



Potential benefits of statins on morbidity and mortality in chronic obstructive pulmonary disease: a review of the evidence

R P Young,¹ R Hopkins,¹ T E Eaton²

¹ Department of Medicine, University of Auckland, Auckland; ² Respiratory Services, Auckland City Hospital, Auckland, New Zealand

Correspondence to: Dr R Young, Department of Medicine, Auckland Hospital, Private Bag 92019, Auckland, New Zealand; roberty@adhb.govt.nz

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ABSTRACT

Studies show reduced forced expiratory volume in 1 s (FEV₁) in patients with chronic obstructive pulmonary disease (COPD) is an important independent predictor of cardiovascular death and is characterised by both pulmonary and systemic inflammation. Evidence shows statins have important anti-inflammatory effects in both the lungs and arteries. Although randomised control trials are yet to be reported, non-randomised studies have consistently shown benefit in COPD patients taking statins compared with those not. These include reductions in both cardiovascular and respiratory morbidity/mortality. Other potential benefits include a reduced decline in FEV₁ and reduced risk of lung cancer. It is argued that confounding by a "healthy user effect" is unlikely to explain the observed benefit. Given the undisputed benefit of statins in high risk populations and the growing body of data suggesting statins may benefit patients with COPD, the question arises "Should statins be considered more often in patients with COPD?".

Patients with chronic obstructive pulmonary disease (COPD) die primarily from complications of smoking, specifically coronary artery disease (CAD), COPD related complications (respiratory failure with or without chest infection), lung cancer and stroke.^{1–5} Collectively these account for over 80% of deaths in COPD.^{1–7} CAD is the most common cause of death, estimated to affect between 20–50%,^{1–5} but both lung cancer and COPD related complications are also common, estimated at 20–30% and 10–30% of deaths, respectively.^{1–6}

COPD and reduced forced expiratory volume in 1 s (FEV₁) are both powerful predictors of mortality. Studies show that the severity of COPD, based on FEV₁, predicts survival with an estimated mortality of 50% over 5 years.^{3,8,9} This is comparable to mortality from advanced CAD and many forms of cancer. Nevertheless, to date only smoking cessation, long term oxygen, and lung reduction surgery have shown benefit in this regard.¹⁰ Bronchodilating and anti-inflammatory treatment for COPD have been shown to have only a limited effect on decline in lung function¹¹ and limited reduction on survival.^{9,10,12–15} Despite being the fourth leading cause of death in developed countries, COPD is significantly under diagnosed^{16,17} and predicted to be the third leading cause in the coming years. Urgent efforts are required to address this major public health problem.

LUNG FUNCTION AND CARDIOVASCULAR MORTALITY

Reduced FEV₁ is a powerful marker for CAD^{18–20} and mortality from cardiovascular disease^{21,22} after

controlling for several potential confounders.²³ Although smoking is implicated in both COPD and CAD, it is those smokers with poor lung function, estimated to be 20–30% of all smokers,^{10,24,25} who are at greatest risk of a coronary death.^{3,6} Indeed for men, the combination of reduced FEV₁ and smoking exposure are better predictors of future mortality from heart disease than serum cholesterol values.¹⁰ In this study, where FEV₁ was compared with traditional risk factors, it is striking that reduced FEV₁ ranks second only to smoking, well above blood pressure, social class and cholesterol^{19,20} as a predictor for all cause mortality in both men and women. Further support for the importance of FEV₁ in cardiovascular risk assessment comes from two studies showing that patients with COPD have a higher prevalence of coexisting cardiovascular risk factors than those with normal lung function^{26,27}; specifically, those with COPD had a higher prevalence (and presumed risk) for diabetes, hypertension and cardiovascular disease.²⁶ This study showed that by including COPD (based on spirometry) with traditional risk factors, further refinement of cardiovascular risk could be achieved. Although the second study showed that the relationship between lung function and cardiovascular death was reduced after adjustment for traditional risk factors,²⁷ COPD remained an independent and significant risk factor in its own right. This observation is consistent with the hypothesis that the tendency to exaggerated systemic inflammation underlies both COPD and cardiovascular disease (discussed further below).²⁸ Given the increased CAD risk associated with COPD (or reduced FEV₁), it seems very reasonable to consider drug treatment to address this risk specifically. On this basis alone, it could be argued that HMG CoA reductase inhibitors (statins) would benefit many patients with COPD for primary prevention of CAD.

To exemplify the extent to which lung function is relevant to cardiovascular mortality, the authors highlight data from several studies.^{21–23} In these studies, reduced FEV₁ is shown to be more important than smoking exposure after adjustment for other variables (fig 1), not only in cardiovascular mortality but in death from all causes. Among smokers of comparable smoking exposure, reduced FEV₁ was associated with as much as a 3–4 fold greater cardiovascular mortality.^{21–23} Remarkably, this effect also extends to non-smokers where poor FEV₁ predicts a risk 2–3 fold greater than that of heavy smokers with normal lung function.^{21,22} We conclude that FEV₁ is an

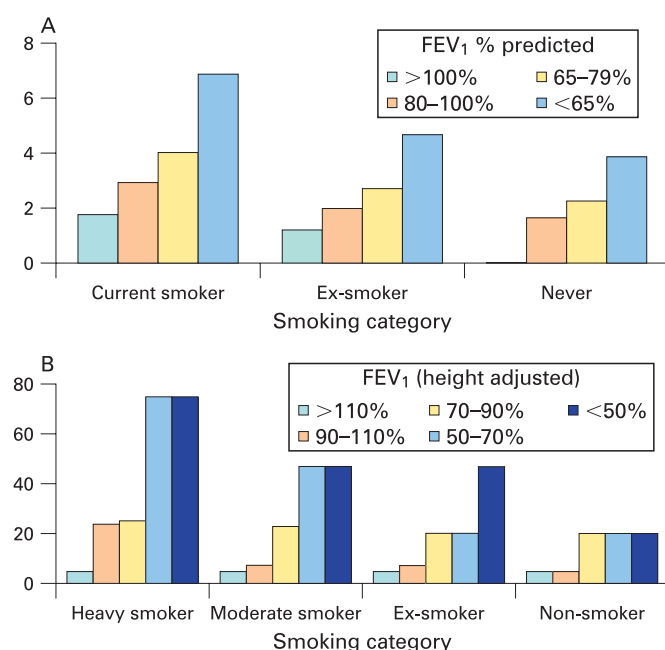


Figure 1 Relationship between forced expiratory volume in 1 s (FEV₁), smoking status and (A) odds ratio for cardiovascular mortality (modified from Tockman *et al*⁷¹) and (B) all cause mortality rate (%) (modified from Olofson *et al*⁷²).

important marker of future cardiovascular mortality and that its effects on mortality are both independent of and synergistic with those from smoking. The underlying mechanism for this may relate to systemic inflammation which has been implicated in COPD and cardiovascular disease.

COPD AND LUNG CANCER

Although smoking exposure has a central role in both, only approximately 10–15% of chronic smokers develop lung cancer²⁹ while 20–30% develop COPD.^{10 24 30} Epidemiological studies show that smokers with COPD are at considerably higher risk of lung cancer than smokers with normal lung function,^{31–33} contributing over 50% of all lung cancer cases.^{34 35} There is growing evidence that COPD and lung cancer result from common pathological responses to inflammatory processes in the lung,^{16 36–38} and that the individual smoker's response to these processes are genetically determined.^{39–42} Collectively, these studies show that an overlapping subgroup of smokers (and ex-smokers), characterised by reduced FEV₁, are at increased risk of CAD, COPD and lung cancer.

COPD AND SYSTEMIC INFLAMMATION

Recent studies have shown a consistent association between biomarkers of systemic inflammation, primarily C reactive protein (CRP), and severity of COPD.^{43–49} In a population based study (NHANES III), those with severe airways obstruction (FEV₁ % predicted <50%) were twice as likely to have an elevated CRP value.⁴³ This study also reports an additive effect between the presence of moderate–severe COPD and elevated CRP on risk of cardiac injury.⁴³ The finding of an association between systemic inflammation in both moderate and severe COPD support epidemiological data showing that even small reductions in FEV₁ can increase cardiac morbidity and mortality 2–3 fold in the general community.^{44 45} Surprisingly, this relationship with CRP exists across smokers, ex-smokers and non-smokers,^{18 46–49}

although one small population study failed to identify any association.⁵⁰ Two studies have examined the predictive utility of CRP in outcome for patients with COPD, although the findings were inconclusive.^{51 52} There is certainly a greater tendency to consider COPD a systemic disease where weight loss predates lung function decline⁵³ and non-pulmonary manifestations include diseases such as anaemia and osteoporosis.^{26 45–47 53}

In summary, there is growing evidence that COPD is associated with systemic inflammation that is exaggerated by, but not dependent on, cigarette smoking. It is possible other aero-pollutants are important here⁵⁴ and that this susceptibility to systemic inflammation may be in part genetically conferred.^{55 56} These observations would be consistent with the hypothesis that lung function is not just a “barometer” to the lung's response to airway aero-pollutant exposure but also a marker of a more general systemic response.³⁹ If this were true, then drug treatment with systemic anti-inflammatory benefits may be beneficial in reducing other inflammatory based diseases such as CAD, lung cancer or stroke. Interestingly, in a population study from Norway, statin use was associated with a decrease in CRP concentration.⁵⁷ More importantly, statin use in a recently reported randomised control trial of 18 000 healthy people with elevated CRP and normal lipid profile reported reductions of 40–60% in cardiovascular end points.⁵⁸ If systemic inflammation is considered an important determinant of mortality in COPD and a target for preventive treatment (as it is in CAD), then statins may have significant additional benefits in COPD where elevated CRP is a feature^{43–49} and existing treatments target pulmonary inflammation only.⁵⁹ In this regard, statin treatment may represent a new and much needed adjunct treatment in the management of COPD.

STATINS AND THEIR ANTI-INFLAMMATORY EFFECTS ON ARTERIES AND THE LUNGS

In the management of coronary artery disease, statins play a central role by significantly reducing the serum cholesterol concentration. However, their role in reduction of mortality and morbidity in CAD is thought to relate as much to their anti-inflammatory effects as to their cholesterol lowering effects (that is, pleiotropy).⁶⁰ Studies in both primary and secondary prevention show that statin use is associated with a relative 30% reduction in mortality (table 1).⁶¹ The absolute benefit of statin treatment in secondary prevention (in terms of absolute risk reduction) is much greater and thus more cost effective than in those at lower risk.⁶² To maximise the benefit of statin therapy, treatment is targeted at patients who have established CAD or those who have a very high baseline risk of having a heart attack. People in the latter group are best identified by assessing their risk based on several clinical parameters such as age, cholesterol value, blood pressure and family history (for example, Framingham score).

There is now considerable evidence suggesting that statins have immunomodulatory effects that could attenuate the inflammatory effects of smoking on the lung,^{63–66} not just the arteries. These include reducing neutrophil migration, cytokine production, adverse matrix remodelling, small airways inflammation, and apoptosis.^{64–68} Of note, neutrophil migration into the mouse lung following lipopolysaccharide (LPS) induced inflammation is inhibited by statins.⁶⁸ As neutrophil mediated inflammation is central to smoking effects on the lung in COPD,^{63–65 67 68} this effect of statins may be additive to those of inhaled corticosteroids.^{67 68} Persistence of neutrophils in COPD due to inhibition of neutrophil apoptosis and/or phagocytic clearance might also be relevant to attenuating persisting

Table 1 Risk reduction associated with statin therapy in the observational studies compared with primary prevention randomised controlled trials (RCTs) in coronary artery disease

Cohort	No	OR (95% CI)	Relative risk reduction	Reference
COPD	19720	0.53 (0.42 to 0.62)	47% risk reduction for death or MI in high risk COPD patients	Mancini <i>et al</i> ⁶⁰
COPD	854	0.57 (0.38 to 0.87)	43% risk reduction for death after hospital discharge for COPD exacerbation	Soyseth <i>et al</i> ⁶¹
COPD	76232	0.62 (0.43 to 0.91) 0.19 (0.08 to 0.47)	38% risk reduction for death following hospitalisation with chest infection 81% risk reduction for death following hospitalisation with COPD exacerbation	Frost <i>et al</i> ⁶²
US Veterans	483733	0.45 (0.42 to 0.48)	55% risk reduction of lung cancer with > 6 months of statin use	Farwell <i>et al</i> ⁶³
US Veterans	62842	0.70 (0.60 to 0.81)	30% risk reduction of lung cancer	Karp <i>et al</i> ⁶⁴
US Veterans	8652	0.54 (0.42 to 0.70)	46% risk reduction of death following hospitalisation for pneumonia	Mortensen <i>et al</i> ⁶⁵
Primary prevention RCT*	21087	0.71 (0.56 to 0.91) 0.70 (0.62 to 0.79)	29% risk reduction for death following an MI 30% risk reduction for having a MI	Pignone <i>et al</i> ⁶¹

CI, confidence interval; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; OR odds ratio.

*Based on a meta-analysis of randomised controlled trials.

neutrophilic inflammation.⁶⁸ We suggest that identifying smokers with significant air flow limitation (%predicted FEV₁ <70%) could be considered analogous (in terms of future cardiovascular risk) to identifying those with elevated cholesterol.^{7, 39} Evidence of airflow limitation, together with other CAD risk factors (for example, smoking, elevated blood pressure or family history) should prompt consideration of primary preventive treatment with statin therapy in those with multiple risk factors. Given the substantial risk of CAD conferred by a reduced FEV₁, it would not be surprising that patients with COPD might gain greater cardiovascular benefit from statin therapy than those with normal lung function from the primary prevention studies.

STATINS IN COPD: FINDINGS FROM OBSERVATIONAL STUDIES

Given the importance of reduced FEV₁ in cardiovascular risk, we support others who propose that FEV₁ be used in conjunction with commonly used risk markers,^{5, 7, 68, 69} such as blood pressure and serum cholesterol, to assess risk and target preventive treatment. Such an approach may improve outcomes as suggested by three recent large prospective observational studies reporting that patients with COPD on statins had substantial reductions in both morbidity and mortality compared with those with COPD who were not.⁷⁰⁻⁷² Strikingly, those with COPD who took statins had as much as a 50% reduction in all cause mortality,^{70, 71} 50% reduction in myocardial infarction,⁷⁰ and 30% reduction in hospitalisation from COPD (table 1).⁷⁰ These findings were replicated in another observational study of patients with peripheral vascular disease that, after a median 5 year follow-up, showed those with COPD taking statins had mortality reduction of 30–40% compared with non-users.⁷³

In a recently reported non-randomised study of lung function screening in smokers and ex-smokers with COPD (n = 319), compared with those not on statins, those taking statins had a significantly reduced annual FEV₁ decline (+5 ml/year compared with –86 ml/year in those with mild COPD not taking a statin) and 37% reduction in COPD related hospitalisation.⁷⁴ This is consistent with other studies purporting a 90–110 ml/year loss in

FEV₁ in smokers most susceptible to COPD,^{75, 76} versus the normal annual decline of approximately 10–20 ml.^{10, 16, 24} We note that the decline of FEV₁ in clinical trial patients, with mild to moderate COPD, is estimated to be in the order of 50 ml/year.^{77, 78} As a randomised clinical trial is needed to confirm that statins attenuate FEV₁ decline, studies involving mild to moderate COPD might require greater numbers (to improve power) than those reported in these observational studies. The observation that statins might attenuate FEV₁ decline⁷⁴ is consistent with data reported in a subpopulation of the Normative Aging Study involving 803 men and 2136 measurements over a 10 year follow-up period.⁷⁹ Across a wide range of baseline lung function, the average yearly decline in FEV₁ was 24 ml/year in those not on statins and 11 ml/year in those on statins. Importantly, in both studies^{74, 79} this effect was found regardless of smoking status, suggesting statin therapy benefits both smokers and ex-smokers. When the lung function findings from these studies^{74, 79} are extrapolated over a 20 year period, the preservation of lung function in a COPD patient taking statin therapy would be comparable to that achieved from quitting smoking (fig 2). Although data from randomised studies are needed to confirm these interesting findings, they suggest that statins could be one of the first pharmacological agents to preserve lung function, to date the only intervention other than smoking cessation to do so. Although smoking cessation is and must remain the priority in all patients, the addition of statins to current treatment appear to confer protective effects on the lung and may be useful in those ex-smokers with COPD where lung function continues to decline.

These observational data are remarkably consistent and suggest the mortality benefit in COPD patients taking statins was approximately twofold greater than the mortality benefit seen with inhaled corticosteroid treatment (up to 25% reduction)⁸⁰ or corticosteroid treatment combined with long acting bronchodilators (up to 35% reduction).⁸¹ Moreover, the reduction in hospitalisation with the statin treatment was comparable to that achieved with locally acting inhaled corticosteroids, considered by many as routine therapy.⁸¹ The apparent benefit of statins over

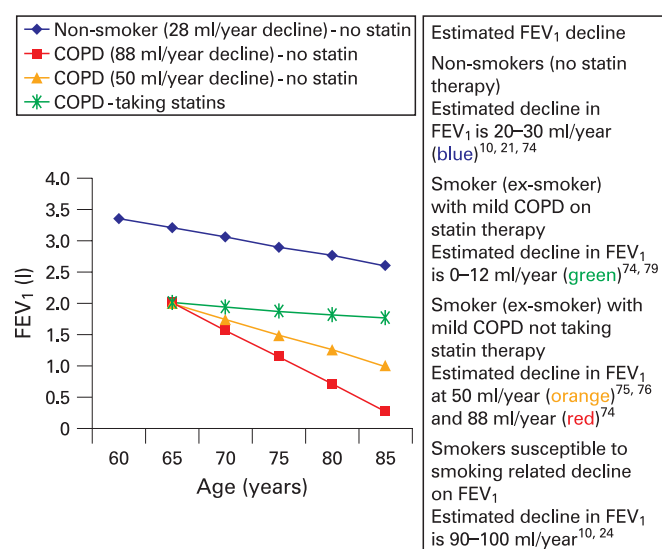


Figure 2 Estimated effect of statin treatment on forced expiratory volume in 1 s (FEV₁) decline in non-randomised prospective studies.^{74–79} COPD, chronic obstructive pulmonary disease.

corticosteroids may reflect their greater attenuating effect on neutrophilic inflammation and/or apoptosis, both of which are key features of COPD.^{63–68} Perhaps of greater significance was that the reduction in myocardial infarction seen with statin treatment was twofold greater in patients with COPD than was seen in the coronary artery primary prevention studies.⁶¹

Lastly, statin use has also been associated in three large observational studies with reduced risk of lung cancer (table 1).^{82–84} Two US studies reported data from the Veterans Affairs Healthcare System involving 480 000 patients (from south Central VA) and 60 000 (from New England). In the former case-control study, statin use for >6 months was associated with a 55% reduction in lung cancer risk compared with those not taking statins.⁸² This reduction was seen across all ages and independent of other cardiovascular risk factors such as smoking and the presence of diabetes. In the New England study, with a median 5 year follow up, there was a 30% risk reduction for lung cancer after adjustment for confounding variables.⁸³ The third study reported data on 60 000 patients and reported a 35–47% reduction in the incidence of lung cancer after 7 years of follow up.⁸⁴ In another Veteran Affairs study, statin use was associated with a 50% reduction in 30 day mortality in those hospitalised with community acquired pneumonia,⁸⁵ although the benefit of statin use in sepsis remains controversial.^{86–88} Just as was seen in the COPD related studies above, there appears consistency in both the direction and magnitude of effect with statin use and reduced lung cancer risk. Although these studies consistently report benefit over harm, with reductions in statin users ranging between 30–50%, history shows that the real magnitude of the benefit of statin use may be less and best estimated from randomised clinical trials. This is because all these statin studies have been observational studies,^{70–78 82–85} where the potential for confounding exists (see “healthy user effect” below).

STATINS: FINDINGS FROM AN INTERVENTIONAL STUDY

The Heart Protection Study (HPS) was a large randomised clinical trial of secondary prevention in 20 000 patients with vascular disease or diabetes.⁸⁹ It concluded that statin users had a 17% reduction in vascular deaths although no significant

effect on non-vascular death was found. Over the 5 year period of the study no increase in mortality from diseases such as cancer (and specifically lung cancer) was observed, but it should be noted that this was a relatively young cohort to be exploring effects on cancer incidence. In a sub-analysis, there was a non-significant trend to reduced death from all respiratory diseases and hospital admission for COPD. Findings showed death from all respiratory diseases were reduced in statin users compared with non-users (26 (0.3%) simvastatin vs 39 (0.4%) placebo, for respiratory death—relative reduction of 34%, relative risk (RR) 0.66, 95% confidence interval (CI) 0.41 to 1.08, $p = 0.10$; and 88 (0.9%) vs 110 (1.1%) for COPD admission—relative reduction of 21%, RR 0.79, 95% CI 0.60 to 1.05, $p = 0.10$). This was a small subsample from a large RCT, where there was no selection (or sub-analysis) for patients with COPD. In this setting dilution effects may be large and result in under-powering for any effect between statins and respiratory morbidity/mortality. No significant difference in absolute FEV₁ was observed on the final visit in a subgroup taking simvastatin compared with placebo. It is difficult to interpret this last finding as no lung function was done at baseline, smoking prevalence was low, and it is not clear whether the two groups were matched for relevant factors such as smoking exposure. As approximately 70–80% of smokers maintain normal or near normal lung function,³⁰ any beneficial effect of statin treatment over a 5 year period may be lost (or diluted) by those unlikely to benefit. The latter group will be large and comprise non-smokers (estimated at 80% of the cohort) and smokers who have maintained normal or near normal lung function despite smoking (estimated as 15% of the cohort). Thus, an estimated 95% of the HPS cohort, where little statin effect on lung function would be expected, might obscure the beneficial effect of statin use in those who were smokers and had COPD (remaining 5%). This is because the positive effects statins might confer on the lungs come from mitigating the inflammatory effects from smoking (see effects of statins on the lungs). Any benefit would thus be found primarily in those smokers where the inflammatory effects of smoking are exaggerated or maladaptive (that is, in “susceptible” smokers with COPD), leading to remodelling in both the airways and/or lung parenchyma.

THE “HEALTHY USER EFFECT”

The observation that patients with COPD taking statins do better than those not taking statins has been attributed to the “healthy user effect”.⁹⁰ This effect means any benefits associated with taking statins is actually secondary to other factors such as co-existing disease, underlying COPD severity, other lifestyle factors (for example, smoking), drug compliance and factors related to health care quality or access. In other words, those taking statins are doing other things that improve their health status (for example, attending the doctor more, smoking less, are otherwise healthier with better lung function or generally are more compliant with their medications). Accordingly, improved outcomes in statin users are not due to taking statins per se but some other unrecognised factor associated with being prescribed statins (that is, statin use is confounding the observed better outcomes). Although the “healthy user effect” may explain the mixed results from statin use in reducing mortality in infection (sepsis or pneumonia),^{85–88} to attribute this effect to the consistently reported mortality and morbidity benefits of statin use in the COPD studies outlined above requires detailed analysis. The benefit of statin use on mortality is greatest in COPD patients with pre-existing cardiovascular disease⁷⁰ and may relate to effects on reducing

systemic inflammatory cytokines linked to coronary disease (for example, interleukin 6 (IL6)).⁸⁸ Such an effect may also be of importance in the lungs and we note with interest the consistently reported statin effect on reducing FEV₁ decline^{74–79} and reducing lung cancer risk^{82–84} where pulmonary inflammation is likely to be most relevant.^{16–36–38}

First, patients taking statins have been recognised to have established CAD or risk factors for CAD in contrast to those non-statin users who presumably have not. In the New England Veterans study of 60 000 participants, statin users had significantly higher diabetes prevalence, smoking prevalence, low density lipoprotein (LDL) values, “lung diseases”, and “cardiovascular disease”.⁸³ Only hypertension and mental illness were marginally higher in the non-statin user group compared with the statin users. We conclude that baseline health status, and thus expected mortality, appears worse in statin users compared with non-users. Given how well statins are tolerated,⁹¹ the proportion of patients not taking statins because they do not tolerate them is likely to be small and non-contributory.

Second, although those taking statins have been shown to seek out other health preventive services⁹² such as influenza vaccination, pneumococcal vaccination or cancer screening, there are several reasons why such activities might not explain a 50% reduction in mortality. Only the minority of the population undertake these activities (influenza vaccine 38%, pneumococcal vaccine 6%, mammography 21% of women, and prostate specific antigen (PSA) testing 21% of men). Furthermore, the magnitude of the difference was small (the relative frequency of influenza vaccination use among statin users was only 21% higher than in those not taking statins with an absolute difference of 10%). Given that the difference in uptake of these “preventive therapies” is modest and that fewer than half of statin users actually use these treatments, it would require a substantial benefit on mortality for any of these to account for a 50% reduction in mortality. To date, none of these “preventive therapies” have been convincingly shown to reduce cardiorespiratory mortality or morbidity and therefore are unlikely to account for a confounding effect from statin use. Similarly, if statin use was associated with better drug compliance with COPD related treatments such as inhaled corticosteroid use, the latter is unlikely to account for a 50% reduction in mortality across all those with COPD. In one observational study, where the effect of a statin was compared in those taking or not taking corticosteroids, little further risk reduction came from steroid

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use.⁷⁰ It is not apparent what other treatments the statin users were taking which might confer this degree of effect.

Third, both population and observational studies show there are much higher rates of cardiovascular disease in those with COPD taking statins compared with non-users.^{26–27–65–71–74–76} As there is no evidence that having COPD increases your lipid concentrations, it would seem likely that statin users are inherently at greater risk of cardiovascular disease (with greater expected mortality) than those not prescribed them. One of the observational studies attempted to look at this by subdividing their COPD cohort according to baseline CAD risk⁷⁰ and found significantly reduced rates of COPD related hospitalisation and deaths in the low risk group, although myocardial infarction reduction was no longer evident. Similarly, the benefits of taking inhaled corticosteroids did not contribute to better outcomes in this study.⁷⁰

Another factor associated with statin use was a higher frequency of screening for cancer.⁹² Screening for cancer may reduce cancer mortality through early diagnosis and treatment, but does not reduce cancer prevalence. In the previously discussed observational study from New England, the lung cancer prevalence was lower in statin users compared with non-users.⁸² This is unlikely to be due to a greater proclivity for, or awareness of, screening in lung cancer.

Several of the observational studies have controlled for other lifestyle factors such as smoking and still find a mortality benefit with statin use. Protective lifestyle factors such as intake of fresh fruits and vegetables may be higher in statin users compared with non-users, but again the proportion of people involved and the magnitude of the effect are likely to be too small to account for the mortality benefit seen in the observational studies. One possibility is that the combined effects of all these potential confounding variables might explain the benefit associated with statin use; however, this would suggest these beneficial confounders were relevant across all populations studied by these observational studies.

Lastly, there are only limited data on just how frequently statins are prescribed in patients with COPD and no evidence to suggest that statin use is more common in those with milder forms of COPD (that is, confounding by severity of COPD). Data from observational studies suggest that the proportion of patients with COPD prescribed statins to be on average 26% (range 20–50%).^{72–74–79–80} This correlates with other population based studies that report 29% of patients diagnosed with COPD

Table 2 Statin use and lung function in a tertiary centre chronic obstructive pulmonary disease clinic

Characteristic	Statin user (n = 125)	Statin non-user (n = 137)
Mean age (years)	69	67
Male gender (%)	62%	60%
Pack years	48	44
Current smoker	34%	44%
Lung function		
FEV ₁ (litres)	1.86	1.81
%predicted FEV ₁	67%	65%
FEV ₁ /FVC	59%	58%
Past medical history		
Cardiovascular event (%)*	45%	8%
Pneumonia (%)	37%	38%
COPD exacerbation	41%	39%

COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

*p<0.05.

Key learning points

- ▶ Reduced forced expiratory volume in 1 s (FEV₁) is associated with systemic inflammation and is an independent marker of cardiovascular morbidity and mortality.
- ▶ Reduced FEV₁ is also an independent marker for risk of lung cancer and stroke.
- ▶ Statins have anti-inflammatory effects in both arteries and airways through attenuation of neutrophilic inflammation.
- ▶ Reported benefits of statin use in patients with chronic obstructive pulmonary disease (COPD) include reduced cardiovascular mortality, reduced respiratory morbidity/mortality, reduced lung function decline, and reduced risk of lung cancer.
- ▶ Although these benefits have yet to be confirmed in randomised controlled trials, they are unlikely to be explained by the “healthy user effect”.

were taking statins⁸⁴ and 34% with “lung disease”.⁸³ We examined this variable in a small audit of our COPD clinic patients and found no difference in demographic variables or lung function between those taking and not taking statins (table 2). However, among the 48% (n = 125) who were currently taking statins, nearly a half (45%, 56/125) reported having had a cardiovascular event (angina, myocardial infarction, coronary revascularisation or stroke) compared with 8% (11/137) in the non-statin group. Similar findings have been reported by others.^{73 74}

Given the evidence to date, it seems the “healthy user effect” is very unlikely to explain the consistent reductions in mortality and morbidity in those taking statins in these large observational studies. In the USA alone there are over 90 million smokers or ex-smokers and an estimated 15 million with COPD who might benefit from the use of statin treatment as a preventive agent for not just CAD but COPD and lung cancer as well. Collectively these diseases account for 70–80% of premature death in smokers.⁹³ Statins are currently one of the most widely prescribed drugs and are generally well tolerated with a safe side effect profile.^{89 94 95} Analogous to the clinical situation in CAD, there could be targeting of smokers and ex-smokers for preventive statin treatment using a risk marker such as reduced FEV₁. We conclude from these data that although it is possible that an as yet unidentified confounding factor associated with statin use might explain a 50% mortality reduction, to date, no convincing explanation has been reported.

SUMMARY

Based on growing epidemiological, laboratory and clinical studies, there is now considerable evidence to suggest that statin treatment could improve outcomes in COPD. This could have considerable impact on this important disease. Given the importance of reduced FEV₁ in predicting cardiovascular disease, we support others who propose that it be used in conjunction with accepted risk markers,^{37 50 54 61 62 69} such as blood pressure, CRP and serum cholesterol, to assess risk and target preventive treatment. Targeted treatment could also be based on more sophisticated models such as the BODE index.⁹⁶ Such an approach may improve outcomes in the most cost effective manner.

The magnitude of this respiratory benefit may be as much as twofold greater than that from existing treatments (for example, inhaled corticosteroids), while the magnitude of the cardiovascular benefit may be nearly twofold greater than that

Current research questions

- ▶ In a randomised control trial, how does the anti-inflammatory benefit of statin treatment compare with inhaled corticosteroids?
- ▶ Will randomised control trials replicate the diverse morbidity and mortality benefits of statin treatment consistently reported in observational studies?

currently seen in heart attack prevention where mortality has halved since the introduction of statins. Although it is possible that this statin benefit is confounded by other factors independently associated with statin use (the so called “healthy user effect”), there is no good evidence to suggest this is the case. The observational studies typically show that statin users tend to be older and have more co-morbidities (such as coronary artery disease, dyslipidaemia and diabetes) than non-users—that is, not healthier than non-users. There is no apparent difference in lung function between those prescribed and not prescribed statins. Moreover, the “preventive” factors reported to be associated with statin use appear insufficient in frequency and effect size to account for the morbidity and mortality benefits seen with statin use.

We and others have previously reported that reduced FEV₁ is an independent predictor of mortality from both cardiovascular disease (CAD and stroke) and respiratory disease (COPD and lung cancer).^{39 45} We have also proposed that reduced FEV₁ provides a non-invasive marker of susceptibility to aero-pollutant exposure and tendency to systemic inflammation.³⁹ Here we suggest that patients with COPD be considered for statin treatment for three reasons. Firstly, a diagnosis of COPD (or reduced FEV₁) is in its own right a powerful marker of increased risk of coronary artery disease.^{7 8} This risk is greater than that of other well established risk factors usually prompting statin treatment (elevated cholesterol, smoking, family history, diabetes and elevated blood pressure). Second, there is consistency in the studies showing benefit over harm with clinically significant morbidity and mortality reductions with statin use that have not yet been attributed to confounding effects. Third, currently recommended therapies for COPD merely control symptoms and have not been shown to reduce morbidity or mortality convincingly.⁹⁷ Novel treatments such as statins, that have been shown to attenuate neutrophilic inflammation by reducing recruitment and/or activation of inflammatory cells in the lungs,⁹⁷ should be considered. To date, approximately 20–30% of patients with COPD are prescribed statins. However, given the impressive safety data on long term statin use,⁹¹ in particular that lowering cholesterol does not increase risk of cancer nor does it increase mortality,^{82 83 85 94 95} should we be considering statins more often in patients with COPD? Based on the evidence to date showing clinically relevant reductions in cardiovascular mortality in high risk populations (20–30%) and the benefits of adding statins to existing COPD treatment (consistent morbidity and mortality reductions of 30–50%), the answer is quite possibly yes.

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AFTER THE REFERENCES)

1. Based on the observational studies, which one of the following potential benefits of statin use in patients with COPD is false?

- Reduced risk of lung cancer
- Reduced decline in FEV₁
- Reduced cardiovascular and all cause mortality

- D. Reduced hospitalisation and mortality from infective exacerbations
- E. Reduction in symptoms and quality of life

2. Based on the animal and human studies, which one of the following has not been attributed to statin effects in the lungs?

- A. Reduced apoptosis in the lung
- B. Reduced neutrophil influx and/or migration in to the lung
- C. Bronchodilatation and smooth muscle relaxation
- D. Reduced cytokine production in the lung
- E. Reduced small airway inflammation

3. Which of the following statements regarding reported observations between CRP and COPD is false?

- A. Elevated CRP is inversely related to impaired FEV₁ in patients with COPD, after adjustment for smoking
- B. Elevated CRP in COPD patients is unrelated to cardiovascular mortality
- C. Elevated CRP and reduced FEV₁ have been associated in cross-sectional studies
- D. Statin use is associated with a reduction in CRP
- E. Elevated CRP is association with increased mortality in patients with COPD

4. Which of the following statements about the use of statins in COPD is false?

- A. Benefits of statin use from observational studies suggest significant reduction in respiratory morbidity even after adjustment for conventional treatment such as corticosteroids
- B. Given the high cardiovascular risk associated with COPD, statins may be beneficial in many patients with COPD
- C. Benefits from statins over existing treatments for COPD may be attributed to their apparent anti-neutrophilic effects
- D. From observational data, it appears statins are taken by the majority of patients with COPD
- E. In a sub-analysis of a large randomised controlled trial examining statin use and their effect on cardiovascular disease, a trend for benefit on respiratory morbidity/mortality was seen despite the inclusion of non-smokers and subjects with normal lung function

5. Which of the following statements with respect to potential statin benefits in COPD is unlikely to account for “the healthy user effect”?

- A. COPD patients taking statins have a higher prevalence of cardiovascular disease and higher mortality risk.
- B. COPD patients taking statins have greater impairment in lung function compared with those not taking statins
- C. COPD patients taking statins have morbidity/mortality benefits irrespective of concomitant use of inhaled corticosteroids.
- D. COPD patients taking statins with low baseline cardiovascular risk had reductions in respiratory morbidity
- E. COPD patients taking statins undertake “preventive interventions” at a slightly higher rate than those not taking statins but is unlikely to account for the apparent beneficial effects of statins

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Answers

1. A (T); B (T); C (T); D (T); E (F)
2. A (T); B (T); C (F); D (T); E (T)
3. A (T); B (F); C (T); D (T); E (T)
4. A (T); B (T); C (T); D (F); E (T)
5. A (T); B (F); C (T); D (T); E (T)