Intravenous Antithrombotic Agents: Before, During, Instead of the Cath Lab

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Conflict of Interest Statement

"Intravenous Antithrombotic Agents: Before, During, Instead of the Cath Lab"

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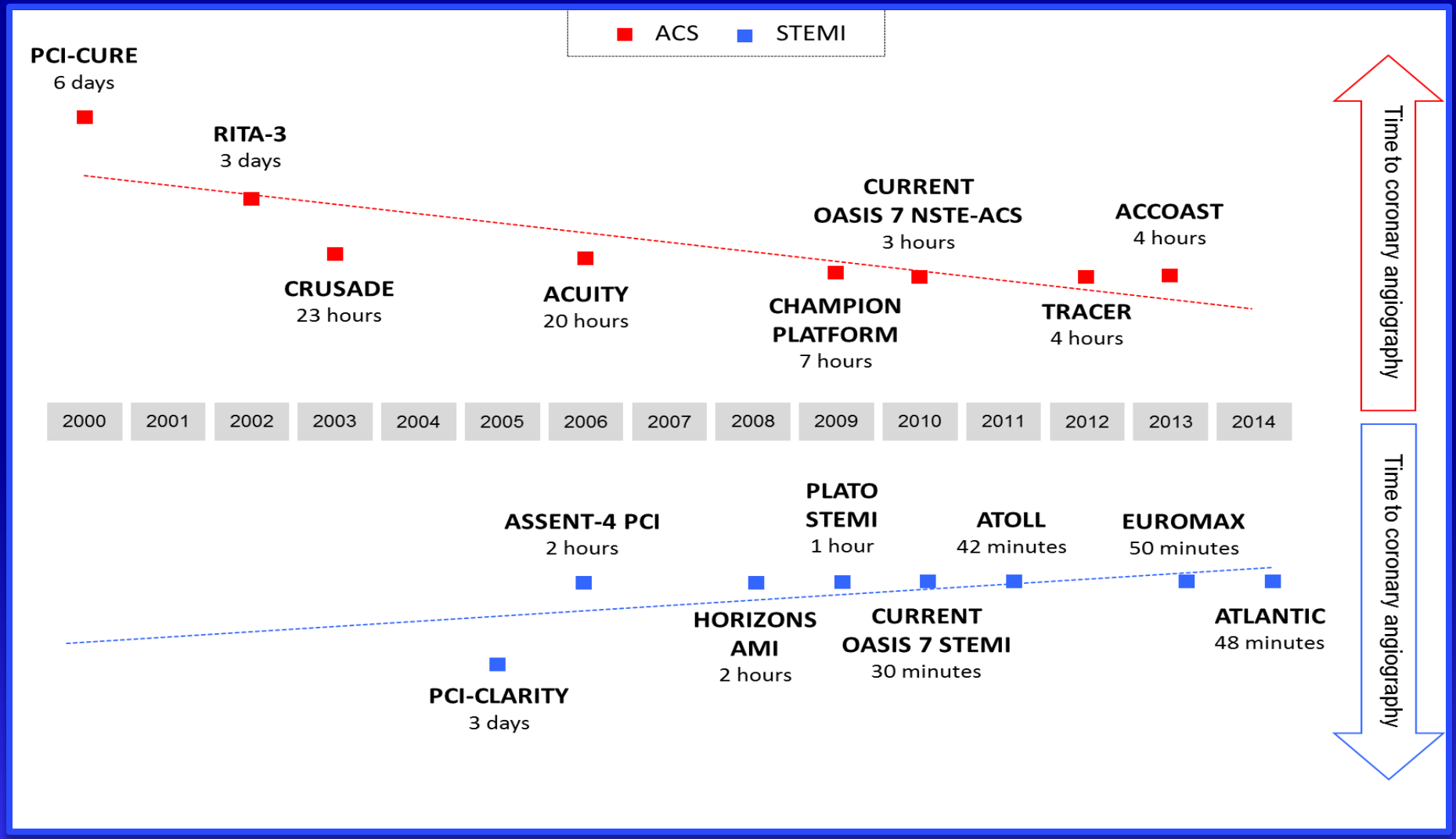
DSMB: Janssen Pharmaceuticals (GEMINI Study)

Research Grant: Astra Zeneca (Steering Committee: TWILIGHT Study)

IV Antithrombotic Choices

- What are the immediate goals?
  - Prevent peri-procedural thrombosis
  - Minimize bleeding risk
- Are there any unique thrombotic risks?
- Are there unique bleeding risks?
- Are their drug-drug interactions?
- What is available and lab experience?
- What are the cost implications?
- Are there relevant future events to consider?

Admission to Angiography Time



Capodanno D, Angiolillo DJ. Circ Cardiovasc Inter 2015

Delayed drug absorption

Intravenous Antithrombotics

Antiplatelets

- Aspirin
- Thienopyridines
  - Clopidogrel
  - Prasugrel
  - Ticagrelor
  - Cangrelor
- GP IIb/IIIa
  - Abciximab
  - Eptifibatide
  - Tirofiban

Antithrombins

- Heparin
- LMWH
  - Dalteparin
  - Enoxaparin
  - Fondaparinux
- DTI
  - Lepirudin
  - Bivalirudin
  - Argatroban
  - Dabigatran

Antithrombotic Options

Numerous Class I Permutations

- Aspirin: (3 options)
  - None; low; high first dose
- Thienopyridines: (12 options)
  - Cangrelor alone or in transition
  - Clopidogrel, Prasugrel, Ticagrelor
  - Short or long DAPT course
- Antithrombin (4 options)
  - Heparin, LMWH, Fondaparinux
  - Bivalirudin
- Oral factor IIa or Xa inhibitors (#? of options)

2014 ESC/EACTS Guidelines

Recommendations	Class[a]	Level[b]	Ref[c]
Antiplatelet therapy			
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.), and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A	774,776,794
A $P2Y_{12}$ inhibitor is recommended in addition to ASA, and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A	337,341,825
• Prasugrel (60 mg loading dose, 10 mg daily dose) in patients in whom coronary anatomy is known and who are proceeding to PCI if no contraindication	I	B	337
• Ticagrelor (180 mg loading dose, 90 mg twice daily) for patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy including those pre-treated with clopidogrel if no contraindication	I	B	341
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated	I	B	812,825
GP IIb/IIIa antagonists should be considered for bail-out situation or thrombotic complications.	IIa	C	
Pre-treatment with prasugrel in patients in whom coronary anatomy is not known, is not recommended.	III	B	826
Pre-treatment with GP IIb/IIIa antagonists in patients in whom coronary anatomy is not known, is not recommended.	III	A	357,815

Windecker S et al. Eur Heart J 2014;35:2541-2619

2014 ESC/EACTS Guidelines

Anticoagulant therapy			
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during PCI.	I	A	180
The anticoagulation is selected according to both ischaemic and bleeding risks, and according to the efficacy–safety profile of the chosen agent.	I	C	
Bivalirudin (0.75 mg/kg bolus, followed by 1.75 mg/kg/hour for up to 4 hours after the procedure) is recommended as alternative to UFH plus GP IIb/IIIa receptor inhibitor during PCI.	I	A	815–817
UFH is recommended as anticoagulant for PCI if patients cannot receive bivalirudin.	I	C	
In patients on fondaparinux (2.5 mg daily s.c.), a single bolus UFH (85 IU/kg, or 60 IU/kg in the case of concomitant use of GP IIb/IIIa receptor inhibitors) is indicated during PCI.	I	B	827
Enoxaparin should be considered as anticoagulant for PCI in patients pre-treated with subcutaneous enoxaparin.	IIa	B	788
Discontinuation of anticoagulation should be considered after an invasive procedure unless otherwise indicated.	IIa	C	
Crossover of UFH and LMWH is not recommended.	III	B	820

Windecker S et al. Eur Heart J 2014;35:2541-2619

ESC Guidelines

European Heart Journal (2016) 37, 267–315
doi:10.1093/eurheartj/ehv320

ESC GUIDELINES

2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)

Authors/Task Force Members: Marco Roffi* (Chairperson) (Switzerland), Carlo Patrono* (Co-Chairperson) (Italy), Jean-Philippe Collet† (France), Christian Mueller† (Switzerland), Marco Valgimigli† (The Netherlands), Felicita Andreotti (Italy), Jeroen J. Bax (The Netherlands), Michael A. Borger (Germany), Carlos Brotons (Spain), Derek P. Chew (Australia), Baris Gencer (Switzerland), Gerd Hasenfuss (Germany), Keld Kjeldsen (Denmark), Patrizio Lancellotti (Belgium), Ulf Landmesser (Germany), Julinda Mehilli (Germany), Debabrata Mukherjee (USA), Robert F. Storey (UK), and Stephan Windecker (Switzerland)

Roffi M et al. Eur Heart J 2016;37:267-315

Anticoagulation in NSTEMI

Recommendations	Class[a]	Level[b]	Ref.[c]
Parenteral anticoagulation is recommended at the time of diagnosis according to both ischaemic and bleeding risks.	I	B	227
Fondaparinux (2.5 mg s.c. daily) is recommended as having the most favourable efficacy–safety profile regardless of the management strategy.	I	B	218, 228, 229
Bivalirudin (0.75 mg/kg i.v. bolus, followed by 1.75 mg/kg/h for up to 4 h after the procedure) is recommended as an alternative to UFH plus GPIIb/IIIa inhibitors during PCI.	I	A	205, 222, 223
UFH 70–100 IU/kg i.v. (50–70 IU/kg if concomitant with GPIIb/IIIa inhibitors) is recommended in patients undergoing PCI who did not receive any anticoagulant.	I	B	219, 229
In patients on fondaparinux (2.5 mg s.c. daily) undergoing PCI, a single i.v. bolus of UFH (70–85 IU/kg, or 50–60 IU/kg in the case of concomitant use of GPIIb/IIIa inhibitors) is recommended during the procedure.	I	B	219
Enoxaparin (1 mg/kg s.c. twice daily) or UFH are recommended when fondaparinux is not available.	I	B	218, 230
Enoxaparin (1 mg/kg s.c. twice daily) or UFH are recommended when fondaparinux is not available.	I	B	218, 230
Enoxaparin should be considered as an anticoagulant for PCI in patients pretreated with s.c. enoxaparin.	IIa	B	211
Additional ACT-guided i.v. boluses of UFH during PCI may be considered following initial UFH treatment.	IIb	B	231
Discontinuation of anticoagulation should be considered after PCI, unless otherwise indicated.	IIa	C	
Crossover between UFH and LMWH is not recommended.	III	B	216

Roffi M et al. Eur Heart J 2016;37:267-315

Anticoagulation During PCI

European Heart Journal (2016) **37**, 3376–3385
doi:10.1093/eurheartj/ehw061

REVIEW

Controversies in cardiovascular medicine

Anticoagulation in coronary intervention

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Percutaneous coronary intervention (PCI) induces thrombin generation and is associated with the risk of acute, subacute, or long-term ischaemic events. Therefore, intravenous anticoagulation is recommended to minimize thrombotic complications. The intensity and duration of anticoagulation needed are dependent on the clinical presentation (elective PCI for stable coronary artery disease, PCI for non-ST elevation acute coronary syndromes, or primary PCI for ST-segment elevation myocardial infarction) and procedural features. As both ischaemic and periprocedural bleeding complications are associated with acute and long-term mortality, the optimal level of anticoagulation and the best agents are a matter of debate. Despite a number of limitations and the lack of large randomized clinical trials, unfractionated heparin (UFH) is still been used in the majority of interventions. Intravenous enoxaparin, a low-molecular-weight heparin, leads to a more predictable level of anticoagulation and has been compared with UFH in patients with elective PCI and primary PCI with favourable results. The direct thrombin inhibitor bivalirudin has been studied in numerous trials and consistently shown to reduce bleeding complications when compared with UFH with or without glycoprotein IIb/IIIa inhibitors. This review will summarize the current status of anticoagulation for PCI and the results of most recent trials and give recommendations for different clinical scenarios.

Keywords Percutaneous coronary intervention • Anticoagulation • Thrombin inhibition

Zeymer U et al. Eur HeartJ 2016;37:3376-3385

Anticoagulation During PCI

Table 4 Recommendations for anticoagulation in different indications in the current ACC/AHA and ESC guidelines

	UFH	Enoxaparin	Fondaparinux	Bivalirudin
Stable coronary artery disease				
ESC 2014	I	IIa	Not mentioned	I (in patients with HIT) IIa (in patients with high bleeding risk)
ACC/AHA 2011	I	IIb	III	I
NSTE-ACS				
ESC 2015	I (in patients who cannot receive bivalirudin)	IIa (in patients pre-treated with enoxaparin)	I (if used additional UFH during PCI)	I
ACC/AHA 2014	I	IIb (in patients pre-treated with enoxaparin)	III as sole anticoagulant during PCI	I
STEMI				
ESC 2014	I	IIa	III	IIa
ACC/AHA 2013	I	Not mentioned	III	I

Zeymer U et al. Eur HeartJ 2016;37:3376-3385

Anticoagulation During PCI

Intravenous antiplatelet therapy			
GPIIb/IIIa inhibitors during PCI should be considered for bailout situations or thrombotic complications.	IIa	C	
Cangrelor may be considered in $P2Y_{12}$ inhibitor–naive patients undergoing PCI.	IIb	A	158–161
It is not recommended to administer GPIIb/IIIa inhibitors in patients in whom coronary anatomy is not known.	III	A	198, 199

Zeymer U et al. Eur HeartJ 2016;37:3376-3385

Anticoagulation During PCI

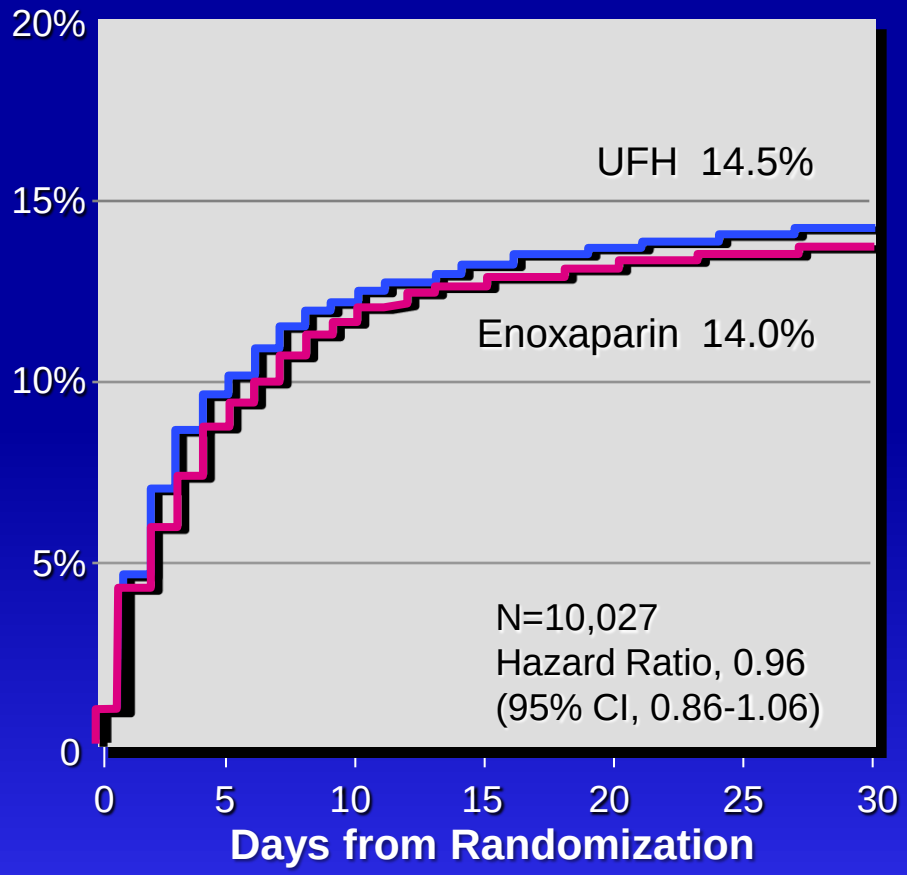
Recommendations for combining antiplatelet agents and anticoagulants in non-ST-elevation acute coronary syndrome patients requiring chronic oral anticoagulation

Recommendations	Class[a]	Level[b]	Ref.[c]
Patients undergoing coronary stenting			
Anticoagulation			
During PCI, additional parenteral anticoagulation is recommended, irrespective of the timing of the last dose of all NOACs and if INR is <2.5 in VKA-treated patients.	I	C	
Uninterrupted therapeutic anticoagulation with VKA or NOACs should be considered during the periprocedural phase.	IIa	C	

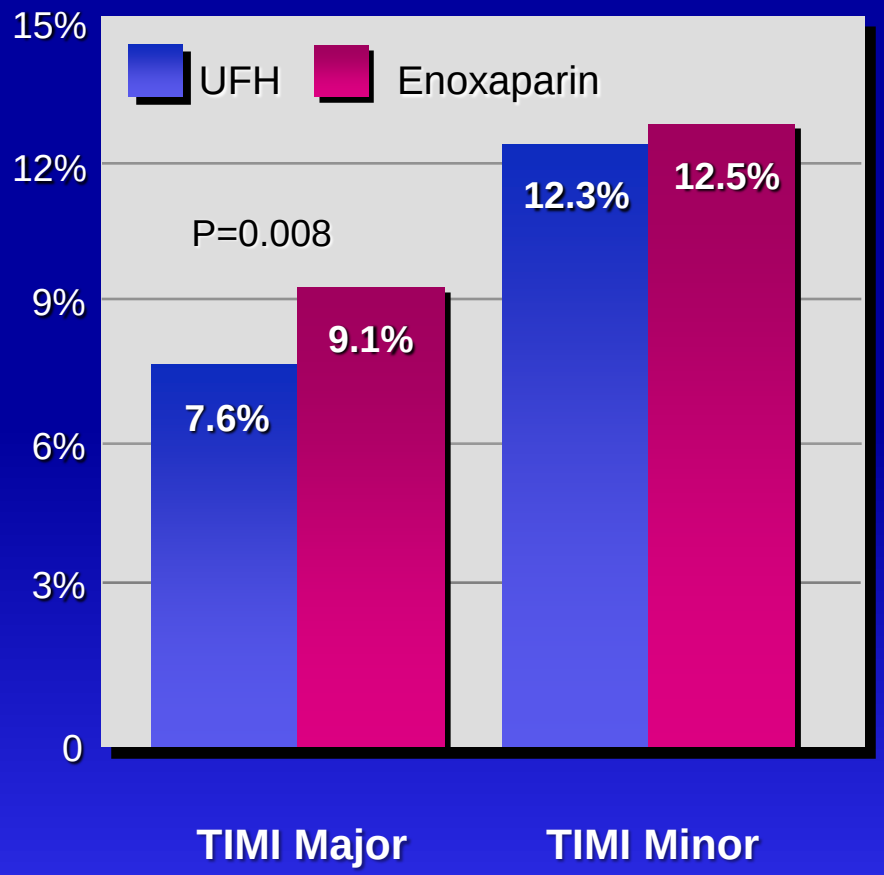
Zeymer U et al. Eur HeartJ 2016;37:3376-3385

SYNERGY

30-Day Death or MI



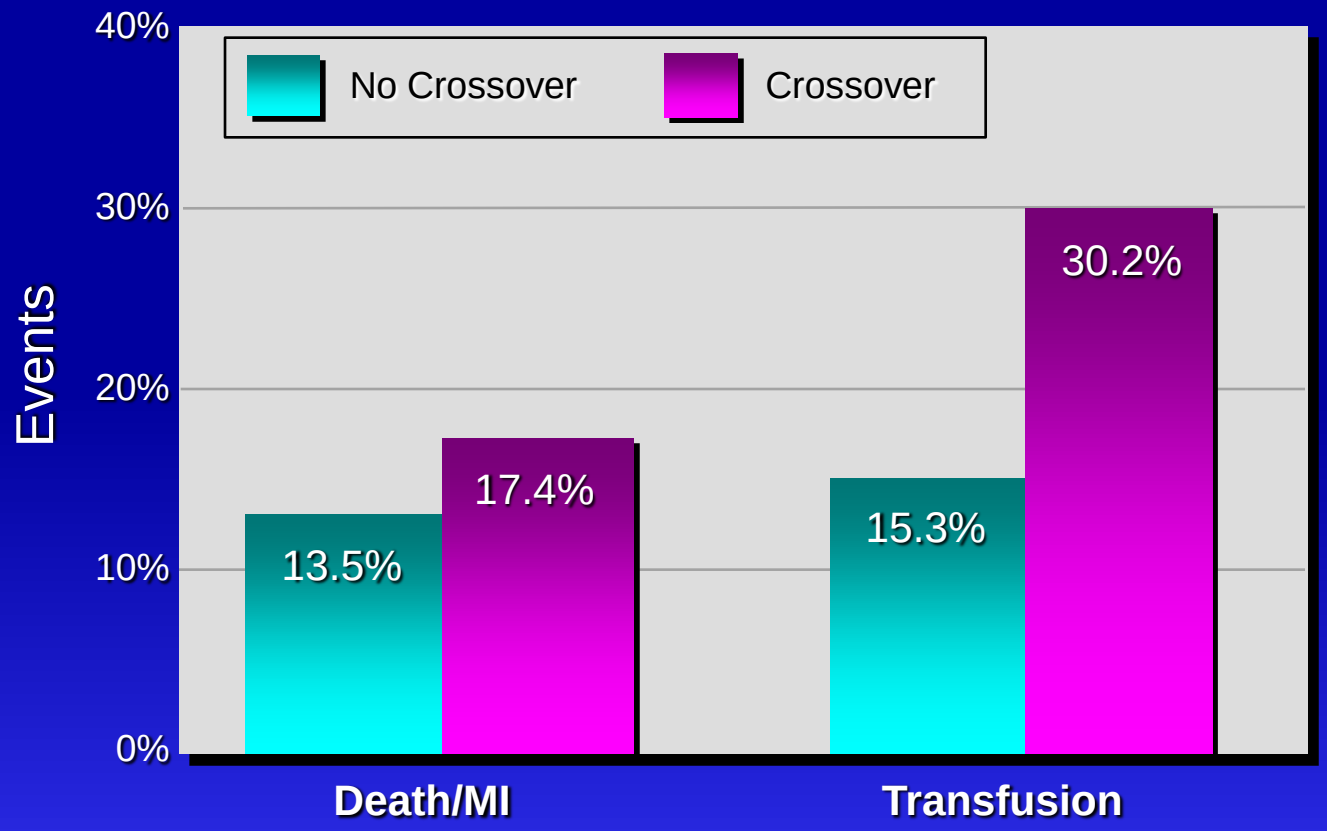
Bleeding



SYNERGY Trial Investigators. JAMA 2004;292:45-54

SYNERGY

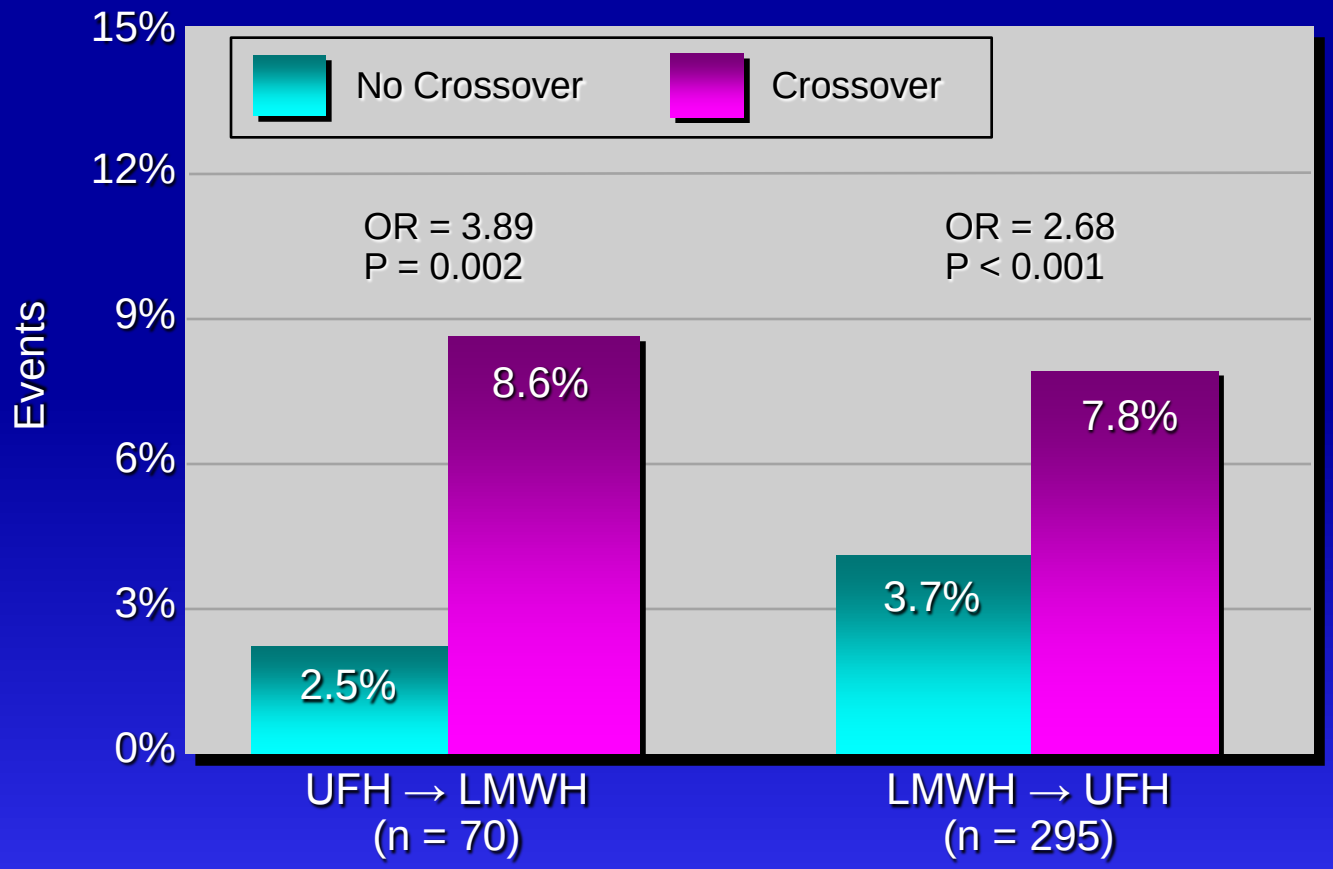
Crossovers from LMWH to UFH



The SYNERGY Trial Investigators. JAMA 2004;292:52

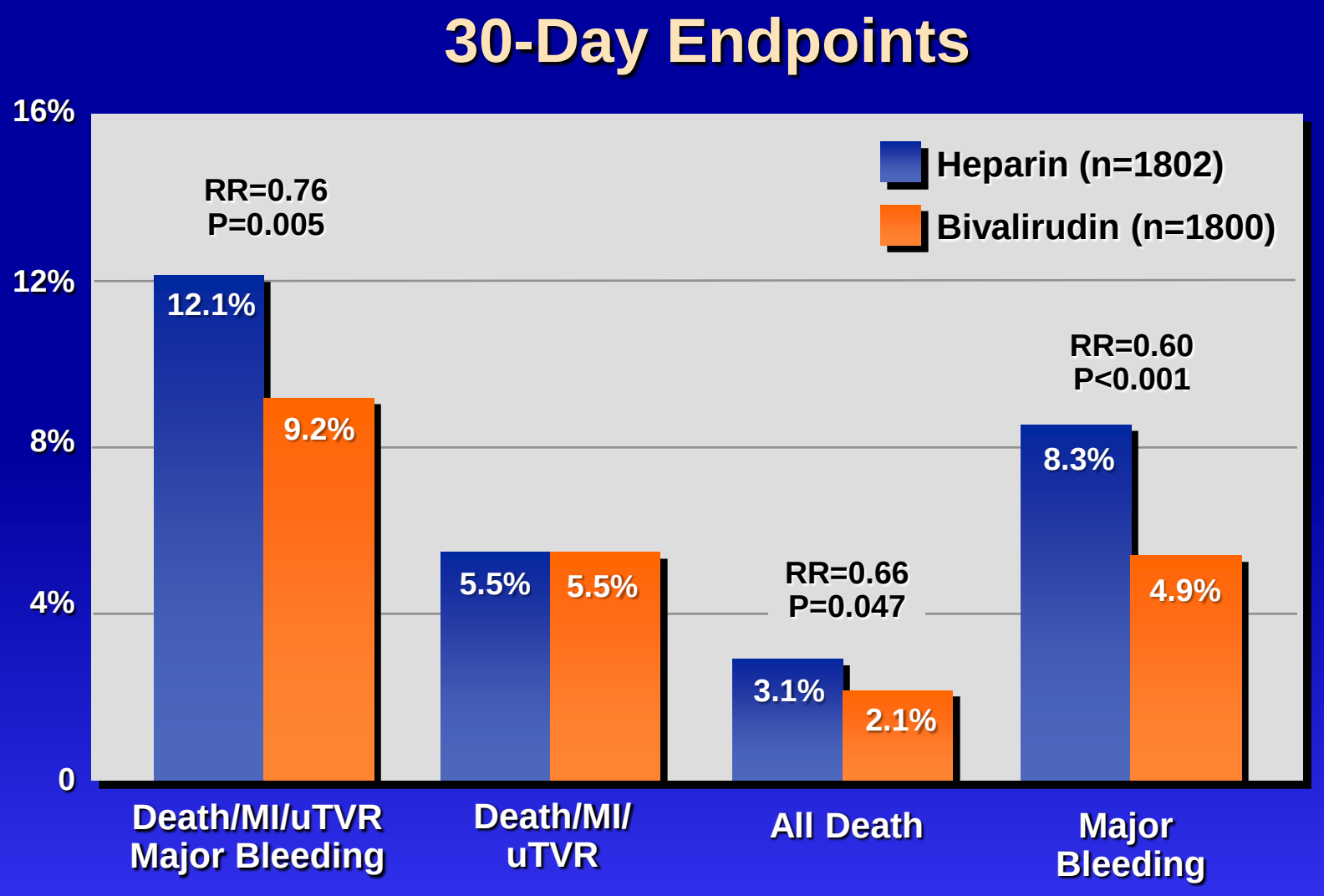
SYNERGY: PCI Cohort

TIMI Major Bleeding Among Crossovers



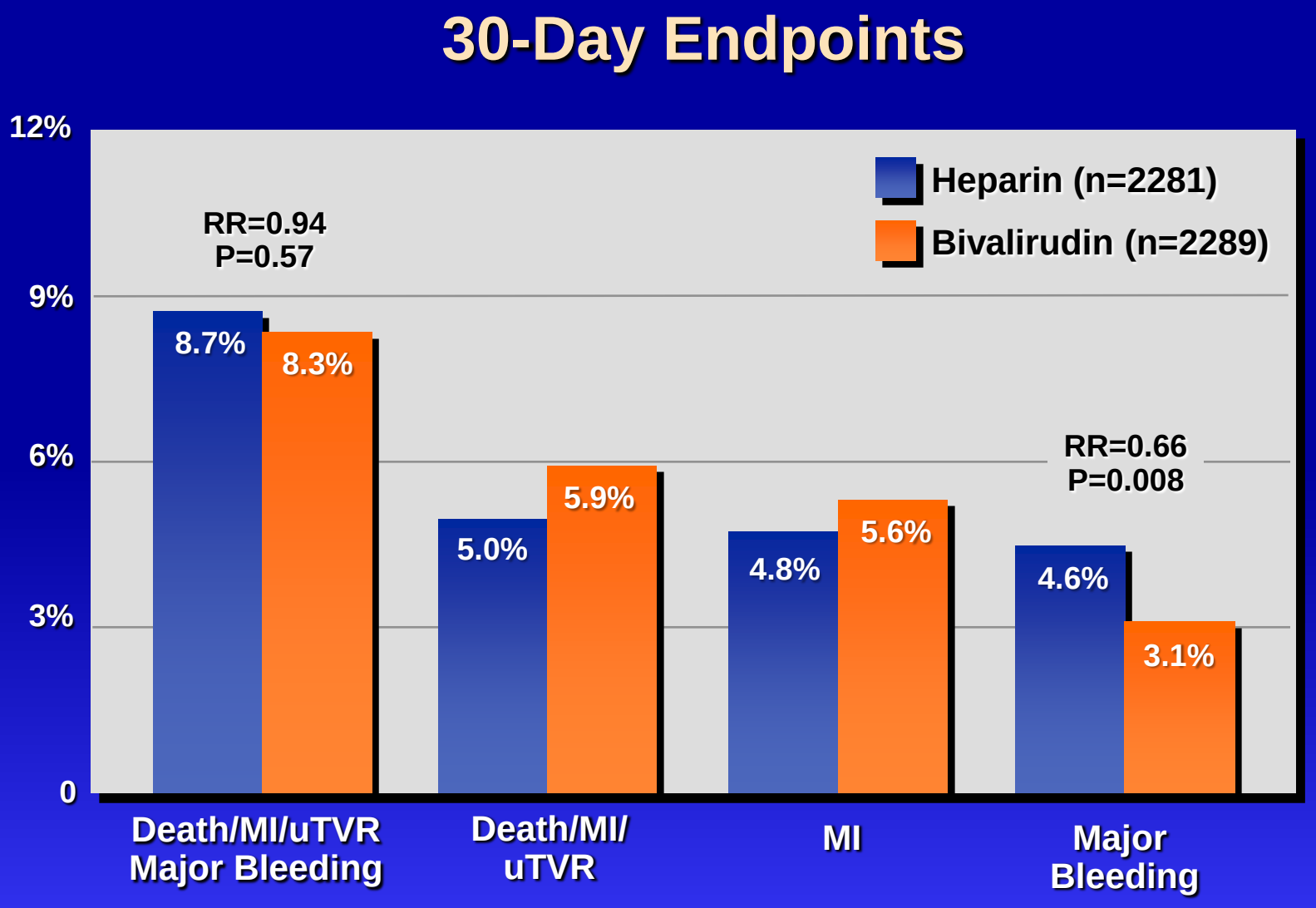
White HD et al. Am Heart J 2006;152:1042

HORIZONS-AMI



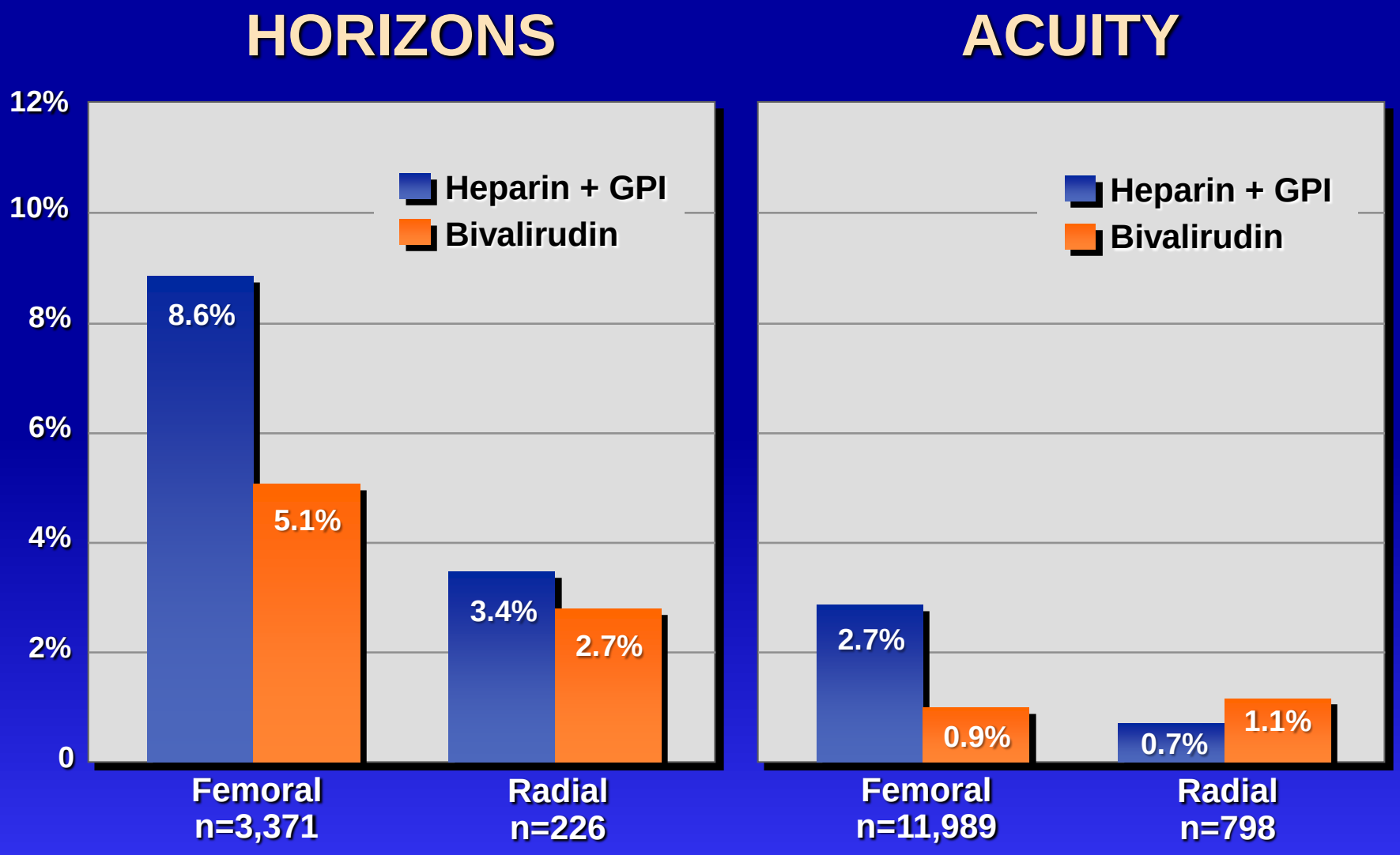
Stone GW et al. N Engl J Med 2008;358:2218-2230

ISAR-REACT 3

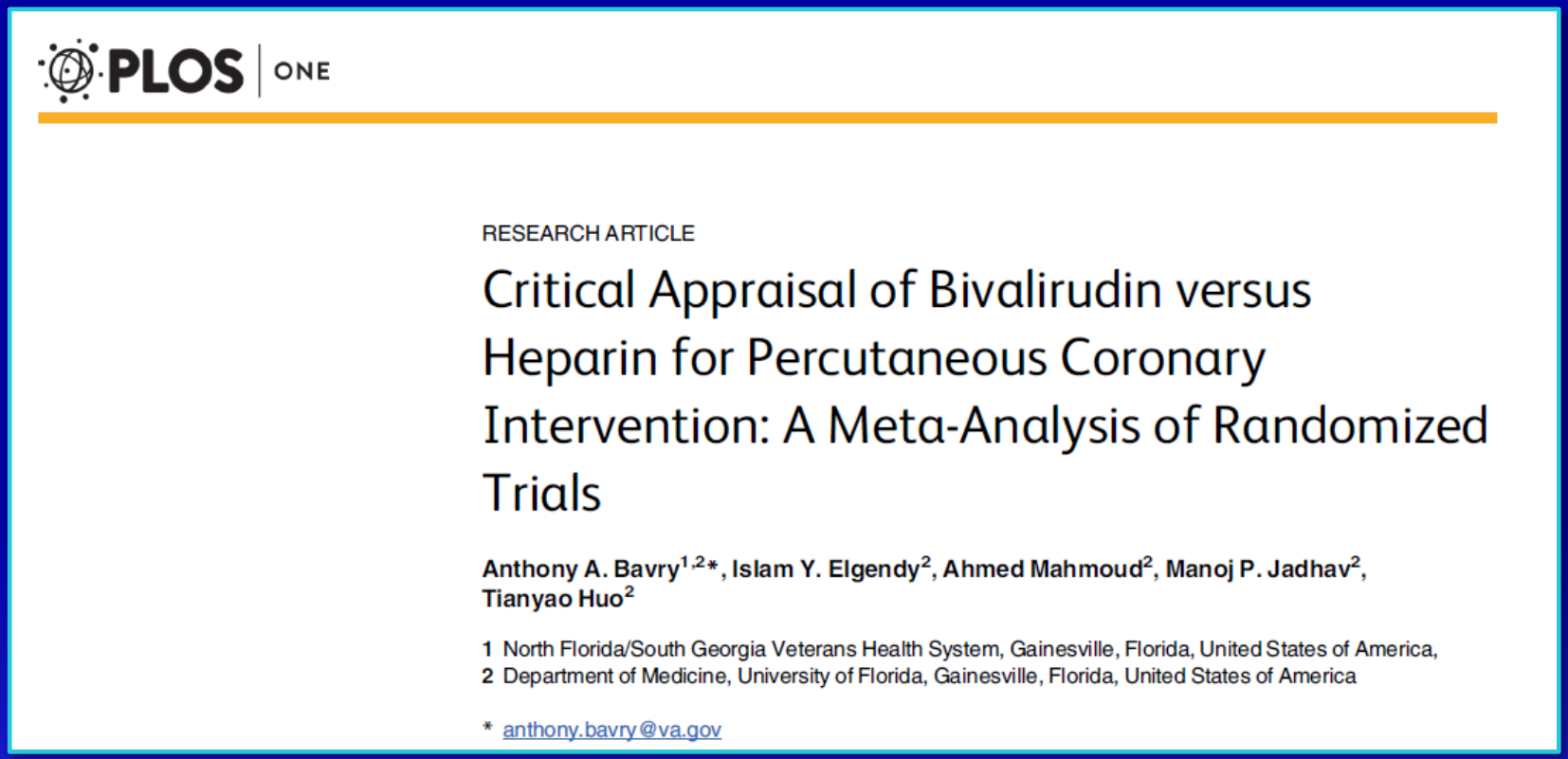


Kastrati et al. N Engl J Med 2008;359:688

Major Bleeding by Access Site



Bivalirudin Meta-analysis



PLOS ONE

RESEARCH ARTICLE

Critical Appraisal of Bivalirudin versus Heparin for Percutaneous Coronary Intervention: A Meta-Analysis of Randomized Trials

Anthony A. Bavry[1,2]*, Islam Y. Elgendy[2], Ahmed Mahmoud[2], Manoj P. Jadhav[2], Tianyao Huo[2]

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2 Department of Medicine, University of Florida, Gainesville, Florida, United States of America

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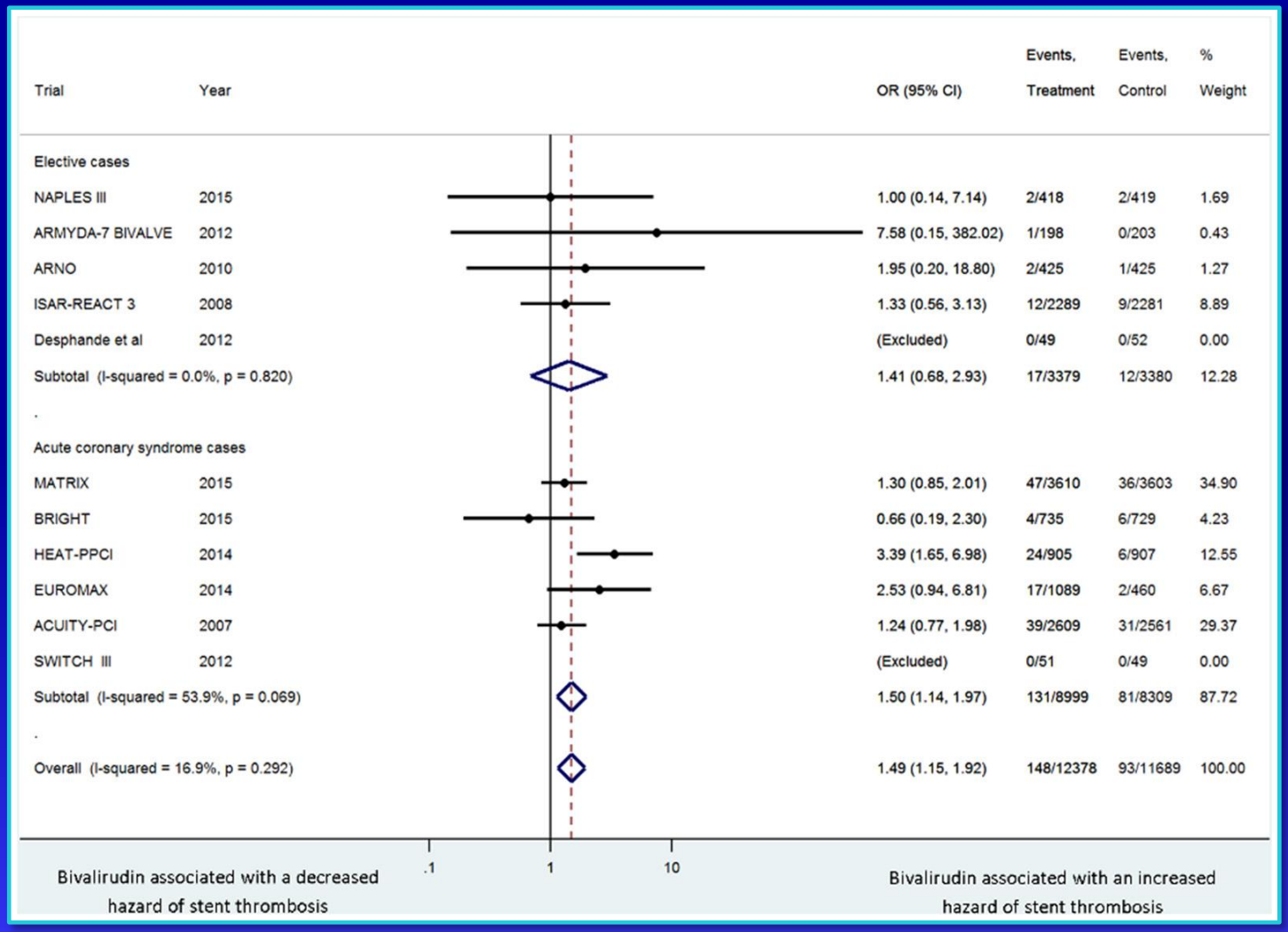
- 15 PCI RCTs of bivalirudin versus heparin with 30-day outcome
- N = 25,824 (STEMI, NSTEMI, and elective cases)
- Similar intended use of GP IIb/IIIa inhibtors between groups

Bavry A et al. PlosOne 2015;10:e0127832

Bivalirudin Meta-analysis

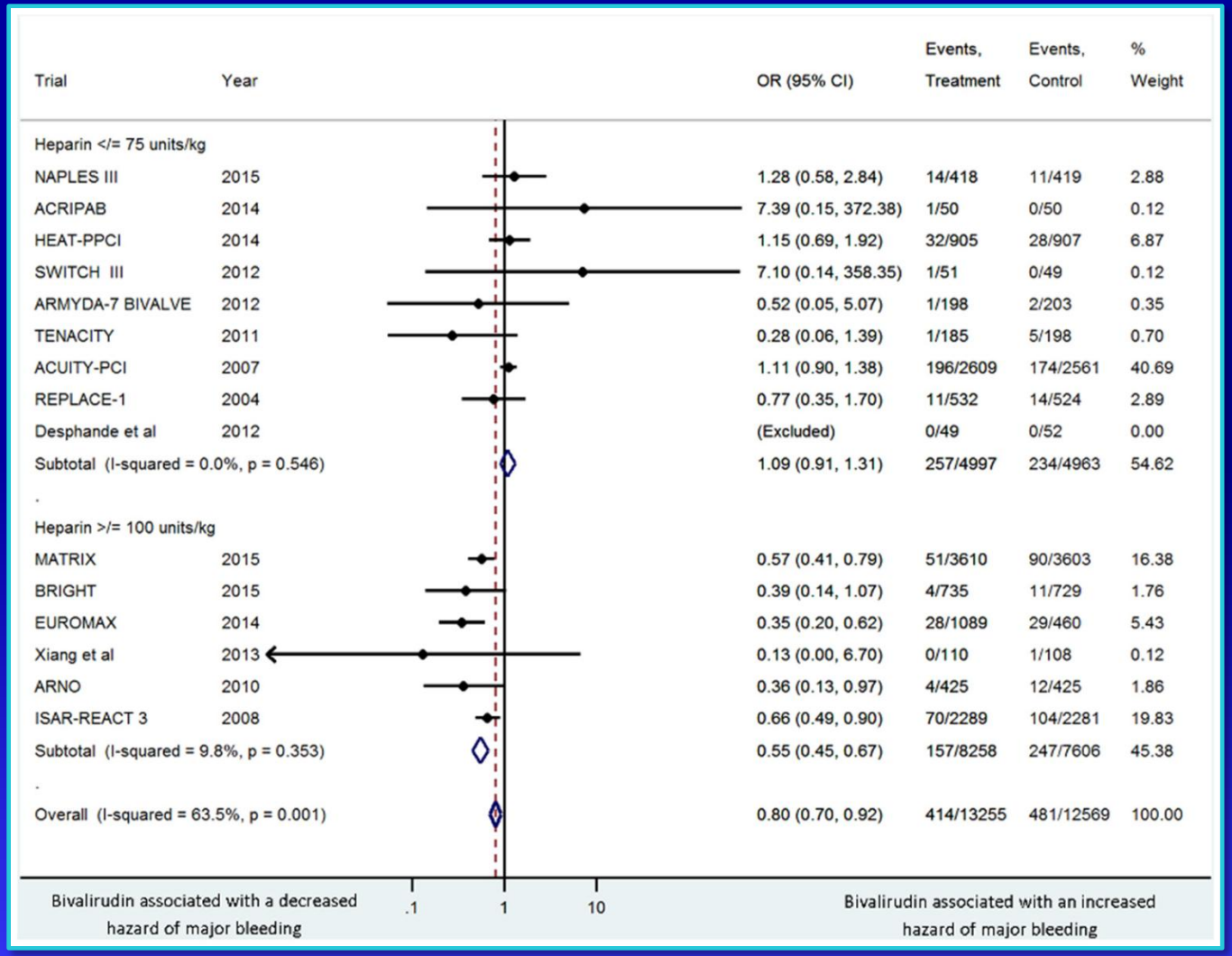
Stent Thrombosis



Bavry A et al. PlosOne 2015;10:e0127832

Bivalirudin Meta-analysis

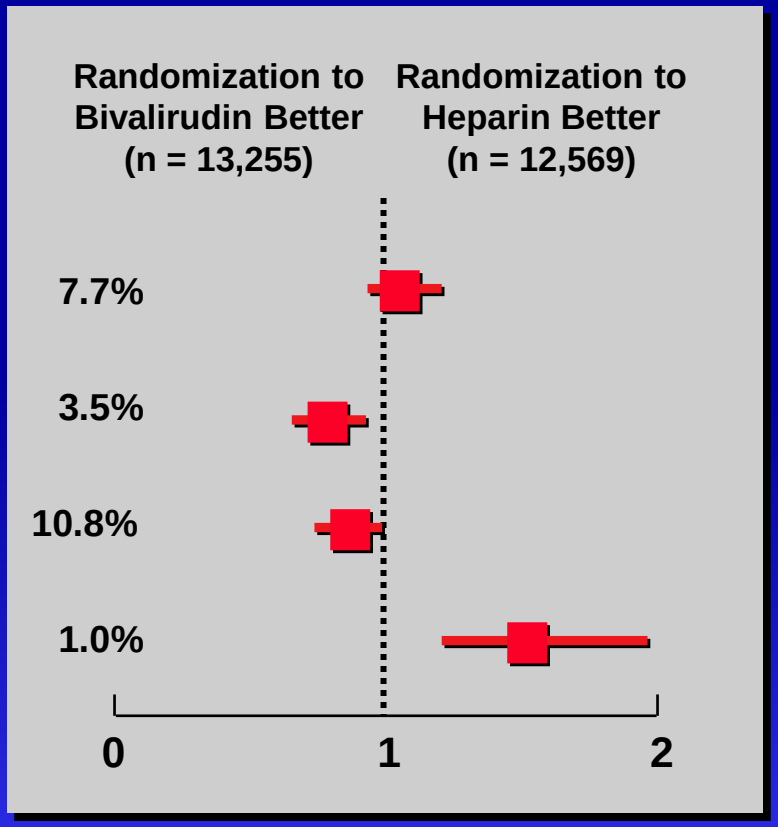
Major Bleeding



Bavry A et al. PlosOne 2015;10:e0127832

Bivalirudin Meta-analysis

30-Day Events



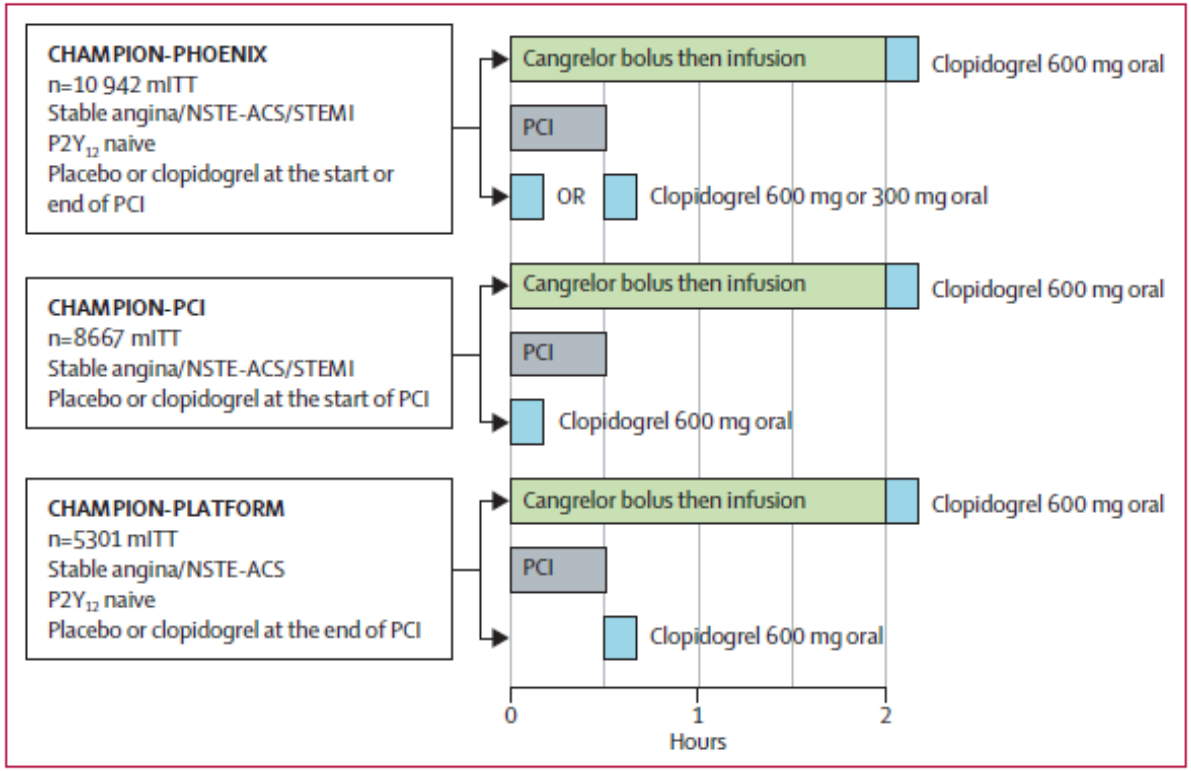
Outcome		OR (95% CI)	P
MACE	7.7%	1.04 (0.94 – 1.14)	0.46
Major Bleeding	3.5%	0.80 (0.70 – 0.92)	0.001
NACE	10.8%	0.91 (0.84 – 0.99)	0.028
Stent Thrombosis	1.0%	1.49 (1.15 – 1.92)	0.002

Bavry A et al. PlosOne 2015;10:e0127832

CHAMPION Trials

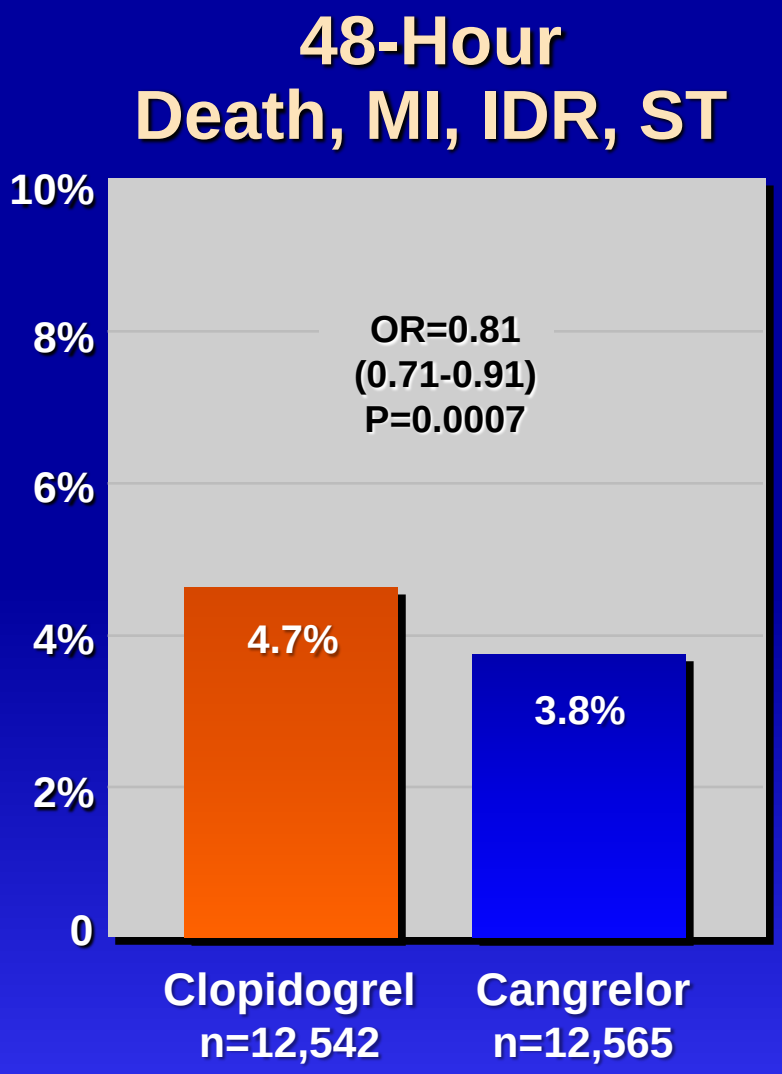
Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data

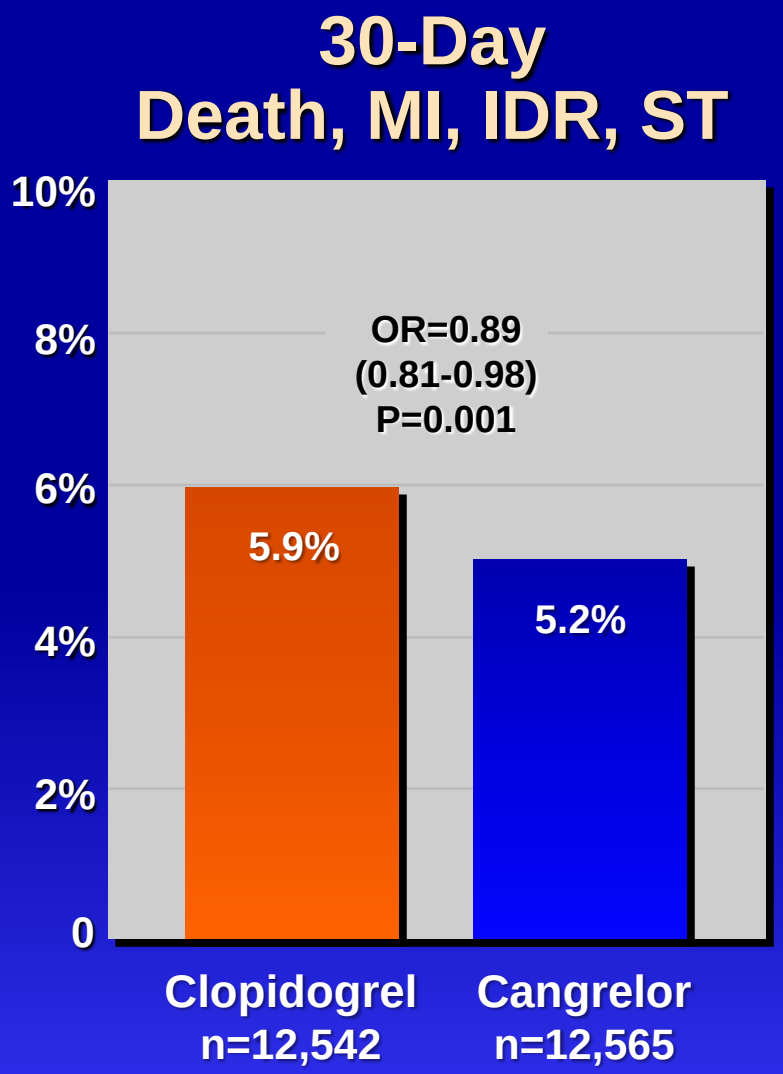
Philippe Gabriel Steg, Deepak L Bhatt, Christian W Hamm, Gregg W Stone, C Michael Gibson, Kenneth W Mahaffey, Sergio Leonardi, Tiepu Liu, Simona Skerjanec, Jonathan R Day, Robert S Iwaoka, Thomas D Stuckey, Harinder S Gogia, Luis Gruberg, William J French, Harvey D White, Robert A Harrington, for the CHAMPION Investigators



Steg PG et al. Lancet 2013;382:1981-1992

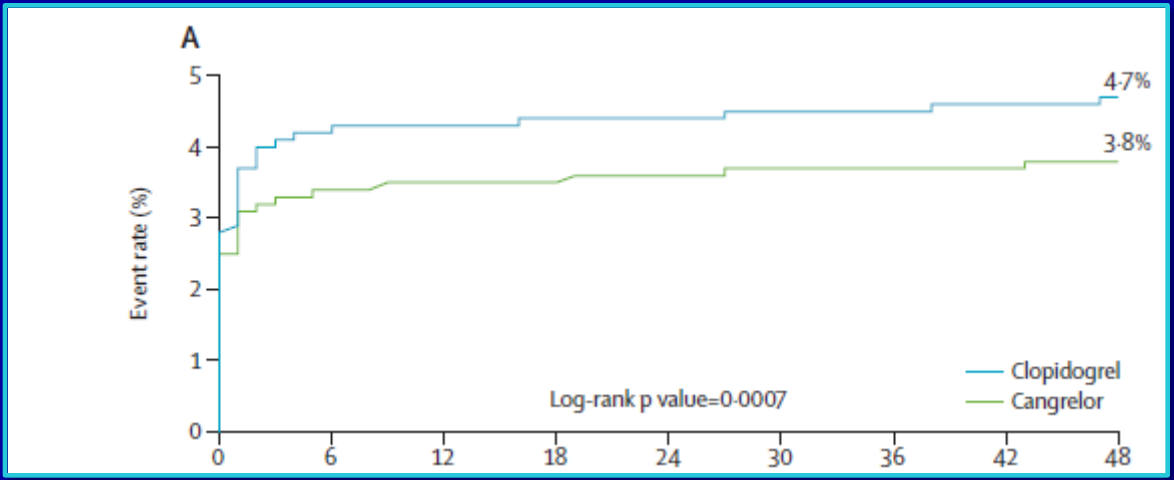
CHAMPION Trials



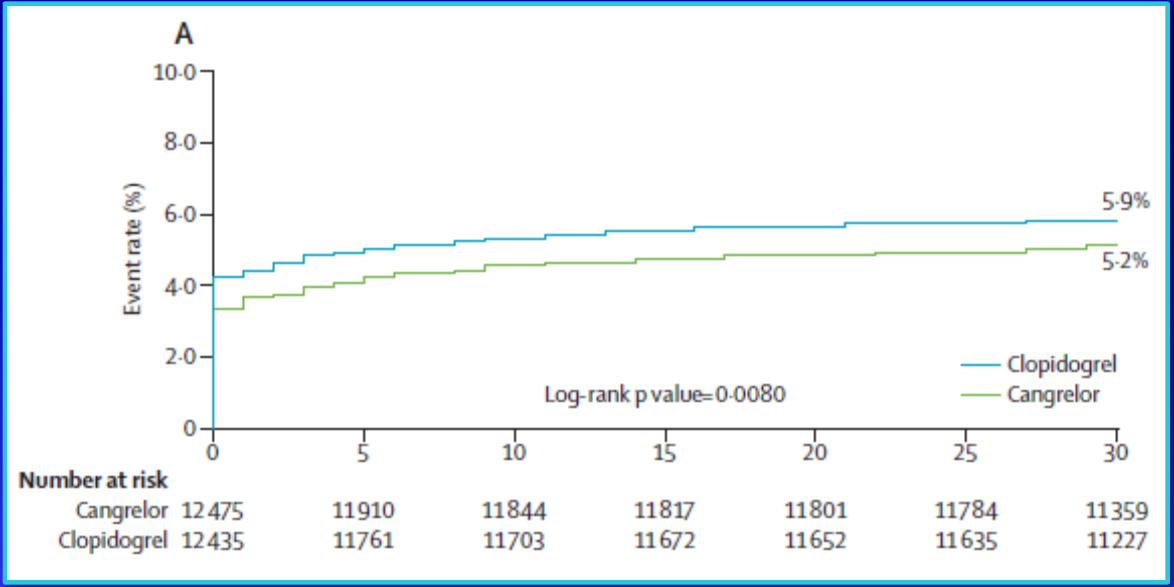


Steg PG et al. Lancet 2013;382:1981-1992

CHAMPION Trials



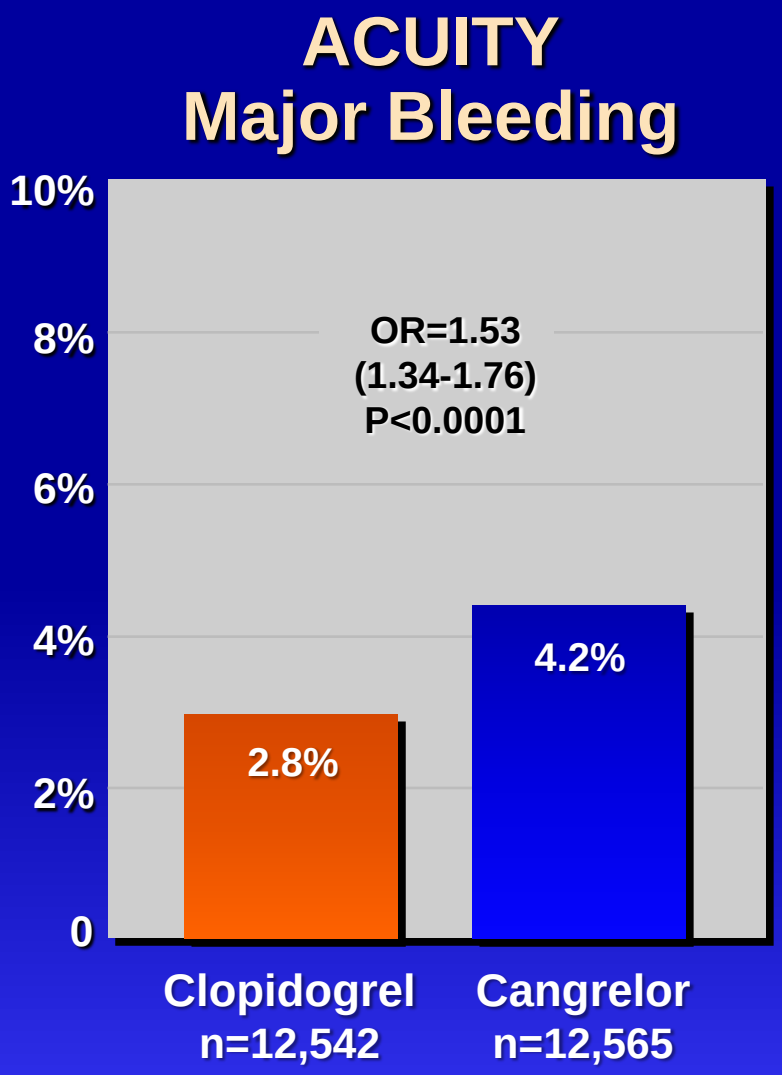
At 48 Hours
0.9% ARR
19% RRR
OR 0.81 (0.71-0.91)
P=0.007

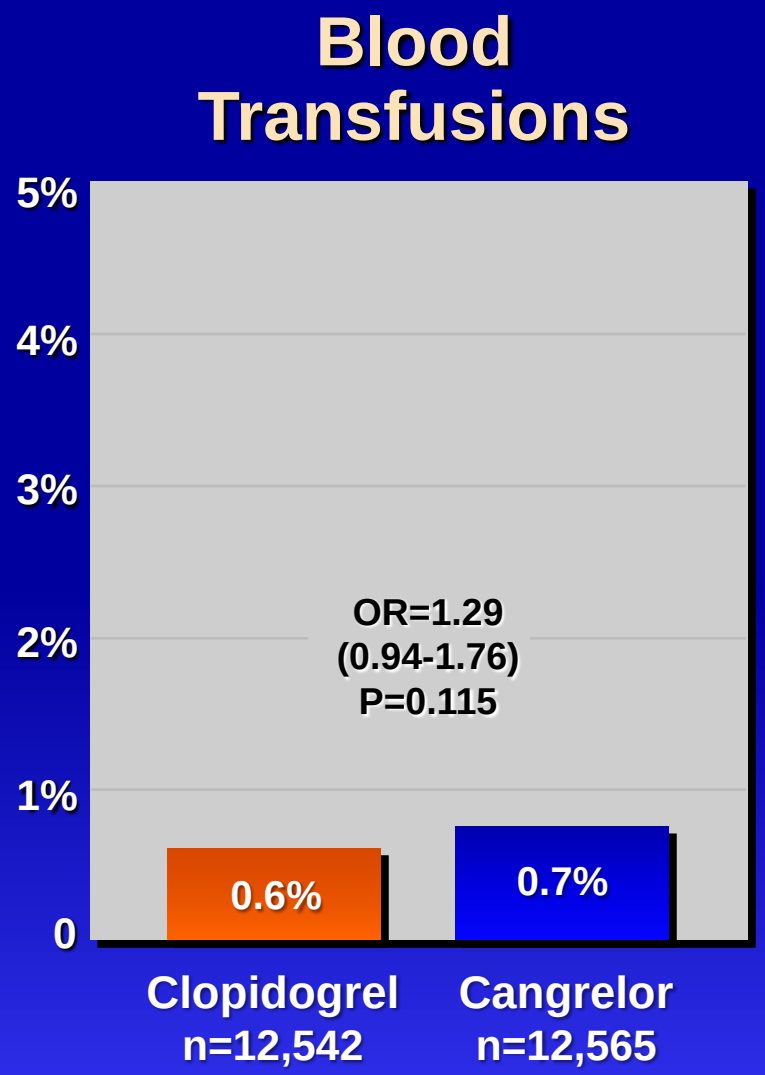


At 30 Days
0.7% ARR
13% RRR
OR 0.87 (0.78-0.97)
P=0.001

Steg PG et al. Lancet 2013;382:1981-1992

CHAMPION Trials





Steg PG et al. Lancet 2013;382:1981-1992

CHAMPION Trials

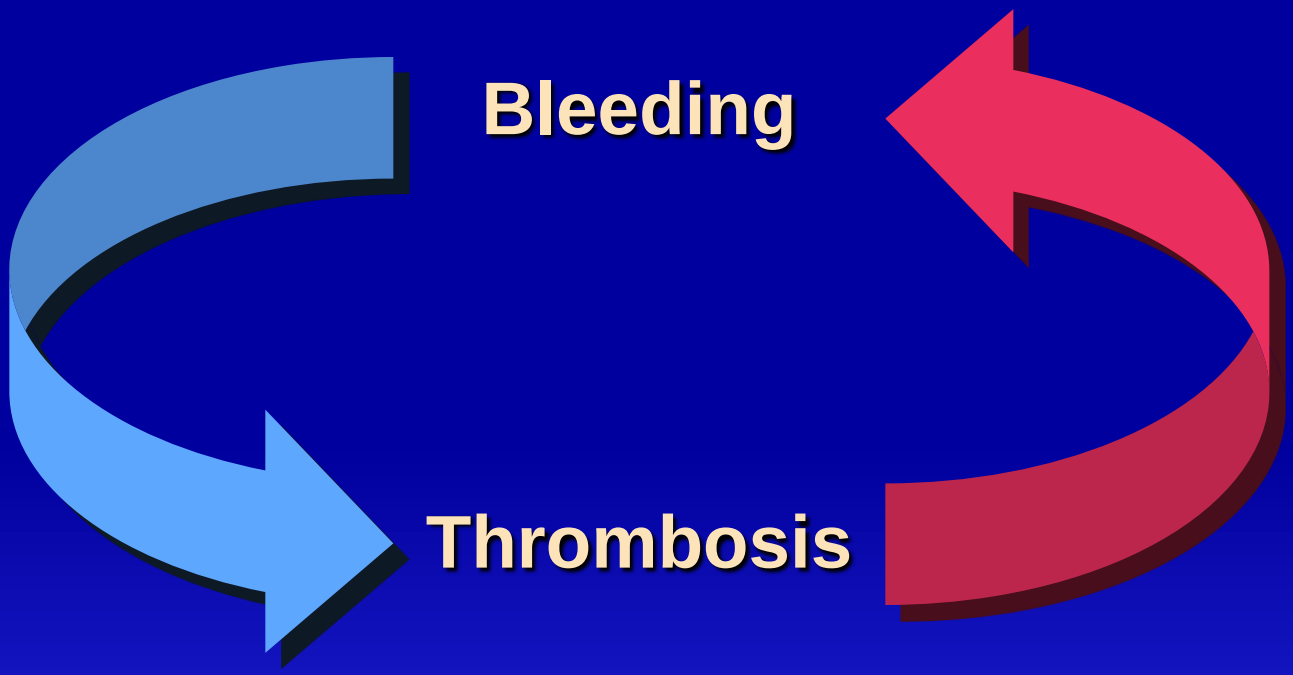
	Cangrelor (n=12 565)	Clopidogrel (n=12 542)	OR (95% CI)	p*
GUSTO bleeding				
Severe/life threatening	28 (0·2%)	23 (0·2%)	1·22 (0·70–2·11)	0·4875
Moderate	76 (0·6%)	56 (0·4%)	1·36 (0·96–1·92)	0·0828
Severe/moderate	103 (0·8%)	79 (0·6%)	1·30 (0·97–1·75)	0·0762
Mild	2109 (16·8%)	1627 (13·0%)	1·35 (1·26–1·45)	<0·0001
Mild, excluding ecchymosis, oozing, and <5 cm haematoma	707 (5·6%)	515 (4·1%)	1·39 (1·24–1·56)	<0·0001
Any GUSTO bleed	2196 (17·5%)	1696 (13·5%)	1·35 (1·26–1·45)	<0·0001
TIMI bleeding				
Major	32 (0·3%)	28 (0·2%)	1·14 (0·69–1·90)	0·6101
Minor	77 (0·6%)	51 (0·4%)	1·51 (1·06–2·15)	0·0218
TIMI major/minor	109 (0·9%)	79 (0·6%)	1·38 (1·03–1·85)	0·0290
ACUITY bleeding				
Major	534 (4·2%)	353 (2·8%)	1·53 (1·34–1·76)	<0·0001
Major excluding haematoma ≥5 cm	169 (1·3%)	123 (1·0%)	1·38 (1·09–1·74)	0·0071
Minor	1738 (13·8%)	1381 (11·0%)	1·30 (1·20–1·40)	<0·0001
Minor excluding ecchymosis, oozing, and <5 cm haematoma	293 (2·3%)	255 (2·0%)	1·15 (0·97–1·36)	0·1053
ACUITY major/minor	2196 (17·5%)	1696 (13·5%)	1·35 (1·26–1·45)	<0·0001
Any blood transfusion	90 (0·7%)	70 (0·6%)	1·29 (0·94–1·76)	0·1154

ACUITY=Acute Catheterization and Urgent Intervention Triage Strategy. CABG=coronary artery bypass graft. GUSTO=Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. TIMI=Thrombolysis In Myocardial Infarction. *p value for OR based on the χ^2 test.

Table 5: **Non-CABG-related bleeding events at 48 h**

Steg PG et al. Lancet 2013;382:1981-1992

Optimal Anticoagulation—does it exist?



intensity x duration

Summary

- Summary—for ACS/PCI there are between 30 and 1200 different combinations of options for the anticoagulation strategy
- Ischemic events are lowered by 1-1.5% and bleeding events are increased by 1-1.5%
- Advice—become very knowledgeable and comfortable with one drug at a time and then with one combination of anticoagulants, before exploring the next