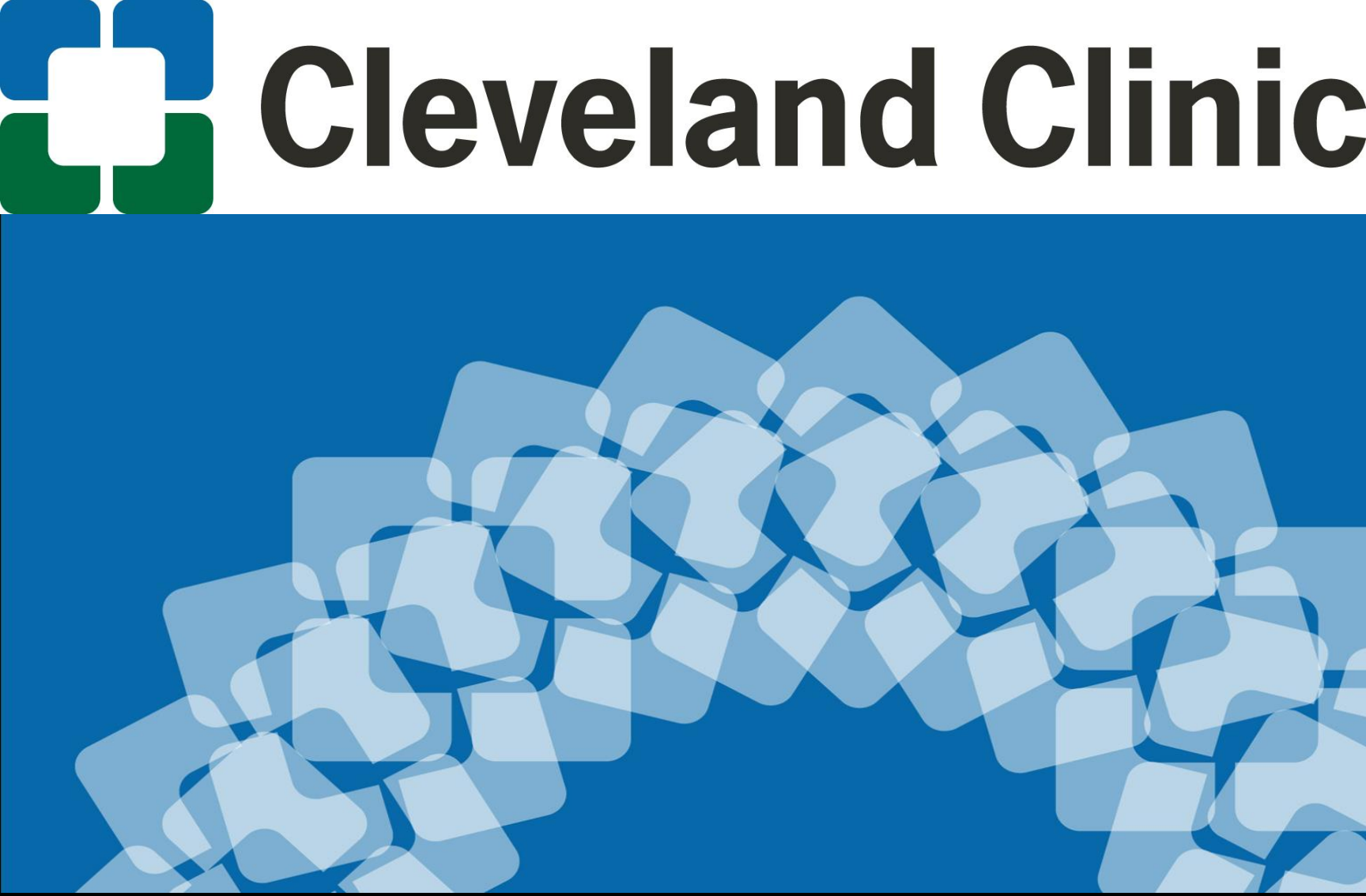

Cleveland Clinic
Department of OUTCOMES RESEARCH

# Causes of Death

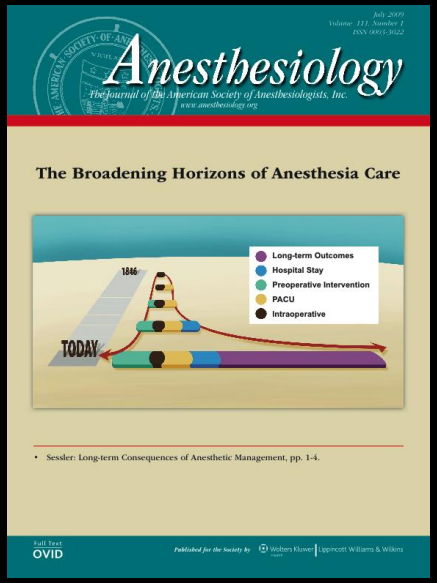
Death due to diseases of the heart *(CDC)*

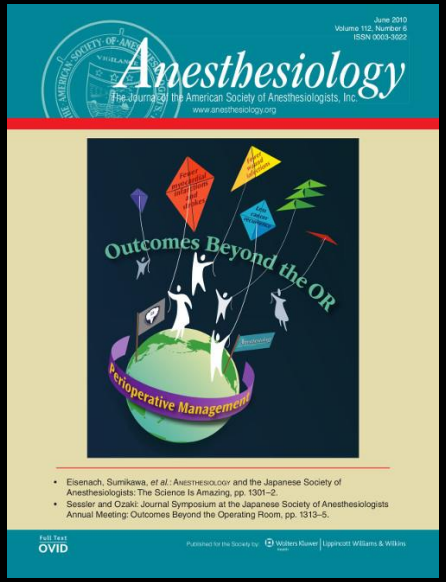
Death due to malignant neoplasms *(CDC)*

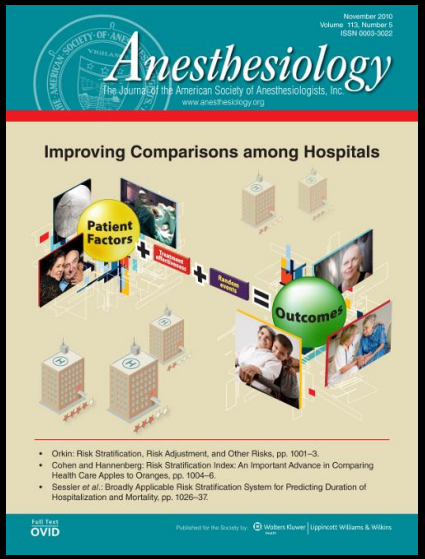
Death within 30 days of admission for surgery *(NIS)*

Death due to cerebrovascular diseases *(CDC)*

Bartels, *et al.*, 2013, Anesthesiology





Wound Infection
Cancer Recurrence
Red Cell Transfusion
Glycemic Control
Myocardial Infarction
Anesthetic Toxicity
Persistent Pain
Delirium & POCD
Mortality

# Long-term Outcomes of Anesthesia

Interventions to improve outcomes weeks, months, and years after surgery

- Blood loss and transfusion
  - Red cell storage duration
- Regional analgesia and cancer
- Perioperative myocardial injury

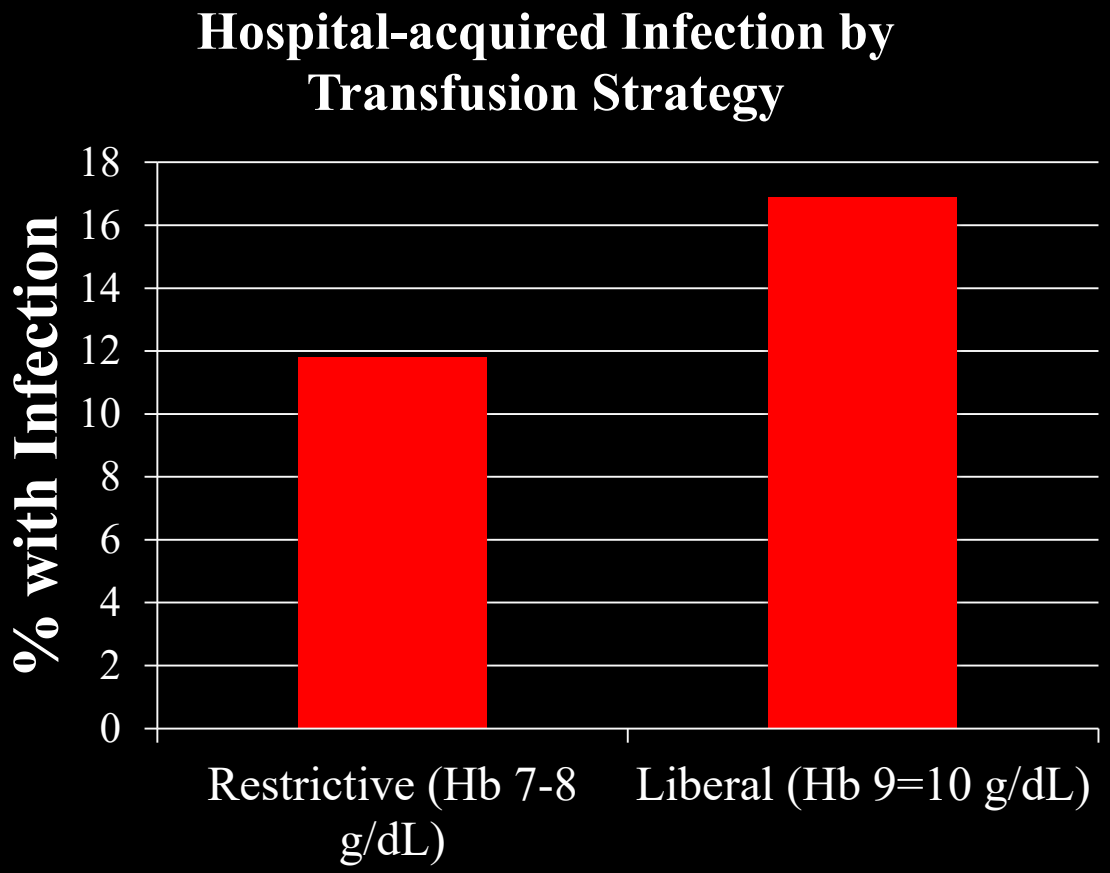
# Blood Transfusion

Transfusion can save lives
- Appropriate triggers unknown

Associated with complications
- Viral infection *not* major risk
- Most commonly transmitted infection is babesiosis

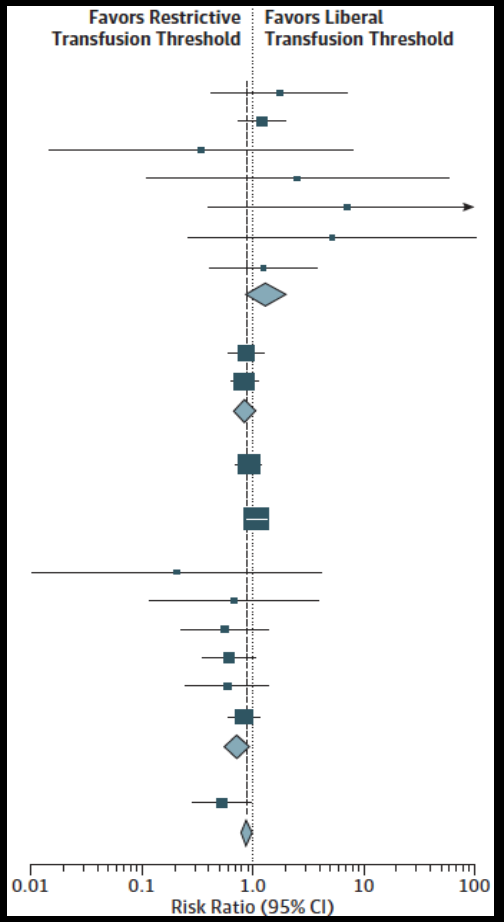
Potential risk mechanisms
- Highly immunogenic
- Nitric oxide depletion

# Randomized Trials: Infection

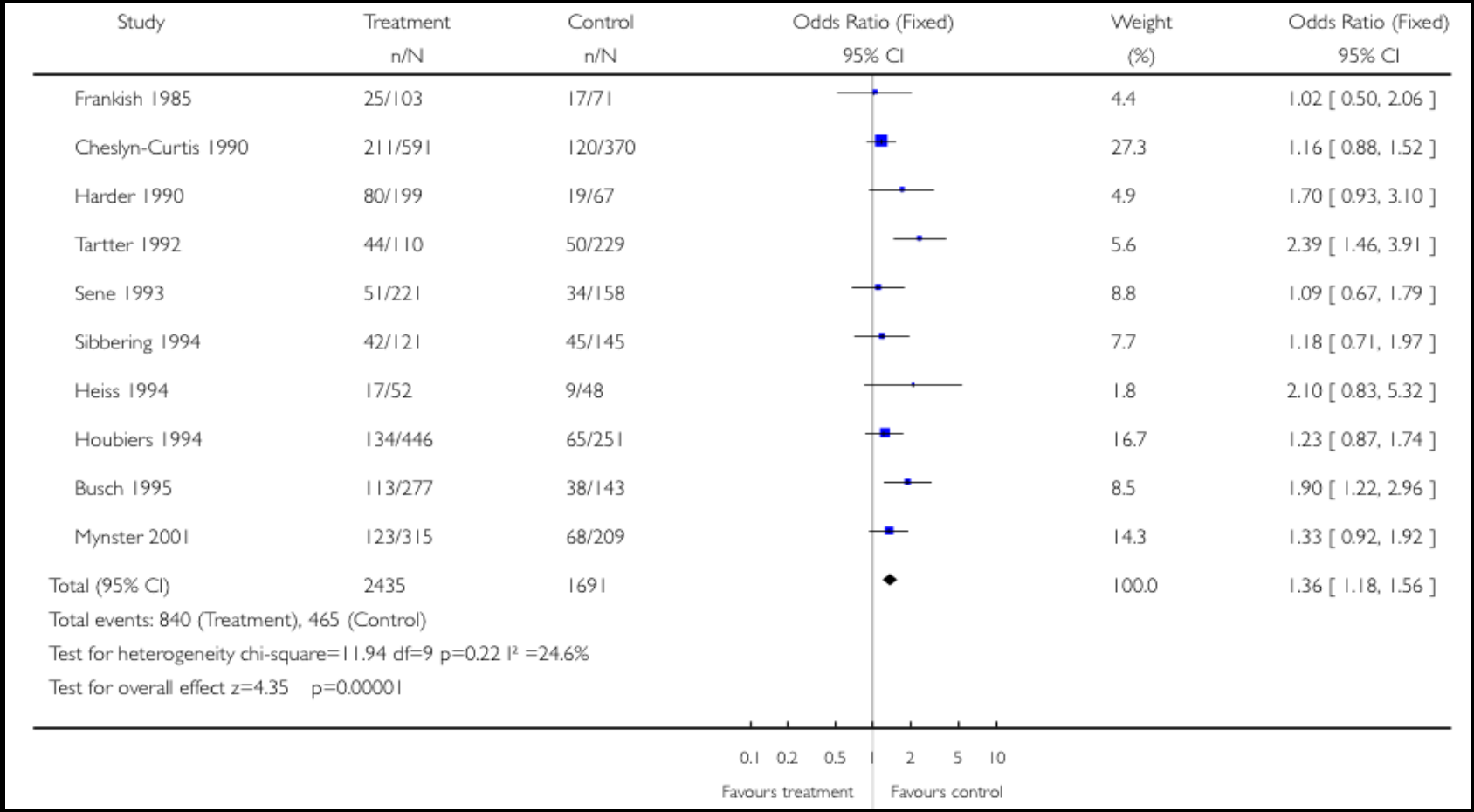



Rohde, et al, JAMA, 2014

RR = 0.82



# Randomized Trials: Cancer Recurrence



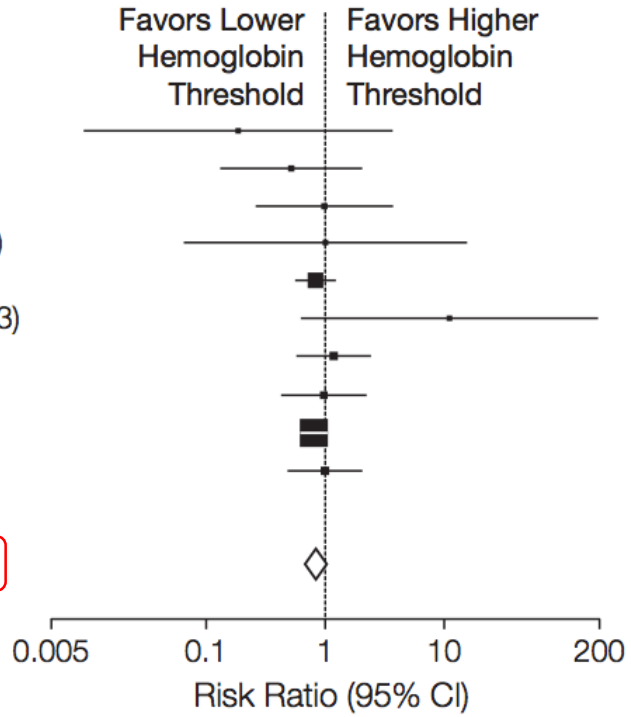

RR=1.36, P=0.03

Amato *et al*, Cochrane 2006

# Transfusion and Mortality

| Source | 30-d Mortality: Lower Hemoglobin Threshold, Events, No. | Lower Hemoglobin Threshold, Total, No. | Higher Hemoglobin Threshold, Events, No. | Higher Hemoglobin Threshold, Total, No. | Risk Ratio (95% CI) |
|---|---|---|---|---|---|
| Blair, 1986 | 0 | 26 | 2 | 24 | 0.19 (0.01-3.67) |
| Bracey, 1999 | 3 | 215 | 6 | 222 | 0.52 (0.13-2.04) |
| Bush, 1997 | 4 | 50 | 4 | 49 | 0.98 (0.26-3.70) |
| Carson, 1998 | 1 | 42 | 1 | 42 | 1.00 (0.06-15.47) |
| Carson, 2011 | 43 | 1009 | 52 | 1007 | 0.83 (0.56-1.22) |
| Foss, 2009 | 5 | 60 | 0 | 60 | 11.00 (0.62-194.63) |
| Hajjar, 2010 | 15 | 249 | 13 | 253 | 1.17 (0.57-2.41) |
| Hebert, 1995 | 8 | 33 | 9 | 36 | 0.97 (0.42-2.22) |
| Hebert, 1999 | 78 | 418 | 98 | 420 | 0.80 (0.61-1.04) |
| Lacroix, 2007 | 14 | 320 | 14 | 317 | 0.99 (0.48-2.04) |
| Lotke, 1999 | 0 | 62 | 0 | 65 | NA |
| **Overall random effects model** | | | | | **0.85 (0.70-1.03)** |

Heterogeneity: $I^2 = 0\%$
Test for overall effect: $P = .10$

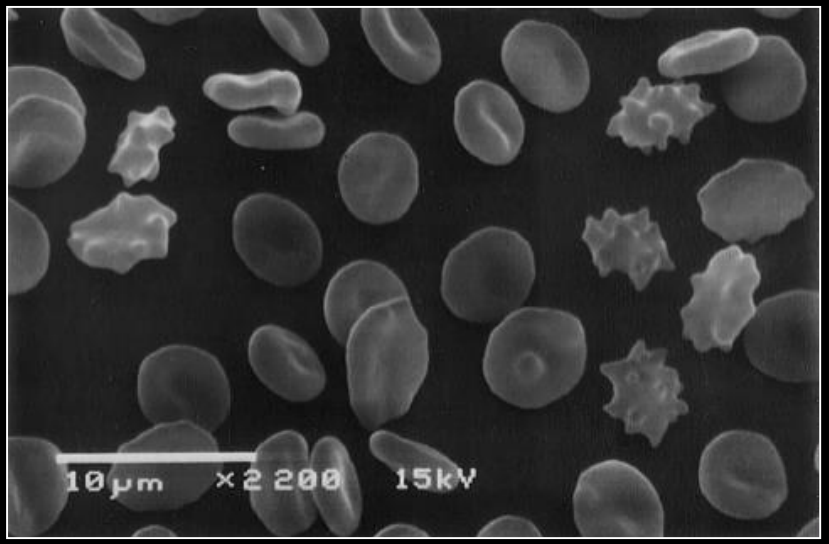



RR=0.85, $P = 0.1$

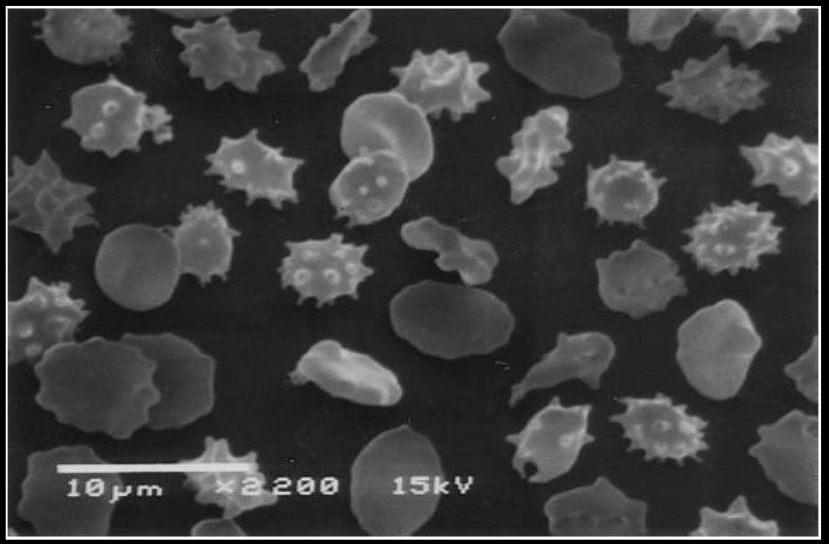
Carson, JAMA 2013

# Stored Blood Degrades Over Time

Younger blood



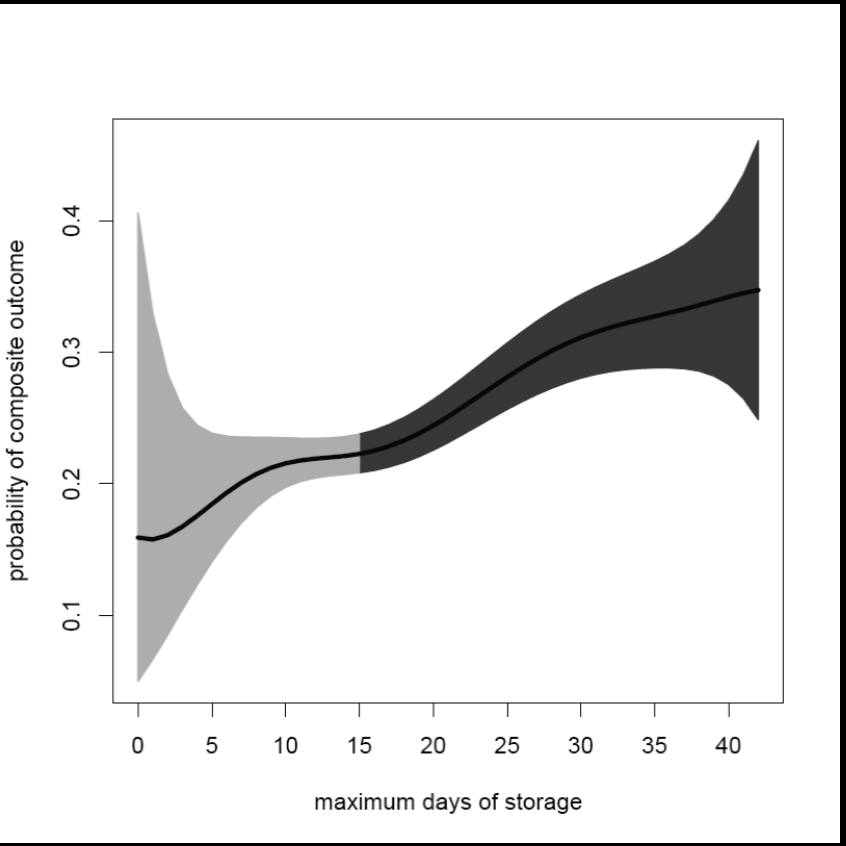

Older blood

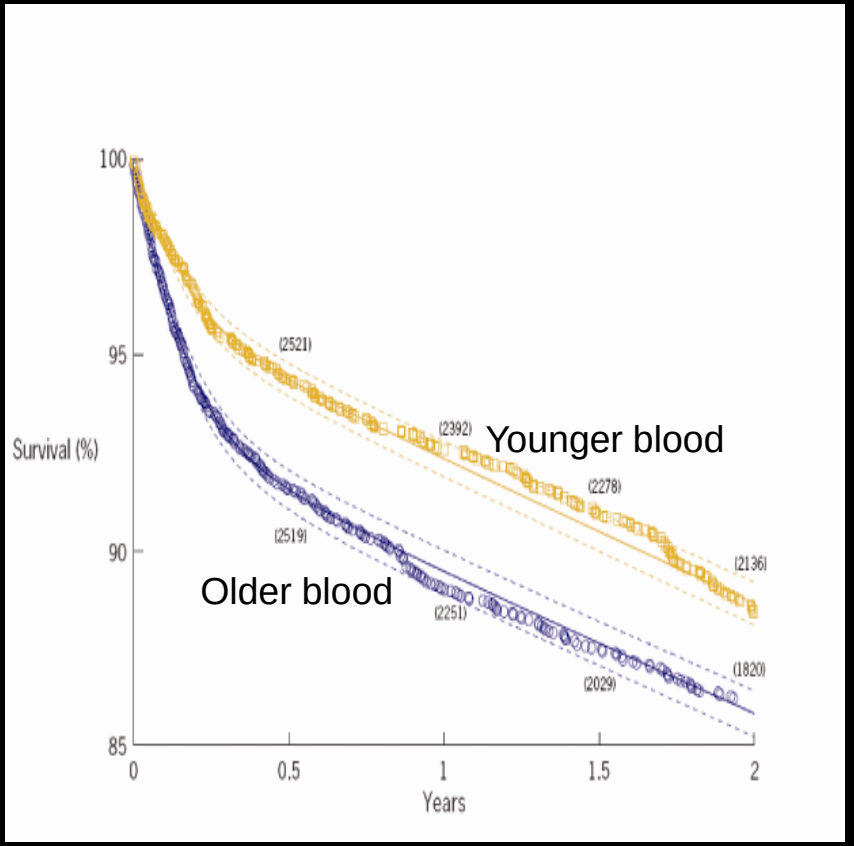



Berezina, J Surg Res, 2002

Free hemoglobin in stored blood scavenges NO, provoking systemic and pulmonary vasoconstriction

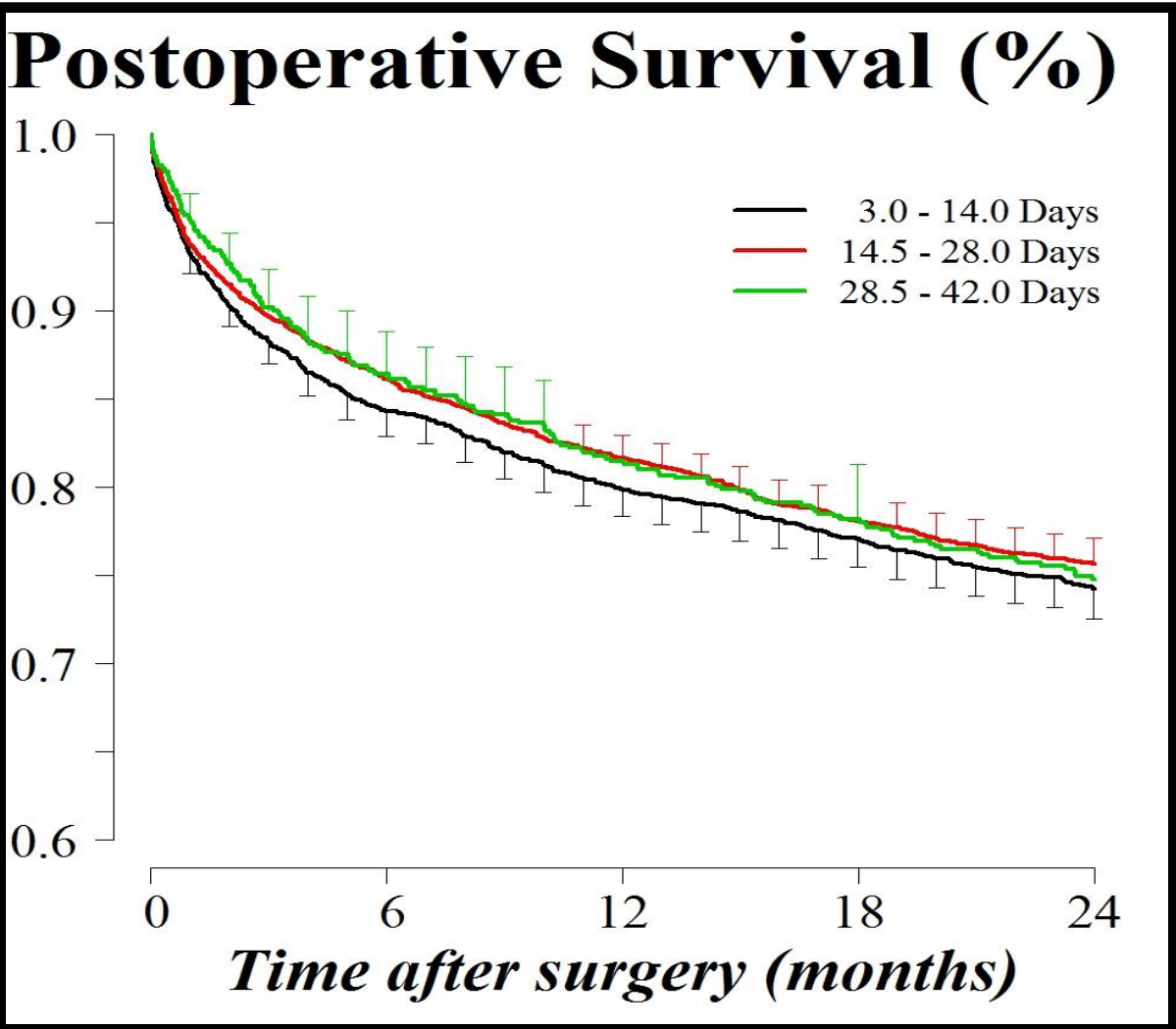
# Storage Duration and Survival



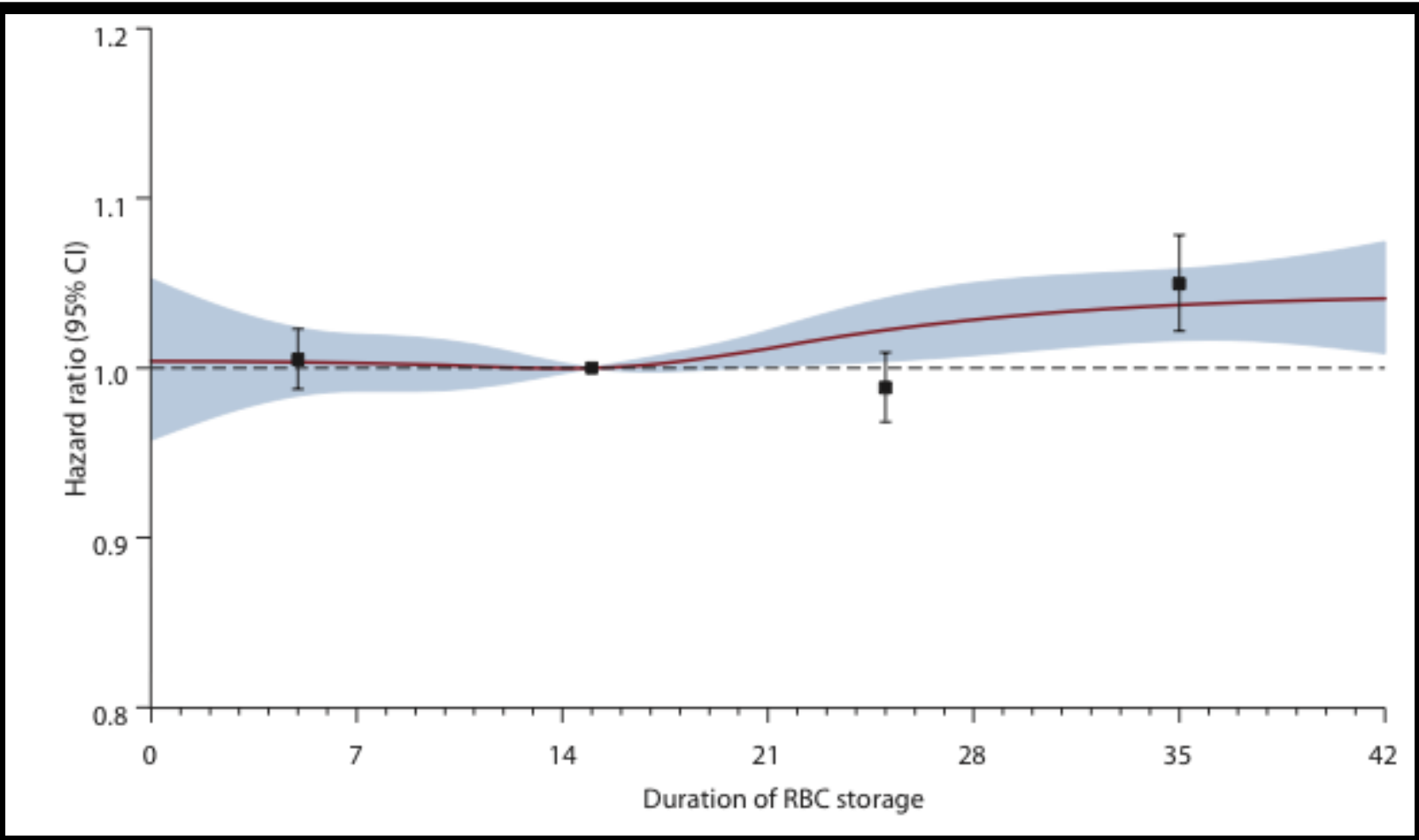




Koch, NEJM, 2008

# Storage Duration, Non-cardiac

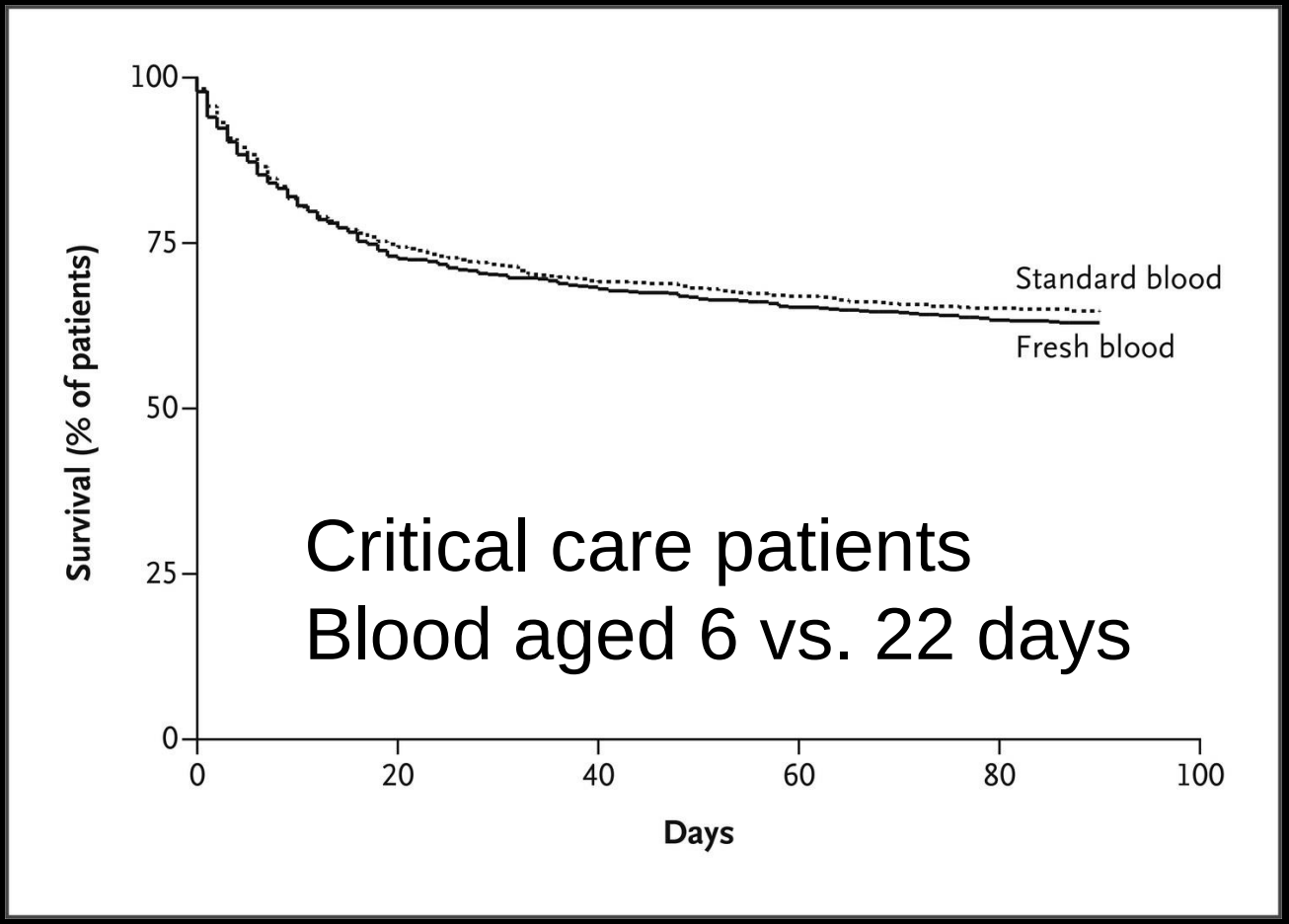


# Observational Mortality, n=380,000




Edgren, Transfusion 2011

# ABLE Trial (n=2,430)




Lacroix et al. N Engl J Med 2015

# Recess Trial (n=1,098)

| Subgroup | No. of Patients | ≤10 Days | ≥21 Days | Adjusted Between-Group Difference (95% CI) | P Value for Interaction |
|---|---|---|---|---|---|
| | | *adjusted mean ΔMODS* | | | |
| Overall | | 8.49 | 8.66 | −0.17 (−0.60 to 0.26) | |
| ABO blood group | | | | | 0.06 |
| Group O | 439 | 8.53 | 8.54 | −0.02 (−0.69 to 0.66) | |
| Group A | 475 | 8.55 | 8.87 | −0.32 (−0.97 to 0.32) | |
| Group B | 127 | 7.64 | 8.65 | −1.01 (−2.25 to 0.24) | |
| Group AB | 46 | 9.75 | 7.52 | 2.23 (0.16 to 4.31) | |
| Group O vs. other blood groups | | | | | 0.56 |
| Group O | 439 | 8.53 | 8.55 | −0.02 (−0.69 to 0.66) | |
| All non-O | 648 | 8.46 | 8.74 | −0.28 (−0.83 to 0.28) | |
| Sex | | | | | 0.87 |
| Male | 471 | 8.59 | 8.79 | −0.21 (−0.85 to 0.44) | |
| Female | 616 | 8.42 | 8.55 | −0.13 (−0.70 to 0.43) | |
| Age | | | | | 0.12 |
| ≤65 yr | 279 | 8.66 | 8.26 | 0.40 (−0.45 to 1.25) | |
| >65 yr | 808 | 8.44 | 8.81 | −0.37 (−0.87 to 0.12) | |

Cardiac surgery patients
Blood aged 7 vs. 28 days

**Steiner et al. N Engl J Med 2015**

# CCF Cardiac Surgery Trial

Randomized trial of younger *versus* older blood

Cardiac surgical patients

Target n=2,838 transfused patients

- n≈1,200 so far
- Next interim analysis at n=1,814

Primary outcome

- STS Composite of serious complications

Koch, et al.

# INFORM Trial

Randomized trial of younger *versus* older blood

Virtually all patients at five centers

- Not restricted to surgical patients

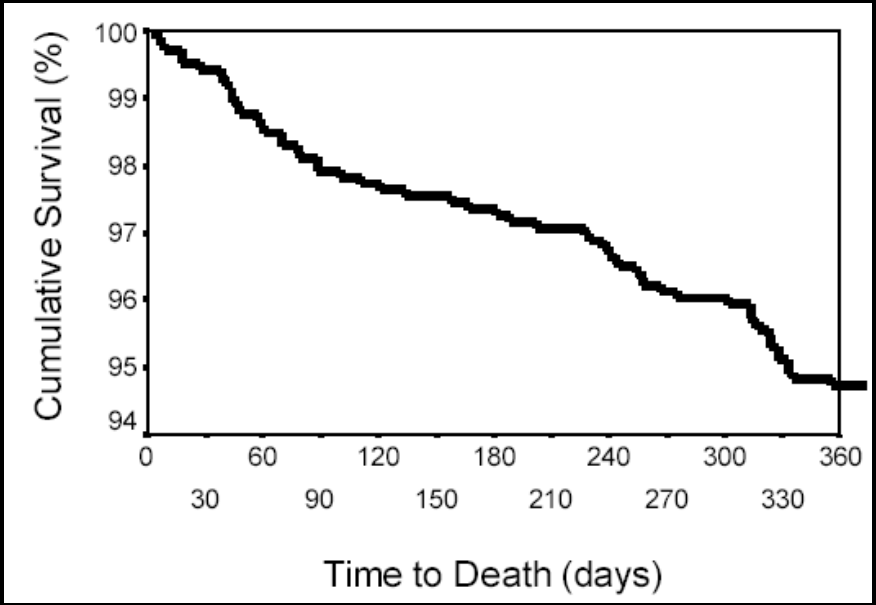
Target n=31,500 transfused patients

- >24,000 so far

Primary outcome: in-hospital mortality

Eikelboom, et al.

# Causes of Long-term Mortality




≈10% one-year mortality in patients ≥65 yrs

| *Cause of Death* | *%* |
|---|---|
| Cancer | 52% |
| Cardiovascular | 17% |
| Renal/Liver Failure | 5% |
| Respiratory Failure | 4% |
| Pulmonary Emboli | 2% |
| Sepsis/Infection | 2% |

Monk, A&A 2005

# Cancer Surgery

Cancer recurrence is usually lethal

Surgery remains primary treatment
- Releases tumor cells into blood stream
- There is *always* minimal residual disease

Natural killer (NK) cells are major defense
- Spontaneously recognize and kill tumor cells

Surgery and anesthesia impair NK Cell function
- Neuroendocrine stress response to surgery
- Volatile anesthetics
- Opioids

# Regional Analgesia Protective?

Regional anesthesia & analgesia

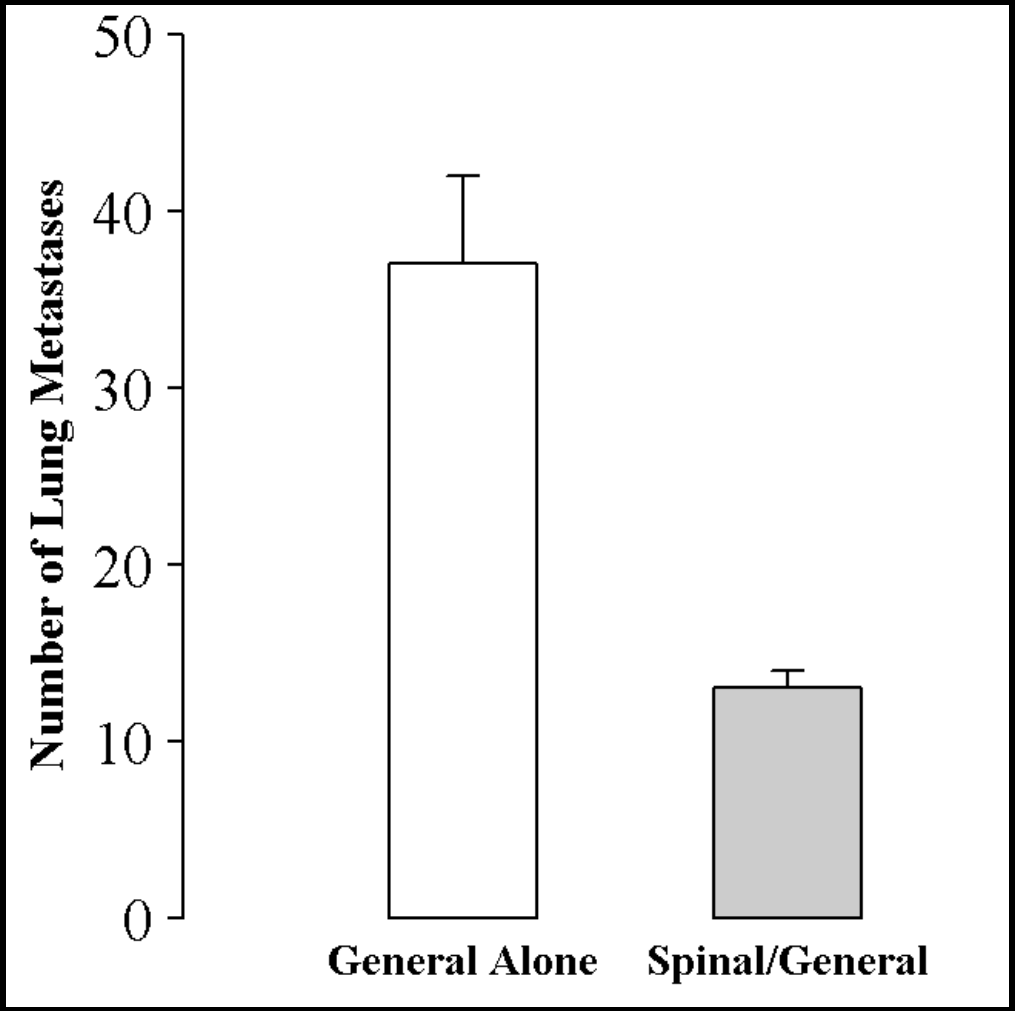
- Reduces stress response to surgery
- Reduces or eliminates general anesthetics
- Obviates need for postoperative opioids

All three help preserve NK cell function

Hypothesis:

- Regional anesthesia & analgesia reduces risk of cancer recurrence

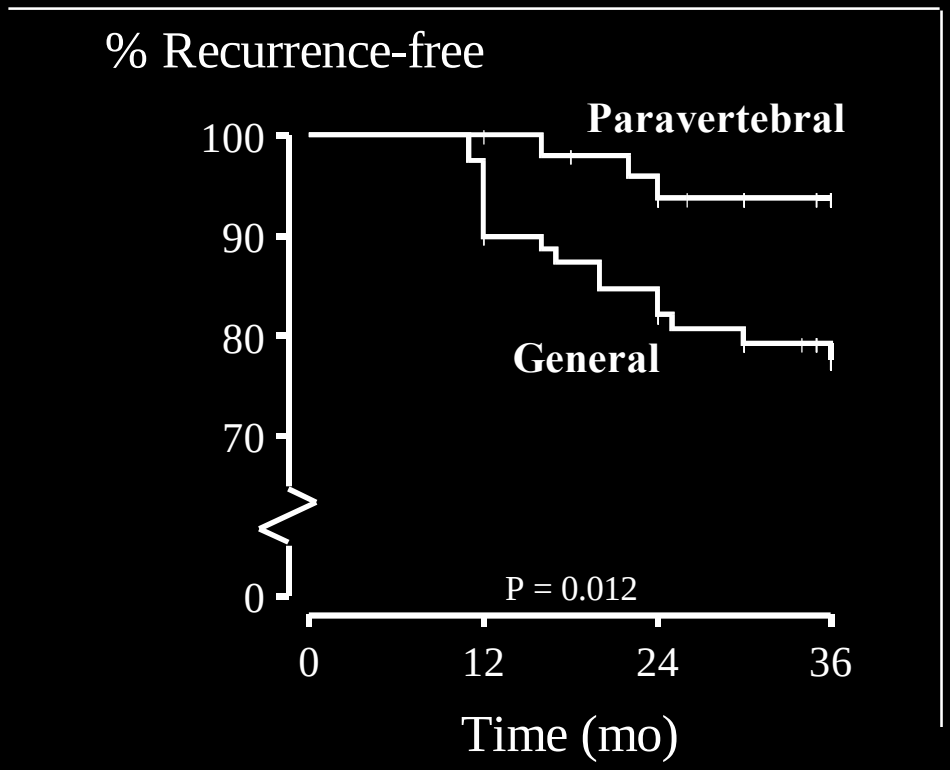
# Rats: Bar-Yusof, Anesthesiology 2001



# Paravertebrals & Breast Cancer

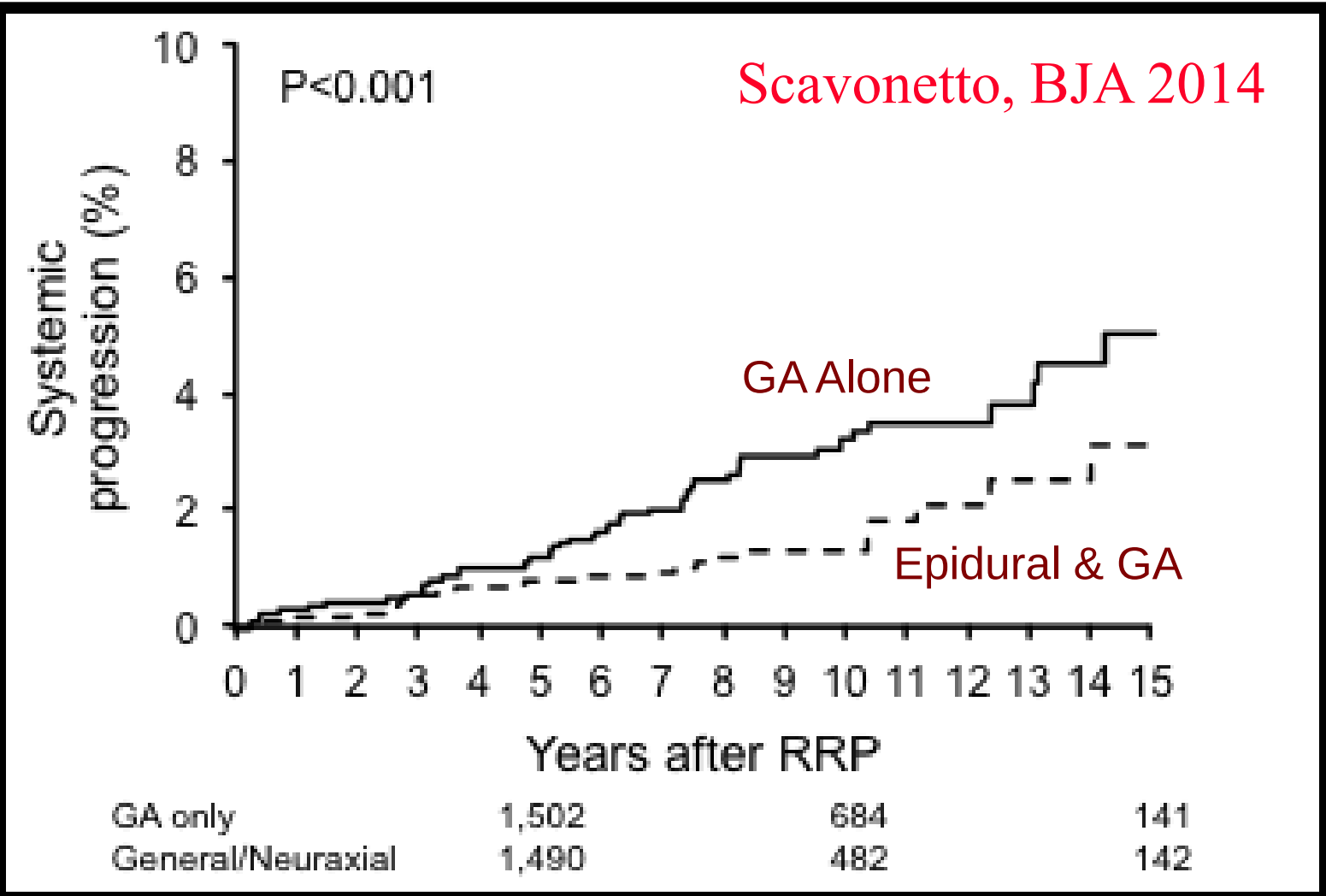
Retrospective analysis of 129 mastectomies for CA

- 50 had combined general & paravertebral analgesia
- 79 had general and morphine analgesia




Exadaktylos, Anesthesiology 2006

# Epidurals & Prostate Cancer



# Negative Retrospective Results

Ismail et al: BJA 2010
- Brachytherapy for cervical cancer
  - 63 neuraxial vs. 69 general anesthesia

Gottschalk et al: Anesthesiology 2010
- Colectomy for colon cancer
  - 256 epidural vs. 253 general anesthesia

Tsui et al: CJA 2010
- Epidural analgesia for prostate cancer
  - 49 epidural vs. 50 general anesthesia

Forget et al: EJA 2011
- Epidural analgesia for prostate cancer
  - 578 epidural vs. 533 general anesthesia

Day et al: BJA 2012
- Laparoscopic colectomy
- 107 epidural; 144 spinal; and 173 general alone

And others…

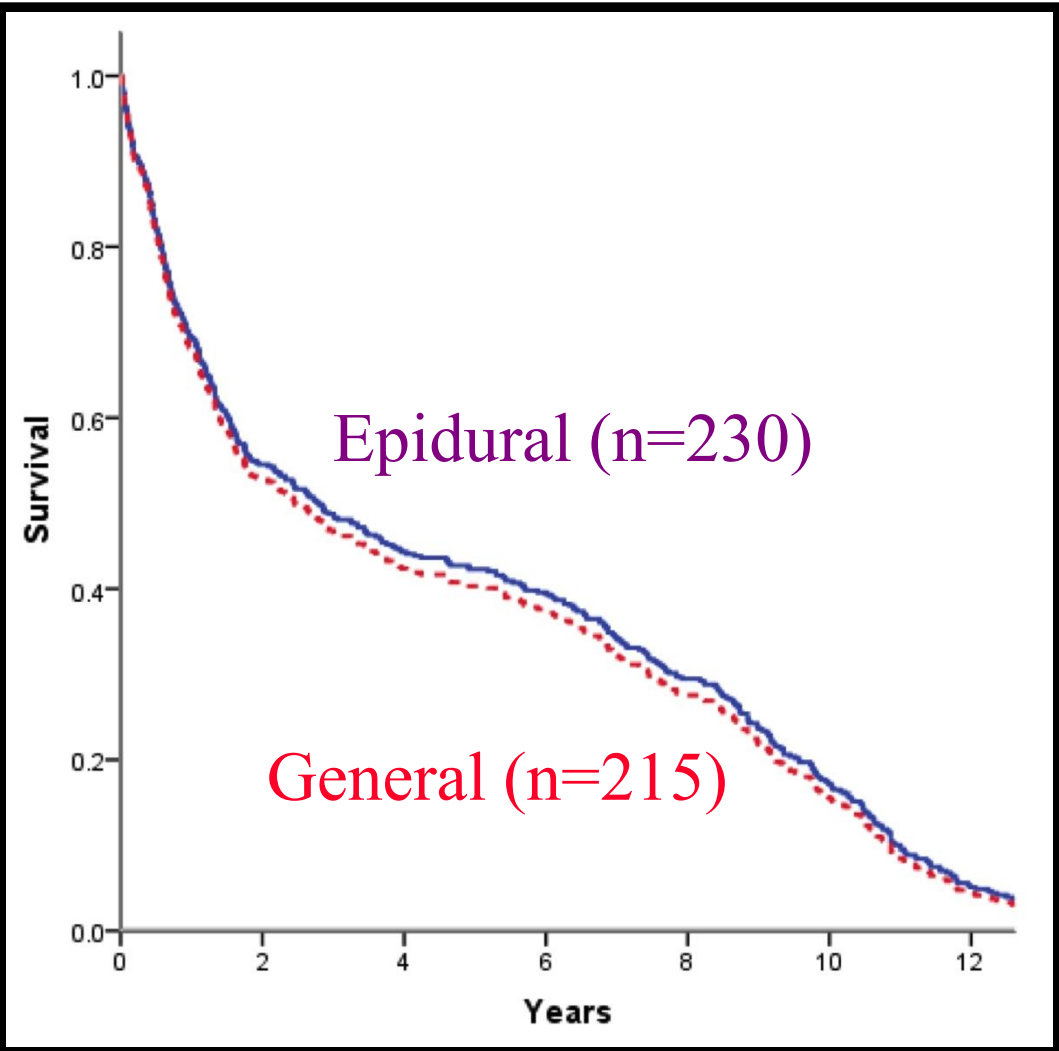
# MASTER Trial Follow-up

Myles, BMJ, 2011

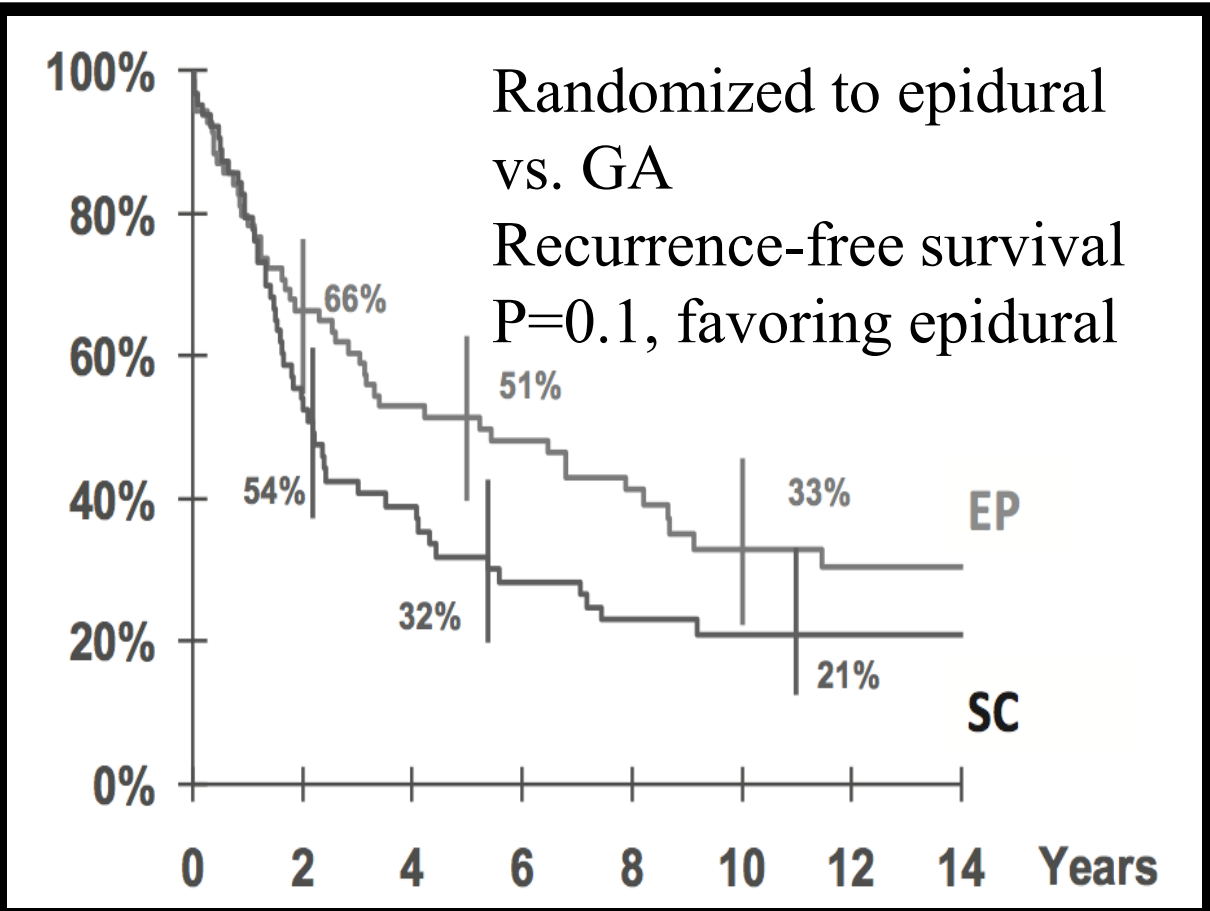
Also negative:

Tsui 2010

Christopherson 2008



# Binczak, et al 2013 (n=132)




Trials of breast and lung cancer in progress

Major abdominal surgery

# Perioperative Mortality

Intraoperative mortality rare

Thirty-day postoperative mortality

- 1% nationwide in United States
- 80% of one-month deaths during initial hospitalization
- Mostly cardiovascular or consequent

Postoperative MI poorly understood

- Etiology?
- Prediction?
- Prevention? (today's focus)
- Treatment?

# Postoperative MIs are Common

≈230 million non-cardiac operations / year

MI incidence 8% among inpatients >45 years

- ≈10 million postoperative infarctions per year

Nearly all *non*-ST segment elevation

- Plaque rupture?
- Supply-demand mismatch?
- Thrombus?

VISION: JAMA 2012 and Anesthesiology 2014

# Silent and Deadly

80% of MIs *only* detected by troponin
- Most do not have chest pain, SOB, ECG changes

Mortality identical after apparent & silent MIs
- It's not just "troponitis"

Mortality is 10% at 30 days
- Twice as high as non-operative infarctions
  - Different?
  - Unrecognized?
  - Untreated?

VISION: JAMA 2012 and Anesthesiology 2014

# Troponin Predicts Mortality

"Prognosis define diagnosis"

Even slight troponin elevations predict death

| Peak Troponin (ng/ml) | 30-day Mortality (%) | Time to death (days) |
|---|---|---|
| <0.01 | 1 | — |
| 0.02 | 4 | 13 |
| 0.03-0.29 | 9 | 9 |
| ≥0.3 | 17 | 6 |

# ENIGMA-2

Background

- $N_2O$ increases plasma homocysteine
- $N_2O$ impairs endothelial function

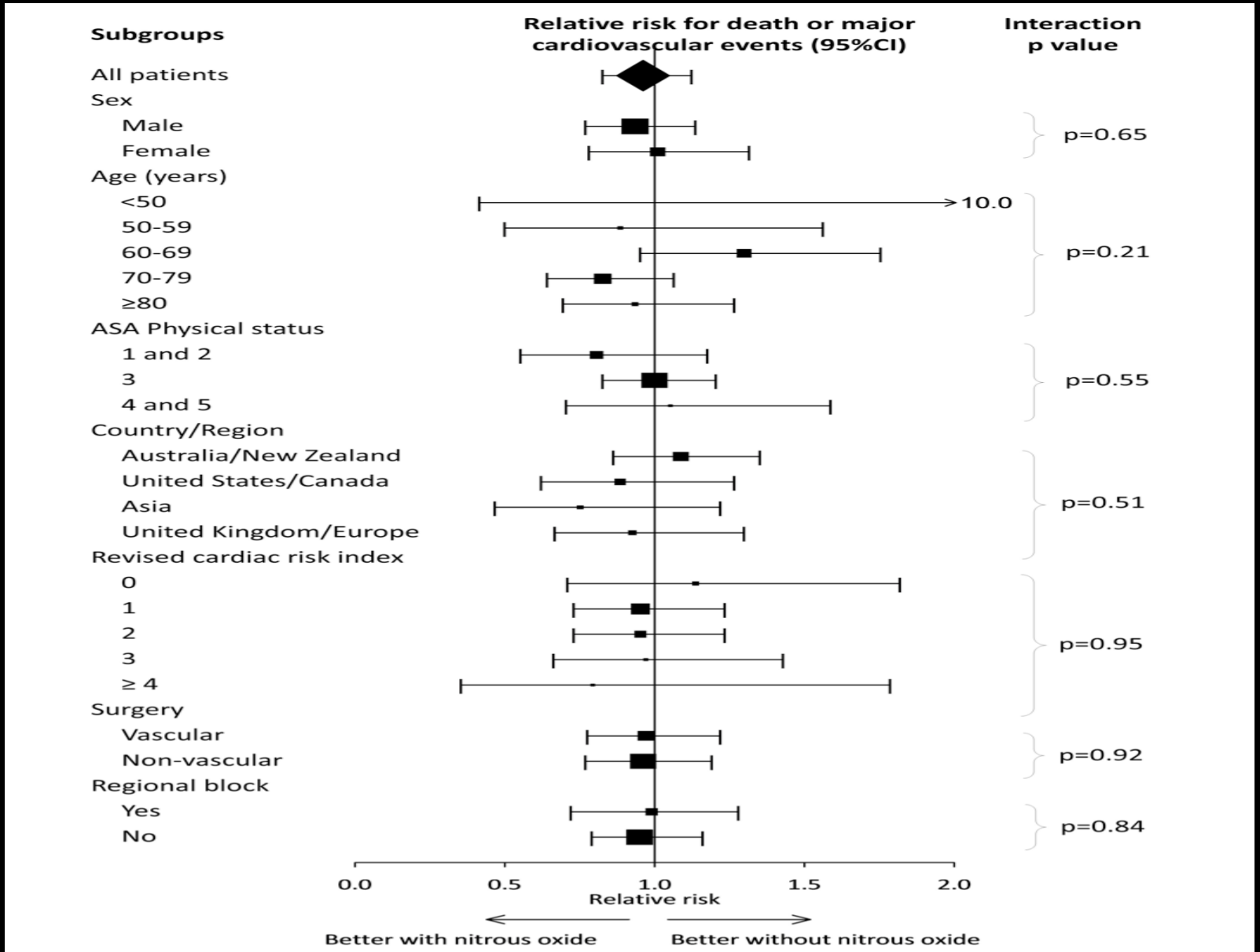
Hypothesis

- $N_2O$ increases 30-day death or major CV events
- MI required troponin elevation & clinical event

Randomized trial in 7,000 high-risk patients

- 70% nitrous oxide
- 70% nitrogen

Myles, Lancet, 2014


Subgroups
Relative risk for death or major cardiovascular events (95%CI)
Interaction p value
All patients
Sex
Male
Female
p=0.65
Age (years)
<50
50-59
60-69
70-79
≥80
10.0
p=0.21
ASA Physical status
1 and 2
3
4 and 5
p=0.55
Country/Region
Australia/New Zealand
United States/Canada
Asia
United Kingdom/Europe
p=0.51
Revised cardiac risk index
0
1
2
3
≥ 4
p=0.95
Surgery
Vascular
Non-vascular
p=0.92
Regional block
Yes
No
p=0.84
0.0
0.5
1.0
1.5
2.0
Relative risk
Better with nitrous oxide
Better without nitrous oxide

# POISE-2 Background

Surgery
- Inflammatory response activates platelets
- Promotes tachycardia

Aspirin
- Impairs platelet aggregation
- Prevents non-operative primary & secondary MI

Clonidine
- Moderates central sympathetic activation
- Heart rate control
- Less hypotension than beta blockers
- Analgesic and anti-inflammatory

# POISE-2 Design

10,000 inpatients >45 yrs at cardiovascular risk

Blinded 2 X 2 factorial trial

- Aspirin 100 mg/day *vs.* placebo for 7 or 30 days
- Clonidine 75 μg/day *vs.* placebo for 72 hours

Primary outcome

- Death or MI within 30 days
- MI required troponin elevation and clinical events

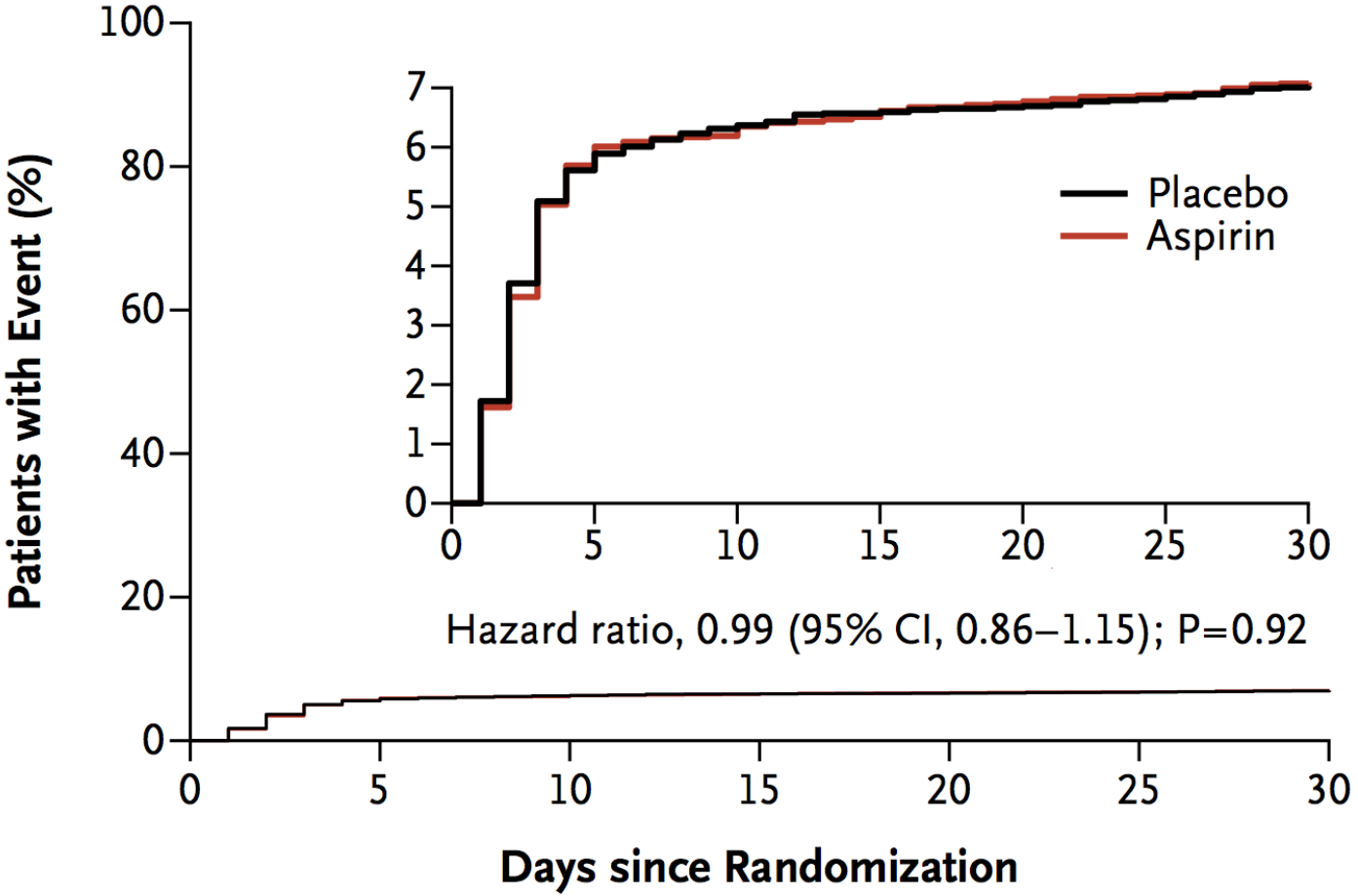
# POISE-2 Results, Aspirin

| Outcome | Aspirin (4998) | Placebo (5012) | HR (95% CI) | P |
|---|---|---|---|---|
| 1$^{O}$ outcome: death or nonfatal MI | 351 (7.0) | 355 (7.1) | 0.99 (0.86-1.15) | 0.92 |
| Major bleed | 229 (4.6) | 187 (3.7) | 1.23 (1.01-1.49) | 0.04 |
| Stroke | 16 (0.3) | 19 (0.4) | 0.84 (0.43-1.64) | 0.62 |

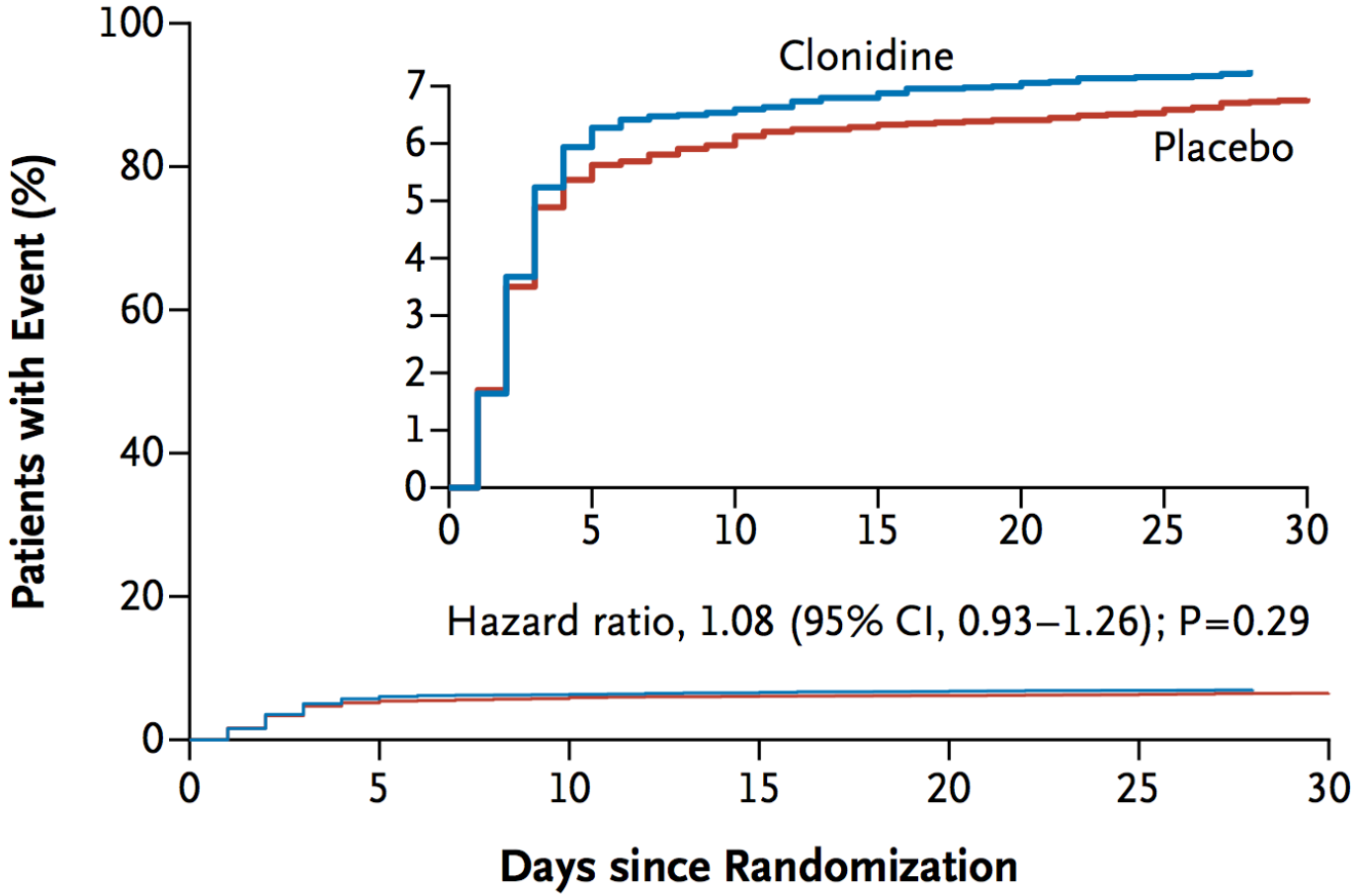
No interaction with clonidine

Devereaux, NEJM 2014

# Aspirin, Death & MI



# Clonidine, Death & MI



# POISE-2, Clonidine Results

| Outcome | Clonidine (5009) | Placebo (5001) | HR (95% CI) | P |
|---|---|---|---|---|
| Clinically important hypotension | 2385 (48) | 1854 (37) | 1.32 (1.24-1.40) | <0.001 |
| Clinically important bradycardia | 600 (12) | 403 (8) | 1.49 (1.32-1.69) | <0.001 |
| Stroke | 18 (0.4) | 17 (0.3) | 1.06 (0.54-2.05) | 0.87 |

No interaction with aspirin

Devereaux, NEJM 2014

# POISE-2 Conclusions

Aspirin

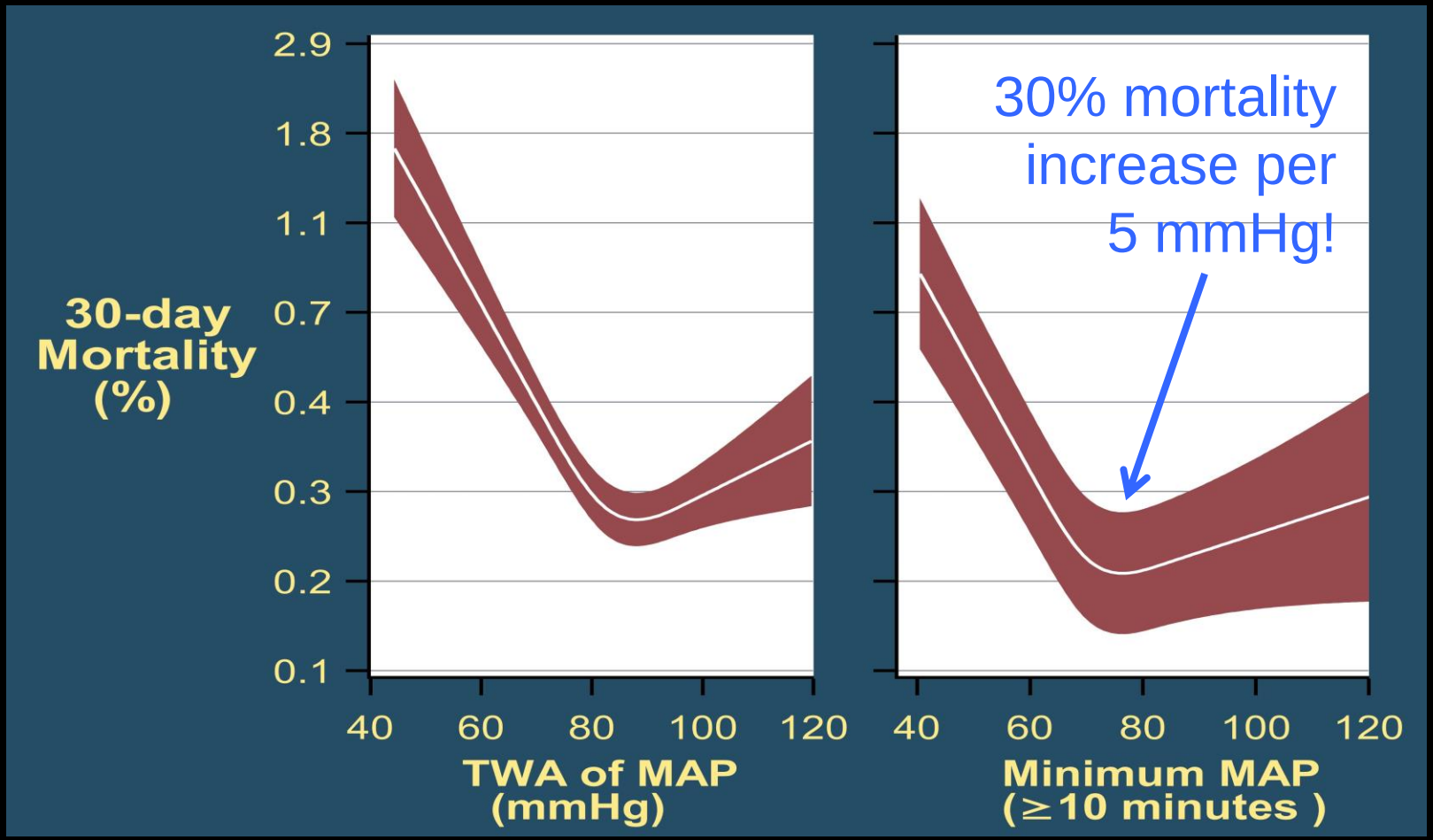
- Does not prevent death or MI
- Increases life-threatening bleeding
- Should not be used for MI prophylaxis

Clonidine

- Does not prevent death or MI
- Causes clinically important hypotension
- Should not be used for MI prophylaxis

A safe and effective way to prevent perioperative myocardial infarctions remains unknown

# Association with MAP




Mascha, Anesthesiology, in press

# Summary of Long-Term Outcomes

## Prolonged storage of transfused red cells

- Association with complications in some studies
- Randomized trials in progress

## Regional analgesia and cancer recurrence

- Immunologic & animal data suggest reduced risk
- Current human data poor and conflicts
- Randomized trials in progress

## Perioperative heart attacks

- Common, silent, and deadly
- Predication, etiology, prevention, and treatment remain unknown

# Cleveland Clinic