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Novel Lipoprotein Subfraction and Size Measurements in Prediction of Mortality in Maintenance Hemodialysis Patients

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Summary

Background and objectives Conventional lipid profiles usually cannot predict cardiovascular outcomes in chronic disease states. We hypothesized that novel lipoprotein subfraction concentrations and LDL particle size measurements better predict mortality in maintenance hemodialysis (MHD) patients.

Design, setting, participants, & measurements Mortality-predictability of LDL particle diameter and lipoprotein subfraction concentrations, measured by novel ion mobility, was examined in a cohort of 235 hemodialysis patients who were followed for up to 6 years using Cox models with adjustment for important covariables.

Results Patients were 54 ± 14 years old (mean ± SD) and included 45% women with total, LDL and HDL cholesterol levels of 143 ± 42, 76 ± 29, and 37 ± 12 mg/dl, respectively. Over 6 years, 71 patients (31%) died. Conventional lipid profile was not associated with mortality. The death hazard ratio (HR, 95% confidence interval) of the highest *versus* lowest quartiles of very small and large LDL particle concentrations were 2.43 (1.03 to 5.72) and 0.38 (0.15 to 0.96), respectively. Across increasing quartiles of LDL particle diameter, death HRs were 1.00, 0.93 (0.46 to 1.87), 0.43 (0.21 to 0.89), and 0.45 (0.31 to 1.00), respectively.

Conclusions Whereas conventional lipid profile cannot predict mortality in MHD patients, larger novel LDL particle diameter or higher large LDL particle concentrations appear predictive of greater survival, whereas higher very small LDL particle concentration is associated with higher death risk. Examining lipoprotein subfraction modulation in chronic diseases is indicated.

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Introduction

The number of maintenance dialysis patients in the United States is currently over 400,000 and still growing fast (1). Two-thirds of all dialysis patients die within 5 years of initiation of dialysis treatment, a 5-year survival rate worse than that of many cancers (1). Approximately half of all dialysis patients die of cardiovascular disease (CVD) (1). In the general population, conventional serum levels of LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C) predict incident atherosclerotic CVD (2). Nevertheless, similar to individuals with chronic heart failure (CHF), the conventional CVD risk factors such as hypercholesterolemia are not associated with mortality in these patients; indeed in both dialysis and CHF patients, a low, rather than a high, serum total cholesterol (TC) or LDL-C is associated with higher mortality, a phenomenon known as lipid paradox or reverse epidemiology (3–6). Hence, novel CVD biomarkers including novel lipid measures are needed to more reliably risk-stratify dialysis or CHF patients.

Each lipoprotein class consists of a continuous spectrum of particles of different size, density, metabolism, and atherogenic effect (7). Various studies have evaluated the associations of small LDL subfraction concentration (8), total LDL particle concentration (LDL-Pc) (8), specific HDL subfractions (9,10), and combined measures such as the LDL-C/HDL-C and apoB/apoA-I ratios (11–13) with cardiovascular risk. However, studies on chronic kidney disease (CKD) patients are scarce and often limited to conventionally measured TC and LDL-C (3–6). What remains to be determined is what measures of lipoprotein help better identify high risk dialysis patients and whether LDL-altering strategies are more effective in this population than LDL-lowering medications. Measuring novel lipoprotein particle concentrations, diameter, and subfractions may be a means to this end. To directly measure lipoprotein particle diameter and subfraction concentrations with high resolution, we used a novel ion mobility method, to our knowledge for the first time in CKD patient population (14,15).

This study examines which of the different aspects of conventional (triglycerides [TGs] and cholesterol) and novel lipoprotein measurements (total particle concentration (Pc) including HDL-Pc and LDL-Pc, LDL particle diameter [LDL-Pd] and subfraction-Pc) can better identify maintenance hemodialysis (MHD) patients with an increased death risk. We hypothesized that lipoprotein-Pc and LDL-Pd can better predict prospective mortality in MHD patients when compared with conventional lipid profiles.

Study Population and Methods

Patient Population

We studied MHD patients who participated in the Nutritional and Inflammatory Evaluation in Dialysis (NIED) Study (16). The original patient cohort was derived over 5 years from a pool of over 3000 MHD outpatients in eight DaVita chronic dialysis facilities in the South Bay Los Angeles area (see the NIED Study website at www.NIED-Study.org for more detail) (17–20). Included were outpatients who underwent MHD treatment for at least 8 weeks, who were 18 years or older, and who signed the institutional review board–approved consent form. Participants with an anticipated life expectancy of <6 months (*e.g.* metastatic malignancy or advanced AIDS) were excluded. From October 1, 2001, through December 31, 2006, a total of 893 MHD patients from eight DaVita dialysis facilities in the Los Angeles South Bay area provided informed consent to participate in the NIED study. Approximately one-fourth of these patients (235 patients including 106 women) were invited randomly to come to the Harbor-UCLA General Clinical Research Center to undergo additional tests including lipid profile and body composition tests (16).

Anthropometric Measures

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively. Portable near infrared (NIR) interactance technology was utilized in the eight participating dialysis clinics to estimate lean body mass. A commercial near-infrared interactance sensor with a coefficient of variation of 0.5% for total body-fat measurements (portable Futrex 6100, Gaithersburg, MD, www.futrex.com) was used. NIR measurements were performed by placing a Futrex sensor on the nonvascular-access upper arm for several seconds and entering the required data (date of birth, gender, weight, and height). NIR measurements of body fat have been shown to correlate significantly with other body-fat measures in MHD patients (20).

Laboratory Tests

Predialysis blood samples and postdialysis serum urea nitrogen were obtained on a mid-week day in the fasting state. The single-pool Kt/V was used to represent the weekly dialysis dose (21). Except as indicated below, all of the laboratory measurements were performed by DaVita Laboratories (Deland, FL) using automated methods. In this study, 3-month averaged values were used, and all of the laboratory measurements used established assays with well known coefficients of variation. Serum C-reactive protein (CRP) was measured by a turbidometric immunoassay (WPCI, Osaka, Japan, unit: mg/L, normal range < 3.0 mg/L). Circulating IL-6 and TNF-α cytokines were measured with immunoassay kits (R&D Systems, Minneapolis, MN; units: pg/ml; normal range: IL-6 < 9.9 pg/ml, TNF-α < 4.7 pg/ml). CRP and the cytokines were measured in the General Clinical Research Center Laboratories of Harbor-UCLA (22). Total homocysteine was determined by high-performance liquid chromatography, and serum transthyretin (prealbumin) was determined by immunoprecipitation analysis (23).

LDL-C concentration levels were calculated with Friedewald formula, except when TG exceeded 400 mg/dl. Lipoproteins were fractionated into very small, small, medium, and large LDL subfractions from archived baseline plasma samples using an ion mobility method as described previously (14,15). This method uses an ion separation/particle detector system that fractionates lipoprotein particles from the small HDL particles to the large very LDL (VLDL) particles and directly counts each lipoprotein particle to permit the determination of lipoprotein particle concentration. Since the original publication of the method, refinements to the technique have been made that address concerns about the method (15). These refinements were fully incorporated into the ion mobility measurements used for this study and are described in previous studies (14,15). Assay characteristics for the ion mobility are as follows: interassay variation for LDL-Pd was <1.0% for higher concentration subfractions, HDL and LDL, the CV ranged from 13 to 20% and for lower concentration subfractions, intermediate density lipoprotein (IDL) and VLDL, CVs were 17 to 30%. The diameter ranges (in angstroms, Å) used for each subfraction are as follows: HDL small, 76.5 to 105.0; HDL large, 105.0 to 145.0; LDL very small, 180.0 to 208.2; LDL small, 208.2 to 214.1; LDL medium, 214.1 to 220.0; LDL large, 220.0 to 233.3; IDL small, 233.0 to 250.0; IDL large, 250.0 to 296.0; VLDL small, 296.0 to 335.0; VLDL medium, 335.0 to 424.0; and VLDL large, 424.0 to 520.0. The ratio of large/small LDL-Pc was calculated using the concentrations of the two subfractions in the sizes listed above. Figure 1 shows a schematic diagram of different aspects of conventional and novel LDL and HDL measurements.

Statistical Methods

Spearman correlation coefficient (r) was used for analyses of linear associations. ANOVA or Kruskal-Wallis tests were used as appropriate to examine differences across groups. Death hazard ratios (HRs) were obtained using Cox proportional hazard models after controlling for the relevant covariates. We performed incremental levels of multivariate adjustment: (*1*) Case-mix variables included age, gender, race/ethnicity, diabetes, dialysis vintage, modified Charlson comorbidity score, and dialysis dose (single pool Kt/V); (*2*) lipids included LDL and HDL-C and TG concentrations; (*3*) malnutrition-inflammation complex syndrome (MICS) variables included serum or blood levels of phosphorus, albumin, creatinine, calcium, ferritin, hemoglobin, normalized protein catabolic rate; and body mass index (BMI); and (*4*) adjustment for three inflammatory markers (CRP, IL-6, and TNF-α). We used quartile analyses to disclose nonlinear associations. To examine interaction between lipoprotein measures and

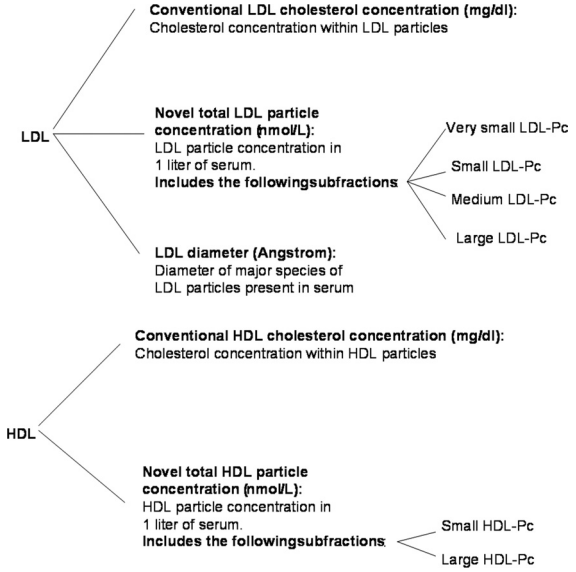

Figure 1. | Schematic diagram of different aspects of LDL and HDL measurements.

MICS, a composite variable combining serum albumin, CRP, and IL-6 levels was used to dichotomize the study population into two subgroups on the basis of the presence or absence of MICS defined as achievement of *a priori* cutoffs for any of the three variables according to the study by Liu *et al.* (5), *i.e.* serum albumin < 3.6 mg/dl, CRP > 10 mg/L, and IL-6 > 11 pg/ml, corresponding to the 10^{th}, 90^{th}, and 75^{th} percentiles of these three markers, respectively, from the Third National Health and Nutrition Examination Survey (NHANES-III) (15). If P values for interaction were significant (<0.05), patients were stratified into corresponding groups. A restricted cubic spline graph was utilized on the basis of Cox regression models to illustrate systematic relations between LDL size and mortality. This method also served to examine the nonlinear associations as an alternative to assumptions concerning linearity (24). Descriptive and multivariate statistics were carried out with the statistical software Stata version 10.0 (Stata Corporation, College Station, TX).

Results

Baseline demographic, clinical, and laboratory values in the 235 MHD patients according to gender and BMI are shown in Table 1. The patients' mean age ± SD was 54 ± 14 years; 45% of patients were women ($n = 106$), and 26% ($n = 61$) were African American. The median (interquartile range) of dialysis vintage was 44 months (range, 29 to 71 months). TG, TC, and LDL-C were highest among women with high BMI, and HDL-C was highest among women with low BMI. Table 2 shows the correlation coefficients of relevant measures with the subfractions of LDL-Pc and HDL-Pc. The four conventional lipid measures, serum TC, LDL-C, HDL-C, and TG, were correlated with all subfractions of LDL-Pc. HDL-C was associated negatively with small and medium LDL-Pc and positively with large HDL-Pc. LDL-Pd was correlated positively with very small and large LDL-Pc and negatively with small HDL-Pc. Scatter plots of correlations of conventional serum LDL-C and HDL-C with novel large LDL-Pc and large HDL-Pc concentrations indicated correlation coefficients of $r = 0.34$ ($P < 0.01$) and $r = 0.23$ ($P < 0.01$), respectively (see supplemental Figure S1).

Over the 6 years of the cohort, 71 MHD patients (31%) died. We calculated the death HR across the quartiles of conventionally measured serum LDL-C and HDL-C and novel LDL-Pc and HDL-Pc. As shown in Table 3, no association was observed between LDL-C, HDL-C, or LDL-Pc and mortality in MHD patients. However, the highest quartile of the total HDL-Pc was associated with 2.2-fold higher death risk. VLDL and IDL cholesterol concentrations were not associated with increased or decreased mortality either (data not shown).

We also examined the mortality-predictabilities of novel lipid-Pc and LDL-Pd measures by calculating the death HR across their quartiles, highest *versus* lowest. Figure 1 shows schematic diagrams of different aspects of LDL and HDL measurements.

Among novel subfractions of LDL-P, the highest concentrations of very small and large LDL-P were associated with highest and lowest mortality, respectively, especially after adjustment for case mix, conventional lipids, MICS and inflammation (Table 4). No association was observed between novel small and large HDL-Pc and mortality (see supplemental Table S1 in supplemental materials).

The death HRs were also calculated for the quartiles of LDL-Pd (Table 5) and large/small LDL-Pc ratio (see supplemental Table S1). There was no significant association in the unadjusted models. However, both measures were associated with decreased mortality after adjustment for case mix, conventional lipids, MICS, and inflammation. The death HRs (first to fourth quartiles) for quartiles were 1.0, 0.93 (0.46 to 1.87), 0.43 (0.21 to 0.89), and 0.45 (0.31 to 1.00) for LDL-Pd and 1.0, 0.64 (0.31 to 1.32), 0.51 (0.25 to 1.02), and 0.43 (0.20 to 0.95), respectively, for quartiles of the large/small LDL-Pc ratio (see supplemental Table S1). These relationships were verified in cubic spline analyses examining Cox based multivariate-adjusted association between smaller LDL-Pd and higher mortality (see supplemental Figure S2). Hence, in Cox-based multivariate-adjusted analysis, smaller LDL-Pd was associated with higher mortality. We also calculated the net reclassification improvement for LDL particle diameter, very small and large LDL. They were 0.05 ($P = 0.25$), 0.22 ($P < 0.01$), and 0.03 ($P = 0.47$), respectively.

To investigate whether the novel lipid measures can help better risk-stratify MHD patients, we examined the mortality predictability of the combinations of novel LDL-Pd with conventional LDL-C by dichotomizing all subjects into below-median *versus* above-median LDL-C (median: 73 mg/dl) as well as below-median *versus* above-median LDL-Pd (median: 216.5 Å), leading to four (2×2) mutually exclusive groups. As shown in Figure 2, above-median LDL-C combined with above-median LDL-Pd was associated with the lowest death risk. This figure illustrates the statistical interactions, in that above-median *versus* below-median serum LDL-C appeared paradoxically protective in the context of above-median LDL-Pd but within the below-median LDL-Pd, above-median serum LDL-C was

Table 1. Baseline demographic, clinical, and laboratory values in 235 MHD patients according to sex and BMI

	Total	Women (n = 106)		Men (n = 129)		P
		BMI < 27	BMI ≥ 27	BMI < 27	BMI ≥ 27	
n	235	57	49	80	49	
Age (year)	54 ± 14	57 ± 14	56 ± 15	51 ± 15	52 ± 13	0.06
BMI (kg/m^2)	27.4 ± 6.8	22.8 ± 2.6	33.5 ± 6.0	23.3 ± 2.1	33.5 ± 7.1	<0.01
African Americans (%)	26	21	33	26	24	0.59
Hispanic (%)	52	54	45	49	61	0.37
Diabetes mellitus (%)	58	47	67	55	67	0.09
Charlson comorbidity score	1.8 ± 1.5	1.7 ± 1.3	1.8 ± 1.4	1.8 ± 1.5	2.3 ± 1.6	0.20
Dialysis vintage (months)	44 (29 to 71)	46 (34 to 78)	34 (23 to 73)	47 (29 to 74)	39 (26 to 63)	0.21
Body fat (%) via NIR	45.0 ± 29.3	36.5 ± 25.9	75.6 ± 25.9	23.8 ± 10.7	58.6 ± 33.3	<0.01
Dialysis dose, Kt/V (sp)	1.67 ± 0.31	1.79 ± 0.30	1.70 ± 0.34	1.62 ± 0.29	1.56 ± 0.25	<0.01
Serum albumin (mg/dl)	4.05 ± 0.45	3.92 ± 0.41	3.94 ± 0.32	4.15 ± 0.40	4.04 ± 0.31	<0.01
Creatinine (mg/dl)	9.7 ± 2.8	9.0 ± 2.7	8.9 ± 2.0	10.3 ± 3.0	10.4 ± 2.9	<0.01
CRP (mg/dl)	3.5 (1.7 to 6.7)	2.2 (1.1 to 5.0)	4.7 (2.7 to 7.3)	2.9 (1.3 to 5.8)	4.7 (2.7 to 7.8)	<0.01
IL-6(mg/dl)	6.0 (3.8 to 12.0)	4.9 (3.4 to 11.4)	8.0 (4.4 to 10.9)	5.9 (3.4 to 12.9)	7.3 (4.2 to 12.8)	0.32
TNF-α (mg/dl)	3.5 (2.4 to 4.6)	3.5 (1.9 to 4.6)	3.7 (2.1 to 4.5)	3.5 (2.6 to 4.4)	3.5 (2.5 to 5.1)	0.86
Conventional lipid measurements						
triglyceride (mg/dl)	153 ± 11	118 ± 52	196 ± 113	133 ± 86	180 ± 160	<0.01
total cholesterol (mg/dl)	143 ± 42	135 ± 37	166 ± 50	133 ± 34	146 ± 42	<0.01
LDL-C (mg/dl)	76 ± 29	68 ± 26	88 ± 29	72 ± 28	80 ± 32	<0.01
HDL-C (mg/dl)	37 ± 12	43 ± 15	37 ± 14	36 ± 10	32 ± 9	<0.01
Novel LDL particle measures						
total LDL-Pc (nmol/L)	255 ± 154	215 ± 156	299 ± 171	241 ± 149	281 ± 162	0.02
very small LDL-Pc (nmol/L)	101 ± 66	87 ± 46	119 ± 78	95 ± 63	111 ± 73	0.04
small LDL-Pc (nmol/L)	30 ± 22	23 ± 13	38 ± 29	27 ± 17	37 ± 27	<0.01
medium LDL-Pc (nmol/L)	34 ± 25	27 ± 19	42 ± 30	32 ± 23	40 ± 27	<0.01
large LDL-Pc (nmol/L)	89 ± 64	79 ± 65	100 ± 69	87 ± 62	94 ± 57	0.34
LDL-Pd (angstrom)	215 ± 10	217 ± 10	213 ± 10	217 ± 10	214 ± 10	0.06
Novel HDL particle measures						
total HDL-Pc (nmol/L)	2773 ± 3500	2921 ± 3805	2324 ± 1873	3038 ± 4084	2616 ± 3387	0.69
small HDL-Pc (nmol/L)	2228 ± 3309	2328 ± 3575	1777 ± 1768	2511 ± 3852	2101 ± 3252	0.66
large HDL-Pc (nmol/L)	566 ± 399	603 ± 426	547 ± 377	583 ± 432	514 ± 331	0.66

Both conventional and novel lipid measures are included for comparison. All of the values are presented as the means ± SD or percentages except for variables that are not normally distributed (vintage, CRP, IL-6, and TNF-α), for which we used interquartile range. All of the analyses are ANOVA, except for variables that are not normally distributed (vintage, CRP, IL-6, and TNF-α), for which we used a Kruskal-Wallis test. LDL-C, LDL cholesterol; LDL-Pc, LDL particle concentration; LDL-Pd, LDL particle diameter; HDL-C, HDL cholesterol; TG, triglyceride; CRP, C-reactive protein; BMI, body mass index; NIR, near infrared.

Table 2. Spearman's correlation coefficients showing r values among traditional and novel lipid measurements and other relevant variables in 235 maintenance MHD patients

	Novel LDL particle measures				Novel HDL particle measures	
	Very small LDL-Pc	Small LDL-Pc	Medium LDL-Pc	Large LDL-Pc	Small HDL-Pc	Large HDL-Pc
Age	0.05	−0.04	0.02	−0.01	−0.17[c]	0.08
Vintage	−0.11	−0.13[c]	−0.11	−0.10	0.05	−0.06
Charlson comorbidity score	0.01	−0.02	0.01	0.02	0.05	0.00
BMI	0.18[d]	0.17[d]	0.16[c]	0.08	0.00	−0.02
NIR fat mass percent	**0.21**[d]	0.09	0.07	0.03	0.01	0.00
TG[a]	**0.39**[d]	**0.43**[d]	**0.43**[d]	**0.33**[d]	0.15	0.01
TC[a]	**0.33**[c]	**0.36**[d]	**0.38**[d]	**0.37**[d]	0.09	0.01
LDL-C[a]	**0.21**[d]	**0.28**[d]	**0.29**[d]	**0.33**[d]	0.04	−0.06
HDL-C[a]	−0.07	**−0.23**[d]	**−0.21**[d]	−0.15[c]	−0.07	0.14[c]
Total LDL-Pc[b]	**0.87**[d]	**0.96**[d]	**0.93**[d]	**0.89**[d]	**0.34**[d]	**0.35**[d]
Very small LDL-Pc[b]	—	**0.87**[d]	**0.77**[d]	**0.66**[d]	**0.41**[d]	**0.33**[d]
Small LDL-Pc[b]	**0.87**[d]	—	**0.95**[d]	**0.84**[d]	**0.35**[c]	**0.25**[d]
Medium LDL-Pc[b]	**0.77**[d]	**0.95**[d]	—	**0.93**[d]	**0.27**[d]	**0.24**[d]
Large LDL-Pc[b]	**0.66**[d]	**0.84**[d]	**0.93**[d]	—	**0.25**[d]	**0.29**[d]
Total HDL-Pc[b]	**0.55**[d]	**0.29**[d]	**0.21**[d]	0.17[c]	**0.85**[d]	**0.52**[d]
Small HDL-Pc[b]	**0.41**[c]	**0.35**[d]	**0.27**[d]	0.01	—	0.11
Large HDL-Pc[b]	**0.33**[d]	**0.25**[d]	**0.24**[d]	**0.25**[d]	0.11	—
LDL-Pd[b]	**0.31**[d]	−0.11	−0.02	**0.29**[d]	**−0.20**[d]	−0.09
CRP	−0.01	0.00	0.00	−0.06	−0.01	−0.09
IL-6	−0.11	−0.12	−0.15[c]	−0.14[c]	0.00	0.00
TNF-α	−0.06	−0.06	−0.04	−0.03	0.02	−0.17[d]
Dietary data						
energy intake	0.03	0.00	−0.06	−0.09	−0.16	0.04
SAFA intake	0.04	0.02	−0.07	−0.10	−0.15	0.07
MUFA intake	−0.02	−0.01	−0.09	−0.12	−0.11	0.01
PUFA intake	−0.10	−0.13	**−0.20**	−0.19	−0.13	−0.03
SGA	−0.12	−0.16[c]	−0.15[c]	−0.12	−0.03	−0.02

NIR: near infrared; LDL-C, LDL cholesterol; LDL-Pc, LDL particle concentration; HDL-C, HDL cholesterol; TG, triglyceride; TC, total cholesterol; CRP, C-reactive protein; SAFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, poly unsaturated fatty acid; SGA, subjective global assessment.
[a]Conventional (traditional) lipid markers.
[b]Novel lipoprotein markers.
[c]$P < 0.05$.
[d]$P < 0.01$ (r values ≥ 0.20 are bold).

associated with a trend toward a 47% higher death risk. Figure 3 shows the Kaplan-Meier proportion of surviving according to the four aforementioned categories of LDL-Pd and LDL-C concentration, which were consistent with the Cox models. We also implemented the same 2 × 2 approach to examine the mortality predictability of the four combinations of total LDL-Pc and LDL-Pd by dichotomizing each into above-median *versus* below-median. The median value for total LDL-Pc was 216 nmol/L. We also calculated death hazard ratios of conventional LDL-C, HDL-C, and novel total LDL-P concentrations across above-median and below-median values of novel LDL-P diameter, in that median values were used to dichotomize each measure forming a two-by-two table. After multivariate adjustments, above-median total LDL-Pc combined with above-median LDL-Pd was associated with the lowest death risk, *i.e.* 74% lower mortality compared with below-median total LDL-Pc combined with below-median LDL-Pd. However, *P* values for interaction with LDL-Pd were NS (>0.17).

Discussion

We examined the mortality predictability of both traditional and novel measures of lipoproteins and their particle and subfraction concentrations including LDL-Pd in a cohort of 235 MHD patients who were followed for up to 6 years and found that novel lipoprotein measures could better predict outcomes of MHD patients. Prior studies have indicated a lipid paradox in dialysis patients, in that lower serum TC and LDL-C are paradoxically associated with higher death risk (3,4,25). Hence, novel lipoprotein measures may more accurately reflect the increased cardiovascular risk in this patient population (26). To our knowledge, this is the first investigation in any group of patients with chronic disease states to describe an association between such novel lipoprotein subfractions including LDL-Pd and prospective outcomes including mortality.

We found that conventional TC, LDL-C and HDL-C were not able to predict mortality, consistent with the previous literature in CKD and CHF patient population. Higher HDL-Pc was associated with higher death risk.

Table 3. Death hazard ratios (95% confidence intervals) according to quartiles of conventional LDL-C and HDL-C and novel LDL-Pc and HDL-Pc in 235 maintenance MHD patients who were followed for up to 6 years (2001 to 2007)

	Q1	Q2	Q3	Q4	*P* for trend
Conventional LDL					
n	62	58	59	56	
LDL-C (mg/dl)	<55	55 to 72	73 to 94	>94	
unadjusted	1	1.25 (0.66 to 2.37)	0.88 (0.44 to 1.78)	1.16 (0.61 to 2.20)	0.90
case mix[a] + lipids[b]	1	1.11 (0.56 to 2.19)	0.98 (0.47 to 2.05)	1.21 (0.58 to 2.50)	0.71
previous + MICS[c+] inflammation[d]	1	1.41 (0.68 to 2.89)	1.16 (0.52 to 2.58)	1.43 (0.65 to 1.15)	0.49
Conventional HDL					
n	64	55	62	54	
HDL-C (mg/dl)	<29	29 to 34	35 to 44	>44	
unadjusted	1	0.95 (0.48 to 1.92)	1.10 (0.58 to 2.13)	1.52 (0.80 to 2.91)	0.19
case mix + lipids	1	0.77 (0.37 to 1.62)	0.92 (0.44 to 1.90)	0.85 (0.40 to 1.81)	0.80
previous + MICS[+] inflammation	1	0.92 (0.41 to 2.02)	1.19 (0.52 to 2.74)	0.99 (0.43 to 2.23)	0.93
Novel LDL particle					
n	60	59	58	58	
total LDL-Pc (nmol/L)	<144	144 to 215	216 to 315	>315	
unadjusted	1	0.89 (0.46 to 1.73)	0.93 (0.47 to 1.82)	0.87 (0.45 to 1.69)	0.72
case mix + lipids	1	0.76 (0.37 to 1.55)	1.29 (0.61 to 2.73)	1.04 (0.48 to 2.27)	0.60
previous + MICS[+] inflammation	1	0.46 (0.20 to 1.04)	1.36 (0.62 to 2.98)	0.84 (0.35 to 2.03)	0.65
Novel HDL particle					
n	59	59	59	58	
total HDL-Pc (nmol/L)	<936	936 to 1466	1467 to 2919	>2919	
unadjusted	1	0.86 (0.42 to 1.77)	1.03 (0.52 to 2.08)	1.50 (0.78 to 2.87)	0.18
case mix + lipids	1	1.00 (0.47 to 2.11)	1.58 (0.76 to 3.27)	1.69 (0.86 to 3.32)	0.07
previous + MICS[+] inflammation	1	1.05 (0.48 to 2.29)	1.44 (0.67 to 3.11)	**2.22 (1.02 to 4.81)**[e]	**0.03**

LDL-C, LDL cholesterol; LDL-Pc, LDL particle concentration; HDL-C, HDL cholesterol.
[a]Case mix included age, gender, race/ethnicity, diabetes mellitus, dialysis vintage, modified Charlson comorbidity score and dialysis dose (single pool Kt/V).
[b]Lipids included total LDL and HDL particle concentrations and triglyceride.
[c]Malnutrition-inflammation complex syndrome (MICS) variables included serum or blood levels of phosphorus, albumin, creatinine, calcium, ferritin, hemoglobin, normalized protein catabolic rate (also known as normalized protein nitrogen appearance), and body mass index.
[d]Inflammatory markers include serum concentrations of C-reactive protein, interleukin-6, and tumor necrosis factor-α.
[e]Significant values are in bold ($P < 0.05$).

Prognostic factors for survival in these patients were, however, novel LDL-P subfraction concentrations and LDL-Pd. Decreased LDL-Pd, indicating smaller LDL particle size, was associated with an increased death risk even after adjustment for demographics, comorbidities, and conventional measurements of lipids, nutritional status, and inflammation. Higher concentrations of very small LDL-P were associated with higher mortality, whereas higher concentrations of large LDL-P were associated with greater survival. We also found that larger (above-median) LDL-Pd with either above-median or below-median total LDL-Pc was associated with greater survival. As it might be expected, with below-median LDL-Pd, the highest risk of mortality was associated with above-median levels of LDL-C. However, somewhat surprisingly, above-median LDL-Pc combined with below-median LDL-Pd had a lower risk of mortality than below-median LDL-Pd and below-median LDL-Pc. Whereas neither one of these groups reached statistical significance, it is interesting to note that the trends of each are in different directions with below-median LDL-Pd, above-median LDL-C, and above-median LDL-Pc showing increased and decreased risk, respectively. This would suggest that the LDL-C content of the LDL particles in this population may not be proportional to the LDL-Pd. It is generally assumed that the larger the LDL particle, the more cholesterol it contains. Our data may indicate a difference in particle composition in dialysis patients. We also found that larger LDL-Pd with either above-median or below-median total HDL-C tended to correlate with greater survival. These observations need to be investigated further.

Conventional chemical measures of lipid concentration have long been the most used clinical measurements of lipid profile. However, in chronic disease states such as CKD and CHF, these measures do not appear to predict outcomes (27). There is increasing evidence and recognition of the value of more sophisticated lipid measurements. Total LDL-Pc and LDL-Pd show tighter correlation with atherosclerotic progression and cardiovascular events than conventional LDL-C (28,29). Indeed, conventional LDL-C can be low, yet total LDL-Pc may be high, and cardiovascular events rates may be increased. Conversely, conventional LDL-C can be high, yet total LDL-Pc low, especially in the setting of low cardiovascular risk. These scenarios are more likely to be the case in chronic disease

Table 4. Death hazard ratios (95% confidence intervals) according to quartiles of the novel LDL-P subfractions (very small LDL-P, small LDL-P, medium LDL-P, and large LDL-P) in 235 maintenance MHD patients who were followed for up to 6 years (2001 to 2007)

	Q1	Q2	Q3	Q4	*P* for trend
Very small LDL-P					
n	58	60	59	58	
very small LDL-Pc (nmol/L)	<57	57 to 87	88 to 121	>121	
unadjusted	1	0.84 (0.42 to 1.70)	0.93 (0.45 to 1.91)	1.54 (0.82 to 2.89)	0.13
case mix[a] + lipids[b]	1	0.90 (0.43 to 1.90)	1.18 (0.53 to 2.59)	**2.44 (1.10 to 5.44)**[e]	**0.02**
previous + MICS[c+] inflammation[d]	1	0.67 (0.29 to 1.55)	0.88 (0.38 to 2.05)	**2.43 (1.03 to 5.72)**[e]	**0.03**
Small LDL-P					
n	62	60	59	54	
small LDL-Pc (nmol/L)	<15	15 to 24	25 to 36	>36	
unadjusted	1	1.57 (0.83 to 2.97)	1.68 (0.56 to 2.34)	0.92 (0.45 to 1.89)	0.63
case mix + lipids	1	1.60 (0.84 to 3.06)	1.43 (0.69 to 2.93)	1.40 (0.61 to 3.19)	0.43
previous + MICS[+] inflammation	1	1.36 (0.67 to 2.73)	1.73 (0.82 to 3.61)	1.23 (0.49 to 3.12)	0.41
Medium LDL-P					
n	64	55	57	59	
medium LDL-Pc (nmol/L)	<17	47 to 26	27 to 46	>46	
unadjusted	1	1.42 (0.74 to 2.72)	1.32 (0.67 to 2.58)	0.87 (0.43 to 1.78)	0.65
case mix + lipids	1	1.50 (0.76 to 2.97)	1.64 (0.80 to 3.33)	1.17 (0.51 to 2.68)	0.60
previous + MICS[+] inflammation	1	1.24 (0.60 to 2.58)	2.07 (0.98 to 4.37)	1.15 (0.46 to 2.91)	0.37
Large LDL-P					
n	63	55	59	58	
large LDL-Pc (nmol/L)	<44	44 to 76	77 to 105	>105	
unadjusted	1	0.70 (0.37 to 1.34)	0.88 (0.47 to 1.62)	**0.45 (0.22 to 0.92)**[e]	**0.05**
case mix + lipids	1	0.63 (0.31 to 1.28)	0.68 (0.34 to 1.37)	**0.37 (0.16 to 0.87)**[e]	**0.04**
previous + MICS[+] inflammation	1	0.51 (0.23 to 1.12)	0.96 (0.45 to 2.05)	**0.38 (0.15 to 0.96)**[e]	0.13

LDL-Pc, LDL particle concentration.
[a]Case mix included age, gender, race/ethnicity, diabetes mellitus, dialysis vintage, modified Charlson comorbidity score and dialysis dose (single pool Kt/V).
[b]Lipids included LDL and HDL cholesterol concentrations and triglyceride plus large LDL and very small LDL in the analysis of quartiles of very small LDL and large LDL, respectively.
[c]Malnutrition-inflammation complex syndrome (MICS) variables included serum or blood levels of phosphorus, albumin, creatinine, calcium, ferritin, hemoglobin, normalized protein catabolic rate (also known as normalized protein nitrogen appearance), and body mass index.
[d]Inflammatory markers include serum concentrations of C-reactive protein, interleukin-6, and tumor necrosis factor-α.
[e]Significant values are in bold ($P < 0.05$).

Table 5. Death hazard ratios (and 95% confidence intervals) according to quartiles of the novel LDL-Pd in 235 maintenance MHD patients who were followed for 6 years (2001 to 2007)

LDL particle diameter quartiles	Q1	Q2	Q3	Q4	*P* for trend
n	61	57	59	58	
LDL particle diameter (A)	<211.4	211.4 to 216.4	216.5 to 222.1	>222.8	
unadjusted	1	0.76 (0.40 to 1.43)	0.65 (0.34 to 1.23)	0.70 (0.37 to 1.33)	0.22
case mix[a] + lipids[b]	1	0.97 (0.50 to 1.86)	**0.49 (0.25 to 0.96)**[e]	0.52 (0.25 to 1.09)	**0.03**
previous + MICS[c+] inflammation[d]	1	0.93 (0.46 to 1.87)	**0.43 (0.21 to 0.89)**[e]	**0.45 (0.31 to 1.00)**[e]	**0.02**

[a]Case mix included age, gender, race/ethnicity, diabetes mellitus, dialysis vintage, modified Charlson comorbidity score, and dialysis dose (single pool Kt/V).
[b]Lipids included LDL and HDL cholesterol concentrations and triglyceride.
[c]Malnutrition-inflammation complex syndrome (MICS) variables included serum or blood levels of phosphorus, albumin, creatinine, calcium, ferritin, hemoglobin, normalized protein catabolic rate (also known as normalized protein nitrogen appearance), and body mass index.
[d]Inflammatory markers include serum concentrations of C-reactive protein, interleukin-6, and tumor necrosis factor-α.
[e]Significant values are in bold ($P < 0.05$).

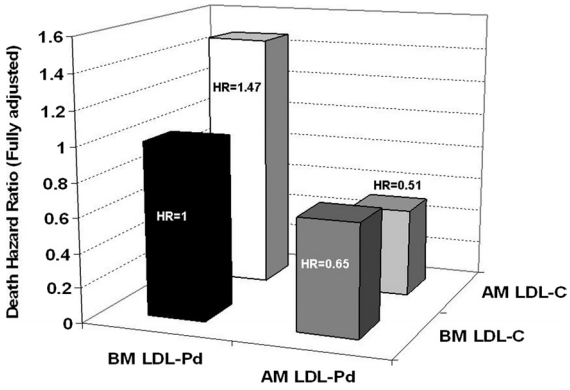

Figure 2. | Bar diagram of hazard ratio of death according to categories (above median [AM] or below median [BM]) of LDL-C and LDL-P diameter after full adjustment. Median values for LDL-C and LDL-Pd are 73 mg/dl and 216.5 A, respectively. Full adjustment means adjustment for case mix (age, gender, race/ethnicity, diabetes mellitus, dialysis vintage, modified Charlson comorbidity score, and dialysis dose [single pool Kt/V]), lipids (triglyceride, LDL, and HDL particle concentration), malnutrition-inflammation complex syndrome (serum or blood levels of phosphorus, albumin, creatinine, calcium, ferritin, hemoglobin, normalized protein catabolic rate [also known as normalized protein nitrogen appearance], and body mass index), and inflammation (CRP, IL6, and TNF-α).

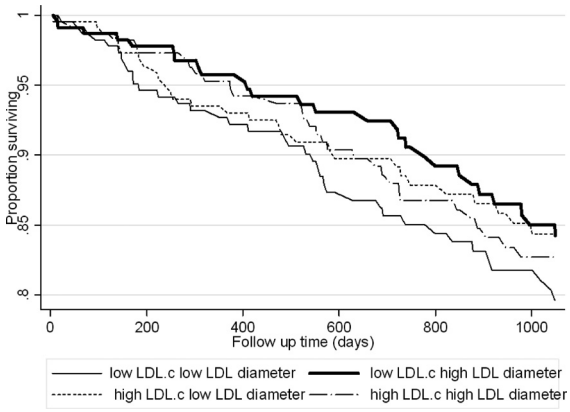

Figure 3. | Kaplan-Meier proportion of surviving MHD patients after 5 years of observation according to the categories of LDL cholesterol concentration and LDL particle diameter in 235 MHD patients.

states such as CKD and CHF where conventional lipid concentrations may be confounded by wasting syndrome and MICS (30).

Conventional lipid measurements such as LDL-C and HDL-C have not proven to be of great assistance in MHD patients in assessing cardiovascular or death risk (27). This was also observed in our current study where measurement of LDL-Pd and LDL-P subfraction concentration better identified MHD individuals at increased risk of death for up to 6 years thereafter. It is unclear whether the increased risk associated with very small LDL-Pc is a reflection of an increased atherogenic potential of very small LDL particles or simply a consequence of the broader pathophysiology of which very small LDL-P is a part. The association of LDL-Pd and its subfraction concentrations with death was independent of conventional LDL-C and HDL-C or inflammation. In our study, adjustments for case mix and lipids as well as MICS increased the robustness of the ion mobility measured novel LDL parameter for predicting mortality, suggesting that the LDL-Pd and subfraction concentrations are superior predictors of mortality independent of conventional lipid measurements.

Our study should be qualified for its limited sample size, which excludes further analysis on the association of lipoprotein subfractions and CVD mortality or subgroup analyses. Second is the selection bias during enrollment, in that healthier patients were more likely to enroll leading to a substantially lower mortality rate compared with the national data (1). Another type of selection bias known as the prevalence-incidence or survivor bias is also likely because we recruited prevalent patients. However the latter types of biases would bias the results toward the null; therefore, without this bias, our results may have been even stronger. Third is the observational design rather than interventional. Fourth is the lack of information regarding dialysis access, dialysis membrane, and several other factors related to treatment, although in DaVita dialysis clinic treatment, patterns are rather uniform. Fifth is the potential confounding of therapy with cholesterol-lowering agents (statins), which was not examined because only 12% of the patients received statins at some point in time during the cohort; this low proportion is consistent with prior studies (31) and likely related to an inherently low LDL levels among most U.S. dialysis patients (3). Finally, relatively high CVs for some of the assays may have diluted potentially positive associations, and hence some null findings should be interpreted with caution. There are several strengths to this study including the relatively long follow-up period (up to 72 months), comprehensive laboratory evaluations, the concomitant assessments of body composition data, and the detailed evaluation of the clinical and comorbid states of the patients by study physicians. A unique feature of this study is its novelty in assessing lipoprotein subfractions, because we used a novel ion mobility method (14,15) that directly measures lipoprotein-Pc and size with high resolution.

Conclusions

In MHD patients, smaller-sized LDL-Pd and higher concentrations of very small LDL-P are associated with increased mortality, whereas a higher concentration of larger sized LDL-P is associated with decreased risk of death. Given that no prior study in the general population has evaluated the incremental value of lipoprotein subfractions beyond traditional cardiovascular risk factors, the clinical utility of these measurements requires additional studies including randomized controlled trials to examine whether modulation of lipoprotein subfraction can improve outcomes.

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Disclosures

M.P.C., W.A.S., and R.E.R. are employees of Quest Diagnostics, which has developed the lipid particle measurement methods.

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