Technological Advance in Cholesterol Medication Meets Physician Learning: A Non-Parametric Bounding Approach

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Abstract

In this paper we investigate the relation between technological advance, in terms of product innovation or information shock, and learning of physicians and patients. We focus on the case of statins, a medication used to manage high cholesterol levels, for which newly produced evidence altered the scientific consensus regarding their side effects. Early common wisdom was that statins may cause liver damages and therefore patients should regularly test for changes in liver enzyme levels. At the end of 2010 GREACE, a randomized controlled trial, suggested instead that the medication could be continued despite elevated liver enzymes, and then patients on this cure need not be tested regularly. This major change gives us the opportunity to test how physicians prescription and testing behaviour and patients adherence to therapy respond to a technological advance. We test our model using a unique dataset representative of the Italian population, that links patients to doctors over the period 2003-2014. To take into account the possible non-random sorting of patients into specific medication, we exploit a randomly assigned instrument. A distinctive feature of our analysis is the non-parametric bounding approach, that takes into account the selection mechanism (unlike the OLS) and refers to the entire population (unlike the standard instrumental variable). Our results show that doctors promptly respond to technological advance.

JEL classification: I18, J18, C21
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*We thank ... Replication files and additional results will be available at the webpage: http://sites.google.com/site/domdepalo/. The views expressed in this paper are those of the authors and do not imply any responsibility of their institutions. Corresponding address: Domenico Depalo, Banca d'Italia, Economics and Statistics Department, Via Nazionale, 91 - 00184 Roma, Tel.: 39-06-4792 5989, e-mail: domenico.depalo@bancaditalia.it

1 Introduction

Medical practice is, in theory, based on developments in medical science. Such developments may include new drug products, new knowledge about physiological mechanism, and new information about existing technologies. Important new technological developments should in principle lead to changes in optimal medical practice by physicians. This is especially true if the new evidence convincingly contradicts prior common medical wisdom. Patients behavior such as adherence to prescribed therapy may, in principle, also change in response to new technological developments. This may happen because patients themselves become aware of the new evidence, or because of changes in prescribed therapy chosen by their doctor that make side effects appear less likely or less severe. In short, important new technologies and new medical information should disrupt medical practice. In this paper, we analyze the effects of an information shock that altered the scientific consensus on the side effect profile associated with statin medication, an important pharmaceutical product used to manage hypercholesterolemia.

Hypercholesterolemia is defined as high levels of cholesterol in the blood stream. High levels of low density lipoprotein (LDL) cholesterol is of medical concern because patients with high LDL levels are more likely to develop atherosclerosis and associated heart disease. Statin medications are among the most commonly used pharmaceutical products both because the prevalence of hypercholesterolemia is high, and because these medications have been shown in randomized trials to be safe and effective way to reduce serum LDL levels and reduce mortality. For instance, the 1994 Scandinavian Simvastatin Survival Study (among the earliest large randomized trials of statin medications) found that patients randomized to statins enjoyed a 35% reduction in LDL cholesterol and a 30% reduction in mortality hazard relative to placebo controlled patients

(Scandinavian Simvastatin Survival Study Group, 1994).

However, like every drug, statin medications can cause adverse side effects. In the case of statins, an increase in blood levels of liver enzymes like alanine aminotransferase (ALT) – which in some cases indicate liver damage – was historically seen as the most common side effect. An early randomized study found fifteen times higher rates of elevated liver enzymes among patients assigned to high dose statins relative to placebo or low dose statins (Bradford et al., 1991). Physicians viewed this evidence of side effects as salient; in studies of statin initiation, physicians were found to be reluctant to prescribe statin therapy because of the risk of hepatotoxicity (Rzouq et al., 2010). A finding of elevated liver function tests (LFTs) might lead a physician to recommend discontinuing statin therapy, lowering statin doses, or changing the stain molecule prescribed (Calderon et al., 2010). Given the concern about liver damage, until 2011 clinical guidelines suggested that physicians who prescribe statins for their patients should regularly test for changes in liver enzyme levels (McKenney et al., 2006; Gillett and Norrell, 2011). In fact, even in the early days of statin medications, there were non-randomized studies that found that elevated liver function tests did not necessarily indicate permanent liver damage as it was readily reversible (Mölgaard et al., 1991). However, given the evidence from the early statin RCTs, the general consensus in the medical community was that statins had the potential to cause this side effect.

In late 2010, the GREACE study of statin medication use in a population of Greek patients with abnormal liver tests was published in *Lancet*, a leading medical journal (Athyros et al., 2010). The study showed that despite elevated liver enzyme levels, patient randomized to statin medications actually experienced *lower* rates of liver enzymes relative to control patients, with a better cardiovascular response. This study was striking because its results were so

unexpected given what most physicians believed about the effects of statins. If patients with liver disease show improvements in liver function after statin therapy is started, then the prior conventional wisdom that statins can cause low grade liver damage in patients without liver disease is most likely incorrect. This in turn means that a finding of elevated liver function tests in the context of statin therapy should not be taken as evidence that the statin medication is leading liver damage. The GREACE results suggested that statin medications could be continued despite elevated liver enzymes, and hence that patients on statins need not to be tested regularly with LFTs (Pastori et al., 2015).[1]

Ultimately, this reasoning led experts to reverse the recommendations in previous guidelines. American practice guidelines were modified in 2014 to recommend that patients on statins did not need have their liver enzyme levels checked regularly. They suggest instead that liver function tests are needed only when statin therapy is initiated and when the statin dose or type of statin prescribed is changed (Bays, Cohen, Chalasani, Harrison, and The National Lipid Association's Statin Safety Task Force, Bays et al.). Though the Italian guideline for ordering liver function tests in the context of statin therapy has not changed, the GREACE study was widely known among Italian physicians.[2]

Our main aim with this study is to test how physicians prescription and testing behavior changed in response to changing evidence about the side effect profiles of statin medication in an Italian context. Given the history we recount above, we divide our data into three distinct periods: (1) an early period when most physicians believed that statins may cause liver damage, and hence regular liver function testing is necessary; (2) a period where some observational studies suggested that statins might not be the cause of liver function abnormalities in

[1] The GRAECE study did not contradict a previous finding that in some rare cases, statins can cause rhabdomyolosis, a serious condition involving muscle degradation that can lead to extensive liver and kidney damage. This rare side effect cannot typically be prevented or detected early with regular liver function tests.

[2] Personal communication with Dr. Cortese, lipidologist at the University of Rome.

patients taking statins; and (3) after the publication of the GREACE trial, which established that statins may actually help patients with liver function abnormalities. A secondary aim of this paper is to understand how patient adherence to therapy changed in response to this changing evidence. Together, we aim to estimate how both doctors and patients react to new information in a discrete setting.

To do this, we analyze data from a large longitudinal sample of Italian patients who have been diagnosed with high cholesterol levels between 2004 and 2014. The dataset includes the identity of the primary care physician who manages the patient's statin prescription during this period. The data set includes biometric information, such as the measured LDL cholesterol level, as well as information on the identity and dose of statins prescribed at each time point, and information about the ordering of lab tests such as liver function tests.

To generate estimates that may be interpreted causally from this observational database, we employ recently developed econometric bounding methods that permit us to explore the effects of progressively stronger assumptions (Manski, 1990; Shaikh and Vytlacil, 2011). We believe that the methods we apply in this paper could be widely and routinely applied to other prescription drugs in real world as a way to augment the information available from randomized trials. The bounding methods we employ – in contrast to more traditional point estimators employed by randomized and observational studies alike – permit us to measure the range of treatment effects that are consistent with observational data without the strong structural assumptions that are necessary to guarantee point identification.

The rest of the paper is organized as follows. Section 2 presents our data set. Section 3 illustrates a simple principal-agent theoretical model which helps

the understanding the economic insights behind our empirical results. Section 4 provides a brief description of the recent econometric literature on bounding methods, and develops a small extension of these methods to continuous outcomes that we employ in this paper. Section 5 presents our quantitative results, and finally, in Section 6, we conclude providing some reflections on what our results suggest about the role of randomized evidence in medicine..

2 Data and Summary Statistics

In this section, we describe our dataset and inclusion and exclusion criteria, our measures of drug potency and patient adherence to therapy, and finally we present some important summary statistics about our population.

2.1 Italian Health Search Database

Our empirical analysis is based on data obtained from the Health Search Database (HSD), a longitudinal observational database collected by the Italian College of General Practitioners (SIMG) since 1998. The HSD contains patient level data from computer-based patient records reported by General Practitioners (GPs) throughout Italy. GP participation is on a voluntary basis, but nevertheless GP represented are in fact representative of the National Health Service (NHS) regional organization. The number of patients tracked in the HSD are in proportion to the size of the Italian adult population within each region (Fabiani et al., 2004).[3]

Patient data are linked through a unique anonymous identifier to drug prescriptions, clinical events and diagnoses, hospital admissions, and causes of death. Information available include prescription dispensing date and drug char-

[3]Data have been collected routinely since 2000. More details on the representativeness of the database can be found at `https://www.healthsearch.it/` (Official website of the HSD project).

acteristics (Anatomical Therapeutic Chemical or ATC code which indicates the quantity and type of active ingredient and number of pills). Other observable characteristics are discussed in Section 2.3. We limit our sample to patient records collected between 2003 and 2014, inclusive, because prior to 2003 serum cholesterol level data were not accurately recorded by all GPs.

We selected patients based on two main inclusion criteria: *i)* patients who receive a diagnosis of "pure hyper-cholesterolemia" (or familiar hyper-cholesterolemia) and received at least one statin prescription between 2003 to 2012; and *ii)* patients born between 1925 and 1975, inclusive. This leads to a twelve year unbalanced panel, with 11 years of follow-up for the cohort of patients who were observed to be on statins in 2003 and only two years of follow-up for the 2012 cohort (that is, 2013 and 2014).

Since the initial sample consists of daily observations, after having constructed and transformed all variables used in the analysis, data have been collapsed to obtain patient-quarter level observations. Our choice of the patient-quarter as the unit of observation represents a compromise aimed at reducing the number of observations with a zero in drug consumption, while permitting relatively frequent changes in treatment and outcomes. The final sample is then organized as a quarterly unbalanced panel with data from 2004 to 2014, which consists of 112,331 patients (57,244 women and 46,493 men) for a total of 1,792,595 observations.

We do not exclude patients who initiated statin therapy prior to 2003 for two reasons. First, the half life of statin molecules in humans depends on the molecule, but in all cases we consider, is less than 20 hours (Plakogiannis and Cohen, 2007). Half-life, here, is a physiological property of a molecule, and indicates the amount of time it takes for half of the initial dose to be excreted from the body through the kidney, or metabolized into a biologically inactive

form in the liver. Since the half-life of statin medications are so short, the effect of the drug on cholesterol levels (and other outcomes) for someone who initiates therapy before 2003 will depend primarily on the extent to which the patient takes the statin during 2003 (and not on drug-taking behavior before then). Second, including people who are already on therapy in 2003 may lead us to underestimate the effect of statin medications on cholesterol levels. Someone who has routinely taken statin medications for some time prior to the start of our sample in 2003 is likely to have a low measured cholesterol level at the start of the observation window. Continuing to take the statin medication through 2003 and after will not lead to a yet lower cholesterol level since the patient is already at his or her steady-state cholesterol level.

2.2 Measuring Drug Potency and Patient Adherence

We characterize the prescribed treatment regime according a univariate measure called the equipotency score. This score relies on the physiological fact that some molecules are more active than others in blocking cholesterol synthesis in the liver. This measure also accounts for the fact that higher doses of a molecule will have a more potent cholesterol synthesis blocking effect than lower doses. Table 1 shows this conversion formula for the three statin molecules that we analyze in this study (simvastatin, atorvastatin, and rosuvastatin). This table follows the work of Maron et al. (2000).

According to this table, a one unit increase in equipotency for the same molecule by doubling the dose. For example, going from 20 mg to 40mg of Simvastatin increases the expected LDL cholesterol reduction by one equipotency unit. Similarly, switching from 20mg of simvastatin to 20mg of atorvastatin or to 10mg of rosuvastatin leads to an increase in the equipotency score because rosuvastatin is more biologically active than atorvastatin, and atorvastatin is

more biologically active than simvastatin. Analogously, switching from 40mg of simvastatin to 20mg of atorvastatin or 5mg of rosuvastatin maintains the same equipotency level.

A key characteristic of interest is a patient's adherence with the prescribed treatment regimen. This is important because a drug cannot have an effect if a patient decides not to take it. Given our data, there are various ways we could measure patient adherence.[4] In this study, we measure patient adherence to care using the Mean Possession Ratio (MPR) (Cramer et al., 2008; Atella et al., 2017). This is defined as:

$$MPR = \left(\frac{\text{Sum of days' supply for all fills in quarter}}{\text{Number of days in quarter}} \right) \tag{1}$$

The MPR is thus the fraction of days over the course of a quarter covered by all prescriptions for a drug. Low values of MPR are consistent with poor adherence because a patient who is poorly adherent to therapy does not need a refill prescription.

2.3 Other Observable characteristics

The Health Search Database also includes detailed information on patients clinical histories. As a summary of the general individual health condition, we construct the Charlson et al. (1987) index, a composite measure for the seriousness of diseases that increases as health conditions become worse (i.e., the assigned weight for AIDS is 6, the maximum, while for flu, it is 0, the minimum). We have also information about the presence of several chronic diseases, such as diabetes, hypertension, congestive heart failure, atrial fibrillation,

[4] According to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), medication compliance is commonly measured by adherence and persistence to prescribed medical treatment. Adherence refers to the proportion of prescribed doses taken in the prescribed time interval, while persistence refers to the continued use of a prescribed therapy over time (Hughes et al., 2001).

vascular diseases, a history of cardiac bypass surgery or percutaneous coronary intervention (PCI), ischemic heart disease, or other cardiac conditions, which will be useful in order to control for comorbidities. In terms of diagnostic tests, we observe the number of patient specific prescribed tests by each physician for alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumine and bilirubin. These tests represent our key variables for the empirical analysis as they allow to estimate the effects of informational shocks on patient prescription and physician adherence behaviours. Finally, a set of socio-demographic indicators includes age, sex, and the geographical region.

2.4 Summary Statistics

Table 2 reports the list of variables used in this analysis with their relative descriptive statistics by gender status. The dependent variable is the yearly rate of change in LDL-cholesterol at the patient level. As we can see in the table, men and women reduce their LDL cholesterol by an average of 2.4% and 2.6% (respectively) per year that they are in our sample. However, the median change is much lower, in the range of 1%. This marked difference between mean and median change suggests a left skewed distribution, denoting also a high heterogeneity in the effect of drug treatment on LDL cholesterol levels across patients.

In our selected population, 55.0% are female. Mean age is around 69 years for women and 65 for men. In accordance with the distribution of the Italian population, the majority of the patients are concentrated in the north of Italy (25.0% North-west, 20.0% North-east), with the center accounting for about 18.0%, and the south and the islands (Sardinia and Sicily) account for another 25%. The Initial level of cholesterol (that is, the first observed cholesterol level

for a patient in our sample) is higher for women (129 mmol/L) than for men (118 mmol/L). The Charlson et al. (1987) index is similar by gender (about 1.0); in about one third of the observations also diabetes is present and hypertensions in two third of observations. Tests for aspartate aminotransferase and alanine aminotransferase are the mode among the available test and are prescribed about once per year (or 0.25 per quarter).

Table 3 reports the sum of all prescriptions recorded from 2004 to 2014 in our dataset by sex, dosage and active ingredient. This table thus reflects specific GP prescription patterns for simvastatin, atorvastatin, and rosuvastatin in Italy. As is evident in the table, the most prescribed active ingredients/dose combinations are Simvastatin 40mg, Atorvastatin 40mg and Rosuvastatin 20mg. Low dosage statins are hardly prescribed, with some exception for Rosuvastatin 10mg which is actually at a high equipotency level.

3 Theoretical model

We interpret the results on the base of a stylized theoretical model. In order to reduce cholesterol as much as possible, a rational patient use drugs up to a point where the associated costs are not greater than benefits. Formally, this may be represented as:

$$\max \qquad -Y = f(D, \underbrace{Q}_{+}) \tag{2}$$

$$\text{such that} \qquad B - C \geq 0, \tag{3}$$

where Y is the reduction of cholesterol, which is a function of the prescribed treatment indexed by D and the quantity of drug (Q), $B - C$ is the net benefit, where B represents the reduction in cholesterol and C depends on liver function abnormalities induced by statin medications and on monetary costs

of medications necessary to reach a specific target. Monetary costs amount to $P \times Q$, where P is the price of the drug and Q is the amount of active ingredient prescribed. Finally, Q is affected by non-monetary components, namely technology.

We define the latter as $t = [t_1, t_2]$: this vector representation takes into account both the product innovation (t_1) and information shock (t_2), like those produced by new RCTs. We thus use the compact notation ($C = g(P, Q; t)$), with $g(\cdot)$ a monotonic function of its argument.

Whilst costs increase with prices and quantities, the effect of technology is uncertain, because it depends on its interaction with the other arguments of $g(\cdot)$. For example, the clinical information related to the consequences of drugs in terms of increase in alanine aminotransferase, may have induces a *lower* adherence of patients and thus less quantities and lower costs. In contrast, the information provided by GREACE may have induced an *higher* adherence of patients, thus pushing up quantities and, therefore, costs. Finally, due to the half-life of statins, we do not consider here the lag between drugs and effectiveness. Nevertheless, patients and doctors may take some time to 'see the effectiveness of the therapy': in this case, a better representation of eq. 2 could be based on Q_{t-i}. In case we observe a further reduction as going from $t-1$ to $t-2$, this would be the effect of persistence in the treatment.

The economic framework of Eq. 2-3 can be understood as a principal-agent problem. In order to maximize the cholesterol reduction of a patient (the agent), the doctor (the principal) has three options: switch the treatment of the patient to a *lower* level of drug equivalence; switch the treatment to an *higher* level of equipotency; leave the prescribed regime at the same level of drug equivalence. We refer to the first two cases as $D = 1$ and to the last case as $D = 0$. The last possibility might appear the least relevant from a clinical point of view but it is

the most useful from an empirical point of view, as the outcome of these patients is the natural benchmark against which to compare those of patients who switch therapy. Indeed, the patients who switch therapy do so because they expect a sufficiently high reduction of cholesterol $f(D = 1, Q) > f(D = 0, Q)$, such that $(B - C) \geq 0$ (Roy, 1951). The principal-agent framework makes clear an important complication of our model, that limits its ability to draw conclusions. In a real world setting, the decision to adhere to a prescribed regime is a patient choice. In fact, if only the doctor was involved, we could expect $E[-Y] \geq 0$. As patients play a major role in this process, the final outcome depends on their actual adherence.

Based on our simple stylised model, and using standard comparative static techniques, we can compare outcomes across patients who either switch or not treatment regime. Let's then first focus on those patients whose treatment is switched towards a lower scale of equivalence. In this case, the drug price may reduce, which implies that the patient is ready to accept a smaller reduction of cholesterol (but still an improvement with respect to the no-switch situation). At this point, based on our model characteristics, the patient consumption is unpredictable: to the extent that the switch is due to side effects, e.g. liver problems, the net benefit increases, as patient adherence (i.e. the quantity) increases and cholesterol will decrease in response. On the contrary, to the extent that adherence remains constant (or even decreases), e.g. because the perceived risk decreases, this effect will add up to the price effect because the drug is less effective (i.e., $f(D = 1, Q) < f(D = 0, Q)$). This simple reasoning implies that we cannot have prior expectations for this case, until we have a look into compliance level (on which we cannot predict anything). If compliance increases enough after the switch, a reduction of cholesterol is expected and, vice-versa, if compliance does not increase cholesterol is expected to increase.

In case of a switch towards a higher scale of equipotency the reasoning is pretty much the same: if the price goes up, then a larger reduction of cholesterol is required to switch. If the quantity of drug does not decrease, the reduction of cholesterol under the new drug will be unambiguously higher than under the previous treatment. If the compliance decreases, the argument is a bit more complicated. To the extent that the higher equipotency compensates the lower quantity the expected effect on cholesterol is still positive (i.e., $f(D=1,Q_1) \geq f(D=0,Q_0)$, even if $Q_1 < Q_0$), otherwise it is still possible that the cholesterol increases with respect to the previous situation.

	Switch to:			
Variable	Higher lev.		Lower lev.	
P	$\uparrow$	$\uparrow$	$\downarrow$	$\downarrow$
Q	$\uparrow$	$\downarrow$	$\uparrow$	$\downarrow$
Cholesterol	$\downarrow$	$f(D,Q)$	Q vs. P	$\uparrow$

Table 3 summarizes these predictions for the relevant quantities. The stylized fact summarized in the table are coherent with the assumptions underlying the model. The price of statin is monotonically increasing in the equivalence class, for both groups of patients (switchers and non-switchers) and, for each equipotency class the price for switchers is higher than for non-switchers. For quantity, there is no clear pattern nor across classes of equivalence nor across groups of patients.

As discussed in 1, during our window period, the GREACE study produced a huge information shock, which can be easily analysed using the comparative static of our model. The evidence produced are expected to lead to a larger adherence (i.e., an increase in Q) to regime, as GP and patients are now aware that the observed side effects are not caused by statins. However, whether we should expect a larger or a smaller effect (in absolute value) is an empirical question, because the compliance resulting after the new information is provided

increases for both groups of patients (switchers and non-switchers).

4 Methods

In this section we review the methodologies that allow us to learn about the model 2–3. The model describes a situation for an individual chosen at random from the population, like RCT do. As suggested in Section 3, the parameter of interest is the difference between two potential outcomes under treatment (Y_1) and non-treatment (Y_0). This is the Average Treatment Effect (ATE) for the entire population (Imbens and Wooldridge, 2009). From now on, and consistent with the majority of the existing literature, we no more specify that this parameter refers to the entire population. As clinical indicator we consider the reduction of cholesterol (Y), due to a treatment that changes the equivalence of statins (in which case $d \in D$ takes value 1; otherwise, it takes value 0). Hence, a formal representation for the ATE is

$$\begin{aligned} \Delta &= E[Y_1] - E[Y_0] \\ &= E[Y_1|D=1]\,P[D=1] + E[Y_1|D=0]\,P[D=0] \\ &- E[Y_0|D=1]\,P[D=1] + E[Y_0|D=0]\,P[D=0], \end{aligned} \tag{4}$$

If we could observe the outcome under the two states of the world for a randomly chosen individual (Heckman et al., 2006), the identification of ATE would be straightforward. In fact, the sampling process is informative only about the outcome under treatment for treated individuals ($E[Y_1|D=1]$) and about the outcome under non-treatment for non-treated individuals ($E[Y_0|D=0]$). The main challenge of the analysis is thus recovering the outcome for treated patients had they not been treated, or $E[Y_1|D=0]$, and vice versa for non treated patients.

In Section 3 we emphasized that the sample of treated individuals is not completely at random, in the terminology of Little (1995). If we can add a set of characteristics (for ease of notation we omit them, which are kept implicit in what follows) that drive who is treated (selection on observables), the selection process would be at random. In contrast, problems arise when dealing with unobservable patient and physician traits and characteristics which are unknown to researchers, like genetic endowments, that lead to liver abnormalities. **intro? This is a standard problem in non-experimental/observational data in health economics, although not quite simple to address.** This represents a critical issue when we want to disentangle the true effect of the treatment from these unobservable confounding factors. The Roy model of Section 3 suggests that this might likely be our situation.

Formally, we are interested in the average treatment effect under the following reference model:

$$\begin{aligned} Y_d &= r(D) + \epsilon_d \\ D^* &= s(Z) - v \qquad D = 1(D^* > 0), \end{aligned} \tag{5}$$

where D^* is the selection rule that determines who is treated, on the basis of a binary variable $z \in Z$ (our instrument) that affects the selection mechanism, but not the outcome; ϵ_d and v are unobservable disturbances. An example of Z is the communication skill of the doctor (but not his/her clinical ability, which presumably has a direct effect on the reduction of cholesterol).

Depending on which assumptions we are willing to impose on the relation between ϵ_d and v, different alternatives are available to evaluate the effect of the treatment.

In the simplest case, when $\epsilon_d \perp v$ we have that $E[Y_d|D=1] = E[Y_d|D=0]$. It then follows that $E[Y_1|D=0] = E[Y_1|D=1]$ and $E[Y_0|D=0] = E[Y_0|D=1]$

which can be substituted in eq. 4 to derive $\Delta = E[Y_1|D = 1] - E[Y_0|D = 0]$. This parameter is valid for the entire population, but it is not robust to possible endogeneity of the treatment indicator with respect to the outcome variable. As such, it is incoherent with our stylized economic model.

An estimator robust to sorting into treatment would be based on an Instrumental Variable (IV) under the following conditions (Imbens and Angrist, 1994; Angrist et al., 1996):

1. potential outcomes are unrelated to the treatment status of other workers (also known as SUTVA);

2. the randomly assigned instrument is correlated with compliance indicator, i.e. relevant or first stage;

3. the instrument does not affect the outcome, i.e. en exclusion restriction,

4. monotonicity (i.e., $D_1 \geq D_0$ for each patient, where D_z is the potential treatment with the instrument $Z = z$), such that there is no one who does the opposite of his/her assignment of instrument.

Under these hypotheses, we identify

$$\frac{E[Y_1|Z = 1] - E[Y_0|Z = 0]}{E[D_1|Z = 1] - E[D_0|Z = 0]} = E[Y_1 - Y_0|D_1 > D_0]. \tag{6}$$

Whilst the estimate of the treatment effect is robust to endogeneity, it does not recover ATE. In fact, the IV approach identifies a *local* average treatment effect (LATE), valid for the subpopulation of patients who are induced to be treated by a change in the instrument. Patients belonging to this subpopulation, defined compliers (Angrist et al., 1996), cannot be flagged on the basis of the observable covariates, although their characteristics can be described (Angrist, 2004). Since different instruments affect different subpopulations, it is not surprising that in

general a LATE estimated with an instrument Z differ from a LATE estimated with an instrument $Z' \neq Z$; more than this, even the same instrument estimates different marginal returns as moving from z to z', with $\{z, z'\} \in Z$ (Heckman, 2010).

Though, it is important to emphasize that under special circumstances the LATE is informative also about ATE. This happens when the effect is homogeneous within the population, or when the entire population is made of compliers, or when patients do not select on the basis of their idiosyncratic return (Heckman, 1997; Blundell et al., 2005).

The above discussion is not against or in favour of IV-LATE. It only aims at clarifying the identification power of the IV. Indeed, when the interest is in a given policy that targets a specific subpopulation (of compliers), as for example would be the case of a subsidy provided to a low-income population for preventive care **Jay: example??**, IV-LATE is the parameter of main interest. When the interest is in the treatment effect *for the entire population*, as is the case in this analysis, IV-LATE might not be the best option, unless one may argue that one of the special circumstances mentioned above is satisfied, or some external information excludes specific subpopulations (Oreopoulos, 2006).

The definition of IV-LATE is also very useful to point out that the main challenge we face when we want to identify the ATE for the entire population under endogeneity, is that Y_0 is never observed for always-takers ('at') and Y_1 is never observed for never-takers ('nt'), in the terminology of Angrist et al. (1996). For a more clear exposition the following decomposition is very useful:

$$ATE = \pi_{at}\, LATE_{at} + \pi_c\, LATE_c + \pi_{nt}\, LATE_{nt}, \tag{7}$$

where π is the share of the attached component.[5]

[5]Under the assumptions discussed in Imbens and Angrist (1994); Angrist et al. (1996),

In this paper, we review some useful assumptions that allow to recover ATE. This comes at the cost of losing point-identification in favour of partial/set identification (i.e., 'bounds') of the population average treatment effect (Manski, 1990). As a general rule, the larger the set of assumptions, the smaller the width of the bounds. To fix ideas, consider the simplest possible example. We don't know the outcome $E[Y_i]$ in the unobservable state of the world, but suppose we know $Y \in [k_0, k_1]$ with $k_0 \leq k_1$. In this case, we know that even in the unobservable state of the world, the outcome would have been *at least* equal to k_0, thus identifying a lower bound of the level of the outcome, and *at most* equal to k_1, thus identifying a upper bound of the level of the outcome. Therefore the upper bound of the treatment effect would be equal to the difference between the upper bound of the outcome under treatment and the lower bound under non-treatment (Manski, 1990). Upon substitution in eq. 4, it follows that

$$Lower \quad : \quad E[Y_1|D=1]\,P[D=1] + k_1\,P[D=0] - \{k_0\,P[D=1] + E[Y_0|D=0]\,P[D=0]\} \tag{8}$$

$$Upper \quad : \quad E[Y_1|D=1]\,P[D=1] + k_0\,P[D=0] - \{k_1\,P[D=1] + E[Y_0|D=0]\,P[D=0]\} \tag{9}$$

Although these bounds are very useful to understand how set identification works, they are usually very large and not much informative. The reason is that the amount of information exploited by them is very small. In this paper we consider various alternatives to narrow the identified set of the population average treatment effect, exploiting further information as done by Shaikh and Vytlacil (2011); Bhattacharya et al. (2008, 2012); Chen et al. (2017). Shaikh and Vytlacil (2011); Bhattacharya et al. (2008, 2012) are based on binary outcomes and impose a monotonicity condition at individual level (similar to that

there are no 'defiers' ('df'), and therefore $\pi_{df} = 0$ (or equivalently, $\pi_{at} + \pi_c + \pi_{nt} = 1$). Also, two of the special cases mentioned for LATE informative for ATE are clear from eq. 7: if $LATE_{at} = LATE_c = LATE_{nt} = LATE$, then $ATE = (\pi_{at} + \pi_c + \pi_{nt})\,LATE = LATE$; if $\pi_c = 1$, then $ATE = 0\,LATE_{at} + 1\,LATE_c + 0\,LATE_{nt} = LATE$.

of the IV-LATE). Chen et al. (2017) generalize the results to consider continuous outcomes and monotonicity in the treatment of the average outcomes of specified subpopulations. More precisely, besides the IV-LATE conditions of Imbens and Angrist (1994); Angrist et al. (1996), we impose:

1. $Y \in [K_0, K_1]$;
2. $E[Y_1|S] \leq E[Y_0|S]$ for $S \in at, nt, c$ (or viceversa);
3. $E[Y_0|at] \geq E[Y|Z = 0, D = 0]$ and $E[Y_1|nt] \leq E[Y|Z = 1, D = 1]$, or the reduction of cholesterol under non treatment for those patients that are compliant with the treatment no matter the instrument (the always-taker) is smaller that when $[Z = 0, D = 0]$ (and similarly for never takers).

The last condition might be critical and deserves discussion. We impose it for several reasons. On the empirical side, notice that $E[Y|D = 0, Z = 0] = \frac{\pi_c}{\pi_c+\pi_{at}} Y_C + \frac{\pi_{nt}}{\pi_c+\pi_{nt}} Y_{nt}$, therefore testable implications when the treatment effect is positive are $E[Y|D = 1, Z = 0] \geq E[Y|D = 0, Z = 0]$ (related to the always takers part) and $E[Y|D = 1, Z = 1] \geq E[Y|D = 0, Z = 1]$ (related to the never takers part). Therefore, if $LATE_C \geq 0$, rejecting these hypotheses would be strong evidence against them (Chen et al., 2017). When the treatment effect is negative, even rejecting the hypothesis, it may still be that $E[Y_0|at] \geq E[Y|D = 0, Z = 0] \geq E[Y|D = 1, Z = 0]$, if the treatment effectively reduces cholesterol. Therefore, if $LATE_C \leq 0$, non-rejecting the hypothesis is a strong argument in favour of them.

This condition is also consistent with our economic model: always takers basically do not have alternatives to drugs, or otherwise their cholesterol would be higher than the rest of the population, so that the benefit from drug overcome costs; never taker in contrast can substitute drugs for healthier behaviour (e.g., sport) as argued in Atella et al. (2017), and the balance between benefits and

costs is more complicated. If this is true, the pre-treatment conditions of always takers (never takers) are expected to be worse (better) than for other sub-populations. In the empirical application (Section 5), we successfully check all these conditions.

The bounds obtained imposing these assumptions are:

$$
\begin{aligned}
&\text{if:} && E[Y|Z=1] - E[Y|Z=0] > 0: \\
LB &= && E[Y|Z=1] - E[Y|Z=0] \\
UB &= && E[Y|D=1,Z=1] - E[Y|D=0,Z=0]
\end{aligned}
$$

$$
\begin{aligned}
&\text{if:} && E[Y|Z=1] - E[Y|Z=0] < 0: \\
LB &= && E[Y|D=1,Z=1]\,E[D=1|Z=1] - E[Y|D=0,Z=0]\,E[D=0|Z=0] + \\
& && + K_0\,E[D=0|Z=1] - K_1\,E[D=1|Z=0] \\
UB &= && E[Y|D=1,Z=1]\,E[D=1|Z=1] - E[Y|D=0,Z=0]\,E[D=0|Z=0] + \\
& && + \min\{E[Y|D=0,Z=1], E[Y|D=1,Z=1]\}\,E[D=0|Z=1] + \\
& && - \max\{E[Y|D=1,Z=0], E[Y|D=0,Z=0]\}\,E[D=1|Z=0]
\end{aligned} \tag{10}
$$

Bhattacharya et al. (2008, 2012) discuss the relation between these bounds and those obtained by Manski and Pepper (2000) imposing Monotone Treatment Response (MTR). Depalo (2017) shows the one-to-one relation between the heterogeneity in the population and width of bounds.

Before proceeding, it may be useful a summary of the properties of all of the estimators. The table below shows whether the estimator is robust to possible endogeneity, whether the parameter identifies an effect for the population at large or it is a local effect, and what kind of identification provides:

Method	End.	Pop.	Id.	Acronym
OLS	x	v	Point	OLS-ATE
IV	v	x	Point	IV-LATE
Bounds	v	v	Set	various

Bounds in eq. 10 involve minima and maxima. In finite sample these estimators are biased, typically providing conservative (i.e., smaller) bounds. Nowadays, corrections have been proposed by Chernozhukov et al. (2013); Kreider and Pepper (2007). In this paper we employ the method by Kreider and Pepper (2007), that is based on nonparametric bootstrap. Define T_n the sample analog of the consistent estimator of the parameter θ, by definition the bias $b_n = E[T_n] - \theta$. The nonparametric bootstrap delivers $\hat{b} = E^*[T_n] - T_n$, where $E^*[\cdot]$ is the expectations with respect to the bootstrap distribution. The bootstrap bias-corrected estimator can now be calculated as $T_n^c = T_n - \hat{b} = 2T_n - E^*[T_n]$. Kreider and Pepper (2007) provide evidence in favour of this approach.[6]

Based on the bootstrap bias-corrected estimator, Kreider and Pepper (2007) provide the associated confidence interval. McCarthy et al. (2015) propose to use either Kreider and Pepper (2007) altogether or the method of Kreider and Pepper (2007) for the finite-sample correction and the asymptotic inference suggested by Imbens and Manski (2004).

5 Results

5.1 Data Subsetting and the Three Eras in Cholesterol Management

We start the discussion of our results by showing how physician behavior with respect to cholesterol prescribing and liver function testing changed between 2004 and 2014 in Italy. We divide our analysis into three time periods (before

[6]The method by Chernozhukov et al. (2013) is based on precision-corrected estimate of the sample analog estimator $\hat{\theta(p)} + k(p)\, s(x)$, with $s(x)$ the standard error of $\hat{\theta(x)}$, and $k(p)$ is a critical value that is based on an adaptive inequality selection procedure proposed on purpose. In our application we rely on Kreider and Pepper (2007) for several reasons: 1) it is easier to understand and to implement (notice however that Chernozhukov, 2015 provide a Stata-routine for the method); 2) it is computationally much faster than the alternative Chernozhukov et al., 2013; Chernozhukov, 2015; 3) the correction in Kreider and Pepper (2007) performs well based on Montecarlo evidence provided by the authors.

2006, 2006-2010 inclusive, and 2011+) based on information in the literature on the effect of cholesterol testing on liver function. Recall that in the early period, the conventional wisdom was that statins may cause liver damage in some cases. In the middle period, there was some non-randomized evidence that the effect of statins on liver function might not be directly causal. Finally, in the late period (after the GREACE randomized trial) statins were known to protect against liver dysfunction. Therefore, all our analyses are conducted separately on those three sub-periods.

A key point here is that the nature of the technological advance involved new information about the properties of an existing drug (t_1), rather than any physical change in the molecule itself or its formulation (t_2). Thus, there is no reason to expect a change in the effect of drug on cholesterol reduction except through changes in physician and patient patterns in the use of drug.

In our point-identified results, our conditioning set includes the Charlson index (a composite comorbidity score explained in Section 2), age, sex, geographical region, and indicators of the presence of chronic diseases like diabetes, hypertension, congestive heart failure, atrial fibrillation, vascular diseases, a history of cardiac bypass surgery or percutaneous coronary intervention (PCI), ischemic heart disease, or other cardiac conditions. We include this extensive set of covariates in these regressions to reduce the chance of bias due to observed differences between patients assigned different statin molecule/dose combinations.[7]

For the bounding estimators, by contrast, we do not condition on observable covariates, and instead verify that the assumptions imposed to generate bounds

[7]Pepper (2000) present an illuminating discussion about the different role of covariates in point and set identifications. For traditional point-identified estimators, like the OLS estimator, covariates generally serve the purpose of reducing bias due to relevant observable differences between the treated and untreated groups. In the bounding estimators, covariates are used to define subgroups of the population for whom separate treatment effect estimates are of some policy (or in this case, clinical) interest; there is no bias problem as long as the (relatively weak) assumptions underlying the estimator are met.

are met using methods described in Pepper (2000). (Please see Section 5.7). For the bounding estimators, not conditioning does not create any bias as long as the assumptions we impose to generate the bounds are met. [8]

5.2 Physician Habits as an Instrumental Variable

While it may be tempting to compare outcomes for patients on different statin equipotency combinations to estimate the effects of statins, this procedure is not possible, given that the set of patients who change statin therapy over time in our data is not randomly assigned. In fact, the decision to switch depends on a variety of clinical and economic factors known to both patients and physicians, but not always known to researchers. This is consistent with our theoretical model, which emphasizes the importance of the costs and benefits of switching on observed switching behavior.

To address this problem of differences between treated and non-treated patients, we propose an instrumental variable – the physician-specific share of patients who switch between molecules or equipotency class. This instrument is calculated for each patient by calculating the switching behavior of all the other patients that the patient's physician manages. This calculation purges any mechanically induced correlation between the *instrument* and the outcome, and is consistent with the stable-unit of treatment value assumption (SUTVA) condition of Imbens and Angrist (1994). Empirically, we find that our instrument is strongly correlated with a patient's own switching behavior (the F-Stat from first-stage suggested in Bound et al., 1995 much greater than 10).

One possible concern about the instrument is that the selection process that matches patients to GPs is not random. However, in the Italian medical care

[8] In an online appendix, we calculate our bounding results separately for men and women because it is in principle possible that the physiological effect of statins on cholesterol, as well as medication adherence, differ by sex. In practice, we find little substantively different between the sexes in our results, so we present combined results here to save space.

system, the choice of general physician is strongly influenced by the location of the physician and the patient. General practitioners are not allowed to reject a patient for service on the basis of the severity of the patient's medical condition. Different values of our instrument, then, are more likely to reflect distinct practice styles of the practitioners (due perhaps to differences in physician training), rather than unobserved differences in physician behavior due to the underlying condition of the patient.

Even if the reader is skeptical about our choice of instrument, we argue that a violation of our IV assumption would likely tend to produce an attenuation bias on our results. Suppose that the argument in this paragraph is wrong, and a physician's propensity to switch is in fact correlated with a patient's unobserved health status. In the case of statins, one of the few reasons why a physician might recommend switching to an alternate therapy is that the current molecule and dose is not producing a sufficient reduction in LDL cholesterol level. Thus switches will be most likely to occur (and physician propensity to switch will be highest) when the observed change in cholesterol level is smallest.

We use a binary version of our instrumental variable, consistent with the description of the estimator we adopt in Section 4. To generate this binary instrument, we calculate the average value of the continuous version of our instrument. Then, we assign our binary instrument a value of one if the patient sees doctor who has an average switching rate above the mean switching rate for all doctors in the sample, and zero otherwise. This approach may be understood as a comparison of each physisian's practice style with relative to the community norm.

5.3 Treatment Adherence Results

A key idea underlying the economic background that we describe in Section 3, is the fact that adherence to therapy exerts a positive impact on the reduction of cholesterol: a patient not taking the prescribed statin will see little change in their cholesterol level. In this section, we conduct a test of this assumption with the data at hand.

In Table 4 we report the bounds of Section 4 (with the correction proposed by Kreider and Pepper, 2007), as well as analogous OLS and IV results. We also include some useful descriptive statistics: (log) cholesterol level change after six months (Y) conditional on adherence during this period of more than 75% ($D = 1$) and adherence during this period of less than 75%. We report these results for each type of statin molecule, as well as for each of the three treatment eras. The numbers in this table are all negative because these drugs tend to reduce cholesterol levels.

The OLS estimates tend to show small changes in LDL cholesterol levels correlated with patient adherence. Adherent patients experience (roughly) a 2% reduction in cholesterol levels relative to non-adherent patients. This is entirely consistent, not surprisingly, with the mean changes observed in the right-most columns of Table 4. Though potentially biased because of the endogeneity of adherence behavior, the OLS results are interesting because they represent an estimate of the population level average treatment effect. The OLS treatment effect is smaller in later treatment eras; this is consistent with the idea that the set of people under statin treatment expanded as the fear of liver damage diminished, namely those with worse unobservable health conditions.

The IV results uses an instrument analogous to the one described in Section 5.2: an indicator for whether a doctor's patients adhere to their prescription more than patients seen by the average doctor (not including each patient's ad-

herence status). As is the case with the OLS results, we find that adherent patients (in nearly all of the cases) see a greater decrease in their cholesterol than non-adherent patients.

The IV results are interesting because they address the endogeneity of adherence, but the drawback is that it is consistent only for the local average treatment effect, rather than the population average treatment effect. In this case, the local average treatment effect applies to the set of patients who adhere to therapy if they are seeing a doctor whose other patients comply at a rate higher than the overall adherence rate in the population. There is no reason to think that the treatment effect of adherence in this "complier" population should coincide with the population treatment effect. This population is not particularly interesting to clinicians since it is impossible in general to identify whether any particular patient belongs it *a priori* (or indeed *ex post*). Because it is not clear who these compliers are, we should not interpret the changes in the IV estimates in earlier vs. later treatment eras as the response due to a technological shift.

Finally, the BSV bounds in Table 4 are fairly wide; the lower bounds show reductions in cholesterol on the order of 50%. These numbers may seem large, but in fact are consistent with the effect size measured in the clinical trials (Scandinavian Simvastatin Survival Study Group, 1994). These bounds are robust to non-random sorting (unlike OLS) *and* apply to the entire population (unlike IV).

Overall, the results in Table 4 are consistent with our hypothesis that adherence to therapy leads to lower cholesterol levels in the population at large.

5.4 Effect of Switching Equipotency Levels on Cholesterol

In this section, we explore the effect of changes in prescribed equipotency level on serum LDL cholesterol levels. In one sense, one might think that the answer to this question is available from the numerous randomized trial data, which show that increasing statin dose leads to substantial reductions in serum cholesterol levels reported in Table 1. However, the story in actual practice is complicated by two phenomena that are not present in the randomized trials. First, the set of people who are treated in the population include many patients who have health conditions that were not represented in the initial trials. Though subsequent RCTs may be conducted that expand the set of patients exposed to treatment (such as the GREACE trial which included patients with liver disease), physicians are free to prescribe statins to patient groups not represented in the trial (and often do). Thus, the treatment effect in the population may differ from what is observed in the trials.

Second, the set of people who participate in the randomized trials are typically much more likely to adhere to prescribed therapy than are patients in the population at large. In trials, investigators regularly remind patients to stick to the therapy they have been randomly assigned; low adherence presents problems for investigators in calculating the "true" treatment effect of the drug, so they take actions to increase adherence. This is less common in real world treatment settings, where patients make their own decisions about whether to follow their doctors' recommendations. The model we present in Section 3 posits that patients adhere to therapy if the net benefits from doing so are sufficiently high. For instance, if a drug at a given dose causes many perceived side effects, many patients may decide not to adhere to therapy. Suppose a doctor in that case decides to reduce the recommended dose in a bid to reduce perceived side effects. If the patient's adherence increases in response, then the effect of the

drug on the main endpoint (LDL cholesterol) may actually increase.

We divide our discussion of the effect of switching the recommended equipotency level of the drugs on LDL cholesterol into two cases: a recommendation to decrease the effective dose, and a recommendation to increase the effective dose.

The results for the first case are in shown in Table 5. The OLS estimates suggest mixed results – lowering drug dose or equipotency class led to decreased LDL cholesterol levels in the pre-2006 era, but led to increased LDL cholesterol levels in the later two eras. This particular mix is hard to interpret, and is consistent with the idea that the OLS estimator is biased.

The IV results (that is, the local average treatment effect results) show that decreasing dose led to decreasing LDL cholesterol levels in the pre-2006 and 2006 to 2011 eras, but led to a small increase (almost zero change) in LDL cholesterol in the post-2011 period. This result is consistent the fact that we observe an increase in adherence after a doctor prescribes a lower equipotency class. In fact, adherence under increases from 63.3% of patients taking their prescription more than 75% of the time to 66.1% of patients in the overall population. Since the IV results suggest either a decrease or no change in LDL after a dose decrease, this increase in adherence must be the true in the complier population as well.

Finally, the BSV bounds suggest that in all three eras, the population average treatment effect of decreasing dose was negative, with effects as large as a 60% reduction and more consistent with the data (as well as effects as small as a 0.2% reduction in LDL cholesterol possible). These results confirm our interpretation that the rise in adherence from lowering the effective dose outweighs the direct mechanical effect of the lower dose in terms of its net effect on LDL cholesterol in the overall patient population.

Next, we discuss the consequences of physicians raising the prescribed equipo-

tency level of the statin medication. These results are presented in Table 6. A doctor might decide to recommend a higher dose, for instance, if the current dose has not produced a sufficiently large reduction in LDL cholesterol, *a*nd there is no evidence of side effects or lack of adherence at the current dose. In such a case, our theoretical prediction is that the mechanical effect of increasing the effective dose will dominate, and the switch will produce a decrease in LDL cholesterol. This is in fact what we empirically observe in all three treatment eras, and with all three estimators. When physicians raise the prescribed effective dose, then, both compliers and the population at large enjoy decreases in serum LDL.

One caveat: the result in Table 6 does not mean that increasing the effective dose would always be effective, and that therefore all physicians should recommend that their patients do so. Rather, the result implies that physicians are good at predicting when an increase in the prescribed effective dose would not lead a patient to adhere less to therapy, and thereby gain the full benefit from a recommendation of a the higher dose.

5.5 Comparing Always Takers, Never Takers, and Compliers Over Treatment Eras

In this section, we discuss how the clinical characteristics of the treated population has changed over the treatment eras.

Table 7 presents a wide variety of health and health economic variables for the patients in the sample. In addition to conditioning on the era of treatment, we divide the sample up into four groups based on their values of the instrument and whether doctors recommended a change in the equipoteency level of the prescribed medication during a quarter. These four groups are the "always-takers" (who has a change in equipotency recommended despite being seen by

a doctor who recommends equipotency changes less frequently than average), "never-takers" (who do not have a switch recommended, despite being seen by a doctor who recommends equipotency changes more frequently than average), as well as "compliers" (Angrist, 2004). The last group consists of two distinct types of patients: (1) patients who are seen by doctor who recommends equipotency changes more frequently than average and who have a switch recommended; and (2) patients who are seen by doctor who recommends equipotency changes less frequently than average and do not have a switch in their recommended prescribed regimen. The first of these two "complier" groups include "always-takers" mixed in with the actual compliers, while the second of these two include "never-takers" mixed in. Thus the clinical characteristics we report in this table for these two "complier" groups are weighted combinations of actual compliers and some other population.

The first important finding from Table 7 is that on many important clinical and demographic characteristics, the "never-taker", "always-taker", and "complier" groups are indistinguishable from one another on average. The characteristics where we observe clinically small differences include: age, sex, the number of liver function tests ordered (serum albumin, ALT, AST, blirubin), anemia prevalence, asthma prevalence, body weight or obesity prevalence, exercise habits, chronic obstructive pulmonary disease prevalence, HDL and LDL cholesterol levels, history of cardiac bypass surgery or balloon angioplasty, history of cancer, diabetes prevalence, atrial fibrillation prevalence, hypertension prevalence, ischemic heart disease prevalence, heart attack history, and history of vascular disease. These lack of differences across these groups can be summarized nicely by the fact that the distribution of Charleson Index scores (which is a summary measure of the presence of chronic diseases in a patient) does not differ across the four groups in a clinically signficant way (Charlson et al., 1987).

The "always-takers" do have higher levels of adherence, higher expenditures on drugs, and higher total medical expenditures, than the "never-takers", but this just indicates that they tend to comply more with doctor orders.

One important consequence of this (lack of) finding is that trying to develop a model to predict whether a doctor is likely to recommend a swtich in therapy conditional on these observed clinical and demographic characteristics (perhaps using machine learning methods) would be a difficult challenge. There is clearly too much clinical overlap between the groups to permit an easily observable distinction. Doctors recommend switches in equipotency dose on the basis of characteristics that we do not observe, despite the fact that we observe so many clinical characteristics.

By contrast with the results across patient types, Table 7 shows substantial change in the clinical characteristics of the population in the direction of sicker patients under treatment over time. For all subgroups of patients, health conditions (either in general, such as the Charleson Index, or those specifically related to LDL cholesterol) become worse, while the number of liver function tests per quarter decreases. This trend is particular striking in the post-GREACE trial era. As new information about the side effect profiles of statin became available, the set of patients under treatment expanded to include patients who were previously thought to be poor candidates for the drug.

5.6 Relationship Between Switching and Testing

In Table 8 we report the probability of a change in recommended equipotency level as a function of number of liver tests. For all patients (see the 'Overall' column), the probability of a change in therapy is an increasing function of the number of tests: patient who take at least four tests are more likely to switch than patients who have their liver function tested no more than three

times. This is consistent with both the pre-GREACE guidelines and the post-GREACE American guidelines, which suggest testing liver function tests at the time of a recommended switch in therapy. Our results suggest that Italian doctors are following these guidelines, at least on average.

If we fix the period of analysis and compare different groups of switchers, patients who are prescibed a higher equipotency class undergo a larger number of liver function tests. This is consistent with physician concern that raising the dose, or prescribing a stronger molecule may result in a higher risk of liver side effects. higher equipotency levels may be more effective, but physicians are concerned that they may also be more damaging.

Next, we examine changes across treatment eras, holding fixed switcher groups. This "vertical" comparison is motivated by the information shock provided by GREACE, as well as the observational evidence piling up before 2010.

For all groups of patients, there is an abrupt change in "testing behaviour" that is evident in the post-GREACE era. For example, with respect to the baseline category of no liver function tests, the probability of switching the therapy to a lower class of equivalence with four tests was larger than 2% (0.02138) before 2006, compared with less than two percent between 2006 and 2010 (0.01839), or a decrease of about 15%;[9] after the results of the GREACE trial became available, the probability of switching conditional on at leat four tests went further down (again, with respect to the baseline category) to about 1%, or a decrease of 30%. Similar results can be seen for patients switching to an higher equipotency class. The probability of switching the therapy to an higher equipotency class with four or more liver tests was slightly smaller than 15% before 2006, and decreased marginally in the following period (a decrease equal to 3.5%); and a larger drop of 25%. C learly, the GREACE information shock affected

[9] Given the large difference in the absolute values of the probability, we find the comparison of these relative risk more fair than the comparison of the attributable risk. For a more thorough discussion on this kind of comparisons and for similar conclusions, see Manski (2009).

liver function testing behavior for all groups of patients, with those switching to a lower equipotency class more affected. This pattern of results is consistent with the idea that Italian GPs change their practice in response to new scientific information, and relatively quickly.

5.7 Testing Monotonicity and Exogeneity

We also tested the non-rejection of the validity of exogeneity and monotonicity assumptions using a test proposed by Mourifie and Wan (2016). **to be written!**

6 Conclusion

TO BE COMPLETED

The length of the bounds suggest that even though *ranges are for the cattle*, giving a single number may be too restrictive: the more heterogeneous the population, the larger the range. In these cases providing a single number may be not adequate. Depending on the specific bound, the width is an increasing function of admissible range of values in Manski (1990), the distance between average outcomes and admissible range of values, the distance between average outcomes for compliers and defiers in Bhattacharya et al. (2012).

If one is in search of a single number, then the heterogeneity of the population will be a pity, but if one is also looking for a more realistic description of the population, the heterogeneity in the population should be considered and the width will not be less informative than the number. Horowitz and Manski (2000) emphasize this concept with the argument that "bounds reflects the information available from the data *per se* about the population parameters of interest. The width also indicates the relative importance of the data and untestable assumptions in determining the values of point estimates. If bounds obtained without making untestable assumptions are very wide, then the data

per se provide little information about the population parameters of interest. When this happens, point estimates are largely consequences of one's untestable identifying assumptions, not of information contained in the data. This does not necessarily mean that one should avoid point-identifying assumptions, but analysts should be honest about what is going on if the bounds are wide. Readers should be told that the point estimates are sensitive to untestable assumptions and that different assumptions could produce widely different results" (p.88).

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Table 1: Statin conversion table

Class	% LDL red.	Simva	Ator	Rosu
1	<24	5	-	-
2	25–32	10	-	-
3	31–39	20	10	-
4	37–45	40	20	5
5	48–52	80	40	10
6	55–60	-	80	20
7	60–63	-	-	40

Table 2: Descriptive statistics

	Women			Men		
Variabile	Mean	S.D.	Median	Mean	S.D.	Median
Age	68.94675	9.31172	70.00000	65.53925	10.28141	66.00000
North W	0.24379	0.42937	0.00000	0.26874	0.44331	0.00000
Nort E	0.21095	0.40799	0.00000	0.21464	0.41057	0.00000
Center	0.18273	0.38645	0.00000	0.17311	0.37834	0.00000
South	0.24468	0.42990	0.00000	0.23888	0.42640	0.00000
LDL	120.70131	36.26905	115.77856	110.84665	34.90859	106.31404
Δ Chol.	-0.03812	0.19161	-0.01911	-0.03776	0.18461	-0.02010
Adherence	0.64299	0.28583	0.62921	0.69568	0.28073	0.67416
Charlson ind.	1.00882	1.15930	1.00000	1.22023	1.26860	1.00000
Diabetes	0.24669	0.43109	0.00000	0.29706	0.45696	0.00000
Hypert.	0.72070	0.44865	1.00000	0.68348	0.46512	1.00000
Congestive heart failure	0.02697	0.16200	0.00000	0.03852	0.19246	0.00000
Atrial fibrillation	0.05063	0.21925	0.00000	0.06261	0.24225	0.00000
Vasc. Deas.	0.01009	0.09994	0.00000	0.01934	0.13772	0.00000
PCI	0.00132	0.03629	0.00000	0.00511	0.07132	0.00000
Ischemic heart	0.01392	0.11714	0.00000	0.01733	0.13050	0.00000
Other Heart	0.13643	0.34324	0.00000	0.31022	0.46258	0.00000
ALP	0.06080	0.25567	0.00000	0.05228	0.24262	0.00000
ALT	0.29048	0.50879	0.00000	0.28997	0.51597	0.00000
AST	0.27201	0.49636	0.00000	0.26991	0.50155	0.00000
Albumin	0.02888	0.17698	0.00000	0.02967	0.18138	0.00000
Birilubin	0.02181	0.15431	0.00000	0.02190	0.15578	0.00000
Birilubin (Tot & Fract.)	0.04222	0.21578	0.00000	0.04308	0.22302	0.00000
simvastatin	0.44051	0.49645	0.00000	0.39973	0.48984	0.00000
atorvastatin	0.34151	0.47422	0.00000	0.38324	0.48618	0.00000
rosuvastatin	0.21797	0.41287	0.00000	0.21703	0.41223	0.00000

Table 3: Number of prescription by active ingredient and dosage

		Statin		
Variable	**mg**	**Simva.**	**Ator.**	**Rosu.**
Men	5	0	0	18705
	10	14282	105253	132127
	20	246066	166173	26579
	40	70926	42047	2455
	80	0	4131	0
Women	5	0	0	25440
	10	24684	137788	158079
	20	331071	164907	24892
	40	68835	24946	1684
	80	0	1525	0

Table 4: Reduction of Cholesterol and Compliance

	BSV		Point		Averages		
Statin	Lower	Upper	OLS	IV	$[Y\|D=0]$	$[Y\|D=1]$	ΔY
All							
Simva.	-0.43723	-0.01157	-0.01251	-0.01308	-0.04134	-0.03007	-0.01127
Ator.	-0.46379	-0.01975	-0.02165	-0.01657	-0.04707	-0.02688	-0.02019
Rosu.	0.00123	-0.02041	-0.02530	0.00980	-0.05739	-0.03277	-0.02462
All	-0.47357	-0.01834	-0.02006	-0.01417	-0.04830	-0.02930	-0.01899
Before 2006							
Simva.	-0.45963	-0.01669	-0.01806	-0.02855	-0.04528	-0.02740	-0.01788
Ator.	-0.51893	-0.02529	-0.02597	-0.02141	-0.06181	-0.03687	-0.02493
Rosu.	-0.64166	-0.06810	-0.05002	-0.14422	-0.14016	-0.08948	-0.05068
All	-0.51053	-0.03823	-0.03431	-0.05770	-0.06857	-0.03488	-0.03368
2006-2011							
Simva.	-0.54417	-0.00949	-0.01173	-0.00578	-0.03910	-0.02887	-0.01023
Ator.	-0.46309	-0.01973	-0.01995	-0.02327	-0.03948	-0.02035	-0.01914
Rosu.	-0.53721	-0.02585	-0.02913	-0.00823	-0.06408	-0.03580	-0.02828
All	-0.49780	-0.02149	-0.02228	-0.02125	-0.04809	-0.02694	-0.02114
After 2011							
Simva.	-0.43583	-0.00995	-0.01190	-0.01282	-0.04269	-0.03242	-0.01027
Ator.	-0.49167	-0.02229	-0.02297	-0.03021	-0.05001	-0.02915	-0.02086
Rosu.	-0.68864	-0.01726	-0.02091	0.00281	-0.04214	-0.02118	-0.02095
All	-0.48126	-0.01644	-0.01670	-0.02839	-0.04500	-0.02944	-0.01556

Table 5: Reduction of Cholesterol and change in therapy (lower equivalence)

	BSV		Point		Averages		
Statin	Lower	Upper	OLS	IV	$[Y\|D=0]$	$[Y\|D=1]$	ΔY
				All			
Simva.	0.00059	0.00378	0.00436	0.01418	-0.03039	-0.03525	0.00486
Ator.	-0.97901	-0.00767	0.00728	0.00049	-0.03080	-0.03850	0.00770
Rosu.	-0.60358	-0.00106	0.00674	-0.01006	-0.04323	-0.04983	0.00660
All	-0.48837	-0.00164	0.00372	-0.00765	-0.03645	-0.03984	0.00339
				Before 2006			
Simva.	0.00000	-0.00611	-0.00967	0.00785	-0.04066	-0.03081	-0.00984
Ator.	0.00005	-0.00780	-0.00771	0.00956	-0.05118	-0.04351	-0.00766
Rosu.	-0.75974	-0.02254	-0.02455	-2.53065	-0.14155	-0.11806	-0.02349
All	-0.60369	-0.00314	-0.00672	-0.02256	-0.04993	-0.04299	-0.00693
				2006-2011			
Simva.	-0.55072	-0.00046	0.00164	-0.09297	-0.03049	-0.03256	0.00207
Ator.	-0.54995	-0.00141	0.00118	-0.04504	-0.02697	-0.02819	0.00122
Rosu.	0.00081	0.00494	0.00559	0.01260	-0.04876	-0.05424	0.00548
All	-0.53356	-0.00374	0.00251	-0.03002	-0.03406	-0.03599	0.00194
				After 2011			
Simva.	0.00005	-0.00252	0.00183	0.02434	-0.03495	-0.03634	0.00139
Ator.	-0.60091	-0.00775	-0.00471	-0.11980	-0.04370	-0.03917	-0.00453
Rosu.	-0.73430	-0.00826	-0.00634	-0.02890	-0.04085	-0.03404	-0.00681
All	-0.61513	-0.00237	0.01058	0.00219	-0.02710	-0.03720	0.01010

Table 6: Reduction of Cholesterol and change in therapy (more equivalence)

	BSV		Point		Averages		
Statin	Lower	Upper	OLS	IV	$[Y\|D=0]$	$[Y\|D=1]$	ΔY
				All			
Simva.	-0.49904	-0.00212	0.00190	-0.02847	-0.03266	-0.03525	0.00260
Ator.	-0.83348	-0.00458	0.00748	-0.00218	-0.03090	-0.03850	0.00759
Rosu.	0.00139	0.00594	0.00470	0.02398	-0.04483	-0.04983	0.00500
All	-0.48351	-0.00115	0.00321	-0.00874	-0.03634	-0.03984	0.00349
				Before 2006			
Simva.	-0.53458	-0.00356	-0.00489	-0.05249	-0.03603	-0.03081	-0.00521
Ator.	-0.81169	-0.00425	0.00016	-0.02591	-0.04292	-0.04351	0.00059
Rosu.	0.00768	0.01504	0.05387	0.56251	-0.06833	-0.11806	0.04973
All	-0.55246	-0.01077	-0.00505	-0.06541	-0.04779	-0.04299	-0.00480
				2006-2011			
Simva.	-0.53372	-0.01425	-0.00753	-0.10426	-0.04007	-0.03256	-0.00752
Ator.	-0.52549	-0.00284	0.00031	-0.06596	-0.02796	-0.02819	0.00023
Rosu.	-0.67786	-0.00589	0.00355	-0.15750	-0.04927	-0.05424	0.00498
All	-0.53549	-0.00808	-0.00510	-0.05547	-0.04080	-0.03599	-0.00481
				After 2011			
Simva.	-0.53709	-0.01023	-0.00644	-0.06850	-0.04312	-0.03634	-0.00678
Ator.	-0.57831	-0.00142	-0.00053	-0.04750	-0.04009	-0.03917	-0.00092
Rosu.	-0.62203	-0.00232	-0.00212	-0.25837	-0.03649	-0.03404	-0.00245
All	-0.54537	-0.01037	-0.00833	-0.03535	-0.04589	-0.03720	-0.00869

Table 7: Characterization of subpopulations

	Never				D=0, Compliers				D=1,Compliers				Always			
Variable	All	Pre	Dur.	Post	All	Pre	Dur.	Post	All	Pre	Dur.	Post	All	Pre	Dur.	
age	67.42	64.78	67.04	68.86	68.02	64.93	67.09	69.01	67.06	64.03	66.15	67.72	66.93	63.89	65.95	6
albumina num	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.02	0.03	0.03	0.04	0.03	0.03	0.04	0.03	
alp num	0.06	0.06	0.06	0.06	0.05	0.05	0.06	0.06	0.06	0.05	0.06	0.06	0.06	0.06	0.06	
alt gpt num	0.28	0.30	0.30	0.27	0.27	0.29	0.28	0.26	0.31	0.33	0.34	0.32	0.30	0.34	0.32	
anem	0.08	0.03	0.06	0.11	0.07	0.03	0.06	0.10	0.09	0.03	0.07	0.12	0.08	0.04	0.07	
asma	0.06	0.04	0.05	0.07	0.05	0.03	0.05	0.07	0.06	0.04	0.05	0.09	0.06	0.04	0.05	
ast got num	0.27	0.29	0.29	0.25	0.24	0.27	0.26	0.24	0.30	0.32	0.33	0.29	0.27	0.33	0.30	
bilirub tot e fraz num	0.05	0.03	0.04	0.05	0.04	0.02	0.04	0.04	0.05	0.02	0.04	0.05	0.04	0.03	0.04	
bilirub tot num	0.02	0.03	0.02	0.02	0.02	0.03	0.02	0.02	0.02	0.03	0.02	0.02	0.02	0.03	0.02	
bmi	28.58	28.36	28.62	28.50	28.62	28.60	28.73	28.57	28.58	28.23	28.69	28.66	28.62	28.54	28.61	2
bpco	0.07	0.05	0.07	0.08	0.07	0.05	0.07	0.08	0.08	0.06	0.06	0.09	0.07	0.06	0.07	
col hdl	1.41	1.43	1.41	1.42	1.44	1.44	1.41	1.44	1.40	1.44	1.39	1.40	1.40	1.43	1.38	
col ldl	2.98	3.29	3.04	2.84	2.97	3.33	3.06	2.85	3.09	3.54	3.22	3.12	3.10	3.54	3.24	
col tot	5.12	5.53	5.19	4.95	5.13	5.57	5.22	4.99	5.29	5.85	5.42	5.26	5.30	5.85	5.46	
compliance	0.64	0.54	0.66	0.69	0.63	0.53	0.66	0.68	0.70	0.62	0.74	0.74	0.70	0.61	0.74	
du area1	0.22	0.26	0.26	0.23	0.30	0.25	0.26	0.29	0.22	0.27	0.26	0.21	0.29	0.25	0.26	
du area2	0.16	0.20	0.20	0.22	0.28	0.26	0.24	0.20	0.15	0.20	0.19	0.22	0.27	0.22	0.23	
du area3	0.21	0.20	0.16	0.17	0.15	0.14	0.19	0.19	0.21	0.20	0.19	0.16	0.14	0.17	0.17	
du area4	0.26	0.22	0.25	0.25	0.22	0.26	0.23	0.23	0.26	0.20	0.24	0.25	0.24	0.27	0.24	
du area5	0.15	0.12	0.12	0.13	0.06	0.09	0.09	0.08	0.16	0.12	0.12	0.16	0.07	0.09	0.10	
du bypass pci	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.01	0.00	0.01	0.01	
du decesso	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
du diab	0.26	0.22	0.28	0.28	0.25	0.22	0.27	0.27	0.29	0.21	0.30	0.29	0.27	0.22	0.29	
du fib atr	0.05	0.03	0.05	0.07	0.06	0.03	0.05	0.07	0.05	0.03	0.04	0.07	0.06	0.04	0.05	
du hyper	0.71	0.62	0.71	0.74	0.71	0.63	0.70	0.73	0.71	0.61	0.70	0.74	0.69	0.60	0.69	
du ictus	0.12	0.08	0.12	0.16	0.13	0.09	0.12	0.14	0.14	0.09	0.14	0.19	0.15	0.09	0.14	
du isch	0.01	0.01	0.02	0.02	0.02	0.01	0.01	0.01	0.02	0.01	0.02	0.02	0.02	0.01	0.02	
du malcor	0.18	0.22	0.21	0.19	0.17	0.23	0.21	0.19	0.25	0.25	0.28	0.24	0.26	0.27	0.31	
du sc card	0.03	0.02	0.03	0.04	0.03	0.02	0.03	0.03	0.04	0.03	0.03	0.04	0.04	0.03	0.03	
du vasc d	0.01	0.02	0.02	0.01	0.01	0.02	0.01	0.01	0.02	0.02	0.02	0.01	0.02	0.02	0.02	
ducharlson1	0.40	0.49	0.39	0.34	0.40	0.48	0.40	0.37	0.37	0.49	0.36	0.31	0.36	0.47	0.36	
ducharlson2	0.32	0.30	0.33	0.32	0.32	0.30	0.32	0.32	0.32	0.29	0.33	0.32	0.32	0.31	0.33	
ducharlson3	0.17	0.13	0.17	0.19	0.17	0.14	0.17	0.18	0.18	0.14	0.19	0.20	0.18	0.14	0.18	
ducharlson4	0.11	0.08	0.11	0.15	0.11	0.07	0.11	0.13	0.13	0.08	0.12	0.17	0.14	0.08	0.13	
female	0.54	0.55	0.53	0.54	0.55	0.54	0.53	0.55	0.53	0.55	0.52	0.54	0.53	0.53	0.50	
fumo	0.03	0.05	0.03	0.03	0.03	0.04	0.03	0.03	0.03	0.04	0.03	0.03	0.03	0.04	0.03	
fumo ex	0.04	0.03	0.03	0.04	0.03	0.03	0.03	0.04	0.03	0.03	0.03	0.04	0.04	0.03	0.03	
fumo no	0.05	0.05	0.04	0.06	0.05	0.05	0.04	0.05	0.05	0.04	0.04	0.06	0.04	0.05	0.03	
i bmi	28.33	27.88	28.28	28.39	28.34	28.06	28.37	28.46	28.30	27.96	28.31	28.53	28.31	27.95	28.24	2
i p max	135.53	137.80	136.50	134.76	136.27	138.46	136.23	134.85	135.78	137.53	136.64	134.27	135.89	137.38	135.94	1
i p min	79.42	80.95	79.90	78.41	79.36	81.13	79.67	78.42	79.51	81.02	79.93	78.52	79.34	80.87	79.52	7
mrge	0.19	0.10	0.16	0.26	0.17	0.09	0.16	0.22	0.21	0.11	0.18	0.29	0.19	0.11	0.17	
obes	0.08	0.06	0.08	0.10	0.10	0.06	0.08	0.10	0.08	0.06	0.09	0.11	0.09	0.06	0.09	
parkinson	0.01	0.00	0.01	0.01	0.01	0.00	0.01	0.01	0.01	0.00	0.01	0.01	0.01	0.00	0.01	
q a	9.51	8.56	9.74	10.76	10.02	8.52	9.90	10.04	10.34	8.78	10.54	12.37	10.83	9.52	10.86	1
q a 2	0.34	0.36	0.39	0.30	0.31	0.35	0.35	0.29	0.38	0.38	0.42	0.35	0.35	0.39	0.40	
s a	64.21	54.28	67.50	69.49	62.55	52.42	63.40	66.42	70.39	55.70	73.98	78.94	69.78	58.26	74.18	7
s a 2	6.91	7.40	8.14	6.08	6.43	7.20	7.40	5.93	7.54	7.67	8.68	6.86	7.43	7.91	8.48	
s t	218.16	248.75	228.68	215.73	209.19	239.46	226.66	213.45	242.92	254.08	255.51	231.79	247.17	264.78	263.84	2
s tot	282.37	303.03	296.18	285.22	271.75	291.88	290.06	279.88	313.31	309.78	329.49	310.73	316.96	323.04	338.02	3
sport leggero	0.07	0.08	0.07	0.08	0.08	0.09	0.08	0.07	0.07	0.08	0.07	0.08	0.08	0.08	0.09	
sport medio	0.01	0.02	0.01	0.01	0.02	0.03	0.02	0.01	0.01	0.03	0.01	0.01	0.02	0.02	0.02	
sport no	0.08	0.10	0.09	0.09	0.09	0.08	0.08	0.08	0.09	0.08	0.09	0.10	0.08	0.08	0.07	
sport pesante	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
tiroide	0.21	0.12	0.18	0.25	0.19	0.12	0.18	0.23	0.21	0.13	0.17	0.27	0.19	0.12	0.18	
trigli	1.65	1.84	1.70	1.58	1.61	1.85	1.71	1.58	1.77	2.01	1.82	1.69	1.78	2.09	1.89	
tum	0.11	0.08	0.11	0.14	0.12	0.09	0.11	0.13	0.11	0.07	0.10	0.13	0.11	0.07	0.10	

Table 8: Pattern of behaviuour of liver test

Number	Overall	Lower lev.	Higher lev.
	All		
1	0.07212 ***	0.00930 ***	0.06789 ***
2	0.08176 ***	0.01049 ***	0.07588 ***
3	0.07025 ***	0.00807 ***	0.06623 ***
4	0.12224 ***	0.01636 ***	0.11572 ***
5	0.12011 ***	0.01623 ***	0.11528 ***
	Before 2006		
1	0.07886 ***	0.00849 ***	0.07493 ***
2	0.08679 ***	0.01040 ***	0.07847 ***
3	0.08698 ***	0.01106 ***	0.07847 ***
4	0.14324 ***	0.02138 ***	0.13541 ***
5	0.16685 ***	0.02690 ***	0.16181 ***
	2006-2010		
1	0.08341 ***	0.00849 ***	0.08015 ***
2	0.08738 ***	0.01081 ***	0.08301 ***
3	0.08126 ***	0.00956 ***	0.07738 ***
4	0.13702 ***	0.01839 ***	0.13055 ***
5	0.13595 ***	0.01750 ***	0.12986 ***
	After 2010		
1	0.06654 ***	0.01071 ***	0.06123 ***
2	0.08120 ***	0.00991 ***	0.07674 ***
3	0.06299 ***	0.00618 ***	0.06022 ***
4	0.10443 ***	0.01296 ***	0.09897 ***
5	0.09365 ***	0.01250 ***	0.08811 ***