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## COPD Treatment in Real Life and Randomized Controlled Trials: Is There Any Difference between Both Settings?

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### Editorial

In the last decade, for treatment of patients with chronic obstructive pulmonary disease (COPD) a myriad of new medications, mostly administered in new inhalation devices were introduced on the market. In addition, All, but one (Roflumilast) of these “new” drugs rely on old and well proven principles of long acting bronchodilation. Nonetheless, for gaining regulatory approval many randomized controlled trials (RCT’s) were accomplished for long-acting beta2 agonists (LABA’s) and long-acting anticholinergics (LAMA’s) and their fixed combinations, respectively, Inhaled corticosteroids (ICS) as anti-inflammatory therapy are available on the market for a long time, but their indication for COPD is controversial [1,2] and new fixed combinations emerged. Hence even more RCT’s for pharmacological treatment of COPD were recently completed. Therefore, enough high grade evidence from RCT’s should exist for pharmacological treatment of COPD patients.

For efficacy of a treatment for a given indication, RCT’s are generally considered as the gold standard study design. In other words, they have the highest internal validity. On the other hand, the external validity of the above mentioned RCT’s is highly biased by low external validity, i.e. effectiveness of the treatment in a large “real life” population. This is due to several well-known factors. Strict inclusion and exclusion criteria in RCT’s apply to a small minority of real life patients with COPD. This proportion can be as low as 5% [3,4]. For example the most delicate patients with co-morbidities are mostly excluded. Severity distribution of in RCT included patients can also differ from real life cohorts. Probably a much less recognized fact is, that outcome targets of pivotal trials, in COPD usually exacerbations and FEV1 are determined by regulatory authorities, i.e. Food and Drug Administration (FDA) and European Medicine Agency (EMA). Symptoms like dyspnoea, cough, exercise capacity, and other important patient related outcomes are frequently not proven. Moreover, persistence on treatment and real life treatment adherence cannot be tested in RCT’s. What are, if any, the alternatives?

Register studies are retrospective in nature and use data from electronic healthcare registries. They are large and

observational, but register data are seldom complete and often miss disease severity and symptoms. Moreover, robustness of register diagnoses is questionable and in COPD important information on smoking habits is usually missing.

The “A two-year evaluation of the ‘real life’ impact of COPD on patients in Germany: The DACCORD observational study” published in *Respiratory Medicine* 2017 [5] will add to fill the gaps of RCT’s and register studies. DACCORD (Die ambulante Versorgung mit langwirksamen Bronchodilatoren: COPD Register in Deutschland, English translation: Outpatient Care with Long-Acting Bronchodilators: COPD Registry in Germany) is an ongoing observational, non-interventional study being conducted in almost 500 German primary and secondary care centres. This large study aims to describe the impact of disease (including exacerbations) and treatments over 2 years on ‘real-life’ patients. More than 6000 patient were included, all with both clinical and spirometry diagnosis of COPD. GOLD 2011 diagnostic criteria were used for inclusion and patient were included if at inclusion they had a change in their maintenance COPD medication. Except asthma no exclusion criteria applied. According to the German healthcare system patients had about four routine clinical visits per year, data on symptoms and health status (using CAT; COPD Assessment Test), exacerbation, lung function and current treatment were collected. Thus, DACCORD balanced successfully for many above mentioned limitations of RCT’s, however at the cost of a high attrition rate: at year two only some 3100 patients could be evaluated.

### What adds DACCORD to our knowledge on real life COPD?

First, DACCORD shows that in contrast to RCT populations enriched with exacerbating patients exacerbations in real life remain infrequent events. In DACCORD only every 4th patient (26.2% in the first year and 23.2% in the second year) reported exacerbations at all. As could have been shown in ECLIPSE, another observational study [6] also in DACCORD the most important predictor for exacerbations is the exacerbation history. While the non-exacerbator phenotype remains stable over the 2 years’ period, the exacerbation frequency for first year exacerbators is varying in the second year. Overall, the

exacerbation rate is slightly diminishing from 0.390 during the first year to 0.347 during the second year.

Taken together, the first lesson learned from DACCORD, additional treatments like ICS merely targeting prevention of COPD exacerbations is not the focus for roughly 75% of the real-life population. Nonetheless, in real life in Germany much more patients are treated with ICS [7].

The second important point is about disease progression. It was a common held hypothesis, that COPD is an inevitably progressive disease. For the first time the ECLIPSE study [8] identified different phenotypes with and without progression as defined by FEV1 decline. COPD progression as assessed by changes in CAT score in a moderately symptomatic population with CAT mean value around 20 at baseline shows only in 22% (first year) and 29% (two years) a clinically meaningful (i.e.  $\geq 4$  unit) deterioration. In contrast, approximately 50% of patients experienced unexpectedly a clinically relevant improvement and 38.7% a sustained improvement at each of the yearly assessments.

The third point is about insights on treatment persistence over two years - also a unique feature of non-interventional studies like DACCORD. At inclusion about half of all patients were treated with LAMA monotherapy or ICS/LABA/LAMA triple therapy, respectively. Other treatment classes included LABA monotherapy, LABA+LAMA combination, ICS/LABA fixed combination and a small proportion ICS plus LAMA or phosphodiesterase inhibitors. In two years 71.4% of all patients didn't change the medication class. The highest variation was in the LABA monotherapy group, where 8.8% of patient had add on therapy, i.e. mostly conversion to LABA/LAMA fixed combination. At the time of the two years study several LABA/LAMA fixed dose combinations were launched on the German market.

Finally, analysis of real life population data supported the 2017 change in GOLD COPD assessment, where severity of obstruction was taken out from estimation for exacerbation risk. In DACCORD, 76% of GOLD 2011 group D patients (that equals

24.9% of all patients) where categorized as D according only to low lung function, which is a poor predictor of exacerbations and potentially misleads to recommendation of ICS containing treatments.

In summary, RCT's alongside with large real-life observational trials like DACCORD complement each other in developing evidence for treatment of COPD. In this large German COPD study new data were collected on real-life exacerbation frequency, symptoms progression, treatment persistence and support for change in 2011 GOLD classification of COPD severity.

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