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Introduction

In June 2004, almost 1,000 delegates attended the Third Atorvastatin Global Investigators Meeting in Toronto, Ontario, Canada. Presentations were held on recent 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) trial results, on the implications of these results for cardiovascular disease (CVD) prevention guidelines, and on future directions for statin therapy. Each of the articles published in this supplement to The American Journal of Medicine reflects the issues highlighted during a particular presentation at this meeting.

Results from clinical trials drive the development of guideline recommendations, and over the last few years, many important statin trials have been completed. The medical community has gained an increasingly accurate understanding from these trials of the benefits of lipid-lowering therapy in patients with or at risk for CVD. The authors in the first section of this supplement, Advances in Lipid-Lowering Therapy, present data from some of these trials.

In the first article, Dr. Peter S. Sever describes the results of the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA). In ASCOT-LLA, patients at risk for CVD but with only moderately elevated cholesterol levels who were randomized to statin therapy experienced significant cardiovascular benefit compared with those randomized to placebo. Dr. Sever stresses the importance of determining a patient’s global cardiovascular risk based on all coexistent risk factors, rather than on the risk associated with an individual risk factor, when considering the most appropriate treatment strategy.

The second article, by Dr. John Betteridge, presents data from the Collaborative Atorvastatin Diabetes Study (CARDS) that had not been available at the time of the Third Atorvastatin Global Investigators Meeting. The results from CARDS show that, compared with placebo, statin therapy reduced cardiovascular events in patients with type 2 diabetes mellitus who did not have clinically evident CVD. Dr. Betteridge proposes that patients with diabetes but without CVD may be candidates for statin therapy regardless of low-density lipoprotein (LDL) cholesterol levels.

The last 3 articles in this section focus on whether intensive lipid-lowering therapy provides greater benefit than more moderate lipid-lowering therapy. In his article, Dr. Michael J. Koren explains that in the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) trial, intensive statin treatment significantly reduced cardiovascular events compared with usual care in patients with coronary heart disease (CHD) in a managed care setting. Similarly, greater benefits with intensive versus moderate lipid-lowering therapy in patients with CHD were evident in the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, as described in the article by Dr. Steven E. Nissen. In REVERSAL, intravascular ultrasonographic imaging showed that with intensive statin therapy (atorvastatin 80 mg/day) atherosclerotic progression stopped, whereas with moderate therapy (pravastatin 40 mg/day) atherosclerotic progression continued. Although the results from REVERSAL suggest that a greater reduction in cardiovascular events was likely with intensive compared with more moderate therapy, it was the findings from the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial, a large clinical end point trial that compared the same treatment regimens as REVERSAL but in patients with acute coronary syndromes, that verified this assumption. In his article, Dr. Jean Rouleau reviews the rationale, study design, and results of the PROVE IT–TIMI 22 trial.

Having established the benefits of statin therapy, the 2 articles in the second section of this supplement, Applying Guideline Recommendations to Clinical Practice, address strategies to improve patients’ lipid profiles in clinical practice. Dr. Leif R. Erhardt provides data showing that many patients are unaware of their risk for CVD and that physicians overestimate their patients’ knowledge of the disease as well as the extent to which guidelines are implemented in clinical practice. His contribution is followed by that of Prof. Ian Graham, who emphasizes the cardiovascular benefits associated with lowering LDL cholesterol levels beyond existing guideline goals, particularly in light of recent data from the Treating to New Targets (TNT) study. Prof.
Graham states that future guideline emphasis may lie in preventive rather than drug therapy.

The articles in the third and final section of this supplement, New Directions for Statin Therapy, provide a shift of focus to some of the exciting new areas of statin research. The first and perhaps most surprising area is whether statins are of benefit in the treatment of Alzheimer disease (AD). The number of cases of AD is estimated to increase 4-fold in the next 50 years, and AD is a disease for which there is currently no cure. The article by Dr. Steven T. DeKosky reviews data from epidemiologic and observational studies, the results of which suggest that statin therapy may offer some clinical benefits in patients with AD. Another novel area is described by Dr. R. Preston Mason in an article that focuses on the combination of amlodipine and atorvastatin in a single tablet for the treatment of coprevalent hypertension and dyslipidemia. Specifically, Dr. Mason describes the synergistic effect of both compounds on increasing nitric oxide availability, thus potentially enhancing their combined impact on cardiovascular outcomes. In the final article of the section, Dr. Scott Kinlay looks beyond the lowering of LDL cholesterol levels and summarizes the other vascular benefits offered by statins that may be responsible in part for the clinical benefits associated with this drug class. Improved understanding of the vascular benefits of statins may aid the identification of new targets for preventing atherosclerotic vascular disease and may result in new indications.

In summary, the articles herein offer a broad picture of our most recent knowledge of the benefits of statin therapy. They present the implications of this knowledge for clinical practice and provide a tantalizing glimpse of what the future may hold.

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Lipid-lowering therapy and the patient with multiple risk factors: what have we learned from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)?

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The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) was the first trial of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) to assess the benefits of lipid lowering in the primary prevention of coronary heart disease (CHD) in patients with hypertension who were not deemed to have dyslipidemia by conventional measures. A total of 19,342 patients with hypertension and ≥3 cardiovascular risk factors, but without CHD, were enrolled in ASCOT. Of these, 10,305 patients with a serum cholesterol level of ≥250 mg/dL (≥6.5 mmol/L) were randomized to either atorvastatin (10 mg/day) or placebo in the ASCOT lipid-lowering arm (ASCOT-LLA). Follow-up was planned for an average of 5 years. The ASCOT-LLA was stopped after 3.3 years owing to the superiority of atorvastatin 10 mg over placebo in reducing the primary end point of nonfatal myocardial infarction (MI) and fatal CHD. Patients receiving atorvastatin experienced a significant reduction in total cholesterol (50 mg/dL [1.3 mmol/L]) and low-density lipoprotein cholesterol (46 mg/dL [1.2 mmol/L]) levels after 1 year compared with those who received placebo. Cholesterol lowering with atorvastatin was associated with a highly significant reduction in the primary end point of nonfatal MI and fatal CHD (36%, P = 0.0005). The observed benefit was consistent across the secondary end points and the 18 prespecified subgroups. The ASCOT-LLA findings have influenced lipid-lowering guidelines and support the concept that treatment strategies to reduce cardiovascular disease should be based on the assessment of all cardiovascular risk factors, rather than on numerical thresholds of individual risk factors, to determine treatment strategies.

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KEYWORDS: Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT); Atorvastatin; Clinical trial

Hypertension and dyslipidemia are highly prevalent, independent, modifiable risk factors for cardiovascular disease (CVD). The importance of hypertension and dyslipidemia as risk factors is underscored by the knowledge that they contribute to 12 million deaths per year, of which at least half now occur in the developing world. In both the United States and the United Kingdom, it is suggested that approximately two thirds of coronary heart disease (CHD) deaths can be ascribed to elevated blood pressure and elevated cholesterol levels.

In addition to the presence of either hypertension or dyslipidemia in isolation, these 2 risk factors commonly coexist. Observational data indicate that the coexistence of hypertension and dyslipidemia exerts a greater than additive effect on the risk of developing CHD (Figure 1). In 2002 it was estimated that 27 million people in the United States (15% of the population) and 7.7 million people in the United Kingdom (16% of the population) were at risk of CHD due to concomitant hypertension and dyslipidemia.
Anglo-Scandinavian Cardiac Outcomes Trial

Rationale

The aim of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) was to determine the answers to several important questions relating to the management of hypertension, in particular whether a combination of newer antihypertensive agents—a dihydropyridine calcium channel blocker and an angiotensin-converting enzyme (ACE) inhibitor—produces greater benefits in terms of reducing CHD events than does the standard β-blocker and diuretic combination. Preliminary results from the ASCOT blood pressure–lowering arm (ASCOT-BPLA) were presented in March 2005 and are available on the ASCOT Web site. The final data have recently been published.

The ASCOT lipid-lowering arm (ASCOT-LLA) was incorporated by factorial design into the ASCOT blood pressure trial and was designed to determine whether lipid lowering with a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) provides additional beneficial effects in patients with hypertension who have average or below-average levels of serum total cholesterol. Before ASCOT-LLA, no study had assessed the benefits of cholesterol lowering in the primary prevention of CHD in patients with hypertension who by contemporary guidelines were not deemed to have dyslipidemia.

Design

ASCOT was an independent, investigator-led, multicenter, randomized trial to assess treatment strategies for the prevention of CHD in patients with hypertension who had multiple risk factors but no history of CHD. The study comprised 2 treatment comparisons in a factorial design (Figure 2).

The ASCOT hypertension arm was a prospective, randomized, open, blinded end point design comparing 2 antihypertensive regimens. The second arm, ASCOT-LLA, was a double-blind, placebo-controlled trial of atorvastatin in a subsample of patients with hypertension and total cholesterol levels ≤250 mg/dL (≤6.5 mmol/L). The primary objective of ASCOT-LLA was to compare the effect of atorvastatin 10 mg/day versus placebo on the incidences of nonfatal myocardial infarction (MI) and fatal CHD in patients with treated hypertension. Of the 19,342 patients randomized in ASCOT, 10,305 were further randomly assigned either atorvastatin 10 mg daily (5,168 patients) or a matching placebo (5,137 patients) in ASCOT-LLA.

Inclusion criteria

Patients eligible for inclusion in ASCOT were men and women, aged 40 to 79 years at randomization, with hypertension and ≥3 prespecified cardiovascular risk factors. Risk factors included male sex, current smoking, age ≥55 years, microalbuminuria/proteinuria, type 2 diabetes mellitus, left ventricular hypertrophy (LVH), electrocardiographic abnormalities, a history of early CHD in a first-degree relative, ratio of plasma total cholesterol to high-density lipoprotein (HDL) cholesterol of ≥6, peripheral vascular disease, and a history of cerebrovascular events. Because this was a primary prevention study, patients were not permitted to have had a prior major coronary event (previous clinical MI or currently treated angina pectoris) or a cerebrovascular event within 3 months of study onset.

Subjects not receiving antihypertensive medication at study entry were required to have either systolic blood pressure of ≥160 mm Hg and/or diastolic blood pressure of ≥100 mm Hg at both the screening and randomization visits. Patients who had not achieved blood pressure control but who were taking antihypertensive medication before study entry were required to have a systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg at randomization. Individuals eligible for inclusion in ASCOT-LLA were those patients eligible for the antihypertensive regimen comparison who had a serum cholesterol level at screening of ≥250 mg/dL (≥6.5 mmol/L) and who were not currently taking a statin or a fibrate.

End points

The primary end point, which was the same for both treatment comparisons, was a composite of nonfatal MI and fatal CHD events. The effect of atorvastatin on the primary end point of ASCOT was assessed in 18 prespecified subgroups, with stratification including diabetes, age, sex, renal function, LVH, and smoking. Secondary end points included all-cause mortality, cardiovascular mortality, fatal and nonfatal stroke, total coronary events, and total cardiovascular events and procedures.

Statistical methods

Assuming a sample size of 9,000 patients, ASCOT-LLA was powered at >90% (α = 0.01) to detect a 30% relative treatment effect on the primary end point. The time to first primary end point event in the atorvastatin and placebo groups was compared on an intention-to-treat basis. For the main analyses, the log-rank procedure and the Cox proportional hazards model to calculate confidence interval (CI) was used. Cumulative incidence curves were generated by the Kaplan-Meier method for all major end points in the active treatment and placebo groups.
Results of ASCOT–LLA

ASCOT–LLA was stopped in October 2002 after 3.3 years on the recommendation of the Data and Safety Monitoring Board. The recommendation to end ASCOT–LLA early was made on the grounds that atorvastatin treatment had resulted in a highly significant reduction in the primary end point compared with placebo and a significant reduction in the incidence of stroke. This recommendation was ratified by the steering committee, as it was deemed unethical and unjustifiable to continue the study because of the magnitude of benefit conferred upon those assigned to atorvastatin. All patients in ASCOT–LLA were offered atorvastatin 10 mg daily until the end of the ASCOT blood pressure trial.

Baseline characteristics for the atorvastatin and placebo treatment groups in ASCOT–LLA were well matched. Patients were characterized as predominantly male, white, with a mean age of 63 years, mean total cholesterol level of 213 mg/dL (5.5 mmol/L), and poor blood pressure control (Table 1). At the close of follow-up for ASCOT–LLA, complete information was obtained on 10,186 (98.8%) of the 10,305 patients originally randomized. The structured approach to hypertension treatment used in
ASCOT resulted in an average systolic blood pressure reduction of 26 mm Hg (164/95 mm Hg at baseline to 138/80 mm Hg) after 3.3 years.

At 1 year follow-up, levels of total cholesterol and low-density lipoprotein (LDL) cholesterol in the atorvastatin treatment group were significantly reduced relative to levels in the placebo group by 24% (50 mg/dL [1.3 mmol/L]) and 35% (46 mg/dL [1.2 mmol/L]), respectively (Figure 3). Compared with placebo, atorvastatin reduced triglyceride levels by approximately 17% (27 mg/dL [0.3 mmol/L]) at 1 year. Changes in HDL cholesterol concentrations were minimal in the 2 groups.

### Cardiovascular outcomes

The observed reductions in total and LDL cholesterol were associated with reductions in the incidence of cardiovascular events. Atorvastatin therapy significantly reduced the risk of reaching the primary end point (nonfatal MI and fatal CHD) by 36% (P = 0.0005) compared with placebo (Figure 4), with benefits evident within the first year of treatment. Reduction in the risk of the primary end point was observed regardless of baseline cholesterol levels; the risk reduction (37%) in atorvastatin-treated patients with a low baseline total cholesterol level of <193 mg/dL (<5.0 mmol/L) was comparable to that observed in the overall population. Relative to placebo, atorvastatin therapy also significantly reduced the risk of several secondary end point measurements, including fatal and nonfatal stroke (27%, P = 0.024), total cardiovascular events and procedures (21%, P = 0.0005), and total coronary events (29%, P = 0.0005). All-cause mortality was nonsignificantly reduced by 13%, with nonsignificantly fewer cardiovascular deaths and no excess of deaths from cancer (81 assigned statin vs. 87 assigned placebo) or due to other noncardiovascular causes (111 statin vs. 130 placebo).

Owing to the small number of events in the prespecified subgroups, a test of heterogeneity was the most appropriate analysis to determine whether any individual

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**Table 1** Baseline characteristics of patients randomized in the Anglo-Scandinavian Cardiac Outcomes Trial lipid-lowering arm (ASCOT-LLA)

<table>
<thead>
<tr>
<th>Patients’ characteristics</th>
<th>Atorvastatin (n = 5,168)</th>
<th>Placebo (n = 5,137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>979 (18.9)</td>
<td>963 (18.7)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>4,189 (81.1)</td>
<td>4,174 (81.3)</td>
</tr>
<tr>
<td>Age, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60.0 yr</td>
<td>1,882 (36.4)</td>
<td>1,853 (36.1)</td>
</tr>
<tr>
<td>&gt;60.0 yr</td>
<td>3,286 (63.6)</td>
<td>3,284 (63.9)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>63.1 (8.5)</td>
<td>63.2 (8.6)</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>4,889 (94.6)</td>
<td>4,863 (94.7)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>1,718 (33.2)</td>
<td>1,656 (32.2)</td>
</tr>
<tr>
<td>Laboratory values, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>164.2 (17.7)</td>
<td>164.2 (18.0)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>95.0 (10.3)</td>
<td>95.0 (10.3)</td>
</tr>
<tr>
<td>BMI</td>
<td>28.6 (4.7)</td>
<td>28.7 (4.6)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.5 (0.8)</td>
<td>5.5 (0.8)</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>3.4 (0.7)</td>
<td>3.4 (0.7)</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.3 (0.4)</td>
<td>1.3 (0.4)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.7 (0.9)</td>
<td>1.6 (0.9)</td>
</tr>
<tr>
<td>Number of risk factors, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>485 (9.4)</td>
<td>516 (10.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1,258 (24.3)</td>
<td>1,274 (24.8)</td>
</tr>
<tr>
<td>LVH (on ECG or ECHO)</td>
<td>744 (14.4)</td>
<td>729 (14.2)</td>
</tr>
<tr>
<td>ECG abnormalities other than LVH</td>
<td>741 (14.3)</td>
<td>729 (14.2)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>261 (5.1)</td>
<td>253 (4.9)</td>
</tr>
<tr>
<td>Other relevant CVD</td>
<td>188 (3.6)</td>
<td>207 (4.0)</td>
</tr>
<tr>
<td>Previous antihypertensive treatments, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1,021 (19.8)</td>
<td>996 (19.4)</td>
</tr>
<tr>
<td>1</td>
<td>2,314 (44.8)</td>
<td>2,279 (44.4)</td>
</tr>
<tr>
<td>≥2</td>
<td>1,833 (35.5)</td>
<td>1,862 (36.2)</td>
</tr>
</tbody>
</table>

BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; ECG = electrocardiogram; ECHO = echocardiogram; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LVH = left ventricular hypertrophy; TIA = transient ischemic attack.

Adapted from *Lancet.*

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subgroup was different from the total study population. No significant heterogeneity was evident for either the primary end point or total cardiovascular events and procedures in any of the prespecified subgroups. Therefore, it is justifiable to apply the results obtained for the total trial population to each of the prespecified subgroups.

One subgroup of particular importance was patients with type 2 diabetes, because they can be considered as at CHD risk equivalent to that of patients without diabetes who already sustained an MI. Of the 10,305 patients randomized to treatment with either atorvastatin or placebo, approximately 25% (n = 2,532) had type 2 diabetes. Although a subgroup analysis of patients with diabetes was not sufficiently powered to detect reductions in individual components of the composite end point, analysis of all cardiovascular events and procedures elicited enough events to permit a comparison of atorvastatin with placebo. This comparison revealed that, compared with placebo, atorvastatin treatment resulted in a 23%
risk reduction in patients with diabetes—a reduction that was similar to that seen in patients without diabetes (20%).

Safety

The incidences of noncardiovascular deaths, cancer, serious adverse events, and liver enzyme test abnormalities were not significantly different between patients assigned to atorvastatin or placebo. There was 1 nonfatal case of rhabdomyolysis in a patient receiving atorvastatin, although causation was confounded by alcohol abuse and recent febrile illness.

Summary

In patients with hypertension at modest risk of CHD but who were not conventionally deemed to have dyslipidemia, cholesterol lowering with atorvastatin 10 mg/day was associated with a highly significant reduction in the primary end point of nonfatal MI and fatal CHD events. Significant reductions in the secondary end points of stroke, all cardiovascular events and procedures, and total coronary events also were observed. Reductions in incidence of major cardiovascular events were large, given the short follow-up time, and appeared to occur earlier than in previously published statin trials. CVD risk reductions were unrelated to baseline cholesterol levels, and benefits occurred with low doses of statin. Overall, the findings from ASCOT-LLA suggest that patients with hypertension and multiple cardiovascular risk factors should receive lipid-lowering therapy, regardless of baseline cholesterol levels.

Wider implications of the Anglo-Scandinavian Cardiac Outcomes Trial

Patients randomized to treatment in ASCOT achieved excellent blood pressure control. The average systolic blood pressure for the ASCOT population was reduced by 26 mm Hg to between 130 and 140 mm Hg after a study period of 4 years. Using data from previous hypertension trials, the observed reduction in blood pressure can be estimated to be associated with a reduction in CHD of >40% and a stroke reduction of >60%. The ASCOT-LLA data showed that, against a background of good blood pressure control, patients assigned atorvastatin benefited from a 36% reduction in coronary disease events and a 27% reduction in incidence of stroke. Because the benefits of statin treatment are likely to be additive to those of good blood pressure control, the overall results of ASCOT imply that it may be possible to have an impact of >60% risk reduction on CHD outcomes.

The findings of ASCOT-LLA add further support to the concept that treatment strategies to reduce CVD should be based on global assessment of risk rather than on numeric thresholds of individual risk factors, and that benefits of lipid lowering are apparent across the whole range of serum cholesterol concentrations. The placebo group in ASCOT-LLA experienced the equivalent of a combined 10-year risk of first stroke or CHD event of approximately 16.5%. However, had these patients not received aggressive blood pressure–lowering treatment, it could be estimated that their cardiovascular risk would have been >20% over 10 years, which is increasingly accepted as a reasonable treatment threshold for lipid lowering. The findings from ASCOT-LLA therefore reinforce the need to treat patients based on their cardiovascular risk and to not restrict lipid-lowering therapy to those with high cholesterol levels.

In conjunction with data from other recent cardiovascular outcome trials (including the Heart Protection Study [HPS] and Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 [PROVE IT–TIMI 22] trial), the ASCOT results have influenced the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines. Previously, NCEP ATP III guidelines did not recommend LDL cholesterol–lowering therapy in patients at moderately high risk in whom serum LDL cholesterol was <130 mg/dL (<3.4 mmol/L). However, in ASCOT a significant proportion of the patients who had an LDL cholesterol level of <130 mg/dL (<3.4 mmol/L) and who were at moderately high risk by NCEP ATP III criteria had a significantly reduced CVD risk when treated with atorvastatin 10 mg/day. The 2004 modification to the NCEP ATP III guidelines emphasized that drug intervention should be considered for patients at moderately high risk (≥2 risk factors [10-year risk, 10% to 20%]) with an LDL cholesterol level of 100 to 129 mg/dL (2.6 to 3.3 mmol/L).

Summary

In conclusion, the ASCOT results have not only influenced contemporary guidelines for the primary prevention of CHD but also have had a major impact on clinical practice. The findings of ASCOT-LLA lend further support to the concept that treatment strategies to reduce CVD should depend on global assessment of risk rather than on numeric thresholds of individual risk factors.

References


Benefits of lipid-lowering therapy in patients with type 2 diabetes mellitus

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The incidence of type 2 diabetes mellitus is expected to increase dramatically over the next decade. Patients with type 2 diabetes are at a much greater risk for cardiovascular disease (CVD) than are nondiabetic individuals. Consequently, the treatment of CVD risk factors is a healthcare priority in this patient population. Dyslipidemia is a major cardiovascular (CV) risk factor in patients with type 2 diabetes, and it is characterized by elevated triglyceride levels, low high-density lipoprotein (HDL) cholesterol levels, and a preponderance of small, dense low-density lipoprotein (LDL) particles. Subgroup analyses of clinical trial data suggest that treatment of the entire range of lipid abnormalities may reduce CV risk in this patient population. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the best therapy for LDL cholesterol reduction. A number of statin trials have shown significant CV risk reduction through LDL cholesterol lowering in subgroups of patients with diabetes. The recently published Collaborative Atorvastatin Diabetes Study (CARDS), a placebo-controlled trial conducted solely in patients with type 2 diabetes, terminated 2 years earlier than its anticipated length owing to the significant reduction in number of CV events observed in patients randomized to receive low-dose atorvastatin versus placebo. These results suggest that low-dose statin therapy with atorvastatin results in significant reduction of CV events in patients with type 2 diabetes without prior CVD or high LDL cholesterol levels. Based on this evidence, patients with type 2 diabetes may be candidates for statin therapy regardless of LDL cholesterol level and in the absence of a previous CV event.

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KEYWORDS:
Diabetes;
Dyslipidemia;
Fibrates;
Statins

The incidence of type 2 diabetes mellitus is expected to reach almost epidemic proportions in the next decade. By 2010, it is estimated that approximately 221 million people worldwide will have this condition, representing a 46% increase over just 10 years. Type 2 diabetes is becoming more common in increasingly younger populations and is now observed even in adolescents.

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with diabetes, and the degree of coronary heart disease (CHD) risk in patients with diabetes but without a prior history of CHD is similar to that of patients without diabetes but with existing CHD. Once symptomatic disease develops in patients with diabetes, prognosis is poor. For instance, in the Finnish Contribution to the World Health Organization (WHO) Multinational Monitoring of Trends and Determinants of Cardiovascular Disease project (FINMONICA), diabetes independently increased risk of death by 57% in patients with non-Q-wave myocardial infarction (MI) and unstable angina. With growing numbers of younger patients with diabetes, more people will live with the burden of CVD risk for a longer
Evidence of cardiovascular benefit in treating dyslipidemia in patients with type 2 diabetes

The lipid profile of patients with diabetes

Patients with diabetes exhibit a distinctive lipid profile characterized by mild hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol levels, a preponderance of small, dense low-density lipoprotein (LDL) particles, and an accumulation of cholesterol-rich remnant particles. This dyslipidemic profile tends to remain even when glucose-related factors have been targeted by the physician. Nevertheless, diabetic dyslipidemia is open to therapeutic intervention.

In the general population, elevated total cholesterol and LDL cholesterol levels have been identified as major CVD risk factors. Numerous clinical trials with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have shown that lowering LDL cholesterol is associated with a reduction in risk of CVD events in patients with, or at risk for, CVD. Consequently, many guidelines set total cholesterol and/or LDL cholesterol goals for the treatment and prevention of CVD. Although LDL cholesterol levels in patients with diabetes are not typically elevated compared with the general population, this does not imply that LDL cholesterol is not a major CVD risk factor in this patient population. Indeed, in patients with diabetes, LDL particles tend to be smaller, denser, and more atherogenic than in the general population. As a result, in patients with diabetes, lowering LDL cholesterol levels may lead to a greater benefit in terms of CVD risk reduction than in patients without diabetes.

Statin treatment for patients with diabetes

Data from the diabetes subgroup analysis of the Scandinavian Simvastatin Survival Study (4S) clearly illustrated the increased risk for CHD in patients with diabetes compared with patients without diabetes and the potential benefits offered by lowering LDL cholesterol with statin therapy. In 4S, patients with elevated cholesterol levels and a history of CHD were randomized in a double-blind fashion to either simvastatin 20 mg/day, with titration up to 40 mg/day, or to placebo. Follow-up was for a median 5.4 years. Mean LDL cholesterol levels at baseline were elevated in both the subgroup with diabetes (186 mg/dL [4.8 mmol/L]) and the overall population. LDL cholesterol levels at baseline were elevated in both the subgroup with diabetes (190 mg/dL [4.9 mmol/L]). During follow-up, 45.4% of patients with diabetes assigned to placebo experienced a major CHD event (defined as CHD death or nonfatal MI), compared with only 27.2% of patients without diabetes who were assigned to placebo (Figure 1). In patients with diabetes, simvastatin therapy was associated with a 55% reduction in risk for a major CHD event compared with placebo, whereas in patients without diabetes who were assigned to receive simvastatin, the reduction in risk for a major CHD event was 32% compared with the placebo group.

Evidence from other subgroup analyses of major statin trials also supports the benefit of statin therapy in patients with type 2 diabetes. Table 1 shows that in many primary and secondary CHD prevention trials, patients with diabetes experienced CHD risk reductions similar to those observed in the overall population.

For example, the Heart Protection Study (HPS) randomized 20,536 patients at risk of occlusive arterial disease to simvastatin 40 mg/day or placebo. This patient population included a subgroup of 5,963 patients with known diabetes. At the end of the 5-year treatment period, patients in the overall population who were treated with statin experienced a 24% reduction in major vascular events (i.e., CHD death, nonfatal MI, stroke, and revascularization) compared with patients given placebo. The risk reduction was similar in the subgroup with diabetes, with a 22% reduction in major vascular events observed in patients treated with statins compared with those receiving placebo.

Additional data from HPS illustrated the impact of low HDL cholesterol on cardiovascular (CV) risk in patients with diabetes (Figure 2). In the diabetic subgroup in HPS, a greater risk for vascular events was observed in placebo-treated patients with low baseline HDL cholesterol levels (31.1%) than in placebo-treated patients with high baseline LDL cholesterol levels (27.9%), suggesting that strategies that target low levels of HDL cholesterol may result in CV...
benefit in addition to those that target high levels of LDL cholesterol.

The benefits of lowering LDL cholesterol levels in patients with diabetes also have been demonstrated in a recently completed "real-world" end point trial. In the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study, 1,600 patients with CHD were randomized to receive open-label atorvastatin or usual care. The atorvastatin dose was doubled every 6 weeks, from 10 mg/day to a maximum of 80 mg/day, to achieve an LDL cholesterol goal of 100 mg/dL (2.6 mmol/L). In the atorvastatin group, LDL cholesterol levels were reduced by 46%, whereas in the usual-care group, LDL cholesterol levels were lowered by only 5%. In the treated group, 95% of patients achieved National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) goals compared with only 3% in the usual-care group. Approximately 20% of all patients recruited had type 2 diabetes. Compared with the usual-care group, patients receiving atorvastatin experienced a 51% reduction in risk for the primary end point (nonfatal MI, unstable angina, coronary heart failure, stroke, and revascularization); in the subgroup with diabetes the corresponding risk reduction was 58% (P <0.0001 vs. the usual-care group). These results suggest that lowering LDL cholesterol levels robustly in patients with diabetes and established CHD may be associated with a significant reduction in risk for a further CHD event.

The results from the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 trial (PROVE IT–TIMI 22) also support a strategy of intensive lipid lowering with statins in patients with diabetes. The PROVE IT–TIMI 22 trial randomized 4,162 patients who had been hospitalized for an acute coronary syndrome to either pravastatin 40 mg/day or atorvastatin 80 mg/day. In this trial, 18% of all patients recruited had type 2 diabetes. The primary end point was death from any cause, MI, documented unstable angina requiring hospitalization, revascularization, and stroke. After a mean follow-up of 2 years, atorvastatin therapy yielded a 16% reduction in risk for the primary end point compared with pravastatin therapy, and a similar reduction (17%) was observed for atorvastatin in the diabetes subset.

Fibrate treatment for patients with diabetes

Clearly, there are considerable data to suggest that the use of statin therapy to reduce LDL cholesterol levels in patients with diabetes may provide CV benefit. Less information is available regarding the potential benefits of treatment with fibrate drugs in patients with diabetes.

The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) recruited 2,531 men with CHD and normal LDL cholesterol levels but with low levels of HDL cholesterol. In VA-HIT, 25% of the patients randomized to gemfibrozil 1,200 mg/day or placebo had diabetes. Gemfibrozil, a fibrate, elevates HDL cholesterol and lowers triglycerides but has a minimal impact on LDL cholesterol concentrations. After a median follow-up of 5.1 years, patients with diabetes receiving gemfibrozil experienced smaller changes in their HDL cholesterol levels (+5% for patients with diabetes; +8% for patients without diabetes; P = 0.02) and triglyceride levels (−20% for patients with diabetes; −29% for patients without diabetes; P <0.001) compared with patients with a normal fasting glucose level. Nevertheless, the patients with diabetes experienced greater risk reductions in the incidences of CHD death (41% reduction) and stroke (40% reduction) than did patients without diabetes (3% reduction in CHD death and 10% reduction in stroke). These findings from VA-HIT suggest that increasing HDL cholesterol levels and decreasing triglyceride levels may confer greater CV benefit in patients with diabetes than in patients without diabetes.
Recent evidence for benefit of statin therapy in patients with diabetes

Recently, the evidence from subgroup analyses suggesting a benefit of statin therapy in patients with diabetes has been confirmed by randomized trial data from the Collaborative Atorvastatin Diabetes Study (CARDS).25 To date, CARDS is the only published statin trial that specifically recruited patients with type 2 diabetes. Furthermore, CARDS recruited patients with relatively low LDL cholesterol levels (≤160 mg/dL [≤4.14 mmol/L]), triglyceride levels ≤600 mg/dL (≤6.78 mmol/L), no history of CVD, but with 1 other risk factor for CHD in addition to diabetes. A total of 2,838 patients were randomized in a double-blind fashion to receive placebo or atorvastatin 10 mg/day. The combined primary end point was an acute CHD event, coronary revascularization procedure, and stroke. The trial was originally planned for 5 years but was terminated at 3.9 years by its data safety monitoring board because a substantial reduction in the incidence of CV events was observed in favor of the group treated with atorvastatin. Compared with placebo recipients, patients receiving atorvastatin 10 mg/day experienced a 37% reduction in the incidence of the primary end point (Figure 3).25 When the components of the primary end point were assessed separately, atorvastatin therapy was associated with a 36% reduction in coronary

Figure 2  The Heart Protection Study (HPS) diabetic cohort. Benefits of treatment with simvastatin by baseline low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels.

Table 1 Coronary heart disease (CHD) prevention trials with statins in subgroup analyses of patients with diabetes mellitus

<table>
<thead>
<tr>
<th>Trial</th>
<th>Statin</th>
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<th>CHD Risk Reduction (%)</th>
<th>P Value</th>
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<td>Pravastatin</td>
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AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; CARE = Cholesterol and Recurrent Events trial; 4S = Scandinavian Simvastatin Survival Study; HPS = Heart Protection Study; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease study; NS = not significant.
events, a 31% reduction in coronary revascularization procedures, and a 48% reduction in stroke compared with placebo. There was no heterogeneity of effect for sex or baseline age, lipid concentrations below or above the median, systolic blood pressure, retinopathy, albuminuria, smoking status, or glycosylated hemoglobin.

The results from CARDS not only support the view that statin therapy can substantially reduce the risk for CVD in patients with diabetes but also suggest that the benefit is obtained even when pretreatment LDL cholesterol levels are not elevated. At entry, 66% of patients had LDL cholesterol levels at or below the threshold of $\geq 130\, \text{mg/dL} \approx 3.35 \, \text{mmol/L}$ recommended by the American Diabetes Association (ADA). The median LDL cholesterol level achieved by patients randomized to atorvastatin was $77\, \text{mg/dL} \approx 2.0 \, \text{mmol/L}$, and 25% of patients treated with atorvastatin achieved LDL cholesterol levels $< 68\, \text{mg/dL} < 1.7 \, \text{mmol/L}$. Thus, the risk reductions in CVD events and in stroke established in CARDS are related to both starting lipid-lowering therapy and achieving LDL cholesterol levels below those recommended in current guidelines.

**Summary**

With the worldwide incidence of diabetes projected to increase dramatically in the next decade, and the increased risk for CVD that coexists with diabetes, the prevention and treatment of CVD in patients with diabetes is an urgent healthcare priority. Evidence is mounting steadily that CV benefits can be obtained by reducing LDL cholesterol levels in these individuals.

The recently published results from CARDS have convincingly corroborated the potential CV benefit of statin therapy in patients with type 2 diabetes and no history of CVD; they also indicate that there is no lower threshold for baseline LDL cholesterol levels. These benefits were obtained with a low statin dose over a shorter time than previously demonstrated in other trials. Treatment benefit without increased risk also was seen when LDL levels obtained were substantially lower than current guideline recommendations.

It remains to be seen whether future guidelines will advocate lower LDL cholesterol goals for diabetic populations. However, after ensuring that patients implement the relevant lifestyle changes—such as smoking cessation, improved diet, and increased exercise—the results from the studies outlined here provide evidence that physicians should target LDL cholesterol levels aggressively in their patients with diabetes to circumvent the increased risk for CVD.

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Statin use in a “real-world” clinical setting: aggressive lipid lowering compared with usual care in the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) trial

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KEYWORDS: Atorvastatin; Cardiovascular prognosis; Coronary artery disease; Hyperlipidemia; “Real-world trial”; Statin therapy

Clinical trials that incorporate elements of “real-world” experience are of great value to practicing physicians. Using a trial design adapted to approximate clinical settings, the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) trial compared a focused treatment strategy using atorvastatin with usual medical care. Patients eligible for study participation were predefined based on diagnosis codes for coronary heart disease from US managed care database records; 66% of these patients were taking lipid-lowering medications at study entry. In contrast to standard clinical trials, ALLIANCE maintained a real-world environment by limiting the interactions of investigators with patients after dose titration of aggressive treatment to a low-density lipoprotein (LDL) cholesterol goal < 80 mg/dL (2.1 mmol/L) or maximum atorvastatin dose of 80 mg/day. After 51.5 months of follow-up, the study showed that aggressive treatment with atorvastatin was associated with significantly lower LDL cholesterol levels (147 mg/dL [3.8 mmol/L] to 95 mg/dL [2.5 mmol/L]) over usual care (146 mg/dL [3.8 mmol/L] to 111 mg/dL [2.9 mmol/L]). This greater reduction in LDL cholesterol was accompanied by improved outcomes in the composite primary end point of cardiovascular events (17% with atorvastatin vs. usual care; P = 0.02) and particularly in the end point of nonfatal myocardial infarction (47% with atorvastatin vs. usual care; P = 0.0002). No safety difference was noted between the 2 treatment groups. These results indicate that usual-care treatment was not equivalent to targeted statin therapy, even in a trial conducted to minimize potential bias owing to traditional patient selection and trial design methods.

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In the mid 1990s, results from placebo-controlled clinical trials provided convincing evidence for the morbidity and mortality benefits of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) therapy in patients both with and without coronary heart disease (CHD).1–3 These positive early trial outcomes led to questions regarding the implementation of clinical strategies to maximize lipid-lowering benefits. Do the benefits of statin therapy in “real-world” clinical settings match those demonstrated in highly structured clinical trials? What would constitute a reasonable and effective lower limit for low-density lipoprotein (LDL) cholesterol levels? Finally, can high-dose statin therapy, if proved to provide additional benefit, be used safely? The Aggressive Lipid-Lowering Initiation Abates New Cardiac
Events (ALLIANCE) trial, initiated in 1995 and recently published, was designed to address some of these issues in patients with stable CHD.

The value of real-world trials

The value of real-world personal experience for clinicians trying new drugs and new drug regimens is an indisputable truth of contemporary medicine. Clinical feedback contributes substantially to information gleaned from clinical trials. In fact, randomized and controlled clinical trials were introduced to the medical community only 50 years ago. Real-world trials involving typical patients receiving “usual care” have been referred to as “effectiveness” (versus “efficacy”) or “pragmatic” (versus “explanatory”) trials. Such trials have been in demand in recent years, although no best approach for designing them has been described. Indeed, in heart failure, the need for clinically relevant information has led researchers to evaluate the specific differences in demographics and disease characteristics that exist between patients enrolled in clinical trials and those encountered in daily practice.

The Aggressive Lipid-Lowering Initiation Abates New Cardiac Events study design

The design of the ALLIANCE trial is shown in Figure 1. Although many of its basic elements parallel standard trial protocols, several unique aspects were introduced to best reflect real-world practices. The ALLIANCE study compared 2 clinical strategies, both of which involved active treatments. Patients received either atorvastatin (10 mg/day to 80 mg/day) or usual care. The usual-care patients were maintained on the individualized lipid-lowering regimen they were following at the time of enrollment. Adjustments to medication in these patients were made at the discretion of the treating physician. Usual-care treatment could in-clude modifications in diet, behavior, or antihyperlipidemic medication. Atorvastatin could be added to the usual-care regimen after its approval in 1997 (ALLIANCE enrollment occurred between July 1995 and June 1998, with follow-up until July 2002). Finally, usual-care treatment could evolve over the course of the trial, unconstrained by protocol-mandated interventions, and thus reflected changing trends in individual practice habits and lipid regulation.

The ALLIANCE study used a novel approach to enrollment so as to ensure a study population that reflected the types of patients usually seen by practicing clinicians in their offices. Rather than asking investigators to recruit from their own practice populations, a predefined patient cohort was identified using diagnosis codes for CHD from US managed healthcare organization or US Department of Veterans Affairs (VA) databases. Letters were sent to these patients inviting them to participate, and eligible patients were randomized to the aggressive atorvastatin arm or usual care after an initial screening visit. The use of a predetermined patient cohort minimized both the potential for selection bias among physician-investigators and variations in recruitment styles across study centers. Moreover, presenting the potential study participants to the investigators led to a distinct approach to framing the research question at hand. Whereas the standard clinical trial deals with the question of whether treatment A is better than treatment B, the research issue more fitting for ALLIANCE was how to get the best results in a given patient population.

It should be noted that approximately 66% of randomized patients were on lipid-lowering therapy at baseline. Patients were not taken off lipid-lowering therapy for their baseline laboratory measurements; consequently, LDL cholesterol inclusion values were lower for patients receiving lipid-regulating medications (between 110 mg/dL [2.8 mmol/L] and 200 mg/dL [5.2 mmol/L]) than for patients who were not taking such medications (between 130 mg/dL [3.4 mmol/L] and 250 mg/dL [6.5 mmol/L]) at screening. Patients were not subjected to a washout period before receiving study drug in either therapy arm. Given these trial design features, the efficacy outcomes in ALLIANCE in large part represented incremental benefits of aggressive lipid-lowering therapy versus usual care in an actively treated, managed care–based patient population.

Several additional nuances of trial conduct should be noted for ALLIANCE. First, the recruitment scheme described above ensured that all patients had a medical plan and health insurance at the time of enrollment, thereby eliminating bias based on differential access to healthcare...
resources. Second, the study setting, typically of little concern in randomized controlled trials, mirrored real-world clinical experience. Study centers had to be a staff model health maintenance organization (HMO), a community physician open-provider HMO, or a VA system facility. Usual-care patients had limited contact with study personnel and investigators, because visits were not required by the trial protocol. Although patients in this arm were invited to a center every 6 months for adverse event (AE) reporting, it was commonly found that these evaluations were, in fact, performed by telephone. Patients in the atorvastatin treatment arm were seen every 4 weeks during the dose-titration period and at 6-month intervals thereafter.

Despite providing a valuable comparison in a real-world patient population, the ALLIANCE trial design also had some shortcomings. The dropout rate for patients in both study arms seemed high (complete end point assessments were made for 78% of atorvastatin-treated patients and 77% of usual-care patients; partial end point assessments were made for the other 543 patients, who dropped out of the study for various reasons) compared with standard clinical trials. However, this dropout rate may be an inevitable consequence of the real-world approach taken in this trial. It is well known that patient adherence to preventive healthcare interventions can be poor. Because, by design, ALLIANCE limited investigator–subject interactions, it is not surprising that adherence rates may have been closer to those seen in clinical practice rather than in standard structured clinical trials. Frequent changes in healthcare plans among ALLIANCE patients, as well as investigator concerns about Health Insurance Portability and Accountability Act (HIPAA) rules, also were cited as factors contributing to a higher dropout rate than anticipated.

The unanticipated instability in the healthcare market in the late 1990s also gave rise to gaps in interim trial data for the usual-care group. Managed care databases often were unavailable, owing to company failures or mergers and to patients switching healthcare plans. Although laboratory values were measured by a central facility at baseline and end of study, data were incomplete for interim medications, lipid values, side effects, reasons for discontinuations, and postevent lipid values for the usual-care patient group. Of note, investigators were able to obtain information on all patients known to have been hospitalized as well as on the presence of serious AEs.

Patient population and lipid profiles

The details of the ALLIANCE protocol have been published. A total of 2,442 patients were recruited from among approximately 100,000 patients identified through managed care databases in 16 communities throughout the United States. Of these, 1,217 patients were assigned to the atorvastatin arm and 1,225 to the usual-care group. The study enrolled both men and women (aged 18 to 78 years) with a history of CHD. For trial purposes, CHD was defined as acute myocardial infarction (MI) >3 months before screening, percutaneous transluminal coronary angioplasty >6 months before screening, or coronary artery bypass grafting or unstable angina >3 months before screening.

The mean age for both treatment groups was 61 years, and 82% of randomized patients were men. Risk factors were comparable across the 2 treatment groups (Table 1) and patients were followed, on average, for 51.5 months. The mean LDL cholesterol levels at baseline were similar: 147 mg/dL (3.8 mmol/L) in atorvastatin-treated patients and 146 mg/dL (3.8 mmol/L) in the usual-care group.

As stated previously, usual-care patients were treated completely at the discretion of their physician. Patients in the focused treatment arm were treated with atorvastatin 10 mg/day with the option of doubling the dose every 4 weeks until an LDL cholesterol level of <80 mg/dL (<2.1 mmol/L) or a maximum dose of 80 mg/day was achieved. The median dose of atorvastatin received by patients in this arm was 40.5 mg/day and slightly <50% of patients were taking 80 mg/day. By study end, LDL cholesterol levels in the atorvastatin group had decreased by 34% to 95 mg/dL (2.5 mmol/L), and LDL cholesterol levels in the usual-care group were reduced by 23% to a value of 111 mg/dL (2.9 mmol/L; $P < 0.0001$ for atorvastatin vs. usual care). A summary of lipid profile changes in the ALLIANCE study is shown in Figure 2.

For both treatment groups, LDL cholesterol values at study end point were above the target levels projected at study inception. It was expected that atorvastatin-treated patients would achieve LDL cholesterol levels <80 mg/dL (<2.1 mmol/L) and that usual-care patients would be managed based on the National Cholesterol Education Program (NCEP) goal of <100 mg/dL (<2.6 mmol/L). Maximum-dose atorvastatin therapy (80 mg/day) has been associated with LDL cholesterol levels <80 mg/dL (<2.1 mmol/L) in several structured trials in a similar patient population. The failure to achieve these respective LDL cholesterol goals likely reflects the “treatment gap” that occurs in real-world settings, largely related to patient nonadherence. The confirmation of this treatment gap in the real-world ALLIANCE study supports the concept of targeting lower individual treatment goals knowing that these aggressive goals may be required to achieve a more modest population-based treatment objective.

Trial outcomes: efficacy end points

The primary end point for ALLIANCE was the time from randomization to the first occurrence of a primary cardiovascular event. Primary events included cardiac death, nonfatal MI, resuscitated cardiac arrest, cardiac revascularization, and unstable angina requiring hospitalization.
tion. The Kaplan-Meier curves for the composite end point of all primary events are shown in Figure 3.

Based on a Cox regression model, patients treated with a focused regimen of atorvastatin attained a 17% reduction in the risk of a primary cardiovascular outcome when compared with usual care (hazard ratio [HR] = 0.829; P = 0.02). This benefit of targeted atorvastatin treatment was due in large part to a significant reduction in incidence of nonfatal MI in this cohort (Figure 4). For nonfatal MI, the Cox regression analysis estimated a 47% reduction in risk for patients in the atorvastatin group (HR = 0.526; P = 0.0002) versus usual care. The Kaplan-Meier curves for nonfatal MI separated quite early in the trial, suggesting that the benefits of atorvastatin treatment for this outcome may have become evident within the first few months.

Atorvastatin-treated patients experienced numerically fewer primary events for each of the remaining components of the composite end point (cardiac death, resuscitated cardiac arrest, cardiac revascularization, and unstable angina requiring hospitalization). These differences were not statistically significant, although the outcome for cardiac death verged on significance (P = 0.057 for focused atorvastatin therapy over usual care). Given this trend toward signifi-
cance, a post hoc analysis was performed on the combined end points of nonfatal MI and cardiac death. Patients in the targeted atorvastatin group experienced a 43% reduction in these 2 “hard” end points compared with the usual-care group (HR = 0.574; \( P = 0.0001 \)).

**Trial outcomes: safety**

The occurrence of serious AEs was similar in the atorvastatin and usual-care groups (40% vs. 42%). Routine laboratory testing, mandated by protocol for the atorvastatin treatment group only, showed abnormal aspartate aminotransferase levels (>3 times the upper limit of normal [ULN]) in 8 (0.7%) patients and abnormal alanine aminotransferase levels (>3 times the ULN) in 16 (1.3%) patients. There were no documented cases of creatine phosphokinase >10 times the ULN in the atorvastatin group, and no documented cases of rhabdomyolysis or myopathy in either group.

**Summary**

ALLIANCE was the first trial comparing targeted statin therapy and usual care in a patient population whose degree
of lipid regulation was representative of the general population with CHD. Using a novel trial design tailored to mimic a real-world setting, ALLIANCE demonstrated that an aggressive statin-based management plan outperformed usual care with respect to lipid levels achieved as well as clinical outcomes.

References

Halting the progression of atherosclerosis with intensive lipid lowering: results from the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial

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Intravascular ultrasonography is a catheter-based technique used to provide 3-dimensional views of the vessel lumen as well as the size and distribution of atherosclerotic plaques. This imaging technique was used in the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study, an 18-month, randomized, controlled, multicenter trial comparing the effects of intensive versus moderate lipid-lowering therapy on plaque progression in patients requiring coronary angiography. A total of 253 patients were randomized to atorvastatin 80 mg/day (intensive lipid lowering) and 249 patients were randomized to pravastatin 40 mg/day (moderate lipid lowering). Low-density lipoprotein (LDL) cholesterol levels decreased from a baseline mean of 150 mg/dL (3.9 mmol/L) in both groups to 79 mg/dL (2.0 mmol/L) in the atorvastatin group and 110 mg/dL (2.9 mmol/L) in the pravastatin group. High-sensitivity C-reactive protein (hs-CRP) levels decreased by 36.4% in the atorvastatin group versus 5.2% in the pravastatin group (P < 0.001). For the primary end point of percent change in total atheroma volume, a significantly lower rate of progression from baseline was observed with atorvastatin (−0.4%) than with pravastatin (2.7%) (P = 0.02). Linear regression analysis showed an inverse relation between lipid reduction and plaque progression for both groups; however, at any given level of LDL cholesterol, the progression rate was lower with atorvastatin compared with pravastatin. Both regimens were well tolerated. The results show that intensive lipid lowering with atorvastatin 80 mg/day for 18 months halted the progression of coronary atherosclerosis, whereas more moderate lipid lowering with pravastatin 40 mg/day was associated with progression. The differences in the progression rate are likely to be a result of greater reduction in atherogenic lipoproteins and hs-CRP with intensive therapy.

Coronary atherosclerosis is an insidious process that remains silent for many years, or even decades, before the onset of the clinical manifestations of the disease. In >50% of cases, the occurrence of a major coronary event (myocardial infarction or sudden death) is the first and only indication of the presence of underlying coronary atherosclerosis. Although most events occur after the age of 40 years, necropsy studies have demonstrated that the disease process can begin as early as the teenage years. Several factors explain the long and silent course of coronary atherosclerosis. Contrast angiography, the traditional method for detecting the presence of coronary plaque, relies on assessment of a silhouette of the vessel lumen to detect the presence of disease. Thus, using angiography, plaque burden is determined exclusively by measuring the size of the
**Intravascular ultrasonography**

Intravascular ultrasonography (IVUS) is a relatively new catheter-based technique that is used as an adjunct to contrast angiography to view coronary vessels. IVUS equipment consists of an ultrasonicographic imaging catheter with a miniaturized transducer and a console used to reconstruct the images. Once the catheter is placed within the coronary vessel, a motorized pullback device is typically used to withdraw the transducer at a constant speed while recording the images continuously. Unlike angiography, which provides only a planar view of the vessel lumen, IVUS provides a 3-dimensional view of the vessel, allowing assessment of lumen size and the extent and distribution of atherosclerotic plaque. IVUS studies have confirmed the Glagov hypothesis, revealing significant atheroma burden within the walls of coronary vessels that appear completely normal by angiography. IVUS studies have also confirmed that this disease begins early in life, with the majority of the population exhibiting atherosclerotic changes by the age of 30 years.

**The Reversal of Atherosclerosis with Aggressive Lipid Lowering study**

**Background and objectives**

Although it is well established that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) reduce levels of atherogenic lipoproteins, as well as the incidence of cardiovascular morbidity and mortality, the optimal intensity for statin therapy in secondary prevention remains unclear. Even less is known about the effect of statins on the atherosclerotic disease process occurring within the vessel wall. Over the past decade, several angiographic trials have shown that statins are effective in slowing the progression of atherosclerosis; however, none of these trials has unequivocally demonstrated that statins can arrest progression or promote regression of the disease. In angiographic trials, low to moderate doses of statins were used and low-density lipoprotein (LDL) cholesterol levels were rarely lowered to <100 mg/dL (<2.6 mmol/L). The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study was the first IVUS trial specifically designed to compare the impact on plaque progression of intensive statin therapy designed to lower LDL cholesterol levels well below current guidelines.

**Study design**

REVERSAL was an 18-month, randomized, controlled, multicenter trial comparing the effects of intensive lipid-lowering therapy (atorvastatin 80 mg/day) with moderate lipid-lowering therapy (pravastatin 40 mg/day) in patients requiring coronary angiography for a clinical indication. Pravastatin 40 mg/day was selected because it had been widely studied in both primary and secondary coronary heart disease (CHD) prevention studies with proven morbidity and mortality benefits. The 40-mg dose carried a US Food and Drug Administration (FDA)–approved indication for slowing the progression of atherosclerosis and was also the highest available dose at the time of the study. Atorvastatin 80 mg/day was selected as intensive therapy because this regimen was known to produce the most pronounced reductions in LDL cholesterol of any available therapy. In the study design, LDL cholesterol reductions of approximately 30% with pravastatin 40 mg/day and 50% to 55% with atorvastatin 80 mg/day were anticipated.

In contrast to previous angiography trials, which were conducted over 2 to 3 years, REVERSAL was designed to use IVUS as its assessment tool. Because of the ability of IVUS to visualize angiographically invisible plaque, it was anticipated that this imaging technique could detect a difference between the effects of intensive and moderate statin therapy in only 18 months. IVUS examinations were performed at baseline and after 18 months of therapy along a ≥30-mm segment of a single target vessel. During the motorized pullback, images were obtained at 30 frames per second and were recorded on videotape. The recorded images were analyzed by selecting a distal fiducial site as the beginning point and analyzing every 60th frame, thereby producing a series of cross-sections exactly 1 mm apart. Additional details on the IVUS technique and study methods are provided in the original publication.

The primary efficacy end point was percent change in total atheroma volume (TAV) (determined as TAV at follow-up minus baseline), where TAV was calculated as the sum of plaque areas for each evaluable slice. Because of the effects of coronary remodeling, despite modest angiographic disease burden, use of IVUS found that the average patient in REVERSAL (who required only 20% stenosis of the coronary artery for study entry) had almost 200 mm³ of atherosclerotic plaque.
Primary and secondary outcomes

Of the 654 patients randomized to treatment, 502 completed the study (253 in the atorvastatin group and 249 in the pravastatin group) and were included in the primary analysis. At baseline, the 2 treatment groups were well balanced, with identical mean LDL cholesterol levels (150 mg/dL [3.9 mmol/L]). After 18 months’ treatment, LDL cholesterol was reduced by 46%, to 79 mg/dL (2.0 mmol/L), in the atorvastatin group, compared with a 25% reduction, to 110 mg/dL (2.9 mmol/L), in the pravastatin group (Table 1). Greater reductions were also observed with atorvastatin for total cholesterol and triglyceride levels, compared with pravastatin.14

For the primary end point (percent change in TAV), a significantly slower rate of progression from baseline to study end was observed with atorvastatin compared with pravastatin (P = 0.02) (Figure 1). There was unequivocal progression of the atheroma in the pravastatin group (TAV percent change, +2.7%; 95% confidence interval [CI], 0.24 to 4.67), whereas patients in the atorvastatin group had slightly less plaque after 18 months than at baseline (TAV percent change, −0.4%; 95% CI, −2.35 to 1.49), indicating a halting of disease progression (Figure 1). Thus, treatment with a moderate dose of a first-generation statin led, on average, to atheroma progression, whereas treatment with a maximum dose of a higher-efficacy statin halted the progression of coronary atherosclerosis. This was confirmed for all 3 prespecified secondary end points: change in percentage atheroma volume (P <0.001), nominal change in atheroma volume, and change in volume for the 10-mm subsegment with the greatest atheroma burden (P <0.01). The results of the 3 outcomes were numerically consistent across all 22 prespecified subgroups, including those delineated by age, sex, smoking status, history of diabetes mellitus, history of statin use, and baseline LDL cholesterol levels.14

Plaque progression as a function of low-density lipoprotein cholesterol reduction

The baseline level of LDL cholesterol before randomization was not a determinant of the extent of benefit of intensive therapy. The superiority of the more intensive regimen was similar for patients with baseline lipid levels throughout the entire range of LDL cholesterol values. For patients receiving either atorvastatin or pravastatin, linear regression analysis showed an inverse relation between LDL cholesterol reduction and plaque progression, whereby each 10% reduction in LDL cholesterol (15 mg/dL [0.4 mmol/L]) resulted in an approximate 1% reduction in atheroma volume. Although lower LDL cholesterol levels clearly yielded a more favorable outcome, the results were not exclusively a function of achieved LDL cholesterol values. For any given level of LDL cholesterol, the rate of atheroma progression was lower with atorvastatin than with pravastatin therapy (Figure 2),14 suggesting that additional drug effects beyond LDL cholesterol lowering were affecting the outcome.

Anti-inflammatory effects

In the pravastatin arm, high-sensitivity C-reactive protein (hs-CRP) was reduced by 5.2%, whereas intensive therapy with atorvastatin reduced hs-CRP by 36.4% (P <0.001) (Table 1). A post-hoc analysis of the REVERSAL trial results revealed that reduction in hs-CRP concentration was an important independent predictor of the slowing of atherosclerosis.15 Thus, the superiority of the intensive atorvastatin regimen was related to both the greater reduction in LDL cholesterol and the more effective reduction in hs-CRP levels.

Safety

Both the moderate and intensive regimens were well tolerated. There was 1 death in each group, and no cases of muscle enzyme elevations were reported in either group. Elevations of alanine aminotransferase >3 times the upper limit of normal (ULN) were observed in 5 patients (1.6%) in the pravastatin arm and in 7 patients (2.3%) in the atorvastatin arm; 2 patients (0.6%) in each arm experienced elevations of aspartate aminotransferase >3 times the ULN.
Clinical implications

The results of the REVERSAL study have several important implications for clinical practice. The study demonstrated that intensive lipid-lowering therapy with atorvastatin 80 mg/day to a mean LDL cholesterol level of 79 mg/dL can halt the progression of atherosclerosis in secondary prevention patients. A more moderate regimen consisting of pravastatin 40 mg/day was associated with continued disease progression. The difference between the 2 treatment regimens was consistent regardless of baseline LDL cholesterol level, suggesting that more intensive therapy benefits patients regardless of their LDL cholesterol levels.

These findings also have implications for future cardiovascular risk prevention guidelines. Current guidelines recommend an LDL cholesterol goal of <100 mg/dL (<2.6 mmol/L) for secondary prevention of CHD, with a further optional target of 70 mg/dL (1.8 mmol/L) for patients at very high risk of CHD. The results of the current study support this lower target, demonstrating that intensive LDL cholesterol lowering to well below 100 mg/dL (2.6 mmol/L) further retards disease progression. Although disease regression was not observed for the entire study population on average, significant regression was observed in individual patients during the 18 months of intensive lipid-lowering therapy (Figure 3).

Figure 1  Percent change in total atheroma volume (TAV). Moderate lipid lowering with pravastatin was associated with significant atherosclerotic progression from baseline, whereas intensive therapy with atorvastatin caused no significant change from baseline. †P = 0.001; †P = 0.98.

Figure 2  Low-density lipoprotein cholesterol (LDL-C) reduction versus change in atheroma volume. Disease progression continued at all levels of LDL cholesterol reduction with moderate pravastatin therapy, whereas progression was lessened at all levels with intensive atorvastatin therapy. The solid line indicates the relationship between mean change in low-density lipoprotein cholesterol and change in atheroma volume from linear regression analysis. The dashed lines indicate the upper and lower 95% confidence limits for the mean values.

(Reprinted with permission from JAMA.14)
The rate of disease progression at any given level of LDL cholesterol was lower with the intensive atorvastatin regimen than with the moderate pravastatin regimen, suggesting that factors independent of LDL cholesterol lowering influenced the rate of disease progression. Greater reductions in total cholesterol, triglycerides, and apolipoprotein B were observed with the atorvastatin regimen, which may have contributed to the observed benefits. However, consistent with previous studies, significantly greater reductions in the inflammatory marker hs-CRP also were observed with the atorvastatin 80 mg/day regimen compared with pravastatin 40 mg/day. This finding suggests that more robust reductions in hs-CRP may help explain the therapeutic benefits not related to LDL cholesterol reductions. Accordingly, the anti-inflammatory effects of statins may be an appropriate consideration (in addition to the LDL cholesterol–lowering effect) in the choice of therapy, particularly for high-risk patients. However, further studies are needed to help characterize the relation between achieved hs-CRP levels and the progression of atherosclerotic disease. For example, it remains uncertain whether high doses of other statins or the combination of a statin with a cholesterol absorption inhibitor will produce comparable benefits. 18,19

Although REVERSAL was a surrogate end-point trial, results from subsequent cardiovascular event trials suggest that arresting disease progression with intensive lipid-lowering therapy translates into significant improvements in cardiovascular morbidity and mortality. 20,21 The Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial showed a significant 16% reduction in CHD events or all-cause mortality in patients receiving intensive lipid-lowering therapy with atorvastatin 80 mg/day compared with those receiving moderate lipid-lowering therapy using pravastatin 40 mg/day. 20 Because REVERSAL and PROVE IT–TIMI 22 used identical lipid-lowering regimens, the results of the 2 trials demonstrate the validity of IVUS as an intermediate end point in clinical efficacy trials. More recently, the Treating to New Targets (TNT) study demonstrated that treatment of patients with CHD who had a mean baseline LDL cholesterol level of 98 mg/dL (2.5 mmol/L) using atorvastatin 80 mg/day reduced events by 22% compared with atorvastatin 10 mg/day. 21 In this study the more intensive regimen achieved LDL cholesterol levels similar to those in REVERSAL, specifically a mean of 77 mg/dL (2.0 mmol/L) in the intensive-therapy arm. Results from ongoing trials such as the Incremental Decrease in End-points Through Aggressive Lipid Lowering (IDEAL) study will further establish the role of intensive lipid-lowering therapy through the comparison of atorvastatin and simvastatin and may contribute to a further alteration in practice guidelines, reflecting the broad benefits of more intensive statin therapy in secondary prevention.

References

Improved outcome after acute coronary syndromes with an intensive versus standard lipid-lowering regimen: results from the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial

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The aim of the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial was to determine whether intensive low-density lipoprotein (LDL)–cholesterol lowering to a level of approximately 70 mg/dL (1.8 mmol/L) with atorvastatin 80 mg/day was more efficacious than standard LDL cholesterol lowering to 100 mg/dL (2.6 mmol/L) with pravastatin 40 mg/day in reducing the incidence of cardiovascular events in patients with acute coronary syndrome (ACS). In total, 4,162 men and women aged >18 years, who had been hospitalized for an ACS within the preceding 10 days, were randomized to receive either pravastatin 40 mg/day or atorvastatin 80 mg/day. The median LDL cholesterol levels achieved during follow-up were 95 mg/dL (2.5 mmol/L) in the pravastatin group and 62 mg/dL (1.6 mmol/L) in the atorvastatin group (P <0.001). Standard treatment (statin) with a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (pravastatin 40 mg/day) resulted in a 22% reduction in LDL cholesterol levels at 30 days compared with a 51% reduction with intensive therapy (atorvastatin 80 mg/day). At 2 years, a relative risk reduction of 16% (95% confidence interval, 5%–26%; P = 0.005) in the primary end point rate (death, myocardial infarction, documented unstable angina requiring hospitalization, coronary revascularization, or stroke) was seen in patients receiving intensive statin treatment compared with standard statin therapy. The benefit of intensive treatment was apparent as early as 30 days and was consistent over time. The PROVE IT–TIMI 22 data indicate that patients recently hospitalized for an ACS benefit from early and continued lowering of LDL cholesterol to levels substantially below current guideline recommendations.

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KEYWORDS: Acute coronary syndrome; Cholesterol; Statins

Several large randomized controlled trials have documented that cholesterol–lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) reduces the risk of death or cardiovascular events across a wide range of cholesterol levels, whether or not patients have a history of coronary heart disease (CHD).1–8 In line with the evidence emerging from these trials, current guidelines in the United States, Canada, and Europe recommend a low-density lipoprotein (LDL) cholesterol level <100 mg/dL (<2.6 mmol/L) for patients with established CHD or diabetes mellitus.9–11 However, until quite recently, it was not known whether lowering lipid
levels to well below 100 mg/dL (2.6 mmol/L) in patients with CHD would be associated with incremental clinical benefit.

The relation between low-density lipoprotein cholesterol levels and coronary heart disease risk

To date, the following 3 theoretical models have been proposed to explain the relation between LDL cholesterol levels and the risk of CHD: the linear model, the curvilinear model, and the threshold model (Figure 1). Until recently there has been some dispute over which model is most accurate and, therefore, whether intensive LDL cholesterol lowering should be favored over less intensive LDL cholesterol lowering, which has proven effectiveness.

The linear model suggests that the reduction in CHD risk is directly proportional to the magnitude by which LDL cholesterol is lowered. As such, even at low LDL cholesterol levels (<100 mg/dL [<2.6 mmol/L]), this model proposes that patients receive incremental benefit from further LDL cholesterol lowering. The curvilinear model predicts that at low LDL cholesterol levels, the effects on CHD risk of lowering LDL cholesterol are reduced further and therefore the benefits of therapy are less pronounced. The threshold model proposes that no further reduction in CHD risk is achieved by lowering LDL cholesterol levels below a certain threshold (<116 mg/dL [<3.0 mmol/L]).

A number of early population-based studies, including the Multiple Risk Factor Intervention Trial (MRFIT), supported the curvilinear model; others, such as the Cholesterol and Recurrent Events (CARE) secondary prevention study, supported the threshold model. In the CARE study, patients who had experienced a myocardial infarction (MI) and had an LDL cholesterol level of 115 to 174 mg/dL (mean, 139 mg/dL [3.6 mmol/L]) were randomized to either pravastatin 40 mg/day or placebo. The LDL cholesterol levels achieved during treatment were associated with reductions in incidence of coronary events down to an LDL cholesterol level of approximately 125 mg/dL (3.2 mmol/L). Lowering LDL cholesterol levels to <125 mg/dL (<3.2 mmol/L) during treatment was not associated with incremental benefit.

Even so, a growing body of evidence suggests that a threshold LDL cholesterol level does not truly exist, at least as far as patients with CHD or vascular disease and high-risk patients with diabetes are concerned. For example, in the Scandinavian Simvastatin Survival Study (4S), which enrolled patients with coronary atherosclerosis, no marked threshold of LDL cholesterol lowering on CHD risk was apparent. Additionally, in the Heart Protection Study (HPS)—a more recent landmark trial that investigated the effect of simvastatin 40 mg/day versus placebo in patients with coronary disease, other occlusive arterial disease, or diabetes—significant beneficial effects of statin treatment were observed even in those patients presenting with LDL cholesterol levels <116 mg/dL (<3.0 mmol/L). The significant reductions in relative risk of major vascular events observed in the 3 predefined pretreatment LDL cholesterol subgroups (LDL cholesterol levels: subgroup 1, >135 mg/dL [>3.5 mmol/L], 19%; subgroup 2, 116 to 135 mg/dL [3.0 to 3.5 mmol/L], 26%; subgroup 3, <116 mg/dL [<3.0 mmol/L], 21%) correlated with comparable reductions in LDL cholesterol levels (subgroup 1, 39%; subgroup 2, 37%; subgroup 3, 35%). This finding demonstrates that lowering LDL cholesterol levels can produce substantial reductions in the incidence of major vascular events regardless of the pretreatment LDL cholesterol level.
Effects of robust low-density lipoprotein cholesterol lowering on atherosclerosis

There also appears to be a consensus developing supporting the view that intensive versus standard LDL cholesterol-lowering therapy produces a superior effect on measurements of atherosclerotic progression at clinically important sites. In the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) study,\footnote{H11021} carotid intima media thickness (CIMT) decreased by 0.031 mm (95% confidence interval [CI], −0.021 mm to −0.041 mm; \( P = 0.0017 \)) after treatment with atorvastatin 80 mg/day for 2 years, whereas in the simvastatin 40 mg/day group it increased by 0.036 mm (95% CI, 0.014 mm to 0.058 mm; \( P = 0.0005 \)). The change in thickness differed significantly between the 2 groups (\( P = 0.0001 \)). In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) study,\footnote{H11006} intensive statin therapy with atorvastatin 80 mg/day induced progressive CIMT regression over 12 months (change in CIMT, 0.034 ± 0.021 mm), whereas CIMT was stable in the standard pravastatin 40 mg/day therapy group (change in CIMT, 0.025 ± 0.017 mm; \( P = 0.03 \)). These clear effects on CIMT, now established as a valid marker of atherosclerotic progression and as a risk indicator for cardiovascular disease, suggested that marked LDL cholesterol reduction with statin therapy could provide enhanced reductions in clinical coronary events.

The results of the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study\footnote{H11021} extended the findings in carotid atherosclerosis to coronary atherosclerosis. In REVERSAL, a total of 654 patients (mean LDL cholesterol level, 150.2 mg/dL [3.9 mmol/L]) were randomized to receive either intensive statin therapy with atorvastatin 80 mg/day or standard therapy with pravastatin 40 mg/day. At study end (18 months), baseline LDL cholesterol levels were reduced to 79 mg/dL (2.0 mmol/L) and 110 mg/dL (2.8 mmol/L) in the atorvastatin and pravastatin groups, respectively (\( P < 0.001 \)). The primary end point (percentage change in atheroma volume, as measured by intravascular ultrasonography) showed a significantly lower progression rate in the intensive statin therapy group (\( P = 0.02 \)). Similar differences between groups were observed for secondary efficacy parameters, including change in total atheroma volume (\( P = 0.02 \)), change in percentage atheroma volume (\( P < 0.001 \)), and change in atheroma volume in the most severely diseased 10-mm vessel subsegment (\( P < 0.01 \)). Progression of coronary atherosclerosis compared with baseline occurred in the pravastatin group (2.7%; 95% CI, 0.2% to 4.7%; \( P = 0.001 \)). Progression compared with baseline did not occur in the atorvastatin group (−0.4%; 95% CI, −2.4% to 1.5%; \( P = 0.98 \)). Analysis looking at regression and progression according to LDL cholesterol levels showed a positive relation between the reduction in LDL cholesterol level and reduction in atheroma volume, suggesting that further lipid lowering would have greater benefit.

Intensive statin treatment in patients with acute coronary syndrome

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial\footnote{H11005} was specifically designed to assess the clinical benefits of intensive statin therapy (such as prevention of unstable angina [UA], MI, or coronary death) in patients with acute coronary syndrome (ACS). A total of 3,086 adults aged ≥18 years with UA or non–Q-wave acute MI were randomized to receive treatment with either atorvastatin 80 mg/day or placebo within 24 to 96 hours after admission. The primary end point of the trial—time to the first occurrence of death, resuscitated cardiac arrest, nonfatal MI, or recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency hospitalization—was achieved in 17.4% (269 patients) of the placebo group and 14.8% (228 patients) of the atorvastatin group (relative risk reduction, 16%; 95% CI, 0% to 30%; \( P = 0.048 \)). This benefit was due mainly to the significant reduction in recurrent symptomatic ischemia requiring emergency rehospitalization. There were no significant differences in risk of death, nonfatal MI, or cardiac arrest between the atorvastatin group and the placebo group. Despite the mixed findings from the MIRACL study,\footnote{H11006} the overall results were favorable and supported a strategy of implementing lipid-lowering treatment in patients who have been hospitalized for ACS. The observation that, compared with patients who started statin therapy before discharge, patients in whom statin therapy is not initiated before hospital discharge are less likely to be initiated with statin therapy after ACS further supports the early initiation of statin therapy in patients hospitalized for ACS.\footnote{H11006} However, additional confirmatory studies were required to justify very early initiation of aggressive lipid-lowering therapy in this subpopulation of patients.

The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 trial

The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial was designed to establish whether intensive LDL cholesterol lowering to approximately 70 mg/dL (1.8 mmol/L) would achieve a greater reduction in incidence of cardiovascular events than standard LDL cholesterol lowering to an average of 100 mg/dL (2.6 mmol/L) in patients with ACS.\footnote{H11005} Based on data from the CARE trial, it was hypothesized that aggressive statin therapy would be no more beneficial in reducing the incidence of cardiovascular events than standard statin therapy.
Patient population

In total, 4,162 men and women aged >18 years who had been hospitalized for an ACS (either acute MI or high-risk UA) within the preceding 10 days (patients had to be in a stable condition and were enrolled after a percutaneous revascularization procedure if one was planned), were randomized to either standard LDL cholesterol-lowering therapy (pravastatin 40 mg/day) or intensive LDL cholesterol-lowering therapy (atorvastatin 80 mg/day) in a 2 × 2 factorial design. (The 2 × 2 factorial design of PROVE IT–TIMI 22 also enabled assessment of the efficacy of gatifloxacin versus placebo, although data from this part of the study are not presented here.) The mean duration of follow-up was 2 years (Figure 2). The primary end point was time to the first occurrence of any of the following: death, MI, documented UA requiring rehospitalization, coronary revascularization (>30 days after randomization), or stroke.

To be eligible for the study, patients had to have a total cholesterol level of <240 mg/dL (<6.2 mmol/L), measured within the first 24 hours of onset of the ACS or up to 6 months earlier if no sample had been obtained during the first 24 hours. For patients receiving lipid-lowering therapy at the time of their index ACS, total cholesterol levels had to be <200 mg/dL (<5.2 mmol/L) at the time of screening.

Patients were ineligible for the study if they had a comorbidity that shortened expected survival to <2 years; if they were receiving therapy with simvastatin 80 mg/day or atorvastatin 80 mg/day at the time of their index event or if they were receiving lipid-lowering therapy with fibrates or niacin that could not be discontinued before randomization; if they had received strong inhibitors of cytochrome P450 3A4 within 1 month of randomization (to avoid interactions that may affect atorvastatin metabolism); if they had undergone coronary angioplasty within the previous 6 months or coronary artery bypass grafting (CABG) within the previous 2 months or were scheduled to undergo CABG for treatment of qualifying ACS; or if they exhibited liver disease, unexplained creatine kinase (CK) elevations, or a creatinine plasma concentration >2.0 mg/dL (>177 μmol/L).

Results

The pravastatin and atorvastatin groups were well matched with regard to baseline characteristics (Table 1). Determination of concomitant therapies at baseline showed that most patients included in the trial were receiving optimal therapy for ACS.

At the time of randomization (a median of 7 days after the onset of the index event), the median LDL cholesterol levels were 106 mg/dL (2.7 mmol/L) in each group. The median LDL cholesterol levels achieved during follow-up were 95 mg/dL (2.5 mmol/L) in the pravastatin group and 62 mg/dL (1.6 mmol/L) in the atorvastatin group (P <0.001). Standard therapy with pravastatin 40 mg/day resulted in a 22% reduction in LDL cholesterol levels at 30 days, whereas intensive therapy with atorvastatin 80 mg/day resulted in a 51% reduction. However, it should be noted that in PROVE IT–TIMI 22, 25% of the patients were taking statins before study entry and that the response to therapy for ACS lowers LDL cholesterol levels from true baseline.

Primary end point

At 2 years, primary end point event rates were 26.3% in the standard-therapy (pravastatin) group and 22.4% in the
intensive-therapy (atorvastatin) group, representing a 16% relative reduction in favor of atorvastatin ($P / H_{11005} 0.005; 95\% CI, 5\% to 26\%$) (Figure 3).22 The benefit of intensive treatment compared with standard therapy was apparent as early as 30 days after study initiation and was consistent over time (Figure 4).22 At 30 days the relative risk of a primary end point event was reduced by 17% with atorvastatin, with an absolute event rate of 1.9% among atorvastatin-treated patients, compared with 2.2% among pravastatin-treated patients.

Analysis of individual components of the primary end point was consistent with the finding that intensive lipid lowering with atorvastatin was more beneficial than standard treatment with pravastatin. Compared with patients receiving pravastatin, the patients treated with atorvastatin benefited from a 14% relative risk reduction in the need for revascularization ($P / H_{11005} 0.04$), a 29% reduction in the relative risk of recurrent UA ($P / H_{11005} 0.02$), and nonsignificant reductions in the rates of all-cause death (28%; $P = 0.07$) and death or MI (18%; $P = 0.06$). Stroke was infrequent, but the incidence did not differ significantly between the 2 groups.

Analysis also revealed that the benefit of high-dose atorvastatin was consistent across the prespecified subgroups, which included men and women, patients with UA and those with MI, and individuals with or without diabetes. The only observed difference between subgroups was that patients with a baseline LDL cholesterol level $<125 \text{ mg/dL}$ ($<3.2 \text{ mmol/L}$) appeared to benefit less than those with LDL cholesterol levels $>125 \text{ mg/dL}$ ($>3.2 \text{ mmol/L}$), perhaps because those patients were previously treated with a statin. A large proportion of the patients in PROVE IT–TIMI 22 (72%) were receiving clopidogrel, and no interaction was found between clopidogrel and atorvastatin.

### Effect of therapy on high-sensitivity C-reactive protein

Reductions in high-sensitivity C-reactive protein (hs-CRP) were greater with atorvastatin compared with pravastatin (from baseline 12.3 mg/L to 1.3 mg/L with atorvastatin and to 2.1 mg/L with pravastatin; $P <0.001$). Elevated levels of hs-CRP have been correlated with increased cardiovascular risk and mortality.22,23 It is known that hs-CRP binds to oxidized LDL cholesterol and apoptotic cells but not to native LDL cholesterol or healthy cells, suggesting an association with atherosclerotic plaques.24 Reductions in hs-CRP levels achieved with intensive statin therapy appear to correlate with increased clinical benefit in patients who have experienced an ACS.25,26

### Safety

The safety and tolerability of both treatments were comparable. The rates of discontinuation of treatment due to an adverse event or the patient’s preference or for other reasons were 21.4% in the pravastatin group and 22.8% in the atorvastatin group at 1 year ($P = 0.30$) and 33.0% and 30.4%, respectively, at 2 years ($P = 0.11$). The percentage of patients who had elevations in CK levels that were $\geq 3$ times the upper limit of normal were 1.5% in the atorvastatin group and 1.1% in the pravastatin group ($P = 0.24$). Discontinuation due to myalgia or CK elevations were comparable between groups (2.7% of pravastatin-treated patients vs. 3.3% of atorvastatin-treated patients; $P = 0.23$). There were no cases of rhabdomyolysis in either group.

### Discussion

Among patients who had recently had an ACS, an intensive lipid-lowering statin regimen with atorvastatin 80 mg/day
provided greater protection against death or major cardio-
vascular events than did a standard regimen with pravastatin
40 mg/day. Intensive LDL cholesterol lowering (to a me-
dian LDL cholesterol level of 62 mg/dL [1.6 mmol/L])
reduced the risk of all-cause mortality or major cardiovascular
events by 16% (P = 0.005) compared with more moderate lipid-lowering therapy (to a median LDL choles-
terol level of 95 mg/dL [2.5 mmol/L]). The benefits
emerged within 30 days after the ACS and continued
throughout the 2.5 years of follow-up. The benefits ob-
served with atorvastatin therapy were consistent across all
cardiovascular end points (except stroke) and most clinical
subgroups. The findings of PROVE IT–TIMI 22 indicate
that patients recently hospitalized for an ACS benefit from
early and continued lowering of LDL cholesterol to levels
substantially below current target values.

The Aggrastat to Zocor trial conflict

Together, the MIRACL and PROVE IT–TIMI 22 studies
provide evidence that in patients with ACS, lowering LDL
cholesterol levels below those recommended by current

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**Figure 3** Kaplan-Meier estimates of the incidence of the primary end point of death from any cause or a major cardiovascular event. Intensive lipid lowering with the 80-mg dose of atorvastatin, as compared with moderate lipid lowering with the 40-mg dose of pravastatin, reduced the hazard ratio for death or a major cardiovascular event by 16% (relative risk, 16%; 95% confidence interval, 5% to 26%; P = 0.005). (Reprinted with permission from N Engl J Med.)

**Figure 4** Hazard ratio for the primary end point of death from any cause or a major cardiovascular event at 30, 90, and 180 days and at the end of follow-up in the high-dose atorvastatin group, as compared with the standard-dose pravastatin group. Event rates are Kaplan-Meier estimates censored at the time points indicated with the use of the average duration of follow-up (2 years). CI = confidence interval. (Reprinted with permission from N Engl J Med.)
guidelines provides greater benefit in terms of reductions in cardiovascular events than does more moderate lowering of LDL cholesterol levels. In the Aggrastat to Zocor (A to Z) trial—a large randomized, double-blind, controlled trial—an intensive statin regimen (simvastatin 40 mg/day for 1 month and then 80 mg/day thereafter [n = 2,265]) failed to show a statistically significant benefit for reducing the primary composite end point of cardiovascular death, MI, readmission for ACS, or stroke compared with a less intensive regimen (placebo for 4 months and then simvastatin 20 mg/day thereafter [n = 2,232]) (absolute risk reduction, 2.3%; hazard ratio [HR], 0.89; 95% CI, 0.76 to 1.04; \( P = 0.14 \)).

The failure in the A to Z trial to achieve reductions in clinical end points comparable to those observed in the MIRACL and PROVE IT–TIMI 22 trials, despite similar reductions in LDL cholesterol, is perplexing. This disparity raises the possibility that the beneficial effects of statin therapy in ACS cannot be predicted entirely from the degree of LDL cholesterol reduction. The between-group reduction in hs-CRP level observed in A to Z was much smaller (16.7% vs. 34% for MIRACL and 38% for PROVE IT–TIMI 22). It has been proposed that the early benefits of statin therapy observed in MIRACL and PROVE IT–TIMI 22 may be derived partially from the anti-inflammatory effects of the drugs. This view is also supported, at least in part, by the A to Z trial investigators, who commented that the lack of a concurrent anti-inflammatory effect (determined by hs-CRP levels) in the A to Z trial may have contributed to the delayed treatment effect observed.

Future studies

On the basis of the results from PROVE IT–TIMI 22, the recent update of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines now suggest that in patients with ACS, an LDL cholesterol goal of <70 mg/dL (1.8 mmol/L) can be considered. However, in other patient populations, such as those with stable coronary artery disease, the effects of aggressive lipid lowering beyond current guideline recommendations also appear to be beneficial. The results from the Treating to New Targets (TNT) trial provide evidence that the use of intensive atorvastatin therapy to reduce LDL cholesterol levels to <100 mg/dL (<2.6 mmol/L) is associated with substantial clinical benefit in patients with stable CHD. In the TNT study, a total of 10,001 patients with clinically evident CHD and LDL cholesterol levels <130 mg/dL (<3.4 mmol/L) were randomly assigned to double-blind therapy and received atorvastatin 10 mg/day or 80 mg/day. A primary end point, defined as the occurrence of a first major cardiovascular event (death from CHD, nonfatal non–procedure-related MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke) occurred in 434 patients (8.7%) receiving 80 mg/day of atorvastatin, compared with 548 patients (10.9%) receiving 10 mg/day of atorvastatin, representing an absolute reduction in the rate of major cardiovascular events of 2.2% and a 22% relative reduction in risk (HR, 0.78; 95% CI, 0.69 to 0.89; \( P < 0.001 \)). However, confirmatory studies are required to confirm the benefits of lipid lowering to below that recommended by current guidelines in patients with stable CHD and it is hoped that the results from ongoing studies, including the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trial and the Study of the Effectiveness of Additional Reductions of Cholesterol and Homocysteine (SEARCH), will help address this knowledge gap.

Summary

Data from PROVE IT–TIMI 22 provided solid evidence in patients with ACS regarding the benefits of intensive lipid-lowering therapy to reduce levels of LDL cholesterol below those previously recommended in national and international guidelines. Thus, it is now recognized that patients with ACS can be considered for treatment to LDL cholesterol goals of <70 mg/dL (<1.8 mmol/L). Treatment to this new goal has the potential to further reduce cardiovascular morbidity and mortality in this patient population. Results from recently completed and ongoing trials may extend the evidence for these benefits to all patients with CHD.

References

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Barriers to effective implementation of guideline recommendations

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KEYWORDS:
Adherence;
Cardiovascular disease;
Hypercholesterolemia

Cardiovascular disease (CVD) is the leading cause of death worldwide, and its prevention and treatment are important healthcare aims. Hypercholesterolemia is among the most important modifiable risk factors for CVD, and numerous guidelines exist for the treatment of this condition. Nevertheless, despite the existence of well-established and safe pharmacologic therapy for lowering cholesterol and preventing CVD, surveys in the United States and Europe have revealed that many patients have elevated cholesterol levels. There is a clear gap between what is known about treating CVD and the implementation of that knowledge. A survey assessing patients’ knowledge about CVD observed that many patients are unaware of the disease prevalence and have little knowledge about the main risk factors, including the importance of cholesterol. Another survey demonstrated that many physicians overestimate patients’ awareness of CVD and that physicians also overestimate the extent to which guidelines are implemented in clinical practice. Guideline implementation may be improved by narrowing the discrepancies between what patients and physicians believe and the reality. Many physicians claim that lack of time hinders guideline implementation and improvement of patient education. Physicians also appear to lack the motivation to implement lipid-lowering interventions. A multifactorial approach to improving use of guidelines in clinical practice may improve the treatment and prevention of CVD.

Risk factors for cardiovascular disease (CVD), such as hypertension, dyslipidemia, diabetes mellitus, lack of exercise, poor diet, and smoking, are well documented and can be modified to reduce a person’s risk of CVD.1–4 Lifestyle changes, such as increased exercise, improved diet, and smoking cessation, are the primary steps needed for reducing cardiovascular risk. However, many individuals will have persistent hypercholesterolemia and/or hypertension even after implementing lifestyle changes, and in these patients pharmacologic therapy may be necessary. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, are safe and effective agents for the lowering of serum cholesterol levels,5–7 and clinical trials have demonstrated that statin therapy is associated with a significant reduction in risk for coronary heart disease (CHD) in a wide range of patients.8–15 A number of classes of agents are available for the treatment of hypertension, including diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.4 Clinical trials have demonstrated significant reductions in risk for major cardiovascular events, including stroke, CHD, and heart failure, in patients receiving antihypertensive therapy.16,17 As a result, evidence-based guidelines have provided cholesterol and blood pressure goals for the prevention and treatment of CVD,1–4 yet CVD nevertheless continues to be the leading cause of death worldwide and currently accounts for 38.5% of all deaths in the United States.18
The persistence of CVD as a leading cause of death, despite knowledge of the risk factors for the disease and the existence of safe pharmacologic interventions for their modification, may be due to a failure to implement clinical findings into clinical practice. Some barriers to guideline implementation in clinical practice are beyond physicians’ control. For instance, insurance reimbursement systems may be inadequate, formularies may be restrictive, or hospital structures may hinder the operation of optimal clinical practice. The present article suggests strategies to improve implementation of guidelines despite such hurdles.

The treatment gap

Obstacles to and delays in the implementation of knowledge in everyday practice are not a modern phenomenon. As early as 1601, James Lancaster demonstrated that lemon juice prevented scurvy. However, introduction of fresh food into the diet was not formally adopted until 1795 by the British Navy and 1865 by the Merchant Navy. This example, in which it took >200 years before knowledge was communicated and subsequently incorporated into “real-world” settings, illustrates the gap that exists between what we know and what we do. In today’s era of technologic advances and faster communication, this gap can perhaps be narrowed. Nevertheless, a gap is evident between treatment recommendations based on clinical trial data and treatment that is given in clinical practice, with evidence indicating that only a minority of patients with CHD achieve target levels for modifiable risk factors or even receive treatment.19–22

An analysis of data from 1,252 survivors of myocardial infarction (MI) or stroke in the United States revealed that despite the existence of well-established guidelines for the treatment of hypercholesterolemia and hypertension,3,4 almost half (46%) of the patients with previously diagnosed hypercholesterolemia in this high-risk population remained uncontrolled for their condition, and more than half (53%) of those with hypertension had not achieved their blood pressure goals.23 Similar treatment gaps were observed for patients with diabetes, of whom only 52% had adequately achieved their controlled serum glucose levels. Moreover, almost 20% of survivors were still current smokers. From these data, it is clear that even after a stroke or MI, physicians and healthcare systems are unable to provide the best care to these patients.

A similar gap between the existence and the implementation of guideline recommendations is apparent in the treatment of patients at high risk for CHD. In the Lipid Treatment Assessment Project (L-TAP), data were assessed from 4,888 US patients with dyslipidemia who had received the same dietary or lipid-lowering therapy for ≥3 months.21 Patients were defined as at high risk for CHD if they had ≥2 CHD risk factors, including smoking; alcohol consumption; history of CHD or atherosclerotic disease; family history of CHD; hypertension; diabetes; and conditions that affect lipid levels, such as hypothyroidism, nephrotic syndrome, or liver disease. The study revealed that 63% of patients who were at high risk for CHD had not attained their National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) II24 low-density lipoprotein (LDL) cholesterol goals. Furthermore, poor implementation of recommendations was observed in patients with existing CHD, of whom 82% did not attain their NCEP ATP II goal.

Data from 4,148 patients with measured cholesterol levels in the 1999 to 2000 National Health and Nutrition Examination Survey (NHANES) were similar.25 Of 2,262 patients with total cholesterol levels of ≥5.2 mmol/L (≥201 mg/dL), or who were receiving lipid-lowering medications, 35% were aware that they had hypercholesterolemia, 12% were receiving treatment for the condition, and only 5% had attained their cholesterol goal.

The treatment gap appears to be a global phenomenon, with inadequate management of CVD risk factors also prevalent throughout Europe. The first European Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE I) survey of patients with CHD in 9 countries (Czech Republic, Finland, France, Germany, Hungary, Italy, the Netherlands, Slovenia, and Spain) ascertained that 86% of patients had uncontrolled cholesterol levels during 1995 to 1996 and that >50% of those with evaluable data had high blood pressure.19 A second EUROASPIRE survey (EUROASPIRE II), conducted in 1999 to 2000, found little improvement in the management of CVD risk factors (Figure 1).20 Although the prevalence of high serum cholesterol decreased from 82% in EUROASPIRE I to 59% in EUROASPIRE II, many patients still had not achieved their cholesterol goals. Moreover, in EUROASPIRE II, 51% of patients receiving lipid-lowering medications continued to have elevated cholesterol levels, suggesting that patients who received lipid-lowering therapy did not receive the appropriate statin dose and/or were not prescribed a sufficiently efficacious statin. The prevalence of hypertension did not change from 1995 to 1996 and 1999 to 2000; it still affected >50% of the population. Furthermore, from EUROASPIRE I to EUROASPIRE II (Figure 1), there was an increase in the proportion of people who were overweight, who smoked, or who had diabetes.

Together, these studies clearly demonstrate the huge discrepancy between the consolidation of knowledge in guidelines and success in communicating and implementing them in clinical practice.

Patient and physician perceptions

The persistent treatment gap may be due to a mismatch between (1) how physicians and patients perceive the risks of CVD and the extent to which those risks are being treated, and (2) what the actual risks are, and how they should be treated. In this scenario, a first step toward
narrowing the treatment gap will be to alter people’s perceptions so that they match reality.

Two surveys have been conducted to determine (1) patients’ understanding of CVD and its risk factors and (2) current physician treatment practices and how physicians perceive patients’ understanding of CVD. Results from these surveys can be compared with what is actually known about CVD and its treatment in real-world settings.

Mismatches between patient perception and reality

In 2001, the Global Opinions and Awareness of Cholesterol (GOAL) survey assessed European public perception of cardiovascular risk. Interviews for the survey were conducted in person, electronically, and over the telephone in 7 countries (Canada, France, Germany, Great Britain, Italy, the Netherlands, and Spain). Most of the 7,018 respondents were unaware of the prevalence of CVD. Only 33% of patients correctly identified CVD as the leading cause of death worldwide; the largest proportion (40%) of participants believed that cancer was the major cause of death.

Interviewees also greatly underestimated their own risk for CHD. Only 13% of respondents believed that they were at high or very high risk for the disease, even though $\geq 37\%$ of them had $\geq 2$ major CHD risk factors, placing them at high risk for the disease (Figure 2). Moreover, the number of respondents at high risk for CHD may even be $> 37\%$, because some interviewees may have been unaware of having hypercholesterolemia and thus did not report it. This hypothesis is supported by the fact that 83% of respondents did not know what their cholesterol levels were.

Most participants in the survey had only a vague knowledge about the role of cholesterol in CHD. Indeed, $> 40\%$ of respondents did not know of the link between cholesterol and CHD and, although 86% of participants reported knowing that it was important to have healthy cholesterol levels, only 76% could identify what a healthy cholesterol level was.

These results clearly indicate that the general population has a poor understanding of the prevalence of, and the risk factors for, CHD, with many patients underestimating their risk for the disease. As a result, physicians cannot assume that patients already know which factors worsen their risk for CHD; physicians must educate their patients in this respect, so that patients’ perceptions of CHD risk match reality. A large number of respondents of the GOAL survey
did not know their own cholesterol levels, suggesting that physicians need to measure patients’ cholesterol levels more often and to inform patients about the importance of managing their cholesterol levels to improve CVD risk.

Mismatches between physician perception and reality

The Reassessing European Attitudes about Cardiovascular Treatment (REACT) survey obtained responses from 754 physicians, each with >10 years’ experience, from 5 European countries (France, Germany, Italy, Sweden, United Kingdom) to assess whether physicians’ perceptions of CHD management matched their treatment practices and whether their perceptions of patients’ awareness was an accurate reflection of their patients’ understanding.26

The REACT survey revealed a gap between what physicians thought about guideline recommendations and how physicians acted in practice. Although the vast majority (90%) of physicians claimed to agree with the content of cholesterol guidelines, most did not implement international recommendations, and over half (59%) of the physicians surveyed reported that they used their “own practice guidelines.” Few physicians reported use of the European Society of Hypertension (ESH) (22%), European Society of Cardiology (ESC) (17%), or Joint European Societies (15%) guidelines (Figure 3). There was also a gap between how physicians reported they acted and how they believed that other physicians acted. Even though most of the physicians surveyed reported that they did not follow internationally established guidelines, 78% believed that guideline recommendations were implemented by others to a moderate or major extent.

The belief that guideline recommendations are generally well implemented is in conflict not only with physicians’ self-reported practice but also with what is known to be the case. Namely, surveys such as EUROASPIRE I, EUROASPIRE II, and L-TAP have clearly demonstrated that many patients with dyslipidemia who have or who are at risk for CHD are not treated to their LDL cholesterol goal and, therefore, that guidelines are poorly implemented. In contrast to the findings from EUROASPIRE and L-TAP, 80% of physicians in the REACT survey believed that cholesterol is well managed in patients with CHD, and 68% believed that cholesterol is well managed in patients at risk for CHD.

A further perceptual gap exists between what physicians believe their patients understand about CHD and the actual extent of their patients’ knowledge. In the REACT survey, 92% of physicians believed that their patients were aware that elevated cholesterol levels were associated with a greater risk for CHD, whereas the GOAL survey showed that in fact only 58% of patients knew there was a link.

These discrepancies between perception and reality, from the perspective of the patient and of the physician, as well as between the patient and the physician, may be responsible for the poor implementation of guideline recommendations in clinical practice.

Barriers to guideline implementation

In the REACT survey, physicians were asked what the most common barriers were that prevented them from implementing guideline recommendations. The most common barrier, cited by 38% of the respondents, was lack of time (Figure 4). Interestingly, other data from the REACT survey indicated that implementation of guidelines correlated inversely with the number of patient consultations, supporting the claim that time was a factor hindering guideline implementation. Patient adherence was cited as an important barrier by 17% of physicians, which is supported by data showing that within 1 year of receiving statin therapy, approximately 33% of patients stop filling their prescriptions.27

When asked how guideline implementation could be improved, 29% of those asked cited improved physician educa-
tion. A recent online study of 500 randomly selected physicians revealed that physicians’ perception of patients’ CVD risk was the primary factor associated with their CVD preventive recommendations and that physicians were significantly more likely to assign women at intermediate risk to a lower risk category than they would men at intermediate risk. However, in general, the problem appears to be that physicians seem to have a lack of motivation rather than a lack of knowledge. Although they are aware of the importance of controlling cholesterol levels and agree with this aim, their knowledge is rarely implemented in clinical practice. Some 25% of physicians asked believed that improvement of patient education would improve implementation. Physicians’ time could be spared if nurses undertook this role. Most patients receive only a few minutes of advice from physicians regarding the risk factors for CVD; therefore, if nurses were empowered to discuss the importance of risk factor modification and prevention with patients more thoroughly, patients’ motivation might increase and their adherence to medication regimens might improve.

Nevertheless, knowledge alone does not change behavior, as evidenced by the large numbers of people who continue to smoke, despite information about the risks involved. Simplification (17%) and clarification (12%) of guidelines were also mentioned as areas for possible improvement, representing important aims toward which the scientific community can work. The number of guidelines may be confusing, and movement toward consolidated guidelines also may be an appropriate goal. Not only must CVD be treated by targeting all risk factors, but approaches to improving guideline implementation must likewise be treated in a multifactorial fashion—with educating patients, simplifying guidelines, and helping physicians and patients match their perceptions to reality all being considered equally important tasks.

Summary

Data from numerous observational studies demonstrate that in actual practice there is a gap between what physicians know about CVD prevention and how they execute this knowledge. Surveys of patient and physician attitudes suggest that the gap between guideline recommendations and their implementation in clinical practice may be due in part to patients having a highly deficient understanding of CVD risk factors and of the worldwide prevalence of the disease. This lack of understanding may, in turn, lead to a lack of motivation for patients to adhere to their medication regimens. The surveys also indicate that physicians are unaware of how little their patients know about CVD. As a result, physicians do not understand the needs of their patients. If the guidelines gap is to be bridged, adherence programs must take physicians’ as well as patients’ perspectives into account. The problem of barriers to guidelines implementation is not a simple one, and it must be addressed from a multidimensional perspective.

References


What impact will current trial data have on future guideline recommendations?

Ian Graham, FRCPI, FESC

The current Third Joint European Societies’ Guidelines on Cardiovascular Disease Prevention in Clinical Practice reflect an active approach to cardiovascular disease (CVD) prevention. These guidelines have shifted the emphasis from coronary heart disease to total atherosclerotic CVD. A new risk prediction system, Systematic Coronary Risk Evaluation (SCORE), has been developed to define risk in terms of absolute 10-year risk of a fatal cardiovascular event. The definition of high risk has also been refined. The currently recommended goals for total and low-density lipoprotein (LDL) cholesterol are based on the evidence pool that was available at the time of publication. More recent evidence from the Heart Protection Study (HPS), the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA), and the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial indicates that lowering LDL cholesterol levels beyond the currently recommended goals can produce incremental reductions in cardiovascular morbidity and mortality. Results from the recently completed Treating to New Targets (TNT) study lend further support to implementing lower lipid goals than those currently suggested by guidelines. Results from the ongoing Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) trial may provide additional evidence in support of the implementation of lower lipid goals. Nevertheless, the scope of future guidelines extends well beyond lipid targets. Guidelines of the future are likely to provide increasingly comprehensive recommendations on combined risk reduction, to publicize the characteristics of healthy people by highlighting acceptable levels of all cardiovascular risk factors, and to refine the concept of evidence-based medicine by shifting the focus from drug therapy to preventive therapy.

Our understanding of the atherosclerotic disease process has improved substantially in recent times. We now know that atherosclerosis is an insidious and slowly progressing process that begins at a relatively young age and, over time, can lead to the development of clinical coronary disease, often manifesting as an abrupt and life-threatening cardiovascular event. Even though the major causes of cardiovascular disease (CVD) are well known, CVD remains the leading cause of mortality in all developed countries. Current treatment practices give little emphasis to CVD prevention and remain largely reactive.

With >20,000 biomedical journals in current circulation, only a small percentage of which publish information that actually affects treatment practices, it becomes a challenge for clinicians to keep abreast of the most relevant literature. This may result in a gap between the evidence base and actual clinical practice. General acceptance and appropriate use of treatment practice guidelines can help bridge this gap by disseminating peer-reviewed evidence-based consensus recommendations to practicing clinicians.

The first set of European guidelines on coronary heart disease; Prevention; Risk assessment

The recommended European goal for low-density lipoprotein (LDL) cholesterol is <115 mg/dL (<3.0 mmol/L) in asymptomatic patients and <100 mg/dL (<2.6 mmol/L) in patients with established CHD or diabetes. Because extrapolation from current randomized clinical trial data indicates that the relation between on-treatment LDL cholesterol levels and CHD risk is linear for both primary and secondary CHD prevention, it is important to explore whether there exists an LDL cholesterol level below which the CVD benefits cease to be apparent.3

Implications of recent clinical trial data

Results from the Heart Protection Study (HPS)10 provide preliminary evidence that lowering LDL cholesterol levels to below currently recommended targets may lead to further reductions in cardiovascular morbidity and mortality. HPS randomized 20,536 adults in the United Kingdom with CHD, other occlusive arterial disease, or diabetes to simvastatin 40 mg/day or placebo for a mean follow-up of 5 years. Changes in LDL cholesterol levels and cardiovascular event rates for patients with baseline LDL cholesterol levels of <116 mg/dL (<3.0 mmol/L) or ≥135 mg/dL (≥3.5 mmol/L) are presented in Table 2. The results show that regardless of baseline LDL cholesterol levels, lowering of LDL cholesterol with statin therapy, even to levels below existing guideline recommendations, produced large reductions in cardiovascular events. Post hoc analyses suggested that these benefits were maintained across different subgroups of patients, including women, patients with diabetes, and patients >70 years of age.10

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) randomized 19,342 patients to 1 of 2 antihypertensive regimens. In the lipid-lowering arm of the trial (ASCOT-LLA),11 10,305 patients with total cholesterol levels ≤250 mg/dL (≤6.5 mmol/L) were also randomized to atorvastatin 10 mg/day or placebo. The LDL cholesterol level in the atorvastatin group was lowered from 133 ± 27.5 mg/dL (3.4 ± 0.7 mmol/L) at baseline to 88 ± 27.5 mg/dL (2.3 ± 0.7 mmol/L) at 3 years. ASCOT-LLA was stopped after a mean follow-up of 3.3 years, by which time a primary end point event (nonfatal myocardial infarction or fatal CHD) had occurred in 1.9% of patients in the atorvastatin 10 mg/day or placebo. The LDL cholesterol level in the atorvastatin group was lowered from 133 ± 27.8 mg/dL (3.4 ± 0.7 mmol/L) at baseline to 88 ± 27.5 mg/dL (2.3 ± 0.7 mmol/L) at 3 years. ASCOT-LLA was stopped after a mean follow-up of 3.3 years, by which time a primary end point event (nonfatal myocardial infarction or fatal CHD) had occurred in 1.9% of patients in the atorvastatin group compared with 3.0% in the placebo group (relative risk reduction, 36.7%; absolute risk reduction, 1.1%). Risk reductions observed with atorvastatin therapy over the course of the study were unrelated to baseline total cholesterol levels. Patients with baseline total cholesterol levels below the goal of 193 mg/dL (5.0 mmol/L) recommended by the European Joint Task Force guidelines experienced a 37% reduction in risk for the primary end point compared with a 31% reduction in risk experienced by patients with baseline total cholesterol levels between 231 mg/dL and 250 mg/dL (6.0 mmol/L and 6.5 mmol/L) (Table 3).

Based on data from HPS, ASCOT, and other recently completed studies such as the Pravastatin or Atorvastatin

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Current joint European recommendations

The current European guidelines include information from both EUROASPIRE audit surveys and differ from earlier versions in several ways. The emphasis has now shifted from CHD to total atherosclerotic CVD. The concept of primacy of total risk evaluation also has been extended by the development of a new risk prediction system called Systematic Coronary Risk Evaluation (SCORE). The SCORE system replaces the previous Framingham-based risk charts for assessing an individual’s CVD risk.6 The data for the SCORE charts are based on approximately 220,000 individuals from 12 European cohorts comprising 3 million person-years of observation and >7,000 fatal CVD events. In contrast, the Framingham risk charts were based on approximately 5,000 individuals from the United States. Separate SCORE charts have been developed for high- and low-risk European countries (Figures 1 and 2).3,7

The SCORE charts define risk in terms of the absolute 10-year probability of a fatal cardiovascular event. In contrast, the US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines use Framingham risk assessment to define risk in terms of the 10-year risk of a fatal or nonfatal CHD event.3,8 The use of CVD mortality allows the risk charts to be calibrated more easily for individual European countries based on national mortality statistics and risk factor distributions. An interactive Web-based version of SCORE, HeartScore, is also available.9 HeartScore is being developed to provide calibrated risk scores for individual European countries, and, unlike existing risk charts, it is designed to integrate new cohort data and risk factors as they become available.

Like the NCEP ATP III guidelines, the current guidelines of the European Joint Task Force reflect the evidence base that was available at the time of publication. Both sets of guidelines show certain similarities with regard to lipid treatment goals in asymptomatic patients and in patients with established CHD (Table 1).
Evaluation and Infection Therapy--Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial,10–12 the NCEP ATP III has published revisions to their existing guidelines, which include consideration of more aggressive lipid lowering for certain patients.13 The revisions introduce the category of patients at very high risk for a CHD event. In these patients an LDL cholesterol goal of $110 \text{ mg/dL}$ ($1.8 \text{ mmol/L}$) can be considered as an option. Factors that favor a decision to treat to this revised goal include the presence of established CVD plus multiple major risk factors, including diabetes, severe and poorly controlled risk factors (e.g., smoking), elevated triglycerides ($\geq 200 \text{ mg/dL}$, $\geq 2.3 \text{ mmol/L}$) and non–high-density lipoprotein (HDL) cholesterol ($\geq 130 \text{ mg/dL}$, $\geq 3.4 \text{ mmol/L}$), and HDL cholesterol $<40 \text{ mg/dL}$ ($<1.0 \text{ mmol/L}$). On the basis of PROVE IT–TIMI 22, patients with acute coronary syndromes may also be considered for the goal of $<70 \text{ mg/dL}$ ($<1.8 \text{ mmol/L}$).

The Treating to New Targets (TNT) study14 went further than the other trials, indicating that all patients with CHD may benefit from the lower LDL cholesterol goal of $<70 \text{ mg/dL}$ ($<1.8 \text{ mmol/L}$). It randomized 10,001 patients with CHD to atorvastatin 10 mg/day or 80 mg/day. During the 5-year follow-up period, mean LDL cholesterol target levels were 101 mg/dL (2.6 mmol/L) for the low-dose atorvastatin group and 77 mg/dL (2.0 mmol/L) for the high-dose atorvastatin group. A 22% relative reduction in risk for major cardiovascular events was observed in patients randomized

Figure 1  The 10-year risk of fatal cardiovascular disease (CVD) in high-risk regions of Europe by sex, age, systolic blood pressure, total cholesterol, and smoking status. Instructions on how to use above chart appear in Figure 2. (Reprinted with permission from *Eur Heart J Cardiovasc Prev Rehabil*.)

![Figure 1](image-url)
Figure 2  The 10-year risk of fatal cardiovascular (CVD) in low-risk regions of Europe by sex, age, systolic blood pressure, total cholesterol, and smoking status. (Reprinted with permission from *Eur Heart J Cardiovasc Prev Rehabil.*7)
to atorvastatin 80 mg compared with patients randomized to atorvastatin 10 mg ($P < 0.001$).

The Incremental Decrease through Aggressive Lipid Lowering (IDEAL) trial will provide further information on the relation between lowering LDL cholesterol to levels below existing guideline recommendations and cardiovascular morbidity and mortality in patients with existing CHD. The IDEAL trial has a prospective, randomized, open-label, blinded end point design and randomized 8,000 patients to atorvastatin 80 mg/day or simvastatin 20 to 40 mg/day.\textsuperscript{15} It will assess whether aggressive high-dose atorvastatin therapy, which is expected to lower LDL cholesterol to levels below those achieved with established treatment from the Scandinavian Simvastatin Survival Study (4S),\textsuperscript{16} produces additional clinical benefits to those observed with more moderate lipid-lowering therapy. The results from IDEAL, together with the results from TNT, will be important in helping the developers of guidelines decide whether to set new LDL cholesterol goals for patients with existing CHD.

Guidelines of the future

The scope of future cardiovascular guidelines is likely to extend far beyond recommendations on target lipid levels. Future guidelines are likely to provide comprehensive recommendations on combined risk reduction, stressing the importance of critical lifestyle changes such as smoking cessation. They may emphasize total cardiovascular health both by publicizing the characteristics of healthy people, such as implementing therapeutic lifestyle changes, and by highlighting acceptable levels of cardiovascular risk factors, such as blood pressure and lipids. They are likely to refine the concept of evidence-based medicine by shifting the

### Table 1 Lipid treatment goals in cardiovascular disease prevention

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>European Joint Task Force</th>
<th>NCEP ATP III</th>
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<tr>
<td></td>
<td>mmol/L mg/dL</td>
<td>mmol/L mg/dL</td>
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<tr>
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<tr>
<td>LDL-C</td>
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<td>$&lt;2.5$ $&lt;100$</td>
</tr>
</tbody>
</table>

LDL-C = low-density lipoprotein cholesterol; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.

*Defined as CVD or diabetes mellitus according to guidelines of the European Joint Task Force.

†Defined as coronary heart disease (CHD) or CHD risk equivalent according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines.

### Table 2 Cardiovascular event rates and low-density lipoprotein cholesterol (LDL-C) levels at follow-up in the Heart Protection Study (HPS)

<table>
<thead>
<tr>
<th>Baseline LDL-C, mg/dL (mmol/L)</th>
<th>LDL-C on Follow-up (mmol/L)</th>
<th>Major Vascular Event Rates (%)</th>
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<tr>
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<td>Simvastatin</td>
<td>Placebo</td>
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<td>$&lt;116$ ($&lt;3.0$)</td>
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<td>2.7</td>
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<td>$\geq 116$–$&lt;135$ ($\geq 3.0$–$&lt;3.5$)</td>
<td>2.2</td>
<td>3.2</td>
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<td>$\geq 135$ ($\geq 3.5$)</td>
<td>2.7</td>
<td>3.7</td>
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</table>

### Table 3 Benefit across the cholesterol range observed in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA)

<table>
<thead>
<tr>
<th>Baseline Total Cholesterol, mg/dL (mmol/L)</th>
<th>Hazard Ratio for Primary End Point</th>
<th>95% Confidence Interval</th>
<th>$P$-Value</th>
</tr>
</thead>
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focus from drug therapy to preventive therapy and nonpharmacologic lifestyle interventions. As the medical community strives to achieve compatibility between the various national and international guidelines, it is important to recognize that inherent differences in risk factors between various ethnic groups or geographic differences in the availability of medical resources may influence treatment practices within certain areas. This subject warrants considerable discussion and debate, and guidelines of the future will need to address differences in treatment recommendations as they apply to different populations.

To close the gap between the evidence and the achieved risk levels, it is important for future guidelines to define implementation and audit strategies to ensure that the consensus recommendations are translated successfully into clinical practice. Most important, the process of preventive care needs to be "demedicalized" through effective patient education, enabling patients to "choose" their own level of cardiovascular risk in the future.

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Alzheimer disease (AD) is a chronic neurodegenerative disorder that is manifested by cognitive decline, neuropsychiatric symptoms, and diffuse structural abnormalities in the brain. Its prevalence is predicted to rise 4-fold in the next 50 years. AD is characterized pathologically by deposition of extracellular β-amyloid and accumulation of neurofibrillary tangles. Neuronal death and specific neurotransmitter deficits also are part of the pathologic picture. Strategies to delay symptom progression have focused on addressing the neurotransmitter deficits. Strategies to delay the onset or biologic progression of AD largely have targeted the plaques formed by the deposition of β-amyloid. AD and cardiovascular disease share common risk factors, notably hypercholesterolemia, and occur together more often than expected by chance. Therapy with the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) is the first-line treatment option for hypercholesterolemia, and observational studies have suggested that the risk of AD is reduced in patients who receive statin therapy in midlife. This reduction in risk of AD observed with statin therapy may be due to statins reducing β-amyloid formation and deposition or to their known anti-inflammatory effects. Two randomized double-blind statin trials in patients with AD to assess the potential for statins to slow disease progression are currently under way. If successful, statin AD primary prevention trials may be developed.

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0002-9343/$ -see front matter © 2005 Elsevier Inc. All rights reserved.
Tant pathologic changes associated with AD include region-specific neuronal death and deficits in neurotransmitters, such as acetylcholine, serotonin, norepinephrine, and glutamate.

**Treatment strategies for Alzheimer disease**

Current preventive strategies for AD focus on delaying the onset or progression of the disease. A strategy that would delay the onset of AD by 5 years has been projected to reduce the prevalence in 50 years by 50%. A delay in onset of 10 years would virtually eradicate AD, because most people would not live long enough to develop the disease.6 If the progression of AD were delayed, the majority of patients with AD would remain in the mild-to-moderate stages of the disease. Fewer patients would progress to the moderate and severe stages, resulting in a higher quality of life for patients and their caregivers as well as a reduced healthcare burden for the state. The optimal treatment strategy would therefore delay both onset and progression of AD, with fewer people developing the disease and with those who do remaining in its earlier stages.3

Treatment strategies largely have targeted the neurotransmitter deficits. In particular, the well-reported cholinergic deficit in patients with AD7–10 has been a major therapeutic target for improving cognition or delaying symptom progression. Controlled clinical trials of acetylcholinesterase inhibitors in patients with AD have demonstrated statistically significant benefits in cognitive and non-cognitive symptoms.11–14 As a result, acetylcholinesterase inhibitors have now become the most widely approved symptomatic therapies available for the treatment of patients with mild-to-moderate AD.15,16

Treatment strategies for delaying the onset of AD have targeted the amyloid plaques. Plaques are observed in all patients with AD and are composed of altered metabolites of the amyloid precursor protein (APP), especially the 40- and 42-amino acid β-amyloid. Under normal conditions APP is cleaved by α-secretase just above the surface of the neuronal membrane, releasing soluble APP.17 In patients with AD, the APP molecule is cleaved further distal from the membrane surface by β-secretase and within the neuronal membrane by γ-secretase, releasing β-amyloid that can become deposited in the center of the amyloid plaque (Figure 1). Efforts to delay the onset of AD have therefore focused on developing β- or γ-secretase inhibitors to prevent abnormal APP cleavage or else focused on developing antibodies to facilitate the removal of β-amyloid, by either active or passive immunization. However, no therapeutic options targeting this mechanism are currently available.

**Commonalities between Alzheimer disease and cardiovascular disease**

A number of cardiovascular risk factors, such as hypertension, hypercholesterolemia, inflammatory states, and diabetes mellitus, have been shown in observational and epidemiologic studies to be associated with AD and dementia.18,19 Furthermore, cardiovascular disease (CVD) and AD occur together more often than would be expected by chance,20 and neuritic plaques have been observed in patients with myocardial infarctions without diagnosed dementia.21 Moreover, vascular injury may lower the threshold for cognitive manifestations of clinical dementia.22

These observations have led to the hypothesis that the 2 diseases may share common or complementary biologic antecedents.23 For instance, β-amyloid can cause vasoconstriction in the brain and reduce endothelium-dependent cerebrovascular dilation.24 Impaired vasodilation and constriction also occur in CVD and lead to inflammation and ultimately to plaque formation. In addition, cerebral ischemia can upregulate local APP expression and increase production of β-amyloid,25 thereby further enhancing the likelihood of impaired vasodilation. Therefore, removal of
β-amyloid under conditions of ischemia would also decrease some of the vasoconstriction and reduce oxidative stress as well as primary AD pathology.

**Hypercholesterolemia and Alzheimer disease**

Hypercholesterolemia is among the major modifiable risk factors for CVD. Although mean cholesterol levels in patients with AD are not higher than in controls, data from large epidemiologic studies and prospective population studies suggest that an elevated cholesterol level in midlife may increase the risk of AD in older age. A survey of a random sample of 1,449 participants who were followed for an average of 21 years revealed that participants with elevated systolic blood pressure or elevated serum total cholesterol levels in midlife had a significantly higher risk of AD in later life than those with normal systolic blood pressure (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.0–5.5) or total cholesterol levels in midlife (OR, 2.1; 95% CI, 1.0–4.4). This observation held even after adjusting for age, body mass index, education, vascular events, smoking status, and alcohol consumption. Similarly, a retrospective study of 444 Finnish men found that early elevated total cholesterol levels predicted later incidence of AD (OR, 3.1; 95% CI, 1.2–8.5), even after controlling for age and the presence of the apolipoprotein E4 allele.

A review of autopsy cases of patients aged ≥40 years revealed that in the youngest patients (40 to 55 years) hypercholesterolemia correlated with the presence of neuritic plaques. The authors concluded that hypercholesterolemia may be an early risk factor for AD. If early elevated cholesterol levels are indeed associated with a risk of AD, then this represents a rationale for lipid-lowering treatments to confer a reduction in risk for AD.

**Statins and their effects on dementia**

Cholesterol-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) has been shown to reduce the risk of death or cardiovascular events in patients with or without CVD and is the therapy of choice for treating hypercholesterolemia. Data from a number of observational studies suggest that statins may have a protective effect against the risk of developing AD.

Data from the Canadian Study of Health and Aging (CSHA) revealed a 74% reduced risk of AD in statin users and in users of any lipid-lowering agent compared with those not using statins or any other lipid-lowering medications. However, the reduction in risk was observed only in patients <80 years of age. A similar effect in favor of statins was revealed in a cross-sectional analysis of 60,349 patients aged ≥60 years. In this study, a 60% to 73% reduction in risk of AD in statin users was observed compared with the total population or with patients receiving other medications typically used in the treatment of CVD.

There is some evidence that statins in particular, rather than low cholesterol levels or lipid-lowering agents in general, are associated with the reduction in risk of AD. A nested case-control study demonstrated a risk reduction of ≥70% for dementia in statin users compared with persons without hypercholesterolemia or persons who used other lipid-lowering agents. In an observational study in postmenopausal women with coronary heart disease, statin users scored higher on the Modified Mini-Mental State Examination (MMSE) than nonusers of statins, independent of lipid levels. There was also a trend for statin users to have a reduced risk of cognitive impairment. These results have led researchers to posit potential mechanisms for the possible benefits of statins in reducing the incidence of AD.

**Potential mechanisms of statins in the treatment of AD**

This section describes a number of physiologic mechanisms by which statin therapy may reduce patients’ risk of AD.

**Endothelial nitric oxide synthase**

Statins upregulate the production of endothelial nitric oxide synthase (eNOS) in cells by which statin therapy may reduce patients’ risk of AD. Interestingly, the upregulating effect of statins on eNOS is independent of statins’ lipid-lowering ability and may reflect the absence of a close association between cholesterol level and cognition.

**Vascular wall mechanisms**

Decreased platelet adhesion is observed with the use of statins and may be associated with decreased risk of vessel wall disease.

**Alterations in β-amyloid production and removal**

There is some evidence to suggest that statins may inhibit the formation of β-amyloid. For instance, in a study in hippocampal neurons in cell culture, formation of β-amyloid was completely inhibited after reducing cholesterol levels by 70% with lovastatin. Statins may also maintain low-density lipoprotein (LDL) receptor–related protein production. LDL receptors are diminished in the vessel walls of patients with AD, and these receptors may facilitate the removal of β-amyloid from the brain.

**Suppression of inflammation**

Inflammation is common in the brains of patients with AD. A number of studies have demonstrated that statins may...
exert anti-inflammatory effects.\textsuperscript{47–49} For instance, statins may upregulate eNOS RNA.\textsuperscript{40} The evidence from observational studies, along with hypothesized mechanisms for a treatment benefit with statins, has provoked interest in conducting trials to assess the safety and efficacy of statins in the treatment of AD.

**Future perspectives**

Opportunities for major public health gains exist in the development of AD prevention therapies. However, AD primary prevention trials are very expensive to conduct, with each study costing in excess of US$25 million. Unlike cardiovascular research, prevention trials in patients with AD often require physicians to work with patients on an individual level to assess cognitive function over extended periods of time. Power calculations based on projections of AD incidence would necessitate the recruitment of ≥3,000 participants in most trials and would have to last for 5 to 7 years or longer. Due to the requirement for double-blind placebo-controlled trial designs, early trials have focused on safe and inexpensive compounds, such as estrogen or *Ginkgo biloba*, to assess the potential for delaying the onset of dementia.\textsuperscript{50,51}

Two major statin trials are currently under way to assess the effects of statins in delaying the progression of AD in patients with serum cholesterol levels that do not require therapeutic intervention. The Cholesterol Lowering Agent to Slow Progression of Alzheimer’s Disease (CLASP) study is a double-blind trial that randomized approximately 400 patients with AD to either simvastatin 20 mg/day or placebo for 6 weeks. Patients then received either simvastatin 40 mg/day or placebo for the remainder of the 18-month study.\textsuperscript{52} Patients continued to receive their acetylcholinesterase-inhibitor medications. This trial is expected to be completed in December 2005. The Lipitor’s Effect in Alzheimer’s Dementia (LEADe) study is a double-blind trial that randomized approximately 600 patients with AD to either atorvastatin 80 mg/day or placebo for a period of 72 weeks. At 72 weeks, patients continued their double-blind therapeutic regimen for a further 8 weeks or had their treatment replaced by matching placebo for 8 weeks. All patients received the acetylcholinesterase inhibitor donepezil 10 mg/day for the duration of the study. The study is due to be completed in 2006. If these trials demonstrate that statin therapy confers symptomatic benefit in patients with AD, they will open up the possibility of AD prevention trials with statins.

**Summary**

AD is a fatal, incurable, and chronic disease, the incidence of which is predicted to rise dramatically over the next 50 years with an increase in associated healthcare burden. Current treatment options focus on delaying the symptomatic progression of the disease. Data from observational studies suggest that statin therapy may delay the onset of AD by a variety of proposed mechanisms, such as suppression of β-amyloid metabolism, vascular effects, and anti-inflammatory effects. Clinical trials are currently under way that will assess the effect of statins on cognitive function in patients with AD. If successful, statin trials for the primary prevention of AD may be developed.


A rationale for combination therapy in risk factor management: a mechanistic perspective

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Endothelial dysfunction contributes to mechanisms of atherogenesis and its clinical manifestations, including coronary heart disease. Cardiovascular risk factors have been linked directly to a loss of endothelial function, such as endothelium-dependent nitric oxide (NO) release, resulting in abnormal vasodilation in response to various stimuli. There is evidence that multiple risk factors, including hypertension and hyperlipidemia, lead to a synergistic effect on endothelial dysfunction, likely through oxidative stress mechanisms. Damage to the endothelium leads to reduced NO bioavailability and facilitates vessel wall permeability to low-density lipoprotein. Certain agents, including the antihypertensive drug amlodipine and the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) atorvastatin, are known to influence endothelial function and NO bioavailability directly; these properties may contribute to clinical benefits. Recent experimental evidence at the cellular level indicates that these agents stimulate NO release from human endothelial cells in a highly synergistic fashion. The clinical implications of these observations are discussed in this article in the context of cardiovascular risk factor management strategies.

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KEYWORDS:
Calcium channel blockers; Endothelium; Nitric oxide; Statins

Treatment of modifiable cardiovascular risk factors is essential to reducing the incidence of cardiovascular disease (CVD). Hypertension and dyslipidemia are 2 frequently comorbid risk factors; these conditions contribute substantially to the burden of CVD. Indeed, >50% of the condition known as the metabolic syndrome can be attributed to elevated blood pressure and elevated lipid levels.1 Despite this knowledge, treatment rates for these risk-elevating conditions remain alarmingly low. Data from the Third National Health and Nutrition Examination Survey (NHANES III) indicate that >15% of individuals surveyed have concomitant hypertension and dyslipidemia and, of these, <10% are at recommended target levels for blood pressure and cholesterol.2 Furthermore, studies such as the Multiple Risk Factor Intervention Trial (MRFIT)3 have demonstrated a large and disproportionate increase in cardiovascular risk associated with having high blood pressure and concomitant high levels of cholesterol, compared with having either risk factor alone.3,4 Even moderately elevated lipid levels can increase risk. Results from recent trials indicate that patients with hypertension and concomitant multiple cardiovascular risk factors can benefit from lipid-lowering therapy regardless of their baseline lipid levels.5

Integrated perspective on cardiovascular risk factors and vascular disease

Cardiovascular risk factors are highly interactive and thereby contribute synergistically to mechanisms of atherosclerotic disease, including endothelial dysfunction, oxida-
To slow the progression of vascular disease effectively, it is essential to treat modifiable cardiovascular risk factors in a comprehensive manner. This article summarizes the pathophysiology of atherosclerosis as a rationale for effective and comprehensive treatment of multiple cardiovascular risk factors, particularly hypertension and dyslipidemia.

**Cardiovascular disease at the level of the vessel wall: endothelial dysfunction**

Endothelial dysfunction is characterized by changes in the vascular endothelium, from a smooth nonthrombogenic surface to one whose cells respond abnormally to stimuli of vasodilation while also expressing adhesion molecules that bind circulating leukocytes. As endothelial dysfunction progresses, there is loss in the production of functional nitric oxide (NO) along with its atheroprotective actions. Cardiovascular risk factors, including hypertension and dyslipidemia, contribute to endothelial dysfunction. Endothelial dysfunction leads to smooth muscle cell proliferation and increased levels of thromboxane A$_2$, a potent stimulus of platelet aggregation (Figure 1). Concomitantly with other signs of endothelial dysfunction, there is evidence of increased endothelial permeability to low-density lipoprotein (LDL). Finally, potent vasoconstrictors such as endothelin I are released, further compromising normal hemodynamics (Figure 1).

**The role of modified (oxidized) LDL**

Under “normal” conditions, LDL is taken up by high-affinity LDL receptors in the liver for ultimate removal from peripheral circulation. However, under conditions of high oxidative stress, as observed in patients with hypertension, dyslipidemia, or diabetes mellitus, or in those who smoke, the LDL particle is modified or oxidized. This acetylated, modified particle has reduced affinity for the high-affinity LDL receptor. The oxidized LDL particles tend to aggregate and contribute to foam cell formation through uptake by scavenger receptors associated with macrophages. Studies have shown that lowering plasma LDL while increasing its resistance to oxidation may provide important benefits with respect to vascular function.

Oxidized LDL is highly atherogenic, more so than “normal” (nonoxidized) LDL, although both compromise the ability to produce NO. Vergnani and colleagues exposed aortic endothelial cells to successively higher levels of nonoxidized and oxidized LDL. For normal LDL, there was a precipitous drop-off in the ability of cells to produce NO at levels >50 mg/dL (>1.3 mmol/L). This effect was more pronounced and occurred at an even lower concentration (>20 mg/dL [0.52 mmol/L]) with oxidized LDL (Figure 2). It is therefore of primary importance to lower oxidized LDL, because it appears to be more deleterious in reducing NO bioavailability than is nonoxidized LDL. These data also provide strong support for a more aggressive approach to lipid lowering, as advocated in the recent call to update the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) guidelines. Evaluation of oxidized lipid biomarkers suggests that these markers are highly predictive of coronary events. For example, a longitudinal study analyzing serum samples from 634 participants of the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) who had documented coronary disease revealed that patients with a high baseline level of oxidized LDL had a
much greater risk of developing cardiovascular events compared with patients who had low levels of oxidized LDL.16

**Oxidative stress and uncoupling of endothelial NO synthase: early forerunners to endothelial dysfunction**

Oxidative stress can be linked to various enzymatic processes, including a loss in normal NO synthase function, or uncoupling of endothelial NO synthase (eNOS). During eNOS uncoupling, the enzyme transfers electrons to molecular oxygen, instead of to L-arginine, resulting in the formation of superoxide. This free radical then reacts with NO to form a toxic product known as peroxynitrite (ONOO–).19 This is consistent with studies that have linked increased superoxide (O2–) formation to loss of endothelial function due to eNOS uncoupling and increase in reduced nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase activity.20,21 Interestingly, a recent study in African Americans has revealed higher levels of superoxide in this patient population, even among healthy individuals, which may explain why this population is particularly at risk for CVD.22,23

**Cell membrane microdomains: structural changes in the vessel wall leading to endothelial dysfunction**

Elevations in both cellular free cholesterol and oxidative stress lead to the formation of membrane cholesterol domains and extracellular crystals that cannot be removed by reverse cholesterol transport mechanisms.17,24–27 These crystals are toxic and have been observed in various cell culture systems under conditions of hypercholesterolemia.28 Examination of the initial stages of the crystal-formation process by x-ray diffraction methods has demonstrated that cholesterol begins to organize into microscopic crystalline structures within the cell membrane.27,28 The primary target of therapy, therefore, should be to block the formation of these crystalline structures within the cell membrane because cholesterol in this state does not respond well to pharmacologic interventions that promote lesion regression.24

The complexity of the cell membrane is being increasingly recognized, as is its pivotal role in the onset of CVD.29 During atherogenesis, microscopic structures are formed in the cell membrane that are related to an increase in the number of caveolae (Figure 3).29 Caveolae are enriched with free cholesterol and sphingolipid and contain a key NO synthase–binding protein, caveolin-1, which blocks activation of this enzyme.29 Understanding how changes in the endothelial cell occur in response to cardiovascular risk factors, particularly at the level of the cell membrane, has contributed to our further understanding of the underlying pathophysiology of atherosclerosis.

**Restoring endothelial function**

Endothelial dysfunction is a compelling central pathway by which cardiovascular risk factors such as hypertension and dyslipidemia are related to the underlying disease process. Both hypertension and dyslipidemia independently contribute to a marked impairment in NO-mediated vasodilation.11 Agents that help restore endothelial function and increase NO bioavailability—for example, angiotensin-converting enzyme (ACE) inhibitors, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), and certain dihydropyridine-type calcium channel blockers—have beneficial antiatherogenic activities and can improve cardiovascular outcomes.6,30–34 Both the long-acting dihydropyridine calcium channel blocker amlodipine and the statin atorvastatin have been associated with slowing the progression of coronary and carotid atherosclerosis, a surrogate marker for CVD and cerebrovascular disease.31,35–38 These agents also have been shown to reduce the incidence of clinical events in large randomized trials.5,36,39

Beyond causing vasodilation through inhibition of calcium channels, long-acting calcium channel blockers such as amlodipine have been demonstrated to produce clinical benefits that may be independent of effects on blood pressure in patients with coronary artery disease (CAD).31,40 For example, in PREVENT, amlodipine provided significant clinical benefits compared with placebo, including a marked reduction in cardiovascular morbidity and a reduction in the progression of carotid atherosclerosis.31 Such beneficial effects have not been widely observed with other dihydropyridine-type calcium channel blockers, suggesting that this agent may have distinct vascular benefits beyond calcium channel blockade.

The effects of statins on the vascular endothelium are well documented.17,33,34,41 In brief, statins decrease oxidative stress pathways by reducing LDL and oxidized LDL. In endothelial cells, these metabolic changes contribute to favorable effects on NO bioavailability.11 Additionally it has been demonstrated that statins can significantly reduce the expression of caveolin-1, secondary to blocking cholesterol synthesis in endothelial cells.41

**Amlodipine: improving endothelial function**

Laboratory studies have demonstrated that amlodipine has beneficial effects on endothelial dysfunction.42–44 One early investigation recorded the effects on human arterial vessels with the administration of different antihypertensive agents, including an ACE inhibitor and a calcium channel blocker.43 The aim of this study was to determine the effect of amlodipine on NO production in failing human hearts along with the role of kinins. Results demonstrated that amlodipine significantly increased nitrite (a byproduct of NO) production in coronary microvessels. The increase in nitrite in response to the highest dose of amlodipine (79%) was similar in magnitude to that of the ACE inhibitor...
ramipril (74%), indicating that amlodipine can promote coronary NO production in vessels from failing human hearts and that this effect is dependent on a kinin-mediated mechanism. The effect was dose dependent and apparent at therapeutic levels.\textsuperscript{43}

A more recent study in patients with hypertension showed that treatment with amlodipine or an ACE inhibitor significantly improved forearm blood flow in response to increasing levels of acetylcholine.\textsuperscript{45} Amlodipine and ACE inhibitors both enhance NO bioavailability through a kinin-dependent pathway, although via different molecular mechanisms.\textsuperscript{42} In addition, amlodipine may improve endothelial function through a potent antioxidant mechanism\textsuperscript{46–48} resulting from its high lipophilicity.\textsuperscript{49,50} These physicochemical properties also enable amlodipine to inhibit aggregation of oxidized LDL, a key step in foam cell formation.\textsuperscript{51}

The Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study compared the incidence of cardiovascular events among 1,991 patients with angiographically documented CAD and normal blood pressure (mean blood pressure at baseline, 129/78 mm Hg), randomized to amlodipine 10 mg/day, enalapril 20 mg/day, or placebo.\textsuperscript{36} Results showed a significant reduction in the incidence of cardiovascular events with amlodipine compared with placebo (hazard ratio, 0.69; 95% confidence interval [CI], 0.54 to 0.88.

\begin{figure}[h]
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\caption{Stimulated peak nitric oxide (NO) production, shown as change from baseline versus concentration of low-density lipoprotein (LDL). n-LDL = normal (nonoxidized) LDL; ox-LDL = oxidized LDL. (Adapted with permission from \textit{Circulation}.\textsuperscript{14})}
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\caption{Role of endothelial cell membrane microdomains in atherosclerosis. Ca\textsuperscript{2+} = calcium; eNOS = endothelial nitric oxide synthase; NAD(P)H = reduced nicotinamide adenine dinucleotide phosphate; NO = nitric oxide; O\textsubscript{2} = superoxide. ① = calveolae; ② = detergent-resistant membrane domain; ③ = cholesterol crystalline membrane domain; ④ = extracellular crystals. (Adapted with permission from \textit{Circulation}.\textsuperscript{29})}
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Atorvastatin: reducing oxidative stress on the vessel wall

A recent study by Shishehbor and colleagues recorded a significant reduction in the concentration of protein markers of oxidation in 35 patients with hypercholesterolemia and no CAD following only 12 weeks of treatment with atorvastatin 10 mg/day. The reduction in protein markers was indicative of a novel effect of atorvastatin on key sources of oxidative stress. A more detailed analysis of this effect identified the active metabolite of atorvastatin as the key component contributing to this effect. In fact, and uniquely among the statins, the metabolites of atorvastatin are equally active as those of the parent compound: the majority (~70%) of the HMG-CoA reductase inhibition is achieved via the hydroxyl metabolite of atorvastatin. So, independent of its LDL-lowering efficacy, the active metabolite of atorvastatin is a potent inhibitor of oxidative stress under normal pharmacologic conditions.

Analysis of the structure of the atorvastatin metabolite has revealed that the basis of this distinct antioxidant ability is its phenoxy group, which is capable of proton donation and electron stabilization. Additionally, the membrane location of the phenoxy group facilitates efficient electron transfer with the phospholipid acyl chains. Other statins do not possess these physicochemical properties and, consequently, the effect cannot be replicated with the other agents.

Rationale for combining amlodipine and atorvastatin therapy

From a clinical perspective, it is obvious that cardiovascular risk factors such as hypertension and dyslipidemia act to augment risk of disease via damage to the vascular endothelium, increased oxidative stress, and acceleration of inflammatory processes. It therefore is not unreasonable to suggest that a combination of agents that specifically target hypertension and lipid lowering will potentially produce a more than additive benefit in terms of improvement of clinical outcomes and reduction in vascular risk.

Both amlodipine and atorvastatin have been associated with reduced risk of events associated with CVD. Close examination of the molecular structures of amlodipine and atorvastatin reveals that these agents have complementary chemical properties. Atorvastatin has negative polarity associated with its heptanoic side chain, whereas amlodipine is distinct among the dihydropyridines in having a formal positive charge on its aminoethoxy side chain.

Both amlodipine and atorvastatin are lipophilic and share high affinity for the cell membrane. Recent analysis suggests that both agents partition into the membrane lipid bilayer: the concentration of amlodipine and atorvastatin in the cell membrane is much higher than that found in the surrounding aqueous environment. This is an important common property of the 2 compounds that may facilitate interactions with novel receptor sites in vascular cell membranes.

Effect of amlodipine and atorvastatin on NO

We have evaluated the separate versus combined effects of amlodipine and atorvastatin on endothelium-dependent NO release. In isolated human umbilical vein endothelial cells, we measured the release of NO with electrochemical nanosensors. Under these conditions, statins generally have limited effects on NO release; conversely, amlodipine has a significant ability to stimulate NO release. The amlodipine-atorvastatin combination, however, has a much more pronounced, synergistic effect on NO (Figure 4). It appears that the endothelial activity of amlodipine is actually enhanced by the presence of atorvastatin, thereby facilitating a greater NO-releasing effect. We attribute this synergistic effect to electron transport mechanisms between the molecules that facilitate antioxidant activity. Clinical investigations are under way to test these separate and combined effects in vivo on vasodilation of coronary vessels through an endothelium-dependent pathway.

Effect of amlodipine and atorvastatin on vascular compliance

The Avalon Arterial Wall Compliance (AWC) trial was designed to determine the effect of coadministered amlodipine 5 mg/day plus atorvastatin 10 mg/day on the compliance/elasticity of the microcirculation (C2) and large conduit arteries (C1) in patients with concomitant hypertension and dyslipidemia. Statistically significant improvements in C2 were observed with coadministered amlodipine and atorvastatin compared with amlodipine alone or placebo, indicating a potentially synergistic vascular effect of coadministration of the 2 agents.

Clinical studies of simultaneously administered amlodipine and atorvastatin

Laboratory examination has indicated the potential vascular benefits of combining amlodipine and atorvastatin treatment. Several recent studies have tested the combination treatment in a clinical trial setting, demonstrating the efficacy, safety, and clinical utility of simultaneously administered amlodipine and atorvastatin.
One double-blind placebo-controlled study in 1,660 patients with concomitant hypertension and dyslipidemia has shown that amlodipine (5 mg and 10 mg) does not interfere with the LDL cholesterol–lowering efficacy of atorvastatin and, equally, atorvastatin (10 mg, 20 mg, 40 mg, and 80 mg) does not compromise the blood pressure–lowering efficacy of amlodipine when the 2 therapies are coadministered. Amlodipine and atorvastatin are also available as a single-pill combination therapy, which has been shown (at the amlodipine 5 mg/atorvastatin 10 mg and amlodipine 10 mg/atorvastatin 80 mg daily doses) to be bioequivalent to either component in isolation. The recently completed Gemini Study was designed to determine the clinical utility of the single-pill amlodipine/atorvastatin therapy for the simultaneous treatment of hypertension and dyslipidemia. Gemini was a 14-week, open-label, noncomparative, multicenter trial in 1,220 patients with concomitant hypertension and dyslipidemia. All 8 then-available doses (11 doses are now available in the United States) of the amlodipine-atorvastatin single pill were titrated, at the clinician’s discretion, to improve blood pressure and lipid control, with 58% of patients attaining goals for both conditions at week 14 after 3 titrations.

The development of combination therapies represents an important step in the effective treatment of cardiovascular risk factors, especially given our understanding of how such factors contribute in a multiplicative fashion to mechanisms of vascular disease.

**Summary**

Endothelial dysfunction is a systemic disorder and a key factor in the pathogenesis of atherosclerosis and its complications. Current evidence suggests that endothelial status is not determined solely by the individual’s risk factor burden but rather may be regarded as a broader indication of vascular function. Hypertension and dyslipidemia are 2 modifiable cardiovascular risk factors that frequently are comorbid. Amlodipine and atorvastatin are well-known therapies for, respectively, reducing blood pressure and improving the lipid profile. However, in addition to their separate effects on blood pressure and lipids, the synergistic effects of this drug combination on human endothelial function, as shown by means of isolated cells, represent an additional mechanism of action in the treatment of CVD. To halt the progression of atherosclerosis effectively, it is important to treat an individual’s overall cardiovascular risk. Single-pill combination therapy that targets multiple risk factors represents an important step in improving the management of patients at risk of CVD.

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Potential vascular benefits of statins

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Atherosclerosis is associated with a number of functional abnormalities that affect endothelium-dependent vasomotor function, inflammation, and thrombosis. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have effects on many of these functions, likely explaining their benefit in reducing the incidence of clinical events in patients at high risk of cardiovascular disease. Statins may improve this vascular biology by lowering levels of low-density lipoprotein (LDL) or potentially by a number of non–LDL-related mechanisms. Cell culture and some animal studies have demonstrated LDL-independent effects of statins. The non-LDL mechanisms include effects on isoprenoid production and function, interactions between caveolin and nitric oxide synthase, and direct immunomodulatory effects. Although these mechanisms are clearly demonstrated in the experimental setting, their relevance to the clinical use of statins is unknown. From a purely pragmatic viewpoint, the debate of lipid versus nonlipid effects of statins matters little to clinical practice. Their proven effect on vascular biology and risk reduction justifies their important therapeutic role.

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Atherosclerosis is a dynamic process characterized by important changes in the biology of arteries in addition to the hemodynamic effects related to plaque growth and disruption. The disordered vascular biology associated with atherosclerosis and its risk factors include vasomotor dysfunction and plaque inflammation as well as a prothrombotic/antifibrinolytic state.

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) reduce the risk of atherosclerotic events in patients with clinically evident atherosclerosis and those at high risk of events due to diabetes mellitus, peripheral arterial disease, hypertension, and multiple risk factors. Statins have little impact on the extent of atherosclerosis, but they do have potent effects to reverse the dysfunctional vascular biology of atherosclerosis.

Statins may improve vascular biology by a number of mechanisms related to changes in lipids and potentially by a number of nonlipid effects on vascular biology. Although these effects are clearly demonstrated in cell culture and some animal studies, their relative importance in clinical practice is still debated. An understanding of these mechanisms reinforces the therapeutic value of statins in atherosclerosis and may help to develop novel therapies that can further assist in disease prevention.

Vasomotor function

The healthy endothelium produces a number of important substances that promote vasodilation, inhibit inflammation, and prevent thrombus formation. Of these, nitric oxide (NO) is particularly important in medium-sized arteries and is increased in response to a number of stimuli, including shear stress and bradykinin. NO produced by the endothelium diffuses across the artery wall to vascular smooth
muscle and promotes vasorelaxation and dilation of arteries to improve blood flow to distal organs.1 Atherosclerosis and its risk factors have important adverse effects on endothelium-dependent vasomotor function.2–7 Lack of NO (through lack of production or increased degradation) prevents dilation and may lead to inappropriate vasoconstriction and ultimately to organ ischemia.1 Improvement in a number of atherosclerotic risk factors, including lowering low-density lipoprotein (LDL) by apheresis, LDL lowering by resins, and increasing physical activity reverses this abnormal physiology.8–14

Statins also improve vasomotor function, potentially by decreasing LDL cholesterol levels and perhaps by other direct mechanisms described below. Lowering plasma LDL reduces the amount of LDL and oxidized LDL in the artery wall15,16 thereby removing a potent factor that reduces NO bioavailability. Clinical studies clearly show that long-term use of statins improves endothelium-dependent dilation.8,9,14 By improving NO bioavailability, statin therapy decreases the likelihood of ischemia17,18 and has other effects related to NO’s impact on vascular inflammation and thrombosis.

### Lipid and nonlipid effects of statins

Statins have a number of lipid and nonlipid effects that could improve vascular biology and reduce cardiovascular risk. The relative importance of these actions to the clinical use of statins is not known, but it is under investigation.

### Lipid effects of statins

Statins can decrease plasma LDL cholesterol by as much as 50% to 60%, and these changes are associated with a reduction in LDL and, particularly, oxidized LDL in plaque.15,16,24 Oxidatively modified LDL cholesterol has a number of adverse effects on NO bioavailability, including decreasing the production of NO by NO synthase (NOS) and increasing NO destruction by oxygen-derived free radicals.1,36 The decrease in bioavailability of NO promotes the adverse changes in vascular biology described above.

In addition to their LDL effects, statins increase high-density lipoprotein (HDL) by 5% to 10%, and potent statins can decrease triglycerides by up to 20%. The changes in HDL and triglycerides are smaller than the changes in LDL, but small changes in HDL are associated with important changes in arterial function and cardiovascular risk.37–39 HDL cholesterol removes cholesterol from macrophages and other cells in the artery wall by interactions between apolipoprotein A-I on HDL and the adenosine triphosphate binding cassette transporter–1 (ABCI) on peripheral cells.40 Increasing HDL may further help to reduce the residency of LDL in the artery wall and to reverse abnormal vascular function related to modified LDL.41 In addition, HDL has a number of antioxidants that may help prevent oxidation processes in the artery wall. These include the specific antioxidant paraoxonase as well as the indirect antioxidant effects related to less LDL in the artery wall.40 Plasma triglycerides can deliver cholesterol to peripheral tissue and may participate in some of the abnormalities in vascular biology associated with atherosclerosis.42 Results of clinical trials using external and intravascular ultrasonography suggest that statin regimens intensively lower LDL cholesterol and are more successful in prevent-
ing plaque progression than are more modest LDL-lowering strategies. These findings suggest that statins affect lipid flux across the artery wall and other vascular changes that lead to the progression of atherosclerosis.

**Nonlipid effects of statins**

In addition to effects that are mediated by their impact on lipid metabolism, statins may improve several facets of vascular biology through direct actions on other molecular processes.

**Isoprenoids and vascular function**

The mevalonate pathway divides into a cholesterol limb and an isoprenoid limb (Figure 1). Because statins inhibit HMG-CoA reductase activity, they not only decrease levels of cholesterol but also reduce the production of a number of isoprenoids such as geranylgeranyl pyrophosphate. Isoprenoids activate the G-protein rho, leading to its translocation from the cytoplasm to the cell membrane. Activation of rho, rho kinase, and related G-proteins inhibits NOS activity and the production of NO, affects cell structure, and promotes inflammation. These effects are largely independent of cholesterol and, because they are inhibited by statins, provide a plausible mechanism for the lipid-independent effects of statins on vascular function.

**Effects on caveolin and NOS**

Endothelial NOS, the enzyme that produces NO, largely resides in clefts in the luminal surface of endothelial cells called caveolae. In the resting state, NOS is inhibited by binding to caveolin—a protein in the cell membrane of caveolae. In the healthy state, shear stress and other stimuli increase enzymes that activate NOS by phosphorylation and increase the competitive inhibitor of caveolin, the calcium-calmodulin complex (Figure 2). These stimuli allow NOS to dissociate from caveolin and increase NO production.

Hyperlipidemia increases caveolin in cell culture, and statins decrease the expression of caveolin-1. Thus statins may increase NOS activity by lowering LDL cholesterol level and by direct effects on caveolin concentration in the cell membrane. Statins also enhance the activation of NOS by promoting the phosphorylation of heat shock protein–90 and its subsequent association with serine threonine kinase.

**Immunomodulatory effects**

Statins may inhibit immunomodulatory signaling events via 2 mechanisms: (1) preventing T-lymphocyte activation by decreasing the expression of the major histocompatibility complex–II and (2) interfering with integrin-mediated interactions between leukocytes and antigen-presenting cells (or endothelial cells) by preventing the normal function of the lymphocyte function-associated antigen–1. These actions tend to occur in cell culture at high concentrations, but they are potentially lipid-independent anti-inflammatory effects of statins.

**From bench to bedside: are lipid-independent effects relevant clinically?**

Although nonlipid effects of statins are clearly apparent in cell culture and in some animal studies, we are uncertain...
of their relevance to statin use in clinical practice. Human studies that attempt to address the nonlipid effects of statins are almost always confounded by changes in LDL cholesterol that occur even within a week of initiating statin therapy.

Other studies tackle this question by demonstrating a lack of association between changes in LDL cholesterol and changes in plasma markers of inflammation or atherosclerosis growth. However, these methods fail to acknowledge the impact of intraindividual variability on the measurement of all these parameters. This variability tends to drive associations to the null and is an entirely unsatisfactory method for demonstrating lipid independence.

**Clinical markers of vascular biology**

The impact of endothelial function, inflammation, and thrombosis mechanisms on our understanding of this disease cannot be underestimated. Although of limited use clinically, greater comprehension of vascular biology has revolutionized the understanding of atherosclerotic vascular disease as well as the approach to its treatment.

Early studies of statin effects on endothelial function were some of the first to demonstrate that the adverse vascular biology associated with atherosclerosis was reversible by risk factor modification in general and statin therapy in particular. These studies helped link risk factors such as elevated LDL cholesterol, hypertension, and cigarette smoking to the development of atherosclerosis and emphasized the importance of risk factor modification to disease management.

More recently, plasma markers of inflammation, including C-reactive protein, serum amyloid A, shed cellular adhesion molecules, and products of activated macrophages, provide a window into the inflammation processes related to atherosclerosis. Average concentrations in groups of individuals help us to understand the effects of risk factor modification on atherosclerosis biology. Numerous studies demonstrate that statins reduce the level of inflammatory markers in patients with elevated risk factors, stable angina, and acute coronary syndromes. Average changes in inflammatory markers track the average reduction in risk in groups of subjects and provide support for the role of statins in stabilizing atherosclerosis to prevent clinical events.

**Summary**

Statins have revolutionized the treatment of patients with high cardiovascular risk. They also have contributed to the understanding of this disease process by demonstrating improvements in the vascular biology important to atherosclerosis progression and destabilization. Although the relative importance of lipid and nonlipid effects garners much attention, this is of little relevance to the practicing clinician or to the patient receiving therapy. Endothelium-dependent vasodilation, inflammatory markers, and thrombolic markers continue to advance our knowledge of atherosclerotic vascular disease, but their relatively great intraindividual variability limits their clinical utility. Currently, change in LDL cholesterol levels is still the best guide to the success of statin therapy. Greater understanding of lipid and nonlipid mechanisms of statins may help in the development of new therapies that could provide additional benefits in the form of risk reduction.

**References**


