CTS GUIDELINE

Benefit?
If so, how much?
Harms?
Cost?
**NNTs... diminishing returns?** *(ballpark)*

<table>
<thead>
<tr>
<th>Scenario</th>
<th>LAMA or LABA vs. SABD (scheduled or prn)</th>
<th>LAMA+LABA vs. LAMA or LABA</th>
<th>Adverse events:</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 mod-severe AECOPD</td>
<td>16-29</td>
<td>42</td>
<td>NO DIFFERENCE</td>
</tr>
<tr>
<td>≥ 1 severe AECOPD</td>
<td>36</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>MCID on dyspnea score</td>
<td>6</td>
<td>6-15</td>
<td></td>
</tr>
<tr>
<td>MCID on QoL score</td>
<td>8-10</td>
<td>8-15</td>
<td></td>
</tr>
</tbody>
</table>

*Adverse events: NO DIFFERENCE (how well is this collected and reported?)*

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Thorax 2016;71:15-25  
Int J COPD 2017;12 907-922  
Respir Res 2017;18:196  
COPD: What to Do with all These New Inhalers? Dalhousie CPD Academic Detailing Service, 2017
### BACK IN TIME...

**AECOPD VS. PNEUMONIA IN CONTEXT**

<table>
<thead>
<tr>
<th>Study</th>
<th>Time span for NNT</th>
<th>COPD exacerbation</th>
<th>Pneumonia</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CI at end of study</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ICS</td>
<td>No ICS</td>
<td>NNT</td>
</tr>
<tr>
<td><strong>TORCH</strong>(^1)</td>
<td>3 years</td>
<td>0.922(^*)</td>
<td>0.945(^*)</td>
<td>44</td>
</tr>
<tr>
<td><strong>INSPIRE</strong>(^4)</td>
<td>2 years</td>
<td>0.578(^\dagger)</td>
<td>0.590(^\dagger)</td>
<td>83</td>
</tr>
<tr>
<td>Kardos(^3)</td>
<td>44 weeks</td>
<td>0.47</td>
<td>0.55</td>
<td>13</td>
</tr>
<tr>
<td>Ferguson(^5)</td>
<td>1 year</td>
<td>0.58</td>
<td>0.66</td>
<td>13</td>
</tr>
<tr>
<td>Anzueto(^6)</td>
<td>1 year</td>
<td>0.60</td>
<td>0.67</td>
<td>14</td>
</tr>
</tbody>
</table>

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Patients (n=3362)
- At least one moderate exacerbation in the past year
- 75% were GOLD stage D (i.e. severe)

Results:
- 0.21 less exacerbations/pt/yr for LAMA+LABA
- 1.8 point difference in QoL (SGRQ)
- ¼ puff less/day of rescue inhaler
- Pneumonia: NNH = 63 for LABA+ICS

So, LAMA+LABA modestly better than LABA+ICS in the highest risk patient, and safer
NOTABLE TRIPLE TRIALS:

OPTIMAL WISDOM SUNSET TRIBUTE KRONOS IMPACT

Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD

WHO? FEV1 = 45%, ≥1 AECOPD/yr (55% had ≥2)
WHAT? LABA+LAMA+ICS (fluticasone) vs. LABA+LAMA vs. ICS+LABA

What did they find @ 1yr?

- ↓ mod-severe AECOPD = 0.3/pt/yr
- ↓ hospitalizations = 0.06/pt/yr
- ↓ mortality = 0.83%, NNT=120

Did patients FEEL BETTER? → well...

- SQRQ -1.8 → NNT MCID = 13
- TDI change not reported → MCID NNT = 17?

IMPACT? → yes, a bit

What’s the CATCH?

- you could have history of ASTHMA
- >70% on ICS pre-randomization

NNH (pneumonia) = 34
DYNAMIC **DUO** VS. **TRIPLE THREAT**
(LAMA+LABA) vs. (LAMA+LABA+ICS)

3 meta-analyses:

- Reduction in **AECOPD** (Cazzola, *Eur Resp J* 2018)
  \[ \text{NNT} = 39 \] (for triple)

  \[ \text{NNH} = 38\text{-}39 \] (against triple)

But, did they at least feel better day-to-day?
Ballpark estimates of the benefits seen from inhalers on clinically important outcomes

St George’s Respiratory Questionnaire - MCID = -4
(NNT to reach MCID)

NNT = 12
mono vs triple ~41→
dual vs triple ~43→
Baseline ~45

Transition Dyspnea index - MCID = -1

mono vs triple no change→
dual vs triple
Baseline not reported

Rescue inhaler puffs per day

mono vs triple 2→
dual vs triple no change→
Baseline ~2.5

Exacerbations/year (moderate/severe)
(NNT to prevent one exacerbation)

NNT = 21
mono vs triple ~0.9→
dual vs triple ~1.0→
Baseline ~1.3

Exacerbations/year (severe)

mono vs triple ~0.1→
dual vs triple ~0.15→
Baseline 0.2
### NNTs... diminishing returns? (ballpark)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>LAMA or LABA vs. SABD (scheduled or prn)</th>
<th>LAMA+LABA vs. LAMA or LABA</th>
<th>LAMA+LABA+ICS vs. LAMA+LABA</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 mod-severe AECOPD</td>
<td>16-29</td>
<td>42</td>
<td>38</td>
</tr>
<tr>
<td>≥ 1 severe AECOPD</td>
<td>36</td>
<td>NS</td>
<td>0.05 less/pt/yr</td>
</tr>
<tr>
<td>MCID on dyspnea score</td>
<td>6</td>
<td>6-15</td>
<td>NA</td>
</tr>
<tr>
<td>MCID on QoL score</td>
<td>8-10</td>
<td>8-15</td>
<td>17</td>
</tr>
</tbody>
</table>

**Adverse events:** NO DIFFERENCE

**Pneumonia:** 39

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**References:**
- Thorax 2016;71:15–25
- CDSR 2018, Issue 12, Art. No.: CD012620
- Int J COPD 2017;12 907–922
- Respir Res 2017;18:196
- COPD: What to Do with all These New Inhalers? Dalhousie CPD Academic Detailing Service, 2017
ETHOS


Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to- Very-Severe COPD

WHO? FEV1 = 43%, ≥1 AECOPD/yr (57% had ≥2)
WHAT? LABA+LAMA+ICS (budesonide 320mcg or 160mcg) vs. LABA+LAMA vs. ICS+LABA

What did they find @ 1yr?
→ ↓ mod-severe AECOPD = 0.35/pt/yr (or ~1 saved in 3 yrs)
→ ↓ hospitalizations = NS
→ ↓ mortality = 1.0% NNT=100 (320mcg), 0.47% (NNT=212)(160mcg)

Did patients FEEL BETTER? → well...
→ SQRQ change -1.9 (320mcg), -1.5 (160mcg) → NNT MCID = 13-15
→ TDI change 0.4 (both doses) @24 wks → MCID NNT not reported

Efficacy in context of other triple trials... VERY SIMILAR

What’s the CATCH?

• you could have history of ASTHMA
• 80% on ICS pre-randomization ✹

NNH (pneumonia) = 59
IMPACT: 
EFFECT OF ICS USE AT BASELINE ON AECOPD

Am J Respir Crit Care Med;101(12):1508–1516, Jun 15, 2020

Table 3. Rates of On-Treatment Moderate/Severe Exacerbations in IMPACT by Medication at Study Entry

<table>
<thead>
<tr>
<th>Baseline Medication*</th>
<th>FF/UMEC/VI (95% CI)</th>
<th>FF/VI (95% CI)</th>
<th>UMEC/VI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.91 (0.87–0.95)</td>
<td>1.07 (1.02–1.12)</td>
<td>1.21 (1.14–1.29)</td>
</tr>
<tr>
<td>ICS/LAMA/LABA</td>
<td>1.21 (1.13–1.28)</td>
<td>1.43 (1.35–1.53)</td>
<td>1.72 (1.58–1.87)</td>
</tr>
<tr>
<td>ICS/LABA</td>
<td>0.70 (0.64–0.77)</td>
<td>0.85 (0.78–0.92)</td>
<td>0.94 (0.83–1.06)</td>
</tr>
<tr>
<td>LAMA/LABA</td>
<td>0.84 (0.73–0.98)</td>
<td>1.11 (0.95–1.29)</td>
<td>1.05 (0.86–1.29)</td>
</tr>
<tr>
<td>LAMA</td>
<td>0.65 (0.54–0.78)</td>
<td>0.75 (0.64–0.89)</td>
<td>0.61 (0.47–0.80)</td>
</tr>
</tbody>
</table>

"...more than 70% were receiving an ICS, and patients with a history of asthma were included. Thus, for the patients assigned to the LAMA–LABA group, many of whom were actually stepping down in their treatment, ICS were abruptly withdrawn at the time of randomization... This design peculiarity, compounded by the probable inclusion of some patients who could have met a standard case definition of asthma, could explain the rapid surge in exacerbations observed in the first month after randomization in the LAMA–LABA group; during the subsequent 11 months of follow-up, the incidence of exacerbation with LAMA–LABA was practically identical to that with triple therapy."

Suissa, Drazen, NEJM April 18, 2018 NEJM
ETHOS & IMPACT:
EFFECT OF ICS USE AT BASELINE ON MORTALITY

ETHOS

IMPACT

AJRCCM Articles in Press. Published November 30, 2020
as 10.1164/rccm.202006-2618OC

Am J Respir Crit Care Med;101(12):1508–1516,
Jun 15, 2020
IMPACT:
EFFECT OF ICS USE AT BASELINE ON MORTALITY

ICS at screening

No ICS at screening

Am J Respir Crit Care Med;101(12):1508–1516, Jun 15, 2020
## PRIMARY CARE vs. TRIALS

*Plos One 2014;9(3):e90145*

**Table 2.** Baseline comparison of the UNLOCK studies versus large COPD studies, including independent sample t-tests.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>(primary care) UNLOCK studies</th>
<th>Large COPD studies (LPCS)</th>
<th>Mean difference between UNLOCK - LPCS (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>3508</td>
<td>23860</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>66.1 (2.3)</td>
<td>63.7 (0.9)</td>
<td>-2.4 (-4.6 — -0.3)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Male, %</td>
<td>60.9 (16.7)</td>
<td>73.3 (4.1)</td>
<td>12.4 (-3.1 — 27.9)</td>
<td>0.1</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>42.9 (9.5)</td>
<td>40.7 (8.6)</td>
<td>-2.2 (-13.2 — 8.8)</td>
<td>0.67</td>
</tr>
<tr>
<td>Pack years</td>
<td>43.6 (13.5)</td>
<td>44.9 (4.03)</td>
<td>1.3 (-15.2 — 17.8)</td>
<td>0.84</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.3 (0.5)</td>
<td>25.6 (0.9)</td>
<td>-0.7 (-2.6 — 0.6)</td>
<td>0.23</td>
</tr>
<tr>
<td>Postbronchodilator FEV₁, % predicted</td>
<td>63.8 (8.7)</td>
<td>47.4 (2.4)</td>
<td>-16.4 (-24.4 — -8.2)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>FEV₁:FVC, %</td>
<td>55.7 (0.7)</td>
<td>46.5 (4.0)</td>
<td>-9.2 (-14.1 — -4.2)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td><strong>GOLD distribution</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild GOLD I</td>
<td>20.7 (13.2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Moderate GOLD II</td>
<td>53.3 (6.2)</td>
<td>45 (6.3)</td>
<td>-8.3 (-16.6 — -0.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>Severe GOLD III</td>
<td>21 (10.1)</td>
<td>44.5 (3.1)</td>
<td>23.6 (13.9 — 33.1)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Very severe GOLD IV</td>
<td>5.8 (5.2)</td>
<td>11.5 (3.5)</td>
<td>5.7 (-0.71 — 12)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Patient-reported outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGRO</td>
<td>32.6 (6.2)</td>
<td>48.4 (1.9)</td>
<td>15.8 (6.3 — 25.4)</td>
<td>0.01*</td>
</tr>
<tr>
<td>CCQ (mean)</td>
<td>1.6 (0.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MRC (mean)</td>
<td>2.1 (0.8)</td>
<td>2.7 (1.1)</td>
<td>0.6 (-1.5 — 2.7)</td>
<td>0.5</td>
</tr>
<tr>
<td>MRC score &gt; 2 (%)</td>
<td>32.3 (17)</td>
<td>51.5 (2.1)</td>
<td>19.2 (1.3 — 37)</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

* proportion of primary care patients eligible for inclusion in large RCTs → 17% - 42%

- Better FEV₁
- Less GOLD
- Better QoL

[https://www.trelegy.com](https://www.trelegy.com)
THERE ARE A LOT OF “IFs”:
YOU GOTTA HAVE FAITH (OR HOPE)?

2 possible approaches:

1) PREVENTATIVE
   → prescribe knowing that AECOPD are reduced overall
      • AECOPD occur relatively infrequently
      • seasonal fluctuations not uncommon

2) SYMPTOM-based
   → prescribe the inhaler → assess if patient feels better
      • COPD symptoms often fluctuate widely day-to-day/wk-to-wk
         (often > than differences in RCTs)
      • When are new inhalers started? → when patient feeling worse

HOPE patient is one of the few that gets
□ AECOPD

Keeping in mind…

Difficult or impossible to determine

Problems…