9-6-2005

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Background—National Cholesterol Education Program Adult Treatment Panel III guidelines recommend therapeutic lifestyle changes (TLC) and drug therapy to reduce cardiovascular disease (CVD) risk. These guidelines have been revised recently (ATP III-R); however, the risk of CVD mortality within each intervention window and the effects of cardiorespiratory fitness (CRF) and metabolic syndrome on CVD mortality within the framework of the guidelines are unknown.

Methods and Results—Risk factor and CRF data from 19 125 men (aged 20 to 79 years) who attended a preventive medical clinic between 1979 and 1995 were used. Mortality follow-up was completed until December 31, 1996. Participants were assigned to ATP III-R groups (LDL-C goal, TLC initiation, and drug consideration), and risk of CVD mortality was assessed by Cox proportional hazards regression. There were 179 CVD deaths over an average 10.2 years of follow-up. Compared with the LDL-C goal group, men in the TLC initiation and drug consideration groups had an elevated risk of CVD mortality (TLC initiation: HR=2.65, 95% CI 1.67 to 4.19; drug consideration: HR=6.44, 95% CI 4.49 to 9.25). Compared with LDL-C goal/fit, CVD mortality risk was higher in the LDL-C goal/unfit (4.8, 2.5 to 9.1), TLC initiation/fit (3.0, 1.7 to 5.3), TLC initiation/unfit (7.5, 3.7 to 15.2), drug consideration/fit (7.2, 4.6 to 11.4), and drug consideration/unfit (14.9, 9.1 to 24.4) groups. A similar gradient was observed for metabolic syndrome across intervention windows.

Conclusions—Men eligible for TLC or drug consideration under ATP III-R were at elevated risk of CVD mortality compared with men who met the LDL-C goal. Furthermore, men who were physically fit or who did not have the metabolic syndrome had a lower risk of CVD mortality. (*Circulation*. 2005;112:1478-1485.)

Key Words: epidemiology ■ death, sudden ■ risk factors ■ follow-up studies ■ exercise

Global risk assessment and physician treatment algorithms are accepted aids to decision making in cardiovascular medicine, owing in large part to the clinical guidelines of the National Cholesterol Education Program (NCEP) Expert Panel. In 2001, the third NCEP report (Adult Treatment Panel; ATP III) recommended focusing on LDL cholesterol (LDL-C) as the primary target for coronary heart disease (CHD) risk reduction.[1] These guidelines have since been revised (ATP III-R)[2] to incorporate the results of recent "statin" (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) trials and their efficacy in lowering LDL-C. Like the previous version, the revised guidelines also emphasize the importance of therapeutic lifestyle change (TLC; diet, physical activity, and weight management) in the prevention and treatment of atherosclerosis in primary and secondary care, a position that has been reinforced by a statement from the American Heart Association's Council on Clinical Cardiology.[3]

The current guidelines use an evidence-based global risk assessment approach to identify immediate and long-term risk, while identifying opportunities for intervention. To apply the ATP III-R guidelines, the number of traditional CHD risk factors is counted (0 to 5) and used to classify a patient into a preliminary risk status category (lower, moderate, moderately high, and high risk). Within each risk status category, patients are classified into 1 of 3 intervention groups based on their LDL-C level: (1) at or below LDL-C goal ("LDL-C goal"); (2) initiate TLC ("TLC initiation"), and (3) consider drug therapy ("drug consideration"). Beyond LDL-C lowering, ATP III-R also recognizes the importance of the metabolic syndrome and physical activity in defining CHD risk. Furthermore, within the high-risk status group, universally low LDL-C targets are recommended for all patients with diabetes, those with high Framingham risk scores, and those with previous coronary events.

Risk Category	LDL-C Goal	TLC Initiation	Drug Consideration
High Risk CHD or CHD Risk Equivalents (10-y risk >20%)	<2.59 mM (optional goal: <1.81 mM)	≥2.59 mM	≥2.59 mM (<2.59 mM: consider drug options)
Moderately High Risk 2+ risk factors (10-y risk 10% to 20%)	<3.36 mM	≥3.36 mM	≥3.36 mM (2.59-3.35 mM: consider drug options)
Moderate Risk (10-y risk <10%)	<3.36 mM	≥3.36 mM	≥4.14 mM
Lower Risk 0-1 risk factor*	<4.14 mM	≥4.14 mM	≥4.91 mM (4.14-4.90 mM: LDL-C lowering drug optional)

Figure 1. ATP III-R treatment eligibility groups. The present study compared the risk of CVD mortality across LDL-C goal, TLC initiation, and drug therapy consideration groups. Adapted from Grundy et al.[2] See Methods for further details. *Almost all people with 0 or 1 risk factor have a 10-year risk <10%, and 10-year risk assessment in people with 0 or 1 risk factor is thus not necessary. To convert LDL-C in mmol/L to mg/dL, multiply by a factor of 38.67.

To date, little is known about the clinical application of these guidelines. Given the widespread adoption of previous NCEP reports, a critical investigation of the effectiveness of ATP III-R guidelines in predicting hard end points such as cardiovascular disease (CVD) mortality is both warranted and timely.

The primary aim of the present study was to quantify the association across baseline ATP III-R group classification (LDL-C goal, TLC initiation, and drug consideration) with CVD mortality. Secondary aims of this study were to (1) explore the influence of the metabolic syndrome and cardiorespiratory fitness (CRF) on CVD mortality risk within the ATP III-R classification groups and (2) explore the risk of CVD mortality across subgroups of the high-risk category.

Methods

Participants and Mortality Ascertainment

All men who attended the Cooper Clinic (Dallas, Tex) for a preventive medical examination and a maximal exercise test between 1979 and December 31, 1995 were eligible for inclusion in the Aerobics Center Longitudinal Study (ACLS). Although there are women participants in the ACLS, the number of CVD deaths is at present insufficient to perform the analyses reported here. ACLS men are predominantly white, college- or university-educated professionals. Follow-up was available until December 31, 1996, or death. Thus, the cohort used in the present analysis can be considered to be largely in the prestatin era, before a marked increase in statin use in the late 1990s. Mortality was ascertained by linkage with the US National Death Index, and official death certificates were obtained from each state's public health department. Primary causes of death were coded by a nosologist according to the Ninth Revision of the International Classification of Disease Clinical Modification (ICD-9),[4] and CVD mortality was defined as "diseases of the circulatory system" (390 to 448.9). The study protocol was reviewed and approved by the Institutional Review Board of The Cooper Institute on an annual basis. All men provided written informed consent.

Complete data were available for classification of 23 437 men into ATP III-R treatment categories within the age range (20 to 79 years) to which the adapted Framingham risk algorithm applies. To reduce the potential influence of covert disease on ATP III-R classification, the final sample was limited to 19 125 men who were free of cancer at baseline and had at least 1 year of follow-up. The 4312 men who were excluded tended to be older (mean age 45.9 versus 43.2 years; t=14.8, P<0.0001) than the men in the final study sample; however, there were no differences in the prevalence of being physically unfit between the 2 groups (both 13.8%, χ^2=0.14, P=NS).

Clinical Measurements

Participants reported to the Cooper Clinic after a 12-hour fast for examination by one of the clinic's physicians. All men completed a general health habit questionnaire detailing personal and family medical history in addition to a demographic profile before undergoing a complete clinical battery of blood chemistry, resting blood pressure, and anthropometric measurements. Blood pressures were obtained with a mercury sphygmomanometer by auscultatory methods, and plasma was drawn for total and HDL cholesterol (HDL-C) determination. The Friedewald equation was used to calculate LDL-C, where triglycerides <4.52 mmol/L.[5] All assays were conducted by Cooper Clinic technicians in accordance with the Centers for Disease Control and Prevention lipid standardization program (coefficients of variation <3%).[6]

CRF was assessed by a maximal treadmill test (according to a modified Balke protocol)[7] that began at a speed of 88 m/min and 0% elevation and increased to 2% on completion of the first minute. The elevation was increased by 1% each subsequent minute until 25 minutes had passed, at which point elevation was held at 25% and the speed was increased by 5.4 m/min each minute. Time to volitional fatigue (r=0.92 with directly measured $\dot{V}O_2$max)[8] was translated into metabolic equivalents [METs=(1.44×treadmill time/60+14.99)/3.5]. Age-adjusted METs were then divided into fifths; the bottom quintile (≤20th percentile) was considered "unfit" and the top 4 quintiles (21st to 100th percentile) "fit." These fitness criteria are from previous reports on the cohort.[9]

Body weight and height were measured on a standard physician's balance beam scale and stadiometer, and the body mass index (BMI) was calculated (kg/m²). Waist circumference (WC; cm) was measured with an inelastic anthropometric tape at the level of the umbilicus.

Placement Into ATP III-R Groups

As described in Figure 1, placement into ATP III-R groups involves 4 steps. The first step in identifying LDL-C targets that alter CHD risk is counting of core risk factors.[2] Risk factors that modify the LDL-C goals for ATP III-R treatment are as follows: (1) age ≥45 years,(2) family history of premature CHD (myocardial infarction [MI] or sudden death of male first-degree relative before age 55 years or first-degree female relative before age 65 years), (3) current cigarette smoking, (4) hypertension (≥140/90 mm Hg or a history of physician-diagnosed hypertension), and (5) low HDL-C (<1.03 mmol/L); if HDL-C is ≥1.55 mmol/L, 1 risk factor is removed from the count. Approximately 24% of men had 0 risk factors (an additional 4% also had a high HDL-C level that qualified as a negative risk factor), 34.5% had 1 risk factor, and 37.5% had ≥2 risk factors. In the second step of ATP III-R, men with ≥2 risk factors are indicated for an assessment of their 10-year risk of "hard" coronary events (MI and coronary-related death) with the adapted Framingham algorithm, an index of CHD risk based on categories of age, age-adjusted total cholesterol, HDL-C, systolic blood pressure (treated and untreated), and age-adjusted cigarette smoking (0=nonsmoker, 1=any in past month). Of men with ≥2 core risk factors, the median Framingham 10-year risk of coronary events was 8% (range 1% to 30%), with 32.7% and 11.7% having a 10% to 20% and >20% 10-year risk, respectively. In the present study, ACLS men only had

1 baseline blood lipid measurement rather than the recommended average of two,[2] and cigarette smoking was based on self-report (0=quitter or nonsmoker, 1=current smoker). Also, information on use of blood pressure medication such as β-blockers or diuretics was not universally available, but information on physician-diagnosed hypertension was available in the medical record. Finally, family history of premature coronary events was defined as a parental heart attack, bypass surgery, or angina under the age of 50 years.

In the third step of the ATP III-R, 4 CHD risk categories are identified to indicate target thresholds for LDL-C lowering: men with (1) 0 to 1 risk factor (lower risk); (2) ≥2 risk factors with <10% 10-year CHD risk (moderate risk); (3) ≥2 risk factors and 10% to 20% 10-year CHD risk (moderately high risk); and (4) established CHD or CHD risk equivalents (other vessel disease, diabetes, >20% 10-year CHD risk; high risk). In the ACLS, men were coded as diabetic (n=470; 2.5%) in the presence of high fasting blood glucose (≥7.0 mmol/L) or a self-reported previous physician diagnosis of diabetes. A previous heart attack was self-reported in 326 men (1.7% of sample), and another 335 men (1.8%) had a 10-year CHD risk >20%. Multiple CHD risk equivalents were found in 53 men; thus, 1076 men (5.6% of the sample) were automatically placed in the high-risk category for which aggressive LDL-C lowering treatment is recommended.

In the final step of the ATP III-R, men are assigned to LDL-C goal, TLC initiation, or drug consideration groups on the basis of the LDL-C target of each participant's respective core risk factor category (Figure 1). The LDL-C thresholds for TLC initiation were 4.14, 3.36, 3.36, and 2.59 mmol/L across the low-, moderate-, moderately high-, and high-risk categories, respectively. Corresponding LDL-C thresholds for drug consideration (4.91, 4.14, 3.36, and 2.59 mmol/L) were also applied and represent a lowering of the high-risk LDL-C goal for drug consideration (from 3.36 to 2.59 mmol/L) in ATP III-R, with an optional LDL-C goal of 1.81 mmol/L in those at very high immediate risk.

Secondary Targets of ATP III-R

Secondary targets of risk reduction include TLC approaches to the metabolic syndrome, a constellation of atherogenic risk factors, once elevated LDL-C has been addressed. According to the ATP III working definition,[1] the metabolic syndrome is defined by 3 or more of (1) abdominal obesity (WC >102 cm), 2) high triglycerides (≥1.69 mmol/L), (3) low HDL-C (≤1.03 mmol/L), (4) high blood pressure (≥130/85 mm Hg), or (5) high fasting blood glucose (≥6.11 mmol/L). According to the revised guidelines, TLC initiation is automatically indicated in the presence of (1) high triglycerides (>2.26 mmol/L), (2) high BMI (≥30 kg/m^2), (3) physical inactivity, or (4) the metabolic syndrome, when core risk factor status is moderately high or high. In application of ATP III-R to the ACLS cohort, we have substituted the lowest quintile of age-adjusted METs (physically unfit) for "physical inactivity." Indeed, previous research has indicated that CRF is a good marker for physical activity levels in the months preceding a fitness test.[10]

Statistical Analysis

Survival characteristics (follow-up length and crude and adjusted CVD death rates/10 000 man-years) of each ATP III-R group were generated, and survival curves were estimated by the Kaplan-Meier method and compared with log-rank statistics. Deaths that were not cardiovascular in origin were treated as right-censored observations. The proportional hazards assumption of the log-linear Cox regression model was assessed by visual inspection of negative log by negative log survival plots, and a formal test of proportionality with age- and time-dependent ATP III-R groups was conducted. This test revealed no violation of proportional hazard assumptions (Wald χ^2=3.43, df=3, P=0.33).

To investigate the primary study aims, risk of CVD mortality across baseline ATP III-R groups was assessed by entering dummy coded TLC initiation (0=no; 1=TLC initiation) and drug consideration (0=no; 1=drug consideration) variables into the time-fixed regression model,[11] with adjustment for year of examination. Second, to examine the persistent effect of age, interactions with ATP

III-R groups were probed, and age-stratified (20 to 39 years; 40 to 59 years; and 60 to 79 years) analyses were conducted.

To explore our secondary aims, we fit Cox regression models under 2 conditions: (1) ATP III-R without inclusion of the metabolic syndrome as an automatic inclusion for TLC initiation in the moderately high and high core risk factor categories but with cross-classification into "metabolic syndrome" and "no metabolic syndrome" within each ATP III-R group, and (2) ATP III-R without inclusion of "unfit" as an automatic inclusion, with cross-classification into "unfit" and "fit" within the ATP III-R groups, as above. Furthermore, to provide insight into the relative risk across subgroups of the risk equivalents in the high core risk factor category, men were classified into 4 mutually exclusive subsets, representing men with (1) previous coronary events, (2) diabetes, (3) Framingham risk scores >20%, and (4) 2+ risk equivalents, compared with lower, moderate, and moderately high categories combined. Finally, the additive effects of BMI, WC, and CRF on CVD mortality beyond ATP III-R classification were assessed in 6 subsequent Cox regression models of increasing complexity. All statistical analysis were conducted in SAS version 8.0, and statistical significance was set at an α-level of 0.05.

Results

Description of Study Population

Table 1 presents the baseline characteristics of the sample. In this sample, 58% were classified as being in the LDL-C goal group, whereas 18% were eligible for TLC initiation and 24% for drug consideration. As expected, there was a positive gradient of the component risk factors (eg, 10-year risk of CHD, metabolic syndrome, diabetes, and cigarette smoking) across the LDL-C goal, TLC initiation, and drug consideration groups. There was also a strong age-related gradient in the prevalence of drug consideration.

Survival Analysis by ATP III-R Categories

There were a total of 489 deaths, 179 of which were cardiovascular in origin. CHD represented ≈60% of all CVD deaths and a proportionally similar (P=NS) number across ATP III-R groups (Table 2). Of all CHD deaths, the most common causes of death were acute MI (ICD-9 410; 67 deaths) and coronary atherosclerosis (ICD-9 414; 46 deaths).

Differences in survival probabilities across LDL-C goal, TLC initiation, and drug consideration groups (log-rank χ^2=134.3, df=2, P<0.001) are shown in Figure 2 and represent approximately 4, 9, and 23 deaths per 10 000 man-years, respectively. Overall, after adjustment for year of examination, the TLC initiation (hazard ratio [HR]=2.65, 95% CI 1.67 to 4.19) and drug consideration (HR=6.44, 95% CI 4.49 to 9.25) groups were at markedly elevated risk of CVD mortality compared with the LDL-C goal group (Figure 3A). The observed HRs were attenuated by the addition of age to the model. Evidence for age as an effect modifier was also apparent. There was a significant age-by-drug consideration interaction, whereas age did not modify the TLC initiation–mortality relationship. Drug consideration in the 40-to-59-year-old group was associated with a greater relative risk of CVD mortality than either the younger or older age groups (Figure 3B). Although ATP III-R is intended to prevent CHD-related morbidity and mortality, risk of all-cause mortality was also elevated in the TLC initiation (HR=1.57, 95% CI 1.22 to 2.01) and drug consideration (HR=2.80, 95% CI 2.29 to 3.40) groups by comparison to

TABLE 1.   Characteristics of Participants Across ATP III-R Groups

	LDL-C Goal (n=11 132)	TLC Initiation (n=3420)	Drug Consideration (n=4573)
Age, y	40.6±9.2	44.2±9.0§	48.9±9.2‖#
BMI, kg/m^2	25.7±3.4	26.9±3.5§	27.3±3.6‖#
WC, cm	91.5±10.1	95.4±10.0§	97.3±10.3‖#
Total cholesterol, mmol/L	4.87±0.71	5.87±0.69§	6.48±1.15‖#
LDL-C, mmol/L	3.07±0.59	4.00±0.60§	4.59±1.08‖#
HDL-C, mmol/L	1.23±0.31	1.13±0.28§	1.07±0.26‖#
Triglycerides, mmol/L	1.25±0.71	1.61±0.82§	1.79±0.81‖#
Systolic blood pressure, mm Hg	118.3±11.8	120.9±12.5§	123.7±14.2‖#
Diastolic blood pressure, mm Hg	78.9±8.8	81.6±9.3§	83.4±9.7‖#
Framingham 10-year CHD risk, %	3±3	5±4§	12±7‖#
Prevalence, %			
Age category			
20–39 y	74.6	14.5§	10.8‖#
40–59 y	49.7	20.4§	29.9‖#
60–79 y	33.0	16.1§	50.9‖#
Metabolic syndrome	9.4	22.5§	33.0‖#
Current smoker*	12.2	14.6§	32.4‖#
No alcohol consumption†	25.0	27.1	26.5
Obese (BMI ≥30 kg/m^2)	9.7	17.1§	19.0‖
High WC (>102 cm)	13.9	23.1§	28.3‖#
Physically unfit‡	10.0	15.1§	22.1‖#
Diabetes	0.2	1.2§	8.9‖#

Plus-minus values are mean±SD.

*Self-reported current cigarette smokers.

†Self-report of no regular weekly alcohol consumption.

‡Top four fifths of age-adjusted METs (21st to 100th percentile).

One-way ANOVA across ATP III-R categories (Scheffe planned contrasts $P<0.01$); χ^2 test between groups (Bonferroni corrected pairwise comparisons $P<0.01$): §TLC initiation vs LDL-C goal; ‖drug consideration vs LDL-C goal; #drug consideration vs TLC initiation.

the LDL-C goal group, after adjustment for year of examination.

## Influence of Secondary Targets on Survival

When we compared risk of CVD mortality for men with and without the metabolic syndrome within ATP III-R categories, men with the metabolic syndrome in the drug consideration group (HR=1.51, 95% CI 1.02 to 2.23) but not those in the LDL-C goal (HR=1.93, 95% CI 0.86 to 4.32) or TLC initiation (HR=1.06, 95% CI 0.43 to 2.61) groups, were at a

significantly greater risk of CVD mortality than those without the metabolic syndrome. Figure 4A depicts a trend for higher CVD mortality across strata of ATP III-R and the metabolic syndrome. Thus, compared with men in the LDL-C goal/no metabolic syndrome group, men in the drug consideration/ metabolic syndrome group (HR=8.2, 95% CI 5.3 to 12.8) were at greatest risk of CVD mortality.

Within ATP III-R categories, physically unfit men in the LDL-C goal (HR=5.61, 95% CI 3.06 to 10.29) and drug consideration (HR=2.07, 95% CI 1.40 to 3.08) groups were

TABLE 2.   Causes of CVD Mortality According to ICD-9 Codes

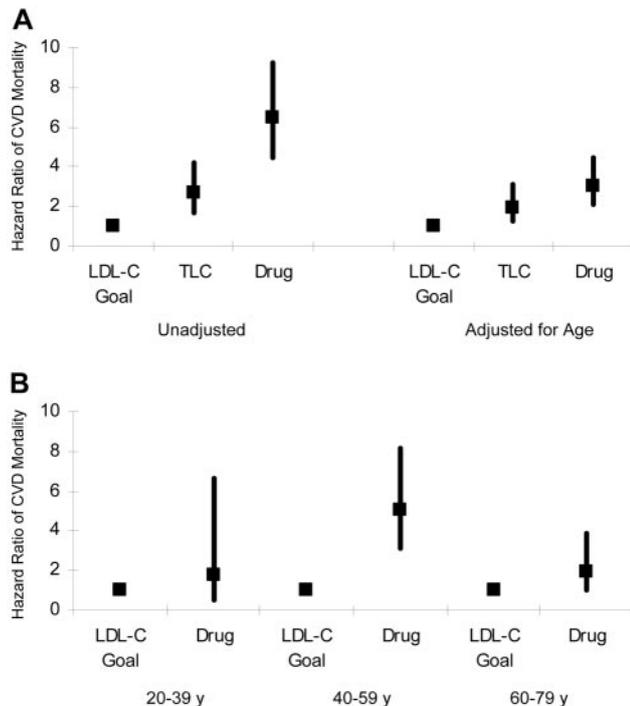|	LDL-C Goal (n=11 132)	TLC Initiation (n=3420)	Drug Consideration (n=4573)	Total (n=19 125)
Hypertensive disease (401–404)	2	0	4	6
CHD (410–414)	24	24	65	113
Diseases of pulmonary circulation (415–417)	0	0	1	1
Other forms of heart disease (420–429)	10	8	17	35
Cerebrovascular disease (430–438)	4	1	12	17
Diseases of arteries, arterioles, and capillaries (440–448)	1	0	6	7
CVD-related deaths	41	33	105	179
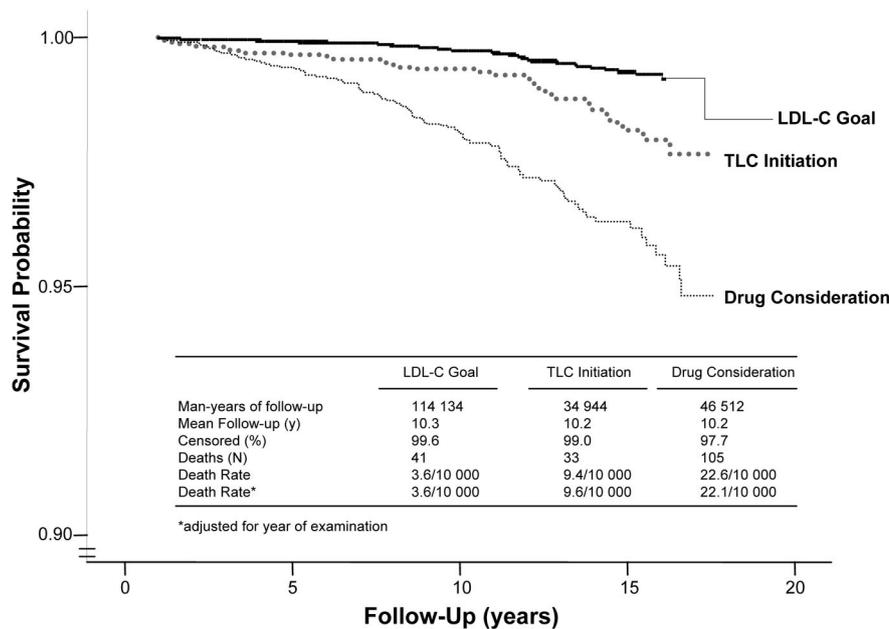
Figure 2. Kaplan-Meier survival probability across baseline ATP III-R risk categories. Censored % is the percentage of the sample who were survivors or those who died of causes that were not cardiovascular in origin. Log-rank χ^2=134.3, *df*=2, *P*<0.001.

at significantly increased risk of CVD mortality compared with fit men, whereas the relationship was not significant in the TLC initiation group (HR=1.88, 95% CI 0.83 to 4.26). A gradient of increasing risk of CVD mortality emerged both within and between CRF categories such that men in the drug consideration/unfit group were at markedly elevated risk (HR=14.89, 95% CI 9.11 to 24.35) compared with men in the LDL-C goal/fit group (Figure 4B).


Figure 3. A, Comparison of risk of CVD mortality by baseline ATP III-R treatment groups. B, Comparison of risk of CVD mortality in drug consideration vs LDL-C goal groups across age categories. All models were adjusted for year of examination. Error bars represent 95% CIs.

Table 3 describes the influence (per SD) of adiposity (BMI and WC) and CRF on risk of CVD mortality in the TLC initiation and drug consideration groups by comparison with the LDL-C goal group. Owing to collinearity between BMI and WC (*r*=0.86), no model included both BMI and WC. In separate models, BMI and WC moderately attenuated the risk of CVD mortality associated with TLC initiation and drug consideration status; however, the inclusion of METs in a separate model resulted in an approximate 50% reduction in the risk associated with drug consideration. The addition of either BMI or WC to models that already included METs did not further reduce risk of CVD mortality associated with TLC initiation or drug consideration.

To investigate whether CVD mortality risk was similar across the high core risk factor subgroups, we compared coronary risk equivalents. By comparison with lower-, moderate-, and moderately high–risk men combined, those with a combination of 2 or more risk equivalents were at markedly elevated risk of CVD mortality (HR=28.9, 95% CI 14.7 to 57.0), followed by those who reported a previous coronary event (HR=14.6, 95% CI 9.7 to 22.1), diabetics (HR=6.3, 95% CI 3.7 to 10.8), and men with a high Framingham risk score (HR=4.5, 95% CI 2.3 to 9.0; Figure 5). Across high-risk men, 47% of the CVD deaths occurred in those reporting a previous coronary event, 25% in diabetics, and 15.8% in men with a high Framingham risk score, and the remaining 12.5% were men with multiple risk equivalents. There were also differences in the cause of death within each subgroup, with ischemic events being most common in men reporting a previous coronary event.

Discussion

Primary Aims

Results of this study indicate that the relative risk of CVD-related mortality was more than twice as high in men in the TLC initiation group at baseline and almost 7-fold higher in
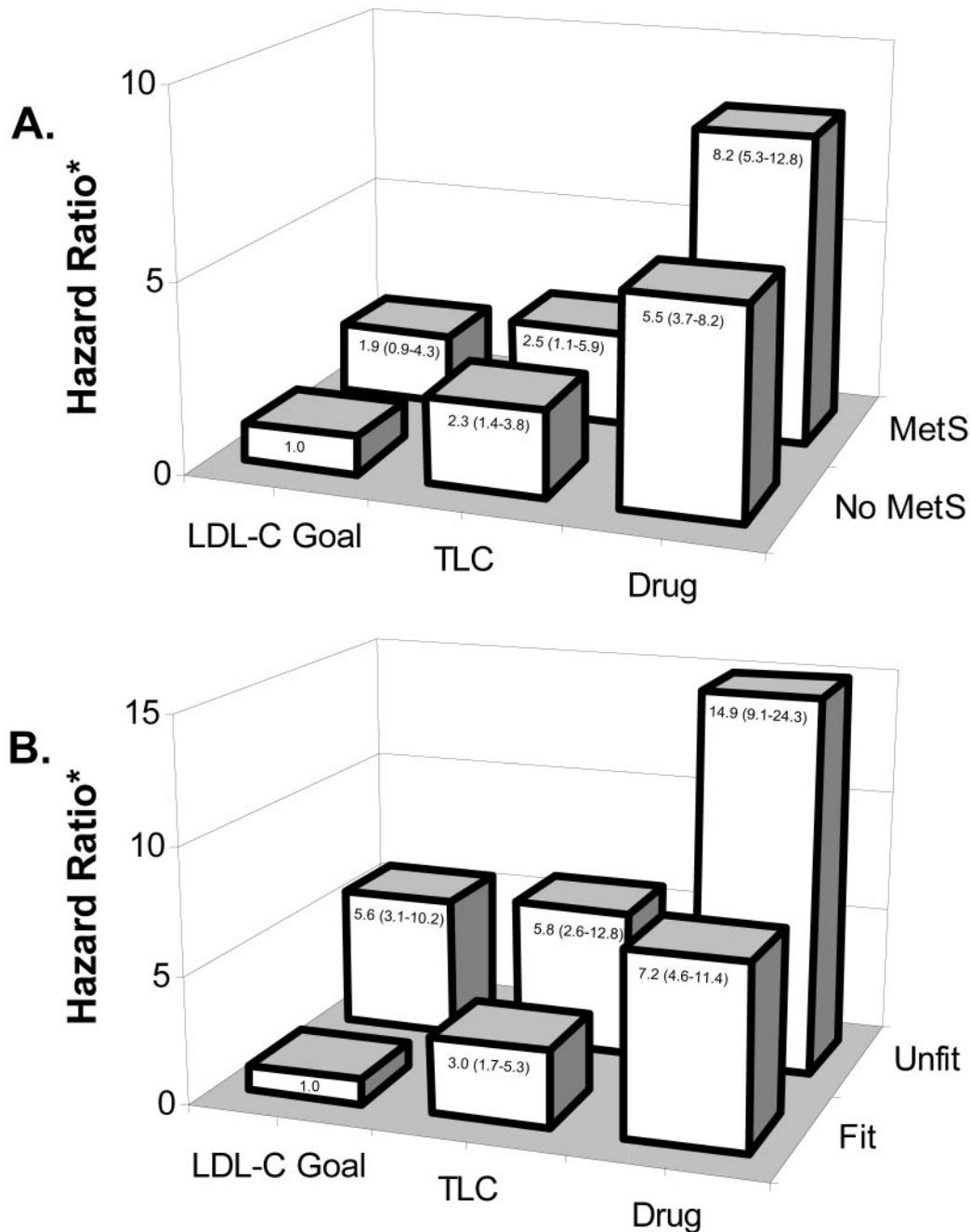
Figure 4. Risk of CVD mortality across ATP III-R treatment groups and metabolic syndrome (MetS; A) and physical fitness groups (B). *Adjusted for year of examination. Unfit indicates lowest 20% of age-adjusted treadmill METs; Fit, top 80%. Values are HRs (95% CIs).

men eligible for drug consideration under ATP III-R. Given that approximately one fourth of Americans (aged 20 to 79 years) were eligible for aggressive lipid-lowering therapy under ATP III,[12] lowering the threshold for consideration of lipid-lowering drug therapy in those at high immediate and long-term risk (ie, ATP III-R) is likely to have important implications for both population health and healthcare utilization. In the present study, the relative risk of CVD mortality in men in the drug consideration group was higher when the ATP III-R guidelines were applied (HR=6.44, 95% CI 4.49 to 9.25) by comparison with the original ATP III guidelines (HR=4.75, 95% CI 3.39 to 6.65), which suggests that the

new criteria are effective at identifying men at a high risk of CVD mortality.

Secondary Aims
In 2001, ATP III released a working definition of the metabolic syndrome that is now included within ATP III-R as a target for TLC in individuals with moderately high and high core risk factor status. The inclusion of the metabolic syndrome as a therapeutic target of global risk assessment is an important advance in treatment for the estimated 25% of the US population that has the metabolic syndrome.[13] In ACLS men, 45% of those with the metabolic syndrome were in the

TABLE 3. Contribution of BMI, WC, and CRF (METs) to Risk of CVD Mortality in TLC Initiation and Drug Consideration, Compared With Men in the LDL-C Goal Group

	TLC Initiation*	Drug Consideration*	BMI	WC	METs
Model 1	2.65 (1.67–4.19)	6.44 (4.49–9.25)			
Model 2	2.49 (1.57–3.95)	5.93 (4.11–8.56)	1.20 (1.05–1.38)		
Model 3	2.41 (1.52–3.82)	5.60 (3.87–8.09)		1.30 (1.14–1.49)	
Model 4	1.85 (1.16–2.93)	3.01 (2.06–4.40)			0.35 (0.30–0.42)
Model 5	1.88 (1.18–2.98)	3.03 (2.08–4.43)	0.86 (0.74–0.99)		0.33 (0.28–0.40)
Model 6	1.88 (1.18–2.99)	3.05 (2.09–4.46)		0.89 (0.77–1.03)	0.34 (0.28–0.40)

Results are HR (95% CI) and are expressed per SD of BMI (kg/m^2), WC (cm), and METs.

*All models include TLC initiation and drug consideration groups compared with LDL-C goal group (referent not shown).

Because of multicollinearity, BMI and WC are presented in separate models with METs.

Model 1 included year of examination as a covariate; Model 2, BMI and year of examination as covariates; Model 3, WC and year of examination as covariates; Model 4, METs and year of examination as covariates; Model 5, BMI, METs, and year of examination as covariates; and Model 6, WC, METs, and year of examination as covariates.

drug consideration group compared with an estimated eligibility for drug consideration of 39.2% among Americans with the metabolic syndrome.[14] Because LDL-C is not always elevated in those with the metabolic syndrome, inclusion of the metabolic syndrome in ATP III-R global risk assessment is a potentially essential element to identify individuals at elevated risk of CHD.[14] In the ACLS, cross-classification of those with and without the metabolic syndrome demonstrates a trend toward increased risk of CVD mortality across ATP III-R strata. Compared with healthy men, the risk of CVD mortality has been shown to be ≈2-fold greater[15,16] when the metabolic syndrome is present, similar to the results presented in Figure 4.

Results from the present study also suggest that within a given ATP III-R risk category, CRF is associated with a 50% lower risk of CVD mortality. The amount of physical activity associated with being in the physically fit group in the present study is approximately 4 to 5 bouts of 30 minutes' duration (equivalent to walking between 130 and 138 minutes per week),[17] which is consistent with recommendations from the *Surgeon General's Report on Physical Activity and Health*.[18] It is also clear that the optimal approach to improving total cholesterol, LDL-C, triglycerides, blood pressure, blood glucose, and insulin resistance should include lifestyle modification.[2,19] Despite the acknowledged genetic contributions to CRF, physical activity is the only way by which an individual can increase his or her CRF; thus, despite difficulties with long-term physical activity intervention, it continues to be a necessary component to lowering long-term CVD risk. This reinforces our position that physical activity and CRF should be emphasized as a concomitant therapy in both TLC initiation and drug consideration groups.

Subset analysis of CHD risk equivalents in men in the high-risk category also suggests that all CHD risk equivalents may not be equal. Here, we report that relative risk of CVD mortality is highest in men with a previous coronary event and lowest in those with a high Framingham risk score. However, this analysis should be viewed as exploratory; in addition to small sample sizes in the subgroup analysis, it is also not yet fully clear whether more aggressive LDL-C treatment targets or different therapeutic approaches can improve CVD outcomes in each of the above subgroups.

Study Limitations

This study has some limitations that warrant recognition. We were unable to address the potential influence of prescription drug use on ATP III-R classification and subsequent mortality. Even though data for the present study were ascertained in the prestatin era, it is possible that other lipid-lowering drugs may have influenced the observed relationships. At baseline, ≈25% of men reported taking a medication other than insulin. Although medication use was an independent predictor of CVD mortality when included in a model with ATP III-R categories (HR=2.55, 95% CI 1.41 to 4.61), its inclusion as a covariate did not alter the relationship between ATP III-R categories and CVD mortality. Given that higher-risk men in this cohort with excellent access to medical care would perhaps be more likely to receive pharmacological treatments and coronary revascularization, the lack of complete data on CVD morbidity would likely bias the results toward the null.

Because only baseline measurements were used, it is unclear what changes in lifestyle factors or medical history
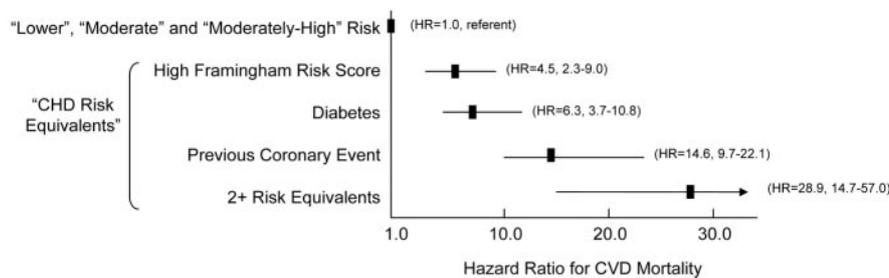
Figure 5. Subset analysis of ATP III-R risk equivalents for CVD mortality, by comparison with lower-risk men combined. Within the pooled referent group (lower, moderate, and moderately high risk), there were 17 941 men, and within the risk equivalent group, there were 1184 men (diabetics: n=470; previous coronary events: n=326; >20% 10-year risk: n=335; 2+ risk equivalents: n=53). Values are HRs (95% CIs).

occurred over the follow-up period and how these changes influenced the observed relationships. Additionally, the ACLS is composed of predominantly non-Hispanic white, college- or university-educated, upper-middle-class men, which limits the generalizability of the findings. However, the proportion of the sample in the drug consideration group in the present study (24%) is similar to the 26% that has been reported for American men for aggressive lipid-lowering therapy.[12] The number of deaths among women in the ACLS is not yet sufficient to perform parallel analyses.

Finally, although the NCEP guidelines are intended to identify target thresholds that lower atherosclerosis and CHD risk, we elected to predict all CVD deaths. In a post hoc analysis, we fit a Cox regression model, adjusted for year of examination, to CHD-related mortality (ICD-9 410 to 414). Results were similar to those seen in the CVD analysis (LDL-C goal HR=1.00, TLC initiation HR=3.30 [95% CI 1.87 to 5.80], and drug consideration HR=6.85 [95% CI 4.29 to 10.94]). Future studies should address these issues with incident CVD and specific categories of CVD (eg, CHD and stroke).

Summary

The present study supports the evidence-based clinical update of the NCEP and indicates that inclusion of the metabolic syndrome as a secondary target of cardiovascular risk reduction in men is appropriate. However, these data also suggest that the risk of CVD mortality may not be uniform across CHD risk equivalents in high-risk men. The inclusion of physical inactivity as an automatic rationale for TLC initiation in moderately high- and high-risk categories is an important advance in ATP III-R risk prediction. Given the magnitude of the relative risk associated with the additional stratification by CRF, all patients should be encouraged to be physically active and to maintain adequate levels of physical fitness.

Acknowledgments

Disclosure

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