High-density Lipoprotein Cholesterol and Prognosis After Myocardial Infarction

Prepared for the Coronary Drug Project Research Group by KENNETH G. BERGE, M.D., PAUL L. CANNER, PH.D., AND ADRIAN HAINLINE, JR., PH.D.

SUMMARY  The Coronary Drug Project was a randomized, placebo-controlled trial of lipid-influencing drugs in men who had recovered from one or more documented myocardial infarctions. Determinations of high-density lipoprotein (HDL) cholesterol were made at baseline in a group of 354 men randomized to the placebo group. Five-year mortality was highest (33.0%) in men with baseline serum HDL cholesterol levels of less than 35 mg/dl; it was 15.9%, 17.7%, and 21.8% in men with levels of 35-39, 40-44, and ≥ 45 mg/dl, respectively (for the linear inverse relationship between HDL cholesterol and 5-year mortality, p = 0.029). Adjustment for 40 baseline variables had a minimal effect on this relationship (p = 0.042).

IN RECENT YEARS, several epidemiologic studies have indicated that low levels of high-density lipoprotein (HDL) cholesterol in the blood are associated with an increase in incidence and severity of coronary heart disease and with ischemic cerebrovascular disease. To our knowledge, no prospective data have been reported regarding possible prognostic significance of HDL cholesterol levels determined after recovery from acute myocardial infarction (MI). Limited data available from the baseline period of the Coronary Drug Project allow an assessment of HDL cholesterol in this circumstance.

Methods

The Coronary Drug Project was a randomized, double-blind, placebo-controlled trial of lipid-influencing drugs in the secondary prevention of coronary heart disease. Men ages 30–64 years (mean 52.4 years) who had recovered from one or more documented MIs were recruited by 53 project clinical centers. Men with chronic conditions other than coronary heart disease were excluded from the study; thus, 88% of the deaths were from cardiovascular causes. As part of their baseline clinical assessment, three sets of lipid determinations were carried out under fasting conditions in the morning, after a low-fat meal the previous evening. During the early phases of the enrollment period, baseline lipid analyses included determination of the HDL cholesterol to be used in later assessment of adherence to the estrogenic treatment groups. This procedure was discontinued after such sets of data were obtained on 1038 men, including 354 men randomized to the placebo group. The latter group forms the basis of this report.

Laboratory Methods

Total cholesterol was determined by the AutoAnalyzer N-24a method modified to give results comparable to the method of Abell et al. Serum HDL cholesterol was determined by the method of Walton and Scott, which was modified to permit measurement of cholesterol by the AutoAnalyzer on the supernatant obtained by precipitation of low-density lipoproteins by a reagent composed of dextran sulfate, barbital and calcium chloride. Serum triglyceride was determined on the AutoAnalyzer using the chromotropic acid reaction with a silicic acid chloroform extract of serum. Univariate and multivariate linear regression analyses were used to determine the relationship of baseline HDL cholesterol levels to 5-year mortality in the placebo group, both unadjusted and adjusted for 40 base-
line variables. Statistical significance of this relationship was assessed by means of t values (i.e., the estimated regression coefficients divided by their standard errors) and their associated p values.17,18 Five-year mortality rates for four groups of patients defined by baseline HDL cholesterol levels (i.e., < 35, 35–39, 40–44 and ≥ 45 mg/dl) adjusted for 40 baseline variables were computed by including in the regression equation three "dummy" (or 0,1) variables denoting the HDL cholesterol groups.19

**Results**

The mean level of serum HDL cholesterol for men in the placebo group (n = 354) was 41.4 ± 10.3 mg/dl (± sd).

Eighty of the 354 men (22.6%) died within 5 years. The 5-year all-cause mortality was highest (33.0%) in men with baseline serum HDL cholesterol levels of less than 35 mg/dl; it was 15.9% and 17.7% in men with levels of 35–39 and 40–44 mg/dl, respectively, and 21.8% in men with levels of 45 mg/dl or higher (table 1). A simple linear regression analysis of baseline HDL cholesterol and 5-year mortality yielded a t value for the slope of −2.18 (p = 0.029), a statistically significant relationship. A quadratic term added to the regression equation yielded a t value of 1.84 (p = 0.066), denoting borderline significance. Upon adjustment for 40 baseline variables including serum total cholesterol and triglyceride (the complete list of these variables has been published elsewhere4), the significance of the quadratic term diminished (t = 1.11, p = 0.27), while the linear effect maintained its strength (t = −2.03, p = 0.042) (fig. 1). Use of the ratio HDL cholesterol to total cholesterol in the regression analysis yielded similar results.

Five-year mortality rates by baseline HDL cholesterol are listed in table 1 for subgroups of patients defined by total cholesterol, triglyceride, relative body weight (defined elsewhere18) and cigarette smoking status at baseline. In every case, the minimum mortality is associated with an intermediate level — either 35–39 or 40–44 mg/dl — of HDL cholesterol. While the values listed in table 1 suggest that the relationships of mortality to baseline HDL cholesterol may differ somewhat between men with lower and those with higher baseline triglyceride levels and between smokers and nonsmokers, regression analyses indicate that the differences are not significant.

Seven of the 80 deaths were due to cancer. Within the four levels (< 35, 35–39, 40–44 and ≥ 45 mg/dl) of baseline HDL cholesterol, there were 3, 1, 1 and 2 cancer deaths, respectively.

**Discussion**

Limited data from the placebo group of the Coronary Drug Project indicate that low levels (i.e., < 35 mg/dl) of HDL cholesterol are associated with an increase in subsequent mortality in men who have recovered from MI. This finding is compatible with the growing body of data relating low levels of HDL cholesterol with an increased risk of atherosclerotic cardiovascular disease.

The number of cancer deaths (seven) in this group of men is too small either to support or to contradict the finding by Keys7 of a positive correlation between HDL cholesterol and death due to neoplasms.

**References**


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**TABLE 1. Five-year Mortality by Baseline High-density Lipoprotein Cholesterol for Various Baseline Subgroups**

<table>
<thead>
<tr>
<th>Baseline subgroup</th>
<th>Serum HDL cholesterol (mg/dl)</th>
<th>&lt; 35</th>
<th>%</th>
<th>n</th>
<th>35–39</th>
<th>%</th>
<th>n</th>
<th>40–44</th>
<th>%</th>
<th>n</th>
<th>≥ 45</th>
<th>%</th>
<th>n</th>
<th>All</th>
<th>%</th>
<th>n</th>
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<tbody>
<tr>
<td>Serum total cholesterol &lt; 250 mg/dl</td>
<td>32.6</td>
<td>46</td>
<td>12.8</td>
<td>39</td>
<td>17.1</td>
<td>35</td>
<td>20.8</td>
<td>48</td>
<td>21.4</td>
<td>168</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Serum total cholesterol ≥ 250 mg/dl</td>
<td>33.3</td>
<td>48</td>
<td>18.4</td>
<td>49</td>
<td>18.5</td>
<td>27</td>
<td>22.6</td>
<td>62</td>
<td>23.7</td>
<td>186</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Serum triglyceride &lt; 5 mEq/l</td>
<td>30.3</td>
<td>33</td>
<td>29.4</td>
<td>34</td>
<td>7.9</td>
<td>38</td>
<td>23.1</td>
<td>78</td>
<td>22.4</td>
<td>183</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Serum triglyceride ≥ 5 mEq/l</td>
<td>34.4</td>
<td>61</td>
<td>7.4</td>
<td>54</td>
<td>33.3</td>
<td>24</td>
<td>18.8</td>
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<td>22.8</td>
<td>171</td>
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<tr>
<td>Relative body weight &lt; 1.15</td>
<td>27.3</td>
<td>44</td>
<td>12.2</td>
<td>49</td>
<td>13.5</td>
<td>37</td>
<td>20.3</td>
<td>64</td>
<td>18.6</td>
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<tr>
<td>Relative body weight ≥ 1.15</td>
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<td>50</td>
<td>20.5</td>
<td>39</td>
<td>24.0</td>
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<td>23.9</td>
<td>46</td>
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<tr>
<td>Non–cigarette smoker</td>
<td>36.2</td>
<td>47</td>
<td>22.4</td>
<td>49</td>
<td>16.2</td>
<td>37</td>
<td>18.6</td>
<td>70</td>
<td>23.2</td>
<td>203</td>
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<tr>
<td>Cigarette smoker</td>
<td>29.8</td>
<td>47</td>
<td>7.7</td>
<td>39</td>
<td>20.0</td>
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<td>27.5</td>
<td>40</td>
<td>21.9</td>
<td>151</td>
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<tr>
<td>All patients</td>
<td>33.0</td>
<td>94</td>
<td>15.9</td>
<td>88</td>
<td>17.7</td>
<td>62</td>
<td>21.8</td>
<td>110</td>
<td>22.6</td>
<td>354</td>
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</tbody>
</table>

*To convert total and HDL cholesterol to millimoles per liter, multiply by 0.02586; to convert triglyceride to millimoles per liter, multiply by 0.333.

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**Figure 1. Five-year mortality by baseline levels of high-density lipoprotein (HDL) cholesterol and best-fitting linear regression line, adjusting for 40 baseline variables.**

Appendix

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CIRCULATION Vol. 66, No 6, December 1982

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High-density lipoprotein cholesterol and prognosis after myocardial infarction.

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Circulation. 1982;66:1176-1178
doi: 10.1161/01.CIR.66.6.1176

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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