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Primary and secondary prevention of heart failure with statins

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Statins are effective in the prevention of coronary heart disease (CHD), a leading cause of heart failure (HF). Secondary analyses from 11 randomized clinical trials of patients with high-risk acute or stable coronary heart disease, but without HF, suggest that statins may prevent new-onset HF or HF-related hospitalization. In persons with established HF, several cohort studies found an approximate 35% relative risk reduction in all-cause mortality. While ongoing randomized clinical trials will help to determine the efficacy of statins in persons with established HF, it is reasonable to consider this class of medications in patients with a history of cardiovascular disease, dyslipidemia or diabetes mellitus, and who have either developed, or who remain at risk of, HF.

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3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are safe and efficacious drugs for the primary and secondary prevention of coronary heart disease (CHD) and stroke [1]. Although congestive heart failure (HF) and left ventricular (LV) dysfunction may have several etiologies, coronary artery disease (CAD) is the leading cause within the western world [2]. It is estimated that 50% of incident cases of HF in those under the age of 75 years are due to CHD [3].

It is conceivable that statins may protect against HF by lowering the onset or progression of CHD. The following review examines the relationship between dyslipidemia and HF, and the evidence that statins may prevent new-onset HF among those with established HF.

Epidemiology of CHD & HF

The Framingham heart study established a strong link between antecedent CHD and the subsequent development of HF [4], an observation confirmed by others [5–8]. In autopsy studies of HF patients who experienced sudden death, CAD is found in approximately 50% of cases as the likely cause of death [9], and CHD remains the most influential risk factor in the development of LV dysfunction [10].

As more people now survive their incident episode of an acute coronary syndrome (ACS), HF has become a more prevalent 'complication' thereafter, accounting for many rehospitalizations and consumption of healthcare resources [11–13]. In lieu of the latter, randomized clinical trials of HF therapies now typically include hospitalization for HF as part of their composite cardiovascular end point.

Epidemiology of dyslipidemia & HF

The association between dyslipidemia, CHD and HF is recognized as a sequence of pathophysiological processes [2–8,14]. A high concentration of serum low-density lipoprotein cholesterol (LDL-C) is an independent risk factor for developing HF [4,10], but total cholesterol (TC) alone is not [10,15]. In fact, a high serum TC concentration is associated with higher survival in HF patients, improving by 25% per 1 mmol/l increase in serum TC [15,16]. A few points may help explain this apparent paradox: first, lowering of LDL-C may be more important for the prevention or recurrence of CHD than reducing TC [1]. Second, persons with advanced HF often display cachexia, malnutrition, chronic inflammation and metabolic catabolism [17]. Similar to individuals receiving dialysis [18], the latter state is reflected by lower concentrations of serum

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TC; thus, a decline in the concentration of TC may simply mirror the poorer state of health seen in HF patients, rather than it being protective.

It has been proposed that once HF is established, particularly if it is of nonischemic etiology, the overall poor prognosis may preclude any potential benefit of LDL-C reduction, in terms of CHD protection. This should caution us about assuming that statins can do no harm, especially in a frail population whose nutrition is suboptimal, and who are receiving several concomitant medications. However, if statins are beneficial among some patients with ischemic or nonischemic advanced HF then perhaps this is partly independent of their action on lipids, as discussed below.

Statins & CHD

The efficacy of statins in the treatment of people with established ischemic heart disease, and those at high risk of developing CHD, has been demonstrated in several large randomized clinical trials [1,19–34]. For example, the Scandinavian Simvastatin Survival Study (4S) established the benefit of simvastatin in the treatment of hypercholesterolemia in CHD patients [19]; the West Of Scotland COronary Prevention Study Group (WOSCOPS) [20], the Cholesterol And Recurrent Events (CARE) [21] and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study [22] trials also demonstrated the benefit of statin therapy in persons at high risk for CHD, with and without hyperlipidemia. The Heart Protection Study (HPS), a randomized clinical trial (RCT) comprising over 20,000 patients, demonstrated a 24% relative risk reduction in cardiovascular events with simvastatin in high-risk patients [24]. The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial also showed a benefit of statins in elderly patients [25]. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial was the first study to demonstrate the benefit of early initiation of statin therapy in the setting of ACSs [26], while the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial – Lipid Lowering Trial (ALLHAT-LLT) [27], Anglo–Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA) [28] and Collaborative AtoRvastatin Diabetes Study (CARDS) [29] trials showed a significant benefit in favor of statin therapy among high-risk patients with hypertension and/or diabetes mellitus (DM), in the absence of known cardiovascular disease (CVD).

Given the results of earlier trials, where a reduction in LDL-C provided a proportionate reduction in CVD risk [1], several studies compared intensive- versus moderate-dose statin therapy. The PRavastatin Or atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT–TIMI) 22 [30], REversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) [31], Phase Z of the A to Z [32], Treating to New Targets (TNT) [33] and IDEAL [34] trials proved that high-dose statin therapy was better at reducing CVD events in high-risk patients than low-dose statins, but at a cost of more frequent medication-related side effects.

The overall evidence suggests that statins reduce CVD mortality in persons at high risk of CVD, or those with established CVD. Since many patients with HF fall into the latter two categories, it is logical to question whether they too may benefit from statins.

Pleiotropic & physiological effects of statin therapy in HF

The positive biological effects of statin therapy in HF patients may extend beyond their reduction in LDL-C (BOX 1) [35,36]. *In vitro* and *in vivo* studies have shown statins to favorably modify the ischemic milieu, through their anti-inflammatory and antioxidative properties [37–41], stabilization of the atherosclerotic plaque [42], reduction of endothelial dysfunction [43,44], antithrombotic effects [45] and attenuation of myocardial remodeling [46]. Additionally, statins appear to delay the progression of existing HF through improvement in LV ejection fraction (LVEF) and exercise tolerance (TABLE 1) [38–41,46,47].

Statins may attenuate neurohormonal activation by normalizing sympathetic outflow and reflex regulation in exposed rabbits [48], and their use is associated with a reduced risk of new-onset atrial fibrillation in adults with stable CHD (adjusted relative risk [RR]: 0.37; 95% confidence interval [CI]: 0.18–0.76) [49]. These protective effects are likely to be relevant in HF patients, since both high catecholamine production and atrial fibrillation are independent risk factors for death in affected individuals [50,51].

Box 1. Potential beneficial & harmful actions of statin therapy in heart failure.

Potential benefit:

- Slows atherosclerosis progression
- Reduces ischemic heart disease events
- Reduces atrial and ventricular arrhythmias
- Improves endothelial dysfunction
- Reduces aortic stiffness
- Reduces proinflammatory cytokines
- Antithrombotic effects
- Reduces left ventricular hypertrophy and adverse remodeling
- Reduces proteinuria
- Reduces neurohormonal activation

Potential harm:

- Lowering of cholesterol is correlated with poor prognosis in advanced heart failure
- Lowering of cholesterol may increase risk of lipopolysaccharide-induced production of deleterious cytokines
- Reduces ubiquinone (coenzyme Q10), which correlates with left ventricular function and exercise tolerance

Table 1. Prospective studies of the change in left ventricular ejection fraction comparing statin users and nonusers.

Author	Study design	Patients included (n)	Criteria for study entry at baseline	Statin studied	Study outcome	Mean absolute change in LVEF (%)			Ref.
						Statin	*Control*	*Statistical significance of mean change*	
Node *et al.*	RCT	51	Nonischemic dilated cardiomyopathy and HF with LVEF < 40%	Simvastatin 5–10 mg daily	Change in LVEF at 12 weeks	+7.0	+1.0	$p < 0.05$	[38]
Laufs *et al.*	RCT	15	Nonischemic dilated cardiomyopathy with NYHA class II–III	Cerivastatin over a mean of 20 weeks	Change in LVEF at mean 20 weeks	+4.3	-2.8	$p > 0.50$	[39]
Sola *et al.*	RCT	89	Nonischemic HF with NYHA class II–IV and LVEF ≤ 35%	Atorvastatin 20 mg daily	Change in LVEF at 12 months	+4.0	-2.0	$p = 0.004$	[40]
Wojnicz *et al.*	RCT	71	Inflammatory dilated cardiomyopathy with NYHA class II–III	Atorvastatin 40 mg daily	Increase in LVEF > 5% at 6 months	+7.0	+1.0	$p = 0.012$	[41]

HF: Heart failure; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; RCT: Randomized clinical trial.

Four small randomized clinical trials have examined the effects of statins on LVEF in persons with nonischemic dilated cardiomyopathy (TABLE 1) [38–41]. After low-dose statin therapy for 12–24 weeks, there was an approximate 6% absolute increase in LVEF observed in these studies. The absence of known CHD in these participants offers some support to the notion that statins may be efficacious in HF beyond their effects on the coronary arterial plaque and/or its tendency to thrombose.

There are theoretical concerns regarding the reduction of LDL-C in persons with established HF, since low levels of TC may be associated with higher mortality in small studies of patients with advanced HF (BOX 1) [15,16]. However, these proposed deleterious mechanisms, including endotoxin cytokine activation or ubiquinone (coenzyme Q10) reduction, have not been confirmed in clinical trials, and remain largely theoretical [38–41,44,52].

Primary prevention of HF or related hospitalization in prospective studies of statin use for CVD

A total of 11 prospective studies, ten of which were randomized clinical trials, reported on the risk of new onset or worsening HF-related hospitalization among 67,111 patients (TABLE 2) [25–28,32–34,53–56]. All 11 studies were originally designed to examine the impact of statins on the primary or secondary prevention of CVD in high-risk populations. Most participants were free of HF at enrollment, but had active CHD. These studies rarely describe how HF was either defined or adjudicated as a secondary or post hoc study outcome.

Kjekshus and colleagues were the first to observe a significantly lower risk of new-onset HF with statins among persons with stable CHD (TABLE 2). At a daily dose of 20–40 mg of simvastatin, the RR of HF was 0.81 (95% CI: 0.67–0.97) after 5 years [53]. The following year, the authors of the CARE trial reanalyzed their data for patients treated with pravastatin after myocardial infarction (MI) and discovered a trend towards a protective effect against new-onset HF with pravastatin among those aged 65–75 years (RR: 0.77; 95% CI: 0.56–1.1) but not among younger patients, whose incidence of HF was less common [54]. Another cohort of patients who had survived an MI, some of whom were receiving a statin, followed for 3 years were also observed to have an adjusted RR of 0.52 (95% CI: 0.43–62) for new-onset HF in favor of statins [55]. In the remaining studies, where no benefit was observed, treatment was either provided for a mere 16 weeks immediately after ACS [26], or low-risk persons without preexisting CHD were enrolled [25,27,28]. For example, in the ASCOT-LLA study, where atorvastatin 10-mg daily was compared with placebo in persons at high risk for CVD but who were free of CHD, there was no evident reduction in the risk of new-onset fatal or nonfatal HF (hazard ratio [HR]: 1.1; 95% CI: 0.73–1.8) [28].

Four large randomized clinical trials compared HF outcomes between moderate- versus intensive-dose statin therapy among patients with both acute and stable CHD (TABLE 2). PROVE IT-TIMI 22 compared standard-dose pravastatin 40-mg daily versus a more intensive strategy of atorvastatin 80-mg daily [30,56]. Similarly, the Phase Z of the A to Z study of ACS patients compared simvastatin 80-mg daily to a four-month regimen of placebo followed by simvastatin 20-mg daily [32]. In the TNT and IDEAL trials, which were conducted in persons with stable CHD, they assessed study outcomes after a median of almost 5 years, comparing atorvastatin 80-mg daily to a daily dose of either atorvastatin

Table 2. Primary prevention of heart failure or related hospitalization within prospective studies of statin use for the prevention or treatment of cardiovascular disease.

Author	RCT acronym	Study features				Study outcomes			Ref.
		Study design	*Patients included (n)*	*Criteria for study entry at baseline*	*Statin*	*Heart failure-related study outcome*	*Absolute risk of study outcome in the control group*	*Risk (95% CI) for study outcome, statin vs control*	
Kjekshus *et al.*	4S	RCT *post hoc* analysis	4444	CHD	Simvastatin 20–40 mg daily	New-onset HF at 5 years	10.3%	Crude RR 0.81 (0.67–0.97)	[53]
Lewis *et al.*	CARE	RCT subgroup	2876	Post-MI and age < 65 years	Pravastatin 40 mg daily	New-onset HF at median 5 years	4.9%	Crude RR 1.1 (0.77–1.5)	[54]
		RCT subgroup	1283	Post-MI and age 65–75 years	Pravastatin 40 mg daily	New-onset HF at median 5 years	13.8%	Crude RR 0.77 (0.56–1.1)	
Aranow *et al.*		Prospective cohort study	1410	Post MI	Any	New-onset clinical HF at 3 years	42%	Adjusted RR 0.52 (0.43–0.62)	[55]
Shepherd *et al.*	PROSPER	RCT	5804	History of, or at risk for, CVD	Pravastatin 40 mg daily	HF hospitalization at mean 3.2 years	4.2%	Crude HR 0.91 (0.71–1.2)	[25]
	ALLHAT-LLT	RCT	10,355	HTN, dyslipidemia and ≥ 1 other CHD risk factor	Pravastatin 20–40 mg daily	HF-related hospitalization or death at mean 4.8 years	0.4%	Crude RR 0.99 (0.83–1.2)	[27]
Sever *et al.*	ASCOT-LLA	RCT	10,305	HTN and 3 other CVD risk factors, but no prior HF or CHD	Atorvastatin 10 mg daily	New-onset fatal or nonfatal HF at median 3.3 years	0.22/100 person-years	Crude HR 1.1 (0.73–1.8)	[28]
Schwartz *et al.*	MIRACL	RCT	3086	Mean 63 h post unstable angina or non-Q wave MI	Atorvastatin 80 mg daily vs placebo	New or worsening HF hospitalization at 16 weeks	2.8%	Crude RR 0.94 (0.62–1.4)	[26]
Scirica *et al.*	PROVE IT	RCT	4162	Median 7 days post-ACS	Atorvastatin 80 mg daily vs Pravastatin 40 mg daily	HF hospitalization at a mean of 2 years	3.1% (Pravastatin 40 mg daily)	Crude HR 0.55 (0.35–0.85)	[56]
de Lemos *et al.*	A to Z	RCT	4497	Median 1 month post-ACS	Simvastatin 80 mg daily vs Simvastatin 20 mg daily	HF hospitalization or HF medication initiation at median 2 years	5.0% (Simvastatin 20 mg daily)	Crude HR 0.72 (0.53–0.98)	[32]
LaRosa *et al.*	TNT	RCT	10,001	Stable CHD	Atorvastatin 80 mg daily vs Atorvastatin10 mg daily	HF hospitalization at median 4.9 years	3.3% (Atorvastatin 10 mg daily)	Crude HR 0.74 (0.59–0.94)	[33]
Pedersen *et al.*	IDEAL	RCT	8888	Median 22 months post-MI	Atorvastatin 80 mg daily vs Simvastatin 20–40 mg daily	HF hospitalization at median 4.8 years	2.8% (Simvastatin 20–40 mg daily)	Crude HR 0.81 (0.62–1.1)	[34]

ACS: acute coronary syndrome; ALLHAT-LLT: Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial – Lipid Lowering Trial; ASCOT-LLA: Anglo–Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm; CARE: Cholesterol and Recurrent Events Trial; CHD: Coronary heart disease; CVD: Cardiovascular disease; HF: Heart failure; HR: Hazard ratio; HTN: Hypertension; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; MIRACL: Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; PROSPER: PROspective Study of Pravastatin in the Elderly at Risk; PROVE IT-TIMI: PRavastatin Or atorVastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction; RCT: Randomized clinical trial; RR: Risk ratio; TNT: Treating to New Targets.

Table 3. Secondary prevention of morbidity and mortality within studies comparing statin use among individuals with known HF or left ventricular dysfunction

Author	Study features				Study outcomes			Ref.
	Study design	*Patients included (n)*	*Criteria for study entry at baseline*	*Statin*	*Study outcome*	*Absolute risk of study outcome in the control group*	*Risk (95% CI) for study outcome, statin vs control*	
Sacks *et al.*	RCT subgroup	706	Post-MI and LVEF 25–40%	Pravastatin 40 mg daily	Death from CHD or nonfatal MI or revascularization at median 5 years	32%	Crude HR 0.72 (0.55–0.96)	[21]
Mitchell *et al.*	Nested cohort study within a RCT	362	Post ventricular arrhythmia and CHD and LVEF < 40%	Any	Recurrent ventricular arrhythmia at mean 28 months	NA	Adjusted HR 0.60 (0.42–0.85)	[57]
					All-cause mortality at mean 28 months	NA	Adjusted HR 0.64 (0.32–0.85)	
Mozaffarian *et al.*	Nested cohort study within a RCT	1153	Ischemic and nonischemic HF, NYHA class IIIB-IV and LVEF < 30%	Any	All-cause mortality at mean 15 months	31/100 patient-years	Adjusted HR 0.44 (0.26–0.75)	[58]
					Sudden death at mean 15 months	NA	Adjusted HR 0.48 (0.22–1.0)	
					Pump failure death at mean 15 months	NA	Adjusted HR 0.36 (0.15–0.90)	
Horwich *et al.*	Prospective cohort study	551	Ischemic and nonischemic HF clinic patient, LVEF < 40%	Any	All-cause mortality at 1 year	18%	Crude HR 0.52 (0.30–0.90)	[59]
					Sudden death at 1 year	NA	Crude HR 0.47 (0.16–1.4)	
					Pump failure death at 1 year	NA	Crude HR 0.46 (0.20–1.1)	
			Subgroup with ischemic HF		All-cause mortality or urgent transplant at 1 year	43%	Crude HR 0.35 (0.19–0.62)	
			Subgroup with nonischemic HF		All-cause mortality or urgent transplant at 1 year	29%	Crude HR 0.27 (0.11–0.69)	
Ezekowitz *et al.*	Prospective cohort study database	6427	Clinical HF and angiographically proven CHD	Any	All-cause mortality at 1 year	NA	Adjusted HR 0.84 (0.74–0.95)	[60]
Fukuta *et al.*	Prospective cohort study	137	HF clinic patients with inactive CHD and LVEF ≥ 50%	Any	All-cause mortality at a mean of 21 months	Approximatel y 6.3/100 patient-years	Adjusted RR 0.20 (0.06–0.62)	[61]

CHD: Coronary heart disease; HF: Heart failure; HR: Hazard ratio; HTN: Hypertension; LV: Left ventricular: LVEF; Left ventricular ejection fraction; MI: Myocardial infarction; NA: Not applicable; NYHA: New York Heart Association; RCT: Randomized clinical trial; RR: Relative risk.

Table 3. Secondary prevention of morbidity and mortality within studies comparing statin use among individuals with known HF or left ventricular dysfunction (cont.)

Author	Study features				Study outcomes			Ref.
	Study design	*Patients included (n)*	*Criteria for study entry at baseline*	*Statin*	*Study outcome*	*Absolute risk of study outcome in the control group*	*Risk (95% CI) for study outcome, statin vs control*	
Sola *et al.*	Prospective cohort study	446	Ischemic and non-ischemic HF clinic patients, NYHA class II–III and LVEF ≤ 35%	Any	All-cause mortality at median 2 years	33%	Crude HR 0.71 (0.57–0.84)	[62]
Anker *et al.*	Retrospective cohort study	3132	Ischemic and nonischemic LV dysfunction (mean LVEF 31%)	Any	All-cause mortality at median 1 year	12%	Adjusted HR 0.61 (0.44–0.84)	[63]
			Subgroup with ischemic HF			NA	Adjusted HR 0.59 (0.43–0.82)	
			Subgroup without ischemic HF			NA	Adjusted HR 0.49 (0.15–1.5)	
	Retrospective cohort study database	2068	Ischemic and nonischemic HF clinic patients	Any	All-cause mortality at median 3 years	33%	Adjusted HR 0.58 (0.44–0.77)	
			Subgroup with ischemic HF		All-cause mortality at median 2 years	NA	Adjusted HR 0.54 (0.37–0.80)	
			Subgroup with nonischemic HF		All-cause mortality at median 2 years	NA	Adjusted HR 0.58 (0.35–0.97)	
Ray *et al.*	Retrospective cohort study database	28,828	Hospitalized with a primary diagnosis of HF and aged ≥ 65 years	Any	All-cause mortality, nonfatal MI or stroke at mean 17 months	21.8/100 patient-years	Adjusted HR 0.72 (0.63–0.83)	[64]
					All-cause mortality at mean 17 months	19.1/100 patient-years	Adjusted HR 0.67 (0.57–0.78)	
Foody *et al.*	Retrospective cohort study database	54,960	Hospitalized with a primary diagnosis of HF and aged ≥ 65 years	Any	All-cause mortality at 3 years	62.2%	Adjusted HR 0.82 (0.79–0.85)	[65]

CHD: Coronary heart disease; HF: Heart failure; HR: Hazard ratio; HTN: Hypertension; LV: Left ventricular: LVEF; Left ventricular ejection fraction; MI: Myocardial infarction; NA: Not applicable; NYHA: New York Heart Association; RCT: Randomized clinical trial; RR: Relative risk.

10 mg [33] or simvastatin 20–40 mg [34]. HF was defined according to the need for HF-related hospitalization, except in A to Z trial, which additionally included newly treated HF (TABLE 2) [32]. All four trials found that high-dose statin therapy was associated with a reduced risk of new-onset HF (TABLE 2). A meta-analysis of these trials revealed a highly significant 27% reduction in HF hospitalization and within PROVE IT, the benefit in HF outcome with intensive statin therapy was independent of recurrent ischemic events or B-type natriuretic peptide concentrations [56].

There are probable explanations for why there are conflicting results about the efficacy of statins for the prevention of new-onset HF in the 11 cited studies (TABLE 2). One reason is that these trials were not originally designed to examine HF-related complications as a major study end point. Secondly, since not all patients with HF require hospitalization, some would be missed in these studies. Accordingly, the accuracy of documented HF as a 'hard' outcome may be questioned. Also, as mentioned above, the protective effect of statins against CHD-related mortality may only be realized in high-risk individuals. Thus, persons with pre-existing CHD and who are followed for a long duration, appear to benefit most from high-dose statins. Finally, participants randomized to statins (vs placebo) may experience fewer fatal CVD and survive longer and, thus, are more likely to develop HF.

Secondary prevention of mortality & morbidity in cohort studies & clinical trials of statins in patients with HF or LV dysfunction

A series of mainly observational studies have examined whether statins are associated with a reduced risk of ventricular arrhythmia or death in persons with pre-existing HF or LV impairment (TABLE 3) [21,57–65]. The relevance of this question relates to the fact that 30–50% of all deaths in patients with HF patients are sudden, presumably due to ventricular arrhythmias [66–68]. A total of 98,770 persons were included in these studies, of which three were nested within previously completed randomized clinical trials of statin therapy [21,57–58], four were prospective cohort studies [59–62] and four were large retrospective cohort studies [63–65]. All but one study, which examined pravastatin exclusively in a randomized fashion [21], compared users of any statin with nonuser controls (TABLE 3). Within those studies that measured LVEF at baseline, the majority included persons whose LVEF was below 40% [21,57–60,62–63], while one considered patients with diastolic HF and a preserved LVEF [61].

Despite some differences in the duration of follow-up, nonrecipients of statins experienced roughly the same annual mortality rate of 15–30% [58,59,62–65], or death in conjunction with recurrent CVD events (TABLE 3) [21,64]. Statins were associated with approximately a 35% RR reduction in all-cause mortality, and an even more pronounced reduction in the risk of ventricular arrhythmia [57], sudden death [58–59] and death due to pump failure (TABLE 3) [58].

These observational studies may have been biased by a 'healthy user effect', in that persons who are less ill, or whose cause of HF is reversible, tend to be prescribed a statin. This would be expected to produce a degree of bias that cannot be fully captured or controlled for. However, of the three analyses that included patients with HF due to a nonischemic etiology, one observed a 42% significantly lower RR of death with statin use [63], and the other a 73% lower RR of death or need for cardiac transplantation (TABLE 3) [59]. While the latter does not eliminate the presence of a healthy user bias, it certainly raises intriguing questions about the benefits of statins in persons who are less likely to receive beneficial therapies for reversible CHD. In addition, given the prominent and consistent reduction in mortality across all 11 studies, the overall findings are certainly thought provoking.

Conclusions

The effectiveness of the statins in persons with CHD has been established by the completion of large randomized clinical trials. Given that one major sequelae of CHD is LV dysfunction and HF, it is logical to assume that statins can protect against both. Moreover, it should follow that statins might prevent the complications of HF, including sudden-, arrhythmic- or pump failure-related death in persons with CHD or LV impairment.

Not all secondary analyses from RCTs of persons with CHD were associated with a reduction in the future risk of HF or HF-related hospitalization (TABLE 2). Completed cohort studies – which focused on patients with HF rather than CHD alone – were more likely than RCTs to be biased by a healthy user effect; nonetheless, they all demonstrated a protective benefit from statin use (TABLE 3). There are some plausible reasons for why this might be so, as outlined in BOX 1.

Future clinical trials are now underway to examine the efficacy of statins for the protection against CVD events and an improvement in survival in persons with established HF [69,70]. The COntrolled ROsuvastatin multiNAtional study in heart failure (CORONA) trial is a 5-year RCT designed to evaluate the effects of rosuvastatin, at a daily dose of 10 mg, among elderly adults with stable ischemic HF. Study entry requires a patient to have New York Heart Association (NYHA) class II symptoms and an LVEF up to 35%, or NYHA class III-IV symptoms with an LVEF up to 40% [69]. The GISSI-HF trial uses a two-by-two factorial design to compare high-dose rosuvastatin and fish poly-unsaturated fatty acids with placebo among persons with HF of both ischemic and nonischemic etiologies [70].

The pressing question is whether there exists a sufficient level of evidence to recommend the use of statins in HF patients, or to adopt a more conservative 'watch and wait' approach. We recommend prescribing a statin for the prevention of HF in high-risk patients who have a concomitant history of CHD or cerebrovascular disease [1], dyslipidemia or DM [29]. Moreover, no clinical trial to date has demonstrated harm to patients with HF patients

Key issues

- Statins are effective for the prevention of coronary heart disease (CHD), a leading cause of heart failure (HF).
- Secondary analyses from 11 randomized clinical trials in patients with CHD, or those at high risk for its development, suggest that statins are efficacious for the prevention of new-onset HF.
- In patients with established HF, several cohort studies have demonstrated an approximate 35% relative risk reduction for all-cause mortality, sudden death and death due to ventricular arrhythmias or pump failure.
- Small randomized clinical trials have demonstrated that statins may improve left ventricular function among patients with HF.
- In patients with a history of ischemic cardiovascular disease, dyslipidemia or diabetes mellitus, statin therapy may lower their risk of incident HF.
- Ongoing clinical trials will determine the efficacy of statins in patients with established HF.

who were prescribed a statin. Among those with isolated HF and none of the aforementioned comorbid conditions – a minority of patients with HF – we advise waiting for the completion of ongoing clinical trials.

Expert commentary

Current studies suggest that statins are effective in patients with a history of ischemic heart disease, stroke, dyslipidemia or DM. Such treatment may also reduce their risk of new-onset HF. Among persons with established HF and a history of cardiovascular disease, statin therapy may lower the risk of ventricular arrhythmias, sudden death and progressive ventricular pump failure.

Five-year view

Clinical trials, being conducted over the next 5 years, should resolve the issue of whether or not statins benefit people with established HF but no concurrent cardiovascular disease.

References

Papers of special note have been highlighted as:
- • of interest
- •• of considerable interest

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