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Mild Hypercholesterolemia and Premature Heart Disease: Do the National Criteria Underestimate Disease Risk?

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OBJECTIVES To determine the frequency of hospital admissions for acute coronary syndrome in young adults and to examine the risk factors that predispose to the development of premature heart disease.

BACKGROUND Significant coronary heart disease (CHD) is considered rare in the young adult. Current guidelines do not recommend treatment of mild cholesterol abnormalities for primary prevention of CHD in the young.

METHODS This is a large case series of 449 adults (≤50 years) admitted to the hospital with acute coronary syndrome. A history of cardiovascular risk factors and lipid profile were recorded. The presence and extent of CHD were established.

RESULTS Mean patient age was 44 ± 6 years. Documented CHD was present in 61% of hospital admissions. Multivariate analysis revealed that history of hypercholesterolemia, history of smoking and diabetes were independently associated with premature CHD. The fasting lipid profiles were only borderline to mildly abnormal. Serum total cholesterol, low-density lipoprotein (LDL) and triglyceride levels were not different in cases compared with control subjects. Nearly half (49%) of those with LDL levels of ≥160 mg/dl had only one additional risk factor or none. Despite this, a history of hypercholesterolemia had independent and incremental value on other risk factors for the likelihood of premature CHD.

CONCLUSIONS The magnitude of hospital admissions relating to premature CHD is high. In this population, the presence of borderline or mild hypercholesterolemia has significant effects on the development of premature CHD. These observations have significant implications in the development of guidelines for primary prevention of premature CHD. (J Am Coll Cardiol 2000;35:1178–84) © 2000 by the American College of Cardiology

The association between abnormal cholesterol metabolism and coronary heart disease (CHD) is no longer in doubt. Several epidemiologic studies have shown a direct, continuous, graded and perhaps linear relationship between serum cholesterol levels and cardiovascular events risk (1–4). Additionally, randomized-control clinical trials have consistently demonstrated that treatment of elevated cholesterol levels is associated with significant reductions in recurrent event rates in people with documented coronary disease. In people without coronary disease, there is evidence that certain high risk groups do benefit from treatment. However, confusion exists in the treatment of young men and women with mild or moderate cholesterol abnormalities.

The National Cholesterol Education Program (NCEP) is a national effort to increase both professional and public awareness of the dangers of high cholesterol levels (4). The NCEP has developed guidelines for both primary and secondary prevention of coronary disease. The guidelines do not recommend pharmacologic therapy for young adults with moderate cholesterol elevations in the absence of concomitant risk factors. Several reasons may be accountable for the lack of endorsement of drug therapy. First, it is generally believed that premature CHD is rare, and that the absolute risk for a young adult with hypercholesterolemia developing coronary disease is low (5). Second, the relationship between cholesterol levels and CHD may be linear in that the likelihood of cardiovascular events is relatively low for people with mild and moderate cholesterol abnormalities without multiple risk contributors (6). Third, there is currently no evidence that treatment of mild cholesterol abnormalities in the young is cost-effective. Fourth, the long-term safety of the current medications remains unknown.

However, the extent to which these assumptions remain true for rural communities that may bear little or no
presence of cardiovascular risk factors was noted. Body mass index was calculated for all patients and expressed as weight in kilograms divided by the square of height in meters ($\text{kg/m}^2$). Obesity was defined as body mass index $\geq 27.8$ and $\geq 27.3$ for men and women, respectively. Hypertension was defined as systolic blood pressure $\geq 140$ mm Hg, diastolic pressure of $\geq 90$ mm Hg or current use of antihypertensive medication. Cigarette smoking (yes or no) was ascertained for current and previous use. History of smoking was defined as total abstention for at least four weeks before hospital admission. History of diabetes was considered present if the individual was receiving therapy with either insulin or an oral hypoglycemic agent. Additional criteria included a fasting blood glucose level in excess of 150 mg/dl on two occasions. Family history was defined as premature CHD in first-degree relatives at age 55 years or younger and 65 or younger for men and women, respectively. Only lipid profiles drawn within initial 48 h of hospital admission were included. History of hypercholesterolemia was taken from physician’s hospital admission notes. The final diagnoses were confirmed by hospital discharge records.

The hospital has a defined catchment area and provides services to patients living in 19 counties in western Wisconsin, southeastern Minnesota, and northeast Iowa. The service area population is 530,697 persons. Approximately 78% of these individuals live in rural regions. The racial make-up of the service area is 98% white, 1% Southeast Asian and 1% Hispanic. The study population does not differ from the population of this geographic area.

Statistical analysis. The data were analyzed with software (SAS software Version 6.12; Cary, North Carolina: SAS Institute; 1996). For the univariate analysis, the categorical variables were compared using Fisher’s exact two-tailed test, Pearson’s chi-square test or test for linear trend. The continuous variables, which are expressed as mean $\pm$ SD, were compared by Student $t$ test. For the multivariate analysis, the following variables were tested for risk for premature CHD using stepwise logistic regression: smoking, diabetes, history of hyperlipidemia, obesity, family history of premature coronary disease and hypertension. This stepwise regression was set to enter variables into and remove variables from the model in such a way that each forward step is followed by a backward elimination. Variables must have met the $p = 0.05$ criteria to be entered and remain in the model. The odds ratio as an estimate of multivariate relative risk (RR) and the 95% confidence intervals before and after adjustment of confounding variables were calculated by logistic regression. The hypothesis testing and the estimation of 95% confidence intervals were performed using the standard error estimate for logistic coefficient estimates.

RESULTS

General. There were 449 patients (only initial hospital admission was counted in the case of multiple admissions) of age 50 years or younger with acute coronary syndrome in
the two-year period. This represented 22% of all hospital admissions (N = 2,042) for acute coronary syndrome during that period. The mean patient age was 44 ± 6 years. There were 132 (29.4%) women. Documented premature coronary artery disease (≥70% stenosis) was present in 61 (46%) and 212 (67%) women and men, respectively. The medications at the time of hospital admission were as follows: beta-adrenergic blocking agents (20.0%), calcium blockers (13.5%), angiotensin-converting enzyme inhibitors (6.9%) and alpha-blockers (1.6%). Thirty-five patients (7.8%) were receiving statins, and an additional seven (1.6%) were receiving either niacin or gemfibrozil. Table 1 presents a more detailed description of the demographic profile.

Patients were categorized into group 1 if there was irrefutable evidence of premature CHD (n = 274; 61%). Group 2 was comprised of the patients without definite evidence of CHD. This included patients who were ruled out for MI or who were classified as having low probability for significant disease and therefore were not offered coronary angiography, as well as patients with normal angiograms. The mean age for our population was 45 ± 6 years. The mean age for our population was 45 ± 6 years in group 2 (p = NS). Among the women with premature coronary disease, 36% suffered acute MI compared with 47% of the men (p < 0.14).

### Table 1. Patient Demographic Profile

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>317 (71%)</td>
<td>132 (29%)</td>
</tr>
<tr>
<td>% with CHD</td>
<td>67%</td>
<td>46%</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>45 ± 5.0</td>
<td>44 ± 4.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>39%</td>
<td>35%</td>
</tr>
<tr>
<td>Hypercholesterolemia (Hx)</td>
<td>46%</td>
<td>35%</td>
</tr>
<tr>
<td>History of smoking</td>
<td>75%</td>
<td>59%</td>
</tr>
<tr>
<td>Obesity</td>
<td>67%</td>
<td>61%</td>
</tr>
<tr>
<td>Family history</td>
<td>42%</td>
<td>29%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12%</td>
<td>16%</td>
</tr>
</tbody>
</table>

*CHD = coronary heart disease; Hx = history.

### Angiographic disease

Among the 274 patients with premature CHD, left main involvement was present in 5%. The distributions of coronary lesions in the remaining patients were one vessel (27%), two vessels (28%) and three vessels (22%). In another 15%, the extent of disease was unknown. This included those with documented, uncomplicated MI who did not undergo diagnostic coronary angiography, and those in whom the angiographic disease was poorly documented. Insignificant coronary disease was documented in 2% of patients. History of known cardiovascular disease was as follows: previous angiography (n = 98), previous percutaneous transluminal coronary angioplasty (n = 26), previous MI (n = 54) and previous coronary artery bypass graft (n = 17).

### Risk factors

Table 2 provides a summary of the details of the risk factor distribution in the patients with and without premature CHD (group 1 and group 2, respectively). The risk factors examined were history of smoking, current smoking, family history of premature CHD, obesity, diabetes mellitus and lipid profile. After adjusting for gender, multivariate analysis revealed that history of hypercholesterolemia (RR 3.0, p < 0.0001), history of smoking (RR 2.8, p < 0.0001) and diabetes mellitus (RR 2.7, p < 0.007) were independently associated with premature CHD. Among the entire group, 186 patients (42%) gave history of having hypercholesterolemia, and 168 (38%) admitted having hypertension. As many as 315 (70%) and 231 (51%) had history of smoking or were current smokers, respectively. The occurrence rate for obesity as defined by body mass index was 65%.

Group 1 patients had a significantly higher ratio of history of hypercholesterolemia and smoking (both current and history), as well as diabetes, than group 2 patients. There was a trend for higher rates of hypertension (p = 0.058) and family history of premature coronary disease (p = 0.053) in group 1 compared with group 2. The

### Table 2. Frequency of Risk Factors by Group

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>n</th>
<th>Group 1 % With CHD</th>
<th>Group 2 % Without CHD</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>449</td>
<td>78% (213/274)</td>
<td>59% (104/175)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia (Hx)</td>
<td>438</td>
<td>53% (144/274)</td>
<td>26% (42/164)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hx of hypertension</td>
<td>440</td>
<td>42% (114/274)</td>
<td>33% (54/166)</td>
<td>0.058</td>
</tr>
<tr>
<td>Hx of smoking</td>
<td>449</td>
<td>80% (219/274)</td>
<td>55% (96/175)</td>
<td>0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>449</td>
<td>58% (160/274)</td>
<td>41% (71/175)</td>
<td>0.001</td>
</tr>
<tr>
<td>Family Hx CHD</td>
<td>438</td>
<td>42% (114/274)</td>
<td>32% (53/164)</td>
<td>0.053</td>
</tr>
<tr>
<td>Obesity</td>
<td>438</td>
<td>66% (180/274)</td>
<td>65% (106/164)</td>
<td>0.822</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>436</td>
<td>16% (45/274)</td>
<td>8% (13/162)</td>
<td>0.013</td>
</tr>
<tr>
<td>LDL ≥160 mg/dl</td>
<td>233</td>
<td>29% (51/178)</td>
<td>25% (14/55)</td>
<td>0.644</td>
</tr>
<tr>
<td>Low HDL*</td>
<td>259</td>
<td>58% (115/199)</td>
<td>38% (23/60)</td>
<td>0.008</td>
</tr>
<tr>
<td>Total cholesterol ≥240 mg/dl</td>
<td>277</td>
<td>23% (48/207)</td>
<td>26% (18/70)</td>
<td>0.668</td>
</tr>
</tbody>
</table>

*Low HDL ≤35 mg/dl for men; ≤45 mg/dl for women.
CHD = coronary heart disease; HDL = high-density lipoprotein; Hx = history; LDL = low-density lipoprotein.
patients had total cholesterol values of $48$ h of hospital admission. Of these, only $66$ (23.8%) vs. 65%).

Comparison with NCEP guidelines. There was a total of 277 patients who had total cholesterol level checked within 48 h of hospital admission. Of these, only 66 (23.8%) patients had total cholesterol values of $\geq 240$ mg/dl. A total of 233 patients had an analysis of low-density lipoprotein (LDL) cholesterol performed. Only 63 (27.2%) had fasting LDL values of $\geq 160$ mg/dl, and 123 (52.8%) had LDL values of $\geq 130$ mg/dl. Among those with a LDL cholesterol level of $\geq 160$ mg/dl, 8% had no identifiable risk factor (n = 5), 41% (n = 26) had only one additional cardiovascular risk, 31.7% (n = 20) had two, 16% (n = 10) had three and 3.2% (n = 2) had more than three additional risk factors present (Fig. 1). In other words, as many as 49% of subjects with LDL cholesterol levels $\geq 160$ mg/dl had only one or no recognized cardiovascular risk factor. Two hundred fifty-nine patients had high-density lipoprotein (HDL) cholesterol levels recorded, of whom 53% had low HDL levels. The analysis was repeated counting low HDL levels ($\leq 35$ mg/dl for men and $\leq 45$ mg/dl for women). With HDL levels considered, 6.3% and 28.6% had either none or one additional risk factor, respectively. However, the number of risk factors present was associated with severity of disease (F = 19.9, p = 0.000). Patients with one-vessel disease had significantly more risk factors than those without disease and significantly less risk factors than those with three diseased vessels. The mean total cholesterol level was not different among the group without CHD compared to those with documented disease ($201 \pm 52.4$ vs. $207 \pm 51$ mg/dl, p = 0.4). Similarly, LDL cholesterol and triglyceride levels were not different for the two groups ($128 \pm 38$ vs. $135 \pm 40$ mg/dl, p = 0.3 and $201 \pm 171$ vs. $225 \pm 158$, p = 0.3, respectively). Conversely, the group with CHD had significantly lower HDL cholesterol levels ($37.7 \pm 10.5$) compared to those without disease ($44.3 \pm 10.0$, p < 0.0001).

Influence of cholesterol and other risk factors. We analyzed the lipoprotein profile according to smoking status. The mean total cholesterol level among nonsmokers was significantly lower compared with the mean total cholesterol level of smokers ($192 \pm 49$ vs. $211 \pm 51$ mg/dl, p < 0.005). Similarly, LDL cholesterol level was significantly lower among nonsmokers ($122 \pm 35$ vs. $139 \pm 41$ mg/dl, p < 0.003). There was no difference in the mean HDL or triglyceride levels in smokers compared with levels in nonsmokers. History of hypercholesterolemia and smoking were independent predictors of disease and their presence together increased the probability of disease significantly. The results of the stepwise logistic regression model are illustrated in Table 3. The risk ratio for premature CHD is 3.0 for a patient with history of hypercholesterolemia (p < 0.0001). The logistic regression model was repeated with all variables simultaneously forced into the analysis. The results showed that family history (p = 0.7) and hypertension (p = 0.2) were not statistically significant in predicting disease. Obesity showed a trend toward significance (p = 0.055), although the odds ratio was less than one.

DISCUSSION

The main findings of our study are three-fold. First, the study shows that contrary to current beliefs, a high proportion (22%) of hospital admissions for acute coronary syndrome occur in young adults and as many as 61% have significant angiographic disease. Second, the proportion of patients with multivessel disease may suggest that the onset of coronary disease in this population is early or that the disease progression is rapid. Third, a significant number of people do not get lipoprotein analysis, suggesting missed opportunities for prevention of coronary disease.

A report issued by the National Heart, Lung and Blood Institute Task Force on Research in Epidemiology and Prevention of Cardiovascular Diseases in 1994 noted that CHD death rates vary among geographic regions in the U.S. (9). Studies done over the past five decades show that cardiovascular disease mortality rates are highest in the southeastern, northeastern and Appalachian states and lowest in the Rocky Mountain and western states (10,11). Our understanding of the contribution of modifiable, environmental risk factors to the development of CHD has improved. It is also true that the extent and distribution of each known cardiovascular risk factor is dynamic within any community and this may account, at least in part, for the decreasing age-adjusted mortality rates for CHD (12–14).
The differential effect of each risk factor on the onset of disease and prevalence rates, however, is yet to be documented. Based on currently available epidemiologic studies it is generally believed that development of significant CHD is rare in the young (5,15–17). This is believed to be particularly true in the absence of diabetes (18), cocaine abuse (19) or severely abnormal serum cholesterol levels with multiple risk factors (20–24). The question then is why so many young men and women in this geographic area present with premature CHD. In just a two-year period, a total of 449 patients 50 years or younger (22% of all hospital admissions for acute coronary syndrome) were admitted to the hospital with acute coronary syndrome, of whom 61% had documented significant coronary artery disease. One may ask if this is a local phenomenon limited to our geographic catchment area. After all, the population here is homogenous and stable with common ancestry from northern Europe. It is possible that the population may carry a genetic susceptibility for premature CHD. Furthermore, smoking is habitual among the youth and obesity is a prevalent problem in this area. Nevertheless, we believe that it is entirely possible that the findings of this study are representative of many other similar communities.

First, our current understanding of the epidemiology of CHD is derived from studies that have been done from a few select communities that are defined by proximity to large educational and urban centers (25–28). In reality, although many people live in rural settings, very few studies have been done in these areas. In addition, recent studies portray particularly troubling trends in the health profile of U.S. adolescents such as increasing rates of cigarette smoking (29), obesity (30) and physical inactivity (31). Moreover, a recent autopsy report from the Bogalusa study showed that even in children and young adults who died from noncardiac causes, there was atherosclerotic disease in the aorta and coronary arteries. The degree of atherosclerotic involvement was correlated with the presence and number of traditional coronary risk factors (32). The Bogalusa study is consistent with previous reports involving young soldiers who died in both the Korean (33) and Vietnam (34) conflicts as well as the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study (35). We postulate that this is true for most U.S. communities and that progression to clinically significant disease in the young adult is variable and dependent on the presence and extent (duration and severity) of atherogenic risk factors such as smoking and obesity. This may partly explain why as many as 55% of the patients had multivessel disease, whereas other studies show that young adults with premature CHD usually have single-vessel disease with discrete lesions (36).

One interesting finding from the current study concerns the lipid analysis and the risk factor profile of the patients. The best way to deal with premature coronary disease is prevention. For this reason, we asked how well could these patients be identified prior to the events. Could these events be prevented by current guidelines? Current guidelines on hypercholesterolemia are not as clear or assertive on primary prevention compared with secondary prevention. The American College of Physicians does not recommend cholesterol screening for young men (<35 years) or women (<45 years) unless history and physical examination suggest a familial lipoprotein disorder or at least two other characteristics that increase the risk for CHD. Screening for primary prevention is considered appropriate but not mandatory for men 35 to 65 years of age and for women 45 to 65 years of age (37). If one considers that 22% of all our hospital admissions for acute coronary syndrome occurred in this group of patients 50 years or younger, clearly this strategy would not have helped these patients. The NCEP guidelines recommend fasting lipoprotein analysis only when total cholesterol level is elevated to ≥240 mg/dl. Therapy is not recommended for primary prevention unless the LDL cholesterol level is ≥160 mg/dl and there are concomitant risk factors (4). In our group of patients, only 24% had total cholesterol values of ≥240 mg/dl, and only 27% had fasting LDL values of ≥160 mg/dl. Among those with LDL values of ≥160 mg/dl, approximately 49% had either none or only one additional risk factor. Although the values for total cholesterol, LDL and HDL cholesterol and triglycerides were only borderline or mildly abnormal, history of hypercholesterolemia carried a significant independent and incremental risk by multivariate analysis.

What then should be the target lipid profile for primary prevention in this area? We believe the best strategy for primary prevention should be aggressive reduction of all modifiable risk factors. The rate of smoking in our patients and indeed this community is unacceptably high. The extent of obesity should be reduced and physical activity encouraged. What level of cholesterol abnormalities to treat cannot be answered in this study, but the issue of cost-effectiveness of treating mild hypercholesterolemia may need to be revisited for few reasons. Current assumptions are based on the belief that absolute risk for development of premature CHD is low. This may not be true for this area and it is possible that there are several other rural communities that have similarly high rates that remain unrecognized. Second, the lipoprotein analysis in our group suggests that most patients may benefit from strategies that improve HDL values. Furthermore, in a population with high rates of premature CHD, preventing symptomatic CHD may be cheaper in the long run because it is expensive to treat MI. Once MI develops, the combined cost of secondary preventive measures, coronary angiography, revascularization and eventual development of ischemic cardiomyopathy becomes extremely expensive. We reiterate the observation by Brown and Goldstein (38) that total cholesterol of 200 mg/dl is much too high. We agree with their suggestion that the total cholesterol level in the population needs to be much lower than the NCEP recommended criteria (38).

**Study limitations.** The current study is observational and deserves necessary caution in the interpretation of the
results. Patients admitted to our hospital are unselected and reflect our community. However, the findings may not be generalized to other communities where the population differs from ours. We believe there are several other rural communities that may share similarly high rates of premature CHD. In this regard, we believe the findings of this study are important. Another limitation of our method is that it does not allow us to derive incidence and prevalence values by which we could compare with national data. We recognize this weakness, but in reality the essential finding of unacceptably high hospital admission rates for young adults here calls for reevaluation of the extent of premature CHD and current preventive strategies. Unfortunately, lipid profile was not available for all patients, which is problematic in using a retrospective design. Although we categorized our patients into two groups based on irrefutable evidence of coronary disease, in reality the groups may not be different. It can be argued that they all have clinical manifestations of disease (acute ischemic syndromes for which they were admitted to the hospital). A control group composed of patients without chest pain would be preferable. Viewed from this perspective, the findings of this study become even more impressive, since one would expect the differences between groups to be magnified if such a control group was used.

CONCLUSIONS

We present our experience showing high hospital admission rates for patients with premature CHD. Our study offers new clinical and scientific information in cardiovascular medicine, which includes the following. Many young adults presenting with clinical evidence of premature CHD are not adequately evaluated for prevention. A large number of these patients have borderline or only mildly abnormal lipid profiles. Only a few have multiple risk factors, yet many do have multivessel disease. These findings suggest that in a high risk population with high rates of smoking and obesity, the incremental impact of borderline to mild cholesterol abnormalities is significant. Furthermore, the high percentage of multivessel involvement does argue for early disease onset or rapid progression and that prevention should be started early and the criteria for therapy need review. This suggests a need for protocols to reflect all modifiable risk factors, including smoking, obesity, hypertension and hypercholesterolemia.

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REFERENCES

24. Ferrieres J, Sing CF, Roy M, Davignon J, Lussier-Cacan S. Apoli-
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