CVD, Risks and Risk Reduction Strategies

MBBS I
2010

RCT’s

• Special kind of prospective cohort study where conditions are specified by investigator

• Involves an intervention

• At least two groups
  • experimental
  • control or comparison

• Individuals are followed to ascertain effects of intervention
Advantages & Disadvantages of Randomised Controlled Trials

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• randomisation</td>
<td>• difficult to conduct and design</td>
</tr>
<tr>
<td>• unbiased distribution of confounders</td>
<td>• expensive - time and costs</td>
</tr>
<tr>
<td>• blinding of subject and/or investigator possible</td>
<td>• problems related to ethics and feasibility</td>
</tr>
<tr>
<td>• establishment of timing and event direction</td>
<td>• generalisability may be limited</td>
</tr>
<tr>
<td>• best evidence on which to make a judgment about the existence of a cause-effect relationship</td>
<td>• potential for loss-to-follow-up</td>
</tr>
</tbody>
</table>

Risk Prediction

• Cohort study
  – next in study design hierarchy if RCT not feasible.
  – overcomes ethical problems of RCT
  – Multiple outcomes can be studied from one large cohort, so cheaper.
  – Thus, can follow up for decades.
**CER = Control Event rate**  
**EER = Experimental Event Rate**

**Relative risk:** The ratio of risk in the treated group to the risk in the control group: RR=EER/CER

**Absolute risk reduction:** The difference in the rates of adverse events between study and control populations (ie: the difference in risk between the control group and the treated group: ARR=CER-EER)

**Relative risk reduction:** The extent to which a treatment reduces a risk, in comparison with patients not receiving the treatment of interest (ie., the percent reduction in events in treated compared to controls: RRR=\((CER-EER)/CER\) or 1 - RR.

**Number needed to treat (NNT):** The number of patients who must be exposed to an intervention before the clinical outcome of interest occurred; for example, the number of patients needed to treat to prevent one adverse outcome. Equal to the inverse of the absolute risk reduction:  

\[NNT = \frac{1}{ARR} = \frac{1}{CER-EER}.\]

**Number needed to harm** = 1 / ARR when outcome is worse in the experimental group.

NB. Always state the time period involved, eg. 1 year, 5 years etc.
NZ CV Risk Calculator

• Based on population cohorts such as Framingham

• Chart listing the number of CHD events prevented with treatment and the NNT for each risk level

• 5-year absolute risk in 8 categories

• Risk color coded and given qualitative description ranging from mild to very high

• Provides a guide to risk but may not accurately estimate risk for some groups — for example because of differences between the base population and the Australian population.

In particular, the New Zealand Cardiovascular risk calculator is not accurate for predicting risk in

1. People who have experienced a cardiovascular event
2. People aged >70 years
3. Special groups: Aboriginal or Torres Strait Islander people
4. People with very high blood pressure (systolic blood pressure > 180 mmHg) or very high cholesterol concentration (total cholesterol > 8.0 mmol/L)
5. Familial hypercholesterolaemia
6. Atrial fibrillation
7. Known kidney disease or impairment.
NZ CV Risk Calculator

• Quantifying risk clarifies treatment decisions
• May motivate the patient to engage in lifestyle change
• May underestimate risk in high risk individuals

RALPH

CVD Risk Factors
- Male
- Age 53yrs
- Positive family history of CVD
- Smoker
- TC:HDL = 7.0/1.8 = 3.9 (normal)
- BP – normal
- Non-diabetic

CURRENT RISK = 5-10%
EFFECT OF SMOKING CESSATION?
(hint: use mid-point of the range i.e. 7.5%)

Absolute Risk Reduction (ARR)
- $7.5 - 3.75 = 3.75\%$.
- The absolute difference in the rate of CVD events between smokers and non-smokers is 3.75%.

Relative Risk Reduction (RRR)
- $(7.5 - 3.75) / 7.5 = 50\%$.
- Quitting smoking reduced the risk of a cardiovascular event by 50%.

Number Needed to Treat (NNT)
- $1 / \text{ARR} = 1/0.0375 = 27$.
- 27 people would need to quit smoking to prevent one CVD event from occurring.

MR J.P.
Mr JP is a 43 year old non-insulin-dependent diabetic whose total cholesterol is 6.3mM and HDL cholesterol is 0.9mM. His BP is 160/95 and he smokes 40 cigarettes per day. His current interventions include a low-sugar, low-fat diet for his diabetes plus a low dose of an oral hypoglycaemic, which has kept him in reasonable control. He has no symptoms of CVD.

- Identify his cardiovascular risk factors, and use the Risk Factor charts in your workbook to ascertain his 5-year risk of a CVD event.
Mr J.P.

CVD Risk Factors

- Male
- Age 43 yrs
- Diabetes
- Smoker
- TC:HDL = 6.3/0.9
- BP = 160/95

CURRENT RISK = 15-20%

STATINS = 10-15%

Quitting Smoking = 5-10%

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>No Diabetes</th>
<th>Men</th>
<th>Diabetes</th>
<th>No Diabetes</th>
<th>Men</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-smoker</td>
<td>Smoker</td>
<td>Non-smoker</td>
<td>Smoker</td>
<td>Non-smoker</td>
<td>Smoker</td>
</tr>
<tr>
<td>180/105</td>
<td>4.5 6 7 8</td>
<td>4 5 6 7 8</td>
<td>4.5 6 7 8</td>
<td>4 5 6 7 8</td>
<td>4.5 6 7 8</td>
<td>4 5 6 7 8</td>
</tr>
<tr>
<td>160/95</td>
<td>4.5 6 7 8</td>
<td>4 5 6 7 8</td>
<td>4.5 6 7 8</td>
<td>4 5 6 7 8</td>
<td>4.5 6 7 8</td>
<td>4 5 6 7 8</td>
</tr>
<tr>
<td>140/90</td>
<td>4.5 6 7 8</td>
<td>4 5 6 7 8</td>
<td>4.5 6 7 8</td>
<td>4 5 6 7 8</td>
<td>4.5 6 7 8</td>
<td>4 5 6 7 8</td>
</tr>
<tr>
<td>120/75</td>
<td>4.5 6 7 8</td>
<td>4 5 6 7 8</td>
<td>4.5 6 7 8</td>
<td>4 5 6 7 8</td>
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</tr>
</tbody>
</table>

Key to Risk Tables

- "High" indicated patients with very high level of cholesterol or blood pressure, or patients with total cholesterol > 200 mg/dL or triglycerides > 150 mg/dL. Statins may be indicated.
- "Moderate" indicated that treatment may be considered to lower absolute CVD risk.
- "Low" indicates that treatment may be considered to lower absolute CVD risk.

Quitting smoking = 5-10%
Assuming that Mr JP’s TC:HDL is lowered to 6 and he quits smoking his absolute risk is ~7.5% (middle of the range).

Absolute Risk Reduction (ARR)
= 17.5 – 7.5 = 10%

Relative Risk Reduction (RRR)
= (17.5 – 7.5) / 17.5 = 57%

Number Needed to Treat (NNT)
= 1 / ARR = 1/0.10 = 10

Prior to discharge, Ralph has a fasting blood test for lipid levels. The results are as follows:

Cholesterol: 5.4 mM (< 5.5 mM)
Triglycerides 1.2 mM (< 2 mM)
HDL 1.1 mM (0.9-2.2 mM).
LDL 4.3 mM (< 4.6 mM)

Since his total cholesterol and LDL cholesterol are now within the normal range, you consider whether or not he would benefit from a lipid-lowering agent.

You decide to search the literature for the best evidence.
Formulate an Answerable Clinical Question

P = patient or problem
  • 53yr old man with a past history of MI and borderline lipid levels

I = intervention or indicator
  • treatment with a statin

C = comparison
  • comparison (none)

O = CV events and / or mortality
  • CV events and/or mortality

“In a 53 year old man with a past history of myocardial infarction and borderline lipid levels, will treatment with a statin reduce CV events and/or mortality?”

Clinical Question:

PICO: In a 53 year old man with a past history of myocardial infarction and borderline lipid levels, will treatment with a statin reduce CV events and/or mortality?

Ideal Study Design
  • RCT: (Blinding, Use of placebo)

Database:
  • Cochrane, Pubmed Clinical Queries (therapy), Medline, Embase

Search Terms:
  • myocardial infarction AND statin* AND secondary prevention (can also consider outcomes in search terms)
<table>
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<tr>
<th>Question</th>
<th>Answer</th>
</tr>
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<tbody>
<tr>
<td>Was the assignment of patients to treatments randomised?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the groups similar at the start of the trial?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients who entered the trial accounted for at its conclusion?</td>
<td>Yes. (Loss to FU?)</td>
</tr>
<tr>
<td>Were they analysed in the groups to which they were randomised?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the patients and clinicians kept ‘blind’ to which treatment was being received?</td>
<td>Yes</td>
</tr>
<tr>
<td>Aside from the experimental treatment, were the groups treated equally?</td>
<td>Yes: Usual care by doctors</td>
</tr>
</tbody>
</table>
EXCELLENT EXAMPLE OF WELL-CONDUCTED CLINICAL TRIAL
therefore, results should be valid

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Pravastatin</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
</tr>
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<tbody>
<tr>
<td>Death (CHD)</td>
<td>373 (8.3%)</td>
<td>287 (6.4%)</td>
<td>23%</td>
<td>1.9%</td>
<td>53</td>
</tr>
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RRR: Pravastatin reduced the risk of death due to CHD by 23%

ARR: The absolute difference in the rate of deaths due to CHD between placebo and Pravastatin group is 1.9%

NNT: 53 people would need to treat with Pravastatin to prevent one death due to CHD.
## COMPLETE TABLE

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<tr>
<td>Death (CVD)</td>
<td>433 (9.6%)</td>
<td>331 (7.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death (Any Cause)</td>
<td>633 (14.1%)</td>
<td>498 (11.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any MI</td>
<td>463 (10.3%)</td>
<td>336 (7.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Stroke</td>
<td>204 (4.5%)</td>
<td>169 (3.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Would you prescribe a statin based on these results?

Other factors to consider
• Harms of treatment (Harm verses benefit?)
• Patient’s wishes
• Cost (cost benefit analysis needed)

➢ Relative risk reduction measures biological impact and remains same despite differences in absolute rate of events.

➢ Absolute risk reduction measures patient impact and reflects underlying susceptibility of patients

➢ Number needed to treat provides a useful measurement of the clinical effort that must be expended to avoid bad events
Cardiovascular disease risk factors

- CVD risk multi-factorial
- Risk factors present in different combinations
  - eg. Most MI patients do not have high cholesterol
- Risk calculator allows individualisation of risk
  eg. Treat BP and high cholesterol at lower thresholds in diabetics and renal disease.

Reminder
Read detailed info on critical appraisals at the end of your book