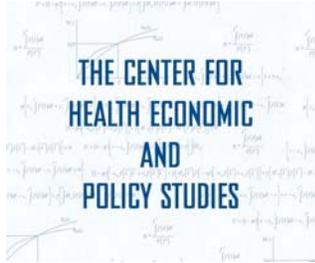


Effect of Direct to Consumer Advertising for Cholesterol Treatment

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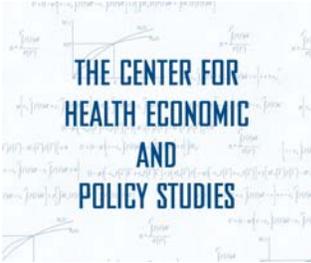
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* This paper was funded by grants from the Agency for Healthcare Research and Quality (1 R01 HS011326-01A2) and from the National Heart Lung and Blood Institute (1 R01 HL077841-01).



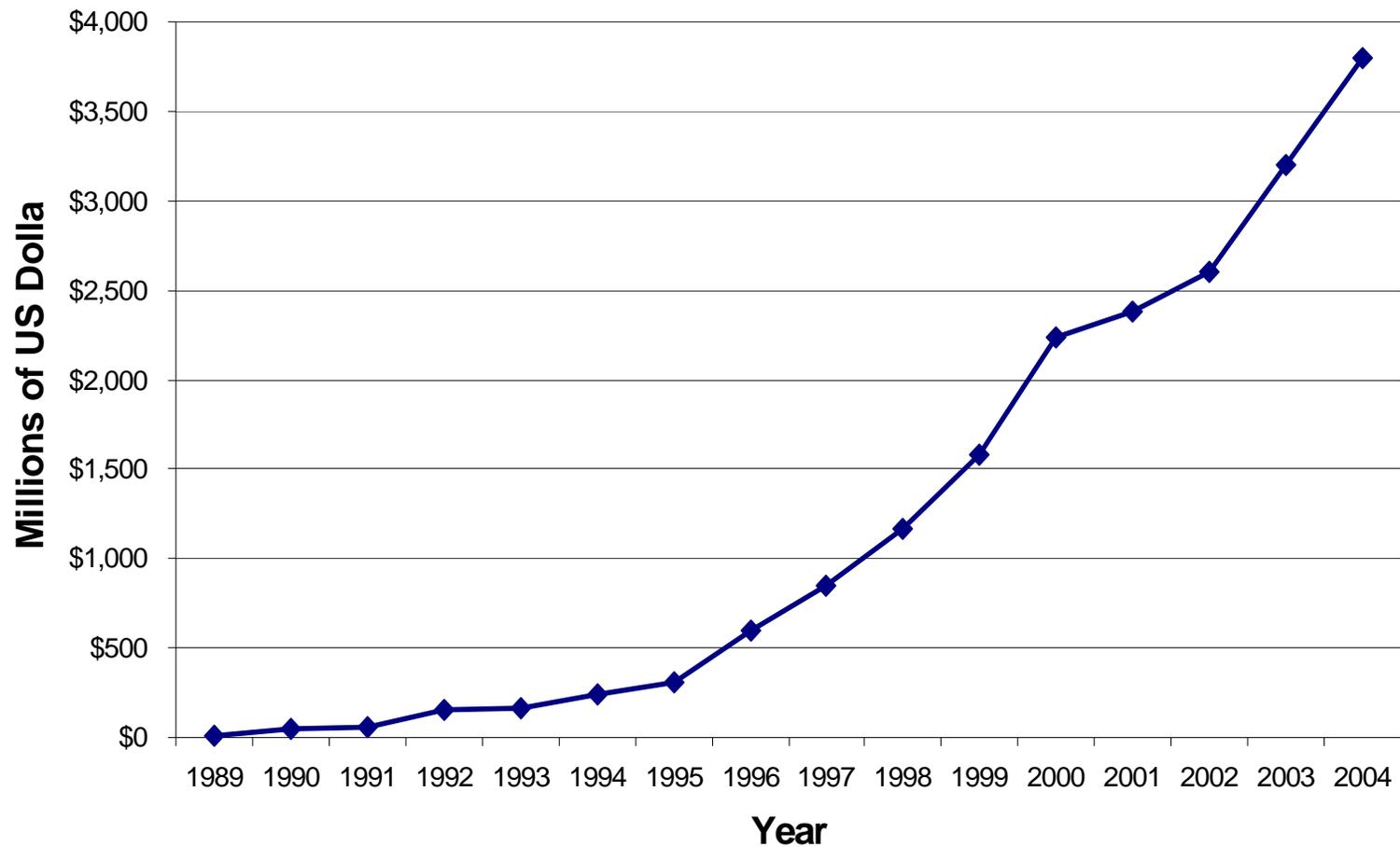
Introduction

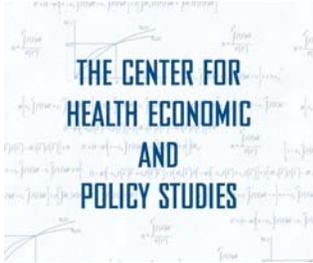
- Other than New Zealand, the United States is the only industrialized country to allow relatively unrestricted DCA for prescription drugs.
- In August of 1997 the FDA relaxed the apparent restrictions on television and radio DCA, permitting for the first time advertisers to mention both the name of the product, and the diseases and/or symptoms that the product treats in the same ad (as long as certain conditions were met).
- This policy switch has created a great deal of controversy, and the FDA continues to hold hearings to evaluate the policy.



Introduction

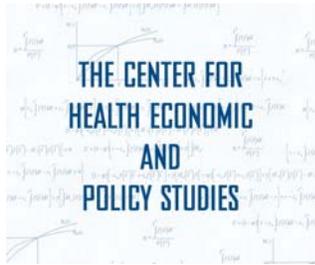
Spending of DCA in the United State
(in millions of \$US)





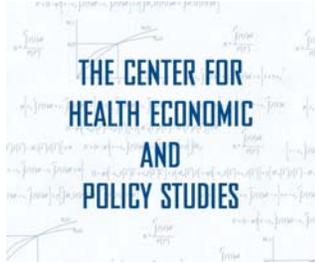
Introduction

- Purpose of this research is three-fold:
 - Determine whether DCA has any effect on the likelihood that patients are compliant with prescribed therapy.
 - Determine whether DCA can increase the likelihood that therapies are successful.
 - Determine whether DCA affects patients differently according to their clinical need.
- We selected hypercholesterolemia as the disease category, and statin drugs (e.g., Lipitor, Pravacol, Zocor) as the study drug class.



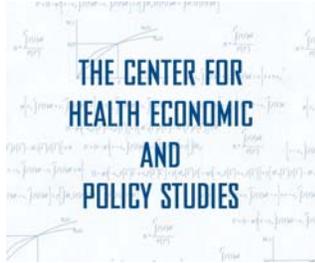
Literature on DCA in Pharmaceuticals

- Effect of DTC on overall prescribing:
 - Iizuka and Jin (2005) used visit data from the National Ambulatory Medical Care Survey and found that physician visits substantially increased during months of increased advertising spending, although DTC did not prompt significant changes to actual physician prescribing.
 - Rosenthal et al. (2003) show that DTCA increased category sales in several drug categories, but had no statistically significant impact on brand sales.
 - Wosinska (2002) and Narayanan et al (2004) found positive but small market share effects on drug prescribing / usage that was dependent on the drug's formulary status (in the case of Wosinska).
- Effect of DTC on adherence:
 - Donohue et al. (2004) used administrative data of actual anti-depressant prescriptions filled at the patient level. They found that DTC led to higher rates of diagnosing and prescribing, but much smaller increases in appropriate adherence to therapy.
 - Wosinska (2005), used a four-year panel of data from Blue-Shield of California, and found that patient adherence to statin therapy did rise in response to class-level DTC, but that the effect was small in magnitude.



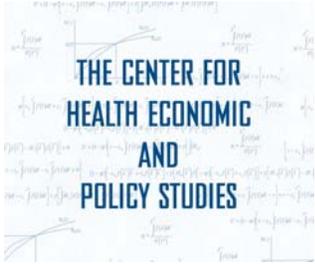
Our Previous Research on Cox-2 Inhibitors

- With respect to DCA on physician practices Bradford et al (2006) found:
 - general support for the hypothesis that DCA will attract patients to physician practices for treatment;
 - evidence of a class effect, where advertising for Vioxx stimulates demand for Celebrex;
 - evidence that Vioxx advertising may have brand effect, found in positive own-advertising Vioxx response.
- With respect to individual patient delays until use, we found that some aspects of DCA may help improve the efficiency of treatment:
 - DCA tends to shorten the delays to adoption for patients with gastrointestinal comorbidities.
 - DCA tends to lengthen the delay to adoption for patients with cardiovascular comorbidities, but only after August 2001.



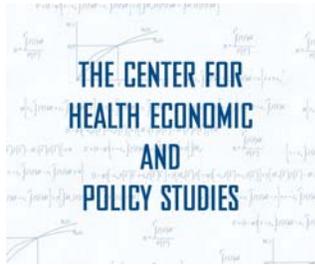
Rationale for Hypotheses in this Paper

- Our research on Cox-2 inhibitors is supportive of view that DCA is
 - encouraging patients to consult with physicians, where presumably positive agency relationships are at work, and
 - assisting patients/physicians in matching therapies
- If so, then for our statin research we should observe some difference in clinical outcomes in response to DCA:
 - Better adherence to lipid reducing pharmacotherapy
 - Better lipid control



Rationale for Hypotheses

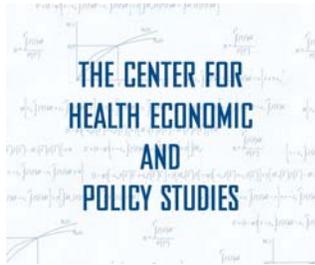
- We test this by identifying a set of patients who have already sought care, and already chosen to take some lipid lowering drug.
- We measure the dollars in national and local advertising for the most popular statin drug therapies (Lipitor, Pravacol, and Zocor).
- We identify which patients initiated their therapy during a month of very high local or national DCA (upper 25th percentile).
- We test whether beginning therapy with a greater “DCA dose” is associated with staying on therapy for 6 months, and improving cholesterol levels by 6 months.



Data Sources: Clinical and DTC Data

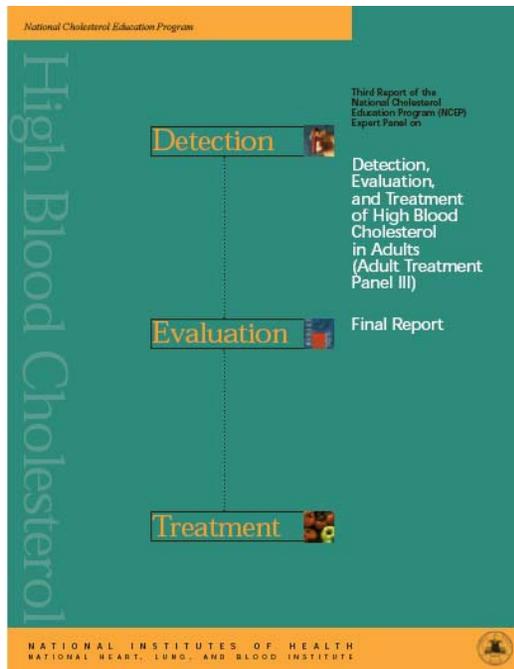
- Commercial EMR system extracts from 106 practices from 35 states
- Time period is 1998-2004.
- Collected monthly data on dollars spent on ads by:
 - Specific brand
 - Media market
- Data collected in largest 75 media markets
- Physician practices linked to closest media markets
- 51,100 patients from 88 practices with a prescription for any lipid lowering drug

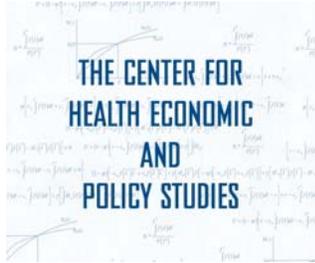




LDL Cholesterol as an Intermediate Clinical Outcome

- Cholesterol is a fat-like substance that travels through the blood, which tends to cling to vessel walls, leading to the buildup of plaque and blockage.
- There are three classes of lipids:
 - High Density Lipoprotein (HDL) – may be protective
 - Very Low Density Lipoprotein (VLDL) – may have some negative effects.
 - Low Density Lipoprotein (LDL) – main culprit in developing of plaques.
- Elevated levels of LDL cholesterol in the blood (hypercholesterolemia) is a precursor for CHD
- Consequently, control of serum LDL has been identified as a significant clinical path to reducing the onset of CHD from cholesterol.
 - Lifestyle modification – reduce saturated fat intake, increase exercise, control weight
 - Drug therapy – nicotinic acid, fibric acids, bile acid sequestrants, statins

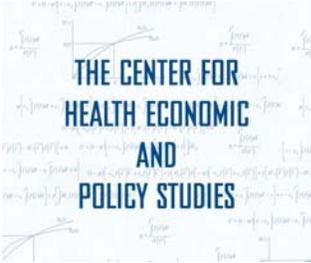




Dependent Variables

Identifying Duration of Treatment

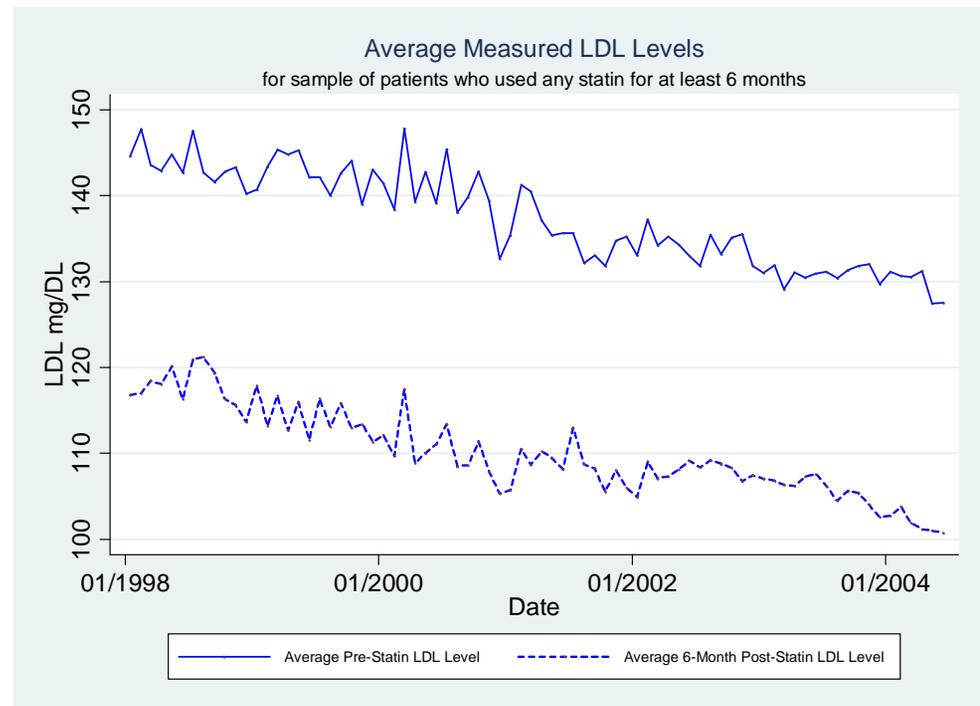
- Treatment spells:
 - Begin with the first date of issuance for any lipid-lowering drug
 - Continue for as many days as there are “daily doses” in the initial prescription and any refills, including a switch to another lipid lowering drug
 - End when the patient has been out of daily doses for 90 days
- First dependent variable is whether the spell lasts at least 6 months.

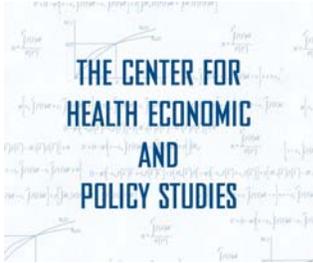


Dependent Variables

Measured LDL Levels in Our Data

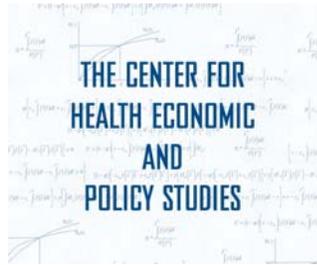
- Average pre-treatment LDL levels are falling, suggesting differing selection of patients into treatment.
- Average post-treatment LDL levels are also falling, but it's not clear the difference is changing.
- Could DCA be factor?





DTC and LDL Levels

- Not immediately obvious that DCA tracks well with changing post-treatment LDL.
- If physicians are titrating toward some clinical goal, then change in LDL levels are poor measure for DCA effect.
- But, not everyone has the same LDL goal that would trigger statin therapy – 100 mg/DL is not necessarily “right”.
- So, to test impact of DCA, we want an unambiguous clinical indicator.



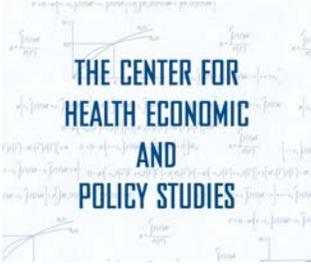
Dependent Variables Defining Cholesterol Goals

- Second dependent variable is whether patients individual LDL goals have been met.

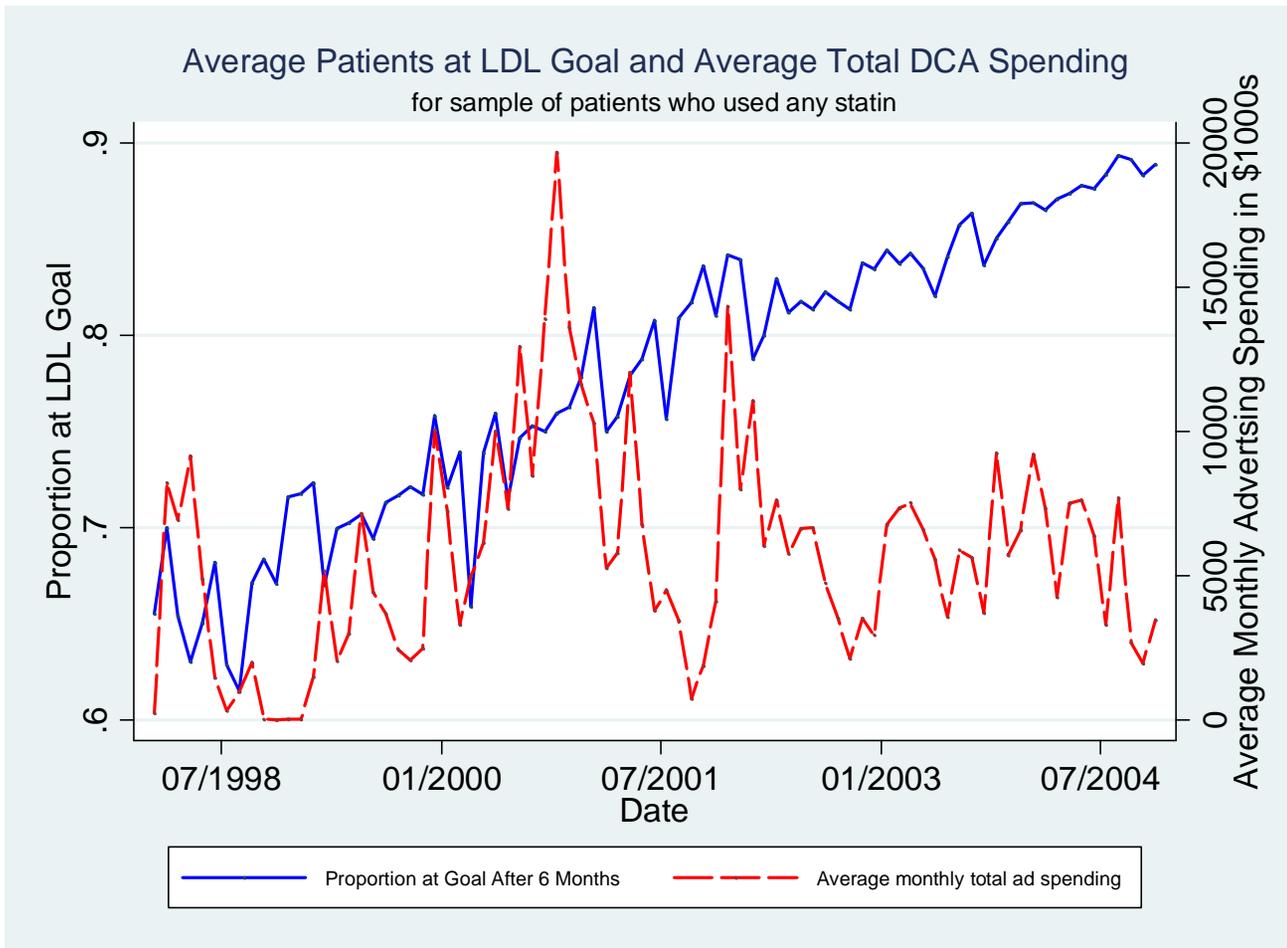
Table 1: Defining LDL Goals

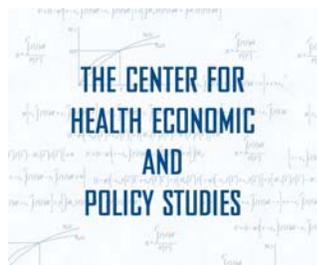
LDL Goal (mg/dL)	Risk Factors	
	<i>Hypertension, HDL < 40 mg/dL, Age > 44 (men) or 54 (women) Diagnosed with COPD (smoking proxy)</i>	
	<i>Diagnosed CVD</i>	
<160	Zero or one	No
<130	Two or three	No
<100	Not applicable	Yes

Source: Adapted to observable data from National Heart Lung and Blood Institute. National Institutes of Health. *Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)*.



Relationship Between Achieving LDL Goal and DCA

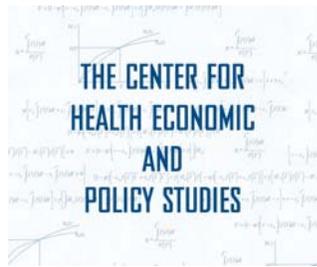




Raw Rates of Achievement

Table 2:
Percent of Population at LDL Target
Overall, and by advertising market level

Target LDL (mg/DL)	Number (%)	Overall Number at Target (%)	High DCA Exposure Number at Target (%)	Low DCA Exposure Number at Target (%)
<100	18,929 37.0%	10,795 57.0%	2,785 58.6%	2,000 52.9%
<130	13,681 26.8%	11,034 80.7%	2,742 81.4%	2,029 78.9%
<160	18,490 36.2%	16,944 91.6%	4,199 92.1%	3,156 91.9%
All	51,100 100.0%	38,773 82.0%	9,726 76.7%	7,185 73.4%



Empirical Model

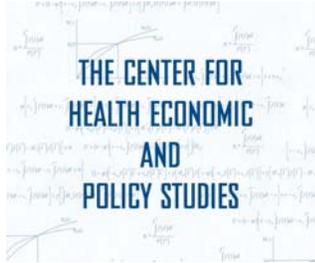
Bivariate Probit

- Estimate two joint probabilities that a patient adheres ($Y_1=1$) and achieves their LDL goal ($Y_2 = 1$) by 6 months:

$$\Phi(Y_1 = 1, Y_2 = 1) = \int_{-\infty}^{X\beta_1} \int_{-\infty}^{X\beta_2} f_{\rho}(t, s) \partial t \partial s$$

- In the bivariate probit model, the marginal effect for $\Pr(Y_1 = 1 \ \& \ Y_2 = 1)$:

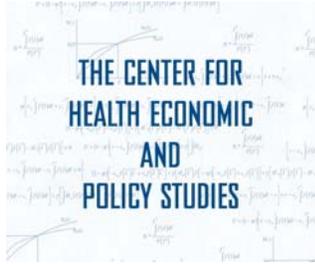
$$d\Phi / dX = F((X\beta_2 - \rho X\beta_1) / (1 - \rho^2)^{0.5}) f(X\beta_1) \beta_1 + F((X\beta_1 - \rho X\beta_2) / (1 - \rho^2)^{0.5}) f(X\beta_2) \beta_2$$



Independent Variables

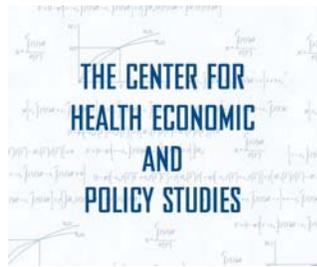
Advertising Measures

- We can construct separate measures for local and national advertising dollars for Lipitor, Pravacol and Zocor in any month in our data.
- Since there is not likely a linear dose response, we use an approach similar to Donohue *et al.* and define an indicator variable which =1 when the month is in the upper 25th percentile of local and national (separately) ad spending.
- Recall, however, that our “in treatment” indicator is any lipid lowering drug, not just one of these three statins.



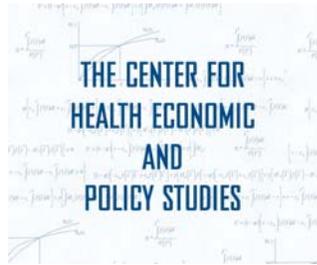
Independent Variables Other Covariates

- Age
- Female indicator
- LDL level measured prior to beginning of treatment spell
- Year indicators
- Relevant clinical indicators:
 - CVD
 - Hypertension
 - COPD
 - Diabetes
- Some versions of the model:
 - Physician practice fixed effects
 - High DCA and LDL goal indicator interactions



Results:

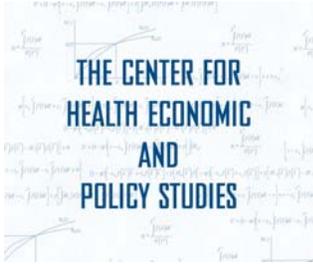
Table 4						
Coefficients on National and Local Advertising						
Across LDL Goals						
<i>(t-statistics in parentheses)</i>						
	<i>Without Fixed Effects</i>			<i>With Fixed Effects</i>		
	LDL Goal = 100	LDL Goal = 130	LDL Goal = 160	LDL Goal = 100	LDL Goal = 130	LDL Goal = 160
Adherence						
Local Advertising	0.243 (2.00)	0.254 (2.01)	0.246 (1.94)	0.207 (6.01)	0.218 (6.07)	0.167 (3.93)
National Advertising	0.093 (3.26)	0.029 (1.89)	0.123 (3.98)	0.101 (3.93)	0.079 (2.81)	0.142 (4.48)
Attain LDL Goal						
Local Advertising	0.0097 (0.27)	0.103 (2.72)	0.039 (0.97)	0.0085 (0.26)	0.081 (2.74)	0.00047 (0.01)
National Advertising	0.063 (2.69)	0.053 (1.91)	0.026 (0.81)	0.063 (2.68)	0.052 (1.86)	0.029 (0.66)
# of Obs./	18,929/	13,681/	18,490/	18,929/	13,681/	18,490/
% adherence/	65.75%/	65.97%/	65.19%/	65.75%/	65.97%/	65.19%/
% reaching goal	57.03%	80.65%	91.64%	57.03%	80.65%	91.64%
<i>Also included as regressors, but not shown: patient pre-treatment LDL level, age, gender, diagnosis of hypertension, year indicators, and (where appropriate) physician practice fixed effects.</i>						



Results:

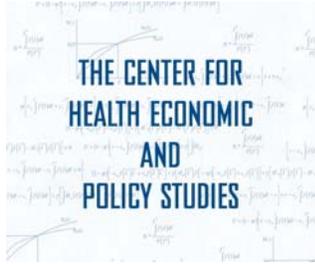
Table 5
Marginal Effects
On Joint Probability of Adherence and Reaching Goal
(t-statistics in parentheses)

	Without Fixed Effects			With Fixed Effects		
	LDL Goal = 100	LDL Goal = 130	LDL Goal = 160	LDL Goal = 100	LDL Goal = 130	LDL Goal = 160
Local Advertising	0.051 (1.86)	0.090 (2.38)	0.087 (1.95)	0.043 (4.00)	0.076 (6.75)	0.057 (3.69)
National Advertising	0.036 (4.17)	0.025 (2.46)	0.044 (4.43)	0.037 (4.85)	0.031 (3.32)	0.050 (4.81)



Conclusions

- Coronary Heart Disease (CHD) is the leading cause of mortality in the United States. Over 12 million people in the U.S. have some history of CHD.
- Statins have benefits of $\approx 42\%$ relative risk reduction in coronary mortality. Clinicians still struggle to increase the rate of use among their patients.
- Thus, if DCA for branded statin drugs prompt better matching or improved adherence it could be a useful tool toward improving patient lipid levels.



Conclusions

- Our results indicate that DCA advertising for statins has important health benefits for patients.
 - High local and national advertising increases prescription adherence for all patients.
 - High national increases the probability that patients with LDL goals of 100 mg/DL attain their LDL goals, while high local advertising has a similar effect for patients with LDL goals of 130 mg/DL.
 - Overall, exposure to high levels of DCA prior to adopting statin therapy raises the joint probability that patients both adhere to treatment and attain their LDL goals from between 3 to 7 percent.