

Prophylactic Perioperative Beta Blockers

Glenn Gravlee

UCD & HSC

Aurora

Perioperative Prophylactic Beta-blockers

- *Prospective Studies*
- Retrospective studies (selected)
- Meta-analyses and systematic reviews
- ACC/AHA 2006 Beta-blocker update
- Statins instead?
- Conclusions / recommendations

Prophylactic β -blockers

What started the buzz?

- McSPI group – late 90s
- 200 general surgery Pts with cardiac risk factors randomized to atenolol from day of surgery to 7 days post-op
- Atenolol: lower incidence of ischemia by Holter monitoring (24% vs 39%)
- ND in periop MI or mortality, but decreased mortality in subsequent 6 mos (1% vs 10%)
 - Wallace A et al. Anesthesiology 1998;88:7-17

Prophylactic β -blockers

The buzz gets louder

- Poldermans et al., NEJM 1999;341:1789-4
- Vascular surgery: 112 Pts with new RWEMAs on Dobut Stress Echo randomly assigned to bisoprolol or placebo
- Rx begins 7 days or more pre-op, continues to 30 days post-op
- Resting HR < 60 pre-op, <80 intra- and post-op

Results – Poldermans et al.

- Reduced cardiac death: 3.4% vs 17%
- Reduced nonfatal MI: 0% vs 17%

NEJM 1999; 341:1789

Net result ~ 2000-2004

- Enthusiasm over prophylactic beta-blockers
- Pressure to establish local protocols
- Common establishment of protocols
- But without clear consensus about how best to do it (and in whom)
- Hence protocol implementation has been spotty, even in institutions with well-defined protocols

Step 1. Patient undergoing high-risk surgical procedure (e.g., intraperitoneal procedure, intra-thoracic procedure, suprainguinal vascular procedure)

Step 2: Does patient have any one of the following:

- Patient currently receiving a beta blocker as an outpatient
- History of coronary disease, which includes any one of the following: clinical history of myocardial infarction or angina, positive stress test (symptoms or not), presence of pathological Q waves on EKG, or prior CABG or PCI.
- History of peripheral vascular disease, which includes any one of the following: known carotid artery disease (for example: obstructive plaque, transient ischemic attack or cerebrovascular disease), prior endarterectomy, known thoracic or abdominal aneurysm, previous AAA repair, prior or planned peripheral vascular bypass, confirmation by doppler studies, or strong history of claudication.

Step 2: Does patient have any two of the following:

- Current or recent smoker.
- History of renal insufficiency (> 2 mg/dl)
- History of diabetes mellitus

No criteria are met.

Yes, one criterion are met

Yes, two criteria are met

No criteria are met or only
One criterion is met.

Patient not a candidate
for peri-operative beta blocker use

Step 3. Evaluate for absolute contraindications

Patient not a candidate
for peri-operative beta blocker use

- Cardiac conduction anomalies (e.g., 2nd or 3rd degree AV heart block in the absence of a pacemaker).
- Severe aortic stenosis (i.e., gradients > 50 mmHg or aortic valve area < 0.85 cm²).
- Resting heart rate less than 60 beats/minute or a systolic blood pressure less than 100 mmHg.
- Symptoms of heart failure or an ejection fraction < 35%.
- Evidence of pulmonary edema.
- Evidence of right ventricular dysfunction (greater than moderate)

Yes one or more
are met

Page Cardiology
Fellow

No criteria are meet

Step 3. Evaluate for relative contraindications

Yes one or more is met

1. Severe COPD
2. Severe reactive airway disease
3. Pulmonary hypertension

Consider lower dose of metoprolol
or esmolol (refer to pre operative
order set)

No criteria are meet

Refer to Pre/Post-operative beta blocker order set

Further studies from the Poldermans group (Rotterdam)

- 1,476 Pts @ 5 centers, abd aortic or infrainguinal vasc surgery
- Risk stratification by screening: low (0 AHA risk factors), intermed. (1-2), or high (≥ 3)
- Intermed Risk randomly assigned to stress testing or none: If surgery could be delayed, cor. angio and consideration of revasc
- Perioperative β -blockers for all Pts adjusted to resting pre-op HR 60-65, periop HR at that level or below ischemic HR threshold

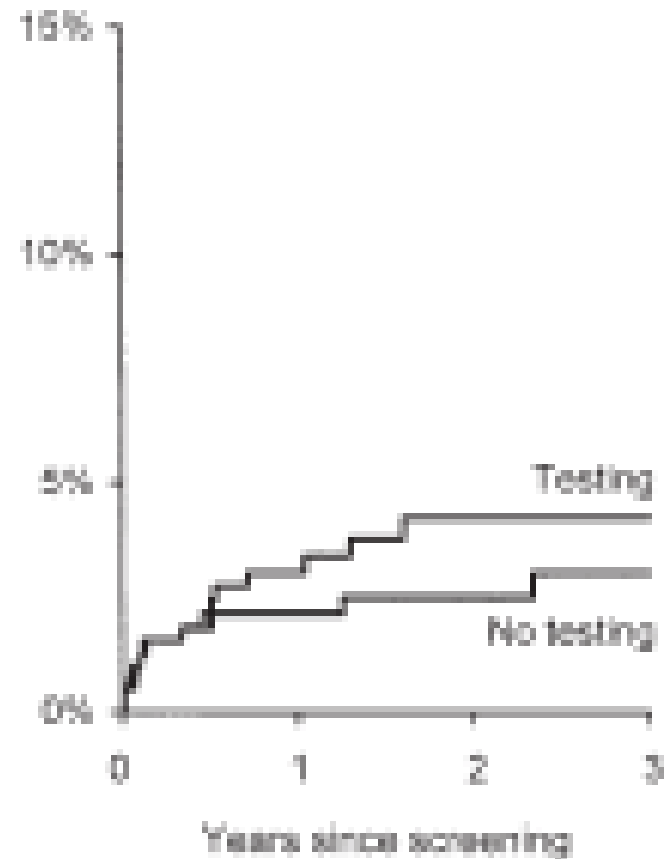
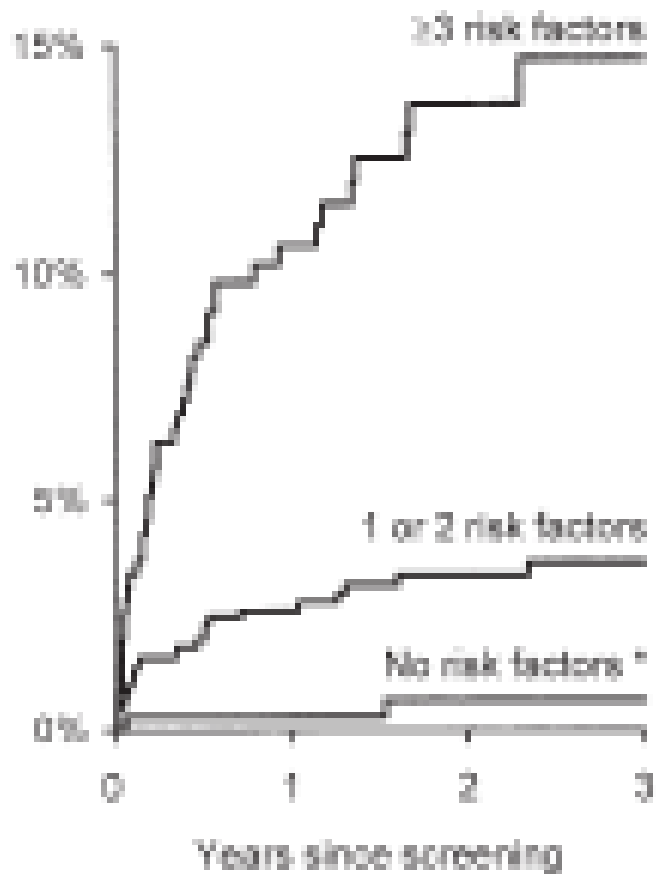
Poldermans D, JACC 2006;48:964-9

Poldermans, JACC 2006;48:964

Results

- Stress testing showed ischemia in 99 Pts (26%), severe in 34 (9%): revascularization was feasible in 12 (~3%)
- ND in cardiac morbidity with or without stress testing (Odds ratio 0.78, CI .28-2.1)
- No testing: Surgery 3 weeks earlier
- HR < 65: Lower risk (OR 0.24, CI 0.09-0.66)
- Conclude: No need for stress testing with intermed risk if HR controlled

Poldermans: Assuming HR control, It's about the risk profile, not the stress testing (JACC 2006;48:964)



Patients at risk 1478 1044 738 388

770 558 300 202

Further studies from the Poldermans group (Rotterdam)

JACC 2007;49:1763-9

- N=1,889 Major Vasc below diaphragm, if ≥ 3 AHA risk factors: stress testing, if positive (≥ 5 segments or ≥ 3 walls): random assignment to cor. revasc. All Pts had β -blockade with target HR 60-65
- End Points: All-cause death or MI at 30 d and 1 year.

Poldermans JACC 2007;49:1763-9

- 101 Pts randomized to cor revasc vs none
- 2 VD in 24%, 3 VD in 67%, L main 8%
- CABG N=17, Drug-stent N=30, Bare metal stent N=2
- Median revasc.-to-surgery interval: CABG 29 D (13-65), Stent 31 D (19-31, surgery without aspirin / clopidogrel interruption, transfusion median 2 vs 3 units (NS))

Poldermans JACC 2007;49:1763-9

- 2 Pts in revasc group died pre-op from ruptured aneurysm, 1 had a nonfatal MI (no pre-op events in non-revasc group)
- Overall, revasc did not improve 30-day (43 vs 33%) or 1-year outcome (49 vs 44%).
- Concludes that Cor. Revasc does not improve outcome in setting of tight periop HR control

Prophylactic Beta-blockers: Recent Negative Studies

Powell JT, J Vasc Surg 2005;41:602-9 (Pobble)

- Prospective, placebo-cont. infrarenal vasc without previous MI, unstable angina, or positive stress test (lower risk than Poldermans)
- Metoprolol or placebo, start 1 day pre-op through 7 d post-op, no HR target (low HR/BP interrupts)
- ND in 30-D or periop CV events, shorter LOS (10 vs 12) with β -B, greater need for intra-op “inotrope” with β -B (92 v 64%)

Prophylactic Beta-blockers: Recent Negative Studies

Juul AB, BMJ 2006;332:1482

- 921 Diabetics for major noncard. surg (predominantly orthopedic and nonvasc intra-abdominal)
- Random: Metoprolol fixed dose v. placebo from 1 D pre-op to D/C (max 8 days), outcomes were mortal, card. mortal, non-fatal cardiac morbidity
- ND in 1^o outcomes (21 v 20%) or mortality (16 v 16%) out to 18 mos
- Metoprolol: Higher incidence of low HR (<65) or BP (< 100): 32 v 17%

Prophylactic Beta-blockers: Recent Negative Studies

Yang H, Am Heart J 2006;152:983-90

- 496 elective major vascular (subdiaphragm), blinded, randomized
- Metoprolol v placebo, 2 hrs pre-op to D/C (max 5 d), outcomes: 30 days: MI, unstable angina, CHF, new dysrhythmia needing Rx, cardiac death.
- ND in 1^o outcomes: Metop 10.2 %, Placebo 12.0 %
- Bradycardia needing Rx: 53* v 19, hypotension needing Rx 114* v 84, BUT aggressive metoprolol regimen (80 kg Pt gets 100 mg 2 hrs pre-op, then 15 mg IV q6hrs apparently without a HR or BP minimum)

Perioperative Prophylactic Beta-blockers

- Prospective Studies
- *Retrospective studies (selected)*
- Meta-analyses and systematic reviews
- ACC/AHA 2006 Beta-blocker update
- Statins instead?
- Conclusions / recommendations

β Bs with mixed results

Lindenauer PK, NEJM 2005;353:349-61

- Retrospective review of 700K noncardiac surgery Pts at 329 US hospitals
- Retrieved data on β Bs given within 2 days of hospitalization vs none
- Propensity scoring to reduce confounding factors
- Used a cardiac risk index score to assess effect of β Bs on outcomes

βBs with mixed results

Lindenauer PK, NEJM 2005;353:349-61

- Pts with risk index of 3 or higher (Hx CAD, Hx CVD, Renal insuffic., DM, or high-risk surgery all = 1) were less likely to die in the hospital if they received βBs
- Pts with risk index of 1 or 2: no difference
- Pts with Risk index of 0: more likely to die if *given* a βB
 - But why did they get a βB? Complication perhaps?

Further studies from the Poldermans group (Rotterdam)

N=211 Major Vasc, extensive pre-op screening, *observational* study

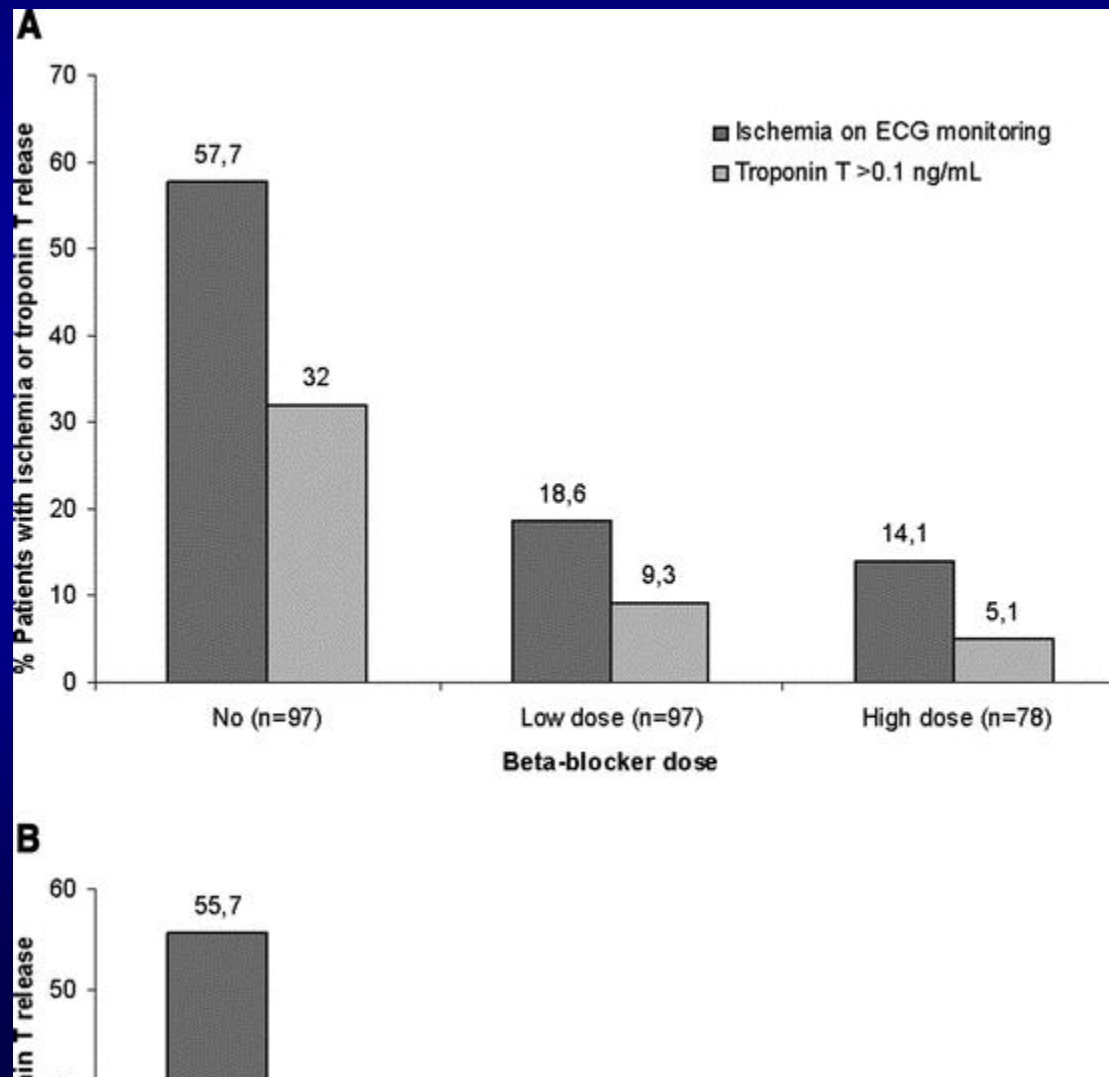
- Pt groups: No β -blockers, low-dose β -blockers, high-dose β -blockers (high if >25% of max recommended daily dose)
- Over 60% bisoprolol (cardioselective)
 - Pre-op HR 76 ± 13 (N=97), 66 ± 12 (97), 64 ± 11 (78)

Higher β -block doses reduce:

- Myocardial ischemia incidence (Hazard Ratio 0.62, 95% CI .51-.75)
- Troponin T release (HR 0.63, .49-.80)
- Long-term mortality (HR 0.86, .76-.97)

Ischemia vs B-blocker dose

Feringa HHH, Circulation 2006; 114: I-344



Further studies from the Poldermans group (Rotterdam)

- Observational @ 11 hospitals, vasc. surg., risk stratification/ adjustment, continuity of B-blocker use assessed: Beta-blocker withdrawal assoc with higher 1 yr. mortality (Haz. Ratio 2.7, CI 1.2-5.9) Hoeks SE, Eur J Vasc Endovasc Surg 2007;33:13-19
- Severe LV dysfunction (EF<30), observational, vasc. surg.: Use of β -blockers assoc. w/ decreased risk-adjusted hosp (OR 0.18, CI .04-.74) and long-term (OR .38, CI .22-.65) mortality
 - Did risk adjustment lack severity of CHF?
 - Feringa HHH, Eur J VAsc Endovasc Surg 2006;31:351

Perioperative Prophylactic Beta-blockers

- Prospective Studies
- Retrospective studies (selected)
- *Meta-analyses and systematic reviews*
- ACC/AHA 2006 Beta-blocker update
- Statins instead?
- Conclusions / recommendations

2003 Meta-analysis of 11 trials

Stevens RD, Anesth Analg 2003;97:623

- (Not all trials were randomized or blinded)
- Noncardiac surgery
- Decreased ischemic episodes, nonfatal MIs, and cardiac death
- Number needed to treat to
 - Prevent MI = 23
 - Prevent cardiac death = 32

Prophylactic β -B Systematic Review

Devereaux PJ, BMJ: 2005; 331:313-21

- 22 Randomized trials with 2437 Pts for noncardiac surgery
- Outcomes: 30 day mortality, CV mortality, non-fatal MI, card arrest, stroke, CHF, hypotension, bradycardia, bronchospasm
- No benefit to B-Bs for any individual outcome, RR 0.44 (.20-.97) for composite outcomes of CV mortal., non-fatal MI, and non-fatal cardiac arrest
- RR for bradycardia needing Rx 2.27 (1.53-3.36), hypotension needing Rx 1.27 (1.04-1.56)
- Study methodologies varied and often weak, much heterogeneity: Further study recommended

Peri-op beta-blockers for M&M Prevention: Systematic Review and Meta-analysis Wiesbauer et al., A&A 2007;104:27-41

- 69 Randomized Trials met criteria (all but 24 were Cardiac Surgical Pts only)
- Principal findings for noncardiac surgery:
 - *Reduced ischemia* (OR 0.38 [0.21-0.69])
 - No difference in arrhythmias, mortality, MI, or length of hospital stay

Systematic Review and Meta-analysis

Wiesbauer F, Anesth Analg 2007;104:27-41

- Noncardiac Surgery **MI** Category: 12 of 69 clinical trials reviewed (45-921 Pts)
- Drugs: Metoprolol 5, Atenolol 2, Esmolol 1, Propranolol 1, Bisoprolol 1, Esm/metop 1, aten/labet/oxpren 1
- Surgery type: Vascular 5, “noncardiac” 3, lung 1, Ortho or intra-abd 1, total knee 1, General or Vasc 1,

Study	1 wk	1D	Preop	Preind	PACU	D/C	30 D
1							
2							
3							
4							
5							
6							
7							
8					?		
9							
10							
11							
12							

Perioperative Prophylactic Beta-blockers

- Prospective Studies
- Retrospective studies (selected)
- Meta-analyses and systematic reviews
- *ACC/AHA 2006 Beta-blocker update*
- Statins instead?
- Conclusions / recommendations

Strength of Recommendation

- Class I: Strong evidence of usefulness and efficacy, benefit >>risk (do it)
- Class II: Conflicting evidence
 - IIA: Weight of evidence favors (reasonable)
 - IIB: Less well established (consider it)
- Class III: Evidence/general agreement for lack of usefulness/efficacy, possibility for harm (don't do it)

Quality of Evidence

- Level A: Multiple (3-5) population risk strata evaluated, multiple randomized trials, general consistency of direction and magnitude of effect
- Level B: Limited (2-3) population risk strata evaluated, single rand. trial or non-randomized trials
- Level C: Very limited (1-2) population risk strata evaluated, consensus of experts or case studies

Perioperative Beta Blockers

Class I Recommendations

- Continue β Bs if on them for ACC/AHA Class I indications (ang, arrhyth, HT, etc.)(C)
- Give them to vasc surg Pts at high cardiac risk as a result of ischemia found on pre-op testing (B)

Perioperative Beta Blockers

Class IIa Recommendations

- Vasc Surgery plus known CAD (B)
- Vasc Surgery plus high cardiac risk (mult risk factors) (B)
- Intermed or Hi-risk nonvasc surgery plus known CAD or high card. Risk (B)

Perioperative Beta Blockers

Class IIb Recommendations

- Intermediate or High-risk procedure PLUS Intermediate Cardiac Risk (1 factor) (C)
- Vascular surgery with low cardiac risk who aren't currently taking BBs

AHA/ACC 2006 β B Update

Their commentary

- Inadequate # randomized trials, often underpowered, often unblinded, highly variable Pt populations
- Titration of therapy (target HR) insufficiently established
- Optimal β Bs or β B-subtypes not established
- ***Implementation timing, route, monitoring, and duration not well-established***

Editorial: Where did we go wrong?

McCullough PA, Am Heart J 2006;152:815-818

- Some trials were too small and unblinded
- Differences in Pt selection, risk profiles, end points, drug, route, duration
- As cor. Revasc becomes more prevalent, the prevalence of Pts with severe unrevasc CAD may decrease
- Plaque rupture and thrombosis may be unaffected by β -Bs (But what about their consequences?)
- Larger trials still ongoing (Canada - POISE)

McCullough Editorial

Am Heart J 2006;152:815-818

Stone, 1988, n = 128

Mangano, 1996, n = 200

Poldermans, 1999, n = 112 (unblinded)

Raby, 1999, n = 26

Zaug, 1999, n = 63 (no placebo)

Urban, 2000, n = 107

Total N = 636

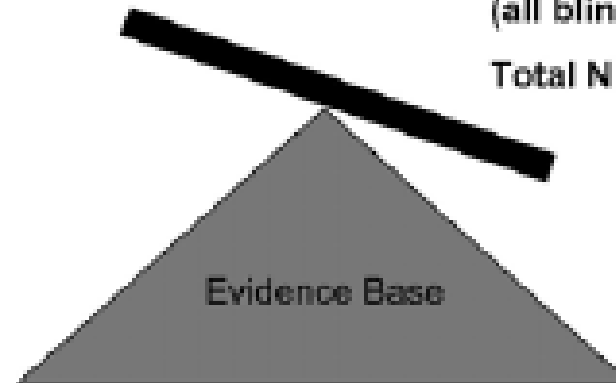
POBBLE, 2005, n = 103

MAVS, 2006, n = 296

DIPOM, 2005 n = 921

(all blinded, placebo-controlled)

Total N = 1320



Protective Effect of Beta-Blockade

No Effect of Beta-Blockade

Perioperative Events In Patients Undergoing Non-cardiac Surgery

However, collective works of the Rotterdam group suggest (in infradiaphragmatic vascular surgery)

- Either tight HR control or extended pre-op and post-op β -block matters (or both)
 - Only their group has done it this way
- Extended pre-op/post-op β -B with tight HR control MAY be as good as pre-surgical coronary revascularization
 - Particularly appealing in view of confused state of affairs for drug-eluting stents: Clopidogrel D/C, optimal timing of surgery post-stent

Perioperative Prophylactic Beta-blockers

- Prospective Studies
- Retrospective studies (selected)
- Meta-analyses and systematic reviews
- ACC/AHA 2006 Beta-blocker update
- *Statins instead?*
- Conclusions / recommendations

Statins – Better than Beta-blockers?

Brief overview of evidence to date

Prospective Statin Studies

Perler BA, Perspect Vasc Surg Endovasc Ther 2007;19:240

2 prospective studies in major vascular surg.

- 30-40 days pre-op and continued post-D/C
- Reduced CV events (8 v 26%), combined MI/death (9 v 15%)
- Higher infrainguinal graft patency @ 2 years but no change in limb salvage or survival

Retrospective Statin Studies

Perler BA, Perspect Vasc Surg Endovasc Ther 2007;19:240

Retrospective: all favoring statins

- Mortality and adverse events in CABG: 2 studies
- PTCAs or stents: 1 study
- Noncardiac vascular: 3 studies
- Higher infrainguinal graft patency at 2 years
- Decreased long-term restenosis after CEA
- Hopkins CEAs: Independently decreases odds of stroke threefold, death fivefold
- W. Ontario CEA: 75% reduction in odds of death, 45% reduction in odds of stroke or death in Sx Pts

Statins and Length of Stay

Van de Pol MA, Am J Cardiol 2006;97:1423-6
(Poldermans group)

- Retrospective multivariate analysis of factors affecting LOS after vascular surgery
- Factors prolonging: COPD, DM, Renal failure, Hx CHF
- Factors shortening: Aspirin, HTN, Male gender, statins (beta-blockers with CAD)
- Model accounts for 14% of observed variation

Retrospective Multicenter VA Study

Barrett TW, J Hosp Med 2007;2:241-252

- 3,062 Vascular Surgery Pts, 1998-2005
- Stratified by chronic use of β -B, statin, both, or neither
- Survival analysis with risk adjustment
- Both drugs conferred survival benefit
 - Beta-blocker: HR 0.84 (.73-.96), NNT=30
 - Statin: HR 0.78 (.67-.92), NNT=22
 - Both: HR 0.56 (.42-.74), **NNT=9**
- Drug combo was beneficial at all levels of risk

Statins: Not just about Cholesterol

Perler BA, Perspect Vasc Surg Endovasc Ther 2007;19:240

So-called pleiotropic effects

- Improved endothelial function: increased endothelial eNOS and NO, decreased adhesion molecules (ICAM-1, E-selectin)
- Inflammation/Plaque stabilization: decreased macrophage activation, chemoattractants, inflam.cytokine release, proteolytic enzymes, increased anti-inflam cytokines
- Mild anticoagulant: decreased TF, PAI-1, vWF, Factors II/V/VII/VIII activity, inc tPA

Statins - cautions

- Contraindications: Active liver disease or pregnancy
- Precautions: aortic stenosis (hypotension) elevated risk of renal failure from rhabdomyolysis, recent stroke, heavy EtOH, liver disease, myalgias,
 - concomitant use of cyclosporine, erythromycin, some antifungals, fibric acid derivatives (risk of myalgia/ rhabdomyolysis)
 - COX 2 inhibitors theoretically inhibit protective effects mediated by prostaglandins

The Wall Street Journal

MY ONLINE JOURNAL

February 19, 2008

Can a drug help hearts but impair heads?

BY MELINDA BECK THE WALL STREET JOURNAL ASIA

Word Count: 1,188 | Companies Featured in This Article: Pfizer

COGNITIVE SIDE EFFECTS like memory loss and fuzzy thinking aren't listed on the patient information sheet for Lipitor, the popular cholesterol-lowering drug. But some doctors are voicing concerns that in a small portion of patients, statins like Lipitor may be helping hearts but hurting minds.

"This drug makes women stupid," Orli Etingin, vice chairman of medicine at New York Presbyterian Hospital, declared at a recent luncheon discussion sponsored by Project A.L.S. to raise awareness of gender issues and the brain. Dr. Etingin, who is also founder and director of the Iris Cantor Women's Health Center

Spousal dilemma

- Stupider husband who lives longer
- More stimulating companionship for a shorter period

The following message may be very disturbing

- Low cholesterol is associated with violent death (suicide is a big player)
- In the community in general
- In violent populations specifically
- In patients undergoing cholesterol-lowering therapy
- In men more than women
- Subject of a large ongoing study, mechanism may be reduced CNS serotonin

Golomb BA, Ann Intern Med 1998;128:478-487

But the good news is:

Increase in violent death has NOT
been associated with statin-
induced decreased cholesterol

Prophylactic Statins and Surgery

- Evidence is limited and mostly retrospective
- Nevertheless: Quite encouraging
- Needs further prospective study
- Will this be another β -blocker deal?
 - Initial enthusiasm and overreaction followed by a reality-check

Perioperative Prophylactic Beta-blockers

- Prospective Studies
- Retrospective studies (selected)
- Meta-analyses and systematic reviews
- ACC/AHA 2006 Beta-blocker update
- Statins instead?
- ***Conclusions / recommendations***

Conclusions/Recommendations

- Major Vascular Surgery below the diaphragm: Beta-blockers are probably good for most of these Pts
 - How long and how intense?
- Other surgeries: Benefit not yet proven. Possibly harmful if low cardiac risk profile
- Beta-blockers *may* be as good as pre-op coronary revascularization
- Expect more bradycardia and hypotension

Conclusions/ Recommendations

Statins may have an important prophylactic role as well

As compared to beta-blockers

- Perhaps as good or better
- More widely applicable risk profiles?
- May complement or be synergistic with B-Bs

Wild Speculation

- If you need vascular surgery and you aren't already on a B-blocker and lack a contraindication to them:
 - Maybe you *should* be
 - Like, *permanently*
 - *And maybe you need a statin too*
 - **[But stay away from firearms]**
 - And ski slopes?

Beta-blockers are Good

- Prospective Studies
- Retrospective studies and meta-analyses
- ACC/AHA 2006 Beta-blocker update
- Conclusions and recommendations

5 Commandments for using beta-blocker prophylaxis for QI or P4P

- I. Thou shalt only use Class I indicators to judge deficiency
 - Continuation in Pts taking β -blockers for angina, arrhythmias, hypertension, or other ACC/AHA Class I guidelines
 - Initiation in vascular surgery Pts at high cardiac risk as judged by finding ischemia on pre-op testing
- Corollary A: If you don't want to be deficient, don't test for ischemia pre-op in vascular surgical patients
- Corollary B: Corollary A will work better if you have a low threshold for pre-op β -blockers in leg revasc.

5 Commandments for β -blocker prophylaxis – (cont.)

- II. Thou shalt not penalize a physician for failing to implement indicated β -blockers prior to the day of surgery
 - It's likely best to initiate blockade at least several days pre-op, but the jury is out

5 Commandments for β -blocker prophylaxis – (cont.)

- III. Thou shalt not give demerits for prophylactic β -blockers unless used for a Class III “indication”
 - Pts who have contraindications to β -blockers
 - This leaves room for judgment in Class IIa indications: Vasc surg plus stable CAD, Vasc surg plus multiple risk factors, Intermediate or high risk surgery plus multiple risk factors

5 Commandments for β -blocker prophylaxis – (cont.)

- IV. Thou shalt not penalize a physician for failing to reach a target pre-op HR (e.g., <60) when (indicated) β -blockers are used
 - It's probably good to reach a target resting HR, and 60 is as good as any, but it's only substantiated by one study group (REPEATEDLY)
 - May be MORE IMPORTANT to avoid perioperative tachycardia (HR >90 (?) in Pts with CAD or strong CAD risk factors). If Pt cardiac stress tested: avoid ischemic threshold

5 Commandments for β -blocker prophylaxis – (cont.)

- V. Thou shalt neither honor nor condemn physicians who use prophylactic β -blockers for Class IIb indications:
 - Intermediate or high-risk procedures with a single clinical risk factor
 - Vascular surgery Pts with low cardiac risk who are not taking β -blockers chronically

Prospective or Favorable
studies

Prophylactic β -blockers

What started the buzz?

- McSPI group – late 90s
- 200 general surgery Pts with cardiac risk factors randomized to atenolol from day of surgery to 7 days post-op
- Atenolol: lower incidence of ischemia by Holter monitoring (24% vs 39%)
- ND in periop MI or mortality, but decreased mortality in subsequent 6 mos (1% vs 10%)
 - Wallace A et al. Anesthesiology 1998;88:7-17

Prophylactic β -blockers

The buzz gets louder

- Poldermans et al., NEJM 1999;341:1789-4
- Vascular surgery: 112 Pts with new RWEMAs on Dobut Stress Echo randomly assigned to bisoprolol or placebo
- Rx begins 7 days or more pre-op, continues to 30 days post-op
- Resting HR < 60 pre-op, <80 intra- and post-op

Results – Poldermans et al.

- Reduced cardiac death: 3.4% vs 17%
- Reduced nonfatal MI: 0% vs 17%

NEJM 1999; 341:1789

2003 Meta-analysis of 11 trials

Stevens RD, Anesth Analg 2003;7?:623

- (Not all trials were randomized or blinded)
- Noncardiac surgery
- Decreased ischemic episodes, nonfatal MIs, and cardiac death
- Number needed to treat to
 - Prevent MI = 23
 - Prevent cardiac death = 32

Unfavorable Studies

Peri-op beta-blockers for M&M Prevention: Systematic Review and Meta-analysis Wiesbauer et al., A&A 2007;104:27-41

- 69 Randomized Trials met criteria (all but 24 were Cardiac Surgical Pts only)
- Principal findings for noncardiac surgery:
 - *Reduced ischemia* (OR 0.38 [0.21-0.69])
 - No difference in arrhythmias, mortality, MI, or length of hospital stay

Systematic Review and Meta-analysis

Wiesbauer F, Anesth Analg 2007;104:27-41

- Noncardiac Surgery **Ischemia** Category: 10 of the 69 clinical trials (27-497 Pts)
- Drugs: Metoprolol 5, Atenolol 2, Atenolol/oxprenolol/labetalol 1, esmolol 1, esmolol/metoprolol 1
- Surgery type: Vascular 4, Gen or Vasc 1, Gen surg 1, “noncardiac” 1, orthopedic or intra-abdom 1, chole or ing hernia 1, total knee 1

Beta-blocker admin (ischemia): Meta/anal Wiesbauer A&A 2007

Study	1D pre	Preop	Preind	PACU	D/C	2 wks
1	Red	Red	Red	Red	Red	Dark Blue
2	Red	Red	Red	Red	Red	Dark Blue
3	Dark Blue	Light Blue	Light Blue	Light Blue	Light Blue	Light Blue
4	Dark Blue	Light Green	Light Green	Light Green	Light Green	Dark Blue
5	Dark Blue	Light Green	Light Green	Light Green	Light Green	Dark Blue
6	Dark Blue	Light Green	Light Green	Light Green	Light Green	Dark Blue
7	Dark Blue	Dark Red	Dark Blue	Dark Blue	Dark Blue	Dark Blue
8	Dark Blue	Dark Blue	Yellow	Dark Blue	Dark Blue	Dark Blue
9	Dark Blue	Dark Blue	Yellow	Dark Blue	Dark Blue	Dark Blue
10	Dark Blue	Dark Blue	Dark Blue	White	White	Dark Blue

Systematic Review and Meta-analysis

Wiesbauer F, Anesth Analg 2007;104:27-41

- Noncardiac Surgery **MI** Category: 12 of 69 clinical trials reviewed (45-921 Pts)
- Drugs: Metoprolol 5, Atenolol 2, Esmolol 1, Propranolol 1, Bisoprolol 1, Esm/metop 1, aten/labet/oxpren 1
- Surgery type: Vascular 5, “noncardiac” 3, lung 1, Ortho or intra-abd 1, total knee 1, General or Vasc 1,

Study	1 wk	1D	Preop	Preind	PACU	D/C	30 D
1							
2							
3							
4							
5							
6							
7							
8					?		
9							
10							
11							
12							

Bradycardia and Hypotension

Wiesbauer A&A 2007: 104:27

- Similar problems with consistency of design among 11 studies
- 7 drugs or combinations of drugs
- 10 different surgical procedure types
- 7 different spans of administration
- No standardization of observation period
- No comments on responsiveness to management

β Bs with mixed results

Lindenauer PK, NEJM 2005;353:349-61

- Retrospective review of 700K noncardiac surgery Pts at 329 US hospitals
- Retrieved data on β Bs given within 2 days of hospitalization vs none
- Propensity scoring to reduce confounding factors
- Used a cardiac risk index score to assess effect of β Bs on outcomes

βBs with mixed results

Lindenauer PK, NEJM 2005;353:349-61

- Pts with risk index of 3 or higher were less likely to die in the hospital if they received βBs (Hx CAD, Hx CVD, Renal insuffic., DM, or high-risk surgery all = 1)
- Pts with risk index of 1 or 2: no difference
- Pts with Risk index of 0: more likely to die if *given* a βB
 - But why did they get a βB? Complication perhaps?

Q: Why worry about myocardial O₂ supply/demand when 50% of MIs are unrelated to it?

A: Because 50% of them ARE

Beta-blockers 2005 Update

Perioperative Beta-blockers

AHA/ACC 2006 Update

CAD or High Cardiac Risk

- Vasc Surg: I-IIa (Level B)
- Other Hi/Intermed Risk Surg: IIa (B)
- Low-risk Surg: insuffic. data

Intermediate Cardiac Pt Risk

- Vasc Surg: IIb (C)
- Other Hi/Intermed Risk Surg: IIb (C)
- Low-risk Surg: Insuffic. Data

Perioperative Beta-blockers

AHA/ACC 2006 Update

Low Cardiac Pt risk:

- Vascular Surgery: Ib (C)
- Other hi/intermediate or low risk surgery:
insufficient data

Perioperative Beta Blockers

Class I Recommendations

- Continue BBs if on them for ACC/AHA Class I indications (ang, arrhyth, HT, etc.)(C)
- Give them to vasc surg Pts at high cardiac risk as a result of ischemia found on pre-op testing (B)

Perioperative Beta Blockers

Class IIa Recommendations

- Vasc Surgery plus known CAD (B)
- Vasc Surgery plus high cardiac risk (mult risk factors) (B)
- Intermed or Hi-risk nonvasc surgery plus known CAD or high card. Risk (B)

Perioperative Beta Blockers

Class IIb Recommendations

- Intermediate or High-risk procedure PLUS Intermediate Cardiac Risk (1 factor) (C)
- Vascular surgery with low cardiac risk who aren't currently taking BBs

AHA/ACC 2006 BB Update

Their commentary

- Inadequate # randomized trials, often underpowered, often unblinded, highly variable Pt populations
- Titration of therapy (target HR) insufficiently established
- Optimal BBs or BB-subtypes not established
- ***Implementation timing, route, monitoring, and duration not well-established***

Perioperative Beta-blockers

What should we do?

- Vascular surgery: Just do it
- High/intermediate risk surgery plus CAD or 2+ cardiac risk factors: do it
- Other situations: judgmental
- Avoid if contraindicated
- Start days/weeks pre-op if possible, but don't delay surgery because of absence
- Target resting HR: 50-60 probably, Target peak HR < 80

Commandments/Conclusions

Step 1. Patient undergoing high-risk surgical procedure (e.g., intraperitoneal procedure, intra-thoracic procedure, suprainguinal vascular procedure)

Step 2: Does patient have any one of the following:

- Patient currently receiving a beta blocker as an outpatient
- History of coronary disease, which includes any one of the following: clinical history of myocardial infarction or angina, positive stress test (symptoms or not), presence of pathological Q waves on EKG, or prior CABG or PCI.
- History of peripheral vascular disease, which includes any one of the following: known carotid artery disease (for example: obstructive plaque, transient ischemic attack or cerebrovascular disease), prior endarterectomy, known thoracic or abdominal aneurysm, previous AAA repair, prior or planned peripheral vascular bypass, confirmation by doppler studies, or strong history of claudication.

Step 2: Does patient have any two of the following:

- Current or recent smoker.
- History of renal insufficiency (> 2 mg/dl)
- History of diabetes mellitus

No criteria are met.

Yes, one criterion are met

Yes, two criteria are met

No criteria are met or only
One criterion is met.

Patient not a candidate
for peri-operative beta blocker use

Step 3. Evaluate for absolute contraindications

Patient not a candidate
for peri-operative beta blocker use

- Cardiac conduction anomalies (e.g., 2nd or 3rd degree AV heart block in the absence of a pacemaker).
- Severe aortic stenosis (i.e., gradients > 50 mmHg or aortic valve area < 0.85 cm²).
- Resting heart rate less than 60 beats/minute or a systolic blood pressure less than 100 mmHg.
- Symptoms of heart failure or an ejection fraction < 35%.
- Evidence of pulmonary edema.
- Evidence of right ventricular dysfunction (greater than moderate)

Yes one or more
are met

Page Cardiology
Fellow

No criteria are meet

Step 3. Evaluate for relative contraindications

Yes one or more is met

1. Severe COPD
2. Severe reactive airway disease
3. Pulmonary hypertension

Consider lower dose of metoprolol
or esmolol (refer to pre operative
order set)

No criteria are meet

Refer to Pre/Post-operative beta blocker order set

5 Commandments for using beta-blocker prophylaxis for QI or P4P

- I. Thou shalt only use Class I indicators to judge deficiency
 - Continuation in Pts taking β -blockers for angina, arrhythmias, hypertension, or other ACC/AHA Class I guidelines
 - Initiation in vascular surgery Pts at high cardiac risk as judged by finding ischemia on pre-op testing
- Corollary A: If you don't want to be deficient, be conservative about pre-op testing in vascular surgical patients
- Corollary B: Corollary A will work better if you have a low threshold for pre-op β -blockers in leg revasc.

5 Commandments for β -blocker prophylaxis – (cont.)

- II. Thou shalt not penalize a physician for failing to implement indicated β -blockers prior to the day of surgery
 - It's likely best to initiate blockade at least several days pre-op, but the jury is out

5 Commandments for β -blocker prophylaxis – (cont.)

- III. Thou shalt not give demerits for prophylactic β -blockers unless used for a Class III “indication”
 - Pts who have contraindications to β -blockers
 - This leaves room for judgment in Class IIa indications: Vasc surg plus stable CAD, Vasc surg plus multiple risk factors, Intermediate or high risk surgery plus multiple risk factors

5 Commandments for β -blocker prophylaxis – (cont.)

- IV. Thou shalt not penalize a physician for failing to reach a target pre-op HR (e.g., <60) when (indicated) β -blockers are used
 - It's probably good to reach a target resting HR, and 60 is as good as any, but it's only substantiated by one controversial study
 - It's probably MORE IMPORTANT to avoid perioperative tachycardia (HR >90 in Pts with CAD or strong CAD risk factors). If Pt cardiac stress tested: avoid ischemic threshold

5 Commandments for β -blocker prophylaxis – (cont.)

- V. Thou shalt neither honor nor condemn physicians who use prophylactic β -blockers for Class IIb indications:
 - Intermediate or high-risk procedures with a single clinical risk factor
 - Vascular surgery Pts with low cardiac risk who are not taking β -blockers chronically

Poor man's approach to Prophylactic Peri-op Beta-blockade

- Vascular surgery below the diaphragm unless there's a contra-indication
- Symptomatic CAD unless there's a contra-indication

Poor Man's Approach – cont.

How to do it

- Ideally start at least several days pre-op
 - Atenolol better than metoprolol? Maybe
- Continue peri-operatively with IV/PO as appropriate, monitor VS and keep max HR < 90 (80?)
- Continue post-op for at least a week unless resting HR drops below 50

Reduced myocardial ischemia and/or Enzyme release: ***Good enough for me***

- True: Most perioperative ischemia doesn't lead to MI, VT/fib, CHF
- Yet most periop MI is preceded by sustained ischemia – the link will eventually emerge
- So: oversensitive marker that has a low Positive Predictive Value, but it identifies a group at increased risk that probably benefits from β -blockade

Q: Why worry about myocardial O₂ supply/demand when 50% of MIs are unrelated to it?

A: Because 50% of them ARE

ACC/AHA Risk Factors

Quality of Evidence

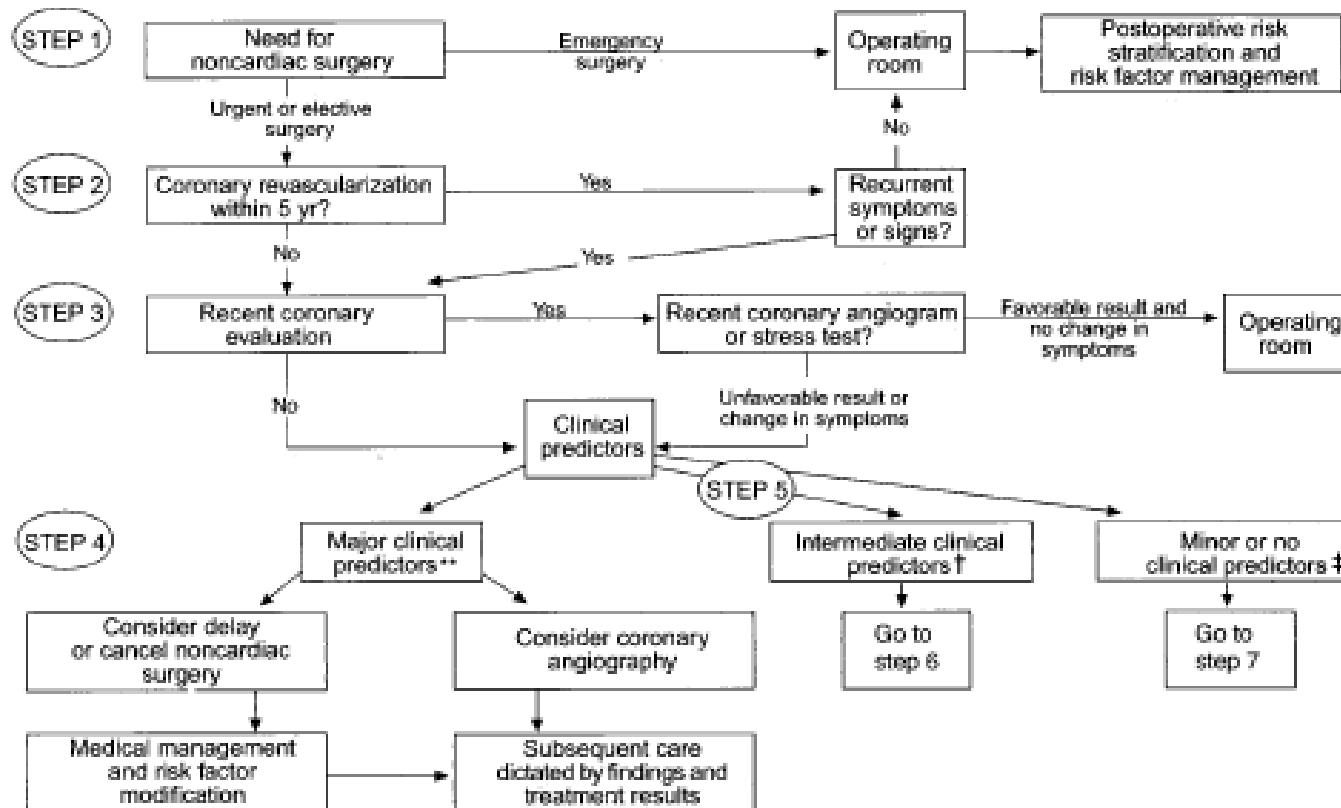
- Level A: Multiple (3-5) population risk strata evaluated, multiple randomized trials, general consistency of direction and magnitude of effect
- Level B: Limited (2-3) population risk strata evaluated, single rand. trial or non-randomized trials
- Level C: Very limited (1-2) population risk strata evaluated, consensus of experts or case studies

Strength of Recommendation

- Class I: Strong evidence of usefulness and efficacy, benefit >>risk (do it)
- Class II: Conflicting evidence
 - IIA: Weight of evidence favors (reasonable)
 - IIB: Less well established (consider it)
- Class III: Evidence/general agreement for lack of usefulness/efficacy, possibility for harm (don't do it)

ACC/AHA Preoperative Cardiac Predictors: Major

- Unstable coronary syndromes/
 - Acute/recent MI (<30 d), unstable/severe ang
- Decompensated heart failure
- Significant arrhythmias
 - Hi grade AVB, Sx vent arrhyth w/ heart Dz, SV arrhyth w/ uncontrolled vent. rate
- Severe valvular disease



Major Clinical Predictors **

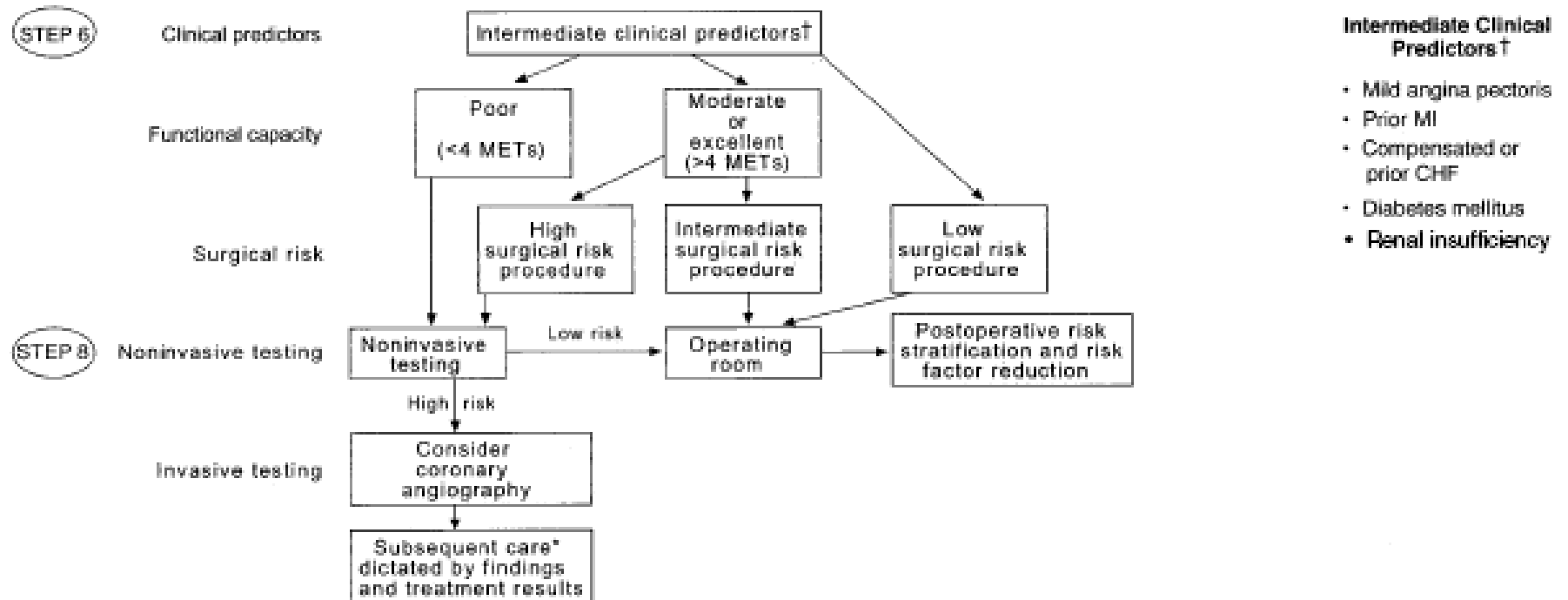
- Unstable coronary syndromes
- Decompensated CHF
- Significant arrhythmias
- Severe valvular disease

ACC/AHA Cardiac Predictors: Intermediate

- Mild angina pectoris
- Previous MI by Hx or Q waves
- Compensated or prior CHF
- Diabetes mellitus (espec Insulin-dependent)
- Renal insufficiency (Cr > 2.0 for sure, maybe > 1.4)

Cardiac Risk by Surgical Procedure: High Risk (>5%)

- Emergencies
- Aortic and “other major vascular”
- Peripheral vascular surgery
- Anticipated prolonged surgery with large fluid shifts and/or blood loss



ACC/AHA Cardiac Predictors: Minor

-“unproven to independently increase cardiac risk”

- Advanced Age
- Abnormal ECG (LVH, LBBB, ST-T changes)
- Rhythm other than sinus
- Low functional capacity (gen < 4 mets)
- Hx of stroke
- Uncontrolled systemic hypertension

Cardiac Risk by Surgical Procedure: Intermediate (1-5%)

- Carotid endarterectomy
- Head and neck
- Intraperitoneal or intrathoracic (intermediate?)
- Orthopedic (joints vs ditzels)
- Prostate (TURP vs open vs robotic)

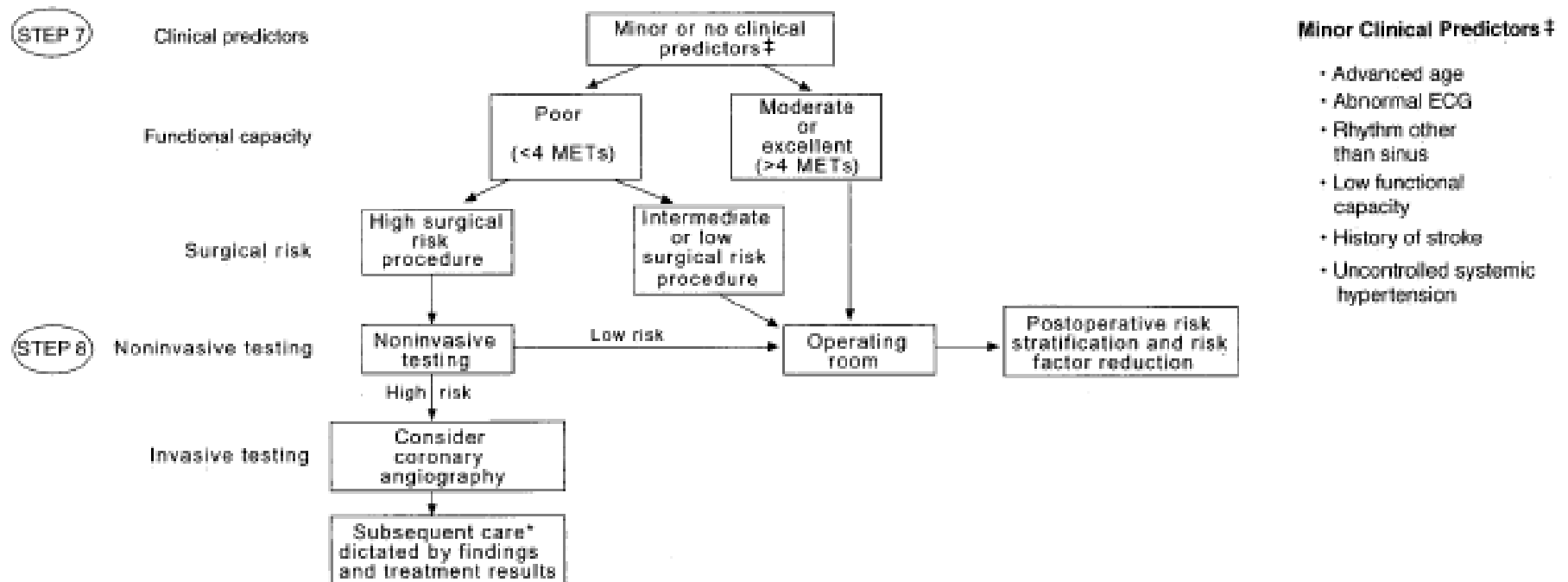
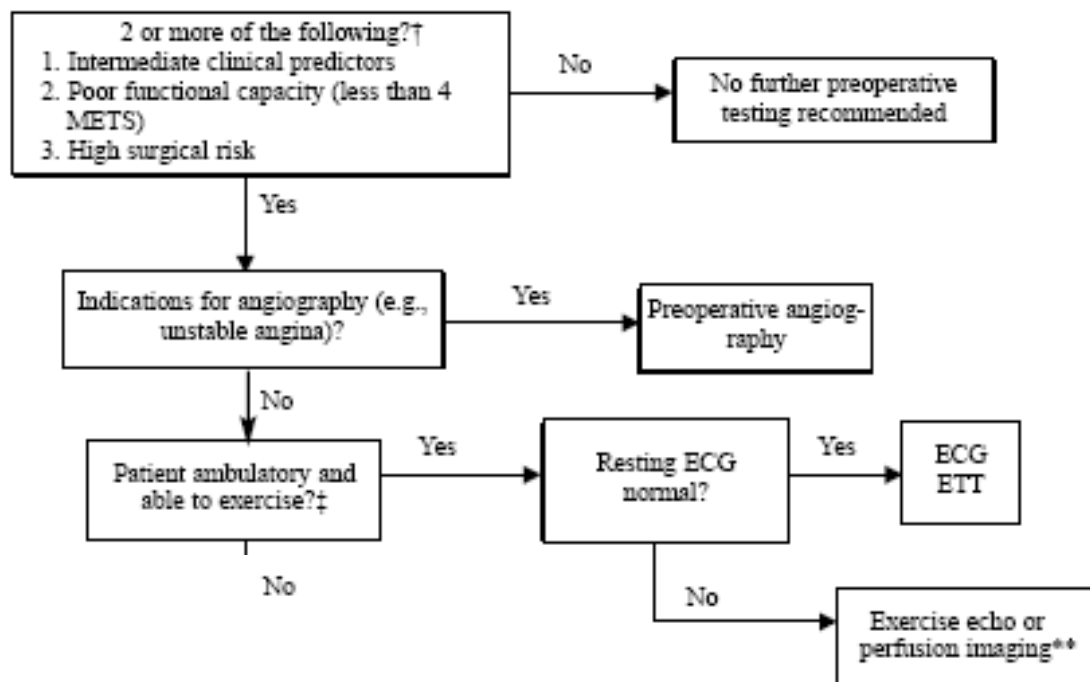


Figure 1. Stepwise approach to preoperative cardiac assessment. Steps are discussed in text. *Subsequent care may include cancellation or delay of surgery; coronary revascularization followed by noncardiac surgery, or intensified care. CHF indicates congestive heart failure; ECG, electrocardiogram; MET, metabolic equivalent; MI, myocardial infarction.



*Testing is only indicated if the results will impact care.

[†]See Table 1 for the list of intermediate clinical predictors, Table 2 for the metabolic equivalents, and Table 3 for the definition of high-risk surgical procedure.

[‡]Able to achieve more than or equal to 85% MPPHR.

**In the presence of LBBB, vasodilator perfusion imaging is preferred.

See next slide

From previous slide

No

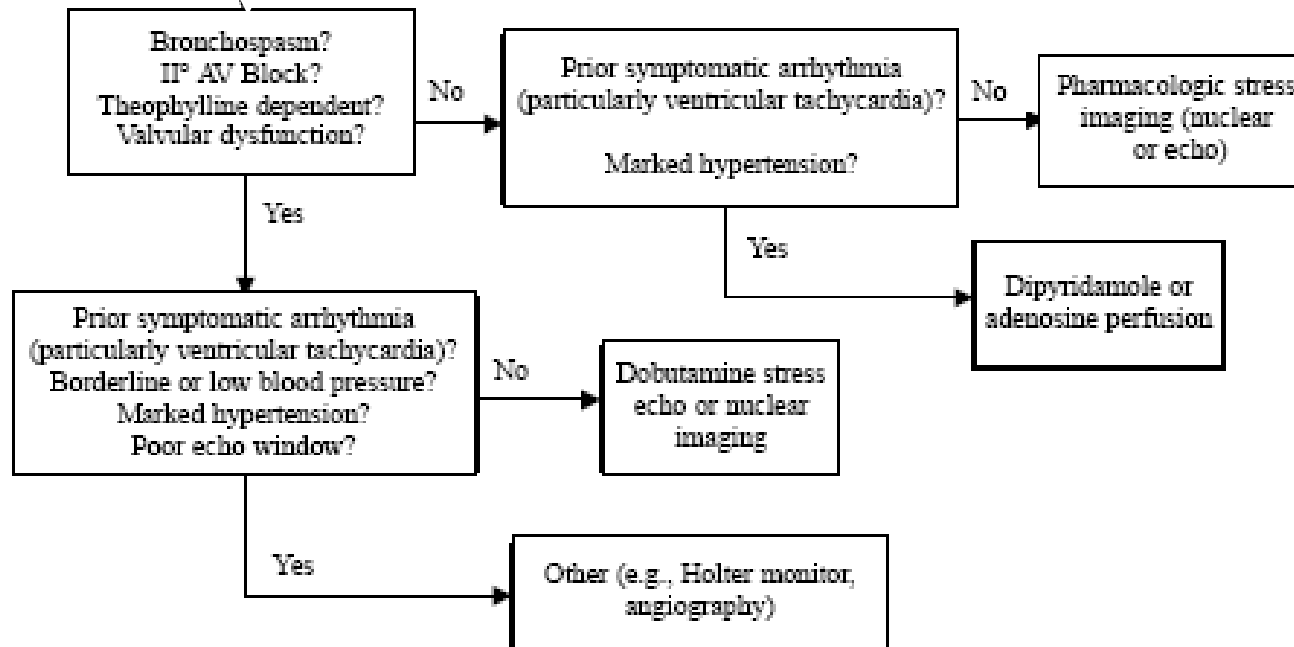


Figure 3. Supplemental Preoperative Evaluation: When and Which Test. Testing is only indicated if the results will impact care.

Cardiac Risk by Surgical Procedure: Low (<1%)

- Endoscopic (covers a lot of ground)
- Superficial
- Cataract
- Breast

Future Issues

Future Issues

- 2 large randomized trials are underway
- Genetic polymorphisms may play an increasing role
- Is there a role for statins?

Reduced myocardial ischemia and/or Enzyme release: ***Good enough for me***

- True: Most perioperative ischemia doesn't lead to MI, VT/fib, CHF
- Yet most periop MI is preceded by sustained ischemia – the link will eventually emerge
- So: oversensitive marker that has a low Positive Predictive Value, but it identifies a group at increased risk that probably benefits from β -blockade

Poor man's approach to Prophylactic Peri-operative Beta-blockade

Give Beta-blockers in the following clinical settings:

- [Assuming no contraindication]
- Vascular surgery below the diaphragm
- Symptomatic CAD

Does the specific B-blocker matter?

- One study suggests that metoprolol is too short-acting: tendency for “valleys” to reduce blockade efficacy vs atenolol
- Overall, no evidence of outcome superiority of one B-blocker over another

Further studies from the Poldermans group (Rotterdam)

- Common themes: high risk Pts, long β -blocker window (30 pre-, 60 post-), low target HR
- 2006: N=511, major vascular with LVEF < 30%, dobutamine stress echo, retrospective, hence some Pts without β -blockers
 - β -blockers reduced risk-adjusted in-hospital and long-term mortality (median F.U. of 7 years)
 - Feringa HHH, Eur J Vasc Endovasc Surg 2006; 31: 351-8