HOUSTON Methodist
DEBAKEY HEART & VASCULAR CENTER

Bridging patients with Stents for Non-Cardiac Surgery

Neal S. Kleiman MD

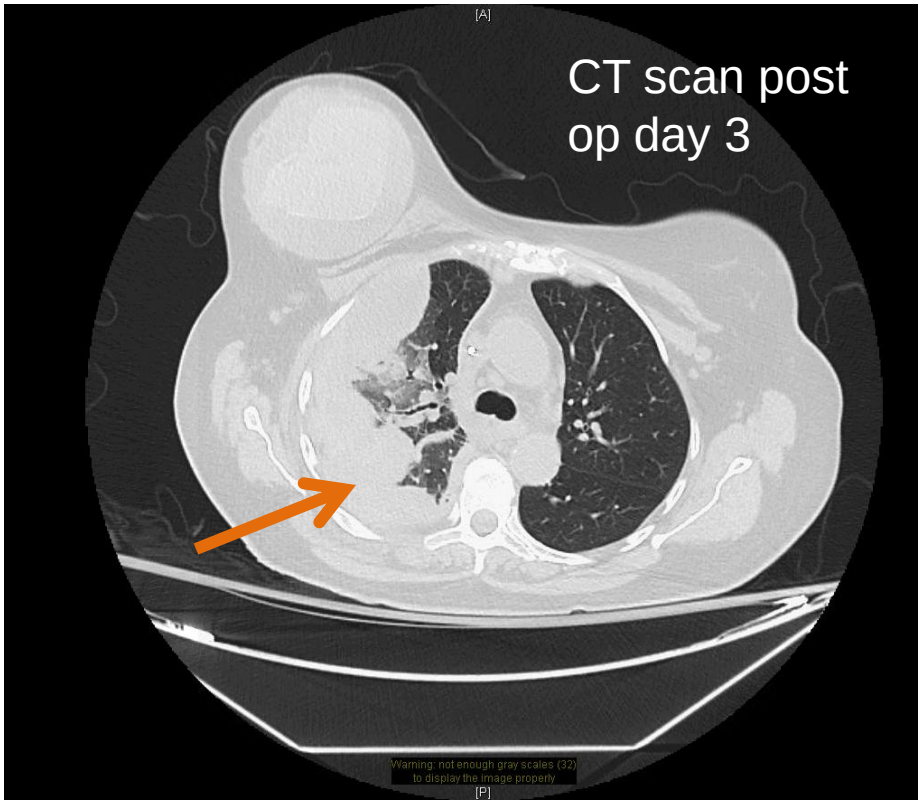
Houston Methodist DeBakey Heart Center

Houston, Texas

Clinical Case

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

- 59 yo woman with ischemia on treadmill June 2014 followed by 2.5 x 23 mm EES; treated with prasugrel/aspirin
- Three thorocenteces for recurrent bloody pleural effusion
- Decortication/biopsy off prasugrel
- *Persistent chest tube drainage* with hemoglobin drop to 6.5 g/dL – **off** P2Y12 antagonists



- Reexploration planned for post op day 6
- **When would you bridge and for how long?**

A Growing Problem

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

- In Europe, it is estimated that the number of patients undergoing surgery will increase by 25% by 2020. Over the same time period, the elderly population will increase by 50%.

- The total number of surgical procedures may increase even faster because of the rising frequency of interventions with age.

Courtesy of Dr Darek Dudek

Journal of the American College of Cardiology
© 2000 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 35, No. 5, 2000
ISSN 0735-1097/00/$20.00
PII S0735-1097(00)00521-0

Catastrophic Outcomes of Noncardiac Surgery Soon After Coronary Stenting

Grzegorz L. Kałuża, MD, PHD, Jane Joseph, Joseph R. Lee, MD, Michael E. Raizner, MD, Albert E. Raizner, MD, FACC

Houston, Texas

OBJECTIVES To assess the clinical course of patients who have undergone coronary stent placement less than six weeks before noncardiac surgery.

BACKGROUND Surgical and percutaneous transluminal coronary angioplasty revascularization performed before high-risk noncardiac surgery is expected to reduce perioperative cardiac morbidity and mortality. Perioperative and postoperative complications in patients who have undergone coronary stenting before a noncardiac surgery have not been studied.

METHODS Forty patients who underwent coronary stent placement less than six weeks before noncardiac surgery requiring a general anesthesia were included in the study (1–39 days, average: 13 days). The records were screened for the occurrence of adverse clinical events, including myocardial infarction, stent thrombosis, peri- and postoperative bleeding and death.

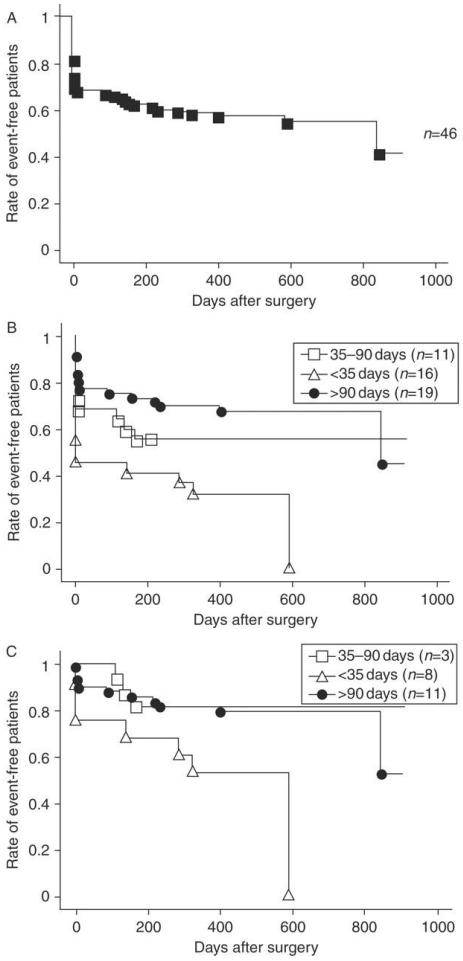
RESULTS In 40 consecutive patients meeting the study criteria, there were seven myocardial infarctions (MIs), 11 major bleeding episodes and eight deaths. All deaths and MIs, as well as 8/11 bleeding episodes, occurred in patients subjected to surgery fewer than 14 days from stenting. Four patients expired after undergoing surgery one day after stenting. Based on electrocardiogram, enzymatic and angiographic evidence, stent thrombosis accounted for most of the fatal events. The time between stenting and surgery appeared to be the main determinant of outcome.

CONCLUSIONS Postponing elective noncardiac surgery for two to four weeks after coronary stenting should permit completion of the mandatory antiplatelet regimen, thereby reducing the risk of stent thrombosis and bleeding complications. (J Am Coll Cardiol 2000;35:1288–94) © 2000 by the American College of Cardiology

Austrian Study of Non-Cardiac Surgery After Stenting

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

- 103 Patients with non-cardiac surgery < 1 year after stenting; 46% had an event
- Antiplatelets, aspirin, clopidogrel continued or stopped < 3 days preop
  - Cardiac death 4.9%
  - MI 4%
  - Bleeding 4%



Vicenzi. Br. J. Anaesth. 2006;96:686

Findings From the EVENT Registry

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

- In the first 7 days after surgery, 4 of the 206 patients (1.9%) suffered a MACE: 1 died and 3 suffered MI.
- No patient suffered definite stent thrombosis

Table 4. Multivariate Analysis of the Occurrence of Cardiac Death, MI, or Stent Thrombosis in the 7 Days After Surgery

Variable	p Value	Hazard Ratio	95% CI for Hazard Ratio
Noncardiac surgery	<0.0001	27.113	9.916–74.136
Age	0.4044	0.994	0.979–1.008
Sex	0.9767	1.005	0.702–1.439
Use of at least 1 Taxus stent	0.1855	0.796	0.569–1.115
CHF	<0.0001	2.796	1.871–4.178
Creatinine >2.0 mg/dl	0.0005	2.783	1.568–4.939
LAD lesion	0.3333	0.842	0.595–1.192
Bifurcation lesion	0.6463	0.891	0.544–1.458
Total stent length	0.6770	1.002	0.992–1.012
No. of lesions	0.0843	1.312	0.964–1.784
Maximum balloon diameter	0.0675	0.744	0.541–1.022

- The performance of noncardiac surgery was associated with a 27-fold increased risk of ischemic complications during the week following surgery

J Am Coll Cardiol Intv 2010;3:920 –7

Independent preoperative risk factors for cardiovascular and haemorrhagic complications (RECO Study)

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

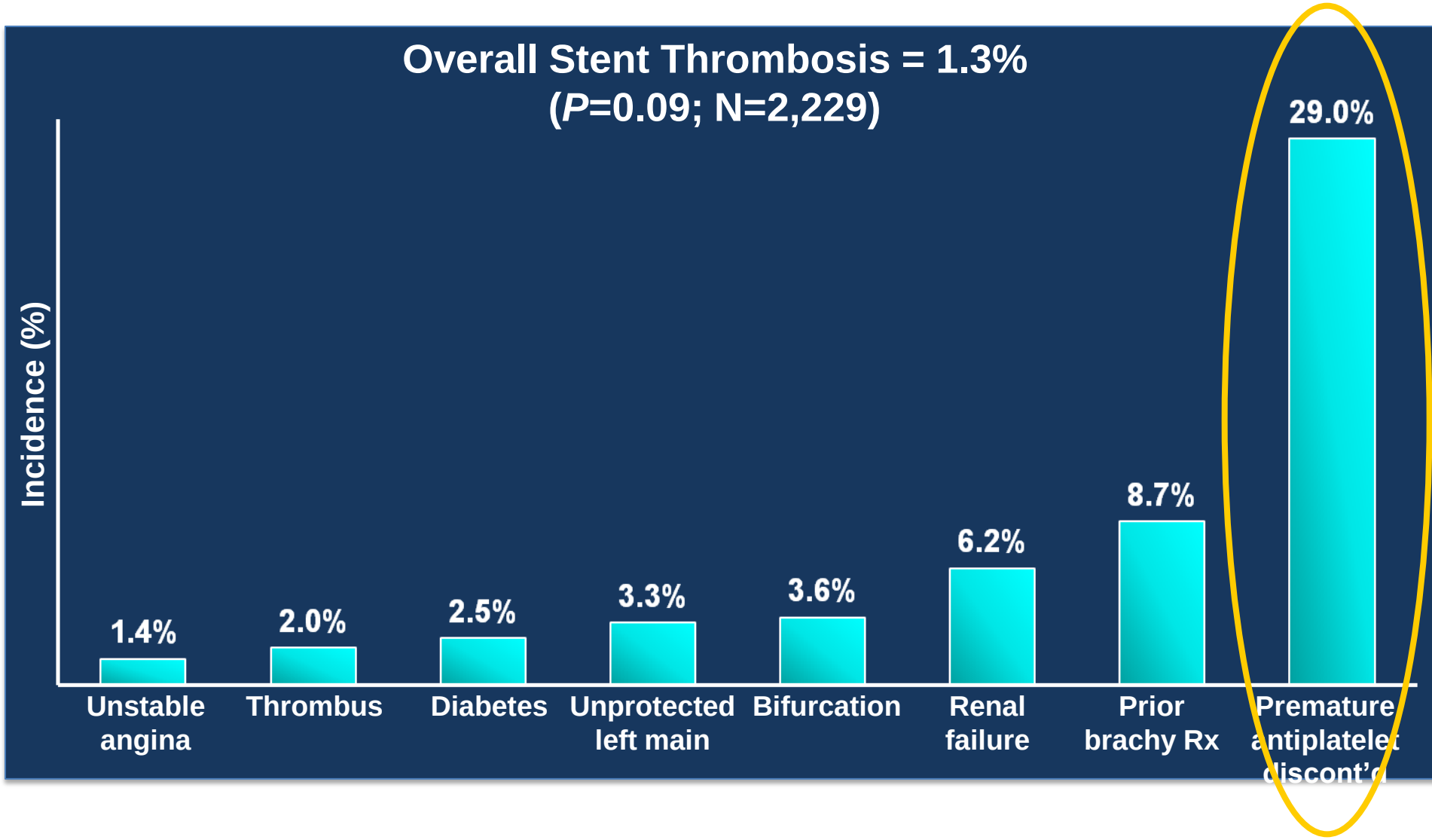
	MACCE		Bleeding complications	
	OR (95% CI)	p	OR (95% CI)	p
Complete OAT interruption				
No interruption	Reference		Reference	
≤5 days	0.67 (0.32 to 1.37)	0.272	0.72 (0.35 to 1.47)	0.366
>5 days	2.11 (1.23 to 3.63)	0.007	0.93 (0.48 to 1.79)	0.826
Preoperative haemoglobin				
>12 g/dl (or missing)	Reference		Reference	
10–12 g/dl	1.13 (0.62 to 2.08)	0.691	1.37 (0.75 to 2.48)	0.308
<10 g/dl	3.00 (1.23 to 7.29)	0.016	2.61 (1.04 to 6.55)	0.041
Creatinine clearance				
>60 ml/min (or missing)	Reference		Reference	
30–60 ml/min	1.32 (0.79 to 2.21)	0.287	1.96 (1.19 to 3.24)	0.008
<30 ml/min	3.51 (1.54 to 8.04)	0.003	1.96 (0.76 to 5.03)	0.162
Time between PCI and surgery				
0–3 months	0.97 (0.45 to 2.07)	0.938	2.91 (1.53 to 5.52)	0.001
4–6 months	1.11 (0.48 to 2.58)	0.803	0.96 (0.38 to 2.44)	0.928
7–12 months	0.70 (0.28 to 1.73)	0.437	1.07 (0.46 to 2.52)	0.874
More than 12 months	Reference		Reference	
Urgent surgery	3.08 (1.74 to 5.47)	<0.001	1.77 (0.94 to 3.31)	0.075
High-risk surgery	3.59 (2.34 to 5.51)	<0.001	3.31 (2.11 to 5.18)	<0.001

- Observational cohort study of 1134 consecutive patients with coronary stents.
- Independent preoperative correlates for MACCE were **complete OAT interruption for >5 days prior to surgery**, preoperative haemoglobin <10 g/dl, creatinine clearance of <30 ml/min and emergency or high-risk surgery.

Courtesy of Dr Darek Dudek

Premature Discontinuation of Antiplatelet Therapy is the Most Powerful Risk Factor for Stent Thrombosis

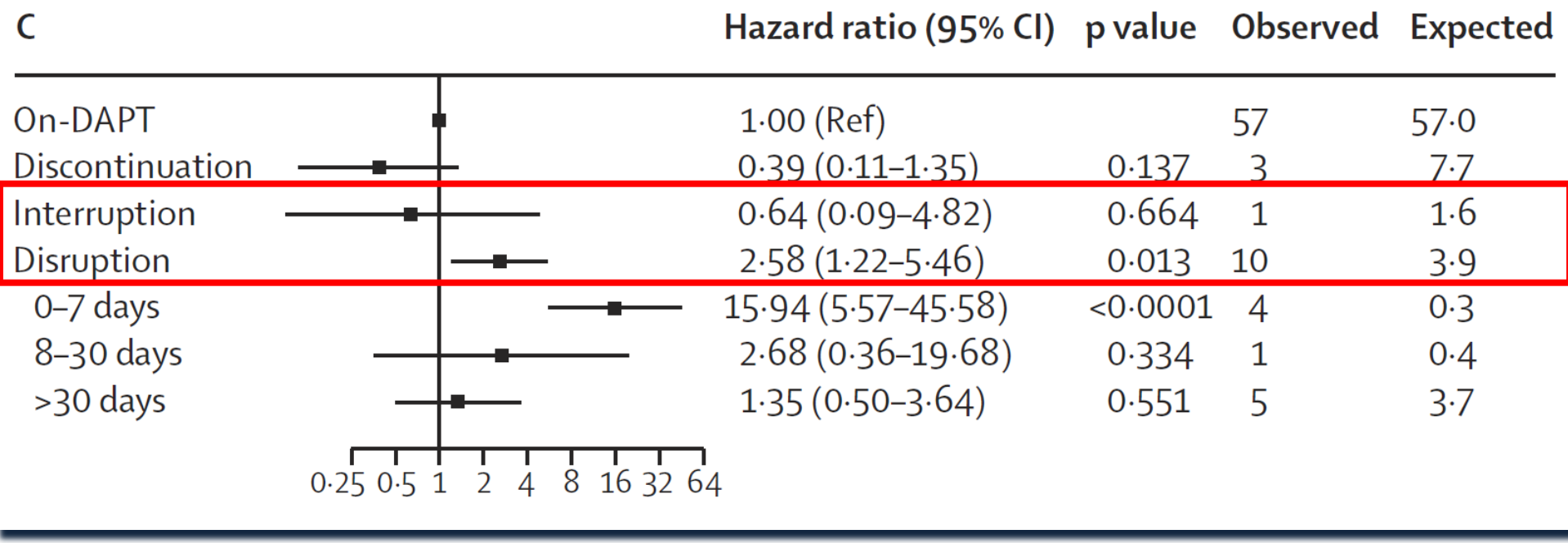
HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER



Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS)

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

Risk of definite or probable stent thrombosis



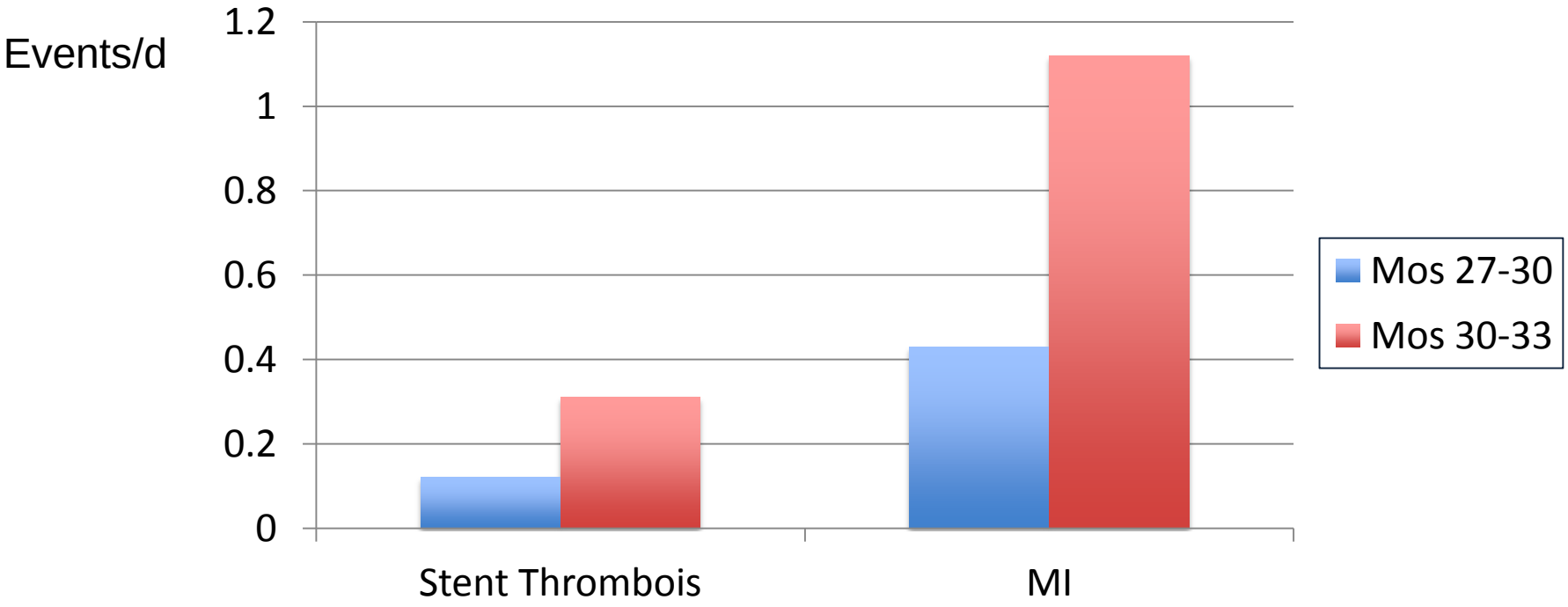
C	Hazard ratio (95% CI)	p value	Observed	Expected
On-DAPT	1·00 (Ref)		57	57·0
Discontinuation	0·39 (0·11–1·35)	0·137	3	7·7
Interruption	0·64 (0·09–4·82)	0·664	1	1·6
Disruption	2·58 (1·22–5·46)	0·013	10	3·9
0–7 days	15·94 (5·57–45·58)	<0·0001	4	0·3
8–30 days	2·68 (0·36–19·68)	0·334	1	0·4
>30 days	1·35 (0·50–3·64)	0·551	5	3·7

For patients undergoing PCI and discharged on DAPT, cardiac events after DAPT cessation depend on the clinical circumstance and reason for cessation and attenuates over time.

Courtesy of Dr Darek Dudek

Possible Clopidogrel Rebound Effect (DAPT Trial)

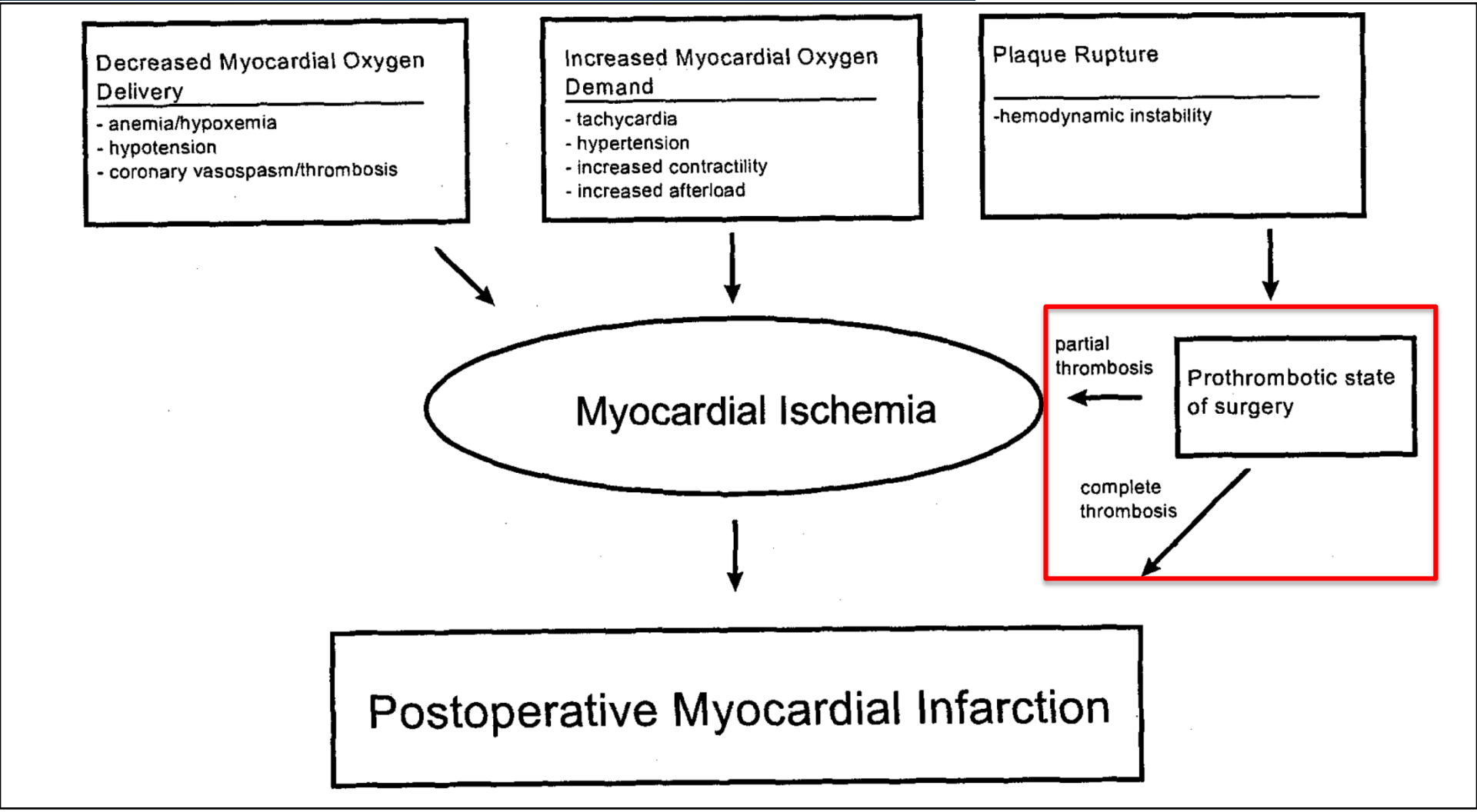
HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER



Mauri, MEJM.2014;371:2155

Physiological alterations related to surgery which may contribute to the pathophysiology of perioperative MI

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

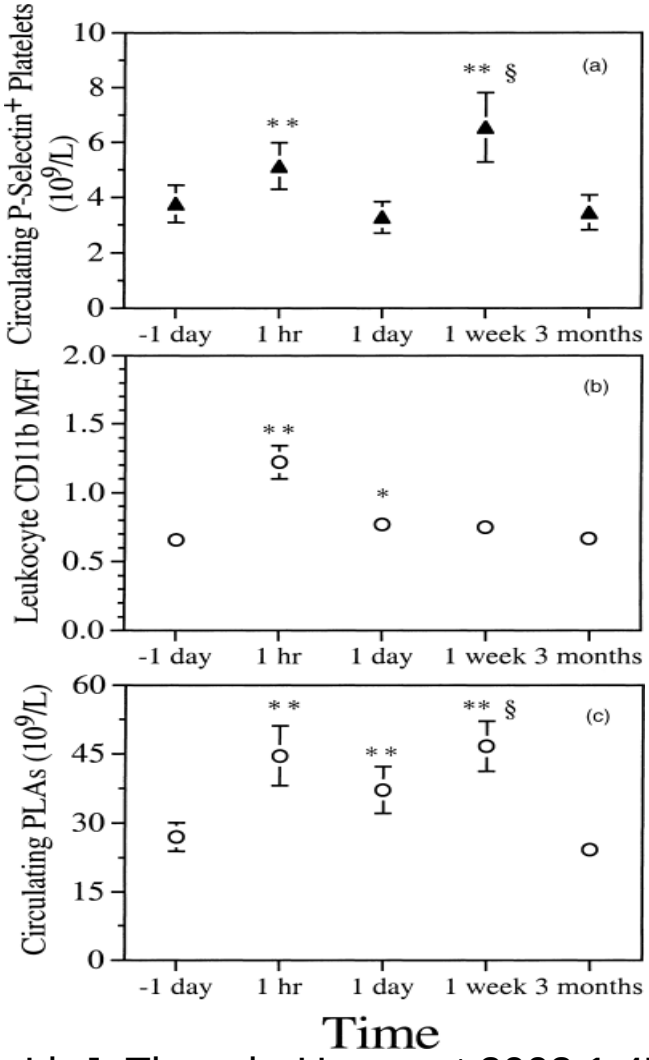


Courtesy of Dr Darek Dudek

Prothrombotic State After Cardiac and Non Cardiac Surgery

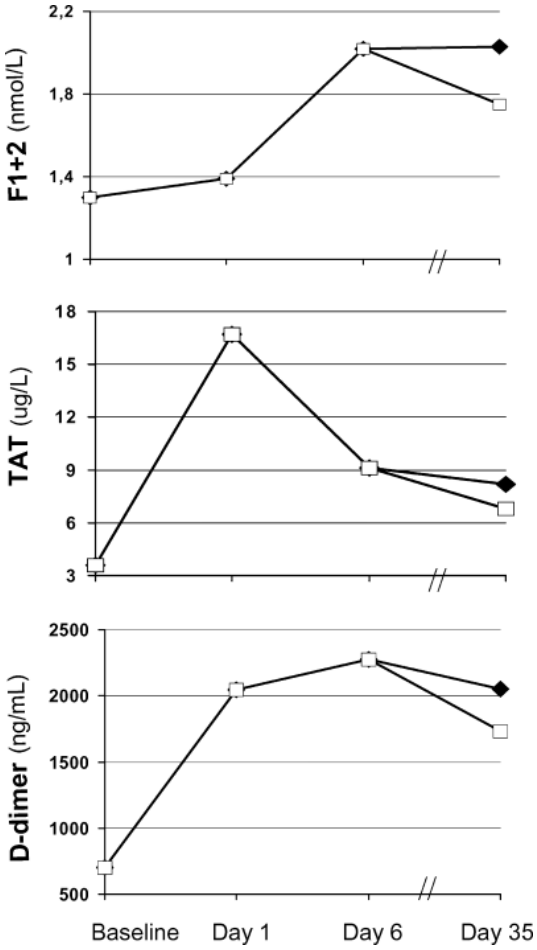
HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

Cardiac Surgery



Li. J. Thromb. Haemost.2003;1:471

Hip Surgery



Arnesen. J Thromb. Haemost.2003;1:971

The Paradigm

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

- Surgery in patients with recent stent placement is characterized by a high risk of stent thrombosis and myocardial infarction.
- Surgeons dislike P2Y12 antagonists intensely because of bleeding risk.
- Short acting antithrombotic drugs modulate the risk of stent thrombosis, and should be used preoperatively.

Bleeding complications in patients with coronary stents during non-cardiac surgery (RECO study)

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

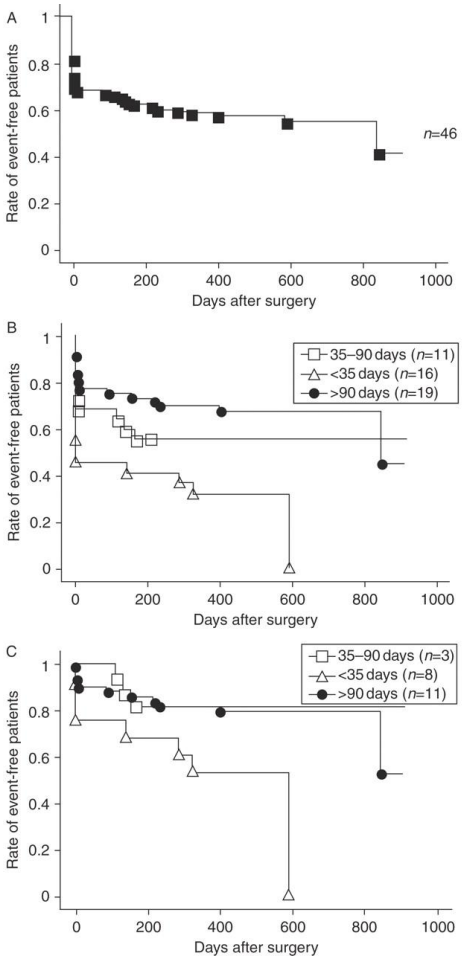
- Observational cohort study of 1134 consecutive patients with coronary stents.
- 108 (9.5%) experienced a postoperative hemorrhagic complication (with a median time to occurrence of 5.3 days).
- In 20 (18.5%) of patients reoperation was required.
- Mortality in patients with a hemorrhagic complication was 12% (n=13).

Thrombosis Research 134 (2014) 268–272

Austrian Study of Non-Cardiac Surgery After Stenting

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

- 103 Patients with non-cardiac surgery < 1 year after stenting; 46% had an event
- Antiplatelets, aspirin, clopidogrel continued or stopped < 3 days preop
  - Cardiac death 4.9%
  - MI 4%
  - Bleeding 4%



Vicenzi. Br. J. Anaesth. 2006;96:686

The Problems

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

1. Most myocardial infarctions occur after surgery (as far as we know) while bridging is done before surgery
2. There is no effective replacement for aspirin/P2Y12 antagonists during surgery and during the period of post-op oozing.
3. The risk may be lessened with modern stents and stenting techniques.

Antiplatelet Therapy at the Time of Late Stent Thrombosis (LST)

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

	Time from Stent to LST (mos)	AP Therapy at LST	Time from DC of Clopidogrel
1	2	--	5 d
2	7	ASA	28 d
3	6	ASA	21 d
3b	11	--	5 d
4	14.5	--	5 d
5	8	ASA	60 d
6	25	ASA	19 mo
7	26	ASA	19 mo

Ong; JACC: 2005: 45; 2088

Journal of the American College of Cardiology
© 2006 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 48, No. 12, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.10.026

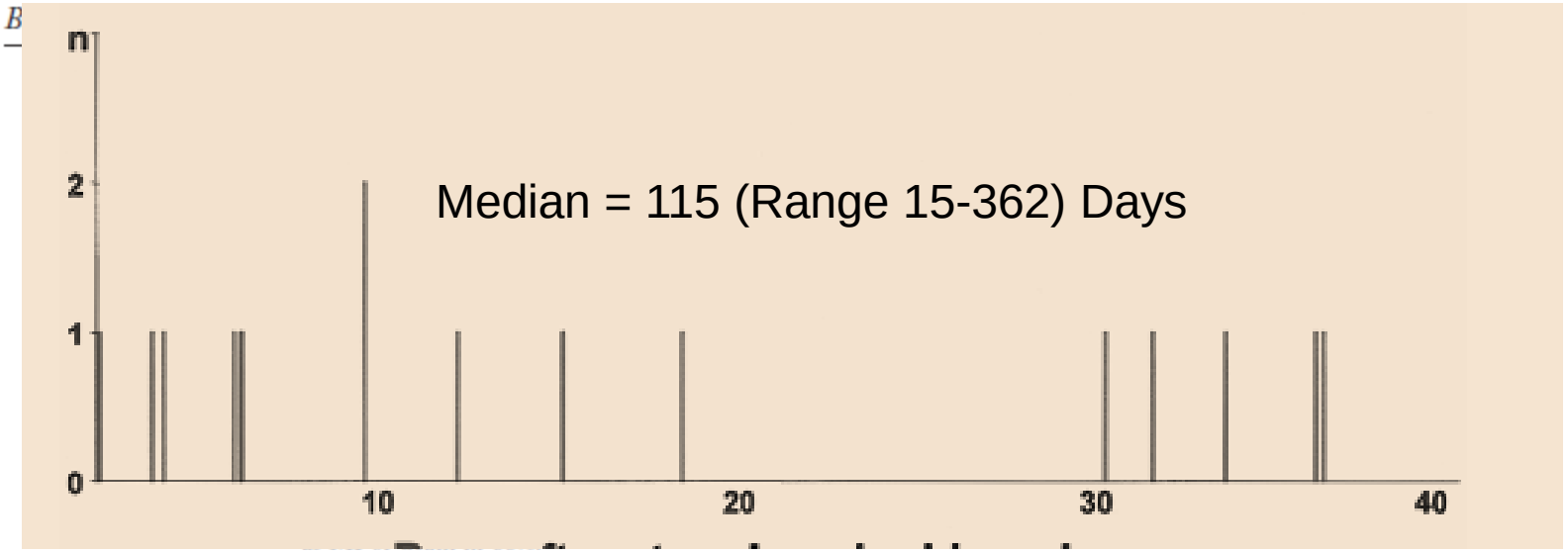
HOUSTON Methodist HEART & CENTER

EXPEDITED REVIEWS

Late Clinical Events After Clopidogrel Discontinuation May Limit the Benefit of Drug-Eluting Stents

An Observational Study of Drug-Eluting Versus Bare-Metal Stents

Matthias Pfisterer, MD, FACC,* Hans Peter Brunner-La Rocca, MD,* Peter T. Buser, MD, FACC,* Peter Rickenbacher, MD,§ Patrick Hunziker, MD,† Christian Mueller, MD,‡ Raban Jeger, MD,* Franziska Bader, RN,* Stefan Osswald, MD, FACC,* Christoph Kaiser, MD,* for the BASKET-LATE Investigators



CONCLUSIONS After the discontinuation of clopidogrel, the benefit of DES in reducing target vessel revascularization is maintained but has to be balanced against an increase in late cardiac death or nonfatal MI, possibly related to late stent thrombosis. (J Am Coll Cardiol 2006;48: 2584–91) © 2006 by the American College of Cardiology Foundation

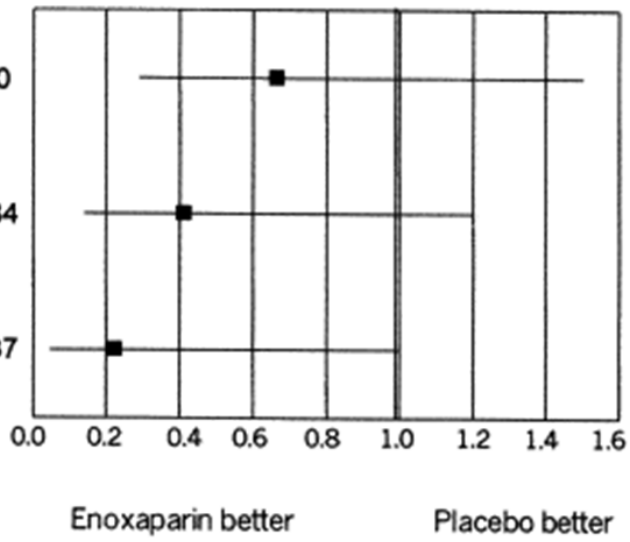
Bridging is most likely to be performed during a period when nothing is likely to happen anyway.

ATLAST Trial of Enoxaparin After Stenting

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

- 1,102 of planned 2,000 patients with high risk features post stenting randomized to placebo or enoxaparin SQ BID
- 14 Day follow-up
- Terminated for low event rate

Event	Enoxaparin	Placebo	P
Death, Infarction, or UR	1.8%	2.7%	0.30
Death or Infarction	0.9%	2.2%	0.084
Infarction	0.4%	1.6%	0.037



Batchelor. J. Am. Coll. Cardiol.2001;68;E1308

Scan for Author Video Interview

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

Bridging Antiplatelet Therapy With Cangrelor in Patients Undergoing Cardiac Surgery

A Randomized Controlled Trial

Dominick J. Angiolillo, MD, PhD
Michael S. Firstenberg, MD
Matthew J. Price, MD
Pradyumna E. Tummala, MD
Martin Hutyra, MD
Ian J. Welsby, MD
Michele D. Voeltz, MD
Harish Chandna, MD
Chandrashekhar Ramaiah, MD
Miroslav Brtko, MD, PhD
Louis Cannon, MD
Cornelius Dyke, MD
Tiepu Liu, MD, PhD
Gilles Montalescot, MD
Steven V. Manoukian, MD
Jayne Prats, PhD
Eric J. Topol, MD
for the BRIDGE Investigators

Context Thienopyridines are among the most widely prescribed medications, but their use can be complicated by the unanticipated need for surgery. Despite increased risk of thrombosis, guidelines recommend discontinuing thienopyridines 5 to 7 days prior to surgery to minimize bleeding.

Objective To evaluate the use of cangrelor, an intravenous, reversible $P2Y_{12}$ platelet inhibitor for bridging thienopyridine-treated patients to coronary artery bypass grafting (CABG) surgery.

Design, Setting, and Patients Prospective, randomized, double-blind, placebo-controlled, multicenter trial, involving 210 patients with an acute coronary syndrome (ACS) or treated with a coronary stent and receiving a thienopyridine awaiting CABG surgery to receive either cangrelor or placebo after an initial open-label, dose-finding phase (n=11) conducted between January 2009 and April 2011.

Interventions Thienopyridines were stopped and patients were administered cangrelor or placebo for at least 48 hours, which was discontinued 1 to 6 hours before CABG surgery.

Main Outcome Measures The primary efficacy end point was platelet reactivity (measured in $P2Y_{12}$ reaction units [PRUs]), assessed daily. The main safety end point was excessive CABG surgery–related bleeding.

Results The dose of cangrelor determined in 10 patients in the open-label stage was 0.75 μg/kg per minute. In the randomized phase, a greater proportion of patients treated with cangrelor had low levels of platelet reactivity throughout the entire treatment period compared with placebo (primary end point, PRU <240; 98.8% (83 of 84) vs 19.0% (16 of 84); relative risk [RR], 5.2 [95% CI, 3.3-8.1] $P<.001$). Excessive CABG surgery–related bleeding occurred in 11.8% (12 of 102) vs 10.4% (10 of 96) in the cangrelor and placebo groups, respectively (RR, 1.1 [95% CI, 0.5-2.5] $P=.763$). There were no significant differences in major bleeding prior to CABG surgery, although minor bleeding episodes were numerically higher with cangrelor.

Conclusions Among patients who discontinue thienopyridine therapy prior to cardiac surgery, the use of cangrelor compared with placebo resulted in a higher rate of maintenance of platelet inhibition.

Trial Registration clinicaltrials.gov Identifier: NCT00767507

JAMA. 2012;307(3):265-274 www.jama.com

DUAL ANTIPLATELET THERAPY with aspirin and an oral $P2Y_{12}$ receptor inhibitor is the standard of care to prevent the short- and long-term risk of recurrent atherothrombotic events in high-risk settings, such as patients with an acute coronary syndrome (ACS) and those undergoing percutaneous coronary intervention (PCI).[1-4] However, the ischemic benefit associated with more

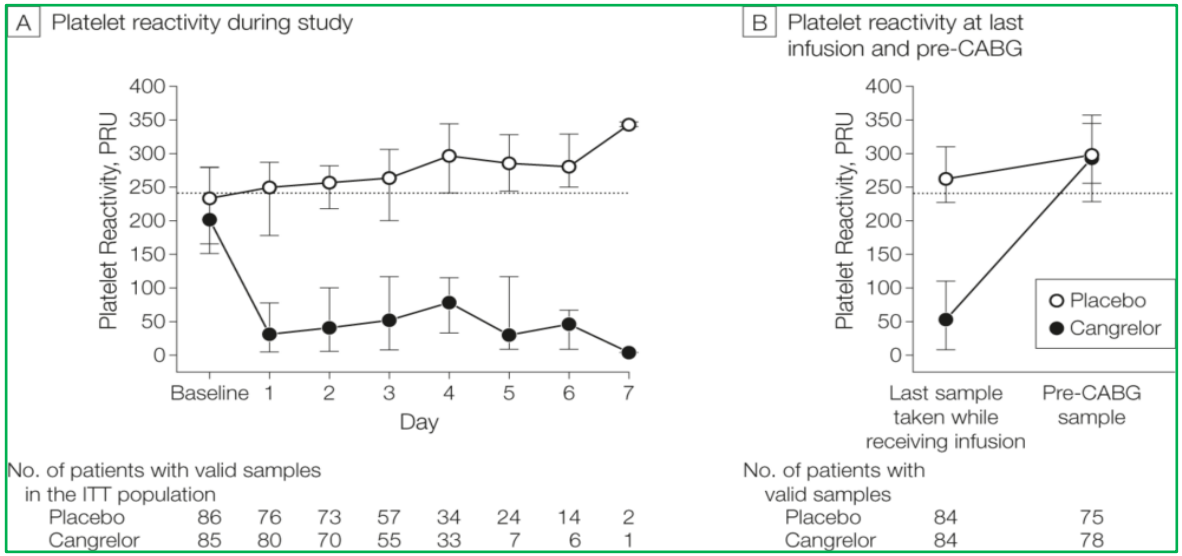
BRIDGE Study

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

- 210 Patients on thienopyridine prior to planned cardiac surgery
- 5-7 days off thienopyridine but on cangrelor until 1-6 hours before surgery.
- Platelet reactivity was measured using VerifyNow.
- Primary EPs:
  - % of patients with Verify now > 240 PRU
  - % of patients with excessive perioperative bleeding

Anigolillo.JAMA. 2012;307:265-274

Cangrelor Bridging

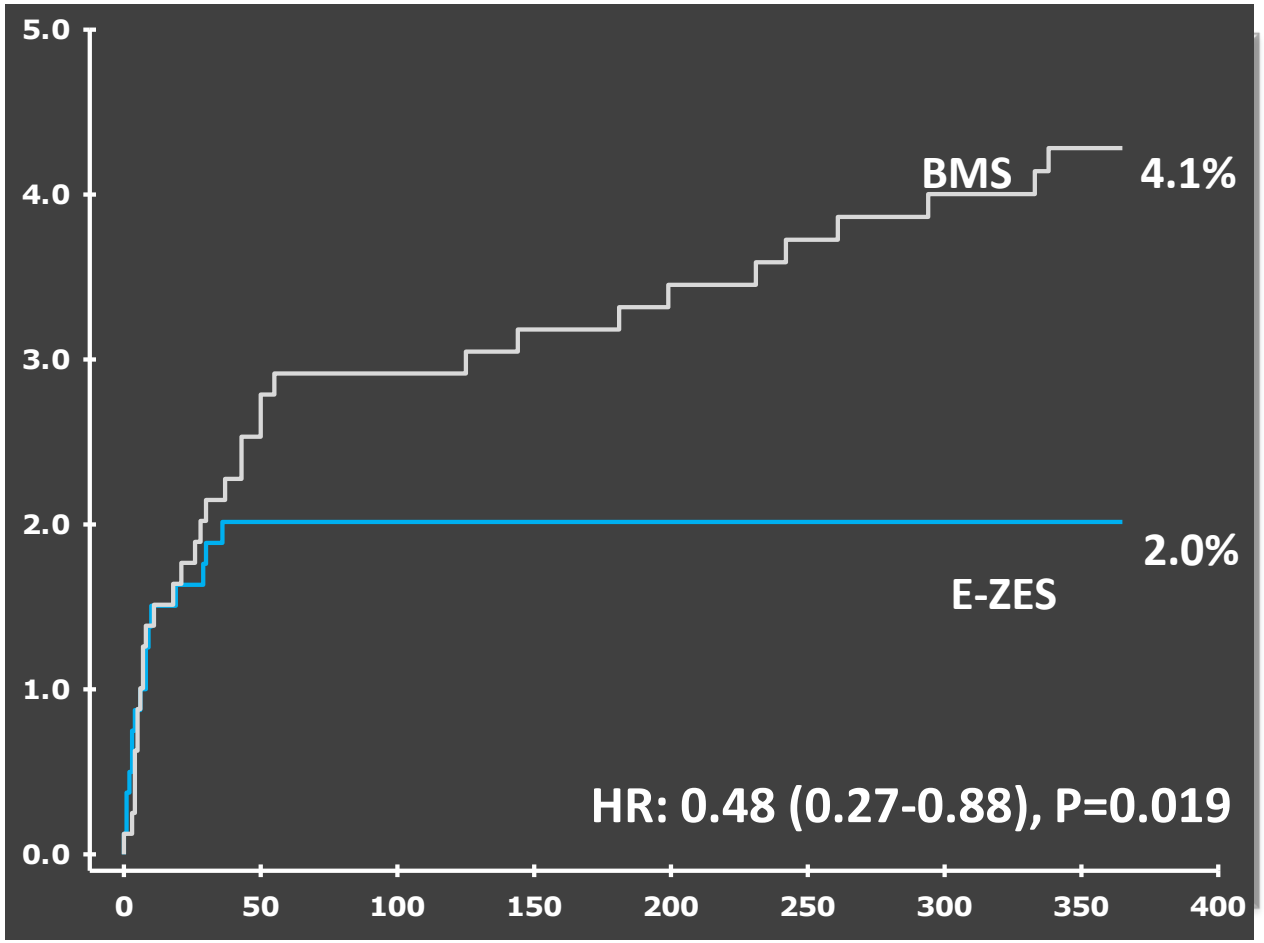


- 98.8% of patients treated with cangrelor had <240 PRU
- No differences were observed in perioperative bleeding.

Angiolillo.JAMA. 2012;307:265-274

Definite or Probable Stent Thrombosis

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER



No. at Risk								
BMS	804	763	739	723	712	701	692	685
E-ZES	802	767	758	741	733	721	713	708

HOUSTON Methodist HEART & R CENTER

Modifying effect of dual antiplatelet therapy on incidence of stent thrombosis according to implanted drug-eluting stent type

Edoardo Camenzind[1]*, Eric Boersma[2], William Wijns[3], Laura Mauri[4], Tessa Rademaker-Havinga[5], Farzin Fath Ordoubadi[6], Maarten J. Suttorp[7], Mohammad Al Kurdi[8], and Ph Gabriel Steg[9,10,11,12], on behalf of the PROTECT Steering Committee and Investigators[†]

[1]University of Geneva, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva, Switzerland; [2]Erasmus Medical Center, Rotterdam, the Netherlands; [3]Cardiovascular Center, OLV Hospital, Aalst, Belgium; [4]Brigham and Women's Hospital, Boston, MA, USA; [5]Cardialysis, Rotterdam, the Netherlands; [6]Manchester Royal Infirmary Hospital, Manchester, UK; [7]St Antonius Ziekehuis, Nieuwegein, the Netherlands; [8]Prince Salman Cardiac Center, King Fahd Mec
Paris, France; [11]Département Hospitalo-Universitaire FIRE, Hôpital Bichat, A
Hospital, London, UK

Received 11 November 2013; revised 27 January 2014; accepted 3 February 20

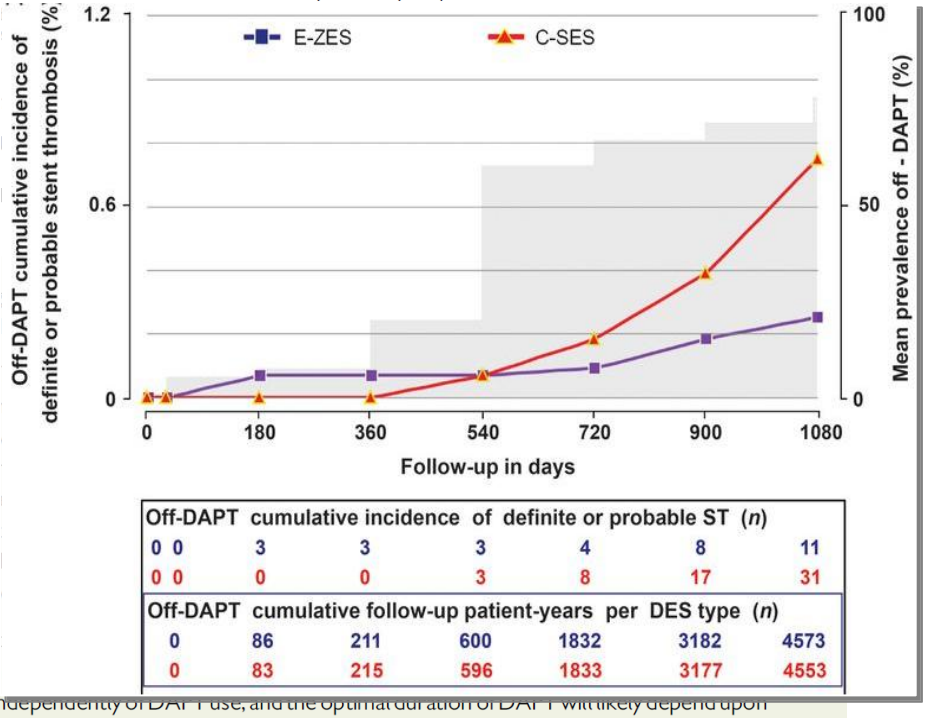
This paper was guest edited by Stephan Windecker, MD,

See page 1914 for the editorial comment on this article (c

Aim To investigate the putative modifying
years in patients randomized to End

Methods and results Of 8709 patients in PROTECT, 435
and clopidogrel/ticlopidine for ≥3 r
or probable stent thrombosis at 3 y
their interaction as the main outcom
and C-SES groups (79.6% at 1 yea
($P = 0.0052$) heterogeneity in treat
bosis was lower with E-ZES vs. C-S
presence of DAPT, no difference w

Conclusion A strong interaction was observed b
healing response induced by the im
DES trials should not be evaluated independently of DAPT use, and the optimal duration of DAPT will likely depend upon
stent type (Clinicaltrials.gov number NCT00476957).



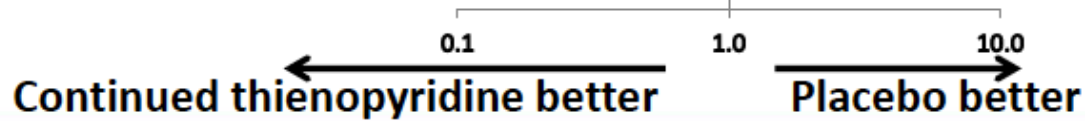
Off-DAPT cumulative incidence of definite or probable ST (*n*)						
0	3	3	3	4	8	11
0	0	0	3	8	17	31

Off-DAPT cumulative follow-up patient-years per DES type (*n*)						
0	86	211	600	1832	3182	4573
0	83	215	596	1833	3177	4553

Consistency of Treatment Effect MACCE (12-30 Months)

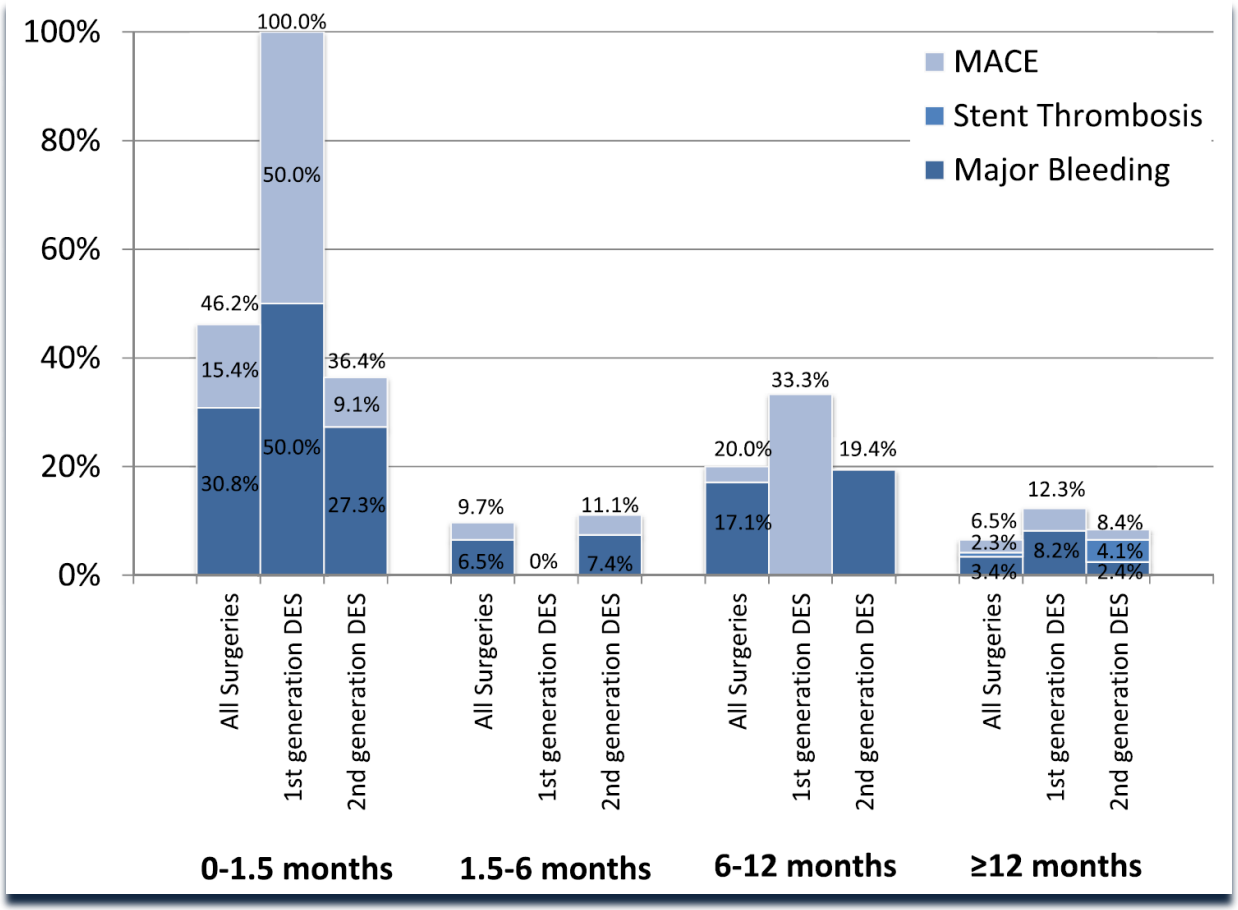
DAPT STUDY

Factor	N	HR and 95% CI	Interaction P
< 75 Years	N=8929	0.69 (0.57,0.83)	0.22
>= 75 Years	N=1032	0.95 (0.59,1.52)	
Male	N=7435	0.69 (0.56,0.85)	0.46
Female	N=2526	0.81 (0.56,1.17)	
No diabetes	N=6924	0.59 (0.46,0.74)	0.01
Diabetes	N=3037	0.95 (0.72,1.25)	
No Risk Factors for ST	N=5162	0.78 (0.60,1.03)	0.41
Risk Factors for ST	N=4799	0.67 (0.53,0.86)	
Clopidogrel	N=6500	0.80 (0.64,1.01)	0.03
Prasugrel	N=3461	0.52 (0.38,0.71)	
Sirolimus	N=1118	0.54 (0.31,0.93)	
Zotarolimus	N=1264	0.76 (0.44,1.30)	0.048
Paclitaxel	N=2666	0.52 (0.37,0.71)	
Everolimus	N=4703	0.89 (0.67,1.18)	



Perioperative complications after noncardiac surgery in patients with insertion of second-generation DES

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

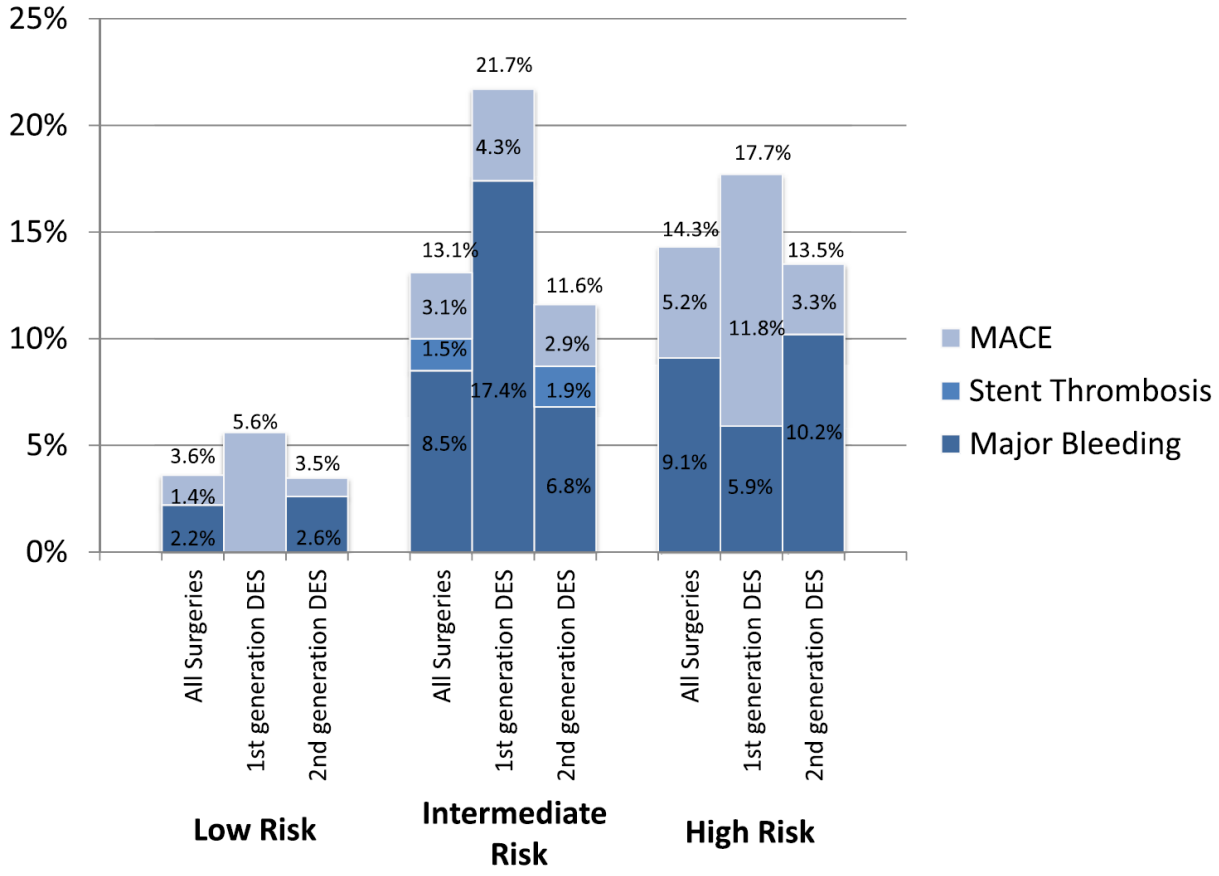


Rates of perioperative MACE, stent thrombosis, and major bleeding classified according to time from DES implantation to noncardiac surgery.

Courtesy of Dr Darek Dudek

Perioperative complications after noncardiac surgery in patients with insertion of second-generation DES

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER



Rates of perioperative MACE, stent thrombosis, and major bleeding classified according to surgical risk.

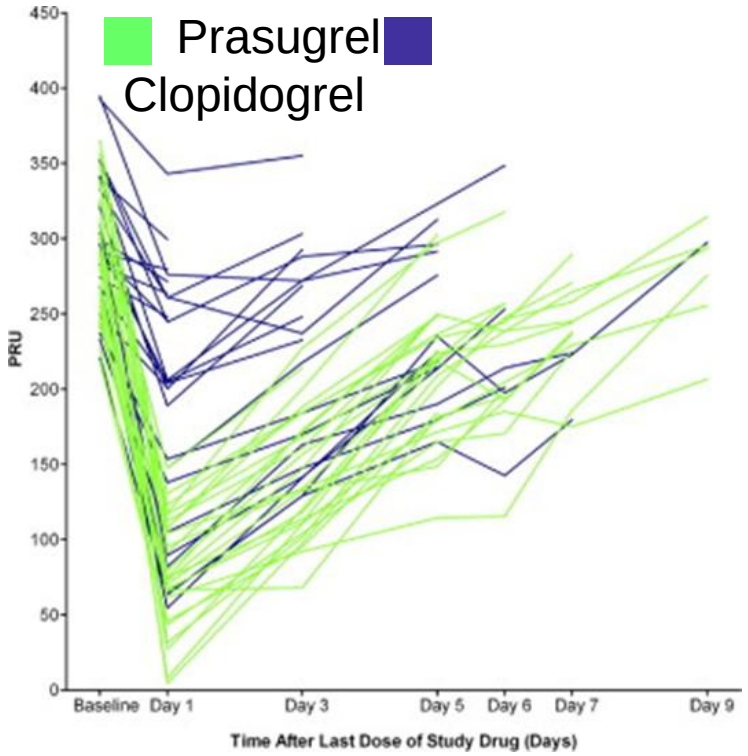
Courtesy of Dr Darek Dudek

Am J Cardiol 2014;114:230-235

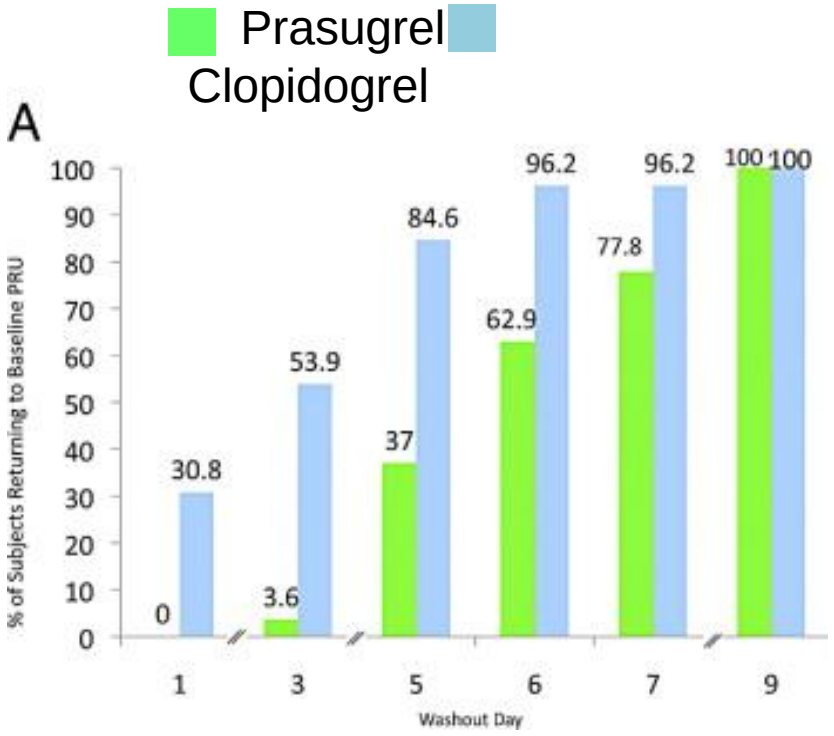
Clopidogrel/Prasugrel Washout After Drug Cessation

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

Individual Reactivity (VerifyNow)



Return to Baseline Value

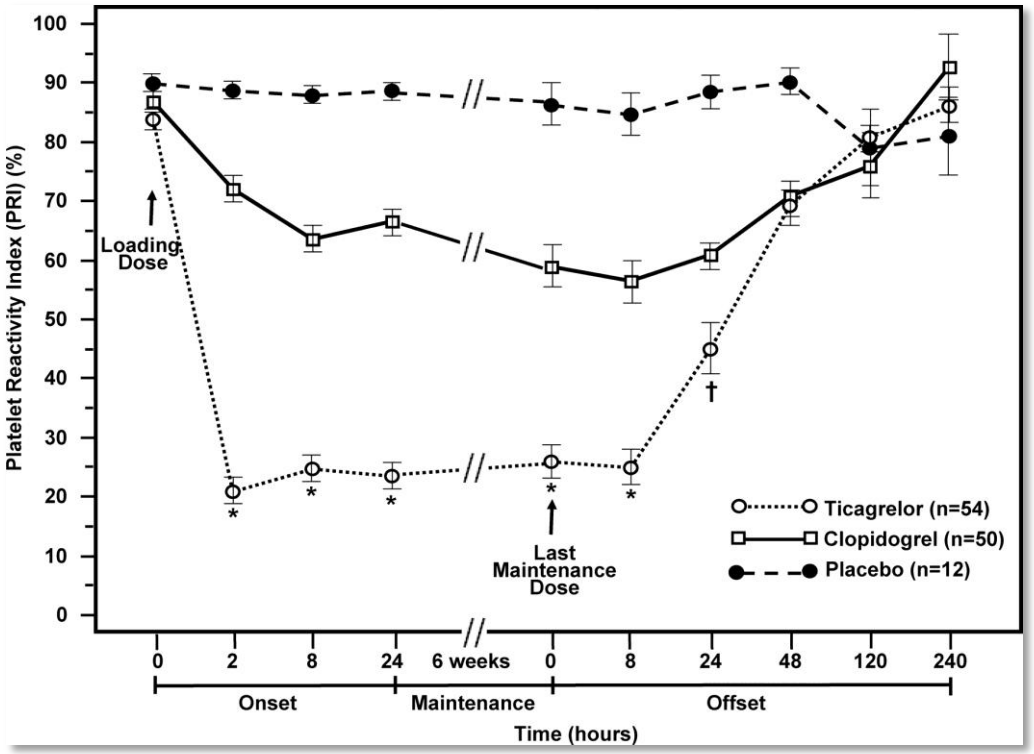


Price. J. Am. Coll. Cardiol;59:2338

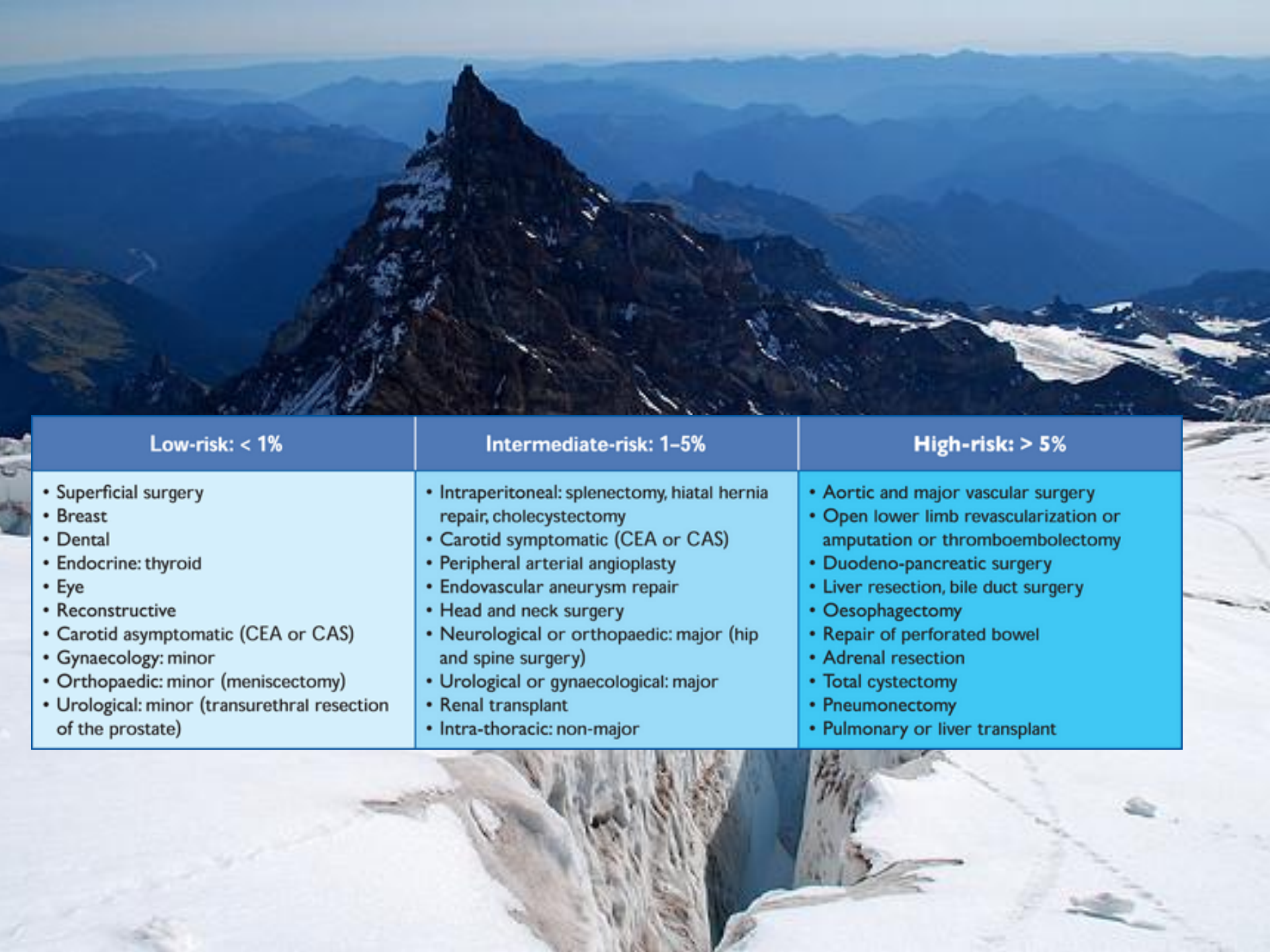
Ticagrelor

HOUSTON Methodist DEBAKEY HEART & VASCULAR CENTER

- Adenosine agonist (cyclopentyl-triazolo-pyrimidine)
- Direct P2Y12 antagonist, unlike the thienopyridines
- Relatively rapid on/off
- Requires BID dosing
- PLATO: High risk ACS and STEMI



Gurbel, P. A. et al. Circulation 2009;120:2577-2585



Low-risk: < 1%	Intermediate-risk: 1–5%	High-risk: > 5%
• Superficial surgery • Breast • Dental • Endocrine: thyroid • Eye • Reconstructive • Carotid asymptomatic (CEA or CAS) • Gynaecology: minor • Orthopaedic: minor (meniscectomy) • Urological: minor (transurethral resection of the prostate)	• Intraperitoneal: splenectomy, hiatal hernia repair, cholecystectomy • Carotid symptomatic (CEA or CAS) • Peripheral arterial angioplasty • Endovascular aneurysm repair • Head and neck surgery • Neurological or orthopaedic: major (hip and spine surgery) • Urological or gynaecological: major • Renal transplant • Intra-thoracic: non-major	• Aortic and major vascular surgery • Open lower limb revascularization or amputation or thromboembolectomy • Duodeno-pancreatic surgery • Liver resection, bile duct surgery • Oesophagectomy • Repair of perforated bowel • Adrenal resection • Total cystectomy • Pneumonectomy • Pulmonary or liver transplant