NON-RENAL OUTCOMES IN RENAL TRIALS

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Disclosure of Interests

- Ionis Pharmaceuticals - consultancy
- Bayer - consultancy
- Abbott Diagnostics – research grant (in-kind)
Overview

• Why non-renal outcomes?
• General considerations
• Composite outcomes
• Surrogate outcomes
Why non-renal outcomes?

CKD / ESRD / Transplant / Autoimmune kidney disease

- Anemia
- Arrhythmia
- Coronary disease
- Heart failure
- Infections
- Mineral bone disease
- Relapses of autoimmune disease
- Strokes
- Uremia and side effects

Reduced Quantity and Quality of Life
Fit for Purpose Outcomes

• How is the intervention expected to help?
  – Knowledge / model of disease process
  – Knowledge / model of action of intervention

• What is the purpose of the trial?
  – Understand mechanism?
  – Understand if likely worth proceeding development?
    • Expected biological effect? Safe? Patients able to take?
  – Understand patient-important benefits?
What is the purpose of the trial?

Balancing biological effects with unequivocally patient-important effects

Other causes that diminish the role (and effect) of intended treatment

- Cause specific non-fatal events
- Cause specific mortality
- Overall Mortality

(Putative) biology of disease

- Disease specific symptoms
- Relevant HRQoL Domain
- Overall HRQoL
PATHOPHYSIOLOGY OF CKD-MBD

Causes of cardiovascular disease in chronic kidney disease

- Cardiomyopathy
- Vasculopathy

Left ventricular pressure overload
- Maladaptive left ventricular hypertrophy, myocyte death
  - Heart failure

Left ventricular volume overload
- Critical stenosis of large vessels
  - Ischemic heart disease, peripheral vascular disease, cardiovascular disease
  - Heart failure, ischemic heart disease
  - Cardiac arrest

Atherosclerosis
- Arteriosclerosis

Dilation, noncompliance of conduit vessels

Bone pain, fractures, increased cardiovascular mortality

Source: South Med J © 2012 Lippincott Williams & Wilkins
Fit for Purpose Outcomes

• Criticisms
  – Lots of assumptions in causal model
  – Impact of components of model on quantity and quality of life suspect
  – Robust association between high PO4 and death (25% increase risk of death)
  – Simpler to look for effect on death from any cause
Effect of “noise” events

• Assume:
  – 10/100 per year death rate
    • 50% CV deaths = 5/100 per year
      – 50% of CV death due to MBD = 2.5/100 per year
        » Intervention reduces MBD death rate 50% = 1.25/100 deaths per year avoided
          » RRR on MBD = 50%
          » RRR on all cause death = 12.5%
Effect of “noise” events

• All-cause death outcome
  – Control group = 10 events per 100 patient years
  – Treatment group = 8.75 events per 100 patient years
  – Alpha 0.05, power 80%
  – 17,070 participants
    • Total 1,280 events
Effect of “noise” events

• CV death outcome
  – Control group = 2.5 events per 100 patient years
  – Treatment group = 1.25 events per 100 patient years
  – Alpha 0.05, power 80%
  – 3,700 participants
  • Total of 70 events
Key points

• Choose event definitions that are:
  – Responsive to treatment
  – Appropriate for goal of trial
• More events only useful if right type of events
• Large trials with carefully considered event definitions highest probability of reliably identifying treatments with patient important benefits
Composite Outcomes
Composite Outcomes

• Participant considered to reach the outcome when any one of a number of events occur

• Potential Uses
  – Power
  – Avoid complexity
  – Competing risks
Composite Outcomes

• Potential problems
  – Differing treatment effects → reduced power
  – Differing patient importance → difficult interpretation
Composite Outcomes

• User’s Guide to choosing components
  – Similar treatment effect
  – Similar importance (to patients)
  – Similar rates

Potential Problems

• POISE trial
  – Perioperative metoprolol vs placebo in non-cardiac surgery
  – 8,351 participants
  – Hypothesized metoprolol reduced fatal and non-fatal cardiovascular events after surgery
**Potential Problems - POISE**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Metoprolol (n=4174)</th>
<th>Placebo (n=4177)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary (CV death, non-fatal MI, non-fatal stroke)</td>
<td>243 (5.8%)</td>
<td>290 (6.9%)</td>
<td>0.83 (0.70 – 0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>151 (3.6%)</td>
<td>215 (5.1%)</td>
<td>0.70 (0.56 – 0.86)</td>
<td>0.0007</td>
</tr>
<tr>
<td>CV death</td>
<td>75 (1.8%)</td>
<td>58 (1.4%)</td>
<td>1.30 (0.92 – 1.83)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Interaction p = 0.002

Choosing Components

(Putative) biology of disease

Cause specific non-fatal events

Cause specific mortality

Overall Mortality

Other causes that diminish the role (and effect) of intended treatment

Lipid metabolism

Atherosclerosis

Angina

Myocardial Infarction

Ischemic stroke

CHF

Arrhythmia

CV death

Revascularization
Choosing Components

(Putative) biology of disease → Cause specific non-fatal events → Cause specific mortality → Overall Mortality

Other causes that diminish the role (and effect) of intended treatment

Lipid metabolism
Atherosclerosis

Angina
Myocardial Infarction
Ischemic stroke
Revascularization

CHF
Arrhythmia
CV death
Key points

• Several reasons to consider composite outcomes
  – Feasibility
  – Improved signal to noise

• Each component should be “fit for purpose” as stand alone

• Classification of sub-classes of events may be difficult and introduce measurement error
Biomarker and Surrogate Outcomes
Definitions

• Patient Important Outcome
  – Variable that reflects how the patient feels functions or survives (something meaningful to patients)

• Surrogate Outcome:
  – Variable which predicts clinical benefit (or harm) based on epidemiologic, therapeutic or scientific evidence

• Biomarkers and correlates:
  – Associated with the clinical endpoint but does not necessarily modify predictably with intervention

Evidence Hierarchy

- Patient Important Endpoint
- Surrogates
- Clinical Correlates
- Non-patient important endpoints
Why Use a Surrogate?

- Shorter follow-up time
- Easier to measure
- Rare disease prevalence
- Smaller sample sizes
- Cost
- Feasibility
Why use a surrogate?

<table>
<thead>
<tr>
<th>Study</th>
<th>True Endpoint</th>
<th>Surrogate Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>Death 4,000</td>
<td>Vessel Flow 200</td>
</tr>
<tr>
<td>MI</td>
<td>Death 4,000</td>
<td>EF 30</td>
</tr>
<tr>
<td>Stroke</td>
<td>Stroke 25,000</td>
<td>DBP 200</td>
</tr>
</tbody>
</table>

Proposed Role of Surrogates

Scientific Discovery

Clinical Practice

Conclusions

Established Surrogate

RCT

Clinical Outcomes

Candidate Surrogate

Conclusions

RCT 2:
New Therapy

KDIGO Controversies Conference on Challenges in the Conduct of Clinical Trials in Nephrology
September 8-11, 2016 | Paris, France
Limitations of Surrogates

• Validation requires demonstration of patient-important effect
  – How many treatments are we confident have patient important benefits?
• Typically only predicts one outcome
  – Limits assessment of other outcomes
• Extrapolation beyond drug and disease validation can be misleading
  – E.g. bone mineral density and fluoride
Key points

• Valid surrogate endpoints could speed development
  – Need to acknowledge serious limitations

• Areas with accepted surrogates still tend to do large trials with clinical outcomes
Conclusions

• Outcome should reflect
  – Plausible pathways
  – Goal of trial

• Careful consideration required
  – Substantial unknowns

• Large trials needed to address patient-important problems and uncertainty in outcome selection / definitions
YOU MUST CHOOSE...

BUT CHOOSE WISELY.
Discussion