Role of evidence from observational studies in the process of health care decision making

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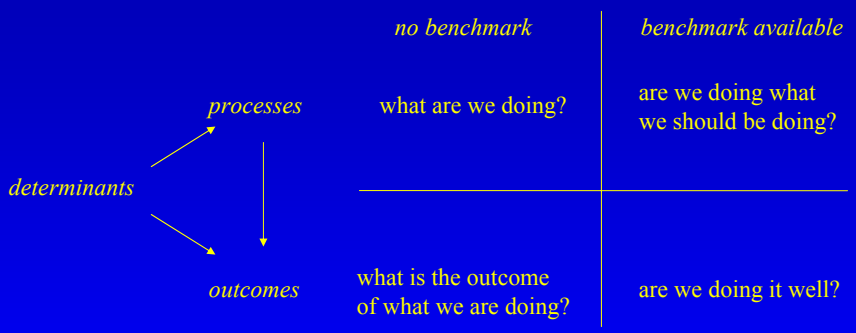
Core activity:

- Assessing the quality of surgical care in the UK

Also:

- Carrying out research on clinical and cost effectiveness
- Developing clinical practice guidelines

Assessing the quality of care: basic questions



Role of evidence from observational studies to compare health care interventions

Randomisation may be:

- Unnecessary
  - Dramatic effect -> confounding irrelevant
- Inappropriate
  - Rare outcomes, outcomes far in the future
  - Impact of random allocation on effectiveness
- Impossible
  - Lack willingness to participate (clinicians and patients)
  - Ethical or political objections
  - Contamination
  - Scale
- Inadequate
  - Clinicians not representative, patients atypical
  - Efficacy rather than effectiveness

N Black, BMJ 1996;312:1215

Sources of bias in studies comparing health care interventions

- Selection for inclusion
- Treatment allocation -> confounding by indication
- Co-intervention
- Loss to follow-up
- Assessment of outcomes

Remedies against bias

	RCT	Non-randomised study
Selection for inclusion	Explicit in- and exclusion criteria	Explicit in- and exclusion criteria
Treatment allocation	Randomisation	Case-mix adjustment
Co-intervention	Blinding	Measurement of interventions
Loss to follow-up	Completeness of follow-up	Completeness of follow-up
Assessment of outcome	Blinded outcome assessment	Blinded outcome assessment

RCT and non-randomised studies of arthroplasty versus internal fixation for fractured neck of femur

- 14 randomised studies (n=3108) and 13 non-randomised studies (n=1901)

	RR for arthroplasty	
	RCT	Non-randomised
Mortality	1.04	1.44
Revision	0.24	0.38

- Authors are "unable to identify reasons for these differences"

*

M Bhandari et al, Arch Orthop Trauma Surg 2004;124:10

Review of empirical comparisons of randomised and non-randomised studies

Reviews were included if

- They compared quantitative results between RCTs and non-randomised studies of the same technique
- They had accumulated results from several of these comparisons across healthcare interventions

- Eight reviews were found with considerable overlap
- 7 medical interventions and 1 psychological intervention

J Deeks et al, Health Technol Assess 2003:7(27)

Review of empirical comparisons of randomised and non-randomised studies
cont'd

- Conflicting results:
  - 5 studies concluded that there were differences between randomised and non-randomised studies, but without a consistent pattern indicating systematic bias
  - 1 study (oldest 1982) found overestimation of effect with non-randomised studies
  - 2 studies concluded that results of randomised and non-randomised studies were "remarkably similar"
- Other results:
  - 1 study concluded that results of RCTs were more consistent and 1 study that they were less consistent
  - 2 studies agreed that case-mix adjustment did not reduce differences between randomised and non-randomised findings

Review of empirical comparisons of randomised and non-randomised studies
cont'd

- Critical evaluation of reviews
  - Publication bias of primary study and of the reviews
  - Differences between RCTs and non-randomised studies in
    - participants, interventions and outcomes
    - study methodology
  - Large variation in criteria for what is "different" or "similar"

Conclusions

- Results of RCT and non-randomised studies sometimes, but not always, differ
- Similarities and differences might be explicable by other confounding factors (e.g. era, populations, dosage, length of follow-up) -> comparison "unfair" due to meta-confounding

Observational data to "enhance" results of RCTs

PROWESS trial:

- Recombinant human activated protein C versus placebo for severe sepsis on intensive care
- Trial was stopped after interim analysis showed reduced 28-day mortality with agent (24.7% versus 30.8%)
- Are these results generalisable to intensive care practice in UK (or Germany?)

A Padkin et al, BMJ 2001;323:923

Observational data to "enhance" results of RCTs

Cont'd

UK audit of patient outcome on intensive care to assess:

- Generalisability of PROWESS results to UK practice
  - 28% of all intensive care admissions met definition for severe sepsis used in PROWESS trail
  - Hospital mortality in UK is 44.7% compared to 30.8% at 28 days in PROWESS
- Financial implications of recommending use of agent
  - About 10,000 patients eligible for drug each year -> potential costs £ 30m - £ 50
- Effectiveness of agent after introduction in UK practice
  - May include patients not eligible for PROWESS trial
  - Case-mix adjustment important !

Observational data to "enhance" results of RCTs

Before RCT

- Identify uncertainty and generate hypotheses
- Estimate the parameters for sample size calculations

After RCT

- Evaluate outcome over longer period, in wider context and in different populations
- Study link between "efficacy" and "effectiveness"
- Explore impact on clinical practice / health service
- Examine uptake of new treatment

Observational data to support individualised decision making

- Not every patient is the same
- RCTs do not give *the* answer for individual patients
- "Clinical profile" of patients important
- Implications for clinical research
  - Trial design: anticipate "individual risk management / subgroup analysis
  - Observational studies for prognostic information
  - Decision analysis to combine data from RCTs and studies on prognosis.

European Carotid Surgery Trial

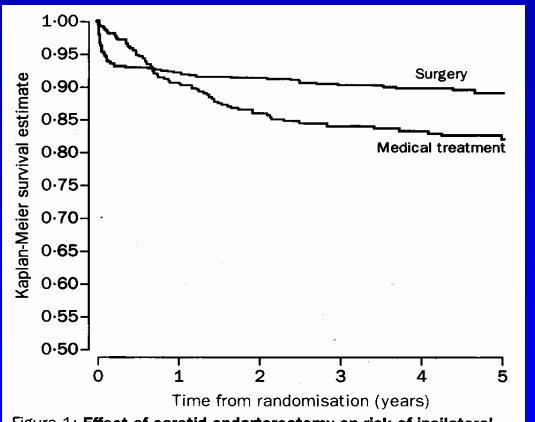


Figure 1: **Effect of carotid endarterectomy on risk of ipsilateral carotid territory major ischaemic stroke and operative major stroke or death in patients with 70–99% carotid stenosis, censoring non-stroke death**

PM Rothwell, Lancet 1999;353:2105

Individualised decision making for carotid endarterectomy

- Decision for individual patients depends on balance between
  - risk of stroke and death *resulting from surgery*
  - *extra* risk of ipsilateral stroke *without surgery*
- Crucial question: can we differentiate patients in terms of
  - stroke risk?
  - surgical risk?

Prognostic variable	Hazard ratio (95% CI)	p	Risk points*	Predictive score
Medical model				
Cerebral *vs* ocular events	2·45 (1·09–3·71)	0·02	1	1
Plaque surface irregularity[17,18]	2·09 (1·21–3·62)	0·008	1	1
Any events within past 2 months	1·82 (1·02–3·18)	0·04	1	1
Carotid stenosis (per 10% stenosis)	1·30 (1·10–1·40)	0·001	0–2†	0–2
Surgical model				
Female	2·05 (1·29–3·24)	0·002	1	−0·5‡
Peripheral vascular disease§	2·48 (1·51–4·13)	0·0004	1	−0·5‡
Systolic blood pressure >180 mm Hg	2·21 (1·29–3·79)	0·004	1	−0·5‡

*Derived by rounding hazard ratio to nearest whole number and subtracting 1.
†70–79% (0 points); 80–89% (1 point); 90–99% (2 points).
‡In risk-factor model applied to 70–99% stenosis group, surgical risk points are subtracted (ie, become negative) and their weighting is decreased by 50%.
§Claudication or previous peripheral vascular surgery for ischaemia.

Table 1: **Hazard ratios, risk points, and predictive score for independent predictors of outcome in medical and surgical models**

Number of risk points	Cases	Strokes	5-year actuarial risk (95% CI)
0	7	0	0
1	48	2	6·0% (0–14)
2	141	14	13·1% (7–20)
3	123	22	21·0% (13–29)
4	63	21	45·2% (31–60)
5	12	4	38·1% (9–68)

5-year actuarial risk for patients with 4 or more risk points was 43·4% (95% CI 30–57).

Table 2: **5-year actuarial risk of ipsilateral carotid territory major ischaemic stroke in 394 patients with 70–99% stenosis in medical-treatment group**

Number of risk points	Cases	Strokes or deaths	30-day risk (95% CI)
0	238	14	4·7% (2·6–7·6)
1	234	17	7·3% (4·3–11)
2	58	7	12·1% (5·0–23)
3	6	1	16·7% (4·2–64)

30-day risk of endarterectomy in patients with 2 or more risk points was 12·5% (95% CI 5·6–23·0).

Table 3: **30-day risk of any major stroke or death after carotid endarterectomy in 596 patients with 70–99% stenosis in surgery group**

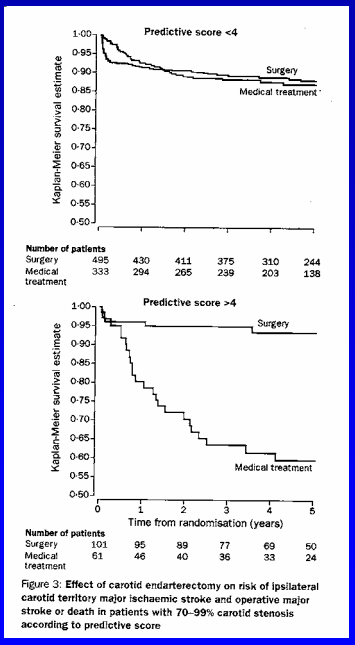


Figure 3: **Effect of carotid endarterectomy on risk of ipsilateral carotid territory major ischaemic stroke and operative major stroke or death in patients with 70–99% carotid stenosis according to predictive score**

Most important question of evidence-based medicine: whom to treat with what

RCT evidence from selected and homogenous groups

Observational data on prognosis

Individualised decision making incorporating patients' preferences and circumstances

Summary

- Role for observational studies in absence of RCTs to evaluate interventions
- Differences between results of non-randomised studies and RCTs can not be predicted
- Observational data can enhance results from RCTs
- Observational data needed for individualised decision making