



TRITON TIMI-38

**TRial to Assess Improvement in
Therapeutic Outcomes by Optimizing
Platelet Inhibition N with Prasugrel**

**TRITON-TIMI 38
AHA 2007
Orlando, Florida**

Disclosure Statement:

The TRITON-TIMI 38 trial was supported by a research grant to the Brigham and Women's Hospital from Daiichi Sankyo Co. Ltd and Eli Lilly & Co.

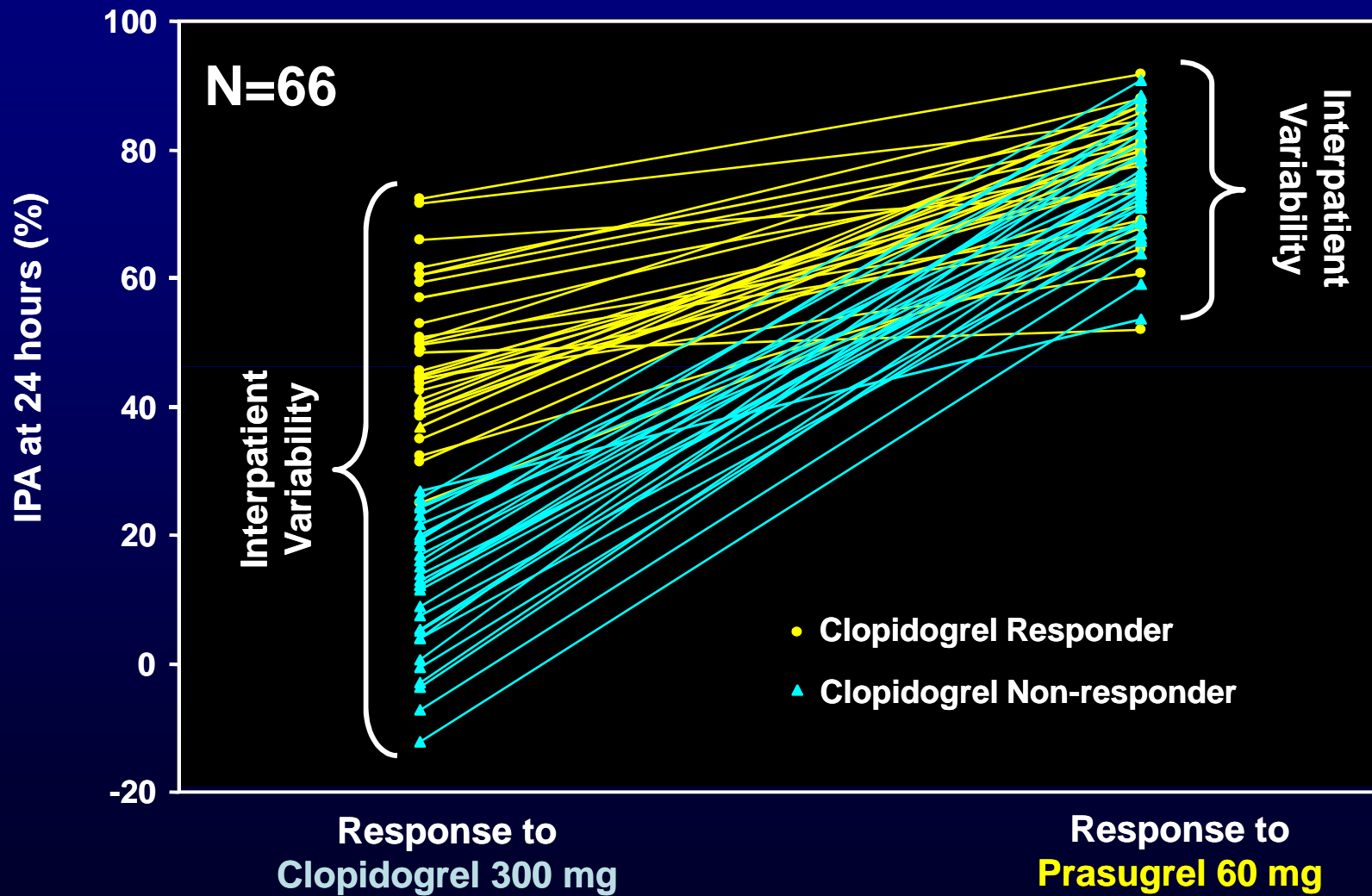


Antiplatelet Therapy for PCI

- **Dual antiplatelet Rx (ASA + thienopyridine) is standard of care:**
 - Ticlopidine → Clopidogrel**
- **Clinical need to improve on benefits observed with clopidogrel**
- **Prasugrel**
 - Novel thienopyridine**
 - Efficient generation of active metabolite**
 - High levels of IPA achieved rapidly**
 - High IPA in clopidogrel “hyporesponders”**
 - Encouraging Phase 2 data**



Healthy Volunteer Crossover Study



1. To test the hypothesis that higher and less variable IPA prevents clinical ischemic events.
2. To evaluate the safety of a regimen that produces higher IPA.

These goals were achieved by evaluating the efficacy and safety of **prasugrel** compared to **clopidogrel** in mod/high risk patients with ACS undergoing PCI on a background of ASA.

Trial Organization

Trial Leadership: TIMI Study Group

Eugene Braunwald, Chairman, Elliott M. Antman, PI,
Stephen D. Wiviott, Gilles Montalescot, Carolyn H. McCabe,
Sabina A. Murphy, Susan McHale

Sponsors: Daiichi Sankyo and Eli Lilly

J. Anthony Ware, Jeffrey Riesmeyer, William Macias,
James Croaning, Govinda Weerakkody, Francis Plat,
Tomas Bocanegra

Data Center and Site Management: Quintiles Inc

Data Safety Monitoring Board

David Williams (Chair) , Christophe Bode, Spencer King,
Ulrich Sigwart, David DeMets

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

1° endpoint: CV death, MI, Stroke
2° 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

• Inclusion Criteria

Planned PCI for :

Known { Mod-High Risk UA/NSTEMI (TRS \geq 3)
Anatomy { STEMI: \leq 14 days (ischemia or Rx strategy)
STEMI: Primary PCI

• Major Exclusion Criteria:

- Severe comorbidity
- Increased bleeding risk
- Prior hemorrhagic stroke or any stroke \leq 3 mos
- Any thienopyridine within 5 days
- No exclusion for advanced age or renal function



Enrollment: Nov 2004 - Jan 2007
N = 13,608 (ITT)

Argentina (195)

Australia (217)

Austria (182)

Belgium (287)

Brazil (225)

Canada (251)

Chile (114)

Czech Rep (340)

Denmark (33)

Estonia (134)

Finland (116)

France (146)

Germany (999)

Hungary (695)

Iceland (10)

Israel (1219)

Italy (782)

Latvia (21)

Lithuania (54)

Netherlands (390)

New Zealand (49)

Poland (1938)

Portugal (67)

Slovakia (140)

South Africa (404)

Spain (178)

Sweden (154)

Switzerland (136)

United Kingdom (73)

United States (4059)

30 Countries

707 Sites

LTFU = 14 (0.1%)



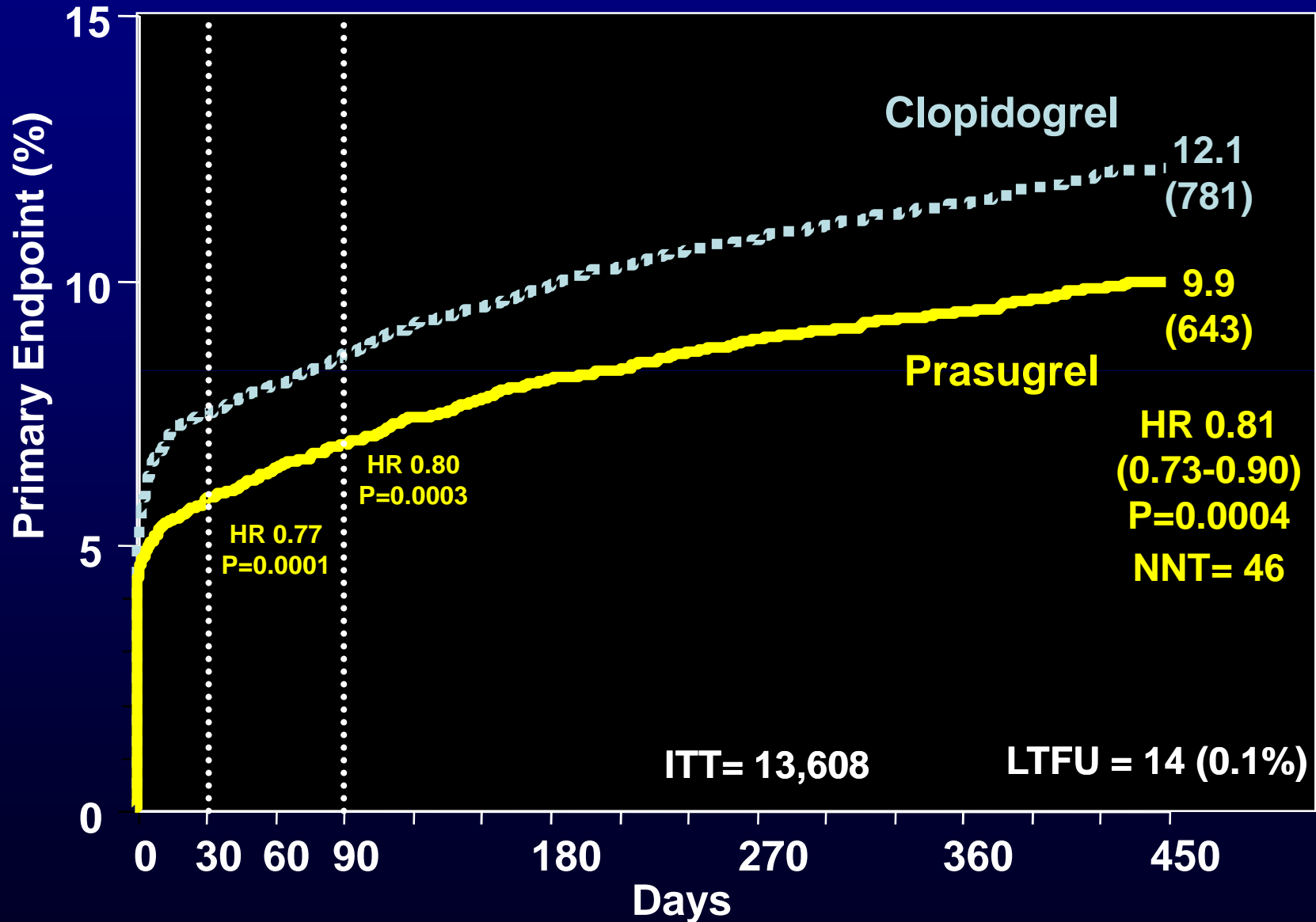
Baseline Characteristics

	Clopidogrel (N=6795) %	Prasugrel (N=6813) %
UA/NSTEMI	74	74
STEMI	26	26
Age, median (IQR)	61 (53,69) y	61 (53, 70) y
≥75 y	13	13
Wgt, median (IQR)	83 kg (72, 92)	84 kg (73, 93)
< 60 kg	5.3	4.6
Female	27	25* *P<0.05
Diabetes	23	23
Prior MI	18	18
CrCl (ml/min)		
≥60	88	89
<60	12	11

	Clopidogrel (N=6795) %	Prasugrel (N=6813) %
PCI / CABG	99 / 1	99 / 1
Any Stent	95	94
BMS	47	48
DES	47	47
Multivessel PCI	14	14
UFH / LMWH / Bival	65 / 8 / 3	66 / 9 / 3
GP IIb/IIIa	55	54
LD of Study Rx		
Pre PCI	25	26
During PCI	74	73
Post PCI	1	1

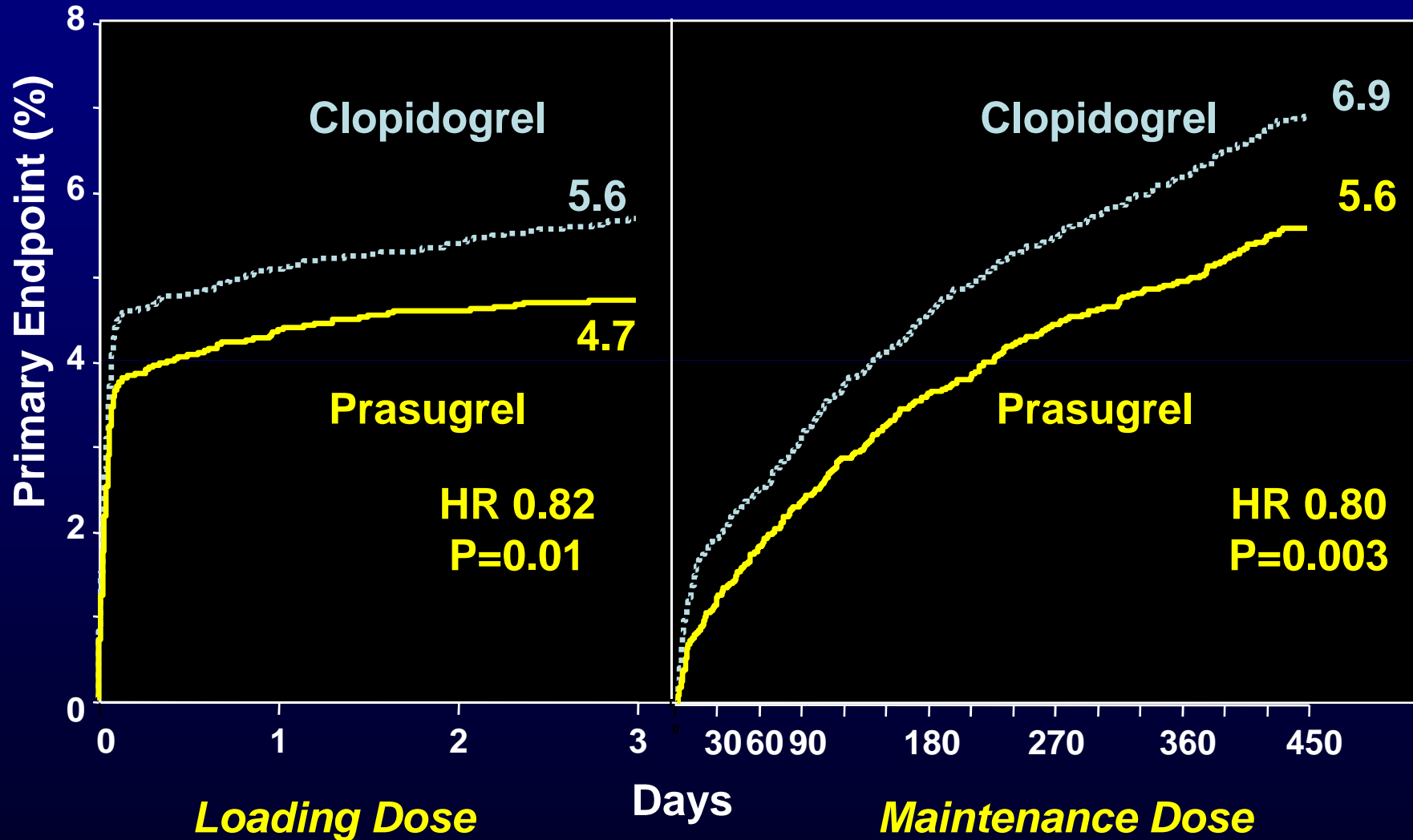


Primary Endpoint CV Death,MI,Stroke



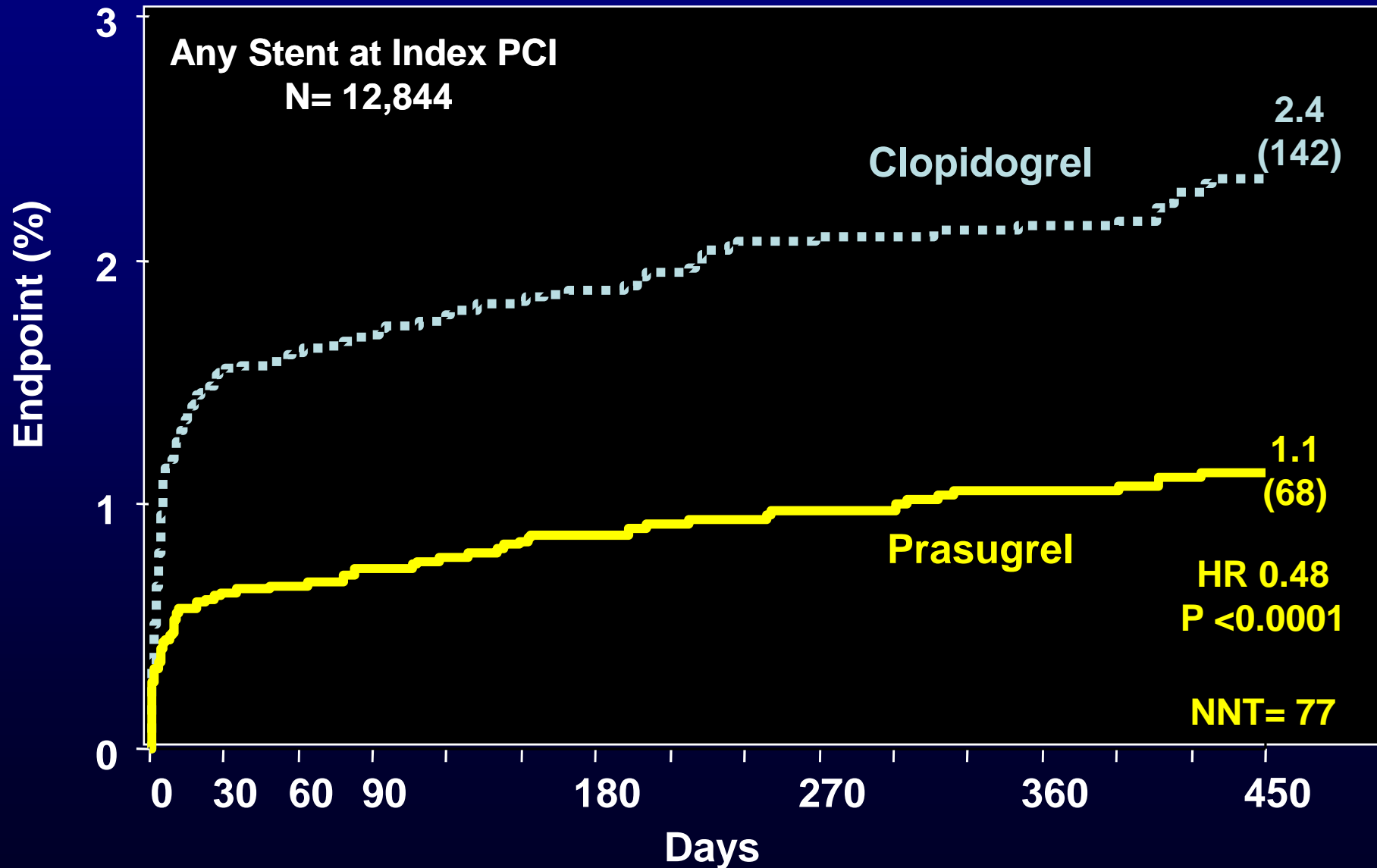


Timing of Benefit (Landmark Analysis)



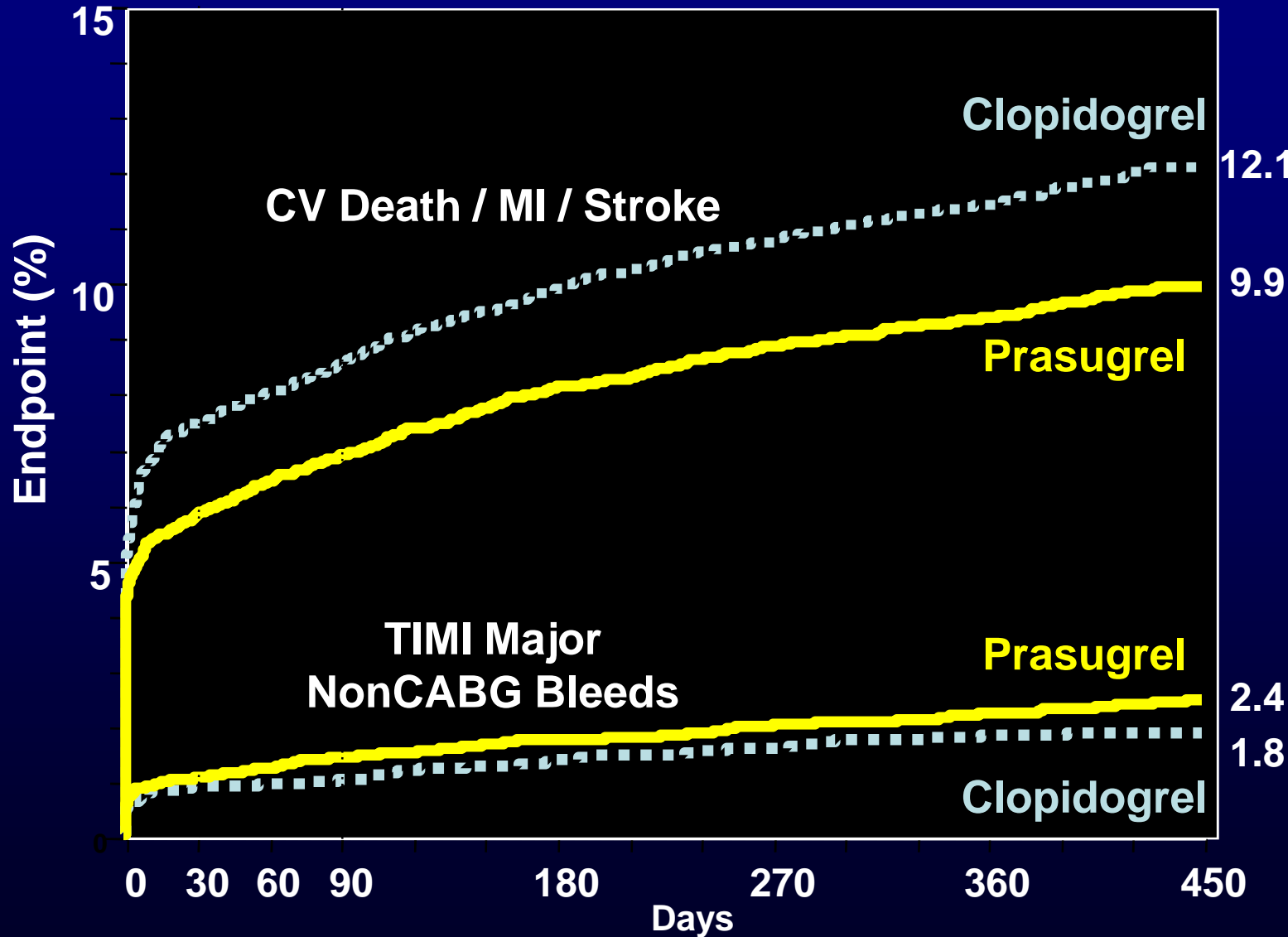


Stent Thrombosis (ARC Definite + Probable)





Balance of Efficacy and Safety



↓ 138 events

HR 0.81
(0.73-0.90)
P=0.0004
NNT = 46

↑ 35 events

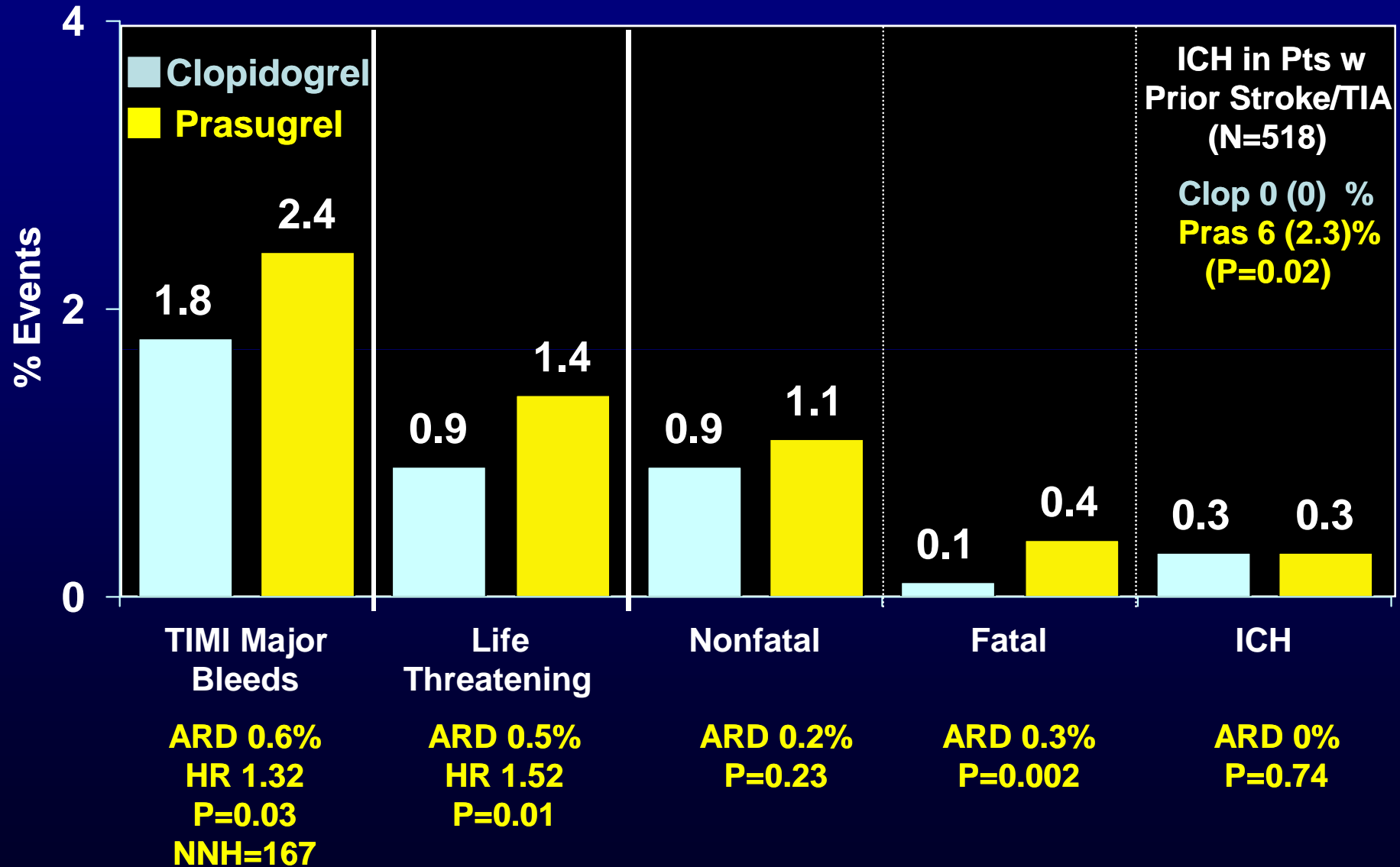
HR 1.32
(1.03-1.68)
P=0.03

NNH = 167



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Bleeding Events Safety Cohort (N=13,457)

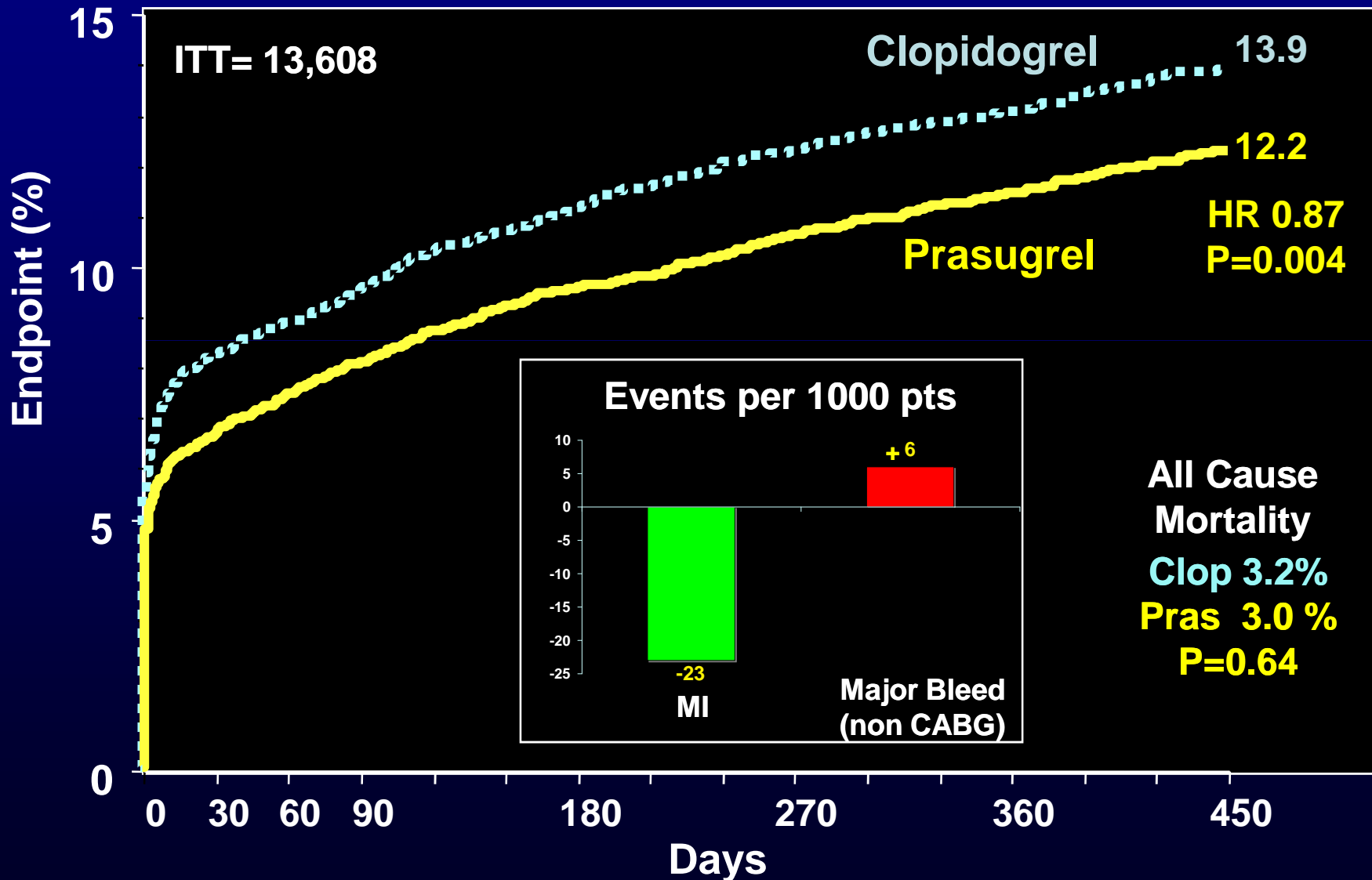




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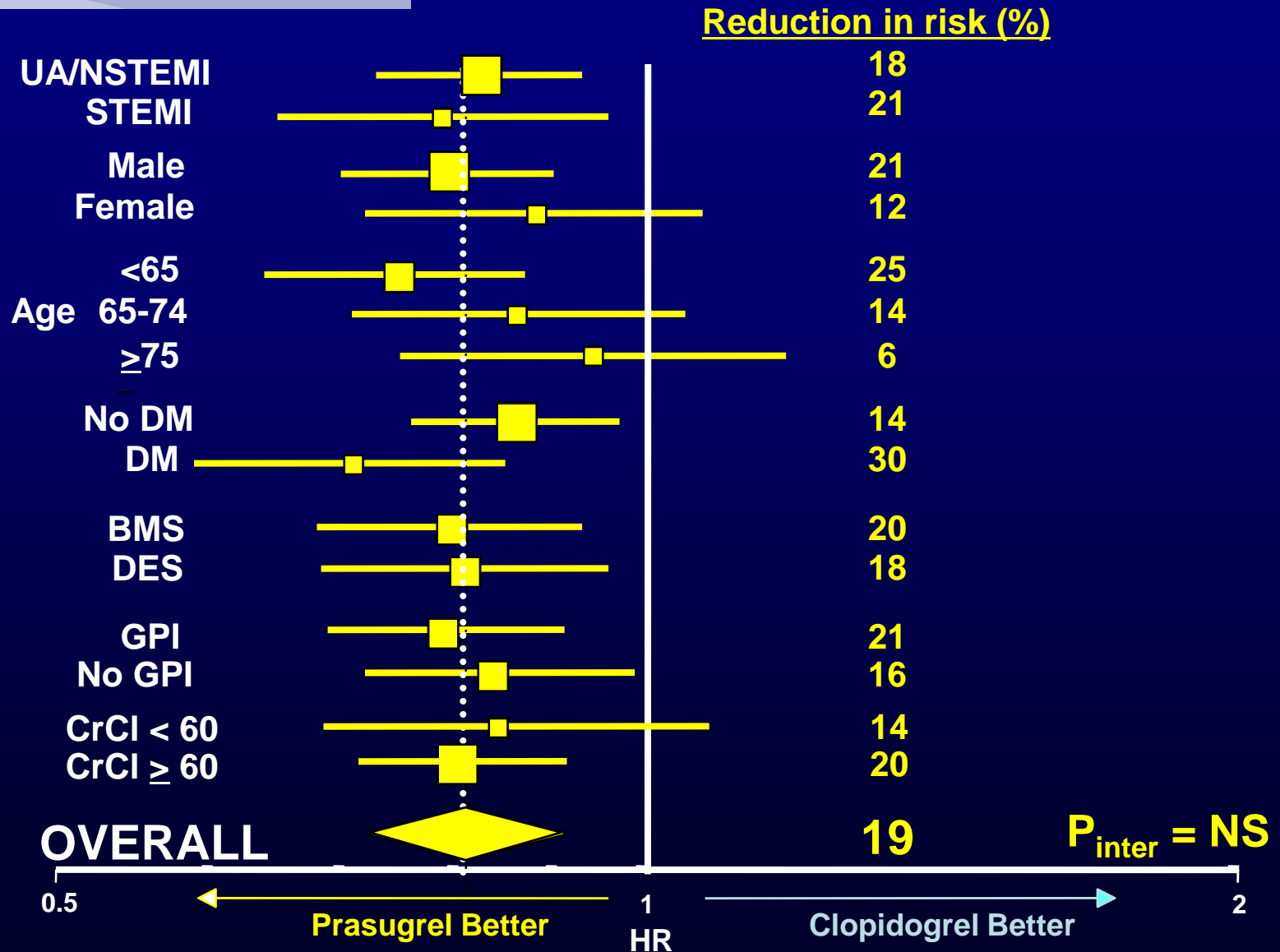
Net Clinical Benefit

Death, MI, Stroke,
Major Bleed (non CABG)





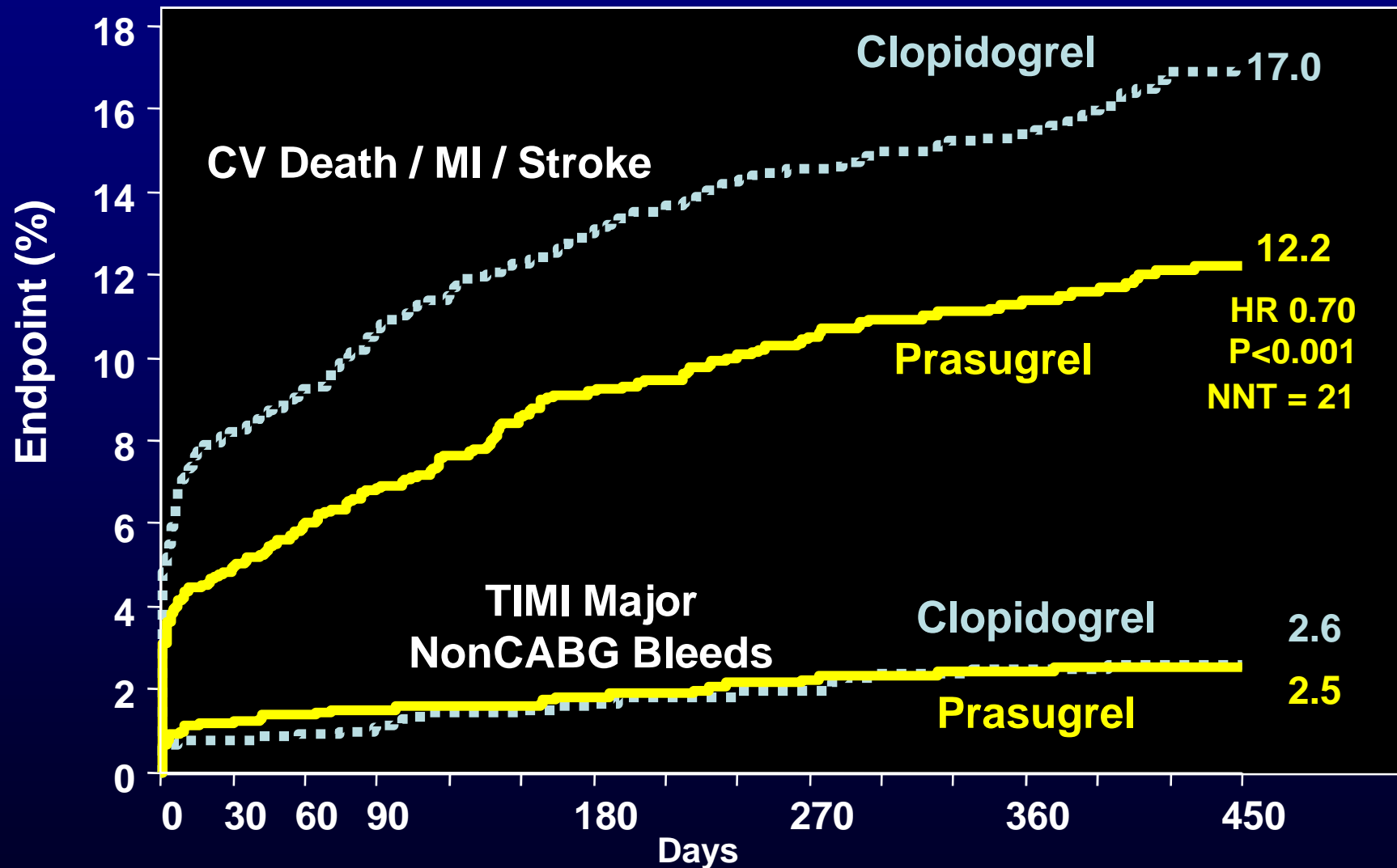
CV Death, MI, Stroke Major Subgroups





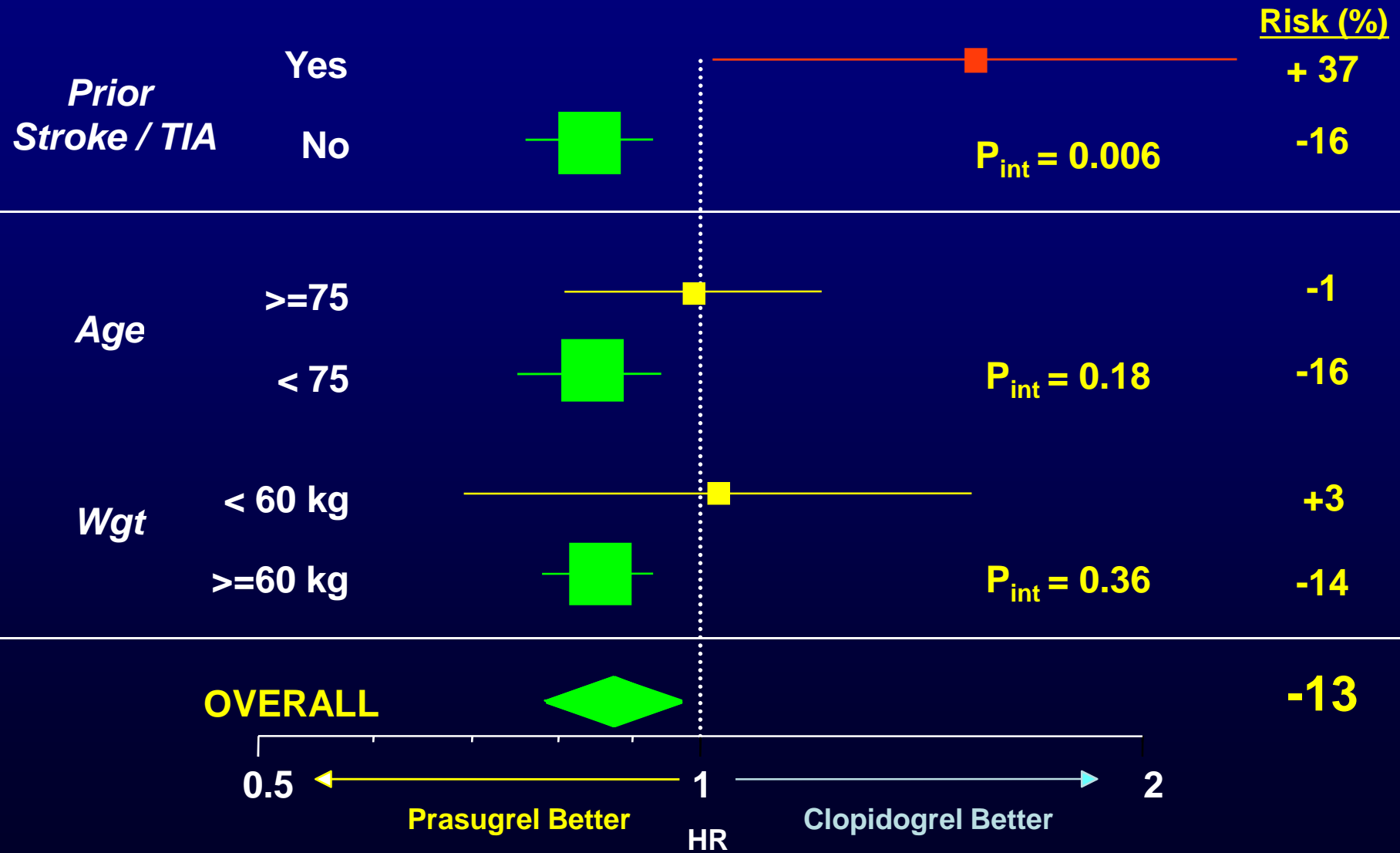
Diabetic Subgroup

N=3146



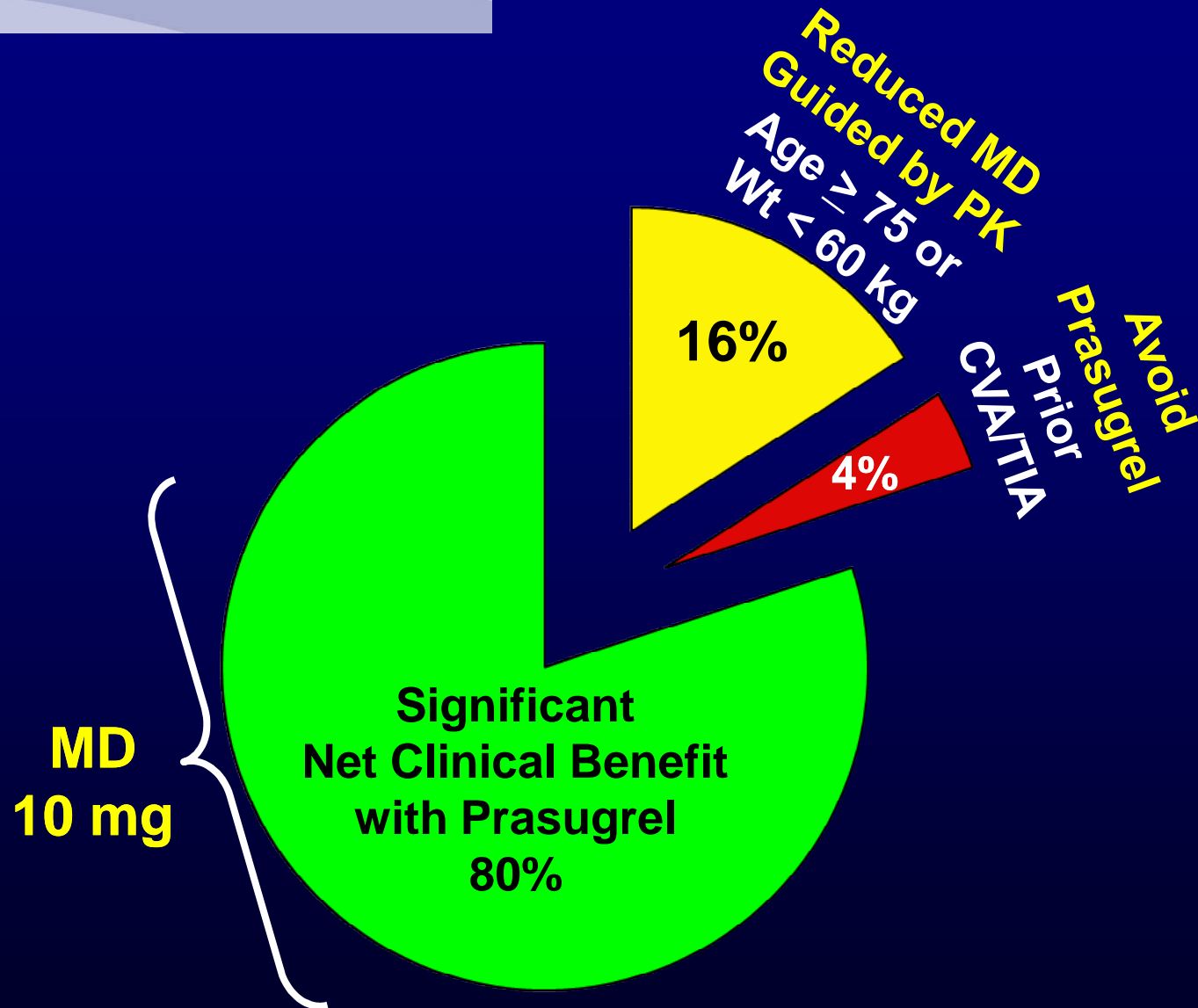


Net Clinical Benefit Bleeding Risk Subgroups Post-hoc analysis





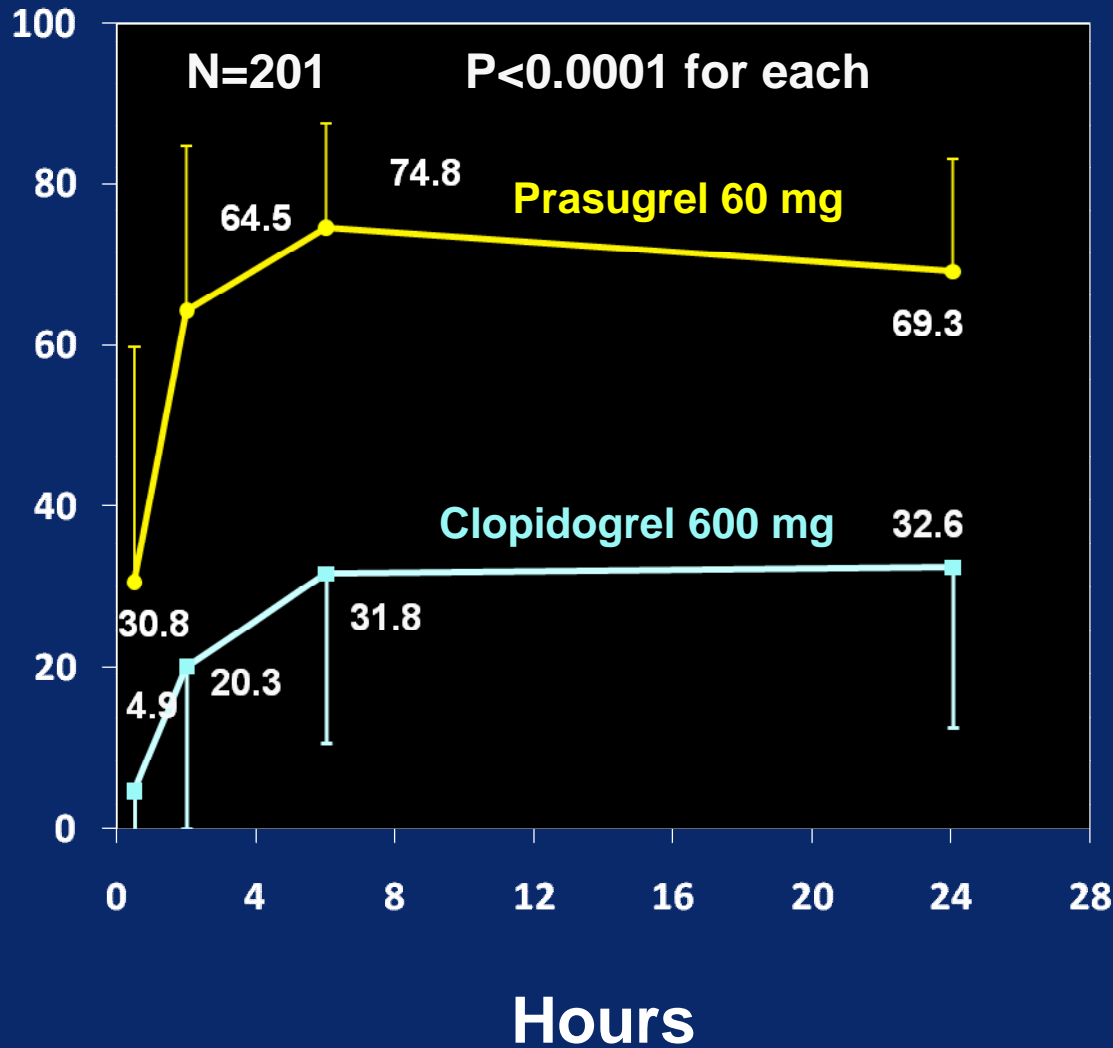
Bleeding Risk Subgroups Therapeutic Considerations



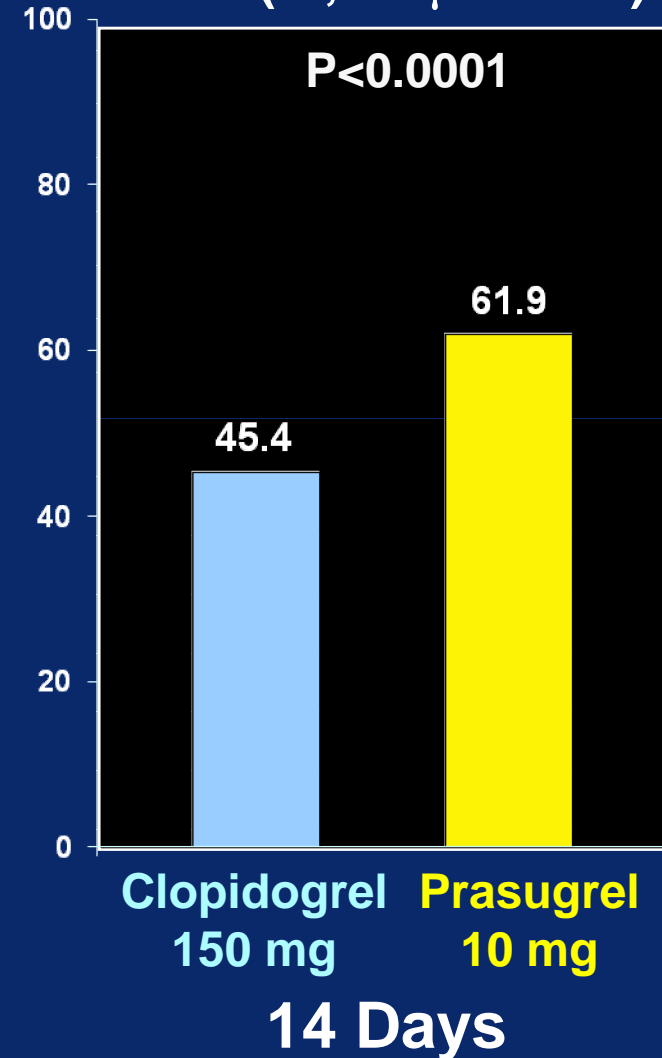


Comparison with Higher Dose Clopidogrel

IPA (%; 20 μ M ADP)



IPA (%; 20 μ M ADP)



Conclusions

Higher IPA to Support PCI

Prasugrel 60 mg LD/10mg MD vs Clopidogrel 300 mg LD/ 75 mg MD

Efficacy

1. A significant reduction in:

CV Death/MI/Stroke	19%
Stent Thrombosis	52%
uTVR	34%
MI	24%

2. An early and sustained benefit

3. Across ACS spectrum

Safety

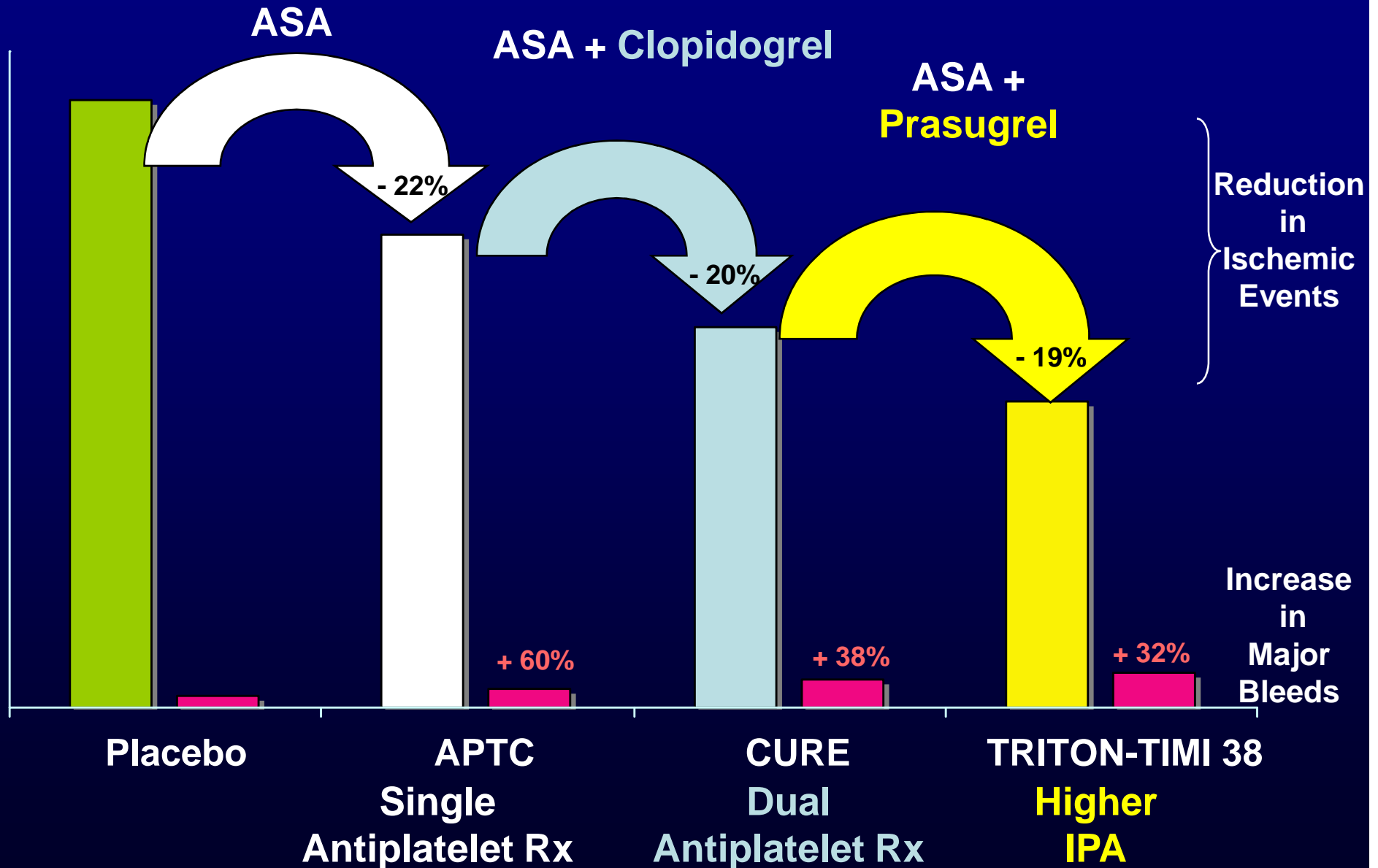
Significant
increase in
serious bleeding
(32% increase)

**Avoid in pts with
prior CVA/TIA**

Net clinical benefit significantly favored Prasugrel

**Optimization of Prasugrel maintenance dosing in a minority of patients
may help improve the benefit : risk balance**

Antiplatelet Therapy in ACS



Publication of Primary Results

The NEW ENGLAND JOURNAL *of* MEDICINE

NEJM 357: 2001-2015, 2007

www.NEJM.org

Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

Stephen D. Wiviott, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D., Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D., Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesmeyer, M.D., Govinda Weerakkody, Ph.D., C. Michael Gibson, M.D., and Elliott M. Antman, M.D., for the TRITON-TIMI 38 Investigators*

**Slides and Full Listing of Trial Participants at
www.TIMI.org**

