Using Secondary Data in Statistical Analysis

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Meta-analysis Definition

- Glass 1976, “the statistical analysis of a large collection of results from individual literature for the purpose of integrating their respective findings.”
- Two basic purposes:
  1. Determine if similar treatment effects exist for a therapy in independent studies to estimate a net effect for this therapy
  2. Alternatively, if treatment effects differ substantially for a therapy among independent studies, to examine factors that may explain these differing effects

Education Research 1976

Techniques of Meta-Analysis

Step One: Formulating the Question

- Validity and importance are contingent on this step
- Poorly conceived research hypothesis will usually lead to an analysis of dubious value

Techniques of Meta-Analysis

Step Two: Defining Eligibility Criteria

- Protocols for study inclusion should be prospective, systematic, and explicit
- Ideally, randomized trials similar in diagnosis, outcome, patient characteristics, and treatment groups

Techniques of Meta-Analysis

Step Two: Defining Eligibility Criteria Cont'd

- Including all available studies, regardless of size, design, or quality results in an analysis that is broadly representative but may compromise accuracy
- Alternatively, exclusion of poorly done studies may increase the statistical validity but limit the ability to generalize findings

Techniques of Meta-Analysis

Step Three: Identifying Studies and Data Abstraction

- Usually begins with a search of online databases such as MEDLINE, Current Contents, Best Evidence, Cochrane, and HealthSTAR
- Title and abstract perused to exclude studies

Techniques of Meta-Analysis

Step Three: Identifying Studies and Data Abstraction Cont'd

- Full texts of the remaining articles retrieved and thoroughly studied
- Reference lists of these articles are reviewed
- Once a study selected for inclusion, data should be extracted by more than one reviewer onto structured forms

Techniques of Meta-Analysis

Step Four: Analysis

- A common measure of treatment effect must be determined
- Fixed versus random effect model used to combine data

Techniques of Meta-Analysis

Step Four: Analysis Cont'd

- Cochran's Q statistic and I^2 calculated
- Consider metaregression when $I^2 > 30\%$ and $P < 0.10$
- Publication bias examined
  - Funnel Plot

Techniques of Meta-Analysis

Step Five: Reporting and Interpreting Results

- To improve overall quality of reporting for meta-analysis, a checklist and a flow chart should be constructed
- Quality of Reporting of Meta-analyses (QUOROM) conference provides guidelines for reporting searches, study selection, validity assessment, data abstraction, study characteristics and data synthesis

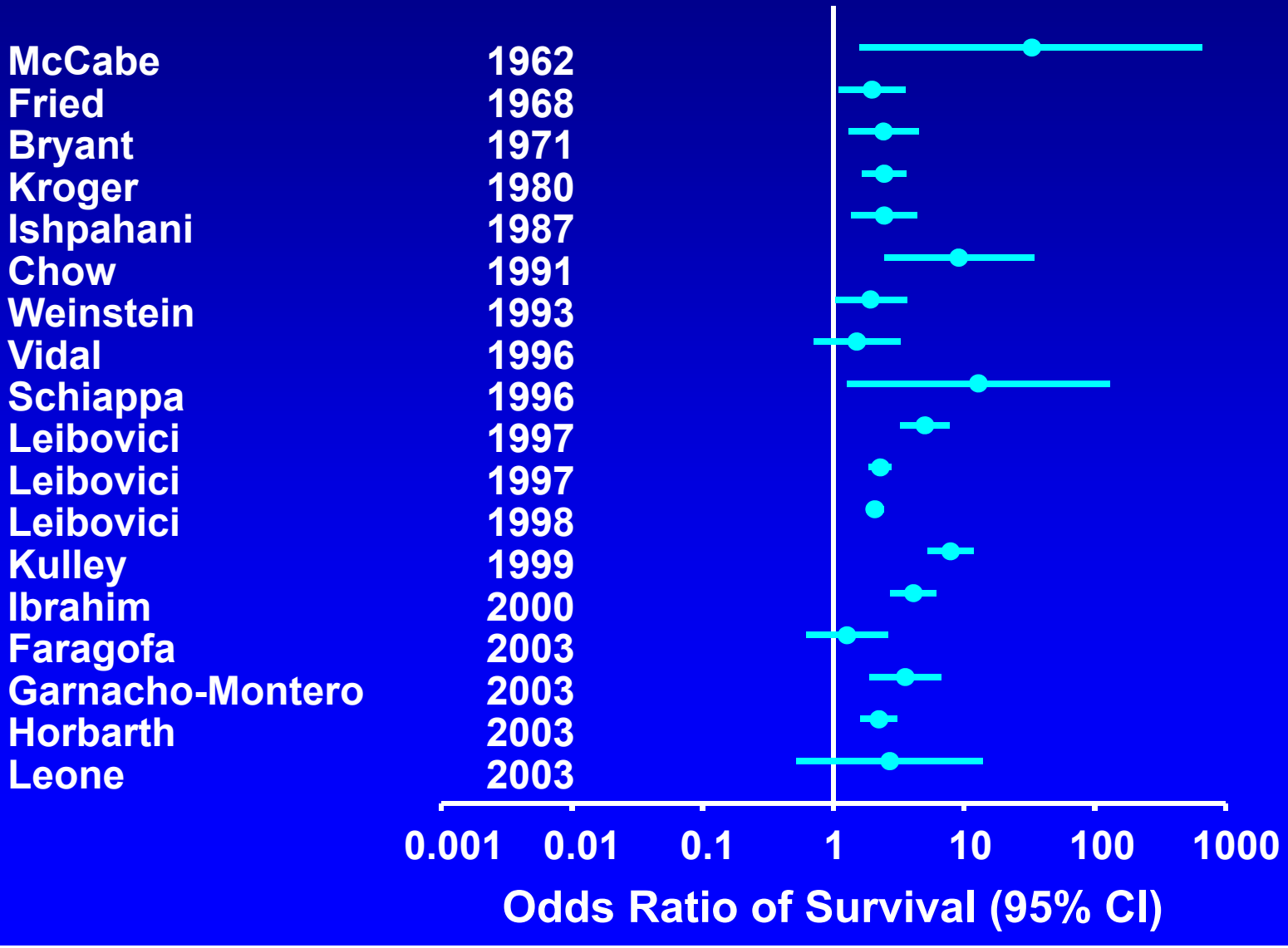
Lancet, 1999.

Meta-analysis of Clinical Trials in Sepsis

Septic Shock Management

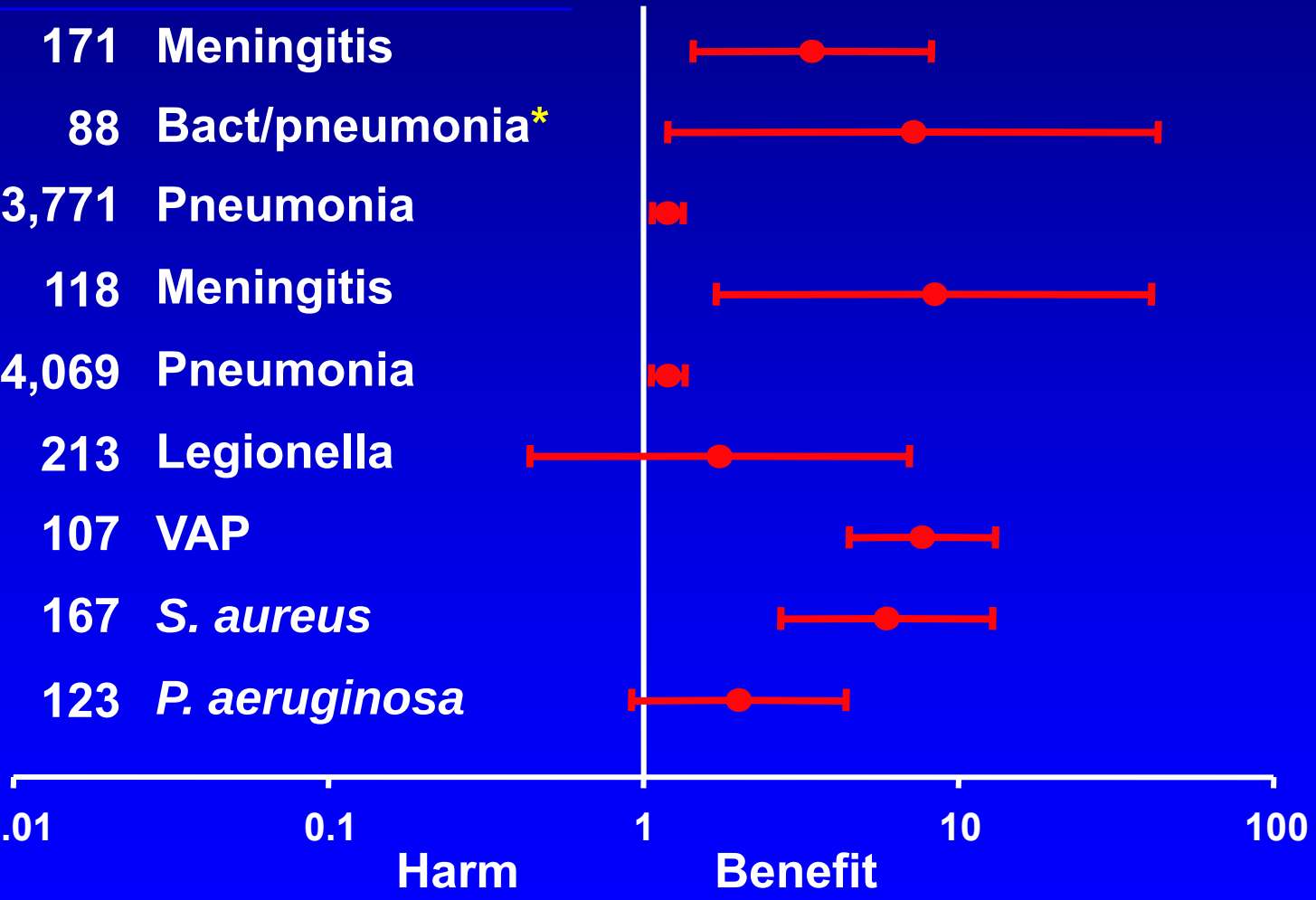
- Early recognition
- The right antibiotics right away
- Rapid fluid resuscitation
- Judicious use of vasopressors
- Promptly address removable nidi

Benefits of Starting Appropriate Antibiotic Therapy



Benefit of Early *versus* Late Antibiotics

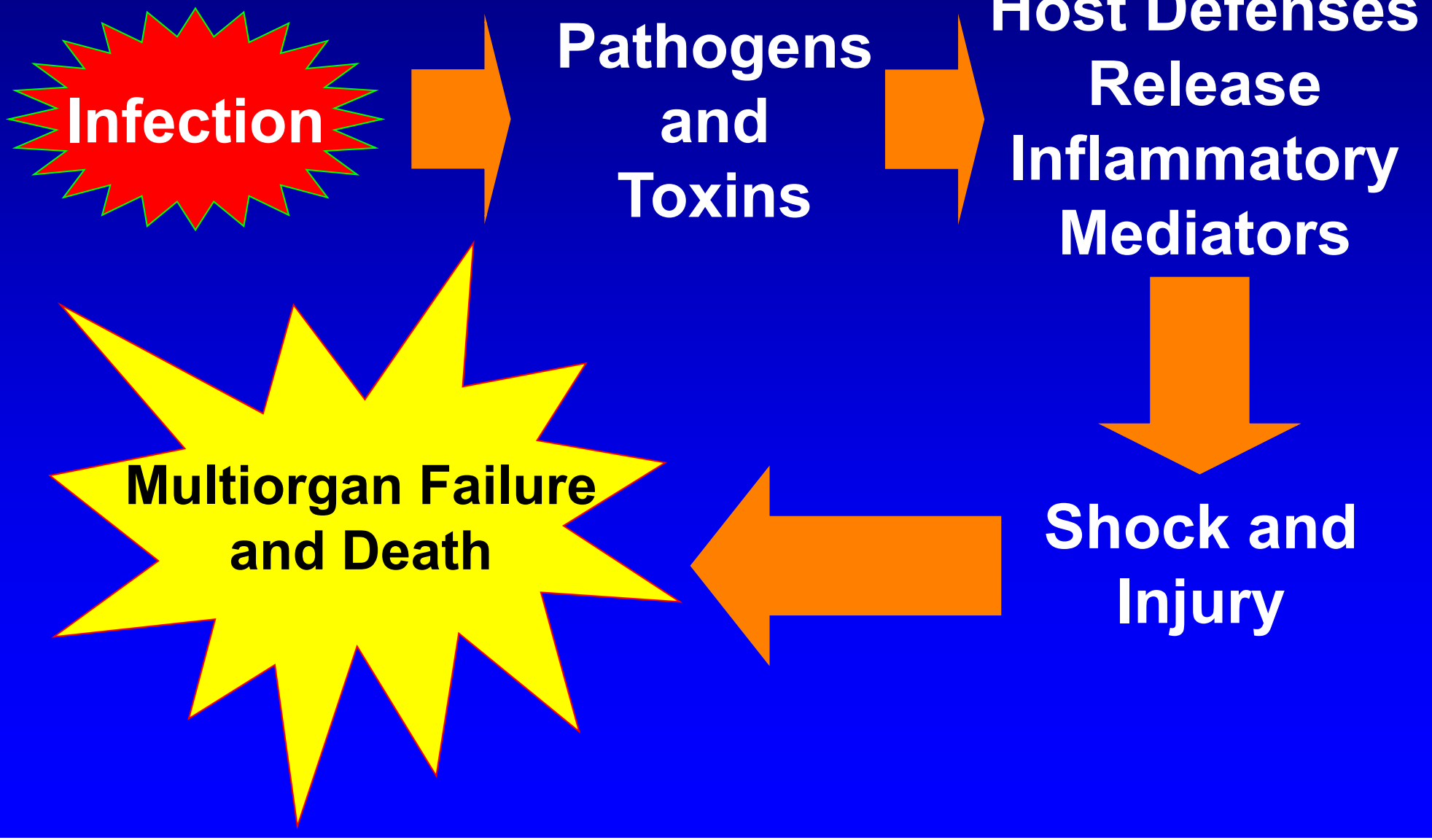
Author	Year	*N*	Diagnosis
Miner	2001	171	Meningitis
Larche	2002	88	Bact/pneumonia*
Houck	2004	13,771	Pneumonia
Proulx	2005	118	Meningitis
Meehan	1997	14,069	Pneumonia
Gacouin	2002	213	Legionella
Iregui	2006	107	VAP
Lodis	2003	167	*S. aureus*
Kang	2003	123	*P. aeruginosa*



* Patients with cancer

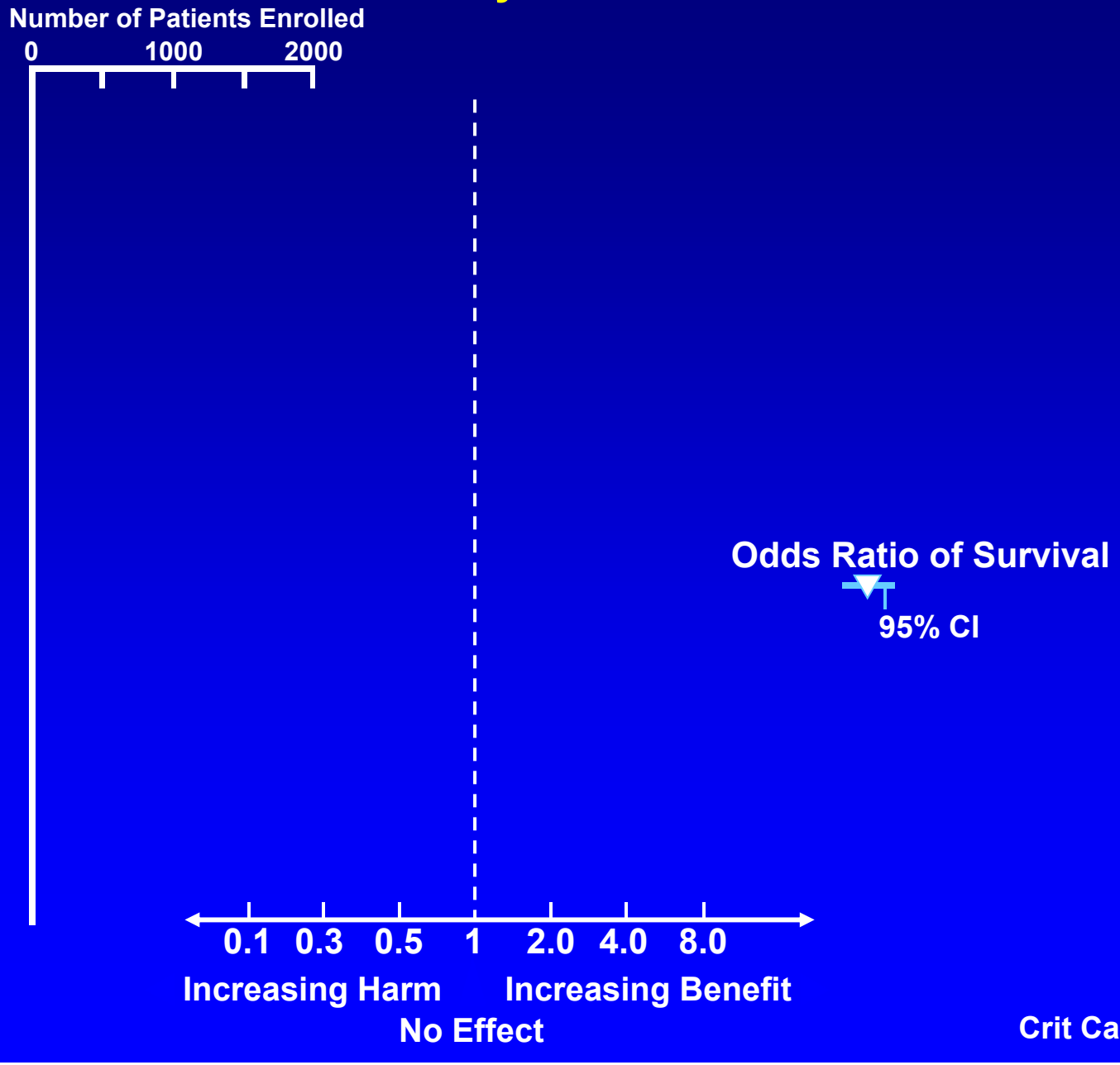
The Host Inflammatory Response Hypothesis: What went wrong?

Pathogenesis of Septic Shock



Human Clinical Trials of Anti-Inflammatory Therapies in Sepsis

Ranked by Size



Crit Care Med 1998

Human Clinical Trials of Anti-Inflammatory Therapies in Sepsis

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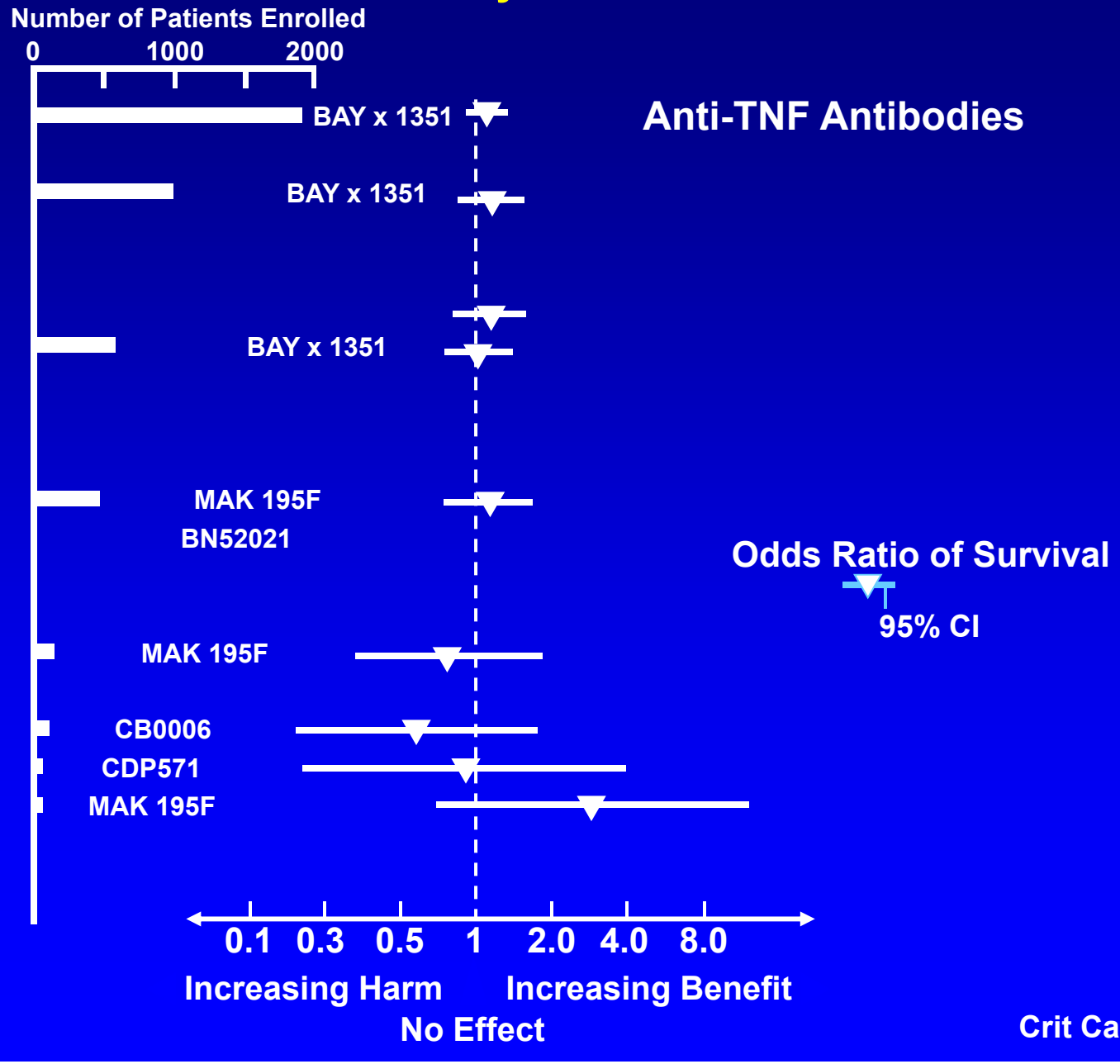

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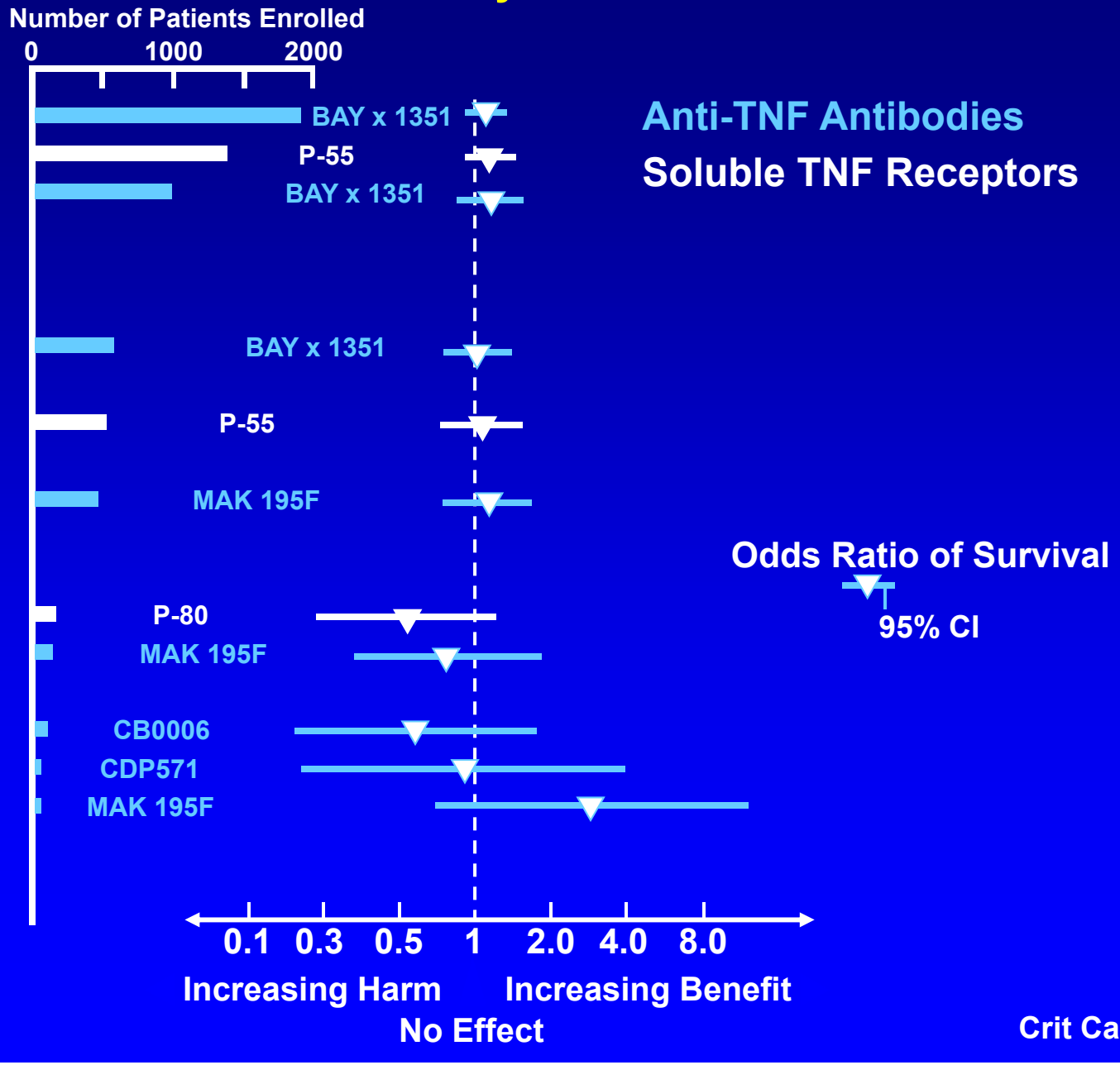

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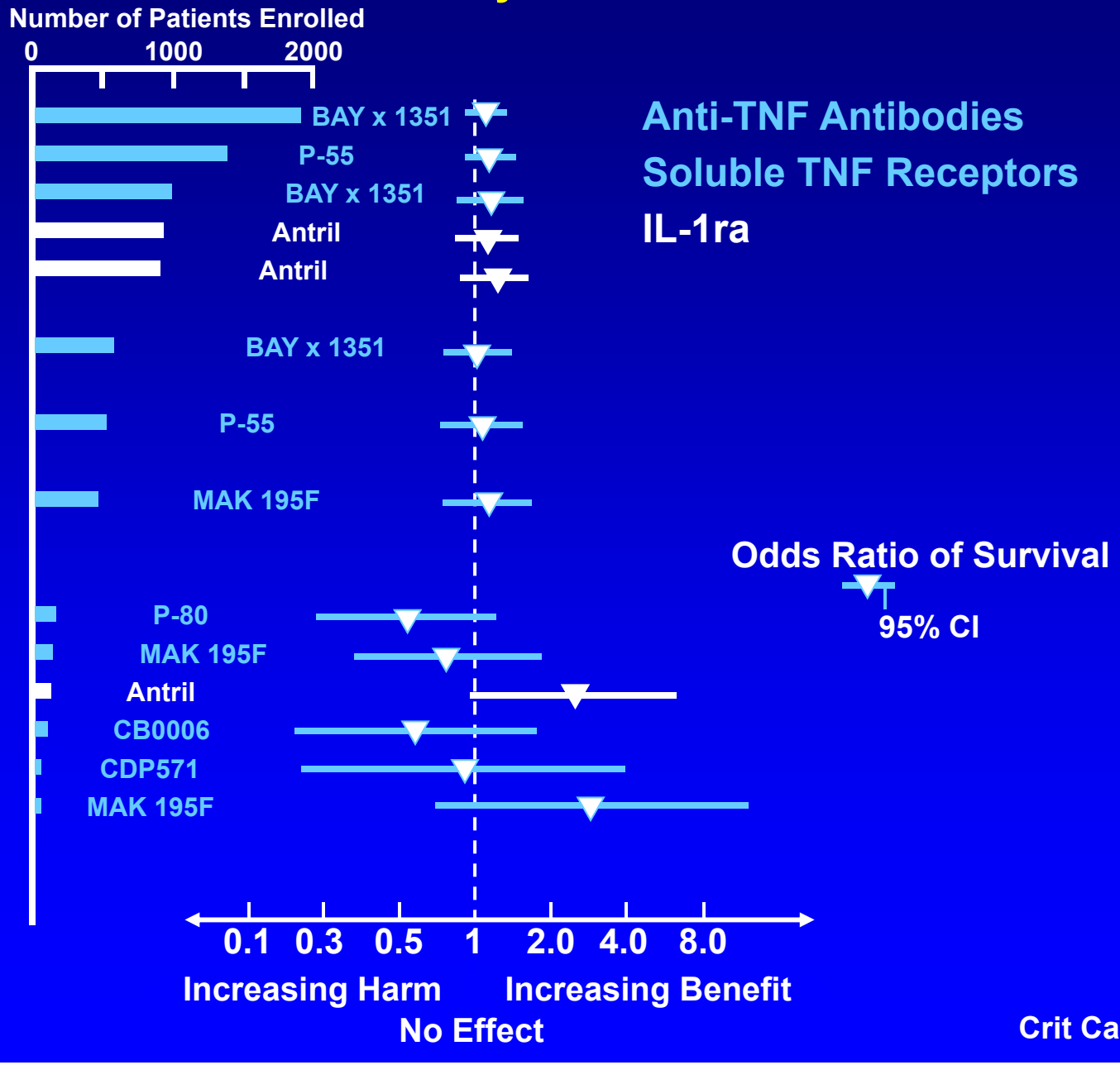

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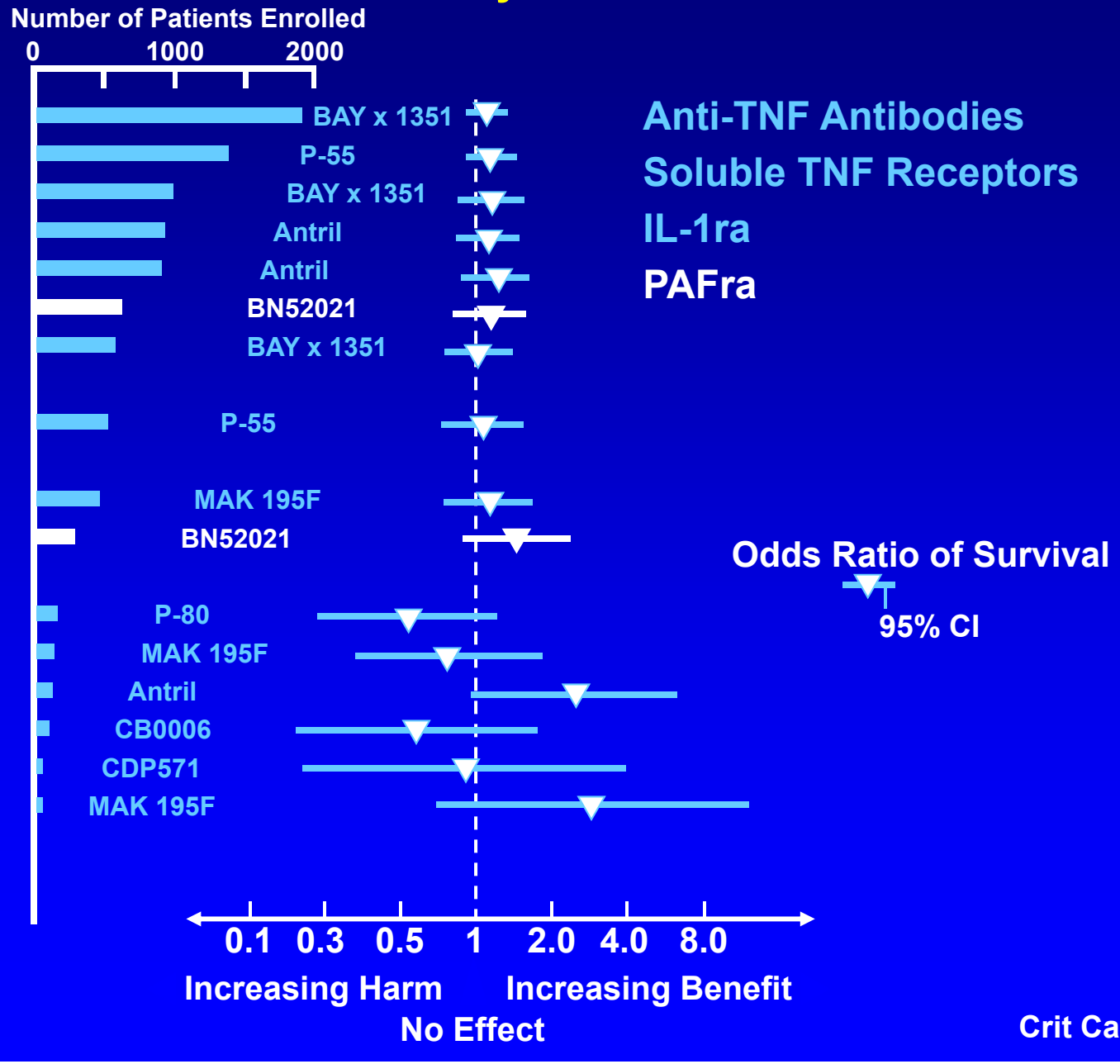

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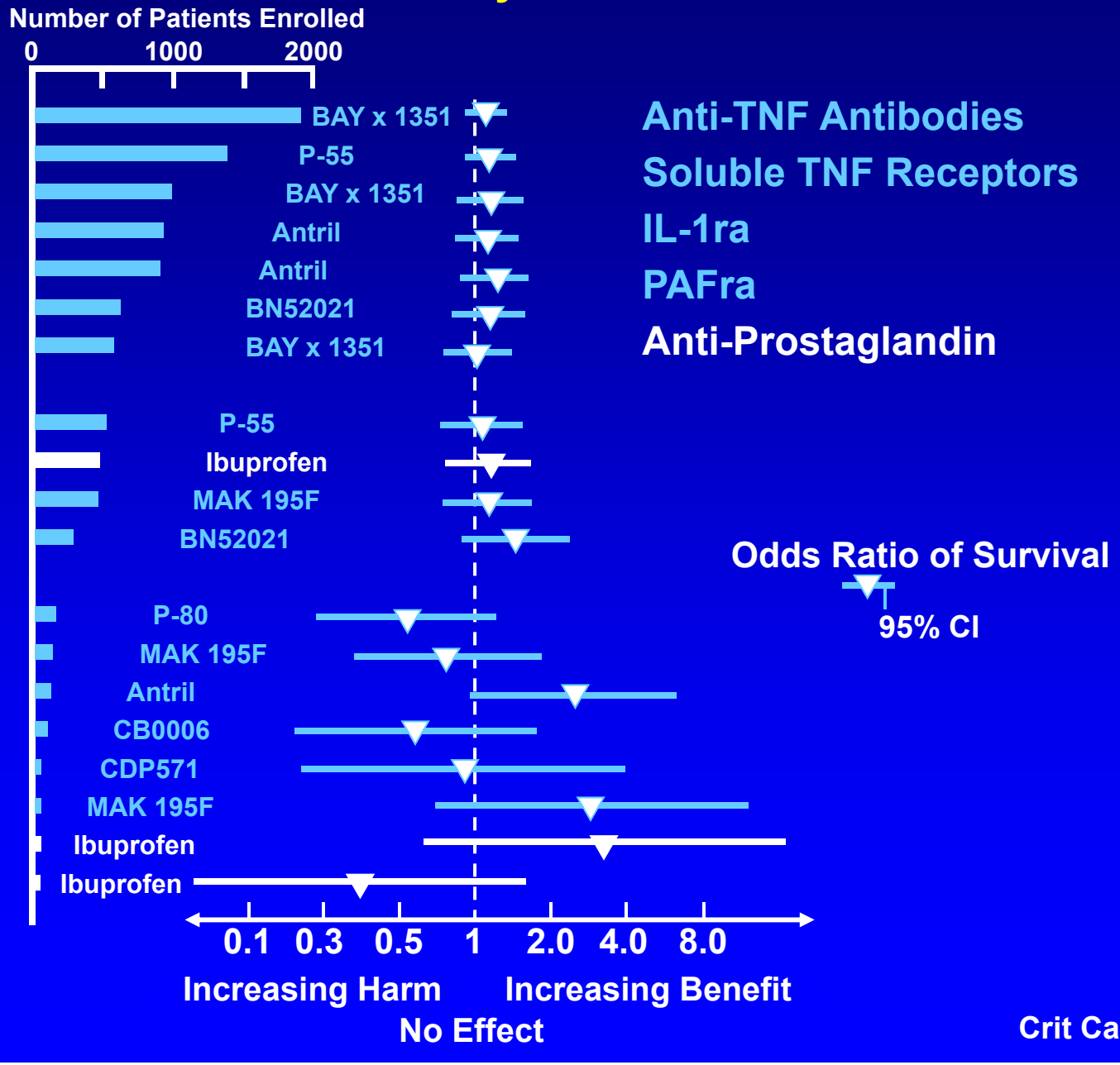

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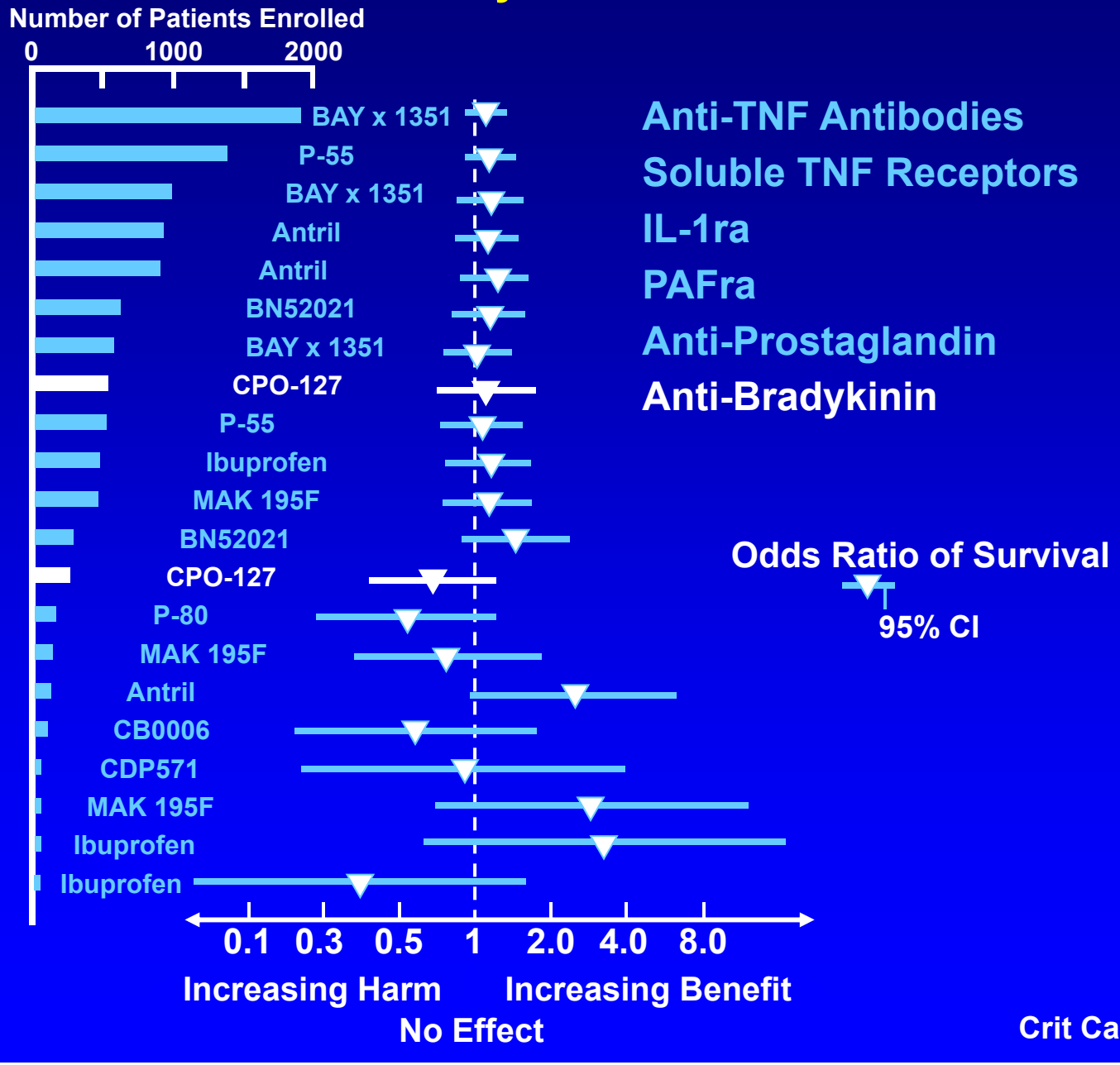

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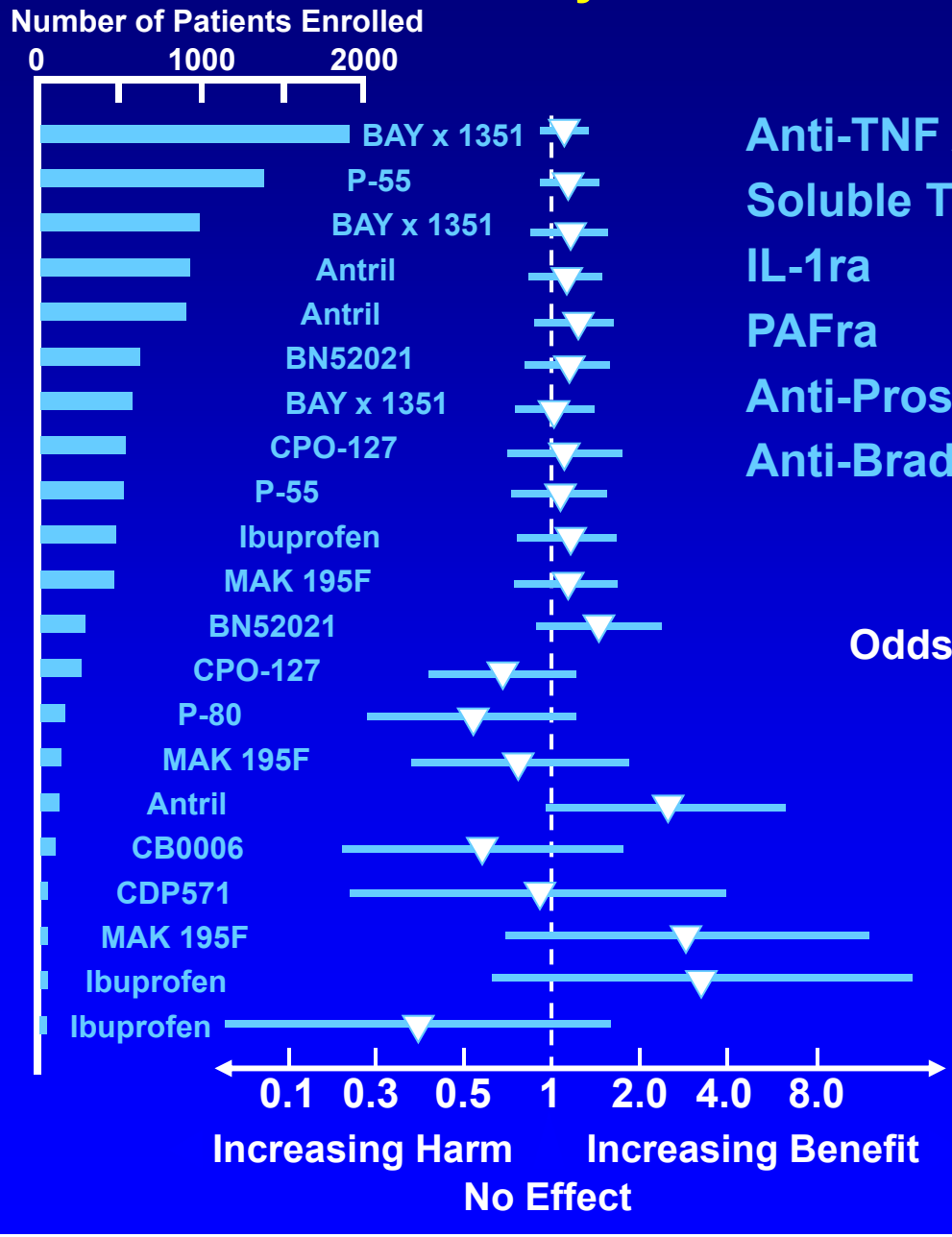
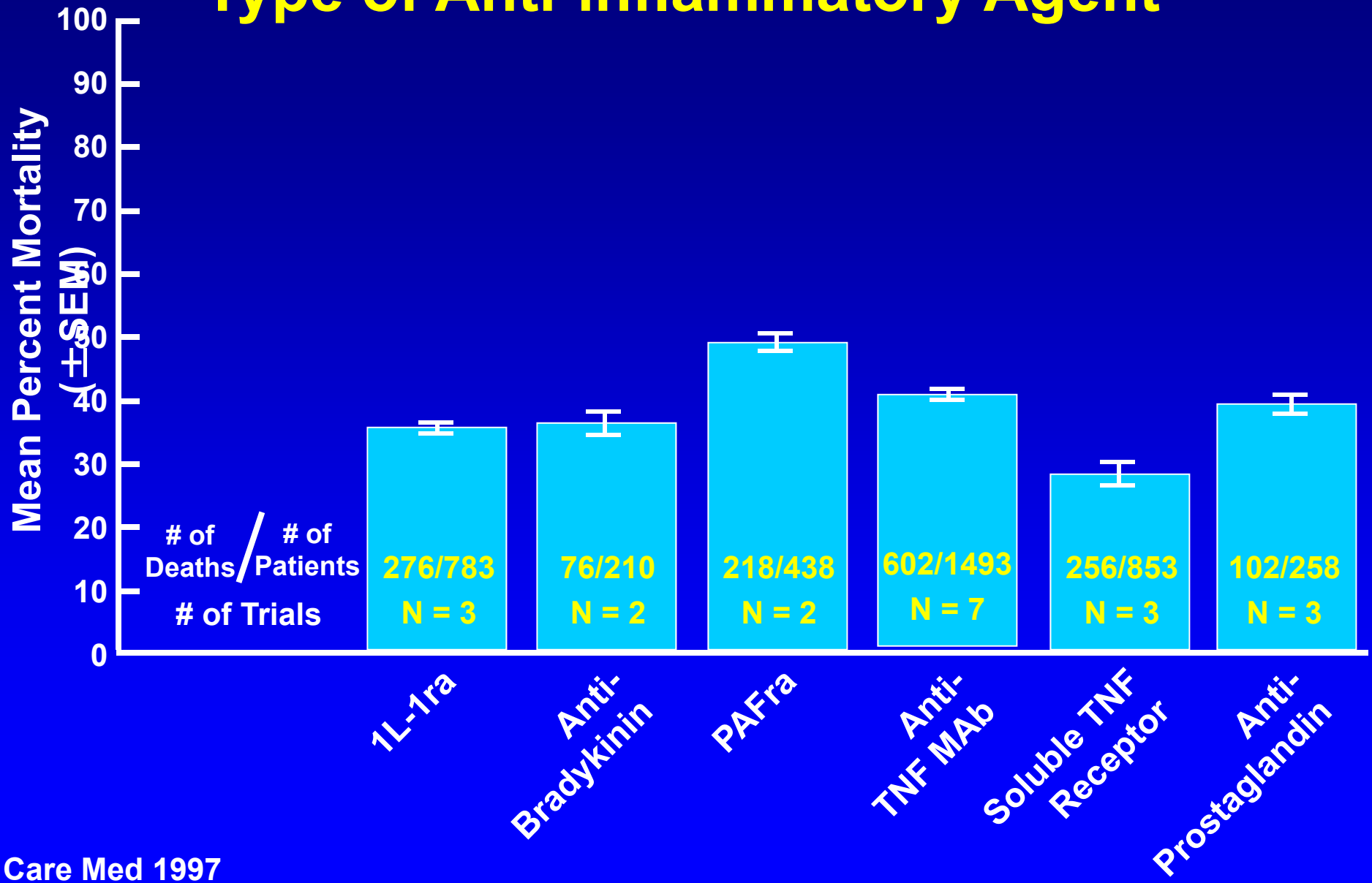


Anti-TNF Antibodies
Soluble TNF Receptors
IL-1ra
PAFra
Anti-Prostaglandin
Anti-Bradykinin

Odds Ratio of Survival
95% CI

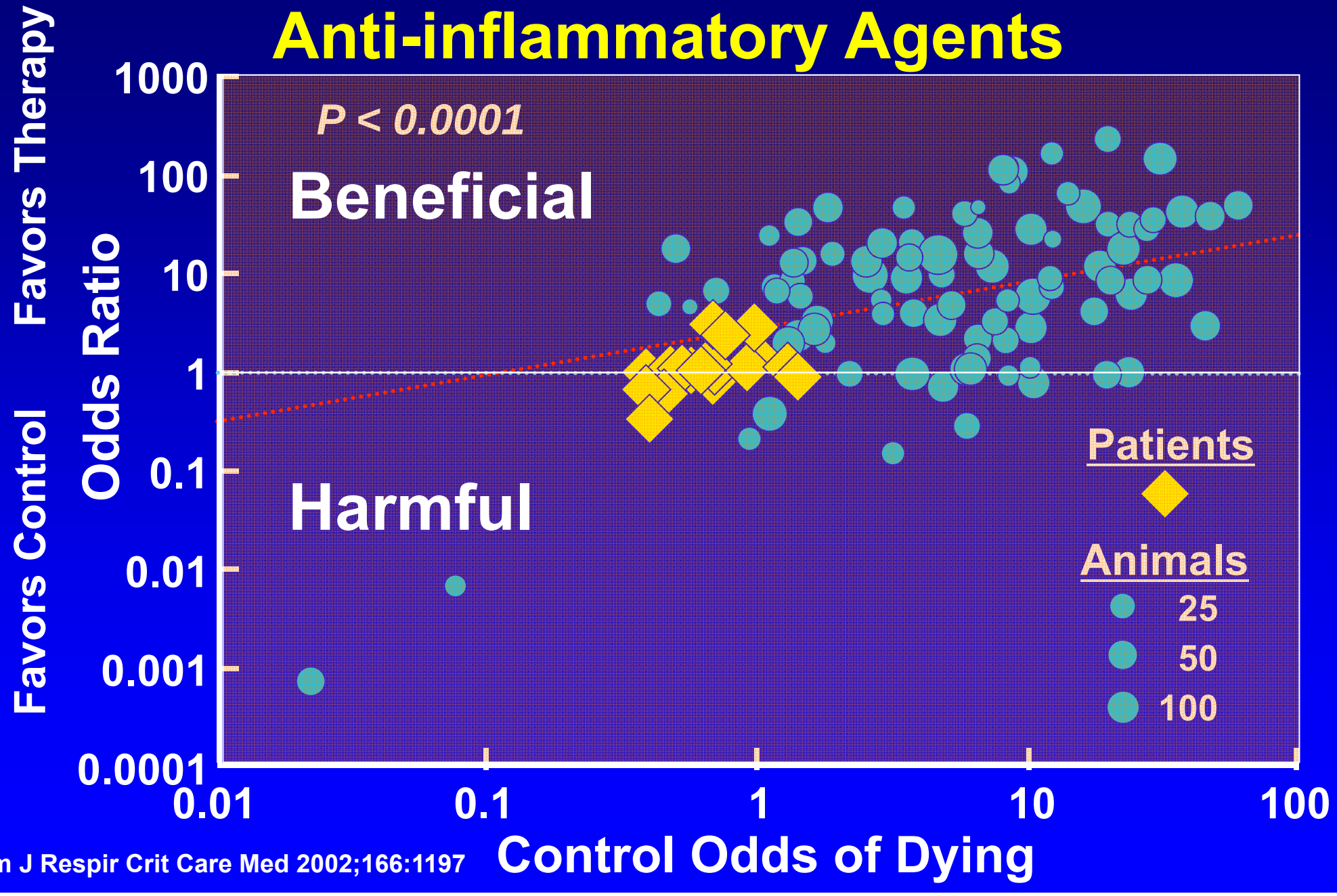
Crit Care Med 1998

Control Arm Mortality Rates by Type of Anti-inflammatory Agent



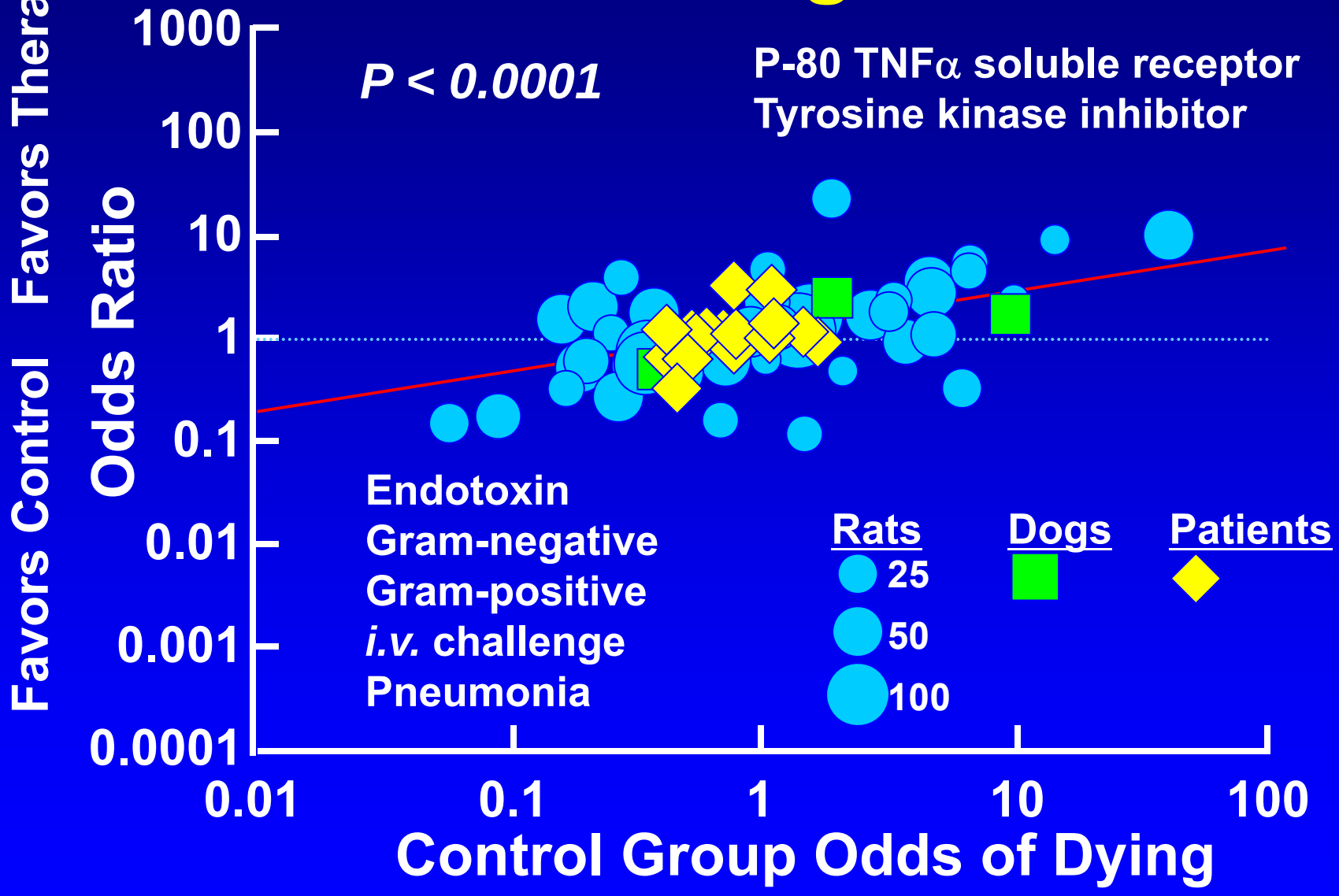
Crit. Care Med 1997

Preclinical Studies of Anti-inflammatory Agents



Am J Respir Crit Care Med 2002;166:1197

Prospective Animal Studies of Selected Agents



Am J Respir Crit Care Med 2002;166:1197

Summary
Anti-Inflammatory Agents in Sepsis

- **Meta-analysis:**
  - **treatment effects are small (3%), but statistically significant**
- **Meta-regression analysis:**
  - **Efficacy dependent on risk of death**
    - **Beneficial at high risks of death,**
    - **ineffective or harmful when risk was moderate or low**

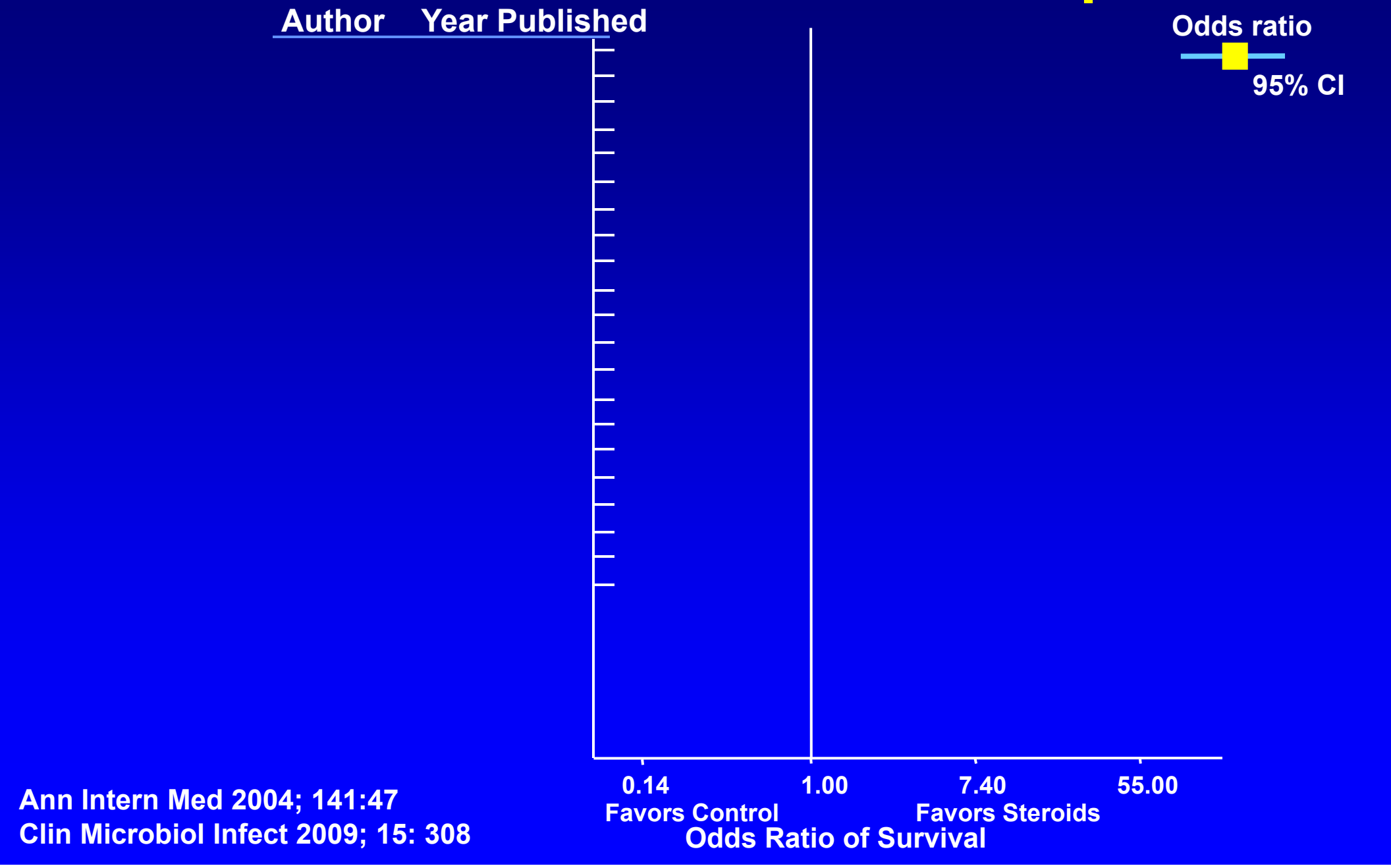
Paradox of Corticosteroids in Sepsis

Less may have benefits, but only in sickest patients

Corticosteroids in Sepsis

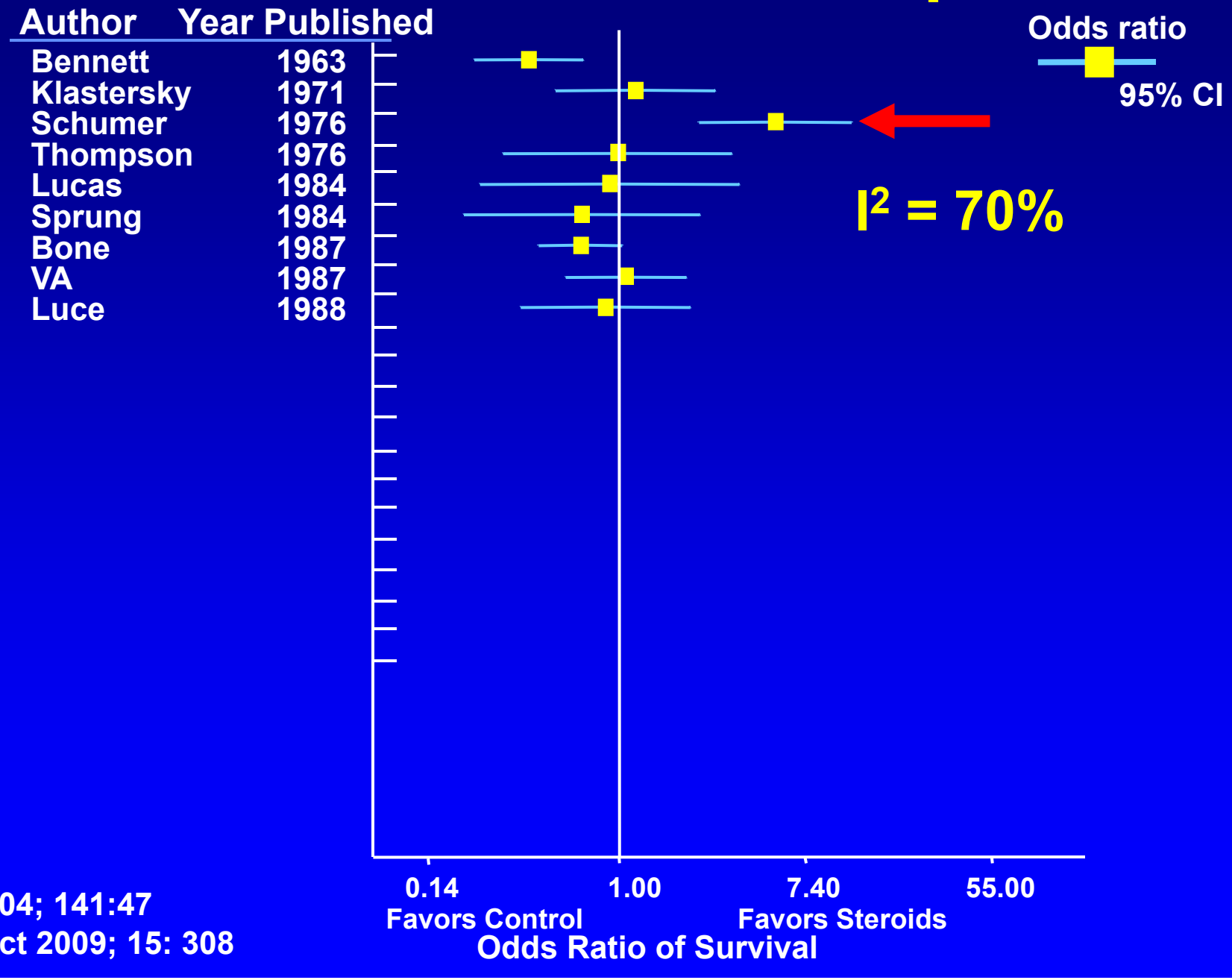
- Investigated since the 1960s
- By early 1990s, shown to be ineffective or possibly harmful
- Renewed interest and new trials over the last decade

Trials of Corticosteroids in Sepsis



Ann Intern Med 2004; 141:47
Clin Microbiol Infect 2009; 15: 308

Trials of Corticosteroids in Sepsis



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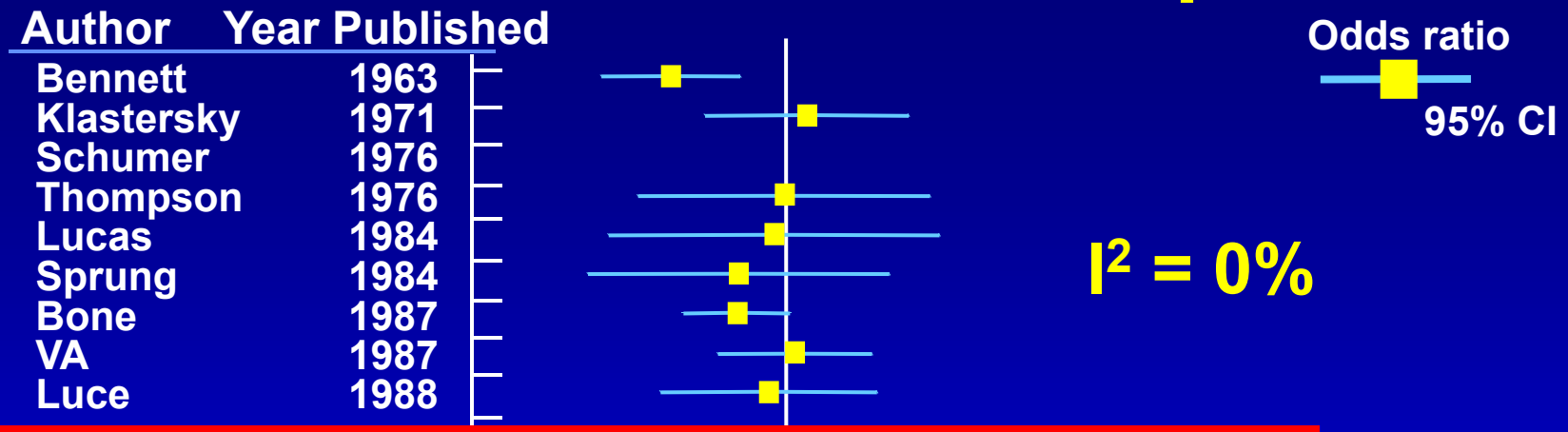
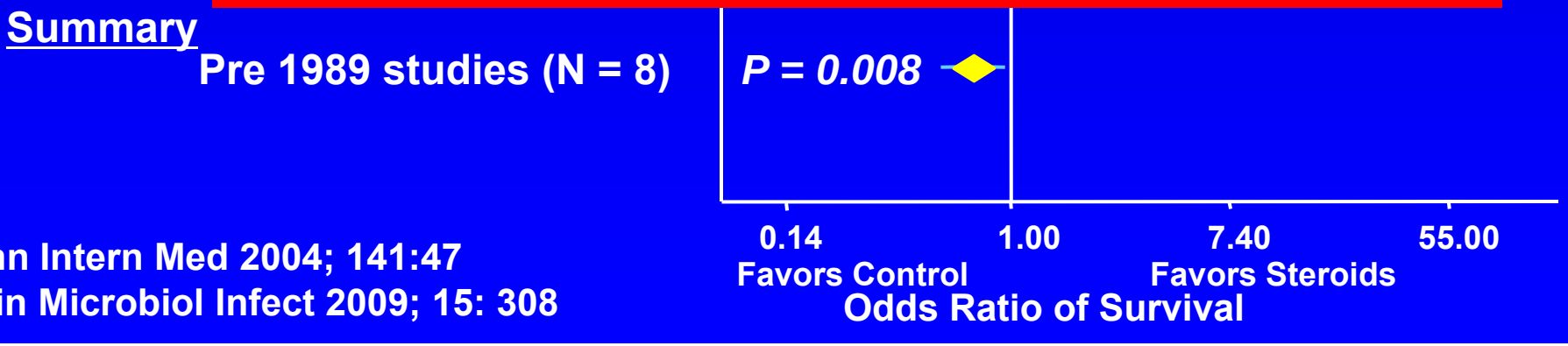


Short course (24 h) high dose corticosteroids (median - 24,000 mg of hydrocortisone equivalents) worsened survival



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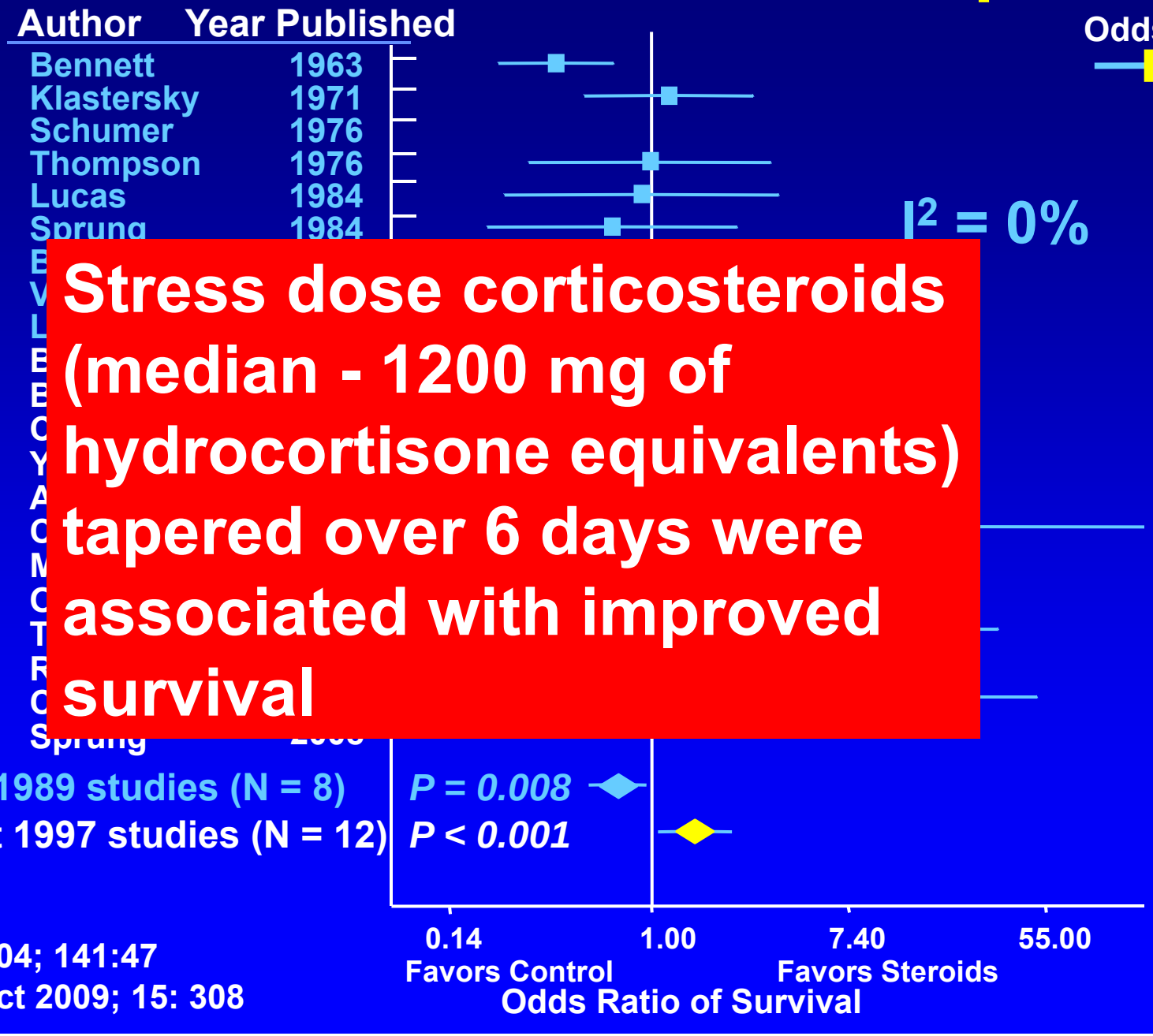
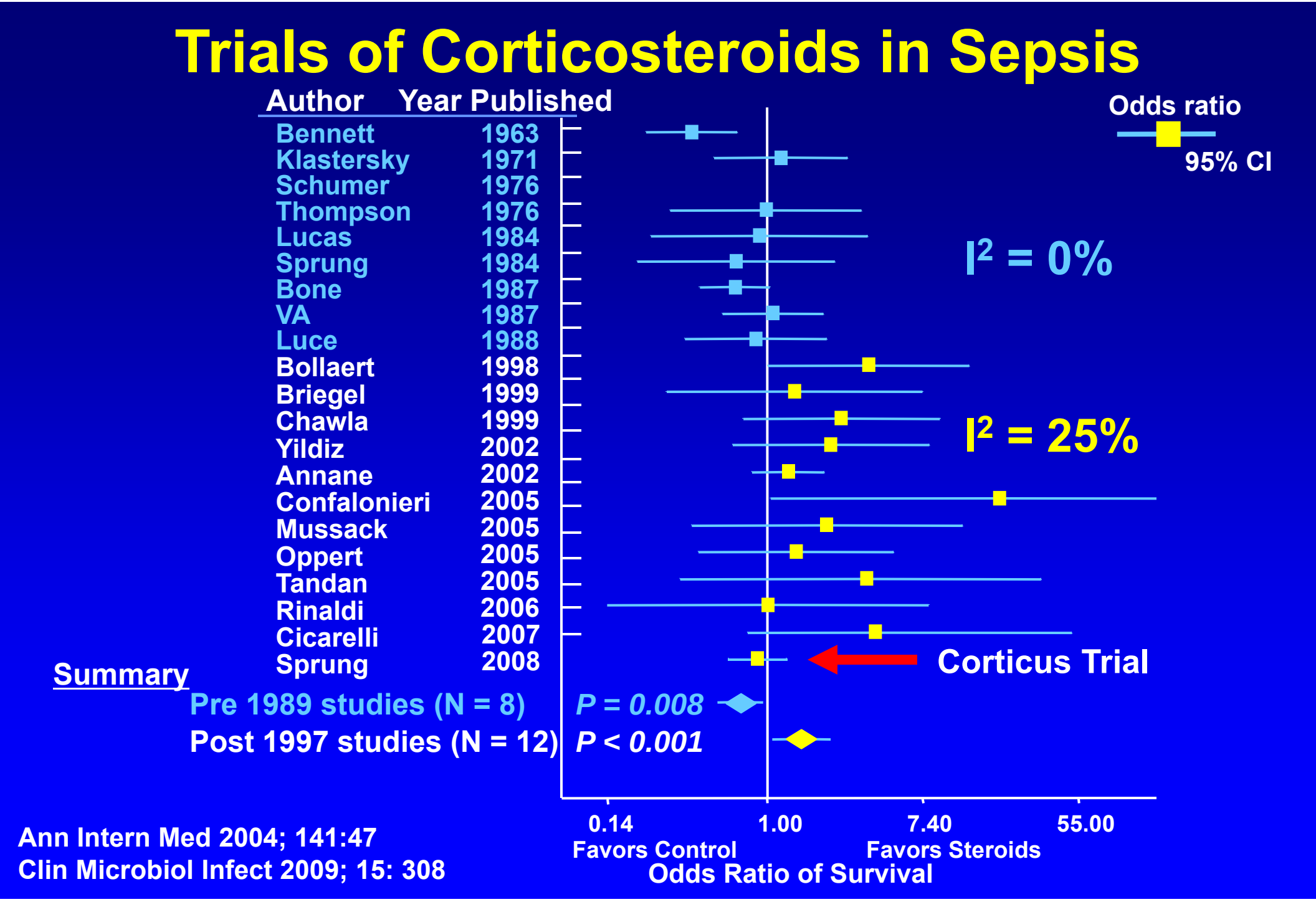


Stress dose corticosteroids (median - 1200 mg of hydrocortisone equivalents) tapered over 6 days were associated with improved survival

Ann Intern Med 2004; 141:47
Clin Microbiol Infect 2009; 15: 308

Trials of Corticosteroids in Sepsis



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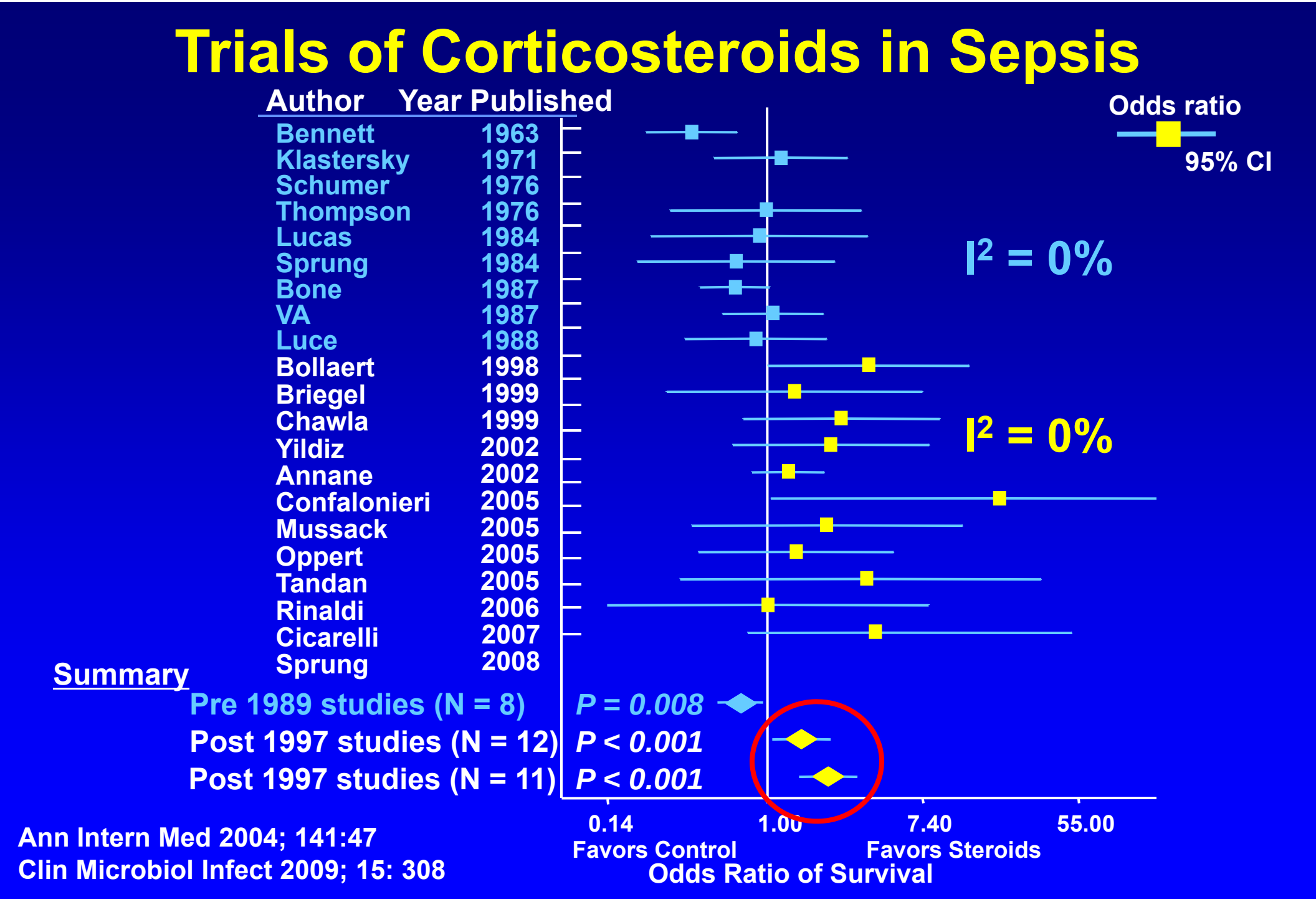
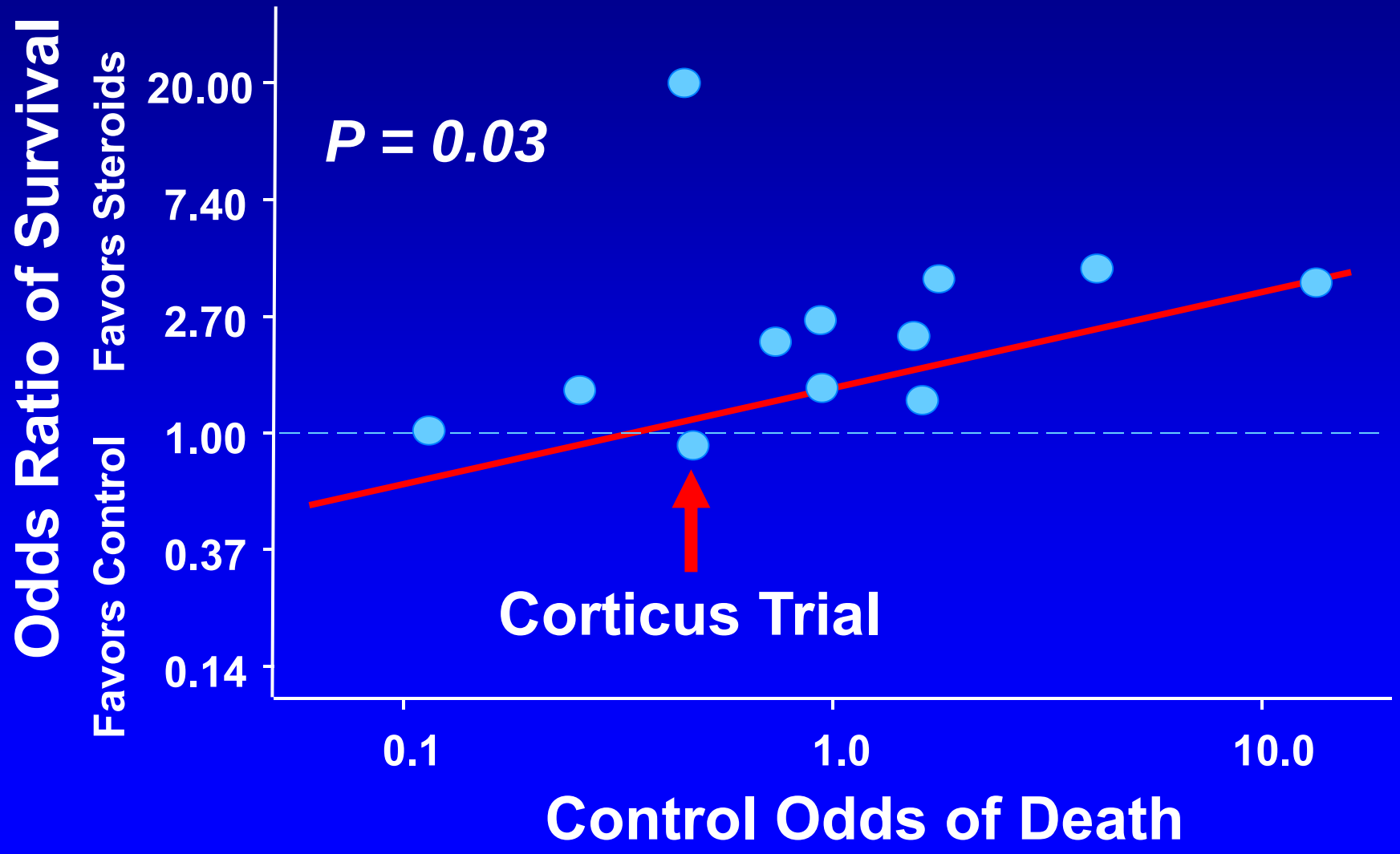


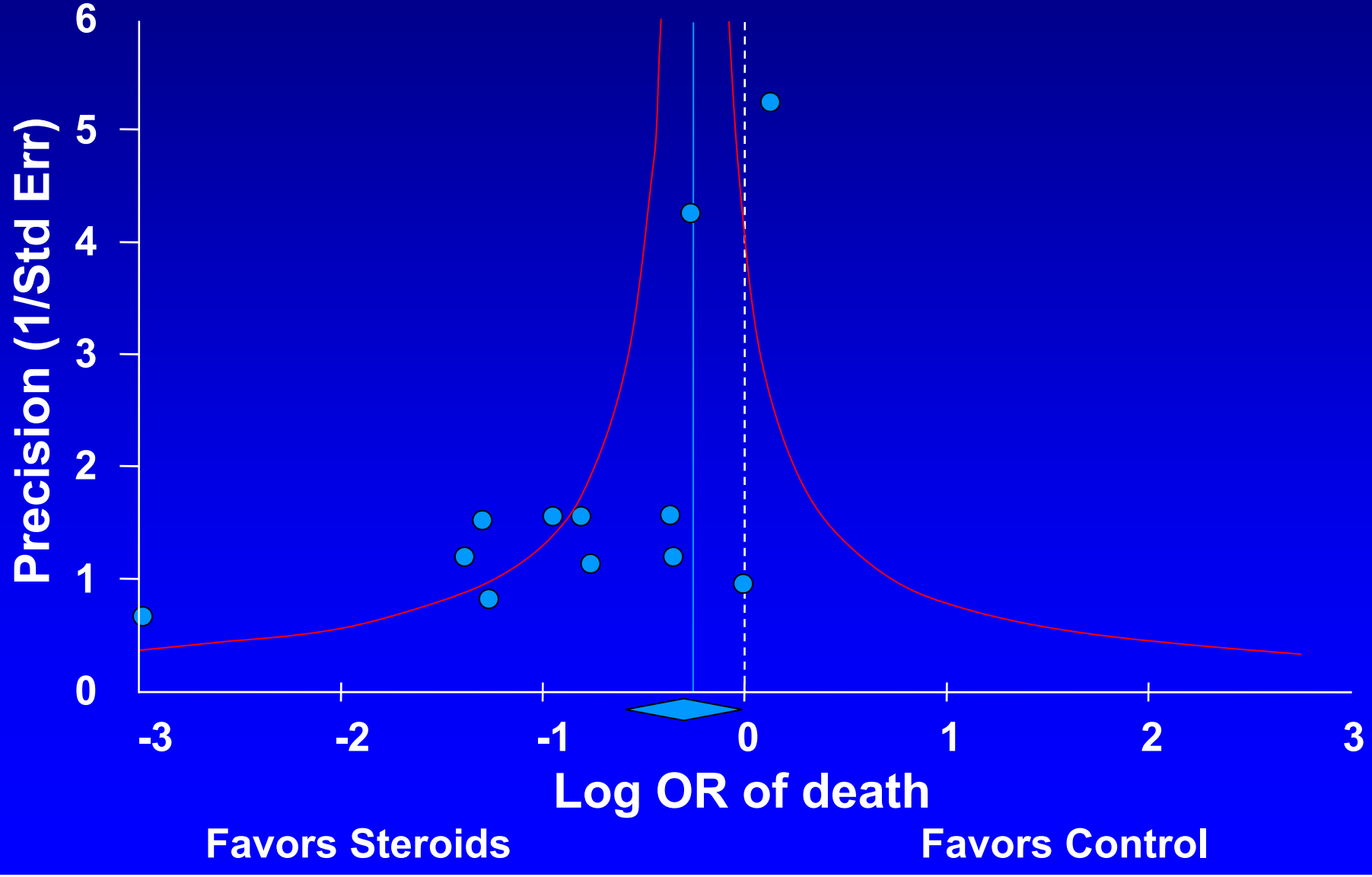
Ann Intern Med 2004; 141:47
Clin Microbiol Infect 2009; 15: 308

How is Corticus Different from the 11 Other Trials of Low-Dose Steroids?

Effect of Corticosteroids During Sepsis Dependent on the Severity of Illness

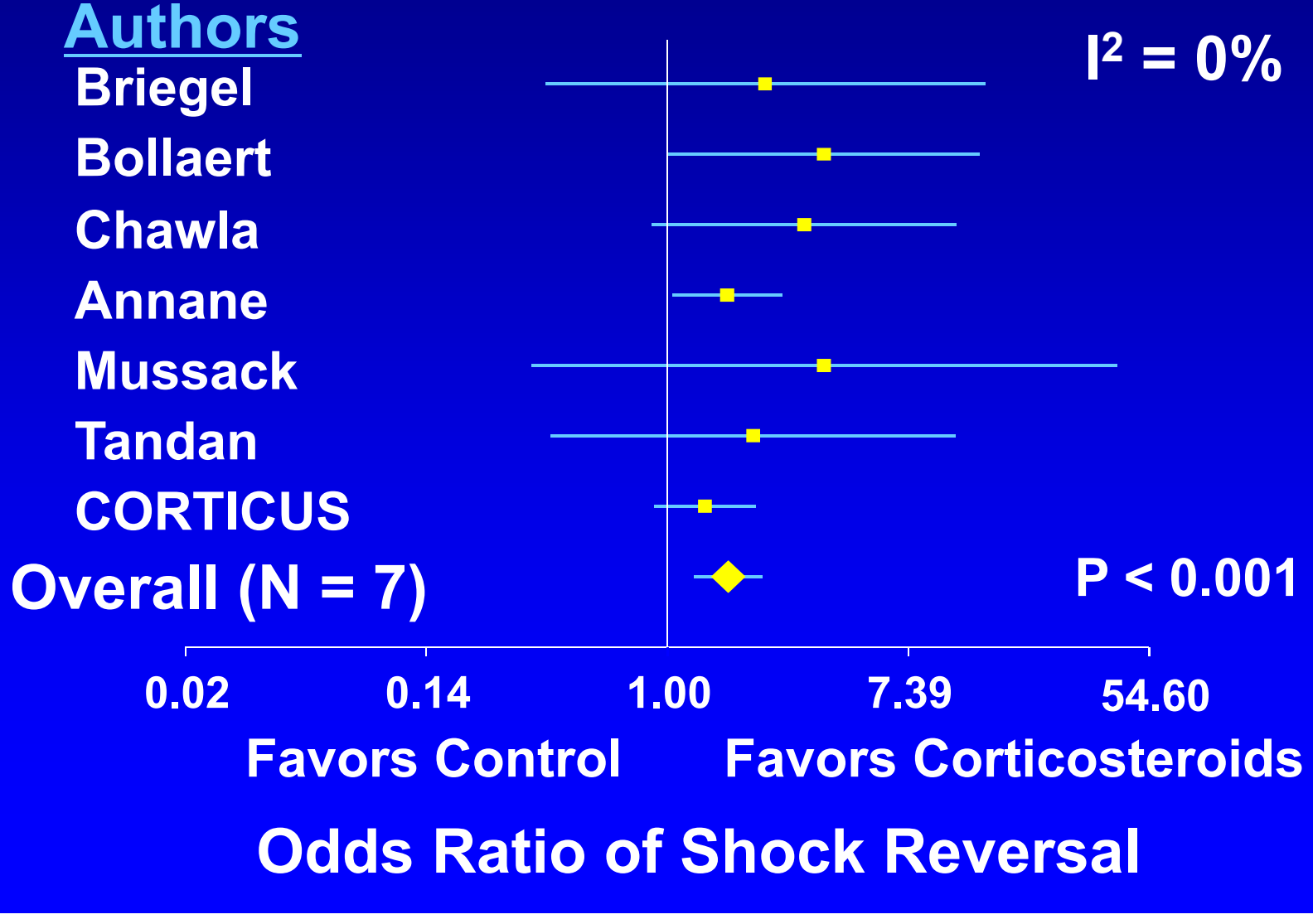


Funnel Plot of Sepsis Trials of Low Dose Steroids



Corticosteroid Effect on Shock

Low Dose Corticosteroids Trials Reporting Shock Reversal



Summary

- Corticosteroid effects during sepsis depend on **dose** and **severity** of illness
- Le… se va… s ar… sal

High dose corticosteroids increase mortality

Low dose corticosteroids improve survival in severely ill patients

Limitations

- At present, the beneficial effects of low doses of corticosteroids are based on small trials (median 40 patients, IQR 41-44) confounded by publication bias
- The largest trial of low dose cortico-steroids (CORTICUS, n = 499) studied a relatively low risk population
- Benefit from low dose corticosteroids has not been confirmed in a large multicenter trial of high risk patients

Conclusions

- Until new data are available, the decision to administer low dose steroids for septic shock should be individualized:
  - Severity of illness
  - Assessment of risk

The New England
Journal of Medicine

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INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.SC., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D., FRANS BRUYNINCKX, M.D., MIET SCHETZ, M.D., PH.D., DIRK VLASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D., PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.

Endorsement of Glycemic Control as Standard of Care for the Critically Ill

- JCAHO
  - Core quality of care - all Medicare hospitals
- American College of Endocrinology
- Volunteer Hospital Association
  - Care bundle
- Institute for Healthcare Improvement
  - Sepsis bundle
  - Post cardiac surgery
- Surviving Sepsis Campaign
  - Sepsis bundle

Am J Resp Crit Care Med 2005; 172:1358

Selected Baseline Characteristics

	Conventional Insulin: glucose 180 - 200 mg/dl N = 783	Intensive Insulin: glucose 80 - 110 mg/dl N = 765
Men	557 (71%)	544 (71%)
Age (yr)	62.2 ± 13.9	63.4 ± 4.4
Reason for ICU care:		
Cardiac Surgery	493 (63%)	477 (62%)
Non-cardiac indications	290 (37%)	288 (38%)
Apache II (median, IQR)	9 (7 - 13)	9 (7 - 13)

N Engl J Med 2001;345:1359

Mortality Associated with Conventional *versus* Intensive Insulin

Death in ICU	# of patients	Conventional Insulin	Intensive Insulin	Δ deaths
Cardiac Surgery	970	25 (5%)	10 (2%)	15
Thoracic	122	10 (18%)	5 (7.6%)	5
Other	70	6 (17%)	0 (0%)	6
Neuro, Vascular, Trauma,Transplant	386	22 (11%)	20 (11%)	2
All patients	**1548**	**63 (8%)**	**35 (5%)**	**28***

N Engl J Med 2001;345:1359

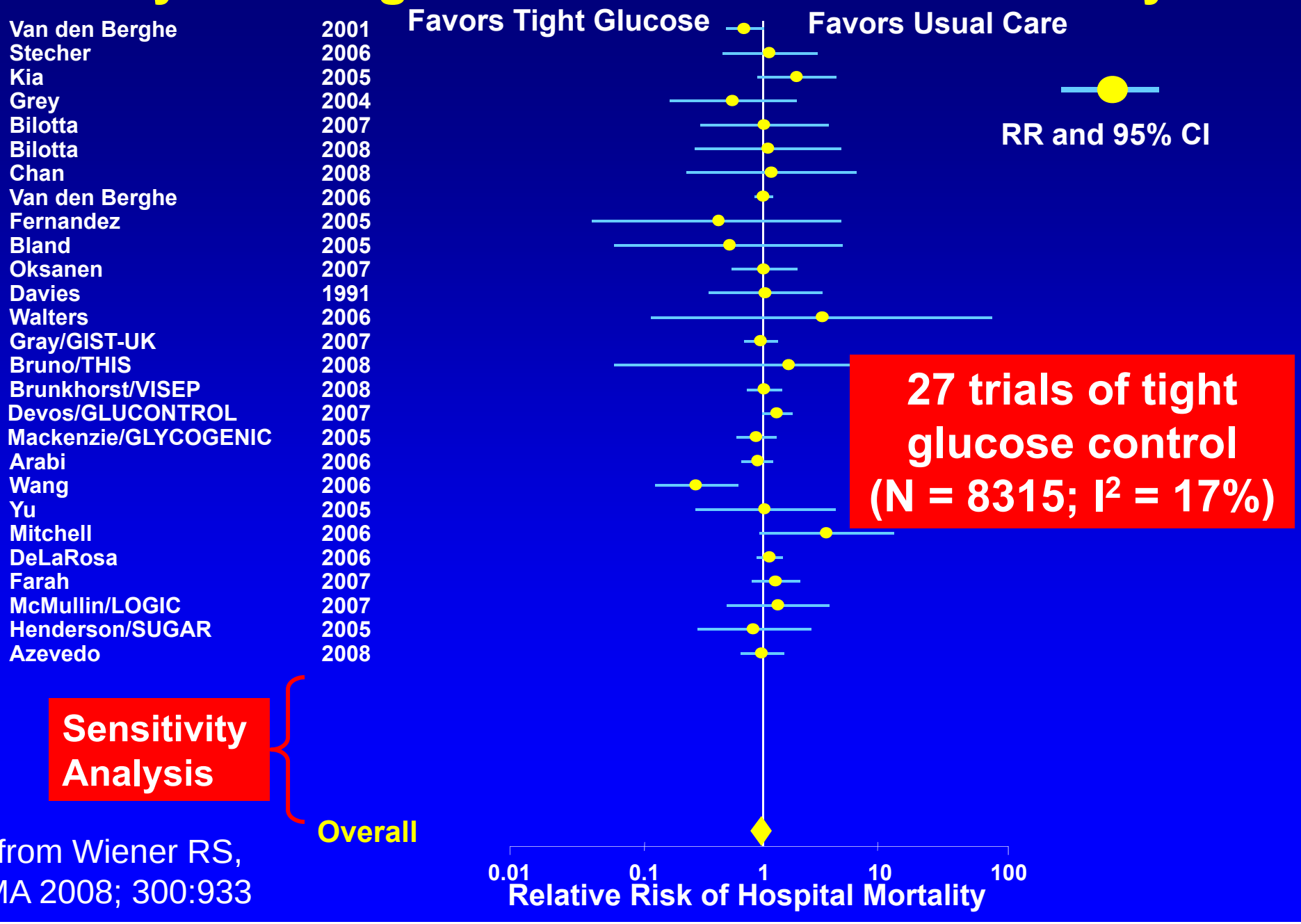
** P < 0.04*

Limitations

- Single center, unblinded study
- Relatively high mortality among cardiac surgery patients in control group (5.1%)
- Immediate post-operative *i.v.* glucose (200-300 g per day: ~ 2 - 3 L D10 or D20) and early feeding (enteral or parenteral)
  - Not routine care for cardiothoracic surgery patients

N Engl J Med 2001;345:1359

Meta-analysis of Tight Glucose Control in Critically Ill



Modified from Wiener RS, et al. JAMA 2008; 300:933

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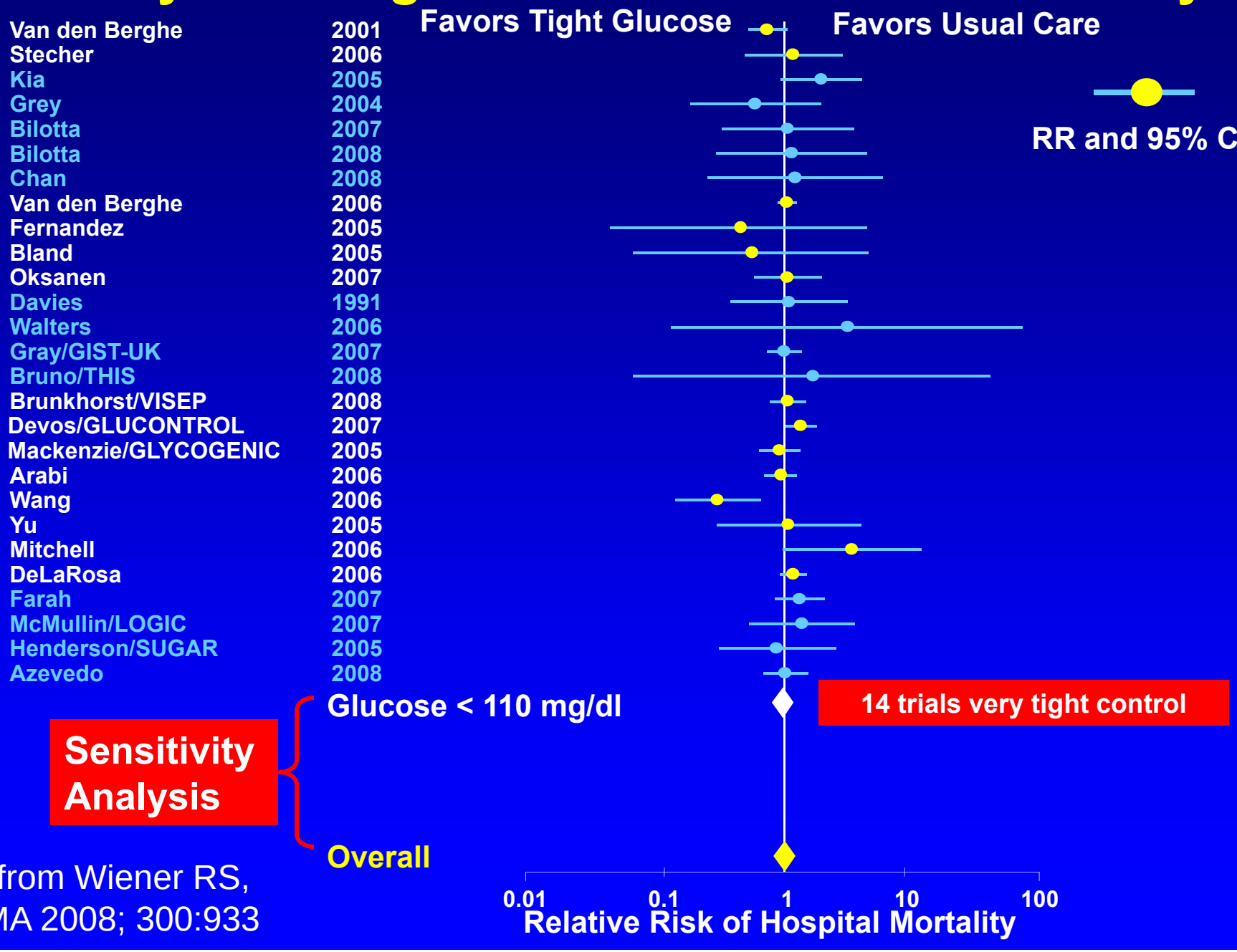

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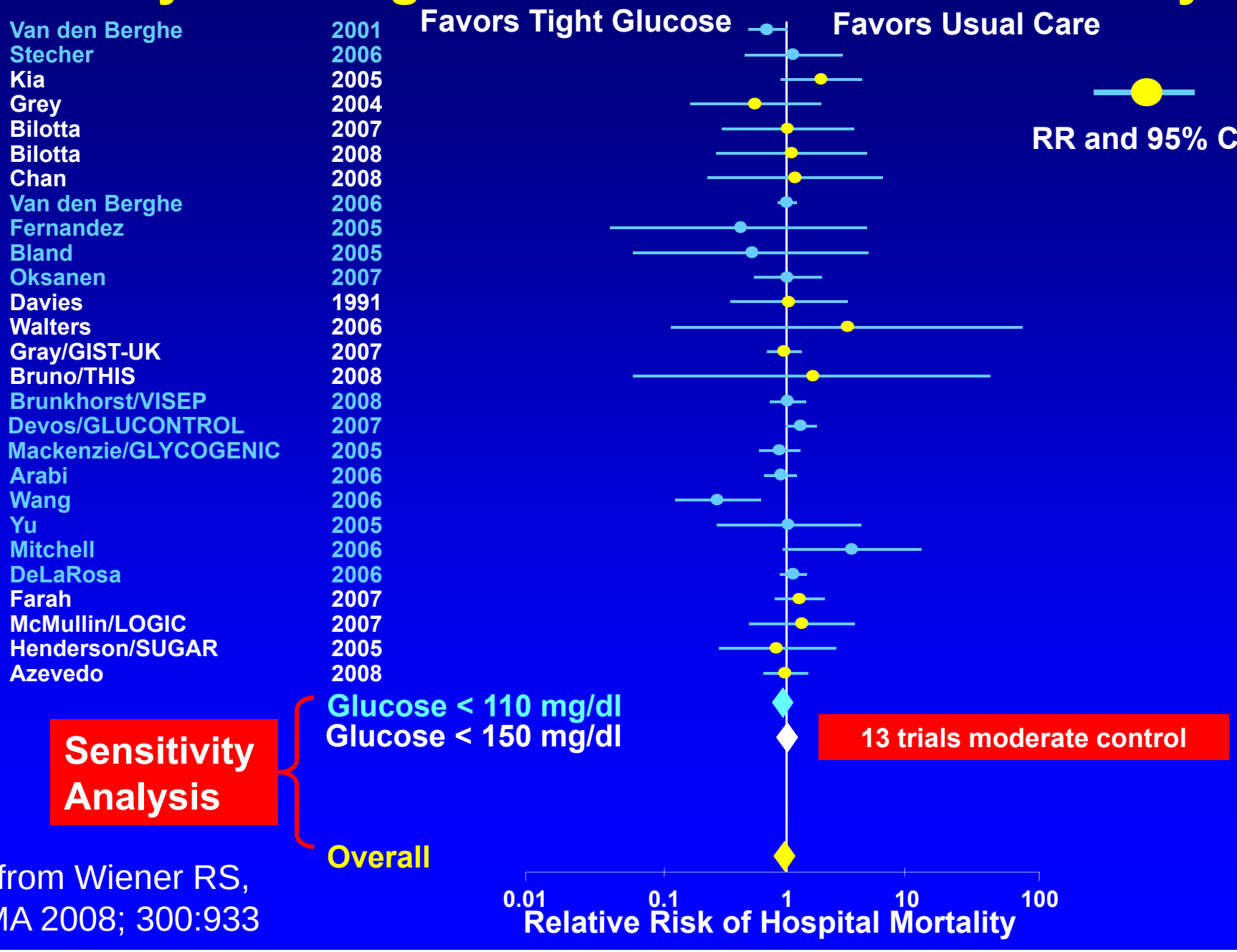

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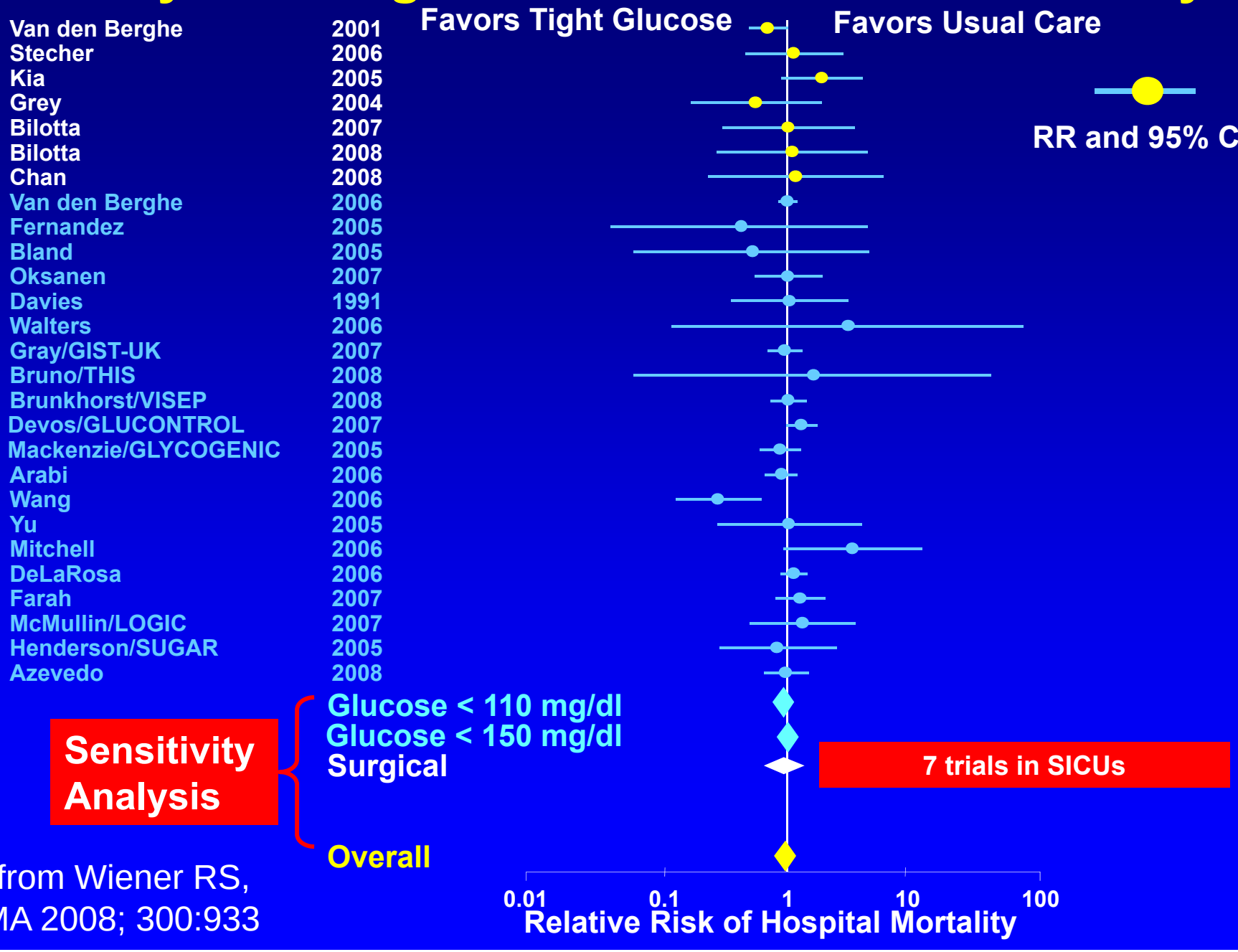

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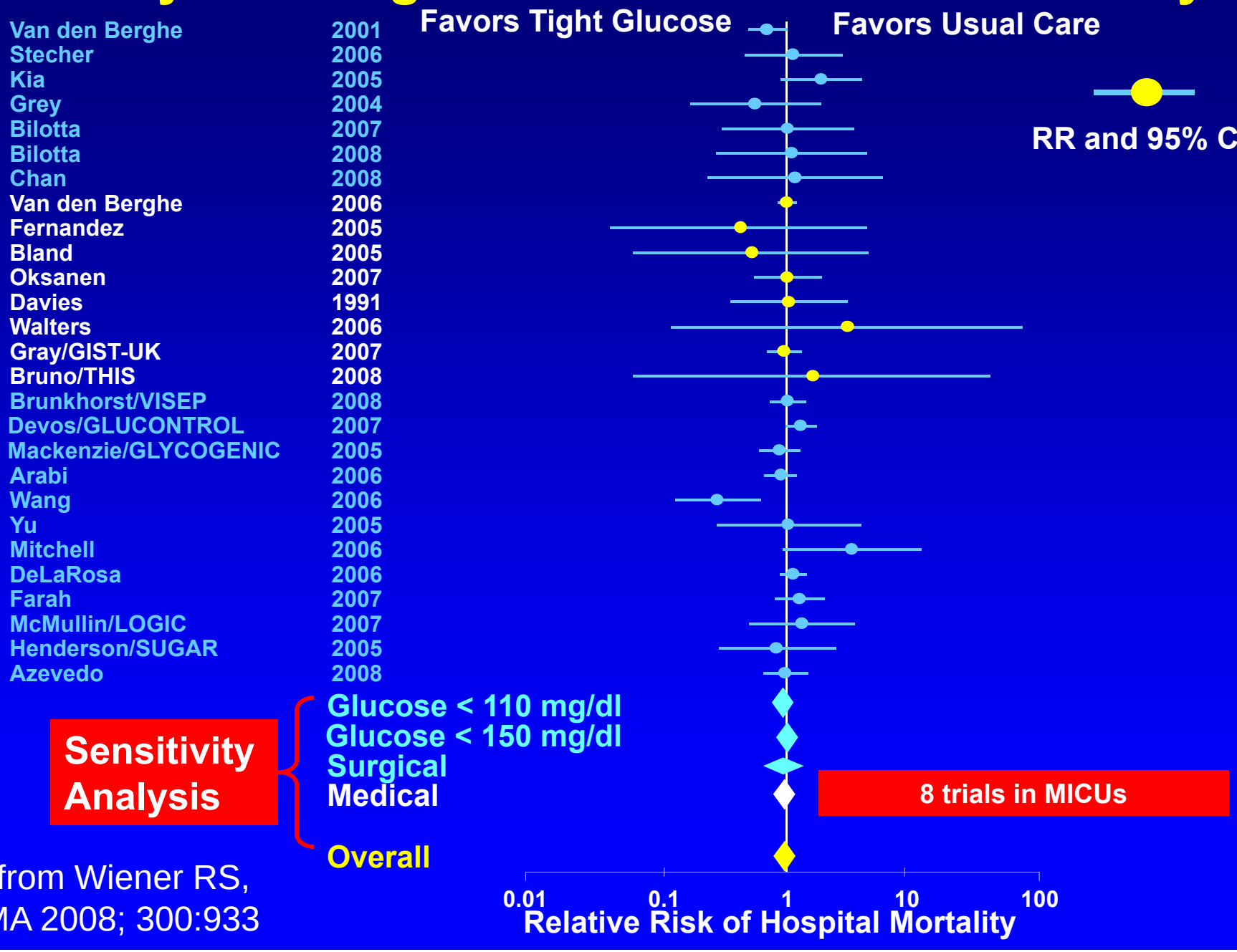

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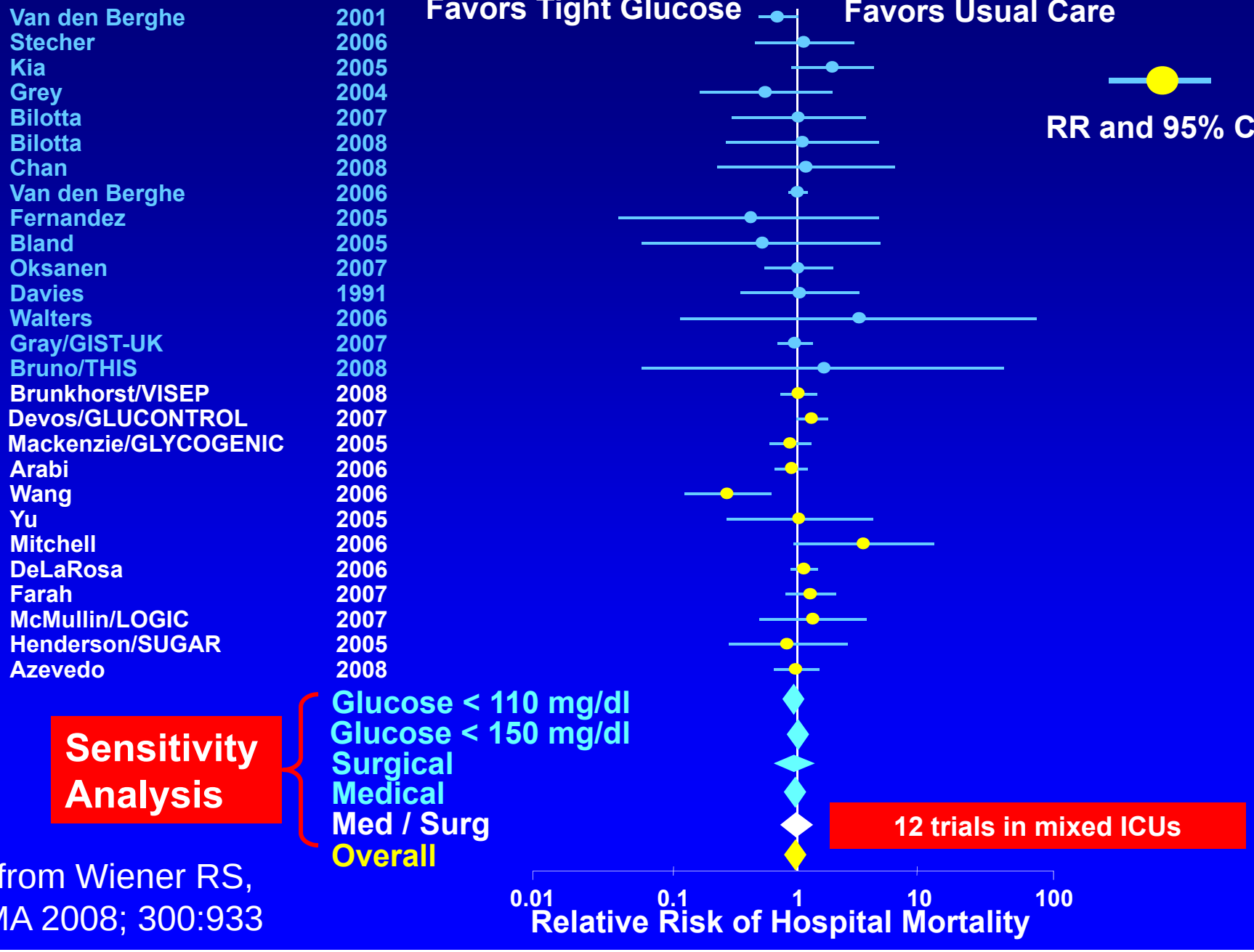

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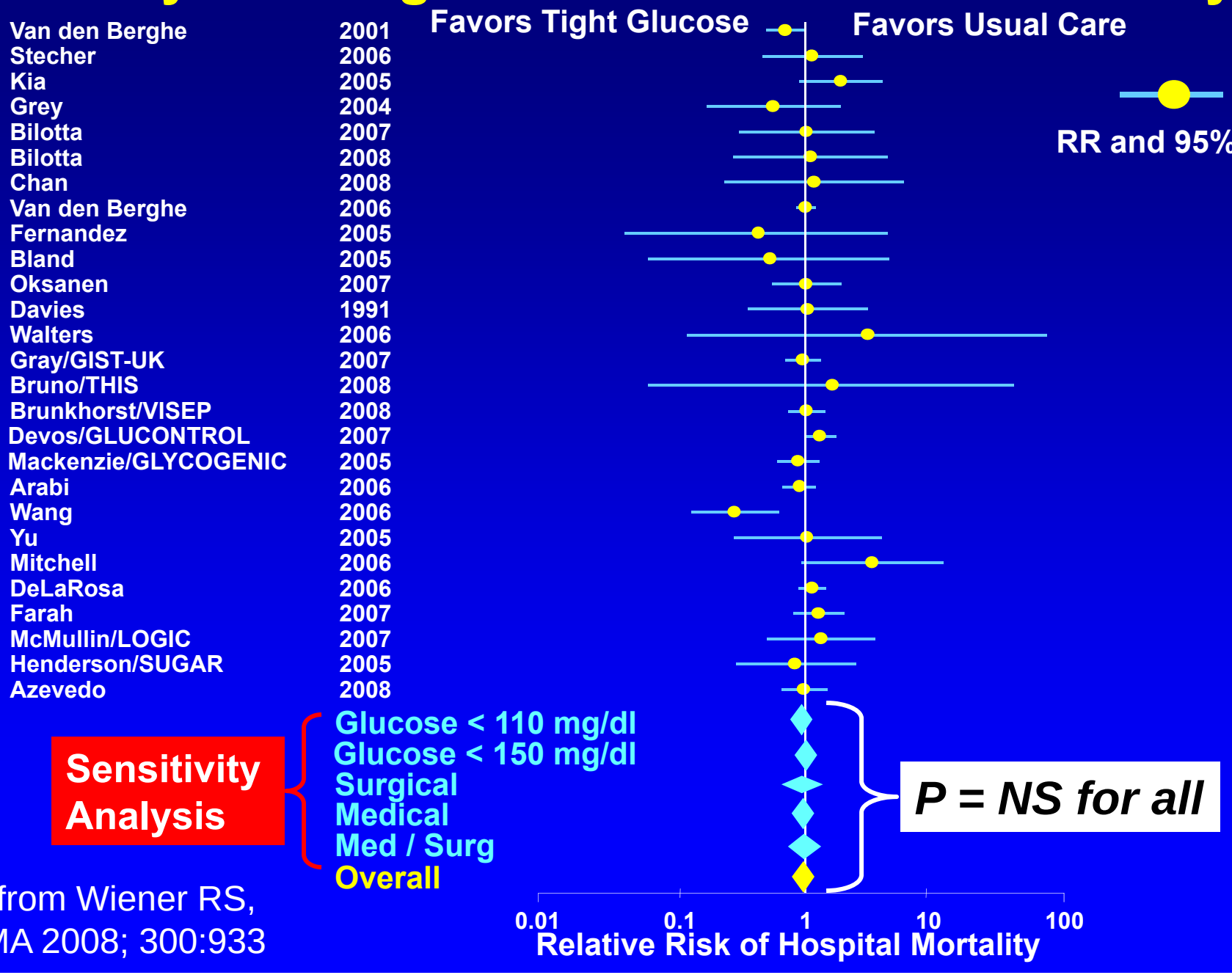

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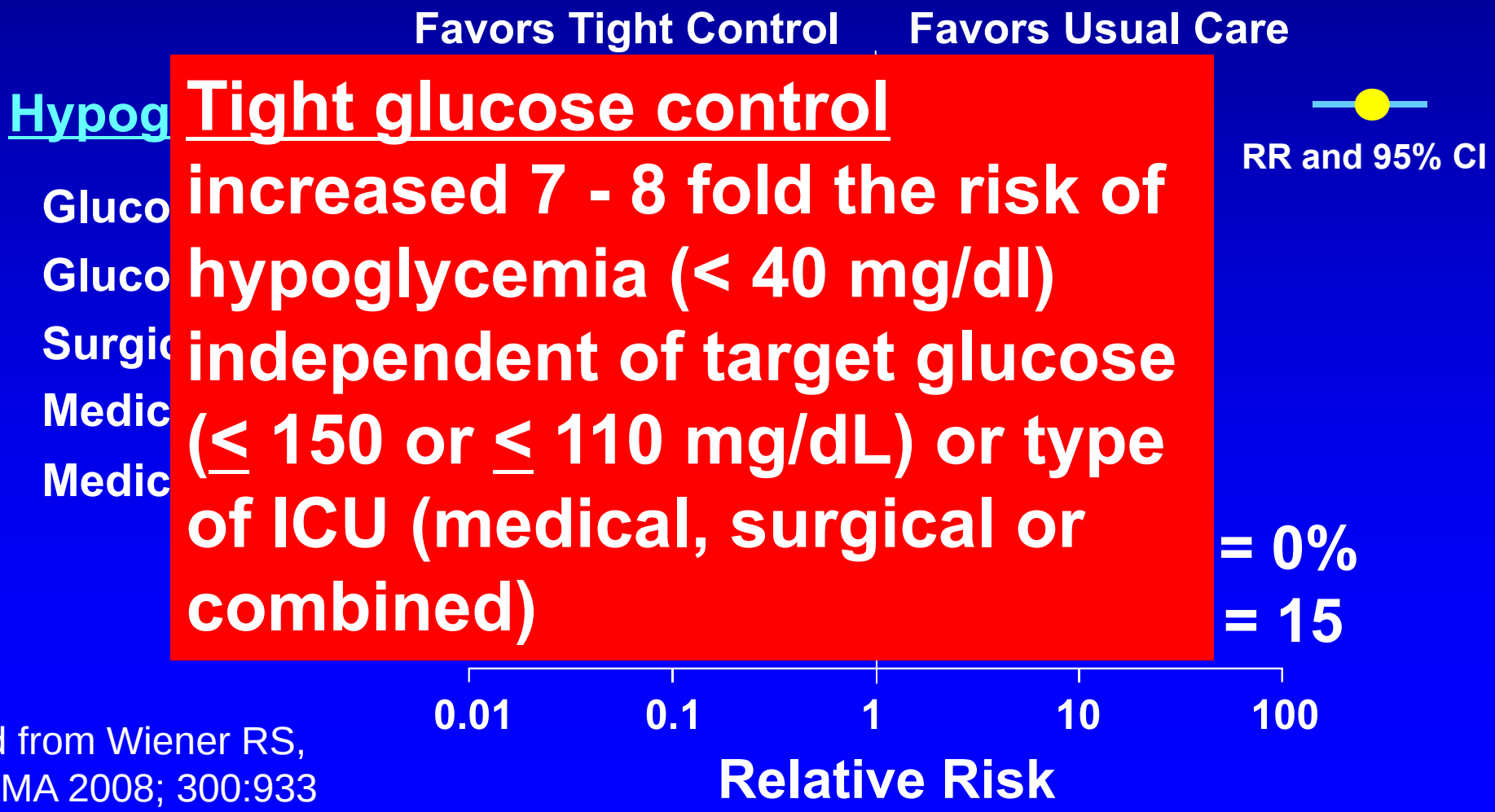
Tight Glucose Control and the Risk of Hypoglycemia



Tight glucose control increased 7 - 8 fold the risk of hypoglycemia (< 40 mg/dl) independent of target glucose (≤ 150 or ≤ 110 mg/dL) or type of ICU (medical, surgical or combined)

Modified from Wiener RS, et al. JAMA 2008; 300:933

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 26, 2009 VOL. 360 NO. 13

Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

NICE-Sugar Trial
Baseline Characteristics

	Intensive Insulin	Conventional Insulin
Enrolled (N)	3054	3050
Surgical	37%	37%
Apache II > 25	31%	31%
Severe Sepsis	22%	21%
Mech Ventilator	94%	94%

N Engl J Med 2009; 360:1283

NICE-Sugar Trial
Outcomes

In 6014 critically ill patients, tight glucose control was associated with hypoglycemia and increased mortality at 90 days.

"On the basis of [these] results we do not recommend use of the lower target (81 - 110 mg/dL) in critically ill patients."

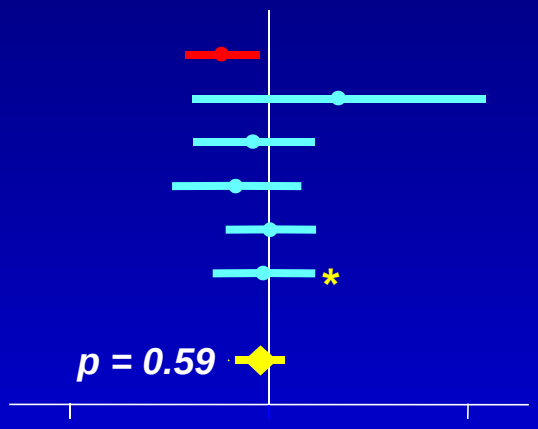
N Engl J Med 2009; 360:1283

Meta-analyses of Sepsis Trials with at Least One Significant Benefical Trial

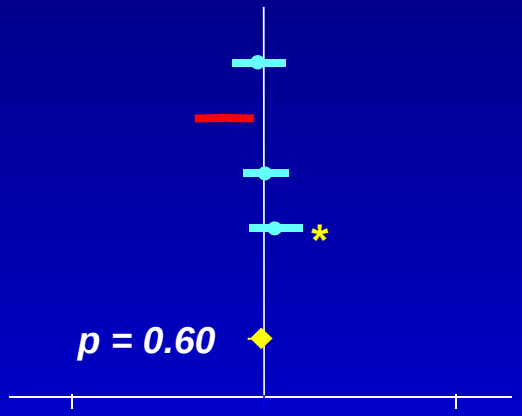
Summary

Anti-Endotoxin

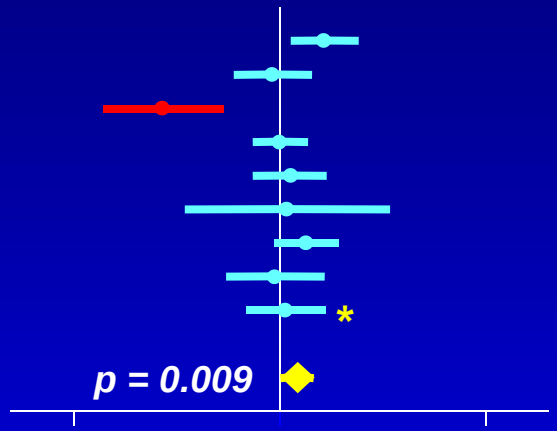
J5 Antiserum



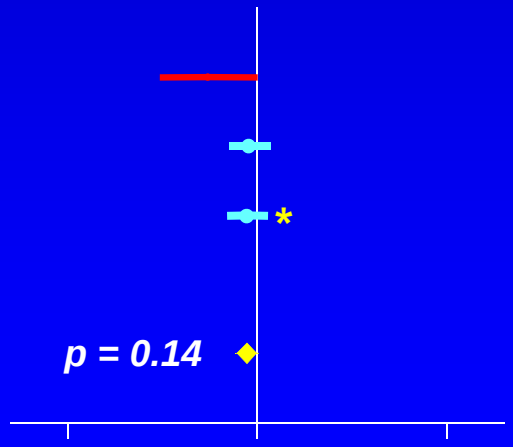
Monoclonals



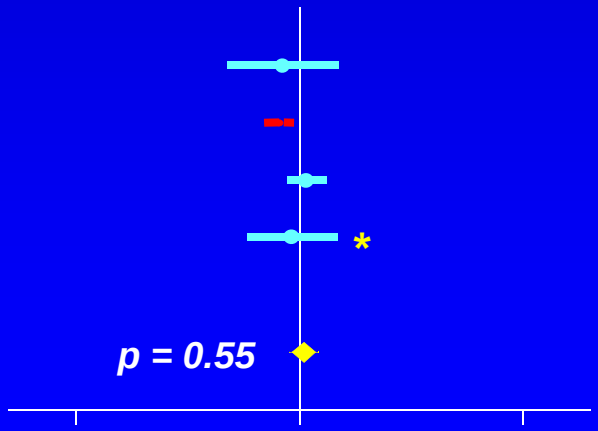
High Dose Corticosteroids



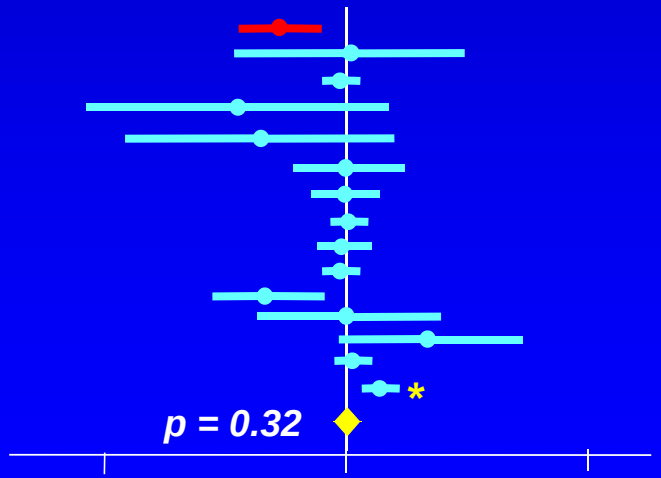
IL-1RA



Activated Protein C



Intensive Insulin



* Shift from beneficial to last trial, p = 0.003

The randomized control trial minimizes bias but does not eliminate the need for reproducibility which is the *sine qua non* (i.e. the indispensable and essential condition) of scientific evidence