Chronic obstructive pulmonary disease (COPD) is a global health issue with high social and economic costs. Concomitant chronic cardiac disorders are frequent in patients with COPD, likely owing to shared risk factors (e.g., aging, cigarette smoke, inactivity, persistent low-grade pulmonary and systemic inflammation) and add to the overall morbidity and mortality of patients with COPD. The prevalence and incidence of cardiac comorbidities are higher in patients with COPD than in matched control subjects, although estimates of prevalence vary widely. Furthermore, cardiac diseases contribute to disease severity in patients with COPD, being a common cause of hospitalization and a frequent cause of death. The differential diagnosis may be challenging, especially in older and smoking subjects complaining of unspecific symptoms, such as dyspnea and fatigue.

The therapeutic management of patients with cardiac and pulmonary comorbidities may be similarly challenging: bronchodilators may have cardiac side effects, and, vice versa, some cardiac medications should be used with caution in patients with lung disease. The aim of this review is to summarize the evidence of the relationship between COPD and the three most frequent and important cardiac comorbidities in patients with COPD: ischemic heart disease, heart failure, and atrial fibrillation. We have chosen a practical approach, first summarizing relevant epidemiological and clinical data, then discussing the diagnostic and screening procedures, and finally evaluating the impact of lung–heart comorbidities on the therapeutic management of patients with COPD and heart diseases.

Keywords: dyspnea; aging; comorbidities; metabolic syndrome; smoking

Chronic obstructive pulmonary disease (COPD) as a disease characterized by persistent and usually progressive airflow limitation, associated with typical risk factors—most notably cigarette smoke. Chronic dyspnea, cough, and sputum dominate the clinical presentation. Although spirometry (e.g., FEV₁/FVC < 0.70 or FEV₁/FVC below the lower limits of normal) is required to confirm the presence of airflow limitation and thus the diagnosis of COPD (2), many smokers have the same clinical presentation even if their spirometry is normal (3, 4).

Although the lung is usually identified as the primary target organ, smoking greatly affects other organs, such as the heart (5), suggesting that patients with COPD are at...
increased risk of cardiac diseases (6, 7). Also, reduced lung function has been independently correlated with increased risk of heart failure (HF) (8, 9), myocardial infarction (MI) (10), and atrial fibrillation (AF) (11). Undeniably, COPD and cardiac diseases share recognized risk factors, such as older age, smoking, and unhealthy lifestyle choices. However, the open question is whether COPD and cardiac disorders are linked beyond these risk factors. Altered, persistent, and low-grade systemic inflammation likely plays a role: raised inflammatory markers, such as C-reactive protein and different cytokines, have been repeatedly related to atherosclerosis and subsequent ischemic heart disease (IHD), HF, and AF (12). Such inflammatory markers are raised in many patients with COPD (13). Furthermore, exacerbation frequency in COPD relates to higher levels of inflammation and to a higher risk of MI (14). Clusters of subjects may present an altered systemic inflammatory response, probably triggered by genetic as well as environmental risk factors, and be at increased risk of developing COPD as well as cardiac diseases (6). However, the development of chronic diseases is a complex and multifactorial process that cannot be explained just by a single mechanism. Furthermore, there are no definite data to suggest that suppression of inflammation prevents COPD with or without concomitant heart diseases. Hence, the debate is ongoing.

In this review we summarize the evidence on the relationship between COPD and the three most frequent cardiac comorbidities—HF, IHD, and AF—focusing on a practical (i.e., diagnostic and therapeutic) approach. We will not discuss other cardiovascular diseases, such as hypertension, cerebrovascular diseases, peripheral artery diseases, pulmonary hypertension, or pulmonary embolism.

### Data Source

Three parallel electronic literature searches were conducted via PubMed (May 30, 2016) using the following search terms: “COPD OR Chronic Obstructive Pulmonary Disease OR Emphysema OR Chronic Bronchitis AND” (1) “Heart Failure”; (2) “Ischemic Heart Disease OR Coronary Artery Disease OR Myocardial Infarction OR Myocardial Ischemia OR Atherosclerosis OR Arteriosclerosis”; (3) “Arrhythmias OR Dysrhythmia OR Atrial Fibrillation OR Tachycardia,” restricted for English language, abstract availability, and human species. Both observational and experimental clinical trials, as well as reviews, commentaries, and perspectives published in peer-reviewed journals were considered in a first screening for relevance. This primary inspection included title and abstract review, and articles were excluded mainly for not discussing the topic of interest. Publications were deemed relevant when targeting the topic of cardiac comorbidities in a population of patients with COPD or, vice versa, when exploring the role of COPD in cardiac patients; records had to provide clear and meaningful data either on epidemiology, clinical/prognostic characteristics peculiar to these patients, and diagnostic, therapeutic, or drug safety indication. Secondary inspection included full-text review (212, 164, and 151 potentially relevant publications, respectively), curated manually for their clinical relevance. The search was not restricted to specific years, but priority was given to more recent works. Screening of the reference lists of relevant review articles completed the search.

### Cardiac Diseases in COPD: The Size of the Problem

The prevalence (Table 1) and incidence of HF, IHD, and arrhythmias, most notably AF, are higher in patients with COPD than in matched control subjects (7, 15). The relevance of cardiac diseases in patients with COPD in everyday practice is undeniable: IHD, HF, and arrhythmia are common causes of hospitalization in patients with COPD, with aggregate rates higher than hospitalization for COPD itself (27). Progressive respiratory failure accounts for approximately just one-third of the COPD-related mortality (26), whereas cardiac diseases account for about one out of every four deaths in COPD (39). Moreover, coexisting cardiac diseases and COPD have been repeatedly identified as negative prognostic factors and have been correlated with higher rates of hospitalization, mortality, and lower quality of life in the setting of HF (39, 40), IHD (41, 42), and AF as well (43).

### HF and COPD

#### Background

According to the latest definition (44), HF is a clinical syndrome with typical symptoms caused by a structural and/or functional cardiac abnormality and resulting in reduced cardiac output and/or elevated intracardiac pressures. HF is defined according to left ventricular ejection fraction (EF): HF with preserved EF (HFP EF) (i.e., EF ≥ 50%) or HF with reduced EF (HFrEF) (i.e., EF < 40%); the range of 40 to 49% represents a gray area, now termed HF midrange EF (44). This distinction is important, as disease-modifying therapies have proven to reduce morbidity and mortality only in patients with HFrEF (45).

When evaluating the clinical characteristics and therapeutic studies of patients with COPD and HF, the literature includes two different (but related) perspectives on this topic. On the one hand, there is the perspective of cardiologists, who are interested in understanding the effects of COPD in patients with HF (hence, they compare HF with COPD against HF alone). On the other, there is the perspective of pulmonologists, whose main objective is to understand the effects of HF in patients with COPD (hence, they compare COPD with HF against COPD alone). These two perspectives have one group in common—patients who have both diseases—but, importantly, their comparison group is different: HF for the cardiologists and COPD for the pulmonologists. This difference may be relevant (and probably complementary) for a proper interpretation of available evidence, especially when extrapolating study results to the general population.

#### The Size of the Problem

Prevalence estimates of HF in patients with COPD are higher than those reported in the general adult population (10–30% vs. 1–2%), with an estimated annual incidence of about 3.7% (7) and a pooled odds ratio of 2.57 (95% confidence interval [CI], 1.90–3.47; P < 0.0001) (15). Similarly, COPD is frequent and often undiagnosed (hence, untreated) among patients with HF, at rates of 13 to 39% (46, 47) (see Table E2 in the online supplement). Moreover, according to a recent metaanalysis (48), COPD is associated with higher mortality in patients with HF (hazard ratio, 1.24–1.7).
Rest, higher pulmonary artery pressures, to have significant differences. Likewise, they tend to have similar EF, worse New York Heart Association class (49). Hence, they tend to be older, males, smokers, have more associated comorbidities, and, despite having a similar EF, worse New York Heart Association class (52), with no significant differences between HFrEF and HFpEF (53).

Diagnostic challenges. The differential diagnosis of COPD in patients with HF, and vice versa, may be challenging, especially in older, dyspneic, and smoking subjects. Spirometry is required to detect airflow limitation, and thus COPD (2, 3).

Nevertheless, the correct interpretation of spirometry in patients with HF may be challenging: spirometry should be avoided in acutely decompensated patients (risk of overdiagnosis of COPD) (68). However, even in stable and euvoletic conditions, patients with HFrEF may present a 20% reduction in both FEV₁ and FVC compared with matched control subjects; fortunately, the FEV₁/FVC ratio is not affected and retains diagnostic validity (69). Body plethysmography is an important additional test in the correct identification of COPD in patients with HFrEF (70). To conclude, clinical judgement and evidence of exposure to risk factors, coupled with spirometry performed in the stable phase of disease and eventually complemented with body plethysmography, should allow the identification of COPD in the majority of patients with HF.

On the other hand, when evaluating a patient with clinical features of HF, echocardiography and ECG, complemented with natriuretic peptides (71, 72), are necessary but cannot always confirm the diagnosis. Moreover, there is no validated gold standard for HFpEF. This is a major challenge when dealing with coexisting lung disease: because the clinical presentation is fundamental in the diagnosis of HF (it is defined as a clinical syndrome), and HF and COPD share both risk factors and clinical characteristics.

Clinical Characteristics and Diagnostic Challenges

Stable patients with HF and COPD versus HF alone: the cardiologist’s view. Patients with HF with COPD (compared with HF alone) tend to be older, males, smokers, have more associated comorbidities, and, despite having a similar EF, worse New York Heart Association class (49). Likewise, they tend to have significantly worse lung function at rest, higher pulmonary artery pressures, and reduced exercise capacity compared with patients with HF alone (50, 51). COPD is significantly associated with increased cardiovascular morbidity and mortality (52), with no significant differences between HFrEF and HFpEF (53).

Stable patients with COPD and HF versus COPD alone: the pulmonologist’s view. As in the cardiologist’s view, patients with HF and COPD tend to be older, males, and have greater symptoms and more coexisting diseases, including IHD, compared with patients with COPD alone (54, 55). In a primary care setting, a history of IHD, high body mass index, laterally displaced apex beat, and elevated heart rate in stable patients with COPD are independent clinical indicators of the presence of concomitant HF (56).
presentation (56, 69), making the correct diagnosis may be difficult (73). However, within the appropriate clinical context, an EF less than 40% confirms the diagnosis of HFrEF (44, 71). In this context, we have to keep in mind that “reduced EF” is the most frequently cited criterion in the literature to diagnose HF in patients with COPD (74).

Alternatively, in the absence of EF reduction, beyond the presence of symptoms and/or signs, all the following criteria are required for the diagnosis in the nonacute setting: (1) elevated levels of natriuretic peptides (brain natriuretic peptide [BNP] > 35 pg/ml and/or N-terminal prohormone brain natriuretic peptide [NT-proBNP] > 125 pg/ml), (2) “preserved” EF (>50% for HFrEF; 40–49% for HF midrange EF), (3) objective evidence of cardiac structural-functional alteration (e.g., increased left ventricular [LV] mass index or left atrial size, or diastolic dysfunction defined by echocardiography) (44). In this regard, patients with COPD represent a peculiar population, because COPD can influence heart function, thus confounding the results of diagnostic tests. For example, a direct association between NT-proBNP and FEV1 has been observed in elderly subjects without HF (9).

Nevertheless, NT-proBNP improves the diagnostic accuracy of HF in stable COPD (e.g., receiver operating characteristic area increased from 0.70 to 0.77 [56]) (75). Echocardiography remains the cornerstone for the diagnosis of HF, but in patients with pulmonary emphysema, echocardiographic acoustic windows may be impeded by gas trapping, resulting in unsatisfactory image quality in 10 to 50% of patients (73). Cardiovascular magnetic resonance imaging may identify previously unknown left-sided chronic HF in patients with mild/moderate COPD (76), but its use in clinical practice is limited by availability and high cost.

In conclusion, when assessing an older smoker with nonspecific symptoms such as dyspnea and/or “fatigue,” a careful clinical evaluation is essential. An obstructive spirometric pattern and a reduced EF support the diagnosis of coexisting COPD and HFrEF. The diagnosis of HFrEF is more challenging, as it must rely on other data, such as echocardiography, patient history, and natriuretic peptides (77) (Figure 1).

In the acute setting, the differential diagnosis of dyspnea is similarly challenging and has been the target of different trials.

Figure 1. Schematic representation of the diagnostic flow chart in chronic obstructive pulmonary disease (COPD) and heart failure (HF). COPD and HF require a careful assessment of patient symptoms and signs (i.e., of clinical presentation) coupled with diagnostic tests. The top blue box presents the symptoms suggesting COPD, and the top red box shows those suggesting HF. As some symptoms are common in both diseases, they are presented in the center (purple) and should warrant further diagnostic assessment for both COPD and HF. The second part of the figure summarizes the minimum requirements for the diagnosis of COPD and/or HF (see text for further details). Positive history of coronary artery disease or other cardiac disorders, hypertension, and exposure to cardiotoxic drugs, increase the likelihood of HF, as well as signs of congestion and overload (e.g., rales, jugular venous dilatation). Spirometry is required to make the diagnosis in the appropriate clinical context and must show a post-bronchodilator fixed ratio of FEV1/FVC < 70%. An objective cardiac cause must be identified (see text). BNP = brain natriuretic peptide; HFrEF = heart failure with midrange ejection fraction; HFrEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; NT-proBNP = N-terminal prohormone brain natriuretic peptide.

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<td>Orthopnoea</td>
<td>Chronic cough and sputum</td>
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<td>Ankle swelling</td>
<td>Recurrent exacerbations of respiratory symptoms</td>
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<td>Paroxysmal nocturnal dyspnea</td>
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<td>Elevated jugular venous pressure</td>
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<th>Assessment of HF probability</th>
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<td>ECG (any abnormality)</td>
<td>risk factors (mostly cigarette smoking)</td>
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<td>BNP &gt;35 pg/mL and/or NT-proBNP &gt;125 pg/mL</td>
<td>Spirometry</td>
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**STATE OF THE ART**

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(78). Natriuretic peptides are helpful, because the diagnosis of concomitant AHF is unlikely with normal values (cutoffs are higher in the acute setting [i.e., BNP < 100 pg/ml or NT-proBNP < 300 pg/ml]). However, cutoff values in patients with coexisting pulmonary disease are still debated (72, 79). Similarly, the comet-tail sign on lung ultrasound indicates pulmonary edema (80). In patients with known COPD and acute respiratory symptoms, these findings should prompt further evaluation of cardiac structure and function, to diagnose or exclude coexisting HF. On the other hand, because spirometry is not indicated in the acute setting, clinicians will have to rely on patient history and clinical presentation to suspect concomitant COPD and wait to confirm the diagnosis in the stable phase (69, 81).

**Treatment Indications**

Given that HF and COPD may be confused due to the common cardinal symptom of dyspnea, caution is warranted for their therapeutic management.

**Treatment of HF in patients with COPD.** There is no evidence that HFrEF or HFP EF should be treated differently in the presence of COPD. Thus, HF should be treated according to usual guidelines (44, 45). Some potential caveats are discussed below.

Despite clear survival benefits in patients with HFrEF, β-blockers are underprescribed due to perceived concerns regarding adverse effects on pulmonary function (62, 82). Such practice goes against evidence that β-blockers in patients with COPD, especially cardioselective β1-receptor antagonists (i.e., bisoprolol, metoprolol succinate, or nebivolol), are generally safe (83, 84). It should be noted that guidelines and expert opinion favor using cardioselective β-blockers in COPD. However, the volume of evidence comparing efficacy and safety of selective versus nonselective β-blockers in patients with COPD is limited. One such trial was conducted in a small cohort of patients with COPD with HF and showed that, although NT-proBNP levels were lower with carvedilol than with metoprolol or bisoprolol, FEV1 was lowest with carvedilol and highest with bisoprolol. New York Heart Association functional class, 6-minute-walk distance, and LVEF did not change, and switching between a β1-selective to a nonselective β-blocker was well tolerated (85). A larger retrospective analysis from an HF registry showed that β-blocker selectivity was not associated with a difference in outcome for patients with HF with COPD as compared with those with HF but without COPD (86). On the contrary, other data showed that β-blocker titration for HF in patients with moderate/severe COPD was better tolerated for bisoprolol than carvedilol, although the final number of subjects who achieved target doses was quite low (56% bisoprolol, 42% carvedilol) (87). Interestingly, bisoprolol appeared to reduce the incidence of HF and/or COPD exacerbations (88). All in all, the benefits of β-blocker treatment in HF, preferably with selective drugs, clearly outweigh any potential risks, even in patients with severe COPD (73, 89).

Angiotensin-converting enzyme inhibitors and mineralocorticoid receptor antagonists have proven beneficial in HFrEF and are thus recommended, with patients with COPD not being an exception (90, 91). The new compound LCZ696 sacubitril/valsartan is indicated as a replacement for an angiotensin-converting enzyme inhibitor in patients with HFrEF who remain symptomatic despite optimal medical treatment, but no specific data on COPD are available. Furthermore, ivabradine, a sinus node I1 current inhibitor, is indicated in a subset of patients with HFrEF and persistently elevated heart rate (44) to reduce mortality and hospitalization; in patients with coexisting COPD, ivabradine maintains its efficacy, compared with placebo (92). Finally, diuretics are useful to reduce congestion in all spectrums of HF, including HFrEF, HF due to right ventricular (RV) failure, and AHF. In the acute setting, noninvasive ventilation, added to conventional therapy, improves the outcome of patients with acute respiratory failure due to hypercapnic ECOPD (44).

**Treatment of COPD in patients with HF.** The cardiac safety of bronchodilators has been widely discussed. However, evidence-based specific data on HF are limited: whether these drugs specifically increase the risk of HF in patients with COPD or if patients with COPD with known HF are at increased risk of adverse events is questions still partially unanswered. For example, most clinical trials have concluded that no cardiovascular safety signals exist with long-acting β2-agonists (LABA) (93), but this may not fully apply to patients with HF, who seem to have an alteration of the β-receptor system (e.g., down-regulation of β1-receptors while maintaining unchanged levels of β2-receptors [94]) and may present a higher susceptibility to the inotropic stimulation. Accordingly, users of an LABA and tiotropium combination may be more likely to have a hospitalization or an emergency department visit for HF, especially in the first 2 to 3 weeks (odds ratio compared with nonuser of 1.42 [95% CI, 1.10–1.83] and 1.31 [95% CI, 1.08–1.60], respectively) (95). Similarly, previous observational studies have demonstrated a dose–response relationship between risk of HF hospitalization or death and use of inhaled β-agonists in patients with HFrEF (96, 97), although these studies analyzed the effects of older short-acting β-agonist compounds. In contrast, other studies have not reported an increased risk of cardiac events, including HF, with the use of LABA (98) or an independent association between use of LABA and mortality in patients with HF (99).

Similarly, the cardiac safety of inhaled antimuscarinic agents has been debated for more than a decade (17, 100). Short-acting bronchodilators, such as ipratropium, may slightly increase the risk of HF (101), whereas there seems to be no additional risk of incident HF due to tiotropium use (102, 103) or with newer long-acting antimuscarinic antagonists (LAMAs) (i.e., glycopyrronium [104], aclidinium [105], and umeclidinium [106]) or even with the LABA/LAMA combination indacaterol/glycopyrronium (107).

Likewise, the cardiac safety of the newer combination of LABA/LAMA agents does not differ significantly from the monocomponents (107, 108). Similarly, safety data from placebo-controlled trials with rolumlilast did not show cardiovascular safety signals when treating patients with COPD (109), and inhaled corticosteroids (ICS) do not seem to increase the risk of HF either (110, 111). The recently published SUMMIT (Study to Understand Mortality and Morbidity) trial, the largest survival study to date of LABA (vilanterol) and ICS (fluticasone) in patients with COPD with heightened cardiovascular risks, confirmed the cardiovascular safety of these drugs (112). However, patients with severe HFrEF (EF < 30%) were excluded, and no specific analysis on HF has been presented to date.
In conclusion, LAMA agents may be slightly preferred over β₂-agonists to treat patients with COPD with HFrEF (113). It seems reasonable to suggest close follow-up during the first weeks of treatment with bronchodilators (95), particularly in those with HFrEF, but overall there is no direct evidence that COPD should be treated differently in the presence of HF (2).

**Right Heart Failure in COPD**

When suspecting coexisting HF in COPD, the functionality of the right heart should be carefully assessed as well (114). As for the left ventricle, the key diagnostic tool is echocardiography. The “classic paradigm” indicates that chronic lung disease has a detrimental effect on RV function, causing RV hypertrophy/dilatation (115), with clinically relevant RV dysfunction occurring only in the very late stages of pulmonary disease and predicting poor prognosis (116, 117). Recently, however, this paradigm has been slightly challenged: the abnormalities of the RV structure associated with lung disease are multifaceted and may occur in stages other than severe lung disease. For example, RV hypertrophy has been documented in moderate and normoxic COPD (118). In the 2014 MESA (Multi-Ethnic Study of Atherosclerosis) study, patients with COPD displayed lower RV volumes than control subjects, with the authors concluding that smaller rather than larger RV size appeared to be the more common phenotype in COPD (120). Among hospitalized patients with moderate/severe COPD, 48% demonstrated at least one abnormality of RV structure/function, with RV enlargement being the most common (29.9%) (119). Finally, overt RV failure confers a poor prognosis in COPD (121, 122). The treatment of HF due to right ventricular failure in COPD is mostly symptomatic, with diuretics being useful in managing the effects of volume overload (44); other drugs (e.g., those used in primary pulmonary hypertension) do not seem beneficial in patients with COPD (123).

**IHD and COPD**

**Background**

IHD describes a broad spectrum of heart disorders related to atherosclerotic narrowing or occlusion of the coronary arteries typically causing myocardial ischemia and necrosis (124). There is a major difference in the clinical presentation and the pathophysiology of coronary artery disease between acute and stable syndromes. The acute syndrome occurs when an acute (usually abrupt) intraluminal obstruction leads to MI with or without ST-segment elevation (STEMI) or unstable angina (UA). The stable syndrome is typically characterized by symptoms of angina pectoris (125), due to reversible myocardial supply/demand mismatch provoked by exercise or stress (126). Finally, the term “myocardial infarction” indicates necrosis in the setting of ischemia, but not all situations are the same: spontaneous or type I MI is an event related to the rupture/ulceration of an atherosclerotic plaque. However, myocardial necrosis may occur in conditions other than complicated coronary plaque: type II MI indicates those conditions where myocardial injury and necrosis relate to supply and demand imbalance, for example during arrhythmias, anemia, respiratory failure, and hypotension (124). Such precipitants are common in patients with COPD and present diagnostic and therapeutic challenges.

As with HF, evidence on IHD and COPD can be broadly divided into two subtle but potentially important perspectives: those of cardiologists and those of pulmonologists, as discussed below.

**The Size of the Problem**

There is a strong epidemiologic link between IHD and COPD (Table 1). Although still unclear whether the presence of IHD relates to the severity of COPD (22), very high rates (i.e., 59%) of angiographically proven coronary artery disease have been reported in patients with severe COPD awaiting a lung transplant (127).

Similarly, the prevalence of COPD is remarkably high among patients with established IHD (Table E3), but, as in HF, COPD is grossly underdiagnosed (128, 129). According to recent data, airflow limitation was documented in 30.5% of patients with documented IHD, although largely undiagnosed (130). In the largest study to date among patients undergoing percutaneous coronary intervention, patients with concomitant COPD had a 30% increased risk of death and 20% higher rate of repeat revascularization at 1 year compared with patients with IHD without COPD (131).

**Clinical Characteristics and Diagnostic Challenges**

**Stable patients with IHD and COPD compared with IHD alone: the cardiologist’s view.** Overall, there are few studies analyzing the features of patients with IHD and COPD, compared with IHD alone. Patients with both disorders have poor prognostic features, such as older age, higher prevalence of previous MI, and more coronary artery vessels affected by atherosclerosis (132). Patients with IHD and airflow limitation have more respiratory symptoms and increased BMI-Obstruction-Dyspnea Index, Systematic Coronary Risk Evaluation score and Framingham risk score, compared with patients with IHD alone (130). Interestingly, along with higher cardiovascular mortality, patients with COPD with IHD are at increased risk of developing HF (133). In the general population, atypical presentation of IHD (i.e., absence of chest pain, and nonpain symptoms such as nausea, weakness, sweating, and dyspnea) is more frequent in women, individuals with diabetes, or older subjects. However, coexisting COPD is not correlated with higher rates of atypical presentation (134, 135).

**Stable patients with COPD and IHD compared with COPD alone: the pulmonologist’s view.** Once again, patients with COPD with coexisting IHD compared with control subjects are more likely to be older, male, smokers (136), and have significantly worse health status, with lower exercise capacity, more dyspnea, and longer recovery time during episodes of exacerbations (137). Cardiac deaths represent a large share of all-cause mortality in patients with COPD, with estimates ranging from 20 to 30% of total deaths (138–140).

**Acutely ill patients with IHD and COPD.** As in HF, acutely ill patients may manifest both diseases, and acute coronary events may be associated with an exacerbation of COPD (59, 141–143). Interestingly, the presence of COPD seems to hinder the recognition of MI and delay in the diagnosis: patients with COPD are more likely to receive an initial diagnosis other than definite STEMI, despite having an acute coronary event and a final diagnosis of STEMI, than subjects without COPD (41). The short- and long-term outcomes of patients with acute IHD and COPD are worse (i.e., complicated hospital
course, higher in-hospital mortality [144], higher rehospitalization rates, and reduced overall health status ([145]).

**Diagnostic challenges.** Identification of COPD in patients with known IHD requires spirometry to detect the presence of airflow limitation (2). Spirometry should be avoided in unstable cardiovascular status: 1 week after acute MI, most patients are deemed stable, but waiting 1 month may be better (146). Despite this rather simple approach, COPD is underdiagnosed and undertreated in patients with established IHD.

On the other hand, identification of MI and IHD in patients with COPD can be challenging. In the stable setting, IHD can usually be suspected from the patient’s history, risk factors, and symptoms (147). In patients with stable COPD, slightly elevated levels of troponin have been reported (148) and have been correlated with systemic inflammation and RV overload (149). Similarly, ischemic ECG changes are common in patients with stable COPD and are related to poorer clinical outcome (150). These findings should be evaluated on an individual basis: clinical risk stratification tools, noninvasive imaging (124), stress tests, and, if indicated, cardiac catheterization should be undertaken to ensure that patients with COPD receive appropriate therapy. The differential diagnosis becomes more challenging in hospitalized patients with COPD, as cardiac biomarkers and ECG changes, fundamental tools for the diagnosis of MI, are often increased (151). Thus, the everyday question is whether such findings should be interpreted as coronary related, as mismatch myocardial damage, or as nonspecific findings. According to published data, about 1 in 12 patients with severe/very severe airflow limitation meet the criteria for MI (60).

Moreover, available data clearly indicate that cardiac troponin elevation during ECOPD is an independent prognostic marker of all-cause mortality (152). These findings suggest that exacerbation episodes may be associated with a certain degree of myocardial damage, which in turn may contribute to future cardiac events (14). However, whether this damage is due to supply–demand mismatch in the acute respiratory patient or to a primary coronary event is an open question, which should be answered individually in each case.

Finally, there is controversy about whether the risk of IHD increases with COPD severity, as there is tremendous heterogeneity in cardiovascular risk across and within each GOLD spirometric grade (153). For example, previous large epidemiological studies in the general population have documented an inverse association between the severity of airflow limitation and the incidence of IHD/death from IHD (154–156). Smaller studies in subjects with COPD have demonstrated a similar correlation, with increasing severity of coronary atherosclerosis with increasing severity of airflow limitation (157).

However, other authors could not find a relationship between the prevalence of IHD and COPD severity (158). Similarly, coronary atherosclerosis and calcification are higher in patients with COPD than in those without COPD, but without significant differences among GOLD groups (159) or percent predicted FEV₁ (160). However, in COPD, as in the general population, global cardiovascular risk scores are helpful in assessing the risk of cardiac events and death in patients with COPD (147, 153).

The bottom line is that, because IHD has a relatively high prevalence in patients with COPD (and vice versa), clinicians should actively search for cardiac risk factors. As for HF, IHD and COPD may share common features (e.g., dyspnea, reduced exercise tolerance). However, there is a major difference: although HF and COPD have the same cardinal symptom (i.e., dyspnea), the chief symptom of IHD is angina/chest pain, which is not so common in COPD. This important clinical difference, coupled with well-defined diagnostic criteria and diagnostic tests, should direct the clinician toward the correct diagnosis (Figure 2).

**Treatment Indications**

**Treatment of IHD in patients with COPD.** The long-term therapeutic management of IHD includes oral antiplatelet therapy, inhibitors of the renin-angiotensin-aldosterone system, β-adrenergic blockers, and statins, as indicated by cardiology guidelines (125, 126). As in HF, there is no convincing evidence that IHD should be treated differently in patients with coexisting COPD. Single or dual antiplatelet therapy should be given according to the clinical presentation of IHD and the revascularization technique used, irrespective of the presence of COPD (161). Although statins do not reduce the risk of exacerbations in COPD (162), they are indicated in patients with IHD. Similarly, the use of β-blockers should follow cardiac indication (i.e., useful in MI with reduced LV function, but uncertain utility in stable IHD with preserved LV function) and should not be withdrawn because the patient has COPD; as stated above, β-blockers are generally safe and effective, decreasing mortality by up to 50% compared with no β-blocker therapy (83). Moreover, during hospitalization for ECOPD, β-blockers—particularly β₁-selective—in patients with IHD have proved to be safe (84, 163).

Most patients with IHD and coexisting COPD should tolerate percutaneous coronary interventions as well as patients without COPD, although COPD is associated with worse long-term outcomes after coronary interventions (164, 165). On the contrary, the presence and the severity of COPD are well-recognized negative prognostic markers in cardiac surgery (166); severe COPD, for instance, has been associated with higher early mortality after coronary artery bypass (167). Thus, coexisting COPD may discourage cardiologists and surgeons from choosing an invasive revascularization technique.

**Treatment of COPD in patients with IHD.** Although there are few data on the possible benefits of bronchodilators and other inhaled therapies directly assessed in patients with COPD and concomitant IHD, the results from previous trials suggest that LABA and LABA/ICS are safe and effective (see previous HF section) (93, 168, 169). Similarly, the rates of fatal MI, UA, and coronary revascularization were practically identical between patients treated with LABA/LAMA (indacaterol/glycopyrronium) and LABA/ICS (salmeterol/fluticasone) in the recently published FLAME (Effect of Indacaterol–Glycopyrronium vs. Fluticasone–Salmeterol on COPD Exacerbations) trial (107). The recently released SUMMIT trial was unique, as it was the first large trial to focus on cardiovascular risk (enrolled patients had a history of or were at increased risk of cardiovascular diseases, including IHD and MI). Study results demonstrated that the rates of MI and UA were not significantly different between the combination of vilanterol/fluticasone, monocomponents, and placebo, supporting the safety of these drugs in cardiovascular patients (112).
**AF and COPD**

**Background**

Atrial fibrillation (AF) is the most common supraventricular arrhythmia in the general population and in patients with COPD as well (7). It is characterized by rapid disorganized atrial activation and ineffective atrial contraction, with irregular conduction to the ventricle (170). The diagnosis is based on surface ECG (170), where normal P waves are replaced by rapid waves that vary in amplitude, shape, and timing and are associated with an irregular ventricular response (171) (Figure 3).

**The Size of the Problem**

Prevalence and incidence estimates of arrhythmic disorders in COPD are variable (Table 1) and often lack detail regarding the type of arrhythmia. However, available evidence is strongest for the association between AF and COPD, albeit atrial tachycardia, atrial flutter, ventricular tachycardia, and conduction disorders have also been cited (172, 173). The prevalence of AF in stable COPD ranges from 4.7 to 15% (174), with significantly higher rates in very severe COPD (about 20–30%) (29).

Moreover, severity of airflow limitation has been repeatedly related to increased incidence of AF (175).

Conversely, COPD prevalence estimates in patients with AF range around 10 to 15%, reaching 23.2% in patients older than 65 years (171, 176). As always, the prevalence of COPD in AF varies widely depending on the population studied (177) (Table E3).

**Clinical Characteristics and Diagnostic Challenges**

**Patients with AF and COPD compared with AF alone: the cardiologist’s view.** Evidence on both diseases is limited and focuses on the prognostic impact of coexisting COPD in patients with AF, revealing a significant association with hospital admissions and all-cause mortality (177). Concurrent COPD is a negative prognostic factor for AF progression from paroxysmal AF to persistent AF (178), immediate and long-term success of cardioversion (179), and recurrence of atrial tachyarrhythmia after catheter ablation (180).

**Patients with COPD and AF compared with COPD alone: the pulmonologist’s view.** There is no clear evidence that the clinical features of stable patients with COPD with...
AF differ from those without AF, except for the well-described negative prognostic factor of associated cardiac comorbidities (29). However, AF may present with uncontrolled ventricular rate, causing dyspnea or manifest pulmonary edema, and thus be misdiagnosed as ECOPD (Figure 4) (142). Alternatively, altered gas exchange, hypoxia and hypercapnia, and oxidative stress due to a “true” ECOPD can be proarrhythmogenic (181).

**Diagnostic challenges.** AF may be symptomatic or asymptomatic, but it is simply diagnosed by standard ECG. Likewise, the coexistence of COPD does not present a particular diagnostic challenge per se, because spirometry confirms the presence of airflow limitation. Yet, identifying coexisting AF is not trivial clinically, because AF has been repeatedly identified as a negative prognostic factor in COPD for (1) increased risk of hospitalization, with an estimated risk ratio of 2 to 2.5 (22); (2) lower quality of life and health status (182); and (3) all-cause mortality, with an estimated relative risk of 1.2 to 3 (174, 183–185).

The surface ECG is a simple and readily available tool to diagnose persistent/permanent AF. As in the general population, in patients with COPD, the diagnostic challenges are mainly related to the diagnosis of paroxysmal (i.e., episodic) AF (186). Differences in P waves and P-wave dispersion on surface ECG are related to paroxysmal AF in COPD (187) but have inadequate validation for routine clinical application. Prolonged rhythm recording is the key to identify paroxysmal AF: 24-hour Holter-ECG monitoring is usually readily available and is the most commonly prescribed test (172). However, longer recording (e.g., 72-h Holter, or implantable loop recorder) improves the detection rate of silent paroxysmal AF—although available data derive from ischemic stroke survivors (188, 189), whereas specific trials in patients with COPD are lacking. Given the high rate of AF in patients with COPD, and the higher risk of progression compared with the general population (178), studies are needed to determine the utility of periodic ECG and Holter-ECG recording in those with suspected paroxysmal AF.

In conclusion, AF may be asymptomatic (and thus overlooked) or symptomatic, including the induction of dyspnea. Given the importance of anticoagulation in reducing strokes, and simplicity of diagnosis by clinical examination and resting ECG, efforts should be directed to identification of AF. Paroxysmal forms are more challenging, and the optimal strategy for screening is yet undefined.

### Treatment Indications

**Treatment of AF in patients with COPD.** Considering the presence of COPD is included in the treatment algorithm of patients with AF, but, given the lack of strong evidence, all recommendations are level C (171, 186). The general management...
strategy for AF, including rhythm versus rate control (i.e., restoration/maintenance of sinus rhythm vs. control of the heart rate) and prevention of thromboembolism, also applies to patients with COPD. When pursuing a rhythm-control strategy, however, the presence of COPD reduces the likelihood of maintaining sinus rhythm after cardioversion (179) or catheter ablation (180).

Amiodarone is a key element of rhythm-control strategies (171), although its use is associated with pulmonary toxicity (variable incidence, from 1–10%). The pathogenesis of this side effect is incompletely understood but seems to involve direct drug toxicity and abnormal inflammatory response; different forms of pulmonary damages have been described, including interstitial pneumonitis, organizing pneumonia, acute respiratory distress syndrome, and diffuse alveolar hemorrhage (190). Pulmonary toxicity seems higher in patients with preexisting lung disease (191), and one study has reported higher incidence of pulmonary toxicity in patients with COPD (192). However, most data are quite old and inadequate to justify an absolute contraindication of such an effective drug in patients with COPD (171). Nevertheless, caution and closer clinical surveillance are advisable in patients with COPD treated with amiodarone.

For rate control treatment, nondihydropyridine calcium channel antagonists receive a class I level of evidence C recommendation for patients with COPD and AF (172). Cardioselective β-blockers may also be used for rate control and are associated with lower mortality (193, 194). However, nonselective β-blockers and other antiarrhythmic drugs, such as sotalol, propafenone, and adenosine, are generally contraindicated in patients with bronchospasm (186), especially in asthma (195, 196). Contraindications could be extended to COPD with severe airflow limitation, even though evidence is limited (91, 197).

Anticoagulation (e.g., warfarin or direct thrombin and factor Xa inhibitors) to prevent thrombotic events (198) should be evaluated in all subjects with documented AF, regardless of the coexistence of COPD, according to the individual’s risk of ischemia or bleeding (199).

**Treatment of COPD in patients with AF.** Treatment of COPD in patients with concomitant AF should be the same as those without AF. Bronchodilators have been described as potential proarrhythmic agents (200, 201), but available evidence suggests an overall acceptable safety profile for using LABA, LAMA, and ICS (202, 203). For example, tiotropium does not increase the overall risk of cardiac arrhythmias (204), whereas a slightly higher incidence of AF has been reported in patients treated with glycopyrroinum compared with placebo, despite an overall good safety profile (104). On the contrary, caution is advised when using short-acting β₂-agonists (205, 206) and theophylline, which may precipitate AF and worsen ventricular rate control (207, 208).

**Complexity of Cardiac Diseases**

Finally, we should address the topic of coexisting IHD, HF, and AF in a single patient, as each disease may be a cofactor for another (209). For example, (1) patients with IHD have a higher incidence of AF, and AF increases the risk of long-term cardiovascular events (210); (2) although hypertension and diabetes are contributing factors, approximately two-thirds of HFrEF is attributable to IHD (211); and (3) MI is a frequent cause of so-called “secondary” AF (18% of cases in the Framingham Heart Study) (212). Thus, the literature on “complex cardiac patients” is wide and ample.

In clinical practice, complex cardiovascular patients are common, with or without concomitant pulmonary disease. However, when HF, IHD, or AF are considered in the medical literature, each disease is usually analyzed separately or as a global entity under the rubric of “cardiovascular comorbidities.” Therefore, data on the relationship between the “complex cardiac patient” and COPD are scarce. Given the clinical relevance of the topic, there is a pressing need for...
high-quality data on how best to diagnose, manage, and educate these patients.

**Nonpharmacologic Treatment**

Dyspnea and “fatigue” are among the cardinal symptoms that limit the participation in activities of daily living in individuals with chronic cardiopulmonary diseases. Beyond pharmacological treatments, other interventions, such as lifestyle changes, exercise training, and rehabilitation, are feasible approaches to improve outcomes in these patients.

Patient education, including indication for a correct lifestyle, is indicated in all chronic conditions: for example, smoking cessation is of paramount importance in COPD as well as in patients with IHD, for both primary and secondary prevention (213). Similarly, a well-balanced diet, rich in vegetables and fruits, with high fiber intake and low saturated fatty acids, as well as caloric restriction (when appropriate) is beneficial for the health of the heart (213) and the lung (214). Moreover, it seems that a correct dietary style may reduce accelerated aging, thus being useful in patients with multimorbidity (215). Likewise, rehabilitation is important for patients with COPD (216, 217) and for patients with cardiac disorders as well. Pulmonary rehabilitation is an evidence-based comprehensive intervention, including exercise training as well as nutritional support and patient education, that improves clinical outcomes in COPD. Comorbidities have been differently associated with rehabilitation outcomes, with some authors claiming a reduction in treatment success and others stating the opposite (218). Severe symptoms, such as dyspnea or chest pain at rest/low work rates, recent MI (<3 wk), moderate/severe valvular diseases, or new-onset AF are usually considered contraindications to exercise training. However, in the majority of cases, pulmonary rehabilitation with exercise training is deemed beneficial (218, 219). Similarly, cardiac rehabilitation is a well-established beneficial intervention in patients with IHD (220) and chronic HF (221). Comorbidities, including COPD, are related to lower referral rates but do not negatively affect the outcomes (222, 223). For example, in a large, randomized trial, including patients with severe HFREF and concomitant COPD, adding exercise training to conventional treatment proved beneficial on the absolute change in exercise capacity and health status (53). To conclude, rehabilitation is usually beneficial in patients with chronic cardiac and pulmonary diseases and should not be denied to these subjects due to the presence of comorbidities. Although high-intensity exercise usually produces greater benefit, intensity should be tailored to patient characteristics, with low-intensity training likely more indicated in individuals with significant COPD and cardiac comorbidities (224).

**Integrated Approach**

Finally, multimorbidity is a daily challenge for physicians, with COPD, HF, IHD, and AF representing an important share of it. Given all the data presented so far, an integrated approach to the cardiopulmonary patient is warranted. How this integrated approach should be implemented is a matter of debate. Clearly, in patients hospitalized for ECOPD, it is important to screen for coexisting heart disorders and undergo appropriate diagnostic procedures, and, vice versa, COPD should not be overlooked in the hospitalized cardiac patient. Recovered from the acute phase, the chronic management of the cardiorespiratory patient is similarly, if not more, challenging. In this scenario, a joint approach between respiratory and cardiac health professionals using cardiopulmonary outpatient clinics could truly be beneficial. Such facilities should ideally integrate respiratory and cardiac medicine, including rehabilitative and educational programs. Something is already stirring in this direction (225), such as local cardiopulmonary rehabilitation clinics or breathlessness support services, which aim to improve symptoms and quality of life in individuals with comorbid disease, possibly reducing hospitalization rates. We hope that integrated approaches become widely available in the nearer future.

Cardiac disease in COPD is the paradigm of complexity. As in any organization, healthcare or otherwise, complexity must be addressed through standardization, processes and structure, transparency and accountability, monitoring and metrics, networks and communication. What does this mean in the healthcare environment? COPD needs chronic disease registries and interfaced electronic medical records and information systems; integrated and automated clinical decision support; screening programs for cardiac disease; standardized assessment and treatment of risk factors; and local, regional, national and international audit.

Until then, pulmonologists and cardiologists, along with primary care physicians, need to work closely together by using the clinical tools available to provide the best available treatment for COPD and all the cardiovascular comorbidities, as outlined in this review.

**Conclusions**

Published evidence indicates that patients with COPD are at increased risk of suffering from IHD, HF, and AF—and vice versa. This correlation has important clinical implications, as multimorbidity may represent a diagnostic and therapeutic challenge. Whether the overlap between COPD and cardiac diseases is causal (e.g., altered inflammatory response that triggers both) or simply the result of smoking and other shared risk factors is still a matter of debate; however, these are complex and multifactorial chronic diseases, and it is unlikely that one size fits all. Most likely, there are clusters of individuals who have a predisposition to develop cardiac and pulmonary diseases and are likely to have an overall poor prognosis. To date, low-grade, persistent systemic inflammatory response seems to be an important trigger for such predisposition, but subsequent clinical applications are limited (e.g., statin in COPD did not prove beneficial [162], and LABA/ICS does not modify cardiac mortality [112]). Ideally, in the near future, common etiological mechanisms will be described more clearly, and it will be possible to identify accurately which patients with COPD are at higher risk of suffering from cardiac comorbidities, which will enable tailoring of therapeutic approaches to each patient risk. Thus, both cardiologists and pulmonologists need to look beyond their specific field, as the contemporary patient is often a complex, multimorbid patient.

**Author disclosures** are available with the text of this article at www.atsjournals.org.
References


State of the Art


