EVIDENCE BASED MEDICINE / Nephrology

Mucsi István

EVIDENCE BASED MEDICINE

EBM is

- "the conscientious,
- explicit and
- judicious

use of current best evidence in making decisions about the care of the individual patient.

- It means integrating individual clinical expertise with the best available external clinical evidence from systematic research (D. Sackett)

EVIDENCE BASED MEDICINE

- Clinical expertise refers to the clinician's cumulated experience, education and clinical skills.
- The patient brings to the encounter his or her own personal and unique concerns, expectations, and values.
- The best evidence is usually found in clinically relevant research that has been conducted using sound methodology

EVIDENCE BASED MEDICINE

- The full integration of these three components into clinical decisions enhances the opportunity for optimal clinical outcomes and quality of life

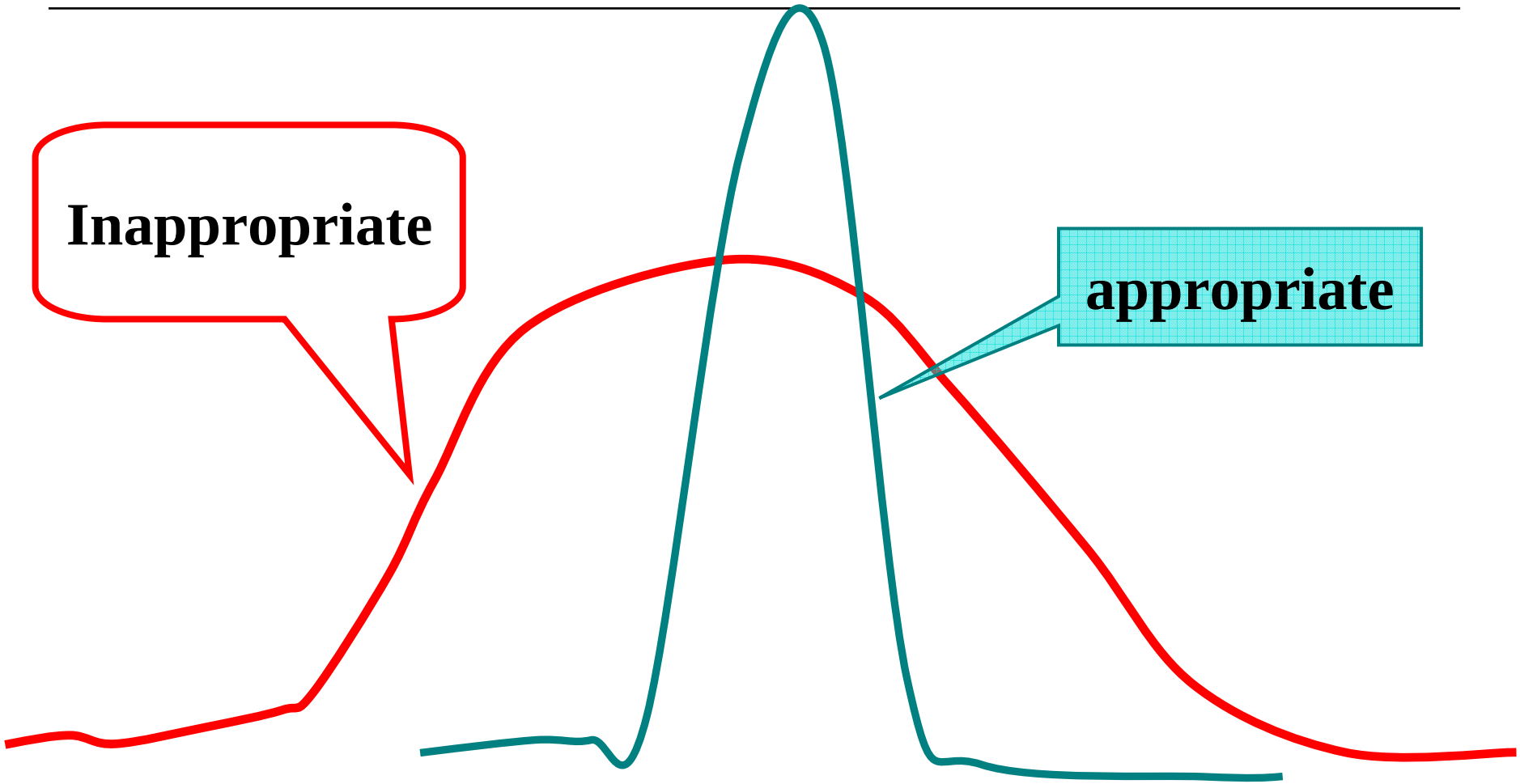
- **In other words: best possible quality of medical care**

Practice variations

- **Inappropriate variations of everyday medical practice/practice patterns**

- **Variations which can not be explained by:**
  - **Differences in natural history of the disease**
  - **Differences is socio-demographic or clinical characteristics of the patients**
  - **Differences in effectiveness of the treatment methods**
  - **Diffferences in cost-effectiveness of treatments**

Practice variations



One question:

- 60 yrs old male, T2DM for 7 yrs, BP 130/80, wt: 80 kg
- Se kreat 240 microM, electrolytes OK, 24 UTP 1 g/l, se alb 41 g/l
- Eats 80 g protein/day
- What do you do?
  - Continoue with 80 g protein
  - Reduce to 55 g protein
  - Reduce to 40 g protein

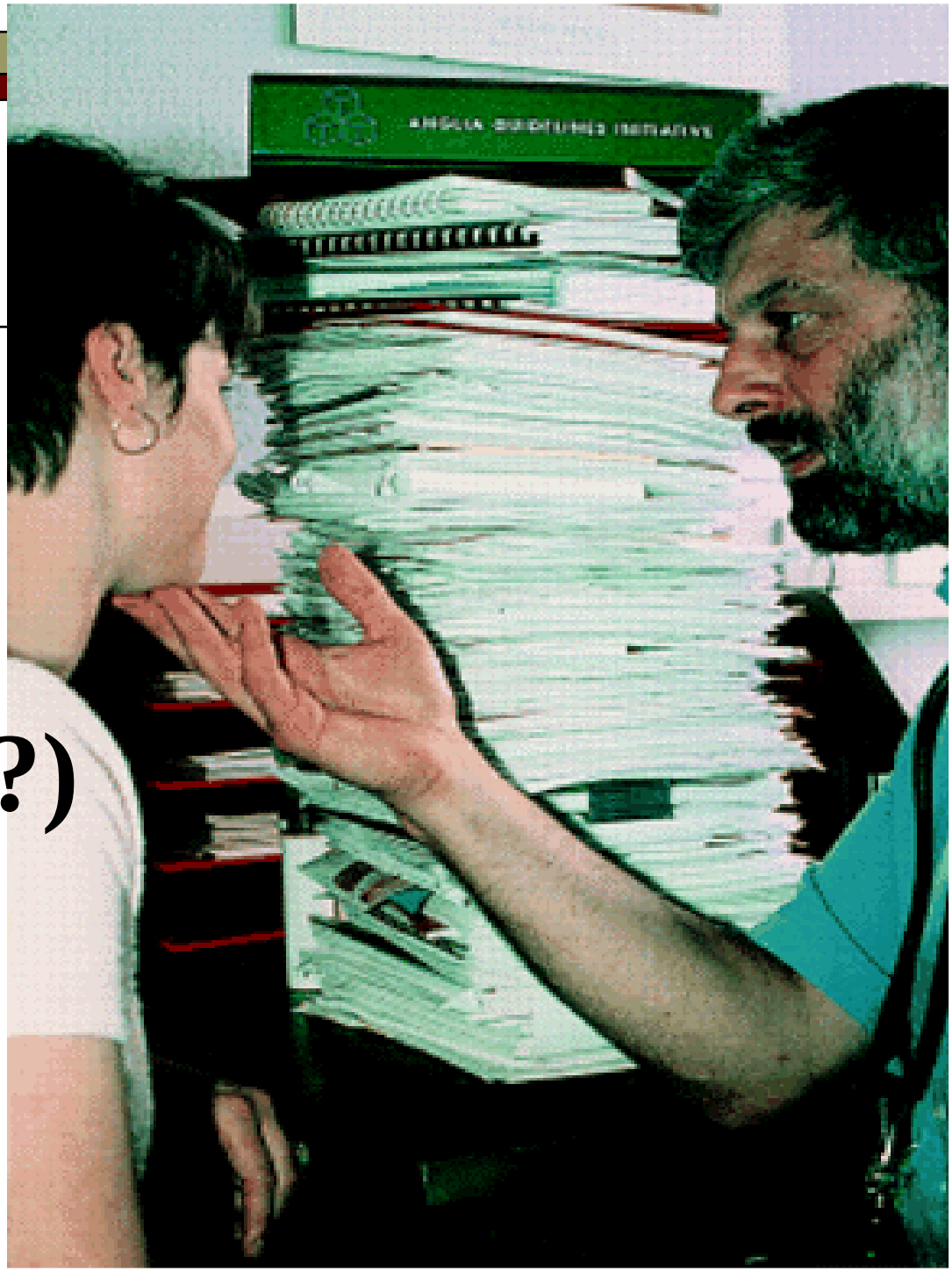
More questions:

- How much dialysis – how frequently?
- PD vs HD?
- HDF vs HD vs Psychosocial care
- Hb at 110 vs 120 vs 130?
- Need for SW vs psychologist vs dietician vs pharmacist vs Pt ??? in team?
- Single vs double vs triple blockade of RAAS?
- Native vs activated vitamin D?

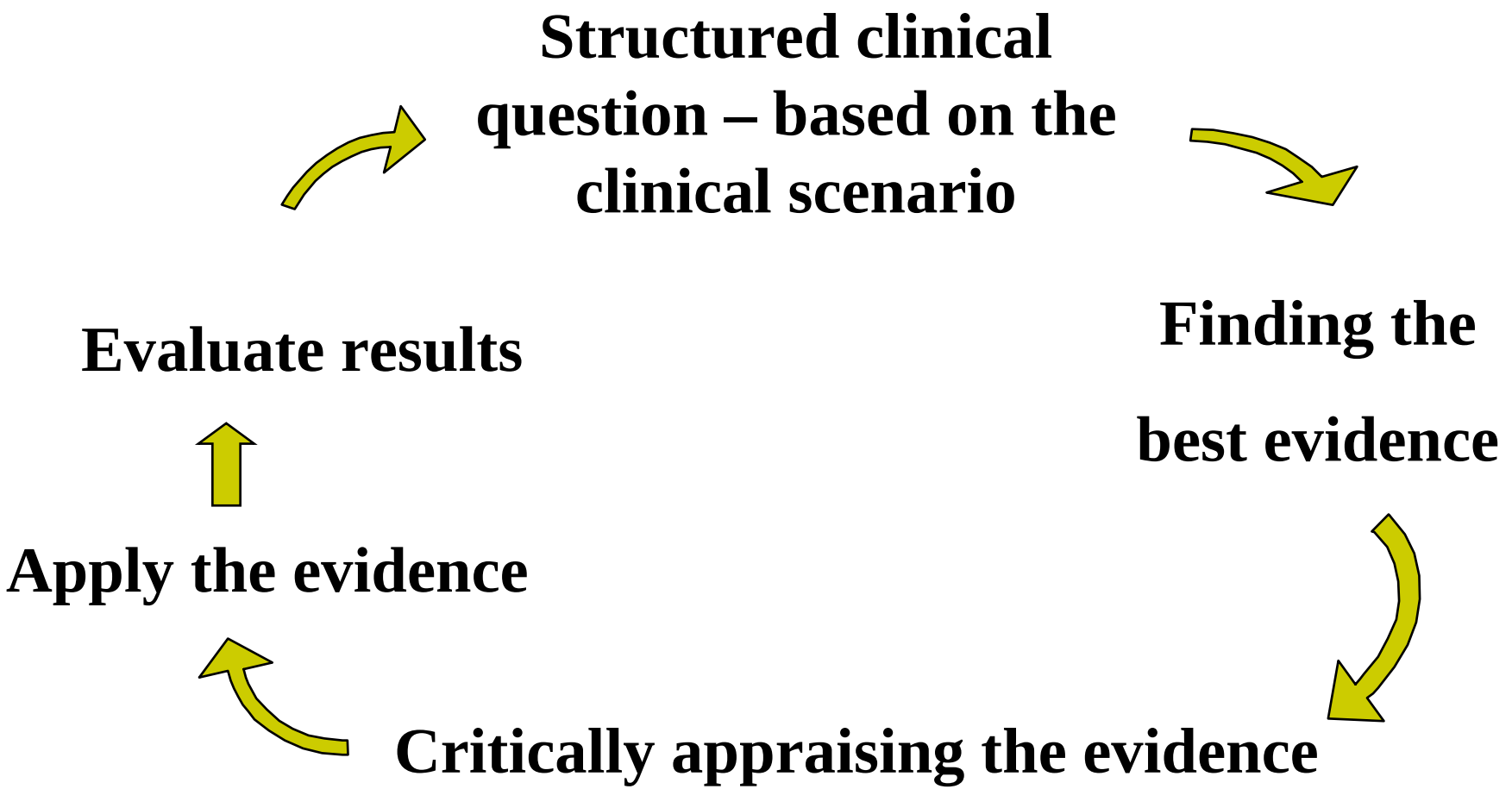
Evidence Based Practice

- Gaps between evidence and practice
- Methods to get evidence into practice
- How to narrow the gap at the
  - Individual
  - Team, and
  - Systems levels?
- How to reduce practice variations?
- How to improve quality?

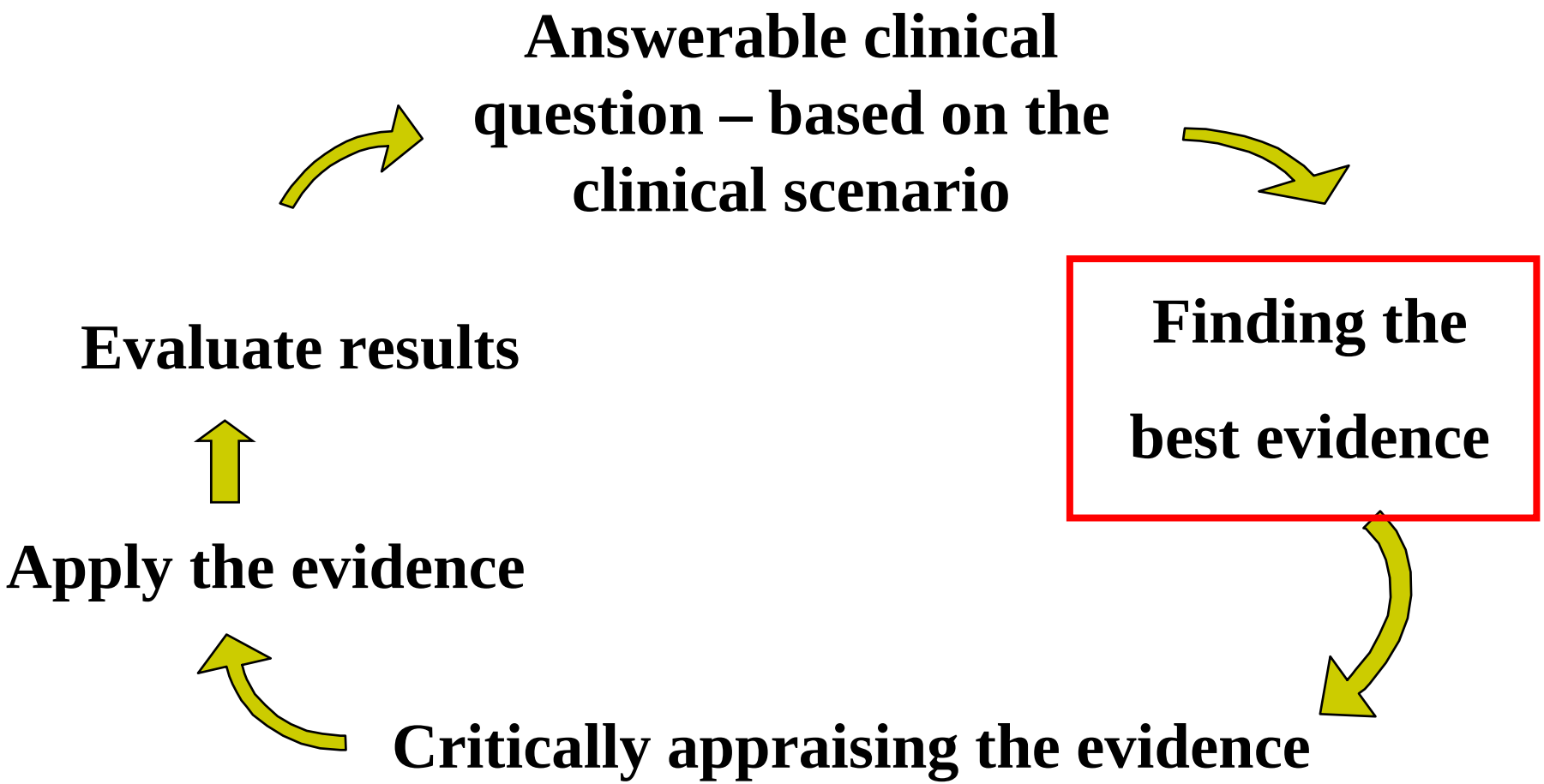
We need guidelines… (?)



Evidence based practice



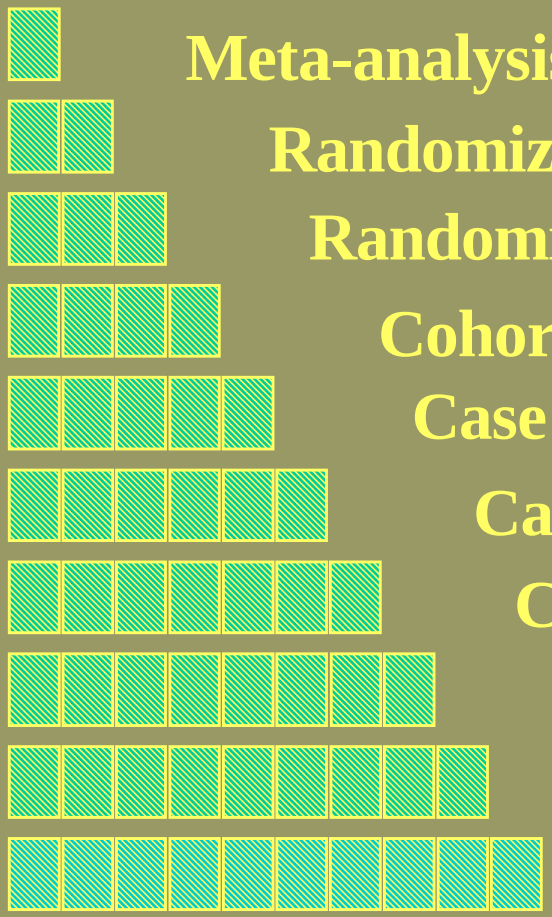
Evidence based practice



Finding the evidence ….

- University studies
- Handbooks
- Colleagues
- Personal experience (memories)
- Literature
- Systematic reviews
- Pharamaceutical industry
- Internet

Evidence pyramid – hierarchy of evidence



Meta-analysis of RCTs

Randomized Controlled Double Blind Studies

Randomized Controlled Studies

Cohort Studies

Case Control Studies

Case Series

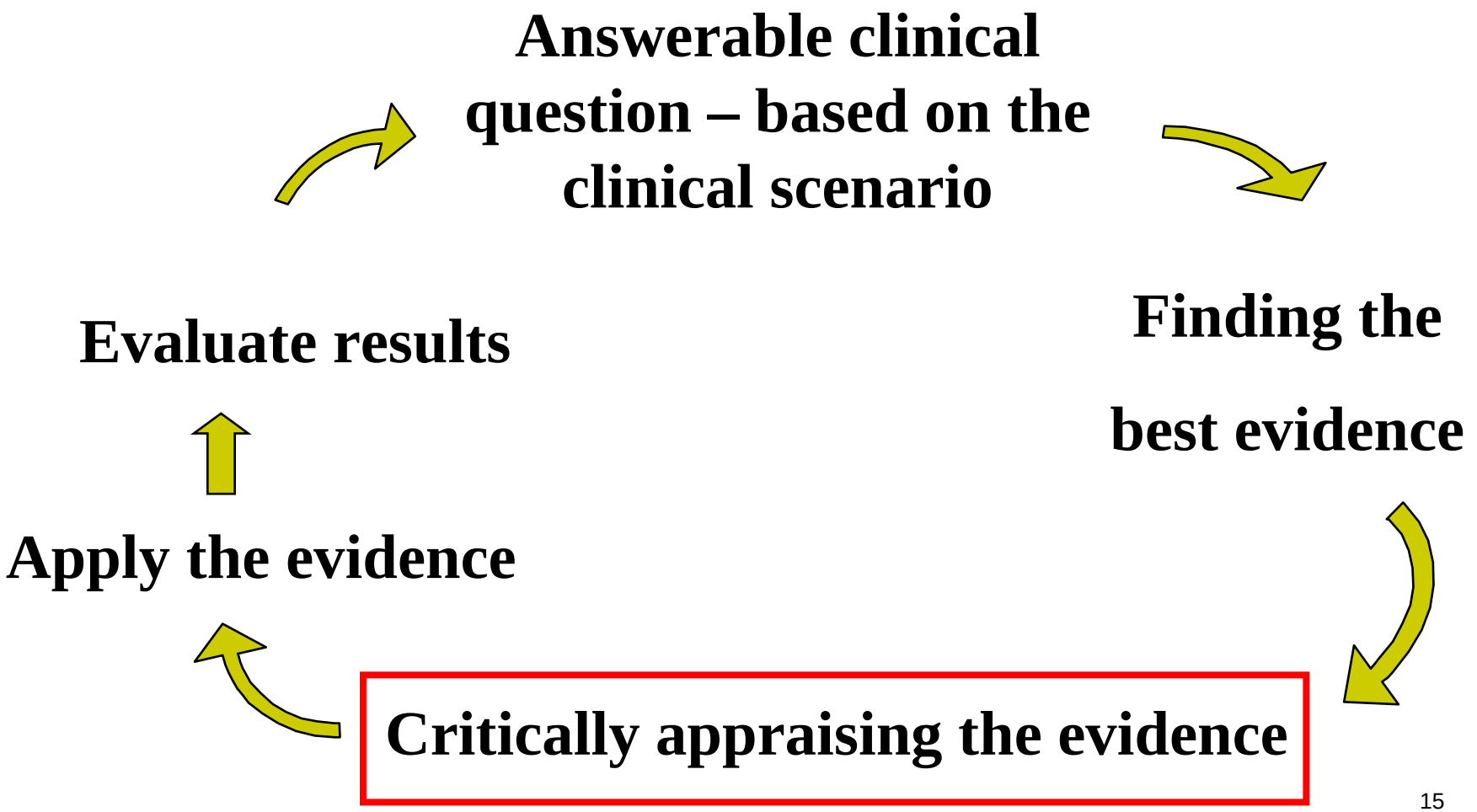
Case Reports

Opinions, Editorials etc.

Animal Research

Basic Research

Evidence based practice



What is clinical epidemiology?

Why is it important?

Critical appraisal

- Are the results valid?
- Are the results important?
- Can I apply the evidence to the specific clinical situation for the specific patient?

What is clinical epidemiology?

- Clinical epidemiology provides the methodology with which to assess the effectiveness of medical care/ specific interventions
- to improve the health of the public

- The field concerned with applying epidemiological principles in a clinical setting
- linking principles and methods of classic epidemiology, biostatistics, and clinical medicine

Selected concepts of clinical epidemiology

- study design,
- hypothesis testing,
- treatment effect,
- diagnostic performance
- outcomes assessment,
- data management
- statistical analysis.

What is epidemiology?

- **Epidemiology** is the study of
  - factors affecting the health and illness of populations,
  - Frequency of diseases in populations
  - Distribution of diseases in populations

- and serves as the foundation and logic for interventions made in the interest of public health and preventive medicine.

Selected milestones in classic epidemiology - I

- **Edward Jenner** (1749-1823) – vaccine against smallpox

- **Dr. John Snow** - suppression of an 1854 outbreak of cholera in London's Soho district. He identified the cause of the outbreak as a public water pump on Broad Street and had the handle removed, thus ending the outbreak. (It has been questioned as to whether the epidemic was already in decline when Snow took action.)

- Another important pioneer was Hungarian physician **Ignac Semmelweis**, who in 1847 brought down infant mortality at a Vienna hospital by instituting a disinfection procedure. His findings were published in 1850, but his work was ill received by his colleagues

Selected milestones in classic epidemiology - II

- 1954 - British Doctors Study (Richard Doll and Austin Bradford Hill): strong statistical support to the suspicion that tobacco smoking was linked to lung cancer Early case-control study. Smoking and carcinoma of the lung: Preliminary report. [Br. Med. J. 2:739, 1950]

- Cohort study: longitudinal study in a population (cohort) : Framingham study. 10,000 inhabitant of the town have been enrolled at baseline. F/U cca 50 yrs. [Annals New York Academy of Sciences 107:539;1963]

Basic principles of clinical studies - I

1. **Research question – we do need one**

About natural history, etiology, prognosis or treatment of diseases (population level).

Basic principles of clinical studies - II

2. **Design**

Dependent variable (outcome)
Independent variable(s) (exposure)
Population studied
Temporality; directionality
Prospective, Retrospective, cross-sectional

- case definition/event definition
- collection/documentation of „caseness”/ events
- planning/timing the study; selecting the setting;

designing the population (inclusion/exclusion/sample size)
Ethical considerations (conifdentiality; appropriateness; consent)

Basic principles of clinical studies - III

3.**Realization of the study**

Proper representation of the target population; selection process; non-response.

Observation/data collection; availability, reliability, validity, consistency, standardized protocol, coding manual & training of quality control data management.

Basic principles of clinical studies - IV

4. **Analysis**

Quality of data – data capture, data entry, quality assessment; cleaning;

Desciptive statistics

- frequency, association

Hypothesis testing

- statistics

Basic principles of clinical studies - V

5. **INTERPRETATION**

bias, validity, generalizability, consequences, importance, strengths and limitations – new and additional questions, hypotheses

- Formulate a concise clinical question
- Identify the best type of study to answer clinical questions;
- Identify major sources of bias and their likely effects on results;
- Understand and interpret: 95% confidence intervals; p values; and power estimates;
- Understand and interpret: prevalence; incidence; relative risk; risk ratio; odds ratio; risk difference;

Types of clinical studies

TYPES OF CLINICAL QUESTIONS

Diagnosis	What is the likelihood for a patient having a specific symptom or yielding „positive” on a specific test to have the disease?
Therapy	Is the therapy in question more effective in achieving a particular outcome than an alternative therapy (including no therapy)?
Prognosis	What is the likelihood of a particular outcome in this patient?
Etiology	What is the cause of the disease? OR: how likely is a particular intervention to cause a specific side effect?)

TYPES OF CLINICAL QUESTIONS

	„Exposure”	“effect”
diagnosis	result of a test	disease
therapy	medication, surgery	recovery side effect
prevention	e.g. pt. information, medication	no disease
prognosis	risk factor	eg. morbidity

Types of clinical studies - I

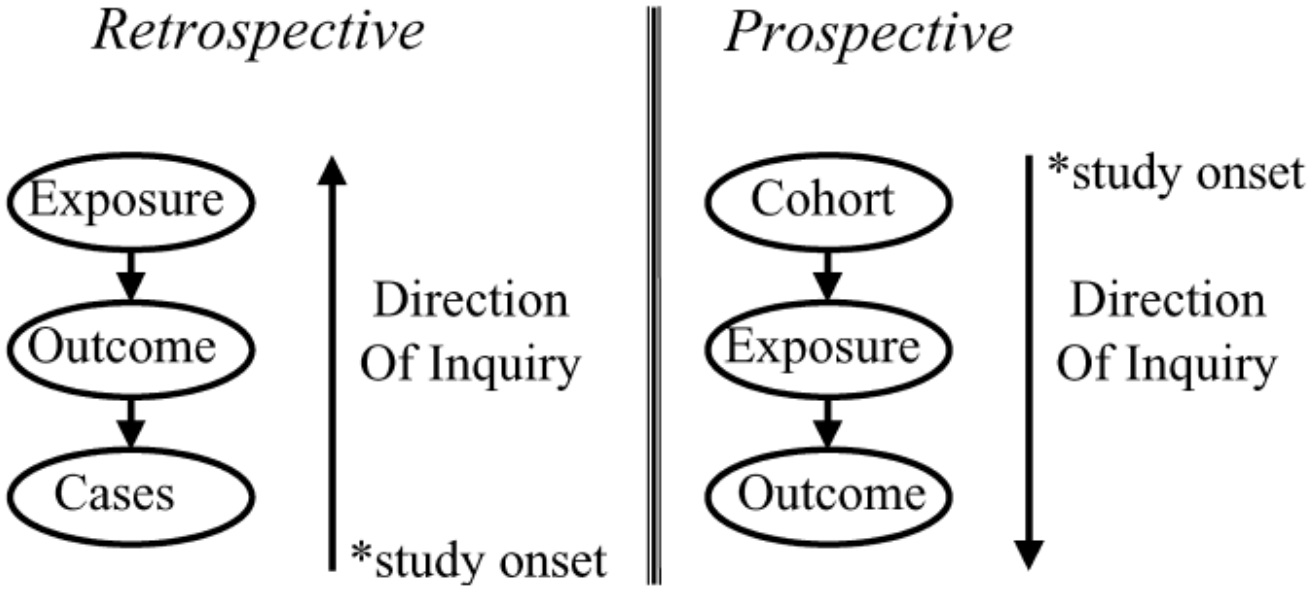
- In *observational studies* researchers observe patient groups

- without allocation of the intervention, whereas in *experimental studies* researchers allocate the treatment.

Types of clinical studies - II

- Studies may be
  - *retrospective*, meaning that the direction of inquiry is backward from the cases and that the events of interest transpired before the onset of the study.
  - *prospective*, meaning that the direction of inquiry is forward from the cohort inception and that the events of interest transpire after the onset of the study

Types of clinical studies - III



Types of clinical studies - IV

- *Cross-sectional* studies are used to survey one point in time.
- *Longitudinal* studies follow the same patients over multiple points in time.

GENERAL STRUCTURE OF A CLINICAL STUDY

“effect”

(eg. disease, recovery)

„Exposure” **(eg. risk factor, medication)**	**yes**	**no**
yes	**a**	**b**
no	**c**	**d**

Measures of the effect: eg. Relative risk [a/(a+b)/c/(c+d)]

CROSS SECTIONAL STUDY

- Advantages

  cheap, simple, fast

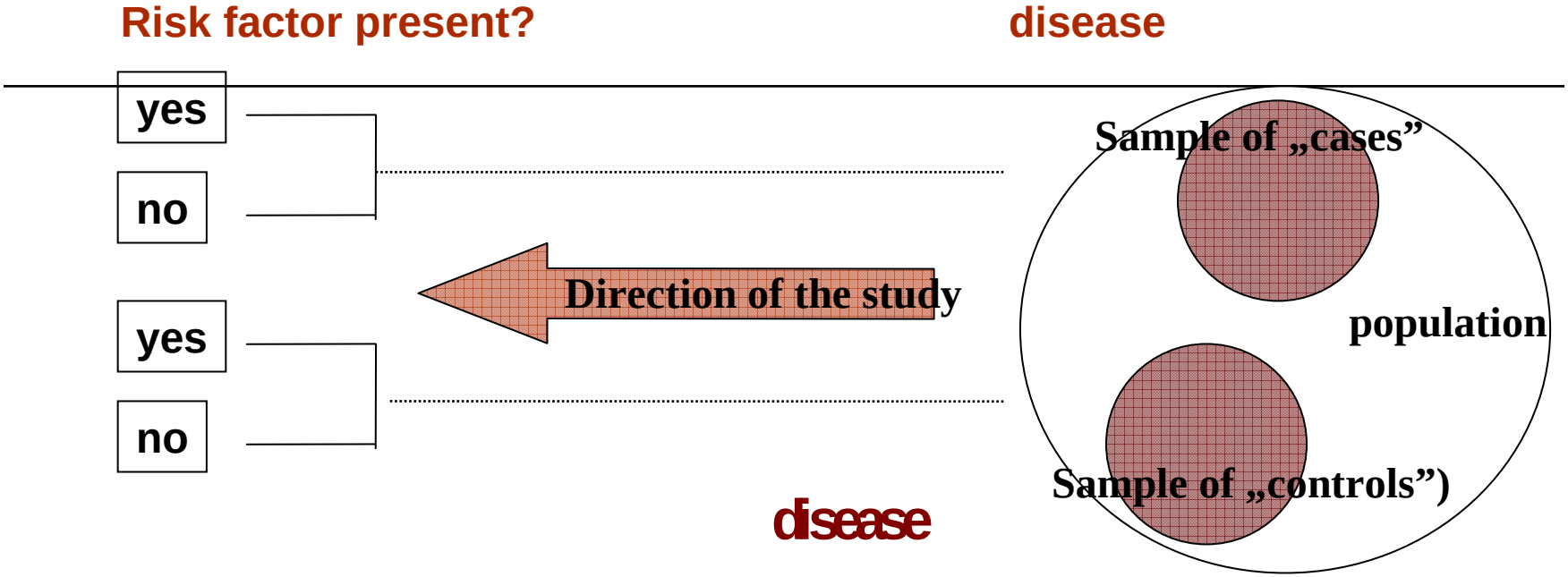
  - No ethical problem
- disadvantages
  - It may suggest association but not causality
  - Bias
  - Distribution of confoundings may be unequal
  - Group size may be different
  - Neyman bias

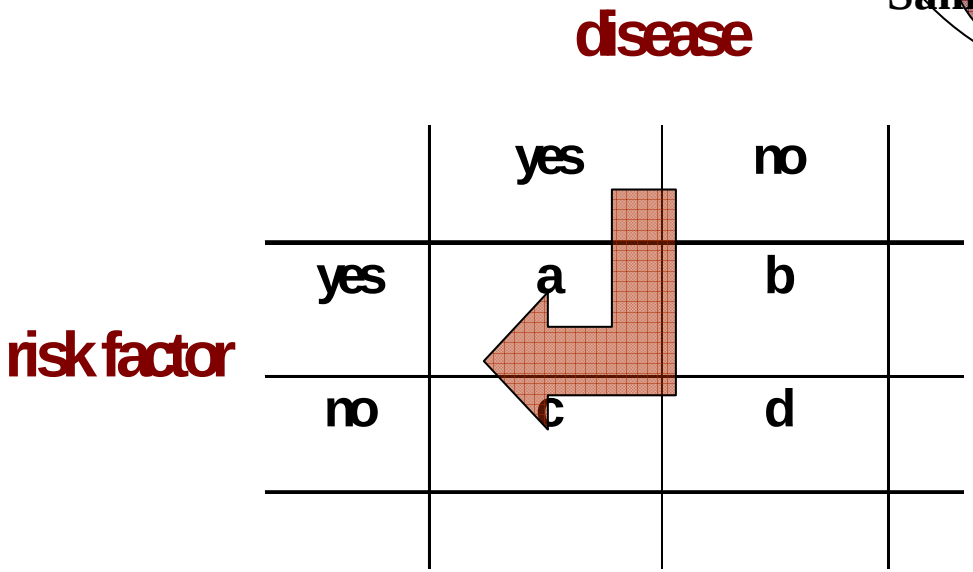
CASE-CONTROL STUDIES

- After selecting „cases” and „controls” one compares the presence or absence of a hypothetical „cause” or exposure in the past in the two groups

- It is important to make the „controls” as similar to „cases” as possible (except the presence of the symptom or disease)

CASE-CONTROL STUDIES





CASE-CONTROL STUDIES

Diuretics, beta-blockers, and the risk for sudden cardiac death in hypertensive patients **Ghoes AW. et al. NEJM 1995;123:481-7**

- Question: Is there a correlation between the use of K-sparing diuretics and sudden death?
- Method: review of charts of 257 pts with HTN who died of sudden death vs 257 alive pts with HTN („contols”) (usage of diuretics)

sudden death

diuretics	**case**	**controls**	
yes	**33**	**23**	**OR= 1,50**
no	**224**	**234**	
	257	**257**	

CASE-CONTROL STUDIES

- advantages:
  - effective, cheap, fast – there is no F6u
  - Usually less patients are needed than for a cross-sectional study
  - The only feasible design for very rare disorders or for ones with very long latency periode;

- diadvantage:
  - Potential for bias (selection bias, recall bias – problems with documentation, etc.)
  - Confoundings;
  - selection of control groups is difficult
  - Temporality may be questionable

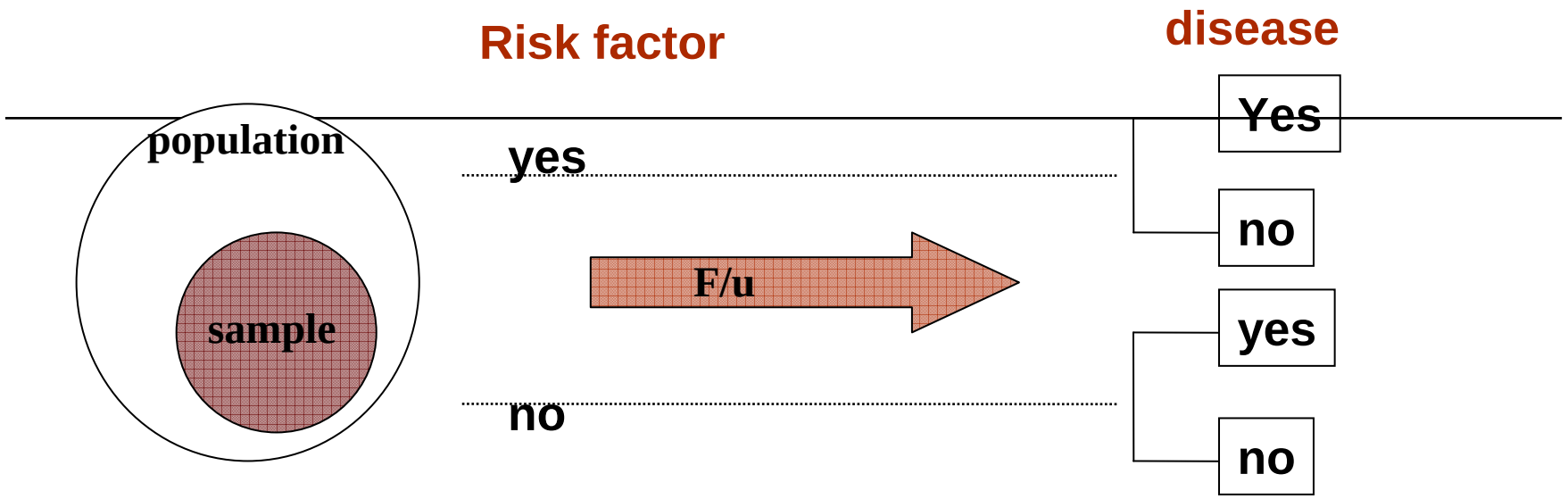
COHORT STUDY

COHORT STUDY

- F/u of groups („cohorts”) of pts exposed versus not exposed to a given factor (risk factor) than a comparison of a pre-specified outcome (e.g. appearance of a disease) between the two groups

- *To make the two groups as similar as possible*
- At the beginning no one shows the symptoms

COHORT STUDY



"disease"

risk factor

	yes	no	
yes	a	b	
no	c	d	

COHORT STUDY

Sodium sensitivity and cardiovascular events in patients with essential hypertension. **Morimoto A et al. Lancet 1997;350:1734-7**

- Question: Is salt sensitivity a risk factor for cardiovascular events?
- Method: 62 salt-sensitive (propsed "cause") and 94 salt-resistant pts, 7,3 yrs f/u, outcome ("effect") CV events

CV event

	yes	no	
SS	**17**	**45**	**62**
SR	**14**	**80**	**94**

RR= 1,87

COHORT STUDY

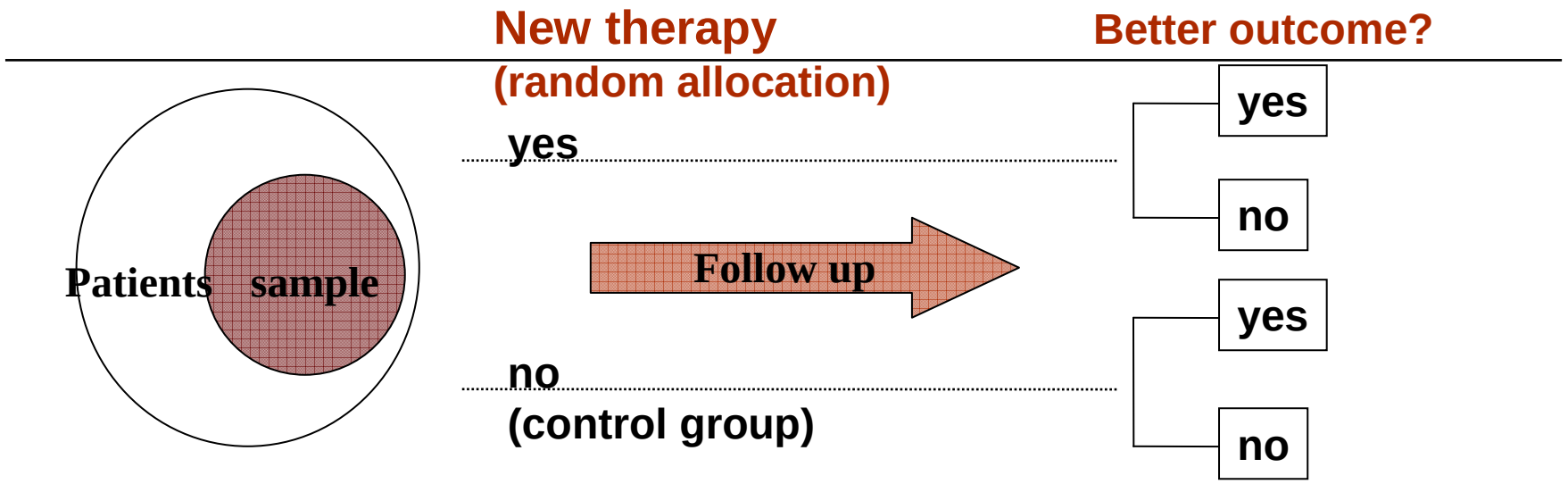
- **advantages**
  - No ethical problems
  - It can determine temporality and directionality
  - The only way to establish the role real risk factors in humans
  - Exclusion and inclusion criteria can be standardized
  - One can look at several outcomes
  - Cheaper and more simple than RCT
- D**isadvantages**
  - Effect of a confounding can not be ruled out
  - Still expensive, takes time,
  - It is difficult and not feasible for rare disorders or for ones with long latency-periods
  - Groups may not be comparable

RANDOMIZED CONTROLLED TRIAL

- Randomized (by chance) allocation of patients into experimental (e.g. new medication) or contol (e.g. placebo or conventional therapy) group than patients are followed prospectively and outcomes are compared between the two groups

- A special „cohort” study
- Randomization renders the two groups comparable

RANDOMIZED CONTROLLED TRIAL



outcome

	good	bad
New therapy	a	b
Control	c	d

RANDOMIZED CONTROLLED TRIAL

Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study
Gaede P et al. Lancet 1999;353:617-22

- Qestion: Is intensive risk factor management more effective to prevent nephropathy than standard therapy?
- Method: randomization- 80 pts intensive therapy, 80 pts standard therapy, 3,8 yrs f/u, outcome - diabetic nephropathy

	nephropathy		
	yes	no	
intenzive	8	72	80
standard	19	61	80

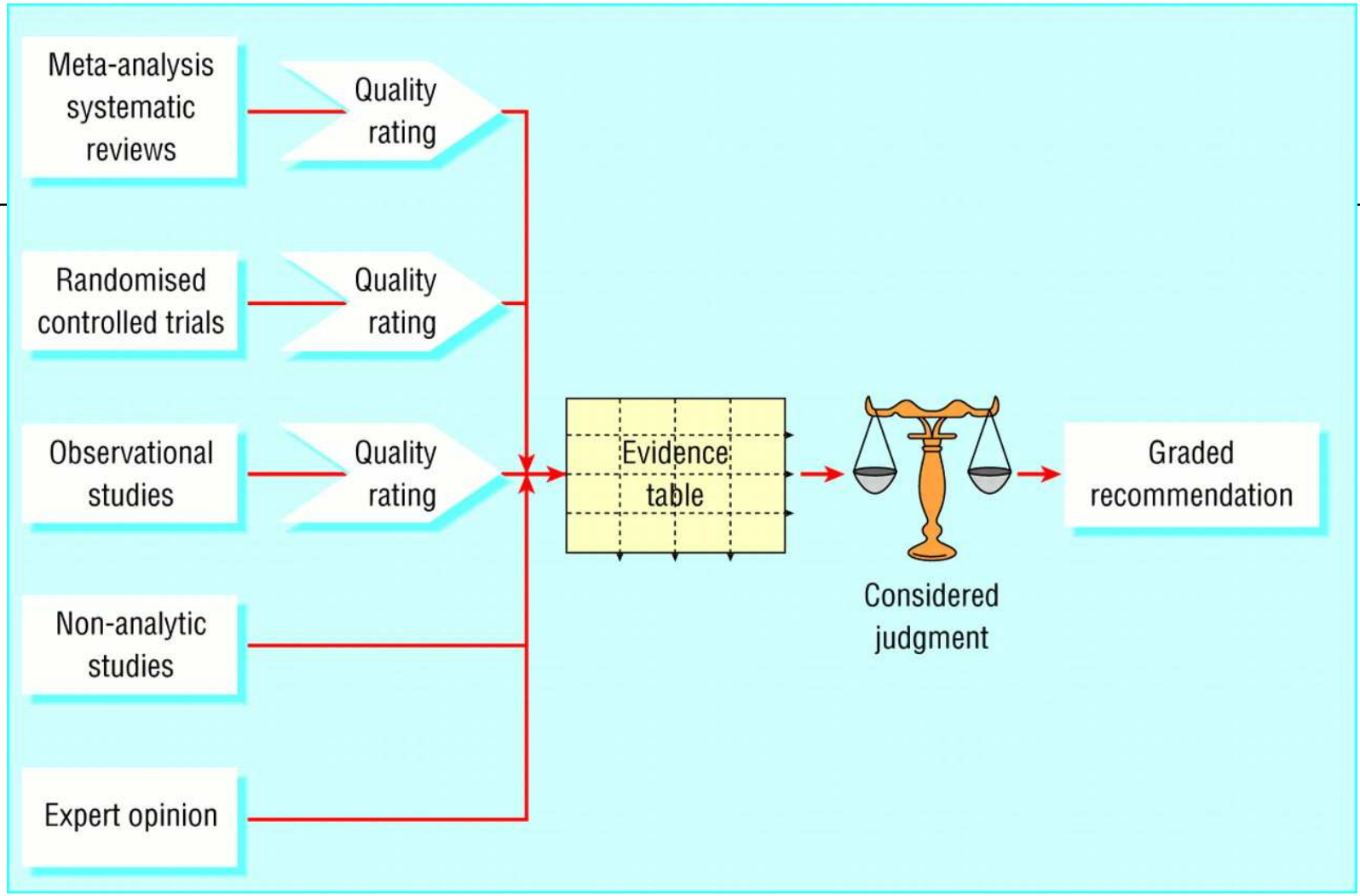
RR= 0,42

RANDOMIZED CONTROLLED TRIAL

- advantage
  - Equal distribution of potential confoundings
  - „blinding” is possible
  - Randomization facilitates statistical comparison
  - Secondary analyses

- disadvantage
  - Ethical difficulties
  - expensive, complicated
  - volunteer bias

Diagnosis	What is the likelihood for a patient having a specific symptom or yielding „positive” on a specific test to have the disease??	Cross sectional study
Therapy	Is the therapy in question more effective in achieving a particular outcome than an alternative therapy (including no therapy)?	Prospective, randomized, controlled study
Prognosis	What is the likelihood of a particular outcome in this patient?	Longitudinal cohort-study
Etiology	What is the cause of the disease? OR: how likely is a particular intervention to cause a specific side effect?)	Studies comparing “cases” and “controlles” (RCT, case-control or cohort- study)



Harbour, R. et al. BMJ 2001;323:334-336

BMJ

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LEVELS OF EVIDENCE (therapy)

- Ia: Systematic review of RCTs SR (with homogeneity) of RCTs
- Ib: At least one good RCT (with narrow Confidence Interval)
- II.a: SR (with homogeneity) of cohort studies
- II.b: Individual cohort study (including low quality RCT; e.g., <80% follow-up)
- III.a: SR (with homogeneity) of case-control studies
- III.b: Individual Case-Control Study
- IV. Case-series (and poor quality cohort and case-control studies)
- V. Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

Grade of Recommendation*	Benefit vs Risk and Burdens	Methodologic Quality of Supporting Evidence	Implications
Strong recommendation, high-quality evidence, Grade 1A	Desirable effects clearly outweigh undesirable effects, or *vice versa*	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances; further research is very unlikely to change our confidence in the estimate of effect
Strong recommendation, moderate-quality evidence, Grade 1B	Desirable effects clearly outweigh undesirable effects, or *vice versa*	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances; higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Strong recommendation, low or very low-quality evidence, Grade 1C	Desirable effects clearly outweigh undesirable effects, or *vice versa*	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Weak recommendation, high-quality evidence, Grade 2A	Desirable effects closely balanced with undesirable effects	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient or society values; further research is very unlikely to change our confidence in the estimate of effect
Weak recommendation, moderate-quality evidence, Grade 2B	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Best action may differ depending on circumstances or patient or society values; higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Weak recommendation, low or very low-quality evidence, Grade 2C	Desirable effects closely balanced with undesirable effects	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate

Quality of evidence	Numbers	Letters	Circles	Stars	Multiple
High	1	A	●	☆☆☆☆	⊕⊕⊕⊕
Moderate	2	B	◕	☆☆☆	⊕⊕⊕🧍
Low	3	C	◑	☆☆	⊕⊕🧍🧍
Very low	4	D	◔	☆	⊕🧍🧍🧍

Action based on balance between benefit and harm	Numbers	Letters	Traffic lights	Thumbs	Arrows
Do	1	A			↑↑
Probably do	2	B			↑?
Probably don't do	3	C			↓?
Don't do	4	D			↓↓

- RCT? Vs observational data
- Decisions for an individual based on data from populations - Typical? If not then what?
- MDRD, HEMO, DECOR, etc – **$$$$$$$$$**

- Observational – hypothesis : what happens to the hypotheses?
- What happens meanwhile or at all?