Published in: International journal of clinical practice (2014), vol. 68, iss. 2, pp. 144-151.
Status: Postprint (Author's version)

Lipid-lowering drug therapies and chronic obstructive pulmonary disease: lung failure or just heart failure?

A. S. Wierzbicki,[1] R. Louis[2]

[1]*Guy's & St. Thomas' Hospitals, St Thomas' Hospital Campus, London, UK*

[2]*Department of Pneumology, University of Liège, CHU Liège, Belgium*

COPD and atherosclerosis share many risk factors so statins may improve lung function by improving cardiac function.

Introduction

Lipids are intimately involved in metabolism in the lung. Lipid-lowering drugs, primarily statins, are prescribed for patients both with established and with developing cardiovascular disease (CVD) (1). Statins improve microvascular and endothelial function (1,2). As statins inhibit early in the pathway of cholesterol synthesis, they also reduce isoprenoid intermediates involved in the control of protein prenylation and rho kinase, which modulate inflammation (1,2). Statins have been suggested as potential treatments for lung diseases including acute lung injury (3), pneumonia (4), pulmonary fibrosis, pulmonary hypertension (5) and for chronic obstructive pulmonary disease (6). Most studies have suggested benefits in lung disease, but some studies of statins in interstitial lung disease showed adverse effects, although these have not been reproduced recently in a large cohort study (7). The most common clinical situations where lipid-lowering drug therapy is likely to be used are in patients with asthma and/or chronic obstructive pulmonary disease (COPD). The question addressed in this review is whether these drugs contribute anything to the management of common lung diseases as well as of CVD risk factors in the general population.

Search strategy

This review was based on searches of PubMed databases for studies using the terms statin, fibrate and niacin (including individual drug names), as well as asthma (statin, $n = 63$), chronic obstructive airways disease (statin, $n = 102$), lung (statin, $n = 582$) and of clinical trial databases using similar search terms in English from 1980 to 2013. Systematic reviews of statins in asthma and COPD were also abstracted in detail for papers not in PubMed.

Lipoprotein metabolism and the lung

The role of lipoproteins in lung metabolism is underestimated (8). Both LDL receptors and SR-B1 (the principal HDL receptor) are found in lung tissue and phospholipids are the source of fatty acids and other lipid-related moieties required for surfactant production. The Niemann-Pick C lysosomal pathway is involved in cholesterol homeostasis and surfactant production in lung alveolar cells (9). Serum cholestenoic acid and 27-hydroxy-cholesterol [whose production is regulated by a farnesoid-X receptor (FXR)-controlled pathway in the liver] have been suggested to be plasma markers of lung lipid metabolism and to relate to the degree of pulmonary alveolar proteinosis (10). Excess cholesterol impairs surfactant function through changes in surface chemistry (11). Macrophages are a key component of alveoli and are profoundly affected by cholesterol analogous to the effects seen in atheroma formation. Thus, proteins involved in cholesterol or oxidised lipid transport such as the export transporters ABC-A1 and ABC-G1, the scavenger receptors for cholesterol, fatty acids and sterols (SR-B1; CD36; SR-A1/2) located on macrophages are also involved in lung biology (8). Activation of macrophages and the changes induced in macrophage lipid metabolism and receptor expression also occur secondary to infective stimuli, e.g. lipopoly-saccharide (LPS). Mice deficient in apolipoprotein (apo) A-1, the key structural protein of HDL, show increased airway resistance, inflammation and alveolar fibrosis (12). The apoE-deficient mouse model of atherosclerosis has impaired macrophage cholesterol export, but also shows abnormal alveolar development and increased airway resistance (13). ABC-A1-deficient mice (homologous to human Tangier

disease), deficient in cholesterol export of early HDL apoA1-phospholipid discs, show reticuloendothelial lipid accumulation in the liver and spleen but also in the lungs allied with alveolar proteinosis and respiratory dysfunction (14). Similarly, ABC-G1-deficient mice, where the primary defect is in the later loading of partially lipidated HDL discs, also have a respiratory distress phenotype allied with immune activation, which may be a model or indeed a homologue of human pulmonary alveolar proteinosis (15). ABC-G1-deficient mice show abnormal lymphocyte responses with a reduction in the TH2 response, increased alveolar neutrophils, reduced eosinophils and enhanced LPS and bacterial responses. Some of these responses may be dependent on oxysterols, which are made following oxidation of cholesterol in surfactant by extraneous (e.g. bacterial) or immunological (neutrophil/macrophage oxidative bursts) mechanisms (16) and may help regulate specific liver-X receptors found on both macrophages and lung epithelial cells.

Oxidised phospholipids also trigger activation of toll receptors (e.g. TLR4) and the interplay of oxidation, inflammation and lipids including glycolipids (ceramides, sphingosine derivatives) in the lung (17) may resemble that seen in the liver in the pathogenesis of non-alcoholic steatohepatitis (18). Sphingolipids are known to play roles in alveolar function (19) and sphingosine-1-phosphate receptors (especially type 1) linked to rhoA have been suggested as possible drug targets for acute lung injury and COPD (20-22).

Statins and asthma

Basic mechanisms pertaining to asthma

Interest in the role of statins in asthma dates from the early studies that showed their possible immunomodulatory properties, e.g. in renal disease (23). In mouse models, statins reduce alveolar eosinophils, other inflammation-associated cells, interleukins (IL) 4-6, 18 prostaglandins, IFN-gamma, CCL17 and CXCL10, and improve airway responsiveness (24-26). The mechanism involved phosphorylation of peroxisomal proliferator-activating receptor alpha (PPAR-α) as PPAR-α-deficient macrophages show no additional response to LPS if treated with statins (25). Statins inhibit this phosphorylation by LPS-activated protein kinase C-alpha (PKC-α) acting through nuclear factor kappa B (NFκB). Some of these effects were reversed by mevalonic acid - a known antagonist of the isoprenoid effects of statins (27). Statins down-regulate IL-17-induced allergen response, CD11c(+) antigen presentation and lymphocyte TH1 and TH2 responses leading to reduced eosinophilia and IgE production through mevalonate-dependent mechanisms (28).

Statins reduce the proliferation of alveolar smooth muscle cells and matrix synthesis (29). Molecular dissection of the cellular response showed that the effects of statins could be mimicked by GGTI-286, a geranyl-geranyl transferase-I inhibitor, C3 exoenzyme, an inhibitor of Rho, and Y-27632, an inhibitor of Rho-kinase (29,30). In animal models, statins reduce airway inflammation, hyper-responsiveness and remodelling. These effects correlate with changes in nitric oxide biochemistry - a known effect of statins (31). Both asymmetric dimefhylarginine and inducible nitric oxide synthase levels are reduced by statins, but eNOS expression was increased. Statins also reduced nitro-tyrosine levels, a marker of oxidative stress in endothelium and the airway epithelium, as well as markers of alveolar cell injury and apoptosis, including cytochrome C, caspases 3 and 9 and apoptotic protease-activating factor 1 (Apaf-1) (31).

Clinical studies of Statins in asthma

Studies of human cohorts are less clear. A population database survey in Taiwan compared 3965 patients with asthma who had received statins and with 7843 age, gender-matched controls with asthma alone. The statin-treated group predictably included more patients with CVD, diabetes, hypertension and chronic kidney disease. In 974 patients with severe asthma, statin use was associated with an 18% (5-29) reduction in hospitalisation rate ($p = 0.006$) (32). A propensity score matched retrospective cohort study of 479 statin-treated patients and 958 non-treated individuals found a 55% (16-73) reduction in hospitalisations over a period of 1 year (33).

Only small-scale randomised clinical trials (RCTs) of statins have been performed in asthma. In a trial in 16 patients with asthma receiving inhaled corticosteroids, simvastatin 20-40 mg/day failed to reduce airway inflammation as assessed by exhaled NO and sputum eosinophil content or lung function assessed by bronchial hyper-responsiveness (34). In 8-week study of atorvastatin 40 mg, statins had no effect on peak expiratory flow rates, FEV1, methacholine bronchial hyper-responsiveness or asthma control despite a large LDL-C reduction (35). Other small trials show similar effects (36).

Corticosteroids activate indoleamine 2,3-dioxygenase (IDO) activity through increased IL-10 secretion acting through glucocorticoid-induced TNF receptor ligand, activation of p52 and the non-canonical NFκB pathway

(37). The control of dioxygenases is often related to PPAR mechanisms and leukotrienes are one of the group of fatty acids ligands for these receptors (38). An 8-week trial of 10 mg simvastatin in 50 patients showed that statin therapy allied to budesonide reduced sputum eosinophils counts and increased IL-10 and IDO activities (37). A further RCT in 71 smokers using the same statin dose and inhaled steroids showed no difference in FEV1 though an improvement in quality of life scores (39). In a small RCT in 12 patients, simvastatin 40 mg did not show any corticosteroid-sparing effect in eosinophilic asthma, although when patients were completely weaned off steroids, those receiving statins had lower symptom scores, better lung function and a reduced sputum eosinophil counts (40).

Summarising these trials, a systematic review in 2012 identified eight small studies: RCTs (Table 1) and two observational studies (41). Statin use was not associated with any consistent improvements in any clinical or respiratory function parameter, but improvements were observed in inflammation markers. The only data not included in the review were the spirometry performed in the Heart Protection Study (HPS). In HPS, FEV1 was similar in both groups (simvastatin 2.06 l vs. 2.05 l for placebo ($p = 0.5$); as was forced vital capacity (FVC) (2.82 l vs. 2.82 l ($p = 0.9$) and both were independent of pretreatment cholesterol levels (42). Overall, the studies of statins in asthma are too small and too short-term for conclusions to be drawn.

Table 1 *Randomised controlled trials identified in systematic reviews of statins in asthma (41) and chronic obstructive pulmonary disease (COPD) (44,52)*

Study first author	Number	Daily Statin dose	Duration (weeks)	End-point	Result
Asthma trials (41)					
Braganza (39)	71 smokers	Atorvastatin 40 mg	4	Lung function Hyper-responsiveness Airway inflammation Asthma control (ACQ) and quality of life (QoL)	Quality of life improved
Maneechotesuwan (37)	47 steroid treated	Simvastatin 10 mg	8	Airway inflammation	Sputum Eosinophils reduced Sputum IL-10 increased
Cowan (40)	43 steroid treated	Simvastatin 40 mg	12	Corticosteroid-sparing effect	Nil
Hothersall (35)	54 steroid treated	Atorvastatin 40 mg	24	Lung function Airway hyper-responsiveness Airway inflammation Asthma control (ACQ)	Sputum macrophages, leukotriene B4 reduced
Fahimi (36)	17	Atorvastatin 10 mg	4	Lung function	Nil
Menzies (34)	16 steroid-naive	Simvastatin 20/40 mg	4	Lung function Airway hyper-responsiveness Airway inflammation	Nil
COPD trials (44,52)					
Lee (53)	125 Pulmonary hypertension	Pravastatin 40 mg	26	Exercise tolerance time	Improved in statin group compared with baseline

Statins and COPD

Chronic obstructive pulmonary disease is a chronic condition usually affecting elderly people involving sometimes an asthmatic component (this is not seen in the majority of patients), frequent infective exacerbations and physiological dysfunction (ventilation-perfusion mismatching) allied to destructive lung disease (43). COPD combines elements of infection and airways disease (asthma), so the discussions of asthma above are relevant to COPD.

Basic mechanisms pertaining to COPD

Statins exert several anti-inflammatory effects, which are potentially beneficial to the asthma component of

COPD (see above). Statins also inhibit Th17 cells, which promote neutrophil-driven inflammation and also stimulate the uptake of apoptotic neutrophils by alveolar macrophages (efferocytosis), which is impaired in COPD. Satins also reduce the release of TGF-β from epithelial cells, a growth and remodelling factor potentially involved in small airway fibrosis (22). Animal studies have shown that statins inhibit the development emphysema following smoke or elastase lung exposure (44).

Clinical studies of statins in COPD

Studies of statins in COPD are based on case-control and cohort designs. Statins were originally reported to reduce rates of sepsis by 85% in a cohort study of 361 patients of whom 82 had received statin therapy (45), but this finding has not been reproduced in larger cohort studies (4). A matched cohort study (n = 76,232) and two case-control studies (397 influenza and 207 COPD deaths) found a reduced OR for influenza/pneumonia death [OR, 0.60(0.44-0.81)] and COPD death [0.17(0.07-0.42)] in the cohort study and improved hazard ratios in patients on statin therapy (46). A study in China of 1584 cases with COPD exacerbations and 5950 matched controls showed that any statin use was associated with a 30% (12-44) decreased risk of COPD exacerbations with a 40% (19-56) reduction seen with current statin use as well as a dose-dependent relationship (47). In a cohort study in Scotland, which included 1017 patients with COPD, use of statins reduced CVD morbidity and mortality in 443 secondary prevention patients by 65% (13-85) after a 0.52 mmol/l reduction in total cholesterol and non-significantly by 16% (-89 to +73) in 1274 primary prevention patients despite a 0.86 mmol/l reduction; far less than would be predicted (48). However, statin therapy was associated with a reduction in all-cause mortality in both primary and secondary prevention cohorts by 42% (3-65) and 39% (15-57) respectively (49). In the Veterans Administration Normative Aging Study, statin usage attenuated the decline in FEV1 (11 vs. 24 ml/year), a key feature of COPD, in a retrospective study of 803 men over 10 years after correction for other factors (50). Statin therapy was associated with reduced requirement for intubation and a reduction in the frequency of exacerbations and possibly an improvement in survival post exacerbation in a retrospective survey of 185 patients (51).

Systematic reviews of statins in COPD in 2012 identified nine studies (four retrospective cohorts, one nested case-control study of a retrospective cohort, one retrospective cohort and case series, two population-based analyses and one RCT (Table 1) (44,52). All these small studies showed a reduction in COPD exacerbations (n = 3), number of and time to COPD-related intubations (n = 1), improved pulmonary function (e.g. FEV(l) and FVC) (n = 1), exercise capacity (n = 1), COPD (n = 2) and all-cause mortality (n = 3) (44,52). The only RCT included 125 patients with COPD and pulmonary hypertension (53) and used a walking distance end-point that might be affected by statin-mediated improvement in endothelial function (5) rather than reflecting any improvement in COPD. A review of statin studies (n = 18) in community-acquired pneumonia as opposed to COPD found publication bias and a small potential benefit of statin therapy (54).

The HPS, which recruited patients at high risk of CVD, was not included in these reviews. In HPS, deaths from COPD were non-significantly reduced [simvastatin 26 (0.3%) vs. 39 (0.4%) placebo; RR 0.66; p = 0.1] but numbers were small. No difference was seen in all combined respiratory deaths and admissions [simvastatin 811 (7.9%) vs. 820 (8.0%) placebo; RR 0.98; p = 0.7], but there was a trend towards a reduction in this end-point for COPD [88 (0.9%) vs. 110 (1.1%); RR 0.79; p = 0.1) (42).

Other lipid-lowering drugs and lung function

Statins are the best known and most universally efficacious of the lipid-lowering drug therapies. They are not the only ones. Although statins primarily lower LDL-C, they can have secondary effects on other lipoprotein pathways. Statins enhance clearance of apoB-100-containing lipoproteins through the LDL ($apoB_{100}$/apoE) receptor and thus reduce triglyceride-rich lipoproteins (TGRL) in a dose proportional manner. Most statins are mild inhibitors of cholesterol ester transfer protein (CETP) function and they may regulate PPAR-α function through secondary phosphorylation (55); these effects may underlie the small increase in HDL-C seen with statin therapy (55). Thus, if LDL-C reduction is not the mechanism behind the postulated effects of statins on lung function, other lipid-lowering drugs acting on these alternative pathways also have potential roles in lung disease (20).

Triglyceride-modulating drugs

Peroxisomes are present in alveolar cells and are involved in alveolar lipid metabolism (56). Little is known about the relationship of PPAR agonists and lung disease. Fibrates (PPAR-α) agonists and thiazo-lidinediones (PPAR-γ agonist hypoglycaemic therapies) have been used for many years. Fibrates (PPAR-α agonists) also

have microvascular effects in atheroma-reducing proteinuria and retinopathy in patients with diabetes (57), but no studies have been performed with these drugs in lung disease. Both PPAR-α (58) and PPAR-γ are involved in the control of inflammation (58) and PPAR-α function influences liver-X-receptor function that may be responsible for the anti-inflammatory effects of these drugs. PPAR-γ may be relevant to lung disease given its associations with asthma, hypoxia, lung injury and fibrosis (59-62). Any effects seen in cohort studies may correlate with changes in HDL-C and triglycerides rather than cholesterol in studies of fibrates or pioglitazone in lung disease, although the pioglitazone effect may be confounded (especially in COPD) by its aldosterone - raising effect and consequent fluid retention.

HDL-modulating drugs

The functional biology of HDL is extremely complicated (63). It is difficult to measure HDL turnover as, unlike LDL, cholesterol and proteins have profoundly different kinetics; thus, HDL-C levels in plasma are a poor guide to HDL turnover. Reverse cholesterol transport (e.g. functions of ABC-A1 and ABC-G1) is only one component of the activity of HDL particles, which also includes apolipoproteins, which modulate immune function (63-65). ApoA-1 is a core component of HDL, whereas apoE is transferred to HDL from TGRL. ApoA-I (e.g. D-4F) and apoE mimetic peptides reduce alveolar eosinophil and neutrophil concentrations and improve cytokine and oxidative stress profiles in mouse models of asthma (66). HDL is known to be a highly effective anti-inflammatory, to contain specific enzymes to degrade lipid epoxides (paraoxonase) and proteins safely able to carry oxidised lipids and LPS (63) all with potential relevance to asthma and COPD.

Fibrates have indirect actions on HDL metabolism, but their prime action is to increase the turnover of TGRL and thus LDL clearance (67). Niacin has multiple actions on lipid profiles of which the largest component is to raise HDL-C through a decrease in its clearance rate (68). In mouse models of LPS-induced lung injury, niacin reduces lung inflammation markers through an action via NFκB (69). Niacin increases skin dendritic and Langerhans cell production of prostaglandins (D2 more than E2), thromboxane and leukotrienes, which might exacerbate asthma (70). There are no data on niacin and the incidence of asthma in man, although it may be possible to identify a signal if it exists in the 28,000 patient Heart Protection 2-THRIVE study (71). The greatest increase in HDL-C levels is seen with CETP inhibitors. These act to stop particle remodelling through cholesterol and triglyceride transfer and also reduce LDL-C levels. CETP inhibitors promote cholesterol efflux from cells to HDL particles through the ABC-A1 and ABC-G1 pathways. Their effects on lung cell function or physiology are unknown.

Atherosclerosis, chronic cardiac failure and COPD

Atherosclerosis and COPD share many risk factors including prior smoking, a male gender predominance, and greater incidence in patients with diabetes or renal disease. The presence and exacerbations in COPD are known to drive progression of atherosclerosis (72,73). In the OMEGA trial of omega-3 fatty acids, postacute myocardial infarction COPD was associated with a 1.77 [1.01-3.10]-fold increase in CVD events (74). Severe airflow limitation (FEV1 < 50% predicted) in COPD was associated with CVD risk factors and CRP levels in 3877 men in the Tromso heart study (75). A New Zealand cohort study of 1687 patients (age 71 years) admitted with COPD included 596 on statin and 1091 not on treatment. Patients prescribed statins were more often men (59% vs. 49%), have CVD (59% vs. 25%), heart failure (48% vs. 25%) or diabetes (35% vs. 12%). In this study, 671 deaths occurred during 4 years and statin use was associated with a 31% (16-42) reduction in mortality after adjustment for CVD risk factors and frusemide use (a crude proxy for the presence of heart failure) (76). Coronary atherosclerosis is associated with LDL-C-induced endothelial dysfunction, including erectile dysfunction, another marker of CVD (77) as well as left ventricular dysfunction and chronic heart failure (CHF). Deterioration in CHF often occurs secondary to infections as well as predisposing to them. Thus, CHF and COPD could be closely linked. The association of markers of COPD with CHF has been shown in epidemiological studies of CVD. Cases of new-onset CHF were identified in 13,600 patients in the Atherosclerosis Risk in Communities cohort (78). After 15 years of follow-up, 1369 (10%) participants developed CHF. Age- and height-adjusted odds ratios for CHF increased with quartiles of FEV1 with gender, race and smoking. After adjustment for CVD risk factors and height, the hazard ratios for quartile 1 vs. quartile 4 were 3.91(2.40-6.35) for FEV1 in white women, 3.03 (2.12-4.33) for white men, less for African Americans, but all remained significant after adjustment for markers of inflammation. An association with CHF was also seen for reported new diagnoses of COPD, but not for asthma. Similarly, in 3642 patients from the Multi-Ethnic Study of Atherosclerosis where emphysematous damage was measured on thoracic computerised tomography, carotid intima media thickness (cIMT), a known marker of atheroma burden (79), was associated with reduced FEV1 especially in smokers even after adjustment for CVD risk factors and inflammation (80). Ankle-brachial index (a marker of peripheral arterial disease, PAD) was associated with extent of emphysema, but no relation

was found with coronary artery calcium scores. In a subgroup analysis of 253 patients with COPD from the Rotterdam cohort study (all aged > 55 years), the presence of COPD was associated with a twofold increase in the prevalence of carotid artery thickening (cIMT > 2.5 mm) and the presence of lipid-rich plaque on magnetic resonance imaging (81).

Atherosclerosis affects multiple vascular beds and thus patients with PAD almost always have coronary atherosclerosis. In a study including 3371 patients with PAD, the presence of COPD was associated with an increased risk of both lung and extra-pulmonary cancer mortality (82). Similar data were reported from Japan (83). A cohort study in the Netherlands compared 330 patients with PAD and COPD treated with statins with 480 patients with PAD alone. Statin use was associated with a 52% [0-77] improvement in 30-day survival and a 33% (14-48) improvement in 1-year survival, but only high-dose statin therapy was associated with improved short-term survival (84).

Statins improve coronary and peripheral endothelial function and thus would be expected to improve lung perfusion secondary to larger effects on extracellular fluid volumes through actions on cardiac and renal function. Their direct effects on pulmonary endothelium have been demonstrated in pulmonary hypertension (5), but are less extensive than those induced by inhibition of phosphodiesterase-5 or endothelin-1. The presence of subclinical left ventricular dysfunction or CHF could be a significant comorbidity that is the real target of statin therapy in COPD with predictable improvements in endothelial function and other surrogate markers (5) such as the 6-min walk distance by analogy with studies in pulmonary hypertension and one trial in COPD trial (53). Coronary artery disease, left ventricular hypertrophy (with added risk of ischaemia) and inflammation may contribute to raised troponins in COPD (85,86). Fourfold elevations in troponins are routinely found in COPD exacerbations (86,87). Many patients with COPD show evidence of left ventricular dysfunction including elevations in N-terminal B-type natriuretic peptide (BNP) and troponins (86,88). The only systematic data from a large CVD prevention statin study is that collected in HPS where statin therapy was associated with a small non-significant decrease in COPD deaths or admissions. No data have been published on BNP or troponin concentrations from this trial. This may be an indication for trials of statins and renin-angiotensin-modulating therapies in COPD.

Conclusions

There are good theoretical and biochemical reasons why statins should benefit patients with acute and chronic lung dysfunction. Lipids, isoprenoid cholesterol intermediates and dysfunctional macrophages are found in both atherosclerosis and chronic lung disease. It may be possible to identify subtypes of COPD based on airway response, inflammation, biochemical and imaging markers that would respond well to lipid-lowering therapies (89). One recent trial has compared the use of an inflammation-based algorithm to define a subtype of COPD in which to institute statins as well as other therapies in 35 patients. The St George's respiratory questionnaire score was improved by 14 vs. 3.5 points ($p < 0.001$) with parallel improvements in quality of life scores (90). Small scale but highly specific studies using imaging technologies may also be used to investigate the role of lipid-lowering therapies on the progression of COPD (91). However, currently in COPD, clinical studies of lipid-lowering therapies remain small, cohort studies inadequate and randomised control trials vastly underpowered to detect any significant clinical effects (2). Well-designed surrogate marker studies and large-scale clinical trials on clinical pulmonary end-points are still required to identify whether statins or other lipid-lowering drugs have a role in the treatment of lung disease.

The basic biochemical mechanisms of how lipid-lowering drugs affect lung cell function may be clinically irrelevant. The meta-analyses of small-scale trials show little effect for statins to date and there are no data for any other lipid-lowering drugs. The interesting link between inflammation and infection and destabilisation of atherosclerotic plaque may also occur in exacerbations of asthma and COPD with their increases in plasma cytokines and immune cell activation. Thus, the actions of statin in preventing plaque destabilisation and secondary cardiac insufficiency may explain their epidemiological association with better outcomes in asthma and COPD. Despite these associations, statins, beta-blockers and acute coronary intervention are underused in patients with COPD despite the high rate of occurrence of CVD risk factors in this population (92).

Disclosure

None.

References

1 Wierzbicki AS, Poston R, Ferro A. The lipid and non-lipid effects of statins. *Pharmacol Ther* 2003; 99(1): 95-112.

2 Beri A, Sural N, Mahajan SB. Non-atheroprotective effects of statins: a systematic review. *Am J Cardiovasc Drugs* 2009; 9(6): 361-70.

3 Kor DJ. Statins and acute lung injury: Holy Grail or the next to fail? *Crit Care Med* 2012; 40(5): 1661-3.

4 Janda S, Young A, Fitzgerald JM, Etminan M, Swiston J. The effect of statins on mortality from severe infections and sepsis: a systematic review and meta-analysis, *J Crit Care* 2010; 25(4): 656-22.

5 Katsiki N, Wierzbicki AS, Mikhailidis DP. Pulmonary arterial hypertension and statins: an update. *Curr Opin Cardiol* 2011; 26(4): 322-6.

6 Young RP, Hopkins R, Eaton TE. Pharmacological actions of statins: potential utility in COPD. *Eur Respir Rev* 2009; 18(114): 222-32.

7 Saad N, Camus P, Suissa S, Ernst P. Statins and the risk of interstitial lung disease: a cohort study. *Thorax* 2013; 68(4): 361-4.

8 Gowdy KM, Fessier MB. Emerging roles for cholesterol and lipoproteins in lung disease. *Pulm Pharmacol Ther* 2013; 26(4): 430-7.

9 Roszell BR, Tao JQ, Yu KJ, Huang S, Bates SR. Characterization of the Niemann-Pick C pathway in alveolar type II cells and lamellar bodies of the lung. *Am J Physiol Lung Cell Mol Physiol* 2012; 302 (9): L919-32.

10 Meaney S, Bonfield TL, Hansson M, Babiker A, Kavuru MS, Thomassen MJ. Serum cholestenoic acid as a potential marker of pulmonary cholesterol homeostasis: increased levels in patients with pulmonary alveolar proteinosis, *J Lipid Res* 2004; 45 (12): 2354-60.

11 Leonenko Z, Gill S, Baoukina S et al. An elevated level of cholesterol impairs self-assembly of pulmonary surfactant into a functional film. *Biophys J* 2007; 93(2): 674-83.

12 Wang W, Xu H, Shi Y et al. Genetic deletion of apolipoprotein A-I increases airway hyperrespon-siveness, inflammation, and collagen deposition in the lung, *J Lipid Res* 2010; 51(9): 2560-70.

13 Massaro D, Massaro GD. ApoetmlUnc mice have impaired alveologenesis, low lung function, and rapid loss of lung function. *Am J Physiol Lung Cell Mol Physiol* 2008; 294(5): L991-7.

14 Bates SR, Tao JQ, Collins HL, Francone OL, Rothblat GH. Pulmonary abnormalities due to ABCA1 deficiency in mice. *Am J Physiol Lung Cell Mol Physiol* 2005; 289(6): L980-9.

15 Wojcik AJ, Skaflen MD, Srinivasan S, Hedrick CC. A critical role for ABCG1 in macrophage inflammation and lung homeostasis. *J Immunol* 2008; 180 (6): 4273-82.

16 Pulfer MK, Murphy RC. Formation of biologically active oxysterols during ozonolysis of cholesterol present in lung surfactant, *J Biol Chem* 2004; 279 (25): 26331-8.

17 Imai Y, Kuba K, Neely GG et al. Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. *Cell* 2008; 133 (2): 235-49.

18 Wierzbicki AS, Oben J. Nonalcoholic fatty liver disease and lipids. *Curr Opin Lipidol* 2012; 23(4): 345-52.

19 Uhlig S, Gulbins E. Sphingolipids in the lungs. *Am J Respir Crit Care Med* 2008; 178(11): 1100-14.

20 Zhou Q, Gensch C, Liao JK. Rho-associated coiled-coil-forming kinases (ROCKs): potential targets for the treatment of atherosclerosis and vascular disease. *Trends Pharmacol Sci* 2011; 32(3): 167-73.

21 Edmonds Y, Milstien S, Spiegel S. Development of small-molecule inhibitors of sphingosine-1-phosphate signaling. *Pharmacol Ther* 2011; 132(3): 352-60.

22 Barnes PJ. Future treatments for chronic obstructive pulmonary disease and its comorbidities. *Proc Am Thorac Soc* 2008; 5(8): 857-64.

23 Holdaas H, Fellstrom B, Cole E et al. Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study. *Am J Transplant* 2005; 5(12): 2929-36.

24 McKay A, Leung BP, Mclnnes IB, Thomson NC, Liew FY. A novel anti-inflammatory role of simvastatin in a murine model of allergic asthma. *J Immunol* 2004; 172(5): 2903-8.

25 Paumelle R, Blanquart C, Briand O et al. Acute antiinflammatory properties of statins involve peroxisome proliferator-activated receptor-alpha via inhibition of the protein kinase C signaling pathway. *Circ Res* 2006; 98(3): 361-9.

26 Montero MT, Hernandez O, Suarez Y et al. Hydroxymethylglutaryl-coenzyme A reductase inhibition stimulates caspase-1 activity and Thl-cytokine release in peripheral blood mononuclear cells. *Atherosclerosis* 2000; 153(2): 303-13.

27 Zeki AA, Franzi L, Last J, Kenyon NJ. Simvastatin inhibits airway hyperreactivity: implications for the mevalonate pathway and beyond. *Am J Respir Crit Care Med* 2009; 180(8): 731-40.

28 Imamura M, Okunishi K, Ohtsu H et al. Pravastatin attenuates allergic airway inflammation by suppressing antigen sensitisation, interleukin 17 production and antigen presentation in the lung. *Thorax* 2009; 64(1): 44-9.

29 Schaafsma D, Dueck G, Ghavami S et al. The mevalonate cascade as a target to suppress extracellular matrix synthesis by human airway smooth muscle. *Am J Respir Cell Mol Biol* 2011; 44(3): 394-403.

30 Takeda N, Kondo M, Ito S, Ito Y, Shimokata K, Kume H. Role of RhoA inactivation in reduced cell proliferation of human airway smooth muscle by simvastatin. *Am J Respir Cell Mol Biol* 2006; 35(6): 722-9.

31 Ahmad T, Mabalirajan U, Sharma A et al. Simvastatin improves epithelial dysfunction and airway hyperresponsiveness: from asymmetric dimethyl-arginine to asthma. *Am J Respir Cell Mol Biol* 2011; 44(4): 531-9.

32 Huang CC, Chan WL, Chen YC et al. Statin use in patients with asthma: a nationwide population-based study. *Eur J Clin Invest* 2011;41(5): 507-12.

33 Lokhandwala T, West-Strum D, Banahan BF, Bentley JP, Yang Y. Do statins improve outcomes in patients with asthma on inhaled corticosteroid therapy? A retrospective cohort analysis *BMJ Open* 2012; 2(3): pii: e001279.

34 Menzies D, Nair A, Meldrum KT, Fleming D, Barnes M, Lipworth BJ. Simvastatin does not exhibit therapeutic anti-inflammatory effects in asthma. *J Allergy Clin Immunol* 2007; 119(2): 328-35.

35 Hothersall EJ, Chaudhuri R, McSharry C et al. Effects of atorvastatin added to inhaled corticosteroids on lung function and sputum cell counts in atopic asthma. *Thorax* 2008; 63(12): 1070-5.

36 Fahimi F. Do statins improve lung function in asthmatic patients? A randomized and double blind trial. *Iranian J Pharm Sci* 2009; 5(1): 13-20.

37 Maneechotesuwan K, Ekjiratrakul W, Kasetsinsombat K, Wongkajornsilp A, Barnes PJ. Statins enhance the anti-inflammatory effects of inhaled corticosteroids in asthmatic patients through increased induction of indoleamine 2, 3-dioxygenase. *J Allergy Clin Immunol* 2010; 126(4): 754-62.

38 Zhao J, O'Donnell VB, Balzar S, St Croix CM, Trudeau JB, Wenzel SE. 15-Lipoxygenase 1 interacts with phosphatidylethanolamine-binding protein to regulate MAPK signaling in human airway epithelial cells. *Proc Natl Acad Sci USA* 2011; 108(34): 14246-51.

39 Braganza G, Chaudhuri R, McSharry C et al. Effects of short-term treatment with atorvastatin in smokers with asthma - a randomized controlled trial. *BMC Pulm Med* 2011; 11: 16.

40 Cowan DC, Cowan JO, Palmay R, Williamson A, Taylor DR. Simvastatin in the treatment of asthma: lack of steroid-sparing effect. *Thorax* 2010; 65(10): 891-6.

41 Suva D, Couto M, Delgado L, Moreira A. A systematic review of statin efficacy in asthma. *J Asthma* 2012; 49(9): 885-94.

42 Heart Protection Study Group. The effects of cholesterol lowering with simvastatin on cause-specific mortality and on cancer incidence in 20,536 high-risk people: a randomised placebo-controlled trial [ISRCTN48489393]. *BMC Med* 2005; 3: 6.

43 van Eeden SF, Sin DD. Chronic obstructive pulmonary disease: a chronic systemic inflammatory disease. *Respiration* 2008; 75(2): 224-38.

44 Janda S, Park K, Fitzgerald JM, Etminan M, Swiston J. Statins in COPD: a systematic review. *Chest* 2009; 136(3): 734-43.

45 Almog Y, Shefer A, Novack V et al. Prior statin therapy is associated with a decreased rate of severe sepsis. *Circulation* 2004; 110(7): 880-5.

46 Frost FJ, Petersen H, Tollestrup K, Skipper B. Influenza and COPD mortality protection as pleiotropic, dose-dependent effects of statins. *Chest* 2007; 131(4): 1006-12.

47 Wang MT, Lo YW, Tsai CL et al. Statin use and risk of COPD exacerbation requiring hospitalization. *Am J Med* 2013; 126(7): 598-606.

48 Baigent C, Blackwell L, Emberson J et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010; 376 (9753): 1670-81.

49 Sheng X, Murphy MJ, Macdonald TM et al. Effect of statins on total cholesterol concentrations, cardiovascular morbidity, and all-cause

mortality in chronic obstructive pulmonary disease: a population-based cohort study. *Clin Ther* 2012; 34(2): 374-84.

50 Alexeeff SE, Litonjua AA, Sparrow D, Vokonas PS, Schwartz J. Statin use reduces decline in lung function: VA Normative Aging Study. *Am J Respir Crit Care Med* 2007; 176(8): 742-7.

51 Blamoun AI, Batty GN, DeBari VA, Rashid AO, Sheikh M, Khan MA. Statins may reduce episodes of exacerbation and the requirement for intubation in patients with COPD: evidence from a retrospective cohort study. *Int J Clin Tract* 2008; 62(9): 1373-8.

52 Dobler CC, Wong KK, Marks GB. Associations between statins and COPD: a systematic review. *BMC Pulm Med* 2009; 9: 32.

53 Lee TM, Chen CC, Shen HN, Chang NC. Effects of pravastatin on functional capacity in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *Clin Sci (Lond)* 2009; 116(6): 497-505.

54 Khan AR, Riaz M, Bin Abdulhak AA et al. The role of statins in prevention and treatment of community acquired pneumonia: a systematic review and meta-analysis. *PLoS ONE* 2013; 8(1): e52929.

55 Yamashita S, Tsubakio-Yamamoto K, Ohama T, Nakagawa-Toyama Y, Nishida M. Molecular mechanisms of HDL-cholesterol elevation by statins and its effects on HDL functions, *J Atheroscler Thromb* 2010; 17(5): 436-51.

56 Karnati S, Baumgart-Vogt E. Peroxisomes in mouse and human lung: their involvement in pulmonary lipid metabolism. *Histochem Cell Biol* 2008; 130(4): 719-40.

57 Ansquer JC, Foucher C, Aubonnet P, Le MK. Fibrates and microvascular complications in diabetes - insight from the FIELD study. *Curr Pharm Des* 2009; 15(5): 537-52.

58 Belvisi MG, Hele DJ. Peroxisome proliferator-activated receptors as novel targets in lung disease. *Chest* 2008; 134(1): 152-7.

59 Spears M, McSharry C, Thomson NC. Peroxisome proliferator-activated receptor-gamma agonists as potential anti-inflammatory agents in asthma and chronic obstructive pulmonary disease. *Clin Exp Allergy* 2006; 36(12): 1494-504.

60 Kulkarni AA, Woeller CF, Thatcher TH, Ramon S, Phipps RP, Sime PJ. Emerging PPARgamma-independent role of PPARgamma ligands in lung diseases. *PPAR Res* 2012; 2012: 705352.

61 Bauer CM, Zavitz CC, Botelho FM et al. Treating viral exacerbations of chronic obstructive pulmonary disease: insights from a mouse model of cigarette smoke and H1N1 influenza infection. *PLoS ONE* 2010; 5(10): e13251.

62 Lakatos HF, Thatcher TH, Kottmann RM, Garcia TM, Phipps RP, Sime PJ. The role of PPARs in lung fibrosis. *PPAR Res* 2007; 2007: 71323.

63 Florentin M, Liberopoulos EN, Wierzbicki AS, Mikhailidis DP. Multiple actions of high-density lipoprotein. *Curr Opin Cardiol* 2008; 23(4): 370-8.

64 Sorci-Thomas MG, Thomas MJ. High density lipoprotein biogenesis, cholesterol efflux, and immune cell function. *Arterioscler Thromb Vasc Biol* 2012; 32(11): 2561-5.

65 Wierzbicki AS. Lipoproteins: from A to B and maybe C-III. *Int J Clin Pract* 2008; 62(5): 674-6.

66 Yao X, Remaley AT, Levine SJ. New kids on the block: the emerging role of apolipoproteins in the pathogenesis and treatment of asthma. *Chest* 2011; 140(4): 1048-54.

67 Wierzbicki AS. Fibrates in the treatment of cardiovascular risk and atherogenic dyslipidaemia. *Curt Opin Cardiol* 2009; 24(4): 372-9.

68 Wierzbicki AS. Niacin: the only vitamin that reduces cardiovascular events. *Int J Clin Pract* 2011; 65(4): 379-85.

69 Kwon WY, Suh GJ, Kim KS, Kwak YH. Niacin attenuates lung inflammation and improves survival during sepsis by downregulating the nuclear factor-kappaB pathway. *Crit Care Med* 2011; 39(2): 328-34.

70 Popp L, Haussier A, Olliges A et al. Comparison of nociceptive behavior in prostaglandin E, F, D, prostacyclin and thromboxane receptor knockout mice. *Eur J Pain* 2009; 13(7): 691-703.

71 HPS2-THRIVE Investigators. A randomized trial of the long-term clinical effects of raising hdl cholesterol with extended release niacin/laropiprant. Heart protection study 2-treatment of HDL to reduce the incidence of vascular events (HPS2-THRIVE). Clini-calTrials.gov 2009 February 2NCT00461630. http:// clinicaltrials.gov/ct2/show/NCT00461630 (accessed 1 June 2013).

72 van Eeden S, Leipsic J, Paul Man SF, Sin DD. The relationship between lung inflammation and cardiovascular disease. *Am J Respir Crit Care Med* 2012; 186(1): 11-6.

73 Man SF, van Eeden S, Sin DD. Vascular risk in chronic obstructive pulmonary disease: role of inflammation and other mediators. *Can J*

Cardiol 2012; 28(6): 653-61.

74 Liosis S, Bauer T, Schiele R et al. Predictors of 1-year mortality in patients with contemporary guideline-adherent therapy after acute myocardial infarction: results from the OMEGA study. *Clin Res Cardiol* 2013; 102(9): 671-7.

75 Melbye H, Halvorsen DS, Hartz I et al. Bronchial airflow limitation, smoking, body mass index, and statin use are strongly associated with the C-reactive protein level in the elderly. The Tromso Study 2001. *Respir Med* 2007; 101(12): 2541-9.

76 Lawes CM, Thornley S, Young R et al. Statin use in COPD patients is associated with a reduction in mortality: a national cohort study. *Prim Care Respir J* 2012; 21(1): 35-40.

77 Blanker MH, Bohnen AM, Groeneveld FP et al. Correlates for erectile and ejaculatory dysfunction in older Dutch men: a community-based study. *J Am Geriatr Soc* 2001; 49(4): 436-42.

78 Agarwal SK, Heiss G, Barr RG et al. Airflow obstruction, lung function, and risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study. *Eur J Heart Fail* 2012; 14(4): 414-22.

79 Wierzbicki AS. New directions in cardiovascular risk assessment: the role of secondary risk stratification markers. *Int J Clin Pract* 2012; 66(7): 622-30.

80 Barr RG, Ahmed FS, Carr JJ et al. Subclinical atherosclerosis, airflow obstruction and emphysema: the MESA Lung Study. *Eur Respir J* 2012; 39(4): 846-54.

81 Lahousse L, van den Bouwhuijsen Q, Loth DW et al. Chronic obstructive pulmonary disease and lipid core carotid artery plaques in the elderly: the Rotterdam Study. *Am J Respir Crit Care Med* 2012; 187(1): 58-64.

82 van Gestel YR, Hoeks SE, Sin DD et al. COPD and cancer mortality: the influence of statins. *Thorax* 2009; 64(11): 963-7.

83 Ishida W, Kajiwara T, Ishii M et al. Decrease in mortality rate of chronic obstructive pulmonary disease (COPD) with statin use: a population-based analysis in Japan. *Tohoku J Exp Med* 2007; 212(3): 265-73.

84 van Gestel YR, Hoeks SE, Sin DD et al. Effect of statin therapy on mortality in patients with peripheral arterial disease and comparison of those with versus without associated chronic obstructive pulmonary disease. *Am J Cardiol* 2008; 102(2): 192-6.

85 Stone IS, Barnes NC, Petersen SE. Chronic obstructive pulmonary disease: a modifiable risk factor for cardiovascular disease? *Heart* 2012; 98: 1055-62.

86 Stone IS, Petersen SE, Barnes NC. Raised troponin in COPD: clinical implications and possible mechanisms. *Heart* 2013; 99(2): 71-2.

87 Soyseth V, Bhatnagar R, Holmedahl NH et al. Acute exacerbation of COPD is associated with fourfold elevation of cardiac troponin T. *Heart* 2013; 99(2): 122-6.

88 Marcun R, Sustic A, Brguljan PM et al. Cardiac biomarkers predict outcome after hospitalisation for an acute exacerbation of chronic obstructive pulmonary disease. *Int J Cardiol* 2012; 161(3): 156-9.

89 Barker BL, Brightling CE. Phenotyping the heterogeneity of chronic obstructive pulmonary disease. *Clin Sri (Lond)* 2013; 124(6): 371-87.

90 McDonald VM, Higgins I, Wood LG, Gibson PG. Multidimensional assessment and tailored interventions for COPD: respiratory Utopia or common sense? *Thorax* 2013; 68(7): 691-4.

91 Galban CJ, Han MK, Boes JL et al. Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. *Nat Med* 2012; 18(11): 1711-5.

92 Stefan MS, Bannuru RR, Lessard D, Gore JM, Lindenauer PK, Goldberg RJ. The impact of COPD on management and outcomes of patients hospitalized with acute myocardial infarction: a 10-year retrospective observational study. *Chest* 2012; 141 (6): 1441-8.