COMPARISON OF C-REACTIVE PROTEIN AND LOW-DENSITY LIPOPROTEIN CHOLESTEROL LEVELS IN THE PREDICTION OF FIRST CARDIOVASCULAR EVENTS

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ABSTRACT

Background Both C-reactive protein and low-density lipoprotein (LDL) cholesterol levels are elevated in persons at risk for cardiovascular events. However, population-based data directly comparing these two biologic markers are not available.

Methods C-reactive protein and LDL cholesterol were measured at base line in 27,939 apparently healthy American women, who were then followed for a mean of eight years for the occurrence of myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes. We assessed the value of these two measurements in predicting the risk of cardiovascular events in the study population.

Results Although C-reactive protein and LDL cholesterol were minimally correlated (r=0.08), base-line levels of each had a strong linear relation with the incidence of cardiovascular events. After adjustment for age, smoking status, the presence or absence of diabetes mellitus, categorical levels of blood pressure, and use or nonuse of hormone-replacement therapy, the relative risks of first cardiovascular events according to increasing quintiles of C-reactive protein, as compared with the women in the lowest quintile, were 1.4, 1.6, 2.0, and 2.3 ($P<0.001$), whereas the corresponding relative risks in increasing quintiles of LDL cholesterol, as compared with the lowest, were 0.9, 1.1, 1.3, and 1.5 ($P<0.001$). Similar effects were observed in separate analyses of each component of the composite end point and among users and nonusers of hormone-replacement therapy. Overall, 77 percent of all events occurred among women with LDL cholesterol levels below 160 mg per deciliter (4.14 mmol per liter), and 46 percent occurred among those with LDL cholesterol levels below 130 mg per deciliter (3.36 mmol per liter). By contrast, because C-reactive protein and LDL cholesterol measurements tended to identify different high-risk groups, screening for both biologic markers provided better prognostic information than screening for either alone. Independent effects were also observed for C-reactive protein in analyses adjusted for all components of the Framingham risk score.

Conclusions These data suggest that the C-reactive protein level is a stronger predictor of cardiovascular events than the LDL cholesterol level and that it adds prognostic information to that conveyed by the Framingham risk score. (N Engl J Med 2002;347:1557-65.)

BECAUSE of its critical importance in atherogenesis, low-density lipoprotein (LDL) cholesterol is the focus of current guidelines for the determination of the risk of cardiovascular disease.[1] However, atherothrombosis often occurs in the absence of hyperlipidemia, and recent consensus panels assembled by the National Heart, Lung, and Blood Institute and the Centers for Disease Control and Prevention have concluded that population-based data on other risk factors are urgently needed.[2,3]

Among the biologic markers considered by those panels, there was particular interest in C-reactive protein, a marker of inflammation that has been shown in several prospective, nested case–control studies to be associated with an increased risk of myocardial infarction,[4-9] stroke,[4,6,10,11] sudden death from cardiac causes,[12] and peripheral arterial disease.[13] Although the results of these studies are highly consistent, limitations inherent in the design of nested case–control studies make it difficult to assess the relative merit of C-reactive protein. In particular, population-based cutoff points for C-reactive protein remain uncertain, and reliable data describing receiver-operating-characteristic curves for C-reactive protein have not been available. Moreover, there are insufficient data from prospective cohort studies directly comparing the predictive value of C-reactive protein with that of LDL cholesterol.

In a previous hypothesis-generating report limited to 122 women in whom cardiovascular disease developed (case patients) and 244 controls who were participants in the Women's Health Study, we observed that several markers of inflammation, including C-reactive protein, had prognostic value for the detection of first vascular events over a three-year period.[6] However, the relatively small number of events and the short follow-up limit the reliability of those data. Furthermore, because of the matched-pairs case–control study design, we were unable to define general population-

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based cutoff points or to evaluate directly characteristics of C-reactive protein used as a diagnostic test.

To overcome these limitations, we measured C-reactive protein and LDL cholesterol in all 27,939 participants in the Women's Health Study who provided usable base-line blood samples; these women had been followed for a mean of eight years. Using these data, we were able to calculate survival curves associated with C-reactive protein levels, to compare the predictive value of C-reactive protein and LDL cholesterol directly in a large, representative population sample, and to define the population distribution of C-reactive protein levels. We also determined the predictive value of each biologic marker among users and nonusers of hormone-replacement therapy; this is a clinically relevant issue, since hormone-replacement therapy affects levels of both C-reactive protein and LDL cholesterol.[14-16] Finally, we evaluated whether C-reactive protein provided prognostic information on risk after adjustment for all components of the Framingham risk score.

METHODS

Study Design

The Women's Health Study is an ongoing evaluation of aspirin and vitamin E for the primary prevention of cardiovascular events among women 45 years of age or older. Participants were enrolled between November 1992 and July 1995, at which time they provided information regarding demographic, behavioral, and lifestyle factors. All participants were followed for the occurrence of first cardiovascular events, including nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization procedures, and death from cardiovascular causes. The occurrence of myocardial infarction was considered confirmed if symptoms met the criteria of the World Health Organization and if the event was associated with abnormal levels of cardiac enzymes or diagnostic electrocardiographic criteria. Stroke was confirmed if the participant had new neurologic deficits that persisted for more than 24 hours. Computed tomographic scans or magnetic resonance images were available for the great majority of events and were used to distinguish hemorrhagic from ischemic events. The performance of either percutaneous coronary revascularization or coronary-artery bypass surgery was confirmed by a review of hospital records. Deaths from cardiovascular causes were confirmed by review of autopsy reports, death certificates, medical records, and information obtained from family members.

Before randomization, blood samples were collected in tubes containing EDTA from 28,345 study participants and stored in liquid nitrogen until the time of analysis. Samples were then transferred to a core laboratory facility, where they were assayed for C-reactive protein with a validated, high-sensitivity assay (Denka Seiken) and for LDL cholesterol with a direct-measurement assay (Roche Diagnostics). This laboratory is certified for the measurement of lipids and is a core facility for ongoing standardization programs regarding the measurement of C-reactive protein. Of the samples received, 27,939 could be evaluated and were assayed for C-reactive protein and LDL cholesterol.

Statistical Analysis

Because hormone-replacement therapy affects levels of C-reactive protein and LDL cholesterol, we first established population-based distributions for each analyte among the 15,745 women who were not taking hormone-replacement therapy at study entry — a method consistent with the guidelines of the Department of Health and Human Services for lipid standardization.[17] We then divided these population data into increasing quintiles with respect to C-reactive protein and LDL cholesterol and constructed Kaplan–Meier curves for event-free survival. The relative risks of new cardiovascular events were computed for quintiles 2 through 5, as compared with the lowest quintile, in both crude Cox proportional-hazards models and models adjusted for risk factors. Stratified analyses were used to address the predictive value of LDL cholesterol and C-reactive protein among users and nonusers of hormone-replacement therapy at base line. To evaluate whether different cutoff points might affect the risk estimates for users of hormone-replacement therapy, we repeated the analysis among users with cutoff points for C-reactive protein and LDL cholesterol defined by the values in the 12,139 women who were using hormone-replacement therapy at base line. The 55 women for whom hormone-replacement status was unknown were excluded from the stratified analyses.

To estimate the discriminative value of predictive models, we calculated the C statistic on the basis of the minimal follow-up time of six years for both C-reactive protein and LDL cholesterol in crude and risk-factor–adjusted models. This statistic is analogous to the area under the receiver-operating-characteristic curve.[18] To compute the C statistic, we compared each woman's status with respect to cardiovascular disease (present or absent) at six years with the predicted six-year probability of event-free survival, estimated from the Cox proportional-hazards model. Subjects whose data were censored before six years of follow-up (less than 1 percent) were excluded from this calculation.

We tested for trend across the quintiles of C-reactive protein or LDL cholesterol by entering a single ordinal term for the quintile in the Cox regression model. In addition, we tested for deviation from linearity by comparing models containing quintile indicators with those containing a linear term in a likelihood-ratio test with 3 degrees of freedom. We also tested the additional prognostic

TABLE 1. DISTRIBUTION OF C-REACTIVE PROTEIN AND LDL CHOLESTEROL LEVELS AMONG 15,745 STUDY PARTICIPANTS WHO WERE NOT TAKING HORMONE-REPLACEMENT THERAPY AT THE TIME OF THE BASE-LINE BLOOD COLLECTION.

AGE GROUP	NO. OF WOMEN	PERCENTILE						
		5TH	10TH	25TH	50TH	75TH	90TH	95TH
		milligrams per liter						
C-reactive protein								
45–54 yr	10,075	0.17	0.25	0.52	1.31	3.18	6.15	8.80
55–64 yr	3,604	0.25	0.39	0.82	1.89	4.12	7.47	9.76
65–74 yr	1,862	0.33	0.46	0.91	1.99	3.92	6.79	8.77
≥75 yr	204	0.29	0.43	0.80	1.52	3.55	7.56	13.33
Total	15,745	0.19	0.29	0.61	1.52	3.48	6.61	9.14
		milligrams per deciliter*						
LDL cholesterol								
45–54 yr	10,075	72.7	82.1	97.6	117.3	139.6	162.5	178.2
55–64 yr	3,604	83.4	94.9	113.4	134.4	158.8	181.9	198.3
65–74 yr	1,862	86.4	97.0	115.1	137.0	157.9	183.5	199.3
≥75 yr	204	91.2	100.4	117.3	139.3	159.6	178.4	189.4
Total	15,745	75.8	85.3	102.4	123.7	147.4	170.5	187.2

*To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

contribution of quintiles of C-reactive protein or LDL cholesterol to models containing the other variable with a likelihood-ratio test with 4 degrees of freedom.

To evaluate joint effects, we repeated the analyses after classifying all study participants in one of four groups on the basis of whether their C-reactive protein and LDL cholesterol levels were above or below the respective study medians. Finally, using these data, we assessed whether C-reactive protein had independent predictive value after simultaneous adjustment for all components of the Framingham risk score[19] (including age, smoking status, categorical levels of blood pressure, presence or absence of diabetes mellitus, and high-density lipoprotein and LDL cholesterol levels) and whether C-reactive protein contributed information on risk beyond that conveyed by the 10-year risk calculated with the Framingham risk score and beyond the risk associated with LDL cholesterol, as defined by current guidelines.[1] All P values are two-tailed, and 95 percent confidence intervals were calculated.

RESULTS

Base-Line Characteristics

The mean age of the 27,939 women at base line was 54.7 years. Forty-four percent were current users of hormone-replacement therapy, 25 percent had hypertension, 12 percent were current smokers, and 2.5 percent had diabetes mellitus. The mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 25.9.

Distribution of C-Reactive Protein and LDL Cholesterol Levels

Table 1 presents data on the distribution of C-reactive protein and LDL cholesterol values among the

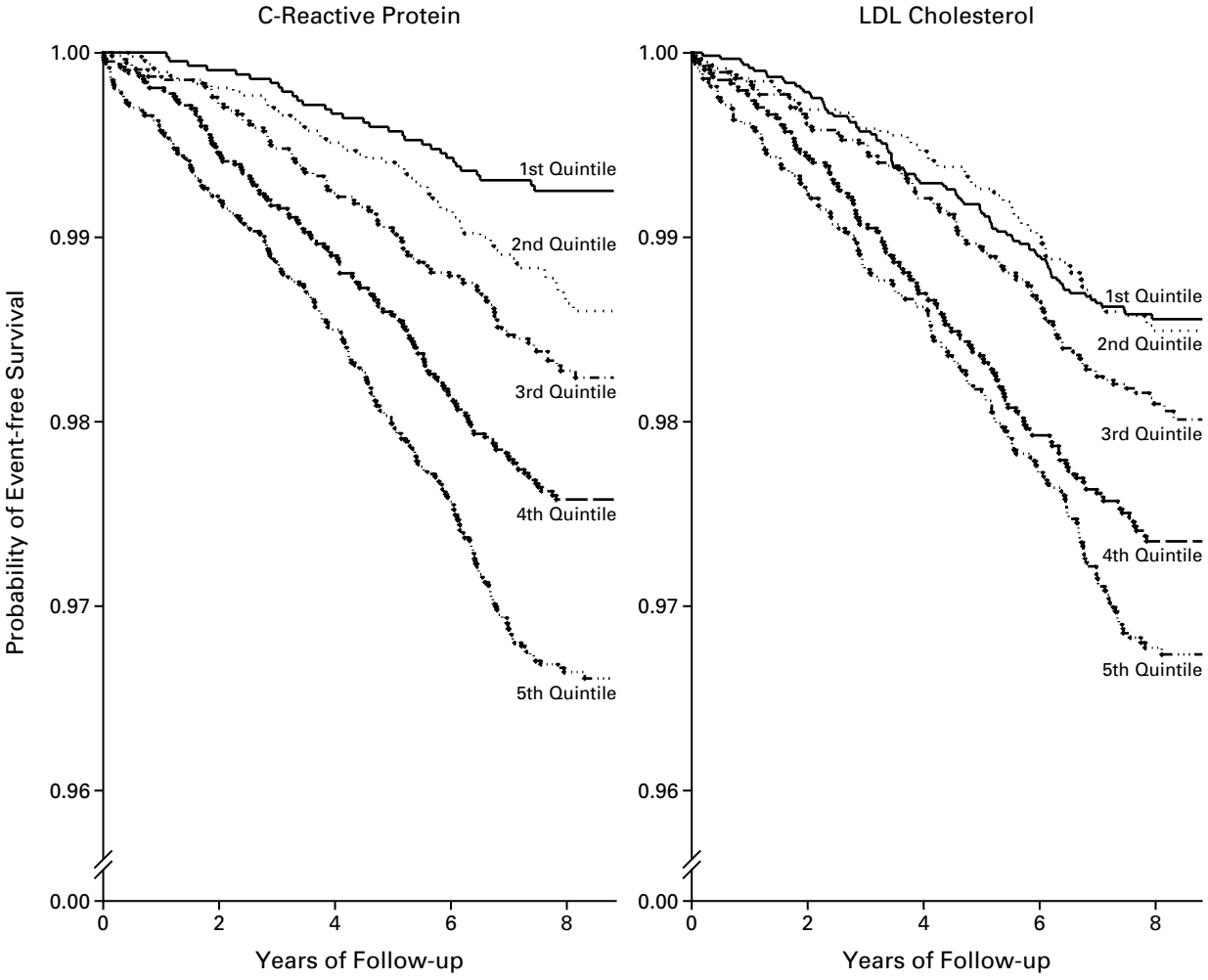

Figure 1. Event-free Survival According to Base-Line Quintiles of C-Reactive Protein and LDL Cholesterol.

The range of values for C-reactive protein was as follows: first quintile, ≤0.49 mg per liter; second quintile, >0.49 to 1.08 mg per liter; third quintile, >1.08 to 2.09 mg per liter; fourth quintile, >2.09 to 4.19 mg per liter; fifth quintile, >4.19 mg per liter. For LDL cholesterol, the values were as follows: first quintile, ≤97.6 mg per deciliter; second quintile, >97.6 to 115.4 mg per deciliter; third quintile, >115.4 to 132.2 mg per deciliter; fourth quintile, >132.2 to 153.9 mg per deciliter; fifth quintile, >153.9 mg per deciliter. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586. Note the expanded scale on the ordinate.

15,745 women who were not using hormone-replacement therapy at the time of blood collection. These distributions are very similar to those reported for men and women in previous U.S. and European studies. On the basis of this sample, the cutoff points for quintiles of C-reactive protein were less than or equal to 0.49, more than 0.49 to 1.08, more than 1.08 to 2.09, more than 2.09 to 4.19, and more than 4.19 mg per liter.

Event-free Survival

The probability of event-free survival for all study participants is presented in Figure 1 according to base-line quintiles of C-reactive protein and LDL cholesterol. Table 2 presents crude relative risks of a first cardiovascular event according to increasing quintiles of base-line C-reactive protein and LDL cholesterol, along with relative risks adjusted for age and other risk factors. For both C-reactive protein and LDL cholesterol, strong linear risk gradients were observed. After adjustment for age, smoking status, the presence or absence of diabetes, blood pressure, and use or nonuse of hormone-replacement therapy, the multivariable relative risks of a first cardiovascular event for women in increasing quintiles of C-reactive protein were 1.0 (the first quintile was the reference category), 1.4, 1.6, 2.0, and 2.3 ($P<0.001$), whereas the relative risks associated with increasing quintiles of LDL cholesterol were 1.0 (the first quintile was the reference category), 0.9, 1.1, 1.3, and 1.5 ($P<0.001$). No significant deviations from linearity in the log relative risks were detected in either model. The apparent superiority of C-reactive protein over LDL cholesterol in terms of the prediction of risk was observed in similar analyses of the individual components of the composite end point (coronary heart disease, stroke, and death from cardiovascular causes) (Fig. 2).

Predictive Models

Table 2 also presents results of the C statistic analyses (area under the receiver-operating-characteristic curve). In models of crude rates including the entire cohort (27,939 women), the calculated area under the receiver-operating-characteristic curve was 0.64 for C-reactive protein and 0.60 for LDL cholesterol. In prediction models including age, smoking status, presence or absence of diabetes, blood pressure, use or nonuse of hormone-replacement therapy, and treatment assignment, the ability of the model based on C-reactive protein to discriminate events from nonevents was virtually identical to that of the model based on LDL cholesterol (C statistic for both models, 0.81). However, the likelihood-ratio chi-square statistic was higher for the model based on C-reactive protein than for that based on LDL cholesterol (716.4 vs. 706.0, both with 16 df). This statistic, a more sensitive measure of model fit than the rank-based C statistic, suggests that the model based on C-reactive protein has better discrimination than the model based on LDL cholesterol. In addition, in likelihood-ratio tests of the contribution of each variable, the addition of C-reactive protein to the model based on LDL cholesterol was stronger (chi-square=25.4, 4 df;

TABLE 2. CRUDE, AGE-ADJUSTED, AND RISK-FACTOR–ADJUSTED RELATIVE RISK OF A FIRST CARDIOVASCULAR EVENT ACCORDING TO THE QUINTILE OF C-REACTIVE PROTEIN AND LDL CHOLESTEROL AT BASE LINE.*

VARIABLE	QUINTILE OF C-REACTIVE PROTEIN						
	1 (≤0.49 mg/liter)	2 (>0.49–1.08 mg/liter)	3 (>1.08–2.09 mg/liter)	4 (>2.09–4.19 mg/liter)	5 (>4.19 mg/liter)	P VALUE	AREA UNDER ROC CURVE
Crude relative risk (95% CI)	1.0	1.8 (1.1–2.7)	2.3 (1.5–3.4)	3.2 (2.2–4.8)	4.5 (3.1–6.6)	<0.001	0.64
Age-adjusted relative risk (95% CI)	1.0	1.5 (1.0–2.4)	1.8 (1.2–2.8)	2.5 (1.7–3.7)	3.6 (2.5–5.2)	<0.001	0.74
Risk-factor–adjusted relative risk (95% CI)	1.0	1.4 (0.9–2.2)	1.6 (1.1–2.4)	2.0 (1.3–3.0)	2.3 (1.6–3.4)	<0.001	0.81
	QUINTILE OF LDL CHOLESTEROL						
	1 (≤97.6 mg/dl)	2 (>97.6–115.4 mg/dl)	3 (>115.4–132.2 mg/dl)	4 (>132.2–153.9 mg/dl)	5 (>153.9 mg/dl)	P VALUE	AREA UNDER ROC CURVE
Crude relative risk (95% CI)	1.0	1.0 (0.8–1.4)	1.3 (1.0–1.8)	1.8 (1.4–2.4)	2.2 (1.7–2.9)	<0.001	0.60
Age-adjusted relative risk (95% CI)	1.0	0.9 (0.7–1.3)	1.1 (0.9–1.5)	1.5 (1.1–1.9)	1.7 (1.3–2.2)	<0.001	0.73
Risk-factor–adjusted relative risk (95% CI)	1.0	0.9 (0.7–1.2)	1.1 (0.8–1.4)	1.3 (1.0–1.7)	1.5 (1.1–2.0)	<0.001	0.81

*P values are for tests of trend across quintiles. ROC denotes receiver operating characteristic, and CI confidence interval. Risk-factor–adjusted relative risks have been adjusted for age, smoking status, the presence or absence of diabetes mellitus, blood pressure, and use or nonuse of hormone-replacement therapy. All models have been adjusted for treatment assignment. For all relative risks, the reference category is the first quintile. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

P< 0.001) than the addition of LDL cholesterol to the model based on C-reactive protein (chi-square= 15.0, 4 df; P=0.005).

Effects of Hormone-Replacement Therapy

Table 3 presents stratified analyses according to the use or nonuse of hormone-replacement therapy at base line. Among women who did not use hormone-replacement therapy, the multivariable-adjusted relative risks of a first cardiovascular event in increasing quintiles of C-reactive protein were 1.0, 1.8, 1.8, 2.4, and 3.0 (P<0.001), whereas the multivariable-adjusted relative risks in increasing quintiles of LDL cholesterol were 1.0, 0.8, 0.9, 1.1, and 1.4 (P=0.002). Among users of hormone-replacement therapy, risk estimates were lower for both C-reactive protein and LDL cholesterol but remained significant in crude and age-adjusted models. Risk estimates based on C-reactive protein among users of hormone-replacement therapy were similar regardless of whether the quintiles were defined by measurements in nonusers or users of hormone-replacement therapy.

Interactions between C-Reactive Protein and LDL Cholesterol

Of all events in the study participants, 77 percent occurred among those with LDL cholesterol levels below 160 mg per deciliter (4.14 mmol per liter), and 46 percent occurred among those with LDL cholesterol levels below 130 mg per deciliter (3.36 mmol per liter). However, C-reactive protein and LDL cholesterol levels were minimally correlated (r=0.08), suggesting that each biologic marker was detecting a different high-risk group. We therefore constructed survival curves after dividing the study participants into four groups on the basis of whether they were

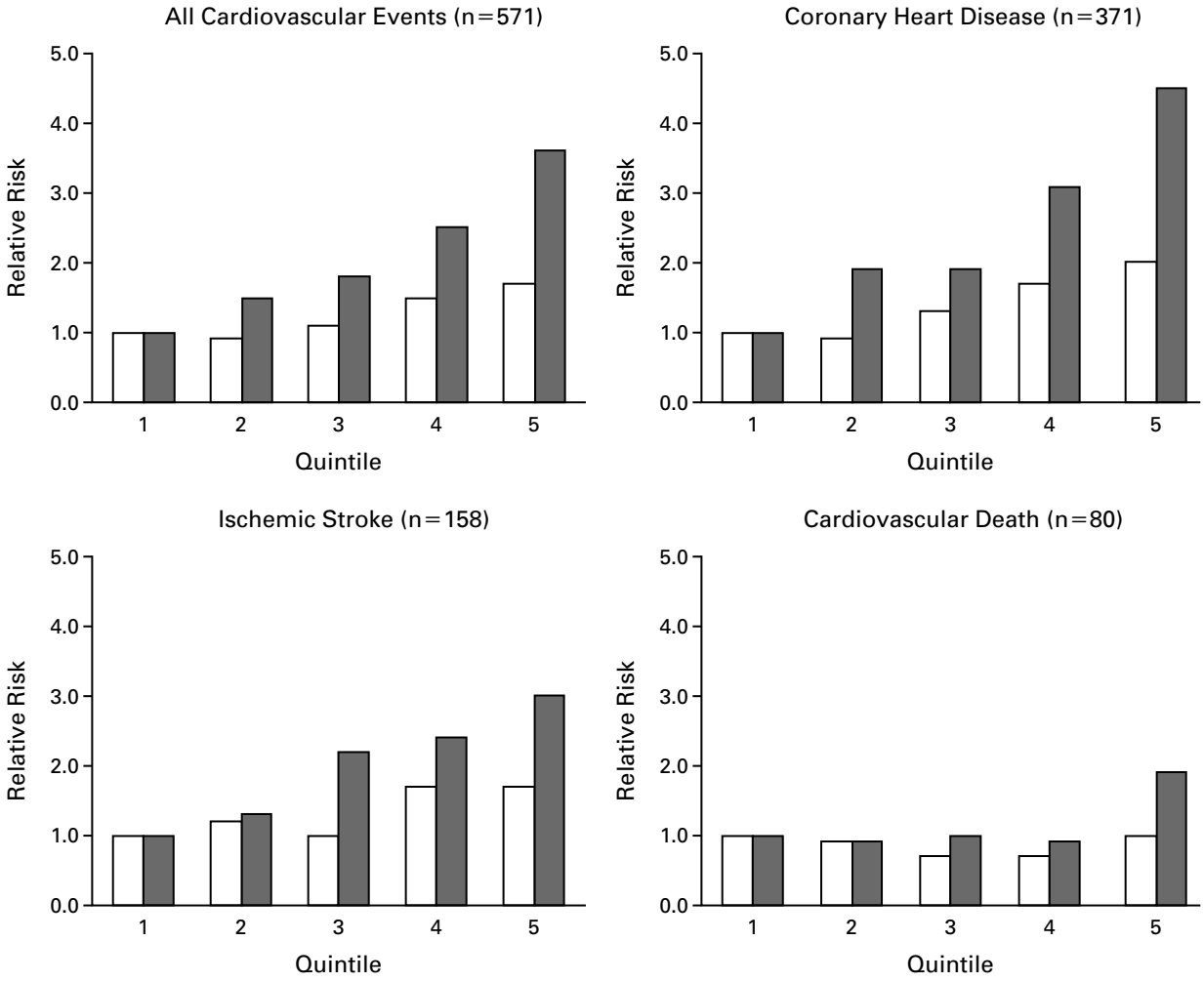

Figure 2. Age-Adjusted Relative Risk of Future Cardiovascular Events, According to Base-Line C-Reactive Protein Levels (Solid Bars) and LDL Cholesterol Levels (Open Bars).

TABLE 3. CRUDE, AGE-ADJUSTED, AND RISK-FACTOR–ADJUSTED RELATIVE RISK OF A FIRST CARDIOVASCULAR EVENT, ACCORDING TO THE QUINTILE OF C-REACTIVE PROTEIN AND LDL CHOLESTEROL AT BASE LINE, AMONG 12,139 WOMEN WHO USED POSTMENOPAUSAL HORMONE-REPLACEMENT THERAPY AND 15,745 WOMEN WHO DID NOT USE SUCH THERAPY.*

VARIABLE	QUINTILE OF C-REACTIVE PROTEIN						
	1	2	3	4	5	P VALUE	AREA UNDER ROC CURVE
Nonusers of HRT							
Crude relative risk	1.0	2.3	2.8	4.3	6.9	<0.001	0.67
Age-adjusted relative risk	1.0	1.9	2.2	3.2	5.4	<0.001	0.78
Risk-factor–adjusted relative risk	1.0	1.8	1.8	2.4	3.0	<0.001	0.84
Users of HRT							
Crude relative risk	1.0	1.0	1.5	1.9	2.4	<0.001	0.60
Age-adjusted relative risk	1.0	0.9	1.3	1.6	2.1	<0.001	0.69
Risk-factor–adjusted relative risk	1.0	0.9	1.1	1.3	1.3	0.08	0.77
	QUINTILE OF LDL CHOLESTEROL						
	1	2	3	4	5	P VALUE	AREA UNDER ROC CURVE
Nonusers of HRT							
Crude relative risk	1.0	1.0	1.2	1.8	2.6	<0.001	0.61
Age-adjusted relative risk	1.0	0.8	1.0	1.3	1.6	<0.001	0.75
Risk-factor–adjusted relative risk	1.0	0.8	0.9	1.1	1.4	0.002	0.84
Users of HRT							
Crude relative risk	1.0	1.1	1.5	1.8	1.7	0.001	0.58
Age-adjusted relative risk	1.0	1.1	1.3	1.7	1.5	0.005	0.68
Risk-factor–adjusted relative risk	1.0	1.0	1.3	1.5	1.5	0.02	0.77

*ROC denotes receiver operating characteristic, and HRT hormone-replacement therapy. P values are for tests of trend across quintiles. Risk-factor–adjusted relative risks have been adjusted for age, smoking status, presence or absence of diabetes mellitus, and blood pressure. All models have been adjusted for treatment assignment. For all relative risks, the reference category is the first quintile. For 55 women in the study, status with regard to hormone-replacement therapy was unknown.

above or below the median C-reactive protein value (1.52 mg per liter) and the median LDL cholesterol value (123.7 mg per deciliter [3.20 mmol per liter]). For the entire cohort (Fig. 3), the multivariable-adjusted relative risks were as follows: low C-reactive protein–low LDL cholesterol, 1.0 (this was the reference category); low C-reactive protein–high LDL cholesterol, 1.5 (95 percent confidence interval, 1.0 to 2.1); high C-reactive protein–low LDL cholesterol, 1.5 (95 percent confidence interval, 1.1 to 2.1); and high C-reactive protein–high LDL cholesterol, 2.1 (95 percent confidence interval, 1.5 to 2.8). The corresponding age-adjusted rates of events per 1000 person-years of follow-up were 1.3, 2.0, 2.6, and 3.9, respectively.

On the assumption that recent evidence from clinical trials will lead to a marked reduction in the use of hormone-replacement therapy among American women,[20] we sought to increase the generalizability of our findings by repeating these analyses including only the 15,745 women who were not using hormone-replacement therapy at base line. In this analysis, the multivariable-adjusted relative risks were as follows: low C-reactive protein–low LDL cholesterol, 1.0 (the reference category); low C-reactive protein–high LDL cholesterol, 1.5 (95 percent confidence interval, 1.0 to 2.4); high C-reactive protein–low LDL cholesterol, 1.7 (95 percent confidence interval, 1.1 to 2.6); and high C-reactive protein–high LDL cholesterol, 2.4 (95 percent confidence interval, 1.6 to 3.6). The corresponding age-adjusted rates of events per 1000 person-years were 1.2, 1.9, 3.1, and 4.5, respectively. As in the total cohort, event-free survival among nonusers of hormone-replacement therapy was worse in the high C-reactive protein–low LDL cholesterol group than in the low C-reactive protein–high LDL cholesterol group (Fig. 3).

C-Reactive Protein, LDL Cholesterol Categories, and the Framingham Risk Score

We performed several further analyses to evaluate the addition of measurements of C-reactive protein to the Framingham risk score and to the LDL cholesterol categories of less than 130, 130 to 160, and more than 160 mg per deciliter, which are defined in current guidelines for risk detection.[1] After adjustment for all components of the Framingham risk score,[19] quintiles of C-reactive protein remained a strong, independent predictor of risk in the cohort as a whole (relative risks of future cardiovascular events in increasing quintiles, 1.0, 1.3, 1.4, 1.7, and 1.9; $P<0.001$) and among nonusers of hormone-replacement therapy (relative risks, 1.0, 1.6, 1.5, 1.8, and 2.2; $P=0.001$). As shown in Figure 4, increasing levels of C-reactive protein were associated with increased risk of cardiovascular events at all levels of estimated 10-year risk based on the Framingham risk score.[19] Similarly, increasing C-reactive protein levels were associated with increased risk of cardiovascular events at LDL cholesterol levels below 130, 130 to 160, and above 160 mg per deciliter (Fig. 4).

DISCUSSION

The current study suggests that C-reactive protein, a marker of systemic inflammation, is a stronger predictor of future cardiovascular events than LDL cholesterol. In this study, C-reactive protein was superior to LDL cholesterol in predicting the risk of all study end points; this advantage persisted in multivariable analyses in which we adjusted for all traditional cardiovascular risk factors and was clear among users as well as nonusers of hormone-replacement therapy at base line. However, C-reactive protein and LDL cholesterol levels were minimally correlated. Thus, the combined evaluation of both C-reactive protein and LDL cholesterol proved to be superior as a method of

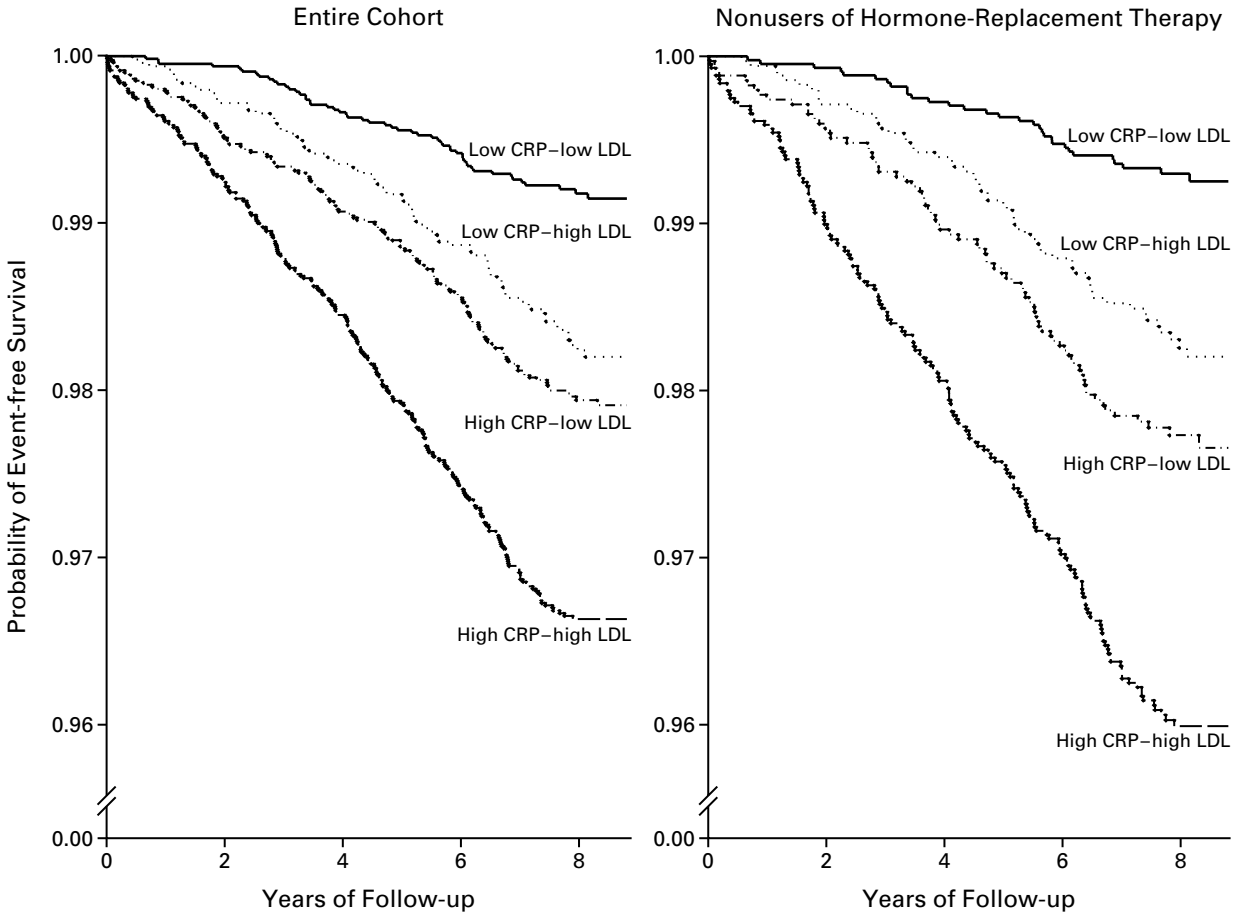

Figure 3. Event-free Survival among Women with C-Reactive Protein (CRP) and LDL Cholesterol Levels above or below the Median for the Study Population.

Data are shown for the entire cohort (27,939 women) and for women who were not taking hormone-replacement therapy at base line (15,745 women). The median values were as follows: for C-reactive protein, 1.52 mg per liter; for LDL cholesterol, 123.7 mg per deciliter (3.20 mmol per liter). Note the expanded scale on the ordinate.

risk detection to measurement of either biologic marker alone. Finally, at all levels of estimated 10-year risk for events according to the Framingham risk score and at all levels of LDL cholesterol, C-reactive protein remained a strong predictor of future cardiovascular risk.

In addition to their pathophysiological implications with regard to inflammation and atherothrombosis,[21-23] we believe these data have implications for the detection and prevention of cardiovascular disease. Seventy-seven percent of first cardiovascular events among the 27,939 women in this study occurred in those with LDL cholesterol levels below 160 mg per deciliter, and 46 percent occurred in those with levels below 130 mg per deciliter. Thus, large proportions of first cardiovascular events in women occur at LDL cholesterol levels below the threshold values for intervention and treatment in the current guidelines of the National Cholesterol Education Program.[1]

Our data also help establish the population distribution of C-reactive protein. That the cutoff points for the quintiles in the current population are very close to those previously described in smaller studies from the United States and Europe is reassuring and consistent with evidence describing the stability and reproducibility of values obtained for C-reactive protein with new, high-sensitivity assays.[24] These data also demonstrate that a single set of cutoff points for C-reactive protein in women can be used regardless of their status with regard to hormone-replacement therapy — an issue that has been of concern in previous work.[14-16]

The current data also have implications for the targeting of preventive therapies. We previously demonstrated in a randomized trial that statin therapy may have clinical value for primary prevention among persons with elevated C-reactive protein but low LDL cholesterol levels.[25] According to the survival analy-

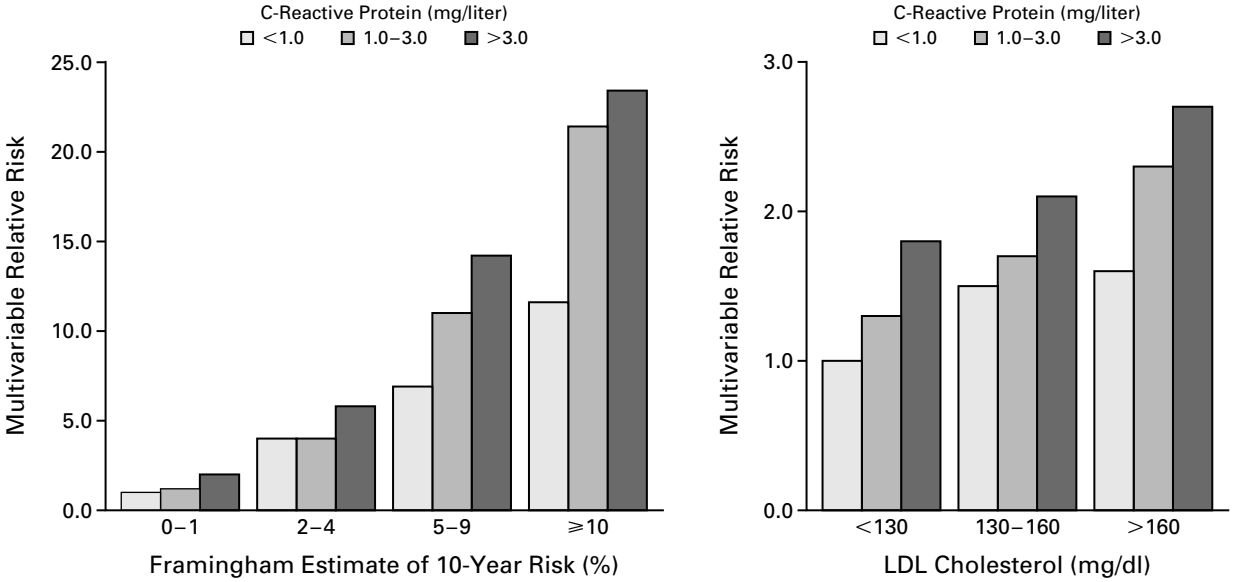

Figure 4. Multivariable-Adjusted Relative Risks of Cardiovascular Disease According to Levels of C-Reactive Protein and the Estimated 10-Year Risk Based on the Framingham Risk Score as Currently Defined by the National Cholesterol Education Program and According to Levels of C-Reactive Protein and Categories of LDL Cholesterol.

To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

ses in the current study (Fig. 3), women in the high C-reactive protein–low LDL cholesterol subgroup were at higher absolute risk than those in the low C-reactive protein–high LDL cholesterol subgroup, yet it is only the latter group for whom aggressive prevention is likely to be considered by most physicians. These observations suggest that continued reliance on LDL cholesterol to predict the risk of cardiovascular events will not lead to optimal targeting of statin therapy for primary prevention; this suggestion is consistent with data from the Heart Protection Study, in which LDL cholesterol levels did not predict the efficacy of statins for secondary prevention.[26] Our data thus strongly support the need for a large-scale trial of statin therapy among persons with low levels of LDL cholesterol but high levels of C-reactive protein.[27]

Unlike other markers of inflammation, C-reactive protein levels are stable over long periods, have no diurnal variation, can be measured inexpensively with available high-sensitivity assays, and have shown specificity in terms of predicting the risk of cardiovascular disease.[24,28-30] However, despite the consistency of prospective data in diverse cohorts,[4-13,16,25,31] decisions regarding the clinical use of C-reactive protein remain complex. To evaluate fully the clinical usefulness of any new biologic marker requires more than a direct comparison with LDL cholesterol or the Framingham risk score; other factors, such as lipid subfractions, triglycerides, Lp(a) lipoprotein, homocysteine, insulin resistance, and hypofibrinolysis, either in combination with or in place of other traditional markers, must also be taken into account. Furthermore, it is increasingly clear that no single common pathway is likely to account for all cardiovascular events and that interactions between novel biologic markers and more traditional risk factors, such as high blood pressure, smoking, obesity, diabetes, low levels of physical activity, and use of hormone-replacement therapy, may be more or less important for individual patients. Thus, as our findings indicate, new biologic and statistical approaches will be needed as information from basic vascular biology begins the transition into clinical practice.

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