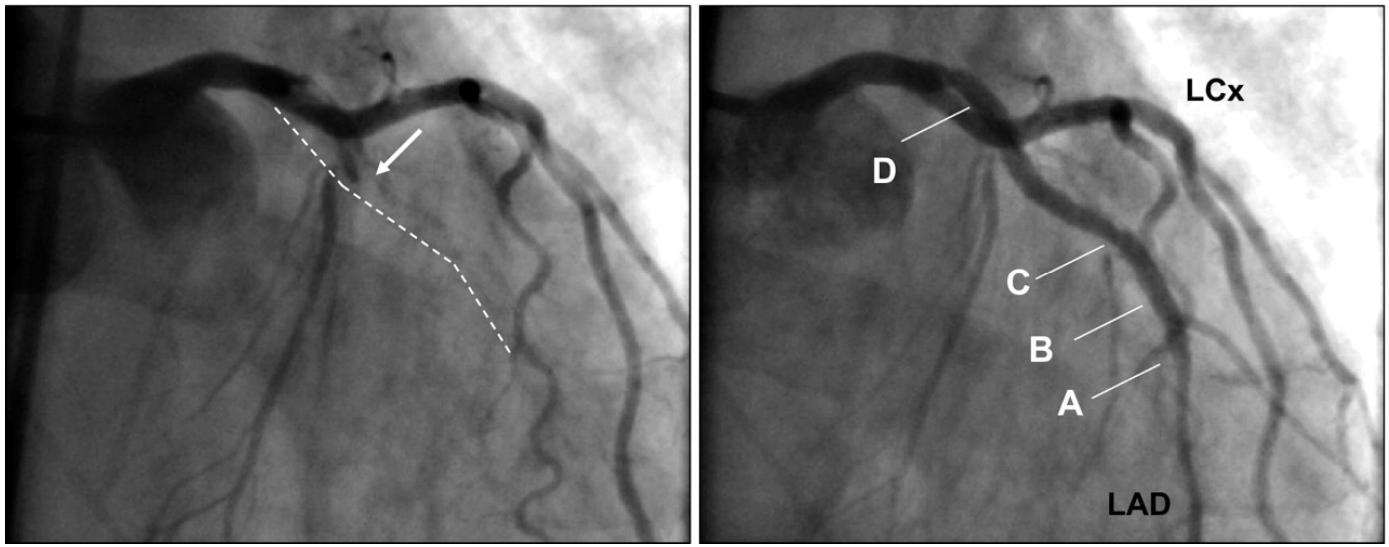
Late Stent Thrombosis: Pursuing the Elusive Goal

Spencer King MD MACC
St Joseph's Heart and Vascular Institute
Professor of Medicine Emeritus
Emory University
Atlanta, USA

Coronary Angiogram

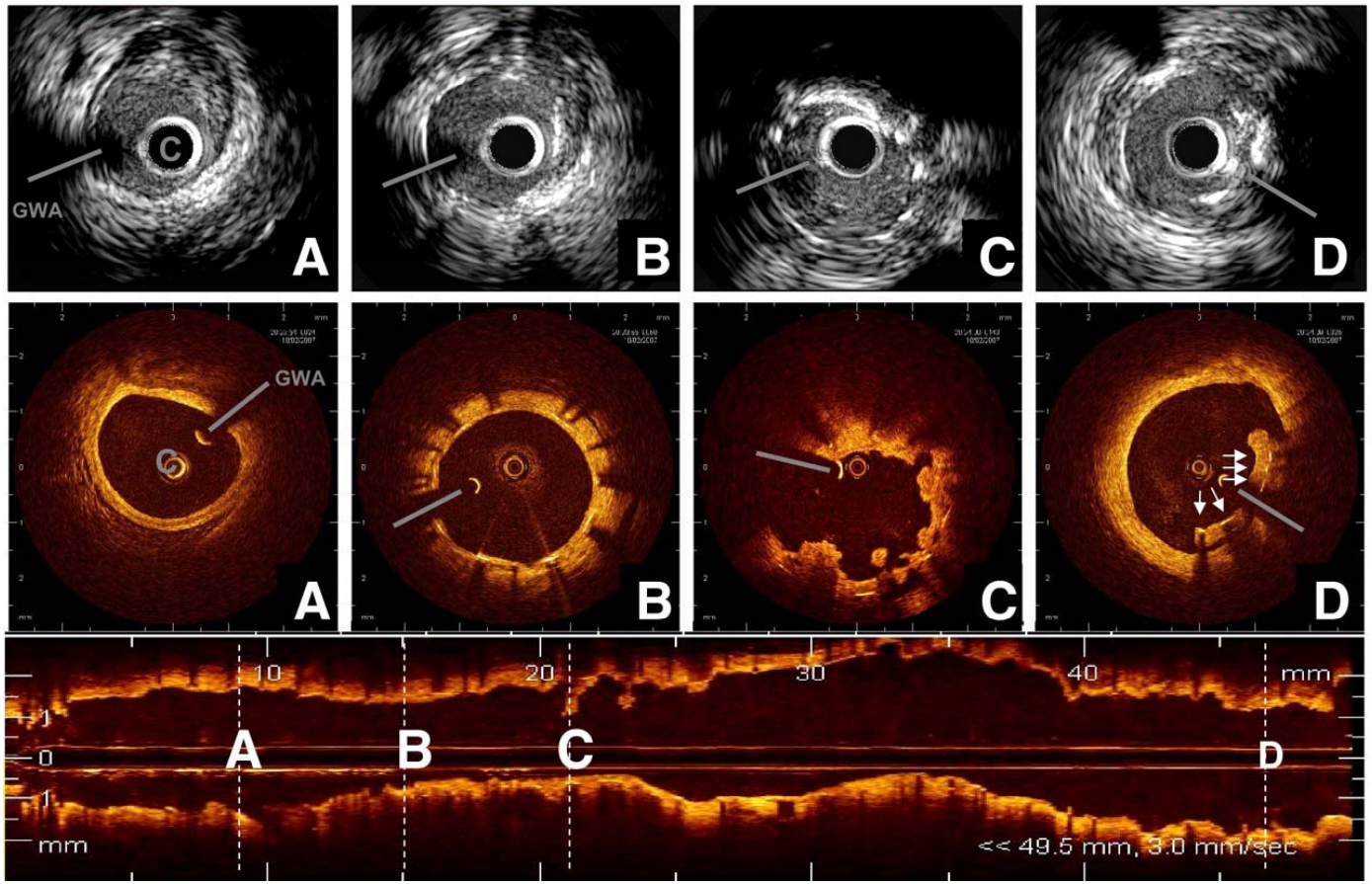


Schinkel, A. F.L. et al. J Am Coll Cardiol Intv 2008;1:449-451

Copyright ©2008 American College of Cardiology Foundation. Restrictions may apply.

JACC Cardiovascular Interventions

Intracoronary Imaging After Thrombus Aspiration

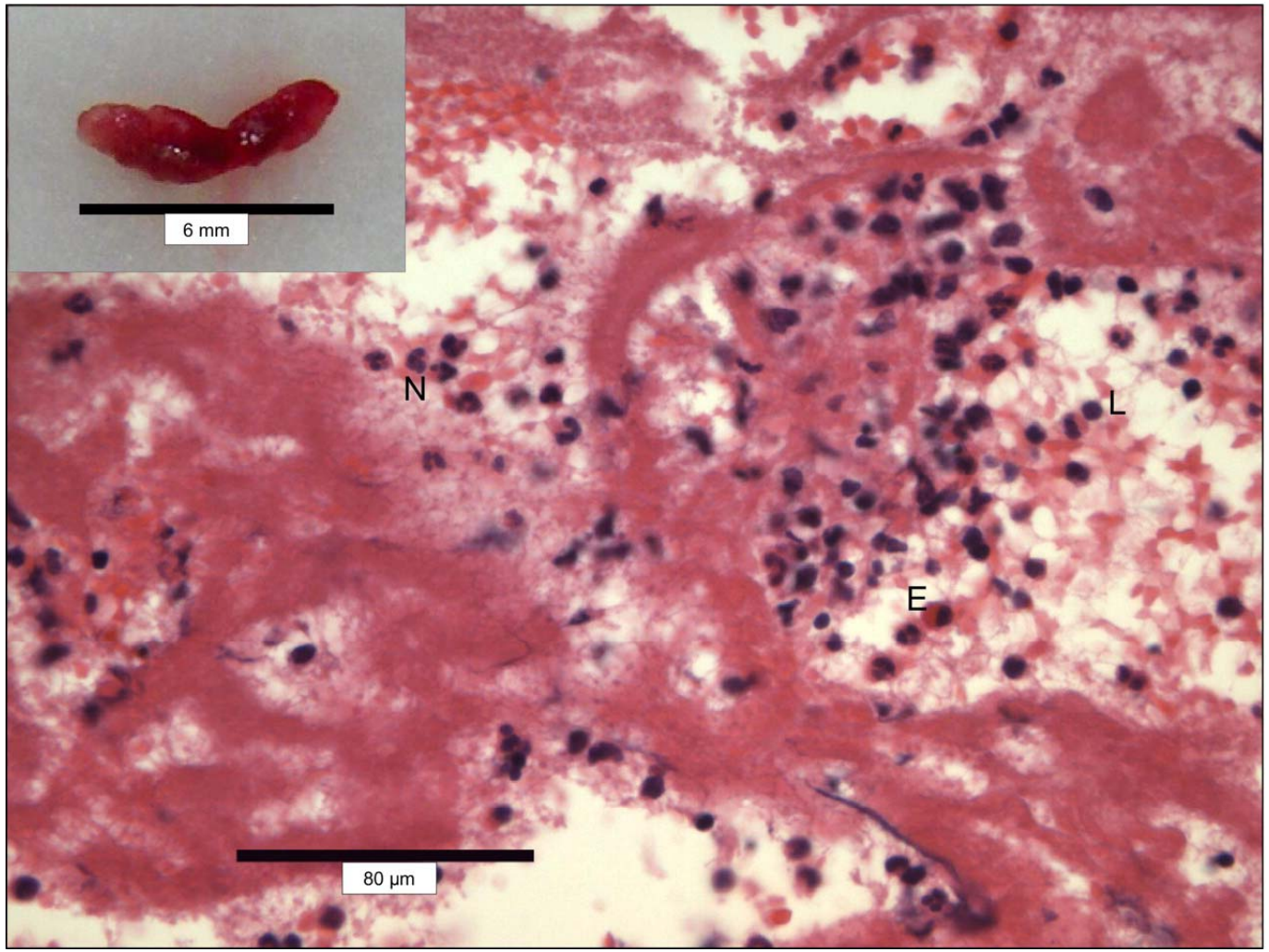


Schinkel, A. F.L. et al. J Am Coll Cardiol Intv 2008;1:449-451

Copyright ©2008 American College of Cardiology Foundation. Restrictions may apply.

JACC Cardiovascular Interventions

Histology of the Aspirated Thrombus



Schinkel, A. F.L. et al. J Am Coll Cardiol Intv 2008;1:449-451

Copyright ©2008 American College of Cardiology Foundation. Restrictions may apply.

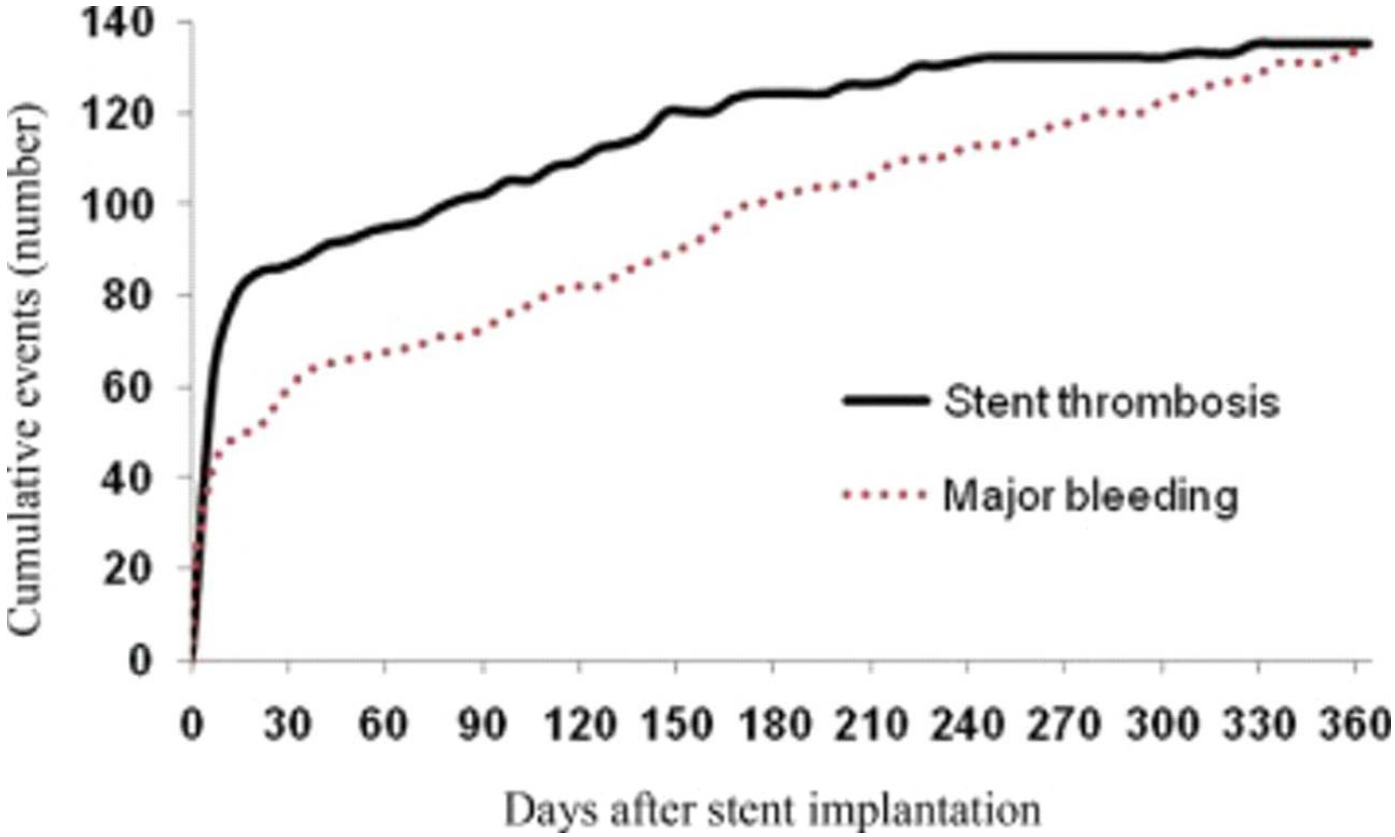
JACC Cardiovascular Interventions

Stent Thrombosis

- Most ST occurs acutely or sub acutely
- Late ST is not rare
- The occurrence of late ST is linear over time
- The etiology of late ST is still being defined
- The measures to reduce the chance of late ST are still being investigated

What is the time course of stent thrombosis?

Incidence of Definite or Probable Stent Thrombosis and Major Bleeding

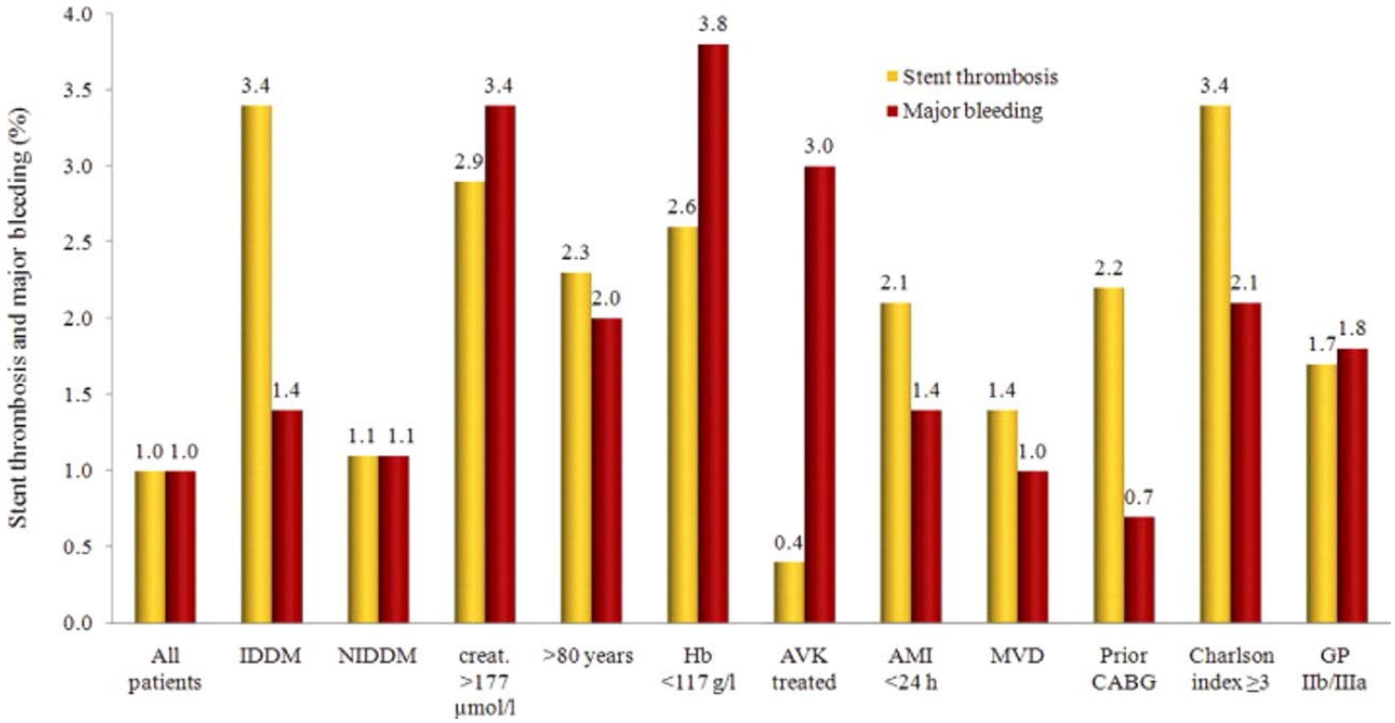


Urban, P. et al. J Am Coll Cardiol 2011;57:1445-1454

Copyright ©2011 American College of Cardiology Foundation. Restrictions may apply.

Bleeders or Clotters?

Stent Thrombosis and Major Bleeding in Selected Patient Subgroups



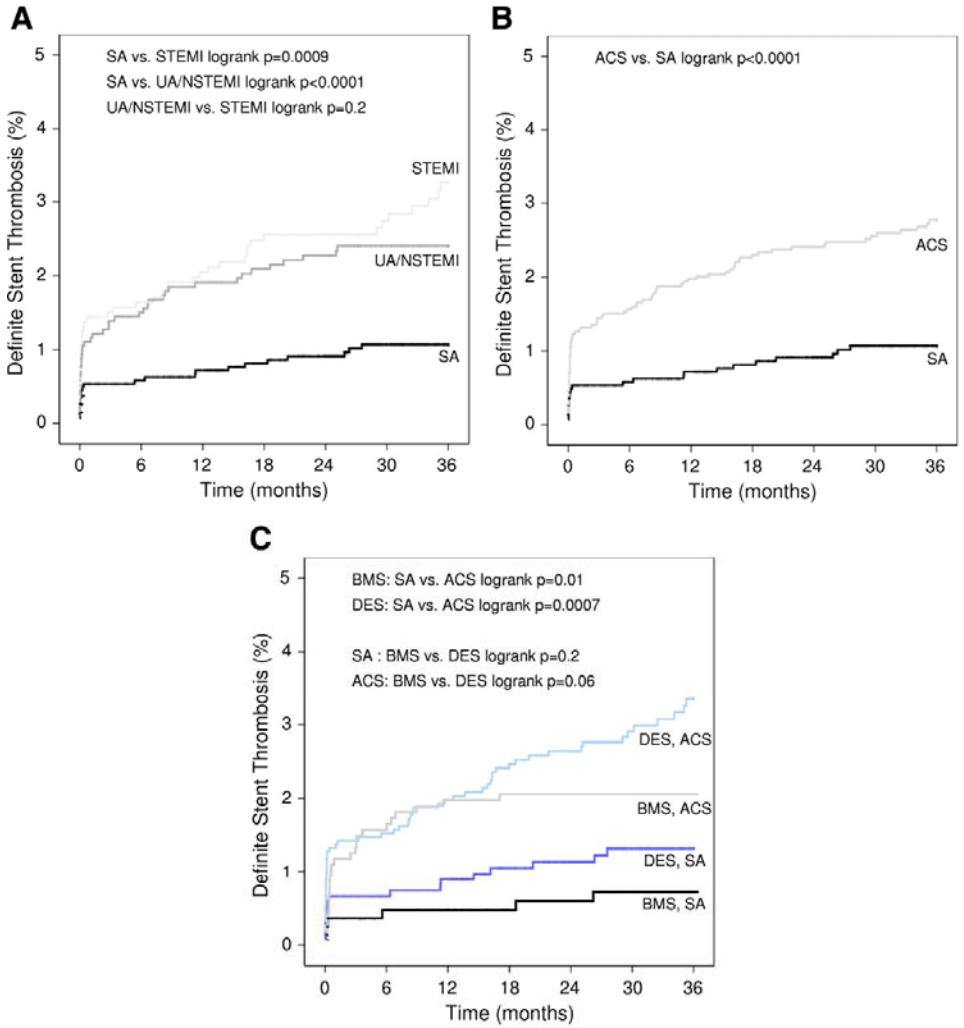
Urban, P. et al. J Am Coll Cardiol 2011;57:1445-1454

Copyright ©2011 American College of Cardiology Foundation. Restrictions may apply.

JACC Journal of the American College of Cardiology

Patients with ACS are at higher risk of early or late stent thrombosis with either DES or BMS but very late ST is almost unique to DES.

Cumulative Incidence of Stent Thrombosis According to Clinical Presentation, in Stable and Unstable Patients, and According to Presentation and Stent Type

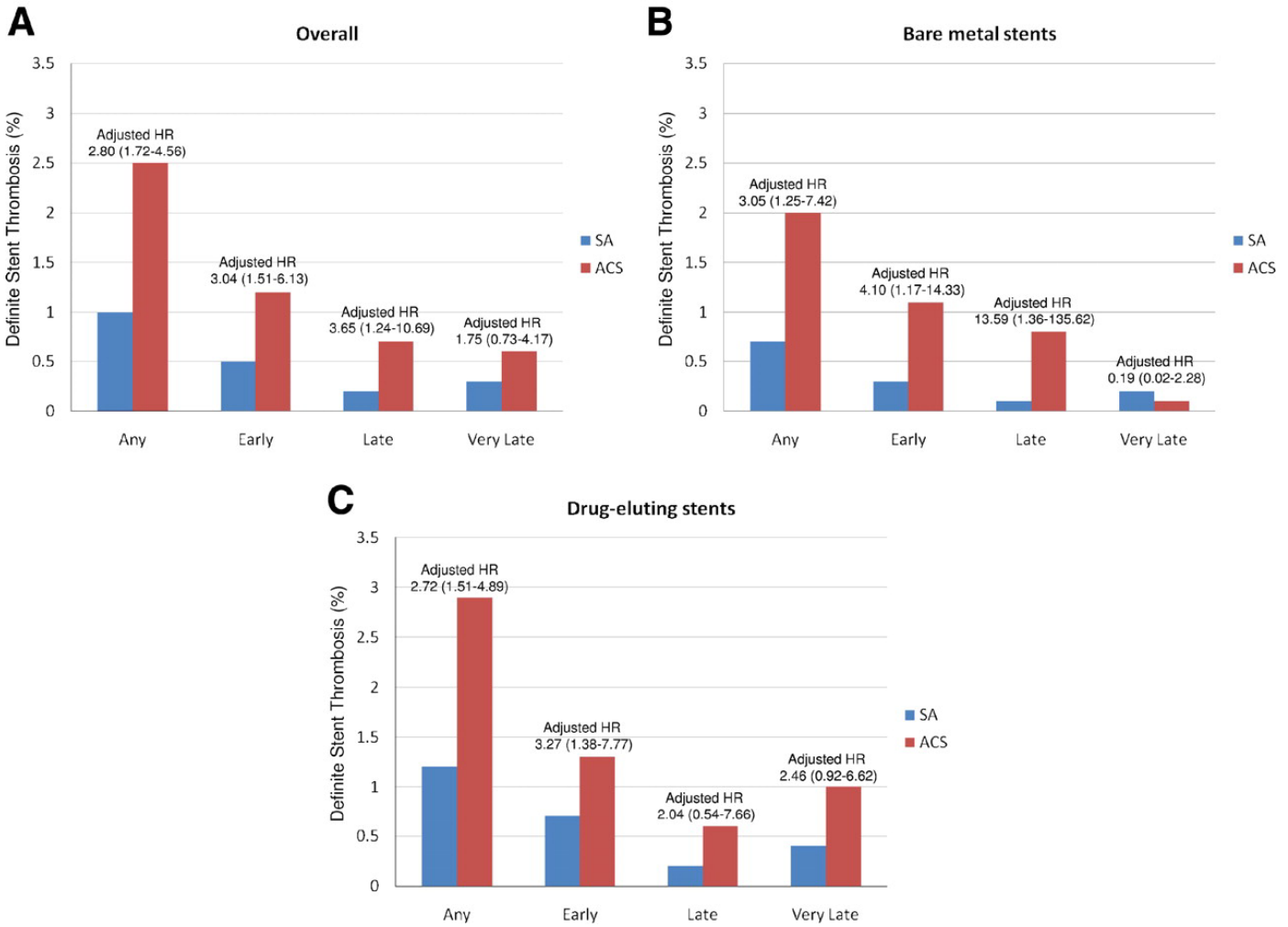


Kukreja, N. et al. J Am Coll Cardiol Intv 2009;2:534-541
(Thoraxcenter n=5816)

Copyright ©2009 American College of Cardiology Foundation. Restrictions may apply.

JACC Cardiovascular Interventions

Classification of Stent Thrombosis Timing for All Patients, BMS, and DES

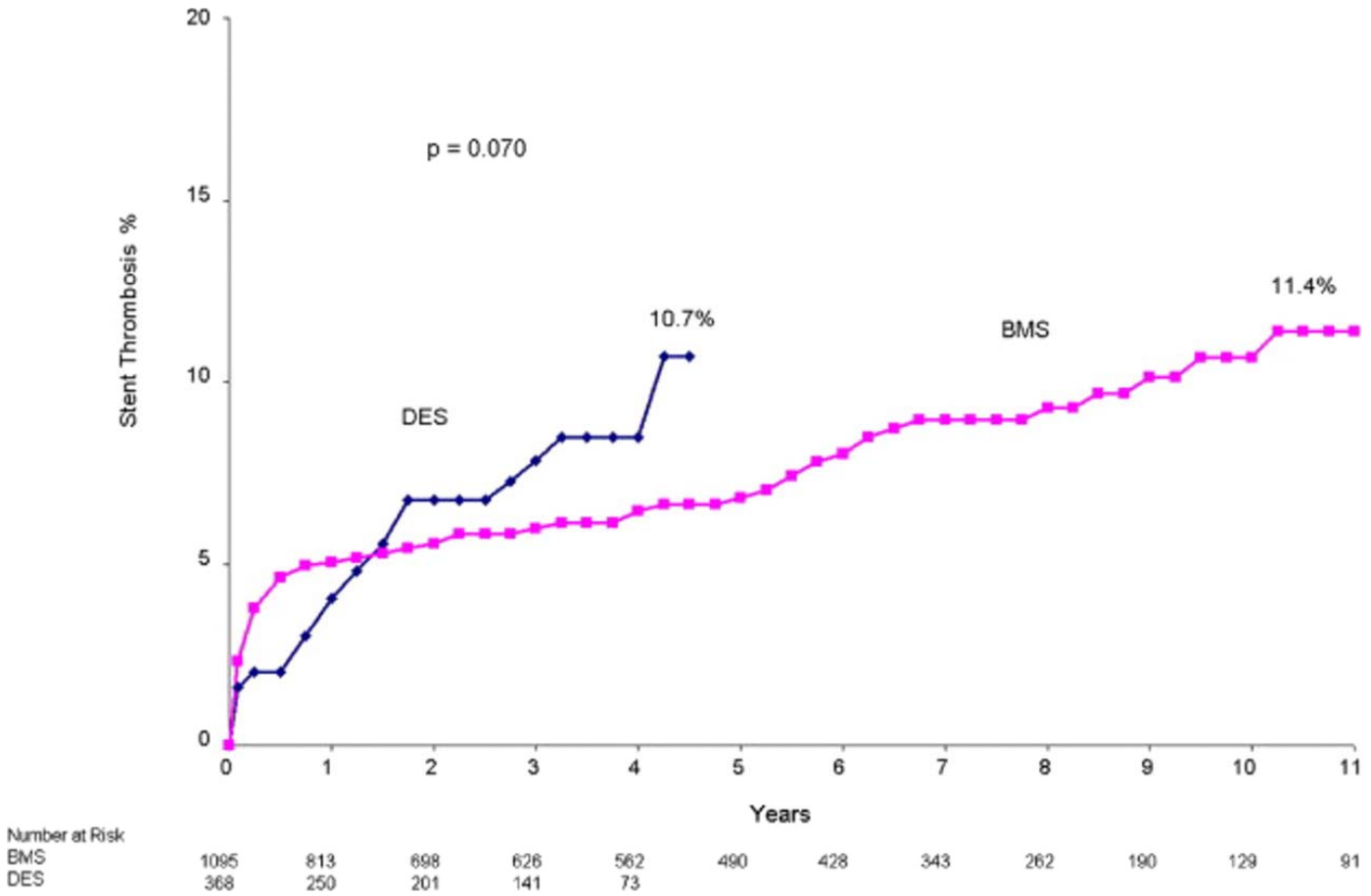


Kukreja, N. et al. J Am Coll Cardiol Intv 2009;2:534-541

Copyright ©2009 American College of Cardiology Foundation. Restrictions may apply.

JACC Cardiovascular Interventions

Kaplan-Meier Estimates of ST Rates After Primary PCI With BMS and DES for STEMI

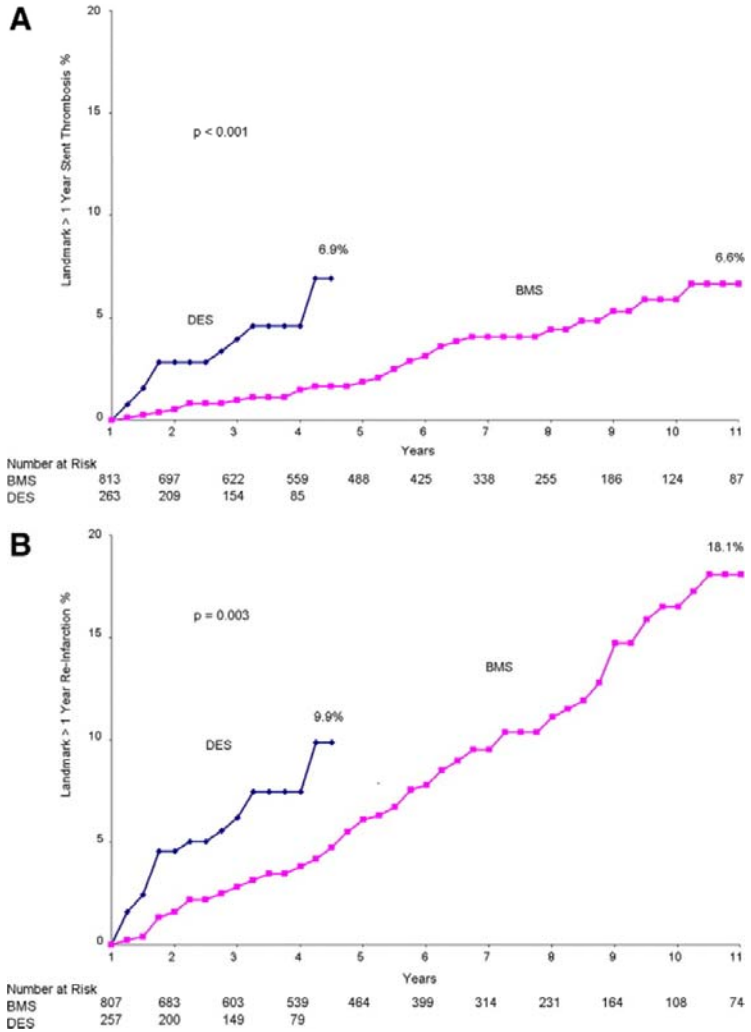


Brodie, B. et al. J Am Coll Cardiol Intv 2011;4:30-38

Copyright ©2011 American College of Cardiology Foundation. Restrictions may apply.

JACC Cardiovascular Interventions

Landmark Analysis Showing Kaplan-Meier Estimates of VLST and Reinfarction After Primary PCI With DES and BMS for STEMI



Brodie, B. et al. J Am Coll Cardiol Intv 2011;4:30-38

Copyright ©2011 American College of Cardiology Foundation. Restrictions may apply.

JACC Cardiovascular Interventions

Frequency and Predictors of Stent Thrombosis After Percutaneous Coronary Intervention in Acute Myocardial Infarction

George D. Dangas, MD, PhD*; Adriano Caixeta, MD, PhD*; Roxana Mehran, MD; Helen Parise, ScD; Alexandra J. Lansky, MD; Ecaterina Cristea, MD; Bruce R. Brodie, MD; Bernhard Witzenbichler, MD; Giulio Guagliumi, MD; Jan Z. Peruga, MD; Dariusz Dudek, MD; Martin Möeckel, MD; Gregg W. Stone, MD; for the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial Investigators

Background—Concerns persist regarding the risk of stent thrombosis in the setting of primary percutaneous coronary intervention for ST-segment elevation myocardial infarction.

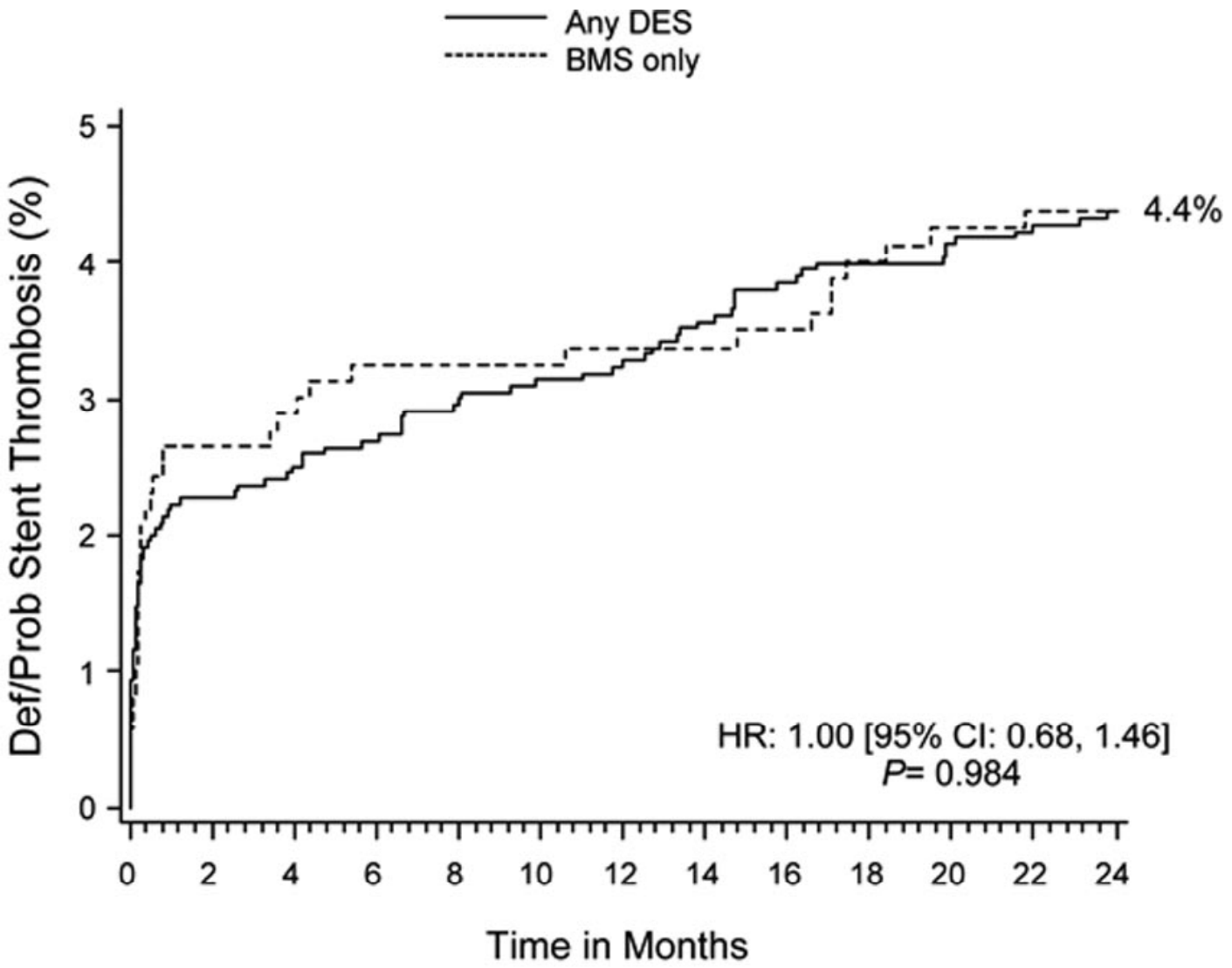
Methods and Results—The Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial included 3602 patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention who were randomized to heparin plus a glycoprotein IIb/IIIa inhibitor (GPI) (n=1802) versus bivalirudin monotherapy (n=1800). Stents were implanted in 3202 patients, including 2261 who received drug-eluting stents and 861 who received only bare metal stents. Definite or probable stent thrombosis within 2 years occurred in 137 patients (4.4%), including 28 acute events (0.9%), 49 subacute events (1.6%), 32 late events (1.0%), and 33 very late events (1.1%). The 2-year cumulative rates of stent thrombosis were 4.4% with both drug-eluting stents and bare metal stents ($P=0.98$) and 4.3% versus 4.6% in patients randomized to bivalirudin monotherapy versus heparin plus a GPI, respectively ($P=0.73$). Acute stent thrombosis occurred more frequently in patients assigned to bivalirudin compared with heparin plus a GPI (1.4% versus 0.3%; $P<0.001$), whereas stent thrombosis after 24 hours occurred less frequently in patients with bivalirudin compared with heparin plus a GPI (2.8% versus 4.4%; $P=0.02$). Prerandomization heparin and a 600-mg clopidogrel loading dose were independent predictors of reduced acute and subacute stent thrombosis, respectively.

Conclusions—Stent thrombosis is not uncommon within the first 2 years after primary percutaneous coronary intervention in ST-segment elevation myocardial infarction, and occurs with similar frequency in patients receiving drug-eluting stents versus bare metal stents and bivalirudin alone versus heparin plus a GPI. Optimizing adjunct pharmacology including early antithrombin therapy preloading with a potent antiplatelet therapy may further reduce stent thrombosis in ST-segment elevation myocardial infarction.

Clinical Trial Registration:—http://www.clinicaltrials.gov. Unique identifier: NCT00433966. (***Circulation***. **2011;123:1745-1756.**)

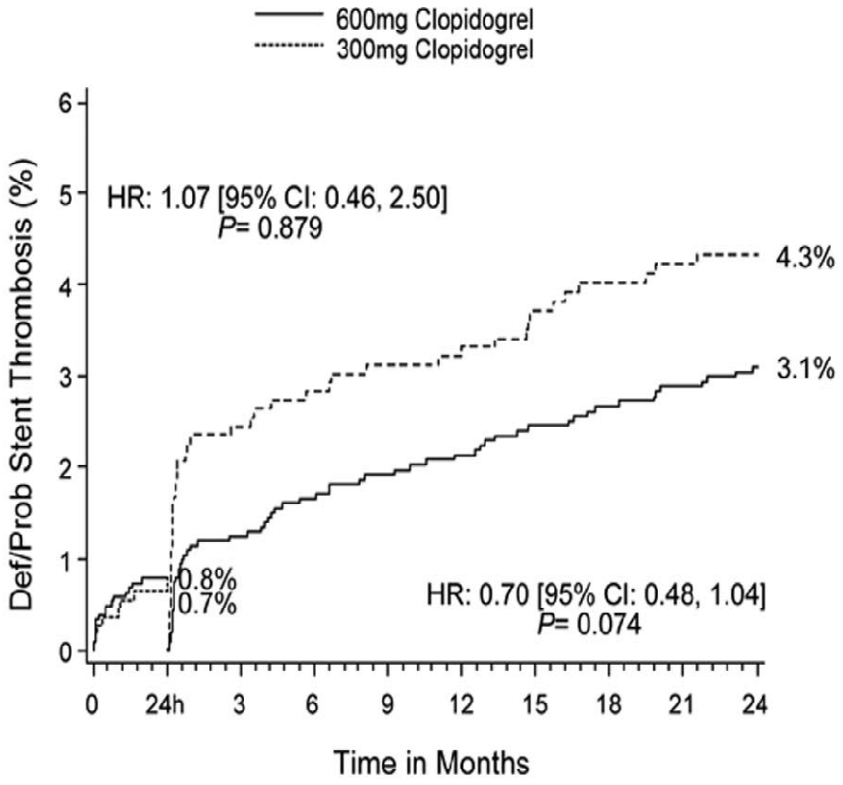
Key Words: myocardial infarction ■ stents ■ thrombosis

American Heart Association
Circulation



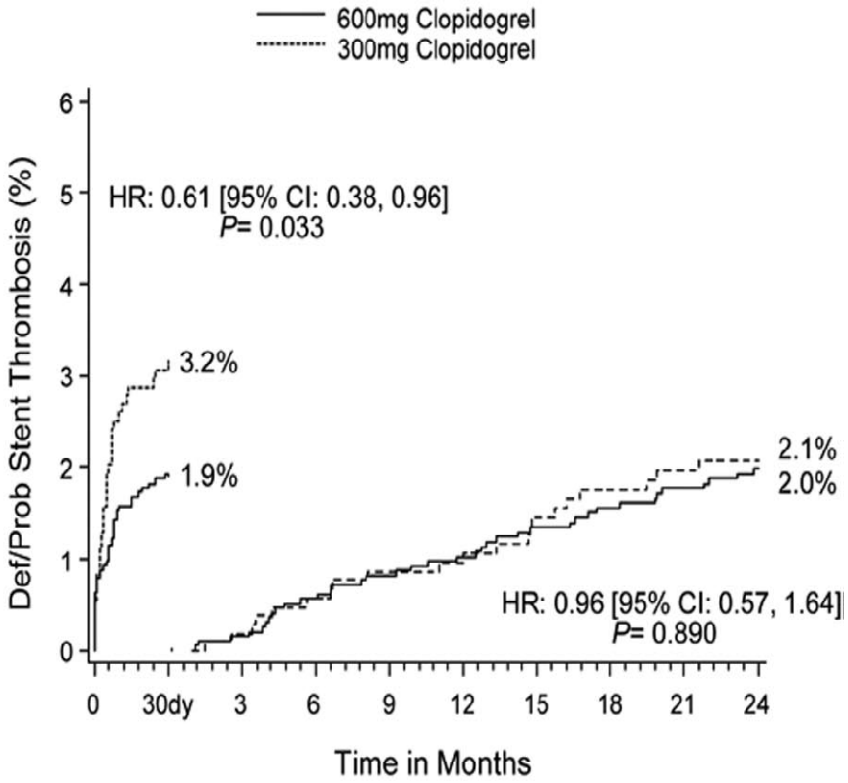
Number at risk

Any DES	2261	2142	2114	2077	2022	2006	1679
BMS only	872	813	798	793	771	760	634



Number at risk

600 mg	2031	2005	1909	1868	1813	1487
300 mg	1087	1070	1011	986	949	812

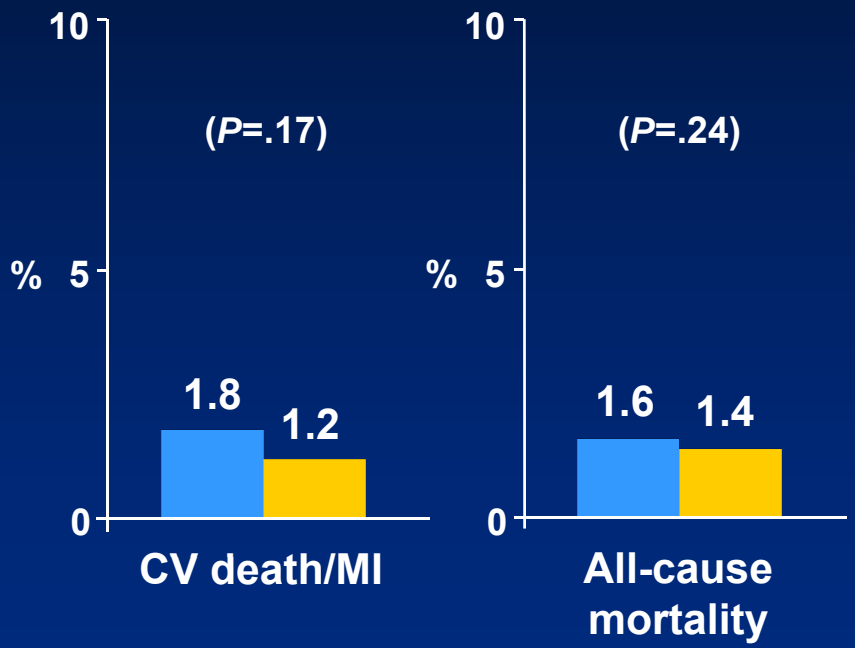


t risk

2031	1982	1935	1894	1839	1510
1087	1056	1035	1009	970	829

DES-LATE

Trial design: Patients on dual antiplatelet therapy (DAT) and with no adverse events 12 months after DES implantation were randomized to continuation of DAT for 2 years or aspirin alone. Patients were followed for a mean of 19.2 months.



Results

- CV death/MI similar between DAT and aspirin arms (HR, 1.65; 95% CI, 0.8-3.36)
- MI: 0.8% vs 0.7%, *P*=.49; definite stent thrombosis: 0.4% vs 0.4%, *P*=.76
- TIMI major bleeding similar (0.2% vs 0.1%, *P*=.35)

Conclusions

- Optimal duration of DAT following DES implantation unclear; current trial suggests aspirin similar to DAT beyond 12 months
- Significantly lower (<25%) event rate than anticipated; trial may be underpowered to detect differences in clinical outcomes
- Results from ongoing trials are awaited

www.cardiosource.org

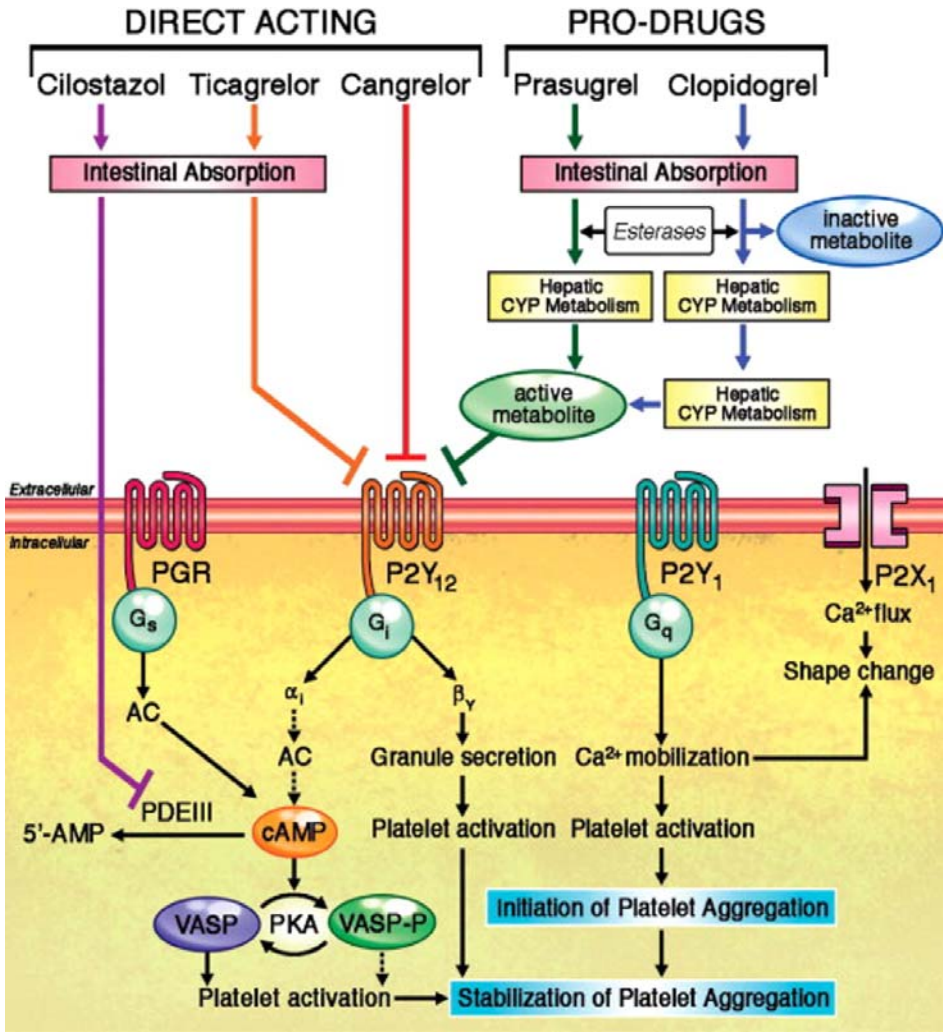
Park SJ, et al. *N Engl J Med*. 2010;362(15):1374-1382.

STRIVE®

Should other antiplatelet strategies be considered?

STRIVE®

Therapeutic Options for Optimizing Platelet Inhibition in Clopidogrel Poor Metabolizers



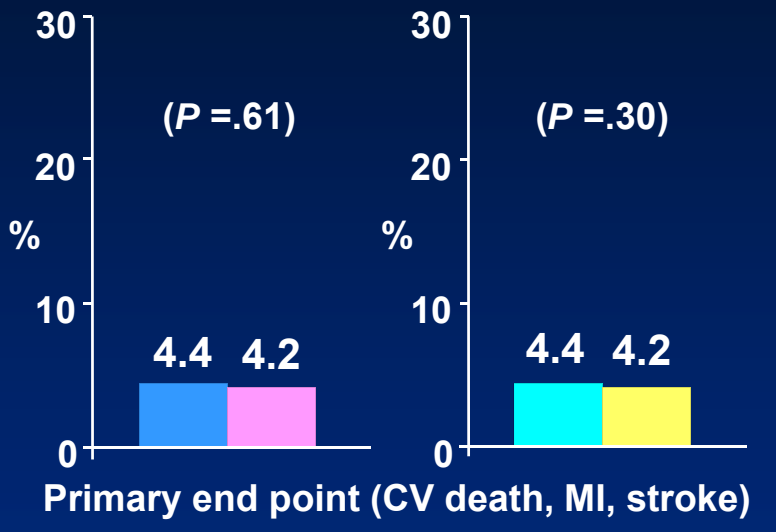
Angiolillo, D. J. et al. J Am Coll Cardiol Intv 2011;4:411-414

Copyright ©2011 American College of Cardiology Foundation. Restrictions may apply.

JACC Cardiovascular Interventions

CURRENT–OASIS 7

Trial design: Patients with ACS (STEMI or NSTEMI) referred for an early invasive strategy were randomized in a 2 x 2 factorial design to either low-dose or high-dose aspirin (ASA), and standard-dose or high-dose clopidogrel. Patients were followed for 30 days.



Results

- No difference in primary end point between low- and high-dose ASA (*P*=.61); benefit noted in high-dose arm on high-dose clopidogrel (*P*=.04)
- No difference in primary end point between standard- and high-dose clopidogrel overall (*P*=.30), but significant interaction with ASA dose; benefit noted in high-dose clopidogrel arm undergoing PCI (*P*=.03)
- Major bleeding similar in both ASA arms, but higher in high-dose clopidogrel arm (*P*=.01)

Conclusions

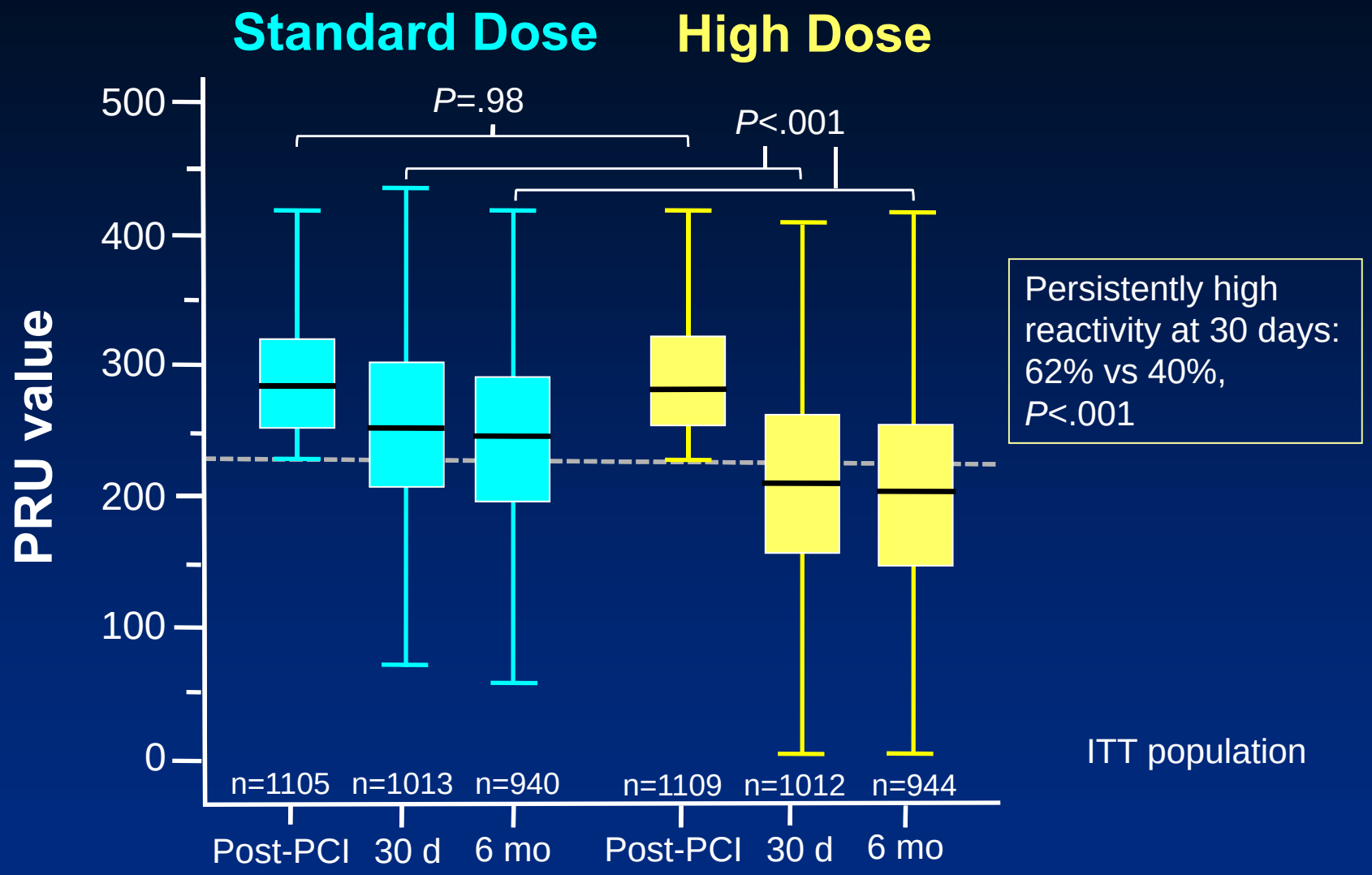
- Treatment with high-dose ASA and high-dose clopidogrel not associated with significant clinical benefit at 30 days in ACS patients. However, benefit noted in PCI subset receiving high-dose clopidogrel
- Bleeding complications higher with high-dose clopidogrel, but not ASA
- Important findings; likely to be in future guidelines

www.cardiosource.org

CURRENT-OASIS 7 Investigators. *N Engl J Med.* 2010;363(10):930-942.

STRIVE®

GRAVITAS: Pharmacodynamics



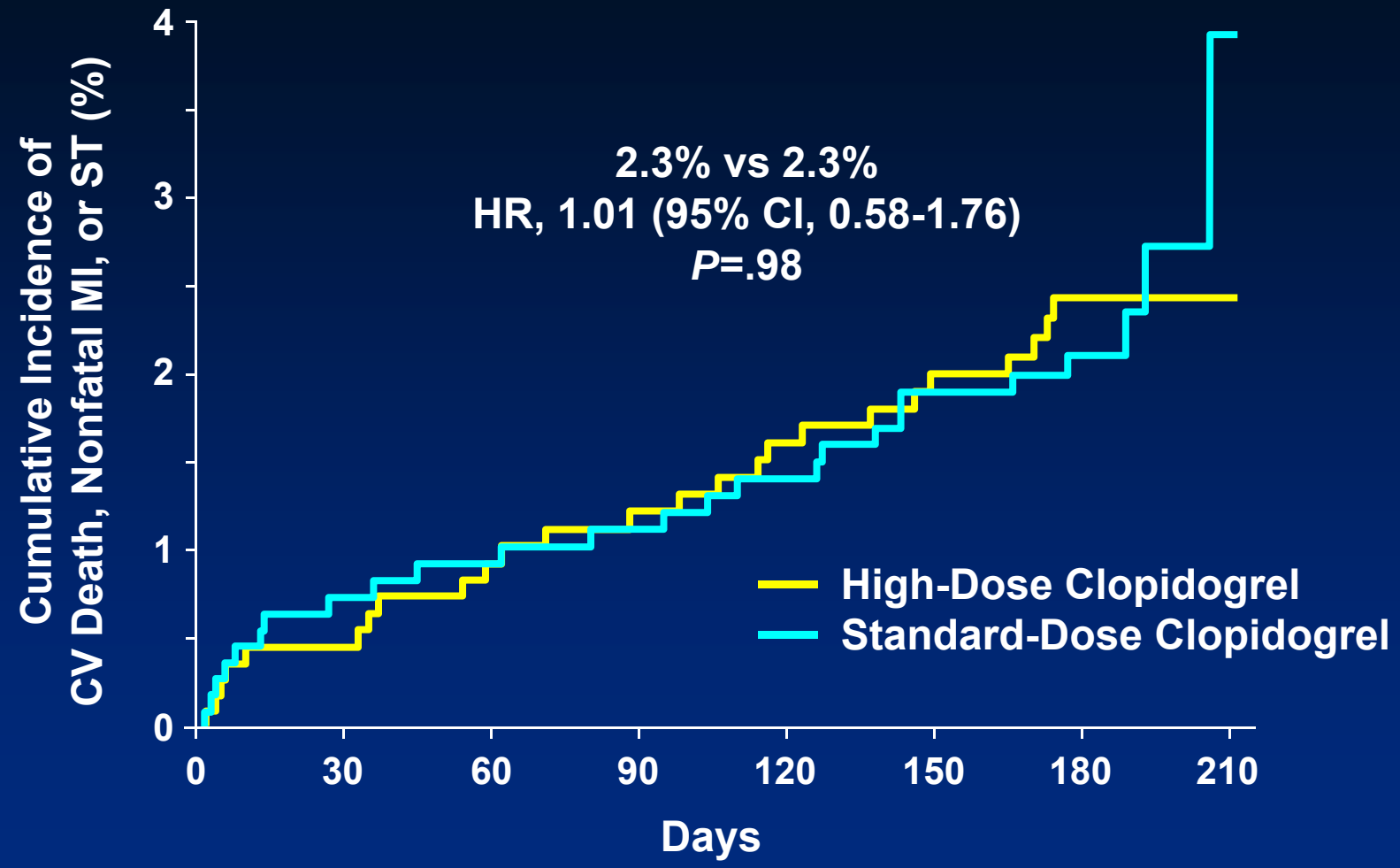
Persistently high reactivity at 30 days: 62% vs 40%, *P*<.001

ITT population

Price MJ. Presented at: American Heart Association Scientific Sessions 2010; November 16, 2010; Chicago, IL.

STRIVE®

GRAVITAS: Primary End Point

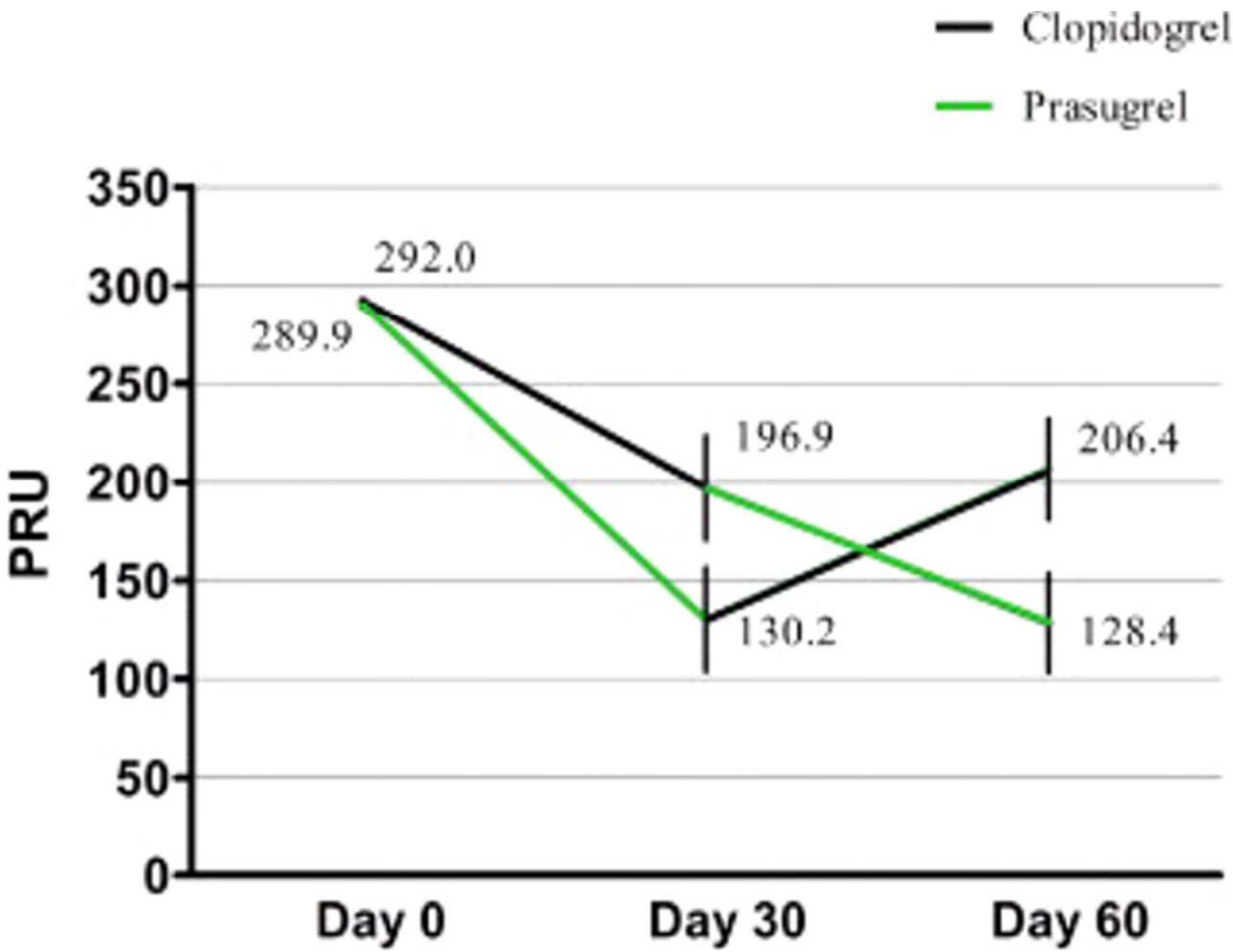


ST, stent thrombosis.

Price MJ. Presented at: American Heart Association Scientific Sessions 2010; November 16, 2010; Chicago, IL.

STRIVE®

PR by Treatment Sequence



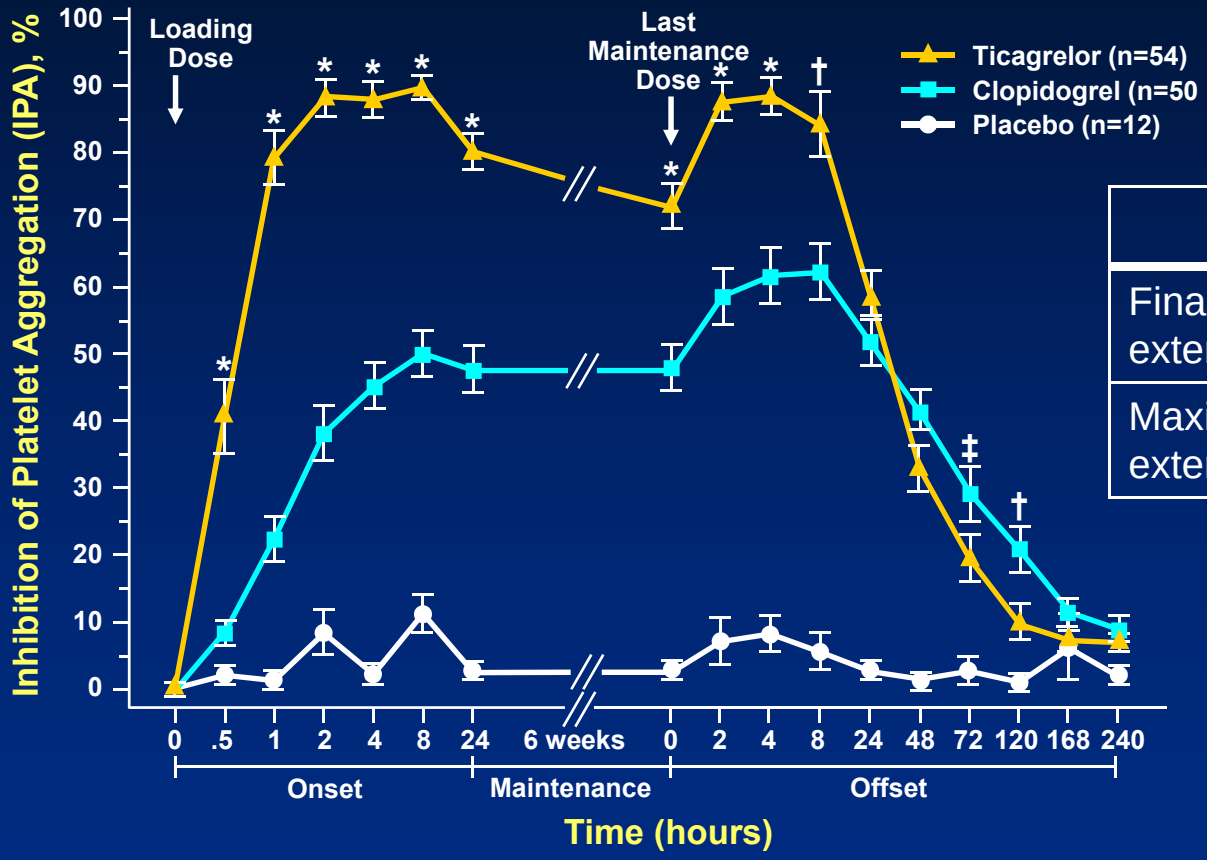
Alexopoulos, D. et al. J Am Coll Cardiol Intv 2011;4:403-410

Copyright ©2011 American College of Cardiology Foundation. Restrictions may apply.

JACC Cardiovascular Interventions

ONSET/OFFSET Study: Antiplatelet Effect of Ticagrelor vs Clopidogrel

IPA (%; 20 µmol/L ADP, Final Extent) by Protocol Time and Treatment



IPA (20 µmol/L ADP) at 2 Hours After First Dose

	Ticag. (n=54) IPA, %	Clop. (n=50) IPA, %	*P*
Final extent	88±15	38±33	<.0001
Maximum extent	65±17	25±23	<.0001

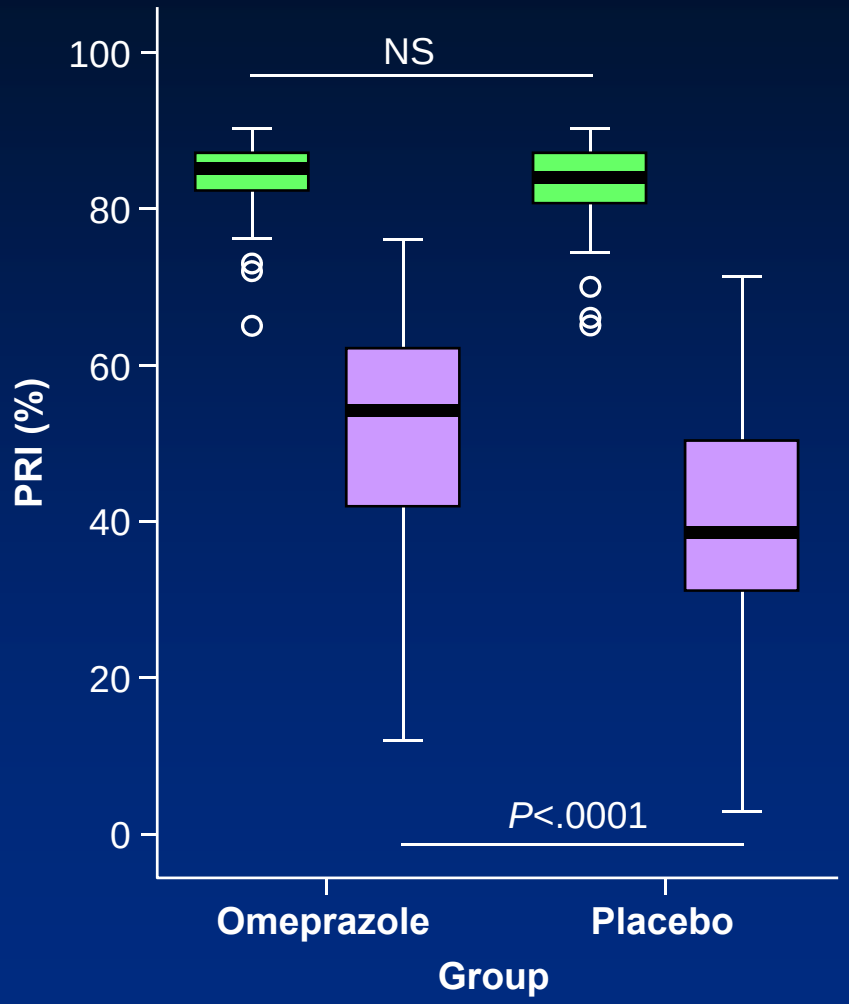
*P<.0001, †P<.005,‡P<.05, ticagrelor vs clopidogrel.

Reprinted with permission from Gurbel PA, et al. *Circulation.* 2009;120(25):2577-2585.

STRIVE®

The problem? (with PPI’s)

Effect of PPIs on Antiplatelet Action of Clopidogrel: OCLA Study



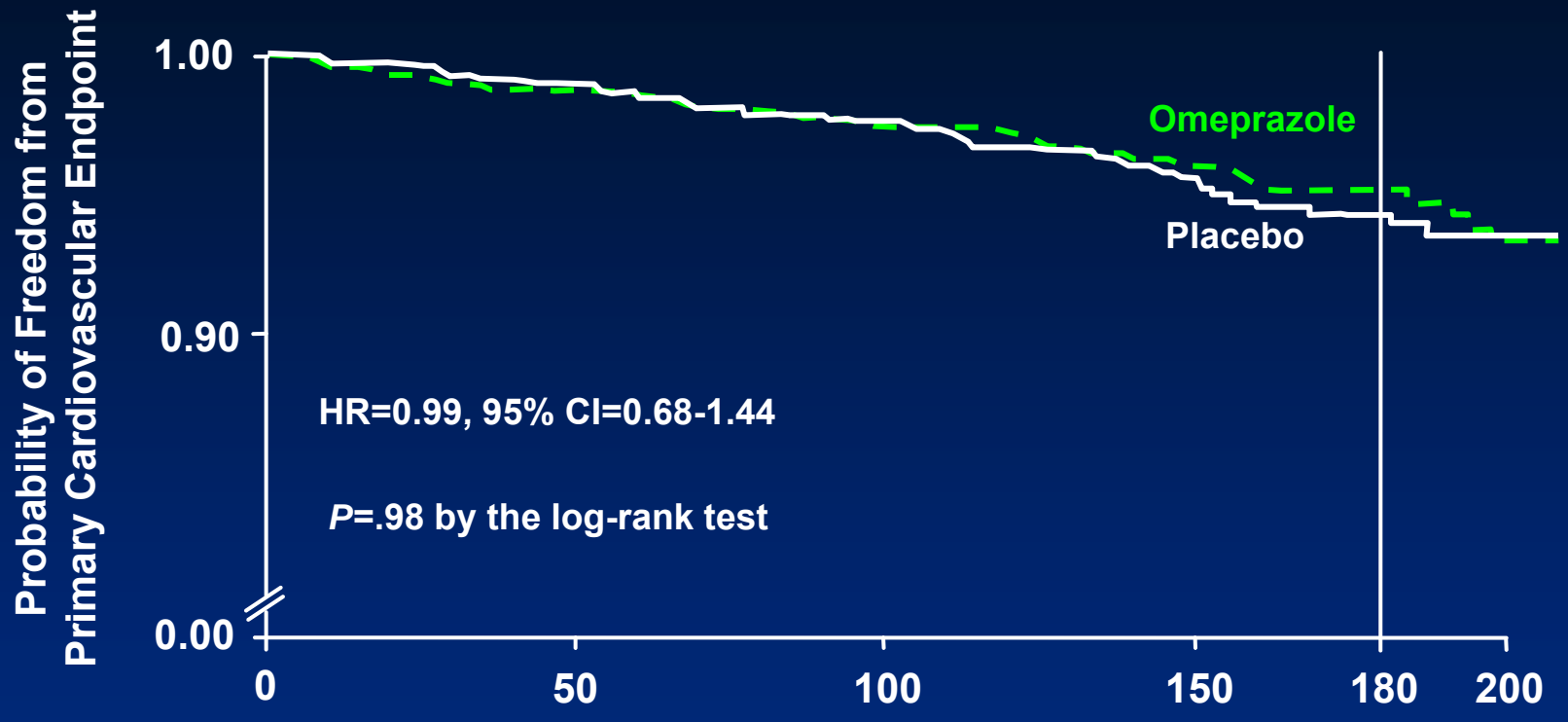
VASP PRI (%) on Day 1

VASP PRI (%) on Day 7

NS, nonsignificant; OCLA, Omeprazole CLopidogrel Aspirin; PRI, platelet reactivity index; VASP, vasodilator-stimulated phosphoprotein.

Reproduced with permission from Gilard M, et al. *J Am Coll Cardiol.* 2008;51(3):256-260.

COGENT Trial: Effect of PPI on Composite Cardiovascular Events



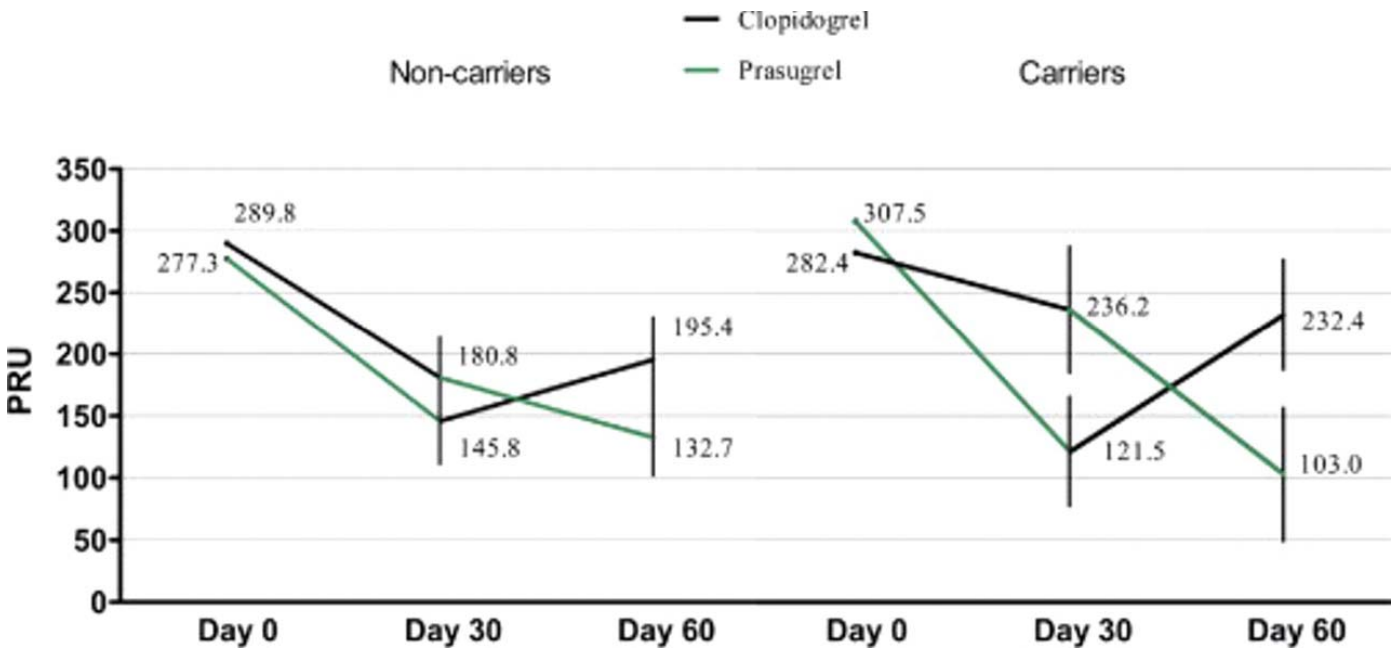
No. at Risk

Placebo	1885	1449	945	515	250	218
Omeprazole	1876	1488	966	537	242	205

Bhatt DL, et al. *N Engl J Med.* 2010;363(20):1909-1917.

STRIVE®

PR by Treatment Sequence in Noncarriers and Carriers of CYP2C19*2 Allele



Alexopoulos, D. et al. J Am Coll Cardiol Intv 2011;4:403-410

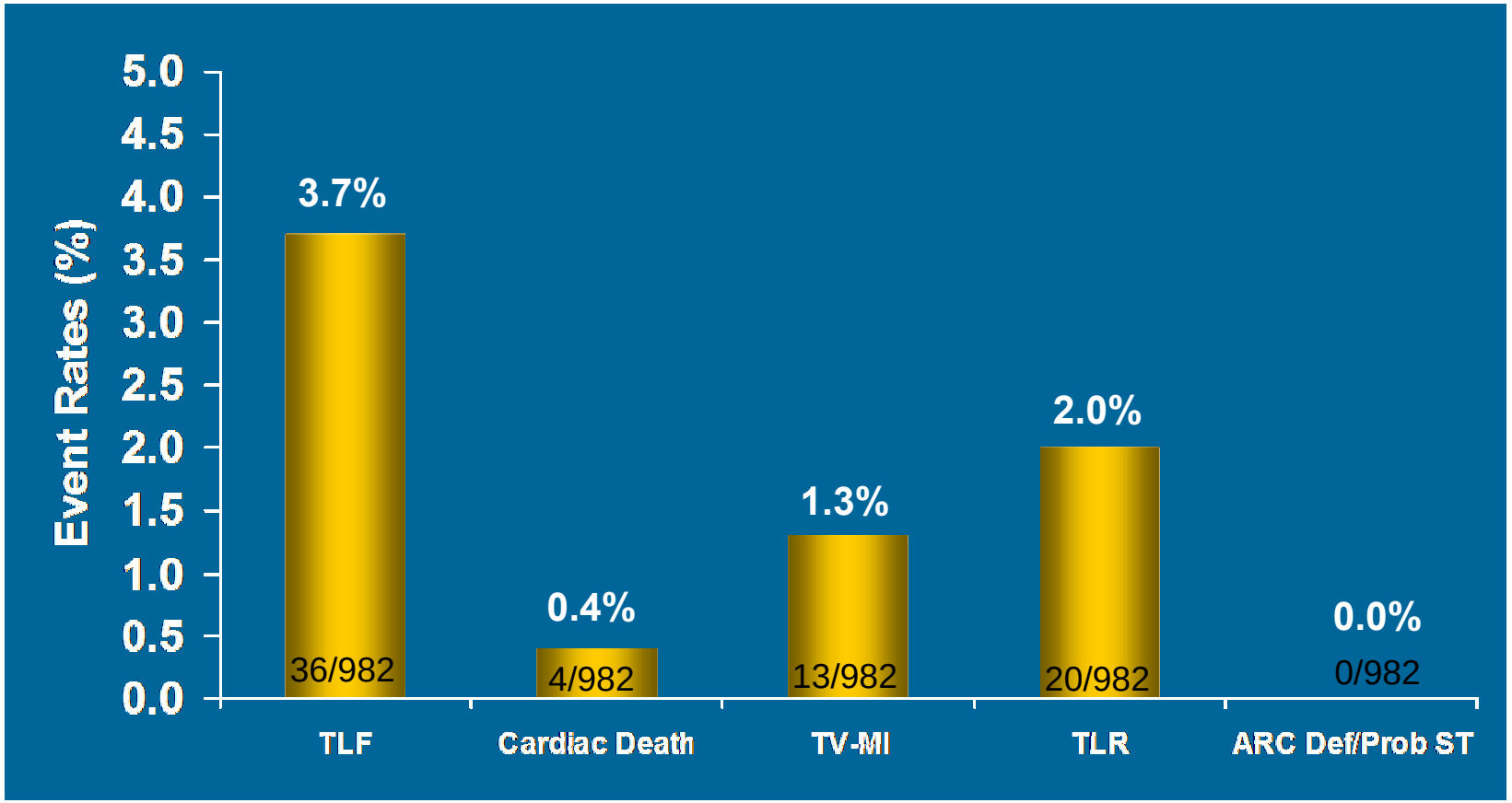
Copyright ©2011 American College of Cardiology Foundation. Restrictions may apply.

JACC Cardiovascular Interventions

New stents

RESOLUTE US: Main Cohort

Clinical Endpoints at 12 Months



Remaining Management Questions?

- Is point of care testing important?
- Is Genomic testing important?
- Should selection of DES or BMS be a major consideration
- What is the comparative effectiveness of stenting or not stenting borderline lesions?

Remaining pharmacologic questions?

- How potent antiplatelet therapy should be?
- Should agents with more uniform effect be used?
- How long should antiplatelet therapy be given? Should it differ? If so on what basis?

Remaining Stent Development Questions?

- Is metal a problem?
- Is polymer a problem?
- Is drug a problem?

- What is the next frontier in endovascular therapeutics?

Technologies of humility

Researchers and policy-makers need ways for accommodating the partiality of scientific knowledge and for acting under the inevitable uncertainty it holds.

Sheila Jasanoff

The great mystery of modernity is that we think of certainty as an attainable state. Uncertainty has become the threat to collective action, the disease that knowledge must cure. It is the condition that poses cruel dilemmas for decision-makers; that must be reduced at any cost; that is tamed with scenarios and assessments; and that feeds the frenzy for new knowledge, much of it scientific.

For a long time we accepted lack of certainty as humankind's natural lot. What has happened to reverse that presumption? Perhaps it is the spread of binary thinking that frames the future in terms of determinate choices between knowable options. Boolean algebra and digital logics are not only built into our computers, mobile phones and other information and communication technologies, they dominate the framing of social problems and the options for dealing with them.

Thus, statistics offers a choice between Type 1 and Type 2 errors. The first lead to false positives that promote too much risk avoidance, the second to false negatives that keep us from acting when we ought. Implicitly, error follows a binary trail. Philosophy casts moral dilemmas as trolley problems, in which possible solutions are represented as choices encountered at forks in the track. One option is to let the trolley run its course and infinitely complex, and for any given problem, science offers only part of the picture. Climate scientists can tell us with high certainty that human activities are raising Earth's mean surface temperature, that extreme weather events will occur, and that melting ice caps will cause abrupt changes in the global climate. But it takes time and money to produce such certainty, and for all the doors that science even provisionally closes, others relevant to policy remain beyond closure by science alone.

D. PARKINS

Science fixes our attention on the knowable, leading to an over-dependence on fact-finding. Even when scientists recognize the limits of their own inquiries, as they often do, the policy world, implicitly encouraged by scientists, asks for more research. For most complex problems, the pursuit of perfect knowledge is asymptotic. Uncertainty, ignorance and indeterminacy are always present.

We need disciplined methods to accommodate the partiality of scientific knowledge and to act under irredeemable uncertainty. Let us call these the technologies of humility. These technologies compel us to reflect on the sources of ambiguity, indeterminacy and complexity. Humility instructs us to think harder about how to reframe problems so that their ethical dimensions are brought to light, which new facts to seek and when to resist asking science for clarification. Humility directs us to alleviate known causes of people's vulnerability to harm, to pay attention to the distribution of risks and benefits, and to reflect on the social factors that promote or discourage learning.

Policies based on humility might: redress inequality before finding out how the poor are hurt by climate change; value greenhouse gases differently depending on the nature of the activities that give rise to them; and uncover the sources of vulnerability in fishing communities before installing