Beta blockers are harmful – is it a question of dosage?

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No Disclosures

The Potential Risks and Dangers of BETA BLOCKERS

Lets review RCT data

Peri-operative Management

Beta-blocker Rx (Atenolol)\(^1,2\)
200 pts with or at risk for CAD
Atenolol → Discharge

Peri-op Ischemia
No. of Hosp D/MI

0 180 360 540 720
Days after Surgery

0 10 20 30 40 50 60 70 80 90 100
Event-Free Survival (%)

0 20 40 60 80 100
Beta Blockers

Placebo

↓

P<0.01

Peri-operative Management:

DECREASE

Beta-blocker Rx (Bisoprolol)\(^3\)
High risk vasc surgery
Bisoprolol 5-10 mg 7-89 days pre-op (mean 37)

P<0.001

Percentage of Patients

0 10 20 30 40
6 7 14 21 28
Days after Surgery

Standard care

Bisoprolol

P<0.001

CONT 17 17 0.02
BIS 3.4 0 0.001

Promising results, but…

\(^3\)Poldermans D, et al. NEJM 1996;334:1759-64.
Methodologic Concerns: DECREASE Trials

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Research Question</th>
<th>Main Concern</th>
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<tbody>
<tr>
<td>DECREASE I 1999</td>
<td>Effect of beta blockers in high risk patients undergoing vascular surgery</td>
<td>Not investigated</td>
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<tr>
<td>DECREASE II 2006</td>
<td>Effect of cardiac stress testing in addition to tight blood pressure control in intermediate risk patients</td>
<td>Fictitious method of establishing outcome</td>
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<tr>
<td>DECREASE III 2008</td>
<td>Effect of statins in high risk patients undergoing vascular surgery</td>
<td>No source data to investigate, only when witnessed statements</td>
</tr>
<tr>
<td>DECREASE IV 2009</td>
<td>Effect of beta blockers and/or statins in intermediate risk patients undergoing non-cardiac surgery</td>
<td>Events (e.g., MI) did not match hospital records or discharge summaries</td>
</tr>
<tr>
<td>DECREASE V (pilot) 2009</td>
<td>Effect of coronary revascularization in high risk patients undergoing vascular surgery</td>
<td>Falsified method of patient risk profile assessment (MI and renal failure)</td>
</tr>
<tr>
<td>DECREASE VI (pilot) 2006</td>
<td>Utility of NT-pro-BNP, in addition to clinical data and stress echo data in predicting perioperative cardiac events in patients undergoing vascular surgery</td>
<td>97% of patients did not undergo a stress echo and the surgery as specified</td>
</tr>
</tbody>
</table>

Perioperative Ischemic Evaluation POISE Trial

<table>
<thead>
<tr>
<th>8351 Patients*</th>
<th>Toprol XL 3.6% / Placebo 5.1% / P-value &lt;0.001</th>
</tr>
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<tbody>
<tr>
<td>Toprol XL 100 mg 2-4 Hrs Preop – 30 Days</td>
<td>Placebo</td>
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POISE – I Results: 1-Year Mortality Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Metoprolol N=4174 no. (%)</th>
<th>Placebo N=4177 no. (%)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All cause mortality</td>
<td>410 (10)</td>
<td>356 (9)</td>
<td>1.16 (1.01-1.34)</td>
<td>0.036</td>
</tr>
<tr>
<td>• CV mortality</td>
<td>182 (4)</td>
<td>167 (4)</td>
<td>1.10 (0.89-1.36)</td>
<td>0.37</td>
</tr>
<tr>
<td>• Non-CV mortality</td>
<td>228 (6)</td>
<td>189 (5)</td>
<td>1.22 (1.01-1.48)</td>
<td>0.043</td>
</tr>
</tbody>
</table>

At 1-year, B-blockers caused 54 excess deaths c/w placebo!

Implications of POISE I at 1 Year

1,000 Patients Treated with B-Blocker

- Benefit: Prevent 12 MI's
- Harm: Cause 6 CVA

At 1-year, B-blockers caused 54 excess deaths c/w placebo!

Perioperative β-blockade (POBBLE) for patients undergoing infra-vascular surgery: Results of a randomized double-blind controlled trial

- RCT
- 50-100 mg metoprolol day before and on surgery day
- Mortality and CV events

Implications of POISE I at 1 Year
• RCT
• 100 mg metoprolol at least 2 hrs prior to OR (after test dosing)
• Cont’d to day 8
• Was controlled in those with bradycardia or hypotension

Composite outcome of death and CV morbidities

Am Heart J 2006;152:983

The effects of perioperative β-blockade: Results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial

Same dosing regimen as prior studies

Am Heart J 2006;152:983

Meta-analysis of secure randomised controlled trials of β-blockade to prevent perioperative death in non-cardiac surgery

Comparison of effect of perioperative β-blockade on non-fatal strokes in secure and non-secure trials
May be just as much an issue of too large a dose as too short of time

B-Blockers to Lower Vascular Surgical Risk: Influence of Pre-op Heart Rate

So what to do?

- Keep your patients on b-blockers if on them already such as HF
- If at high risk for periop MI (+ stress), would consider starting low dose metoprolol (12.5 – 25mg) or atenolol 15-30d in advance
- Titrate HR to 55-65 bpm
- Avoid dose on morning of surgery, continue for use post op
- Need RCT of titrated low dose BB in high risk patients
Thank you!

Who does all the research work.

Who gets all the credit.