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REVIEW

Lipid-lowering therapy: who can benefit?

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Abstract: Cardiovascular disease (CVD) is the leading cause of death in the US. Despite the decline in CVD-associated mortality rates in recent years, coronary heart disease (CHD) still causes one in every six deaths in this country. Because most CHD risk factors are modifiable (eg, smoking, hypertension, obesity, onset of type 2 diabetes, and dyslipidemia), cardiovascular risk can be reduced by timely and appropriate interventions, such as smoking cessation, diet and lifestyle changes, and lipid-modifying therapy. Dyslipidemia, manifested by elevated low-density lipoprotein cholesterol (LDL-C), is central to the development and progression of atherosclerosis, which can be silent for decades before triggering a first major cardiovascular event. Consequently, dyslipidemia has become a primary target of intervention in strategies for the prevention of cardiovascular events. The guidelines of the Adult Treatment Panel (ATP) III, updated in 2004, recommend therapeutic lifestyle changes and the use of lipid-lowering medications, such as statins, to achieve specific LDL-C goals based on a person's global cardiovascular risk. For high-risk individuals, such as patients with CHD and diabetic patients without CHD, an LDL-C target of < 100 mg/dL is recommended, and statin therapy should be considered to help patients achieve this goal. If correctly dosed in appropriate patients, currently approved statins are generally safe and provide significant cardiovascular benefits in diverse populations, including women, the elderly, and patients with diabetes. A recent primary prevention trial also showed that statins benefit individuals traditionally not considered at high risk of CHD, such as those with no hyperlipidemia but elevated C-reactive protein. Additional evidence suggests that statins may halt or slow atherosclerotic disease progression. Recent evidence confirms the pivotal role of statins in primary and secondary prevention.

Keywords: atherosclerosis, coronary heart disease, dyslipidemia, lipid lowering, primary prevention, statin therapy

Introduction

Coronary heart disease (CHD) remains the leading cause of death in both men and women in the US.[1] In 2006, 18 million of the estimated 81 million adults in the US with cardiovascular disease (CVD) had CHD, and more than 400,000 Americans died of CHD. CHD is the cause of one in every six deaths in the US.[1] However, although these statistics are sobering, the age-adjusted death rates for CVD and CHD decreased substantially from 1996 to 2006 by 30% and 36%, respectively.[1] Population studies using validated statistical models have provided compelling evidence that the decrease in CHD-related mortality rates is attributable to reductions in modifiable CHD risk factors and improvements in evidenced-based medical therapies.[2,3]

Smoking, hypertension, obesity, type 2 diabetes, and dyslipidemia have long been established as important risk factors for CHD.[4] The contribution of dyslipidemia

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to cardiovascular risk was illustrated in a multicenter, case-control study conducted in 52 countries showing that abnormal lipid levels accounted for approximately 50% of the attributable risk for myocardial infarction (MI) in the population.[5] Consequently, reductions in total cholesterol by dietary and other lifestyle changes have been associated with more than 20% of the recently observed decrease in CHD mortality rates.[2,3] Another important factor contributing to this positive trend has been the availability of powerful lipid-lowering therapies, particularly statins. The lipid-lowering potency of statins and their clinical benefit in terms of CHD risk reduction have been established in numerous randomized controlled trials.[6] Between 1% and 5% of the recent decrease in CHD mortality rates has been attributed to the use of statins in primary prevention (ie, individuals without established CHD)[2,3] and another 9% to the use of statins by patients with chronic stable coronary artery disease.[3] Together, these findings confirm that controlling lipid levels through lifestyle changes and/or medical treatment is a key strategy for primary and secondary prevention of major cardiovascular events.

Cardiovascular events, such as MI, often represent the end result of years of atherosclerotic disease progression. Atherosclerosis typically starts in early adulthood or even youth (in high-risk individuals) and may progress silently for decades before CHD symptoms manifest.[7] The importance of dyslipidemia as a likely CHD risk factor is related to the central role of specific lipoprotein particles, especially low-density lipoprotein (LDL), in the development and progression of atherosclerosis.[8] Atherosclerosis is initiated by complex interactions between oxidatively modified lipoproteins and components of the immune system in the arterial wall that lead to the formation of fatty streaks and fibrous plaques. Plaque build-up and rupture may ultimately lead to progressive stenosis and thrombosis.[8] The continuum of atherosclerotic disease progression provides a strong rationale for early intervention with lipid-lowering therapy in patients with dyslipidemia to prevent the development of CHD later in life. This review discusses the role of lipid-lowering therapy in primary and secondary prevention, with particular focus on recent outcome studies of statins. An important question that will be examined is: who can benefit from lipid-lowering therapy?

Lipid goals

Lipid management is the focus of the current guidelines (last updated in 2004) for the reduction of cardiovascular risk issued by the National Cholesterol Education Program Adult Treatment Panel (ATP) III (available at http://www.nhlbi.nih.gov/guidelines/cholesterol/).[9,10] The ATP III guidelines recommend specific lipid goals based on a person's global risk for CHD: the higher the risk, the lower the goal (Table 1). For example, an LDL cholesterol (LDL-C) goal of < 100 mg/dL was recommended for high-risk persons – ie, those with CHD or CHD risk equivalents – while an LDL-C goal of < 130 mg/dL was recommended for moderate-risk persons who had ≥ 2 risk factors but no CHD or CHD risk equivalents.[9,10]

Table 1 NCEP ATP III–recommended LDL-C targets based on a person's global risk for CHD[10]

Risk category	LDL-C goal	Non–HDL-C goal[a]	Initiate therapeutic lifestyle changes	Consider drug therapy
Very high risk: CHD + other risk factors or ACS	<70 mg/dL (optional)	<100 mg/dL	≥100 mg/dL	≥100 mg/dL (<100 mg/dL: consider drug options)
High risk: CHD or risk equivalents (10-year risk > 20%)	<100 mg/dL	<130 mg/dL	≥100 mg/dL	≥100 mg/dL (<100 mg/dL: consider drug options)
Moderately high risk: ≥ 2 risk factors (10-year risk 10%–20%)	<130 mg/dL (optional: <100 mg/dL)	<160 mg/dL	≥130 mg/dL	≥130 mg/dL (100 to 129 mg/dL: consider drug options)
Moderate risk: ≥ 2 risk factors (10-year risk < 10%)	<130 mg/dL	<160 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk: 0 to 1 risk factor	<160 mg/dL	<190 mg/dL	≥160 mg/dL	≥190 mg/dL (160 to 189 mg/dL: consider drug options)

Note: [a]In patients with elevated triglycerides (≥ 200 mg/dL).
Abbreviations: ACS, acute coronary syndrome; CHD, coronary heart disease; non–HDL-C, non–high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III guidelines.

Lipid management in the US has improved since the 2004 update of the ATP III guidelines. Based on a 2003 survey, 67% of adults at risk of CHD achieved the ATP III–recommended LDL-C goals.[11] This number increased to 76% in a more recent survey conducted in 2006 and 2007.[12] However, substantial room for improvement in lipid goal attainment remains, especially for persons at high risk or very high risk of CHD. In both surveys, treatment success rates were considerably lower for these persons than for persons at low risk.[11,12]

Therapeutic lifestyle changes for all at-risk persons

Therapeutic lifestyle changes – increased physical activity, weight loss, smoking cessation, and adoption of a healthier diet – effectively reduce cardiovascular risk in primary[13–15] and secondary prevention.[16,17] Lifestyle changes should be the primary focus and first step of a cardiovascular risk reduction strategy for any person at risk for CHD.[10] However, it is important to acknowledge that lifestyle intervention is not always an achievable or successful approach for attaining recommended lipid goals. Some individuals may be unable or unwilling or may lack the opportunity to fully comply with dietary and other lifestyle recommendations. Others may not be able to reach their lipid goals despite their best efforts at lifestyle changes.

Who can benefit from lipid-lowering therapy?

Evidence before updated ATP III

The 2001 ATP III guidelines recommend the use of lipid-lowering pharmacotherapy for individuals who are unable to meet their recommended LDL-C goals with therapeutic lifestyle changes and for higher-risk individuals.[9] Taking into account new evidence from five outcome trials of statin therapy, the guidelines were updated in 2004 (Table 1).

The Heart Protection Study was a placebo-controlled primary prevention study of simvastatin conducted in the UK in more than 20,000 adults at high risk of a cardiovascular event. The study results revealed a 13% lower all-cause mortality rate ($P = 0.0003$) and a 24% lower rate in major vascular events ($P < 0.0001$) for simvastatin vs placebo.[18] Subgroup analyses of the study further suggested that the vascular benefits of simvastatin extended to a wide variety of high-risk individuals, including women, older individuals, individuals with no CHD but with other vascular diseases or diabetes, and individuals with LDL-C < 116 mg/dL or total cholesterol < 193 mg/dL.[18,19] In study participants with diabetes, simvastatin vs placebo reduced the occurrence of a first major vascular event by 22% ($P < 0.0001$).[19] Diabetic individuals who benefited from simvastatin therapy included those without occlusive arterial disease and those with LDL-C < 116 mg/dL at baseline.[19] Thus, the findings from the Heart Protection Study strongly suggested that lipid-lowering therapy with statins can provide primary prevention benefits for high-risk individuals, even in the absence of hyperlipidemia.

The efficacy of statin therapy in elderly patients with or at high risk of stroke or CVD was demonstrated in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). In this study, pravastatin was associated with a modest but significant reduction in the risk for the composite end point of CHD mortality, stroke, and nonfatal MI, compared with placebo (hazard ratio [HR]: 0.85; $P = 0.014$).[20]

The results of the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) study provided evidence that in patients who have acute coronary syndrome (ACS), an intensive lipid-lowering statin regimen may be warranted. In this comparative study, intensive therapy with atorvastatin 80 mg was significantly more effective than standard therapy with pravastatin 40 mg in reducing LDL-C levels well below the 100-mg/dL goal for high-risk patients (62 mg/dL with intensive therapy vs 95 mg/dL with standard therapy). Importantly, the more effective LDL-C reduction with intensive therapy was accompanied by a significantly greater reduction in the risk of the composite primary end point of death from any cause, MI, unstable angina requiring rehospitalization, revascularization, and stroke (relative risk [RR] reduction: 16%; $P = 0.005$).[21]

Two primary prevention studies evaluated the clinical benefits of statin therapy in hypertensive and moderately hypercholesterolemic patients at moderately high risk for CHD. In the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT–LLA), the addition of atorvastatin to antihypertensive therapy decreased LDL-C to 87 mg/dL (placebo, 133 mg/dL) – a level substantially below the goal of 130 mg/dL for moderate-risk patients – and significantly reduced the incidence of nonfatal MI and fatal CHD (HR: 0.64; $P = 0.0005$).[22] In contrast, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT–LLT) found no significant reduction in the risk of all-cause mortality (primary end point) or in the risk

of CHD events with pravastatin vs usual care in this patient population. A possible explanation for this negative result is the modest difference observed between the mean LDL-C values achieved with pravastatin (111 mg/dL) and usual care (135 mg/dL) after 2 years of treatment.[23]

The results of these five statin trials led to the 2004 update of the ATP III guidelines (originally published in 2001).[10] For high-risk and moderate-risk persons, the updated guidelines recommend LDL-C goals of < 100 mg/dL and < 130 mg/dL, respectively (Table 1). Regardless of the recommended goal, lipid-modifying therapy in a high-risk or moderate-risk person should have sufficient intensity to achieve at least a 30% to 40% reduction in LDL-C. For persons at very high risk, such as those with established CHD plus additional risk factors (eg, type 2 diabetes), LDL-C < 70 mg/dL is recommended as an optional therapeutic goal.[10]

Evidence since updated ATP III guidelines

The significant clinical benefits of statin therapy across populations with a wide variety of patient characteristics are well established. The results of a prospective meta-analysis of data from 90,056 participants in 14 randomized statin trials suggested that the absolute benefits of treatment in terms of risk reduction largely depend on the risk at baseline and the absolute reduction in LDL-C achieved.[24] The benefits of statin therapy were confirmed recently by the results of a large network meta-analysis of 76 randomized controlled trials with a total of more than 170,000 participants.[25] Statin therapy vs placebo or usual care was associated with significant reductions in the risk of death from any cause (RR: 0.90; $P \leq 0.0001$), death from cardiovascular causes (RR: 0.80; $P < 0.0001$), nonfatal MI (RR: 0.74; $P \leq 0.001$), and revascularization procedures (RR: 0.76; $P \leq 0.0001$).[25] Importantly, a highly significant reduction in the incidence of death from CVD with statin therapy vs control was observed both in individuals with established CHD (RR: 0.82; 95% confidence interval [CI]: 0.76–0.88) and in primary prevention (RR: 0.81; 95% CI: 0.75–0.87).[25]

Secondary prevention

The meta-analysis by Mills et al[25] included 42 studies of patients with CHD as the primary study population. In these patients, statin therapy vs control was associated with a RR reduction of 18% for cardiovascular death.[25] A number of previous meta-analyses also demonstrated the clinical benefits of statin therapy in secondary prevention (Table 2). A meta-analysis of nine placebo-controlled trials of statins that included previously unpublished data demonstrated a 22% reduction in all-cause mortality among elderly patients (aged 65–82 years) with CHD (Table 2).[26] In addition, two meta-analyses of data from patients with ACS suggested that more intensive lipid-lowering therapy is associated with greater benefits in this population. In the first meta-analysis, data from 13 randomized controlled trials in patients with ACS showed that intensive statin therapy, compared with standard statin therapy, reduced the incidence of adverse cardiovascular outcomes when started within 14 days of hospitalization for ACS[27] (Table 2). Similarly, in the second meta-analysis, data from patients with ACS or stable CHD who participated in the Treating to New Targets (TNT), Incremental Decrease in End Points Through Aggressive Lipid-Lowering (IDEAL), PROVE IT–TIMI 22, or Aggrastat-to-Zocor (A-to-Z) studies showed significantly greater efficacy of high-dose vs standard-dose statin therapy in reducing the risk of cardiovascular events, including coronary death (Table 2).[28]

Despite the overwhelming evidence for significant clinical benefits of statin therapy in patients with CHD, trials designed to demonstrate similar benefits in patients with heart failure have been unsuccessful. The Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) evaluated the effects of rosuvastatin 10 mg/day on the composite primary end point of cardiovascular death, nonfatal MI, or nonfatal stroke in more than 5000 patients aged ≥ 60 years with systolic heart failure.[29] Although rosuvastatin significantly reduced the incidence of hospitalization for cardiovascular causes, compared with placebo, it provided no significant benefit related to the primary end point (Table 2).[29] Similarly, in a recent placebo-controlled study conducted in Italy, rosuvastatin 10 mg had no significant effects on the primary end point of death or hospitalization for cardiovascular reasons in patients with chronic heart failure (Table 2).[30] Lipid-lowering therapy with statins also has not been shown to provide significant benefits in patients with end-stage kidney disease requiring maintenance hemodialysis.[31,32] However, in the Study of Heart and Renal Protection (SHARP), which included more than 9000 patients with chronic kidney disease but no history of MI or coronary revascularization, the combination of simvastatin 20 mg and ezetimibe 10 mg provided a significant 17% reduction (95% CI: 6–26; $P = 0.002$) in atherosclerotic events (including first nonfatal MI, coronary death, nonhemorrhagic stroke, and coronary or noncoronary revascularization), compared with placebo.[33]

Primary prevention

The updated ATP III guidelines emphasize that lipid-lowering therapy can provide benefits for high-risk individuals, including those with diabetes, even if they have no obvious signs of hyperlipidemia. The results of the Collaborative Atorvastatin

Table 2 Clinical effects of statins in secondary prevention: findings from recent meta-analyses and randomized controlled clinical outcomes trials

Study	Follow-up	Population	Treatments	Mean LDL-C (mg/dL)[a]		Outcome	
				Baseline	During treatment	Event	Hazard ratio (95% CI)
Meta-analysis by Hulten et al[27]	Median 6 months	N = 17,963 (13 trials) ACS; statins initiated ≤14 days of hospitalization	High-dose statin Usual care, placebo, or lower-dose statin	N/A N/A	–34 CFB –6 CFB	Death and cardiovascular events over 2 years	0.81 (0.77–0.87) $P < 0.001$
Meta-analysis by Afilalo et al[26]	Weighted mean 4.9 years	N = 19,569 (9 trials) Established CHD; age ≥ 65 years	Statin Placebo	N/A N/A	N/A N/A	All-cause mortality	0.78 (0.65–0.89)
Meta-analysis by Cannon et al[28]	~2 (ACS) or 5 years (stable CHD)[b]	N = 27,548 (4 trials) ACS or stable CHD	High-dose statin Standard-dose statin	130 130	75 101	Coronary death or any cardiovascular event	0.84 (0.80–0.89) $P < 0.0001$
CORONA[29]	Median 32.8 months	N = 5011 Systolic heart failure; age ≥ 60 years	Rosuvastatin 10 mg Placebo	137 136	76 at 3 months 138 at 3 months	Primary outcome: death from cardiovascular causes, nonfatal MI, or nonfatal stroke	0.92 (0.83–1.02) $P = 0.12$
GISSI-HF[30]	Median 3.9 years	N = 4574 Chronic heart failure	Rosuvastatin 10 mg Placebo	122[c] 121[c]	83[c] at 1 year 130[c] at 1 year	Primary outcome: time to death (and time to death or hospitalization for cardiovascular reasons)	1.00 (0.90–1.12) $P = 0.943$ (1.01 [0.91–1.11] $P = 0.903$)

Notes: [a]Values are pooled means for meta-analyses; [b]mean or median follow-up time for the meta-analysis is not available; values shown are follow-up durations of individual trials included in the meta-analysis (24 months [mean] or 721 days [median] for post-ACS patients; 4.8 or 4.9 years [median] for patients with stable CHD); [c]values are converted from mmol/L to mg/dL.

Abbreviations: ACS, acute coronary syndrome; CFB, change from baseline; CHD, coronary heart disease; CI, confidence interval; CORONA, Controlled Rosuvastatin Multinational Study in Heart Failure; GISS-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insuffi cienza cardiaca Heart Failure; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; N/A, not available.

Diabetes Study (CARDS) confirmed the primary prevention benefit of statin therapy in diabetic patients without high LDL-C.[34] CARDS showed that atorvastatin 10 mg daily reduced the rate of first major cardiovascular events, including ACS, coronary revascularization, and stroke, by 37% ($P = 0.001$) compared with placebo (Table 3).[34] Patients with diabetes generally have higher triglycerides and lower high-density lipoprotein cholesterol (HDL-C) levels, which are associated with an increased risk for cardiovascular events.[35] In the FIELD trial, fenofibrate, a drug that lowers triglycerides and increases HDL-C, was shown to provide some benefits for patients with type 2 diabetes, such as reducing the rate of nonfatal MI and coronary revascularization, but beneficial effects on CHD-related mortality could not be demonstrated.[36] Results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Study further suggest that addition of fenofibrate to simvastatin provides no cardiovascular benefits for patients with diabetes beyond those conferred by simvastatin alone.[37] However, combination therapy with fenofibrate and simvastatin may be appropriate for patients with diabetes with mixed dyslipidemia (triglycerides $\geq$ 204 mg/dL and HDL-C $\leq$ 34 mg/dL), based on the results of a prespecified subgroup analysis of ACCORD showing that addition of fenofibrate to simvastatin lowered the incidence of CVD events by 31% in these patients.[37]

Findings from the recent Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) (Table 3) demonstrated that statin therapy may provide cardiovascular benefits for healthy individuals who do not meet the current ATP III criteria for high CVD risk.[38] JUPITER was a large, double-blind, placebo-controlled study that evaluated the efficacy of rosuvastatin in the primary prevention of cardiovascular death and vascular events in 17,802 men (aged $\geq$ 50 years) and women (aged $\geq$ 60 years) from 26 countries who had LDL-C $<$ 130 mg/dL but plasma concentrations of high-sensitivity C-reactive protein $\geq$ 2 mg/L.[38] Compared with placebo, rosuvastatin 20 mg/day significantly reduced the incidence of major cardiovascular events by 44%, including MI (HR: 0.46; 95% CI: 0.30–0.70), stroke (HR: 0.52; 95% CI: 0.34–0.79), and arterial revascularization (HR: 0.54; 95% CI: 0.41–0.72).[38] Because the differences in clinical efficacy between rosuvastatin and placebo were of high clinical and statistical significance, JUPITER was halted by an independent data and safety monitoring board after a median follow-up period of 1.9 years.[38]

Despite the results of JUPITER, which showed a significant reduction in all-cause mortality with rosuvastatin vs placebo in patients without CHD, the effect of statin therapy on all-cause mortality in primary prevention remains a subject of controversy. Although many meta-analyses of primary prevention trials clearly demonstrated that statin therapy may provide important cardiovascular benefits in individuals without CHD, findings for all-cause mortality have been mixed in terms of the statistical significance of statin-related benefit (Table 4).[6,39–42] A recent meta-analysis of eleven primary prevention trials that included 65,229 adults without clinically manifest CHD found a 9% reduction in the risk of all-cause mortality for statin therapy vs placebo that missed statistical significance (Table 4).[39] In contrast, another recently published meta-analysis of ten primary prevention studies comprising 70,388 individuals found that statin therapy vs placebo significantly reduced the risk of all-cause mortality by 12% (Table 4).[42] In the latter analysis, 6% of participants had had a previous cardiovascular event. Exclusion from the analysis of the three studies that recruited these individuals did not affect the outcome substantially because statin therapy was still associated with a significant reduction of 13% in the RR of all-cause mortality. In addition, even after the exclusion of JUPITER from the meta-analysis, RR reduction in all-cause mortality with statin therapy (11% vs placebo) remained statistically significant.[42] Consistent with these findings, a recently published Cochrane database analysis of 14 primary prevention studies (not including JUPITER) across diverse study populations found statistically significant reductions with statins in risks of all-cause mortality (RR: 0.83; 95% CI: 0.73–0.95), combined fatal and nonfatal CVD events (RR: 0.70; 95% CI: 0.61–0.79), and revascularization (RR: 0.66; 95% CI: 0.53–0.83).[40] The differences in the results of these meta-analyses regarding the effects of statins on all-cause mortality may be due at least in part to the differences in the selection of trials and data, potentially resulting in differences in the representation of risk categories among analysis populations (Table 4). Moreover, in study populations with substantial proportions of low-risk individuals, much longer follow-up times may be required to demonstrate a significant treatment effect on all-cause mortality than to demonstrate significant benefits related to composite end points.

Effect of lipid-lowering therapy on atherosclerotic disease progression

Several clinical studies evaluated the effect of statins on atherosclerotic disease progression in individuals with or without CHD. For patients with established CHD, the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial showed that intensive therapy with high-dose atorvastatin reduced the progression of coronary atherosclerosis compared with standard-dose pravastatin.[43] A Study

Table 3 Clinical effects of statins on major cardiovascular events in primary prevention: findings from recent large randomized controlled clinical outcomes trials

Study	Follow-up	Population	Treatments	Mean LDL-C (mg/dL)[a]		Primary outcome	
				Baseline	During treatment	Event	Hazard ratio (95% CI)
CARDS[34]	Median 3.9 years	N = 2838 Type 2 diabetes, no CVD, LDL-C ≤160 mg/dL	Atorvastatin 10 mg	117	72 at 1 year	Acute CHD, coronary revascularization, or stroke	0.63 (0.48–0.83) $P = 0.001$
			Placebo	117	120 at 1 year		
ASPEN[49]	Median 4 years	N = 1905 Type 2 diabetes, no prior MI or interventional procedure, LDL-C ≤160 mg/dL	Atorvastatin 10 mg	114	–30.5 CFB at study end	CV death, nonfatal MI, nonfatal stroke, arterial revascularization, hospitalization for unstable angina	0.97 (0.74–1.28)
			Placebo	114	–0.5 CFB at study end		
MEGA[50]	Mean 5.3 years	N = 7832 Japanese patients without CHD or stroke, total cholesterol 220–270 mg/dL	Pravastatin 10 to 20 mg + diet	156	127 at 1 year	CHD	0.67 (0.49–0.91) $P = 0.01$
			Diet	156	153 at 1 year		
JUPITER[38]	Median 1.9 years	N = 17,802 No CHD, LDL-C <130 mg/dL, hsCRP ≥ 2 mg/L	Rosuvastatin 20 mg	108[b]	55 at 1 year[b]	MI, stroke, arterial revascularization, hospitalization for unstable angina, or CV death	0.56 (0.46–0.69) $P < 0.00001$
			Placebo	108[b]	110 at 1 year[b]		

Notes: [a]Values are converted from mmol/L to mg/dL; [b]values are medians.

Abbreviations: ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-insulin-dependent diabetes mellitus; CARDS, Collaborative Atorvastatin Diabetes Study; CFB, change from baseline; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; hsCRP, high-sensitivity C-reactive protein; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C, low-density lipoprotein cholesterol; MEGA, Members of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; MI, myocardial infarction.

Table 4 Clinical effects of statins on all-cause mortality in primary prevention: findings from recent meta-analyses

Meta-analysis	Follow-up[a]	Population	LDL-C		All-cause Mortality	
			Baseline	Reduction	No. of deaths/no. of patients	Risk reduction (95% CI)
Thavendiranathan et al[41]	3.2–5.2 years	N = 42,848 (7 trials)[b] 90% without CVD	147 mg/dL (mean)	–26.1%	N/A	0.92 (0.84–1.01) $P = 0.09$
Mills et al[6]	1.0–5.3 years[c]	N = 63,899 (19 trials)[b] 59.6%–100% without CHD	N/A	N/A	N/A	0.93 (0.87–0.99) $P = 0.03$
Brugts et al[42]	4.1 years	N = 70,388 (10 trials) 94% without CVD	140 mg/dL[d] (mean)	–25.6%	1725/33,683[e] 1925/33,793[f]	0.88 (0.81–0.96)
Ray et al[39]	3.7 years	N = 65,229 (11 trials) 100% without CVD	138 mg/dL	–40 mg/dL[g]	1346/32,623[e] 1447/32,606[f]	0.91 (0.83–1.01)
Taylor et al[40]	1.0–5.3 years	N = 34,272 (14 trials)[b] ≥ 90% without CVD	153 mg/dL[d] (median)	–36 mg/dL[d,g]	794/28,161 (2.8%)	0.83 (0.73–0.95)

Notes: [a]Based on mean and median follow-ups of the individual studies; [b]did not include JUPITER; [c]values shown are follow-up durations or patient characteristics of individual trials included in the meta-analysis; [d]converted from SI units (mmol/L) using 38.61 as conversion factor; [e]statin group; [f]control group; [g]vs control.
Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C, low-density lipoprotein cholesterol; N/A, not available.

to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) further demonstrated that intensive lipid lowering with high-dose rosuvastatin, achieving average LDL-C levels of 61 mg/dL (53% reduction) and HDL-C increases of 6 mg/dL (15%), resulted in significant regression of coronary atherosclerosis.[44] Similarly, the Stop Atherosclerosis in Native Diabetics Study (SANDS) showed that intensive therapy lowering LDL-C to ≤ 70 mg/dL resulted in the regression of carotid intima-media thickness (CIMT) in patients with type 2 diabetes and no prior cardiovascular event.[45] Statins have also been shown to provide benefits for asymptomatic patients with subclinical atherosclerosis. In the Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin (METEOR) study, 2 years of intensive therapy with rosuvastatin, compared with placebo, significantly slowed the progression of carotid atherosclerotic lesions in patients with low Framingham risk scores, slightly elevated LDL-C, and modestly increased CIMT.[46]

Overall, the findings from these studies are consistent with the clinical benefits of intensive lipid-lowering therapy observed in trials with clinical end points and suggest that the aggressive LDL-C goal of < 70 mg/dL may be beneficial for specific patient groups, such as high-risk patients with established CHD or type 2 diabetes. In addition, some findings suggest that statins may slow the progression of atherosclerosis in asymptomatic low-risk patients, for whom the ATP III guidelines currently do not recommend the use of statins. These findings need to be confirmed in randomized controlled trials evaluating vascular outcomes.

Safety

Statin therapy is generally safe and well tolerated, and adverse events associated with statins are well documented.[24,25] Among adverse effects of statin therapy, abnormalities in liver metabolism and myopathy are of particular concern. Symptoms of myopathy, such as myalgia, vary widely among persons taking statins in routine clinical practice (0.3% to 33%), but rhabdomyolysis, a serious and potentially fatal myopathy, is rare.[47] A meta-analysis of 76 randomized controlled statin trials found that statin therapy significantly increased levels of aspartate aminotransferase (odds ratio [OR]: 1.12; $P = 0.005$) and alanine aminotransferase (OR: 1.3; $P \leq 0.001$), but not creatine kinase (OR: 1.07; $P = 0.66$).[25] Most importantly, statin therapy, compared with control treatment, was not associated with a significantly increased risk of rhabdomyolysis (OR: 1.04; $P = 0.73$). Overall, rates of rhabdomyolysis were low and virtually identical (0.25%) in statin and control groups across 35 studies that included data from more than 130,000 participants.[25] However, although the absolute risk of statin-related rhabdomyolysis is generally low, it may be increased in specific patients by a number of patient and treatment characteristics, including high statin doses, statin cytochrome metabolism, advanced age, specific comorbidities (eg, liver dysfunction), drug interaction of statins with concomitant medications, and genetic risk factors.[47]

A recently emerged concern is the increase in incident diabetes observed with statin therapy in some clinical studies.[22,29,38] A meta-analysis of 13 major cardiovascular trials that evaluated the incidence of diabetes in more than 90,000 nondiabetic participants found that statin therapy was associated with a small risk of developing diabetes

(OR: 1.09; 95% CI: 1.02–1.17) over a period of 4 years.[48] The increased risk of diabetes primarily affected elderly individuals and appeared not to be associated with the extent of LDL-C reduction.[48] These findings suggest that it is important to closely monitor older patients on statin therapy for signs of dysglycemia. However, it is also important to emphasize that the large cardiovascular benefits of statin therapy in primary and secondary prevention clearly outweigh the relatively small risk of incident diabetes associated with statin use.[48]

Conclusion

Clinical data published during the past decade have provided compelling evidence that lipid-lowering therapy with statins is a powerful therapeutic approach in the primary and secondary prevention of negative cardiovascular outcomes. Statin therapy may benefit high-risk individuals with diverse demographic and clinical characteristics, including women, the elderly, patients with type 2 diabetes, and high-risk individuals without hyperlipidemia. Moreover, recent results suggest that the treatment benefits of statins may extend to individuals traditionally not considered at high risk for CHD, such as those with elevated C-reactive protein but normal lipid levels. The demonstrated efficacy of statins in primary prevention together with their potential to slow atherosclerotic disease progression provides a strong argument in favor of starting lipid-lowering therapy as early as possible. In patients with established CHD, intensive lipid-lowering therapy is more effective than less-intensive therapy in reducing lipid levels to recommended goals and in reducing the risk of cardiovascular events, CHD mortality, and all-cause mortality. The failure to demonstrate significant benefits of statin therapy in patients with heart failure and in those requiring hemodialysis suggests that in many patients with very advanced stages of disease, intervention with statins may be too late to affect outcomes or impact end-of-life events not related to cardiovascular risk reduction.

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