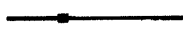







# Five vs Four Courses of Therapy for Acute Myeloid Leukemia

Timepoint	Deaths/Patients		Statistics		HR & 95% CI		Odds Redn. (SD)
	Five courses	Four courses	(O-E)	Var.	Five courses :	Four courses	
1997	7/102	15/100	-4.6	5.5			57% (29); 2P = 0.05

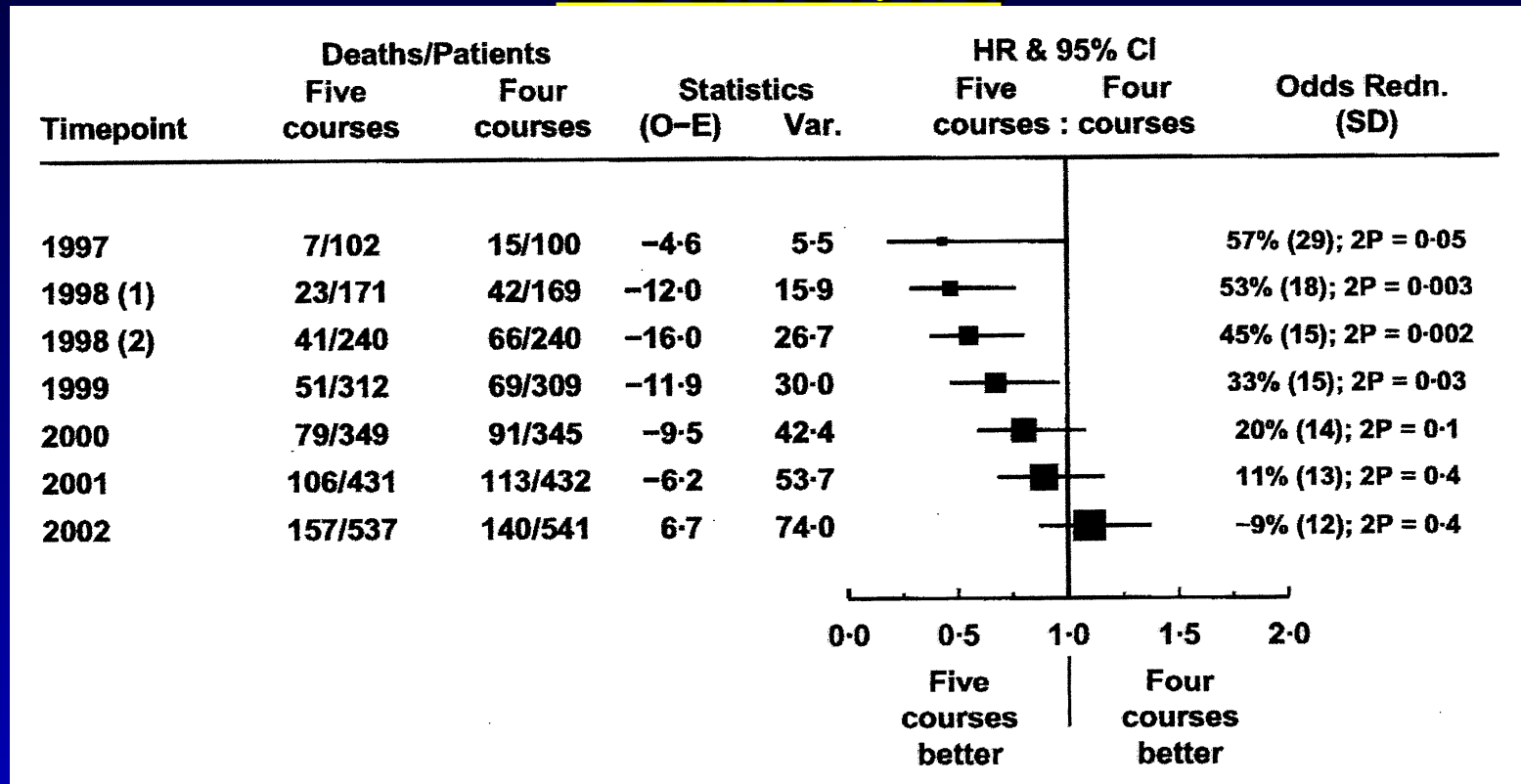
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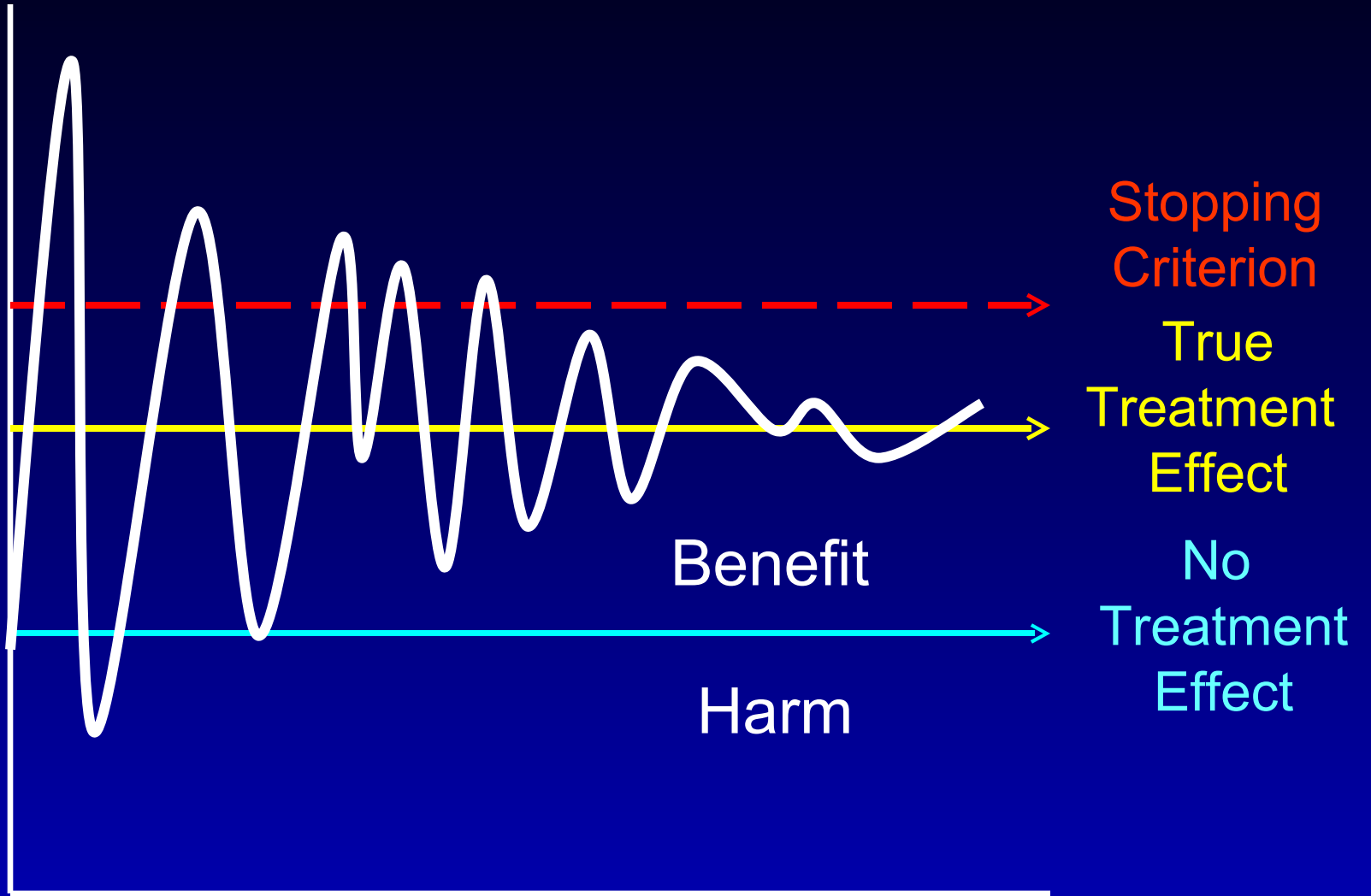
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1998 (1)	23/171	42/169	-12.0	15.9			53% (18); 2P = 0.003
1998 (2)	41/240	66/240	-16.0	26.7			45% (15); 2P = 0.002

# Five vs Four Courses of Therapy for Acute Myeloid Leukemia



Wheatley K, Clayton D. Controlled Clinical Trials 2003;24:66-70



# A systematic review of trials stopped early for benefit

- eligibility
  - RCTs reported stopped early because of finding in favor of experimental intervention
- search
  - MEDLINE, Embase, Current Contents
  - databases including full text of journals (*OVID, ScienceDirect, Ingenta, and Highwire Press, Lancet, New England Journal of Medicine, JAMA, Annals of Internal Medicine, and BMJ*)
- duplicate assessment of eligibility, data extraction

# Systematic review

- 141 eligible trials

- increasing use

- 1975-1979: 1/6574 (0.001%)	0/620 (0%)
- 1980-1984: 1/12653 (0.008%)	1/1175 (0.1%)
- 1985-1989: 10/21807 (0.05%)	9/1938 (0.5%)
- 1990-1994: 18/38712 (0.05%)	14/1306 (0.5%)
- 1995-1999: 40/52060 (0.07%)	34/3594 (0.9%)
- 2000-2004: 71/58537 (0.12%)	47/3859 (1.2%)

- $\chi^2_{\text{trend, df=1}} P < .0001$

$P < .0001$

# Where exactly?

- low impact/specialty: 51
- BMJ: 2
- Archives Int Med: 2
- JAMA: 6
- Lancet: 26
- NEJM: 54



# Systematic review

- 74 of 141 did not report 1 or more of
  - planned sample size
  - interim analysis after which trial stopped
  - whether stopping rule informed decision
- only 7 reported all 3 + adjusted estimate

# Systematic review

- median 68 events (IQ range 23-200)
- for 124 RCTs dichotomous outcomes
  - median RR 0.53 (IQ range 0.30-0.66)
  - fewer events larger treatment effects
    - OR 31, CI 12-82

# 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 conventional ventilation
- RR 0.09, 95% CI 0.02 to 0.37,  $P < 0.001$ 
  - adjusted RR 0.22, 95% CI 0.06 to 0.92,  $p = 0.04$
- likelihood large overestimate very high
- latest RCT 496 patients
  - 19 events in beta blocker, 22 placebo

# Conclusions

- epidemic of early stopped trials
- large number in top journals
  - NEJM and Lancet big offenders
- often methodologically flawed
- majority events < 100
- majority implausibly large effects
  - fewer the events, greater the effect
- view early stopped trials skeptically, specially if:
  - don't report planned sample size, stopping rule
  - stopping rule > 2 looks
  - *few events; large effect*