The “Promise” of Comparative Effectiveness Research

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Goals for Today

- Clarify the definition and scope of CER

- Brief look at the history of CER

- Discuss the rationale for proposing observational studies in CER - examples

- Consider the “promise” of observational databases for CER
Comparative effectiveness research is the conduct and synthesis of systematic research comparing different interventions and strategies to prevent, diagnose, treat and monitor health conditions. Its purpose is to inform patients, providers, and decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances. To provide this information, comparative effectiveness research must assess a comprehensive array of health-related outcomes for diverse patient populations. Interventions compared may include medications, procedures, medical and assistive devices and technologies, behavioral change strategies, and delivery system interventions. This research necessitates the development, expansion, and use of a variety of data sources and methods.
Defining Characteristics of CER

- Compares two or more treatment strategies, but one may be “usual care” or watchful waiting.

- Aims to inform pragmatic clinical questions at the level of the individual patient or the population (i.e. policy decisions).

- Requires data from “real world” patients, settings and treatments.

- Careful attention given to possible heterogeneity of treatment effects - “what works for whom”
Effectiveness - Not Efficacy

- Must compare treatments as they are or would be used in practice
- Must include the broad range of patients in whom the treatments are or would be used
- Must consider a range of outcomes
Defining Characteristics of CER

- No suggestion that CER is only, or even predominantly observational – only that the patients and practice be highly representative of real world practice.

- In the IOM’s 2009 report on national priorities in CER, RCTs were recommended for 49 of the top 100 priorities.
History of CER – ca 2003
Medicare Modernization Act of 2003

This legislation authorizes and appropriates $50 million for FY 2004 for the Secretary through AHRQ to conduct research to address the scientific information needs and priorities related to improving outcomes, clinical effectiveness and appropriateness of specified health services and treatments including prescription drugs identified by the Medicare, Medicaid, and State Children Health Insurance Programs and to improving the efficiency and effectiveness of these Programs. The Secretary is required to establish a process for developing research priorities. The Secretary must establish an initial list of priorities no later than 6 months after enactment.

Medicare Modernization Act of 2003
History of CER – ca 1990

AHCPR & Patient Outcomes Research Teams (PORTs)

PORTs...represent the coming of age of health services research as a useful, clinically relevant discipline, whereby the evaluative sciences for the first time are, with the help and support of Congress, going to become directly relevant to clinical decision making in a way that they haven't before. They're going to have to carry the same burdens of scrutiny that clinical trials and other kinds of clinical research have carried.

David Blumenthal, Institute of Medicine Workshop, 1990
Outcomes management is a technology of patient experience designed to help patients, payers, and providers make rational medical care-related choices based on better insight into the effect of these choices on the patient’s life. It consists of a common patient-language of health outcomes; a national database containing information and analysis on clinical, financial, and health outcomes, as well as the relation between health outcomes and money. It would pool clinical and outcomes data on a massive scale. Its closest relative is the clinical trial. It would be a “clinical trials machine.”

History or CER – *ca 1988*

And Before...

Since one of my proclivities is to give *old ideas* new labels, let’s label this technology “outcomes management.......”

Rationale for Observational CER

What’s wrong with RCTs?

- Nothing…. Except:
  - Highly selected population – volunteers
  - Highly restricted population
  - Tend to be short duration
  - Underpowered to detect unexpected adverse effects – both rare and “common”
  - Underpowered to detect heterogeneity of treatment effects
  - They cost too much
  - Sometimes not feasible
Rationale for Observational CER

What’s wrong with RCTs?

“The paradox of the clinical trial is that it is the best way to assess whether an intervention works, but is arguably the worst way to assess who will benefit from it.”

D Mant
Can randomised trials inform clinical decisions about individual patients?
Bias Due to Selection into RCTs
The EC/IC Bypass Study

- 1,377 eligible patients from multiple centers with symptomatic carotid ischemia
- 115 pts reported to have refused randomization
- 2572 patients from same centers had surgery outside trial
- 633 to surgery
- 714 to best medical care

No evidence of benefit from surgery

Bias Due to Selection into RCTs
Day Hospital vs. Outpatient Tx for CD

1073 eligible patients referred for initial CD treatment

- 668 agreed to be randomized
  - 310 to Day Hosp.
  - 358 to Outpt.

- 405 refused randomization and self-selected
  - 211 chose Day Hosp.
  - 194 chose Outpt.

No significant differences in outcomes (though all favored DH slightly)

6-month abstinence rates significantly higher for DH – 64 vs 47%, p<0.002

Rationale for Observational CER
Advantages of Large Clinical Databases

- Not restricted – captures all use
- No selection due to nonparticipation in research
- Much larger potential size
- Longer-term follow-up
- Remarkably rich data on potential confounders – disease severity, comorbidity
- Data on mechanisms of effectiveness – e.g., adherence to medications.
- Offer possibilities for identifying and studying natural experiments.
Anticoagulation Therapy for Stroke Prevention in Atrial Fibrillation
How Well Do Randomized Trials Translate Into Clinical Practice?

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Yuchiao Chang, PhD
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Daniel E. Singer, MD

Context Warfarin has been shown to be highly efficacious for preventing thromboembolism in atrial fibrillation in randomized trials, but its effectiveness and safety in clinical practice is less clear.

Objective To evaluate the effect of warfarin on risk of thromboembolism, hemorrhage, and death in atrial fibrillation within a usual care setting.

Design Cohort study assembled between July 1, 1996, and December 31, 1997, and followed up through August 31, 1999.

Setting Large integrated health care system in Northern California.

Patients Of 13,559 adults with nonvalvular atrial fibrillation, 11,526 were studied, 43% of whom were women, mean age 71 years, with no known contraindications to anticoagulation at baseline.

Main Outcomes Ischemic stroke, peripheral embolism, hemorrhage, and death according to warfarin use and comorbidity status, as determined by automated databases, review of medical records, and state mortality files.

Results Among 11,526 patients, 397 incident thromboembolic events (372 ischemic strokes, 25 peripheral embolism) occurred during 25,341 person-years of follow-up, and warfarin therapy was associated with a 21% (95% confidence interval [CI], 39%-60%) lower risk of thromboembolism compared with no warfarin therapy (either no antithrombotic therapy or aspirin) after adjusting for potential confounders and likelihood of receiving warfarin. Warfarin was effective in reducing thromboembolic risk in the presence or absence of risk factors for stroke. A nested case-control analysis estimated a 64% reduction in odds of thromboembolism with warfarin compared with no antithrombotic therapy. Warfarin was also associated with a reduced risk of all-cause mortality (adjusted hazard ratio, 0.69; 95% CI, 0.51-0.97). Intracranial hemorrhage was uncommon, but the rate was moderately higher among those taking vs those not taking warfarin (0.46 vs 0.23 per 100 person-years, respectively; P = .003, adjusted hazard ratio, 1.97; 95% CI, 1.24-3.13). However, warfarin therapy was not associated with an increased adjusted risk of nonintracranial major hemorrhage. The effects of warfarin were similar when patients with contraindications at baseline were analyzed separately or combined with those without contraindications (total cohort of 13,559).

Conclusions Warfarin is very effective for preventing ischemic stroke in patients with atrial fibrillation in clinical practice while the absolute increase in the risk of intracranial hemorrhage is small. Results of randomized trials of anticoagulation translate well into clinical care for patients with atrial fibrillation.
Rationale for Observational CER Cohort Study- Anticoagulation in AF

- Multiple RCTs had demonstrated a benefit of warfarin for preventing stroke in AF.
- Trials were restricted to younger patients with few co-morbidities no relative contraindications
- Doubts remained about *efficacy* in older, sicker patients
- Doubts remained about *safety* of anti-coagulation in community practice settings
Rationale for Observational CER Cohort Study- Anticoagulation in AF

- All AF found – searched ECG tracings as well as inpt. And outpt diagnoses for 5 yrs
- Eliminated patients with valvular heart disease
- Identified contraindications and co-morbid conditions
- Used time-varying propensity score methods to adjust for confounders as they appeared or changed during observation period
- Analyzed data separately by age group, level of risk, presence of relative contraindications.
MULTIPLE RANDOMIZED trials have demonstrated warfarin therapy to be highly efficacious in reducing risk of ischemic stroke and other systemic thromboembolism in patients with atrial fibrillation, with relatively low rates of bleeding. Aspirin has substantially less efficacy, particularly among patients at moderate to high risk of stroke. However, concerns persist about the effectiveness and safety of anticoagulation with warfarin in persons treated in usual clinical care because the randomized trials enrolled highly selected patients, included few very elderly patients, and closely monitored anticoagulation. This has important clinical implications because atrial fibrillation occurs commonly, particularly among the elderly. Ischemic stroke, peripheral embolism, hemorrhage, and death according to warfarin use and comorbidity status, as determined by automated databases, review of medical records, and state mortality files.

Results Among 11,526 patients, 397 incident thromboembolic events (372 ischemic strokes, 25 peripheral embolism) occurred during 25,341 person-years of follow-up, and warfarin therapy was associated with a 51% (95% confidence interval [CI], 39%-60%) lower risk of thromboembolism compared with no warfarin therapy (either no antithrombotic therapy or aspirin) after adjusting for potential confounders and likelihood of receiving warfarin. Warfarin was effective in reducing thromboembolic risk in the presence or absence of risk factors for stroke. A nested case-control analysis estimated a 64% reduction in odds of thromboembolism with warfarin compared with no antithrombotic therapy. Warfarin was also associated with a reduced risk of all-cause mortality (adjusted hazard ratio, 0.69; 95% CI, 0.61-0.77). Intracranial hemorrhage was uncommon, but the rate was moderately higher among those taking vs those not taking warfarin (0.46 vs 0.23 per 100 person-years, respectively; \( P = 0.003 \), adjusted hazard ratio, 1.97; 95% CI, 1.24-3.13). However, warfarin therapy was not associated with an increased adjusted risk of nonintracranial major hemorrhage. The effects of warfarin were similar when patients with contraindications at baseline were analyzed separately or combined with those without contraindications (total cohort of 13,559).

Conclusions Warfarin is very effective for preventing ischemic stroke in patients with atrial fibrillation in clinical practice while the absolute increase in the risk of intracranial hemorrhage was small.
Rationale for Observational CER Comparing β-blockers in CHF

- Cohort of 7,946 patients who received β-blocker after hospitalization for CHF – two sites, KPNC and Harvard Pilgrim
- Followed cohort for up to 12 mos. for mortality
- Monitored ongoing exposure and switches among β-blockers
- Used time-varying exposure variable
- Propensity score analysis included exclusion of extreme deciles of propensity to receive carvedilol.

Rationale for Observational CER
Beta-blockers in CHF - Confounding

<table>
<thead>
<tr>
<th></th>
<th>Atenolol (n=3069)</th>
<th>Metoprolol (n=3443)</th>
<th>Carvedilol (n=926)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (yrs)</td>
<td>74</td>
<td>73</td>
<td>68</td>
</tr>
<tr>
<td>% Female</td>
<td>53</td>
<td>48</td>
<td>33</td>
</tr>
<tr>
<td>Prior CHD (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>68</td>
<td>59</td>
<td>44</td>
</tr>
<tr>
<td>On Digoxin (%)</td>
<td>14</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>Aldosterone Recept, Antagonists (%)</td>
<td>3.5</td>
<td>3.5</td>
<td>13</td>
</tr>
</tbody>
</table>

Rationale for Observational CER
Beta-blockers in CHF – Results

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (95% CI) (vs. Atenolol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metoprolol</td>
</tr>
<tr>
<td>Full cohort</td>
<td>1.16 (1.01-1.34)</td>
</tr>
<tr>
<td>Subgroup (n=2929) with documented Systolic Dysfunction</td>
<td>1.14 (0.78-1.67)</td>
</tr>
</tbody>
</table>

“Our findings raise the possibility that carvedilol may not have significantly greater effectiveness than atenolol and that metoprolol tartrate may be inferior to atenolol for reducing mortality in HF. However, our results should be interpreted cautiously, and future randomized comparisons should be considered that include a broader set of different β-blockers in this population.”

Rationale for Observational CER
Other Studies Underway

- Comparison of outcomes by type of bariatric surgery in persons with diabetes – (GJ Bypass, vs. Band vs Sleeve → diabetes resolution/recurrence, re-operation, fractures)

- Beta-blockers vs. ACE-inhibitors as 2nd-line therapy in hypertension

- Immediate vs. delayed initiation of metformin in newly diagnosed T2 diabetes
Limitations of Observational Studies

- Confounding by indication
- Confounding by self-selection
- (In large clinical datasets) missing data on covariates
The “Promise” of CER
The Special Case of Natural Experiments

- Sometimes treatments are distributed among patients for reasons unrelated to health status or prognosis –
  - formulary decisions of different health plans or over time
  - variation due to individual clinician preferences
  - Other “natural experiments” related to innovation in some locales (or times) but not in others

- Higher level or “ecological” differences in exposures create opportunities for observational evaluations that avoid much of the risks of confounding by indication/self-selection

- There is, however, the risk of confounding by other differences at the ecological level – e.g., differing quality of care, or population socioeconomic status
Combining ecological and individual variables to reduce confounding by indication:
Case study—subarachnoid hemorrhage treatment

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Ecological studies may reduce the problem of confounding by indication; however, these studies introduce new biases not present in level analyses. To study the potential for ecological variables to reduce confounding by indication, we used a large database of
The “Promise” of Observational CER
Endovascular Coil vs. Surgical Clip for SAH

- Data from 80 university hospitals
- Hospitals’ use of endovascular coiling in SAH ranged from 0 to 40% of treated cases
- **Individual-level analyses**: mortality for surgery vs. coil with adjustments for patient variables
- **Ecologic analyses**: hospital mortality rate by % treated with coils with adjustment for hospital variables.
- **Two-level analysis**: individual mortality by % treated with coils at hospital with adjustment for both patient and hospital variables.
The “Promise” of Observational CER
Coil vs. Surgery Coil for SAH - Results

**Individual-Level Analysis:**

<table>
<thead>
<tr>
<th>Adjusted Mortality Odds Ratio (95% CI) - Coil vs. Surgery</th>
<th>1.30 (0.85, 2.00)</th>
</tr>
</thead>
</table>

**Ecologic Analyses (Regression):**

<table>
<thead>
<tr>
<th>Δ hospital mortality per 10% increase in % treated by EV</th>
<th>-1.0% (-3.0, +0.9)</th>
</tr>
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</table>

**Two-level Analyses:**

<table>
<thead>
<tr>
<th>Adjusted Mortality Odds Ratio for 10% change in % treated by EV</th>
<th>0.89 (0.82, 0.96)</th>
</tr>
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</table>
The “Promise” of CER
Beyond Observation

- Pragmatic clinical trials – large, “simple” trials in real world settings with real world treatments, multiple outcomes, attention to subgroup differences

- Cluster randomized trials – help to facilitate placement of RCTs within real world settings – with and sometimes without individual informed consent