Pros and Cons of Noninferiority Trials: The Case of CVOT in CKD-Anemia

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Disclosure Slide

• I am NOT a trial statistician
• Salary mostly supported from federal grants
• Balance of salary from clinical work and endowed Gordon A. Cain Chair in Nephrology
• Advisory Boards/Consultancies (Akebia/Otsuka, AstraZeneca, Bayer, GlaxoSmithKline, Janssen, Merck, Pharmacosmos, Reata, Relypsa)
• Associate Editor, JAMA (stipend)
• Co-Chair, Kidney Disease: Improving Global Outcomes (unpaid)
History of CKD-Anemia Treatment

- 1906: existence of *hémopoïétine* postulated (Paul Carnot)
- 1968: Goldwasser & Kung purified EPO from sheep urine; succeeded after 9 years (1977)
- 1970s: John Adamson and Joseph W. Eschbach established clinical potential
- 1985: EPO gene isolated and cloned (Jacobs; Lin)
- rhEPO synthesis patented at Columbia University and licensed to Amgen
History of CKD-Anemia Treatment

Recombinant human erythropoetin

• Eschbach et al: *NEJM* 1987; 316:73 (Phase I-II)

  – Phase III study – single arm evaluation
    • 333 patients on maintenance hemodialysis
    • In: Hematocrit <0.30; clinically stable; iron replete
    • Out: poorly controlled hypertension (dBP>100 mmHg)
    • Starting dose of 300 (150) U/kg
    • Titrate dose to target hematocrit 0.32-0.38

Recombinant human erythropoietin

Figure 1. The mean hematocrit values at biweekly intervals for 35 patients receiving 300 U rHuEpo/kg body weight (circles) or 201 patients receiving 150 U (diamonds) rHuEpo/kg. The rHuEpo was given intravenously three times per week.

Figure 2. Transfusion requirements (units/patient) per month for 6 months before initiation of rHuEpo therapy (pre) and at 4-week intervals thereafter. At week 52, one patient autodonated three units in the previous month for elective hip surgery.

Recombinant human erythropoietin

Other desired outcomes:
- Reduced iron overload (ferritin: 962→628 μg/L; TSAT: 41→30%)
- Significant improvements (observed up to 10 months) in
  - physical functioning (Karnowsky),
  - activity level,
  - energy level
  - Nottingham health profile scores

Adverse events (within 3 months):
- Increase in BP (35% had dBP increased by >10 mmHg or required increase in antihypertensive medications)
- Seizures (5.4%)
- Iron deficiency (43% developed ferritin <30 μg/L or TSAT <20%)

Recombinant human erythropoietin

Value proposition:
• reduction of transfusion rates (shown),
• improvement of hrQoL (maybe)
• reduction in CV morbidity/mortality (proposed),
• [reduction in immune-sensitization of kidney transplant candidates (suggested much later)]

US FDA approved epoetin alfa on June 1, 1989
Anemia Targets and CV Outcomes

Testing the hypothesis that treating anemia (using ESAs) more aggressively improves hard (cardiovascular) endpoints.

Using **superiority trial designs**

\[ H_0: \text{Treatments A and B (or placebo) yield outcomes that are statistically not different} \]

\[ H_A: \text{Treatment A yields better (or worse) outcomes than Treatment B (placebo) at a statistical significance threshold, usually p<0.05} \]
Anemia Targets and CV Outcomes

- “Normal hematocrit study”
- 1233 patients, HD, w/ CHF or IHD
- Randomized to hematocrit target 0.30 vs. 0.42
- Primary endpoint: death or nonfatal MI

Anemia Targets and CV Outcomes

Stopped early for futility.
RR: 1.3 (95% CI: 0.9-1.9)
Increased risk of HD vascular access thrombosis in normal-hematocrit group (39% vs. 29%; p<0.001).

Anemia Targets and CV Outcomes

Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta – CREATE

603 patients w/ CKD eGFR 15-35 mL/min/1.73 m²
Randomized to hemoglobin target of 11-12.5 vs. 13-15 g/dL

Primary endpoint: composite CV endpoint (sudden death, MI, stroke/TIA, acute HF, hospitalized arrhythmia, hospitalized angina, PVD w/ necrosis or requiring amputation)

Drueke et al. NEJM 2006; 335:2071
Anemia Targets and CV Outcomes

Primary CV Composite:
HR, 0.78; 95% CI, 0.53 to 1.14; adjusted P = 0.20
Results robust when censoring for initiation of dialysis.

Drueke et al. NEJM 2006; 335:2071
Anemia Targets and CV Outcomes

Correction of Hemoglobin and Outcomes in Renal Insufficiency – CHOIR

1432 patients w/ CKD eGFR 15-50 mL/min/1.73 m²
Randomized to hemoglobin target of 10.5-11 vs. 13-13.5 g/dL (amended to 11.3 vs. 13.5 g/dL)
Primary endpoint: composite CV endpoint (death, MI, stroke, hospitalization for heart failure).

Singh et al. *NEJM* 2006; 335:2085
Anemia Targets and CV Outcomes

Stopped early for lack of conditional power.
Primary CV Composite:
HR, 1.34; 95% CI, 1.03 to 1.74; P = 0.03

Singh et al. *NEJM* 2006; 335:2085
Regulatory Action

BLACK BOX
Regulatory Action

• Black Box (9/3/2007) and other label updates
• CRDAC (9/11/2007)
  – Voted against market withdrawal for epoetin alfa and darbepoetin alfa (approved in 2001)
  – Deferred any recommendation for action until data from ongoing TREAT would be available
• Quiet (?) shift in approach by FDA towards additional requirements for innovators in CKD anemia space
  – Registrational evidence solely focusing on anemia treatment/control no longer sufficient (inference)
  – CVOTs now appear required for NDAs in CKD-anemia (at least broadly for ESAs; apparently not for iron treatments)
Anemia Treatment and CV Outcomes

Trial to Reduce Cardiovascular Events with Aranesp Therapy – TREAT (darbepoetin alfa)

4038 patients w/ CKD (eGFR 20-60 mL/min/1.73 m^2), type 2 DM, anemia (hemoglobin <10.5 g/dL)

Randomized to darbepoetin treatment w/ target of 13 g/dL vs. placebo w/ rescue at hemoglobin <9 g/dL

Co-primary endpoints:

A) composite CV endpoint (death, stroke, HF, MI, hospitalized myocardial ischemia);
B) death or time to renal replacement therapy

Pfeffer et al. NEJM 2009; 361:2019
Anemia Treatment and CV Outcomes

Pfeffer et al. *NEJM* 2009; 361:2019
## Anemia Treatment and CV Outcomes

**Table 2. Composite and Component End Points.**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Darbepoetin Alfa (N=2012)</th>
<th>Placebo (N=2026)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end points</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cardiovascular composite end point;‡</td>
<td>632 (31.4)</td>
<td>602 (29.7)</td>
<td>1.05 (0.94–1.17)</td>
<td>0.41</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>412 (20.5)</td>
<td>395 (19.5)</td>
<td>1.05 (0.92–1.21)</td>
<td>0.48</td>
</tr>
<tr>
<td>Myocardial infarction§</td>
<td>124 (6.2)</td>
<td>129 (6.4)</td>
<td>0.96 (0.75–1.22)</td>
<td>0.73</td>
</tr>
<tr>
<td>Stroke§</td>
<td>101 (5.0)</td>
<td>53 (2.6)</td>
<td>1.92 (1.38–2.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure§</td>
<td>205 (10.2)</td>
<td>229 (11.3)</td>
<td>0.89 (0.74–1.08)</td>
<td>0.24</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>41 (2.0)</td>
<td>49 (2.4)</td>
<td>0.84 (0.55–1.27)</td>
<td>0.40</td>
</tr>
<tr>
<td>Renal composite end point (ESRD or death)</td>
<td>652 (32.4)</td>
<td>618 (30.5)</td>
<td>1.06 (0.95–1.19)</td>
<td>0.29</td>
</tr>
<tr>
<td>ESRD</td>
<td>338 (16.8)</td>
<td>330 (16.3)</td>
<td>1.02 (0.87–1.18)</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Additional adjudicated end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>259 (12.9)</td>
<td>250 (12.3)</td>
<td>1.05 (0.88–1.25)</td>
<td>0.61</td>
</tr>
<tr>
<td>Cardiac revascularization</td>
<td>84 (4.2)</td>
<td>117 (5.8)</td>
<td>0.71 (0.54–0.94)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* ESRD denotes end-stage renal disease.
† P values have not been adjusted for multiple comparisons.
‡ A patient may have had multiple cardiovascular events of different types. The cardiovascular composite end point reflects only the first occurrence of any of the components.
§ This category includes both fatal and nonfatal events.

Pfeffer et al. *NEJM* 2009; 361:2019
Anemia Treatment and CV Outcomes

• TREAT was the first placebo-controlled CVOT for an ESA to treat CKD-anemia
  – Superiority design (failed to reject the $H_0$)
  – Lots of regulatory response (not covered today)

• Subsequent trials of INDs used non-inferiority designs
  – Paradigm shift
  – Design insufficiently understood by many
Noninferiority Trials

• Test whether a Treatment A is not unacceptably worse relative to an outcome of interest compared with a Treatment B.
  – “The intent of an NI trial, however, is not to show that the new drug is equivalent, but rather that it is not materially worse than the control.” -- FDA
  – Do not per se determine better or worse

Anonymous. FDA, CDER, CBER, 2016
Superiority vs. Noninferiority Trials

Figure 1. Possible Results of a Placebo-Controlled Superiority Study (Point Estimate and 95% Confidence Interval (CI))

Favors Placebo (control drug) → Favors Test drug

Figure 2. Possible Results of an NI Study Showing Control Drug–Test Drug Differences (Point Estimate and 95% CI)

Favors Test drug ← M1 → Favors Control drug

(1-6)
Superiority vs. Noninferiority Trials

- Superiority trials are straightforward to interpret.
- The null value is fixed
- Rejection of $H_0$ and acceptance of $H_A$ if $p<0.05$.
- Biases limited and usually towards the null (conservative bias).
Superiority vs. Noninferiority Trials

Figure 1. Possible Results of a Placebo-Controlled Superiority Study (Point Estimate and 95% Confidence Interval (CI))

Figure 2. Possible Results of an NI Study Showing Control Drug–Test Drug Differences (Point Estimate and 95% CI)

Favors Placebo  ←  Favor Test drug

Favors Test drug  ←  Favors Control drug

Anonymous. FDA, CDER, CBER, 2016
Superiority vs. Noninferiority Trials

- Noninferiority trials are not straightforward to interpret.
- How to determine the non-inferiority margin, $M_1$?
- Noninferiority $p<0.05$ (95% CI does not cross $M_1$) needs to be interpreted in light of key assumptions.
- Biases usually directed towards increased likelihood of (inappropriately) accepting noninferiority (nonconservative bias).
Superiority vs. Noninferiority Trials

Example 1: Inclusion of types of events that cannot plausibly be affected by treatment.

E.g., accidental death (MVA, GS, drug overdose, brick falling from roof)

Question for today: might anemia treatment A vs. B reduce accidental death? (Not plausibly)

Impact of inclusion of accidental death in composite endpoint (remember -- occurs at similar rates in both arms):

**Superiority trial:** fewer events that might be affected by treatment get counted => dilution of power, effect estimate pulled towards the null (not desirable for anyone; conservative bias ↑ false negative conclusion).

**Noninferiority trial:** fewer events that might be affected by treatment get counted => augmentation of power, effect estimate, CI get pulled towards the null (not desirable for some; non-conservative bias; ↑ false positive conclusion).
Superiority vs. Noninferiority Trials

Example 2: Inclusion of timing of events that cannot plausibly be affected by treatment.
E.g., including events long after treatment discontinuation or crossover
Question for today: might treatment A vs. B reduce (CV) events weeks or months after assigned treatment was discontinued? (Maybe? Or not?)
Impact of inclusion of (CV) events that occurred long after treatment discontinuation. What if this occurs at dissimilar rates between arms?
Superiority trial: fewer events get counted during time periods when a treatment effect is plausible => dilution of power, effect estimate pulled towards the null (not desirable for anyone, conservative bias, ↑ false negative conclusion).
Noninferiority trial: fewer events get counted during time periods when there is a plausible treatment effect => augmentation of power, effect estimate pulled towards the null (not desirable, non-conservative bias; ↑ false positive conclusion).
Superiority vs. Noninferiority Trials

What if discontinuation rates are high and different between treatments?
Bad! But ‘badder’ for NI trials.

ITT a useful fix (and gold standard) for superiority trials
ITT not a fix for noninferiority trials.
On treatment? OT +7? OT +28?
Back to Anemia Trials
Peginesatide

ORIGINAL ARTICLE

Peginesatide in Patients with Anemia Undergoing Hemodialysis

Steven Fishbane, M.D., Brigitte Schiller, M.D., Francesco Locatelli, M.D., Adrian C. Covic, M.D., Ph.D., Robert Provenzano, M.D., Andrzej Wieczek, M.D., Ph.D., Nathan W. Levin, M.D., Mark Kaplan, M.D., Iain C. Macdougall, M.D., Carol Francisco, Ph.D., Martha R. Mayo, Pharm.D., Krishna R. Polu, M.D., et al., for the EMERALD Study Groups*

ORIGINAL ARTICLE

Peginesatide for Anemia in Patients with Chronic Kidney Disease Not Receiving Dialysis

Iain C. Macdougall, M.D., Robert Provenzano, M.D., Amit Sharma, M.D., Bruce S. Spinowitz, M.D., Rebecca J. Schmidt, D.O., Pablo E. Pergola, M.D., Ph.D., Raja I. Zabaneh, M.D., Sandra Tong-Starksen, M.D., Martha R. Mayo, Pharm.D., Hong Tang, M.S., Krishna R. Polu, M.D., Anne-Marie Duliege, M.D., et al., for the PEARL Study Groups*

CV Composite: death, MI, stroke, HF, angina, arrhythmia

$M_1$: HR=1.3

Peginesatide

EMERALD and PEARL pooled

EMERALD pooled

PEARL pooled

Peginesatide

- FDA approved 3/26/2012, for CKD on dialysis
- Broad rollout of the drug in the FMC-NA dialysis network in the fall of 2012

Anaphylaxis and Hypotension after Administration of Peginesatide

This letter describes serious adverse events (three fatal cardiorespiratory arrests and two grade 4 anaphylaxis and hypotension events) related to the administration of peginesatide during surveillance in patients undergoing dialysis. As a result, the drug was removed from the market.
Roxadustat (FG-4592) for the Treatment of Anemia in Patients with Chronic Kidney Disease (CKD)

July 15, 2021
FibroGen
Cardiovascular and Renal Drugs Advisory Committee

CV Composite: death, MI, stroke
$M_1: \text{HR}_{\text{FDA}} = \text{N.D.}; \text{HR}_{\text{EMA}} = 1.3$
Roxadustat

NDD and NDD-ND (Censored at Dialysis): MACE Comparable for Roxadustat and Placebo

CO-71

DD: Proportion of Patients Without MACE Comparable Between Groups

CO-77

NDD and NDD-ND: MACE+ and Components 95% CIs Cross 1.0

CO-72

DD: Incidence of MACE+ Components Comparable to Epoetin Alfa

CO-78

Fibrogen Slides for FDA CRDAC July 15 2021
FDA Committee Votes Against Approval of Roxadustat for Anemia of Chronic Kidney Disease

WEDNESDAY, SEPTEMBER 1, 2021

The FDA’s Cardiovascular and Renal Drugs Advisory Committee (CRDAC) has decided not to recommend the approval of roxadustat for the treatment of patients with chronic kidney disease-related anemia. The panel voted 13 to one against approving the treatment for patients who are not on dialysis and voted 12 to two against its approval for dialysis-dependent patients.

Healthcare & Pharmaceuticals

U.S. FDA declines to approve FibroGen's anemia drug

Reuters

After FDA snub, EMA backs FibroGen, Astellas’ roxadustat

Phil Taylor

August 20, 2021

The EU regulator has approved FibroGen and Astellas Evrenzo for adults with anaemia caused by chronic kidney disease (CKD), just days after the FDA turned down the drug in the US.
Vadadustat

Safety and Efficacy of Vadadustat for Anemia in Patients Undergoing Dialysis


Vadadustat in Patients with Anemia and Non–Dialysis-Dependent CKD


CV Composite: death, MI, stroke
M1: HRF DA =1.25

Vadadustat (CKD-DD)

Hazard ratio, 0.96 (95% CI, 0.83–1.11)
*P* = 0.5 by log-rank test stratified according to trial

<table>
<thead>
<tr>
<th>Months since Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
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<tr>
<td>0</td>
</tr>
</tbody>
</table>

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Vadadustat</th>
<th>Darbepoetin alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1947</td>
<td>1881</td>
<td>1883</td>
</tr>
<tr>
<td>1810</td>
<td>1615</td>
<td>1607</td>
</tr>
<tr>
<td>1372</td>
<td>1040</td>
<td>1053</td>
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<tr>
<td>711</td>
<td>491</td>
<td>491</td>
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<td>262</td>
<td>89</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td></td>
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</table>

*Eckardt KU, et al NEJM 2021; 384:1601*
### INNO2VATE MACE, Expanded MACE & Other Safety Endpoints

<table>
<thead>
<tr>
<th>Safety Endpoint</th>
<th>Vadadustat (n/N)</th>
<th>Darbepoetin Alfa (n/N)</th>
<th>Treatment Comparison Vadadustat/Darbepoetin Alfa</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>355/1947</td>
<td>377/1955</td>
<td></td>
<td>0.96 (0.83, 1.11)</td>
</tr>
<tr>
<td>Expanded MACE(^a)</td>
<td>420/1947</td>
<td>449/1955</td>
<td></td>
<td>0.96 (0.84, 1.10)</td>
</tr>
<tr>
<td>Cardiovascular MACE(^b)</td>
<td>225/1947</td>
<td>242/1955</td>
<td></td>
<td>0.95 (0.80, 1.14)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>150/1947</td>
<td>160/1955</td>
<td></td>
<td>0.96 (0.77, 1.20)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>291/1947</td>
<td>310/1955</td>
<td></td>
<td>0.95 (0.81, 1.12)</td>
</tr>
</tbody>
</table>

\(^a\) Not adjusted for baseline platelet count
\(^b\) Benchmark event as MACE in primary analysis

**Favors Vadadustat**

**Favors Darbepoetin Alfa**
Vadadustat (CKD-NDD)

Chertow GM, et al NEJM 2021; 384:1589
Vadadustat (CKD-NDD)

PRO2TECT MACE, Expanded MACE and other Safety Endpoints

<table>
<thead>
<tr>
<th>Safety Endpoint</th>
<th>Vadadustat (n/N)</th>
<th>Darbepoetin Alfa (n/N)</th>
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<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>382/1739</td>
<td>344/1732</td>
<td></td>
<td>1.17 (1.01, 1.36)</td>
</tr>
<tr>
<td>Expanded MACE\textsuperscript{a}</td>
<td>451/1739</td>
<td>424/1732</td>
<td></td>
<td>1.11 (0.97, 1.27)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>319/1739</td>
<td>307/1732</td>
<td></td>
<td>1.09 (0.93, 1.27)</td>
</tr>
<tr>
<td>Cardiovascular MACE\textsuperscript{b}</td>
<td>198/1739</td>
<td>178/1732</td>
<td></td>
<td>1.16 (0.95, 1.42)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>127/1739</td>
<td>131/1732</td>
<td></td>
<td>1.01 (0.79, 1.29)</td>
</tr>
</tbody>
</table>

\textit{Age as a dichotomous variable in the Cox model}

ASN Kidney Week 2020
Daprodustat

Daprodustat for the Treatment of Anemia in Patients Undergoing Dialysis


Daprodustat for the Treatment of Anemia in Patients Not Undergoing Dialysis


CV Composite: death, MI, stroke

M₁: HR_FDA = 1.20 (amended to 1.25)

and DOI: 10.1056/NEJMoa2113380
Daprodustat (CKD-NDD)

CV MACE: 11.0% dapro vs. 10.0% darbepoetin alfa. Hazard ratio 1.11 (0.91, 1.35)

Singh AK, et al NEJM 2021; published online ahead of print, Nov 5 2021
CV MACE: 15.2% dapro vs. 17.4% ESA control. Hazard ratio 0.86 (0.72, 1.03)

Singh AK, et al NEJM 2021; published online ahead of print, Nov 5 2021
Conclusion

• Noninferiority trials are more difficult to interpret
• Valid inference can be jeopardized by inclusion of events that are
  – Implausibly affected by treatment
  – Occur (long) after treatment has been discontinued
• Particular challenge when treatment discontinuation is high and, especially, when differential between randomized groups
• ITT is not a fix and may make things even worse
• The noninferiority margin $M_1$ becomes less relevant
• Acceptance of noninferiority spuriously optimistic
• And remember in the special case of CKD-anemia trials: standard of care has a Boxed Warning
Have fun and be controversial

Thank you