# Large trials: key factors for obtaining clear answers

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# Proliferation of laws and "guidelines" may make trial results LESS reliable (and so harm, not help, patients)

Clinical trial conduct:

- ICH Guideline for GCP
- EU Clinical Trials Directive
- NHS Research Governance

Data access/confidentiality:

- 1998 Data Protection Act
- GMC guidance on confidentiality
- Health & Social Care Act/PIAG

Ethics & consent:

- Helsinki Declaration

# Declaration of Helsinki 2000: obstacle to research in developing countries

*"The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods…….. At the conclusion of the study, every patient entered into the study should be assured of access to the best proved prophylactic, diagnostic and therapeutic methods identified by the study."*

Committee on Publication Ethics
(established by journal editors)

*"….. the incidence of research misconduct in clinical trials of drugs is around 1%"*

Sunday Telegraph, August 1997
quoted in 1998 COPE report

## Headline: “Drug trials risk to patients”

*“Trials of new medicines ….. are so badly flawed that they endanger the health of the patients ….. according to scientists who have been auditing them in confidence for 10 years ….. The scientists’ company, Good Clinical Research Practices, is called in by pharmaceutical companies to establish whether trials meet international standards”*

Guardian (UK newspaper) July 1999

# Potential conflicts of interest among those who promote more regulation

Petitions for compulsory winding-up
Week ending 18 June 1999
(www.insolvency.co.uk)

14/07/99 Good Clinical
Research Practices Ltd

## MRC review: Potential for EU Clinical Trials Directive (2001) to be a major obstacle to important trials

- Increased bureaucracy due to requirement for single sponsor (possibly the funding source)
- Burdensome drug authorisation and supply (GMP & labelling) processes
- Threat to trials of emergency treatments for patients unable to give consent
- Rigid approach to pharmacovigilance and site monitoring (through over-interpretation)
- Substantial increases in costs could result in fewer important trials being conducted

# Impact of EU Clinical Trials Directive (2001) on non-commercial cancer trials in UK (Eur J Cancer 2006)

- Doubling in costs of running non-commercial cancer trials and 6-12 month delays to starting
- Major concerns about correct interpretation due to lack of central guidance, lack of clarity regarding interpretation of guidance notes, and increased documentation
- Clinical trial units unable or unwilling to start in non-UK centres due to different interpretations in different European countries

# New EU Directive 2005/28/EC (Recital 11): simplified procedures for non-commercial trials

*"Non-commercial clinical trials conducted by researchers without the participation of the pharmaceutical industry may be of great benefit to the patients concerned…*
*…. The conditions under which the non-commercial research is conducted by public researchers, and the places where this research takes place, make the application of certain of the details of good clinical practice unnecessary or guaranteed by other means."*

Consultation on draft guidance on "specific modalities" for non-commercial trials during June-Sept 2006

# EU definition of “non-commercial” trials

- Sponsor is university, hospital, public scientific organisation, non-profit institution, patient organisation or researcher;
- Data from trial belongs to this non-commercial sponsor;
- Design, conduct, recording and reporting under their control;
- No agreement in place between sponsor and third parties that allows use of trial data for regulatory or marketing purposes; and
- Trial should not be part of the development programme for a marketing authorisation of a medicinal product.

N.B. Supplying a product free or at reduced cost and/or providing support in a limited way does not imply industry is “participating”.

# ICH GCP: Guidance on monitoring

*"… extent and nature of monitoring should be based on considerations such as the objectives, purpose, design, complexity, blinding, size and endpoints of the trial. In general there is a need for on-site monitoring before, during and after the trial; however … central monitoring …can assure appropriate conduct of the trial in accordance with GCP"*

ICH GCP 5.18.3

# Range of options for on-site monitoring

Arrangements for site visiting may vary:

- Routine visits to all sites
- Visits to random selection of sites
- Targeted visits to less experienced sites, or those for which central monitoring suggests possible problems

MRC/DH joint project (www.cl-toolkit.ac.uk)

# COMMIT (clopidogrel in acute MI): lack of value of on-site data audits

- Site visits to highest recruiting 300 of 1250 hospitals (representing 66% of randomised patients) plus 44 randomly selected hospitals
- Coordinating centre selected ~10 patients (50% with relevant events) at each hospital for note review
- No material discrepancies between hospital notes and study records for patient characteristics or study outcomes (e.g. death always correctly reported and 98% of reported reinfarction/stroke confirmed)

# Central monitoring by coordinating centre

Record checks for:

- Patient eligibility (eg, pathology report to substantiate diagnosis)
- Patient existence (eg, ONS flagging or imaging investigation)
- Outcome (eg, ONS flagging for death; investigation results)

Statistical checks for:

- Missing or invalid data (eg, range checks)
- Calendar checks (eg, dates of recruitment)
- Unusual patterns (eg, digit preference, rounding or unusual frequency distribution)
- Reporting rates (eg, frequency of adverse events or missing data)
- Repeated measures (eg, variability and within-individual changes)

MRC/DH joint project (www.cl-toolkit.ac.uk)

# COMMIT: Example of central checks indicating problem at one of 1250 participating hospitals

| | Hospital (n=93) | All hospitals | |
|---|---|---|---|
| Patients/month | 2.1 | 1.0 | |
| Female | 39.8% | 27.6% | * |
| ST↓ only | 1.1% | 6.8% | |
| Fibrinolytic <12 h | 73.3% | 65.3% | |
| Pain onset <6 h | 33.3% | 33.6% | |
| 6-12 h | 59.1% | 30.2% | * |
| >12 h | 7.5% | 36.2% | |
| MI confirmed | 100.0% | 96.0% | * |
| Antiplatelet stopped | 0% | 7.3% | * |
| All i.v. BB given | 98.9% | 93.2% | * |
| Oral BB stopped | 0% | 11.1% | * |
| Possible side-effects | 0.4% | 3.5% | * |
| Major adverse events | 0.1% | 3.3% | * |
| Death | 0% | 8.0% | * |

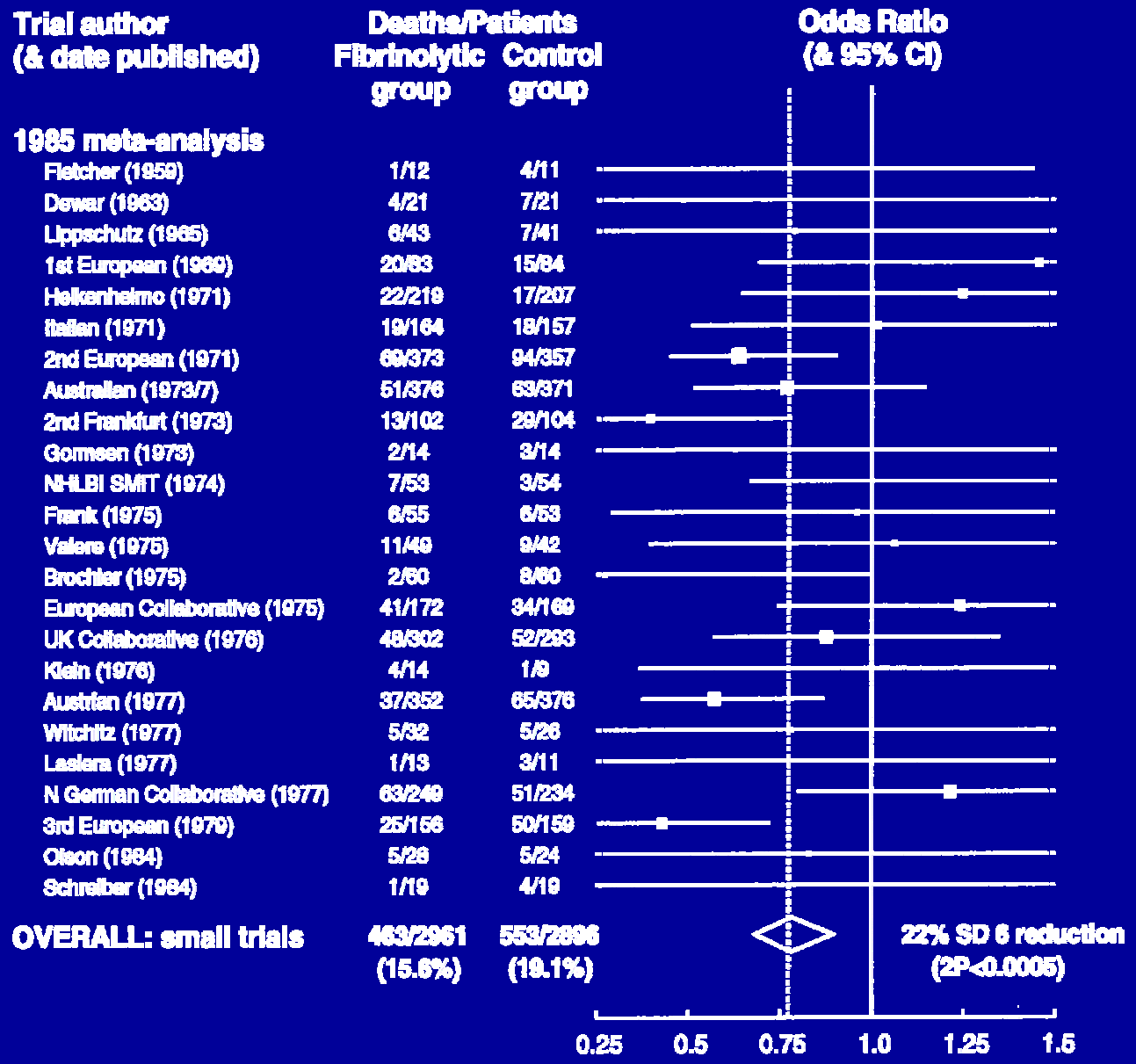
(NB: More than 4 significant differences led to on-site auditing of all patients)

# Prevention of misconduct by better trial design (rather than by more policing)

- *Relax eligibility criteria:* Excessively restrictive entry criteria may lead to entry data being altered
- *Assess compliance crudely:* Detailed pill counts may be unnecessary (& random sampling better)
- *Limit data collected:* Important adverse events may be under-reported if data collection is excessive
- *Accept missing values:* Undue pressure for complete data may lead to values being invented

More cost-effective design allows much larger numbers to be randomised, yielding smaller random errors

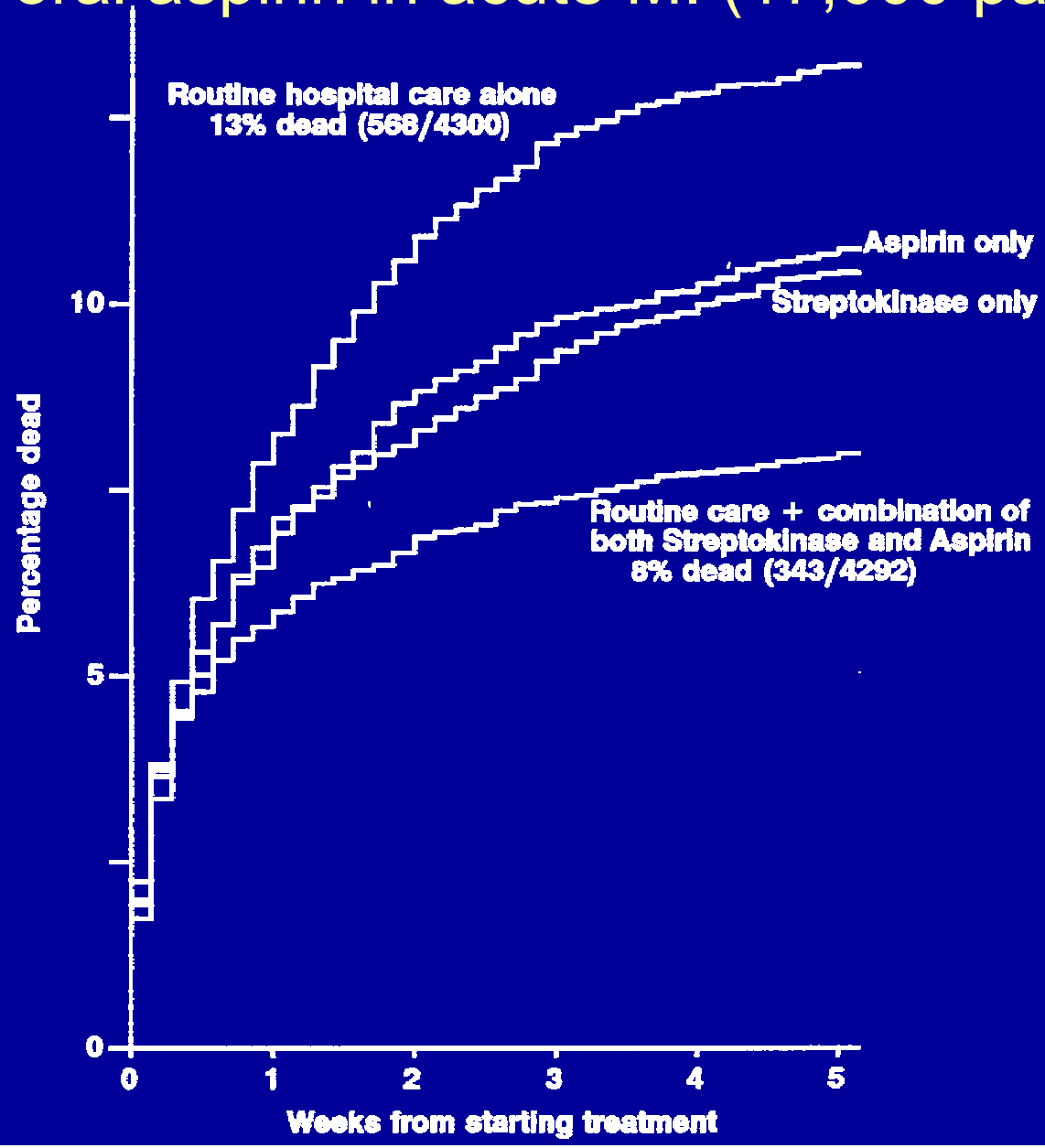
# Meta-analysis of small fibrinolytic trials (1959-85)



# “Uncertainty principle” for trial eligibility

- If the responsible doctor is, for **any** reasons, reasonably certain that trial treatment is clearly indicated, or clearly contraindicated, for a particular patient then that patient is **not** eligible.
- All remaining patients, for whom the responsible doctor is **substantially uncertain** whether or not to recommend the trial treatment, are eligible for randomisation.

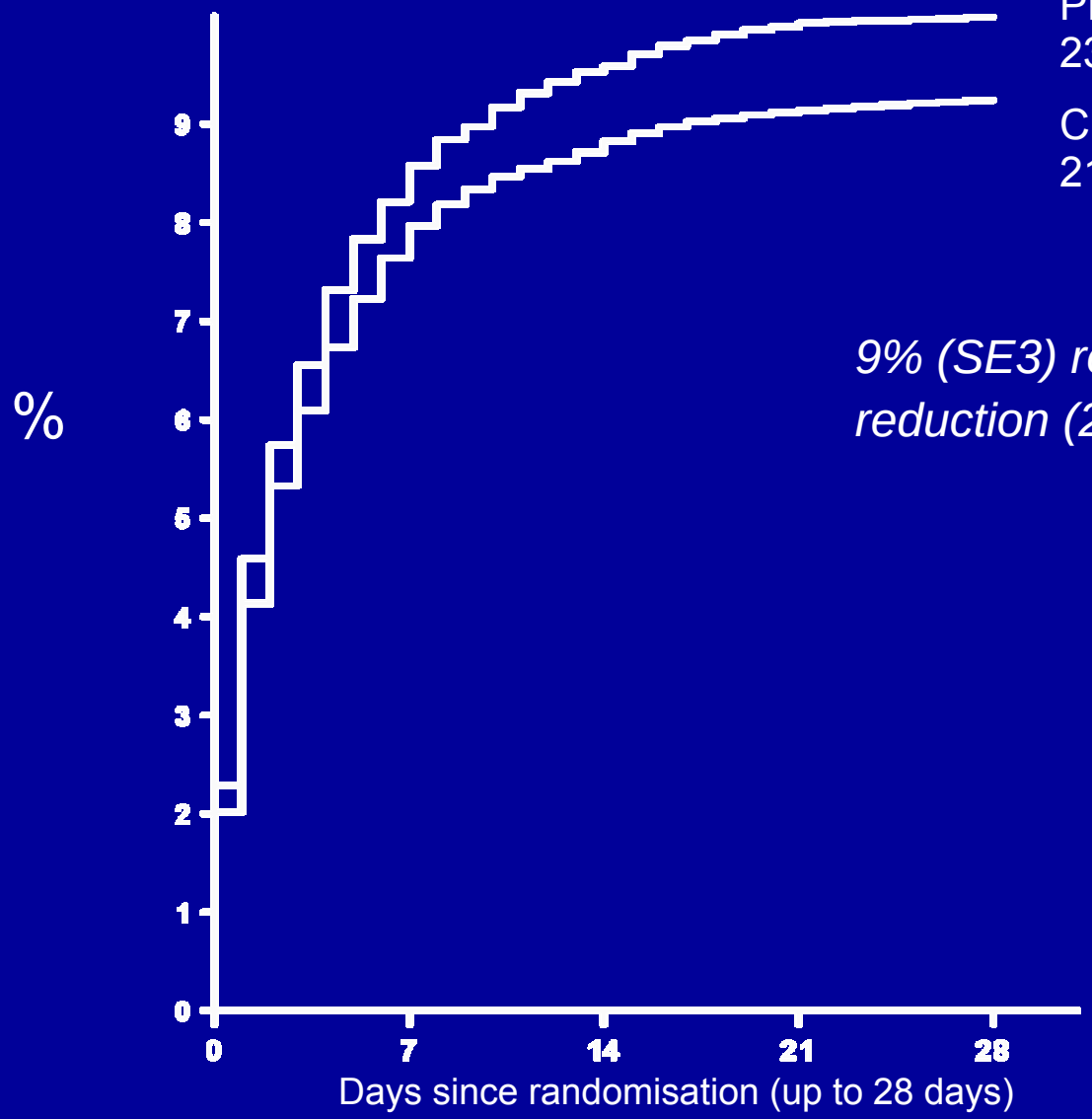
# ISIS-2: 2 x 2 “factorial” study of iv streptokinase and of oral aspirin in acute MI (17,000 patients)



## Reliable evidence can change practice rapidly: BHF surveys of UK physicians reporting fibrinolytic therapy use for heart attacks

| Year of survey | Routinely for most patients | Sometimes (or as part of a trial) | Rarely or never |
|---|---|---|---|
| 1987 | 2% | 45% | 53% |
| 1989 | 68% | 28% | 3% |

# COMMIT: Effect on death/re-MI/stroke of adding clopidogrel during heart attack (45,000 patients)




Placebo + ASA:
2310 with event (10.1%)

Clopidogrel + ASA:
2121 with event (9.2%)

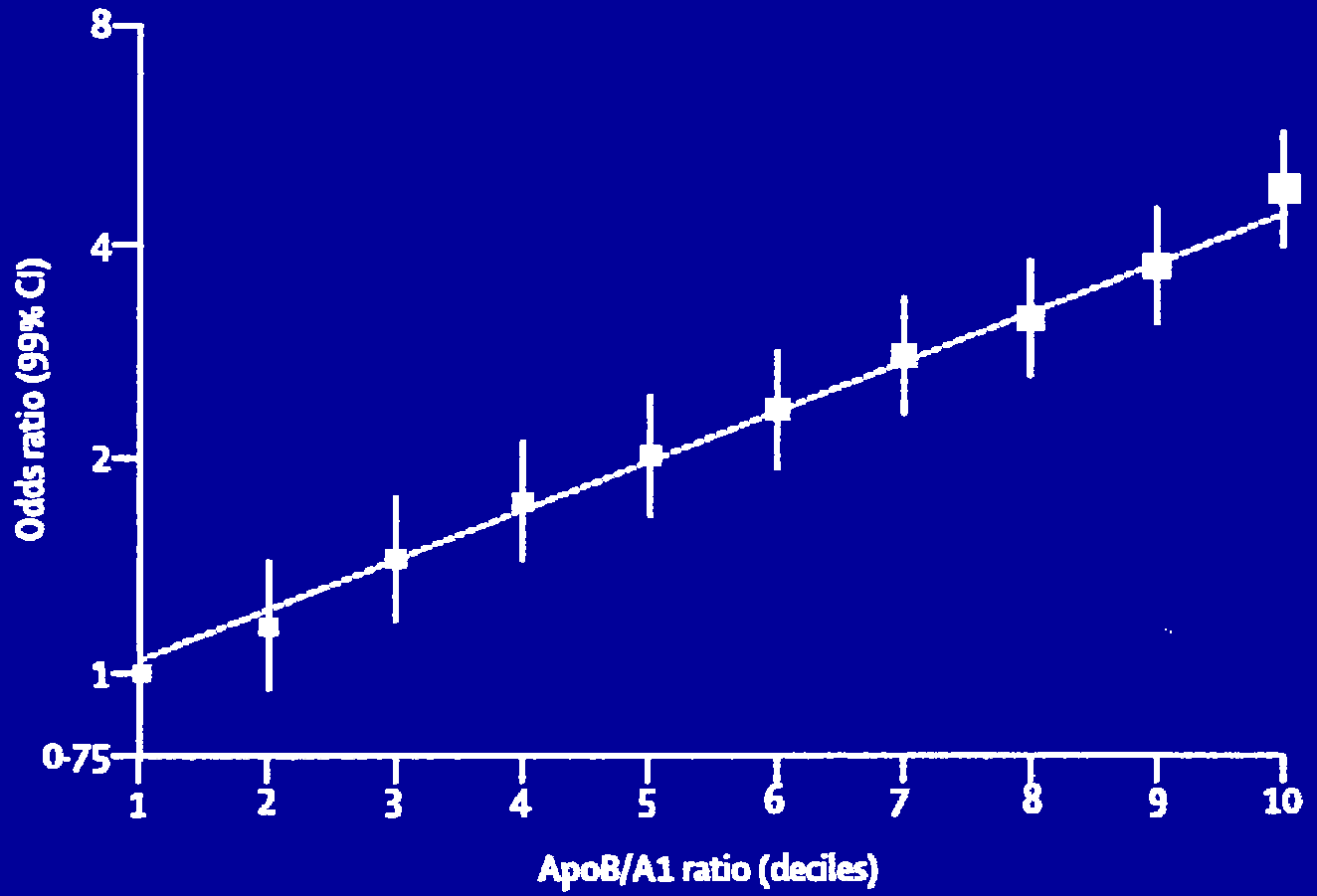
*9% (SE3) relative risk reduction (2P=0.002)*

# From ISIS-2 to COMMIT: Effects of aspirin and clopidogrel on death/re-MI/stroke

| | | | |
|---|---|---|---|
| *ISIS-2:* | Placebo | 14% | |
| | | ↓ | ~40 per 1000 |
| | ASA | 10% | |
| *COMMIT:* | ASA | 10% | |
| | | ↓ | ~10 per 1000 |
| | ASA + Clop. | 9% | |

ASA + Clopidogrel vs nil: ~50 per 1000 treated

# INTERHEART: ApoB/ApoA1 ratio and MI risk in an international case-control study




| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Number of controls | 1210 | 1206 | 1208 | 1207 | 1210 | 1209 | 1207 | 1208 | 1208 | 1209 |
| Number of cases | 435 | 496 | 610 | 720 | 790 | 893 | 1063 | 1196 | 1366 | 1757 |
| Median | 0·43 | 0·53 | 0·60 | 0·66 | 0·72 | 0·78 | 0·85 | 0·93 | 1·04 | 1·28 |

# CARE: Effect on coronary events of lowering cholesterol subdivided by baseline LDL-cholesterol

| LDL (mmol/l) | Pravastatin | Placebo | Risk reduction (& 95% CI) |
|---|---|---|---|
| <3.2 | 89/410 (22%) | 93/441 (21%) | -3% (23% to -38%) |
| 3.2-3.9 | 239/1183 (20%) | 311/1172 (27%) | 26% (38% to 13%) |
| >3.9-4.5 | 102/488 (21%) | 145/465 (31%) | 35% (50% to 17%) |
| ALL PATIENTS | 430/2081 (21%) | 549/2078 (26%) | 28% (37% to 16%) |

# Inappropriate guidelines based on inadequate data: ATP III LDL goals and cutpoints for people with CHD (and CHD risk equivalents*)

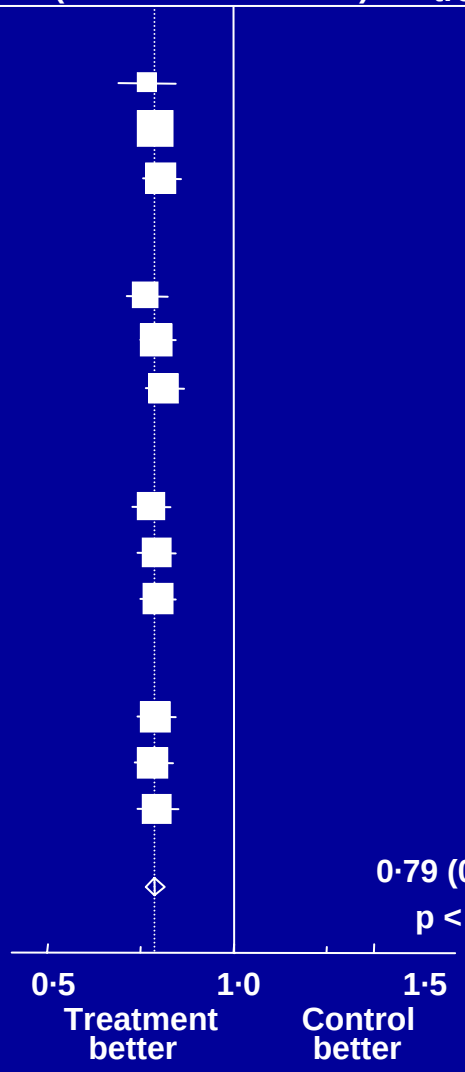
| Estimated 10 y CHD risk | LDL level to consider drug | LDL goal of treatment |
|---|---|---|
| >20% | ≥3.4 mmol/l (2.6-3.3 optional) | <2.6 mmol/l |

*CHD risk equivalents include other clinical atherosclerotic disease and diabetes

NHLBI, May 2001

# Meta-analysis of effects on major vascular events per mmol/L LDL reduction by baseline lipid levels

| Groups (mmol/L) | Events (%) Treatment | Events (%) Control | Heterogeneity/ trend p-value |
|---|---|---|---|
| **Total cholesterol:** | | | |
| ⩽5.2 | 1465 (13·5) | 1808 (16·6) | |
| 5.2-6.5 | 3312 (13·9) | 4159 (17·4) | p = 0·3 |
| >6.5 | 1547 (15·2) | 1992 (19·7) | |
| **LDL cholesterol:** | | | |
| ⩽3.5 | 2237 (13·4) | 2776 (16·7) | |
| 3.5-4.5 | 2680 (14·2) | 3344 (17·6) | p = 0·1 |
| >4.5 | 1364 (15·8) | 1773 (20·4) | |
| **HDL cholesterol:** | | | |
| ⩽0.9 | 2277 (18·2) | 2876 (22·7) | |
| 0.9-1.1 | 1813 (14·3) | 2278 (18·2) | p = 0·6 |
| >1.1 | 2223 (11·4) | 2789 (14·2) | |
| **Triglycerides:** | | | |
| ⩽1.4 | 2125 (13·4) | 2665 (16·8) | |
| 1.4-2.0 | 1821 (13·8) | 2389 (18·0) | p = 0·9 |
| >2.0 | 2357 (15·3) | 2868 (18·8) | |
| **Overall** | **6354 (14·1)** | **7994 (17·8)** | **0·79 (0·77 – 0·81)** **p < 0·00001** |



# HPS: Efficient strategies allowed large sample size (20,000 patients) at relatively low cost

- Contact details of potentially eligible patients obtained centrally from hospital records
- Coordinating centre sent appointments at local hospital clinics to specific types of patients
- Active pre-randomisation Run-in to assess lipid response and exclude non-compliers
- Recording of only study outcomes and other serious adverse events during follow-up
- Detailed lipid assays during follow-up in random sample (not all) of the participants

*"….. fraud in clinical trials is so rare and ….. generally inconsequential, that the public may be far more misguided by studies that are poorly designed, wrongly analysed and inappropriately reported than by fraud"*

ISCB subcommittee on fraud
Stat Med 1999

# Progress in clinical trials

**1950-1990:** False POSITIVES increasingly well controlled by randomisation

**1990-2000:** False NEGATIVES increasingly well controlled by “mega-trials” and “meta-analyses”

**2000 & beyond:** Increasing regulation (without appropriate interpretation) may prevent many important public health questions from being answered reliably