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Outcomes Research
Outcomes Research

- Safety
- Effectiveness
  - e.g. RALES
- Equity
- Efficiency
- Timeliness
- Patient-centeredness

Validity

• Internal Validity (believable?)
  – No bias
• External Validity (relevant?)
  – Appropriate sample
• Tradeoff between internal and external validity
Background
Stents useful in PTCA
- Prevented periprocedural vessel recoil and collapse

However, stents were associated with in-stent restenosis due to proliferation of fibrous tissue

DES were developed to decrease this complication

However, reports of DES association with subacute (<=30 days) and late (>30 days) in-stent thrombosis

Unclear about this tradeoff

RCTs powered to show reduction in revascularization, not in-stent thrombosis
Study Design and Methods
Study Design, Setting, and Patients

• Study Design: Observational Study

• The investigators used a 100% national sample of all Part A hospital claims submitted to the Centers for Medicare & Medicaid Services for the 2002-2005 period to identify patients 65 years or older enrolled in traditional, fee-for-service Medicare programs who had received a coronary stent.
  
  o The Part A data contain a record for each Medicare hospitalization that includes unique identifiers for the hospital and patient, the dates of admission and discharge, an admitting diagnosis and priority, procedures performed, and additional diagnoses representing comorbid conditions, among other information.
Study Design, Setting, and Patients

- Patients undergoing a percutaneous coronary intervention with stent placement were identified by the presence of a hospital claim for a bare-metal stent, drug-eluting stent, or both.
  - For analysis purposes, patients coded as having placement of both types of stents during their first PCI hospitalization were classified as having a drug-eluting stent.

- Patients were excluded if:
  1) the admission was emergent as noted on the index claim
  2) a diagnosis code for MI was present on the index claim
  3) they were admitted within 7 days of discharge from a prior hospitalization
  4) they were within 1 year of coronary artery bypass surgery or a prior PCI
  5) they had evidence of bypass graft disease on their index claim to eliminate patients who might have had an intervention on a bypass graft rather than on a native coronary artery.
The bare-metal stent era cohort consisted of 38,917 Medicare patients who underwent nonemergent coronary stenting from October 2002 through March 2003.

The drug-eluting stent era cohort consisted of 28,086 similar patients who underwent nonemergent coronary stenting from September through December 2003, when 61.5% of patients received a drug-eluting stent and 38.5% received a bare-metal stent.

- Because of concerns about the selective use of the CYPHER stent shortly after it had received FDA approval on April 24, 2003, the drug-eluting stent era cohort included patients undergoing stent placement from September 1 through December 31, 2003, by which time drug-eluting stent use had stabilized.
Use of Bare-metal vs. Drug-eluting Stents

Figure 1. Numbers of Medicare Enrollees Undergoing Coronary Stenting, February 2002 through December 2004
Patient Comorbidities

• Using information from the index admission, they identified the following comorbid conditions:
  
  o history of MI
  o congestive heart failure
  o peripheral vascular disease
  o pulmonary disease
  o diabetes without complications
  o diabetes with complications
  o mild liver disease
  o moderate or severe liver disease
  o dementia
  o renal disease
  o nonmetastatic cancer
  o metastatic solid tumor
Outcomes

- Measure of effectiveness: rate of repeat coronary revascularization (PCI or CABG)
  - Only the first subsequent revascularization was counted for each patient

- Outcomes of interest: death and ST-elevation MI
  - To avoid confusing a technical complication of the procedure with an adverse outcome secondary to subacute thrombosis, only patients who survived for at least one day following their procedure were included and in the analysis.

- Follow-up data were available through December 31, 2005 ensuring at least a 2-year follow-up for all patients.
Differences in baseline patient characteristics between the 2 cohorts were assessed using a $\chi^2$ test for categorical variables and a $t$ test for continuous variables. Crude risks of outcomes were compared using a $\chi^2$ test. Crude rates of outcomes were plotted using Nelson-Aelen cumulative hazard estimators. The hazard distributions were compared using the log-rank test.

Propensity scoring was to control for any differences between the population of patients undergoing coronary stenting during the bare-metal stent era (whose only option was a bare-metal stent) and those receiving stents during the drug-eluting stent era (when patients could receive either a bare-metal stent or drug-eluting stent at the discretion of the interventionalist).
Data Analysis II

- They estimated adjusted survival weighting by the propensity score and expressed differences in survival between the 2 cohorts as a hazard ratio with 95% confidence intervals. They repeated the propensity score adjustment using both nearest neighbor matching (with random matching for ties) and stratification matching. They also compared outcomes between the 2 era cohorts using direct adjustment for risk adjusters.

- To determine whether there was an increased risk of death or STEMI for patients who stopped taking their thienopyridine after stent placement, a landmark analysis was performed to examine the adverse event rates for patients who had not died or had a STEMI during the first 3 months following stent placement, the recommended duration of dual antiplatelet therapy in 2003 for patients receiving a sirolimus-eluting stent.
Results
<table>
<thead>
<tr>
<th></th>
<th>Bare-Metal Stent Era (n = 38917)</th>
<th>Drug-Eluting Stent Era (n = 28086)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-eluting stent</td>
<td>0 (0.0)</td>
<td>17273 (61.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>74.7 (5.89)</td>
<td>74.6 (5.84)</td>
<td>.01</td>
</tr>
<tr>
<td>Women</td>
<td>15917 (40.9)</td>
<td>11656 (41.5)</td>
<td>.07</td>
</tr>
<tr>
<td>African American</td>
<td>4320 (11.1)</td>
<td>3174 (11.3)</td>
<td>.51</td>
</tr>
<tr>
<td>History of MI</td>
<td>4047 (10.4)</td>
<td>2949 (10.5)</td>
<td>.82</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3347 (8.6)</td>
<td>2331 (8.3)</td>
<td>.29</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>4553 (11.7)</td>
<td>3342 (11.9)</td>
<td>.48</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>5059 (13.0)</td>
<td>3764 (13.4)</td>
<td>.20</td>
</tr>
<tr>
<td>Dementia</td>
<td>117 (0.3)</td>
<td>112 (0.4)</td>
<td>.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9807 (25.2)</td>
<td>7330 (26.1)</td>
<td>.009</td>
</tr>
<tr>
<td>Liver disease</td>
<td>39 (0.1)</td>
<td>28 (0.1)</td>
<td>.97</td>
</tr>
<tr>
<td>Renal disease</td>
<td>156 (0.4)</td>
<td>84 (0.3)</td>
<td>.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>1635 (4.2)</td>
<td>1123 (4.0)</td>
<td>.18</td>
</tr>
<tr>
<td>Multivessel PCI</td>
<td>6995 (18.0)</td>
<td>5046 (18.0)</td>
<td>.83</td>
</tr>
</tbody>
</table>

Abbreviation: MI, myocardial infarction; PCI, percutaneous coronary intervention.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Bare-Metal Stent Era (n = 38,917)</th>
<th>Drug-Eluting Stent Era (n = 28,086)</th>
<th>P Value</th>
<th>Hazard Ratios (95% Confidence Interval) of Drug-Eluting Stent vs Bare-Metal Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI, mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2569 (6.5)</td>
<td>1939 (6.8)</td>
<td>.05</td>
<td>1.06 (1.00-1.13)</td>
</tr>
<tr>
<td>6</td>
<td>4243 (10.8)</td>
<td>2753 (9.7)</td>
<td>&lt;.001</td>
<td>0.90 (0.86-0.94)</td>
</tr>
<tr>
<td>12</td>
<td>5917 (15.2)</td>
<td>3681 (13.1)</td>
<td>&lt;.001</td>
<td>0.86 (0.83-0.90)</td>
</tr>
<tr>
<td>24</td>
<td>7785 (20.0)</td>
<td>4804 (17.1)</td>
<td>&lt;.001</td>
<td>0.85 (0.82-0.88)</td>
</tr>
<tr>
<td>CABG surgery, mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>272 (0.7)</td>
<td>140 (0.5)</td>
<td>&lt;.001</td>
<td>0.66 (0.53-0.81)</td>
</tr>
<tr>
<td>6</td>
<td>740 (1.9)</td>
<td>281 (1.0)</td>
<td>&lt;.001</td>
<td>0.54 (0.47-0.62)</td>
</tr>
<tr>
<td>12</td>
<td>1129 (2.9)</td>
<td>478 (1.7)</td>
<td>&lt;.001</td>
<td>0.57 (0.51-0.64)</td>
</tr>
<tr>
<td>24</td>
<td>1635 (4.2)</td>
<td>759 (2.7)</td>
<td>&lt;.001</td>
<td>0.64 (0.58-0.69)</td>
</tr>
<tr>
<td>PCI or CABG surgery, mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2803 (7.0)</td>
<td>2051 (7.2)</td>
<td>.40</td>
<td>1.03 (0.97-1.09)</td>
</tr>
<tr>
<td>6</td>
<td>4827 (12.3)</td>
<td>2978 (10.5)</td>
<td>&lt;.001</td>
<td>0.85 (0.82-0.90)</td>
</tr>
<tr>
<td>12</td>
<td>6734 (17.3)</td>
<td>4046 (14.4)</td>
<td>&lt;.001</td>
<td>0.82 (0.79-0.86)</td>
</tr>
<tr>
<td>24</td>
<td>8875 (22.8)</td>
<td>5338 (19.0)</td>
<td>&lt;.001</td>
<td>0.82 (0.79-0.85)</td>
</tr>
</tbody>
</table>

Abbreviations: CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

a Adjusted for age, sex, race, history of myocardial infarction, congestive heart failure, vascular disease, pulmonary disease, dementia, diabetes, liver disease, kidney disease, cancer.
Unadjusted Cumulative Hazard of Repeat Revascularization for Patients Undergoing Coronary Stenting in the Bare-Metal Stent vs. Drug-Eluting Stent Eras

![Graph showing the unadjusted cumulative hazard of repeat revascularization for patients undergoing coronary stenting in the bare-metal stent vs. drug-eluting stent eras. The graph includes a table with the number of patients at risk at different time points: 38,917, 35,610, 33,155, and 30,437 for the bare-metal stent era; 28,086, 25,660, 24,386, and 22,737 for the drug-eluting stent era. The Log-rank test statistic is provided as *P < 0.001.*]
Table 3. Crude Risks and Hazard Ratios of Death and STEMI for Bare-Metal Stent vs Drug-Eluting Stent Eras

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. (%)</th>
<th>Hazard Ratios (95% Confidence Interval) of Drug-Eluting Stent vs Bare-Metal Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bare-Metal Stent Era (n = 38 917)</td>
<td>Drug-Eluting Stent Era (n = 28 086)</td>
</tr>
<tr>
<td>Death, mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>545 (1.4)</td>
<td>393 (1.4)</td>
</tr>
<tr>
<td>6</td>
<td>973 (2.5)</td>
<td>702 (2.5)</td>
</tr>
<tr>
<td>12</td>
<td>1751 (4.5)</td>
<td>1208 (4.3)</td>
</tr>
<tr>
<td>24</td>
<td>3269 (8.4)</td>
<td>2359 (8.4)</td>
</tr>
<tr>
<td>STEMI, mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>350 (0.9)</td>
<td>197 (0.7)</td>
</tr>
<tr>
<td>6</td>
<td>506 (1.3)</td>
<td>281 (1.0)</td>
</tr>
<tr>
<td>12</td>
<td>701 (1.8)</td>
<td>393 (1.4)</td>
</tr>
<tr>
<td>24</td>
<td>934 (2.4)</td>
<td>562 (2.0)</td>
</tr>
<tr>
<td>Death or STEMI, mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>856 (2.2)</td>
<td>534 (1.9)</td>
</tr>
<tr>
<td>6</td>
<td>1401 (3.6)</td>
<td>927 (3.3)</td>
</tr>
<tr>
<td>12</td>
<td>2296 (5.9)</td>
<td>1489 (5.3)</td>
</tr>
<tr>
<td>24</td>
<td>3931 (10.1)</td>
<td>2696 (9.6)</td>
</tr>
</tbody>
</table>

Abbreviation: STEMI, ST-elevated myocardial infarction.

<sup>a</sup> Adjusted for age, sex, race, history myocardial infarction, congestive heart failure, vascular disease, pulmonary disease, dementia, diabetes, liver disease, kidney disease, cancer.
A Landmark Analysis of the Unadjusted Cumulative Hazard of Death or ST-Elevation Myocardial Infarction for Patients Undergoing Coronary Stenting in the Bare-Metal stent vs. Drug-Eluting Stent Eras Among Patients Who Were Event-Free for 3 Months Following Their Initial Stent Procedure
Conclusions
Study Conclusions

• “The widespread adoption of drug-eluting stents into routine practice was associated with a decline in the need for repeat revascularization procedures and had similar 2-year risks for death or ST-elevation myocardial infarction to bare-metal stents.”
Revascularization Rates

• Smaller difference than previously reported in RCT
  – Only 61% pts received DES
  – No true assessment of revascularization
  – Lack of angiographic criteria/Off-label use
  – Financial incentive for incremental use
  – Use of sirolimus eluting (Cypher) stents only

• Similar to findings of other observational studies
Inferred Conclusions?

• “We speculate that whatever the increased risk of stent thrombosis associated with drug-eluting stent use is, it is more than offset by a decrease in the risk of developing restenosis and the attendant risk of a procedure to treat that restenosis”
Cohort Selection

- Why not compare DES to BMS in the DES era?
  - Increased death rates with BMS immediately following release of DES, implies confounding

- Possible confounders:
  - Better health of DES pts
  - High volume/quality centers adopted DES earlier
Mortality and ST-Elevation Myocardial Infarction Rates for Patients Receiving Bare-Metal Stents vs. Drug-Eluting Stents

Malenka, D. J. et al. JAMA 2009;301:34.
Strengths / Weaknesses
Strengths

• Has sufficient power to detect difference in outcomes due to stent thrombosis; moreso than prior RCTs

• Used Medicare patients—large number / inclusive

• Better reflect on-label and off-label stent use as seen in real-life practice

• Answers whether this new technology, on average, is hurting patients
Weaknesses

• Observational study → potential biases:
  – Unobserved differences in case mix
  – Differences in coronary anatomy in bare-metal vs. DES
  – Changes in perioperative or post-procedural care over time period
  – Changes in threshold of when patients received a stent
  – Difficult to establish causality due to study design
Weaknesses

- Lack of specific data on cardiac catheterizations involved, which could have revealed selection bias on those receiving DES vs. bare metal
- Factors contributing to outcomes:
  - Procedural characteristics (e.g. completeness of revascularization)
  - Use of antiplatelet agents
  - Improved overall quality of cardiovascular care
  - Change in physicians’ practices? (increased PCI)
    - PCI to lesions at low risk for restenosis/adverse events
    - Multivessel stenting (at high risk for restenosis/adverse events)
Weaknesses

- Limited to sirolimus-eluting stent (not paclitaxel-eluting stent)
- Direct attribution of death and MI to stent thromboses difficult
- Doesn’t tell us the true rate of stent thrombosis in bare-metal vs. DES