

Perioperative Inflammation, Ischemia, and Infarction

John E. Ellis MD
Adjunct Professor
University of Pennsylvania

johnellis1700@gmail.com

vascularanesthesia.com

Conflicts of Interest

- Baxter
- The Medicines Company

Three “I”s

- Pharmacologic protection - updates
 - Beta blockers
 - Statins
- Surgical population
 - Cardiac
 - Vascular
 - Other high-risk noncardiac

Personal recommendations

- Routine pharmacologic prophylaxis
 - Beta blockade
 - Statins
 - Aspirin +/- clopidogrel

Coronary Artery Disease Stenosis vs. Plaque Rupture?

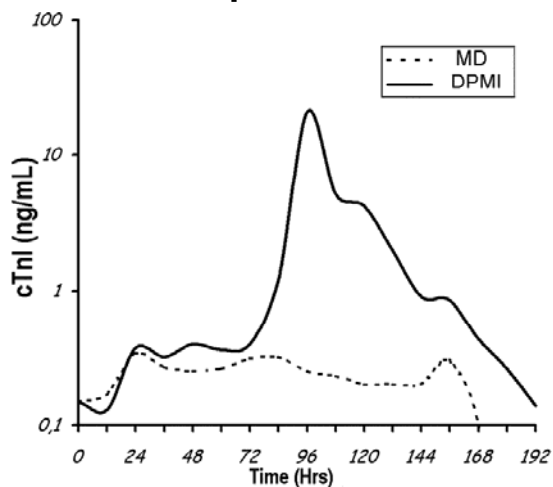


Mechanisms of perioperative MI

- Supply/demand mismatch
 - Subendocardial MI
 - ST changes, Troponin rise
- Plaque rupture
- Plaque hemorrhage
- Thrombosis
 - Transmural MI
 - Q wave, ↑ Troponin rise

Anesthesiology. 2005 May;102(5):885-91

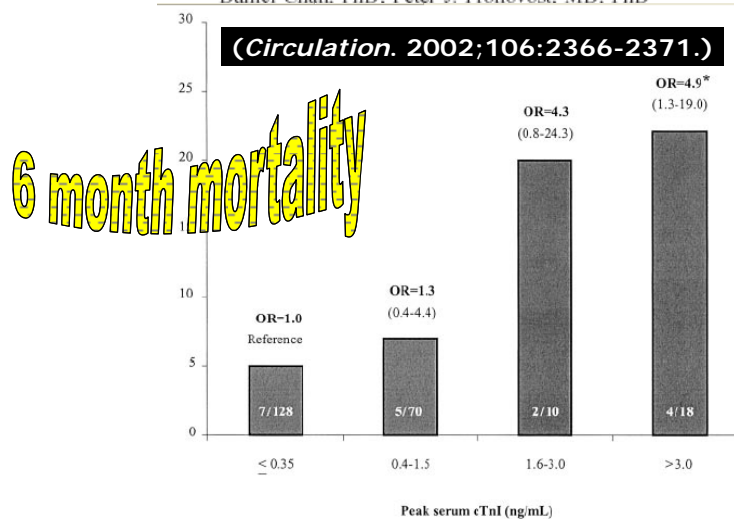
Two patterns of injury / troponins



Anesthesiology: 102(5) 2005pp 885-891

Cardiac Troponin I Predicts Short-Term Mortality in Vascular Surgery Patients

Lauren J. Kim, MPH; Elizabeth A. Martinez, MD; Nauder Faraday, MD; Todd Dorman, MD; Lee A. Fleisher, MD; Bruce A. Perler, MD; G. Melville Williams, MD; Daniel Chan, PhD; Peter J. Pronovost, MD, PhD



Intense Cardiac Troponin Surveillance for Long-Term Benefits is Cost-Effective in Patients Undergoing Open Abdominal Aortic Surgery: A Decision Analysis Model

Srinivas Mantha, MD*

Joseph Foss, MD†

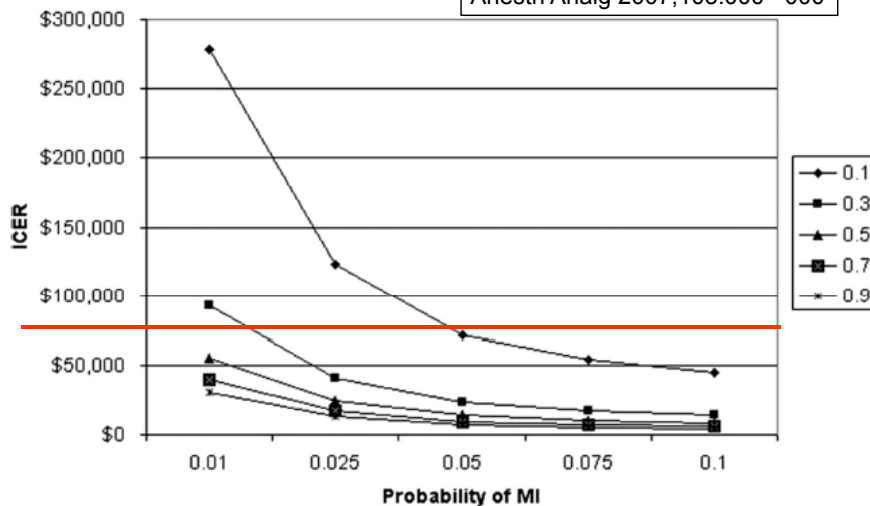
John E. Ellis, MD‡

Michael F. Roizen, MD†

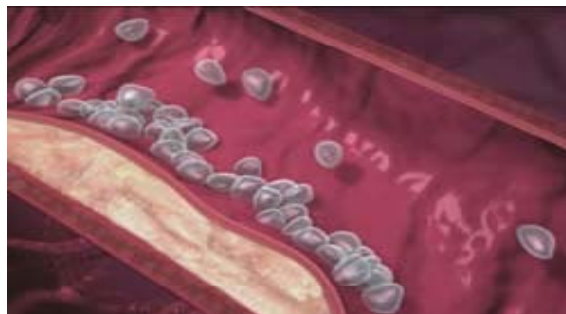
Anesth Analg 2007;105:000-000

Intense Cardiac Troponin Surveillance for Long-Term Benefits is Cost-Effective in Patients Undergoing Open Abdominal Aortic Surgery: A Decision Analysis Model

Anesth Analg 2007;105:000-000



Surgery is a hypercoagulable state



Hypercoagulability associated with thrombotic events

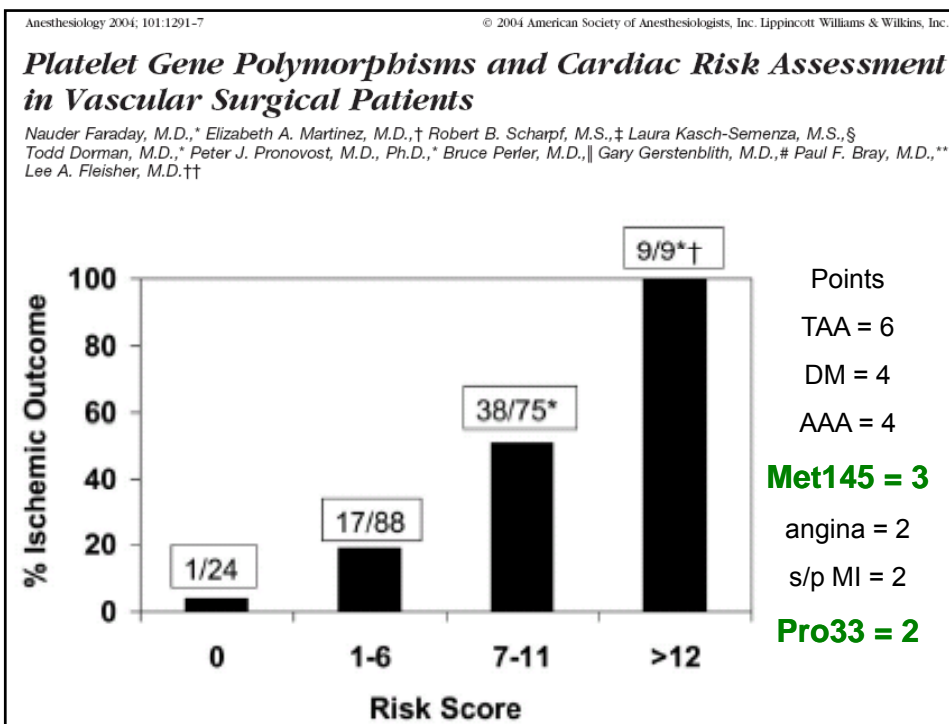
Anesthesiology 2004; 101:1291-7

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Platelet Gene Polymorphisms and Cardiac Risk Assessment in Vascular Surgical Patients

Nauder Faraday, M.D.,* Elizabeth A. Martinez, M.D.,† Robert B. Scharf, M.S.,‡ Laura Kasch-Semenza, M.S.,§
Todd Dorman, M.D.,* Peter J. Pronovost, M.D., Ph.D.,* Bruce Perler, M.D.,|| Gary Gerstenblith, M.D.,# Paul F. Bray, M.D.,**
Lee A. Fleisher, M.D.††

- Platelets are known to play a significant role in coronary thrombosis in nonoperative settings
- Polymorphisms in the genes encoding platelet glycoprotein (GP) IIIa and GPIb α are associated with myocardial ischemic morbidity in nonsurgical settings



■ CASE REPORTS

Anesthesiology 2007; 106:1057-9 Copyright © 2007, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Late Thrombosis of a Drug-eluting Stent Presenting in the Perioperative Period

Duncan G. de Souza, M.D.,* Victor C. Baum, M.D.,† Natalie M. Ballert, M.D.‡

1058 CASE REPORTS

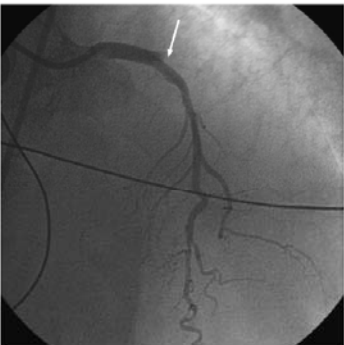


Fig. 1. Coronary angiography showing acute thrombosis (white arrow) in the proximal circumflex artery at the site of the drug-eluting stent.

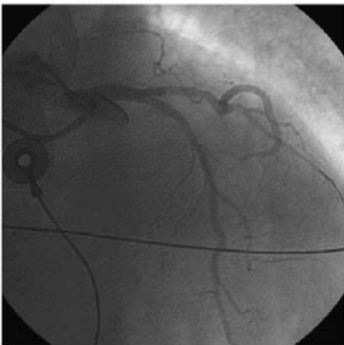
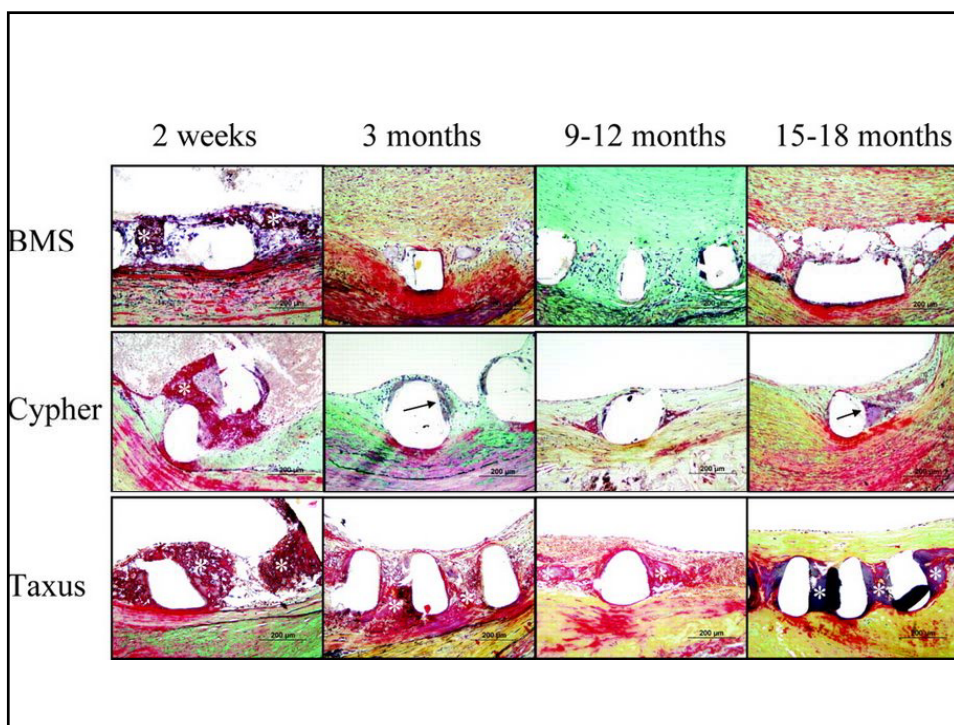
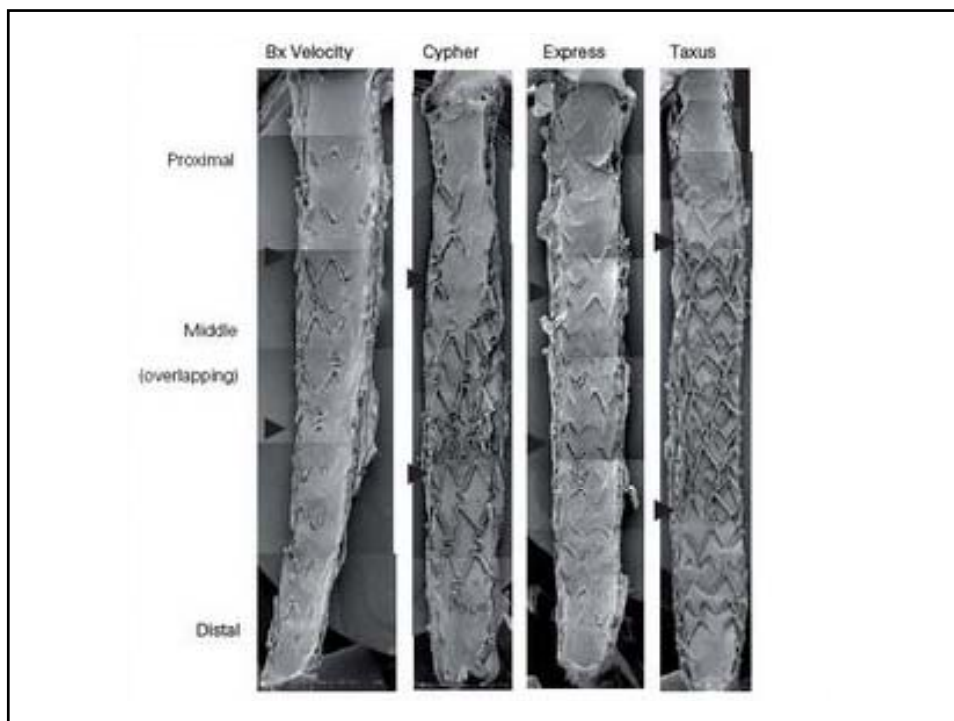


Fig. 2. Balloon angioplasty has restored vessel patency.

case demonstrates that patients with DES are not free



Beta blockade 2009

- Earlier trials show protection
- More recent trials questionable
- POISE (n>8000)
 - Less MI, but more CVA

POISE – the definitive trial??

Outcome	Metoprolol (n=4174), n (%)	Placebo (n=4177), n (%)	Hazard ratio	p
Primary composite	243 (5.8)	290 (6.9)	0.83	0.04
Nonfatal MI	151 (3.6)	215 (5.1)	0.70	0.0007
Total mortality	129 (3.1)	97 (2.3)	1.33	0.03
Stroke	41 (1.0)	19 (0.5)	2.17	0.005

AHA 2007



VS.



-Fig.2-

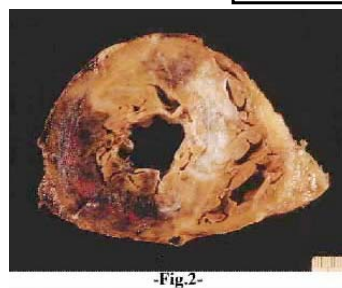
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AHA 2007



VS.



-Fig.2-

POISE – the definitive trial??

Outcome	Metoprolol (n=4174), n (%)	Placebo (n=4177), n (%)	Hazard ratio	p
Revascularization	11 (0.3)	27 (0.6)	0.41	0.01
Atrial fibrillation	91 (2.2)	120 (2.9)	0.76	0.04
Significant hypotension	626 (15.0)	404 (9.7)	1.55	<0.0001
Significant bradycardia	274 (6.6)	101 (2.4)	2.71	<0.0001

AHA 2007

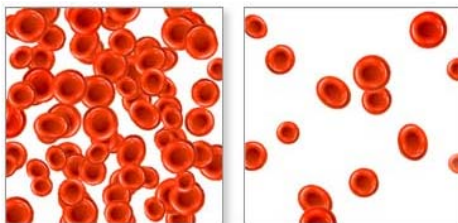
Lancet editorial re: POISE

- Poldermans and Fleisher suggest that patients in the POISE trial were **overdosed** with metoprolol, receiving functionally twice the dose of patients in the DECREASE-V trial.

Lancet. 2008 May 31;371(9627):1813-4.

ASA 2008 – Toronto (Beattie)

- Death/MI was higher for patients administered beta blockers when Hgb decreases postop more than 30%



ASA 2008 A846

Inflammatory Gene Polymorphisms and Risk of Postoperative Myocardial Infarction After Cardiac Surgery

M.V. Podgoreanu, MD; W.D. White, MPH; R.W. Morris, PhD; J.P. Mathew, MD;
M. Stafford-Smith, MD; I.J. Welsby, MD; H.P. Grocott, MD; C.A. Milano, MD;
M.F. Newman, MD; D.A. Schwinn, MD;
Perioperative Genetics and Safety Outcomes Study (PEGASUS) Investigative Team

- 3 polymorphisms were independent predictors of PMI
 - proinflammatory cytokine interleukin 6
 - intercellular adhesion molecule-1 (ICAM1)
 - E-selectin

(Circulation. 2006;114[suppl I]:I-275–I-281.)

Statins 2009

- Stroke
- Death
- MI
- Atrial fibrillation
- Aortic stenosis (slows progression)
- Renal failure?
- Sepsis?
-

Journal of Cardiothoracic and Vascular Anesthesia
Volume 23, Issue 3, June 2009, Pages 430-436

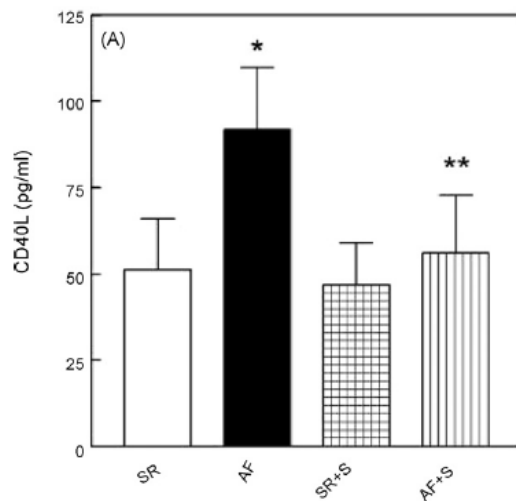
Statins 2009

- Small randomized trials show benefit
- Many retrospective studies, and now meta-analyses show benefit
- Many benefits besides lipid lowering
 - Reduced inflammations
 - NOS
- Risks of rhabdomyolysis very low

Simvastatin reduces platelet–endocardium adhesion in atrial fibrillation

Massimo Chello *, Cristiano Spadaccio, Giuseppe Patti, Mario Lusini, Raffaele Barbato,
Costanza Goffredo, Germano Di Sciascio, Elvio Covino

*Interdisciplinary Center for Biomedical Research (CIR), Department of Cardiovascular Sciences,
University Campus BioMedico of Rome, Italy*

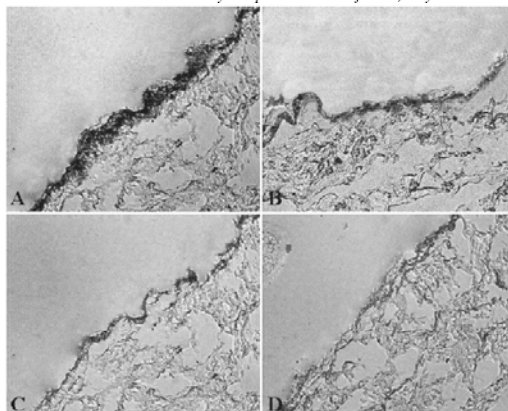


M. Chello et al. / Atherosclerosis 197 (2008) 588–595

Simvastatin reduces platelet–endocardium adhesion in atrial fibrillation

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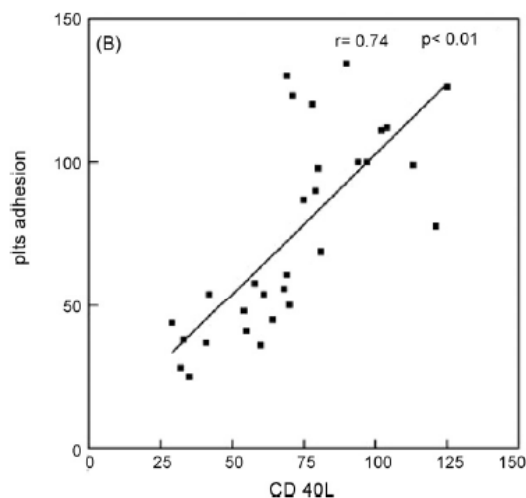
Immunohistochemical analysis of atrial specimens with anti-CD41 primary antibodies. (A) Atrial fibrillation, (B) atrial fibrillation in the presence of 5M simvastatin, (C) sinus rhythm and (D) sinus rhythm in the presence of 5M simvastatin.

M. Chello et al. / Atherosclerosis 197 (2008) 588–595

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M. Chello et al. / *Atherosclerosis* 197 (2008) 588–595

Mannacio et al

Acquired Cardiovascular Disease

Effect of rosuvastatin pretreatment on myocardial damage after coronary surgery: A randomized trial

Vito A. Mannacio, MD,^a Domenico Iorio, MD,^a Vincenzo De Amicis, MD,^a Francesco Di Lello, MD,^a and F. Musumeci, MD^b

TABLE 3. Postoperative biochemical features

	Placebo		RSV	
	n = 100	Mean peak values	n = 100	Mean peak values
Troponin I	65%	0.32 ± 0.26 ng/mL	35%	0.16 ± 0.15 ng/mL
Myoglobin	72%	98.31 ± 31 ng/mL	39%	72.25 ± 25 ng/mL
CK-MB mass	40%	9.3 ± 8.1 ng/mL	22%	3.9 ± 3.3 ng/mL
hsCRP	88%	17.2 ± 3.4 mg/L	58%	15.4 ± 2.5 mg/L

RSV, Rosuvastatin; CK-MB, creatine kinase-MB; hsCRP, high-sensitivity C-reactive protein.

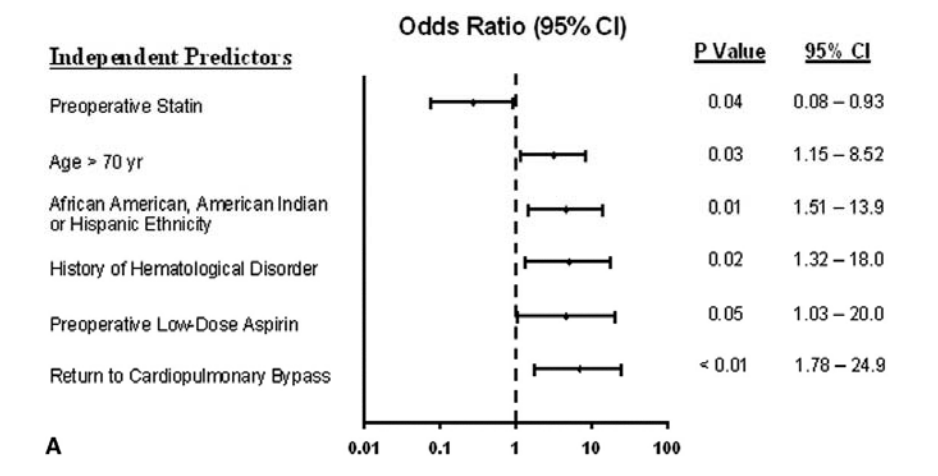
P < 0.01 for all

J Thorac Cardiovasc Surg 2008;136:1541-8

Preoperative statin therapy is associated with reduced cardiac mortality after coronary artery bypass graft surgery

The Journal of Thoracic and Cardiovascular Surgery August 2006

Charles D. Collard, MD,^a Simon C. Body, MBChB, MPH,^b Stanton K. Shernan, MD,^b Shirley Wang, PhD,^c and Dennis T. Mangano, PhD, MD,^a for the Multicenter Study of Perioperative Ischemia (MCSPI) Research Group, Inc, and the Ischemia Research and Education Foundation (IREF) Investigators*



Perioperative Statin Therapy Is Associated With a Significant and Dose-Dependent Reduction of Adverse Cardiovascular Outcomes After Coronary Artery Bypass Graft Surgery

Alexandre Ouattara, MD, PhD,* Hamina Benhaoua, MD,* Yannick Le Manach, MD,* Nejma Mabrouk-Zerguini, MD,* Omar Itani, MD,* Amer Osman, MD,* Marc Landi, MD,* Bruno Riou, MD, PhD,† and Pierre Coriat, MD*

Table 2. Independent Risk Factors of Postoperative Cardiovascular Outcomes

	Odds Ratio (95% CI)	p Value
Left ventricular ejection fraction	0.93 (0.91-0.95)*	0.001
Perioperative statin therapy	0.46 (0.25-0.85)	0.01
CARE score	1.6 (1.1-2.3)†	0.02
Preoperative atrial fibrillation	6.1 (2.1-18.1)	0.001
Cardiopulmonary bypass time	1.02 (1.01-1.03)‡	0.003
Surgical re-exploration	9.0 (1.3-62.7)	0.03

NOTE. The Hosmer-Lemeshow goodness-of-fit chi-square test statistic was 9.95 ($p = 0.27$). The C-index for this model was 0.81.

Abbreviations: CI, confidence interval; CARE, Cardiac Anesthesia Risk Evaluation.

*Per percent of increase.

†Per point of CARE score.

‡Per minute bypass time increase.

Journal of Cardiothoracic and Vascular Anesthesia, Vol xx, No x (Month), 2009:

Perioperative Statin Therapy Is Associated With a Significant and Dose-Dependent Reduction of Adverse Cardiovascular Outcomes After Coronary Artery Bypass Graft Surgery

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Nejma Mabrouk-Zerguini, MD,* Omar Itani, MD,* Amer Osman, MD,* Marc Landi, MD,*
Bruno Riou, MD, PhD,† and Pierre Coriat, MD*

- There was a dose-dependent effect of statins in reduced CV complications
 - OR high-dose vs no statin therapy = 0.38
 - (95% CI, 0.17-0.85; $p < 0.05$)

Journal of Cardiothoracic and Vascular Anesthesia, Vol xx, No x (Month), 2009:

Journal of the American College of Cardiology
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Published by Elsevier Inc.

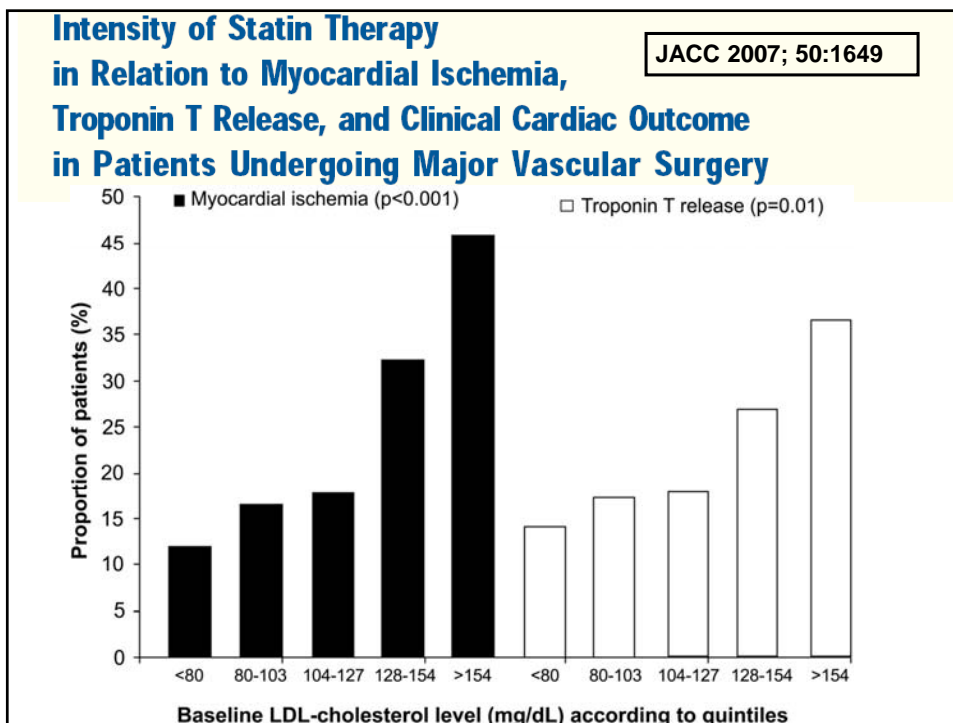
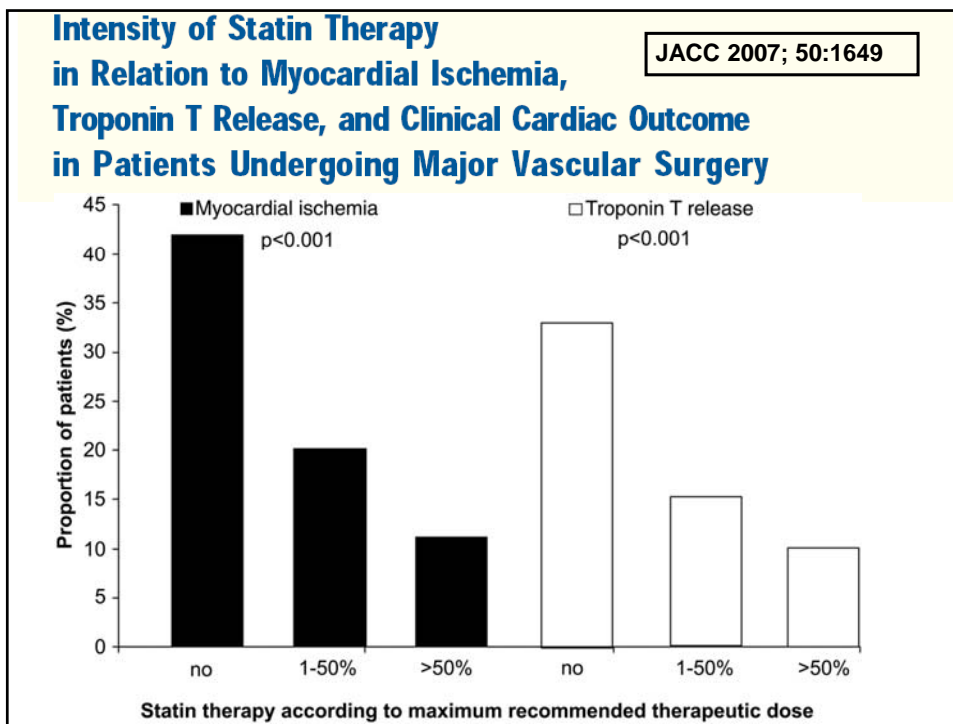
Vol. 50, No. 17, 2007
ISSN 0735-1097/07/\$32.00
doi:10.1016/j.jacc.2007.06.046

Coronary Artery Disease

**Intensity of Statin Therapy
in Relation to Myocardial Ischemia,
Troponin T Release, and Clinical Cardiac Outcome
in Patients Undergoing Major Vascular Surgery**

Harm H. H. Feringa, MD,* Olaf Schouten, MD,† Stefanos E. Karagiannis, MD,* Jasper Bruggts, MD,*
Abdou Elhendy, MD,§ Eric Boersma, PhD,* Radosav Vidakovic, MD,*
Marc R. H. M. van Sambeek, MD,† Peter G. Noordzij, MD,‡ Jeroen J. Bax, MD,¶
Don Poldermans, MD‡

Rotterdam and Leiden, the Netherlands; and Marshfield, Wisconsin



CMC **The Impact of Postoperative Discontinuation or Continuation of Chronic Statin Therapy on Cardiac Outcome After Major Vascular Surgery**

Yannick Le Manach, MD*

Gilles Godet, MD*

Pierre Coriat, MD*

Claire Martinon, MD*

Michèle Bertrand, MD*

Marie-Hélène Fléron, MD*

Bruno Riou, MD, PhD†



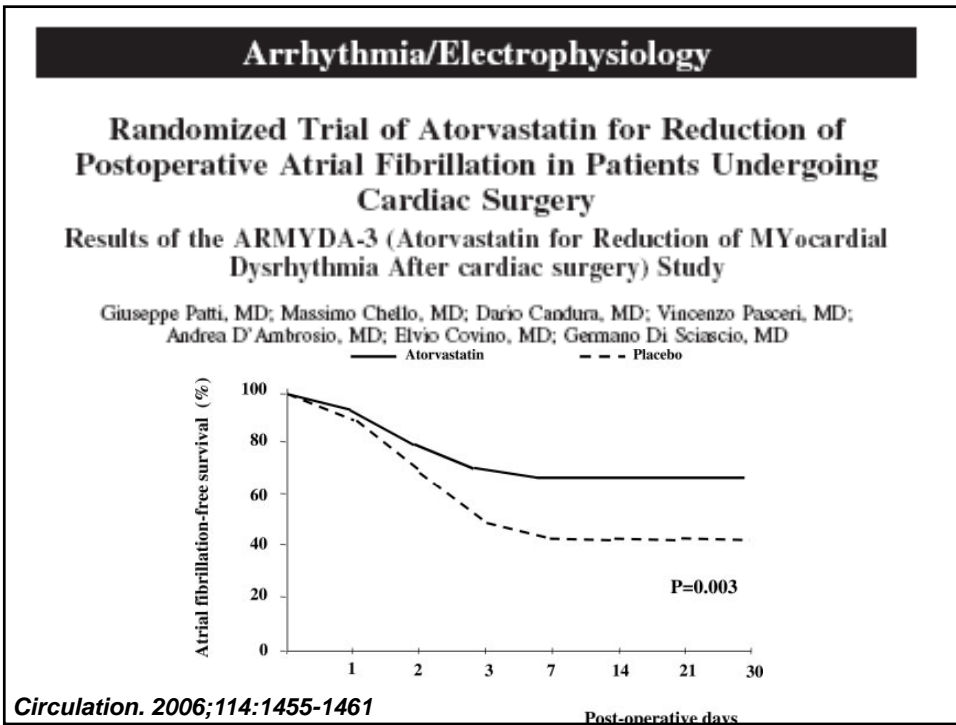
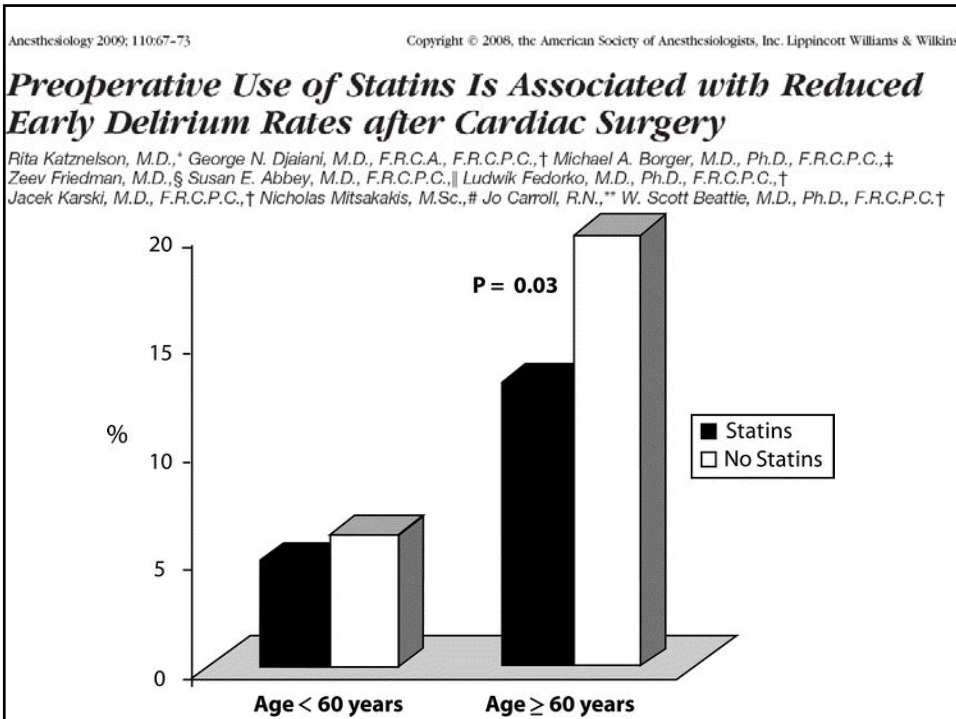
Le Manach Y et al. Anesth Analg 2007;104:1326

Table 4. Independent Variables Associated with Postoperative Cardiac Myonecrosis in Patients Chronically Treated with Statins Regardless of the Period of Study Where Delay Between Surgery and Restarting of Statins was Known ($N = 262$)

Variables	Odds ratio (95% confidence interval)	<i>P</i> value
Obliterative vascular disease	1.8 (1.1–3.2)	0.04
Coronary artery disease	1.8 (1.1–3.2)	0.03
Age >75 yr	2.0 (1.1–3.7)	0.03
Statin withdrawal = 4 days	2.9 (1.6–5.5)	0.001
Reintervention (any type)	3.7 (1.9–7.1)	<0.001
PRBC >3 units	4.1 (2.4–7.2)	<0.001

PRBC = Packed red blood cell units.

Le Manach Y et al. Anesth Analg 2007;104:1326



**Recent Advances in Perioperative Medicine: Highlights From the Literature
for the Cardiothoracic and Vascular Anesthesiologist**

John G.T. Augoustides, MD, FASE, FAHA, and Prakash Patel, MD



Journal of Cardiothoracic and Vascular Anesthesia
Volume 23, Issue 3, June 2009, Pages 430-436

Statins 2009

- "...concluded that preoperative statins significantly improve multiple clinical outcomes after cardiac surgery.
- Although data are compelling, ... caution against empiric statins for all patients scheduled for cardiac surgery **until supported by evidence from adequately powered future RCTs.**

Journal of Cardiothoracic and Vascular Anesthesia
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Fish Oil (omega-3)?



DECREASE 3

- **Randomized clinical trial**
- ~500 patients for **vascular surgery**
- All on beta blockers
- European Society Cardiologists 2008

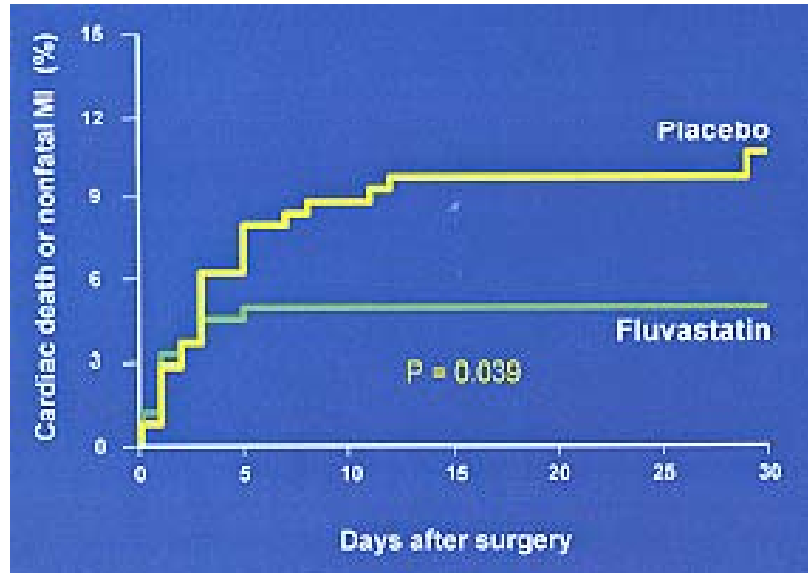
Primary endpoint: myocardial ischemia

- continuous ECG registration during 72 hours postoperatively
- troponin T measurement on day 1, 3, 7, and 30
- ECG recordings on day 7 and 30.

Secondary endpoint

- The composite of cardiovascular death and nonfatal MI within 30 days after surgery.

DECREASE 3 MI/cardiac death



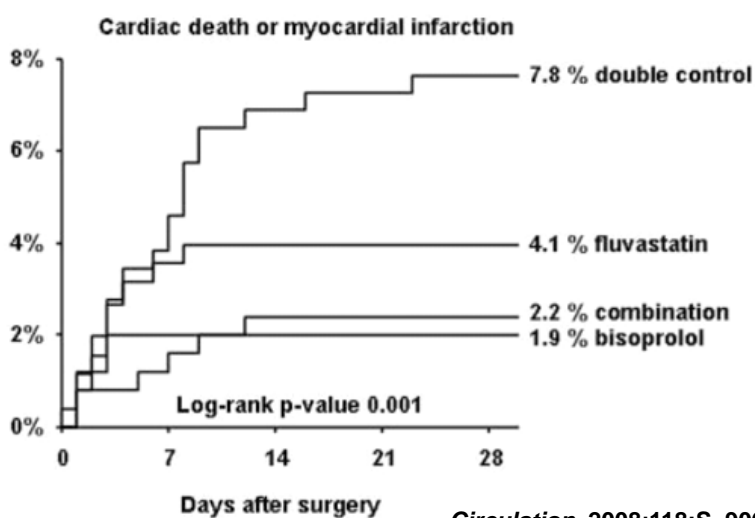
DECREASE 4

- ~1100 patients randomized according to an open-label, factorial design to
 - 1) β -blocker therapy (bisoprolol),
 - 2) statin (fluvastatin XL 80mg daily)
 - 3) combination of β -blockers and statins (bisoprolol and fluvastatin) and
 - 4) neither β -blockers nor statins (control group).

DECREASE 4

- By design, study medication could be started up to the day of surgery
 - median 34 days preprocedure
 - interquartile range 21 to 53 days
- Continued until 30 days after surgery.

DECREASE 4



An aside....

- SCA committee is designing an anesthesia module for the STS database
- Input is appreciated

“Breakfast of Champions!”

