Costs and Effectiveness of Cholesterol Screening in the Elderly

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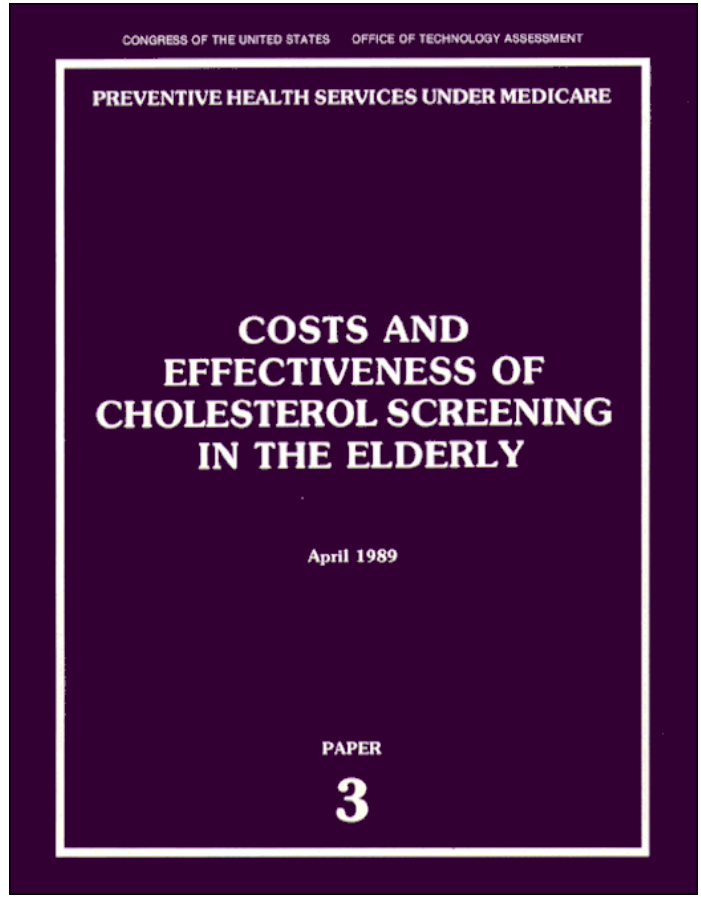

Costs and Effectiveness of Cholesterol Screening in the Elderly

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Cardiovascular disease is the most common cause of death among elderly (i.e., age 65 or older) Americans. In the general population, an elevated serum cholesterol level is associated with an increased risk of contracting and dying from cardiovascular disease. This paper reviews the evidence that elevation of serum cholesterol (hypercholesterolemia) is an independent risk factor for cardiovascular disease in the elderly and that the detection and treatment of hypercholesterolemia in an elderly individual who does not have clinically apparent heart disease will diminish overall morbidity or mortality. It also estimates health care expenditures associated with screening and treatment of hypercholesterolemia in the elderly.

Cholesterol and Heart Disease in the Elderly

Cholesterol is a fat, or lipid, that circulates in the bloodstream bound to proteins in complexes called lipoproteins. Cholesterol-containing lipoproteins are generally grouped into four categories, each containing different proportions of cholesterol, other lipids, and proteins. Low-density lipoproteins (LDLs) are 50 to 60 percent cholesterol; high-density lipoproteins (HDLs) are only 18 to 25 percent cholesterol; very low-density lipoproteins (VLDLs) contain between 20 and 30 percent cholesterol; and chylomicrons are only about 2 percent cholesterol (15). The serum cholesterol is the total amount of cholesterol circulating in all molecular forms.

Prolonged hyperlipoproteinemia or hyperlipidemia (elevated levels of lipids in the blood) has long been thought to contribute to the risk of heart disease. Hypercholesterolemia--long believed to be the most important form of hyperlipidemia--has been shown to be a major risk factor for coronary heart disease (CHD) in middle-aged men. However, epidemiologic studies suggest that the cholesterol level does not have the same significance as a risk factor for cardiac disease in the elderly as in middle-aged and younger populations. Relatively few studies have addressed whether the cholesterol level at age 65 or older predicts CHD risk; the results of these are conflicting and vary with gender. Almost all studies of elderly men failed to find an association between cholesterol level and CHD incidence or mortality (4,5,8,22,44,115,126). The single exception was conducted on a population with a very low CHD mortality rate (13). In elderly women, cholesterol level was found to predict CHD or CHD mortality (13,51,1 15, 126). Although it is not certain why cholesterol might be a better predictor of CHD or CHD mortality in elderly women than in elderly men, women begin to develop symptoms of CHD at more advanced ages than men, so from the standpoint of cardiac disease, an elderly woman may bear risks similar to those of a middle-aged man. It is possible that future studies, conducted in populations with lower rates of CHD mortality, may confirm that cholesterol is a risk factor in both elderly men and women, but today the evidence that cholesterol is an important CHD risk factor at advanced ages remains equivocal.

Whatever its association with CHD incidence or mortality, the cholesterol level does not appear to be an independent predictor of overall survival in the elderly. The few studies that investigated this issue found either that the cholesterol level does not predict total mortality at all (5,8,13) or that it is a statistically significant predictor of lower morality (1 15). Since the cholesterol level is not associated with mortality in the elderly, and since the development of CHD is only

weakly associated with the cholesterol level, the epidemiologic evidence does not confirm that detecting and treating hypercholesterolemia in the elderly will increase their longevity.

The HDL level may be a better predictor of cardiac risk in the elderly (higher levels indicating lower risk). However, HDL assays in routine clinical use are not well standardized. Because of the resulting inaccuracies, the HDL level may not predict cardiac risk as accurately as the well-standardized HDL assays used in the epidemiologic studies that have found an association between HDL and cardiac risk.

Treatment of High Cholesterol In the Elderly

The effects of cholesterol-lowering treatment in the elderly have not been studied extensively. In middle-aged men without evidence of heart disease, treatment of hypercholesterolemia lowers CHD incidence and CHD mortality but has not been shown to affect overall survival. In the elderly, the efficacy of cholesterol reduction has not been tested, and the adverse effects of treatment may be more frequent and more severe. Consequently, there is no firm evidence to suggest that cholesterol screening and subsequent treatment would prolong the lives of elderly individuals who have no evidence of heart disease.

Costs of Screening and Treatment

Recommendations for periodic cholesterol screening have recently been promulgated by the National Heart, Lung, and Blood Institute's National Cholesterol Education Program (NCEP) (l16). These recommendations call for a total cholesterol determination at least every 5 years beginning at age 20. They also specify diagnostic followup and treatment regimens for individuals identified at screening with high cholesterol levels. OTA estimated the annual health care expenditures implied by the NCEP protocol if the protocol were fully implemented in the elderly population. This model estimates the national health care expenditures associated with full compliance with the NCEP screening and treatment regimens.

The estimates of national health expenditures represent total incremental health expenditures associated with cholesterol screening and subsequent treatment of those requiring it in the asymptomatic elderly population compared to no screening or treatment in that population. Because many elderly people are presently screened and treated for high cholesterol, some of these costs are already incurred today. A Medicare cholesterol screening benefit would further increase cholesterol screening and treatment rates and the health care costs associated with them.

Expenditures for actual screening are relatively low compared to the costs of treating hypercholesterolemia; hence, total health care expenditures associated with the NCEP protocols are very sensitive to the costs of medications. Full compliance with NCEP screening and treatment protocols would result in treatment, either with diet or medication, of between 47 and 57 percent of the elderly population. In 1995, total health care expenditures associated with the NCEP protocols for cholesterol screening and treatment of the elderly would be between $2.9 billion and $14.3 billion (in 1988 prices) depending on the prevalence of certain risk factors in the elderly and the mix of medications prescribed by physicians treating elderly patients with hypercholesterolemia.

Whether the elderly would fully comply with cholesterol screening and treatment regimens even under full Medicare funding is questionable, so the actual impact of NCEP or Medicare coverage on health expenditures is probably substantially less than the estimates imply. For example, if only 25 percent of the elderly were to comply with the screening and treatment protocols specified by the NCEP, national health care

expenditures for cholesterol screening and treatment of the elderly would range between $800 million and $3.6 billion in 1995. It is worth noting, however, that the extent to which the actual costs of the NCEP protocol turn out to be lower than the costs estimated for full compliance is a reflection of the failure of the NCEP to achieve its stated goal of full participation in cholesterol screening.

Implications for Medicare

Medicare currently pays 80 percent of allowed charges after the beneficiary has met an annual deductible. Assuming that Medicare similarly were to pay 80 percent of screening expenditures, Medicare costs for screening only (not including treatment) would be roughly $46 million in 1995. In addition, Medicare would pay 80 percent of allowed charges for physician services and diagnostic procedures necessary for monitoring drug therapy, which would range from about $250 to $550 annually for each treated individual. If the entire elderly population were to comply fully with the NCEP guidelines, Medicare expenditures for testing and monitoring would range from $1 billion to $5.4 billion in 1995, depending on the frequency of risk factors and the monitoring required for prescribed medications. With a 25 percent compliance rate in the elderly, Medicare's expenditures (net of outpatient prescription drug benefits) would be reduced proportionately to between $261 million and $1.3 billion. Under the recently enacted Medicare Catastrophic Coverage Act of 1988 (Public Law 100-360), Medicare would also likely bear some portion of the cost of drugs used to treat hypercholesterolemia. A1though some cholesterol-lowering drugs by themselves are unlike] y to cause beneficiaries' drug expenses to exceed the required deductible, many elderly taking cholesterol-lowering drugs would qualify for the drug benefit because they use multiple prescription medications.

Heart disease is the most common cause of death among elderly Americans, killing 2.5 percent of American men and 1.9 percent of American women aged 65 and over in 1984 (121). Prolonged hyperlipidemia, or elevated levels of lipids (fats) in the blood,[1] has long been thought to contribute to the risk of heart disease. Biological, epidemiological, pathological, and clinical evidence has shown that the most important form of hyperlipidemia, hypercholesterolemia (elevation of the blood cholesterol level), is an important risk factor for coronary heart disease (CHD), the leading form of heart disease in adults. hypercholesterolemia is thought to result in CHD by causing atherosclerosis (the accumulation of fat deposits in blood vessels) in the arteries supplying blood to the heart. Atherosclerosis can affect other organs as well, leading to severe limb pain, gangrene, kidney failure, and strokes. Interest in cholesterol screening has sprung from the hope that the detection and treatment of hypercholesterolemia will help avert the pain, suffering, and mortality of these diseases.

Several randomized controlled trials conducted in the past decade have shown that treatment of hypercholesterolemia can diminish the incidence of CHD and reduce the number of cardiovascular deaths. At the same time, inexpensive tests have become available for measuring the cholesterol level in blood serum. The trend toward identifying and treating hypercholesterolemia has culminated in the report of the National Cholesterol Education Program (NCEP), an expert consensus group, which has recommended that all Americans 20 years of age and over be screened for hypercholesterolemia at least once every 5 years. Treatment should be determined according to the cholesterol level and the presence of other risk factors (1 16). Public awareness of cholesterol as a risk factor for cardiac disease has increased in the wake of concerted educational campaigns of the National Institutes of Health, the American Heart Association, and others. Interest in screening for hypercholesterolemia is at an all-time high, at least among the medical profession (105).

Most of the evidence about cholesterol as a risk factor and about the treatment of hypercholesterolemia has been obtained from populations of middle-aged men. The elderly may be different. Medications often have more severe and frequent side-effects in the elderly (95,101). Many of the elderly metabolize some drugs more slowly than younger people; they may take more medications, risking adverse drug interactions; and they are particularly likely to suffer from multiple illnesses that affect their ability to tolerate medications. Because of these and other factors, the benefits and risks of cholesterol reduction in elderly men and women may be different from those of middle-aged men.

This paper addresses two questions: (1) will cholesterol screening improve the health of asymptomatic elderly Americans? and (2) what are the implications of cholesterol screening and treatment in the elderly for health care expenditures? The population considered in this paper excludes individuals who have clinical evidence of diabetes mellitus or heart disease. Heart disease includes the presence of angina pectoris (brief episodes of chest pain caused by narrowing or blockages of the coronary arteries), a previous myocardial infarction (heart attack), arrhythmia (disturbances of the heart rhythm), congestive heart failure, or hypertension (high blood pressure). Such individuals, whose conditions put them at high risk of heart attack and death, should be under the treatment of physicians and are likely to be taking

1 Fats present in the blood are usually combined with proteins to form "lipoproteins." Because the disorders considered in this document are characterized by excess lipoproteins, some authors use the term "hyperlipoproteinemia" rather than "hyperlipidemia."

medications that affect their cholesterol level. Cholesterol determinations may be important in these individuals for the purpose of monitoring rather than the detection of a risk factor. A discussion of this use of cholesterol testing is beyond the scope of this paper.

Although this paper emphasizes the effects of cholesterol on mortality, it also discusses its role in causing symptoms and diseases that result in hospitalization. The argument in favor of cholesterol screening rests upon the following premises: First, the risk factor it detects is important because it is common. Second, the cholesterol test identifies a group of individuals at excess risk of a serious disease. Third, treatment of hypercholesterolemia is more effective in reducing overall mortality and morbidity if initiated before it causes symptoms. After critically examining these premises, the paper turns to evidence about the current utilization of cholesterol assays among Medicare recipients to discover whether liberalized reimbursement policies would increase participation in cholesterol screening programs. Finally, it addresses the implications of such changes for national health care expenditures.

hypercholesterolemia (elevation of the blood cholesterol level) is a health problem because it predisposes to diseases that cause significant morbidity and mortality.

Diseases Associated With hypercholesterolemia

Stroke

Stroke refers to brain injury that results from inadequate blood flow to the brain. Common causes include congenital abnormalities of cerebral arteries and hypertensive damage to cerebral blood vessels. In addition, atherosclerosis can cause stroke in three ways: atherosclerotic deposits can block arteries carrying blood to the brain; fragments of the deposits in the major arteries to the brain or elsewhere can dislodge and block smaller arteries; or atherosclerotic deposits can develop in small vessels in the brain causing hemorrhage and stroke. The role of atherosclerosis in the sequence of events leading to a stroke has led many to suspect that hypercholesterolemia might be a risk factor for this syndrome.

Stroke is important because it is a common cause of death and because nonfatal stroke can lead to severe disability and institutionalization. More than 2.6 percent of all men and 2.2 percent of all women aged 65 and over were admitted to hospitals in 1984 with a diagnosis of cerebrovascular disease. The number of stroke deaths per 100,000 men and women aged 65 and over was 447.7 and 495.1, respectively, in 1984 (121). Stroke is the second most common cause of death in Americans aged 85 and over, and the third most common cause in 65 to 84 year-olds.

Peripheral Vascular Disease

Peripheral vascular disease (PVD) refers to obstructive disease of blood vessels of the extremities. Although some authors include disease of the veins and lymphatic vessels in the definition of PVD, this paper will discuss only disease of the arteries, which is more likely than venous or lymphatic disease to be related to hypercholesterolemia. Most PVD is thought to be due to atherosclerotic occlusion of the arteries supplying blood to the lower extremities.

PVD can affect any large artery of the extremities. The most common syndromes are intermittent claudication, a severe exercise-related pain in the calves or buttocks; coldness and numbness in an extremity; impotence; and loss of strength in an affected leg. Severe PVD can lead to skin ulceration, gangrene, and loss of the extremity.

The prevalence of symptomatic PVD is uncertain. Since many individuals with severe PVD have concomitant diabetes and/or coronary heart disease (CHD), it has been difficult to discern the independent effect of PVD on mortality. However, it can produce severe disability since even minimal walking may precipitate severe claudication pain.

Coronary Heart Disease

Ischemic or coronary heart disease refers to the clinical syndromes that result from impaired blood flow to the myocardium (heart muscle), Ischemia, or inadequate blood flow, reflects an imbalance between blood supply and demand and is usually associated with obstructive deposits of cholesterol- rich material in the coronary arteries (coronary atherosclerosis). CHD includes angina pectoris, a characteristic chest pain syndrome; myocardial infarction (heart attack); sudden death, or death occurring within an hour of the onset of symptoms and in the absence of a known cause; l and coronary insufficiency, or unstable angina, a syndrome of prolonged chest pain associated with electrocardio-

1 Some authors use a longer time limit for sudden death, including all deaths that occur within 24 hours of the onset of symptoms in the definition.

graphic abnormalities, but lacking the chemical or electrocardiographic evidence of definite myocardial infarction.

CHD is the most common cause of death among adult Americans, and it is a very common disease. Most symptomatic CHD occurs in the elderly; more than 17 percent of men and 11 percent of women aged 65 and over who are not in nursing homes or other institutions report that they suffer from ischemic heart disease (120). In 1984, 8.4 percent of all men and 6.9 percent of all women aged 65 and over were admitted to a hospital because of heart disease (121). Most of these admissions were due to CHD or consequences of CHD, such as congestive heart failure. These admissions accounted for more than 7.6 million and 10 million days of hospital care for men and women, respectively (121). The National Vital Statistics system reported that in 1985 heart disease killed more than 1 percent of all Americans who were between the ages of 65 and 74, 2.7 percent of 75 to 84 year-olds, and 7.3 percent of Americans aged 85 and over (122).

The Distribution of Serum Cholesterol Levels Among Elderly Americans

According to a recent consensus statement from the National Heart, Lung, and Blood Institute (NHLBI) and other experts, serum cholesterol levels of 240 milligrams per deciliter of blood serum (mg/dl) and above are "high-risk" even in the absence of other cardiac risk factors. In the presence of other risk factors, a cholesterol level of 200 mg/dl or more should lead to further evaluation (1 16). As table 1 demonstrates, most adult Americans have cholesterol levels that exceed the "desirable" level of 200 mg/dl or less.

If the 240 mg/dl cutoff is used, about 30 percent of men and 50 percent of women aged 65 to 74 are at high risk. Even at the higher cutoff of 260 mg/dl for high risk proposed by an earlier NHLBI--sponsored consensus conference (11 4), 18 percent of men and 34 percent of women aged 65 to 74 fall into the high-risk category (121). If a "high-risk" cholesterol level mandates treatment, a vast number of elderly Americans will need to undergo therapy.

Evidence That hypercholesterolemia Is Associated With Increased Morbidity and Mortality

Although hypercholesterolemia may contribute to other illnesses, its most important impact is on CHD. Many studies of middle-aged and younger men have demonstrated that the cholesterol level predicts CHD incidence, CHD mortality, and mortality from all causes (39). The evidence comes from international comparisons of CHD incidence and death rates (66), as well as epidemiologic and clinical studies. This section describes the evidence that the cholesterol level is a predictor of the incidence of stroke, peripheral vascular disease, and CHD, and of mortality from CHD and from all causes.

Serum Cholesterol as a Predictor of Stroke Incidence

Because there are substantial similarities between the pathology of atherosclerosis of the coronary arteries and the lesions responsible for stroke, many authors have suggested that hypercholesterolemia may be an independent predictor of morbidity from stroke. Three main lines of evidence are available to test this hypothesis. First, several authors have compared the cholesterol levels in stroke victims to those without strokes. A binational cooperative study compared stroke victims to controls in Japan and Minnesota (14) and found no difference in the cholesterol levels of the cases and controls within each country. A report on stroke in adults less than 50 years old (35) found no difference between the cholesterol levels of the victims and local population averages.

More direct evidence comes from longitudinal studies that have examined cholesterol as a predictor of stroke. The Honolulu Heart

Table 1.-- Mean Serum Cholesterol Levels of Men and Women, SEM, Age-Adjusted Values, Selected Percentiles, Number of Examined Persons, and Estimated Population, by Race and Age: United States, 1978-1980

Age	Number of persons examined	Estimated population in thousands	Mean	SEM	Percentile[a] 5th	10th	15th	25th	50th	75th	85th	90th	95th
Men													
All races:													
20-74	5604	63611	211	1.2	144	156	165	179	206	239	258	271	291
20-24	676	9331	180	1.7	129	136	145	155	176	202	215	227	246
25-34	1067	15895	199	1.5	141	152	159	172	194	220	240	254	275
35-44	745	11367	217	2.0	153	166	173	187	215	244	262	275	293
45-54	690	11114	227	1.8	159	176	182	197	223	255	271	283	303
55-64	1227	9607	229	1.8	164	176	184	198	225	254	277	288	307
65-74	1199	6297	221	1.8	153	167	175	191	217	249	265	279	301
White:													
20-74	4883	55808	211	1.2	145	157	166	179	207	239	258	271	291
20-24	581	8052	180	1.8	131	138	146	155	176	202	216	229	244
25-34	901	13864	199	1.7	144	153	161	172	194	220	239	254	273
35-44	653	9808	217	1.8	153	166	173	187	214	244	260	272	291
45-54	617	9865	227	1.8	160	177	181	198	222	254	271	283	303
55-64	1086	8642	230	2.0	164	178	185	199	225	255	278	289	307
65-74	1045	5576	222	2.0	153	167	175	191	217	250	266	281	301
Black:													
20-74	607	6102	208	2.5	133	146	156	171	200	238	260	273	301
20-24	79	1043	171	3.7[b]	b	128	134	149	170	193	210	211	b
25-34	139	1546	199	4.1[b]	129	136	144	163	192	226	248	259	301
35-44	70	1112	218	8.3[b]	b	156	168	176	202	238	275	283	b
45-54	62	1044	229	7.1[b]	b	174	184	195	232	261	268	279	b
55-64	129	801	223	4.8[b]	157	168	172	183	218	254	271	299	312
65-74	128	555	217	4.2	149	163	173	183	216	244	261	277	299
Age-adjusted values:													
All races, 20-74	MA	*MA*	211	1.1	MA	MA	MA	MA	MA	NA	MA	MA	MA
White, 20-74	MA	*MA*	211	1.1	MA	NA	NA	MA	MA	MA	MA	MA	MA
Black, 20-74	MA	*MA*	209	2.5	MA	NA	MA	NA	NA	NA	MA	MA	MA
Women													
All races:[b]													
20-74	6260	69994	215	1.2	143	156	166	179	210	245	266	282	305
20-24	738	9994	184	1.9	132	140	145	157	180	204	216	230	250
25-34	1170	16856	192	1.4	135	145	154	164	188	215	233	243	263
35-44	844	12284	207	1.8	147	158	164	177	202	231	248	260	276
45-54	763	11918	232	2.2	164	178	188	199	228	257	275	290	306
55-64	1329	10743	249	2.0	180	193	203	215	242	277	299	314	336
65-74	1416	8198	246	1.6	173	189	198	214	241	274	295	309	327
White:													
20-74	5418	60785	216	1.3	143	156	166	179	210	246	267	282	305
20-24	624	8408	184	2.1	133	140	147	159	181	204	215	230	249
25-34	1000	14494	192	1.5	135	145	153	164	188	215	235	244	261
35-44	726	10584	207	1.9	147	157	164	177	203	231	248	250	277
45-54	647	10369	232	2.6	166	179	188	199	228	257	274	290	308
55-64	1176	9601	249	1.7	180	193	203	215	244	277	298	312	330
65-74	1245	7329	246	1.7	174	190	199	214	242	275	296	309	328
Black:													
20-74	729	7579	212	3.1	140	154	166	176	205	237	263	279	308
20-24	94	1304	185	4.9[b]	b	136	144	156	178	204	220	237	b
25-34	145	1953	191	4.1	129	144	156	167	190	212	226	235	267
35-44	103	1415	206	4.5[b]	143	158	170	175	194	233	254	274	279
45-54	100	1215	230	7.2[b]	150	172	181	200	226	263	277	291	306
55-64	135	959	251	8.0[b]	178	185	198	211	233	280	318	336	345
65-74	152	733	243	4.2	173	189	198	211	237	269	290	308	322
Age-adjusted values:													
All races, 20-74	MA	*MA*	215	1.2	MA	MA	MA	MA	MA	MA	MA	MA	NA
White 20-74	MA	*MA*	215	1.2	MA	MA	MA	MA	MA	MA	MA	MA	MA
Black 20-74	MA	*MA*	214	2.7	MA	MA	MA	MA	NA	MA	MA	MA	MA

[a] Serum cholesterol values are given in milligrams per deciliter. To convert values to millimoles per liter, multiply by 0.02586.

[b] Includes data for races not shorn separately.

ABBREVIATIONS: SEM = standard error of the mean, NA = not applicable.

SOURCE: Reproduced from Adult Treatment Panel, National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institute of Health, U.S. Department of Health and Human Services, "Report of the National Cholesterol Education Program Expert Panel on Detection, Evacuation, and Treatment of High Blood Cholesterol in Adults," Arch. Intern Med. 148:36-69, 1988.

Program reported a statistically significant U-shaped association between cholesterol and subsequent incidence of stroke (97). Stroke rates were higher at both very low and high cholesterol levels than for cholesterol levels in the middle range. However, in a similar analysis of transient ischemic attacks (a stroke-like syndrome that resolves within 24 hours), the predictive ability of cholesterol disappeared when hypertension and cigarette smoking were considered (98).

Westlund (127) and Balodimos (1 1) each reported that cholesterol is a significant predictor of stroke when examined alone (i.e., in a univariate analysis). Another univariate analysis, a 10-year followup of residents of Shikoku Island, Japan found no association between cholesterol and stroke (109). None of these reports included a multivariate analysis. Only a multivariate analysis, which measures the independent or separate effects of each of several risk factors, can distinguish the effect of cholesterol from the effect of other risks, such as cigarette smoking, that are also correlated with the cholesterol level.

Studies that control for the impact of other potential risk factors suggest that cholesterol is not independently associated with the risk of stroke. Two Italian reports of fatal and nonfatal strokes in men between 40 and 59 years of age found no independent role for cholesterol as a risk factor (33,86). A 7-year followup of a cohort of adults 35 to 39 years old in Eastern Finland found hypertension, age, tobacco use, prior stroke, and diabetes to be independent predictors of stroke, while the independent association with cholesterol was not significant (102), A 13-year study of 50-year-old men found that the diastolic blood pressure, smoking habits, and the erythrocyte sedimentation rate were significant predictors (3). Once again, the association with cholesterol was insignificant. An 8-year followup of adults 40 to 69 years of age in a farming village in Akita, Japan ascribed a similarly insignificant independent role to cholesterol (111). Finally, the Framingham Heart Study (an ongoing prospective epidemiologic study of several thousand adults from Framingham, Massachusetts, that was begun in the late 1940s) found that the cholesterol level was not associated with the risk of stroke except in subjects who also had other risk factors (65). In multivariate analyses of the 2-year risk of stroke from Framingham, the independent effects of the cholesterol level on the risks of stroke and transient ischemic attack were not statistically significant in either men or women with the exception of women aged 65 to 74.

In summary, case-control studies as well as multi variate longitudinal analyses have suggested that the serum cholesterol does not appear to be independently associated with the risk of stroke. The apparent relation between cholesterol and stroke is due to the relation between cholesterol and other variables, particularly smoking and hypertension, that appear to be much stronger predictors of stroke risk.

Serum Cholesterol as a Predictor of Peripheral Vascular Disease Incidence

Just as hypercholesterolemia would be expected to predispose individuals to stroke, it also is a potential risk factor for peripheral artery disease. Few studies have examined whether there is a significant association between cholesterol level and the incidence of PVD.

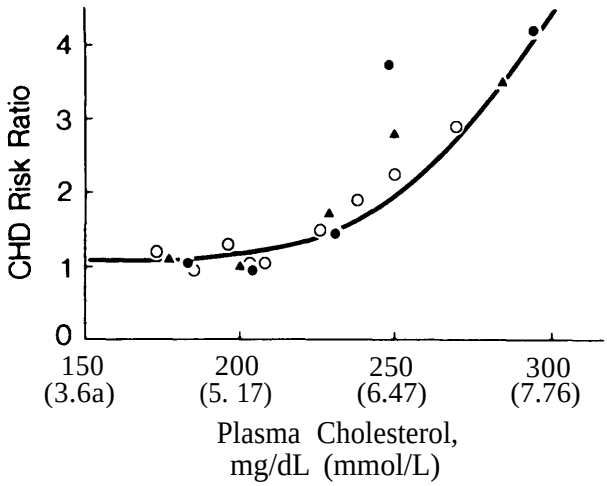
Two studies found that the cholesterol level was a significant predictor of the subsequent development of PVD in univariate analyses, but none of these studies controlled for the effect of other risk factors (1 1, 127), One report from the Framing ham Study found that intermittent claudication, a clinical marker for PVD, was more common in hypercholesterolemic subjects but failed to apply multivariate analysis (45). A recently reported 25-year evaluation of two rural Italian communities found that deaths from PVD were so rare (0,72 percent over 25 years) that no statistical relations to to cholesterol could be determined (86).

Studies could not be located that assessed whether the serum cholesterol level has an association with PVD that is independent of such confounding variables as cigarette smoking and the blood pressure level. Because the serum cholesterol level is associated at the population level with cigarette smoking, the association of cholesterol level and PVD independent of those factors is likely to be smaller than the association found in univariate analyses.

Serum Cholesterol as a Risk Factor for Coronary Heart Disease Incidence and Death

Numerous multi variate studies of middle-aged men have shown that, over a wide range of cholesterol values, the probability that an asymptomatic individual will subsequently develop angina or suffer a myocardial infarction or sudden cardiac death rises in an approximately exponential fashion with his or her cholesterol level. Thus, the same increment in cholesterol has a much more pronounced effect at higher levels than at lower levels of serum cholesterol. For example, among 361,662 men screened in the Multiple Risk Factor Intervention Trial (MRFIT), individuals whose cholesterol exceeded 263,[2] placing them at or above the 90th percentile, had four times the risk of coronary death of the bottom 20 percent, whose cholesterol level was less than 182 (85). In the Whitehall study, the 10-year CHD mortality ranged from 2.85 percent in the lowest quintile, to 3.44 percent in the next lowest quintile, to 5.37 percent in the highest quintile of cholesterol levels (99). A pattern of slowly rising risk of CHD at lower cholesterol levels and rapidly rising risk at higher levels was observed in the Framingham Study (63), which examined CHD incidence, and in a prospective study of Israeli civil servants (41), which examined CHD mortal it y. The relation between cholesterol level and relative risk of developing CHD in three prospective studies is illustrated in figure 1 (48). Epidemiologic studies have also found that the effect of hypercholesterolemia is highly dependent on the presence of other risk factors. Cholesterol interacts in a synergistic fashion with other risk factors to increase the risk of coronary disease. Cigarette smoking and hypertension, in particular, produce greater increases in CHD mortality in people with hypercholesterolemia than would be predicted on the basis of each risk factor alone (64,93).

Figure 1--- Relation Between Plasma Cholesterol Level and Relative Risk of Coronary Heart Disease (CHD) in Three Prospective Studies



SOURCE : Reproduced w ith permi ss i on from S. M. Grundy,"Cholesterol and Coronary Heart Disease, ' J. A.M.A. 256:2849-58, 1986. Copyright 1986, American Medical Associ at ion.

2 Unless otherwise noted, throughout this document "cholesterol" refers to the serum cholesterol level and is reported i n units of mg/dl. Cholesterol levels in many countries are reported i n units of mmol/L (S1 units); to convert f ran mg/dl to mmol/L, multiply by 0.02586.

undoubtedly be clarified when more data become available. Relatively few studies have addressed whether the cholesterol level predicts CHD risk at age 65 or older, although the Stockholm Prospective Study (22), Framingham, and a few others included elderly individuals. Investigators in the Framingham Study reported several years ago that total cholesterol is not a significant risk factor for the development of CHD in the elderly, despite its clear predictive power in younger individuals (44). Two later publications based on 30 years of followup from the Framing ham Heart Study indicated that cholesterol is a risk factor for CHD in elderly women, but not elderly men. In a multivariate logistic regression analysis, Framingham investigators reported that the cholesterol level was not a statistically significant independent predictor of the incidence of CHD among men aged 65 and over, although it was a significant predictor for women (1 15).

The second Framingham publication used Cox-type proportional hazards analysis[3] to relate the development of CHD to putative cardiac risk factors in individuals 65 years of age and over (5 1). For this study, the cholesterol level was divided into four categories: <200 mg/dl; 200 to 239 mg/dl; 240 mg/dl to the 90th percentile (306 mg/dl for women and 275 mg/dl for men); and 90th percentile and above. The risk of CHD was significantly elevated for those individuals whose cholesterol was at the 90th percentile or greater, when men and women were pooled; the elevated risk for those in the category between 240 mg/dl and the 90th percentile reached borderline statistical significance. The association between cholesterol category and risk of CHD was much stronger for women than for men. When men and women were analyzed separately, the risk of developing heart disease was 2.3 times as great for women whose cholesterol exceeded 305 mg/dl as for women whose cholesterol level was less than 200 mg/dl. This risk elevation was statistically significant. There was a trend toward increasing risk of CHD with increasing cholesterol level for both men and women, but aside from the single category of women whose cholesterol levels were in the top 10 percent, the association between cholesterol level and CHD risk did not achieve statistical significance. Thus both of these reports from the Framingham Heart Study suggest that very high cholesterol levels are associated with an elevated risk of developing CHD for elderly women, but not necessarily for the elderly men.

In the Glostrup prospective epidemiologic study of 230 men and 210 women aged 70 and above from nine Danish municipalities, the cholesterol level at age 70 did not predict the development of cardiovascular disease (CVD) during the succeeding ten years, when suspected risk factors that are correlated with cholesterol-- triglycerides, glucose intolerance (diabetes), and a prior history of CVD--were taken into account. CHD was not reported separately; CVD included CHD as well as cerebrovascular disease and intermittent claudication. These results were true for men and women (4,5). In univariate analyses of the Busselton (Australia) Study, the cholesterol level did not predict the development of CHD in the succeeding 6 years among men or women who were 60 years of age or older; multi variate results were not presented (126). A univariate 9-year fol-1owup study of Swedish men found that the serum cholesterol level did not predict the subsequent development of CHD among men who were aged 60 or over at the time the cholesterol was drawn (22).

The relation between cholesterol and CHD death rates is similar to the relation with CHD incidence. In the Glostrup study of 70 year-olds (5), the serum cholesterol was not a significant independent predictor of

3 Proportional hazards analysis is a biostatistical method for ana 1 yz i ng the association between r i sk factors and variation in survival (27).

cardiovascular mortality. In the Busselton study, total cholesterol did not predict CHD or CVD mortality in men or women aged 60 to 69, or in men aged 70 and above, although cholesterol was significant at the 5 percent level in predicting CHD mortality among women aged 70 and above (126). In the 30-year followup of the Framingham Study, the serum cholesterol predicted CHD death rates in elderly women, but not in elderly men (1 15).

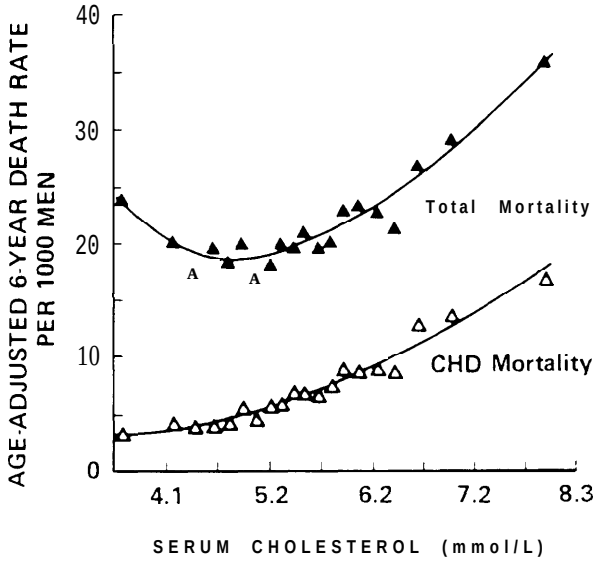
This review located only one published study that found cholesterol is a significant independent predictor of CHD death rates among both elderly men and women. This study, in adults between 50 and 79 years of age in Southern California, reported results of a Cox-type proportional hazards analysis that found that total cholesterol was a significant independent predictor ($p<0.01$) of CHD mortality among men and women aged 65 to 70. Among women aged 65 to 79, it was significant at the 5 percent level. The authors explained the disparity with other studies by noting that they conducted their investigation more recently. Because of falling CHD mortality rates, "subjects with high levels of risk factors [were] no longer weeded out by age 50 or even by age 65. Consequently, the impact of selective mortality may be delayed so that these risk factors still have expression at later ages" (13). Their hypothesis was supported by the low CHD mortality rate in their study population compared to other studies and compared to the general U.S. population (the risk ratios for men and women were 0,40 and 0.27, respectively). Unpublished observations from the Lipid Research Clinics followup study, a major epidemiologic study conducted by several collaborating institutions, also suggest that the total cholesterol level is a significant predictor of CHD incidence and mortality in the elderly (19).

Collectively, these studies demonstrate that the blood cholesterol level is an independent risk factor for the development of CHD in middle-aged men and elderly women. Although it is not certain why cholesterol seems to retain its importance as a risk factor in elderly women more than in elderly men, women begin to develop symptoms of CHD at more advanced ages than men, so from the standpoint of cardiac disease, an elderly woman may bear risks similar to those of a middle-aged man. It is possible that newer studies will confirm that cholesterol is a risk factor in elderly men and women, as the work of Barrett-Connor and colleagues and the results from the Lipid Research Clinics followup suggest. However, there is currently little evidence that cholesterol is a CHD risk factor in men who have reached the age of 65 without manifesting heart disease.

The Serum Cholesterol Level as a Risk Factor for All-Cause Mortality

Does the relation between overall mortality and cholesterol level parallel the relation between CHD risk and cholesterol level? Univariate analyses have found that, for individuals whose cholesterol is below the tenth or twentieth percentile, mortality actually decreases as cholesterol levels increase; at higher cholesterol levels, further increases in cholesterol are associated with rising mortality (see figure 2). The MRFIT study found that middle-aged men whose cholesterol levels were in the bottom decile had a significantly increased rate of cancer death early in the trial (before the intervention could have been responsible for an increased cancer risk). Adjusted for age, smoking status, and randomization group, the MRFIT participants who died of cancer experienced much greater falls in serum cholesterol levels after enrollment than did survivors. Furthermore, the drop in cholesterol was greatest among the men who died of cancer early in the trial, which has been interpreted to mean that cancer causes the serum cholesterol to fall (106), rather than that a falling cholesterol causes cancer. Other large studies have also found that at very low cholesterol levels, declines in cholesterol are associated with increased all-cause mortality. In the Israeli civil servants study, age-adjusted overall mortality at 15 years was

Figure 2--- Age-Adjusted 6-year CHD and Total Mortality per 1,000 Men Screened for MRFIT According to Serum Cholesterol



Entire cohort of 361,662 men was divided into approximate twentieths, and each point represents the mortality (either CHD or total) and the mean cholesterol level in one of those twentieths. Modified lines are drawn through the points.

ABBREVIATION: CHD = coronary heart disease.

SOURCE: Reproduced with permission from M.J. Martin, S.B. Hulley, and U.S. Browner, "Serum Cholesterol, Blood Pressure, and Mortality: Implications From a Cohort of 361,662 Men," Lancet 2:933-936, 1986.

lowest for individuals in the third decile, corresponding to a serum cholesterol of 177 to 187 mg/dl (41). All-cause mortality in the bottom decile, corresponding to a cholesterol level of less than 161 mg/dl, was about the same as mortality in the seventh decile, corresponding to a cholesterol level of 217 to 227 mg/dl,

Not all studies have found a negative association between cholesterol level and noncardiovascular mortality. The inconsistent findings of epidemiologic studies have led some experts to question whether a low cholesterol level is associated with elevated cancer mortality (34,107), but most of the studies were not designed to examine the relation between cardiovascular risk factors and noncardiovascular mortality. More controversial than the existence of an association is its interpretation; many cardiovascular experts doubt that a declining cholesterol level leads to elevated total mortality, while others (104) believe that a low cholesterol level may be more than a preclinical marker of cancer. Whether the low cholesterol level causes cancer or cancer causes the cholesterol level to fall, the relation with total mortality suggests that there is little reason to further reduce an already low cholesterol level in middle-aged men, while rises in their cholesterol levels clearly place them at higher risk if their cholesterol is already elevated.

In the elderly, the total cholesterol level does not appear to be an independent predictor of survival. The few studies that investigated this issue found either that the cholesterol level does not predict total mortality at all (5,8,13) or, in the case of the Framingham Study, that it is a statistically significant predictor of lower mortality for both men and women (l15). The insignificant or negative association may reflect the much higher incidence of death from noncardiovascular causes in old age. For example, among white males in 1985, the death rate from malignant neoplasms between the ages of 35 and 44 was 39.5 per 100,000, while the death rate was 1,061 per 100,000 at ages 65 to 74 and 1,820 per 100,000 between ages 75 and 84 (115). Cancer death rates for white females are lower than for white males but also rise dramatically with age. If cancer, occult or overt, lowers the serum cholesterol, it may cause the association between cholesterol and total mortality to weaken or reverse with age.

In the absence of studies that directly assess the effects of cholesterol reduction in the elderly, further investigation of the reasons for the lack of association (or negative association) between cholesterol level and total mortality in the elderly is important. If the cholesterol level is not associated with mortality in the elderly, and if the develop-

ment of CHD is only weakly associated with the cholesterol level, the epidemiologic evidence does not confirm that detecting and treating hypercholesterolemia in the elderly will increase their longevity.

Do Other Lipoprotein Levels Predict Mortality and Morbidity in the Elderly?

Cholesterol and triglycerides are the two major lipids that circulate in blood. Both circulate as constituents of lipoproteins. Tests to detect hyperlipoproteinemia include serum cholesterol and triglyceride levels as well as measurements of specific lipoprotein classes (sometimes called "lipoprotein fractions"). Besides the serum cholesterol level, the triglyceride level and the levels of two classes of lipoproteins--HDL and low-density lipoprotein (LDL)--are widely used to assess hyperlipoproteinemia. What is the role of these tests in the identification of individuals at high risk of CHD?

Whether the triglyceride level is an independent risk factor for CHD at any age is controversial. In univariate analyses, the triglyceride level appears to predict CHD risk. However, hypertriglyceridemia is associated with cigarette smoking, obesity, diabetes mellitus, and other potential cardiac risk factors (such as a low HDL level). Among asymptomatic individuals who are not obese, who do not have diabetes or a family history of hyperlipidemia, and who do not have hypercholesterolemia, the triglyceride level does not appear to be an independent risk factor for CHD (12,58,59). Perhaps the most important confirmation of the importance of a risk factor comes from studies that show that health is improved by eliminating the risk factor. It appears that no randomized trials have been conducted of triglyceride reduction alone, but a randomized trial of gemfibrozil, a drug that raises HDL levels and lowers total and LDL cholesterol and triglyceride levels found that the decline in CHD incidence correlated with changes in HDL, LDL, and total cholesterol levels, but not with the fall in triglycerides (84).

Studies of (primarily) nonelderly populations have shown that the level of HDL (sometimes called the "scavenger" or "good" cholesterol) is inversely related to the risk of developing CHD, and that the LDL level is positively related to CHD risk (128). The ratio of LDL to HDL and the ratio of HDL to the serum cholesterol 1evel may also be reliable predictors of cardiac risk (62). Most commonly, the HDL and LDL levels are viewed as adjuncts to the measurement of serum cholesterol; many experts recommend first obtaining a serum cholesterol level and then determining HDL and LDL levels if the cholesterol is elevated. Usually the LDL is a calculated value that requires a serum cholesterol measurement (see below), so the LDL cannot be substituted for a cholesterol measurement. The serum cholesterol level is highly correlated with the LDL but not with the HDL level (table 2), so high-risk individuals who have a low HDL level in association with a low serum cholesterol may not be detected if LDL and HDL measurement (referred to as fractionation) is limited to hypercholesterolemic subjects (54,58,75).

Few studies have evaluated the HDL or LDL levels as risk factors for CHD incidence in the elderly, and this review did not locate any studies that reported on the relation between HDL or LDL and either CHD mortality or total mortality in the elderly. Investigators from the Framingham Study reported that HDL was a much better predictor of CHD incidence among the elderly than the total cholesterol level (43). Among men aged 60 to 69, the HDL level was a significant predictor ($p<0.05$) of CHD but it was not significant for men aged 70 to 79. Among women at age 60 to 69 or 70 to 79, the HDL level was not a significant predictor of CHD risk. In these analyses, the LDL level was significant ($p<0.05$) in predicting the risk of CHD among men aged 60 to 69 and 70 to 79, and significant at the 1 percent level in predicting CHD incidence among women aged 60 to 69. Another report from the Framingham Study (44) published the same year stated that both the HDL and LDL choles-

Table 2--- Simple Pearson Correlation Coefficients Between Various Plasma Lipids and Lipoprotein Fractions From Various Studies

study	Correlation between: HDL and TC	HDL and LDL	LDL and TC
Framingham:			
Hen (n=1 ,025)	0.10	-0.04	0.84
Women (n=I,445)	0.07	-0.16	0.88
Ages 49-82 years			
Hawaii:			
Japanese men (n=2,019)	0.03	-0.01	0.78
Ages 50-72 years			
Cooperative Lipoprotein Phenotyping Study:[a]			
Men (n=4,898)	0.03 to 0.18	-0.01 to -0.31	0.78 to 0.88
Women(n=I,683)	0.06 to 0.24	-0.09 to -0.16	0.88 to 0.89
Ages 40-70 years			
MRFIT:			
Men (n=301)	NA	-0.08	NA
Ages 35-57 years			

[a]The correlation coefficients reported for the Cooperative Lipoprotein Phenotyping Study represent the range for the five geographic sites of the study.

ABBREVIATIONS: HDL = high-density lipoprotein; LDL = low-density lipoprotein; MRFIT = Multiple Risk Factor Intervention Trial; TC = total cholesterol; NA = not applicable.

SOURCE: Office of Technology Assessment, 1989; adapted from C.E. Davis, D. Gordon, J. LaRosa et al., "Correlations of Plasma High Density Lipoprotein Cholesterol Levels Uith Other Plasma Lipid and Lipoprotein Concentrations: The Lipid Research Clinics Program Prevalence Study," Circulation 62(supp.IV):IV-24--IV-30, 1980.

terol levels were highly significant predictors of CHD risk among men and women aged 49 to 82 years. This study did not report the number of participants who were aged 65 and above, nor did it report results for the elderly (aged 65 and over) separately. Because the HDL and LDL levels were not measured as part of the Framingham Study until 1968, the results of both of these publications were based on only about 4 years of followup. A more recent publication from the Framingham investigators, based on 12 years of fol-10WUP, reported that the HDL cholesterol is a particularly strong indepen-dent predictor of one form of CHD--myocardial infarction--among older women, and is of borderline significance for older men (l).

Taken as a whole, the evidence from the Framingham Study indicates that at least among some groups of the middle-aged and the elderly HDL and LDL levels predict CHD incidence.

Summary

Do the cholesterol level, HDL level, or LDL level predict the risk of significant cardiac events and death among the asymptomatic elderly? The epidemiologic studies that included elderly individuals have found, in some cases, that the total cholesterol level may predict CHD risk among the elderly, but the effect is not nearly as striking or as consistent as the relation among the middle-aged. The relation between cholesterol level and CHD mortality has not been reported as frequently, and here the relation is even weaker. Furthermore, some of the studies that report the relation between cholesterol level and CHD mortality include individuals who have already manifested symptoms (such as angina)

or signs (such as hypertension) of heart disease, in whom the relation between cholesterol level and CHD death may be stronger. The HDL and LDL levels may be better predictors of CHD risk in the elderly than the total cholesterol level. The studies that have reported on the association between the total cholesterol level and overall mortality have found that the cholesterol level either is a significant negative predictor of mortality in the elderly (the opposite is observed in middle-aged and younger individuals), or does not predict overall mortality rates at all.

Why does the relation between cholesterol and CHD events weaken with age, and why does the association with total mortality reverse? One might speculate that individuals who have hypercholesterolemia and remain free of CHD when elderly may have a different mix of apolipoproteins,[4] or for some other reason may tolerate hypercholes - terolemia better than those who went on to develop heart disease at earlier ages. Their selective CHD-free survival may explain why the individuals who survive to old age with hypercholesterolemia and no evidence of CHD subsequently seem to suffer few deleterious consequences from their hypercholesterolemia. At younger ages, the cholesterol level does not seem to be associated with non-CHD mortality, except at very low cholesterol levels, where non-CHD mortality may rise as the cholesterol level falls. Several studies have found that the elevated mortality at low cholesterol levels is associated with cancer, though this is not a uniform finding. The role of the serum cholesterol level at advanced age is of great concern because of the large potential at tributable risk of hypercholesterolemia. Attributable risk refers to the expected number of excess deaths due to the presence of a risk factor. It is usually distinguished from the relative risk, or the ratio of the number of deaths in persons with the risk factor to the number of deaths in persons without the risk factor. The attributable risk is superior to the relative risk as a measure of the impact of a risk factor on overall survival, since the relative risk of an uncommon event can be very high without significantly affecting survival rates, For example, about 2.7 percent of Americans between the ages of 75 and 84 died of heart disease in 1985 compared to 0.15 percent of 45 to 54 year-olds (122). Suppose that a risk factor increases the relative risk of CHD death at all ages by 10 percent (i.e., the ratio of the rate of CHD death among individuals with the risk factor to the rate in individuals without it is 1.1). Then the attributable risk of the factor is about 0.27 percent among 75 to 84 year-olds (i.e., almost 27 additional deaths per 10,000 people in this age group would occur each year), but it is only 0.015 percent among 45 to 54 year-olds (i. e., 2 additional deaths per 10,000 people in the age group would occur).

Most of the epidemiologic studies cited in this paper indirectly measured the impact of cholesterol on attributable risk, not relative risk, but they did not find that it had a statistically significant effect. Because the estimates were often imprecise, they are consistent with a large impact on attributable risk of CHD, but they are also consistent with a small or even negative impact on attributable risk. With prolonged followup of larger numbers of elderly individuals, the attributable risk of CHD due to elevations in the cholesterol level may prove to be large, but existing studies provide weak support for such a speculation.

4 Apolipoproteins are parts of the 1 ipoproteins to wh i ch cholesterol binds.

Recommendations for Cholesterol Measurement Among the Elderly

The National Heart, Lung, and Blood Institute's National Cholesterol Education Program (NCEP) established an Adult Treatment Panel composed of outside experts that published guidelines in 1988 for the measurement and treatment of hypercholesterolemia (116). NCEP categorized cholesterol levels according to increasing risk of coronary heart disease (CHD). For serum cholesterol, the panel considered measurements under 200 mg/dl as "normal," between 200 and 239 mg/dl as "borderline high," and 240 mg/dl or above as "high." Although it did not provide separate screening guidelines for persons over 65 years old, the panel recommended that all adults over the age of 20 should have their total serum cholesterol measured at least *every* 5 years. The full set of recommendations developed by this group for diagnosing and treating hyperlipidemia are summarized in appendix C.

The conclusions of the Adult Treatment Panel supersede an earlier National Institutes of Health Consensus Conference (114) that concluded, without documentation, that a cholesterol determination during annual physician office visits would be cost-effective for adults.

The American Heart Association (AHA) publishes general guidelines for the prevention of CHD (6,49). Representatives of the A HA participated in NCEP. Like the Adult Treatment Panel, AHA recommends that healthy people should have routine measurement of cholesterol and triglycerides every 5 years until age 60. But for older patients, these tests are considered optional if baseline measurements have been well-established. Like NCEP, AHA categorizes cholesterol levels into normal (<200 mg/dl), borderline high (200 to 239 mg/dl), and high (> 240 mg/dl) categories and recommends that physicians take other risk factors for CHD into account when prescribing treatment for persons whose lipid levels fall outside the normal range.

The U.S. Department of Health and Human Services' Preventive Services Task Force (a group of experts from outside the government) is currently considering screening for hyperlipidemia as well as other conditions. Its recommendations for cholesterol screening are expected to be released in the summer of 1989.

In Canada, a task force convened by the Department of National Health and Welfare to make recommendations on the frequency and content of the periodic health examination considered cholesterol screening in its initial report (20). The Canadian Task Force (CTF) concluded that there was insufficient medical evidence to warrant routine screening of cholesterol or triglycerides. However, this group did suggest that physicians may wish to measure blood lipids for other reasons, such as the presence of other CHD risk factors. CTF has not reevaluated its position since 1979.

Cholesterol Measurement Techniques

The hundreds of assays that have been used to measure cholesterol in blood (90, 108) can be divided into three categories. The first includes multi-stage techniques based on the modified Abell-Kendall method, which is considered the "standard reference method" (2,31). Application of the standard reference method is more demanding than many laboratory procedures, requiring relatively sophisticated facilities and technical skills. The laboratories of the Lipid Research Clinics and others that use this method have made extensive efforts to standardize and improve the quality of testing. These laboratories are thought to supply the most nearly error-free results in clinical use. The test requires a few milliliters of blood, and labora-

tories can generally provide results within 24 to 72 hours of receiving the specimen. These methods are used by the Centers for Disease Control (CDC) and Lipids Research Clinics around the country.

The second kind of assay is based on automated analyzers. This less exacting procedure is used mainly by general clinical laboratories, such as those available in most hospitals and freestanding clinics. Often, the measurement is performed as part of a panel of blood chemistry assays. Inaccuracy in these tests, partly due to variability in technical competence among the thousands of clinical laboratories in the country, is a major concern (1 17). Although the results of these assays may be less reliable than those produced by a reference laboratory, they are convenient because a number of measurements in addition to cholesterol can be performed on the same tube of blood. Results can be available within minutes.

The third kind of assay, a one-step enzymatic method that has recently become available, is particularly convenient for both patients and providers of care. These tests require only a few drops of blood from a finger stick and give results in 3 to 8 minutes. The equipment can be operated in a physician's office, clinic, or community screening site by personnel without a special background in clinical chemistry. These methods have a low per-screening cost (less than $3 in one large-scale community screening program (47)). Preliminary reports, generated under ideal circumstances of operator training and attention to calibration and technique, have found that assays are accurate (18). It is not known whether this level of accuracy will be maintained when the technology is used more widely.

Factors That Influence Cholesterol Measurements

The measured cholesterol level is influenced by long-term or clinically significant biologic factors, transient or insignificant biologic factors, and measurement error. The main determinants of the cholesterol level are genetic characteristics, diet, exercise, and lipid-lowering medications. To the extent that these factors can be altered, the serum cholesterol level may be lowered and the risk of adverse outcome may be influenced.

A variety of other factors influence the measured cholesterol level (73). Patient posture (reclining, sitting, or standing) and venous stasis (blood pooling in an extremity, which sometimes occurs during blood-drawing when a tourniquet is applied) can change the plasma volume enough to alter reported cholesterol levels by 5 to 12 percent. The cholesterol level increases slightly at ovulation and substantially during pregnancy (75 percent over nonpregnant subjects). Although recent food ingestion, alcohol intake, and exercise are thought not to influence cholesterol, there is some evidence that transient emotional stress may elevate the level. Medications, especially those used to treat high blood pressure, can elevate the cholesterol level (74). Seasonal variation can be responsible for temporary changes (1 10). In the placebo group of the Lipid Research Clinics-Coronary Primary Prevention Trial, which studied men aged 35 to 59 years whose plasma cholesterol levels[1] exceeded 265 mg/dl after a brief trial of diet, the measured cholesterol averaged 7.4 mg/dl higher on December 30 than on June 30 (42). Other studies (reviewed in Hegsted, 1987) have found that even when an individual adheres to a strictly controlled diet, his or her measured cholesterol varies substantially over short periods of time. A number of technical factors can also influence the reported level of cholesterol after the specimen has been collected. The cholesterol level obtained in some assays is affected by hemolysis (mechanical disruption of the blood that can occur when blood is withdrawn from a vein).

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1 Plasma cholesterol levels are consistently 3 percent lower than serum cholesterol.

The most important source of variability in the reported cholesterol level is, however, the clinical laboratory (1 17). Most of the epidemiologic studies that have contributed to our knowledge of cholesterol as a risk factor used meticulously standardized methods that were periodically tested against a central reference laboratory. Although laboratory error has diminished over the last 40 years, and although NCEP has urged clinical laboratories to redouble their efforts to standardize, measurements remain imprecise (117). Variation in reported cholesterol levels is partially the consequence of the varied methods used to test cholesterol, but substantial variation occurs even among laboratories using the same method. The College of American Pathologists sent a sample specimen whose cholesterol concentration was determined by CDC to be 262.6 mg/dl to 5,000 clinical laboratories. The cholesterol values reported by the surveyed laboratories ranged from 101 to 524 mg/dl (1 17). Current standards established by NCEP call for a coefficient of variation[2] of less than 3 percent. However, recent studies show the coefficient of variation to be at least 6 percent (1 17).

Errors in the cholesterol level may arise from bias in a particular laboratory method, meaning that even when standardized well, the reading will differ repeatedly from the true cholesterol level. A study conducted by Kroll and colleagues (70) compared the performance of the reference standard method to other assays, including the SMAC™ (Technicon Instruments Corp., Tarrytown, NY) and the aca™ (DuPont Co., Medical Products Department, Wilmington DE), the most widely used methods for cholesterol determinations in clinical laboratories. For a true cholesterol value between 170 mg/dl and 260 mg/dl, the aca method had an upward bias of between 4.0 and 4.8 percent, while the SMAC method had a 2.6 percent upward bias,[3] A more recent report showed that one laboratory, with careful attention to standardization and proper performance of the tests, was able to produce highly accurate and precise results using three commonly employed assays for cholesterol (69). The bias and coefficient of variation in each of these tests were less than 3 percent when compared to the standard reference method. Laboratories that do not strictly adhere to quality control measures are unlikely to achieve results as accurate as those of either Kroll or Koch. The physician who orders a serum cholesterol level risks misinterpreting the test result if he or she does not know the laboratory's assay method or if the laboratory fails to standardize properly.

The new one-step enzymatic techniques have not been tested extensively, but they appear to be accurate if well-standardized and properly performed. In preliminary results, collected under near-ideal conditions, three of these methods were evaluated when used by a family medicine physician. The degree of imprecision was less than the *3* percent coefficient of variation recommended by NCEP. However, two of the three methods produced cholesterol values that were 2.5 to 8.1 percent higher than the reference method (18). If not properly standardized, these methods are not likely to perform as accurately in physicians' offices, drug stores, field-screening programs, and other settings.

In order to achieve their goals of biases of 3 percent or less, and coefficients of variation of 3 percent or less for all assays and laboratories, NCEP's Laboratory Standardization Panel has endorsed a campaign to educate physicians and laboratories about the components of accurate and precise measurement methods. In addition, they have encouraged the use of reference serum samples produced by CDC and the National Bureau of

2 The coefficient of variation is the standard deviation of a probability distributions as a percentage of the mean. This statistical allows comparison of variation among distribution with different means.

3 This bias may be due to a "matrix effect" (92). The "matrix" is the environment in which the compound being measured exists. For cholesterol, the matrix is usually serum (11 7).

Standards with which laboratories can test and calibrate their assays. They have also encouraged participation in proficiency testing programs sponsored by the College of American Pathologists and the American Association of Bioanalysts (91,117).

Reliability of HDL and LDL Measurements

Many clinical laboratories can measure the high-density lipoprotein (HDL) cholesterol level directly. However, direct measurement of the low-density lipoprotein (LDL) level requires specialized equipment, so the LDL level is usually calculated from the total cholesterol, HDL cholesterol, and triglyceride levels (37).[4]

When HDL and LDL levels and ratios based on these levels are used for routine screening, they are unlikely to predict CHD risk as accurately as they did in a research setting. In routine clinical use, HDL assays are not as reproducible as serum cholesterol measurements, nor are they standardized as well as the HDL assays used in epidemiologic studies. The calculated LDL suffers from the same flaw because the components of the formula are often inaccurate. In a recent survey of chemistry laboratories *(23),* a standardized specimen whose "true" HDL value (as measured by CDC) was 34.6 mg/dl was sent to a large number of laboratories. Measurements reported by the participants were grouped according to which of eight methods the laboratory used. There was significant variation between the methods and among laboratories using the same method. The mean for each method ranged from 29.0 to 39.4 mg/dl. The method that produced a mean value of 39.4 mg/dl had a standard deviation of 7.9, implying that an HDL level of 34.6 mg/dl would be reported as 47 mg/dl or greater 16 percent of the time, denoting a much lower risk of heart disease than actually exists.

The variability in measured HDL levels is reflected in the coefficient of variation of the test results obtained by different laboratories. The coefficient of variation for the serum HDL among laboratories using the same method ranged from 11.1 to 20.0 percent. The striking variation in reported HDL levels indicates that routine HDL assays are imprecise, and are unlikely to predict risk as well as the meticulously standardized HDL assays used in epidemiologic studies.

Costs of Lipoprotein Measurement

The costs of lipoprotein testing depend on the method used and the combination of tests performed. Although the incremental costs of performing these tests are not easily determined, the charges reported to third-party payers provide a useful estimate of the likely costs of implementing a testing program. Table *3* summarizes the average allowed charges for lipoprotein determination procedures reported by two payers and a community-based screening program. Of the two payers, Blue Shield of California reports somewhat higher charges than the national Medicare program. The community-based screening program in Rochester, New York used an analyzer representative of the fingerstick method (the Retroflon™ manufactured by Boehringer-Mannheim). This equipment costs $5,000 for the analyzer and $1.10 per reagent strip. The organizers of the screening program estimated the costs to be $2.78 per determination (47).

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4 The "Friedewald formula" for calculating the LDL level is:

LDL = total cholesterol - HDL cholesterol - triglycerides/5.

This formula is considered accurate when the triglyceride level does not exceed 400 mg/dl. A triglyceride level of 400 mg/dl is very uncommon in the general population, so this formula can usually be applied. The 95th percentile for serum triglyceride levels in American men and women is well below 400 mg/dl at all ages, at least 6 years and above (75).

Table 3--- Selected Charges for Lipoprotein Measurement

	Blue Shield California[a]	Medicare[b]	community screening program[c]
Total cholesterol	$14.26	$6.35	$2.78
Lipoprotein cholesterol fractionation (by calculation formula)	23.80	15.80	NA
Complete lipid profile (HDL, cholesterol, and triglycerides)	39.06	NA	NA

[a] Blue Shield average allowed charges (R. Schaffarzick, Blue Shield of California, personal communication, November 1988).

[b] Medicare average allowed charges (M. Newton, Health Care Financing Administration, Baltimore, MD, personal communication, October 1988).

[c] Estimated cost of cholesterol determination in community screening program using the Retroflon™ fingerstick method (P. Greenland, J.C. Levenkron, M.G. Radley et al., "Feasibility of Large-Scale Cholesterol Screening: Experience With a Portable Capillary-Blood Testing Device," Am. J. Pub. Health 77:73-75, 1987).

ABBREVIATIONS: HDL = high-density lipoprotein; NA = not applicable.

SOURCE: Office of Technology Assessment, 1989.

Followup Testing

Followup testing for hypercholesterolemia can include repeating the cholesterol determination and performing assays for lipoprotein fractions and triglycerides. Although apolipoprotein determinations may eventually prove to be an important component of the followup testing for individuals found to have hypercholesterolemia, these tests are experimental at this time.

NCEP recommends that all subjects with an initial cholesterol of 200 mg/dl or greater have one or two repeat determinations. If the average of the two readings remains over 240 mg/dl, lipoprotein analysis is advised. The recommended threshold for lipoprotein analysis is 200 mg/dl in subjects with known CHD or two risk factors (including male sex). Further treatment advice is based on the calculated LDL-cholesterol level.

Importance of the Locale of Testing

A successful screening program depends upon characteristics of the test procedure, the population screened, and the efficacy of treatment. All of these may vary with the setting for testing. The most obvious problem for cholesterol is accurate testing procedures. Because most current methods require careful calibration, extra precautions must be taken to assure valid reporting when assays are performed away from a highly standardized clinical laboratory. Although newer fingerstick methods show promise for making accurate cholesterol assays available in the field, they have not yet been validated.

The completeness of followup testing is likely to vary with the locale of the original cholesterol test. An individual who is screened as part of a mass screening program or in a nonmedical setting will almost always need to go to another site for followup testing. This may deter some Medicare recipients from obtaining further tests. Similarly, when a cholesterol test is ordered or performed in a doctor's office or hospital clinic, it will be simpler to institute treatment than if screening is performed elsewhere.

Finally, the place where testing is performed may influence the feasibility of reimbursement under the Medicare program. A cholesterol measurement obtained as part of a battery of tests, in a physician's office or a hospital, could be reimbursed like other covered services under Medicare Part A or Part B. It is likely that the administrative costs would be large relative to the size of the reimbursement if cholesterol was measured as a single test, without any associated services. Consequently, while screening in shopping centers and drug stores might be inexpensive, reimbursement by Medicare or any other third-party payer is likely to be impractical.

5 A lipoprotein test that analyzes their protein composition.

Dietary Treatment of Cholesterolemia

The dietary treatment of hypercholesterolemia has been reviewed elsewhere (72). Cholesterol-lowering diets involve the reduction of overall fat and cholesterol intake, and the substitution of polyunsaturated vegetable oils for saturated fats and complex carbohydrates for sugars (116). Many people have reduced their cholesterol levels dramatically by diet alone. However, when averaged across many individuals, the reduction in serum cholesterol in the randomized trials of dietary interventions has been modest. In the Multiple Risk Factor Intervention Trial (MRFIT), diet reduced the cholesterol level by an average of about 7 percent.

Dietary treatment, although generally safer than pharmacologic approaches, is not entirely without cost. Significant changes in eating habits may reduce the quality of life. The monetary and utility costs of dietary modification have not been well studied. Other than the potential for loss of pleasure in eating, however, dietary changes have few known side effects.

Oat bran is a soluble fiber that reduces serum cholesterol. With a dietary intake of 1 to 1.5 cups of dry bran per day, serum cholesterol falls by 13 to 19 percent (7,9, 10,67,89). When used with other soluble fibers, the sustained reduction in serum cholesterol can be 20 to 25 percent. At current prices, a 90 gm daily dose of oat bran costs less than $0.40, if purchased in bulk. The cost does not include the time or money required to convert the oat bran to palatable food, such as bread or muffins.

Certain foods, especially fish containing omega-3 fatty acids, may have a beneficial effect on serum cholesterol (46,52,53,112). In one study *of* healthy persons, a fish diet reduced low-density lipoprotein (LDL) cholesterol and very low-density lipoprotein (VLDL) cholesterol with variable effects on high-density lipoprotein (HDL) cholesterol (124). There have been no reported long-term studies of omega-3 fatty acids in hypercholesterolemic patients (125).

Drug Treatment of hypercholesterolemia

Bile Acid Sequestrants: Cholestyramine and Colestipol

The bile acid sequestrants, which interrupt the circulation of bile acids in the body and cause the liver to synthesize new bile acids from cholesterol, are commonly used to reduce the LDL-cholesterol level. These drugs can reduce total serum cholesterol by 20 percent and LDL-cholesterol by 27 percent if taken in full doses (77), with a proportionate loss in effect when compliance is imperfect (79).

The bile acid sequestrants are difficult to take regularly, in part because some people have difficulty swallowing the slurry in which they are administered and in part because of minor but unpleasant side effects. The resin is administered in a liquid suspension and must be drunk quickly to avoid settling. Nausea, abdominal discomfort, and indigestion are common, and constipation occurs in as many as 45 percent of patients treated with cholestyramine (77). Impaction of stool may occur and be particularly troublesome in the elderly. The resins also bind other drugs in the intestine, decreasing their absorption. Despite their favorable effects on the LDL cholesterol, bile acid sequestrants can raise the triglyceride level.

Nicotinic Acid

Nicotinic acid (niacin) is an inexpensive and effective cholesterol-lowering medication.

The frequent occurrence of side effects has limited its acceptance. Nicotinic acid lowers the levels of plasma triglycerides and LDL cholesterol and raises HDL cholesterol. Nicotinic acid reduced total serum cholesterol by an average of 10 percent in the Coronary Drug Project (26) but can reduce cholesterol by as much as 40 percent in combination with bile acid sequestrants (61).

In the Coronary Drug Project, the incidence of the most common side effects of nicotinic acid, skin flushing and itching, were 92 and 49 percent, respectively. These side-effects may be less common when the dose is gradually escalated, or when each dose is preceded by a dose of aspirin. Vomiting, diarrhea, and dyspepsia (indigestion) are also common. Nicotinic acid can cause hepatitis (rarely), elevate serum liver enzyme levels without causing apparent disease, and raise blood sugar levels in diabetics.

HMG CoA reductase inhibitors

The enzyme 3-hydroxy-3-methyl glutaryl coenzyme-A (HMG CoA) reductase regulates the rate of cholesterol synthesis in humans. The drugs that inhibit this enzyme lower total and LDL cholesterol by reducing the rate of cholesterol synthesis. Formerly known as mevinolin, lovastatin is the first HMG CoA reductase inhibitor to be released in the United States. Lovastatin raises or does not affect plasma HDL.

There have been several multicenter trials of lovastatin (80,82,123). In one of these studies, there was a dose-dependent reduction of 32 percent in total cholesterol and 39 percent in plasma LDL cholesterol (80). HDL cholesterol increased 13 percent. When patients take cholestyramine in addition to lovastatin, plasma LDL cholesterol falls by 50 percent.

Side effects of lovastatin are uncommon and usually mild. None of the 101 patients in one study had a side effect that required stopping the drug. Liver enzymes (the transaminases) often rise in patients treated with lovastatin, but the enzyme levels seldom exceed twice the upper limit of the normal range. While clinical liver disease is rare *(80),* monitoring serum liver enzymes is recommended every 4 to 6 weeks for 15 months after starting lovastatin. Periodic eye examinations are recommended because of a possible association with cataracts (80). Because the drug is new, the side effects of long-term therapy, if any, have yet to be identified.

Fibric Acid Derivatives

Two fibric acid derivatives are currently used in the United States to treat hyperlipidemia. The first, clofibrate, was initially hailed as an important drug, but the indications for its use have narrowed as the results of randomized trials have become known. In the Coronary Drug Project, clofibrate reduced serum cholesterol by only 6 percent (26). In at least one large clinical trial, clofibrate significantly increased overall mortality and did not reduce coronary heart disease (CHD) mortality (24,25).

Clofibrate is generally well-tolerated, although it produces a variety of side effects in a small proportion of patients. Increased appetite (5 percent), decreased libido (14 percent), and breast tenderness (9 percent) are significantly more frequent among clofibrate-treated patients than in subjects given a placebo (26). Some patients get a flu-like syndrome with severe muscle cramps whenever they take the drug. Clofibrate is also associated with an increased incidence of gallstones (3.5 percent over 5 years) (26). Because clofibrate causes significant side effects, does not appear to reduce cardiovascular mortality, and may increase overall mortality, most experts no longer recommend it as a first-line drug for treating hypercholesterolemia.

Gemfibrozil, a newer fibric acid derivative, primarily lowers triglyceride levels. It also lowers LDL and raises HDL levels. In

one multicenter, placebo-controlled, randomized trial, total cholesterol decreased by 10 percent, non-HDL cholesterol fell 11 percent, and HDL cholesterol rose 11 percent (84). In this study, patients on gemfibrozil had a lower incidence of coronary heart disease than patients on placebo.

Gemfibrozil is generally well-tolerated. Gastrointestinal distress is the principal side effect. In the Helsinki Heart Study, moderate to severe upper gastrointestinal symptoms occurred in 11 percent of patients on gemfibrozil and 7 percent of patients on placebo, a highly significant difference (36). These symptoms were much less frequent after the first year of the study. Although gemfibrozil may promote gallstone formation, this complication appears to be less frequent than with clofibrate (17).

Other fibric acid derivatives, such as fenofibrate, bezafibrate, and ciprofibrate, are available in Europe but not in the United States. Experience overseas suggests that these drugs may have somewhat more favorable effects on the lipid profile than gemfibrozil or clofibrate and may be better tolerated. In a short-term randomized trial in the United States, fenofibrate decreased total cholesterol levels by 17.5 percent, lowered LDL-cholesterol levels by 20.3 percent, and raised HDL-cholesterol levels by 11.1 percent among individuals with hypercholesterolemia and normal triglyceride levels. In individuals who had elevations of triglycerides as well as cholesterol, fenofibrate cut total and LDL cholesterol by 16 and 6 percent, respectively, and raised HDL cholesterol by 15.3 percent (68).

Probucol

Probucol reduces serum LDL cholesterol by 10 to 15 percent. However, it also lowers serum HDL cholesterol, often to a greater degree than LDL cholesterol. There are no studies of its effect on survival or primary coronary heart disease events. The mechanism of action of probucol is unknown. Probucol is well-tolerated, with gastrointestinal symptoms occurring in about 10 percent of patients (17). Because of its adverse effect on HDL levels, probucol is not widely used.

Costs of Treatment

Table 4 details the annual cost of using the currently approved medications. Total costs per year of treatment include both retail drug prices, the costs of diagnostic procedures and physician services associated with monitoring the potential side-effects of treatment, and the costs of semiannual lipoprotein analysis to monitor the effectiveness of the treatment. These cost figures assume that:

- doctors prescribe the recommended dose to achieve maximal cholesterol-lowering effect,
- patients are compliant,
- laboratory monitoring as described in the manufacturers' package insert is performed regularly, and
- physicians' fees average $200 per patient per year for monitoring and adjusting therapy.

In order to estimate the retail cost of each prescription drug, OTA obtained average allowed charges from a New Jersey State pharmaceutical reimbursement program available to all non institutionalized persons over age 65 (60,81). For niacin and slow-released niacin, which are available without a physician's prescription, OTA obtained retail prices for generic versions of the compound from a Washington, DC retail drugstore chain (38).

Under these assumptions, the least expensive regimen, nicotinic acid, costs over $500 per year. Cholestyramine, often described as the agent of first choice, costs $1,200 per year when purchased in bulk and over $2, 100 annually when the more convenient pre-measured packets are employed. Gemfibrozil costs $850 per year including monitoring costs. The newest, and possibly most effective, agent is lovastatin. It costs

Table 4--Costs of Treating Hypercholesterolemia (in 1988 dollars)

Drug	Lipids[a] No.	Lipids[a] Cost	Chemistries[b] No.	Chemistries[b] Cost	CBC No.	CBC Cost	ECG No.	ECG Cost	Eye exam[c] No.	Eye exam[c] Cost	Annual cost of physician services	Annual monitoring cost[d]	Size	Daily dose[e]	Annual retail cost[f]	Total annual treament cost (includes monitoring)
Lovastatin	3	$58	12	$203	NA	NA	NA	NA	1	$86	$200	$547	20mg tablet	40mg	$1,141	$1,687
Colestipol	3	$58	NA	NA	NA	NA	NA	NA	NA	NA	$200	$258	5g packet	30g	$1,309	$1,567
													500g can		1,000	1,258
Niacin (nicotonic acid)	1	$19	6	$101	NA	NA	NA	NA	NA	NA	$200	$321	50mg tablet	3g	$194	$515
													100mg tablet		104	425
Niacin (nicotonic acid, slow release)	1	$19	6	$101	NA	NA	NA	NA	NA	NA	$200	$321	125mg tablet	3g	$312	$633
													250mg tablet		205	525
estyramine	3	$58	3	$51	NA	NA	NA	NA	NA	NA	$200	$309	9g packet	54g	$2,150	$2,459
													378g can		1,198	1,507
Gemfibrozil	3	$58	3	$51	3	$35	NA	NA	NA	NA	$200	$343	300mg capsule	1,200mg	$506	$850
Probucol	3	$58	NA	NA	NA	NA	2	$67	NA	NA	$200	$325	250mg tablet	1,000mg	$554	$879
													500mg tablet		534	859

[a]Lipid panel [illegible] and calculated low density lipoprotein.

[b]Chemistries are blood chemistry panel including three or more tests: glucose, liver function tests including transaminases, and total cholesterol.

[c]Eye Exam is a limited consultation for slit lamp exam by ophthalmologist.

[d]Recommended monitoring procedures were taken from the manufacturers' package inserts. "Periodically" was taken to mean three times per year and "frequently" was taken to mean six times per year. Monitoring costs include average allowed Medicare charges from a Northern California group practice laboratory.

[e]Daily doses are taken from Adult Treatment Panel; National Cholesterol Education Program; National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services, "Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults," Arch. Intern. Med. 148:36-69, 1988.

[f]Annual retail costs are average allowed costs from the New Jersey Pharmaceutical Assistance to the Aged and Disabled Program (S. Luger, Chief Pharmaceutical Consultant, New Jersey Pharmaceutical Assistance to the Aged and Disabled Program, Trenton, NJ, personal communication, Dec. 5, 1988; and D. Iozzia, Drug Reimbursement Analyst, Blue Cross/Blue Shield of New Jersey, Newark, NJ, personal communication, Feb. 10, 1989), except for niacin for which costs were estimated from retail prices in a District of Columbia chain pharmacy (D. Fukuzawa, Foer's Pharmacy, Washington, DC, personal communication, Dec. 5, 1988). Cost assumes full patient compliance.

ABBREVIATIONS: CBC = complete blood count; ECG = resting electrocardiogram; NA = Not applicable; No. = number of tests recommended per year.

SOURCE: Office of Technology Assessment, 1989.

over $1,600 per year, including monitoring Costs . Even purchasing at wholesale and using the lowest cost laboratory available, as might be the case for a public clinic or health maintenance organization, these regimens are expensive. Only nicotinic acid, available as a generic product, costs less than several hundred dollars per year.

As more products become available (new HMG CoA reductase inhibitors are in the preliminary phases of approval by the Food and Drug Administration) and as alternative agents (psyllium or oat bran, for instance) are evaluated, price competition may lower the costs of treatment.

Health Outcomes of Treatment

There is little information about the effects of treating hypercholesterolemia in the elderly. None of the randomized controlled clinical trials of the treatment of hypercholesterolemia included significant numbers of the elderly. Virtually all that is known about the effects of treatment is based on studies of middle- aged men. Several large randomized trials have addressed the effects of pharmacologic treatment in this population. Several other trials have assessed dietary therapy.

Several lines of evidence suggest that treatment might be effective. For example, animal (83) and human studies (16,76) have found that cholesterol reduction can slow or even reverse the progression of atherosclerosis. Clinical trials have shown that treatment can impede the development of heart disease in hypercholesterolemic individuals. At least two studies found that reducing cholesterol levels that start above 260 mg/dl can diminish cardiovascular mortality, and one study has shown that a cholesterol-lowering medication reduces 15-year all-cause mortality among survivors of myocardial infarction.

Table 5 displays key findings from several major studies of interventions to reduce mortality by lowering cholesterol. Asymptomatic, hypercholesterolemic individuals, such as those who would be identified in a screening program, were the subjects of several primary prevention trials. These trials have shown that moderate cholesterol reduction lowers both the incidence of and mortality from CHD among individuals who have no clinical evidence of CHD. However, the interventions did not significantly affect all-cause mortality. The Lipid Research Clinics-Coronary Primary Prevention Trial (LRC-CPPT) is widely cited as the first randomized trial to show that drug therapy of hypercholesterolemia in asymptomatic subjects reduces coronary disease morbidity and mortal it y. The LRC-CPPT enrolled 3,806 men aged 35 to 59 whose serum cholesterol, after an attempt at dietary management, was at least 265. Both the intervention and control groups continued to receive a dietary intervention after the start of the trial. At an average of 7 years of followup, the choles - tyramine-treated group suffered less morbidity and mortality from ischemic heart disease than the control group. There was a statistically significant ($p<0.01$) reduction in the incidence of angina, which was experienced by 15 percent of the control group and 12 percent of the treatment group. CHD mortality was also reduced by the intervention; 2.3 percent of the control group died from definite or suspected CHD death, compared with 1.7 percent of the cholestyramine group. However, all-cause mortality was 3.7 percent and 3.6 percent in the control and cholestyramine-treated groups, respectively, a difference that was not statistically significant (78). Analysis of the cholestyramine-treated patients showed that an 8-percent reduction in serum total cholesterol was associated with a 19-percent reduction in CHD incidence. The magnitude of the reduction in the incidence of CHD corresponded to the degree of reduction in total cholesterol levels. Thus, the individuals who adhered closely to the intervention tended to have larger declines in cholesterol and a lower incidence of CHD (79). However, CHD incidence in the control group did not show a statistically significant

Table 5.--Randomized Trials of Cholesterol Reduction and Mortality

Study	Number of patients	Characteristics[a]	Intervention	Mean followup (in years)	Mean change[b]	Mortality[c]			
						Coronary heart disease		All causes	
						Intervention	Control	Intervention	Control
Lipid Research Clinics[d]	1,906	Age 35-59 plasma cholesterol ≥ 265 (mean 279)	Cholestyramine	7.4	8.5%	1.6	2.0[e]	3.6	3.7
Helsinki Heart Study[f]	2,051	Age 40-55, non-HDL cholesterol >200 (mean total cholesterol 289)	Gemfibrozil	5	1%	0.7	0.9	2.2	2.1
Coronary Drug Project:	1,119	Age 30-64, survivors of myocardial infarction (mean cholesterol 253)	Niacin	6	10.1%	18.8	18.9	21.2	20.9
■ Coronary Drug Project Research Group, 1975[g]									
■ Canner et al., 1986[h]				15		36.5	41.3[e]	52	58.2[e]
World Health Organization:	5,331	Age 30-59 upper one-third of cholesterol distribution (mean cholesterol 249)	Clofibrate	5.3	9%	0.13	0.12	0.62	0.52[j]
■ Committee of Principal Investigators, 1984[i]									
■ Committee of Principal Investigators, 1984[k]				13.2		0.36	0.35	0.86	0.79
Multiple Risk Factor Intervention Trial[l]	6,428	Age 35-57, high-risk (mean cholesterol 254)	Diet, smoking reduction, blood pressure control	7	2%	1.8	1.9	4.1	4
Wadsworth Veterans Administration Hospital[m]	424	Age 55-89, residing in Veterans domicile (mean cholesterol 233)	Diet	8[n]	12.7%	9.6	14.2[o]	41	41.9
Oslo Study[p]	604	Age 40-49 cholesterol 290-380, high risk (mean cholesterol 323)	Diet, smoking reduction	5	13%	1	2.2[e]	2.6	3.8

(footnotes found on next page)

[a]Cholesterol are levels reported in units of mg/dl.

[b]Percent of change is the difference between intervention group and control group cholesterol levels, expressed as percentage of original cholesterol level.

[c]Mortality figures are the cumulative numbers of deaths per 100 subjects during the followup period, with exception of the World Health Organization trial, where deaths per 100 subjects per annum are reported.

[d]Lipid Research Clinics Program, "The Lipid Research Clinics Coronary Primary Prevention Trial Results: I. Reduction in Incidence of Coronary Heart Disease," J.A.M.A. 251:351-364, 1984; and Lipid Research Clinics Program, "The Lipid Research Clinics Coronary Primary Prevention Trial Results: II. The Relation Of Reduction in Incidence of Coronary Heart Disease to Cholesterol Lowering," J.A.M.A. 251:365-374, 1984.

[e]difference between intervention and control groups is significant at p<0.05. two-tailed test.

[f]M.H. Frick, O. Elo, K. Haapa et al., "Helsinki Heart Study: Primary-Prevention Trial With Gemfibrozil in Middle-Aged Men With Dyslipidemia," N. Engl. J. Med. 317:1237-1245, 1987.

[g]Coronary Drug Project Research Group, "Clofibrate and Niacin in Coronary Heart Disease," J.A.M.A. 231:360-381, 1975.

[h]P.L. Canner, K.G. Berge, N.K. Wenger et al., "Fifteen year Mortality in Coronary Drug Project Patients: Long-Term Benef t With Niacin," J. Am. Coil. Cardiol. 8:1245-1255, 1986.

[i]Committee of Principal Investigators, "A Cooperative Trial in the Primary Prevention of Ischaemic Heart Disease Using Clofibrate: Report From the Committee of Principal Investigators," Brit. Heart. J. 40:1069-1118, 1978.

[j]Difference between intervention and control groups is significant at p<0.05, two-tailed test, but in wrong direction.

[k]Committee of principal Investigators, "WHO Cooperative Trial on Primary prevention of Ischaemic Heart Disease With Clofibrate To Lower Serum Cholesterol: Final Mortality Follow-up, 2:600-604, 1984.

[l]Multiple Risk Factor Intervention Trial Research Group, "Multiple Risk Factor Intervention Trial: Risk Factor Changes and Mortality Results," J.A.M.A. 248:1465-1477, 1982.

[m]S. Dayton, M. Pearce, S. Hashimoto et al., "A Controlled Clinical Trial of a Diet High in Unsaturated Fat in Preventing Complications of Atherosclerosis, " Circulation 40(suppl. 2):II-1--II-63, 1969.

[n]Entire followup period; mean not reported.

[o]Statistical significance not reported in study.

PI. Hjermann, K.V. Byre, 1. Holme et al., "Effect of Diet and Smoking Intervention on the Incidence of Coronary Heart Disease: Report From the Oslo Study Group of a Randomized Trial in Healthy Men," Lancet 2:1303-1310, 1981.

ABBREVIATION: HDL = high-density lipoprotein.

SOURCE: A. Garber, B. Littenberg, and H. Sex, "Screening for Cardiac Risk Factors: Serum Cholesterol and Triglycerides," forthcoming in Ann. Intern. Med.

relation to the degree of cholesterol lowering due to diet (71). In summary, the LRC-CPPT trial showed that cholestyramine given to hypercholesterolemic, asymptomatic men without a prior myocardial infarction diminishes morbidity and mortality from CHD but does not reduce overall 7-year mortality.

The Helsinki Heart Study, another medication trial, obtained similar results in 4,081 asymptomatic, hypercholesterolemic men aged 40 to 55 who were randomly assigned to receive either placebo or gemfibrozil (36). Beyond 2 years of followup, gem fibrozil decreased total and LDL cholesterol by about 9 percent each and raised HDL cholesterol levels by 9 percent. At 5 years of followup, compared to the controls, the gemfibrozil group experienced significantly fewer cardiac events but the same overall mortality rate. Most of the excess noncardiac deaths in the treatment groups of both the LRC-CPPT trial and the Helsinki Heart Study were due to accidents and violence.

The Oslo Study (56), which enrolled more than 1,200 men whose cholesterol levels ranged from 290 to 380 mg/dl (average value, 328.9 mg/dl), found that a combined diet and smoking intervention produced a large but statistically insignificant fall in all-cause mortality. By the end of the trial (averaging 5 years of observation), 2.6 percent of the intervention group died, compared with 3.8 percent of the control group (P=0.246). Nearly 80 percent of the men smoked cigarettes at the time of enrollment, and the combined intervention decreased tobacco consumption by 45 percent. In a followup study conducted after the termination of the trial (between 8.5 and 10 years after enrollment), the difference in overall mortality approached statistical significance. By that time, 3.15 percent of the intervention group and 4.94 percent of the control group had died, corresponding to a one-sided p-value of approximately 0.05, not adjusted for multiple comparisons (57). Because the intervention substantially reduced cigarette smoking during the trial, the trend toward a significant decline in overall mortality could not be attributed to cholesterol reduction alone. This trial enrolled men whose cholesterol levels were higher than in the populations included in the LRC-CPPT and Helsinki studies, and its small sample size limited its power to detect clinically significant differences in outcomes.

Other trials that were designed to lower coronary disease and death rates by reducing cholesterol did not show a benefit from the intervention. In at least one case, there may have been no benefit because the intervention did not lower the cholesterol level substantial y. In MRFIT, which tested a multifaceted intervention (designed to alter diet, promote smoking cessation, and control blood pressure), the cholesterol level in the intervention group fell by only 2 percent more than in the control group, and neither CHD nor all-cause mortality was lower in the intervention group.

Evidence from trials of individuals with established CHD complements the findings from primary prevention studies of cholesterol reduction. Established CHD might not seem to be amenable to preventive efforts, so trials targeted toward middle-aged men who have CHD might not seem directly relevant to a screening population of asymptomatic elderly men and women. Despite such concerns, these studies provide important clues to the likely effects of cholesterol reduction in asymptomatic individuals. Men with CHD are at such a high risk of death from CHD and of recurrent cardiac morbidity that secondary prevention might show a benefit from cholesterol reduction in this population, despite a relatively short period of observation. The Coronary Drug Project, a secondary prevention trial that tested several cholesterol-lowering interventions in this population, has provided evidence that cholesterol reduction leads to lower all-cause mortality. This study showed that nicotinic acid, when given to 30 to 64 year-old male

survivors of myocardial infarction, reduced cholesterol levels by about 10 percent (21). It had no effect on mortality at a followup period averaging 6 years. However, at an average of 15 years after the inception of the trial, the men treated with nicotinic acid had an all-cause mortality rate that was 11 percent lower than the placebo group (p=0.0004), even though the Coronary Drug Project regimen only lasted for about 6 years. The mortality reduction was primarily due to a fall in the CHD mortality rate. Larger benefits were reported in another secondary prevention trial, the Stockholm Ischemic Heart Disease Study (1 00), which found a 29 percent reduction in 5-year all-cause mortality among survivors of myocardial infarction treated with a combination of clofibrate and nicotinic acid. However, only limited conclusions can be drawn from this trial, It was small and not double-blinded; the authors did not report whether the all-cause mortality difference was statistically significant; and 24 percent of the intervention group withdrew from the trial (as against only 10 percent of the control group).

In the absence of direct evidence pertinent to the elderly, these studies must serve as the most important basis for inferring the effects of cholesterol reduction in older Americans. Although cholesterol reduction can reduce the incidence of CHD and the rate of CHD death among middle-aged asymptomatic men without clinical evidence of heart disease, it has not been shown to lower overall mortality in this population. These studies may not have had sufficient years of followup or numbers of subjects to detect an overall mortality benefit, but benefits delayed for many years might not be pertinent to the elderly, who have a high rate of death from other causes. If the elderly suffer more side effects from medication or dietary interventions than the subjects of these trials did, the case for treating hypercholesterolemia will be weakened.

Implications of Cholesterol Screening in the Elderly for Total Health Care Expenditures

The literature reviewed in the preceding chapters suggests that the health benefits, particularly as measured by total mortality, of cholesterol screening in the elderly are unproven and may be smaller than in middle-aged people:

- Cholesterol assays in routine clinical use are not as reliable as those employed in epidemiologic studies and may not predict risk as accurately.
- The evidence that cholesterol level is a risk factor for coronary heart disease (CHD) in the elderly is not as consistent and conclusive as the evidence for middle-aged men. Furthermore, it appears not to be a risk factor for overall mortality in the upper ages.
- There are no randomized trials of the impact of cholesterol reduction on CHD or overall morbidity or mortality in the elderly, and no randomized trial has proven that cholesterol reduction lowers overall mortality in the populations that have been studied, with the exception of a study of male survivors of myocardial infarct ion.
- Apart from diet, treatment in the elderly may have more adverse side effects than treatment in younger populations. The elderly take more drugs on a regular basis than do other patients. Multiple drug therapies increase the risk of interactions among the different chemical compounds. In addition, as individuals age, they may be less able to tolerate the unpleasant side effects of cholesterol-lowering drugs themselves.

Cholesterol reduction has been found to reduce CHD morbidity and mortality in middle-aged men, but it did not improve overall survival during the study periods of the randomized trials (usually less than 10 years). Consequently, data about existing treatments do not provide convincing evidence that cholesterol reduction would increase life expectancy among the elderly. Cholesterol reduction might improve quality of life by reducing the symptoms of CHD, but it would also require changes in diet or suffering the side effects of medication.

Because no study has documented the survival or morbidity benefits of cholesterol reduction in the asymptomatic elderly, a precise estimate of the costs and effectiveness of cholesterol screening is impossible. However, the National Institutes of Health has sponsored the development of recommended cholesterol screening and treatment protocols for the elderly (as well as for other age groups) and has widely disseminated these recoin - mendations to physicians and the public (1 16). Therefore, OTA estimated the annual national health care expenditures associated with full implementation of the National Cholesterol Education Program (NCEP) screening and treatment protocols in the elderly population,

The model, described in detail in appendix C, estimates both screening expenditures and expenditures associated with treating all diagnosed hypercholesterolemia in 1995. The number of people who would be treated for hypercholesterolemia, either with dietary guidelines or ultimately, with medication, was estimated with data on the distribution of serum cholesterol and low-density lipoprotein (LDL) levels in the elderly (1 18,1 19). When data on important elements of the model were unavailable, a range of costs was generated to reflect the probable boundaries for specific estimates. For example, the NCEP guidelines call for dietary treatment in certain cholesterol and LDL ranges only when two or more other risk factors (such as being male,

Table 6--- Estimated Total Health Care Costs of Full Compliance With National Cholesterol Education Program Protocol[a] in the Elderly Population in 1995 (in millions of 1988 dollars)

	Percent of population treated	Screening and diagnostic costs	Total costs
Risk factor prevalence 30%:			
Low cost regimen[b]	47%	$57.7	$ 2,905
High cost regimen[c]	47	57.7	9,207
Risk factor prevalence 50%:			
Low cost regimen	52%	$57.6	$ 3,610
High cost regimen	52	57.6	11,472
Risk factor prevalence 70%:			
Low cost regimen	57%	$57.4	$ 4,314
High cost regimen	57	57.4	14,252

[a] Adult Treatment Panel, National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services, 'Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults," Arch. Intern. Med. 148:36-69, 1988.

[b] Assumes that patients receiving medication pay $525 per year for niacin and related monitoring.

[c] Assumes that patients receiving medication pay $1,687 per year for lovastatin and related monitoring.

SOURCE: Office of Technology Assessment, 1989.

hypertensive, a smoker, or having diabetes) are present. Because data on the frequency with which such risk factors occur in the elderly population are unavailable, the number of elderly treated under the NCEP protocols was estimated for frequencies ranging from 30 to 70 percent of the population.

In other cases, where uncertainty exists about specific factors, the model is constructed to underestimate costs. For example, the health care costs associated with monitoring people who are successful in controlling cholesterol with diet are assumed to be zero. Moreover, dietary intervention was assumed to lower LDL levels by 10 percent, an effectiveness rate that is reasonably optimistic relative to the existing empirical evidence (32). Medication costs were based on prices paid by a State pharmaceutical assistance agency on behalf of its beneficiaries. These prices may be lower than the average retail prices that would be paid by Medicare beneficiaries.

The results of the analysis are presented in table 6. The costs of performing the laboratory tests associated with screening and followup are a very small part of the total costs of screening and treatment. Treatment costs, particularly the costs of medications, constitute the vast majority of annual total costs of the NCEP. Even if relatively inexpensive medications are chosen, the cost of treating hypercholesterolemia is much greater than the cost of detecting it. In 1995, the costs of screening and followup testing would be about $57 million, while total national health care expenditures associated with screening and treatment would range from at least $2.9 billion to $14.2 billion.

The cost estimates in table 6 show what would be spent nationally if all elderly people were to comply with screening recommendations and adhere to the cholesterol lowering therapy called for by the NCEP. Full compliance with the NCEP treatment guidelines

would result in 47 to 57 percent of all elderly Americans on some form of treatment, either diet or medication. Many elderly people are currently receiving cholesterol-lowering therapy, so some of these costs are already being incurred. But many others probably would not comply with the recommended screening or treatment protocols, even if Medicare were to pay for cholesterol screening. For example, in a large well-established and prevention-oriented health maintenance organization in the Northeastern United States, only 75 percent of elderly enrollees had had a serum cholesterol test within the previous 5 years (40). If compliance with the NCEP screening and therapy guidelines were as low as 25 percent, then only 12 to 14 percent of the elderly would actually enter cholesterol-lowering treatment, and the annual health care costs of screening and treatment in the elderly would range from $782 million to $3.6 billion in 1995.

Although these cost estimates are based on optimistic assumptions about the effectiveness of diet in controlling cholesterol and LDL, total estimated costs are extremely sensitive to this assumption. If, for example, a dietary intervention were shown to be able to produce a permanent reduction in LDL levels by 15 percent in the elderly, then national health care costs associated with full compliance in the elderly would fall somewhere between $1.9 billion to $10 billion in 1995. At present, however, there is no reason to expect such a level of effectiveness to be obtained through dietary intervention in the elderly.

Costs to Medicare

Medicare currently does not pay for serum cholesterol or other lipoprotein measurement on a screening basis. However, these procedures are all covered as diagnostic services or as part of the management of previously diagnosed CHD or hypercholesterolemia. Medicare currently pays 80 percent of allowed charges after the beneficiary has met an annual deductible. Assuming that Medicare similarly were to pay 80 percent of screening expenditures, Medicare costs for screening only (including initial testing and-followup, but not treatment) would be between $50 million and $62.6 million in 1995 under a regimen of full compliance with the NCEP guidelines. In addition, Medicare would pay 80 percent of allowed charges for physician services and diagnostic procedures necessary for monitoring drug therapy, which would range from about $250 to $550 annually for each treated individual. If the entire elderly population were to comply fully with the NCEP guidelines, these Medicare expenditures would range from $1 billion to $5.4 billion in 1995, depending on the frequency of risk factors and the mix of medications prescribed for the population. With a 25 percent compliance rate in the elderly, Medicare's expenditures would be reduced proportionately to between $261 million and $1.3 billion.

Expenditures associated with actual drug purchases would be covered by the prescription drug benefit of the Medicare Catastrophic Coverage Act of 1988 (Public Law 100-360). Cholesterol-lowering medications will first be eligible for reimbursement in 1991, with each beneficiary facing a $600 annual deductible on all prescription drug purchases and a 50 percent copayment. Starting in 1993, the deductible will be indexed so that 16.8 percent of all Medicare beneficiaries will have drug expenses that exceed the deductible. The coinsurance rate will be 20 percent. Precise estimates of the Medicare burden for the costs of treating hypercholesterolemia diagnosed through a screening program are not possible. Although only three of the cholesterol-lowering drugs currently available are so expensive that they are highly likely to exceed the annual deductible (lovastatin, colestipol, and cholestyramine; see table 4), Medicare beneficiaries using the other cholesterol-lowering drugs may still become eligible for reimbursement if their total annual prescription drug expenses exceed the deductible. For those elderly who use multiple prescription drugs, a cholesterol screening

benefit would substantially increase Medicare's financial burden for the treatment of hypercholesterolemia. Only one choles-terol-lowering drug--niacin--whose annual retail costs are estimated to be between $100 and $300, would not be eligible for reimbursement under the Catastrophic Coverage Act because it does not require a physician's prescription.

Use of Cholesterol Screening Services

Current Utilization

Little information exists on the current use of cholesterol screening by the elderly. None of the national household surveys conducted to date by the National Center for Health Statistics have collected data on the frequency of cholesterol measurements. The Health Care Financing Administration's (HCFA) Medicare Procedures Database (BMAD) allows estimation of the number of procedures and allowed charges reimbursed under the Medicare program. The database records the use of all medical and surgical procedures as defined in the Current Procedural Terminology (CPT) manual performed in hospitals, ambulatory clinics, and physicians offices.

HCFA provided OTA with data from its BMAD files for all lipoprotein measurement procedures paid by Medicare during calendar year 1986 (see table 7). However, these numbers provide little information about the proportion of elderly with no history of hyperlipidemia or CHD who receive periodic cholesterol screening. First, since Medicare currently reimburses cholesterol measurement only when a patient has symptoms or has been given a diagnosis, the BMAD numbers theoretically should not include any tests done purely for screening purposes. In addition, since the BMAD database records use by procedures rather than by persons, the numbers in table 7 represent more than one test for some Medicare beneficiaries.

Table 7.--Total Number of Lipoprotein Measurement Services Allowed Under Medicare in 1986 by Type of Procedure

CPT[a] code	Name of procedure	Number of allowed services[b]
82465	Total serum cholesterol	678,666
82470	Total serum cholesterol and esters	7,605
83700	Total blood lipids	57,484
83705	Fractionated cholesterol (cholesterol, triglycerides, and phospholipids)	
83719	High-density lipoproteins by ultracentral fugation	32,833
83720	Lipoprotein fractionation by calculation formula	91,578

[a] Physician's Current Procedural Terminology, v. 1. A. Coy, C.M. Fanta, A.J. Finkel et al. (eds.) (Chicago, IL: American Medical Association, 1988).

[b] Data supplied by M. Newton, Health Care Financing Administration, Baltimore, MD, personal communication, October 1988.

SOURCE: Office of Technology Assessment, 1989.

Implementing a Cholesterol Screening Benefit

A decision to include cholesterol screening under Medicare would present at least two issues concerning payment for such services:

1. Paying for cholesterol screening as part of a physician's office visit .-- OTA's analysis of expenditures associated with the diagnosis of hypercholesterolemia in the elderly only includes the charges for specific screening procedures; it does not include the cost of visiting the physician's office. Because many (if not most) cholesterol screenings would take place in the physician's office, this model implicitly assumes that all elderly have their cholesterol checked while visiting their doctor for some other reason. For reimbursement purposes, this assumption is not unreasonable, because each procedure performed as part of a screening program already can be billed separately from the office visit charge

and has an assigned CPT code used by Medicare in paying for services (28). However, if beneficiaries make a special visit to the physician just to have their cholesterol checked, the cost of the office visit becomes part of the true cost of the screening benefit. It is also possible that the introduction of a cholesterol screening benefit would lead to an increase in the number of physician office visits and other medical services used by Medicare beneficiaries by simply encouraging individuals to pay greater attention to their own health.

2. Paying for cholesterol screening in community settings.--As the analysis in this paper indicates, the technology exists to perform cholesterol measurement in community settings with "desk-top" analyzers. Current data suggest that the cost of screening in community settings with such technology is lower than charges for such procedures in physicians' offices and laboratories. However, there currently is no mechanism by which Medicare pays for medical services offered in community facilities, such as churches or senior citizens' centers. If Medicare covered cholesterol screening in these settings, HCFA would have to develop reimbursement policies for them. As suggested in OTA's earlier analysis of glaucoma screening for the elderly, HCFA might pay the sponsors of community screening programs--hospitals, nonprofit organizations, etc---a set rate per patient for all Medicare beneficiaries screened (96). Because the accuracy and precision of desk-top analyzers are, in part, a direct function of the proficiency and care of individuals using the technology, policy makers would also need to consider how to monitor the quality of testing in community settings.

Costs and Effectiveness of Cholesterol Screening

Is routine cholesterol screening a cost-effective approach to the prevention of coronary heart disease in the elderly? Cost-effectiveness analysis usually assesses the cost associated with a defined increase in a measure of benefits. In health care, the most commonly employed measure of effectiveness is the change in life expectancy (or "quality-adjusted" life expectancy) brought about by a health intervention. However, the cost-effectiveness ratio (the ratio of the incremental costs of the interventions to the incremental health effects) is undefined when there are no health effects or when the intervention has deleterious effects on health.

Because there have been no randomized controlled trials of the health effects of cholesterol reduction in the elderly, particular weight must be placed on observational and epidemiologic data about cholesterol as a risk factor in the elderly. As reviewed above, cholesterol is not as powerful a risk factor for CHD in the elderly as it is in the middle-aged. Furthermore, epidemiologic studies have found that the cholesterol level is either not associated with overall mortality rates or is inversely associated with all-cause mortality. In addition, randomized controlled trials of the health effects of cholesterol reduction have not included elderly participants. It would be difficult to infer from available evidence that elderly individuals with an elevated blood cholesterol level would benefit from cholesterol reduction, even if the cholesterol could be lowered without side effects from medication or dietary change.

However, several developments may increase the effectiveness of cholesterol screening in coming years. First, cholesterol measurements in clinical laboratories and in other

settings are likely to become more accurate, in large part because of the efforts of the Laboratory Standardization Panel of NCEP. Standardization of high-density lipoprotein and low-density lipoprotein measurements is likely to improve as well, and one or both of these lipoproteins may become the primary screening tests for CHD risk in the elderly. The powerful new medications to lower cholesterol that have recently become available seem to have few short-term side effects and may prove to be more effective at lowering cardiovascular risk than previously available treatments. If studies demonstrate that cholesterol-lowering interventions reduce CHD and all-cause mortality among the elderly, the rationale for screening could become more persuasive.

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APPENDIX B: ACKNOWLEDGMENTS

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APPENDIX C: EXPENDITURE MODEL FOR DIAGNOSIS AND TREATMENT OF hypercholesterolemia IN THE ELDERLY

In order to analyze the cost implications of a cholesterol screening benefit under Medicare, OTA developed a model to estimate annual total direct health care expenditures associated with screening and treatment of hypercholesterolemia in the elderly, This appendix describes the model. The text of the paper discusses the results of the analysis.

The Model

Several expert groups have recommended periodic screening for hypercholesterolemia. The most recent of these guide lines--formulated by the Adult Treatment Panel of the National Cholesterol Education Program (NCEP)--provides a suggested model for the detection and subsequent management of hypercholesterolemia. OTA has neither evaluated nor endorsed the protocol outlined by the Adult Treatment Panel. However, because of the protocol's wide dissemination throughout the medical community, it is the basis for estimating direct expenditures associated with cholesterol screening and treatment in the elderly.

The recommended protocol of NCEP is as follows (1 16):

- All adults should have their total serum cholesterol measured at least once every 5 years.
- If the cholesterol level is found to be less than 200 mg/dl, it is classified as "desirable, " and no specific management is required (educational materials about diet and cardiac risk factors should be provided).
- If the cholesterol level is at least 200 mg/dl, the cholesterol test is repeated. If the average of the two readings is between 200 and 239 mg/dl, it is classified as "borderline-high" cholesterol. If the average of the two readings is less than 200 mg/dl, further management is the same as for individuals with a desirable cholesterol level.

Table 8.--- NCEP Risk Factors for Coronary Heart Disease

- Male gender
- Family history of premature CHD (definite myocardial infarction or sudden death before age 55 in a parent or sibling)
- Cigarette smoking (currently >10 cigarettes per day)
- Hypertension[a]
- Diabetes mellitus[a]
- History of definite cerebrovascular disease (stroke) or occlusive peripheral disease
- Severe obesity (>30% overweight)
- Known history of low-HDL-cholesterol level (<35mg/dl confirmed by repeated measurement)

[a]NCEP does not specify the criteria for categorizing patients as diabetic or hypertensive.

ABBREVIATIONS: CHD=coronary heart disease; HDL = high density lipoprotein; NCEP = National Cholesterol Education Program.

SOURCE: Office of Technology Assessment, 1989.

- If the average of two readings is greater than 239 mg/dl, or if it is at least 200 mg/dl and the individual has either a history of coronary heart disease (CHD) (defined as prior myocardial infarction, or myocardial ischemia such as angina pectoris), or two other CHD risk factors, as shown in table 8, lipoprotein analysis is recommended. Lipoprotein analysis includes measurement of fasting total cholesterol, triglycerides, and high-density lipoproteins (HDL), and calculation of the low-density lipoprotein (LDL) level (from the Friedewald formula).
- For persons who receive lipoprotein analysis, further management is based on the calculated LDL level. If it is less than 130 mg/dl, the individual is considered to have "desirable LDL cholesterol," and no specific further management is required. Management of an LDL level above 130 mg/dl depends on the presence of other risk

factors. All patients are started on a dietary intervention for 6 months. If at the end of that time they have failed to achieve a desirable cholesterol level, medications may be added, depending on the LDL level, and the physician's discretion. These recommendations for testing and therapy are summarized in Figure 3.

Using an adaptation of this protocol, OTA performed an analysis of the likely health care expenditures associated with an ongoing cholesterol screening and treatment program for Medicare recipients. Because the costs of medications vary widely, expenditures for a range of medical regimens were estimated in 1988 prices.

Assumptions

The assumptions used in this analysis appear in table *9*. The basis for the assumptions is as follows:

Size of the population to be screened---The analysis uses the projected number of American men and women aged *65* and over in 1995 (113). The year *1995* was chosen because it would represent the first year in which full screening of the population could be anticipated under an every-5-year screening program.

Participation. --OTA estimated the cost. of full compliance with the NCEP protocols by all elderly people. Of course, not all Medicare recipients will avail themselves of the screening program or will comply with drug therapy. For example, one health maintenance organization that provided OTA with information on the use of preventive services reported that of members over *65* years old, 75 percent had their cholesterol measured at least once during a 5-year period (40). Consequently, the model was constructed to estimate costs under various assumptions about levels of compliance. Results are presented in the main body of this report indicating how costs would change if compliance with the NCEP screening and therapy guidelines were only 25 percent in the elderly.

Table 9--- Assumptions for Cholesterol Expenditure Model

	1995 Over-65 population (in thousands)
Men	13,441
Women	20,447

Fraction screened annually	0.2
Compliance with screening and therapy	0.25-1.00
Fraction with risk factors	0.3-0.7
Response to dietary therapy	10-15%
Fraction of drug expenditures incurred in the first year for persons who begin medication after failing to respond to dietary therapy	0.5

Cost assumptions	
Total cholesterol measurement	$ 6.79
LDL measurement	16.89
Annual costs of drug and monitor:	
low-cost medication (niacin)	525.00
high-cost medication (lovastatin)	1,678.00

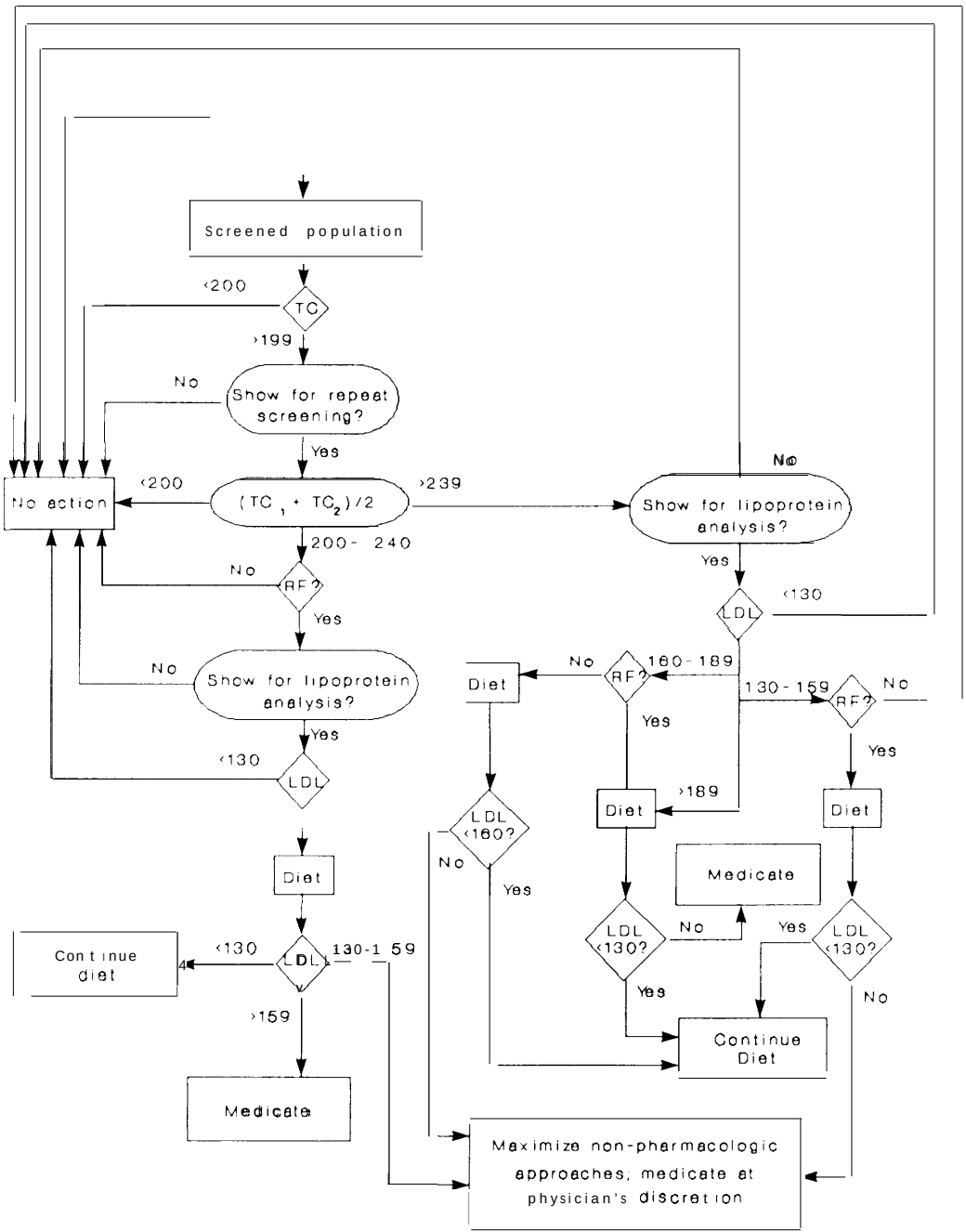
Lipid distributions	Men	Women
Total cholesterol (mg/dl)		
Mean	221.00	246.00
Standard deviation	62.33	60.21
LDL cholesterol (mg/dl)		
Mean	149.00	162.00
Standard deviation	40.00	44.00
Correlation, total and LDL cholesterol	0.84	0.88
Proportion with		
cholesterol under 200 (mg/dl)	0.37	0.22
cholesterol under 240 (mg/dl)	0.62	0.46

ABBREVIATION: LDL = low-density lipoprotein.

SOURCE: Office of Technology Assessment, 1989.

Prevalence of risk factors.--The NCEP protocol for determining lipoprotein fractions and treatment depends not only on the serum cholesterol but also on the presence of other risk factors. A high-risk individual is identified as one with 2 or more of the risk factors. Information is unavailable about the prevalence of other risk factors in relation to the cholesterol level in the elderly. It seems likely that a substantial number of Medicare recipients will either have a history of CHD or have two of the risk factors: about 20 percent of men and 15 percent of women

Figure 3--- Protocol for Cholesterol Screening in the Elderly



ABBREVIATIONS: LDL = low-density lipoprotein; RF = risk factors; TC = total cholesterol.

SOURCE: Office of Technology Assessment, 1989. Adapted from Adult Treatment Panel, National Cholesterol Education Program, National Institutes of Health, U.S. Department of Health and Human Services, "National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults," Arch. Intern. Med. 148:36-69, 1988.

aged 65 and over are current smokers (122), nearly 14 percent report that they have CHD, and one half of Americans aged 65 to 74 have definite hypertension (121).

Because the precise number of elderly individuals who have CHD or two other risk factors is unknown, the analysis includes calculations for three different assumptions:

- the low-prevalence estimates assume that 30 percent of the Medicare recipients are high-risk based on a history of CHD or two risk factors for CHD (other than hypercholesterolemia),
- the middle-prevalence estimates assume that 50 percent have the risk factors, and
- the high-prevalence estimates assume that 70 percent have risk factors.

OTA assumed that the prevalence of the risk factors is not correlated with the cholesterol level; this assumption probably leads to an underestimate of the number of persons who will need treatment, since it is likely that the risk factors are more common among individuals whose cholesterol levels are elevated than among those whose cholesterol levels fall below 200 mg/dl. Given that male sex is a risk factor according to the NCEP framework, the high-prevalence assumption (70 percent) may be the most likely value for men over 65 years old.

Number of participants requiring further testing or treatment .--The analysis assumes that the repeat cholesterol assay will give the same result as the initial assay. This assumption will underestimate screening expenditures because it does not count the costs of repeat total cholesterol screening for those people whose initial readings are greater than 199 mg/dl, but who receive no further management on the basis of the second screening. The magnitude of this effect should be slight but depends on the accuracy and precision of the screening tests.[1]

The number of people in alternative treatment groups (e.g., those who do not have a history of CHD or two other CHD risk factors, but do have a cholesterol level in excess of 200 mg/dl and an LDL cholesterol level above 190 mg/dl) is calculated by assuming that the total cholesterol and the LDL - cholesterol level have a joint bivariate normal distribution.

Followup testing. --In order to calculate how many individuals will have repeat cholesterol determinations, lipoprotein fractionation, and recommendations for testing, OTA used data from the National Health and Nutrition Examination Survey, reproduced in the NCEP report. The analysis assumes that the total cholesterol level and the LDL - cholesterol level have a bivariate normal distribution in the Medicare population, and use the published figures for the mean and standard deviation of cholesterol and LDL for the 65 to 74 year-old age group. The correlation between LDL cholesterol and total cholesterol is assumed to be 0.84 for men, and 0.88 for women, based on the Framingham Heart Study, as shown in table 2. The predicted number of people whose cholesterol is less than 200 mg/dl or less than 240 mg/dl is consistent with the percentiles noted in table 1.

Response to diet. --The model assumes that individuals treated with diet will uni -

1 While the accuracy and precision of cholesterol measurement is important i n eva 1 uat i ng the **effectiveness** of a screening benefit, it is of less importance in estimating the **health care expenditures** associated with such a benefit. Hence, OTA did not build into its model more sophisticated mechanisms for model linghowwell the various screening technologies work.

formly achieve a 10-percent reduction in LDL. This is an optimistic assumption regarding the effectiveness of dietary interventions in lowering LDL levels. The Multiple Risk Factor Intervention Trial of middle-aged men led to a 7-percent reduction in LDL with diet. Even in the subset of participants with "best adherence," LDL fell by 8.6 percent (32).

Although the effectiveness of diet control interventions appears to be limited, if a way were found to reduce LDL levels more dramatically through diet alone, the estimated cost of the NCEP program would be greatly reduced. Therefore, OTA also calculated how costs might change if a 15 percent reduction in LDL could be expected from diet.

Costs of testing. --The marginal cost of performing lipoprotein analyses is uncertain. Laboratory and physician charges for cholesterol determinations are highly variable. For this analysis, total cholesterol measurements were assumed to cost $6.79 per determination (which includes drawing the blood and performing the analysis), the Medicare average allowed charge in 1986 inflated to 1988 prices by the Medicare Economic Index (87,94). This is more expensive than the retail price of fingerstick cholesterol determinations (47). The analysis assumes that fractionation (measurement of HDL, triglycerides, and total cholesterol, with a calculated value of LDL) costs $16.89, the average allowed Medicare charge in 1988 dollars.

As is discussed in greater detail in the text, the model does not include the cost of a physician visit in estimating expenditures for screening. It assumes that cholesterol screening either would take place in a community setting or would occur as part of a patient's visit to the physician for some other purpose. It is possible, however, that the introduction of a cholesterol screening benefit would increase the number of physician office visits for Medicare beneficiaries and the health care costs of the program would rise accordingly.

Costs of treatment protocols. --The analysis assumes that diet imposes no direct health care costs. This assumption underestimates treatment expenditures, since most patients participating in dietary therapy require counseling with physicians or dietitians in the establishment and monitoring of their diets. The NCEP protocol recommends that people on dietary therapy have a "complete clinical evaluation. " The costs of such an evaluation are not included in the model.

Under certain conditions, if improvement in LDL levels with diet is totally inadequate, the NCEP protocol leaves it at the physician's discretion whether to continue with diet or to initiate therapy with medication. The model assumes that physicians will always be conservative in decisions and will not initiate medication. Thus, the model is extremely conservative in estimating the number of elderly people who would end up on medication and the costs of their treatment.

For medications, OTA calculated the estimated annual expenditures in 1988 dollars for a low cost regimen of $525 per patient per year for niacin, and a high cost regimen of $1,687 for lovastatin, including the costs of followup testing. The figures are obtained from table 4, and the text of the paper describes how they were derived.

A HA	--American Heart Association
BMAD	--Medicare Procedure Database
CDC	--Centers for Disease Control
CHD	--Coronary heart disease
CPT	--Current procedural terminology
CTF	--Canadian Task Force
CVD	--Cardiovascular disease
EDTA	--Ethylenediaminetetraacetate
HCFA	--Health Care Financing Administration
HDL	--High-density lipoprotein
HMG CoA	--3-hydroxy-3-methyl glutaryl coenzyme-A reductase
LDL	--Low-density lipoprotein
LRC-CPPT	--Lipid Research Clinics-Coronary Primary Prevention Trial
MRFIT	--Multiple Risk Factor Intervention Trial
NCEP	--National Cholesterol Education Program
NHLBI	--National Heart, Lung, and Blood Institute
PVD	--Peripheral vascular disease
VLDL	--Very low-density lipoprotein

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