Evidence-Based Pharmacotherapy Recommendations for PCI, NSTEMI, and STEMI:

The Forest and the Trees

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Evidence-based Clinical Decision-Making:
Seeing the forest through the trees

Evidence-based Clinical Decision-Making:
Seeing the forest through the trees

Anticoagulants (21+):

Unfractionated heparin

Low molecular weight heparins (8): Enoxaparin, Bemiparin, Certoparin, Dalteparin, Nadroparin, Parnaparin, Reviparin, Tinzaparin

Anti-thrombins (4): Bivalirudin, Dabigatran, Argatraban, Lepirudin

Factor Xa inhibitors (7+): Fondaparinux, Rivaroxiban, Apixaban, Otamixaban, Letaxaban, Betrixaban, Danaparoid, others

Vitamin K antagonists: Warfarin

Antiplatelet agents (12+):

Aspirin

First gen oral ADP antagonists (2): Ticlopidine and Clopidogrel

Second gen oral ADP antagonists (2): Prasugrel and Ticagrelor

GPIIb/IIIa inhibitors (3): Abciximab, Eptifibatide, Tirofiban

IV (±oral) ADP antagonists (2): Cangrelor, Elinogrel

TR antagonists (2+): Vorapaxar, Atopaxar, others

Evidence-based Clinical Decision-Making:
Seeing the forest through the trees

Evidence-based Clinical Decision-Making:

Seeing the forest through the trees

What really matters to the patient?

pruritis/rash

claudication

depression

infections

sleep

Mortality
Stroke
Myocardial infarction
Unplanned revascularization
Angina
Dyspnea
Bleeding
Thrombocytopenia
Renal insufficiency
Fatigue
Hospitalization

hepatitis

arrhythmias

mylagias

convenience

cost

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Evidence-based Clinical Decision-Making:
Seeing the forest through the trees

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What really matters to the patient?

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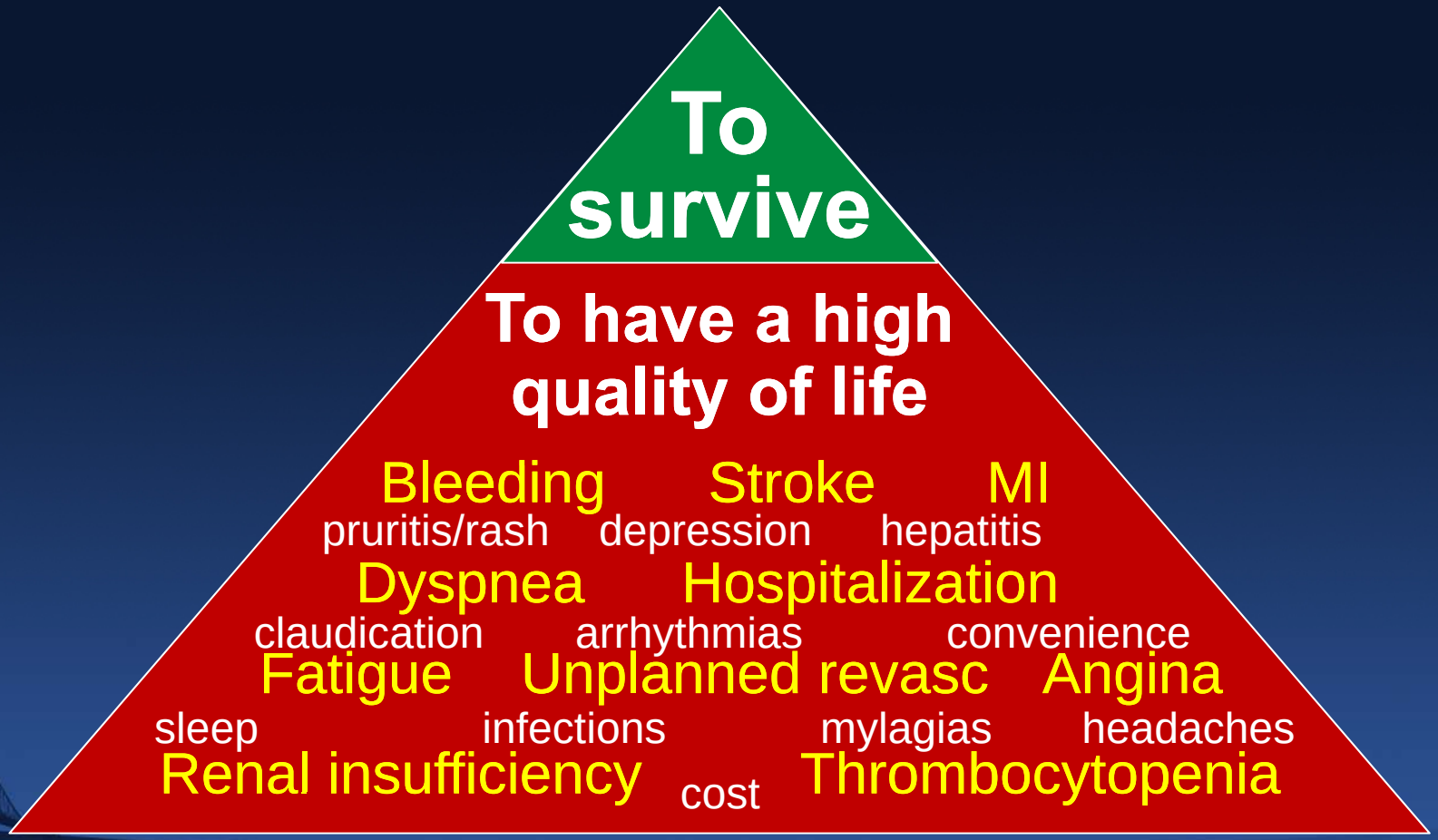
Evidence-based Clinical Decision-Making:

Seeing the forest through the trees

What really matters to the patient?



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High-risk ACS: Etiology and solutions

The Cause

Ruptured thin-cap fibroatheroma and luminal thrombus in the setting of systemic inflammation and platelet activation

The Solution

Revascularization with stenting (in most pts) to stabilize the ruptured plaque

NSTEACS: PCI ~70%

STEMI: PCI ~90%

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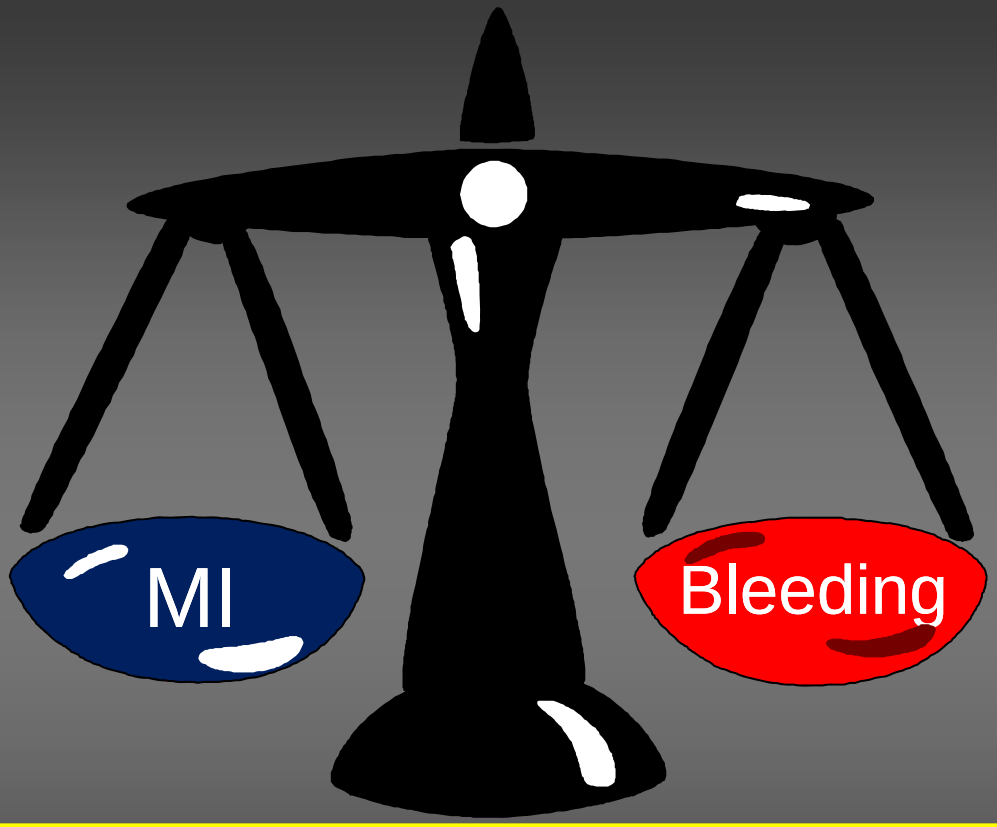
Impact of Myocardial Infarction and Bleeding on Subsequent Mortality

- Large MIs are prognostically important (esp Q-wave and those with angiographic complications)

- Spontaneous MIs are more important than peri-procedural MI (and deserve different thresholds for dx).



-Major and moderate bleeding are as prognostically important as MI, & impact late as well as early mortality

-Bleeding defns should be broad to capture most events, except possibly isolated hematomas

Both bleeding and MI must be suppressed for survival to be improved in ACS and PCI. Recognition of individual pt risks for atheroembolic vs. hemorrhagic complications should permit personalized decision-making to optimize outcomes on a case by case basis.

Optimal pharmacotherapy as an adjunct to PCI is necessary to:

1) Allow the PCI procedure to be performed safely
2) Provide long-term prophylaxis

Anticoagulants:

Unfractionated heparin

Low molecular weight heparins (8): Enoxaparin, Bemiparin, Certoparin, Dalteparin, Nadroparin, Parnaparin, Reviparin, Tinzaparin

Anti-thrombins (4): Bivalirudin, Dabigatran, Argatraban, Lepirudin

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TRA inhibitors (2+): Vorapaxar, Atopaxar, others

Optimal pharmacotherapy as an adjunct to PCI is necessary to:

1) Allow the PCI procedure to be performed safely

2) Provide long-term prophylaxis

Focus on agents that reduce mortality

Anticoagulants:

Heparin (UFH or LMW) + GPI vs. Bivalirudin

Antiplatelet agents:

Clopidogrel vs. Prasugrel and Ticagrelor

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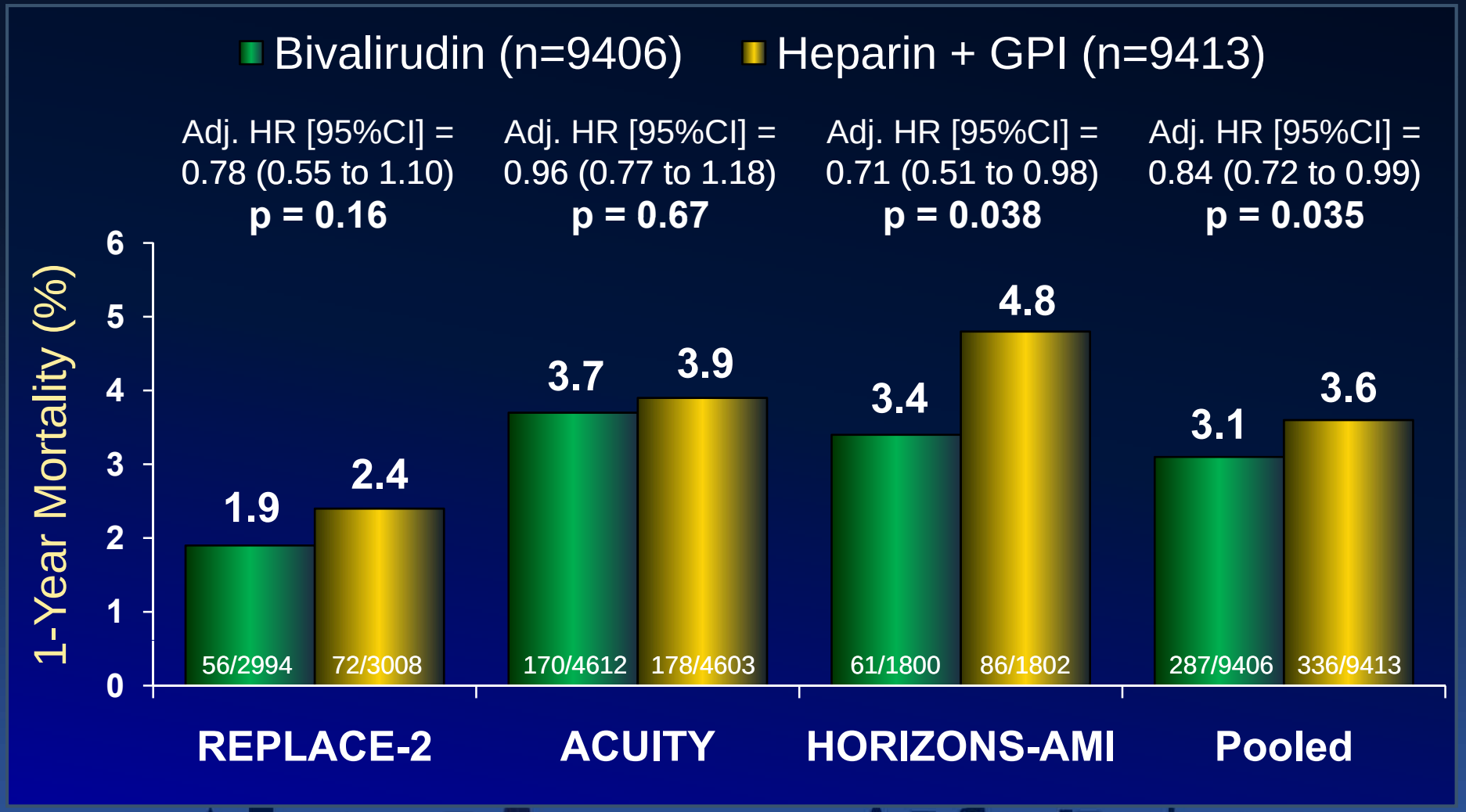
Bivalirudin vs. Heparin + GPI (n=18,819)
Mortality at 1-year by treatment and study



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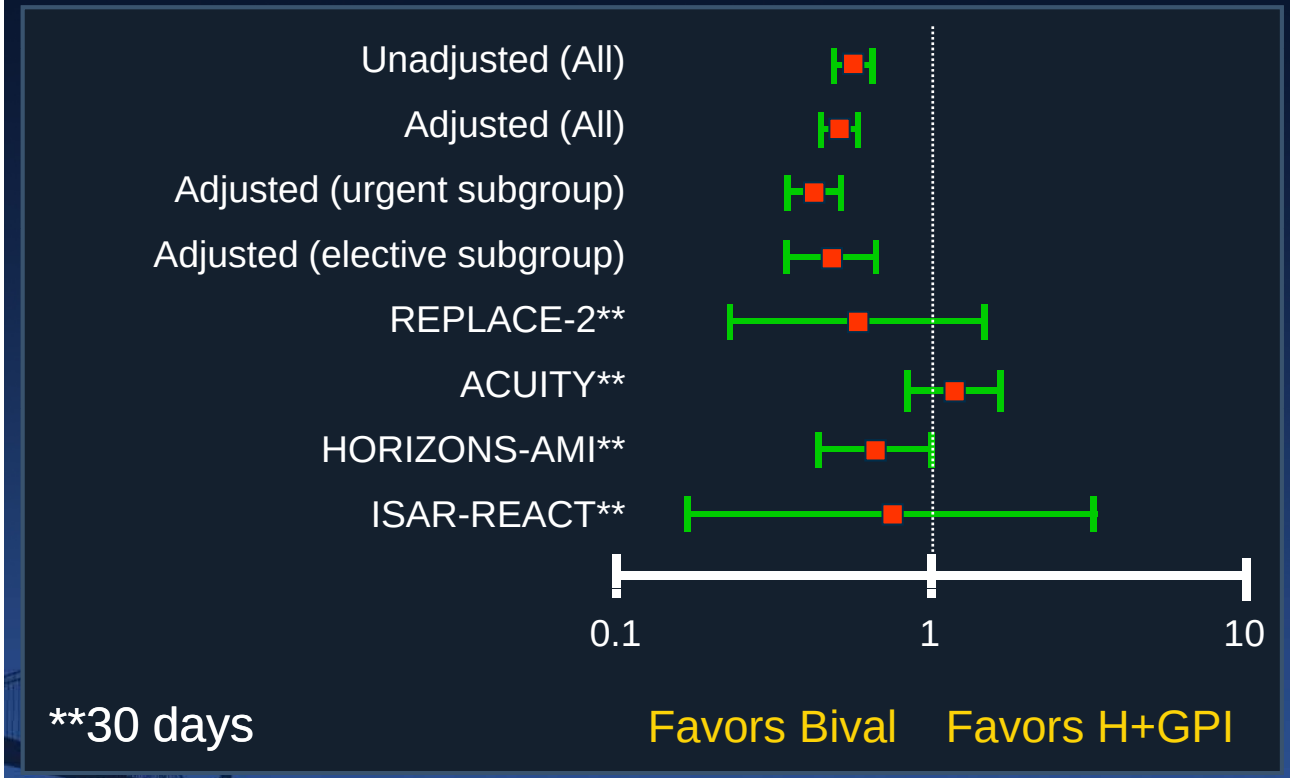
Bivalirudin vs. Heparin + GPIIb/IIIa

N = 127,185 pts undergoing PCI 2003-2006

(Premier Perspective Database, ~1/6th of all US hosps; bival in 26%)

In-hospital death



Bivalirudin	H+GPI
0.8%	2.1%

Adjusted HR [95%CI]

0.51 [0.44 – 0.60]

49% ⇩ Death

Rassen JA et al. EHJ 2010;31:561-72

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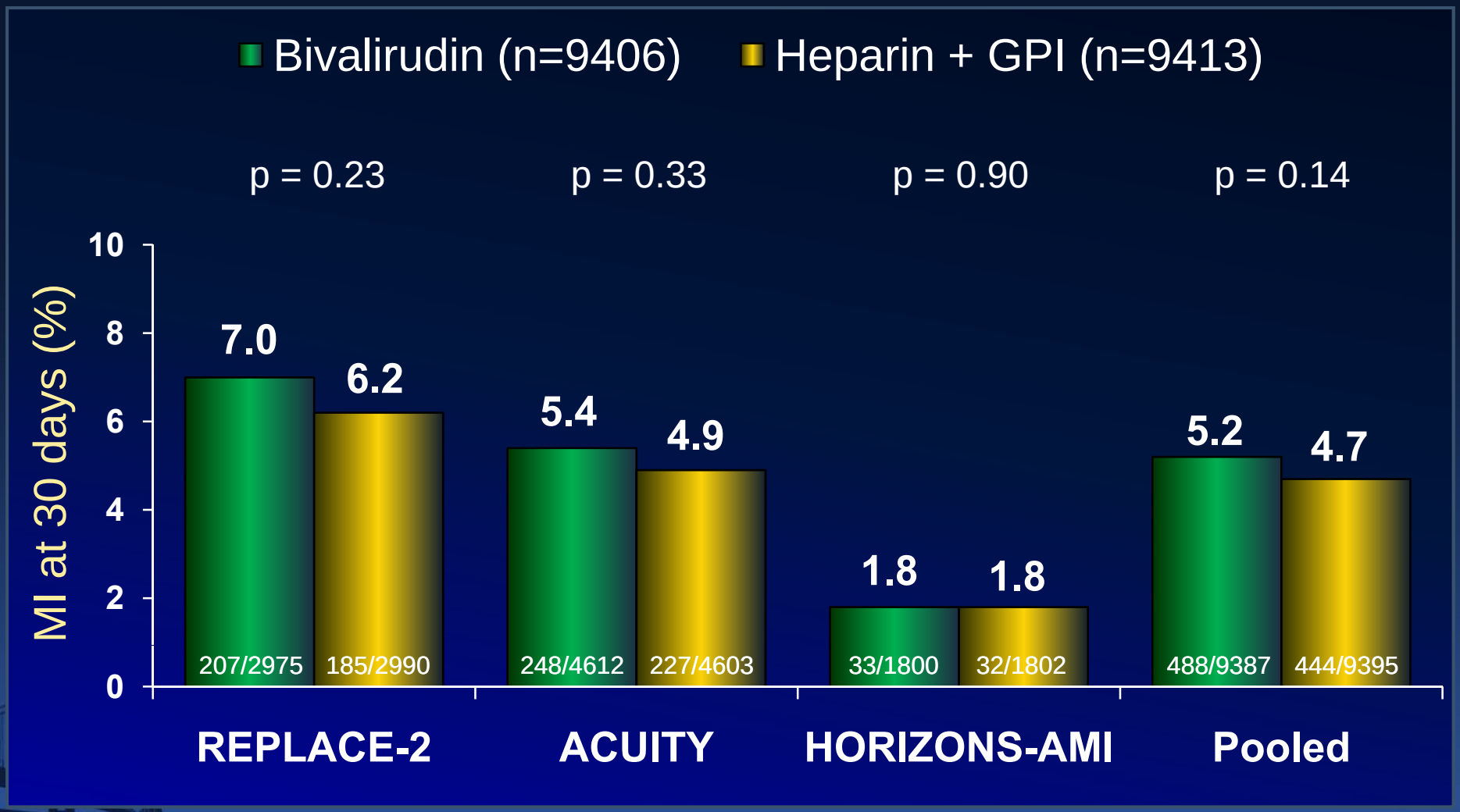
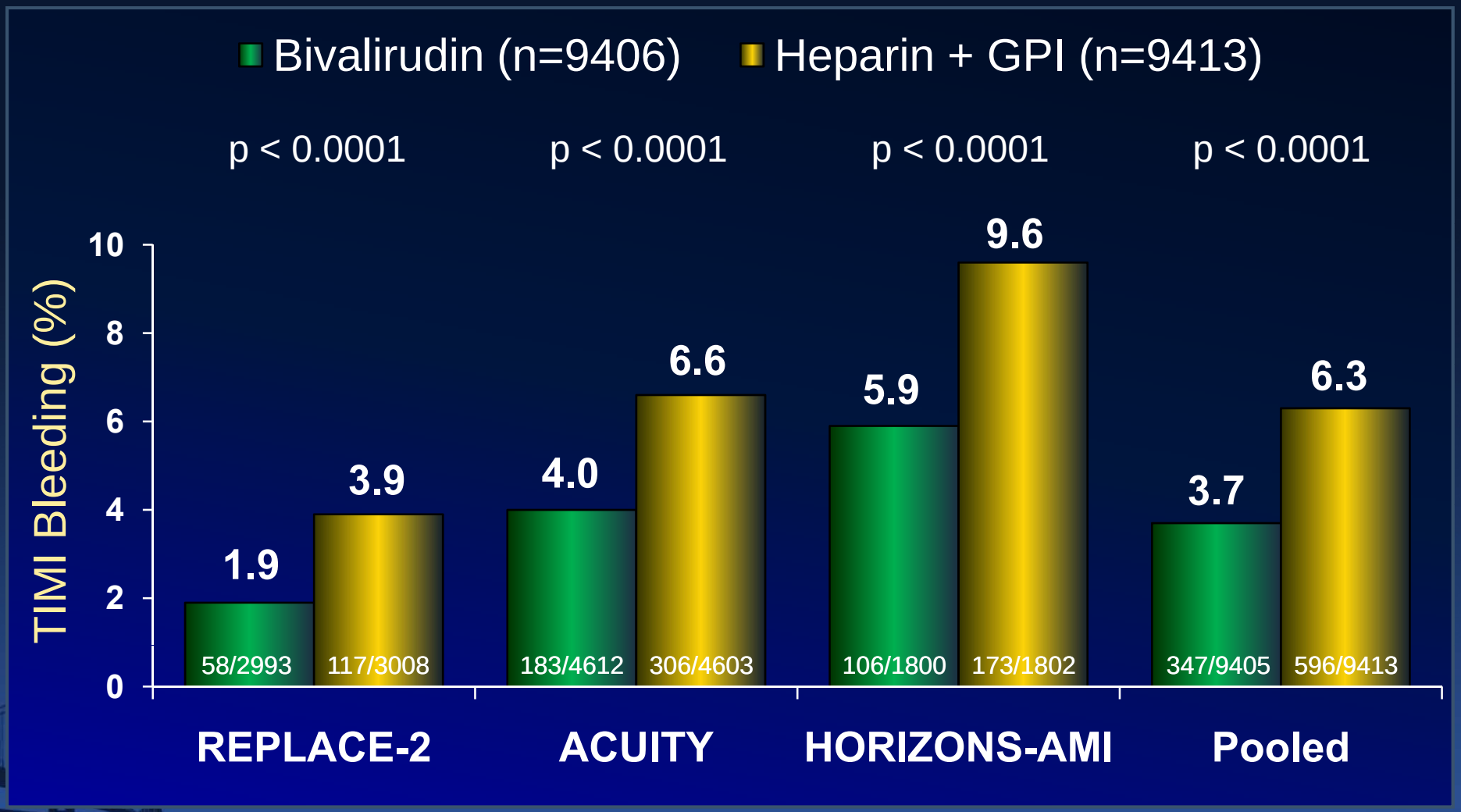
Bivalirudin vs. Heparin + GPI (n=18,819)
30d MI by treatment and study



Bivalirudin vs. Heparin + GPI (n=18,819)

30d TIMI major or minor bleeding by treatment and study



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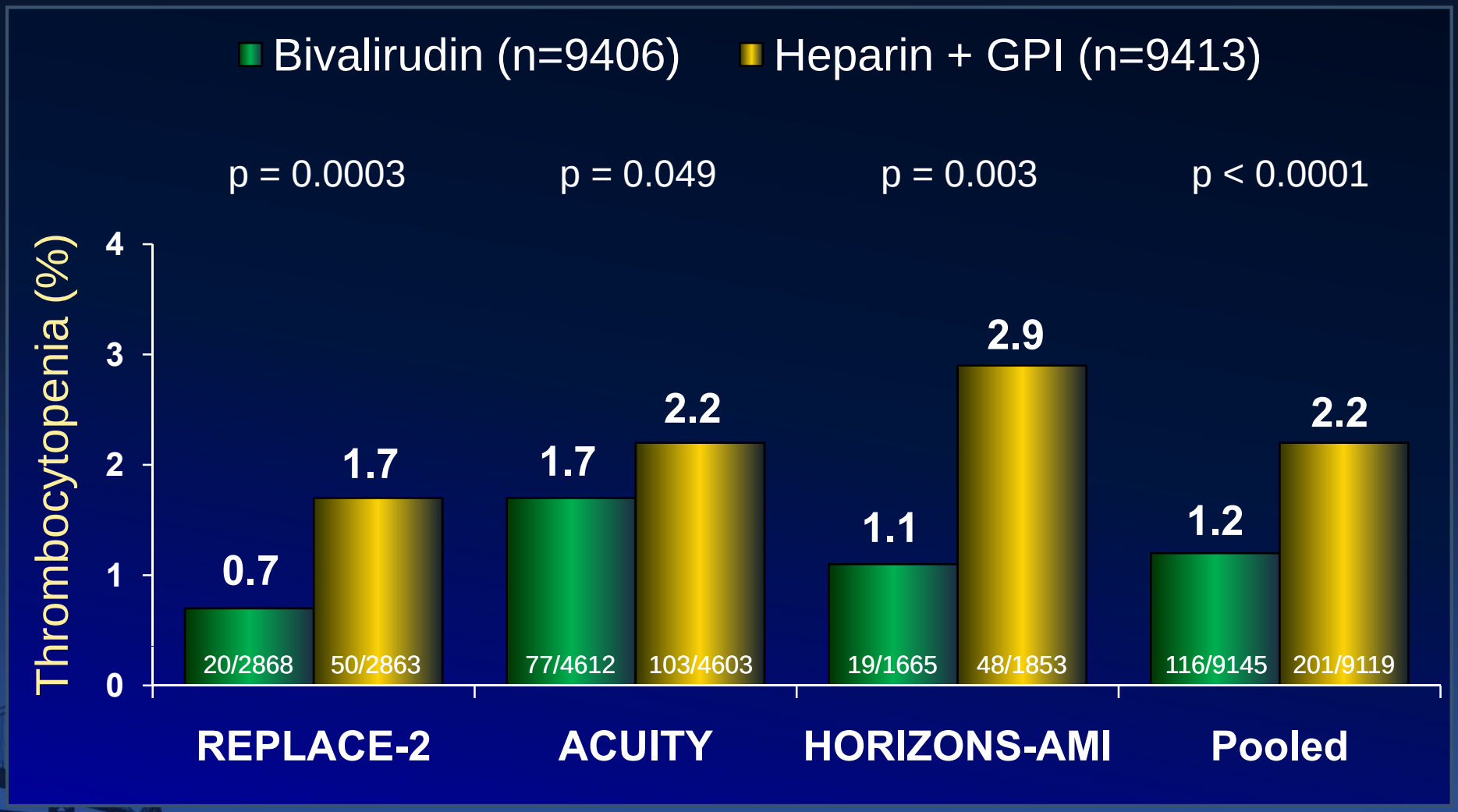
Bivalirudin vs. Heparin + GPI (n=18,819)

Acquired thrombocytopenia (<100,000) by treatment and study



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Bivalirudin vs. Heparin + GPIIb/IIIa

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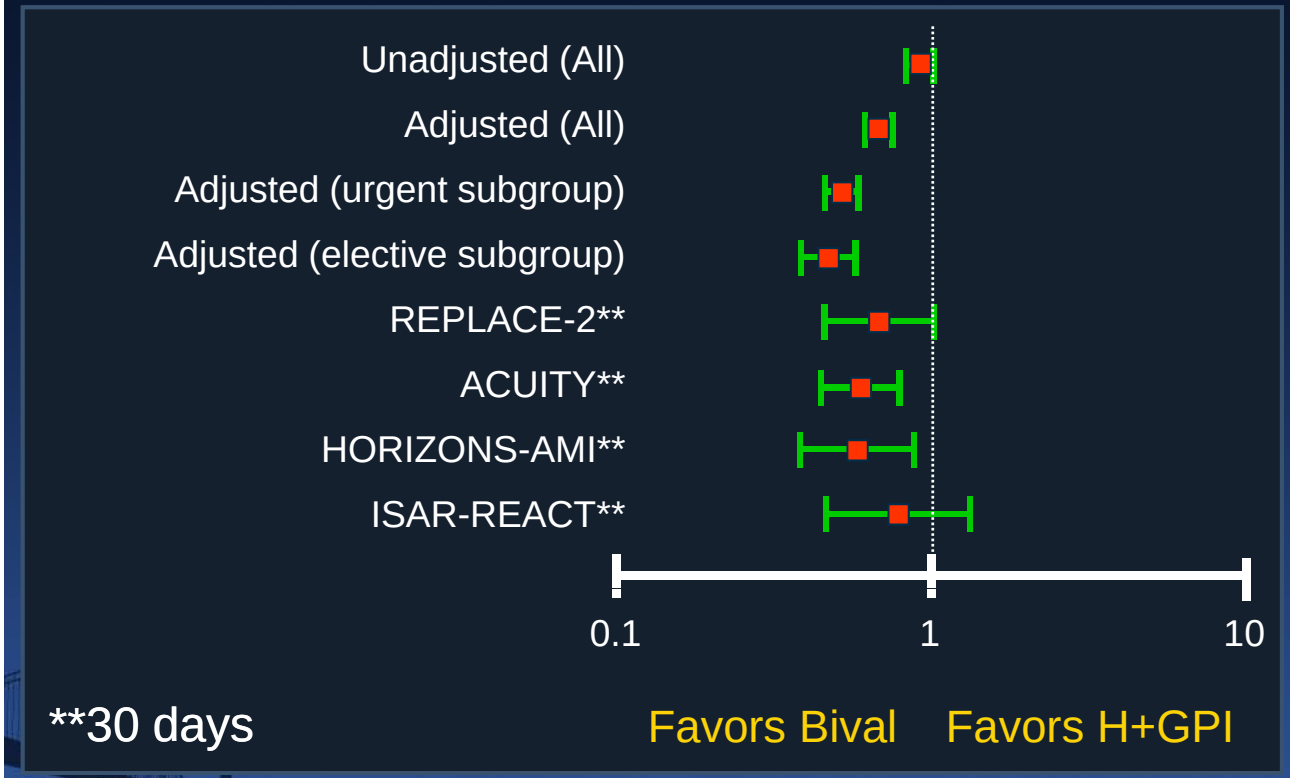
In-hospital transfusion



Bivalirudin	H+GPI
3.0%	4.6%

Adjusted HR [95%CI]

0.67 [0.61 - 0.73]

33% ⇩ Transfusion

Rassen JA et al. EHJ 2010;31:561-72

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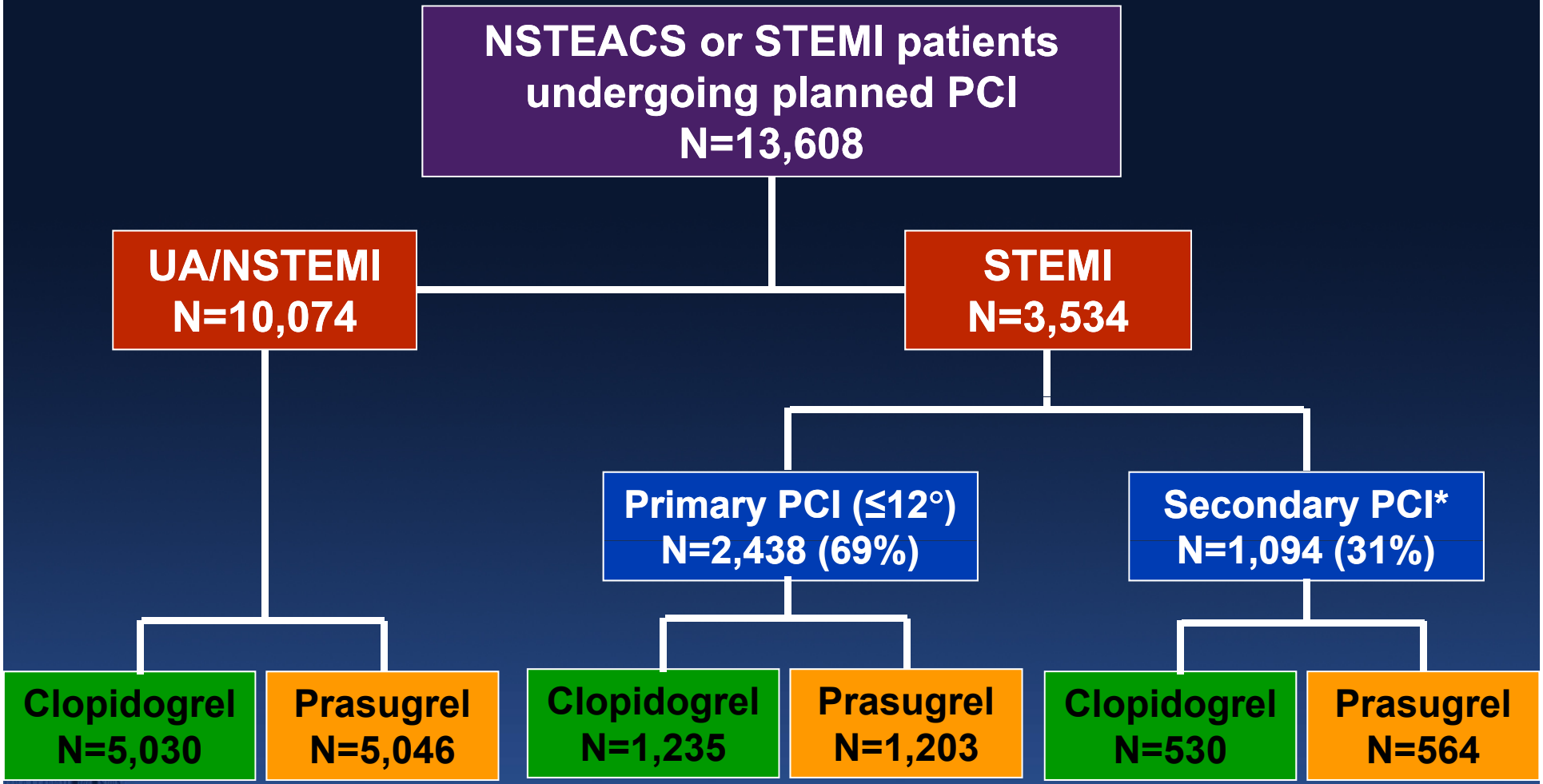
TRITON TIMI-38

Patient Flow



*enrolled between 12 h and 14 days after symptom onset

Montalescot G et al. Lancet 2009;373:723-31

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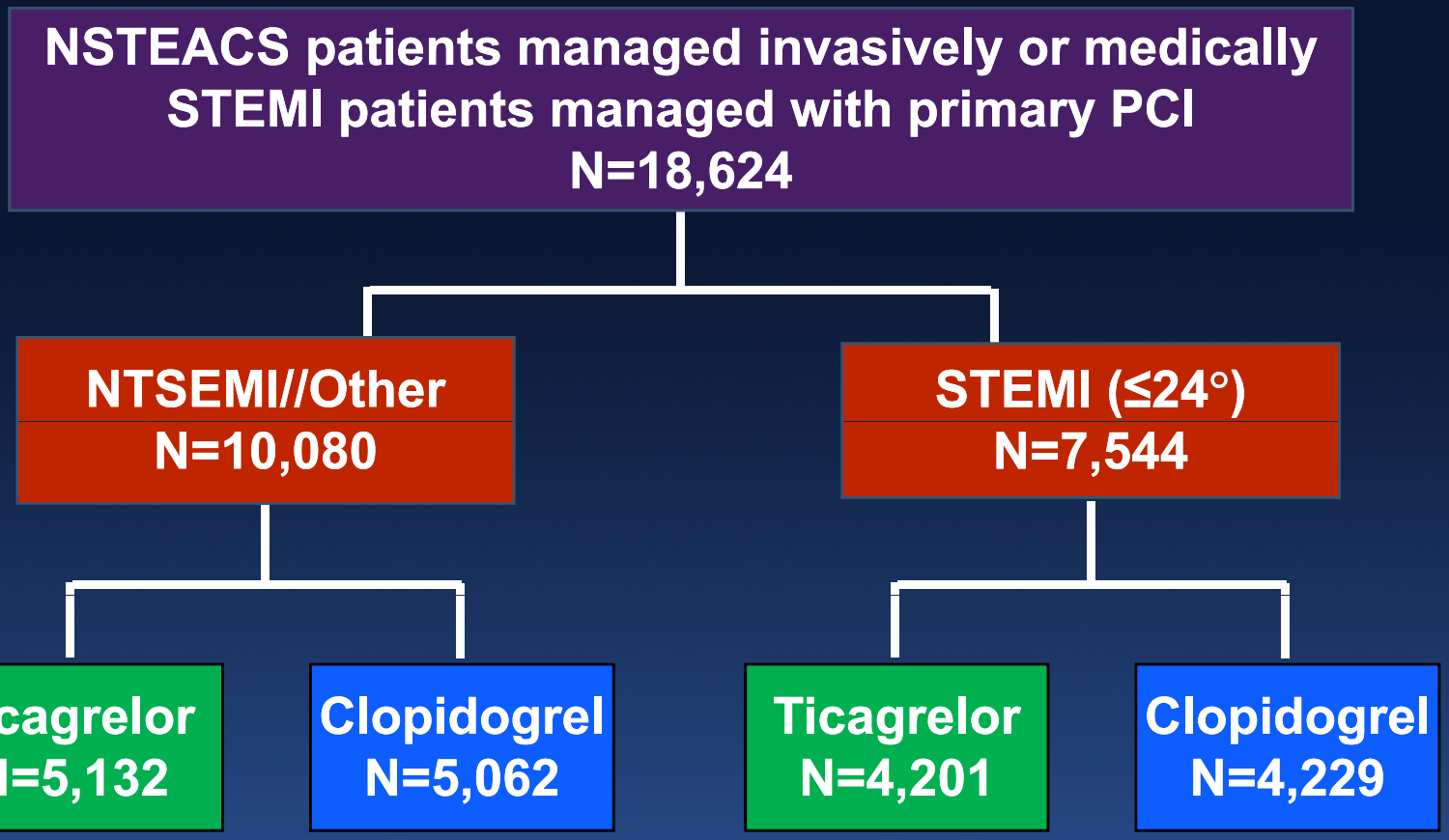
Patient Flow



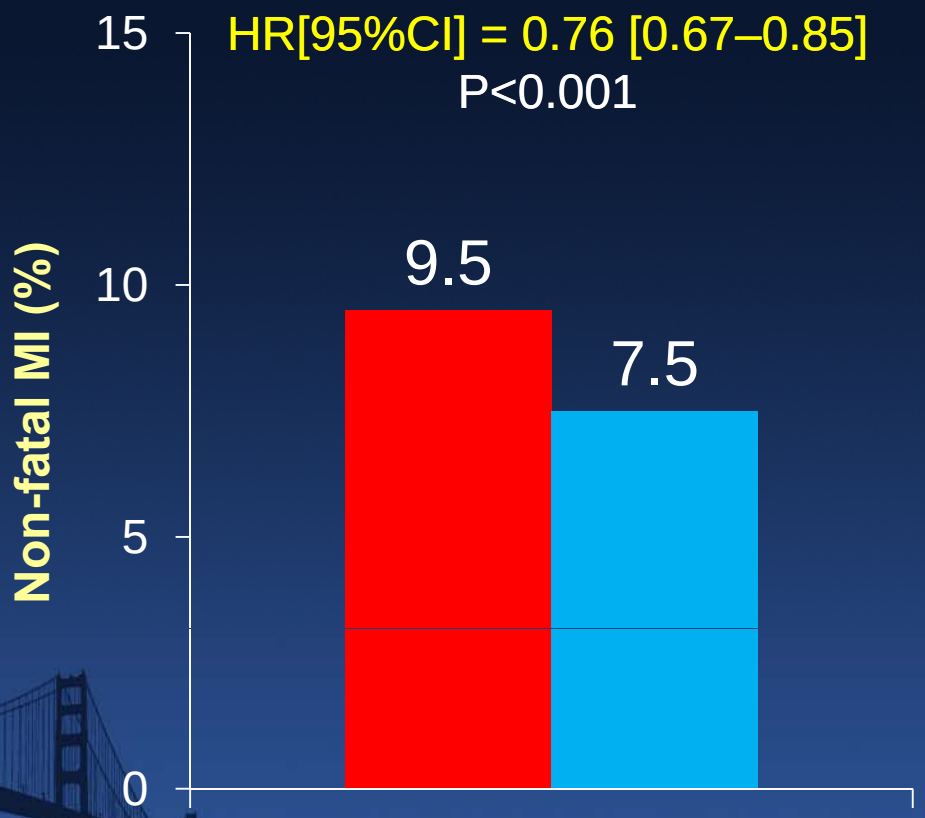
Steg PG et al. Circulation. 2010;122:2131-2141

Prasugrel and Ticagrelor in ACS

Myocardial infarction

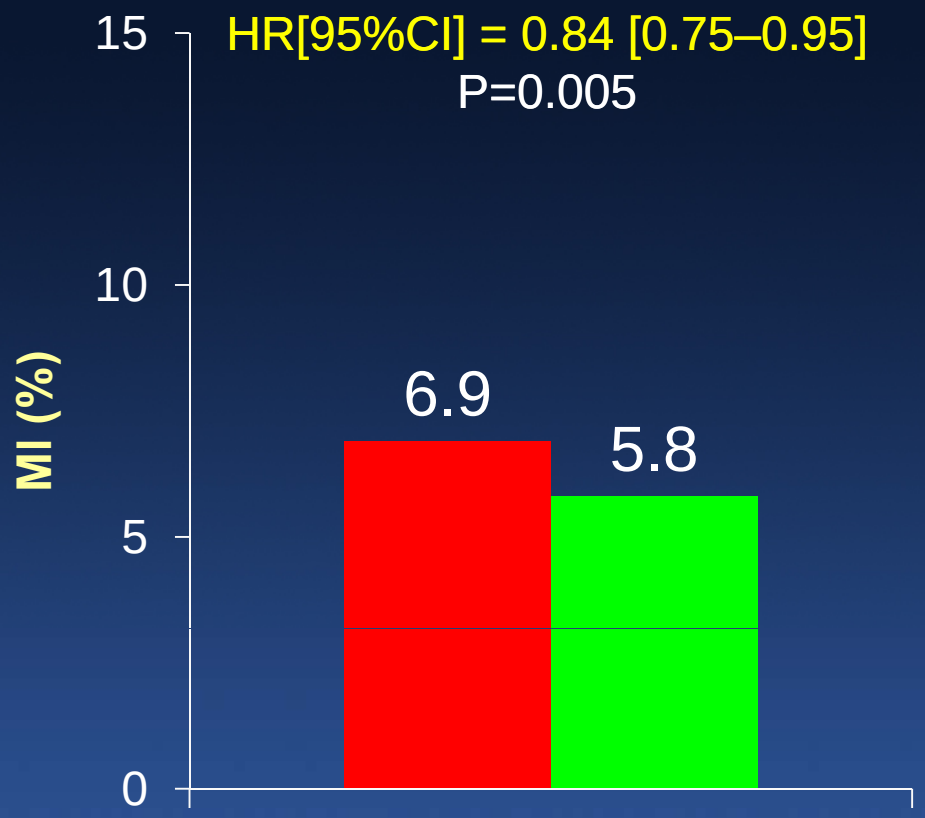
TRITON-TIMI-38 (n=13,608)

15 months



PLATO (n=18,624)

12 months



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

Wallentin L et al. N Engl J Med 2009;361:1045-57

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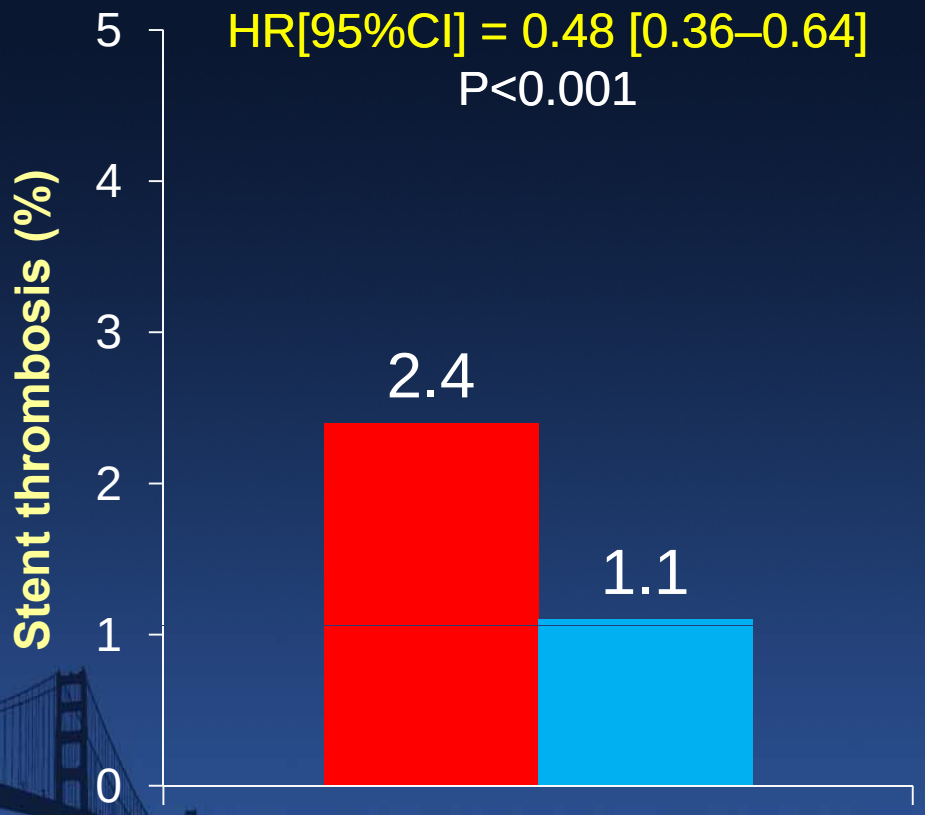
Prasugrel and Ticagrelor in ACS

Stent thrombosis

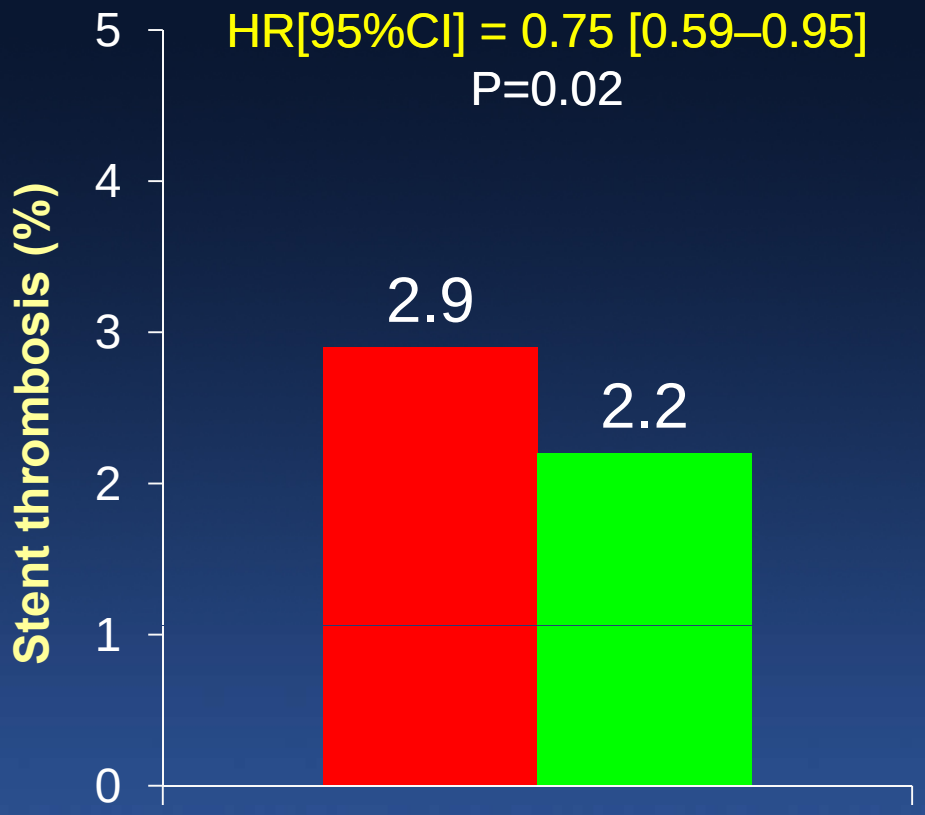
TRITON-TIMI-38 (n=13,608)
15 months

Clopidogrel (n=6795) Prasugrel (n=6813)



PLATO (n=18,624)
12 months

Clopidogrel (n=9291) Ticagrelor (n=9333)



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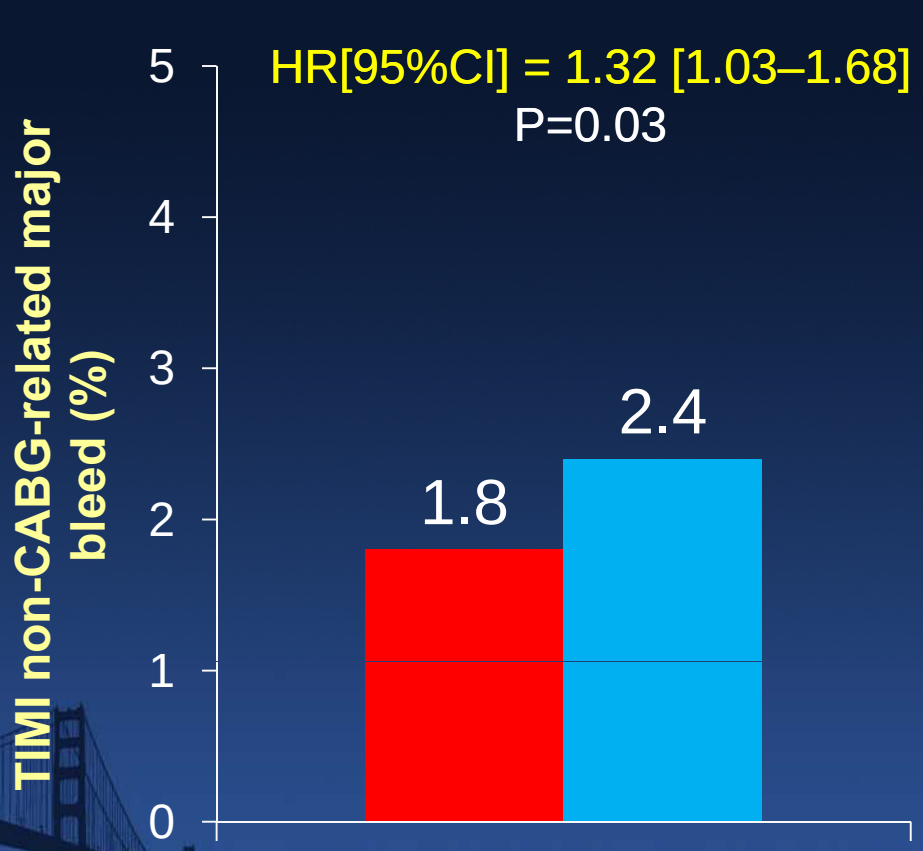
Prasugrel and Ticagrelor in ACS

TIMI non-CABG-related major bleeding

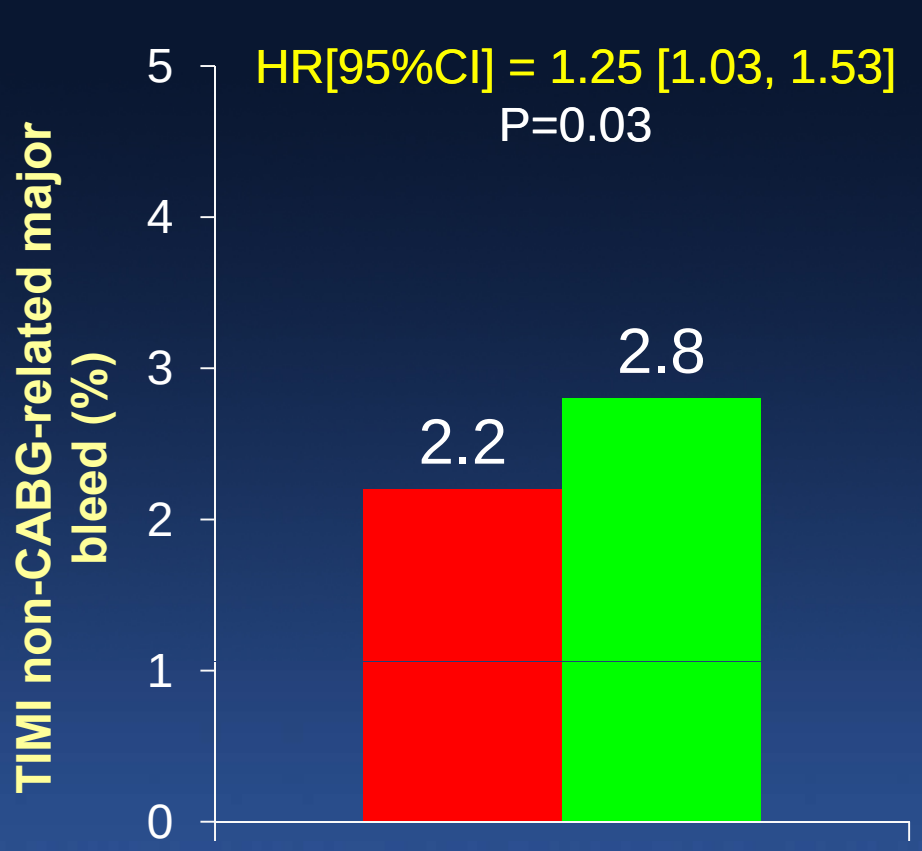
TRITON-TIMI-38 (n=13,608)

15 months



PLATO (n=18,624)

12 months



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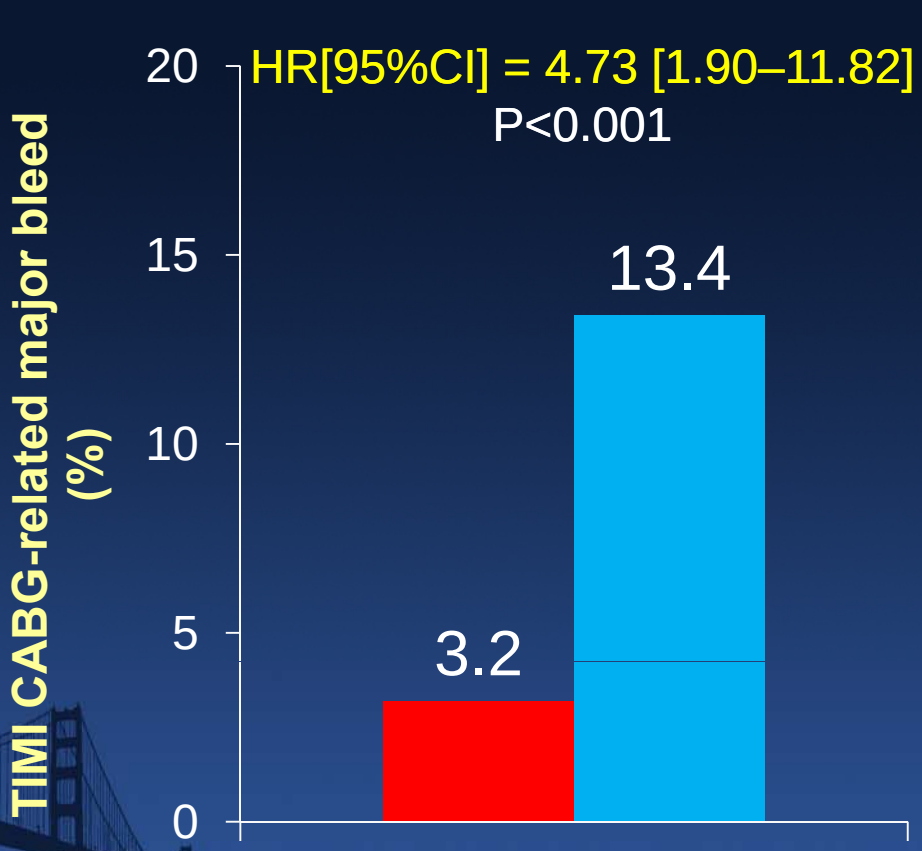
Prasugrel and Ticagrelor in ACS

TIMI CABG-related major bleeding

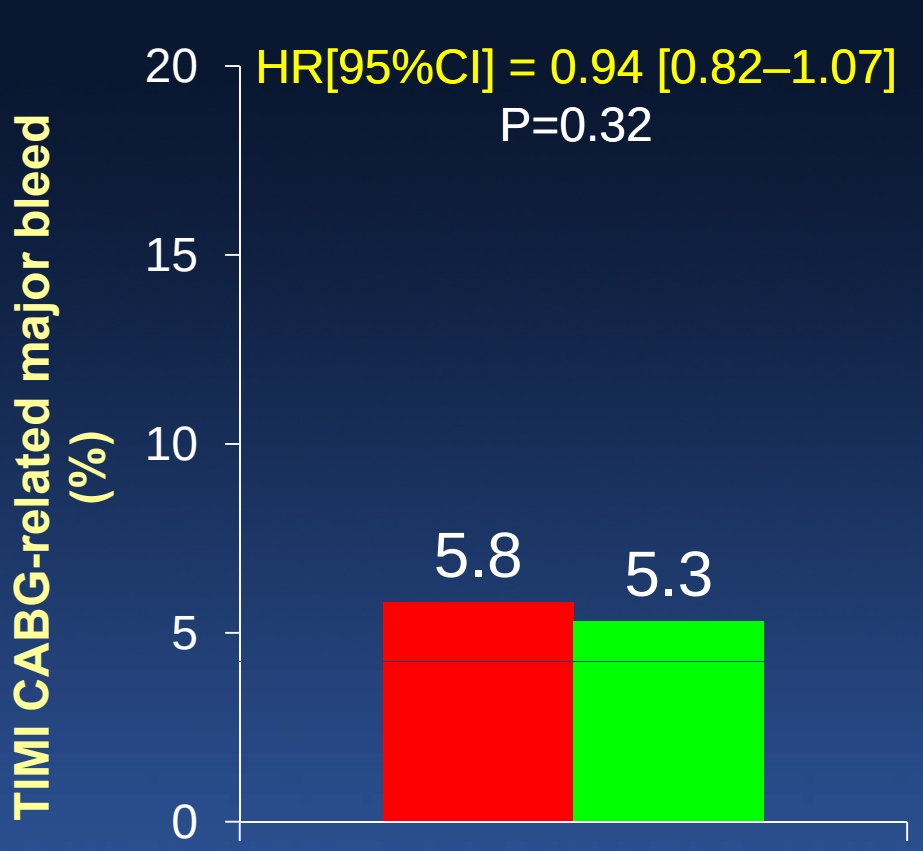
TRITON-TIMI-38 (n=13,608)

15 months



PLATO (n=18,624)

12 months



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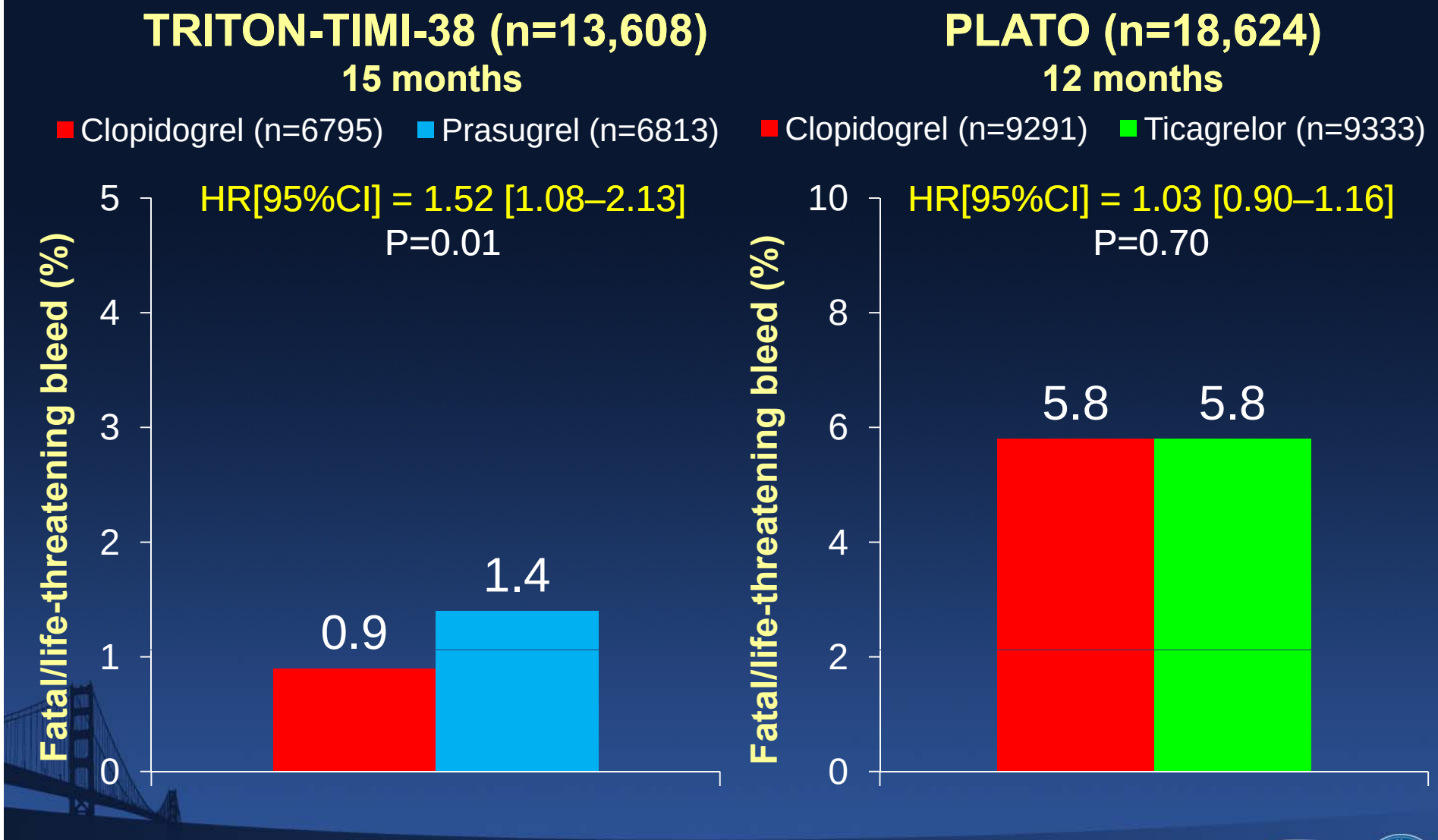
Prasugrel and Ticagrelor in ACS

Fatal or life-threatening bleeding



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Prasugrel and Ticagrelor in ACS

Mortality

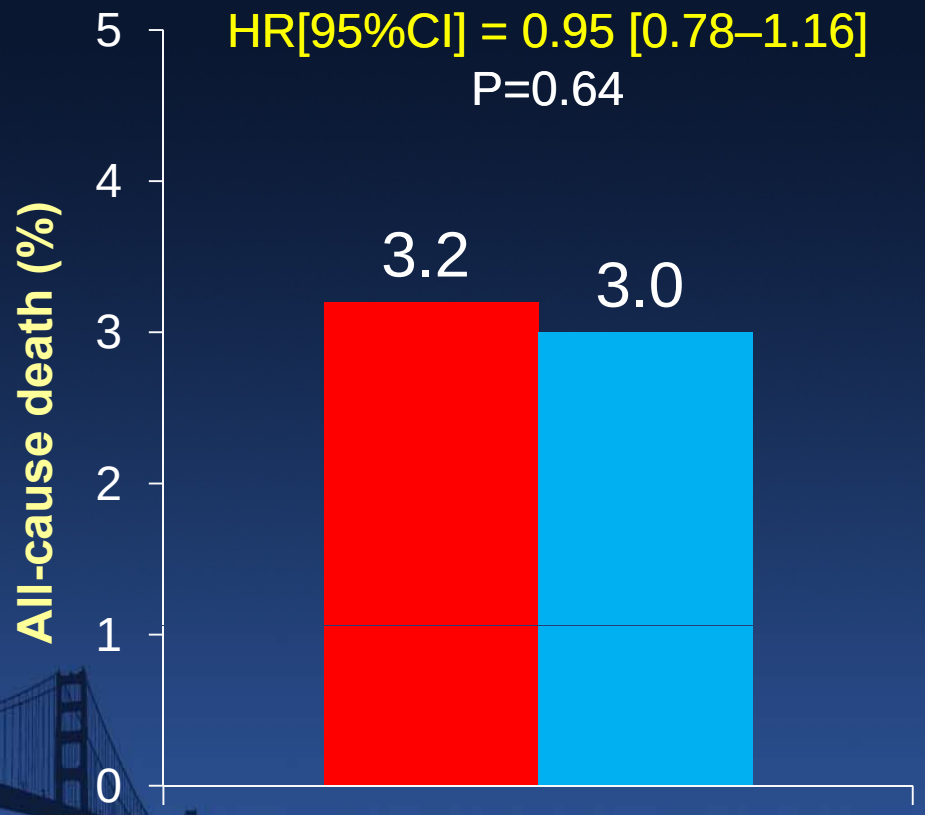
TRITON-TIMI-38 (n=13,608)

15 months

Clopidogrel (n=6795) Prasugrel (n=6813)

HR[95%CI] = 0.95 [0.78–1.16]

P=0.64



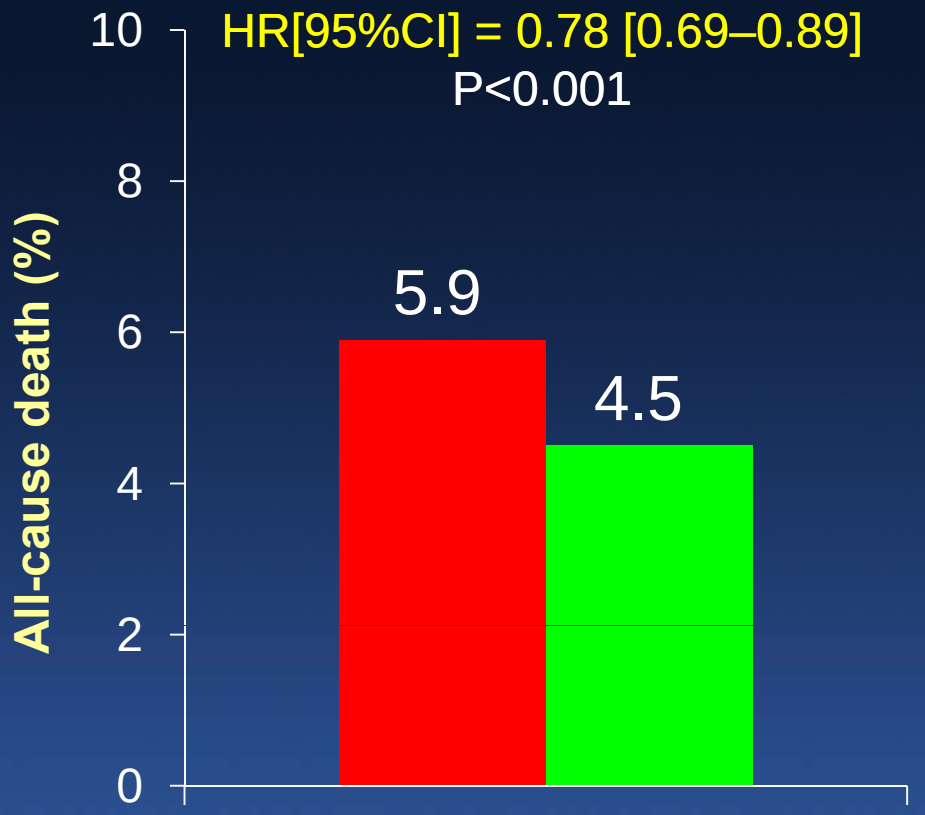
PLATO (n=18,624)

12 months

Clopidogrel (n=9291) Ticagrelor (n=9333)

HR[95%CI] = 0.78 [0.69–0.89]

P<0.001



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Why does Ticagrelor, but not Prasugrel, Reduce Mortality in ACS?

1. Both agents significantly reduce hard ischemic events, but only ticagrelor is able to do so without increasing life-threatening or fatal bleeding (shorter $t_{1/2}$, reversible)

OR

2. Ticagrelor (but not prasugrel) has favorable off-target effects (blocks rbc adenosine re-uptake)

But it's probably mostly about ischemia vs. bleeding!

Evidence-based Medicine Pharmacotherapy Decisions: Conclusions I

1. Effective treatment for most patients with angina, ischemia and high-risk ACS requires revascularization
2. Antithrombin and antiplatelet agents are necessary to suppress short- and long-term ischemia and MI, but must be used appropriately so potential hemorrhagic complications do not outweigh their benefits

Evidence-based Medicine Pharmacotherapy Decisions: Conclusions I

3. The risk-benefit profile of bivalirudin has been strongly associated with improved early and late survival

4. The potent ADP antagonist ticagrelor has been shown to further reduce mortality in ACS given its ability to suppress ischemia without increasing life-threatening or fatal bleeding (and/or blocking adenosine re-uptake); thus, absent a head-to-head trial against prasugrel, ticagrelor should be the agent of choice in most pts with STEMI or NSTEMI

   - Ticagrelor (and prasugrel) should be highly synergistic with bivalirudin, although data in this regard are also lacking

Finally: If you can see the forest through the trees….

If you can see the forest through the trees….

You'll find a happy and healthy patient

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