Perioperative Myocardial Ischemia/Infarction in Non-Cardiac Sx

H Yang
Professor & Chair
Department of Anesthesia
Conflict of Interest

- No payment by industry
- No shares in industry
Choose the best response

A. Beta-blocker prophylaxis prevents periop MI (POMI)
B. Coronary critical stenosis account for 90% of POMI
C. Cardiac risk indices have high sensitivity & specificity to predict POMI
D. Postop myocardial ischemia is rarely seen before POMI
Objectives

• Understand the implications of perioperative myocardial infarctions (POMI)
• Review status of prophylaxis against POMI
• Describe pathophysiology (Mechanism) of perioperative myocardial ischemia/infarction
• Discuss pre-op risk stratification in preventing POMI
• Discuss alternative management options
Perioperative MI / Ischemia

- 11.6% of MI died within 30 days
  - OR for death (asymptomatic) 3.45 [2.20 – 5.4]
  - OR for death (symptomatic) 3.31 [1.78 – 6.15]
    POISE. Lancet 2008; 371(9627):1839-47

- TnI > 1.5 ng/ml on POD 1 – 3, at 6 months
  - Mortality OR 5.9 [1.6 – 22.4]
  - MI OR 27.1 [5.2 – 142.7]
    Circulation 2002; 106(18):2366 - 71

- TnT ≥ 0.02 ng/ml (ischemia → MI)
  - HR for death 2.41 [133 – 3.77]
    VISION. JAMA 2012; 307(21):2295 – 304
  - Caution: association vs causation
GUIDELINES
Poldermans described a very difficult situation with the whistleblower, a fellow who was responsible for the now-defunct DECREASE VI trial. His tasks included enrolling eligible patients and obtaining consent. Even if the fellow was himself guilty of the misconduct, Poldermans accepts that he, Poldermans, must accept the blame and responsibility. Poldermans told me that he had no direct involvement in the misconduct of the fellow, but he admits that he should have been suspicious, because there were numerous warning signs. It was clear, said Poldermans, that the fellow was overburdened with his clinical work on top of his research work with Poldermans. The fellow began doing his research work for Poldermans on...
POISE Primary Outcomes

HR(95%CI)=0.83 (0.70-0.99), p=0.035

# at Risk

0 10 20 30

M 4174 3959 3909 3879

P 4177 3915 3873 3853

Metoprolol

Placebo

POISE. Lancet 2008; 371:1839-47
POISE. Lancet 2008; 371:1839-47

POISE Non-fatal MI

HR(95%CI)=0.70(0.56-0.86), p=0.0007

Risk

0.0 0.02 0.04 0.06 0.08

0 10 20 30 Days

Metoprolol

Placebo

POISE. Lancet 2008; 371:1839-47
POISE All Cause Mortality

HR(95%CI)=1.33(1.02-1.74), p=0.032

POISE. Lancet 2008; 371:1839-47
Perioperative mischief: the price of academic misconduct.

Abstract: Recent allegations of fraud committed by one of the most prolific researchers in perioperative medicine, Don Poldermans, have left many clinicians in a state of disbelief. With over 500 peer-reviewed publications, Poldermans heavily influenced the clinical practice of perioperative beta-blockers and statins in noncardiac surgery, shaping guidelines and national policies on the use of these treatments. The effects of fraud in perioperative medicine are particularly caustic owing to a profound domino effect. Many investigators devoted their academic careers to following the footsteps of investigators such as Poldermans. Similarly, funding agencies supported this line of enquiry, incurring significant cost and expense. Most importantly, hundreds of patients were exposed to treatments that may have been harmful in an effort to advance this research agenda. How should perioperative clinicians utilize beta blockade now that a considerable portion of the literature is enshrouded in uncertainty …………..

Clinical Significance
• The evidence regarding the cardiac benefit of perioperative beta blockade is in doubt owing to allegations of research fraud.
• Perioperative beta blockade must be administered appropriately and judiciously in a narrow spectrum of patients.
• Whenever implemented, attention to hemodynamic parameters is critical to ensure the safety of perioperative beta blockade.
• Greater oversight and structural reform is necessary to prevent perioperative research misconduct

Listed as an author in 500+ papers, 16 cited at least 100 times, one over 700 times
Please choose all that apply

A. I don’t believe in β-blocker prophylaxis
B. I believe in β-blocker prophylaxis for high risk patients
C. I believe in β-blocker prophylaxis for non-vascular patients
D. I believe in β-blocker prophylaxis for emergency patients
## Large Database Propensity Matched Studies

<table>
<thead>
<tr>
<th></th>
<th>Lindenauer</th>
<th>London</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total matched</strong></td>
<td>335,922</td>
<td>75610</td>
</tr>
<tr>
<td><strong>RCRI 0</strong></td>
<td>1.43 (1.29 – 1.58)</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>(n=141,916)</td>
<td>(n=24,500)</td>
</tr>
<tr>
<td><strong>RCRI 1</strong></td>
<td>1.13 (0.99 – 1.30)</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>(n= 137,353)</td>
<td>(n=32,114)</td>
</tr>
<tr>
<td><strong>RCRI 2</strong></td>
<td>0.90 (0.75 – 1.08)</td>
<td>0.63 (0.50 – 0.80)</td>
</tr>
<tr>
<td></td>
<td>(n=53,238)</td>
<td>(n=13,590)</td>
</tr>
<tr>
<td><strong>RCRI 3</strong></td>
<td>0.71 (0.56 – 0.91)</td>
<td>0.54 (0.39 – 0.73)</td>
</tr>
<tr>
<td></td>
<td>(n=12,260)</td>
<td>(n=4,180)</td>
</tr>
<tr>
<td><strong>RCRI ≥ 4</strong></td>
<td>0.57 (0.42 – 0.76)</td>
<td>0.40 (0.25 – 0.73)</td>
</tr>
<tr>
<td></td>
<td>(n=1065)</td>
<td>(n=1226)</td>
</tr>
</tbody>
</table>

JAMA, 2013; 309(16):1704 - 13
Perioperative Mortality

541297 (did not receive \( \beta \)-blockers)

10771 (1.98%)

RCRI Factors \( \leq 1 \)

8443 (1.73%)

78% of all mortality

RCRI Factors \( \geq 2 \)

2328 (4.23%)

22 % of all mortality
Effect of β-blockers in Postop Hip & Knee Replacements

<table>
<thead>
<tr>
<th>Class</th>
<th>PMI (n=77)</th>
<th>No PMI (n=5081)</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>28 (36.4%)</td>
<td>4502 (88.6%)</td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>32 (41.6%)</td>
<td>502 (9.9%)</td>
<td>10 (6.1–17)</td>
</tr>
<tr>
<td>Class III</td>
<td>15 (19.5%)</td>
<td>63 (1.2%)</td>
<td>38 (19–75)</td>
</tr>
<tr>
<td>Class IV</td>
<td>2 (2.6%)</td>
<td>14 (0.3%)</td>
<td>23 (5.0–106)</td>
</tr>
</tbody>
</table>
Fig. 4. The incidence of postoperative myocardial infarction, stratified across Revised Cardiac Risk Index classes, beta-blocker prescription status, and postoperative hemoglobin (A) greater than 100 g · l¹ and (B) less than 100 g · l¹.
CVC by Sx urgency and treatment assignment

Number at risk:
- Elective Surgery + Placebo: 3736, 3571, 3530, 3515, 3506, 3500, 3494
- Emergent Surgery + Placebo: 438, 401, 397, 393, 391, 390, 389
- Elective Surgery + Metoprolol: 3729, 3606, 3572, 3558, 3550, 3539, 3533
- Emergent Surgery + Metoprolol: 440, 407, 401, 398, 395, 393, 392
Mortality by surgical urgency and treatment assignment

Number at risk:

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective Surgery + Placebo</td>
<td>3736</td>
<td>3719</td>
<td>3698</td>
<td>3687</td>
<td>3678</td>
<td>3672</td>
<td>3666</td>
</tr>
<tr>
<td>Elective Surgery + Metoprolol</td>
<td>438</td>
<td>428</td>
<td>420</td>
<td>417</td>
<td>413</td>
<td>407</td>
<td>406</td>
</tr>
<tr>
<td>Emergent Surgery + Placebo</td>
<td>3729</td>
<td>3709</td>
<td>3692</td>
<td>3676</td>
<td>3660</td>
<td>3647</td>
<td>3639</td>
</tr>
<tr>
<td>Emergent Surgery + Metoprolol</td>
<td>440</td>
<td>426</td>
<td>414</td>
<td>407</td>
<td>400</td>
<td>396</td>
<td>394</td>
</tr>
</tbody>
</table>
PATHOPHYSIOLOGY
Type 1
Plaque Rupture

Unstable Plaque

Hemodynamics (↓BP, ↑HR)
Coronary Vasoconstriction
↑ Sympathetic Tone (pain)
↓ volume

Plaque Rupture

Type 1 ACS MI

↑ inflammation (statins)
↑ coagulability (ASA, clopidogrel)

Type 2
Supply & Demand

Stable CAD

↑ MVO2
↑ HR
↑ LVEDP
↑ afterload (BP)
↑ contractility
↓ Supply
↓ Hb
↓ O2
↑ LVEDP
↓ BPd
↑ HR

Type 2 ACS MI
Please choose the best response

1. Panels A & B are prone to plaque rupture
2. Panels C & D are prone to plaque rupture
Type 1 vs Type 2 ACS

• Postmortem
  – ≈ 40 – 50% plaque rupture / thrombus

• Angiography
  – Thrombotic (26%), demand (55%), non-obstructive (19%)

  Catheterization and Cardiovascular Interventions 80:768–776 (2012)

• Angiography
  – Thrombotic (9/120) + Ambrose II (54/120) + complex lesions (68/120), non-obstructive (7/120)

What do we know so far?

• Vulnerable Heart (Supply & Demand)
  – Conventional risk group
  – Preop Tc99 or angiogram
• Vulnerable Plaque
  – Not an insignificant group, whatever the proportion
  – Not yet predictable pre-op (IVUS, CT-A)
• What’s this “non-obstructive?”
Non-Obstructive
Supply & Demand
No Culprit Lesions

Type 1
Plaque Rupture

Unstable Plaque

Hemodynamics (↓BP, ↑HR)
Coronary Vasoconstriction
↑ Sympathetic Tone (pain)
↓ volume

Plaque Rupture

Type 1 ACS MI

Plaque Erosion

↑ inflammation (statins)
↑ coagulability (ASA, clopidogrel)

Type 2
Supply & Demand

Stable CAD

↑ MVO2
↑ HR
↑ LVEDP
↑ afterload (BP)
↑ contractility
↓ Supply
↓ Hb
↓ O2
↑ LVEDP
↓ BPd
↑ HR

ACS MI

↑ LVEDP
↓ BPd
↑ HR

ACS MI

↑ MVO2
↑ HR
↑ LVEDP
↓ BPd
↑ HR

ACS MI
PREDICTABLE PREOP?
# POISE: Table 5

<table>
<thead>
<tr>
<th>Death</th>
<th>Adjusted odds ratio (95% CI)</th>
<th>Frequency of risk factor n (%)</th>
<th>PAR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative independent predictors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No use of statin in 24 h before surgery</td>
<td>1.73 (1.22–2.46)</td>
<td>5674 (67.9%)</td>
<td>33.7% (18.3–53.6)</td>
</tr>
<tr>
<td>Age ≥70 years</td>
<td>1.65 (1.20–2.26)</td>
<td>4387 (52.5%)</td>
<td>29.3% (16.2–47.0)</td>
</tr>
<tr>
<td>Emergent/urgent surgery</td>
<td>3.71 (2.68–5.14)</td>
<td>878 (10.5%)</td>
<td>24.4% (18.0–32.2)</td>
</tr>
<tr>
<td>Serum creatinine &gt;175 μmol/L</td>
<td>2.67 (1.75–4.08)</td>
<td>401 (4.8%)</td>
<td>9.5% (5.4–16.0)</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>1.76 (1.14–2.72)</td>
<td>535 (6.4%)</td>
<td>6.0% (2.5–13.6)</td>
</tr>
<tr>
<td>Use of low-molecular-weight heparin in 24 h before surgery</td>
<td>1.74 (1.14–2.68)</td>
<td>556 (6.7%)</td>
<td>5.9% (2.4–13.8)</td>
</tr>
<tr>
<td>Intraoperative and postoperative predictors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically significant hypotension</td>
<td>4.97 (3.62–6.81)</td>
<td>1029 (12.3%)</td>
<td>37.3% (29.5–45.8)</td>
</tr>
<tr>
<td>Myocardial infarction without ischaemic symptoms</td>
<td>3.45 (2.20–5.41)</td>
<td>271 (3.3%)</td>
<td>10.6% (6.4–17.0)</td>
</tr>
<tr>
<td>Significant bleeding</td>
<td>1.67 (1.14–2.44)</td>
<td>553 (6.6%)</td>
<td>9.4% (4.3–19.5)</td>
</tr>
<tr>
<td>Stroke</td>
<td>18.97 (9.93–36.25)</td>
<td>60 (0.7%)</td>
<td>8.0% (5.0–12.5)</td>
</tr>
<tr>
<td>Clinically significant bradycardia</td>
<td>2.13 (1.37–3.32)</td>
<td>351 (4.2%)</td>
<td>7.9% (3.9–15.3)</td>
</tr>
<tr>
<td>Myocardial infarction with ischaemic symptoms</td>
<td>3.31 (1.78–6.15)</td>
<td>144 (1.7%)</td>
<td>4.2% (1.9–9.2)</td>
</tr>
<tr>
<td>Total explained</td>
<td></td>
<td></td>
<td>85.5% (78.8–90.4)</td>
</tr>
</tbody>
</table>
### Population Attributable Risk: Pre-op

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR (95%CI)</th>
<th>Frequency of at risk Factor n(%)</th>
<th>PAR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td>1.520(1.087,2.126)</td>
<td>5674(67.94%)</td>
<td>0.274(0.064,0.462)</td>
</tr>
<tr>
<td>Age &gt; 70</td>
<td>1.990(1.475,2.684)</td>
<td>4311(51.67%)</td>
<td>0.361(0.201,0.501)</td>
</tr>
<tr>
<td>Emergent Sx</td>
<td>3.302(2.441,4.466)</td>
<td>878(10.51%)</td>
<td>0.242(0.128,0.349)</td>
</tr>
<tr>
<td>Creat &gt; 175</td>
<td>3.312(2.246,4.885)</td>
<td>401(4.80%)</td>
<td>0.114(0.05,0.177)</td>
</tr>
<tr>
<td>CHF</td>
<td>1.674(1.103,2.541)</td>
<td>499(5.98%)</td>
<td>0.052(-0.006,0.11)</td>
</tr>
<tr>
<td>LMWH</td>
<td>1.507(1.004,2.261)</td>
<td>556(6.66%)</td>
<td>0.049(-0.016,0.113)</td>
</tr>
</tbody>
</table>

Full PAR (95% CI) 0.696 (0.373, 0.869)
## Population Attributable Risk: Post-op

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR (95%CI)</th>
<th>Frequency of at risk Factor n(%)</th>
<th>Par(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypotension</td>
<td>4.684(3.451,6.358)</td>
<td>1029(12.32%)</td>
<td>0.424(0.213,0.597)</td>
</tr>
<tr>
<td>MI wo sympt</td>
<td>3.338(2.156,5.169)</td>
<td>279(3.34%)</td>
<td>0.143(0.023,0.26)</td>
</tr>
<tr>
<td>Bleed</td>
<td>1.750(1.207,2.538)</td>
<td>553(6.62%)</td>
<td>0.12(-0.014,0.249)</td>
</tr>
<tr>
<td>Stroke</td>
<td>14.762(7.914,27.535)</td>
<td>60(0.72%)</td>
<td>0.156(0.022,0.285)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2.085(1.368,3.178)</td>
<td>351(4.20%)</td>
<td>0.089(0.006, 0.17)</td>
</tr>
<tr>
<td>MI w sympt</td>
<td>3.023(1.659,5.509)</td>
<td>164(1.96%)</td>
<td>0.043(0.007,0.079)</td>
</tr>
</tbody>
</table>

Full PAR (95% CI) 0.592 (0.262 , 0.798 )
Performance of RCRI

• “not appropriate for peri-operative cardiovascular risk stratification in vascular surgery patients”

• “The RCRI substantially underestimates in-hospital cardiac events in patients undergoing elective or urgent vascular surgery”

• “The RCRI did not predict cardiac morbidity in our patients undergoing major spine fusion surgery”
  Spine. 2014 May. DOI 10.1097/brs.0000000000000405
Figure 1. Sensitivity (open bars) and specificity (solid bars) of selected preoperative predictors in patients with and without perioperative cardiac complications. Dripps-A.S.A. = Dripps-American Society of Anesthesiologists; RWMA = regional wall motion abnormality.
Non-Obstructive Supply & Demand

No Culprit Lesions

Type 1
Plaque Rupture
Predictable

Unstable Plaque
Stable CAD

↑ inflammation (statins)
↑ coagulability (ASA, clopidogrel)

Plaque Rupture
Type 1 ACS MI

Type 2
Supply & Demand
Non-predictable

Stable CAD

Unstable Plaque

↑ MVO2
↑ HR
↑ LVEDP
↑ afterload (BP)
↑ contractility
↓ Supply
↓ Hb
↓ O2
↓ LVEDP
↓ BPd
↑ HR

ACS MI

Pre-op
Predictable

Stable CAD

↑ inflammation (statins)
↑ coagulability (ASA, clopidogrel)

Plaque Rupture
Type 1 ACS MI

Pre-op
Non-predictable

Unstable Plaque

↑ MVO2
↑ HR
↑ LVEDP
↑ afterload (BP)
↑ contractility
↓ Supply
↓ Hb
↓ O2
↓ LVEDP
↓ BPd
↑ HR

ACS MI

No Culprit Lesions
Pre-op
Predictable

Stable CAD

↑ inflammation (statins)
↑ coagulability (ASA, clopidogrel)

Pre-op
Non-predictable

Unstable Plaque

Hemodynamics (↓BP, ↑HR)
Coronary Vasoconstriction
↑ Sympathetic Tone (pain)
↓ volume

↑ MVO2
↑ HR
↑ LVEDP
↑ afterload (BP)
↑ contractility
↓ Supply
↓ Hb
↓ O2
↑ LVEDP
↓ BPd
↑ HR

No Culprit Lesions
“It’s the postop care!”

• The action shifts to the postop period
• These are EARLY explorations
• BNP pre-op ≥ 50 ng/ml + Tnl post-op ≥ 2 ng/ml
  – HR for MACE 25.2, CI 5.0 – 128.4
• TnT ng/ml post-op & 30-day mortality rates
  – ≤ 0.01: 1.0%, 0.02: 4.0%, 0.03-0.29: 9.3%, and ≥ 0.30: 16.9%
OUTCOMES
## Review: Event rate with postop ischemia

**Comparison:** 01 Postop ischemia and events

**Outcome:** 02 Cardiac events (random effects)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Ischemia n/N</th>
<th>No ischemia n/N</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ouyang 1989</td>
<td>8/15</td>
<td>1/9</td>
<td>3.65 (9.14) [0.90, 92.40]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mangano 1991</td>
<td>11/42</td>
<td>2/58</td>
<td>7.09 (9.94) [2.07, 47.72]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McHugh 1991</td>
<td>2/93</td>
<td>0/15</td>
<td>2.15 (0.85) [0.04, 18.50]</td>
<td></td>
<td></td>
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<tr>
<td>Raby 1992</td>
<td>14/35</td>
<td>2/80</td>
<td>7.17 (26.00) [5.47, 123.48]</td>
<td></td>
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<tr>
<td>Beattie 1993</td>
<td>5/18</td>
<td>0/37</td>
<td>2.32 (30.56) [1.58, 590.33]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Christopherson 1993</td>
<td>7/40</td>
<td>1/60</td>
<td>4.20 (12.52) [1.48, 106.18]</td>
<td></td>
<td></td>
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<tr>
<td>Landesberg 1993</td>
<td>11/88</td>
<td>2/63</td>
<td>7.28 (4.36) [0.93, 20.40]</td>
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<td></td>
</tr>
<tr>
<td>Nelson 1993</td>
<td>6/12</td>
<td>0/15</td>
<td>2.24 (31.00) [1.51, 634.42]</td>
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<td></td>
</tr>
<tr>
<td>Berlatzky 1994</td>
<td>7/40</td>
<td>0/85</td>
<td>2.43 (38.28) [2.13, 689.16]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edward 1995</td>
<td>2/26</td>
<td>1/74</td>
<td>3.31 (6.08) [0.53, 70.10]</td>
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<td></td>
</tr>
<tr>
<td>Gannedahl 1995</td>
<td>13/30</td>
<td>0/8</td>
<td>2.36 (13.11) [0.69, 247.87]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hollenberg 1995</td>
<td>0/12</td>
<td>0/12</td>
<td>Not estimable</td>
<td></td>
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</tr>
<tr>
<td>Bois 1997</td>
<td>11/21</td>
<td>12/93</td>
<td>12.72 (7.43) [2.60, 21.20]</td>
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</tr>
<tr>
<td>Landesberg 1997</td>
<td>17/129</td>
<td>2/276</td>
<td>7.76 (20.79) [4.73, 91.49]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gozal 1998</td>
<td>0/15</td>
<td>0/41</td>
<td>Not estimable</td>
<td></td>
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<td>Anderson 2004</td>
<td>26/59</td>
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<td>2.54 (166.91) [9.90, 2813.44]</td>
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<td>Dogan 2008</td>
<td>0/3</td>
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<tr>
<td>Fayad 2011</td>
<td>3/59</td>
<td>6/253</td>
<td>8.33 (2.21) [0.54, 9.09]</td>
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<td>Bassuoni 2012</td>
<td>0/40</td>
<td>0/126</td>
<td>Not estimable</td>
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</tbody>
</table>

**Total (95% CI):**

Total events: 179 (Ischemia), 35 (No ischemia)

Test for heterogeneity: Chi² = 22.25, df = 19 (P = 0.27), I² = 14.6%

Test for overall effect: Z = 10.04 (P < 0.00001)
Vascular Study Group of Northern New England

- 22 centers, 117 surgeons
- Members from Rhode Island, Massachusetts; Connecticut;
- Affiliate members from Carolinas; Texas; Florida; California; Ontario Canada
- 14,000 patients
  - CEA or stent; open or stent AAA; lower extremity revascularization
  - 1 year follow-up > 85% of patients
Fig 3. Percentage of patients (VSGNE) started on perioperative beta blockers over time.
Fig 4. A, Percentage of patients on beta blockers (chronic plus perioperative) by surgeon (blue, 2003; red, 2008) (VSGNE, with permission from Goodney et al\textsuperscript{27}). B, Percentage of patients on beta blockers (chronic plus perioperative) by center (blue, 2003-2005; maroon, 2006-2008) (VSGNE, with permission from Goodney et al\textsuperscript{27}).
No Change in Mortality Over Time

Fig 5. Beta blocker utilization (diamonds), one-year mortality (dots), and postoperative MI rate (squares) over time in quarterly intervals (VSGNE, with permission from Goodney et al27).
EVALUATION OF TREATMENTS
Prophylactic β-blocker

- Subtypes of β-blockers
  - Metoprolol vs atenolol vs bisoprolol
- Dosage
- Pharmacogenomics
- Timing of β-blocker prophylaxis
- Emergency vs Elective prophylaxis
Fig. 5. Meta-regression of odds ratio of mortality from β-adrenergic receptor blockers (β-blockers) by β-1 relative selectivity of
Fig. 1. Mean steady-state plasma concentration of metoprolol and atenolol after administration of metoprolol CR/ZOC 100 mg, metoprolol conventional tablet (CT) 100 mg and atenolol tablet 50 mg
Fig. 3. Mean exercise-induced tachycardia in relation to placebo after once-daily dosing for 4 days with metoprolol CR/ZOC (100 mg and 200 mg) and atenolol (50 and 100 mg).
Bioavailability of Metoprolol CR

- Bioavailability after first pass effect
  - Metoprolol tartrate (conventional) 78%
  - Metoprolol succinate (CR) 71%

- Metoprolol CR 200 mg
  = metoprolol 65 mg q12h
Pharmacogenomics

- CYP2D6 genotype
  - Impacts on cytochrome P450 & metoprolol metabolism
- 50 HBP patients - No correlation between genotypes and BP or adverse effects
Pharmacogenomics

- 52 patients: 27 – 2 functional alleles; 22 – 1 function allele; 3 no functional allele
- Median dose-adjusted S-metoprolol concentrations 6.3 & 3.2 X higher in 0 or 1 versus 2 functional alleles
- “no relationships between CYP2D6 genotype and dose or clinical effects could be shown”
Pharmacogenomics

- 121 patients enrolled in prospective 6-week multi-center study on metoprolol
  - 5 ultra-rapid (UM) CYP2D6 metabolizers; 91 extensive metabolizers (EM); 21 intermediate metabolizers (IM); 4 poor metabolizers (PM)
    - UM 0.0088 ng/mL, EM 0.047 ng/mL, IM 0.34 ng/mL, and PM 1.34 ng/mL ($P < .0001$)
- No association with BP or HR
- No association with side effects except cold extremities and sexual dysfunction
Pharmacodynamics

Pharmacogenomics

Pharmacokinetics
Fig. 4. Meta-regression of odds ratio of mortality from β-adrenergic receptor blockers (β-blockers) by interaction of length of titration period and β-blockers using cytochrome P-450 metabolism. Ln(odds ratio) of 0 indicates odds ratio = 1. Values of Ln(odds ratio) less than 0 indicate benefit from β-blockers. BBSA = β Blocker in Spinal Anesthesia⁴; DECREASE I = Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography I²⁴; DECREASE IV = Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography I²⁵; DIPOM = Diabetes postoperative mortality and morbidity²⁶; MSPI = Multicenter Study of Perioperative Ischemia Research Group¹⁶; POISE = Perioperative Ischemic Evaluation²⁷
Statins

- Meta-analysis
- Statin naïve patients started perioperatively
- 2 non-cardiac, 2 vascular, 11 cardiac studies
  - Non-cardiac studies are from Poldermans’ group
  - Total of vascular studies = 206 patients

Rhabdomyolysis

- Data from 11 managed care health plans 1998 – 2001
- 252,460 patients on lipid lowering drugs
- 24 cases of rhabdomyolysis
- Per year of therapy, 1 case of rhabdomyolysis per 22727 for statin monotherapy

JAMA 2004; 292(21):2585 - 90
Fig. 2 Mean C-reactive protein levels. C-reactive protein levels are mg·L\(^{-1}\).
Fig 4  Cumulative meta-analysis assessing the effect of perioperative β blockers on the 30 day risk of major perioperative cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal cardiac arrest) in patients having non-cardiac surgery. The Lan-DeMets sequential monitoring boundary, which assumes a 10% control event rate and a 25% relative risk reduction with 80% power and a two sided α=0.01, has not been crossed, indicating that the cumulative evidence is inconclusive.
ALTERNATIVE MANAGEMENT
Molecular Phenotype of MSC Treated Septic Mice

dos Santos et al, AJP 2012
A preliminary report on the prognostic significance of preoperative brain natriuretic peptide and postoperative cardiac troponin in patients undergoing major vascular surgery

Figure 1. Clinical course for the 133 patients, divided based on the preoperative brain natriuretic peptide (BNP) and postoperative cardiac troponin (cTn) I levels. MACE = major adverse cardiac event; pts = patients.
VISION Study

• Recruitment period for 4th generation Trop T
  – August 6, 2007 to Jan 11, 2011
• 16,087 patients recruited
  – 68% of eligible patients based on screening logs
  – 954 patients excluded from Trop T analyses
    • 146 patients had peak Trop T reported as <0.04, <0.03, or <0.02
    • 779 patients did not have Trop T measured
      – 29 died before Trop T measured
      – 750 did not have Trop T measured b/f discharge
    • 29 patients missing data on >1 of 24 variables assessed in prognostic model
• 15,333 patients completed
• However, mortality not confirmed to be PMI or cardiac
## Perioperative Myocardial Ischemia

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Pre-op (%)</th>
<th>Intra-op (%)</th>
<th>Post-op (%)</th>
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<tr>
<td>Mangano</td>
<td>474</td>
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<td>NEJM 1990</td>
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<td>Raby</td>
<td>115</td>
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<td>JAMA 1992</td>
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</table>
## Event rate with postop ischemia

### Comparison: 01 Postop ischemia and events

### Outcome: 02 Cardiac events (random effects)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Ischemia n/N</th>
<th>No ischemia n/N</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
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<tbody>
<tr>
<td>Ouyang 1989</td>
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<td>3.65 9.14 [0.90, 92.40]</td>
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<td>2/80</td>
<td>7.17 26.00 [5.47, 123.48]</td>
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<td>Beattie 1993</td>
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<td>2.32 30.56 [1.58, 590.33]</td>
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<td>4.20 12.52 [1.48, 106.18]</td>
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<td>7.28 4.36 [0.93, 20.40]</td>
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<td>Nelson 1993</td>
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<td>7.76 20.79 [4.73, 91.49]</td>
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Total (95% CI) 1066 2154
Total events: 179 (Ischemia), 35 (No ischemia)
Test for heterogeneity: Chi² = 22.25, df = 19 (P = 0.27), I² = 14.6%
Test for overall effect: Z = 10.04 (P < 0.00001)
Patient 241

• 64 y/o for radical prostatectomy
• MI 2002
• Angioplasty 2007
• Nuclear Scan 2008 – small infarct scar without ischemia
• HTN
• Meds: Crestor, Metoprolol, Micardis
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<th>Date</th>
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01-Feb-2012 04:20:01

- **Heart Rate (HR)**: 77
- **PR Interval (PR)**: 148
- **QRS Duration (QRS)**: 88
- **QT Interval (QT)**: 432
- **QTc**: 489

---

**Axes**
- **P Axis**: 70
- **QRS Axis**: 39
- **T Axis**: 103

**ECG Details**
- **Previous ECG**: 01-Feb-2012 03:09:16 - Abnormal Confirmed
- **Confirmed for**: Megan, Joal 02 Feb 2012 16:53:29

**Device Information**
- **Device**: PACU
- **Speed**: 25 mm/sec
- **Lead**: 10 mm/mV
- **Chest**: 10 mm/mV

**Display Settings**
- **Frequency (F)**: 60-0.5-100 Hz
- **Mode**: PHD05A
Choose the best response

A. Beta-blocker prophylaxis prevents periop MI (POMI)
B. Coronary critical stenosis account for 90% of POMI
C. Cardiac risk indices have high sensitivity & specificity to predict POMI
D. Postop myocardial ischemia is rarely seen before POMI
Summary

• Pathophysiology
  – At least 25% of PMI is Type 2
  – “non-obstructive” category exists
  – Hemodynamic → Type 1 & Type 2

• Pre-op risk stratification is limited by unpredictable intra- & post-op events

• The new paradigm is post-op
  – TnI (risk stratification)
  – Remote real-time ECG ST monitoring (early intervention)