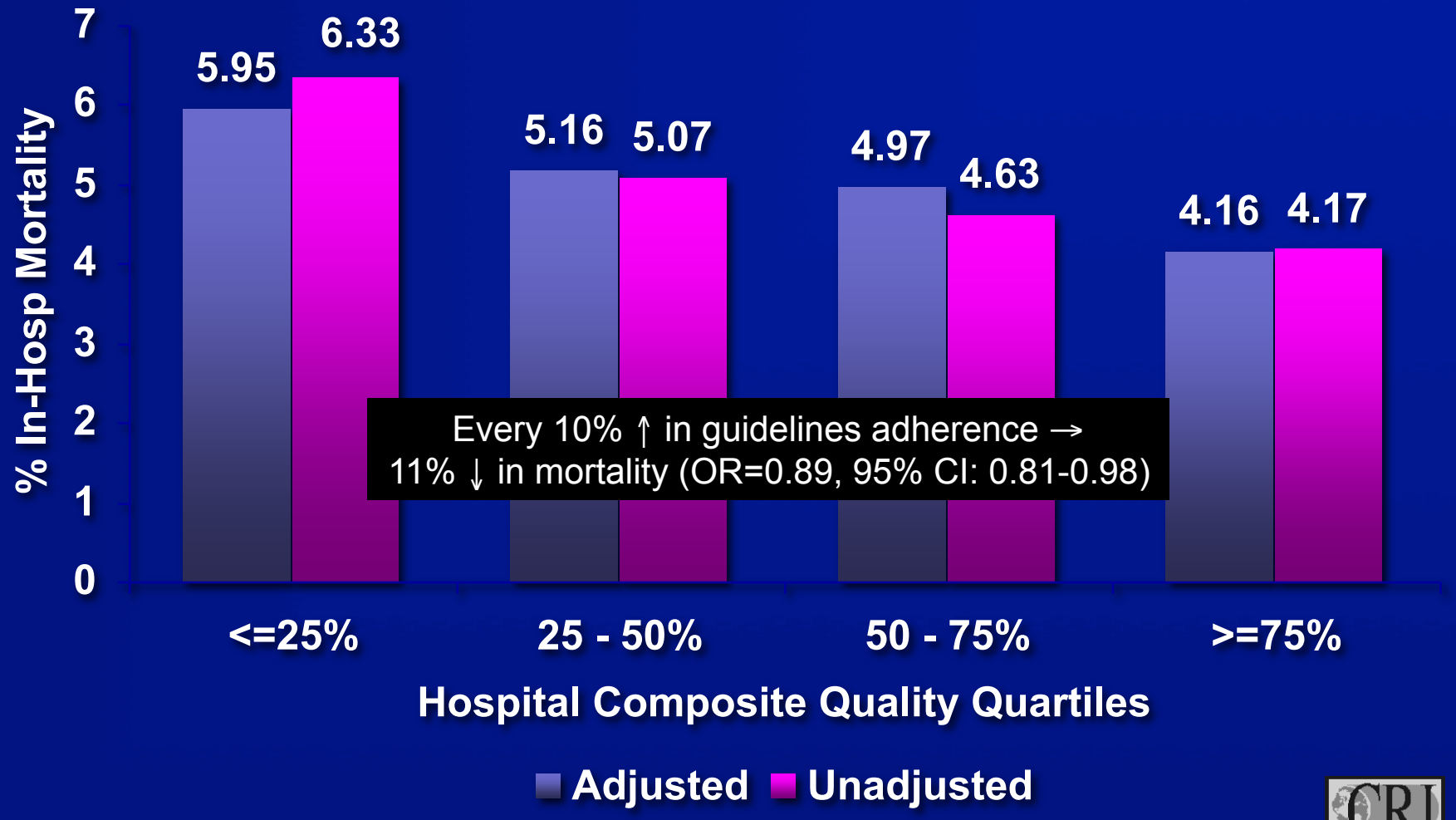
Paul W. Armstrong[1] and Robert A. Harrington[2]

[1]University of Alberta, 251 Medical Sciences Building, Edmonton AB T6G 2H7, Canada; and [2]Duke Clinical Research Institute, Durham, NC, USA

Online publish-ahead-of-print 31 January 2012

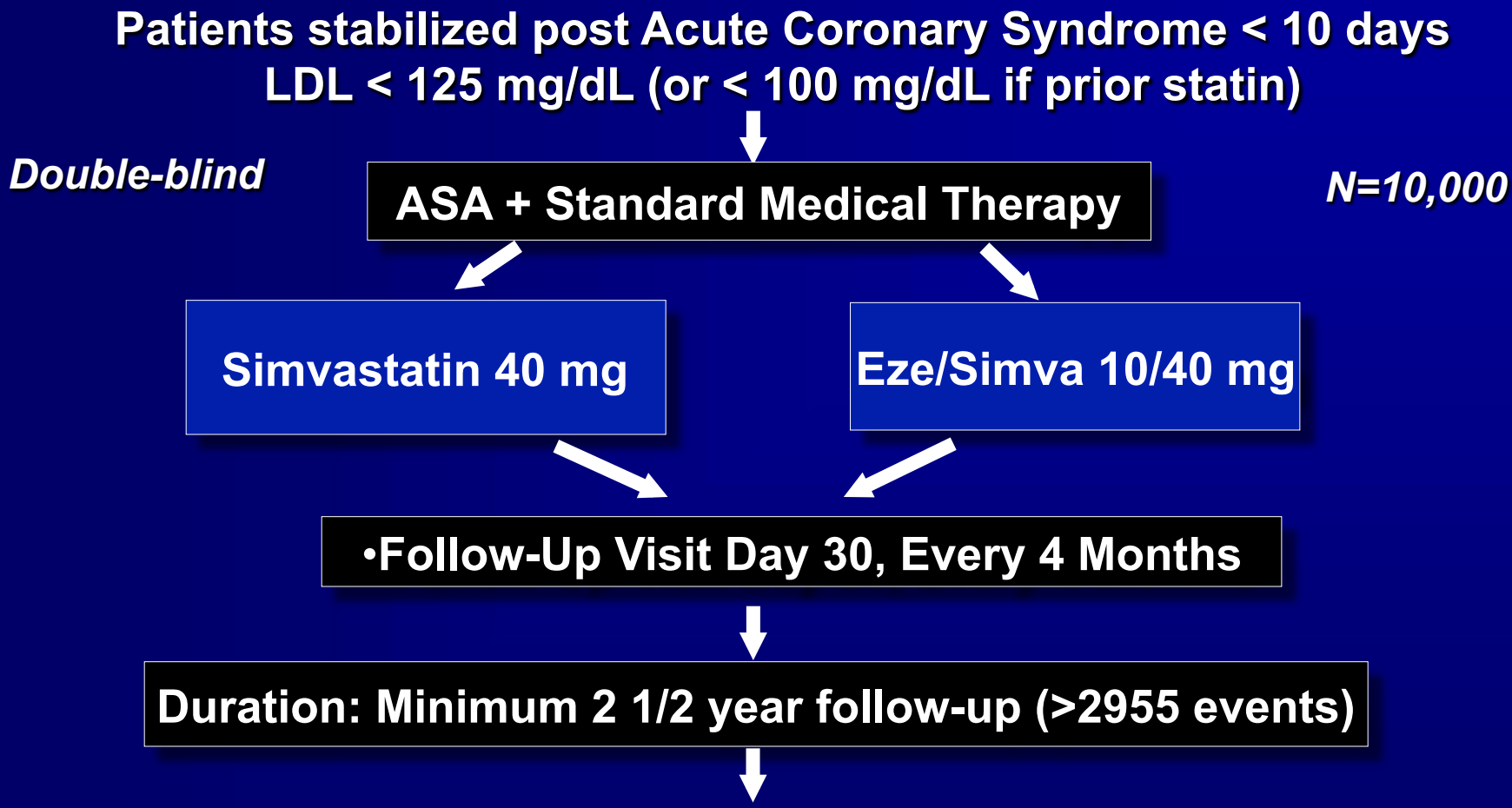


Link Between Overall Guidelines Adherence and Mortality



-Peterson E et al. JAMA 2006

IMPROVE IT Study Design



High Risk ACS: What Are the Concerns

Stanford MEDICINE

- Initial assessment of acute chest pain
  - Based on 12-lead ECG (STE versus NSTE)
  - Cardiac biomarkers (information from CKMB and troponin)
- Evolution of risk scores
  - For prognosis
  - For therapeutic decision making
- Moving from acute to long term care
- General concepts of antithrombotic therapy use
  - Balancing ischemia and bleeding
- What's next?
  - Adherence
  - Lipids
  - inflammation

Minimizing Readmission Rates Post-ACS: Why Should Clinicians Care & What Can They Do About It?

Jeffrey L. Anderson, MD, FACC, FAHA, MACP

Director, Cardiovascular Research

Intermountain Medical Center

Professor of Medicine

University of Utah

Salt Lake City, Utah

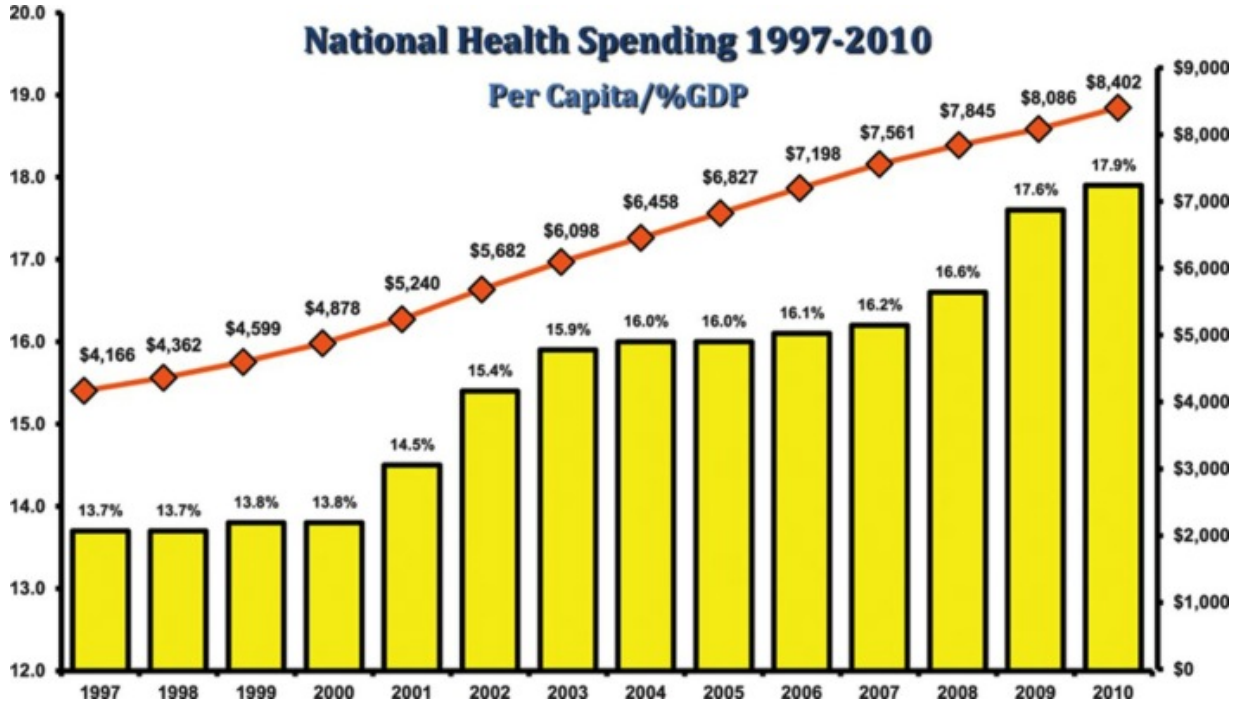
Readmissions After ACS: Why Should Clinicians Care?

- "On October 1, 2012, the Centers for Medicare & Medicaid Services (CMS) began to penalize hospitals for higher standardized early (30 day) readmission rates for heart failure, **acute myocardial infarction**, and pneumonia. It is anticipated that these penalties will increase and also expand to include other diseases, making this provision one of the most severe penalties mandated by the Patient Protection and Affordable Care Act."

Vaduganathan et al. JAMA 2013; 309:345-6.

The Rise in National Health Spending: An Unsustainable Trend

National Health Spending 1997–2010.



Anderson J L et al. Circulation. 2014;129:2329-2345

American Heart Association.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

ACC/AHA Statement on Cost/Value Methodology in Clinical Practice Guidelines and Performance Measures: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines

Jeffrey L. Anderson, Paul A. Heidenreich, Paul G. Barnett, Mark A. Creager, Gregg C. Fonarow, Raymond J. Gibbons, Jonathan L. Halperin, Mark A. Hlatky, Alice K. Jacobs, Daniel B. Mark, Frederick A. Masoudi, Eric D. Peterson and Leslee J. Shaw

Circulation. 2014;129:2329-2345; originally published online March 27, 2014;
doi: 10.1161/CIR.0000000000000042
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Cost Impact of Readmissions

- "Using 2005 Medicare data, the Medicare Payment Advisory Commission estimated that 13.3% of 30-day hospital readmissions were potentially preventable and cost an additional **$12 billion**."
- CMS chose to initially target heart failure, acute coronary syndromes, and pneumonia as the biggest contributors to readmission costs.

Axon and Williams. JAMA 2011; 305:504-5.

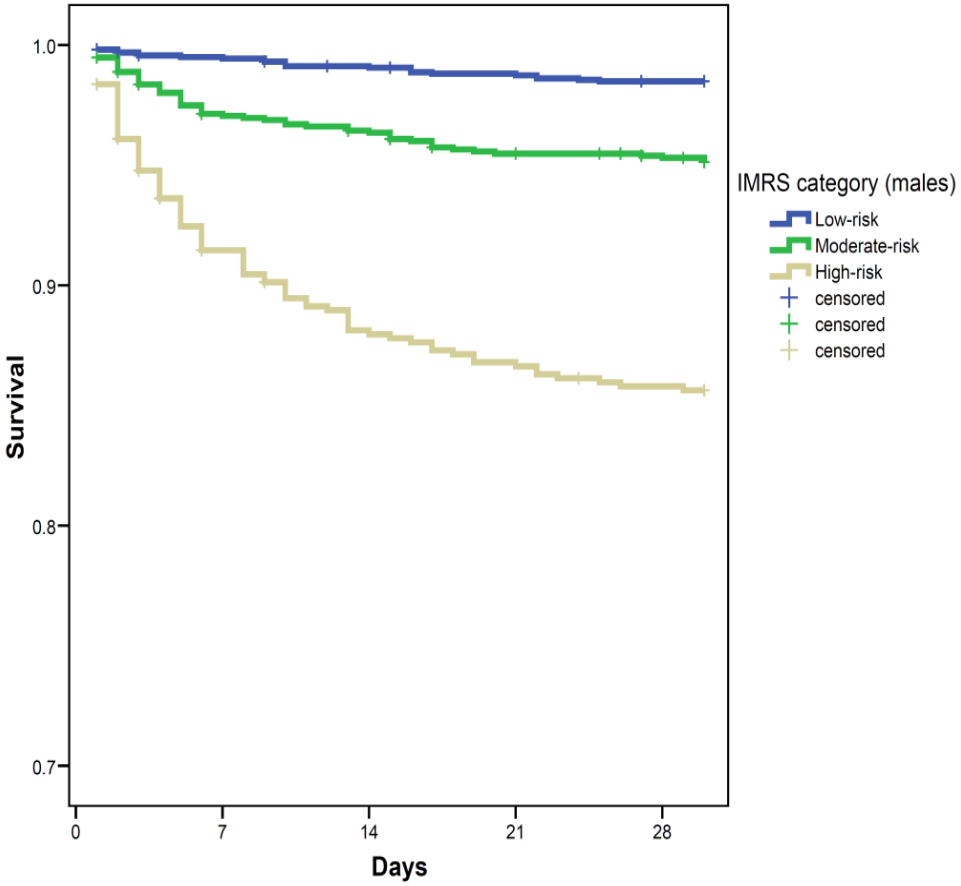
Critique of Readmission Rate as a Quality Metric

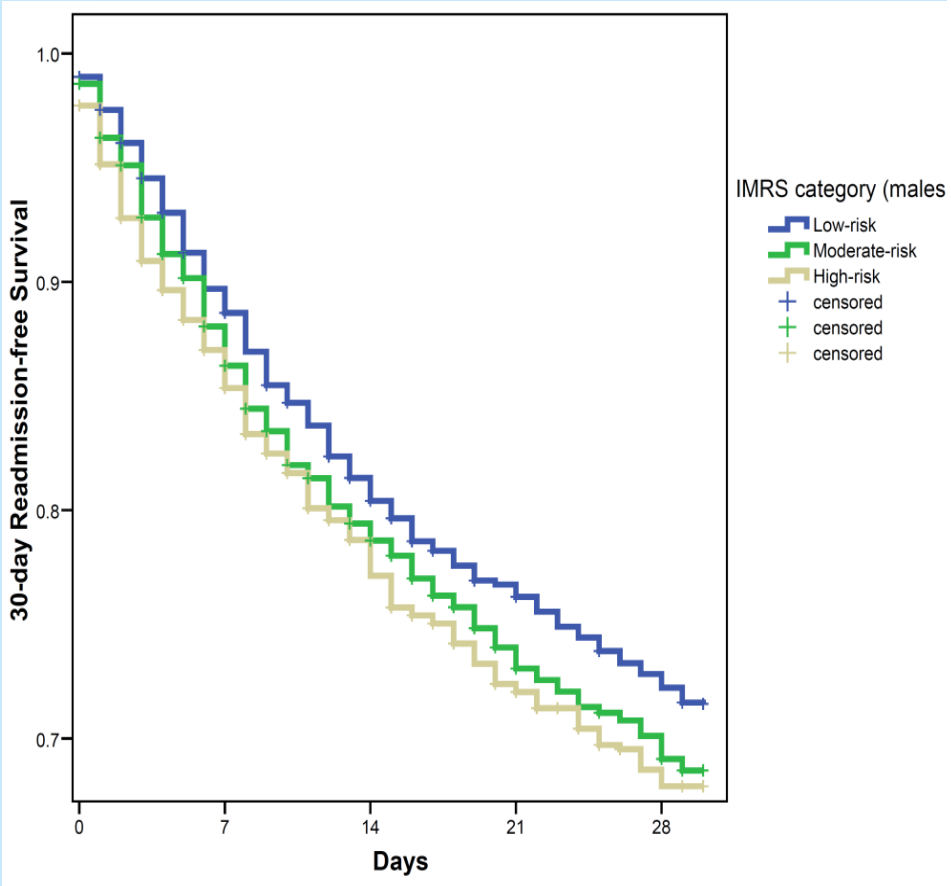
- 30-day readmission rate fails the premise that a quality metric should be rigorously tested and validated in target populations before implementation to ensure feasibility and effectiveness in improving clinical outcomes.
- CMS algorithms are proprietary (i.e., cannot be externally tested, validated) and poorly predictive (c-stat ≈ 0.6).
- No distinction made between "good" and "bad" readmissions and between readmissions related and unrelated to primary condition (i.e., ACS).
- Lower mortality rates may predispose to higher readmission rates (survivor bias).
- No adjustment made for socioeconomics: may penalize hospitals caring for poor, minorities, disadvantaged.
- No demonstration that readmission rate tracks with improvements in care processes or patient outcomes.

Vaduganathan et al. JAMA 2013; 309:345-6; Axon and Williams. JAMA 2011; 305:504-5

What Factors Predict 30-Day Readmission Rates After ACS?

The Intermountain Risk Score for Post-ACS Mortality Does Not Predict Readmission*

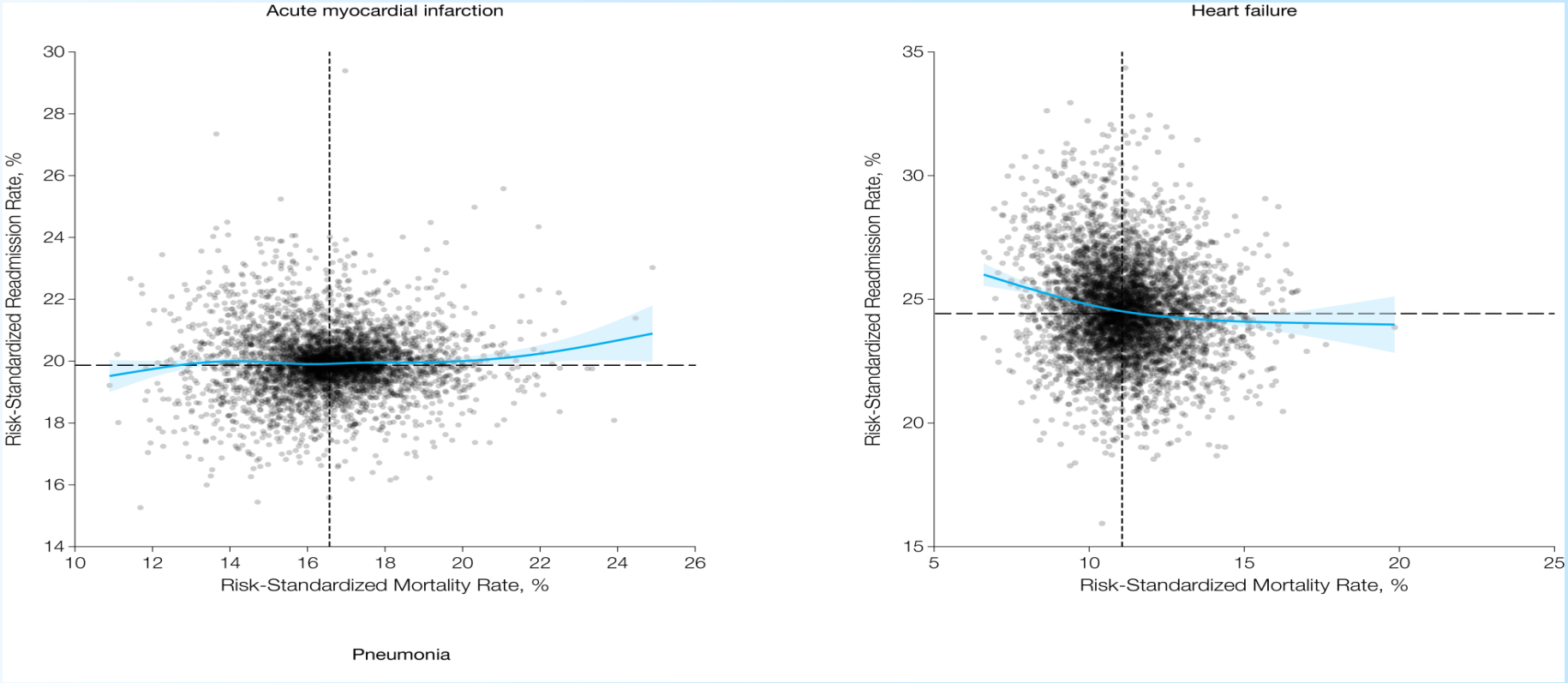




*Based on age, sex, CBC, BMP.

Horne et-al. Circulation 2012; 126 (suppl): A16794.

No Relationship Between Hospital Readmission and Mortality Rates in Patients with MI or HF

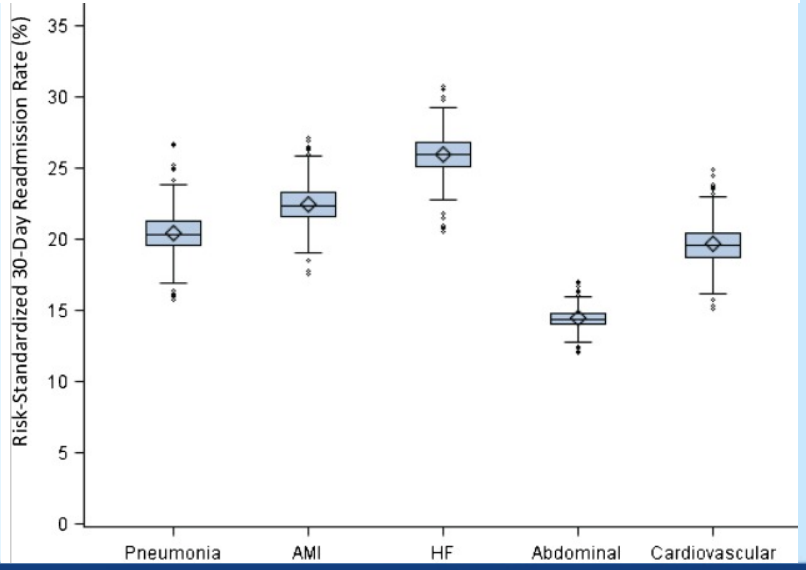


Krumholz et all. JAMA 2013; 309:587-93

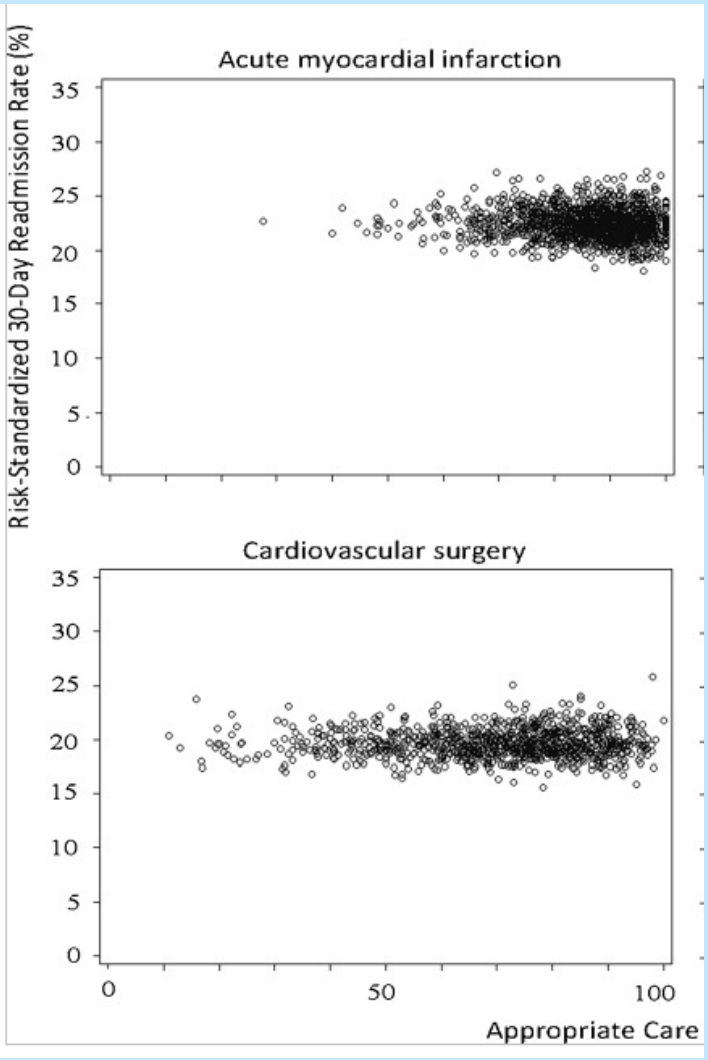
Do Hospital Performance Measures Predict 30-Day Readmission Rates?

Condition-Specific Process of Care Performance Measures

Acute Myocardial Infarction (AMI)	
AMI-1	Aspirin use at arrival
AMI-2	Aspirin prescribed at discharge
AMI-3	Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker
AMI-4	Adult smoking cessation advice/counseling
AMI-5	Beta blocker prescribed at discharge
AMI-6	Beta blocker at arrival
AMI-7a	Thrombolytic agent received within 30 min of arrival

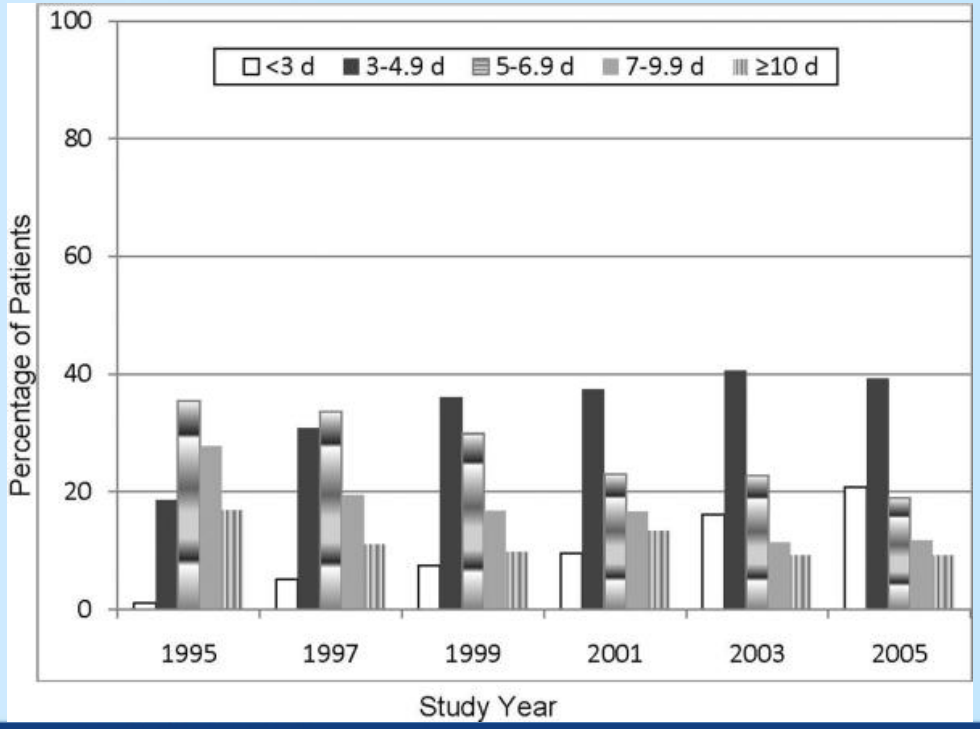


Stefan et al.
J Gen Intern Med
2013; 28:377-85.



Declining Lengths of Stay Do Not Impact Readmission Rates

- Compared with patients hospitalized for shorter than the median length of stay during 2003 and 2005 (4 days), those who were hospitalized for 4 or more days had lower rates of rehospitalization at 7 days (5.7% vs 5.0%) but higher rates at 1 month (14.5% vs 17.9%), 3 months (24.7% vs 31.0%), and 1 year (41.3% vs 48.4%) after hospital discharge.



Saczynski et al. Am J Med 2010; 123: 1007-15

IMPROVING PATIENT CARE | ORIGINAL RESEARCH

Associations Between Reduced Hospital Length of Stay and 30-Day Readmission Rate and Mortality: 14-Year Experience in 129 Veterans Affairs Hospitals

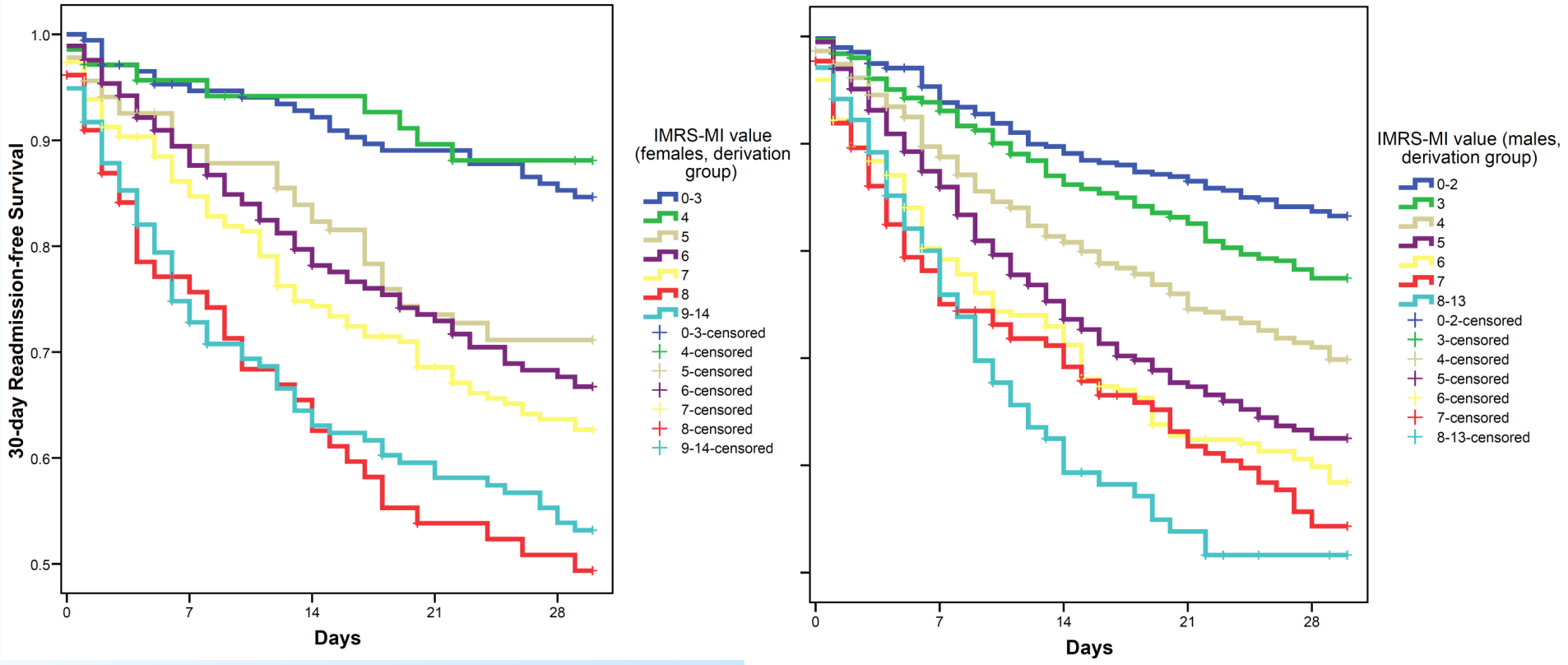
Peter J. Kaboli, MD, MS; Jorge T. Go, MD, MS; Jason Hockenberry, PhD; Justin M. Glasgow, BS, MS; Skyler R. Johnson, BS, MS; Gary E. Rosenthal, MD; Michael P. Jones, PhD; and Mary Vaughan-Sarrazin, PhD

Conclusion: Veterans Affairs hospitals demonstrated simultaneous improvements in hospital LOS and readmissions over 14 years, suggesting that as LOS improved, hospital readmission did not increase. This is important because hospital readmission is being used as a quality indicator and may result in payment incentives. Future work should explore these relationships to see whether a tipping point exists for LOS reduction and hospital readmission.

Kaboli et al. Ann Intern Med 2012; 157:837-45

A New Intermountain Risk Score for 30-Day Readmission After MI

- Derived from 4,101 patients based on age, sex, CBC, BMP, and 31 other risk factors and diagnostic and treatment variables; validated in 1,919. Derivation c-stats 0.64, 0.61 for women, men; validation c-stats 0.62, 0.59.



Horne et al. Circulation 2012; 126 (suppl): A16794

An Improved Analytics Approach to Predicting 30-Day Avoidable Readmissions After MI

- Medicare pays out $17 billion/year on 20% of patients readmitted within 30 days of discharge.
- Current models poorly predict readmission risk (c-stat≈0.6).
  - Do not discriminate planned vs unnecessary readmissions
  - Do not consider h/o readmissions and change in risk factors.
- A tree-based classification method was developed to estimate readmission probability incorporating patient h/o readmissions and changes in risk factors over time.
- Method was validated in 2011-12 VHA database for AMI, HF, pneumonia, and COPD in Michigan.
- Results show improved discrimination (c-stat >0.80) and good calibration.

Shams et al. Health Care Manag Sci 2014 May 3 [Epub ahead of print]

Psychological Stress as a Predictor of 30-Day All-Cause Readmission in ACS Patients

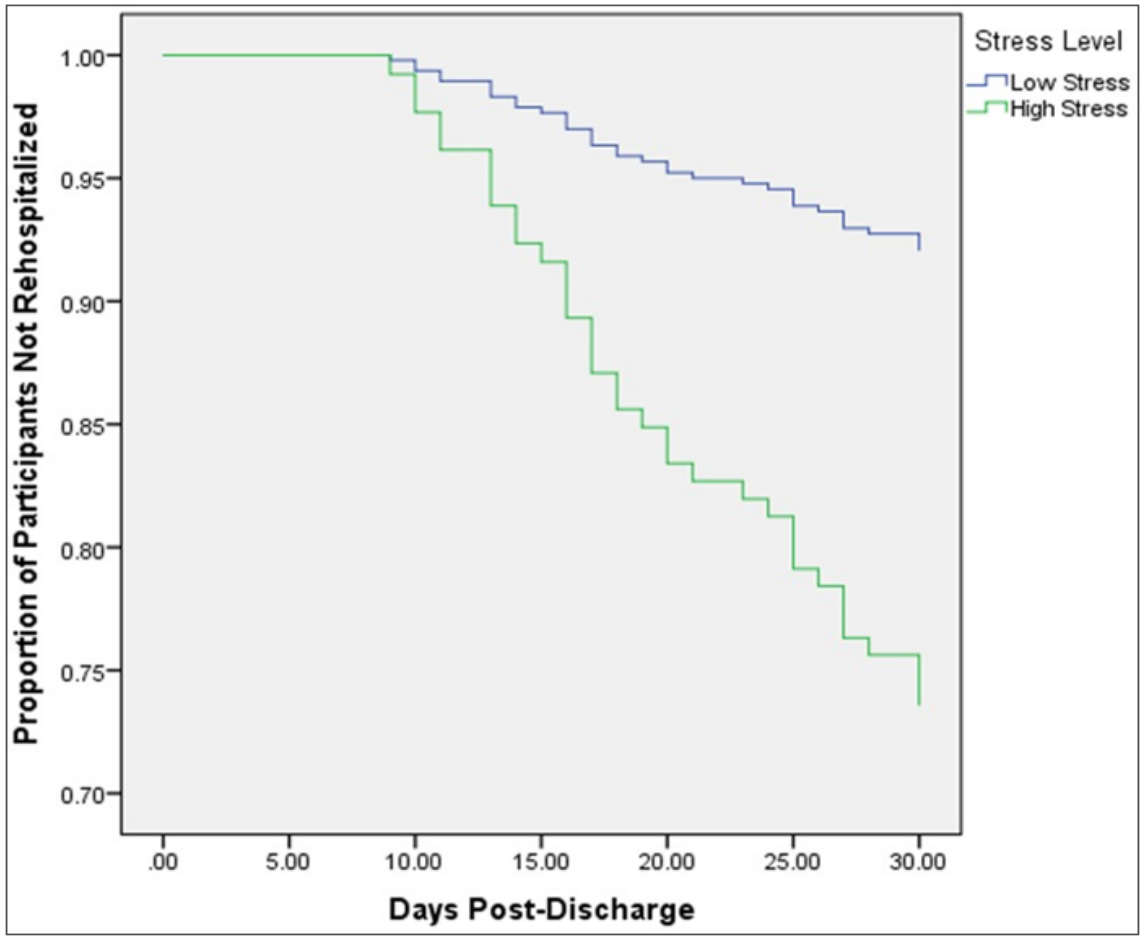


Figure 1

Cox proportional hazards regression analysis predicted survival curves for acute coronary syndrome (ACS) patients by stress category, adjusted for age, sex, race, ethnicity, type of ACS, Charlson comorbidity index score, Global Registry of Acute Coronary ...

Edmondson et al. Plos One 2014; 12; 9(3):d91466

Adding Socioeconomic Data Markedly Narrows the Range of Variation in Calculated (Predicted) Hospital Readmission Rates

Exhibit 1

Hospital Risk–Standardized Readmission Rates, By Calculation Method, June 2009 To May 2012

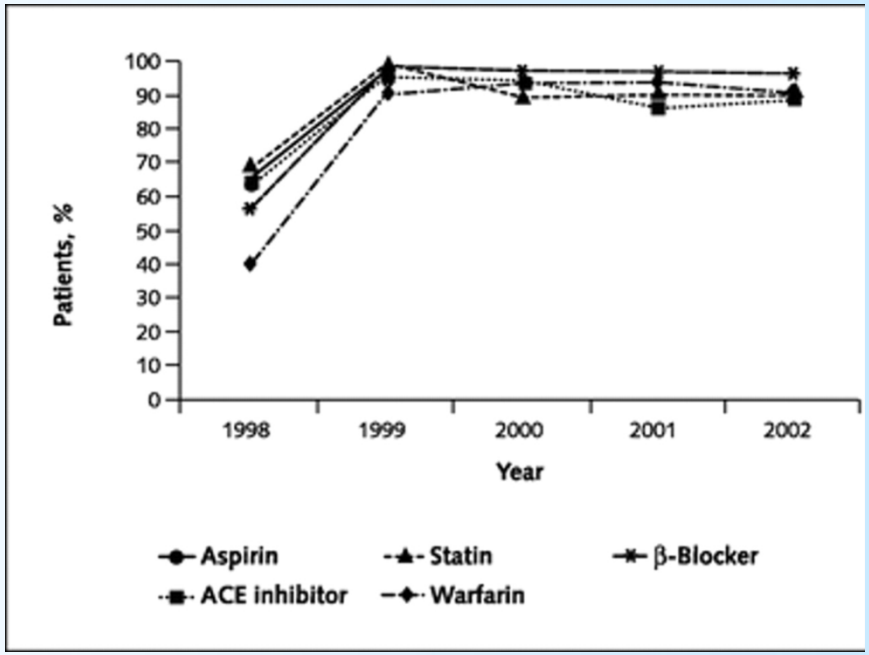
		Hospital risk-standardized readmission rates			
		Baseline model		Socioeconomic-factor-enriched model	
Principal diagnosis	No. of hospitals	Mean (%)	Range (%)	Mean (%)	Range (%)
Acute myocardial infarction	49	16.4	14.0–20.5	16.3	15.3–17.1
Heart failure	100	19.3	14.5–28.5	19.5	17.6–25.0
Pneumonia	109	15.1	11.2–18.6	15.1	13.4–17.1

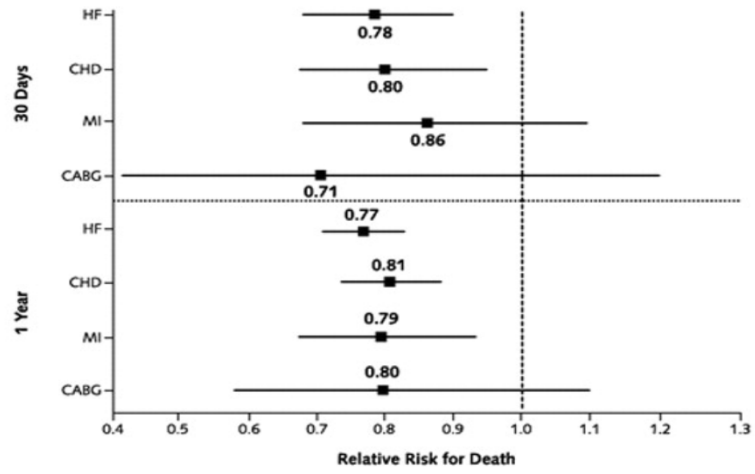
Nagasako et al. Health Aff (Millwood) 2014; 33:786-91

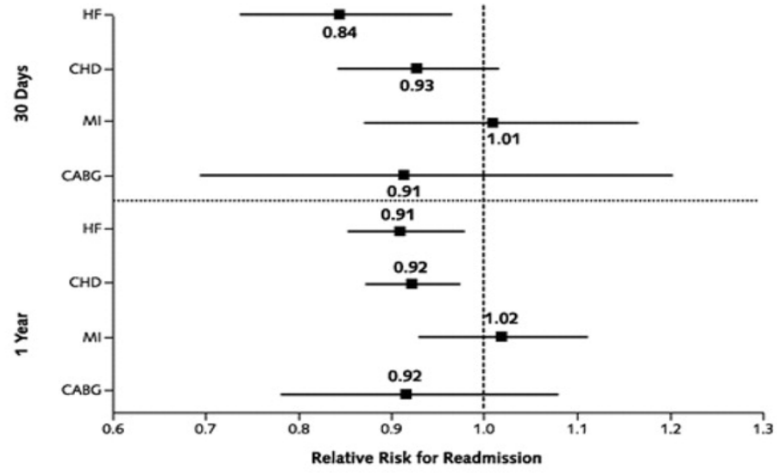
What Interventions Impact 30-Day Hospital Readmissions After ACS?

Improvements in 1-Year Cardiovascular Clinical Outcomes Associated with a Hospital-Based Discharge Medication Program

Jason M. Lappé, MS; Joseph B. Muhlestein, MD; Donald L. Lappé, MD; Rodney S. Badger, MD; Tami L. Bair, BS; Ruth Brockman, RN, MBA; Thomas K. French, MStat; Linda C. Hofmann, MS, BSN; Benjamin D. Horne, MStat, MPH; Susan Kralick-Goldberg, RN, MSN; Nan Nicponski, RN, MBA; Janette A. Orton, RN, MS; Robert R. Pearson, BS; Dale G. Renlund, MD; Holly Rimmasch, RN, MSN; Colleen Roberts, RN, MS; and Jeffrey L. Anderson, MD



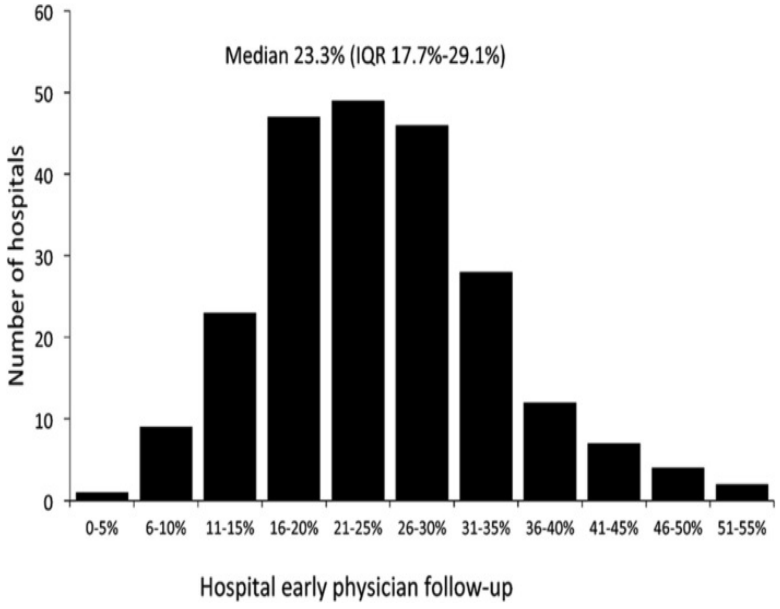




Lappe' et al. Ann Intern Med 2004; 141:446-53

No Relation Between Early (≤7-Day) Physician Follow-up and 30-Day Readmissions After NSTEMI

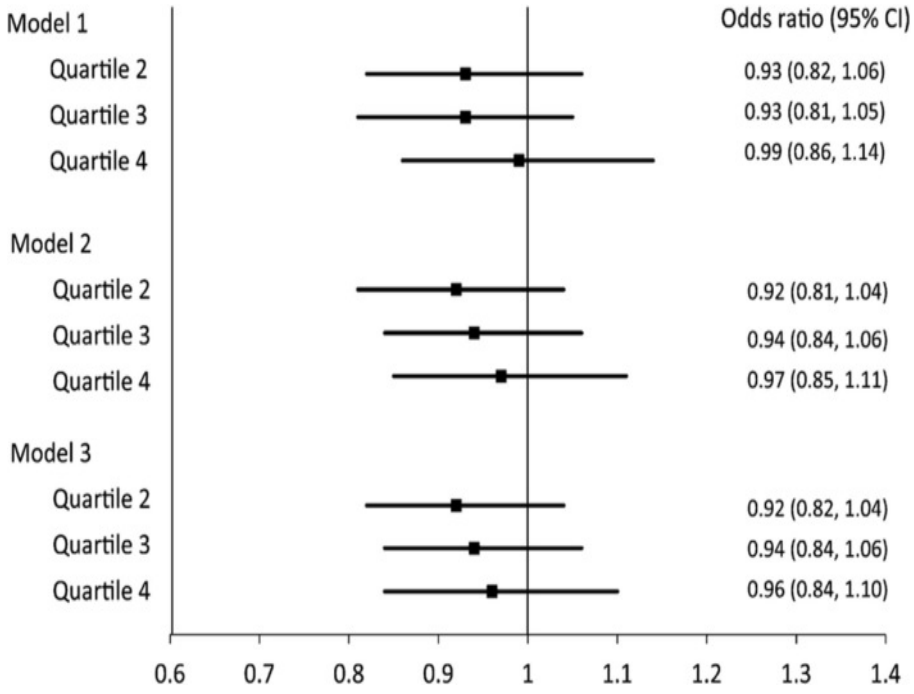
Variation in hospital-level early physician follow-up.



Hess C N et al. Circulation. 2013;128:1206-1213

American Heart Association.

Adjusted 30-day all-cause readmission by hospital-level early physician follow-up.



Hess C N et al. Circulation. 2013;128:1206-1213

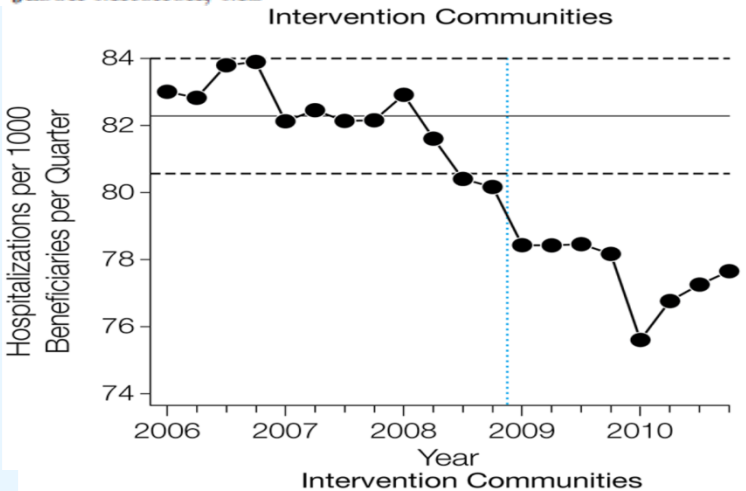
American Heart Association.

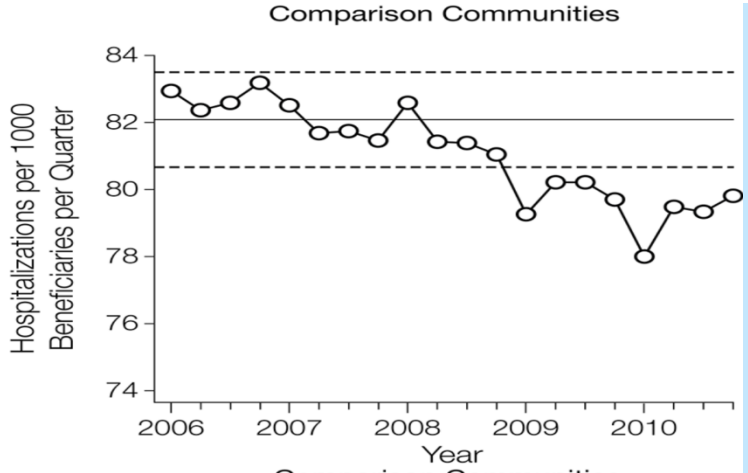
Hess et al. Circulation 2013; 128:1206-13

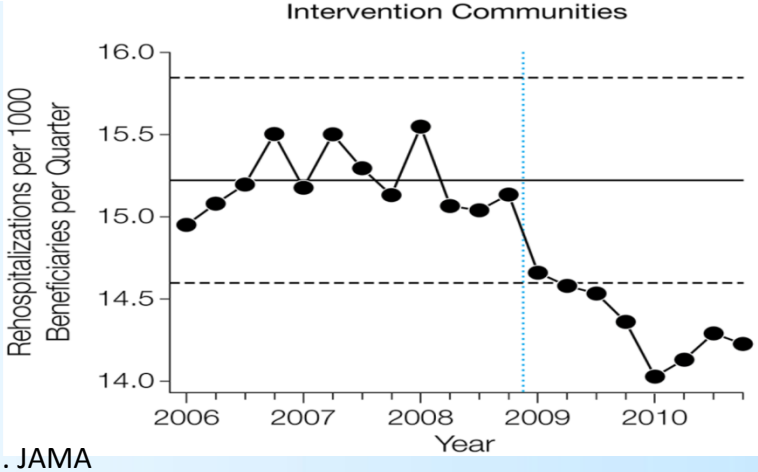
Association Between Quality Improvement for Care Transitions in Communities and Rehospitalizations Among Medicare Beneficiaries

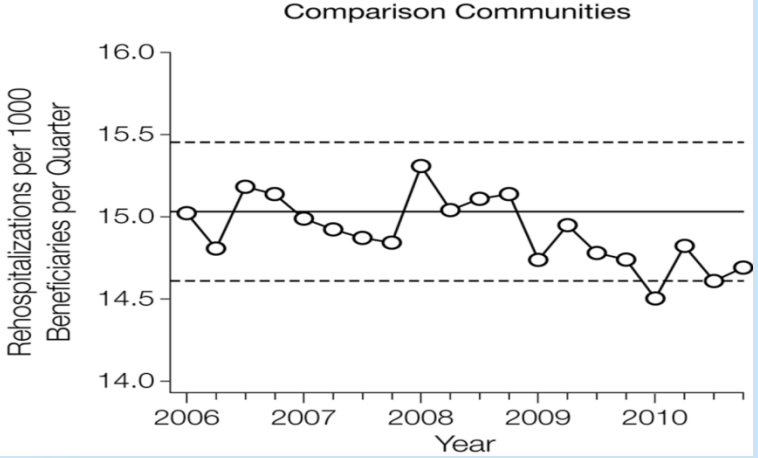
Jane Brock, MD, MSPH
Jason Mitchell, MS

Importance Medicare beneficiaries experience errors during transitions among care settings, yielding harms that include unnecessary rehospitalizations.









Brock et-al. JAMA 2013; 309; 381-91

Pre- vs. Post- between group differences were NS: (0.22%, p=0.14)

Does Improved Coordination of Care Using Health Information Technology (i.e., Health Information Exchange Program) Decrease Readmission Rates?

Unadjusted and Adjusted Readmission Rates by % of Participation in Health Information Exchange

Condition	Health Information Exchange Participant	Unadjusted Readmission Rate (%)	*P Value (Relative to Reference)*	Adjusted Readmission Rate (%)	*P Value (Relative to Reference)*
AMI	**No**	20.0	*Ref*	19.9	*Ref*
	Yes	19.8	0.14	19.8	0.18
Heart Failure	**No**	24.6	*Ref*	24.4	*Ref*
	Yes	24.3	0.003	24.2	0.11
Pneumonia	**No**	18.2	*Ref*	18.2	*Ref*
	Yes	18.1	0.68	18.1	0.68

Jones et al. AMIA Annu Symp Proc 2011; 2011:644-53

REVIEW | Annals of Internal Medicine

Transitional Care Interventions to Prevent Readmissions for Persons With Heart Failure

A Systematic Review and Meta-analysis

Cynthia Feltner, MD, MPH; Christine D. Jones, MD, MS; Crystal W. Cené, MD, MPH; Zhi-Jie Zheng, MD, PhD, MPH; Carla A. Sueta, MD, PhD; Emmanuel J.L. Coker-Schwimmer, MPH; Marina Arvanitis, MD; Kathleen N. Lohr, PhD, MPhil, MA; Jennifer C. Middleton, PhD; and Daniel E. Jonas, MD, MPH

Category	Impact on 30-d readmissions	Strength of Evidence
High-intensity home-visiting program	↓ All-cause readmission or death	Low SOE
Structured telephone support	Insufficient evidence	----
Multidisciplinary-HF clinics	No data available	----
Telemonitoring	Insufficient evidence	----
Educational interventions	No data available	----

Feltner et al. Ann Intern Med 2014; 160:774-84

Current Summary and Future Possibilities

- 30-day readmission rate after ACS is a reportable statistic with reimbursement implications.
- Current determination of expected readmission rate by CMS fails to discriminate between appropriateness/type of readmission and does not incorporate socioeconomic data.
- Current models poorly predict readmission rates, and how and whether readmissions can be reduced is unclear. Improved predictive models are clearly needed.
- A more nuanced and comprehensive approach will be required to effectively alter the post-discharge course of ACS pts.
- Robust risk adjustment must account for mental and physical comorbidities and socioeconomic factors.
- Specific post-hospital quality of care metrics should be rigorously tested and validated before implementation.

Panel Discussion

Moderator: Deepak L. Bhatt, MD, MPH
Discussants: Jeffrey L. Anderson, MD
Robert A. Harrington, MD
P. Gabriel Steg, MD

ARS QUESTION 1

A 73-year-old female comes in with a NSTEMI and receives a DES to the proximal left circumflex artery. In addition to aspirin, which antiplatelet agent would you discharge her on?

A. Clopidogrel

B. Prasugrel

C. Ticagrelor

ARS QUESTION 2

A 78-year-old male comes in with a NSTEMI and is found to have diffuse three vessel disease. Medical management is elected. In addition to aspirin, which antiplatelet agent would you discharge him on?

A. Clopidogrel

B. Prasugrel

C. Ticagrelor