Thrombolysis in Myocardial Infarction (TIMI) Study Group

ASCO/IOM Workshop:
Implementing a National Cancer Clinical Trials System for the 21st Century, February 11, 2013

Marc S. Sabatine, MD, MPH

Chairman, TIMI Study Group
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TIMI Study Group

BWH BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

What is the TIMI Study Group?

An Academic Research Organization (ARO) dedicated to advancing the knowledge and care of patients suffering from cardiovascular disease and its risk factors

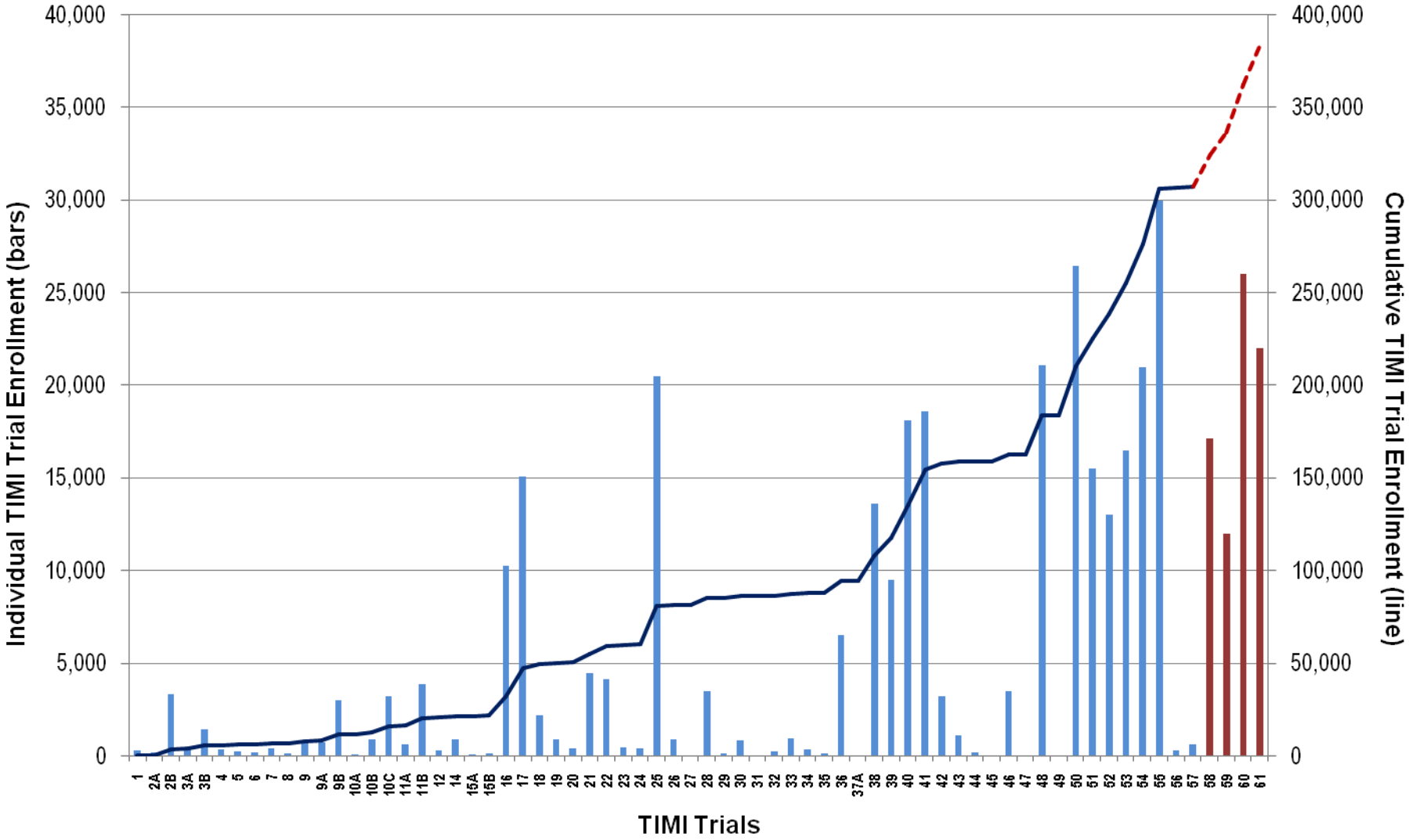
TIMI Trials: *1984 to present*

65 Clinical Trials (59 completed, 6 ongoing)

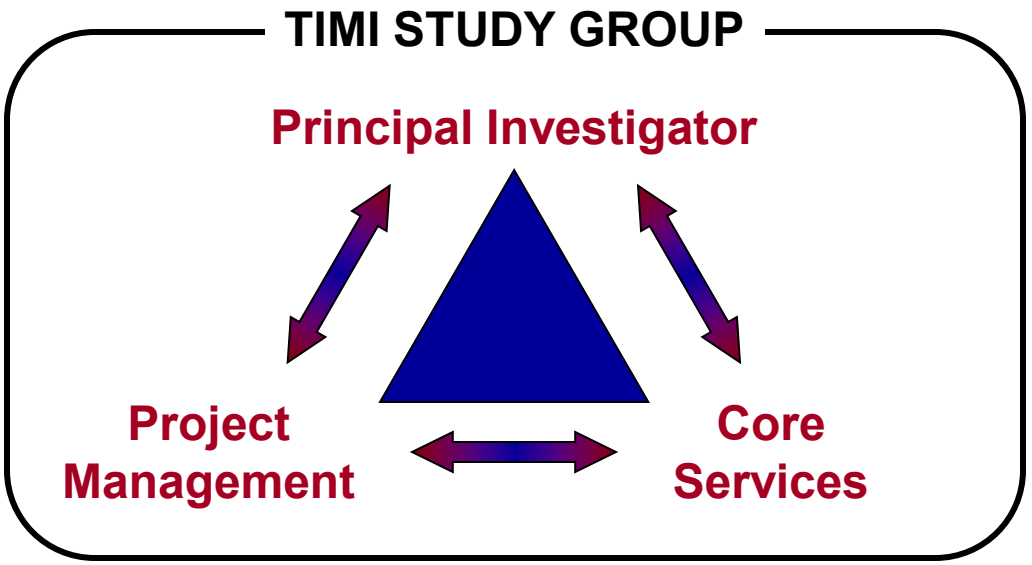
More Than:

- **>300,000 Patients enrolled to date**
- **>4000 Sites worldwide**
- **>8000 Investigators worldwide**
- **52 Countries**
- **6 Continents**

TIMI Trial Enrollment



TIMI Integrated Approach



TIMI Physicians

- **Clinicians (on staff at Brigham and Women's Hosp)**
  - Experts in practice of cardiovascular medicine
  - On national professional society guideline committees
- **Scientists (on faculty of Harvard Medical School)**
  - Experienced at framing and refining hypotheses
  - Long track record of high impact publications (*NEJM*, *JAMA*, *Lancet*)
  - **Dedicate career to research (75-80% research time)**
- **Clinical Trialists (TIMI Investigators)**
  - Highly experienced in the design of clinical trials: protocol, eCRF, ICF, CEC charter, IDMC charter
  - Integral part of Trial Team, **working daily** with Senior Project Director on implementation of trial
  - Provide **physician-to-physician** guidance & motivation

Project Management

- **Director of Operations**
  - Oversees all trials
  - Ensures appropriate resources; problem solves
- **Project Directors**
  - ~10 years of experience with multiple CV mega-trials
  - Leads trial ops team
  - Works hand-in-hand with TIMI Trial PI, Co-PI
- **Project Managers** (1-2 per trial)
- **Research Assistants** (10-12 per trial)

Core Services

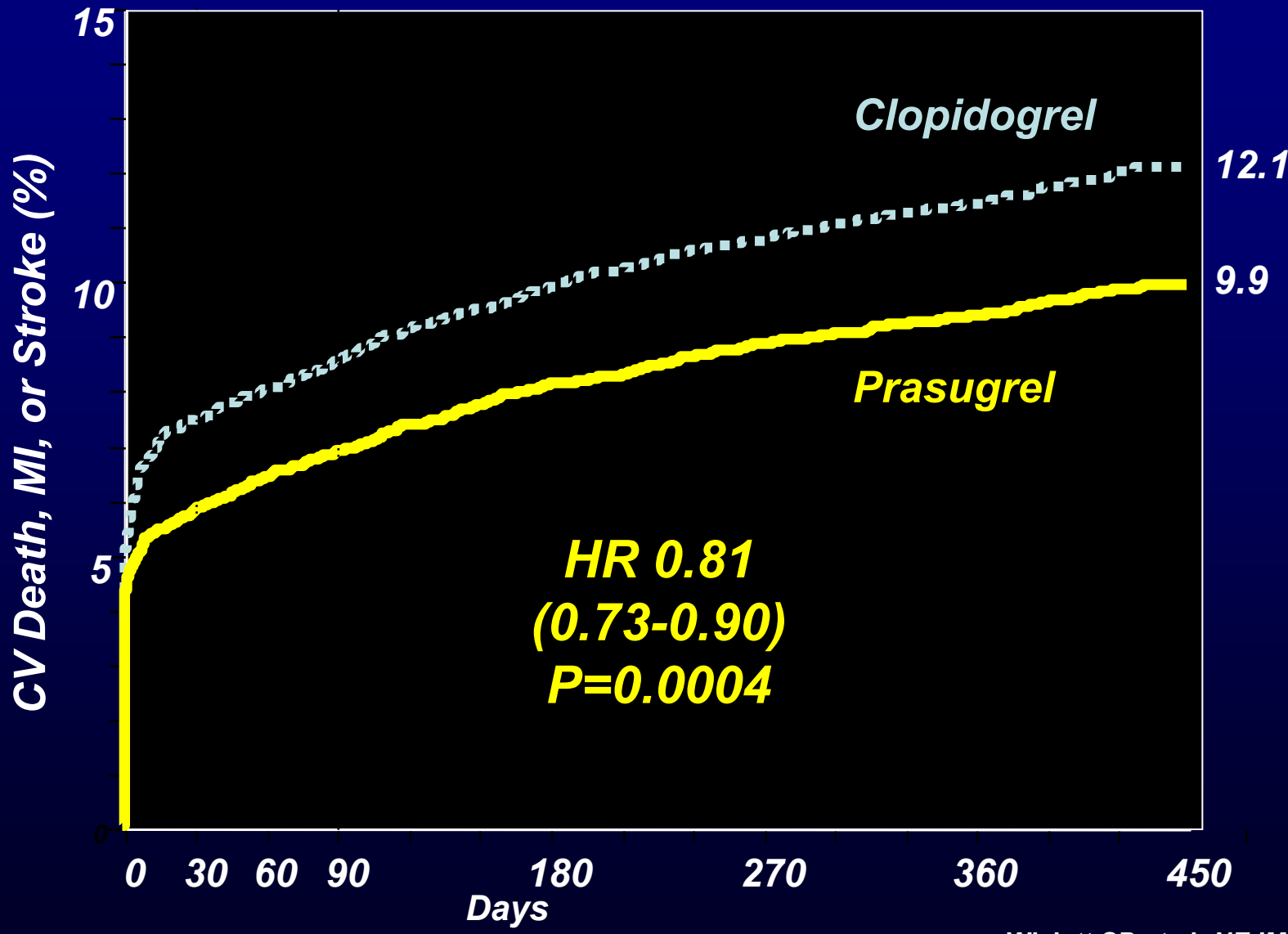
- Clinical Events Committee
- Safety Desk
- QA/Regulatory Team
- Trial Hotline
- Biomarker Core Laboratory
- Genetics Core Laboratory
- ECG Core Laboratory
- Independent Biostatistics

Trial Design

- **Protocol**
  - Right patient population
  - Right dose
  - Right endpoints
- **Case Report Form**
  - Gather all the necessary information to test trial's hypothesis
  - Expand knowledge of disease state
  - Ask the right questions the right way
  - Streamline, make easy for sites, minimize queries
- **Statistical Analysis Plan**
  - Define correct datasets (efficacy vs. safety, censoring rules)
  - Appropriate analyses of secondary endpoints given multiple hypothesis testing

TRITON TIMI·38

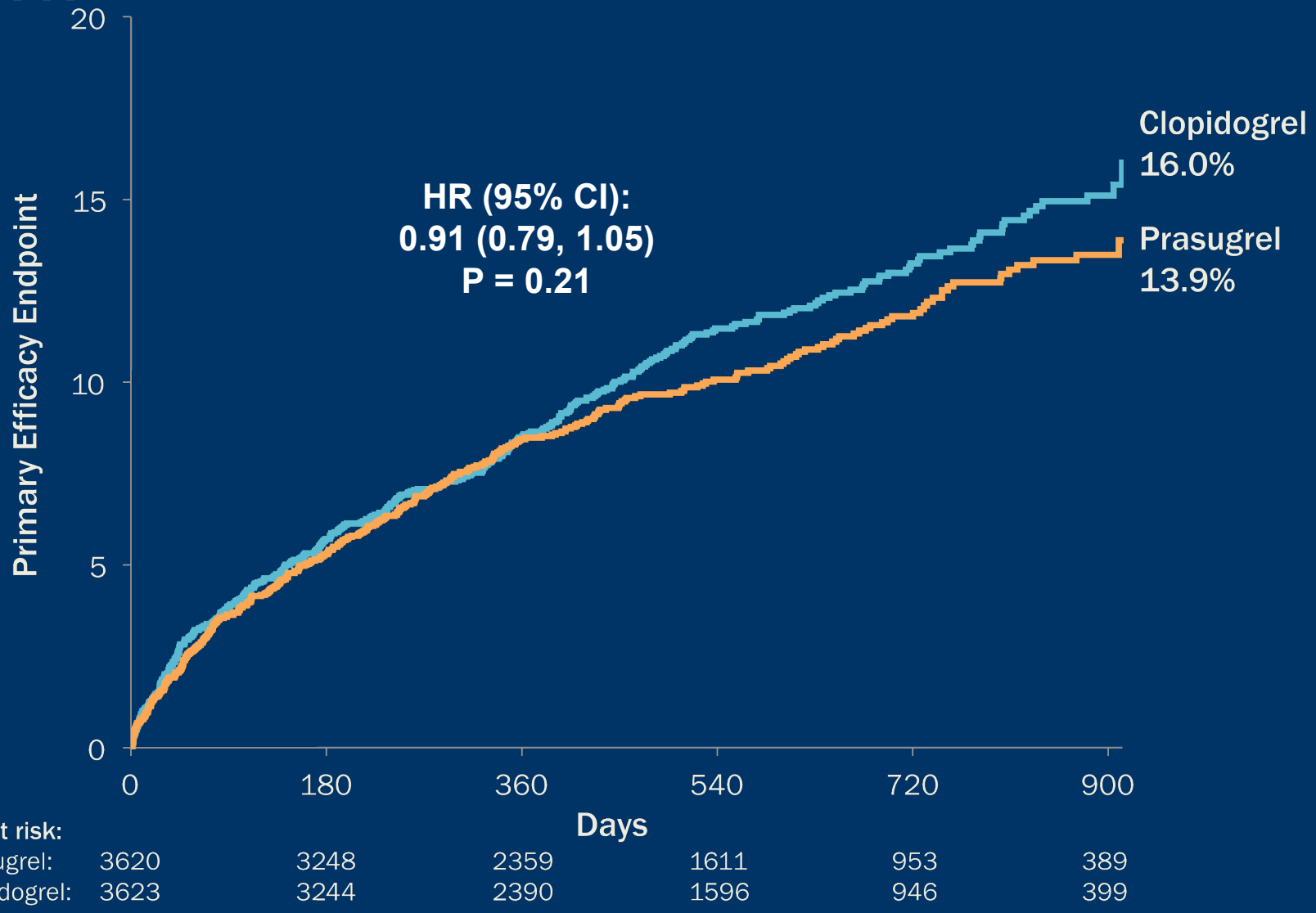
13,608 Patients with ACS and Planned PCI Randomized to Prasugrel (60/10) vs. Clopidogrel (300/75)



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

Prasugrel in Medically Managed Patients

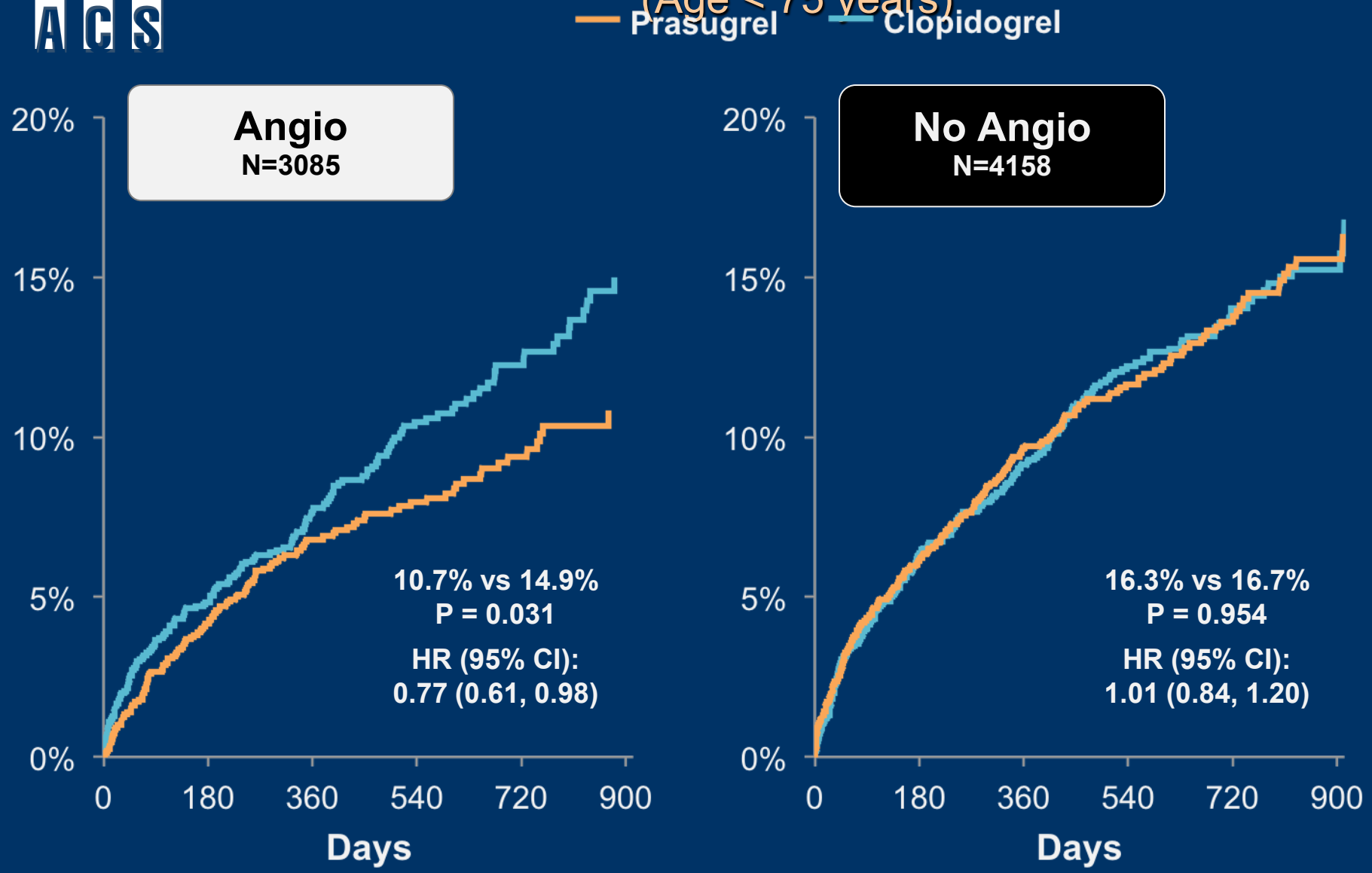
(Age < 75 years)



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

Primary Efficacy Endpoint to 30 Months

(Age < 75 years)



P interaction = 0.08

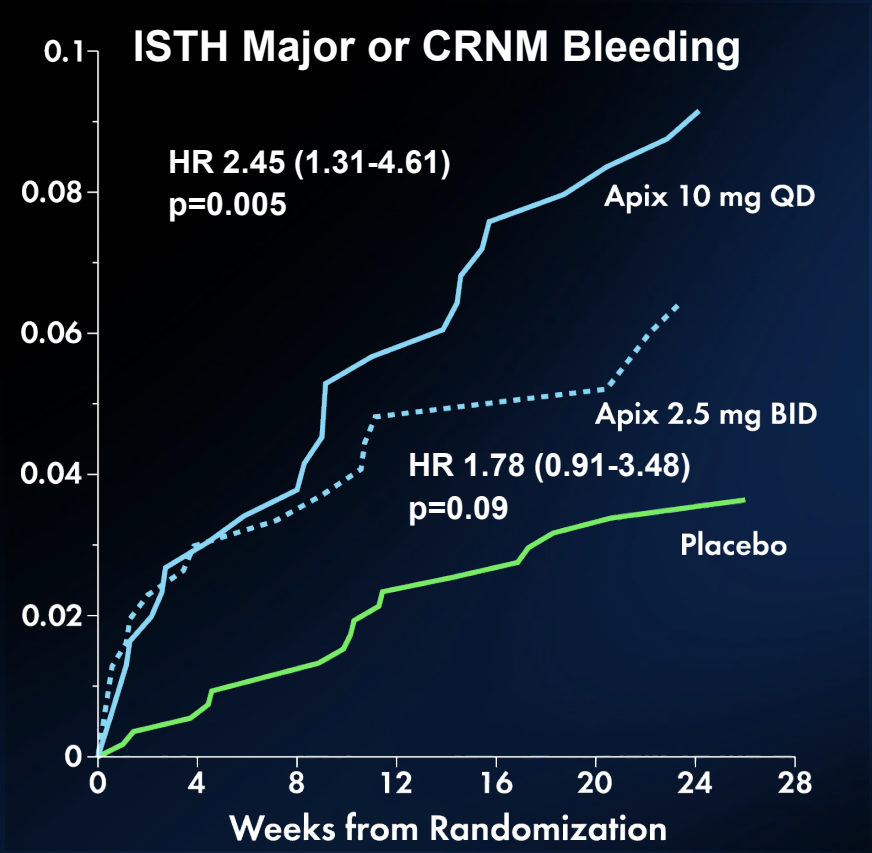
Wiviott et al TCT 2012

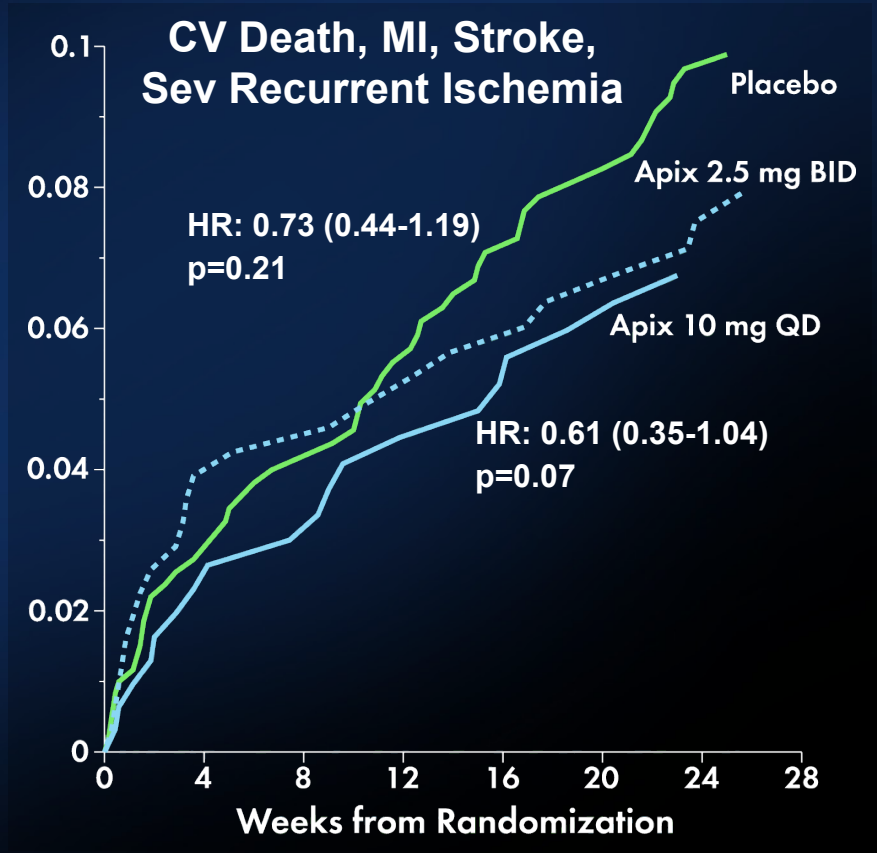
APPRAISE-1 Trial of Apixaban (Factor Xa Inhib)

Phase 2, 1715 patients, recent acute coronary syndrome

Apixaban 2.5 mg BID, 10 mg QD, 10 mg BID, 20 mg QD, placebo

Apixaban 10 mg BID & 20 mg QD stopped due to excess bleeding

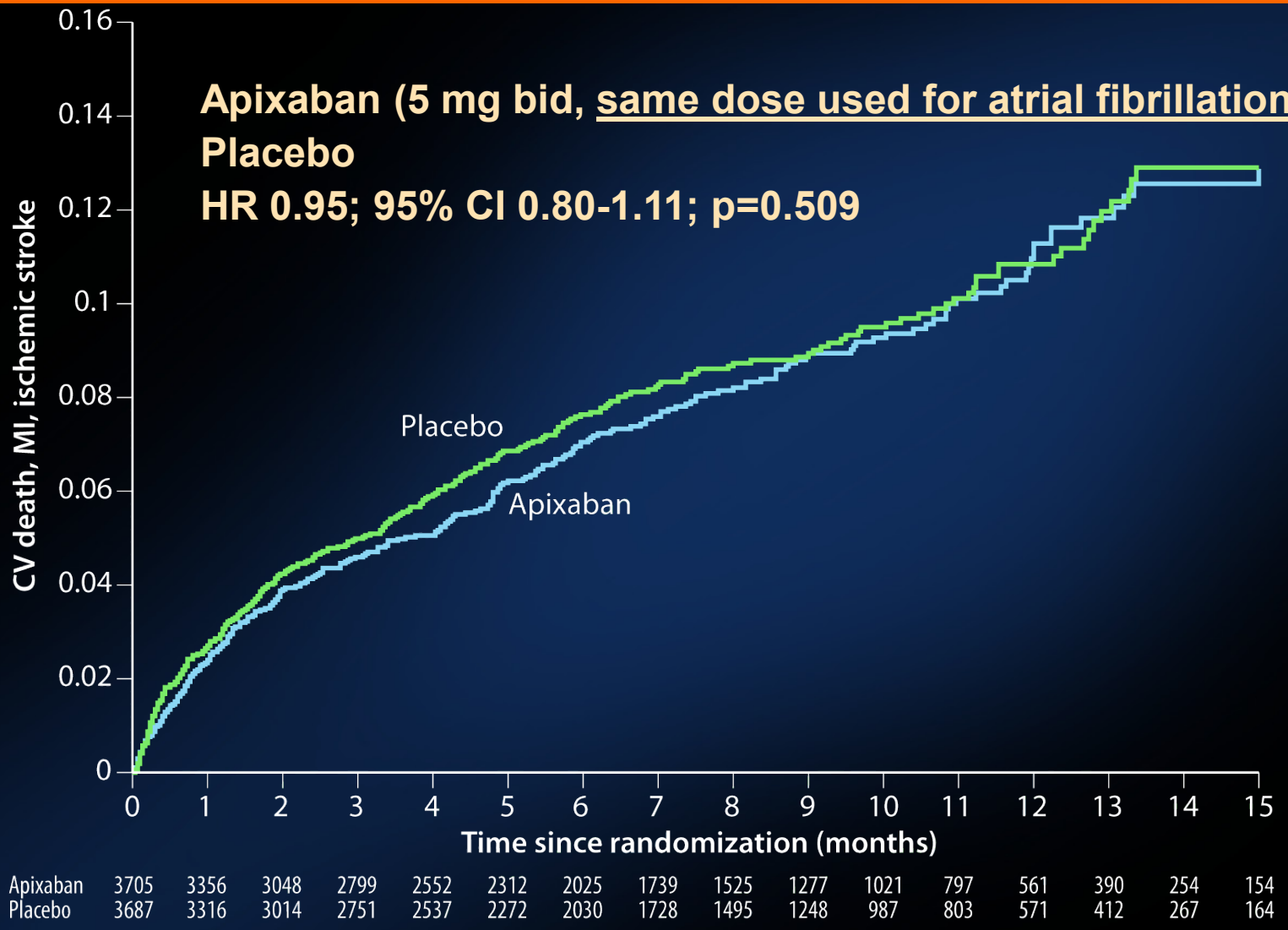




Alexander JH. Circulation 2009;119:2877–85.

APPRAISE 2: Primary Outcome

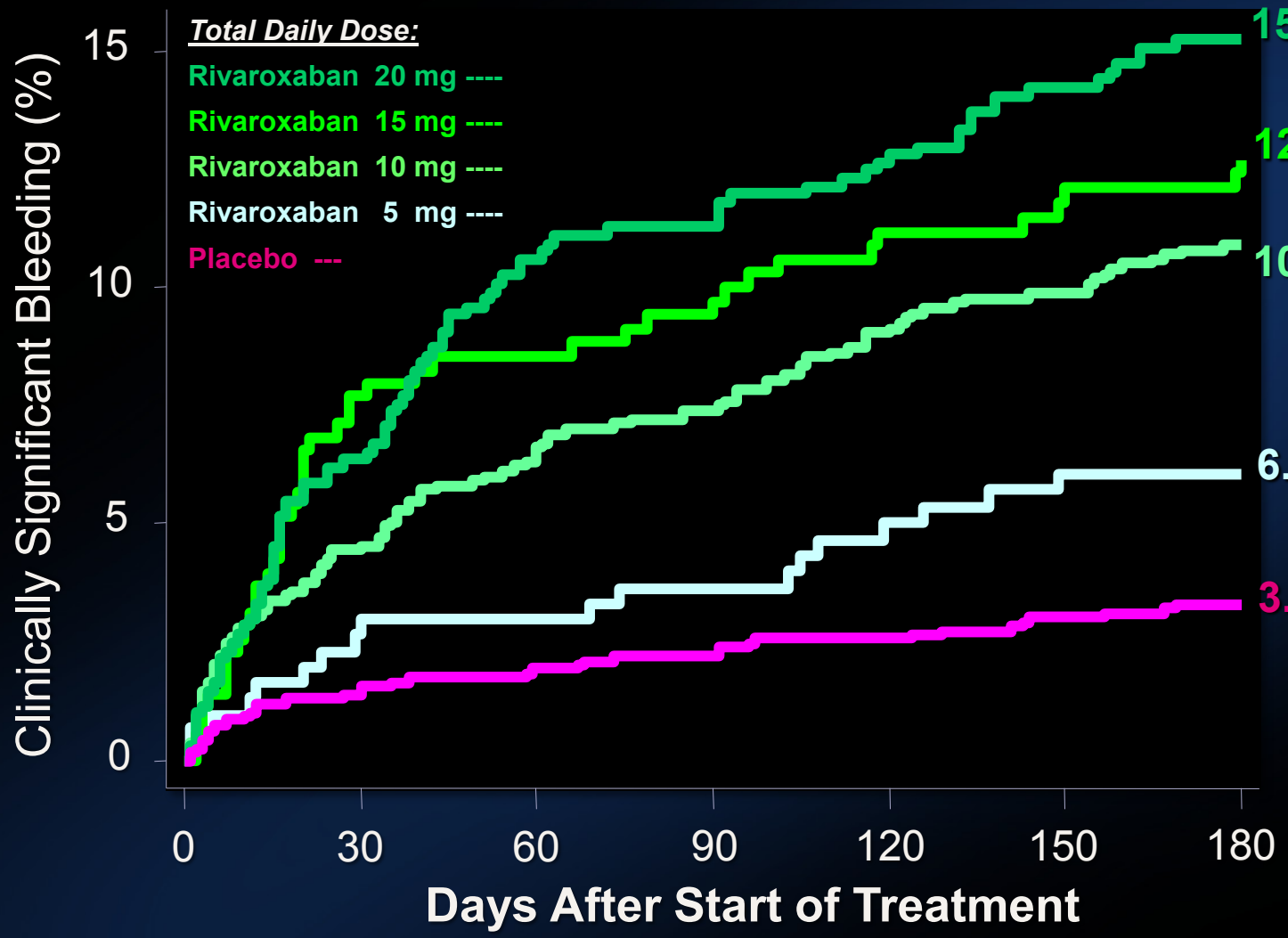
CV Death, MI, Ischemic Stroke



N Engl J Med 2011; 365:699-708

Rivaroxaban (Factor Xa Inhib) post ACS Ph2 Trial (n=3491); 1° Safety Endpoint

(= TIMI Major, TIMI Minor, Bleed Req. Med. Attn.)



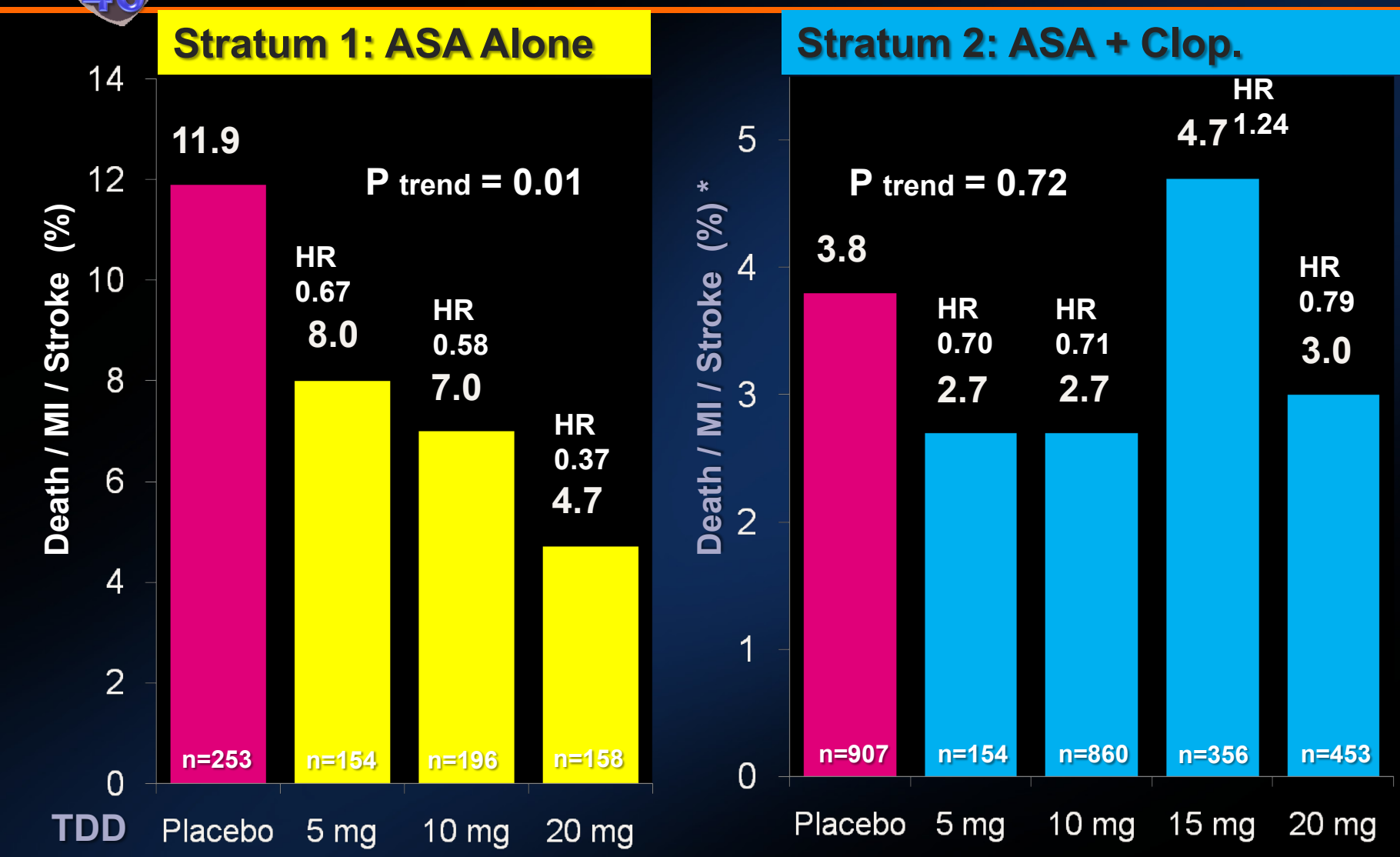
		HR
Rivaroxaban 20 mg	15.3%	5.1 (3.4-7.4)
Rivaroxaban 15 mg	12.7%	3.6 (2.3-5.6)
Rivaroxaban 10 mg	10.9%	3.4 (2.3-4.9)
Rivaroxaban 5 mg	6.1%	2.2 (1.25-3.91)
Placebo	3.3%	

*p<0.01 for placebo Vs Riva 5mg. p<0.001 for Riva 10,15,20mg vs placebo

Mega JL et al. *Lancet* 2009;374:29-38.

SECONDARY EFFICACY ENDPOINT:

Incidence of Death / MI / Stroke



Mega JL et al. *Lancet* 2009;374:29-38.

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

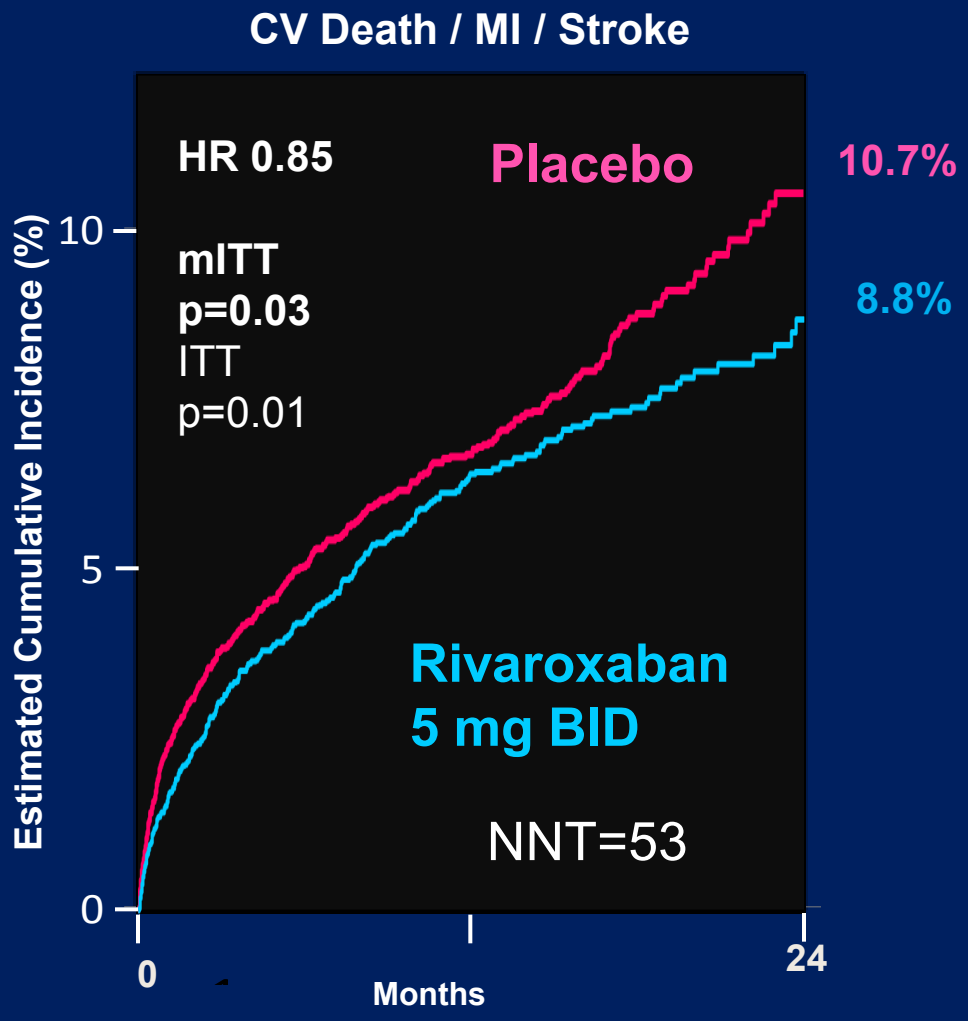
PRIMARY ENDPOINTS:
EFFICACY: CV Death, MI, Stroke (Ischemic, Hemorrhagic, or Uncertain Origin)
SAFETY: TIMI major bleeding not associated with CABG

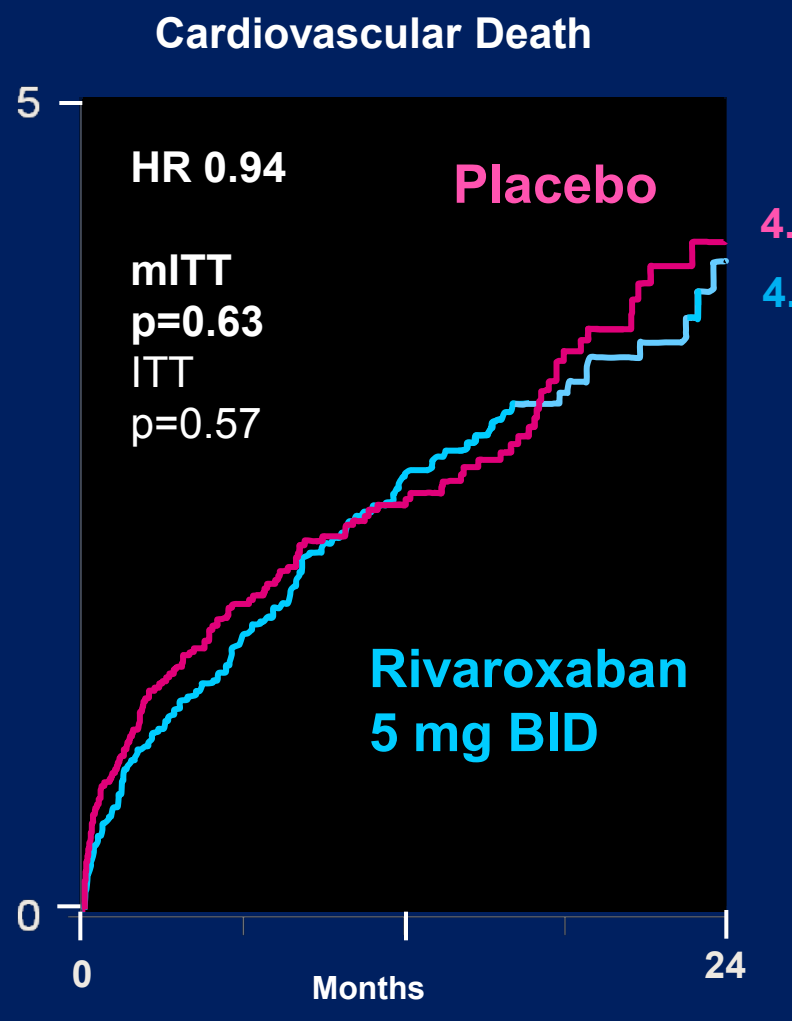
Event driven trial with 1,002 primary efficacy events

Mega JL et al. *NEJM* 2012;366:9-19

ATLAS ACS 2 TIMI 51

EFFICACY ENDPOINTS: Low Dose 5.0 mg BID



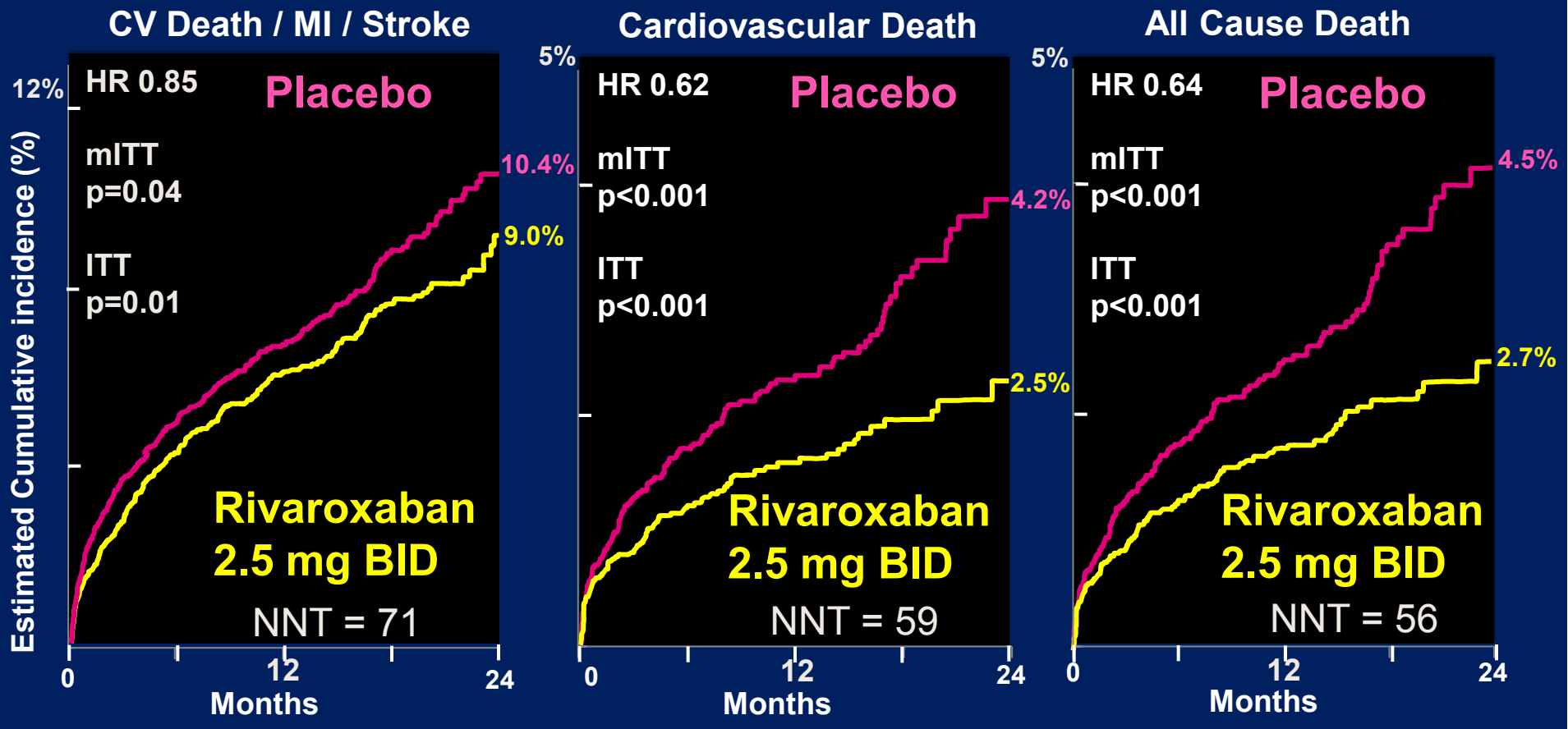


Mega JL et al. *NEJM* 2012;366:9-19

ATLAS ACS 2 TIMI 51

EFFICACY ENDPOINTS: Very Low Dose 2.5 mg BID

Patients Treated with ASA + Thienopyridine

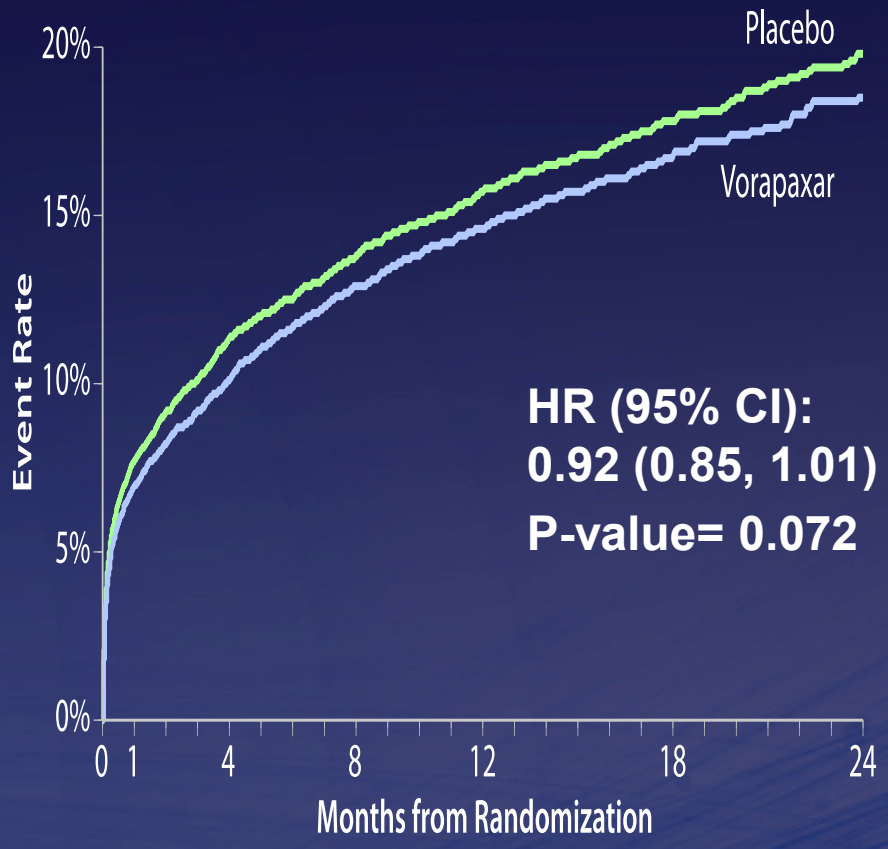


Mega JL et al. *NEJM* 2012;366:9-19

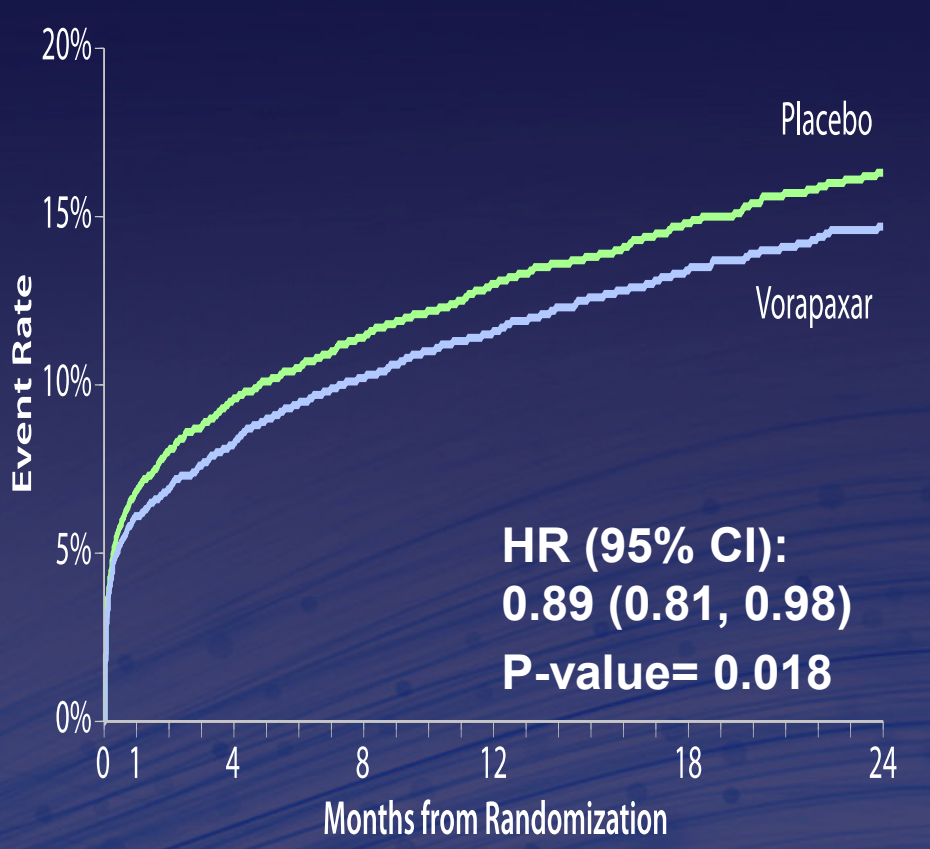
Vorapaxar (PAR-1 inhibitor) in ACS

TRA·CER

Primary Endpoint:
CV Death, MI, Stroke, Hosp for Ischemia, Urgent Revasc



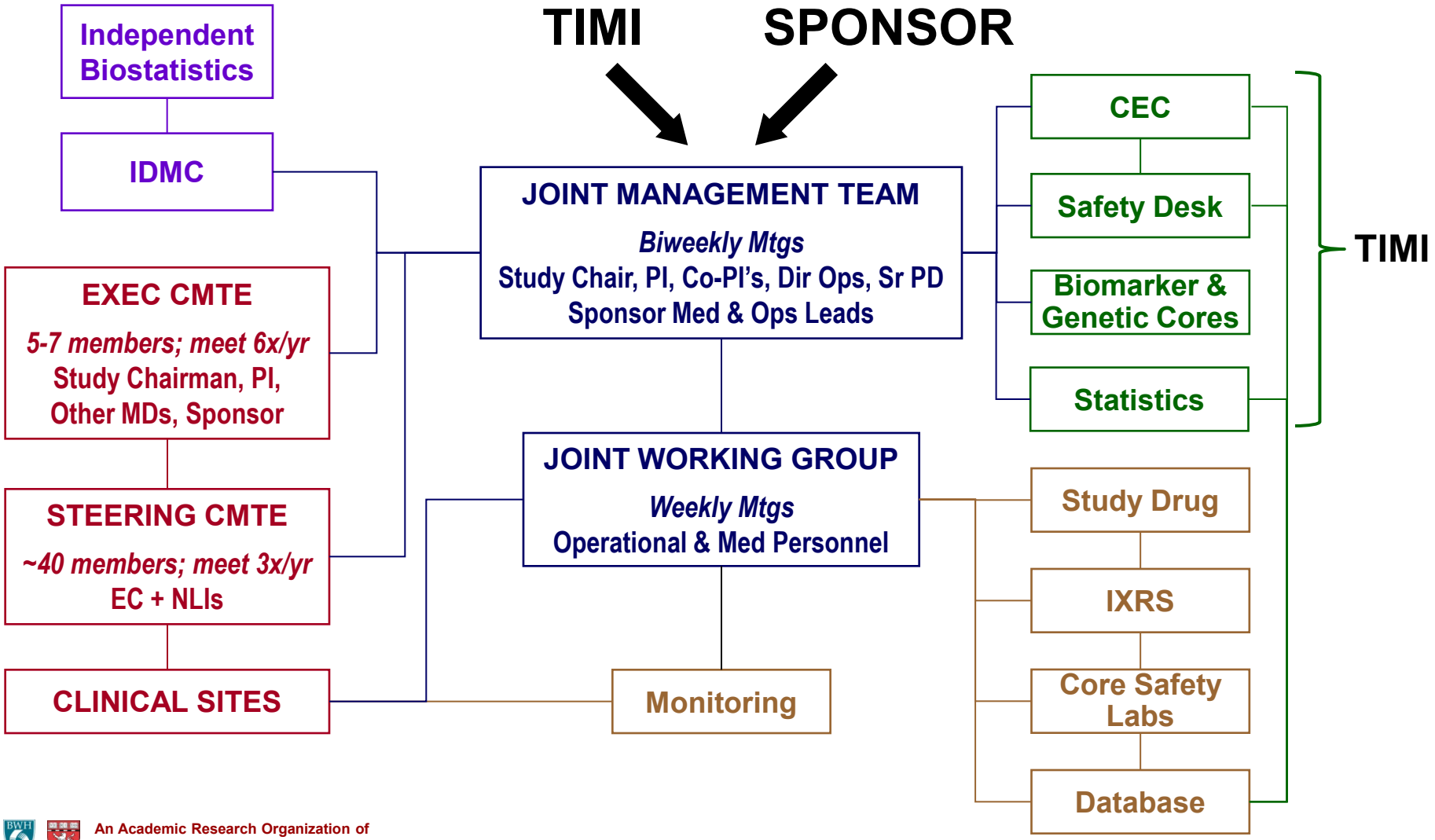
Secondary Endpoint:
CV Death, MI, Stroke



Duke Clinical Research Institute

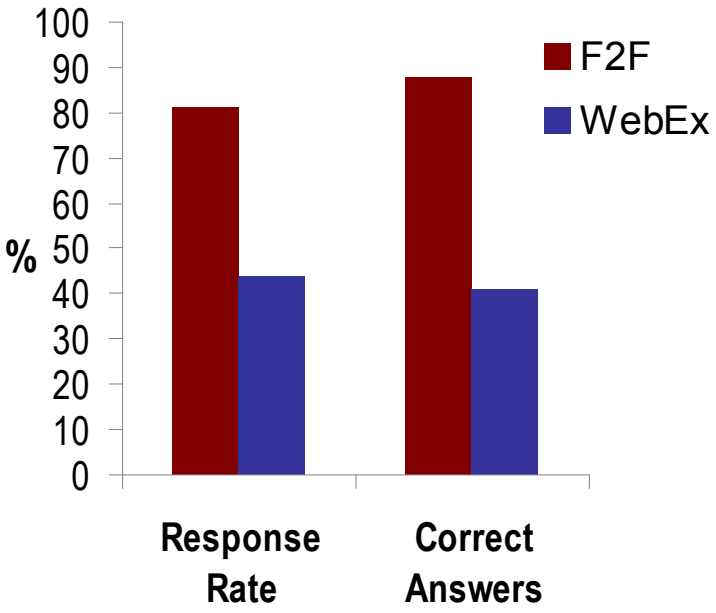
Tricoci P et al. *New Engl J Med* 2012;366:20-33

Trial Organization

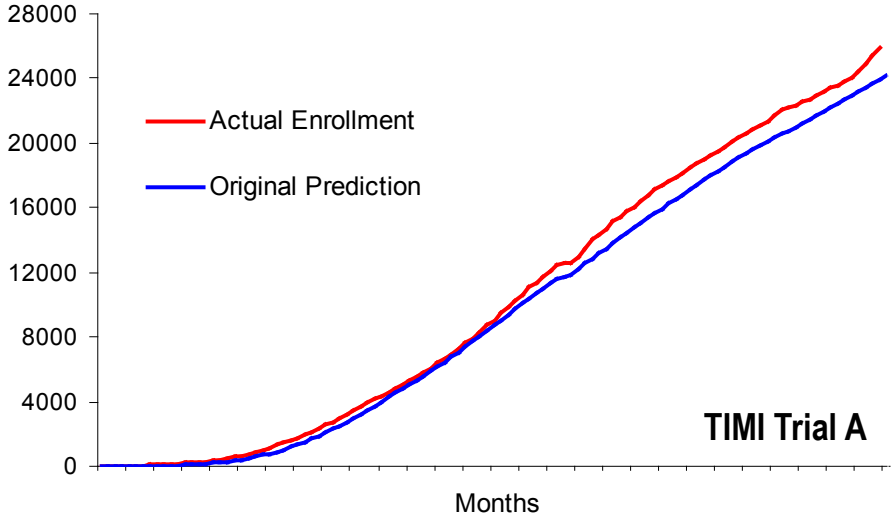


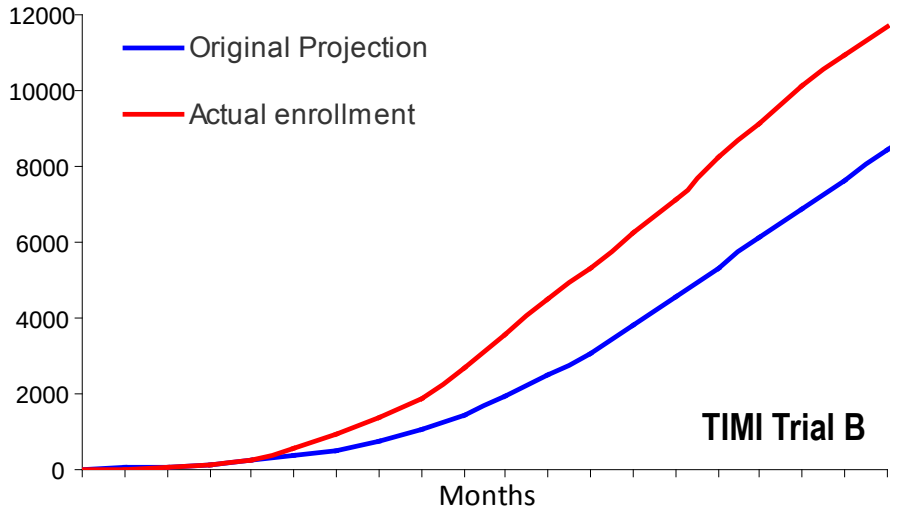
Training & Communication

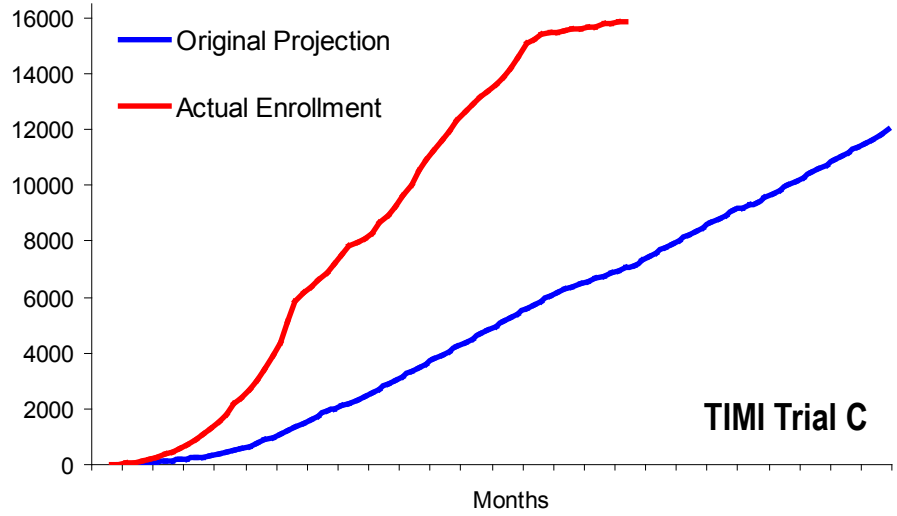
- Training
  - Face-to-face mtgs led by TIMI
  - Interactive regional mtgs w/ NLIs (and translation)
  - Separate sessions tailored to person's role
  - Audience Response Questions
- Communication
  - Numbered memos; ensure global consistency
  - Written by Global PI & Proj Director
- Trial "Hotline"
  - Responds to all medical and operational inquiries
  - Staffed 24/7 by TIMI
  - Learn from ?s what is unclear/problematic → site retraining vs. global clarification

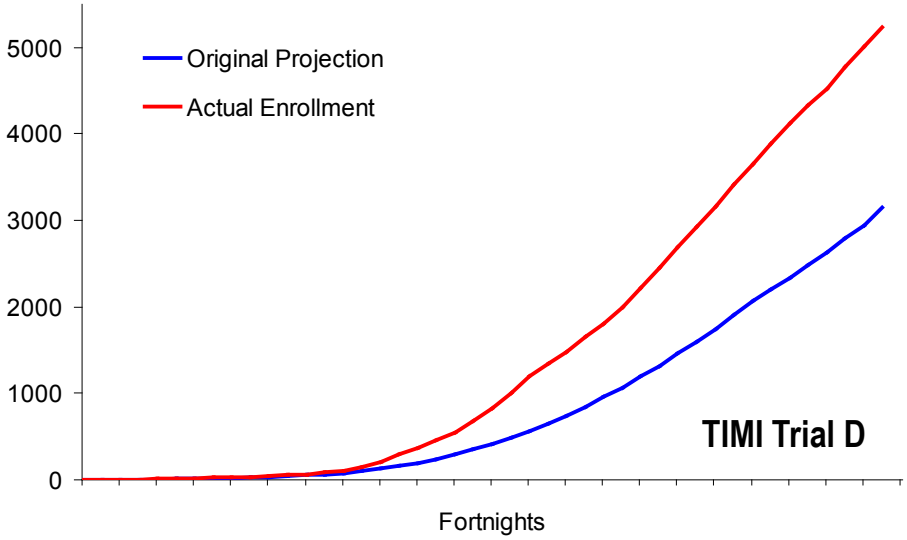


TIMI Trial Enrollment





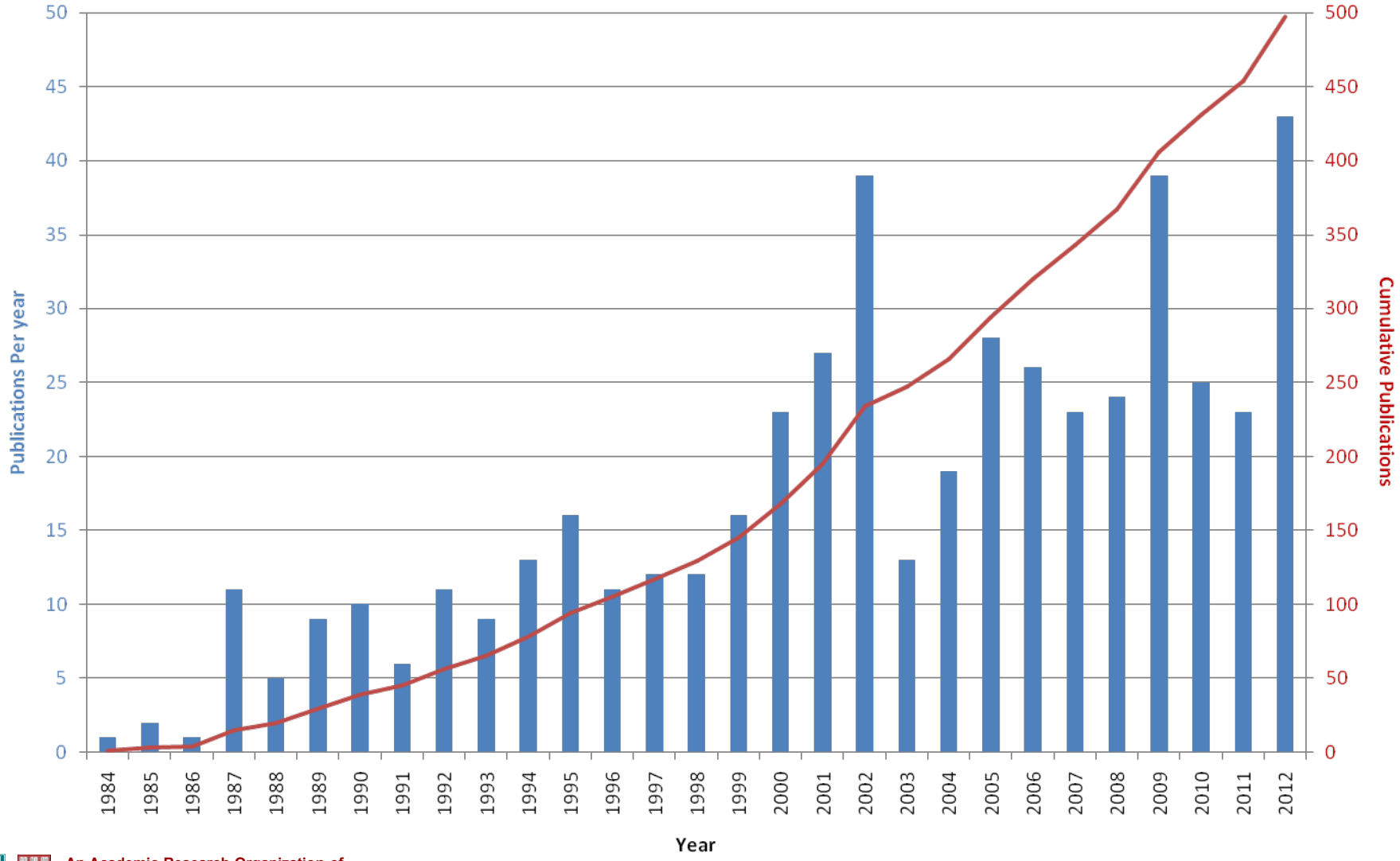




Biostatistics

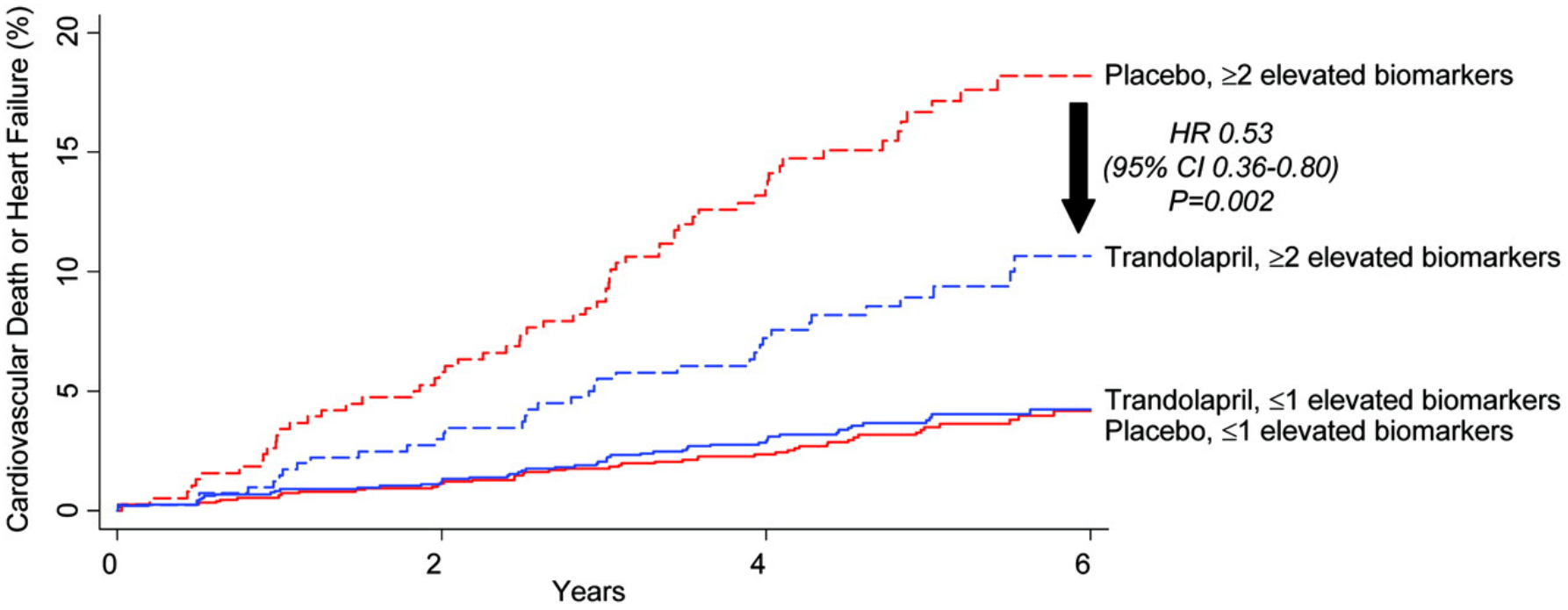
- **Pre-Trial**
  - Analysis of TIMI Trial Databases to aid in refining inclusion & exclusion criteria
  - Review SAP, verify power calcs & alpha spending
- **Pre-DB Lock**
  - Projections based on aggregate data as needed
  - Review DB fields, validate programming
- **Post-DB Lock**
  - Receive raw database
  - Perform primary analyses, validate sponsor results
  - Perform secondary analyses

TIMI Study Group Publications



Novel Biomarkers of Cardiovascular Stress to Guide Therapy

Effect of ACEI Trandolapril on Incidence of CV death or Heart Failure in 3717 Patients with Stable CAD, Stratified by Levels of Biomarkers of CV Stress



Biomarkers included MR-proANP, MR-proADM, and CT-proET1.
Levels in top quartile were considered to be elevated

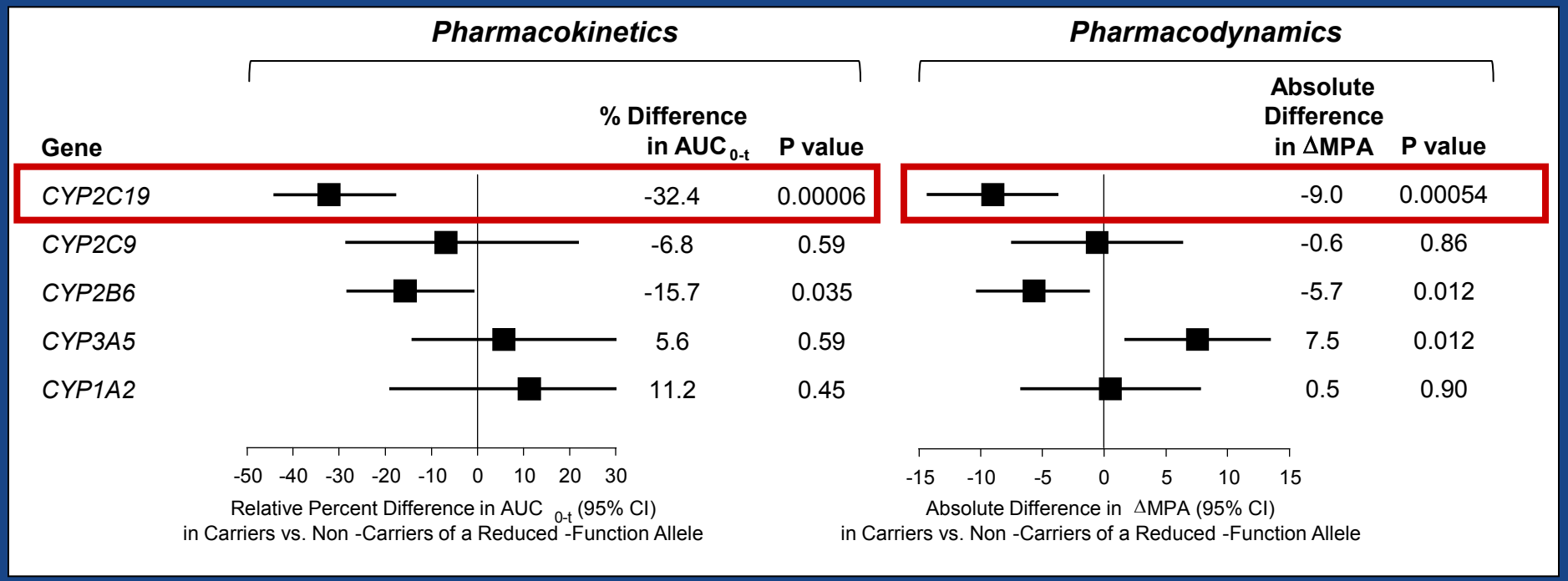
Sabatine MS et al. *Circulation* 2012;125:233-40

CYP450 Genetic Variants & Pharmacokinetics & Pharmacodynamics of Clopidogrel

162 healthy individuals

PK: active metabolite measured by LC-MS

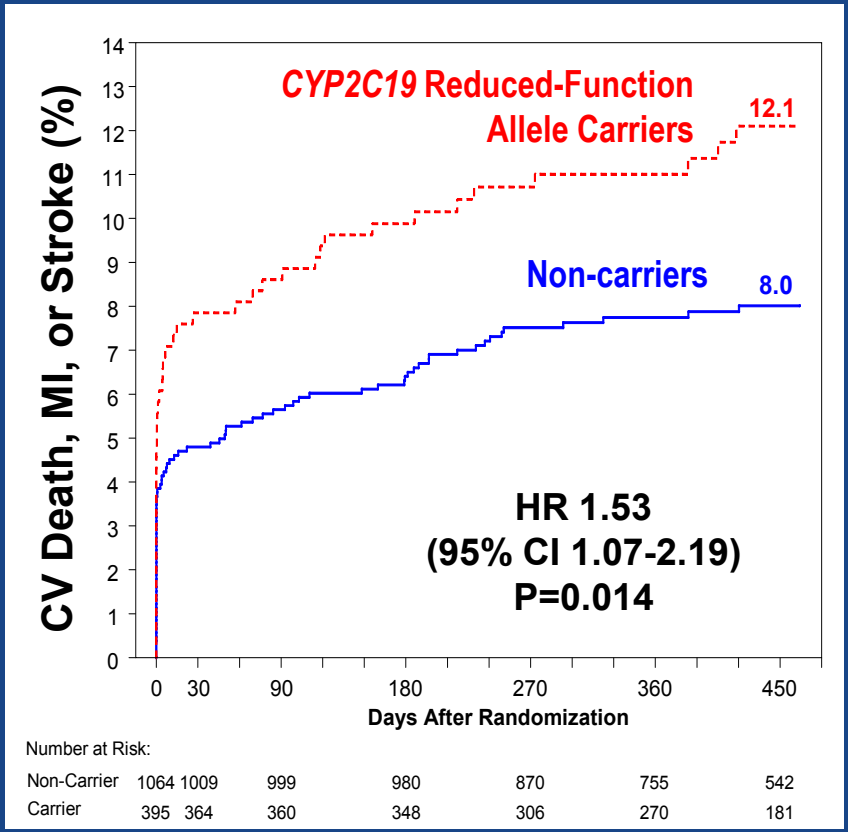
PD: LTA w/ 20 μM ADP; ΔMPA = abs ↓ max plt agg from BL (overall 36.0±20.5%)

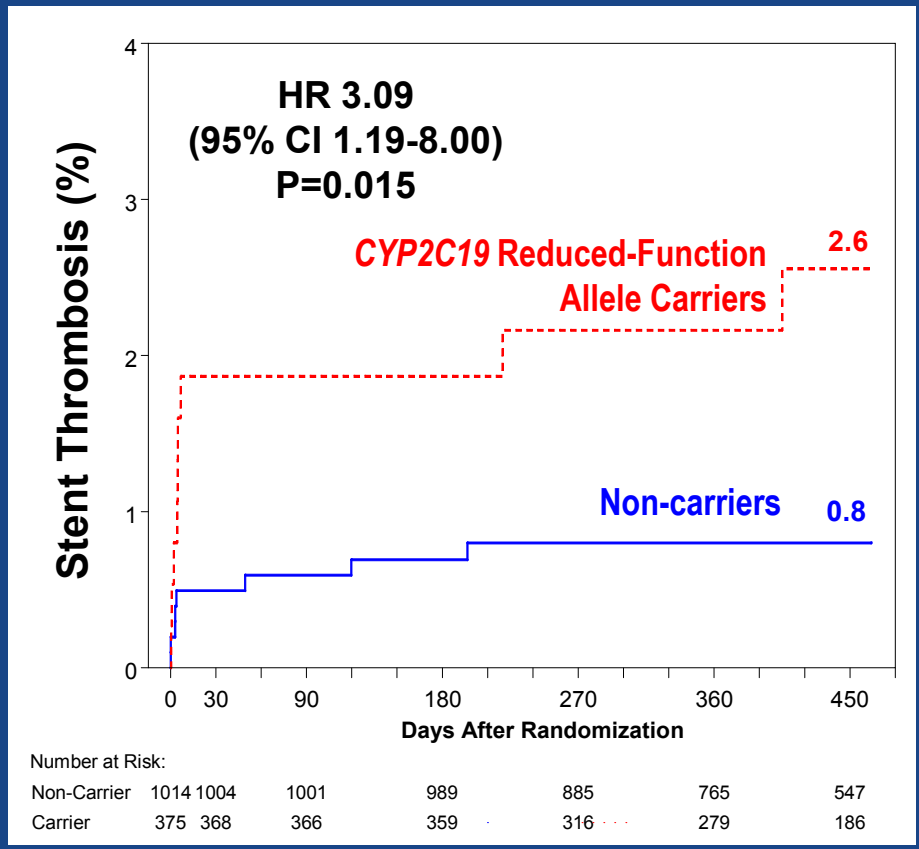


Mega JL et al. & Sabatine MS. *N Engl J Med* 2009;360:354-62.

CYP2C19 & Clinical Outcomes

1477 Patients w/ ACS and planned PCI Rx'd w/ clopidogrel





Carriers ~30% of the population

Mega JL et al. & Sabatine MS. *N Engl J Med* 2009;360:354-62.

AY 2012-2013

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Chairman

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Founding Chairman

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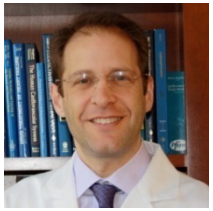

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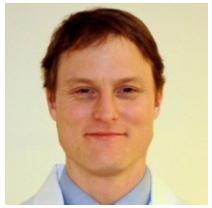

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