Lessons from 25+ Years of Clinical Trials in Cardiology:
The TIMI Study Group Experience

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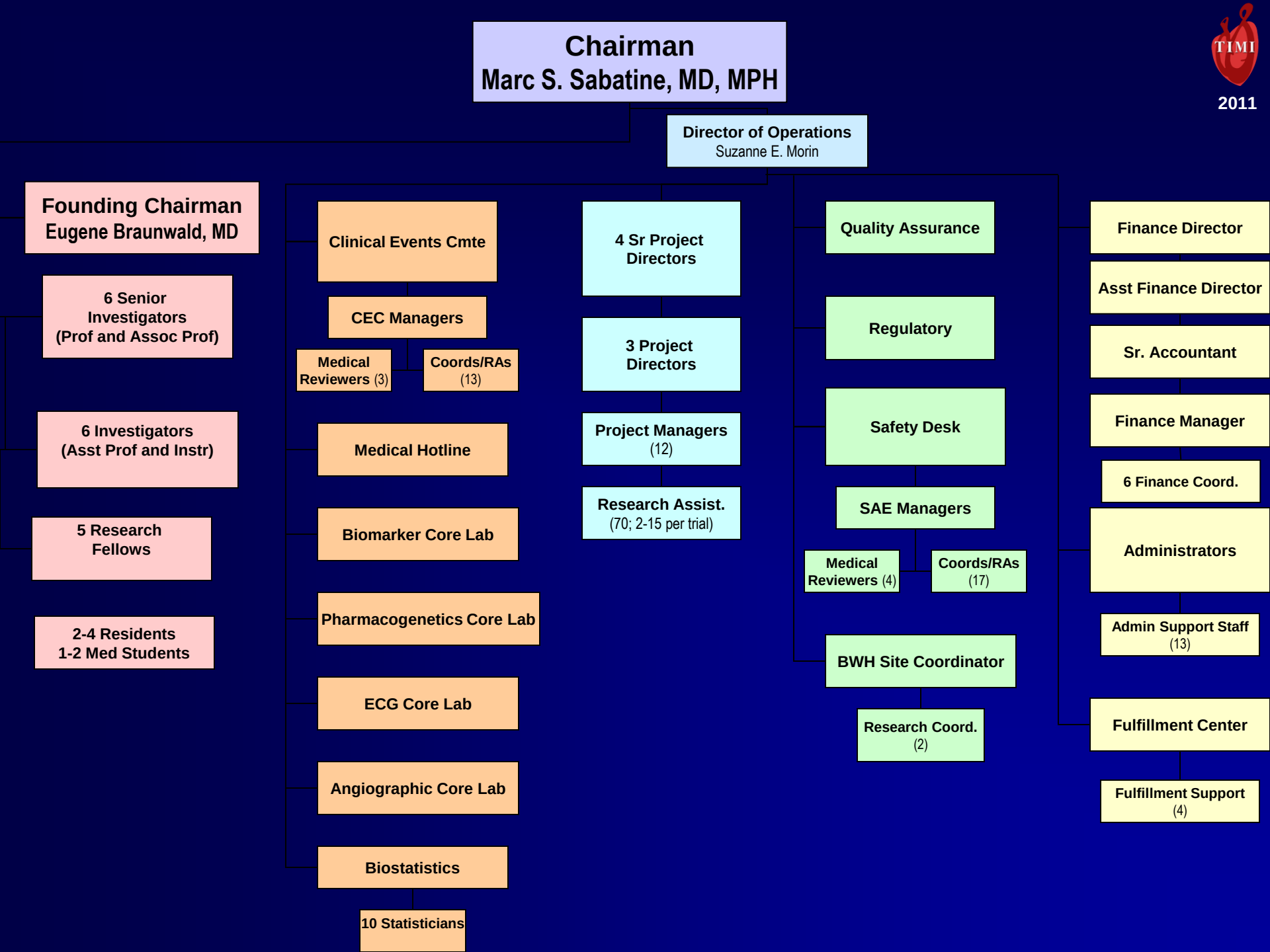
TIMI STUDY GROUP
Thrombolysis in Myocardial Infarction

TIMI
2011

MISSION STATEMENT:

The TIMI Study Group organized in 1984 by Eugene Braunwald, MD at Brigham and Women's Hospital, Boston, MA, is committed to advancing the knowledge and care of patients suffering from acute coronary syndromes by performing clinical research.


Chairman
Marc S. Sabatine, MD, MPH
TIMI
2011
Director of Operations
Suzanne E. Morin
Founding Chairman
Eugene Braunwald, MD
6 Senior Investigators (Prof and Assoc Prof)
6 Investigators (Asst Prof and Instr)
5 Research Fellows
2-4 Residents
1-2 Med Students
Clinical Events Cmte
CEC Managers
Medical Reviewers (3)
Coords/RAs (13)
Medical Hotline
Biomarker Core Lab
Pharmacogenetics Core Lab
ECG Core Lab
Angiographic Core Lab
Biostatistics
10 Statisticians
4 Sr Project Directors
3 Project Directors
Project Managers (12)
Research Assist. (70; 2-15 per trial)
Quality Assurance
Regulatory
Safety Desk
SAE Managers
Medical Reviewers (4)
Coords/RAs (17)
BWH Site Coordinator
Research Coord. (2)
Finance Director
Asst Finance Director
Sr. Accountant
Finance Manager
6 Finance Coord.
Administrators
Admin Support Staff (13)
Fulfillment Center
Fulfillment Support (4)

TIMI TRIALS
1984-2011

2011

62 Cardiac Trials (more than 50 completed)

- 300,000 Pts enrolled to date
- 4000 Hospitals worldwide
- 8000 Investigators worldwide
- 52 Countries
- 6 Continents

TIMI BIBLIOGRAPHY: >500 PEER REVIEWED PUBLICATIONS

COLLABORATIVE PARTNERS

2011

TIMI STUDY GROUP

Non Profit
AHA
ACC

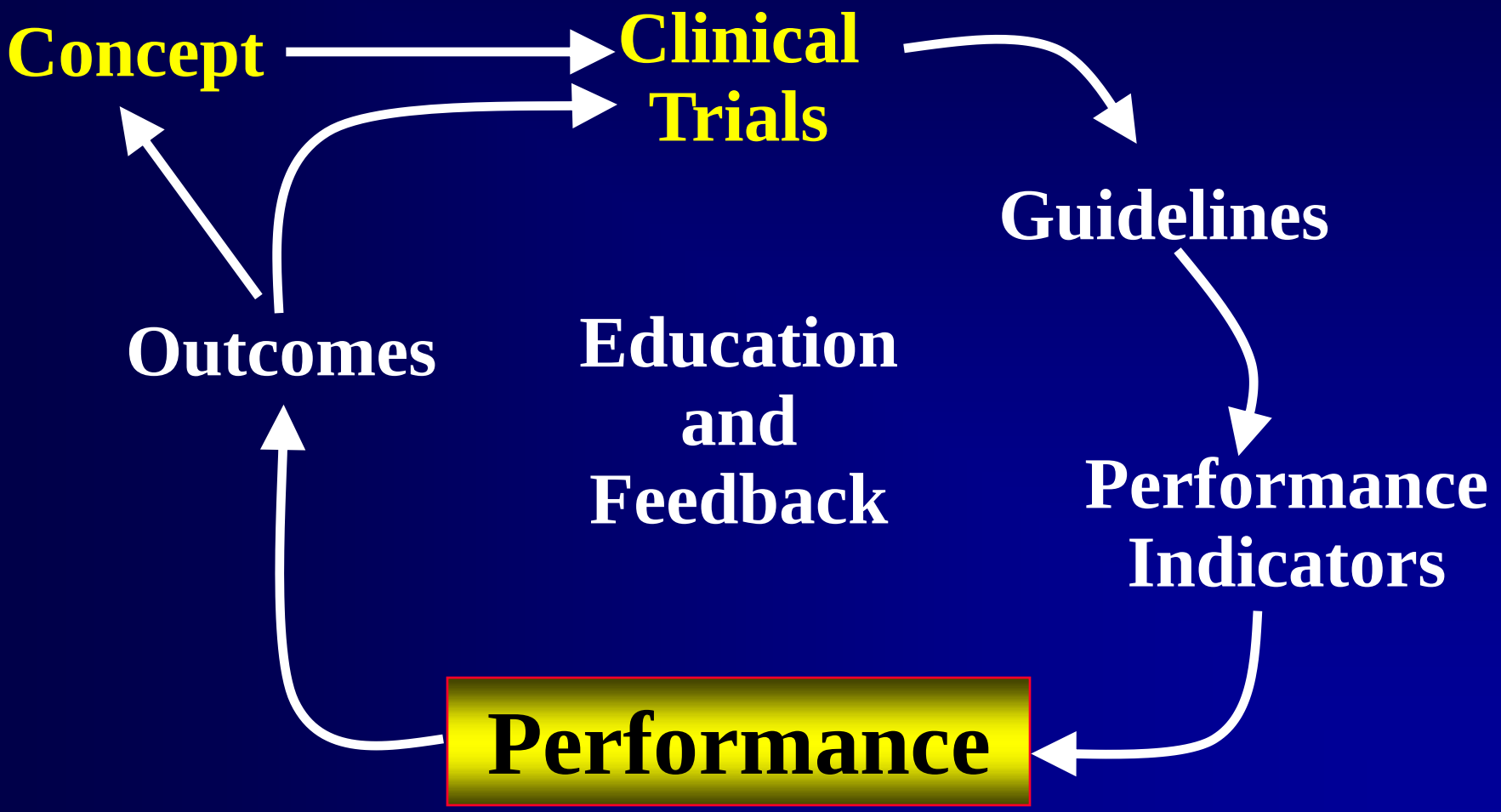
National Institute of Health
NHLBI-Contracts and Investigator Initiated

CROs
Parexel
Covance
Quintiles
WCT
ICON

AROs
DCRI
HCRI
CHRC
LCC
NCRL

Pharmaceuticals
Smith Kline Beecham
Ciba Geiqy
Biogen
Genentech
Rhone Poulenc Rorer
Centocor
Searle
Bristol Myers Squibb
Merck
Cor Therapeutics
Aventis
Lilly
Sunol
Sanofi Synthelabo
Millennium
British Biotech
Corvas
Astra Zeneca
Schering Plough
Daiichi Sankyo
Inotek
CV Therapeutics
Sanofi-Aventis
Novartis
Nuvelo
Johnson & Johnson PRD
GlaxoSmithKline
Amgen

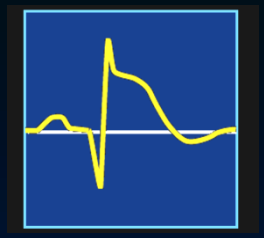
The Cycle of Clinical Therapeutics



Top 10 Lessons 1984-1999

TIMI 2011

1. Better epicardial flow results in lower mortality
2. Development of grading scale for bleeding
3. Speed of flow (frame count) and perfusion of myocardial tissue (perfusion grade) are impt
4. tPA is better than SK at opening arteries
5. Single bolus TNK-tPA is safe and effective
6. Enoxaparin is superior to unfractionated heparin
7. Risk score predicts outcomes, can guide therapy
8. Early invasive approach is better in UA/nSTE-MI
9. Prehospital lytic is feasible and speeds reperfusion
10. Multimarker approach improves prognostic ability



ACC/AHA 2009 STEMI Focused Update: Acute Medical Therapy

General treatment measures	• Aspirin, nitrates, oxygen, analgesics (morphine)
Infarct size limitation	• **β-blockers** (not for acute use in patients with evidence of heart failure)
Reperfusion	• **Thrombolysis (within 30 min) or primary PCI (within 90 min)**
Anticoagulant and antiplatelet therapy	• **UFH, enoxaparin**, fondaparinux[a], or bivalirudin[b] • **Clopidogrel 75 mg/d added to aspirin for patients undergoing fibrinolysis; 300 mg loading dose for patients <75 y who receive fibrinolytic therapy or who do not receive reperfusion therapy** • **If PCI: clopidogrel, prasugrel, GP IIb/IIIa inhibitors**

[a] Because of the risk of catheter thrombosis, fondaparinux should not be used as the sole anticoagulant to support PCI. An additional anticoagulant with anti-IIa activity should be administered.

[b] For primary PCI with 600 mg clopidogrel

Kushner FG, et al. Circulation. 2009;120:2271-2306.

STRIVE™

2007 ACC/AHA nSTE-ACS Guidelines

Immediate ASA; Clopidogrel if ASA contraindicated

Aspirin + clopidogrel for up to 1 month

Enoxaparin or UFH for invasive or conservative mgt

Bivalirudin (invasive) or fondaparinux (conservative)

β-blocker (IV→oral) if not contraindicated

Non-dihydropyridine Ca^{2+} blckr if β-blocker contraindicated and no LV dysfcn, for rec ischemia

ACE-I if ↑ BP with NTG+ β-blocker, if CHF or DM

Any GPI all patients, if cath/PCI planned

Ept or tiro for high-risk* if early cath not planned

Any GP IIb/IIIa inhibitor for patients already on ASA + Heparin + clopidogrel, if cath/PCI is planned

Anderson JL, *JACC* 2007;50:1-157

TIMI Trials 2000-present

Population	Experimental Therapy
Fibrinolytic	clopidogrel, enoxaparin
Primary PCI	GPI timing, half-dose lytic+GPI
UA/nSTE-MI	anticoag, antiplt, anti-ischemic
Post ACS	lipids, antibiotics, renin inhibitor, oral factor Xa, Lp-PLA_2 inhibitor
PCI	antiplt, anticoag
Atrial Fib	oral factor Xa
DM	DPP-4 inhibitor

TIMI

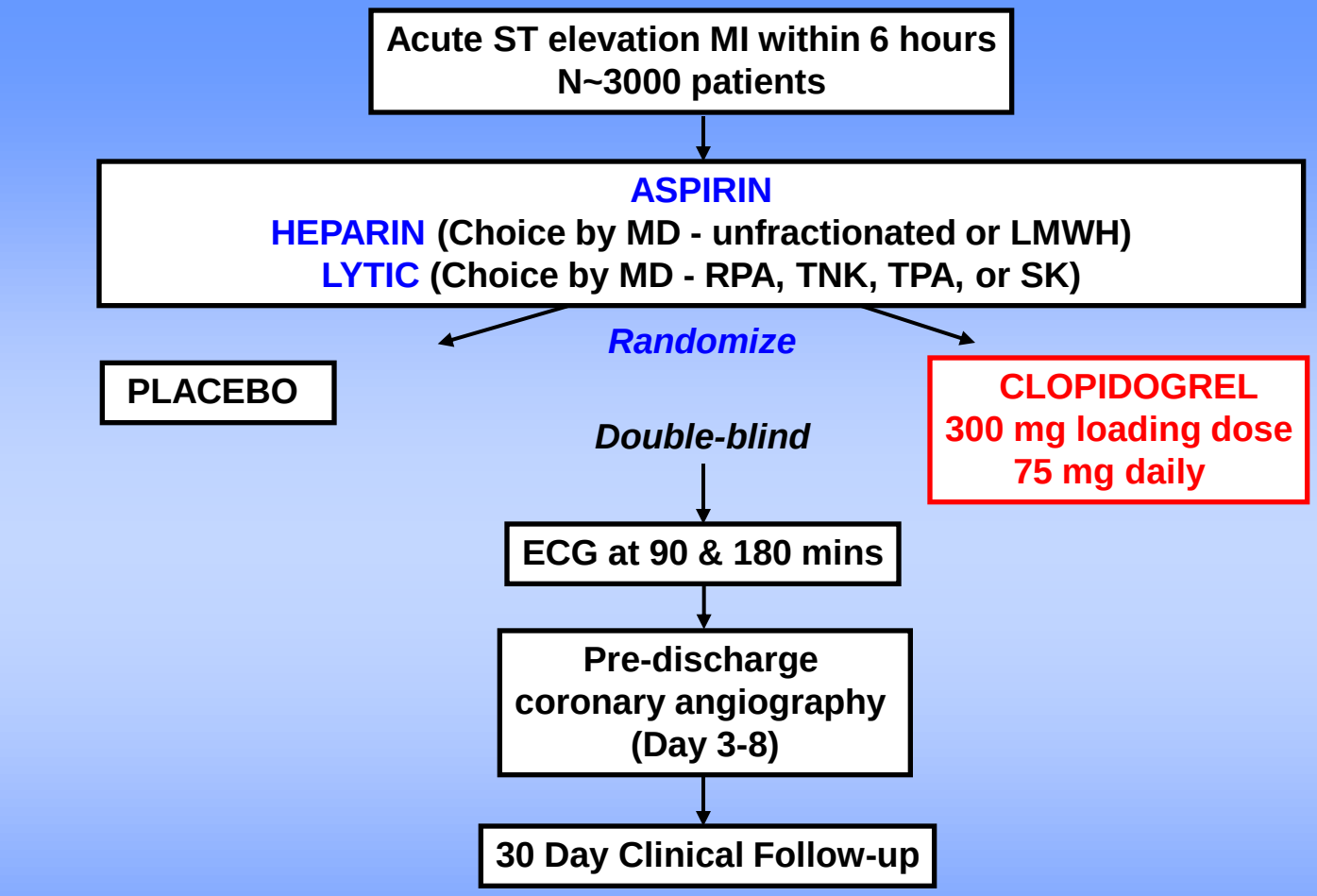
2011

CLARITY - TIMI 28

*CL*opidogrel as *A*djunctive *R*eperfus*I*on *T*herap*Y*

2011

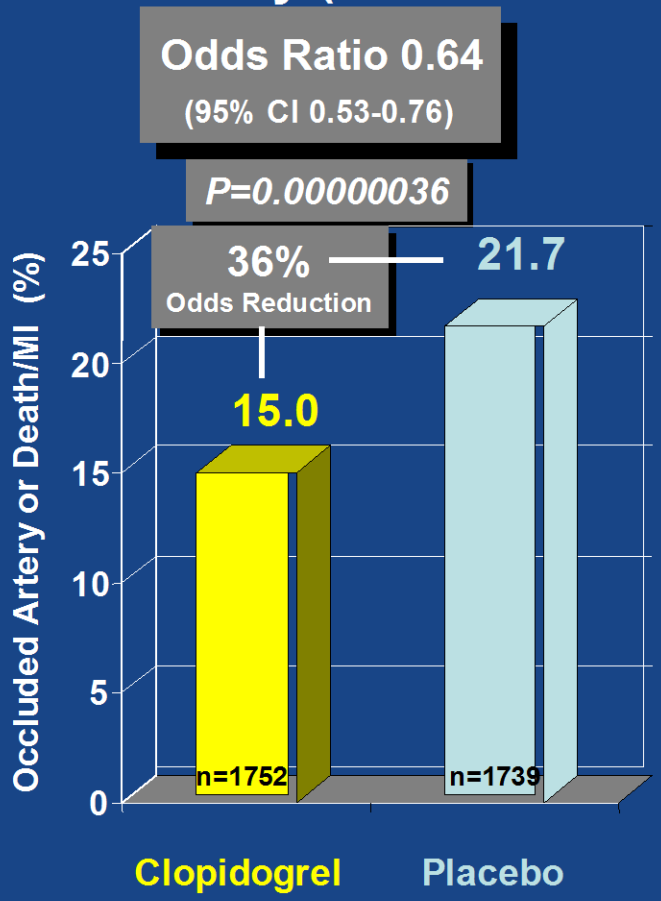
Protocol Design



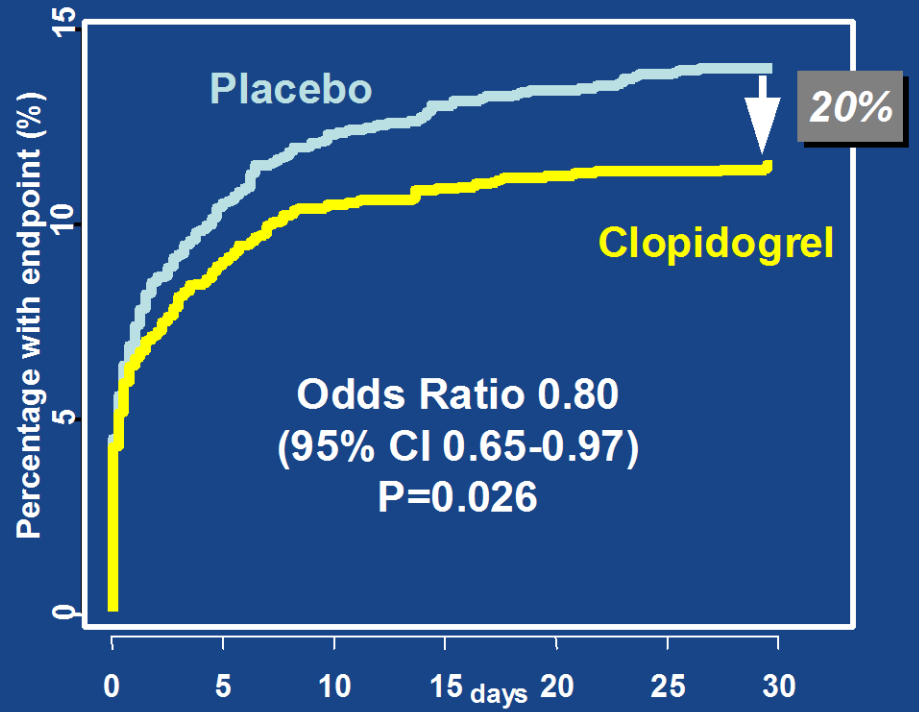
CLARITY-TIMI 28 Main Results

2011

Primary Endpoint: Occluded Artery (or D/MI thru Angio/HD)



CV Death, MI, RI

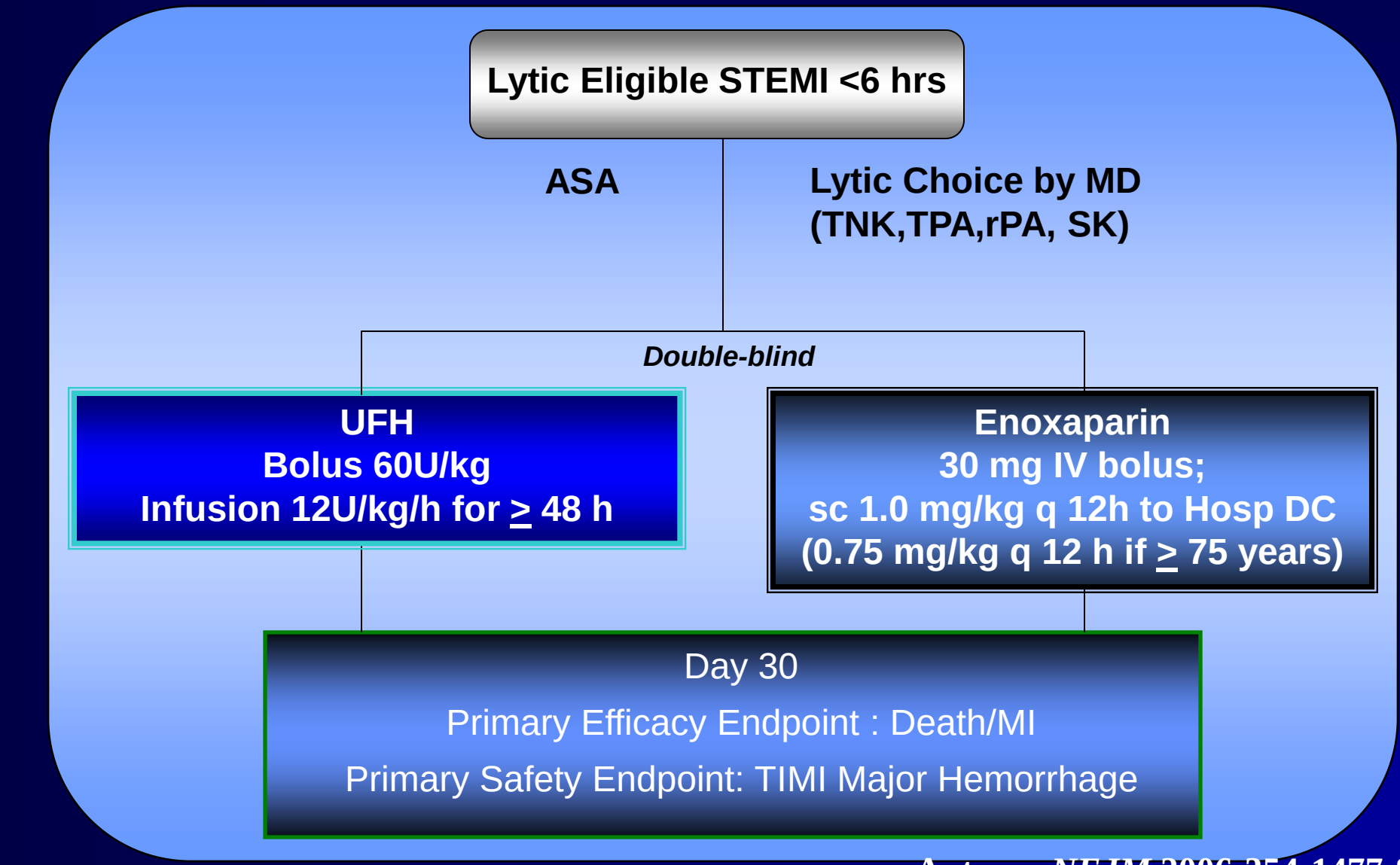


No difference in TIMI bleeding

Sabatine MS, et al. N Engl J Med 200;352:1179-89

ExTRACT - TIMI 25

Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment

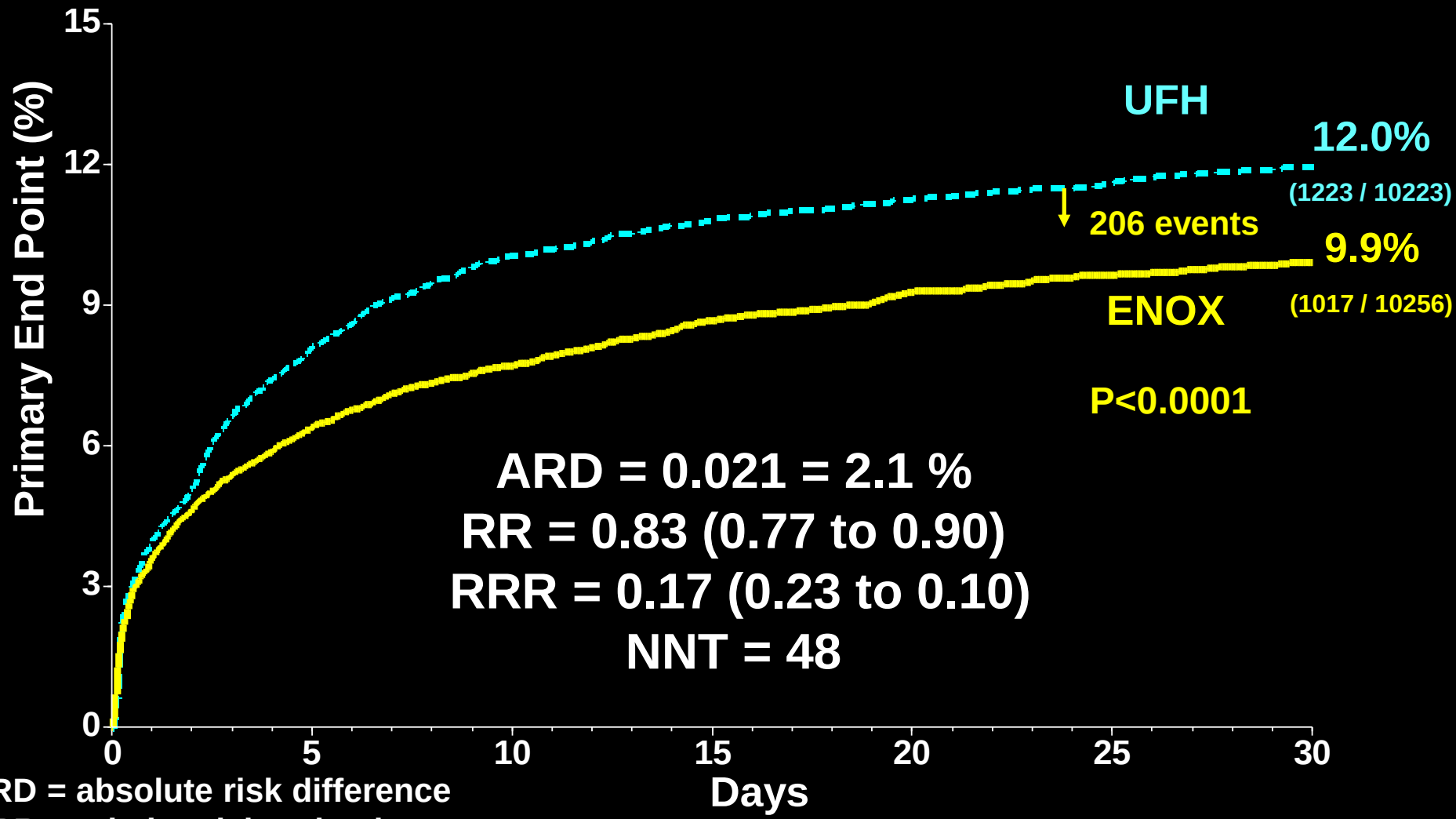


Antman *NEJM* 2006;354:1477-88

Primary End Point (ITT) Death or Nonfatal MI

N Engl J Med 2006;354:1477-88.

2011



ARD = absolute risk difference

RRR = relative risk reduction

Antman *NEJM* 2006;354:1477-88

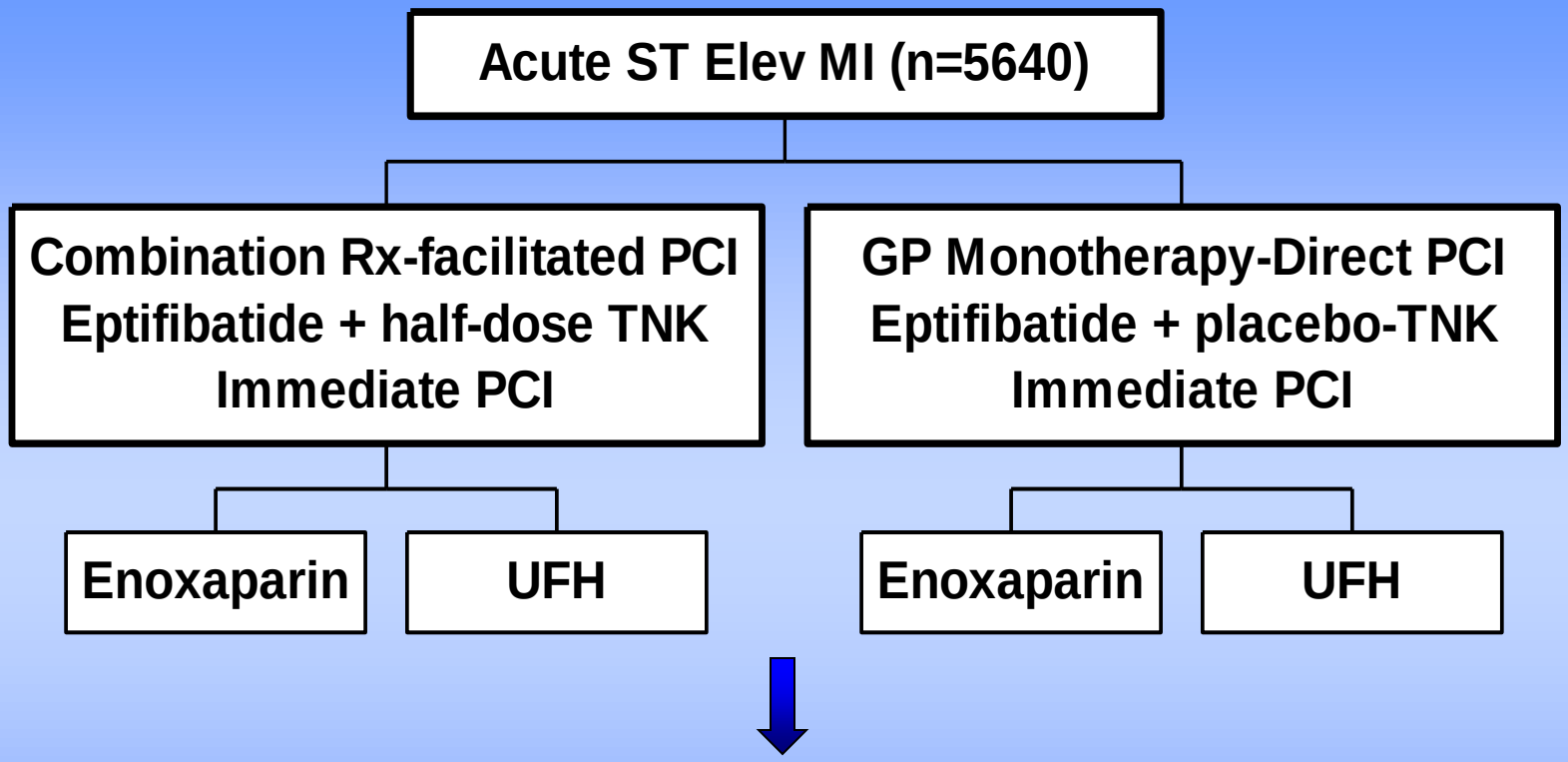
TIMI Trials 2000-present

Population	Experimental Therapy
Fibrinolytic	clopidogrel, enoxaparin
Primary PCI	**GPI timing, 1/2-dose lytic+GPI**
UA/nSTE-MI	anticoag, antiplt, anti-ischemic
Post ACS	lipids, antibiotics, renin inhibitor, oral factor Xa, Lp-PLA_2 inhibitor
PCI	anticoag, antiplt
Atrial Fib	oral factor Xa
DM	DPP-4 inhibitor

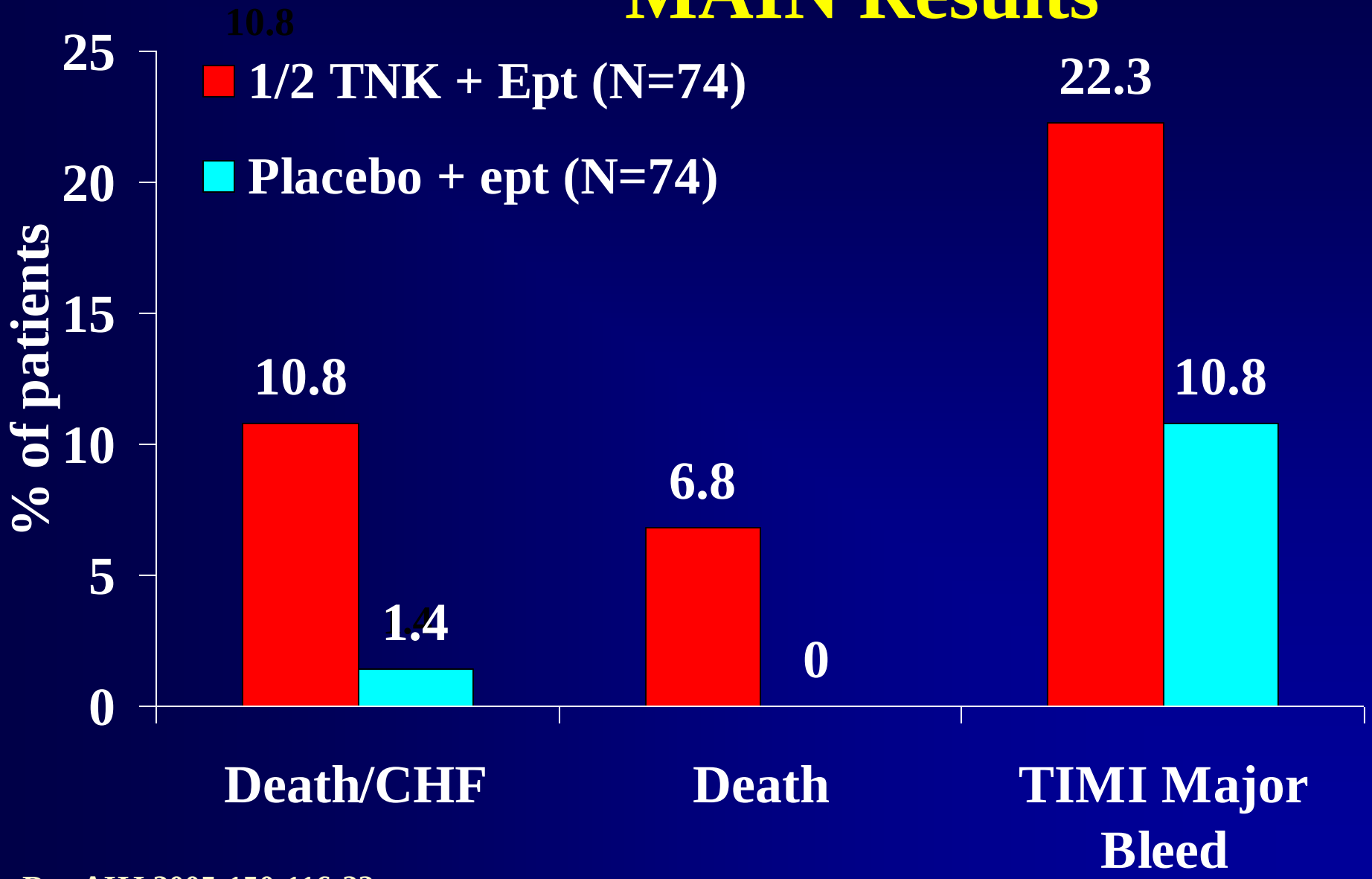
ADVANCE MI

ADdressing the ***V***alue of ***P***rimary ***AN***gioplasty after ***C***ombination therapy or ***E***ptifibatide monotherapy in acute ***M***yocardial ***I***nfarction

2011



ADVANCE MI – MAIN Results



Roe AHJ 2005;150:116-22

TIMI Trials 2000-present

Population	Experimental Therapy
Fibrinolytic	clopidogrel, enoxaparin
Primary PCI	GPI timing, half-dose lytic+GPI
UA/nSTE-MI	**anticoag, antiplt, anti-ischemic**
Post ACS	lipids, antibiotics, renin inhibitor, oral factor Xa, Lp-PLA_2 inhibitor
PCI	anticoag, antiplt
Atrial Fib	oral factor Xa
DM	DPP-4 inhibitor

TIMI

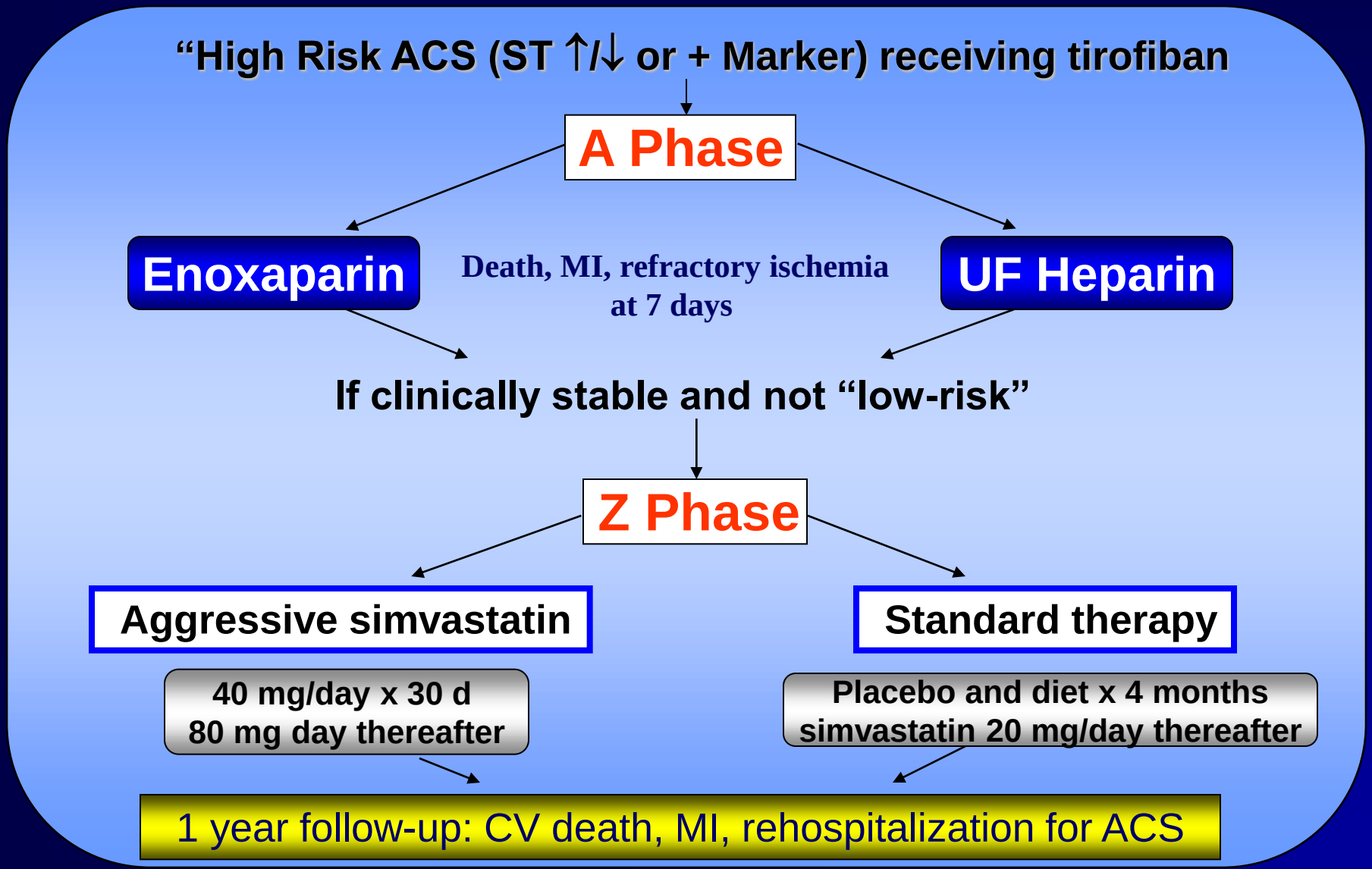
2011

A2Z

Aggrastat to Zocor

Protocol Design

2011



AGGRASTAT > ZOCOR

Preliminary Results

7 Day Primary Endpoint
Composite of Death, MI and Refractory Ischemia

TIMI 2011

Primary Analysis					
Population	ENOX	UFH	Hazard Ratio	P-value	Upper Bound One-Sided 95% CI
Intent to Treat	8.4%	9.4%	0.88	0.23	1.05

Non-inferiority = upper bound of one-sided 95% CI < 1.144

Blazing *JAMA* 2004;292:55

PROXIMATE -TIMI 27

PROXimal Inhibition of coagulation using a Monclonal Antibody to Tissue factor (Sunol cH36) - TIMI 27

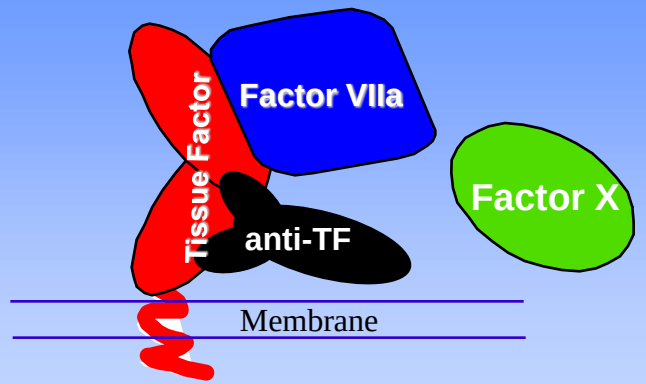
TIMI 2011

Protocol Design

Stable CAD Receiving ASA (n = 28)

- **cH36 Bolus Dose # 1 n = 7**
- **cH36 Bolus Dose # 2 n = 7**
- **cH36 Bolus Dose # 3 n = 7**
- **cH36 Bolus Dose # 4 n = 7**

If no safety concerns, proceed to higher dose



Measured at multiple time points:

- **cH36 levels**
- **Factor Xa activity**
- **Hgb/Hct**
- **PT/PTT/fibrinogen**
- **Platelet count**
- **Serum chemistries**
- **Human anti-chimeric ab**

Morrow DA EHJ 2004

PROXIMATE - TIMI 27

Bleeding Events 2011

PROXimal **I**nhibition of coagulation using a **M**onclonal **A**ntibody to **T**issu**e** factor (*Sunol cH36*)-TIMI 27

	Dose Sunol cH36				
	0.03	0.06	0.08	0.10	0.30
Enrolled, N	8	4	4	7	3
Major bleeding (pts)	0	0	0	0	0
Minor bleeding (pts)					
Spontaneous	1 (13)	2 (50)	2 (50)	6 (86)	3 (100)
Provoked	2 (25)	1 (25)	0	1 (14)	1 (33)
Any minor*	2 (25)	3 (75)	2 (50)	6 (86)	3 (100)
(Exact CI %)	(3, 65%)	(19, 99%)	(7, 93%)	(44,100%)	(29,100%)

*Individual pts may be classified as having both spontaneous & provoked episodes. Provoked bleeds were those that occurred at the site of IV insertion or as the result of minor trauma; all others were classified as spontaneous.

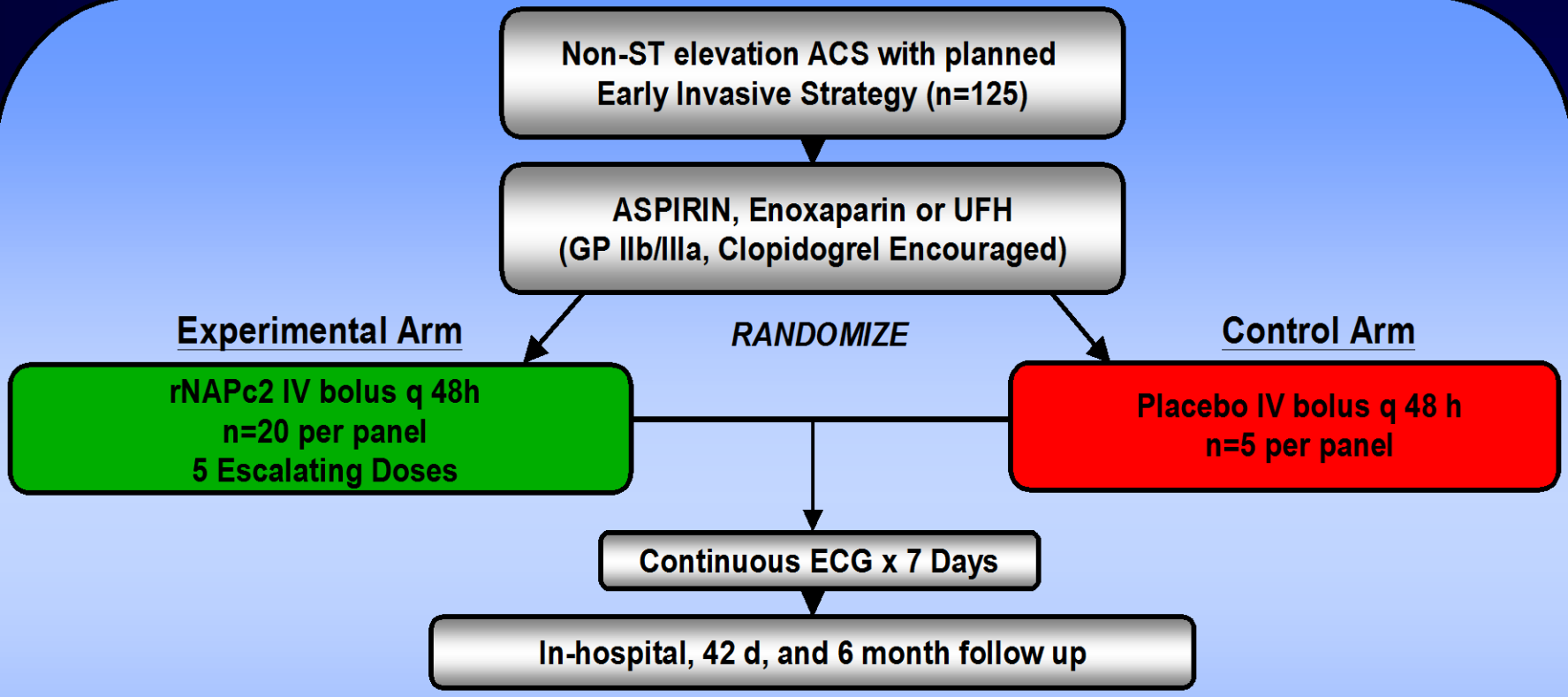
Morrow DA EHJ 2004

ANTHEM – TIMI 32

*A*nticoagulation with *N*APc2 *T*o *H*elp *E*liminate *M*ACE

2011

Protocol Design



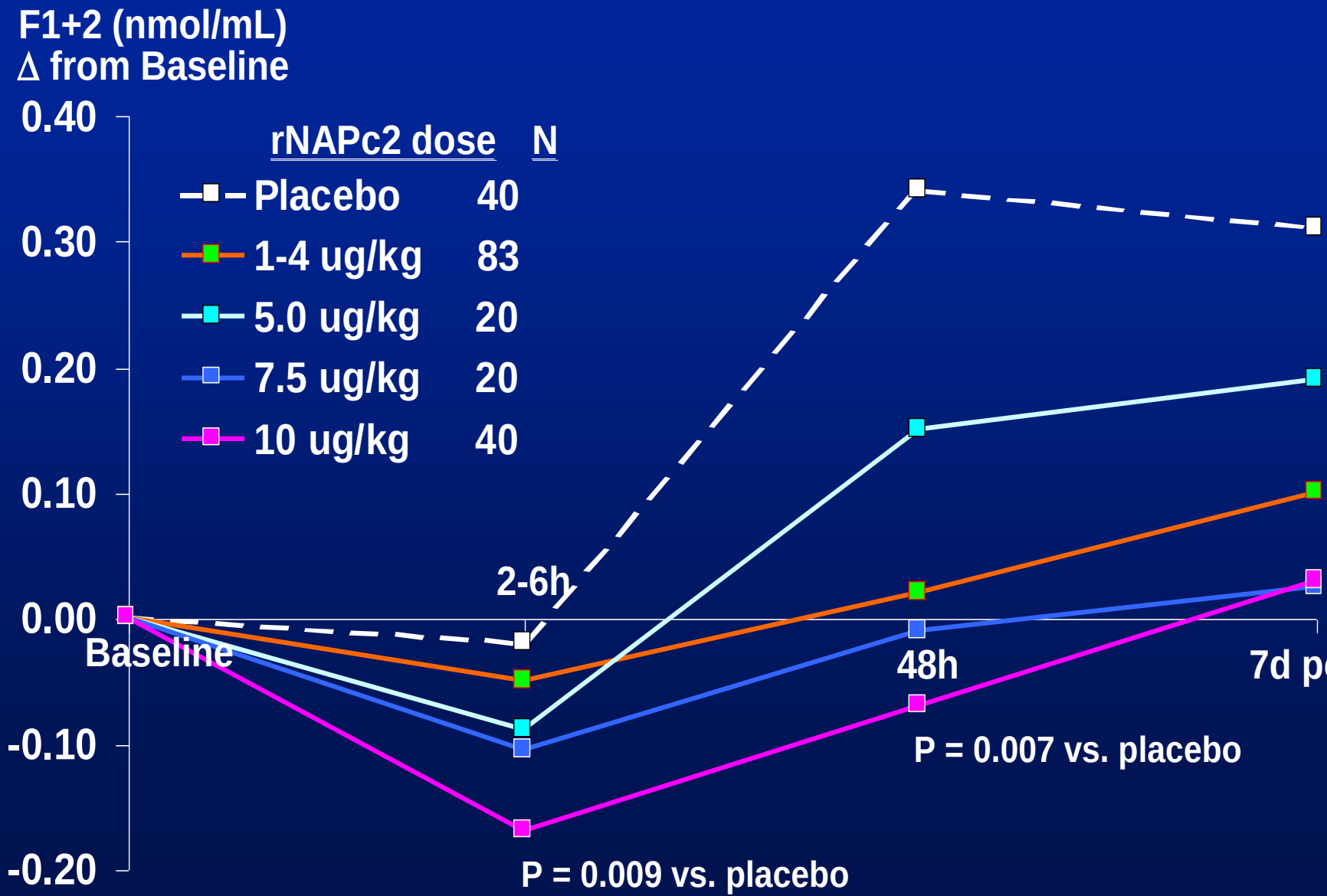
Primary Endpoints:
Safety: Significant Hemorrhage
Efficacy: PK, PD

Secondary Endpoints:
Death, MI, Recurrent Ischemia
Ischemia by Continuous ECG

A Randomised, Double-blind Placebo-controlled Study to Assess the Efficacy and Safety of Factor VIIa/Tissue Factor Inhibitor, Recombinant Nematode Anticoagulant Protein c2 (rNAPc2), in Subjects With Non-ST-Elevation Acute Coronary Syndromes.

Giugliano RP et al. *JACC* 2007; 49:2398-2407

F1+2 Concentration:
A Measure of New Thrombin Generation



Giugliano RP et al. *JACC* 2007; 49:2398-2407

TRÎTON TIMI·38

TRITON – TIMI 38

Protocol Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA

N= 13,000

Double-blind

PRASUGREL

CLOPIDOGREL

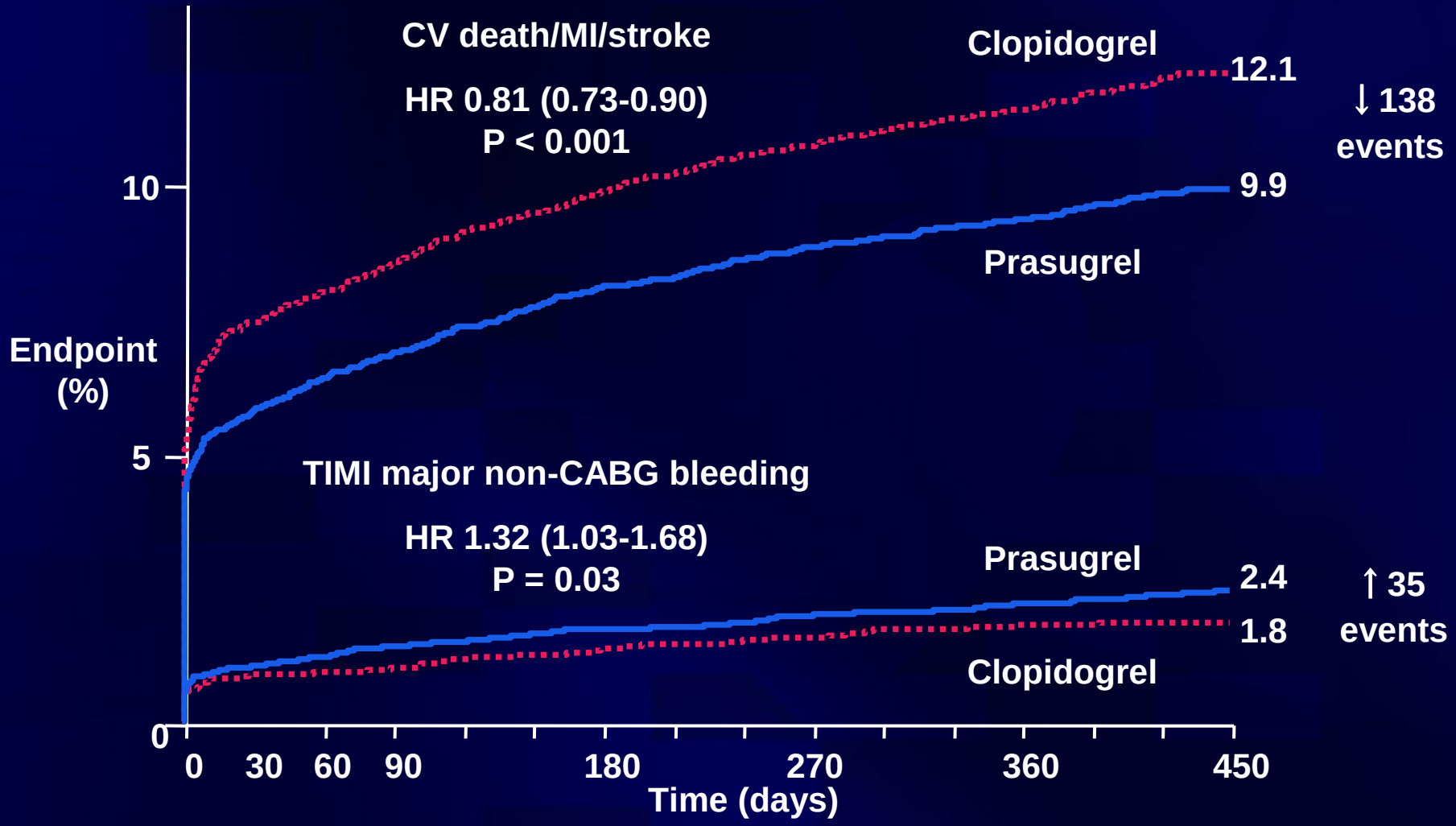
Median duration of therapy - 12 months

1º endpoint: CV death, MI, Stroke

2º endpoints: CV death, MI, Stroke, Re-ischemia

CV death, MI, UTVR

2011 TRITON-TIMI 38: Treatment effects on primary efficacy and key safety endpoints



HR = hazard ratio

Wiviott SD et al. *N Engl J Med.* 2007;357:2001-15.

EARLY ACS

Early (<12h) Eptifibatide in Pts with High-Risk ACS

10,500 pts ≥ 2 of the following:

1. ↑ MB or Tn
2. New STD ≥ 1mm
3. Age ≥ 60

Stratified by early clopidogrel

Eptifibatide 180/2/180 | UPSTREAM | Matching Placebo

Cath >12 h after randomization

Ept allowed at PCI

Optional Study Drug in Cath Lab
Blinded Placebo / Eptifibatide

Primary Endpoint: D/MI/UR/TBO at 96h
Secondary Endpoint: D/MI at 30 days

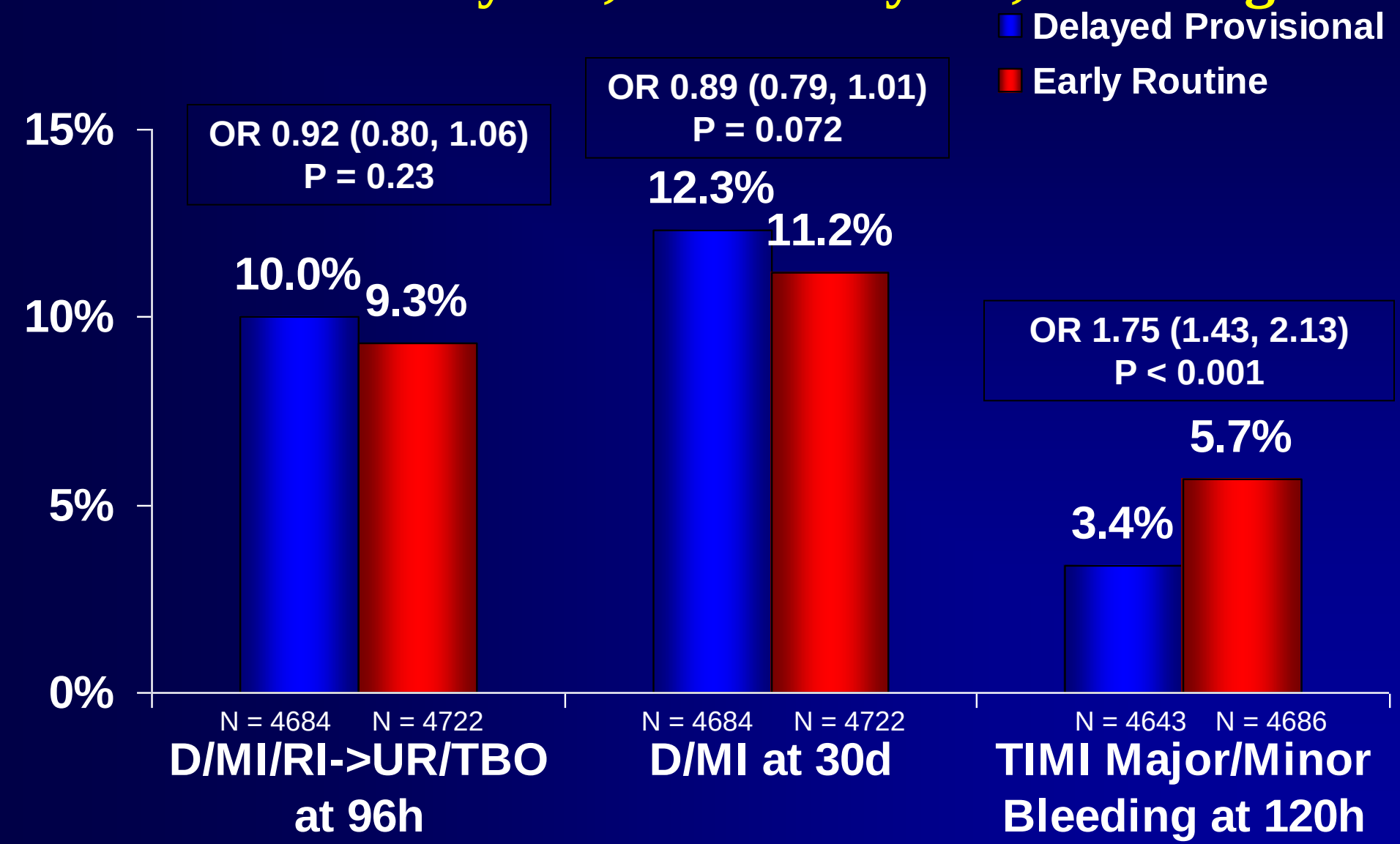
Giugliano *AHJ* 2005

EARLY ACS

TIMI

2011

Key Findings: Primary EP, Secondary EP, Bleeding

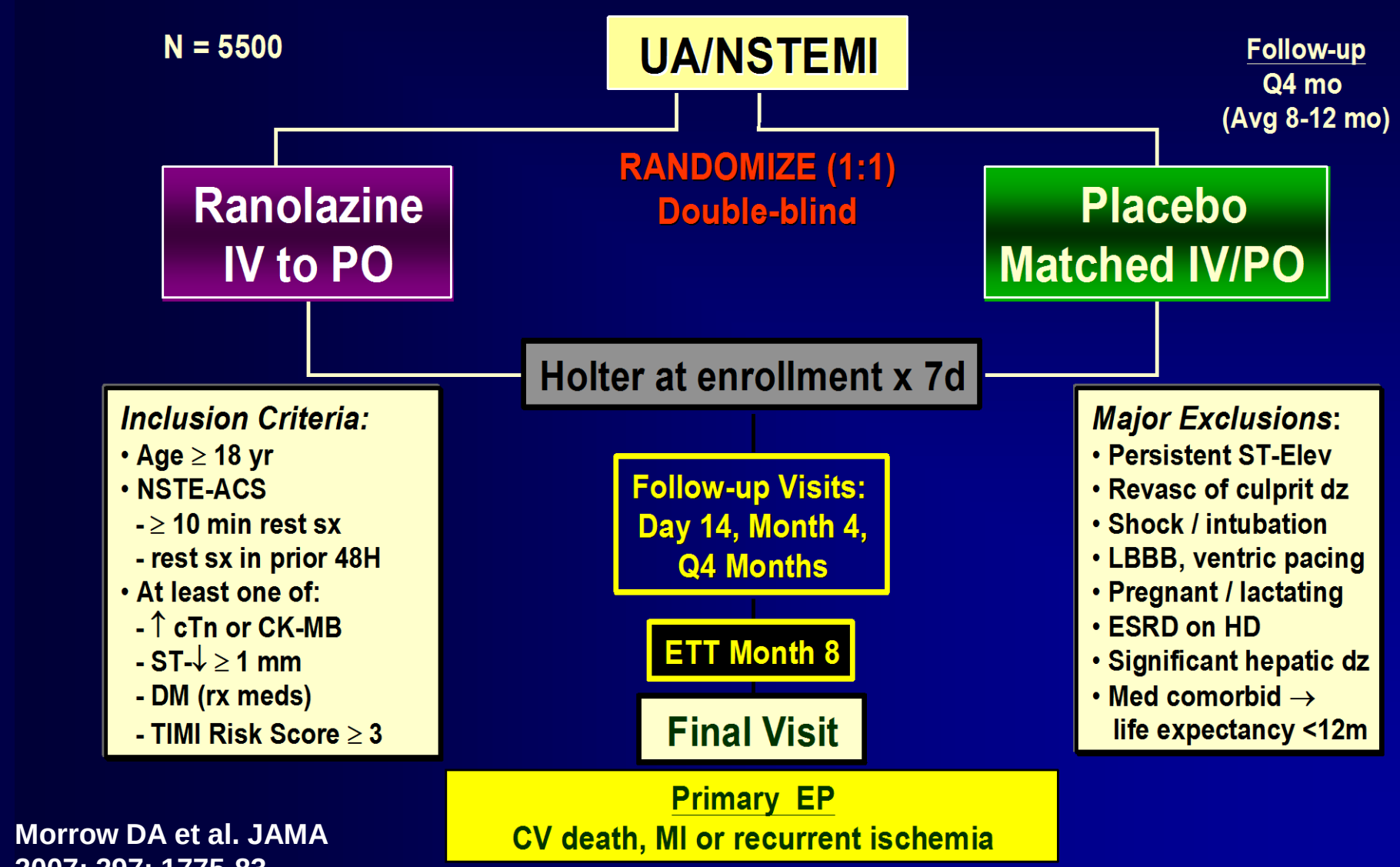


Giugliano RP et al. NEJM 2009;360:2176-90

MERLIN – TIMI 36

Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST elevation Acute Coronary Syndromes

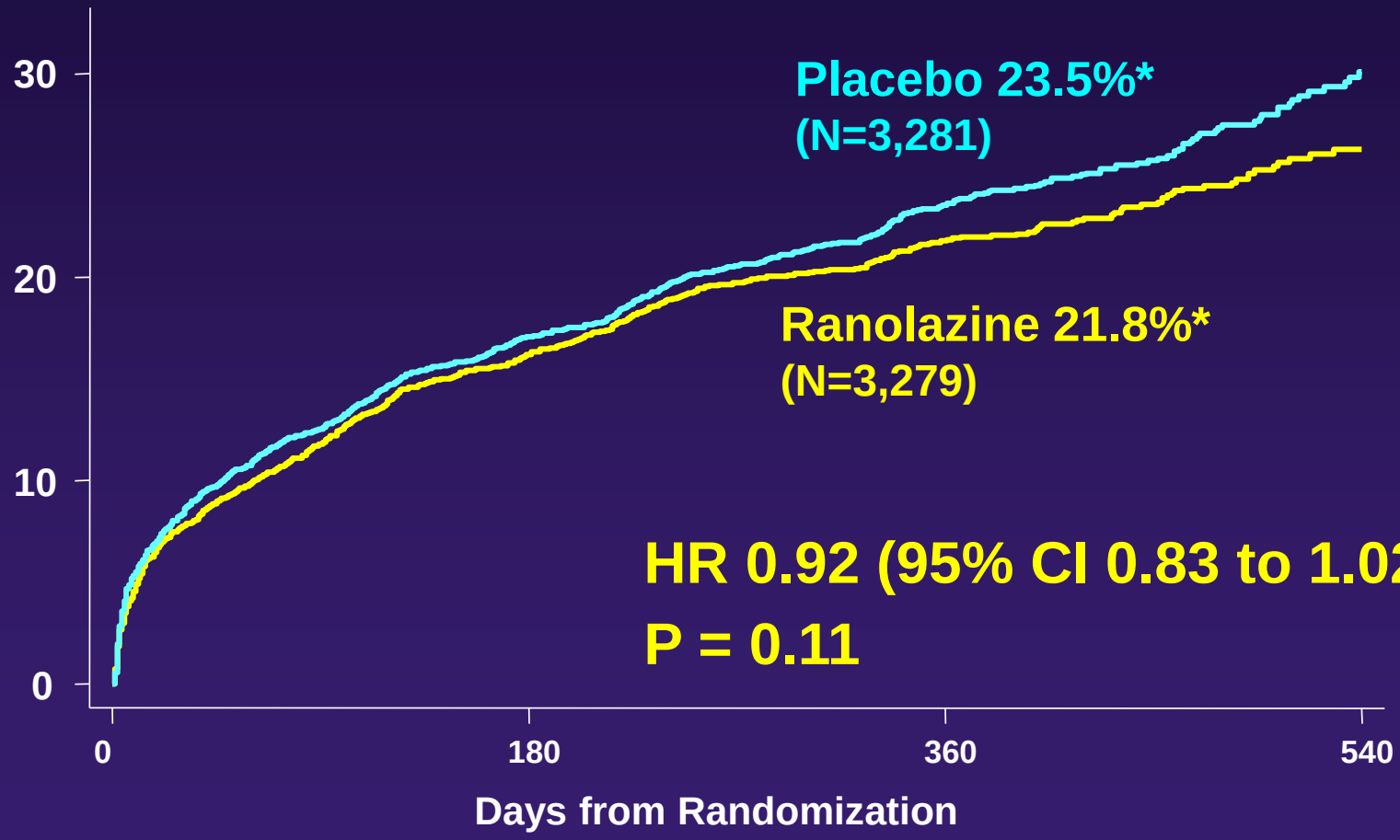
Protocol Design



Morrow DA et al. JAMA 2007; 297: 1775-83

Primary Endpoint

CV Death, MI, or Recurrent Ischemia (%)



*KM cumulative incidence (%) at 12 months

Morrow DA et al. JAMA 2007; 297: 1775-83

TIMI Trials 2000-present

Population	Experimental Therapy
Fibrinolytic	clopidogrel, enoxaparin
Primary PCI	GPI timing, half-dose lytic+GPI
UA/nSTE-MI	anticoag, antiplt, anti-ischemic
Post ACS	lipids, antibiotics, renin inhibitor, oral factor Xa, Lp-PLA_2 inhibitor
PCI	anticoag, antiplt
Atrial Fib	oral factor Xa
DM	DPP-4 inhibitor

TIMI

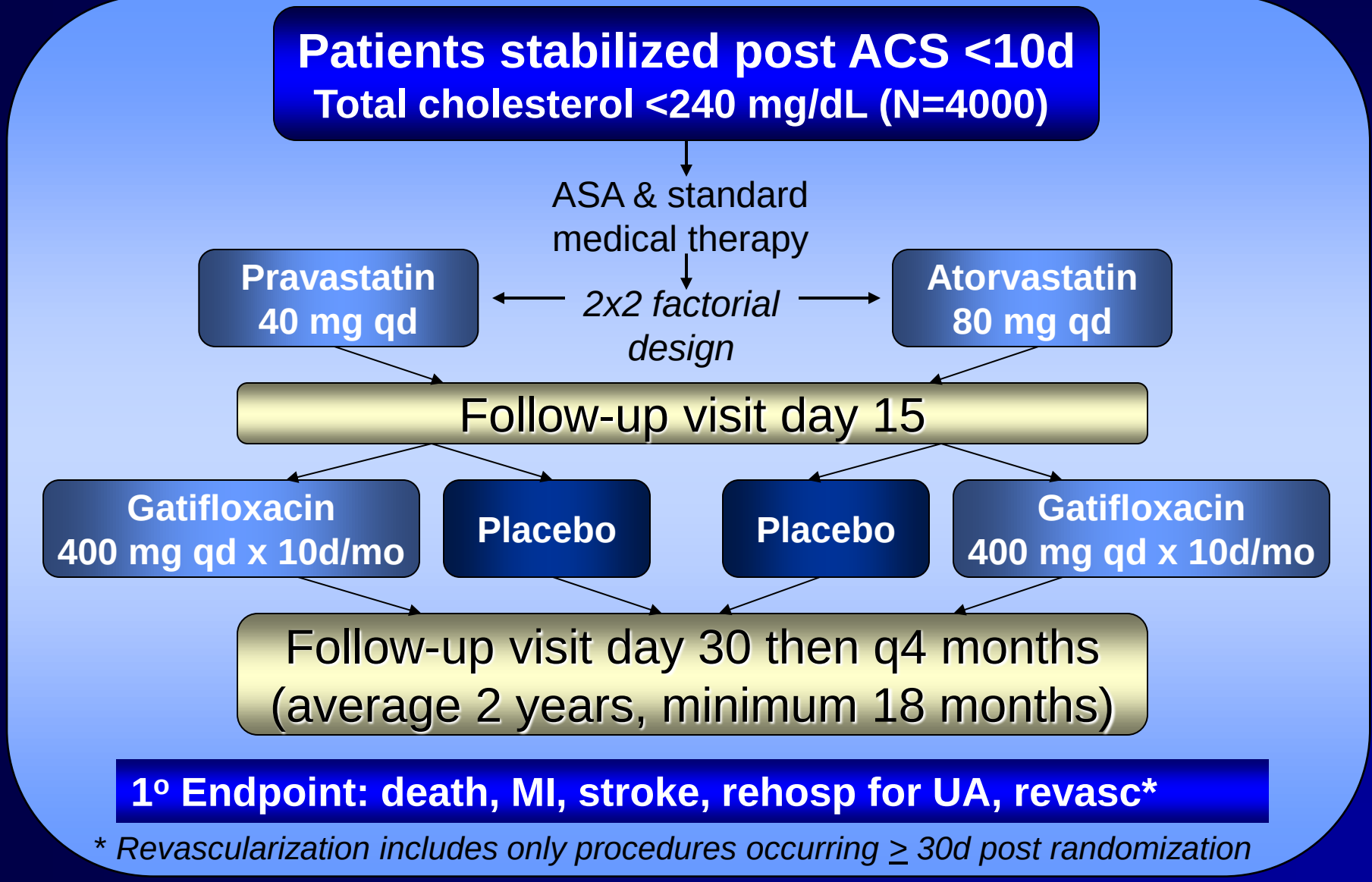
2011

PROVE IT - TIMI 22

***PR*avastatin *O*r Atorvastatin Evaluation and *I*nfection *T*herapy**

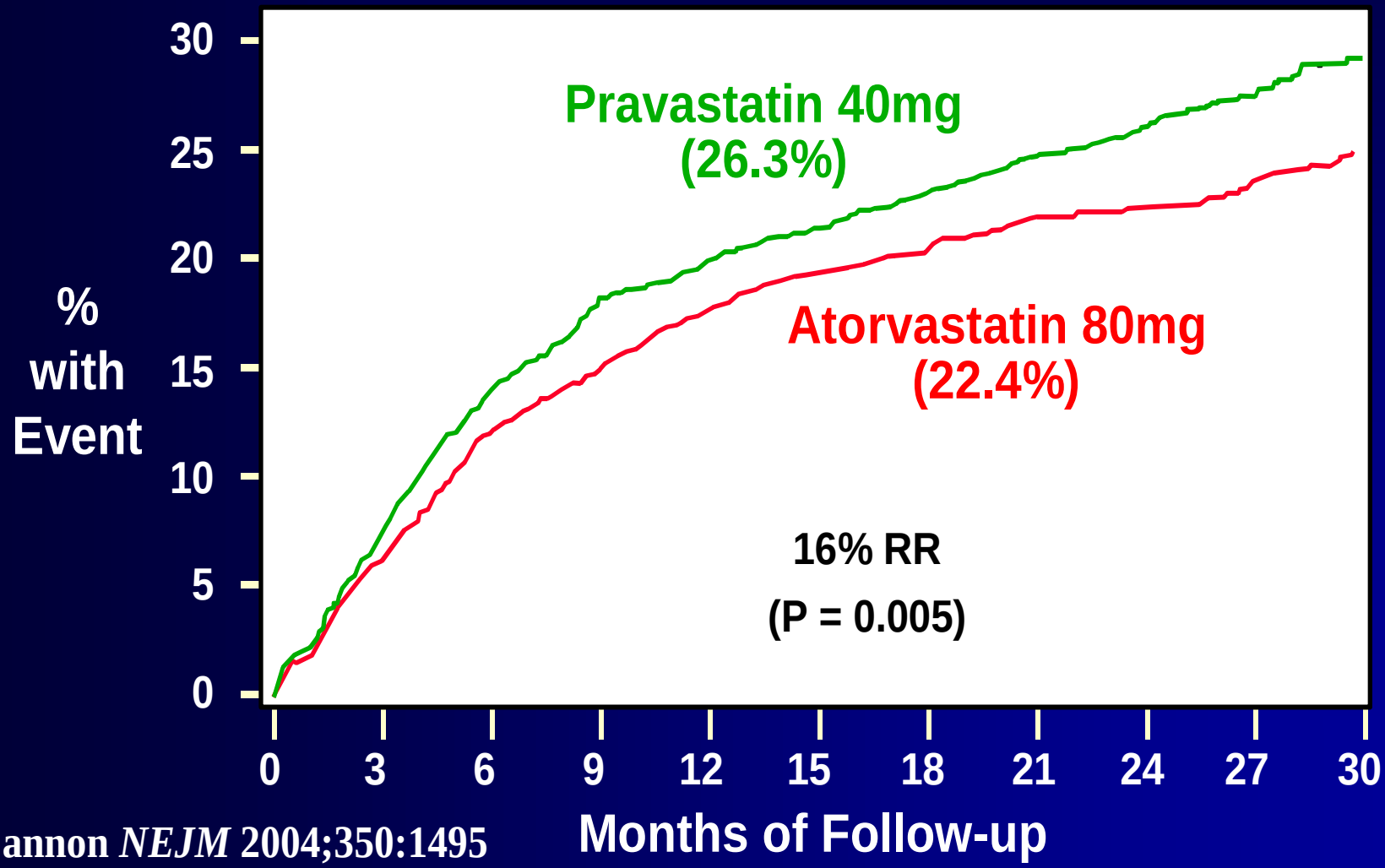
2011

Protocol Design



PROVE IT TRIAL TIMI 22

All-Cause Death or Major CV Events in All Randomized Subjects



Cannon *NEJM* 2004;350:1495

Study Design

ELEVATE TIMI 56

TIMI 2011

Investigator-Initiated Study
IND #: 107635

335 Patients Enrolled
Stable CAD Pts on Clopidogrel 75 mg daily
(>4 Weeks and <6 Months Post-MI or PCI)

2 Not Genotyped

333 Blinded Genotyping

247 *CYP2C19*2* Non-Carriers

Randomized to various blinded sequences of daily doses of clopidogrel

75 mg | 150 mg | 75 mg | 150 mg

86 *CYP2C19*2* Carriers

(80 Heterozygotes; 6 Homozygotes)

Randomized to various blinded sequences of daily doses of clopidogrel

75 mg | 150 mg | 225 mg | 300 mg

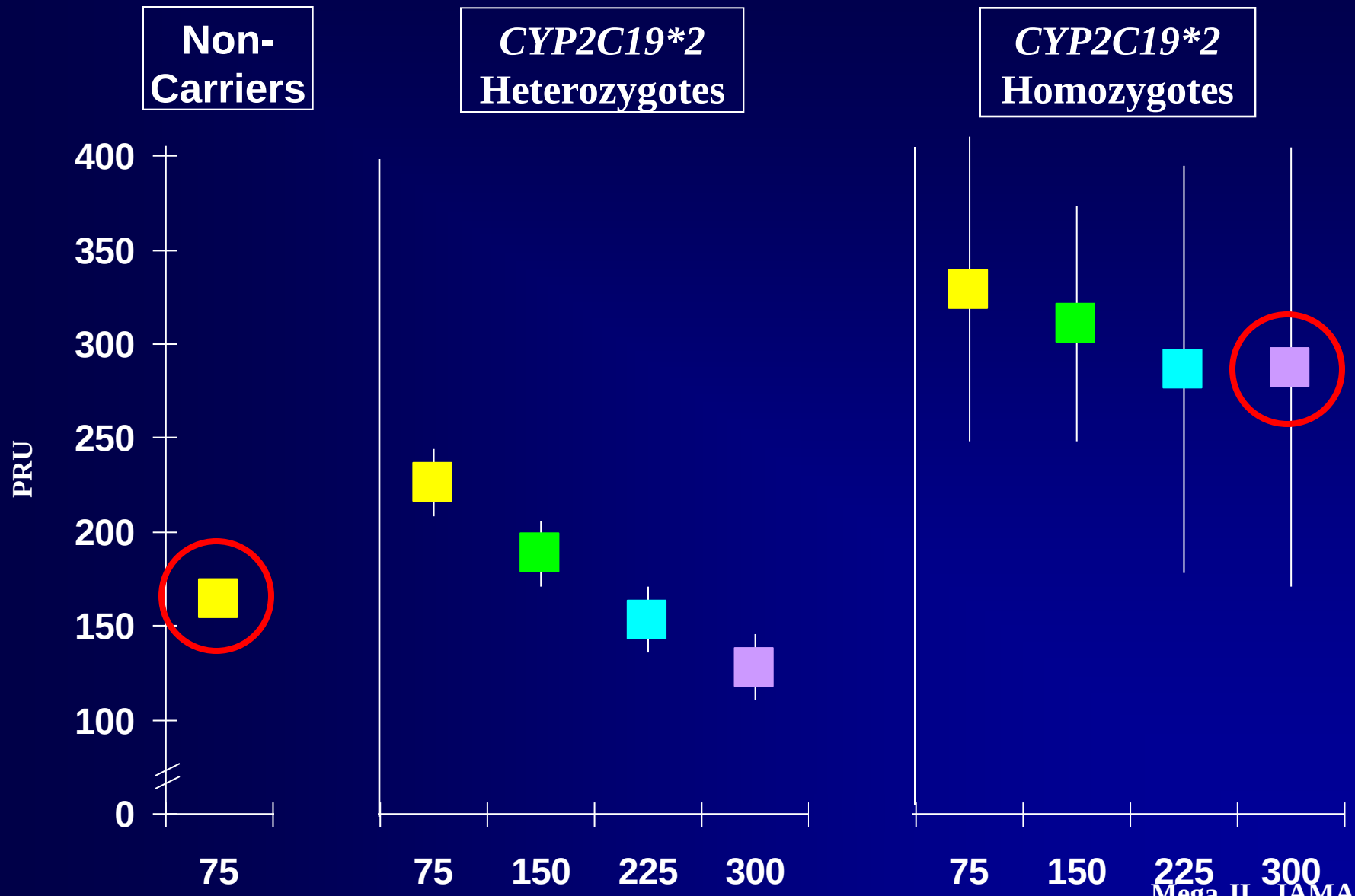
Each dose given for ~14 days followed by platelet function testing (VASP and VerifyNow $P2Y_{12}$ assays) and assessment for events

Mega JL, JAMA. 2011;306(20):2221-2228

ELEVATE
TIMI 56

Platelet Reactivity with ↑ Clopidogrel

2011



Squares represent the means and vertical lines the 95% confidence intervals.

Mega JL, JAMA. 2011; 306(20):2221-2228

Recent ACS: STEMI, NSTEMI, UA

Stabilized 1-7 Days Post-Index Event

Exclusions: increased bleeding risk, warfarin use, ICH, prior stroke if on ASA + thienopyridine

ASA 75 to 100 mg/day

Stratified by Thienopyridine Use at MD Discretion

Placebo	Rivaroxaban 2.5 mg BID	Rivaroxaban 5.0 mg BID
n=5,176	n=5,174	n=5,176

PRIMARY ENDPOINTS:

EFFICACY: CV Death, MI, Stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

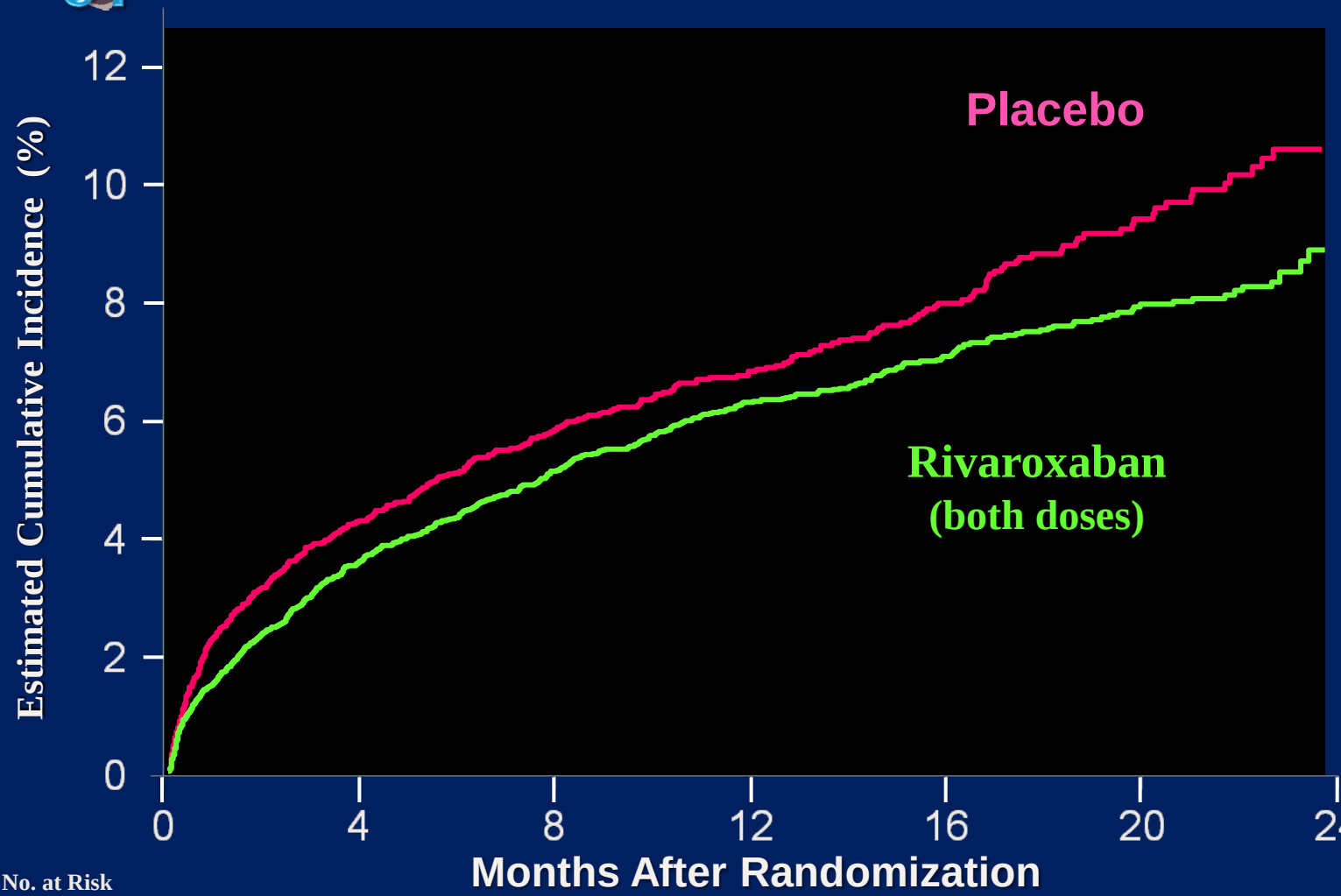
SAFETY: TIMI major bleeding not associated with CABG

Event driven trial with 1,002 primary efficacy events

Gibson CM, *Am Heart J* 2011

PRIMARY EFFICACY ENDPOINT:

CV Death / MI / Stroke



2 Yr KM Estimate

10.7%

8.9%

HR 0.84 (0.74-0.96)

mITT p = 0.008
ITT p = 0.002

ARR 1.8%
NNT = 56

No. at Risk							
Placebo	5113	4307	3470	2664	1831	1079	421
Rivaroxaban	10229	8502	6753	5137	3554	2084	831

HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches.

Mega JL, *NEJM* 2011

Current TIMI Trials

2011

Follow-up Phase (N=5)

IMPROVE-IT (T40)	Ph3 – Ezetimibe post ACS
ENGAGE AF-TIMI 48	Ph3 – Edoxaban in AFib
ICE-T – TIMI 49	Ph3 – IC TNK in Primary PCI
TRA 2P-TIMI 50	Ph3 – Vorapaxar in CVD
SOLID-TIMI 52	Ph3 – PLA2 inhibitor in CAD

Currently Enrolling (N=4)

SAVOR-TIMI 53	Ph3 – DPP4 in DM
PEGASUS-TIMI 54	Ph3 – Ticagrelor post MI
HPS3-TIMI 55/Reveal	Ph3 – Anacetrapib in CAD
LAPLACE-TIMI 57	Ph2 - PCSK9 Inhibitor in ↑Chol

Future TIMI Trials

Treatments

Old and new antiplatelet agents
More proximal and oral anticoagulants
Novel lipid-modifying therapies
Diabetes treatment / prevention
Cardioprotective agents
Non-pharmacologic Rx

Strategies

Earlier therapy
Aggressive vs conservative
Markers of high-risk (genetic, clinical, biochemical)

Summary

Important Lessons from TIMI 1-50+

- Clinical trials form a key step in the cycle of clinical therapeutics between the concept and the established guidelines
- Completed trials have helped established standards of care across ACS spectrum (lysis, anticoag, antiplts, lipid Rx, inv vs cons)
- Ongoing studies will further refine use of antithrombotics, anti-ischemics, lipid Rx, and other therapies in patients with CAD/ACS

Ezetimibe + Simvastatin vs Simvastatin Alone post ACS

IMPROVE-IT

Patients stabilized post Acute Coronary Syndrome < 10 days
LDL ≤ 125*mg/dL (or ≤ 100**mg/dL if prior lipid-lowering Rx)

Double-blind

ASA + Standard Medical Therapy

N=18,000

Simvastatin 40 mg

Eze/Simva 10/40 mg

Follow-Up Visit Day 30, Every 4 Months

*3.2mM
**2.6mM

Duration: Minimum 2 1/2 year follow-up (>5250 events)

Primary Endpoint: CV Death, MI, Hospital Admission for UA, revascularization (> 30 days after randomization), or Stroke

Cannon et al. *AHJ* 2008; 156:826-832

Edoxaban (oral FXa inhibitor) in Atrial Fib

Engage AF TIMI 48

TIMI 2011

N = 21,105

AF on Electrical Recording ≤ 12 mo
Intended oral A/C
$CHADS_2 \geq 2$

DOUBLE BLIND DOUBLE DUMMY

R

Randomization Stratified By
1. $CHADS_2$ 2-3 vs 4-6
2. Drug Clearance

Low Exposure Strategy
Edoxaban 30 mg QD
(n ≈ 7000)

High Exposure Strategy
Edoxaban 60 mg QD
(n ≈ 7000)

Active Control
Warfarin
(n ≈ 7000)

Median Duration of Followup 24 months

Primary Objective
Edoxaban: Therapeutically as Good as Warfarin

1º EP = Stroke or SEE (Noninferiority Boundary HR 1.38)
2º EP = Stroke or SEE or All-Cause Mortality
Safety EP's = Major Bleeding, Hepatic Function

SEE = systemic embolic event

Ruff CR. AHJ 2010

EVENT DRIVEN

ICE T – TIMI 49: Intracoronary TNK in Primary PCI

ASA 160-325 mg
Clopidogrel 300-600 mg

STEMI < 6 hours for 1° PCI

n=40 | 8 sites

UFH
Glycoprotein IIb/IIIa inhibitor

TIMI 0/1 Flow in Culprit Artery
During Diagnostic Angiography

R

n=20 — **IC Tenecteplase (4mg)**

Saline (Placebo) — n=20

PCI with stent

IC Tenecteplase (4mg)

Saline (Placebo)

Post-treatment Angiography (epicardial flow and myocardial perfusion)

Primary Endpoint: Improvement in % diameter stenosis after1st administration of study drug

*T*hrombin *R*eceptor *A*ntagonist in *Secondary P*revention of Atherothrombotic Ischemic Events (TRA 2°P)-TIMI 50

2011

Prior MI, Ischemic CVA, or PAD

Standard care, including oral antiplt rx

Vorapaxar (SCH 530348)

RANDOMIZE 1:1 DOUBLE BLIND
Stratify by CAD, CVD or PAD and intent to use thienopyridine

Placebo

Trial Features
Global: 31 countries
~1000 sites
~26,500 subjects
Double-blind
Event-driven

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

Final Visit

Primary EP
CV Death, MI, Stroke, Urgent Coronary Revascularization

Major Secondary EP: CV death, non-fatal MI, non-fatal stroke

Morrow DA et al. *AHJ* 2009;158:335-341e3

TRA 2°P TIMI 50

Stabilization Of pLaques usIng Darapladib (Lp-PLA$_2$ inhibitor)-TIMI 52

SOLID TIMI 52

TIMI 2011

High-risk* patients ≤30 days post-ACS:
UA, NSTEMI or STEMI

* Must meet ≥1 enrichment criteria

Guideline-recommended background Rx, including statins and antiplatelet drugs

Double-blind

Randomize 1:1

Darapladib (160mg daily)

Placebo (daily)

Event driven
Total N ~11,500
Total events ~ 1500

Anticipated median f/u ~ 3y

Primary Endpoint: CV Death, Non-fatal MI, or Non-Fatal Stroke

Saxagliptin (DPP-4 inhibitor) Assessment of Vascular Outcomes Recorded in DM - TIMI 53

savor TIMI 53

TIMI 2011

Documented Type 2 Diabetes

N ~ 12000

Established CV disease or Multiple Risk Factors

RANDOMIZE 1:1 DOUBLE BLIND

Dosing based on eGFR

All other DM Rx per treating MD

SAXAGLIPTIN 2.5 or 5 mg/d

PLACEBO

Follow-up
Min. 3 yr

Duration
Event driven (n=1040)
Estimated time ~ 5 yr

Follow up Visits Q6 months

Final Visit

Primary EP
CV Death, Non-fatal MI, Non-Fatal Ischemic Stroke

Major Secondary EP: CV death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure, unstable angina pectoris, or coronary revascularization

PEGASUS TIMI 54

TIMI

2011

History of MI 1-3 yrs prior + ≥1 additional atherothrombosis risk factor*

N ~ 21,000

** Age ≥65 yrs, diabetes, 2nd prior MI, multivessel CAD, or chronic non-end stage renal dysfunction*

RANDOMIZE
DOUBLE BLIND

Planned treatment with ASA 75 – 150 mg & Standard background care

- **Ticagrelor 90 mg bid**
- **Ticagrelor 60 mg bid**
- **Placebo**

Follow-up Visits
Q4 mos for 1st yr, then Q6 mos

Min 12 mos and median 26 mos follow-up
Event-driven trial

Primary Efficacy Endpoint: CV Death, MI, or Stroke

Primary Safety Endpoint: TIMI Major Bleeding

REVEAL

hps3·TIMI55

Randomized EValuation of the Effects of Anacetrapib through Lipid-modification

Age ≥ 50 *and* ≥1 *of following:*
Hx of prior MI, CVD, PAD, or Diabetes with Symptomatic CAD

Total Cholesterol ≤ 155mg/dL

Anacetrapib 100mg/d + Atorvastatin

Minimized Randomization

Double-blind

Placebo + Atorvastatin

Follow up Visits
At month 2 and 6, and every 6 months thereafter.

Final visit

Primary Endpoint

- CV death / MI / Coronary Revascularization

Trial features

- ~30,000 subjects
- ~400 hospitals
- Event driven
- ~4y median f/u

Major Secondary Endpoints: CV death, coronary death or MI, coronary revascularization procedure, or ischemic stroke

CTSU Oxford University *and* TIMI Study Group

LAPLACE-TIMI 57

Trial Design