Disease progression in COPD:
• What is it?
• How should it be measured?
• Can it be modified?

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Disease progression – as measured by FEV$_1$

Fletcher et al, 1976.
Rate of decline of FEV₁: the ISOLDE trial

**Graph:**
- **Y-axis:** FEV₁ (litre)
- **X-axis:** Months
- **Lines:**
  - Orange line: Fluticasone propionate*
  - Blue line: Placebo
- **Key Points:**
  - Fluticasone propionate line:
    - 0 months: 1.45 litres
    - 3 months: 1.40 litres
    - Increase: 76 ml
    - Rate of decline: 50 ml/year
  - Placebo line:
    - 0 months: 1.40 litres
    - Rate of decline: 59 ml/year
  - Statistical significance: p=0.16

**Annotation:**
- *Not licensed for COPD

**References:**
- Burge et al BMJ 2000; 320:1297
TORCH: Exacerbation rate and FEV\textsubscript{1} decline

Exacerbations per year

Adjusted for smoking status, gender, baseline FEV\textsubscript{1}, region, BMI, prior exacerbations, treatment, time, time by treatment and covariate by time

Celli et al AJRCCM 2008; 178: 332
Exacerbations and worsening in health status over 3 years

ANOVA p<0.0003

Exacerbation Category

None in 3 years
Infrequent <1.65/yr
Frequent >1.65/yr

SGRQ slope (units/yr)

Getting worse faster

Change in steps per day over 3 years

Daily activity is lower after 3 years with all degrees of severity

FEV₁ and SGRQ changes

SGRQ, St George’s Respiratory Questionnaire
Five-year study of male outpatients with stable COPD (n=137)

Oga et al; Respir Med; 2007; 101; 146-153
ECLIPSE: Post-bronchodilator FEV1 rate of decline over 3-years

Half of people with COPD (as determined by FEV$_1$) do not appear to have abnormal rates of FEV$_1$ decline.

FEV$_1$ decline in early COPD cohort

TR3 = 53 ml/yr (47% of COPD population)
TR4 = 27 ml/yr (53% of COPD population)

At time of diagnosis – no knowledge of how the patient reached this point

Reference: 1. Adapted from Lange P et al. NEJM 2015 Vol 373: 111-122  2. supplementary appendix
Long-term trial issues
TORCH: Early study withdrawal on placebo: FEV$_1$ rate of decline

"Healthy survivor issue"

Placebo patients with 3-years of data annual decline = 54 ml/year

Early withdrawal patients annual decline = 76 ml/year

Annual decline in last 6-months leading to withdrawal >100ml/year

Clinically Important Deterioration (CID) - Rationale
A composite approach to assess short-term worsening in COPD

Measurable deterioration

- Loss of lung function
- Occurrence of first exacerbation
- Deterioration in health status

Naya I et al. Thorax. 2015; 70(3): A34 (S57)
Clinically Important Deteriorations (CID) in COPD

- Decrease of \( \geq 100 \text{ mL} \) from baseline in trough FEV\(_1\)  
  \textit{and/or}\n
- Deterioration in SGRQ \( \geq 4 \) units  
  \textit{and/or}\n
- Moderate/severe COPD exacerbation
Long term risk based on composite CID status (+) or (-) at 6-months (TORCH post hoc analysis):

At 6 months CID+ (n=2870 [54%])

- Placebo n=1524
- Salmeterol n=1521
- Fluticasone n=1534
- FP/ SAL combination n=1533

Reason for CID+ status

- Exacerbation = 33%
- FEV₁ = 23%
- SGRQ = 17%
- 2 or more causes = 27%

Naya I et al. Thorax. 2015; 70(3): A34 (S57)
Naya et al; European Respiratory Society Congress 2016 (PA304)
TORCH: 3-year outcome on FEV$_1$ & SGRQ based on composite CID status at 6-months

FEV$_1$ (mL) deterioration over time

- Patients CID -
  - FEV$_1$ Mean change (95% CI)
  - Time after day 182 (weeks)
  - -117 ml
  - p<0.001

- Patients CID +
  - FEV$_1$ mean change (95% CI)
  - Time after day 182 (weeks)
  - + 6.4 units
  - p<0.001

SGRQ total score deterioration over time

- Patients CID +
  - SGRQ mean change (95% CI)
  - Time after day 182 (weeks)

- Patients CID -
  - SGRQ mean change (95% CI)

Naya I et al. Thorax. 2015; 70(3): A34 (S57), DOF: RF/CPD/0041/16
TORCH: 3-year risk assessments based on composite CID status at 6-months

All treatment groups combined in TORCH. At 6-Mo. 2870 [54%] patients were CID (CID+) and 2422 [46%] were (CID-).

Future risk of exacerbations on treatment

- Patients CID+ [73%]
- Patients CID- [60%]

CID+ patients had a 61% increased risk of an exacerbation (p<0.001)

Future risk of all cause mortality on treatment

- Patients CID+ [8.3%]
- Patients CID- [6.6%]

CID+ patients had a 41% increased risk of all-cause death (p<0.001)

All treatment groups combined in TORCH. At 6-Mo. 2870 [54%] patients were CID (CID+) and 2422 [46%] were (CID-).

Naya et al; European Respiratory Society Congress 2016 (PA304)
CID in short-term trials
Time to first clinically important deterioration: Relative Risk (RR) reduction

Relative Risk (RR) reduction: 43% (95% CI 31, 53; $p<0.001$)

UMEC/VI 55/22mcg
TIO 18mcg

Singh et al. Int J COPD; 2016; 11; 1413
All components of the composite endpoint were significantly better with UMEC/VI vs. tiotropium

Singh et al. Am J Respir Crit Care Med 2015;191; A5760 (poster presentation)
Preventing short-term worsening: comparison between dual and mono bronchodilator therapy

Post hoc analysis of time to a first composite ClD

(A) Dual bronchodilator therapy (UMEC/VI) vs. tiotropium

- Tiotropium n=869
- UMEC/VI n=878

HR 0.62 (0.54, 0.71)
P<0.001

56%
41%

Singh et al ERS abstract PA1487

(B) Dual bronchodilator therapy (UMEC/VI) vs. placebo

- Placebo n=280
- UMEC/VI n=413

HR 0.37 (0.30, 0.45)
P<0.001

44%
75%

Malaki-Yazdi et al ERS abstract PA1001

(C) Open triple therapy (ICS/LABA + UMEC) vs. ICS/LABA + placebo

- ICS/LABA + PBO n=818
- ICS/LABA + UMEC n=819

HR 0.52 (0.45, 0.59)
P<0.001

68%
46%

Singh et al ERS abstract PA1487
Summary

• All components contribute to CID worsening
• CID distinguishes between treatments in the short-term
• Short term worsening measured over 6 months may predict long-term outcome
• Prevention of short-term worsening looks a promising therapeutic target
  • As a surrogate for long term trials
  • To identify potential disease modifying treatments more quickly