Perioperative Beta Blockers: Order from Confusion

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Case

A 56 year old man with htn and colon CA is referred to your preoperative clinic for cardiac evaluation prior to his total colectomy next month.
Recent exercise treadmill test with nuclear imaging shows reversible defects compatible with two vessel CAD.

You tell the surgeon
A. To surgery as is, no beta blocker
B. Start a beta blocker now
C. Cancel surgery, he has CAD
D. Start a beta blocker the AM of surgery
**Perioperative MI**

- **Plaque Rupture**
  - Unpredictable based on angiographic appearance
  - Unpredictably impacted by surgical changes
    - Prothrombotic milieu
    - Increased sympathetic tone
    - Vasoconstriction

- **Mismatch of Oxygen Supply and Demand**
  - Hyperdynamic state of surgery
    - Increased myocardial oxygen demand
  - Fixed coronary lesions
  - Potential for prolonged ischemia

**Why Beta Blockers?**

- Reduction of HR can decrease myocardial O2 demand
- BB can attenuate sympathetic driven vasoconstriction
- Reduction of hyperdynamic state can decrease shear stress on vulnerable plaques
The Good- Mangano

- 200 pts with known or 2 traditional risk factors for CAD undergoing high risk non cardiac surgery (NCS)
- Atenolol started before anesthesia and 7 days postop
  - Continued long term in most pts
- No difference in cardiac outcomes during hospitalization
- Atenolol arm had lower mortality at:
  - 6 months (0 vs 8%)
  - 2 years (10 vs 21%)

Mangano DT et al. NEJM 1996;335(23:1713-20

The Good- Mangano

- In hospital deaths excluded from final analysis
- Role of increased use of preoperative beta blockers in study group.
- Role of abrupt stoppage of beta blockers in placebo group.

Mangano DT et al. NEJM 1996;335(23:1713-20

The Good- DECREASE I

- 173 patients with + DSE undergoing vascular surgery
- Bisoprolol started on average 37 days before surgery and continued during hospitalization
- Endpoint= cardiac death or non fatal MI
  - 3.4% bisoprolol group
  - 34% placebo group

Poldermans NEJM 1999;341:1789-1794
The Good- **DECREASE**

- Trial stopped early because of unanticipated large treatment effect
- Bisoprolol highly beta-1 selective

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The Bad- **DIPOM**

- 921 patients with DM undergoing NCS > 1 hour
- Randomized to 100 mg metoprolol or placebo
  - Preop day 1 to postop day 4-8
- Composite primary outcomes
  - Time to all cause mortality
  - Acute MI
  - Unstable angina
  - CHF

Juul AB et al. BMJ.2006;332:1482

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The Bad- **DIPOM**

- Median follow up 18 months
- Primary outcome reached in 20% of both groups
- All cause mortality in 16% both groups
- Applicable to patients you’ll be seeing
  - Diabetics undergoing mod/high risk surgery of all types
  - 40% had low risk procedure

Juul AB et al. BMJ.2006;332:1482
**The Bad- MAVS**

- 496 pts undergoing major vascular surgery
- Randomized to metoprolol or placebo
  - 2 hours before surgery to POD 5
  - >80% pts had RCRI < 2
- Primary outcome is 30 day:
  - Cardiac death
  - Non fatal MI
  - CHF
  - Unstable Angina
  - Dysrhythmia requiring treatment

Yang H et al. Am Heart J. 2006; 152:983-90

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**The Bad- MAVS**

- Primary outcome:
  - 12% placebo
  - 10.2% metoprolol
  - No change by RCRI
- Increased incidence of intraoperative hypotension and bradycardia requiring treatment in metoprolol arm

Yang H et al. Am Heart J. 2006; 152:983-90

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**How Important is Heart Rate?**

- Observational cohort study of 272 major vascular surgery patients
- Divided into no, low or high dose beta blocker
- Outcomes:
  - myocardial ischemia
  - Troponin leak
  - Long term mortality

Feringa HH et al. Circulation. 2006;114(supp):I344
How Important is Heart Rate?

Effect of Beta Blockers on Mortality
- Very large retrospective study evaluating cardiac mortality and perioperative beta blockade
- Patients stratified by RCRI
- Relationship between perioperative beta blockade and risk of death correlates directly with increasing risk

RCRI
- CAD
- Cr>2
- Diabetes
- CHF
- CVA
- High Risk Surgery
**Effect of Beta Blockers on Mortality**

POISE

- 8300 pts
- Patients >45 undergoing non-cardiac surgery who had a history of CAD, PVD, CVA, CHF; or major vascular surgery
- Randomized to placebo or metoprolol 200 mg/day for 30 days.
- Primary endpoint was a 30 day composite of cardiovascular death, non-fatal myocardial infarction or non-fatal cardiac arrest.


<table>
<thead>
<tr>
<th></th>
<th>Metoprolol (n = 4174)</th>
<th>Placebo (n = 4177)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>5.8%</td>
<td>6.9%</td>
<td>.04</td>
</tr>
<tr>
<td>Non Fatal MI</td>
<td>3.65%</td>
<td>5.1%</td>
<td>.0007</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>3.12%</td>
<td>2.3%</td>
<td>.03</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.0%</td>
<td>0.5%</td>
<td>.005</td>
</tr>
</tbody>
</table>
POISE
- Risk associated with PBB is real
- Is it beta blockers or study design?
- MI not the only pitfall of perioperative period
  - VTE
  - Sepsis
  - Pain
  - Hypovolemia

DECREASE IV
- 1000 pts randomized to bisoprolol vs placebo
- Intermediate risk pts undergoing noncardiac, non vascular surgery
- Bisoprolol started 1 month prior to surgery, titrated to HR <70
- Combined CV endpoint
  - 2.1% bisoprolol
  - 6% placebo
- No difference in stroke, hypotension, bradycardia


Data Review
- DECREASE I suggests starting BB early associated with improved outcomes
- DIPOM, MAVS suggest starting immediately preoperatively not helpful
- POISE suggests empiric large doses reduce cardiac outcomes with serious collateral damage
- DECREASE IV establishes safety and efficacy of titration of BB
- Lindenauer’s paper suggests harm in low risk patients
Back to the Case

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Beta Blocker Guidelines to Consider

- Beta blockers should not be routinely started preoperatively in patients whose only risk are traditional RF’s for CAD
- Start BB for
  - **RCRI >2**
  - Consider for RCRI = 2
- For pts with CAD as only RCRI, use timing and ability to titrate dose to guide decision to start BB
Beta Blocker Guidelines to Consider

- Patients already on beta blockers should have them continued in the perioperative period.
- Beta blockers are indicated in patients with coronary artery disease although it is unclear if starting them immediately prior to surgery is helpful, and may be associated with increased risk of death and stroke.

If beta blockade is initiated, it should be titrated to preoperative heart rate of sixty and postoperative heart rate of sixty to eighty.
- Patients on beta blockers in the perioperative period should be carefully monitored for pain, sepsis, hypovolemia and pulmonary embolus as their clinical signs can be masked by beta blockade.

Perioperative Beta Blocker Dosing:
New ACC/AHA Recommendation

- “Available evidence suggests, but does not prove that, when it is possible, BB should be started several days or weeks before elective surgery, with the dose titrated to achieve a resting HR b/w 50-60 bpm, to assure that the patient is indeed receiving the benefit of BB and should continue during the intraoperative and post operative period to maintain a HR < 80 bpm.”
- No definitive evidence that one drug is best.

Flesher, JACC 2006;47:2343-2354