Current Heart Failure Reports (2024) 21:163–173
https://doi.org/10.1007/s11897-024-00660-2

Chronic Obstructive Pulmonary Disease in Heart Failure: Challenges in Diagnosis and Treatment for HFpEF and HFrEF

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Accepted: 20 March 2024 / Published online: 28 March 2024

Abstract

Purpose of Review Chronic obstructive pulmonary disease (COPD) is common in heart failure (HF), and it has a significant impact on the prognosis and quality of life of patients. Additionally, COPD is independently associated with lower adherence to first-line HF therapies. In this review, we outline the challenges of identifying and managing HF with preserved (HFpEF) and reduced (HFrEF) ejection fraction with coexisting COPD.

Recent Findings Spirometry is necessary for COPD diagnosis and prognosis but is underused in HF. Therefore, misdiagnosis is a concern. Also, disease-modifying drugs for HF and COPD are usually safe but underprescribed when HF and COPD coexist.

Summary Patients with HF-COPD are poorly enrolled in clinical trials. Guidelines recommend that HF treatment should be offered regardless of COPD presence, but modern registries show that undertreatment persists. Treatment gaps could be attenuated by ensuring an accurate and earlier COPD diagnosis in patients with HF, clarifying the concerns related to pharmacotherapy safety, and increasing the use of non-pharmacologic treatments. Acknowledging the uncertainties, this review aims to provide key clinical resources to support better physician-patient co-decision-making and improve collaboration between health professionals.

Keywords Ventricular dysfunction · Obstructive deficit · Lung disease · Betablockers · Bronchodilators · Rehabilitation

Abbreviations

COPD	Chronic obstructive pulmonary disease
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with preserved ejection fraction
QoL	Quality of life
HF-COPD	Coexistence of HF and COPD
FEV_1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ATS	American Thoracic Society
ERS	European Respiratory Society
KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire—Total Symptom Score
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire—Clinical Symptom Score
DLCO	Diffusing capacity of lung for carbon monoxide
TLC	Total lung capacity
FOT	The forced oscillation technique
ACE	Angiotensin converting enzyme
ARB	Angiotensin receptor blocker
ARNi	Angiotensin receptor/neprilysin inhibitor
MRA	Mineralocorticoid receptor antagonists
LABA	Long acting beta-agonists
LAMA	Long acting muscarinic antagonists

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most prevalent comorbidities among patients with HF, especially in HF with preserved ejection fraction (HFpEF) [1]. Moreover, in patients where HF and COPD coexist, the prevalence of diabetes, hyperlipidemia, chronic kidney disease, and atherosclerosis is greater than in patients with HF alone [2]. Coexisting COPD and HF may manifest after long exposure to shared risk factors (smoking, air pollution, inflammation). Poor lung function not reaching the threshold of clinical lung disease is associated with an increased risk of incident HF, independently of other risk factors [3]. In addition, early identification of lung dysfunction is challenging in patients at risk for HF or with pre-HF. Although such finding may represent an opportunity for early intervention, the best approach for an early diagnosis for lung dysfunction in patients with pre-HF and effective preventive or therapeutic strategies are yet to be defined [4, 5].

Considering the clinical aspects of patients with HF and COPD, the clinician is challenged to understand their overlapping symptoms, assess the implications of HF for interpreting lung function assessments, and be aware of the best available evidenced-based treatment for both diseases. The diagnosis of COPD in the setting of HF is especially difficult considering that dyspnea and exercise impairment are the cornerstone complaints for the diagnosis of both diseases. In addition, spirometry is essential to diagnose COPD [6••, 7], but might be influenced by anatomic and functional HF alterations.

This review aims to (1) describe the dual burden of COPD and HF, (2) highlight the potential sources of misdiagnosis where HF and COPD overlap, and (3) provide information to improve the prescription of the best available pharmacologic and non-pharmacologic therapies.

Epidemiology: The Heart Failure Patient With Chronic Obstructive Pulmonary Disease

Signs and symptoms of HF, such as dyspnea, fatigue, exercise intolerance, edema, and pulmonary crackles, are manifestations of a structural and/or functional cardiac abnormality, which reduces cardiac output and/or elevates intracardiac pressures [4, 5]. Although sensitive (> 80%), these signs/symptoms lack specificity (< 35%) to diagnose HF [8]. COPD can mimic HF or can exacerbate underlying HF. This is particularly worrisome for HFpEF, where echocardiographic alterations are more subtle compared to HFrEF and N-terminal pro B-type natriuretic peptide (NT-proBNP) concentrations might not distinguish between HF and COPD [9•]. Therefore, other tools are needed to correctly diagnose isolated or combined HF and COPD, especially when the left ventricular ejection fraction is > 50%.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as "*a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction*" [6••]. Airway obstruction (forced expired volume in 1 s and forced vital capacity ratio (FEV_1/FVC) < 0.7 post-bronchodilator) is needed for diagnosis. Alternatively, the American Thoracic Society and the European Respiratory Society (ATS/ERS) considers the 5th percentile of the lower limit of predicted FEV_1/FVC rather than fixed cutoffs, to account for aging [7] (Table 1).

The prevalence of HF among COPD patients and COPD among HF patients varies substantially. The reported prevalence of HF among COPD patients ranges from 7 to 21% and is higher when structured and adjudicated HF criteria are used [1, 10]. Similarly, the prevalence of COPD in HF registries ranges from 10 to 40% and is higher when GOLD criteria for COPD diagnosis are used [10–12]. In HFpEF, the COPD prevalence ranges from 6 to 38% and is higher than in HF with reduced ejection fraction (HFrEF) in most cohorts enrolling both HF phenotypes [13]. In HF trials, COPD prevalence is lower than in registries, ranging from 9 to 15%, and is often similar between HFrEF and HFpEF [9•, 11, 14•, 15•].

These significant differences in COPD across cohorts and between registries and trials may be attributed to misdiagnosis of HF decompensation as COPD exacerbation (or vice versa), specialty bias (cardiologist or pneumologist), obstructive deficit criterion used (ATS/ERS or GOLD), spirometry performed with volume overload (enhancing obstructive airway deficit), self-reported only COPD, and exclusion of COPD in HF trials. Awareness of these sources of variation can be critical to interpreting clinical findings and avoiding potential COPD misdiagnosis in HF care.

Clinical Impact COPD in Patients With HF

Clinical Characteristics

Patients with HF and COPD have an increased burden of risk factors, comorbidities, and poorer health indicators than patients with HFrEF or HFpEF alone. In OPTIMIZE-HF, among 20,118 patients with HF (median age 73 years and > 60% males), 25% had COPD. Importantly, patients with both HF and COPD were more likely to be smokers

Table 1 Key parameters for interpreting lung function tests in patients with heart failure (HF) and chronic obstructive pulmonary disease (COPD)

	COPD	*Heart failure*	*Heart failure + COPD*
Spirometry	Obstructive deficit: • $FEV_1/FVC < 0.7$ [6••] or < 5th percentile [7] • Severity dependent decrease in FEV_1 greater than FVC decrease	• Chronic HF: FVC decrease (congestion, space occupying cardiomegaly, vascular pruning and remodeling, ventilatory muscle weakness) [21] • Acute HF: FEV_1 variable non-linear decrease (airway and alveolar edema, vascular congestion). Reduction FEV_1 attenuates after clinical compensation [59] No particular HFrEF or HFrEF distinction	• Additional decrease in FVC [21] • Greater decrease in FEV_1, particularly in acute HF, can be misdiagnosed as COPD exacerbation • In HFpEF, acute COPD exacerbation and HF decompensation can be clinically difficult to distinguish, so other tests and reassessment can be necessary • It is recommended that patients with HF should be compensated, stable and euvolemic for 3 to 4 months to perform spirometry to avoid misclassification
Lung volumes	• Normal or increased total lung capacity (hyperinflation) [38••] • Increased residual volume (air trapping)	• Decreased total lung capacity (similar mechanisms of lower FVC) [38••] • Normal or small increase in residual volume • At least mild restrictive deficit is frequent [33]	• Obstructive and restrictive deficit (combined) can be found [33] • Air trapping is not influenced by pulmonary congestion, so may be necessary to determine true COPD [34] • No particular HFrEF or HFrEF distinction
Forced oscillation technique [35]	• High resistance [36, 37] • High compliance • Pros: no forced maneuvers necessary, sampling in tidal volume, 2 min execution • Cons: no clear references, may have complex interpretation	• Slightly increased or normal resistance [37] • Low compliance • Very limited data available • Unavailable data for HFpEF. Needs further research	• Potential overlapping patterns • Needs further research, particularly at bedside evaluation, to discriminate dyspnea driver • Unavailable data for HFpEF. Needs further research
Lung diffusion capacity for carbon monoxide	• Reduced [38••]	• HFrEF: reduced [38••] • HFpEF: reduced (resting and exercise) [23]	• Sum effect of impairing gas exchange from both alveoli and circulatory components • Disproportional reduction to the degree of obstruction on COPD may suggest underlying HF [38••] • No particular HFrEF or HFrEF distinction
Cardiopulmonary exercise testing [38••]	• Reduced ventilatory reserve • Reduced ventilatory efficiency (high ventilation per unit of CO_2 produced or O_2 consumed) • Early hypoxemia with low workloads	• Low ventilatory threshold (early use of other ATP resynthesis sources) • Early heart rate increase • Decreased O_2 uptake per heart beat (low systolic volume) and/or early and steady-sustained curve throughout exercise • Blunted blood pressure increase and circulatory power [41] • In HFpEF, invasive monitoring shows increased or normal intracardiac pressure with significant increase early after exertion [23]	• Additional limitation to achieve peak VO_2 [41], with even lower %predicted VO_2 at peak than individual COPD and HF • Lower relationship between the change in O_2 uptake and change in work rate [40] • Earlier and greater decrease in pulse oximetry saturation • Additional reduction in ventilatory efficiency indices • Increased excess of ventilation [39] • Lower end tidal CO_2 pressure No particular HFrEF or HFrEF distinction

COPD, chronic obstructive pulmonary disease; *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *HFrEF*, heart failure with reduced ejection fraction; *HFpEF*, heart failure with preserved ejection fraction; *ATP*, adenosine tri-phosphate; *VO_2*, oxygen uptake

(31% versus 16%), hyperlipidemic (38% versus 33%), have peripheral vascular disease (19% versus 12%), have renal insufficiency (21% versus 18%), and several other conditions, than those without COPD [2]. Similarly, patients with HFpEF and COPD were also more frequently smokers (62% vs 35%) and more likely to have had prior coronary artery bypass graft surgery, percutaneous coronary intervention, or stroke compared to those without COPD [9•].

Symptoms and Quality of Life

Patients with HF and COPD are more symptomatic and have lower QoL than patients with isolated HF. In the DAPA-HF trial, the frequency of NYHA III/IV in HFrEF was 43% among those with COPD and 31% in those without. In DAPA-HF, HF patients with COPD had lower QoL: the median Kansas City Cardiomyopathy Questionnaire—Total Symptom Score (KCCQ-TSS) was 71 (53–85) versus 79 (60–93) points in those without COPD [15•]. Likewise, in the PARAGON-HF trial, 24% of the patients with HFpEF and COPD had NYHA III/IV versus 19% of those without COPD, and the median KCCQ-CSS was 69 (55–83) versus 76 (61–89) in those with versus without COPD, respectively [9•].

Prognosis

COPD is independently associated with an increased risk of all-cause mortality and hospitalization in both HFpEF and HFrEF [1, 15•, 16, 17]. In a UK population-based nested case–control study, COPD conferred an excess mortality risk of 31% (odds ratio [OR]: 1.31; 1.26–1.36), and excess all-cause hospitalization risk of 33% (OR 1.33; 1.26–1.39), compared to HF alone after accounting for confounders [18]. This risk appears to be greater in HFpEF than in HFrEF [19, 20]. In PARAGON-HF [9•], COPD was independently associated with an increased risk of HF hospitalization (relative risk [RR] 1.54; 1.24–1.90), CV death (RR 1.42; 1.10–1.82), and non-CV death (RR 1.67; 1.23–2.27) in patients with HFpEF.

Potential Mechanisms Associated With Poorer Outcomes

Cardiac dysfunction impacts lung function [21]. In patients with acute HF, lung function can be directly influenced by volume overload with increased interstitial fluid in lung parenchyma, in bronchi and alveoli, or vascular congestion, which can enhance airway obstruction. In chronic HFrEF, lung function is affected by vascular remodeling, decreased expansibility due to cardiomegaly and ventilatory muscle weakness [21], leading to reduced vital capacity. In HFpEF, mechanisms of lung dysfunction are less clear, but ventilatory muscle weakness [22], increased ventricular filling pressure (worsened in exercise), remodeling of the pulmonary vascular bed, and impaired diffusing capacity of lung for carbon monoxide (DLCO) are common findings [23].

Lung dysfunction impacts cardiac function. The extent of emphysema and magnitude of airflow obstruction are both associated with smaller left ventricle size, lower stroke volume, and lower cardiac output, irrespective of ejection fraction (EF) [24]. Possibly, hyperinflation impairs ventricular filling, with loss of lung parenchyma and the associated capillary beds, even in early disease stages. COPD also has been associated with LV hypertrophy even in normoxic and normotensive COPD patients [25], possibly related to systemic neurohumoral activation from intermittent hypoxia [26].

The mechanisms linking COPD to heightened risk of HF hospitalization are not entirely clear, particularly in HFpEF, given its debatable diagnosis and possibly delayed COPD confirmation [1]. COPD, especially less severe disease, may be misdiagnosed as a HF exacerbation due to overlapping signs and symptoms, including dyspnea, edema, airflow limitation, and hypoxemia [27]. However, it is also plausible that the lower cardiopulmonary reserve in patients with HF and COPD lowers the threshold for HF or respiratory decompensation, resulting in an increased likelihood of hospitalization. Therefore, clinicians must consider this complex interplay for investigation and therapeutic decision-making.

Diagnostic Investigation

Lung Function Assessment

Spirometry is a widely available assessment and necessary for COPD diagnosis, stratification, and therapy adjustments [6••, 7]. However, it remains surprisingly underused in patients with HF. While more than 80% of patients with HF and COPD undergo echocardiography, only in approximately 40% is spirometry is performed [18, 28, 29]. Patients with HF and COPD who underwent spirometry are more likely to be older men, with lower body mass index than those without COPD, and have moderate to severe airflow limitations [18]. Therefore, there is an unmet need to lower the threshold to refer patients with HF to spirometry, leading to earlier diagnosis and treatment.

Clinicians must interpret spirometry cautiously in HF (key findings are summarized in Table 1). First, obstructive deficit criteria in GOLD (fixed ratio) or in ATS/ERS (lower limit of normal) slightly differ and can be associated with different outcomes in patients with HF. In a meta-analysis of 13 observational studies of isolated COPD, airflow limitation by each individual criterion was associated with higher

mortality; however, only patients who met the GOLD criterion were more likely to exacerbate [30]. Therefore, interpretation of the criteria in patients with versus without HF might differ.

Second, spirometry may not identify the cause of an obstructive deficit. In patients with HF and COPD with acute or subacute HF decompensation, congestion can additionally reduce small airways lumen, decreasing the FEV_1/FVC ratio. Thus, HF hospitalization is a critical moment when COPD exacerbation can be misdiagnosed due to new or worsened obstructive deficits [31]. Using spirometry only, COPD misclassification ranges from 40 to 80% in patients with HF [32]. It is recommended to only perform spirometry in stable, euvolemic HF patients, even though euvolemic misjudgment and timing of assessment may still overestimate COPD diagnosis [31].

Further investigations may be necessary to appropriately diagnose and manage COPD. The measurement of volumes and capacities (body plethysmography, helium dilution, or nitrogen washout) can reveal increased air trapping (high residual volume) and lung hyperinflation (high total lung capacity), diagnostic for COPD. Hyperinflation is present in more severe COPD, whereas a decreased total lung capacity (TLC) is often found in both HFpEF and HFrEF, with at least a mild restrictive ventilatory pattern [31, 33, 34]. Because air trapping (i.e., hyperinflation) is not influenced by pulmonary congestion, even among those with fluid overload, lung volume measurement can be used to diagnose COPD when HF is present. Therefore, in addition to spirometry, lung volume measurement should be considered to increase the chance of correctly diagnosing COPD when HF is present [34].

However, equipment for volume measurement may be unavailable at bedside, or patients may be unable to perform vigorous spirometric maneuvers, particularly if dyspnea is present. Here, an interesting alternative is the forced oscillation technique (FOT). FOT estimates the mechanical characteristics of the airway tree over the tidal volume, through the resonance of acoustic waves from a mouthpiece [35, 36]. Following spirometry, FOT further inspects obstruction severity, especially for small- and mid-airway dysfunction [37]. Considering the different pathophysiology of airway obstruction in COPD (inflammatory lumen narrowing and hyperinflation) and HF (luminal and alveolar edema), FOT could potentially be useful to identify the predominant mechanism of airway obstruction. This hypothesis was tested only in one small study, which compared FOT patterns in the acute setting [37]. In patients with dyspnea, admitted for COPD exacerbation ($n=25$), acute HF ($n=24$), and 11 controls, FOT was performed in 3 reproduceable attempts (10 breaths each, 20–25 s/measurement). The respiratory system in COPD showed greater compliance (hyperinflation) and higher resistance—the hallmark of the disease—while patients with HF had lower compliance and slightly increased or normal resistance [37].

Therefore, it is plausible that the unique ability of FOT to investigate mid and small airways can add information to other lung function tests and help to discriminate between HF and COPD. It is important to note that reference values for FOT are still lacking for patients with HF and COPD. Nonetheless, considering the advantages of FOT (it requires minimal collaboration, is less dependent on the technician than spirometry is, and execution lasts less than 2 min), investigating whether FOT can differentiate between HF and COPD deserves further research.

Global Functional Assessment

Other tools can be used for the diagnosis and stratification of patients with HF and COPD. The cardiopulmonary exercise test uniquely integrates several simultaneous measures of physiological reserves. It can be used for the differential diagnosis of dyspnea, and can also quantify the main drivers of exercise limitation, and the extent to which COPD (predominantly mechanical-ventilatory constraints and hypoxemia) and HF (poorer O_2 deliver with leg discomfort, preserved mechanical reserves, and impaired stroke volume) contribute [38••, 39] (Table 1). Objective parameters of cardiac and ventilatory function performances under submaximal and maximal effort can guide treatment adjustments and rehabilitation targets and even support surgery planning or identify transplant candidates [40, 41].

Probably the most frequent non-heart/lung consequence of HF and COPD is muscle dysfunction. Sarcopenia prevalence ranges from 34 to 66% in HF [42•] and from 15 to 37% in COPD [43] and is independently associated with a higher mortality risk and lower QoL. Skeletal muscle alterations in structure and function, particularly in the diaphragm, are a leading cause of effort limitation, well described for both HF and COPD, and worsened when HF and COPD coexist [44, 45]. Inspiratory muscle weakness is prognostic in COPD [46], HFpEF [22], and HFrEF [47]. Yet, muscle dysfunction is usually underappreciated and undertreated in clinical practice, and pharmacologic interventions do not reverse muscle atrophy [44].

Therapeutic Interventions

Pharmacologic Treatment

The most important recommendation is that HF evidence-based therapy should not be withheld because of coexisting COPD [4, 5]. Vice versa, COPD evidence-based treatment should be offered independently of HF [6••].

Use of HF Medication in Patients With Versus Without COPD

There are ongoing concerns regarding interactions of HF drugs with worsening lung function and vice versa, leading to underuse of therapies for HF and COPD (most relevant issues are summarized in Table 2). In 4133 HFrEF patients from the EVEREST trial, patients with COPD were less likely to receive betablockers (71% vs 63%), angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) (85% vs 80%), or mineralocorticoid receptor antagonists (MRAs) (55% vs 43%). Interestingly, only 57% of patients with HF and COPD received any COPD medications [2]. Recent clinical trials showed that betablockers were widely prescribed in HF, but less used when COPD was also present at enrollment. Among patients with HFrEF in the DAPA-HF trial, betablockers were used by 97% of patients without COPD and 92% with COPD. Similarly, MRAs and RAAS inhibitors were less often used by patients with than those without COPD [15•]. In patients with HFrEF from the PARADIGM-HF trial, betablockers were used by 94% non-COPD ($n=6877$) and 86% by COPD patients ($n=934$), without differences in MRAs [14•]. In patients with HFpEF from the PARAGON-HF trial, betablockers were also more used in non-COPD (80%) than in COPD (75%) patients [9•]. The underuse of HF medications in patients with HF and COPD is even greater in registries [18, 48].

Betablockers

Betablockers are one of the fundamental treatments for patients with HFrEF [4]. Data on the safety of betablockers in patients with COPD is mixed. Data from HF trials comparing patients with and without COPD [9•, 14•, 15•] and from several HF registries [1, 12, 49] did not highlight any safety concerns.

Among 24,999 patients from a Danish cohort, the use of the non-selective betablocker carvedilol was associated with increased likelihood for HF hospitalization in patients with COPD when compared to cardioselective b1-antagonists (bisoprolol, metoprolol succinate, or nebivolol), after adjustment for confounders [48]. In the few randomized controlled trials available which compared betablockers, FEV_1 was lower in patients treated with carvedilol compared to b1-selective antagonists and highest with bisoprolol in patients with COPD [50]. The potential association of carvedilol with increased airway muscle tone and the competition with b2-agonists might be plausible explanations of the association of carvedilol with worsening symptoms. However, carvedilol prescription was also associated with lower use of inhaled corticosteroids or bronchodilators prescriptions in the previous Danish study. This underuse could be an explanation for the increased hospitalization risk [48].

The positive effects of cardioselective betablockers in HFrEF might outweigh the risks, even in patients with more severe COPD [12, 38••]. The BLOCK-COPD trial investigated if COPD patients treated with metoprolol had lower rates of exacerbation [51]. The trial was interrupted for futility with 532 patients of 1028 planned enrollees. However, the rates of severe and very severe COPD exacerbation were greater in the metoprolol group than placebo, suggesting possible safety concerns for using metoprolol in patients with COPD. Two other ongoing trials are currently investigating the effectiveness and safety of bisoprolol in COPD [52, 53].

The clinician treating patients with HF and COPD needs to weigh the benefits of betablockers for HF against potential harms to COPD. For patients with HFrEF, betablockers confer clear survival benefits. Therefore, ESC and AHA guidelines recommend the use of betablockers in patients with HF and COPD. However, clinicians might prefer cardioselective betablockers and avoid metoprolol. For patients with HFpEF, betablockers are not indicated.

RAAS and SGLT2 Inhibitors

RAAS inhibitors and MRAs are underprescribed in patients with HF and COPD [18]. RAAS inhibitors have been associated with a survival benefit in patients with obstructive lung disease [54]. Furthermore, the prognostic benefit of MRAs in patients with HF is consistent in patients with and without COPD [55•]. One potential explanation for underuse of RAAS inhibitors might be the greater likelihood of patients with HF and COPD to have renal failure, which may limit their use at target dose [28].

Similarly, the beneficial effects of more recent HF medications, including ARNIs and sodium-glucose cotransporter-2 inhibitors, are consistent in patients with and without COPD [9•, 14•, 15•].

COPD Medications

In patients with COPD, concurrent bronchodilator and betablocker use is a clinical concern [38••]. Data mostly from observational HFrEF registries suggest that beta-agonists are associated with increased mortality and HF hospitalization risk [12]. This might be explained by the cardiovascular effects of these medications, which include tachycardia, arrhythmias, and ischemia, but it might also be that there was residual confounding in those studies [56].

Trials using COPD dual or triple therapy showed no safety concerns [49, 57, 58]. However, patients with HF were commonly not included in these studies [49, 57, 58]. Well-designed randomized controlled trials are necessary to

Table 2 Summary of clinical concerns of first-line therapy prescription for patients with heart failure (HF) and chronic obstructive pulmonary disease (COPD) (see text for more details)

	COPD	*Heart failure*	*Heart failure + COPD*
Betablockers (bb)	- GOLD recommends no restriction - But non-selective bb (carvedilol) decreases FEV_1, may induce bronchoconstriction - Metoprolol may increase COPD exacerbation - Other selective beta1-antagonists may be safer, but are being studied	- Pilar 1st-line therapy, with mortality, hospitalization, and quality of life benefit - Low impact on lung function for selective beta1-antagonists - No clinical benefit in RCTs specifically for HFpEF and should be used only if other indications are present	- Potential benefits in general outweigh risk - Selective beta1-antagonists may be used at minimally effective dose - Gradual dose increase may be necessary - Severe COPD are more vulnerable even to a lesser degree of bb-induced bronchoconstriction - Shared decision-making is essential - Should be avoided in HFpEF given potential harm and no proportional benefit
ACEi, ARBs, ARNi, and aldosterone inhibitors	- Despite cough may be a consequence of ACEi, RAS inhibition improves outcomes in COPD - No reasons to avoid	- HFrEF: pilar 1st-line therapy, with mortality, hospitalization, and quality of life benefit - HFpEF: no clinical benefit in RCTs, potential benefit for aldosterone inhibitors	- No reasons to avoid any of them - HFrEF: spironolactone is associated with gas exchange improvement - The benefit for HFrEF is consistent regardless of COPD; however, these classes are still underprescribed - Kidney failure is more prevalent in HF-COPD patients which may limit their use
Sodium-glucose cotransporter-2 (SGLT2) inhibitors	- No direct study	- HFrEF: pilar 1st-line therapy, with mortality, hospitalization, and quality of life benefit - HFpEF: 1st-line therapy, with mortality, hospitalization, and quality of life benefit	- Benefits are consistent regardless of COPD status - No reasons do avoid
Beta-agonists	- Inhaled drugs have less systemic cardiovascular effects (tachycardia, arrhythmias, ischemia) - Delivery of prescription dose must be ensured by adequate inhaler use	- HF usually excluded from COPD trials - Pooled data: long acting beta-agonists are overall safe	- GOLD recommends use, on tolerated dosing, irrespective of HF - HF also reduces adherence to COPD medications and several confounders may mediate potential harm of beta-agonists described in registries - The risk of HF decompensation may be greater with short acting beta-agonists use; therefore, long acting beta-agonists are preferred with close monitoring - Lower doses may be effective with the combination with other bronchodilators, but trials are lacking - No consensus yet on what medications have the best net benefit to use in HF

Table 2 (continued)

	COPD	*Heart failure*	*Heart failure + COPD*
Muscarinic antagonists [38••]	- Similar safety profile to beta-agonists - Trials show overall cardiovascular safety for long acting muscarinic antagonists	- Evidence is lacking given HF is usually excluded from COPD trials	- GOLD recommends use, on tolerated dosing, irrespective of HF - Similarly, long acting antimuscarinic are preferred - No consensus yet on the best medication to use in HF - Despite potential pharmacologic harmful interactions, longitudinal studies show that this class in generally safe among the subgroup with COPD-HF coexistence
Other medications [38••]	- Inhaled corticosteroids are useful to be added if exacerbations are frequent - Xanthines are third-line therapies used for severe cases	- No direct harm for inhaled corticosteroids in HF - Xanthines may be pro-arrhythmic; however, bamifylline may have minor effects on the heart	- Addition of inhaled corticosteroids as a second or third drug to avoid exacerbations may indirectly help HF stability, but can increase the likelihood of opportunistic airway infections. So, HF should not directly guide pro or against its prescription - If a xanthine is necessary, oral bamifylline may have a safer profile

COPD, chronic obstructive pulmonary disease; *GOLD*, Global Initiative for Chronic Obstructive Lung Disease; FEV_1, forced expiratory volume in 1 s; *HFrEF*, heart failure with reduced ejection fraction; *HFpEF*, heart failure with preserved ejection fraction; *ACEi*, angiotensin-converter enzyme inhibitor; *ARBs*, angiotensin receptor blocker; *ARNi*, angiotensin receptor/neprilysin inhibitor; *RAS*, renin angiotensin system

answer which combination of COPD drugs (LABA/LAMA and corticosteroids) are safe in HF and COPD. In accordance with HF guidelines, it is suggested that COPD treatment should be prescribed to patients with COPD regardless of their HF status. Furthermore, LABA/LAMA are preferred, combined with close monitoring, particularly in initial weeks of treatment [6••, 31, 49].

Non-pharmacological Interventions

Non-pharmacologic interventions are commonly considered less controversial, yet are not often prescribed in clinical practice. Patient education strategies targeting adherence and self-monitoring should be part of HF and COPD management [4–6••]. Importantly, special attention is necessary to teach adequate inhaler use, particularly in elderly and sicker patients.

Other non-pharmacological interventions are related to the lifestyle of the patient. Smoking cessation is important, especially when considering that 28% of patients with both COPD and HF and 12% of patients with HF alone in PARADIGM-HF were current smokers [14•]. Another important point is vaccination, as PARADIGM-HF observed influenza vaccination rates of 28% in those with COPD and 20% in those without [14•]. Less than half of patients with and without COPD had a formal exercise prescription [14•]. These concerning results were similar in PARAGON-HF and DAPA-HF [9•, 15•]. Promoting smoking cessation, physical activity, structured rehabilitation programs, and flu vaccination are recommended in both COPD and HF guidelines [4–6••], yet remain an unmet need in clinical practice.

Conclusion

COPD and HF often coexist; however, diagnosing COPD in the setting of HF is challenging and clinicians should be aware of the challenges that HF poses on the diagnosis of COPD. Furthermore, patients with coexisting COPD and HF have lower QoL, receive less guideline-directed medical therapy, and have worse clinical outcome compared to patients with isolated COPD or HF. Careful consideration of pharmacological and non-pharmacological treatment is warranted in order to improve QoL and clinical outcomes.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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