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Michael A. Kortt and Edward P. Armstrong

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Department of Economics
University of New England
Armidale
New South Wales 2351
Australia

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A PHARMACOECONOMIC REVIEW OF CHOLESTEROL-LOWERING THERAPY INTERVENTIONS.

Michael A. Kortt and Edward P. Armstrong[#]

The purpose of this paper is to review the literature on the pharmacoeconomics of cholesterol-lowering therapy interventions for patients with elevated cholesterol levels. In this review, the emphasis is on study methodology because, in the field of pharmacoeconomics, there appears to be a shift from only clinical trial-based pharmacoeconomic evaluations to a broader health systems-based approach. This shift has been identified and addressed in the US literature. To begin with, this paper distinguishes between clinical trial-based and health systems-based pharmacoeconomic evaluations of therapy interventions. Following this, the pharmacoeconomics of cholesterol-lowering therapy interventions is reviewed. Although no published studies on cholesterol-lowering therapy interventions explicitly employed a health systems-based perspective a discussion of these studies is presented. More specifically, issues such as the use of clinical data, the selection of patient populations, and the relevance of cost-outcome ratios as decision variables is addressed. Finally, this paper highlights the advantages of using a health systems-based methodology and puts forth a proposed research agenda for continuing research.

1. INTRODUCTION

Cholesterol, a fat-like substance that is present in cell membranes,[1-2] travels through the blood, containing both lipids and proteins. These particles are commonly referred to as lipoproteins. The three major lipoproteins found in the blood of an individual are: low density lipoproteins (LDL), high density lipoproteins (HDL), and very low density lipoproteins (VLDL). Due to the fact that LDL cholesterol is the major atherogenic lipoprotein, it is usually the primary target of many cholesterol-lowering strategies.[1-2]

The scientific literature indicates that there is a positive association between elevated cholesterol levels and the risk of cardiovascular diseases.[3-6] The findings from the Lipid Research Clinics (LRC) Coronary Prevention Trial in 1984 provided strong scientific evidence of an association between elevated cholesterol levels and

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[#] Michael A. Kortt is a PhD student in the Department of Economics at the University of New England, Armidale, Australia. Edward P. Armstrong is Associate Professor in the College of Pharmacy at the University of Arizona, Tucson, USA. The authors would like to thank Kevin Parton and Jonathan Baldry for comments on an earlier version of this paper.

cardiovascular diseases.[3-4] The LRC findings were then followed by the National Cholesterol Education Program (NCEP) guidelines for the detection and treatment of hypercholesterlemia in adults.[7-8] These guidelines, originally published in 1988, have been recently revised by the NCEP. In addition, another set of guidelines have also been developed by the American College of Physicians.[8]

Treatment strategies designed to lower elevated cholesterol levels are outlined in the revised National Cholesterol Education Program (NCEP) guidelines.[1-2] Broadly speaking, treatment strategies can be classified as either being primary or secondary. Primary prevention treatment strategies can be targeted for either the entire population or high-risk subjects only. Alternatively, secondary treatment strategies focus on those individuals who already have pre-existing cardiovascular disease.

2. METHODOLOGY

In reviewing the literature on the pharmacoeconomics of cholesterol-lowering therapy interventions it is important to distinguish between clinical trial-based pharmacoeconomic evaluations as opposed to the more broader (or global) health systems-based approach. Within the field of pharmacoeconomics a methodological shift in relation to both theoretical developments[9-12] and the introduction of guidelines for drug purchasers[13] has been identified. This methodological shift is associated with the economic concept of equilibrium.[14-15] For instance, if a new cholesterol-lowering product is introduced to a patient population, then physicians may switch patients from the one therapy option to the another based on therapeutic outcome. Subsequently, a new equilibrium position in the distribution of the patient population (and associated costs and outcomes) will emerge.[9]

The health systems-based approach to pharmacoeconomic evaluation is most evident in North America and this is primarily due to the accessibility of relatively large health care databases such as medical and pharmacy claims data. Despite the availability of such data, however, there does not appear to be any studies which have used these data to evaluate the cost of treating patients with elevated cholesterol levels. There are also no known studies that have determined the cost to achieve the cholesterol goal for a population of patients.

2.1 Clinical Trial-Based Pharmacoeconomic Evaluations

Clinical trial-based pharmacoeconomic evaluations primarily use cost-outcome ratios to evaluate competing therapy options. These studies often have a narrow focus and use data drawn primarily from clinical trials. As a result, the use of efficacy data (as opposed to effectiveness data) will result in best-case cost-outcomes ratios. This

occurs because clinical trials do not reflect a real-world treating environment. By design clinical trails control for a variety of patient characteristics such as the presence of co-morbidities and non-compliance.[9-11]

Moreover, clinical trial-based pharmacoeconomic evaluations are based on the assumption that constant returns to scale are maintained. This means that while competing therapy options may present different average cost-outcome relationships, the ranking of these alternatives, by incremental cost-outcomes ratios requires that each therapy option displays constant costs and outcomes regardless of the number (or proportion) of patients treated in a given disease area.[11] This limitation is rarely, if ever, addressed in clinical trial-based pharmacoeconomic studies.

2.2 Broader Health Systems-Based Pharmacoeconomic Evaluations

It is important to note that health systems-based pharmacoeconomic evaluations are new and just beginning to be used in the evaluation of alternative therapy interventions. In essence, this approach to pharmacoeconomic analysis involves estimating the global health systems "impact of introducing a new therapy, or switching existing therapies, on the profile of costs and outcomes in a disease or treatment area."[12] For example, a health system-based pharmacoeconomic evaluation would take into account: (i) treatment protocols, (ii) patient characteristics of the patient population, (iii) the cost profiles used to support therapy interventions, and (iv) the impact of therapy switching on the outcomes profiles of the treated patient population.[12]

In the United States a health systems-based perspective would be particularly useful in a disease state management setting where a broad range of information pertaining to patient profiles, resource utilization, and outcome measurements are of importance. However, with a health systems-based perspective, the focus of this analysis is concerned with assessing the introduction of alternative therapy options within a given treatment area and the impact of therapy switching (as opposed to therapy comparison) on the cost and outcomes profiles of the patient population.[12]

3. CHOLESTEROL-LOWERING THERAPY INTERVENTIONS

The studies reviewed in this paper were identified using MEDLINE.® The key words used in the search criteria included: cost, cholesterol, cost-effectiveness analysis, and pharmacoeconomics. The reference section for each paper was examined to identified other studies that were not captured by the MEDLINE® database.

A review of the medical and pharmaceutical literature identified 18 pharmacoeconomic research papers that analyzed the benefits of cholesterol-lowering therapy interventions.[16-33] These studies, grouped by methodological technique, are summarized in the Table 1. The categories in Table 1 include: authors/type of study, study sample, cholesterol level(s), principal finding, and results.
Overall, these studies can be grouped according to the following methods: (i) cost-of-illness evaluation, (ii) cost-effectiveness analysis, and (iii) computer simulations. It should be noted that, to date, there are no known pharmacoeconomic studies, within the cholesterol literature, that have explicitly employed a health systems-based perspective.

3.1 Cost-of-Illness Evaluation

In 1986, Oster and Epstein[16] examined the economic benefits associated with lowering elevated cholesterol levels in adult men with total cholesterol levels greater than 260 mg/dl. The authors used an incidence-based cost-of-illness framework, combining incidence-based estimates of the cost of CHD with known reductions in future CHD risk factors. The estimate of the benefits associated with a reduction in cholesterol levels therefore "reflect the present value of lifetime economic savings that the average individual could expect to experience because of diminished risk of CHD."[16]

This study reports that the discounted lifetime direct benefits, of a 15% reduction in total cholesterol level, of $3 to $208 per person, and an additional discounted lifetime indirect benefit of $1 to $8,946.[16] The authors indicate that patients most likely to benefit from treatment are those with a high initial cholesterol level. The benefits are reduced with increase patient age. Oster and Epstein[16] conclude that cholesterol-lowering strategies are unlikely to yield a substantial direct saving to the US health care system. However, the authors determine that the indirect benefits of cholesterol-lowering strategies are relatively high for both middle-aged adults and high risk individuals.

3.2 Cost-Effectiveness Analysis

Cost-effectiveness analysis has been used in a number of studies that have examined the economic benefits gained from a reduction in cholesterol levels. The first cost-effectiveness study was performed by Weinstein and Stason[17] on the lipid-lowering agent cholestyramine. The authors based their analysis on US men aged 45 to 50 with cholesterol levels greater than 265 mg/dl. These characteristics were consistent with the patient profiles in the Lipid Research Clinics (LRC) Coronary Primary Prevention Trial. Drawing upon information collected in this trial, Weinstein and

Stason[17] combined data collected from the Framingham Heart Study to estimate the cost per year of life saved. Weinstein and Stason[17] estimate the cost-effectiveness of cholestyramine treatment to be $126,000 per year of life saved (1984 $US, assuming a 5% discount rate). Interestingly, Kinosian and Eisenberg[18] also evaluated the cost-effectiveness of a program designed to reduce cholesterol levels by comparing the use of cholestyramine, colestipol, and oat bran. Kinosian and Eisenberg[18] also based their analysis on patient characteristics that were consistent with the patient profiles in the LRC Coronary Primary Prevention Trial. The authors estimated the cost-effectiveness of cholestyramine to be $117,400 per year of life saved. For colestipol and oat bran the estimated cost-effectiveness ratios were 70,900 and $17,800 per year of life saved, respectively (in 1985 $US).[18]

In two studies, Martens et al.[19-20] estimated the cost-effectiveness of cholestyramine versus simvastatin for The Netherlands. Estimates of the incidence of coronary heart disease (CHD) were generated from a CHD model developed by the authors. Future CHD incidence rates were estimated using logistic regression and data from the Framingham Heart Study. Results from this study[19] indicate that for men with total cholesterol levels greater than 310 mg/dl, the cost effectiveness ratio for cholestyramine (expressed in Dutch guilders) ranged from approximately 220,000 to 510,000 guilders per year of life saved. Alternatively, the cost-effectiveness ratio from simvastatin ranged from 50,000 to 110,000 guilders per year of life saved. These results suggest that simvastatin is cost-effective when compared to cholestyramine. These findings were also consistent with the subsequent study by Martens et al. in 1990.[20]

In another study, Schulman and colleagues[21] evaluated the cost-effectiveness of the following cholesterol-lowering agents: cholestyramine, colestipol, gemfibrozil, lovastatin, niacin, and probucol. Cost-effectiveness analysis was used to compare the resources consumed in the treatment of elevated cholesterol levels, with modification in lipid levels used as an outcome variable. The authors report that niacin was the most efficient drug for reducing LDL cholesterol levels. Over five years, the average cost of niacin was $139 per percent reduction in LDL cholesterol levels. Lovastatin was also relatively efficient with an estimated $177 per percent reduction. The least efficient cholesterol-lowering agent was cholestyramine at $347 per percent reduction.

Hay and associates[22] performed an economic evaluation of lovastatin for cholesterol-lowering and coronary artery disease (CAD) reduction. The authors estimated the costs and benefits of cholesterol-lowering in primary prevention of

CAD using a lifetime therapy of lovastatin for adults between the age of 35 and 55. The benefits of reducing CAD risk were based on estimates from the Framingham Heart Study. Results indicate that for men with total cholesterol levels between 220 mg/dl and 380 mg/dl, the cost per life-year saved ranged from $9,000 to $106,00 (1989 US dollars). Hay et al. conclude that current cholesterol medication "could be economically justified, particularly for persons with high levels of primary CAD risk factors."[22]

In 1995, Hilleman et al.[23] estimated the cost-effectiveness of bile sequestrants (i.e., resins), statins, and a combination of both treatment options in patients with elevated cholesterol levels. Of a total sample of 141 patients, 42 patients were on resin alone, 56 were on statins, and 43 were on combination therapy. The cost-effectiveness ratios were calculated as the dollar per patient per mg/dl reduction per year. The results of this study were as follows: (i) the cost per patient per mg/dl LDL reduction was $49 for resins alone, (ii) $25 dollars for statins alone, and (iii) $30 for combination therapy of resins and statins. The authors report that the selection of cholesterol-lowering therapy should be determined by the magnitude of LDL cholesterol reduction required. Statins and combination therapy provided more favorable cost-effective ratios than resins alone.

Ashraf et al.[24] estimated the cost-effectiveness of pravastatin in the secondary prevention of coronary artery disease (CAD). The projected risk model in 445 male subjects with CAD and elevated cholesterol levels used data from the following placebo-controlled trials: (i) pravastatin limitation of atherosclerosis in coronary arteries, and (ii) the pravastatin of atherosclerosis in carotids. Furthermore, data from the Framingham Heart Study were also used to project the risk of mortality 10 years after myocardial infarction. The authors also used a Markov process to estimate life-years saved. Moreover, decision analysis was used to estimate the cost. The mid-range estimated cost per life year saved with pravastatin ranged from $7,124 to $12,665. The authors consider this cost-effectiveness ratio to be "favorable."[24]

Jönsson et al.[25] performed a cost-effectiveness analysis of simvastatin based on the results from the Scandinavian Simvastatin Survival Study (4S). The authors examined the cost-effectiveness of treating coronary heart disease (CHD) patients with simvastatin, using both survival and cost data from 4S. The 4S data were collected prospectively on: (i) hospital admissions associated with revascularization procedures and acute cardiovascular events, and (ii) the usage of simvastatin.[25] These data were then combined with cost data from Sweden to estimate a cost-

effectiveness ratio of simvastatin. The cost-effectiveness ratio of simvastatin in 4S were 56,400 Swedish kronor (SEK) per life-year saved. The authors indicate that the "cost per life-year of simvastatin . . . is well within the range normally considered to be cost-effective."[25]

In a more recent study, Johannesson et al.[26] also estimated the cost-effectiveness of simvastatin treatment using data from 4S. Men and women, 35 to 70 years of age, with cholesterol levels of 213 to 309 mg/dl were included in the study. The authors report that when the analysis included only direct costs, the cost per year of life gained ranged from $3,800 for 70 year old men with cholesterol level of 309 mg/dl to $27,000 for 35 year old women with cholesterol levels of 213 mg/dl. The authors conclude that in "patients with coronary heart disease, simvastatin therapy is cost effective among both men and women at the ages and cholesterol levels studied."[26]

In an interesting study, Johannesson et al.[27] evaluated the cost-effectiveness of four alternative treatment strategies for reducing elevated cholesterol level in middle-aged men based on the cost-effectiveness of the lipid lowering (CELL) trial. The four alternative treatment strategies considered by the authors were: (i) usual advice only, (ii) usual advice combined with pharmacotherapy, (iii) intensive advice only, and (iv) intensive advice combined with pharmacotherapy. The authors estimated the cost per life-year gained based on the change in cholesterol level and the net cost of the four treatment strategies. Of the four treatment options, usual advice combined with pharmacotherapy (versus no treatment) was the cost-effective treatment strategy. The estimated cost-effectiveness ratio was about $61,000 (1991 US dollars) per year of life gained.

Pharoah and Hollingworth[28] estimated the cost-effectiveness of reducing cholesterol levels using statins in patients with and without pre-existing coronary heart disease (CHD). The authors used a life table approach to model the effect of statin treatment over 10 years on the survival of men and women aged 45 to 64.[28] Pharoah and Hollingworth[28] report that the average cost-effectiveness of treating men aged between 45-64 with no history of CHD for 10 year, with a statin, was £136,000 per life year saved. The authors state that although statins are safe, the "treatment for all whom treatment is likely to be effective is not suitable within the current NHS [National Health Service] resources."[28]

3.3 Computer Simulations

Several studies[29-33] have used computer simulations to evaluate the cost-effectiveness of cholesterol-lowering therapy interventions. The studies by Goldman et al.[29-30] and Hamilton et al.[31] make use of the Coronary Heart Disease (CHD) Policy Model. This computer simulated model estimates the "benefits of lifelong risk factor modification."[31] In 1991, Goldman et al.[29] estimated the cost-effectiveness of HMG-CoA reductase inhibitors (such as lovastatin) for primary and secondary prevention of coronary heart disease using the CHD Policy Model. This work, was based on earlier research by Goldman et al.[30] The authors report that, for secondary prevention, 20 mg/dl of lovastatin was estimated to save lives and save costs in younger men with elevated cholesterol levels of about 250 mg/dl. For secondary prevention the cost-effectiveness ratio for lovastatin, in both men and women of all ages, was less than $20,000 per year of life saved. However, for primary prevention lovastatin had "favorable" cost-effectiveness ratios in selected subgroups.[29]

Hamilton et al.[31] evaluated the lifetime cost-effectiveness of lovastatin using cost data (1992-1993 Canadian dollars) added to the CHD computer model. The authors calculated the cost-effectiveness, from a societal perspective, and evaluated the net cost of drug therapy (i.e., lovastatin) against its net effectiveness. Additional years of life expectancy was defined as the outcome variable. Results from this study indicate that the cost-effectiveness of lovastatin varied by age and gender and was sensitive to the presence of non-lipid CHD risk factors. In addition, non-CHD costs due to increased life expectancy may be substantial in an elderly population.

Kinlay et al.[32] demonstrated a new method for assessing the cost-effectiveness of a strategy designed to reduce CHD by lowering cholesterol levels. Using Australian data from a community surveillance study of CHD risk factors and incidence rates, Kinlay and colleagues[32] were able to apply a logistic regression equation to estimate the number of CHD-events prevented. This study was designed to estimate the number of CHD-events avoided and the cost-effectiveness of an intervention proposed to identify and treat men with elevated cholesterol levels with dietary therapy and cholestyramine. The assumptions used to estimate the "effectiveness and costs of the intervention were entered into a computer model."[32] The cost of implementing this strategy was estimated at $A50.1 million dollars to prevent 104 CHD events. The cost-effectiveness ratio was $A482,224 per CHD averted and the direct medical costs avoided were approximately $A500,000 over five years.

Glick and associates[33] provide a detailed description of a computer model designed to evaluate the cost-effectiveness of cholesterol-lowering strategies. This computer model is based on the Framingham Study logistic risk functions. The authors demonstrate the application of the model by evaluating the cost-effectiveness of cholestyramine and simvastatin therapy for 50 year old men in the United Kingdom with cholesterol levels of 290 mg/dl. Results indicate that, conditional upon the patient's coronary risk profile, the cost of cholestyramine ranges from £36,000 to £86,000 per year of life saved (1989 £UK). It was estimated that the cost of simvastatin ranges from £9,600 to £22,900.[33]

4. DISCUSSION

Following a review of the pharmacoeconomics of cholesterol-lowering therapy interventions it is important to consider the main points from these studies. To begin with, initial pharmacoeconomic studies evaluated the cost-effectiveness of cholestyramine.[17-18] However, as pharmacological treatment options changed, the majority of these studies evaluated the cost-effectiveness of statins, especially simvastatin. Although it is difficult to make comparisons across studies, it should be noted that several research papers have indicated that simvastatin is a cost-effective therapy intervention.[19-20,25-26,33] It is important to note, however, that favorable cost-outcome ratios for statins may be influenced by the selection of the patient population. There is evidence to suggest that the most cost-effective ratios for statins were obtained with high-risk patient subgroups.[34]

Furthermore, the emphasis of many of these studies is directed at middle-aged men. For instance, in the US, approximately half of the individuals who use cholesterol-lowering agents are 65 years of age and over.[35] Ito[35] has examined whether health care resources should be targeted at treating the elderly, especially considering that the strength of the association between elevated cholesterol levels and coronary artery disease is "controversial in persons older than 65."[35] Ito recommends that good clinical judgement is required in treating elderly individuals with elevated cholesterol levels. For example, care should be taken when dietary advice is given to elderly individuals as certain dietary restrictions could potentially contribute to other medical problems. This raises an important point: should the focus on cholesterol-lowering therapy interventions be directed at actually treating elevated cholesterol levels as opposed to, say, treatment to goal? That is, obtaining a desired cholesterol level according to the NCEP guidelines. Treatment to goal is likely the more important outcome for health systems to consider.

In addition, there are a limited number of studies examining cholesterol-lowering strategies in both women and the very young. For instance, Davidson and colleagues[36] indicate that about a 10% of fourth graders, in a Southern California school district, had a blood cholesterol levels of 200 mg/dl or more. This raises the issue of whether the current NCEP cholesterol guidelines should be revised to include a wider range of people.

Overall, several comments can be made in relation to the current body of literature. To date, the evaluation of cholesterol-lowering strategies have been modeled using a clinical trial-based pharmacoeconomic framework. For instance, a number of these studies used clinical data drawn from previously conducted research--such as the Multiple Risk Factor Intervention Trial, the Lipid Research Clinics Program, or the Framingham Heart Study--and combined this efficacy data with cost data. As indicated previously the use of clinical data will result in best-case cost-outcome ratios.

Another important point to consider is whether the studies just reviewed provide useful information to drug purchasing agencies? From the perspective of managed care organizations, cholesterol-lowering therapy interventions (and issues such as whether to switch patients from cholestyramine to statins) would be of interest, especially considering the current climate to contain rising health care costs. Managed care organizations, however, would be more interested in the potential economic benefits for their specific patient populations. Since the current studies of cholesterol-lowering therapy interventions are clinically-driven (and narrowly focused) it is reasonable to argue that this type of information would have limited appeal to managed care organizations. It is important to note that this should not detract from the quality of the many studies reviewed. However, this implies that there is a demand (and indeed a market for) health systems-based pharmacoeconomic evaluations. For example, a health systems-based perspective could be used to evaluate drug utilization and expenditure patterns of competing lipid-lowering therapy options for those individuals who are members of a managed care organization. Equilibrium changes in drug treatment patterns and costs could be determined. Conditional upon the patient mix and cholesterol levels, managed care organizations could benefit from knowing the preferred treatment options. In fact, a major advantage of the health systems-based approach is that it could assist a managed care organization in deciding whether to switch patients from one therapy intervention to another. Moreover, it is possible to perform this type of analysis due to the availability of relatively large health care databases in United States managed care organizations.[37]

5. CONCLUSION

This paper reviewed the pharmacoeconomics of cholesterol-lowering therapy interventions. This review indicated that, to date, the current body of literature has employed a clinical trial-based framework to evaluate the pharmacoeconomic benefits of reducing cholesterol levels. It should be noted, however, that there are no known studies have used a health systems-based perspective. From a pharmacoeconomic perspective, further research is required. There is a distinct need for pharmacoeconomic studies to provide a broader health system view to assess a range of alternative cholesterol-lowering treatment options. A health systems-based perspective is extremely useful in assisting drug purchasing agencies within United States managed care organizations.

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TABLE 1: EVALUATION OF CHOLESTEROL-LOWERING THERAPY INTERVENTIONS BY METHOD

Authors/Method	Study Sample	Cholesterol Level(s)	Principal Finding	Results
Cost-of-illness evaluation				
Oster & Epstein[16] Incidence-based COI evaluation.	US adult men.	> 260 mg/dl.	Study reports that the discounted lifetime direct benefits, of a 15% reduction in total cholesterol level, of $3 to $208 per person.	Cholesterol-lowering interventions are unlikely to result in significant direct savings to the health care system.
Cost effectiveness analysis				
Weinstein & Stason[17] CEA of cholestyramine.	US men (45-50) years.	> 265 mg/dl.	$126,000/YOLS (1984).	Drug therapy is not cost-effective.
Kinosian & Eisenberg[18] CEA of cholestyramine, colestipol, and oat bran.	US men (48 years).	> 265 mg/dl.	Cost per YOLS ranges from $117,400 (cholestyramine) to $70,900 (colestipol) and $17,800 (oat bran).	Drug therapy is associated with substantial costs.
Martens et al[19] CEA of cholestyramine and simvastatin.	Dutch men and women (35-60 years).	290, 310, and 330 mg/dl.	For simvastatin the ratio ranges from 50,000 to 110,000 Dutch guilders per YOLS.	Simvastatin is cost-effective.
Martens et al[20] CEA of cholestyramine and simvastatin.	Dutch men and women (35-60 years).	271, 310, and 348 mg/dl.	For simvastatin the ratio ranges from 46,000 to 98,000 Dutch guilders per YOLS.	Simvastatin is cost-effective.

COI -- Cost-of-illness evaluation. CEA -- Cost-effectiveness analysis. YOLS -- Years of life saved.

TABLE 1 -- CONTINUED

Authors/Method	Study Sample	Cholesterol Level(s)	Principal Finding	Results
Schulman et al[21] CEA of cholestyramine, colestipol, gemfibrozil, lovastatin, niacin, and probucol,	US patients.	Analysis assumed that patients eligible for cholesterol-lowering agents followed NCEP guidelines.	Average cost of niacin over 5 years was $139 per percent reduction in cholesterol levels.	Niacin is cost-effective.
Hay et al[22] CEA of simvastatin and cholestyramine.	US men and women (35-84 years).	220, 260, 300, 340, and 380 mg/dl.	For average risk men the cost per YOLS ranged from $9,000 to $106,000. For women the ratio ranged from $35,000 to $297,000.	Results are favorable compared with previous studies.
Hilleman et al[23] CEA of bile sequestrants (resins) alone, HMG Co-A reductase inhibitors alone, and a combination treatment option.	US patients in a lipid clinic.	> 160 mg/dl.	The cost per patient per year per mg/dl was $49 for resins alone, $25 for HMG inhibitors alone, and $30 for combination therapy.	Selection of lipid-lowering therapy should be determined by the amount of cholesterol reduction needed.
Ashraf et al[24] CEA of pravastatin.	US men (mean age 60 years).	N/A.	Mid-range cost per YOLS with pravastatin varied from $7,124 to $12,665.	The authors considered these estimates to be "favorable."
Jönsson et al[25] CEA of simvastatin.	Scandinavian men and women.	N/A.	The cost of simvastatin per YOLS was 56,400 Swedish Kronor (£5,502).	The cost per YOLS for simvastatin is "well within the range normally considered cost-effective."
Johannesson et al[26] CEA of simvastatin	Scandinavian men and women (35-70 years).	213-309 mg/dl.	The cost per YOLS ranged from $3,800 for 70 year old men to $27,000 for 35 year old women.	Simvastatin is cost-effective.

COI -- Cost-of-illness evaluation. CEA -- Cost-effectiveness analysis. YOLS -- Years of life saved.

TABLE 1 -- CONTINUED

Authors/Method	Study Sample	Cholesterol Level(s)	Principal Finding	Results
Johannesson et al[27] CEA of two types of advice to reduce cardiovascular risk with and without pharmacotherapy.	Swedish men (30-59 years).	6.84 mmol/l.	The cost per life-year gained of drug therapy compared to no treatment was about $61,000.	Doubtful whether the use of drug therapy in primary prevention is cost-effective.
Pharoah & Hollingworth[28] CEA of statins.	UK men and women (45-64 years).	> 5.4, > 6.4, and 7.2 mmol/l.	Average cost-effectiveness of treatment men with a statin was £136,000 per life-year saved.	Treatment of elevated cholesterol levels "is not sustainable within the current NHS resources."
Computer Simulations				
Goldman et al[29] CEA of lovastatin.	US men and women (35-55 years)	< 250, 250-299 mg/dl, and ≥ 330 mg/dl.	Less than $20,000 per YOLS.	Lovastatin is cost-effective.
Goldman et al[30] CEA of lovastatin.	US men and women (34-64 years).	350-430 mg/dl.	Results support use of low-to-moderate doses of high cost medications for primary prevention.	Lovastatin is cost-effective.
Hamilton et al[31] CEA of lovastatin.	US men and women (30-70 years).	Cholesterol levels equal to the 90th percentile of the US distribution.	For men (age 50) the lowest cost-effectiveness ratio was $20,882 per YOLS. For women (age 60) the ratio was $36,627.	Cost effectiveness of statins varied by age and gender and was sensitive to the presence of non-lipid CHD risk factors.
Kinlay et al[32] CEA of cholestyramine and dietary therapy.	Australian men (35-64 years).	> 6.5 mmol/l.	The authors estimate a cost-effectiveness ratio of $A482,224 per coronary heart disease averted.	The direct medical costs avoided were approximately $A500,00 over 5 years.
Glick et al[33] CEA of cholestyramine and simvastatin.	UK men (50 years).	290 mg/dl.	The cost of simvastatin ranged from £9,600 to £22,900 per YOLS,	Simvastatin is cost-effective.

COI -- Cost-of-illness evaluation. CEA -- Cost-effectiveness analysis. YOLS -- Years of life saved.

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