

Chronic Obstructive Pulmonary Disease: Lessons from the Important Treatment Trials

Peter M.A. Calverley, DSc and Paul P. Walker, MD

University of Liverpool, and University Hospital Aintree, Liverpool, United Kingdom

ABSTRACT

Since 1999, clinical trials have more precisely defined the impact of various treatments on important patient-centred outcomes, allowing the development of treatment guidelines and leading to personalised treatment. The use of larger populations, seen in the Toward a Revolution in COPD Health (TORCH), Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) and The Study to Understand Mortality and Morbidity (SUMMIT) trials, has allowed hypotheses to be answered clearly albeit not always positively. Notwithstanding, each study has provided important information, often through secondary outcomes, which have been prospectively tested in other trials. Nearly two decades on, we are clearer as to the role of lung volume reduction procedures, who should and shouldn't be prescribed inhaled steroids and long-acting bronchodilators and in what combinations, and who may benefit from roflumilast. Unexpected findings such as pneumonia risk from inhaled steroids and use of eosinophil count to direct their use have an important clinical impact now and in the future. (BRN Rev. 2017;3:286-98)

Corresponding author: Peter Calverley, pmacal@liverpool.ac.uk

Key words: Chronic obstructive pulmonary disease. Clinical trial. Therapeutics. Statistics.

Correspondence to:

Peter Calverley
Clinical Science Centre
University Hospital Aintree
Lower Lane, Liverpool, L9 7AL
E-mail: pmacal@liverpool.ac.uk

Received in original form: 06-04-2017
Accepted in final form: 13-05-2017
DOI: 10.23866/BRNRev:2017-0051

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has never been an easy condition to research. Its long natural history, pathological heterogeneity and the relative inaccessibility of the lungs to tissue sampling have all limited our understanding of COPD. Respiratory physiological measurements have helped fill this gap and the first major treatment intervention trials in COPD showed in just over 300 subjects that long-term domiciliary oxygen treatment could prolong life in persistently hypoxaemic COPD patients who were at appreciable risk of dying during the 3 years of these studies¹. The high reproducibility of forced expiratory volume in one second (FEV₁) measurement meant that only modest numbers of people need be studied over relatively short periods to confirm that inhaled bronchodilators improved spirometry. However, the size of studies had to increase if rate of decline of FEV₁ was to be measured or indeed other non-normally distributed outcomes such as exacerbations. Ultimately, the needs of regulators and the desire to identify genetic factors pre-disposing to COPD have led to very large observational studies which have been pooled to increase their statistical power.

The conduct and outcomes of these large scale randomised controlled trials have been reviewed previously^{2,3} and some general conclusions have been drawn about them. A recent series of review articles in the *New England Journal of Medicine* provides many insights into issues of trial design and conduct⁴, although the only large-scale respiratory trial to be mentioned is the Toward a Revolution in COPD Health (TORCH) study^{4,5}. In this review, we will offer some general thoughts

about our experience with clinical trials over the last twenty years. Although all our examples are drawn from COPD studies, we believe that they have wider applicability. To make these lessons more memorable, we have reduced our messages to a series of aphorisms derived from popular music and culture but, we hope, supported by evidence.

BIG IS BEAUTIFUL BUT SIMPLE IS BEST

Conducting a successful clinical trial requires considerable organisational skill, attention to detail and resources. Not all clinically relevant questions need a large trial to answer them, but given the heterogeneity of COPD and the interventions available, big trials have been needed to try to provide clear answers. The success of any study depends on the patients recruited, the outcomes selected and the intervention studied. Clearly the study should recruit sufficient patients to ensure that a negative outcome is truly negative, but it has been difficult to do this when the observed event rate in the control arm of the study has been lower than expected. Considerations about statistical power were minimal in the United Kingdom (UK) long-term oxygen study when the annual mortality in the control group was 22%, which was reduced to 11% with oxygen treatment⁶. The National Emphysema Treatment Trial (NETT) recruited 1,218 patients to surgery or routine medical care and its primary outcome based on intention to treat was negative, although much attention was spent in the manuscript in presenting clinically plausible subgroups who benefitted from surgery⁷. The TORCH study recruited some 6,000 patients followed

TABLE 1. Exacerbation rate in selected placebo controlled COPD clinical trials. Exacerbation rate often appears higher in 'real world' studies

Year	Clinical trial	Subject number	FEV ₁ (L /% predicted) post-bronchodilator	Comparison	Annual exacerbation rate
2000	ISOLDE ¹⁶	751	1.4 L; 50% predicted	Placebo versus fluticasone propionate	1.32
2003	TRISTAN ⁹	1,022	0.98 L; 36% predicted	Placebo versus budesonide versus formoterol versus budesonide/formoterol	1.8
2005	BRONCUS ¹⁸	523	1.65 L; 57% predicted	Placebo versus N-acetylcysteine	1.31
2007	Roflumilast I ²⁸	1,513	1.15 L; 41% predicted	Placebo versus roflumilast	0.92
2007	TORCH ⁸	6,112	1.22 L; 44% predicted	Placebo versus fluticasone propionate versus salmeterol versus fluticasone propionate	1.13
2008	UPLIFT ²⁴	5,993	1.32 L; 47% predicted	Placebo versus tiotropium bromide	0.85
2009	M2-124/125 ¹⁰	3,091	1.11 L; 36% predicted	Placebo versus roflumilast	1.37
2011	Azithromycin ¹⁹	1,142	1.12 L; 40% predicted	Placebo versus azithromycin	1.83
2015	REACT ²⁷	1,945	1.1 L; 35.5% predicted	Placebo versus roflumilast	0.92
2016	RESPOND ³¹	2,354	0.97 L; 33% predicted	Placebo versus roflumilast	1.43
2016	SUMMIT ¹⁷	16,458	1.7 L; 60% predicted	Placebo versus fluticasone furoate versus vilanterol versus fluticasone furoate/vilanterol	0.35
2016	Salford Lung ¹¹	2,799	1.62 L	Placebo versus fluticasone furoate/vilanterol	1.9

FEV₁: forced expiratory volume in one second; ISOLDE: inhaled steroids in obstructive lung disease in Europe; TRISTAN: trial of inhaled steroids and long-acting b2-agonists; BRONCUS: bronchitis randomized on NAC cost-utility study; TORCH: toward a revolution in COPD health; UPLIFT: understanding potential long-term impacts on function with tiotropium; REACT: severe chronic obstructive pulmonary disease uncontrolled by combination therapy; RESPOND: roflumilast effect on exacerbations in patients on dual [LABA/ICS] therapy; SUMMIT: survival in chronic obstructive pulmonary disease with heightened cardiovascular risk; SLS: Salford lung study.

for 3 years and failed to conclusively show an effect of inhaled corticosteroid (ICS)/long-acting beta-agonist (LABA) treatment on mortality⁸. However, the event rate in the placebo arm was lower than the 6% per year powered from historical control data and in part reflecting cross over to use of trial medication after withdrawal from the study. The likelihood of exacerbating in clinical trials has fallen steadily over the years from around 2 events/year⁹ to 0.9 or less, even among patients reporting exacerbations previously (Table 1)¹⁰. Interestingly, this may reflect the complexity of trial entry criteria, as the "real world" randomised controlled trial conducted in Salford, UK, had much higher exacerbation rates than seen in more classical studies¹¹. Whatever the reason, the decision to power a study on historically

observed exacerbation rates can be a hazardous one, as the likely event rate can be substantially less than anticipated. One way to avoid these problems is to simplify the trial protocol as much as possible and focus on your primary outcome. Thus, both the Prevention of Exacerbations with Tiotropium (POET) (7,000 subjects) and the event-driven Tiotropium Safety and Performance in Respimat (TIOspir) studies (17,135 subjects) did not monitor spirometry regularly and had relatively simple designs focussed on the primary outcome (exacerbations and mortality respectively)^{12,13}. Happily, both gave rise to a clear result. Notwithstanding, the use of exacerbation rate as a primary study endpoint can be challenging, due to the relative subjectivity of some exacerbation definitions, an example

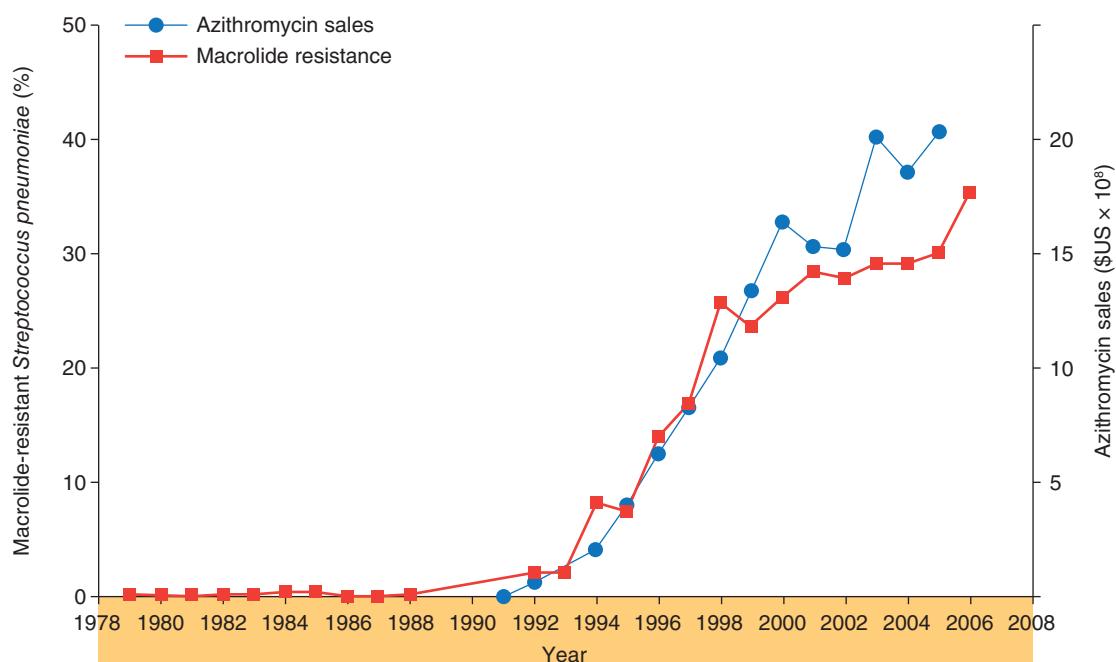


FIGURE 1. Prevalence of macrolide resistant *Streptococcus pneumoniae* and use of azithromycin in United States of America (USA) since its introduction in 1991 (reproduced with permission from Serisier D et al.²⁰).

being the definition used in the Simvastatin Therapy for Moderate and Severe COPD (STATSCOPE) study¹⁴. Use of diary cards can, at least in part, ameliorate this effect but significantly increase the work involved for both subject and researcher.

YOU DON'T ALWAYS GET WHAT YOU WANT ...

A high proportion of large COPD studies have failed to meet their primary endpoint. This may reflect over-optimistic assumptions about the numbers needed to identify an effect as in the early studies of ICS in COPD^{15,16} or relatively ineffective interventions as was the case with ICS and/or LABA treatment in moderate

COPD and cardiovascular risk in the The Study to Understand Mortality and Morbidity (SUMMIT) study¹⁷ and N-acetylcysteine in the Bronchitis Randomized On NAC Cost-Utility (BRONCUS) trial¹⁸. Even when the trial is positive, as was the case in the National Heart, Lung and Blood Institute (NHLBI) funded study of azithromycin in exacerbation prevention¹⁹, concerns about the wider risks of treatment (in this case the risk of antibiotic resistance) may limit the application of the results (Fig. 1)²⁰.

... BUT YOU MIGHT JUST GET WHAT YOU NEED

Even if the primary outcome of trials (when it is not based on short-term lung function change)

often seems to fail, many of the treatments studied do seem to have important effects on nominated secondary endpoints. Although this feels like having multiple bites of the cherry, in an individual study the consistency with which these secondary effects are confirmed suggests that the treatment effects are real. This is likely to be due to the rather weak relationship between the secondary and primary outcomes. Exacerbations are associated with increased COPD mortality, but this association is relatively weak for those managed without hospitalisation and so treatment can reduce the frequency of these events without immediately impacting the death rate²¹. Much the same holds true for rate of decline of FEV₁, which is only slightly faster among patients who are treated but still exacerbate²². The Randomised, double blind, placebo controlled study of fluticasone propionate (ISOLDE) study was the first to report a reduction in exacerbations with ICS, a secondary outcome confirmed repeatedly by others and then extended to long-acting inhaled bronchodilator studies¹⁶. This effect was a driver for the improvement in health status evidenced for the first time in ISOLDE by repeated measurements of the St. George's Respiratory Questionnaire (SGRQ)²³. This questionnaire has been widely employed ever since and can identify large changes in health status with pulmonary rehabilitation and lung volume reduction^{7,24}.

Sometimes, the design of one study can be better suited to establishing that the primary endpoint of another is actually positive. Thus, secondary analysis of the carefully collected spirometry in TORCH suggested that all three active treatment arms had a lower rate of FEV₁ decline than the placebo²⁵. By contrast, the Understanding Potential Long-Term Impacts on

Function with Tiotropium (UPLIFT) failed to show an effect of tiotropium on lung function decline but up to 70% of patients in the control arm were using one of the drugs which the TORCH data suggested might be effective²⁶. Conversely, as subjects in UPLIFT did not drop out as frequently as in TORCH and this 5,885-patient trial had only two comparison arms over four years, there was sufficient power to show a reduction in mortality with tiotropium, at least when the data were analysed appropriately²⁷.

Occasionally, the investigator needs to hold their nerve and (funding permitting) continue to explore some of the plausible secondary outcomes from an initial study (Fig. 2). Despite high hopes, the phosphodiesterase-4 (PDE4) inhibitor roflumilast did not change the exacerbation rate in its pivotal one-year trial²⁸. However, the event rate was much lower than expected and there were signs of effect in patients with worse lung function, a history of exacerbations and chronic bronchitis²⁹. When prospectively tested in this subgroup of patients, the drug did prevent exacerbations¹⁰ but only when this finding was confirmed in patients with very frequent exacerbations or a high risk of being hospitalised and who also took LABA/ICS and LAMA, was it possible to finally establish a treatment group where the intrusive side effects of treatment produced clinically important benefits^{30,31}.

'LIES, DAMN LIES AND STATISTICS'

This quotation from the 19th century British Prime Minister Benjamin Disraeli emphasises the scepticism which many non-statisticians have for the way in which apparently straightforward numbers can be modified to suit the

Roflumilast Effect on Exacerbations in Patients on Dual [LABA/ICS] Therapy (RESPOND) (2016)

2,354 subjects with severe or very severe COPD, 2+ exacerbation or hospitalisation previous year, chronic bronchitis and prescribed LABA/ICS +/- LAMA

Given placebo or roflumilast 500 mcg daily

Outcomes

53 ml improvement FEV₁ over 1 year

Similar rate of moderate or severe AE (1.31 versus 1.47; $p = 0.09$) versus placebo

Benefit in subjects with 3+ AE or hospitalisation. Benefit in subjects already taking fluticasone propionate/salmeterol

Roflumilast on Exacerbations in Patients with Severe Chronic Obstructive Pulmonary Disease Uncontrolled by Combination Therapy (REACT) (2015)

1,945 subjects with severe or very severe COPD, 2+ exacerbation previous year and chronic bronchitis

Given placebo or roflumilast 500 mcg daily

Outcomes

56 ml improvement FEV₁ over 1 year

Lower rate of AE (0.74 versus 0.92; $p < 0.01$) versus placebo. Lower rate of hospitalisation

Similar overall withdrawal, higher in roflumilast first 12 weeks

Roflumilast II (2009)

3,091 subjects with severe or very severe COPD, 1+ exacerbation previous year and regular cough and phlegm

Given placebo or roflumilast 500 mcg daily

Outcomes

55 ml improvement FEV₁ over 1 year

Lower rate of AE (1.13 versus 1.37; $p < 0.001$) versus placebo

Similar overall withdrawal, higher in roflumilast first 12/52

Roflumilast I (2007)

1,513 subjects with COPD

Given placebo or roflumilast 500 mcg daily

Outcomes

39 ml improvement FEV₁ over 1 year

No change AE rate. No change SGRQ.

More withdrawals roflumilast in first 4/52

Very severe COPD (higher AE rate) lower rate of AE – 1.01 versus 1.59; $p < 0.03$ – versus placebo

FIGURE 2. The evolution of roflumilast with each study allowing further development of the place of therapy in COPD management. AE: acute exacerbations; COPD: chronic obstructive pulmonary disease; FEV₁: forced expiratory volume in one second; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic-antagonist.

purpose in hand. We are all sadly learning to live with “alternative facts” promoted by a variety of politicians, but we can have more faith in the statistical input to most of our randomised controlled trials (RCTs). Indeed, the major problems are likely to come from our imperfect understanding of what the statistics

are telling us rather than any malevolence on the statistician’s part.

RCTs remain the best way available to decide whether an intervention can work, which is not the same as saying it will work. That conclusion should be drawn from effectiveness

TABLE 2. Sources of bias in randomised controlled trials

Type of bias	How this affects the trial	How to obviate this potential bias
Selection bias	Systematic differences between baseline characteristics of the groups that are compared	Sequence generation – pre-determined random sequence Allocation sequence concealment – concealment of unpredictable sequence
Ascertainment bias	Knowledge of the intervention by the researcher(s), subject or analyst influences the administration of the intervention, the reporting or the analysis of outcomes Subjects could receive different alternative interventions (co-intervention bias), report outcomes differently (participant ascertainment bias) or the researcher(s) could report outcomes differently (observer bias)	Blinding of the researcher, subject and data analyst
Study design bias	Choice of study design, population studied, the intervention selected, the control intervention and the outcome measure(s) affect the generalisability and applicability of the study findings Study design can be influenced by a desire to achieve a specific outcome, funding limitation or by regulatory authorities. Skewed populations and complexity can affect the generalisability of the study. Timing of the intervention and the outcomes selected can affect the study results and relevance of the study	Careful consideration of the research question, the population, the intervention and outcome measures. External review of proposals
Attrition bias	Systematic differences in withdrawal from trials leading to incomplete data and the risk of over or understating the effect of the intervention	Intention-to-treat analysis: all study participants are included in the study assigned to their allocated groups regardless of drop out Sensitivity analysis: allocation of the worst outcomes to subjects in the best performing group and allocation of the best outcomes to subjects from the worst performing group
Reporting bias	Reporting of trial focuses on significant rather than non-significant differences	Pre-determination and prior publication of primary and secondary outcomes. Effective peer review
Publication bias	Studies with positive results are more likely to be published. Delay in publishing of negative studies (time lag bias)	Compulsory registration of trials at inception and publication of all trials

studies and they are in short supply. Although they are well designed and conducted, our current RCTs have problems. The selection of representative patients has already been mentioned and Table 2 lists a series of other biases that can affect the interpretation of the data. Indicators of statistical significance are important to pre-specify but some common sense is needed in the interpretation of borderline p values as suggested by Pocock et al.³². The need to conduct interim safety analyses and potentially stop a trial lowers the p value needed before significance can be declared, but is seldom accounted for when powering a trial. The need to discount all

secondary analyses if the primary outcome is not met seems foolish if the secondary outcomes are only tangentially related to the primary one. However, we do need clear rules to stop anarchy breaking out when trials are unblinded. Our concern is that intelligent interpretation of the results and the generation of new hypotheses can be inhibited by too rigorous an implementation of perceived statistical norms.

Meta-analysis of several studies can either suggest an effect of treatment not shown in individual studies or simply reduce the confidence interval around the estimate of the trial effect.

It works well when the studies are homogeneous in their selection criteria and the results are clinically plausible. Unfortunately, by chance, differences may arise and these do not always favour the active therapy. A salutatory case of this arose when the registration studies of tiotropium delivered as a soft mist were reported³³. Although the primary lung function and exacerbation outcomes were clearly positive, mortality, which was a minor secondary outcome in a study not powered to detect a difference, was higher in the treatment group than the controls. This led a spate of meta-analyses largely of the same data set and the proposal that this delivery system was uniquely dangerous³⁴. In fact, the problem was not that the tiotropium treated patients were dying too frequently (their mortality rate was in line with many similar study populations) but that the death rate in placebo-treated patients was unusually low. Once raised, such concerns are not easily allayed and it was not until over 17,000 patients were recruited to the TIOSPIR study that the soft mist system was shown to be safe³⁵.

EXPECT THE UNEXPECTED

Part of the joy of being involved in clinical trials for the investigator (if not the sponsor) is the occurrence of an unanticipated new finding. This most often occurs when a large trial reports, as it has the size and/or duration to identify associations which have previously escaped detection. The observation that clinically reported pneumonia was more frequent in COPD patients taking fluticasone propionate, was a complete surprise to the TORCH investigators³⁶ but has subsequently been confirmed in other large studies and in trials with a high

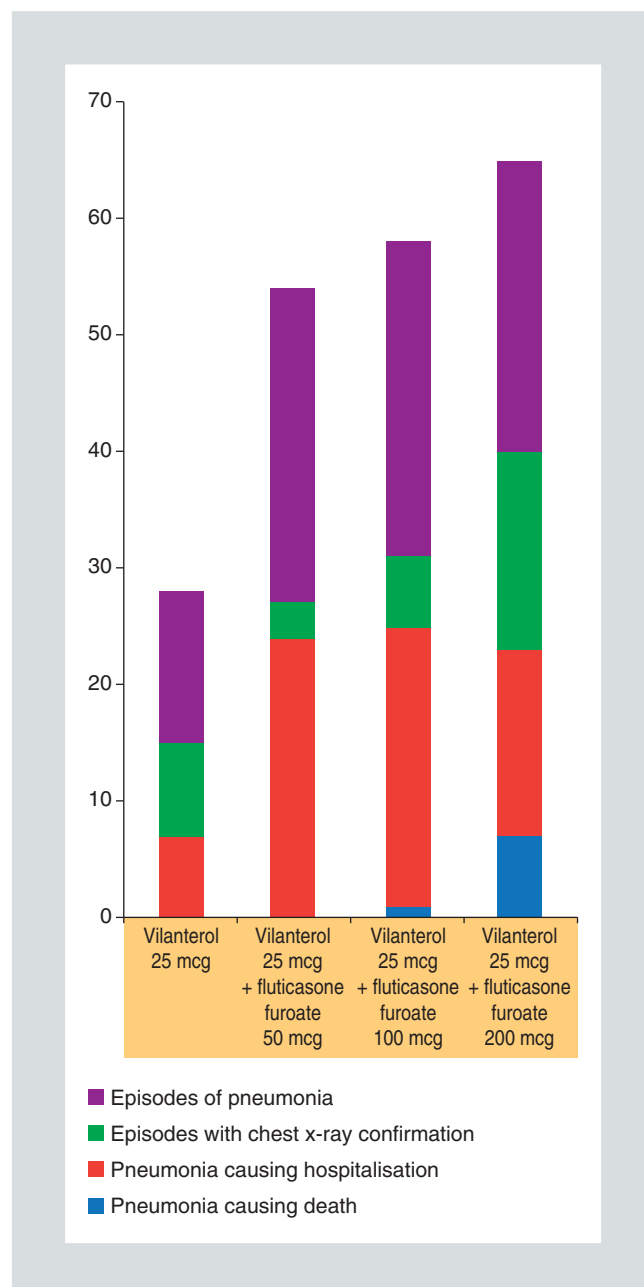


FIGURE 3. Number of episodes of pneumonia, with or without radiological confirmation, and causing hospitalisation and death in patients taking vilanterol with or without differing doses of fluticasone furoate (*reproduced with permission from Dransfield MT et al.³⁷*).

rate of radiological confirmation of the diagnosis³⁷ (Fig. 3). Whether this excess of pneumonias is due to increased susceptibility or an inability to resolve earlier exacerbations³⁸ is still unclear, as is the association of all ICS

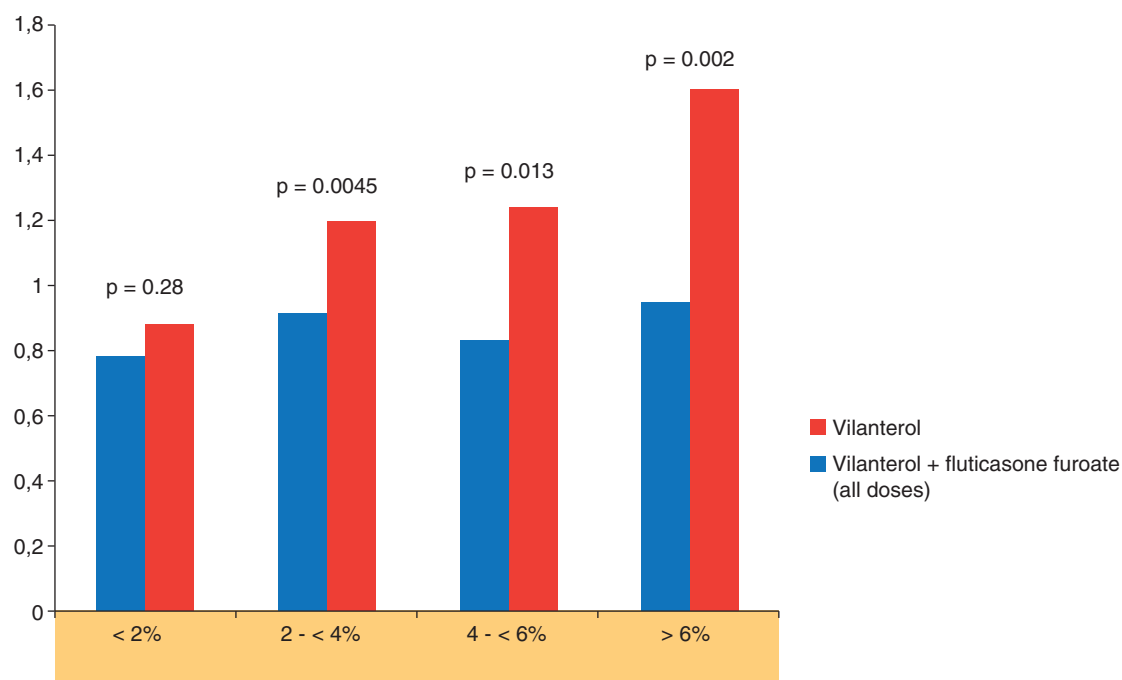


FIGURE 4. Annual exacerbation rate (patient per year) of chronic obstructive pulmonary disease (COPD) patients when taking vilanterol with or without fluticasone furoate stratified according to blood eosinophil count below 2%, 2-4%, 4-6% and above 6% of total white blood cell count (reproduced with permission from Pascoe et al.⁴⁰).

drugs with these events³⁹. However, the clinical perception of the value of ICS in more severe COPD was changed by these observations.

Equally unlikely, although identified in this case by *post-hoc* analysis, was the discovery that patients with a blood eosinophil count above 2% were the ones who had fewer exacerbations when treated with ICS and LABA rather than LABA alone⁴⁰ (Fig. 4). A series of further *post-hoc* analyses in other data sets confirmed this observation^{41,42} although there was no particular benefit in this subgroup when ICS/LABA was compared to a LABA/ long-acting muscarinic antagonist (LAMA) combination⁴³. Data from the large

Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) trial showed that ICS could be safely stopped in patients with severe COPD and an exacerbation history provided they continued with LABA and LAMA treatment⁴⁴. *Post-hoc* scrutiny of these results suggested that there was benefit from continuing the ICS if the eosinophil count was above 300 cells/mm³^{3,45}. Prospective confirmation of these findings was seen in the recently published Single Inhaler Extrafine Triple Therapy versus long-acting Muscarinic Antagonist Therapy for Chronic Obstructive Pulmonary Disease (TRINITY) study albeit the “cut-off” point remains unclear⁴⁶.

The search for genetic and other biological markers of COPD in large observational cohorts like Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) and Genetic Epidemiology of COPD (COPDGene) has proven to be elusive. However, these investigators were pleased to find that a previous history of frequent exacerbations was much the strongest predictor of recurrent events⁴⁷, that the six-minute walk test had a smaller minimally important clinical difference than expected⁴⁸, and that serial computed tomography (CT) imaging could identify emphysema progression or in the case of an enlarged pulmonary artery the risk of future exacerbations⁴⁹. Hypotheses need to work with information and these studies have generated this in abundance.

GRAB THE LOW HANGING FRUIT CAREFULLY

After the uncertainties of studies to modify disease progression, the recent focus of registration trials on combined LAMA/LABA drugs should have been an easy win. These studies have been reviewed in detail elsewhere⁵⁰ (Table 3) but suffice to say the lung function endpoints immediately and over time were all better with the combination than its components, irrespective of which particular LAMA/LABA preparation was studied. The incremental benefit was not additive suggesting a ceiling effect at the doses used. This may explain why it has been harder to confirm that these modest changes in FEV₁ translate into clinical noticeable improvements in breathlessness or general respiratory health. Carefully conducted crossover studies confirm that the combination improves breathlessness more

than does LAMA alone⁵¹ while large scale well powered parallel group studies have identified improvements in health status with dual bronchodilator therapy⁵², but even here the difference between the groups is relatively modest. Dual bronchodilators do reduce total exacerbation numbers compared to LAMA drugs⁵³ but the difference in moderate/severe exacerbation rate is very small and barely significant. Further large studies are underway to clarify how large a difference we might expect. However, the findings of the Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone (FLAME) study, a non-inferiority comparison of LABA/LAMA and LABA/ICS, have changed perceptions as the combination was clearly superior in all types of exacerbation compared to LABA/ICS⁴³. Clearly not all unexpected findings are unwelcome ones.

WHAT GOES AROUND COMES AROUND... AND MAY BE BETTER

The last twenty years have seen clinical trials move from a focus on changes in the FEV₁ to encompass a variety of clinically more relevant outcomes which have been more complex to measure. It took almost ten years before the non-random distribution over time in exacerbation could be appropriately modelled statistically⁵⁴. Studying the individual's exercise capacity was greatly aided by the advent of computerised exercise testing equipment. Together with insights about the role of dynamic hyperinflation in limiting exercise in COPD, it became possible to study a range of respiratory drugs and understand by how much and why they improved exercise

TABLE 3. Currently available combinations of long-acting beta-agonist and long-acting muscarinic-antagonist (LABA/LAMA) with selected trials and outcomes

LABA/LAMA Combination	Trial Name	Comparator and subject numbers	Trial length	Baseline Characteristics	Outcomes
Formoterol/ aclidinium	AUGMENT ⁵⁹	Aclidinium/formoterol (2 doses – 400/12 & 400/6) versus aclidinium formoterol placebo	24 weeks	1692 subjects FEV ₁ = 53% predicted	A/F 400/12 dose: Trough FEV ₁ – improved versus formoterol and placebo Health status (SGRQ) – improved versus placebo Breathlessness (TDI) – improved versus placebo
	ACLIFORM-COPD ⁶⁰	Aclidinium/formoterol (2 doses – 400/12 & 400/6) versus aclidinium formoterol placebo	24 weeks	1729 subjects FEV ₁ = 54% predicted	Trough FEV ₁ – improved versus placebo Breathlessness (TDI) – improved vs. all groups
Indacaterol/ glycopyrronium	FLAME ⁴³	Indacaterol/glycopyrronium versus Salmeterol/fluticasone	52 weeks	3362 subjects FEV ₁ = 44% predicted	I/G: Annual exacerbation rate – lower than S/F Trough FEV ₁ – improved versus S/F Health status (SGRQ) – improved versus S/F
	SPARK ⁵³	Indacaterol/glycopyrronium versus glycopyrronium Tiotropium	64 weeks	2224 subjects FEV ₁ = 37% predicted	I/G: Moderate/severe exacerbations – lower than G Trough FEV ₁ – improved versus G & T
Vilanterol/ umeclidinium	Decramer et al. ⁶¹	Vilanterol/umeclidinium (2 doses – 125/25 & 62.5/25) versus vilanterol umeclidinium tiotropium	24 weeks	2332 subjects	V/U 62.5/25 dose: Trough FEV ₁ – improved versus vilanterol and tiotropium
Olodaterol/ tiotropium	Buhl et al. ⁵²	Olodaterol/tiotropium (2 doses – 2.5/5 and 5/5) versus olodaterol tiotropium	24 weeks	5162 subjects FEV ₁ = 50% predicted	O/T 5/5 dose: Trough FEV ₁ – improved versus both groups Health status (SGRQ) – improved versus both groups

A: aclidinium; AUGMENT: aclidinium/formoterol fumarate combination for investigative use in the treatment of moderate to severe COPD; F: formoterol; FEV₁: forced expiratory volume in one second; FP: fluticasone propionate; G: glycopyrronium; I: indacaterol; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic-antagonist; O: olodaterol; S: salmeterol; SGRQ: St. George's respiratory questionnaire; SPARK: analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium; T: tiotropium; TDI: transition dyspnoea index; U: umeclidinium; V: vilanterol.

performance⁵⁵. The failure to translate this greater capacity into increases in daily activity remains a challenge. The need to identify patients suitable for medical lung volume reduction procedures who had upper lobes that did not exhibit significant collateral ventilation has led to a revival of interest in physiological

methods of detecting this previously obscure phenomenon. When carefully selected using these methods the results of trials of a variety of methods to promote lobar collapse are encouraging⁵⁶⁻⁵⁸. Respiratory physiological measurement as a tool for patient selection is staging something of a comeback.

CONCLUSIONS

As indicated in this far from comprehensive review of the large number of COPD trials conducted in the last twenty years, we have learned much but still have more to discover. We understand our outcome measures better, especially the new more behaviourally determined ones like health status and exacerbations. We are more rigorous about identifying which outcomes matter before we begin a study and in trying to produce manageable clinical protocols to help deliver it without exhausting our patients in the process. We do need to ensure that the statistical power of a study is likely to match contemporary rather than historical event rates. We should be a little more optimistic when interpreting our *post-hoc* analyses as a surprising number of these have been confirmed when tested prospectively. Patient selection remains crucial, whether in terms of their representativeness of the generality of COPD patients or in the presence of the key characteristics under study. We should always be prepared to face this disappointment of a negative trial result but do our best to ensure that whatever we tried really did not work rather than failing through lack of numbers or operational failures on our part. Crucially, we need to move away from just identifying small treatment gains in severe COPD and look earlier in the natural history of the disease to consider intervention at a stage when less permanent damage has occurred and the clinical trajectory of the patient can be changed. These are the challenges for the next 20 years.

CONFLICT OF INTEREST

Professor Peter M.A. Calverley, has advised Boehringer Ingelheim, GSK, AstraZeneca and

Recipharm on the design and conduct of clinical trials and has spoken at meetings sponsored by these companies. He has no stock holdings in any pharmaceutical company or connection with the tobacco industry. Doctor Paul P. Walker has nothing to disclose.

REFERENCES

1. Cranston JM, Crockett AJ, Moss JR et al. Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2005;4: CD001744.
2. Calverley PM, Rennard SI. What have we learned from large drug treatment trials in COPD? *Lancet.* 2007;370:774-85.
3. De Soyza A, Calverley PM. Large trials, new knowledge: the changing face of COPD management. *Eur Respir J.* 2015;45:1692-703.
4. Rosenblatt M. The Large Pharmaceutical Company Perspective. *N Engl J Med.* 2017;376:52-60.
5. Pocock SJ, Stone GW. The Primary Outcome Fails - What Next? *N Engl J Med.* 2016;375:861-70.
6. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet.* 1981;1:681-6.
7. Fishman A, Martinez F, Naunheim K et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med.* 2003;348:2059-73.
8. Calverley PM, Anderson JA, Celli B et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med.* 2007;356:775-89.
9. Calverley PM, Boonsawat W, Cseke Z et al. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J.* 2003;22:912-9.
10. Calverley PM, Rabe KF, Goehring UM et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet.* 2009;374:685-94.
11. Vestbo J, Leather D, Diar Bakerly N et al. Effectiveness of Fluticasone Furoate-Vilanterol for COPD in Clinical Practice. *N Engl J Med.* 2016;375: 1253-60.
12. Vogelmeier C, Hederer B, Glaab T et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med.* 2011;364:1093-103.
13. Wise RA, Anzueto A, Cotton D et al. Tiotropium Respiat inhaler and the risk of death in COPD. *N Engl J Med.* 2013;369:1491-501.
14. Criner GJ, Connett JE, Aaron SD et al. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. *N Engl J Med.* 2014;370:2201-10.
15. Vestbo J, Sørensen T, Lange P et al. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet.* 1999;353:1819-23.
16. Burge PS, Calverley PM, Jones PW et al. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ.* 2000; 320:1297-303.
17. Vestbo J, Anderson JA, Brook RD et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet.* 2016;387:1817-26.
18. Decramer M, Rutten-van Molken M, Dekhuijzen PN et al. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet.* 2005;365:1552-60.

19. Albert RK, Connett J, Bailey WC et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med*. 2011;365:689-98.
20. Serisier DJ. Risks of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. *Lancet Respir Med*. 2013;1:262-74.
21. Martinez FJ, Vestbo J, Anderson JA et al. Effect of Fluticasone Furoate and Vilanterol on Exacerbations of COPD in Patients with Moderate Airflow Obstruction. *Am J Respir Crit Care Med*. 2017;195:881-888.
22. Donaldson GC, Seemungal TA, Bhowmik A et al. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax*. 2002;57:847-52.
23. Spencer S, Calverley PM, Sherwood Burge P et al. Health status deterioration in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2001;163:122-8.
24. Griffiths TL, Burr ML, Campbell IA et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet*. 2000;355:362-8.
25. Celli BR, Thomas NE, Anderson JA et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med*. 2008;178:332-8.
26. Tashkin DP, Celli B, Senn S et al; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359:1543-54.
27. Celli B, Decramer M, Kesten S et al. Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2009;180:948-55.
28. Calverley PM, Sanchez-Toril F, McIvor A et al. Effect of 1-year treatment with roflumilast in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007;176:154-61.
29. Rennard SI, Calverley PM, Goehring UM et al. Reduction of exacerbations by the PDE4 inhibitor roflumilast—the importance of defining different subsets of patients with COPD. *Respir Res*. 2011;12:18.
30. Martinez FJ, Calverley PM, Goehring UM et al. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial. *Lancet*. 2015;385:57-66.
31. Martinez FJ, Rabe KF, Sethi S et al. Effect of Roflumilast and Inhaled Corticosteroid/Long-Acting β_2 -Agonist on Chronic Obstructive Pulmonary Disease Exacerbations (RE(2)SPOND). A Randomized Clinical Trial. *Am J Respir Crit Care Med*. 2016;194:559-67.
32. Pocock SJ, Stone GW. The Nature of the P Value. *N Engl J Med*. 2016;375:2205-6.
33. Bateman E, Singh D, Smith D et al. Efficacy and safety of tiotropium Respimat SMI in COPD in two 1-year randomized studies. *Int J Chron Obstruct Pulmon Dis*. 2010;5:197-208.
34. Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2012;7:CD009285.
35. Wise RA. Tiotropium and the risk of death in COPD. *N Engl J Med*. 2014;370:482.
36. Crim C, Calverley PM, Anderson JA et al. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. *Eur Respir J*. 2009;34:641-7.
37. Dransfield MT, Bourbeau J, Jones PW et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med*. 2013;1:210-23.
38. Calverley PM, Stockley RA, Seemungal TA et al. Reported pneumonia in patients with COPD: findings from the INSPIRE study. *Chest*. 2011;139:505-12.
39. Sin DD, Tashkin D, Zhang X et al. Budesonide and the risk of pneumonia: a meta-analysis of individual patient data. *Lancet*. 2009;374:712-9.
40. Pascoe S, Locantore N, Dransfield MT et al. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med*. 2015;3:435-42.
41. Pavord ID, Lettis S, Locantore N et al. Blood eosinophils and inhaled corticosteroid/long-acting β_2 -agonist efficacy in COPD. *Thorax*. 2016;71:118-25.
42. Siddiqui SH, Guasconi A, Vestbo J et al. Blood Eosinophils: A Biomarker of Response to Extrafine Beclomethasone/Formoterol in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 2015;192(4):523-5.
43. Wedzicha JA, Banerji D, Chapman KR et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. *N Engl J Med*. 2016;374(23):2222-34.
44. Magnussen H, Disse B, Rodriguez-Roisin R et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *N Engl J Med*. 2014;371:1285-94.
45. Watz H, Tetzlaff K, Wouters EF et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir Med*. 2016;4(5):390-8.
46. Vestbo J, Papi A, Corradi M et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. *Lancet*. 2017 Apr 3. pii: S0140-6736(17)30188-5. doi: 10.1016/S0140-6736(17)30188-5.
47. Hurst JR, Vestbo J, Anzueto A et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010;363:1128-38.
48. Polkey MI, Spruit MA, Edwards LD et al. Six-minute-walk test in chronic obstructive pulmonary disease: minimal clinically important difference for death or hospitalization. *Am J Respir Crit Care Med*. 2013;187:382-6.
49. Coxson HO, Dirksen A, Edwards LD et al. The presence and progression of emphysema in COPD as determined by CT scanning and biomarker expression: a prospective analysis from the ECLIPSE study. *Lancet Respir Med*. 2013;1:129-36.
50. Calverley P, Vlies B. A rational approach to single, dual and triple therapy in COPD. *Respirology*. 2016;21:581-9.
51. Mahler DA, Decramer M, D'Urzo A et al. Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: the BLAZE study. *Eur Respir J*. 2014;43:1599-609.
52. Buhl R, Maltais F, Abrahams R et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). *Eur Respir J*. 2015;45:969-79.
53. Wedzicha JA, Decramer M, Ficker JH et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med*. 2013;1:199-209.
54. Keene ON, Calverley PM, Jones PW et al. Statistical analysis of exacerbation rates in COPD: TRISTAN and ISOLDE revisited. *Eur Respir J*. 2008;32:17-24.
55. Langer D, Ciavaglia CE, Neder JA et al. Lung hyperinflation in chronic obstructive pulmonary disease: mechanisms, clinical implications and treatment. *Expert Rev Respir Med*. 2014;8:731-49.
56. Shah PL, Slebos DJ, Cardoso PF et al. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomised, sham-controlled, multicentre trial. *Lancet*. 2011;378:997-1005.
57. Klooster K, ten Hacken NH, Hartman JE et al. Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation. *N Engl J Med*. 2015;373:2325-35.
58. Deslée G, Mal H, Dutau H et al. Lung Volume Reduction Coil Treatment vs Usual Care in Patients With Severe Emphysema: The REVOLENS Randomised Clinical Trial. *JAMA*. 2016;315:175-84.
59. Singh D, Jones PW, Bateman ED et al. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. *BMC Pulm Med*. 2014;14:178.
60. D'Urzo AD, Rennard SI, Kerwin EM et al. Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomised, placebo-controlled AUGMENT COPD study. *Respir Res*. 2014;15:123.
61. Decramer M, Anzueto A, Kerwin E et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. *Lancet Respir Med*. 2014;2:472-86.