Module C2: Clinical Research Methodology

Randomised controlled trials (RCTs)

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What is a clinical trial

Definition

A planned experiment on human subjects which is designed to evaluate the effectiveness of one or more healthcare technology/intervention.

Intervention

Any maneuver that improves health status.

Types of interventions

- drug
- surgical procedure
- diet
- physiotherapy
- behavioural therapy
- diagnostic test
- prevention strategy

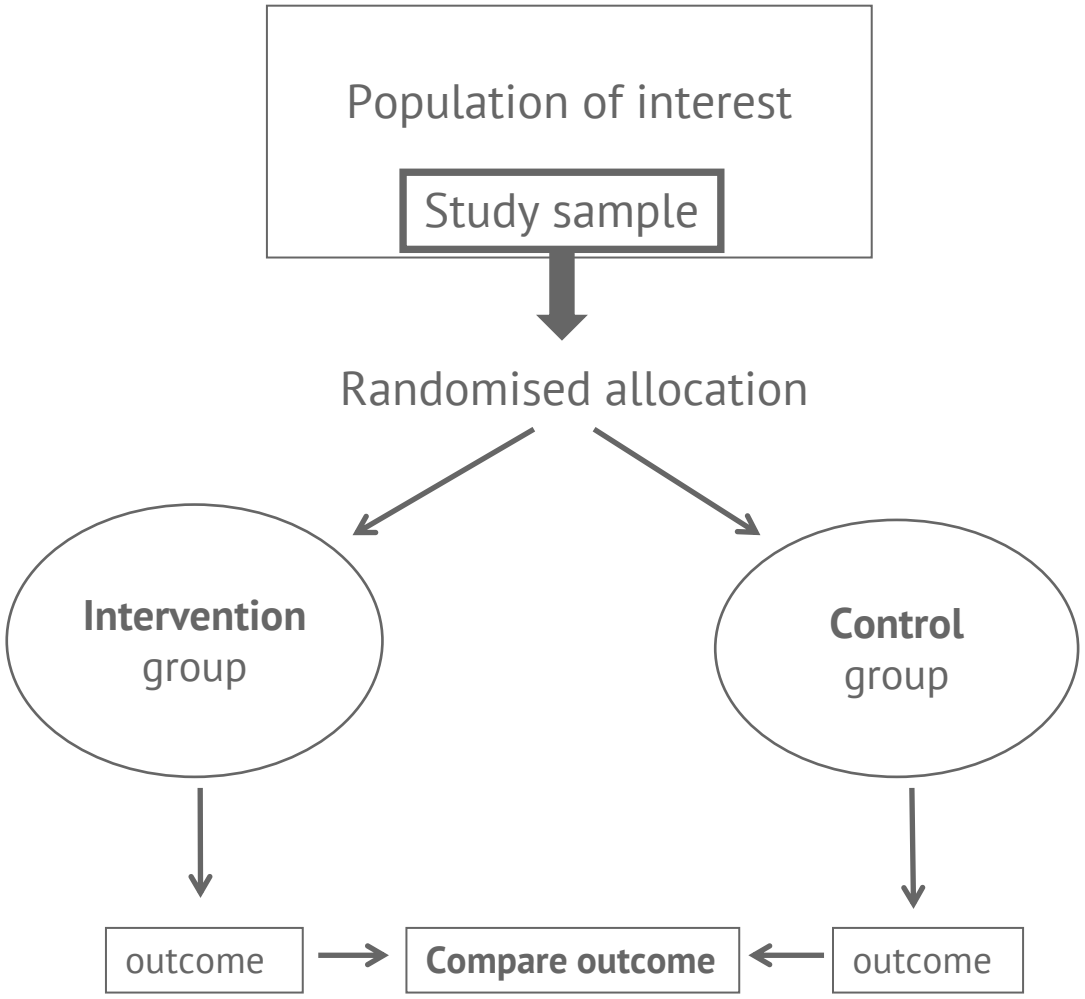
The need for a comparator (control)

- It is natural to begin investigation of a new treatment by assessing it on some patients without a comparator group

- This type of study is uncontrolled

- Many early studies of this type have suggested that a new treatment was effective, only to be proven false after careful evaluation in RCTs

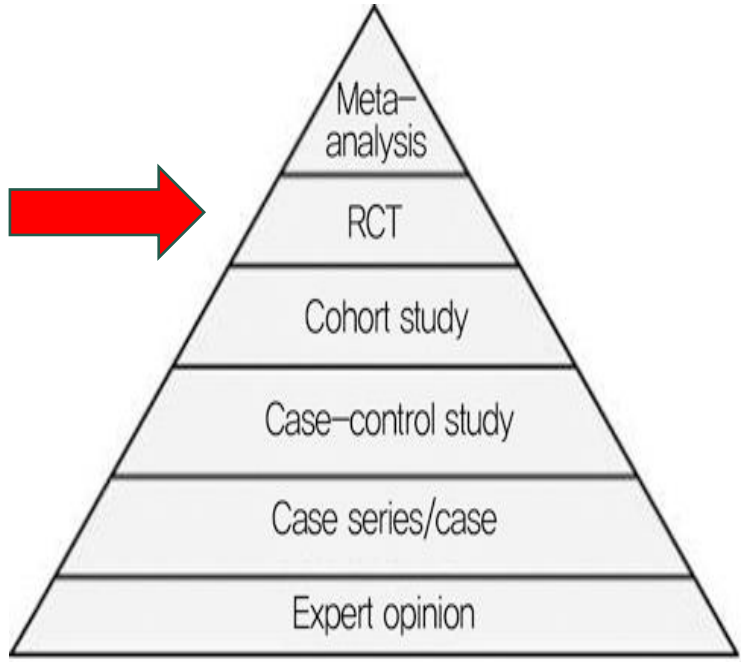
Basic structure of a RCT



RCTs in the hierarchy of evidence

- The most scientifically rigorous method of hypothesis testing available

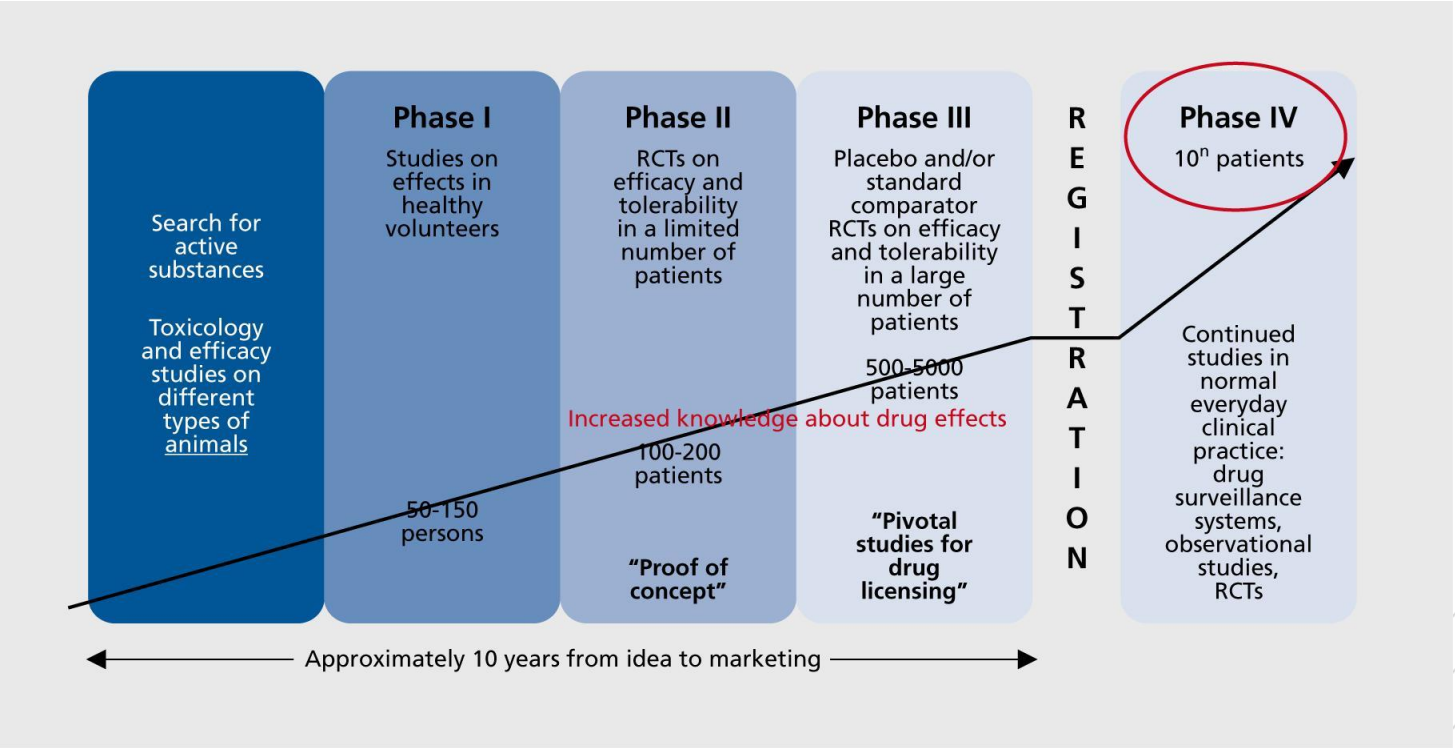
- The gold standard for evaluating healthcare technologies



Correlation vs. causation

Phases of clinical trials

1. Phase I: Is the treatment safe?
2. Phase II: Does the treatment work?
3. Phase III: Is it better than what's already available?
4. Phase IV (post-marketing): What else do we need to know?



RCTs are an interventional type of study!

On March 13th, 2006 eight healthy volunteers took part in a clinical trial of an experimental drug known as TGN1412.

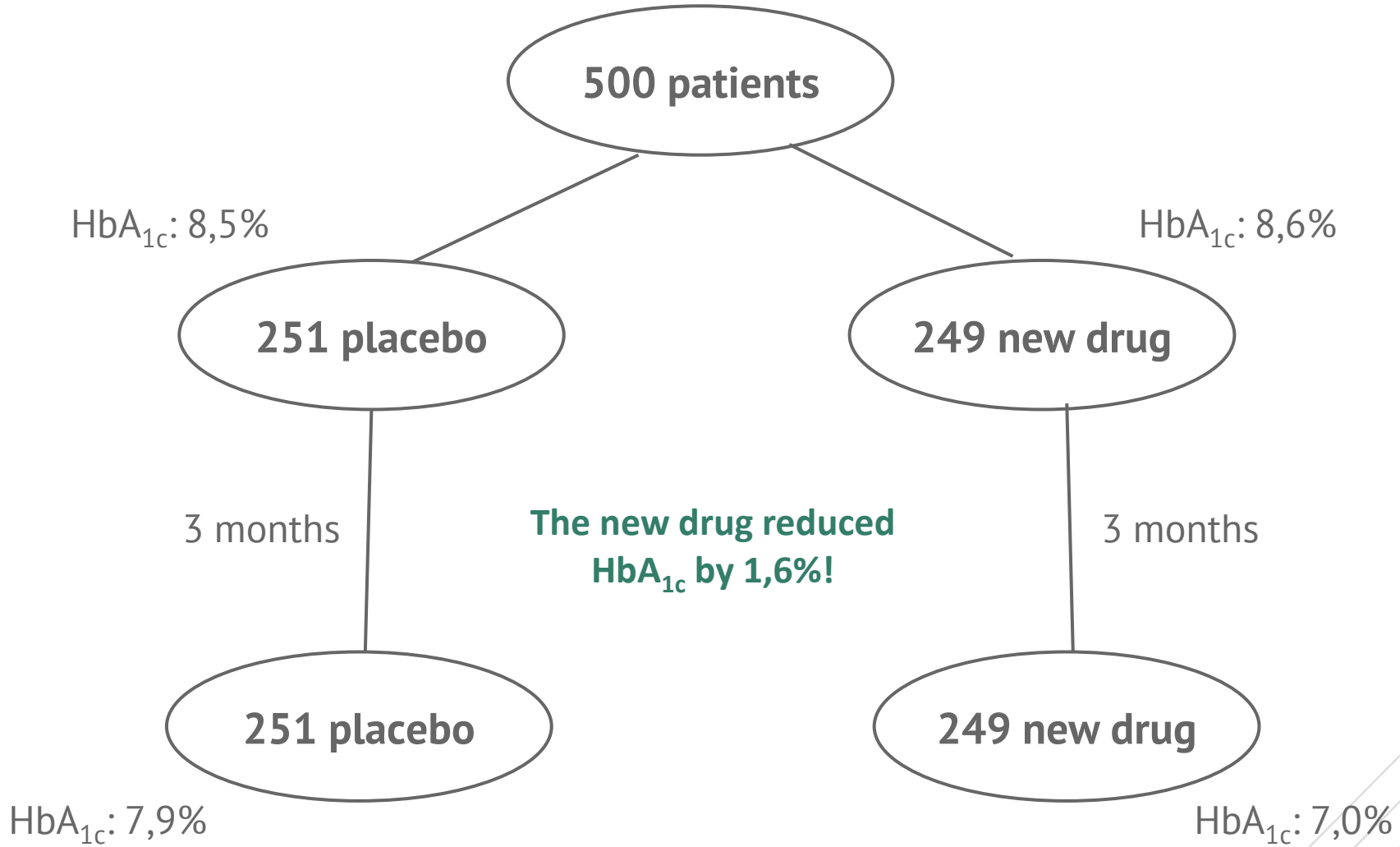
The drug was indented to treat leukaemia and had already been successfully tested on monkeys but never on humans.

The trial soon spiraled into one of the most infamous medical emergencies in recent British history.

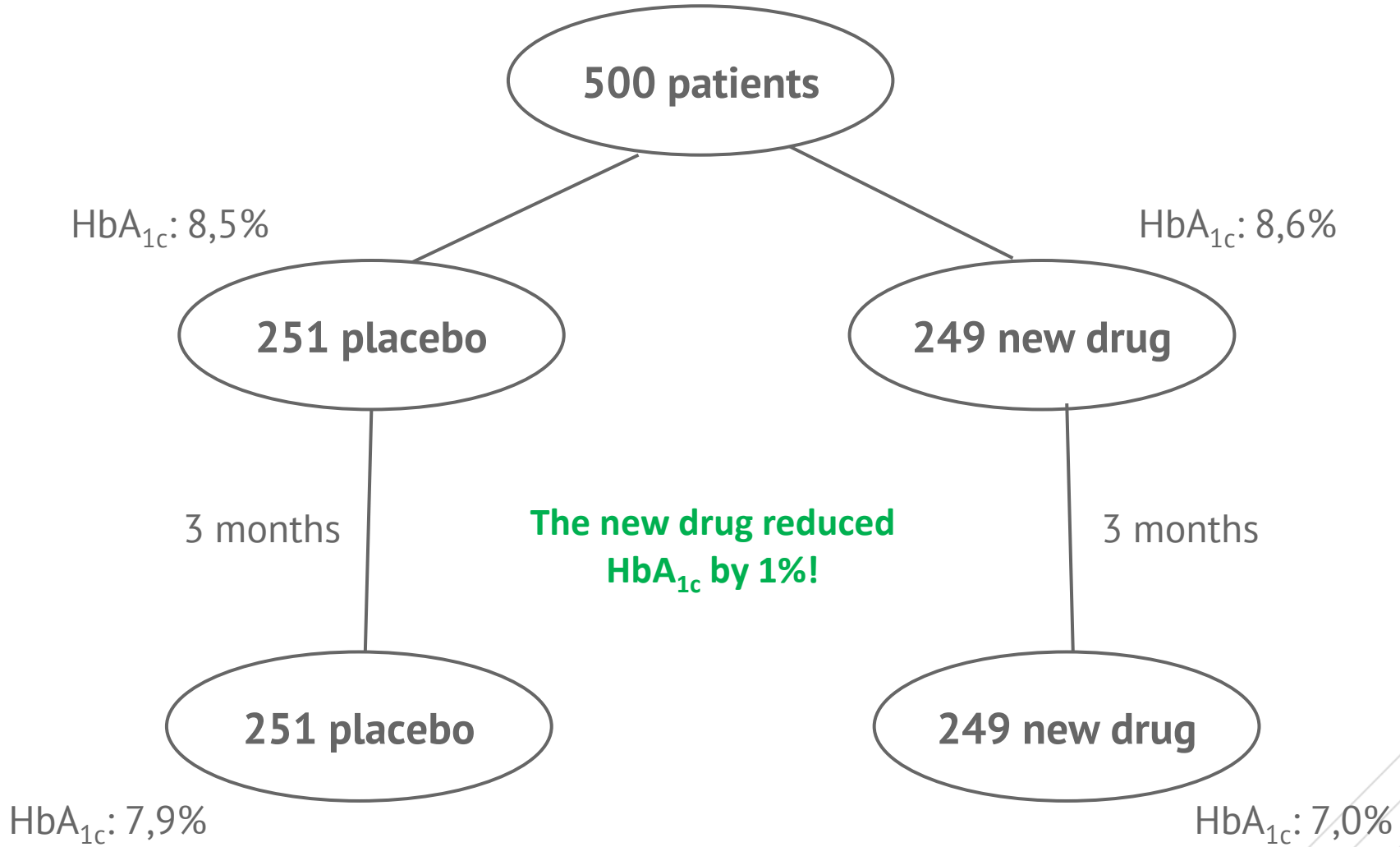
https://www.youtube.com/watch?v=a9_sX93RHOk

RCT stats and metrics

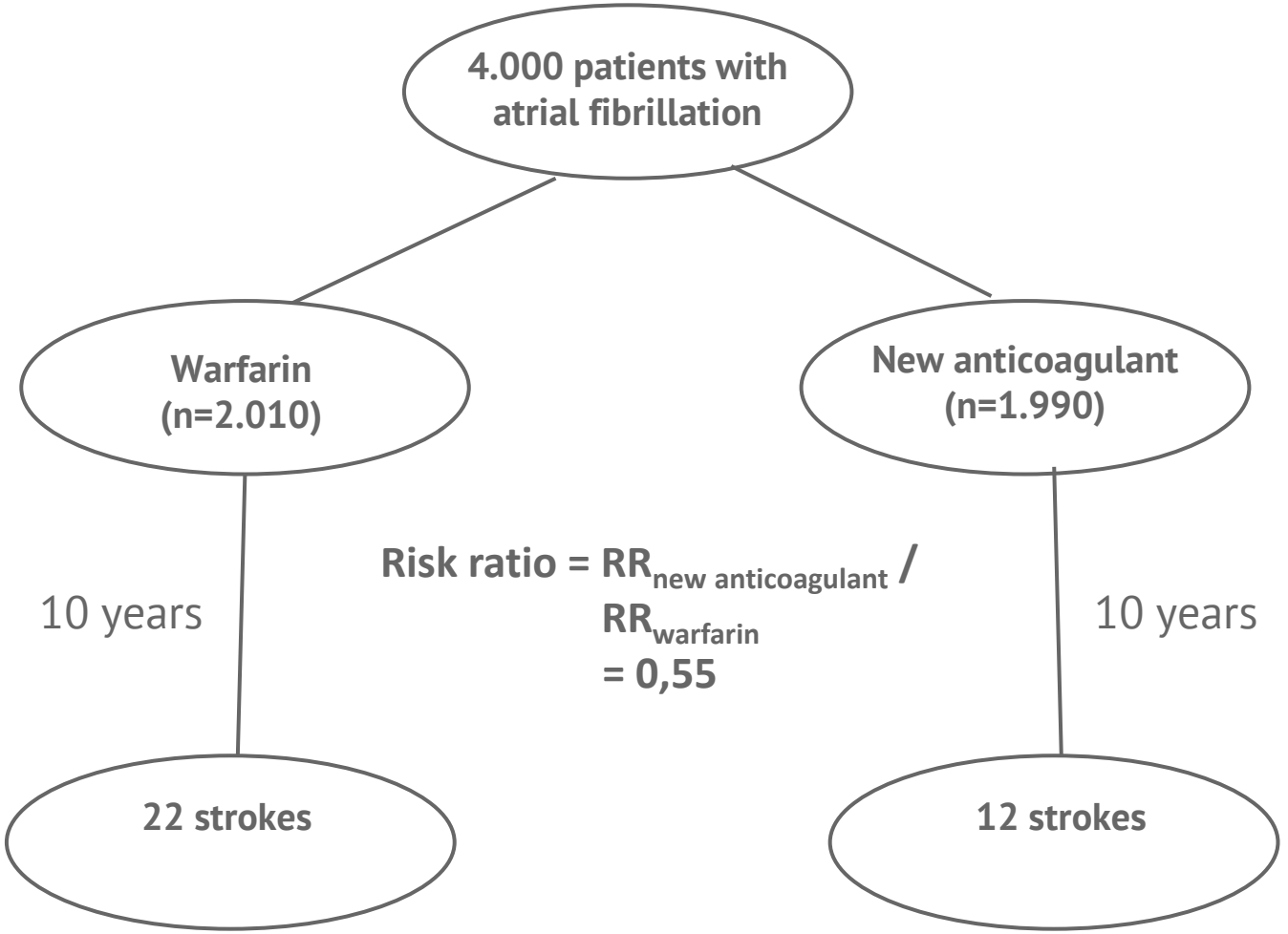
Continuous outcomes - Mean Difference



Continuous outcomes - Mean Difference



Dichotomous outcomes – Risk Ratio



Risk ratio = $RR_{new\ anticoagulant}$ / $RR_{warfarin}$ = 0,55

$RR_{warfarin}$ = 22/2.010 = 0,011 or 1,1%

$RR_{new\ anticoagulant}$ = 12/1.990 = 0,006 or 0,6%

Dichotomous outcomes

	Outcome present	Outcome absent
Experimental group	a	b
Control group	c	d

Risk in experimental group: a / a + b

Risk in control group: c / c + d

Risk ratio: (a / a + b) / (c / c + d)

Odds(p): p / (1 − p)

Odds ratio: (a /c) / (b / d) = (a * d) / (c * b)

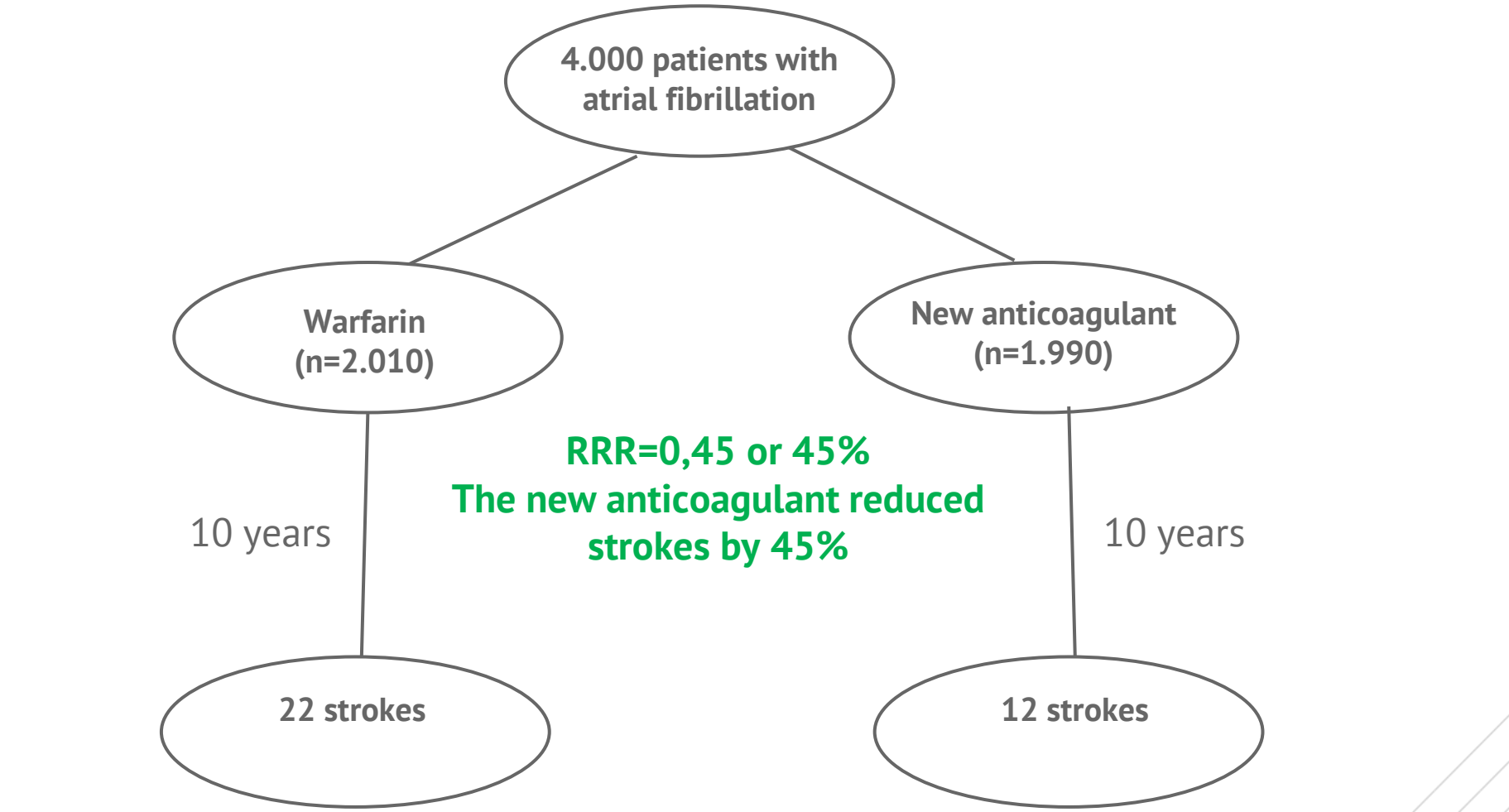
Risk ratio (RR) or Odds ratio (OR)

- For low event rates (close to 1), RR and OR are virtually the same and can be used interchangeably

- For increasing event rates, a dissociation between the two outcome measures is observed (OR > RR)

- RRs produce less impressive (more conservative) results and are more straightforward for clinicians to interpret

Relative Risk Reduction (RRR)



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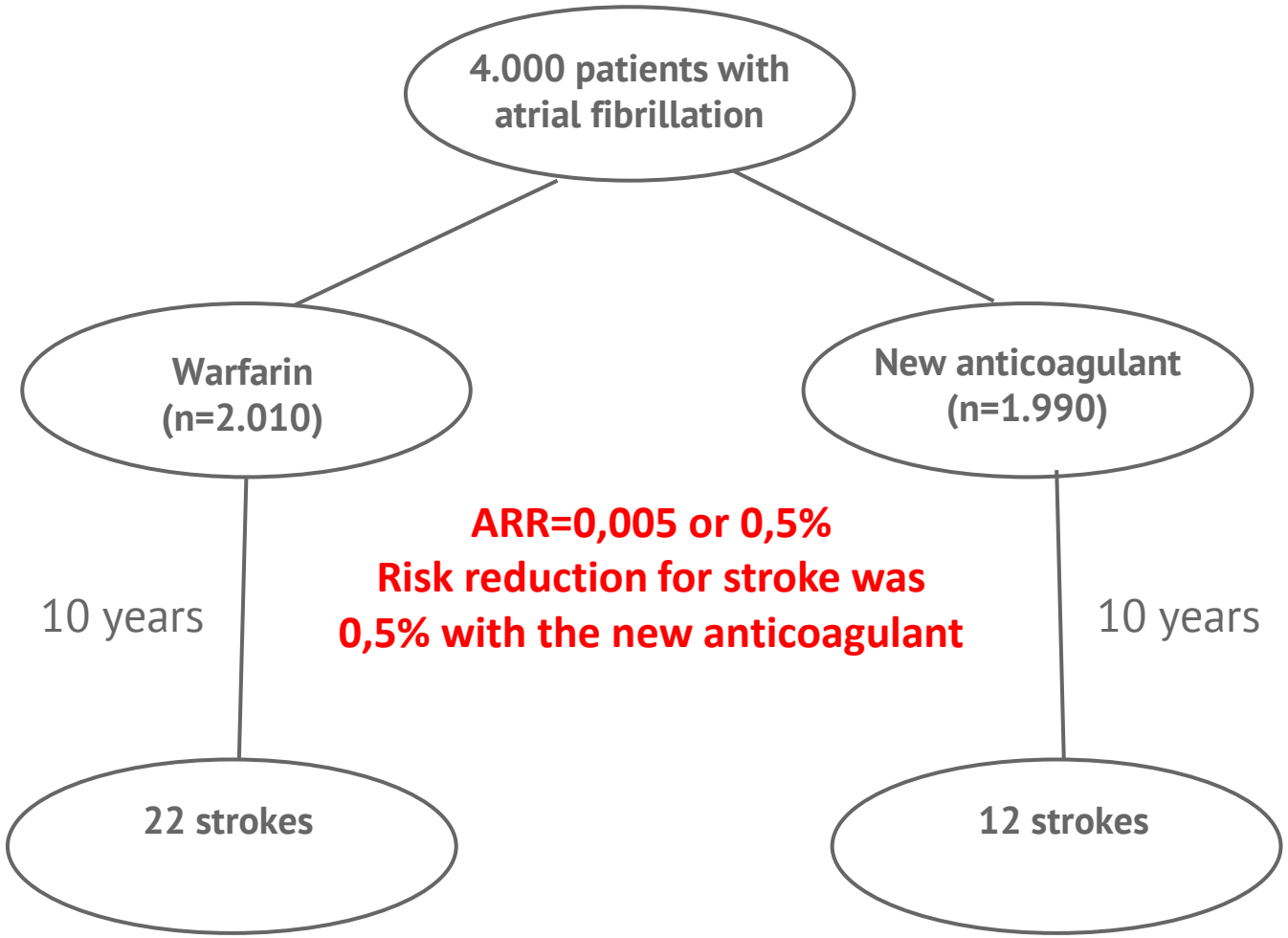
Absolute Risk Reduction (ARR)



$RR_{warfarin}$ = 22/2.010 = 0,011 or 1,1%

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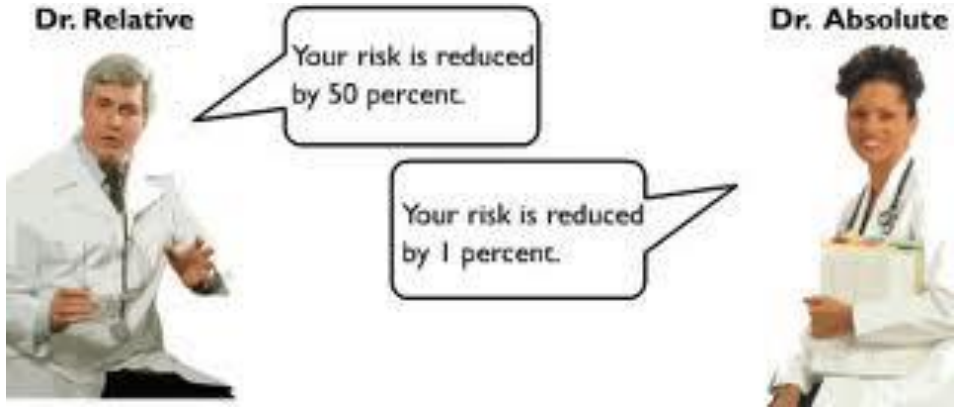
ARR vs. RRR

- RRR – definitely more impressive
- RRR – cannot discriminate between small and large treatment effects
- The lower the control event rate, the higher the dissociation between RRR and ARR is



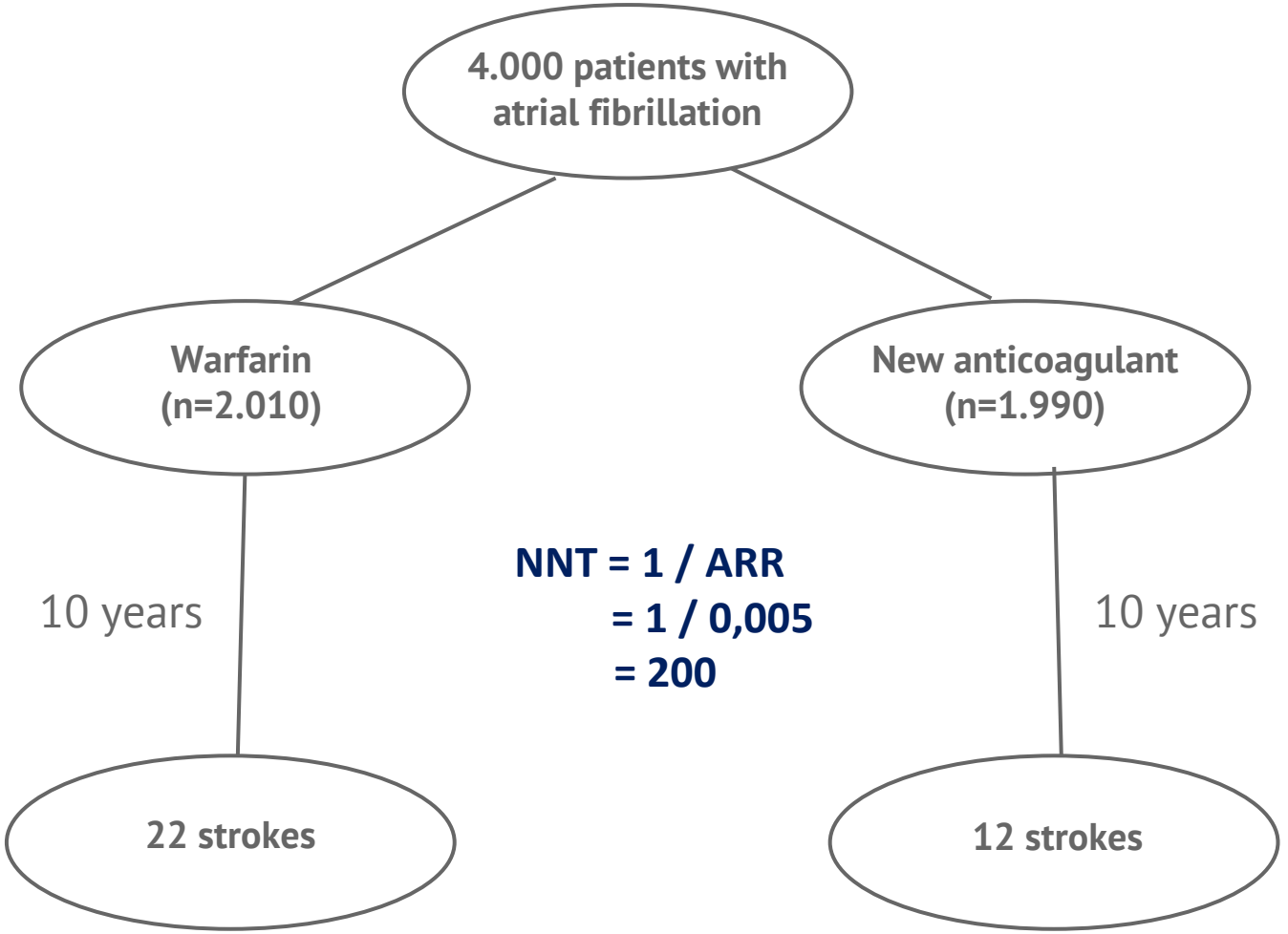
Number Needed to Treat (NNT)

- The number of patients who need to be treated to achieve one extra favourable outcome

NNT = 1/ARR or NNT = 100/ARR%

- Should always be interpreted in the context of follow-up duration

Number Needed to Treat (NNT)

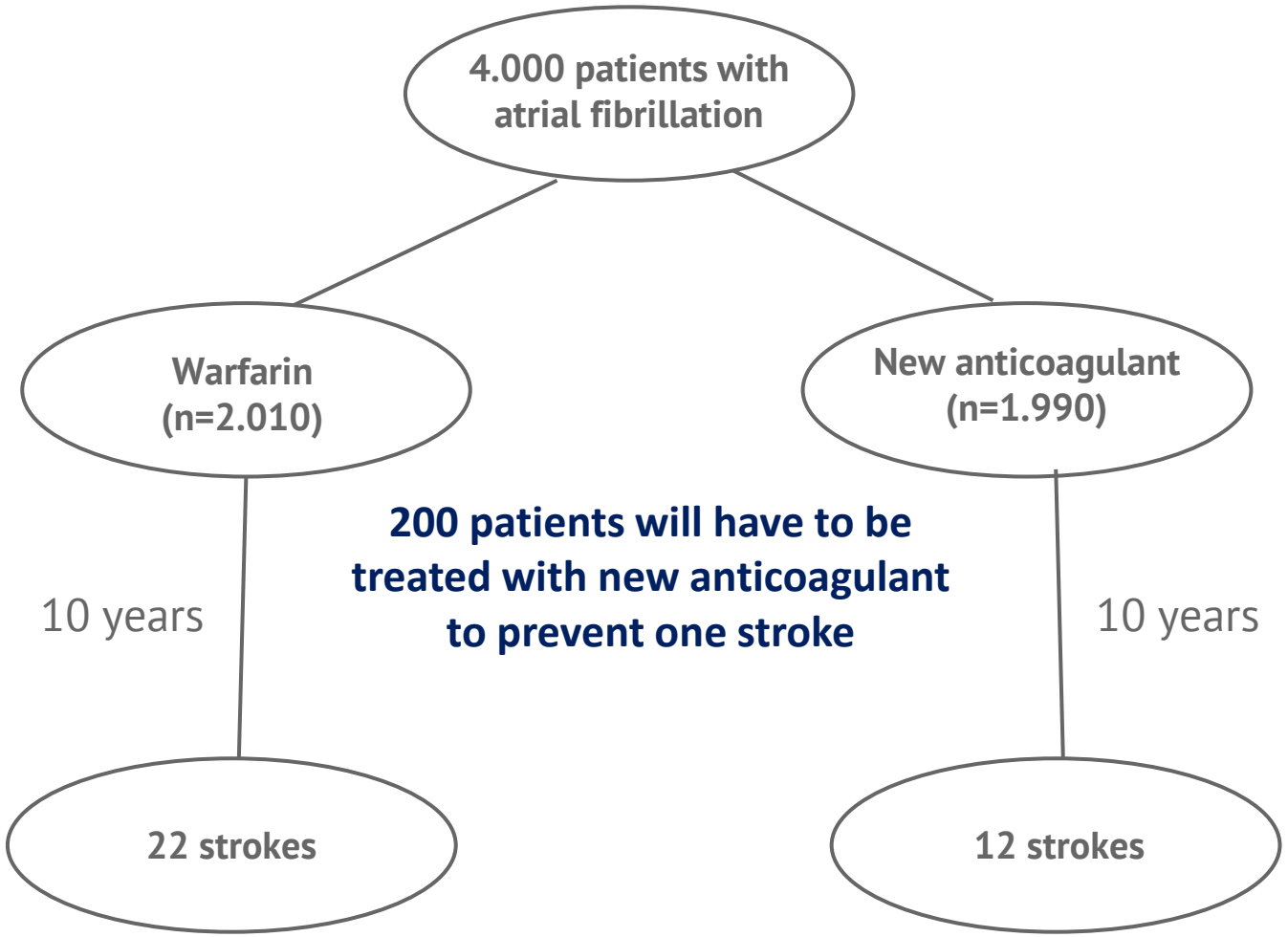


NNT = 1 / ARR
= 1 / 0,005
= 200

$RR_{warfarin}$ = 22/2.010 = 0,011 or 1,1%

$RR_{new\ anticoagulant}$ = 12/1.990 = 0,06 or 0,6%

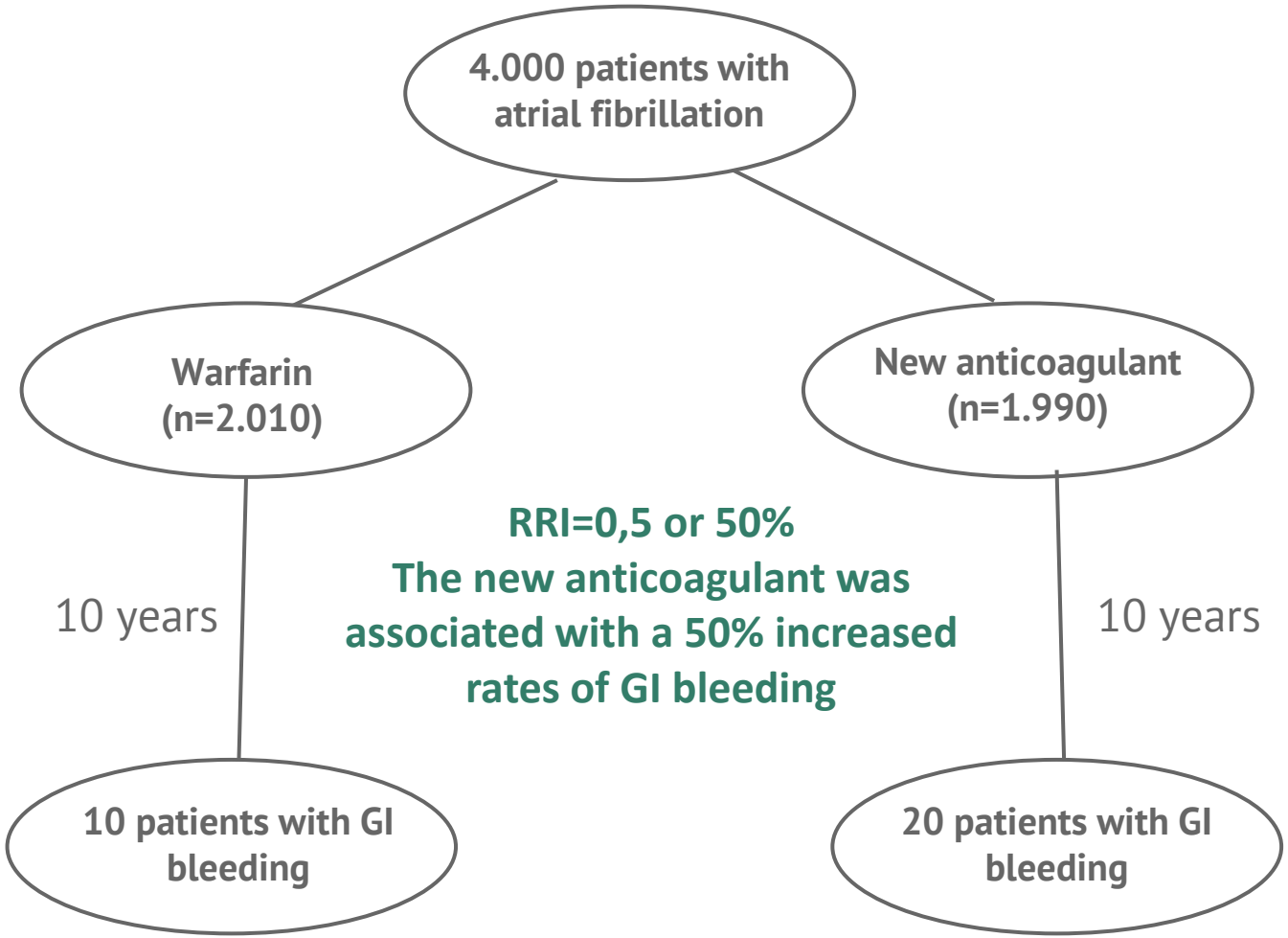
Number Needed to Treat (NNT)



$RR_{warfarin}$ = 22/2.010 = 0,011 or 1,1%

$RR_{new\ anticoagulant}$ = 12/1.990 = 0,006 or 0,6%

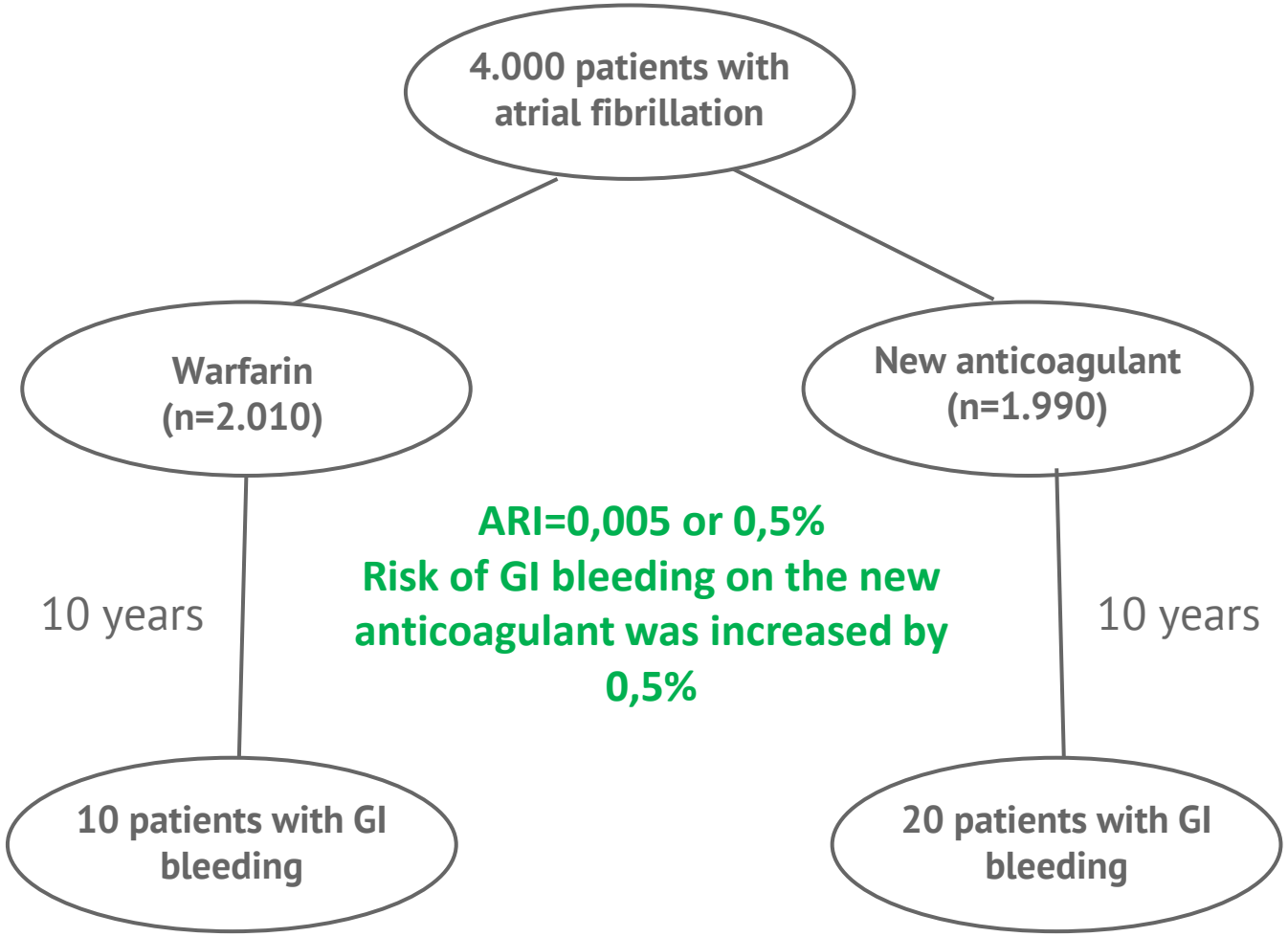
Relative Risk Increase (RRI)



$RR_{warfarin}$ = 10/2.010 = 0,005 or 0,5%

$RR_{new\ anticoagulant}$ = 20/1.990 = 0,01 or 1%

Absolute Risk Increase (ARI)



$RR_{warfarin}$ = 10/2.010 = 0,005 or 0,5%

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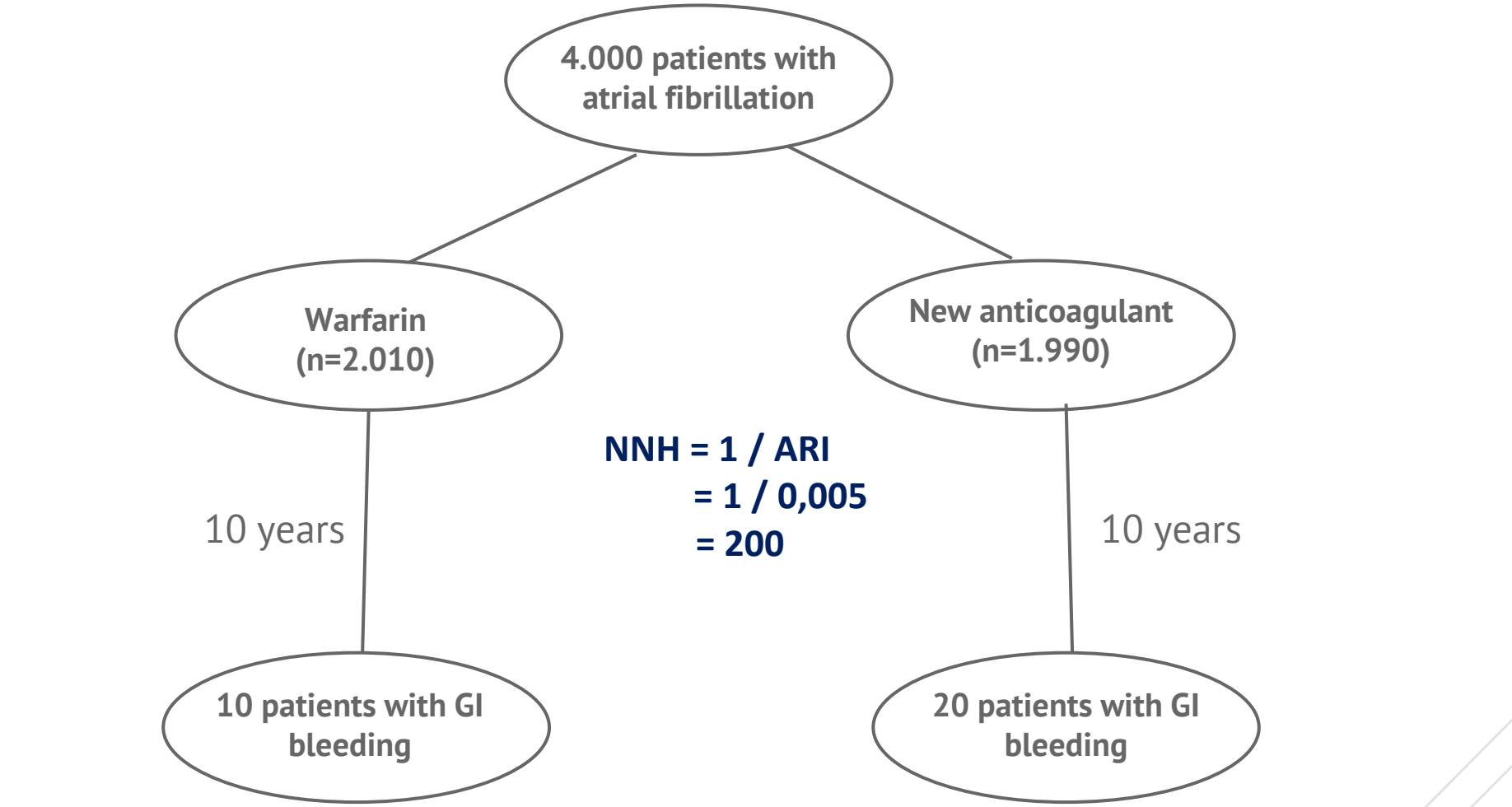
Number Needed to Harm (NNH)



NNH = 1 / ARI
= 1 / 0,005
= 200

$RR_{warfarin}$ = 10/2.010 = 0,005 or 0,5%

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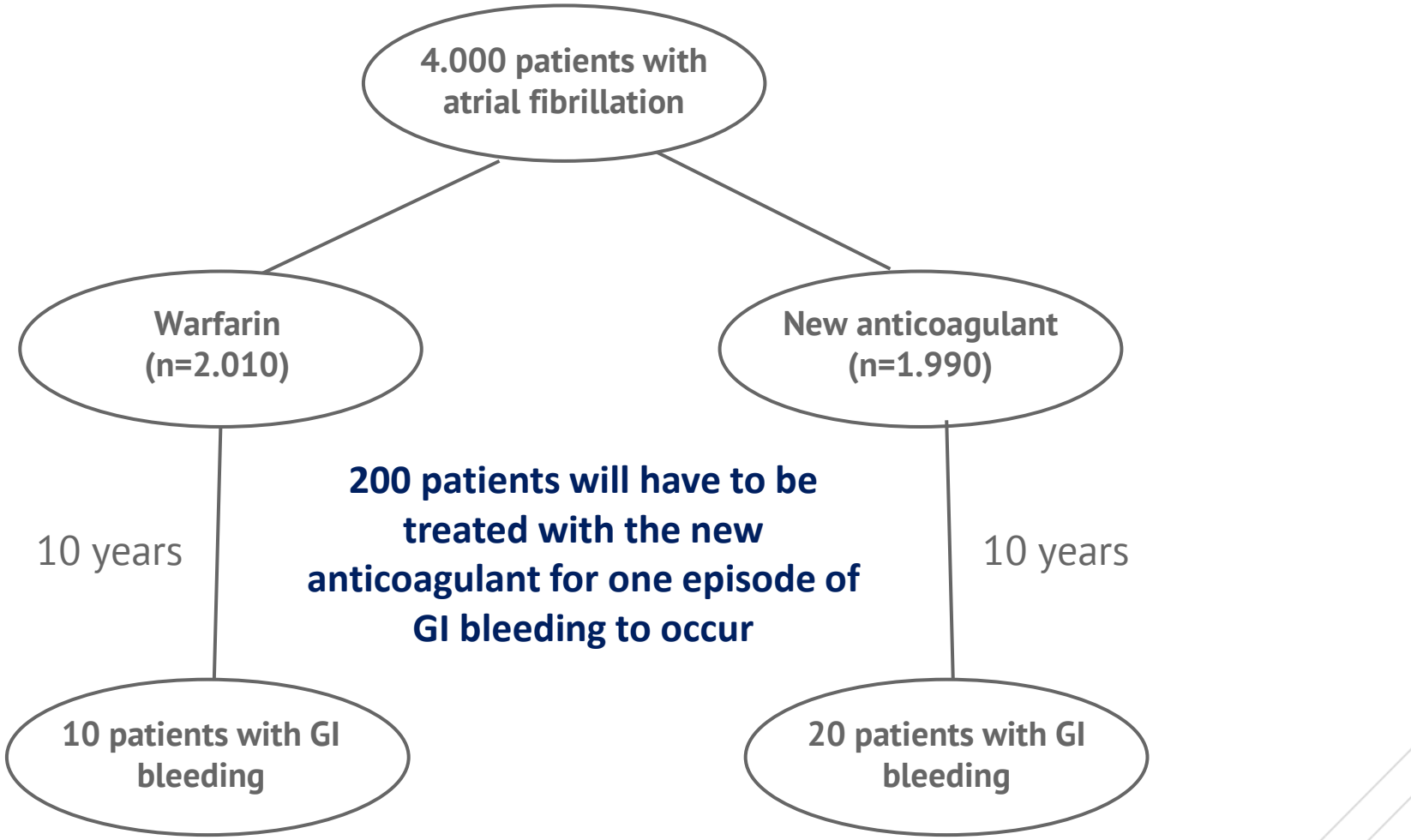
Number Needed to Harm (NNH)



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Which NNT is sufficiently low to justify initiation of a medical intervention?

Table 2: Benefit table for patients with cardiovascular problems

Clinical question	Event rate, %		ARR, %	NNT
	Control group	Treatment group		
What is the reduction in risk of stroke within 5 years among 60-year-old patients with hypertension who are treated with diuretics?[11]	2.9	1.9	1.00	100
What is the reduction in risk of death within 2 years after MI among 60-year-old patients treated with β-blockers?[12]	9.8	7.3	2.50	40
What is the reduction in risk of death within 5 weeks after acute MI among 60-year-old patients treated with streptokinase?[13]	12.0	9.2	2.80	36

Note: MI = myocardial infarction, ARR = absolute risk reduction, NNT = number needed to treat.

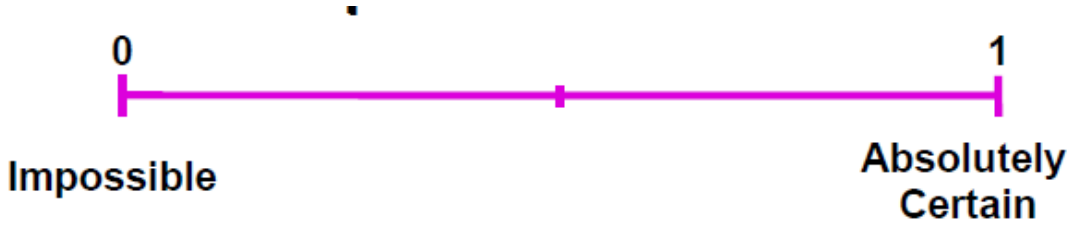
Barratt et al. *CMAJ* 2004;171(4):353-8

P value

- Refers to the possibility that the observed treatment effect is due to chance

- The lower the *P* value (arbitrarily < 0.05) the less likely it is that the observed treatment effect is due to chance

- A *P* value < 0.05 means that the possibility that the treatment effect is due to chance is less than 5% or 1 out of 20



p=0.001	Very unlikely	1 in 1000
p=0.05	Fairly unlikely	1 in 20
p=0.5	Fairly likely	1 in 2
p=0.75	Very likely	3 in 4

Confidence interval (CI)

- Range in which the true treatment effect possibly lies
- If the experimental study was to be repeated 100 times, 95 times we would get a result within the confidence interval
- The larger the study sample, the narrower the confidence interval is

Example A

Compared with aspirin risk ratio for stroke for a new antiplatelet agent was 0.6 (95% CI 0.3 to 0.9).

Example B

Compared with atorvastatin a new hypolidaemic drug reduced LDL cholesterol by −10 mg/dL (95% CI −30 to 10 mg/dL).

Sample size calculation

- If the sample size it too small:
  - a statistically significant difference between the study arms cannot be detected (wide confidence intervals)
  - resources will be wasted
  - it is unethical for participants to enroll in a trial that is not adequately powered to answer the research question

- If the sample size is too large:
  - resources will be unnecessarily wasted
  - the research proposal is unlikely to receive funding

Sample size calculation (continued…)

- Sample size is usually calculated based on the primary outcome
- Sample size depends on:
  - level of significance (type I error rate)
  - power of the study (type II error rate)
  - the minimally clinically important difference
  - standard deviation in the population
  - the underlying event (rate) prevalence in the population
- Other parameters to consider for sample size calculation:
  - the expected drop-out rate
  - the allocation ratio
  - secondary outcomes or subgroup analyses