

## Comparative Cost-Effectiveness of Bile Acid Sequestering Resins, HMG Co-A Reductase Inhibitors, and Their Combination in Patients with Hypercholesterolemia

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### OBJECTIVE:

To determine the cost-effectiveness of bile acid sequestrants (resins) alone, HMG Co-A reductase inhibitors alone, and a combination of a resin with an HMG Co-A reductase inhibitor in patients with hypercholesterolemia.

### DESIGN:

Retrospective, open-label, cost-effectiveness analysis.

### SETTING:

University-based outpatient lipid clinic.

### PARTICIPANTS:

Patients managed in our lipid clinic with an LDL-cholesterol (LDL-C) greater than 160 mg/dL following eight weeks on an American Heart Association Step 1 diet were eligible for this study.

### INTERVENTIONS:

Patients were treated with a bile acid sequestrant alone, an HMG Co-A reductase inhibitor alone, or a combination of both

drugs to achieve an LDL-C of less than 130 mg/dL. Costs included in the analysis were initial and concomitant drug acquisition (*Redbook* average wholesale price), safety and efficacy monitoring tests (liver function, creatine phosphokinase, eye examinations, lipid profiles), clinic visits (\$28/visit), managing side effects. Patients were followed for one year after initiation of lipid-lowering therapy. Cost-effectiveness was calculated as dollars spent per year per mg/dL reduction in LDL-C.

### MEASUREMENTS:

Percent reduction of LDL cholesterol, total cost of treatment, and cost per mg/dL reduction in LDL cholesterol.

### RESULTS:

A total of 141 patients were included in the analysis: 42 patients on resins alone, 56 patients on HMG inhibitors alone, and 43 on a combination resin-HMG inhibitor. Total yearly per patient costs for treatment was \$1,532 for resins, \$1,635 for HMG inhibitors, and \$2,556 for combination therapy.

Cost per patient per year per mg/dL LDL-C reduction was \$49 for resins alone, \$25 for HMG inhibitors alone, and \$30 for combination therapy. Low-dose resin therapy was more cost-effective than high-dose resin therapy in patients treated with either monotherapy (\$20 versus \$57) or combination therapy (\$26 versus \$33).

### CONCLUSION:

The selection of lipid-lowering therapy should be determined by the magnitude of LDL-C reduction required and the cost-effectiveness of therapy. HMG inhibitors alone and bile acid sequestrant-HMG inhibitor combinations are the most cost-effective. When combination regimens are used, low-dose resin therapy is preferable.

### KEY WORDS:

Pharmacotherapy, Pharmacoeconomics, LDL-cholesterol, Lipid-lowering therapy, Hypercholesterolemia, Bile acid sequestrants, HMG Co-A Reductase Inhibitors.

J Managed Care Pharm 1995; 1: 188-192.

Pharmacotherapy is a cost-beneficial choice in medical care. Pharmacologic advances have afforded a significant reduction in morbidity and mortality, particularly among the cardiovascular diseases.<sup>1-5</sup> However, inappropriate use can result in a lack of therapeutic effect, endangered health, and wasted resources. In this era of health care reform and limited economic resources, medical interventions must undergo evaluations not only of efficacy and safety, but cost-effectiveness relative to other treatment alternatives in-

cluding no therapy at all. Cost analyses must globally incorporate all costs of consumed medical resources when assessing the cost-effectiveness of a pharmacotherapy decision.<sup>6,7</sup>

Pharmacoeconomics is defined as the description and analysis of the costs and outcomes of drug therapy to the healthcare system and to society.<sup>8</sup> Such a process incorporates not only product costs, but also the costs associated with preparation and administration, monitoring, and both

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ACKNOWLEDGEMENT: This study was sponsored in part by a grant from the Upjohn Pharmacy Science Liaison.

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the positive and negative effects of therapy.<sup>6,7</sup> Unfortunately, the term cost-effective remains widely misused. Cost-effectiveness is often used to describe cost savings alone or that an agent is merely effective.<sup>9</sup> For most major disease states where drug therapy is the mainstay of treatment, there is a paucity of adequately designed pharmacoeconomic studies in the literature.

In the case of lipid-lowering therapy, the landmark publication of Schulman and colleagues has a number of limitations.<sup>10</sup> In this study, efficacy rates of lipid-lowering therapy were extrapolated from 57 published studies and pooled to create a single percentage change induced by various drugs for each lipid fraction. Obviously, patient populations varied widely in terms of demographic and clinical characteristics among these 57 separate studies. The only criterion for inclusion of studies in this analysis was the availability of data concerning the percent reduction in total cholesterol. Not all studies actually reported complete lipid profiles. Differential effects of various drugs on other lipid fractions were estimated based on results from those studies that did report complete lipid profiles. In the case of niacin, for example, complete lipid profiles were available in only two studies. Results of short-term and long-term studies were homogenized. As no long-term studies were available for lovastatin or probucol, the long-term efficacy of these drugs was computed based on the results of gemfibrozil. In addition, only patients receiving monotherapy were included; the common practice of using combinations of lipid-lowering therapy was not evaluated. Perhaps of greatest concern was the assumption that efficacy and safety outcomes in general practice would be similar to outcomes observed in controlled clinical trials (where medication and clinic visits are free, poor medication compliance is an exclusion criteria, and patients are motivated by full-time research personnel).

The objective of this study was to compare the cost-effectiveness of three pharmacologic approaches to the treatment of patients with hypercholesterolemia using outcome data from a university-based outpatient lipid clinic. The three pharmacologic treatment approaches included: bile acid sequestrants alone, HMG Co-A reductase inhibitors alone, and a combination of a bile acid sequestrant and an HMG Co-A reductase inhibitor.

## METHODS

**Patients** This study was an open-label, retrospective chart review. Consecutive hypercholesterolemic patients satisfying the inclusion/exclusion criteria were included in this cost-effectiveness analysis. Patients with a diagnosis of hypercholesterolemia without manifest coronary artery disease comprised the study group. Entry criteria included an LDL-cholesterol (LDL-C) > 190 mg/dL at baseline with an LDL-C > 160 mg/dL following eight weeks on an American Heart Association Step I diet. Patients were followed for 12 months after initiation of therapy with a bile acid sequestering resin alone, an HMG Co-A reductase inhibitor alone, or a combination of a bile acid se-

questering resin and an HMG Co-A reductase inhibitor. Drug doses of lipid-lowering therapy were titrated to achieve an LDL-C of < 130 mg/dL. Doses were titrated at > four-week and < eight-week intervals. Patients were excluded for the following reasons: age less than 25 years or greater than 75 years; triglycerides greater than 300 mg/dL; women of child-bearing potential; and insulin-dependent diabetes mellitus. Patients with a compliance rate less than 80%—based on prescription refill records averaged over the year of follow-up—were excluded from the study.

**Events Outcomes** Included in the outcome events were the number and type of physician visits (routine or unscheduled), drugs administered and their dosages, laboratory tests ordered, and side effects. Incidence and type of side effects were recorded only if they were specifically noted by the physician in the medical record as a side effect secondary to a lipid-lowering drug.

**Cost Outcome** The cost-effectiveness analysis was performed from the perspective of the institution. Total health care costs, including costs related to the routine treatment of hypercholesterolemia, as well as the toxic effects of the drugs, were calculated using a direct cost accounting technique (adding the costs of all visits, medications, and toxic effects). Cost-effectiveness calculations were performed using event rates and costs as determined by the review of patients' records. Total costs and costs per mg/dL reduction in total cholesterol and LDL-C are reported. All costs used in the analysis were direct costs to the institution, rather than patients' charges.

**Cost Analyses** In the direct cost accounting method, costs of visits were calculated by determining the total number of outcome events multiplied by the cost per event (\$28 per scheduled clinic visit and \$300 per emergency room visit). Outcome event costs incorporated labor costs, nonlabor costs, and overhead costs into the computation. The costs of medications included drug acquisition costs and an indirect inventory cost (35% of drug acquisition cost). These costs were based on *Redbook* average wholesale prices.<sup>11</sup> The costs of side effects included the costs of medications to treat the side effect, diagnostic tests employed, clinic or emergency room visits, and services of consulting physicians. All costs were calculated from the start of therapy to the end of one year of follow-up.

**Statistics** Comparability of demographic and baseline characteristics among treatment groups was assessed using one-way analysis of variance for continuous variables and Pearson's  $\chi^2$  for dichotomous and categorical data. Change in blood lipids with treatment was analyzed using one-way analysis of variance.

Drug acquisition costs were reported as yearly averages for each treatment group. Other costs (laboratory, clinic, side effects) were also calculated from the time of initiation of therapy through the one year of follow-up and reported as means for each treatment group. A one-way analysis of variance (ANOVA) was used to compare the mean treatment costs be-

Table 1. Demographics and Clinical Characteristics of Patients in the Treatment Groups

| Characteristics   | Resins<br>(n = 42) | HMG Co-A Reductase<br>Inhibitors<br>(n = 56) | Combination<br>Therapy<br>(n = 43) |
|---|--------------------|--|------------------------------------|
| Age (years)   | 59.1 ± 9.3         | 59.4 ± 12.8                                  | 57.0 ± 9.5                         |
| Gender (M/F)  | 28/14              | 33/23  | 28/15                              |
| No. smokers(%)  | 17 (40%)           | 24 (43%)                                     | 18 (42%)                           |
| No. patients with (%) Hypertension                          | 3 (7%)             | 1 (2%)                                       | 0                                  |
| No. patients with (%) Congestive heart failure              | 1 (2%)             | 0  | 0                                  |
| No. of patients with (%) Diabetes Mellitus <sup>a</sup>     | 4 (10%)            | 1 (2%)                                       | 0                                  |
| No. patients (%) with Peripheral vascular disease           | 2 (5%)             | 0  | 0                                  |
| No. patients (%) with Chronic obstructive pulmonary disease | 1 (2%)             | 0  | 0                                  |
| No. patients (%) with Atrial fibrillation                   | 1 (2%)             | 0  | 0                                  |

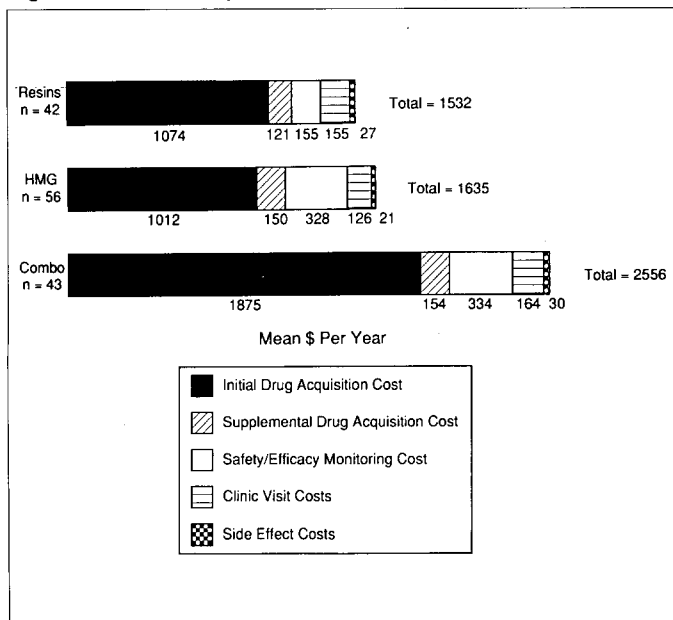
<sup>a</sup> P < 0.05.

Table 2. Final Daily Drug Doses Used in Study

| Drug           | Mean (± S.D.) Dose |                     |
|----------------|--------------------|---------------------|
|                | Monotherapy        | Combination Therapy |
| Cholestyramine | 18.9 ± 6.7 g       | 14.7 ± 7.1 g        |
| Colestipol     | 23.3 ± 2.4 g       | 20.5 ± 4.9 g        |
| Lovastatin     | 31.1 ± 16.1 mg     | 23.7 ± 10.9 mg      |
| Pravastatin    | 41.8 ± 10.18 mg    | 37.0 ± 10.7 mg      |
| Simvastatin    | 25.7 ± 15.7 mg     | 12.5 ± 3.5 mg       |

variate. The regression approach was used where the main effects and co-variables were assessed simultaneously with each being adjusted for all others. When age, gender, and co-morbid conditions were not significant in accounting for cost differences between the treatment groups, a one-way analysis of variance was used to compare treatment costs between drug therapy groups. Continuous data was presented as mean ± SD. For all analyses, a p value of < 0.05 was considered statistically significant.

Figure 1. Annual Comprehensive Cost of Lipid-Lowering Therapy.



**RESULTS**

**Patients** Approximately 435 patients were screened to yield 141 patients meeting the inclusion/exclusion criteria. Clinical and demographic characteristics of the three treatment groups are summarized in Table 1. A total of 42 patients were treated with resins alone, 56 patients with HMG inhibitors alone, and 43 patients with a combination of a resin plus an HMG inhibitor. Final daily doses of the resins, HMG inhibitors, and combination therapy are listed in Table 2.

**Drug Effectiveness** The maximal effect of resins, HMG inhibitors, and their combination on serum total cholesterol, LDL-C, and HDL-C concentrations is summarized in Table 3. The efficacy of drug therapy in reducing serum total cholesterol and LDL-C concentrations was significantly greater for combination therapy compared to resins alone and to HMG inhibitors alone (p < 0.0001). Reductions in total cholesterol and LDL-C concentrations were significantly greater with the HMG inhibitors alone compared with resins alone (p < 0.0001). Increases in HDL-C were significantly greater for both HMG inhibitors alone and combination therapy compared with resins (p < 0.05). The magnitude of the difference in the effect of HMG inhibitors alone and combination therapy on HDL-C was not significantly different.

Within the group of patients treated with resins, the effect of differing doses on total cholesterol and LDL-C reduction was minimal. Patients receiving ≤ 10 g/day colestipol (mean 8.5 g/day) or ≤ 8 g/day cholestyramine (mean 7.0 g/day) had a

tween drug therapy groups and also to compare mean treatment costs between the specific drugs within each drug therapy group. A modified least-significant difference multiple range test was used for multiple comparisons with the effect of age, gender, functional class, and the presence of co-morbid conditions, and drug class as main effects and age as the co-

Table 3. Drug Effect on Serum Total Cholesterol, LDL-Cholesterol, and HDL-Cholesterol Concentrations

|                          | Serum Concentrations (mg/dL) |           |                     |                  |
|--------------------------|------------------------------|-----------|---------------------|------------------|
|                          | Baseline                     | Treatment | Absolute Difference | % Change         |
| <b>Total Cholesterol</b> |                              |           |                     |                  |
| Resin                    | 269 mg/dL                    | 229 mg/dL | 40 mg/dL            | 15% <sup>a</sup> |
| HMG inhibitors           | 278 mg/dL                    | 210 mg/dL | 67 mg/dL            | 24% <sup>a</sup> |
| Combination therapy      | 268 mg/dL                    | 181 mg/dL | 88 mg/dL            | 33% <sup>a</sup> |
| <b>LDL-Cholesterol</b>   |                              |           |                     |                  |
| Resins                   | 203 mg/dL                    | 169 mg/dL | 34 mg/dL            | 17% <sup>a</sup> |
| HMG inhibitors           | 223 mg/dL                    | 159 mg/dL | 64 mg/dL            | 29% <sup>a</sup> |
| Combination therapy      | 215 mg/dL                    | 125 mg/dL | 89 mg/dL            | 41% <sup>a</sup> |
| <b>HDL-Cholesterol</b>   |                              |           |                     |                  |
| Resin                    | 39 mg/dL                     | 39 mg/dL  | 0 mg/dL             | 0%               |
| HMG inhibitors           | 39 mg/dL                     | 43 mg/dL  | 4 mg/dL             | 10% <sup>b</sup> |
| Combination therapy      | 40 mg/dL                     | 45 mg/dL  | 5 mg/dL             | 12% <sup>b</sup> |

a = P < 0.001; all drugs differ from each other.

b = P < 0.05; HMG inhibitors and combination therapy differ from resin alone.

Table 4. Cost-Effectiveness of Lipid-lowering Therapy (\$ per mg/dL Reduction per Year)

|                     | Total Cholesterol | LDL-C           |
|---------------------|-------------------|-----------------|
| Resins              | \$58.80 ± 36.40   | \$48.70 ± 27.60 |
| HMG inhibitors      | \$27.40 ± 14.40   | \$25.00 ± 12.30 |
| Combination therapy | \$31.60 ± 11.70   | \$30.60 ± 12.00 |

+ = P < 0.0001 versus other treatments.

14% reduction in total cholesterol and a 16% reduction in LDL-C, respectively. This compares with a 16% reduction in total cholesterol and an 18% reduction in LDL-C achieved by patients receiving higher doses of resins [ $> 10$  g/day colestipol (mean 21.8 g/day) or  $> 8$  g/day cholestyramine (mean 19.5 g/day)]. A similar outcome was observed for patients receiving higher versus lower doses of resins as part of a combination therapy regimen.

**Therapy Costs** The annual comprehensive costs of treating patients for one year are summarized in Figure 1. Total yearly treatment costs with combination therapy (\$2,556) were significantly greater than treatment costs with resins alone (\$1,532) or HMG inhibitors alone (\$1,635). The difference in treatment costs between HMG inhibitors and resins was not significantly different. The primary reason for the higher cost of the combination regimen was the higher acquisition cost of drugs. Concomitant drug therapy acquisition costs, clinic visits, and side effect costs were not significantly different among the three treatment groups. Monitoring costs including laboratory tests and other diagnostic testing were doubled for HMG inhibitors alone and combination therapy compared with resins alone (~\$330 vs \$155).

**Cost-Effectiveness** The cost-effectiveness of lipid-lowering therapy (dollars per patient per mg/dL reduction per year) is summarized in Table 4. Resin therapy alone was significantly

less cost-effective than HMG inhibitors alone or a combination of a resin plus an HMG inhibitor. Lower-dose resin therapy ( $\leq 8$  g/day cholestyramine or  $\leq 10$  g/day colestipol) was more cost-effective than higher-dose resin therapy. The cost per year per mg/dL reduction in LDL-C for resin monotherapy was  $\$40.20 \pm 26.90$  for lower doses compared with  $\$57.20 \pm 32.7$  for higher doses. The cost per mg/dL reduction in LDL-C for combination therapy was  $\$26.40 \pm 10.70$  for lower doses of resin, compared with  $\$33.02 \pm 12.40$  for higher doses of resins.

## DISCUSSION

Lipid-lowering therapy in patients with coronary artery disease has been shown to be cost beneficial.<sup>12-19</sup> A number of trials using pharmacologic manipulation of cholesterol have demonstrated a reduction in the need for revascularization, a reduction in clinical events, and a stabilization of coronary atherosclerosis.<sup>12-19</sup> The findings of these large clinical endpoint trials are valuable in confirming the hypothesis that lowering LDL-C with drugs is beneficial. However, these same trials are not very useful concerning decisions about product selection or treatment approaches from the perspective of an institution or an individual practitioner.

Our study was designed to assess the direct costs of treating patients with hypercholesterolemia using three common treatment approaches. All of our patients had failed diet therapy before the initiation of drug therapy. We found that HMG inhibitors alone or a combination of an HMG inhibitor plus a resin were more cost-effective than a resin alone. The primary reason the resins were less cost-effective was that even though the resins total cost was similar to that of the HMG inhibitors, they reduced LDL-C by only 17% compared with a 29% reduction observed with the HMG inhibitors. We also observed

a fairly flat dose-response with resin therapy. Lower-dose resin therapy resulted in an LDL-C reduction similar to that observed with higher-dose resin therapy. As a result, lower doses of resins ( $\leq 8$  g/day cholestyramine and  $\leq 10$  g/day colestipol) were more cost-effective than higher-dose resins, whether used as monotherapy or as part of a combination regimen. The results of our trial were actually similar to those previously demonstrating a flat-dose response change with colestipol.<sup>20,21</sup>

Limitations of our study include the use of data derived from a retrospective chart review. The strength of the data relies heavily on the quality of its documentation. Only clinical outcomes and events with written documentation in the medical record were included. This approach may have underestimated events or missed occurrences of patients seeking medical care with other physicians at other institutions. In addition, because of the retrospective nature of the study, patients were nonrandomly assigned to their initial drug therapy. However, with the exception of diabetes mellitus, baseline demographic and clinical characteristics were not significantly

different between treatment groups. We also did not have sufficient information to assess the functional status of patients or their subjective well-being while receiving the two drugs. Thus, quality of life was not considered in this cost-effectiveness analysis.

## CONCLUSION

Cost-effectiveness has become an important tool for making drug product selection and formulary decisions. Although many cost-effectiveness evaluations are not useful in making decisions by clinicians on an everyday basis, we believe our analysis is important in terms of judging the cost-effectiveness of three common lipid-lowering strategies. Clearly the use of an HMG inhibitor alone is cost-effective if an LDL reduction of 25–30% is required, while a combination regimen would be most cost-effective if an LDL reduction of more than 30% is needed. Selection of lipid-lowering therapy must be determined by the magnitude of LDL-reduction required and the cost-effectiveness of therapy.

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