

DISCONTINUATION OF ANTIHYPERLIPIDEMIC DRUGS — DO RATES REPORTED IN CLINICAL TRIALS REFLECT RATES IN PRIMARY CARE SETTINGS?

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Abstract Background. Discontinuation rates for drugs used to treat chronic conditions may affect the success of therapy. However, the discontinuation rates reported in clinical trials may not reflect those in primary care settings.

Methods. We conducted a cohort study using computerized research files and medical records on 2369 new users of antihyperlipidemic therapy at two health maintenance organizations (HMOs) from 1988 through 1990. The rates of drug discontinuation in these primary care settings were compared with the rates reported in clinical trials published from 1975 through 1993, located with the Medline data base.

Results. In the HMOs, the one-year probability of drug discontinuation was 41 percent for bile acid sequestrants (95 percent confidence interval, 38 to 44 percent), 46 percent for niacin (95 percent confidence interval, 42 to 51

percent), 15 percent for lovastatin (95 percent confidence interval, 11 to 19 percent), and 37 percent for gemfibrozil (95 percent confidence interval, 31 to 43 percent). For the bile acid sequestrants, niacin, and gemfibrozil, the risks of discontinuation were substantially higher in the HMOs than in randomized clinical trials, in which the summary estimates of this risk were 31 percent, 4 percent, and 15 percent, respectively, for trials of one year or longer. The rates of discontinuation in open-label studies were similar to those in the HMOs.

Conclusions. The discontinuation rates reported in randomized clinical trials may not reflect the rates actually observed in primary care settings. The effectiveness and tolerability of antihyperlipidemic medications should be studied further in populations that typically use the agents. (N Engl J Med 1995;332:1125-31.)

FIVE large-scale, randomized clinical trials of antihyperlipidemic drugs¹⁻⁵ have suggested that most patients continue receiving the agents for long periods of time. Reported rates of discontinuation or dropping out range from approximately 4 percent¹ to 15 percent^{2,3} in the first year of antihyperlipidemic treatment and from approximately 11 percent¹ to 30 percent^{2,4,5} with five or more years of follow-up.

In clinical trials, the services made available to patients to manage drug side effects and improve compliance are usually more extensive than those provided in routine clinical practice. Selection criteria intended to provide a clear therapeutic contrast may produce study groups that tolerate drug therapy better than typical populations of patients. Four of the aforementioned trials^{1,2,4,5} enrolled only middle-aged men, and each excluded patients with diseases or conditions that are common in populations requiring antihyperlipidemic therapy. These included coronary heart disease,^{2,4,5} diabetes mellitus requiring treatment with insulin¹⁻⁵ or

oral hypoglycemic agents,³⁻⁵ hypertension,^{4,5} and notable obesity.⁴ Subjects unlikely to have good compliance^{1,4} were also excluded.

Because lifelong treatment is generally necessary in persons with high lipid levels, the discontinuation of antihyperlipidemic drugs signals a failure of therapy due to the patient's intolerance or to therapeutic ineffectiveness. To obtain more representative estimates of the rate of discontinuation of antihyperlipidemic drugs in primary care settings, we evaluated the risks of discontinuation in patients enrolled in two health maintenance organizations (HMOs) and compared them with discontinuation rates for the same drugs reported in long-term clinical trials.

METHODS

Cohort Study

A retrospective cohort study (unpublished data) was performed with the computerized files and full-text medical records of the Fallon Community Health Plan (FCHP) and the Harvard Community Health Plan (HCHP), two HMOs operating in central and eastern Massachusetts. The study population consisted of all FCHP members with a diagnosis of hyperlipidemia (codes 272.00 to 272.90 of the *International Classification of Diseases, Ninth Revision*) from January 1, 1988, through December 31, 1990, and all HCHP members with diagnosed lipid disorders (Computer-Stored Ambulatory Record code B001, B003, B005, B006, B160, or S122 or laboratory evidence of a lipid abnormality) from October 1, 1988, through September 30, 1990, who began antihyperlipidemic therapy with the bile acid sequestrants cholestyramine and colestipol or with niacin, lovastatin, gemfibrozil, probucol, dextrothyroxine, or clofibrate and who had prescription-drug coverage throughout the study period. For all eligible study subjects, data on sex, date of birth, concomitant drug use, concomitant diagnoses, dosage of any antihyperlipidemic drugs, serum lipid levels (HCHP members only), and referral to the Lipid Clinic (FCHP members only) were acquired through the computerized data bases of the two HMOs.

Potential discontinuation of antihyperlipidemic therapy was flagged by identifying patients who switched from one antihyperlipidemic agent to another during the study period, patients for whom more than six months elapsed between the last refill of a prescription for an antihyperlipidemic drug and the end of the study period.

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riod or the termination of participation in the plan, and patients for whom omitted or inactive antihyperlipidemic therapies were flagged in the clinical-encounter files (HCHP members only). For each patient so identified, additional information on the discontinuation of antihyperlipidemic therapy and the reason for it was obtained by reviewing the medical chart. Drug courses that were discontinued by the physician because the patient had acceptable serum cholesterol levels or that were stopped temporarily were not considered to constitute discontinuations for the purposes of the primary analyses. For each drug and for all drug therapies combined, curves were constructed by the product-limit method⁶ to show the cumulative incidence (or risk) of drug discontinuation, drug discontinuation due to adverse effects, and drug discontinuation due to therapeutic ineffectiveness during a particular period. The rates of discontinuation of clofibrate, dextrothyroxine, probucol, and specific combinations of two or more agents are not reported but are included in the overall estimate.

Reported Long-Term Clinical Trials

We used the Medline data base to locate all primary reports of clinical trials published in English from January 1975 through December 1993 that examined the efficacy or safety of cholestyramine, colestipol, niacin, lovastatin, or gemfibrozil in treating lipid disorders or preventing morbidity or mortality from coronary heart disease in adults. We excluded studies that had lasted less than six months, that had enrolled fewer than 30 patients in the treatment group of interest, or that included ambiguous information on the number of subjects enrolled or dropping out. We used the overall reported dropout rates, which included but were not limited to discontinuations due to adverse effects and therapeutic ineffectiveness. We excluded subjects who did not meet the eligibility criteria for the study^{7,8} and those who were given substandard formulations of the agents.⁸ When more than one dosage or formulation was assessed, we chose the mean rate of discontinuation. We used the reported rate of discontinuation for the entire study population, including other treatment groups, when the investigators did not report regimen-specific discontinuation rates but did indicate that there was no significant difference in rates between the groups.^{9,10}

We also obtained published open-label drug studies that met the same criteria as the clinical trials. For the purposes of our analysis, reported deaths were not considered to be discontinuations. Asymptotic 95 percent confidence intervals for the risks of discontinuation were calculated from the reported standard errors or from the raw counts, where available.

To estimate summary values, we summed the logit of the risk of discontinuation ($\log[R/(1-R)]$) for each study, weighted by the inverse variance $[R(1-R)/SE]^2$, where R is the reported rate of discontinuation and SE the standard error. The variance of the weighted sum was taken as the inverse of the sum of the weights. Overall estimates of the rate of discontinuation were then recalculated from the logit values.

RESULTS

Cohort Study

There were 2369 eligible study subjects, including 1309 FCHP members and 1060 HCHP members. The mean age of the FCHP members was 58 years, and 55 percent were female. The mean age of the HCHP members was 55 years, and 48 percent were female. In all, these patients were exposed to 3223 courses of therapy. The characteristics of the patients, including concomitant diagnoses and drug use, are shown in Table 1.

Data on the frequency with which antihyperlipidemic drugs were discontinued in the HMOs are presented in Table 2 according to the type of drug and the reason for discontinuation. Of the 3223 courses of antihyperlipidemic treatment, a total of 1047 courses (32 percent) were discontinued. An additional 38 courses of

Table 1. Characteristics of the HMO Patients Who Were Receiving Antihyperlipidemic Therapy during the Study Period.

CHARACTERISTIC	COURSES OF THERAPY* no. (%)
Demographic information	
Female sex	1713 (53.1)
Age (yr)	
<40	327 (10.1)
40 to <50	624 (19.4)
50 to <60	835 (25.9)
60 to <70	1039 (32.2)
≥70	398 (12.3)
Dietary counseling before drug therapy†	609 (42.8)
Lipid Clinic referral before drug therapy‡	251 (13.9)
Previous discontinuation of antihyperlipidemic drug	723 (22.4)
Base-line serum cholesterol (mg/dl)†§	
Total cholesterol	
<240	143 (10.0)
240 to <270	356 (25.0)
270 to <300	383 (26.9)
≥300	360 (25.3)
Unknown	181 (12.7)
LDL cholesterol	
<160	123 (8.6)
160 to <200	473 (33.2)
≥200	507 (35.6)
Unknown	320 (22.5)
Concomitant disease or condition	
Hypertension	1713 (53.1)
Diabetes	380 (11.8)
Obesity	685 (21.3)
Hypothyroidism	114 (3.5)
Concomitant drug use	
Beta-adrenergic blockers	589 (18.3)
Calcium-channel blockers	534 (16.6)
Angiotensin-converting-enzyme inhibitors	411 (12.8)
Thiazide diuretic agents	365 (11.3)
Oral hypoglycemic agents	139 (4.3)
Insulin†	55 (3.9)
Smoking status at start of antihyperlipidemic therapy¶	
Current smoker	29 (19.3)
Past smoker	42 (28.0)
Nonsmoker	75 (50.0)
Unknown	4 (2.7)

*Data are based on a total of 3223 courses of therapy, except as indicated.

†Data are based on a total of 1423 courses of therapy in the HCHP group.

‡Data are based on a total of 1800 courses of therapy in the FCHP group.

§To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

¶Data are based on a random sample of 150 courses of therapy.

treatment (1 percent) were stopped temporarily because of hospitalizations or transient side effects.

Among the 1047 discontinued courses of therapy, 582 (56 percent) were followed by a switch to a new therapy, 120 (11 percent) by treatment with agents in addition to the one originally prescribed, 27 (3 percent) by treatment with one agent of a combination originally prescribed, and 318 (30 percent) by no further drug therapy during the study period. The median time from the start of observation to the discontinuation of therapy or the completion of the observation period was 190 days (range, 1 to 1093).

The principal reasons for the discontinuation of drug

Table 2. Courses of Antihyperlipidemic Therapy Discontinued during the Study Period in the Patients from the Two HMOs, According to the Reasons for Discontinuation.*

REASON FOR DISCONTINUATION	ALL DRUGS	BILE ACID SEQUESTRANTS	NIACIN	LOVASTATIN	GEMFIBROZIL
Total no. of courses	3223	1335	729	537	453
	<i>number (percent)</i>				
No. of discontinuations†	1047 (32.5)	453 (33.9)	325 (44.6)	68 (12.7)	127 (28.0)
Adverse effect‡	587 (18.2)	280 (21.0)	192 (26.3)	35 (6.5)	46 (10.2)
Clinical adverse effect	555 (17.2)	275 (20.6)	177 (24.3)	28 (5.2)	43 (9.5)
Laboratory abnormality	45 (1.4)	1 (0.1)	30 (4.1)	8 (1.5)	3 (0.7)
Drug ineffectiveness	324 (10.1)	116 (8.7)	102 (14.0)	13 (2.4)	67 (14.8)
Noncompliance	65 (2.0)	36 (2.7)	16 (2.2)	1 (0.2)	5 (1.1)
Other	69 (2.1)	31 (2.3)	16 (2.2)	10 (1.9)	5 (1.1)
Unknown	85 (2.6)	33 (2.5)	21 (2.9)	14 (2.6)	12 (2.6)

*The numbers shown for the specific treatments do not total the overall numbers because data on clofibrate, dextrothyroxine, probucol, and specific combinations of two or more agents are not reported separately but are included in the overall data.

†More than one reason for the discontinuation of drug therapy was noted in 78 instances.

‡Data on eight courses are not shown because the type of adverse effect could not be determined.

therapy were adverse effects (in 18 percent of all courses given), therapeutic ineffectiveness (in 10 percent), and noncompliance (in 2 percent). Other reasons, from the perspective of the patient, included a lack of desire to continue receiving the medication (often due to a preference for nonpharmacologic methods of lowering cholesterol levels or anxiety about potential side effects of the drug), hospitalization, and concomitant serious illness. In 78 cases, more than one reason was listed for discontinuing the drug.

Adverse effects were noted as a contributing factor in 587 of the 1047 discontinued courses of drugs (56 percent), and therapeutic ineffectiveness was noted in 324 such courses (31 percent). These contributing causes were present in similar proportions at the two study sites.

The frequency of drug discontinuation due to adverse effects ranged from 7 percent in patients receiving lovastatin to 26 percent in patients receiving niacin. The frequency of discontinuation due to therapeutic ineffectiveness ranged from 2 percent with lovastatin to 15 percent with gemfibrozil. For both adverse effects and therapeutic ineffectiveness, the proportional number of discontinuations differed significantly ($P < 0.001$) according to the agent received. Among discontinuations with known causes, the relative contribution of adverse effects as a documented cause was 67 percent with the bile acid sequestrants (280 of 420), 63 percent with niacin (192 of 304), 65 percent with lovastatin (35 of 54), and 40 percent with gemfibrozil (46 of 115). The relative contribution of therapeutic ineffectiveness as a documented cause of drug discontinuation was 28 percent with the bile acid sequestrants (116 of 420), 34 percent with niacin (102 of 304), 24 percent with lovastatin (13 of 54), and 58 percent with gemfibrozil (67 of 115). The overall differences between types of drugs were apparent at both study sites.

The cumulative incidence of discontinuation associated with each antihyperlipidemic drug at the HMOs is shown in Figure 1, both overall and according to

cause. For all treatments combined, the cumulative incidence of discontinuation after one year was 38 percent. The estimated one-year risk of discontinuation was similar for all the drugs except lovastatin: it was 41 percent for the bile acid sequestrants (95 percent confidence interval, 38 to 44 percent), 46 percent for niacin (95 percent confidence interval, 42 to 51 percent), 15 percent for lovastatin (95 percent confidence interval, 11 to 19 percent), and 37 percent for gemfibrozil (95 percent confidence interval, 31 to 43 percent). The cause-specific risks of discontinuation for the various drugs were proportionate to the overall risks, with adverse effects as the predominant cause except in the case of

gemfibrozil, for which the principal reason for discontinuation was therapeutic failure.

Rates of Drug Discontinuation in Long-Term Clinical Trials

We examined 30 long-term clinical trials^{1-4,7-31} that evaluated the safety or efficacy of antihyperlipidemic agents. These trials ranged in length from six months to seven years; there were 17 randomized trials^{1-4,7,9,10,12-15,17,18,26-28,30} and 13 open-label studies.^{8,11,14,16,19-25,29,31} Tables 3 and 4 list the principal findings of the randomized clinical trials and open-label trials, respectively, and show estimates of the frequency of discontinuation of antihyperlipidemic therapy as compared with our findings in the two HMOs.

Figure 2 shows the risk estimates for the discontinuation of antihyperlipidemic drugs reported in randomized clinical trials of one year or more as compared with the risks in the HMOs after one year and (where appropriate) two years. The reported estimates of the discontinuation rates in the six trials of bile acid sequestrants^{4,9,13,14,27,30} and one of the lovastatin trials¹² were calculated for periods in excess of 1 year (range, 36 months to 7 years). The life-table estimates of the failure rate for the bile acid sequestrants, niacin, and gemfibrozil all differed significantly between the HMOs. However, the differences between the two HMOs in estimated one-year discontinuation rates were relatively minor and were less substantial than the discrepancies in rates between the HMOs and the published clinical trials.

Each agent studied except lovastatin was discontinued at higher rates in the HMOs than in randomized clinical trials over similar periods. The summary estimates of discontinuation rates for randomized trials of one year or more were as follows: 31 percent (95 percent confidence interval, 30 to 33 percent) for the bile acid sequestrants, 4 percent (95 percent confidence interval, 3 to 5 percent) for niacin, 16 percent (95 percent confidence interval, 15 to 17 percent) for lovastatin, and 15 percent (95 percent confidence interval, 13

to 16 percent) for gemfibrozil. The estimated rates in the open-label studies were similar to the rates observed in the HMOs.

DISCUSSION

The risk of discontinuing antihyperlipidemic drugs in the two HMOs one year after the start of therapy

ranged from 15 percent for lovastatin to 46 percent for niacin. For the bile acid sequestrants, gemfibrozil, and niacin, the risks observed in the HMOs were substantially higher than the summary estimates of discontinuation rates reported in randomized clinical trials, which ranged from 4 percent with niacin to 31 percent with the bile acid sequestrants. Substantial heterogene-

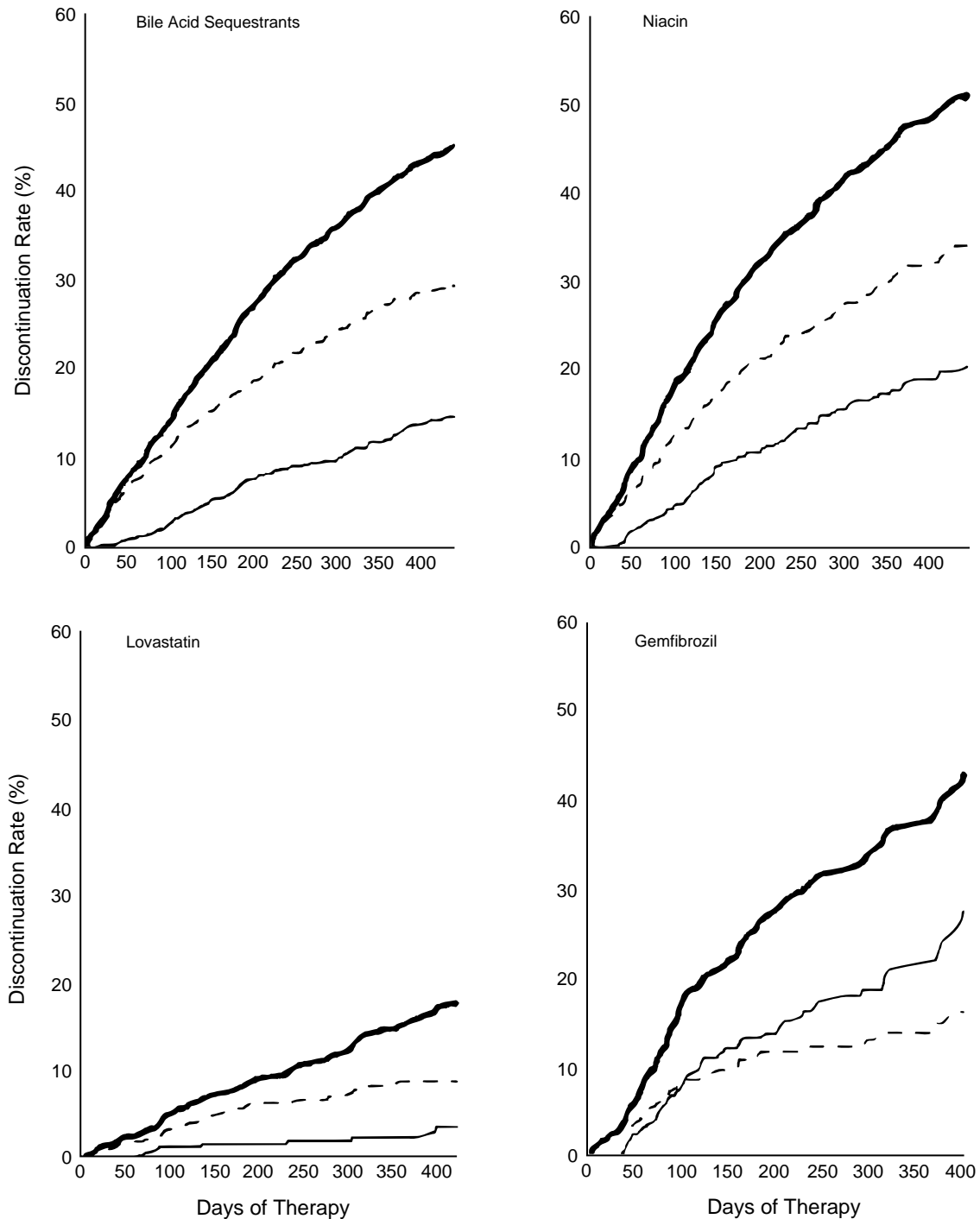


Figure 1. Cumulative Incidence of Drug Discontinuation in the Patients from the Two HMOs, According to Cause of Discontinuation.

The thick lines indicate the overall risk of drug discontinuation, the broken lines the risk of discontinuation due to adverse effects, and the thin lines the risk of discontinuation due to therapeutic ineffectiveness.

Table 3. Long-Term Randomized Clinical Trials of Antihyperlipidemic Agents.

STUDY	PERIOD USED FOR RISK ESTIMATE	NO. OF SUBJECTS IN TREATMENT GROUP*	RISK OF DISCONTINUATION (95% CI) FOR ENTIRE STUDY PERIOD†
Bile acid sequestrants			
Lipid Research Clinics ⁴	7.4 yr	1906	27.0 (25.0–29.0)
Brensike et al. ¹³	5 yr	71	7.0 (1.1–13.0)
Watts et al. ^{30‡}	3 yr	30	20.0 (5.7–34.4)
Dorr et al. ⁹	1–3 yr	1149	38.1 (35.3–40.9)
Cooper and Michel ¹⁴	2 yr	76	48.7 (37.4–59.9)
Ryan et al. ²⁷	≤36 mo	44	2.3 (0.6–6.7)
Betteridge et al. ⁷	6 mo	41	12.2 (2.2–22.2)
Pravastatin group ²⁶	6 mo	61	19.7 (9.7–29.6)
HMO	1 yr	—	41 (38–44)
Niacin			
Coronary Drug Project ¹	1 yr	1119	4.0 (2.9–5.2)
HMO	1 yr	—	46 (42–51)
Lovastatin			
Blankenhorn et al. ¹²	2 yr	134	8.2 (3.6–12.9)
Bradford et al. ³	1 yr	6582	16.5 (15.6–17.4)
Farmer et al. ¹⁰	6 mo	272§	7.7 (4.5–10.9)
Goldberg et al. ¹⁸	6 mo	50	10.0 (1.7–18.3)
Sahni et al. ^{28‡}	6 mo	79	2.5 (0–6.0)
HMO	1 yr	—	15 (11–19)
Gemfibrozil			
Frick et al. ²	1 yr	2051	14.7 (13.1–16.2)
Frick et al. ¹⁷	1 yr	311	16.1 (12.0–20.2)
Crepaldi et al. ¹⁵	6 mo	192	8.9 (4.8–12.9)
Goldberg et al. ¹⁸	6 mo	52	7.7 (0.5–14.9)
HMO	1 yr	—	37 (31–43)

*The number of subjects studied in the HMOs is not reported because many subjects were treated with more than one course of therapy.

†Risks shown are per 100 courses. CI denotes confidence interval.

‡Investigators and subjects in this study were aware of the treatment status of the patients.

§Data assume equal randomization between treatment groups.

ity was found among the estimates of the discontinuation rates reported in the trials, but those reported in each randomized trial of bile acid sequestrants, niacin, or gemfibrozil were lower than the corresponding rates in the HMOs for comparable periods. Similarly, Thurner et al.³² reported a marked difference in effectiveness between antihypertensive therapy in primary care settings and the benefits reported in randomized clinical trials.

Although this study evaluated discontinuations of drug therapy that were initiated by the patient or the physician and did not specifically assess overall adherence to a regimen of medication, the estimated discontinuation rates are similar to the 23 to 50 percent frequencies of noncompliance in studies of therapy for hypertension and other chronic diseases.^{33–36} Long-term clinical trials of antihypertensive drugs have reported discontinuation rates of approximately 30 percent,^{37,38} and community-based studies with one or more years of follow-up have reported dropout rates of approximately 50 percent from antihypertensive care in private practice³⁹ and clinic^{40,41} settings.

The open-label studies we examined reported discontinuation rates similar to those obtained from the HMOs. Thus, although open-label studies are generally considered inferior to randomized trials in the evaluation of therapeutic efficacy, such studies may reflect the success of therapy in primary care settings more accurately when drug discontinuation is taken as the measure of drug failure. Whether this is the result of less

stringent patient care or of differences in the study populations is uncertain.

Unlike previous studies that reported high frequencies of discontinuation of antihyperlipidemic drugs in primary care settings,^{42–44} our study used survival analysis to account for varying lengths of follow-up. In this manner, we were able to include all the observations, regardless of the length of follow-up, and to estimate the risk of drug discontinuation according to the duration of therapy. We also used this approach to assess specific causes of drug discontinuation, counting courses of drugs as censored that were terminated for reasons other than those used in the study. Our review of the medical records suggested that the reasons for discontinuation were often mixed, even when a predominant reason was cited. The adverse effects of a drug and its ineffectiveness may not be independent factors in causing the discontinuation of the drug, and our analyses of the reasons for discontinuation are presented to permit examination of the balance among specific reasons, without our suggesting a relation of cause and effect.

Data from clinical trials on intolerance to drugs and on therapeutic failures are likely to be more accurate than the information we could obtain from records of clinical practice. In clinical trials, information on drug discontinuation was collected prospectively, and more complete ascertainment was possible. In our cohort study, the use of the computerized files of the HMOs to identify possible drug discontinuations may have led to an underascertainment of the actual discontinuations. Reviewing the medical charts for a random sample of antihyperlipidemic treatments for which the computer-

Table 4. Long-Term Open-Label Trials of Antihyperlipidemic Agents.

STUDY	PERIOD USED FOR RISK ESTIMATE	NO. OF SUBJECTS IN TREATMENT GROUP*	RISK OF DISCONTINUATION (95% CI) FOR ENTIRE STUDY PERIOD†
Bile acid sequestrants			
Cooper and Michel ¹⁴	2 yr	30	53.3 (35.5–71.2)
HMO	2 yr	—	53 (49–57)
Niacin			
Knopp et al. ^{21‡}	6 mo	71	21.1 (11.6–30.6)
Luria ²⁴	6 mo	55	40.0 (27.1–52.9)
Yovos et al. ³¹	6 mo	40	17.5 (5.7–29.3)
HMO	6 mo	—	29 (26–33)
Lovastatin			
Bates et al. ¹¹	6 mo	56	3.6 (0–8.4)
Itskovitz et al. ¹⁹	6 mo	38	21.1 (8.1–34.0)
Kannel et al. ²⁰	6 mo	489	8.2 (5.8–10.6)
HMO	6 mo	—	8 (6–11)
Gemfibrozil			
Koskinen et al. ^{22‡}	1 yr	322	20.8 (16.4–25.2)
Eisalo and Manninen ¹⁶	6 mo	34	8.8 (0–18.4)
Gotto et al. ^{8‡}	6 mo	652	19.8 (16.7–22.8)
Kundu et al. ²³	6 mo	37	29.7 (15.0–44.5)
Olsson et al. ²⁵	6 mo	34	23.5 (9.3–37.8)
Varthakavi et al. ²⁹	6 mo	36	22.2 (8.6–35.8)
HMO	6 mo	—	26 (21–30)

*The number of subjects studied in the HMOs is not reported because many subjects were treated with more than one course of therapy.

†Risks shown are per 100 courses. CI denotes confidence interval.

‡Patients in this study were randomly assigned to receive two or more formulations of the same drug.

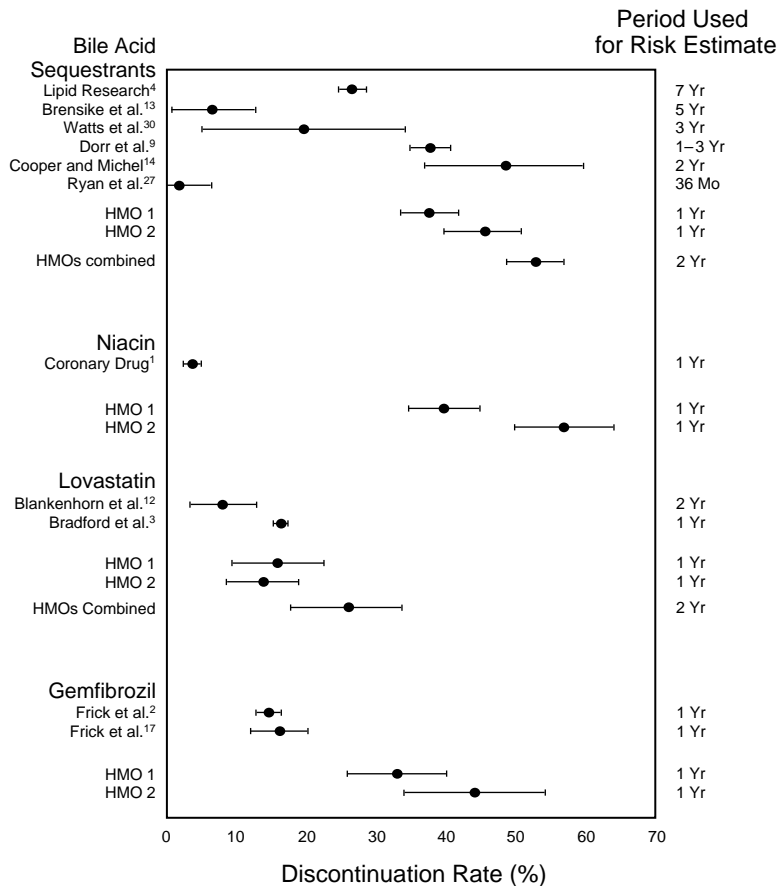


Figure 2. Risks of Drug Discontinuation over Periods of One Year or More as Reported in Randomized Clinical Trials and in the Two HMOs Studied.

HMO 1 and HMO 2 refer to the two HMOs studied. Bars represent 95 percent confidence intervals.

ized files showed no evidence of a drug discontinuation revealed that according to the charts, 7 percent of the treatments had been discontinued (unpublished data). Thus, among the approximately 1300 additional patients with no evidence of drug discontinuation for whom a medical chart was not reviewed, additional drug discontinuations were likely to have been missed. In addition, we excluded approximately 100 patients from the study who were initially flagged by the computer as having potentially discontinued antihyperlipidemic drug use; in these cases, the medical chart did not show adequate documentation of such use (unpublished data). All these sources of error would tend to reduce the apparent distinction between clinical trials and HMO practice, making our findings of substantial differences all the more striking.

Antihyperlipidemic agents are generally distributed without cost to patients in clinical trials. This factor was not, however, markedly different from the situation in the HMOs we studied. All HMO members included in the cohort study had insurance coverage for prescription drugs and paid only a nominal copayment for each prescription.

We also explored the influence of other characteristics of the study populations on the rates of discontinu-

ation of antihyperlipidemic drugs in order to determine plausible factors contributing to the marked disparity in rates between the HMOs and the randomized trials. In the HMOs, the discontinuation rate was 33 percent higher among women than among men, a difference entirely explained by the fact that the rate of discontinuation due to the incidence of adverse effects was 79 percent higher among women. Age had no consistent influence on drug discontinuation. However, patients who had previously discontinued therapy with an antihyperlipidemic drug were more likely to discontinue subsequent therapy. In the long-term randomized clinical trials of lovastatin, the selection criteria were less stringent. Women were enrolled, as well as patients with various disease states and concomitant use of non-study drugs, and the discontinuation rates estimated in these trials were similar to those in the HMO populations.

Bias in patterns of prescribing the lipid-lowering drugs was likely to be present in this cohort study, but such bias would not discount the observed differences in rates between the randomized trials and the primary care settings. However, this bias prevents legitimate comparison of the agents within the HMO settings with respect to safety and effectiveness. As has been noted, users of secondary agents at the HMOs were more likely to discontinue therapy. However, patients in whom all other available agents had failed might be more likely to continue receiving suboptimal therapy.

The high frequency of discontinuation of antihyperlipidemic drugs due to adverse effects and therapeutic ineffectiveness in our HMO population suggests that the discontinuation rates reported in randomized clinical trials may not give an accurate reflection of the tolerability or effectiveness of therapy in the general population. Whereas randomized clinical trials are often regarded as the gold standard in the assessment of drug efficacy, they may provide inferior information with regard to certain outcomes. Reports from such trials may imply that antihyperlipidemic agents have an overly optimistic success rate, thereby distorting the judgment of both practicing physicians and the policy makers who assess the cost effectiveness of these drugs. Evaluations of cholesterol-lowering therapy have reported that early drug discontinuation has a substantial influence on the cost of treatment.^{45,46} Our findings suggest a need for further study of the effectiveness and tolerability of these agents.

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