Are There MACE-Specific Endpoints That Should Be Considered?

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Disclosures

- NHLBI institutional training grant
- 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
- Antiarrythmics
- 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.*

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

Niewoehner DE *et al., Ann Int Med* 2005; 143:317 Tashkin DP *et al., NEJM* 2008; 359:1543

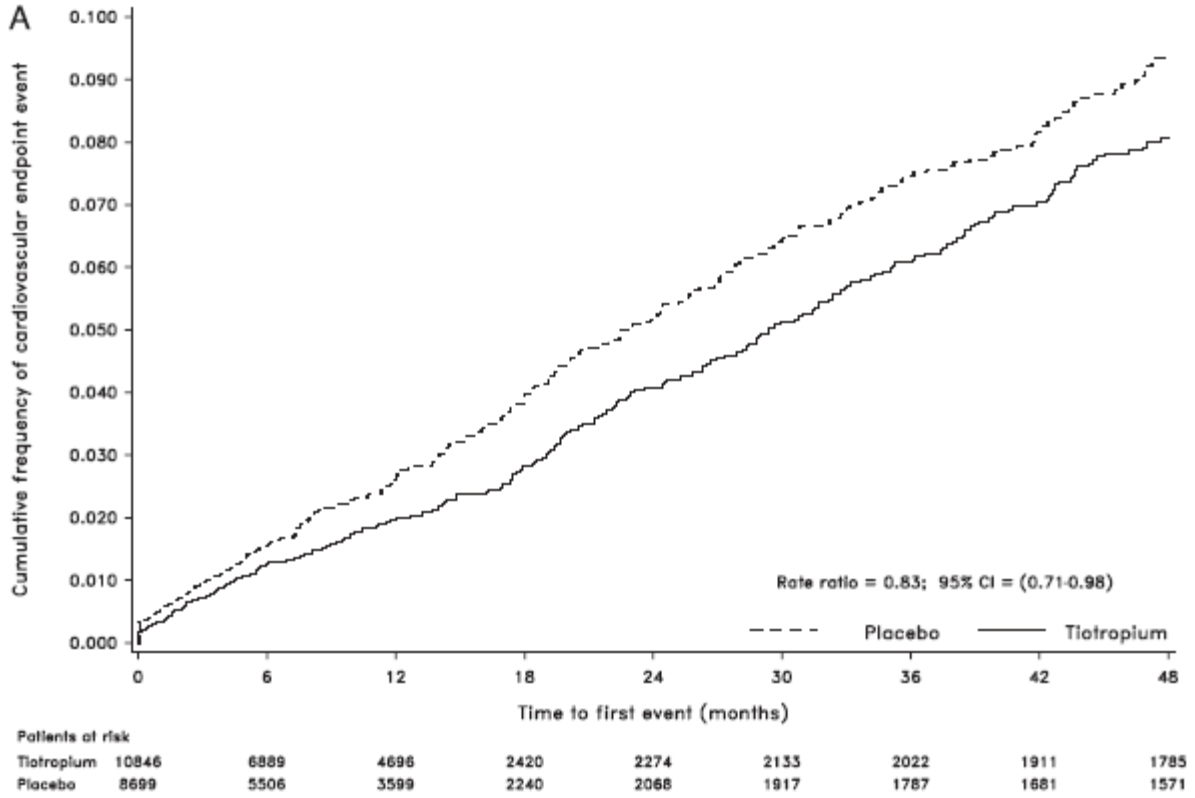
ACCLAIM: aclidinium v. placebo

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)

System organ class	Adverse event preferred term	ACCLAIM/COPD I		ACCLAIM/COPD II	
		Aclidinium 200 µg (n = 627) n (%)	Placebo (n = 216) n (%)	Aclidinium 200 µg (n = 600) n (%)	Placebo (n = 204) n (%)
Cardiac disorders	Atrial fibrillation	3 (0.5)	2 (0.9)	3 (0.5)	0 (0.0)
	Atrial flutter	0 (0.0)	0 (0.0)	2 (0.3)	1 (0.5)
	Sinus tachycardia	2 (0.3)	1 (0.5)	1 (0.2)	0 (0.0)
	Tachycardia	3 (0.5)	0 (0.0)	3 (0.5)	1 (0.5)
	Ventricular extrasystoles	1 (0.2)	1 (0.5)	3 (0.5)	0 (0.0)
Eye disorders	Dry eye	1 (0.2)	1 (0.5)	5 (0.8)	0 (0.0)
	Eye irritation	0 (0.0)	0 (0.0)	3 (0.5)	1 (0.5)
	Eye pain	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
	Vision blurred	0 (0.0)	0 (0.0)	3 (0.5)	1 (0.5)
	Visual acuity reduced	0 (0.0)	0 (0.0)	2 (0.3)	1 (0.5)
Gastrointestinal disorders	Constipation	4 (0.6)	0 (0.0)	13 (2.2)	4 (2.0)
	Dry mouth	6 (1.0)	2 (0.9)	2 (0.3)	3 (1.5)
Infections and infestations	Urinary tract infection	0 (0.0)	0 (0.0)	29 (4.8)	10 (4.9)

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?