Evidence-Based Medicine Interventions – 1

Component 2 / Unit 5

Using EBM to assess questions about interventions

- Questions concerning benefit of a clinical intervention to treat or prevent disease
- Can include drug therapy, diet therapy, surgery, alternative medicine, etc.
- Best evidence comes from a randomized controlled trial (RCT) or meta-analysis of RCTs
  - Patients similar in all regards with exception of intervention applied

Why are RCTs the best evidence for interventions?

- Reduction in bias
  - Vitamin C to prevent the common cold (Douglas, 2004)
  - Women's Health Initiative (2002)
- Emphasis on clinical end-points and patient-oriented outcomes
  - Cardiac Arrhythmia Suppression Trial (Epstein, 1993)
- "New" treatments are not necessarily better
  - In radiation oncology, trials of new treatments are as likely as not to be successful (Soares, 2005)

Other issues for RCTs

- Quality of study inversely related to magnitude of treatment effect (Moher, 1998)
- Lower-quality (e.g., non-RCT) studies more likely to be later "overturned" (Ioannidis, 2005)
- But well-designed observational studies may be just as good (Benson, 2000)

History of RCTs

- James Lind, British naval doctor and surgeon (1717-1794) demonstrated that lemons and oranges improved health of sailors with scurvy over those who did not receive them (Lindemann, 1999)
- First true RCT performed in UK in 1940s, demonstrating superiority of streptomycin over placebo for tuberculosis (BMJ, 1948)

How do we critically appraise an intervention study?

- Remember the questions to be asked of any study
  - Are the results valid?
  - What are the results?
  - Can the results be applied to patient care?

Questions to ask about a study on intervention

- Are the results valid?
  - Did experimental and control groups begin the study with a similar prognosis?
    - Were patients randomized?
    - Was randomization concealed (blinded or masked)?
    - Were patients analyzed in the groups to which they were randomized?
    - Were patients in treatment and control groups similar with respect to known prognosis?

A study on an intervention (cont.)

- Are the results valid? (cont.)
  - Did experimental and control groups retain a similar prognosis after the study started?
    - Were patients aware of group allocation?
    - Were clinicians aware of group allocation?
    - Were assessors aware of group allocation?
    - Was follow-up complete?

A study on an intervention (cont.)

- What are the results?
  - How large was the treatment effect?
    - What was the relative risk reduction?
    - What was the absolute risk reduction?
  - How precise was the estimate of treatment effect?
    - Were the confidence intervals or p-values stated?

A study on an intervention (cont.)

- Can the results be applied to patient care?
  - Were the study patients similar to my patient?
  - Were all clinically important outcomes considered?
  - Are the likely treatment benefits worth the potential harm and costs?

How large was the treatment effect?

Events Intervention	Had event	No event	Total
Control	a	b	a+b
Experimental	c	d	c+d

Assuming statistical significance:
- Control event rate (CER) = a / a+b (risk of event from control intervention)
- Experimental event rate (EER) = c / c+d (risk of event from exp. intervention)
- Relative risk (RR) = EER / CER
  - Related to RR is hazard ratio (HR), which is used in treatment context as "survival" over time
- Relative risk reduction (RRR) = 1 - RR
- Absolute risk reduction (ARR) = CER - EER
- Number needed to treat (NNT) = 1 / ARR

How precise was the estimate of treatment effect?

- True risk for population is unknown; need to assess with sample
- Study result gives point estimate, but true result can vary due to chance (and bias if study not performed properly)
- Assess possible range of results by calculating confidence interval (CI)
  - Range of values that includes true value 95% of the time

Critical appraisal of some interventions

- Low-molecular-weight heparin (LMWH) versus graduated compression stockings (GCS) to prevent deep venous thrombosis (DVT) in knee arthroscopy
- Eradication of *H. pylori* for recurrence of gastric cancer
- Primary prevention of coronary heart disease with statins
- Hormone replacement therapy in postmenopausal women – Women's Health Initiative (WHI)
- Tight control of diabetes mellitus to prevent complications
- Screening to reduce mortality from prostate cancer

LMWH vs. GCS to prevent DVT (Camporese, 2008)

	DVT	No DVT	Total
GCS (Control)	21	639	660
LMWH (Exp.)	6	651	657

- Primary outcome: asymptomatic proximal DVT or symptomatic DVT within 7 days of surgery

- Control event rate (CER) = 21 / 660 = .032
- Experimental event rate (EER) = 6 / 657 = .009
- Relative risk (RR) = .009 / .032 = .28
- Relative risk reduction (RRR) = 1 - .28 = .72
- Absolute risk reduction (ARR) = .032 - .009 = .023
- Number needed to treat (NNT) = 1 / .023 = 43

Eradication of *H. pylori* for recurrence of gastic cancer (Fukase, 2008)

	Recurrence	No recurrence	Total
No eradication (Control)	24	248	272
Eradication (Exp.)	9	263	272

- Eradication with lansoprazole, amoxicillin, and clarithromycin
- Primary outcome: metachronous gastric tumor

- Control event rate (CER) = 24 / 272 = .088
- Experimental event rate (EER) = 9 / 272 = .033
- Relative risk (RR) = .033 / .088 = 0.38
- Relative risk reduction (RRR) = 1 - .38 = .62
- Absolute risk reduction (ARR) = .088 - .033 = .055
- Number needed to treat (NNT) = 1 / .055 = 18

Primary prevention of heart disease with atorvastatin (ASCOT; Sever, 2003)

	Fatal CHD + Nonfatal MI	No CHR or MI	Total
Placebo	154	4983	5137
Atorvastatin	100	5068	5168

- Primary outcome: fatal coronary heart disease or nonfatal MI
- Study terminated early due to statistically significant benefit (letters to editor)

- Control event rate (CER) = 154 / 5137 = .030
- Experimental event rate (EER) = 100 / 5168 = .019
- Relative risk (RR) = .019 / .030 = .633
- Relative risk reduction (RRR) = 1 - .633 = .367
- Absolute risk reduction (ARR) = .030 - .019 = .011
- Number needed to treat (NNT) = 1 / .011 = 91
  (Many needed to treat for one benefit)

Other outcomes from ASCOT trial (Simon, 2003)

Outcomes	Atorvastatin	Placebo	RRR (95% CI)	NNT (CI)
Fatal CHD + nonfatal MI	1.9%	3.0%	36% (17-50%)	94 (68-200)
Fatal CHD + nonfatal MI without silent events	1.7%	2.7%	38% (19-58%)	99 (65-198)
Total cardiovascular events	7.5%	9.5%	20% (10-30%)	53 (36-111)
Total coronary events	3.4%	4.8%	28% (14-40)	74 (52-153)
Fatal and nonfatal stroke	1.7%	2.4%	27% (4-44)	156 (96-1054)

- More information at www.ascotstudy.org
- All-cause mortality not statistically significantly different

Some issues in primary prevention of heart disease

- Many studies; need to look to systematic reviews although studies are not homogeneous
  - West of Scotland study (Shepherd, 1995) showed similar benefit
  - Follow-up in West of Scotland (Ford, 2007) and ASCOT (Sever, 2008) showed persistent benefit
  - ALLHAT-LLT (JAMA, 2002) showed no benefit but had excess crossover
  - Retrospective cohort study in large Israeli HMO found increasing benefit with "proportion of days covered" (PDC) by statins, with 45% RR for >90% PDC (Shalev, 2009)
- Classic example of impressive RRR but small ARR (and high NNT)
- Assess your own absolute risk from Framingham data
  - http://hp2010.nhlbihin.net/atpiii/calculator.asp
- What is a 50-ish healthy living informatics professor with a low LDL but also a low HDL (or you with your profile) to do?