REVIEW

Pharmacological actions of statins: potential utility in COPD

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ABSTRACT: Chronic obstructive pulmonary disease (COPD) is characterised by minimally reversible airflow limitation and features of systemic inflammation. Current therapies for COPD have been shown to reduce symptoms and infective exacerbations and to improve quality of life. However, these drugs have little effect on the natural history of the disease (progressive decline in lung function and exercise tolerance) and do not improve mortality. The anti-inflammatory effects of statins on both pulmonary and systemic inflammation through inhibition of guanosine triphosphatase and nuclear factor-κB mediated activation of inflammatory and matrix remodelling pathways could have substantial benefits in patients with COPD due to the following. 1) Inhibition of cytokine production (tumour necrosis factor-α, interleukin (IL)-6 and IL-8) and neutrophil infiltration into the lung; 2) inhibition of the fibrotic activity in the lung leading to small airways fibrosis and irreversible airflow limitation; 3) antioxidant and anti-inflammatory (IL-6 mediated) effects on skeletal muscle; 4) reduced inflammatory response to pulmonary infection; and 5) inhibition of the development (or reversal) of epithelial-mesenchymal transition, a precursor event to lung cancer. This review examines the pleiotropic pharmacological action of statins which inhibit key inflammatory and remodelling pathways in COPD and concludes that statins have considerable potential as adjunct therapy in COPD.

KEYWORDS: Chronic obstructive pulmonary disease, statins

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Chronic obstructive pulmonary disease (COPD) occurs as a result of the combined effects of smoking exposure and genetic susceptibility to the damaging effects of smoking. COPD is characterised by progressive, minimally reversible airflow limitation that results from varying combinations of parenchymal destruction (emphysema) and fixed small airways disease from smooth muscle hypertrophy and airway fibrosis [1–3]. COPD is also a systemic disease with progressive muscle wasting of the skeletal and respiratory system, which further limits exercise capacity [4–6]. Other systemic manifestations of COPD include coronary artery disease (CAD), osteoporosis and anaemia [4, 7]. Although goblet cell hyperplasia and excessive mucus production are also clinical manifestations in COPD they do not appear to be associated with poor outcomes in COPD, unlike reduced expiratory volumes and systemic inflammation [3].

PATHOPHYSIOLOGY OF COPD
Smoking has been shown to account for ~85% of cases diagnosed with COPD, while exposure to other aero-pollutants such as organic and inorganic work dusts, heavy air pollution or precipitants of allergic inflammation may also play a role [3]. The potential effects of smoking on the lung, systemic circulation and muscle is shown in figure 1. Smoking initiates a ubiquitous inflammation orchestrated by the bronchial epithelium with release of interleukin (IL)-8 and subsequent sequestration of neutrophils from the pulmonary capillaries into respiratory bronchioles and airway lumen [8–10]. IL-8 stimulates further release of neutrophils from the bone marrow [9]. Activated neutrophils in the pulmonary tissue (respiratory bronchioles and alveolar walls) release neutrophil elastase which contributes to elastin degradation [8]. Other proteases with possible roles in COPD include sereine proteases, cysteine proteases or chymotrypsin. Smoke exposure also incites the release of other inflammatory cytokines from a variety of cells including IL-6, tumour necrosis factor (TNF)-α, IL-1β, transforming growth factor (TGF)-β1 and granulocyte-monocyte colony-stimulating factor (GM-CSF) [1, 11]. Inhalation of cigarette smoke results in a huge exogenous oxidant load on the

lung from reactive oxygen species (ROS), which inactivates many of the anti-protease mediators, most notably α_1-antitrypsin (and possibly α_1-anti-chymotrypsin and serine antiproteases), resulting in an acquired anti-protease deficiency [12, 13]. The effect of IL-8 and neutrophil influx into the pulmonary parenchyma is accompanied by the influx of macrophages and CD8+ T-lymphocytes [14]. Macrophages are thought to become activated and release a number of matrix metalloproteases (most notably MMP1, MMP2, MMP9, MMP12 and MMP15), which have the ability to degrade both elastin and collagen leading to further lung parenchymal damage [10, 11, 15]. The neutrophils are known to release a high concentration of endogenous oxidants, which add to those derived from smoking and worsen the global anti-protease effect through inactivation of systemic anti-pro-teases (*e.g.* α_1-antitrypsin) and inhibition of local anti-proteases (*e.g.* tissue inhibitors of metalloproteinases) [8].

The oxidant load derived from the lung (exogenous and endogenous) crosses the endothelium where, in combination with elevated circulating cytokines, it results in systemic inflammation in the vascular system [4, 7, 12]. Nicotine from smoke provides agonist activity to the nicotine acetylcholine

receptor found throughout the airways and is thought to initiate the release of fibronectin leading to pulmonary airway fibrosis by fibroblasts [16, 17]. The latter is thought to be mediated by IL-8 and TGF-β1 is released as part of the inflammatory responses [16, 17] leading to excess collagen relative to elastin (impaired repair). Finally, recent studies suggest that dysregulated apoptosis (programmed cell death) of structural cells (epithelial and endothelial cells) and inflammatory cells (polymorphic neutrophils) occurs in patients with COPD [18, 19]. It has been shown that neutrophil apoptosis is reduced in the sputum of patients with COPD and is associated with elevated IL-6 and IL-8 levels [19]. This observation was found to be mediated by nuclear factor (NF)-κB activation and is consistent with other studies that show these cytokines are associated with inhibition of apoptosis [20]. Prolonging the lifespan of neutrophils in the lung would result in persisting neutrophil-mediated inflammation and matrix remodelling.

It has also been proposed that high levels of cytokines (primarily IL-6), inflammatory mediators and/or ROS in the systemic circulation, derived in a large part from the
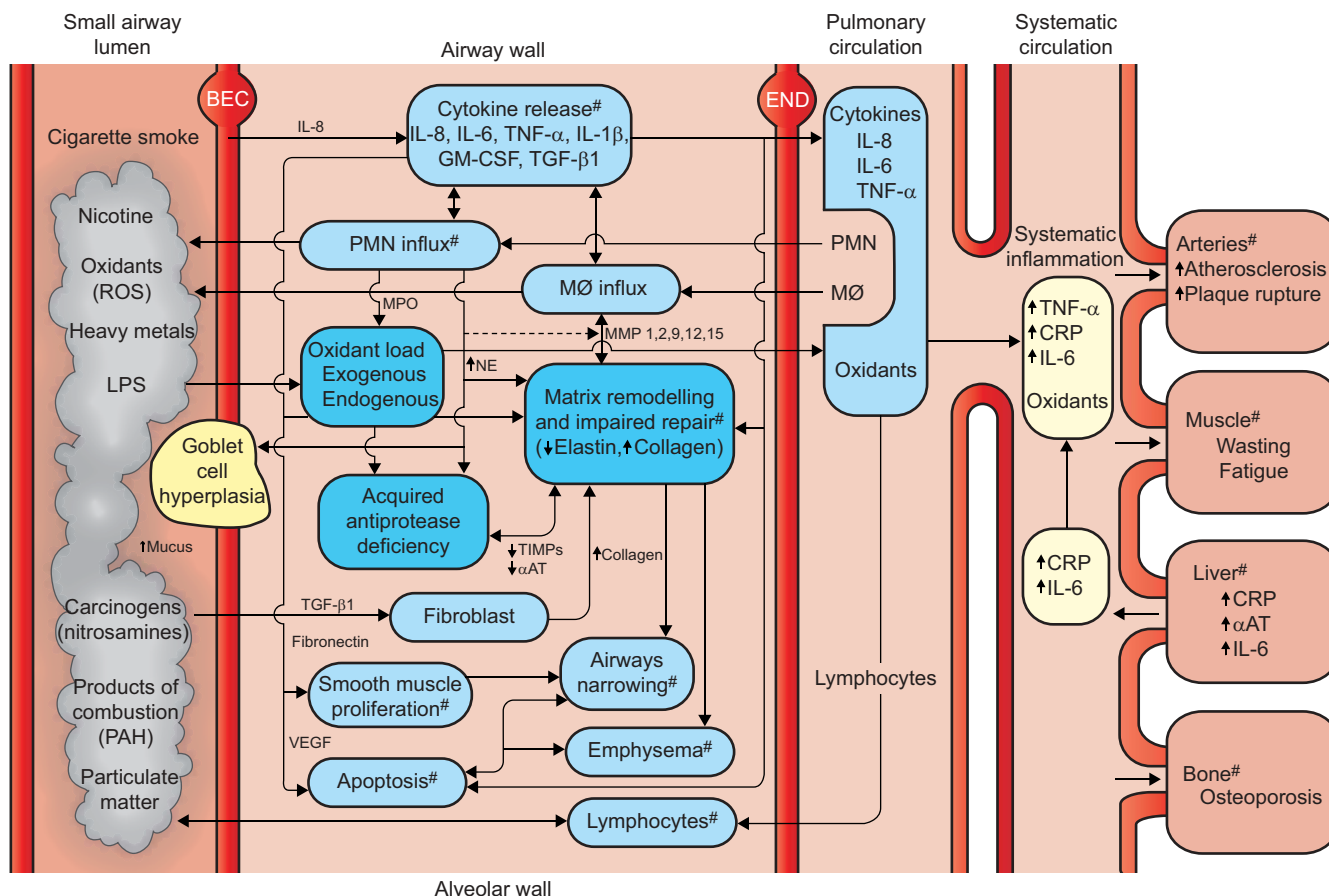
FIGURE 1. Proposed pathogenesis of chronic obstructive pulmonary disease. ROS: reactive oxygen species; LPS: lipopolysaccharide; PAH: polyaromatic hydrocarbons; BEC: bronchial epithelial cell; IL: interleukin; TNF: tumour necrosis factor; GM-CSF: granulocyte-monocyte colony-stimulating factor; TGF: transforming growth factor; PMN: polymorphic neutrophil; MPO: myeloperoxidase; MØ: macrophage; MMP: matrix metalloproteinase; NE: neutrophil elastatse; TIMP: tissue inhibitors of metalloproteinase; αAT: α_1-antitrypsin; VEGF: vascular endothelial growth factor; END: endothelial cell; CRP: C-reactive protein. #: denotes the site of action of statins.

pulmonary circulation (the ''spill over'' effect) [4, 7], may lead to muscle wasting and decreased muscle function [17–22]. Apoptosis has also been implicated in muscle wasting, as seen in COPD patients [18, 19], and may be important in survival [19–22]. Collectively, smoking appears to incite an inflammatory response and high oxidant load that, over time, prematurely ages the body [23] through lung destruction (emphysema), poor elastic recoil of tissues (reduced airway compliance), maladaptive or excessive healing (airway fibrosis), and wasting of skeletal and respiratory muscles resulting in poor exercise tolerance. These processes are ''exaggerated'' in smokers who are genetically predisposed to COPD and result in progressive loss of lung function, muscle wasting and exercise intolerance.

There is growing epidemiological and molecular evidence that COPD is closely associated with lung cancer [24–26]. Like COPD, lung cancer develops in only the minority of long-term smokers, estimated to be 10–15% [27]. Recently, it has been shown that 60–90% of those diagnosed with lung cancer have pre-existing impaired lung function (consistent with COPD) and/or emphysema on computed tomography scanning [24–26]. This relationship is comparable to that observed between obesity and type 2 diabetes. These epidemiological studies suggest that factors conferring susceptibility to COPD may also confer susceptibility to lung cancer mediated through genetic variants underlying the pathogenic pathways, as described above and as shown in figures 1 and 2 [28].

There is also a growing interest in the role that epithelial-mesenchymal transition (EMT) plays in lung carcinogenesis (fig. 2) [29, 30]. In this process, bronchial epithelial cell (BEC) integrity and function is disrupted by matrix remodelling and growth factor release that underlies COPD, such as TGF-β and MMPs, and promotes EMT. The effect of growth factors on EMT has been shown to be promoted by collagen 1, linking remodelling (COPD) with EMT [30]. In animal models, the guanosine triphosphatase (GTPase) proteins (*i.e.* GTP-binding proteins *e.g.* Ras, Rho and Rac) have been linked to the development of lung cancer, with NF-κB mediating this effect in a COPD mouse model [31]. *In vitro* studies show that inhibition of GTPase can reverse EMT and restore the epithelium to its normal morphology [32]. Finally, there is a link between EMT and damage to DNA which results in the formation of DNA adducts and somatic mutations forming oncogenes (*e.g.* k-Ras) and inhibiting tumour suppressor genes, which are thought to underlie lung cancer development [31]. Although several pathological pathways are likely to be involved in the development of COPD and EMT (figs 1 and 2), many are mediated intracellularly by GTPases [29]. These signalling molecules require isoprenylation to be active and, as described above, are critical for cellular function through up-regulating effects on transcription binding factors, such as NF-κB and activator protein-1, central to gene expression in COPD [33] and lung cancer development [29]. If EMT is an important pre-malignant event then the inflammation and matrix remodelling processes that lead to COPD may also lead to lung cancer, thereby explaining this close relationship in an overlapping group of genetically susceptible smokers [28]. If this were true, then any pharmacological agent that could attenuate the inflammatory and matrix remodelling processes

underlying COPD might also reduce the risk (and development) of lung cancer.

EPIDEMIOLOGY OF COPD

Despite the inflammatory and aging effects of smoking on not just the lungs but the arteries and muscles of the body, why do only an estimated 20% of smokers develop clinically significant COPD [3]? Numerous studies have shown that COPD and lung function have a strong genetic component, especially in the presence of smoking history [34–36]. Based on widely divergent drug metabolite levels, classic pharmacogenetic studies have been able to define high or low drug metabolisers that were subsequently linked to genetic variants of metabolising enzymes [37]. Similarly, after ⩾40 yrs of smoking, forced expiratory volume in 1 s (FEV1) in smokers can be categorised according to approximately bi- or tri-modal distribution with the majority (70–80%) maintaining normal (or near normal) lung function (termed resistant smokers), while the remainder have accelerated decline in FEV1 and are identified as susceptible [3, 38–40]. This latter group may eventually be diagnosed with COPD; however, due to the insidious breathlessness and under-utilisation of spirometry, 50–80% of people with COPD remain undiagnosed [41].

This susceptibility to the effects of smoking is conferred by a variable combination of low penetrant variants in genes encoding proteins that are closely linked to the pathogenic pathways described above [42]. It has been proposed that reduced FEV1 in smokers is a general barometer of a smoker's susceptibility to the adverse effects of smoking and explains the reported two to five-fold increased risk of other smoking related complications, such as CAD, lung cancer and stroke, in comparison to smokers with normal lung function [38]. It has been shown that both cardiovascular and all-cause mortality are more closely linked to reduced FEV1 than to smoking status [43, 44], and maybe mediated by over-lapping inflammatory mediators (*e.g.* C-reactive protein (CRP), TNF-α and IL-6). Therefore, smoking is an accelerant to an established pro-inflammatory tendency which may be genetically conferred [28, 45] and may lead to premature aging of the lungs and arteries.

CURRENT TREATMENT IN COPD

The mainstay of treatment in COPD is short- and long-acting β-agonist therapy to relax smooth muscle and dilate airways [2]. This approach is very successful in relieving the brocho-constriction in asthma where hyperreactive airways and smooth muscle constriction are important. The bronchodilating response to this treatment is considerably less in COPD due to small airway fibrosis and emphysema secondary to matrix remodelling (imbalance of elastin/collagen content). Inhaled corticosteroids are also used to inhibit airway inflammation of COPD although it is strongly neutrophil driven rather than the T-helper (TH) type-2 inflammatory response of asthma, where activated lymphocytes are thought to play a central role [2]. Given these significant differences in pathogenic pathways underlying COPD and asthma, it is perhaps not surprising that current treatments in COPD modestly improve symptoms but do no restore patients back to normal lung function. Given that corticosteroids do little for neutrophilic inflammation [2, 11], it is also not surprising that COPD is characterised by a
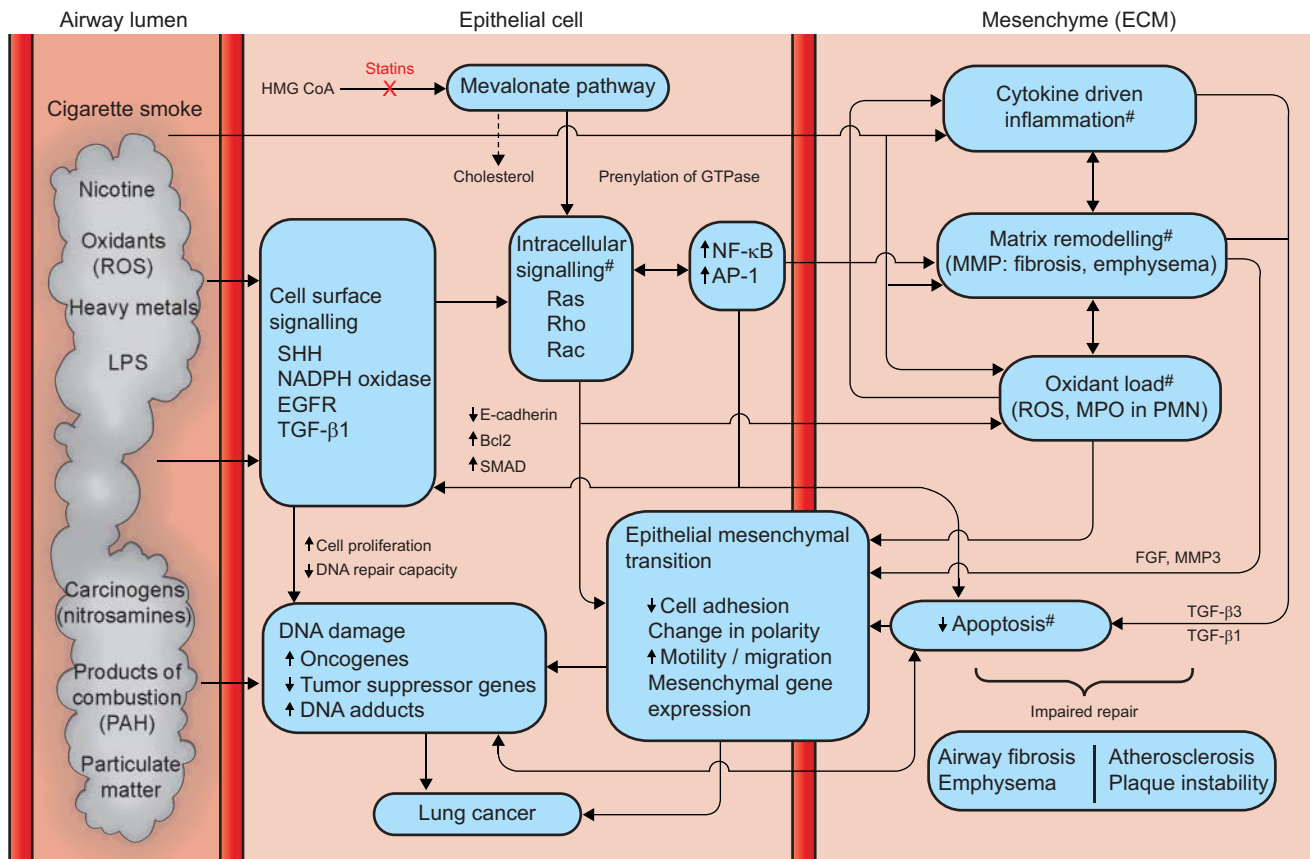
FIGURE 2. Proposed pathogenesis of lung cancer. ECM: extracellular matrix; ROS: reactive oxygen species; LPS: lipopolysaccharide; PAH: polyaromatic hydrocarbons; HMG CoA: 3-hydroxy-3-methylglutaryl coenzyme A; GTPase; guanosine triphosphatase; SHH: sonic hedgehog homologue; NADPH: reduced nicotinamide adenine dinucleotide phosphate; EGFR: epidermal growth factor receptor; TGF: transforming growth factor; NF-κB: nuclear factor-κB; AP-1: activator protein-1; MMP: matrix metalloproteinase; MPO: myeloperoxidase; PMN: polymorphic neutrophil; FGF: fibroblast growth factor. #: denotes the site of action of statins.

progressive decline in lung function, exercise tolerance and premature death despite these treatments. Although some studies suggest marginal benefits on mortality from inhaled corticosteroids or combined β-agonist/corticosteroid therapy, the data are not terribly convincing [46–48]. Based on these limitations [49, 50], interest has turned to treatments with greater impact on neutrophil or macrophage derived inflammation [50–53].

COPD AND SYSTEMIC INFLAMMATION

There are a growing number of studies showing that CRP is a marker of systemic inflammation and a possible effector molecule in vascular disease [4–6]. Several cross-sectional and prospective studies have shown the close inverse relationship between high-sensitivity CRP and lung function [54–56]. CRP is synthesised and released by the liver into the systemic circulation in response to IL-6 released by inflammatory stimuli. This link between IL-6, CRP and COPD is supported by population studies showing an inverse relationship between serum IL-6 levels and FEV1 [5, 57, 58], and murine models of emphysema resulting from IL-6 overexpression [59]. Interestingly, α_1-antitrypsin is also an acute-phase protein released by the liver at the time of inflammation. It should be

noted that serum IL6 and IL-8 levels are elevated in smokers with COPD in excess of those with normal lung function [8, 11, 19]. It would appear conceivable that, in those disposed to COPD, smoking initiates an increase in the cytokines IL-6 and IL-8 which might underlie the systemic (''spill over'' effect [4, 7]) and pulmonary inflammation, respectively. This could explain the observation that patients with COPD have a greater than two-fold risk of coronary heart disease [6]. Genetic variation may confer important effects on the expression of these effector molecules (*e.g.* CRP, IL-6 and IL-8) that then mediate the downstream effects on COPD [60] and lung cancer [45, 61, 62]. The heavy oxidant load derived from smoking has effects both locally in lung parenchyma and systemically on muscle function. Given these diverse pathways and anatomically distant events, what evidence exists to suggest that statin therapy (or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) might affect any of these pathological events?

STATIN EFFECTS ON CLINICAL OUTCOMES IN COPD: AN OVERVIEW

Statins are known to inhibit endogenous cholesterol synthesis in hepatocytes by blocking the synthesis of cholesterol in the mevalonate pathway. This explains the ability of statins to

lower serum cholesterol. However, evidence from both human and animal studies has shown that statins have strong immune-modulating effects in both the systemic [63] and pulmonary circulation [64, 65], which may have useful anti-inflammatory actions in COPD (table 1) [52, 65–88].
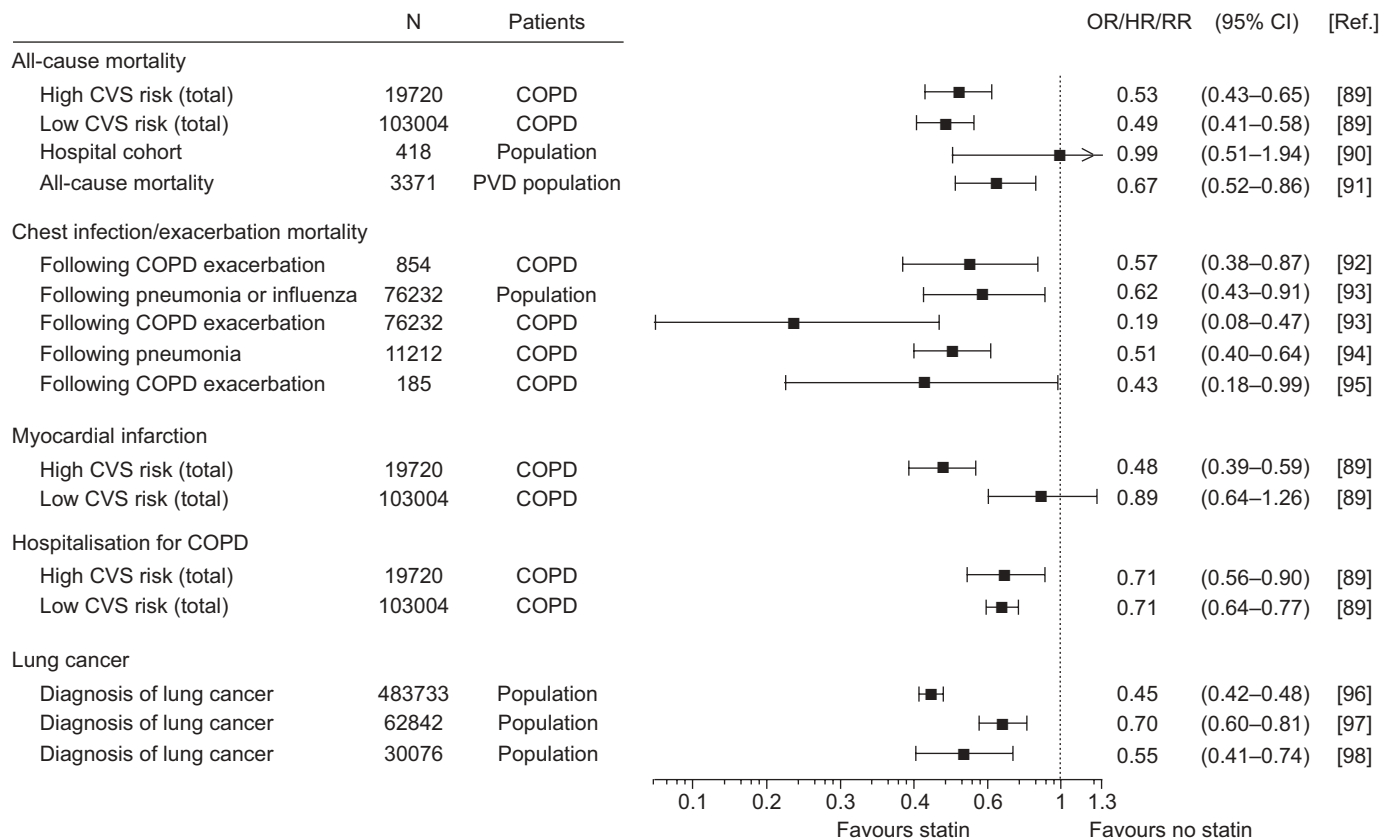
Recently, there have been a number of observational studies suggesting that patients with COPD and taking statins have reduced hospitalisation for COPD exacerbations, lower mortality from COPD exacerbations (or chest infections) and lower cardiovascular mortality compared to those not taking statins (fig. 3) [89, 91–95]. In three recently published reviews, beneficial effects were consistently found in those taking statins [66, 99, 100] and appear to be irrespective of concomitant corticosteroid use [67]. In addition to these reported benefits, several observational studies have shown that statin use also reduces decline in FEV1 and lowers the risk of lung cancer (fig. 3) (reviewed in [66, 90, 96–98, 101]). A number of observational studies have also examined the effect of taking statins in patients from the general population with

TABLE 1	Summary of statin mediated pharmacological effects on pulmonary inflammation and remodeling		
COPD pathway	**Study type**	**Statin effect on pathogenic pathways**	**[Ref.]**
Cytokine production	MM, HM *in vitro* (liver cell line), HM *in vivo* (mononuclear cells)	Reduce IL-6 induced CRP production by hepatocytes	[52, 67, 68]
	HM *in vitro* (VSM cells and PBE cells)	Reduce IL-8 production by VSM cells	[69, 70]
	MM	Inhibition of neutrophil accumulation and IL-8 and TNF-α concentration in BALF in rats	[71]
	HM *in vivo* (serum), MM	Reduce production of IL-β1 and TNF-α	[52, 72]
	MM	Reduced expression of IFN-γ TNF-α and MMP12 in whole lung	[73]
Matrix remodelling	MM	Reduced lung parenchymal destruction and MMP 9 activity in smoke exposed rat lung	[74, 75]
	HM *ex vivo* (bronchial epithelial cells)	Reduce release of MMP2 and MMP9 from bronchial epithelial cells from lung transplant patients	[70]
Neutrophil/macrophage influx	HM *ex vivo* (bronchial epithelial cells), HM *in vivo* (PMN)	Reduce neutrophil influx in lung transplant recipients by inhibiting release of IL-8 and GM-CSF from bronchial epithelial cells	[70, 76, 77]
	HM *in vitro* (PMN), HM *in vivo* (serum)	Reduce neutrophil endothelial adhesion and transendothelial migration	[76, 78–80]
	MM	Reduce neutrophil influx and inhibit the development of elastase induced pulmonary emphysema in mice	[74, 75]
	MM, HM *ex vivo* (human monocytes)	Reduce CRP-induced monocyte migration by inhibition of ICAM-1 in human monocytes	[81]
	MM, HM *in vitro* (endothelial cells), HM *in vivo* (BALF)	Reduced concentration of neutrophils and lymphocytes in BALF	[74, 75]
	MM, HM *in vitro*	Reduce chemokine and adhesion molecule expression to reduce migration of inflammatory cells into the airways	[74, 81, 82]
Epithelial/endothelial integrity	MM	Promotes alveolar cell regeneration and restores endothelial cell function	[75]
	MM	Reduce LPS-induced IL-6 gene expression leading to reduced lung vascular leak and pulmonary inflammation in mice lung	[83]
	HM *in vitro* (endothelial and smooth muscle cells)	Inhibition of VEGF in smooth muscle cells and endothelial cells	[84]
Apoptosis	HM *in vitro* (macrophages and PMN)	Enhances clearance of apoptotic cells in alveolar macrophages from patients with COPD	[85]
	HM *in vitro* (endothelial cells), HM *in vitro* (endothelial and smooth muscle cells)	Increase apoptosis in human vascular endothelial cells	[84, 86]
Oxidant response	HM *in vivo* (PMN)	Reduce IL-8 release from neutrophils and neutrophil derived reactive oxidant species	[77]
	HM *in vivo* (serum), MM	Strong anti-oxidant properties	[87, 88]
Mucus production	MM	Reduced LPS-induced goblet cell hyperplasia in bronchial epithelium and Muc5A induced mucus hypersecretion	[71]
CRP level	HM *in vitro* (liver cell)	Reduce CRP levels at the transcriptional level thorough Rac-1 mediated inhibition of STAT3 phosphorylation	[67]

COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; MM: murine model; HM: human model; VSM: vascular smooth muscle; PBE: primary bronchial epithelial; PMN: polymorphic neutrophil; BALF: bronchoalveolar lavage fluid; IL: interleukin; TNF: tumour necrosis factor; IFN: interferon; MMP: matrix metalloproteinase; GM-CSF: granulocyte-monocyte colony-stimulating factor; ICAM: intracellular adhesion molecule; LPS: lipopolysaccharide; VEGF: vascular endothelial growth factor.

	N	Patients		OR/HR/RR	(95% CI)	[Ref.]
All-cause mortality						
High CVS risk (total)	19720	COPD		0.53	(0.43–0.65)	[89]
Low CVS risk (total)	103004	COPD		0.49	(0.41–0.58)	[89]
Hospital cohort	418	Population		0.99	(0.51–1.94)	[90]
All-cause mortality	3371	PVD population		0.67	(0.52–0.86)	[91]
Chest infection/exacerbation mortality						
Following COPD exacerbation	854	COPD		0.57	(0.38–0.87)	[92]
Following pneumonia or influenza	76232	Population		0.62	(0.43–0.91)	[93]
Following COPD exacerbation	76232	COPD		0.19	(0.08–0.47)	[93]
Following pneumonia	11212	COPD		0.51	(0.40–0.64)	[94]
Following COPD exacerbation	185	COPD		0.43	(0.18–0.99)	[95]
Myocardial infarction						
High CVS risk (total)	19720	COPD		0.48	(0.39–0.59)	[89]
Low CVS risk (total)	103004	COPD		0.89	(0.64–1.26)	[89]
Hospitalisation for COPD						
High CVS risk (total)	19720	COPD		0.71	(0.56–0.90)	[89]
Low CVS risk (total)	103004	COPD		0.71	(0.64–0.77)	[89]
Lung cancer						
Diagnosis of lung cancer	483733	Population		0.45	(0.42–0.48)	[96]
Diagnosis of lung cancer	62842	Population		0.70	(0.60–0.81)	[97]
Diagnosis of lung cancer	30076	Population		0.55	(0.41–0.74)	[98]

0.1   0.2   0.3   0.4   0.6   1   1.3
Favours statin   Favours no statin

FIGURE 3. Morbidity and mortality benefits with statin use in observational studies on a logarithmic scale. CVS: cardiovascular; COPD: chronic obstructive pulmonary disease. Data are presented as odds ratio (95% confidence interval), except hospital cohort which is presented as relative risk (95% confidence interval) and following COPD exacerbation which is presented as hazard ratio (95% confidence interval).

community acquired pneumonia (table 2) [102–109]. However, unlike the studies in COPD, the results in pneumonia are not consistent. This probably reflects the heterogeneity of the study populations with respect to many possible confounding factors (*e.g.* sampling, age and smoking) but specifically the presence of COPD (where systemic-pulmonary inflammation is pre-existing) [7].

Such diverse and clinically significant benefits in patients with COPD might, at first glance, appear unlikely to be attributable to a single drug (figs 1 and 2). Indeed, some benefits from statin use have been attributed to the ''healthy user effect''; however, there is little, if any, convincing data to support this hypothesis [66]. Importantly, statin use in patients with COPD should be associated with greater mortality (confounding by indication) due to the consistently higher incidence of coexisting cardio-vascular diseases [89–93, 96–98, 101]; 48% of statin users have CAD *versus* 8% in nonusers [66]. Yet in patients with COPD, despite comparable lung function [66], statin use consistently confers lower mortality compared to nonuse. It was estimated from the observational studies that 25–30% of patients with COPD are currently prescribed statins [66].

The data from randomised control trials (RCTs) examining statin use in COPD is limited to just two studies [110, 111]. In a sub-analysis of a large randomised trial of statin therapy and its effects on cardiovascular disease (the Heart Protection

Study), a trend towards reduced respiratory death (30% reduction) and reduced COPD exacerbations (20% reduction) was reported [110]. The only RCT of statin therapy specifically in patients with COPD was reported from 125 patients in Taiwan and showed that those randomised to pravastatin for 6 months had a 54% increase in exercise tolerance [111]. Therefore, both observational and randomised studies have reported clinically important benefits of statin therapy in patients with COPD. What is more compelling is that, in the absence of further confirmatory RCT data, the known pharmacological actions of statins on systemic and pulmonary inflammation can explain all the beneficial effects reported to date (table 1).

STATINS EFFECTS ON SYSTEMIC INFLAMMATION IN COPD

In a prior review, YOUNG *et al.* [38] argued that impaired lung function is a strong predictor of cardiovascular death, both independent of and additive with the risk conferred by smoking. It has also been proposed that CAD in patients with COPD results, in part, from the spill over effect of pulmonary derived inflammatory cytokines (*e.g.* IL-6 and TNF-α) underlying COPD [4, 7]. As stated previously, both cross sectional and prospective studies show that serum CRP and IL-6 are inversely related to FEV1 implying a possible causal relation-ship [54–56]. A recent study showed that, at a therapeutic dose,

TABLE 2	Mortality benefit of statin use in the general population diagnosed with community acquired pneumonia			
Cohort	**Subject n**		**Risk reduction**	**[Ref.]**
Retrospective cohort study in teaching hospital	787	0.36 (0.14–0.92)	64% reduction in 30-day mortality	[102]
Population based prospective cohort study	3415	0.78 (0.57–1.07)	22% reduction in mortality or admission to an ICU	[103]
Population based retrospective nested case–control	6089	0.47 (0.25–0.88)	53% reduction in fatal pneumonia	[104]
Prospective hospital based observational study	1007	0.46 (0.25–0.85)	54% reduction in 30-day mortality	[105]
Population based cohort study	29900	0.69 (0.58–0.82)	31% reduction in 30-day mortality	[106]
		0.75 (0.65–0.86)	25% reduction in 90-day mortality	
Retrospective national cohort study	8652	0.54 (0.42–0.70)	46% reduction in 30-day mortality	[107]
Population based case–control study	2235	0.81 (0.46–1.42)	19% reduction in risk of pneumonia (after excluding those with CAD)	[108]
Population based cohort study	3681	0.33 (0.19–0.58)	67% reduction in 30-day mortality	[109]
		0.45 (0.32–0.62)	55% reduction in long-term mortality	

Data are presented as odds ratio (95% confidence interval). Data for population based case–control study and cohort study are presented as hazard ration (95% confidence interval). ICU: intensive care unit; CAD: coronary artery disease.

statin therapy was associated with a 50% reduction in GTPase (Rho) activity of circulating polymorphic neutrophils that correlated with a reduction in serum CRP [112]. NOHRIA *et al.* [112] proposed that this effect might explain the significant mortality reduction seen with statin use in subjects with normal lipids (Jupiter RCT [113]), which again correlated with CRP reduction [113]. In summary, when statins inhibit systemic inflammation (*e.g.* CRP and IL-6 derived from pulmonary inflammation), a clinically important reduction in mortality can be achieved. As death from CAD is common in COPD patients [7, 53, 66] and reduced $FEV1$ is itself a marker of increased CAD risk, it could be argued that on this basis alone statins might be prescribed for patients with COPD.

Patients with COPD may be profoundly limited by exertional breathlessness attributed, in a large part, to skeletal muscle wasting and atrophy. This limitation of physical activity is not in keeping with airflow limitation ($FEV1$) and has been attributed to the combined effects of elevated oxidative stress and IL-6, *i.e.* another systemic inflammation based comorbidity [7, 17–22]. In the only RCT of statin therapy in COPD, statin use was associated with a 54% increase in exercise tolerance [111]. This increase correlated with a reduction in high sensitivity-CRP and IL-6 suggesting a reduction in systemic inflammation mediated this clinically important end-point [111]. The question remains, through what mechanisms could statins modify pulmonary inflammation and related remodelling effects in patients with COPD (or even smokers with mild airflow limitation) in addition to traditional inhaler therapies?

STATIN EFFECTS ON PULMONARY INFLAMMATION IN COPD

It has been recently appreciated that statins have profound anti-inflammatory effects that might explain their beneficial role in reducing respiratory morbidity and mortality in COPD (table 1) [66–101, 114–121]. Studies have shown that statins reduce neutrophil influx in the lung which might have a strong effect on attenuating the downstream inflammatory events, such as macrophage influx, lymphocyte activation and inhibition of cytokine release, in particular IL-8 that appears central to the neutrophil inflammation of the lung [67–77, 80–88]. The inhibition of IL-6, IL-8 and GM-CSF expression by statins has been shown in cell cultures of human BEC [65, 70]. Statins have also been shown to modify airway inflammation in animal models and matrix remodelling, notably inhibiting emphysema formation [73–75]. Statins also have effects on IL-6 levels in the systemic circulation and the effects of anti-oxidants on muscle atrophy [70, 73–77, 80, 87, 88]. Statins also inhibit apoptosis, which has been linked to both COPD and lung cancer [83–86, 116]. The many pathways affected by statins are shown in figures 1 and 2, where the site of an inhibitory effect of statins based on animal or human studies are clearly shown (table 1).

Statins could conceivably affect these pathways through their inhibition of intracellular prenylation and inhibition of the GTP-binding proteins that underlie these inflammatory pathways [76, 117, 118]. Given these diverse actions on key components of the pathways underlying COPD, it is possible that such effects might explain the benefits observed in the observational studies. In particular, if statins reduce the release of IL-8 in the lungs of COPD patients, then attenuation of neutrophilic inflammation could have considerable downstream effects, such as reduced inflammatory cells in the lungs [81] and reduced remodelling of lung tissue to restore elastin content relative to collagen. If statins reduce the oxidant burden in the systemic circulation [87, 88] and the catabolic state conferred by IL-6 release, then wasting and respiratory muscle function might be improved [21, 22, 87, 88]. It is interesting to note that the inhibitory effect of statins in hepatocytes in blocking cholesterol synthesis might also block cytokine production (primarily IL-6), underlying the premature aging and associated morbidities from smoking-induced systemic inflammation [21].

Statins have also been shown in murine models, through inhibition of GTPase (prenylation), to reverse the hypoxia-induced pulmonary hypertension [119, 120]; a known late complication of COPD causing heart failure. Given the suspected relationship between inflammation, apoptosis and malignant transformation (particularly EMT), it is possible that

statin therapy may have chemo-preventive actions on lung cancer [28, 85]; as suggested by the three large observational studies reporting up to a 50% reduction in lung cancer risk (fig. 3) [96–98].

Further support for the protective role of statins on lung inflammation comes from lung transplant studies that show concomitant use of statins reduces post-transplant bronchiolitis and improves lung function compared to patients not receiving statins [70, 76, 82, 121]. This is an inflammatory-based complication of lung transplantation with over lapping pathology with COPD, including small airway inflammation dominated by airway fibrosis (bronchiolitis obliterans). Similar pharmacological effects from statins on tissue inflammation and remodelling has been seen in atherosclerosis [122–124] and cardiac transplantation [125].

SUMMARY

Current therapy in COPD relieves symptoms and reduces hospitalisation but does not change the natural history of the disease (pulmonary inflammation, systemic inflammation and lung function decline) or outcome (respiratory mortality, cardiovascular mortality or all-cause mortality) [50, 126]. Statin therapy may improve all these outcomes to some degree, as suggested by an extensive review of the observational studies [66] and two recent systematic reviews [99, 100], which all consistently show benefit over harm. A large RCT, underpowered to address a statin effect on respiratory outcomes, showed a trend towards lower respiratory death and COPD exacerbations [110]. A small RCT of statin therapy in COPD patients showed an improvement in exercise tolerance [111], probably mediated through systemic inflammation [4, 7, 49]. Clearly, large RCTs are needed to specifically test these potential benefits in patients with COPD. However, based merely on the robust observation that reduced FEV_1 is an independent marker of cardiovascular disease and that the latter is a common cause of death in patients with COPD, statin therapy could be initiated for this indication alone [7, 39, 66]. Based on new incites into the pleiotropic effects of statins on matrix remodelling, response to oxidant load and, most importantly, cytokine driven inflammation in the lung and circulation (spill over effect) [4, 7], there is compelling evidence to suggest statins may confer considerably wider benefits to patients with COPD.

STATEMENT OF INTEREST

None declared.

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