# Using Secondary Data in Statistical Analysis

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Bethesda, MD

## 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

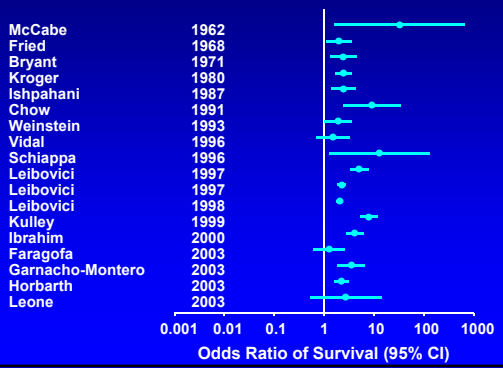
Lancet, 1999.

## Meta-analysis of Clinical Trials in Sepsis

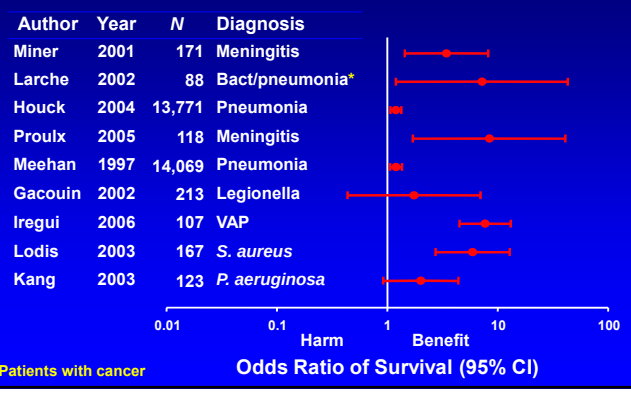
## Septic Shock Management

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

## Benefits of Starting Appropriate Antibiotic Therapy

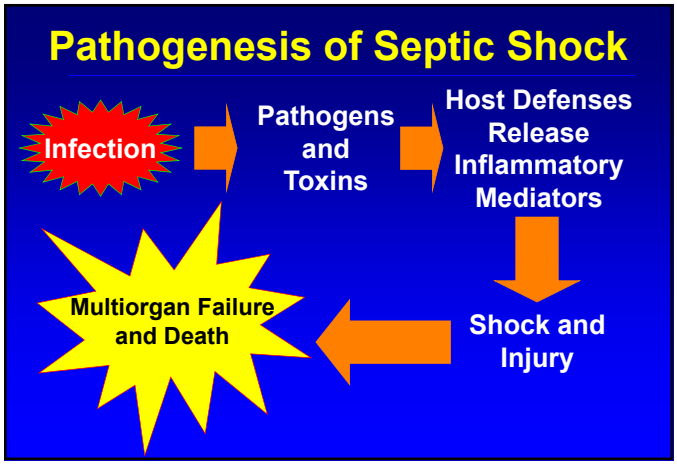


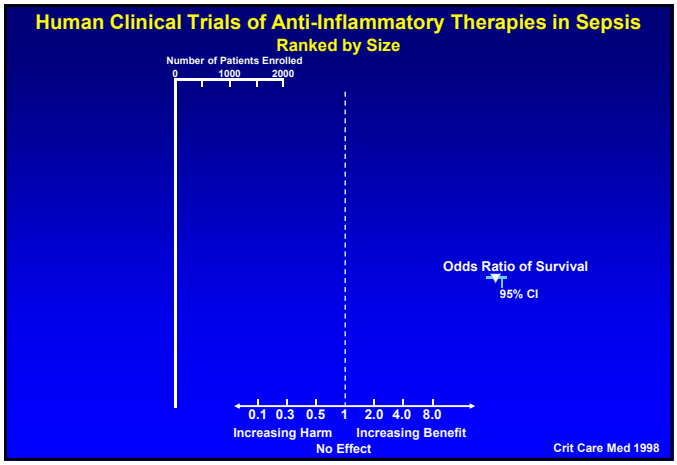

## Benefit of Early *versus* Late Antibiotics

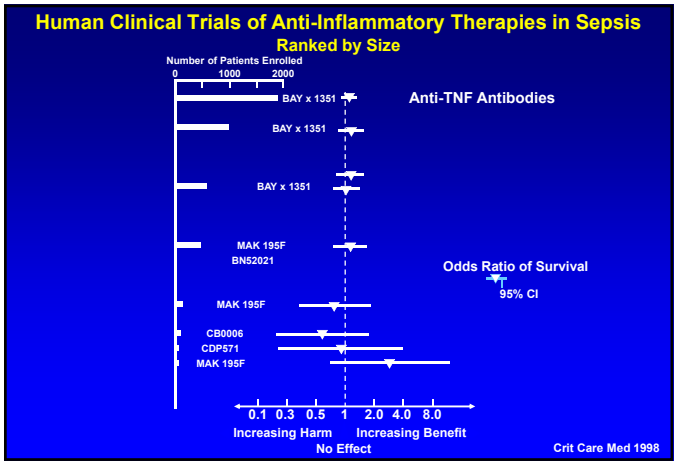



* Patients with cancer

## The Host Inflammatory Response Hypothesis: What went wrong?


Pathogenesis of Septic Shock
Infection
Pathogens and Toxins
Host Defenses Release Inflammatory Mediators
Shock and Injury
Multiorgan Failure and Death


Human Clinical Trials of Anti-Inflammatory Therapies in Sepsis
Ranked by Size
Number of Patients Enrolled
0
1000
2000
Odds Ratio of Survival
95% CI
0.1 0.3 0.5 1 2.0 4.0 8.0
Increasing Harm
Increasing Benefit
No Effect
Crit Care Med 1998


Human Clinical Trials of Anti-Inflammatory Therapies in Sepsis
Ranked by Size
Number of Patients Enrolled
0
1000
2000
BAY x 1351
BAY x 1351
BAY x 1351
Anti-TNF Antibodies
MAK 195F
BN52021
MAK 195F
CB0006
CDP571
MAK 195F
Odds Ratio of Survival
95% CI
0.1 0.3 0.5 1 2.0 4.0 8.0
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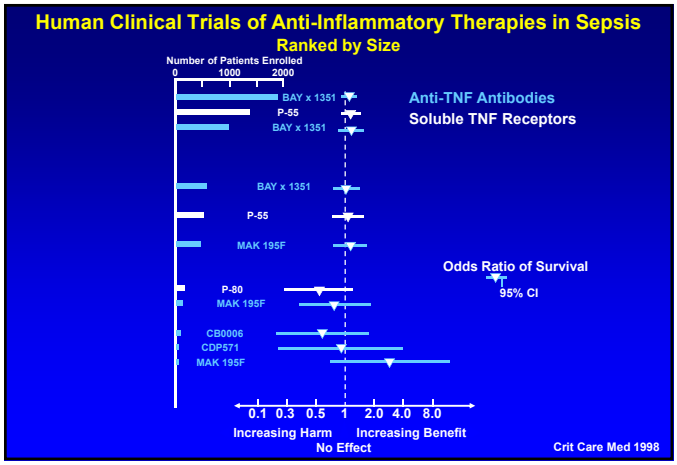
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P-55
BAY x 1351
BAY x 1351
P-55
MAK 195F
P-80
MAK 195F
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MAK 195F
Anti-TNF Antibodies
Soluble TNF Receptors
Odds Ratio of Survival
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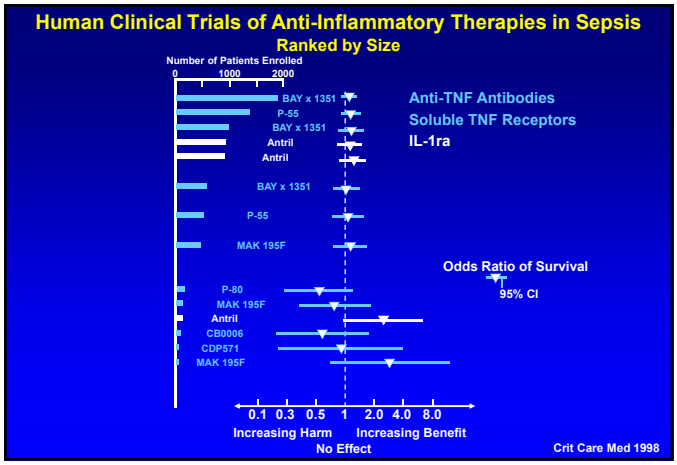
Human Clinical Trials of Anti-Inflammatory Therapies in Sepsis
Ranked by Size
Number of Patients Enrolled
0
1000
2000
BAY x 1351
P-55
BAY x 1351
Antril
Antril
BAY x 1351
P-55
MAK 195F
P-80
MAK 195F
Antril
CB0006
CDP571
MAK 195F
Anti-TNF Antibodies
Soluble TNF Receptors
IL-1ra
Odds Ratio of Survival
95% CI
0.1 0.3 0.5 1 2.0 4.0 8.0
Increasing Harm
Increasing Benefit
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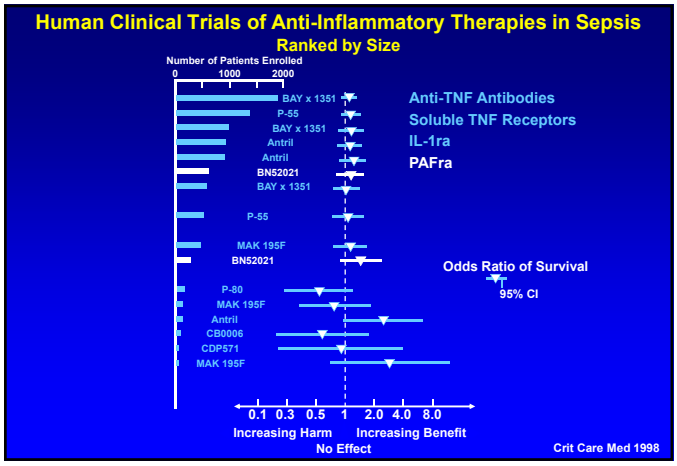
Crit Care Med 1998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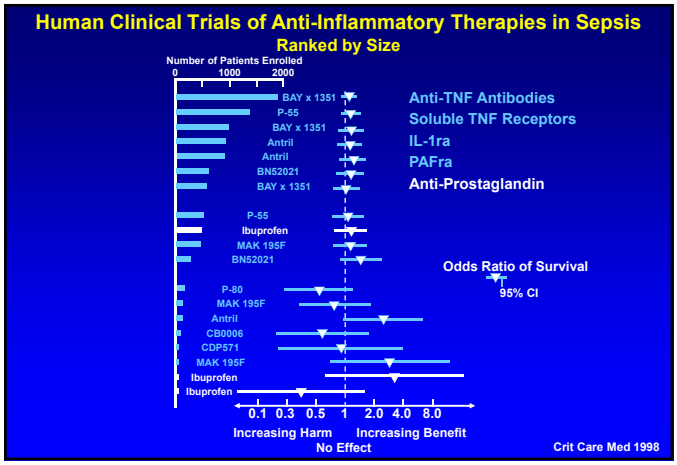
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BAY x 1351
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Antril
BN52021
BAY x 1351
P-55
Ibuprofen
MAK 195F
BN52021
P-80
MAK 195F
Antril
CB0006
CDP571
MAK 195F
Ibuprofen
Ibuprofen
Anti-TNF Antibodies
Soluble TNF Receptors
IL-1ra
PAFra
Anti-Prostaglandin
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95% CI
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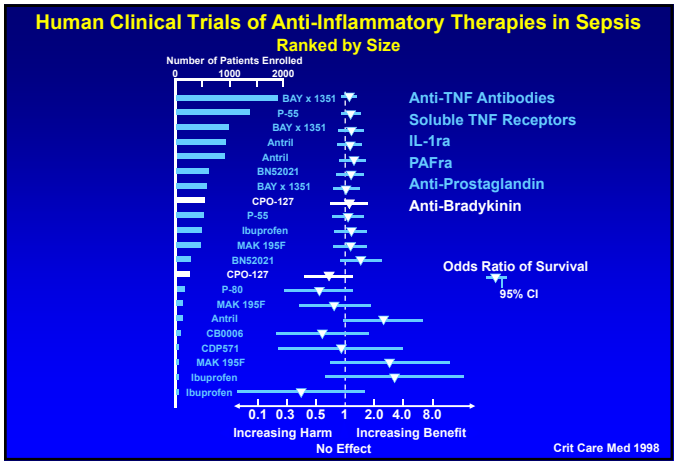
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Antril
Antril
BN52021
BAY x 1351
CPO-127
P-55
Ibuprofen
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CPO-127
P-80
MAK 195F
Antril
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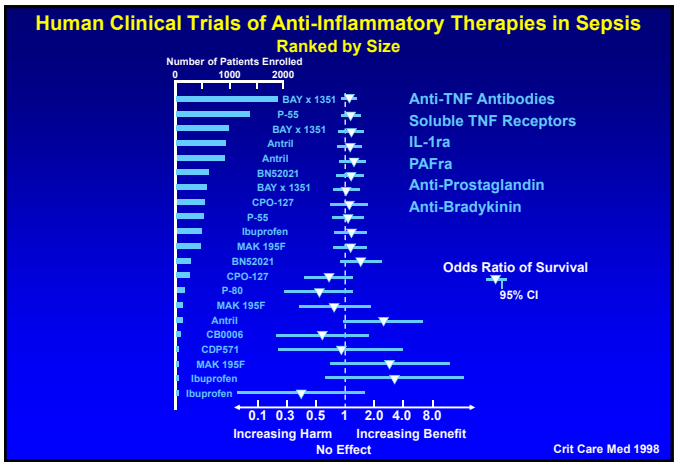
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2000
BAY x 1351
P-55
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Antril
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BN52021
BAY x 1351
CPO-127
P-55
Ibuprofen
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Anti-Prostaglandin
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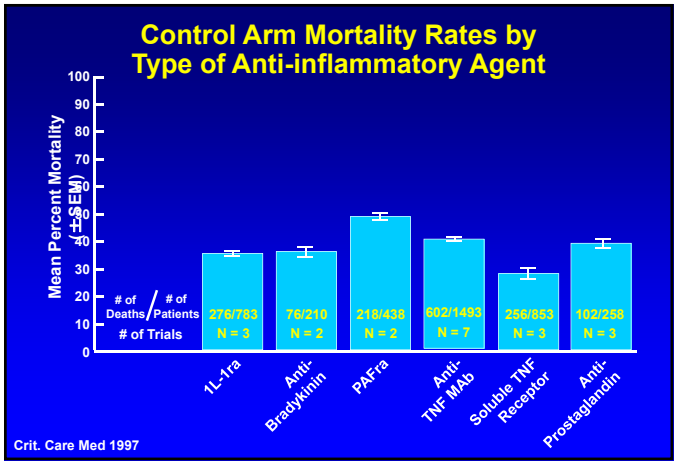
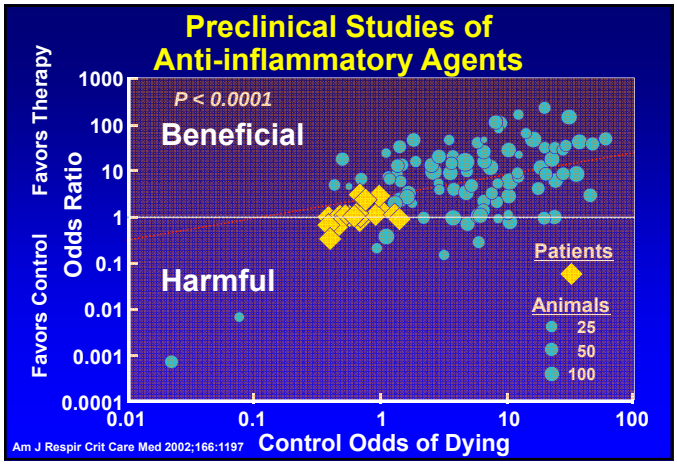
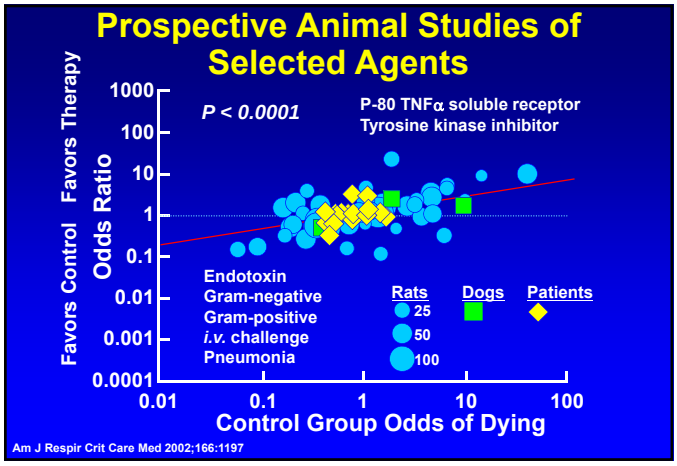
Increasing Harm
Increasing Benefit
No Effect
Crit Care Med 1998


Control Arm Mortality Rates by Type of Anti-inflammatory Agent
Mean Percent Mortality (±SEM)
100
90
80
70
60
50
40
30
20
10
0
# of Deaths / # of Patients
# of Trials
276/783 N = 3
76/210 N = 2
218/438 N = 2
602/1493 N = 7
256/853 N = 3
102/258 N = 3
1L-1ra
Anti-Bradykinin
PAFra
Anti-TNF MAb
Soluble TNF Receptor
Anti-Prostaglandin
Crit. Care Med 1997


Preclinical Studies of Anti-inflammatory Agents
Favors Therapy
Favors Control
Odds Ratio
1000
100
10
1
0.1
0.01
0.001
0.0001
P < 0.0001
Beneficial
Harmful
Patients
Animals
25
50
100
0.01
0.1
1
10
100
Control Odds of Dying
Am J Respir Crit Care Med 2002;166:1197


Prospective Animal Studies of Selected Agents
Favors Therapy
Favors Control
Odds Ratio
1000
100
10
1
0.1
0.01
0.001
0.0001
P < 0.0001
P-80 TNFα soluble receptor
Tyrosine kinase inhibitor
Endotoxin
Gram-negative
Gram-positive
i.v. challenge
Pneumonia
Rats
Dogs
Patients
25
50
100
0.01
0.1
1
10
100
Control Group Odds of Dying
Am J Respir Crit Care Med 2002;166:1197

## Summary
## Anti-Inflammatory Agents in Sepsis

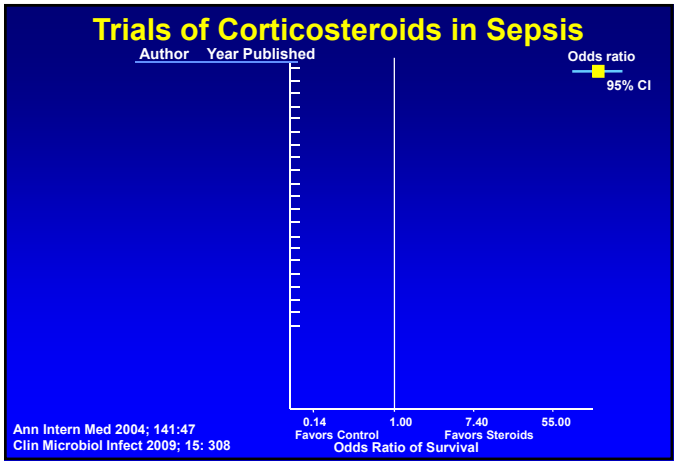
- Meta-analysis:
  - treatment effects are small (3%), but statistically significant
- Meta-regression analysis:
  - Efficacy dependent on risk of death
    - Beneficial at high risks of death,
    - ineffective or harmful when risk was moderate or low

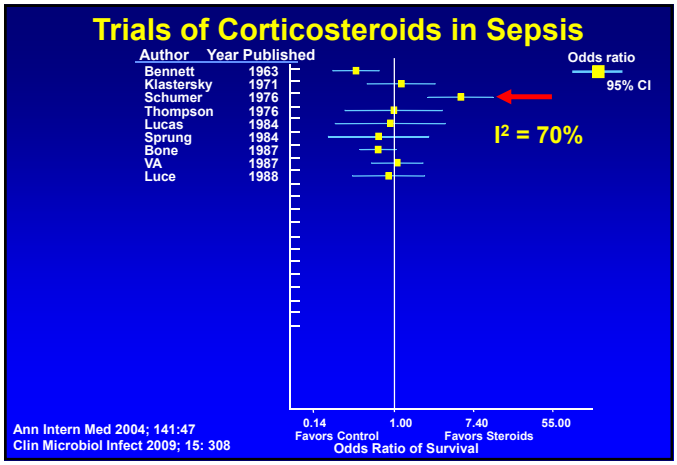
## Paradox of Corticosteroids in Sepsis

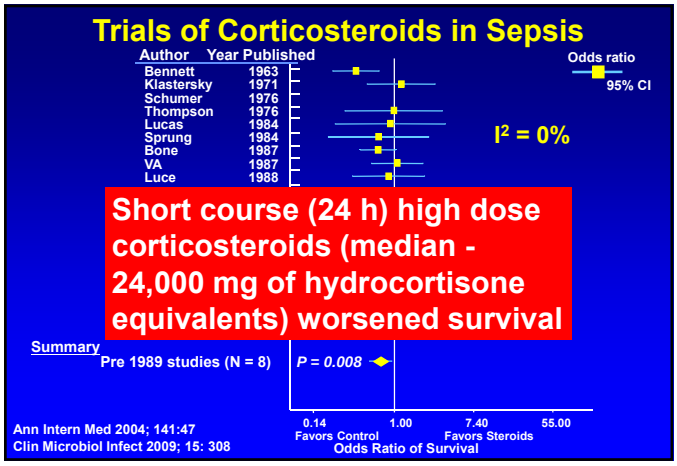
Less may have benefits, but only in sickest patients

## 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
Author Year Published
Odds ratio
95% CI
0.14
1.00
7.40
55.00
Favors Control
Favors Steroids
Odds Ratio of Survival
Ann Intern Med 2004; 141:47
Clin Microbiol Infect 2009; 15: 308


Trials of Corticosteroids in Sepsis
Author Year Published
Bennett 1963
Klastersky 1971
Schumer 1976
Thompson 1976
Lucas 1984
Sprung 1984
Bone 1987
VA 1987
Luce 1988
Odds ratio
95% CI
I² = 70%
0.14
1.00
7.40
55.00
Favors Control
Favors Steroids
Odds Ratio of Survival
Ann Intern Med 2004; 141:47
Clin Microbiol Infect 2009; 15: 308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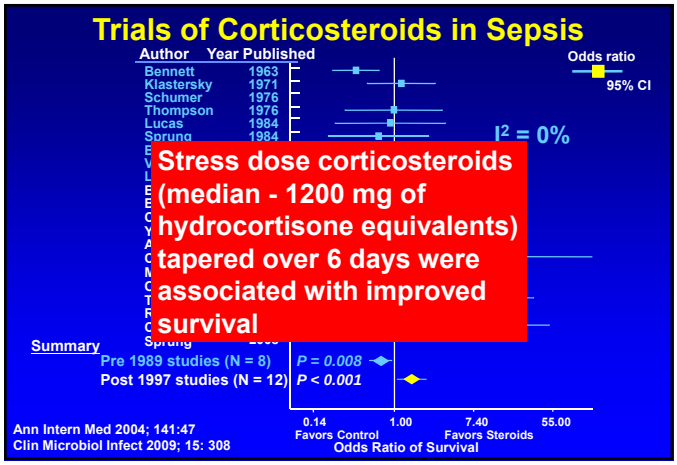
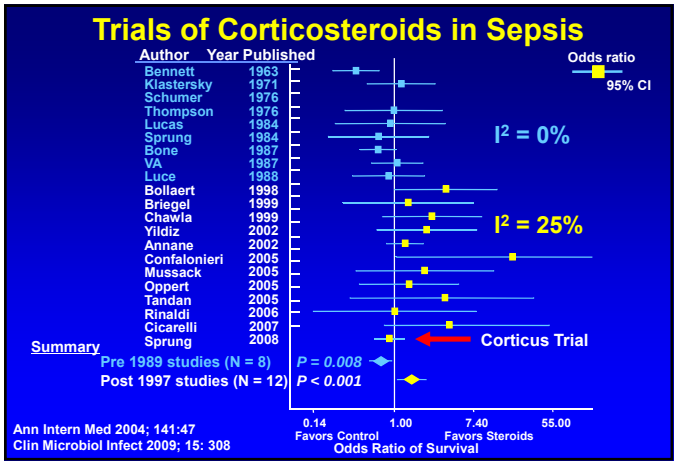
Schumer 1976
Thompson 1976
Lucas 1984
Sprung 1984
Bone 1987
VA 1987
Luce 1988
Odds ratio
95% CI
I² = 0%
Short course (24 h) high dose corticosteroids (median - 24,000 mg of hydrocortisone equivalents) worsened survival
Summary
Pre 1989 studies (N = 8)
P = 0.008
0.14
1.00
7.40
55.00
Favors Control
Favors Steroids
Odds Ratio of Survival
Ann Intern Med 2004; 141:47
Clin Microbiol Infect 2009; 15: 308


Trials of Corticosteroids in Sepsis
Author Year Published
Odds ratio
95% CI
Bennett 1963
Klastersky 1971
Schumer 1976
Thompson 1976
Lucas 1984
Sprung 1984
I² = 0%
Stress dose corticosteroids (median - 1200 mg of hydrocortisone equivalents) tapered over 6 days were associated with improved survival
Summary
Pre 1989 studies (N = 8) P = 0.008
Post 1997 studies (N = 12) P < 0.001
0.14 1.00 7.40 55.00
Favors Control Favors Steroids
Odds Ratio of Survival
Ann Intern Med 2004; 141:47
Clin Microbiol Infect 2009; 15: 308


Trials of Corticosteroids in Sepsis
Author Year Published
Odds ratio
95% CI
Bennett 1963
Klastersky 1971
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Thompson 1976
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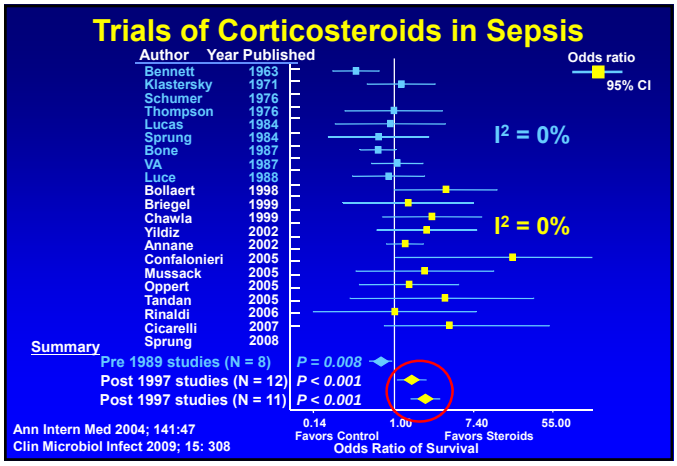
Luce 1988
Bollaert 1998
Briegel 1999
Chawla 1999
Yildiz 2002
Annane 2002
Confalonieri 2005
Mussack 2005
Oppert 2005
Tandan 2005
Rinaldi 2006
Cicarelli 2007
Sprung 2008
I² = 0%
I² = 25%
Corticus Trial
Summary
Pre 1989 studies (N = 8) P = 0.008
Post 1997 studies (N = 12) P < 0.001
0.14 1.00 7.40 55.00
Favors Control Favors Steroids
Odds Ratio of Survival
Ann Intern Med 2004; 141:47
Clin Microbiol Infect 2009; 15: 308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Author Year Published
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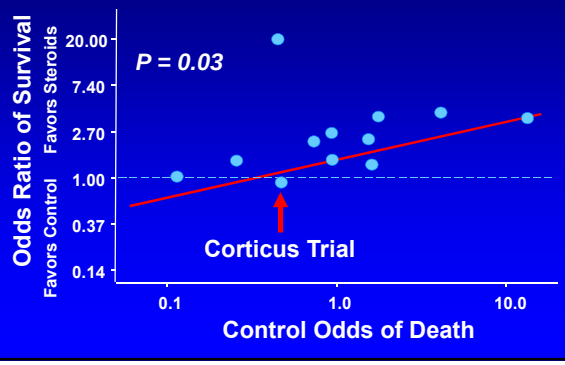
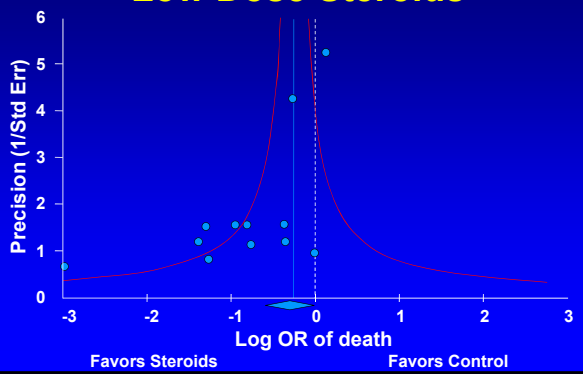
Sprung 2008
I² = 0%
I² = 0%
Summary
Pre 1989 studies (N = 8) P = 0.008
Post 1997 studies (N = 12) P < 0.001
Post 1997 studies (N = 11) P < 0.001
0.14 1.00 7.40 55.00
Favors Control Favors Steroids
Odds Ratio of Survival
Ann Intern Med 2004; 141:47
Clin Microbiol Infect 2009; 15: 308

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

## Effect of Corticosteroids During Sepsis Dependent on the Severity of Illness

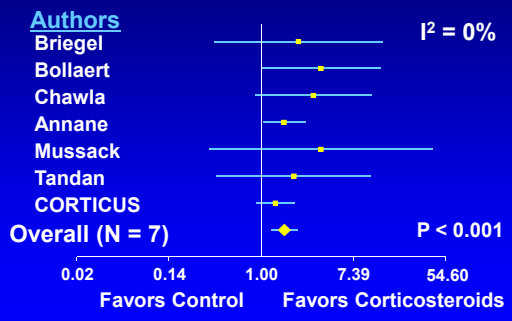



## Funnel Plot of Sepsis Trials of Low Dose Steroids



## Corticosteroid Effect on Shock

## Low Dose Corticosteroids Trials Reporting Shock Reversal




## Summary

- Corticosteroid effects during sepsis depend on dose and severity of illness
- L… se va… … an… …al

High dose corticosteroids increase mortality

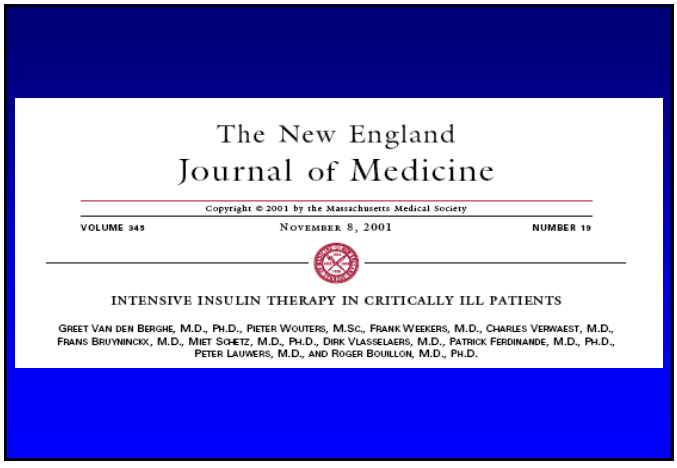
Low dose corticosteroids improve survival in severely ill patients

## 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



VOLUME 345 NOVEMBER 8, 2001 NUMBER 19

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

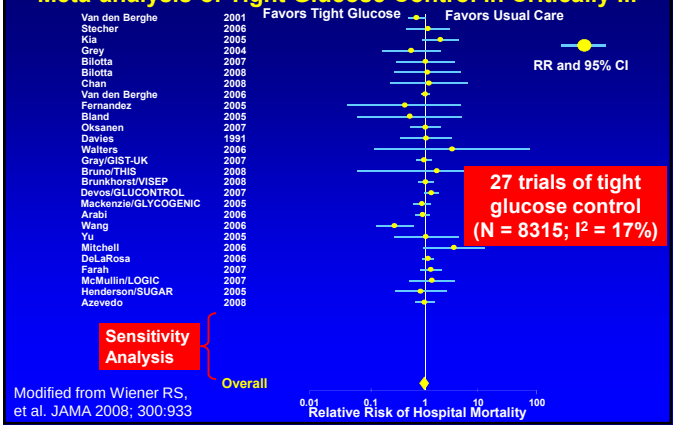
** P < 0.04*

# 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

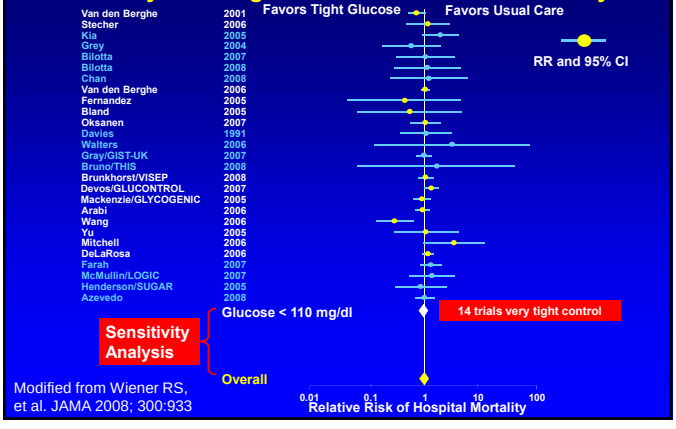
N Engl J Med 2001;345:1359

## Meta-analysis of Tight Glucose Control in Critically Ill

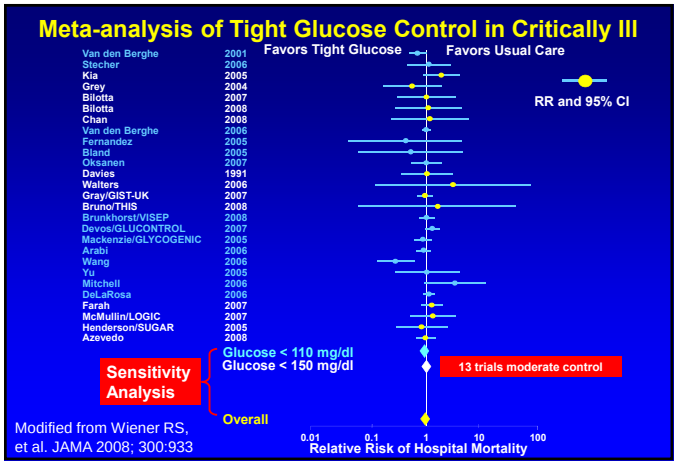



Modified from Wiener RS, et al. JAMA 2008; 300:933

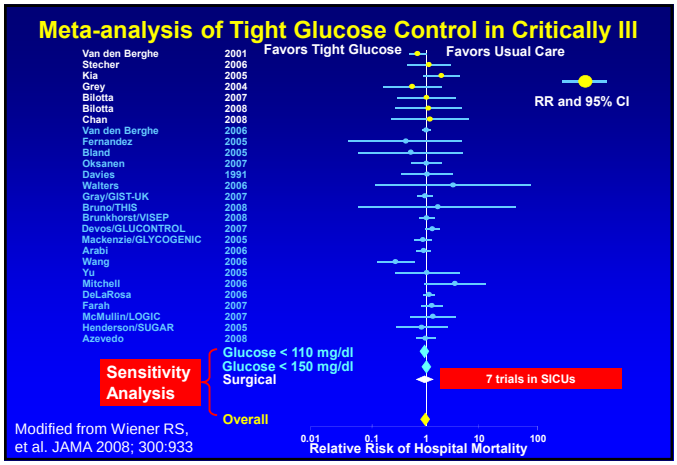
## Meta-analysis of Tight Glucose Control in Critically Ill



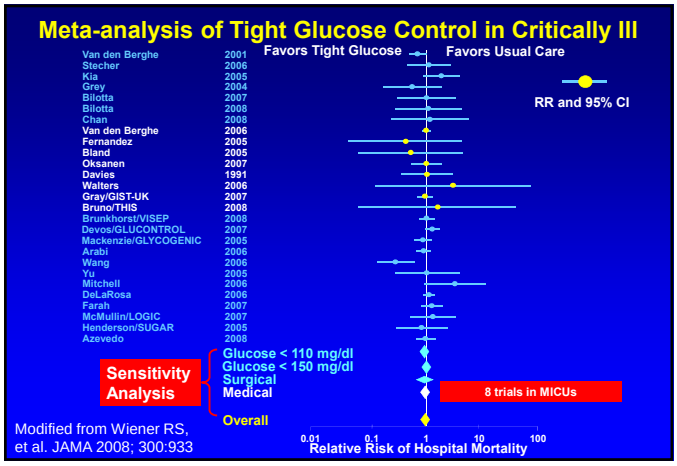

Modified from Wiener RS, et al. JAMA 2008; 300:933



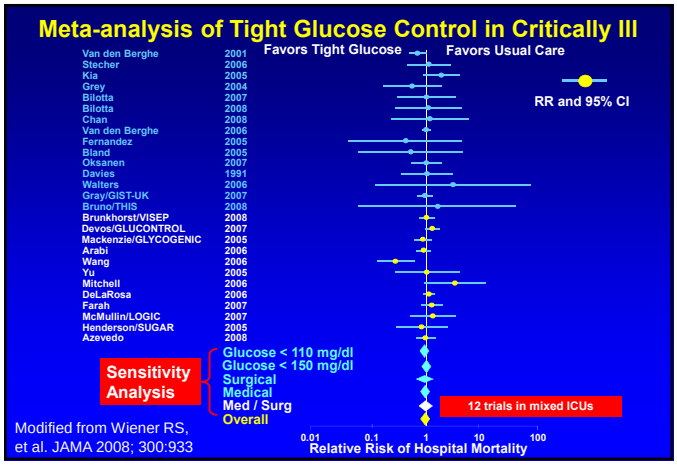
Modified from Wiener RS, et al. JAMA 2008; 300:933



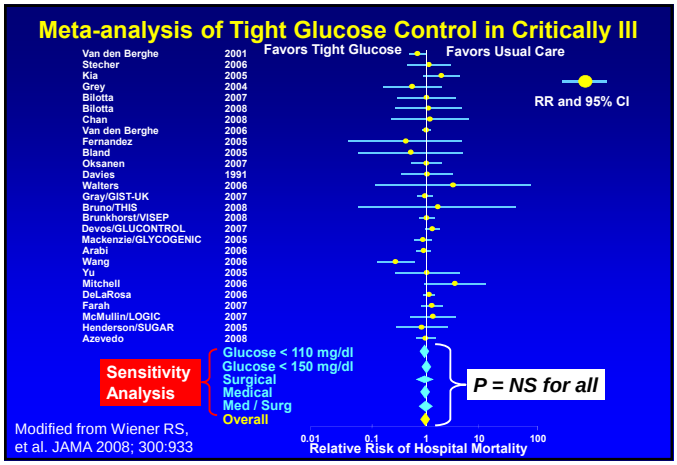
Modified from Wiener RS, et al. JAMA 2008; 300:933



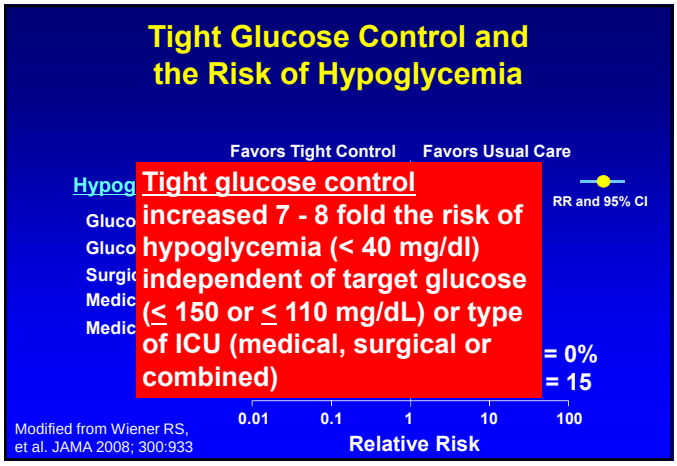
Modified from Wiener RS, et al. JAMA 2008; 300:933



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



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



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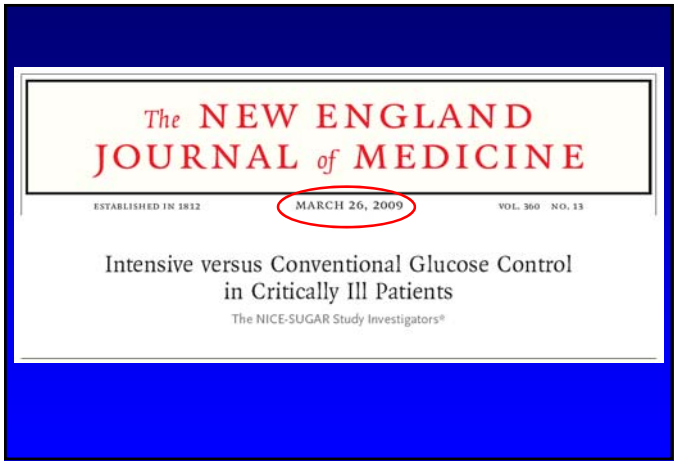



## NICE-Sugar Trial
### Baseline Characteristics

| | 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

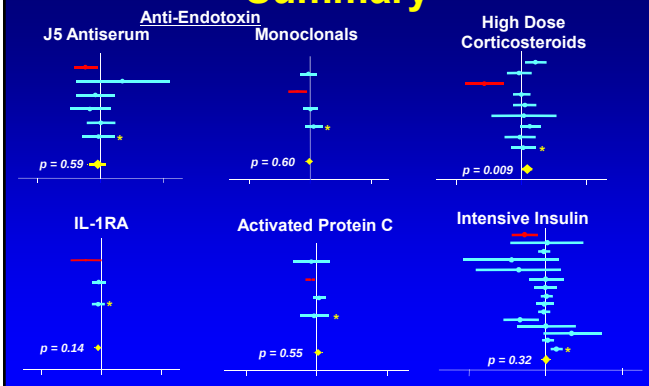
**In 6014 critically ill patients, tight glucose control was associated with hypoglycemia and increased mortality at 90 days.**

**"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




* 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