Non-inferiority trials

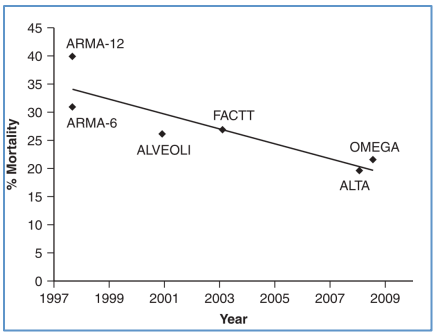
1. The IKEA principle

"Much cheaper – almost as good"

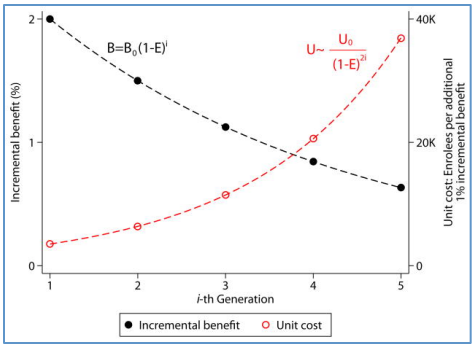
gain ***delta***

The trade-off between accepting slightly lower efficacy of new treatment in exchange for other benefits, e.g. less toxicity, lower cost, more convenience etc…

2. The law of diminishing returns:

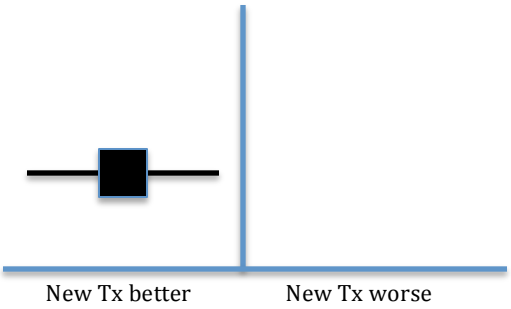


Spragg AJRCCM 2010



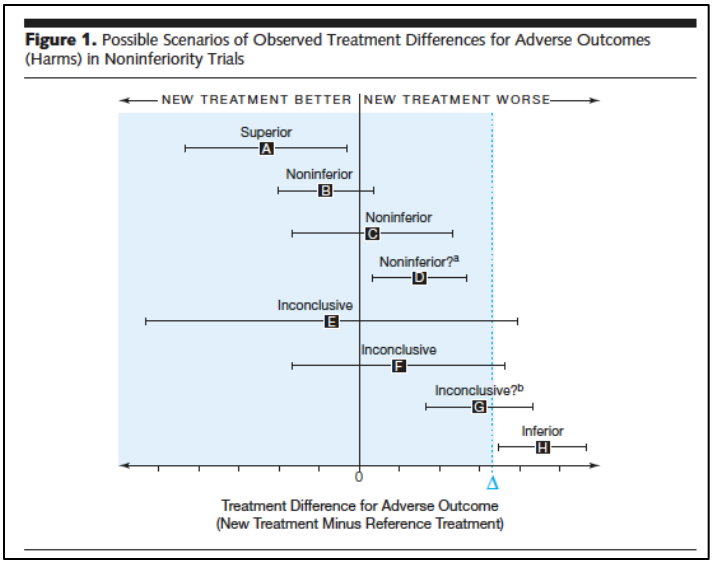
Kent DM JAMA 2009

3. All you need to look at when examining a treatment effect

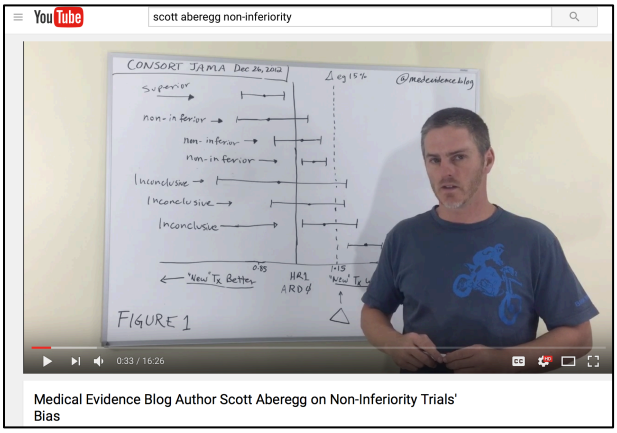


1. Direction: on which side of line of equality, i.e. benefit or harm
2. Magnitude: how far away from line of equality?
3. Precision: how narrow the confidence interval?
4. Significance: does the CI cross the line of equality?

4. The forest plot of non-inferiority trials

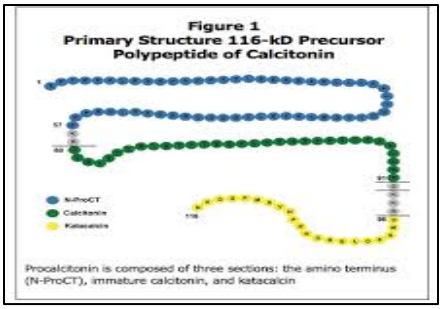


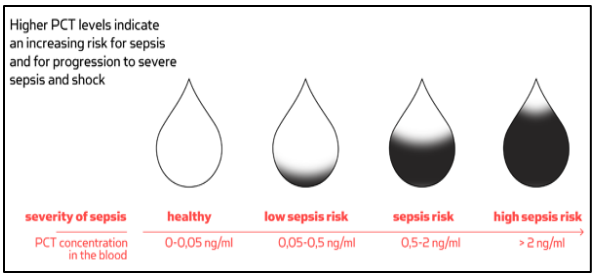
For a very critical review of this diagram, watch the following video from an EBM zealot.
https://www.youtube.com/watch?v=1tlepjqJaJA

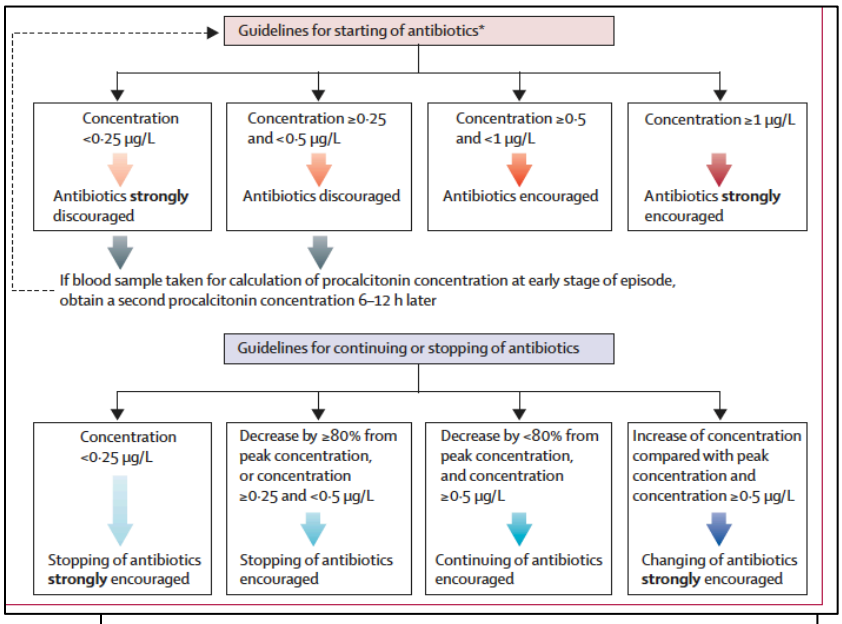


Medical Evidence Blog Author Scott Aberegg on Non-Inferiority Trials' Bias

De Jong et al. Lancet ID 2016.







Population

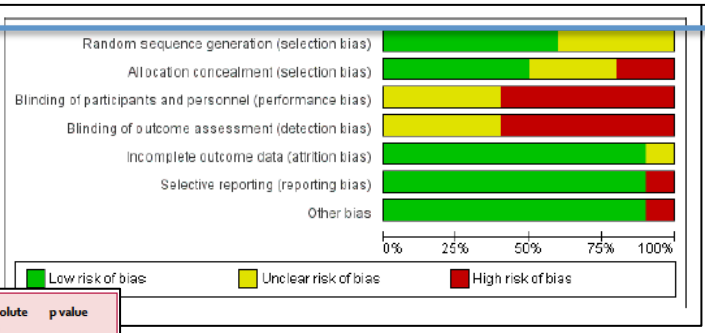
Intervention

Comparator

Outcomes

Design:

- Superiority for Abx use and duration, LOS, Cost-effectiveness
- Non-inferiority for 28d mortality and recurrent infections
- Delta = 8% relative increase in mortality (28% risk in standard of care group, 30% in PCT group)



	Procalcitonin-guided group (n=761)	Standard-of-care group (n=785)	Between-group absolute difference in means (95% CI)	p value
Antibiotic consumption (days)				
Daily defined doses in first 28 days	7·5 (4·0 to 12·8)	9·3 (5·0 to 16·5)	2·69 (1·26 to 4·12)	<0·0001
Duration of treatment	5·0 (3·0 to 9·0)	7·0 (4·0 to 11·0)	1·22 (0·65 to 1·78)	<0·0001
Antibiotic-free days in first 28 days	7·0 (0·0 to 14·5)	5·0 (0 to 13·0)	1·31 (0·52 to 2·09)	0·0016
Mortality (%)				
28-day mortality	149 (19·6%)	196 (25·0%)	5·4% (1·2 to 9·5)	0·0122
1-year mortality	265 (34·8%)	321 (40·9%)	6·1% (1·2 to 10·9)	0·0158
Adverse events				
Reinfection	38 (5·0)	23 (2·9)	−2·1% (−4·1 to −0·1)	0·0492
Repeated course of antibiotics	175 (23·0)	173 (22·0)	−1·0% (−5·1 to 3·2)	0·67
Time (days) between stop and reinstitution of antibiotics	4·0 (2·0 to 8·0)	4·0 (2·0 to 8·0)	−0·22 (−1·31 to 0·88)	0·96
Costs				
Total cumulative costs of antibiotics	€150 082	€181 263	NA	NA
Median cumulative costs antibiotics per patient	€107 (51 to 229)	€129 (66 to 273)	€33·6 (2·5 to 64·8)	0·0006
Length of stay (days)				
On the intensive care unit	8·5 (5·0 to 17·0)	9·0 (4·0 to 17·0)	−0·21 (−0·92 to 1·60)	0·56
In hospital	22·0 (13·0 to 39·3)	22·0 (12·0 to 40·0)	0·39 (−2·69 to 3·46)	0·77

Data are median (IQR), n (%), or mean (95% CI). Between-group absolute differences were calculated using the mean values, percentage differences, and 95% CIs. NA=not applicable.

Table 2: **Primary and secondary outcome measures**

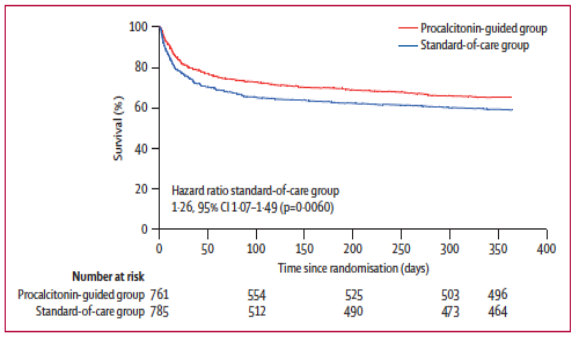
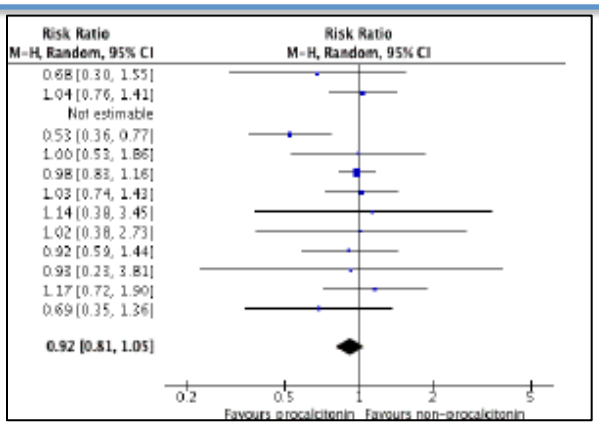


Figure 2: **Kaplan-Meier plot for probability of survival from random assignment to day 365, in the modified intention-to-treat population**



14. We suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients (weak recommendation, low quality of evidence).
15. We suggest that procalcitonin levels can be used to support the discontinuation of empiric antibiotics in patients who initially appeared to have sepsis, but subsequently have limited clinical evidence of infection (weak recommendation, low quality of evidence).

Surviving Sepsis Guidelines 2016

XXIV. Should Discontinuation of Antibiotic Therapy Be Based Upon PCT Levels Plus Clinical Criteria or Clinical Criteria Alone in Patients With HAP/VAP?

Recommendation

1. For patients with HAP/VAP, we suggest using PCT levels plus clinical criteria to guide the discontinuation of antibiotic therapy, rather than clinical criteria alone *(weak recommendation, low-quality evidence)*.

IDSA HAP/VAP 2016