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2015-04

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Kankaanranta , H , Harju , T , Kilpelainen , M , Mazur , W , Lehto , J T , Katajisto , M , Peisa , T , Meinander , T & Lehtimeki , L 2015 , ' Diagnosis and Pharmacotherapy of Stable Chronic Obstructive Pulmonary Disease : The Finnish Guidelines ' , Basic & Clinical Pharmacology & Toxicology , vol. 116 , no. 4 , pp. 291-307 . <https://doi.org/10.1111/bcpt.12366>

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<http://hdl.handle.net/10138/208480>

<https://doi.org/10.1111/bcpt.12366>

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## Diagnosis and Pharmacotherapy of Stable Chronic Obstructive Pulmonary Disease: The Finnish Guidelines

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(Received 29 September 2014; Accepted 7 December 2014)

**Abstract:** The Finnish Medical Society Duodecim initiated and managed the update of the Finnish national guideline for chronic obstructive pulmonary disease (COPD). The Finnish COPD guideline was revised to acknowledge the progress in diagnosis and management of COPD. This Finnish COPD guideline in English language is a part of the original guideline and focuses on the diagnosis, assessment and pharmacotherapy of stable COPD. It is intended to be used mainly in primary health care but not forgetting respiratory specialists and other healthcare workers. The new recommendations and statements are based on the best evidence available from the medical literature, other published national guidelines and the GOLD (Global Initiative for Chronic Obstructive Lung Disease) report. This guideline introduces the diagnostic approach, differential diagnostics towards asthma, assessment and treatment strategy to control symptoms and to prevent exacerbations. The pharmacotherapy is based on the symptoms and a clinical phenotype of the individual patient. The guideline defines three clinically relevant phenotypes including the low and high exacerbation risk phenotypes and the neglected asthma–COPD overlap syndrome (ACOS). These clinical phenotypes can help clinicians to identify patients that respond to specific pharmacological interventions. For the low exacerbation risk phenotype, pharmacotherapy with short-acting  $\beta_2$ -agonists (salbutamol, terbutaline) or anticholinergics (ipratropium) or their combination (fenoterol–ipratropium) is recommended in patients with less symptoms. If short-acting bronchodilators are not enough to control symptoms, a long-acting  $\beta_2$ -agonist (formoterol, indacaterol, olodaterol or salmeterol) or a long-acting anticholinergic (muscarinic receptor antagonists; aclidinium, glycopyrronium, tiotropium, umeclidinium) or their combination is recommended. For the high exacerbation risk phenotype, pharmacotherapy with a long-acting anticholinergic or a fixed combination of an inhaled glucocorticoid and a long-acting  $\beta_2$ -agonist (budesonide–formoterol, beclomethasone dipropionate–formoterol, fluticasone propionate–salmeterol or fluticasone furoate–vilanterol) is recommended as a first choice. Other treatment options for this phenotype include combination of long-acting bronchodilators given from separate inhalers or as a fixed combination (glycopyrronium–indacaterol or umeclidinium–vilanterol) or a triple combination of an inhaled glucocorticoid, a long-acting  $\beta_2$ -agonist and a long-acting anticholinergic. If the patient has severe-to-very severe COPD ( $FEV_1 < 50\%$  predicted), chronic bronchitis and frequent exacerbations despite long-acting bronchodilators, the pharmacotherapy may include also roflumilast. ACOS is a phenotype of COPD in which there are features that comply with both asthma and COPD. Patients belonging to this phenotype have usually been excluded from studies evaluating the effects of drugs both in asthma and in COPD. Thus, evidence-based recommendation of treatment cannot be given. The treatment should cover both diseases. Generally, the therapy should include at least inhaled glucocorticoids (beclomethasone dipropionate, budesonide, ciclesonide, fluticasone furoate, fluticasone propionate or mometasone) combined with a long-acting bronchodilator ( $\beta_2$ -agonist or anticholinergic or both).

The Finnish Medical Society Duodecim has created a system for the production of national guidelines on the most important diseases. These guidelines provide the basis of evidence-based treatment of about 100 common health problems and are based on a rigorous evaluation of evidence and production of the guidelines in a specific format including formal level of evidence statements (A–D; see table 1) [1], and this level of

evidence is also referred in the current MiniReview. The major difference between the current guideline and most other guidelines for chronic obstructive pulmonary disease (COPD) is that the short reviews of the literature presenting the evidence supporting the claim for a certain level of evidence (A–D) are publicly available [1,2]. These guidelines and statements (in the Finnish language) are published on the website of the medical society Duodecim [1,2] and are available to all physicians as well as to the general public in Finland. In addition, patient versions are occasionally published. During summer 2012, the Finnish Medical Society Duodecim and the Finnish

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Table 1.

Grading of the evidence in the Current Care Guidelines.

Level of evidence	Description ( <i>verbal expression in the text</i> )
A	Strong research-based evidence (multiple, relevant, high-quality studies with homogeneous results – e.g. two or more randomized, controlled trials or a systematic review with clearly positive results)
B	Moderate evidence (e.g. one randomized, controlled trial or multiple adequate studies) (... <i>apparently</i> ...)
C	Limited research-based evidence (e.g. controlled, prospective studies) (... <i>may</i> ...)
D	No evidence (e.g. retrospective studies or the consensus reached in the absence of good-quality evidence)

Adapted from reference [1].

Respiratory Society invited members to a group aiming to update the previous guideline on COPD. The production of the novel guideline was started in October 2012, and the final version of the guideline (in Finnish) was accepted and published on 13 June 2014 after a long review process [2].

In Finland, the diagnostics and treatment of common respiratory diseases such as asthma and COPD are mainly performed in primary health care by general practitioners, and only a part of the patients are treated by respiratory specialists. The Finnish Medical Society Duodecim represents the whole medical community in Finland, and the society necessitates that the guideline should serve especially the general practitioners working in primary health care. However, the guideline is also widely used by respiratory specialists and other healthcare specialists such as nurses and pharmacists. Thus, the main requirements for the guideline were that it should be evidence based, accurate, clear and simple enough to be used in a busy general practice.

The need to update the guideline for the treatment of COPD was aroused by the prevalence of COPD in the Finnish patients and its importance and costs to patients and to the healthcare system as well as the paradigm shift in the treatment of COPD started by the GOLD (Global Initiative for Chronic Obstructive Lung Disease) report [3]. This guideline greatly owes to the international GOLD report [3] as well as to the innovative guideline for COPD by the Spanish Respiratory Society [4]. The present guideline introduces a modified and hopefully, simplified version of pharmacological treatment based on the assessment of exacerbation risk presented in the GOLD report [3] and Spanish guideline [4]. It takes into the account the neglected phenotype of COPD–asthma as presented in the Spanish COPD guideline [4,5] or asthma–COPD overlap syndrome (ACOS) as termed by the recent GINA report [6]. Asthma and COPD are generally diagnosed, treated and managed by the same personnel (nurses and general practitioners) in Finland. As there are some crucial differences in the treatment of these two common diseases, accurate diagnosis and clear treatment guidelines are of utmost importance. Thus, in the preparation of the present guideline, the diagnostic section was co-ordinated with the recently published asthma guideline as three members served in this group (H.K., T.H. and L.L.) who were also involved in the production of the asthma guideline [7]. Special attention was drawn to the diagnosis of COPD, differential diagnosis between asthma and COPD, and the inclusion of the ACOS. In addition, the phar-

macological treatment section was developed to pursue readiness, simplicity and in-depth precision at the same time. This Finnish COPD guideline in the English language covers only a part of the original guideline [2,8,9], that is the diagnostics, comprehensive assessment and pharmacological treatment of stable COPD. Other sections such as epidemiology, screening, tobacco cessation, oxygen therapy, ventilatory support, surgical treatments, pulmonary rehabilitation, management of acute exacerbations and palliative care can be found in the original document in Finnish [2,9]. This version of the guideline has been updated to contain some novel compounds (e.g. umeclidinium), fixed combinations of long-acting bronchodilators (glycopyrronium–indacaterol and umeclidinium–vilanterol) and fixed combinations of inhaled glucocorticoids (ICS) and long-acting  $\beta_2$ -agonists (beclomethasone dipropionate–formoterol and fluticasone furoate–vilanterol) not included in the earlier published Finnish version [2,8] and now available in Finland. In addition, new relevant literature has been cited.

### Diagnosics

The diagnosis of COPD is based on relevant exposure history, symptoms and airway obstruction that is not fully reversible (post-bronchodilator forced expiratory volume in one-second/forced vital capacity < 0.70; FEV<sub>1</sub>/FVC < 0.70).

#### *Evaluation of predisposing factors.*

The following predisposing factors should be assessed in the diagnostic evaluation: smoking history (in pack-years), current smoking, passive smoking, occupational exposures, previous respiratory infections, asthma and respiratory diseases in the family.

#### *Symptoms.*

Typical symptoms of COPD include dyspnoea, chest tightness, wheezing, cough and sputum production [3], but the diagnosis of COPD cannot be based on symptoms alone, as some patients are symptom free and similar symptoms can be caused by other diseases [10]. However, symptoms suggestive of COPD in an individual with exposure to tobacco or other risk factors should lead to spirometry and other diagnostic evaluations. In patients with established COPD, the level of symptoms and the presence of exacerbations should be assessed as these are used to guide the treatment

[3]. COPD is a progressive disease and symptoms tend to worsen, especially if the patient continues smoking, and dyspnoea at rest or light exercise, cough, weight loss and frequent exacerbations are often present in advanced severe-to-very severe COPD [11].

#### Physical examination.

The diagnosis of COPD cannot be based on clinical signs, but these can be suggestive of COPD and its degree of severity [3]. Wheezing may be heard during auscultation of the chest, but pulmonary sounds can also be normal. Increased respiratory rate at rest, the use of accessory respiratory muscles and signs of right-sided heart failure may be present in severe COPD.

#### Pulmonary function testing.

In diagnosing COPD, spirometry should be conducted with bronchodilation test. COPD can be diagnosed if  $FEV_1/FVC$  is  $<0.70$  in a post-bronchodilation spirometry [3]. This criterion causes some over-diagnosis in elderly people [12,13] and possibly also in women [14] and under diagnosis in individuals younger than 45 years [13], but it is sensitive in detecting COPD clinically assessed by a physician [15–17]. This criterion is also associated with mortality risk [18].

Significant reversibility in the bronchodilation test ( $FEV_1$  increases at least 12% and 200 ml) can be detected in approximately 25–50% of individuals with COPD (see Differential diagnosis below). Classification of severity of airway obstruction is presented in table 2, but this is only one aspect of the clinical severity of COPD.

#### Radiological imaging.

The diagnosis of COPD cannot be based on chest X-ray, but a chest X-ray should be included in the initial evaluation to exclude other diseases such as pulmonary cancer, tuberculosis, pneumonia, heart failure and pleural diseases.

In mild COPD, chest X-ray is almost always normal. In advanced disease flattening of the diaphragm, long narrow heart, over-inflation with thinning of blood vessels and emphysematous bullae can be seen. Computerized tomography of the chest is not routinely needed, but may be used by specialists in cases of problematic differential diagnosis to detect bronchiectasis and in the evaluation for surgical treatment of COPD [19].

#### Blood tests and sputum cultures.

There are no specific blood tests to be used in diagnosing COPD, but some basic tests may be used to rule out other diseases and to assess infections and respiratory failure during acute exacerbations. Bacterial culture of sputum is not useful in stable COPD. If COPD is found in a person with exceptionally young age ( $<45$  years) or with a low smoking history ( $<20$  pack-years), serum levels of alpha-1-antitrypsin (A1AT) should be measured to rule out alpha-1-antitrypsin deficiency. This recommendation may differ from that of other guidelines [3]. However, screening for A1AT is not recommended for all patients in Finland, because there is no A1AT replacement therapy available in Finland. Thus the only relevant therapeutic option is counselling for smoking cessation and the smoking cessation is recommended for all patients with COPD despite the knowledge of A1AT levels.

#### Comprehensive evaluation of the patient.

Symptoms, quality of life and the impact of the disease can be assessed with validated questionnaires such as COPD Assessment Test<sup>®</sup> (CAT<sup>®</sup>) and modified Medical Research Council Dyspnea Scale (mMRC) [3]. Six-minute walking test or ergometry can be used to assess exercise tolerance. The clinical severity of COPD is assessed based on the degree of airway obstruction, level of symptoms, exacerbations and co-morbidities (table 2). Extra-pulmonary manifestations and co-morbidities such as cardiovascular diseases, metabolic syndrome, osteoporosis and depression are more prevalent in individuals with COPD than in non-COPD individuals with

Table 2.

Classification of the severity of obstruction and the clinical severity of chronic obstructive pulmonary disease (COPD).

	Severity of obstruction (assessed after bronchodilation)	Clinical severity of COPD
Mild	$FEV_1 \geq 80\%$ predicted	Good quality of life (CAT <sup>®</sup> $< 10$ ), no frequent exacerbations and $FEV_1 > 50\%$ predicted
Moderate	$50\% \leq FEV_1 < 80\%$	One of the following: <ul style="list-style-type: none"> <li>• <math>FEV_1 &lt; 50\%</math> predicted</li> <li>• At least two exacerbations a year or one hospitalization because of COPD</li> <li>• COPD has a medium impact on life (e.g. CAT<sup>®</sup> <math>\geq 10</math> points) or causes poor quality of life or impaired exercise tolerance</li> </ul>
Severe	$30\% \leq FEV_1 < 50\%$	
Very severe	$FEV_1 < 30\%$	One of the following: <ul style="list-style-type: none"> <li>• <math>FEV_1 &lt; 30\%</math> predicted</li> <li>• Chronic respiratory failure</li> <li>• Frequent exacerbations or hospitalizations regardless of treatment to COPD</li> <li>• COPD has a high or very high impact on life (e.g. CAT<sup>®</sup> <math>\geq 20</math> points) or causes very poor quality of life or exercise tolerance</li> </ul>

similar smoking history. Nutritional status and especially unintended loss of weight should be assessed.

#### *Differential diagnosis.*

The most important differential diagnoses include asthma, chronic bronchitis, lower airway infections (including tuberculosis), lung cancer, interstitial lung diseases and heart diseases.

A common diagnostic problem is to distinguish between asthma and COPD. Although these diseases are often treated with the same medication, they differ in basic pathology, aetiology and prognosis. COPD and asthma are often found in the same individual, and in smoking asthma patients, the cellular components of inflammation may resemble that found in COPD [3,6]. The differential diagnosis of asthma and COPD cannot be based on pulmonary function tests alone, but a comprehensive approach including smoking history, symptoms, co-morbidities and family history is needed [3,6].

Bronchodilation test in spirometry cannot reliably distinguish between asthma and COPD [3], as asthmatic individuals do not always present with significant reversibility and approximately 25–50% of individuals with COPD have significant reversibility [20–22].

Glucocorticoid therapy test does not always differentiate between asthma and COPD [23], as a considerable proportion of individuals with COPD benefit from ICS [24]. On the other hand, some of the asthmatic individuals are not responsive to ICS alone [25]. However, if an individual patient clearly benefits from using ICS (i.e. as assessed based on improvement in lung function or based on a reduction of symptoms or exacerbations), it should be continued regardless of the diagnosis (asthma or COPD). As the response to oral glucocorticoids does not predict responsiveness to ICS [26,27], the possible treatment trials should be conducted using ICS at moderate (to high) doses for (4 to) 8 weeks.

Normalization of lung function by ICS treatment excludes COPD and strongly supports the diagnosis of asthma. If the lung function is not significantly changed by ICS treatment, the diagnosis is more likely COPD than asthma.

#### **Aims of the Treatment of COPD**

The goals of the therapy of COPD can be divided into four major aims:

- 1 Controlling symptoms and improving the quality of life.
- 2 Reducing future risk, that is preventing exacerbations.
- 3 Slowing down the progression of the disease.
- 4 Reducing mortality.

#### **Multimodal Therapy of COPD**

The therapy of COPD includes both non-pharmacological and pharmacological means. Non-pharmacological treatment modalities include smoking cessation [28], oxygen therapy, physical exercise and pulmonary rehabilitation, ventilator support and surgical therapy. Palliative care in patients nearing death is discussed in detail in the original document and may

include a trial of opioids for refractory dyspnoea [2,9]. The risk of physical inactivity in patients with COPD is vastly increased (A) [29], and the patients should be encouraged to do physical exercise. Physical activity reduces the risk of mortality and hospitalizations. In contrast, physical inactivity predicts increased mortality (A) [30,31]. Exercise-based pulmonary rehabilitation courses should be available for COPD patients with continued dyspnoea despite the use of bronchodilators, or when they are physically inactive and suffer from frequent exacerbations, or have exercise intolerance. These recommendations can be found in detail in the original document [2,8,9]. Pharmacological therapies include bronchodilators, combinations of ICS and long-acting bronchodilators, phosphodiesterase 4 (PDE4) inhibitors or theophylline and influenza and pneumococcal vaccination.

#### **Vaccination**

In the general population, vaccination of persons aged >65 years against influenza has been found to reduce pneumonia, hospitalization and deaths by 50–68%. A majority of patients with COPD belong to this age group. Vaccination against influenza reduces COPD exacerbations (A) [32]. Vaccination annually against influenza is recommended for all patients with COPD.

Pneumococcal vaccination apparently reduces pneumonia of pneumococcal origin in patients with COPD (B) [33–35]. Pneumococcal vaccination is recommended for patients with COPD.

#### **Pharmacotherapy of Stable COPD**

##### *Principles of regular long-term pharmacotherapy of COPD.*

- 1 There exist two main goals with the current pharmacotherapy of COPD. They are (1) to control symptoms and (2) to reduce future risk (i.e. the exacerbations of COPD). The grounds for the use of any particular treatment in COPD may be either one of these goals or both goals together. The continuation or termination of a specific therapy is decided based on which goal is targeted (fig. 1).
- 2 If a particular pharmacotherapy is started in an effort to achieve both goals, the decision whether to continue or discontinue is made based on goal 2, that is the aim to reduce future risk (exacerbations). This is because the ability or inability of any particular drug to improve lung function or symptoms is not known to predict its ability to reduce exacerbations of COPD.
- 3 The pharmacological groups of inhaled drugs and the compounds used in the pharmacotherapy of COPD are shown in table 3.
- 4 The effects of several pharmacotherapies of COPD as well as the effects of smoking cessation and exercise on different end-points and goals in the treatment of COPD are shown in table 4.
- 5 The pharmacotherapy of COPD is based on the individual patient phenotype, on the level of symptoms and the risk of exacerbations. These are described in the section

Long-term pharmacological treatment of COPD has two separate aims, but same medication may help in achieving therapeutic benefit in both aims.

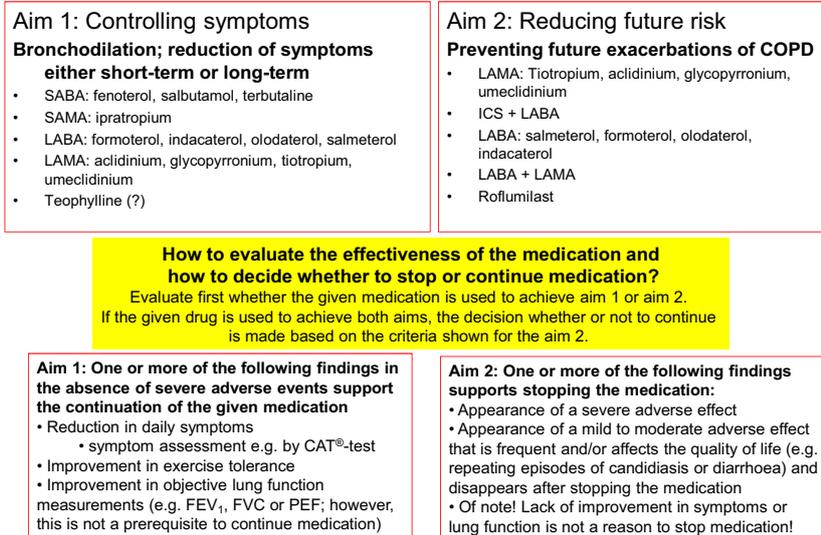


Fig. 1. Aims of the pharmacotherapy of chronic obstructive pulmonary disease (COPD) and principles for the evaluation whether to continue or discontinue the current medication.

‘COPD phenotypes and phenotype-specific pharmacotherapy of COPD’. Grouping of patients to three different phenotypes is shown in fig. 2.

- 6 Phenotype and phenotype-based pharmacotherapy (fig. 2) should be evaluated at every visit to health care as the phenotype may change when the disease progresses (especially with regard to an increase in exacerbation risk) [36].
- 7 So far, no pharmacotherapy has definitively been shown to slow down disease progression (annual FEV<sub>1</sub> decline) or reduce mortality [37–43], even though preliminary findings suggesting such effects have been published.
- 8 The principles for combining different drugs in the treatment of COPD are shown in table 5.
- 9 A short-acting bronchodilator to be used on as-needed basis is considered beneficial for most patients treated with long-acting bronchodilators or combination therapy including long-acting bronchodilators.

#### Bronchodilators.

Drugs that relieve bronchial obstruction by reducing bronchial smooth muscle contraction are called bronchodilators. Usually, they improve spirometric values reflecting obstruction such as FEV<sub>1</sub>. These compounds generally improve also emptying of the lungs and reduce air trapping (dynamic hyperinflation/restriction) both at rest and during exercise [44]. These effects cannot be predicted based on the ability of the particular compound to improve FEV<sub>1</sub> [45–48]. The dose–response effect of all bronchodilators at the currently used doses is relatively flat, which means that a small increase (e.g. doubling) in the dose is not expected to produce a vast increase in the bronchodilatory action [49–51]. The adverse effects are generally dose-related. Increase in the dose of short-acting inhaled  $\beta_2$ -agonist and anticholinergic, especially when given nebulized, may relieve sub-

jective dyspnoea in acute setting during an exacerbation of COPD but may not help as a long-term therapy [52,53].

Bronchodilators can be divided into short acting (duration of bronchodilatory effect generally 3–6 hr) and long acting (duration of bronchodilatory effect generally 12–24 hr). There are two different classes of bronchodilators that have basically similar bronchodilatory action in the treatment of COPD but different mechanism of action. These pharmacological classes are  $\beta_2$ -agonists and muscarinic receptor (M<sub>1</sub>, M<sub>2</sub> and M<sub>3</sub>) antagonists (termed anticholinergics) [54,55]. Both of these pharmacological classes contain short-acting and long-acting preparations. Bronchodilators are usually administered on either as-needed (usually short-acting preparations) or regularly (usually long-acting preparations) to treat or prevent the occurrence of symptoms.

A short-acting bronchodilator to be used as-needed is considered beneficial for most patients even though they were treated with long-acting bronchodilators or combination therapy including long-acting bronchodilators. Instead, the use of regular, high-dose (nebulized, etc.), short-acting bronchodilator or their combination in patients treated with long-acting bronchodilators is not evidence based [3] and should only be reserved to treatment of the most difficult cases. In such a situation, the need for long-acting bronchodilators should be carefully evaluated as well as the ability of the patient to properly inhale them.

#### Short- and long-acting $\beta_2$ -agonists (SABA, LABA).

The main beneficial effect of  $\beta_2$ -agonists is the reduction of bronchial smooth muscle contraction that leads to relief of bronchial obstruction. The duration of the effect of short-acting  $\beta_2$ -agonists is usually 3–6 hr. Short-acting  $\beta_2$ -agonist used either as-needed or regularly reduce symptoms of COPD and improve lung function [56]. The effect of long-acting  $\beta_2$ -

Table 3.

Pharmacological compounds used in the therapy of chronic obstructive pulmonary disease.

Pharmacological group and its abbreviation	Compounds belonging to the group
Short-acting $\beta_2$ -agonists	Salbutamol Terbutaline
Long-acting $\beta_2$ -agonist (LABA)	Formoterol Indacaterol Olodaterol Salmeterol Vilanterol
Short-acting anticholinergic	Ipratropium
Long-acting anticholinergic (LAMA)	Aclidinium Glycopyrronium Tiotropium Umeclidinium
Inhaled glucocorticoids (ICS)	Beclomethasone dipropionate Budesonide Ciclesonide Fluticasone propionate Fluticasone furoate Mometasone
Fixed combination of inhaled glucocorticoid and long-acting $\beta_2$ -agonist (ICS + LABA)	Budesonide–formoterol Beclomethasone dipropionate–formoterol Fluticasone propionate–salmeterol Fluticasone furoate–vilanterol
Fixed combination of long-acting anticholinergic and long-acting $\beta_2$ -agonist (LAMA + LABA)	Glycopyrronium–indacaterol Umeclidinium–vilanterol
Phosphodiesterase 4 (PDE4) inhibitors	Roflumilast
Others	Theophylline

agonists lasts 12 hr (formoterol or salmeterol) or 24 hr (indacaterol, olodaterol or vilanterol). The bronchodilatory action of formoterol/indacaterol/olodaterol/vilanterol starts sooner (within 5 min.) than that of salmeterol (within 20–30 min.). Indacaterol improves lung function (e.g. FEV<sub>1</sub>), reduces dyspnoea during exercise and improves the quality of life, but the evidence on the reduction of COPD exacerbations is still preliminary [57–60]. The efficacy of indacaterol, olodaterol or vilanterol, when measured using FEV<sub>1</sub> or quality of life, is at least as good as that of formoterol or salmeterol [58,61–63] or the long-acting anticholinergic tiotropium [58,61,64].

Generally,  $\beta_2$ -agonists are well tolerated. Typical adverse effects include tremor, tachycardia and palpitations that have been reported in <1% of patients. Headache, muscular cramps and an increase in the blood glucose and a decrease in potassium levels are possible, even though these events occur almost as often in patients treated with placebo [65]. It has been suggested that activation of heart  $\beta_2$ -receptors by  $\beta_2$ -agonists might induce ischaemia, cardiac insufficiency and arrhythmias or increase the risk of sudden death. However, in controlled clinical studies recruiting patients with COPD, there is no indication for the increase of arrhythmias or cardiac deaths [65] or overall mortality [66] by  $\beta_2$ -agonists. Based on a case–control study [67], an increase in the risk of severe arrhythmias is possible. Thus, the benefits of

using long-acting  $\beta_2$ -agonist in patients with severe cardiac disease should be carefully considered.

The use of long-acting  $\beta_2$ -agonists in the treatment of asthma in the absence of simultaneous ICS is prohibited [7] because there is evidence that treatment of asthma with long-acting  $\beta_2$ -agonists in the absence of ICS increases mortality due to asthma [68]. In contrast, in the treatment of COPD, a long-acting  $\beta_2$ -agonist can be used as the sole therapy as it does not increase mortality in COPD according to the studies published [65,66]. According to some cohort studies, use of long-acting  $\beta_2$ -agonist may even reduce the mortality of patients with COPD [69,70].

#### Short- and long-acting anticholinergics (SAMA, LAMA).

Anticholinergic compounds block muscarinic receptors (M<sub>1</sub>, M<sub>2</sub> and M<sub>3</sub>), thus antagonizing acetylcholine-induced bronchial smooth muscle contraction. The duration of the effect of short-acting anticholinergic (ipratropium) is usually somewhat longer (even up to 8 hr) than that of the short-acting  $\beta_2$ -agonists (3–6 hr), but starts more slowly [54,55]. The effect of long-acting anticholinergics lasts either 12 hr (aclidinium) or approximately 24 hr (glycopyrronium, tiotropium or umeclidinium). Of these, tiotropium has been most extensively studied and used. The bronchodilatory action of aclidinium and glycopyrronium starts sooner than that of tiotropium.

Tiotropium improves lung function and quality of life and reduces symptoms and exacerbations of COPD (A) [71]. In contrast, tiotropium does not affect the progression of the disease as judged by the annual decline in FEV<sub>1</sub> [72]. Tiotropium may be more effective than salmeterol in reducing exacerbations of COPD [73]. Both aclidinium and glycopyrronium have been shown to induce bronchodilation, improve lung function and quality of life and reduce the need for rescue medication [74,75], and their efficacy roughly equals to that of tiotropium. Aclidinium, glycopyrronium and umeclidinium have been shown to reduce COPD exacerbations in studies lasting up to 1 year [76–78], but long-term studies lasting more than 1 year, similar to those made with tiotropium [72,73], are still lacking.

Inhaled anticholinergics are generally well tolerated, and adverse effects occur relatively seldom. Typical adverse effects, such as dry mouth, blurred vision, throat irritation, rhinitis, constipation and nausea, are due to blocking of muscarinic receptors. Other possible adverse effects include also arrhythmias, urinary retention/obstruction, elevated intraocular pressure and acute or worsening of narrow-angle glaucoma [79].

The short-acting anticholinergic ipratropium has been suspected to induce cardiac adverse effects [79]. With the long-acting anticholinergics, no similar increase in cardiac adverse effects has been reported with certainty [79]. The 4-year-long UPLIFT trial reported that there were statistically significantly less cardiac adverse effects and the total mortality was numerically, although not statistically, lower in patients treated with tiotropium [72].

Recently, it has been proposed that dosing of tiotropium with Respimat<sup>®</sup> device (Boehringer Ingelheim, Ingelheim,

Table 4.

Effects of smoking cessation, exercise and various pharmacotherapies in the treatment of chronic obstructive pulmonary disease (COPD).

	Smoking cessation	Exercise	Short-acting bronchodilator ( $\beta_2$ -agonist or anticholinergic)	Long-acting $\beta_2$ -agonist	Long-acting anticholinergic	Addition of inhaled glucocorticoid in severe COPD <sup>1</sup>	Roflumilast in severe COPD
Symptoms	+	+	+	+	+	(+)	–
Obstruction	+	–	+	+	+	(+)	(+)
Exacerbations	+	+	–	+	+	+	+
Disease progression (annual FEV <sub>1</sub> decline)	+	?	–	–	–	(+)	?
Mortality	+	+	–	–	–	(+)	?

+ : definite beneficial effect; (+): small or possible beneficial effect; –: no effect; ?: no evidence.

<sup>1</sup>In practice means terminating long-acting  $\beta_2$ -agonist and prescribing a combination product containing both inhaled glucocorticoid and long-acting  $\beta_2$ -agonist.

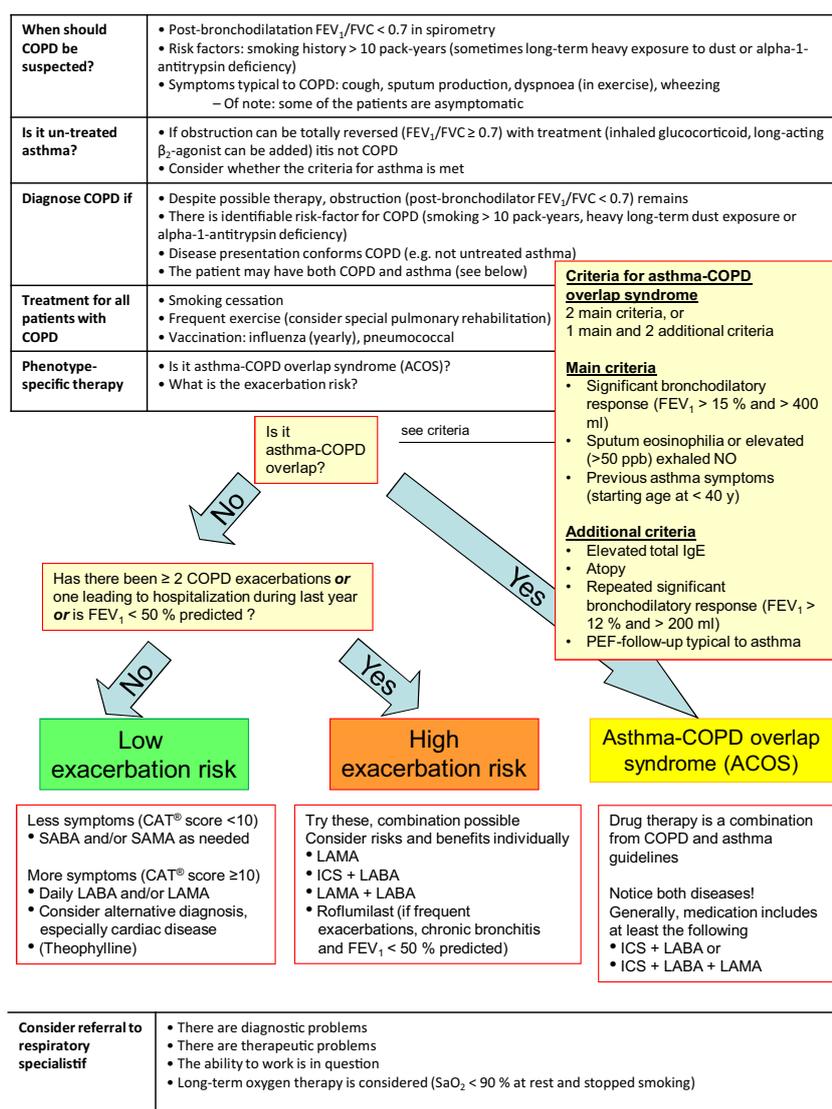


Fig. 2. The principles of diagnostics and phenotype-specific therapy of chronic obstructive pulmonary disease (COPD). Of note, the current indication for the use of different fixed combinations of inhaled glucocorticoid ICS and long-acting  $\beta_2$ -agonist (LABA) in COPD is frequent exacerbations despite the use of appropriate bronchodilator therapy, but the FEV<sub>1</sub> ranges from <50% predicted (budesonide–formoterol, beclomethasone dipropionate–formoterol) to <60% predicted (fluticasone propionate–salmeterol) and to <70% predicted (fluticasone furoate–vilanterol).

Table 5.

The principles of combining drugs used to treat chronic obstructive pulmonary disease (COPD). The general rule of drug therapy of COPD is that two drugs belonging to the same group or having similar mechanism of action should not be combined. The exception to this rule is the simultaneous use of short- and long-acting  $\beta_2$ -agonists that is allowed and often is meaningful.

If there is a clinical indication to combine drugs from the following groups, there is no pharmacological reason to prevent the combination. To a single patient, only one compound or product can be selected from the following groups of drugs

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Short-acting bronchodilators ('reliever medication') <sup>1</sup>
Short-acting $\beta_2$ -agonist (fenoterol, salbutamol, terbutaline)
Short-acting anticholinergic (ipratropium) <sup>2</sup>
Long-acting bronchodilators <sup>1</sup>
Long-acting $\beta_2$ -agonist (formoterol, indacaterol, olodaterol, salmeterol, vilanterol)
Long-acting anticholinergic (aclidinium, glycopyrronium, tiotropium, umeclidinium) <sup>2</sup>
Glucocorticoids
Inhaled glucocorticoids (beclomethasone, budesonide, fluticasone, mometasone, ciclesonide)
Oral medications
Phosphodiesterase 4 inhibitors (roflumilast) <sup>3</sup>
Theophylline <sup>3</sup>

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<sup>1</sup>The duration of action of the compound does not prevent the combination. For example, two long-acting bronchodilators can be combined as long as they have a different mechanism of action (i.e. tiotropium and indacaterol can be combined). Similarly, short-acting anticholinergic (ipratropium) can be combined with short-acting  $\beta_2$ -agonist (e.g. salbutamol). Instead, two different  $\beta_2$ -agonists with similar duration of action should not be combined (e.g. indacaterol should not be combined with formoterol or salmeterol). Use of a short-acting  $\beta_2$ -agonist as needed with a regular long-acting  $\beta_2$ -agonist is acceptable.

<sup>2</sup>Use of short-acting anticholinergic (ipratropium) with long-acting anticholinergic is not recommended.

<sup>3</sup>Phosphodiesterase 4 inhibitors and theophylline should not be combined because of the risk of adverse effects.

Germany) would cause more deaths than its dosing with Handihaler<sup>®</sup> device (Boehringer Ingelheim, Ingelheim, Germany) [79]. However, a direct comparison of the two devices for a mean of 2.3 years indicated that there were no differences in mortality, serious cardiac adverse effects or exacerbations of COPD [80].

#### Combination bronchodilator therapy.

Bronchodilators with a different mechanism or duration of action can be relatively freely combined (table 5), and the combination may have a better bronchodilatory effect [81]. For example, combination of a short-acting anticholinergic with a short- or long-acting  $\beta_2$ -agonist improves FEV<sub>1</sub> better than any of the single agents [81,82]. Short- or long-acting  $\beta_2$ -agonist can be combined with a long-acting anticholinergic if a single agent is not improving symptoms enough [81–83]. The combination of tiotropium and a long-acting  $\beta_2$ -agonist apparently improves the lung function and quality of life somewhat better than tiotropium alone (B) [83]. The use of short- and long-acting anticholinergic compounds together is not recommended. Even though this combination may improve results of lung function tests better than the single agents, it will increase the risk of adverse effects such as urinary retention [84]. Combination of a short-acting  $\beta_2$ -agonist with a long-acting anticholinergic will result in at least as good a response in lung function parameters without a risk of anticholinergic adverse effects. Thus, if a patient is using a long-acting anticholinergic, the rescue medication should be a short-acting  $\beta_2$ -agonist [84].

After the finalization of the Finnish guideline [2,8,9], two fixed-dose combinations of a long-acting  $\beta_2$ -agonist and a long-acting anticholinergic have been approved to be used in the treatment of COPD, namely indacaterol–glycopyrronium

and vilanterol–umeclidinium. In most studies, both of these fixed combinations have been shown to improve lung function (e.g. trough FEV<sub>1</sub>) and health status and to reduce dyspnoea better than the single monocomponents alone in patients with moderate-to-severe COPD with no apparent safety concerns [64,85–89]. In addition, the fixed-dose combination of indacaterol–glycopyrronium has been reported to reduce moderate-to-severe COPD exacerbations better than glycopyrronium alone [90].

#### Inhaled glucocorticoids.

In the treatment of asthma, the therapeutic and adverse effects of ICS depend on the dose used [91]. Instead, in the treatment of COPD, the dose dependency of the therapeutic and adverse effects of ICS is not known [92,93]. In long-term trials, only moderate and high doses of ICS have been used [92,93]. Regular long-term (>6 months) therapy with ICS in COPD reduces exacerbations and slows down the decline in the quality of life [93]. Generally, patients with mild disease and without previous exacerbation history do not benefit from ICS [3,93]. The response to ICS in COPD cannot be foretold from the response to oral glucocorticoids or by measuring hyper-reactivity or response to bronchodilators (bronchodilator test in spirometry) [93]. Discontinuation of ICS may precipitate exacerbation of the disease in some patients with COPD [94] but may be safely performed in others to decrease risk of long-term adverse effects [95]. ICS alone do not affect mortality due to COPD or the rate of decline of lung function (annual FEV<sub>1</sub> decline) [93]. Adverse effects include candida infection in the mouth and hoarseness. Also, there is evidence that use of ICS is associated with an increased risk of pneumonia [93] and fractures [96]. Initiation of ICS therapy has been associated with increased risk of diabetes in respiratory

patients in general in a registry-based study [97], but in a retrospective analysis of shorter placebo-controlled, double-blind studies in patients with asthma or COPD, it has not been confirmed [98].

Long-term therapy with ICS in addition to other therapy is recommended only for patients with ACOS or patients with a high risk of exacerbations of COPD, that is with severe or very severe obstruction in spirometry (table 2) and a history of frequent exacerbations (fig. 2) [99]. The use of ICS as the sole long-term therapy of COPD should be avoided as the combination of inhaled glucocorticoid with long-acting  $\beta_2$ -agonist is more efficient in reducing exacerbations of the disease and possibly better in reducing mortality and improving lung function and quality of life [100]. The use of ICS outside the current indications is not recommended as long-term therapy with these may increase the risk of pneumonia [92,93], osteoporosis and fractures [96].

#### *Combination of inhaled glucocorticoid and long-acting $\beta_2$ -agonist.*

In COPD, the current indication for the use of different fixed combinations of ICS and long-acting  $\beta_2$ -agonist is frequent exacerbations despite the use of appropriate bronchodilator therapy, but the accepted FEV<sub>1</sub> ranges from <50% predicted (budesonide–formoterol, beclomethasone dipropionate–formoterol) to <60% predicted (fluticasone propionate–salmeterol) and to <70% predicted (fluticasone furoate–vilanterol). The combination of inhaled glucocorticoid and a long-acting  $\beta_2$ -agonist reduces exacerbations and improves lung function and quality of life in COPD (A) [101]. In addition, combination of inhaled glucocorticoid and a long-acting  $\beta_2$ -agonist is better than placebo or any of its components in improving lung function and health status and reducing exacerbations in patients with COPD [100,102–105]. In a large, prospective 3-year trial with a combination of inhaled glucocorticoid and a long-acting  $\beta_2$ -agonist, there was no statistically significant effect on mortality [106]. However, in a subsequent meta-analysis, it was found that a combination of inhaled glucocorticoid and a long-acting  $\beta_2$ -agonist may reduce mortality (number needed to treat NNT = 36 to prevent one extra death; 95% CI 21; 258) [104].

The use of a combination of an inhaled glucocorticoid and a long-acting  $\beta_2$ -agonist is associated with adverse effects typical for both its components. The increased risk of pneumonia is considered as the most significant in patients with COPD [99,104]. At present, it remains uncertain to what extent increased risk of pneumonia is associated with other ICS or combinations of ICS and long-acting  $\beta_2$ -agonists, but a combination of inhaled fluticasone propionate and salmeterol may cause a higher risk [107–110].

Even though COPD is largely an under-diagnosed and under-treated disease [3], over-treatment of mild-to-moderate COPD (spirometric GOLD classification; table 2) with combinations of ICS and long-acting  $\beta_2$ -agonists was recently reported [111]. This cannot be recommended and leads to unnecessary adverse effects and costs [111].

Addition of a combination of an inhaled glucocorticoid and a long-acting  $\beta_2$ -agonist to tiotropium therapy has been reported to improve lung function and the quality of life, and it may even further reduce the occurrence of exacerbations, particularly severe exacerbations [112–115], but more and longer studies are needed. Preliminary evidence suggests that the triple therapy is cost-effective in Finland and other Scandinavian countries [116].

#### *Roflumilast.*

Roflumilast inhibits the inflammatory reaction associated with COPD by inhibiting enzyme phosphodiesterase 4 (PDE4) and by increasing intracellular cyclic adenosine monophosphate (cAMP) content [57]. Roflumilast is given orally as one tablet daily. It is not a bronchodilator and cannot be used to relieve acute bronchial obstruction, even though during long-term therapy in patients already on salmeterol or tiotropium, roflumilast further increases FEV<sub>1</sub> by 50–80 ml [57,117–119].

Roflumilast reduces exacerbations of COPD and improves lung function, but it also has significant adverse effects (A) [117]. Roflumilast reduces moderate (requiring systemic glucocorticoids) and severe (leading to hospitalization or death) exacerbations in patients with COPD who have severe COPD (FEV<sub>1</sub> < 50% predicted), chronic bronchitis and frequent exacerbations despite long-acting bronchodilators [57,117,118]. In contrast, the effects on the quality of life and symptoms are less pronounced [57,117].

Typical adverse effects of roflumilast are gastrointestinal complaints and headache. Weight loss is also common, and the weight should be followed [117,118].

#### *Other pharmacological treatments used for long-term therapy.*

*Oral glucocorticoids.* A treatment trial with oral glucocorticoids is not recommended in patients with COPD to identify those who will respond to ICS. A response to oral glucocorticoids has not been shown to predict the response to other treatments [23–27]. However, this does not prevent us from treating exacerbations with a course of oral steroids or trying a course of oral steroids in a patient with difficult symptoms.

Even though a high dose (equalling  $\geq 30$  mg oral prednisolone per day) of oral glucocorticoids improves lung function in the short run, there is no evidence of long-term benefits of oral glucocorticoids at low or moderate to high doses [120]. In contrast, there is evidence to suggest increased risk of adverse effects [120]. Thus, long-term therapy of COPD with oral glucocorticoids should be avoided as it may even worsen the long-term outcome of the patient [121]. Oral glucocorticoids have several significant adverse effects – one of the most important in the treatment of COPD being steroid myopathy which presents with symptoms such as muscular weakness, impaired physical activity and respiratory insufficiency in patients with very severe COPD [122]. Regular long-term oral glucocorticoid therapy has several well-known adverse effects, and thus, it is easy to understand that there exist no studies on its use in the treatment of stable COPD [3].

*Theophylline.* The exact mechanism of action of theophylline remains unknown, but it has both bronchodilatory and anti-inflammatory effects. The pharmacokinetics of theophylline varies between individuals and is prone to drug–drug interactions [123,124]. For this reason, its blood concentrations need to be followed and the dosing needs to be adjusted. The duration of effect in COPD is not known even in the case of currently used slow-release preparations [3].

The reports on the effects of theophylline in COPD are controversial. Theophylline apparently improves lung function in COPD, but the risk of adverse effects increases (B) [125–127]. Theophylline may improve the function of inspiratory muscles [123]. The effect of theophylline on lung function and symptoms in COPD is less than that of long-acting  $\beta_2$ -agonists formoterol and salmeterol [126,128]. Addition of theophylline to salmeterol improved FEV<sub>1</sub> and reduced dyspnoea better than salmeterol alone [128]. Small dose of theophylline (100 mg twice daily) reduced COPD exacerbations statistically significantly, but did not improve lung function as judged by post-bronchodilator spirometry [127].

The therapeutic concentration range of theophylline is narrow, and widespread toxicity is easily a problem [3,123,124]. The most usual adverse effects include gastric irritation, nausea, vomiting, diarrhoea, increased diuresis and signs of stimulation of central nervous (headache, nervousness, anxiety and agitation) and cardiac electrical (arrhythmias, specially tachycardia) systems [54,55,123,124,129]. For this reason, the use of theophylline has diminished, and it is recommended for the treatment of COPD only as an additional therapy to patients with severe symptoms.

#### *Antimicrobial compounds.*

A recent meta-analysis reported that regular use of macrolides (erythromycin, clarithromycin and azithromycin) in six studies (lasting 3–12 months) resulted in a 37% decrease in COPD exacerbations as compared with placebo. In addition, hospitalization was reduced by 21%, and the share of patients suffering from exacerbations was reduced by 68% but at the expense of increased risk of hearing loss [130,131]. However, a widespread use of macrolides is restrained by the fear of increased resistance of bacteria to macrolides [130].

#### *Compounds affecting sputum production or consistency (mucolytics).*

The group of mucolytic drugs consists of several compounds with varied mechanisms of actions, part of which remain unknown [54,55]. The regular use of mucolytics in COPD has been a subject of several studies with conflicting results [3,132].

Mucolytics apparently reduce COPD exacerbations, but they do not improve lung function or induce significant adverse effects (B) [132].

#### *Choice of the inhaler.*

A significant proportion of the patients commit errors in using their inhalers [133], so the correct use should be taught and controlled when starting the treatment and also at control visits.

The use of dry powder inhaler (DPI) does not require co-ordination of actuating the device and inhalation, but sufficient inspiratory strength is needed to create high enough inspiratory flow.

The use of pressurized, metered dose inhaler (pMDI) does not require high inspiratory flow, but the patient needs to be able to co-ordinate the actuation of the inhaler at the beginning of inhalation.

The use of valved holding chambers or spacer devices alleviates the problem with co-ordination, and they diminish oral and pharyngeal deposition when suspension aerosols are used [134].

Inspiratory flow is not always sufficient for the use of DPI in individuals with a more severe COPD [135]. A pMDI should then be used, and, if needed, holding chamber with or without mask and assistance from a caregiver can also be used. The basic principles of choosing a correct inhaler are shown in table 6 [136].

### **COPD Phenotypes and Phenotype-Specific Pharmacotherapy of COPD**

- 1 The pharmacotherapy of COPD is based on the individual patient phenotype, on the level of symptoms and the risk of exacerbations. Grouping of patients to three different phenotypes is shown in fig. 2.

Table 6.

Choosing a suitable inhaler.

Choosing a suitable inhaler

1. Assess the patients' ability to co-ordinate actuation of the pMDI and inhalation
2. Assess the patients' ability to create sufficient inspiratory flow for using DPI

Good co-ordination

Poor co-ordination

Good co-ordination		Poor co-ordination	
Inspiratory flow > 30 l/min.	Inspiratory flow < 30 l/min.	Inspiratory flow > 30 l/min.	Inspiratory flow < 30 l/min.
DPI	pMDI	DPI	pMDI + spacer
pMDI	SMI	BA-MDI	(SMI)
SMI	(nebulizer)	pMDI + spacer	(nebulizer)
BA-MDI		(SMI)	
(nebulizer)		(nebulizer)	

DPI, dry powder inhaler; pMDI, pressurized, metered dose inhaler; SMI, soft mist inhaler; BA-MDI, breath-actuated metered dose inhaler. Modified from reference [136].

2 Phenotype and phenotype-based pharmacotherapy (fig. 2) should be evaluated at every health care visit as the phenotype may change when the disease progresses (especially with regard to exacerbation risk) [36].

#### Low risk of exacerbations.

A phenotype of COPD that is characterized by a low risk of exacerbations based on infrequent previous exacerbations and relatively good lung function (i.e.  $FEV_1 \geq 50\%$  predicted) and the patient is not presenting with the typical features of ACOS (fig. 2). The patients are divided into two groups: those with less symptoms (CAT<sup>®</sup> score < 10 or mMRC score < 2) or those with more symptoms (CAT<sup>®</sup> score  $\geq 10$  or mMRC score  $\geq 2$  points) and limitations of physical activity or quality of life due to COPD.

- 1 In patients with less symptoms, a short-acting bronchodilator, either  $\beta_2$ -agonist or anticholinergic, is recommended. If a single compound is not enough to control the symptoms, a combination of short-acting  $\beta_2$ -agonist and anticholinergic can be used, even though there is not much evidence to support this treatment option [81].
- 2 If a short-acting bronchodilator is not enough to control the symptoms or the patient is having plenty of symptoms, a long-acting bronchodilator, either  $\beta_2$ -agonist or anticholinergic, can be used. In patients with more symptoms, long-acting bronchodilators are more effective than short-acting bronchodilators and thus are recommended [82,137].
- 3 At the moment, there is not enough evidence available to recommend one class ( $\beta_2$ -agonist or anticholinergic) of long-acting bronchodilators over the other as initial therapy in COPD [3]. The choice of a long-acting bronchodilator for long-term use should be made based on the symptomatic benefit experienced by the patient.
- 4 A combination of tiotropium and a long-acting  $\beta_2$ -agonist apparently improves the quality of life and lung function better than tiotropium alone (B) [58,83].
- 5 A combination product of long-acting bronchodilators (glycopyrronium and indacaterol) apparently improves spirometric lung function test results and quality of life better than any of its components alone (B) [85,90].
- 6 Theophylline can be combined to the bronchodilators described above, but the evidence to recommend its use alone or as a combination is limited. Theophylline apparently improves lung function in COPD, but the risk of adverse effects increases (B) [125–127].
- 7 If the patient is experiencing more symptoms and his/her lung function is only moderately reduced (i.e.  $FEV_1$  is  $\geq 50\%$  predicted), then consider the possibility of additional or alternative diagnosis, especially cardiac disease or lung cancer [36,138].

#### High risk of exacerbations.

A phenotype that is characterized by a high risk of exacerbations either based on previous exacerbation history or severe to very severe airflow limitation (i.e.  $FEV_1$  is <50% predicted) and the patient is not presenting with the typical features of

ACOS. The main aim of the pharmacotherapy in this patient group in addition to relieving symptoms is to prevent and to reduce the severity of exacerbations of COPD.

The recommended first choice of pharmacotherapy is as follows:

- 1 A long-acting anticholinergic or a combination of inhaled glucocorticoid and long-acting  $\beta_2$ -agonist:
  - The combination of inhaled glucocorticoid and a long-acting  $\beta_2$ -agonist reduces exacerbations and improves lung function and quality of life in COPD (A) [101].
  - Tiotropium improves lung function and quality of life and reduces symptoms and exacerbations of COPD (A) [71].
  - There is not enough evidence available to recommend one of these options over the other as initial therapy in high exacerbation risk phenotype of COPD [139].

Other treatment options:

- 1 Combination of two long-acting bronchodilators:
  - Long-acting anticholinergics [71] and long-acting  $\beta_2$ -agonists [140] reduce exacerbations of COPD, even though studies evaluating the effects of a combination of long-acting bronchodilators administered via separate inhalers are still scarce [58,83].
  - A combination product of long-acting bronchodilators (glycopyrronium and indacaterol) apparently improves spirometric lung function test results and quality of life better than its components alone (B) [85,90] and may reduce COPD exacerbations better than long-acting anticholinergic alone [90] and thus may be used.
- 2 Roflumilast:
  - If the patient is having severe-to-very severe COPD ( $FEV_1 < 50\%$  predicted), chronic bronchitis and frequent exacerbations despite long-acting bronchodilators, the pharmacotherapy may include also roflumilast.
  - Roflumilast reduces exacerbations of COPD and improves lung function, but it also has significant adverse effects (A) [117].
- 3 Triple therapy:
  - If the patient is having more symptoms in addition to exacerbations, a combination of three agents (i.e. an inhaled glucocorticoid, a long-acting  $\beta_2$ -agonist and a long-acting anticholinergic) may be used. The evidence of the usefulness of this triple combination is mainly based on short trials [112–115].
- 4 Inhaled glucocorticoid and long-acting anticholinergic:
  - This is not a therapy based on strong evidence, but in theory it is considered sensible. The reason for the absence of evidence most probably is due to the lack of interest by the pharmaceutical industry rather than not being a rational combination [3].
- 5 Long-acting  $\beta_2$ -agonist:
  - Long-acting  $\beta_2$ -agonist (formoterol or salmeterol) reduces exacerbations and hospitalizations due to COPD and improves lung function (A) [106,140,141]. Both com-

pounds also improve significantly the quality of life and reduce the need for rescue medication, but do not reduce mortality due to COPD or the annual decline in FEV<sub>1</sub> [106,140].

- Long-acting  $\beta_2$ -agonist as the sole therapy of high-risk phenotype of COPD is not, however, recommended because these studies were not carried out in patients prone to COPD exacerbations [140] and because there is solid evidence of the efficacy of both the long-acting anticholinergic [71] and the combination of inhaled glucocorticoid and long-acting  $\beta_2$ -agonist [104] in this indication.

#### 6 Theophylline:

- Theophylline can be combined with inhaled glucocorticoid and/or long-acting bronchodilators, but the evidence of its efficacy in reducing COPD exacerbations as part of a combination therapy or alone is very limited [127]

#### 7 Antibiotics

- Regular use of macrolides (erythromycin, clarithromycin and azithromycin) reduces COPD exacerbations [130], but widespread use of macrolides is restrained by the fear of increased resistance of bacteria to macrolides. For this reason, long-term therapy with antimicrobial compounds should be restricted to patients who suffer from repeated exacerbations leading to hospitalization despite adequate pharmacotherapy of COPD [92]. The decision to start and to follow up on this kind of therapy always necessitates specialist consultation.

#### 8 Compounds affecting sputum production or consistency (mucolytics)

- Mucolytics apparently reduce COPD exacerbations, but they do not improve lung function or induce significant adverse effects (B) [132].
- The long-term use of mucolytics in the routine therapy of COPD is not recommended. However, some patients presenting with severe over-production of viscous mucus may benefit from them [132]. At the moment, no clear evidence exists to guide the use of mucolytics in COPD (i.e. which compound, to which kind of patients and for how long).

#### *Asthma–COPD overlap syndrome.*

- 1 This is a phenotype of COPD in which there are features that comply both with asthma and with COPD (fig. 2). Patients belonging to this phenotype have been usually excluded from studies evaluating the effects of drugs both in asthma and in COPD [142–144]. Thus, evidence-based recommendation of treatment cannot be given. Furthermore, there exist no generally accepted criteria for this condition [6,142].
- 2 In patients fulfilling the criteria for both asthma and COPD and who were using ICS, addition of tiotropium improved lung function test results and reduced the need for rescue medication [145].
- 3 The treatment should cover both diseases, and, generally, the therapy includes at least ICS combined with long-acting bronchodilator ( $\beta_2$ -agonist or anticholinergic or both)

(the reader is strongly advised to familiarize him-/herself also with the Asthma guidelines) [6,7].

#### Conclusion

Optimal therapy of patients with COPD requires a tailored and multidisciplinary approach focusing on the symptoms and the individual future risk of the patient [3,4,146,147]. In addition, the personal needs and wishes should be taken into account [3–5,146]. The current guideline emphasizes early diagnosis with structured evaluation of the phenotype of each patient. The therapy should be started early in the course of the disease and should be phenotype-directed. The phenotype may change during the course of the disease and should be re-evaluated during each follow-up visit, and the pharmacotherapy should be changed according to the changed phenotype of the disease.

The paradigm shift in the treatment of COPD initiated by the GOLD (Global Initiative for Chronic Obstructive Lung Disease) report [3] offers a basis for the assessment of the future risk of the individual patient. However, at the same time, there is a huge lack of knowledge on the effects of pharmacotherapies on the symptoms and risks of different phenotypes of COPD as well as on patients with different comorbidities. Future studies with drugs directed towards COPD should take into consideration the different phenotypes of the disease and include patients with comorbidities and also follow-up for future risk end-points such as exacerbations, hospitalizations and mortality.

We recognize several limitations of the present guideline, and the reader may identify several deficiencies in the recommendations as well as topics that remain undiscussed. Several topics that were raised by the reviewers of the original Finnish guideline [2,8] as well as the present version in the English language remain untouched due to lack of evidence or due to very conflicting evidence. In fact, much more evidence is needed to evaluate the effectiveness of different therapies in COPD and its specific phenotypes. However, we have very little evidence that a specific pharmacotherapy would not help in COPD. Thus, the reader should not consider the ‘lack of evidence that a treatment works’ as a synonym for ‘evidence that a specific treatment does not help’ in COPD [3].

#### *Limitation of responsibility.*

The practice guidelines of the Finnish Medical Society Duodecim are summaries on the diagnostics and effectiveness of therapy on single diseases and are produced by experts. They do not replace the judgement of a physician or other health-care specialist on the best possible diagnostics and therapy of an individual patient.

#### References

- 1 Ketola E, Kaila M, Honkanen M. Guidelines in context of evidence. *Qual Saf Health Care* 2007;**16**:308–12.
- 2 Chronic Obstructive Pulmonary Disease (online). Current Care Guidelines. Working Group Set Up by the Finnish Medical Society Duodecim and the Finnish Respiratory Society. The Finnish

- Medical Society Duodecim, Helsinki, 2014. [www.kaypahoito.fi](http://www.kaypahoito.fi) (last accessed on 9 September 2014).
- Global strategy for the diagnosis, management and prevention of COPD, global initiative for chronic obstructive lung disease (GOLD) 2014. [www.goldcopd.org](http://www.goldcopd.org) (last accessed on 03 March 2014).
  - Miravittles M, Soler-Cataluna JJ, Calle M, Molina J, Almagro P, Quintano JA *et al.* Guia Espanola de la EPOC (GesEPOC). Tratamiento farmacologico de la EPOC estable. *Arch Bronconeumol* 2012;**48**:247–57.
  - Miravittles M, Soler-Cataluna JJ, Calle M, Molina J, Almagro P, Quintano JA *et al.* A new approach to grading and treating COPD based on clinical phenotypes: summary of the Spanish COPD guidelines (GesEPOC). *Prim Care Respir J* 2013;**22**:117–21.
  - Global strategy for asthma management and prevention, global initiative for asthma (GINA) 2014. <http://www.ginasthma.org/> (last accessed on 22 May 2014).
  - Haahntela T, Lehtimäki L, Ahonen E, Harju T, Jartti T, Kankaanranta H *et al.* Update on Current Care Guidelines: asthma. *Duodecim* 2013;**129**:994–5.
  - Harju T, Kankaanranta H, Katajisto M, Kilpeläinen M, Lehtimäki L, Lehto J *et al.* Keuhkohtaumatauti. Käypä hoito-suositus, päivitystiivistelmä. *Duodecim* 2014;**130**:1774–6.
  - Harju T, Kankaanranta H, Katajisto M, Kilpeläinen M, Lehtimäki L, Lehto J *et al.* Keuhkohtaumatauti. Käypä hoito-suositus [Update on Current Care Guideline: chronic obstructive pulmonary disease (COPD)]. *Duodecim* 2014;**130**:hoi06040.
  - Zwar NA, Marks GB, Hermiz O, Middleton S, Comino EJ, Hasan I *et al.* Predictors of accuracy of diagnosis of chronic obstructive pulmonary disease in general practice. *Med J Aust* 2011;**195**:168–71.
  - Blinderman CD, Homel P, Billings JA, Tennstedt S, Portenoy RK. Symptom distress and quality of life in patients with advanced chronic obstructive pulmonary disease. *J Pain Symptom Manage* 2009;**38**:115–23.
  - Schermer TR, Smeele IJ, Thoonen BP, Lucas AE, Grootens JG, van Boxem TJ *et al.* Current clinical guideline definitions of airflow obstruction and COPD overdiagnosis in primary care. *Eur Respir J* 2008;**32**:945–52.
  - Vollmer WM, Gíslason T, Burney P, Enright PL, Gulsvik A, Kocabas A *et al.* Comparison of spirometry criteria for the diagnosis of COPD: results from the BOLD study. *Eur Respir J* 2009;**34**:588–97.
  - Jordan RE, Miller MR, Lam KB, Cheng KK, Marsh J, Adab P. Sex, susceptibility to smoking and chronic obstructive pulmonary disease: the effect of different diagnostic criteria. Analysis of the Health Survey for England. *Thorax* 2012;**67**:600–5.
  - Güder G, Brenner S, Angermann CE, Ertl G, Held M, Sachs AP *et al.* GOLD or lower limit of normal definition? A comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study. *Respir Res* 2012;**13**:13.
  - Mohamed Hoesein FA, Zanen P, Sachs AP, Verheij TJ, Lammers JW, Broekhuizen BD. Spirometric thresholds for diagnosing COPD: 0.70 or LLN, pre- or post-dilator values? *COPD* 2012;**9**:338–43.
  - Mohamed Hoesein FA, Zanen P, Lammers JW. Lower limit of normal or FEV1/FVC < 0.70 in diagnosing COPD: an evidence-based review. *Respir Med* 2011;**105**:907–15.
  - Mannino DM, Diaz-Guzman E. Interpreting lung function data using 80% predicted and fixed thresholds identifies patients at increased risk of mortality. *Chest* 2012;**141**:73–80.
  - Xie X, de Jong PA, Oudkerk M, Wang Y, Ten Hacken NH, Miao J *et al.* Morphological measurements in computed tomography correlate with airflow obstruction in chronic obstructive pulmonary disease: systematic review and meta-analysis. *Eur Radiol* 2012;**22**:2085–93.
  - Calverley PM, Burge PS, Spencer S, Anderson JA, Jones PW. Bronchodilator reversibility testing in chronic obstructive pulmonary disease. *Thorax* 2003;**58**:659–64.
  - Tashkin DP, Celli B, Decramer M, Liu D, Burkhart D, Cassino C *et al.* Bronchodilator responsiveness in patients with COPD. *Eur Respir J* 2008;**31**:742–50.
  - Albert P, Agustí A, Edwards L, Tal-Singer R, Yates J, Bakke P *et al.* Bronchodilator responsiveness as a phenotypic characteristic of established chronic obstructive pulmonary disease. *Thorax* 2012;**67**:701–8.
  - Broekhuizen BD, Sachs AP, Moons KG, Cheragwandi SA, Damste HE, Wignands GJ *et al.* Diagnostic value of oral prednisolone test for chronic obstructive pulmonary disorders. *Ann Fam Med* 2011;**9**:104–9.
  - Callahan CM, Dittus RS, Katz BP. Oral corticosteroid therapy for patients with stable chronic obstructive pulmonary disease. A meta-analysis. *Ann Intern Med* 1991;**114**:216–23.
  - Woolcock AJ. Corticosteroid-resistant asthma. Definitions. *Am J Respir Crit Care Med* 1996;**154**:S45–8.
  - Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA. Prednisolone response in patients with chronic obstructive pulmonary disease: results from the ISOLDE study. *Thorax* 2003;**58**:654–8.
  - Chavannes NH, Schermer TR, Wouters EF, Akkermans RP, Dekhuijzen RP, Muris JW *et al.* Predictive value and utility of oral steroid testing for treatment of COPD in primary care: the COOPT study. *Int J Chron Obstruct Pulmon Dis* 2009;**4**:431–6.
  - Tobacco Dependence and Cessation (online). Current Care Guidelines. Working Group Set Up by the Finnish Medical Society Duodecim and the Finnish Association for General Practice. The Finnish Medical Society Duodecim, Helsinki, 2014. [www.kaypahoito.fi](http://www.kaypahoito.fi) (last accessed on 11 November 2014).
  - Vorriink SN, Kort HS, Troosters T, Lammers JW. Level of daily physical activity in individuals with COPD compared with healthy controls. *Respir Res* 2011;**12**:33.
  - Waschki B, Kirsten A, Holz O, Müller KC, Meyer T, Watz H *et al.* Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. *Chest* 2011;**140**:331–42.
  - García-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. *Thorax* 2006;**61**:772–8.
  - Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;**1**:CD002733.
  - Walters JA, Smith S, Poole P, Granger RH, Wood-Baker R. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2010;**11**:CD001390.
  - Lee TA, Weaver FM, Weiss KB. Impact of pneumococcal vaccination on pneumonia rates in patients with COPD and asthma. *J Gen Intern Med* 2007;**22**:62–7.
  - Alfageme I, Vazquez R, Reyes N, Munoz J, Fernandez A, Hernandez M *et al.* Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. *Thorax* 2006;**61**:189–95.
  - Agusti A, Edwards LD, Celli B, MacNee W, Calverley PMA, Mullerova H *et al.* Characteristics, stability and outcomes of the 2011 GOLD COPD groups in the ECLIPSE cohort. *Eur Respir J* 2013;**42**:636–46.
  - Decramer M, Celli B, Kesten S, Lystig T, Mehra S, Tashkin DP. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. *Lancet* 2009;**374**:1171–8.

- 38 Jenkins CR, Jones PW, Calverley PM, Celli B, Anderson JA, Ferguson GT *et al.* Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. *Respir Res* 2009;**10**:59.
- 39 Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. 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.
- 40 Celli BR, Thomas NE, Anderson JA, Ferguson GT, Jenkins CR, Jones PW *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.
- 41 Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS *et al.* Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA* 1994;**272**:1497–505.
- 42 Pauwels RA, Löfdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB *et al.* Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. *N Engl J Med* 1999;**340**:1948–53.
- 43 Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 1999;**353**:1819–23.
- 44 Thomas M, Decramer M, O'Donnell DE. No room to breathe: the importance of lung hyperinflation in COPD. *Prim Care Respir J* 2013;**22**:101–11.
- 45 O'Donnell DE, Fluge T, Gerken F, Hamilton A, Webb K, Aguilaniu B *et al.* Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004;**23**:832–40.
- 46 O'Donnell DE, Sciruba F, Celli B, Mahler DA, Webb KA, Kalberg CJ *et al.* Effect of fluticasone propionate/salmeterol on lung hyperinflation and exercise endurance in COPD. *Chest* 2006;**130**:647–56.
- 47 Berger R, Smith D. Effect of inhaled metaproterenol on exercise performance in patients with stable “fixed” airways obstruction. *Am Rev Respir Dis* 1988;**138**:624–9.
- 48 Hay JG, Stone P, Carter J, Church S, Eyre-Brook A, Pearson MG *et al.* Bronchodilator reversibility, exercise performance and breathlessness in stable chronic obstructive disease. *Eur Respir J* 1992;**5**:659–64.
- 49 Gross NJ, Petty TL, Friedman M, Skorodin MS, Silvers GW, Donohue JF. Dose response to ipratropium as a nebulized solution in patients with chronic obstructive pulmonary disease. A three-center study. *Am Rev Respir Dis* 1989;**139**:1188–91.
- 50 Higgings BG, Powell RM, Cooper S, Tattersfield AE. Effect of salbutamol and ipratropium bromide on airway calibre and bronchial reactivity in asthma and chronic bronchitis. *Eur Respir J* 1991;**4**:415–20.
- 51 Vathenen AS, Britton JR, Ebdon P, Cookson JB, Wharrad HJ, Tattersfield AE. High-dose albuterol in severe chronic airflow limitation. *Am Rev Respir Dis* 1988;**138**:850–5.
- 52 O'Driscoll BR, Kay EA, Taylor RJ, Weatherby H, Chetty MC, Bernstein A. A long-term prospective assessment of home nebulizer treatment. *Respir Med* 1992;**86**:317–25.
- 53 Jenkins SC, Heaton RW, Fulton TJ, Moxham J. Comparison of domiciliary nebulized salbutamol and salbutamol from a metered-dose inhaler in stable chronic airflow limitation. *Chest* 1987;**91**:804–7.
- 54 Kankaanranta H, Moilanen E. Hengitysteiden sairauksien hoidossa käytettävät lääkkeaineet [Drugs used to treat respiratory diseases]. In: Koulu M, Mervaala E (eds). *Farmakologia ja Toksikologia [Pharmacology and Toxicology]*, 9th edn. Kustannusosakeyhtiö Medicina Oy, Kuopio, Finland, 2013;513–40.
- 55 Kankaanranta H, Mäkelä M. Tukkeavat keuhkosairaudet. [Obstructive lung diseases]. In: Neuvonen PJ, Backman JT, Himberg J-J, Huupponen R, Keränen T, Kivistö KT (eds). *Kliininen farmakologia ja Lääkehoito [Clinical Pharmacology and Drug Therapy]*, 2nd edn. Kandidaattikustannus Oy, Helsinki, Finland, 2011;323–45.
- 56 Sestini P, Renzoni E, Robinson S, Poole P, Ram FSF. Short-acting beta2-agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2002;**3**:CD001495.
- 57 Kankaanranta H. Keuhkoastmataudin uudet lääkkeet indakateroli ja roflumilasti [review in Finnish]. *Suom Lääkäreilehti* 2013;**68**:299–306.
- 58 Chung VCH, Ma PHX, Hui DSC, Tam WWS, Tang JL. Indacaterol for chronic obstructive pulmonary disease: systematic review and meta-analysis. *PLoS ONE* 2013;**8**:e70784.
- 59 Han J, Dai L, Zhong N. Indacaterol on dyspnea in chronic obstructive pulmonary disease: a systematic review and meta-analysis of randomized placebo-controlled trials. *BMC Pulm Med* 2013;**13**:26.
- 60 Donohue JF, Singh D, Kornmann D, Lassen C, Kramer B. Safety of indacaterol in the treatment of patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2011;**6**:477–92.
- 61 Cope S, Donohue JF, Jansen JP, Kraemer M, Capkun-Niggli G, Baldwin M *et al.* Comparative efficacy of long-acting bronchodilators for COPD – a network meta-analysis. *Respir Res* 2013;**14**:100.
- 62 Koch A, Pizzichini E, Hamilton A, Hart L, Korducki L, De Salvo MC *et al.* Lung function efficacy and symptomatic benefit of olodaterol once daily delivered via Respimat<sup>®</sup> versus placebo and formoterol twice daily in patients with GOLD 2-4 COPD: results from two replicate 48-week studies. *Int J Chron Obstruct Pulmon Dis* 2014;**9**:697–714.
- 63 Feldman GJ, Bernstein JA, Hamilton A, Nivens MC, Korducki L, LaForce C. The 24-h FEV1 time profile of olodaterol once daily via Respimat<sup>®</sup> and formoterol twice daily via Aerolizer<sup>®</sup> in patients with GOLD 2-4 COPD: results from two 6-week cross-over studies. *Springerplus* 2014;**3**:419.
- 64 Decramer M, Anzueto A, Kerwin E, Kaelin T, Richard N, Crater G *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 multicenter, blinded, randomized controlled trials. *Lancet Respir Med* 2014;**2**:472–86.
- 65 Decramer ML, Hanania NA, Lötvald JO, Yawn BP. The safety of long-acting  $\beta_2$ -agonists in the treatment of stable chronic obstructive disease. *Int J Chron Obstruct Pulmon Dis* 2013;**8**:53–64.
- 66 Kew KM, Mavergames C, Walters JAE. Long-acting beta2-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2013;Art. No.:CD010177.
- 67 Wilchesky M, Ernst P, Brophy JM, Platt RW, Suissa S. Bronchodilator use and the risk of arrhythmia in COPD: part 2: reassessment in the larger Quebec cohort. *Chest* 2012;**142**:305–11.
- 68 Cates CJ, Cates MJ. Regular treatment with salmeterol for chronic asthma: serious adverse events. *Cochrane Database Syst Rev* 2008;**3**:CD006363.
- 69 Lee TA, Pickard AS, Au DH, Bartle B, Weiss KB. Risk of death associated with medications for recently diagnosed chronic obstructive pulmonary disease. *Ann Intern Med* 2008;**149**:380–90.

- 70 Mapel DW, Nelson LS, Lydick E, Soriano J, Yood MU, Davis KJ. Survival among COPD patients using fluticasone/salmeterol in combination versus other inhaled steroids and bronchodilators alone. *COPD* 2007;**4**:127–34.
- 71 Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012;**7**:CD009285.
- 72 Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S *et al.* A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;**359**:1543–54.
- 73 Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-van Mölken MP, Beeh KM *et al.* Tiotropium versus salmeterol for the prevention of exacerbations in COPD. *N Engl J Med* 2011;**364**:1093–103.
- 74 Sims MW, Panettieri RA Jr. Profile of aclidinium bromide in the treatment of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2011;**6**:457–66.
- 75 Ulrik CS. Once-daily glycopyrronium bromide, a long-acting muscarinic antagonist, for chronic obstructive pulmonary disease: a systematic review of clinical benefit. *Int J Chron Obstruct Pulmon Dis* 2012;**7**:673–8.
- 76 Jones PW, Rennard SI, Agusti A, Chanez P, Magnussen H, Fabri L *et al.* Efficacy and safety of once-daily aclidinium in chronic obstructive pulmonary disease. *Respir Res* 2011;**12**:55.
- 77 Kerwin E, Hebert J, Gallagher N, Martin C, Overend T, Alagappan VKT *et al.* Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. *Eur Respir J* 2012;**40**:1106–14.
- 78 Donohue JF, Niewoehner D, Brooks J, O'Dell D, Church A. Safety and tolerability of once-daily umeclidinium/vilanterol 125/25 mcg and umeclidinium 125 mcg in patients with chronic obstructive pulmonary disease: results from a 52-week, randomized, double-blind, placebo-controlled study. *Respir Res* 2014;**15**:78.
- 79 Sharafkhaneh A, Majid H, Gross NJ. Safety and tolerability of inhalational anticholinergics in COPD. *Drug Healthc Patient Saf* 2013;**5**:49–55.
- 80 Wise RA, Anzueto A, Cotton D, Dahl R, Devins T, Disse B *et al.* Tiotropium Respimat inhaler and the risk of death in COPD. *N Engl J Med* 2013;**369**:1491–501.
- 81 Appleton S, Jones T, Poole P, Pilotto L, Adams R, Lasserson TJ *et al.* Ipratropium bromide versus short acting beta-2 agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;**2**:CD001387.
- 82 Appleton S, Jones T, Poole P, Lasserson TJ, Adams R, Smith B *et al.* Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;**3**:CD006101.
- 83 Karner C, Cates CJ. Long-acting beta2-agonist in addition to tiotropium versus either tiotropium or long-acting beta2-agonist alone for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012;**4**:CD008989.
- 84 Cole JM, Sheehan AH, Jordan JK. Concomitant use of ipratropium and tiotropium in chronic obstructive disease. *Ann Pharmacother* 2012;**46**:1717–21.
- 85 Bateman ED, Ferguson GT, Barnes N, Gallagher N, Green Y, Henley M *et al.* Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. *Eur Respir J* 2013;**42**:1484–94.
- 86 Donohue JF, Maleki-Yazdi MR, Kilbride S, Mehta R, Kalberg C, Church A. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. *Respir Med* 2013;**107**:1538–46.
- 87 Vincken W, Aumann J, Chen H, Henley M, McBryan D, Goyal P. Efficacy and safety of coadministration of once-daily indacaterol and glycopyrronium versus indacaterol alone in COPD patients: the GLOW6 study. *Int J Chron Obstruct Pulmon Dis* 2014;**9**:215–28.
- 88 Wedzicha JA, Dahl R, Buhl R, Schubert-Tennigkeit A, Chen H, D'Andrea P *et al.* Pooled safety analysis of the fixed-dose combination of indacaterol and glycopyrronium (QVA149), its monocomponents, and tiotropium versus placebo in COPD patients. *Respir Med* 2014;**108**:1498–507.
- 89 Ulrik CS. Clinical benefit of fixed-dose dual bronchodilation with glycopyrronium and indacaterol once daily in patients with chronic obstructive pulmonary disease: a systematic review. *Int J Chron Obstruct Pulmon Dis* 2014;**9**:331–8.
- 90 Wedzicha JA, Decramer M, Ficker JH, Niewoehner DE, Sandström T, Fowler Taylor A *et al.* Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomized, double-blind, parallel-group study. *Lancet Respir Med* 2013;**1**:199–209.
- 91 Kankaanranta H, Lahdensuo A, Moilanen E, Barnes PJ. Add-on therapy options in asthma not adequately controlled by inhaled corticosteroids: a comprehensive review. *Respir Res* 2004;**5**:17.
- 92 Lopez-Campos JL, Acuna CC. What is in the guidelines about the pharmacological treatment of chronic obstructive pulmonary disease? *Expert Rev Respir Med* 2013;**7**(2 Suppl):43–51.
- 93 Yang IA, Clarke MS, Sim EHA, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012;**7**:CD002991.
- 94 van der Valk P, Monnikhof E, van der Palen J, Zielhuis G, van Herwaarden C. Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease: the COPE study. *Am J Respir Crit Care Med* 2002;**166**:1358–63.
- 95 Magnussen H, Disse B, Rodriguez-Roisin R, Kirsten A, Watz H, Tetzlaff L *et al.* Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *N Engl J Med* 2014;**371**:1285–94.
- 96 Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. *Thorax* 2011;**66**:699–708.
- 97 Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. *Am J Med* 2010;**123**:1001–6.
- 98 O'Byrne PM, Rennard S, Gerstein H, Radner F, Peterson S, Lindberg B *et al.* Risk of new onset diabetes mellitus in patients with asthma or COPD taking inhaled corticosteroids. *Respir Med* 2012;**106**:1487–93.
- 99 Price D, Yawn B, Brusselle G, Rossi A. Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD. *Prim Care Respir J* 2013;**22**:92–100.
- 100 Nannini LJ, Cates CJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta-agonist in one inhaler versus inhaled steroids for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007;**4**:CD006826.
- 101 Nannini LJ, Poole P, Milan SJ, Holmes R, Normansell R. Combined corticosteroid and long-acting beta2-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2013;**11**:CD003794.
- 102 Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta2-agonist in one inhaler versus long-acting beta2-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012;**9**:CD006829.
- 103 Dransfield MT, Bourbeau J, Jones PW, Hanania NA, Mahler DA, Vestbo J *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.
- 104 Nannini LJ, Cates CJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007;**4**:CD003794.

- 105 Wedzicha JA, Singh D, Vestbo J, Paggiaro PL, Jones PW, Bonnet-Gonod F *et al.* Extrafine beclomethasone/formoterol in severe COPD patients with history of exacerbations. *Respir Med* 2014;**108**:1153–62.
- 106 Calverley PMA, Anderson AMA, Ferguson GT, Jenkins C, Jones PW, Yates JC *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;**356**:775–89.
- 107 Rabe KF, Wedzicha JA. Controversies in treatment of chronic obstructive pulmonary disease. *Lancet* 2011;**378**:1038–47.
- 108 Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. *Thorax* 2013;**68**:1029–36.
- 109 Janson C, Larsson K, Lisspers KH, Ställberg B, Stratelis G, Goike H *et al.* Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroids and long acting  $\beta_2$  agonist: observational matched cohort study (PATHOS). *Br Med J* 2013;**346**:f3306.
- 110 Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014;Art. No.:CD010115.
- 111 White P, Thorntoh H, Pinnock H, Georgopoulou S, Booth HP. Overtreatment of COPD with inhaled corticosteroids – implications for safety and costs: cross-sectional observational study. *PLoS ONE* 2013;**8**:e75221.
- 112 Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R *et al.* Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomised trial. *Ann Intern Med* 2007;**146**:545–55.
- 113 Welte T, Miravittles M, Hernandez P, Eriksson G, Peterson S, Polanowski T *et al.* Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009;**180**:741–50.
- 114 Cazzola M, Ando F, Santus P, Ruggeri P, Di Marco F, Sanduzzi A *et al.* A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium to the airflow obstruction of patients with severe-to-very severe COPD. *Pulm Pharmacol Ther* 2007;**20**:556–61.
- 115 Karner C, Cates CJ. Combination inhaled steroid and long-acting beta2-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2011;**3**:CD008532.
- 116 Nielsen R, Kankaanranta H, Bjermer L, Lange P, Arnetorp S, Hedegaard M *et al.* Cost effectiveness of adding budesonide/formoterol to tiotropium in COPD in four Nordic countries. *Respir Med* 2013;**107**:1709–21.
- 117 Chong J, Poole P, Leung B, Black PN. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2011;**5**:CD002309.
- 118 Calverley PMA, Rabe KF, Goehring U-M, Kristiansen S, Fabbri LM, Martinez FJ *et al.* Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet* 2009;**374**:685–94.
- 119 Fabbri LM, Calverley PMA, Izquierdo-Alonso JL, Bundschuh DS, Brose M, Martinez FJ *et al.* Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with long-acting bronchodilators: two randomised clinical trials. *Lancet* 2009;**374**:695–703.
- 120 Walters JAE, Walters EH, Wood-Baker R. Oral corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005;**3**:CD005374.
- 121 Schols AMWJ, Wesseling G, Kester ADM, de Vries G, Mostert R, Slangen J *et al.* Dose dependent increased mortality risk in COPD patients treated with oral glucocorticoids. *Eur Respir J* 2001;**17**:337–42.
- 122 Man WD-C, Kemp P, Moxham J, Polkey MI. Skeletal muscle dysfunction in COPD: clinical and laboratory observations. *Clin Sci (Lond)* 2009;**117**:251–64.
- 123 Barnes PJ. Theophylline. *Am J Respir Crit Care Med* 2013;**188**:901–6.
- 124 Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. *Pharmacol Rev* 2012;**64**:450–504.
- 125 Ram FS, Jones P, Jardim J, Castro AA, Atallah AN, Lacasse Y *et al.* Oral theophylline for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2002;**3**:CD003902.
- 126 Rossi A, Kristufek P, Levine BE, Thomson MH, Till D, Kottakis J *et al.* Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. *Chest* 2002;**121**:1058–69.
- 127 Zhou Y, Wang X, Zeng X, Qiu R, Xie J, Liu S *et al.* Positive benefits of theophylline in a randomized, double-blind, parallel-group, placebo-controlled study of low-dose, slow-release theophylline in the treatment of COPD for 1 year. *Respirology* 2006;**11**:603–10.
- 128 ZuWallack RL, Mahler DA, Reilly D, Church N, Emmett A, Rickard K *et al.* Salmeterol plus theophylline combination therapy in the treatment of COPD. *Chest* 2001;**119**:1661–70.
- 129 Lehtimäki L, Saano V, Moilanen E. Hengityselimistöön vaikuttavat lääkeaineet [Drugs affecting respiratory system]. In: Pelkonen O, Ruskoaho H, Hakkola J, Huupponen R, MacDonald E, Moilanen E, Pasanen M, Scheinin M, Vähäkangas K (ed.). *Lääketeollinen farmakologia ja toksikologia [Medical Pharmacology and Toxicology]*. Kustannus Oy Duodecim, Helsinki, Finland, 2014;733–56.
- 130 Donath E, Chaudhry A, Hernandez-Aya LF, Lit L. A meta-analysis on the prophylactic use of macrolide antibiotics for the prevention of disease exacerbations in patients with chronic obstructive pulmonary disease. *Respir Med* 2013;**107**:1385–92.
- 131 Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JAD Jr, Criner GJ *et al.* Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011;**365**:689–98.
- 132 Poole P, Black PN, Cates CJ. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012;**8**:CD001287.
- 133 Yawn BP, Colice GL, Hodder R. Practical aspects of inhaler use in the management of chronic obstructive pulmonary disease in the primary care setting. *Int J Chron Obstruct Pulmon Dis* 2012;**7**:495–502.
- 134 Laube BL, Janssens HM, de Jongh FH, Devadason SG, Dhand R, Diot P *et al.* What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J* 2011;**37**:1308–31.
- 135 Wieshammer S, Dreyhaupt J. Dry powder inhalers: which factors determine the frequency of handling errors? *Respiration* 2008;**75**:18–25.
- 136 Chapman KR, Voshaar TH, Virchow JC. Inhaler choice in primary practice. *Eur Respir Rev* 2005;**14**:117–22.
- 137 Barr RG, Bourbeau J, Camargo CA Jr. Tiotropium for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005;**2**:CD002876.
- 138 Lange P, Marott JL, Vestbo J, Olsen KR, Ingebrigtsen TS, Dahl M *et al.* Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification. A study of the general population. *Am J Respir Crit Care Med* 2012;**186**:975–81.
- 139 Wedzicha JA, Calverley PMA, Seemungal TA, Hagan G, Ansari Z, Stockley RA *et al.* The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008;**177**:19–26.

- 140 Appleton S, Poole P, Smith BJ, Veale A, Lasserson TJ, Chan MMK *et al.* Long-acting beta2-agonists for poorly reversible chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;**3**:CD001104.
- 141 Marchetti N, Criner GJ, Albert RK. Preventing acute exacerbations and hospital admissions in COPD. *Chest* 2013;**143**:1444–54.
- 142 Piras B, Miravittles M. The overlap phenotype: the (missing) link between asthma and COPD. *Multidiscip Respir Med* 2012;**7**:8.
- 143 Carolan BJ, Sutherland ER. Clinical phenotypes of chronic obstructive pulmonary disease and asthma: recent advances. *J Allergy Clin Immunol* 2013;**131**:627–34.
- 144 Louie S, Zeki AA, Schivo M, Chan AL, Yoneda KY, Avdalovic M *et al.* The asthma-chronic obstructive pulmonary disease overlap syndrome: pharmacotherapeutic considerations. *Expert Rev Clin Pharmacol* 2013;**6**:197–219.
- 145 Magnussen H, Bugnas B, van Noord J, Schmidt P, Gerken F, Kesten S. Improvements with tiotropium in COPD patients with concomitant asthma. *Respir Med* 2008;**102**:50–6.
- 146 Koblizek V, Chlumsky J, Zindr V, Neumannova K, Zatloukal J, Zak J *et al.* Chronic obstructive pulmonary disease: official diagnosis and treatment guidelines of the Czech Pneumological and Phthisiological Society; a novel phenotypic approach to COPD with patient-oriented care. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2013;**157**:189–201.
- 147 Russi EW, Karrer W, Brutsche M, Eich C, Fitting JW, Frey M *et al.* Diagnosis and management of chronic obstructive pulmonary disease: the Swiss guidelines. Official guideline of the Swiss respiratory society. *Respiration* 2013;**85**:160–74.