

Ethnic, Gender, and Age-related Differences in the Treatment of Dyslipidemia

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Abstract

Coronary heart disease (CHD) remains the leading cause of mortality in the United States, and factors such as age, gender, or race/ethnicity have a significant impact on cardiovascular risk. More than 80% of people who die from CHD are 65 years or older. Because women experience myocardial infarction (MI) at older ages than men, their mortality from MI is greater than it is for men. The largest disparity can clearly be seen between white women and black women. CHD death rates are higher among blacks than whites and the discrepancy in rates of premature CHD death is even more pronounced. Given this information, aggressive treatment of CHD risk factors is critical in black individuals, older individuals, and women. Although abundant randomized, controlled clinical data exist to support the efficacy of lipid-lowering therapy in preventing CHD events, these populations have traditionally been underrepresented in intervention-based clinical trials, despite their high prevalence of CHD. This article will explore the evidence for instituting statin therapy as part of a risk-reducing strategy in older individuals, women, and ethnic minorities.

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Coronary heart disease (CHD) remains the leading cause of mortality in the United States, regardless of age, sex, or race/ethnicity.¹ However, these factors impact cardiovascular risk significantly. The average age at the time of a first myocardial infarction (MI) is 65.8 years in men and 70.4 years in women.¹ Further, more than 83% of people who die from CHD are 65 years or older.¹ Moreover, because women experience MI at older ages than men, their mortality from MI is greater than for men: 38% of women die within 1 year of a recognized MI compared with 25% of men.¹ The largest disparity can clearly be seen between white women and black women. Whereas age-adjusted mortality due to heart disease is 19% greater for black men compared with white men, black

women are one third more likely to die from heart disease than white women.²

CHD death rates per 100 000 are higher among blacks than whites,¹ and the discrepancy in rates of premature CHD death is even more pronounced. The higher CHD prevalence and CHD mortality among blacks is partly attributable to a greater risk factor burden in this ethnicity.³ The presence of multiple CHD risk factors is 50% more likely in blacks than whites.³ Hypertension and diabetes are more prevalent in blacks than whites; and the highest rate of obesity is found in black women (49%). Although the prevalence of lipid abnormalities is similar in blacks and whites, the pattern of dyslipidemia is somewhat different between these groups.

Abundant randomized, controlled clinical data exist to support the efficacy of statins in preventing CHD events. Unfortunately, black individuals, older individuals, and women are undertreated with statin therapy in clinical practice.

This article will explore the evidence for instituting statin therapy as part of a risk-reducing strategy in older individuals, women, and ethnic minorities. It will focus specifically on black individuals as the racial/ethnic group with the highest mortality from CHD; data are accumulating for other ethnic groups.

CHD in Older Individuals

The Scandinavian Simvastatin Survival Study (4S),^{4,5} Prospective Study of Pravastatin in the Elderly (PROSPER),⁶ and the Heart Protection Study (HPS)⁷ provide sufficient evidence that statin therapy should

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not be denied to at-risk patients because of advanced age. These landmark trials support the efficacy of statin therapy in preventing mortality and CHD events in older patients.

In 4S,⁴ 51% of the study population was 60 years of age or older. In this age group, simvastatin treatment for a median duration of 5.4 years was associated with a 27% reduction in all-cause mortality and a 29% reduction in the incidence of major coronary events relative to placebo. Moreover, in a post-hoc analysis of 1021 subjects in 4S aged 65 years or older,⁵ the reductions in total and CHD mortality in simvastatin recipients were similar among those 65 years of age or older and those younger than 65 years. The absolute reduction in all-cause and CHD mortality with simvastatin treatment was twice as great in the older individuals than with the younger patients, owing to the increased risk of these end points in the older cohort.

HPS⁷ included 10 697 persons aged 65 years or older among its total study population of 20 536 patients with serum total cholesterol levels greater than 135 mg/dL with or without previous CHD or MI. Significant reductions in all-cause mortality, any vascular death, major coronary events, stroke, revascularization (coronary or noncoronary), and any major vascular events were observed in patients randomized to 40 mg/day of simvastatin compared with placebo; and the benefits of active treatment were similar when stratified by age (40-64 years, 65-69 years, and 70-80 years).

PROSPER⁶ was the first prospective study of statin therapy to enroll older patients exclusively. It included 5804 men and women aged 70 to 82 years with either established vascular disease or risk factors for vascular disease. Patients randomized to pravastatin 40 mg/day experienced a 15% reduction in the primary composite end point of coronary death, nonfatal MI, and fatal or nonfatal stroke after a mean follow-up of 3.2 years, with reductions in CHD death and nonfatal MI accounting for pravastatin's beneficial effect on the primary end point.

CHD in Women

Data to support statin therapy in women are not as compelling as in older at-risk patients. In the large landmark statin trials, especially the secondary prevention trials, statins demonstrate the same benefit in women for reducing vascular events as in men.

In 4S, 827 of the 4444 patients enrolled were women.⁵ The relative risk of a major coronary event was reduced 34% in women assigned to simvastatin, which was identical to the relative risk reduction in men randomized to simvastatin in 4S. However, because of the low incidence of CHD death and total mortality among the entire cohort of women, a mortality advantage to simvastatin treatment in women could not be demonstrated.⁴

The Cholesterol and Recurrent Events (CARE) study randomized men and postmenopausal women to pravastatin 40 mg/day or placebo⁸; 14% of the 4159 patients randomized were postmenopausal women. The effect of pravastatin on the primary end point (death from CHD or nonfatal MI) was greater in women than men (46% risk reduction vs 20%; $P = .001$ for both).

Pravastatin's effect on cardiovascular events and mortality was examined separately with the 1516 women enrolled in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study.⁹ Although LIPID was not adequately powered to show separately significant effects of pravastatin therapy in women, the relative risk reductions in all prespecified cardiovascular events in the overall study population were not different between men and women.

In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),¹⁰ 997 postmenopausal women were enrolled. A prespecified analysis found no statistical differences in reductions in risk for first major coronary event between men and women assigned to lovastatin versus placebo. As with most of the other major statin efficacy trials, reductions in end points with lovastatin treatment did not achieve statistical significance in women because of the small number of women enrolled relative to men.

HPS⁷ included 5082 women, which constituted about one fourth of the total HPS study population. The relative reductions in mortality and major vascular events with simvastatin allocation relative to placebo allocation were similar in the women and men, at approximately 25%.

CHD in African Americans

Traditional risk factors predict CHD in blacks as well as in whites, but the prevalence and influence of these risk factors differs by ethnicity.^{11,12} The relationship between total cholesterol and CHD risk is similar in blacks and whites, as demonstrated by the Multiple Risk Factor Intervention Trial, which included 23 490 black men in its sample.¹³ Furthermore, type 2 diabetes, designated as a CHD risk equivalent by the National Cholesterol Education Program Adult Treatment Panel III,³ is common in blacks, as is hypertension, which is a strong predictor of CHD in this population. The current cholesterol guidelines paradigm determines low-density lipoprotein cholesterol (LDL-C) goal based on global cardiovascular risk, which is clearly elevated in this group, and the newest data suggest that in high-risk patients, the LDL-C goal really is “the lower, the better.”

Dyslipidemia is as common among blacks as it is among white individuals, although the pattern tends to be somewhat different in these ethnicities.³ Mean levels of LDL-C tend to be lower in blacks, although LDL-C levels are more frequently elevated in that population group (due to a cluster of patients with high LDL-C). Mean levels of high-density lipoprotein cholesterol (HDL-C) are higher among black men than among white men, whereas mean HDL-C levels are similar between black and white women. Whether the higher HDL-C level observed in black men is protective against CHD, however, is unclear. Triglyceride levels are lower in both black men and women compared with their white counterparts.

Blacks and other racial minorities have been woefully underrepresented in statin safety and efficacy trials as well as outcomes trials, making their benefits assessment difficult in these groups. The only major lipid intervention trial in which a large number

of black persons were enrolled was the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial—Lipid Lowering Trial (ALLHAT-LLT).¹⁴ In this study, 10 355 subjects (37% of whom were black) enrolled in ALLHAT were further randomized to either pravastatin 40 mg/day or usual care. In the overall study population, the rates of all-cause mortality and CHD death were not significantly different between those randomized to pravastatin or usual care. However, pravastatin had a significantly favorable effect on CHD events in the black versus nonblack populations (relative risk, 0.73 vs 1.02; $P = .03$). The lack of an effect on CHD events in the overall ALLHAT-LLT study group was attributed to increasing statin use during the trial's 5-year duration in patients assigned to usual care, who could be treated with lipid-modifying therapies at the discretion of their treating physicians. This drop-in treatment in the usual care group resulted in only a modest difference in the final LDL-C levels between the 2 groups. The high rate of lipid treatment in the usual care group, however, did not extend to the black patients enrolled, which likely accounted for the significant reduction in CHD events for the black patients randomized to pravastatin versus usual care.

Variability exists in drug response, including the response to statins, among individuals of various races. Simon and colleagues found that race/ethnicity was 1 of 5 variables significantly associated with LDL-C response to simvastatin.¹⁵ White patients had an average 3-mg/dL greater reduction in LDL-C ($P < .01$) and a 1-mg/dL greater increase in HDL-C ($P < .01$) in response to 6 weeks of treatment with 40 mg/day of simvastatin compared with black patients.

The African American Rosuvastatin Investigation of Efficacy and Safety (ARIES) trial was the first prospective, large-scale, comparative trial of statin therapy in an exclusively African American population comparing the efficacy and safety of statin therapies in hypercholesterolemic African American adults. The ARIES trial enrolled 774 African American adults with LDL-C levels between 160 and 300 mg/dL and fasting triglycerides less than 400 mg/dL.¹⁶

Table. Rosuvastatin Versus Atorvastatin in African American Patients: Baseline Lipid Parameters and Mean Percent Change at 6 Weeks

Lipid Measure	Rosuvastatin		Atorvastatin	
	10 mg (n = 186)	20 mg (n = 189)	10 mg (n = 179)	20 mg (n = 178)
LDL-C				
Baseline (mg/dL)	191.8 ± 27.2	189.6 ± 23.4	189.1 ± 24.0	191.9 ± 26.6
% Change	-37.1 ± 1.3*	-45.7 ± 1.3 [†]	-31.8 ± 1.3	-38.5 ± 1.3
TC				
Baseline (mg/dL)	270.7 ± 31.9	270.9 ± 29.4	269.4 ± 28.1	270.8 ± 30.6
% Change	-26.6 ± 1.0*	-33.0 ± 1.0 [†]	-23.1 ± 1.0	-28.7 ± 1.0
HDL-C				
Baseline (mg/dL)	51.5 ± 11.2	52.6 ± 14.2	52.5 ± 12.0	49.9 ± 12.8
% Change	+7.0 ± 0.9 [‡]	+6.5 ± 0.9	+5.6 ± 1.0	+3.7 ± 1.0
Triglycerides				
Baseline (mg/dL)	136.5 ± 49.7	143.7 ± 55.9	139.3 ± 56.4	146.3 ± 49.7
% Change	-16.0 ± 1.9	-20.9 ± 1.9	-17.1 ± 1.9	-19.6 ± 1.9
Non-HDL-C				
Baseline (mg/dL)	219.1 ± 30.3	218.3 ± 26.6	216.9 ± 28.1	221.0 ± 29.7
% Change	-34.3 ± 1.2*	-42.3 ± 1.2 [†]	-29.8 ± 1.3	-35.6 ± 1.2
Apo B				
Baseline (mg/dL)	164.9 ± 25.9	165.4 ± 22.7	166.7 ± 26.5	167.3 ± 25.9
% Change	-29.3 ± 1.2*	-37.2 ± 1.2 [†]	-25.3 ± 1.3	-31.4 ± 1.3
Apo A-1				
Baseline (mg/dL)	154.4 ± 24.5	159.1 ± 31.3	158.6 ± 25.4	153.8 ± 27.5
% Change	+5.4 ± 1.0 [‡]	+4.0 ± 1.0 [‡]	+2.7 ± 1.0	+0.7 ± 1.0

Baseline data are presented as mean ± standard deviation; percent changes as mean ± standard error.

$P < .017$ for *rosuvastatin 10 mg vs atorvastatin 10 mg; [†]rosuvastatin 20 mg vs atorvastatin 20 mg; and [‡]rosuvastatin 10 mg vs atorvastatin 20 mg (Bonferroni-adjusted critical P values). Comparison of least-squares mean percent change and P value from analysis of variance.

LDL-C indicates low-density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; Apo, apolipoprotein. Adapted with permission from Reference 16.

Participants were randomized to open-label rosuvastatin 10 or 20 mg/day or atorvastatin 10 or 20 mg/day for 6 weeks. The reductions in LDL-C, triglycerides, non-HDL-C, and apolipoprotein B concentrations from baseline to week 6 were greater with rosuvastatin versus the milligram-equivalent doses of atorvastatin. Increases in HDL-C and apolipoprotein A-1 were greater with rosuvastatin versus the milligram-equivalent doses of atorvastatin (Table). Furthermore, more rosuvastatin-treated patients than atorvastatin-treated patients in ARIES achieved their National Cholesterol Education Program Adult Treatment Panel III goals for LDL-C (for rosuvastatin 20 mg vs atorvastatin 20 mg: 78.8% vs 61.8% overall achieved goal; 62.5% vs 27.0% in the high-risk category). The trial was not, however, powered to assess clinical outcomes.

Myalgia rate in ARIES was 2.5% and was similar between treatment groups. There were no myopathy cases, creatine kinase elevations greater than 10 times the upper limit of normal (ULN), or liver enzyme elevations more than 3 times the ULN reported. The overall safety profile within the 4 treatment groups was similar.

Studies similar to ARIES have recently been concluded in people of South Asian (Investigation of Rosuvastatin In South Asian Subjects [IRIS]) and Hispanic (Study Assessing Rosuvastatin in Hispanic Population [STARSHIP]) ethnicity,¹⁷ and demonstrated that rosuvastatin was again superior to atorvastatin in these ethnic groups in reducing LDL-C levels and non-HDL-C levels, and in achieving LDL-C goals.^{17,18}

Conclusions

Although the available evidence to support statin treatment of older individuals, women, and black individuals is robust as for white men, it seems to strongly suggest that statin therapy is beneficial in these patient groups as well. The increased risk and therefore the need to aggressively manage risk factors in these groups has been clearly established, and we now have evidence of risk reduction associated with statin therapy treatment in the elderly, women, and black individuals. Although the scientific community will need to continue to focus on inclusion of these important populations in these essential clinical trials, the medical community must strive to concentrate their efforts on ensuring that these populations are adequately taking full advantage of these effective and much-needed therapies.

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