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National Cholesterol Education Panel III performance in preventing myocardial infarction in young adults

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BACKGROUND: Only one published trial has directly evaluated the utility of the new National Cholesterol Education Program (NCEP) guidelines in young adults and that study population consisted of young Americans. We examined the utility of the latest NCEP Adult Treatment Panel III (ATP III) guidelines in a group of young Lebanese adults.

METHODS: A group of 234 young adults admitted for myocardial infarction at a Lebanese teaching hospital over a 2-year period were evaluated retrospectively. The Framingham risk predictor model was used to calculate the 10-year risk for coronary events in all subjects.

RESULTS: Two hundred young Lebanese adults with a mean age of 49.7±7.6 years were included in the analysis. The majority of the study population had a history of smoking (67%) and LDL cholesterol <130 mg/dL(70.5%) and were considered overweight and obese (80.5%). As a group, 80% did not meet the criteria to qualify for antilipemic pharmacotherapy prior to their presentation.

CONCLUSION: The predictive model did not detect the majority of these patients. Clinicians should treat modifiable risk factors with the same intensity given to cholesterol even if the patient has a normal lipid profile.

Coronary heart disease (CHD) continues to be the leading cause of mortality and a significant cause of morbidity among North Americans. In the United States, CHD claimed over 650 000 lives in 2003, about one of every five deaths.[1] A high level of cholesterol, or hypercholesterolemia, is an important risk factor for CHD. Aggressive medical therapy has substantially reduced morbidity and mortality in patients with CHD over the past four decades and is largely ascribed to the newer treatment modalities such as reperfusion and early invasive interventions.[2,3] In addition, secondary prevention, including beta-blockers,[4-7] angiotensin converting enzyme inhibitors,[8-10] anti-platelets,[11-14] statins,[15-18] and lifestyle modification,[19-23] contributed to a great extent in the reduction of major cardiac events in patients with established disease. Despite the fact that risk factors for CHD are well recognized, their modification did not lessen the occurrence of acute coronary syndrome.[1]

Since the Framingham Heart Study showed the correlation between cholesterol levels and mortality, cholesterol management has become the cornerstone of primary CHD prevention. The National Cholesterol Education Program (NCEP) has created guidelines for the management and prevention of CHD.[24] The third report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel [ATP] III) was released in May 2001,[24] and updated in July 2004 to include evidence from more recent trials.[25] In ATP III, target low density lipoprotein cholesterol (LDL-c) levels depend on the patient's risk of heart disease, medical history, and initial LDL-c level. Patients who have type II diabetes without known CHD, peripheral or carotid vascular disease, and patients who have multiple risk factors and a 10-year risk of CHD >20% are considered as having "CHD equivalents." The term means that the criteria for using drug therapy and the LDL target are the same as for patients who have a history of CHD. The addition of "CHD equivalents" to the ATP III increased the number of patients who required treatment. To our knowledge, there has only been one published trial that

directly evaluated the utility of the new NCEP guidelines in a group of young adults and that study population consisted of Americans.[26] Risk factors for coronary heart disease in young Lebanese adults may vary from other countries, especially blood pressure, blood cholesterol, smoking, physical activity, genetics and diet. Therefore, the objective of this study was to investigate the utility and the application of the latest guidelines in a group of young Lebanese adults. Using the modified Framingham risk predictor model,[24] we calculated a 10-year risk for coronary events on all patients. This calculation will evaluate the model's accuracy in identifying candidates for prophylactic pharmacotherapy.

METHODS

The methodology used in this study was published previously[26] and permission to use it was granted. This study was conducted at Makassed General Hospital (MGH), Beirut, Lebanon. Medical records for patients admitted to the Coronary Care Unit (CCU) between January 1999 and January 2001 were reviewed retrospectively. Only men ≤55 years and women ≤65 years classified as having acute myocardial infarction (MI) were eligible for inclusion. Acute MI was defined as two of the following: chest pain, electrocardiographic changes, or elevated enzymes (creatine kinase, creatine kinase-myocardial band isoenzymes, and troponin). Patients with a history of CHD or a CHD equivalent were excluded.

A clinical pharmacist reviewed the medical records for all eligible patients. The patient's age, gender, weight, height, vital signs, past medical and family history of CHD, smoking status, lipid profile, and other risk factors were noted on a pre-approved form. Body mass index (BMI) was used for indicating weight status in our young adult population. The BMI is a quotient of body mass that takes into account both weight and height measured as kg/m^2. Body weights are currently defined according to BMI as follows: normal weight 18.5-24.9 kg/m^2; overweight 25-29.9 kg/m^2; and obesity ≥30.0 kg/m^2 for both men and women.[27] Cigarette smoking was determined as being a current smoker or with a history of smoking. The designation "current smoker" applied to any cigarette smoking in the month prior to the acute MI. A history of smoking was established if the person reported smoking cessation for longer than one month before the event. A history of hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or current use of antihypertensive medication. A family history of premature CHD was defined as CHD in a first-degree relative at age ≤55 years and ≤65 years for men and women, respectively. For all CCU patients at MGH, a fasting lipid profile is drawn within 24 hours of admission. The data was analyzed with Jandel Sigmastat Statistical Software (version 2.0, Jandel Corp, San Rafael, California). Frequency distributions were reported and the Student's t test was used to determine differences between genders.

RESULTS

A total of 234 young adults were admitted to MGH for acute MI during the period between January 1999 and January 2001. According to the NCEP guidelines, 34 patients (14.5%) would have been classified as having CHD or a CHD equivalent before their MI and therefore were excluded; the remaining 200 were included in the analysis. There were 138 males (69%) and 62 female (31%) with a mean age of 49.71±7.60 years (Table 1).

Overweight and obese patients comprised 80.5% (47.5% and 33%, respectively) of this study population, with a group population mean±SD for BMI equal to 28.69±4.46 kg/m^2. In addition, 72.5% of this population was noted to have a history of smoking (considered relatively high) and 67% were considered current smokers. Based on the updated NCEP ATP III guidelines, the major risk factors include the following: smoking, hypertension, low high-density lipoprotein (HDL) cholesterol (<40 mg/dL), family history of CHD (CHD in male first degree relative <55 years, in female first degree relative <65 years), and age (men ≥45 years, women ≥55 years). In this study population, 181 (90.5%) patients presented with multiple risk factors (two or more), and 19 (9.5%) patients had either none or one risk factor.

The mean total cholesterol (190.9 mg/dL), low-density lipoprotein (LDL) cholesterol (115.9 mg/dL), and

Table 1. Demographics and risk factor profile (N=200).

Age (yrs)	49.71±7.60*
Gender	
Male	138 (69%)
Female	62 (31%)
Overweight (BMI=25-29.9 kg/m^2)	95 (47.5%)
Obese (BMI ≥30 kg/m^2)	66 (33%)
Smoker	134 (67%)
Ever smoked	145 (72.5%)
Hypertension	82 (41%)
Family history of premature CHD	93 (46.5%)

BMI=body mass index, CHD=coronary heart disease, *Mean±standard deviation

Table 2. Lipid profile in the study population.

	Study Population	Male	Female	NCEP Criteria
TC	190.9±62.2	189.8±34.1	193.3±99.9	<200
LDL-c	115.9±33.4	118.3±30.9	110.6±38.2	<130
HDL-c	40±9.3	37.8±10.3	42.37±9.2	>40
TG	190.3±111.6	203.8±152.3	176.2±87.7	<150

Values are mean±SD (mg/dL). HDL-c=high-density lipoprotein cholesterol, LDL-c=low-density lipoprotein cholesterol, NCEP=National Cholesterol Education Program, TC=Total cholesterol, TG=Triglycerides

HDL cholesterol (40 mg/dL) were all within the normal range as recommended by NCEP ATP III (Table 2). Only 20 patients (10%) had LDL cholesterol of 160 mg/dL or higher, 141 patients (70.5%) had LDL cholesterol of <130 mg/dL and 66 patients (33%) had LDL cholesterol of <100 mg/dL.

According to the number of major risk factors present and LDL cholesterol level in the study population, the 10-year CHD risk was stratified. Fourteen (7%) patients were considered at high risk and 62 (31%) patients at moderate risk, of which 10 and 22 patients, respectively, were qualified for pharmacotherapy. Very few patients with a low risk qualified for therapy (6% of people with 10-year risk <10%, and 1% of people with no or one risk factor). Remarkably, 124 (62%) patients were stratified into these two lowest risk categories. As a group, 160 patients (80%) did not meet the criteria to qualify for pharmacotherapy.

Thirty-one percent of the patient population was female. The differences in the mean total cholesterol, LDL cholesterol, and triglyceride between both males and females, as shown in Table 2, were not statistically significant. The mean HDL cholesterol was statistically significantly higher in females (42.3±9.2 mg/dL) versus males (37.8±10.3 mg/dL) with P=.004. The mean number of major risk factors was higher in men than in women (2.52 vs. 2.0 risk factors, P<.05). Only 3.5% of women (vs. 43% of males) in this study had a risk score probability of a 10-year event between 10% and 20% and only one woman (vs. 13 males) had a calculated risk of >20%. Therefore the majority of women had a 10-year risk of <10%.

DISCUSSION

Despite advances in the detection of risk factors, CHD continues to affect many patients worldwide and accounts for nearly one-third of all global deaths.[1] The major emphasis of the NCEP ATP III guidelines is the primary prevention of CHD in at-risk patients by lowering levels of LDL cholesterol.[24,25] While it is crucial to achieve lipid goals, it is important to realize that half of all acute MIs occur in patients with normal lipid levels, below the current NCEP guidelines for intervention and treatment. The new and updated guidelines build on previous reports; however, several changes have been made, including raising diabetes mellitus to a CHD risk equivalent, utilizing the Framingham 10-year risk assessment to adjust initiation of therapy for higher-risk patients, focusing on metabolic syndrome as a risk factor, defining the optimal LDL cholesterol level to be <100 mg/dL, raising the low HDL cholesterol cut-off point to <40 mg/dL, recommending treatment of, and focusing more attention on, elevated triglycerides, recommending that the initial lipid workup include total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides, and stressing the importance of continued therapeutic lifestyle changes and drug therapies. Despite all these new features, the focus of ATP III remains on LDL cholesterol as the primary target of lipid-modifying therapy. Furthermore, utilizing the new ATP III guidelines, pharmacotherapy will be offered to many people for aggressive medical treatment, who in previous reports would not be included.[28,29] It is recommended that absolute risks for a cardiac event in 10 years be calculated for all individuals for primary prevention. In spite of all these changes, the use of these guidelines has yet to be tested among young adults except in one small study in a specific population.[30,31]

The goal of this study was to determine each individual level of risk and whether or not they would have met criteria for medical management if they had presented to their physicians before the events. Two hundred and thirty-four young adults with known acute MI were screened. Only 34 (14.5%) patients were excluded due to known CHD or CHD-equivalents and were qualified for secondary prevention. The remaining 200 patients would have been candidates for primary prevention if they had presented to their physicians for evaluation prior to the MI. As many as 80% did not qualify for pharmacotherapy. The prediction model, as shown

Table 3. Ten-year risk profile in the study population.

	LDL Cholesterol (mg/dL)				Total
	<100	100-129	130-159	≥160	
2+ risk factors, 10-year risk >20%Ω	0 (0%)	4 (2%)	8 (4%)*	2 (1%)*	14 (7%)
2+ risk factors, 10-year risk 10-20%Δ	12 (6%)	28 (14%)	12 (6%)*	10 (5%)*	62 (31%)
2+ risk factors, 10-year risk <10%∏	43 (21.5%)	40 (20%)	16 (8%)	6 (3%)*	105 (52.5%)
0-1 risk factor ∏	11 (5.5%)	3 (1.5%)	3 (1.5%)	2 (1%)*	19 (9.5%)
Total	**66 (33%)**	**75 (37.5%)**	**39 (19.5%)**	**20 (10%)**	

Values are numbers of subjects and percent of cohort. *Indicates those patients who are qualified for medical management; CHD= coronary heart disease; LDL = low-density lipoprotein. Ω: High risk; Δ: Moderate risk; ∏: Low risk

Table 4. Framingham point scores by age and smoking status.

Age range (years)	20-39	40-49	50-59	60-69	70-79
Nonsmoker	0	0	0	0	0
Smoker (men)	8	5	3	1	1
Smoker (women)	9	7	4	2	1

in Table 3, is more accurate for moderate- to high-risk patients; identifying 42% of the people in this category. Only 16% of the entire cohort was in that group. Based on the data presented in this study, this predictive model did not detect these patients as expected, leading to a postulation that these guidelines do not perform well in young Lebanese adults. We can only offer the following assumptions: Young adults have seldom been evaluated in large, multi-centered, and randomized trials. Furthermore, the clinical and risk factor profiles of young Lebanese adults with MI may vary from other young adults and from what is traditionally believed.[28-31] In addition, premature CHD was usually seen in young adults with specific conditions such as cocaine abuse, familial hyperlipidemia, or diabetes.

In this study population, the frequency of smoking is considered high, and the new guidelines stratify smoking according to age, with higher scores assigned to younger ages (Table 4). This system of scoring fails to account for the intensity of exposure (duration and number of packs) to tobacco. In the risk assessment of young adults, the intensity of smoking may be a better basis for stratification than age. In addition, over 80% of the study population is considered to be overweight or obese. Looking at the new NCEP ATP III guidelines, obesity, in all of its types, is not directly counted in the risk assessment scoring system. Its effect may be accounted for in metabolic syndrome and hypercholesterolemia. Looking at our patient population in Lebanon, with a high frequency of being overweight, the rate of obesity in CHD may be unappreciated and may need to be re-evaluated in future guidelines, especially since the obesity rate is increasing. Furthermore, approximately 47 percent of the study population had a family history of premature CHD. Family history of premature CHD is an important and independent risk factor especially for early-onset disease. Family history is not included as a risk factor in the Framingham risk estimate. Therefore, the Framingham score may underestimate CHD risk for individuals with a family history, particularly at young ages when prevention could have substantial benefits given the risk for early-onset disease. Finally, elevated levels of homocysteine and/or certain apolipoproteins (e.g. apo B) that may be overpresented in the study population and contributed to this result, however, were not performed.

Our study results corroborated the findings of a previous study[26] showing the important role of risk factors in determining the qualification for pharmacotherapy prophylaxis for primary prevention in young adults. Akosah et al investigated the utility of these guidelines in a group of young adults from Wisconsin.[26] A group of 222 patients were included in this retrospective study. The mean lipid levels were within the normal range and the rate of smoking and obesity were high. Only 25% met the criteria to qualify for pharmacotherapy. The vast majority of our young adult population in this study did not have high total cholesterol or LDL cholesterol levels. Over 70% had LDL cholesterol levels less than or equal to 130 mg/dL with a high percentage

of multiple risk factors. All of the above-discussed factors may contribute to the poor performance of current guidelines for prevention of premature CHD in this population.

Based on our results, to help reduce CHD events in young Lebanese adults, clinicians should emphasize treating modifiable risk factors with the same intensity given to cholesterol, even if the patient has a normal lipid profile.

The NCEP ATP III was developed to incorporate new evidence and evidence-based strategies to reduce CHD events. While ATP III maintains attention to intensive treatment of patients with CHD, its major new feature is a focus on primary prevention in persons with multiple risk factors. In spite of this, the new guidelines fail to appreciate the need for validation among different age population groups.

Based on our findings, the majority of young Lebanese adults presenting with MI had a normal lipid profile and did not require any pharmacotherapy prior to presentation based on NCEP ATP III. In addition, the rate of obesity was relatively high and its effect on CHD may need to be re-evaluated. A large controlled, prospective and randomized trial to validate the performance of these guidelines in young adults is recommended.

At the time this research was conducted, Drs Alameddine, Geitany, and Afiouni were Pharm.D. candidates at the Lebanese American University.

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