The translational story of the relationship between reversible pulmonary obstructive disease and AAA

Jes S Lindholt

on behalf of:
Disclosure of Interest

Speaker name: Jes S. Lindholt

• I do not have any potential conflict of interest
Background

• COPD is a well known risk factor for aneurysmal rupture

• However, spirometry studies in the Viborg study showed all screening diagnosed AAA had obstructive pulmonary disease.

• Lindholt JS, Jørgensen B, Klitgaard NA, Henneberg EW. Systemic levels of cotinine and elastase, but not pulmonary function, are associated with the progression of small abdominal aortic aneurysms. Eur J Vasc Endovasc Surg. 2003;26:418-22.

• Only 13% used bronchodilators, indicating only a small fraction of AAA patients have some component of reversible obstructive pulmonary disease (ROPD).

• Use of bronchodilators was associated with transient increased growth rate, while the FEV1/expected FEV1 ratio (Pulmonary function) were not – indicating other still unknown important mechanisms
Methods and material
3 step translational research

• 1. VIVA: Subgroup study of all participants from the population-based randomized Viborg Vascular (VIVA) screening trial (615 AAA and 18,238 controls).

• 2. DCCS: Population-based, Danish, nationwide, case-control study included all patients with a first-time admission for rAAA and up to five age- and sex-matched AAA controls without rupture in Denmark from 1996-2012 (N=4,747 rAAA and 17,272 intact AAA)

• 3. Experimental angiotensin II AAA mice +/- ovalbumin sensitization and challenge to develop allergic lung inflammation (ALI)
Pharmacoepidemiological results

VIVA trial  \( (ATVB\; 2016;36:570-8) \)

- In the VIVA trial, anti-asthma medication showed 45\% significantly increased risk of AAA regardless of adjustment for smoking or other risk factors  (Crude OR=1.45, Adj. OR=1.46).

- YKL-40 were significant higher in AAA patients compared to controls, and among users of bronchodilators compared to non-users

<table>
<thead>
<tr>
<th></th>
<th>AAA</th>
<th>Controls</th>
<th>P-value</th>
<th>Use of bronchodilator</th>
<th>No use of Bronchodilator</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>YKL-40</td>
<td>106.6 (102.8)</td>
<td>91.9 (147.6)</td>
<td>&lt;0.001</td>
<td>122.0 (129.8)</td>
<td>100.7 (116.9)</td>
<td>0.049</td>
</tr>
</tbody>
</table>
DCCS: Pharmacoepidemiological results

(ATVB 2016;36:570-8)

Hospital diagnosed asthma
- Ever
  - Within 360 days of index date
  - Within 180 days of index date

Bronchodilator use
- Ever
  - Within 360 days of index date
  - Within 180 days of index date
  - Within 90 days of index date

Selective beta-2-adrenergic receptor agonists
- Ever
  - Within 360 days of index date
  - Within 180 days of index date
  - Within 90 days of index date

Anti-cholinergics
- Ever
  - Within 360 days of index date
  - Within 180 days of index date
  - Within 90 days of index date

Inhaled glucocorticoids
- Ever
  - Within 360 days of index date
  - Within 180 days of index date
  - Within 90 days of index date

Theophylline
- Ever
  - Within 360 days of index date
  - Within 180 days of index date
  - Within 90 days of index date

Crude odds ratio (95% C.I.)

Adjusted odds ratio (95% C.I.)
Experimental results I

- Simultaneous production of acute lung inflammation in AAA mice
  - doubled abdominal aortic diameter
  - increased macrophage and mast cell content, arterial SMC loss a.o

- ALI also increased plasma IgE, reduced plasma interleukin-5, and increased bronchialveolar total inflammatory cell and eosinophil accumulation.
Experimental results II

- Systemic inflammatory response?
- Intraperitoneal administration of an anti-IgE antibody* suppressed AAA lesion formation and reduced lesion inflammation, plasma IgE, and bronchioalveolar inflammation.

*: Commercially available
Conclusions

Pharmacoepidemiological population-based studies showed reversible obstructive pulmonary disease as Asthma - especially recent active asthma-, significantly increases risk of AAA and AAA-rupture.

An association between ALI and AAA in Ang-II–induced AAA mice was established. Mice with ALI from an inhaled allergen showed significantly enhanced AAA progression, before, during, or after AAA induction. Anti-IgE reduced significantly that cross-talk

These translational findings document and furnish novel links between airway disease and AAA, two common diseases that share inflammatory aspects opening a potential novel treatment
THANK YOU for your ATTENTION!