What Can We Learn From Observational Studies – Examples from the DOPPS

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Dialysis Outcomes and Practice Patterns Study (DOPPS)

- International longitudinal study of hemodialysis facility practices and patient outcomes:
  - DOPPS I: 7 countries, 1996-2001 (n >17000)
  - DOPPS II: 12 countries, 2002-2004 (n >12800)
  - DOPPS III: 12 countries, 2005-2008 (n >11000)

- Representative samples of dialysis units (>300 /phase), random patient selection within each unit

- Supported by Amgen and in Japan by Kirin Pharma (without publication restrictions, >115 papers published)

- Coordinated by Arbor Research Collaborative for Health, (formerly URREA) Ann Arbor, MI, USA
Large Mortality Variations Across US Dialysis Facilities

Standardized Mortality Ratio (SMR)

No. of Facilities

0.25-0.4 0.4-0.55 0.55 0.7 0.85 1 1.15 1.3 1.45 1.6 1.75 1.9 2.05 2.2 2.35
Key Points

Ho: Large differences in survival between country & facilities partially due to variations in modifiable facility practices

Improvements in HD Practices

Improved Patient Survival
DOPPS: A Facility Practice-Based Study

Patient Demographics

+ Patient Comorbidities

+ Practice Patterns

Patient Outcomes
• Mortality
• Hospitalization
• Vascular access
• Quality of life

Goal: Live longer – Live better!
DOPPS 3

340 randomly selected facilities stratified by unit type and geographic region
[detailed data from >40,000 HD patients since DOPPS I (1996)]

Japan
Canada & US
Europe
Australia & New Zealand
Canada & US

≥2 Country Investigators per country
Inclusion of Multiple Countries Increases Observable Variability

Probability Distribution

Practice Pattern or Outcome
Constrasting Randomized Controlled Clinical Trials versus Observational Studies
Double-blind Randomized Controlled Trials

When perfectly executed,

- such trails are ideal for evaluating treatments since randomization makes “all else equal”
- difference in outcomes can be attributed to the treatment = Causal relationship
### RCT “Balances” Patient Characteristics in Treated vs Control Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>High-Hemoglobin Group (N=715)</th>
<th>Low-Hemoglobin Group (N=717)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>66.0±14.3</td>
<td>66.3±13.5</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>56.2</td>
<td>54.1</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>62.3</td>
<td>61.1</td>
</tr>
<tr>
<td>Black</td>
<td>28.6</td>
<td>29.3</td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>3.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Other</td>
<td>5.6</td>
<td>6.0</td>
</tr>
<tr>
<td>Hispanic ethnic background (%)</td>
<td>12.5</td>
<td>13.5</td>
</tr>
<tr>
<td>History of smoking tobacco (%)</td>
<td>47.5</td>
<td>44.6</td>
</tr>
<tr>
<td>Cause of chronic kidney disease (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>46.8</td>
<td>50.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29.9</td>
<td>27.5</td>
</tr>
<tr>
<td>Other</td>
<td>23.3</td>
<td>21.6</td>
</tr>
<tr>
<td>Cardiovascular history (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>95.8</td>
<td>93.2†</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>16.4</td>
<td>15.0</td>
</tr>
<tr>
<td>CABG</td>
<td>17.4</td>
<td>13.5‡</td>
</tr>
<tr>
<td>PCI</td>
<td>10.9</td>
<td>11.9</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>24.4</td>
<td>22.9</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9.4</td>
<td>8.6</td>
</tr>
<tr>
<td>Stroke</td>
<td>9.8</td>
<td>10.0</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>16.4</td>
<td>16.4</td>
</tr>
<tr>
<td>Myocardial infarction, stroke, CABG, PCI, or amputation of a lower limb</td>
<td>36.3</td>
<td>34.5</td>
</tr>
</tbody>
</table>

Singh et al NEJM 2006
Randomized Controlled Trials: Aspects to be Considered

• Narrow entry criteria → Non-representative
• Inadequate sample size (power)
• Withdrawals – may make study groups unequal
• Imperfect blinding
• Ethically not feasible to address some questions
• Expensive
Observational Studies*

Advantages:
• Test numerous hypotheses
• Can be representative of all patients
• Can study the range of actual practices
• Lower cost than randomized trials

Requirements:
• Statistical adjustments
• Look for potential confounding and apply special techniques

* e.g. DOPPS
Problem with Observational Data

You have to deal with Treatment-by-Indication Biases

(Because of this confounding, must avoid making conclusions of causality)
### Hypothetical Example of Outcomes for a Drug Given Preferentially to Older Patients with Severe Comorbidities

**A) Results from Observational Data**

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>RR of death (Drug A vs No Drug)</th>
<th>Adjusted RR (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.79 (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.40 (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Demographics plus many comorbidities</td>
<td>1.20 (p&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>

Even after extensive adjustment, one still doesn’t know how much of the 20% higher risk is due to effects of Drug A versus due to unmeasured confounders associated with patients receiving Drug A.

**RCT run later gives an RR = 0.90 (p<0.05)**
Therapy Preferentially Given to Patients Having Certain Conditions (Treatment-by-Indication Bias)

Difficult to determine how much of the benefit or harm associated with the therapy is due to the therapy versus due to patients who receive the therapy being either more healthy or less healthy than those not receiving therapy.
Common Statistical Methods for Reducing the Effect of TBIB

- Statistical adjustment via Cox regression models
- Propensity score analysis
- Marginal Structural Models (MSMs)

**Problem**: these account for measured covariates but do not fully account for unmeasured confounders
Is there another way to analyze observational data to free ourselves more from Treatment-by-Indication Bias (TBIB)?
YES – there is another way to analyze observational data to free ourselves more from Treatment-by-Indication Bias (TBIB)

Use Facility Practice-based methodology = patient treatment aggregated to facility or provider level

(also referred to as “instrumental variable” analysis)
Challenge in Facility-based Analyses:
Assess treatment effects in a setting in which treatment assignment (facility’s practice) is not tightly linked to patient characteristics.

This goal is similar to the RCT design in which assignment to treatment groups occurs irrespective of patient characteristics (i.e. patient characteristics are balanced across treatment groups)
Facilities and physicians greatly differ in deciding who should receive treatment for many different types of HD practices.
Examples of Large Variation in Prescribing Therapy for HD patients

- % facility patients using a catheter: 0 to 86%
- % facility patients using AV fistula: 0 to 100%
- % facility patients with a spKt/V<1.2: 0 to 73%
- % facility patients given vitamin D: 6 to 92%
- Facility mean Epo dose: 2000 – 25,000 units/wk
Regional Variation in Facility AVF Use

Facility AVF Use (% of patients)

% of Facilities

Japan (n=59) 92%
EUR/ANZ (n=157) 74%
North Amer (n=96) 36%

DOPPS II: 2002-2003
Facility Preferences to Treat: Major Determinant of Receiving Therapy

Facility Catheter Use

- 7% of variance explained by Pt Char
- 23% by Facility effects + Pt Char

Facility Catheter Use:

Treatment (T) → Outcome (O)

Pt Char
Relationships Can Differ Greatly When Viewed from Patient vs Provider Perspectives

• Is it good to have hospitals?
  – People in hospitals have higher death rates than those not in hospitals.
  – However, countries with more hospitals have longer lifetimes than those with few hospitals.

• Is it good to take an antibiotic?
  – People taking an antibiotic are more likely to have an infection and die of pneumonia.
  – However, death rates due to pneumonia have declined in countries since using antibiotics
Example: EPO Dose & TBIB

• EPO Dose is prescribed based on patient EPO responsiveness which in part reflects patient health status
  – Sicker ⇒ higher EPO dose
  – Healthier ⇒ lower EPO dose

• ⇒ Treatment by indication bias (TBIB)

• Many covariates are available, but cannot completely explain TBIB
Scatter plot of Patient Hemoglobin by Patient Epo Dose

Hemoglobin (g/dl)

Epo Dose (units/week)
In 1989-91 (during introduction of EPO) patients at facilities using EPO had higher Hgb than patients at facilities not yet using EPO.
Example: Catheter Use & TBIB

- Patients dialyzing with a catheter tend to have poorer health status
Older Mean Age and Greater Comorbidity Burden in Patients Using a Catheter Versus AVF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AVF (n=10,530)</th>
<th>Graft (n=3980)</th>
<th>Catheter (n=2324)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yrs</td>
<td>60.2</td>
<td>62.1**</td>
<td>63.7**</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>26.5</td>
<td>46.8**</td>
<td>44.6**</td>
</tr>
<tr>
<td>PAD, %</td>
<td>19.8</td>
<td>29.2**</td>
<td>33.6**</td>
</tr>
<tr>
<td>CAD, %</td>
<td>34.4</td>
<td>52.3**</td>
<td>53.3**</td>
</tr>
<tr>
<td>CHF, %</td>
<td>21.6</td>
<td>42.7**</td>
<td>43.7**</td>
</tr>
<tr>
<td>Cerebrovascular disease, %</td>
<td>14.0</td>
<td>19.5**</td>
<td>22.0**</td>
</tr>
<tr>
<td>Other CV disease, %</td>
<td>32.9</td>
<td>37.1**</td>
<td>39.8**</td>
</tr>
<tr>
<td>HTN, %</td>
<td>77.2</td>
<td>84.2</td>
<td>80.4**</td>
</tr>
<tr>
<td>Lung disease, %</td>
<td>8.2</td>
<td>11.1</td>
<td>16.6**</td>
</tr>
<tr>
<td>Cancer, %</td>
<td>9.0</td>
<td>10.4</td>
<td>14.3**</td>
</tr>
<tr>
<td>Psychological disorder, %</td>
<td>15.6</td>
<td>23.1</td>
<td>27.3**</td>
</tr>
</tbody>
</table>

**p<0.01 adjusted for study phase and region; DOPPS I+II, prevalent cross-section
Vascular Access: Mortality Risk
Patient Based Model

RR of Death

- Catheters: 1.32 (p<0.0001)
- Grafts: 1.21 (p<0.0001)
- AVF: 1 (Ref.)

Grafts vs AVF (in US) RR of death = 1.17 (p=0.001)

Pisoni et al ASN, 2005

* DOPPS I+II, 1996-2004; n=25,806; adjusted for age, gender, black race, yrs with ESRD, 14 comorbidity classes, baseline Hgb, Kt/V, serum albumin, calcium, PO₄, accounted for facility clustering effects; stratified by continent [Japan, US, EUR (Fr,Ge,It,Sp,UK); RR based upon access in use at study entry.
(1) However, catheter use is tightly linked to patients with poorer health status.

(2) Outcomes, even with adjustments, are expected to be worse for patients using a catheter since unmeasured confounders are not accounted for in the patient-level analyses.
Are Patient Characteristics More Balanced When Looking at Catheter Use as a Facility Practice?
Facilities Differing in Catheter Use Display Few Differences in Comorbidity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Facility Case-mix Adjusted Catheter Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;9% (n=3270)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>29</td>
</tr>
<tr>
<td>CerebroVasc Dis, %</td>
<td>15</td>
</tr>
<tr>
<td>Lung disease, %</td>
<td>8</td>
</tr>
</tbody>
</table>

*p=0.01- 0.05; DOPPS 1+2; adjusted for region and phase; no significant trend in prevalence of other comorbidities with increasing levels of facility case-mix adjusted catheter use.

When many measured confounders do not differ across different levels of a facility practice, such balance suggests: practice is provided independently of MEASURED patient factors, and the practice likely is also provided independently of most UNMEASURED confounders.
Vascular Access: Mortality Risk Facility Based Model

RR of Death among Facility Patients per 20% more facility use of indicated access type

Catheters  Grafts  Fistulae

1.2  1.09  1

p<0.0001  p=0.007  Ref.

*DOPPS I+II, 1996-2004; n=27,360; adjusted for age, gender, black race, yrs with ESRD, 14 comorbidity classes, baseline Hgb, Kt/V, serum albumin, calcium, PO4, accounted for facility clustering effects; stratified by continent [Japan, US, EUR (Fr,Ge,It,Sp,UK)]; RR based upon access in use at study entry. Facility access use is adjusted for facility case-mix.

Pisoni et al, ASN 2005
Statistical Analysis of Patient Outcomes by Facility Practice

• Define facility practice pattern
  - % facility patients within lab limits (e.g. Hgb ≥11)
  - % patients using certain drug, vascular access type, etc

• Attribute the “practice pattern” to every patient in the facility

• Model = Patient’s risk of the outcome related to the facility’s practice level while simultaneously adjusting for a patient’s characteristics
### Effect of Added Covariates on a Patient-based versus Facility-based Predictor

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Catheter use: Pt vs facility models</th>
<th>Graft use: Pt vs facility models</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR of death (Graft vs AVF)</td>
<td>RR of death for 20% more facility catheter use*</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.79 (p&lt;0.001)</td>
<td>1.26 (p&lt;0.001)</td>
</tr>
<tr>
<td>+ demographics</td>
<td>1.67 (p&lt;0.001)</td>
<td>1.23 (p&lt;0.001)</td>
</tr>
<tr>
<td>+ demographics and many comorbidities</td>
<td>1.45 (p&lt;0.001)</td>
<td>1.20 (p&lt;0.001)</td>
</tr>
</tbody>
</table>
Adjustment for patient factors will have little effect on the relationship of mortality with a strong instrument (facility practice predictor) that is not tightly linked to patient characteristics.
Facility Practice-based Modeling: Important to Account for Other Facility Practices & Characteristics
Facility % Catheter Use

Treatment (Pt Access Use)

Pt Char

Outcome (O)

Other Facility Practices & Char
## Effect of Accounting for Other Facility Practices on the Relationship of Mortality with Facility VA use

<table>
<thead>
<tr>
<th>Adjustments</th>
<th>Catheter use</th>
<th>Graft use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR of death for 20% more facility catheter use*</td>
<td>RR of death for 20% more facility graft use*</td>
</tr>
<tr>
<td>Demographics, many comorbidities</td>
<td>1.20 (p&lt;0.001)</td>
<td>1.09 (p=0.005)</td>
</tr>
<tr>
<td>+ facility median TT, % phos &gt;5.5, and % Ca &gt;10 mg/dl</td>
<td>1.19 (p&lt;0.001)</td>
<td>1.08 (p=0.008)</td>
</tr>
<tr>
<td>+ facility % spKt/V&lt;1.2, % hgb &lt;10, % albumin &lt;3.2</td>
<td>1.14 (p&lt;0.001)</td>
<td>1.07 (p=0.02)</td>
</tr>
</tbody>
</table>

Note: practices in the final model may be a consequence of facility catheter use and as such would then be expected to explain away some of the facility catheter use effect; careful analysis is required not to adjust for practices that are a consequence of the practice being studied.
Advantage of Facility-Level Analyses

- Prior DOPPS work has indicated that for many practices:
  - facility-level analyses often are superior to patient-level analyses in reducing treatment-by-indication bias

- When many measured confounders do not differ across different levels of a facility practice, such balance suggests:
  - practice is provided independently of MEASURED patient factors
  (the practice likely is also provided independently of most UNMEASURED confounders)

- In these cases, the facility practice has the potential to be substantially free of both measured AND unmeasured confounding, thereby providing more reliable findings

- The question can then be tested: Is there a survival benefit for patients treated in facilities having greater use of a particular practice?
Conclusions

• Facility level or IV analyses have the potential power to substantially reduce unmeasured confounding and bias.

• Checking IV assumptions is necessary
  – Checking balance across facility-level treatment measures in
    • Patient-level characteristics
    • Facility characteristics

Newhouse & McClellan (1998)
Ann Rev Pub Health 19: 17-34
Thank you very much!

Additional information and slides available at: www.dopps.org or www.arborresearch.org