

Optimal Management of Heart Failure and Chronic Obstructive Pulmonary Disease: Clinical Challenges

Joseph J Cuthbert^{1,2}, Pierpaolo Pellicori³, Andrew L Clark²

¹Centre for Clinical Sciences, Hull York Medical School, Kingston Upon Hull, East Riding of Yorkshire, UK; ²Department of Cardiology, Hull University Teaching Hospital Trust, Kingston Upon Hull, East Riding of Yorkshire, UK; ³Robertson Centre for Biostatistics and Glasgow Clinical Trials Unit, University of Glasgow, Glasgow, UK

Correspondence: Joseph J Cuthbert, Department of Cardiorespiratory Medicine, Centre for Clinical Sciences, Hull York Medical School, Hull and East Yorkshire Medical Research and Teaching Centre, Castle Hill Hospital, Cottingham, Kingston Upon Hull, HU16 5JQ, UK, Tel +44 1482 461776, Fax +44 1482 461779, Email joe.cuthbert@hyms.ac.uk

Abstract: Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are common causes of breathlessness which frequently co-exist; one potentially exacerbating the other. Distinguishing between the two can be challenging due to their similar symptomatology and overlapping risk factors, but a timely and correct diagnosis is potentially lifesaving. Modern treatment for HF can substantially improve symptoms and prognosis for many patients and may have beneficial effects for patients with COPD. Conversely, while many inhaled treatments for COPD can improve symptoms and reduce exacerbations, there is conflicting evidence regarding the safety of some inhaled treatments for COPD in patients with HF. Here we explore the overlap between HF and COPD, examine the effect of one condition on the other, and address the challenges of managing patients with both conditions.

Keywords: chronic obstructive pulmonary disease, heart failure, management, outcomes, comorbidities

Introduction

Breathlessness on exertion is an enormously common presenting complaint, affecting between 10% and 20% of the adult population,¹⁻³ and up to two-thirds of those aged over 60 years.⁴⁻⁶ Distinguishing between heart failure (HF), chronic obstructive pulmonary disease (COPD), both, or neither can be challenging due to the large overlap in symptoms, clinical signs, co-morbidities and risk factors – especially smoking history. Furthermore, the pre-existing diagnosis of one condition may obscure the diagnosis of the other, as clinicians might fail to consider additional causes of breathlessness.⁷

Distinguishing between the two – and identifying one despite the presence of the other – is essential for controlling symptoms and improving prognosis. Medical management of HF due to a reduced ejection fraction (HFrEF) can almost double life expectancy.⁸ There is little data to suggest inhaled treatments for COPD have a prognostic benefit;⁹⁻¹² the recent ETHOS and IMPACT trials of inhaled therapies for patients with COPD have suggested a reduced mortality for patients treated with triple therapy (inhaled glucocorticoid, long-acting antimuscarinic, and long acting beta-agonist) compared to dual therapy but event rates were low and neither trial was powered to detect a mortality difference.^{13,14} Inhaled therapies can substantially improve symptoms and reduce the risk of exacerbations for patients with COPD,¹⁵ but may have harmful effects in patients with HF.¹⁶⁻¹⁸ Conversely, loop diuretics can greatly improve symptoms of congestion in patients with HF,¹⁹ but would have minimal impact on the symptoms of patients with airway obstruction.

Prevalence of COPD in Patients with HF

The prevalence of COPD in patients with HF varies depending on the population and the definition used (Figure 1). Using a non-standard definition (either self-reported by the patient or based on physician assessment, COPD treatment, or from review of the medical notes) the prevalence ranges between 10 and 25% (Table 1).²⁰⁻²⁸ Using spirometry to define

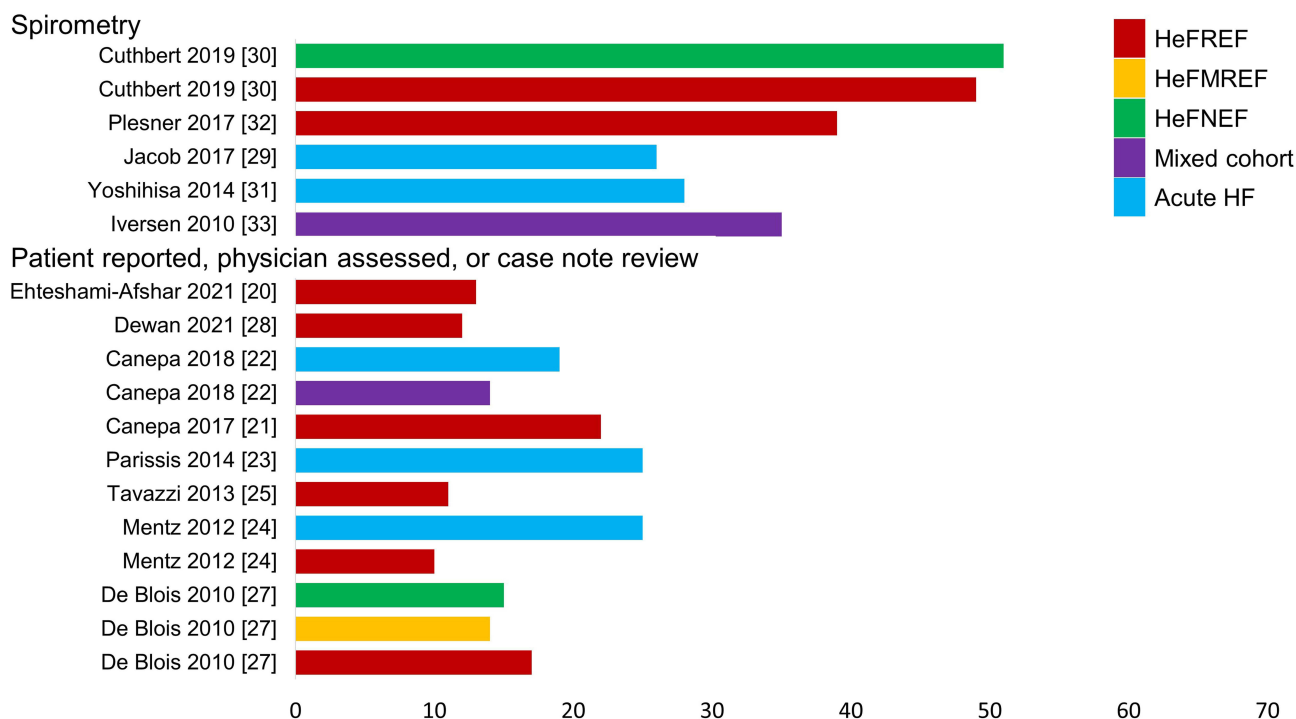


Figure 1 Prevalence of COPD in patients with HF by definition and HF phenotype.

Note: Reference citation in square brackets.

Abbreviations: HFREF, heart failure with a reduced ejection fraction; HeFMREF, heart failure with a mildly reduced ejection fraction; HeFNFEF, heart failure with a normal ejection fraction; HF, heart failure; COPD, chronic obstructive pulmonary disease.

the presence of COPD, the prevalence is higher and ranges between 25 and 50% (Table 2).^{29–33} The reasons for this discrepancy is unclear, but it may be due to undiagnosed COPD in patients with HF: the patient is breathless and the clinician has objective evidence of cardiac dysfunction (raised natriuretic peptide levels and/or reduced left ventricular ejection fraction (LVEF)), another potential cause of the symptoms may go overlooked. Alternatively, abnormal findings on spirometry may be due to HF rather COPD.³⁴ Pulmonary congestion may compress small airways causing an obstructive clinical picture on spirometry that resolves with adequate treatments, particularly diuresis.³⁵ In one small study (N = 272), half of patients with HF and obstructive spirometry at baseline had normal spirometry after 6 months of treatment with loop diuretics, angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), beta-blocker, and mineralocorticoid receptor antagonist.³⁶ However, while abnormal spirometry is common amongst patients admitted with heart failure, a restrictive pattern is nearly three times more common than an obstructive, or mixed, pattern.³⁷

COPD (among other causes of breathlessness) should be considered in all patients with HF who are breathless despite having no signs of congestion, although the prognostic benefits of diagnosing and treating COPD in patients with established HF remain questionable. Of those studies which used non-standardised definitions of COPD, some suggest that the co-diagnosis of COPD and HF is associated with a 20–30% greater risk of death compared to HF alone,^{19,25,26} while others suggest no,^{21,22} or only weak,^{20,23,24} associations between the presence of COPD and greater risk of adverse outcome.

In the two largest cohorts which diagnosed COPD via spirometry (N~11,000 combined), the presence of COPD in patients with HF was not associated with a greater risk of mortality^{29,30} but was associated with an increased risk of readmission in the month following discharge following an admission with HF.²⁹

Prevalence of HF in Patients with COPD

Although there is a large overlap in risk factors for HF and COPD, COPD may be an independent risk factor for incident HF: exacerbations are associated with an increased risk of myocardial infarction (among other cardiovascular events) which is the most common cause of HeFREF.³⁸ Amongst those with COPD, the prevalence of HF based on the findings from examination,

Table I Studies of COPD Prevalence in Patients with HF Not Using Spirometry

Study	Cohort	HF Phenotype	Definition of COPD	Prevalence of COPD	Beta-Blocker (COPD vs No COPD)	Results
De Blois (2010) ²⁷	N=4132 Norwegian HF registry	>90% HeFREF CHF	ICD 9	20%	74% vs 84%	COPD associated with increased risk of all-cause mortality in (HR=1.19; p=0.03)
Mentz (2012) ²⁶	N=4133 EVEREST trial cohort	HeFREF AHF	Medical record	10%	63% vs 71%	COPD not associated with mortality or hospitalisation after adjustment for other variables
Mentz (2012) ²⁴	N=20118 OPTIMIZE-HF registry	HeFREF AHF	Investigator reported	25%	66% vs 75%	COPD not associated with in-hospital or post discharge mortality after adjustment for other variables
Tavazzi (2013) ²⁵	N=6505 SHIFT trial cohort	HeFREF CHF	Medical record	11%	69% vs 92%	COPD associated with an increased risk of HF hospitalisation or CV mortality (HR 1.22; p=0.006)
Canepa (2018) ²²	N=16329 ESC HF long-term registry	73% HeFREF 57% CHF	Investigator reported	19% in AHF 14% in CHF	72% vs 85%	COPD associated with an increased risk of all-cause hospitalisations but not associated with mortality after adjustment for other variables
Canepa (2017) ²¹	N=6975 GISSI-HF trial cohort	~90% HeFREF CHF	Investigator reported	22%	44% vs 71%	COPD associated with an increased risk of all-cause mortality (HR 1.28; p<0.001) and CV hospitalisation (HR 1.23; p<0.001)
Ehteshami-Afshar (2021) ²⁰	N=8399 PARADIGM-HF cohort	HeFREF CHF	Investigator reported	13%	87% vs 94%	COPD associated with an increased risk of CV hospitalisations but not mortality
Dewan (2021) ²⁸	N=4744 DAPA-HF cohort	HeFREF CHF	Investigator reported	12%	92% vs 97% No difference in proportion of patients achieving $\geq 50\%$ of target dose	COPD associated with an increased risk of worsening HF or CV mortality (HR = 1.44; P<0.001)

investigations, or information in the medical record ranges between from 5% to 20% (Figure 2).^{39–49} However, up to 50% of patients with COPD have high serum natriuretic peptide concentrations (a key diagnostic criterion for HF suggestive of underlying cardiac dysfunction).^{43,46,50}

The presence of HF in patients with COPD is consistently associated with an increased risk of morbidity and mortality compared to COPD alone. Patients with high natriuretic peptide concentrations may have significant underlying cardiac dysfunction regardless of whether they fit the current diagnostic criteria for HF,⁵¹ and the presence of raised NP concentrations is associated with a higher mortality in patients with COPD.^{52,53}

Medical treatment for HFREF is associated with a 50–60% reduction in the risk of HF hospitalisation or cardiovascular mortality.⁸ Thus, identifying and treating HF in a patient with COPD may have an enormous beneficial effect on prognosis.

Distinguishing HF from COPD and Vice Versa

History & Clinical Examination

An accurate history alone is unlikely to be able to distinguish HF from COPD but may give some clues. Patients with either condition predominantly present with progressive breathlessness, which may be interpreted as a sign of old age, or

Table 2 Studies of COPD Prevalence in HF Populations Using Spirometry

Study	Cohort	HF Phenotype	Definition of COPD	Prevalence of COPD	Beta-Blocker (COPD vs No COPD)	Results
Iversen (2010) ³³	N=527 ECHOS trial cohort	58% HeFREF CHF	Post-bronchodilator FEV ₁ ; FEV ₁ :FVC GOLD criteria	35%	17% vs 32%	Lower FEV ₁ associated with an increased risk of mortality but lower FEV ₁ :FVC was not regardless of HF phenotype
Brenner (2013) ³⁶	N=619 Sub-group of Interdisciplinary Network HF Study	HeFREF AHF	Post-bronchodilator FEV ₁ ; FEV ₁ :FVC GOLD criteria	23%	88% vs 92%	COPD associated with increased risk of all-cause mortality (HR=1.64; P=0.04)
Yoshihisa (2014) ³¹	N=378 Hospitalised with HF	Mixed cohort AHF	No bronchodilator FEV ₁ ; FEV ₁ :FVC	28%	58% vs 70%	Mild COPD not associated with outcomes but moderate COPD (FEV ₁ :FVC <0.7 and FEV ₁ 50–80% of predicted) associated with increased risk of all-cause mortality
Jacob (2016) ²⁹	N=8099 EAHFE cohort – patients presenting to ED with ADHF	Mixed cohort AHF	No bronchodilator FEV ₁ ; FEV ₁ :FVC	26%	30% vs 45%	COPD associated with an increased risk of re-hospitalisation but not mortality.
Plesner (2017) ³²	N=573 Stable out-patients with HF	HeFREF CHF	No bronchodilator FEV ₁ ; FEV ₁ :FVC	39%	75% vs 78%	COPD associated with an increased risk of all-cause mortality (HR = 2.07; P<0.01)
Cuthbert (2019) ³⁰	N=4986 Stable outpatients with HF	83% HeFREF CHF	No bronchodilator FEV ₁ ; FEV ₁ :FVC	50%	55% vs 63%	COPD not associated with HF hospitalisation or all-cause mortality after multivariable adjustment

fatigue – another symptom common in HF.⁴⁴ Obesity might impair respiratory mechanics,⁵⁴ but carrying a substantial excess of body fat might also cause exertional breathlessness. Ankle swelling is a non-specific symptom of cardiac dysfunction that may go unrecognised by patients and their clinicians.⁵⁵ However, advanced lung disease can cause raised pulmonary arterial pressures – type III pulmonary hypertension or *cor pulmonale* – which itself can cause peripheral oedema and ankle swelling.

Daytime cough is a common symptom of COPD, particularly in chronic smokers, but is also seen, less commonly, in patients with HF. Cough in patients with HF is most likely to be due to pulmonary congestion, and rarely due to treatment with an ACEI. Nocturnal cough and breathlessness (paroxysmal nocturnal dyspnoea) due to lying flat is an indication of worsening pulmonary congestion in patients with HF.⁵⁰ Nocturnal symptoms are claimed to be uncommon in patients with COPD,⁵⁶ but up to 20% of patients with severe COPD may suffer from chest tightness, breathlessness, or cough which are worse at night.⁵⁷ Sputum production is a common feature of COPD but rare in patients with HF (except in the case of frank pulmonary oedema in which patients may produce pink, frothy sputum). Symptoms of advanced disease, such as weight loss and frailty, are common to both conditions.^{58,59}

Concurrent medications may also offer useful clues: chronic use of medications such as loop diuretics or digoxin might indicate underlying cardiac dysfunction and is associated with a greater risk of cardiovascular events, even in the absence of a heart failure diagnosis.⁵⁵

Based on examination & investigations†

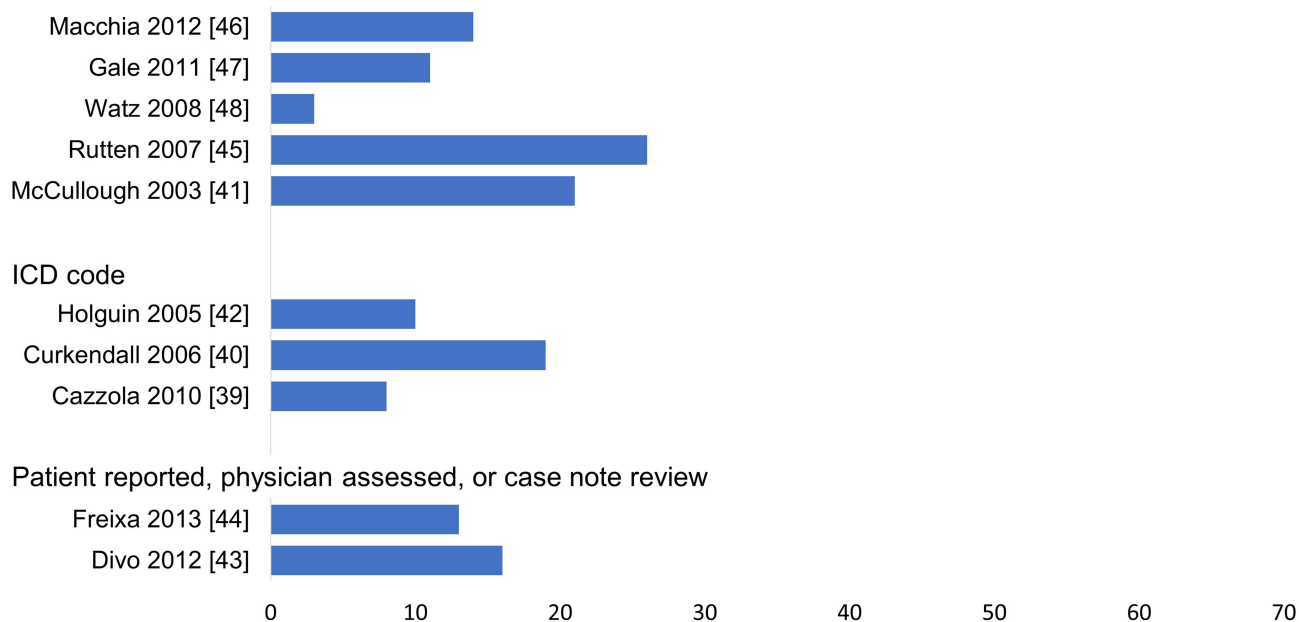


Figure 2 Prevalence of HF in patients with COPD.

Note: †Not including natriuretic peptide testing except for Gale et al 2011.

Abbreviations: ICD, international classification of diseases; HF, heart failure; COPD, chronic obstructive pulmonary disease.

Clinical signs of bronchoconstriction (such as wheeze) or congestion (such as a raised jugular venous pulse) are often difficult to elicit,^{60,61} lack specificity,^{61,62} and may only be present with severe disease.⁶³ Further investigation is usually essential.

Investigations

Unless there is pulmonary oedema, the chest X-ray (CXR) findings listed in textbooks in patients with either HF or COPD are often non-specific and a normal CXR excludes neither condition.^{64,65} The real value of a CXR in a patient presenting with breathlessness and/or cough is to exclude other possible pathologies such as pneumonia, lung cancer, or pulmonary fibrosis. Conversely, a normal electrocardiogram (ECG) has a negative predictive value of 98% for the presence of significant cardiac dysfunction,⁶⁶ but would not rule out COPD.⁶⁷ The finding of x-ray changes consistent with COPD in a patient with HF, or ECG changes in a patient with COPD should not be ignored and prompt investigation for the other pathology.

Measuring serum natriuretic peptide concentration in patients with breathlessness and suspected HF is recommended by international specialist guidelines.^{50,68} As with a normal ECG, normal natriuretic peptide concentrations make a diagnosis of HF highly unlikely. Very high concentrations, on the other hand, are associated with a poor prognosis regardless of underlying conditions or left ventricular systolic function. However, there are multiple causes of raised serum NP concentration, including COPD, although concentrations tend to be lower than in patients with left ventricular systolic dysfunction,⁴⁸ even during an exacerbation.⁶⁹ The underlying cause of raised NP concentrations in patients presenting with breathlessness is rarely clear from history, examination, and blood tests alone: in a patient with COPD, it may indicate the presence of pulmonary hypertension due to severe lung disease, the presence of left ventricular systolic dysfunction, or atrial fibrillation. Thus, when NPs are abnormal, assessment of cardiac structure and function is required, most commonly via transthoracic echocardiography (TTE).

Echocardiography and Spirometry

Approximately half of patients with the superficial “heart failure syndrome” – breathlessness, signs of congestion, and raised NP concentrations – will have a left ventricular ejection fraction (LVEF) within the normal range (>50%), variously termed HF with a preserved or normal ejection fraction (HFpEF/HFnEF).⁵⁰

Echocardiography can also give an estimate of pulmonary artery systolic pressure using Doppler imaging, thereby indicating the presence of pulmonary hypertension but offers only limited information on the aetiology of high pulmonary pressures. Echocardiography may also raise the suspicion of amyloidosis or other rarer cardiomyopathies which require further investigation.

However, the main purpose of a TTE in patients with breathlessness and raised NP concentrations is to identify or exclude HFrEF or severe valve disease, both of which can be treated with profound beneficial effects on symptoms and prognosis.⁵⁰ While low LVEF on TTE makes the management plan easier, it does not exclude concurrent COPD. Spirometry is the standard test for diagnosing COPD. If the ratio of forced expiratory volume in 1 second (FEV₁) to forced vital capacity (FVC) is below 0.7 despite the administration of bronchodilator, there is obstructive pulmonary disease.⁷⁰ However, just as with LVEF measured on echocardiography, spirometry can be misleading – as many as 1 in 4 patients with an FEV₁/FVC ratio <0.7 on one day may have a normal ratio on a different day in whom a differential diagnosis of asthma ought to be considered.^{70,71} Many patients with normal spirometry have symptoms, signs, radiographic evidence of, and frequent exacerbations consistent with COPD.^{72,73} Furthermore, many patients with heart failure also have obstructive spirometry which improves with diuresis.^{35,36}

Both conditions have “quick-fix” symptomatic treatments – loop diuretics in the case of HF; short-acting beta-agonists in the case of COPD. Given the inherent difficulties with establishing a diagnosis, a trial of treatment with either (but not both together) may be the best way to clarify the diagnosis or, in the case of concurrent HF and COPD, clarify which condition has the greatest symptomatic impact. However, symptomatic improvement is not a valid excuse to not investigate for other diagnoses, should the clinical suspicion remain.⁷⁴

Patients can have as many diseases as they damn well please.

Hickam’s dictum. John Hickam 1914–1970.⁷⁵

Effect of HF Treatments on Patients with COPD

Renin Angiotensin Aldosterone System Inhibitors

Drugs that inhibit the renin angiotensin aldosterone system (RAAS) – angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), and angiotensin receptor neprilysin inhibitors (ARNI) – are the cornerstone of medical management of HFrEF, but there is increasing evidence that they may provide prognostic benefit for some patients with HF and a higher LVEF.⁵⁰

RAAS activation may also be implicated in the pathogenesis of COPD. In vivo and in vitro studies have found that angiotensin II (AngII) stimulates the release of inflammatory cytokines such as interleukin, tumour necrosis factor α , and monocyte chemoattractant protein 1.⁷⁶ The latter activates tissue mast cells in response to alveolar hypoxia, thus potentially driving the local and systemic inflammatory response in patients with COPD.⁷⁷ AngII also increases inflammatory cell migration, epithelial cell apoptosis, and fibroblast activity in the lung parenchyma.^{78,79} It enhances bronchoconstriction driven by muscarinic receptor activation,⁸⁰ and drives the cytokine mediated immune response to lung injury.⁸¹ In human tissue, expression of angiotensin receptor 1 (AT1) is higher in fibrosed lung of patients with COPD compared to those with no pulmonary disease.⁸² AngII may thus contribute to the development and progression of lung inflammation and fibrosis associated with COPD and losartan – an AT1 blocker can inhibit some aspects of lung injury.^{79,83}

ACEIs or ARBs can improve histological appearances, lung compliance, exercise capacity, and reduce lung fibrosis in animal models of pulmonary disease.^{84–86} Retrospective data suggest that patients with COPD who either take an ACEI or ARB have slower decline in lung function,⁸⁷ and slower progression of emphysematous changes on computed tomography than those that do not.⁸⁸ However, trials of the effect of ACEI or ARB on pulmonary function or exercise capacity in patients with COPD have produced inconsistent results.^{89–92} Of note, in a double-blind randomised controlled trial (RCT) (N = 80), treatment with enalapril for 10 weeks, alongside a cardiopulmonary exercise rehabilitation programme, was associated with improved peak work rate in patients with at least moderate COPD compared to those undergoing the rehabilitation programme alone.⁹³ No prospective randomised clinical trial has investigated the effect of RAAS inhibitors on morbidity and mortality in patients with COPD and no cardiovascular indication for treatment.

The use of ACEI or ARB tends to be lower amongst patients with HF and COPD compared to those with HF alone. The reasons for this are unclear but may be due to clinicians overlooking other causes of breathlessness in patients with an established diagnosis of COPD and not treating HF effectively as a result.⁹⁴ The benefits of medications that inhibit the RAAS in patients with HFrEF are clear and, in the case of ACEI or ARB, may also benefit patients with COPD (Figure 3).

Beta-Blockers

Initially thought to be detrimental in patients with HF, beta-blockers are now considered first-line treatment with perhaps the greatest prognostic benefit for patients with HFrEF.^{8,95} There is often great unease regarding the safety of beta-blocker in patients with COPD.

Almost all HF registry and trial data report that a lower proportion of patients with HF and COPD are treated with beta-blockers compared to patients with HF but without COPD.⁹⁶ Anxiety about beta-blocker induced bronchoconstriction and concerns that beta-blockers might also reduce the efficacy of inhaled beta-agonist treatment have some evidence to support them.⁹⁷ In those with obstructive lung disease, treatment with beta-blockers is associated with a fall in FEV₁ and an increase in wheeze; non-selective beta-blockers (such as carvedilol which antagonises β_1 , β_2 , and α_1 adrenoceptors) reduce FEV₁ by ~100 mL more than do cardio-selective beta-blockers (such as metoprolol or bisoprolol which antagonises β_1 only).^{98–100} Some observational data suggest that the rate of hospitalisation with COPD is greater within 60 days of starting a non-selective beta-blocker in patients with HFrEF and concurrent COPD compared to HF alone,¹⁰¹ and that the risk of death in patients with COPD on long-term oxygen therapy is higher among those taking beta-blockers.¹⁰¹

COPD, like HF, is associated with adrenergic activation and high concentrations of circulating inflammatory cytokines.^{102,103} Activation of one system increases activation of the other, particularly in the context of an exacerbation.^{97,104} Cardiovascular death is common amongst patients with COPD,¹⁰⁵ and use of beta-blockers is

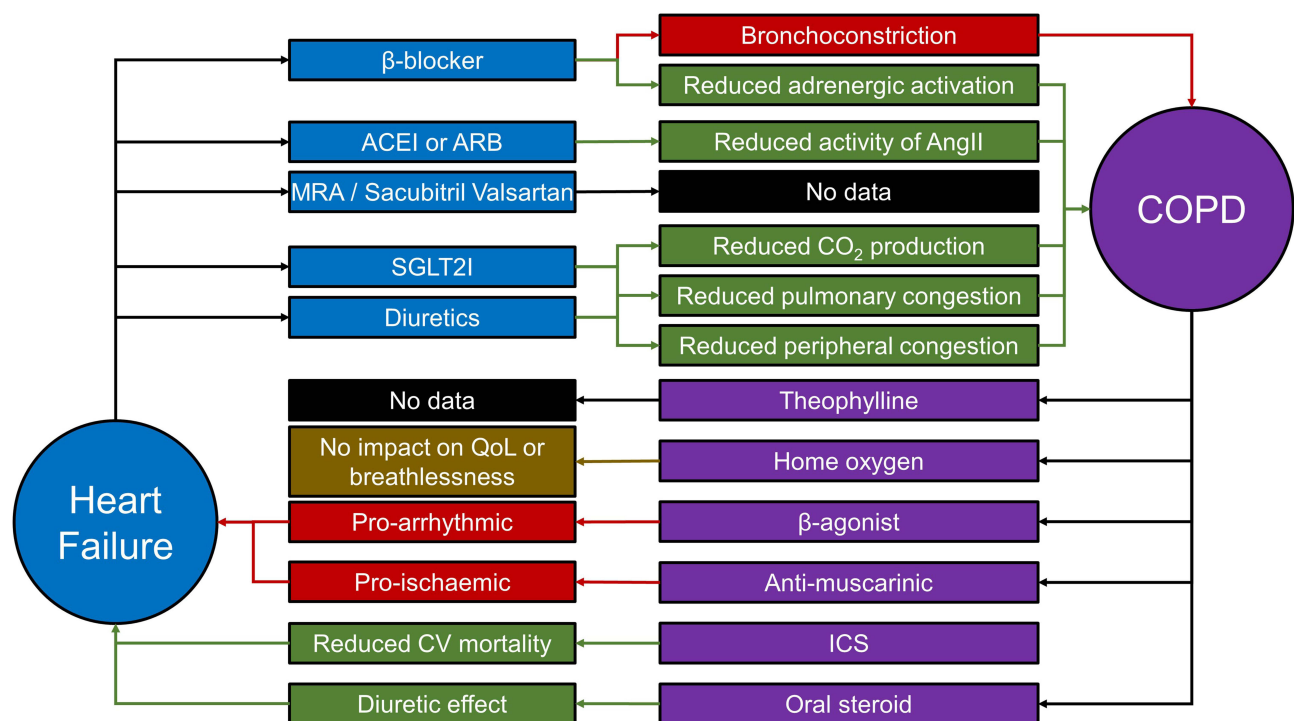


Figure 3 Proposed interactions of medical therapy for HF and COPD.

Note: Data from References 76–93; 98–100;102–105; 120–125; 136–161.

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; SGLT2I, sodium-glucose co-transporter 2 inhibitor; ICS, inhaled corticosteroid; QoL, quality of life; AngII, angiotensin II; CO₂, carbon dioxide; COPD, chronic obstructive pulmonary disease.

associated with a reduced risk of mortality amongst patients with COPD in some observational cohorts.^{106,107} However, the only RCT to assess beta-blocker use in patients with moderate or severe COPD and no other cardiovascular indication (N = 532) was stopped prematurely because of futility and safety concern: patients randomised to metoprolol had a 91% greater risk of developing a severe COPD exacerbation compared to those assigned to placebo.¹⁰⁸ Further trials are ongoing.^{109,110}

In practice, beta-blockers are well tolerated in the majority of patients with COPD, even during exacerbations,^{111,112} but are only tolerated in half of patients with asthma.¹¹³ While beta-blockers may be associated with worse COPD-related outcomes in those with severe COPD, their benefit in patients with HFREF is profound and well established and widely recommended, regardless of a COPD diagnosis.⁵⁰ In clinical practice, for patients with HF and COPD, cardio selective beta-blockers should be preferred and started at a low dose, closely monitoring for early signs of airway obstruction.

Sodium Glucose Co-Transporter-2 Inhibitors

Sodium glucose co-transporter 2 inhibitors (SGLT2i) were developed as anti-hyperglycaemic medications. The sodium glucose co-transporter 2 is responsible for reabsorption of sodium and glucose in the proximal convoluted tubule, thus inhibition of the transporter induces glycosuria and natriuresis.¹¹⁴ Initially investigated in patients with diabetes, Phase III studies found a reduction in HF hospitalisation regardless of the presence of HF at baseline.^{115,116} Subsequent trials confirmed prognostically beneficial effects of SGLT2i in patients with heart failure regardless of LVEF or a diagnosis of type II diabetes.^{117,118}

A meta-analysis of 9 large RCTs of SGLT2i in various patient populations suggested that treatment with SGLT2i may reduce the risk of hospital admission with COPD exacerbation compared to placebo (hazard ratio 0.77 (95% confidence interval 0.61–0.97; P = 0.03)).¹¹⁹ The underlying mechanisms of benefits of SGLT2i are much debated but are likely to be due, mostly, to the osmotic diuretic effect of glycosuria.¹²⁰ Thus, in those with HF, SGLT2i might decrease pulmonary congestion,¹²¹ and theoretically improve lung function, reducing the risk of infective COPD exacerbations (Figure 3). Overall, in clinical trials, SGLT2i has been well tolerated in different populations and there is no indication that patients with COPD are more likely to be intolerant of the treatment.

Diuretics

Loop diuretics are vital for controlling symptoms of venous congestion in HF.⁵⁰ Venous congestion is also a feature of *cor pulmonale*, and thus loop diuretics are prescribed to some patients with COPD with no diagnosis of left ventricular dysfunction. Pulmonary congestion may cause worsening of lung function and obstructive physiology on spirometry.³⁶ Titration of HF medications (including diuretics) to reduce pulmonary artery pressure is associated with a lower rate of hospitalisation due to respiratory infection.¹²² A large observational analysis of patients in primary care in the UK suggests that early diagnosis and better management of HF, including a more appropriate use of diuretics, are associated with a lower risk of COPD exacerbation (Figure 3).¹²³

There are other potential mechanisms of benefit with loop diuretics: air hunger (the sensation of inadequate inspiration, reduced by taking deep breaths) is a common feature of respiratory disease, most likely due to stimulation of stretch receptors (slowly adapting pulmonary stretch receptors) in the lung parenchyma.¹²⁴ Increased intracellular sodium concentration may increase activation of these stretch receptors,^{125,126} and furosemide (which inhibits Na⁺/K⁺/2Cl⁻ co-transporters increasing sodium concentrations in lung parenchyma) is associated with increased activity of the stretch receptors in animal models.¹²⁷ Although nebulised furosemide reduces the sensation of air hunger in healthy volunteers,¹²⁸ it has no effect on breathlessness in patients with lung disease.¹²⁹ There are no trial data on the symptomatic or prognostic effect of loop diuretics in patients with COPD.

Management of COPD in Patients with HF

Inhaled Treatments

Short- and long-acting beta-agonists improve respiratory function and symptoms for patients with COPD and are the first-line treatment for COPD.⁵⁶ Before the discovery of the benefits of RAAS and adrenergic system antagonism in the

1980s and '90s, small studies in patients with HF found that β -2 selective *agonists* increased LVEF and cardiac output.^{130,131}

However, the partial beta agonist xamoterol caused a three-fold higher mortality after 3 months of treatment in patients with HFrEF compared to placebo.¹³² The CIBIS I trial found that a beta-receptor *antagonist*, bisoprolol, was associated with improved symptoms and quality of life with a signal of improved outcomes.¹³³ As more trials demonstrated the beneficial effects of beta-blockers, enthusiasm for investigating beta-agonists for the treatment of HF evaporated. Indeed, some observational data suggests that inhaled beta-agonists are associated with an increased risk of HF hospitalisation or death in patients with HFrEF.^{13,14}

Tiotropium and ipratropium inhalers are often used in combination with long-acting beta-agonists in patients with COPD who remain breathless despite frequent use of a short-acting treatment.⁵⁶ Both tiotropium and ipratropium are associated with improved symptoms and a reduced risk of COPD exacerbation.¹³⁴ However, both are also associated with an increased risk of cardiovascular and all-cause mortality in meta-analyses,^{18,135} possibly due to pro-ischaemic or pro-arrhythmic effects (Figure 3).^{136,137}

While inhaled corticosteroids (ICS) are as effective as long-acting inhaled beta-agonists for improving symptoms and reducing the risk of exacerbation in patients with COPD,¹³⁸ there is little evidence of additional benefit on top treatment with long-acting beta-agonists or antimuscarinic inhalers.^{139,140} Guidelines recommend ICS use is reserved for patients with severe disease or frequent exacerbations,⁵⁶ yet they remain one of the most commonly prescribed inhaled therapies for patients with COPD.¹⁴¹

ICS are associated with increased risk of several conditions such as osteoporosis, cataracts, diabetes, and perhaps most relevant to patients with HF or COPD: pneumonia. Respiratory infection is a common reason for hospital admission and death amongst patients with HF.^{142,143} Use of ICS may expose the patient with COPD and HF to a higher risk of adverse outcome with little benefit.

However, the associations between inhaled therapies and adverse cardiovascular outcomes are far from certain. For example, in a meta-analysis of 23 RCTs involving >20,000 patients there was no difference in the cardiovascular adverse event rate between long-acting beta-agonist (LABA) plus long-acting muscarinic antagonists (LAMA) combinations versus LAMA alone.¹⁴⁴ Furthermore, the association between tiotropium use and increased mortality in meta-analyses was confined to those taking the soft mist inhaler only¹⁸ and was not reproduced in a large-scale RCT comparing mortality in patients randomised to soft mist or dry powder preparations.¹⁴⁵

Moreover, there are some data from RCTs suggesting that the addition of ICS to combined LAMA/LABA therapy may be associated with reduced cardiovascular mortality compared to LAMA/LABA therapy alone.^{13,14} COPD is associated with increased platelet activation,¹⁴⁶ potentially increasing the risk of thrombotic cardiovascular events. Thus, ICS may reduce the risk of ischaemic heart disease by dampening systemic inflammation (Figure 3). However, the only RCT which has addressed this specific question – the SUMMIT trial – showed no mortality benefit with the addition of ICS.¹²

Ultimately, the data regarding the safety of inhaled treatments for COPD in patients with HF are conflicting. If they offer symptomatic benefit, short- or long-acting beta agonists or muscarinic antagonists should not be withheld based on concerns regarding detrimental cardiovascular effects, most of which come from confounded observational data. However, de-prescribing inhaled therapy may be safe for some patients with COPD,^{147,148} and could be considered for some patients, particularly those with HF, if only for the sake of reducing treatment burden.

Oral Treatments and Home Oxygen

Oral steroids are a common treatment for a COPD exacerbation but rarely used as a long-term treatment. Despite historical concerns that long-term steroid treatment may increase salt and water retention, a particular problem in the context of co-existing HF, there are few data to back this up.¹⁴⁹ In fact, short course steroid treatment can induce a profound diuresis in patients with HF and severe venous congestion who are not responding to conventional diuretic therapy,¹⁵⁰ and may be associated with better outcomes amongst patients hospitalised with HF.¹⁵¹ There are no prospective trials of long-term oral steroids in patients with HF and the significant side-effect profile which may override any positive effects in patients with either COPD or HF.

Oral theophylline and mucolytics may be used in patients with severe COPD, but data on their use in patients with HF are limited. In a small study of euvoalaemic patients with HF and central sleep apnoea, a 5-day course of theophylline reduced the number of apnoeic and hypopnoeic episodes and was well tolerated.¹⁵² However, theophylline metabolism may be reduced in patients with HF,¹⁵³ potentially increasing the risks of adverse effects of the medication including arrhythmia.¹⁵⁴

Similarly, home oxygen is often prescribed to patients with end-stage COPD, and may improve outcomes for those with severe hypoxaemia.^{155–157} In the only RCT of home oxygen therapy for patients with severe HF, there was no difference in quality of life or measures of breathlessness after 6 months of treatment in patients randomised to oxygen compared to those receiving medical therapy alone.¹⁵⁸

Summary

Heart failure and COPD share common risk factors and pathophysiological mechanisms; thus, it is no surprise they frequently co-exist. A diagnosis of HF in a patient with COPD has a profound adverse effect on prognosis, but the additional diagnosis of COPD in a patient with HF seems to have little impact. Distinguishing one from the other is an enormous clinical challenge, even using “gold-standard” diagnostic tests but timely identification and treatment of the underlying disease process has a large impact on symptoms, quality of life and, in the case of HFrEF, long-term outcomes. Once a diagnosis of HFrEF has been established, early treatment with optimal medical therapy is essential. Caution is advised with beta-blockers, but the co-existence of COPD should not be a reason to withhold treatment: if there are concerns with bronchoconstriction with non-selective beta-blockers such as carvedilol switching to a cardio-selective beta-blocker such as bisoprolol may help. Bear in mind that most treatments for HFrEF, including loop diuretics, may also have favourable aspects on COPD in patients with both diagnoses. There are conflicting data regarding whether treatments for COPD are harmful to patients with HF: in selected cases, de-escalation of inhaled therapies should be considered in patients with co-existing COPD and HF. Establishing an accurate diagnosis and getting the balance of long-term treatments right are difficult but essential to improve management of both conditions.

Acknowledgments

Dr. Pellicori has received a research grant (Scotland Grant) from Heart Research UK (RG2676/18/21). The authors would like to thank Dr Michael Crooks of the Respiratory Research Group at the Hull York Medical School for his advice while drafting the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Voll-Aanerud M, Eagan TM, Wentzel-Larsen T, Gulsvik A, Bakke PS. Respiratory symptoms, COPD severity, and health related quality of life in a general population sample. *Respir Med*. 2008;102(3):399–406. doi:10.1016/j.rmed.2007.10.012
2. Currow DC, Plummer JL, Crockett A, Abernethy AP. A community population survey of prevalence and severity of dyspnea in adults. *J Pain Symptom Manage*. 2009;38(4):533–545. doi:10.1016/j.jpainsymman.2009.01.006
3. Bowden JA, To TH, Abernethy AP, Currow DC. Predictors of chronic breathlessness: a large population study. *BMC Public Health*. 2011;12:11–33.
4. Barberger-Gateau P, Chaslerie A, Dartigues JF, Commenges D, Gagnon M, Salamon R. Health measures correlates in a French elderly community population: the PAQUID study. *J Gerontol*. 1992;47(2):S88–95. doi:10.1093/geronj/47.2.S88
5. Ho SF, O'Mahony MS, Steward JA, Breay P, Buchalter M, Burr ML. Dyspnoea and quality of life in older people at home. *Age Ageing*. 2001;30(2):155–159.
6. Abramson M, Matheson M, Wharton C, Sim M, Walters EH. Prevalence of respiratory symptoms related to chronic obstructive pulmonary disease and asthma among middle aged and older adults. *Respirology*. 2002;7(4):325–331.
7. Wong CW, Tafuro J, Azam Z, et al. Misdiagnosis of heart failure: a systematic review of the literature. *J Card Fail*. 2021;27(9):925–933.
8. Vaduganathan M, Claggett BL, Jhund PS, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet*. 2020;396(10244):121–128.
9. Calzetta L, Rogliani P, Matera MG, Cazzola M, Systematic Review A. With meta-analysis of dual bronchodilation with LAMA/LABA for the treatment of stable COPD. *Chest*. 2016;149(5):1181–1196.

10. Rojas-Reyes MX, García Morales OM, Dennis RJ, Karner C. 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.* 2016;2016(6):CD008532.
11. Tricco AC, Striffler L, Veroniki AA, et al. Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis. *BMJ Open.* 2015;5:e009183. doi:10.1136/bmjopen-2015-009183
12. Vestbo J, Anderson JA, Brook RD, et al.; SUMMIT Investigators. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet.* 2016;387:1817–1822. doi:10.1016/S0140-6736(16)30069-1
13. Rabe KF, Martinez FJ, Ferguson GT, et al.; ETHOS Investigators. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med.* 2020;383(1):35–48. doi:10.1056/NEJMoa1916046
14. Lipson DA, Barnhart F, Brealey N, et al.; IMPACT Investigators. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med.* 2018;378(18):1671–1680. doi:10.1056/NEJMoa1713901
15. Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. *Pharmacol Rev.* 2012;64(3):450–504. doi:10.1124/pr.111.004580
16. Au DH, Udris EM, Fan VS, Curtis JR, McDonnell MB, Fihn SD. Risk of mortality and heart failure exacerbations associated with inhaled beta-adrenoceptor agonists among patients with known left ventricular systolic dysfunction. *Chest.* 2003;123:1964. doi:10.1378/chest.123.6.1964
17. Au DH, Udris EM, Curtis JR, McDonnell MB, Fihn SD; ACQUIP Investigators. Association between chronic heart failure and inhaled beta-2-adrenoceptor agonists. *Am Heart J.* 2004;148(5):915–922. doi:10.1016/j.ahj.2004.03.048
18. Singh S, Loke YK, Enright PL, Furberg CD. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. *BMJ.* 2011;342:d3215. doi:10.1136/bmj.d3215
19. Clark AL, Cleland JG. Causes and treatment of oedema in patients with heart failure. *Nat Rev Cardiol.* 2013;10(3):156–170. PMID: 23319101. doi:10.1038/nrcardio.2012.191
20. Ehteshami-Afshar S, Mooney L, Dewan P, et al. Clinical characteristics and outcomes of patients with heart failure with reduced ejection fraction and chronic obstructive pulmonary disease: insights from PARADIGM-HF. *J Am Heart Assoc.* 2021;10(4):e019238. doi:10.1161/JAHA.120.019238
21. Canepa M, Temporelli PL, Rossi A, et al.; GISSI-HF Investigators. Prevalence and prognostic impact of chronic obstructive pulmonary disease in patients with chronic heart failure: data from the GISSI-HF Trial. *Cardiology.* 2017;136(2):128–137. doi:10.1159/000448166
22. Canepa M, Straburzynska-Migaj E, Drozd J, et al.; ESC-HFA Heart Failure Long-Term Registry Investigators. Characteristics, treatments and 1-year prognosis of hospitalized and ambulatory heart failure patients with chronic obstructive pulmonary disease in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur J Heart Fail.* 2018;20(1):100–110. doi:10.1002/ejhf.964
23. Parissis JT, Andreoli C, Kadoglou N, et al. Differences in clinical characteristics, management and short-term outcome between acute heart failure patients chronic obstructive pulmonary disease and those without this co-morbidity. *Clin Res Cardiol.* 2014;103(9):733–741. doi:10.1007/s00392-014-0708-0
24. Mentz RJ, Fiuzat M, Wojdyla DM, et al. Clinical characteristics and outcomes of hospitalized heart failure patients with systolic dysfunction and chronic obstructive pulmonary disease: findings from OPTIMIZE-HF. *Eur J Heart Fail.* 2012;14(4):395–403. doi:10.1093/eurjhf/hfs009
25. Tavazzi L, Swedberg K, Komajda M, et al.; SHIFT Investigators. Clinical profiles and outcomes in patients with chronic heart failure and chronic obstructive pulmonary disease: an efficacy and safety analysis of SHIFT study. *Int J Cardiol.* 2013;170(2):182–188. doi:10.1016/j.ijcard.2013.10.068
26. Mentz RJ, Schmidt PH, Kwasny MJ, et al. The impact of chronic obstructive pulmonary disease in patients hospitalized for worsening heart failure with reduced ejection fraction: an analysis of the EVEREST trial. *J Card Fail.* 2012;18(7):515–523. doi:10.1016/j.cardfail.2012.04.010
27. De Blois J, Simard S, Atar D, Agewall S; Norwegian Heart Failure Registry. COPD predicts mortality in HF: the Norwegian heart failure registry. *J Card Fail.* 2010;16(3):225–229. doi:10.1016/j.cardfail.2009.12.002
28. Dewan P, Docherty KF, Bengtsson O, et al. Effects of dapagliflozin in heart failure with reduced ejection fraction and chronic obstructive pulmonary disease: an analysis of DAPA-HF. *Eur J Heart Fail.* 2021;23(4):632–643. doi:10.1002/ejhf.2083
29. Jacob J, Tost J, Miró Ò, Herrero P, Martín-Sánchez FJ, Llorens P; ICA-SEMES Research Group. Impact of chronic obstructive pulmonary disease on clinical course after an episode of acute heart failure. EAHFE-COPD study. *Int J Cardiol.* 2017;227:450–456. doi:10.1016/j.ijcard.2016.11.013
30. Cuthbert JJ, Kearsley JW, Kazmi S, et al. The impact of heart failure and chronic obstructive pulmonary disease on mortality in patients presenting with breathlessness. *Clin Res Cardiol.* 2019;108(2):185–193. doi:10.1007/s00392-018-1342-z
31. Yoshihisa A, Takiguchi M, Shimizu T, et al. Cardiovascular function and prognosis of patients with heart failure coexistent with chronic obstructive pulmonary disease. *J Cardiol.* 2014;64(4):256–264. doi:10.1016/j.jjcc.2014.02.003
32. Plesner LL, Dalsgaard M, Schou M, et al. The prognostic significance of lung function in stable heart failure outpatients. *Clin Cardiol.* 2017;40(11):1145–1151. doi:10.1002/clc.22802
33. Iversen KK, Kjaergaard J, Akkan D, et al.; ECHOS Lung Function Study Group. The prognostic importance of lung function in patients admitted with heart failure. *Eur J Heart Fail.* 2010;12(7):685–691. doi:10.1093/eurjhf/hfq050
34. Güder G, Brenner S, Störk S, Hoes A, Rutten FH. Chronic obstructive pulmonary disease in heart failure: accurate diagnosis and treatment. *Eur J Heart Fail.* 2014;16(12):1273–1282. doi:10.1002/ejhf.183
35. Light RW, George RB. Serial pulmonary function in patients with acute heart failure. *Arch Intern Med.* 1983;143(3):429–433. doi:10.1001/archinte.1983.00350030039007
36. Brenner S, Güder G, Berliner D, et al. Airway obstruction in systolic heart failure--COPD or congestion? *Int J Cardiol.* 2013;168(3):1910–1916. doi:10.1016/j.ijcard.2012.12.083
37. Kawakami R, Nakada Y, Hashimoto Y, et al. Prevalence and prognostic significance of pulmonary function test abnormalities in hospitalized patients with acute decompensated heart failure with preserved and reduced ejection fraction. *Circ J.* 2021;85(9):1426–1434. doi:10.1253/circ.CJ-20-1069

38. Rothnie KJ, Connell O, Müllerová H, et al. Myocardial infarction and ischemic stroke after exacerbations of chronic obstructive pulmonary disease. *Ann Am Thorac Soc*. 2018;15(8):935–946. doi:10.1513/AnnalsATS.201710-815OC
39. Cazzola M, Bettoncelli G, Sessa E, Cricelli C, Biscione G. Prevalence of comorbidities in patients with chronic obstructive pulmonary disease. *Respiration*. 2010;80(2):112–119. doi:10.1159/000281880
40. Curkendall SM, DeLuise C, Jones JK, et al. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. *Ann Epidemiol*. 2006;16(1):63–70. doi:10.1016/j.annepidem.2005.04.008
41. McCullough PA, Hollander JE, Nowak RM, et al.; BNP Multinational Study Investigators. Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department. *Acad Emerg Med*. 2003;10(3):198–204. doi:10.1197/aemj.10.3.198
42. Holguin F, Folch E, Redd SC, Mannino DM. Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. *Chest*. 2005;128(4):2005–2011. doi:10.1378/chest.128.4.2005
43. Divo M, Cote C, de Torres JP, et al.; BODE Collaborative Group. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012;186(2):155–161. doi:10.1164/rccm.201201-0034OC
44. Freixa X, Portillo K, Paré C, et al.; PAC-COPD Study Investigators. Echocardiographic abnormalities in patients with COPD at their first hospital admission. *Eur Respir J*. 2013;41(4):784–791. doi:10.1183/09031936.00222511
45. Rutten FH, Cramer MJ, Zuithoff NP, et al. Comparison of B-type natriuretic peptide assays for identifying heart failure in stable elderly patients with a clinical diagnosis of chronic obstructive pulmonary disease. *Eur J Heart Fail*. 2007;9(6–7):651–659. doi:10.1016/j.ejheart.2007.01.010
46. Macchia A, Rodriguez Moncalvo JJ, Kleinert M, et al. Unrecognised ventricular dysfunction in COPD. *Eur Respir J*. 2012;39(1):51–58. doi:10.1183/09031936.00044411
47. Gale CP, White JE, Hunter A, et al. Predicting mortality and hospital admission in patients with COPD: significance of NT pro-BNP, clinical and echocardiographic assessment. *J Cardiovasc Med*. 2011;12(9):613–618.
48. Watz H, Waschki B, Boehme C, Clausen M, Meyer T, Magnussen H. Extrapulmonary effects of chronic obstructive pulmonary disease on physical activity: a cross-sectional study. *Am J Respir Crit Care Med*. 2008;177(7):743–751. doi:10.1164/rccm.200707-1011OC
49. Pellicori P, McConnachie A, Carlin C, Wales A, Cleland JGF. Predicting mortality after hospitalisation for COPD using electronic health records. *Pharmacol Res*. 2022;179:106199. doi:10.1016/j.phrs.2022.106199
50. McDonagh TA, Metra M, Adamo M, et al.; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599–3726.
51. Cleland JGF, Pfeffer MA, Clark AL, et al. The struggle towards a universal definition of heart failure-how to proceed? *Eur Heart J*. 2021;42(24):2331–2343.
52. Hawkins NM, Khosla A, Virani SA, McMurray JJ, FitzGerald JM. B-type natriuretic peptides in chronic obstructive pulmonary disease: a systematic review. *BMC Pulm Med*. 2017;17(1):11.
53. Pavasini R, Tavazzi G, Biscaglia S, et al. Amino terminal pro brain natriuretic peptide predicts all-cause mortality in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis. *Chron Respir Dis*. 2017;14(2):117–126.
54. Dixon AE, Peters U. The effect of obesity on lung function. *Expert Rev Respir Med*. 2018;12(9):755–767. doi:10.1080/17476348.2018.1506331
55. Cuthbert JJ, Gopal J, Crundall-Goode A, Clark AL. Are there patients missing from community heart failure registers? An audit of clinical practice. *Eur J Prev Cardiol*. 2019;26(3):291–298.
56. National Institute of Health and Care Excellence. NICE guideline [NG115]. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. Available from: <https://www.nice.org.uk/guidance/ng115/chapter/Recommendations>. Accessed May 5, 2022.
57. Kessler R, Partridge MR, Miravittles M, et al. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. *Eur Respir J*. 2011;37(2):264–272.
58. Sepúlveda-Loyola W, Osadnik C, Phu S, Morita AA, Duque G, Probst VS. Diagnosis, prevalence, and clinical impact of sarcopenia in COPD: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle*. 2020;11(5):1164–1176.
59. Sze S, Pellicori P, Zhang J, Weston J, Clark AL. Identification of Frailty in Chronic Heart Failure. *JACC Heart Fail*. 2019;7(4):291–302.
60. Pellicori P, Shah P, Cuthbert J, et al. Prevalence, pattern and clinical relevance of ultrasound indices of congestion in outpatients with heart failure. *Eur J Heart Fail*. 2019;21(7):904–916.
61. Lleman DR, Simel DL. Does the clinical examination predict airflow limitation? *JAMA*. 1995;273:313–319.
62. Drazner MH, Hellkamp AS, Leier CV, et al. Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. *Circ Heart Fail*. 2008;1(3):170–177.
63. Zile MR, Bennett TD, St John Sutton M, et al. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation*. 2008;118(14):1433–1441.
64. Clark AL, Coats AJ. Unreliability of cardiothoracic ratio as a marker of left ventricular impairment: comparison with radionuclide ventriculography and echocardiography. *Postgrad Med J*. 2000;76(895):289–291.
65. Wallace GM, Winter JH, Winter JE, Taylor A, Taylor TW, Cameron RC. Chest X-rays in COPD screening: are they worthwhile? *Respir Med*. 2009;103(12):1862–1865.
66. Davie AP, Francis CM, Love MP, et al. Value of the electrocardiogram in identifying heart failure due to left ventricular systolic dysfunction. *BMJ*. 1996;312(7025):222.
67. Ferry OR, Huang YC, Masel PJ, et al. Diagnostic approach to chronic dyspnoea in adults. *J Thorac Dis*. 2019;11(Suppl 17):S2117–S2128.
68. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *Circulation*. 2022;145(18):e895–e1032.
69. Adrish M, Nannaka VB, Cano EJ, Bajantri B, Diaz-Fuentes G. Significance of NT-pro-BNP in acute exacerbation of COPD patients without underlying left ventricular dysfunction. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1183–1189.
70. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. *Eur Respir J*. 2017;49(3):1700214.
71. Perez-Padilla R, Wehrmeister FC, Montes de Oca M, et al.; PLATINO group. Instability in the COPD diagnosis upon repeat testing vary with the definition of COPD. *PLoS One*. 2015;10(3):e0121832.

72. Woodruff PG, Barr RG, Bleecker E, et al.; SPIROMICS Research Group. Clinical significance of symptoms in smokers with preserved pulmonary function. *N Engl J Med.* 2016;374(19):1811–1821.
73. Regan EA, Lynch DA, Curran-Everett D, et al.; Genetic Epidemiology of COPD (COPDGene) Investigators. Clinical and radiologic disease in smokers with normal spirometry. *JAMA Intern Med.* 2015;175(9):1539–1549.
74. Pellicori P, Fitchett D, Kosiborod MN, et al. Use of diuretics and outcomes in patients with type 2 diabetes: findings from the EMPA-REG OUTCOME trial. *Eur J Heart Fail.* 2021;23(7):1085–1093.
75. Radiopaedia. Hickam's dictum. Available from: <https://radiopaedia.org/articles/hickams-dictum>. Accessed May 5, 2022.
76. Hanif K, Bid HK, Konwar R. Reinventing the ACE inhibitors: some old and new implications of ACE inhibition. *Hypertens Res.* 2010;33(1):11–21.
77. Chao J, Donham P, van Rooijen N, Wood JG, Gonzalez NC. Monocyte chemoattractant protein-1 released from alveolar macrophages mediates the systemic inflammation of acute alveolar hypoxia. *Am J Respir Cell Mol Biol.* 2011;45(1):53–61.
78. Kaparianos A, Argyropoulou E. Local renin-angiotensin II systems, angiotensin-converting enzyme and its homologue ACE2: their potential role in the pathogenesis of chronic obstructive pulmonary diseases, pulmonary hypertension and acute respiratory distress syndrome. *Curr Med Chem.* 2011;18(23):3506–3515.
79. Marshall RP, Gohlke P, Chambers RC, et al. Angiotensin II and the fibroproliferative response to acute lung injury. *Am J Physiol Lung Cell Mol Physiol.* 2004;286(1):L156–64.
80. Brown AJ, Nally JE. Hydrocortisone abolishes the angiotensin II-mediated potentiation of endothelin-1 in bovine bronchi. *Clin Sci.* 2001;100(1):19–23.
81. Wong MH, Chapin OC, Johnson MD. LPS-stimulated cytokine production in type I cells is modulated by the renin-angiotensin system. *Am J Respir Cell Mol Biol.* 2012;46(5):641–650.
82. Bullock GR, Steyaert I, Bilbe G, et al. Distribution of type-1 and type-2 angiotensin receptors in the normal human lung and in lungs from patients with chronic obstructive pulmonary disease. *Histochem Cell Biol.* 2001;115(2):117–124.
83. Shrikrishna D, Astin R, Kemp PR, Hopkinson NS. Renin-angiotensin system blockade: a novel therapeutic approach in chronic obstructive pulmonary disease. *Clin Sci.* 2012;123(8):487–498.
84. Raupach T, Lüthje L, Kögler H, et al. Local and systemic effects of angiotensin receptor blockade in an emphysema mouse model. *Pulm Pharmacol Ther.* 2011;24(2):215–220.
85. Podowski M, Calvi C, Metzger S, et al. Angiotensin receptor blockade attenuates cigarette smoke-induced lung injury and rescues lung architecture in mice. *J Clin Invest.* 2012;122(1):229–240.
86. Uhal BD, Li X, Piasecki CC, Molina-Molina M. Angiotensin signalling in pulmonary fibrosis. *Int J Biochem Cell Biol.* 2012;44(3):465–468.
87. Tejwani V, Fawzy A, Putcha N, et al.; COPDGene Investigators. Emphysema progression and lung function decline among angiotensin converting enzyme inhibitors and angiotensin-receptor blockade users in the COPDGene cohort. *Chest.* 2021;160(4):1245–1254.
88. Parikh MA, Aaron CP, Hoffman EA, et al. Angiotensin-converting inhibitors and angiotensin ii receptor blockers and longitudinal change in percent emphysema on computed tomography. the multi-ethnic study of atherosclerosis lung study. *Ann Am Thorac Soc.* 2017;14(5):649–658.
89. Di Marco F, Guazzi M, Vicenzi M, et al. Effect of enalapril on exercise cardiopulmonary performance in chronic obstructive pulmonary disease: a pilot study. *Pulm Pharmacol Ther.* 2010;23(3):159–164.
90. Kanazawa H, Hirata K, Yoshikawa J. Effects of captopril administration on pulmonary haemodynamics and tissue oxygenation during exercise in ACE gene subtypes in patients with COPD: a preliminary study. *Thorax.* 2003;58(7):629–631.
91. Oliver RM, Peacock AJ, Fleming JS, Waller DG. Renal and pulmonary effects of angiotensin converting enzyme inhibition in chronic hypoxic lung disease. *Thorax.* 1989;44(6):513–515.
92. Andreas S, Herrmann-Lingen C, Raupach T, et al. Angiotensin II blockers in obstructive pulmonary disease: a randomised controlled trial. *Eur Respir J.* 2006;27(5):972–979.
93. Curtis KJ, Meyrick VM, Mehta B, et al. Angiotensin-converting enzyme inhibition as an adjunct to pulmonary rehabilitation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2016;194(11):1349–1357.
94. Pellicori P, Cleland JGF, Clark AL. Chronic Obstructive pulmonary disease and heart failure: a breathless conspiracy. *Heart Fail Clin.* 2020;16(1):33–44.
95. Packer M, McMurray JJV. Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction. *Eur J Heart Fail.* 2021;23(6):882–894.
96. Lipworth B, Skinner D, Devereux G, Thomas V. Underuse of β -blockers in heart failure and chronic obstructive pulmonary disease. *Heart.* 2016;102(23):1909–1914.
97. Baker JG, Wilcox RG. β -Blockers, heart disease and COPD: current controversies and uncertainties. *Thorax.* 2017;72(3):271–276.
98. Loth DW, Brusselle GG, Lahousse L, Hofman A, Leufkens HG, Stricker BH. β -Adrenoceptor blockers and pulmonary function in the general population: the Rotterdam study. *Br J Clin Pharmacol.* 2014;77(1):190–200.
99. Clague HW, Ahmad D, Carruthers SG. Influence of cardioselectivity and respiratory disease on pulmonary responsiveness to beta-blockade. *Eur J Clin Pharmacol.* 1984;27(5):517–523.
100. van der Woude HJ, Zaagsma J, Postma DS, Winter TH, van Hulst M, Aalbers R. Detrimental effects of beta-blockers in COPD: a concern for nonselective beta-blockers. *Chest.* 2005;127(3):818–824. doi:10.1378/chest.127.3.818
101. Sessa M, Mascolo A, Mortensen RN, et al. Relationship between heart failure, concurrent chronic obstructive pulmonary disease and beta-blocker use: a Danish nationwide cohort study. *Eur J Heart Fail.* 2018;20(3):548–556. doi:10.1002/ejhf.1045
102. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve--an integrative interface between two supersystems: the brain and the immune system. *Pharmacol Rev.* 2000;52(4):595–638.
103. Malerba M, Montuschi P, Radaeli A, Pirisi M. Role of beta-blockers in patients with COPD: current perspective. *Drug Discov Today.* 2015;20(1):129–135. doi:10.1016/j.drudis.2014.09.005
104. Padro CJ, Sanders VM. Neuroendocrine regulation of inflammation. *Semin Immunol.* 2014;26:357–368. doi:10.1016/j.smim.2014.01.003
105. Müllerova H, Agusti A, Erqou S, Mapel DW. Cardiovascular comorbidity in COPD: systematic literature review. *Chest.* 2013;144:1163–1178. doi:10.1378/chest.12-2847

106. Short PM, Lipworth SI, Elder DH, Schembri S, Lipworth BJ. Effect of beta blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study. *BMJ*. 2011;342:d2549. doi:10.1136/bmj.d2549
107. Rutten FH, Zuithoff NP, Hak E, Grobbee DE, Hoes AW. Beta-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. *Arch Intern Med*. 2010;170(10):880–887. doi:10.1001/archinternmed.2010.112
108. Dransfield MT, Voelker H, Bhatt SP, et al.; BLOCK COPD Trial Group. Metoprolol for the prevention of acute exacerbations of COPD. *N Engl J Med*. 2019;381(24):2304–2314. doi:10.1056/NEJMoa1908142
109. Cotton S, Devereux G, Abbas H, et al. Use of the oral beta blocker bisoprolol to reduce the rate of exacerbation in people with chronic obstructive pulmonary disease (COPD): a randomised controlled trial (BICS). *Trials*. 2022;23(1):307. doi:10.1186/s13063-022-06226-8
110. Sundh J, Magnuson A, Montgomery S, Andell P, Rindler G, Fröbert O; BRONCHIOLE investigators. Beta-blockers in patients with chronic obstructive pulmonary disease (BRONCHIOLE) - Study protocol from a randomized controlled trial. *Trials*. 2020;21(1):123. doi:10.1186/s13063-019-3907-1
111. Rutten FH, Groenwold RH, Sachs AP, Grobbee DE, Hoes AW. β -Blockers and All-cause mortality in adults with episodes of acute bronchitis: an observational study. *PLoS One*. 2013;8(6):e67122. doi:10.1371/journal.pone.0067122
112. Dransfield MT, Rowe SM, Johnson JE, Bailey WC, Gerald LB. Use of beta blockers and the risk of death in hospitalised patients with acute exacerbations of COPD. *Thorax*. 2008;63(4):301–305. doi:10.1136/thx.2007.081893
113. Kotlyar E, Keogh AM, Macdonald PS, Arnold RH, McCaffrey DJ, Glanville AR. Tolerability of carvedilol in patients with heart failure and concomitant chronic obstructive pulmonary disease or asthma. *J Heart Lung Transplant*. 2002;21(12):1290–1295. doi:10.1016/S1053-2498(02)00459-X
114. Brown E, Rajeev SP, Cuthbertson DJ, Wilding JPH. A review of the mechanism of action, metabolic profile and haemodynamic effects of sodium-glucose co-transporter-2 inhibitors. *Diabetes Obes Metab*. 2019;21(Suppl 2):9–18. doi:10.1111/dom.13650
115. Mahaffey KW, Neal B, Perkovic V, et al.; CANVAS Program Collaborative Group. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS program (canagliflozin cardiovascular assessment study). *Circulation*. 2018;137(4):323–334. doi:10.1161/CIRCULATIONAHA.117.032038
116. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117–2128. doi:10.1056/NEJMoa1504720
117. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet*. 2020;396(10254):819–829. doi:10.1016/S0140-6736(20)31824-9
118. Anker SD, Butler J, Filippatos G, et al.; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385(16):1451–1461. doi:10.1056/NEJMoa2107038
119. Yin DG, Qiu M, Duan XY. Association between SGLT2i and cardiovascular and respiratory diseases: a meta-analysis of large trials. *Front Pharmacol*. 2021;12:724405. doi:10.3389/fphar.2021.724405
120. McMurray J. EMPA-REG - the “diuretic hypothesis”. *J Diabetes Complications*. 2016;30(1):3–4. doi:10.1016/j.jdiacomp.2015.10.012
121. Nassif ME, Qintar M, Windsor SL, et al. Empagliflozin effects on pulmonary artery pressure in patients with heart failure: results from the EMBRACE-HF trial. *Circulation*. 2021;143(17):1673–1686. doi:10.1161/CIRCULATIONAHA.120.052503
122. Krahnke JS, Abraham WT, Adamson PB, et al.; Champion Trial Study Group. Heart failure and respiratory hospitalizations are reduced in patients with heart failure and chronic obstructive pulmonary disease with the use of an implantable pulmonary artery pressure monitoring device. *J Card Fail*. 2015;21(3):240–249. doi:10.1016/j.cardfail.2014.12.008
123. Axson EL, Bottle A, Cowie MR, Quint JK. Relationship between heart failure and the risk of acute exacerbation of COPD. *Thorax*. 2021;76(8):807–814. doi:10.1136/thoraxjnl-2020-216390
124. Chowieniczek S, Javadzadeh S, Booth S, Farquhar M. Association of descriptors of breathlessness with diagnosis and self-reported severity of breathlessness in patients with advanced chronic obstructive pulmonary disease or cancer. *J Pain Symptom Manage*. 2016;52(2):259–264. doi:10.1016/j.jpainsymman.2016.01.014
125. Yu J, Wang YF, Zhang JW. Structure of slowly adapting pulmonary stretch receptors in the lung periphery. *J Appl Physiol*. 2003;95(1):385–393. doi:10.1152/jappphysiol.00137.2003
126. Matsumoto S, Takahashi T, Tanimoto T, Saiki C, Takeda M, Ojima K. Excitatory mechanism of veratridine on slowly adapting pulmonary stretch receptors in anesthetized rabbits. *Life Sci*. 1998;63(16):1431–1437. doi:10.1016/S0024-3205(98)00410-X
127. Sudo T, Hayashi F, Nishino T. Responses of tracheobronchial receptors to inhaled furosemide in anesthetized rats. *Am J Respir Crit Care Med*. 2000;162(3 Pt 1):971–975. doi:10.1164/ajrccm.162.3.2001001
128. Grogono JC, Butler C, Izadi H, Moosavi SH. Inhaled furosemide for relief of air hunger versus sense of breathing effort: a randomized controlled trial. *Respir Res*. 2018;19(1):181. doi:10.1186/s12931-018-0886-9
129. Hollowell RW, Schwartzstein R, O'Donnell CR, Sheridan A, Banzett RB. Controlled delivery of 80 mg aerosol furosemide does not achieve consistent dyspnea relief in patients. *Lung*. 2020;198(1):113–120. doi:10.1007/s00408-019-00292-7
130. Sharma B, Goodwin JF. Beneficial effect of salbutamol on cardiac function in severe congestive cardiomyopathy. Effect on systolic and diastolic function of the left ventricle. *Circulation*. 1978;58(3 Pt 1):449–460. doi:10.1161/01.CIR.58.3.449
131. Mifune J, Kuramoto K, Ueda K, et al. Hemodynamic effects of salbutamol, an oral long-acting beta-stimulant, in patients with congestive heart failure. *Am Heart J*. 1982;104(5 Pt 1):1011–1015. doi:10.1016/0002-8703(82)90433-1
132. The Xamoterol in Severe Heart Failure Study Group. Xamoterol in severe heart failure. *Lancet*. 1990;336(8706):1–6. doi:10.1016/0140-6736(90)91517-E
133. CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation*. 1994;90(4):1765–1773. doi:10.1161/01.CIR.90.4.1765
134. Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2014;2014(7):CD009285.
135. Dong YH, Lin HH, Shau WY, Wu YC, Chang CH, Lai MS. Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials. *Thorax*. 2013;68(1):48–56. doi:10.1136/thoraxjnl-2012-201926

136. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA*. 2008;300(12):1439–1450. doi:10.1001/jama.300.12.1439
137. Singh S, Loke YK, Enright P, Furberg CD. Pro-arrhythmic and pro-ischaemic effects of inhaled anticholinergic medications. *Thorax*. 2013;68(1):114–116. doi:10.1136/thoraxjnl-2011-201275
138. Spencer S, Evans DJ, Karner C, Cates CJ. Inhaled corticosteroids versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2011;10:CD007033.
139. Calverley P, Pauwels R, Vestbo J, et al.; TRIal of Inhaled STeroids ANd long-acting beta2 agonists study group. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet*. 2003;361(9356):449–456. doi:10.1016/S0140-6736(03)12459-2
140. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA; INSPIRE Investigators. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med*. 2008;177(1):19–26. doi:10.1164/rccm.200707-973OC
141. 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(1):92–100. doi:10.4104/pcrj.2012.00092
142. Drozd M, Garland E, Walker AMN, et al. Infection-related hospitalization in heart failure with reduced ejection fraction: a prospective observational cohort study. *Circ Heart Fail*. 2020;13(5):e006746. doi:10.1161/CIRCHEARTFAILURE.119.006746
143. Walker AMN, Drozd M, Hall M, et al. Prevalence and predictors of sepsis death in patients with chronic heart failure and reduced left ventricular ejection fraction. *J Am Heart Assoc*. 2018;7(20):e009684. doi:10.1161/JAHA.118.009684
144. Rodrigo GJ, Price D, Anzueto A, et al. LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis*. 2017;12:907–922. doi:10.2147/COPD.S130482
145. Wise RA, Anzueto A, Cotton D, et al.; TIOSPIR Investigators. Tiotropium respimat inhaler and the risk of death in COPD. *N Engl J Med*. 2013;369(16):1491–1501. doi:10.1056/NEJMoa1303342
146. Maclay JD, McAllister DA, Johnston S, et al. Increased platelet activation in patients with stable and acute exacerbation of COPD. *Thorax*. 2011;66(9):769–774. doi:10.1136/thx.2010.157529
147. Magnussen H, Disse B, Rodriguez-Roisin R, et al.; WISDOM Investigators. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *N Engl J Med*. 2014;371(14):1285–1294. doi:10.1056/NEJMoa1407154
148. Chapman KR, Hurst JR, Frent SM, et al. Long-term triple therapy de-escalation to indacaterol/glycopyrronium in patients with chronic obstructive pulmonary disease (SUNSET): a randomized, double-blind, triple-dummy clinical trial. *Am J Respir Crit Care Med*. 2018;198(3):329–339. doi:10.1164/rccm.201803-0405OC
149. Massari F, Mastropasqua F, Iacoviello M, Nuzzolese V, Torres D, Parrinello G. The glucocorticoid in acute decompensated heart failure: Dr Jekyll or Mr Hyde? *Am J Emerg Med*. 2012;30(3):517.e5–10. doi:10.1016/j.ajem.2011.01.023
150. Liu C, Liu G, Zhou C, Ji Z, Zhen Y, Liu K. Potent diuretic effects of prednisone in heart failure patients with refractory diuretic resistance. *Can J Cardiol*. 2007;23(11):865–868. doi:10.1016/S0828-282X(07)70840-1
151. Miró Ò, Takagi K, Davison BA, et al. Effect of systemic corticosteroid therapy for acute heart failure patients with elevated C-reactive protein. *ESC Heart Fail*. 2022;9(4):2225–2232. PMID: 35393762. doi:10.1002/ehf2.13926
152. Javaheiri S, Parker TJ, Wexler L, Liming JD, Lindower P, Roselle GA. Effect of theophylline on sleep-disordered breathing in heart failure. *N Engl J Med*. 1996;335(8):562–567. doi:10.1056/NEJM199608223350805
153. Kurata Y, Muraki S, Hirota T, Araki H, Ieiri I. Reduced theophylline clearance due to hepatic congestion secondary to right heart failure - A population pharmacokinetic study. *Drug Metab Pharmacokinet*. 2021;41:100403. doi:10.1016/j.dmpk.2021.100403
154. Bittar G, Friedman HS. The arrhythmogenicity of theophylline: a multivariate analysis of clinical determinants. *Chest*. 1991;99(6):1415–1420. doi:10.1378/chest.99.6.1415
155. Cranston JM, Crockett AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2005;2005(4):CD001744.
156. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med*. 1980;93(3):391–398. doi:10.7326/0003-4819-93-3-391
157. Report of the Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet*. 1981;1(8222):681–686.
158. Clark AL, Johnson M, Fairhurst C, et al. Does home oxygen therapy (HOT) in addition to standard care reduce disease severity and improve symptoms in people with chronic heart failure? A randomised trial of home oxygen therapy for patients with chronic heart failure. *Health Technol Assess*. 2015;19(75):1–120.

Publish your work in this journal

The International Journal of General Medicine is an international, peer-reviewed open-access journal that focuses on general and internal medicine, pathogenesis, epidemiology, diagnosis, monitoring and treatment protocols. The journal is characterized by the rapid reporting of reviews, original research and clinical studies across all disease areas. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-general-medicine-journal>