CV safety in COPD?

Impact of Guidances and Whitepaper
Regulatory position in Europe?

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Disclaimer:

The views and opinions expressed in the following slides are those of the individual presenter and should not be attributed to any of the organisations the presenter is affiliated with (MHRA, EMA/CHMP or NHS organizations).

Disclosures.

I have no Financial interests to declare, only a risk averse attitude (necessary evil).

I make predictions only in retrospect (and so am rarely wrong)

Available Guidances

- Current regulatory Guidances
  - ICH Clinical Safety guidelines. (E1 and E2A-F)
  - QT– ICH E-14
  - ICH- Safety pharmacology guidelines
- White papers on
  - cardiac conduction
  - General cardiac safety
  - evaluation of BP in Drug development
  - WP on Heart rate.
- Few clinical guidances ?!!

Specific reference to COPD is not a feature of these.. DOES it need to be?!

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Background

- There is considerable of overlap of COPD and CVD as comorbidities
- There is evidence that patients with COPD are at increased CV risk.[1-2]
- Epidemiological evidence that COPD is an independent risk factor for CV morbidity.[3]

1. Chest 2012; 142(5):1118-25
2. Thorax, 2010;65: 956-62.
3. International J of COPD. 2009;4: 337-349

Background

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- Treatments for COPD associated[3] with
  - Increased heart rate, Arrhythmias
  - Effect on QT (??)
  - Heart failure,
  - High blood pressure
  - CV death and myocardial infarction

- Lung Health study[4] - ↑ CV death with ipratropium.

- Meta-analysis-tiotropium & ipratropium[5] 17 RCTs – anti-cholinergics increase MACE in COPD.

- Meta-analysis tiotropium Respimat trials[6] (2011) – raised request for withdrawal from the market.

3. International J of COPD. 2009;4: 337-349.
4. AJRRCM 2002;166:333-339
5. JAMA, 2008; 300: 1439-1450
6. BMJ, 2011; 342: d3215

Where do we stand?

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- Inconsistency/ Variability with the evidence
  - RCTS; UPLIFT(2009) and Tiospir (2013) – but are they generalisable ?
  - Meta-analysis.

Other safety concerns resulted in guidances / WPs- but were consistent and related to MOAs/ off target effects

- QT and E-14
- Diabetes and CV outcome trials.
- Review of NSAIDS & withdrawal of Cox-2 inhibitors.

What if we apply same guidances?

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There is need for clarity and definition of risk.

- MOA:
  - with LAMA → ↑ Heart rate/ Arrhythmia;
  - ↑ HR associated with mortality[7-10.] Apply to COPD treatments?
  - Question is what magnitude of change; 5 Bpm or 10 Bpm
  - Time scale for evaluation?
  - Do we apply the same to LABA?

- No Data on blood pressure ?
  - Should BP measurement be a requirement?
  - What magnitude of change? 2-3 mmhg or > 5mm Hg

7. AHJ, 1987; 113:1489-94
8. EHJ, 2008; 29: 2772–2781
9. EHJ, 2010; 31: 2271–2279
10. PLoS ONE 6(8): e21310.

Questions

- Exposure
  - Do events relate to exposure and if so for inhaled products with very low concentrations a dose response will need to be established.
  - Is it time dependent? i.e., to ↑sed risk of HR and BP limited to long term treatment and if so, how long?

- There is need to balance this risk with benefit related to the MOA?

QTc evaluation in COPD;

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- ICH E-14 guidance is established.
- However, heart correction issue is debatable. There is a white paper on heart rate corrections, but it is unclear if this is regularly applied.
- Given the low exposure of inhaled products, there is inconsistency in the corrections applied thus far.
- There is also inconsistent assessment of effect on heart rate it self.

European Guidances in COPD

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Identifier	Guidance title	CV safety ?
EMA/CHMP/483572/2012	Clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD)	General safety HR increase as a general measure
CPMP/EWP/562/98	Points to Consider on Clinical Investigation of Medicinal Products in the Treatment of Patients with Chronic Obstructive Pulmonary Disease (COPD)	
CPMP/EWP/4151/00 Rev. 1	Requirements for clinical documentation for orally inhaled products (OIP) (COPD and Asthma)	NI or equivalence relating to safety expected but not CV safety.
CPMP/180/95	PMS Studies for Metered Dose Inhalers with New Propellants	
CHMP/EWP/311890/07	Clinical investigation of medicinal products for cardiovascular disease prevention	Not specific to COPD, but CV prevention.

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CV safety & COPD Rx in Europe!.

Recognised as a significant and controversial issue.

MHRA issued a drug safety update in 2011- *Tiotropium: safety studies of Spiriva Respimat▼:*

Identified the issues and the variability of data.

CHMP;

Is consistently seeking evaluation of CV safety aspects for most LAMA or LAMA/LABA combinations.

Pharmacovigilance and Risk assessment Committee;

Regular review of safety and advice to CHMP. Includes LAMAs, LABAs and even SABAs in certain clinical situations.

Requirements for CV safety for recent compounds!.

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LAMA or LAMA+LABA

- Need Post authorisation studies for CV safety-Mostly cohort studies
- Drug utilisation studies in those with CV co-morbidity in the post authorisation period.

- Risk management Plans
  - Need to identify CV safety and mortality as a safety concern.
  - Includes HR, Myocardial infarction, cardiac arrhythmia, stroke and heart failure.
  - RCT requirement is not applied consistently.

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Summary/ Conclusions

Current paradigm

- Few Guidances specific to CV risk in COPD.
- Need careful consideration of need for evaluation of CV risk.
- Are outcome studies the answer and do we need them for all LAMAs as a class? If, so when?

Any new paradigm

- Need to know the direction
- Need evaluation of impact--