

Nouveaux anti-agrégants et anti-thrombotiques dans le syndrome coronarien aigu

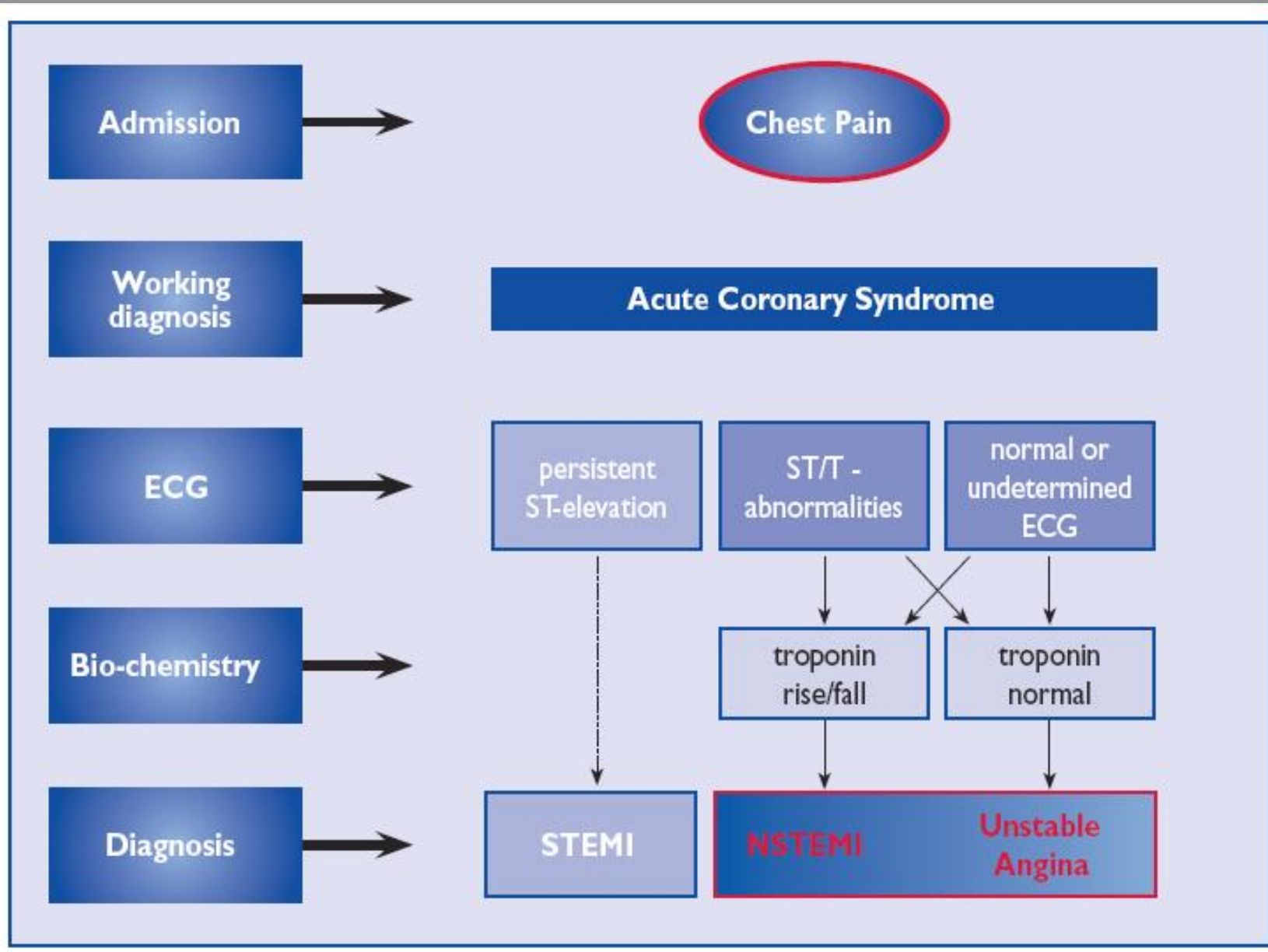
Daniel R. Wagner
Bourginster, Février 2012



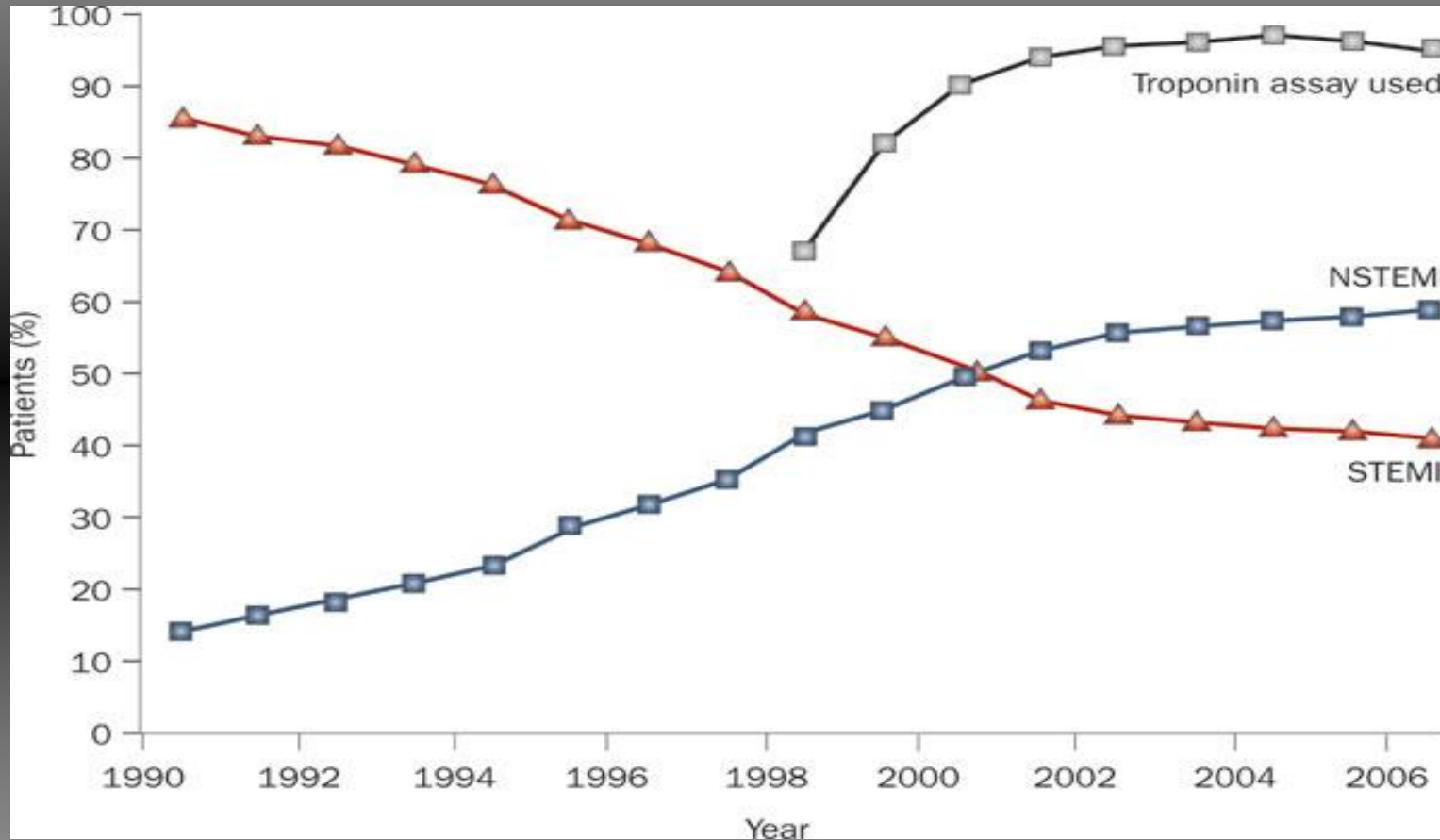
Agenda

- ◆ ACS: background
- ◆ New kid on the block # 1: Prasugrel
- ◆ New kid on the block # 2: Ticagrelor
- ◆ New kid on the block # 3: Rivaroxaban
- ◆ ACS: guidelines ESC 2010/2011
- ◆ Our favorite





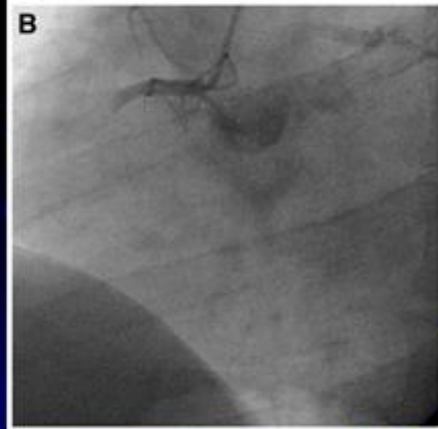
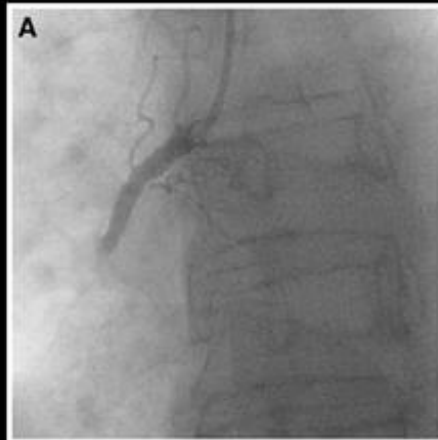
Prevalence of STEMI and NSTEMI



EF/ELB/04/2010/252



60 min



6 Hours

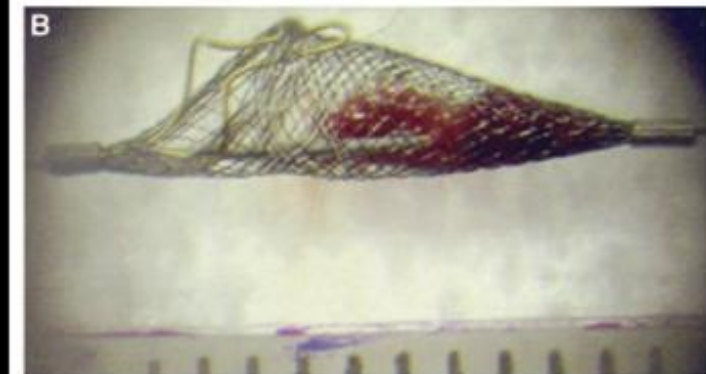
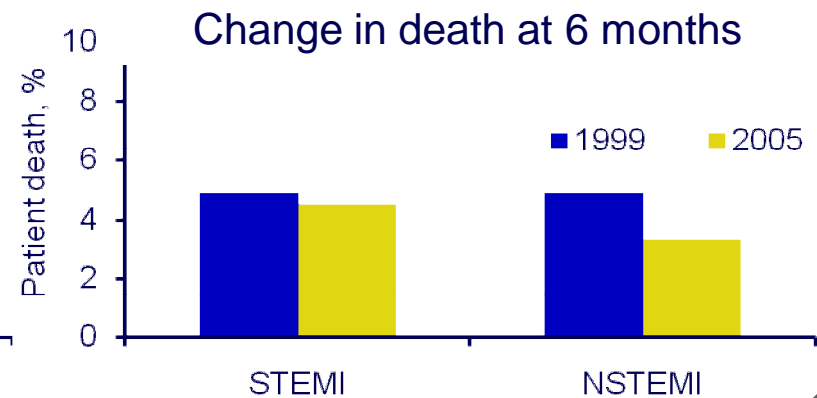
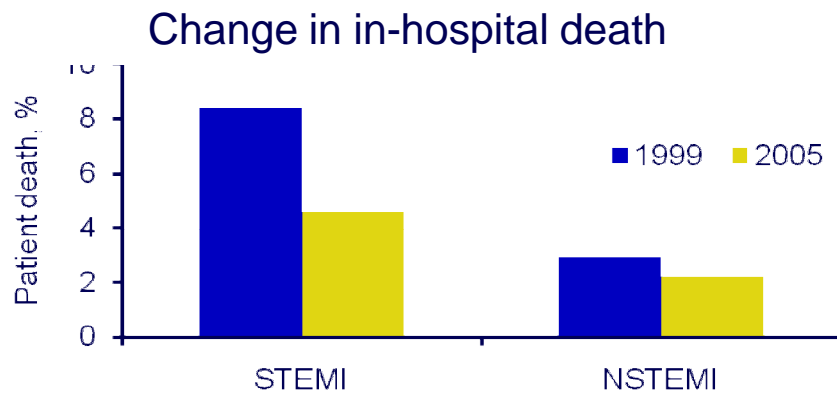
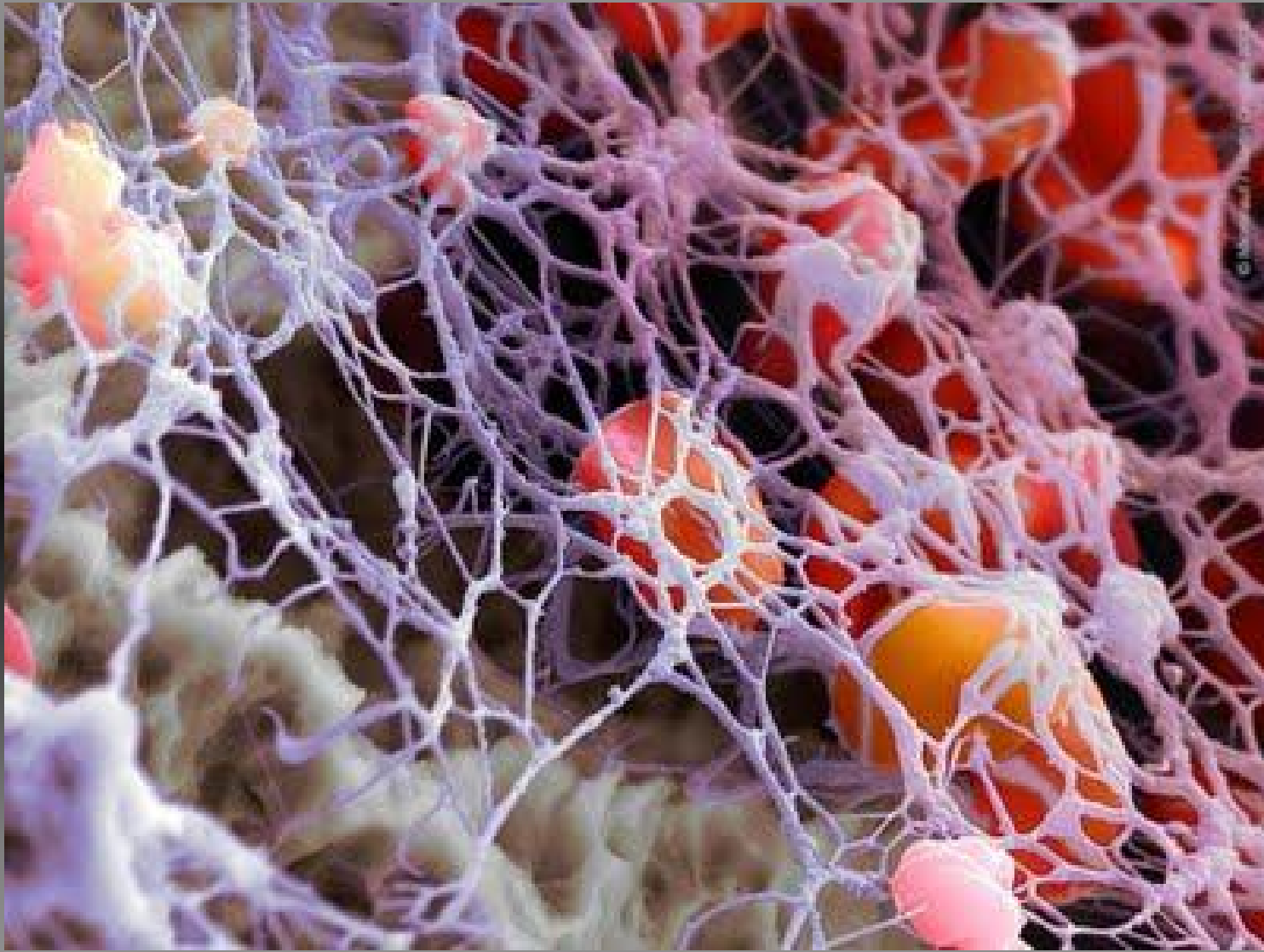


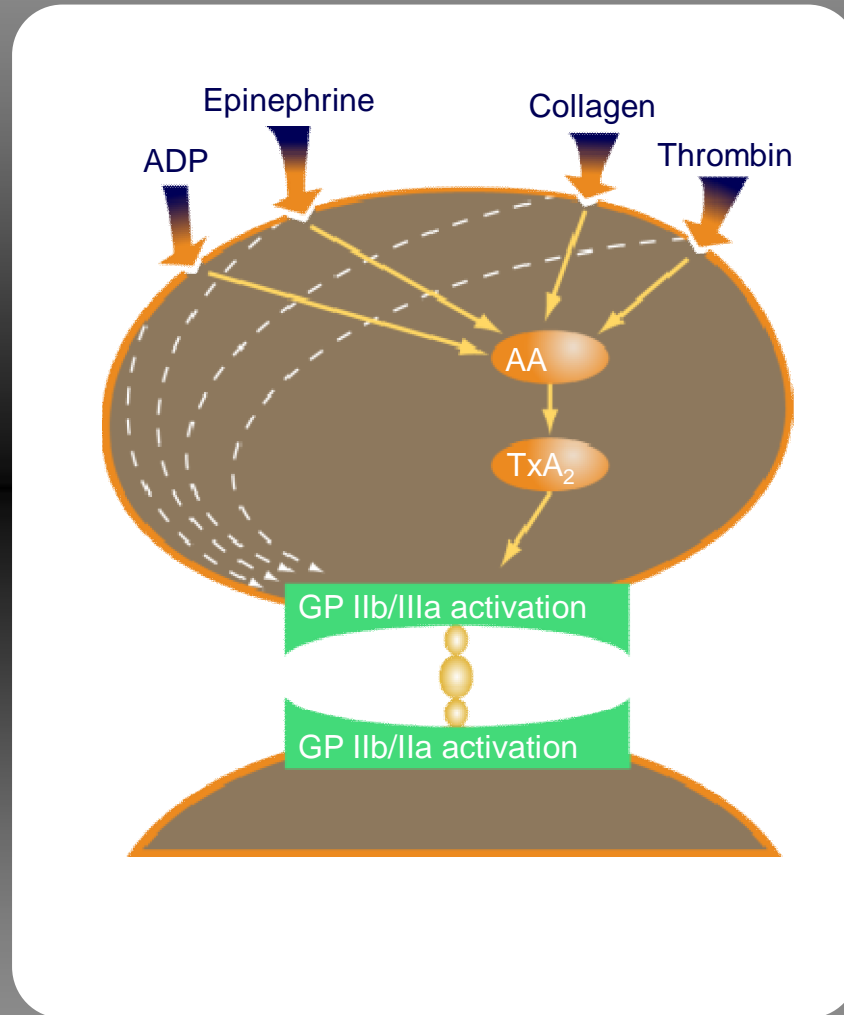
Figure 4. White (A) and red (B) thrombus trapped in the Spider filters in patients 1 and 2.

Clinical outcomes



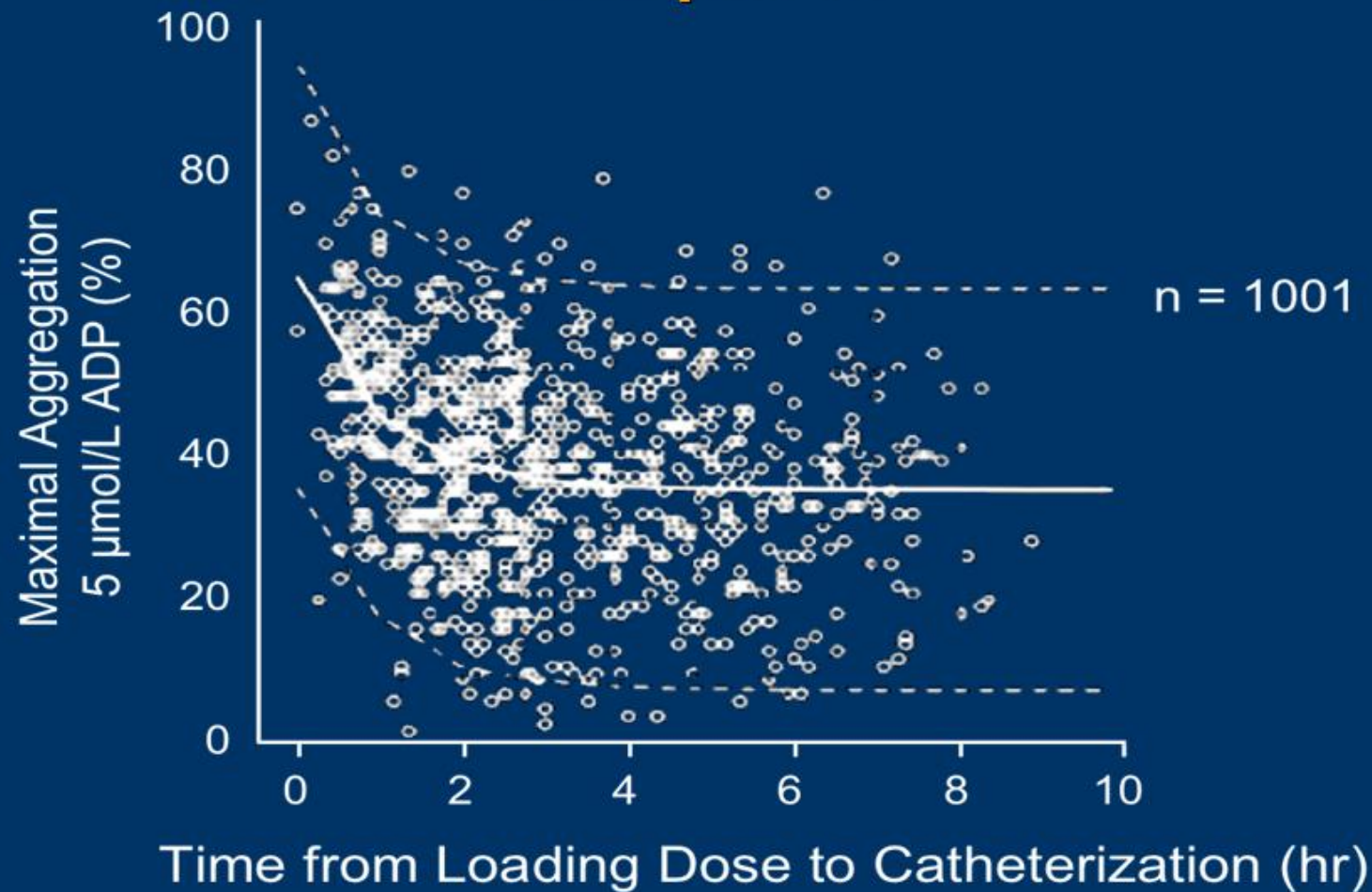


Platelet activation



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Variability in Inter-Individual Clopidogrel Response



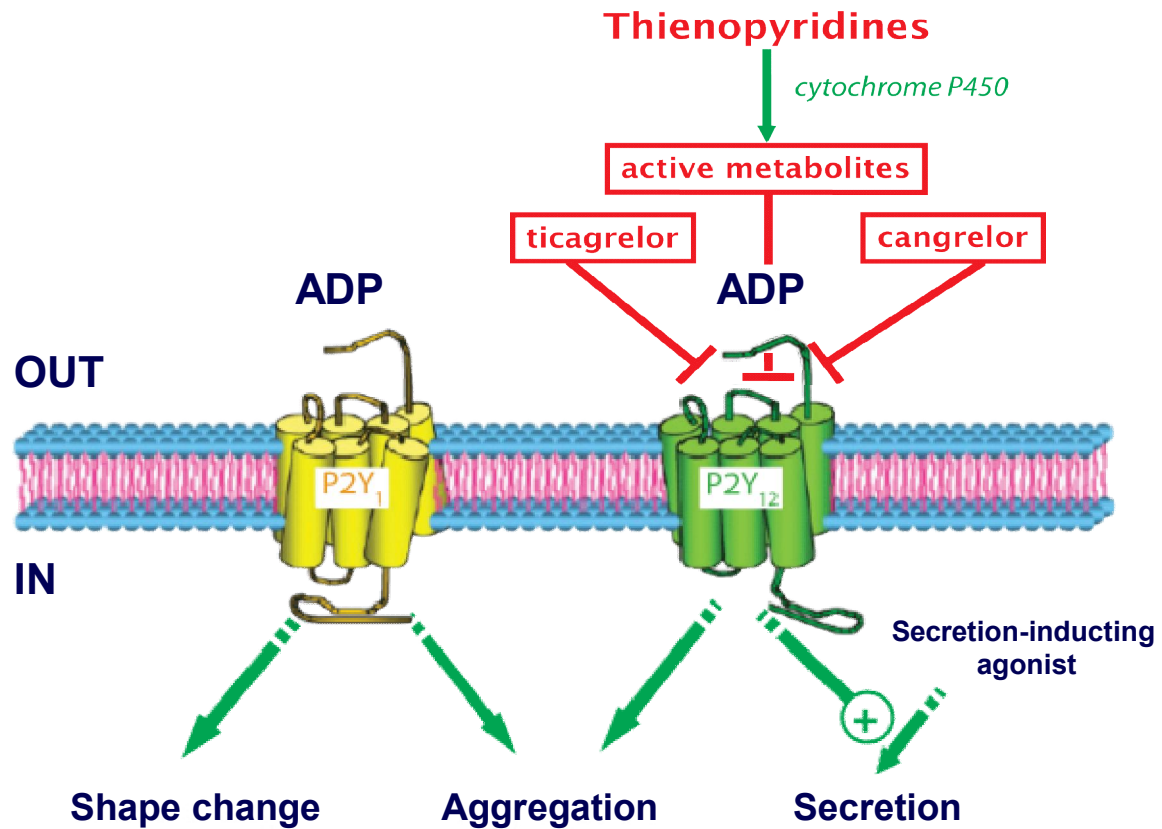
Poor clopidogrel responders with ACS: RECLOSE 2 ACS

- 248/1789 patients had high residual platelet reactivity with clopidogrel/aspirin. 2 year F/u.
- If non-responder
 - cardiac mortality 9.7% vs. 4.3%
 - stent thrombosis 6% vs. 2.9%

GRAVITAS

- ◆ 5429 patients on the regular clopidogrel dose underwent platelet-function testing
- ◆ If high residual platelet reactivity: 150-mg
- ◆ At six months, the composite primary end point of cardiovascular death/MI/stent thrombosis was identical in both groups, at 2.3%.

P2Y₁₂ receptor

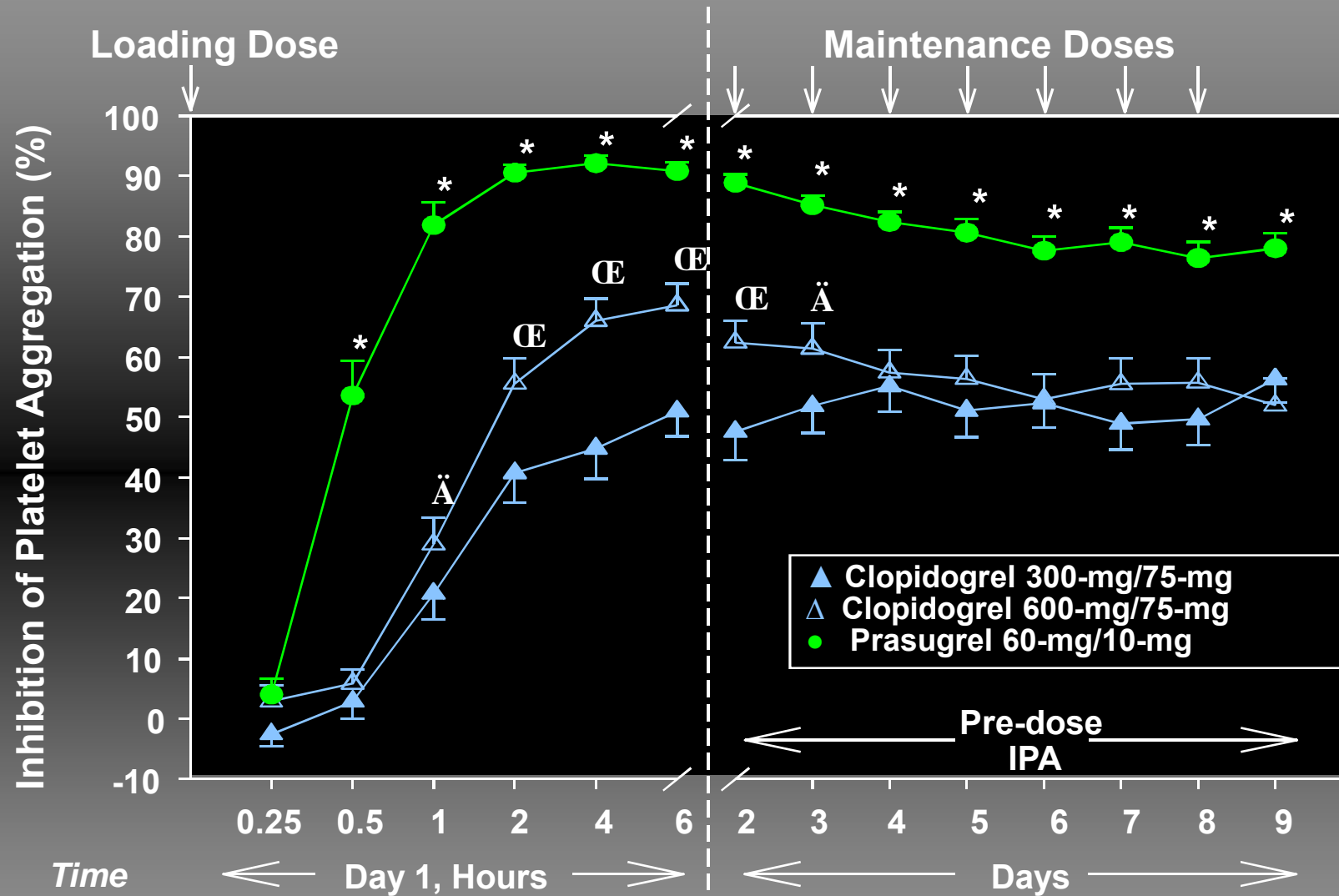


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Table 8 P2Y₁₂ inhibitors

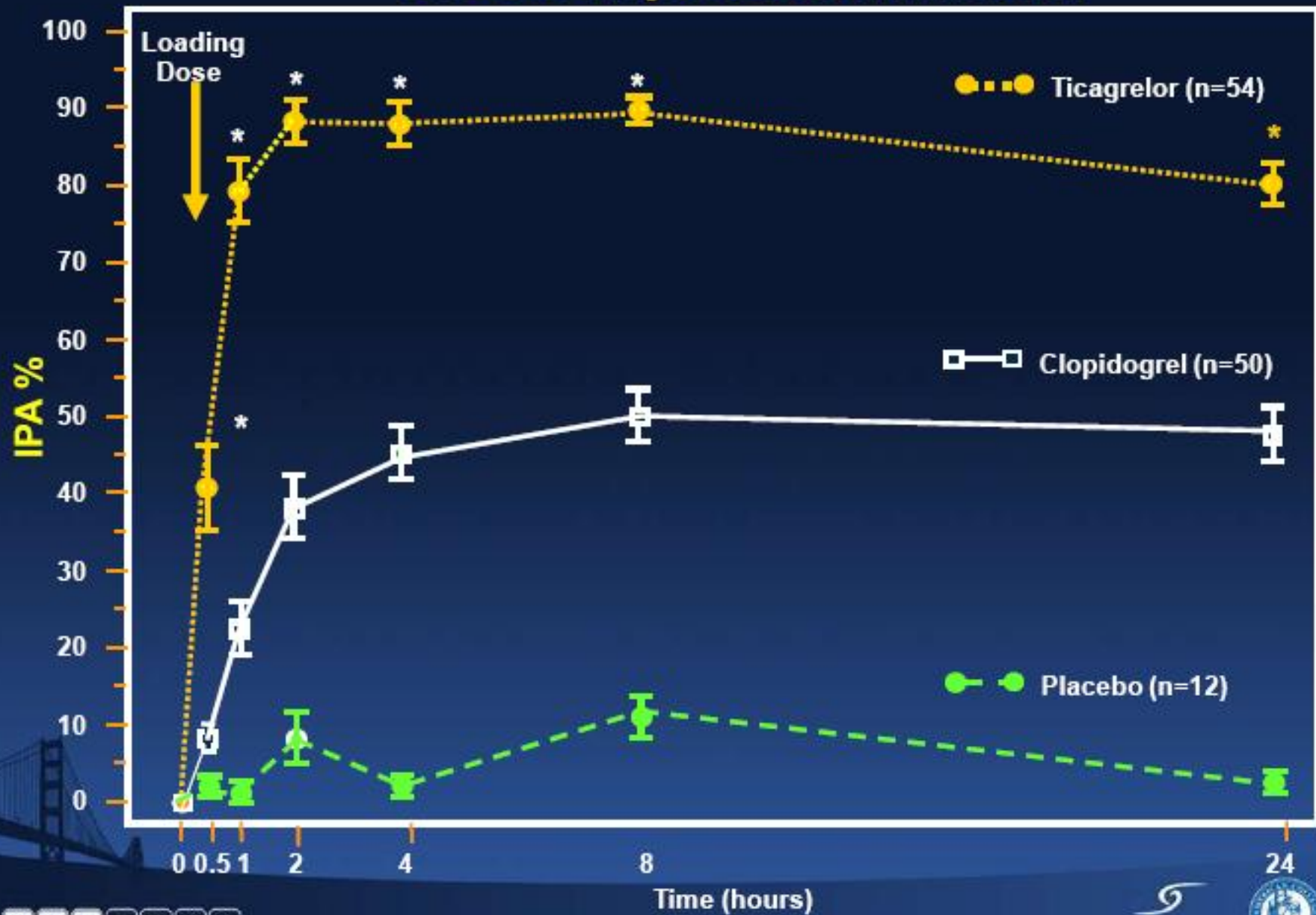
| | Clopidogrel | Prasugrel | Ticagrelor |
|---------------------------------|--------------------------------|------------------------------------|--------------------|
| Class | Thienopyridine | Thienopyridine | Triazolopyrimidine |
| Reversibility | Irreversible | Irreversible | Reversible |
| Activation | Prodrug, limited by metabolism | Prodrug, not limited by metabolism | Active drug |
| Onset of effect ^a | 2–4 h | 30 min | 30 min |
| Duration of effect | 3–10 days | 5–10 days | 3–4 days |
| Withdrawal before major surgery | 5 days | 7 days | 5 days |

Inhibition of Platelet Aggregation

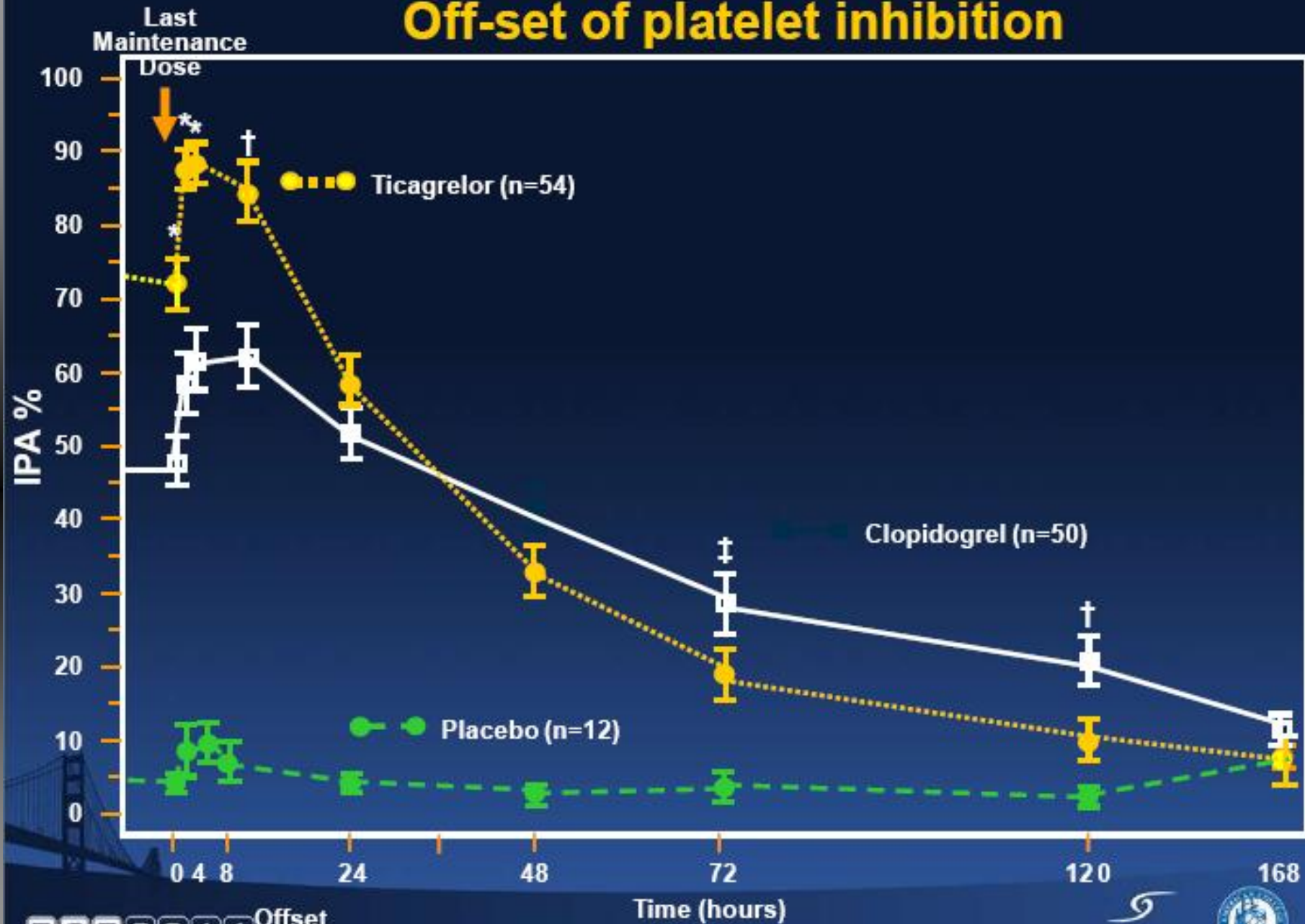


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On-set of platelet inhibition



Off-set of platelet inhibition



TCT 2011 Offset

(Gurbel PA et al. *Circulation*, 2009)



20210214/111111

Criteria for minor and minimal bleeding

| TIMI | PLATO |
|---------------------|--|
| <i>Minor</i> | <i>Minor</i> |
| hemoglobin 3-5 g/dL | Requires medical intervention to stop or treat bleeding |
| <i>Minimal</i> | <i>Minimal</i> |
| hemoglobin <3 g/dL | All others not requiring intervention (eg, bruising, bleeding gums, oozing from injection sites, etc) |

Definition of major bleeding criteria

| TIMI | PLATO |
|-------------------------|--|
| <i>Major</i> | <i>Major (fatal/life-threatening)</i> |
| Fatal | Fatal |
| Intracranial hemorrhage | Intracranial hemorrhage |
| ≥5 g/dL hemoglobin | ≥5 g/dL hemoglobin |
| | ≥4 unit transfusion |
| | Hypotension requiring pressors or surgery |

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TRITON TIMI-38

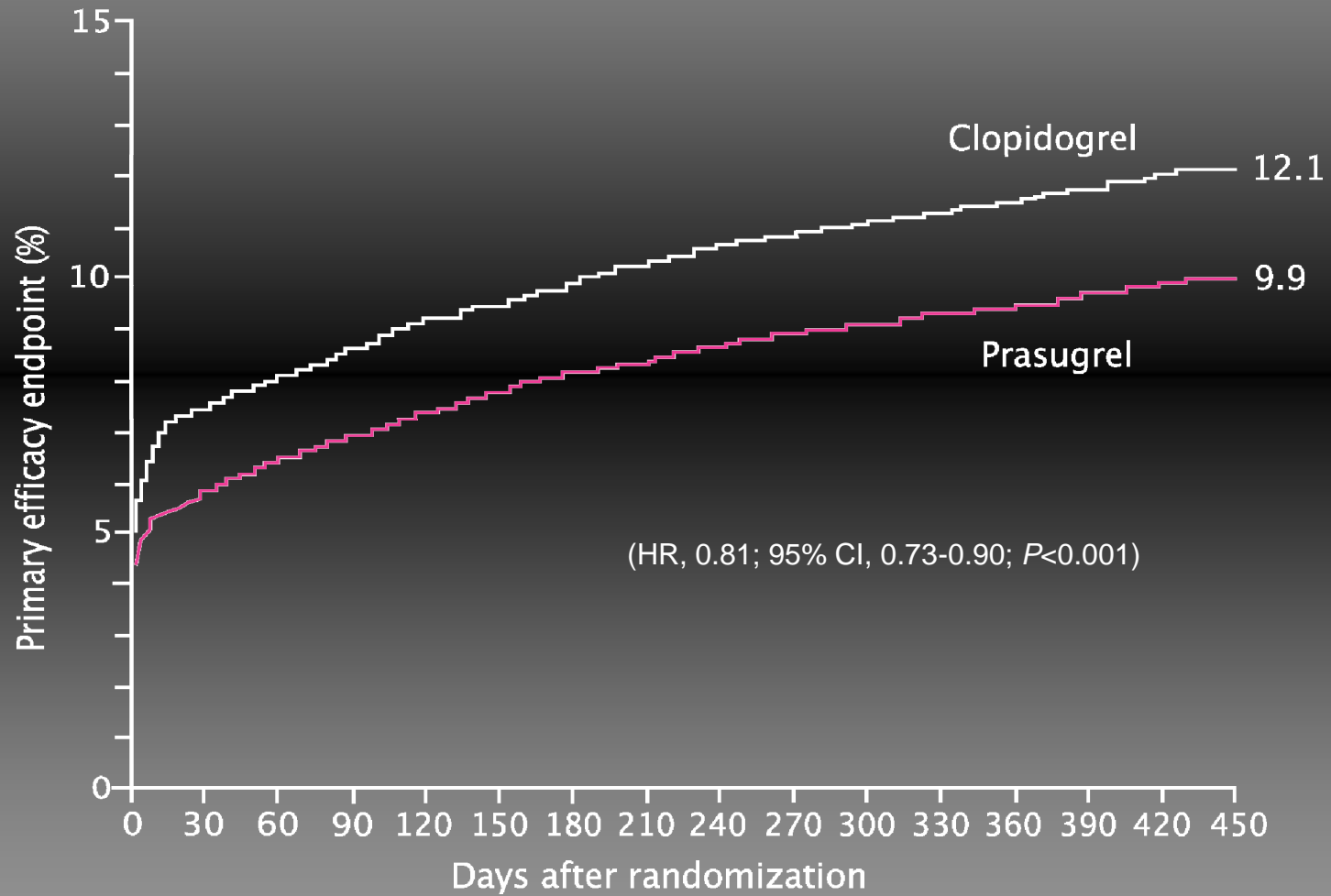
Acute coronary syndrome with scheduled PCI
All received aspirin (75-162 mg daily)
randomized within 72 hours (UA/NSTEMI) or 12 hours (STEMI)
of onset of symptoms
(N=13,608)

Prasugrel
Loading dose: 60 mg
Daily maintenance: 10 mg

Clopidogrel
Loading dose: 300 mg
Daily maintenance: 75 mg

TRITON TIMI-38

death from CV causes, nonfatal MI or nonfatal stroke



EF/ELB/04/2010/252

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

TRITON TIMI-38

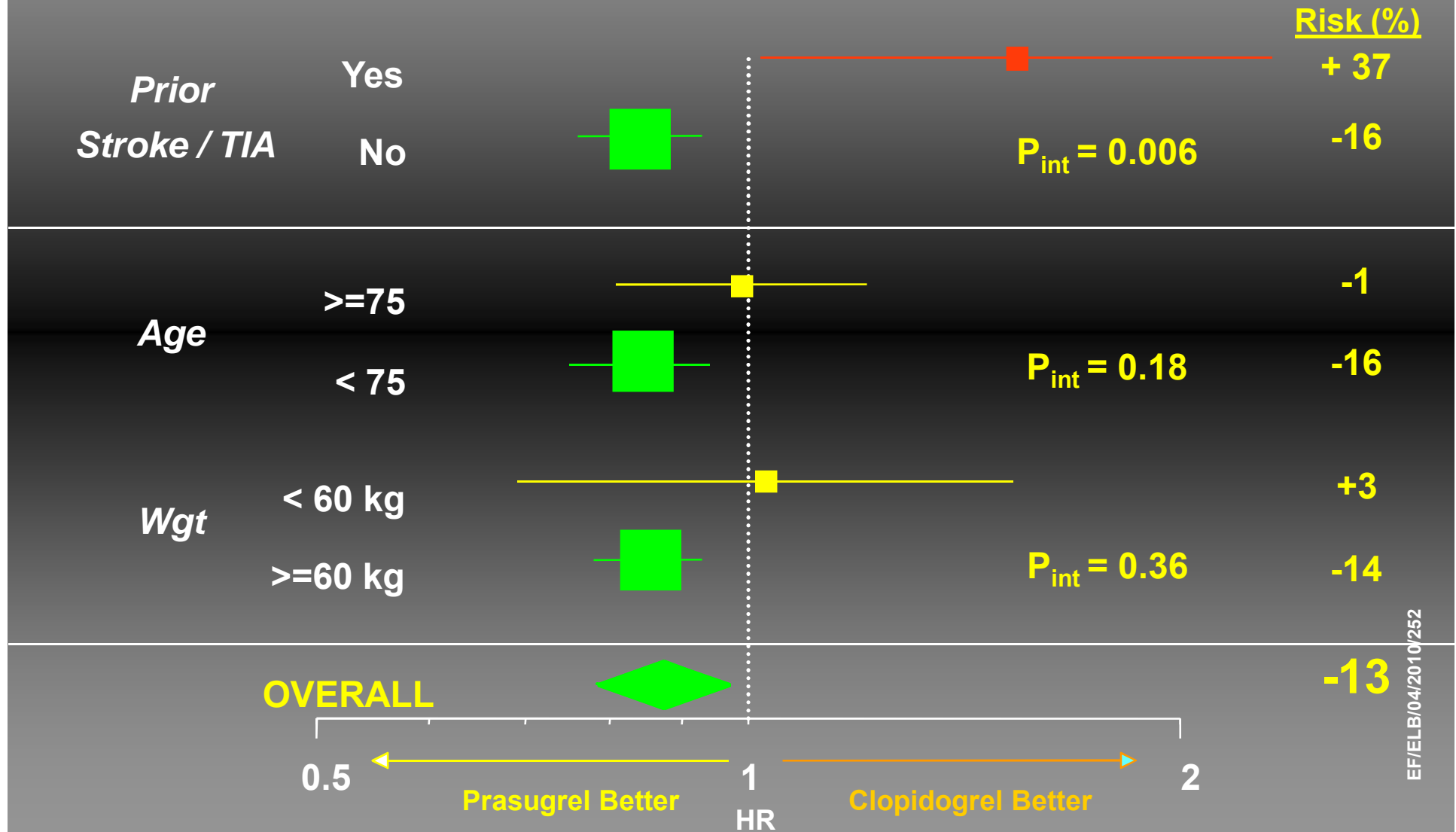
primary endpoint components and secondary endpoints

| Endpoint ^a | Prasugrel (N=6813) | Clopidogrel (N=6795) | Hazard ratio (95% CI) | P value |
|---|-----------------------|-------------------------|--------------------------|------------------|
| | N (%) | | | |
| CV death/nonfatal MI/nonfatal stroke | 643 (9.9) | 781 (12.1) | 0.81 (0.73-0.90) | <0.001 |
| CV death | 133 (2.1) | 150 (2.4) | 0.89 (0.70-1.12) | 0.31 |
| Nonfatal MI | 475 (7.3) | 620 (9.5) | 0.76 (0.67-0.85) | <0.001 |
| Nonfatal stroke | 61 (1.0) | 60 (1.0) | 1.02 (0.71-1.45) | 0.93 |
| Death from any cause | 188 (3.0) | 197 (3.2) | 0.95 (0.78-1.16) | 0.64 |
| Death from any cause, nonfatal MI, or nonfatal stroke | 797 (12.3) | 938 (14.6) | 0.84 (0.76-0.92) | <0.001 |
| Stent thrombosis | 68 (1.1) | 142 (2.4) | 0.48 (0.36-0.64) | <0.001 |

TRITON TIMI-38: bleeding endpoints

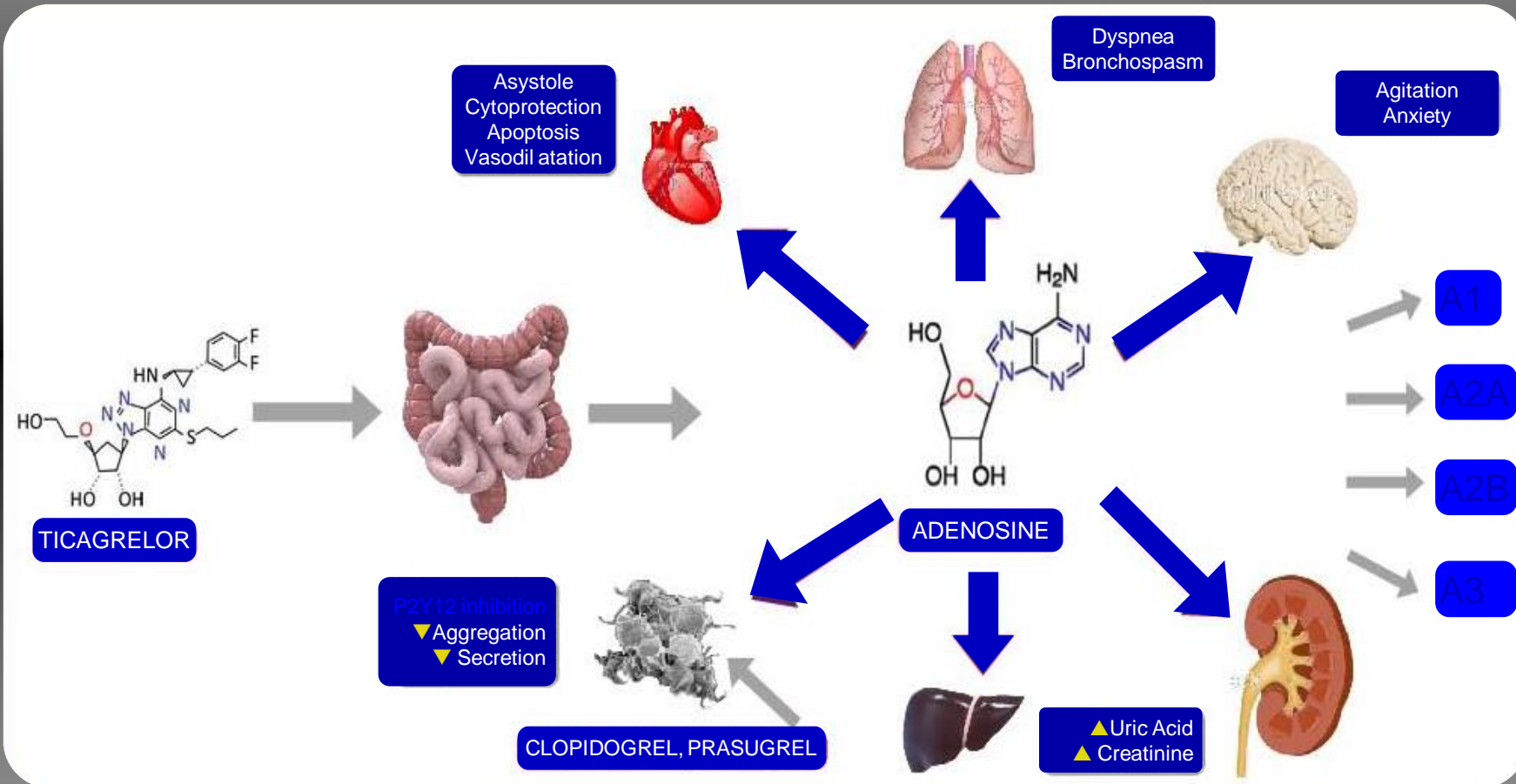
| Endpoint | Prasugrel | Clopidogrel | Hazard ratio (95% CI) | <i>P</i> value |
|-------------------------------------|-----------------|----------------|--------------------------|----------------|
| | N (%) | | | |
| NonCABG-related TIMI Major bleeding | 146 (2.4) | 111 (1.8) | 1.32 (1.03-1.68) | 0.03 |
| Life-threatening | 85 (1.4) | 56 (0.9) | 1.52 (1.08-2.13) | 0.01 |
| Fatal | 21 (0.4) | 5 (0.1) | 4.19 (1.58-11.11) | 0.002 |
| Nonfatal | 64 (1.1) | 51 (0.9) | 1.25 (0.87-1.81) | 0.23 |
| Intracranial | 19 (0.3) | 17 (0.3) | 1.12 (0.58-2.15) | 0.74 |
| Major or Minor TIMI bleeding | 303 (5.0) | 231 (3.8) | 1.31 (1.11-1.56) | 0.002 |
| Bleeding requiring transfusion | 244 (4.0) | 182 (3.0) | 1.34 (1.11-1.63) | <0.001 |
| CABG-related TIMI Major bleeding | 24 (13.4) | 6 (3.2) | 4.73 (1.90-11.82) | <0.001 |

TRITON-TIMI 38: Net Clinical Benefit Post-hoc Analyses in Selected Subgroups



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Ticagrelor



Study of PLAtelet Inhibition and Patient Otcomes PLATO

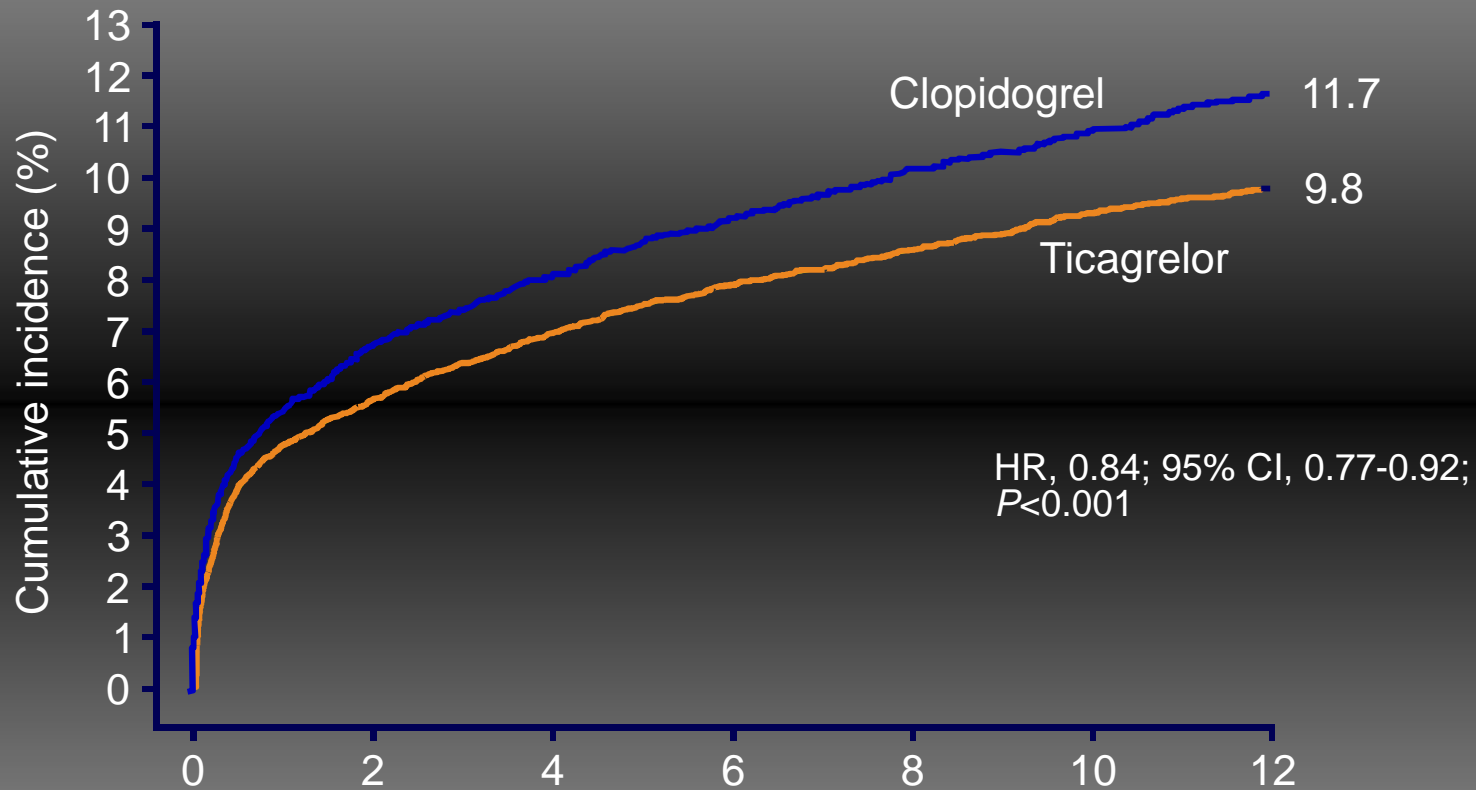
ACS patients with UA/NSTEMI (moderate-to-high risk) or STEMI (if primary PCI)
All received aspirin (75-100 mg daily); clopidogrel-treated or clopidogrel-naive;
randomized within 24 hours of index event
(N=18,624)

Clopidogrel
300 mg loading dose
then 75 mg od maintenance

Ticagrelor
180 mg loading dose, then
90 mg bid maintenance

PLATO

CV death, MI or stroke



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Wallentin L, et al. *N Engl J Med.* 2009;361:1045-1057.

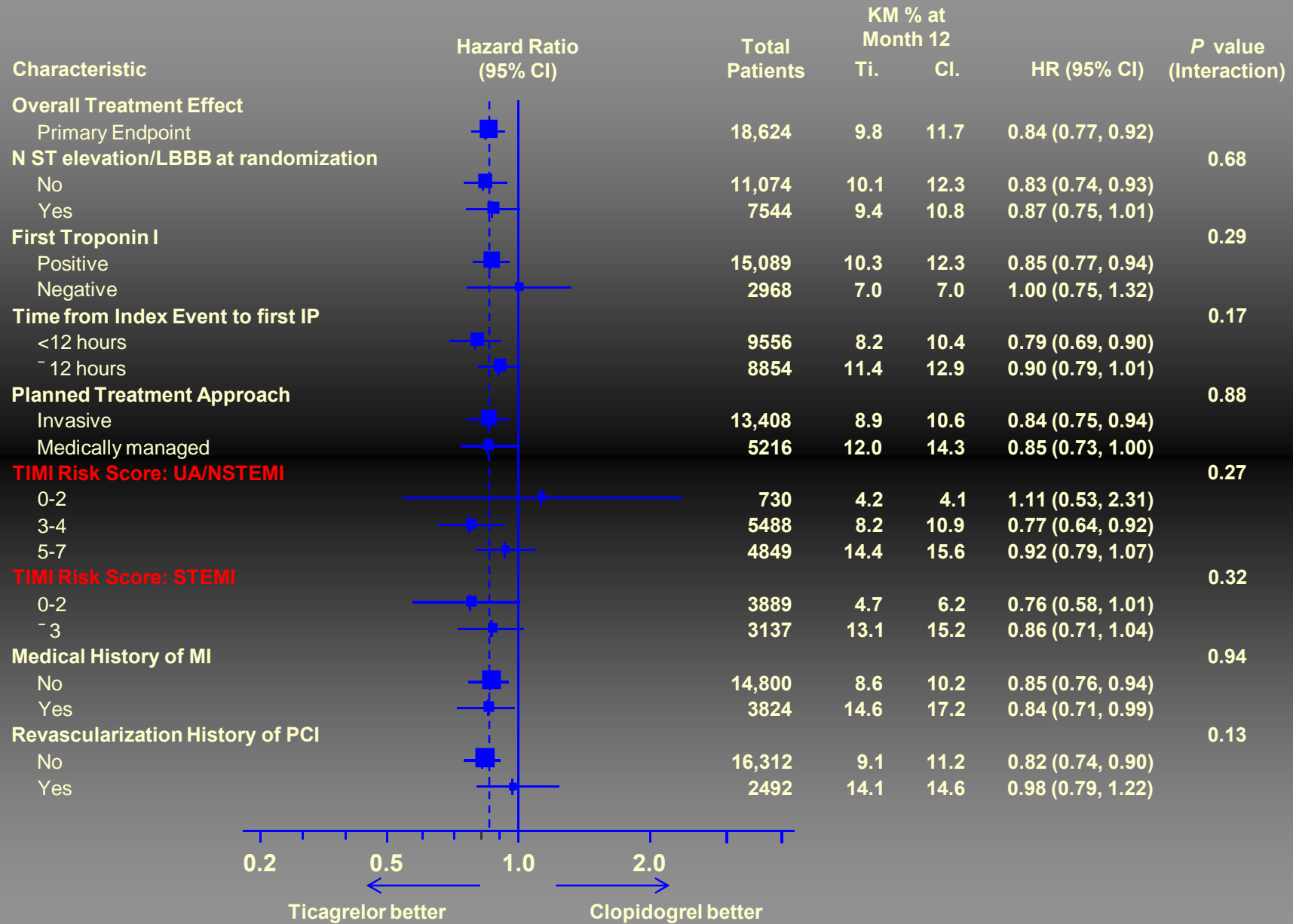
PLATO: secondary endpoints

| Endpoint | Ticagrelor (N=9333) n (%) | Clopidogrel (N=9291) n (%) | Hazard ratio (95% CI) | <i>P</i> value |
|--|---------------------------------|----------------------------------|--------------------------|------------------|
| Death from vascular causes, MI, or stroke in planned invasive treatment | 569 (8.9) | 668 (10.6) | 0.84 (0.75-0.94) | 0.003 |
| Death from any cause, MI, or stroke | 901 (10.2) | 1065 (12.3) | 0.84 (0.77-0.92) | <0.001 |
| CV death, MI, stroke, recurrent ischemia, TIA, or arterial thrombotic events | 1290 (14.6) | 1456 (16.7) | 0.88 (0.81-0.95) | <0.001 |
| MI | 504 (5.8) | 593 (6.9) | 0.84 (0.85-0.95) | 0.005 |
| Death from vascular causes | 353 (4.0) | 442 (5.1) | 0.79 (0.69-0.91) | 0.001 |
| Stroke | 125 (1.5) | 106 (1.3) | 1.17 (0.91-1.52) | 0.22 |
| Death from any cause | 399 (4.5) | 506 (5.9) | 0.78 (0.69-0.89) | <0.001 |

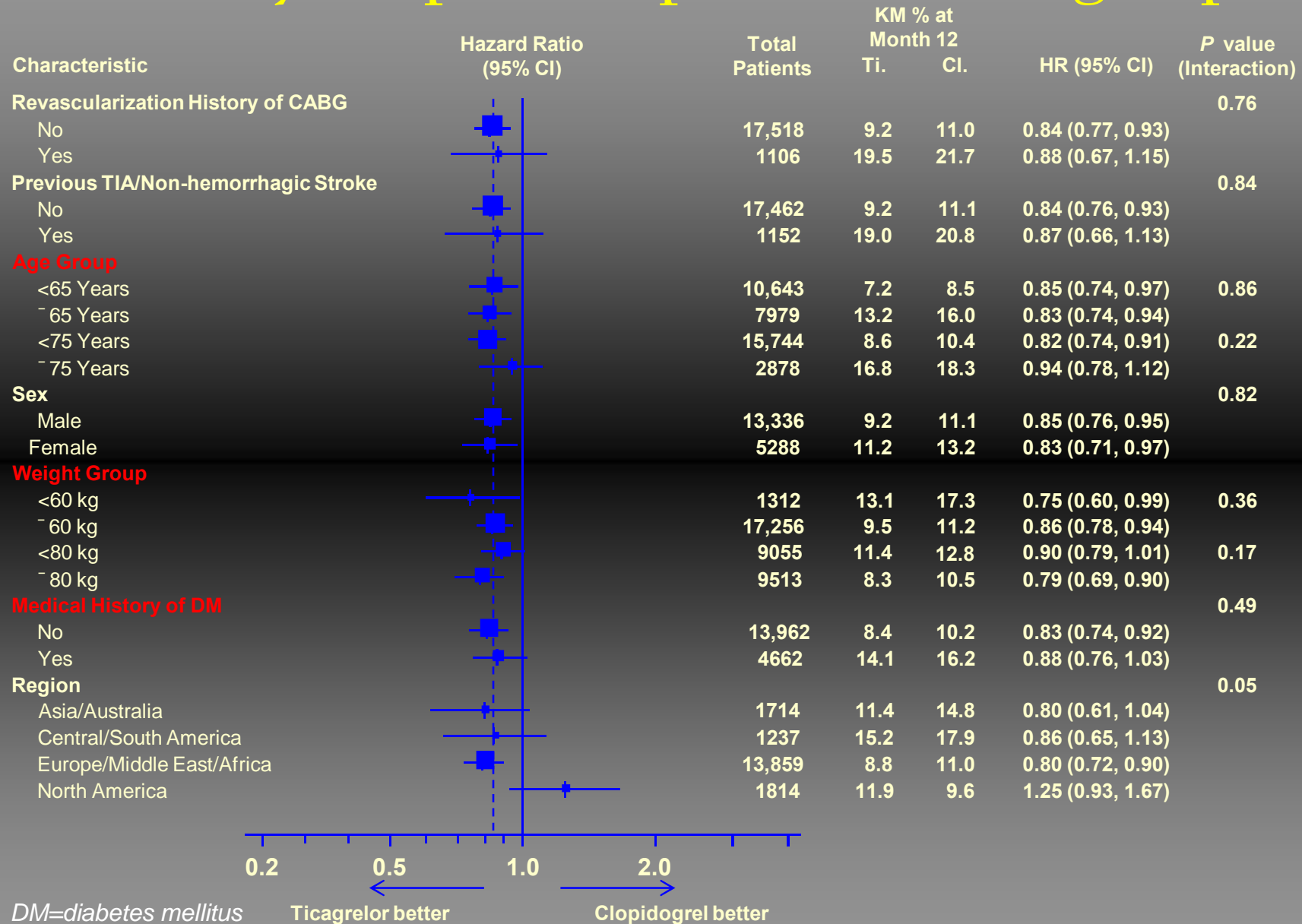
PLATO: stent thrombosis

| Patients with intent for invasive treatment* | Ticagrelor (n=6732) | Clopidogrel (n=6676) | HR for ticagrelor (95% CI) | Pvalue |
|--|---------------------|----------------------|----------------------------|--------|
| Stent thrombosis, n (%) | | | | |
| <i>Definite</i> | 71 (1.3) | 106 (1.9) | 0.67 (0.50-0.91) | 0.0091 |
| <i>Probable + Definite</i> | 118 (2.1) | 158 (2.8) | 0.75 (0.59-0.95) | 0.0167 |
| <i>Possible + Probable + Definite</i> | 155 (2.8) | 202 (3.6) | 0.77 (0.62-0.95) | 0.0131 |

Primary endpoint in predefined subgroups



Primary endpoint in predefined subgroups



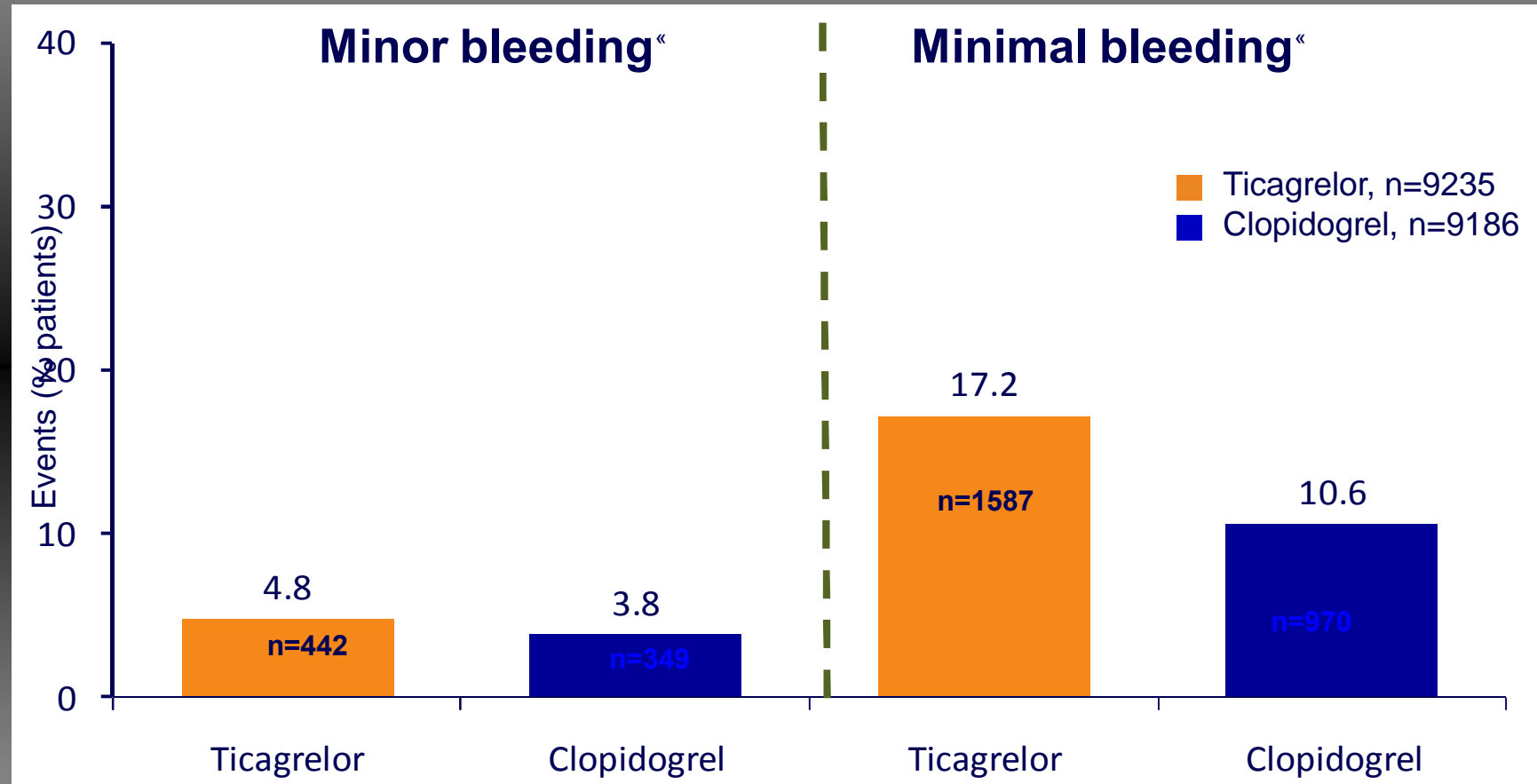
DM=diabetes mellitus
[Wallentin 2009-3:A]

Ticagrelor better

Clopidogrel better

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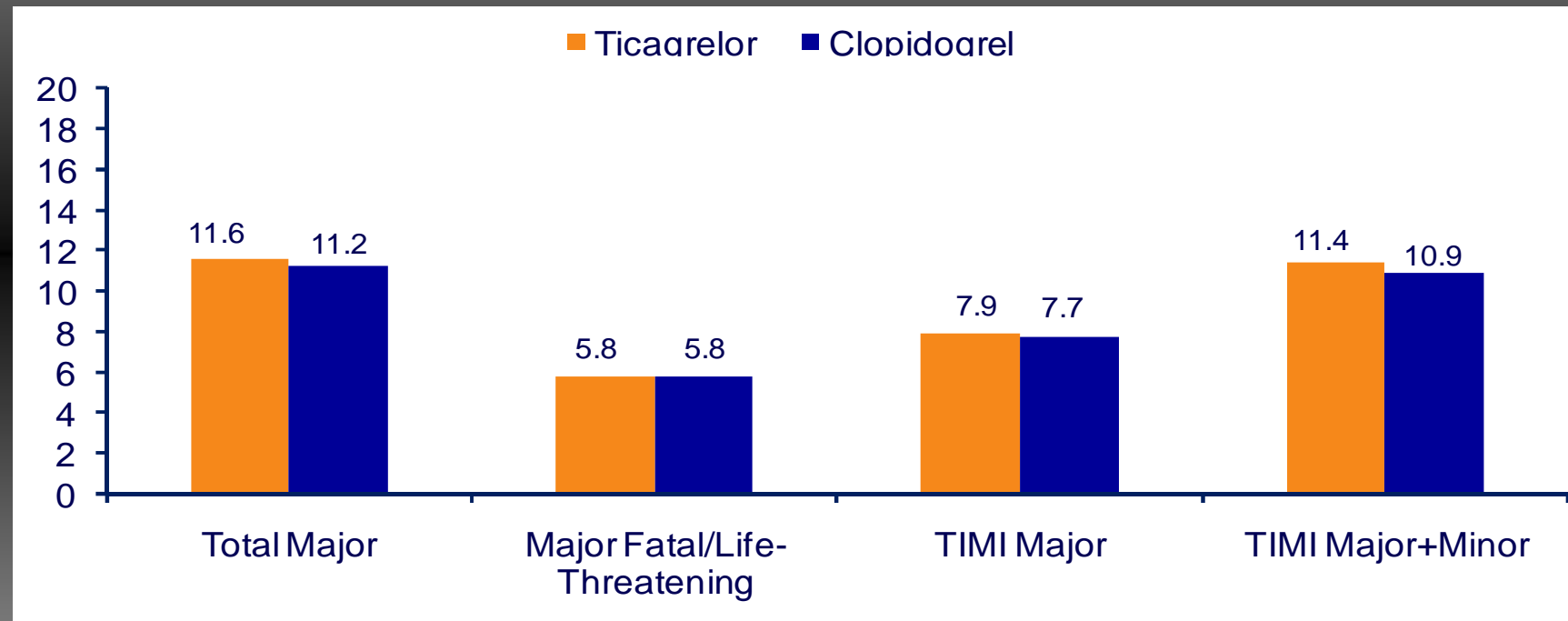
PLATO: minor and minimal bleeding



Major bleeding: PLATO and TIMI criteria

PLATO bleeding criteria

TIMI bleeding criteria



PLATO: total fatal bleeding

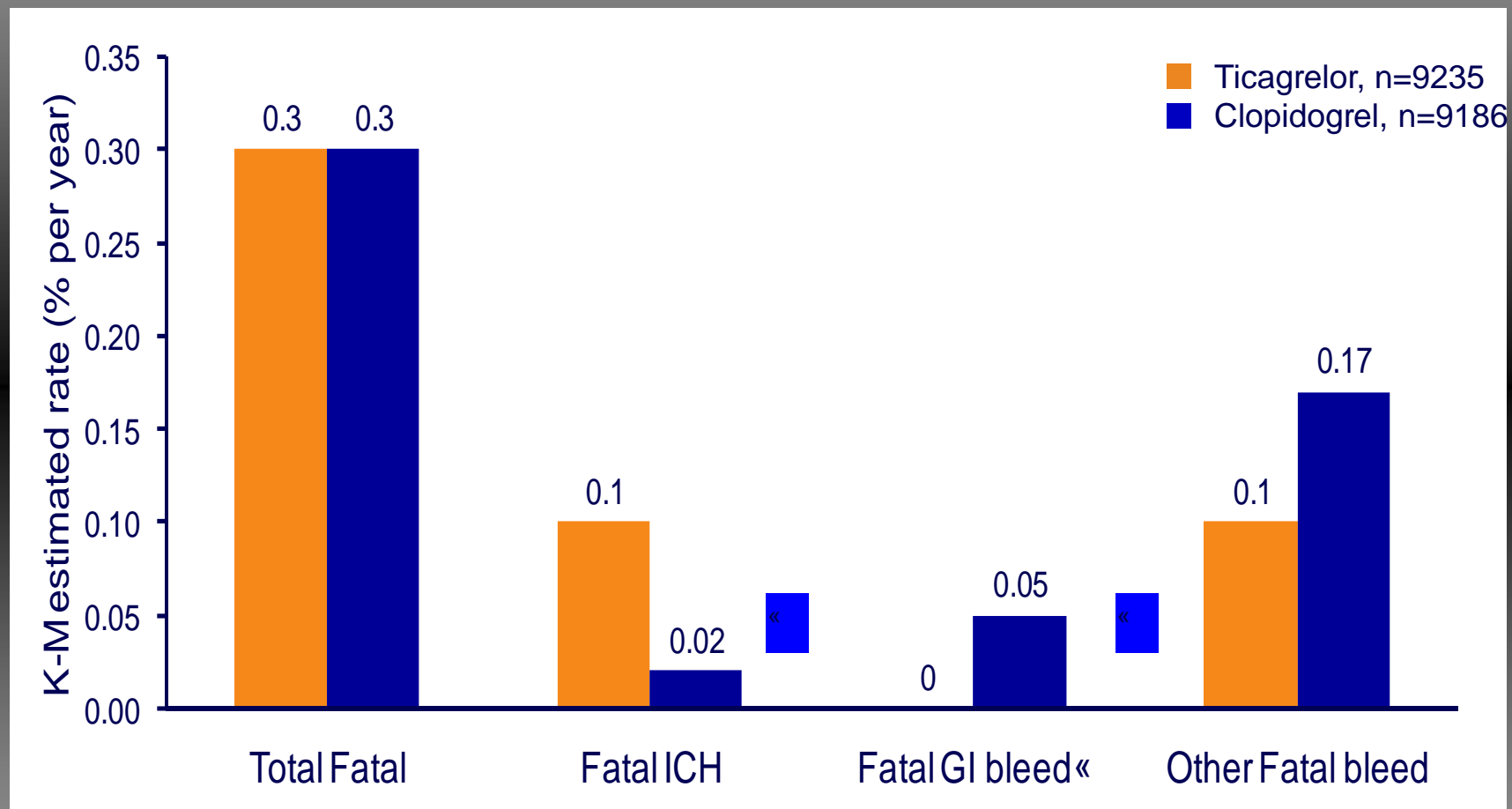


Table 3 Fatal bleeding: sites and management

| | Ticagrelor | Clopidogrel |
|--|------------|-------------|
| Total | 20 | 23 |
| Primary location of bleed ^a | | |
| Intracranial | 11 | 2 |
| Pericardial | 2 | 4 |
| Gastrointestinal | 0 | 5 |
| Cardiac cath/percutaneous coronary intervention access site | 2 | 2 |
| Subcutaneous/dermal | 0 | 2 |
| Retroperitoneal | 0 | 2 |
| Haemoptysis | 1 | 0 |
| Other bleeding site ^b | 5 | 7 |
| Not reported | 0 | 2 |

PLATO: bradycardia-related events

| All Patients | Ticagrelor (n=9235) | Clopidogrel (n=9186) | Pvalue |
|--------------------------------------|------------------------|-------------------------|--------|
| Bradycardia-related event | | | |
| <i>Pacemaker insertion</i> | 82 (0.9) | 79 (0.9) | 0.87 |
| <i>Syncope</i> | 100 (1.1) | 76(0.8) | 0.08 |
| <i>Bradycardia</i> | 409 (4.4) | 372 (4.0) | 0.21 |
| <i>Heart Block</i> | 67 (0.7) | 66 (0.7) | 1.00 |
| Holter monitor first week | (n=1451) | (n=1415) | |
| <i>Ventricular pauses ≥3 seconds</i> | 84 (5.8) | 51 (3.6) | 0.01 |
| <i>Ventricular pauses ≥5 seconds</i> | 29 (2.0) | 17 (1.2) | 0.10 |
| Holter monitor at 30 days | (n=985) | (n=1006) | |
| <i>Ventricular pauses ≥3 seconds</i> | 21 (2.1) | 17 (1.7) | 0.52 |
| <i>Ventricular pauses ≥5 seconds</i> | 8 (0.8) | 6 (0.6) | 0.60 |

PLATO: laboratory parameters

| All Patients | Ticagrelor (n=9,235) | Clopidogrel (n=9,186) | <i>P</i> value |
|---|-------------------------|--------------------------|----------------|
| Mean % increase (\pm SD) in serum creatinine from baseline | | | |
| At 1 month | 10 \pm 22 | 8 \pm 21 | <0.001 |
| At 12 months | 11 \pm 22 | 9 \pm 22 | <0.001 |
| 1 month after end of treatment | 10 \pm 22 | 10 \pm 22 | 0.59 |
| Mean % increase (\pm SD) in serum uric acid from baseline | | | |
| At 1 month | 14 \pm 46 | 7 \pm 44 | <0.001 |
| At 12 months | 15 \pm 52 | 7 \pm 31 | <0.001 |
| 1 month after end of treatment | 7 \pm 43 | 8 \pm 48 | 0.56 |

Dyspnea in PLATO

- Dyspnea was reported more frequently by patients on ticagrelor than clopidogrel (13.8% vs 7.8%; $P < 0.001$)
 - Most episodes lasted less than a week
 - Ticagrelor-associated dyspnea was mostly mild to moderate and did not affect efficacy
 - Determine BNP to exclude HF
- Few patients discontinued study drug because of dyspnea (0.9%)

Ticagrelor

◆ Bleeding

- Do not use if H/O intracranial hemorrhage
- STOP 5 days before CABG
- Suspect bleeding if hypotension

◆ Biliary Elimination and Metabolized by CYP3A4/5

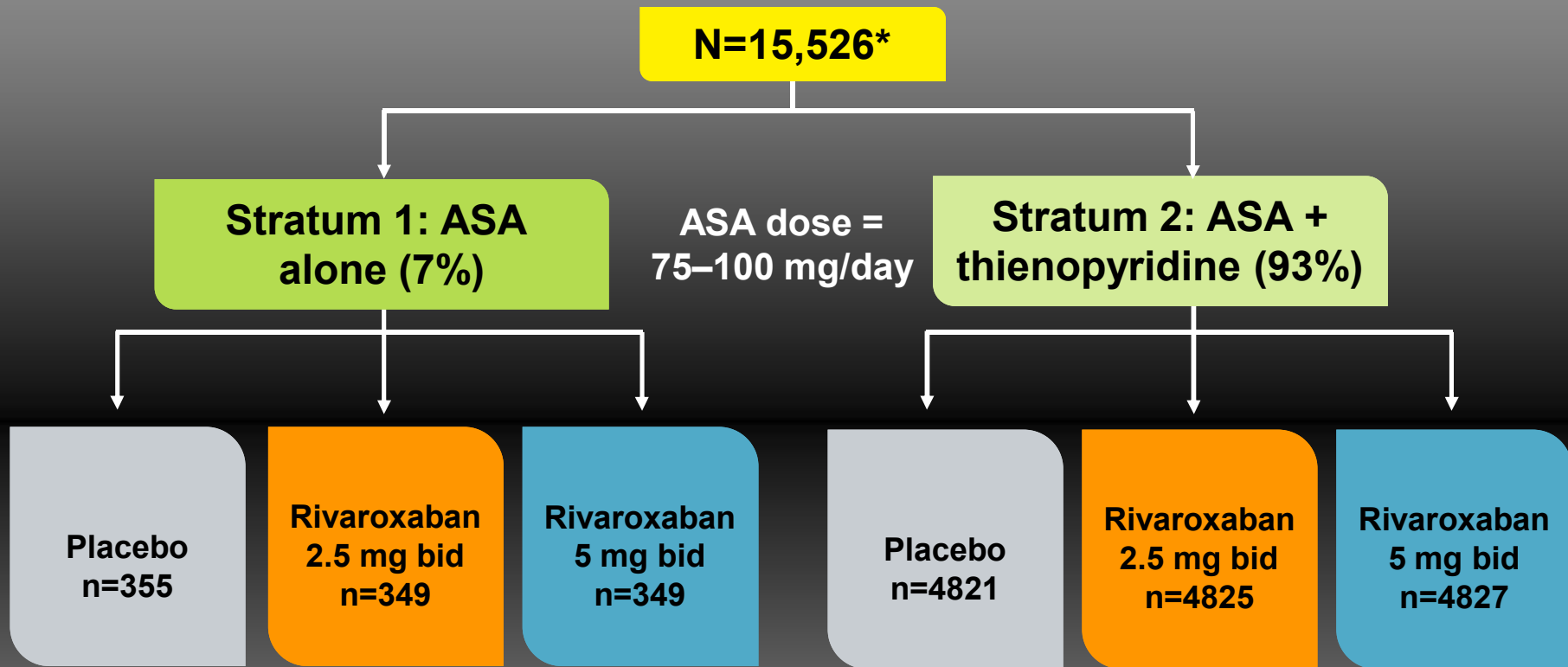
- Avoid simvastatin > 40 mg and lovastatin > 40 mg
- Avoid clarithromycin, ketoconazole and antivirals
- Monitor digoxin levels

PLATO Conclusions

Do you believe in magic?

- ◆ Highly significant reduction of mortality (HR 0.78, $p < 0.001$)
- ◆ The only other antiplatelet agent with mortality reduction: aspirin (ISIS-2)
- ◆ Benefit of Ticagrelor delayed and growing slowly:
ADENOSINE

ATLAS ACS 2 TIMI 51: UA/NSTEMI/STEMI



EF/ELB/04/2010/252

Mega et al, NEJM 2011

Efficacy

| | Rivaroxaban 2.5 mg bid (n=5114) | Rivaroxaban 5 mg bid (n=5115) | Placebo (n=5113) |
|--|---------------------------------------|-------------------------------------|---------------------|
| Composite primary endpoint | | | |
| K-M estimate at 2 years | 9.1% | 8.8% | 10.7% |
| HR versus placebo (95% CI) | 0.84 (0.72–0.97) | 0.85 (0.73–0.98) | |
| <i>p</i> value versus placebo | 0.02 | 0.03 | |
| CV death | | | |
| K-M estimate at 2 years | 2.7% | 4.0% | 4.1% |
| HR versus placebo (95% CI) | 0.66 (0.51–0.86) | 0.94 (0.75–1.20) | |
| <i>p</i> value versus placebo | 0.002 | 0.63 | |
| MI | | | |
| K-M estimate at 2 years | 6.1% | 4.9% | 6.6% |
| HR versus placebo (95% CI) | 0.90 (0.75–1.09) | 0.79 (0.65–0.97) | |
| <i>p</i> value versus placebo | 0.27 | 0.02 | |
| Stroke (haemorrhagic and ischaemic) | | | |
| K-M estimate at 2 years | 1.4% | 1.7% | 1.2% |
| HR versus placebo (95% CI) | 1.13 (0.74–1.73) | 1.34 (0.90–2.02) | |
| <i>p</i> value versus placebo | 0.56 | 0.15 | |

Safety

| | Rivaroxaban 2.5 mg bid (n=5115) | Rivaroxaban 5 mg bid (n=5110) | Placebo (n=5125) |
|-------------------------------------|---------------------------------------|-------------------------------------|---------------------|
| Non-CABG TIMI major bleed | | | |
| K-M estimate at 2 years | 1.8% | 2.4% | 0.6% |
| HR versus placebo (95% CI) | 3.46 (2.08–5.77) | 4.47 (2.71–7.36) | |
| <i>p</i> value versus placebo | <0.001 | <0.001 | |
| TIMI minor bleed | | | |
| K-M estimate at 2 years | 0.9% | 1.6% | 0.5% |
| HR versus placebo (95% CI) | 1.62 (0.92–2.82) | 2.52 (1.50–4.24) | |
| <i>p</i> value versus placebo | 0.09 | <0.001 | |
| TIMI medical attention bleed | | | |
| K-M estimate at 2 years | 12.9% | 16.2% | 7.5% |
| HR versus placebo (95% CI) | 1.79 (1.55–2.07) | 2.39 (2.08–2.75) | |
| <i>p</i> value versus placebo | <0.001 | <0.001 | |

ESC guidelines 2011: NSTEMI

12. Antiplatelet treatment

- Aspirin lifelong for all.
- A P2Y₁₂ inhibitor should be added and kept for 12 months unless there are contraindications such as excessive bleeding risk.
- Ticagrelor indicated in all-comers, prasugrel only prior PCI in clopidogrel naïve patients without prior stroke/TIA whose anatomy is known, clopidogrel if ticagrelor and prasugrel are not an option.
- Glycoprotein IIb/IIIa in high risk PCI patients, but not routinely upstream.
- A proton pump inhibitor in combination with DAPT is recommended in patients at risk with a previous history of gastrointestinal haemorrhage or peptic ulcer.

ESC guidelines 2011: NSTEMI

- Fondaparinux best benefit/ risk profile.
- Add UFH on top of fondaparinux in patients undergoing PCI.
- Enoxaparin in low bleeding risk patients.
- Other low molecular weight heparins or unfractionated heparin are less recommended options as they were not compared to fondaparinux.
- Bivalirudin in high risk bleeding as alternative to GP IIb/IIIa + UFH in patients undergoing PCI.

| | | | |
|--|-----|---|---------------|
| Crossover of heparins (UFH and LMWH) is not recommended. | III | B | 171, 183, 193 |
|--|-----|---|---------------|

ESC guidelines 2010: STEMI

| STEMI | | | | |
|-----------------------------|--|-----|---|----------|
| Antiplatelet therapy | | | | |
| | ASA | I | B | 55, 94 |
| | Clopidogrel ^f (with 600 mg loading dose as soon as possible) | I | C | — |
| | Prasugrel ^d | I | B | 246, 252 |
| | Ticagrelor ^d | I | B | 248, 253 |
| | + GPIIb–IIIa antagonists (in patients with evidence of high intracoronary thrombus burden) | | | |
| | Abciximab | IIa | A | 55, 94 |
| | Eptifibatide | IIa | B | 259, 260 |
| | Tirofiban | IIb | B | 55, 94 |
| | Upstream GPIIb–IIIa antagonists | III | B | 86 |
| Anticoagulation | | | | |
| | Bivalirudin (monotherapy) | I | B | 255 |
| | UFH | I | C | — |
| | Fondaparinux | III | B | 256 |

Take home message: No free lunch

◆ Bleeding

- Clopidogrel < Ticagrelor < Prasugrel

◆ Efficacy

- Clopidogrel < Prasugrel < Ticagrelor

◆ Side effects

- Clopidogrel = Prasugrel < Ticagrelor

STEMI (<12h)

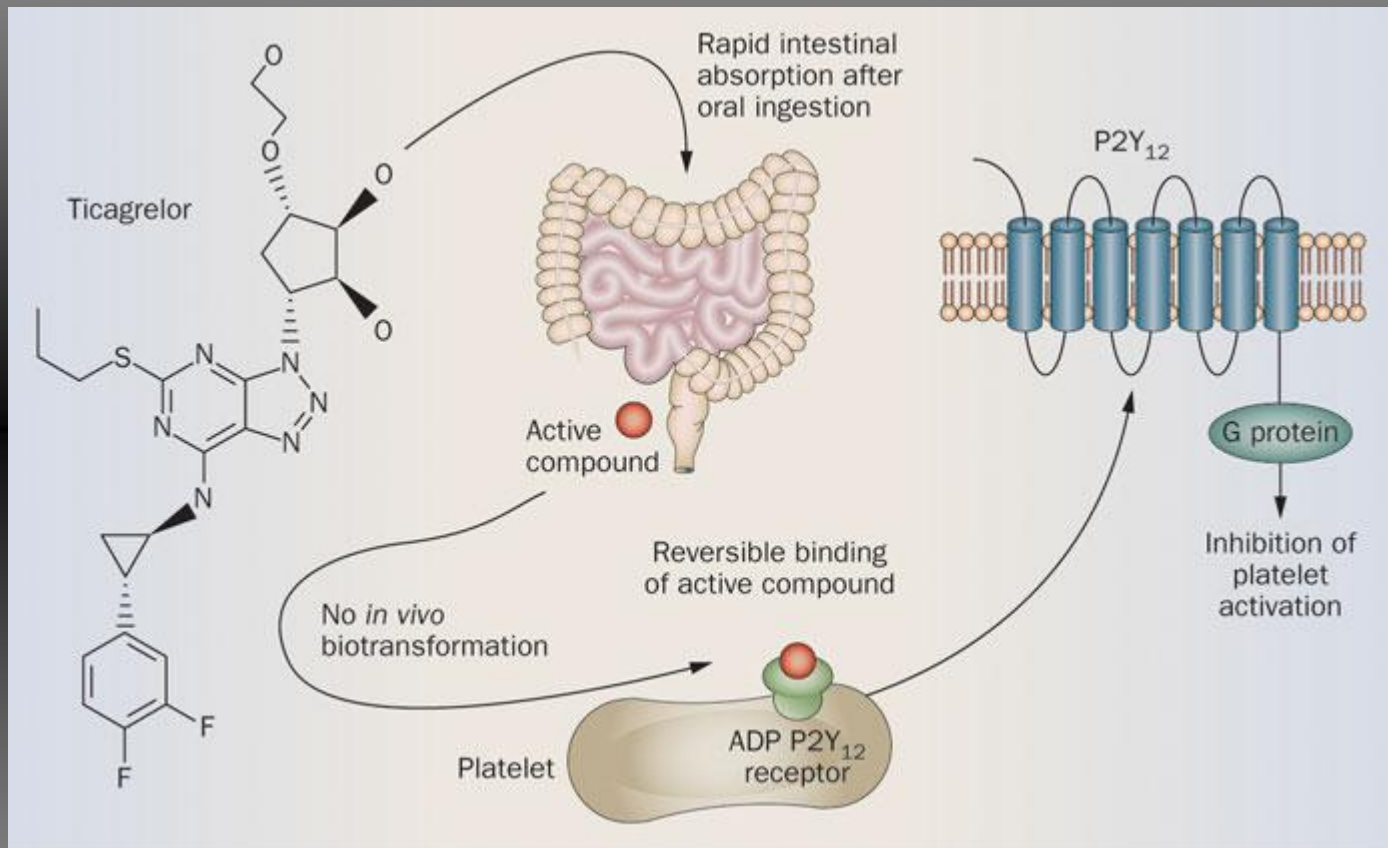


| Produit | Patients | Dose |
|--------------------------|---------------|-------------------|
| Aspirine | tous | 500 mg i.v. |
| Heparine | tous | 5000 u i.v. |
| Ticagrelor (Brilique) | Tous sauf AVC | 2 cp à 90 mg p.o. |

Transfert immédiat INCCI

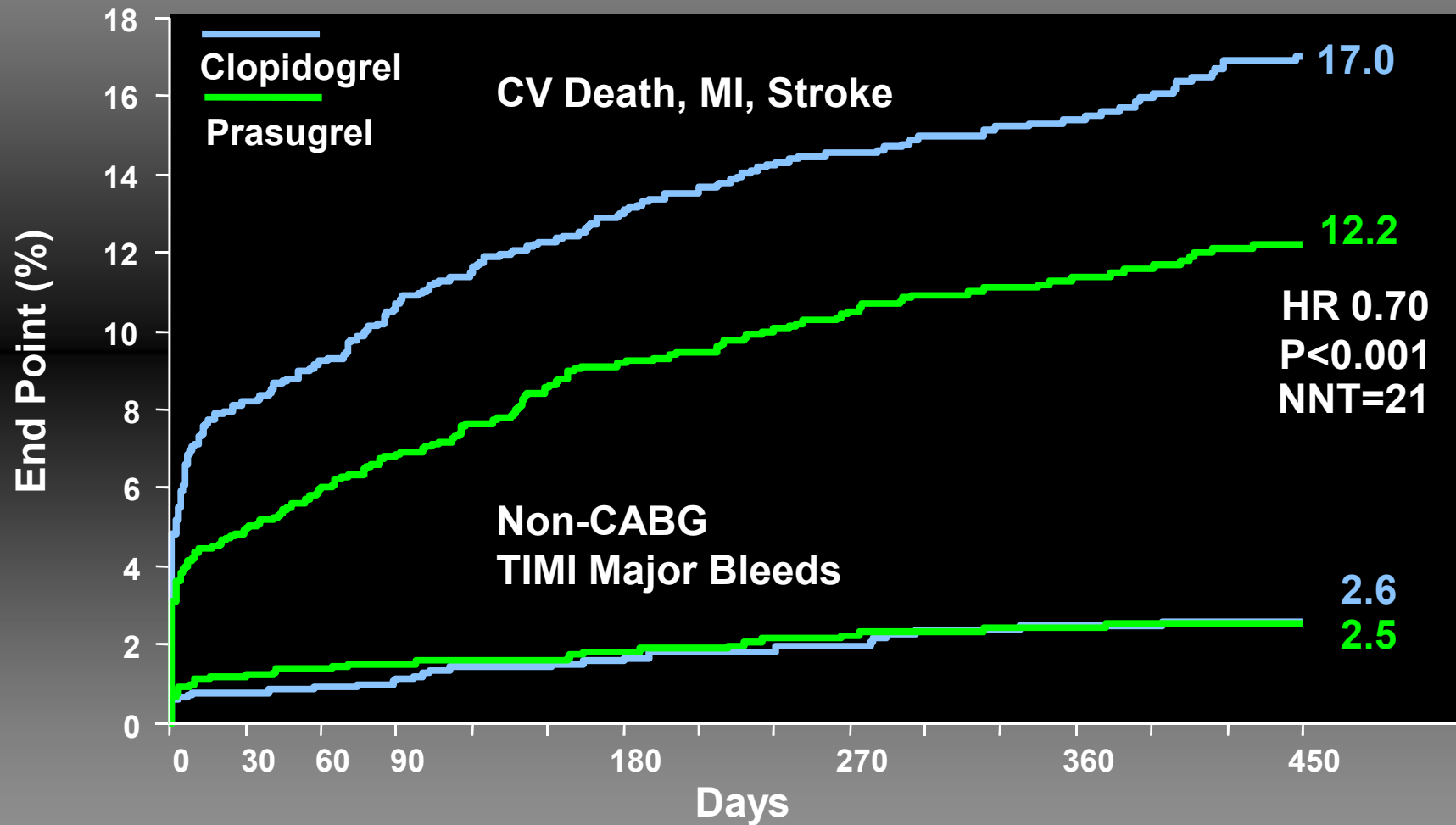
Telephone 2626 2727





Nature Reviews Cardiology, 2009

TRITON-TIMI 38: Diabetic Subgroup Analysis (n=3,146)



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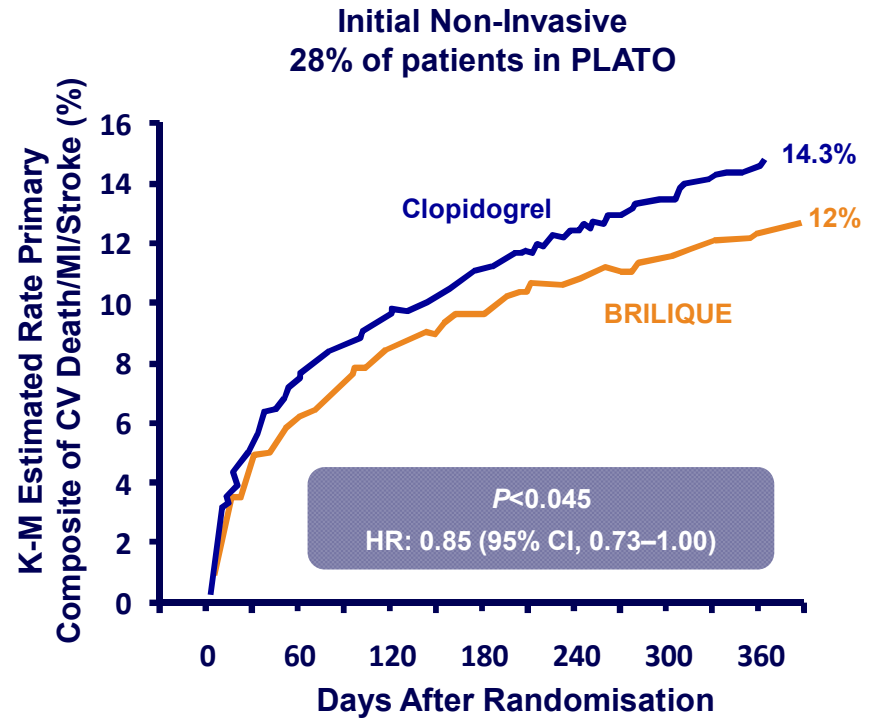
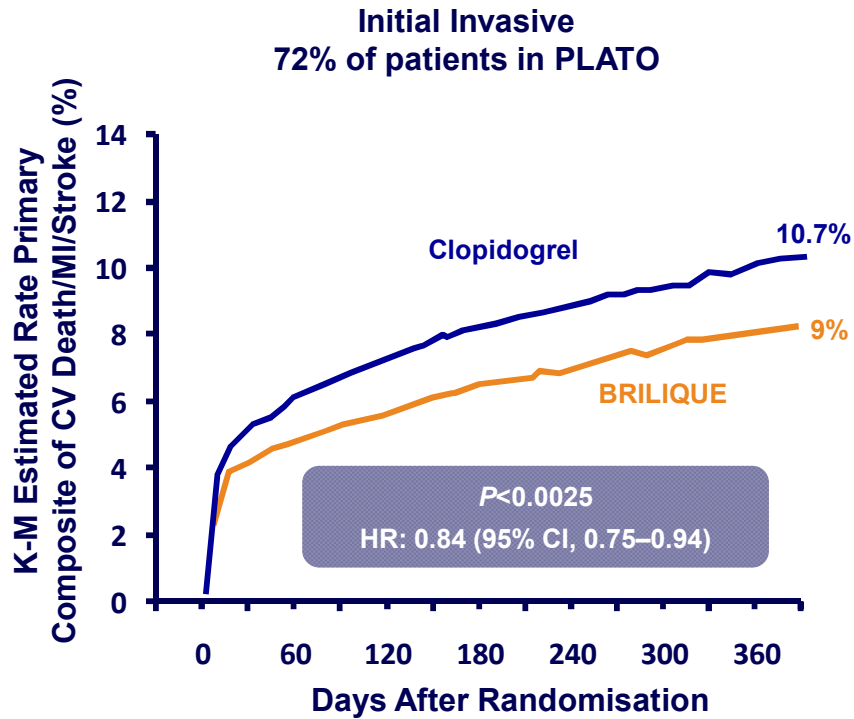
PLATO: final diagnosis of index event

| Diagnosis | Ticagrelor n=9333 | Clopidogrel n=9291 | Total n=18,624 |
|-----------------|----------------------|-----------------------|-------------------|
| | n (%) | | |
| STEMI | 3496 (37.5) | 3530 (38.0) | 7026 (37.8) |
| NSTEMI | 4005 (42.9) | 3950 (42.5) | 7955 (42.7) |
| Unstable angina | 1549 (16.6) | 1563 (16.8) | 3112 (16.7) |

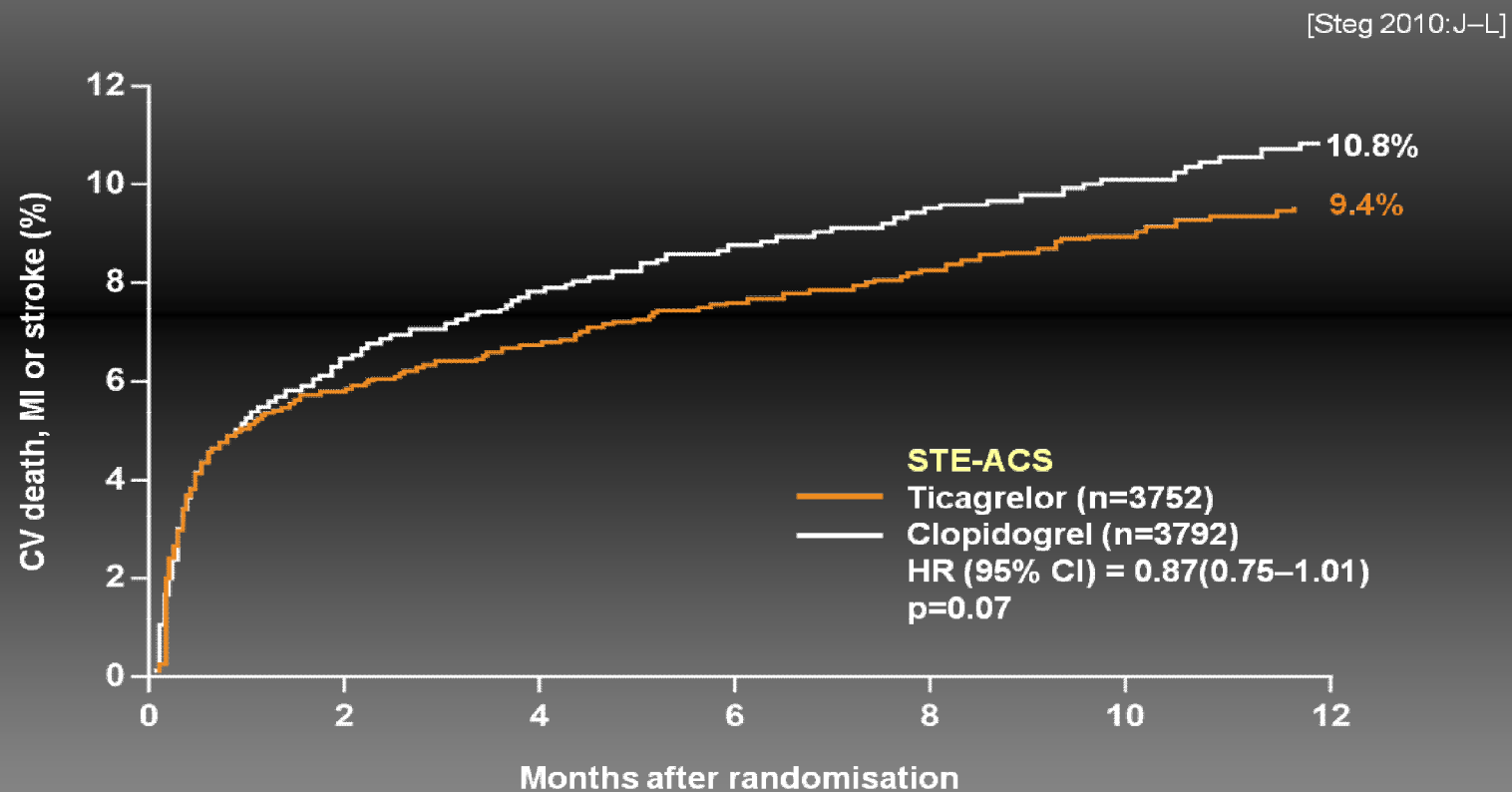
PLATO: invasive procedures

| | Ticagrelor (n=9333) | Clopidogre l (n=9291) | <i>P</i> value |
|---|------------------------|--------------------------|-------------------|
| Invasive procedure at index hospitalization, n (%) | | | |
| <i>Coronary angiography</i> | 7599 (81.4) | 7571 (81.5) | 0.91 |
| <i>PCI during index hospitalization</i> | 5687 (60.9) | 5676 (61.1) | 0.83 |
| <i>Cardiac surgery</i> | 398 (4.3) | 434 (4.7) | 0.19 |

PLATO Invasive vs Non-Invasive Management

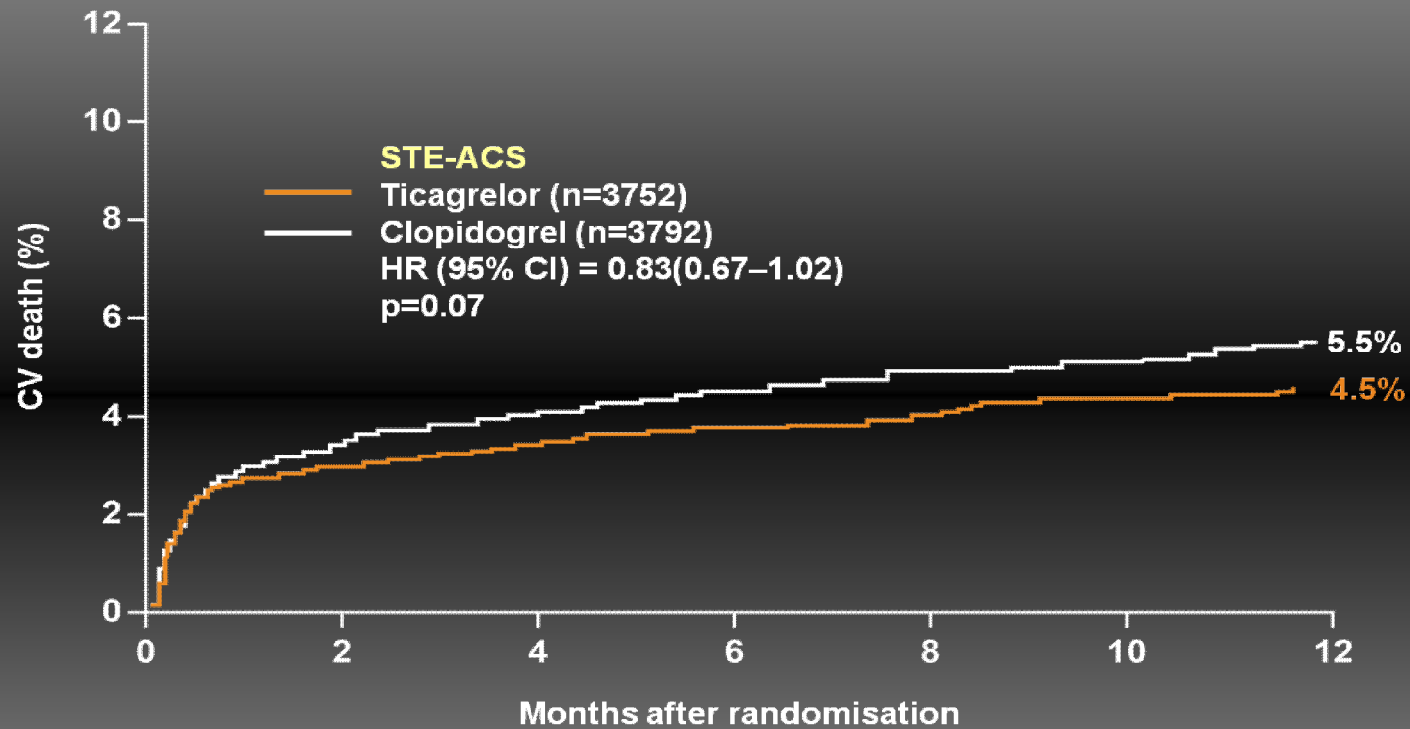


PLATO STEMI: Primary composite endpoint



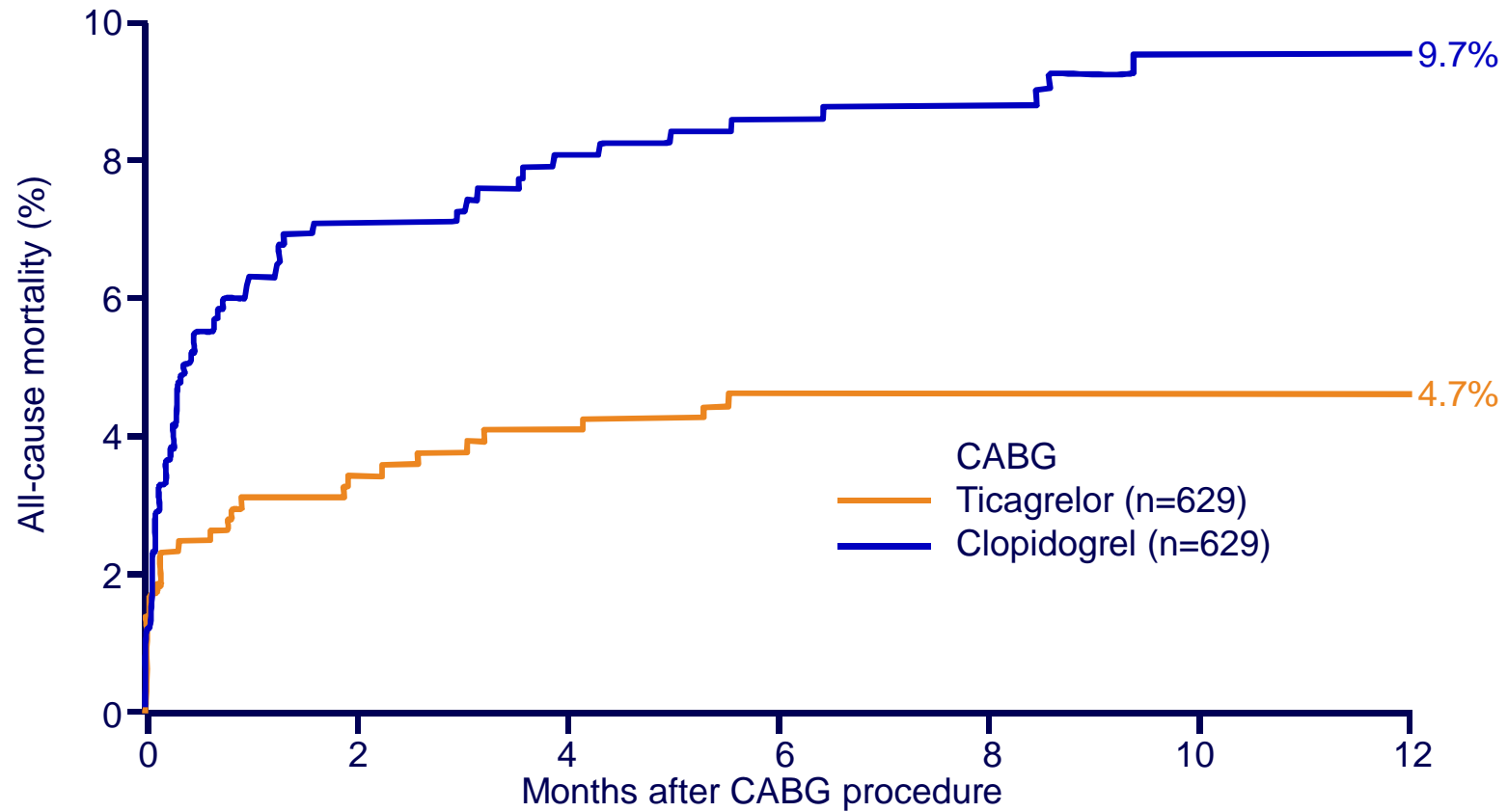
PLATO STEMI: CV death

[Steg 2010:J,K,M]

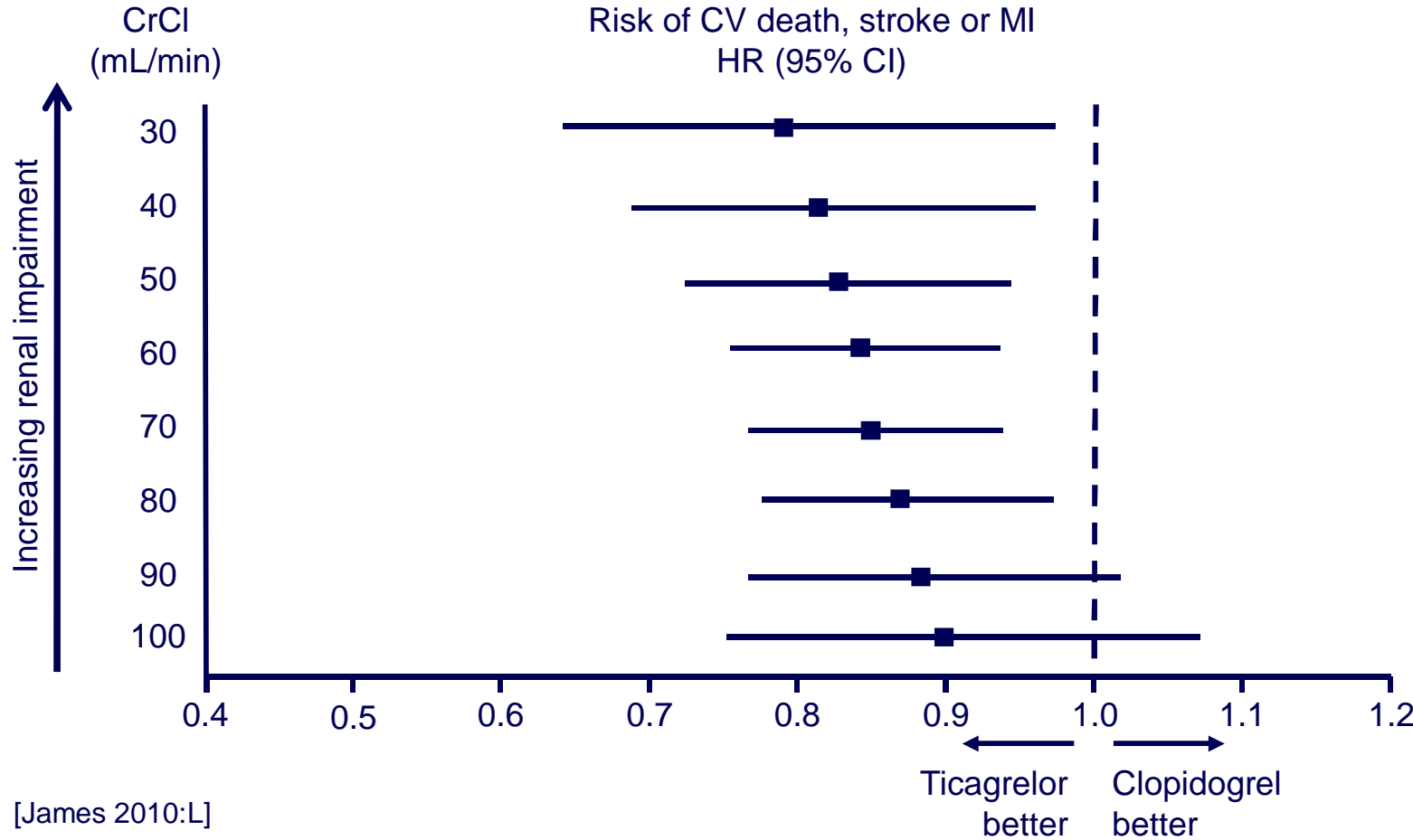


CV death benefit with ticagrelor was consistent with the overall PLATO trial results^[Wallentin 2009:J]

PLATO CABG: All-cause mortality

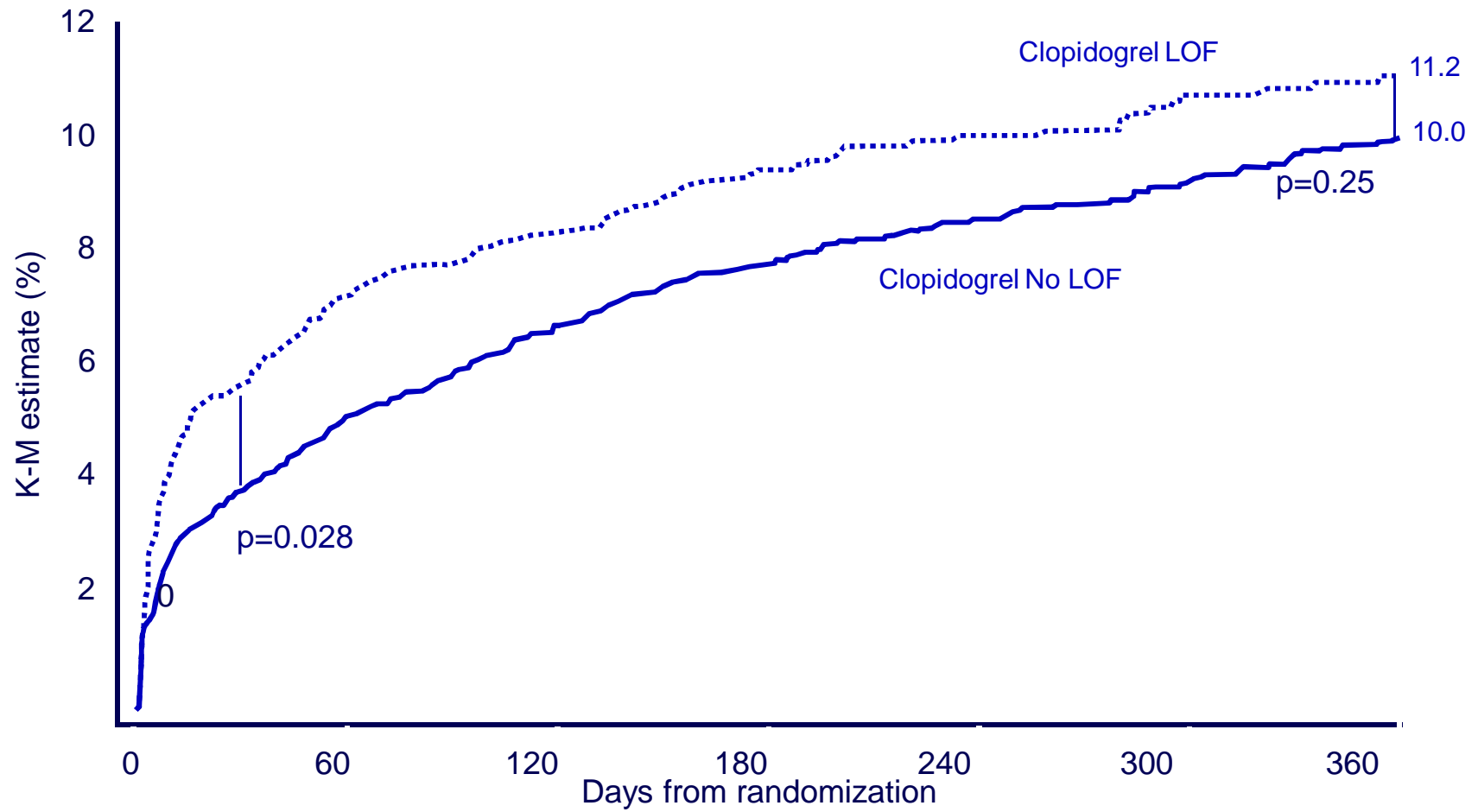


Renal function and outcomes in PLATO



[James 2010:L]

PLATO CYP2C19 LOF



Platelet-Mediated Thrombosis Targets

