Determining the Usefulness of Therapy Articles

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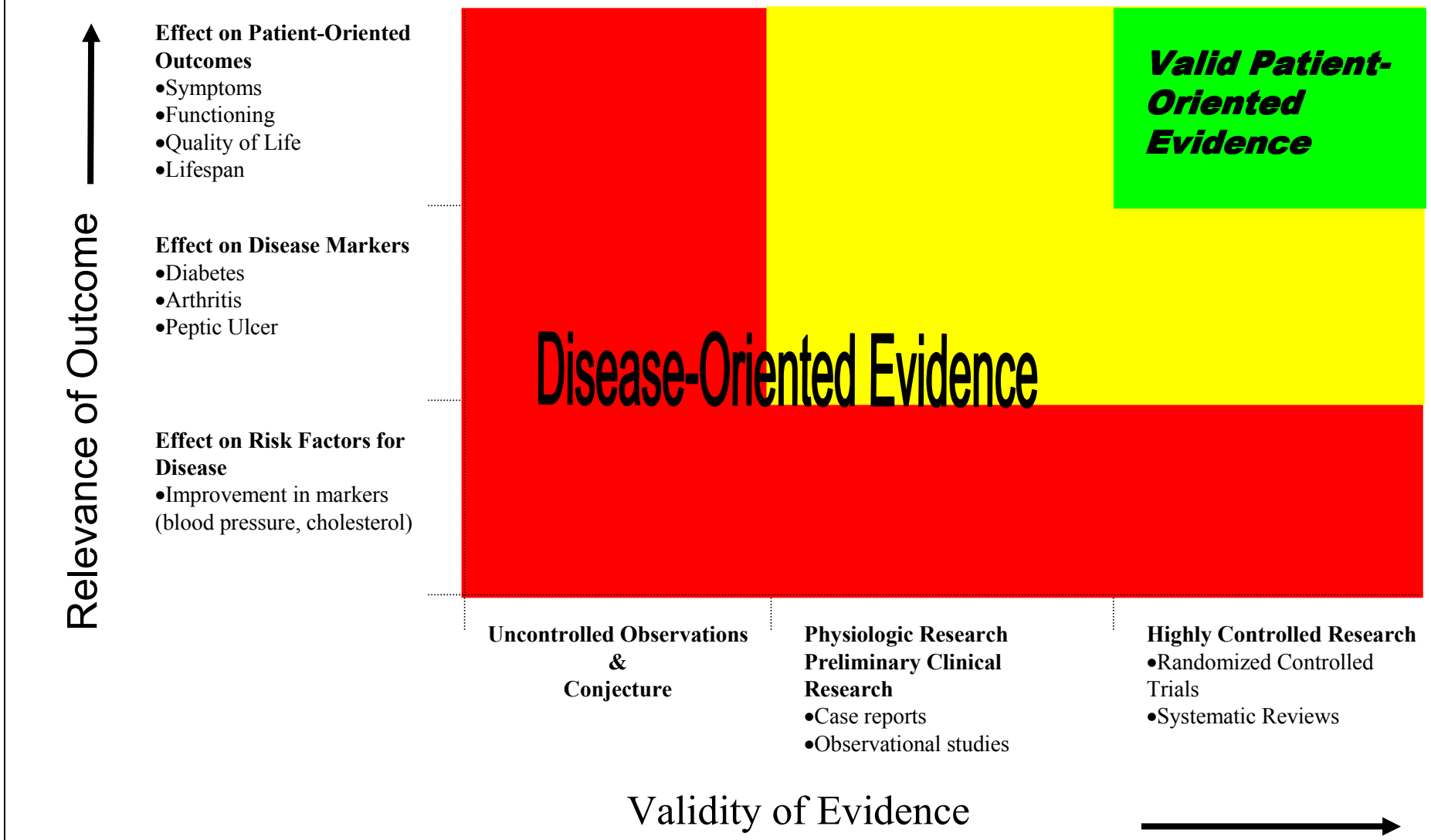
Case

You are seeing a 34 y/o woman with recurrent migraine headaches 3-4 times per month. All attempts to prevent them have had minimal success. She heard some vitamin supplement may help.

PICO: In women with frequent migraines unresponsive to usual therapies is there a vitamin that is more effective than placebo to decrease the frequency of migraine?

Study Methods to Answer This Question

- **Epidemiology**: Patients taking a vitamin are less likely to have migraines
- **Pharmacology**: Drug x affects cerebral vasculature in rat brain isolates
- **Case report**: "It worked on one patient"
- **Case-series**: "It worked on a bunch of patients"
- **Randomized controlled trial**: 1/2 get drug, 1/2 placebo. No one knows who until the end who took what


Relevance of Outcome
Effect on Patient-Oriented Outcomes
•Symptoms
•Functioning
•Quality of Life
•Lifespan
Effect on Disease Markers
•Diabetes
•Arthritis
•Peptic Ulcer
Effect on Risk Factors for Disease
•Improvement in markers (blood pressure, cholesterol)
Valid Patient-Oriented Evidence
Disease-Oriented Evidence
Uncontrolled Observations & Conjecture
Physiologic Research Preliminary Clinical Research
•Case reports
•Observational studies
Highly Controlled Research
•Randomized Controlled Trials
•Systematic Reviews
Validity of Evidence

Article Evaluation Tool

Relevance

validity

A Worksheet for Articles about Treatment

Determine *Relevance* *Is this article worth taking the time to read? If the answer to any of these questions is No, it may be better to read other articles first.*

Based on the conclusion of the abstract:

A. Did the authors study an outcome that patients would *care* about? (Be careful to avoid results that require extrapolation to an outcome that truly matters to patients.)

Yes (go on.) No **(stop)**

B. Is the problem studied one that is *common* to your practice and the intervention feasible?

Yes (go on.) No **(stop)**

C. Will this information, if true, require you to *change* your current practice?

Yes (go on.) No **(stop)**

Determine *Validity*: *If the answers to all three questions above are Yes, then continued assessment of the article is mandatory.*

D. Population

1. Are the studied patients similar enough to your patients that you can apply the results in your practice? Yes No **(Stop)**

E. Study design

1. Was it a controlled trial? Yes No **(Stop)**
2. Were the subjects randomly assigned? Yes No **(Stop)**
3. Were steps taken to conceal the treatment assignment from study personnel entering patients into the study? Yes No
4. Were patients, providers and outcome assessors "blind" to treatment? Yes No

F. Study conduct

1. Were all patients who entered the trial properly accounted for at its conclusion?
   a. Was follow-up complete? Yes No
   b. Were patients analyzed in the groups to which they were randomized ("intention-to-treat" analysis)? Yes No
2. Were the intervention and control groups similar? (Table 1) Yes No

G. Study results

1. What were the results? _____

   _____

2. Are the results clinically as well as statistically significant? Yes No
3. If a negative trial, was the power of the study adequate? Yes No
4. Were there other factors that might have affected the outcome? Yes No
5. How will it change your practice?

1. Determine Relevance

Read the title and the conclusion of the abstract:

1. Did the authors study an outcome that patients would *care* about?
2. Is the problem studied one that is *common* to your practice and the intervention feasible?
3. Will this information, if true, require you to *change* your current practice?

2. Determine Validity

- **Internal validity**: How well was the study done? Do the results reflect the *truth*?

- **External validity**: can I apply these results to **MY** patients?

2. Determine Validity

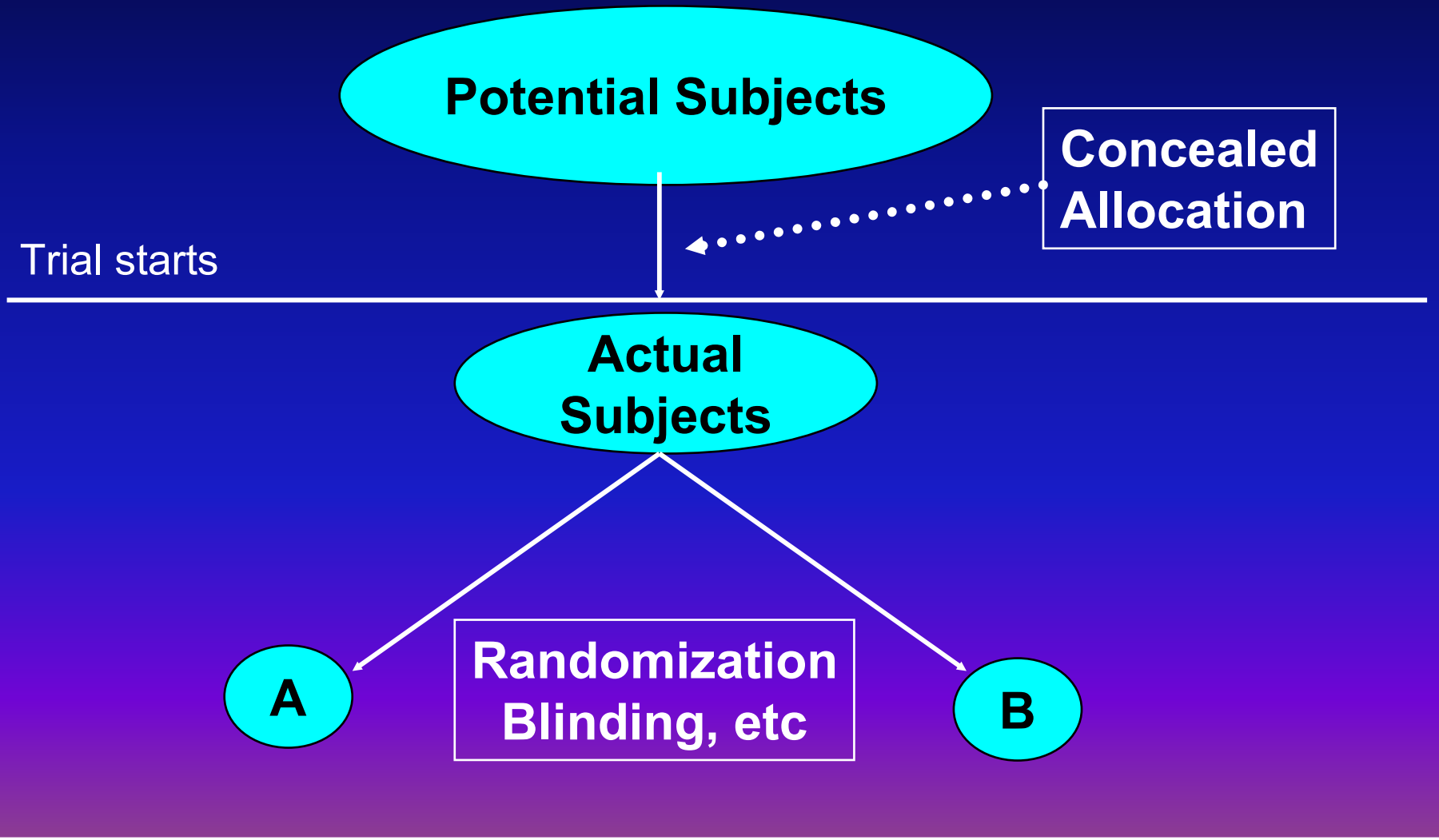
- Read the methods section
  - Answer questions on lower half of worksheet
  - Study design flaws are *common*, but are they "***fatal***"?
    - "Stop" questions = fatal flaws

Methods Section

The Four Pillars of the RCT

1. Randomization
2. Allocation Concealment
3. Blinding
4. Completeness of follow-up

Conducting a Study



Fatal Flaw #1
Was it a randomized controlled trial?

Randomization is the best protection against being mislead

How is it done?

The value of randomization

- 32 controlled trials of anticoagulation in acute MI
- Results by type of study:

	Relative Risk Reduction	Case fatality rate
Historical control	42%	38.3%
Controlled trial	33%	29.2%
Randomized controlled trial	31%	19.6%
Concealed Allocation	18%	12.1%

Chalmers TC, et al. N Engl J Med 1977;297:1091-6.

The value of randomization

To ensure equal distribution of important known and unknown prognostic factors

Fatal Flaw #2
Was allocation assignment concealed?

Did investigators know to which group the potential subject would be assigned **before** enrolling them?

Allocation concealment Reporting

- Opaque sealed envelopes
- Computerized
- Main study center

Importance of concealed allocation

Trials with unconcealed allocation consistently overestimate benefit by ~40%

Schulz KF, Chalmers I, Hayes RJ, et al. JAMA 1995;273:408-12

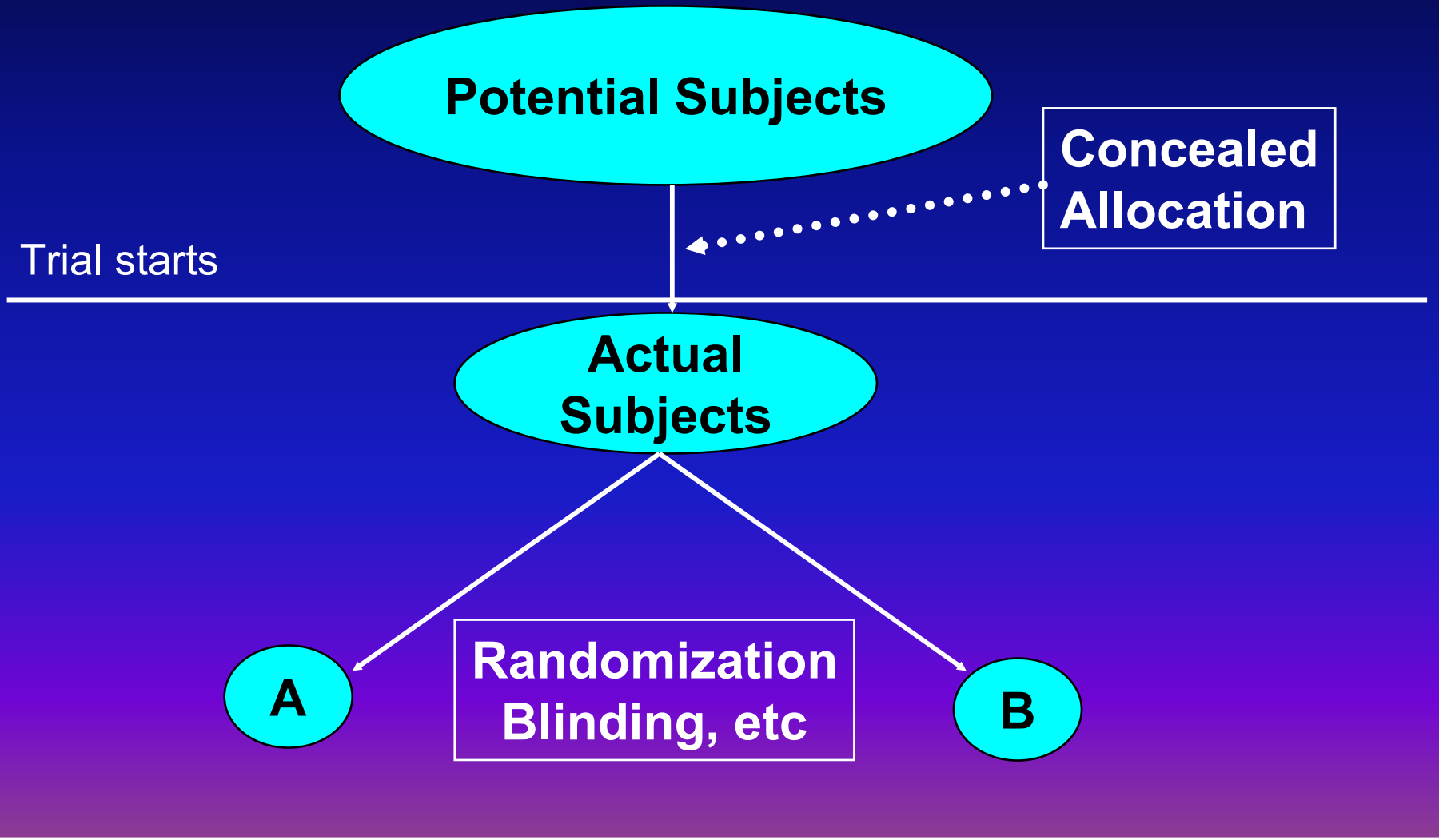
Schulz KF, Grimes DA. Lancet 2002;359:614-18.

Was allocation assignment "concealed"?

- Concealed allocation ≠ blinding
  - Blinding can occur without concealed allocation
    - UVA example- surfactant in the NICU
  - Allocation can be concealed in an unblinded study
    - PT vs surgery for knee DJD

Moseley JB, O'Malley K, Petersen NJ, et al. N Engl J Med 2002; 347:81-8.

Conducting a Study



Blinding
Was study "double-blinded"?

- Did the **patients** know to which group they were assigned?
- Did the ***treating*** physician know?
- Did investigators **assessing** outcomes know ("triple-blinding" – up to 7 levels!)?
  - Judicial assessor blind + allocation concealment = surgery RCTs

Schulz KF. Ann Int Med 2002;136:254-9.

Blinding
Why to blind?

To avoid Co-intervention bias

Are the study patients similar to yours?

Addresses generalizability of results to your practice (external validity)

Are the study patients similar to yours?

Methods. *Patients.* The study was conducted in six centers in Belgium and the Grand Duchy of Luxemburg under the sponsorship of the Belgian Migraine Society. Patients were recruited between March 1995 and March 1996, and the trial was completed on July 31, 1996. The design was in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Faculty of Medicine, University of Liège. Patients (ages 18 to 65 years) were eligible for the study if they met the International Headache Society (IHS) diagnostic criteria for migraine with or without aura[14] and had a history of migraine of at least 1 year, had between two and eight attacks per month, had no more than 5 days of interval headaches per month, had no analgesic or ergotamine overconsumption, and had no serious organic or psychiatric disease. Women were required to have adequate contraceptive protection. Written informed consent was obtained.

Table 1 *Characteristics of patients*

	Placebo (n = 26)	Riboflavin (n = 28)
Age* (y)	35.2 (19–53)	36.9 (18–62)
No. of women	21	21
Attack frequency* (mo)	3.71 (2–7)	3.83 (2–6)
Attack duration* (hr)	32.35 (6–72)	35.42 (6–84)
Migraine history		
Diagnosis		
Migraine without aura	19	23
Migraine with aura	2	1
Both types	5	4
Disease duration* (y)	13.9 (1–47)	11.8 (1–40)

* Values are means, with ranges in parentheses.

Were all the patients properly accounted for at its conclusion?

- Complete follow-up? (conventional# 80%)
- "Intention to treat" analysis?
  - Patients are analyzed in the groups to which they are assigned
  - Attempts to reflect "real world" clinical situations in which not all patients are compliant
  - Watch when they compare only compliers with compliers and non-compliers
    - Compliant subjects always do better overall

Results Section

Were intervention and control groups similar?

- See Table 1 of most studies
- Randomization is best way to avoid bias, though imbalances still can occur (especially if allocation was not concealed)
- Small differences sometimes are important

Were intervention and control groups similar?

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Results

Statistics . . . . .

$$SS_{\text{total}} = \sum_{j=1}^{k} \sum_{i=1}^{n_j} [(x_{ij} - \bar{x}_{.j}) + (\bar{x}_{.j} - \bar{x}_{..})]^2$$

$$= \sum_{j=1}^{k} \sum_{i=1}^{n_j} (x_{ij} - \bar{x}_{.j})^2 + 2 \sum_{j=1}^{k} \sum_{i=1}^{n_j} (x_{ij} - \bar{x}_{.j})(\bar{x}_{.j} - \bar{x}_{..})$$

$$+ \sum_{j=1}^{k} \sum_{i=1}^{n_j} (\bar{x}_{.j} - \bar{x}_{..})^2$$

Users of statistics don't have to be statisticians

- I am a **user** of statistics, not a statistician (I have friends, however, who are statisticians)
- You don't have to know a lot about statistics to effectively use statistics
- Don't focus on whether the statistics are *right*
  - Learn to figure out *what* the statistics are trying to **tell you**

Statistics….

- **The purpose of statistics: a way to approximate the truth**
- **Present some easy definitions of common statistical terms**
- **Differentiate between *statistical* and *clinical* significance**

Which measure was used to compare the two groups?

Outcome	Binary	Continuous
Effect Estimate	OR, RR, RD NNT	MD and SMD

What do you need to know?

- Calculation
- Interpretation

Relative Risk

RR=1 means no difference

EER= 5/50=0.1

CER= 10/50=0.2

RR=EER/CER
=0.1/0.2=0.5

RRR=1-RR
=1-0.5=0.5

	MI +	MI -
Aspirin	5	45
Placebo	10	40

Risk Difference or ARR

RD=0 means no difference

EER= 5/50=0.1
CER= 10/50=0.2

RD=EER-CER
=0.1-0.2=0.1

NNT= 1/RD
= 1/0.1=10

	MI +	MI -
Aspirin	5	45
Placebo	10	40

Odds Ratio

OR=1 means no difference

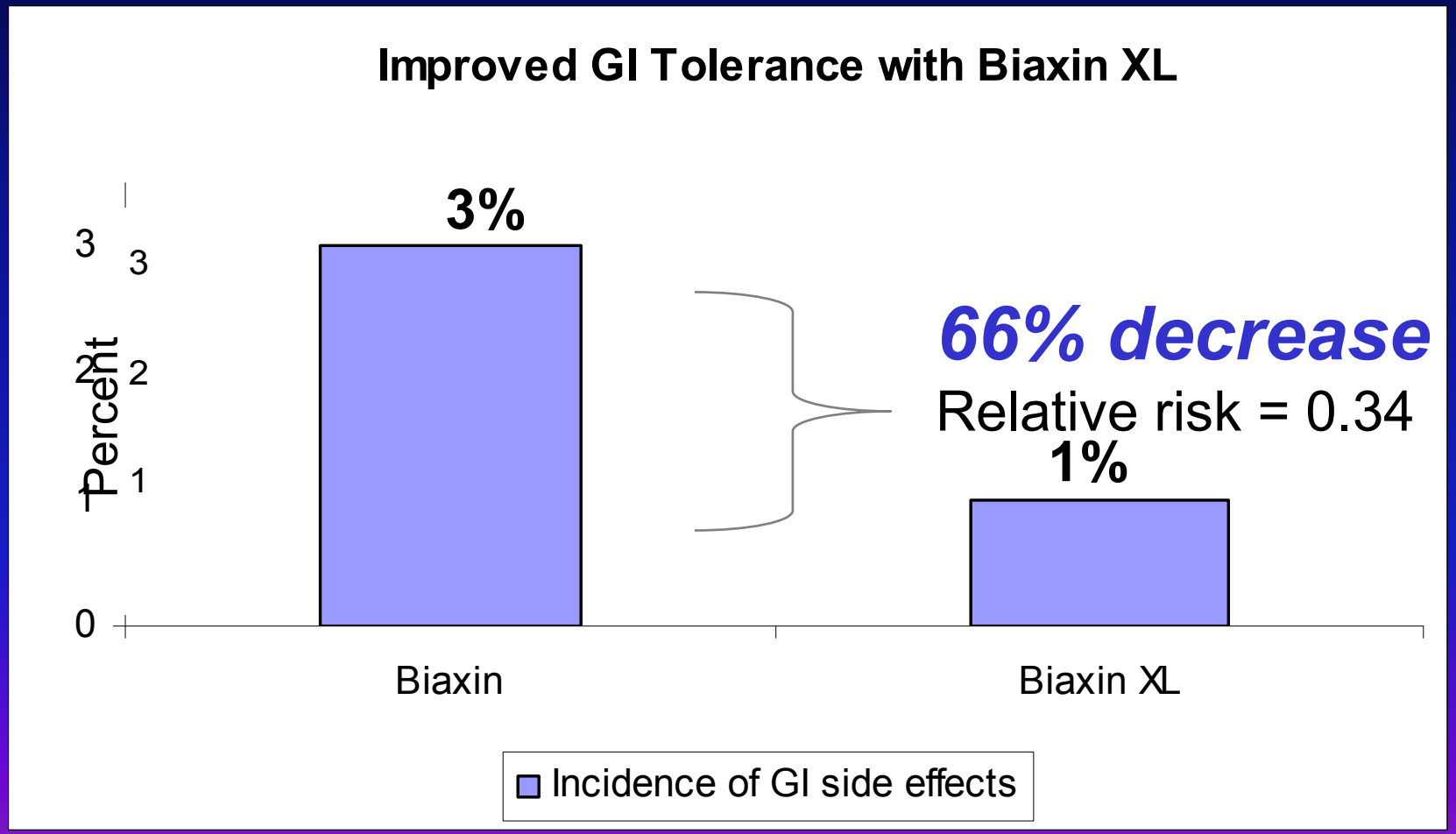
Odds ratio= ad/cb
= 200/450= 0.44

	MI +	MI -
Aspirin	5 a	45 b
Placebo	10 c	40 d

RRR Vs ARR

	Example 1	Example 2
CER (y)	(20%) 0.2	(0.2%) 0.002
EER (x)	(10%) 0.1	(0.1%) 0.001
RRR	(50%) 0.5	(50%) 0.5
ARR	(10%) 0.1	(0.1%) 0.001

RRR Vs ARR


Improved GI Tolerance with Biaxin XL
3%
1%
66% decrease
Relative risk = 0.34
Percent
0
1
2
3
Biaxin
Biaxin XL
Incidence of GI side effects

NNTs for Prevention

Condition	Treatment	Outcome	NNT
Heart failure (NHYA I or II)	Enalapril vs. placebo	1 death at one year	100
Hypertension in patients with type 2 diabetes	HTN treatment	1 diabetes-related death over 10 years	15
Hyperlipidemia – primary prevention	Simvastatin vs no treatment	1 death over 1 years	163
Hyperlipidemia – secondary prevention	Various vs. placebo	1 MI or CVA over 5 years	16 (13-19)
DVT	Warfarin (target INR = 1.5-2.0) vs placebo for 1 yr	1 VTE over 1 year	22

NNTs for Treatment

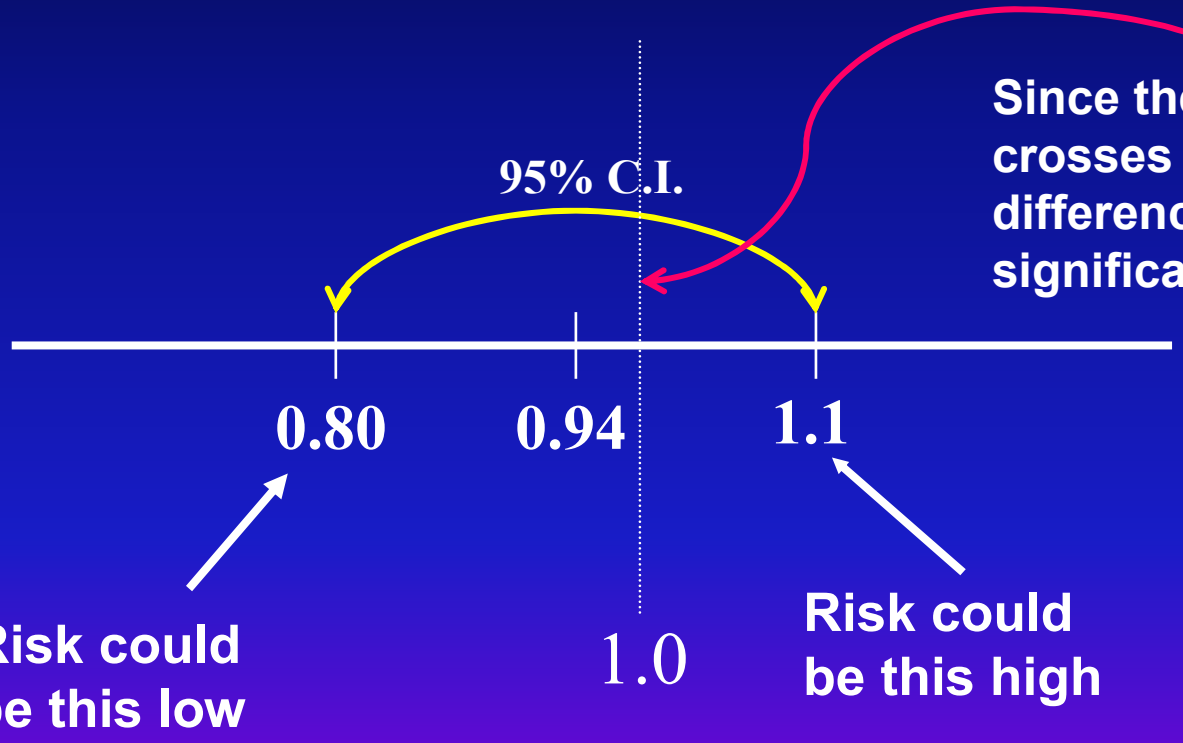
Condition	Treatment	Outcome	NNT
H. Pylori	Triple therapy	Eradication	1.1
Peptic Ulcer	H. Pylori tx vs. H_2 tx for 6-8 wks	Ulcer cure at 1 year	1.8
Migraine	1 dose sumatriptan vs. placebo	Headache relief at 2 hours	2.6
Bacterial conjunctivitis	Topical abx vs. placebo	For early clinical remission (3-5 days)	5
Herpes Zoster	Acyclovir vs. placebo	Prevent PHN at 6 months	Not effective

How Precise is the effect size

Confidence Interval

- An upper and lower boundaries
- What does it mean?
- Statistics are estimates
  - Confidence intervals tells us the upper and lower possibilities of our statistical estimates

All-cause mortality	489	213	17·9	18·9	0·44	0·94 (0·80–1·10)



Example: Results from the UKPDS

	Patients with clinical endpoints		Absolute risk: events per 1000 patient-years		Log-rank p	RR for intensive policy (CI)
AGGREGATE ENDPOINT	Intensive (n=2729)	Conventional (n=1138)	Intensive	Conventional		
Any diabetes-related endpoint	963	438	40·9	46·0	0·029	0·88 (0·79–0·99)
Diabetes-related deaths	285	129	10·4	11·5	0·34	0·90 (0·73–1·11)
All-cause mortality	489	213	17·9	18·9	0·44	0·94 (0·80–1·10)
Myocardial infarction	387	186	14·7	17·4	0·052	0·84 (0·71–1·00)
Stroke	148	55	5·6	5·0	0·52	1·11 (0·81–1·51)
Amputation or death from PVD	29	18	1·1	1·6	0·15	0·65 (0·36–1·18)
Microvascular	225	121	8·6	11·4	0·0099	0·75 (0·60–0·93)

Can I apply the results to my patient?

Can I apply the results to my patient?

Were the study patients similar to the patients) in my practice?

Were all clinically important outcomes considered?

Are the likely treatment benefits worth the potential harms and costs?

Don’t feel bad if you are still confused