Are There MACE-Specific Endpoints That Should Be Considered?

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Disclosures

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• No commercial interests
Overview

• The traditional MACE endpoint
• Qualities of an ideal COPD-specific MACE endpoint for cardiac safety
• Cardiovascular Endpoints Reported in Selected recent COPD clinical trials
• Possible components of a COPD-specific MACE endpoint
Traditional MACE Endpoint

• Cardiovascular death
• Myocardial infarction
• Stroke
• All probably required for COPD trials
  – Even in absence of *a priori* mechanistic association between drug and outcome
  – Multiple common risk factors for CAD and COPD
The Ideal COPD-Specific MACE Cardiovascular Endpoint

- A composite endpoint is only as strong as its weakest component
- Clinical significance of components should be at least comparable
- Components should be reasonably simple to adjudicate
  - Unlikely to overlap much with primary efficacy endpoints in COPD trials
Cardiovascular Outcomes Reported in selected COPD Clinical Trials

...but not necessarily adjudicated
TORCH: Salmeterol/Fluticasone

Reported

• Only cardiovascular death reported in primary manuscript
• No other cardiovascular events specified in published protocol
• No routine ECG monitoring specified

Collected

Cardiovascular events
- Cardiac disorders (SOC)
  - Coronary artery disorders
  - Cardiac arrhythmias
  - Heart failures
  - Cardiac disorder signs and symptoms
  - Myocardial disorders
  - Cardiac valve disorders
  - Pericardial disorders
- Nervous system disorders (SOC)
  - Central nervous system vascular disorders
- Vascular disorders (SOC)
  - Arteriosclerosis, stenosis, vascular insufficiency and necrosis
  - Aneurysms and artery dissections
  - Embolism and thrombosis

Ischaemic events
- Ischaemic coronary artery disorders
- Coronary artery disorders NEC
- Heart failures NEC
- Right ventricular failures
- Left ventricular failures
- Cardiomyopathies
- Pericardial disorders NEC
- Non-infectious pericarditis

Stroke events
- Central nervous system vascular disorders (HLGT)

Cardiovascular medications
- ACE inhibitors
- Angiotensin II antagonists
- Antihypertensives
- Beta blockers
- Calcium channel blockers
- Antiarrhythmics
- Cardiac glycosides
- Adrenergic and dopaminergic agents
- Organic nitrates

NEC, not elsewhere classified.

Calverley PMA et al., NEJM 2007; 356:775  Calverley PMA et al., Thorax 2010; 65:719
# UPLIFT: tiotropium v. placebo

**Table 4. Incidence Rate of Serious Adverse Events per 100 Patient-Years.**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Tiotropium (N = 2986)</th>
<th>Placebo (N = 3006)</th>
<th>Relative Risk for Tiotropium vs. Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>3.56</td>
<td>4.21</td>
<td>0.84 (0.73–0.98)†</td>
</tr>
<tr>
<td>Angina</td>
<td>0.51</td>
<td>0.36</td>
<td>1.44 (0.91–2.26)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.74</td>
<td>0.77</td>
<td>0.95 (0.68–1.33)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>0.61</td>
<td>0.48</td>
<td>1.25 (0.84–1.87)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.29</td>
<td>0.48</td>
<td>0.59 (0.37–0.96)†</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0.21</td>
<td>0.37</td>
<td>0.58 (0.33–1.01)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.69</td>
<td>0.97</td>
<td>0.71 (0.52–0.99)†</td>
</tr>
<tr>
<td>Lower respiratory</td>
<td>11.32</td>
<td>13.47</td>
<td>0.84 (0.77–0.92)†</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>0.37</td>
<td>0.31</td>
<td>1.20 (0.73–1.98)</td>
</tr>
<tr>
<td>COPD exacerbation</td>
<td>8.19</td>
<td>9.70</td>
<td>0.84 (0.76–0.94)†</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0.38</td>
<td>0.62</td>
<td>0.61 (0.40–0.94)†</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3.28</td>
<td>3.46</td>
<td>0.95 (0.81–1.11)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>0.90</td>
<td>1.31</td>
<td>0.69 (0.52–0.92)†</td>
</tr>
</tbody>
</table>

Tashkin DP et al., *NEJM* 2008; 359:1543
### ACCLAIM: aclidinium v. placebo

#### Table 5 Patients with ≥2 possible anticholinergic adverse events in any group in ACCLAIM/COPD I or ACCLAIM/COPD II (by system organ class and preferred term)

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Adverse event preferred term</th>
<th>ACCLAIM/COPD I</th>
<th>ACCLAIM/COPD II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Acldinum 200 µg (n = 627) n (%)</td>
<td>Placebo (n = 216) n (%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Atrial fibrillation</td>
<td>3 (0.5)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td></td>
<td>Atrial flutter</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Sinus tachycardia</td>
<td>2 (0.3)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
<td>3 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Ventricular extrasystoles</td>
<td>1 (0.2)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Dry eye</td>
<td>1 (0.2)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Eye irritation</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Eye pain</td>
<td>3 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Vision blurred</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Visual acuity reduced</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Constipation</td>
<td>4 (0.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>6 (1.0)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Urinary tract infection</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Jones PW et al., Respir Res 2011; 12:55
Meta-Analyses

Singh S. et al., JAMA 2008; 300:1439

Celli B. et al., Chest 2010; 137:20
Toward a CV-MACE Endpoint for COPD

- Cardiovascular death, MI, stroke
  - Probably required for COPD even in absence of *a priori* concern for association between the investigational drug and the endpoint

- Right heart failure, pulmonary hypertension
  - Logical cardiovascular outcomes in lung disease
  - ...but may be more complex to define

- ECG changes & arrhythmias
  - Important and relevant to COPD
  - Variable significance relative to death or ischemic events
  - Would need careful attention to adjudication and identifying “major” events

- We have focused mainly on inhaled beta agonists & anticholinergics
  - “One MACE fits all” may not be reasonable
  - What about antibiotics, steroids, & devices?