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Chris J. Packard, DSc; Ian Ford, PhD; Michele Robertson, BSc; James Shepherd, MD; Gerard J. Blauw, MD; Michael B. Murphy, MD; Edward L.E.M. Bollen, MD; Brendan M. Buckley, FRCPI; Stuart M. Cobbe, MD; Allan Gaw, MD; Michael Hyland, FRCPI; J. Wouter Jukema, MD; Adriaan M. Kamper, MD; Peter W. Macfarlane, DSc; Ivan J. Perry, MD; David J. Stott, MD; Brian J. Sweeney, FRCPI; Cillian Twomey, FRCPI; Rudi G.J. Westendorp, MD; for the PROSPER Study Group

Background—Statins are important in vascular disease prevention in the elderly. However, the best method of selecting older patients for treatment is uncertain. We assessed the role of plasma lipoproteins as predictors of risk and of treatment benefit in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER).

Method and Results—The association of LDLc and HDLc with risk was examined in the 5804 70- to 82-year-old subjects of PROSPER. Baseline LDLc showed no relation to risk of the primary end point in the placebo group ($P=0.27$), nor did on-treatment LDLc in the pravastatin group ($P=0.12$). HDLc was inversely associated with risk in subjects on placebo ($P=0.0019$) but not in those on pravastatin ($P=0.24$). Risk reduction on pravastatin treatment was unrelated to baseline LDLc ($P=0.38$) but exhibited a significant interaction with HDLc ($P=0.012$). Subjects in the lowest 2 quintiles of HDLc (<1.15 mmol/L) had a risk reduction of 33% (hazard ratio, 0.67; 95% confidence limits, 0.55, 0.81; $P<0.0001$), whereas those with higher HDLc showed no benefit (RR, 1.06; 95% confidence limits, 0.88, 1.27; $P=0.53$). During follow-up, there was no relation between achieved level of LDLc or HDLc and risk. However, the change in the LDLc/HDLc ratio on statin treatment appeared to account for the effects of therapy.

Conclusions—In people >70 years old, HDLc appears to be a key predictor of risk and of treatment benefit. Findings in PROSPER suggest that statin therapy could usefully be targeted to those with HDLc <1.15 mmol/L or an LDLc/HDLc ratio >3.3. **(*Circulation*. 2005;112:3058-3065.)**

Key Words: coronary disease ■ risk factors ■ cholesterol ■ drugs

Ischemic vascular disease is a major cause of death and morbidity in older people in the developed world. It affects the majority; in some surveys, 75% to 80% of 80-year-olds exhibit signs or symptoms of arteriosclerosis,[1] and vascular disease is the primary cause of death in almost half of those >65 years. Furthermore, the outcome of surviving a major coronary or cerebrovascular event can be disability, with consequences for the individual, the immediate family, and society. Prevention of vascular disease in the elderly is therefore, a key objective in the promotion of healthy ageing.

Statins, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, are established as first-line therapy for cholesterol lowering to prevent coronary heart disease (CHD), both in those with clinically evident vascular disease and in asymptomatic individuals. A series of landmark trials[2–6] have demonstrated that these drugs are able to reduce risk by 20% to 40%. Remarkably, in studies completed so far, it appears that the benefit of statin therapy is independent of lipid phenotype, background risk factor status, or previous history of vascular disease. For example, in the Heart Protection Study,[5] the relative risk (RR) reduction was the same whether LDL cholesterol (LDLc) levels were elevated or normal, whether subjects were diabetic or not, and whether or not patients had previously experienced a myocardial infarction (MI) or stroke. Until recently, although a number of trials included a significant proportion of older people (ie, >65 years of age) among their recruits,[4–7] none addressed specifically the prevention of cardiovascular and cerebrovascular

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From the Department of Vascular Biochemistry (C.J.P., J.S.), Division of Cardiovascular and Medical Sciences (S.M.C., P.W.M.), and Department of Geriatric Medicine (D.J.S.), University of Glasgow, Glasgow, Scotland; Clinical Trials Unit (A.G.), North Glasgow Division, Greater Glasgow Health Board, Glasgow, Scotland; Robertson Centre for Biostatistics (I.F., M.R.), University of Glasgow, Glasgow, Scotland; Department of Pharmacology and Therapeutics (B.M.B., M.B.M.), Cork University Hospital, Wilton, Cork, Ireland; Department of Epidemiology and Public Health (I.J.P.), Departments of Geriatric Medicine (M.H., C.T.), and Department of Neurology (B.S.), Cork University Hospital, Wilton, Cork, Ireland; Section of Gerontology and Geriatrics (G.J.B., R.G.J., A.M.K.) and Departments of Cardiology (J.W.J.) and Neurology (E.L.E.M.), Leiden University Medical Centre, Leiden, The Netherlands.

Correspondence to Prof C.J. Packard, Glasgow Royal Infirmary, Department of Vascular Biochemistry, 4th Floor, University Block, Glasgow G31 2ER, UK. E-mail chris.packard@clinmed.gla.ac.uk

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TABLE 1. Plasma Lipoprotein and Apo Levels at Baseline and Lipoprotein Levels on Treatment in Pravastatin-Treated Subjects in PROSPER

			Men*		Women*		Primary*		Secondary*	
	Baseline	3 Months	Baseline	3 Months	Baseline	3 Months	Baseline	3 Months	Baseline	3 Months
n	2891	2758	1396	1340	1495	1418	1585	1514	1306	1244
Plasma cholesterol, mmol/L	5.7 (0.9)	4.4 (0.8)	5.3 (0.8)	4.1 (0.7)	6.0 (0.9)	4.6 (0.8)	5.7 (0.9)	4.4 (0.8)	5.7 (0.9)	4.3 (0.8)
Plasma triglyceride, mmol/L	1.5 (0.7)	1.3 (0.6)	1.5 (0.7)	1.3 (0.7)	1.6 (0.7)	1.3 (0.6)	1.5 (0.7)	1.3 (0.6)	1.6 (0.7)	1.4 (0.7)
LDLc, mmol/L	3.8 (0.8)	2.5 (0.7)	3.6 (0.7)	2.4 (0.6)	4.0 (0.8)	2.6 (0.7)	3.8 (0.8)	2.5 (0.7)	3.8 (0.8)	2.5 (0.7)
HDLc, mmol/L	1.3 (0.4)	1.4 (0.4)	1.2 (0.3)	1.3 (0.4)	1.4 (0.4)	1.5 (0.4)	1.3 (0.4)	1.4 (0.4)	1.2 (0.3)	1.3 (0.4)
ApoA1, g//L	1.3 (0.2)	ND	1.2 (0.2)	ND	1.4 (0.2)	ND	1.4 (0.3)	ND	1.3 (0.2)	ND
ApoB, g/L	1.2 (0.2)	ND	1.1 (0.2)	ND	1.2 (0.2)	ND	1.1 (0.2)	ND	1.2 (0.2)	ND

ND indicates not determined. Other abbreviations are as defined in text. Values are mean and (SD). Values given are the average of 2 baseline estimations, and the on-treatment level was determined at 3 months of therapy. No data are provided for the placebo group.

*Pravastatin group refers to all those allocated to pravastatin treatment. Levels are given also for the group split by sex or by prevention status.

diseases in the elderly. PROSPER (the PROspective Study of Pravastatin in the Elderly at Risk) was designed to examine these issues.[8] The rationale for the study was not only to focus on a growing health problem but also to test statin use in an age range wherein plasma cholesterol concentration was a much weaker predictor of relative CHD risk than at midlife.[9–11] The principal findings of the study were that pravastatin at 40 mg/d reduced the risk of CHD by 19% to 24% but did not influence stroke rate.[8] It could be argued on the basis of this result that statins should be prescribed to all older people, but there was evidence in the trial for heterogeneity of response, raising the possibility that these drugs could be targeted to those who would benefit most. This topic is explored further in the present report, as is the issue of which plasma lipoprotein or apolipoprotein best predicts CHD risk in the elderly. Current guidelines, derived mainly from middle-aged cohorts, may not offer the best treatment algorithms for older people, in whom the association of plasma lipid levels with vascular disease appears considerably attenuated.

Methods

Subjects

PROSPER recruited in 3 countries (Scotland, Ireland, and the Netherlands) 5804 subjects (3000 women, 2804 men) to a trial of statin use in an older population. Principal inclusion criteria were a history of vascular disease (in 2565 subjects, 44% of the total) or high CHD risk arising from hypertension, smoking habit, or diabetes and an age of 70 to 82 years. Plasma cholesterol (total) was required to be 4.0 to 9.0 mmol/L and plasma triglyceride <6.0 mmol/L.[12] Institutional ethics committees approved the study, and written, informed consent was obtained from each subject. Follow-up lasted for an average of 3.2 years.

Measurements

Plasma lipids and lipoproteins were measured twice during the screening phase, ie, at the beginning and end of the single-blind, placebo "run-in" phase according to the standardized[13] Lipid Research Clinics protocol.[14] Baseline levels were taken as the average of these 2 determinations. Tests were repeated at 3 months and annually thereafter. Apolipoprotein (apo) A1 and apoB were tested once on samples collected at baseline by turbidimetric assays (Hitachi/Roche catalog Nos. 03032612 and 03032639, respectively).

Statistical Analysis

To test the association of baseline lipoprotein levels with vascular disease, subjects were divided into quintiles of LDLc, HDLc, LDLc/HDLc ratio, and total/HDLc ratio. Risk (unadjusted incidence rates) of the primary end point (CHD death, nonfatal MI, and fatal plus nonfatal stroke) was estimated separately for the placebo- and pravastatin-allocated subjects in each quintile. The RR of the primary end point was derived for quintiles of LDLc, HDLc, LDLc/HDLc, and total/HDLc after adjustment for potential confounding factors, ie, age, sex, smoking status, history of diabetes, history of hypertension, baseline blood pressure, and LDLc or HDLc, as appropriate. The RR reduction on pravastatin therapy was computed for each quintile, and a test for interaction (quintile×treatment effect) was performed. In addition, the trial cohort was divided according to sex and history of vascular disease, and the association of HDLc with the coronary component (CHD death plus nonfatal MI) of the primary end point was determined in these subgroups. ApoA1 and apoB were analyzed as continuous variables, adjusted for the same confounding factors, with hazard ratios and confidence intervals (CIs) produced for a change of 1 SD.

The efficacy of treatment was examined also in those with a combination of low HDLc (<1.03 mmol/L in men, <1.29 mmol/L in women) and high triglyceride (>1.7 mmol/L in both sexes) values compared with the remainder of the cohort.

On-treatment lipoprotein levels determined at 3 months were related to the risk of the primary end point, again by dividing each treatment arm into quintiles of lipoprotein level. Cox proportional-hazards models for the entire cohort were constructed with lipoprotein levels as continuous variables to determine the extent to which baseline level, achieved level, or change from baseline explained the risk reduction.

Results

At baseline, women had higher levels of LDLc ($P<0.0001$) and HDLc ($P<0.0001$) than men. Subjects with a history of vascular disease (secondary prevention) had lower HDLc levels ($P<0.0001$) but similar LDLc levels ($P=0.47$) compared with those who had not had an event (primary prevention; Table 1).

Baseline Lipoprotein Levels and Risk in the Placebo Group

LDLc at baseline showed no association with the observed (unadjusted) incidence of the primary end point in the placebo group during the 3.2 years of follow-up (Figure 1), and this was also the case when the adjusted RR of the

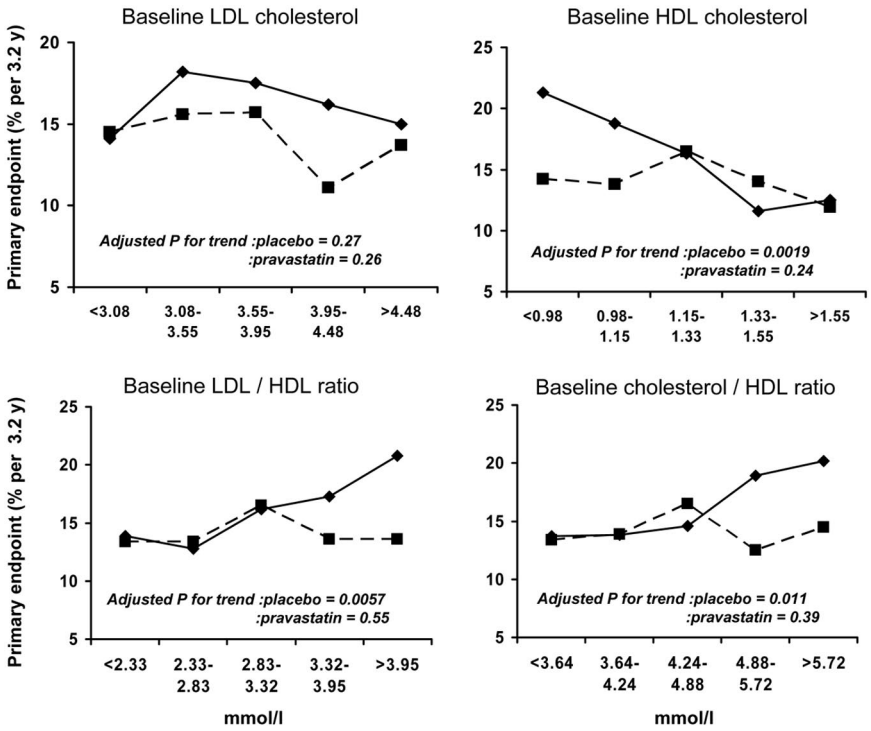

Figure 1. Relation between baseline lipoprotein levels and incidence of the primary end point. Subjects in PROSPER were divided into quintiles according to LDLc, LDLc/HDLc, or total/HDLc at baseline. Crude (unadjusted) event rates for the primary end point during the average 3.2 years of follow-up were calculated separately for subjects allocated to placebo (diamonds) or pravastatin (squares). Probability values for the association of quintiles with event rate, adjusted for age, sex, blood pressure, smoking, history of hypertension, and history of diabetes are quoted for each treatment arm. Abbreviations are as defined in text.

primary end point was estimated for each quintile of LDLc ($P=0.27$; Figure 2). HDLc on placebo treatment exhibited an inverse association with the incidence of the primary end point (Figures 1 and 2) and showed a significant relation to risk ($P=0.0019$) in multivariate models adjusted for age, sex, smoking, blood pressure, history of diabetes, history of hypertension, and LDLc (Figure 2). The ratios of LDLc to HDLc and of total cholesterol to HDLc exhibited positive associations with the incidence of the primary end point when examined by quintile (Figure 1). These relations were attributable to the coronary component of the primary end point, because the risk of stroke was not related to any of the variables (data not shown).

To examine the association of HDLc with risk in the major prespecified subgroups in PROSPER, subjects were divided by sex and history of vascular disease. These analyses suffer, of course, from reduced statistical power, and hence, we chose to focus on the secondary end point of coronary events, wherein the relations were likely to be most evident. HDLc divided by quintiles was related significantly to risk of a coronary event in men ($P=0.0009$) but not in women ($P=0.10$), whereas an inverse association between HDLc and risk was evident in both primary ($P=0.051$) and secondary ($P=0.024$) prevention categories. Similar trends were seen for the primary end point, but associations were weaker.

Baseline Lipoprotein Levels and Risk in the Pravastatin Group

In subjects given pravastatin, LDLc was, on average, 33.9% lower than at baseline (Table 1). This brought the average level on treatment to within the therapeutic goal of <2.6 mmol/L (100 mg/dL).[15] Concomitantly, plasma triglycerides fell by an average of 13.0% while HDLc rose 7.2%. The changes in lipoprotein levels were similar in the major subgroups in the study, ie, men versus women and those with versus without a history of vascular disease (Table 1). As in a previous trial,[16] variation in the percentage of LDLc reduction was seen across all quintiles of baseline LDLc (LDLc fell by 30.9%, 32.7%, 34.0%, 34.9%, and 37.1% in quintiles 1 through 5; $P<0.001$ for trend), and greater percent rises in HDLc were observed in subjects with the lowest HDLc at baseline (HDLc rose by 10.7%, 8.2%, 6.5%, 5.5%, and 4.8% in quintiles 1 through 5).

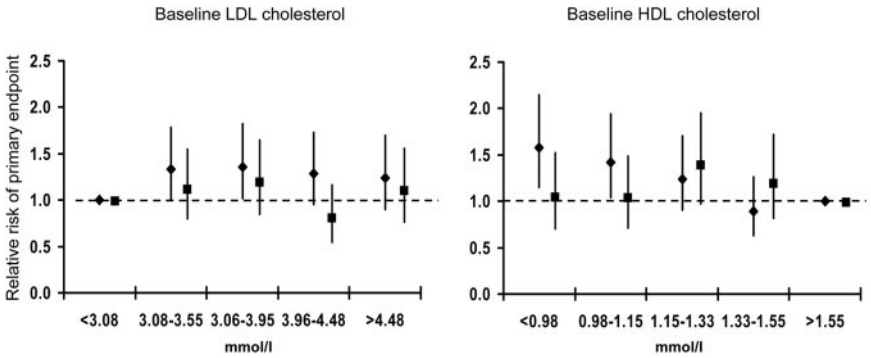

Figure 2. RR of primary end point by quintile of baseline LDLc and baseline HDLc. With the predicted lowest-risk quintile as the referent (bottom LDLc quintile, highest HDL quintile), adjusted mean RR and 95th percentile CI were estimated for the remaining quintiles of LDLc and HDLc. Factors included in the model are given in the legend to Figure 1. Subjects in the placebo arm are represented by diamonds and those in the pravastatin arm by squares. Abbreviations are as defined in text.

TABLE 2. Pravastatin Treatment Effect by Quintile (Q) of Baseline Lipoprotein Levels

	RR Reduction in Primary End Point					Interaction
Variable	Q1	Q2	Q3	Q4	Q5	*P*
LDLc	−4%	16%	12%	34%	10%	0.38
HDLc	36%	31%	−2%	−24%	3%	0.012
LDLc/HDLc	4%	−4%	−2%	23%	39%	0.062
Total/HDLc	1%	2%	−14%	35%	34%	0.029

Abbreviations are as defined in text. Subjects were divided into quintiles according to ranges in Figure 1. The RR reduction was adjusted for age, sex, smoking, history of diabetes, history of hypertension, baseline blood pressure, and LDLc or HDLc, as appropriate. Negative numbers represent a higher event rate in pravastatin-treated subjects. *P* values are the significance of interaction term for quintile×treatment effect.

Subjects who received pravastatin experienced, for a given baseline LDLc, had a lower risk of the primary end point (Figure 1), as would be expected. The risk reduction across quintiles of baseline LDLc did not vary systematically (Table 2), and the interaction term that examined whether treatment effect was related to quintile of baseline LDLc was not significant ($P=0.38$, Table 2). It was noteworthy that an inverse association of HDLc with risk was absent in the pravastatin-treated group ($P=0.24$; Figures 1 and 2). For the top 3 quintiles of HDLc, incidence rates for the primary end point were similar in the placebo and pravastatin groups (Figure 1), and the risk reduction was negligible (Table 2). A treatment effect of an approximate one-third risk reduction was observed in the lowest 2 quintiles of baseline HDLc, with an RR of 0.67 (95% CI, 0.55 to 0.81; $P<0.0001$), whereas pravastatin-treated subjects in the upper 3 quintiles of baseline HDLc had an RR of 1.06 (95% CI, 0.88 to 1.27; $P=0.53$). Similarly, for the top 2 quintiles of LDLc/HDLc and total/HDLc, the RR was 0.69 (95% CI, 0.56 to 0.85; $P=0.0004$) and 0.66 (95% CI, 0.54 to 0.81; $P<0.00001$), respectively. For the bottom 3 quintiles, the RR for LDLc/HDLc was 1.00 (95% CI, 0.84 to 1.19; $P=0.99$), and for total/HDLc, it was 1.03 (95% CI, 0.86 to 1.22; $P=0.77$). For these variables, the interaction term with treatment was close to or within the $P<0.05$ significance limit (Table 2).

Patients were divided into those who, at baseline, had a low HDL/raised triglyceride pattern (as in the metabolic syndrome[15]) and those who did not. In the former group (n=1267), pravastatin treatment was associated with a hazard ratio of 0.78 (95% CI, 0.59 to 1.02; $P=0.07$) for the primary end point and of 0.63 (95% CI, 0.46 to 0.88; $P=0.01$) for coronary events. In the latter group, the corresponding hazard ratios on pravastatin treatment were 0.88 (95% CI, 0.75 to 1.02; $P=0.09$) and 0.87 (95% CI, 0.73 to 1.04; $P=0.13$). The interaction term low HDLc/high triglyceride pattern×treatment was not significant for the primary end point ($P=0.39$) or for coronary events ($P=0.087$). LDLc reduction on pravastatin therapy was the same in the 2 groups.

Baseline Apolipoprotein Levels and Risk

Relations between baseline apoA1 and apoB concentrations and risk of an event mirrored the findings for HDLc and LDLc. In multivariate analysis, apoA1 in the placebo group exhibited a strong, negative association with risk of the primary end point; the hazard ratio for a 1-SD change was 0.72 (95% CI, 0.60 to 0.86; $P<0.001$). Like HDLc, apoA1 was unrelated to risk in the pravastatin group (hazard ratio for primary end point for a 1-SD change in apoA1 was 0.89; 95% CI, 0.73 to 1.09; $P=0.26$). ApoB concentration was unrelated to risk of an event in either treatment arm. The hazard ratios for the primary end point for a 1-SD change were 1.04 (95% CI, 0.85 to 1.29; $P=0.68$) in the placebo group and 0.84 (95% CI, 0.68 to 1.02; $P=0.081$) in the pravastatin group.

On-Treatment Lipoprotein Levels and Risk

To examine the relations between lipoprotein levels on treatment and the subsequent risk of an event, the cohort was divided into quintiles of achieved levels of LDLc, HDLc, LDLc/HDLc, and total/HDLc as measured at the 3-month visit (Figure 3). Whereas subjects in the 2 treatment arms were nearly evenly distributed across the range of HDLc levels, those in the pravastatin group were shifted predictably to lower values of LDLc, LDLc/HDLc, and total/HDLc. In the pravastatin group, the on-treatment level of LDLc was unrelated to risk, as was the level of this lipoprotein in the placebo group (similar to the situation for baseline LDLc; Figure 1). Within the region of overlap, ie, 2.25 to 3.95 mmol/L, the incidence of the primary end point appeared higher in the placebo compared with the pravastatin group (Figure 3). The ability of achieved level on treatment to explain the effect of pravastatin was explored further in a series of multivariate analyses of the whole PROSPER cohort (Table 3; for clarity, this shows only the lipid variables, whereas a typical complete model is shown in Table 4). In model 1c (Table 3), it appears that the on-treatment LDLc was not related to risk ($P=0.12$), and neither was treatment allocation ($P=0.40$). HDLc at 3 months exhibited the same divergent associations with risk in the placebo and pravastatin groups (Figure 3), as was observed at baseline (Figures 1 and 2), and in a model of the full cohort, baseline HDLc was no longer a significant predictor of outcome, presumably because of the influence of pravastatin (model 2a). Achieved HDLc did not account for the treatment effect, and there was a significant interaction term for HDLc×treatment ($P=0.02$; model 2c, Table 3).

When subjects in both treatment arms were divided into quintiles according to on-treatment LDLc/HDLc, there was a close concordance in the incidence rate of the primary end point for a given LDL/HDL (Figure 3). Achieved LDLc/HDLc was significantly associated with risk as a continuous variable (model 3c, Table 3), and in the model that included this ratio, treatment allocation gave a hazard ratio close to unity, ie, 0.95 ($P=0.54$) and hence, was not needed as an explanatory variable over the on-treatment level of this ratio. Similar results were seen for total/HDLc (models 4b and 4c in Table 3).

In an attempt to examine whether a change in any lipoprotein variable could explain the treatment effect, multivariate models were constructed that included baseline values, treatment allocation, and the pravastatin-induced lipoprotein changes (models 1b, 2b, 3b, and 4b in Table 3). Change in LDLc and HDLc was not related significantly to risk in the

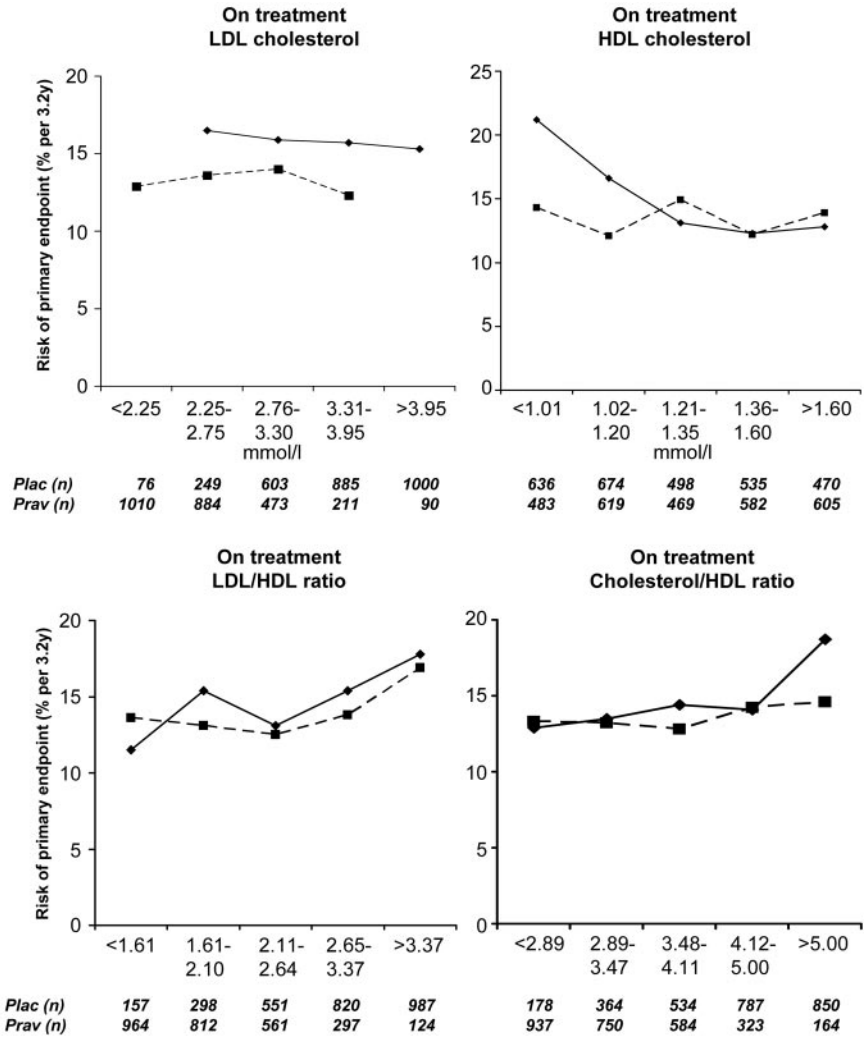

Figure 3. Relation between on-treatment lipoprotein levels and risk of the primary end point. Subjects in both treatment arms were divided into quintiles of on-treatment lipoprotein levels measured at the 3-month follow-up visit. Numbers in the placebo and pravastatin groups in each quintile are shown beneath the figure. Crude (unadjusted) event rates for the primary end point are shown separately for the placebo group (diamonds) and the pravastatin group (squares), for which the number of subjects in a quintile was ≥100. Abbreviations are as defined in text.

whole cohort, although once change in LDLc was included in model 1, the pravastatin term became nonsignificant. The magnitude of the absolute change in LDLc/HDLc or total/HDLc was related to the on-treatment risk of an event (models 3b and 4b), whereas percent change was unrelated to outcome (data not shown).

Discussion

In people >70 years old, HDLc appears to be a predictor not only of coronary risk but also of those who will benefit most from statin treatment. LDLc, in contrast, was not related to the risk of a coronary or cerebrovascular event, and neither a change in LDLc nor its achieved level on therapy was linked to risk reduction, in contrast to the findings of other statin trials.[17,18] These findings raise questions as to which lipoprotein measurements are most appropriate to determine CHD risk in the elderly, how the efficacy of lipid-lowering drugs should be gauged, and how applicable current guidelines are to this growing section of the population.

Studies on how age impacts the association between plasma cholesterol and CHD have revealed that although the absolute risk of a coronary event is high in older people, the RR associated with having a higher versus a lower cholesterol level is reduced.[9–11] In the large Whitehall study, it was calculated that for every increment of 10 years in the age of screening, the difference in plasma cholesterol between those who had a coronary death and those who did not fell by 0.15 mmol/L.[9] From these findings, it can be estimated that at the mean age of entry into our study (75 years), the impact of variation in plasma cholesterol on the risk of CHD death would be minimal. This prediction is borne out in the present analysis: baseline measures of total and LDLc in the placebo group were unrelated to the risk of either the primary end point or its component parts, CHD and stroke; the lack of an association of cholesterol with stroke is, of course, well established in the literature.[19,20] ApoB, which has been reported to predict risk in circumstances where plasma cholesterol or LDLc does not, also did not show any relation to coronary events. Furthermore, on-treatment LDLc levels in both the placebo- and pravastatin-treated groups showed no association with risk of an event. In this regard, PROSPER differs from previous trials that reported a relation between achieved LDLc levels on statin treatment and future risk of CHD.[17,18] PROSPER participants, men and women with or at a high risk of developing vascular disease, are precisely the segment of the elderly population in whom it is important to

TABLE 3. Lipoprotein Variables in Models of Outcome in the Whole PROSPER Cohort

Model*	Variable	HR	CI†	P
1a	Baseline LDLc	1.04	0.95–1.14	0.42
	Pravastatin treatment	0.84	0.73–0.97	0.02
1b	Baseline LDLc	1.07	0.97–1.18	0.18
	Change in LDLc	1.12	0.97–1.30	0.13
	Pravastatin treatment	0.97	0.77–1.22	0.79
1c	On-treatment LDLc	1.08	0.98–1.18	0.12
	Pravastatin treatment	0.93	0.77–1.11	0.40
2a	Baseline HDLc	0.83	0.67–1.04	0.10
	Pravastatin treatment	0.84	0.73–0.97	0.02
2b	Baseline HDLc	0.84	0.68–1.05	0.12
	Change in HDLc	1.32	0.85–2.04	0.22
	Pravastatin treatment	0.83	0.72–0.96	0.01
2c	On-treatment HDLc	0.72	0.54–0.96	0.02
	Pravastatin treatment	0.47	0.28–0.78	0.0036
	Interaction HDL×pravastatin treatment	1.59	1.08–2.32	0.02
3a	Baseline LDLc/HDLc	1.06	0.99–1.14	0.08
	Pravastatin treatment	0.84	0.73–0.97	0.02
3b	Baseline LDLc/HDLc	1.11	1.03–1.20	0.0083
	Change in LDLc/HDLc	1.17	1.02–1.35	0.02
	Pravastatin treatment	1.01	0.82–1.24	0.91
3c	On-treatment LDLc/HDLc	1.11	1.03–1.20	0.0067
	Pravastatin treatment	0.95	0.81–1.12	0.54
4a	Baseline total/HDLc	1.05	1.00–1.11	0.07
	Pravastatin treatment	0.84	0.73–0.97	0.02
4b	Baseline total/HDLc	1.08	1.02–1.15	0.0065
	Change in total/HDLc	1.14	1.03–1.27	0.02
	Pravastatin treatment	1.00	0.82–1.21	0.97
4c	On-treatment total/HDLc	1.09	1.03–1.15	0.0043
	Pravastatin treatment	0.94	0.80–1.10	0.44

HR indicates hazard ratio. Other abbreviations are as defined in text. CI is given for a 1-SD change in lipoproteins as continuous variables or for the categorical variable of treatment allocation.

*Models included age, sex, blood pressure, smoking, history of hypertension, and history of diabetes (see Table 4).

predict CHD risk to apply an appropriate intervention strategy. The present findings indicate that the level of LDLc by itself is unhelpful as a guide to the aggressiveness of intervention or as a goal for therapy.

HDLc is established as a cardioprotective factor that shows an inverse relation to CHD.[21,22] This lipoprotein is believed to act in a number of ways to prevent progression of atherosclerosis and the appearance of its clinical manifestations. HDLc is thought to mediate the process of reverse cholesterol transport, whereby cholesterol in peripheral tissues is carried back to the liver for export from the body.[23] Recently, it has been reported that HDLc also possesses antioxidant and anti-inflammatory properties and so may block key pathways in atherogenesis.[21] The finding in PROSPER of an inverse relation between HDLc and risk of coronary events in the elderly is concordant with other recent studies[24,25] and indicates strongly that assessment of this lipoprotein fraction is critical in the prediction of risk in older people. PROSPER subjects in the lowest compared with the highest quintile of HDLc had an ≈2-fold increase in CHD risk. Pravastatin treatment, it appears, virtually eliminated the link between low HDLc and risk, with those on active therapy showing no discernible association of HDLc with event rate. Furthermore, patients with an initial HDLc in the top 3 quintiles (>1.15 mmol/L) showed little benefit from receiving pravastatin, whereas the RR reduction for the 40% (bottom 2 quintiles) with low HDLc (<1.15 mmol/L) was substantial, approximately one third. This blunting of the relation between HDLc and risk has been reported before for the Air Force/Texas Coronary Atherosclerosis Prevention study[26] but is not a usual feature of statin treatment. In the majority of trials, HDLc remained as strong a determinant of CHD risk in statin-treated subjects as it did in those on placebo.[17,18,27]

TABLE 4. Representative Multivariate Model of Treatment Effect on Lipid Levels*

Variable	HR	CI	P
Baseline LDLc/HDLc†	1.11	1.03–1.20	0.0083
Change in LDLc/HDLc†	1.17	1.02–1.35	0.02
Pravastatin treatment	1.01	0.82–1.24	0.91
Age	1.05	1.03–1.07	<0.0001
Systolic blood pressure†	1.08	0.99–1.17	0.08
Diastolic blood pressure†	0.89	0.82–0.97	0.0075
Smoker, yes	1.10	0.92–1.30	0.29
History of hypertension, yes	1.08	0.92–1.27	0.34
Male sex	1.49	1.29–1.72	<0.0001
History of diabetes, yes	1.45	11.19–1.78	0.0003

HR indicates hazard ratio. Other abbreviations are as defined in text.

*The complete multivariate analysis for model 3b is given in Table 3. Nonlipid risk factors are featured similarly in the other models in Table 3.

†Change in risk associated with a 1-SD change in the variable. For age, HR was for a 1-year increment.

The apparent ability of pravastatin to ameliorate the risk associated with low HDLc in the elderly has a number of potential explanations. For example, if the deleterious effect of low HDLc is due to inflammation, then statins, which have anti-inflammatory actions,[28,29] may act as an effective substitute and eliminate this risk. Alternatively, the drug may have promoted the process of reverse cholesterol transport, which was compromised by the low HDLc level, although the pravastatin-induced rise in HDLc was modest, so it is unlikely that an increase in the circulating mass of this lipoprotein was responsible. More likely, pravastatin redressed an imbalance between the rate of cholesterol deposition in arteries, mediated by LDLc, and the capacity for reverse cholesterol transport. The ratio of LDLc to HDLc or of total cholesterol to HDLc provides a crude index of forward versus reverse cholesterol transport. It was of interest to observe that these ratios were positively related to risk in PROSPER, and their achieved value on statin therapy appeared to explain adequately the effects of the drug. Regardless of mechanism, these analyses suggest that statin use in the elderly corrects the increased CHD risk associated with low HDLc and the consequently elevated LDLc/HDLc.

Current management guidelines,[15,30] formulated mainly from epidemiological studies and trials conducted in middle-aged people, focus correctly on LDLc as a primary indicator of risk and use HDLc as an ancillary factor. This strategy, however, may not be appropriate for an elderly population. Herein, as the present analysis shows, LDLc was a poor predictor of risk and of the benefit achieved by statin therapy. HDLc, on the other hand, moved to the forefront both in the assessment of vascular risk and as an indicator as to which patients to target for lipid-lowering drugs. PROSPER showed that statin use in the elderly produces clear benefit in terms of CHD prevention during a relatively brief (3.2 years) period of treatment. The present report indicates further that a specific subgroup received most of the benefit, ie, those with an HDLc <1.15 mmol/L (<45 mg/dL) or an LDLc/HDLc >3.3. In such individuals, the risk reduction for coronary events was ≈33% rather than the 19% seen in the whole cohort. Focusing on this group reduces the number needed to treat to prevent 1 coronary event from 40 to 17 and hence, improves the effectiveness of intervention strategies.

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