Statins in Heart Failure

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KEYWORDS

• Statin • Heart failure

Heart failure (HF) is a complex syndrome that is comprised of hemodynamic, metabolic, and neurohormonal abnormalities. It is the leading cause of hospital admissions in the United States. Over the past decade, the mortality and number of hospitalizations caused by HF are surging despite rapid advancements in clinical management. At the organ level, the structural remodeling of the left ventricle leads to progression of HF. At the cellular level, patients who have HF exhibit endothelial dysfunction, increased inflammation and oxidative stress, cellular migration and apoptosis.[1,2] In patients who have New York Heart Association class II through III HF, it has been demonstrated that short-term treatment with atorvastatin improves forearm vasodilatory response to reactive hyperemia and decreases serum levels of cytokines like endothelin-I and coenzyme 10.[3] These findings indicate that statins may be useful in patients who have HF and normal cholesterol levels, by affecting forearm vasodilatory response to reactive hyperemia and inflammatory process.

Coronary artery disease (CAD) is the most common underlying cause of HF. HF occurs in patients who have CAD primarily after they have had a coronary event such as myocardial infarction (MI).[4,5] The structural changes that occur after MI lead to left ventricular (LV) remodeling, which, unless interrupted by neurohormonal modulation, progresses to increasing LV dimensions and geometric changes.[6] Obviously, a therapy effective at preventing the coronary event will be effective in preventing development of HF in most patients who have CAD.

The benefits of statins (3-hydroxy 3-methyl glutaryl coenzyme A reductase inhibitors) in ischemic heart disease have been established to extend beyond their lipid-lowering effects. Pleiotropic effects of statins include inhibition of cellular proliferation and migration, plaque stabilization, and improved endothelial function.[7]

Based on the fact that CAD is the predominant etiology of HF, most patients who have HF would appear to be candidates for statin therapy. Landmark clinical trials of statins, however, largely have excluded patients who have advanced/decompensated HF. Based on limited data from various different clinical trials, several recent reports have shown beneficial effects of statins in patients who have HF. It is important to note that these results are based primarily upon limited data available from small numbers of patients who have stable/mild HF. Therefore, safety and efficacy of statins in HF remain elusive.

This article reviews the results from several recent reports describing the safety and efficacy of statin therapy in the setting of HF. It additionally discusses the ongoing controversy regarding the lipid paradox and possible mechanisms responsible for potential benefit of statin therapy in HF.

THE PLEIOTROPIC EFFECTS OF STATINS

The hallmark of chronic HF (CHF) is the adverse remodeling of the left ventricle associated with progressive LV dilatation and LV dysfunction.[2] It now is recognized increasingly that HF also is associated with systematic and vascular inflammation as denoted by increased levels of inflammatory biomarkers and cell adhesion molecules. This remains an issue despite advancements in medical management and successful employment of Renin Angiotensin Aldosterone System and β-blockers. Statins have been used widely in chronic ischemic heart disease and have been shown to improve vascular endothelial function by amplification of

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endogenous nitric oxide (NO) production[8] and mitigation of inflammatory biomarkers such as C-reactive protein (CRP), oxidized low-density lipoprotein (LDL), and cytokines like tumor necrosis factor α (TNF-α) and interleukin (IL)-6.[9,10] The end result is reduction in hypertrophy and prevention of cardiac remodeling through effects of statins on matrix secretion.[11] A significant reduction in cardiac remodeling also might occur because of a decrease in oxidative stress at the molecular level by statins. This potentially is achieved by local control of the renin angiotensin system, local inflammation, and modulation of cytokine activation.[12] This effect appears to be exclusive to statins and not related to other lipid- lowering agents. In one HF study, simvastatin but not ezetimibe improved endothelial function, despite a similar degree of cholesterol lowering in both groups.[13]

Neurohormonal and Cytokine Effects of Statins in Heart Failure

Progression of HF leads to an activation of the neurohormonal system promoting an overexpression of cytokine as described previously. Monocyte adherence to endothelium in HF is overexpressed and leads to further production of cytokines by endothelium. Reduction of these inflammatory mediators by statin therapy in patients who have HF has been validated in small pilot studies, but this had not been confirmed in randomized clinical trials.[14,15] The effects of statins on anti-inflammatory markers appear to be independent of their effects on cholesterol levels. Tousoulis and colleagues[9,10] have demonstrated reduction in antithrombin III, protein C, IL-6, factor V, tPA, vascular cell adhesion molecule, P-selectin, and TNF-α involving patients who have NYHA class II through IV HF in two different trials. Whether the anti-inflammatory activities of statins directly translate to clinical benefits has yet to be shown in randomized clinical trials.

Myocardial Effects

In several studies of patients with acute MI ST segment Elevation Myocardial Infarction (STEMI) or Non ST segment Elevation Myocardial Infarction (NSTEMI), new or continued use of statins within the first 24 hours of the acute event has been shown to reduce 24-hour morbidity and mortality. In animal models of experimental MI, statins also have been shown to improve endothelial function, increase endogenous production of NO, inhibit platelet activation, and attenuate ventricular remodeling during the postinfarction period. This is postulated to be linked to the effects of statin on protein kinase called Akt, which has been shown to prevent apoptosis.[16,17] In a rat model of cardiomyopathy, Lovastatin reduced LV hypertrophy and fibrosis;[18] however in human studies, the results are conflicting. Observational data from the The Hypertension High Risk Management (HYRIM) trial study showed reduction in LV mass. In this study, patients were followed for up to 4 years on fluvastatin.[19]

Reduced Oxidative Stress with Statins

It is known that there is evidence of increased oxidative stress after MI. In experimental models, use of antioxidants has been shown to impede the adverse remodeling process. Reduced oxidative stress potentially can improve LV dysfunction and reduce ventricular dilatation by virtue of deactivation of matrix metalloproteinases, which drive matrix turnover and advance the left ventricle remodeling that subsequently can lead to progressive LV dysfunction.[20]

Statins have antioxidant properties and inhibit reactive oxygen species (ROS) generation through modulation of nicotinamide adenine dinucleotide phosphate (NADPH) pathway, hence blunting the injurious effects of ROS, including effects on antioxidant enzymes, lipid peroxidation, LDL cholesterol oxidation, and NO synthase.

In HF, an increase in ROS may be driven by various mechanisms, including the activation of the renin angiotensin system, cytokine activation, local inflammation, and mechanical stimuli.[12] Upregulation of angiotensin 2 type 1 (AT1) in HF leads to vasoconstriction, fluid and sodium retention, increased sympathetic activity, and myocyte hypertrophy.[17] Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are highly effective inhibitors of angiotensin 2-dependent NADPH oxidase activation. Statins appear to inhibit the NADPH pathway through small GTPases such as Rac.[21] Several experimental studies have indicated favorable effects of statins on cardiac hypertrophy and remodeling after MI.[17]

DOES LIPID PARADOX EXIST IN HEART FAILURE?

There are limited clinical data supporting the fact that statins may harm patients who have HF. Small observational studies have shown that lower cholesterol concentrations are associated with a poor prognosis and increased mortality in HF. This phenomenon is postulated to be multifactorial and may reflect the onset of cardiac cachexia, liver dysfunction, and impaired nutrition. In theory, statin use in HF remains controversial. This essentially has been based upon the so- called endotoxin hypothesis, which requires the presence of lipoproteins to eliminate bacterial lipopolysacharides

and inhibit cytokine release.[22] On the contrary, lowering of lipoproteins by statins would increase the lipopolysaccharides and promote infection in patients who have HF.[23]

Statins are known to cause a decrease in coenzyme Q10, thus worsening oxidative stress and decreasing mitochondrial and myocardial function.[24] In patients who have HF, cholesterol modulates inflammatory immune activity, in particular endotoxin levels. Therefore, it is conceivable that lowering cholesterol levels with the use of statins may prove detrimental in some patients who have HF.[25] Further studies are needed to elucidate on these aspects of statin therapy in patients who have HF.

CURRENT LEVEL OF EVIDENCE ABOUT ROLE OF STATINS IN HEART FAILURE

Although some experimental evidence from small studies suggest that statins are beneficial in HF, one should exercise caution in interpreting clinical outcome data that largely are obtained from various statin trials and studies done in patients who have HF. In most of the recent reports, the evidence comes primarily from observation made by retrospective analyses. These results are limited further by small and relatively poorly defined cohorts of HF patients in the study. Also, the endpoints are not prespecified pertaining to the impact of statin therapy on HF. Hence, the available information is weak and incomplete regarding the long-term efficacy of statins in HF (**Box 1**).

RETROSPECTIVE ANALYSIS OF STATIN AND HEART FAILURE TRIALS
The Statin Trials

First indirect information about the beneficial effects of statins in HF came from the posthoc analyses of two landmark clinical trials of statin therapy (**Table 1**). In the 4S study,[28] patients who had known CAD and hypercholesterolemia were included. Patients who had symptomatic HF were excluded. Of the 4444 patients on statin therapy, 412 developed symptomatic HF during follow-up. A lower incidence of symptomatic HF was observed in the simvastatin group, compared with the placebo group (184 vs. 228). Also, there was a 19% relative risk reduction (RRR) in 5-year mortality with statin therapy in patients who had HF (25.5% vs. 31.9%, CI not reported).

The Cholesterol and Recurrent Events study[26] was a randomized trial of pravastatin for secondary prevention of cardiovascular events after MI. This study excluded symptomatic patients who

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Box 1
Beneficial and adverse effects of statins in heart failure

Beneficial effects

Reduced in coronary events

Improved endothelial function

Anti-inflammatory effects

Decreased endothelial adhesion markers

Reduced oxidative stress

Increased angiogenesis

Prevention of cardiac remodeling

Reduced platelet activation and thrombosis

Reduction in apoptosis

Reduced myocardial hypertrophy

Improved neurohormonal balance

Improved renal function

Adverse effects

Reduced synthesis of ubiquinone (coenzyme Q10)

Decreased binding of lipopolysaccharides

Probable impairment of cellular function

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had HF or those who had LV ejection fraction (LVEF) less than 25%. Of 4159 patients, 706 had LVEF between 25% and 40%, while the rest had LVEF greater than 40%. A posthoc analysis compared the outcome in two subgroups regarding the rate of cardiovascular death or nonfatal MI, and showed 28% versus 23% RRR, respectively, in patients who had LVEF greater or less than 40%.

The Treat to New Targets (TNT) study evaluated efficacy of atorvastatin in 10,001 patients who had stable CAD and LDL less than 130.[37] A subgroup analysis of 781 patients who had HF demonstrated that 80 mg of atorvastatin reduced HF hospitalizations to a greater extent than 10 mg. This study suggested an incremental benefit of high-dose statin therapy in preventing HF hospitalizations, with an RRR of 26% (hazard ratio [HR] 0.74, CI 0.59 to 0.94, $P = .01$) with high-dose statin. For each 1 mg/dL reduction in LDL cholesterol on treatment, the risk of hospitalization for HF was reduced by 0.6% ($P < .007$). This study was limited by the fact that no information on systolic or diastolic function was available. Also, patients who had advanced HF (NYHA classes III to IV) were excluded.

Subgroup analysis from the Incremental Decrease in Events through Aggressive Lipid

Table 1
Subgroup analysis of heart failure patients in major randomized trails of statin therapy

Study	Population	Major Characteristic	Patients with Heart Failure	Outcomes in Heart Failure Subgroup	Outcomes Result	Statin	Follow-up (Years)
CARE[26]	4159	Myocardial infarction (MI) and high cholesterol	706	Death from coronary artery disease (CAD), ejection fraction >40 versus <40	Reduction	Pravastatin	5
LIPID (1998)[38]	9014	MI and unstable angina	None at baseline	Death	Reduction	Pravastatin	6.1
4S (1999)[28]	4444	CAD and high cholesterol	412	Mortality	Positive effect	Simvastatin	5.4
MIRACL[29]	3086	Unstable angina, NSTEMI	253	Onset of heart failure (HF), rehospitalization	No difference	Atorvastatin	4 wks
PROSPER[27]	5814	Peripheral vascular disease or related risk factors	HF NYHA class III–IV excluded	hospitalization for HF	No difference	Pravastatin	3.2
GREACE[30]	1600	CAD	118	Death, nonfatal MI, unstable angina	Reduction in primary endpoints	Atorvastatin	3
A-Z[31]	4497	Acute coronary syndrome	221	New onset heart failure	Reduction in new onset HF	Simvastatin	0.5-2
GRACE[32]	19,537	ACS	N/A	HF during hospitalization	Reduction	Atorvastatin	3.5
ALLIANCE[33]	2442	CAD	162 HF patients	Hospitalization	Reduction (p = not significant)	Atorvastatin	4.3
IDEAL[34]	8888	Acute MI	537	Risk of hospitalization	No effect	Atorvastatin versus simvastatin	4.8
HYRIM[19]	568	Hypertension	None at baseline	LV mass	Reduction	Fluvastatin	4
PROVE IT (2006)[35]	4162	ACS	N/A	Hospitalization	Reduction	Atorvastatin versus pravastatin	2
HPS (2007)[36]	20,536	Diabetes mellitus, vascular disease	Severe HF excluded	Hospitalization or death	Reduction	Simvastatin	5
TNT (2007)[37]	10,001	Stable CAD and LDL <130	781	Hospitalization	Positive effect	Atorvastatin 10 mg versus 80 mg	4.9

Lowering study[34] also exhibited a 19% nonsignificant reduction (HR 0.81, CI 0.62 to 1.05 $P = .11$) in risk of hospitalization in patients receiving atorvastatin 80 mg/d compared with simvastatin 40 mg/d. In the Aggressive Lipid Lowering to Alleviate New Cardiovascular Endpoints (ALLIANCE) study,[33] treatment with atorvastatin was associated with a 27% reduction in hospitalization because of HF (CI 0.49 to 1.09, $P =$ not significant [NS]), while Pravastatin or Atorvastatin Evaluation and Infection Therapy - Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) reported a 45% reduction in HF hospitalization[35] with 80 mg of atorvastatin (CI 0.35 to 0.85, $P = .008$).

The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID)[38] trial observed mortality benefit of pravastatin in HF ($P < .05$), while the Heart Protection Study (HPS) showed a marginal reduction in mortality (3.4% in simvastatin vs. 3.9% in placebo group) and hospitalization.[36] The A to Z trial[31] showed reduction of new-onset heart failure by 18%. In retrospective analysis of the HYRIM study,[19] a reduction of LV mass was observed over 2 years of follow-up during treatment with fluvastatin ($P = .014$).

Contrary to the previously mentioned reports of benefit with statin therapy, the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)[27] trial included elderly patients (70 to 82 years) with history or risk factors for vascular disease and found no difference in hospitalization for HF between pravastatin and usual care groups. Also, the Myocardial Ischemia Reduction with Acute Cholesterol Lowering (MIRACL)[29] trial showed no difference in onset or hospitalization for HF in patients treated with statins. The MIRACL trial, however, was a short-term study lasting only 16 weeks, and this period might not be sufficiently long enough to have significant impact on HF outcome.

Observation from the Heart Failure Trials

Retrospective reviews of statin use in patients enrolled in HF trials have evaluated the role of statins on the mortality and hospitalization for HF extensively (**Table 2**). First compelling evidence came from the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial, in which data from the subset of 134 HF patients on statin (out of a total of 1153 patients) were evaluated.[45] Ninety-three patients were on statin at enrollment, while others were started on during follow-up. Compared with those not on statin therapy, there was a 62% RRR (HR 0.44, CI 0.26 to 0.75) for total mortality.

Horwich and colleagues[45] also studied effect of statin therapy in patients with systolic HF. In a population of 551 patients, statin therapy improved survival in ischemic and nonischemic cardiomyopathy ($P = .001$ for both). Krum and colleagues[43] reported similar effect in (CIBIS)-II and Valsartan Heart Failure Trial (Val-HeFT) trials.[44] In the Cardiac Insufficiency Bisoprolol (CIBIS)-II trial, survival was compared in patients who had HF on statin/bisoprolol, statin/placebo, placebo/bisoprolol, and placebo-only groups. Overall, statin use was associated with better survival compared with no statin use ($P < .05$), with greatest survival benefit in statin/bisoprolol group. A posthoc analysis of data from the Val-HeFT study examined the effect of statin use at baseline on outcomes in 5010 patients who had NYHA class II to III CHF. Statin use significantly reduced the risk of mortality with 19% RRR (HR 0.81, 95% CI 0.70-0.94). Patients with an ischemic etiology appeared to derive more survival benefit from statin therapy than those with a nonischemic etiology.[44]

In the OPTIMAAL[41] trial, the outcomes were evaluated in patients receiving statin and beta blockers alone, versus both of them or none. In 2467 patients, statin use was associated with reduced hospitalization (RR of 9%, $P < .05$), cardiovascular death as well as all cause mortality and recurrent infarction.

The COMPANION[48] trial enrolled 1520 patients with advanced HF randomized to cardiac resynchronization therapy with or without automatic implantable cardioverter defibrillator compared with medical therapy alone. Of the total 608 patients, 40% were on statin. The patients on statin therapy had a 28% RRR (HR 0.72, CI 0.56 to 0.92) in mortality.

Evaluation of Statin Therapy in Observational Studies of HF Cohorts

Several systematic reviews of HF cohorts also suggest that statins may be beneficial in this patient population (**Table 3**). Ray and colleagues[52] studied the impact of statin therapy in patients hospitalized for newly diagnosed CHF. Of 28,828 patients, only 1146 were on various statins. In the observation period of 1.3 years for statin users and 2 years in nonusers, mortality, nonfatal MI, and stroke were studied as primary outcomes. A 38% RRR (CI 0.63 to 0.83) in combined outcomes and a 33% RRR (CI 0.57 to 0.78) in mortality were observed in patients on statin therapy.

In a recent large retrospective observational study of Medicare beneficiaries hospitalized for HF, Foody and colleagues[54] evaluated the association between statin use and survival using the

Table 2
Statin use from major heart failure trials

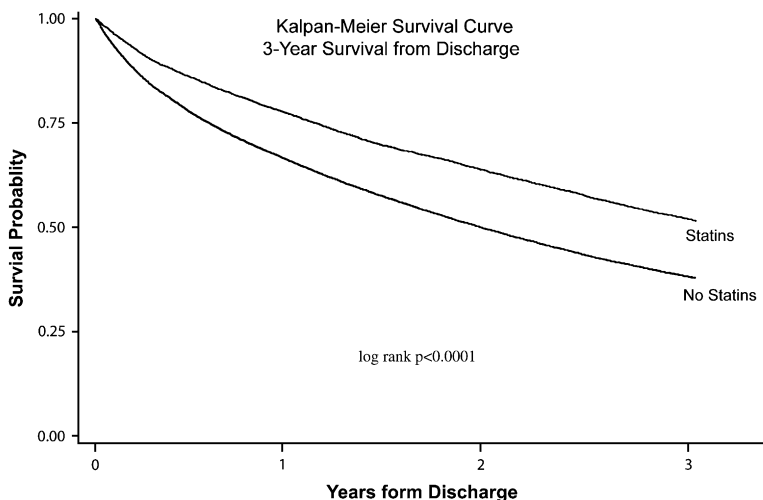| Study	N	Major Characteristics	Patients on Statin	Outcomes in Statin Subgroup	Outcome Results	Statin	Follow-up (Years)
ELITE II[39]	3152	NYHA II–IV, losartan versus captopril	359	Mortality	Positive	Any	1.5
PRAISE[40]	1153	NYHA III–IV, amlodipine versus placebo	134	Mortality, sudden cardiac death	Positive	Lovastatin, pravastatin, simvastatin	1.3
OPTIMAAL[41]	5477	Acute myocardial infarction (MI) associated with heart failure (HF)	2467	All-cause mortality, hospitalization, reinfarction	Positive	Not specified	3.1
Val-HeFT[42]	5010	NYHA II–IV, EF <40	1602	Mortality	Positive	Any	1.9
CIBIS-II[43]	2647	NYHA III–IV, bisoprolol	226	Mortality	Positive	Any	1.3
Val-HeFT[44]	5010	NYHA II–IV, EF <40	1602	Mortality (ischemic vs. nonischemic)	Improved only in ischemic	Any	1.3
Horwich et al[45]	551	HF, EF <40	248	Mortality/cardiac transplantation	Positive	Atorvastatin, simvastatin, pravastatin	2
Ezekowitz et al[46]	6427	Ischemic cardiomyopathy	2545	Mortality	Positive	Any	1
Sola et al[47]	446	NYHA II–III, EF <35	NA	Mortality, hospitalization	Positive	Any	2
COMPANION[48]	1520	NYHA III–IV, cardiac resynchronization therapy versus AICD versus medical therapy alone	608	Mortality	Positive	Any	1.3
ELITE II[49]	3132	NYHA II–IV, losartan versus captopril	398	Mortality	Positive	Any	1
Anker et al[49]	2068	HF	705	Mortality	Positive	Any	1
Dikinson[50]	2521	HF	965	Mortality	Positive	Any	3.8

Table 3
Observational studies of statin therapy in heart failure cohorts

Study	Population	Major Characteristics	Patients on Statin	Outcomes in Statin Subgroup	Results	Statin	Follow-up (Years)
Howlett et al[51]	4888	Heart failure (HF) admission or discharge diagnosis	714	Mortality	Positive	Any	2
Ray et al[52]	23,328	Newly diagnosed HF	1146	Mortality/ myocardial infarction (MI)/ cerebrovascular accident	Positive	Any	2
Jaganmohan et al[53]	32,463	Veterans with HF	19,838	Mortality	Positive	Any	NA
Nul et al[55]	2331	Ambulatory HF	2331	Mortality, admission	Positive	Any	206
Foody et al[54]	54,940	Medicare patients discharged diagnosis HF	9175	Mortality	Positive	Any	3
Go et al[56]	24,598	HF patients eligible for statin therapy	24,598	Mortality	Positive	Any	2.4
Folkeringa et al[57]	840	HF admissions	524	Mortality	Positive	Any	2.5

Cox proportional hazard model. Of the 54,940 patients hospitalized with a primary discharge diagnosis of HF, 16.7% were discharged on statin therapy. Treatment of with a statin at the time of discharge was associated with significant improvements in mortality at 1 and 3 years (HR 0.80, 95% CI 0.76 to 0.84 and HR 0.82, 95% CI 0.79 to 0.85, respectively, **Fig. 1**). This benefit was noted independent of demographics, treatments, physician specialty, and hospital characteristics.

Another study by Go and colleagues[56] evaluated a large (n = 24,589) Kaiser Permanente CHF cohort to confer an association between

Kalpan-Meier Survival Curve
3-Year Survival from Discharge

log rank p<0.0001

Statins

No Statins

Survial Probability

Years form Discharge

Fig. 1. Association of statin use with survival in patients discharged with diagnosis of heart failure. (*From* Foody JM, Shah R, Galusha D, et al. Statins and mortality among elderly patients hospitalized with heart failure. Circulation 2006;113:1090; with permission.)

initiating statin therapy and the risk of death and hospitalization among adults who had HF after a median follow-up of 2.4 years. Statin therapy was associated with a 24% (HR 0.74 CI 0.72 to 0.80) lower risk for death and a 21% (HR 0.79 CI 0.74 to 0.85) lower risk of hospitalization for heart HF. Difference in mortality was independent of total cholesterol level or coronary disease status. It is important to note that statins were more likely to be prescribed in younger patients and those known to have CAD, diabetes, or hypertension.

Jaganmohan and colleagues[53] retrospectively studied 32,463 veterans who had a diagnosis of HF. Of the total, 31% of the patients had an underlying CAD, and 61% (n = 19,838) were on statins. When adjusted for demographics and CAD therapy including aspirin, ACEI, and β-blockers, statin therapy was associated

with 10% RRR (HR 0.9, CI 0.88 to 0.92) in mortality.

Overall, most observational data (see **Table 3**) from these large cohorts of patients with HF have shown that treatment with statins was associated with improvement in survival. It is, however, difficult to assess whether the benefit of statin therapy is related to reduction in coronary events or other direct effect on HF-related processes.

Prospective Trials Evaluating Mechanistic Effects of Statins in Heart Failure

Table 4 summarizes results of several small pilot studies that have evaluated the effects of statin therapy on various parameters related to HF. In general, these are small studies that have evaluated different parameters or biomarkers, and

Table 4
Observational studies of statins therapy in heart failure cohorts

Study	Population	Major Characteristics	Outcomes	Results	Statin	Follow-up (Years)
Node et al[58]	51	NYHA II–III, EF <35, dilated cardiomyopathy	EF, functional class, biomarkers	Positive	Simvastatin	0.25
Hong et al[59]	202	Left ventricular ejection fraction (LVEF) <40, ischemic	Left ventricular (LV), Cardiovascular death, restenosis, CVA	Positive	Simvastatin	0.2
Laufs et al[60]	15	NYHA II–-III, DCM	Functional capacity, quality of life, biomarkers	Positive	Cerivastatin	0.4
Landmesser et al[13]	20	NYHA IV, simvastatin versus ezetimibe	Endothelial function	Positive	Simvastatin	10 wks
Tousoulis et al[9]	35	NYHA II–IV	Angiotensin III, protein C and factory V, tPA and PAI-1	Reduced	Atorvastatin	4 wks
Tousoulis et al[10]	38	NYHA II–IV	Interleukin (IL)-6, tumor necrosis factor (TNF), VCAM-1	Reduced	Atorvastatin	4 wks
Strey et al[3]	24	NYHA II–III, EF <40	Flow mediated vasodilatation, coenzyme Q, ET-1	Positive	Atorvastatin	6 wks
UNIVERSE[61]	87	NYHA II–III, EF <40	LV remodeling	No effect	Rosuvastatin	0.5
Sola et al[62]	108	Non Ischemic cardiomyopathy	LVEF	Positive	Atorvastatin	1

most of them fail to relate changes in these parameters to clinical benefits.

The Rosuvastatin Impact on Ventricular Remodelling Lipids and Cytokines (UNIVERSE) trial[61] was a prospective and randomized trial that analyzed effect of statin therapy in HF. In this trial, 87 patients who had ischemic and nonischemic cardiomyopathy, NYHA class II to III HF, and LVEF less than 40% were randomized to take rosuvastatin 40 mg or placebo in addition to standard HF therapy for 6 months. This study failed to demonstrate an improvement in LVEFor end diastolic volume or reduction in neurohormonal or inflammatory markers.

In contrast, Sola and colleagues[62] evaluated the effects of 20 mg of atorvastatin in a prospective cohort of 108 patients who had nonischemic cardiomyopathy. They demonstrated an improvement in LVEF (0.004), Left Ventricular end systolic dimension ($P = .01$) and Left Ventricular end diastolic dimension ($P = .01$) and statistically significant reduction in inflammatory markers including TNF-α, CRP, IL-6, and erythrocyte superoxide dismutase. Mean NYHA functional class was 2.9 and 2.2, respectively, in treatment and placebo arms. However, there was no difference in hospitalizations or total mortality between the two groups.

In two separate studies, Tousoulis and colleagues[9,10] observed the effect of atorvastatin on flow-mediated vasodilatation in patients who had HF. In a subset of 38 patients who had NYHA class II to IV and LVEF less than 35%, 10 mg of atorvastatin were used, and efficacy was determined by measuring various biomarkers and flow-mediated vasodilatation at baseline and 4 weeks.[9] Reactive hyperemia caused by flow-mediated vasodilatation increased significantly ($P < .01$) and so was reduction in inflammatory markers including IL-6 ($P < .05$), CVAM-1 ($P < .01$) and TNF-α ($P < .01$). In another study of 35 patients who had NYHA class II to IV HF, flow-mediated reactive hyperemia and inflammatory biomarkers were evaluated after 4 weeks of treatment with 10 mg of atorvastatin.[10] Compared with placebo, atorvastatin had no effect on reactive hyperemia. Antithrombin III, protein C and factor V ($P < .01$ for all), and PAI-1 and tPA ($P < .05$ for both) were reduced significantly, however.

Laufs and colleagues[60,63] confirmed beneficial effect of cerivastatin with improved brachial artery flow mediated dilation, quality-of-life score, functional ability, and reduced levels of PAI-1, CRP, and TNF-α. This study refutes the notion that the differences between UNIVERSE and other trials that reported positive results may have been related to the inclusion of ischemic and nonischemic patients in the UNIVERSE trial.

Prospective Randomized Clinical Trials

The inconsistent findings of available studies emphasize the need for large, randomized, double-blind placebo-controlled clinical trials to elucidate the role of statins for treating HF (Table 5). The results from the Controlled Rosuvastatin in Multinational Trial in Heart Failure CORONA[64] and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardica Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-HF)[65] trials have been awaited. Results of the CORONA trial were reported recently, and the GISSI-HF trial is anticipated to provide important information concerning the use of rosuvastatin in HF by 2009.

In the CORONA trial, 5011 elderly patients (age greater than 60), with ischemic cardiomyopathy and NYHA class II to IV HF were enrolled and had a median follow-up of 32.8 months.[64] They randomly were assigned to receive 10 mg/d of rosuvastatin or placebo. The primary composite outcome was cardiovascular death, nonfatal MI, or nonfatal stroke, analyzed as time to the first event. Secondary outcomes included death from any cause, any coronary event, death from cardiovascular causes, and the number of hospitalizations. In the rosuvastatin group, there was a significant reduction in LDL cholesterol (136 vs. 76 mg/dL, 45%, $P < .001$) and also a reduction in high-sensitivity CRP (difference between groups, 37.1%; $P < .001$). The primary events (Fig. 2) occurred in 692 patients in the rosuvastatin group and 732 in the placebo group (HR, 0.92; 95% CI, 0.83 to 1.02; $P = .12$). Deaths from cardiovascular causes (Fig. 3) were in 593 patients in drug group and 581 in control group (HR, 0.97; 95% CI, 0.87 to 1.09; $P = .6$). There was no effect on the cardiovascular outcome, NYHA class or quality of life. Fewer hospitalizations for cardiovascular causes, however, were reported in the rosuvastatin group (2193) compared with the placebo group ($n = 2564$) ($P < .001$).

This trial is limited by the fact that it enrolled elderly patients (mean age 73) in whom the burden of comorbidities may be high, and this may have blunted the benefits in an ailing population. Also raised is potential interaction of the drug with a complex medical regimen in an elderly population. Although the molecular configuration of rosuvastatin helps lower LDL significantly, it might not have a favorable clinical effect in patients who have HF. Further evaluation in prospectively designed clinical trials is needed to compare the effects of rosuvastatin with other statins that have shown beneficial effects in observational studies.

Table 5
Randomized controlled trial of statin use in heart failure

Study	Population	Major Characteristics	Outcomes in Statin Subgroup	Results	Statin	Follow-up (Years)
CORONA[64]	692	NYHA II–IV	Nonfatal myocardial infarction (MI), death, stroke, hospitalization	Improved hospitalization	Rosuvastatin	2.6
GISSI-HF[65]	~7000	NYHA II–IV	Nonfatal MI, all-cause death	Not applicable	Rosuvastatin versus omega-3 fish oil	1.5
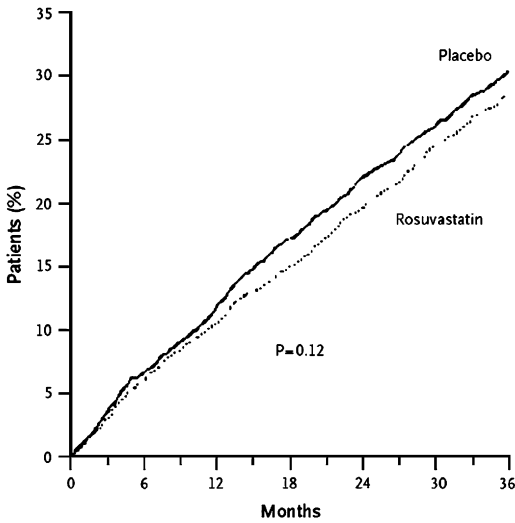
Fig. 2. Controlled Rosuvastatin in Multinational Trial in Heart Failure (CORONA) showed no significant risk reduction in primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke) with use of rosuvastatin in HF. (*From* Kjekshus J, Apetrei E, Barrios V, et al. the CORONA Group. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357:2252; with permission. Copyright © 2007, Massachusetts Medical Society.)
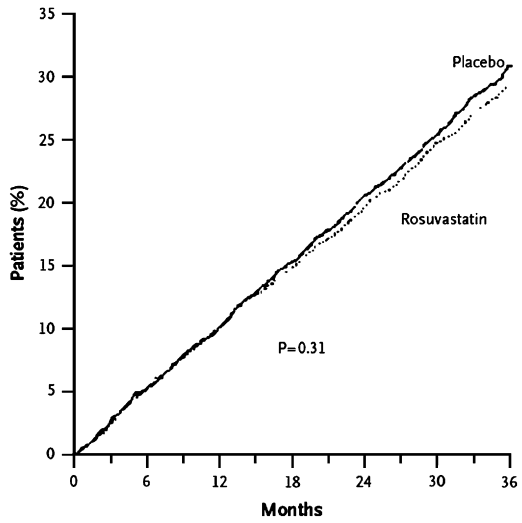

Fig. 3. Controlled Rosuvastatin in Multinational Trial in Heart Failure (CORONA) showed no risk reduction in cardiovascular deaths from use of rosuvastatin in HF. (*From* Kjekshus J, Apetrei E, Barrios V, et al. the CORONA Group. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357:2252; with permission. Copyright © 2007, Massachusetts Medical Society.)

Another ongoing study[65] is the GISSI-HF trial. This trial will randomize around 7000 patients with NYHA functional class II to IV HF regardless of etiology and with ejection fractions less than or equal to 40% to receive either omega-3 polyunsaturated fatty acids or placebo. Patients who have no indication to statin therapy will be randomized to receive rosuvastatin 10 mg or placebo with a follow-up for 18 months. The study endpoints include all-cause mortality or cardiovascular hospitalization. This trial may give a better insight based upon etiology, as patients with nonischemic cardiomyopathy and diastolic HF also will be enrolled. It is expected to be reported in 2009.

Meta-analysis of Statin Use in Heart Failure

A recent meta-analysis of thirteen HF trials[66] estimated survival benefit of statin use in patients who had HF of ischemic and nonischemic etiologies. All trials included in this meta-analysis had evaluated mortality as primary outcome and reported results as HRs. Eleven of the trials included were retrospective, while two were prospective studies. This meta-analysis suggested that statin use among patients who had HF was associated with 26% RRR in mortality (HR, 0.74; 95% CI, 0.68 to 0.8) (**Fig. 4**). A stratified analysis of 8 out of these 13 studies also suggested that statin use was associated with an improved
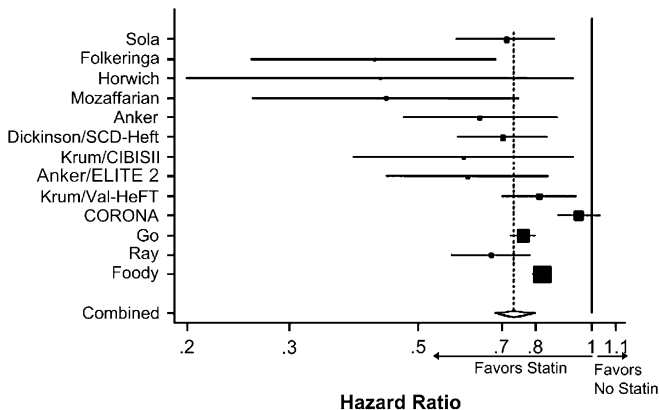
Fig. 4. Meta-analysis of mortality among patients with heart failure (HF). HF patients using statins (n = 30,107); HF patients not using statins (n = 101,323). (*From* Ramasubbu K, Estep J, White DL, et al. Experimental and clinical basis for the use of statins in patients with ischemic and nonischemic cardiomyopathy. J Am Coll Cardiol 2008;51:422; with permission.)
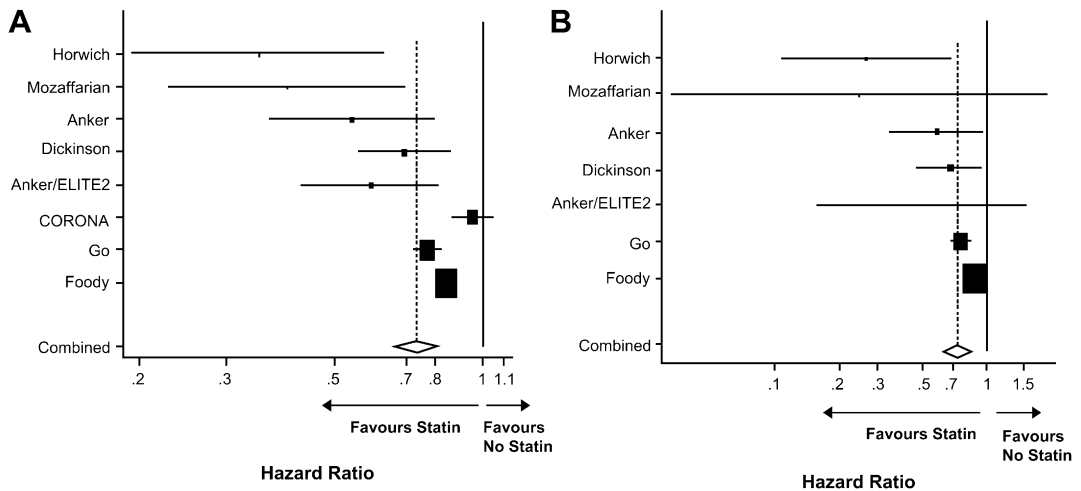
Fig. 5. Mortality among patients with heart failure (HF): ischemic and nonischemic etiology. (*A*) Adjusted mortality among patients with ischemic etiology (n = 62,273) using statins, compared with those not using statins (*B*). Mortality among patients with HF of nonischemic etiology (n = 31,551) using statins compared with those not using statins. (*From* Ramasubbu K, Estep J, White DL, et al. Experimental and clinical basis for the use of statins in patients with ischemic and nonischemic cardiomyopathy. J Am Coll Cardiol 2008;51:423; with permission.)

survival among patients who had HF when added to currently recommended therapy for HF (**Fig. 5**). This effect was noted to be independent of the etiology for HF (for ischemic etiology, HR 0.73; 95% CI 0.65 to 0.82, while for nonischemic etiology, HR, 0.73; 95% CI 0.61 to 0.87).

SUMMARY

As described in the review of clinical data, mostly from the observational studies and posthoc evaluations from the large randomized clinical trials (conducted for various reasons), it seems reasonable to conclude that statin therapy is beneficial in patients who have HV. The third Adult Treatment Panel of the National Cholesterol Education Program recommends the use of statins in HF patients who have underlying CAD.[67] There is no official endorsement for the use of statins in other patients who have HF, as the available data are based upon observational or retrospective, nonrandomized (for statin use) studies. The results of the CORONA trial fail to show any significant benefit, and one must await the results of the GISSI-HF to give further insight regarding the use of statins in all patients who have HF. In summary, patients who have HF should be treated based upon underling cardiac risk factors and etiology of HF. Patients who have ischemic cardiomyopathy and/or diabetes should be treated aggressively with a statin to lower LDL cholesterol levels to at least less than 100 mg/dL and preferably to less than 70 mg/dL. The role of statin therapy in the remaining patients

who have HF remains controversial, and one must wait for the results of the ongoing GISSI-HF trial before making any further recommendations.

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