

# Statins in heart failure: do we need another trial?

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**Abstract:** Statins lower serum cholesterol and are employed for primary and secondary prevention of cardiovascular events. Clinical evidence from observational studies, retrospective data, and post hoc analyses of data from large statin trials in various cardiovascular conditions, as well as small scale randomized trials, suggest survival and other outcome benefits for heart failure. Two recent large randomized controlled trials, however, appear to suggest statins do not have beneficial effects in heart failure. In addition to lowering cholesterol, statins are believed to have many pleotropic effects which could possibly influence the pathophysiology of heart failure. Following the two large trials, evidence from recent studies appears to support the use of statins in heart failure. This review discusses the role of statins in the pathophysiology of heart failure, current evidence for statin use in heart failure, and suggests directions for future research.

**Keywords:** statins, treatment, heart failure, comorbidity, mortality

## Introduction

Heart failure (HF) is a complex clinical syndrome which results from structural and functional disorders of the heart associated with a variety of cardiovascular diseases. HF is mainly characterized by a condition in which the heart cannot pump enough blood to the rest of the body. With an increasing number of patients, HF is becoming a major worldwide public health problem which requires a global response. In recent decades, significant strides have been made in the treatment of HF with the appearance of angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARB),  $\beta$ -blockers, aldosterone antagonists, and device therapies.<sup>1</sup> However, mortality and morbidity is still high and further strategies are needed to avert or reduce adverse outcomes. 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, commonly called statins, are one of the novel but affordable pharmacological agents that have been investigated in patients with HF in recent years.

Statins are a class of drugs that have become one of the most important lipid lowering medications with proven efficacy in treatment of hyperlipidemia. Lovastatin was the first statin introduced into clinical practice in 1987. Now there are seven different statins available for clinical use. Statins are grouped into two main categories according to their origin: (1) naturally occurring statins of fungal origin or semisynthetic analogs, such as lovastatin, pravastatin, and simvastatin; or (2) synthetic statins including fluvastatin, atorvastatin, rosuvastatin, and pitavastatin.<sup>2</sup> Generally, statins are regarded as a remarkably safe and well-tolerated class of drugs, despite the withdrawal of cerivastatin in 2001.<sup>3</sup> Statins lower plasma cholesterol levels by competitive inhibition of the rate-

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determining enzyme HMG-CoA reductase in the mevalonate pathway. It is well-established that statins reduce morbidity and mortality in patients with coronary artery disease (CAD)<sup>4,5</sup> and prevent its progression to HF.<sup>6</sup> The mevalonate pathway also produces isoprenoids (farnesyl pyrophosphate and geranylgeranyl phosphate) as intermediates<sup>7</sup> which mediate the activation of various signaling molecules via the prenylation of small guanosine triphosphate (GTP) binding proteins: Rho, Ras, and Rac. Rho is involved in the activation of inflammatory cytokines and the formation of the actin cytoskeleton which affects intracellular transport, messenger ribonucleic acid (mRNA) stability, and gene transcription.<sup>8,9</sup> The Ras proteins regulate cell proliferation and hypertrophy, whereas Rac are involved in reactive oxygen species (ROS) generation via nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation. By inhibiting HMG-CoA reductase, statins decrease isoprenoid production and consequently downregulate Rho, Ras, and Rac mediated signaling pathways.<sup>7</sup> In addition to lowering cholesterol, statins exert cholesterol-independent effects through mevalonate inhibition; these include the enhancement of endothelial function, reduction of neurohormonal activation, decrease in proinflammatory cytokines, and the attenuation of ventricular remodeling – all of which play a critical role in HF progression and prognosis.

Clinical evidence from observational studies and retrospective and post hoc analyses of data from randomized trials in various cardiovascular conditions suggest the survival benefit of statins for HF.<sup>4,10–14</sup> Statins appear to have many pleiotropic effects believed to influence the pathophysiology to confer survival and further outcome benefits in HF. Notwithstanding these observations, two large scale randomized trials – the Controlled Rosuvastatin Multinational Study in Heart failure (CORONA)<sup>15</sup> and Gruppo Italiano per lo Studio della Sopravvivenza Nell'Insufficienza Cardiaca Heart Failure (GISSI-HF)<sup>16</sup> – which randomized patients to one type of statin at a low dose (rosuvastatin 10 mg) or a matching placebo, did not show improved survival in patients with HF. Clinicians, therefore, withhold statins due to reports of potential harmful effects and lack of substantial clinical trial data to support their use in HF.<sup>17</sup> Moreover, recent studies have not confirmed the detrimental effects of statins in HF reported in the CORONA and GISSI-HF trials.<sup>18,19</sup> The lack of clarity surrounding the effect of statins in HF raises important clinical questions. This review discusses the role of statins in the pathophysiology of HF, current evidence for statin use in heart failure, as well as possible future research directions.

## Potential mechanisms for beneficial effects of statins in the pathophysiology of HF

HF is a complex syndrome typified by hemodynamic and metabolic alterations, elevation of inflammatory and oxidative stress markers, endothelial dysfunction (ED), neurohormonal activation, plaque instability, and adverse cardiac remodeling. Statins show various favorable lipid-dependent and lipid-independent effects which are believed to alter the pathophysiological mechanisms and may bring about clinical benefits in HF.

### Endothelial function

The endothelium is a monolayer of cells lining the innermost surface of blood vessels; it serves as a functional and structural barrier between blood and the vessel wall to prevent platelet and leucocyte aggregation, control the permeability of plasma constituents, and regulate blood flow. The endothelium also regulates vascular tone through balanced production of vasodilators and vasoconstrictors in response to various stimuli.<sup>20</sup> Endothelium produces nitric oxide (NO) – a prime mediator of normal vascular function which dilates smooth muscles and relaxes myofibrils in response to endogenous (bradykinin, acetylcholine, and catecholamines) and exogenous (ischemia, shear stress, and temperature changes) stimulation.<sup>21</sup> The normal endothelium also provides anti-inflammatory and antiproliferative actions, and modulates fibrinolysis and coagulation pathways to maintain the hemostatic properties of blood vessels.<sup>22</sup> ED is characterized by decreased NO bioavailability due to impaired NO production by the endothelium and/or increased NO inactivation by ROS. The after effect is impaired vasodilatation, increased vasoconstriction, platelet aggregation, cytokine release, smooth muscle cell proliferation, and increased oxidative stress.<sup>23</sup> HF severity is associated with NO imbalance and the ensuing ED.<sup>24</sup> Decreased NO mediated vasodilation is common in ED, and appears to impair myocardial perfusion, reduce coronary blood flow,<sup>25</sup> and worsen ventricular function in HF.<sup>24</sup> ED also contributes to increased vascular stiffness and impairs the ability of arteries to distend, resulting in myocardial damage.<sup>26</sup> Furthermore, NO imbalance in ED alters matrix metalloproteinase (MMP) which affects cell migration, cardiac hypertrophy, and atherosclerotic plaque stability.<sup>27</sup> In HF, elevated levels of endothelin-1 (ET-1) – a potent vasoconstrictor – cause increased vasoconstriction, matrix production, and smooth muscle cell growth to worsen endothelial function and accelerate HF progression.<sup>27</sup> Reduced blood flow coupled with increased lactate

production from NO downregulation-mediated catabolism of free fatty acids partly accounts for exercise intolerance seen in patients with HF.<sup>28</sup>

Statins appear to induce NO synthetase (eNOS) – an enzyme which catalyzes the production of NO expression in human endothelial cells.<sup>29</sup> Statins have been shown to prevent the expression of caveolin, which is a negative regulator of eNOS.<sup>30</sup> Atorvastatin and simvastatin also inhibit ET-1 mRNA expression and reduce plasma levels of ET-1.<sup>31–33</sup> The protein kinase Akt has been identified as a major regulator of cell growth, survival,<sup>34</sup> and eNOS activity. Simvastatin induces Akt-mediated phosphorylation of eNOS, which gives rise to heightened NO production and endothelial cell survival.<sup>35</sup> Thus, statins' modulation of Akt activity may partly explain improvement in endothelial function, enhanced tissue perfusion, and reduced cardiovascular events seen in treated patients. Statins further inhibit Rho activation to increase endothelial NO production.<sup>29</sup> Experimental animal models confirm the beneficial effects of statins in ED;<sup>36,37</sup> likewise, clinical studies have demonstrated improved endothelial function with high, optimal, and low doses of statins.<sup>38–40</sup>

## Inflammation

HF is characterized by worsened inflammation due to the activation of proinflammatory cytokines, cell adhesion molecules, endothelial cells, cardiac myocytes,<sup>41,42</sup> the complement system, and cardiac autoantibodies,<sup>18</sup> which are produced by activated macrophages. Elevated proinflammatory cytokines – tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-1, IL-6, IL-10, and C-reactive protein (CRP) – have been implicated in HF morbidity and mortality.<sup>41</sup> These mediators are associated with left ventricular remodeling, enhanced cardiac myocyte apoptosis, ED, and incidence of anorexia and cachexia<sup>41,43</sup> in HF. Statins reduce plasma concentrations of proinflammatory cytokines<sup>44,45</sup> and have been shown in in vitro mononuclear cell cultures of normal human subjects.<sup>46</sup> A couple of in vitro studies suggest statins show anti-inflammatory properties through the inhibition of isoprenoid intermediates which serve as ligand attachments for intracellular signaling molecules in the mevalonate pathway.<sup>45,46</sup> Statins ameliorate inflammation in HF by favorably modulating many signaling pathways which include endothelial NO synthase, tissue-type plasminogen activator, ET-1, and plasminogen activator inhibitor I.<sup>33</sup>

Further, statins have been shown to reduce activation of the transcription factor NF $\kappa$ B,<sup>47</sup> which is associated with the

production of acute-phase proteins such as angiotensinogen, adhesion molecules, and cytokines,<sup>48</sup> and are all known to play an important role in the progression of HF.

## Myocardium remodeling

Myocardial remodeling is a genomic expression that leads to cellular, molecular, and interstitial changes in the heart characterized by change in size, shape, and function. HF progression is closely associated with ventricular remodeling which manifests as myocyte hypertrophy and ventricular dilation. Angiotensin II mediated mechanisms via the angiotensin II type 1 (AT1) receptor stimulation downstream of the mevalonate pathway account for ventricular remodeling in HF.<sup>7</sup> Statins downregulate AT1 receptor mediated negative effects such as enhanced sympathetic activation, vasoconstriction, sodium retention, ROS formation, and cardiac hypertrophy,<sup>49</sup> and thus prevent and/or attenuate myocardial remodeling.

Statins may also prevent remodeling via modulation of the effects of MMPs – protein-degrading enzymes involved in the breakdown and remodeling of tissues and organs including the myocardium. MMPs promote extracellular matrix degradation and remodeling whereas endogenous tissue inhibitors of MMP (TIMP) inhibit these effects.

An imbalance between activated MMP and TIMP promotes extracellular matrix degradation and myocardial remodeling in the development of HF.<sup>50</sup> Myocardial MMP levels increase in dilated cardiomyopathy.<sup>51</sup> Statins suppress expression of MMP-9, MMP-3, and MMP-1 while upregulating the expression of TIMP – a mechanism that could limit extracellular breakdown,<sup>52,53</sup> thereby inhibiting myocardial fibrosis and remodeling.

Studies in human and animal models have confirmed that statins attenuate myocardial remodeling by reducing cardiac myocyte hypertrophy, activation of MMP, fibrosis, and myocardial cell apoptosis.<sup>54,55</sup> A recent study reported that simvastatin inhibits TNF- $\alpha$  induced myofibroblast proliferation and MMP-9 secretion in a concentration dependent fashion in HF.<sup>56</sup> Statins also promote endothelial function and inhibit platelet activation<sup>57</sup> to reduce ventricular remodeling after acute myocardial infarction in coronary artery ligation animal models,<sup>58</sup> and these cardioprotective effects may be attributed to the statins' activation of the protein kinase Akt. The protein kinase Akt acts downstream of the mevalonate pathway to promote production of vascular endothelial growth factor and angiotensin<sup>59</sup> that stimulate endothelial cell survival and promote angiogenesis.

There is some evidence to suggest that statins promote regression of left ventricular mass in patients with angina pectoris<sup>60</sup> and produce antiarrhythmic effects in high-risk patients with HF through downregulation of potential unfavorable effects of AT1 receptor stimulation. Moreover, Krum et al<sup>61</sup> showed that statin therapy has no effect on left ventricular remodeling in patients with New York Heart Association (NYHA) functional class II or III ischemic or nonischemic HF when randomized to either rosuvastatin 40 mg or a placebo in addition to standard therapy for 6 months. The highest effective dose of rosuvastatin (40 mg) used achieved a remarkable 57% reduction in plasma low density lipoprotein (LDL) levels but failed to improve markers of cardiac remodeling. In another study, low dose statins exhibited enhanced endothelial cell proliferation, migration, and differentiation, but the effect was inhibited at high doses after acute coronary syndrome,<sup>62</sup> suggesting a biphasic effect requiring further investigations. Cerivastatin reduces collagen I and fibronectin deposition to prevent ventricular hypertrophy in a transgenic rat model and may ameliorate angiotensin II-induced cardiac hypertrophy, fibrosis, and remodeling, independent of plasma cholesterol levels.<sup>49</sup>

Galectin-3 is secreted by activated macrophages and a member of a family of proteins including soluble  $\beta$ -galactoside-binding lectins that have regulatory roles in fibrogenesis, inflammation, tissue repair, and cell proliferation. In HF, galectin-3 promotes myocardial fibrosis and inflammation, which are involved in myocardial remodeling.<sup>63</sup> Recent studies have reported an association between elevated circulating galectin-3 and poor clinical outcomes in patients with HF.<sup>64-66</sup> A sub-study of the CORONA trial has reported older patients with systolic HF of ischemic origin, receiving modern pharmacotherapy, who have low levels of galectin-3 may benefit from rosuvastatin treatment.<sup>67</sup>

## Neurohormonal activation

HF severity and mortality is linked to sympathetic nervous system activation, which is characterized by the upregulation of the renin-angiotensin-aldosterone system (RAAS), elevated plasma norepinephrine levels,<sup>68,69</sup> and enhanced natriuretic peptide concentration from the myocardium.<sup>70</sup> Statins, by downregulating AT1 receptor activation,<sup>46</sup> reduce sympathetic nerve activity<sup>45</sup> and modulate the vascular functions of ET-1 receptors<sup>71</sup> to attenuate ED and myocardial remodeling in HF.

Further, statins inhibit the RAAS in the vasculature<sup>57</sup> and myocardium<sup>58</sup> to ameliorate angiotensin II mediated

cardiac hypertrophy.<sup>59,72</sup> Simvastatin decreases plasma norepinephrine levels and renal sympathetic nerve activity, and normalizes baroreceptor responses in rat HF models.<sup>73</sup>

The natriuretic peptide axis is another important neurohormonal pathway that plays a fundamental role in HF. Plasma concentrations of natriuretic peptides aid in diagnosis and predict HF severity and prognosis.<sup>74,75</sup> Plasma brain natriuretic peptide (BNP) levels are elevated in ventricular dysfunction.<sup>76,77</sup> Elevated BNP levels are also associated with reduced functional capacity and impaired oxygen uptake at peak exercise in HF.<sup>78</sup> Recently, statins have been shown to modulate plasma BNP and its precursor amino-terminal pro-BNP (NT-proBNP) levels,<sup>79</sup> thus providing evidence for the neurohormonal downregulating effects of statins in HF.

## Ischemia

Recurrent ischemia is associated with the progression of ischemic cardiomyopathy.<sup>73</sup> Ischemia may lead to elevated extracellular matrix collagen reduction, cardiomyocyte necrosis, and apoptosis resulting in HF.<sup>80</sup> Inhibition of cholesterol synthesis reduces macrophage activation, foam cell formation, and plaque thrombogenicity, thus altering the lipid to cell ratio of the atherosclerotic lesion, making the plaque less liable to rupture. Statins promote atherosclerotic plaque stabilization by inhibiting inflammatory macrophages, depleting the lipid core, and strengthening the fibrous cap. Pravastatin inhibits macrophage cholesterol metabolism in *in vivo* and *in vitro* studies.<sup>81</sup> Indeed, statins have been shown to reduce atherothrombotic coronary events in patients with low LDL cholesterol levels,<sup>82</sup> thus extending anti-ischemic effects beyond plaque stabilization. Laboratory evidence demonstrates that statins reduce the extent of myocardial necrosis, preserve myocardial viability, and improve ventricular function in models of myocardial ischemia.<sup>83</sup> Statins improve coronary endothelial function and promote angiogenesis, thus reducing ischemia in HF.<sup>35,84</sup> Statins have also been shown to decrease the incidence of HF in patients with hyperlipidemia through the inhibition of cholesterol biosynthesis and other mechanisms which prevent recurrent ischemia.<sup>85</sup>

## Arrhythmia

Cardiac arrhythmias are common in HF and associated structural heart diseases. Atrial fibrillation (AF) coexists in a third of chronic HF patients and may represent either a cause or a consequence of HF.<sup>86</sup> AF is more common with the increasing severity of HF. Ventricular arrhythmia, which is often commonly seen in HF, is a major cause of

sudden cardiac death. Clinical evidence suggests beneficial effects of statins in atrial and ventricular arrhythmia in HF.<sup>87,88</sup> Data from a multicenter registry of patients with left ventricular systolic dysfunction have shown statin therapy to be associated with a significant reduction in the incidence of AF.<sup>87</sup> The cumulative rate of ventricular arrhythmia or sudden cardiac death was significantly reduced with statin therapy in ischemic cardiomyopathy patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial-II (MADIT).<sup>89</sup>

Statins reduce the incidence of arrhythmia through plaque stabilization, but a significant reduction in sudden death was reported in nonischemic cardiomyopathy,<sup>90</sup> suggesting non-cholesterol-lowering effects in decreasing arrhythmic events. Aside from anti-ischemic properties, other proposed mechanisms for the observed lowered incidence of arrhythmias with statin therapy in HF<sup>18</sup> are membrane-stabilizing and anti-inflammatory properties as well as improved autonomic function. Further, statins appear to improve left ventricular function and prevent remodeling, thereby decreasing the incidence of ventricular arrhythmias.<sup>91</sup> In addition, recent experimental data suggest Rac-1 guanosine triphosphatase (GTPase) may contribute to the pathogenesis of AF<sup>92</sup> and its suppression by statins may reduce arrhythmias. Nonetheless, recent meta-analyses have provided conflicting reports about the effects of statin therapy in patients with AF.<sup>88,93</sup> One such study showed that statin therapy is significantly associated with a decreased risk of incidence or recurrence of AF in patients with various cardiovascular conditions (sinus rhythm with a history of previous AF in those undergoing cardiac surgery or after acute coronary syndrome).<sup>88</sup> This meta-analysis provided robust evidence of the benefit of statins beyond their lipid lowering activity.<sup>88</sup> In a subsequent meta-analysis of published and unpublished studies of statins in various cardiovascular conditions, short term treatment with statins provided compelling evidence of AF prevention, however, long term treatment showed no protective effect of statins on AF.<sup>93</sup> Thus, prospective randomized clinical trials may still be needed to establish whether statins are beneficial and are an appropriate therapeutic option in all subgroups of patients for the treatment of AF, particularly HF.

In conclusion, statins exert pleiotropic effects in tandem with their lipid lowering activity to interfere with the pathophysiology of HF. Statins restore normal neurohormonal balance, prevent ventricular remodeling, prevent recurrent ischemia, reduce inflammation, and improve cardiac function in patients with HF. Statin treatment has been shown to

favorably affect endothelial function, increase capillary density as well as circulating endothelial progenitor cells, and slow the progression of coronary atherosclerosis. These potential beneficial effects result from both cholesterol-dependent and cholesterol-independent actions of statins on the mevalonate pathway. Thus, statins may reverse or attenuate progression and reduce mortality in patients with ischemic and nonischemic HF.

## Potential harmful effects of statins in HF

Statins are often not prescribed for patients with established HF. This is likely to be due to concerns about detrimental effects observed, largely, in retrospective studies. Three hypotheses have been suggested to explain the potential harmful effects of statins in HF.

First, the endotoxin–lipoprotein hypothesis, which postulates that higher levels of cholesterol might be beneficial in HF due to the ability of cholesterol to regulate inflammation.<sup>94</sup> HF is associated with increased inflammatory cytokines, which might be partly linked to elevated endotoxin levels. Endotoxins stimulate the release of cytokines in patients with HF. Circulating cholesterol and triglyceride-rich lipoproteins are natural nonspecific buffers of endotoxins, which are capable of binding and detoxifying bacterial lipopolysaccharides.<sup>95</sup> Thus, lowered circulating cholesterol may result in endotoxemia which is associated with poorer prognosis in HF.

Second, the ubiquinone hypothesis states that inhibition of ubiquinone synthesis in the mevalonate pathway possibly impairs mitochondrial energy production. Ubiquinone is present in all cells and is critical to mitochondrial respiration. Statins inhibit ubiquinone synthesis, which in turn impairs cellular energy production to adversely affect ventricular function and exercise tolerance in HF. Statins also inhibit ubiquinone synthesis, resulting in statin-induced myalgias and myopathy.<sup>96</sup>

Third, the selenoprotein hypothesis postulates that statins interfere with the enzymatic isoprenylation of selenocysteine transfer RNA (tRNA) to inhibit its maturation to functional tRNA molecules, thereby decreasing selenoprotein levels. Statin-induced myopathies have been associated with severe selenoprotein deficiency.<sup>97</sup>

The above three hypotheses, mechanisms, and possible harmful effects of statins in HF are summarized in Table 1. Despite these concerns, statin trials as well as systematic reviews and meta-analyses of statin treatment in heart failure have not established any detrimental effects, but suggest favorable effects in HF populations.<sup>18,19</sup>

**Table 1** Hypothesis, mechanism, and effects of statins in heart failure

Hypothesis	Mechanisms	Effects
Endotoxin–lipoprotein hypothesis	Inhibition of HMG-CoA reductase resulting in reduced circulating plasma cholesterol and triglyceride-rich lipoproteins	<ul style="list-style-type: none"> <li>Lowered cholesterol reduces provision of metabolic reserves and protection in increased resting energy consumption in HF<sup>98</sup></li> <li>Low cholesterol is associated with poorer HF outcomes<sup>94</sup></li> <li>Cholesterol and triglyceride-rich lipoproteins bind and detoxify endotoxin entering into the blood via GIT<sup>95</sup></li> <li>Endotoxin mediates HF progression via activation and release of proinflammatory cytokines</li> <li>Statin enhances circulating endotoxin levels and further elevates proinflammatory cytokines to worsen HF<sup>17</sup></li> </ul>
Ubiquinone hypothesis	Inhibition of ubiquinone synthesis downstream of the mevalonate pathway	<ul style="list-style-type: none"> <li>Ubiquinone is key to mitochondrial respiration in cells</li> <li>Statin decreases ATP production in the myocardium</li> <li>Statins inhibit the antioxidant function of ubiquinone and reduce cellular protection from free radical injury</li> <li>Statins adversely affect ventricular function and exercise tolerance in HF<sup>96</sup></li> <li>Statins inhibit ubiquinone synthesis to cause statin-induced myalgias and myopathy<sup>96</sup></li> </ul>
Selenoprotein hypothesis	Inhibition of selenoprotein synthesis by blockade of HMG-CoA reductase in the mevalonate pathway	<ul style="list-style-type: none"> <li>Selenoproteins are critical in skeletal and cardiac muscle metabolism</li> <li>Statins decrease selenoprotein production to cause skeletal and cardiac muscle myopathy<sup>99</sup></li> </ul>

**Abbreviations:** ATP, adenosine triphosphate; GIT, gastrointestinal tract; HF, heart failure; HMG-CoA, hydroxyl methyl glutaryl-coenzyme A.

## Clinical experience with statins in HF

Owing to potential unfavorable effects, earlier statin trials have excluded patients with symptomatic HF. But their pleiotropic actions suggest HF patients may benefit from statin treatment aside from cholesterol lowering effects. These claims have been partially confirmed, as post hoc analyses of statin trials in various cardiovascular conditions showed improved survival in patients with HF as summarized in Table 2.<sup>4,6,10–13,60,82,100–103</sup> Likewise, retrospective

and subgroup analyses of the effects of statins in HF trials which evaluated outcomes of other therapeutic agents showed reduced hospitalization and mortality.<sup>104–106</sup>

## Evidence from non-randomized studies

Many non-randomized studies have provided evidence to support the use of statins in HF. These non-randomized studies evaluated the effects of statins on outcomes in patients with HF and various cardiovascular conditions.

**Table 2** Retrospective analyses of statin trials in various cardiovascular conditions

Study	Sample	Population	HF in population	Intervention	Duration (years)	Outcomes in HF subgroup	Findings
4S <sup>4</sup>	4444	CAD/↑CHL	412	Simvastatin	5.4	Mortality	↓
CARE <sup>10</sup>	4159	MI/↑CHL	706	Pravastatin	5.0	Death from CAD, EF > 40% versus EF < 40%	↓
LIPID <sup>6</sup>	9014	MI/unstable angina	None at baseline	Pravastatin	6.1	Death	↓
MIRACL <sup>11</sup>	3086	Unstable angina	253	Atorvastatin	0.3	HF onset/rehospitalization	↔
PROSPER <sup>60</sup>	5814	PVD	NYHA class III-IV HF excluded	Pravastatin	3.2	HF hospitalization	↔
GREACE <sup>100</sup>	1600	CAD	118	Atorvastatin	3.0	Death, MI, unstable angina	↓
A-Z <sup>12</sup>	4497	ACS	221	Simvastatin	2.0	New HF onset	↓
GRACE <sup>103</sup>	19537	ACS	N/A	Atorvastatin	3.5	HF during hospitalization	↓
ALLIANCE <sup>13</sup>	2442	CAD	162	Atorvastatin	4.3	Hospitalization	↔
IDEAL <sup>101</sup>	8888	Acute MI	537	Atorvastatin	4.8	Risk of hospitalization	↔
HPS <sup>82</sup>	20536	DM, VD	HF excluded	Simvastatin	5.0	Hospitalization or death	↓
TNT <sup>102</sup>	10001	Stable CAD	781	Atorvastatin	4.9	Hospitalization	↓

**Notes:** ↔, no effect; ↓, decrease; ↑, increase.

**Abbreviations:** ACS, acute coronary syndrome; CAD, coronary artery disease; CHL, cholesterol; DM, diabetes mellitus; EF, ejection fraction; MI, myocardial infarction; PVD, peripheral vascular disease; VD, vascular disease; HF, heart failure.

Generally, statin therapy has been associated with reduced mortality in HF, however, equivocal results have been reported.<sup>103</sup>

A prospective study conducted at the Duke Heart Failure Clinic enrolled 96 consecutive outpatients with ejection fraction (EF) < 40% and NYHA class II to IV symptoms, and 14 healthy volunteers as a control.<sup>107</sup> Enrolled patients were on standard care appropriate to disease severity, were clinically observed directly and/or through family interactions during clinic visits, and had telephone follow-up over a 12-month period. They were observed for the occurrence of adverse events such as death, hospitalization for all causes, worsening heart failure, and angina. Combined therapy of ACE inhibitors and  $\beta$ -blockers was associated with lower CRP levels, improved survival, and reduced outcomes of hospitalization, worsening heart failure, and incidence of angina. Statin therapy had no effect on CRP levels and failed to improve outcome benefits, but did not worsen HF outcomes.<sup>107</sup> In another prospective cohort study, 6427 cardiologist-diagnosed HF patients (mean age of 69  $\pm$  11 years) were followed for 12 months.<sup>14</sup> Enrolled patients had varying degrees of renal insufficiency. In 2545 of the patients observed, statin use was associated with significantly better survival, after adjustment for other medications, even in advanced renal insufficiency compared with non-statin users.<sup>14</sup> In the Kaiser Permanente congestive HF cohort of 24,598 patients, Go et al evaluated the association between initiating statin therapy and risk of death and hospitalization among adults who had HF after a median follow-up of 2.4 years.<sup>108</sup> Statin therapy was associated with a 24% (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.72 to 0.80) lower risk for death and a 21% (HR 0.79, 95% CI 0.74 to 0.85) lower risk of hospitalization for HF. Statins were, however, more likely to be prescribed in younger patients and those known to have CAD, diabetes, or hypertension.

The difference in mortality was independent of cholesterol level or coronary disease.<sup>108</sup>

Foody et al evaluated the association between statin use and survival in a large retrospective observational study of 54,940 Medicare beneficiaries hospitalized for HF.<sup>109</sup> About 16.7% of the patients primarily diagnosed with HF without contraindications were discharged on statin therapy. Treatment with statin at the time of discharge was associated with significant reduction in mortality at 1 (HR 0.80, 95% CI 0.76 to 0.84) and 3 years (HR 0.82, 95% CI 0.79 to 0.85). It is worth noting that the significant reduction in mortality was independent of patient demographics, treatments, physician specialty, and hospital characteristics. There was a significant difference in mortality between statin users and nonusers independent of CAD status or total cholesterol levels.<sup>109</sup>

In conclusion, previous studies have reported decreased hospital admissions, improved surrogate endpoint outcomes, and overall mortality with statin therapy as summarized in Table 3, thus appearing to support its beneficial role in HF.<sup>14,109–112</sup> The equivocal results reported by the Duke Heart Failure Clinic study may be due to the small sample size of the study, which might have introduced type 2 ( $\beta$ ) errors, particularly when it assessed major clinical outcomes.<sup>107</sup> Further, overlap of treatment groups, particularly of patients that received  $\beta$ -blockers and statins created difficulty in detecting the effect of each medication on clinical outcomes. In addition, the assessment of CRP and medication use was determined at a single time point, which might have introduced potential inpatient variability and made longitudinal analysis of the effect of medications on CRP levels impracticable. Statin therapy has been associated with reduced hospital admissions and mortality in non-randomized studies as shown in Table 3. This body of evidence comes from non-randomized studies which are susceptible to confounding and bias and should be interpreted with caution and regarded as “hypothesis-generating.”

**Table 3** Major non-randomized studies evaluating effect of statins in heart failure outcomes

Study	Sample	Statin	Follow-up (months)	Outcome	Findings
Hognestad et al <sup>110</sup>	5301	Any	25	Mortality	Improved mortality
Joynt et al <sup>107</sup>	96	Any	12	C-reactive protein	No effect
Ezekowitz et al <sup>14</sup>	6427	Any	12	Mortality	Improved mortality
Ray et al <sup>111</sup>	28828	Any	96	Mortality	Improved mortality
Sola et al <sup>112</sup>	446	Any	24	Mortality/hospitalization	Improved outcomes
Go et al <sup>108</sup>	24598	Any	29	Mortality/hospitalization	Improved outcomes
Foody et al <sup>109</sup>	54960	Any	36	Mortality	Improved mortality
Senthil et al <sup>113</sup>	10510	Any	31	Mortality	Improved mortality
Maison et al <sup>114</sup>	281	Any	96	Mortality	Improved mortality
Paloma et al <sup>115</sup>	960	Any	109	Mortality	Improved mortality

## Randomized controlled trials (RCTs) of statins in HF

Secondary analyses of statin trials in various cardiovascular conditions show improved HF outcomes, though mechanisms are indistinct. RCTs have evaluated the effects of statin treatment on surrogate endpoints as well as major clinical outcomes (hospital admissions and mortality) in HF (Table 4).

Many small scale RCTs show improved cardiac and endothelial function, reduced inflammation and oxidation markers,<sup>116–121</sup> whereas in other trials, statins had shown neither favorable nor detrimental effects in HF.<sup>61,122,123</sup> Most of the studies appeared to be insufficiently powered to determine major outcomes such as hospital admissions and mortality, but significantly improved surrogate endpoints in HF. Sola et al<sup>119</sup> conducted one such study that randomized 108 nonischemic HF patients to atorvastatin 20 mg/day or a matching placebo and followed them up for 12 months. The study observed changes in left ventricular EF (LVEF) determined by transthoracic echocardiography as the primary endpoint and inflammatory and oxidation markers as the secondary endpoint. It observed a significant reduction in inflammatory and oxidation markers and improved LVEF. Interestingly, atorvastatin failed to reduce the frequency of hospital admissions or mortality in HF.

Laufs et al<sup>124</sup> corroborated the beneficial effect of cerivastatin with improved brachial artery flow mediated dilation, quality of life score, functional ability, and reduced levels of plasminogen activator inhibitor-1 (PAI-1), CRP, and TNF- $\alpha$  in patients with dilated cardiomyopathy in a 4-month follow-up period.

In another study, 60 HF patients of ischemic and nonischemic origin with NYHA class II to III and LVEF < 40% were randomized to atorvastatin 10 mg or a matching placebo for 4 weeks.<sup>125</sup> The efficacy was determined by measuring various biomarkers and flow-mediated vasodilatation at the baseline and at 4 weeks. Reactive hyperemia caused by flow mediated vasodilatation increased significantly and there was a consequent reduction in inflammatory markers such as vascular adhesion molecule-1 (VCAM-1), IL-6, and TNF- $\alpha$ .<sup>125</sup> These evidences suggest statins could be beneficial in both ischemic and nonischemic HF.

Conversely, neither favorable nor detrimental effects on cardiac function, endothelial function, and inflammatory markers were observed with studies that used high doses of statins in HF.<sup>61,123</sup> In one such study, 15 patients with Non-Ischemic Cardiomyopathy (NICM) on optimal heart failure treatment were enrolled in a randomized, double-blind, placebo-controlled, cross over trial.<sup>123</sup> Patients were

**Table 4** Randomized controlled trials of statins in heart failure

Study	Sample	Intervention	Duration (months)	Outcome	Findings
GISSI-HF <sup>15</sup>	4574	Rosuvastatin 10 mg	46	Mortality/CV admission	↔
CORONA <sup>16</sup>	5011	Rosuvastatin 10 mg	32	Mortality/CV admission	↔ mortality, ↓ CV admission
Vrtovec et al <sup>116</sup>	110	Atorvastatin 10 mg	12	Sudden cardiac death	↓
Wojnicz et al <sup>117</sup>	74	Atorvastatin 40 mg	6	LVEF and NYHA class	↑ LVEF; ↓ NYHA class
Xie et al <sup>118</sup>	119	Atorvastatin 10/20 mg	12	LVEF, QTc, and QTcd	↑ LVEF; ↓ QTc and ↓ QTcd
Yamada et al <sup>120</sup>	38	Atorvastatin 10 mg	31	LVEF and BNP	↑ LVEF; ↓ BNP
Krum et al <sup>61</sup>	95	Rosuvastatin 10–40 mg	6	LVEF	↔ LVEF
Sola et al <sup>119</sup>	108	Atorvastatin 20 mg	12	LVEF, markers	↑ LVEF; ↓ markers
Hamaad et al <sup>122</sup>	23	Atorvastatin 40 mg	3	HRV	↔ HRV
Node et al <sup>121</sup>	51	Simvastatin 5–10 mg	3	LVEF, NYHA, markers, and BNP	↑ LVEF; ↓ BNP, and ↓ markers
Erbs et al <sup>126</sup>	42	Rosuvastatin 40 mg	3	LVEF, FMD, CPCs, VEGF, and oxLDL	↑ LVEF, ↑ CPCs, ↑ FMD, ↑ VEGF and ↓ oxLDL
Bleske et al <sup>123</sup>	15	Atorvastatin 80 mg	3	LVEF, markers, BNP, and HRV	↔
Tsutamoto et al <sup>127</sup>	63	Atorvastatin 5/R2.5 mg	6	LVEF, markers, and BNP	↑ A, R ↔
Andreou et al <sup>128</sup>	60	Rosuvastatin 10 mg	1	MPO	MPO ↓
Tousoulis et al <sup>125</sup>	60	Rosuvastatin 10 mg	1	CPCs, FMD, and oxLDL	↑ CPCs, ↑ FMD, ↓ oxLDL ↓
Bielecka et al <sup>129</sup>	68	Atorvastatin 10–40 mg	6	6MWT, NYHA, and markers	↑ 6MWT, ↓ markers, ↓ NYHA
Tousoulis et al <sup>130</sup>	38	Atorvastatin 20 mg	1	Blood flow, markers	↑ Blood flow, ↓ markers
Horwich et al <sup>131</sup>	26	Atorvastatin 10 mg	3	MSNA, LVEF, BNP, and QoL	↔

**Notes:** ↔, No effect; ↑, Increase; ↓, Decrease.

**Abbreviations:** 6MWT, six minute walk test; A, atorvastatin; BNP, brain natriuretic peptide; CPCs, circulating progenitor cells; CV, cardiovascular; FMD, flow-mediated dilation; HRV, heart rate variability; LVEF, left ventricular ejection fraction; markers, inflammatory biomarkers; MPO, myeloperoxidase; MSNA, muscle sympathetic nerve activity; NYHA, New York Heart Association; oxLDL, oxidized low-density lipoprotein; QoL, quality of life; QTc, corrected QT interval; QTcd, corrected QT interval dispersion; R, rosuvastatin; S, simvastatin; VEGF, vascular endothelial growth factor.



randomized to atorvastatin 80 mg/day or matching placebo for the 12-week treatment period with a minimum of an 8-week washout period. The study evaluated surrogate markers such as NT-proBNP, high-sensitivity CRP, oxidized LDL antibody, soluble receptor TNF- $\alpha$ , TNF- $\alpha$ , circulating levels of intercellular adhesion molecule-1 (ICAM-1), VCAM-1, and P-selectin; all are parameters of noninvasive endothelial function and heart rate variability.<sup>123</sup> Statin therapy reduced LDL but was inert to the surrogate endpoints. Statin was neither beneficial nor detrimental as determined by surrogate marker measures. Similarly, the UNIVERSE study randomized 95 ischemic and nonischemic HF patients to rosuvastatin 40 mg/day or a matching placebo in addition to standard optimal therapy for a period of 6 months in a double-blind fashion.<sup>61</sup> The highest dose of rosuvastatin markedly reduced LDL cholesterol, but failed to improve cardiac function among patients in the treatment group.

Generally, many small randomized studies show statins to improve surrogate markers and endpoints, but do not reduce the frequency of hospitalization and mortality in HF (Table 4).<sup>116–121,125,127,128,131</sup> It appears the effect of statins shown in patients with HF varies among the different types of statins employed.

## Evidence from systematic reviews and meta-analyses

Evidence for statin therapy in HF mainly comes from non-randomized studies which evaluated its effects on clinical outcomes in patients with HF and various cardiovascular conditions.<sup>4,6,10–14,60,82,100–103,107,108,110–112</sup> Subgroup and post hoc analyses of statin trials in various cardiovascular conditions and HF trials that evaluated other pharmacological agents too provided substantial evidence for statin use in HF.<sup>104–106</sup>

Several systematic reviews and meta-analyses have been conducted to synthesize evidence for statin therapy in reducing major adverse events in HF. van der Harst et al<sup>19</sup> conducted the first systematic review mainly from retrospective, non-randomized trials and a few prospective randomized studies of statin treatment in HF. The researchers found that there is a paucity of prospective data required to determine the effect of statins on clinical outcomes in HF and concluded that available experimental, post hoc data, observational data, and theoretical considerations are inconsistent. The authors reported that: (1) lower cholesterol levels are associated with poorer outcomes in HF patients and may be related to the function of cholesterol as a scavenger for harmful endotoxins; (2) statins in HF may adversely affect mitochondrial function through inhibition of

ubiquinone; and (3) statins may decrease selenoproteins, which could result in decreased myocardial function. The researchers concluded that statin treatment may favor HF and recommended a large randomized clinical trial.

Ramasubbu et al's<sup>18</sup> meta-analysis from 13 studies – eleven retrospective studies and two prospective studies – reported that statin treatment favored HF with a significant 26% decrease in relative risk of mortality. Conversely, two recent meta-analyses performed on randomized clinical trials did not show improved survival with statin in HF.<sup>132,133</sup> It appears that the majority of patient data came from CORONA<sup>15</sup> and GISSI-HF<sup>16</sup> trials which randomized older patients to low dose rosuvastatin or matching placebo that may have skewed the summary statistic towards the results of these two large trials. From the various studies, low and moderate doses of statins seem to have better outcomes than high doses of statins in patients with HF. However, these claims were not confirmed when investigated with meta regression models and subgroup analysis. Similarly, the age and sex of patients did not influence the outcomes of HF with statin therapy in any of the meta-analyses.

## Recent evidence for statin therapy in HF

To provide more conclusive data on whether or not statins confer survival and other outcome benefits in HF, CORONA (2007)<sup>15</sup> and GISSI-HF (2008)<sup>16</sup> trials were conducted and sufficiently powered to evaluate outcomes of HF with statin treatment.

The CORONA study was a large randomized, placebo controlled trial of rosuvastatin 10 mg versus a placebo in patients with chronic symptomatic systolic HF of ischemic etiology.<sup>15</sup> The study enrolled 5011 patients aged  $\geq 60$  years with NYHA class II symptoms and an EF of  $<35\%$ , or NYHA class III to IV symptoms and an EF of  $<40\%$  with an average of 3 years follow-up. Rosuvastatin did not confer survival benefits, but reduced the number of HF hospitalizations in older patients with systolic HF. The CORONA trial may have failed to improve the primary outcome due to enrollment of elderly patients who may have had many comorbidities which could have attenuated the benefits. Further, the drug may have potentially interacted with the complex medical therapy of the geriatric population.

Moreover, as the CORONA study recruited ischemic HF patients, a significant number of patients could have developed a statin tolerance due to the long period of exposure from treatment of CAD, and prevention and treatment of HF, which meant they may have required a higher dose or a different statin to elicit the desired response to bring about a significant survival benefit. However, it is

reassuring to note that post hoc analyses of the CORONA trial show HF patients of ischemic origin with low levels of galectin-3<sup>67</sup> and NT-proBNP<sup>55</sup> may benefit from rosuvastatin treatment. The findings do not recommend the general use of statins in HF, but endorse their use in ischemic heart disease patients with plasma galectin-3 concentrations lower than 19.0 ng/mL and NT-proBNP less than 103 pmol/L (868 pg/mL). This observation complements that of the Heart Protection Study (HPS), where patients with low levels of BNP benefited from simvastatin treatment.<sup>134</sup> Nonetheless, the presence of HF was not recorded at baseline, and it was impossible to directly estimate the effect of simvastatin in patients with and without HF at randomization in the HPS. This evidence is from a retrospective analysis, which may thus be considered as hypothesis-generating and should be confirmed in a prospective study.

The GISSI-HF trial was a multicenter, randomized, double-blind study that assessed the effect of n-3 polyunsaturated fatty acids and rosuvastatin 10 mg versus placebo on the cardiovascular morbidity and mortality of patients with chronic symptomatic HF.<sup>16</sup> This study enrolled 4574 HF patients and employed broad eligibility criteria, requiring NYHA class II to IV symptoms of any etiology. There were no exclusions based on EF or baseline cholesterol levels. The GISSI-HF trial also did not show any significant effect of rosuvastatin on clinical outcomes in patients with chronic HF of ischemic and nonischemic etiologies after 3 years of follow-up. The GISSI-HF and CORONA studies reported minimal adverse drug events and statin therapy did not worsen HF outcomes, even in older patients with possibly compromised myocardium. Thus, it may be concluded that statins are safe in HF.

A recent study appraised the effect of statin on all-cause mortality in a large cohort of 10,510 consecutive patients (mean age 72 years) from the Veterans Affairs health system, with ischemic and nonischemic HF over 3 years.<sup>113</sup> The study also assessed the effect of incremental duration of statin therapy on mortality. Statin use was associated with significantly lower all-cause mortality among the veterans. Most of the enrolled patients used simvastatin and atorvastatin, which might have accounted for the marked improvement in survival.<sup>113</sup> Patients were comparable to those of the GISSI-HF study,<sup>16</sup> which recounted a nonsignificant 29% mortality compared with the placebo group, as both studies recruited elderly patients with ischemic and nonischemic HF. In this study, patients who used statins for <25% of the 3-year follow-up had no benefit, but survival was apparent when statin use was >25% of the follow-up duration, suggesting compliance as

an important confounding factor. A major weakness of the GISSI-HF study was noncompliance, as about a third of the study population were not compliant with statin treatment for various reasons and may have influenced its result. Likewise the Veterans Affairs study was similar to the CORONA study (mean age: 73 years, mortality rate: 11.9%), but the reason for the disparity in mortality rate recounted remains unclear. Differences in revascularization rates, aggressive lipid control, and other comorbid conditions<sup>135</sup> may have accounted for the disparity in mortality rates. The CORONA and GISSI-HF studies assessed the effect of one type of statin at a low dose, thus the insignificant results provide inconclusive evidence for the class effect of statins in HF. The majority of patients in the Veteran Affairs health system study used simvastatin and atorvastatin; therefore, an evaluation of the effects of various statins in patients with both ischemic and nonischemic HF may be required.

Similarly, a prospective study assessed the effects of statin therapy in 960 elderly HF patients of ischemic and nonischemic etiologies for a maximum follow-up of 9 years.<sup>115</sup> Most patients were prescribed atorvastatin or simvastatin and statin use generally was associated with improved survival (HR 0.45, 95% CI 0.37 to 0.54) for HF.<sup>115</sup> In contrast to the CORONA and GISSI-HF studies, statin was independently and significantly associated with lower mortality after adjusting for all confounders, such as concurrent medication, concurrent therapies, comorbid conditions, gender, HF etiology, HF duration, cholesterol level, LVEF, NYHA class, and sex.

Rosuvastatin, used in the CORONA and GISSI-HF studies, is hydrophilic and employs active transport into hepatocytes to exert its effect.<sup>2,3</sup> It penetrates poorly into extra hepatic tissues; thus, it has less risk of adverse effects, but has a very low uptake by cardiac muscles to exert the pleiotropic effects believed to contribute greatly to attenuate HF symptoms.

Conversely, atorvastatin and other lipophilic statins commonly prescribed in clinics appear to have higher levels of exposure in extra hepatic tissues and very high uptake into cardiac muscles.<sup>2,3</sup> It appears that the effect of statins should not be considered a class effect since small and large scale trials that employed rosuvastatin appeared not to have had a beneficial effect in HF. In addition, a recent meta-analysis of RCTs, which included the CORONA and GISSI-HF trials, suggests lipophilic statins have a significant outcome benefit which was not observed in patients randomized to rosuvastatin or placebo.<sup>133</sup> However, a class effect of statins at relatively low doses has been reported in elderly cohorts

of congestive HF with atorvastatin, simvastatin, pravastatin, and lovastatin without rosuvastatin in a large population study.<sup>136</sup>

Maison et al<sup>114</sup> recently followed a cohort of 281 chronic HF patients after hospital admission through a search of the health insurance and national mortality data base for 1 year and 8 years, respectively. The use of  $\beta$ -blockers and statins was associated with statistically significant survival ahead of ACE inhibitors, spironolactone, and diuretics after controlling for confounders using multivariate analysis. Statin therapy was associated with better survival at 8 years. The findings correspond with those of the prospective study that followed patients for about 9 years, suggesting that statins may reduce mortality after longer follow-ups.<sup>115</sup>

Given that this recent evidence for statin therapy comes from non-randomized studies which suffer from threats of internal validity arising from risk of confounding and bias, the robust study design and statistical analyses employed by Thambidorai et al<sup>113</sup> and Gastelurrutia et al<sup>115</sup> and Maison et al,<sup>114</sup> eliminate or partly address the bias. Granted that, in these studies, the benefit of statins was assessed in real life healthcare settings without strict inclusion criteria questioning the external validity of RCTs, these findings complement previous evidence provided by small RCTs that employed lipophilic statins.<sup>116,117,121</sup> The two recent large trials – CORONA<sup>15</sup> and GISSI-HF<sup>16</sup> – confirmed the surrogate effects exhibited by statins in small randomized trials but failed to ultimately confer survival benefit. The choice of statins, dose, as well as patient background, may possibly have accounted for the findings of the CORONA and GISSI-HF studies in contrast with earlier and recent studies. On the other hand, evidence from recent studies, though non-randomized, complements the findings of the small randomized trials but seems to suggest lipophilic statins provide better outcomes than hydrophilic statins in patients with HF.<sup>113,115</sup>

## Statins and HF comorbid conditions

Comorbidities are common in patients with HF. While some of these contribute to the underlying pathogenesis, others may lead to the progression, associated poor prognosis, and consequently increase mortality in HF patients. Germane to appropriate management of these comorbidities exists the concern of polypharmacy in hitherto overburdened HF patients.

Hypertension causes or coexists with HF and its management in HF could be challenging. Statins possess many pleiotropic effects including improvement in endothelial function, reduction in inflammation and oxidative stress, and downregulation of angiotensin II receptors and endothelin,

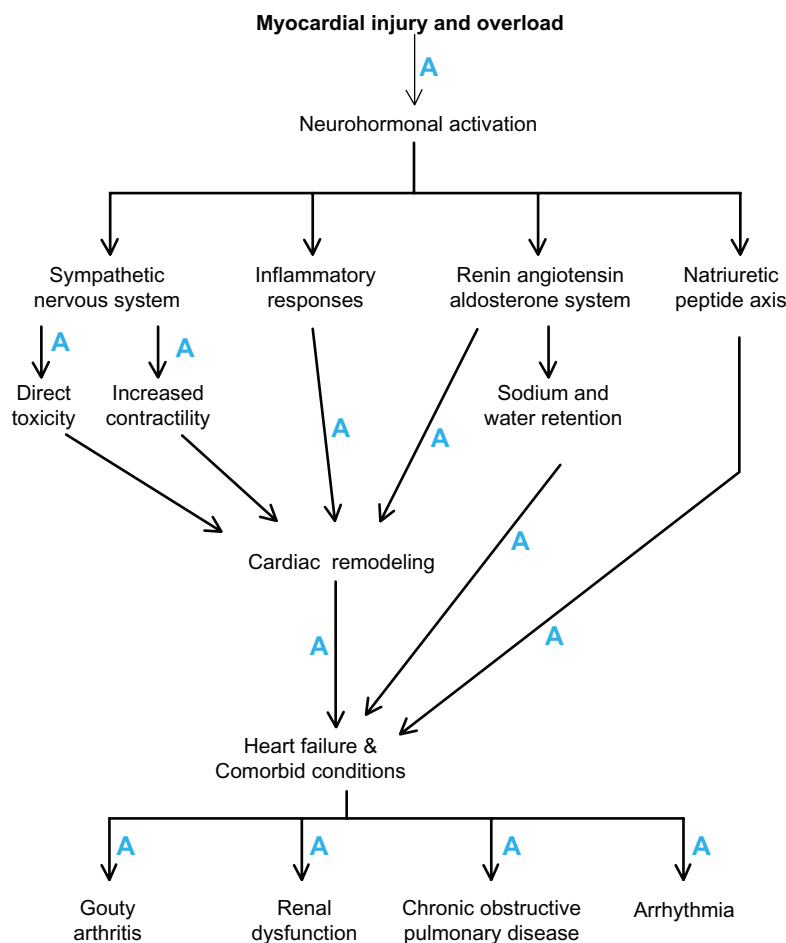
which would suggest that statins may reduce blood pressure in patients with hypertension. Indeed, evidence from various experimental models suggests antihypertensive actions, though clinical evidence has been inconclusive.<sup>137</sup> Statins may augment actions of ACE inhibitors, ARBs, and  $\beta$ -blockers, which double as antihypertensive and conventional pharmacological agents for HF.<sup>138</sup>

Further, hyperuricemia is frequently present in chronic HF and has been attributed to increased production or decreased urinary excretion of uric acid (UA) or both in a compromised circulation.<sup>135</sup> An elevated plasma level of UA is linked with a wide variety of injurious processes comprising increased inflammatory markers, cell apoptosis, and ED,<sup>139</sup> which could cumulatively worsen HF. Serum UA is known to be a marker of HF prognosis and mortality<sup>140–142</sup> and statins have been shown to decrease UA levels by increasing urate excretion.<sup>143,144</sup>

Chronic renal failure (CRF) is a condition which often complicates pharmacotherapy in HF. CRF is also associated with hyperuricemia worsened by diuretic therapy, which is critical in the management of fluid retention, but increases UA levels. Statins have been shown to improve renal function partly through their modulation of the mevalonate pathway to reduce oxidative stress, inflammation, and hypercoagulability,<sup>145</sup> all of which are linked with renal dysfunction via increased atherosclerosis and ED.<sup>144,146</sup>

Chronic obstructive pulmonary disease (COPD) is a common comorbid condition with incidence varying from 20% to 30% in patients with HF.<sup>147</sup> COPD is an independent predictor of mortality in HF.<sup>148</sup> Beta-adrenergic agonists are commonly prescribed as mainstay therapy in COPD, but have been shown in a meta-analysis to significantly increase the risk of cardiovascular events such as tachycardia, AF, myocardial infarction, and HF.<sup>149</sup> The current therapy relieves symptoms and reduces hospitalization, but does not change disease progression or reduce mortality.<sup>150</sup> Statins inhibit isoprenoid production on the mevalonate pathway to reduce inflammation (systemic and pulmonary), thereby improving exercise tolerance and reducing mortality in patients with COPD.<sup>151,152</sup>

Statins exert various molecular mechanisms that may modulate the pathophysiology to an extent that may be identical to or even seem to overlap those of currently recommended HF therapies. Additionally, statins may favorably modulate the pathogenesis of HF comorbidities and possibly reverse and/or reduce progression as well as issues associated with polypharmacy in patients with HF. Figure 1 illustrates how statins influence the pathophysiology



**Figure 1** Statins influence the pathophysiological mechanisms in heart failure (indicated by A).

of HF and its comorbidities. Therefore, statins could merit second line treatment consideration in HF guidelines.

Further research is required to clarify whether statins are still beneficial in HF and warrants consideration into guidelines for the treatment of HF. A sufficiently powered randomized trial to evaluate the effect of other statins apart from rosuvastatin in HF is necessary. In countries where another statin trial in HF is unethical and unlikely, a comparative effectiveness research study is required to compare the efficacies of various statins in patients with HF using data from registries, hospital records, and insurance claims. Alternatively, a direct head to head comparison of the two potent statins (rosuvastatin and atorvastatin) may be ethical since no eligible patients are denied treatment or given a placebo. In addition, an indirect comparison meta-analysis of RCTs which compared statin versus placebo or no statin treatment in HF may be required in the absence of adequately powered head-to-head comparison studies to investigate whether statins are comparable or some types have superior efficacy over others.<sup>153</sup>

## Conclusion

Statin therapy for hypercholesterolemia and primary and secondary prevention of CAD has been established, however, their effects on HF survival remain unclear. The latest evidence from prospective but non-randomized studies complements that of small randomized statin trials in HF and suggests lipophilic statins provide better clinical outcomes than hydrophilic statins. We therefore recommend a randomized trial to evaluate the class effect of statins in HF, but until sufficient evidence is amassed, statin treatment should be based on recommendations from guidelines. Our evidence shows that statins modulate the pathophysiology of HF to an extent that may be identical or even overlap recommended HF therapies. Moreover, statins exert mechanisms on various pathways to reduce or reverse progression of many HF comorbidities beyond the therapeutic actions of some of the mainstay medical therapies and could, in the worse scenario, merit second line or adjuvant therapy consideration in treatment guidelines for HF.

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## Disclosure

The authors report no conflicts of interest in this work.

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