

# Paradigms in chronic obstructive pulmonary disease: phenotypes, immunobiology, and therapy with a focus on vascular disease

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## ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous syndrome that represents a major global health burden. COPD phenotypes have recently emerged based on large cohort studies addressing the need to better characterize the syndrome. Though comprehensive phenotyping is still at an early stage, factors such as ethnicity and radiographic, serum, and exhaled breath biomarkers have shown promise. COPD is also an immunological disease where innate and adaptive immune responses to the environment and tobacco smoke are altered. The frequent overlap between COPD and other systemic diseases, such as cardiovascular disease, has influenced COPD therapy, and treatments for both conditions may lead to improved patient outcomes. Here, we discuss current paradigms that center on improving the definition of COPD, understanding the immunological overlap between COPD and vascular inflammation, and the treatment of COPD—with a focus on comorbid cardiovascular disease.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) represents a major global health burden that is widely recognized as a complex, heterogeneous syndrome rather than a single disease. Epidemiological data reveal three major themes: first, COPD consists of several clinical phenotypes, most of which need further refinement in definition. By understanding these COPD phenotypes, it may be possible to improve treatment. Second, COPD is often recognized as a chronic inflammatory lung disorder with important immunological mechanisms and systemic manifestations. Appreciating the immunobiology of COPD may facilitate better treatment paradigms and shed light on common mechanisms shared between COPD and cardiovascular disease. Third, COPD often exists with and may potentiate cardiovascular disease independent of tobacco smoking. How COPD treatment affects cardiovascular disease, and vice versa, is also unclear.

In this review, we aim to: (1) discuss current COPD phenotypes based on relevant epidemiological biomarker studies; (2) review COPD

immunobiology with a focus on the overlap with cardiovascular disease; and (3) discuss recent advances in COPD treatment, including treatments that can affect both COPD and cardiovascular disease.

## COPD PHENOTYPES

Decades ago, medical schools taught the concept that COPD existed as two basic clinical phenotypes: chronic bronchitis versus pulmonary emphysema. We currently understand that COPD is far more heterogeneous. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) took steps to categorize COPD with greater sophistication beginning in 2001.<sup>1</sup> GOLD has subsequently taken the established staging of COPD by spirometry, primarily forced expiratory volume in 1 s as a percent of forced vital capacity (FEV<sub>1</sub>/FVC or FEV<sub>1</sub>%), and created patient groups that include evaluation of the burden of symptoms and exacerbation frequency in a more comprehensive assessment of the impact of COPD on patient lives. These groups include patients with good lung function and minimal symptoms (GOLD A) to patients with advanced lung disease and a high degree of symptoms (GOLD D). As expected, it also includes a group of patients with COPD with advanced decline in lung function but with relatively few symptoms (GOLD C), and a group with preserved lung function but a high degree of symptoms (GOLD B). Group B and C patients were not a surprise to clinicians, and having an empiric approach to categorizing these complex phenotypes of COPD was welcome.

Large prospective clinical cohort studies have improved our understanding of the heterogeneity of COPD. We review and highlight major discoveries that have emerged from these studies with particular emphasis on phenotyping schemes, contribution of CT scans, and the relationship of COPD with comorbid conditions, including cardiovascular disease.

## Cohort studies

### COPDGene

COPDGene was originally designed to be an observational study to identify genetic factors



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associated with COPD,<sup>2</sup> but it was refined to be a prospective cohort study enrolling 4500 smoker controls between 2008 and 2011 at 21 different clinical centers: 1500 GOLD stage 1, and 4500 GOLD stages 2–4 (total 10,500 subjects). Patients who were classified as ‘smoker controls’ had an FEV<sub>1</sub>/FVC of >0.70 and a FEV<sub>1</sub> >80%, all post-bronchodilator. A small group of non-smoker controls were also included as a comparison for the quantitative CT scan data. Additionally, an interesting subcohort emerged labeled GOLD-U, which was an unclassified COPD cohort of smokers with a decrease in FEV<sub>1</sub> but a preserved FEV<sub>1</sub>/FVC ratio.<sup>2</sup> The study goals were to characterize each of these groups with respect to symptoms, medications, and spirometry; inspiratory and expiratory CT scans; exercise capacity; and genome-wide association patterns to compare within each of these cohorts. At final enrollment, two-thirds of the subjects were non-Hispanic whites while one-third were African-American. The defining contribution of COPDGene is taking existing clinical staging (GOLD) and defining novel phenotypes within these stages.

#### ECLIPSE

The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) was the first large prospective cohort designed to characterize COPD with the goal of discovering novel biomarkers.<sup>3, 4</sup> ECLIPSE enrolled patients over a 3-year period of time including 2164 patients with COPD and 582 control subjects (of whom 337 were smokers). Patients were assessed at eight different time points with the following studies: PFTs (including body plethysmography, spirometry and forced oscillometry, but not carbon monoxide diffusing capacity), biomarkers (including exhaled breath condensate (EBC)), clinical health outcomes (eg, death and disability), CT scans, body impedance, oxygen saturation, and 6 min walk distance. The advantage of the approach in ECLIPSE, as compared with the COPDGene, is that it took the basic definition of COPD and sought to define new phenotypes from that starting point over a 3-year period, for example, the ‘frequent exacerbator’.

#### MESA-LUNG

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study that was designed to study the prevalence and progression of subclinical cardiovascular disease.<sup>5</sup> The MESA cohort enrolled a total of 6814 subjects between the ages of 45 and 84 from six separate clinical sites across the USA. One of the recruitment emphases was to include a highly multiethnic cohort, and the participants included non-Hispanic whites, Hispanics, African-Americans, and Asians. MESA-LUNG is a nested study that uses the data from MESA to test a specific hypothesis: that endothelial dysfunction plays a specific role in the pathogenesis of COPD and, more specifically, emphysema.<sup>6</sup> Initially, MESA-LUNG recruited 3965 randomly sampled participants from MESA that included 24% African-Americans, 23% Hispanics, and 18% Chinese-Americans. These patients had spirometry, quantitative CT scan data, as well as a wide range of genetic and biometric data. MESA-LUNG defined cardiovascular outcomes seeking correlations with COPD within the same cohort.

#### UPLIFT and TIOSPIR

Although not technically a cohort study, the Understanding Potential Long-Term Impact on Function with Tiotropium (UPLIFT) was a large interventional trial that included 5993 subjects with moderate-to-severe COPD.<sup>7</sup> Patients worldwide were randomized to either the long-acting antimuscarinic agent tiotropium or placebo, in addition to their usual respiratory medications. The primary end point was rate of FEV<sub>1</sub> decline. Secondary end points included overall and respiratory-specific death. The addition of tiotropium conferred an improvement in FEV<sub>1</sub> decline, but, surprisingly, the rate of cardiac-specific death was also *reduced* in the tiotropium group<sup>8</sup> (HR 0.86, 95% CI 0.75 to 0.99), despite similar smoking rates of ~30%. UPLIFT identified a subgroup of patients with COPD and cardiovascular disease (occult or known) who benefited from COPD-specific therapy, though pre-existing cardiovascular disease was not among the inclusion/exclusion criteria.

A similar study, Tiotropium Safety and Performance in Respimat (TIOSPIR), randomized subjects with COPD to inhaled tiotropium in different doses and different inhaler delivery devices on top of their usual non-anticholinergic medications.<sup>9</sup> TIOSPIR included >17,000 subjects with GOLD 2–4 disease, and patients with stable cardiovascular disease were included. In addition to showing that tiotropium inhaled as a dry powder using the Handihaler or as a soft mist using the Respimat was equally effective in standard COPD outcomes, TIOSPIR found overall low rates of cardiac events (0.1–0.2% myocardial infarction (MI), 1.2–1.4% cardiac death). The authors found no evidence that one delivery device for tiotropium is safer than the other or was associated with a greater risk of major adverse cardiovascular events.

It is known that a substantial proportion of patients with COPD die from cardiovascular disease,<sup>10</sup> an ‘overlap group’, and the UPLIFT and TIOSPIR trials suggest that this group benefits from COPD treatment. It is noteworthy, however, that some studies have not supported the concept that an ‘overlap group’ may derive cardiovascular benefit from COPD treatment.<sup>11–15</sup> An early meta-analysis by Singh *et al*<sup>12</sup> suggested as much as a 52% increased risk of mortality associated with tiotropium mist inhaler use in patients with COPD, with another meta-analysis supporting a similar conclusion.<sup>13</sup> However, the weight of the evidence, including the large randomized TIOSPIR trial that featured a prespecified subgroup analysis involving patients with underlying cardiovascular disease, supports that tiotropium is safe as the overall hazard of major adverse cardiovascular events, including death, was not increased.<sup>9, 16</sup> Postmarketing surveillance focused on cardiovascular events was recommended by the authors to validate their study findings.

#### Phenotyping and biomarkers

##### Thoracic CT scanning

One common feature in each of the three population studies COPDGene, ECLIPSE, and MESA-LUNG is the incorporation of CT scans to identify novel radiography-based ‘biomarkers’. Washko *et al*<sup>17</sup> validated that CT scan-based measurements of airway wall attenuation are reproducible and correlate to the FEV<sub>1</sub>/FVC ratio. This

study suggests that airway measurements by CT could be complementary to spirometry. A related study determined that the total number of small airways inversely correlated with the percent of emphysema, and that total airway count was predictive of BODE score (the prognostication metric calculated by assessing Body mass index, degree of airflow obstruction, degree of Dyspnea, and Exercise capacity).<sup>18</sup>

Building further on the relationship between airway size, caliber, and parenchymal changes, researchers established that the distensibility of medium-sized to large-sized airways is reduced in individuals with a predominantly emphysema phenotype versus an airway inflammatory phenotype on CT.<sup>19</sup> When Martinez *et al*<sup>20</sup> assessed the correlation between radiological features of COPD, quality of life, and symptom measures, they discovered that patients with airway-limited disease had worse St George Respiratory Questionnaire (SGRQ) scores while those with more emphysema had increased (worse) BODE scores. Measures of air trapping, defined as low attenuation areas of <856 Hounsfield units, were additive to the value of airway measures alone in correlating with FEV<sub>1</sub> and FEV<sub>1</sub>/FVC ratio.<sup>21</sup> The presence of emphysema, separate from evidence of airflow limitation, was found to be associated with a lower total FEV<sub>1</sub> and worse functional status.<sup>22</sup> ECLIPSE showed a higher risk of emphysema progression in women and active smokers. A similar risk related to gender and African-American ethnicity was identified by the COPDgene group.<sup>23</sup> The biomarkers surfactant protein D (SP-D) and soluble receptor for advanced glycation endproducts were more common in the progressive emphysema cohort.<sup>24</sup> However, correlation between COPD and cardiovascular disease outcomes was not the primary purpose of these studies.

Using MRI and CT scans, the MESA-LUNG and MESA-COPD investigators were the first to report that pulmonary microvascular changes are present in patients with mild, moderate, and severe COPD (defined by reduced FEV<sub>1</sub>).<sup>25</sup> This study identified a decrease in the microvascular blood flow that was separate from the degree of emphysema present in those areas. The MESA-LUNG group also reported that CT evidence of pulmonary emphysema occurred in smokers with and without COPD, and that this emphysema was associated with symptoms if it was anatomically centrilobular or panlobular but not paraseptal.<sup>26</sup> MESA-LUNG investigators also commented on the relationship between emphysema and impaired left ventricular filling, concluding that pulmonary vein dimensions are reduced in patients with emphysema and COPD.<sup>27</sup>

#### Serum biomarkers

Chronic persistent inflammation is generally thought to be a central feature of COPD, despite very little evidence that systemic anti-inflammatory therapy improves markers of inflammation. Assessment and discovery of distinct inflammatory patterns in COPD was a goal of all of the prospective cohort studies. Interestingly, Bowler *et al*<sup>28</sup> discovered that decreased levels of interleukin (IL)-16 were associated with emphysema<sup>28</sup> and may be related to the development of autoimmunity.

The hypothesis of systemic inflammation was most comprehensively explored by the ECLIPSE investigators. They

found that inflammation is not present in all patients with COPD, but when present, it appeared to be associated with poorer outcomes.<sup>29</sup> Additionally, they found that combining biomarkers as a composite score of inflammation, including C reactive protein (CRP), fibrinogen, and white cell count, was associated with more frequent exacerbations and comorbidities.<sup>30</sup> Fibrinogen was found to be elevated in 36% of patients with COPD as compared with 5% of control patients, and this has been identified as a candidate biomarker to identify patients at higher risk of frequent exacerbations, hospitalization, or mortality.<sup>31</sup> Interestingly, fibrinogen is also known as a biomarker of cardiac disease.<sup>32</sup>

#### Breath biomarkers

Breath biomarkers are an attractive and novel way to study COPD phenotypes as they are largely non-invasive and may complement existing biomarkers of disease. Until now, there have been efforts to use breath metabolites as a diagnostic matrix from patients with developing COPD<sup>33–35</sup> and smokers at risk of COPD.<sup>36</sup> Studies of exhaled breath condensate (EBC)—the liquid formed from breath passed through a cold tube—identified lower fluid pH and higher hydrogen peroxide levels correlating with COPD.<sup>37–39</sup> Other efforts have looked at EBC conductivity in emphysema,<sup>40</sup> EBC  $\alpha$ -1-antitrypsin levels in acute COPD exacerbations,<sup>41</sup> and fractional exhalation of nitric oxide in subjects with COPD.<sup>42</sup> Although these studies show promise, differing biomarker collection techniques and analytic methods make standardization problematic, and larger scale studies and standardized procedures will surely advance the field. There are limited studies of exhaled biomarkers in patients with cardiovascular disease. Still, non-invasive and low-risk assessment tools that may add an important dimension to phenotyping COPD make breath analysis an exciting area of research.

#### COPD-associated comorbidities

Possibly as a consequence of systemic inflammation, patients with COPD are at a higher risk of developing associated diseases independent of smoking-induced airway disease. COPDgene researchers reported a relationship between COPD and cardiovascular disease. Matsuoka *et al*<sup>43</sup> showed that the cross-section of small pulmonary arteries correlates with the degree of aortic calcification. Another study reported that distal pruning of the pulmonary vasculature is a characteristic signature of smoking-related lung disease and associated with accelerated loss of lung tissue.<sup>44</sup> Researchers have established that seven common comorbid conditions are associated with COPD, including sleep apnea, stroke, coronary disease, peripheral vascular disease, osteoporosis, gastroesophageal reflux, and congestive heart failure (CHF).<sup>45–47</sup> These associations are more pronounced among African-Americans.<sup>47</sup> Additionally, cardiovascular disease was independently associated with COPD.<sup>48</sup> The prevalence of venothromboembolic disease was higher in patients with COPD and comorbid conditions, and the overlap leads to worse exercise performance.<sup>49</sup> Finally, two separate investigations reported an increased association between COPD and diabetes mellitus.<sup>50 51</sup> Similar findings were noted in the ECLIPSE cohort, where comorbid COPD and cardiovascular disease were associated with more

symptoms.<sup>31</sup> Additionally, diabetes was identified as increasing the risk of poor clinical outcomes when associated with COPD. Depression was also identified as being more prevalent in COPD.<sup>52</sup>

### COPD immunobiology with a focus on vascular disease

COPD leads to anatomic distortion of normal airway architecture, resulting in a critical reduction in airway diameter and airflow limitation.<sup>53</sup> The major mechanisms thought responsible for airflow limitation include accumulated debris and mucus in the airway lumen, chronic bronchoconstriction, airway wall thickening, and increased external airway compression from a loss of elastic tissue. However, the rate of development of airflow limitation, that is, lung function loss, varies widely between patients with COPD. Factors such as quantity and quality of toxicant exposure (eg, tobacco smoke), innate and adaptive immune responses, and genetic and epigenetic elements that regulate airway inflammation and remodeling all contribute to the clinical progression in any single person. Clearly, the interplay between immune cells, toxicant exposure, and host background is complex and may evolve over the life of the patient with COPD.

Since COPD stems from abnormal lung and systemic inflammation, and advanced COPD is associated with comorbid vascular disease, there is considerable interest in understanding the immunological links between lung and vascular inflammation. It is known that COPD and coronary arterial disease (CAD) are connected,<sup>54–56</sup> and the dominant theory is that shared risk factors (eg, smoking) elicit a chronic inflammatory response that affects both the lungs and vasculature.<sup>56–58</sup> In fact, patients with COPD with elevated levels of systemic inflammatory markers such as CRP, fibrinogen, and leukocytes have increased rates of MI and CHF based on large cohort studies.<sup>59</sup> Efforts to unravel genetic links by comparing COPD-specific single nucleotide polymorphisms to carotid thickness and CAD are underway.<sup>60</sup> While at present a clear connection is not well established, it is imperative to understand concepts of shared cellular and molecular pathways such as oxidative stress, cell death, airway structural changes and impaired tissue repair underlying both chronic vascular conditions and COPD. The following sections discuss pulmonary structural and inflammatory cells in COPD with a focus on how these may relate to vascular inflammation (figure 1).

### Immune cells, inflammation, and the lung-vascular connection

The gross insult by tobacco smoke to the respiratory tract is the result of repeated and prolonged exposure to a range of toxicants through inflammation and oxidative stress, or to individual toxicants through specific mechanisms.<sup>61</sup> In COPD, damaged epithelial cells express high levels of inflammatory mediators (chemokine (C-X-C motif) ligand (CXCL)-8, IL-1- $\beta$ , and granulocyte-macrophage colony-stimulating factor)<sup>62</sup> and adhesion molecules (soluble intercellular adhesion molecule-1<sup>62</sup> and E-selectin<sup>63</sup>). This inflammatory response facilitates a continuous recruitment and activation of inflammatory cells from the blood. In addition, damaged lung epithelial cells have an altered ability to regulate normal immune functions such as pathogen binding,<sup>64</sup> antigen presentation, and tumor necrosis

factor- $\alpha$  (TNF- $\alpha$ ) expression.<sup>65–68</sup> In addition to its proinflammatory function, the airway epithelium is also responsible for maintaining immune homeostasis and protection against chronic inflammatory changes in the lung and the pulmonary vasculature. The protective function of airway epithelial cells has been attributed to the constitutive production of lung immune modulators called collectins: SP-A and SP-D. Although we currently do not have any direct evidence of a shared mechanism, SP-D-related immune regulatory pathways can be impaired in the development of atherosclerotic plaques<sup>69</sup> and increased levels of SP-D have been observed in heart failure<sup>70</sup> and carotid artery atherosclerosis.<sup>71</sup> These data suggest that SP-D may be a biomarker or may play a putative role in coexistent lung and vascular disease.

Alveolar macrophages are the most abundant immune cell type in the lungs and airways. They function to clear inhaled particles, identify and destroy pathogens, and remove dead or dying cells in the distal air spaces. In COPD, however, the function of these cells is severely impaired<sup>72</sup> despite increased numbers of macrophages in patients with COPD.<sup>73–74</sup> In fact, macrophages, activated locally or recruited during inflammation, can account for many of the known features of COPD.<sup>74–75</sup> Macrophages isolated from the lungs of patients with COPD exhibit reduced apoptosis and increased survival compared with those found in patients with normal lungs. Though this increased survival may be anti-inflammatory in the lung, damaged lung macrophages can produce IL-6,<sup>56–76</sup> which in turn can potentiate coronary endothelial dysfunction.<sup>77</sup> Indeed, bone marrow-derived macrophages in the COPD lung differentiate into the highly proinflammatory M1 subtype and the anti-inflammatory M2 subtype; M1 macrophages have a well-accepted pathogenic role in atherosclerosis and CAD.

Normal, healthy lung parenchyma contains few if any neutrophils. In COPD, damaged epithelial cells, activated macrophages, and T cells (via CXCL-8, CXCL-1, and leukotriene B<sub>4</sub>) cause direct migration of neutrophils toward the airways. Adhesion molecules expressed on endothelial and epithelial cells mediate neutrophil migration with the MAC1/ICAM1 interactions being the most crucial, and patients with COPD who smoke have increased surface expression of MAC1 on their neutrophils.<sup>78</sup> Neutrophils play a major role in COPD exacerbations elicited by air pollution, viral, and/or bacterial infections.<sup>79–81</sup> Recruited neutrophils secrete a number of proinflammatory cytokines that elicit reactive oxygen species (ROS) formation, which further perpetuates neutrophil recruitment.<sup>82</sup> Oxidative stress also causes elevated levels of cytokine and growth factor expression responsible for activating and preventing apoptosis of neutrophils. This effect can lead to either increased survival or necrotic death of these cells. An important feature of the COPD lung is an increased number of dead neutrophils due to necrotic cell death and a reduced ability of alveolar macrophages to perform their scavenger function. As with chronically activated macrophages, chronic neutrophil activity can lead to repeated endothelial exposure to cytotoxic agents (ie, ROS such as myeloperoxidase) and likely potentiate inflammatory changes, recurrent vasoconstriction, and cholesterol dysregulation.<sup>83</sup> In particular, neutrophil-derived ROS can potentiate elastin degradation which has been associated



GOLD Group	First Choice*	Alternate Choice
<b>A</b> FEV <sub>1</sub> ≥ 50%** Low symptoms† <2 exacerbations/yr	Short-acting bronchodilators prn OR Long-acting bronchodilator (LABA or LAMA)	LAMA or LABA added
<b>B</b> FEV <sub>1</sub> ≥ 50%** High symptoms† <2 exacerbations/yr	Long-acting bronchodilator (LABA or LAMA) OR LABA + LAMA	
<b>C</b> FEV <sub>1</sub> < 50%** Low symptoms† ≥2 exacerbations/yr	LAMA OR LABA + LABA	LABA + ICS
<b>D</b> FEV <sub>1</sub> < 50%** High symptoms† ≥2 exacerbations/yr	LABA + LABA OR LABA + LABA + ICS	LAMA OR LABA + ICS OR LABA + LABA + ICS + roflumilast OR LABA + LABA + ICS + macrolides

**Figure 1** Recommended therapy for stable COPD by GOLD category. Figure adapted from the recommendations of the GOLD<sup>1</sup> (<http://www.goldcopd.org>, accessed Jan 2017). \*First choice therapy includes short-acting  $\beta$ -2-agonists or short-acting anticholinergic medications as needed for all categories. First choice therapy also includes the first entry followed by a clinical evaluation. If the patient still has symptoms, then moving to the second entry is advised. \*\*FEV<sub>1</sub> impairment is FEV<sub>1</sub> ≥ 50% predicted for GOLD categories A and B, and FEV<sub>1</sub> < 50% predicted for categories C and D. †Symptoms based on the mMRC scale: 0—SOB with strenuous exertion, 1—SOB with hurrying on level ground or inclines, 2—SOB with normal walking on level ground >100 m, 3—SOB within 100 m, and 4—SOB with daily activities; mMRC < 2 = low symptoms and mMRC ≥ 2 = high symptoms. COPD, chronic obstructive pulmonary disease; CXCL, chemokine (C-X-C motif) ligand; FEV<sub>1</sub>, forced expiratory volume in 1 s; GM-CSF, granulocyte-macrophage colony-stimulating factor; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICAM, intercellular Adhesion molecule; ICS, inhaled corticosteroid; LABA, long-acting  $\beta$ -2 agonist; LAMA, long-acting antimuscarinic; MAC, macrophage adhesion ligand; mMRC, modified Medical Research Council; SOB, shortness of breath; VCAM, vascular cell adhesion molecule.

with significant comorbid cardiac disease in patients with COPD.<sup>84</sup> Although the exact association between lung neutrophil activity and cardiovascular disease is not entirely clear, clinical evidence links circulating myeloperoxidase levels with adverse cardiac outcomes.<sup>85–87</sup>

Lymphocyte accumulation in the pulmonary interstitium and peribronchial areas correlate with the severity of the symptoms of COPD and are considered to be part of the mechanism leading to exacerbation of symptoms brought on by air pollution or infections.<sup>79</sup> Lymphocytes organized in follicular structures with B lymphocyte-containing germinal centers surrounded by CD4+ T helper 1 (Th1) cells have been observed in clinically advanced cases of chronic bronchitis, while increases in the numbers of CD8+ cytotoxic Tc1 lymphocytes in the alveolar wall appear to be proportional to the severity of emphysema.<sup>88</sup> Th1 cells are CD4+ T cells that lead to interferon- $\gamma$  secretion, and this, in turn, helps activate CD8+ cytotoxic Tc1 cells.<sup>89</sup> CD8+ T cells synthesize, store, and release cytokines and cytotoxic substances like TNF- $\alpha$ , granzyme B, and perforins, and their numbers inversely correlate with the FEV<sub>1</sub> of patients suffering from COPD.<sup>90</sup>

#### Pulmonary endothelial cells, COPD, and vascular effects

Often described as the silent player in COPD pathogenesis, the pulmonary vasculature has been increasingly recognized as a major contributor to disease. Beyond their physiological function, endothelial cells also secrete a variety of proinflammatory molecules including cytokines, chemokines,

growth factors, and lipids relevant to COPD.<sup>91</sup> Since COPD itself is a systemic inflammatory condition, both the systemic and pulmonary vasculature have enhanced expression of adhesion molecules (eg, vascular cell adhesion molecule-1) which further promote adherence of activated leukocytes to endothelial surfaces.<sup>76</sup> The pulmonary and airway vasculature also express vascular endothelial growth factor (VEGF) and various adhesion molecules important in the immune response that mediates the transmigration of neutrophils to the airways. As described above, the inflammatory milieu in COPD likely correlates with cardiovascular disease through, in part, endothelial dysfunction. However, a recent study by Chandra *et al*<sup>92</sup> challenges this notion as the authors did not find a significant correlation between endothelial dysfunction and reduced lung function (FEV<sub>1</sub>) in cohorts of patients with atherosclerotic disease. This study underscores the need to better define patients with COPD based on biological parameters other than lung function in order to truly understand the link between COPD and cardiovascular disease.

Alterations in the structure of the pulmonary vasculature in COPD contribute to the development of pulmonary arterial hypertension (PAH) which is associated with reduced survival in COPD and has a higher prevalence in more advanced disease.<sup>93</sup> The underlying dysfunction of the endothelial compartment in COPD leads to an imbalance between vasoconstrictive and vasodilatory mediators further contributing to the development of PAH. This imbalance is in part driven by cigarette smoke which also damages pulmonary endothelial cells via protease activity,

dysregulated apoptosis, and oxidative stress.<sup>94</sup> The development of alveolar destruction and emphysema is in part also due to this vasculopathy. Pulmonary capillary septal endothelial cell apoptosis and reduced local alveolar production of VEGF and its receptor VEGFR2 also contribute to the development of emphysema. Interestingly, in healthy smokers who quit smoking, pulmonary capillary apoptosis is reversible. However, in patients with COPD, this mechanism of endothelial cell apoptosis continues to be active despite smoking cessation further contributing to the development of progressive airflow obstruction.<sup>95</sup> This may explain in part the continued decline in lung function over many years in COPD despite smoking cessation.

### COPD treatment: focusing on comorbid cardiac disease

#### Current COPD therapies

Several excellent reviews of the pharmacological treatment of COPD have been written.<sup>96–98</sup> The GOLD guidelines (2017) use patient grouping (groups A–D) based on spirometry (FEV<sub>1</sub>), frequency of exacerbations, and burden symptoms as assessed by symptom scores to guide treatment considerations. In addition to smoking cessation and vaccines, GOLD treatment guidelines use a step-up approach based on groups A–D with the goals to reduce symptoms with combination bronchodilators and to reduce risks, particularly acute exacerbations with anticholinergic bronchodilators, and, if indicated, inhaled corticosteroids or roflumilast (figure 2). Table 1 summarizes the currently available combination inhalers for maintenance therapy. No current therapies have been demonstrated to change the natural course of COPD except for smoking cessation.

#### Novel and investigative COPD therapies

Several approaches to new drug therapy for COPD are ongoing. These include novel agents that are dual phosphodiesterase (PDE3 and PDE4) inhibitors and other agents that are more specific PDE4 inhibitors. Some of these can potentially be delivered by inhalation.<sup>98</sup> Novel macrolide/fluoroketolide compounds appear to have better anti-inflammatory profiles than current macrolides and may be useful in treating COPD. Agents that are antagonists of the human C-X-C chemokine receptor (CXCR)2 receptor modulating neutrophil trafficking have potential in the treatment and prevention of COPD. The p38 mitogen-activated protein kinase inhibitors also have potential in COPD.<sup>98</sup>

Agents that antagonize matrix metalloproteinases have the potential to inhibit the development of emphysema and small airway fibrosis in animal models but none have been effective in humans. Many new biologic therapies have potential use in the treatment of COPD including humanized monoclonal antibodies directed at IL-5 and IL-17 receptors. Phosphoinositide-3 kinase inhibitors, soluble epoxide hydrolase inhibitors and orally active,  $\gamma$ -selective retinoid agonists are new potential approaches to treating COPD.<sup>98</sup> Exciting new approaches to the treatment and prevention of COPD are on the horizon.

The statin drugs (statins) have garnered much interest as a potential therapy for COPD. Despite several large retrospective studies that suggest that statins have a benefit in preserving lung function and reducing mortality and morbidity in patients with COPD,<sup>99</sup> prospective studies have

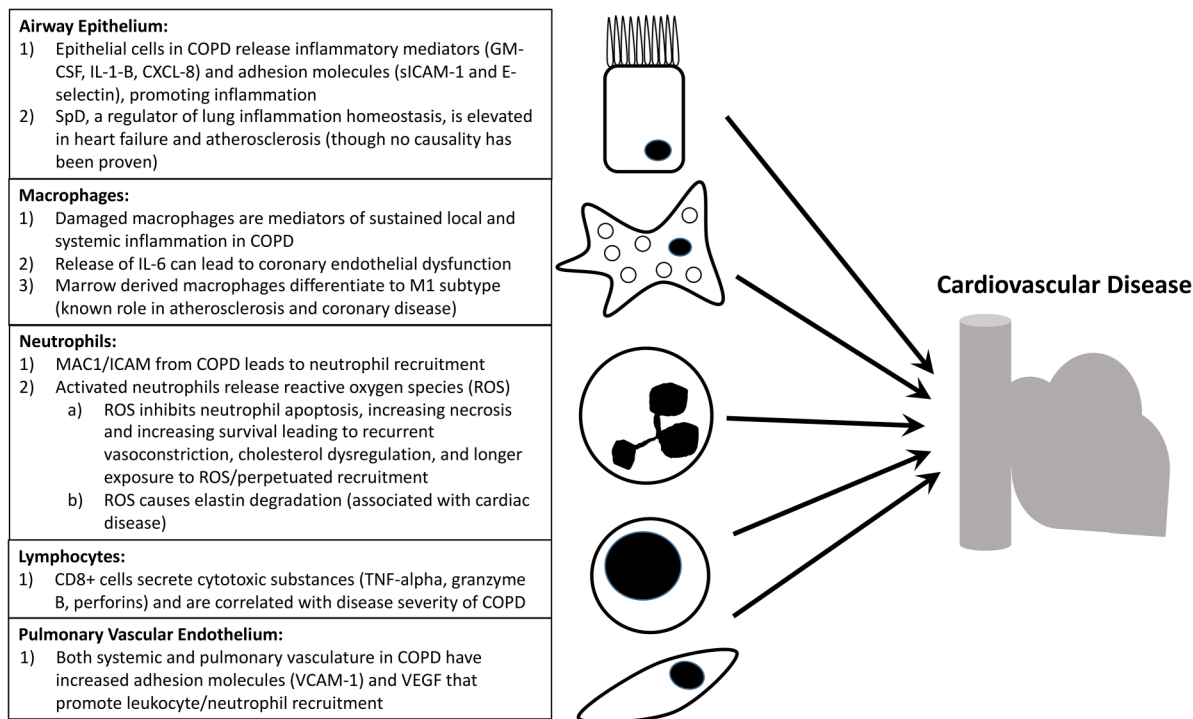
failed to show an advantage in patients with COPD without a significant cardiovascular risk factor.<sup>100</sup> The STATCOPE clinical trial did not show that simvastatin reduced exacerbations in patients with moderate-to-severe COPD.<sup>101</sup> However, smaller clinical trials with pravastatin did show benefit in patients with COPD. In two randomized clinical trials, pravastatin was associated with increased exercise time and reduced systemic inflammation in COPD,<sup>102</sup> and in patients with COPD with pulmonary hypertension treatment with pravastatin increased functional capacity and exercise time, reduced systolic pulmonary pressures, and improved the BORG dyspnea score.<sup>103</sup> Based on these data in sum, statins cannot be recommended for the treatment of COPD, especially with the results of the STATCOPE trial. However, one limitation in the STATCOPE study is that it did not include patients with COPD with overt cardiovascular disease or those with significant cardiac risk factors. STATCOPE excluded the very group of patients with COPD who benefited from statin use in multiple observational studies.<sup>104</sup>

#### Cardiac treatment in patients with COPD

The association of tobacco use and COPD is unequivocal and puts patients with COPD at a higher risk for cardiovascular comorbidities.<sup>105</sup> Patients with COPD are more likely to have cardiovascular disease than matched non-COPD populations (OR=2.46, 95% CI 2.02 to 3.00,  $p<0.00001$ ).<sup>106</sup> This includes a 2–5 time increased risk for MI, cardiac dysrhythmia, CHF, disease of the pulmonary vasculature, and peripheral vascular diseases. Hypertension is also more common in patients with COPD (OR=1.33, 95% CI 1.13 to 1.56,  $p=0.0007$ ).<sup>106</sup> Medications used to treat these cardiovascular comorbidities such as diuretics and  $\beta$ -blockers can have potential detrimental drug–disease interactions and effects in patients with COPD.

The treatment of hypertension in patients with COPD has been reviewed elsewhere.<sup>107</sup> Thiazide (hydrochlorothiazide, chlorthalidone) and loop (furosemide, bumetanide, torsemide) diuretics used in the treatment of hypertension and CHF can cause serious toxicity through urinary potassium losses. This can be exacerbated when diuretics are used with inhaled  $\beta$ -2-receptor agonists, which cause the movement of potassium into the cell. This combination can lead to severe hypokalemia. These drugs can also generate a volume-contraction metabolic alkalosis leading to a further suppression in ventilatory drive, thus resulting in worsening hypoxemia and hypercapnia. Alkalemia also increase the risk for cardiac arrhythmias further exacerbating cardiac disease.

ACE inhibitors are effective in the control of hypertension and the treatment of CHF in patients with COPD. However, since 5–20% of the patients on ACE inhibitors can develop a cough, they must be used with caution in COPD. Prior use of ACE inhibitors has been shown to reduce mortality in patients with COPD admitted with exacerbations.<sup>107</sup> Although ACE inhibitors have been suggested to improve skeletal muscle function in patients with COPD, a recent randomized controlled 3-month trial of the ACE inhibitor fosinopril in patients with COPD failed to show improvement in strength of the quadriceps or exercise performance.<sup>108</sup>



**Figure 2** Schematic showing the overlap between dysfunctional lung structural cells and inflammatory cells in COPD that may have a connection to cardiovascular disease. COPD, chronic obstructive pulmonary disease; IL, interleukin; SP-D, surfactant protein D; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Amiodarone is a class III antiarrhythmic drug used to treat complex and life-threatening cardiac arrhythmias. The use of amiodarone is associated with significant pulmonary toxicity. In a large study of patients with atrial fibrillation, amiodarone use was associated with a nearly 40% increase in pulmonary toxicity in men compared with women (HR=1.37, 95% CI 1.19 to 1.57,  $p < 0.0001$ ) and more than a doubled risk in pulmonary toxicity was seen in patients with COPD (HR=2.53, 95% CI 2.21 to 2.89,  $p < 0.0001$ ).<sup>109</sup> Approximately 3.1% of patients with atrial fibrillation without pre-existing pulmonary disease were found to have pulmonary toxicity after 4 years of taking amiodarone compared with 5.9% ( $p = 0.015$ ) of those patients with pre-existing pulmonary disease in another study.<sup>110</sup> Patients with CHF and COPD who were treated with amiodarone and survived at least 1 year had a significantly greater decrease in lung diffusion capacity (DLCO) compared with patients treated with placebo (2.05 vs 0.09 mL/min per mm Hg,  $p = 0.008$ ) but had no difference in survival free of cardiac deaths.<sup>111</sup> Taken together, these limited data suggest that the risk–benefit ratio must be considered before treating patients who have significant COPD with amiodarone and they need to be carefully monitored with chest imaging and DLCO measurements while on amiodarone.

As noted above, the risk of cardiovascular disease is increased in patients with COPD.<sup>106</sup> The  $\beta$ -blockers are used widely in the treatment of CHF, hypertension, atrial fibrillation, and MI. Non-selective  $\beta$ -blockers such as propranolol have been shown to have a negative effect on lung function (FEV<sub>1</sub>, FVC, and FEV<sub>1</sub>% predicted) as compared with  $\beta$ -1 selective receptor blockers like atenolol. This effect holds

true both at baseline and after albuterol inhalation in patients with COPD or asthma.<sup>112 113</sup> Non-selective  $\beta$ -blocking agents should therefore be avoided in patients with COPD in favor of the more selective  $\beta$ -1-receptor blocker agents.

Use of labetalol, a non-selective  $\beta$ -blocker that also blocks  $\alpha$ -1-receptor, did not affect FEV<sub>1</sub> or the mid-expiratory flow volumes in patients with COPD and hypertension 2 hours after the administration of the maximum labetalol dose.<sup>114</sup> Another non-selective  $\beta$ -blocker/ $\alpha$ -1-receptor blocker, carvedilol, was studied in patients with CHF and COPD and compared with the selective  $\beta$ -1-blockers metoprolol and bisoprolol. A 6 min walk and left ventricular ejection fraction did not change with the three drugs. However, FEV<sub>1</sub> was lowest with carvedilol, better in metoprolol, and best in the patients treated with bisoprolol.<sup>115</sup> In patients with CHF with COPD ( $n = 31$ ) or asthma ( $n = 12$ ), 3.2% of patients with COPD and 25% of patients with asthma developed wheezing after starting carvedilol.<sup>116</sup> In contrast, actual improvement in peak expiratory flow rate of 17% ( $p = 0.04$ ) was seen in patients with COPD and 4% ( $p = \text{NS}$ ) in patients with asthma 2 hours after starting carvedilol. The  $\beta$  and  $\alpha$  adrenergic blocking agents should be used with caution in patients with COPD until more information is available.

In patients with COPD who had an MI, those discharged on  $\beta$ -blockers compared with those who did not had a lower all-cause mortality after adjusting for confounders (HR=0.87, 95% CI 0.64 to 0.95) during a follow-up period that was as long as 7.2 years.<sup>117</sup> More impressive was the survival advantage seen in those patients with COPD discharged on a  $\beta$ -blocker after an MI and who also had CHF (HR=0.77, 95% CI 0.63 to 0.95).

**Table 1** Combination drug inhalers used for maintenance treatment of COPD

Drug 1+drug 2	DI ( $\mu$ g)	DF	Type DD	DD name	Name	
<b>LABA+LAMA</b>						
Indacaterol	Glycopyrronium	110/50	Once a day	DP	Ultibro Breezhaler	QVQ149
Vilanterol	Umeclidinium	25/62.5	Once a day	DP	Ellipta	Anoro
Olodaterol	Tiotropium	3.5/2.5	Once a day	SDM	Respimat	Stiolto
Formoterol	Aclidinium	12/400	two times a day	DP	Genuair	Duaklir
Formoterol	Glycopyrrolate	4.8/9	two times a day	MDI		Bevespi Aerosphere
<b>SABA+SAMA</b>						
Albuterol	Ipratropium	2.5/0.5 (mg)	Every 6 hours	Neb		DuoNeb
Albuterol	Ipratropium	0.1/0.33 (mg)	Every 6 hours	SDM	Respimat	Combivent
<b>LABA +ICS</b>						
Vilanterol	Fluticasone F	25/100	Once a day	DP	Ellipta	Breo
Formoterol	Budesonide	4.5/160 or 80	Two times a day	MDI		Symbicort
Formoterol	Budesonide	6612/100,200,400	Two times a day	DP	Turbuhaler	Symbicort
Formoterol	Mometasone	5/100 or 200	Two times a day	MDI		Dulera <sup>A</sup>
Salmeterol	Fluticasone P	50/100,250,500	Two times a day	DP	Diskus	Advair
Salmeterol	Fluticasone P	21/45,115,230	Two times a day	MDI		Advair HFA <sup>A</sup>

<sup>A</sup>, approved for asthma indication only, all others approved for COPD or COPD+asthma; COPD, chronic obstructive pulmonary disease; DF, dose frequency; DI, dose per inhalation; DP, dry powder; F, furoate; ICS, inhaled corticosteroid; LABA, long-acting  $\beta$ -2 agonist; LAMA, long-acting muscarinic antagonist; MDI, metered dose inhaler; Neb, nebulization; P, propionate; SABA, short-acting  $\beta$ -2 agonist; SAMA, short-acting muscarinic antagonist; SDM, spring driven mist; Type DD, type of delivery device.

Meta-analysis of the use of selective  $\beta$ -1-receptor blockers for hypertension, CHF, and coronary artery disease and during the perioperative period in patients with COPD concluded that they did not produce adverse respiratory effects.<sup>118</sup> However, a large prospective cohort observational trial showed that both cardioselective and non-cardioselective  $\beta$ -blockers in patients without lung disease were associated with significant reductions in FEV<sub>1</sub> measures over a mean of 6.1 $\pm$ 0.5 years. The use of selective  $\beta$ -1-blockers resulted in less reduction in FEV<sub>1</sub> (–118 mL, 95% CI –157 to –78,  $p$ <0.001) than the reduction seen with the use of non-cardioselective  $\beta$ -blockers (–198 mL, 95% CI –301 to –96,  $p$ <0.001).<sup>119</sup> When patients with COPD, asthma, and CHF were included, the same trends held.

In a clinical trial where patients with COPD and CHF were randomized to either the selective  $\beta$ -1-blocker bisoprolol or the non-selective  $\beta$ -blocker/ $\alpha$ -1-blocker carvedilol, both agents reduced the heart rate and had no effect on the N-terminal pro brain natriuretic peptide. Bisoprolol, but not carvedilol, significantly increased FEV<sub>1</sub> by 127 mL.<sup>120</sup> Another randomized triple cross-over trial evaluated carvedilol, metoprolol, and bisoprolol in patients with CHF and found that in those patients with COPD, bisoprolol had the highest and carvedilol the lowest FEV<sub>1</sub> measurements.<sup>115</sup> However, bisoprolol use is also associated with worsening dynamic hyperinflation compared with placebo in patients with moderate-to-severe COPD without reducing the duration of exercise.<sup>121</sup> Conversely, the rate of CHF and/or COPD exacerbations were higher in those patients treated with carvedilol as compared with bisoprolol.<sup>122</sup>

Beyond lung function,  $\beta$ -blockers have been associated with important hard outcomes such as mortality. A mortality advantage was seen with the use of bisoprolol, but not carvedilol or metoprolol, in patients with COPD and CHF.<sup>123</sup> Another study demonstrated reduced mortality

rates in patients with COPD with CHF on bisoprolol or carvedilol (HR=0.41, 95% CI 0.17 to 0.99,  $p$ =0.047). In a large Scottish retrospective cohort study of  $\beta$ -blockers with a mean follow-up of 4.35 years, there was a 22% reduction in overall mortality in patients with COPD taking  $\beta$ -blockers.<sup>124</sup>

Two large trials have demonstrated significant reductions in COPD exacerbations regardless of the severity of airflow obstruction when the patients are on  $\beta$ -blockers.<sup>125–126</sup> A trial of 520 patients with COPD undergoing lung resection found that the use of perioperative  $\beta$ -blockers compared with not using them did not change the rate of postoperative COPD exacerbations (5.4% vs 6.3%).<sup>127</sup> Selective  $\beta$ -1-receptor blockers appear to have an advantage over non-selective  $\beta$ -blockers in patients with COPD with CHF, hypertension and MIs, but the advantages have been small and not always consistent.

## SUMMARY

COPD is the third most common cause of death worldwide. The definition of COPD is evolving, due to complex disease mechanisms, clinical heterogeneity, and variable immune response to inhaled toxicants and environmental pollutants. Large cohort studies are important to help define COPD phenotypes and identify useful biomarkers, and these studies give rise to important and testable clinical questions such as how patients with certain radiological features respond to therapeutic interventions. As our understanding of COPD immunobiology improves, we may better identify specific and effective immune-modulating therapies at various stages of COPD, including monoclonal antibodies in the current age of biologics and precision medicine. The recognition that COPD often coexists with cardiovascular disease underscores the link between these disorders. Therapies directed at both COPD and heart disease seem to confer benefit beyond treating each separately, and the future of COPD research and treatment approaches needs to bear this in mind.



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