The Role of Study Design to Reduce the Potential for Confounding

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UNC Gillings School of Global Public Health,
University of North Carolina at Chapel Hill, USA
Potential Conflicts of Interest

- R01 AG023178 (PI) and R01 AG042845 (Co-I), National Institute on Aging
- R01 CA174453 (Co-I), National Cancer Institute
- IP2PI000075 (PI), Patient Centered Outcomes Research Institute (PCORI)
- AstraZeneca (PI), Amgen (Co-I)
- Center for Pharmacoepidemiology (GlaxoSmithKline, UCB BioSciences, Merck)
- All to University of North Carolina at Chapel Hill
Confounding by Indication

- Good prescribing leads to confounding of drug effects on intended outcomes
- More severe disease more likely to
  - Be treated (with higher doses)
  - Have higher risk of outcomes (we like to prevent)
- Assessment of severity of disease often difficult
- Intractable confounding
- Drug looks BAD compared with NON-USERS!
  - E.g., increased asthma mortality with beta-agonists
Confounding by Frailty in Population Based PE Studies

• Individuals close to death are
  – Less likely to receive preventive treatments
    • E.g., statins, flu vaccination
  – More likely switched to palliative treatments
    • E.g., opiates instead of NSAIDs
  – More likely to receive certain classes of drugs
    • E.g., loop diuretics vs. other diuretics

• Paradoxical drug mortality associations

• Drug looks GOOD compared with NON-USERS!
Intractable Confounding?

- We cannot (well) measure indication nor frailty
- Need other means to control for confounding
  - Randomization, but clearly not feasible to get timely answers for ALL relevant drug related research questions
  - Restriction, very powerful tool to address confounding (e.g., Schneeweiss et al., Med Care 2007)
- Can we (implicitly) restrict to (same) indication?
  - Potential to reduce confounding by indication AND frailty
- Compare treatment alternatives with equipoise for same indication
  - Guideline, clinical practice
- New user, active comparator design
So Much for the Theory, but Does it Really Work?

• Non-selected examples from recent studies on antidiabetics @ UNC
  – Guideline (Diab Care 2015;38:140-149)
  – Metformin versus Sulfonylurea
  – DPP-4 versus TZD/sulfonylurea
  – Glargine versus NPH insulin
### Healthy eating, weight control, increased physical activity, and diabetes education

#### Efficacy

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypo risk</td>
<td>high</td>
<td>low</td>
<td>neutral</td>
<td>low</td>
<td>neutral</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
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</table>

#### Dual therapy

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Thiazolidinedione</td>
<td>DPP-4 inhibitor</td>
<td>SGLT2 inhibitor</td>
<td>GLP-1 receptor agonist</td>
<td>Insulin (basal)</td>
</tr>
<tr>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>moderate risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high risk</td>
</tr>
<tr>
<td>gain</td>
<td>gain</td>
<td>gain</td>
<td>loss</td>
<td>loss</td>
<td>gain</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>edema, HF, fx</td>
<td>low</td>
<td>rare</td>
<td>GU, dehydration</td>
<td>hypoglycemia</td>
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<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>variable</td>
<td>variable</td>
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#### Triple therapy

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Thiazolidinedione</td>
<td>DPP-4 inhibitor</td>
<td>SGLT2 inhibitor</td>
<td>GLP-1 receptor agonist</td>
<td>Insulin (basal)</td>
<td></td>
</tr>
<tr>
<td>or TZD</td>
<td>or SU</td>
<td>or DPP-4-i</td>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td>or DPP-4-i</td>
<td></td>
</tr>
<tr>
<td>or DPP-4-i</td>
<td>or SU</td>
<td>or DPP-4-i</td>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td>or DPP-4-i</td>
<td></td>
</tr>
<tr>
<td>or SGLT2-i</td>
<td>or GLP-1-RA</td>
<td>or GLP-1-RA</td>
<td>or GLP-1-RA</td>
<td>or Insulin 5</td>
<td>or Insulin 5</td>
<td></td>
</tr>
<tr>
<td>or GLP-1-RA</td>
<td>or Insulin 5</td>
<td>or Insulin 5</td>
<td>or Insulin 5</td>
<td>or Insulin 5</td>
<td>or Insulin 5</td>
<td></td>
</tr>
</tbody>
</table>

#### Combination injectable therapy

- If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

- If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

- If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i.
Metformin

- First line treatment pts. with type 2 diabetes
- Reduction of cancer incidence and mortality?
  - Breast, colon and rectum, liver, pancreas, stomach, prostate, esophagus, etc?
  - Some biology
- Time related biases (Suissa & Azoulay 12, 14)
- Active comparator?
  - Guideline: none
  - Empirically: sulfonylureas
## Initiation of Metformin vs. Sulfonylurea, US Medicare

<table>
<thead>
<tr>
<th>Race</th>
<th>Metformin</th>
<th>Sulfonylureas</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>28855 (79.3)</td>
<td>9088 (77.5)</td>
</tr>
<tr>
<td>African American</td>
<td>3858 (10.6)</td>
<td>1590 (13.6)</td>
</tr>
<tr>
<td>Others</td>
<td>3654 (10.0)</td>
<td>1052 (9.0)</td>
</tr>
</tbody>
</table>

### Comorbidity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Metformin</th>
<th>Sulfonylureas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign Breast Disease</td>
<td>1284 (3.5)</td>
<td>290 (2.5)</td>
</tr>
<tr>
<td>Benign neoplasm of breast</td>
<td>55 (0.2)</td>
<td>15 (0.1)</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>2737 (7.5)</td>
<td>1136 (9.7)</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>3199 (8.8)</td>
<td>2036 (17.4)</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>6522 (17.9)</td>
<td>2987 (25.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28332 (77.9)</td>
<td>9139 (77.9)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>4069 (11.2)</td>
<td>1259 (10.7)</td>
</tr>
</tbody>
</table>

Jin-Liern Hong et al., submitted
## Initiation of Metformin vs. Sulfonylurea, US Medicare

<table>
<thead>
<tr>
<th>Medications</th>
<th>Metformin</th>
<th>Sulfonylureas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>2232 (6.1)</td>
<td>491 (4.2)</td>
</tr>
<tr>
<td>Progestin</td>
<td>262 (0.7)</td>
<td>45 (0.4)</td>
</tr>
<tr>
<td>Statins</td>
<td>20268 (55.7)</td>
<td>5413 (46.1)</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>4384 (12.1)</td>
<td>1184 (10.1)</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>13715 (37.7)</td>
<td>4354 (37.1)</td>
</tr>
<tr>
<td>ARBs</td>
<td>7762 (21.3)</td>
<td>2253 (19.2)</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>14412 (39.6)</td>
<td>4978 (42.4)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>10313 (28.4)</td>
<td>3385 (28.9)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>1682 (4.6)</td>
<td>998 (8.5)</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>10479 (28.8)</td>
<td>3676 (31.3)</td>
</tr>
<tr>
<td>Loop Diuretics</td>
<td>5703 (15.7)</td>
<td>2987 (25.5)</td>
</tr>
<tr>
<td>Non-Loop Diuretics</td>
<td>14747 (40.6)</td>
<td>3968 (33.8)</td>
</tr>
</tbody>
</table>
## Table 3. Characteristics in Metformin and Sulfonylureas at Baseline in MCBS 2006-2009

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>SUL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>118 (100.0)</td>
<td>79 (100.0)</td>
</tr>
<tr>
<td>Median Age (IQR)</td>
<td>74.0 (70.0-80.0)</td>
<td>78.0 (75.0-84.0)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>89 (75.4)</td>
<td>59 (74.7)</td>
</tr>
<tr>
<td>Other</td>
<td>29 (24.6)</td>
<td>20 (25.3)</td>
</tr>
<tr>
<td>Median of BMI (IQR)</td>
<td>29.9 (25.6-34.0)</td>
<td>28.6 (25.1-33.1)</td>
</tr>
<tr>
<td>Mean of BMI (Stdev)</td>
<td>30.5 (6.5)</td>
<td>29.9 (6.9)</td>
</tr>
<tr>
<td>BMI Category*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>24 (20.3)</td>
<td>18 (22.8)</td>
</tr>
<tr>
<td>25-30</td>
<td>35 (29.7)</td>
<td>30 (38.0)</td>
</tr>
<tr>
<td>30+</td>
<td>58 <strong>49.2</strong></td>
<td>29 <strong>36.7</strong></td>
</tr>
<tr>
<td>Smoking Status*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>61 (51.7)</td>
<td>48 (60.8)</td>
</tr>
<tr>
<td>Ever Smoking</td>
<td>57 (48.3)</td>
<td>28 (35.4)</td>
</tr>
</tbody>
</table>
Dipeptidyl-peptidase-4 inhibitors

• Introduced (US) in 2006
• Improve glycemic control in type 2 diabetics
• Sitagliptin first in class, saxagliptin (2008), linagliptin (2011) and alogliptin (2012)
• P.O., good tolerability, body-weight neutrality
• 2009: FDA safety communication for acute pancreatitis
• 2011: pancreatic cancer in FAERS (ROR=2.7)
• 2013: increased pancreatic cell proliferation and dysplasia (autopsy study)
# Healthy eating, weight control, increased physical activity, and diabetes education

## Metformin

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Hypo risk</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>low risk</td>
<td>neutral / loss</td>
<td>GI / lactic acidosis</td>
<td>low</td>
</tr>
</tbody>
</table>

If HbA₁c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin +</th>
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<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonlurea</td>
<td>Thiazolidinedione</td>
<td>DPP-4 inhibitor</td>
<td>SGLT2 inhibitor</td>
<td>GLP-1 receptor agonist</td>
<td>Insulin (basal)</td>
</tr>
<tr>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>moderate risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high risk</td>
</tr>
<tr>
<td>gain</td>
<td>gain</td>
<td>low risk</td>
<td>low risk</td>
<td>loss</td>
<td>gain</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>edema, HF, fxs</td>
<td>neutral</td>
<td>GU, dehydration</td>
<td>Gl</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>variable</td>
</tr>
</tbody>
</table>

If HbA₁c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin +</th>
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<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonlurea +</td>
<td>Thiazolidinedione +</td>
<td>DPP-4 inhibitor +</td>
<td>SGLT2 inhibitor +</td>
<td>GLP-1 receptor agonist +</td>
<td>Insulin (basal) +</td>
</tr>
<tr>
<td>or DPP-4-i</td>
<td>or SGLT2-i</td>
<td>or GLP-1-RA</td>
<td>or Insulin</td>
<td>or Insulin</td>
<td>or TZD</td>
</tr>
<tr>
<td>or SU</td>
<td>or DPP-4-i</td>
<td>or TZD</td>
<td>or SGLT2-i</td>
<td>or DPP-4-i</td>
<td>or GLP-1-RA</td>
</tr>
</tbody>
</table>

If HbA₁c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:

Metformin + 1

Basal insulin + Mealtime insulin or GLP-1-RA
Time Trends in Initiation of Oral Antidiabetics: US Medicare

Gokhale et al., unpublished results
<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>DPP-4 inhibitors (N = 29366)</th>
<th>TZD (N = 26332)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Mean (s.d.) age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>66–75 years</td>
<td>16407</td>
<td>55.87</td>
</tr>
<tr>
<td>76–85 years</td>
<td>9782</td>
<td>33.31</td>
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<tr>
<td>≥86 years</td>
<td>3177</td>
<td>10.82</td>
</tr>
<tr>
<td>Male</td>
<td>10590</td>
<td>36.06</td>
</tr>
<tr>
<td>White</td>
<td>22245</td>
<td>75.75</td>
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<tr>
<td>Black</td>
<td>3059</td>
<td>10.42</td>
</tr>
<tr>
<td>Other</td>
<td>4062</td>
<td>13.83</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>9966</td>
<td>33.94</td>
</tr>
<tr>
<td>Depression</td>
<td>4709</td>
<td>16.04</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>5595</td>
<td>19.05</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>5790</td>
<td>19.72</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>7740</td>
<td>26.36</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>6478</td>
<td>22.06</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>2660</td>
<td>9.06</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>5260</td>
<td>17.91</td>
</tr>
<tr>
<td>Diabetic cataract</td>
<td>83</td>
<td>0.28</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>256</td>
<td>0.87</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>316</td>
<td>1.08</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>78</td>
<td>0.27</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>318</td>
<td>1.08</td>
</tr>
</tbody>
</table>
**Dipeptidyl-peptidase-4 inhibitors**

<table>
<thead>
<tr>
<th>Medication use**</th>
<th>DPP-4 inhibitors (N = 29,366)</th>
<th>TZD (N = 26,332)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Insulin</td>
<td>5409</td>
<td>18.42</td>
</tr>
<tr>
<td>Metformin</td>
<td>16,805</td>
<td>57.23</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>13,530</td>
<td>46.07</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>10,907</td>
<td>37.14</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>8,184</td>
<td>27.87</td>
</tr>
<tr>
<td>Statins</td>
<td>19,331</td>
<td>65.83</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>8,294</td>
<td>28.24</td>
</tr>
<tr>
<td>Other diuretics</td>
<td>7,831</td>
<td>26.67</td>
</tr>
<tr>
<td>β-blockers</td>
<td>15,350</td>
<td>52.27</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>10,334</td>
<td>35.19</td>
</tr>
</tbody>
</table>

**Healthcare utilization§**

<table>
<thead>
<tr>
<th></th>
<th>DPP-4 inhibitors (N = 29,366)</th>
<th>TZD (N = 26,332)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood tests</td>
<td>2,675</td>
<td>9.11</td>
</tr>
<tr>
<td>Lipid panel</td>
<td>25,483</td>
<td>86.78</td>
</tr>
<tr>
<td>Influenza vaccinations</td>
<td>16,325</td>
<td>55.59</td>
</tr>
</tbody>
</table>

Gokhale et al., Diabet Obes Metab 2014
Insulin Glargine

- Human insulin analogue
- Implicated with increased risk for cancer (any) in large cohort study from Germany
- Some lab evidence
- Insulin mostly used in type 2 diabetics not controlled by 1st and 2nd line oral antidiab.
- Clinical alternative: human NPH insulin
- New user, active comparator design
## Confounding Control by Design

<table>
<thead>
<tr>
<th>Actual cohorts</th>
<th>Glargine</th>
<th>NPH</th>
<th>Effect on channeling, OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>43,306</td>
<td>9,147</td>
<td></td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td></td>
<td></td>
<td><strong>1.001 (0.999–1.003)</strong></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20,369 (47.0)</td>
<td>3,611 (39.5)</td>
<td><strong>1.29 (1.22–1.37)</strong></td>
</tr>
<tr>
<td>Female</td>
<td>22,937 (53.0)</td>
<td>5,536 (60.5)</td>
<td><strong>1.00 (reference)</strong></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>8,074 (18.6)</td>
<td>1,645 (18.0)</td>
<td><strong>1.01 (0.93–1.09)</strong></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>11,432 (26.4)</td>
<td>2,345 (25.6)</td>
<td><strong>0.90 (0.84–0.95)</strong></td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>9,998 (23.1)</td>
<td>2,110 (23.1)</td>
<td><strong>0.86 (0.81–0.91)</strong></td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>11,613 (26.8)</td>
<td>2,364 (25.8)</td>
<td><strong>0.94 (0.89–1.00)</strong></td>
</tr>
<tr>
<td>Hypertension</td>
<td>35,314 (81.6)</td>
<td>6,842 (74.8)</td>
<td><strong>1.13 (1.06–1.20)</strong></td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td>10,642 (24.6)</td>
<td>2,344 (25.6)</td>
<td><strong>0.98 (0.92–1.05)</strong></td>
</tr>
<tr>
<td>Health care use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalizations (any reason)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8,961 (20.7)</td>
<td>1,922 (21.0)</td>
<td><strong>1.17 (1.07–1.29)</strong></td>
</tr>
<tr>
<td>2</td>
<td>3,144 (7.3)</td>
<td>662 (7.2)</td>
<td><strong>1.15 (1.03–1.28)</strong></td>
</tr>
<tr>
<td>≥3</td>
<td>2,512 (5.8)</td>
<td>515 (5.6)</td>
<td><strong>1.25 (1.11–1.42)</strong></td>
</tr>
<tr>
<td>Days in hospital (any reason)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>2,794 (6.5)</td>
<td>618 (6.8)</td>
<td><strong>0.92 (0.82–1.04)</strong></td>
</tr>
<tr>
<td>3–5</td>
<td>4,251 (9.8)</td>
<td>913 (10.0)</td>
<td><strong>0.95 (0.86–1.06)</strong></td>
</tr>
</tbody>
</table>
OK, But What About BMI?

- BMI probably strongest predictor for adding insulin in T2DM and RF for some cancers
- External validation study
  - Estimate independent effect of BMI on prescribing glargine VERSUS NPH
  - At time of initiation (same indication)
  - Using EMR data (here: MGH, Ochsner)
- Use known effect of BMI on cancer risk to estimate confounding if BMI unbalanced
- Assumption: BMI effect on treatment choice transportable
## Limiting Confounding by Design

Table 4—Effect of BMI on channeling between initiating glargine versus initiating NPH: external validation studies

<table>
<thead>
<tr>
<th></th>
<th>Glargine</th>
<th>NPH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MGH</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²), mean ± SD*</td>
<td>32.7 ± 7.53</td>
<td>32.4 ± 8.43</td>
</tr>
<tr>
<td>BMI (kg/m²), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;19</td>
<td>4 (0.7)</td>
<td>8 (1.9)</td>
</tr>
<tr>
<td>19 to &lt;25</td>
<td>77 (13.4)</td>
<td>67 (16.3)</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>150 (26.1)</td>
<td>105 (25.5)</td>
</tr>
<tr>
<td>30 to &lt;35</td>
<td>146 (25.4)</td>
<td>104 (25.2)</td>
</tr>
<tr>
<td>35 to &lt;40</td>
<td>114 (19.9)</td>
<td>64 (15.5)</td>
</tr>
<tr>
<td>40 to &lt;45</td>
<td>45 (7.8)</td>
<td>36 (8.7)</td>
</tr>
<tr>
<td>≥45</td>
<td>38 (6.6)</td>
<td>28 (6.8)</td>
</tr>
</tbody>
</table>

Sturmer et al. Diabetes Care 2013
Some Differences Remain!

<table>
<thead>
<tr>
<th></th>
<th>Actual cohorts</th>
<th>Effect on channeling, OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glargine</td>
<td>NPH</td>
</tr>
<tr>
<td>n</td>
<td>43,306</td>
<td>9,147</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>61.3 (14.0)</td>
<td>58.9 (17.2)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20,369 (47.0)</td>
<td>3,611 (39.5)</td>
</tr>
<tr>
<td>Female</td>
<td>22,937 (53.0)</td>
<td>5,536 (60.5)</td>
</tr>
<tr>
<td>Metformin</td>
<td>27,347 (63.2)</td>
<td>4,544 (49.7)</td>
</tr>
<tr>
<td>Niacin</td>
<td>810 (1.9)</td>
<td>108 (1.2)</td>
</tr>
<tr>
<td>Nonloop diuretics</td>
<td>7,684 (17.7)</td>
<td>1,397 (15.3)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>593 (1.4)</td>
<td>317 (3.5)</td>
</tr>
<tr>
<td>Other diabetes drugs</td>
<td>9,416 (21.7)</td>
<td>891 (9.7)</td>
</tr>
<tr>
<td>Progestins</td>
<td>407 (0.9)</td>
<td>145 (1.6)</td>
</tr>
<tr>
<td>Statins</td>
<td>23,874 (55.1)</td>
<td>3,792 (41.5)</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>28,399 (65.6)</td>
<td>4,443 (48.6)</td>
</tr>
<tr>
<td>Testosterone</td>
<td>250 (0.6)</td>
<td>30 (0.3)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>275 (0.6)</td>
<td>44 (0.5)</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>14,085 (32.5)</td>
<td>1,954 (21.4)</td>
</tr>
</tbody>
</table>
Additional Design Approaches to Reduce Unmeasured Confounding

- External control for confounding (e.g., Stürmer et al., Med Care 2007)
- Instrumental variables (e.g., Brookhart et al, Epidemiology 2006)
- Excluding patients treated contrary to prediction (in the tails of the PS distribution; Stürmer et al., AJE 2010)
Conclusions Study Design to Control for Unmeasured Confounding

• Conditioning on indication has major impact reducing potential for confounding by indication and frailty
• Can in practice only be achieved with new user, active comparator design (no nonexp. “placebo”)
• Carefully assess potential for remaining confounding by indication (clinician input)
Brief History of New User, Active Comparator Design

• Kramer et al. J Chron Dis 1987;40:1073-85:
  – “For what period of time? The risk posed by a drug for a .. event is not generally the same in the sixth month of chronic therapy as in the first or second week.”
  – “Compared with what? .. it is important to compare that risk with that of some other real therapeutic option for patients with the same clinical indication. Just as in a clinical trial investigating treatment efficacy, any epidemiologic study of treatment risks should compare two or more viable treatment alternatives.”
  – “.. measuring risks conditionally on .. indication is .. essential to reduce confounding”

• Guess. J Clin Epidemiol 1989;42:1179-84:
  – “The possibility of temporally non-constant hazard functions should be considered in the study design. This requires that drug exposure time be measured not only in relation to onset of the study disease but also in relation to start of therapy with the study drug.” (Italics by author)
Brief History of New User, Active Comparator Design

• Moride, Abenhaim. J Clin Epidemiol 1994;47:731-7:
  – “Our results .. are compatible with .. a selection process by which patients who have used the drugs in the past and tolerated them well remain on the drugs while patients who are susceptible to gastropathy select themselves out of the population at risk. This process is analogous to the .. “healthy worker effect”. .. If not taken into account .. it could introduce a selection bias.”


• Ray. Am J Epidemiol 2003;158:915-20:
  – “First, prevalent users are "survivors" of the early period of pharmacotherapy … Second, covariates .. often are plausibly affected by the drug itself.”
  – “A new-user design eliminates these biases by restricting the analysis to persons under observation at the start of the current course of treatment”
Brief History of the New User Active Comparator Design


- Guess. Behavior of the exposure odds ratio in a case-control study when the hazard function is not constant over time. J Clin Epidemiol 1989;42:1179-84.

