A Randomized Trial to Assess Effectiveness and Cost in Clinical Practice: Rationale and Design of the Cholesterol Reduction Intervention Study (CRIS)

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ABSTRACT: To compare the effectiveness and costs of two alternative approaches to the treatment of hypercholesterolemia, a prospective randomized trial is being undertaken at Southern California Kaiser Permanente, a large health maintenance organization. Six hundred and twelve patients with postdiet LDL cholesterol (LDL-C) levels in the range of 190–230 mg/dl (or 160–230 mg/dl for those with coronary heart disease or two or more coronary risk factors) were randomized to a stepped-care regimen (initial treatment with niacin followed by other agents if needed) or to initial use of lovastatin, an HMG–CoA reductase inhibitor. All patients are being followed for 1 year. The study seeks to approximate conditions of typical clinical practice: provider compliance with these plans of treatment is encouraged but not enforced and patients pay for medication as they customarily would. Principal outcomes of interest include the proportion of participants who achieve goal LDL-C at one year, the mean change in total cholesterol and LDL-C levels between baseline and the end of follow-up, and the costs of cholesterol-lowering therapy.

INTRODUCTION

The report of findings from the Lipid Research Clinics Coronary Primary Prevention Trial in 1986 provided what many believed to be definitive evidence of the efficacy of cholesterol reduction in lowering the risk of coronary heart disease (CHD) [1]. Following publication of this report, in 1988 the Expert Panel of the National Cholesterol Education Program (NCEP) released its first set of detailed guidelines for patient screening, diagnostic testing, and treatment of persons found to have elevated cholesterol [2].

For persons requiring drug therapy to attain goal cholesterol levels, the NCEP panel recommended niacin or a bile acid sequestrant for initial use. Treatment with other agents, such as an HMG-CoA reductase inhibitor, was suggested only if cholesterol remained elevated after therapy with first-line medications. The prominence of the NCEP expert panel and the attention its 1988 recommendations received made them an important standard: a number of prepaid health plans adopted screening and treatment guidelines modeled along the lines of the panel's recommendations.

The panel's encouragement of this sequential approach to treatment ("stepped care") may have stemmed in part from the fact that both niacin and cholestyramine had been shown in randomized controlled trials to reduce the risk of CHD and that their long-term safety had been established [1,3]. The rationale for such an approach, however, may also be economic niacin is available at nominal cost and other cholesterol-lowering agents are perceived to be less expensive on a daily basis than the newer HMG-CoA reductase inhibitors, such as lovastatin.

The initial use of less costly medications would be unassailable if all of the drugs were identical in terms of their side effects, dosing regimens, palatability, and overall effectiveness. In fact, however, they are not. Niacin, for example, causes gastrointestinal upset, itching, and flushing in many patients [4]. Although flushing can be attenuated by gradual increase of the dose, taking the medication with meals, and concomitant use of aspirin [5], patient compliance may remain a problem. Similarly, bile acid sequestrants are inconvenient to take and also frequently cause gastrointestinal disturbances [1].

Lovastatin is generally well tolerated [6,7], and may offer advantages in terms of palatability and convenience. In clinical practice, these differences may translate into better compliance and greater numbers of patients attaining target levels of cholesterol. However, it is unclear as to whether these potential advantages would be sufficient to justify the higher drug cost of lovastatin therapy.

Unfortunately, traditional clinical trials shed little light on these issues. While such studies are ideally suited to documenting drug efficacy under controlled conditions of use (thereby maximizing internal validity), they often provide little information on the effectiveness of drugs under typical conditions of use (and hence may have limited external validity and generalizability). In most clinical trials, physician and patient noncompliance with ther-

apy, for example, is actively discouraged. Moreover, the use of a placebo control and a strict treatment protocol may mask the effects of factors that may be important in clinical practice (e.g., dosing form and frequency). Furthermore, although costs of therapy—more specifically, out-of-pocket expenses—may affect patients' willingness to comply with prescribed regimens, the effect of cost on compliance is not addressed in drug-efficacy trials as medication is typically dispensed free of charge. Traditional clinical trials therefore may not yield information about medications that may be important in clinical practice.

Below is described a randomized trial that we designed to mitigate these problems and to increase generalizability to clinical practice. The experiment is designed to assess the effectiveness and costs of two alternative approaches to drug treatment for elevated cholesterol in patients who have not adequately responded to dietary intervention: a stepped-care regimen, beginning with niacin, vs. a treatment program in which patients are prescribed lovastatin initially.

STUDY DESIGN

Overview and Study Objectives

To study two alternative approaches to the treatment of hypercholesterolemia, we are conducting a multicenter, randomized clinical trial at Southern California Kaiser Permanente (SCKP), a multispecialty, group practice health maintenance organization that serves over 2 million members.

The objective of this study is to compare clinical and economic outcomes between patients who are prescribed lovastatin as initial drug treatment for primary hypercholesterolemia and those who are started on a stepped-care regimen. The study seeks to approximate conditions of usual clinical practice to examine the effects of these treatment programs under typical conditions of use. Study intervention will therefore be kept to a minimum during the 1-year period of follow-up, and patients will pay for medication as they customarily would.

Principal outcomes of interest include the proportion of participants who achieve goal LDL cholesterol (LDL-C) at 1 year, as defined by the 1988 NCEP guidelines, which were in effect at the time the study protocol was developed (≤ 160 mg/dl, or ≤ 130 mg/dl if the patient had definite CHD or two or more CHD risk factors [2]; the mean change in total cholesterol (TC) and LDL-C between baseline and the end of follow-up; the costs of cholesterol-lowering medications and selected health care services; and the cost of cholesterol-lowering therapy per patient attaining goal level of LDL-C and per 1% change in LDL-C level.

Second, the study seeks to determine whether these outcomes vary according to the model of care (lipids clinic vs. primary care; see below) in which patients are treated, whether they have insurance coverage for outpatient drugs, and whether they have preexisting CHD.

Additional outcomes of interest include changes (between baseline and the end of follow-up) in HDL-C, triglycerides (TGs), the ratio of LDL-C to HDL-C, patient perceptions of health status, compliance with and side effects

of prescribed medication regimens, discontinuation of medication therapy, patient satisfaction with lipid-lowering care and medical treatment in general, and dietary behavior.

Patients

Patients who were members of SCKP between October 1990 and May 1992 were eligible to participate in the study if they (1) were between 20 and 70 years of age; (2) had an adequate trial period of dietary modification and failed to reach goal LDL-C, or did not wish to modify their diet further; (3) had LDL-C levels in the range of 190-230 mg/dl (or 160-230 mg/dl if they had definite CHD or two or more coronary risk factors as defined by the 1988 NCEP guidelines [2]); (4) had TG <400 mg/dl; (5) had never used a cholesterol-lowering medication; and (6) were under the care of a participating provider (see below). Patients were excluded from the study if they had a medical condition that precluded their participation (Table 1).

Models of Care

Three of ten SCKP medical centers are participating in the study. Two models of care are represented: a primary care model and a lipids clinic model. In the former (two of the medical centers), patients' primary care physicians manage hypercholesterolemia in their customary fashion. In the third center, care is rendered by specially trained registered nurse practitioners under physician guidance. Patients are referred to the lipids clinic by a primary care physician or after routine evaluation by a health-appraisal unit. Patients in the clinic are referred to special diet classes initially. Those who are unable to lower their level of LDL-C to goal are referred to a nurse practitioner to discuss initiation of medication. Patients started on medication receive periodic mailed reminders to have follow-up blood tests. The test results are entered into a computer program. Depending on the results of testing, the computer generates either a letter informing the patient that he or she has achieved goal or a note to the nurse practitioner to telephone the patient and modify therapy.

Interventions

Patients randomized to stepped care were to be started on 50 mg niacin daily, taken with meals, and slowly increased up to a maximum of 3000 mg daily (Fig. 1). If goal LDL-C was not attained with the maximum tolerated dosage of niacin, then a bile acid sequestrant (gemfibrozil, if TG ≥ 250 mg/dl) was to be added or substituted. Lovastatin was to be used only if other medications were ineffective in lowering LDL-C to goal. If any medication was poorly tolerated, treatment was to be discontinued and the patient given the next medication in the sequence. Contraindicated drugs were to be skipped and the next medication prescribed.
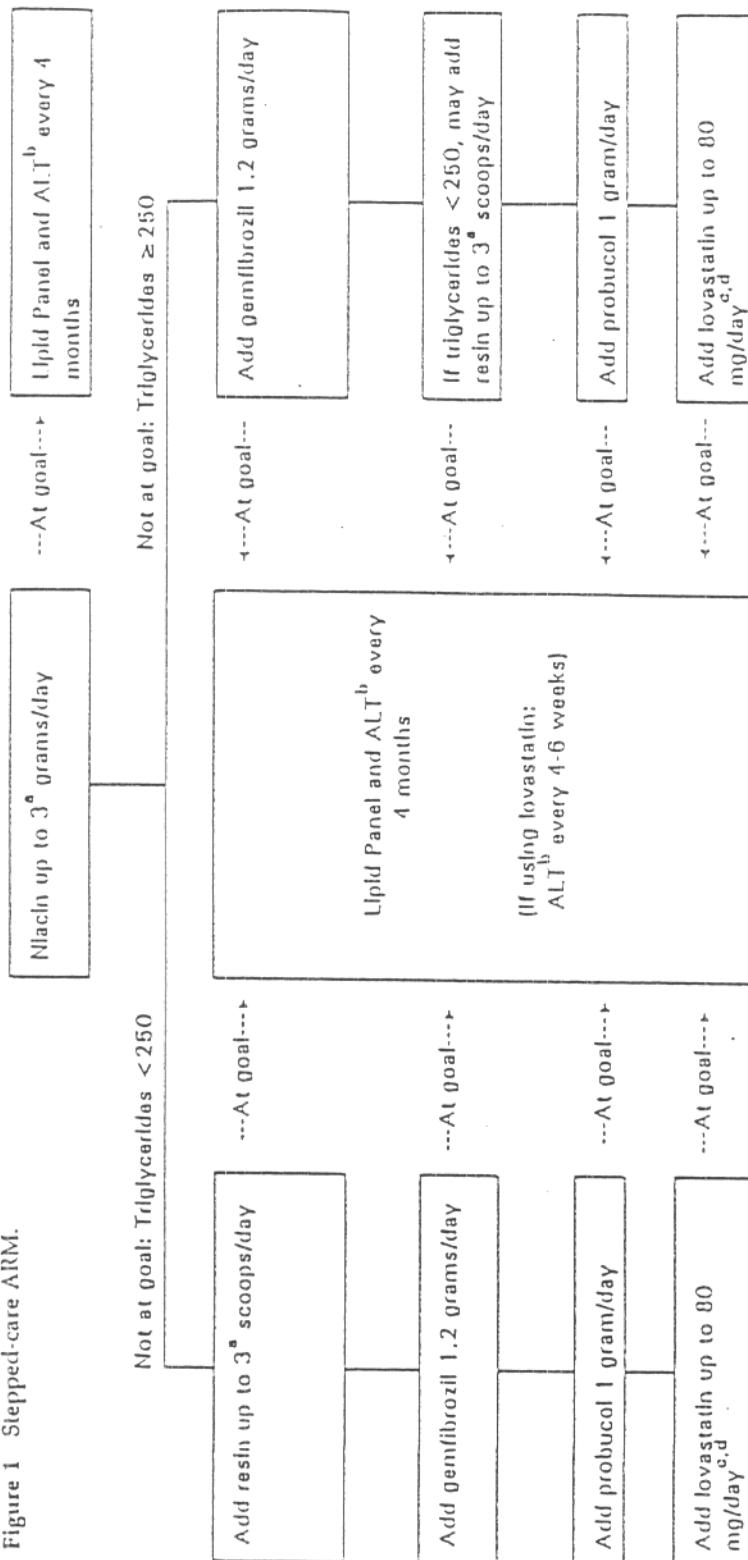
Patients randomized to lovastatin were to be started on lovastatin 20 mg daily with the evening meal (Fig.) 2. If necessary, the dosage could be

Table 1   Trial Entry Criteria

A. INCLUSION CRITERIA

Eligible patients must:

1. Be between 20 and 70 years of age at randomization.
2. Have had an adequate trial of dietary modification and failed to reach goal LDL cholesterol level, or not wish to modify diet further.
3. Have LDL cholesterol levels between 190 mg/dl and 230 mg/dl, or between 160 mg/dl and 230 mg/dl if they have definite coronary heart disease or two or more coronary risk factors, i.e., male sex, family history of premature coronary heart disease, cigarette smoking (10 or more cigarettes per day), hypertension, diabetes mellitus, severe obesity (30% or more above ideal body weight), definite cerebrovascular or peripheral vascular disease, or low HDL cholesterol (below 35 mg/dl).
4. Have triglyceride levels less than 400 mg/dl.
5. Never have used any cholesterol-lowering medication, except niacin at a dosage of 100 mg/day or less (vitamin dose).
6. Be under the care of a participating physician.

Patients who fail to meet all six inclusion criteria will be excluded from the study.

B. EXCLUSION CRITERIA

Eligible patients must not meet any of the following criteria:

1. Myocardial infarction, coronary bypass surgery, or angioplasty in the past 6 months.
2. Current coronary insufficiency, i.e., unstable angina or intermediate coronary syndrome.
3. Ventricular ectopic beats at a rate greater than five per minute, coupling, or R on T phenomenon.
4. Active liver disease, hepatic dysfunction, or unexplained persistent elevations of serum transaminases.
5. Premenopausal women, unless adequately protected against pregnancy, or nursing mothers.
6. Hemoglobin A_1 greater than 10% in the past 6 months.
7. Secondary hypercholesterolemia due to hypothyroidism, nephrotic syndrome, or other cause.
8. Recent history of alcohol or drug abuse; current average daily intake of more than three drinks.
9. Any other condition or therapy which, in the opinion of the investigator, might pose a risk to the patient or confound the results of the study (e.g., renal insufficiency or recently treated cancer).
10. Patients with life expectancy of less than 2 years because of cancer or other serious disease.
11. Inability to cooperate with the requirements of the study.
12. Current therapy with any immunosuppressive agent, anticoagulant, or anticonvulsant.
13. Concurrent participation in another clinical study or current treatment with an investigational drug.

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increased in increments of 20 mg every 4 weeks to a maximum of 80 mg daily. If goal LDL-C was still not attained, another medication (other than gemfibrozil, because of contraindication) could be added. If lovastatin was discontinued for reasons of tolerability or cost, the patient was to be started on the stepped-care regimen (see above).

Because the study sought to approximate conditions of typical clinical

Figure 1 Stepped-care ARM.

Niacin up to 3[a] grams/day

---At goal---→ Lipid Panel and ALT[b] every 4 months

Not at goal: Triglycerides <250

Not at goal: Triglycerides ≥250

Lipid Panel and ALT[b] every 4 months

(If using lovastatin: ALT[b] every 4-6 weeks)

Add resin up to 3[a] scoops/day ---At goal---→

Add gemfibrozil 1.2 grams/day ---At goal---→

Add probucol 1 gram/day ---At goal---→

Add lovastatin up to 80 mg/day[c,d] ---At goal---→

Add gemfibrozil 1.2 grams/day ←---At goal---

If triglycerides <250, may add resin up to 3[a] scoops/day ←---At goal---

Add probucol 1 gram/day ←---At goal---

Add lovastatin up to 80 mg/day[c,d] ←---At goal---

Note. All drugs added to maximum tolerable dose effecting at least a 20 mg/dl fall in LDL cholesterol.
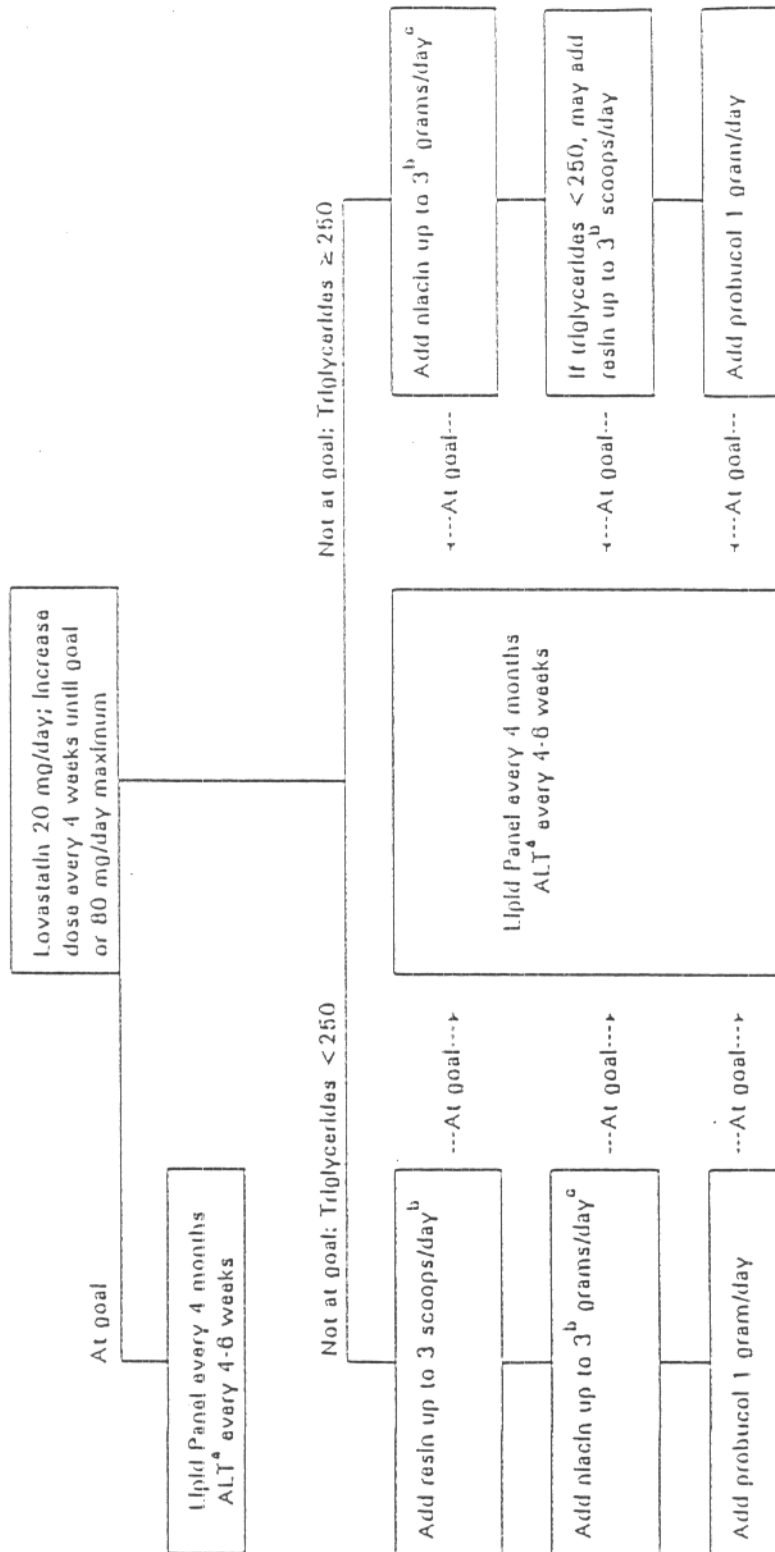
[a] Beyond this dose, combination therapy was recommended. However, if clinical circumstances warranted, higher dosages could be used (up to 6 grams/day for niacin, 6 scoops/day for resin).

[b] Alanine Aminotransferase.

[c] Lovastatin and niacin should be used with caution.

[d] Gemfibrozil must be discontinued if lovastatin is to be added.

Figure 2 Lovastatin ARM.

Lovastatin 20 mg/day; increase dose every 4 weeks until goal or 80 mg/day maximum

At goal

Lipid Panel every 4 months ALT[a] every 4-6 weeks

Not at goal: Triglycerides <250

Add resin up to 3 scoops/day[b]

---At goal--->

Add niacin up to 3[b] grams/day[c]

---At goal--->

Add probucol 1 gram/day

---At goal--->

Lipid Panel every 4 months ALT[a] every 4-6 weeks

Not at goal: Triglycerides ≥ 250

Add niacin up to 3[b] grams/day[c]

---At goal---

If triglycerides <250, may add resin up to 3[b] scoops/day

---At goal---

Add probucol 1 gram/day

---At goal---

Note. All drugs added to maximum tolerable dose effecting at least a 20 mg/dl fall in LDL cholesterol.
[a] Alanine Aminotransferase.
[b] Beyond this dose, combination therapy was recommended. However, if clinical circumstances warranted, higher dosages could be used (up to 6 grams/day for niacin, 6 scoops/day for resin).
[c] Niacin should be used with caution with lovastatin.

Table 2   Patient Recruitment, by Model of Care

Recruitment	Lipids Clinic	Primary Care	Total
Patients meeting initial entry criteria[a]	2049 (100%)	6931 (100%)	8980 (100%)
Patients ineligible because of:			
Prior use of cholesterol-lowering medication	301 (15%)	1617 (23%)	1918 (21%)
Inadequate trial of diet	378 (18%)	2304 (33%)	2682 (30%)
Unwillingness or inability to participate in study	431 (21%)	1466 (21%)	1897 (21%)
Other reason[b]	633 (31%)	1238 (18%)	1871 (21%)
Patients enrolled in study	306 (15%)	306 (4%)	612 (7%)

[a]Age, cholesterol level, seen by participating provider.
[b]Ineligible on exclusion criteria listed in Table 1.

practice, provider compliance with these plans of treatment was encouraged but not enforced.

Provider Participation and Education

Medical providers were recruited to participate in the study in September 1990. All registered nurse practitioners at the lipids clinic and all physicians in the internal medicine and family practice departments at the two primary care sites were invited to participate in the trial. All of the nurse practitioners ($n = 5$) and 78% of the eligible physicians (113 of 145) agreed to participate in the study.

Prior to the start of patient enrollment, all participating providers attended an educational program designed to familiarize them with the study objectives and treatment plans. Study personnel emphasized that all participating provides should attempt to treat each patient according to the plan of treatment to which he or she had been randomized. Finally, each provider was given a packet of written materials containing information covered during the meeting. After this meeting, no additional education regarding the study was provided.

Patient Screening, Recruitment, and Enrollment

To identify potentially eligible patients, the study staff reviewed the results of all routine cholesterol tests performed at the participating centers to determine whether TC $\geq$ 240 mg/dl (or LDL-C $\geq$160 mg/dl). Age–eligible patients under the care of a participating provider were contacted by telephone to ascertain whether they met other selected entrance criteria and were willing to participate in the study. The medical records of all willing patients were then reviewed to determine eligibility on several remaining clinical and laboratory criteria.

Another lipids profile (TC, LDL-C, HDL-C, and TG) was then performed (two if a TC value only was available) to confirm that each patient met the threshold values established for study entry. If LDL-C on repeat testing

using an automated microanalyzer (Hitachi model 717); LDL-C is computed based on the Friedewald equation [11].

Information on dietary behavior is obtained using a 3-day food diary ("Three-Day Cholesterol Control Reporter," Nutrition Scientific Inc.) completed at baseline and the end of the study.

Patients are interviewed periodically over the telephone to ascertain their perceived health status, satisfaction with medical care in general, satisfaction with their cholesterol-lowering program, and self-reported compliance with prescribed drug therapies. Measurement of perceived health status at study entry and at 3, 6, and 12 months is based on two validated scales from the Medical Outcomes Study (MOS) Short-Form General Health Survey: one addresses overall self-perceived health and the other mental and emotional health [12]. We also assessed satisfaction with medical care in general at these times using three items from a previously validated questionnaire [13].

To measure patients' satisfaction with their cholesterol-lowering regimens, we ask them at 3, 6, and 12 months how much they were bothered by the side effects and cost of their treatment and if they were satisfied with its effectiveness as well as its ease and convenience. Patients also are asked to provide an overall rating of their program of treatment. Items pertaining to bother use a five-category response set, ranging from "not at all" to "a great deal." "A great deal" and "quite a bit" will be deemed unfavorable responses. The remaining items also are rated using a five-category response set, ranging from "poor" to "excellent"; "very good" and "excellent" will be deemed to be favorable responses.

To ascertain compliance with the prescribed treatment program, we are using a modified version of an existing four-item scale [14], which we supplemented with a series of questions about compliance with specific cholesterol-lowering medications. Patients are asked to provide the names of the medications they were told to take and asked if they had taken them in the last week. If they had, they are asked how often in relation to when they were supposed to ("never," "hardly ever," "sometimes," "usually," or "always"). If not, they are asked the reason for discontinuation ("cost," "inconvenience," or "side effects").

Costs of care. Data on the utilization of health care services will be obtained from pharmacy records (use of all cholesterol-lowering medications) as well as patient medical records provider services and selected laboratory and diagnostic tests related to monitoring treatment, such as lipid profiles and liver function tests) at the end of the study.

Since actual SCKP costs are not available to us, secondary data will be used to assign dollar values to the numbers of services used. Costs of medication will be estimated using average wholesale prices plus a dispensing fee. Payment rates established under Medicare's Resource-Based Relative Value Scale will be used to estimate the costs of provider services and diagnostic tests [15]. Costs of laboratory tests will be estimated using relative value units from the American College of Pathologists [16] in conjunction with the estimated average cost per relative value unit [17].

Cost effectiveness. The cost effectiveness of initial therapy with lovastatin will be evaluated in terms of its marginal cost (including drugs, provider ser ices, and selected laboratory and diagnostic tests) in relation alternatively to the additional number of patients achieving goal LDL-C at 1 year and the incremental reduction in mean LDL-C.

Data Analysis

An intent-to-treat method will be utilized in all statistical analyses. Since lovastatin is part of the stepped-care program, we expect that some patients randomized to stepped care will be taking lovastatin at the end of the study. Likewise, some patients randomized to the lovastatin arm may receive alternative medications. There will be no study dropouts except for the few patients who die, formally request to be withdrawn from the trial, or leave SCKP. A significance level of 0.01 will be used in all comparisons of secondary outcomes to address concerns of multiplicity. An analytical plan specifies the statistical methods that will be used.

Study Organization and Management

An independent operating committee is solely responsible for study design and conduct. Subcommittees have been assigned responsibility for trial management, data collection, and analysis and report writing. Investigators retain publication rights regardless of study outcome.

Although the trial is open-label, all study investigators involved in data analysis will remain blinded to treatment assignment; the blind will be maintained until the study database is frozen and no analyses will be undertaken prior to that time.

DISCUSSION

The design of scientific investigations is dictated by their specific goals and objectives. With new medications, two common objectives are to determine whether or not they are efficacious and to test if they are superior to existing agents in providing particular benefits. To achieve these objectives, randomized, double-blind, clinical trials are typically undertaken comparing different agents and/or placebo. Placebo control and blinding are used to isolate the effect of the chemical entity and to minimize the impact of other factors. Every effort is made to control sources of variability—for example, by rigidly enforcing dosing regimens, examination schedules, and otherwise limiting the study scope. Such trials play a critical role in medical research by identifying those drugs that have the potential to produce desired clinical outcomes. However, their ability to predict how well these medications actually will work for patients treated in routine clinical practice may at times be limited..

To address these latter issues better, other types of investigations are sometimes undertaken, often involving the use of observational data and nonexperimental research designs [18,19]. The term "outcomes research" has been used in recent years to describe these and similar studies [20]. Although

such research may yield useful information about alternative approaches to patient management, the value of these studies is often limited because of nonrandom treatment assignment and the effects of confounding variables. Also, data on many relevant outcomes of interest (e.g., resource utilization) may not be available.

The study that we are conducting overcomes many of the limitations of these alternative approaches by combining important elements of each. It incorporates features such as randomization and prospectively defined data collection, for example, that are typical of clinical trials. On the other hand, the study is being conducted within the context of routine patient care: external monitoring is minimal, and the costs of medication are borne by patients, who may even insist on alternatives to their randomized treatment while remaining formally in the study. Hybrid studies of this sort have been described previously [21,22], although they are relatively uncommon [23–25]. Our study may serve as a model for other similar investigations.

The interventions we compared are not commonly studied in clinical trials. Most trials of pharmaceutical agents involve a straightforward comparison between one or more drugs used at a defined dosage. In contrast, we randomized patients to treatment programs in which physicians were permitted to determine the frequency of follow-up visits, the dosages of medication prescribed, and the frequency and pace of medication changes. Although at the outset we encouraged physicians to follow defined plans of treatment, compliance was not enforced.

Cost plays two important roles in this study. Costs incurred by patients may influence their willingness to comply with an expensive medical regimen and, as a consequence, its effectiveness. We therefore stratified patients prior to randomization according to whether they had insurance coverage for outpatient medication. Costs are also a key outcome in assessing the cost effectiveness of the different interventions. By collecting information on the costs of medication, laboratory and diagnostic tests, and provider services, we will be able to examine the relation between the marginal costs of lovastatin therapy and the additional percentage of patients achieving goal LDL-C at 1 year and the incremental reduction in mean LDL-C.

New adult treatment guidelines were recently released by the NCEP, which differ in a number of respects from the 1988 recommendations on which our study is based [26]. In the 1993 guidelines, lovastatin and the other HMG-CoA reductase inhibitors have been elevated to status of "major drugs" on an equal footing with niacin and the bile acid sequestrants for initial treatment. Nonetheless, several health care organizations continue to recommend that HMG-CoA reductase inhibitors, such as lovastatin, be used only after treatment with niacin and/or bile acid sequestrants has been attempted. We therefore believe that the questions we are exploring remain timely.

Information from double-blind, placebo-controlled clinical trials is unquestionably important in evaluating the safety and efficacy of new medications. Such trials, however, may be poor guides to the effectiveness of these interventions in typical clinical practice, especially when they are costly to patients, involve regimens that are complicated, or have frequent side effects. In this instance, alternative designs provide additional information that may help guide clinicians in selecting the best therapies for their patients.

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