

The Cholesterol Population Model: US Population Requirements for Treatment of Hypercholesterolemia

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Abstract

This report describes the development of the cholesterol population model to assist managed care and other healthcare providers in designing and benchmarking treatment guidelines and disease management programs for the treatment of hypercholesterolemia. The model enables providers to better answer two questions: (1) In a covered population, what proportion of patients have hypercholesterolemia eligible for treatment according to National Cholesterol Education Program (NCEP) guidelines? (2) How intensively should patients be treated? Based on analysis of the National Health and Nutrition Examination Surveys, which provide an estimate of the lipid levels in the US population by age, gender, and coronary heart disease (CHD) risk factor status, the model estimates the proportion of the general population eligible for pharmacologic therapy under the NCEP-Adult Treatment Panel II Guidelines. Assuming a fairly generous reduction in low-density lipoprotein cholesterol (LDL-C) of 10% with dietary modifications, approximately 7% of the US population (>12 million people) are eligible for pharmacologic therapy. Nearly 90% of these patients have documented CHD or have multiple CHD risk factors, confirming the intuitive clinical impression that efforts should focus on those patients at relatively high risk for cardiovascular events. The model provides an estimate of the proportions of individuals who can achieve their LDL-C goal with various treatment interventions. The model suggests that a majority of patients can achieve their LDL-C goal with disease management programs designed to aggressively lower cholesterol (targeting an average 31% reduction of LDL-C in patients with documented CHD or multiple CHD risk factors). The estimates of the effectiveness of different treatment approaches provided by the model may be useful in guiding managed care organizations in the design of disease management programs for hypercholesterolemia.

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The shift in focus of healthcare delivery to population health management has largely been driven by managed care organizations. To make informed decisions regarding the design of disease management (or case management) approaches, managed care providers need to know the prevalence of a condition within a covered population and the potential of different strategies to achieve treatment objectives.

Because of the prevalence and costs associated with cardiovascular disease, many managed care organizations are already designing and implementing disease management programs for patients at relatively high risk for adverse cardiovascular events. These efforts stem from initiatives undertaken by public health agencies to reduce the incidence of coronary heart disease (CHD) in the US population through education, prevention, and treatment guidelines.

A major emphasis of these programs has been to encourage people to lower their saturated fat and cholesterol intake and to obtain professional dietary counseling or seek treatment intervention if hypercholesterolemia still persists. The concept of target or goal low-density lipoprotein cholesterol (LDL-C) has been advanced and refined through two national consensus conferences. Currently, physicians are encouraged to treat patients more intensively and to counsel them to facilitate attainment of these goals.¹ Despite these initiatives, CHD is still the main cause of mortality in the United States.² Data from the National Health and Nutrition Examination Survey III (NHANES III) show that 30.9% of all adults (>54 million people; Table 1) are still candidates for at least dietary intervention to lower cholesterol levels as part of a CHD risk reduction strategy.^{3,4}

Current primary prevention guidelines for the management of hypercholesterolemia advocate dietary intervention first. However, the efficacy of dietary modification alone is limited—in the range of 3% to 7% total cholesterol reduction.^{5,6} Based on NHANES III data, the proportion of the adult US

Table 1. Number and Percentage of US Adults Who Are Candidates for Therapy to Lower Cholesterol Levels*

Risk Group Category	LDL-C (mg/dL)	LDL-C Category	Number	Percent	
				Risk Group	US Population
CHD	≤100 [†]	At goal	1,775,320	14.3	1.0
	100–129 [†]	Dietary therapy candidate	4,970,896	39.8	2.8
	≥130	Potential drug therapy candidate	5,681,024	45.7	3.2
MRF	<130	At goal	20,061,116	41.7	11.3
	130–159	Dietary therapy candidate	12,959,836	27.1	7.3
	≥160	Potential drug therapy candidate	14,912,688	31.2	8.4
<2RF	<160	At goal	100,838,176	86.1	56.8
	160–189	Dietary therapy candidate	11,184,516	9.6	6.3
	≥190	Potential drug therapy candidate	5,148,428	4.4	2.9
Total		At goal	122,674,612		69.1
		Dietary therapy candidate	29,115,248		16.4
		Potential drug therapy candidate	25,742,140		14.5

*US population data were based on results of the National Health and Nutrition Examination Survey III.³

[†]One percent of the US population has CHD and LDL-C of <100 mg/dL. The National Center for Health Statistics report indicates that 5.7 million people in the United States with CHD have LDL-C of <130 mg/dL.

LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease; MRF = multiple cardiac risk factors; <2RF = fewer than two risk factors for coronary heart disease.

population still eligible for pharmacologic therapy after dietary intervention (assuming that dietary intervention reduces LDL-C by 1%–15%) is estimated to be between 4% and 12%. Assuming a fairly generous 10% estimate for reduction of LDL-C by diet alone, approximately 7% of the US population (>12 million people) are eligible for pharmacologic therapy.

Compelling data have recently become available suggesting that aggressive therapy of patients at relatively high risk for adverse cardiovascular events can reduce total and cardiovascular mortality and resource utilization.⁷⁻⁹ However, the proportion of high-risk patients with hypercholesterolemia in the United States receiving treatment remains relatively low.^{10,11}

One obstacle to the widespread implementation of treatment programs for high-risk patients may be the perception that goal attainment frequently will require the use of therapy involving combinations of high doses of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors with niacin and bile acid-binding resins. Patient compliance with combination therapy is relatively poor; therefore, this therapy is not considered optimal. The frequent side effects associated with niacin therapy, the inconvenient dosing regimens, and the gastrointestinal side effects associated with resins reduce compliance. Furthermore, there are safety concerns regarding the use of combination therapy with niacin and HMG-CoA reductase inhibitors.¹² For example, in a prospective clinical effectiveness trial of cholesterol treatment at Southern California Kaiser Permanente, few patients were treated with combination therapy. Although

combination therapy was specified in the stepped-care treatment algorithm of the study, only 3 of 267 patients randomized to stepped care were actually using combination therapy at the end of 1 year.¹³

Another obstacle to the widespread implementation of treatment programs for high-risk patients, particularly for managed care, may be a perceived need for better information to answer two key questions: (1) In a covered population, what proportion of patients have hypercholesterolemia eligible for treatment according to National Cholesterol Education Program (NCEP) guidelines? (2) How intensively should they be treated?

The purpose of this paper is to outline the development of the cholesterol population model (CPM), which provides a flexible tool that can enable managed care providers and other healthcare providers to answer these critical questions for their covered populations. The model is based on LDL-C and cardiac risk factor distributions in the US population as identified in the NHANES III survey. By using the model, the cholesterol reductions required to achieve NCEP-recommended goal LDL-C levels can be determined. In addition, the model provides an estimate of the proportion of individuals who can achieve LDL-C goal levels with various treatment interventions, according to a managed care organization's local experience with different treatments or the scientific literature. These estimates can be adjusted based on the demographics of an enrolled managed care population and can provide a useful guide to managed care organizations for designing disease management programs for hypercholesterolemia.

Table 2. NCEP-ATP II Guidelines for LDL-C Based on Cardiac Risk Factors

Cardiac Risk Factor Group	LDL-C Goal (mg/dL)	Dietary Intervention Initiation Level (mg/dL)	Drug Treatment Initiation Level (mg/dL)
<2RF	<160	≥160	≥190
MRF	<130	≥130	≥160
CHD	≤100	>100	≥130

NCEP-ATP II = US National Cholesterol Education Program-Adult Treatment Panel II; LDL-C = low-density lipoprotein cholesterol; <2RF = fewer than two risk factors for coronary heart disease; MRF = multiple cardiac risk factors; CHD = coronary heart disease.

Information on the effectiveness of dietary therapy in lowering LDL-C can be modeled by assuming an effect of 1% to 15%. For the purposes of this paper, we made a conservative base-case assumption that dietary therapy can result in an average reduction in LDL-C of 10%.

Guidelines for Treating Hypercholesterolemia

The model uses the US National Cholesterol Education Program-Adult Treatment Panel II (NCEP-ATP II) guidelines as the reference for calculating the proportion of the US population eligible for treatment.¹ These guidelines state that after an adequate trial of dietary intervention to lower lipid levels, individuals eligible for pharmacologic intervention are those who have an elevated serum LDL-C based on coronary heart disease (CHD) risk status. Table 2 summarizes the guidelines from NCEP-ATP II.

Data Elements

The data on serum lipids collected in NHANES III included total serum cholesterol, HDL-C, and triglycerides. The methods of lipid measurement were previously described.¹⁴ Data on total cholesterol and HDL-C were available for 7,775 persons age 20 years of age and over, whereas data on fasting (9 h) triglycerides were available for 3,342 adults. The LDL-C level was calculated from this large subset (n = 3,342) by using the equation of Friedewald and colleagues.¹⁶

Besides demographic data and serum lipids, NHANES III included questions to elicit information necessary for determination of risk factor status: reported history of heart attack in a first-degree relative before the age of 50 years (for family history of premature CHD), current cigarette smoking history, a positive response to the Rose Questionnaire for Angina Pectoris or a history of heart attack (for definite CHD), reported history of diabetes mellitus, and hypertension as calculated from the mean of several measurements of blood pressure.¹⁴

Methodology of the Model

The schema of the model is illustrated in Figure 1. The NHANES III data were used

... METHODS ...

Data Sources

Information on the population-based distribution (by age and gender) of serum lipids and risk factor status was obtained from NHANES III, conducted by the US National Center for Health Statistics between 1988 and 1994.¹⁴ The first phase (1988-1991) was designed to be a national probability sample and is the source of the data in this model. The individuals who were sampled were drawn from the civilian, noninstitutionalized US population.

Information on the efficacy of the HMG-CoA reductase agent used as an example, lovastatin, was obtained from a 1-year safety and tolerability study known as EXCEL.¹⁵ The efficacy results for lovastatin in conjunction with diet at 20 mg, 40 mg, and 80 mg per day showed a mean reduction from baseline in LDL-C of 24% ± 11% (SD), 30% ± 11%, and 40% ± 11%, respectively.

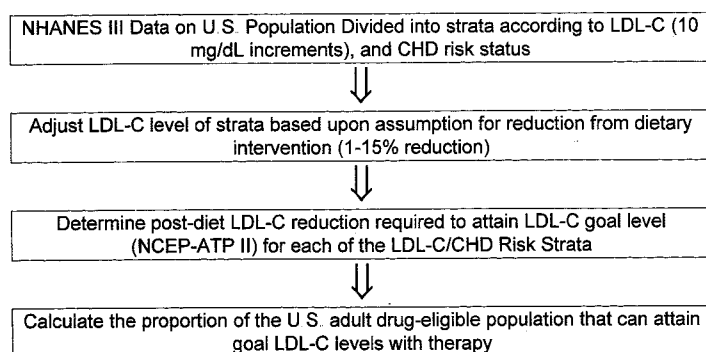


Figure 1. The algorithm employed in the cholesterol population model is illustrated.

NHANES III = National Health and Nutrition Examination Survey III; LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease; NCEP-ATP II = National Cholesterol Education Program-Adult Treatment Panel II.

to divide the US population into subsets based on 10-mg/dL LDL-C increments above 130 mg/dL up to 200 mg/dL (the NCEP guidelines do not suggest drug therapy for any individuals with an LDL-C level below 130 mg/dL). Those with LDL-C levels ≥ 200 mg/dL were assigned a median LDL-C of 211.5 mg/dL and were put into one group because of the small number of survey respondents with these very high levels. The LDL-C interval strata were then further subdivided into LDL-CHD risk strata based on the NHANES III data. NCEP guidelines define three categories of CHD risk factor status: definite CHD (CHD), two or more CHD risk factors and no CHD (MRF; multiple risk factors), and fewer than two CHD risk factors and no CHD (<2RF).

From this distribution, the midpoint of each 10-mg/dL interval was decreased by 10%. This decrease represents the assumed LDL-C reduction as a result of dietary therapy (the model allows the assumed reduction from dietary intervention to be varied from 1% to 15%). To determine the average percentage by which LDL-C must be lowered to reach the goal level for each postdiet LDL-CHD risk stratum, the following was calculated:

$$\frac{(\text{Goal LDL-C for CHD risk status} - \text{postdiet LDL-C midpoint cholesterol}) \times 100}{\text{Postdiet LDL-C midpoint cholesterol}} \quad (1)$$

Thus, for each individual surveyed by NHANES III, we can identify a LDL-C level within a 10-mg/dL interval, the CHD risk status group, and the goal LDL-C level. This information permits calculation of the additional percent reduction of LDL-C necessary to achieve the NCEP goal. Based on risk factor status, the proportion of the US population eligible for pharmacologic treatment can also be calculated.

Finally, using published data on the efficacy of specific drug therapies (mean \pm SD percent lowering of LDL-C from baseline), we could calculate the proportion of drug-eligible patients within each LDL-C/CHD risk stratum that would be expected to reach at least goal levels of LDL-C with a proposed intervention. This calculation is as follows:

$$1 - ZINV \left[\frac{(\text{mean \%LDL-C lowering to attain goal}) - (\text{mean \%LDL-C lowering from intervention})}{(\text{SD of mean \%LDL-C lowering from intervention})} \right] \quad (2)$$

Equation 2 calculates a Z score for the proposed intervention (the amount of required cholesterol lowering as measured in standard deviations from the mean), computes the inverse of that Z score, and subtracts that result from 1 to determine the proportion of the population that will achieve LDL-C control. This equation was applied to each LDL-C/CHD risk stratum in Table 3. For example, if a 23% reduction in LDL-C is required to attain an LDL-C goal and the drug and dose under consideration reduce LDL-C levels on average by 30% (SD = 11%), the calculation is as follows: $1 - Z\text{Inverse} [(.23 - .30)/(.11)] = 0.73$. Therefore, 73% of individuals in the specific LDL-C/CHD stratum could reach the LDL-C goal based on NCEP guidelines.

... RESULTS ...

LDL-C Reduction Required to Attain Goal Levels

The LDL-C distribution for adults in the NHANES III phase I population was projected to the 1990 US population age 20 years and over (see Figure 2). Notice that almost 50% of the population has a serum LDL-C value greater than 130 mg/dL. However, most of these individuals are not eligible for drug therapy based on NCEP guidelines for primary prevention. Of the entire US adult population, 31% would be candidates for dietary therapy. Assuming that dietary intervention decreases LDL-C values by 10% and including a 30-mg/dL gap between the goal LDL-C and the LDL-C threshold for initiating drug therapy, then approximately 7.3% of the population remains eligible for drug therapy (Figure 3, Table 3); all of the persons with initial LDL-C levels between 130 and 140 mg/dL are now ineligible for therapy, as are half of those with initial LDL-C levels between 140 and 150 mg/dL. Of all individuals with postdietary LDL-C levels between 130 and 160 mg/dL, only 6.0% have CHD and are therefore eligible for drug therapy; the remaining patients (without CHD) in this postdiet LDL-C range are not eligible for pharmacotherapy.

The percentage by which LDL-C must be lowered to attain goal levels according to risk factor status is illustrated in Figure 4. Notice that individuals with CHD need substantial LDL-C lowering, ranging from 23% to 48% (weighted average = 31%), depending on their prediet LDL-C level. In contrast, patients in the low-risk-factor group require

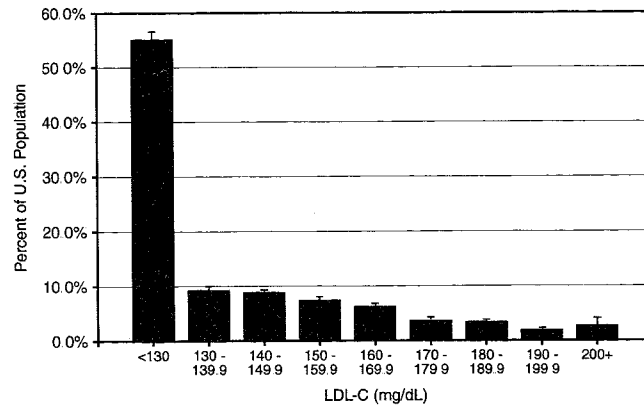


Figure 2. The LDL-C distribution above 130 mg/dL in the adult US population in 10-mg/dL increments, according to data from National Health and Nutrition Examination Survey III.
LDL-C = low-density lipoprotein cholesterol

Table 3. Proportion of US Adult Drug-Eligible Population in Whom Cholesterol-Lowering Medication Can Achieve Goal LDL-C Levels

LDL-C Interval (mg/dL)	Cardiac Risk Factor Status	Percent of US Population	LDL-C After 10% Dietary Reduction	Percent of Each CHD Risk Factor Group Within LDL-C Interval	LDL-C Goal (mg/dL)
<140		64.5			
140-149.9		8.8	130.5		
	<2RF			67.3	≤160
	MRF			27.5	≤130
	CHD			5.2	<100
150-159.9		7.5	139.5		
	<2RF			59.2	≤160
	MRF			31.1	≤130
	CHD			9.8	<100
160-169.9		6.3	148.5		
	<2RF			42.8	≤160
	MRF			48.4	≤130
	CHD			8.7	<100
170-179.9		3.7	157.5		
	<2RF			55.6	≤160
	MRF			39.2	≤130
	CHD			5.2	<100
180-189.9		3.4	166.5		
	<2RF			46.6	≤160
	MRF			47.3	≤130
	CHD			6.1	<100
190-199.9		2.0	175.5		
	<2RF			56.0	≤160
	MRF			36.9	≤130
	CHD			7.2	<100
200+		3.8	190.4		
	<2RF			46.6	≤160
	MRF			42.0	≤130
	CHD			11.4	<100
Total		100.0			

LDL-C = low-density lipoprotein cholesterol; <2RF = fewer than two risk factors for coronary heart disease; MRF = multiple cardiac risk

... CHOLESTEROL POPULATION MODEL ...

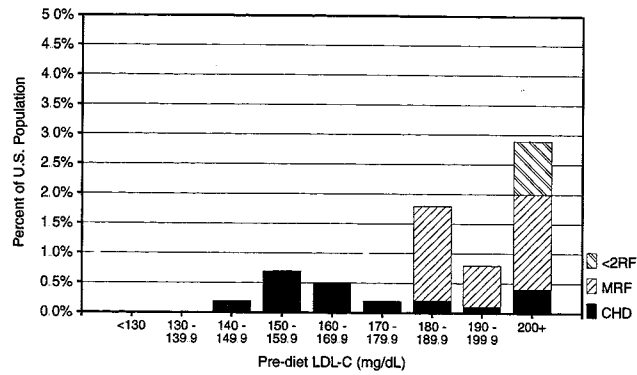


Figure 3. The proportion of the adult US population eligible for drug therapy for hypercholesterolemia after factoring in a 10% dietary reduction in LDL-C levels, according to National Cholesterol Education Program guidelines. All drug-eligible patients with prediet LDL-C levels of <180 mg/dL have definite CHD or atherosclerosis. Among patients with fewer than two CHD risk factors, only those with a prediet LDL-C level of 200 mg/dL are drug eligible. LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease; MRF = multiple cardiac risk factors; RF = fewer than two risk factors for coronary heart disease.

Percent of US Population Eligible for Drug Therapy	Percent of Total Drug Eligible US Population	Percent Decrease in LDL-C Needed to Attain Goal for Drug-Eligible Patients	Z Score	Percent That Can Achieve Goal with Lovastatin 40 mg	Percent of US Population That Can Achieve Goal
0.0	0.0	—	—	—	—
0.0	0.0	—	—	—	—
0.2	3.2	23.4	-0.603	72.7	0.17
0.0	0.0	—	—	—	—
0.0	0.0	—	—	—	—
0.7	10.1	28.3	-0.153	56.1	0.41
0.0	0.0	—	—	—	—
0.0	0.0	—	—	—	—
0.5	7.5	32.7	0.242	40.4	0.22
0.0	0.0	—	—	—	—
0.0	0.0	—	—	—	—
0.2	2.6	36.5	0.592	27.7	0.05
0.0	0.0	—	—	—	—
1.6	21.7	21.9	-0.734	76.9	1.22
0.2	2.8	39.9	0.904	18.3	0.04
0.0	0.0	—	—	—	—
0.7	9.9	25.9	-0.370	64.4	0.47
0.1	1.9	43.0	1.184	11.8	0.02
0.9	12.2	15.9	-1.278	89.9	0.80
1.6	22.1	31.7	0.155	43.8	0.71
0.4	6.0	47.5	1.588	4.6	0.02
7.3	100.0	—	—	—	—

factors; CHD = coronary heart disease.

only a 16% reduction in LDL-C. The latter group, however, represents fewer than 12% of the total drug-eligible population. Patients with multiple risk factors fall in between, requiring LDL-C reductions ranging from 22% to 32%. Because the NCEP guidelines set more stringent LDL-C goals for subsets of higher-risk individuals, the amount of LDL-C lowering required to attain goal LDL-C levels is proportional to the risk.

Projected Proportion of Patients Who Will Reach Goal With Therapy

The EXCEL data were applied to equation 2 for each of the LDL-C/CHD risk strata, and the results were aggregated. Assuming that patients are compliant with lovastatin monotherapy, the total percentages of the drug-eligible population estimated from these data to be able to reach the goal are 39% for the

20-mg strength, 57% for the 40-mg strength, and 81% for the 80-mg strength. The results of this model suggest that the vast majority of patients can achieve current goal LDL-C levels with lovastatin monotherapy. This projection was confirmed in another clinical trial in which patients were treated with lovastatin 40 mg twice a day; 85% of patients achieved goal LDL-C levels.¹⁷

To facilitate the interpretation of the model from a managed care perspective, we calculated the cumulative proportion of a population (which resembles the US population in demographic, CHD risk factor, and LDL-C distribution) that would be expected to attain goal LDL-C levels according to the projected effectiveness of a disease management program that used both dietary and drug intervention. This analysis was performed by aggregating the results for equation 2 across CHD risk strata, varying the mean observed percent reduction in LDL-C as a result of implementation of potential disease management programs from 15% to 50%, and assuming a constant standard deviation of 11% around the mean percent reduction (Figure 5).

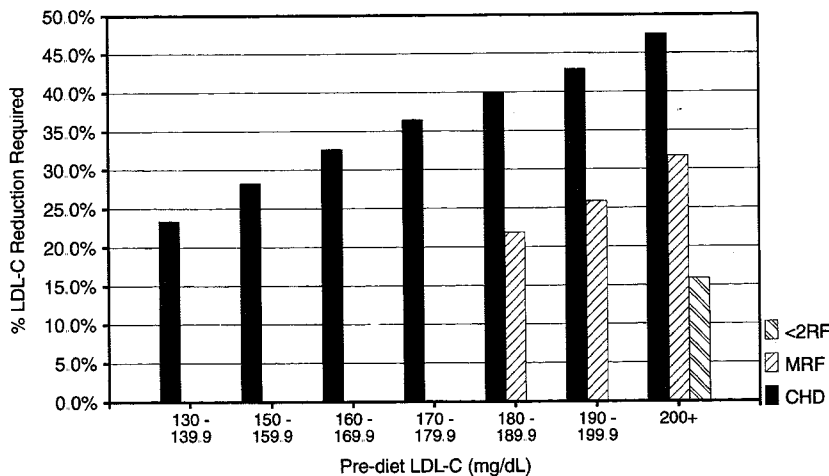


Figure 4. The percent LDL-C reduction needed to attain goal levels according to pre-diet LDL-C 10-mg/dL increments and risk factor status
 LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease; MRF = multiple cardiac risk factors; <2RF = fewer than two risk factors for coronary heart disease

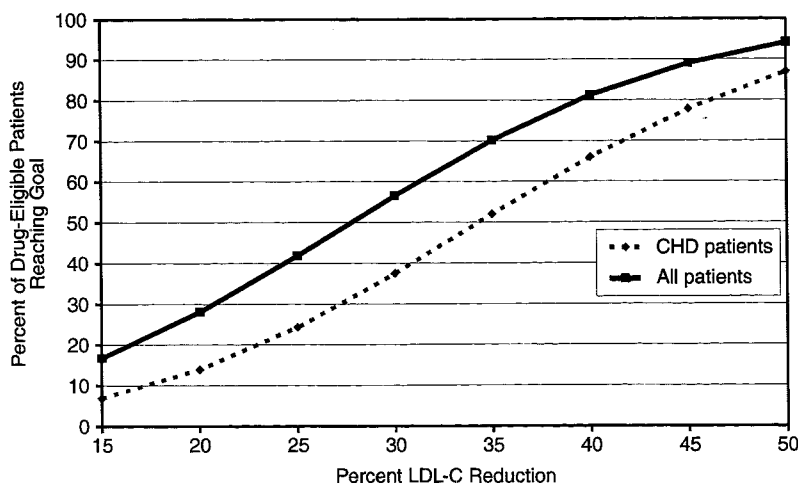


Figure 5. Cumulative percentage of all drug-eligible patients and drug-eligible patients with CHD reaching the National Cholesterol Education Program-Adult Treatment Panel II goal for LDL-C, by the percent LDL-C reduction
 LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease

Discussion

The CPM model allows healthcare providers to assess

(1) the distribution of CHD risk status among drug-eligible patients, (2) how much cholesterol reduction will be required for patients to achieve NCEP-recommended LDL-C goal levels, and (3) what proportion of patients can be expected to reach the NCEP goals based on the expected mean (\pm SD) percent reduction in LDL-C caused by specific pharmacologic agents. This information is critical to the implementation of a rational policy by managed care and other healthcare providers with regards to the management of their covered populations with hypercholesterolemia.

The results confirm the intuitive clinical impression that efforts should focus on persons at relatively high risk for cardiovascular events. Nearly 90% of patients eligible for drug therapy (assuming a dietary LDL-C reduction of 10%) have documented CHD or have multiple CHD risk factors. Varying the assumption of a 10% reduction in LDL-C from dietary intervention does not substantially change this conclusion. Assuming a 5% reduction in LDL-C from dietary intervention, which is more commonly observed in clinical practice,⁵ the model predicts that more than 80% of drug-eligible patients will have either multiple cardiac risk factors or CHD, whereas only 34% of the US adult population is in these groups.

High-risk patients also will benefit most from therapy. Data have recently become available from the Scandinavian Simvastatin Survival Study demonstrating that a mean reduction of 35% in the LDL-C levels of patients with CHD who were treated with simvastatin was associated with a significant (~30%) reduction in all-cause mortality due to a 42% reduction in CHD deaths.⁶ It is pertinent that the CPM indicates that a comparable average reduction in LDL-C levels is required by the US population of drug-eligible CHD patients to attain goal levels. Projecting the clinical benefits of the Scandinavian Simvastatin Survival Study to the segment of the US population that would have been eligible for enrollment in the Scandinavian study indicated a reduction of approximately 140,000 deaths and reductions in cardiovascular-related resource utilization, including an overall decrease in cardiovascular hospitalizations of 831,600 over 5.4 years.¹⁸

The question of how intensively patients should be treated has implications for the design of disease management programs and formulary decisions. The CPM provides clear evidence that intensive treatment is required for patients with CHD or multiple risk factors. Using the base case of a 10% LDL-C reduction from dietary intervention, these patients require an average 31% reduction in LDL-C to achieve goal levels. The average reduction required

increases slightly if one assumes lower LDL-C reductions with diet. It is worth noting that almost 50% of all drug-eligible patients need more than a 25% reduction in LDL-C to achieve goal levels.

Disease management programs can be designed to achieve goal LDL-C levels in a majority of CHD patients. A variety of strategies may be successful, such as the example of lovastatin monotherapy provided in this paper. However, reaching goal levels in clinical practice will depend on appropriate titration of therapy and a variety of other patient management initiatives. Currently, four HMG-CoA reductase inhibitors are marketed in the United States, and they appear to vary significantly in potency in clinical trials.^{19,20} Based on their real-world experience and the scientific literature, managed care providers must be able to estimate the proportion of their covered populations that would achieve goal LDL-C levels with different treatment programs.

A limitation of the model is that the population was divided into categories based on 10-mg/dL increments in LDL-C levels, which necessitated an assumption that patients were normally distributed within each interval. When complete public use data for NHANES III become available, person-level data can be used in the model. Another limitation is that the sample size for some LDL-C/CHD risk factor strata was below the recommended number to make estimates of the US population from complex survey data.¹⁴ These estimates, therefore, must be interpreted with caution. They were employed in the model as "best estimates" since obtaining subgroup population estimates associated with lower standard errors must await future releases of the complete NHANES III data.

The model described here calculates the proportion of a population that can achieve goal LDL-C levels based on the percent reduction in LDL-C reported to be achieved with different interventions. This model may prove useful in designing outcomes research studies that compare the effectiveness of alternative therapies in typical clinical practice. In accordance with NCEP recommendations, this model assists in shifting the short-term emphasis from LDL-C reduction to LDL-C goal attainment. This shift in emphasis is especially helpful to managed care organizations in benchmarking and evaluating disease management strategies.

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