RELATIVE RISK REDUCTION

The RR calculation determines whether there is less risk (RR < 1) or more risk (RR > 1). The relative risk reduction (RRR) is calculated after the RR and indicates <u>how much the risk is reduced</u> in the treatment group, compared to the control group.

RRR Formula

$$RRR = \frac{(\% \text{ risk in control group} - \% \text{ risk in treatment group})}{\% \text{ risk in the control group}}$$

or

$$1 - RR*$$

Decimals or percentages may be used for risks

*Must use decimal form of RR

RRR Calculation

Using the risks previously calculated for HF progression in the treatment and control groups (metoprolol: 16% and placebo: 28%), calculate the RRR of HF progression.

$$RRR = \frac{(28\% - 16\%)}{28\%} = 0.43$$

or

$$RRR = 1 - 0.57 = 0.43$$

Answer can be expressed as a decimal or percentage; the exam question will specify with instructions

RRR Interpretation

The RRR is 43%. Metoprolol-treated patients were 43% <u>less likely</u> to have HF progression than placebo treated patients.
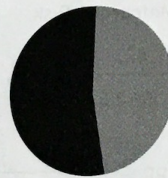
INTERPRETING THE RELATIVE RISK REDUCTION (RRR)

RR: metoprolol patients were 57% <u>as likely</u> (as the control group) to suffer from HF progression.

RRR: metoprolol patients were 43% <u>less likely</u> (than the control group) to suffer from HF progression.

RR 0.57 + RRR 0.43 = 1

RR	AS likely (vs the control)
RRR	LESS likely (vs the control)
Therefore	RR + RRR = 100%

ABSOLUTE RISK REDUCTION

A clinician is listening to a presentation on a drug. The drug manufacturer representative reports that the drug causes 48% less nausea than the standard treatment. The result sounds great; the clinician asks the pharmaceutical representative: what is the absolute risk reduction (ARR)?

The RR and RRR provide relative (proportional) differences in risk between the treatment group and the control group; they have no meaning in terms of absolute risk.

<u>Absolute risk reduction</u> is more useful because it includes the <u>reduction</u> in risk <u>and</u> the <u>incidence rate</u> of the outcome. If the risk of nausea is reduced, but the risk was small to begin with (perhaps the drug caused very little nausea), the large risk reduction has little practical benefit.

It is best if a study reports both ARR and RRR, and for clinicians to understand how to interpret the risk for their patients. If the ARR is not reported, it is possible that the risk reduction, in terms of a decrease in absolute risk, is minimal.

ARR Formula

$$ARR = (\% \text{ risk in control group}) - (\% \text{ risk in treatment group})$$

ARR Calculation

Using the risks previously calculated for HF progression in the metoprolol study, calculate the ARR of HF progression.

| Metoprolol Risk		Control Risk	
$\dfrac{823}{5,123}$	= 0.16	$\dfrac{1,397}{4,988}$	= 0.28

ARR = 0.28 − 0.16 = 0.12 × 100 = 12%

Answer can be expressed as a decimal or a percentage; the exam question will specify with instructions

ARR Interpretation

The ARR is 12%, meaning 12 out of every 100 patients benefit from the treatment. Said another way, for every 100 patients treated with metoprolol, 12 fewer patients will have HF progression.

An additional benefit of calculating the ARR is to be able to use the inverse of the ARR to determine the number needed to treat (NNT) and number needed to harm (NNH). These concepts are discussed next.

RELATIVE RISK REDUCTION COMPARED TO THE ABSOLUTE RISK REDUCTION

RRR

Reduction from treatment

Reduction from placebo
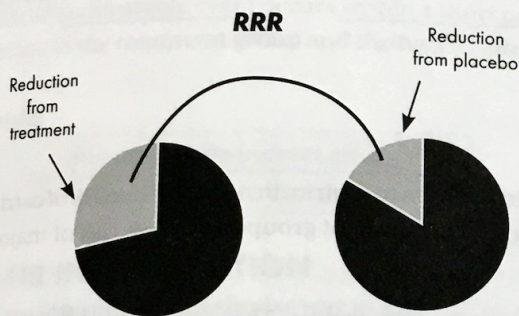
In a relative risk reduction measurement, the risk reduction is a comparison between the two groups.

It's relative (a relation) between the risk reduction in the treatment group and the control group.

ARR

Placebo risk *minus the* Treatment risk = ARR
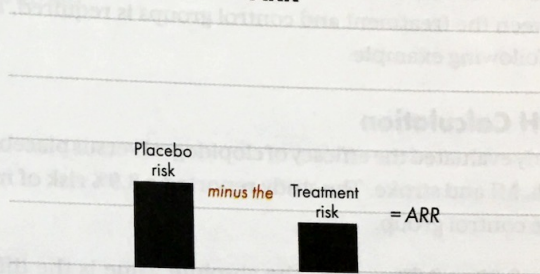
The absolute risk reduction is the true difference in risk between the treatment and the placebo groups.

Said another way, the ARR is the net effect (benefit) beyond the effect obtained from a placebo.

NUMBER NEEDED TO TREAT OR HARM

NNT and NNH help clinicians answer the question: how many patients need to receive the drug for one patient to get benefit (NNT) or harm (NNH)? This information, taken with a consideration of the patient's individual risk, helps guide decision making.

NUMBER NEEDED TO TREAT

The NNT is the number of patients who need to be treated for a certain period of time (e.g., one year) in order for one patient to benefit (e.g., avoid HF progression).

NNT Formula

$$NNT = \frac{1}{(\text{risk in control group}) - (\text{risk in treatment group})^*} \quad \text{or} \quad \frac{1}{ARR^*}$$

*Risk and ARR are expressed as decimals

NNT Calculation

The ARR in the metoprolol study was 12%. The duration of the study period was one year. Calculate the number of patients that need to be treated with metoprolol for one year in order to prevent one case of HF progression.

$$NNT = \frac{1}{0.12} = 8.3, \text{ rounded up to } 9*$$

*Numbers greater than a whole number are rounded up

NNT Interpretation

For every 9 patients who receive metoprolol for one year, HF progression is prevented in one patient.

NUMBER NEEDED TO HARM

The NNH is the number of patients who need to be treated for a certain period of time in order for one patient to experience harm.

NNT and NNH are calculated with the same formula (see the NNT formula above). There are two differences: 1. NNT is rounded up, and NNH is rounded down (see Study Tip Gal) and 2. The absolute value of the ARR is used with NNH; the absolute difference in risk between the treatment and control groups is required, as shown in the following example.

ROUNDING RULES FOR NNT AND NNH

Normal rounding rules do not apply:

- For NNT, anything greater than a whole number, round up to the next whole number. This avoids overstating the potential benefit of an intervention.

  ❏ Example: NNT of 52.1 → round up to 53

- For NNH, anything greater than a whole number, round down to the nearest whole number. This avoids understating the potential harm of an intervention.

  ❏ Example: NNH of 41.9 → round down to 41

NNH Calculation

A study evaluated the efficacy of clopidogrel versus placebo, both given in addition to aspirin, in reducing the risk of cardiovascular death, MI and stroke. The study reported a 3.9% risk of major bleeding in the treatment group and a 2.8% risk of major bleeding in the control group.

ARR = 2.8% − 3.9% = −1.1%; the absolute value is the difference between the two groups. There is a 1.1% higher risk of major bleeding in the treatment group.

$$NNH = \frac{1}{0.011} = 90.9, \text{ rounded down to } 90*$$

*Numbers greater than a whole number are rounded down

NNH Interpretation

One additional case of major bleeding is expected to occur for every 90 patients taking clopidogrel instead of aspirin.

ODDS RATIO AND HAZARD RATIO

ODDS RATIO

Odds represent the probability that an event will occur, versus the probability that it will not occur. Case-control studies, described in the Types of Medical Studies section, are not suitable for relative risk calculations. In order to estimate the risks associated with a treatment or some type of intervention in a case-control study, the odds of unfavorable events are calculated instead.

Case-control studies begin with the presence of a clinical outcome or disease that has already occurred (e.g., lung cancer), and looks backward in the past (retrospectively) to search for possible exposure/s (e.g., smoking) that increased the risk of the clinical outcome or disease. In this case, the odds ratio (OR) is used to calculate the odds of an outcome occurring with an exposure, compared to the odds of the outcome occurring without the exposure.

OR Formula

EXPOSURE/ TREATMENT	OUTCOME PRESENT	OUTCOME ABSENT
Present-Cases	A	B
Absent-Controls	C	D

$$OR = \frac{AD}{BC}$$

OR Calculation

A case-control study was conducted to assess the risk of falls with fracture associated with serotonergic antidepressant (AD) use among a cohort of Chinese females ≥ 65-years-old. Cases were matched with 33,000 controls (1:4, by age, sex, and cohort entry date).

EXPOSURE/ TREATMENT	FALLS W/ FRACTURE-YES	FALLS W/ FRACTURE-NO
CASES (Serotonergic AD-YES)	4,991	18,270
CONTROLS (Serotonergic AD-NO)	3,259	14,730

$$AD = 4,991 \times 14,730 = 73,517,430$$

$$BC = 3,259 \times 18,270 = 59,541,930$$

$$OR = \frac{73,517,430}{59,541,930} = 1.23$$

Conclusion: serotonergic ADs are associated with a 23% increased risk of falls with fracture (see OR and HR Interpretation below).

HAZARD RATIO

In underlined survival analysis (e.g. analysis of death or disease progression), instead of using "risk," a hazard rate is used. A hazard rate is the rate at which an unfavorable event occurs within a short period of time. Similar to RR, the hazard ratio (HR) is the ratio between the hazard rate in the treatment group and the hazard rate in the control group.

HR Formula

$$HR = \frac{\text{Hazard rate in the treatment group}}{\text{Hazard rate in the control group}}$$

OR AND HR INTERPRETATION

OR and HR are interpreted in a similar way to RR:

OR or HR = 1: the event rate is the same in the treatment and control arms. There is no advantage to the treatment.

OR or HR > 1: the event rate in the treatment group is higher than the event rate in the control group; for example, a HR of 2 for an outcome of death indicates that are twice as many deaths in the treatment group.
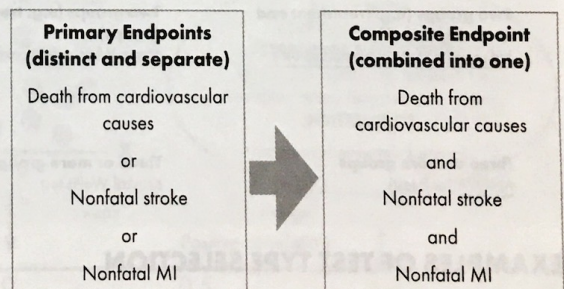
OR or HR < 1: the event rate in the treatment group is lower than the event rate in the control group; for example, a HR of 0.5 for an outcome of death indicates that there are half as many deaths in the treatment group.

PRIMARY AND COMPOSITE ENDPOINTS

The primary endpoint is the main (primary) result that is measured to see if the treatment had a significant benefit. In the metoprolol trial, the primary endpoint was HF progression.

A composite endpoint combines multiple individual endpoints into one measurement. This is attractive to researchers, as combining several endpoints can help the study reach a significant benefit with a smaller, less costly trial.

When a composite endpoint is used, each individual endpoint gets counted toward the same (composite) outcome.

Primary Endpoints (distinct and separate)	Composite Endpoint (combined into one)
Death from cardiovascular causes	Death from cardiovascular causes
or	and
Nonfatal stroke	Nonfatal stroke
or	and
Nonfatal MI	Nonfatal MI

COMPOSITE ENDPOINTS: CAUTION

All endpoints in a composite must be similar in magnitude and have similar, meaningful importance to the patient. For example, the composite endpoint of blood pressure reduction should not be included with heart attack and stroke reduction. The FDA requires each individual endpoint to be measured and reported when a composite endpoint is used. When assessing a composite measurement, it is important to use the composite endpoint value, rather than adding together the values for the individual endpoints. The value of the sum of the individual endpoints will not correlate precisely with the value of the composite endpoint, since a patient can have more than one non-fatal endpoint during a trial.