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## Review

# Exploring new indications for statins beyond atherosclerosis: Successes and setbacks

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Received 3 December 2009; accepted 7 December 2009

Available online 7 January 2010

## KEYWORDS

Alzheimer's  
dementia;  
Aortic stenosis;  
Heart failure;  
Statin

**Summary** Statins have been shown to reduce cardiovascular events across a broad spectrum of patients at risk, irrespective of baseline LDL-cholesterol levels. In a meta-analysis of 14 statin trials involving more than 90,000 participants, statin therapy reduced the 5-year incidence of cardiovascular events by about 20% for each mmol/L of LDL-cholesterol reduction. The results of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study suggest that the degree of reduction in Japanese subjects may be greater than this for the same degree of LDL-cholesterol reduction. Given the success of statins in preventing cardiovascular events, it is not surprising that they have been tested in a variety of related conditions, three of which are discussed in this article.

Heart failure is characterized by inflammation, endothelial dysfunction and neurohumeral activation, conditions that are ameliorated by statin therapy. The Controlled Rosuvastatin Multi-national Trial in Heart Failure (CORONA) showed no significant benefit of rosuvastatin upon the primary endpoint, cardiovascular death, myocardial infarction and stroke. However, subgroups identified by the biomarkers plasma amino-terminal pro-brain natriuretic and C-reactive protein showed a reduction in events.

Aortic stenosis and atherosclerosis share common risk factors, including hypertension and hypercholesterolemia. Although non-randomized cohort studies have suggested that statins slow the progression of aortic stenosis, this was not shown in either of the two randomized placebo-controlled trials testing this hypothesis.

Similarly, Alzheimer's disease shares many risk factors with atherosclerosis, and several observational studies have reported a lower risk of developing this condition in patients taking statins. However, two recently completed clinical trials indicate that neither atorvastatin nor simvastatin slow the progression of early Alzheimer's disease.

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In conclusion, although statins are effective, established therapy for the prevention of vascular events in patients at risk, they have as yet not proven to be successful for these newer indications.

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## Introduction

Statins are arguably the most successful class of drugs in history. Originally discovered by Akiro Endo in the 1970s and developed by Merck Research Laboratories [1], statins first became available in the United States of America in 1987 as a treatment to lower low-density lipoprotein (LDL)-cholesterol. In 1994, the first randomized, placebo-controlled clinical trial showing that a statin reduced cardiovascular events was published [2]. A meta-analysis of 14 statin trials involving more than 90,000 participants, published in 2005, concluded that statin therapy reduced the 5-year incidence of cardiovascular events by about 20% for each mmol/L of LDL-cholesterol reduction [3]. This reduction in events occurred irrespective of baseline LDL-cholesterol level or of other baseline features of the patients. With this strong evidence base from clinical trials, global statin sales totaled \$23 billion in 2006 [4].

## Indications for statin therapy

A statin should be given to patients who are at moderate or elevated risk for a cardiovascular event. This includes all patients with established atherosclerosis irrespective of baseline LDL-cholesterol level [5], and other groups such as patients with diabetes [6] or hypertension plus other risk factors [7]. Statins reduced the risk of cerebrovascular and coronary events after an ischemic stroke or transient ischemic attack [8], and have been shown to reduce events in subjects with normal cholesterol levels, no evidence of vascular disease, but elevated C-reactive protein levels [9]. In patients with stable coronary disease, aggressive LDL-cholesterol lowering with a high dose has been shown to reduce events more than less LDL-cholesterol lowering with a low dose of statin [10].

Statins have proven to be remarkably safe. In clinical trials covering 74,102 subjects, statin therapy was associated with a small excess risk of transaminase elevations, but not of myalgias, creatinine kinase elevations, rhabdomyolysis, or withdrawal of therapy compared to placebo [11]. In clinical practice, the most serious adverse effects of statin treatment are myopathy or rhabdomyolysis; however, these complications are very uncommon and occur mainly

in subjects taking gemfibrozil or drugs metabolized by the cytochrome P450 3A4 [12]. The incidence of new onset diabetes was higher in patients taking rosuvastatin 20mg or atorvastatin 80mg compared to placebo in two clinical trials [8,9,13]. This complication is more common in patients with higher fasting blood glucose levels at baseline or features of the metabolic syndrome.

The efficacy of a statin for reducing cardiovascular events in a Japanese population was clearly demonstrated in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study [14]. In fact, the results of the MEGA trial suggest that the degree of event reduction in Japanese subjects is greater than that seen in non-Japanese populations for the same degree of LDL-cholesterol reduction. The long-term safety of statins has been well documented in Japanese patients [15,16].

Given the success of statins in the prevention of cardiovascular events, it should not be surprising that they have been tested in a variety of related conditions. By blocking the 3-hydroxy-3-methylglutaryl-coenzyme A reductase enzyme, statins not only reduce blood cholesterol levels, but also prevent the synthesis of important isoprenoid intermediates of the cholesterol pathway, ultimately inhibiting the isoprenylation of the small GTP-binding proteins, Ras, Rac, and Rho [17]. These small proteins exert a wide variety of different effects within the body, and thus statins have many potential therapeutic benefits that are unrelated to cholesterol lowering.

Three of the conditions where statins have been evaluated are heart failure, aortic stenosis, and Alzheimer's disease. In each case, animal data and observational studies suggested that statins would improve outcomes; however, the results of clinical trials have been disappointing, as outlined below.

## Statins for the treatment of heart failure

The early statin trials were focused on LDL-cholesterol lowering as the mechanism of benefit, and thus patients with heart failure were mostly excluded. However, heart failure is characterized by inflammation, endothelial dysfunction, and neurohumoral activation, conditions that are ameliorated by statin therapy. In animal studies, statins have favorable effects on left ventricular remodeling after

**Table 1** Incidence of new onset heart failure (HF) or hospitalization for heart failure in selected major statin trials.

Trial	Patients	Drug	Control	HF: drug	HF: control	Hazard ratio (95% CI)
HPS [22]	20,536	Simvastatin 40 mg	Placebo	3.4%	3.9%	0.86 (0.75–1.00)
PROVE-IT [24]	4,162	Atorvastatin 80 mg	Pravastatin 40 mg	1.6%	3.1%	0.55 (0.35–0.85)
TNT [23]	10,001	Atorvastatin 80 mg	Atorvastatin 10 mg	2.4%	3.3%	0.74 (0.59–0.94)
A to Z [25]	4,497	Simvastatin 80 mg	Simvastatin 20 mg	3.7%	5.0%	0.72 (0.53–0.98)
IDEAL [26]	8,888	Atorvastatin 80 mg	Simvastatin 20 mg	2.2%	2.8%	0.80 (0.61–1.05)

myocardial infarction [18]. In clinical studies of patients with non-ischemic cardiomyopathy, simvastatin and atorvastatin have been shown to improve heart failure symptoms and ejection fraction, and to lower plasma levels of proinflammatory cytokines and natriuretic peptides compared to placebo [19,20].

In several of the major randomized trials, statins have exerted a favorable effect upon heart failure, as listed in Table 1 [21–26]. In the Heart Protection Study, 20,536 patients at high-risk for a vascular event were randomized to simvastatin 40 mg/day or placebo and were followed for 5 years. Major vascular events were reduced by 24% in the simvastatin group (95% confidence interval 19–28%). Hospitalization for heart failure was reduced by 14% (95% confidence interval 0–25%) [22] this study, N-terminal pro-B-type natriuretic peptide levels were strongly predictive of major vascular events, including heart failure hospitalizations, and in patients with high baseline levels of this biomarker for heart failure, simvastatin reduced vascular risk, with no evidence of hazard [21].

In the Pravastatin or Atorvastatin Evaluation and Infection Trial (PROVE-IT), 4,162 patients were randomized to atorvastatin 80 mg/day or pravastatin 40 mg/day after an acute coronary syndrome, and were followed for 2 years. The primary endpoint, (a composite of death, myocardial infarction, documented unstable angina requiring hospitalization, stroke, and revascularization after 30 days), occurred in 22.4% of atorvastatin and 26.3% of pravastatin-treated patients (hazard ratio 0.84, 95% confidence interval 0.74–0.95,  $p=0.005$ ). Treatment with atorvastatin significantly reduced the rate of hospitalization for heart failure (1.6% versus 3.1%, hazard ratio 0.55, 95% confidence interval 0.35–0.85,  $p=0.008$ ) [23]. The risk of heart failure hospitalization was higher with increasing levels of B-type natriuretic peptide, and at these higher levels, atorvastatin treatment significantly reduced risk.

In the Treating to New Targets (TNT) trial, 10,001 patients with stable coronary disease were randomized to 10 mg or 80 mg/day of atorvastatin and were followed for 4.9 years. The primary endpoint, (a composite of cardiac death, non-fatal myocardial infarction, and stroke), was reduced from 10.9% to 8.7% in the 80 mg group (hazard ratio 0.78, 95% confidence interval 0.69–0.89,  $p<0.001$ ). Hospitalization for heart failure, a prespecified secondary endpoint of TNT, was reduced from 3.3% in the 10 mg group to 2.4% in the 80 mg group (hazard ratio 0.74, 95% confidence interval 0.59–0.94,  $p=0.012$ ) [23]. The treatment effect of the higher dose was more marked in patients with a history of heart failure, 17.3% and 10.6% in the 10 and 80 mg arms, respectively (hazard ratio 0.59, 95% confidence interval 0.40–0.88,  $p=0.009$ ).

In the Z phase of the A to Z trial, 4,497 acute coronary syndrome patients were randomized to either placebo for 4 months followed by simvastatin 20 or 40 mg/day of simvastatin, increasing to 80 mg/day after 1 month [25]. After a median follow-up of approximately 2 years, the primary endpoint was not significantly reduced in the more aggressively treated group; however, new onset heart failure was reduced from 5.0% to 3.7% (hazard ratio 0.72, 95% confidence interval 0.53–0.98,  $p=0.04$ ). A trend toward a reduction in heart failure hospitalizations was seen in the Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL) trial (hazard ratio 0.80, 95% confidence interval 0.61–1.05), a study where 8,888 patients with a history of myocardial infarction were randomized to 80 mg/day of atorvastatin or 20 mg/day of simvastatin and were followed for 4.8 years [26].

All of the foregoing data suggest that a statin, or a high-dose compared to a low-dose statin, will reduce the risk of hospitalizations for heart failure in patients with coronary disease. However, two large clinical trials have specifically tested whether a statin is of benefit to patients with heart failure, and both yielded disappointing results. In the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA), 5,011 patients aged 60 years or older, with systolic heart failure were randomized to placebo or to rosuvastatin 10 mg/day and were followed for a median of 32.8 months [27]. The primary outcome (a composite of cardiovascular death, myocardial infarction, and stroke) was not significantly reduced in the rosuvastatin group (hazard ratio 0.92, 95% confidence interval 0.83–1.02,  $p=0.12$ ). Fewer hospitalizations for worsening heart failure were seen in the rosuvastatin group (1,109 versus 1,299,  $p=0.01$ ); however, the number of patients with hospitalization for heart failure was not significantly reduced.

In a recent *post hoc* analysis, CORONA patients with a plasma amino-terminal pro-B-type natriuretic peptide level in the lower tercile, below 103 pmol/L, had a lower event rate if assigned to the rosuvastatin group (hazard ratio 0.65, 95% confidence interval 0.47–0.88) [28]. The outcome in the low tercile group was significantly different than in the other two terciles ( $p=0.019$ ). As expected, plasma levels of amino-terminal pro-B-type natriuretic peptide were strongly predictive of adverse outcomes.

Higher C-reactive protein (CRP) levels were also associated with a worse outcome in CORONA [29]. In a retrospective analysis, patients with a baseline CRP level  $\geq 2.0$  mg/L experienced a reduction in cardiovascular death, myocardial infarction or stroke, the primary endpoint of the trial (hazard ratio 0.87, 95% CI 0.77–0.98) [29]. Total mortality was reduced by 11% by rosuvastatin in patients with a baseline CRP level  $\geq 2.0$  mg/L ( $p=0.05$ ) and was increased

by 17% in patients with a baseline CRP level  $< 2.0$  mg/L ( $p = 0.14$ ). It is tempting to speculate that rosuvastatin might produce benefit in heart failure patients with high CRP levels due to its anti-inflammatory activity.

In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca (GISSI) Heart Failure Trial, 4,574 patients with chronic heart failure irrespective of cause were randomly assigned to rosuvastatin 10 mg/day or placebo and followed for a median of 3.9 years [30]. In this trial rosuvastatin had no effect upon the co-primary endpoints, either total mortality or death and hospitalization for a cardiovascular cause.

What conclusions can we draw from all of these data regarding the utility of statins in heart failure? First, 5 of the trials showed that a statin [22,27] or a higher dose of a more potent statin [23–25] reduced hospitalizations for heart failure. This reduction occurred in studies of patients with stable coronary disease [22,23,27] and after acute coronary syndromes [24,25], and with 3 different statins: simvastatin [22,25], high-dose atorvastatin [6,23,24], and rosuvastatin [27]. This benefit of statins is important because hospitalizations for heart failure are frequent and expensive, and interfere with the quality of life of coronary patients.

Second, statins appear to reduce cardiovascular events in patients with mild heart failure. This effect was most clearly seen in the *post hoc* CORONA analysis, where patients with lower natriuretic peptide levels had fewer events with rosuvastatin [28]. In the Heart Protection Study, the absolute benefit of simvastatin was relatively constant across different natriuretic peptide levels, but the absolute benefit was smaller at higher levels [21]. This is consistent with the notion that patients with severe heart failure are more likely to succumb to a fatal arrhythmic event, an endpoint that is unaffected by statins.

## Statins for the treatment of aortic stenosis

Aortic stenosis is the most common acquired valvular disorder in developed countries, with a prevalence of 2–4% in subjects over age 65 years [31,32]. Aortic stenosis and coronary atherosclerosis share common risk factors, including hypertension, and hypercholesterolemia [31,33]. In mouse models of early aortic stenosis, aortic valve histopathological abnormalities are accelerated by elevated cholesterol levels, and can be stabilized and reversed by cholesterol lowering, including with a statin [34,35].

Statins have been reported to slow the progression of aortic stenosis in non-randomized, retrospective cohort studies, using either serial Doppler echocardiography [36–40] or electron beam computed tomography [41]. In a prospective, non-randomized study of 121 asymptomatic patients with moderate to severe aortic stenosis followed for a mean of 73 weeks, aortic valve area decreased less ( $p = 0.041$ ) and aortic valve velocity increased less ( $p = 0.007$ ) in patients treated with rosuvastatin 20 mg/day compared to controls [42].

On the other hand, the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) randomized 155 patients to either placebo or atorvastatin 80 mg/day and followed them for a mean of 25 months [43]. The primary endpoints, change in aortic-jet velocity by Doppler echocar-

diography and change in aortic valve calcium score by helical computed tomography, were not significantly different in the two treatment groups.

The largest study to assess the effect of a statin on aortic stenosis is the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) Trial [44]. In this study, 1,873 patients with asymptomatic, mild-to-moderate aortic stenosis were randomized to simvastatin 40 mg plus ezetimibe 10 mg/day or to placebo and were followed for a median of 52 months. As shown in Fig. 1, fewer patients experienced ischemic cardiovascular events in the simvastatin–ezetimibe group (15.7% versus 20.1%; hazard ratio 0.78, 95% confidence interval 0.63–0.97,  $p = 0.02$ ). However, aortic valve replacement was performed in 28.3% of the simvastatin–ezetimibe patients compared to 29.9% of placebo-treated patients (hazard ratio 1.00, 95% confidence interval 0.84–1.18). No significant difference was seen in peak aortic-jet velocity between the two treatment groups during the follow-up period, as shown in Fig. 2.

Why did SALTIRE and SEAS fail to confirm the benefit of statins for aortic stenosis that was suggested by earlier studies? An obvious explanation is that non-randomized, observational studies are often misleading due to inherent, unrecognized bias, and that animal models do not adequately mirror the complexities of human disease. It is also possible that a statin might be effective in the early stages of aortic stenosis, but that by the time a gradient has developed, the pathologic abnormalities are irreversible, and will progress despite treatment [45]. Supporting this concept, one observational study found that statins slowed progression in aortic sclerosis and mild aortic stenosis, but not in moderate aortic stenosis [46]. Finally, because multiple mechanisms contribute to the progression of aortic stenosis, it may be unrealistic to expect treatment with only one agent to be effective.

## Statins and Alzheimer's disease

Alzheimer's disease is a chronic, progressive neurodegenerative condition that is a major cause of disability and institutionalization among older persons. Currently available treatment for Alzheimer's disease, cholinesterase inhibitors and an N-methyl-D-aspartate receptor antagonist, have some effect on disease symptoms but do not halt progression of the disease [47]. The cause of Alzheimer's disease is thought to be the accumulation of  $\beta$ -amyloid ( $A\beta$ ) in the brain. Cholesterol modulates the processing of amyloid precursor protein-related  $A\beta$  production in animal models and *in vitro* [48]. Excess cholesterol increases the processing of amyloid precursor protein and the production of  $A\beta$ , whereas removing cholesterol slows production of  $A\beta$  in experimental models [49,50]. Simvastatin has been shown to have a similar effect on the processing of amyloid precursor protein and the production of  $A\beta$  [51].

High cholesterol levels, along with diabetes, smoking, hypertension, obesity and a sedentary lifestyle, are risk factors for the development of Alzheimer's disease in later life [52,53]. Several observational studies indicate that the risk of developing Alzheimer's disease is lower in patients taking statins [54–57]. In two clinical trials of statins for cardiovascular disease prevention in patients at high-risk, (the

Heart Protection Study and PROSPER), no differences were detected in cognition tests or new onset dementia between statin-treated and placebo-treated patients [58].

In patients with mild Alzheimer's disease, statins were reported to slow disease progression in a non-randomized, observational study [59]. In a small randomized clinical trial involving only 67 patients with mild-to-moderate Alzheimer's disease, atorvastatin appeared to produce borderline statistically significant benefit in some measures of cognition compared to placebo [60].

The Lipitor's Effect in Alzheimer's Dementia (LEADe) study is the first adequately powered, randomized trial to assess the effect of a statin on the progression of Alzheimer's disease [61]. A total of 640 patients with mild-to-moderate impairment, all receiving donepezil 10 mg/day, were randomized in a double-blind manner to atorvastatin 80 mg/day or to placebo. The follow-up period was 72 weeks. The co-primary endpoints, change in cognition and change in global function as assessed by standardized tests, declined to a similar extent in both treatment groups. The high dose of atorvastatin was well tolerated in this elderly age group, and no unexpected adverse events were observed.

The Cholesterol Lowering Agent to Slow Progression of Alzheimer's Disease (CLASP) Study planned to randomize 400 patients with mild-to-moderate Alzheimer's disease to sim-

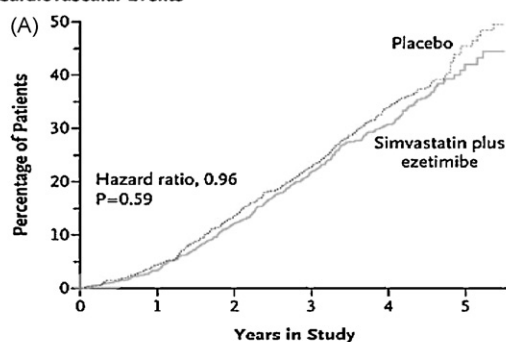
vastatin 20–40 mg/day or to placebo and to follow them for 18 months [62]. This trial has been completed and the results have been reported as showing no benefit for simvastatin; however, the results have not yet been published.

Why do we again find a disparity between the positive results of observational studies and encouraging data from animal models on the one hand, and the negative results of randomized, placebo-controlled trials on the other? One possibility is that statins might be effective in preventing the onset of the disease, but that once even mild symptoms have appeared, the pathological processes may be too advanced for statins to exert a beneficial effect. More likely, our understanding of the mechanisms causing Alzheimer's disease is incomplete, and we are not aiming our therapy at the optimal target.

## Statins for other diseases

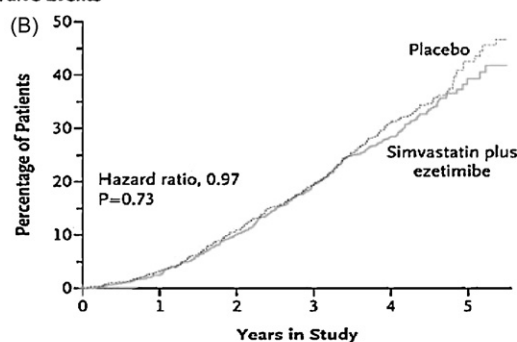
Statins stimulate bone formation in experimental models [63] and the majority of observational studies show that statin users have fewer fractures [64]. However, randomized controlled trials have demonstrated that neither simvastatin nor atorvastatin improves bone mineral density in postmenopausal women [65,66].

### Major Cardiovascular Events



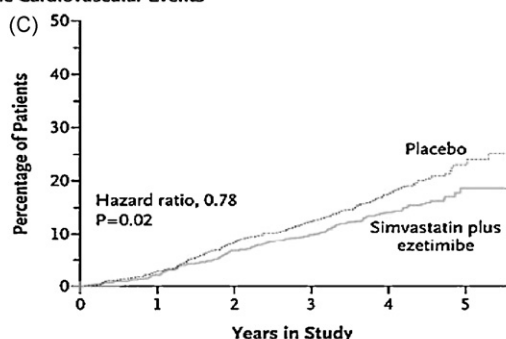
No. at Risk					
Simvastatin plus ezetimibe	906	817	713	618	53
Placebo	884	791	696	586	56

### Aortic-Valve Events



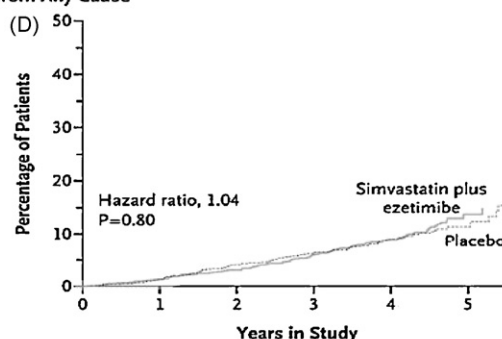
No. at Risk					
Simvastatin plus ezetimibe	914	836	732	635	55
Placebo	895	814	725	611	58

### Ischemic Cardiovascular Events



No. at Risk					
Simvastatin plus ezetimibe	917	867	823	769	76
Placebo	898	838	788	729	76

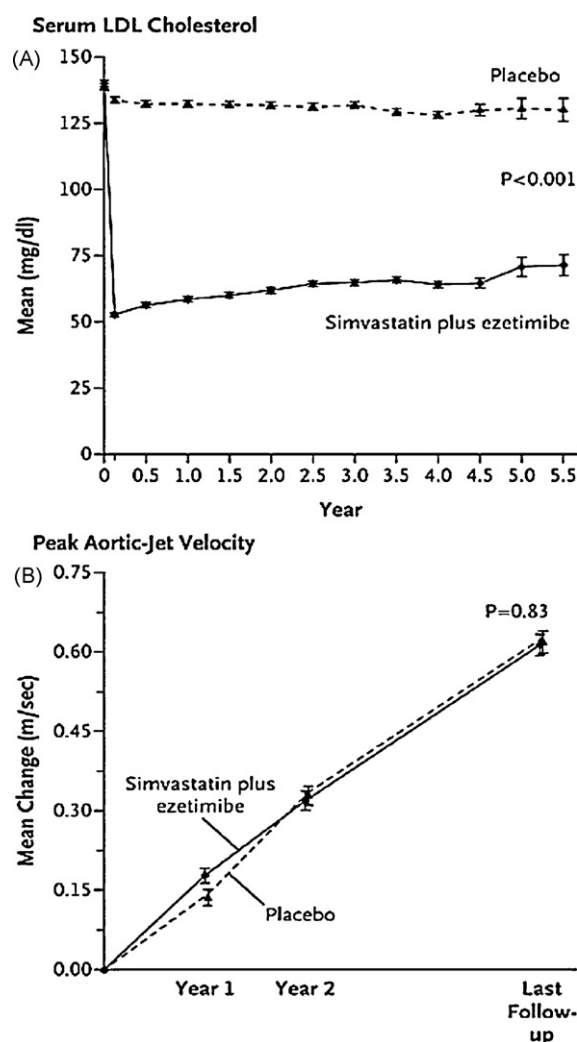
### Death from Any Cause



No. at Risk					
Simvastatin plus ezetimibe	930	912	884	855	89
Placebo	916	890	865	835	94

**Figure 1** Outcome events in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) Trial [44]. No significant differences between the simvastatin plus ezetimibe and placebo groups were seen for major cardiovascular events (panel A), aortic valve events (panel B), or death from any cause (panel D). However, ischemic cardiovascular events were significantly reduced in the active treatment group (panel C). See text for details. Reproduced, with permission, from Rossebo et al. [44].





**Figure 2** In the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) Trial, serum low-density lipoprotein (LDL)-cholesterol (panel A) was reduced by 61% to a mean of  $53 \pm 23$  mg/dL in the active treatment group. However, peak aortic-jet velocity as measured by Doppler echocardiography (panel B), did not differ during follow-up between the groups. Reproduced, with permission, from Rossebo et al. [44].

Statins improve survival in animal models of sepsis [67]. A recent meta-analysis of 16 cohort studies found that statins prevented infection (hazard ratio 0.57, 95% confidence interval 0.43–0.75) and improved outcome among patients with infection (hazard ratio 0.55, 95% confidence interval 0.36–0.83) [68]. Six ongoing randomized controlled trials are evaluating the efficacy of statins in various types of infection [69].

Statins have also been assessed in other inflammatory conditions. A double-blind, randomized, placebo-controlled trial in just 16 patients with rheumatoid arthritis showed significant improvement in inflammatory biomarkers and functional status in the statin-treated group [70]. In an uncontrolled study of 41 patients with relapsing-remitting multiple sclerosis, statin treatment reduced the number of gadolinium-enhancing lesions, a marker of disease activity [71]. Some (but not all) studies in experimental models sug-

gest that statins might be of benefit in lupus erythematosus [72,73]. Whether statins increase or decrease the risk of developing Parkinson's disease is controversial, with inadequate data available to resolve the issue [74]. However, statins have been reported to produce improvement in a mouse model of this disease [75].

In conclusion, statins are effective, established therapy for the prevention of vascular events in patients at risk. Their widespread use has resulted in a marked decline in cardiovascular events in many countries over the past decade. Attempts to expand the indications of statins, as treatment for heart failure, aortic stenosis, and Alzheimer's disease, have as yet proved unsuccessful.

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