Who can get most benefit from tiotropium in asthma?

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New in GINA 2015

Add-on tiotropium by soft-mist inhaler

- for steps 4 & 5
- as a new ‘other controller option’
- age ≥ 18 yrs
- with history of exacerbations
Spiriva Respimat should **NOT** be used in asthma status **below**

should NOT

① as first-line monotherapy
② as a reliever for acute symptoms
③ for acute exacerbation
**Tiotropium as an add-on Tx**

for uncontrolled asthma despite **ICS ± LABA**

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**Preferred Controller**
- Step 1: low dose ICS
- Step 2: low dose ICS

**Other Controller**
- Consider low dose ICS
- Leukotriene receptor antagonists (LTRA)
  - Low dose theophylline*

**Reliever**
- SABA
- SABA or ICS/Form

**Add tiotropium**
- Med/high dose ICS/LABA
  - Med/high dose ICS/LABA (or + theoph)
- Low dose ICS+LTRA (or + theoph)

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**GINA 2015**

*www.ginasthma.org*
## Tiotropium Respimat for Uncontrolled Asthma despite ICS ± LABA

### RCTs

<table>
<thead>
<tr>
<th></th>
<th>PrimoTinA</th>
<th>MezzoTinA</th>
<th>GraziaTinA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Add-on</strong></td>
<td>medium/high ICS + LABA</td>
<td>low/medium ICS ± LABA</td>
<td>low ICS</td>
</tr>
<tr>
<td><strong>Pri. End Points</strong></td>
<td><strong>FEV₁, Exacerb’n Success</strong></td>
<td><strong>FEV₁, ACQ Success</strong></td>
<td><strong>FEV₁ Success</strong></td>
</tr>
<tr>
<td><strong>Sec. End Points</strong></td>
<td><strong>ACQ Partial Success</strong></td>
<td><strong>FVC, PEF Success</strong></td>
<td><strong>ACQ Fail</strong></td>
</tr>
<tr>
<td><strong>Number of Pts</strong></td>
<td>912</td>
<td>2103</td>
<td>4206</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>48 wks</td>
<td>24 wks</td>
<td>12 wks</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Placebo</td>
<td>Salmeterol, Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>
Tiotropium Respimat for uncontrolled asthma despite Step 4 Tx

- 912 uncontrolled asthma
  - ACQ-7 $\geq 1.5$
  - despite medium/high ICS + LABA
- Age $\geq 18$ yrs
- Lung fxn: moderate obstructive
- Hx of exacerbation $\leq 12$ months

Tiotropium improved lung function & delayed severe exacerbation compared with placebo.

Kerstjens, …, Bateman. NEJM 2012
Study design: double-blind, randomised, placebo-controlled, parallel-group (twin trials)

**Tiotropium Respimat® 5 μg qd, morning**

**Placebo Respimat® qd, morning**

Visit 0 (Screening) | Visit 1 (randomisation) | Visit 2 (randomisation) | Visit 9 (end of treatment) | Visit 10

-4 | 0 | 48 | 52

4-week screening | 4-week follow-up

Three co-primary endpoints: hierarchical testing

1. FEV1 peak (0-3 h) after 24 weeks
2. FEV1 trough after 24 weeks
3. Time to first severe asthma exacerbation in pooled* analysis after 48 weeks

All patients at least on ICS maintenance therapy (≥800 μg budesonide or equivalent/day)+LABA

148 centres, 5 continents
Tio. Improved Lung Function

![Graph showing FEV1 trough response in mL from Week 4 to Week 48 for Tiotropium 5 and Placebo in Trials 1 and 2.](image)
Reduced Severe Exacerbation

HR = 0.79; Risk reduction of 21% (P = 0.03)

Number needed to treat: 15

Patients with at least one severe asthma exacerbation (%)

Time (days)

Tiotropium Respimat® n=122 (26.9%) vs. Placebo Respimat® n=149 (32.8%)

Add-on to ICS+LABA

Kerstjens, …, Bateman. NEJM 2012
Tiotropium Respimat may reduce risk of severe asthma exacerbations independent of allergic status

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Events: placebo/Respimat®/tiotropium Respimat®</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE class (Harrison reference) (P=0.21°)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤430 µg/L (n=352)</td>
<td>52/41</td>
<td>0.75 (0.50, 1.12)</td>
</tr>
<tr>
<td>&gt;430 µg/L (n=394)</td>
<td>60/69</td>
<td>1.05 (0.75, 1.49)</td>
</tr>
<tr>
<td>Blood eosinophilia (Harrison reference) (P=0.748°)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.6 × 10⁹/L (n=696)</td>
<td>104/85</td>
<td>0.81 (0.61, 1.09)</td>
</tr>
<tr>
<td>&gt;0.6 × 10⁹/L (n=186)</td>
<td>39/35</td>
<td>0.75 (0.48, 1.19)</td>
</tr>
<tr>
<td>Clinician judgement of allergic status (P=0.745°)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n=352)</td>
<td>40/33</td>
<td>0.75 (0.47, 1.19)</td>
</tr>
<tr>
<td>Yes (n=555)</td>
<td>109/89</td>
<td>0.82 (0.62, 1.08)</td>
</tr>
</tbody>
</table>

Favor Tiotropium
Favor Placebo
Tiotropium Respimat for uncontrolled asthma despite Step 3 or 4 Tx

- **2103** uncontrolled asthma
  - ACQ-7 ≥ 1.5
  - cf. controlled < 0.5 vs. uncontrolled ≥ 1.0
  - despite low/medium ICS ± LABA
- Age 18 ~ 75 yrs
- FEV₁ 60–90% pred.

Tiotropium improved lung function & asthma control compared with placebo.
Study design

- Three coprimary endpoints:
  1. Peak FEV1 (0-3h) after 24 weeks
  2. Trough FEV1 after 24 weeks
  3. ACQ responder rate rate after 24 weeks in pooled data

- Double-blind, randomised, placebo- and active-controlled, parallel-group (two identical trials)
FEV1 improvement with Tiotripium
Asthma Control

Responders (≥0.5 reduction in ACQ-7)

Worsners (≥0.5 increase in ACQ-7)

Tiotropium 2.5

Placebo

P = 0.03

Lancet Respir Med 2015
Asthma Control

Responders (≥0.5 reduction in ACQ-7)

Worsners (≥0.5 increase in ACQ-7)

Tiotropium 2.5

Salmeterol

Lancet Respir Med 2015
Tiotropium Respimat for symptomatic asthma despite Step 2 Tx

- 4206 symptomatic asthma despite Step 2 Tx
  - mean ACQ = 1.5
  - FEV1 60~90% pred.
  - 18~75 yrs

Tiotropium improved lung function compared with placebo.

GraziaTinA, 200–400 μg budesonide
Study design

**Screening**

- Tiotropium Respimat® 5 μg once daily
- Tiotropium Respimat® 2.5 μg once daily
- Placebo Respimat® once daily

**Follow-up**

- Primary endpoint: Peak FEV1(0-3h) response at Week 12

- Secondary endpoints: Trough FEV1, FEV1 AUC(0-3h), Peak FVC (0-3h), Trough FVC, FVC AUC(0-3h), PEF(am), PEF(pm), ACQ-7 total score

- Double-blind, randomised, placebo-controlled, parallel-group

1:1:1 randomisation
FEV1 improvement with Tiotropium

- Tiotropium 5
- Tiotropium 2.5
- Placebo

- Peak FEV1
- Trough FEV1
- FEV1 AUC

P < 0.001
Safety
## Safety

### Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Tiotropium Respimat® (n\ (%))</th>
<th>Placebo Respimat® (n\ (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>456 (100.0)</td>
<td>456 (100.0)</td>
</tr>
<tr>
<td><strong>Total with any Adverse Event</strong></td>
<td>335 (73.5)</td>
<td>366 (80.3)</td>
</tr>
<tr>
<td><strong>Drug-related adverse event as defined by Investigator</strong></td>
<td>26 (5.7)</td>
<td>21 (4.6)</td>
</tr>
<tr>
<td><strong>Serious adverse event</strong></td>
<td>37 (8.1)</td>
<td>40 (8.8)</td>
</tr>
</tbody>
</table>

No deaths occurred.

Kerstjens, ..., Bateman. NEJM 2012
Japan “Safety” Study

Primary end point: long term safety
Secondary end point: long term efficacy (trough FEV1 & trough PEFR)

RCT across 54 Japanese centers
Tiotropium Respimat 5ug (n=114), 2.5ug (n=114), or placebo (n=57), for 52 weeks

2:2:1 randomisation

N = 114

Tiotropium Respimat® 5 µg evening dosing

114

Tiotropium Respimat® 2.5 µg QD evening dosing

57

Placebo Respimat® QD evening dosing

Visit
0 1 2 3 4 5 6 7 8

Week
-4 0 4 8 12 36 52 55
## Long term safety

<table>
<thead>
<tr>
<th>N(%)</th>
<th>Tiotropium Respimat 5ug (n=114)</th>
<th>Tiotropium Respimat 2.5ug (n=114)</th>
<th>Placebo (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients with AE</td>
<td>101 (88.6)</td>
<td>99 (86.8)</td>
<td>51 (89.5)</td>
</tr>
<tr>
<td><strong>Severe AE</strong></td>
<td>2 (1.8)</td>
<td>1 (0.9)</td>
<td>3 (5.3)</td>
</tr>
<tr>
<td>Drug-related AE*</td>
<td>10 (8.8)</td>
<td>6 (5.3)</td>
<td>3 (5.3)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>2 (1.8)</td>
<td>1 (0.9)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Significant (pre-specified) AE**</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>SAE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Requiring hospitalization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-related</td>
<td>4 (3.5)</td>
<td>4 (3.5)</td>
<td>9 (15.8)</td>
</tr>
<tr>
<td>Fatal</td>
<td>0</td>
<td>0</td>
<td>7 (12.3)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>1 (1.8)***</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 (3.5)</td>
</tr>
</tbody>
</table>
Long term safety

- Incidence of **AE was similar** across Tx groups.
- Most AE were **mild to moderate**
- **No deaths** or life-threatening events

Overall, **10 cardiac** events occurred:
- 9 events (in 5) in Tiotropium 5ug group (4.4%)
- 1 in Tiotropium 2.5ug (0.9%)
- 0 in placebo
Who may use tiotropium with caution in asthma?

<table>
<thead>
<tr>
<th>Concomitant Diseases</th>
<th>≤ 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrhythmia, unstable or life-threatening</td>
<td>≤ 12 months</td>
</tr>
<tr>
<td>Hospitalized for heart failure</td>
<td>≤ 12 months</td>
</tr>
<tr>
<td>NYHA class III or IV</td>
<td></td>
</tr>
</tbody>
</table>

NICE advice [ESNM55] Published date: March 2015
Summary
Tiotropium for Asthma Control

• Add-on tiotropium for steps 4 & 5—“a new controller option”

• Should NOT
  ① first-line monotherapy
  ② as a reliever for acute symptoms
  ③ for acute exacerbation
Thank You