Peri-Operative Management of Hypertension:

An Internist's Perspective

William J. Elliott, M.D., Ph.D

14 OCT 17

Presenter Disclosure Information

William J. Elliott, M.D., Ph.D.

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DISCLOSURE INFORMATION:

Dr. Elliott has received research funding, honoraria, and/or travel expenses from essentially **every** pharmaceutical company that makes, markets, or distributes antihypertensive drugs in the United States (but none in the last 12 months). A former full-time employee of RUSH Medical College, he was prohibited from (and still does not) own individual stocks or financial instruments related to healthcare.

Affidavit of Originality

- The following material is based exclusively on the speaker's own opinion, knowledge and expertise.
- There is no organization, company, or entity that has exercised any control or influence over the content of this presentation, nor has any other person or organization had any part in drafting, scripting or designing its content.
- The information presented is based on the principles of "Evidence-Based Medicine," and is intended to avoid promotion of any specific commercial interest, product, or company.

"Off-Label Use" Disclaimer

WARNING!

During this discussion, attempts will be made to avoid discussion of "off-label" or investigational uses of medicines or devices not yet approved by the US FDA, but very few antihypertensive medicines or devices have been specifically approved for use in the peri-operative period.

DISCLAIMER:

The audience member should interpret each example and every statement in the context of the "local standard of care" regarding medical practice, and judge each allegation regarding drug therapy within the standards approved by the most current product information for each marketed agent, as reflected in the most recent FDA-approved package insert. The speaker assumes no liability for any erroneous interpretation of the information contained herein, stated or implied.

More Disclaimers

- The speaker has participated (with known experts in the field) in writing a "Scientific Statement" from the American Heart Association on the topic of "Treatment of Hypertension in Patients with Coronary Heart Disease." This presentation does **NOT** reflect opinion, consensus, or recommendations from the American Heart Association.
- The speaker currently serves as the Chair of the Continuing Education Committee and on the Education Committee of the American Society of Hypertension, which may be involved in reconciling US hypertension guidelines in the next few months. This process is embargoed, and will **not** be discussed.

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Educational Objectives

- At the end of this 35-minute presentation, the **awake** audience member should be able to:
  - Provide a plan (and appropriate justification for it), for a 68-year old man in your practice whose elective surgery was cancelled at 06:30 on the morning of his scheduled procedure, because of a blood pressure in the pre-anesthesia preparation room of 186/108 mm Hg.
  - Recommend which antihypertensive medications should be held, and which should be taken, on the morning of an elective surgical procedure.
  - Explain why the peri-operative management of hypertensive patients is now inexorably linked with concerns about ethics and scientific integrity.

BP Changes Perioperatively

- Pre-operative BP elevations occur due to:
  - Anxiety, pain, white-coat effect, medication withdrawal
  - Elevated BP ranks as the #1 or #2 reason for postponed surgery in three large series.
- Intubation and induction of anesthesia often raise BP and HR, moreso in chronically hypertensive patients.
- **Hypo**tension is a bigger problem for anesthesiologists, and is exacerbated by:
  - Anesthetic agents (esp. IV drugs)
  - Reduced sympathetic tone (after induction)
  - Blood loss, upright position, intraoperative events
- BP variability (±20%) during surgery is more extreme in chronically hypertensive patients.

J Clin Anesth. 2003;**15**:179-83; *Br J Anaesth*. 2001;**86**:789-93.

Ancients: BP & Surgical Risk

- Smithwick & Thompson, 1953: Hypertensive patients undergoing sympathectomy had 6-fold rate of major CV events, compared to normotensives.
- Lee Goldman and colleagues looked at 1001 operations and 19 post-op fatalities at the MGH in 1977; **neither** acute BP **nor** history of hypertension was a significant predictor of death.
- The National VA Surgical Quality Improvement Program examined data from 417,944 major surgical procedures from 1991-7, and found **neither** pre-op BP **nor** history of hypertension to be among the top 10 predictors of 30-day mortality or morbidity.

JAMA. 1953:**152**:1501-4; *N Engl J Med*. 1977;**297**:845-50; *Ann Surg*. 1999;**228**:491-508.

30-Day M & M Predictors in VAHS

Predictor	Mortality Rank	Morbidity Rank
Serum albumin	1	1
ASA Class	2	2
Cancer	3	
Emergent Operation	4	4
Age	5	7
BUN > 40 mg/dL	6	11
DNR in place	7	
Operative complexity	8	3
SGOT > 40 IU/mL	9	
Weight loss > 10%	10	10

Ann Surg. 1998;**228**:491-507

Hypertension in the Post-Anesthesia Care Unit

In 18,380 general surgical patients in Toronto in 1991-2:

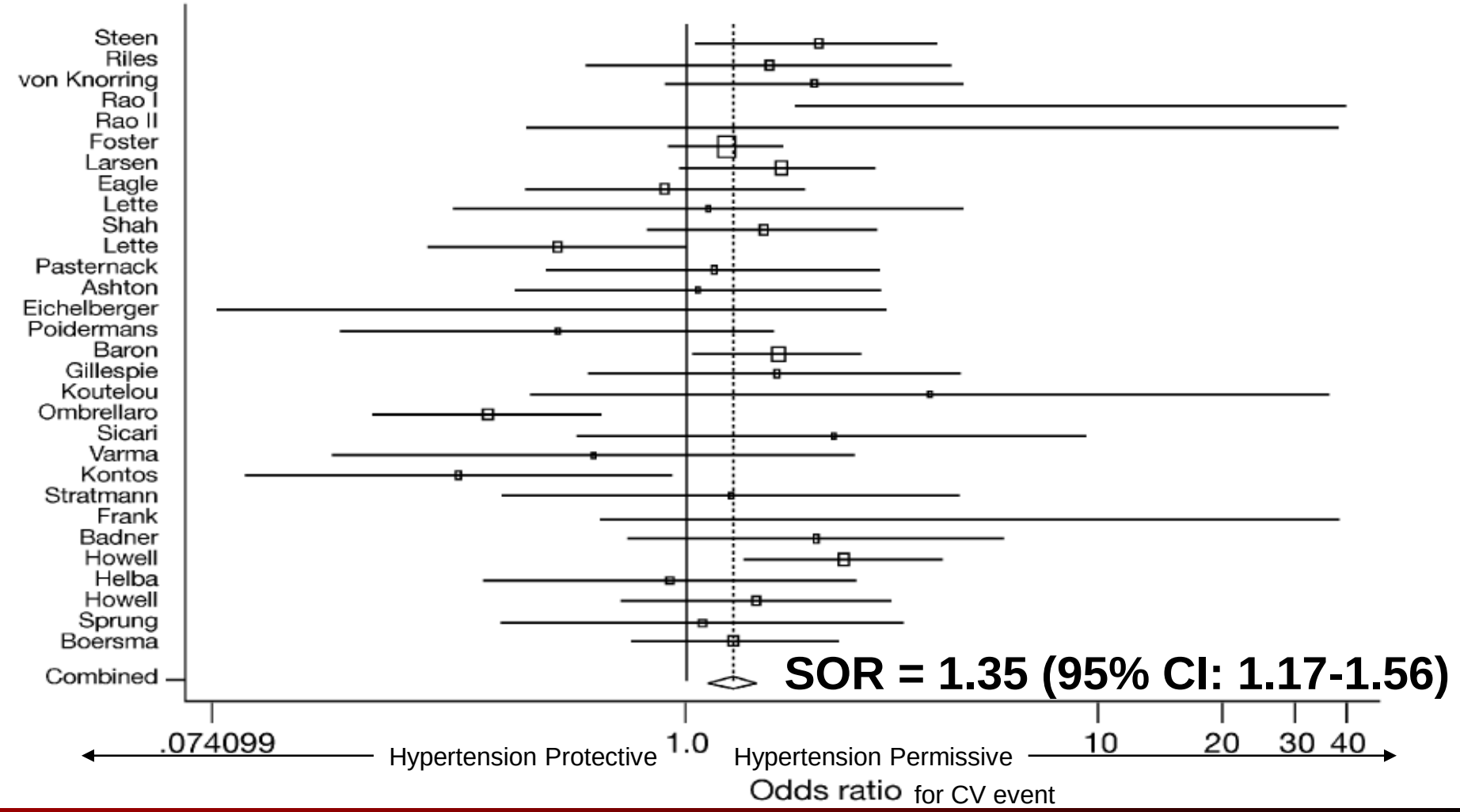
	Hypertension* In the PACU	Tachycardia# in the PACU
Prevalence	2%	0.9%
Unplanned ICU Admission	2.6% vs. 0.2%	4.0% vs. 0.2%
In-hospital mortality rate	1.9% vs. 0.3%	2.3% vs. 0.4%

*SBP > 20% higher than pre-op x 15 min, or > 50% once;
#HR > 120 bpm

Anesthesiology. 1996;**84**:772-81.

Pre-operative BP & CV Risk

30 observational studies, 13,671 patients; 1132 with CV events



Br J Anaesth. 2004;**92**:570-83.

BP and Operative Risk

- Before 2014, most guidelines considered acute hypertension (i.e., BP > **180/110** mm Hg) as only a "minor" risk factor for CV complications after non-cardiac surgery, based on observational studies.
  - As a result, elective procedures were often delayed or deferred if the pre-op BP exceeded this threshold; note that **no** evidence supports this practice.
- "Mild" hypertension (BP between 140/90 and 178/108 mm Hg) prior to anesthesia was **not** an independent risk factor for CV complications, nor was a history of hypertension.

Circulation. 2007;**116**:e418-e500.

2014 Revised Cardiac Risk Index

- **1 Point for each of the following:**
  - Chronic kidney disease (Scr ≥ 2.0 mg/dL)
  - Heart failure
  - Insulin-dependent diabetes mellitus
  - High-risk surgery (intrathoracic, intraabdominal, or suprainguinal vascular procedure)
  - History of stroke or TIA
  - Ischemic heart disease
- **If ≥ 2 points** ("elevated risk"), consider exercise or pharmacological stress testing (and then maybe revascularization, beta-blockade?)

Circulation. 2014;**130**:2215-45;
www.mdcalc.com/revised-cardiac-risk-index-for-pre-operative-risk

2014 Revised Cardiac Risk Index

- Note that hypertension (acute or chronic) is **NOT** listed among the risk factors recommended for peri-operative risk assessment.
- Note that there are **no** BP thresholds that might be used to "delay" or "postpone" surgery.
- Most authorities say we should continue to follow the 2007 guidelines, and probably cancel elective surgery if pre-op BP ≥ 180/110 mm Hg.
- *Yet hypertension is intimately involved in the pathogenesis of 5 of the 6 risk factors...*

Challenges for Evidence-Based Medicine: HTN & Peri-operative Risk

- Few studies have evaluated risk in patients with pre-op BPs between 140-179/90-109 mm Hg.
- No published evidence compared outcomes in patients with pre-op BP > 180/110 whose surgery was delayed, vs. those who underwent surgery anyway.
- Many studies of pre-op BP used a single BP measurement, under less-than-ideal conditions.
- Many studies used only surrogate markers for adverse outcomes (e.g., intra-operative EKGs).

Antihypertensive Agents in the Peri-operative Setting

Older BP Medications

- Because of unpredictable acute BP responses, current guidelines recommend AGAINST first-line, pre-operative institution of:
  - Nitroglycerin
  - Hydralazine
  - Enalapril (or enalaprilat)
  - Sodium nitroprusside (CN^-, SCN^- toxicity)
  - Clonidine (and other α_2-adrenergic agonists)
  - β-Blockers (controversial; see below)

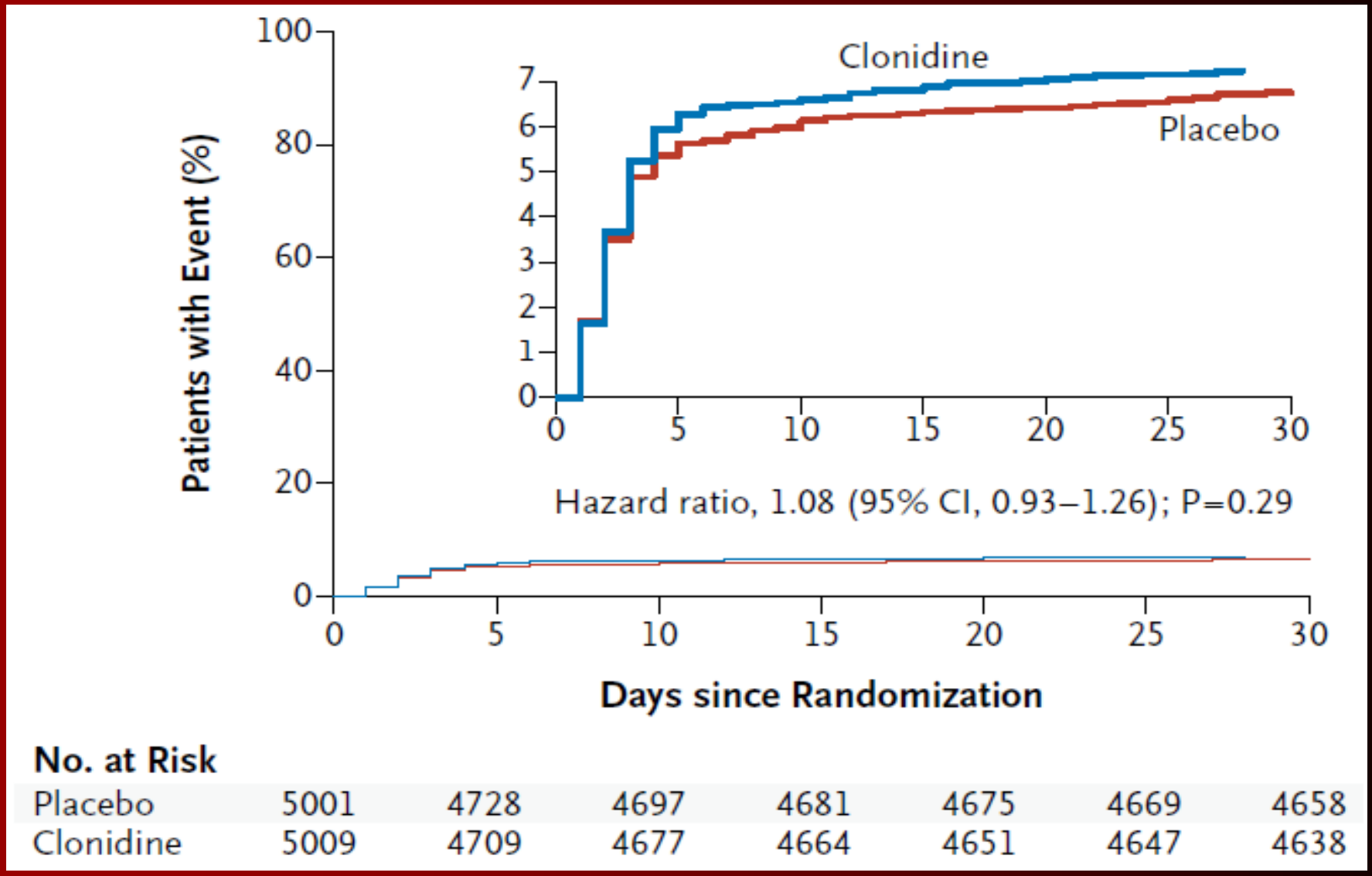
Circulation. 2014;**130**:2215-45

Pre-op Clonidine: Rationale

- Marked activation of the sympathetic nervous system occurs in the peri-operative period.
- Low-dose clonidine, which blunts central sympathetic outflow, might prevent BP surges, tachycardia, myocardial infarction and death, better than placebo?
- A double-dummy, placebo-controlled 2 x 2 factorial design clinical trial (4-6 hours before surgery: clonidine 0.2 mg po + 0.2 mg/day patch x 3 days and aspirin 200 mg x 1, then 100 mg/d for 30 days) enrolled 10,010 subjects.
- Primary outcome: death or nonfatal MI over 30 days.

N Engl J Med. 2014; **370**:1504-13.

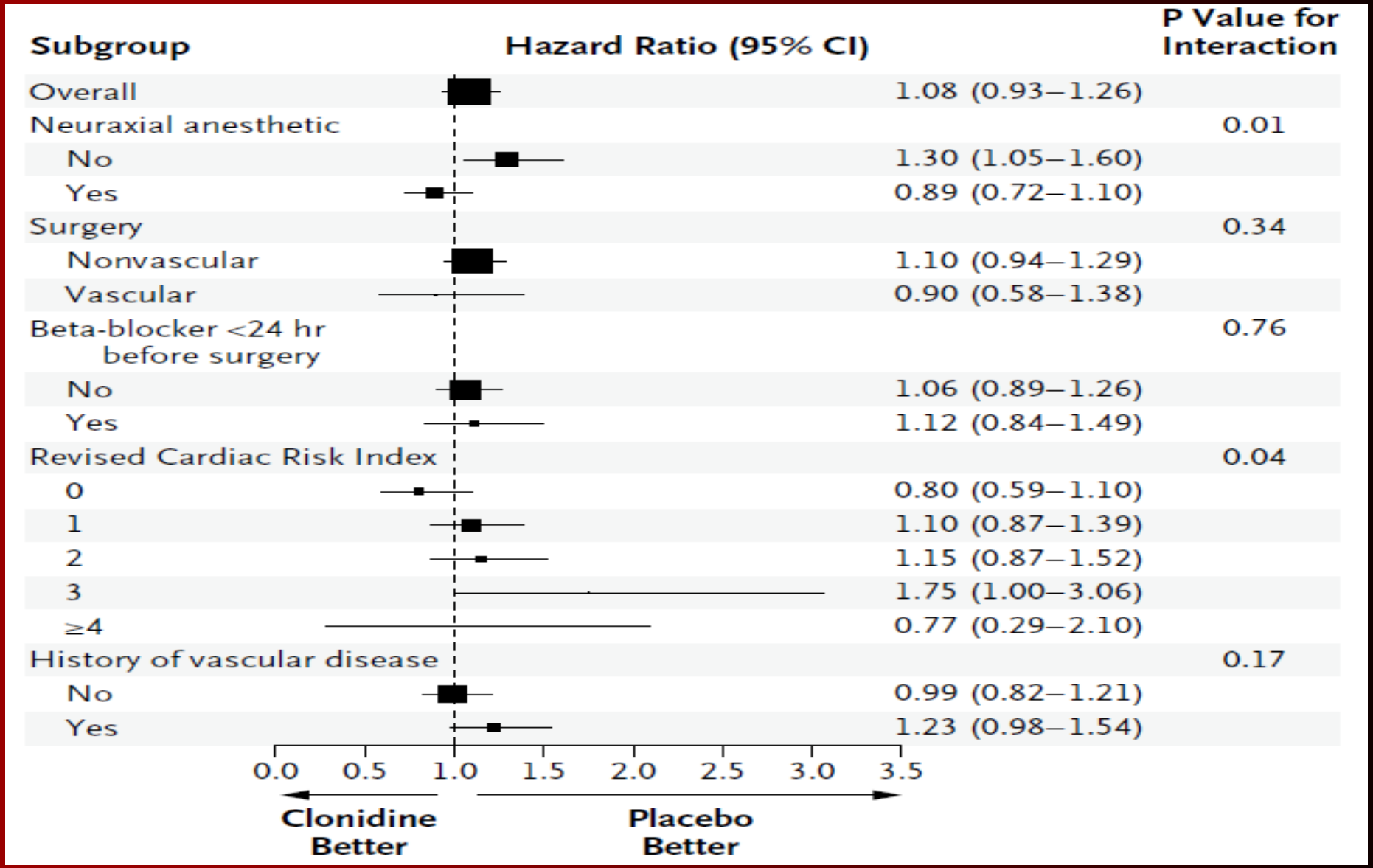
POISE-2 Kaplan-Meier Plots



No. at Risk							
Placebo	5001	4728	4697	4681	4675	4669	4658
Clonidine	5009	4709	4677	4664	4651	4647	4638

N Engl J Med. 2014; **370**:1504-13.

POISE-2 Subgroups



N Engl J Med. 2014; **370**:1504-13.

POISE-2 Endpoints

	Clonidine (n=5009)	Placebo (n=5001)	HR (95% CI)	*P* =
Death/nonfatal-MI	367	339	1.08 (0.93-1.26)	0.29
Death/CV event	380	352	1.06 (0.93-1.25)	0.30
Death	64	63	1.01 (0.72-1.44)	0.94
MI	329	295	1.11 (0.95-1.30)	0.18
Atrial fibrillation	107	96	1.11 (0.84-1.47)	0.45
Dialysis	29	23	1.26 (0.73-2.18)	0.41
Stroke	18	17	1.06 (0.54-2.05)	0.87
HYPOTENSION	2385	1854	1.32 (1.24-1.40)	0.001
BRADYCARDIA	600	403	1.49 (1.32-1.69)	0.001

N Engl J Med. 2014; **370**:1504-13.

POISE-2 Conclusions

- Neither clonidine nor aspirin reduced CV morbidity/mortality when given in the peri-operative period.
- Clonidine was associated with significantly more hypotension and bradycardia; aspirin was associated with significantly more bleeding.
- Neither clonidine nor aspirin can be routinely recommended for pre-and peri-operative reduction of CV risk in general surgery patients.

N Engl J Med. 2014; **370**:1504-13.

ACE-Inhibitors & Operative BP

- From 1984-92, at least 11 reported cases of refractory hypotension after induction of anesthesia were reported in patients taking chronic ACE-inhibitors.
- Coriat et al. therefore randomized 51 subjects to either continue or hold their chronic ACE-inhibitor on the morning of surgery.
  - 16 of 21 patients who took their ACE-inhibitor on the morning of surgery had SBP < 90 mm Hg and required IV ephedrine at induction, compared to 6 of 30 whose ACE-inhibitor was held ($P < 0.005$).

Anesthesiol. 1994;**81**:299-307.

ARBs & Intra-Operative BP

- In 1999, Brabant et al. reported that 12/12 patients treated with chronic ARBs and 18 of 27 treated with chronic ACE-inhibitors developed refractory hypotension (often requiring ephedrine and/or vasopressin), after induction of anesthesia; these were significantly higher than observations in a simultaneous cohort of patients receiving calcium antagonists, beta-blockers, or both.
- They proposed that the morning dose of an ARB or ACE-inhibitor should be held before general anesthesia, to avoid this.

Anesth Analg. 1999;**89**:1388-92.

RAS Blockers & Intra-Op BP

- In 2005, Mayo Clinic investigators studied 267 patients undergoing general surgery; 144 had induction of anesthesia < 10 hours after a dose of an ACE-I or ARB; 123 had their dose held for ≥ 10 hours before anesthesia.
- "Severe hypotension" (SBP < 65 mm Hg) was seen in 21 of 144 and 14 of 123 patients (P = 0.44).
- "Moderate hypotension" (SBP < 90 mm Hg) was seen in 87 of 144 and 57 of 123 patients (P = 0.02; Adjusted odds ratio: 1.74 [1.03-2.93]).

Anesth Analg. 2005;**100**:636-44.

Compromise: RAS Blockers?

- Several small, poorly- or uncontrolled studies have **NOT** shown an increase in perioperative hypotension when RAS blockers were given on the morning before general anesthesia.
- Several small studies have shown **NO** perioperative hypotension after local or regional anesthetics.
- Recent British guidelines say, “Primary care physicians should not try to influence the anaesthetist’s management of the perioperative patient, and anaesthetists should not diagnose or start chronic treatment of patients’ hypertension.”

Anaesthesia. 2016;**71**:326-37.

Controversy: β-Blockers

- Several meta-analyses (17 studies, 12,043 subjects) have concluded that routine β-blocker therapy given to noncardiac surgery patients, pre-and peri-operatively, significantly reduced the subsequent risk of:
  - All-cause mortality.
  - Cardiovascular events, esp. nonfatal MI **(by 31%)**
  - Atrial fibrillation.
- Why is this controversial?
  - The methods and conclusions of the three largest and most often cited trials have been challenged.

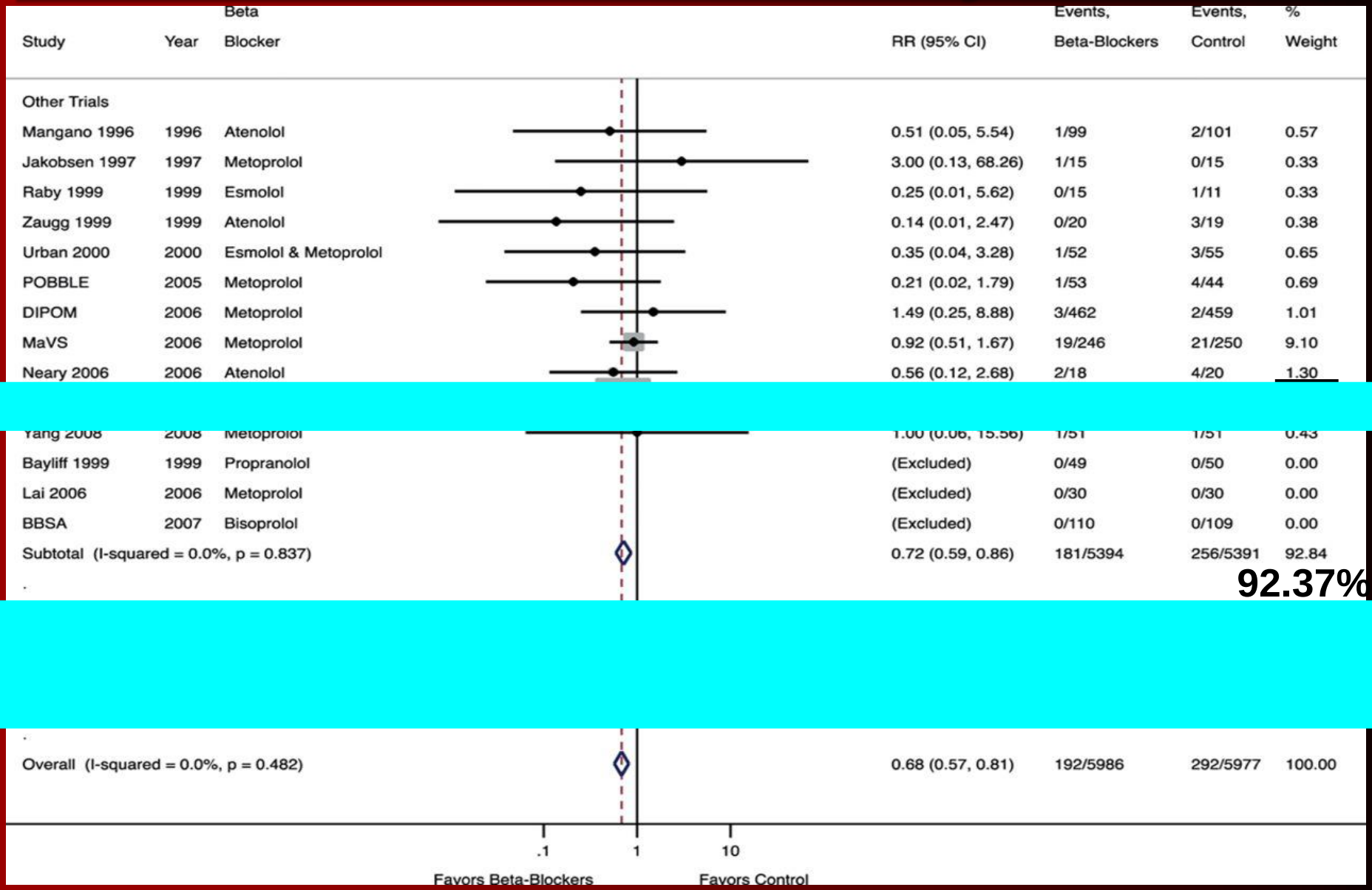
Circulation. 2014;**130**:2246-64; *J Am Coll Cardiol*. 2014;**64**:2406-25.

What Are The Concerns?

- The first author of the DECREASE family of studies resigned from the faculty of The Erasmus University after its Investigative Committee on Academic Integrity concluded that they "were unable to confirm or dispel doubts about the care with which the…study was conducted, or the study's integrity."
- The POISE-1 trial has been criticized because it started 100 mg metoprolol succinate orally, 2-4 hours prior to surgery; its results showed a 27% reduction in 30-day MI rate, but an increase in death (by 33%), stroke (by 117%), hypotension (by 55%) and bradycardia (by 174%).

Eur Heart J. 2015;**36**:633; *Am J Med*. 2012;**125**:953-5; ibid. 2013;**126**:e5-e6.

Risk of Nonfatal MI 30 Days Post-op



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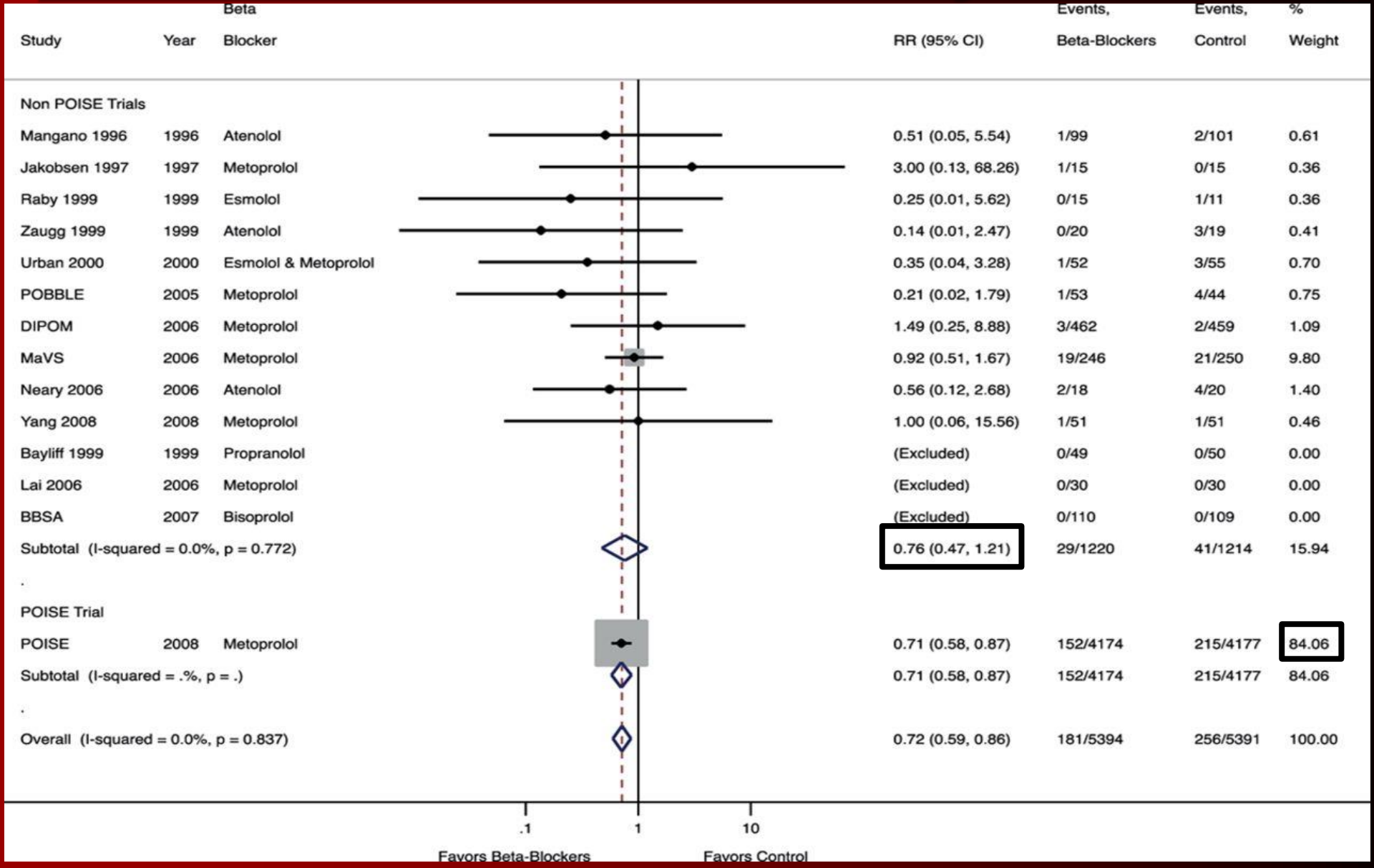


Study	Year	Beta Blocker	RR (95% CI)	Events, Beta-Blockers	Events, Control	% Weight
Non POISE Trials						
Mangano 1996	1996	Atenolol	0.51 (0.05, 5.54)	1/99	2/101	0.61
Jakobsen 1997	1997	Metoprolol	3.00 (0.13, 68.26)	1/15	0/15	0.36
Raby 1999	1999	Esmolol	0.25 (0.01, 5.62)	0/15	1/11	0.36
Zaugg 1999	1999	Atenolol	0.14 (0.01, 2.47)	0/20	3/19	0.41
Urban 2000	2000	Esmolol & Metoprolol	0.35 (0.04, 3.28)	1/52	3/55	0.70
POBBLE	2005	Metoprolol	0.21 (0.02, 1.79)	1/53	4/44	0.75
DIPOM	2006	Metoprolol	1.49 (0.25, 8.88)	3/462	2/459	1.09
MaVS	2006	Metoprolol	0.92 (0.51, 1.67)	19/246	21/250	9.80
Neary 2006	2006	Atenolol	0.56 (0.12, 2.68)	2/18	4/20	1.40
Yang 2008	2008	Metoprolol	1.00 (0.06, 15.56)	1/51	1/51	0.46
Bayliff 1999	1999	Propranolol	(Excluded)	0/49	0/50	0.00
Lai 2006	2006	Metoprolol	(Excluded)	0/30	0/30	0.00
BBSA	2007	Bisoprolol	(Excluded)	0/110	0/109	0.00
Subtotal (I-squared = 0.0%, p = 0.772)			0.76 (0.47, 1.21)	29/1220	41/1214	15.94
POISE Trial						
POISE	2008	Metoprolol	0.71 (0.58, 0.87)	152/4174	215/4177	84.06
Subtotal (I-squared = .%, p = .)			0.71 (0.58, 0.87)	152/4174	215/4177	84.06
Overall (I-squared = 0.0%, p = 0.837)			0.72 (0.59, 0.86)	181/5394	256/5391	100.00

Circulation. 2014;**130**:2246-64; *J Am Coll Cardiol*. 2014;**64**:2406-25.

Conclusions: β-Blocker Meta-Analysis

- Perioperative β-blockade started ≤ 1 day before noncardiac surgery helps to prevent nonfatal MI, but increases stroke, death, hypotension, and bradycardia.
- There are insufficient robust data on the efficacy and safety of perioperative β-blocker regimens that used agents other than metoprolol, or initiated treatment 2-45 days prior to anesthesia.

Circulation. 2014;**130**:2246-64; *J Am Coll Cardiol*. 2014;**64**:2406-25.

2014 AHA/ACCF Guidelines

- β-blockers should be continued in patients undergoing surgery who have taken them chronically. (I, B)
- It is reasonable to use clinical circumstances to guide use of β-blockers after surgery.(IIa,B)
- It may be reasonable to start perioperative β-blockers in patients with ischemia noted on pre-op evaluation. (IIb, C)
- It may be reasonable to start β-blockers before surgery for patients with ≥ 3 RCRI risk factors. (IIa, B)

Circulation. 2014;**130**:2215-45; *J Am Coll Cardiol*. 2014;**64**:e77-e137.

2014 AHA/ACCF Guidelines

- Uncertain benefits accrue after initiating β-blockers to reduce CV risk in pre-surgical patients with a compelling chronic indication for this class of drug, despite having no RCRI risk factors. (IIb, B)
- In patients in whom long-term β-blocker therapy is initiated, it may be reasonable to start the drug more than 1 day before surgery. (IIb, B)
- Starting β-blockers on the day of surgery is very likely harmful, and should **not** be done routinely. (III, B)

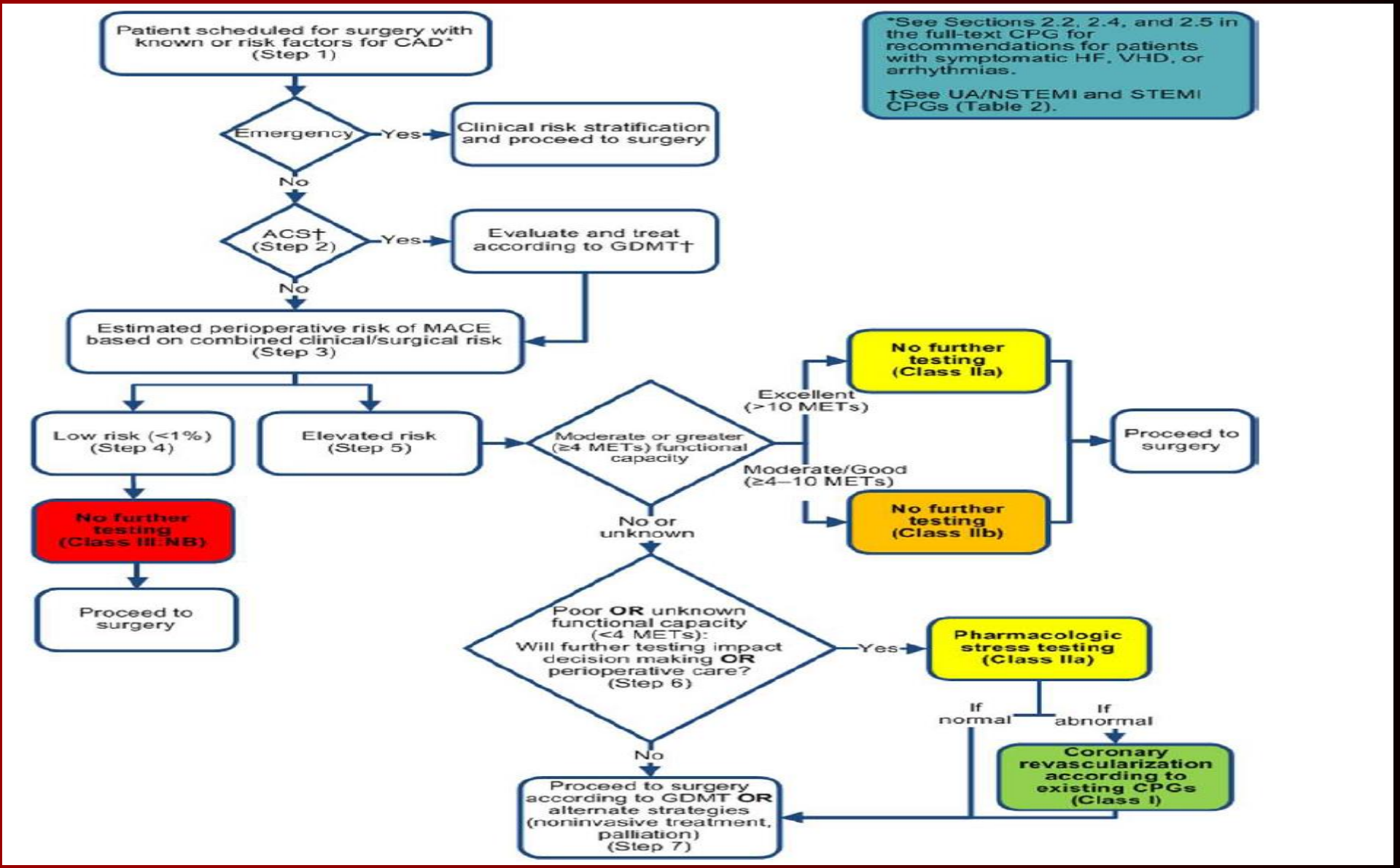
Circulation. 2014;**130**:2215-45; *J Am Coll Cardiol*. 2014;**64**:e77-e137.

AHA/ACCF Recommended Drugs?

- No specific recommendations
- Other authorities favor:
  - Clevidipine (IV)
    - Used in ECLIPSE (significantly lower mortality than nitroprusside, better “tight” BP control than either nitroglycerin or nicardipine)
  - Esmolol (IV)
  - Fenoldopam (IV)
    - No significant difference in renal outcomes during cardiac surgery
  - Metoprolol (IV, po?)

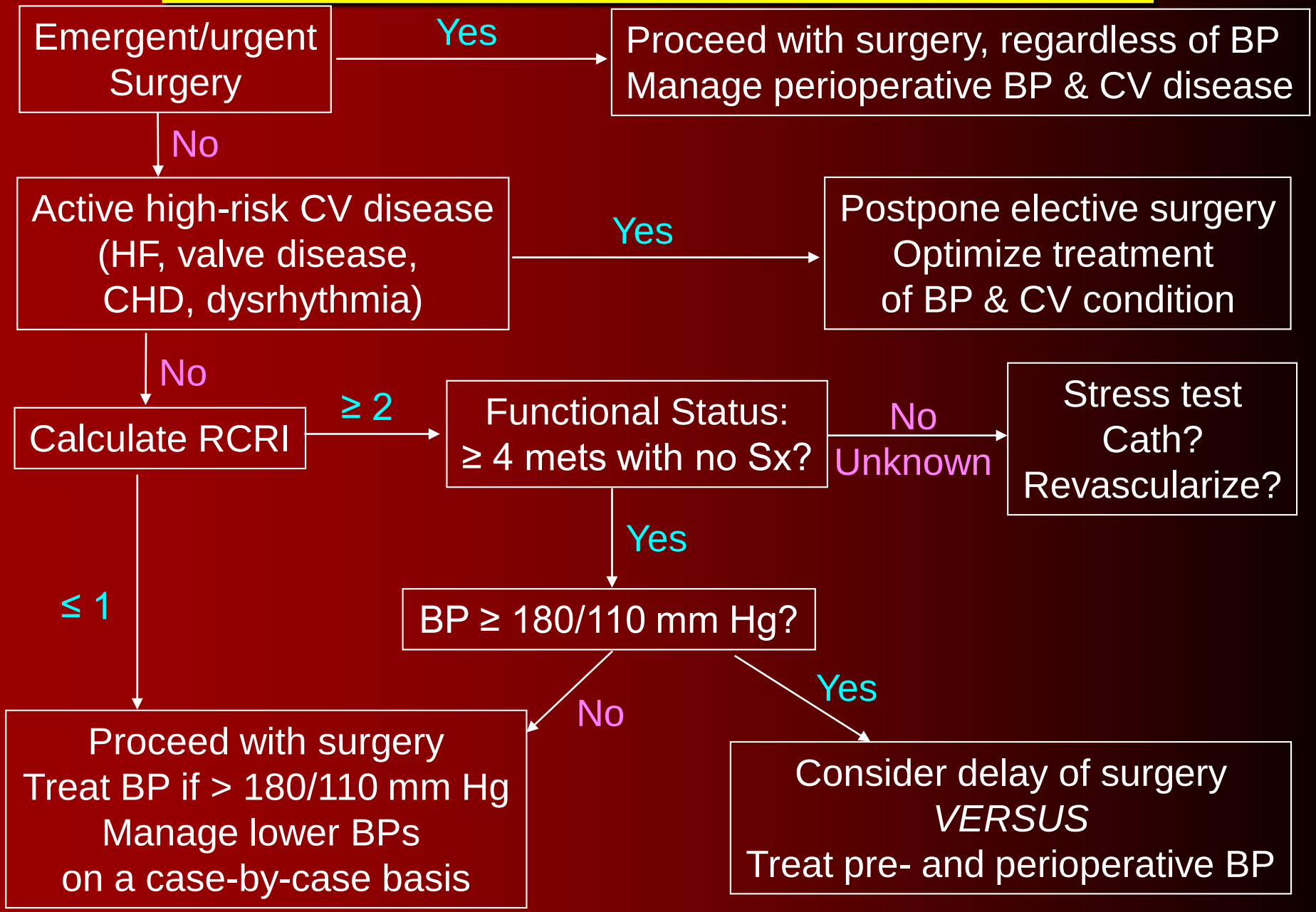
Anesth Analg. 2008;**107**:1110-21; *JAMA*. 2014;**312**:2244-53.

2014 AHA/ACCF Algorithm



Circulation. 2014;**130**:2215-45; *J Am Coll Cardiol*. 2014;**64**:e77-e137.

A Different Algorithm



Conclusions

- Delay of elective surgical procedures due to "too high" BP is common; after it happens, reconsider the timing of antihypertensive drugs, "white-coat" hypertension, and reschedule the procedure.
- Most anesthesiologists recommend taking all antihypertensive agents on the morning of scheduled surgery, except for ACE-inhibitors and ARBs, which may cause excessive hypotension after induction.
- Perioperative initiation of clonidine is not indicated; β-blockers are controversial, but generally discouraged, unless the patient has a compelling condition that should have been so treated before surgery.