Evidence-Based Medicine Interventions – 2

Component 2 / Unit 5

Hormone replacement therapy (HRT) – classic lesson for EBM

- Previous non-RCT studies suggested women who used HRT at any time had lower mortality overall and from heart disease
  - Non-controlled studies always have possibility of differences between groups
- In general, RCTs and observational studies had yielded conflicting results
- Women's Health Initiative (WHI) study was RCT that "settled the issue" (JAMA, 2002; Lowe, 2002)

WHI results

Clinical outcome	HRT	Placebo	HR
Participants	8506	8102	
Cardiovascular disease	694	546	1.22
Cardiovascular death	65	55	
Breast cancer	166	124	1.26
Breast cancer death	3	2	
Colorectal cancer	45	67	0.63
Fractures	650	788	0.76

Why did this study differ from observational studies?

- Problem of any non-controlled study is that the intervention groups are not similar
- Previous observational studies looked at women who chose to take HRT versus those who did not
  - There are likely differences between these groups
- A re-analysis of observational studies found that controlling for socioeconomic status eliminated benefit of HRT (Humphrey, 2002)
  - Women of higher socioeconomic status are healthier, despite their predilection for use of HRT
- Another view: EBM worked! Science adjusts to the facts, which in this case were that less rigorous evidence (observational studies) led to incorrect conclusions

Additional results from WHI

- Estrogen-only arm showed increased risk of stroke and deep venous thrombosis, no heart disease protection, and benefit for fracture (Anderson, 2004)
- Combined therapy also showed
  - Increased risk of cardiovascular disease (Manson, 2003)
  - Adverse effect on cognition (Espeland, 2004)
  - Increased risk of dementia and mild cognitive impairment (Shumaker, 2004)
  - Increased risk of deep venous thrombosis (Cushman, 2004)

Although some may benefit (or not be affected so adversely)

- For women aged 50-59 who had hysterectomy (i.e., closer to menopause), those taking estrogen-only (vs. placebo or estrogen + progesterone) had
  - Less coronary heart disease, although not statistically significant (Rossouw, 2007)
  - Less coronary artery calcification (Manson, 2007)
- For all women, coronary heart disease risk reverted to baseline within 3 years after stopping treatment, although cancer risk did not (Heiss, 2008)

Tight control of diabetes mellitus to prevent complications

- Intensive vs. standard control in veterans with long-standing Type 2 diabetes (Duckworth, 2009)
  - Primary outcome was time to occurrence of a cardiovascular event
  - Experimental group had lower glycated hemoglobin (6.9% vs. 8.4%) but no difference in primary outcome and higher rate of adverse events
- Intensive vs. conventional control in critically ill patients (Finfer, 2009)
  - Target of blood glucose <180 had lower mortality than target of 81-108 and fewer adverse effects

Another intervention is "screening"

- Screening is aim of detecting disease for prevention or early treatment
  - General principle is that we should only screen for diseases for which we have effective treatments, i.e. benefit shown in RCT
  - Goal of screening intervention is to improve outcomes from screening process
- Clinical question: Should men be screened for prostate cancer with the prostate-specific antigen (PSA)?
  - Natural history of prostate cancer is increasing incidence and decreasing aggressiveness with age
  - Many men, especially elderly, die with disease rather than of disease
  - Widespread use of PSA has led to several fold increase in incidence without clear benefit

Prostate cancer and PSA testing

- Treatment can reduce symptoms from complications, but is also associated with significant adverse effects, most notably impotence (25%) and incontinence (2-3%)
- Surgery (radical prostatectomy) is moderately better than "watchful waiting" (Bill-Axelson, 2005)
  - After median follow-up of 8.2 years, 8.6% of men assigned to surgery had died vs. 14.4% assigned to watchful waiting
  - However, all difference was in men <65 years old and not related to PSA or Gleason score
- However, until recently, no evidence for or against PSA screening intervention
  - New studies help but do not completely resolve question (Barry, 2009)

Two RCTs assessing PSA screening

- PLCO trial in US (Andriole, 2009)
  - 76,693 men randomized to screening or usual care
  - Higher rate of cancer diagnosis but no difference in mortality
  - Rates of screening 85% in exp., 40-52% per year in conrol
- European Randomized Study (Schröder, 2009)
  - Seven related clinical trials with subjects randomized to screening or no screening
  - Higher rate of cancer diagnosis and mildly beneficial decreased mortality but
    - ARR of .71 deaths per 1000 men, i.e., 1410 men needed to be screened to prevent one death
- Perspective of urologist vs. health services researcher (Lee, 2009)

Limitations of RCTs

- Sometimes there is incomplete evidence
  - Do parachutes prevent death and injury? No trials, but would you use one? (Smith, 2003)
  - Adverse events not always well-documented, e.g., chemotherapy trials (Fromme, 2004)
  - Publication bias – positive results more likely to be published (Dickersin, 1997), published more quickly (Stern, 1997), and published in English (Egger, 1997)
- Sometimes there is outright fraud – in past and present
  - At least 21 RCTs of pain control in anesthesiology by S Reuben found to have fabricated data (Anesth. News, 2009)
  - Child psychiatrist researcher S Biederman promised results to pharmaceutical company (Harris, 2009)
  - There are many challenges to "cleansing" literature (Sox, 2006)

Limitations of RCTs (cont.)

- Easiest to do with placebo-controlled drug trials; harder (but not impossible) with other interventions
  - Alternative medicine systems may be best assessed with "whole practice" approach (Bell, 2001)
  - Rapidly changing technologies should be assessed with "tracker trials" that focus on best current technology, even if changes over course of trial (Lilford, 2000)
  - Surgical and other interventions requiring considerable skill should be "expertise-based," i.e., controlled for expertise of clinician performing procedure (Devereaux, 2005)
- Call for "practical" clinical trials that compare clinically relevant questions and outcomes from heterogeneous practice settings (Tunis, 2003)

Another problem of RCTs – selective reporting

- A more pernicious form of publication bias, especially when done for economic gain
- It is well known that pharmaceutical companies
  - Manipulate facts and figures in advertising (Wilkes, 1992; Villaneuva, 2003)
  - Occasionally outright suppress results (e.g., Rennie, 1997)
- Studies submitted for US Food and Drug Administration (FDA) approval may not be published in journals
  - For 74 studies registered with FDA assessing antidepressants (Turner, 2008)
    - 37 of 38 positive studies published
    - Of 36 negative studies, 22 not published, 11 conveyed a positive outcome, and 3 published

What to make of this?

- Even science and EBM are fallible to human shortcomings
  - The solution is better science
- In case of RCTs, need
  - Reporting of both absolute and relative risk reductions
  - Registration of trials and adherence to study protocols
  - Clear disclosure of conflict of interest