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Chronic obstructive pulmonary disease and atrial fibrillation: an interdisciplinary perspective

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Chronic obstructive pulmonary disease (COPD) is highly prevalent among patients with atrial fibrillation (AF), shares common risk factors, and adds to the overall morbidity and mortality in this population. Additionally, it may promote AF and impair treatment efficacy. The prevalence of COPD in AF patients is high and is estimated to be ~25%. Diagnosis and treatment of COPD in AF patients requires a close interdisciplinary collaboration between the electrophysiologist/cardiologist and pulmonologist. Differential diagnosis may be challenging, especially in elderly and smoking patients complaining of unspecific symptoms such as dyspnoea and fatigue. Routine evaluation of lung function and determination of natriuretic peptides and echocardiography may be reasonable to detect COPD and heart failure as contributing causes of dyspnoea. Acute exacerbation of COPD transiently increases AF risk due to hypoxia-mediated mechanisms, inflammation, increased use of beta-2 agonists, and autonomic changes. Observational data suggest that COPD promotes AF progression, increases AF recurrence after cardioversion, and reduces the efficacy of catheter-based antiarrhythmic therapy. However, it remains unclear whether treatment of COPD improves AF outcomes and which metric should be used to determine COPD severity and guide treatment in AF patients. Data from non-randomized studies suggest that COPD is associated with increased AF recurrence after electrical cardioversion and catheter ablation. Future prospective cohort studies in AF patients are needed to confirm the relationship between COPD and AF, the benefits of treatment of either COPD or AF in this population, and to clarify the need and cost-effectiveness of routine COPD screening.

Keywords

Atrial fibrillation • Chronic obstructive pulmonary disease • Spirometry • Hyperinflation • Hypoxia

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Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia affecting 33.5 million people globally.¹ Across the developed world, AF increasingly contributes to a rising tide of hospitalization, morbidity and mortality.² At the same time, chronic obstructive pulmonary disease (COPD) is the most common chronic lung disease characterized by persistent airflow limitation with a global prevalence of stage 2 COPD or higher of around 10%.³ Chronic obstructive pulmonary disease is present in up to 23% of AF patients^{3–5} and new-onset AF is twice as common in COPD patients compared with patients without COPD.⁶

The association between AF and COPD is not completely understood. Chronic obstructive pulmonary disease and AF share common risk factors contributing to the onset of both diseases. Additionally, COPD might also directly contribute to the onset of AF by COPD-related pathophysiological mechanisms. Correctly diagnosing COPD in AF patients is important because COPD in patients with AF is a negative prognostic factor for progression from paroxysmal AF to persistent AF⁷ and the efficacy of AF treatment.^{8,9} Additionally, concomitant COPD is associated with increased hospital admissions and all-cause mortality in AF patients.^{4,10} Moreover, among patients with AF, COPD is associated with higher symptom burden, worse quality of life, and worse cardiovascular and bleeding outcomes.¹¹ International professional societies recommend the correction of hypoxaemia and acidosis as initial management for patients who develop AF during an acute pulmonary illness or exacerbation of chronic pulmonary disease.^{12,13} However, recommendations concerning when and how to test for COPD and the long-term management of COPD specifically in AF patients remain uncertain.

This review provides an update on the current understanding of how COPD contributes to a unique dynamic arrhythmogenic substrate for AF. Experimental data pointing to possible pathophysiological mechanisms in AF patients with comorbid COPD as well as diagnostic and therapeutic considerations in AF patients with COPD will be highlighted. Finally, we emphasize the need for larger prospective cohort studies in AF patients to more robustly determine the role of COPD and its treatment in predisposing to incident and recurrent AF and to identify the COPD phenotypes in AF patients.

Atrial arrhythmogenic mechanisms in chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease is a chronic pulmonary disease and is characterized by airflow limitations due to small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema) leading to expiratory flow limitation and hyperinflation.¹⁴ Hyperinflation is defined as an increase in end-expiratory lung volume and can be seen at rest or during exercise, static and dynamic hyperinflation, respectively.¹⁵ Destruction of the alveoli can result in emphysema, low diffusion capacity, and hypoxaemia.¹⁵

Several COPD-related mechanisms contributing to AF onset and progression are summarized in *Figure 1*. Gas exchange abnormalities, such as hypoxaemia and hypercapnia, can lead to pulmonary vasoconstriction and subsequent pulmonary hypertension which may result in right ventricular hypertrophy and diastolic dysfunction.¹⁶ Chronic hypoxaemia modulates the expression of hypoxia-inducible

factor 1 and increases systemic inflammation and oxidative stress promoting pro-fibrotic remodelling of the atrial tissue.¹⁷ Long-term advanced COPD is associated with right heart disease.¹⁴ In rats, induced right heart disease produced a substrate for AF maintenance prominently involving right atrial fibrosis, conduction abnormalities, and right atrial re-entrant activity.¹⁸ Additionally, leucocyte elastase-induced COPD in rabbits increased atrial arrhythmogenesis.¹⁹ Sympathetic overactivity has been observed in both hypoxaemic and normoxemic patients with COPD^{20,21} and is involved in AF progression.²² As a result of dynamic hyperinflation, patients with COPD develop intrinsic positive end-expiratory pressure,¹⁷ which increases pulmonary vascular resistance resulting in interventricular septum encroaching on the left ventricle, compromised left ventricular inflow, and left atrial and pulmonary venous pressure rises.^{2,6,17,23} Concomitant comorbidities like obesity and systemic arterial hypertension may contribute critically to the structural atrial substrate remodelling process. Cardiovascular disease is one of the most important comorbidities. About 30% of patients with heart failure also have COPD.²⁴ Obstructive sleep apnoea (OSA) is also frequently seen in patients with COPD, referred to as 'overlap syndrome'. Co-existing COPD may put OSA patients closer to the steep part of the oxyhaemoglobin dissociation curve leading to more excessive downward drifts in oxygen saturation.²⁵

While atrial structural remodelling is important in providing an AF-maintaining substrate in patients with COPD, AF onset, and paroxysms are often temporally related to acute exacerbations of COPD (AECOPD).^{26–28} During AECOPD, changes in blood gases as well as transmural pressure gradients due to airflow limitation and dynamic hyperinflation result in pulmonary pressure rises with tricuspid regurgitation which particularly impacts the right atrium. In a sheep model with continuous ventilation under autonomic blockade, the transition from hypercapnia back to normal blood gases, rather than longer hypoxic or hypercapnic episodes, was characterized by increased atrial vulnerability due to a differential recovery of right atrial refractoriness and right atrial conduction properties.²⁹ Additionally, intrathoracic pressure swings, as occurring during dynamic hyperinflation as well as during obstructive respiratory events, have been shown to transiently shorten right atrial effective refractory period, right atrial action potential duration and increase AF inducibility by parasympathetic mediated mechanisms in a spontaneously breathing pig model.^{30,31} These factors may create a dynamic arrhythmogenic substrate which transiently increases AF risk during AECOPD. Additionally, AECOPD and the use of sympathomimetic and parasympatholytic medication may also increase trigger formation by changes in pH and autonomic nervous system activation.²²

Epidemiology of chronic obstructive pulmonary disease in atrial fibrillation patients

The global prevalence of COPD ranges at around 11%.³ The estimated prevalence of COPD in patients with AF has been found to be higher, reaching 23% in patients older than 65 years.^{3–5} The prevalence of AF in stable COPD ranges from 4.7% to 15%, with significantly higher rates of about 20–30% in very severe COPD.³²

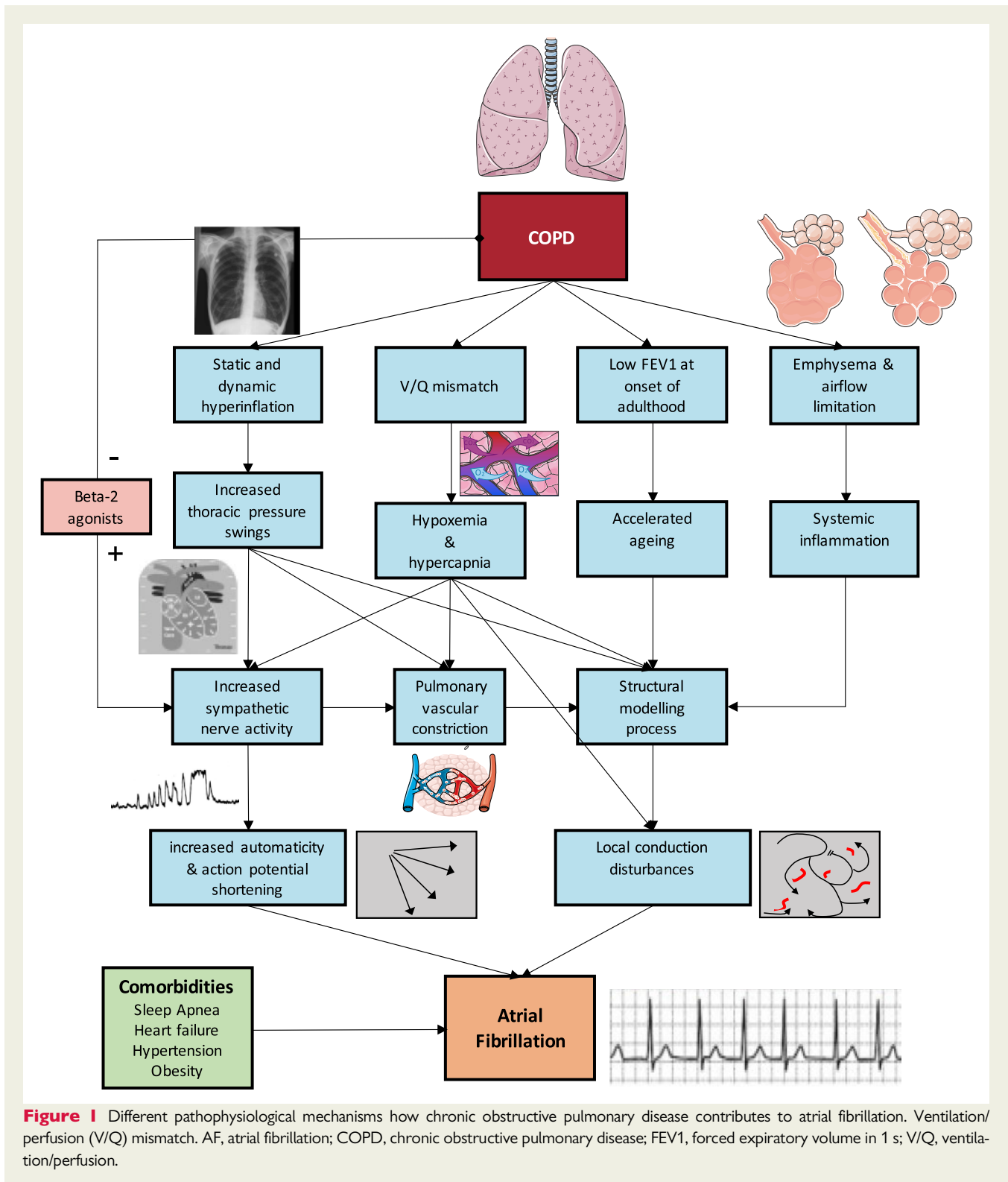


Figure 1 Different pathophysiological mechanisms how chronic obstructive pulmonary disease contributes to atrial fibrillation. Ventilation/perfusion (V/Q) mismatch. AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; V/Q, ventilation/perfusion.

Moreover, severity of airflow limitation has been related to increased incidence of AF in the Copenhagen Heart Study³³ and the Atherosclerosis Risk in Community (ARIC) cohort study.³⁴

Among patients with AF, acute exacerbation of COPD has been shown to be associated with a higher risk of AF-related

hospitalizations in the first 90-day post-acute exacerbation period.^{26,35} About 30% of COPD hospitalizations revealed co-existent arrhythmias, with 22.1% being AF.³⁶

Conversely, the prevalence and incidence estimate of arrhythmic disorders in COPD are variable and often lack detail regarding the

type of arrhythmia. Chronic obstructive pulmonary disease patients had a 28% increased AF risk, which further increased with frequent exacerbations and an enlarged left atrium.²⁸ The presence of COPD increases the hazard ratio for incident AF about five times in patients with CHA₂DS₂VASc score ≤ 1 , while the prognostic significance of COPD was lower in patients with CHA₂DS₂VASc score ≥ 2 .³⁷ Available evidence is strongest for the association between AF and COPD, but also (multifocal) atrial tachycardia, atrial flutter, ventricular tachycardia, and conduction disorders have been related to COPD.³⁸

Assessment and diagnosis of chronic obstructive pulmonary disease in atrial fibrillation patients

Screening and diagnostic tools are summarized in Table 1. Chronic obstructive pulmonary disease should be suspected in everyone with typical respiratory symptoms (e.g. dyspnoea, cough, wheezing, and sputum production) and a history of smoking.³⁹ Spirometry is the cornerstone for the diagnosis of COPD.³⁹ Chronic obstructive pulmonary disease is present if the ratio of forced expiratory volume in 1 s and forced vital capacity (FEV₁/FVC) is below 0.70 after the inhalation of a bronchodilator. The handheld microspirometer is mainly used as a tool to exclude COPD; if the ratio of forced expiratory volume in 1 s and the forced volume in 6 s is above 0.73, COPD is unlikely.⁴⁰ A recent meta-analysis showed that single questionnaires lack specificity and stand-alone handheld microspirometry lacks sensitivity.⁴⁰ A staged approach using both questionnaires (such as the COPD Diagnostic Questionnaire) followed by a handheld microspirometry might be the best diagnostic approach with a sensitivity and specificity of 72% and 97%, respectively.⁴¹ Abnormal handheld microspirometry results should always be followed by a conventional pulmonary work-up, including standard spirometry and body

plethysmography to detect both airway obstruction as well as hyperinflation.

Heart failure as a differential diagnosis

In patients with dyspnoea, heart failure with preserved and reduced ejection fraction is an important differential diagnosis⁴² and the work-up should include the determination of natriuretic peptides and echocardiography according to the Guideline of the European Society of Cardiology.⁴³ Reduced oxygen-extraction in the muscle, increased ventilatory demand and impaired pulmonary mechanical constraints, which have been described in patients with heart failure, contribute to exercise limitation, and could become even more relevant during AF.^{44,45} Moreover, AF is associated with excessive ventricular rate responses and reduced maximum aerobic exercise capacity in patients with concomitant heart failure,^{45,46} which may result in a less efficient gas exchange.

Differentiation between chronic obstructive pulmonary disease-related and atrial fibrillation-related symptoms in atrial fibrillation patients

The overlapping symptom-profile in AF patients with concomitant COPD with or without heart failure creates a diagnostic challenge. Chronic obstructive pulmonary disease-related symptoms may be misinterpreted as symptoms caused by AF, which may trigger unnecessary invasive or pharmacological rhythm control interventions. On the other hand, the acute onset of AF-related symptoms can be misdiagnosed as an exacerbation of COPD or heart failure.

Table 1 Screening and diagnosis

In whom is screening reasonable	Every AF patient with dyspnoea or exercise intolerance as the predominant symptom
How should they be screened	COPD Diagnostic Questionnaire (CDQ) Handheld microspirometry (followed by spirometry to confirm the diagnosis)
Diagnostic options	
Spirometry	Gold standard. COPD confirmed when FEV ₁ /FVC <70%
Handheld microspirometer	Validated in outpatient clinic setting only. COPD can be likely excluded, if FEV ₁ /FEV ₆ > 73%. Negative predicted value is 94%
Questionnaire to screen for COPD	COPD Diagnostic Questionnaire (CDQ). Lacks sensitivity as a stand-alone test and should be followed by microspirometry
Questionnaire for symptom assessment	- mMRC (Modified Medical Research Council) Dyspnoea Scale - NYHA classification - Dyspnoea-12 score and MDP-12 are available to quantify dyspnoea intensity and quality. Not validated in AF patients!
Additive: Cardiopulmonary exercise testing	Diagnostic tool to identify factors contributing to exercise intolerance, to identify if exercising is safe and to serve as a tool to set up an individual training program in multimorbid patients

Chronic obstructive pulmonary disease patients generally demonstrate a ventilatory limitation due to their expiratory flow limitation which can be determined by spirometry.⁴⁶ To identify further mechanisms of exercise limitation, particularly in AF patients with COPD and other concomitant cardiovascular comorbidities, assessment of oxygen saturation, natriuretic peptides echocardiography, and cardiopulmonary exercise testing (CPET) may be useful tools in addition to spirometry to differentiate between cardiac and non-cardiac causes of exercise limitation and symptoms of dyspnoea. Cardiopulmonary exercise testing is sensitive to changes in ventricular function, ventricular rate as well as dynamic hyperinflation and diffusion capacity.

Chronic obstructive pulmonary disease complicates atrial fibrillation management

Rhythm control in COPD patients with AF: COPD in patients with AF is associated with reduced long-term success of cardioversion.^{8,47} In AF patients undergoing AF ablation, COPD is among several demographic and clinical factors associated with reduced short-term outcome, increased hospitalization, stroke, and all-cause mortality.^{9,48–50} In ORBIT-AF, COPD was associated with least improvement in health-related quality of life.⁵¹ There is an increased risk of new-onset AF after flutter ablation in patients with COPD.⁵² During rhythm control procedures requiring deep unconscious sedation, COPD patients may be at higher risk of for impaired ventilation with subsequent CO₂ retention. Amiodarone is known for its pulmonary toxicity, mainly pulmonary fibrosis. Patients with COPD are at an increased risk for amiodaron-induced pulmonary toxicities.⁵³

Rate control in COPD patients with AF: Because of potential side-effects related to bronchoconstriction, beta-blockers are less frequently prescribed in COPD patients.²⁴ However, studies showed a 28% reduction in mortality and a 38% reduction in exacerbation rate in COPD patients treated by beta-1 selective beta-blockers.⁵⁴ Metoprolol did neither shorten nor prolong the time until the first COPD exacerbation among patients with moderate or severe COPD.⁵⁵ Initiating treatment with beta-blockers requires dose titration and monitoring over a period of weeks, and beta-blockers may be less well-tolerated in older patients with COPD who have other comorbidities.²⁴ The Beta-blockers tO patieNts With CHronic Obstructive puLmonary diseasE (BRONCHIOLE) – Study addresses the efficacy of beta-blockers in patients with COPD on patient-related outcomes in patients with COPD.⁵⁶

Chronic obstructive pulmonary disease treatment in atrial fibrillation patients

Pharmacological treatment

Bronchodilators are the mainstay of COPD treatment.³⁹ The recent SUMMIT trial⁵⁷ and ASCENT-COPD⁵⁸ trial have shown that

bronchodilators can be safely used in COPD patients with concomitant cardiovascular disease. Both the inhaled beta2-agonists and anticholinergics have been associated with tachyarrhythmias.⁵⁹ For inhaled beta2-agonists, an increased risk was mainly seen with the new use of inhaled beta2-agonist (prescription within 30 days) and was stronger for short-acting bronchodilators than for long-acting beta2-agonists.^{60,61} The risk for cardiac arrhythmias in patients treated by anticholinergics is much weaker and increased risk of tachyarrhythmias and AF were observed in some but not all studies.^{59,60} Inhaled corticosteroids do not seem to increase AF risk, though in COPD fixed combinations with beta2-agonists are mostly used.^{59,61} Of the oral medications used in COPD, both corticosteroids and theophylline have been associated with an increased risk of AF.^{60–62} The potential effects of COPD medications on AF and potential interactions with drugs frequently used for rate and rhythm control are summarized in *Table 2*.

Correction of hypoxaemia and hypercapnia

Since hypoxaemia and hypercapnia are associated with the onset of AF, guidelines suggest correcting these abnormalities during an AECOPD.¹² In stable disease, COPD patients with AF should be screened for respiratory insufficiency. It seems prudent to correct the underlying hypoxaemia with oxygen therapy and hypercapnia with non-invasive ventilation, though the effect of these treatment modalities on the new onset of AF or progression of AF has not been studied, yet.⁶³

Lifestyle interventions

Exercise interventions, possibly guided by CPET, can be provided through physiotherapy or through specific cardiopulmonary rehabilitation programmes. Beneficial effects of risk factor modification and exercise have been shown individually in AF or in COPD populations.^{64–66} In obese patients with AF, risk-factor management including weight-loss and exercise prescription within a goal-directed programme improves the long-term success of AF ablation.^{64,65} Whether interventions such as weight-loss, cessation of alcohol and smoking, or other lifestyle interventions show antiarrhythmic effects in AF patients with concomitant COPD needs to be further investigated.⁶⁶

Integrated care approach

The diagnosis and treatment of COPD in AF patients requires a close interdisciplinary collaboration between the electrophysiologist, cardiologist, and pulmonologist, and necessitates a structured follow-up. This may be best delivered through an integrated care model and may require multidisciplinary meetings to discuss the most optimal management, based on a combined viewpoint from both specialties. Moreover, comprehensive treatment of COPD and AF, as well as underlying conditions and risk factors should be pursued. Following the integrated approach, the COPD patients with AF should be placed in a central position and actively involved in their care process. This requires continuous patient education: it is crucial that patients understand what COPD and AF are, their treatment and lifestyle management, and how they can contribute to improving clinical outcomes through treatment and lifestyle management. A

Table 2 Chronic obstructive pulmonary disease treatment in patients with atrial fibrillation

Drug group name	Treatment effect ³⁹	Increased risk of atrial fibrillation	Interactions with antiarrhythmic drugs	Other cardiac arrhythmias ^{39,59}
Beta2-agonists				
Short-acting	Improvement of lung function and symptoms	Yes ^{60,61}	- Non-selective beta-blockers can induce bronchoconstriction and attenuate the bronchodilating effect of Beta2- agonists	Resting sinus tachycardia
Long-acting	- Improvement of lung function, symptoms, and health status - Prevention of moderate and severe exacerbations	Yes ^{60,61}	- Non-selective beta-blockers can induce bronchoconstriction and attenuate the bronchodilating effect of Beta2-agonists	Resting sinus tachycardia
Anticholinergics				
Short-acting	- Improvement of lung function and symptoms	No ^{59,60}		Tachyarrhythmias not otherwise specified
Long-acting	- Improvement of lung function and symptoms and health status - Prevention of moderate and severe exacerbations	No ^{59,60}		Tachyarrhythmias not otherwise specified
Methylxanthines				
Theophylline	- Not frequently used anymore - Small improvement of lung function	Yes ^{60,61}	- Calcium antagonists increase the risk of theophylline toxicity - Theophylline-induced hypokalaemia increases the risk of digoxin toxicity	- Sinus tachycardia - Supra-ventricular ectopic beats - Ventricular arrhythmias
Corticosteroids				
Inhaled steroids	- Prevention of moderate and severe exacerbations - Limited improvement of lung function, symptoms, and health status	No ⁶¹		
Oral steroids	- No effect as maintenance therapy - During exacerbation: improve lung function, reduce dyspnoea, reduce treatment failure, reduce relapse rate	Yes ^{61,62}		Ventricular arrhythmias
Antibiotics				
Macrolides	Prevention of exacerbations	No ⁵⁹	Risk of QTc prolongation with amiodarone or sotalol	Prolongation of QTc interval
Phospho-diesterase-4 inhibitors				
Roflumilast	Prevention of exacerbations	No ⁵⁹		

cardiopulmonary nurse as a case manager may be best positioned to provide education and work with the patient to self-manage their condition, and also co-ordinate the care to prevent fragmentation, which may be lurking given that patients will be treated by both cardiology and pulmonology departments.

Figure 2 summarizes a possible pathway for a work-up of AF patients with suspected COPD: Patients with AF and suspected COPD should be screened for COPD and exacerbating factors, like smoking and use of medications. The clinic consultation should also review all medications, address common risk factors, and consider lifestyle changes such as smoking cessation and exercise. If typical symptoms for OSA are present, targeted diagnostics should be

initiated.¹⁷ Handheld microspirometer may be a suitable method to ensure patient access and to implement screening for COPD in the standard work-up of AF patients considered for rhythm control strategies, although specific validation studies in AF populations are needed. Specific dyspnoea questionnaires, like the Modified Medical Research Council (mMRC) Dyspnoea Scale, the Dyspnoea-12 score (D-12), and the Multidimensional Dyspnoea Profile (MDP) might help to quantify and qualify the different dyspnoea sensations. However, these two latter questionnaires are more commonly used in specialized centres. Determination of natriuretic peptides and echocardiography can detect heart failure as a contributing cause of dyspnoea.

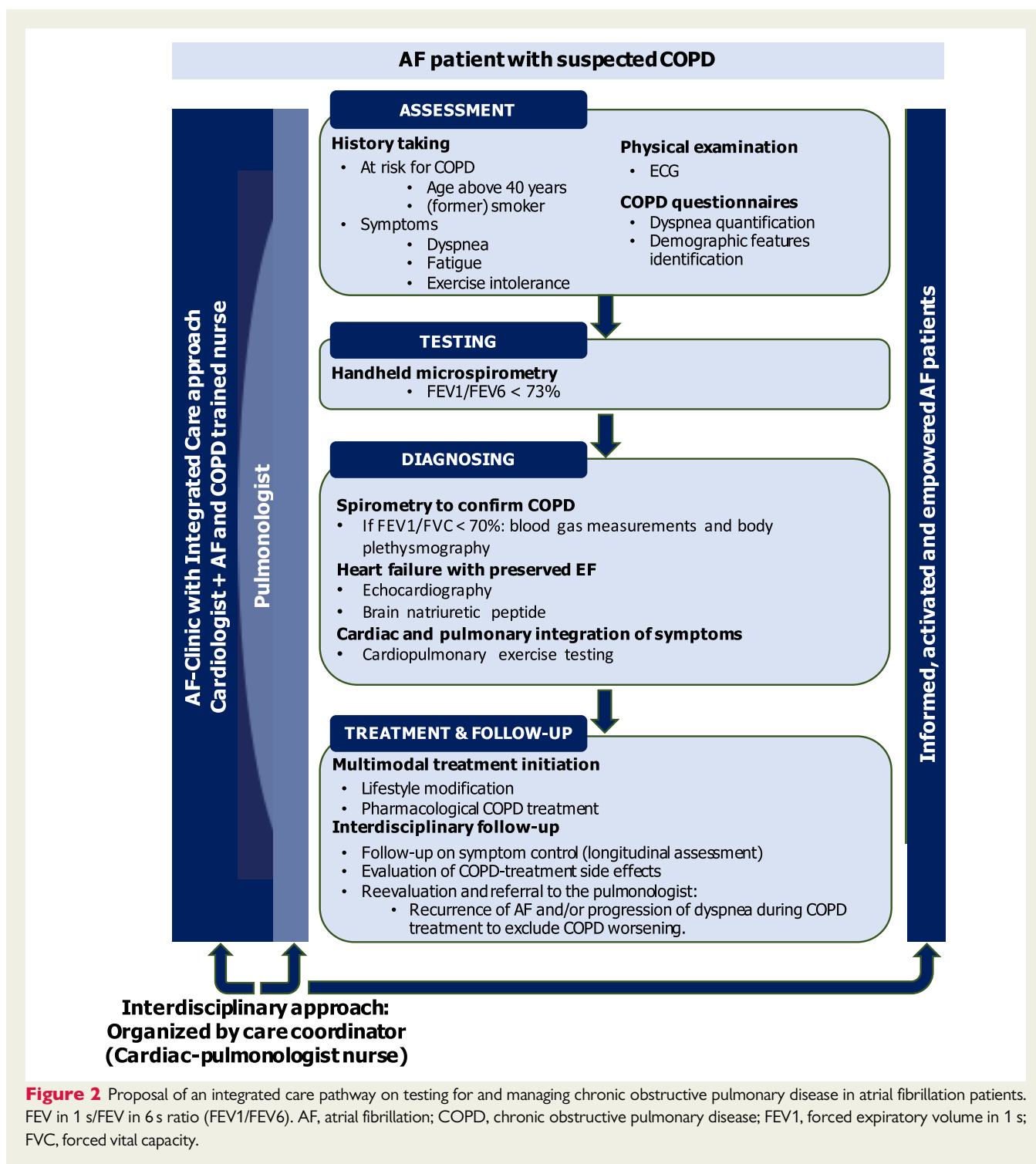


Figure 2 Proposal of an integrated care pathway on testing for and managing chronic obstructive pulmonary disease in atrial fibrillation patients. FEV in 1 s/FEV in 6 s ratio (FEV1/FEV6). AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Professional society recommendations

The 2016 European Society of Cardiology AF-guidelines¹² recommend the correction of hypoxaemia and acidosis as initial management for patients who develop AF during an acute pulmonary illness

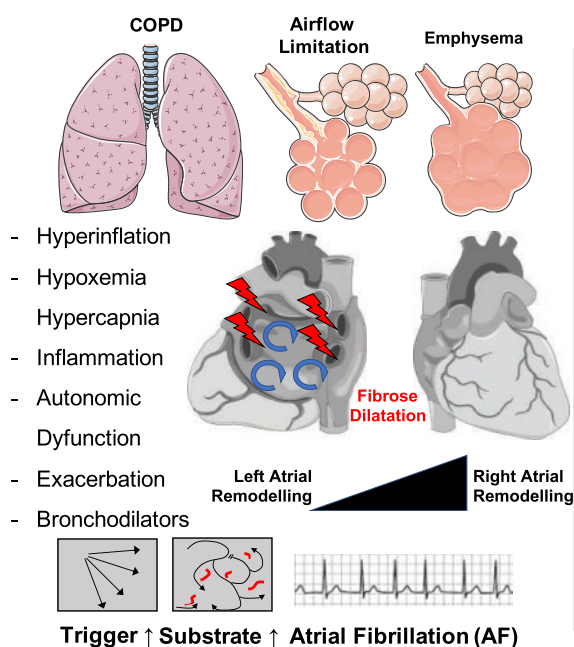
or exacerbation of chronic pulmonary disease. (Class of recommendation IIa 'reasonable to perform', Evidence level C.) Unfortunately, the guideline is weak with respect to statements/standards, that describe how to rule out comorbidities contributing to the non-specific symptoms of dyspnoea due to AF or recommendations concerning rate or rhythm control in AF patients with concomitant COPD.^{12,13}

Table 3 Gaps in evidence

What is the best parameter to determine COPD-severity and guide decision which AF patients require treatment?
 What is the impact of hypoxaemia and its treatment on outcomes in AF patients with underlying COPD?
 Which questionnaires can be used to assess dyspnoea (intensity and quality) in patients with comorbid AF and COPD?
 What is the value of CPET in the diagnosis and management of patients with AF and COPD?
 What are the results of randomized controlled trials regarding the treatment of COPD on prevention of incident and recurrent AF?

CPET, cardiopulmonary exercise testing.

Chronic Obstructive Pulmonary Disease & Atrial Fibrillation



Clinical Facts

Prevalence of COPD in AF patients

→ Approximately 25%.

Observational data suggest that COPD

→ Promotes AF progression
 → Increases AF recurrence after cardioversion
 → Reduces the efficacy of catheter ablation

Diagnosis and treatment

→ Interdisciplinary integrated care approach

Take home figure A summary of different atrial arrhythmogenic mechanisms in patients with chronic obstructive pulmonary disease (left). Clinical facts and observations (right).

Gaps in evidence

There are several diagnostic and therapeutic uncertainties and controversies related to the management of COPD in AF patients (Table 3). In accordance with current recommendations, the severity of COPD in AF patients has been determined in most clinical studies with the FEV1 and the frequency of symptoms. However, given the potentially relevant role of hypoxaemia, inflammation, and autonomic nervous system activation in COPD patients for AF progression, a more detailed characterization of AF patients with concomitant COPD considering these variables may result in a better disease-orientated assessment of COPD, which better reflects COPD-related AF risk and the need for COPD treatment.⁶⁷ Additionally, it is unknown which questionnaires can be used to assess dyspnoea (intensity and quality) and whether CPET can support in the diagnosis

and management of patients with comorbid AF and COPD. The prevalence estimates of COPD in AF patients are based on cross-sectional studies, where often clinical history or diagnostic questionnaires formed the basis of COPD diagnosis and the diagnosis was not always excluded in the non-COPD groups. Large prospective longitudinal population-based studies evaluating the association between untreated COPD and incident AF or randomized controlled trials confirming that treatment of COPD prevents incident and recurrent AF are not available.

Conclusions and perspectives

Data from non-randomized studies of AF patients suggest that COPD is associated with increased AF recurrence after electrical

cardioversion and reduced catheter ablation success rates. Chronic obstructive pulmonary disease is prevalent in up to 23% of all AF patients. Chronic obstructive pulmonary disease should be suspected in every AF patient with chronic dyspnoea or reduced exercise tolerance as the predominant symptom and heart failure should be considered as an important differential diagnosis. Future prospective cohort studies in AF patients are needed to confirm the relationship between COPD and AF, and the benefits of treatment of either COPD or AF in this population, and to clarify the need and cost-effectiveness of routine COPD screening.

Conflict of interest: none declared.

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