How Do We Interpret Unexpected Findings From Large Clinical Trials?

Comparative Effectiveness Research Seminar
May 11, 2010

Some Theory and History

- Interventions are guided by understanding of disease.
- Hippocrates (460-377 BC) described four basic temperaments in relation to physical characteristics known as “homors”
- Galen (129-216 BC) believed that all disease was caused by imbalanced between the four humors
- Galen did detailed studies in anatomy and physiology and employed 20 scribes to help document his findings

Reductionism and Linear Thinking:
Are People Like Cars?

- Sir Isaac Newton -- discrete components assumed to operate independently from one another.
- Ackoff - industrial revolution (18th Century England) initiated ways of thinking that dominated nearly all fields of science for several centuries.
Core concepts:
- reductionism,
- analysis,
- mechanism

Patient Education

- Typically very simple
- Emphasizes linear relationships

What Physiologists Tell Us

- The human body is complex
- Systems interact
- Linear model rarely fits
- Intervening on one system affects other systems

The Outcome Researcher Perspective

Disease: Shortens life or interferes with life quality now or in the future

We Look at Outcomes Differently

- There are only two outcomes of importance
  - Length of life
  - Quality of life
  - Patient reported outcomes
  - Functioning
  - Symptoms/problems
- Physiological measures are only important if they relate to length or quality of life
- Overall outcome represented as QALY
The total mortality problem

Is being dead from cancer worse than being dead from something else?

Cancer mortality in the Health Insurance Plan of New York

- 60,000 women assigned to mammography or usual care
- After 10 years 147 deaths in the mammography group and 192 deaths in usual care group
- 23% reduction in cancer deaths

Sometimes Modifying Risk Factors Does Not Change Outcomes

Helsinki Heart Study

Eight Examples From the Clinical Trial Literature

- Cardiac Arrhythmia Suppression Trial (CAST)
- The Physicians Health Study (PHS)
- Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE)
- Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOR)
- COURAGE
- Woman’s Health Initiative WHI
- Action to Control Cardiovascular Risk in Diabetes (ACCORD)
- Canadian National Breast Screening Study (CNBS)

Mayo Clinic on Preventing Diabetes Complications

- Aggressive care is the best care
- Make a commitment to managing your diabetes.
- Learn the basics of diabetes care and offer support and encouragement along the way.
- Keep your blood pressure and cholesterol under control.
  - Like diabetes, high blood pressure can damage your blood vessels. High cholesterol is a concern, too…
ADA Recommendations for Aggressive Management of Type 2 Diabetes Mellitus

University Group Diabetes Program (UGDP) *Diabetes* 19(5) (supplement 2) 747-830

- Twelve clinical centers,
- 823 patients were randomly assigned to one of five treatment groups (all got diet).
  - Insulin variable dosage
  - Insulin standard
  - Tolbutamide
  - Phenformin (discontinued early)
  - Placebo
- Followed for 8 years 10 months

UGDP Results

- Patients randomly assigned to receive tolbutamide had a significantly increased probability of death due to cardiovascular diseases in comparison to the placebo
- The two insulin groups did not differ significantly from the placebo group.
- The combination of tolbutamide and diet was less effective than diet alone

Reactions

**Feinstein**
- Published a major attack on study and was called:
  - “drug-house horror,”
  - “snake-oil salesman,”
  - and was accused of engaging in activities which represented a “conflict of interest,” “unbridled sensationalism,” and “deliberate destruction”

**Cornfield**
- It was suggested that there was poor randomization in the study, and that groups differed prior to treatment.
  - Yet, the groups did not differ on any of 14 baseline characteristics at the .05 significance level
- More Autopsies in tolbutamide group
  - Too few deaths among women in placebo group
  - When reanalyzed, these issues could account for results

Median Glycated Hemoglobin Levels at Each Study Visit ACCORD Trial *(NEJM, 358:2545-2559)*

Kaplan-Meier Curves for the Primary Outcome and Death from Any Cause ACCORD Trial *(NEJM, 358:2545-2559)*
**Veterans Affairs Diabetes Trial (VADT)**

- 1791 military veterans
  - mean age, 60.4 years
  - mean number of years since the diagnosis of diabetes was 11.5,
  - 40% of the patients had already had a cardiovascular event.
- Randomly assigned
  - intensive-therapy group
  - standard-therapy group.
- Primary outcome time from randomization to the first occurrence of a major cardiovascular event, composite of
  - myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene.

**VADT Outcomes (from NEJM 360:2 January 8, 2009)**

Despite reductions in HbA1c, no noticeable benefit for any outcome. But, there was evidence of harm

**It is not only the ACCORD Study**

- 9306 participants with impaired glucose tolerance and either cardiovascular disease or cardiovascular risk factors randomly assigned to receive
  - nateglinide (up to 60 mg three times daily) or placebo,
  - in a 2-by-2 factorial design with
    - valsartan or placebo,
- Participants followed for a median of 5.0 years for incident diabetes (and a median of 6.5 years for vital status).
Unlike blood glucose level, there is strong evidence that controlling high BP and high blood cholesterol levels significantly reduces both macrovascular and microvascular complications in persons with type 2 DM.
The prevention of progression of arterial disease and diabetes (POPADAD) trial

- Multicentre, randomized, double blind, 2x2 factorial, placebo controlled trial.
- 1276 adults aged 40 or more with type 1 or type 2 diabetes and an ankle brachial pressure index of 0.99 or less but no symptomatic cardiovascular disease.
- Daily, 1) 100 mg aspirin tablet plus antioxidant capsule (n=320), 2) maspin tablet plus placebo capsule (n=318), 3) placebo tablet plus antioxidant capsule (n=320), or 4) placebo tablet plus placebo capsule (n=318).
Post POPADAD Interpretation

- Aspirin is one of the top 10 causes of adverse drug events reported to the Commission on Human Medicines. Gastrointestinal bleeding is associated with general use of non-steroidal anti-inflammatory drugs in over 80% of reported cases, and 87% of that use is associated with aspirin, either alone or with other non-steroidal anti-inflammatory drugs.

Internet Advice on Managing Anemia

- When anemia is caused by decreased production of red blood cells, such as in cancer or severe kidney disease, a medication called epoetin alfa can be used. This medication mimics the action of erythropoietin, the natural hormone that causes the bone marrow to produce more red blood cells.

Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE)

- 603 patients with an estimated glomerular filtration rate (GFR) of 15.0 to 35.0 ml per minute per 1.73 m2 of body-surface area and mild-to-moderate anemia (hemoglobin level, 11.0 to 12.5 g per deciliter) randomly assigned to
  - a target hemoglobin value in the normal range (13.0 to 15.0 g per deciliter, group 1) or the
  - subnormal range (10.5 to 11.5 g per deciliter, group 2). per deciliter – triggered treatment at 10.5 g (group 2).

Percent of Patients Requiring Dialysis in CREATE Study by Group
Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR)

- 1432 patients with chronic kidney disease randomly assigned to:
  - receive a dose of epoetin alfa targeted to achieve a hemoglobin level of 13.5 g per deciliter (N=715)
  - receive a dose targeted to achieve a level of 11.3 g per deciliter (N=717).
- The primary end point was a composite of death, myocardial infarction, hospitalization for congestive heart failure (without renal replacement therapy).

Outcomes in CHIOR Trial

Studies are consistent in meta analysis

Editorial on Erythropoiesis

"A serious reconsideration of the rationale and of the relevance of ongoing studies is necessary, because the effects of erythropoiesis-stimulating agents are not fully understood. Not only do they increase haemoglobin concentrations, but they also might act through alternative dose-dependent pathways that could be harmful" p 349.
Atherosclerosis Timeline

Endothelial Dysfunction
Foam Cells
Fatty streak
Intermediate lesion
Atheroma
Fibrous plaque
Complicated lesion/rupture
From first decade
From third decade
From fourth decade
Growth mainly by lipid accumulation
Smooth muscle and collagen
Thrombosis, inflammation


Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE)
Boden et al, NEJM 356:1503-1516
- 2287 patients who had objective evidence of myocardial ischemia and significant coronary artery disease randomly assigned to patients to undergo
  - PCI with optimal medical therapy (PCI group)
  - optimal medical therapy alone (medical-therapy group).
- Primary outcome was death from any cause and nonfatal myocardial infarction during a follow-up period of 2.5 to 7.0 years (median, 4.6)

Angioplasty with Stent Placement
NHLBI website

COURAGE TRIAL
Kaplan-Meier Survival Curves

COURAGE Results

Kaplan-Meier Survival Curves

**Meta Analysis of PCI Trials**

Katriris, NEJM 2007, 357:414-418

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Medical Treatment</th>
<th>Summary Risk Ratio (95% CI)</th>
<th>P Value</th>
<th>Q Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause</td>
<td>185</td>
<td>2.10</td>
<td>0.09</td>
<td>5.81</td>
</tr>
<tr>
<td>Myocardial infarction or death from cardiac causes</td>
<td>121</td>
<td>1.91 (0.88-1.33)</td>
<td>0.07</td>
<td>10.15</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>242</td>
<td>1.07 (0.83-1.38)</td>
<td>0.55</td>
<td>8.75</td>
</tr>
</tbody>
</table>

* The updated meta-analysis includes 15 studies, involving 5480 patients. The original meta-analysis included data from 11 trials. The updated meta-analysis includes data from the COURAGE trial and the Adenosine Sensitive SPECT Myocardial Perfusion Imaging randomization (ASPECT) trial and updated long-term follow-up data from the MATCH, Angioplasty, or Surgery Trial in Myocardial Infarction, and the randomized comparison of Angioplasty versus Surgery for the Treatment of Acute Myocardial Infarction (RATAM). There were no between-study heterogeneity for any of the three outcomes (p > 0.05). PCI denotes percutaneous coronary intervention.

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**Post-Hoc Discussion of COURAGE**

- Rationale has never been completely clear
- Infarcts do not necessarily occur at the narrowest point in the artery
- Medical therapy stabilizes plaque
- And …..

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**Schwartz et al results**

- Cancer screening is almost always a good idea -- 87%
- Finding cancer early saves lives--74%
- An 80 year old woman who decides not to get a mammogram is irresponsible --41%
- Had a false positive, but still glad I was tested -- 98%

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**Cancer Screening and Public Policy**

- President Obama on cancer screening. From address to joint session of congress, September 9, 2009

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**Cancer Progress**

Welch, 2003

- Atypical Cell
- Carcinoma In-situ
- Invasive Cancer
- Death from Cancer
The simple description of breast cancer…..

Cost-Effectiveness of Pap Smear (from David Meltzer, 2010)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Increase in life expectancy</th>
<th>Increase in cost</th>
<th>Average cost per life year gained</th>
<th>Marginal increase in LE</th>
<th>Marginal increase in cost</th>
<th>Marginal cost/life year saved</th>
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</thead>
<tbody>
<tr>
<td>3 Years</td>
<td>70 days</td>
<td>$500</td>
<td>$2600/YL</td>
<td>70 days</td>
<td>$500</td>
<td>$2600/LY</td>
</tr>
<tr>
<td>2 Years</td>
<td>71 days</td>
<td>$750</td>
<td>$3900/LY</td>
<td>1 day</td>
<td>$250</td>
<td>$9100/LY</td>
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<tr>
<td>1 Year</td>
<td>71 days, 8 hours</td>
<td>$1500</td>
<td>$7300/LY</td>
<td>8 hours</td>
<td>$750</td>
<td>$83000/LY</td>
</tr>
</tbody>
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American Cancer Society On Women Who Question Screening

British National Health Service: “Informational Campaign”

Canadian National Breast Screening Study (Miller et al,
- 50,472 women aged 40-49 years individually randomized
  - an annual mammography and clinical examination, or
  - examined at the first visit and were taught self-examination thereafter
- Followed 13 years
- Comparable study for women 50-59

Cancers detected: Cochrane Review October 2006
Gotzsche & Nielsen
Results of Randomized, Controlled Trials of Mammography among Women 39 to 74 Years of Age

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Age</th>
<th>Median Follow-Up</th>
<th>Breast Cancer Risk for 75% of Women</th>
<th>Relative Risk among Women 10 Years older than controls</th>
<th>Relative Risk among Women 20 Years older than controls</th>
<th>Number Needed to Screen</th>
<th>Relative Risk among Women 30 Years older than controls</th>
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<tr>
<td>Humphrey et al. (2002)</td>
<td>50-69</td>
<td>13.8</td>
<td>81/105/159/310/157/218</td>
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Cochrane Review October 2006
Gotzsche & Nielsen

Do We Understand The Natural History of Breast Cancer?
The Problem of Pseudodisease

Repeated Screening Vs Prevalence
Screening among Norwegian Women
Age 40-64.
(From Zahl, Maehlen, & Welch, Archives of Int Med, Nov 2008)

Is there any evidence for spontaneous regression of advanced cancer?
- Metastatic melanoma (Printz JNCI, 2001)
- Metastatic renal cell (Gleave et al NEJM, 1998)
- National Polyp Study (Int J. Cancer, 2004)
- Pre-cancerous cervical lesions (Moscicki et al, Lancet, 2004)
Alternative Explanations

Were the samples comparable?

Evidence from Trials

- Malmo study estimated that there was 19% higher rate of diagnosis in the screened group 10 years after the trial ended (both groups got screened at exit)
- Canadian trials screen all women at end. Four years later cumulative rates remained 7% higher in the screened group

Evidence from simulation studies

- Wisconsin Breast Cancer Epidemiology Simulation Model (Fryback et al. JNCI 2007)
  - Stochastic simulation to replicate breast cancer incidence and mortality in the US 1975-2000
  - Postulated that 40% in initiated breast cancers were of “limited malignant potential”
  - “progress to a maximum of 1-cm, dwell at this size for 2 years, and then regress if untreated”

Could it be temporal change in incidence of cancer?

- Unlikely. No evidence for an epidemic of breast cancer in Norway at that time.

What Harm Is Done?
100 years of animal experimentation (after Baum and Retsky, 2008)

Cardiac Arrhythmia Suppression Trial (CAST)
- Designed to test the hypothesis that suppression of ventricular ectopy after a myocardial infarction reduces the incidence of sudden death,
- Patients in whom ventricular ectopy randomly assigned to receive
  - active drug (encainide N= 432) and flecainide N=323)
  - or placebo (425 encainide placebo, 318 flecainide placebo)
- After a mean follow-up of 10 months,
  - 43 arrhythmia deaths in active drug group
  - 16 arrhythmia deaths in placebo group; P = 0.0004,
  - Almost all cardiac deaths not due to arrhythmia were attributed to acute myocardial infarction with shock (11 patients receiving drug and 3 receiving placebo) or to chronic congestive heart failure (4 receiving drug and 2 receiving placebo): unknown.

Women’s Health Initiative (WHI)
JAMA. 2002;288:321-333
- Estrogen plus progestin component of the Women's Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which
- 16608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998.
- Participants randomly assigned to
  - conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n = 8506) or
  - placebo (n = 8102)
- Primary outcome coronary heart disease (CHD)
  - nonfatal myocardial infarction and CHD death,
  - invasive breast cancer —primary adverse outcome.
- A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

Conclusions
- Interventions are often guided by mental models of disease
  - These models of often linear
  - Disease is often non linear
- Outcomes researchers focus on different aspects of the data
  - Total mortality
  - Quality of Life
- Aggressive care is not always the best care
- There is still a place for large RCTs
“Make everything as simple as possible…but not simpler”

Albert Einstein