

# Pleiotropic effects of the HMG-CoA reductase inhibitors

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**Abstract:** The HMG-CoA reductase inhibitors (statins) are used extensively in the treatment of hyperlipidemia. They have also demonstrated a benefit in a variety of other disease processes. These secondary actions are known as pleiotropic effects. Our paper serves as a focused and updated discussion on the pleiotropy of statins and emphasizes the importance of randomized placebo-controlled trials to further elucidate this interesting phenomenon.

**Keywords:** HMG-CoA inhibitors, pleiotropic, reductase, review, statins

## Introduction

Statins are a mainstay in the treatment of hyperlipidemia and are used in the primary and secondary prevention of coronary artery disease.<sup>1,2</sup> Recent studies have shown that statins also possess powerful pleiotropic effects that are independent of their cholesterol-lowering properties, a fact that has piqued the interest of the medical community.

The pleiotropic effects of statins are attributed to several processes resulting from the inhibition of HMG-CoA reductase. The main effect of statins is the inhibition of cholesterol and isoprenoid synthesis, which ultimately results in upregulation of endothelial nitric oxide synthase, an enzyme responsible for vascular endothelial function, and thus improved pathophysiologic response.<sup>3,4</sup> Additionally, antioxidant effects via the decreased production of NADPH oxidase leads to decreased amounts of reactive oxidant species in the circulation.<sup>3</sup> Inflammatory markers such as C-reactive protein and nuclear factor-k B have also been shown to be reduced by statins, leading to the hypothesis that statins possess anti-inflammatory properties.<sup>5</sup> Other proposed mechanisms include immunomodulation, normalization of sympathetic outflow, plaque stabilization, decreased activation of the blood coagulation cascade, and inhibition of platelet aggregation (Table 1).<sup>6</sup>

A wide range of disease processes have been linked to better outcomes when patients are treated with statins (Table 2). The following is a review of the current literature and recent studies regarding the potential therapeutic benefits and pleiotropic effects of statins (Table 3).

## Cardiovascular disorders

### Heart failure

Patients in the early or mild stages of heart failure have been shown to benefit from statins via their anti-inflammatory properties and enhancement of endothelial function.<sup>7,8</sup> The CORONA (Controlled Rosuvastatin Multinational Trial in Heart

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**Table 1** Proposed mechanisms of statin pleiotropy

- Upregulation of endothelial nitric oxide synthase and improved pathophysiologic response, including inhibition of vasoconstriction and promotion of re-endothelialization
- Antioxidant effects via the inhibition of nicotinamide adenine dinucleotide phosphate oxidase and thus reactive oxidant species
- Anti-inflammatory properties, including reduction in C-reactive protein, interleukin 6, tumor necrosis factor alpha, and nuclear factor-k B levels
- Downregulation of cytokines and chemokines
- Stabilization of atherosclerotic plaques and inhibition of plaque inflammation
- Decreased activation of the blood coagulation cascade
- Inhibition of platelet aggregation
- Normalization of sympathetic tract outflow
- Induction of autophagy and inhibition of angiogenesis in cancer cells
- Neuroprotection and support of blood–brain barrier function

Failure) trial,<sup>9</sup> a retrospective study of 5011 patients, concluded that those with high sensitivity C-reactive protein >2 mg/L receiving rosuvastatin 10 mg daily had a reduced incidence of the primary outcome (cardiovascular death, myocardial infarction or stroke,  $P = 0.024$ ), coronary events

**Table 2** Overview of statin pleiotropy and medical disorders

System	Disorder
Cardiology	Heart failure
	Atrial fibrillation
	Ventricular arrhythmias
	Acute coronary syndrome and percutaneous coronary intervention
	Aortic stenosis
Pulmonology	Asthma
	Chronic obstructive lung disease
Hematology/oncology	Prostate cancer
	Colon cancer
	Lung cancer
	Pancreatic cancer
	Renal cancer
Neurology	Stroke
	Intracranial hemorrhage
	Multiple sclerosis
	Alzheimer's disease
	Parkinson's disease
Nephrology	Glomerulonephritis
	Renal failure
	Renal transplantation
	Contrast-induced nephropathy
	Rheumatoid arthritis
Rheumatology	Osteoarthritis
	Osteoporosis
	Systemic sclerosis
Miscellaneous	Venous thromboembolism
	Polycystic ovary syndrome
	Macular degeneration
	Influenza
	Infection and sepsis

( $P = 0.017$ ), all-cause mortality or worsening heart failure ( $P = 0.017$ ), and a decreased number of hospitalizations for cardiovascular reasons ( $P < 0.001$ ) or worsening heart failure ( $P = 0.004$ ) compared to placebo. The benefit of reduced incidence of cardiovascular hospitalization was also seen in a study by Kjeskus et al<sup>10</sup> of elderly systolic heart failure patients treated with rosuvastatin ( $P = 0.04$ ).

## Atrial fibrillation

Statins have been shown to prevent structural and electrical remodeling and blunt the development of atrial fibrillation in the setting of atrial tachycardia.<sup>11</sup> Additionally, shortened intra-atrial conduction time, decreased duration of atrial fibrillation, and increased atrial effective refractory period have been shown to be the result of anti-inflammatory properties possessed by statins.<sup>12</sup>

Young-Xu et al<sup>13</sup> prospectively evaluated 449 patients with stable coronary artery disease and no history of atrial fibrillation over five years, and found that statin users had a 59% decreased risk of developing atrial fibrillation ( $P < 0.01$ ). Meanwhile, Kulik et al<sup>14</sup> assessed the incidence of new-onset atrial fibrillation in 29,088 patients after myocardial infarction or coronary revascularization, and found a 10% reduced risk in statin-treated patients ( $P = 0.0006$ ). Siu et al<sup>15</sup> retrospectively studied 62 patients with lone persistent atrial fibrillation of at least three months' duration who underwent successful external electrical cardioversion, and showed that statin use was associated with a significantly decreased risk of recurrence of atrial fibrillation ( $P = 0.032$ ).

The incidence and duration of atrial fibrillation is also decreased by statins in postoperative cardiac patients. In a cohort of 140 patients without prior atrial fibrillation or statin use undergoing elective coronary artery bypass grafting, the incidence of new-onset atrial fibrillation was 14% versus 32% for the control group ( $P = 0.009$ ), with a mean duration of single atrial fibrillation of 3.6 hours versus 5.7 hours ( $P < 0.01$ ) during the first seven postoperative days in those assigned to daily atorvastatin.<sup>16</sup> Furthermore, a recent observational study using data from 64,679 patients enrolled in GRACE (Global Registry of Acute Coronary Events)<sup>17</sup> showed that statin users hospitalized for acute coronary syndrome were not only at lower risk of developing inhospital atrial fibrillation ( $P < 0.0001$ ), but also had a significantly decreased risk of developing ventricular arrhythmias, cardiac arrest, and/or death.

## Ventricular arrhythmias

Studies have shown a correlation between statin use and a decreased incidence of ventricular arrhythmias or

**Table 3** Major trials and studies exhibiting statin pleiotropy

Trial/study	Design	Outcomes with statin treatment
Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) <sup>7,9</sup>	5011 patients with heart failure, reduced left ventricular function, and ischemic heart disease randomly assigned to 10 mg/day rosuvastatin or placebo	Patients with NT-proBNP < 103 pmol/L had 35% reduction in atherothrombotic events or sudden death Patients with hs-CRP > 2 mg/L had better outcomes, decreased all-cause mortality and coronary events, less hospitalizations
Global Registry of Acute Coronary Events (GRACE) <sup>17</sup>	64,679 patients hospitalized for ACS in 1999–2007 were prospectively analyzed in an observational study	Patients taking statins prior to hospital admission had a significantly lower risk of atrial fibrillation, VT/VF, cardiac arrest, and death
Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) <sup>19</sup>	654 patients receiving an ICD were analyzed based on the percentage of days statins were taken during follow-up	≥90% statin usage was associated with a reduced risk of VT/VF or cardiac death
Efficacy of high-dose atorvastatin loading before primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: The STATIN STEMI trial <sup>20</sup>	171 STEMI patients randomized to 600 mg Plavix® plus either 80 mg or 10 mg atorvastatin pre-PCI, with all patients treated with 10 mg atorvastatin post-PCI	High-dose atorvastatin pre-PCI was associated with immediate improvement of coronary flow and microvascular myocardial perfusion when compared with low-dose atorvastatin
Atorvastatin for Reduction of Myocardial Damage during Angioplasty trial (ARMYDA) <sup>21</sup>	153 statin-naïve patients with chronic stable angina undergoing elective PCI randomized to atorvastatin or placebo seven days prior to intervention	Significant reduction in procedural myocardial injury
Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 trial (PROVE IT-TIMI 22) <sup>24</sup>	3745 ACS patients randomized to either 40 mg pravastatin or 80 mg atorvastatin daily	High-dose statin therapy superior in aggressive reduction of both LDL-C and CRP levels, leading to lower risk of recurrent myocardial infarction or vascular death
Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 [PROVE IT-TIMI 22] Substudy (PCI-PROVE IT) <sup>25</sup>	2868 ACS patients who underwent PCI prior to enrollment in PROVE IT-TIMI 22, which randomized patients to 80 mg atorvastatin or 40 mg pravastatin daily	Reduction in major adverse cardiovascular events, as well as target and nontarget vessel revascularization with intensive statin therapy
Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing percutaneous coronary intervention: results of the ARMYDA-RECAPTURE randomized trial <sup>26</sup>	383 long-term statin users with stable angina or NSTEMI undergoing PCI were randomized to atorvastatin reload or placebo pre-PCI, with all patients treated with atorvastatin post-PCI	Decreased 30-day incidence of major adverse cardiovascular events, as well as postprocedural myocardial injury, in patients receiving high-dose pre-PCI atorvastatin reload
Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) <sup>50</sup>	17,802 patients with normal LDL-C and elevated CRP randomly assigned to 20 mg/day rosuvastatin or placebo	Reduced the incidence of stroke by more than 50%; reduction in nonfatal MI and cardiovascular death

**Abbreviations:** NT-proBNP, N-terminal fragment brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; ACS, acute coronary syndrome; VT, ventricular tachycardia; VF, ventricular fibrillation; ICD, implantable cardioverter defibrillator; STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; LDL-C, low density lipoprotein cholesterol; NSTEMI, non-ST-segment elevation myocardial infarction; MI, myocardial infarction.

sudden cardiac death. Chiu et al<sup>18</sup> assessed 281 patients with ischemic cardiomyopathy undergoing implantable cardioverter defibrillator placement with subsequent outpatient follow-up. Those who received statin therapy had a reduced incidence of ventricular arrhythmia requiring use of the defibrillator ( $P = 0.01$ ). The MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) trial<sup>19</sup> looked at 654 patients with ischemic cardiomyopathy and implantable cardioverter defibrillator placement, and found a 35% risk reduction for sudden cardiac death or development of ventricular arrhythmia in patients taking statins ( $P < 0.01$ ). The results observed may be due to mechanisms similar to those seen in atrial

fibrillation, with plaque stabilization also protecting against ischemia-induced arrhythmias.

## Percutaneous coronary intervention and acute coronary syndrome

Statin pleiotropy in patients undergoing percutaneous coronary intervention has been well established. Via their ability to stabilize plaques and exert anti-inflammatory and anti-thrombotic properties, statins increase coronary blood flow and microvascular myocardial perfusion.<sup>20</sup> The ARMYDA (Atorvastatin for Reduction of Myocardial Damage during Angioplasty) trial,<sup>21</sup> which looked at 153 statin-naïve patients with stable angina undergoing elective percutaneous coronary

intervention, found a significantly reduced risk of myocardial injury in patients assigned to 40 mg of atorvastatin daily for seven days prior to percutaneous coronary intervention, with similar results reported in other randomized trials.<sup>22,23</sup> Additionally, recent studies suggest an increased benefit with high-dose therapy as opposed to conservative regimens.<sup>24</sup> Gibson et al<sup>25</sup> assessed the incidence of the primary composite endpoint (all-cause mortality, myocardial infarction, unstable angina leading to hospitalization, 30-day revascularization, or stroke), target vessel revascularization, and nontarget vessel revascularization among 2868 patients undergoing percutaneous coronary intervention in the setting of acute coronary syndrome. Those treated daily with 80 mg of atorvastatin had a decreased incidence of the primary composite endpoint (21.5% versus 26.5%,  $P = 0.002$ ) and target vessel revascularization (11.4% versus 15.4%,  $P = 0.001$ ) compared with patients treated with 40 mg of pravastatin. Furthermore, patients on chronic statin therapy suffering from stable angina or acute non-ST-segment elevation myocardial infarction benefit from reloading with statins before percutaneous coronary intervention, having a 50% reduced risk of major adverse cardiac events (cardiac death, myocardial infarction, or unplanned revascularization) after intervention ( $P = 0.039$ ).<sup>26</sup>

## Aortic stenosis

It has been postulated that the anti-inflammatory effects of statins may help in reducing the progression of aortic stenosis. A retrospective study<sup>27</sup> of 174 patients with mild to moderate aortic stenosis, of whom 57 were on statins, demonstrated a decrease in the aortic valve area of 0.06 cm<sup>2</sup>/year in the statin treatment group compared with 0.11 cm<sup>2</sup>/year in the non-statin group ( $P = 0.03$ ) at the 21-month follow-up. Another retrospective study<sup>28</sup> of 180 patients with mild aortic stenosis and on statin treatment showed a reduction in the increase in the peak systolic gradient across the aortic valve over three years ( $P = 0.009$ ).

A four-year prospective trial by Bellamy et al<sup>29</sup> of 156 patients taking either simvastatin or lovastatin demonstrated that statin users had a slower reduction of aortic valve area of -0.04 cm<sup>2</sup>/year versus 0.09 cm<sup>2</sup>/year in the placebo group ( $P < 0.01$ ). Another prospective study called RAAVE (Rosuvastatin Affecting Aortic Valve Endothelium)<sup>30</sup> compared the effects of rosuvastatin versus placebo in 121 patients with moderate to severe asymptomatic aortic stenosis. At the 18-month follow-up, researchers found a decrease in aortic valve area of 0.05 cm<sup>2</sup> in the rosuvastatin group, compared with 0.10 cm<sup>2</sup> in the placebo group ( $P = 0.041$ , Table 4).

**Table 4** Pleiotropic effects of statins in cardiovascular disorders

Heart failure <sup>7-10</sup>	<ul style="list-style-type: none"> <li>• ↓ risk of coronary events and cardiovascular death</li> <li>• ↓ all-cause mortality</li> <li>• ↓ hospitalizations for cardiovascular reasons or worsening heart failure</li> <li>• Prevent further decompensation of cardiac function</li> </ul>
Atrial fibrillation <sup>13-17</sup>	<ul style="list-style-type: none"> <li>• ↓ duration of atrial fibrillation</li> <li>• 59% ↓ incidence in stable coronary artery disease</li> <li>• 10% ↓ incidence after myocardial infarction or coronary revascularization</li> <li>• ↓ recurrence after electric cardioversion</li> <li>• ↓ incidence after acute coronary syndrome</li> <li>• ↓ incidence and duration in postoperative cardiac patients</li> </ul>
Ventricular arrhythmias <sup>18,19</sup>	<ul style="list-style-type: none"> <li>• ↓ incidence of ICD shocks and 35% ↓ risk of sudden cardiac death in patients with ICD and ischemic cardiomyopathy</li> </ul>
Percutaneous coronary intervention and acute coronary syndrome <sup>21-26</sup>	<ul style="list-style-type: none"> <li>• Significantly reduced risk of myocardial injury in elective PCI in statin-naïve patients</li> <li>• 50% ↓ risk of major adverse cardiac events in statin users reloaded with statin prior to PCI</li> <li>• Superior concomitant reduction in LDL-C and CRP with high-dose statin therapy</li> </ul>
Aortic stenosis <sup>27-30</sup>	<ul style="list-style-type: none"> <li>• Significantly slower reduction of AV area</li> <li>• Slower increase of AV peak systolic gradient</li> </ul>

**Abbreviations:** ICD, implantable cardioverter defibrillator; PCI, percutaneous coronary intervention; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; AV, aortic valve.

## Pulmonary disorders

### Asthma

Statins may play a protective role in asthma patients by curbing inflammation and airway remodeling. A recent study<sup>31</sup> assessed 70 asthmatic patients at baseline and two months after beginning statin therapy. Researchers found a decrease in rescue inhaler use from nine to five times per week ( $P < 0.0001$ ), increased peak flow from 301 L/min two months prior to 335 L/min two months after starting therapy ( $P < 0.0001$ ), and an increase in patients classified as having “mild” disease, with a concurrent decrease in “moderate-to-severe” classifications. Additionally, studies have shown that adult asthmatics receiving statin therapy have a 30% risk reduction for hospitalizations and emergency department visits related to their disease ( $P < 0.001$ ).<sup>32</sup>

### Chronic obstructive lung disease

Blamoun et al<sup>33</sup> retrospectively assessed the incidence of chronic obstructive pulmonary disease exacerbations and intubations in 185 statin users with established obstructive lung disease. At one year, patients not taking statins were

more likely to have suffered an exacerbation ( $P < 0.0001$ ) or have required intubation ( $P < 0.0001$ ) compared with the treatment group. Statins have also been shown to decrease 90-day mortality in patients hospitalized with emphysematous exacerbations<sup>34</sup> and are useful in preservation of lung function in elderly patients with a history of smoking.<sup>35,36</sup>

## Cancers

### Prostate cancer

Studies have shown that statins induce autophagy and cell death in prostate cancer cells while causing no hindrance to normal cells.<sup>37</sup> A retrospective analysis of CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor),<sup>38</sup> which included 7042 men who underwent radical prostatectomy or radiotherapy for prostate cancer, showed a 65% reduction in all-cause mortality after radical prostatectomy and a 41% reduction after radiotherapy with concomitant use of statins. A second study demonstrated improved freedom from biochemical failure and salvage androgen deprivation therapy, as well as improved relapse-free survival rates in statin users who underwent radiotherapy.<sup>39</sup> Furthermore, patients undergoing radical prostatectomy placed on preoperative simvastatin have a 69% reduced risk of intratumoral inflammation, a complication that may lead to prostate cancer progression.<sup>40</sup>

### Colon cancer

Studies have shown that statins inhibit the progression of colon cancer and attenuate tumor burden by inducing apoptosis,<sup>41–43</sup> inhibiting angiogenesis,<sup>41</sup> and decreasing the production of proinflammatory cytokines. A case-control study by Poynter et al<sup>44</sup> found that patients treated with at least five years of statin therapy had a 50% reduced risk of colorectal cancer, adding to prior reports of lower rates of Stage IV carcinomas in statin users.<sup>45</sup> Additionally, patients with a history of adenomatous colon polyps who were on statins had smaller polyp size, a reduced number of polyps, and reduced incidence of pathologic progression or recurrent polyps on 3–5-year colonoscopy follow-up,<sup>46</sup> suggesting that statins may play a preventive role in the development of colorectal cancer.

### Lung, pancreatic, and renal cancer

Khurana et al<sup>47–49</sup> performed a series of retrospective nested case-control studies using the Veterans Affairs database. Patients who used statins for at least six months had a 55% ( $P < 0.01$ ) decreased incidence of lung cancer and a 67% ( $P < 0.01$ ) reduced risk of developing pancreatic cancer,

while patients on statin therapy for longer than four years had an 80% ( $P < 0.01$ ) decreased risk in developing pancreatic cancer. The authors concluded that statins may also play a protective role in the development of renal cell carcinoma (Table 5).

## Neurological disorders

### Stroke and intracranial hemorrhage

Statins have been shown to be beneficial in primary and secondary stroke prevention,<sup>50</sup> preventing ischemia and hemorrhage by increasing cerebral vasomotor reactivity and decreasing vasospasm.<sup>51–53</sup> A meta-analysis of randomized trials that included 165,792 patients found statin users to have a 21% reduced risk of stroke ( $P = 0.009$ ), while patients with prior stroke had a 16% reduced risk of recurrence ( $P = 0.03$ ).<sup>54</sup> Similar effects have been observed in patients with intracranial hemorrhage. Naval et al<sup>55</sup> retrospectively looked at 125 patients with intracranial hemorrhage unrelated to trauma or an underlying lesion. Statin use was associated with decreased mortality and a 12-fold increase in rate of survival ( $P = 0.05$ ). Furthermore, a meta-analysis<sup>56</sup> of randomized trials of patients with aneurysmal subarachnoid hemorrhage found that those who were started on statin therapy at the time of the event had a 27% reduced risk of vasospasm, a 62% reduction in delayed ischemic events, and an 82% reduction in mortality.

### Multiple sclerosis

Statins have synergistic effects when used in combination with conventional multiple sclerosis drugs and may possess reparative properties.<sup>57,58</sup> It is hypothesized that their ability to reduce the amount of lymphocytes and monocytes crossing the blood–brain barrier decreases the amount of perivascular infiltrates that fuel demyelination.<sup>59,60</sup> Vollmer et al<sup>61</sup> prospectively studied 30 patients with relapsing-remitting multiple sclerosis and reported a 44% decrease ( $P < 0.0001$ )

**Table 5** Pleiotropic effects of statins in malignancies

Prostate cancer <sup>38–40</sup>	<ul style="list-style-type: none"> <li>• ↓ all-cause mortality</li> <li>• ↑ relapse-free survival</li> <li>• ↓ risk of intratumoral inflammation</li> <li>• ↓ biochemical failure and androgen deprivation therapy</li> </ul>
Colon cancer <sup>44–46</sup>	<ul style="list-style-type: none"> <li>• 50% ↓ risk of colorectal cancer after 5 years</li> <li>• ↓ rate of stage IV carcinomas</li> <li>• ↓ colon polyp size, number, and progression rate</li> </ul>
Lung cancer <sup>47</sup>	<ul style="list-style-type: none"> <li>• 50% ↓ incidence after 6 months of therapy</li> </ul>
Pancreatic cancer <sup>48</sup>	<ul style="list-style-type: none"> <li>• 67% ↓ incidence after 6 months, 80% ↓ after four years</li> </ul>

in the number and a 41% decrease ( $P < 0.0018$ ) in the volume of gadolinium-enhancing brain lesions after six months of treatment with 80 mg of simvastatin daily. Paul et al<sup>62</sup> verified these findings, showing that patients treated with high-dose atorvastatin had a significantly decreased number ( $P < 0.003$ ) and size ( $P < 0.008$ ) of lesions on magnetic resonance imaging after 6–9 months of therapy.

## Alzheimer's disease

By impairing production of beta-amyloid proteins and apolipoprotein E and exerting anti-inflammatory effects,<sup>63</sup> statins are proposed to decrease the amount of tau fibrilization in the pathophysiologic process of Alzheimer's disease.<sup>64</sup> A recent study by Li et al<sup>65</sup> of 3099 elderly patients reported a 38% reduction in development of Alzheimer's disease in those who began taking statins before the age of 80 years. A second study by Rosenberg et al<sup>66</sup> found a significant reduction in the progression of dementia in Alzheimer's patients taking statins when compared with control subjects ( $P = 0.03$ ).

## Parkinson's disease

Using a mouse model of Parkinson's disease, Ghosh et al<sup>67</sup> observed protection of dopaminergic neurons, striatal neurotransmitter normalization, and stabilization of motor function in mice treated with simvastatin or pravastatin. Analysis of the US Veterans' Affairs database showed a 54% reduced incidence of dementia ( $P < 0.0001$ ) and a 49% reduction in the incidence of newly diagnosed Parkinson's disease in individuals who were taking simvastatin ( $P < 0.0001$ ).<sup>68</sup> Additionally, Wahner et al<sup>69</sup> found that patients who were on statin therapy for at least five years had a 63% reduction in the incidence of Parkinson's disease.

## Renovascular disorders

### Glomerulonephritis and renal failure

By inhibiting signaling pathways that lead to renal inflammation, glomerular scarring, and mesangial proliferation,<sup>70</sup> statins reduce the systemic production and renal infiltration of T cells, T-helper cells, macrophages, and neutrophils.<sup>71</sup> Ozsoy et al<sup>72</sup> studied 31 patients with established glomerulonephritis and proteinuria who were on angiotensin-converting enzyme inhibitor therapy. Adding atorvastatin to their medical regimen conferred a 22% reduction in proteinuria after six weeks of therapy ( $P = 0.005$ ). The benefits of statin therapy have also been observed in hemodialysis patients, who were shown to require significantly lower erythropoietin

administration ( $P < 0.05$ ) for renal failure-associated anemia compared with their untreated counterparts.<sup>73</sup>

## Renal transplantation

Of particular interest are recent studies that have shown statin pleiotropy in patients who have undergone renal transplantation. Pazik et al<sup>74</sup> looked at patients with post-transplant glomerulonephritis and found that maintenance immunosuppression with steroid infusions, alkylating agents, or antiproliferatives did not prolong graft survival. However, patients who had a statin added to their medical regimen had a 63% reduced risk ( $P < 0.02$ ) of graft loss, and when combined with renin-angiotensin-aldosterone system inhibitors, the reduction increased to 76% ( $P < 0.008$ ).

## Contrast-induced nephropathy

The antioxidant and vascular effects of statins are thought to attenuate the development of contrast-induced nephropathy, a serious complication of radiographic and diagnostic procedures that results from decreased renal medullary blood flow and toxic insult to the renal tubules.<sup>75</sup> Khanal et al<sup>76</sup> looked at 29,409 patients who underwent percutaneous coronary intervention and found that chronic statin therapy prior to intervention was associated with a lower risk of contrast-induced nephropathy ( $P < 0.0001$ ) or renal damage requiring dialysis therapy ( $P = 0.03$ ). Similar findings were reported by Patti et al,<sup>77</sup> who observed 434 patients undergoing percutaneous coronary intervention and found that preprocedural statin therapy resulted in a reduced incidence of contrast-induced nephropathy ( $P < 0.0001$ ) and a greater postprocedure creatinine clearance compared with placebo ( $P < 0.0001$ ).

## Rheumatologic disorders

### Rheumatoid arthritis

Via the inhibition and downregulation of proinflammatory cytokines and chemokines,<sup>78,79</sup> statins have been shown to decrease serum C-reactive protein ( $P = 0.025$ ) and tumor necrosis factor-alpha levels ( $P = 0.012$ ) significantly in rheumatoid arthritis patients while improving endothelial function.<sup>80</sup> Recently, Amital et al<sup>81</sup> reviewed a large health maintenance organization database and looked at the incidence of newly diagnosed rheumatoid arthritis over a 10-year period. Statin users had a 40% reduced risk ( $P < 0.001$ ) of developing rheumatoid arthritis, and their protective value was greater the younger the age of the patient ( $P < 0.001$ ).

## Osteoporosis

Statins inhibit osteoclast bone resorption and stimulate the production of specific proteins involved in the development of bone and cartilage,<sup>82,83</sup> thus emerging as a possible therapeutic option for patients with osteoporosis. Tanriverdi et al<sup>84</sup> followed 120 hypercholesterolemic postmenopausal women with osteoporosis or osteopenia over a six-month period. Women treated with risedronate and atorvastatin had a two-fold increase in bone mineral density at the lumbar spine compared with women treated with risedronate alone ( $P < 0.05$ ). A meta-analysis by Hatzigeorgiou et al<sup>85</sup> revealed that patients taking statins had a 40% reduction in hip fractures and improved hip bone mineral density, and statin therapy has also been linked to increased bone mineral density at the femur and femoral neck ( $P < 0.05$ ).<sup>86</sup>

## Systemic sclerosis

Statins are hypothesized to reduce endothelial injury and inhibit defective vasculogenesis and vascular fibrosis in patients with systemic sclerosis.<sup>87,88</sup> Kuwana et al<sup>89</sup> treated eight systemic sclerosis patients with 10 mg of atorvastatin daily for a total of 24 months and found a reduction in flairs of Raynaud's phenomenon, decreased activation of angiogenic factors, and reduced levels of vascular endothelial activation and injury markers. A separate randomized trial by Abou-Raya et al<sup>90</sup> of 84 patients with systemic sclerosis also showed the benefit of statin therapy, as patients treated with 40 mg of atorvastatin daily developed an average of 1.6 new digital ulcers over a four-month treatment period versus 2.5 in the placebo group ( $P = 0.003$ ).

## Miscellaneous disorders

### Venous thromboembolism

Circulating lipid molecules appear to affect vascular endothelial and platelet function and may act as procoagulants, thus lipid-lowering with statins may protect against development of venous thromboembolism.<sup>91</sup> A recent meta-analysis<sup>92</sup> of nearly one million patients from one randomized and nine observational trials who were on statin therapy for cardiovascular risk prevention revealed a 32% decreased risk of venous thromboembolism ( $P < 0.05$ ), a 41% decreased risk of deep vein thrombosis ( $P < 0.05$ ), and a 30% decreased risk of pulmonary embolism ( $P < 0.05$ ). Furthermore, evidence suggests that statins may be of particular benefit in cancer patients, in whom venous thromboembolism and pulmonary embolism are serious sequelae. Khemasuwan et al<sup>93</sup> retrospectively studied 740 patients with solid organ tumors

who were hospitalized and placed on a statin, and found a 67% decreased risk of venous thromboembolism within two months of admission in statin users ( $P < 0.001$ ).

## Polycystic ovary syndrome

A reduction in insulin receptor maturation and inhibition of thecal interstitial cell proliferation are hypothesized to be the pleiotropic mechanisms of statins observed in females suffering from polycystic ovary syndrome.<sup>94,95</sup> Sathyapalan et al<sup>96</sup> studied 40 statin-naïve patients who were placed on 12 weeks of atorvastatin therapy and found significant reductions in testosterone ( $P < 0.01$ ), free androgen index (testosterone/sex hormone binding globulin,  $P < 0.01$ ), and insulin resistance as measured by the homeostasis model assessment for insulin resistance. A study by Banaszewska et al<sup>97</sup> compared 48 polycystic ovary syndrome patients on oral contraceptive treatment with patients on oral contraceptive treatment plus simvastatin, and found that adjuvant statin therapy was associated with an additional 12% reduction in total testosterone ( $P < 0.004$ ), a 23% reduction in free testosterone ( $P = 0.006$ ), a 3.4% decreased incidence in hirsutism ( $P = 0.02$ ), and a 39% reduction in C-reactive protein level ( $P = 0.006$ ) compared with those on oral contraceptive treatment alone.

## Macular degeneration

Statin use has been linked to a 67% reduction in drusen formation,<sup>98</sup> which deprives certain areas of the eye of oxygen and nutrients and is associated with the onset of macular degeneration. Choroidal neovascularization, an early symptom of age-related macular degeneration, has also been shown to be inhibited by statins in vitro.<sup>99</sup> A retrospective study by Wilson et al<sup>100</sup> of 326 patients with age-related macular degeneration reported a 49% reduction in the rate of choroidal neovascularization in statin-treated patients ( $P = 0.01$ ), while a case-control study by McGwin et al<sup>101</sup> found a 70% risk reduction in newly-diagnosed macular degeneration amongst statin users.

## Influenza

Recent data suggest that statins may confer protection against infectious diseases, including the influenza virus. Kwong et al<sup>102</sup> assessed the effects of statin use on hospitalization rates and mortality during the influenza season over a 10-year period using a population-based cohort study of 2.2 million patients. Researchers found an 8% reduced risk of pneumonia hospitalization and a 16% reduction in 30-day

**Table 6** Pleiotropic effects of statins in miscellaneous disorders

Venous thromboembolism <sup>92,93</sup>	<ul style="list-style-type: none"> <li>• 32% ↓ in noncancer patients</li> <li>• 67% ↓ in those with solid organ tumors</li> <li>• 41% ↓ risk of deep vein thrombosis</li> <li>• 30% ↓ risk of pulmonary embolism</li> </ul>
Polycystic ovary syndrome <sup>96,97</sup>	<ul style="list-style-type: none"> <li>• ↓ testosterone levels, free androgen index, insulin resistance, and incidence of hirsutism</li> <li>• Increases therapeutic effects of oral contraceptives</li> </ul>
Macular degeneration <sup>98–101</sup>	<ul style="list-style-type: none"> <li>• 70% ↓ of age-related macular degeneration</li> <li>• 67% ↓ drusen formation</li> <li>• 49% ↓ choroidal neovascularization</li> </ul>
Influenza <sup>102–104</sup>	<ul style="list-style-type: none"> <li>• 8% ↓ risk of hospitalization</li> <li>• ↓ risk of pneumonia, or influenza-related death</li> </ul>
Infection and sepsis <sup>105–108</sup>	<ul style="list-style-type: none"> <li>• ↓ 30-day, in-hospital, bacteremia, sepsis, and mixed infection-related mortality</li> <li>• 35% ↓ incidence of severe sepsis in intensive care unit patients</li> <li>• ↓ risk of <i>Candida</i> infections in hospitalized diabetics</li> </ul>

pneumonia mortality. A separate matched cohort study of 76,232 patients by Frost et al<sup>103</sup> found a 40% reduction in the risk of pneumonia or influenza-related death in moderate-dose statin users, and a recent study<sup>104</sup> presented at the 2010 Infectious Disease Society of America annual meeting showed a 54% reduced risk of death amongst statin users hospitalized for influenza.

## Infection and sepsis

A recent meta-analysis of 20 studies analyzed the effects of statins on mortality from infection and sepsis. Statin therapy was associated with a 39% reduction in 30-day mortality, a 62% reduction in the in-hospital mortality, a 37% reduction in pneumonia-related mortality, a 77% reduction in bacteremia-related mortality, a 60% reduction in sepsis-related mortality, and a 50% reduction in mixed infection-related mortality.<sup>105</sup> Dobesh et al<sup>106</sup> retrospectively assessed the link between statin therapy and severe sepsis in 188 intensive care unit patients and found a 35% reduction ( $P = 0.04$ ) compared with nonusers having APACHE II scores of  $\geq 24$ . Finally, statins have been associated with reduced mortality in solid-organ transplant recipients who developed bacteremia<sup>107</sup> and a decreased risk of *Candida* infection in hospitalized diabetics ( $P = 0.031$ ),<sup>108</sup> indicating that statins may be beneficial in immunocompromised patients or those at risk for opportunistic infections (Table 6).

## Conclusion

The major limitations regarding the current literature on the pleiotropic effects of statins are that the majority of studies

were observational in nature, and usually small in size. There is a lack of data corroboration via large, randomized, placebo-controlled trials. While current evidence is not definitive, there is great potential for the use of statins as adjuvant therapy in a wide range of disease processes and is a worthwhile topic for researchers and clinicians alike.

## Disclosure

The authors report no conflicts of interest in this work.

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