New horizons in early stage COPD — Improving knowledge, detection and treatment

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COPD; Early disease; Treatment; Diagnosis; Case-finding

Summary
Early stage COPD carries a significant healthcare burden that is currently underrecognised, underdiagnosed and undertreated. Furthermore, patients at this stage can rapidly decline to advanced disease, especially if they continue to smoke. The natural history of the disease in early stages remains largely unknown, and emerging evidence indicates that we are able to reduce lung function decline and exacerbations, and improve quality of life, in early stage COPD, mainly through smoking cessation. But new evidence from randomised clinical trials also suggests an impact of pharmacotherapy on clinical outcomes in early disease. Guidelines need to be updated to reflect this greater understanding of early stage disease, and trials need to be conducted to definitively show the benefits of intensive treatment so that we can meet the large, unmet clinical needs of this important patient group.

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The importance of early COPD

Chronic obstructive pulmonary disease (COPD) is one of the main causes of morbidity and mortality in developed countries.\(^1\) The prevalence of spirometrically-confirmed COPD in England was estimated in 2005 at 1.4%, compared with 3.6% for coronary heart disease, 1.5% for stroke, 3.3% for diabetes, 0.5% for cancer, and 5.8% for asthma.\(^3\) The BOLD study, performed in 12 countries using post-bronchodilator spirometry testing plus questionnaires on respiratory symptoms, health status, and exposure to COPD risk factors, revealed that the prevalence of Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II or higher COPD was 10.1% overall, 11.8% in men and 8.5% in women.\(^3\) The overall pooled estimate of the adjusted odds ratio for COPD was 1.94 per 10-year age increment.\(^3\)

Early stage chronic obstructive pulmonary disease is mild or moderate in terms of severity of lung function impairment and is defined differently depending on which classification system is used (see Table 1).\(^4\)\(^-\)\(^6\) However, mild COPD is consistently defined as a forced expiratory volume in 1 s (FEV\(_1\)) of \(\geq 80\%\) predicted and moderate between 51% and 80% predicted.\(^4\)\(^-\)\(^6\) The prevalence of early COPD among patients with COPD is high and varies significantly between countries.\(^3\) In the BOLD study, the prevalence of GOLD stage I COPD ranged from 1% in the Philippines to 16% in Austria, while that of GOLD stage II COPD ranged from 5% in Germany to 12% in South Africa.\(^3\) Other local studies have estimated that, related to spirometry confirmed cases of COPD, 57% of COPD patients have mild and 25% moderate disease in Greece,\(^7\) compared with 42% and 44%, respectively, in England,\(^8\) 56% and 38%, in Spain,\(^9\) 25% and 59%, in Norway,\(^10\) 56% and 38%, in Japan,\(^11\) and 31% and 51%, in Poland.\(^12\) However, most patients with early disease remain undiagnosed in the community. A Spanish study in 1999 of adults aged 40–70 years revealed that, from a prevalence of 9.1%, only 22% of COPD patients had a previous diagnosis of the disease,\(^13\) which rose to just 27% 10 years later.\(^9\) These findings have been replicated around the globe.\(^7\)\(^,\)\(^8\)\(^,\)\(^10\)\(^,\)\(^11\)\(^,\)\(^14\) Overall, 45–85% of COPD patients are not formally diagnosed, as many accept breathlessness and limited exercise tolerance as features of ageing and regard their smoker’s cough as normal and do not request medical attention.\(^15\)

Both patients and physicians play a role in the high rates of COPD underdiagnosis. One survey showed that, of 7000 adult respondents, 33% said that they suffered from chronic respiratory symptoms, but only 56% of those consulted a physician.\(^16\) Of those individuals who consulted a physician with respiratory symptoms, only 42.6% underwent spirometry.\(^16\) Just 56% of primary care practices were found to have a spirometer in a recent nationwide survey of

### Table 1 Definitions of mild-to-moderate COPD in current classification systems.\(^4\)\(^,\)\(^6\)

<table>
<thead>
<tr>
<th></th>
<th>GOLD</th>
<th>ATS/ERS</th>
<th>NICE</th>
<th>ICSI</th>
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<tbody>
<tr>
<td><strong>At risk</strong></td>
<td></td>
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<tr>
<td><strong>Mild</strong></td>
<td></td>
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<tr>
<td>Stage I</td>
<td></td>
<td></td>
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<tr>
<td>FEV(_1)/FVC &lt; 0.70</td>
<td></td>
<td></td>
<td>FEV(_1) &gt;80% predicted</td>
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<tr>
<td>FEV(_1) ≥80% predicted</td>
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<td>FEV(_1) &gt;80% predicted</td>
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<tr>
<td>FEV(_1)/FVC ≤0.70</td>
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<td></td>
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<tr>
<td>FEV(_1) ≥80% predicted</td>
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<td></td>
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<tr>
<td>Moderate</td>
<td></td>
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<td>Stage II</td>
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<tr>
<td>FEV(_1)/FVC &lt; 0.70</td>
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<td></td>
<td>FEV(_1) ≤0.70</td>
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<tr>
<td>FEV(_1) 50–80% predicted</td>
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<tr>
<td>FEV(_1)/FVC ≤0.70</td>
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<tr>
<td>FEV(_1) 50–80% predicted</td>
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FEV\(_1\): forced expiratory volume in 1 s; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ATS/ERS: American Thoracic Society/European Respiratory Society; ICSI: Institute for Clinical Systems Improvement.
Lack of time was cited as a reason for not performing spirometry in 20% of cases. Undiagnosed airflow obstruction is more common than doctor-diagnosed COPD and asthma, with a US study estimating the prevalence of undiagnosed airflow obstruction at 12.0% compared with 3.1% and 2.7% for COPD and asthma, respectively, and, although the undiagnosed airflow is typically very mild, approximately 5% of the general population has an FEV1 <75% predicted. Not all patients with mild airflow obstruction will progress to more severe disease. Yet, despite having milder airflow obstruction than previously diagnosed patients in the same age group, undiagnosed patients have significant impairments in health-related quality of life (HRQoL) and reduced activities of daily living (ADL) compared with individuals without airflow obstruction. As both HRQoL and level of physical activity are important predictors of survival in patients with COPD, these results suggest that, at least in some cases, undiagnosed patients represent earlier disease than diagnosed individuals and highlight the importance of early recognition of the disease in order to implement early intervention, mainly with smoking cessation initiatives. COPD patients also have significantly lower physical activity than patients with rheumatoid arthritis and diabetes, and healthy individuals.

Symptomatic GOLD Stage I COPD patients have increased respiratory care utilisation, including inhaler use, emergency room visits, hospitalisation due to respiratory problems and ambulatory visits, and lower HRQoL than asymptomatic GOLD Stage I patients. These latter are similar to individuals with normal lung function. Even symptomatic mild COPD patients with relatively preserved FEV1, forced vital capacity (FVC) and resting inspiratory capacity have extensive small airway dysfunction that results in troublesome exertional symptoms. Regarding extrapulmonary involvement, GOLD Stage I and II patients also have an approximately 3-fold increased risk of depressive symptoms compared to healthy individuals.

The direct health costs of COPD are substantial, even in early disease. A Spanish 1-year follow-up study estimated that mild COPD incurred a cost of US$1484 per patient (versus US$2911 for severe COPD), with hospitalisations accounting for 41.2%, drug acquisition accounting for 42.5% and clinic visits and laboratory/diagnostic accounting for 16.2% of the costs. In an Italian study, the mean annual direct healthcare cost per patient was approximately €755 for GOLD Stage 0, €1000 for GOLD Stage I and €2000 for GOLD Stage III COPD. It is likely that these may underestimate the true costs of COPD, as COPD is frequently not listed as the primary reason for hospitalisation.

The high prevalence and important social and economic impact of COPD justifies early detection and treatment to prevent the development of severe stages of the disease. In this position paper, we will review strategies to detect early COPD in the community and results reported in large clinical trials in patients with stage II COPD, with particular attention to the possible role of pharmacotherapy in modifying the course of the disease.

Identifying early COPD

While there is a need to improve the recognition of COPD within the community in a cost-effective and efficient manner, there is also a need to ensure that, in addressing any COPD underdiagnosis, the burden of COPD misdiagnosis—both false positives and false negatives—is not increased. Also of concern is the number of individuals currently diagnosed with ‘COPD’ and/or receiving pulmonary medication who do not have a clear or accurate diagnosis of COPD in accordance with guideline standards.

The International Primary Care Respiratory Group (IPCRG) suggests that all smokers aged 35 years and older, individuals who have symptoms suggestive of COPD and those who have positive findings on a COPD risk evaluation questionnaire should either have initial case-identification spirometry or proceed directly to full diagnostic spirometry. This ‘case-finding’ approach of first harnessing symptoms, patient

![Figure 1](https://example.com/figure1.png)

**Figure 1**  Screening strategies for COPD. Adapted from. Two different approaches to identification of individuals with COPD in primary care. In option 1, individuals may be selected for diagnostic spirometry based on the results of the case-identification spirometry in practices in which it is available. Otherwise (option 2), the candidates must be referred for diagnostic spirometry. COPD: chronic obstructive pulmonary disease; IPCRG: International Primary Care Respiratory Group; GOLD: Global initiative for chronic Obstructive Lung Disease; FEV1: forced expiratory volume in 1 s; FEV2: forced expiratory volume in 6 s; FVC: forced vital capacity. *See Price et al. (2006), Table 2; **Patients aged 30 years or older if high risk (eg, family history of COPD, occupational or environmental risk, smoker since childhood).
characteristics and lung function indicators should improve the recognition of COPD (see Fig. 1). \(^{31}\)

The NICE guideline recommends the identification of early COPD and that spirometry be performed in subjects aged over 35 years, current or ex-smokers and those with chronic respiratory symptoms. \(^{32}\) It also suggests that spirometry be considered in patients with chronic bronchitis, as a significant proportion of these will go on to develop airflow limitation. \(^{32}\)

Three major case detection questionnaires have been developed: van Schayck et al\(^{33,35}\); Martinez et al\(^{34}\); and Price et al (see Table 2). \(^{35,36}\) Taking an estimated prevalence of COPD of 10% and two arbitrarily selected cut-off points for each of the questionnaires, the percentage of individuals requiring subsequent spirometry and the percentage of false negatives after application are shown in Table 3. Only for the Price et al questionnaire has there been an attempt at external validation within a population of 676 symptomatic smokers recruited from both the general population and from primary care practices. \(^{35,37}\) For the two previously used cut-off points and the same estimated prevalence of COPD, the percentage needing spirometry and the percentage of false negatives in the original and validation studies are set out as in Table 4. However, doubts have been raised as to the applicability of the validation. As well as differences in the proportion of smokers between the two populations (100% symptomatic smokers versus 44.5% smokers with and without respiratory symptoms in the original population), the Kotz et al patient group was slightly younger than that in the Price et al population, participants were ineligible if they had a prior respiratory diagnosis, were using antidepressants or had undergone spirometry in the preceding 12 months, and the patients were required to have respiratory symptoms. \(^{35,37}\)

While spirometry is an essential part of the clinical diagnosis of COPD, with diagnostic criteria based on an FEV1/FVC ratio <0.7 after inhaled bronchodilator administration, \(^{4}\) 21%–63% of patients registered as having COPD in both primary and secondary care do not fulfil the disease criteria, largely due to a lack of spirometric data. \(^{36–41}\) A survey of COPD care within UK general practices indicated that 74% of

<table>
<thead>
<tr>
<th>Authors</th>
<th>Questions</th>
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| van Schayck et al. (2002) | 1. How many cigarettes do you smoke each day?  
2. Do you have any allergies?  
3. Have you ever had asthma or bronchitis?  
4. Have you started to get tired more quickly in the past few years?  
5. Have you been short of breath more often in the past few years?  
6. Have you coughed more in the past few years?  
7. Have you started to wheeze in the past few years?  
8. Are there any lung diseases in your family? |
| Martinez et al. (2008) | 1. During the past 4 weeks, how much of the time do you feel short of breath?  
2. Do you ever cough up any "stuff", such as mucus or phlegm?  
3. Please select the answer that best describes you in the past 12 months. (strongly agree/agree/unsure/disagree/strongly disagree)  
4. Have you smoked at least 100 cigarettes in your entire life?  
5. How old are you? |
| Price et al. (2006)   | 1. Age group (year)  
2. Body mass index (tertiles)  
3. Smoking intensity (pack years)  
4. Does the weather affect your cough?  
5. Do you ever cough up phlegm (sputum) from your chest when you don’t have a cold?  
6. Do you usually cough up phlegm (sputum) from your chest first thing in the morning?  
7. How frequently do you wheeze?  
8. Do you have or have you had any allergies? |

### Table 3: Percentage of individuals requiring subsequent spirometry and percentage of false negatives with case-finding COPD questionnaires. \(^{33–36}\)

<table>
<thead>
<tr>
<th></th>
<th>Price (&lt;16.5)</th>
<th>Price (&gt;19.5)</th>
<th>Martinez (&gt;4)</th>
<th>Martinez (&gt;5)</th>
<th>van Schayck (1 symptom)</th>
<th>van Schayck (3 symptoms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% needing spirometry</td>
<td>26</td>
<td>46</td>
<td>60</td>
<td>43</td>
<td>61</td>
<td>13</td>
</tr>
<tr>
<td>% false negatives</td>
<td>&gt;4</td>
<td>2</td>
<td>&lt;1</td>
<td>1.5</td>
<td>&gt;2</td>
<td>&gt;7</td>
</tr>
<tr>
<td>PPV</td>
<td>37</td>
<td>30.3</td>
<td>50.3</td>
<td>56.8</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>NPV</td>
<td>89</td>
<td>92.7</td>
<td>91.7</td>
<td>86.4</td>
<td>93</td>
<td>94</td>
</tr>
</tbody>
</table>

PPV = Positive predictive values; NPV = Negative predictive values.
Spirometry is feasible in systematic and opportunistic case-identification programmes targeted at populations at risk of COPD due to smoking, and is likely to benefit patients through earlier interventions.12,43 Screening spirometry performed at a sufficient level to rule out COPD can form part of a strategy to reduce the number of individuals needing full diagnostic spirometry.30 However, its use in a mass population remains controversial.44

Opportunistic primary care case detection has a COPD detection rate of up to 28% in previously undiagnosed smokers.13,45 Case identification of COPD in smokers could also be widened through the participation of healthcare professionals other than doctors, such as pharmacists.46

It is possible to achieve good quality spirometry in primary care,47 and at levels similar to those achieved in the majority of pulmonary function laboratories.31 However, there is marked variability and inconsistency in the use of spirometry to diagnose COPD48,49 and a lack of device calibration and quality control,30 as well as formal and accurate technical training,50 are frequent in primary care. A recent document proposing new standards for general practice diagnostic spirometry that are compliant with ATS/ERS recommendations, and other similar initiatives, seeks to improve operator skills to achieve an acceptable technical standard and quality of spirometry in primary care.51 Furthermore, the aim of case-finding spirometry is not to provide a definitive diagnosis but to exclude those with normal lung function and appropriately guide patients towards further tests. For case identification, it is therefore acceptable to perform a less specific, but highly sensitive test.30 This includes small and simple microspirometers measuring the FEV1/FEV6 ratio, which could be a reliable surrogate for FVC in the detection of obstruction.52,53 The IPCRG has suggested thresholds for excluding COPD using such devices that require study and validation. These are an FEV1/FVC ratio of >0.8 and a FEV1 >80% predicted.30

Clinicians, particularly in primary care, should be offered a range of tools for different levels of COPD identification and diagnosis adapted to their needs and possibilities, including short questionnaires to identify patients warranting additional testing,54 case-identification spirometry and full diagnostic spirometry. Questionnaires should be applied as widely as possible to individuals visiting primary care nurses and pharmacies. As clinicians, we have not succeeded in advocacy to raise awareness on COPD and the importance of early diagnosis, and shown the need for spirometry as an everyday part of primary and secondary care practice. Spirometry should be encouraged during medical school training; and patients should expect to undergo spirometry when they visit their doctor, alongside blood pressure and blood cholesterol levels assessments, as a marker of general health. It is also crucial that clinicians and researchers work with industry to develop spirometry machines that offer better, standardised results and error messages. Current pulmonary equipment cannot always perform spirometry to ATS/ERS standards, and too often industry drives the development of spirometry equipment, rather than clinicians themselves.

### Early treatment of COPD in current guidelines

Over the past decade, five major guidelines have been published on the diagnosis and management of COPD.4–6,32,55 The 2009 updated GOLD report states that, alongside active reduction of risk factors and influenza vaccination, patients with Stage I mild COPD should receive symptomatic treatment with short-acting bronchodilators, while those in Stage II should also have regular treatment with one or more long-acting bronchodilators, plus rehabilitation.4 These recommendations were supported by the 2009 ICSI guidelines.5

The 2010 update of the NICE guidelines recommends that COPD patients with an FEV1 >50% predicted and exacerbations or persistent breathlessness must be offered long-acting bronchodilators and, in those with persisting manifestations, combination therapy with either a long-acting beta-2 agonist plus an inhaled corticosteroid or a long-acting beta-2 agonist plus a long-acting antimuscarinic agent should be recommended.32

The GOLD report emphasises that the underrecognition and underdiagnosis of COPD can lead to significant

<table>
<thead>
<tr>
<th>% needing spirometry</th>
<th>Price (&gt;16.5)</th>
<th>Price (&gt;19.5)</th>
<th>Kotz (&gt;16.5)</th>
<th>Kotz (&gt;19.5)</th>
</tr>
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<tr>
<td></td>
<td>26</td>
<td>46</td>
<td>77</td>
<td>48</td>
</tr>
<tr>
<td>% false negatives</td>
<td>&gt;4</td>
<td>2</td>
<td>1</td>
<td>3.5</td>
</tr>
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</table>

### Figure 2 Hypothetical study randomising patients to intensive intervention and symptomatic treatment

The dashed lines and solid lines represent two possible evolutions after 2 years. Reproduced with permission from.58
underreporting and, crucially, that early diagnosis and implementation of treatment, including smoking cessation, can prevent or delay the course of airflow obstruction or reduce its expression. Central to that is the identification of patients at high risk of COPD. The American College of Physicians concludes that there is evidence to support inhaled treatment in symptomatic patients with an FEV$_1$ <60% predicted and spirometry in symptomatic adults with an FEV$_1$ >60% predicted for determining when to initiate therapy. This has recently been challenged by the findings in TORCH and UPLIFT. Nevertheless, before the early treatment of all COPD patients can be recommended unequivocally, a greater understanding of the natural progression of COPD in the earlier stages is required and, more importantly, the detrimental effects of delaying treatment need to be shown. We therefore need to perform the hypothetical study in Fig. 2. In this study, the effects of early intensive treatment versus symptomatic treatment solely with short-acting bronchodilators on FEV$_1$ and other outcomes would be examined in a group of patients identified with a screening procedure in general practice and after successful smoking cessation. Showing a difference after 1–2 years would not irrefutably show that early treatment is warranted. Intensive treatment would then need to be administered to the patients originally randomised to the symptomatic treatment group. If their outcomes increased to the same levels as the group treated intensively from early on, early treatment would still not be mandatory. If, however, a difference in outcomes persisted, then early treatment would be a necessity.

Early intervention studies such as this will never be carried out without political will and enough resources, especially as treating more patients and treating them better will be more expensive in the short term. However, if early treatment is able to stop the progression of the disease and reduce hospitalisations in the long term, the overall costs of COPD treatment will be reduced. An in-depth cost-effective analysis is the missing link in early COPD intervention and must be the focus of future studies.

**Treatment for early COPD**

The principle that patients with early COPD could benefit significantly from intervention (see Table 5) was established in 1994 by the Lung Health Study, in which 5887 patients with mild-to-moderate airway obstruction (FEV$_1$ 50–90% predicted and FEV$_1$/FVC <70%) who otherwise healthy were randomised to an intensive, long-term smoking cessation program or usual care for 5 years. Those randomised to the smoking cessation program were also randomised to ipratropium bromide 18 µg or placebo three times daily; however, as use of the active bronchodilator was associated with a small noncumulative benefit that disappeared after discontinuation, that treatment arm was omitted from further analyses. Sustained smoking cessation was associated with significantly lower declines in FEV$_1$ than continued smoking, at 31 ml/year and 62 ml/year ($p < 0.001$), respectively, and a significant difference in change in FEV$_1$ percent predicted compared with intermittent smoking, at $+1.98\%$ and $-0.74\%$ ($p < 0.001$), respectively. The European Respiratory Study on Chronic Obstructive Pulmonary Disease (EUROSCOP), published in 1999, investigated the benefits of active treatment in patients with mild-to-moderate COPD. For this study, 1277 individuals with post-bronchodilator FEV$_1$ 50–100% predicted and FEV$_1$/FVC <70% who continued smoking were randomised to budesonide 400 µg or placebo twice daily. After 3 years, there was no difference in the rate of decline in FEV$_1$ in patients treated with budesonide compared with those receiving placebo. An initial improvement in lung function was observed in the first 6 months with budesonide, but no significant change in decline subsequently, at $-57$ ml/year with budesonide versus $-69$ ml/year with placebo ($p = 0.39$), as the study was powered to detect a difference of only $20$ ml/year.

A randomised, double-blind, parallel-group clinical trial nested in the Copenhagen City Heart Study indicated that, in 290 patients with a mean FEV$_1$ 86% predicted, budesonide 400 µg bid, compared with placebo, did not have a significant impact on the rate of decline of FEV$_1$ or the number of exacerbations. In the Lung Health Study II, which compared triamcinolone acetonide 600 µg or placebo bid in 1116 patients with mild-to-moderate COPD, active treatment had, again, a non-significant effect on the rate of decline in FEV$_1$. Nevertheless, there was a significant reduction in respiratory symptoms with triamcinolone acetonide, at 21.1 per 100 person-years versus 28.2 per 100 person-years for placebo ($p = 0.005$), and in visits to a physician due to respiratory illness, at 1.2 per 100 person-years versus 2.1 per 100 person-years for placebo ($p = 0.03$).

A post-hoc analysis of the ISOLDE trial of 751 patients treated with fluticasone propionate 500 µg or placebo bid showed that, in 391 patients with an FEV$_1$ $\geq 50\%$ predicted, fluticasone propionate had no impact on the number of exacerbations per patient per year, at 1.47 versus 1.75 ($p = 0.45$). However, the proportion of patients with $\geq 1$ exacerbations/year treated with oral corticosteroids was reduced significantly with active treatment, at 8% versus 16% for placebo ($p = 0.02$). In the ISOLDE trial as a whole, the annual rate of decline in FEV$_1$ was 50 ml/year in the fluticasone propionate group and 59 ml/year in the placebo group ($p = 0.16$). Again, the study was powered to detect only a difference of only 20 ml/year.

For the BRONCUS study, 523 COPD patients were randomly assigned to N-acetylcysteine (NAC) 600 mg daily or placebo and followed-up for 3 years. NAC was found to have, compared with placebo, no significant effects on either the decline in FEV$_1$ or the decline in vital capacity (VC) in 389 participants with GOLD Stage II COPD. Mean decline in FEV$_1$ was 6 ml/year higher with NAC ($p = 0.589$) and 12 ml/year higher in VC ($p = 0.538$).

The MISTRAL study, published in 2006, randomised 1010 COPD patients to tiotropium 18 µg or placebo once daily for 1 year. Among 426 patients with an FEV$_1$ $>50\%$ predicted, tiotropium was associated with a significant reduction in the number of exacerbations per patient per year, at 1.21 versus 1.97 ($p < 0.001$), alongside which there was a non-significant reduction in the number of patients experiencing $\geq 1$ exacerbation in patients with mild COPD.

TORCH, which compared salmeterol plus fluticasone versus both single substances and placebo, included 2156...
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Duration/ No randomised/ pre-randomisation run-in</th>
<th>Intervention</th>
<th>Agea/% male/FEV1 % predb</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Lung Health Study (1994)59,60 | • 5 years  
• N = 5887  
• No run-in | • SIA  
• SIP  
• US  
• Ratio: 1:1:1 | • SIA: 48.4 years; 60.8% male; 75.1% pred  
• SIP: 48.6 years; 64.0% male; 75.2% pred  
• US: 48.4 years; 63.8% male; 75.1% pred | • Δ FEV1: Q: 31 ml/year; I: 43 ml/year; S: 62 ml/year (p < 0.001, S versus Q)  
• Δ FEV1% pred (1 year): Q: +1.98; I: −1.59; 0.74 (p < 0.001, I versus Q) |
| EUROSCOP (1999)61 | • 3 years  
• N = 1277  
• 6 months run-in | • Bud 400 μg bid  
• Placebo  
• Ratio: 1:1 | • Bud: 52.0 years  
• Placebo: 52.0 years  
• 73% male  
• 77% pred | • Δ FEV1 (6 months): bud: +17 ml; placebo: +81 ml (NS)  
• Δ FEV1 (9 months): bud: −57 ml; placebo: −69 ml (p = 0.39) |
| CCHS (1999)62 | • 3 years  
• N = 290  
• N/Ac | • Bud 800 μg plus  
400 μg daily for 6 months,  
400 μg bid for 30 months  
• Placebo for 36 months  
• Ratio: 1:1 | • Bud: 59.0 years; 58.8% male; 86.2% pred  
• Placebo: 59.1 years; 62.1% male; 86.9% pred | • FEV1: bud: 49.6 ml/year; placebo: 45.1 ml/year (p = 0.70)  
• No. exacerbations: bud: 155; placebo: 161 (NS) |
| Lung Health Study II (2000)63 | • 40 monthsd  
• N = 1116  
• 3 months screening | • Tri 1200 μg per daye  
• Placebo  
• Ratio: 1:1 | • Tri: 56.2 years; 64.0% male; 68.5% pred  
• Placebo: 56.4 years; 62.1% male; 67.2% pred | • Δ FEV1: tri: 44.2 ml/year; placebo: 47.0 ml/year (p = 0.50)  
• Respiratory symptoms: tri: 21.1 per 100 person-years; placebo: 28.2 per 100 person-years (p = 0.005)  
• Visits to a physician due to respiratory illness: tri: 1.2 per 100 person-years; placebo: 2.1 per 100 person/years (p = 0.03)  
• No. exacerbations/patient/year: FP: 1.47; placebo: 1.75 (p = 0.45)  
• Patients with ≥1 exacerbation/year treated with oral corticosteroids: FP: 8%; placebo: 16% (p = 0.02) |
| ISOLDE (2003)64 | • 3 years  
• N = 751 (FEV1 ≥50% pred: 391)  
• 8 week run-in | • FP 500 μg bid  
• Placebo  
• Ratio: 1:1 | • FEV1 ≥50% pred:  
• FP: 63.0 years; 63% male; 61% pred  
• Placebo: 63.0 years; 66% male; 62% pred  
• NAC: 62.0 years; 79% male; 57.0% pred  
• Placebo: 62.0 years; 82% male; 57.0% pred | • No. exacerbations/patient/year: FP: 1.47; placebo: 1.75 (p = 0.45)  
• Patients with ≥1 exacerbation/year treated with oral corticosteroids: FP: 8%; placebo: 16% (p = 0.02) |
| BRONCUS (2005)65 | • 3 years  
• N = 523 (GOLD Stage II: 389)  
• N/A | • NAC 600 mg daily  
• Placebo  
• Ratio: 1:1 | | • Δ decline in FEV1 (NAC versus placebo): −6 ml/year (p = 0.589)  
• Δ decline in VC (NAC versus placebo): −12 ml/year (p = 0.538) |
### MISTRAL (2006)\textsuperscript{67}
- 1 year
- \( N = 1010 \) (FEV\textsubscript{1} >50\% pred: 426)
- 3 weeks screening

### TORCH (2008)\textsuperscript{56,68}
- 3 years
- \( N = 6112 \) (GOLD Stage II: 2156)
- 2 weeks run-in

### UPLIFT (2008)\textsuperscript{57,69}
- 4 years
- \( N = 5993 \) (GOLD Stage II: 2739)
- 14–30 days screening

### O'Donnell et al. (2009)\textsuperscript{71}
- 28 days
- \( N = 16 \)
- N/A

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<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>( N )</th>
<th>GOLD Stage II:</th>
<th>FEV\textsubscript{1} &gt;50% pred:</th>
<th>No. exacerbations/patient/year:</th>
</tr>
</thead>
<tbody>
<tr>
<td>MISTRAL</td>
<td>1 year</td>
<td>1010</td>
<td></td>
<td>64.5 years; 89.0% male; 48.2% pred</td>
<td>Tio: 1.21; placebo: 1.97 (( p &lt; 0.01 ))</td>
</tr>
<tr>
<td>TORCH</td>
<td>3 years</td>
<td>6112</td>
<td>64.9 years</td>
<td>72.0% male; 58.8% pred</td>
<td>Tio: 0.47; placebo: 0.72 (NS)</td>
</tr>
<tr>
<td>UPLIFT</td>
<td>4 years</td>
<td>5993</td>
<td>65.0 years</td>
<td>72.0% male; 59% pred</td>
<td>Tio: 0.56; placebo: 0.70 (( p &lt; 0.0001 ))</td>
</tr>
<tr>
<td>O'Donnell</td>
<td>28 days</td>
<td>16</td>
<td>63.0 years</td>
<td>63.0% male; 90% pred</td>
<td>60 min:</td>
</tr>
</tbody>
</table>

**Notes:**
- FEV\textsubscript{1}: forced expiratory volume in 1 s; Pred: predicted; EUROSCOP: European Respiratory Society Study on Chronic Obstructive Pulmonary Disease; Bud: budesonide SIA: intensive long-term smoking cessation plus ipratropium bromide 18 μg three times daily; SIP: intensive long-term smoking cessation plus placebo; US: usual care; Q: sustained quitters; I: intermittent quitters; S: continuing smokers; Tri: triamcinolone acetonide; ISOLDE: Inhaled Steroids in Obstructive Lung Disease in Europe; Flu: fluticasone propionate; BRONCUS: Bronchitis Randomized on NAC Cost-Utility Study; GOLD: Global Initiative for Chronic Obstructive Lung Disease; NAC: N-acetylcysteine; VC: vital capacity; MISTRAL: Mesure de l’Influence de Spiriva sur les Troubles Respiratoires Aigus à Long terme; Tio: tiotropium; TORCH: Towards a Revolution in COPD Health; UPLIFT: Understanding Potential Long-term Impacts on Function and Tiotropium; Sal: salmeterol; SFC: salmeterol/fluticaone propionate combined; SGRQ: St George’s Respiratory Questionnaire; IB: ipratropium bromide; RV: respiratory volume; sRaw: specific airway resistance.
- a Mean.
- b Postbronchodilator.
- c Nested in epidemiological study.
- d Mean follow-up.
- e Six inhalations bid.
patients with GOLD stage II disease, who had a mean baseline FEV1 of 58.8% predicted.\textsuperscript{56} Post-hoc analysis showed that, compared with placebo, salmeterol plus fluticasone was associated with an increase in FEV1 of 101 ml and a decrease in the decline of FEV1 of 16 ml/year. This compared with an increase in FEV1 of 46 ml and a decrease in the decline of FEV1 of 14 ml/year with fluticasone alone, and with an increase in FEV1 of 67 ml and a decrease in the decline of FEV1 of 20 ml/year with salmeterol alone. Furthermore, combination therapy significantly reduced the number of exacerbations per patient per year compared with placebo, at 0.57 and 0.82, respectively. This compared with rates of exacerbations per patient per year of 0.68 and 0.71 for fluticasone alone and salmeterol alone, respectively.\textsuperscript{56} Reduction of exacerbations in this post-hoc analysis was significant,\textsuperscript{56} and the improvements in lung function and outcomes were in proportion to those observed in the overall study population.\textsuperscript{68}

In UPLIFT, which compared tiotropium bromide versus placebo, 2739 (46%) patients were in GOLD Stage II.\textsuperscript{57,69} Prespecified secondary analysis demonstrated that treatment with tiotropium in this population significantly reduced rates of decline in post-bronchodilator FEV1 compared with placebo (\(-43 \pm 2\) ml/year versus \(-49 \pm 2\) ml/year; \(p = 0.024\)), with improvements in lung function sustained over 4 years. Tiotropium also, compared with placebo, significantly reduced the number of exacerbations per patient per year, at 0.56 versus 0.70 (\(p < 0.0001\)) and significantly increased the median time to the first exacerbation, at 23.1 months versus 17.5 months (\(p < 0.001\)). Active treatment significantly improved SGRQ scores at all time points during follow-up, at reductions in scores ranging from 2.7 to 4.0 (\(p < 0.06\) at all time points).\textsuperscript{57} Importantly, the benefits of tiotropium observed in the MISTRAL and UPLIFT studies occurred despite patients being allowed to receive other drugs, such as ICS (61%–74%), respectively) and/or LABA (32%–72%, respectively).\textsuperscript{67,69} Crucially, a further pre-specified analysis of the UPLIFT data in 810 treatment naive patients, 60% of whom were in GOLD Stage II, showed that tiotropium, compared with placebo, was associated with a significantly lower rate of post-bronchodilator decline in FEV1 (\(42 \pm 4\) ml/year versus \(53 \pm 4\) ml/year; \(p = 0.026\)), a significantly higher morning pre-dose FEV1 at 48 months (134 ml higher for tiotropium; \(p < 0.001\)), and a significantly slower decline in SGRQ total score (difference 1.05 \(\pm 0.34\) units/year; \(p = 0.002\)).\textsuperscript{70}

Early treatment may also have an impact on exercise capacity. A study by O’Donnell et al demonstrated that, in 16 patients with symptomatic GOLD Stage I COPD, nebulised ipratropium bromide 500 \(\mu\)g significantly increased pulmonary function, as measured by FEV1, residual volume and specific airway resistance (\(p < 0.005\) for all), within 2 h. Furthermore, during constant-load exercise, active treatment was associated with a significant reduction in dyspnoea per minute ventilation and a significant increase in tidal volume (\(p < 0.05\) for both).\textsuperscript{71} These trials, overall, demonstrate that, in the early studies, inhaled corticosteroids did not improve lung function and improvements with salmeterol/fluticasone in the TORCH study were confined to patients with an FEV1 between 50% and 60%. All other interventions were associated with negative results, aside from intensive smoking intervention and use of long-acting bronchodilators. In terms of future trials, we need to reconsider the inclusion and exclusion criteria, and multivariate regression analysis of variables will indicate whether treatments are effective. Reversible COPD patients, who are more prevalent in early stages of COPD, should not be excluded. It is also important to note that patients do not complain of FEV1, they complain of symptoms and HRQoL, so these need to be included in all outcomes of trials, and more emphasis needs to be placed on assessing them. In the future, we need to think about different ways of preventing HRQoL reductions, as there is a large, unmet need in terms of impairment. Furthermore, to show treatment benefits, it is important that investigators focus on demonstrating real and tangible benefits by using combined end-points in larger numbers of patients and ensuring that the studies are sufficiently powered to reveal clinical and significant differences. Although there is still room for improvement, trials such as UPLIFT and TORCH have begun to address these problems.

In summary, early stage COPD is underrecognised and underdiagnosed, yet has a substantial impact on patients’ lives that is out of proportion to measurable reductions in lung function. The tools to detect early stage COPD in primary and secondary care are widely available, and emerging evidence strongly suggests that we can improve patients’ lung function and quality of life, as well as reduce exacerbations, with early, intensive treatment. It is time to take these important messages to governments, healthcare providers and patients, and begin the trials that will definitively show the benefits we are already beginning to see.

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Conflict of interest statements

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Marc Miravitlles has received honoraria for speaking at a national and international symposia and for participating in advisory boards from Boehringer Ingelheim and Pfizer.

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Daniel Dusser has no competing interests.

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References


