Effects of Direct-to-Consumer Advertising of Hydroxymethylglutaryl Coenzyme A Reductase Inhibitors on Attainment of LDL-C Goals

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ABSTRACT

Background: Although highly controversial, direct-to-consumer (DTC) television advertising for prescription drugs is an established practice in the US health care industry. While the US Food and Drug Administration is currently reexamining its regulatory stance, little evidence exists regarding the impact of DTC advertising on patient health outcomes.

Objective: The objective of this research was to study the relationship between heavy television promotion of 3 major hydroxymethylglutaryl coenzyme A reductase inhibitors ("statins") and the frequency with which patients are able to attain low-density lipoprotein cholesterol (LDL-C) blood-level goals after treatment with any statin.

Methods: We used logistic regression to determine achievement of LDL-C goals at 6 months after statin treatment, using electronic medical record extract data from patients from geographically dispersed primary care practices in the United States. We identified LDL-C blood levels as being at or less than goal, as defined by risk-adjusted guidelines published by the National Heart, Lung, and Blood Institute from the Adult Treatment Panel III (ATP III) data. A total of 50,741 patients, identified from 88 practices, were diagnosed with hyperlipidemia and had begun therapy with any statin medication during the 1998–2004 time period. In addition, total dollars spent each month on television advertising at the national and local levels for atorvastatin, pravastatin, and simvastatin were obtained. DTC advertising data were merged by local media market where the physician practice was located and by the month in which the patient was first prescribed a statin. The models were run for all patients who initiated therapy, and also on a subsample of patients who continued to receive prescriptions for the drugs for at least 6 months. Logistic regressions were used to predict the likelihood that each patient attained the ATP III LDL-C blood-level goals as a function of DTC advertising and other factors.

Results: High levels of national DTC advertising when therapy was initiated were found to increase the likelihood that patients attained LDL-C goals at 6 months by 6% ($P < 0.001$)—although the effect was concentrated among patients with the least-restrictive ATP III LDL-C goals (≤160 mg/dL). This result was found in both the entire set of patients as well as the restricted sample of patients who maintained therapy for at least 6 months.

Conclusions: The results of this study suggest that higher levels of DTC television advertising of statin treatment were significantly associated with improvements in the likelihood of attaining cholesterol-management goals for at least some patients. While this paper does not address the impact of DTC advertising on the costs of care or on unnecessary switching between statin treatments, the results do suggest that DTC advertising can have beneficial effects, which should be a factor when additional restrictions on DTC advertising are considered. This result—that DTC ad-

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vertising might have beneficial effects—should be weighed against existing studies that have found that patients' suggestions (conceptually which could be induced by DTC advertising) may be associated with overprescribing (eg, in the case of the use of antidepressants for adjustment disorder). (*Clin Ther.* 2006; 28:2105–2118)

Key words: LDL-C, statin, treatment, direct-to-consumer advertising.

INTRODUCTION

The practice of advertising directly to consumers (DTC) through print and broadcast media has been increasing since the mid-1990s. The practice was further reinforced in August 1997, when the US Food and Drug Administration (FDA) clarified and relaxed apparent restrictions on what pharmaceutical companies could say in short television and radio advertisements promoting prescription medications. Despite the ubiquity of this practice today, the FDA has begun hearings to reevaluate its relatively liberal stance.[1]

There are a number of published studies from the peer-reviewed literature that have used survey data to analyze the impact of DTC advertising on prescribing practices.[2–6] The articles can be classified into 2 categories: those that examined how patients feel about DTC advertising,[3,6] and those that examined how physicians feel about DTC advertising.[4,5] With respect to patients, 1 article indicated that younger patients, patients with chronic health conditions, and parents of children with health conditions were positively disposed toward DTC advertising.[3] Older patients, however, appeared more likely to ignore DTC advertising and rely more heavily on their physicians for prescription advice.[3] Survey results also indicated that physicians quite often prescribed something other than what their patients, perhaps driven by DTC advertisements, suggested. The results with respect to physicians' attributes were also mixed. One survey article found that more-experienced physicians, physicians with larger caseloads, and physicians with more exposure to DTC advertising were likely to have more positive attitudes toward such advertising.[4] Another study, however, also found that physicians were more likely to become frustrated with repeated patient questioning in response to DTC advertising than with patients who obtained their information from medical publications.[5]

There are, however, limitations with the use of survey data for policy considerations. Surveys can tell us what people believe about certain issues, and can give us information about their demand for particular consumer products. However, they are not effective in revealing whether DTC advertisements change behavior or improve health outcomes. Some studies have examined the content of DTC advertisements—primarily print advertisements—and found that while many advertisements could be classified as "informative," some lacked adequate clinical information.[7] However, content analysis cannot directly address whether behaviors are changed as a consequence of the advertisements, and if so, how. One recent study reported the results of a randomized trial, in which nearly 300 visits were conducted in family-practice settings using standardized patients who presented with 2 predefined conditions—major depression or adjustment disorder with depressed mood.[8] The investigators suggested that, in the former case, prescribing an antidepressant at the initial visit would be consistent with guideline-based care, although such prescribing in the latter case would not. The standardized patients made a request for a specific drug, a request for nonspecific pharmaceutical treatment, or no specific treatment request. The study found mixed results for the possible impact of patient suggestions. For major depression, a nonspecific request had a larger marginal impact on prescribing than a brand-specific request, although in both cases more prescriptions were written than if the patient made no request. However, patient requests for a specific drug or a general request both were associated with increased prescribing in patients with adjustment disorder ($P < 0.001$ and $P = 0.002$, respectively), in whom a prescription was less clearly warranted. Thus, DTC advertising might be expected to promote some overprescribing in that case.

A limited number of studies of DTC advertising in the peer-reviewed literature have used patient data to determine the association between DTC advertising and prescribing practices.[9–12] One of the first examined whether the demand for the statin class of drugs, determined using data from national aggregate drug sales by class, was increased after the August 1997 FDA policy change, but did not find any significant short-run direct effect.[9] A second study used the National Ambulatory Medical Care Survey, together with national frequencies of advertising of a number of drug classes, to determine the relationship between

advertising frequencies and prescribing practices for the months between 1992 and 1997.[10] While that study found some significant correlations, the measured impacts of DTC advertising were not consistent. More recently, a study in ~31,000 patients examined how likely patients were to use antidepressants when they were diagnosed in months with high spending on DTC advertising compared with those who were diagnosed during DTC advertising low-spending months. That study found that advertising for any brand was associated with increased use of all brands—although the magnitude of the effect was small.[11] Finally, a 2005 study examined the likelihood that patients with high cholesterol complied with recommendations for statin treatment and found that DTC advertisement spending on any statin had small positive effects on adherence, irrespective of the statin being used.[12]

Two other recent studies, although one is still a working paper, are of particular note for this paper.[13,14] Those studies used the same clinical database and examined the impact of DTC advertising on the use of cyclooxygenase (COX)-2 inhibitors (celecoxib and rofecoxib). The first of those studies examined the rate of prescribing of celecoxib and rofecoxib to patients with osteoarthritis at the physician practice level.[13] That paper found that increases in DTC advertising were associated with a greater flow of patients with osteoarthritis into the practice to seek care, consistent with the hypothesis that maintains that DTC advertising will encourage patients who are untreated to seek care. The second paper examined the delay between diagnosis with osteoarthritis and the adoption of daily use of a COX-2 inhibitor.[14] Using patient comorbidities, the investigators identified patients who had indications for COX-2 inhibitor use, and those who had contraindications for it. The results suggested that DTC advertising was associated with increased adoption among patients with favorable indications and discouraging adoption among those with contraindications.

Taken together, these results suggest that DTC advertising has the effect of increasing the rate at which patients seek care and improving the clinical matching of patients with appropriate therapies. However, no study to date has examined whether DTC advertising actually leads to improvements or worsening of clinical conditions. If DTC advertising can: (1) encourage motivated patients to seek care; (2) improve adherence to therapy; and/or (3) improve matching of therapies, then we would expect that greater exposure to DTC advertising might actually have an impact on observable aspects of a patient's health state. We will explore the effect of DTC advertising on 1 such aspect—reducing elevated blood low-density lipoprotein cholesterol (LDL-C) levels to within clinical guidelines.

We used a unique data set consisting of >600,000 patients (including 3.6 million patient-contact records, 3.8 million prescription records, 10.1 million vital-sign measurements, 12 million laboratory records, and 1.3 million preventive-services records) extracted from the electronic medical records of 88 primary care practices in 33 states across the United States. We extracted a subset of these data from patients who had ever been diagnosed with hypercholesterolemia, who had at least 1 physician visit in the years 1998–2004, and who had begun treatment with any statin (including, but not limited to, the 3 statins for which advertising data were available). These patient-level clinical observations were merged with monthly television-advertising measures (dollars spent) for both national and local metropolitan area media-market advertising of 3 brands of statin drugs (atorvastatin,* pravastatin,† and simvastatin‡). These data were used in a regression framework to measure the association between beginning treatment with any statin drug in a location and month that had high DTC advertising and the likelihood of a patient being at his/her guideline-based LDL-C goal after 6 months of therapy.

MATERIALS AND METHODS

Data Collection

Data were obtained from the Practice Partner Research Network (PPRNet), which is headquartered at the Medical University of South Carolina, Charleston, South Carolina. PPRNet is a practice-based learning and research organization among US ambulatory primary care practices that use a common electronic medical record (Practice Partner, Physician Micro Systems, Inc., Seattle, Washington). Practices pooled longitudinal data concerning diagnoses, laboratory studies, medications, vital signs, and other information quarterly for research and quality-improvement

*Trademark: Lipitor® (Pfizer Laboratories, Groton, Connecticut).

†Trademark: Pravachol® (Bristol-Myers Squibb Company, New York, New York).

‡Trademark: Zocor® (Merck & Co., Inc., Rahway, New Jersey).

activities. Using data from the PPRNet,[19] we extracted data from all patients who had a diagnosis of hypercholesterolemia entered into the *diagnosis* field of the electronic medical record from practices active from 1998 through 2004. During this time frame, 88 community-based primary care practices from 33 states were represented.

We obtained national and local advertising information from Competitive Media Reporting, which collects data on media advertising for all products, including pharmaceuticals, at the market (eg, city) level. The data are specific to the brand name of the product and contain information on which products were advertised and how many dollars were spent on advertising on both national and local television each month. We used thousands of dollars in advertising spending by month, summed across the 3 drug brands, as our measure of DTC advertising (thus, we estimated only drug-class level effects, and did not attempt to identify the impact of DTC advertising of the individual brands separately). The DTC advertising effect is measured in terms of dollars per month to capture the differential productivity of advertisements in some markets in generating visits—which would translate into more expensive advertising time per minute. Patients and physician practices were assigned to the nearest local media market (by mileage to the Metropolitan Statistical Area center). We eliminated practices that were >100 miles from the geographic center of the nearest media market. DTC advertising was measured at the time (month) at which a patient began his/her individual spell of treatment with a statin drug. Since the research cited earlier found similar effects between current month DTC advertising and measures of lagged month or a stock (eg, several months' advertising added together) of DTC advertising, we did not include lagged or stock measures of advertising in our models.[13]

Following Donohue et al,[11] we created a dichotomous measure of DTC advertising intensity. We created an indicator variable that equaled 1 if the beginning of the statin use occurred during a month when DTC advertising was in the upper 25th percentile of expenditures. For local advertising this indicator variable corresponded to monthly spending of ≥$7900 on advertising of all 3 statins for which data were available. For national advertising, this indicator variable corresponded to a monthly spending of ≥$7,494,900. While only 3 statins—atorvastatin, pravastatin, and simvastatin—had significant DTC advertising during the time frame of our study, we analyzed data from all patients who received a prescription for any statin for the treatment of hypercholesterolemia.

The inclusion criteria for patients in our sample were that they must have had an indication in the clinical database for hypercholesterolemia and that they must have begun therapy with any statin drug. We also estimated a version of the model on a subsample defined as all such patients whose prescription duration was at least 180 days. In addition, we excluded any patients who did not have a cholesterol laboratory test on record after they began statin therapy. This resulted in a sample of 50,741 patients.

The nature of treatment of dyslipidemias in the United States must drive the specific empiric implementation of the theoretical framework discussed earlier. Clinical management of elevated blood cholesterol levels has evolved over the years as evidence has been generated from randomized drug trials, long panel studies in defined populations, and evaluation of retrospective data sets. The National Cholesterol Education Program (NCEP) periodically conducts expert panel assessments of the evidence and makes recommendations to physicians regarding treatment processes and blood cholesterol targets. As mentioned earlier, the most recent such guidelines—Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel [ATP] III) guidelines—were published by the National Heart, Lung, and Blood Institute in 2001.[20] These guidelines set bands for what would be considered optimal, borderline, high, and very high levels of blood cholesterol—which is best measured as the level of LDL-C (mg/dL). These guidelines represent thresholds, or targets, such that therapies will be adjusted until the target threshold is met.

Thus, while one might be tempted to model the impact of statin treatment (and the derived effect of DTC advertising on the outcome) in terms of changes in measured LDL-C, the resulting estimator would be biased. To see why, consider the treatment process using statins for the treatment of high cholesterol. One characteristic of these drugs is that the effect, in terms of LDL-C reductions, largely depends on the dose of the drug used (and so it is limited by the patient's tolerance for adverse effects). In general, clinicians prescribe the lowest starting dose that they

believe can achieve the goals, and retest the patient. If the goal is not met on retest, then the dose is increased until the target LDL-C level is met. Now, consider 2 hypothetical patients. Assume the first patient presents with 2 risk factors for ischemic heart disease, but has not yet been diagnosed with the condition, and has an LDL-C level of 150 mg/dL. The ATP III guidelines call for a target LDL-C level of ≤130 mg/dL—so the patient begins statin therapy and achieves the goal after a 20-mg/dL decrease in the LDL-C level. A second patient presents with an LDL-C level of 200 mg/dL. This patient's dosage is titrated until she achieves goal (≤130 mg/dL). Although both patients have achieved the recommended treatment goal, one has done so after achieving a 20-mg/dL decrease in blood LDL-C level, while the other has done so after achieving a 70-mg/dL decrease. Both the 20-mg/dL decrease and the 70-mg/dL decrease in LDL-C values achieved—in one meaningful sense—the desired clinical outcome.

How then should one model this process? In essence, there are 2 separate questions: "What effect does DTC advertising have on reducing blood LDL-C levels, irrespective of whether clinical targets are met?" and "What effect does DTC advertising have on helping patients achieve LDL-C clinical goals?" While both are important (since any significant reduction in LDL-C levels is thought to have clinical benefit), it is the latter question that most directly drives the clinical decision-making, and so drives the process that generates the data we observe. Consequently, for this research, we focused on whether the ATP III treatment threshold goals are met. Evidence-based LDL-C goals are defined in the ATP III guidelines.[19] We extracted all relevant clinical information from the PPRNet data (with the exception of smoking status and family history of premature cardiovascular disease [CVD], since these 2 factors were not available in our data). **Table I** summarizes our adaptation of the ATP III guidelines to determine LDL-C goals. Then for each patient, we extracted the LDL-C laboratory result that was measured closest to the date 6 months after the first statin-prescription date. Patients were defined as being at goal if their follow-up LDL-C level was at or below those levels listed in **Table I** for that patient.

Table I. Defining low-density lipoprotein cholesterol (LDL-C) goals.[19]

	Risk Factors	
LDL-C Goal, mg/dL	Hypertension, HDL-C <40 mg/dL, Age >44 (Men) or >54 (Women), Diagnosed with COPD (Smoking Proxy)	Diagnosed CVD
<160	0 or 1	None
<130	2 or 3	None
<100	Any	All

HDL-C = high-density lipoprotein cholesterol; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease.

Statistical Analysis

Data consisted of observations on 50,741 individual patients from 88 different physician practices. Unobservable physician or practice characteristics may affect the degree to which patients adopt or adhere to statin therapy. Thus, we corrected for clustering (repeat observations by physician practice) in the data for all regression models presented below. The data were analyzed using STATA 9.0 (STATA Corporation, College Station, Texas).

We modeled the effect of DTC advertising by examining the impact of high television advertisement spending on the likelihood that patients who initiated any statin therapy achieve their ATP III LDL-C goals within 6 months. In this case, *high* DTC advertising was defined as advertising that occurred during a month (national) or location/month (local) that corresponded to the upper 25th percentile of DTC spending in our data. Postinitiation LDL-C laboratory values were measured as the laboratory values taken nearest the date of initiation plus 6 months, with the exceptions that: (1) the LDL-C level must have been measured at least 45 days after beginning therapy; and (2) the LDL-C test must have occurred no more than 1 year after beginning therapy. Patients who did not have a posttreatment LDL-C measurement conforming to these restrictions were excluded from the analysis. To evaluate the effect of DTC advertising on goal attainment, we estimated 2 logistic models to predict the dichotomous outcome variable (at goal = 1 if blood LDL-C level was below the ATP III goals, and goal = 0 otherwise). The first model included a con-

stant term, clinical risk-adjusters, and the indicator variables for high DTC local and national television advertising during the month in which the patient initiated therapy. The second model included those variables as well as physician practice fixed effects (and excluded 21 patients whose physician practices had too few patient observations to support the fixed-effect estimation). We also estimated the 2 models separately across the subset of 33,047 patients who maintained statin therapy for at least 6 months. All models are adjusted for clustering at the practice level, and are estimated with Huber/White heteroskedasticity-corrected errors using the "robust" option in STATA.

One concern that we addressed prior to estimating the models was how to represent the effect of time in the process of achieving LDL-C blood level goals. Certainly, the medical profession has paid increasing attention to the need to control LDL-C levels as evidence has mounted about the risks associated with elevated blood LDL-C levels. In addition, clinical guidelines support evidence that statin use is associated with a range of protective effects, such that clinicians have become increasingly careful to encourage patients to adopt daily statin therapy.[20] This increased attention to LDL-C control raised 2 questions.

First, we needed to determine whether we were observing a different type of patient population for elevated LDL-C with statins as time progressed. The statistical problem that this raises is that if clinicians were persuading patients with relatively borderline LDL-C levels to begin using statins, then the likelihood of a successful outcome (blood LDL-C levels below those in the ATP III guidelines) could have been increased due simply to the fact that the average patient had less far to go to reach his or her goals. If DTC also generally increased over time, then this selection effect would lead to spurious correlation. **Figure 1** graphs the mean LDL-C blood level prior to initiation of statin therapy from our sample over time. (Recall that all patients in the sample had begun therapy.) There was some apparent downward trend in starting LDL-C levels, which suggested that selection effects may play a role in the process. We controlled for this by including starting blood LDL-C levels as a regressor. (Pretreatment LDL-C levels are missing from some observations since practices did not retroactively enter data from the paper charts when they adopted the electronic medical records. We imputed missing LDL-C levels using a multivariate regression and also included an indicator variable in the estimated models that equaled 1 when pretreatment LDL-C was imputed, and equaled 0 otherwise. The parameter estimates for this nuisance indicator variable are not shown in the tables.)

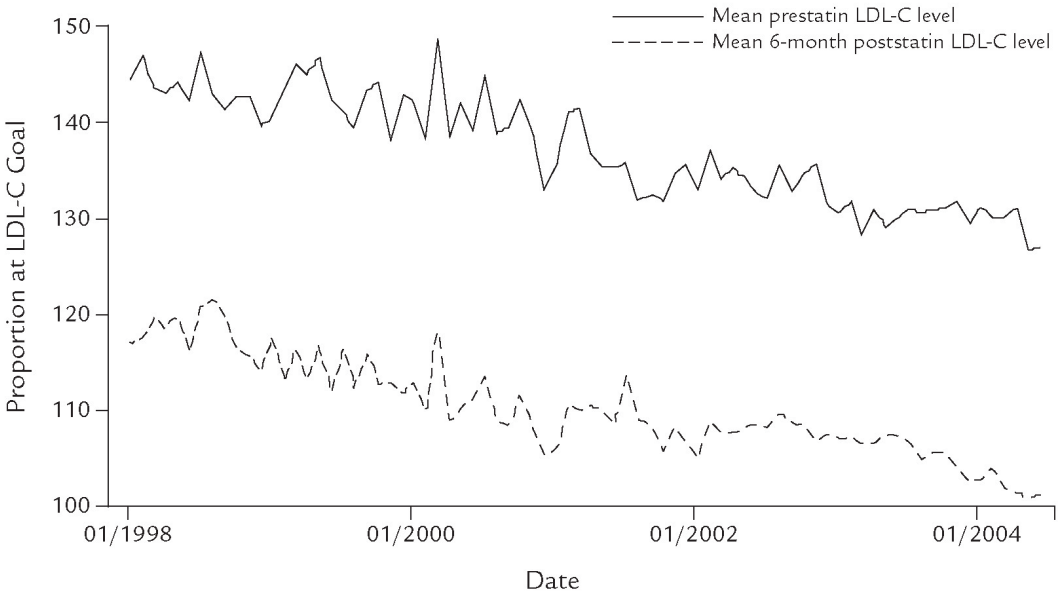

Figure 1. Mean low-density lipoprotein cholesterol (LDL-C) levels.

Figure 1 also sheds light on the second question that was raised regarding the effect of including time in our models. The lower line in **Figure 1** graphs the mean LDL-C level measured posttreatment. Again, these measurements were the lab measurements closest in time to 6 months after initiation of statin treatment. A downward trend in posttreatment LDL-C levels was apparent. The implications were clearer in **Figure 2**, which graphs the percentages of patients who were at goal 6 months after initiating statin therapy, as well as the average total (summed local and national) DTC advertisement spending. Clearly, rates of LDL-C goal attainment were rising over the entire range of the data. In addition, the trend appears to have been relatively linear. Consequently, we needed to control for time in the logistic models. We did so by including "0/1" indicator variables for the year that statin therapy began (with 2004 being the excluded categorical variable).

Finally, we needed to accommodate the fact that DTC advertising may have affected patients differently. Healthier patients—with the less restrictive LDL-C goals of ≤160 and ≤130 mg/dL—may have been more responsive to health messages of all types, including DTC advertising. If so, the impact of DTC advertising on matching therapy or adherence would have differed across patients with different LDL-C goals. To test for this we included interactions between the indicator variables for initiating therapy during a high DTC advertising month and indicator variables for having LDL-C goals of ≤160 and ≤130 mg/dL.

RESULTS

Table II lists the relevant characteristics of our sample.

Table III presents means of LDL-C goals and goal attainment for patients in the entire sample, and those patients who began therapy during a high overall DTC advertising month (defined as being a month in the 75th percentile or higher of total DTC advertisment spending) and a low overall DTC advertising month (defined as being in the 25th percentile or lower of total DTC advertisement spending). Approximately 17.4% of the sample had an LDL-C goal of ≤100 mg/dL, 39.2% had a goal of ≤130 mg/dL, and 43.4% had a goal of ≤160 mg/dL. The groups were different in ways other than their LDL-C goals, as shown in **Table II**: in the group with an LDL-C goal of 100 mg/dL, the mean age was 66.4 years, 37.8% were women, and the average pretreatment LDL-C levels were 117 mg/dL; in the group with the LDL-C

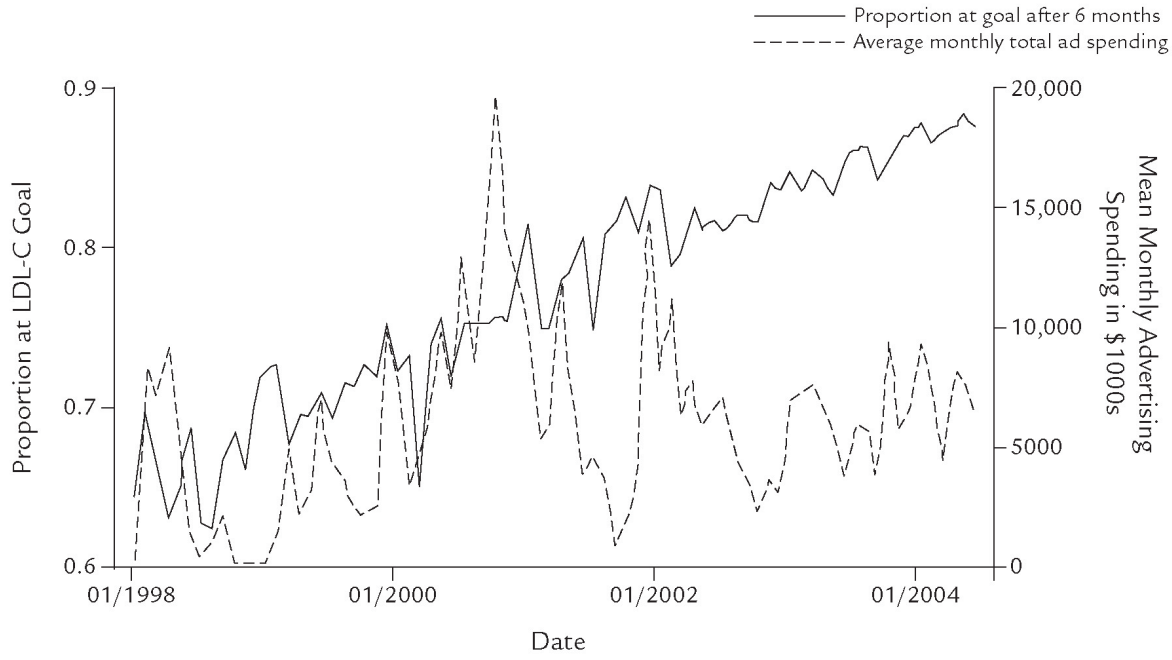

Figure 2. Percentages of patients achieving low-density lipoprotein goals and mean total direct-to-consumer advertisement spending.

Table II. Characteristics of the study sample.

Characteristic	LDL-C Target, mg/dL <100 (n = 8281)	<130 (n = 18,638)	<160 (n = 20,655)	All Patients (N = 47,574)
Age, mean, y	66.4	63.4	55.5	60.6 (SD, 12.33)
Sex, no. (%)				
Male	5089 (62.2)	9580 (51.4)	9006 (43.6)	22,956 (48.3)
Female	3093 (37.8)	9058 (48.6)	11,649 (56.4)	22,902 (48.1)
Baseline LDL-C level, mean, mg/dL	117	131	143	133.4 (SD, 39.41)
Comorbidities, no. (%)				
Hypertension	–	–	–	24,689 (51.9)
Diabetes	–	–	–	12,392 (26.0)
Coronary artery disease	–	–	–	7040 (14.8)
COPD	–	–	–	1878 (3.9)
No. (%) of patients using HMG-CoA drug				
Pravastatin	982 (12.0)	4529 (24.3)	2396 (11.6)	7907 (16.6)
Atorvastatin	3666 (44.8)	2665 (14.3)	10,782 (52.2)	17,113 (36.10)
Simvastatin	2635 (32.2)	6001 (32.2)	4771 (23.1)	13,407 (28.2)
Other*	908 (11.1)	2069 (11.1)	2706 (13.1)	5683 (11.9)
DTC television advertising				
Treatment initiated at high local and metropolitan DTC advertising, no. (%)				13,655 (28.7)
Treatment initiated at high national DTC advertising, no. (%)				12,868 (27.0)
Year treatment was started				
1998	–	–	–	2023 (4.3)
1999	–	–	–	2257 (4.7)
2000	–	–	–	3066 (6.4)
2001	–	–	–	6738 (14.2)
2002	–	–	–	11,102 (23.3)
2003	–	–	–	14,638 (30.8)
2004	–	–	–	7750 (16.3)

LDL-C = low-density lipoprotein cholesterol; COPD = chronic obstructive pulmonary disease; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor ("statin"); DTC = direct-to-consumer.
*Included cerivastatin, fluvastatin, and lovastatin.

goal of ≤130 mg/dL, the mean age was 63.4 years, 48.6% were women, and the average pretreatment LDL-C levels were 131 mg/dL; and in the group with an LDL-C goal ≤160 mg/dL, the mean age was 55.5 years, 56.4% were women, and the average pretreatment LDL-C levels were 143 mg/dL. (Note that in the least-restrictive LDL-C grouping, the average patient had a pretreatment LDL-C level below goal—so that the regression parameters reported subsequently must be interpreted in part as associations between the explanatory variables and maintaining LDL-C goals in at least some of the patients.) Finally, the relative usage of each statin was relatively constant across the 3 groups, with a slightly higher use of simvastatin among the most-restrictive target group (≤100 mg/dL) than the 2 less-restrictive groups. As may be expected, patients

Table III. Rates of low-density lipoprotein cholesterol (LDL-C) target achievement within 12 weeks of treatment with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor ("statin"), by LDL-C goal.

	LDL Target, mg/dL		
Characteristic	<100 (n = 8281)	<130 (n = 18,638)	<160 (n = 20,655)
Achieved target, no. (%)	4771 (57.6)	15,181 (81.5)	18,953 (91.8)
High DTC advertising exposure no. at target	1214 (14.7)	3707 (19.9)	4692 (22.7)
Low DTC advertising exposure no. at target	859 (10.4)	2233 (12.0)	2487 (12.0)

DTC = direct-to-consumer.

whose goals were higher (ie, easier to attain) were more likely to achieve those goals.

We found preliminary evidence that DTC advertising had an effect on goal attainment. For each of the 3 LDL-C blood goal levels, patients who began therapy during a high DTC exposure month had a higher rate of goal attainment than patients who initiated therapy during a particularly low DTC-exposure month.

However, these unadjusted rates did not take the details of patient characteristics or general-practice tendencies (and patient mix) into account. Everything else being equal, one would expect that any impact of DTC advertising would be largest among patients with the LDL-C goals that were least difficult to achieve (≤160 mg/dL). Thus, while the raw rates suggested the counterintuitive result that DTC advertising effects were greater for patients with the most stringent LDL-C goals, a multivariate analysis was needed to ensure that this correlation was not confounded.

Table IV presents the results from our logistic regression models using the entire sample of patients. The estimates are expressed as marginal effects (how a 1-unit change in the variable affected the likelihood of achieving the LDL-C goal). Column 1 of **Table IV** presents the marginal effects for initiating therapy during a heavy local and national DTC-exposure month controlling for patient characteristics, but not practice fixed effects. A clear pattern was found. Neither local nor national advertising had any measured effect on achieving LDL-C goals in the main effect (which represents patients with LDL-C goals of ≤100 mg/dL) or among the patients with the ≤130-mg/dL LDL-C goal. However, patients with the LDL-C goal of ≤160 mg/dL (the least stringent) were between 6% and 7% more likely to be at goal 6 months after treatment initiation during a month of high local and national advertising. These effects were significant at better than the 1% level ($P \leq 0.001$). The results were unaffected by the inclusion of practice-level fixed effects (**Table IV**). Thus it appears that DTC advertising was effective at improving patient LDL-C blood level goal attainment, at least among those patients who had modest goals.

One question that arises is whether this 6% to 7% apparent benefit of high DTC advertising exposure was due to changes in the likelihood that patients would continue on therapy, or some other effect not associated with adherence. To test for this, we reran the models in **Table IV** on the sample of patients whose prescription duration was at least 180 days. If the DTC advertising effect were mediated exclusively through longer periods of active prescriptions then DTC advertising should have had no residual impact in a sample in which everyone had initial prescriptions and renewals that lasted for at least 6 months. **Table V** presents models that estimated the DTC advertising effect conditional in patients who remained on therapy for 6 months. The pattern of effects was consistent with that observed in the entire sample. Beginning therapy during a high local or national DTC advertising month had no effect on patients whose LDL-C goals were ≤100 or ≤130 mg/dL; however, high DTC advertising exposure was associated with a 6% increase in the probability of achieving LDL-C goals in

Table IV. Logistic regression analysis of likelihood of achievement of low-density lipoprotein cholesterol (LDL-C) target.

	No Practice Fixed Effects (n = 45,529)			With Practice Fixed Effects (N = 45,487)		
Variable	ΔP	z Score	P > [z]	ΔP	z Score	P > [z]
Treatment initiated in high local DTC	−0.01	−0.86	0.392	−0.02	−1.59	0.113
Treatment initiated in high national DTC	−0.01	−0.94	0.349	−0.01	−0.94	0.347
LDL-C target <130 mg/dL						
Treatment initiated at high local DTC	−0.01	−0.53	0.597	0.0002	0.01	0.988
Treatment initiated at high national DTC	−0.01	−1.72	0.085	−0.01	−1.53	0.126
LDL-C target <160 mg/dL						
Treatment initiated at high local DTC	0.07	7.69	0	0.07	8.81	0
Treatment initiated at high national DTC	0.06	10.41	0	0.06	11.31	0
Baseline LDL-C level	−0.003	−38.09	0	−0.003	−42.25	0
Age (continuous in years)	−0.0003	−1.84	0.066	−0.0003	−1.67	0.095
Female sex	−0.01	−2.02	0.043	−0.01	−2.27	0.023
Comorbidities						
CVD	−0.31	−25.10	0	−0.31	−28.32	0
Diabetes	0.004	0.74	0.462	0.005	1.03	0.301
Hypertension	−0.05	−9.71	0	−0.05	−10.21	0
COPD	−0.24	−12.44	0	−0.24	−11.36	0
Year treatment was started						
1998	−0.08	−4.74	0	−0.08	−4.73	0
1999	−0.06	−5.21	0	−0.06	−4.58	0
2000	−0.05	−4.79	0	−0.05	−4.78	0
2001	−0.02	−2.90	0.004	−0.03	−4.05	0
2002	−0.02	−4.04	0	−0.03	−4.45	0
2003	−0.02	−2.14	0.032	−0.01	−2.19	0.028

DTC = direct to consumer; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease.

patients whose LDL-C goal was ≤160 mg/dL. This was true whether or not practice fixed effects were included. Consequently, consistent with the literature discussed previously concerning COX-2 inhibitors,[11–13] DTC advertising appeared to have some impact on assisting physicians and patients in matching therapy.

Tables IV and **V** present results for the impact of patient clinical factors on achieving LDL-C blood level goals. In the entire sample, women consistently had an estimated 1% lower likelihood ($P < 0.04$) of achieving LDL-C blood level goals within 6 months than did men (**Table IV**). The marginal effect was the same in the conditional sample (**Table V**), although without fixed effects it was no longer significant at conventional levels. Clinical comorbidities, on the other hand, had large negative effects on achieving goals that were precisely measured in both the entire and conditional samples. Patients with CVD had a likelihood of achieving LDL-C goals that was ~30% lower ($P < 0.001$) than in patients without this comorbidity. Recall, however, that the presence of CVD placed a patient in the ≤100-mg/dL LDL-C goal group—which is the most restrictive goal in the ATP III recommendations. Similarly, the presence of hypertension and chronic obstructive pulmonary disease were associated with reductions in the likelihood of achieving

Table V. Logistic regression analysis of likelihood of achievement of low-density lipoprotein cholesterol (LDL-C) goal if treatment duration ≥180 days.

	No Practice Fixed Effects (n = 31,771)			With Practice Fixed Effects (n = 31,746)		
Variable	Change in Probability	z	$P > [z]$	Change in Probability	z	$P > [z]$
Treatment initiated in high local DTC	−0.002	−0.15	0.883	−0.01	−0.78	0.437
Treatment initiated in high national DTC	−0.01	−1.20	0.231	−0.01	−1.22	0.222
LDL-C target ≤130 mg/dL						
Treatment initiated at high local DTC	−0.01	−0.72	0.470	−0.004	−0.32	0.748
Treatment initiated at high national DTC	−0.02	−1.39	0.163	−0.01	−1.20	0.230
LDL-C target ≤160 mg/dL						
Treatment initiated at high local DTC	0.06	6.72	0	0.06	7.59	0
Treatment initiated at high national DTC	0.06	9.78	0	0.06	10.71	0
Baseline LDL-C level	−0.002	−29.36	0	−0.002	−37.43	0
Age (continuous in years)	−0.0002	−1.45	0.147	−0.0001	−0.85	0.396
Female sex	−0.01	−1.86	0.063	−0.01	−2.09	0.037
Comorbidities						
CVD	−0.31	−23.67	0	−0.30	−27.48	0
Diabetes	−0.0002	−0.04	0.971	0.002	0.50	0.621
Hypertension	−0.05	−7.58	0	−0.05	−8.00	0
COPD	−0.24	−11.26	0	−0.24	−11.57	0
Year treatment was started						
1998	−0.08	−4.56	0	−0.08	−5.61	0
1999	−0.05	−5.59	0	−0.06	−5.13	0
2000	−0.03	−3.48	0.001	−0.04	−3.71	0
2001	−0.01	−1.51	0.130	−0.02	−2.77	0
2002	−0.02	−2.67	0.008	−0.02	−3.35	0
2003	−0.01	−0.98	0.325	−0.01	−0.99	0.32

DTC = direct to consumer; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease.

goals of 5% ($P < 0.001$) and 23% to 24% ($P < 0.001$), respectively. Again, each of these diagnoses also affected the degree to which LDL-C blood levels must be controlled. Interestingly, diabetes was not statistically related to goal attainment. In addition, when we included yearly time variables in all model specifications, patients with higher initial LDL-C levels had a lower likelihood ($P < 0.001$) of achieving their LDL-C goals. We also ran versions of the model that included the distance patients have to go to reach their LDL-C goals (starting LDL-C level minus LDL-C goal) instead of the starting LDL-C level as a regressor. The results are substantially similar. Our rationale for including the starting LDL-C level is that it better correlates to the unobservable patient characteristics (since the distance variable would be a function—albeit nonlinear—of several of the other covariates). With 1 exception, the parameter estimates on the yearly indicator variables were all negative and significant, and generally decreased in absolute value. This is consistent with the generally increasing trend toward goal achievement illustrated in **Figure 2.**

DISCUSSION

In this study, we explored the effect that DTC advertising of 3 drugs (atorvastatin, pravastatin, and sim-

vastatin) had on the outcomes of treatment in patients who used any statin. The outcome of interest was whether a patient had a measured level of blood LDL-C at or below his/her individual ATP III goal 6 months after the initiation of treatment. We measured DTC advertising using a dichotomous (0/1) variable that indicated whether the DTC advertising spending was in the upper quartile at the local and (separately) national levels during the month in which the patient in the data began using 1 of the 3 statins. We found a significant positive association with spending on national advertising in each of our models—but only for the population with the least-restrictive LDL-C goal of ≤160 mg/dL. We found that in this group, the highest levels of DTC advertising just prior to adoption was associated with a 6% and statistically significant ($P < 0.001$) increase in the likelihood of attaining the LDL-C goal.

There were at least 2 possible sources for this positive association between higher DTC advertising spending and statin treatment outcomes. First, despite the fact that most television-based DTC advertising messages were only 30 to 60 seconds in duration, they may have provided important and useful information to patients that help them work with their physicians to more effectively identify or match therapy to their needs. Existing literature suggests reasons that DTC advertising might encourage people to associate symptoms with a disease and seek care, or that DTC advertising might alert people to treatments of which they were previously unaware, which would encourage them to seek care.[18] In support of this conjecture, Keith[17] found that patient suggestions regarding pharmaceuticals (aspirin for CVD) were important determinants in prescription decisions, and that advertising led to more appropriate care as a consequence. More recent research, distributed (but not funded or endorsed) by the American Enterprise Institute,[14] found similar positive associations between television advertising and the prescription of COX-2 inhibitors rofecoxib and celecoxib.

The second possible source of this association between DTC advertising and health outcomes for statin use could have arisen from an adherence effect. As discussed earlier, Wosinska[12] found that DTC advertisement spending for statins had a small positive association with the degree to which patients adhered to prescribed therapy. This is a plausible effect, in that television advertisements are seen not only by people who could benefit from a new prescription, but also by people who have already been prescribed daily statin use but who might have otherwise forgotten or neglected to take the drug. However, when we estimated our models of LDL-C goal achievement in the subpopulation that complied with therapy for at least 6 months, we found an association of high DTC advertising exposure that was approximately the same magnitude as that found in the entire sample (which included individuals who did not adhere continually for 6 months). Thus, while the relationship between DTC advertising and adherence may have played a role in generating the beneficial association we observed, it may have been due to adherence improvements that were <6 months. To completely disentangle the adherence effects, structural modeling of the joint adherence decision and goal attainment will be necessary and will require finding instrumental variables that can identify the decision to adhere from the process that generates goal attainment. More research on this issue is needed in the future.

Study Limitations

Several limitations of the data must be acknowledged. First, our measure of DTC advertising exposure was ecologic in nature. Since our patient database could not capture which advertisements the patients actually saw, if any, our estimates are based on correlations between advertisements broadcast nationally and in the patient's area with rates of LDL-C clinical goal achievement. Thus, while practice-level fixed effects can help to reduce the impact of any secular trends, the possibility of spurious correlation between treatment for elevated LDL-C and DTC advertising cannot be completely eliminated. Additionally, our outcomes measure of achieving ATP III LDL-C goals was intermediate in nature. Whether achieving these goals over a 6-month time horizon leads to long-term LDL-C control or improvements in actual health states is not testable within the scope of this research. There are other marketing factors—such as professional journal advertisement aimed at physicians and pharmaceutical-representative visits with physicians—that we could not control for in the data available to us. Finally, insurance may play a significant role in statin adherence (including the use of multitiered copayments, formulary coverage restrictions, and prior authorization requirements—all mechanisms in effect in the United States during the period of our study). If

these factors were strongly correlated with our ecologic DTC advertising measures, then we would have mismeasured the impact of DTC advertising on LDL-C management goal achievement.

Comment

The FDA has begun a series of public hearings to assist it in reconsidering its relatively permissive stance toward DTC advertising. These results suggest that care should be taken, and more research conducted, before the FDA commits itself to any industry-wide change in policy. At this juncture, our results would argue in favor of leaving the regulations for DTC advertising as they currently stand.

CONCLUSIONS

The results of this study suggest that greater exposure to television advertising just prior to patients' beginning their therapy was associated with persistently measured increases in the likelihood that statin therapy was effective in at least some patient groups; these results suggest that additional restrictions on DTC advertising for statin therapy may not be in society's best interest.

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