GRADE for reducing adverse outcomes

- actions to reduce adverse outcomes should be based on confidence in estimates of effect

- GRADE provides detailed guidance for assessing confidence

- avoids premature quality control initiatives

Confidence assessment criteria

Study Design	Quality of Evidence	Lower if	Higher if
Randomised trial →	High	Risk of bias -1 Serious -2 Very serious	Large effect +1 Large +2 Very large
	Moderate	Inconsistency -1 Serious -2 Very serious	Dose response +1 Evidence of a gradient All plausible confounding
Observational study →	Low	Indirectness -1 Serious -2 Very serious	+1 Would reduce a demonstrated effect or +1 Would suggest a spurious effect when results show no effect
	Very low	Imprecision -1 Serious -2 Very serious Publication bias -1 Likely -2 Very likely	

TRIUMPH: Best Practices in Inpatient Glucose Monitoring

UCLA Clinicians Use IT to Facilitate Innovations in Hyperglycemia Care

Hyperglycemia in the ICU

A landmark clinical trial performed in 2001 changed clinicians' views about stress hyperglycemia in the inpatient setting. The authors of that *New England Journal of Medicine* study, concluded that "Intensive insulin therapy to maintain blood glucose at or below 110 mg per deciliter reduces morbidity and mortality among critically ill patients in the surgical intensive care unit" (Van Den Berghe, et al., 2001).

Van den Berghe, NEJM, 2001

- 1548 patients surgical ICU, ventilated
  - intensive insulin therapy vs conventional

- planned to enroll 2,500

- interim analysis at three month intervals

- $p < 0.01$ ("designed to allow early stopping")

- stopped after 4th interim analysis
  - 98 deaths

Van den Berghe, NEJM, 2001

- ICU mortality
  - 35 of 744 (4.6%) in intensive insulin
  - 63 of 765 (8.0%) in conventional

- RR 0.58 (95% CI 0.38 to 0.78)

Imprecision

- optimal information size
  - # of pts from conventional sample size calculation
  - specify control group risk, α, β, Δ

- 8% mortality, α 0.05, β 0.10, Δ RR 0.75

- 6,838 vs 1,548

- OIS not achieved

# Inconsistency/indirectness/ publication bias

- inconsistency
  - no problem

- indirectness
  - single centre enthusiasts
  - will this be replicable?

- publication bias
  - undetected

Confidence in 42% mortality ↓

risk of bias: no blinding, co-intervention, stopped early

imprecision: well below optimal information size

| no confidence | Very Low | | Low | | Moderate | | High | totally confident |
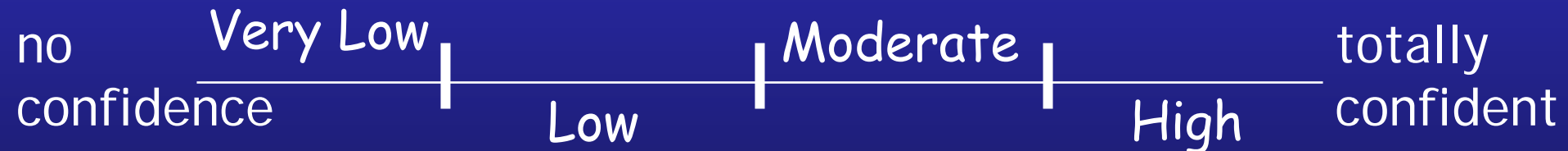
indirectness: single center of enthusiasts

27 trials in 13,572 patients : RR 0.93, 95% CI 0.83 – 1.04

Poldermans, NEJM, 1999

- 112 patients (planned sample size 266)
  - elective vascular surgery
  - positive dobutamine stress echo

- compared bisoprolol to placebo
  - unblinded

- primary endpoint death or nonfatal MI

- prior planned single look at 100 pts
  - stop if exceeded O'Brien-Fleming boundary
    - $p < 0.001$

Poldermans NEJM 1999

- primary endpoint
  - 2 of 59 (3.4%) in bisoprolol group
  - 18 of 53 (34%) in placebo

- RR 0.09, 95% CI 0.02 to 0.37, P< 0.001

ACC/AHA PRACTICE GUIDELINES

ACC/AHA Guideline Update for Perioperative Cardiovascular Evaluation for Noncardiac Surgery—Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery)

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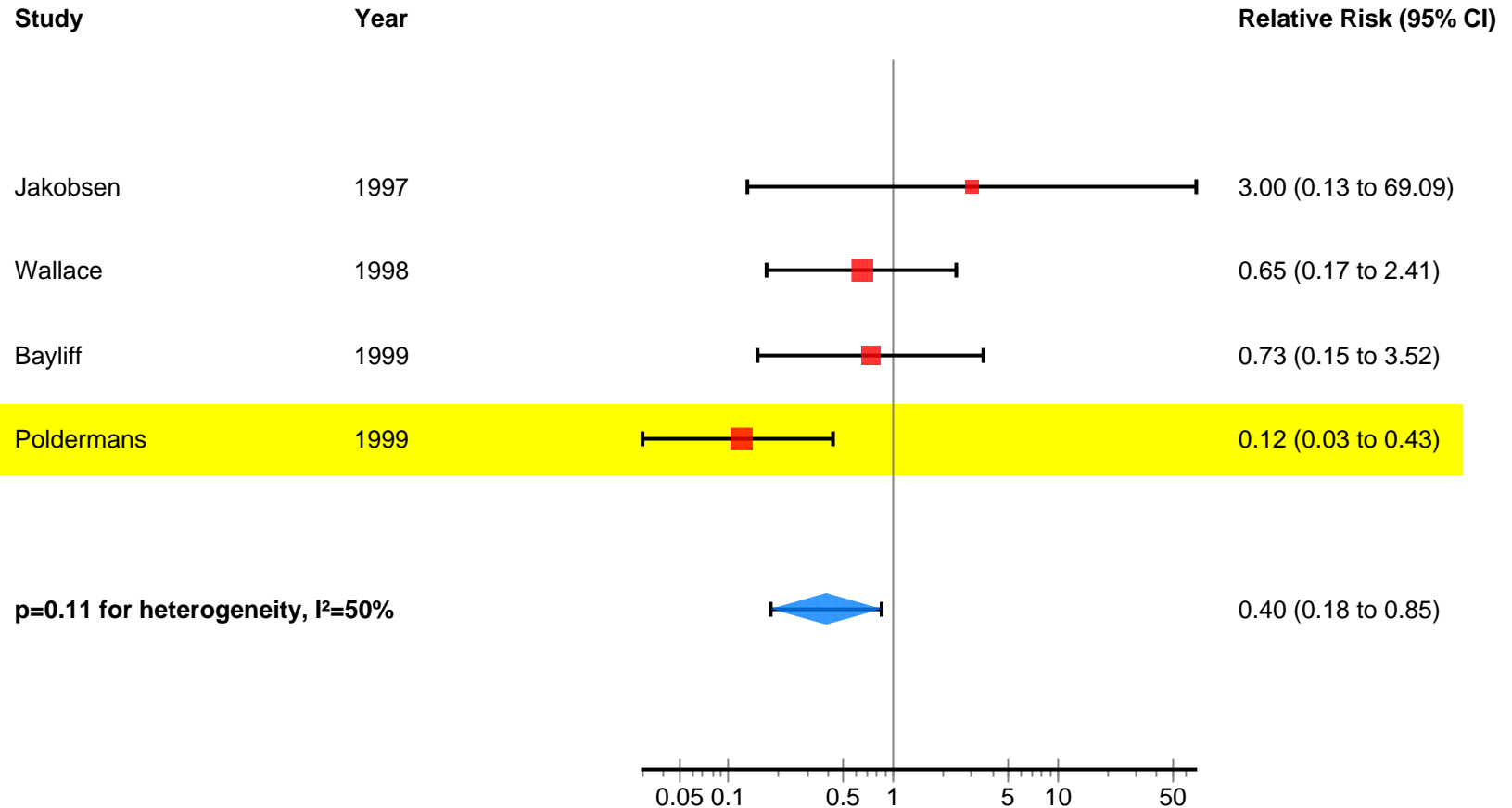KIRSTEN E. FLEISCHMANN, MD, MPH, FACC
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Composite – Fixed Effects

Study	Year		Relative Risk (95% CI)
Jakobsen	1997		3.00 (0.13 to 69.09)
Wallace	1998		0.65 (0.17 to 2.41)
Bayliff	1999		0.73 (0.15 to 3.52)
Poldermans	1999		0.12 (0.03 to 0.43)
p=0.11 for heterogeneity, I²=50%			0.40 (0.18 to 0.85)

0.05 0.1   0.5 1   5   10   50

GRADE assessment

- risk of bias
  - unblinded
  - no documentation of co-intervention
  - stopped early

- precision
  - confidence intervals look OK but...
  - total sample size 447
  - Optimal Information Size
    - 12% events, α 0.05, β 0.10, Δ RR 0.75
    - OIS 4,386

Inconsistency/indirectness/ publication bias

- inconsistency
  - I^2 50%

- indirectness
  - only positive trial odd population

- publication bias
  - undetected

Confidence in 60% mortality ⬇

risk of bias: only positive study no blinding,
co-intervention, stopped early

no
confidence

Very Low | | Moderate | |

Low

High

totally
confident
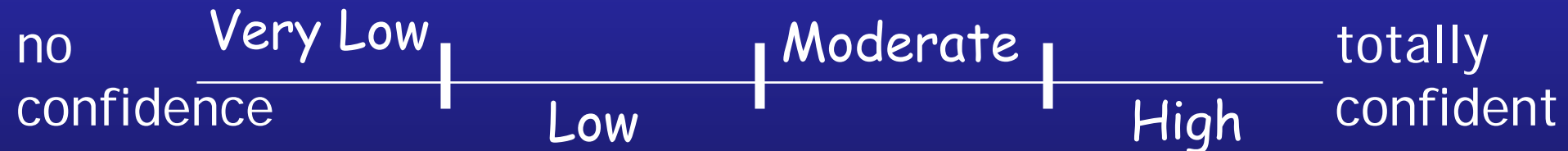
imprecision: well below optimal information size

inconsistency: I^2 50%

indirectness: single center of enthusiasts

Beta blockers in non-cardiac surgery

	Quality Assessment						Summary of Findings		
Outcome	Number of participants (studies)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Quality	Relative Effect (95% CI)	Absolute risk difference
Myocardial infarction	10,125 (9)	No serious limitations	No serious imitations	No serious limitations	No serious limitations	Not detected	High	0.71 (0.57 to 0.86)	1.5% fewer (0.7% fewer to 2.1% fewer)
Mortality	10,205 (7)	No serious limitations	Possiblly inconsistent	No serious limitations	Imprecise	Not detected	Moderate or low	1.23 (0.98 – 1.55)	0.5% more (0.1% fewer to 1.3% more)
Stroke	10,889 (5)	No serious limitaions	No serious limitations	No serious limitations	No serious limitations	Not detected	High	2.21 (1.37 – 3.55)	0.5% more (0.2% more to 1.3% more0

Conclusions

- reducing adverse outcomes requires accurate confidence in estimates

- GRADE provides rigorous, transparent system assessing confidence