Non–HDL Cholesterol, Apolipoproteins A-I and B<sub>100</sub>, Standard Lipid Measures, Lipid Ratios, and CRP as Risk Factors for Cardiovascular Disease in Women

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While measurement of total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) are recommended in most current cardiovascular screening algorithms, several investigations have suggested that superior risk prediction might be achieved by alternatively measuring apolipoproteins B<sub>100</sub> and A-I. At the same time, recent guidelines have emphasized the importance of non–HDL-C as a predictor of cardiovascular risk, while others have strongly advocated use of specific lipid ratios such as total cholesterol to HDL-C, LDL-C to HDL-C, apolipoprotein B<sub>100</sub> to apolipoprotein A-I, and apolipoprotein B<sub>100</sub> to HDL-C.

Despite these varied recommendations, direct comparative data are sparse, particularly among women. To address these issues, we evaluated baseline levels of each of these lipid biomarkers as predictors of first cardiovascular event in a large cohort of initially healthy women who were followed up prospectively over a 10-year period. We additionally compared the predictive value of each lipid marker to that of high-sensitivity C-reactive protein (CRP), which is an inflammatory biomarker previously shown to predict risk in this and other cohorts. To maximize the clinical utility of these data and reduce

Context Current guidelines for cardiovascular risk detection are controversial with regard to the clinical utility of different lipid measures, non–high-density lipoprotein cholesterol (non–HDL-C), lipid ratios, apolipoproteins, and C-reactive protein (CRP).

Objective To directly compare the clinical utility of total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C, non–HDL-C, apolipoproteins A-I and B<sub>100</sub>, high-sensitivity CRP, and the ratios of total cholesterol to HDL-C, LDL-C to HDL-C, apolipoprotein B<sub>100</sub> to apolipoprotein A-I, and apolipoprotein B<sub>100</sub> to HDL-C as predictors of future cardiovascular events in women.

Design, Setting, and Participants Prospective cohort study of 15,632 initially healthy US women aged 45 years or older (interquartile range, 48-59 years) who were enrolled between November 1992 and July 1995. All participants were followed up over a 10-year period for the occurrence of future cardiovascular events.

Main Outcome Measure Hazard ratios (HRs) and 95% confidence intervals (CIs) for first-ever major cardiovascular events (N = 464) according to baseline levels of each biomarker.

Results After adjustment for age, smoking status, blood pressure, diabetes, and body mass index, the HRs for future cardiovascular events for those in the extreme quintiles were 1.62 (95% CI, 1.17-2.25) for LDL-C, 1.75 (95% CI, 1.30-2.38) for apolipoprotein A-I, 2.08 (95% CI, 1.45-2.97) for total cholesterol, 2.32 (95% CI, 1.64-3.33) for HDL-C, 2.50 (95% CI, 1.68-3.72) for apolipoprotein B<sub>100</sub>, 2.51 (95% CI, 1.69-3.72) for non–HDL-C, and 2.98 (95% CI, 1.90-4.67) for high-sensitivity CRP (P < .001 for trend across all quintiles). The HRs for the lipid ratios were 3.01 (95% CI, 2.01-4.50) for apolipoprotein B<sub>100</sub> to apolipoprotein A-I, 3.18 (95% CI, 2.12-4.75) for LDL-C to HDL-C, 3.56 (95% CI, 2.31-5.47) for apolipoprotein B<sub>100</sub> to HDL-C, and 3.81 (95% CI, 2.47-5.86) for the total cholesterol to HDL-C (P < .001 for trend across all quintiles). The correlation coefficients between high-sensitivity CRP and the lipid parameters ranged from −0.33 to 0.15, and the clinical cut points for CRP of less than 1, 1 to 3, and higher than 3 mg/L provided prognostic information on risk across increasing levels of each lipid measure and lipid ratio.

Conclusions Non–HDL-C and the ratio of total cholesterol to HDL-C were as good as or better than apolipoprotein fractions in the prediction of future cardiovascular events. After adjustment for age, blood pressure, smoking, diabetes, and obesity, high-sensitivity CRP added prognostic information beyond that conveyed by all lipid measures.
the potential for uncontrolled confounding, we elected on an a priori basis to adjust all analyses for age, smoking status, blood pressure, diabetes, and body mass index.

METHODS
The study cohort was derived from participants in the Women’s Health Study (WHS), a randomized, double-blind, placebo-controlled, 2 × 2 factorial design trial of aspirin and vitamin E in the prevention of cardiovascular disease and cancer conducted among initially healthy women aged 45 years or older.10-21 Participants were enrolled between November 1992 and July 1995 at which time they provided baseline information on behavioral, lifestyle, and demographic risk factors. All participants have been followed up prospectively for the occurrence of first cardiovascular event including nonfatal myocardial infarction, nonfatal stroke, coronary revascularization procedures, and cardiovascular-related death. The methods of the cohort assembly, follow-up, and end-point validation have been described previously.15-21 All participants in the WHS provided written informed consent and the study protocol was approved by the institutional review board of the Brigham and Women’s Hospital (Boston, Mass).

Among WHS participants, 28,345 provided baseline blood samples that were stored in liquid nitrogen until the time of analysis. These samples underwent lipid analysis and evaluation for high-sensitivity CRP in a core laboratory certified by the National Heart, Lung, and Blood Institute/Centers for Disease Control and Prevention Lipid Standardization program. Levels of total cholesterol and HDL-C were measured enzymatically on a Hitachi 911 autoanalyzer (Roche Diagnostics, Basel, Switzerland) while LDL-C was determined directly (Genzyme, Cambridge, Mass). Levels of apolipoproteins B<sub>100</sub> and A-I were measured by an immunoturbidimetric technique on the Hitachi 911 analyzer.22 The assays for apolipoproteins A-I and B<sub>100</sub> used standards from the World Health Organiza-

tion and the International Federation of Clinical Chemistry and Laboratory Medicine and a validation study of these assays with those used at the Northwest Lipid Research Laboratory (Seattle, Wash) revealed a correlation coefficient of 1.0, intercept of 0.26 mg/dL, and slope of 0.97 for apolipoprotein B<sub>100</sub>, and a correlation coefficient of 0.99, intercept of 0.26 mg/dL, and a slope of 1.0 for apolipoprotein A-I. High-sensitivity CRP was measured using a validated immunoturbidimetric method (Denka Seiken, Tokyo, Japan).23 Of the samples that were received by the core laboratory, 27,748 (98%) underwent successful evaluation for each biomarker. Non–HDL-C was calculated by subtracting HDL-C from total cholesterol.

For the purposes of this lipid-based analysis, we followed guidelines from the Department of Health and Human Services for lipid standardization24 and limited analyses on an a priori basis to women not taking hormone therapy at baseline (N=15,632); there were no missing laboratory data among these women. Population distributions were computed for each biomarker and Spearman correlation coefficients were used to discern interrelationships between the various lipid fractions and each other, as well as high-sensitivity CRP. For each biomarker, we then divided the baseline levels into increasing quintiles and used Cox proportional hazard models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for future cardiovascular events comparing those in each of the quintiles 2 through 5 with those in the lowest (referent) quintile. Proportionality was confirmed by Wald χ² testing of interactions with natural logarithm of follow-up time. Also on an a priori basis, all analyses were simultaneously adjusted for age (years), blood pressure (Framingham categories), diabetes, current smoking status, and body mass index (calculated as weight in kilograms divided by the square of height in meters). Tests for trends across quintiles of each biomarker were addressed by entering a single ordinal term for each quintile based on the median value for that biomarker within each quintile. The magnitude of the likelihood ratio (LR) χ² statistic was used to evaluate the goodness of fit of predictive models associated with each marker individually. All analyses were controlled for randomized treatment assignment to aspirin and vitamin E.

In a prior analysis of this cohort, we demonstrated the predictive value of high-sensitivity CRP levels beyond that achievable by the use of LDL-C alone.23 To extend that analysis, we sought evidence that high-sensitivity CRP might have predictive value across all of the lipid biomarkers measured. This latter analyses was performed after dividing each lipid parameter into increasing tertiles and after classifying high-sensitivity CRP levels using the clinical cut points of less than 1, 1 to 3, and higher than 3 mg/L as recommended jointly by the American Heart Association and the Centers for Disease Control and Prevention.25 Data analysis was conducted using SAS statistical software version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS
Mean (SD) age at baseline for the 15,632 initially healthy women followed up in this study was 54.4 (7.6) years (interquartile range, 48-59 years) and the mean (SD) body mass index was 26.3 (5.3). A total of 1910 women (12%) were current smokers, 527 (3%) had diabetes, 3847 (25%) had a history of hypertension, and 1819 (13%) had a family history of myocardial infarction in a parent before age 60 years.

Baseline distributions of each lipid variable as well as that of high-sensitivity CRP are provided in TABLE 1. Values are similar to those anticipated in populations of healthy middle-aged women not taking hormone therapy.

TABLE 2 presents the Spearman correlation coefficients between each lipid parameter. As expected, strong correlations were observed between LDL-C and apolipoprotein B<sub>100</sub> (r=0.81), between LDL-C and non–HDL-C.
Apolipoprotein ($r=0.92$), between LDL-C and total cholesterol ($r=0.91$), between HDL-C and apolipoprotein A-I ($r=0.80$), between total cholesterol and non-HDL-C ($r=0.94$), and most importantly between non-HDL-C and apolipoprotein B$_{100}$ ($r=0.87$). The correlation coefficients between high-sensitivity CRP and the measured lipid parameters were $r=0.17$ for total cholesterol, $r=0.15$ for LDL-C, $r=-0.33$ for HDL-C, $r=0.27$ for non-HDL-C, $r=-0.19$ for apolipoprotein A-I, and $r=0.29$ for apolipoprotein B$_{100}$.

Over an average of 10 years of follow-up, rates of completed follow-up for the WHS exceeded 97% for morbidity and 99% for mortality. During this period, 464 participants developed a first-ever confirmed cardiovascular end point (131 myocardial infarction, 122 ischemic stroke, 274 coronary revascularization, and 76 cardiovascular death, with many women having $\geq 2$ of these end points). To avoid double counting, only the first event for the participant was used in these analyses.

The HRs for developing future cardiovascular events according to increasing quintiles of each lipid variable and high-sensitivity CRP are shown in Table 3. After adjustment for age (years), blood pressure (Framingham categories), body mass index, diabetes, and current smoking status, each of the measured parameters was strongly associated with risk of future cardiovascular events ($P<.001$ for trend across all quintiles). The assumption of the proportional hazards model was valid in our study in that for each biomarker, the interaction of the HR with $ln$ (time) was not significant ($P>.05$).

Of the lipid measures, the strongest association was observed with the highly intercorrelated variables non-HDL-C and apolipoprotein B$_{100}$ (Table 3). Specifically, the fully adjusted HR for those in the highest compared with lowest baseline quintile of non-HDL-C was 2.51 (95% CI, 1.69-3.72; LR $\chi^2$ statistic = 659.6) whereas the comparable value for apolipoprotein B$_{100}$ was 2.50 (95% CI, 1.68-3.72; LR $\chi^2$ statistic = 660.8). Both non-HDL-C (LR $\chi^2$ statistic = 642.2) and apolipoprotein B$_{100}$ (LR $\chi^2$ statistic = 636.3) showed stronger association than either total cholesterol or LDL-C in these data. By contrast, the magnitude of association for HDL-C appeared to be somewhat greater than that of apolipoprotein A-I.

High-sensitivity CRP levels also were associated with future cardiovascular events (Table 3); the fully adjusted HR for those in the highest compared with lowest baseline quintile of high-sensitivity CRP was 2.98 (95% CI, 1.90-4.67; LR $\chi^2$ statistic = 650.0). The LR $\chi^2$ statistic for high-sensitivity CRP was greater than that of total cholesterol and LDL-C but less than that of apolipoprotein B$_{100}$ and non–HDL-C, most likely reflecting modest correlations between high-sensitivity CRP and some of the nonlipid variables used in the multivariate adjustment. These direct comparative HRs and 95% CIs for those in the extreme quintiles of each measured parameter are presented in Figure 1.

Comparative data on risk associated with the ratios of total cholesterol to HDL-C, LDL-C to HDL-C, apolipoprotein B$_{100}$ to apolipoprotein A-I, and apolipoprotein B$_{100}$ to HDL-C appear in Table 3. By combining information on 2 components of lipid risk into a single clinical variable, all of these lipid ratios provided stronger evi-

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**Table 1.** Distribution of Lipid and C-Reactive Protein Levels at Study Entry Among 15 632 Initially Healthy Women

<table>
<thead>
<tr>
<th>Percentile Cutoffs</th>
<th>5th</th>
<th>10th</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>90th</th>
<th>95th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol, mg/dL</td>
<td>Total</td>
<td>149</td>
<td>161</td>
<td>181</td>
<td>206</td>
<td>234</td>
<td>263</td>
</tr>
<tr>
<td>LDL</td>
<td>76</td>
<td>85</td>
<td>102</td>
<td>124</td>
<td>147</td>
<td>171</td>
<td>187</td>
</tr>
<tr>
<td>HDL</td>
<td>32</td>
<td>35</td>
<td>41</td>
<td>49</td>
<td>59</td>
<td>69</td>
<td>77</td>
</tr>
<tr>
<td>Non-HDL</td>
<td>98</td>
<td>109</td>
<td>129</td>
<td>155</td>
<td>184</td>
<td>213</td>
<td>234</td>
</tr>
<tr>
<td>Apolipoprotein, mg/dL</td>
<td>A-I</td>
<td>110</td>
<td>116</td>
<td>127</td>
<td>140</td>
<td>156</td>
<td>171</td>
</tr>
<tr>
<td>B$_{100}$</td>
<td>62</td>
<td>70</td>
<td>83</td>
<td>99</td>
<td>121</td>
<td>140</td>
<td>153</td>
</tr>
<tr>
<td>High-sensitivity CRP, mg/L</td>
<td>0.2</td>
<td>0.3</td>
<td>0.6</td>
<td>1.5</td>
<td>3.5</td>
<td>6.6</td>
<td>9.1</td>
</tr>
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</table>

**Table 2.** Spearman Correlation Coefficients Between Measured Study Variables

<table>
<thead>
<tr>
<th>Correlation Coefficients</th>
<th>Cholesterol</th>
<th>Apolipoprotein</th>
<th>High-Sensitivity CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1.0</td>
<td>0.91</td>
<td>0.92</td>
</tr>
<tr>
<td>LDL</td>
<td>1.0</td>
<td>-0.03</td>
<td>0.92</td>
</tr>
<tr>
<td>HDL</td>
<td>1.0</td>
<td>-0.20</td>
<td>0.80</td>
</tr>
<tr>
<td>Non-HDL</td>
<td>1.0</td>
<td>-0.09</td>
<td>0.87</td>
</tr>
<tr>
<td>Apolipoprotein</td>
<td>A-I</td>
<td>1.0</td>
<td>-0.12</td>
</tr>
<tr>
<td>B$_{100}$</td>
<td>1.0</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>High-Sensitivity CRP</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
dence of association than that achieved by any of the single variables used alone. However, despite the apparent superiority of apolipoprotein B100 over total cholesterol and LDL-C, the lipid ratio with the strongest association in these data was the more traditional ratio of total cholesterol to HDL-C (top vs bottom quintile HR, 3.81; 95% CI, 2.47-5.86; \(P\leq.001\) for trend; LR \(\chi^2\) statistic = 694.3; Table 3). For comparison, the relative risk in the top quintile of the ratio of apolipoprotein B_{100} to apolipoprotein A-I was 3.01 (95% CI, 2.01-4.50; \(P\leq.001\) for trend; LR \(\chi^2\) statis-

### Table 3. Future Cardiovascular Events Among Initially Healthy Women According to Baseline Lipid Levels, High-Sensitivity C-Reactive Protein, and Calculated Lipid Ratios*

<table>
<thead>
<tr>
<th></th>
<th>Quintile 1</th>
<th>Quintile 2</th>
<th>Quintile 3</th>
<th>Quintile 4</th>
<th>Quintile 5</th>
</tr>
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<tbody>
<tr>
<td><strong>Individual Variables</strong></td>
<td></td>
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<tr>
<td><strong>Cholesterol</strong></td>
<td></td>
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</tr>
<tr>
<td>Total Median (range), mg/dL</td>
<td>161 (&lt;176)</td>
<td>187 (176-197)</td>
<td>207 (198-216)</td>
<td>228 (217-242)</td>
<td>264 (242-242)</td>
</tr>
<tr>
<td>No. of events</td>
<td>41</td>
<td>67</td>
<td>79</td>
<td>118</td>
<td>159</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>1.40 (0.94-2.08)</td>
<td>1.39 (0.94-2.05)</td>
<td>1.71 (1.19-2.48)</td>
<td>2.08 (1.45-2.97)</td>
</tr>
<tr>
<td><strong>LDL</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Median (range), mg/dL</td>
<td>85 (&lt;97.7)</td>
<td>107 (97.7-115.4)</td>
<td>124 (115.5-132.1)</td>
<td>142 (132.2-153.9)</td>
<td>171 (&gt;153.9)</td>
</tr>
<tr>
<td>No. of events</td>
<td>54</td>
<td>66</td>
<td>74</td>
<td>114</td>
<td>156</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>1.06 (0.73-1.54)</td>
<td>1.03 (0.71-1.49)</td>
<td>1.32 (0.94-1.85)</td>
<td>1.62 (1.17-2.25)</td>
</tr>
<tr>
<td><strong>HDL</strong></td>
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</tr>
<tr>
<td>Median (range), mg/dL</td>
<td>35 (&lt;39.5)</td>
<td>43 (39.5-45.9)</td>
<td>49 (46.0-52.6)</td>
<td>57 (52.7-61.5)</td>
<td>69 (&gt;61.5)</td>
</tr>
<tr>
<td>No. of events</td>
<td>171</td>
<td>115</td>
<td>66</td>
<td>63</td>
<td>49</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>0.84 (0.66-1.07)</td>
<td>0.53 (0.39-0.71)</td>
<td>0.54 (0.39-0.73)</td>
<td>0.43 (0.30-0.61)</td>
</tr>
<tr>
<td><strong>Non-HDL</strong></td>
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<td></td>
</tr>
<tr>
<td>Median (range), mg/dL</td>
<td>109 (&lt;123.2)</td>
<td>136 (123.2-144.9)</td>
<td>155 (145.0-165.5)</td>
<td>177 (165.6-191.0)</td>
<td>213 (191.0-213)</td>
</tr>
<tr>
<td>No. of events</td>
<td>32</td>
<td>46</td>
<td>85</td>
<td>116</td>
<td>185</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>1.15 (0.73-1.82)</td>
<td>1.62 (1.06-2.48)</td>
<td>1.88 (1.25-2.83)</td>
<td>2.51 (1.69-3.72)</td>
</tr>
<tr>
<td><strong>Apolipoprotein</strong></td>
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</tr>
<tr>
<td>A-I Median (range), mg/dL</td>
<td>116 (&lt;124.1)</td>
<td>130 (124.1-135.4)</td>
<td>141 (135.5-146.2)</td>
<td>152 (146.3-159.8)</td>
<td>171 (&gt;159.8)</td>
</tr>
<tr>
<td>No. of events</td>
<td>139</td>
<td>116</td>
<td>71</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>0.91 (0.71-1.17)</td>
<td>0.54 (0.40-0.73)</td>
<td>0.54 (0.40-0.74)</td>
<td>0.57 (0.42-0.77)</td>
</tr>
<tr>
<td>B_{100} Median (range), mg/dL</td>
<td>70 (&lt;79.1)</td>
<td>87 (79.1-93.3)</td>
<td>100 (93.4-108.9)</td>
<td>117 (109.0-126.2)</td>
<td>141 (&gt;126.2)</td>
</tr>
<tr>
<td>No. of events</td>
<td>32</td>
<td>52</td>
<td>77</td>
<td>98</td>
<td>205</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>1.22 (0.77-1.92)</td>
<td>1.51 (0.98-2.31)</td>
<td>1.53 (1.00-2.32)</td>
<td>2.50 (1.68-3.72)</td>
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<tr>
<td><strong>High-sensitivity CRP</strong></td>
<td>0.29 (&lt;0.50)</td>
<td>0.75 (0.50-1.08)</td>
<td>1.52 (1.09-2.08)</td>
<td>2.93 (2.09-4.19)</td>
<td>6.62 (&gt;4.19)</td>
</tr>
<tr>
<td>Median (range), mg/L</td>
<td>26</td>
<td>63</td>
<td>79</td>
<td>117</td>
<td>179</td>
</tr>
<tr>
<td>No. of events</td>
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<tr>
<td>RR (95% CI)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Lipid Ratios</strong></td>
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</tr>
<tr>
<td>Total cholesterol to HDL cholesterol Median (range)</td>
<td>2.8 (&lt;3.2)</td>
<td>3.5 (3.2-3.8)</td>
<td>4.1 (3.8-4.5)</td>
<td>4.9 (4.5-5.4)</td>
<td>6.2 (&gt;5.4)</td>
</tr>
<tr>
<td>No. of events</td>
<td>28</td>
<td>49</td>
<td>64</td>
<td>111</td>
<td>212</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>1.63 (1.00-2.64)</td>
<td>1.55 (0.96-2.48)</td>
<td>2.49 (1.59-3.89)</td>
<td>3.81 (2.47-5.86)</td>
</tr>
<tr>
<td>LDL cholesterol to HDL cholesterol Median (range)</td>
<td>1.5 (&lt;1.8)</td>
<td>2.0 (1.8-2.3)</td>
<td>2.5 (2.3-2.8)</td>
<td>3.1 (2.8-3.4)</td>
<td>4.0 (&gt;3.4)</td>
</tr>
<tr>
<td>No. of events</td>
<td>32</td>
<td>46</td>
<td>78</td>
<td>107</td>
<td>201</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>1.24 (0.78-1.98)</td>
<td>1.74 (1.13-2.69)</td>
<td>1.97 (1.29-3.01)</td>
<td>3.18 (2.12-4.75)</td>
</tr>
<tr>
<td>Apolipoprotein B_{100} to apolipoprotein A-I Median (range)</td>
<td>0.46 (&lt;0.54)</td>
<td>0.60 (0.54-0.65)</td>
<td>0.71 (0.65-0.78)</td>
<td>0.85 (0.78-0.94)</td>
<td>1.08 (&gt;0.94)</td>
</tr>
<tr>
<td>No. of events</td>
<td>31</td>
<td>54</td>
<td>65</td>
<td>114</td>
<td>200</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>1.43 (0.91-2.26)</td>
<td>1.45 (0.93-2.25)</td>
<td>1.89 (1.24-2.88)</td>
<td>3.01 (2.01-4.50)</td>
</tr>
<tr>
<td>Apolipoprotein B_{100} to HDL cholesterol Median (range)</td>
<td>1.1 (&lt;1.4)</td>
<td>1.6 (1.4-1.8)</td>
<td>2.0 (1.8-2.3)</td>
<td>2.6 (2.3-3.0)</td>
<td>3.6 (&gt;3.0)</td>
</tr>
<tr>
<td>No. of events</td>
<td>27</td>
<td>54</td>
<td>66</td>
<td>112</td>
<td>205</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>1.76 (1.09-2.83)</td>
<td>1.68 (1.05-2.68)</td>
<td>2.35 (1.50-3.67)</td>
<td>3.56 (2.31-5.47)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RR, relative risk.

*All analyses adjusted for age in years, blood pressure by Framingham categories, body mass index, diabetes, and current smoking status. \(P\leq.001\) for trend across all quintiles.

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tic=674.3). These comparative data and associated 95% CIs also are presented in Figure 1.

Cardiovascular event-free survival according to increasing quintiles of each individual variable and ratios of total cholesterol to HDL-C and apolipoprotein B<sub>100</sub> to apolipoprotein A-I appear in Figure 2. The HRs and 95% CIs for future cardiovascular events after classifying baseline high-sensitivity CRP levels by clinical cut points (<1, 1–3, and >3 mg/L) and baseline levels of non–HDL-C and apolipoprotein B<sub>100</sub> and ratios of total cholesterol to non–HDL-C and apolipoprotein B<sub>100</sub> to apolipoprotein A-I tertile, after adjustment for age (years), blood pressure (Framingham categories), diabetes, current smoking status, and body mass index. CI indicates confidence interval, and CRP, C-reactive protein.

We observed no evidence of effect modification for high-sensitivity CRP by age. In stratified analyses, the fully adjusted HR for those in the highest compared with the lowest quintile of high-sensitivity CRP among women younger than 55 years was 2.9 (P= .008) while the corresponding HR for women aged 55 years or older was 2.8 (P=.002).

**COMMENT**

In this large, prospective cohort of initially healthy US women, we directly compared non–HDL-C, apolipoproteins B<sub>100</sub> and A-I, standard lipid measures, lipid ratios, and high-sensitivity CRP as predictors of future cardiovascular events. Overall, we observed that the magnitude of the association was greater for apolipoprotein B<sub>100</sub> than for either total cholesterol or LDL-C. However, we also observed that apolipoprotein B<sub>100</sub> was highly correlated with non–HDL-C, and that association for non–HDL-C was effectively equal to that of apolipoprotein B<sub>100</sub>. Moreover, the easily calculated ratio of total cholesterol to HDL-C proved to be at least as strongly associated with cardiovascular events as the ratio of apolipoprotein B<sub>100</sub> to apolipoprotein A-I. In these women, high-sensitivity CRP also was strongly associated with risk, but only modestly correlated with any of the lipid parameters.

We believe these data have clinical relevance for several reasons. First, with regard to individual lipid measures, our data are consistent with prior prospective cohort studies indicating that apolipoprotein B<sub>100</sub> is a strong predictor of cardiovascular events independent of the nonlipid covariates typically used in global risk prediction scores. However, in a manner parallel to that observed for apolipoprotein B<sub>100</sub> alone, we also observed that the strength of association for the ratio of apolipoprotein B<sub>100</sub> to apolipoprotein A-I was not superior in these data to the ratio of total cholesterol to HDL-C. Thus, on the basis of the data in this large prospective cohort of initially healthy women as well as other nested case-control studies that have found the ratio of total cholesterol to HDL-C to perform favorably, it would not seem clinically important to replace standard lipid measures with more complex apolipoprotein evaluations—at least for the purpose of primary risk detection. On the other hand, our data and those of several prior studies do suggest that the use of either the ratio of total cholesterol to HDL-C or LDL-C to HDL-C is superior to the use of total cholesterol or LDL-C alone, and thus do not support the portion taken by the European SCORE project, which advocates the use of total cholesterol in isolation.

In the current data, the HR for those in the top vs bottom quintile of high-sensitivity CRP was 2.98 (95% CI, 1.90–4.67), which was greater than that of both non–HDL-C (HR, 2.51; 95% CI, 1.69–3.72) and apolipoprotein B<sub>100</sub> (HR, 2.50; 95% CI, 1.68–3.72). In contrast to the strong correlations observed between lipid measures, the correlation coefficients between high-sensitivity CRP and each lipid parameter were smaller and ranged from –0.33 to 0.15. These observations are consistent with the hypothesis that both inflamma-
tion and hyperlipidemia contribute jointly to the atherothrombotic process. At the same time, the LR statistic in these data for high-sensitivity CRP was greater than that of total cholesterol and LDL-C, but less than that of non–HDL-C and apolipoprotein B_{100}. This latter observation suggests somewhat greater correlations for high-sensitivity CRP than for standard lipids with the nonlipid variables used in our multivariable adjustments, which included both diabetes and obesity. These effects are not surprising because high-sensitivity CRP levels also predict the onset of type 2 diabetes and adipocytes are a proinflammatory tissue.\textsuperscript{28,29}

Our analysis used state-of-the-art assays for all measures (including apolipoproteins A-I and B_{100}) and thus are unlikely to be affected by laboratory issues that have been raised in some earlier studies of both lipid and inflammatory biomarkers. Furthermore, the large-scale prospective cohort approach taken greatly reduces the possibility of chance and bias as alternative explanations for our findings.

However, our study does have some limitations that merit consideration. We evaluated plasma levels only once and thus our data may be susceptible to

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**Figure 2. Probability of Cardiovascular Events According to Increasing Quintiles of Lipid, Apolipoprotein, and C-Reactive Protein Levels**

![Probability of Cardiovascular Events According to Increasing Quintiles of Lipid, Apolipoprotein, and C-Reactive Protein Levels](image-url)

According to increasing quintiles of each measured variable over the 10-year follow-up period.
intra-individual variation. Our study also evaluated middle-aged women and it is known that adverse effects on several blood variables can occur during and after menopause. However, our main findings are consistent with those from a nested case-control study performed within the Nurses’ Health Study in which the average age of women evaluated was older.27 Our lipid-based data are also consistent with prior studies conducted predominantly or exclusively among men.12,26 Finally, we do not have full assessment of triglyceride levels among these women and thus cannot evaluate whether any of the other parameters measured might have greater or lesser value among those with altered triglyceride patterns.

While our analyses support the use of standard lipid measures rather than apolipoproteins A-I and B100 in primary risk detection, these data should not be construed to exclude a potential role for apolipoprotein B100 or the ratio of apolipoprotein B100 to apolipoprotein A-I in monitoring patients taking statins. In this regard, there was virtually no use of statin therapy at the time of enrollment into the WHS and overall usage rates remained very low at all points of follow-up reflecting the low-risk nature of this cohort.19 However, in the Air Force Texas Coronary Atherosclerosis Prevention Study (AF-CAPS/TexCAPS), a randomized trial of lovastatin, the levels of apolipoprotein B100 when participants were receiving treatment and the ratio of apolipoprotein B100 to apolipoprotein A-I were better predictors of future cardiovascular events than LDL-C.30 Levels of apolipoproteins B100 and A-I while participants were receiving treatment also have been found to significantly predict recurrent cardiovascular events in several secondary prevention studies.8,31,32 It has been hypothesized on this basis that the monitoring of apolipoprotein B100 could replace the current standard lipid profile evaluation among patients taking statins.31 With regard to high-sensitivity CRP, recent data suggest potential utility for this inflammatory biomarker as an adjunctive method to monitor statin efficacy not as a replacement for LDL-C.34-36 The possible role of combined apolipoprotein and high-sensitivity CRP evaluation to monitor patients taking statins needs to be evaluated.

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