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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 pathophysiologic 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 FEV1/FVC <70%
Handheld microspirometer	Validated in outpatient clinic setting only. COPD can be likely excluded, if FEV1/FEV6 > 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 amiodarone-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.

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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.

References

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;**129**:837–847.
2. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, Seshadri S, Wolf PA, Vasani RS, Benjamin EJ, Levy D. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* 2015;**386**:154–162.
3. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, Menezes AM, Sullivan SD, Lee TA, Weiss KB, Jensen RL, Marks GB, Gulsvik A, Nizankowska-Mogilnicka E, BOLD Collaborative Research Group. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007;**370**:741–750.
4. Proietti M, Laroche C, Drozd M, Vijgen J, Cozma DC, Drozd J, Maggioni AP, Boriani G, Lip GY, EORP-AF Investigators. Impact of chronic obstructive pulmonary disease on prognosis in atrial fibrillation: a report from the EURObservational Research Programme Pilot Survey on Atrial Fibrillation (EORP-AF) general registry. *Am Heart J* 2016;**181**:83–91.
5. Rodríguez-Mañero M, López-Pardo E, Cordero A, Ruano-Ravina A, Novo Platas J, Pereira-Vázquez M, Martínez-Gómez A, García-Seara J, Martínez-Sande J-L, Peña-Gil C, Mazón P, García-Acuña JM, Valdéz-Cuadrado L, González-Juanatey JR. A prospective study of the clinical outcomes and prognosis associated with comorbid COPD in the atrial fibrillation population. *Int J Chron Obstruct Pulmon Dis* 2019;**14**:371–380.
6. Ganga HV, Nair SU, Puppala VK, Miller WL. Risk of new-onset atrial fibrillation in elderly patients with the overlap syndrome: a retrospective cohort study. *J Geriatr Cardiol* 2013;**10**:129–134.
7. de Vos CB, Pisters R, Nieuwlaar R, Prins MH, Tieleman RG, Coelen R-JS, van den Heijkant AC, Allessie MA, Crijns HJGM. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. *J Am Coll Cardiol* 2010;**55**:725–731.
8. Pisters R, Nieuwlaar R, Prins MH, Le Heuzey J-Y, Maggioni AP, Camm AJ, Crijns HJGM, for the Euro Heart Survey Investigators. Clinical correlates of immediate success and outcome at 1-year follow-up of real-world cardioversion of atrial fibrillation: the Euro Heart Survey. *Europace* 2012;**14**:666–674.
9. Gu J, Liu X, Tan H, Zhou L, Jiang W, Wang Y, Liu Y, Gu J. Impact of chronic obstructive pulmonary disease on procedural outcomes and quality of life in patients with atrial fibrillation undergoing catheter ablation. *J Cardiovasc Electrophysiol* 2013;**24**:148–154.
10. Méndez-Bailón M, Lopez-de-Andrés A, de Miguel-Diez J, de Miguel-Yanes JM, Hernández-Barrera V, Muñoz-Rivas N, Lorenzo-Villalba N, Jiménez-García R. Chronic obstructive pulmonary disease predicts higher incidence and in-hospital mortality for atrial fibrillation. An observational study using hospital discharge data in Spain (2004–2013). *Int J Cardiol* 2017;**236**:209–215.
11. Durheim MT, Holmes DN, Blanco RG, Allen LA, Chan P, Freeman J, Fonarow GC, Go AS, Hylek EM, Mahaffey KW, Pokorney SD, Reiffel JA, Singer DE, Peterson ED, Piccini JP. Characteristics and outcomes of adults with chronic obstructive pulmonary disease and atrial fibrillation. *Heart* 2018;**104**:1850–1858.
12. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendricks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron-Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenk B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K, ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
13. Calkins H, Hindricks G, Cappato R, Kim Y-H, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen P-S, Chen S-A, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, d'Avila A, de Groot NMS(N), Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao H-M, Verma A, Wilber DJ, Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. *Europace* 2018;**20**:157–208.
14. Agust A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. *N Engl J Med* 2019;**381**:1248–1256.
15. Calverley PMA, Koulouris NG. Flow limitation and dynamic hyperinflation: key concepts in modern respiratory physiology. *Eur Respir J* 2005;**25**:186–199.
16. Elia D, Caminati A, Zompatori M, Cassandro R, Lonati C, Luisi F, Pelosi G, Provencher S, Harari S. Pulmonary hypertension and chronic lung disease: where are we headed? *Eur Respir Rev* 2019;**28**:190065.
17. Linz D, McEvoy RD, Cowie MR, Somers VK, Nattel S, Levy P, Kalman JM, Sanders P. Associations of obstructive sleep apnea with atrial fibrillation and continuous positive airway pressure treatment: a review. *JAMA Cardiol* 2018;**3**:532–540.
18. Hiram R, Naud P, Xiong F, Al-u'datt D, Algallarrondo V, Sirois MG, Tanguay J-F, Tardif J-C, Nattel S. Right atrial mechanisms of atrial fibrillation in a rat model of right heart disease. *J Am Coll Cardiol* 2019;**74**:1332–1347.
19. Chan CS, Lin YS, Lin YK, Chen YC, Kao YH, Hsu CC, Chen SA, Chen YJ. Atrial arrhythmogenesis in a rabbit model of chronic obstructive pulmonary disease. *Transl Res* 2020;**223**:25–39.
20. Volterrani M, Scalvini S, Mazzuero G, Lanfranchi P, Colombo R, Clark AL, Levi G. Decreased heart rate variability in patients with chronic obstructive pulmonary disease. *Chest* 1994;**106**:1432–1437.
21. Heindl S, Lehnert M, Criele C-P, Hasenfuss GERD, Andreas S. Marked sympathetic activation in patients with chronic respiratory failure. *Am J Respir Crit Care Med* 2001;**164**:597–601.
22. Linz D, Elliott AD, Hohl M, Malik V, Schotten U, Dobrev D, Nattel S, Böhm M, Floras J, Lau DH, Sanders P. Atrial autonomic innervation: a target for interventional antiarrhythmic therapy? *Int J Cardiol* 2019;**287**:181–188.
23. Watz H, Waschki B, Meyer T, Kretschmar G, Kirsten A, Claussen M, Magnussen H. Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation. *Chest* 2010;**138**:32–38.
24. Canepa M, Franssen FME, Olschewski H, Lainscak M, Böhm M, Tavazzi L, Rosenkranz S. Diagnostic and therapeutic gaps in patients with heart failure and chronic obstructive pulmonary disease. *JACC Heart Fail* 2019;**7**:823–833.
25. Baumert M, Immanuel SA, Stone KL, Litwack Harrison S, Redline S, Mariani S, Sanders P, McEvoy RD, Linz D. Composition of nocturnal hypoxaemic burden and its prognostic value for cardiovascular mortality in older community-dwelling men. *Eur Heart J* 2020;**41**:533–541.
26. Xiao X, Han H, Wu C, He Q, Ruan Y, Zhai Y, Gao Y, Zhao X, He J. Prevalence of atrial fibrillation in hospital encounters with end-stage COPD on home oxygen: national trends in the United States. *Chest* 2019;**155**:918–927.
27. Grymonprez M, Vakaet V, Kavousi M, Stricker BH, Ikram MA, Heeringa J, Franco OH, Brusselle GG, Lahousse L. Chronic obstructive pulmonary disease and the development of atrial fibrillation. *Int J Cardiol* 2019;**276**:118–124.
28. Hirayama A, Goto T, Shimada YJ, Faridi MK, Camargo CA Jr, Hasegawa K. Acute exacerbation of chronic obstructive pulmonary disease and subsequent risk of emergency department visits and hospitalizations for atrial fibrillation. *Circ Arrhythm Electrophysiol* 2018;**11**:e006322.
29. Stevenson IH, Roberts-Thomson KC, Kistler PM, Edwards GA, Spence S, Sanders P, Kalman JM. Atrial electrophysiology is altered by acute hypercapnia but not hypoxemia: implications for promotion of atrial fibrillation in pulmonary disease and sleep apnea. *Heart Rhythm* 2010;**7**:1263–1270.
30. Linz D, Schotten U, Neuberger HR, Böhm M, Wirth K. Negative tracheal pressure during obstructive respiratory events promotes atrial fibrillation by vagal activation. *Heart Rhythm* 2011;**8**:1436–1443.
31. Linz D, Hohl M, Ukena C, Mahfoud F, Wirth K, Neuberger HR, Böhm M. Obstructive respiratory events and premature atrial contractions after cardioversion. *Eur Respir J* 2015;**45**:1332–1340.
32. Konecny T, Park JY, Somers KR, Konecny D, Orban M, Soucek F, Parker KO, Scanlon PD, Asirvatham SJ, Brady PA, Rihal CS. Relation of chronic obstructive pulmonary disease to atrial and ventricular arrhythmias. *Am J Cardiol* 2014;**114**:272–277.

33. Buch P, Friberg J, Scharring H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. *Eur Respir J* 2003;**21**: 1012–1016.
34. Li J, Agarwal SK, Alonso A, Blecker S, Chamberlain AM, London SJ, Loefer LR, McNeill AM, Poole C, Soliman EZ, Heiss G. Airflow obstruction, lung function, and incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 2014;**129**:971–980.
35. Hirayama A, Goto T, Shimada YJ, Faridi MK, Camargo CA Jr, Hasegawa K. Acute exacerbation of chronic obstructive pulmonary disease and subsequent risk of emergency department visits and hospitalizations for atrial fibrillation. *Circ Arrhythm Electrophysiol* 2018;**11**:e006322.
36. Desai R, Patel U, Singh S, Bhuvra R, Fong HK, Nunna P, Zalavadia D, Dave H, Savani S, Doshi R. The burden and impact of arrhythmia in chronic obstructive pulmonary disease: insights from the National Inpatient Sample. *Int J Cardiol* 2019; **281**:49–55.
37. Perticone M, Sciacqua A, Tripepi G, Miceli S, Corrao S, Sesti G, Perticone F. Competitive interaction between chronic obstructive pulmonary disease and CHA2DS2-VASc score in predicting incident atrial fibrillation. *Int J Cardiol* 2018; **255**:74–79.
38. Hayashi T, Fukamizu S, Hojo R, Komiya K, Tanabe Y, Tejima T, Nishizaki M, Hiraoka M, Ako J, Momomura S, Sakurada H. Prevalence and electrophysiological characteristics of typical atrial flutter in patients with atrial fibrillation and chronic obstructive pulmonary disease. *Europace* 2013;**15**:1777–1783.
39. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2019 report. <https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-VMS.pdf> (1 October 2020).
40. Haroon S, Jordan R, Takwoingi Y, Adab P. Diagnostic accuracy of screening tests for COPD: a systematic review and meta-analysis. *BMJ Open* 2015;**5**:e008133.
41. Schermer TR, Vatsolaki M, Behr R, Grootens J, Cretier R, Akkermans R, Denis J, Poels P, van den Bemt L. Point of care microspirometry to facilitate the COPD diagnostic process in primary care: a clustered randomised trial. *NPJ Prim Care Respir Med* 2018;**28**:17.
42. Dubé BP, Agostoni P, Laveneziana P. Exertional dyspnoea in chronic heart failure: the role of the lung and respiratory mechanical factors. *Eur Respir Rev* 2016;**25**: 317–332.
43. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.
44. Dhakal BP, Malhotra R, Murphy RM, Pappagianopoulos PP, Baggish AL, Weiner RB, Houston NE, Eisman AS, Hough SS, Lewis GD. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. *Circ Heart Fail* 2015;**8**:286–294.
45. Keteyian SJ, Ehrman JK, Fuller B, Pack QR. Exercise testing and exercise rehabilitation for patients with atrial fibrillation. *J Cardiopulm Rehabil Prev* 2019;**39**:65–72.
46. O'Donnell DE, Elbehairy AF, Faisal A, Webb KA, Neder JA, Mahler DA. Exertional dyspnoea in COPD: the clinical utility of cardiopulmonary exercise testing. *Eur Respir Rev* 2016;**25**:333–347.
47. Emren SV, Kocabaş U, Duygu H, Levent F, Şimşek EÇ, Yapan Emren Z, Tülüce S. The role of HATCH score in predicting the success rate of sinus rhythm following electrical cardioversion of atrial fibrillation. *Kardiol Pol* 2016;**74**:978–984.
48. Roh SY, Choi JJ, Lee JY, Kwak JJ, Park JS, Kim JB, Lim HE, Kim YH. Catheter ablation of atrial fibrillation in patients with chronic lung disease. *Circ Arrhythm Electrophysiol* 2011;**4**:815–822.
49. Arora S, Lahewala S, Tripathi B, Mehta V, Kumar V, Chandramohan D, Lemor A, Dave M, Patel N, Patel NV, Palamaner Subash Shantha G, Viles-Gonzalez J, Deshmukh A. Causes and predictors of readmission in patients with atrial fibrillation undergoing catheter ablation: a national population-based cohort study. *J Am Heart Assoc* 2018;**7**:e009294.
50. Seara JG, Roubin SR, Gude Sampedro F, Barreiro VB, Sande JM, Mañero MR, Grandio PC, Alvarez B, Juanatey JG. Risk of atrial fibrillation, stroke, and death after radiofrequency catheter ablation of typical atrial flutter. *Clin Res Cardiol* 2014;**103**:543–552.
51. Steinberg BA, Holmes DN, Pieper K, Allen LA, Chan PS, Ezekowitz MD, Freeman JV, Fonarow GC, Gersh BJ, Hylek EM, Kowey PR, Mahaffey KW, Naccarelli G, Reiffel J, Singer DE, Peterson ED, Piccini JP, ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) Investigators and Patients. Factors associated with large improvements in health-related quality of life in patients with atrial fibrillation: results from ORBIT-AF. *Circ Arrhythm Electrophysiol* 2020;**13**:e007775.
52. Chen K, Bai R, Deng W, Gao C, Zhang J, Wang X, Wang S, Fu H, Zhao Y, Zhang J, Dong J, Ma C. HATCH score in the prediction of new-onset atrial fibrillation after catheter ablation of typical atrial flutter. *Heart Rhythm* 2015;**12**:1483–1489.
53. Jackevicius CA, Tom A, Essebag V, Eisenberg MJ, Rahme E, Tu JV, Humphries K, Behloul H, Pilote L. Population-level incidence and risk factors for pulmonary toxicity associated with amiodarone. *Am J Cardiol* 2011;**108**:705–710.
54. Dransfield MT, McAllister DA, Anderson JA, Brook RD, Calverley PMA, Celli BR, Crim C, Gallot N, Martinez FJ, Scanlon PD, Yates J, Vestbo J, Newby DE, SUMMIT Investigators. β -Blocker therapy and clinical outcomes in patients with moderate chronic obstructive pulmonary disease and heightened cardiovascular risk. An observational substudy of SUMMIT. *Ann Am Thorac Soc* 2018;**15**: 608–614.
55. Dransfield MT, Voelker H, Bhatt SP, Brenner K, Casaburi R, Come CE, Cooper JAD, Criner GJ, Curtis JL, Han MK, Hatipoğlu U, Helgeson ES, Jain VV, Kalhan R, Kaminsky D, Kaner R, Kunisaki KM, Lambert AA, Lammi MR, Lindberg S, Make BJ, Martinez FJ, McEvoy C, Panos RJ, Reed RM, Scanlon PD, Sciurba FC, Smith A, Sriram PS, Stringer WW, Weingarten JA, Wells JM, Westfall E, Lazarus SC, Connett JE, BLOCK COPD Trial Group. Metoprolol for the prevention of acute exacerbations of COPD. *N Engl J Med* 2019;**381**:2304–2314.
56. Sundh J, Magnuson A, Montgomery S, Andell P, Rindler G, Fröbert O, the BRONCHIOLE Investigators. Beta-blockers to major cardiovascular events in chronic obstructive pulmonary disease (BRONCHIOLE)—a study protocol from a randomized controlled trial. *Trials* 2020;**21**:123.
57. Brook RD, Anderson JA, Calverley PM, Celli BR, Crim C, Denvir MA, Magder S, Martinez FJ, Rajagopalan S, Vestbo J, Yates J, Newby DE, SUMMIT Investigators. Cardiovascular outcomes with an inhaled beta2 agonist/corticosteroid in patients with COPD at high cardiovascular risk. *Heart* 2017;**103**:1536–1542.
58. Wise RA, Chapman KR, Scirica BM, Bhatt DL, Daoud SZ, Zetterstrand S, Reisner C, Gil EG. Effect of aclidinium bromide on major cardiovascular events and exacerbations in high-risk patients with chronic obstructive pulmonary disease: the ASCENT-COPD randomized clinical trial. *JAMA* 2019;**321**:1693–1701.
59. Lahousse L, Verhamme KM, Stricker BH, Brusselle GG. Cardiac effects of current treatments of chronic obstructive pulmonary disease. *Lancet Respir Med* 2016;**4**:149–164.
60. 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**:305–311.
61. Huerta C, Lanes SF, García Rodríguez LA. Respiratory medications and the risk of cardiac arrhythmias. *Epidemiology* 2005;**16**:360–366.
62. van der Hoof CS, Heeringa J, Brusselle GG, Hofman A, Witteman JC, Kingma JH, Sturkenboom MC, Stricker BH. Corticosteroids and the risk of atrial fibrillation. *Arch Intern Med* 2006;**166**:1016–1020.
63. Köhnlein T, Windisch W, Köhler D, Drabik A, Geiseler J, Hartl S, Karg O, Laiers-Groeneveld G, Nava S, Schönhofer B, Schucher B, Wegscheider K, Criele CP, Welte T. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med* 2014;**2**:698–705.
64. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, Kalman JM, Abhayaratna WP, Sanders P. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol* 2014; **64**:2222–2231.
65. Middeldorp ME, Pathak RK, Meredith M, Mehta AB, Elliott AD, Mahajan R, Twomey D, Gallagher C, Hendriks JML, Linz D, McEvoy RD, Abhayaratna WP, Kalman JM, Lau DH, Sanders P. PREVENTion and regReSSive Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study. *Europace* 2018;**20**:1929–1935.
66. Tsai LL, McNamara RJ, Moddel C, Alison JA, McKenzie DK, McKeough ZJ. Home-based telerehabilitation via real-time videoconferencing improves endurance exercise capacity in patients with COPD: the randomized controlled TeleR Study. *Respirology* 2017;**22**:699–707.
67. Linz D, Baumert M, Catcheside P, Floras J, Sanders P, Lévy P, Cowie MR, Doug McEvoy R. Assessment and interpretation of sleep disordered breathing severity in cardiology: clinical implications and perspectives. *Int J Cardiol* 2018;**271**: 281–288.