Optimizing Perioperative Beta Blockade 2009?

John E. Ellis MD
University of Pennsylvania
johnellis1700@gmail.com

www.vascularanesthesia.com
• Baxter (speakers’ bureau)
  o Esmolol
• The Medicines Company
  o Clevidipine
Merin 1972

• "The cardiothoracic anesthesia group at the Cleveland Clinic .... Four patients who had been receiving from 120-160 mg./day of propranolol within 24 hours of surgery died from intractable heart failure immediately after coming off bypass for CABG....This group will no longer anesthetize a patient for any but the most emergent surgery unless he has been off propranolol for 2 weeks."

Merin 1972

• "On the other hand, several patients at the Massachusetts General Hospital who were taken off propranolol before coronary bypass operations suffered myocardial infarctions before the operation."
Mangano/Wallace

- Atenolol Rx reduced postop Holter ischemia
  - 39% to 24%
- Atenonol Rx reduced HR
  - 87 to 75 bpm
Poldermans

- Bisoprolol preop
- Metoprolol periop prn HR > 80
- Lower HR day 1 (82 vs 71 bpm)

Practice starts to change

- Secular increase in beta blockade
  - Chronic
  - Oral preoperative
  - Oral and intravenous perioperative
- 1997-99 @ U Chicago
  - 33% vascular patients on chronic β-blocker
- 2001-2002 @ Yale
  - 48% vascular patients on chronic β-blocker
Efficacy vs. Effectiveness

• Efficacy
  o How does the treatment perform in the ideal circumstances (e.g. RCT).
  o Maximum achievable effect.

• Effectiveness
  o How does the treatment perform in real circumstances?
  o Benefits vs. side effects
### Included in pivotal trials?

<table>
<thead>
<tr>
<th></th>
<th>CHF</th>
<th>Regional</th>
<th>Asthma</th>
<th>Abnormal ECG (Holter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mangano</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Raby</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Urban</td>
<td>No</td>
<td>Yes (100%)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Poldermans</td>
<td>Yes (12%)</td>
<td>Yes (42%)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Zaugg</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No (non-sinus)</td>
</tr>
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### What followed?

- Guidelines
- Quality improvement
- P4P
Predictors of beta blockade

- Caucasian anesthesiologist
  - Many respondents chose not to identify race
- Larger community hospitals
- Fellowship training
- Never anesthetize patients > 85 yo

- PHYSICIAN FACTORS DOMINATE!
Newest randomized trials

- Metoprolol after Vascular Surgery (MaVS) trial (N=497)
  - Negative results
- DECREASE-V
  - Rotterdam
  - N=770
  - Beta blockade to 60bpm = protective
- PeriOperative ISchemic Evaluation (POISE)
  - N= 8351
  - Australia, Canada, and the United Kingdom
  - THE definitive study?

POISE – the definitive trial??

- The dose of metoprolol:
  - 100 mg preop
  - 100 mg in the 6hr postoperative period
  - 200 mg 12 hours later
  - 200 mg daily thereafter out to 30 days
  - Doses were not titrated
  - Drug stopped for BPs < 100 mm Hg.

Lancet. 2008 May 31;371(9627):1839-47
**POISE – the definitive trial?**

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<tr>
<th>Outcome</th>
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<td>Stroke</td>
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<td>Revascularization</td>
<td>11 (0.3)</td>
<td>27 (0.6)</td>
<td>0.41</td>
<td>0.01</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>91 (2.2)</td>
<td>120 (2.9)</td>
<td>0.76</td>
<td>0.04</td>
</tr>
<tr>
<td>Significant hypotension</td>
<td>626 (15.0)</td>
<td>404 (9.7)</td>
<td>1.55</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Significant bradycardia</td>
<td>274 (6.6)</td>
<td>101 (2.4)</td>
<td>2.71</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
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Lancet. 2008 May 31;371(9627):1839-47
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.


Predictors of Perioperative β-Blockade Use in Vascular Surgery: A Mail Survey of United States Anesthesiologists

John E. Ellis, MD,* Avery Tung, MD,* Hubert Lee, BA,† and Kristen Kasza, MS‡

J Cardiothorac Vasc Anesth. 2007
Comorbidities and the elderly

• Among healthy patients, beta blockers were more likely to be recommended for older patients.
• However, among sick patients, this was reversed.
• p=0.054

J Cardiothorac Vasc Anesth. 2007

Perioperative Beta-Blocker Therapy and Mortality after Major Noncardiac Surgery

Peter K. Lindenauer, M.D., Penelope Pekow, Ph.D., Kaijun Wang, M.S., Dheeresh K. Mamidi, M.B., B.S., M.P.H., Benjamin Gutierrez, Ph.D., and Evan M. Benjamin, M.D.


Propensity-Matched Cohort

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<tr>
<th>RCRI score</th>
<th>Odds Ratio (95% CI)</th>
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<td>0</td>
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Perioperative Strokes and β-Blockade

Don Poldermans, M.D., Ph.D.,* Oefl Schouten, M.D., † Felix van Lee, M.D., ‡ Sanne E. Hoeks, M.Sc., § Louis van de Ven, M.D., Ph.D., † Robert Jan Stoffer, M.D., Ph.D., * Lee A. Fleisher, M.D., ‡

POLDERMANS ET AL.

Fig. 3. Relation between timing of initiation of β-blocker therapy and the risk for perioperative stroke.

DOI 10.1007/s12630-009-9148-0

Delirium following vascular surgery: increased incidence with preoperative β-blocker administration

Rita Katznelson, MD · George Djaiani, MD · Nicholas Mitsakakis, MSc · Thomas F. Lindsay, MDCM · Gordon Tait, PhD · Zeev Friedman, MD · Marcia Wasowicz, MD · W. Scott Beattie, MD, PhD

Received: 27 April 2009 / Accepted: 6 July 2009 / Published online: 27 August 2009
© Canadian Anesthesiologists’ Society 2009
<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient estimate</th>
<th>Odds ratio estimate</th>
<th>95% Wald confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of CVA/TIA</td>
<td>0.9728</td>
<td>2.64</td>
<td>1.57–4.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preoperative depression</td>
<td>1.27</td>
<td>3.56</td>
<td>1.53–8.28</td>
<td>0.003</td>
</tr>
<tr>
<td>Age</td>
<td>0.044</td>
<td>1.04</td>
<td>1.02–1.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preoperative beta-blockers administration</td>
<td>0.7227</td>
<td>2.06</td>
<td>1.18–3.6</td>
<td>0.011</td>
</tr>
<tr>
<td>Preoperative statins administration</td>
<td>-0.2843</td>
<td>0.56</td>
<td>0.37–0.88</td>
<td>0.011</td>
</tr>
<tr>
<td>Type of procedure</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Amputation</td>
<td>1.5396</td>
<td>4.66</td>
<td>1.96–11.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Revascularization of lower extremities</td>
<td>0.5462</td>
<td>1.73</td>
<td>0.77–3.85</td>
<td>0.18</td>
</tr>
<tr>
<td>Aortic reconstructive surgery</td>
<td>1.6744</td>
<td>5.34</td>
<td>2.54–11.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EVAR</td>
<td>1</td>
<td>1</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Thrombectomy/embolectomy</td>
<td>1.1844</td>
<td>3.27</td>
<td>1.41–7.6</td>
<td>0.006</td>
</tr>
<tr>
<td>Other</td>
<td>0.2264</td>
<td>1.254</td>
<td>0.51–3.07</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Marty London opines

- "What I think will happen is that it will become a class 2b indication—possibly effective but based on limited data,"
- "Like it or not, this is a bombshell in the whole area. What it means is that hospitals that have jumped on the beta-blocker bandwagon fairly aggressively, in large respect to try to boost their performance measures, will have to reconsider."


Marty London opines

- Nevertheless, there will always be patients in whom it is necessary to use beta blockers, London concludes.
- "I do a lot of high-risk surgery anesthesia, and I know if I can't control that stress period with an anesthetic drug, I will get a beta blocker out and use that sparingly and carefully. Most of the time, I don't see any big drops in BP or heart rate."

# Table 2. Updates to Section 7.2.1. Recommendations for Perioperative Beta-Blocker Therapy

<table>
<thead>
<tr>
<th>2007 Perioperative Guideline Recommendations</th>
<th>2009 Perioperative Focused Update Recommendations</th>
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<tr>
<td>1. Beta blockers should be continued in patients undergoing surgery who are receiving beta blockers to treat angina, symptomatic arrhythmias, hypertension, or other ACC/AHA Class I guideline indications. (Level of Evidence: C)</td>
<td>1. Beta blockers should be continued in patients undergoing surgery who are receiving beta blockers for treatment of conditions with ACC/AHA Class I guideline indications for the drugs. (Level of Evidence: C)</td>
<td>2007 recommendation remains current in 2009 update with revised wording.</td>
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<td>2. Beta blockers should be given to patients undergoing vascular surgery who are at high cardiac risk owing to the finding of ischemia on preoperative testing. (Level of Evidence: B)</td>
<td></td>
<td>Deleted/cumulative recommendation (class of recommendation changed from I to IIa for patients with cardiac ischemia on preoperative testing).</td>
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<td>1. Beta blockers are probably recommended for patients undergoing vascular surgery in whom preoperative assessment identifies coronary heart disease. (Level of Evidence: B)</td>
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<td>Modified/cumulative recommendation (wording revised and class of recommendation changed from I to IIa for patients with cardiac ischemia on preoperative testing).</td>
</tr>
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</table>
European Society Cardiologists 2009

ESC recommendations on perioperative beta-blocker use

Dose of beta-blockers should be titrated, which requires treatment initiation optimally 30 days and at least one week before surgery. It is recommended to start with a daily dose of 2.5 mg of bisoprolol or 50 mg of metoprolol succinate and then to adjust the dose before surgery to achieve a resting heart rate between 60 and 70 beats per minute with systolic blood pressure > 100 mmHg

Beta-blockers are recommended in patients who have known IHD or myocardial ischaemia according to preoperative stress testing

Beta-blockers are not recommended in patients scheduled for low-risk surgery without risk factors

www.escardio.org

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Class Ia

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Merin 1972

• "On the other hand, several patients at the Massachusetts General Hospital who were taken off propranolol before coronary bypass operations suffered myocardial infarctions before the operation."

We’d never stop beta blockers acutely, would we??

POISE author has suggested that maybe we should even stop chronic beta blockade!
Beta blocker withdrawal

U Chicago '97–'99 Preop Clinic – Vascul:
withdrawal

SCA 2001 (abstract)

Perioperative β-blocker withdrawal and mortality in vascular surgical patients

Jonathan R. Shammas, MD, a Jeffrey C. Trost, MD, b Julie M. Gold, BA, b Jesse A. Berlin, ScD, a Michael A. Golden, MD, d and Stephen E. Kimmel, MD, MS a New York, NY, and Philadelphia, Pa

Am Heart J 2001;141:148-53
Effect of \( \beta \)-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.†

Patients for elective hip or knee (2002-2006; \( n = 5158 \))

POMI was defined as a Troponin \( T > 0.1 \) ng/ml

Patients were divided into three groups:
- Beta-blocker on POD 0 and **throughout** hospital stay
- Beta-blocker on POD 0 but **discontinued**
- No beta-blocker on the day of surgery

Fig. 2. Kaplan-Meier curve showing the cumulative event-free proportion (a myocardial infarction did not occur) during the first 10 postoperative days. The solid line represents patients who were not prescribed a \( \beta \)-blocker on the day of surgery (cumulative event rate 0.8%). The dashed line represents those patients who were prescribed a \( \beta \)-blocker on the day of surgery and in whom this prescription was continued for at least 1 week or until hospital discharge, whichever came first (cumulative event rate 3.0%). The dashed - dotted line represents those who were prescribed a \( \beta \)-blocker on the day of surgery and in whom this prescription was discontinued during the first week after surgery (cumulative event rate 7.9%).
Fig. 3. Kaplan-Meier curve showing the cumulative event-free proportion (death did not occur) during the first 10 postoperative days. The dotted line represents patients who were not prescribed a $\beta$-blocker on the day of surgery (cumulative event rate 0.7%). The solid line represents those patients who were prescribed a $\beta$-blocker on the day of surgery and in whom this prescription was continued for at least 1 week or until hospital discharge, whichever came first (cumulative event rate 0.9%). The dashed-dotted line represents those who were prescribed a $\beta$-blocker on the day of surgery and in whom this prescription was discontinued during the first week after surgery (cumulative event rate 7.5%).

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·l$^{-1}$ and (B) less than 100 g·l$^{-1}$.
ASA 2008 – Toronto (Beattie)

• Death/MI was higher for patients administered beta blockers when Hgb decreases postop more than 30%
Figure. Response surface showing interaction between BIS and MAP on one-year mortality in patients given low end tidal volatile anesthetic concentrations (MAC <0.5) who had a “triple low” state for up to 15 minutes. Baseline one-year mortality was 4.5% in patients who spent no time in the triple low state. One-year mortality increased substantially as BIS decreased and as MAP decreased; the increase was especially great when both BIS and MAP were low. Of note, high mortality was associated with values, such as a BIS of 40 and MAP of 65 mm Hg, that are common during anesthesia and currently do not provoke much concern.

BIS, bispectral index score; MAP, mean arterial pressure

ASA 2009 Abstract A6
Mars and Venus?

• ~1000 vascular surgery patients evaluated retrospectively
• After risk-stratification, the high-risk women who received β-blockade had a statistically worse outcome (36.8% v 5.9%, p = 0.02) because of an increased incidence of CHF.
• By logistic regression, β-blockade improved outcomes in men but not women

John Ellis opines

• Beta blockade may produce hypotension if:
  o Given in fixed doses
  o Other anesthetic drugs are not reduced
    ▪ Volatile agents
    ▪ Opiates
• Beta blockade (BIS titrated)
  o Reduced isoflurane use
  o Reduced fentanyl use
  o Hastened extubation
  o Reduced postop pain scores
  o Reduced postop analgesia needs

CONCLUSIONS

• Studies differ on whether beta blockers are protective or not
• Excessive beta blockade may produce hypotension and hypoperfusion
• Beta blockade may become less of a QI or P4P goal in the future
  o Except for those on them chronically