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**NATIONAL CHOLESTEROL EDUCATION PANEL III
PERFORMANCE IN PREVENTING MYOCARDIAL
INFARCTION IN YOUNG LEBANESE ADULTS**

**Submitted In Partial Fulfillment of the Requirements for
The Degree of Doctor of Pharmacy**

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ABSTRACT

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Purpose: The National Cholesterol Education Program (NCEP) III guidelines have been hailed as an improvement in their potential to identify individuals at risk for coronary heart disease (CHD) complications. Compared with the NCEP II, the new guidelines will increase the number of patients who qualify for medical management. However, the effectiveness of these guidelines to identify young adults at risk for a cardiac event is yet to be studied. The purpose of this study was to investigate the utility of the new NCEP III guidelines in a group of young adults.

Methods: A retrospective review of clinical data from young adults (age ≤ 55 years for men and ≤ 65 years for women) hospitalized for acute myocardial infarction over a two-year period was conducted. Patients with a history of CHD or CHD equivalent were excluded. Using the NCEP III guidelines, we calculated a 10-year risk for coronary events on all patients.

Results: A total of 200 patients met criteria for inclusion. The mean age was 49 years and 31% were women. Mean lipid levels were all within the normal range, however, rates of smoking and obesity were high. When the 10-year risk of these patients was stratified by the number of risk factors and low-density lipoprotein cholesterol level, only 20% met criteria to qualify for pharmacotherapy.

Conclusion: The new guidelines offer multiple new features but have a tendency to under appreciate the risk for disease in young adults. To improve performance in young adults, statistical adjustments may be necessary.

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Introduction.

Coronary heart disease (CHD) is the number one cause of death in both men and women in the United States ⁽¹⁾. Aggressive medical therapy has substantially reduced morbidity and mortality in patients with CHD over the past four decades and this improvement is largely attributed to the newer treatment modalities such as reperfusion and early invasive interventions ^(2,3). In addition secondary prevention strategies including beta-blockers ^(4,5), aspirin ⁽⁶⁾, statins ^(7,8), and lifestyle modifications ^(9,10) contributed to a great extent in the reduction of major cardiac events in patients with established disease. In contrast primary prevention did not decrease the incidence of acute coronary syndrome (ACS) ⁽¹⁾. Despite the fact that risk factors for CHD are well recognized their modification did not lessen ACS occurrence.

Since the Framingham Heart Study that showed the correlation between cholesterol levels and mortality, cholesterol management became the cornerstone of primary prevention of CHD. The National Cholesterol Education Program (NCEP) has created guidelines for the management and prevention of CHD ⁽¹¹⁾. These evidence-based guidelines were based on trials that proved benefit in both the anticipation and the treatment of ACS ^(12,13). The recent National Cholesterol education Panel III reclassified risk based on the probability of an event in 10 years, and it increased

the number of patients who deserve treatment ⁽¹⁴⁾. However the effectiveness of these guidelines was not studied among young adults.

Using the modified Framingham risk predictor model as published in the new NCEP guidelines, we calculate a 10-year risk for coronary events on all patients. This will be performed to evaluate how well we would have identified these young adults for prophylactic pharmacotherapy before their events.

The purpose of this study was to investigate the utility and the application of those guidelines in a group of young Lebanese adults at Makassed General Hospital (MGH).

Methods

Patient selection. This is a retrospective study of adults presenting with first time myocardial infarction (MI) who were admitted to the Coronary Care Unit (CCU) at the MGH, Beirut, Lebanon in a two-year period (January 1, 1999, to January 1, 2001). In this study acute MI was defined as two of the following: angina, electrocardiographic (EKG) changes, or elevated enzymes (creatine kinase, creatine kinase-myocardial band isoenzymes, troponin). Only men ≤ 55 years and women ≤ 65 years classified as having acute MI were included. Patients with history of CHD or diabetes mellitus (DM) were excluded.

Data source and variables. Medical records of all eligible patients were reviewed. The presence of traditional cardiovascular risk factors were noted. Body mass index (BMI) was calculated for all patients and expressed as weight in kilograms divided by the square of height in meters (kg/m^2). Overweight is defined as BMI 25 to 30 kg/m^2 and obesity is defined as BMI $>30\text{kg}/\text{m}^2$ for both men and women. Cigarette smoking (yes or no) is ascertained for current use, which is defined as chronic cigarette smoking up to four weeks

before acute MI. History of smoking is established as if the person reported smoking cessation for longer than four weeks before the event. History of hypertension is defined as systolic blood pressure ≥ 140 mm Hg or current use of antihypertensive medication. Family history of premature CHD is defined as CHD in a first-degree relative at age ≤ 55 years and ≤ 65 years for men and women, respectively. For all CCU patients in MGH, a lipid profile is drawn within 12 h of admission.

Statistical analysis: the data was analyzed with SPSS software (version 9.0 for windows, SPSS Inc, Chicago, Illinois). Frequency distributions were reported and the student t-test was used to determine differences between genders.

Results

General. In the calendar year 1999 through 2001, there were a total of 234 admissions of young adults for acute MI to MGH. According to the NCEP guidelines, 34 (14.5%) would have been classified as having CHD or CHD equivalent before their MI. The remaining 200 comprised the population used in this study (Figure 1). Patients demographics are provided in table 1. The mean age was 49.71 ± 7.60 years. There were 62 women (31%) (Figure 2).

Risk Factors. Table 1 provides a summary of the details of the traditional risk factor distribution in this population. The mean BMI was 28.69 ± 4.46 kg/m². Obesity was present in 27% of the patients and an additional 47.5% were overweight. Thus overweight and obese patients comprise 74.5% of this population (Figure 3). Similarly, a history of smoking was high and accounted for 72.5% of the population (Figure 4). As many as 67% were current smokers. As can be appreciated from Table 1, the frequency rate for each categorical variable was high. Under the new guidelines, major risk factors include: smoking, hypertension (Figure 5), 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 our population, multiple major risk factors were present in 181 (90.5%) patients, whereas 19 (9.5%) patients had either no or only one risk factor (Figure 6).

Lipid levels. Table 2 displays the mean values of the lipoprotein analysis. All 200 young adults had lipid profiles drawn within 12h of admission. As can be appreciated the mean total cholesterol (190.9 mg/dl), low-density lipoprotein (LDL) cholesterol (115.9 mg/dl), and HDL cholesterol (40 mg/dl) were all within the normal range. As a group, only 10% (n=20) had LDL cholesterol 160 mg/dl or higher. The percentage of patients with LDL cholesterol <130 mg/dl was 70.5%, of whom 33% (n=66) of patients had LDL cholesterol <100 mg/dl (Figures 7,8).

10-year calculated risk. The 10-year CHD risk in these patients was stratified according to the number of major risk factors present and LDL cholesterol level. The number of people at high risk, that is a 10-year risk > 20% and two or more major risk factors, was 14 (7%), of whom 10 patients were qualified for pharmacotherapy. Similarly among the 62 patients with moderate risk (10%-20%), only 22 patients (36%) qualified for pharmacotherapy. In contrast, among low-risk groups, very few qualified for therapy (6% of people with 10-year risk < 10%, and 11% of people with no or one risk factor). Remarkably the majority (62%) of young adults were

stratified into these two lowest risk categories ($n = 124$). Overall, 160 patients (80%) did not meet the criteria to be identified as at sufficient risk to qualify for pharmacotherapy. We repeated the analysis using non-HDL cholesterol however the results did not change.

Gender differences. There were 62 women in this study population. A comparison between genders for lipid values was determined using the Student *t* test. The mean total cholesterol was similar in both genders (193.3 ± 99.9 mg/dl and 189.8 ± 34.1 mg/dl in women and men respectively). The mean LDL cholesterol was 110.6 ± 38.2 for women and 118.3 ± 30.9 mg/dl for men with no statistical significance ($p=0.133$). Also the mean triglycerides was 176.2 ± 87.7 for women and 203.8 ± 152.3 for men with no statistical difference. In contrast the mean HDL cholesterol was significantly higher in women versus men (42.3 ± 9.2 mg/dl vs. 37.8 ± 10.3 mg/dl, $p= 0.004$). Counting high HDL cholesterol as a negative risk factor, one male was qualified as having no risk factors. Furthermore, using the Student *t* test, the mean number of major risk factors was higher in men than in women (2.42 vs. 2.11 risk factors, $p<0.05$). In spite of the higher mean of risk factors present in men, one woman in this study had a calculated risk of > 20%. Only 3.5% of women in this study had risk score probability

of 10-year event between 10% and 20%. Thus the majority of women had a 10-year risk of <10%.

Discussion

Although mortality from CAD has declined steadily in the past four decades, rates for acute coronary syndrome have not slowed. Preventing the development of CHD and initial MIs in the first place has been difficult ⁽¹⁶⁾. The new NCEP III guidelines ⁽¹⁷⁾ for the management of dyslipidemia is the best available document for primary prevention. This document has several new features that make it an improvement over previous guidelines. For primary prevention, physicians are encouraged to calculate an individual's absolute risk for a cardiac event in 10 years. The LDL cholesterol targets and goals of treatment are stratified according to the absolute risk. A major advantage of the new guidelines is that many people who did not qualify for aggressive medical management using previous guidelines will be offered pharmacotherapy ^(19,20). However, the utility of these new guidelines has yet to be tested, particularly among young adults, a population in which limitations of the previous guideline have been recently documented ^(18,21).

In this study we applied the new guidelines in a group of 234 young adults with known acute MI. Our goal was to determine each individual's level of risk and whether or not they would have met criteria for medical management if they had presented to their physicians before the event. Of the entire cohort, only 34 people

(14.5%) had known CHD or CHD equivalent and were excluded from this analysis because they qualified for secondary prevention. The remaining 200 would have been candidates for primary prevention if they had presented to their physicians before the MI. As many as 80% did not qualify for medical management. The prediction model as shown in Table 3 is better for moderate- to high-risk patients, identifying 42% of the people in this category. However, only 10% of the entire cohort was in that group.

The infarct these patients had proved they were at high risk. It seems reasonable to expect a predictive model to detect more of these patients than it did. What are some of the reasons that these guidelines did not perform well in our young adult population? We did not study possible mechanistic reasons, but do offer the following speculations. One reason is that young adults have rarely been studied. With the exception of a few studies such as Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPs/TexCAPs) ⁽¹⁴⁾, young adults have been poorly represented in large multicenter trials. Second, the clinical profile of young adults with MI may be different from what is traditionally believed ^(19,21). Premature CHD was considered rare unless certain conditions, such as cocaine abuse, familial hyperlipidemia, or diabetes were present. In our experience, 50% of all acute coronary syndrome hospital admissions were in adults 50 years or younger ⁽¹⁸⁾. Moreover, this young adult population with CHD is

characterized by a high prevalence of individual categorical risk factors, but as many as 9.5% do not have clusters (two or more) of risk factors. Moreover, a significant number of these young adults have LDL cholesterol below 100 mg/dl ⁽²²⁾.

As can be viewed in Table 1, the frequency rate of smoking is exceptionally high. In the new guidelines, smoking is stratified according to age with higher scores assigned to younger ages. For instance, a 20- to 29-year-old smoker is assigned a score of 8, whereas a 50- to 59-year-old smoker is given a score of 3. 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 (defined as number of pack years) may be a better basis for stratification than age.

In addition, overweight/obesity/gross obesity as a traditional risk factor was present in 80.5% of these young adults. In the new guidelines, obesity is not directly scored in risk assessment. The effect of obesity may be accounted for in the role it plays in metabolic syndrome and hypercholesterolemia. However, in a population such as our subjects with high frequency rates of overweight, the full impact of obesity may be unappreciated. The effect of obesity on CHD may need to be re-evaluated in the current era where obesity rates are increasing in all segments of the population.

It may be that (for young adults) long and intense exposure to certain major categorical risk factors may be more detrimental than exposure to multiple marginal risk factors. This may be true for risk factors such as smoking and obesity, both of which are usually acquired early and have a high probability of being maintained.

A distinguishing feature in the clinical profile of our adults is that the vast majority did not have elevated total cholesterol or LDL cholesterol levels. As many as 70.5% had LDL cholesterol levels of 130 mg/dl or less, and 10% do not have multiple risk factors. These factors may contribute to the poor performance of current guidelines for prevention of premature CHD.

Does this mean that cholesterol is not important in young adults? We interpret our results to mean that optimal cholesterol levels do not imply freedom from CHD in young adults with other modifiable risk factors. The message is that we should target all modifiable risk factors with the same intensity given to cholesterol.

A similar study to ours was conducted by Akosah et al evaluated the utility of the new National Cholesterol Education Program (NCEP) III guidelines in a group of young adults admitted to a hospital in Wisconsin. The results were very similar to our study. Concerning the demographics and risk factor profile: the mean BMI was 30 (28.69), obesity was present in 45% (27) and multiple major risk factors were present in 49% (90) of the

patients. About the lipid levels, the percentage of patients with LDL cholesterol <130 mg/dl was 58% (70), of whom 40% (33) had LDL cholesterol <100 mg/dl. Talking about the 10-year CHD risk, the number of people at high risk - that is a 10-year risk >20% - was 12% (7), 70% (62) were stratified into the lowest risk categories and 75% (80) did not meet the criteria to be identified as at sufficient risk to qualify for pharmacotherapy. Finally, concerning the gender differences, there were 25% (31) women in that study, the mean total and HDL cholesterol was similar in both men and women. In contrast, women had a statistically lower mean LDL cholesterol level and a statistically higher triglycerides level (in our study, no gender differences were present except for the mean HDL cholesterol level that was statistically lower in men).

CONCLUSION

The Adult Treatment Panel III guidelines incorporate several new features that may potentially improve primary prevention of premature CHD. However, for clinicians to feel comfortable with these, they may need to be validated across several population groups. We found that many young adults presenting with MI do not have multiple risk factors, and few (10%) have moderately high LDL cholesterol levels. By contrast, the rates of categorical risk factors including overweight/obesity, smoking, and hypertension are high. Young women presenting with MI generally have a higher likelihood of multiple risk factors. In spite of this, the new guidelines failed to appreciate the risk for underlying disease in women. More studies are needed to validate the new guidelines in young adults and to determine the necessary statistical adjustments to improve performance in young adults at risk for MI.

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Appendix I

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 kg/m ²)	95 (47.5%)
Obese (BMI 30-34 kg/m ²)	54 (27%)
Grossly obese (BMI > 35 kg/m ²)	12 (6%)
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

Table 2: Lipid Profile

	Study Population (mg/dl)	NCEP Criteria (mg/dl)
Total cholesterol	190.0 ± 62.2	< 200
LDL cholesterol	115.9 ± 33.4	< 130
HDL cholesterol		
Men	37.8 ± 10.3	> 40
Women	42.37 ± 9.2	
Triglycerides	190.3 ± 111.6	< 150

HDL = high-density lipoprotein, LDL = low-density lipoprotein, NCEP = National Cholesterol Education Program.

Table 3. Ten-Year Risk Profile					
	LDL Cholesterol (mg/dl)				Total
	< 100	100-129	130-159	≥ 160	% cohort
2+ risk factors 10-year risk > 20%	0 (0%)	4 (2%)	8 (4%)	2 (1%)	14(7%)
2+ risk factors 10-year risk 10- 20%	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 (% cohort)	66 (33%)	75 (37.5%)	39 (19.5%)	20(10%)	

Bold type indicates those patients not qualifying for medical management.

CHD = coronary heart disease; LDL = low-density lipoprotein.

Appendix II

Figure 1: Inclusion vs Exclusion

Figure 2: Gender differences

Figure 3: Weight classification

Figure 4: Percentage of smokers

Figure 5: Percentage of hypertensive patients

Figure 6: Family history of premature CHD

Figure 7: Lipid profile

Figure 8: HDL cholesterol levels

Questionnaire

I. Physical Findings

- a. Sex
- b. Age
- c. Height
- d. Weight
- e. BMI

	Normal	Overweight	Obese
BMI			

II. Social History

	Never	Past	Current
Smoking			

III. Past Medical History

	Yes	No
Hypertension		
Diabetes Mellitus		
CHD		
Other		

IV. Past Medication History

	Yes	No
Antihypertensive		
Other		

V. Family History

	Yes	No
Premature CHD		

VI. Laboratory Tests

	Day 1	Day 2	Day 3
BP			
LDL			
HDL			
TG			
TC			