A Cautionary Tale in Comparative Effectiveness Research: Pitfalls and Perils of Observational Data Analysis

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Abstract: Administrative data such as insurance claims offer a potentially powerful data source to examine the relative benefits and costs of competing drug treatments. Motivated by a 2011 FDA warning about possible side effects of angiotensin-II receptor blockers (ARBs), we analyze the benefits and risks of ARBs compared to other classes of hypertension drugs using Medicare Parts A, B, and D data between 2006 and 2009. We study treatment adherence and crossover as well as non-random treatment assignment in detail and illustrate how different approaches to handling these issues impact our results. We find little evidence that ARBs increase cancer rates and weak evidence that they increase stroke rates, but falsification tests raise doubts that any associations are causal. Overall, our results suggest comprehensive, robust analyses are needed in using observational data for comparative effectiveness analysis.

I. Introduction

Comparative effectiveness research (CER) has become increasingly important for payers

and policymakers as health care costs continue to grow rapidly. Such research is usually based

on the results of randomized controlled trials (RCTs). However, determining whether the "blue

pill" or the "red pill" is more effective (and for whom) can be time consuming, challenging, and

expensive. Serious but rare side effects may be missed by an underpowered RCT, making

surveillance important. Moreover, there may be interest in comparing the benefits and costs of

competing drug treatments outside of a clinical trials setting; the populations studied in trials are

almost certainly not representative of all patients who will ultimately consume the drug and trial

participants may also behave differently than people "in the real world."

Conducting CER using observational data presents a potential solution to some of these

problems. Perhaps the most promising source of observational data comes from insurance

claims. Claims data generally include large sample sizes that allow for more precise estimates of

treatment effects than those possible through RCTs. The greater statistical power of claims data

may also permit the detection of rare events not possible with RCTs, such as side effects or

interactions with other drugs. Moreover, some side effects may occur after the conclusion of an

RCT evaluation. The longer time frame of some claims data is thus another reason why claims

data may be particularly well suited to identify drug risks. In addition, RCTs are very expensive

compared to accessing observational data.

The Food and Drug Administration's Mini-Sentinel Project is perhaps the most

prominent example of pharmacovigilance. Using insurance data on roughly 100 million patients

and 2.9 billion prescription drug fills, the project seeks rapid dissemination of safety issues

associated with drugs and adverse reported events. Of course, the lack of randomization is the

trade-off for the greater statistical power and detailed information on past medical histories and drug consumption patterns available with claims data. Accordingly, making valid inferences between treatments becomes much harder and there is a greater need for empirical methods to focus on causality.

The purpose of this paper is to discuss some of the key methodological issues involved in using claims data to conduct CER. Using Medicare claims data from Parts A, B, and D between 2006 and 2009, we discuss the inherent challenges in using claims data and illustrate these issues by analyzing angiotensin II receptor blockers (ARBs) drugs for hypertension. We first document sample contamination observed in the claims—substantial crossover between therapies and discontinuation of hypertension treatment. We then discuss the implications of such sample contamination for CER. As part of our evaluation of drug treatment effectiveness, we focus on stroke—which can result from uncontrolled high blood pressure —and cancer, both of which were flagged by the FDA in 2010 as a potential adverse effect of ARBs. We employ two methods to deal with the non-random treatment assignment. First, we assume that physicians may have underlying propensities to prescribe ARBs, conditional on observed patient characteristics, and we examine the relationship between ARB prescription propensity and our outcomes at the physician level. Our rationale is that if physicians have underlying propensities to prescribe certain hypertension drugs but patients cannot observe such propensities, then we may view the initial prescription as random. Our second approach is to instrument for individual treatment choice using relative price differences between ARBs and substitute hypertension drugs. Using these two strategies to identify treatment effects, we find mixed evidence that ARBs lead to higher cancer rates and some evidence that ARBs lead to higher stroke rates compared to other hypertension drugs. As a falsification test, we rerun our analysis with a

diagnosis of pain as the dependent variable—under the assumption that there should be no relationship between pain and choice of anti-hypertensive. However, we find that ARBs are associated with more pain diagnoses and the magnitudes of the effects are often larger than those for our main outcomes, possibly due to omitted variable bias from individual-level socioeconomic factors. This suggests the relationships between ARBs and cancer or stroke should not be interpreted as causal.

The news is not all bad though. While we document some pitfalls in using observational data to conduct CER, our results also suggest value to using relative price as an instrument for drug treatments, given how well our relative price measure predicts drug use. The remainder of the paper is organized as follows. Section II provides background on ARBs and its possible link with cancer. Section III discusses sample selection and sample contamination, which occurs when people either discontinue treatment or switch treatments. Selection into treatment is discussed in section IV. Two robustness checks are presented in Section V. Section VI compares our findings with those of RCTs. We briefly conclude in Section VII.

II. Background on Hypertension, ARBs, and Cancer Risk

Hypertension is clinically defined as having either high levels of systolic blood pressure (above 140 millimeters of mercury) or diastolic blood pressure (over 90 millimeters of mercury). There is no single cause for hypertension; blood pressure levels are affected by the levels of water, salt, and hormones in the body as well as the condition of the kidneys, nervous system, and blood vessels. As people age, their blood vessels become stiffer, which increases blood pressure. Other risk factors include obesity, diabetes, smoking, and African American.[1]

The major health consequences of hypertension are stroke and heart disease.

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[1] For more background information on risk factors, see http://www.nhlbi.nih.gov/health/health-topics/topics/hbp/.

There are a variety of drugs used to treat hypertension. In this paper, we compare ARBs to common other classes of treatments. In some models, we compare ARBs to ACE inhibitors alone since these drugs represent the closest substitutes, with both operating through the effect of angiotensin (A peptide hormone, angiotensin causes vasoconstriction and also releases aldosterone, both of which lead to an increase in blood pressure). Drug classes we analyze and the mechanism by which they affect blood pressure are summarized below:

- **Angiotensin-II Receptor Blockers (ARBs)**: Relaxes blood vessels by blocking the action of angiotensin II.

- **ACE inhibitors:** Prevents the formation of angiotensin II.

- **Beta blockers:** Blocks the effects of the hormone epinephrine, leading the heart to beat more slowly

- **Diuretics:** Removes salt and water from the body by inducing the kidneys to put more salt into urine, thereby decreasing pressures on artery walls

- **Calcium channel blockers:** Widens and relaxes blood vessels through influencing the muscle cells in the walls of arteries

- **Other antihypertensives (e.g. vasodilators):** Opens blood vessels by preventing muscles from tightening and by stopping the walls in the arteries from narrowing

In July 2010, the FDA issued a safety alert in response to a meta-analysis by Sipahi et al. (2010) suggesting a possible risk of cancer associated with use of ARBs (Food and Drug Administration 2010). The meta-analysis used data on 60,000 patients and found a small but statistically significant increase in new cancer cases among ARB users: 7.2 percent compared to 6.0 percent.[2] The authors considered breast, prostate, and lung cancers and grouped all remaining

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[2] Cancer was not a pre-specified endpoint in several of the trials analyzed by Sipahi et al. (2010). This suggests the difference in cancer deaths observed may have resulted from differential effects of drug use on cancer detection. In particular, ARBs may more cause side effects that prompt a diagnostic workup, which ultimately reveal the presence of cancer, even though there is no causal biological mechanism between ARBs and cancer. We investigated this possibility by calculating prevalence rates of major diagnostic cancer tests among people taking different drugs. To keep the comparison as clean as possible, we also only examined 1-year incident cases—people who did not take any hypertension drug in 2006 and began taking one in 2007—for those on monotherapy (i.e. treatment with a single

cancers together. Over the next year, the FDA pursued further analysis based on 156,000 patients enrolled in RCTs. In June 2011, the FDA released its finding that ARBs do not pose a greater risk of cancer relative to other hypertension drugs (Food and Drug Administration 2011). Although data is currently unavailable to determine how the FDA's 2010 warning impacted drug use, it seems likely that determining within a shorter time frame that ARBs do not cause cancer would generate important benefits to patients. The following sections of the paper describe our attempts to analyze this issue using observational data.

III. Sample Selection and Contamination

Our sample is constructed from individual claims data from Medicare parts A, B, and D between 2006 and 2009. We examine enrollees in standalone prescription drug plans (PDP) only because complete Medicare claims for enrollees in Part C are unavailable. Hypertension cases are classified by use of at least one drug commonly used to treat high blood pressure. Patients taking hypertension drugs for less than 30 days are excluded from our sample. We use the word "treatment" to refer to prescription drugs, but recognize there are other forms of treatment for hypertension, such as exercise and dieting. Ignoring unobservable activities like exercise will only be problematic for our results to the extent that these activities vary differentially across drug classes. One way such differential variation could occur is if certain drugs, due to higher prices, are consumed mainly by patients with higher incomes or education levels and such patients also exercise more often. The inability to control for individual-level socioeconomic factors is an important limitation of our study, and an issue to which we return in the discussion.

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drug). We did not find evidence of higher rates of diagnostic cancer exams among ARB users compared to other classes of drugs, adjusting for differences in age and sex across drug classes.

Sample Selection (Left-censoring)

It is common for patients to take hypertension drugs before age 65, when most beneficiaries become eligible for Medicare. We refer to those already on hypertension drugs when they are first observed in claims as "prevalent cases." For these patients, claims data do not permit the researcher to observe the duration of current treatment or patterns of past treatments prior to age 65. Clearly, this unobservability is problematic for classifying the presence and intensity of drug consumption. An alternative to this left-censoring problem is to restrict the sample to patients enrolled in 2006 who initiate hypertension treatment in 2007. We refer to this group as "incident cases" with a "1-year window." Since hypertension is a chronic condition, incident cases provide a cleaner comparison between ARBs and other drug classes because patients are likely first-time drug users.

Left censoring is a serious analytical problem for evaluating drug treatments, although not necessarily a serious empirical problem. With left censoring, a beneficiary's prior history in terms of both drug consumption and health outcomes is unobserved. Using external information on incident cases that can be linked to Medicare claims, such as the Health and Retirement Study (HRS), to impute "back-dated" information for prevalent cases is not an attractive option because the real analytical danger is the unobservability of switching between drug classes, to be discussed below. To the extent this unobserved switching is correlated with unobserved health status, using prevalent cases creates analytic problems for researchers that are difficult to surmount. Nevertheless, left censoring should not be an empirical problem because the number of incident cases will grow over time with more waves of data.

Contamination Bias

An RCT has a very powerful instrument (randomization) that has a strong effect on treatment assignment. Even in RCTs, however, patients often change treatment as their diseases get managed in the trial. In an observational study, the goal is to classify patients based on patterns of drug consumption, and to group patients with similar histories of drug consumption together into pseudo-treatment and control arms. For reasons of interpretability and statistical power, it would be ideal to have a small number of treatment and control groups. However, there are several challenges to a precise assignment of such groups. If there were only two competing therapies, classification would be relatively simple with only three possible combinations: drug 1 alone, drug 2 alone, or both drug 1 and drug 2. However, dimensionality problems quickly arise when more than a few drugs can be taken possibly in combination. Moreover, the order in which drugs are taken further complicates analysis. Some drugs may generally be taken as first-line therapy while others are prescribed as therapies of "last resort." Indeed, this is the case with hypertension; diuretics are often prescribed first, in line with the Joint National Committee's recommendation, and ARBs are more often prescribed after the patient has tried other drug therapies. By including more therapy groups, we trade off ease of interpretation and greater statistical power against contamination bias resulting from heterogeneity within any single group.

How serious is this problem? We find that most patients discontinue their initial drug treatment within the first year. Table 1 illustrates that over two-thirds of patients stop their initial treatment within 1 year for both prevalent and incident cases—where discontinuation is defined as having a gap in prescription coverage of more than 30 days. However, conditional on maintaining treatment through the first year, most continue through the second year. This pattern

suggests that side effects for a subset of patients or heterogeneity in treatment response may drive adherence patterns. It also suggests that the (selected) groups of patients who have maintained initial therapy for 1 year might make for adequate treatment and control groups.

However, polytherapy also poses a problem. Table 2 documents that conditional on not discontinuing initial treatment in the first year, between 14 and 26 percent of patients take at least one other hypertension drug at some point. Between 9 and 15 percent of such patients take at least two other drugs. So not only do people often discontinue their initial treatments, but those who adhere often take multiple treatments concurrently.

Roughly one third of incident cases are on the same, single monotherapy throughout the sample period (results not shown). The majority of these patients are on either beta blockers or ACE inhibitors. Among combinations of drugs, beta blockers with diuretics are the most common. However, the mix of drugs taken varies widely. We find rates of polytherapy are similar to those cited in the 2003 JNC report, which document more than two-thirds of patients require at least two drugs to control hypertension.

Other studies find greater rates of adherence than we document in Table 1, however. A meta-analysis by Matchar et al. (2007) finds 1-year adherence rates for ARBs and ACE inhibitors range between 40 and 60 percent. Relaxing our restriction that patients must not discontinue treatment for more than 30 days to be considered adhering to 90 days brings our estimates closer to other studies, but they are still at least 10 percentage points lower across drug classes. We suspect that the main driver behind our higher rates of discontinuation is the greater cost sharing under Part D. Simple preliminary analysis reveals that hypertension use decreases in the Doughnut Hole and this is consistent with more general work on drug consumption in Part D plans by Joyce, Sood, and Zissimopolous (2013).

As an example of how various drugs are used in sequence, Figure 1 displays the usage rates of drug treatments among people who ever take an ARB. Over forty percent of ARB users take another drug before starting ARBs, with most taking either diuretics or beta blockers. The figure clearly reveals that ACE inhibitors substitute for ARBs, as is clinically indicated. There is also evidence that diuretics tend to complement ARB use. Finally, many patients who discontinue ARB use subsequently take another drug.

The multitude and timing of drug consumption patterns issues raise the question of how to measure drug consumption in empirical models. We follow two different approaches. The simplest is to classify patients as using a drug if they have ever had at least two fills of the drug, even if they have previously taken other antihypertensives. We term this group "ever users." The second way is to classify patients based on the initial drug therapy prescribed. This represents an intent-to-treat approach. In both of these approaches, treatment is measured as an indicator function.[3] One might be tempted to restrict attention to incident cases who maintain monotherapy for at least 12 months. Doing so, however, would imply throwing away 71 percent of the observed incident cases and 84 percent of all cases (including prevalent hypertension), and this case deletion obviously occurs in a non-random way.

Some of this can be seen in Tables 3 and 4, which present descriptive statistics among "ever users" for prevalent and incident cases, respectively. These unconditional means reveal important differences by drug class. Cancer rates are lowest among ARB and ACE users. The fact that there is much less variation in cancer rates by class among incident users suggests that past history may be very important to determining outcomes. For example, the difference

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[3] A third approach is to model the cumulative exposure to the drug, using a function with an exponential rate of decay. We experimented with this approach by running a series of survival models measuring duration until cancer or stroke instead of using linear IV regressions. The results were qualitatively similar.

between the highest and lowest cancer rates among incident cases is 33.4 per 10,000, but is 81.8 per 10,000 among prevalent cases. Death rates are considerably lower for ARB users in both prevalent and incident cases.

IV. Selection into Treatment

One of the fundamental challenges to using observational data for CER is that treatment assignment is not random. Instead, drug treatment is a decision made between the physician and patient. The decision is likely based on many characteristics of the patient, some of which may be unobserved and may also affect cancer risk. We pursue two approaches to deal with selection into treatment: (1) examine how physician propensities to prescribe ARBs are correlated with health outcomes, and (2) run linear instrumental variables (IV) regressions using relative price to predict treatment choice. These approaches differ conceptually in the power they ascribe to each side of the physician-patient relationship; the first approach implicitly assumes the physician has control over which drug the patient takes and has latent preferences for prescribing certain drugs. By using the out-of-pocket (OOP) cost the patient pays for drugs as an instrument, the second approach implicitly treats the patient as the decision maker and price as the key factor influencing her decision.

Physician propensity to prescribe ARBs

The rationale behind our first approach using physician propensities is to view the initial physician-patient match as random. More precisely, if physicians have underlying propensities to prescribe certain hypertension drugs, conditional on patient characteristics, but patients cannot observe such propensities and thus do not choose physicians based on them, then we may view

the initial prescription as random. In this sense, physicians with a greater propensity to prescribe ARBs are analogous to the randomly assigned treatment group of an RCT (We fully recognize that many patients may shop for doctors in certain clinical circumstances, thereby violating this assumption. However, in the case of anti-hypertensive prescribing, such an assumption seems more plausible.)

To examine physician prescribing decisions, we limit our sample to include only initial therapy choice and do not allow for switching or adding therapies. To fully capture a physician's prescribing tendencies, the sample is restricted to physicians with at least 30 patients on hypertension drugs. Our final dataset for this analysis is composed of 1,176,311 patients and 25,477 physicians, with the average physician treating 46 patients for hypertension.

Following the theoretical model derived by Chandra and Staiger (2011), we model physician's propensity θ to prescribe ARBs based on the fact that some physicians might have a tendency to prescribe ARBs. We regress whether a patient receives ARBs against her chronic conditions, basic demographics, and the physician's propensity effect. Here θ is assumed to be a normally-distributed random effect with mean μ and σ^2. The functional form of $F(.)$ is taken to be logistic. We estimate the mixed-effects model and recover estimates of both μ and σ and use them to construct a posterior distribution of the estimated θ for each physician, which we then use to regress against death and cancer rates.

Results

Figure 2 plots the cancer rate for each physician's set of hypertension patients against the physician's propensity to prescribe ARBs. Our measure of cancer includes breast, prostate, lung, colorectal, and endometrial cancers, which account for the large majority of cancer deaths. Here, the diameter of each circle represents the number of patients with at least one claim to that particular physician. There appears to be a slight positive relationship between ARB use and cancer, which is statistically significant at the 1 percent level based on the large sample size. Perhaps more interestingly, Figure 3 displays a stronger negative relationship between death rates and the propensity to prescribe ARBs. This may be due to an omitted variable, or it may be explained by competing risks; ARBs may reduce increase cancer rates but reduce overall death rates due to fewer occurrences of some other disease(s). Our preliminary analysis has not revealed what this mechanism might be.

Taking these estimates as 'true' causal estimates, the natural question is how many cancer cases and deaths would be avoided (or incurred) if physicians lower their ARB prescribing tendencies. As an illustration, Table 5 displays the results of several simulations. If only the physicians in the right tail of the distribution were to reduce their prescribing rates to two standard deviations above the mean, the changes in outcomes are modest. If physicians above the 25th percentile reduced their prescribing rates to those of the 25th percentile, the implications are, not surprisingly, more dramatic. Doing so would decrease cancer rates by more than 10 percent and increase death rates by 6 percent. These are sizable numbers: saving 3,700 cancer cases through less ARB prescribing involves sacrificing 15,000 lives—hardly an attractive trade-off.

We do not, however, believe these are causal. When we replicate these scatterplots using pain as the dependent variable in the regressions—an outcome we assume is clinically

independent of ARB prescribing—we actually find a stronger relationship between pain and ARB use than that for cancer (Figure 4). This finding unfortunately raises questions about the validity of using physician treatment propensities to identify CER models, at least in the case of anti-hypertensives.

Linear IV Models

Our second approach follows more standard, economic techniques to deal with causality using observational data: instrumental variables regressions. We use the ratio of the average OOP cost of ARBs to the average OOP cost of ACE inhibitors at the regional level using cost sharing information at the plan level. In particular, we calculate the average OOP based on the copayment or the coinsurance rate of the plan multiplied by the average total cost of ARBs and ACE inhibitors at the regional level. We choose to examine ARBs with ACE inhibitors alone for a cleaner comparison since these two drugs represent the closest substitutes for one another. There is little reason to believe that the price difference between ARBs and ACE inhibitors at the regional level should be correlated with health outcomes.

ARBs are nearly always more expensive than ACE inhibitors. In fact, only 10 of 10,087 county-years have cheaper ARBs. On average, ARBs are over 4.5 times as expensive as ACE inhibitors and the standard deviation for this ratio is 1.5. As will be shown in the first stage regressions below, there is still enough variation for price to serve as a good predictor of ARB use.[4]

Our first stage regression is a probit of treatment on relative price, a vector of chronic conditions (diabetes, heart disease, heart failure, depression, Alzheimer's disease, glaucoma,

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[4] Other percentiles of the distribution of relative price are as follows: 1st percentile—2.1; 25th percentile – 3.7; 75th percentile – 5.5; 99th percentile – 9.6.

ischemic heart disease, chronic obstructive pulmonary disease, pelvic/hip fracture, osteoporosis, rheumatoid arthritis/osteoarthritis, cataracts, and chronic kidney disease), age, sex, county-level socioeconomic factors (percent home ownership, education levels, percent African American, average income, percent below poverty line, unemployment rate, percent married, and percent foreign born, all among adults), and state fixed-effects. The second stage is a linear probability model where the dependent variable is an indicator of the health outcome in the two years following the first hypertension prescription. The first hypertension prescription is calculated as the first ARB fill among ARB users or the first fill for another drug class among non-ARB users. We adjust standard errors in all regressions by clustering at the county-level.

Our rationale for examining the incidence of outcomes up to two years post-treatment is to adjust the duration of exposure for the sequencing of drug classes. As described earlier, some treatments, such as ARBs, are often initiated after trying other therapies first. This mechanically reduces the amount of time spent on ARBs compared to other drugs over the time period we observe and so there is also l ess time to be diagnosed with cancer or stroke.[5] We only examine patients with a full two-year window after they begin anti-hypertensives. Since our data extends to December 31, 2009, we exclude anyone beginning hypertension treatment in 2008 or later. By imposing a standard level of follow-up across all drug classes, this improves the comparability of different drugs even when some are routinely prescribed first.

The first stage regressions in Table 6 show that price is a strong predictor of ARB use. For both definitions of treatment, we run four sets of regressions that divide the population based on drug use. The first column includes all patients who are prevalent cases, representing the

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[5] We ran regressions with the number of days without the outcome as the dependent variable along the lines of Basu et al. (2007), but this does not get around the issue of drug therapy sequencing that is prevalent in our data. As part of this alternative analysis, we classified incident hypertension cases using shorter time windows to test whether later initiation of ARBs drove our findings but we did not find support for this hypothesis.

largest number of beneficiaries. The second column includes prevalent cases who either only take ARBs or only take ACE inhibitors. This dramatically reduces sample size, given the popularity of combination therapy. The third column includes all incident cases, comprising slightly more than 10 percent of prevalent cases. The fourth column is the smallest sample and includes only incident ARB or ACE monotherapy users. The comparisons between ARB users and the control group thus become progressively "cleaner" moving from left to right. The second and fourth columns are the same between the two treatment definitions because the ACE monotherapy group is restricted to never be on ARBs.

Figure 5 graphically displays the results of the first stage regressions for incident cases. The binary indicator for treatment (0 or 1) for each patient is plotted against the relative price of ARBs to ACE inhibitors. The downward sloping curve reveals that as ARBs become more expensive, more patients take ACE inhibitors.

There appears to be little evidence that ARBs lead to cancer based on the second-stage regressions. Table 7 presents the results using the "ever use" treatment definition. The point estimate on predicted treatment is negative and statistically significant among all prevalent cases (column 1), with ever using ARBs decreasing the probability of cancer within two years by 1.2 percent. However, the estimate becomes positive and statistically significant among monotherapy users (column 2), increasing the probability of cancer by 2.8 percent. Among incident cases, the point estimates on predicted treatment are positive, but not statistically significant. So as the sample become 'cleaner,' the evidence that ARBs are associated with cancer becomes weaker. Using the intent-to-treat definition as shown in Table 8, the evidence on a link between ARB use and cancer remains weak. Under both treatment definitions, there is

more consistent evidence that ARB users have more strokes, although it is fair to question whether a 5 percent significance level is an appropriate threshold given the large sample size.

V. Robustness checks

Subsample analysis: healthy patients

Healthy patients serve as a first robustness check. Such patients arguably represent cleaner treatment and control groups than the full sample that includes people with a variety of health conditions since healthy patients likely also have fewer unobserved conditions that may be correlated with both ARB use and the outcomes. We classify healthy patients as beneficiaries without any of the 13 CCW chronic conditions measured, which comprises 28 percent of the full sample.

Price is still statistically significant in the first stage IV regressions as shown in Appendix Table 1. However, the F-statistic is lower than in the baseline regressions and below 10 in three of the four specifications. This may be due to the smaller sample size or suggest that chronic conditions are important to explain treatment patterns. In the second-stage regressions, the estimates on predicted treatment are lower than in the baseline regressions and very imprecise. To the extent that the healthy subsample produces more similar control and treatment groups, the IV regressions in Appendix Tables 2 and 3 suggest that there is little meaningful or statistically significant difference between ARBs and other hypertension drugs.

Falsification test: pain

As another check, we rerun our IV regressions with a diagnosis of pain within 1 year of starting hypertension treatment as the dependent variable. Since hypertension drugs should have

little impact on the diagnosis of pain, the magnitude of any association between ARBs and pain should be lower if the effects with cancer and stroke are real. We consider ICD-9 codes for sprains and strains (excluding ankle and back) and open wounds (excluding head wounds) in diagnosing pain. ARBs are associated with less pain as shown in Appendix Table 4, but the magnitude of the coefficient estimates are similar to the results for cancer and stroke, and in some cases larger.[6] As the samples become cleaner, the estimates become smaller in magnitude and less precise. We find a similar pattern if we use the subsample of healthy patients to estimate the incidence of pain (results not shown). Perhaps these results are due to the omitted variable bias, such as individual-level socioeconomic factors, which may drive both treatment choice and the number of office visits (and thus diagnoses) of a patient. Since ARBs are more expensive than other antihypertensives (there are no generic ARBs), one might speculate that higher income patients are more likely to take ARBs. There is also evidence that higher income white Medicare beneficiaries have fewer hospital discharges than lower income beneficiaries (Gornick et al. 1996, Gornick 2003). So if higher incomes patients are also less likely to receive a pain diagnosis due to fewer hospital admissions, then the omission of individual income biases our estimates downward. Overall, our falsification test fails, casting doubt on the validity of the IV regressions of cancer and stroke.

VI. Comparison with Randomized Controlled Trials

The results of RCTs and IV regressions are both relevant for policy, but measure different quantities. In general, RCTs have found weak evidence of any difference in strokes among ARB users compared to users of other hypertension drugs (Wang et al. 2007, Dahlof et

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[6] In case pain followed or preceded a stroke, we also recoded any diagnosis of pain to 0 within a one-month window of a stroke diagnosis. The results were similar as reported in Table 14.

al. 2002, Straus and Hall 2009). RCTs measure the average treatment effect (ATE) while IV regressions measure the local average treatment effect (LATE). Importantly, the parameter in IV regressions is identified only by the subgroup of observations impacted by changes in the instrument (price in our example). This implies that IV regressions are only useful for drawing inferences to people who are impacted by price change. For example, LATE tells us nothing about people who would never consider changing drug treatments because of side effects.

Although RCTs are viewed (rightly) as the gold standard in evaluation, there may still be unobserved behavioral changes between treatment and control groups that bias results. In RCTs, for example, individuals may not always comply with the therapy assigned to them. In comparing the treatment and control groups, assuring that both groups comply at the same rates is critical to obtaining unbiased estimates (Hamilton, 2001). The implication for using observational data is that researchers should also compare groups that are most likely to comply with the therapy prescribed. Additionally, compliance may also depend on whether an individual believes to be assigned to the treatment or control arms of an RCT. Malani (2006) builds a model demonstrating the importance of placebo-effects, where individuals believing to be assigned to the treatment arm are more likely to comply. Using data on the probabilities of assignment to the treatment group of various RCTs, he finds empirical support for this model. So behavior changes within RCTs may be just as important as behavioral patterns in observational data.

VII. Conclusion

This paper highlights some of the perils and pitfalls of using observational data for CER. We document that not only is the lack of randomization a problem, but the existence of competing therapies and prevalence of polytherapy also poses challenges to researchers. To deal

with sample selection problems, we restrict our sample to monotherapy users and incident hypertension cases. While this allows us to sidestep the unobservability of prior drug use, it comes at the price of a sample that is not only small, but also not representative of all drug users. This partly defeats one of the key assets of observational data, which is the potential for greater representativeness than RCTs.

Our empirical approaches to tackle non-random treatment assignment are strong conceptually, albeit unsuccessful. Our first approach of using physician propensities is an innovative solution to initial therapy choice, but does not pass our falsification test using pain. Our second approach using conventional IV methods finds price to be a strong predictor of treatment, but our results are often sensitive to the sample analyzed. Overall, we find little evidence from our IV regressions that ARBs are associated with cancer and weak evidence that ARBs are positively related to strokes. Again, the fact that estimates from our pain regressions are often larger than estimates from cancer or stroke suggest our IV estimates are not causal.

While claims data, in principle, offer several advantages to evaluating drug treatments over RCTs, researchers must be careful to deal with left-censoring, contamination bias, and selection into treatment. By illustrating these pitfalls with the case of ARBs for hypertension, our paper provides a cautionary tale for researchers interested in using claims data for CER. Nevertheless, our results suggest that relative price is a good candidate for an instrument to deal with non-random treatment assignment, which helps overcome perhaps the fundamental disadvantage of observational data.

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Table 1. Adherence of initial treatment by drug class

Prevalent cases

Therapy	Initial treatment	On treatment through 1 year	% of initial users	On treatment through 2 years	% of initial users
ACE inhibitors	608,641	78,932	13	51,973	9
ARBs	300,583	32,357	11	20,193	7
Diuretics	809,900	130,917	16	98,432	12
Calcium Channel Blockers	474,429	63,824	13	41,692	9
Beta blockers	1,010,950	219,443	22	179,434	18
Other antihypertensives	48,119	7,809	16	5,327	11

Incident cases

Therapy	Initial treatment	On treatment through 1 year	% of initial users	On treatment through 2 years	% of initial users
ACE inhibitors	152,561	40,033	26	36,814	24
ARBs	56,005	11,111	20	9,903	18
Diuretics	181,630	54,289	30	50,413	28
Calcium Channel Blockers	91,490	23,144	25	20,849	23
Beta blockers	264,639	84,836	32	78,407	30
Other antihypertensives	9,216	2,423	26	2,144	23

Table 2. Combination therapy by drug class

Total Number of Therapies Ever Taken, Incidence Cases	On initial treatment through 1 year	On 1+ other drugs during 1st year	% of 1-year users	On 2+ other drugs during 1st year	% of 1-year users
ACE inhibitors	78,932	17,692	22	11,033	14
ARBs	32,357	6,060	19	4,912	15
Diuretics	130,917	34,060	26	16,810	13
Calcium Channel Blockers	63,824	10,360	16	5,596	9
Beta blockers	219,443	51,699	24	26,947	12
Other antihypertensives	7,809	1,088	14	765	10

Table 3. Descriptive Statistics, Prevalent Cases

Therapy		age	sex (1=female 0=male)	cancer (per 10,000)	stroke (per 10,000)	death (per 10,000)	avg. # chronic conditions
ARBs	mean	77.5	0.722	182.0	1818.4	526.7	4.99
(N=184,067)	s.d.	7.4	0.448	1336.9	3857.1	2233.7	2.30
ACE inhibitors	mean	77.5	0.647	187.2	1907.1	736.1	4.78
(N=406,100)	s.d.	7.6	0.478	1355.5	3928.6	2611.3	2.33
Beta blockers	mean	78.1	0.677	251.0	1947.2	920.8	5.03
(N=648,429)	s.d.	7.6	0.468	1564.3	3959.9	2891.4	2.27
Calcium channel blockers	mean	78.2	0.725	251.6	1981.9	840.4	4.93
(N=496,334)	s.d.	7.7	0.447	1566.1	3986.4	2774.5	2.31
Other antihypertensives	mean	78.7	0.759	263.8	2897.2	1084.8	5.59
(N=85,437)	s.d.	7.7	0.428	1602.6	4536.4	3109.9	2.34
Diuretics	mean	78.4	0.722	272.2	1821.3	1392.4	4.94
(N=909,615)	s.d.	7.9	0.448	1627.3	3859.5	3461.9	2.34

Table 4. Descriptive Statistics, Incident Cases

Therapy		age	sex (1=female 0=male)	cancer (per 10,000)	stroke (per 10,000)	death (per 10,000)	avg. # chronic conditions
ARBs	mean	77.4	0.669	119.7	1509.6	315.0	4.33
(N=23,143)	s.d.	7.3	0.470	1087.4	3580.2	1746.6	2.29
ACE inhibitors	mean	77.4	0.587	124.5	1613.5	452.3	4.19
(N=63,763)	s.d.	7.4	0.492	1108.9	3678.5	2078.0	2.29
Beta blockers	mean	78.3	0.615	144.2	1705.1	620.5	4.61
(N=104,901)	s.d.	7.5	0.487	1192.2	3760.8	2412.5	2.26
Calcium channel blockers	mean	78.4	0.660	153.1	1773.3	543.0	4.43
(N=64,267)	s.d.	7.6	0.474	1227.8	3819.5	2266.1	2.31
Other antihypertensives	mean	79.2	0.680	148.9	2748.4	842.4	5.06
(N=9,268)	s.d.	7.8	0.467	1211.0	4464.6	2777.6	2.36
Diuretics	mean	78.7	0.663	148.6	1567.7	932.3	4.45
(N=130,572)	s.d.	7.9	0.473	1210.1	3635.9	2907.5	2.36

Table 5. Simulations of Reducing Prescriber Propensity

Cancer	# predicted cancer cases	% of total	Decreased # of cancer cases	% of cancer cases
No restrictions	39,530	3.36%	NA	NA
Restrict those with Propensity in the top 75% to 25%	35,822	3.05%	3,708	10.35%
Restrict those with Propensity greater than 2 std dev	39,455	3.35%	75	0.19%
Restrict those with Propensity greater than 1 std dev	39,096	3.32%	434	1.10%

Death	# predicted deaths	% of total	Increased # of deaths	% of deaths
No restrictions	227,415	19.33%	NA	NA
Restrict those with Propensity in the top 75% to 25%	242,489	20.61%	15,074	6.22%
Restrict those with Propensity greater than 2 std dev	227,718	19.36%	303	0.13%
Restrict those with Propensity greater than 1 std dev	229,179	19.48%	1,764	0.77%

Table 6. First Stage IV Regressions

TREATMENT DEFINITION: PATIENT EVER USED DRUG

	Prevalent cases		Incident cases	
	(1) All drug users	(2) ACE or ARB monotherapy only	(3) All drug users	(4) ACE or ARB monotherapy only
Price	-0.039	-0.035	-0.024	-0.039
	(-60.77)	(-16.83)	(-12.36)	(-7.51)
F-stat	520.99	31.35	55.09	7.75
N	1,406,463	95,386	153,904	19,466

TREATMENT DEFINITION: INTENT TO TREAT

	Prevalent cases		Incident cases	
	(1) All drug users	(2) ACE or ARB monotherapy only	(3) All drug users	(4) ACE or ARB monotherapy only
Price	-0.018	-0.035	-0.020	-0.039
	(-33.02)	(-16.83)	(-11.87)	(-7.51)
F-stat	271.5	31.55	40.35	7.75
N	1,406,469	95,386	153,904	19,466

Cluster-adjusted robust *T*-statistics in parentheses. Regressions also include indicators for age, sex, diabetes, heart disease, heart failure, depression, Alzheimer's disease, glaucoma, ischemic heart disease, chronic obstructive pulmonary disease, pelvic/hip fracture, osteoporosis, rheumatoid arthritis/osteoarthritis, cataracts, and chronic kidney disease, state fixed effects, and the following county-level variables: percent home ownership, percent with high school degree, percent with some college or 2-year degree, percent with 4-year college degree or beyond, , percent African American, average income, percent below poverty line, unemployment rate, percent married, and percent foreign born, all among adults.

Table 7. Second stage IV regressions: Ever-user treatment definition

Cancer	Prevalent cases		Incident cases	
	(1)All drug users	(2) ACE or ARB monotherapy only	(3)All drug users	(4) ACE or ARB monotherapy only
Treatment	-0.012	0.0288	0.0057	0.0273
	(-1.90)	(2.97)	(0.43)	(1.73)
N	1,406,463	95,386	153,904	19,466

Stroke	Prevalent cases		Incident cases	
	(1)All drug users	(2) ACE and ARB users only	(3)All drug users	(4) ACE and ARB users only
Treatment	0.0154	0.0268	0.0234	0.0501
	(1.65)	(2.46)	(1.47)	(2.71)
N	1,406,469	95,386	153,904	19,466

Cluster-adjusted robust *T*-statistics in parentheses. Regressions also include indicators for age, sex, diabetes, heart disease, heart failure, depression, Alzheimer's disease, glaucoma, ischemic heart disease, chronic obstructive pulmonary disease, pelvic/hip fracture, osteoporosis, rheumatoid arthritis/osteoarthritis, cataracts, and chronic kidney disease, state fixed effects, and the following county-level variables: percent home ownership, percent with high school degree, percent with some college or 2-year degree, percent with 4-year college degree or beyond, , percent African American, average income, percent below poverty line, unemployment rate, percent married, and percent foreign born, all among adults.

Table 8. Second stage IV regressions: Intent-to-Treat treatment definition

Cancer	Prevalent cases		Incident cases	
	(1)All drug users	(2) ACE or ARB monotherapy only	(3)All drug users	(4) ACE or ARB monotherapy only
Treatment	-0.0139	0.0288	-0.002	0.0273
	(-1.26)	(2.97)	(-0.13)	(1.73)
N	1,406,469	95,386	153,904	19,466

Stroke	Prevalent cases		Incident cases	
	(1)All drug users	(2) ACE and ARB users only	(3)All drug users	(4) ACE and ARB users only
Treatment	0.041	0.0268	0.0249	0.0501
	(2.40)	(2.46)	(1.32)	(2.71)
N	1,406,469	95,386	153,904	19,466

Cluster-adjusted robust T-statistics in parentheses. Regressions also include indicators for age, sex, diabetes, heart disease, heart failure, depression, Alzheimer's disease, glaucoma, ischemic heart disease, chronic obstructive pulmonary disease, pelvic/hip fracture, osteoporosis, rheumatoid arthritis/osteoarthritis, cataracts, and chronic kidney disease, state fixed effects, and the following county-level variables: percent home ownership, percent with high school degree, percent with some college or 2-year degree, percent with 4-year college degree or beyond, , percent African American, average income, percent below poverty line, unemployment rate, percent married, and percent foreign born, all among adults.

Appendix Table 1. First stage regressions: healthy subpopulation

TREATMENT DEFINITION: PATIENT EVER USED DRUG

	Prevalent cases		Incident cases	
	(1) All drug users	(2) ACE or ARB monotherapy only	(3) All drug users	(4) ACE or ARB monotherapy only
Price	-0.038	-0.019	-0.032	-0.038
	(-21.47)	(-3.95)	(-6.53)	(-3.03)
F-stat	60.11	6.69	9.26	2.22
N	175,346	14,667	22,057	3,259

TREATMENT DEFINITION: INTENT TO TREAT

	Prevalent cases		Incident cases	
	(1) All drug users	(2) ACE or ARB monotherapy only	(3) All drug users	(4) ACE or ARB monotherapy only
Price	-0.014	-0.019	-0.023	-0.038
	(-9.69)	(-3.95)	(-5.51)	(-3.03)
F-stat	44.43	6.69	7.01	2.22
N	175,348	14,667	22,057	3,259

Cluster-adjusted robust T-statistics in parentheses. Regressions also include indicators for age and sex, state fixed effects, and the following county-level variables: percent home ownership, percent with high school degree, percent with some college or 2-year degree, percent with 4-year college degree or beyond, , percent African American, average income, percent below poverty line, unemployment rate, percent married, and percent foreign born, all among adults.

Appendix Table 2. Second stage IV regressions: Ever-user treatment definition, healthy subpopulation

Cancer	Prevalent cases		Incident cases	
	(1)All drug users	(2) ACE or ARB monotherapy only	(3)All drug users	(4) ACE or ARB monotherapy only
Treatment	-0.0209	0.0071	0.0068	0.0399
	(-4.00)	(0.51)	(0.41)	(1.27)
N	175,346	14,667	22,057	3,259

Stroke	Prevalent cases		Incident cases	
	(1)All drug users	(2) ACE and ARB users only	(3)All drug users	(4) ACE and ARB users only
Treatment	-0.0067	-0.0006	-0.0022	0.0054
	(-1.88)	(-0.09)	(-0.17)	(0.32)
N	175,346	14,667	22,057	3,259

Cluster-adjusted robust *T*-statistics in parentheses. Regressions also include indicators for age and sex, state fixed effects, and the following county-level variables: percent home ownership, percent with high school degree, percent with some college or 2-year degree, percent with 4-year college degree or beyond, , percent African American, average income, percent below poverty line, unemployment rate, percent married, and percent foreign born, all among adults.

Appendix Table 3. Second stage IV regressions: Intent-to-treat treatment definition, healthy subpopulation

Cancer	**Prevalent cases**		**Incident cases**	
	(1)All drug users	(2) ACE or ARB monotherapy only	(3)All drug users	(4) ACE or ARB monotherapy only
Treatment	-0.0076	0.0071	0.0134	0.0399
	(-0.90)	(0.51)	(0.71)	(1.27)
N	175,348	14,667	22,057	3,259

Stroke	**Prevalent cases**		**Incident cases**	
	(1)All drug users	(2) ACE and ARB users only	(3)All drug users	(4) ACE and ARB users only
Treatment	0.0068	-0.0006	0.0028	0.0054
	(1.08)	(-0.09)	(0.18)	(0.32)
N	175,348	14,667	22,057	3,259

Cluster-adjusted robust *T*-statistics in parentheses. Regressions also include indicators for age and sex, state fixed effects, and the following county-level variables: percent home ownership, percent with high school degree, percent with some college or 2-year degree, percent with 4-year college degree or beyond, , percent African American, average income, percent below poverty line, unemployment rate, percent married, and percent foreign born, all among adults.

Appendix Table 4. Falsification test: Second-stage regressions for pain

Ever users	Prevalent cases		Incident cases	
	(1)All drug users	(2) ACE and ARB users only	(3)All drug users	(4) ACE and ARB users only
Treatment	-0.0511	-0.0255	-0.0249	-0.0248
	(-5.11)	(-1.95)	(-1.65)	(-1.19)
N	1,406,469	95,386	153,904	19,466

ITT	Prevalent cases		Incident cases	
	(1)All drug users	(2) ACE and ARB users only	(3)All drug users	(4) ACE and ARB users only
Treatment	-0.0718	-0.0255	-0.0329	-0.0248
	(-4.42)	(-1.95)	(-1.73)	(-1.19)
N	1,406,469	95,386	153,904	19,466

Cluster-adjusted robust *T*-statistics in parentheses. Regressions also include indicators for age, sex, diabetes, heart disease, heart failure, depression, Alzheimer's disease, glaucoma, ischemic heart disease, chronic obstructive pulmonary disease, pelvic/hip fracture, osteoporosis, rheumatoid arthritis/osteoarthritis, cataracts, and chronic kidney disease, state fixed effects, and the following county-level variables: percent home ownership, percent with high school degree, percent with some college or 2-year degree, percent with 4-year college degree or beyond, , percent African American, average income, percent below poverty line, unemployment rate, percent married, and percent foreign born, all among adults.

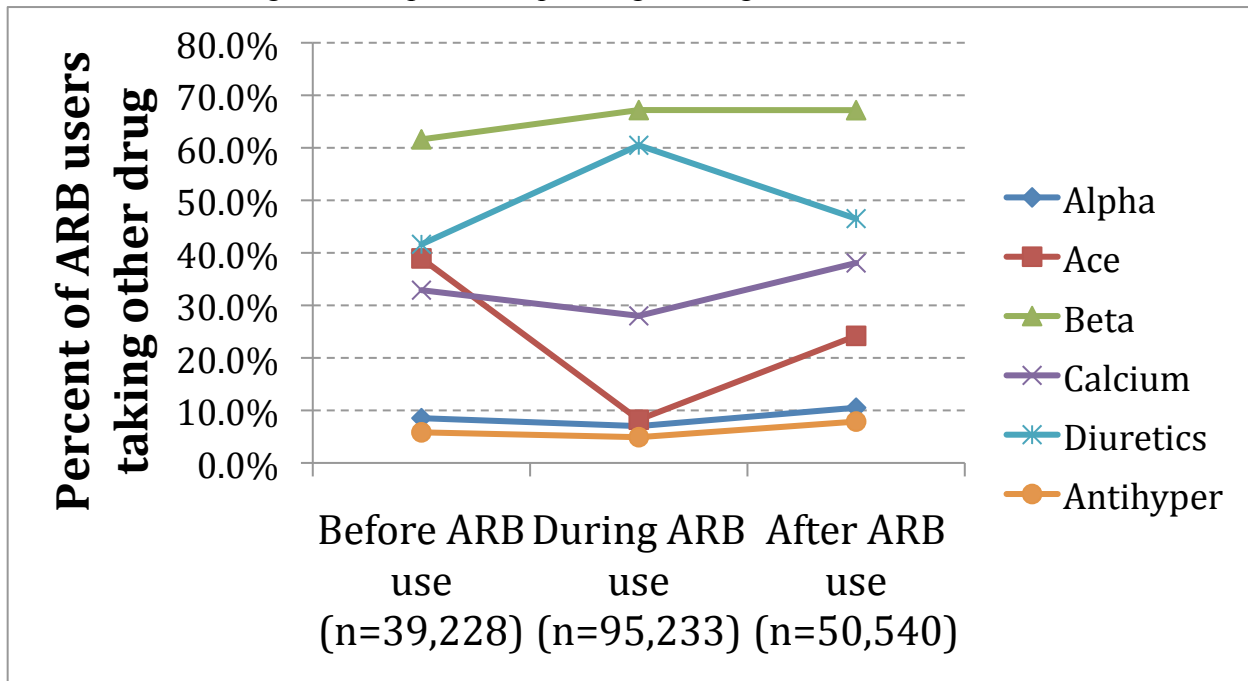Figure 1. Empirical Sequencing of Drug Use for ARB Users

Figure 2. Unconditional Relationship Between Cancer Rate and Propensity to Prescribe ARBs
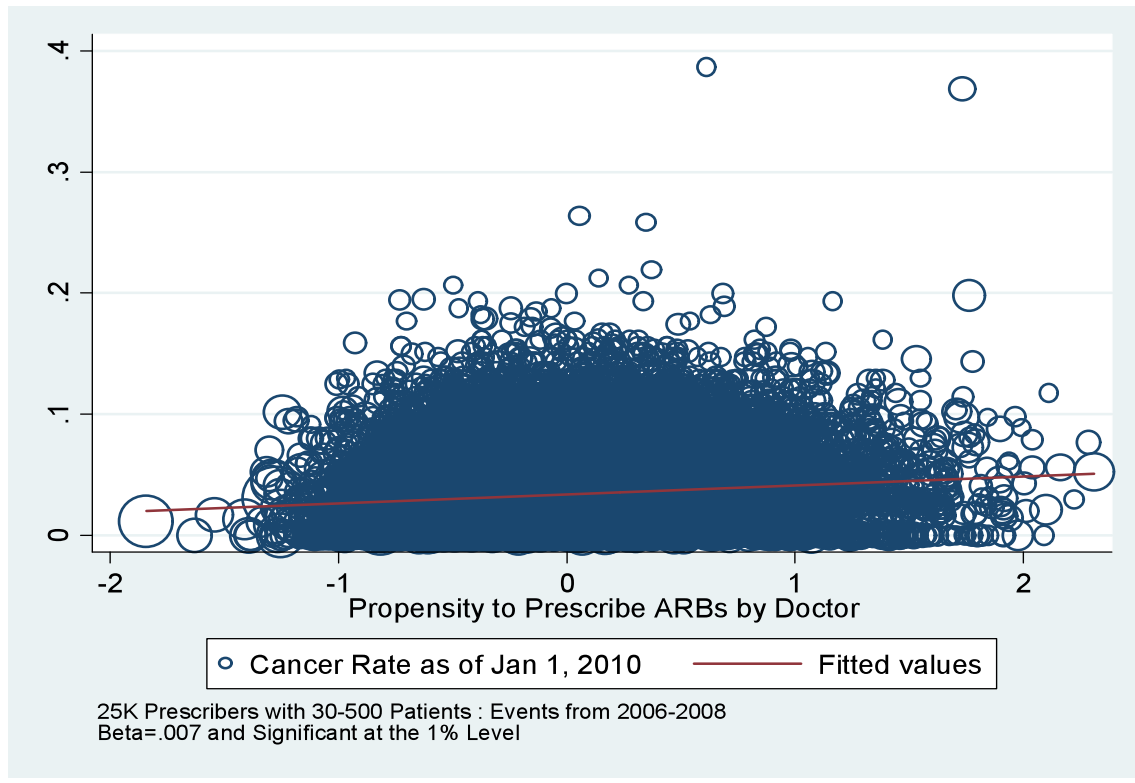

25K Prescribers with 30-500 Patients : Events from 2006-2008
Beta=.007 and Significant at the 1% Level

Figure 3. Unconditional Relationship Between Death Rate and Propensity to Prescribe ARBs

25K Prescribers with 30-500 Patients : Events from 2006-2008
Beta=-.03 and Significant at the 1% Level
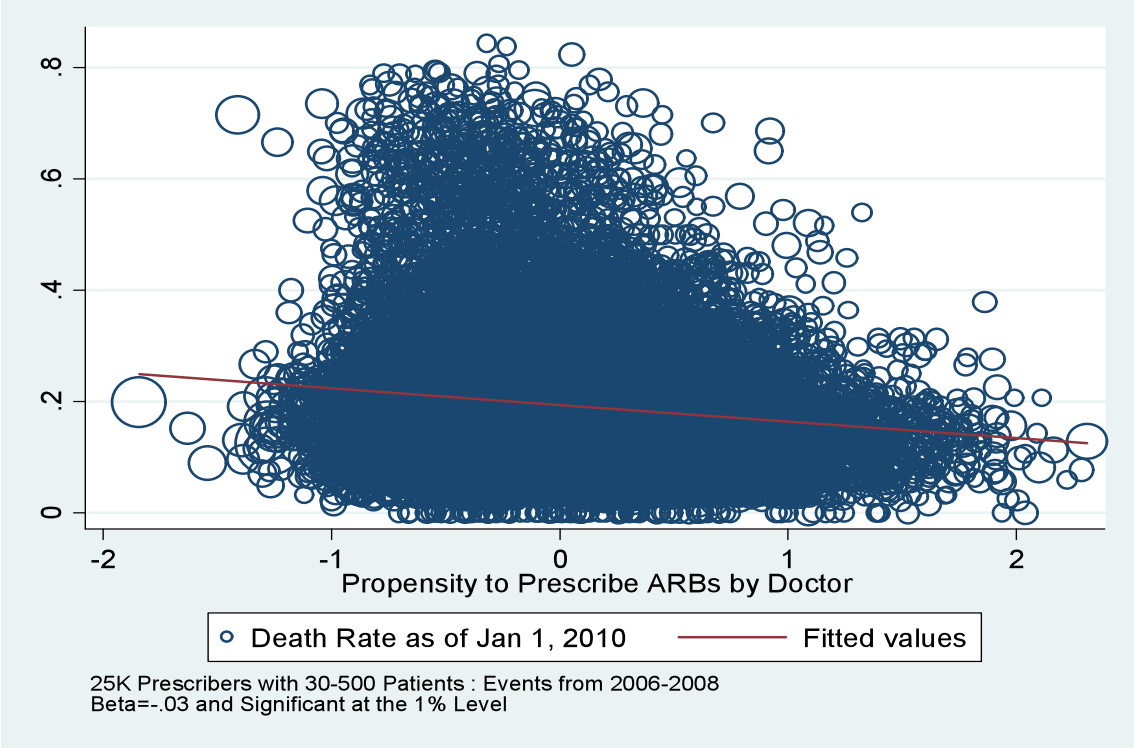
Figure 4. Unconditional Relationship Between Pain Rate and Propensity to Prescribe ARBs

25K Prescribers with 30-500 Patients : Events from 2006-2008
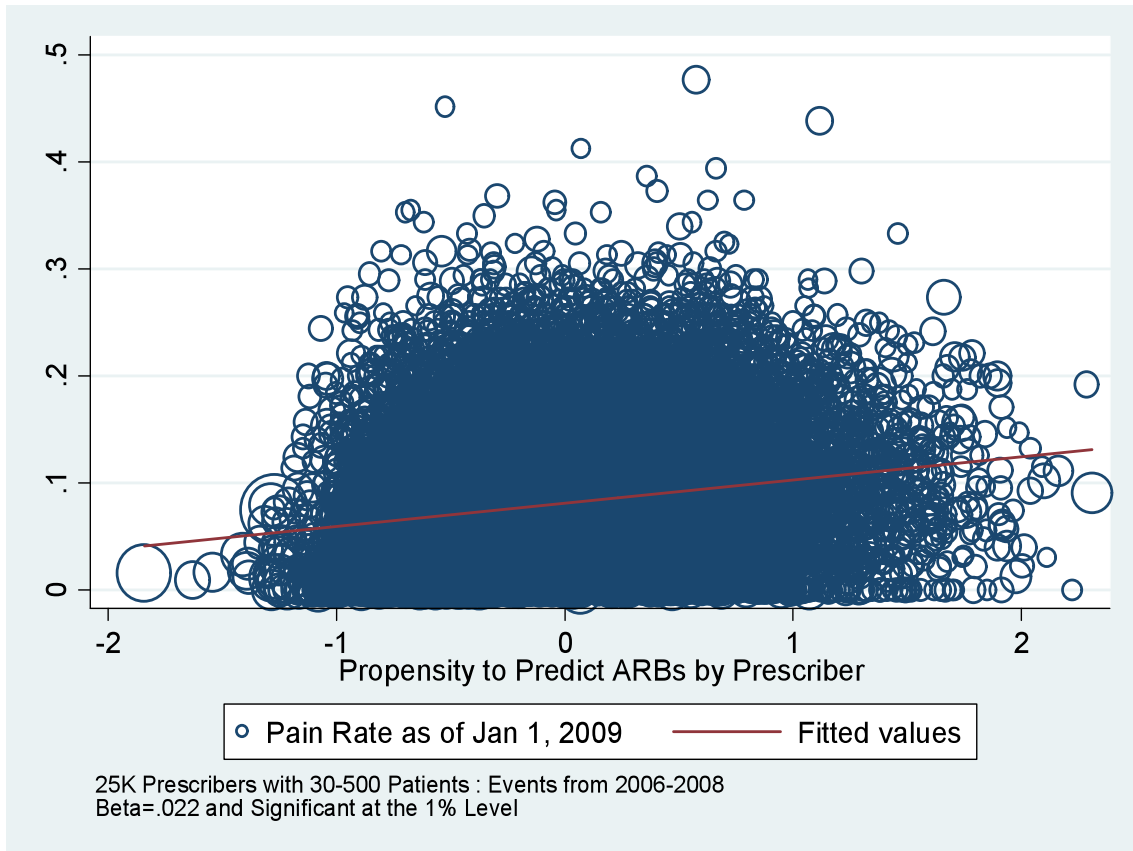Beta=.022 and Significant at the 1% Level

Figure 5. Unconditional Relationship Between ARB Use and Relative Price