TURIN, 20TH—21ST NOVEMBER 2008

GREAT INNOVATIONS IN CARDIOLOGY

4TH JOINT MEETING WITH MAYO CLINIC

4TH TURIN CARDIOVASCULAR NURSING CONVENTION

SESSION III: **HOT SESSION**
NEW THERAPIES AND NEW TREATMENTS

S. D. Kristensen (Aarhus—Denmark)

Part II ACS new therapies and new treatments.
Question and answer

ACS and new anti-thrombotic therapies - questions and answers.

Steen D Kristensen, MD, DMSc, FESC
Department of Cardiology
Aarhus University Hospital
Skejby, Denmark

201108, Turin, Italy

Potential conflicts of interest

Speaker's name: Steen D. Kristensen

I have received lecture fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GSK, Nycomed, Pfizer, Sanofi-Aventis.

ACS and new anti-thrombotic therapies

- Anticoagulation in NSTEMI ACS: Should we use unfractionated heparin, low molecular weight heparin, fondaparinux or bivalirudin?
- Do we need stronger oral antiplatelet drugs in ACS?
- Primary PCI – any news in anti-thrombotic therapy?

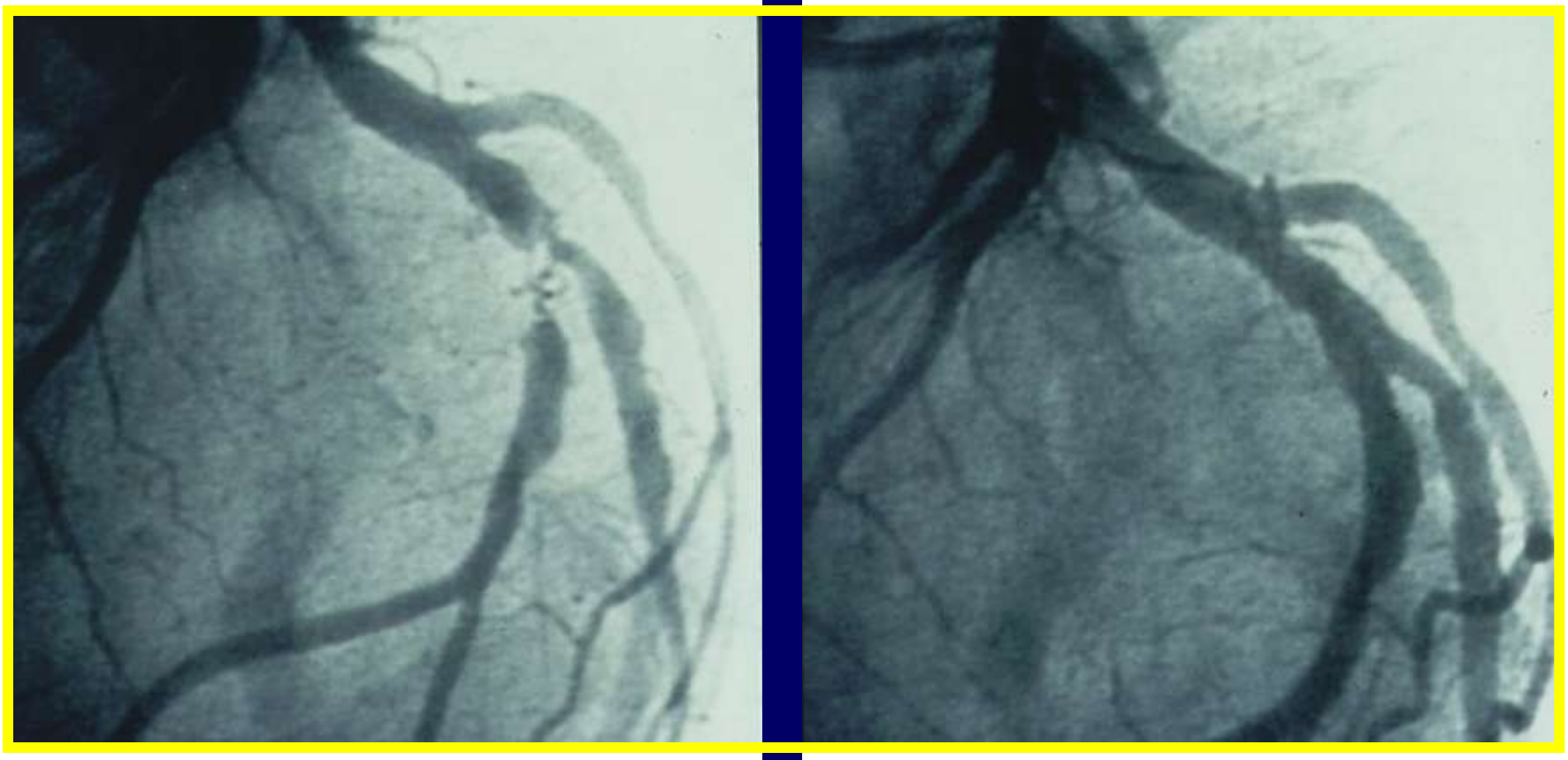
NSTEMI-ACS

Aspirin +

UFH/Enoxaparin/Fondaparinux/Bivalirudin??

+ Clopidogrel + GP2b/3a

+ early CAG(<72 hrs)



Antithrombins: Mechanisms of Action

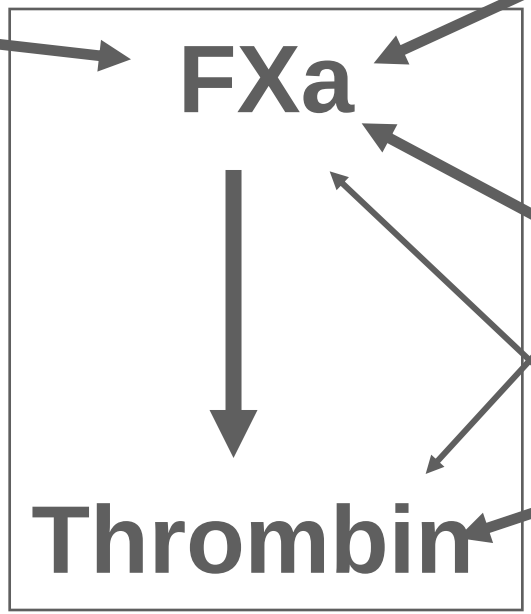
direct inhibition

Rivaroxaban
Apixaban
Otamixaban (i.v.)
LY517717,YM150
DU-176b, DX-9045
AZD-4927

Hirudin

Bivalirudin
Argatroban

Ximelagatran
Dabigatran
SCH 539348 (TRA)



indirect inhibition

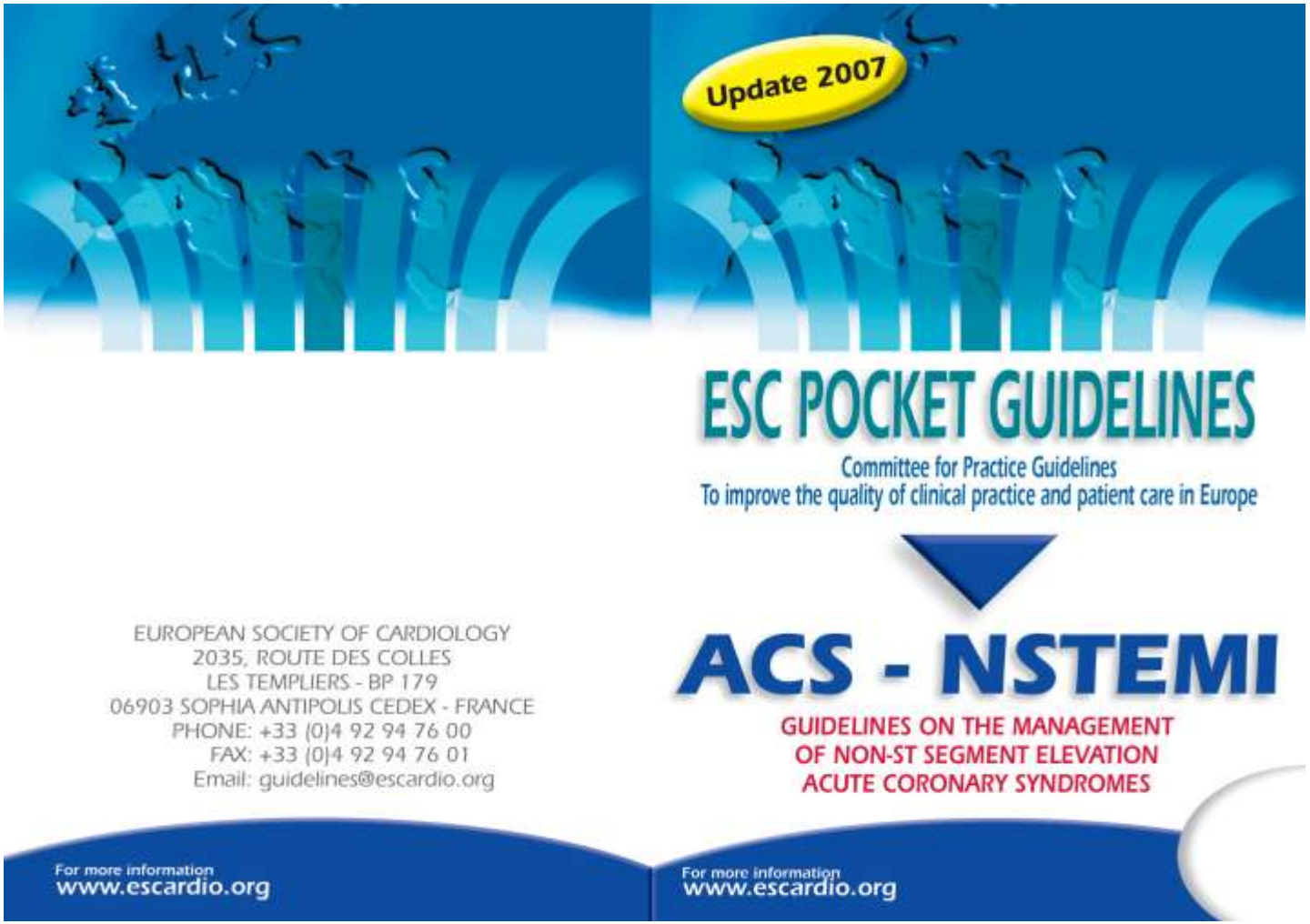
AT-**Pentasaccharid**
Fondaparinux
Idraparinux

AT-LMWH
Enoxaparin

AT-UFH

AT = Antithrombin
UFH = Unfraktioniertes Heparin
NMH = Niedermolekulares Heparin

NSTEMI – recommendations for anti-coagulation ?

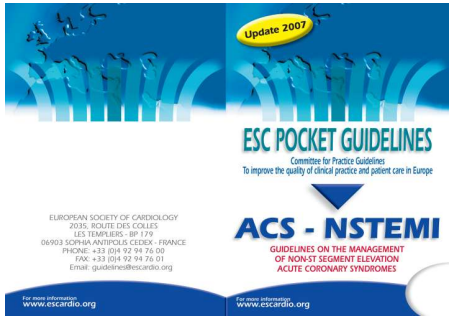


A New Concept is Born

1. Bleeding carries a high risk of death, MI and stroke
2. Rate of major bleeding is as high as the rate of death at the acute phase of NSTE-ACS
3. Prevention of bleeding is equally as important as prevention of ischemic events and results in a significant risk reduction for death, MI and stroke
4. Risk stratification for bleeding should be part of the decision making process

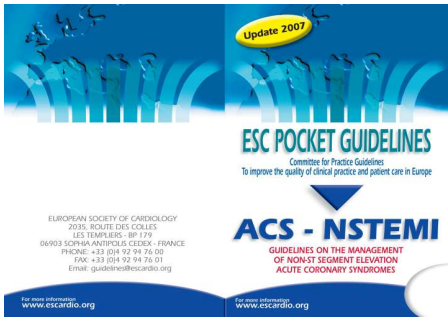
Recommendations for anticoagulation:

- Anticoagulation is recommended for all patients in addition to antiplatelet therapy (I-A)
- Anticoagulation should be selected according to the risk of both ischaemic and bleeding events (I-B)
- Several anticoagulants are available, namely UFH, LMWH, fondaparinux, bivalirudin. The choice depends on the initial strategy (I-B)
- In an urgent invasive strategy UFH (I-C), or enoxaparin (IIa-B) or bivalirudin (I-B) should be immediately started.



Recommendations for anticoagulation:

- In an non-urgent situation, as long as decision between early invasive or conservative strategy is pending:
- Fondaparinux is recommended on the basis of the most favorable efficacy/safety profile. (I-A)
  - Enoxaparin with a less favourable efficacy/safety profile than fondaparinux should be used only if the bleeding risk is low (IIa-B)
  - As efficacy/safety profile of LMWH (other than enoxaparin) or UFH relative to fondaparinux is unknown; these anticoagulants cannot be recommended over fondaparinux (IIa-B)



2007 ESC and ACC/AHA NSTE-ACS Guidelines

Anticoagulation in case of a conservative treatment approach

	ESC	ACC/AHA
UFH	IIa-B	IA
Enoxaparin	IIa-B	IA
Fondaparinux	IA	IB

EUROPEAN SOCIETY OF CARDIOLOGY®

American Heart Association®

Bassand JP, et al. *Eur Heart J*. 2007; 28:1598-1660, Anderson JL, et al. *Circulation*. 2007; 116:e148-304

ESC NSTEMI Guidelines 201008: any change in recommendation for anticoagulation therapy?

NO!!

Antithrombins: Mechanisms of Action

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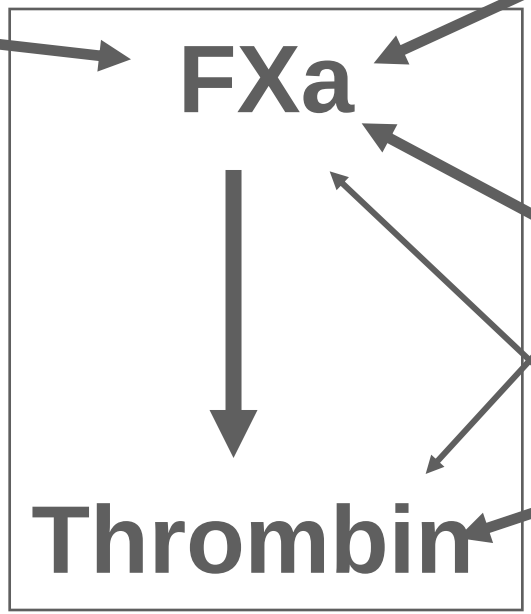

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Summary

New anticoagulants (fondaparinux and bivalirudin) have made it into the guidelines due to their favorable net clinical effect (similar anti-ischemic potential but less bleeding tendency)

New promising agents are under investigation (apixaban, rivaroxaban and dabigatran)

ACS and new anti-thrombotic therapies

- Anticoagulation in NSTEMI ACS: Should we use unfractionated heparin, low molecular weight heparin, fondaparinux or bivalirudin?
- Do we need stronger oral antiplatelet drugs in ACS?
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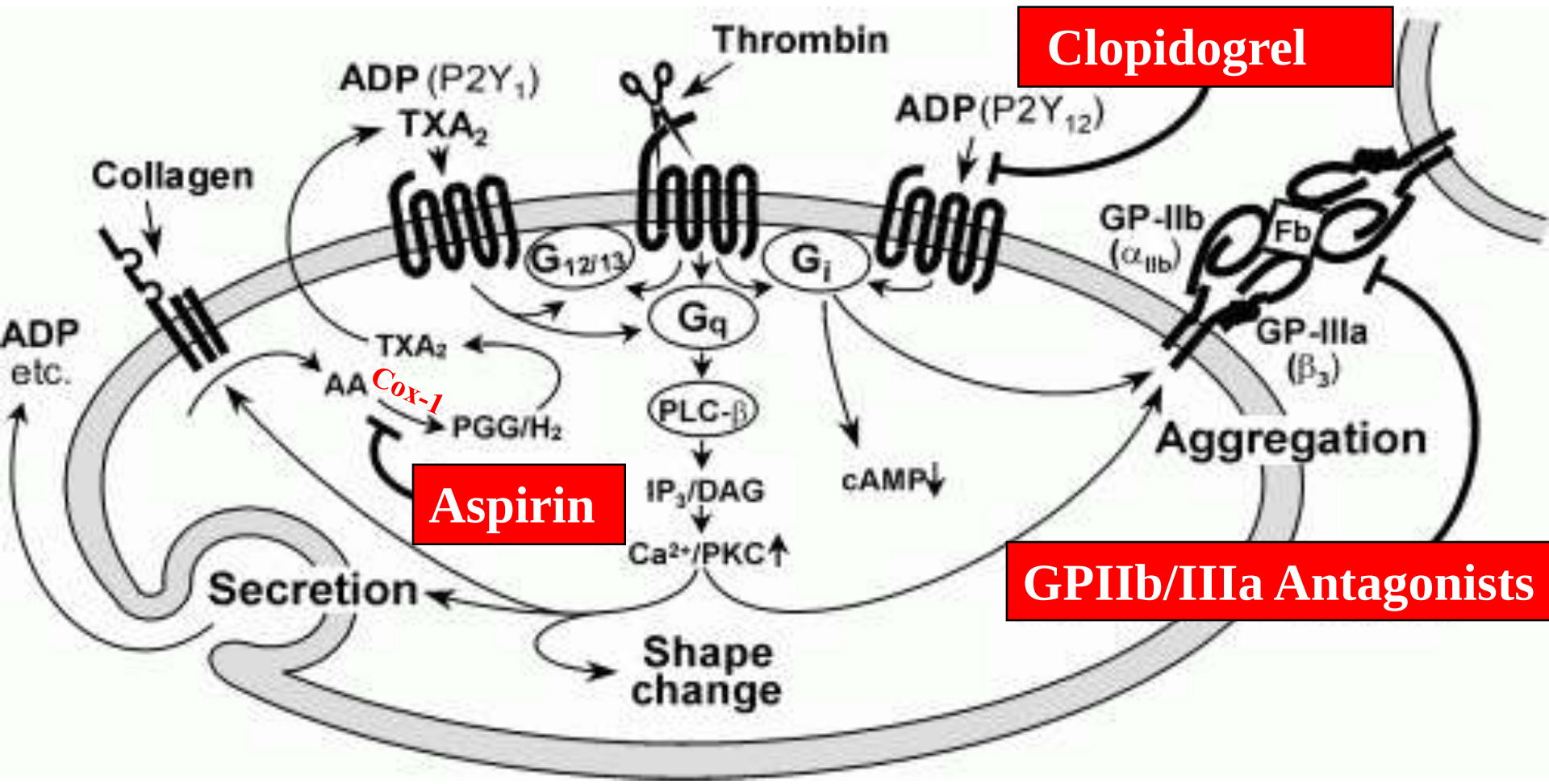
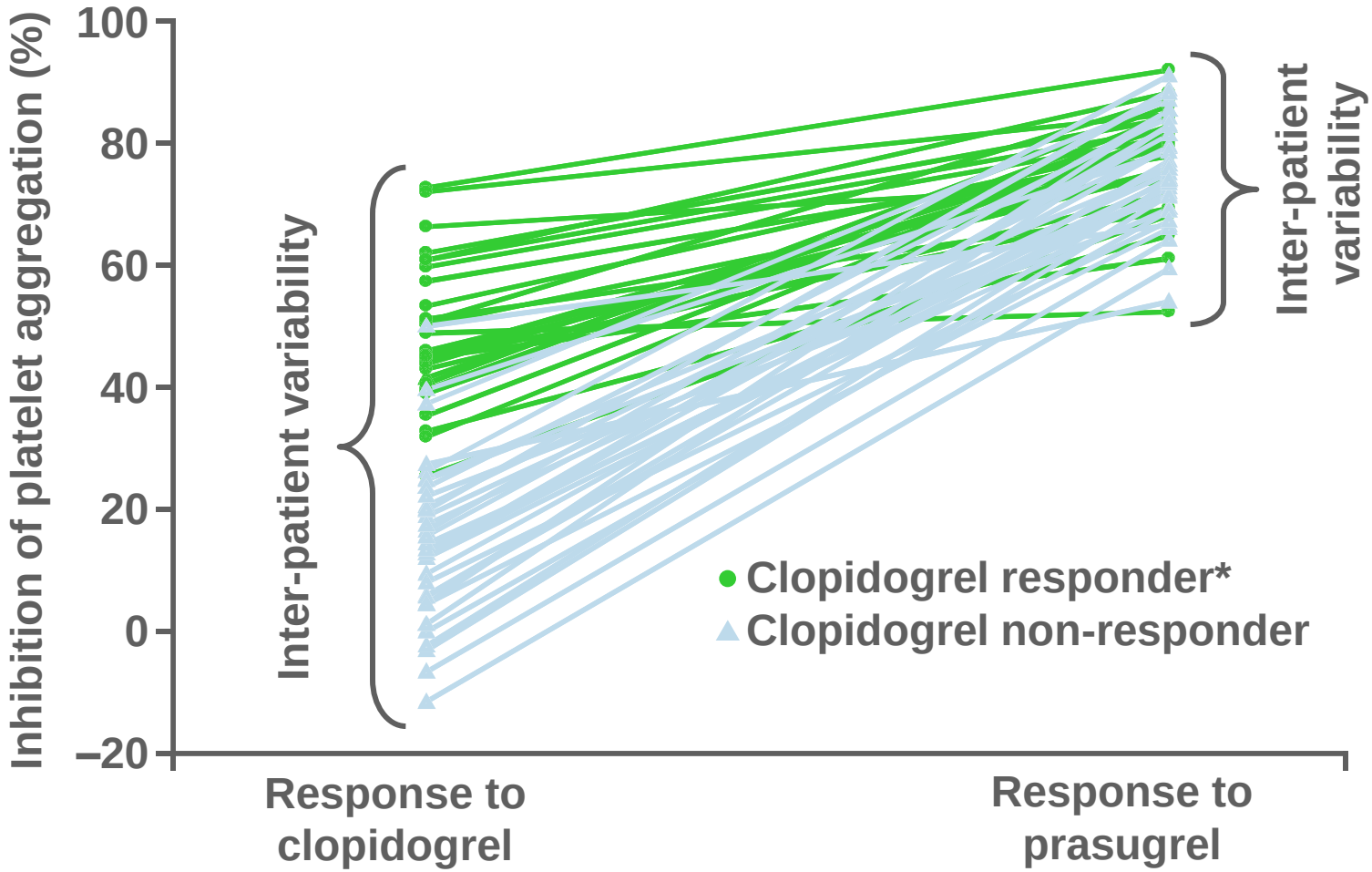
Platelet Receptors



Clopidogrel 2008

- Used in patients that do not tolerate aspirin (CAPRIE)
- Dual antiplatelet therapy indicated for 1 year after ACS and/or PCI (CURE, PCI CURE, CREDO)
- Drug-eluting stents – also 1 year
- Bare-metal stents – 1 to 12 months

Inhibition of platelet aggregation at 24 hours (healthy volunteers)



*Responder = ≥25% IPA at 4 and 24 hours
IPA = inhibition of platelet aggregation

Brandt JT, et al. Am Heart J 2007;153:66.e9–e16

ADP-receptor blockers

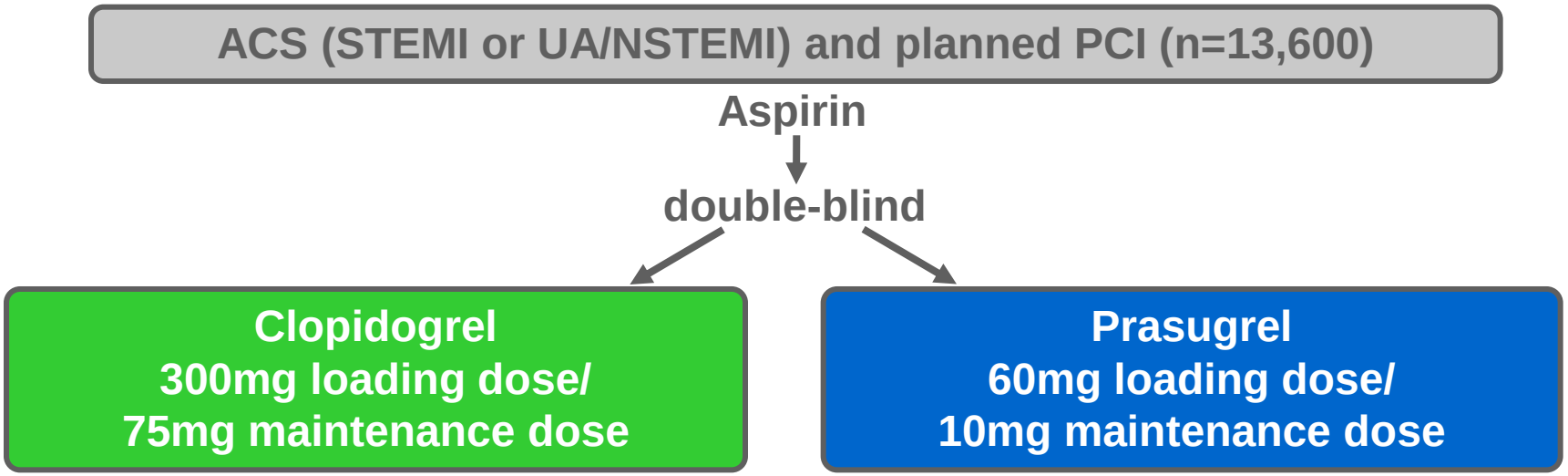
- Irreversible blockers (thienopyridines)
  - ticlopidine
  - clopidogrel
  - **prasugrel**
- Reversible blockers
  - **AZD6140**
  - **cangrelor**

Antiplatelet therapy for PCI

- Dual antiplatelet therapy (aspirin + 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 II data

Wivott SD, et al. Am Heart J 2006;152:627–35

TRITON TIMI 38 study design



Median duration of therapy: 14.5 months

Primary endpoint:	CV death, MI, stroke
Secondary endpoints:	All cause death, MI, stroke
	CV death, MI, stroke, rehospitalisation due to ischaemia
	CV death, MI, urgent target-vessel revascularisation
	Stent thrombosis (ARC: definite/probable)
Safety endpoints:	TIMI major bleeds, life-threatening bleeds
Key substudies:	Pharmacokinetic, genomic

STEMI = ST-segment elevation MI; TIMI = thrombolysis in myocardial infarction; UA = unstable angina; NSTEMI = non-ST-segment elevation MI
ARC = Academic Research Consortium

Wiviott SD, et al. N Engl J Med 2007;357:2001–15

Enrolment criteria

- Inclusion criteria
  - **planned PCI for:**

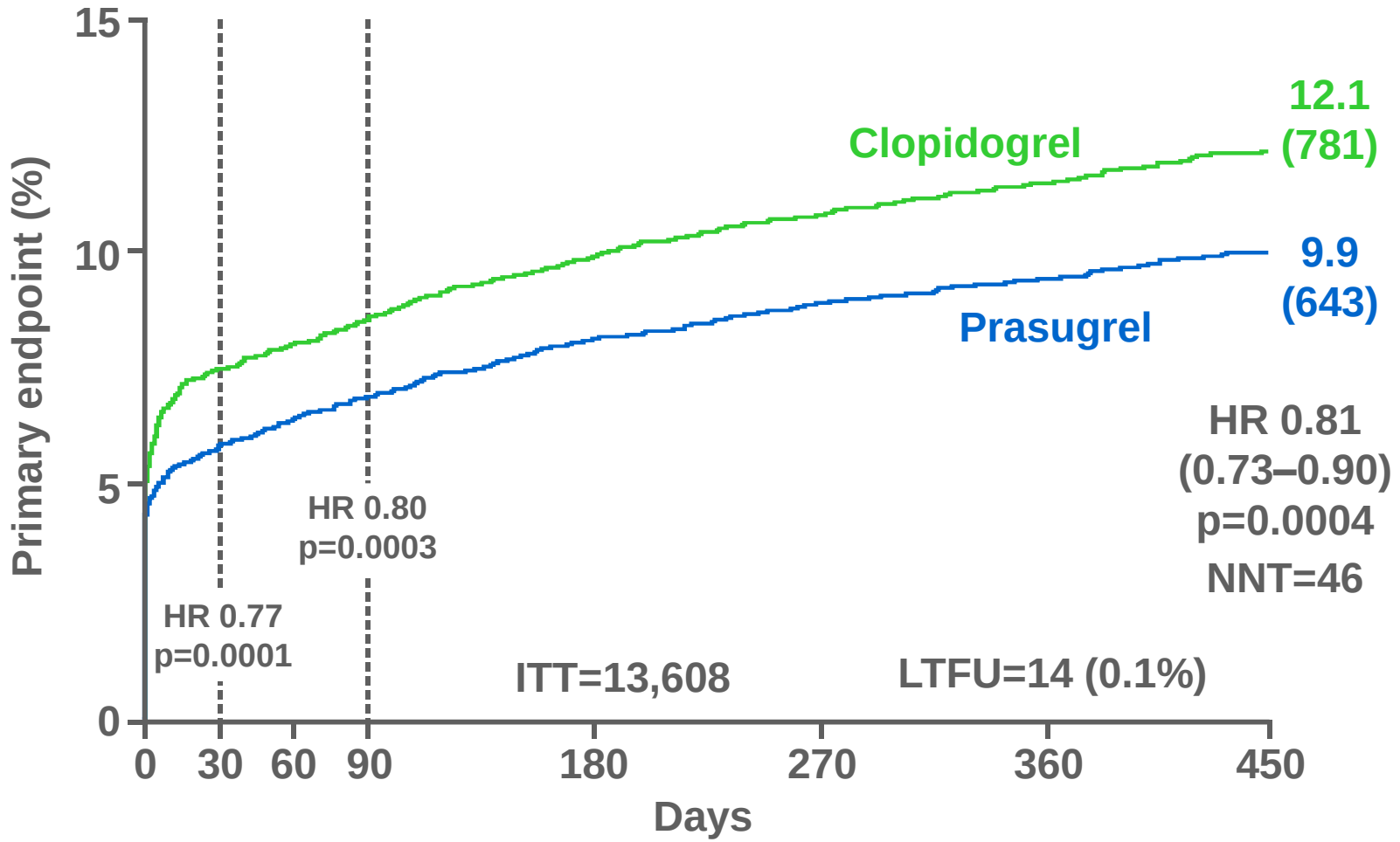
    Known anatomy:
    - **moderate-high risk UA/NSTEMI (TRS ≥3)**
    - **STEMI: ≤14 days (ischaemia or treatment strategy)**
    - **STEMI: primary PCI**

- Major exclusion criteria:
  - severe comorbidity
  - increased bleeding risk
  - prior haemorrhagic stroke or any stroke ≤3 months
  - any thienopyridine within 5 days
  - no exclusion for advanced age or renal function

TRS = TIMI risk score

Wiviott SD, et al. N Engl J Med 2007;357:2001–15

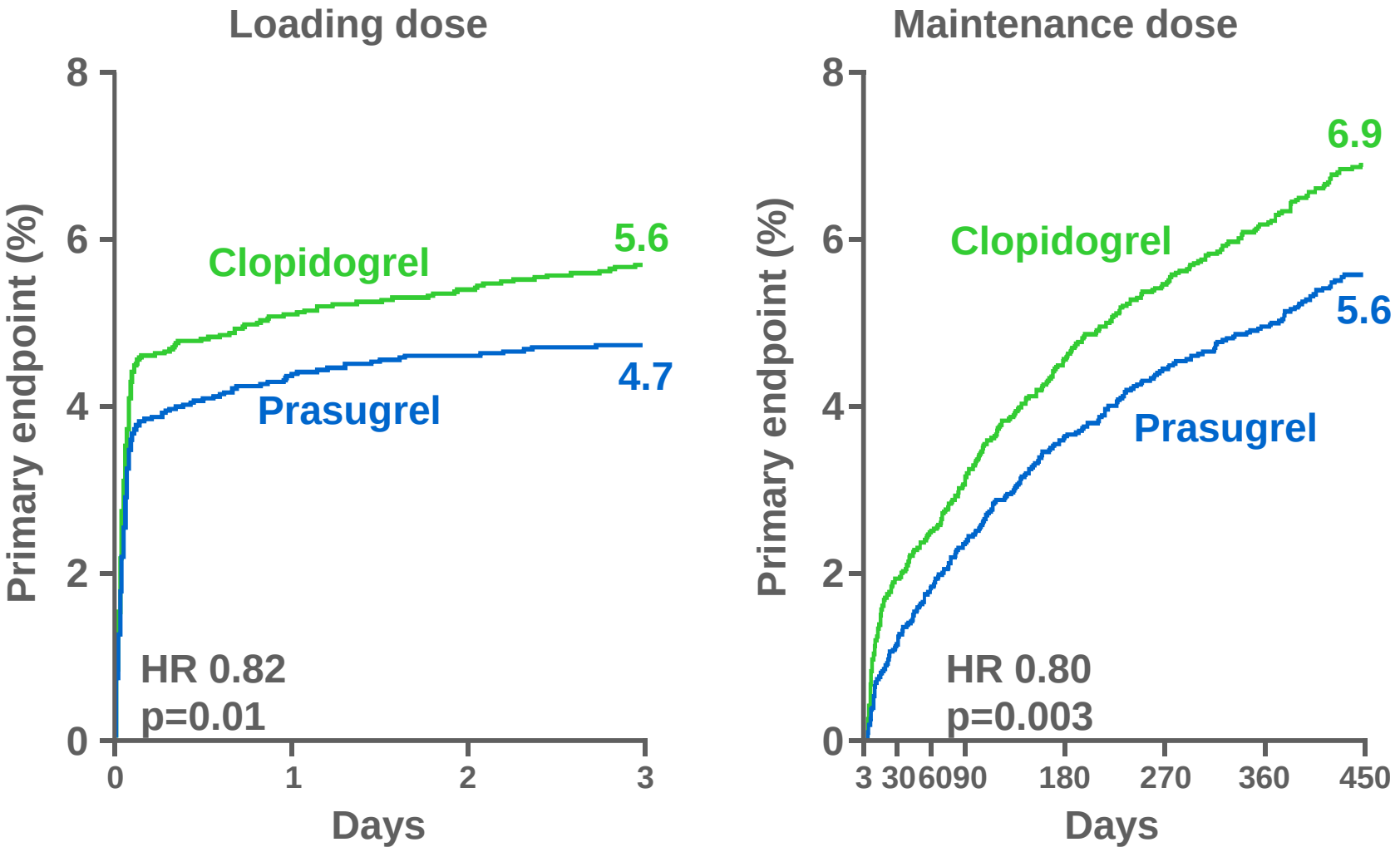
Primary endpoint CV death, MI, stroke



HR = hazard ratio; NNT = number needed-to-treat
ITT = intent-to-treat; LTFU = long-term follow-up

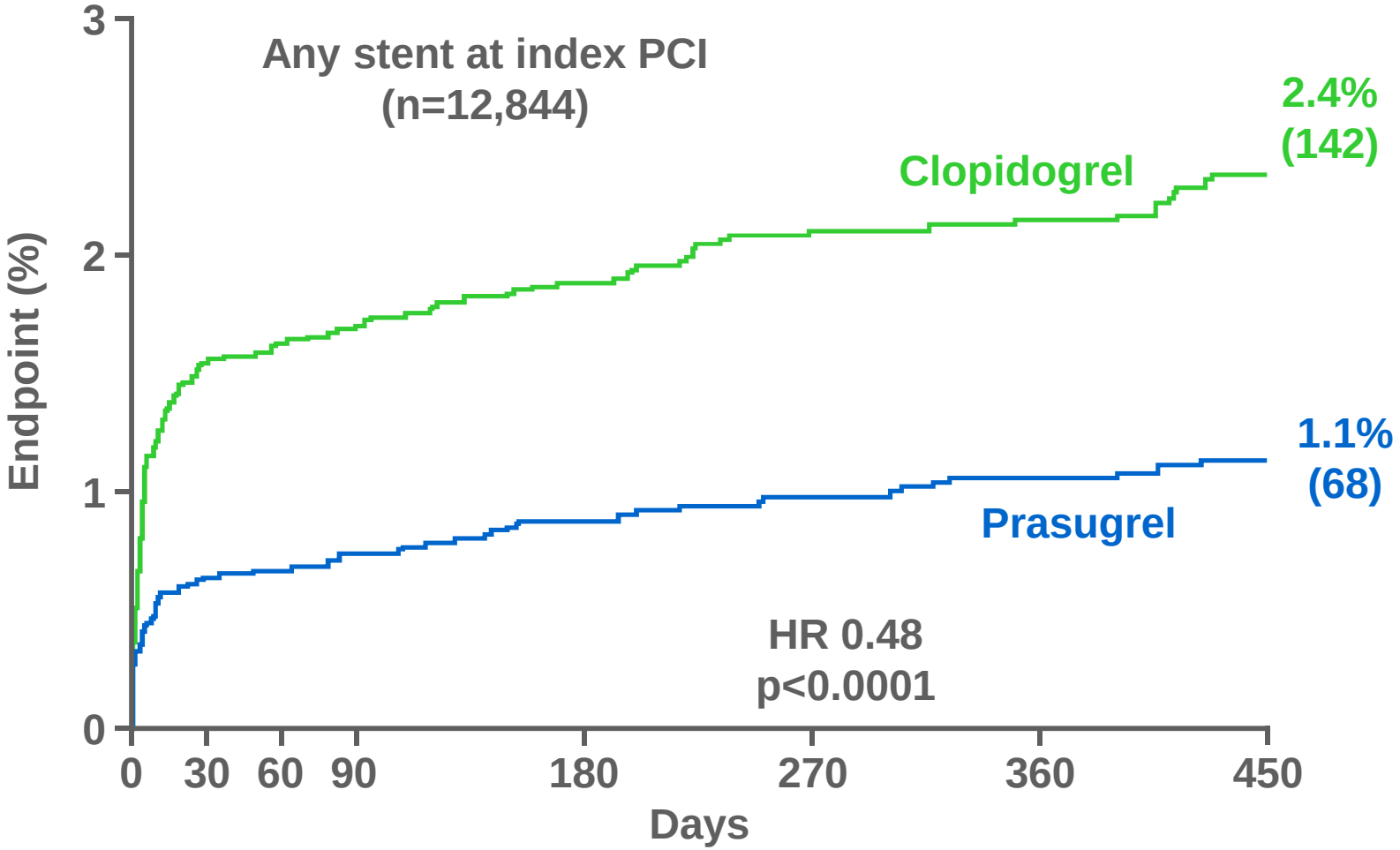
Wiviott SD, et al. N Engl J Med 2007;357:2001–15

Timing of benefit: primary endpoints at day 3 and day 3 to study end (vs landmark analysis)



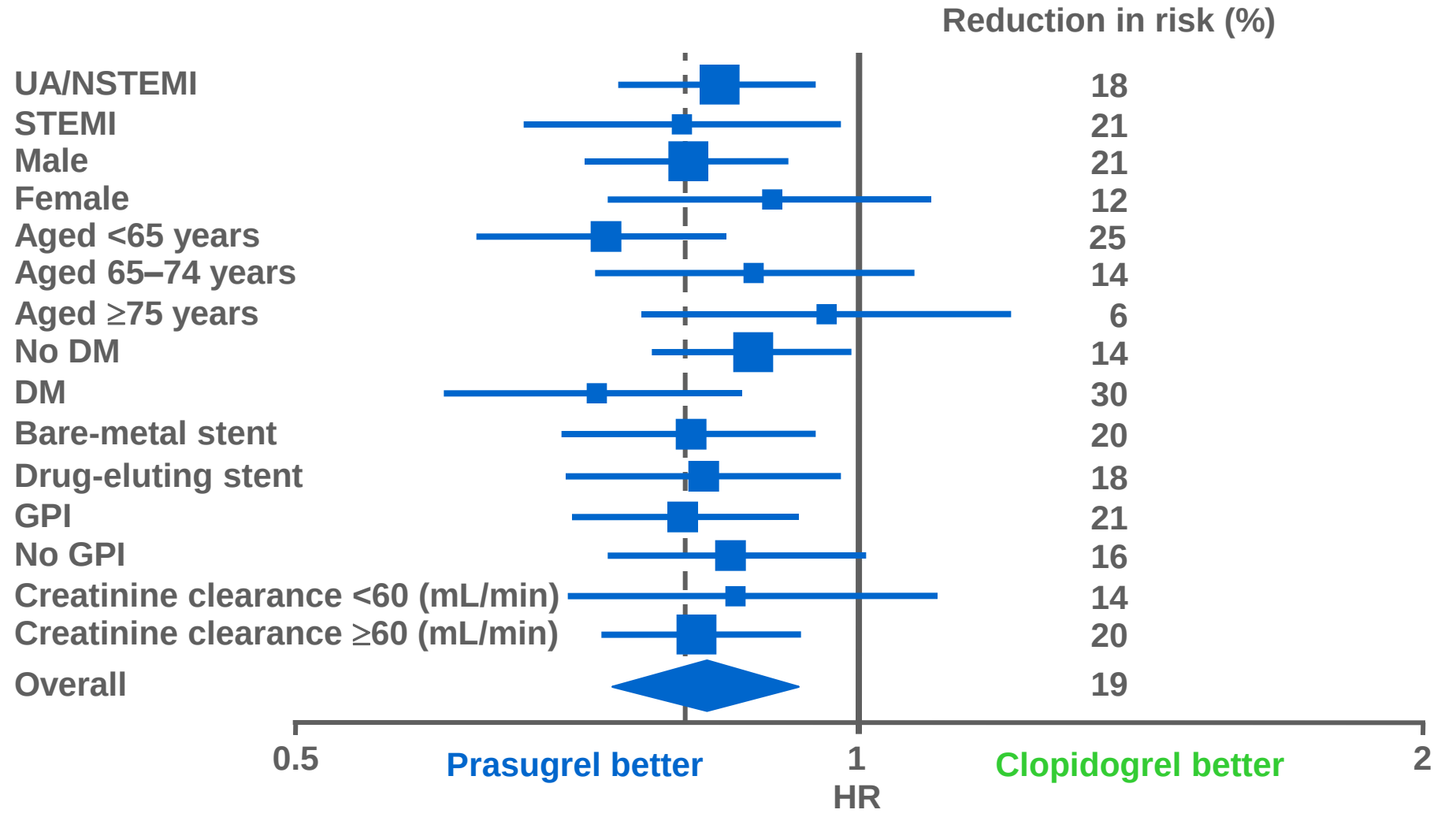
Wiviott SD, et al. N Engl J Med 2007;357:2001–15

Stent thrombosis (ARC definite and probable)



Wiviott SD, et al. Lancet 2008;370:1353–63

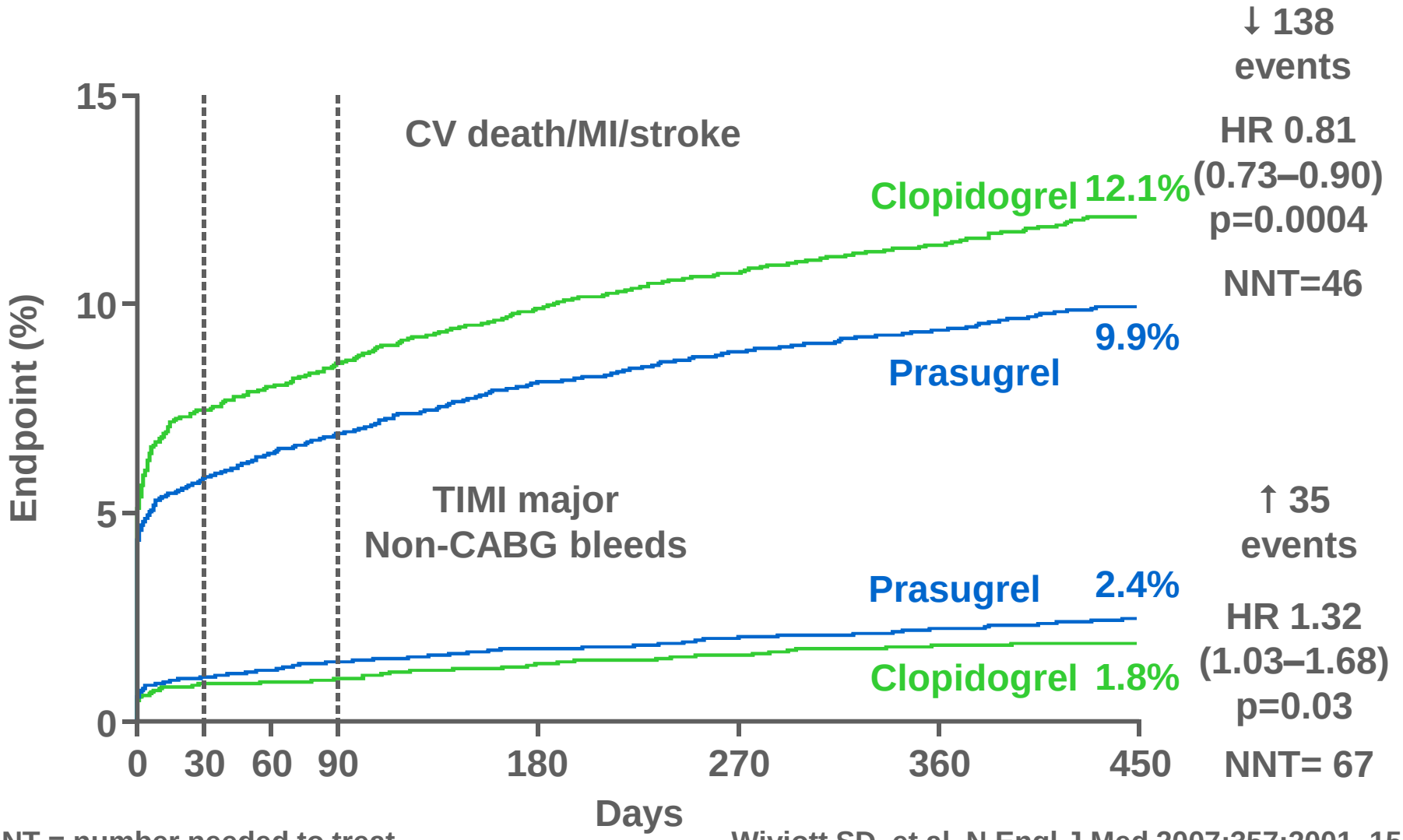
CV death/MI/stroke major subgroups



P_{inter} = NS

Wiviott SD, et al. N Engl J Med 2007;357:2001–15

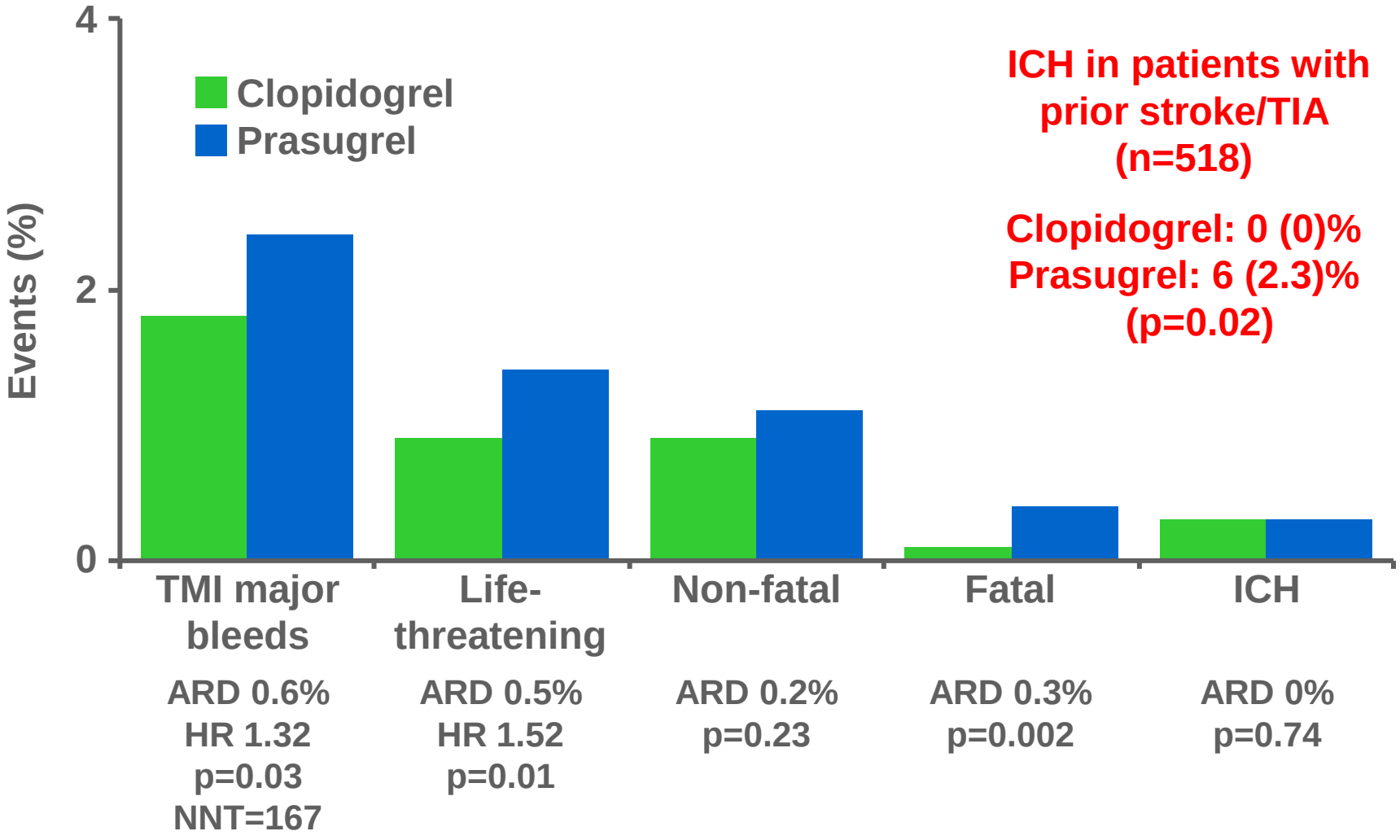
Balance of efficacy and safety



NNT = number needed to treat

Wiviott SD, et al. N Engl J Med 2007;357:2001–15

Bleeding events safety cohort (n=13,457)



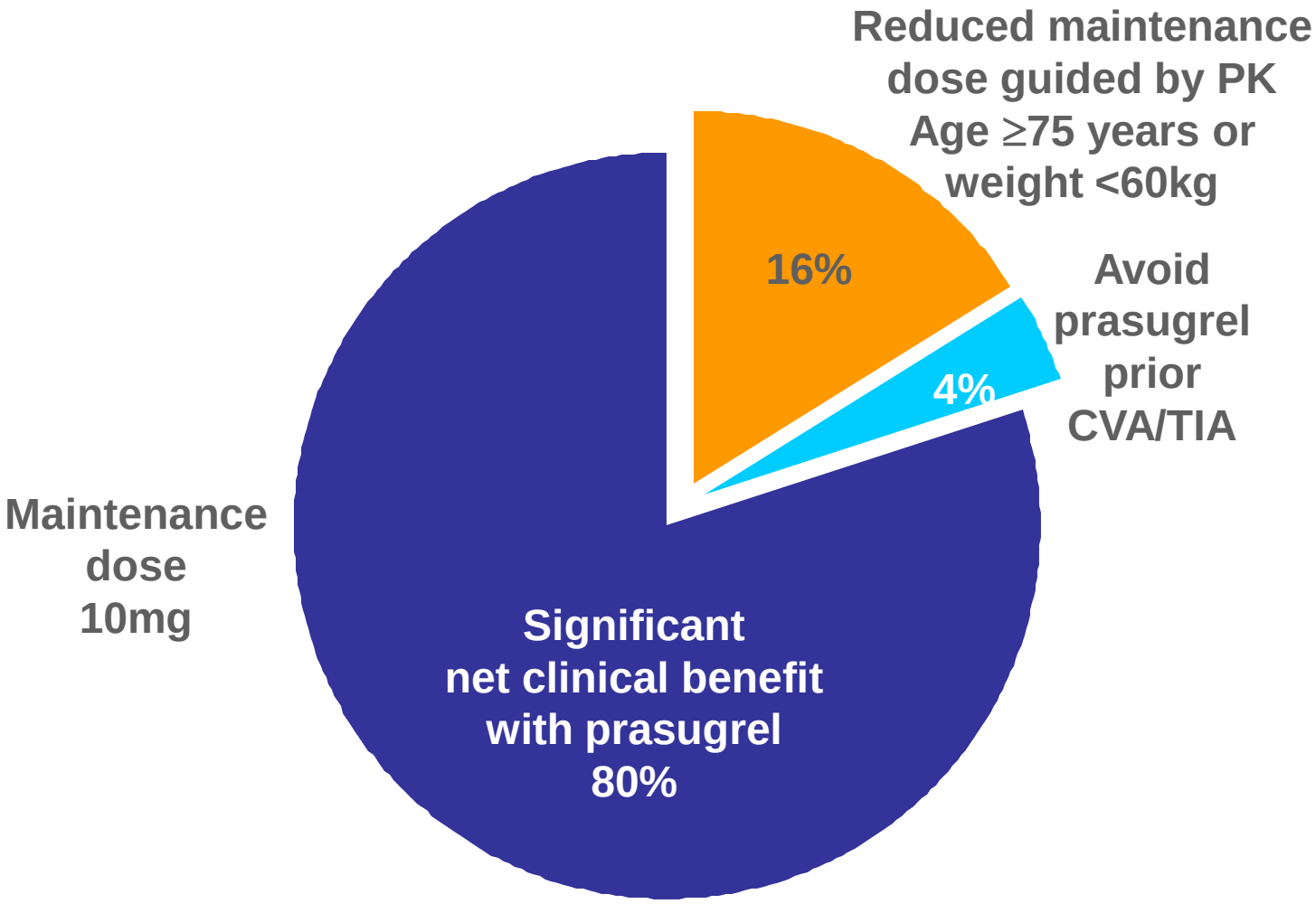
ICH in patients with prior stroke/TIA (n=518)

Clopidogrel: 0 (0)%
Prasugrel: 6 (2.3)%
(p=0.02)

TIA = transient ischaemic attack

Wiviott SD, et al. N Engl J Med 2007;357:2001–15

Bleeding risk subgroups therapeutic considerations



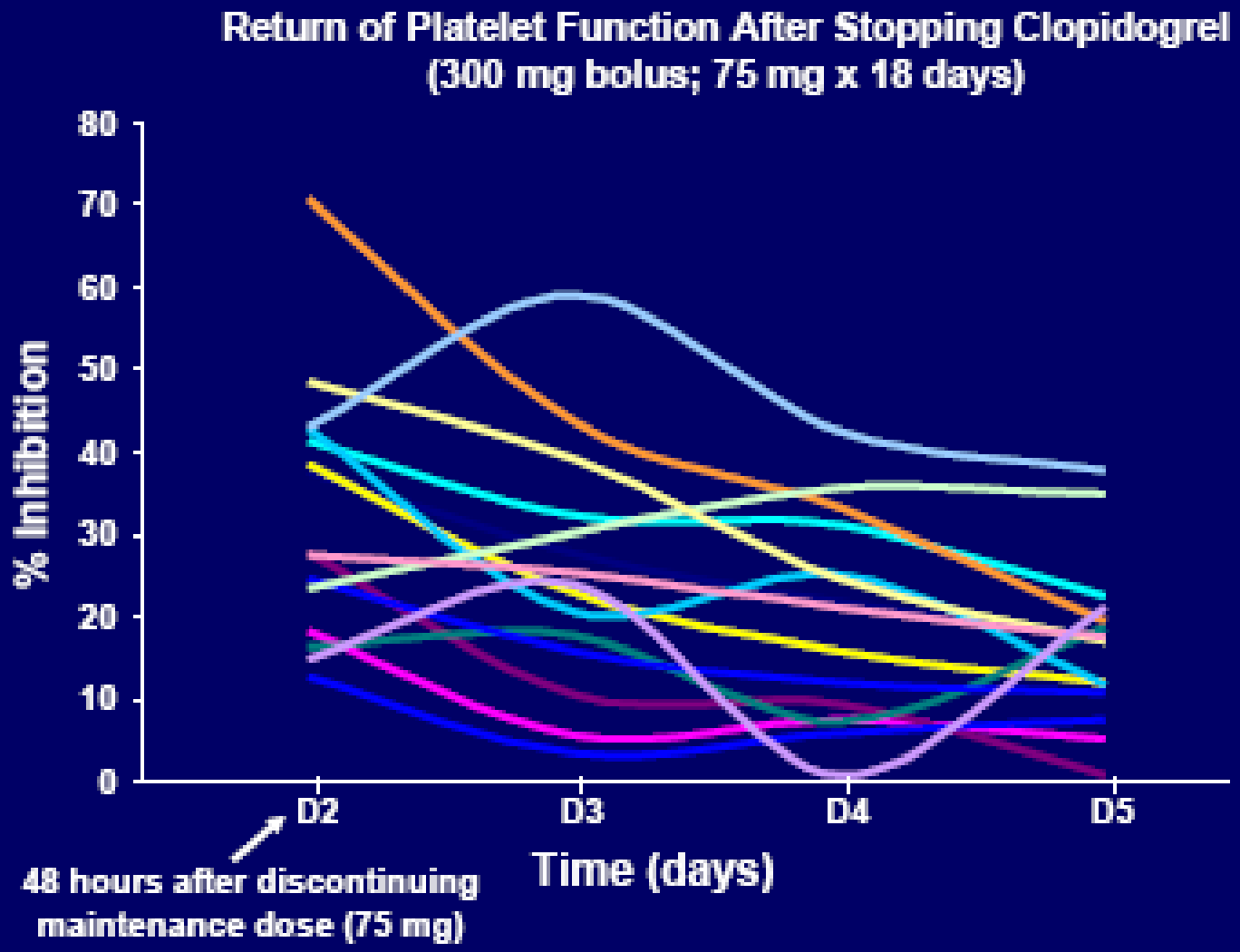
PK = pharmacokinetic

Optimisation of prasugrel maintenance dosing in a minority of patients may help improve the benefit:risk

Current P2Y12 antagonists: possible inprovements

- Potency
- More uniform response
- **Non-reversibility**
- Onset of action

Offset of Platelet Inhibition

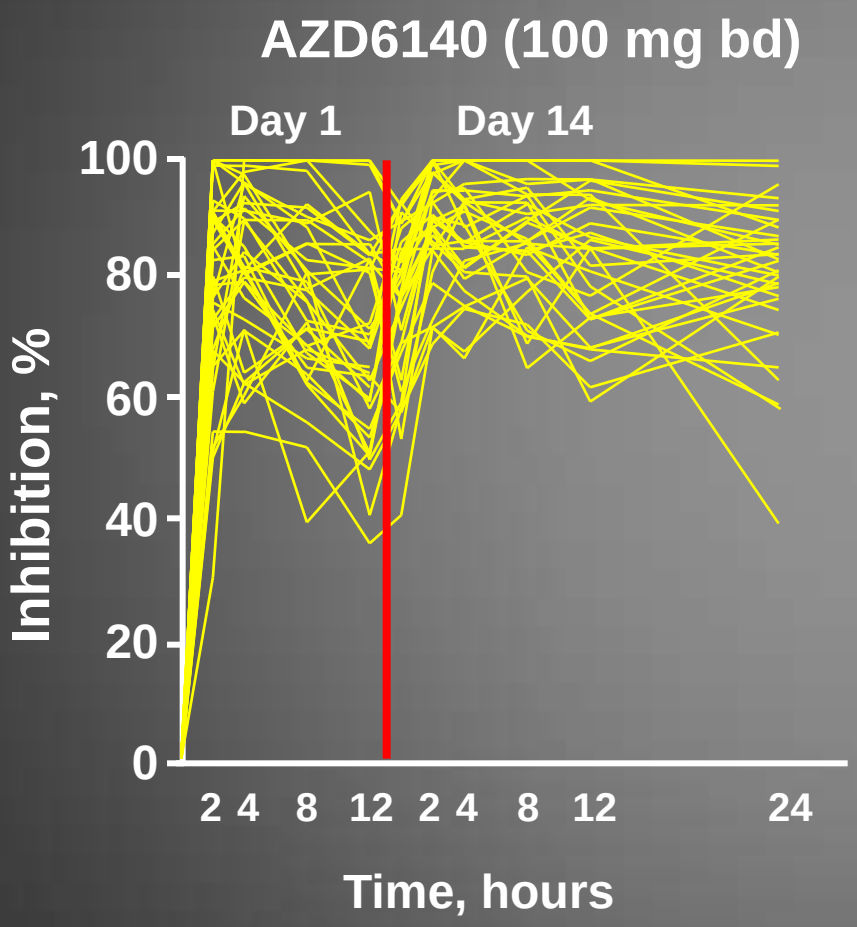


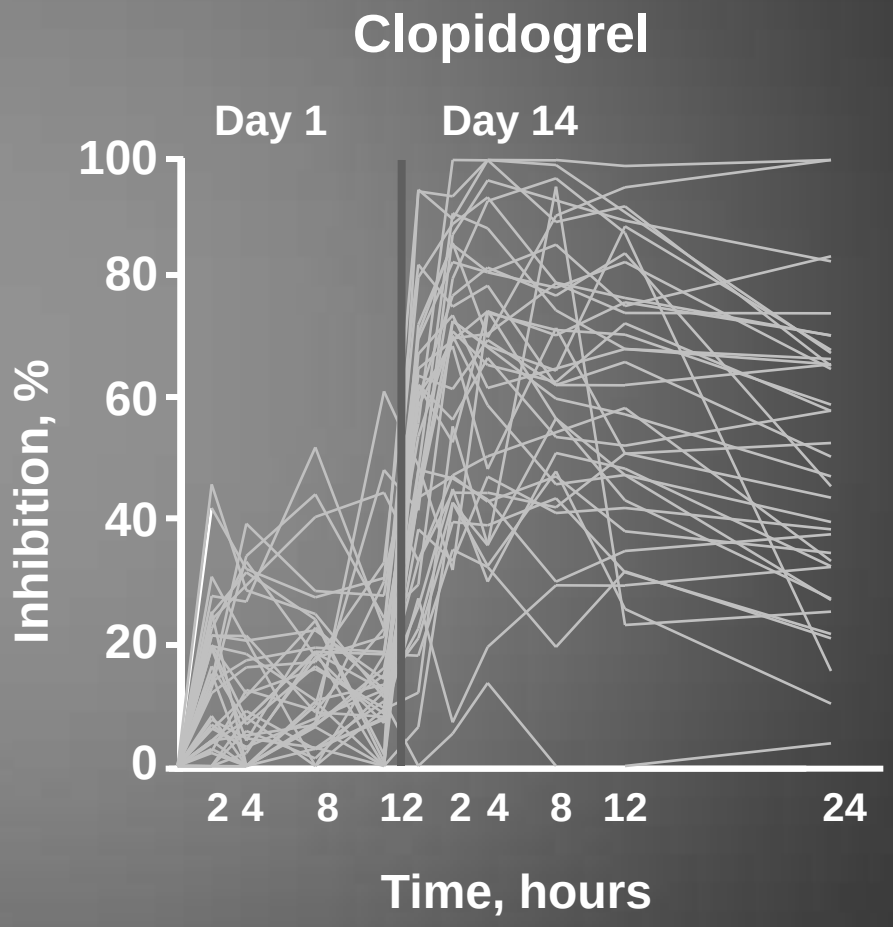
Price et al. *Am J Cardiol*. 2006.

Oral reversible P2Y12 antagonists - AZD6140 -

- the first of a new chemical class of antiplatelet agents, the **cyclopentyltriazolopyrimidines**
- Like the thienopyridines, AZD6140 blocks the platelet **P2Y12 receptor** to inhibit ADP's prothrombotic effects
- Unlike the thienopyridines, which are irreversible antagonists, AZD6140 binds **reversibly** to the P2Y12 receptor and nearly completely inhibits ADP-induced platelet aggregation ex vivo
- Also unlike the thienopyridines, AZD6140 is **orally active without the requirement for metabolic activation**

DISPERSE: Fast and strong IPA with AZD6140





Husted et al, Eur Heart J 2006

Phase III: PLATO PLATelet Inhibition and patient Outcomes)

- Randomised, multinational, multicentre, event driven study
- Comparison of AZD6140 to clopidogrel in a broad patient population (NSTEMI, STEMI, UA)
- Target countries: 40
- Target centres: 1000
- Target patients: 18,000

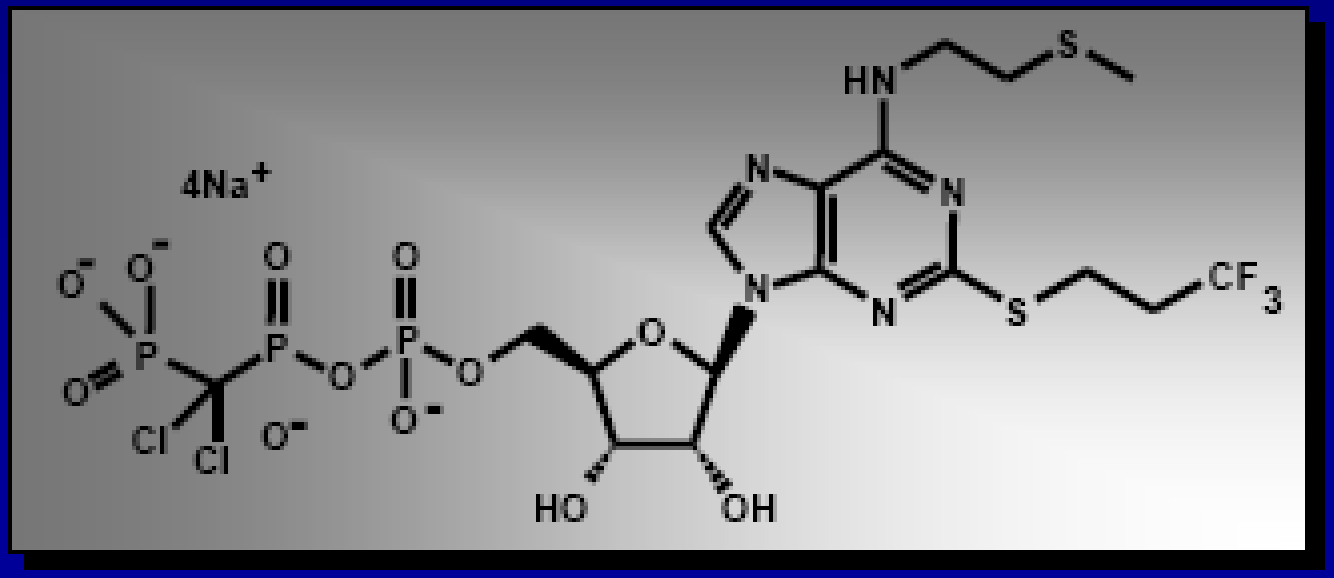
Current P2Y12 antagonists: possible inprovements

- Potency
- Non-reversibility
- Onset of action

Cangrelor (AR-C69931MX)

Parenteral ADP-P2Y12 receptor antagonist

- ATP analogue
- Molecular weight 800 Daltons
- Plasma half-life of 5-9 minutes
- 20 minutes for return to normal platelet function



Cangrelor – Phase 2

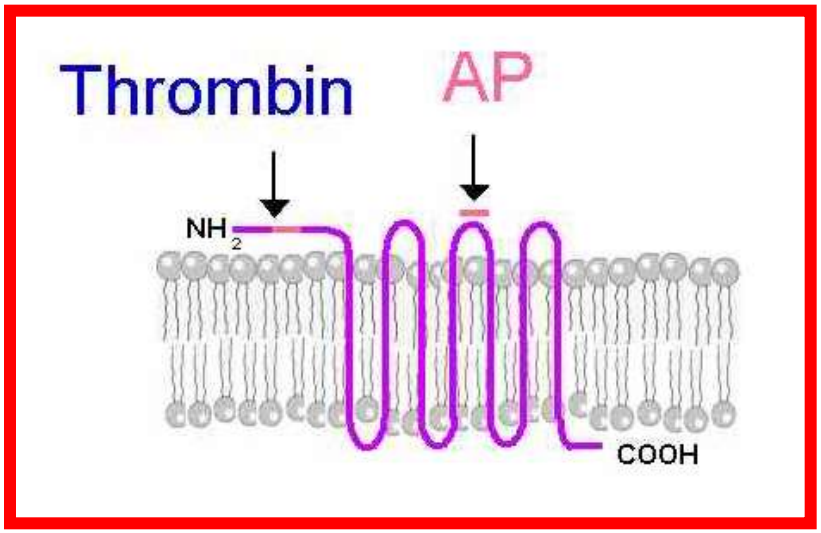
- Acute coronary syndromes without persistent ST-segment elevation and not undergoing PCI, given in conjunction with aspirin and heparin;
- found to be **safe and well tolerated** to a dose of 4 µg/kg per minute, achieving >95% platelet inhibition.

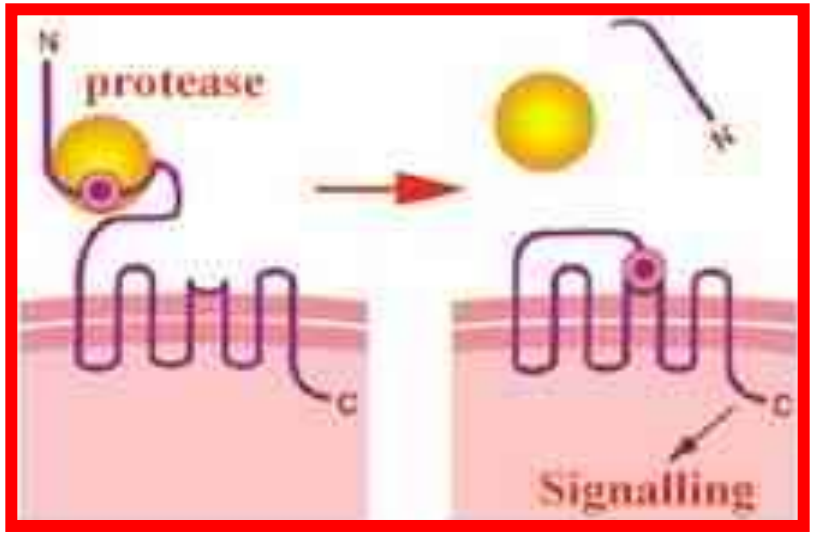
Storey RF, et al. Thromb Haemost 2001;85:401 -7.
Jacobsson F, et al. J Am Coll Cardiol 2000;35(Suppl A):343A.

Cangrelor – Phase III study CHAMPION

- Setting: **Acute Coronary Syndromes undergoing PCI**
- Primary objective: to demonstrate that the efficacy of cangrelor is superior, or at least non-inferior, to that of **clopidogrel** in subjects requiring PCI.
- Primary Outcomes: All-cause mortality, MI, and IDR in the **48 hours** after randomization.
- Secondary Outcomes: All-cause mortality and MI at 48 hours
- Expected Total Enrollment: 9000
- Study start: April 2006

Protease-activated receptors - PAR





Thrombin receptor antagonist: background

- SCH 530348 is an oral, potent, selective thrombin receptor antagonist (TRA) being developed for the prevention and treatment of atherothrombosis.
- Preclinical and early clinical studies have demonstrated SCH 530348 to have antithrombotic properties, with no increase in bleeding time or clotting times (aPTT, PT, ACT).

Galbulimima baccata

- Himbicine derivative
- Bark of the Australian Rhododendron

T·R·A-PCI Design, PI: D Moliterno

Non-Urgent PCI or Cath possible PCI (All Receive Aspirin)
Randomization #1 — 3:1 SCH530348:Placebo (Single Loading Dose)
Sequential Groups: 1=10 mg; 2=20 mg; 3=40 mg, or Placebo

Cardiac Catheterization
Planned PCI (All Receive Clopidogrel and Antithrombin)

Randomization #2 1:1:1
Maintenance Therapy Once Daily for ~ 60 days
SCH 530348 Loading Dose → SCH 530348
Or Placebo Loading Dose → Placebo

SCH 530348

0.5 mg n~100	1 mg n~100	2.5 mg n~100	Placebo n~100

Safety: TIMI Major plus Minor Bleeding
Efficacy: Death/MACE

* *Primary Evaluable Cohort*

No PCI**

CABG

Medical Management

Quantify Postoperative Chest-Tube Drainage, Transfusions, and Re-exploration

Safety: TIMI Major plus Minor Bleeding

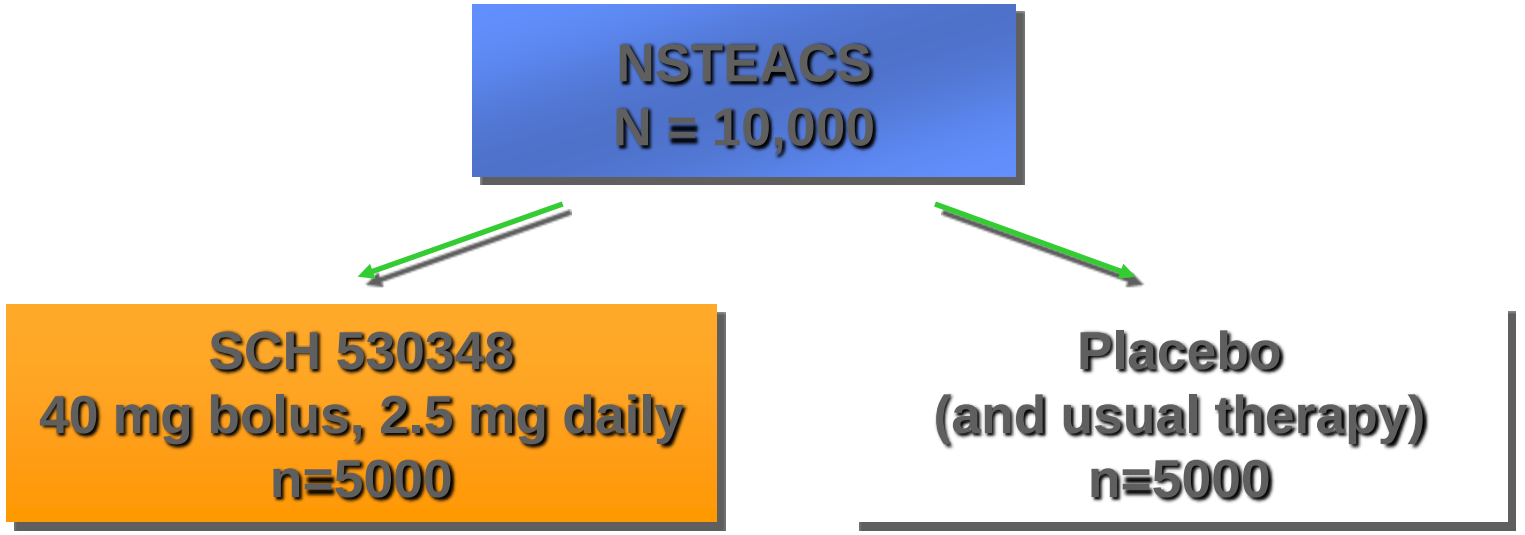
***Secondary Evaluable Cohort*

Conclusions

- **TRA was not associated with an increase in bleeding**
- **Using 15 μM TRAP-induced platelet aggregation:**
  - **40 mg loading dose of SCH 530348 achieved ≥ 80% IPA in 1-2 hours in 68-96% subjects**
  - **1 mg and 2.5 mg maintenance doses sustained ≥ 80% IPA at 30 and 60 days in all subjects**
- **While not statistically significant, SCH 530348 was associated with:**
  - **Death/MACE: ↓32% overall**

TRA•CER

Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome

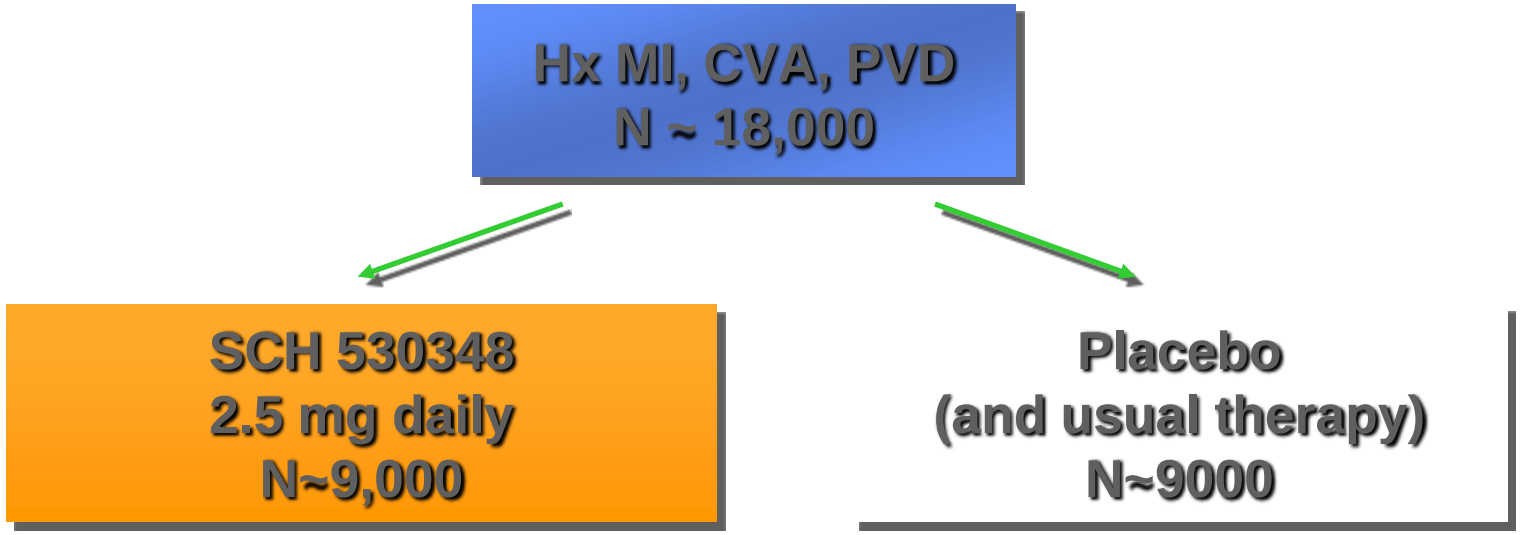


- 1-Year Cardiovascular Death, MI, Stroke, Recurrent Ischemia with Rehosp, Urgent Coronary Revas •

www.clinicaltrials.gov

TRA•2P—TIMI 50

Thrombin Receptor Antagonist for 2° Prevention



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ACS and new anti-thrombotic therapies

- Anticoagulation in NSTEMI ACS: Should we use unfractionated heparin, low molecular weight heparin, fondaparinux or bivalirudin?
- Do we need stronger oral antiplatelet drugs in ACS?
- Primary PCI – any news in anti-thrombotic therapy?

ESC STEMI Guidelines: Van de Werf and coworkers 2008

- Presented at ESC Congress Munich 2008
- Available on the web-site: Eur Heart Journal

Primary PCI is preferred reperfusion therapy IA

- < 12 hours
- Experienced team
- Time delay: 120 minutes (90 minutes in patients presenting early)

Anti-thrombotic therapy - ESC STEMI Guidelines 2008

- **Aspirin:**

  A bolus of 150-325 mg (chewable) or 250-500 mg i.v. followed by life long therapy. **I B**

- **Clopidogrel:**

  Bolus 300 mg or 600 mg. **I C**

- **Heparin:**

  100 U/kg (60 U/kg with GP IIb/IIIa) **I C**

Anti-thrombotic therapy in the cath lab – ESC STEMI Guidelines 2008

GP IIb/IIa inhibitors	
Abciximab	**IIa A**
Eptifibatide	**IIb C**
Tirofiban	**IIb C**
Bivalirudin	**IIa B**
Thrombus aspiration	**IIb B**

New evidence: abciximab

- Abciximab in primary coronary stenting of ST-elevation myocardial infarction: a European meta-analysis on individual patients' data with long-term follow-up.

G Montalescot et al Eur Heart J. 2007; 28(4):443-9.

New evidence: bivalirudin

- Bivalirudin during primary PCI in acute myocardial infarction.
- HORIZONS trial

G Stone et al: N Engl J Med. 2008; 22: 2218-30.

HORIZONS AMI

3602 pts with STEMI with symptom onset ≤12 hours

Aspirin, thienopyridine

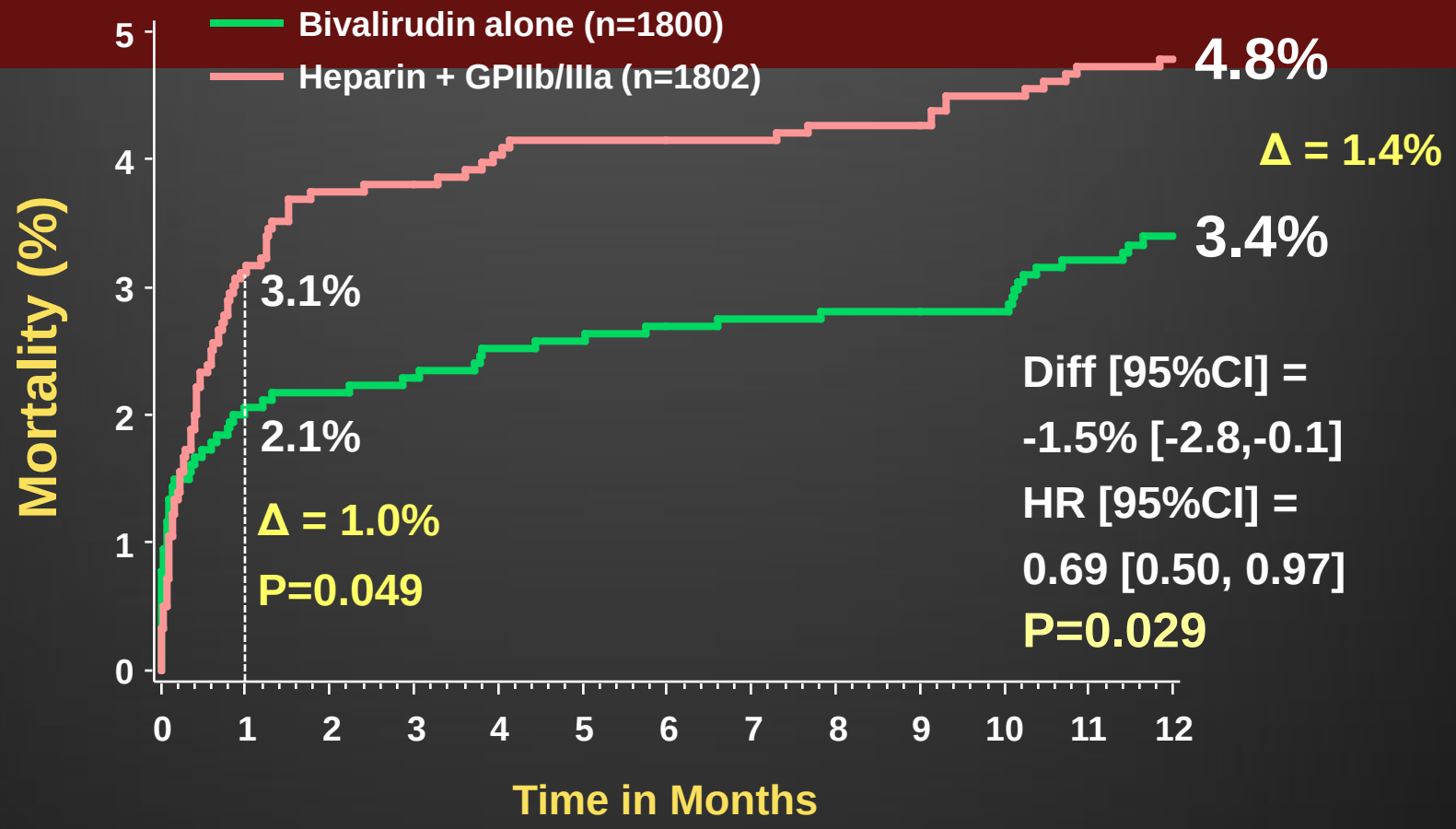
R
1:1

- UFH + GP IIb/IIIa inhibitor (abciximab or eptifibatide)
- Bivalirudin monotherapy (± provisional GP IIb/IIIa)

Pharmacology Arm
Primary and Secondary Endpoints
1-Year
Intention to Treat Population

Outcomes in the 4 randomized groups

1-Year All-Cause Mortality



Number at risk					
Bivalirudin alone	1800	1705	1684	1669	1520
Heparin+GPIIb/IIIa	1802	1678	1663	1646	1486

New evidence: Thrombus aspiration

- Thrombus aspiration during primary percutaneous coronary intervention.
- Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study.

Svilaas T et al, N Engl J Med. 2008;358 :557-67
PJ Vlaar et al, Lancet. 2008;37:1915-20.

Anti-thrombotic therapy - ESC STEMI Guidelines 2008

Adjunctive therapy: primary PCI

- **Not recommended:**

  Upstream therapy with GPI, fibrinolytics or the combination.

  Fondaparinux.

Anti-thrombotic therapy - ESC STEMI Guidelines 2008

Adjunctive therapy: primary PCI

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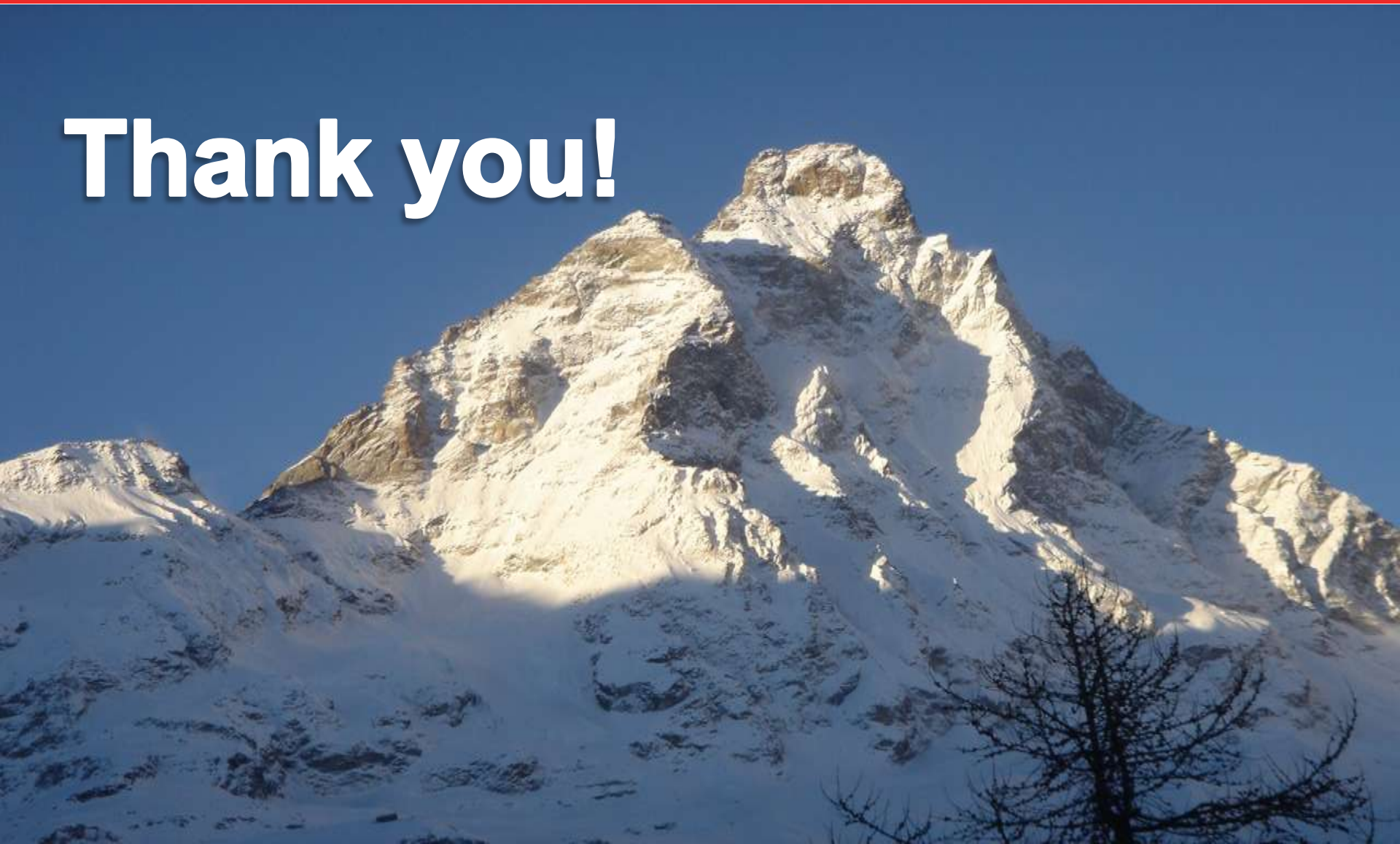
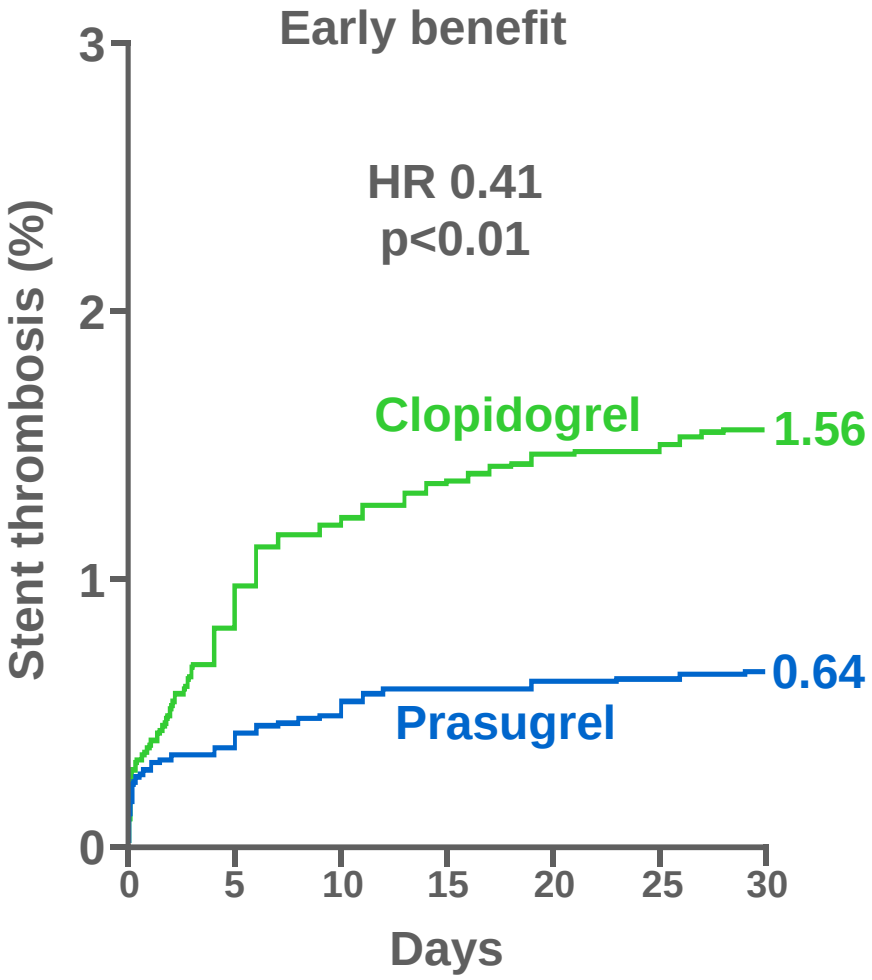
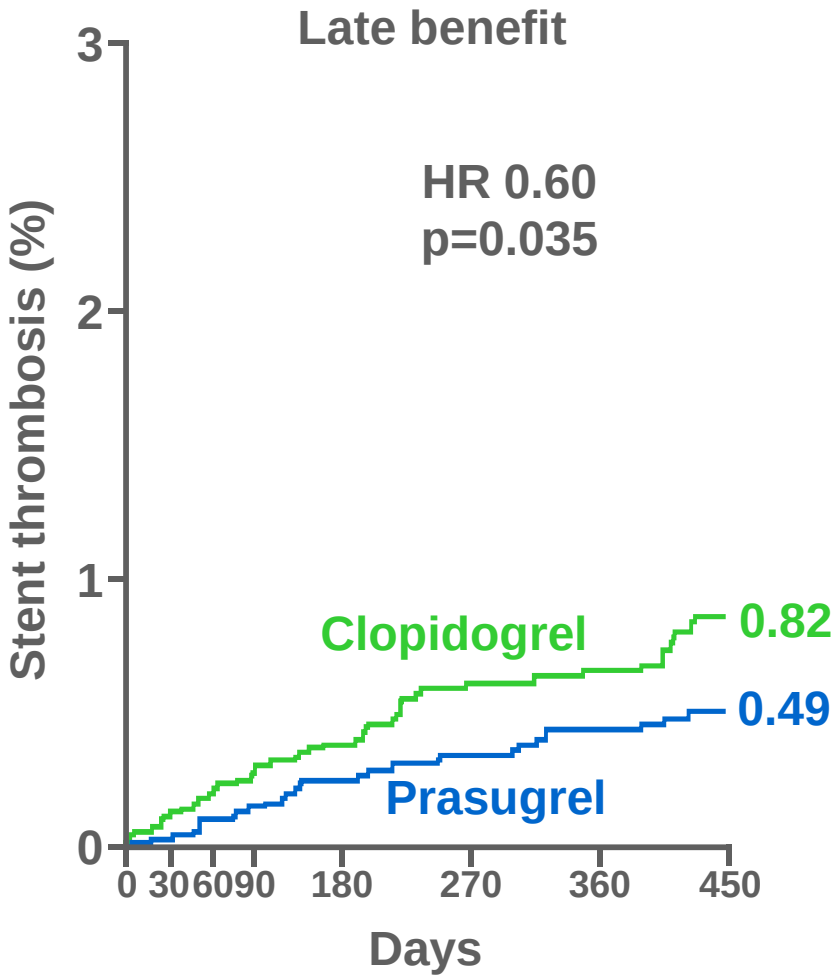
On-time 2 Trial: Tirofiban up-stream
A Van't Hout: Lancet 2008

ACS – antithrombotic therapy – questions???



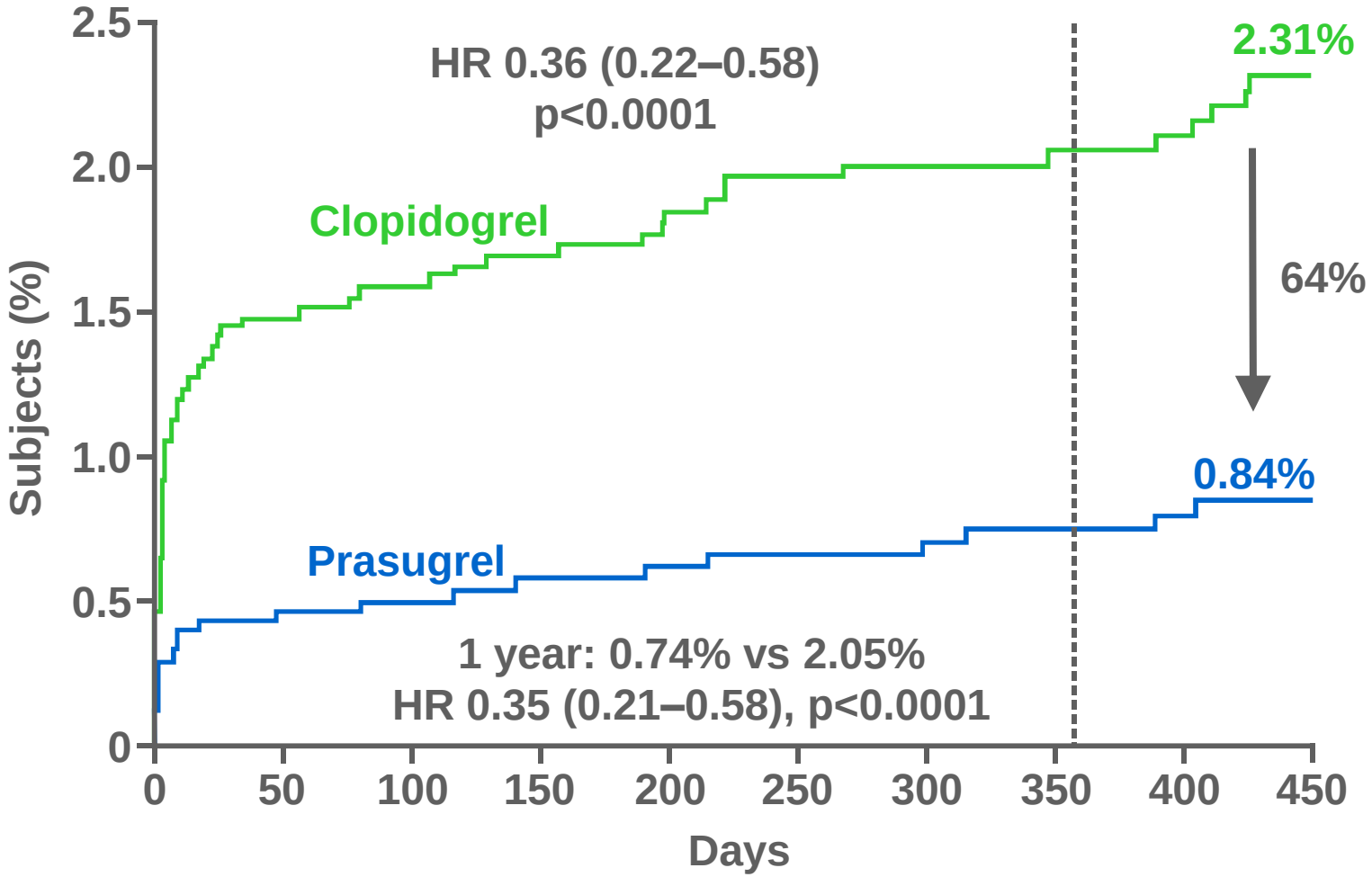
Stent thrombosis (landmark analysis – 30 days)





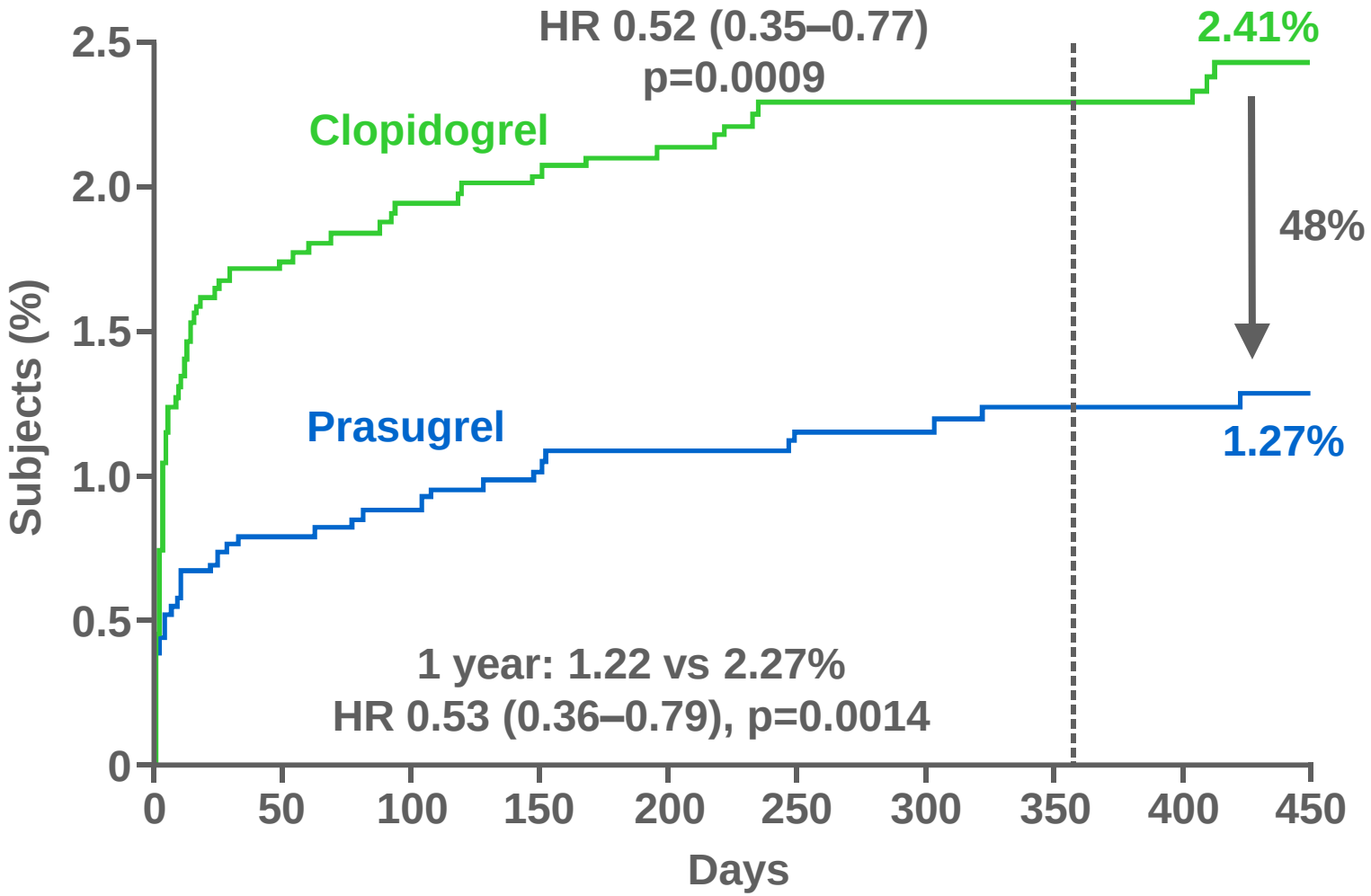
Wiviott SD, et al. Lancet 2008;370:1353–63

Definite/probable stent thrombosis: drug-eluting stent only (n=5,743)



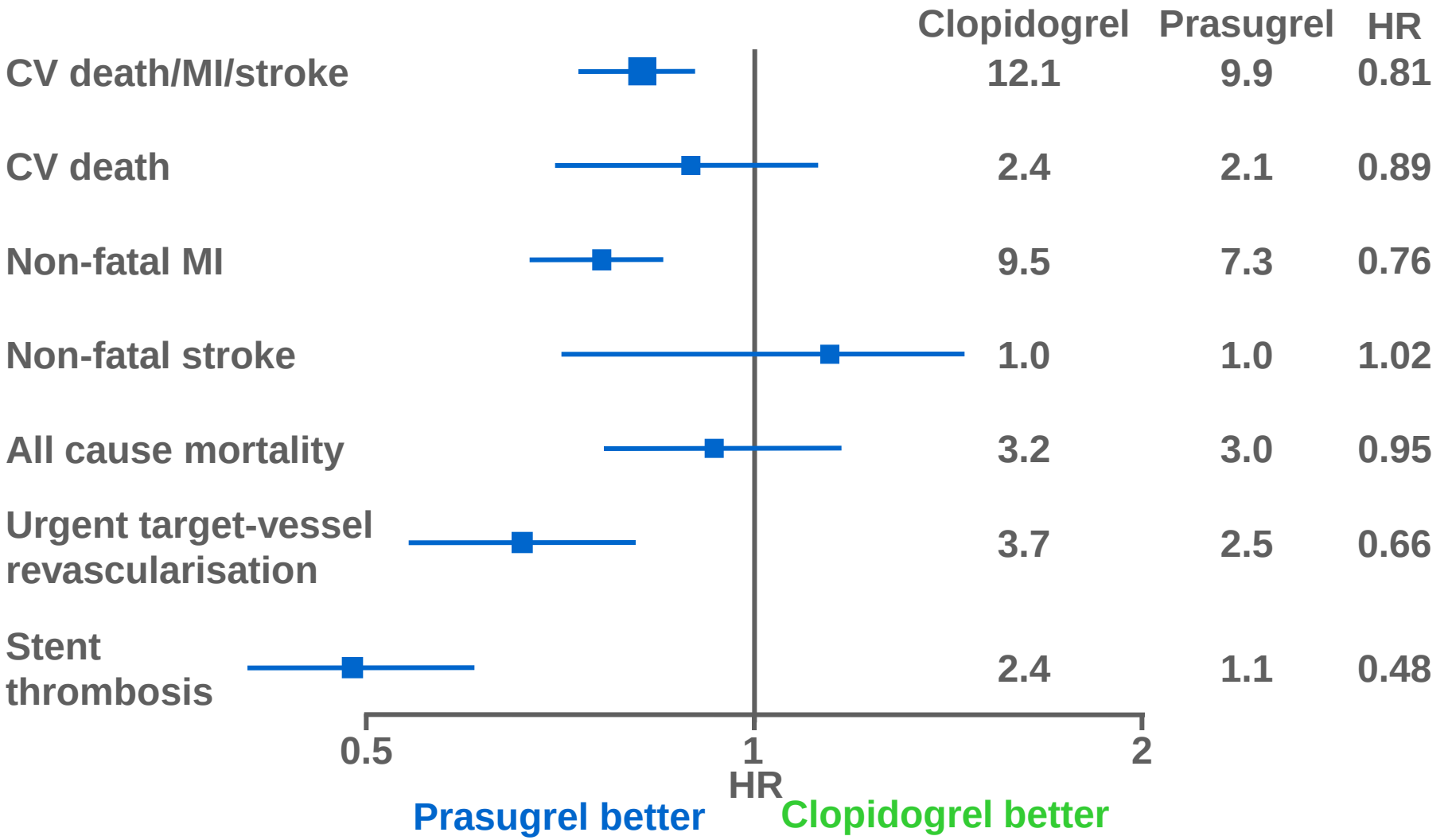
Wiviott SD, et al. Lancet 2008;370:1353–63

Definite/probable stent thrombosis: bare-metal stent only (n=6,461)



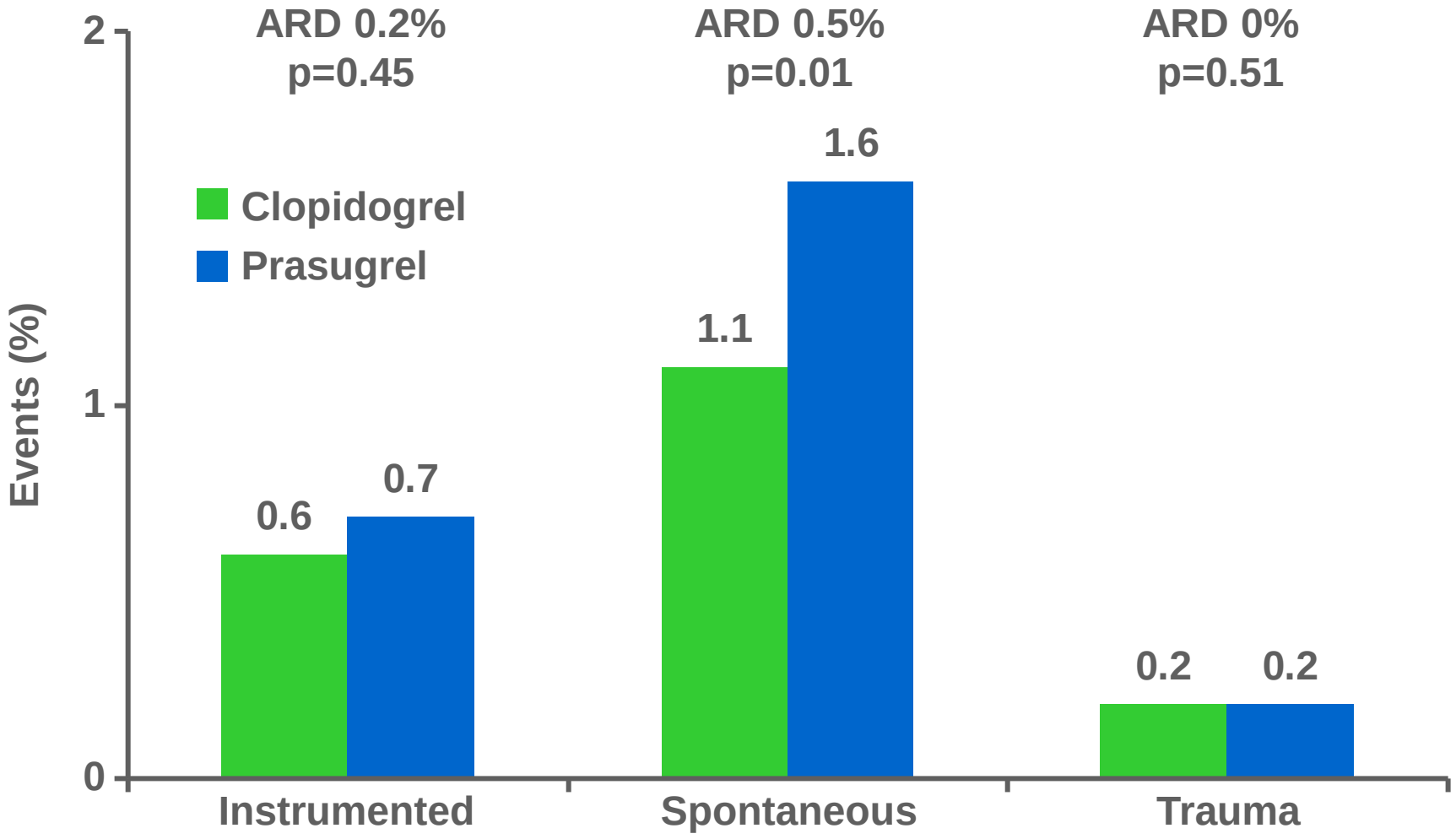
Wiviott SD, et al. Lancet 2008;370:1353–63

Components of endpoints



Wiviott SD, et al. N Engl J Med 2007;357:2001–15

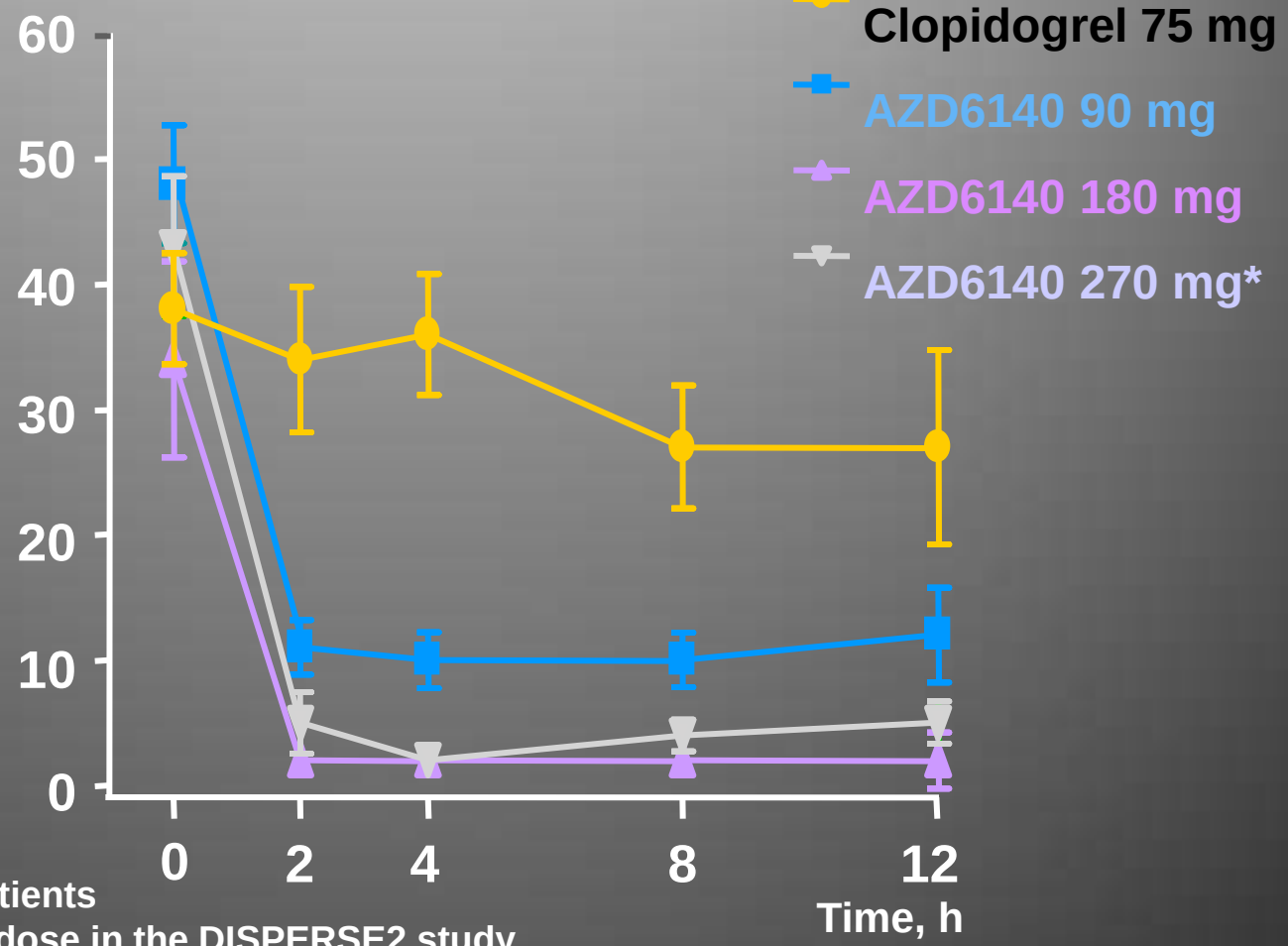
Types of major bleeds (n=13,457)



Wiviott SD, et al. N Engl J Med 2007;357:2001–15

DISPERSE 2 substudy in patients on chronic clopidogrel treatment

Mean ADP-induced platelet aggregation, final extent (% ±SEM)



Note: Substudy included 44 patients
*270 mg dose was the loading dose in the DISPERSE2 study

Storey R et al. Presented at ACC 2006, Atlanta

Which anticoagulant?

- Unfractionated heparin
- LMWH (enoxaparin)
- Bivalirudin
- Fondaparinux

TRITON TIMI 38 study goals

1. To test the hypothesis that higher and less variable IPA prevents clinical ischaemic 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 moderate/high risk patients with ACS undergoing PCI on a background of aspirin

Wiviott SD, et al. N Engl J Med 2007;357:2001–15

Index procedure

	Clopidogrel n=6,795 (%)	Prasugrel n=6,813 (%)
PCI/CABG	99/1	99/1
Any stent	95	94
Bare-metal stent	47	48
Drug-eluting stent	47	47
Multi-vessel PCI	14	14
UFH/LMWH/bivalirudin	65/8/3	66/9/3
GP IIb/IIIa inhibitor	55	54
Loading dose of study therapy		
Pre-PCI	25	26
During PCI	74	73
Post-PCI	1	1

CABG = coronary artery bypass graft
UFH = unfractionated heparin
LMWH = low molecular weight heparin

Wiviott SD, et al. N Engl J Med 2007;357:2001–15

Baseline characteristics

	Clopidogrel n=6,795 (%)	Prasugrel n=6,813 (%)
UA/NSTEMI	74	74
STEMI	26	26
Age, median (IQR), years	61 (53–70)	61 (57–69)
≥75 years	13	13
Female	27	25*
Diabetes	23	23
Prior MI	18	18
Creatinine clearance (mL/min)		
≥60	88	89
<60	12	11

IQR = interquartile range
*p<0.05

Wiviott SD, et al. N Engl J Med 2007;357:2001–15

Conclusions: higher IPA to support PCI

Prasugrel 60mg loading dose/10mg maintenance dose versus clopidogrel 300mg loading dose/75mg maintenance dose

	Efficacy	Safety
1. A significant reduction in:		Significant increase in serious bleeding (32% increase)
CV death/MI/stroke	19%	
Stent thrombosis	52%	
Urgent target-vessel revascularisation	34%	
MI	24%	
2. An early and sustained benefit		Avoid in patients with prior CVA/TIA
3. Across ACS spectrum		

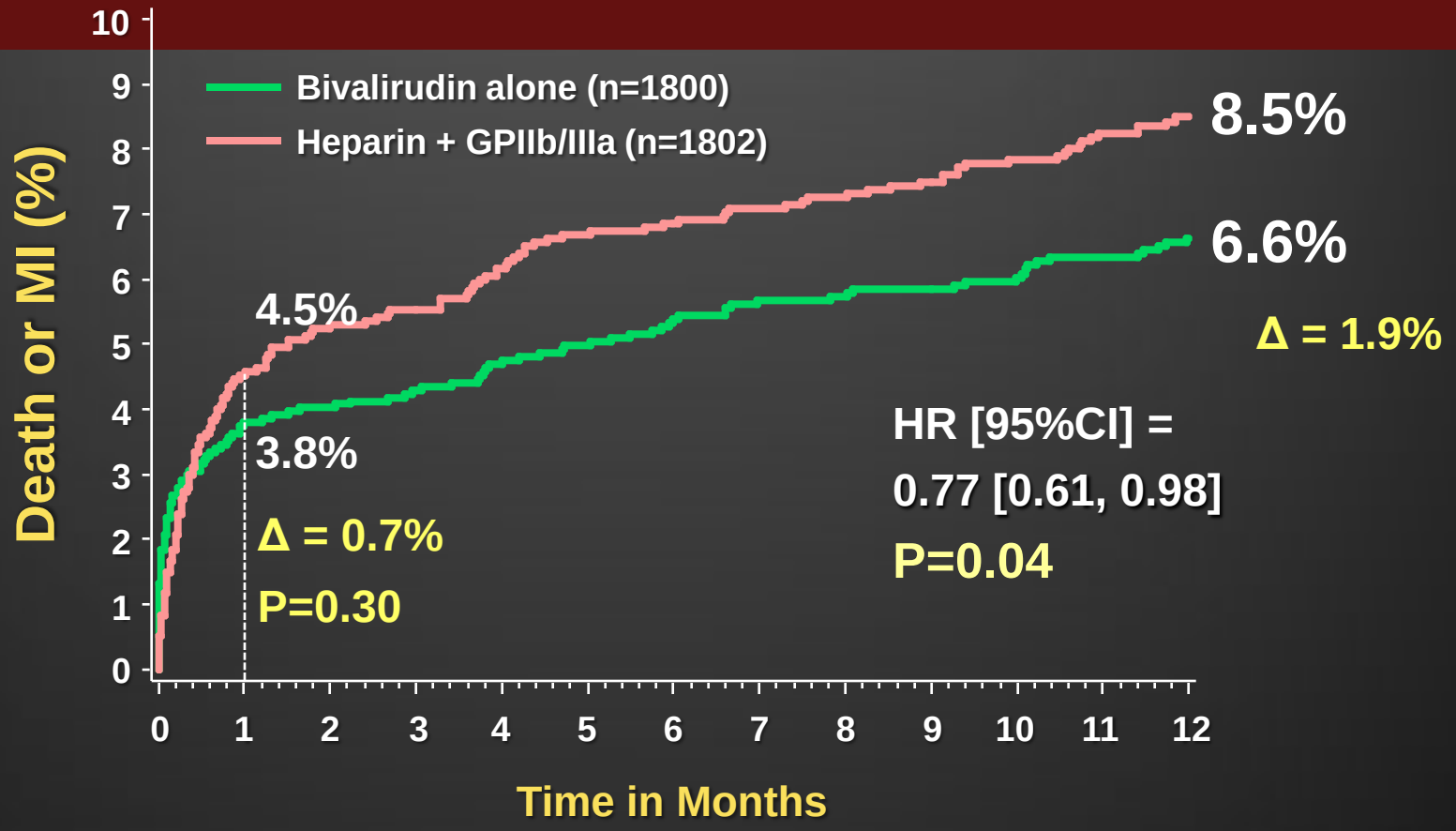
Net clinical benefit significantly favoured prasugrel

Optimisation of prasugrel maintenance dosing in a minority of patients may help improve the benefit:risk balance

ACS = acute coronary syndrome

Wiviott SD, et al. Lancet 2008;371:1353–63
Wiviott SD, et al. N Engl J Med 2007;357:2001–15

1-Year Death or MI: Stone TCT 2008



Number at risk					
Bivalirudin alone	1800	1670	1638	1617	1469
Heparin+GPIIb/IIIa	1802	1648	1617	1593	1431