Perioperative Myocardial Infarction
Which β- Blocker is More Protective?

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Scientist
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Li Ka Shing Knowledge Institute
St. Michael’s Hospital
University of Toronto

St. Michael’s
Inspired Care.
Inspiring Science.

CAS 2014
St. John’s
Disclosures

1) Forest Laboratories Inc.
   Operating grant to study the impact
   of Nebivolol on Cerebral Perfusion During Anemia

2) Johnson & Johnson Medical Companies:
   Academic Salary Support
   Co-Director of Center of Excellence for Patient Blood
   Management at St. Michael’s Hospital
Talk Outline

1) Mechanism of Perioperative MI
2) Is there a belter β-blocker?
3) Anemia as a Diagnostic Interoperative Stress Test
Incidence of Perioperative MI

NUMBER OF MYOCARDIAL INFARCTS

Postoperative Days
Why is Perioperative Myocardial Ischemia Feared?

**High Mortality ~ 30 to 50%**

Nagele P. Anesthesiology, 2011
Ghaferi A.A. NEJM, 2009

**Unknown or Unpredictable Mechanism**

Demand Ischemia ~ 55%
Thrombotic ~ 26%
Non-obstructive ~ 19%

Clinical Question

A 73 yo Woman Present in the PAF for THA tomorrow!
Very limited exercise tolerance (< 4 METS)
EKG-nonspecific ST changes; Hb 110 g/L

The Optimal Approach Includes:

A) Proceed to surgery tomorrow.
B) Prescribe metoprolol 25 BID; proceed to surgery tomorrow.
C) Prescribe metoprolol 25 BID and delay surgery for 1 week.
D) Prescribe bisoprolol 2.5 OD and delay surgery for 1 week.
E) Delay surgery, get a dobutamine echo, consider appropriate β-blockade; diagnose and treat anemia.
Clinical Question

The 73 yo Woman has chest pain in the PACU after THA
Troponin-T > 0.03, HR 105; lateral ST depression; Hb 78 g/L

The optimal Treatment Includes:

A) Admission to the CCU/ICU for monitoring
B) Consider anti-platelet therapy (ASA)
C) Transfusion of 1 U PRBCs
D) Consider acute beta-blockade
E) All of the above
### Which β-Blocker Should We Use?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Solubility</th>
<th>Rec. Spec.</th>
<th>1/2-Life</th>
<th>Metab.</th>
<th>Indication</th>
<th>Dose (Start/Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td><img src="image1" alt="Lipid Soluble" /></td>
<td>β1&gt;β2 + 7</td>
<td>3-7 hrs.</td>
<td><img src="image2" alt="Liver" /></td>
<td>BP, HF CAD, Post-MI,</td>
<td>12.5-25 BID (400 BID)</td>
</tr>
<tr>
<td>Atenolol</td>
<td><img src="image3" alt="Water Soluble" /></td>
<td>β1&gt;β2 ++</td>
<td>6-14 hrs.</td>
<td><img src="image4" alt="Kidney" /></td>
<td>BP, Angina, Post-MI</td>
<td>12.5-25 OD (200 OD)</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td><img src="image1" alt="Lipid Soluble" /></td>
<td>β1&gt;β2 +++</td>
<td>10-12 hrs.</td>
<td><img src="image2" alt="Liver" /></td>
<td>BP</td>
<td>1.25-2.5 OD 20 OD</td>
</tr>
<tr>
<td>Carvedilol</td>
<td><img src="image3" alt="Water Soluble" /></td>
<td>β1/β2 α</td>
<td>6-8 hrs.</td>
<td><img src="image2" alt="Liver" /></td>
<td>Heart Failure</td>
<td>3.125 BID (50 BID)</td>
</tr>
<tr>
<td>Labetalol</td>
<td><img src="image3" alt="Water Soluble" /></td>
<td>β1/β2 α</td>
<td>6-8 hrs.</td>
<td><img src="image2" alt="Liver" /></td>
<td>BP, Angina Preclampsia</td>
<td>100 OD (600 BID)</td>
</tr>
<tr>
<td>Nebivolol</td>
<td><img src="image3" alt="Water Soluble" /></td>
<td>β1&gt;β2 +++++</td>
<td>12-19 hrs.</td>
<td><img src="image2" alt="Liver" /></td>
<td>BP</td>
<td>2.5 OD (40 OD)</td>
</tr>
</tbody>
</table>

- ![Liver](image2) -Liver
- ![Kidney](image4) -Kidney
- ![Water Soluble](image3) -Water Soluble
- ![Lipid Soluble](image1) -Lipid Soluble
Clinical Question

After transfusion to Hb 100 g/L, a dobutamine stress echo demonstrated a lateral wall motion abnormality. You have decided to start a β-blocker for HR control and to minimize risk of ongoing ischemia.

Which drug would you choose?

A) Atenolol 12.5 mg/kg OD
B) Metoprolol 25 mg BID
C) Carvedilol 6.5 mg OD
D) Bisoprolol 2.5 mg OD
E) Nebivolol 2.5 mg OD
The Cardiac Myocyte is the Source of Troponin

**A** Structure of cardiac troponins

- Myofibrillar troponins
  - Myosin
  - cTnI, cTnI
  - Tropomyosin
  - Actin
- Cytosolic troponins
  - cTnI
  - cTnT

**B** Ischemia-induced cardiomyocyte damage

- Ischemic cardiomyocytes

Release of cardiac troponins into the bloodstream

TnC indicates troponin C; cTnI, cardiac troponin I; cTnT, cardiac troponin T.

delemos JAMA 2013
Universal Definition of a Myocardial Infarction

A rise in Troponin:

And one of-

i) Symptoms of myocardial ischemia
ii) New ST-T wave changes or LBBB
iii) New pathological Q wave
iv) Imaging showing new loss of myocardial function
v) Intracoronary thrombus on angiogram
Universal Definition of a Myocardial Infarction

A rise in Troponin:

And one of-
  i) Symptoms of myocardial ischemia
Perioperative MI Caused by:
1) Plaque Rupture and 2) Demand Ischemia

Prolonged-stress-induced infarction  Type-II MI

Plaque rupture – type-I  MI

Coronary stenosis
Perioperative MI Caused by:
1) Plaque Rupture and 2) Demand Ischemia

Revascularization

Landesberg G Circulation 2013
Perioperative MI Caused by:
1) Plaque Rupture and 2) Demand Ischemia

Prolonged-stress-induced infarction  Type-II MI

Treat the Underlying Cause

Plaque rupture – type-I  MI

Coronary stenosis

Probability
Perioperative MI Caused by:
1) Plaque Rupture and 2) Demand Ischemia

Focal MI (Type I)
Plaque Rupture

Global Ischemia (Type II)
Troponin Leak?

TROPONIN

TROPONIN
Perioperative MI Defined by Increased Troponin?

Demand Ischemia (Type II)
Troponin Leak

Oxygen Supply

Oxygen Demand
Perioperative Ischemia leads to MI and Death??

- Surgery and Blood Loss
- Sympathetic Nervous System Activation
- Oxygen Supply/Demand Imbalance (Ischemia)
  - ST Depression
  - Troponin Leak
  - Myocardial Infarction
  - Death
The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION)

Peak TnT level was associated with 30 Day Mortality

Figure 2. Kaplan-Meier Estimates of 30-Day Mortality Based on Peak Troponin T Values

Devereaux PJ JAMA 2012
Re-evaluation of the Definition of Myocardial Injury After Noncardiac Surgery (MINS)

Utilized the VISION data to determine if:
Myocardial injury caused by ischemia (+/- necrosis)
Has a prognostic relevance within 30 Days of surgery

Definition of MINS-TnT >0.03 due to myocardial ischemia

30 Day Mortality with MINS ~9.8% vs. 1.1%
MINS predicted: nonfatal Cardiac arrest (OR 14.6 [CI 5-37])
CHF (OR 10.3 [CI 8-13]), Stroke (OR 4.6 [CI 2-7])

Non-vascular Death 46%; Vascular death 54%
POISE 1, 2- Goal of Perioperative Treatment: To Reduce Risk of Perioperative MI and Death

Pre-Cellular Injury

Optimal Point of Intervention

Cellular Injury

Treat Risk: (POISE-1: β-Blockade) (POISE-2: Clonide)

Supportive Interventions to Optimize Perfusion and Reduce the Risk of Organ Injury & Mortality

Post-Cellular Injury
POISE-2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clonidine in Patients Undergoing Noncardiac Surgery


Devereaux PJ NEJM 2014
POISE 2-Clonidine in Patients Undergoing Non-cardiac Surgery

Assumptions-

Activation of the sympathetic nervous system During surgery leads to O₂ supply demand imbalance and MI.

Clonidine can prevent the increased sympathetic outflow.

Hypothesis-

Perioperative clonidine can prevent 30 day MI and death

Devereaux PJ NEJM 2014
Is it a Good Idea to Impair the Brains Sympathetic Signaling to the Body???
Rationale for POISE-2

Effect of Clonidine on Cardiovascular Morbidity and Mortality after Noncardiac Surgery


![Graph showing survival rates over days after surgery for Clonidine and Placebo groups.](image-url)
POISE 2-Clonidine Did Not Reduce MI + Death

Hazard ratio, 1.08 (95% CI, 0.93–1.26); P=0.29

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Placebo</th>
<th>Clonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5001</td>
<td>5009</td>
</tr>
<tr>
<td></td>
<td>4728</td>
<td>4709</td>
</tr>
<tr>
<td></td>
<td>4697</td>
<td>4677</td>
</tr>
<tr>
<td></td>
<td>4681</td>
<td>4664</td>
</tr>
<tr>
<td></td>
<td>4675</td>
<td>4651</td>
</tr>
<tr>
<td></td>
<td>4669</td>
<td>4647</td>
</tr>
<tr>
<td></td>
<td>4658</td>
<td>4638</td>
</tr>
</tbody>
</table>

Devereaux PJ NEJM 2014
### POISE 2-Clonidine Outcomes

**Table 3. Independent Predictors of Myocardial Infarction.* **

<table>
<thead>
<tr>
<th>Independent Predictor</th>
<th>All Patients (N = 10,010)</th>
<th>Patients with Myocardial Infarction ≤30 Days after Randomization (N = 624)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Population Attributable Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>2268 (22.7)</td>
<td>186</td>
<td>29.8 (26.2–33.4)</td>
<td>1.49</td>
<td>10.3 (6.4–16.3)</td>
</tr>
<tr>
<td>History of peripheral vascular disease</td>
<td>865 (8.6)</td>
<td>100</td>
<td>16.0 (13.1–18.9)</td>
<td>2.10</td>
<td>8.9 (6.1–12.7)</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>337 (3.4)</td>
<td>39</td>
<td>6.2 (4.4–8.1)</td>
<td>1.60</td>
<td>2.5 (1.1–5.7)</td>
</tr>
<tr>
<td>Estimated GFR &lt; 60 ml/min/1.73 m²†</td>
<td>2496 (25.4)</td>
<td>239</td>
<td>38.5 (34.7–42.4)</td>
<td>1.52</td>
<td>13.9 (9.0–20.8)</td>
</tr>
<tr>
<td>Age ≥75 yr</td>
<td>3105 (31.0)</td>
<td>295</td>
<td>47.3 (43.4–51.2)</td>
<td>1.89</td>
<td>23.5 (17.9–30.1)</td>
</tr>
<tr>
<td><strong>Intraoperative and postoperative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically important hypotension</td>
<td>4217 (42.1)</td>
<td>319</td>
<td>51.1 (47.2–55.0)</td>
<td>1.37</td>
<td>14.8 (8.8–23.7)</td>
</tr>
<tr>
<td>Major bleeding.§</td>
<td>527 (5.3)</td>
<td>65</td>
<td>10.4 (8.0–12.8)</td>
<td>1.82</td>
<td>5.0 (2.9–8.4)</td>
</tr>
</tbody>
</table>

Hypotension and **Major Bleeding** Increase the Risk of **MI**
β Blockers in General Medicine: the GOOD

β-blockers are GOOD at reducing mortality after an acute myocardial infarction

MIAMI-Metoprolol in acute myocardial infarction

MIAMI Trial (Metoprolol)
Eur Heart J 1985
POISE 1-Metoprolol in Patients Undergoing Non-cardiac Surgery

Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial

POISE Study Group*

Are β-blockers GOOD at reducing perioperative acute myocardial infarction?
**β Blockers in Perioperative Medicine: the GOOD**

β-blockers are GOOD at reducing perioperative acute myocardial infarction

Devereaux PJ Yang H, POISE 2008
Perioperative MI Defined by Increased Troponin: Beta-Blockers Prevent Perioperative MI

Myocardial Ischemia
Troponin Leak?

Beta-Blockade
Prevents MI
β Blockers Protect Against Perioperative MI

β-Blockers ↓ Non-Fatal MI

Bangalore Lancet 2008

Favors β-Blockade

Favors Control
Perioperative β-Blocker Therapy and Mortality After Major Noncardiac Surgery

Patients at High risk for MI Benefit from β-Blockade.

Lindenauer, NEJM 2005;353:349
Association of Perioperative β-Blockade With Mortality and Cardiovascular Morbidity Following Major Noncardiac Surgery

**Figure 1.** Thirty-Day Mortality Propensity Model

<table>
<thead>
<tr>
<th>All surgery</th>
<th>No. of Patients</th>
<th>No. of Deaths</th>
<th>Favors Exposure</th>
<th>Favors Nonexposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>Exposed 37,805, Not Exposed 37,805</td>
<td>Exposed 426, Not Exposed 583</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of Revised Cardiac Risk Index predictors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12,250, Not Exposed 12,250</td>
<td>67, 53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16,057, Not Exposed 16,057</td>
<td>166, 186</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6,795, Not Exposed 6,795</td>
<td>111, 176</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2,090, Not Exposed 2,090</td>
<td>59, 110</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;4</td>
<td>613, Not Exposed 613</td>
<td>23, 58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

London MJ et al. JAMA 2013
**Current β Blocker Recommendations + Guidelines**

<table>
<thead>
<tr>
<th>Class I (Benefit&gt;&gt;&gt;Risk)</th>
<th>Class II (Benefit&gt;Risk)</th>
<th>Class III (Risk&gt;&gt;Benefit)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Do Not Discontinue β-Blocker Therapy</strong></td>
<td><strong>β Blocker Therapy Indicated for Patients with (\uparrow) Cardiac Risk</strong></td>
<td><strong>Do Not Routinely Treat Low Risk Patients with High Dose β Blockers</strong></td>
</tr>
<tr>
<td><strong>ACCF/AHA</strong></td>
<td><strong>ACCF/AHA</strong></td>
<td><strong>ACCF/AHA</strong></td>
</tr>
<tr>
<td>Continue in patients using β blockers for other AHA Class I Guidelines (Level C)</td>
<td>Vascular or Intermediate risk surgery with a positive stress test or more than 1 risk factor (Level C to B)</td>
<td>High dose β blockers without titration (Level B)</td>
</tr>
<tr>
<td><strong>ESC</strong></td>
<td><strong>ESC</strong></td>
<td><strong>ESC</strong></td>
</tr>
<tr>
<td>Known IHD or myocardial ischemia on stress testing (Level B)</td>
<td>Intermediate risk surgery (Level B)</td>
<td>High dose β blockers without titration (Level A)</td>
</tr>
</tbody>
</table>

β Blockers in Perioperative Medicine: the BAD

β-blockers are BAD because they may impair cardiovascular responses (cardiac output) required for organ perfusion.

Devereaux PJ Yang H, POISE 2008
β Blockers Increase Bradycardia, Hypotension, Perioperative Stroke?

How strong is the evidence for the use of perioperative β blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials

P J Devereaux, W Scott Beattie, Peter T-L Choi, Neal H Badner, Gordon H Guyatt, Juan C Villar, Claudio S Cinà, Kate Leslie, Michael J Jacka, Victor M Montori, Mohit Bhandari, Alvaro Avezum, Alexandre B Cavalcanã, Julian W Giles, Thomas Schricker, Homer Yang, Carl-Johan Jakobsen, Salim Yusuf

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>β blocker (n/N)</th>
<th>Control (n/N)</th>
<th>Relative risk (99% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cucchiara17</td>
<td>0/37</td>
<td>1/37</td>
<td>1.52</td>
<td>0.33</td>
<td>(0.01 to 21.46)</td>
</tr>
<tr>
<td>Liu19</td>
<td>0/16</td>
<td>1/14</td>
<td>1.57</td>
<td>0.29</td>
<td>(0.00 to 17.86)</td>
</tr>
<tr>
<td>Magnusson 198020</td>
<td>4/45</td>
<td>0/15</td>
<td>1.90</td>
<td>9.00</td>
<td>(0.22 to 375.21)</td>
</tr>
<tr>
<td>Stone22</td>
<td>10/39</td>
<td>0/39</td>
<td>1.93</td>
<td>9.33</td>
<td>(0.23 to 376.09)</td>
</tr>
<tr>
<td>Mackenzie23</td>
<td>1/60</td>
<td>0/60</td>
<td>1.51</td>
<td>3.00</td>
<td>(0.06 to 195.17)</td>
</tr>
<tr>
<td>Jakobsen 198025</td>
<td>5/49</td>
<td>1/49</td>
<td>3.41</td>
<td>5.00</td>
<td>(0.31 to 80.06)</td>
</tr>
<tr>
<td>Davies29</td>
<td>12/20</td>
<td>8/20</td>
<td>33.02</td>
<td>1.50</td>
<td>(0.64 to 3.50)</td>
</tr>
<tr>
<td>Wallace31</td>
<td>2/69</td>
<td>1/101</td>
<td>2.68</td>
<td>2.04</td>
<td>(0.09 to 46.84)</td>
</tr>
<tr>
<td>Yang57</td>
<td>53/246</td>
<td>19/250</td>
<td>52.47</td>
<td>2.83</td>
<td>(1.48 to 5.42)</td>
</tr>
<tr>
<td>Total</td>
<td>621</td>
<td>575</td>
<td>100.00</td>
<td>2.27</td>
<td>(1.35 to 3.80)</td>
</tr>
</tbody>
</table>

Total events: 87 (β blocker), 31 (control)
Test for heterogeneity: χ²=3.22, df=8, P=0.41, I²=2.6%
Test for overall effect: z=4.10, P<0.0001

Fig 2 Relative risks for bradycardia needing treatment
**β Blockers Increase Perioperative Stroke?**

**β-Blockers ↑ Non-fatal Stroke**

<table>
<thead>
<tr>
<th>Study</th>
<th>Non-fatal Stroke</th>
<th>(Excluded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-bias risk trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jakolsert et al.</td>
<td>0/50</td>
<td>0/50</td>
</tr>
<tr>
<td>Latif et al.</td>
<td>0/30</td>
<td>0/30</td>
</tr>
<tr>
<td>POBLETI</td>
<td>0/55</td>
<td>0/48</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0/135</td>
<td>0/128</td>
</tr>
<tr>
<td>Low-bias risk trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSSC</td>
<td>0/12</td>
<td>0/12</td>
</tr>
<tr>
<td>GURA</td>
<td>2/44</td>
<td>0/46</td>
</tr>
<tr>
<td>NABIS</td>
<td>4/246</td>
<td>2/150</td>
</tr>
<tr>
<td>POISE</td>
<td>17/4104</td>
<td>14/4107</td>
</tr>
<tr>
<td>Wallace</td>
<td>4/99</td>
<td>1/101</td>
</tr>
<tr>
<td>Bayliss</td>
<td>0/49</td>
<td>0/50</td>
</tr>
<tr>
<td>Cucchiara</td>
<td>0/37</td>
<td>0/37</td>
</tr>
<tr>
<td>Jakolsert</td>
<td>0/9</td>
<td>0/10</td>
</tr>
<tr>
<td>Miller</td>
<td>0/308</td>
<td>0/180</td>
</tr>
<tr>
<td>Rosenberg</td>
<td>0/19</td>
<td>0/19</td>
</tr>
<tr>
<td>Subtotal</td>
<td>38/5575</td>
<td>17/5523</td>
</tr>
</tbody>
</table>

**Favors β-Blockade**  **Favors Control**

Bangalore Lancet 2008
β Blockers Increase Perioperative Stroke?

<table>
<thead>
<tr>
<th>OUTCOMES</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MORTALITY</td>
<td></td>
</tr>
<tr>
<td>POISE</td>
<td>1.33 (1.02-1.73)</td>
</tr>
<tr>
<td>NOT POISE</td>
<td>1.03 (0.63-1.67)</td>
</tr>
<tr>
<td>NON FATAL MI</td>
<td></td>
</tr>
<tr>
<td>POISE</td>
<td>0.70 (0.57-0.86)</td>
</tr>
<tr>
<td>NOT POISE</td>
<td>0.52 (0.32-0.83)</td>
</tr>
<tr>
<td>NON FATAL STROKE</td>
<td></td>
</tr>
<tr>
<td>POISE</td>
<td>1.94 (1.02-3.70)</td>
</tr>
<tr>
<td>NOT POISE</td>
<td>1.93 (0.67-5.50)</td>
</tr>
<tr>
<td>SIGNIFICANT HYPOTENSION</td>
<td></td>
</tr>
<tr>
<td>POISE</td>
<td>1.55 (1.38-1.74)</td>
</tr>
<tr>
<td>NOT POISE</td>
<td>1.62 (1.36-1.92)</td>
</tr>
</tbody>
</table>

Beattie WS 2014
Heart

Brain

β-Blockade

Heart

Brain
## Risk vs. Benefit with β Blockade: Summary of Clinical Trial Outcomes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>Benefit</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS-II</td>
<td>Bisoprolol vs. Placebo-CHF</td>
<td>Reduced Mortality (11.8 vs. 17.3%)</td>
<td>Increased Stroke Rate (31 vs. 16)</td>
</tr>
<tr>
<td>ASCOT-BPLA</td>
<td>Amlodipine + Periindopril vs. Atenolol + Thiazide-HT</td>
<td>Reduce MAP</td>
<td>Increased Stroke Rate (327 vs. 423)</td>
</tr>
<tr>
<td>NOR-DIL</td>
<td>Beta Blocker vs. Diltiazem</td>
<td>Reduce MAP</td>
<td>Increased Stroke Rate (159 vs. 196)</td>
</tr>
<tr>
<td>COMMIT</td>
<td>Metoprolol vs. Placebo-Early MI</td>
<td>Reduced Re-Infarction, VT</td>
<td>Increased Cardiogenic Shock (1141 vs. 885)</td>
</tr>
<tr>
<td>COMET</td>
<td>Carvedilol vs. Metoprolol-CHF</td>
<td>Increased Survival with Carvedilol</td>
<td>Increased Mortality with Metoprolol (512 vs. 600)</td>
</tr>
</tbody>
</table>

Yang and Beattie CJA 2008
Is there a Problem with Metoprolol?

Articles

Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial

Figure 2: All-cause mortality

Lancet 2003
Is there a Problem with Metoprolol?

Perioperative β-Blockade

*Atenolol Is Associated with Reduced Mortality When Compared to Metoprolol*

Anemia Associated with Increased Mortality in Non-Cardiac Surgical Patients

Probability of Mortality

Pre-operative Hemoglobin Concentration
**β Blockers Increase Risk Associated with Perioperative Anemia**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia (WHO gender defined)</td>
<td>2.43 (1.65–3.60)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 70 yr</td>
<td>2.31 (1.64–3.26)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>In-hospital status*</td>
<td>3.51 (2.26–5.44)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>History of CHF</td>
<td>7.99 (4.73–13.5)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Preoperative renal dysfunction†</td>
<td>2.08 (1.22–3.53)</td>
<td>0.0067</td>
</tr>
<tr>
<td><strong>Perioperative medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>β-Blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No β-blockers</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1.67 (1.05–2.68)</td>
<td>0.020</td>
</tr>
<tr>
<td>Atenolol or bisoprolol</td>
<td>0.97 (0.63–1.52)</td>
<td>0.198</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>0.56 (0.33–0.95)</td>
<td>0.033</td>
</tr>
<tr>
<td>CCBs</td>
<td>0.57 (0.34–0.96)</td>
<td>0.036</td>
</tr>
<tr>
<td>Any postoperative NSAID‡</td>
<td>0.58 (0.38–0.88)</td>
<td>0.011</td>
</tr>
<tr>
<td><strong>Transfusion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No blood products</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>1–2 units</td>
<td>1.83 (1.20–2.80)</td>
<td>0.032</td>
</tr>
<tr>
<td>3–4 units</td>
<td>2.99 (1.77–5.07)</td>
<td>0.013</td>
</tr>
<tr>
<td>5–10 units</td>
<td>3.19 (1.62–6.32)</td>
<td>0.021</td>
</tr>
<tr>
<td>More than 10 units</td>
<td>3.43 (1.12–10.5)</td>
<td>0.040</td>
</tr>
</tbody>
</table>

Beattie WS, Anesthesiology 2009
β-Blockade + Anemia Increases Incidence of MI

Acute Surgical Anemia Influences the Cardioprotective Effects of β-Blockade

A Single-center, Propensity-matched Cohort Study


Relative Risk of Major Adverse Cardiac Event with β-blockade: 2.38 (1.43-3.96) p=0.0009

β-Blocked Group

Anesthesiology 2010
Acute β-Blocker Withdrawal Increases MI Risk

Effect of β-blocker Prescription on the Incidence of Postoperative Myocardial Infarction after Hip and Knee Arthroplasty

Wilton A. van Klei, M.D., Ph.D.,* Gregory L. Bryson, M.D., M.Sc.,* Homer Yang, M.D.,† Alan J. Forster, M.D., M.Sc.‡

Van Kei WA, Anesthesiology 2009

Hemoglobin < 100 g/L

β Blocker withdrawal Increased MI incidence

β Blocker treatment increased MI incidence in low risk patients
Increased Stroke Risk In Perioperative Patients

Preoperative Beta Blocker - Multivariate

- History of CVA or TIA
  - Adjusted Odds Ratio: 5.2 (2.7-10.1)
- Age >= 56 years
  - Adjusted Odds Ratio: 3.6 (1.7-7.4)
- Preop Metoprolol Use
  - Adjusted Odds Ratio: 2.3 (1.2-4.7)

Beatiie WS TGH
Clinical Question

After transfusion to Hb 100 g/L, a dobutamine stress echo demonstrated a lateral wall motion abnormality. You have decided to start a β-blocker for HR control and to minimize risk of ongoing ischemia.

Which drug would you choose?

A) Atenolol 12.5 mg/kg OD
B) Metoprolol 25 mg BID
C) Carvedilol 6.5 mg OD
D) Bisoprolol 2.5 mg OD
E) Nebivolol 2.5 mg OD
### Which β-Blocker Should We Use?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Solubility</th>
<th>Rec. Spec.</th>
<th>1/2-Life</th>
<th>Metab.</th>
<th>Indication</th>
<th>Dose (Start/Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td><img src="img1" alt="Lipid Soluble" /> <img src="img2" alt="Water Soluble" /></td>
<td>β1&gt;β2 +</td>
<td>3-7 hrs.</td>
<td><img src="img3" alt="Liver" /></td>
<td>BP, HF CAD, Post-MI,</td>
<td>12.5-25 BID (400 BID)</td>
</tr>
<tr>
<td>Atenolol</td>
<td><img src="img1" alt="Lipid Soluble" /> <img src="img2" alt="Water Soluble" /></td>
<td>β1&gt;β2 ++</td>
<td>6-14 hrs.</td>
<td><img src="img4" alt="Kidney" /></td>
<td>BP, Angina, Post-MI</td>
<td>12.5-25 OD (200 OD)</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td><img src="img1" alt="Lipid Soluble" /> <img src="img2" alt="Water Soluble" /></td>
<td>β1&gt;β2 +++</td>
<td>10-12 hrs.</td>
<td><img src="img3" alt="Liver" /> <img src="img4" alt="Kidney" /></td>
<td>BP</td>
<td>1.25-2.5 OD 20 OD</td>
</tr>
<tr>
<td>Carvedilol</td>
<td><img src="img1" alt="Lipid Soluble" /> <img src="img2" alt="Water Soluble" /></td>
<td>β1/β2 α</td>
<td>6-8 hrs.</td>
<td><img src="img3" alt="Liver" /></td>
<td>Heart Failure</td>
<td>3.125 BID (50 BID)</td>
</tr>
<tr>
<td>Labetalol</td>
<td><img src="img1" alt="Lipid Soluble" /> <img src="img2" alt="Water Soluble" /></td>
<td>β1/β2 α</td>
<td>6-8 hrs.</td>
<td><img src="img3" alt="Liver" /></td>
<td>BP, Angina Preclampsia</td>
<td>100 OD (600 BID)</td>
</tr>
<tr>
<td>Nebivolol</td>
<td><img src="img1" alt="Lipid Soluble" /> <img src="img2" alt="Water Soluble" /></td>
<td>β1&gt;β2 ++++</td>
<td>12-19 hrs.</td>
<td><img src="img3" alt="Liver" /> <img src="img4" alt="Kidney" /></td>
<td>BP</td>
<td>2.5 OD (40 OD)</td>
</tr>
</tbody>
</table>

- **Solubility**: Lipid Soluble (o), Water Soluble (o), Lipid-Water Soluble (o)
- **Metab.**: Liver (L), Kidney (K)
- **Dose**: Start/Max
**Metoprolol Has Lowest $\beta_1$-Adrenergic Receptor Specificity of Commonly Used $\beta_1$-Blockers**

<table>
<thead>
<tr>
<th>$\beta_1$ antagonist</th>
<th>fold selectivity $\beta_1/\beta_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGP 20712A</td>
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</tr>
<tr>
<td>Bisoprolol</td>
<td>13.5</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>6.8</td>
</tr>
<tr>
<td>Atenolol</td>
<td>4.1</td>
</tr>
<tr>
<td>ICI 215001</td>
<td>3.2</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>2.4</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Cross-reactivity with $\beta_2$-ARs may inhibit adrenergic mediated vasodilation.

Baker, Br J Pharmacol, 2005
β Blockers Increase Perioperative Stroke?

LOG ODDS RATIO FOR POST OPERATIVE STROKE

RATIO BETA 1 TO BETA 2 ACTIVITY

Beattie et al TGH
What is the Interaction Between Surgery Anemia and β-Blockade?

Systemic Effect of Surgery

Surgery (Adrenergic Stress)

Acute Blood Loss

Anemia (Blood Loss)

β-Blockade

Medical Intervention
How Does Anemia (Acute Blood loss) Impact Perioperative MI and Stroke?

**POISE-2** – Acute Blood loss ↑ the Risk of MI

**POISE-1** – Acute Blood loss ↑ the Risk of Stroke

### Stroke

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Preoperative</th>
<th>Intraoperative and postoperative</th>
<th>Total explained</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of stroke or transient ischaemic attack</td>
<td>2.80 (1.66–4.73)</td>
<td>1759 (21.1%)</td>
<td>30.5% (17.1–48.2)</td>
</tr>
<tr>
<td>Use of clopidogrel or ticlopidine in 24 h before surgery</td>
<td>3.12 (1.43–6.77)</td>
<td>330 (4.0%)</td>
<td>9.1% (3.2–23.2)</td>
</tr>
<tr>
<td>Clinically significant hypotension</td>
<td>2.14 (1.15–3.96)</td>
<td>1029 (12.3%)</td>
<td>14.7% (5.2–35.4)</td>
</tr>
<tr>
<td>Significant bleeding</td>
<td>2.18 (1.06–4.49)</td>
<td>553 (6.6%)</td>
<td>10.1% (3.0–28.5)</td>
</tr>
<tr>
<td>New clinically significant atrial fibrillation</td>
<td>3.51 (1.45–8.52)</td>
<td>200 (2.4%)</td>
<td>6.9% (2.1–20.4)</td>
</tr>
<tr>
<td>Total explained</td>
<td>51.8% (37.1–66.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: *Lancet* 2008
Anemia-The Ultimate Cardiac and Brain Stress Test!!!!

- Anemia
  - Blood Oxygen Content
  - Cardiac Output
  - Coronary Blood Flow (Oxygen Extraction)

Blood \( \text{O}_2 \) Content

Cardiac Output And Myocardial \( \text{O}_2 \) Demand

\( \text{O}_2 \) Supply-Demand Un-Balanced Troponin Leak?
Anemia-The Ultimate Cardiac and Brain Stress Test!!!!

Human Cardiovascular and Metabolic Response to Acute, Severe Isovolemic Anemia

Richard B. Weiskopf; Maureen K. Viele; John Feiner; et al.
Anemia-The Ultimate Cardiac Stress Test!!!!
Cardiovascular Responses to Acute Anemia in Mice

- **MAP** (Mean Arterial Pressure)
- **CBF** (Carotid Blood Flow)
- **CO** (Cardiac Output)
- **Brain PO₂** (Partial Pressure of Oxygen in the Brain)
Increased Cardiac Output is Preferentially Diverted to the Brain and Heart During Anemia

Anemia-Brain Oxygen Delivery Bioassay

Heart

Brain

Brain Hypoxia

Anemia +/- β-Blockade

Heart
The Impact of $\beta$-Blockade On Cerebral $O_2$ Delivery

Anemia + Metoprolol $\approx$ È Cerebral Hypoxia  
Ragoonana et al. Anesthesiol 2009

$\beta_2$-Blockade $\approx$ Í Cerebral Vasodilation  
El Beheiry et al. J Appl. Physiol 2011

Low Dose $\beta_1$-Blockade Maintained Cerebral $O_2$  
Hu et al. Anesth & Analg 2013

Anemia $\approx$ Mortality È With Metoprolol  
Beattie et al. Anesthesiol 2009

Anemia + $\beta$-Blockade $\approx$ È MACE  
Beattie et al. Anesthesiol 2011

$\beta$-Blockade + Anemia $\approx$ È Stroke (not nebivolol)  
Beattie et al. Anesthesiol 2013
Potential Mechanisms by which Perfusion Limited by β-Blockade During Anemia

Cardiac Output $\Rightarrow$ Resistance Aery

Inadequate Tissue PO$_2$

Beta Blocker

Central Nervous System
Interrupted Oxygen Delivery to Tissue

Inhibit CO Response to Anemia

β-Blockade

Cardiac Output

O$_2$~30 torr

Capillary

O$_2$~20-30 torr

Tissue

O$_2$~10-20 torr?

Brain Cell

Mitochondria
Mouse Brain Perfusion is Limited by Metoprolol

Heart Rate

A

Baseline Saline vs. Drug

Cerebral Blood Flow

B

Baseline Saline vs. Drug

Brain PO$_2$

C

Baseline Saline vs. Drug

El Beheiry J Appl Physiol 2011
Why are Patients at High Risk of Poor Outcomes Following Surgery?

Systemic Effect of Surgery

Adrenergic Stress

β-blockade

Associated Medical Therapy

Acute Blood Loss

Anemia

POISE
Anemia ↑ Stroke Risk by 2X
Potential Mechanisms by which Perfusion Limited by β-Blockade During Anemia

Cardiac Output → Resistance Aertry → Inadequate Tissue PO$_2$

β$_1$ Receptor

Central Nervous System

Pump Regulated Blood Flow

Metoprolol

Brain Heart Kidney
Metoprolol Impairs the Cardiac Response to Anemia

Ragoonanan T et al, Anesthesiology 2009
Metoprolol Dramatically Reduces Brain Tissue PO$_2$
During Acute Hemodilution

- Anemia
- Anemia + β-Blockade

Ragoonanan T, Anesthesiology 2009
Potential Mechanisms by which Perfusion Limited by $\beta$-Blockade During Anemia

Cardiac Output → Resistance Aeryy

$B_2$ Receptor

ICI 118,551

Inadequate Tissue $PO_2$

Brain
Heart
Kidney

Autonomic Nervous System
β₂ Mediated Cerebral Vasodilation

Noradrenergic Perivascular Neurons

β₂ Adrenergic Receptor

Nitrogenergic Neuron

Nitric Oxide Synthase (NOS)

Cerebral Vasodilation and Increased CBF

GTP → GC → cGMP

Vascular Smooth Muscle

Lee et al Am J Physiol 2000;279: H808-16
Inhibition of the $\beta_2$-Adrenoreceptor Accentuated Cerebral Perfusion In Anemic Rats

CAS Richard Knill Research Award 2005

$\beta_2$-Adrenoreceptor Antagonist – ICI 118, 551

Hare GMT. Brit J Anaesth 2006
Metoprolol Impairs Cardiovascular Function

β-blockers may be UGLY because they could impair global perfusion and microvascular vascular function.

Metoprolol

\[ \beta_1 \]

\[ \beta_2 \]

Cardiac Output

\[ \uparrow \]

Vasodilation

\[ \nabla \]

Vasoconstriction

Organ Ischemia
Assessment of Resistance Artery Function by Pressure Myography
Metoprolol Impairs Resistance Artery Dilation to $\beta$-Adrenergic Agonists

Mesenteric Artery

Posterior Cerebral Artery

El Beheiry et al J Appl Physiol 2010
Perfusion Limited by β-Blockade During Anemia

Cardiac Output
Pump
Regulated Blood Flow

Resistance Aery
β Receptor

Inadequate Tissue PO₂
Brain
Heart
Kidney

Metoprolol

Autonomic Nervous System
β Blockers Increase Perioperative Stroke?

Temporally similar to POISE

Ashes et al Anesthesiology 2013
Relationship Between β-blockade, Anemia, Stroke

Probability of Postoperative stroke vs. Lowest recorded Haemoglobin

METOPROLOL

BISOPROLOL

Ashes C, Anesthesiology 2013
Metoprolol Associated with Perioperative Stroke

Perioperative Metoprolol and Risk of Stroke after Noncardiac Surgery

Table 1. Patient Characteristics, Variables, and Univariate Associations with Perioperative Stroke

<table>
<thead>
<tr>
<th>Preoperative β blockers</th>
<th>Stroke—No (N = 57,163)</th>
<th>Stroke—Yes (N = 55)</th>
<th>P Value</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>3,213 (5.6%)</td>
<td>11 (20%)</td>
<td>&lt;0.001</td>
<td>4.2 (2.2–8.1)</td>
</tr>
<tr>
<td>Atenolol</td>
<td>2,666 (4.7%)</td>
<td>2 (3.6%)</td>
<td>1.000</td>
<td>0.8 (0.2–3.2)</td>
</tr>
<tr>
<td>Propranolol</td>
<td>566 (1.0%)</td>
<td>0 (0%)</td>
<td>1.000</td>
<td>1.0 (1.0–1.0)</td>
</tr>
<tr>
<td>Nadolol</td>
<td>221 (0.4%)</td>
<td>1 (1.8%)</td>
<td>0.193</td>
<td>4.8 (0.7–34.6)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>116 (0.2%)</td>
<td>0 (0%)</td>
<td>1.000</td>
<td>1.0 (1.0–1.0)</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>305 (0.5%)</td>
<td>0 (0%)</td>
<td>1.000</td>
<td>1.0 (1.0–1.0)</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>1,027 (1.8%)</td>
<td>1 (1.8%)</td>
<td>1.000</td>
<td>1.0 (0.1–7.3)</td>
</tr>
</tbody>
</table>

Metoprolol was associated with a 4.2 ↑ in stroke incidence.

Mashour GA et al Anesthesiol 2013
Potential Mechanisms by which Perfusion Limited by $\beta$-Blockade During Anemia

- **Cardiac Output**
- **Pump**
- **Regulated Blood Flow**
- **Resistance Aery**
- **Beta Blocker**
- **Inadequate Tissue $PO_2$**
  - Brain
  - Heart
  - Kidney
- **Central Nervous System**
- $\beta_1$ Receptor
- $B_2$ Receptor
- $B_{1,2}$ Receptor
Clinical Question

After transfusion to Hb 100 g/L, a dobutamine stress echo demonstrated a lateral wall motion abnormality. You have decided to start a β-blocker for HR control and to minimize risk of ongoing ischemia.

Which drug would you choose?

A) Atenolol 12.5 mg/kg OD
B) Metoprolol 25 mg BID
C) Carvedilol 6.5 mg OD
D) Bisoprolol 2.5 mg OD
E) Nebivolol 2.5 mg OD
Nebivolol has the Highest $\beta_1$-Adrenergic Receptor Specificity of Available $\beta_1$-Blockers

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<th>fold selectivity $\beta_1/\beta_2$</th>
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</tbody>
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Cross-reactivity with $\beta_2$-ARs may inhibit adrenergic mediated vasodilation.

Baker, Br J Pharmacol, 2005
Bristow et al. 2005
Metoprolol has Relatively Poor $\beta_1$ Selectivity While Nebivolol is much more $\beta_1$ Selective

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\beta_1/\beta_2$ Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Metoprolol</strong></td>
<td><strong>74</strong></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>103</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>321</td>
</tr>
</tbody>
</table>

Bristow et al. (2005)
Can Treatment with Nebivolol Preserve Cerebral Perfusion During Anemia?

Hypothesis:

A highly $\beta_1$ specific antagonist (nebivolol) will NOT attenuate the increase in cerebral blood flow needed to maintain cerebral oxygen delivery during anemia.
Results

nebivolol drug levels are proportional to dose

Affinity ($K_i$) for $\beta_1$ and $\beta_2$ Levels

$\beta_1$: $\sim$0.7 nM
$\beta_2$: $\sim$225 nM

Hu et al A&A 2013
Cardiac Output Effect

Vehicle or Nebivolol Administration

Hemodilution

Cardiac Output Effect

n = 5 per group

Vehicle Control
1.25 Nebivolol
2.5 Nebivolol

Hu et al A&A 2013

Cardiac Output (mL/minute)

Time (minutes)
Cerebral Oxygen Tension Effect

Vehicle or Nebivolol Administration

Hemodilution

* p=0.01 for 1.25 Nebivolol vs. 2.5 Nebivolol (2-way repeated measures ANOVA)

Hu et al A&A 2013
Only High Dose Nebivolol Increases HIF-1α Levels

Hu et al. A&A 2013
A comparison of the $\beta_1$-selectivity of three $\beta_1$-selective $\beta$-blockers

S. L. Nuttall PhD, H. C. Routledge MRCP and M. J. Kendall MD FRCP
Division of Medical Sciences, University of Birmingham, Birmingham, UK
Perfusion Limited by β-Blockade During Anemia

Cardiac Output → Resistance Aery → Inadequate Tissue PO₂ (Brain, Heart, Kidney)

β₁-Receptor

Nebivolol

Autonomic Nervous System
Clinical Question

After transfusion to Hb 100 g/L, a dobutamine stress echo demonstrated a lateral wall motion abnormality. You have decided to start a β-blocker for HR control and to minimize risk of ongoing ischemia.

Which drug would you choose?

A) Atenolol 12.5 mg/kg OD  
B) Metoprolol 25 mg BID  
C) Carvedilol 6.5 mg OD  
D) Bisoprolol 2.5 mg OD  
E) Nebivolol 2.5 mg OD
What about Other Vasodilating β-Blockers?

Meta-Analysis of *Carvedilol* Versus Beta 1 Selective Beta-Blockers (*Atenolol*, *Bisoprolol*, *Metoprolol*, and *Nebivolol*)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Carvedilol Events</th>
<th>Total</th>
<th>Beta-1 Selective Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jonsson 2005</td>
<td>2</td>
<td>118</td>
<td>5</td>
<td>114</td>
<td>11.1%</td>
<td>0.39 [0.88, 1.95]</td>
</tr>
<tr>
<td>Mrdovic 2007</td>
<td>15</td>
<td>155</td>
<td>29</td>
<td>158</td>
<td>85.7%</td>
<td>0.53 [0.29, 0.94]</td>
</tr>
<tr>
<td>Toig 2006</td>
<td>2</td>
<td>50</td>
<td>0</td>
<td>49</td>
<td>3.2%</td>
<td>4.90 [0.24, 99.57]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>323</strong></td>
<td><strong>321</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.55 [0.32, 0.94]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>19</strong></td>
<td><strong>24</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 2.23$, df = 2 ($P = 0.33$); $I^2 = 10$
Test for overall effect: $Z = 2.19$ ($P = 0.03$)

Figure 3. Forest plot of relative risk for all-cause mortality in patients with AMIs.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Carvedilol Events</th>
<th>Total</th>
<th>Beta-1 Selective Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toig 2006</td>
<td>0</td>
<td>50</td>
<td>2</td>
<td>49</td>
<td>5.3%</td>
<td>0.20 [0.01, 3.98]</td>
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<tr>
<td>Jonsson 2005</td>
<td>3</td>
<td>118</td>
<td>6</td>
<td>114</td>
<td>26.8%</td>
<td>0.48 [0.12, 1.86]</td>
</tr>
<tr>
<td>Mrdovic 2007</td>
<td>9</td>
<td>148</td>
<td>12</td>
<td>143</td>
<td>68.8%</td>
<td>0.72 [0.31, 1.67]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>316</strong></td>
<td><strong>306</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.61 [0.31, 1.22]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>12</strong></td>
<td><strong>20</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.92$; df = 2 ($P = 0.66$); $I^2 = 0$
Test for overall effect: $Z = 1.40$ ($P = 0.16$)

Figure 4. Forest plot of relative risk for nonfatal MI in patients with AMIs.

DeNicolantonioAm J Col Cardiol 2013
What is the Next Step for β-Blocker Therapy?

Patients on Chronic β-Blocker Therapy (metoprolol)

- Randomization
  - Continue Metoprolol
  - Convert to Bisoprolol

Assess Composite Clinical Outcome (Stroke-Hypotension-MI-Death)
Non-Stressed → β-Blockade → β-Blockade + Anemia

Brain + Hypoxic Brain + Very Hypoxic Brain

Peri-Operative β Blockade

Protected Heart

Brain

Non-Stressed

β-Blockade

β-Blockade + Anemia

Very Hypoxic Brain

Protected Heart
Acknowledgements:
## Acknowledgements:

<table>
<thead>
<tr>
<th>Dept. of Anesthesia</th>
<th>Research Collaboration</th>
<th>Research Associates &amp; Students</th>
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</tr>
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<td></td>
<td>Dr. D. Wilson</td>
<td>Julie Yu</td>
</tr>
</tbody>
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PSI Foundation

St. Michael’s
Inspired Care. Inspiring Science.
Potential Mechanisms by which Perfusion Limited by β-Blockade During Anemia

Cardiac Output → Resistance Aery → Inadequate Tissue PO₂

- β₁ Receptor
- B₁,₂ Receptor
- B₂ Receptor

Pump
Regulated Blood Flow

Central Nervous System

Brain, Heart, Kidney