Drug compliance, co-payment and health outcomes: Evidence from a panel of Italian patients*

Vincenzo Atella, Franco Peracchi, Domenico Depalo, Claudio Rossetti
University of Rome "Tor Vergata"

May 2005

Keywords: Health outcomes, compliance, health policy reforms, prescription charges, co-payment, natural experiments, panel data.

JEL classification codes: C35, C81, D12, I12.

Abstract

This paper studies the relationship between medical compliance and health outcomes – hospitalization and mortality rates – using a large panel of patients residing in a local health authority in Italy. These data allow us to follow individual patients through all their accesses to public health care services until they either die or leave the local health authority. We adopt a disease specific approach, concentrating on hypertensive patients treated with ACE-inhibitors. Our results show that medical compliance has a clear effect on both hospitalization and mortality rates when we restrict our analysis to male patients under ACE-inhibitor monotherapy: health outcomes clearly improve when patients become more compliant to drug therapy. At the same time, we are able to infer valuable information on the role that drug co-payment can have on compliance, and as a consequence on health outcomes, by exploiting the presence of two natural experiments during the period of analysis. Our results show that drug co-payment has a strong effect on compliance, and that this effect is immediate.

* Financial support from Pfizer is gratefully acknowledged. We thank Alessandro Chinellato and Giulio Nati for many valuable comments and ideas regarding the clinical aspects of the research involved. We also thank Anne Beeson Royalty, Jay Bhattacharya, Partha Deb and Alan Garber for their comments. The usual disclaimers apply. Corresponding author: Vincenzo Atella, Faculty of Economics, University of Rome Tor Vergata, via Columbia 2, 00133 Rome, Italy, e-mail: atella@uniroma2.it, phone: +39 06 7259 5635, fax: +39 06 2020 687.

1 Introduction

The increase in the cost of health care services has produced a vast concern among policy makers, who have enforced restrictive measures to contain those trends. This phenomenon has been particularly relevant for drug costs, who have recorded higher increases (in both volumes and prices) compared to other major components of healthcare spending (Jacobzone 2000). Health economists have studied extensively the effects of such restrictive policies on drug expenditure, and a large literature on this subject is available[1].

Unfortunately, much less we know about the effect of these cost containment measures can have on drug therapy compliance and, as a consequence, on health outcomes, measured through indicators of hospitalization and mortality. Not complying with medication, possibly because of affordability issues, can have serious consequences for health. Two North American studies provide evidence of a negative impact: Soumerai et al. (1994) showed increases in mental health service use, and Tamblyn et al. (2001) linked increased adverse events (e.g. emergency department visits or death) among low-income patients, when cost-sharing was increased. Even interrupting hypertensive treatment by just seven days can increase the risk of stroke (Anonymous 2000). Dracup and Meleis (1982) report evidence that 80% compliance to a medication regimen for hypertension lowers blood pressure to normal, whereas 50% compliance is ineffective. Therefore, reducing dosage below a level that produces a therapeutic effect may also have implications similar to not taking a drug at all.

When a co-payment is established, patients have to contribute in some way towards the cost of their medication and health care use. Several empirical studies have found that the demand for prescription drugs is reduced by a direct contribution from the patient but that the overall impact appears to be quite limited, with estimated price elasticity ranging from -0.1 to -0.6. Unfortunately, as pointed out by Freemantle and Bloor (1996), the key concern with drug reimbursement is that, besides reducing the u se of non-essential drugs, it may also reduce the use of essential drugs. Although the reduction in "discretionary" (or non-essential) drugs has been shown to be greater than the reduction in uptake of essential prescribed medicines (McManus *et al.* 1996), the concern remains that essential medication may be affected.

Following this line of research, Atella *et al.* (2004) have investigated the role that increasing out-of-the-pocket expenditure can have on consumers' attitudes to adopt strategies to contain the

[1] Main studies on the topic include Leibowitz et al. (1985), Soumerai et al. (1987), O'Brien (1989), Harris et al. (1990), Ryan and Birch (1991), Huttin (1994), Hughes and McGuire (1995), Atella (1999, 2003), Atella and Rosati (2002).

cost of medication. Using micro-data from a survey conducted in Italy and the UK, they have shown a tendency for both British and Italian patients suffering from hypertension and dyspepsia to use cost reducing strategies which are strongly influenced by income and drug affordability problems. Reduction in compliance (defined as strategies that either induce patients to not obtain their medication at all, or to select fewer prescribed drugs or lower their dosage) is one of the main strategies used. More recently, Piette, Heisler and Wagner (2004) have found similar evidence in the USA, suggesting that cost remains a significant barrier to health care for many adults, especially among the uninsured and the low-income elderly population.

Further evidence has been provided by Case *et al.* (2004), who explore directly the relationship between income level and medical compliance for hypertensive patients through an ad hoc survey carried out in an urban township of South Africa. They find that the fraction of hypertensive patients who report to be non-compliant is about 47top income quintile, but it jumps to 75% at the bottom the income quintile.

Due to the cross-sectional nature of their data, both Atella *et al.* (2004) and Case *et al.*(2004) have been unable to study the link between compliance and health outcomes. The goal of this paper is to fill this gap by using a unique longitudinal data set collected by the Local Health Authority of Treviso, one of the 107 Italian provinces, covering the period from 1997 to 2002. These data allow us to follow individual patients through all their accesses to public health care services until they either die or leave the local health authority. It is important to mention that our analysis is disease specific, as in Atella *et al.* (2004) and in Case *et al.* (2004). In fact, by concentrating on the sub-sample of patients receiving a specific class of drugs, namely ACE-inhibitors, we almost certainly select those suffering from hypertension.

Unfortunately, while containing extremely rich information on health care services received by patients, our data are quite poor in terms of socio-economic characteristics of the patients. In particular, information on income and education is completely absent. Notwithstanding, we are able to obtain some evidence on the relationship between income and compliance by exploiting the presence of two natural experiments in our time period, respectively in January 2001 and March 2002, when the Italian government first abolished and then allowed each single region to (autonomously) reintroduce the co-payment on all drugs provided by the National Health Service (NHS). Although the abolition of the co-payment corresponds to a price effect, in our context we show that, under reasonable assumptions, it is equivalent to a pure income effect. We then employ a difference-in-difference approach to detect the existence of differences in the behavior

of "compliant" versus "non-compliant" patients "before" and "after" the experiments. Under reasonable assumptions, abolishing the co-payment should lead to a higher increase in the rate of compliance of "non-compliant" patients compared to those who were "compliant" before the experiment.

The remainder of this paper is organized as follows. Section 2 describes the data. Section 3 describes our disease-specific approach. Section 4 discusses our indicator of compliance. Section 5 looks at the relationship between compliance and health outcomes. Section 6 investigates if and how health policy changes affect compliance. Finally, Section 7 offers some conclusions.

2 The data

Our data is based on administrative datasets collected by the Pharmaceutical Service Department of the Local Health Agency (LHA)–ULSS 9–of the Italian province of Treviso. This dataset has been obtained by merging three different administrative registries, containing information about daily access to public health care services by the whole local population: the drug prescription database, the hospitalisation registry, and the death and transfer registry. Data are available from 1993 for drug prescriptions and from 1995 for hospitalizations.The drug prescription database contains records of patient prescriptions, including date of dispensing, amount and ATC code of substance dispensed, unit price and number of packages dispensed. It also includes gender and date of birth of the patient receiving the medications, a unique anonymized patient identifier, a unique anonymized identifier of the practitioner who prescribed the medication, and gender, date of birth and typology–whether general practitioner (GP) or specialist (SP)–of the practitioner. The hospitalization registry contains records of each single patient hospitalization, including date of entry and date of dismissal, primary Diagnosis Related Groups (DRG),and cost of hospitalization. Finally, through the anonymized personal identifiers, we were able to link patient prescription and hospitalization information to the death and transfer registry.

Relative to survey data, these administrative data have both advantages and disadvantages. A very important advantage is that they do not present problems, typical of survey data, such as unit and item non-response, measurement errors and bias effects due to interaction with interviewers. Another advantage is that they contain extremely rich information on health care services received by patients.

The main disadvantage is that the data are quite poor in terms of socio-economic characteristics of the patients. In particular, information on income and education is completely absent. Problems

also arise when patients undergo therapy only for certain periods, based on physician advice.

3 A disease-specific approach

The availability of very rich microdata and the topic under investigation suggest adopting a disease-specific approach. In fact, by observing individual behavior we are forced to adopt a methodology that recognizes that patients behave differently in terms of compliance depending on the particular kind of pathology they suffer from. A chronic "asymptomatic" pathology (such as hypertension) leads to patterns of compliance that are different from those involved in case of acute "painful" pathologies (such as headache). Adopting a disease-specific approach offers the advantage of exploring consumer decision-making in relation to specific clinical conditions and, subsequently, it allows us to derive more precise conclusions concerning the determinants of compliance and the role that compliance can have on health outcome.

There are several reasons why hypertension constitutes an interesting clinical condition. First, hypertension has long-term health implications and affects a large share of the population. In fact, hypertension is a chronic condition: It affects about 20% of the Italian adult population, but its prevalence increases with age (37% at age 55–64, 50% at age 65–7 4 years, and 67% at age 75+). Guidelines for the treatment of hypertension have been published by the Word Health Organization (WHO) (WHO Guidelines Sub-Committee, 1999) and, depending on therapeutic response, this involves either single or combined therapy. Second, hypertension is an asymptomatic condition and, therefore, patients may not generally feel ill because of high blood pressure. In this case, compliance with anti-hypertensives is often problematic (McInnes, 1999). Miller (1997) reports evidence from two large surveys showing that failure to obtain a medication is especially problematic in patients with asymptomatic conditions. The most commonly cited reason for this is the patients' belief that they do not really need the medication. Third, hypertension treatment is generally long-term, and this may have non trivial economic implications as patients receive regular, sometimes multiple, prescriptions, thus incurring regular costs. The large prevalence also affects the public budget. Finally, hypertension is an interesting condition to study from the viewpoint of health outcomes. In fact, left untreated it can lead to serious cardiovascular diseases with potentially observable consequences in terms of mortality and hospitalization rates especially when, as in our case, it is possible to follow patients across several years.

Because our dataset does not include direct information on patient diagnoses, we recover this information indirectly from the specific kind of drugs prescribed. Although this is a difficult task in

general (the same drugs may be prescribed for different pathologies), we believe that this indirect approach works well in the case of hypertension and selects the right kind of patients. In fact, according to international clinical guidelines, hypertensive patients should receive pharmacological treatment based on a specific class of active ingredients: the Angiotensin Converting Enzyme inhibitors (ACE-inhibitors).[2] We are aware that some hypertensive patients do not receive such treatment, and therefore we are not selecting them, but at the same time we are highly confident to avoid selecting non-hypertensive patients. Following this approach, patients with prescriptions in this class may be identified as hypertensive patients.

To improve the probability of selecting patients properly, we excluded from the sample patients receiving low dosage of specific active ingredients (e.g. Enalapril 5mg) which, in the Italian medical practice, are usually prescribed for Congestive Heart Failure. Based on DRG codes, we also excluded from our sample patients who present hospitalization for renal diseases but not for cardiovascular diseases, as ACE-inhibitors are often used for patients with kidney failure.

4 Compliance

In the context of health care, drug compliance has been defined as the extent to which the patient's actual history of drug administration corresponds to the prescribed regimen. According to Miller (1997) there are several reasons to be non-compliant: 1) not having a prescription filled, 2) taking an incorrect dose, 3) taking medication at the wrong time, 4) forgetting to take one or more medication, and 5) stopping medication too soon. Behind this definition of compliance is the implicit assumption that medical advice is good for the patient and that rational patients should follow medical advice precisely.

Therefore, at the individual level, an ideal index of drug compliance would be

$$c^*_{ij} = \frac{C_{ij}}{P_{ij}},$$

[2] ACE-inhibitors block conversion of Angiotensin I into Angiotensin II. Angiotensin II is a very powerful chemical that causes the muscles surrounding blood vessels to contract and thereby narrows the blood vessels. The narrowing of the vessels increases the pressure within the vessels and can cause high blood pressure (hypertension). Angiotensin II is formed from Angiotensin I by the "angiotensin converting enzyme" (ACE). ACE-inhibitors are medications that slow (inhibit) the activity of such enzyme, which then reduces the production of Angiotensin II. As a result, blood vessels can dilate and blood pressure is reduced. Lower blood pressure makes it easier for the heart to pump blood, thus reducing the probability of heart failure. In addition, the progression of kidney disease due to high blood pressure or diabetes is slowed. Because they prevent early death resulting from hypertension, heart failure or heart attacks, ACE-inhibitors are one of the most important groups of drugs. In terms of expenditure, this class is one of the most important for the Italian NHS. In 2000, ACE-inhibitors accounted for about 18% of cardiovascular gross pharmaceutical expenditure (class C of the ATC system) and up to 9% of the total public drug expenditure (OSMED, 2000).

where C_{ij} is consumption of substance (active ingredient) j by patient i in a given time period, and P_{ij} is the optimal amount of substance j that should be prescribed to patient i by a physician, given her health characteristics.

Although such an indicator is straightforward from a theoretical point of view, both the numerator and the denominator are unavailable in our data and, in any case, drug consumption would be very difficult to measure. Most dataset allow only to record purchases of drugs or amount of drugs prescribed. In these case, and in order to be still valid, the index of drug compliance relies on the assumption of an informed and responsible patient, who consumes all the drugs purchased or prescribed.

A second set of problems has to do with the denominator. Our assumption that patients have to be treated according to international or national standards need not to be true in general. Physicians may decide to prescribe different dosages for specific patients under specific conditions. We are aware that "average dosage" or "international standards" may represent an imperfect measure in the construction of an indicator of compliance. For example, in the case of hypertension dosage may be set by blood pressure targets–thus being patient specific–rather than being a natural characteristic of the drug.

Therefore, instead of c^*_{ij}, we work with

$$c_{ij} = \frac{A_{ij}}{\bar{P}_j},$$

where A_{ij} is the amount of substance j purchased by patient i in a given time period, $\bar{P}_j$ is the average amount of substance j that should be prescribed to patients according to international guidelines or national standards.

The relationship between the measured and the ideal index is

$$c_{ij} = c^*_{ij} \frac{A_{ij}}{C_{ij}} \frac{P_{ij}}{\bar{P}_j}.$$

It is plausible to assume that $A_{ij} \geq C_{ij}$, so $c_{ij} \geq c^*_{ij}$ whenever $P_{ij} \geq \bar{P}_j$. The term $P_{ij}/\bar{P}_j$ is likely to cause the most serious problems to our analysis, as it represents an important source of unobserved heterogeneity.

Lacking information on individual prescription, we may work with either international guidelines or national standards. For each active ingredient, the WHO publishes an international standard, the Defined Daily Dose (DDD), that represents the average maintenance dose per day for a substance

used in its main indication on adults.[3] A DDD is a unit of measurement and, therefore, it is not a recommended dose, and may not represent a real dose. However, DDDs of different active ingredients can be added.

The main advantage of constructing a compliance indicator based on DDDs rests on the fact that DDDs are units of measurement, useful to compare drug use. This standardization method is useful since the DDD of one drug is assumed to be functionally equivalent to the DDD of any other drug used for a similar purpose. As a result, the number of DDDs for two or more such drugs can be added together. It is also possible to add together the DDDs of all the drugs in the same broad therapeutic class or of all the drugs given to one or more patients. By extension, compliance across groups of drugs may be compared between patients, practices, health authorities, and regions. This allows us to derive compliance indicators for different active ingredients that are comparable and additive. As a result, we can measure the compliance of a single patient without having to distinguish between active ingredients used, given that we can refer to the sum of compliance for every active ingredient used. For the same reason, by using this method we can account for multi-therapies.[4]

To allow for differences between WHO standards and Italian practice, we work with Prescribed Daily Doses (PDD), defined as the average daily dosage of an active ingredient most commonly prescribed for hypertension in Italy.

Table 1 shows, for each class of active ingredients considered in this study, the DDDs provided by the WHO–according to the 1995 revision–and the daily doses we found appropriate for the Italian drug prescription practice (for short, PDDs). The reason why we compare DDDs from WHO with the Italian PDDs is because DDDs have been defined by the WHO based on international standards. Researches conducted by several agencies around the world show that prescriptions by general practitioners (GPs) in individual countries can differ significantly from international standard. There are at least two reasons why these differences may occur: one is the existence of different indications for the same drug,[5] the other is different prescribing habits of GPs compared

[3] The DDD system, developed and maintained by the WHO, attempts to overcome problems with the measurement of volumes of prescribed drugs in terms of number of items. In fact, a single item (package) can refer to any quantity or to any duration, e.g. 6 months or 1 week and, as such, it is quite an unsatisfactory measure. With the DDD system, each drug is given a value, within its recognized dosage range, that represents the assumed average maintenance dose per day for a drug used on its main indication in adults.

[4] It is important to note that we can add up DDDs of different active ingredients prescribed and dispensed to the same individual because our analysis is based only on plain active ingredients, thus excluding drugs with combinations of active ingredients (see WHO Collaborating Centre for Drug Statistics Methodology), such as drugs composed by "diuretics" and "ACE-inhibitors".

[5] For example, the DDD for quinine is based on the dose used for malaria prophylaxis (1200mg) whereas in

to international standards.[6]

Table 2 compares aggregate measures of DDD consumption in our sample with available national data. In the year 2000, the two averages are quite similar, although aggregate Italian consumption of ACE-inhibitors was 53.02 DDD per 1,000 inhabitants, while in our sample we observe a lower consumption of 46.77 DDD per 1,000 inhabitants (obtained using standard WHO DDDs). Looking inside the class of ACE-inhibitors we observe a larger use of Enalapril in our sample compared to the rest of Italy (26.2 vs. 21.4).

Taking the year as our reference period, our index of annual compliance is

$$\bar{c}_{ij} = \frac{\sum_{t=1}^{T_i} PD_{ijt}}{PDD_j \times T_i} = \frac{\overline{PD}_{ij}}{PDD_j},$$

where $\sum_{t=1}^{T_i} PD_{ijt}$ is total amount of doses of substance j purchased by patient i over the T_i days for which she is observed during a year, and $\overline{PD}_j = T_i^{-1} \sum_{t=1}^{T_i} PD_{ijt}$ is the average daily dosage of substance j purchased by patient i during a year. Thus, our index of annual compliance is simply the ratio between the average daily purchase and the Italian prescribed daily dose. By construction, $\bar{c}_{ij}$ ranges from zero to infinity, with the value of 1 corresponding to the Italian standard.

Since a patient can purchase more than just one active ingredients within the class of ACE-inhibitors, compliance for the ith patient must be computed over all possible active ingredients purchased during the reference period. Thus, by adding over all J active ingredients in the ACE-inhibitor class, we get our measure of annual compliance for the ith patient in the sample

$$\bar{c}_i = \sum_{j=1}^{J} D_{ij}\, \bar{c}_{ij} = \frac{\sum_{j=1}^{J} D_{ij}\, \overline{PD}_{ij}}{\sum_{j=1}^{J} D_{ij}\, PDD_j},$$

where $D_{ij} = 1$ if substance j is included in patient i's therapy and $D_{ij} = 0$ otherwise.

Problems arise when patients undergo therapy only for certain periods, based on physician advice. Consider the case of a patient with recorded prescriptions only for the first six months of the year. Should this patient be considered "fully" compliant or "half" compliant? Similarly, when the therapy is interrupted for a long period of time, we may wonder whether this reflects non-compliance by patients or perfect adherence to medical advices who suggested to stop the therapy. Unfortunately, our panel records patient information only if they interact with the system. We

England the main indication is the treatment of leg cramps (300mg).

[6] Specific examples for Italy are Enalapril and Lisinopril, for which the WHO recommendations is 10 DDDs while the Italian practice is 20 DDDs. For this reason, the PDDs reported in table 1 should be considered as reflecting the actual usage by Italian GPs.

therefore decided to drop from our sample all those patients who present missing values for one year or more over the observation period.

An additional problem is due to the fact that, when patients are hospitalized, drugs are dispensed directly by the hospital pharmacy and are not recorded in the pharmaceutical registry. This would lead to underestimate compliance. We correct the doses purchased by hospitalized patients by assuming that they are treated according to the standards of the Italian practice. Specifically, we impute the doses obtained through hospitals, assuming that daily dosage is equal to the PDDs. We then add imputed doses to the doses purchased through pharmacies. The importance of this correction is larger for older patients, as hospitalization rates tend to increase with age.

5 Compliance and health outcomes

This section looks at the relationship between compliance and health outcomes. We first analyze the determinants of compliance among our sample of patients, and then consider how compliance and other demographic characteristics help explain the variability in health outcomes, such as hospitalization and mortality rates.

5.1 Sample selection criteria

We start with all patients residing in the LHA territory who were prescribed at least one drug belonging to the plain ACE-inhibitor class (ATC class C09AA) at any time during 1993–2002. Because reliable data on hospitalization is only available from 1997, we focus on the 6-year period from 1997 to 2002, resulting in an unbalanced panel of 43,148 patients and 170,083 observations. Given the peculiarity of the condition under scrutiny, we decided to restrict attention to patients born 1910–1960 (2,980 patients and 10,124 observations dropped).[7] We also dropped patients with compliance equal to 0 or greater than or equal to 2 (273 patients and 884 observations dropped), patients who were hospitalized for renal diseases but not for cardiovascular diseases (1,270 patients and 4,943 observations dropped), and patients with no drug consumption for at least one year during the period considered (17,620 patients and 80,143 observations dropped). Finally, we dropped patients with missing values for at least one of the variables used (666 patients and 2,489 observations dropped). Our final sample consists of an unbalanced panel of 20,339 patients and 71,500 observations, with an average of 3.5 annual observations per patient.

[7] The age selection lead to drop 1,518 patients below age 40 and 1,462 above age 90. The fact that the number of patients below age 40 is low may be regarded as a good sign that all patients selected are really suffering of hypertension.

Table 3 shows the panel structure of the initial and the final sample. The fact that the number of patients in the sample increases over time is a consequence of the selection criteria used to obtain our sub-sample from the population. In fact, we select patients based on the prescription of a specific active ingredient in the ATC class C09AA (ACE-inhibitors) at any time during the period 1997–2002 and, since entry into the data set, we follow the patient through all her accesses to the NHS. Thus, if a patient is first recorded receiving a prescription in 1997, we track all her accesses to the NHS for 6 years, until 2002. On the other hand, if a patient is first recorded receiving a prescription in 1998, we track her for only 5 years. This implies that the number of patients is higher in 1998 than in 1997 and, therefore, the stock of patients who received at least one prescription with ACE-inhibitor drugs increases over time.

5.2 Descriptive statistics

Figure 1 compares the distribution by year of birth and gender of our sample–patients with ACE-inhibitor drug prescriptions–with that of patients using any other active ingredient in the class of cardiovascular drugs (ATC class C). The only noticeable difference is represented by the distribution of older women that, as ACE-inhibitor users, are slightly over-represented compared to all other drug classes. Average age of patients is about 68 years, and most of the observations (57.5%) are for patients born between 1920 and 1940, which is consistent with the peculiarity of the cardiovascular diseases considered here. Concerning gender, the fraction of women (51%) is slightly higher than the fraction of men–although, from the epidemiological viewpoint, men are more likely to suffer from cardiovascular diseases, women have a higher life expectancy.

Figure 2 shows the distribution of hospitalisation rates by age, gender and ATC classes. Concerning hospitalization rates related to specific cardiovascular DRG, we observe that patients treated with ACE-inhibitors present higher hospitalization rates. Hospitalization rates for cardiovascular diseases are higher for men than for women almost at all ages. About 25% of patients have been hospitalised for any reason during the period considered, while just 9.1% of patients have been hospitalised for cardiovascular diseases.

Figure 3 presents mortality rates by age, gender and ATC class. About 3.2% of patients died during the period. Mortality rates are very close to zero until age 55 years for men and about age 60 for women. It is only after age 55 that men experience higher mortality rates than women. Finally, data shows no significant difference in mortality rates by ATC class.

Table 4 reports summary statistics of the variables in our dataset. Variables y1997–y2002 are

dummy variables for the years from 1997 to 2002. As the market offers small and large pack sizes (with the large containing a double amount of active ingredient), we have constructed a dummy variable that account for the possibility that physicians may prescribe one of the two. In fact, it may be possible that patients using the large pack size be more compliant. According to our data, patients purchasing large packages are about 60%. Patients whose prescription has been written by a specialist, rather than a GP, are just 0.2%. Average age of prescribing physicians is about 48 years, and the vast majority of them are males. In fact, only 16.8% are female practitioners.

Figure 4 shows the distribution of compliance by active ingredients. The values presented here refer to the sub-sample of patients whose compliance indicator does not exceed 2, thus leading to a loss of 562 observations out of more than 159,000. For all active ingredients, the peaks are located around 0.25, 0.50, 0.75, and 1.

Figures 5 and 6 present summaries of our compliance indicator. Figure 5 shows the histogram of average annual compliance, aggregated across active ingredients, and confirms the peaks observed for each single active ingredient in Figure 4. We also note that the number of patients with compliance values above 1.4 is rather low.

Figure 6 shows mean average annual compliance by age and gender. We observe an inverse U-shaped path of compliance, with compliance increasing until about age 70 for men and then decreasing. On average, compliance is higher for men than for women, with average compliance ranging between 0.45 and 0.60.

To summarize how individual characteristics help explain variations in compliance, we fit by OLS a linear model, separately by for male and female patients, where the outcome variable is our indicator of compliance and the covariates include a cubic polynomial in age, a linear term in the age of the physician, and dummies for calendar year, pack size, gender and typology of the physician. Table 5 shows the estimated coefficients of this linear model. The baseline category is in this case a person aged 55, observed in 2000, consuming a 14-pill package, whose practitioner is a 50 years old male GP. Buying a package with 28 pills increases the patient's compliance and is by far the most significant factor affecting compliance. Ceteris paribus, purchasing a double-dosage package means cutting by half the time spent meeting the practitioner to get a prescription and visiting a pharmacy to cash the prescription. The physician's gender is significant only for women, and in this last case a female physicians is associated with lower compliance by a female patient. Older practitioners tend to reduce patient's compliance, and prescriptions made by a specialist also lead to lower compliance – although specialists are less than 1% of physicians. Finally, the

coefficient on the year 2001 is strongly positive.

5.3 Modeling the probability of hospitalization and mortality

We now present the results of fitting simple parametric models for the probability of hospitalization and mortality in year $t+1$ as function of compliance in year t (entering as a quadratic), controlling for demographic and other characteristics. The model for mortality also controls for hospitalization for cardiac illness in year t.

In an attempt to control for part of the unobserved heterogeneity in the data, we selected the sample by dropping patients with recorded compliance below 0.1 (as they may be affected by mild hypertension, that could be treated simply by healthy diet and by reducing stress factors), and patients with recorded compliance above 1.7 (as they may suffer of specific problems and represent less than 0.5% of the sample). This selection process produced an unbalanced panel of 17,858 patients and 63,003 observations, with an average of 3.5 annual observations per patient.

We further decided to split the sample between patients who have only been prescribed drugs in the ACE-inhibitor class for at least 65% of the time they are observed (mono-therapy) and patients who have been prescribed multiple active ingredients (multi-therapy).[8] Patients who received more than one active ingredient may be in worse health conditions, or present side effects or non response to ACE-inhibitors. By splitting the sample in this way, we isolate confounding effects for which we do not have adequate information.

Our models for the probability of hospitalization and mortality are logit models where the covariates include a second degree polynomial in compliance in the past year, an indicator for using more than one ACE-inhibitor, a third degree polynomial in age, four dummy variables for 10-year birth cohorts, and five time dummies. The basic models have been fitted separately for men and women.

Table 6 reports the estimated coefficients of the hospitalization model.[9] Goodness of fit is rather low, indicating that we do not control for important variables. The intercept corresponds to the log-odds of the baseline category, that is a person aged 55, observed in 1998, with compliance equal to 1 in the previous year, and taking only one kind of ACE-inhibitor. Women have a slightly lower probability to be hospitalized than men. Considering the effect of compliance, the coefficients are highly significant for both men and women. The positive coefficient on the squared term implies a

[8] Results are robust to different specifications of mono/multi-therapy.

[9] The (asymptotic) standard errors are robust to heteroskedasticity and clustering arising from the panel structure of the data.

U-shaped effect of compliance on hospitalization rates.

It is interesting to note that the coefficient on the indicator for the use of more than one active ingredient in the ACE-inhibitor class is highly significant. Because this dummy variable may be proxy for a patient's health status, the positive sign suggests that using more than one active ingredient is associated with an increase in the probability of hospitalization. Age is significant only for men under multi-therapy, while the coefficient on the dummy for the year 2002 is negative and strongly significant for multi-therapy.

Figure 7 plots the observed and predicted probabilities of hospitalization by level of compliance and gender for patients under mono-therapy, along with their asymptotic confidence intervals. The predicted values in these graphs have been obtained by allowing only compliance to vary, while setting all other variables equal to their average values. The graphs indicate a U-shape relationship between hospitalization and compliance, with a minimum around the value of 1 (the optimal value of compliance).

What emerges quite clearly from these graphs is that, for patients under mono-therapy, the probability of future hospitalization for cardiovascular problems falls as current compliance moves toward its optimal value of 1. In particular, the probability of future hospitalization for male patients falls from about 6% when current compliance is near 0.2 to 3% when current compliance is close to 1. For female patients the reduction is less pronounced.

We also fitted the same basic logit model to the probability of future mortality, including an additional dummy variable for hospitalization for cardiac illness in the current year in order to account for different health of the patients. As before, the model was fitted separately to men and women and to patients with mono- and multi-therapy.

Table 7 reports the estimated coefficients. The intercept corresponds to the log-odds for the baseline category, namely a person aged 55, observed in 1998, with current compliance equal to 1, taking only one kind of ACE-inhibitor, and not hospitalized in the current year. The goodness of fit is still low (pseudo R^2 between 0.09 and 0.14), but better than for the hospitalization model. For the baseline case, men have a probability of future death that is twice as high as women. Contrary to the hospitalization model, current compliance is highly significant only in case of men under mono-therapy. Having being hospitalized in the current year has a large positive impact on future mortality, and this impact seems to be larger for women than for men in case of mono-therapy.

Figure 8 plots observed and predicted mortality rates by level of compliance and gender for a patient under mono-therapy. Focusing on male patients, we estimate that increasing current

compliance from 0.2 to 1 reduces future mortality rate by half. As before, the effect of compliance is more marked for patients under mono-therapy compared to those on multi-therapy.

6 Health policy changes and compliance

The results presented in the previous section indicate that compliance helps predict health outcomes. In this section we investigate if and how health policy changes affect compliance. This may have important implications for public policy because, if the relationship between compliance and health outcomes may be interpreted as causal, then health policy changes may affect health outcomes by changing the level of compliance.

Studies by Alan *et al.* (2002, 2003) and Poirier *et al.* (1998) have analyzed the effect of public prescription drug programs on out-of-pocket household drug expenditure in Canada. For Italy, Atella and Rosati (2003), Atella, Rosati and Rossi (2002) and Atella, Bernardi and Rossi (2003) have shown that the drug reforms during the 1990s and in 2001 – although effective in controlling public expenditure – caused undesired redistributive effects, by penalizing mostly the frailest groups in the population. The main limit of these studies is that they only evaluate the impact of policy changes on out-of-pocket expenditure and do not assess their effects on drug compliance and therefore on health outcomes. In this paper we try to fill this gap by exploiting the fact that our time period includes two major policy changes regarding drug co-payment, in 2001 and 2002. These policy changes represent two natural experiments, whose effects on medical compliance an d health outcomes can be evaluated using a difference-in-difference (DID) specification.

6.1 The natural experiments

Our natural experiments correspond to the abolition, on January 1st 2001, of the co-payment on drug prescriptions and its later reintroduction in March 2002. Until January 2001, patients were supposed to pay a fixed amount on each prescription received by his/her physician (the so-called "ticket"). This prescription charge was a flat charge of 3,000 liras (about 1.5 euros) per prescription (each prescription could include at most two packages) that applied equally to all packages, irrespective of the pack size, the dosage or the pharmaceutical form. This implies that changes in the prescription charge produced effects only on the consumer decision process (through a change in out-of-the-pocket expenditures), while leaving unaffected the physician prescription behavior. The aim of the co-payment was twofold: on the one hand it helped reduce public expenditure (financial concern), on the other hand it helped reduce unnecessary consumption (clinical concern).

Patients could be exempted from paying the prescription charges either for clinical reasons or for income status. Hypertensive patients received the exemption if they were diagnosed as such by a specialist (cardiologist), independently of income status. Although hypertension is a chronic condition for which we should expect patients to be exempted from paying prescription charges, our data presents a quite different picture. Table 8 shows the percentage of prescriptions for which patients paid the prescription charge, by year and age group, for all cardiovascular drugs in our sample.[10] About 90% of the adult population pays a ticket - exemptions are more frequent among the oldest old – except in 2001, when the ticket was abolished (in 2002 the fraction of non exempt is lower because the ticket was reintroduced in March).[11]

Being a fixed amount, the co-payment has an intrinsic regressive structure affecting mostly low income patients suffering from chronic conditions. In fact, when the cost containment policy was first introduced, the drug expenditure share went up more for low income patients than for high income patients. At the same time, drug expenditure was reduced more for low income patient with the abolition of the prescription charge in 2001, thus revealing the large distributive effects of such measures.

From an empirical point of view, many studies have confirmed the role of co-payment in reducing the level of drug consumption of low income patients. In this section, we present a simple theoretical framework that allows us to interpret such evidence from an economic point of view. For expositional reasons, let us assume that our patients have to choose between drugs – represented for example by all products in the ACE-inhibitor class - and all other goods. As ACE-inhibitors drugs are provided by the Italian NHS, the drug price is equal to the prescription charge. Therefore, a change in the prescription charge leads to a change in drug consumption (and therefore drug compliance) for each given level of consumption of the other goods.

Figure 9 shows the budget lines and the indifference curves of two types of patients – poor (BC_1) and rich (BC_2) – for the two types of goods – drugs and other goods. Different levels of drug consumption are associated with different levels of drug compliance. When $Y = 1$, patients reach the "recommended" optimal level of compliance. For positive values of drug price, poor patients reach the optimal level of compliance in A_3, where the consumption of all other goods is equal to F_0. As shown in Figure 9, this point may not be compatible with patient utility maximization. In fact, at the corner (A_3) the slope of the indifference curve is higher than the slope of the budget line. This

[10] Results are almost unchanged is we consider only patients under ACE-inhibitor mono-therapy.

[11] This picture is consistent with the data from the ISTAT 1999 Multiscopo Survey. According to this survey, about 10% of the population is exempt for illness reasons. Another 10% is exempt for other reasons (income, unemployment status, invalidity, etc.), although these two groups are for a large part overlapping.

is because hypertension is an asymptomatic condition, and patients may underestimate the long-run utility of consuming an adequate level of antihypertensives drugs, thus leading to a misperception of the correct marginal rate of substitution between drugs and other goods. In turn, this should lead to observe poor patients that trade off dr ugs for higher quantities of other goods, moving down the budget line until reaching points like A_1 or A_2. Atella *et al.* (2005) and Huttin *et al.* (2003) present interesting empirical evidence supporting such behaviour, with poor hypertensive patients who adopt different strategies to reduce drug consumption of anti-hypertensive drugs in Italy, as well as in several other EU countries. On the contrary, rich patients may reach the "recommended" optimal level of compliance compatibly with a higher consumption of other goods in E. For rich patients, the trade-off may be less relevant, as their income allows buying the desired level of other goods without having to trade off drug. In our natural experiment, the price of ACE-inhibitors is set equal to zero, thus leading to the new budget lines BC_1' (poor) and BC_2' (rich).[12] This should lead poor patients to move to a higher level of compliance, say from $Y = 0.4$ to $Y = 1.0$, while for rich patients we should not observe a similar movement as they are already on the optimal level $Y = 1.0$.

6.2 The DID specification

We employ a DID specification to look for differences in the behavior of "compliant" versus "non-compliant" patients "before" and "after" the policy change. If co-payment matters then, after the policy change, we would expect a higher increase in the rate of compliance of "non-compliant" patients relative to those who were "compliant" even before the experiment. This may then indicate a positive relationship between income and compliance.

Our base model is the following:

$$Y_{it} = \alpha_1 + \alpha_2 D_t + \beta_1 C_i + \beta_2 D_t C_i + U_{it}, \qquad i = 1, \ldots, n, \qquad t = 1, 2,$$

where Y_{it} is the indicator of compliance, D_t is a time dummy (equal to 1 for the period after the policy change, and equal to 0 otherwise), C_i is a treatment dummy (equal to 1 for patients with average compliance above a certain threshold before the policy change, and equal to 0 otherwise),[13]

[12] In practice, the budget constraint would probably never become vertical, even in the presence of a zero price for drugs. In fact, on top of the financial cost, we have time costs to obtain the drug prescription from the physician (waiting times in the GP office) and time costs to go to the pharmacy to get the drugs dispensed. All these costs may be either patient or physician specific or both. In any case, even accounting for these costs, the conclusions of the above analysis will not be substantially altered.

[13] The treatment (control) group corresponds to patients who were compliant (non compliant) before January 2001, when the co-payment was abolished. In our base model, patients are considered as compliant if their level of compliance (before January 2001) was greater than 0.55.

and U_{it} is a regression error.

According to the model, $\alpha_1 + \beta_1 = \mu_1^C$ is the average compliance of the compliants in period 1, $\alpha_1 + \alpha_2 + \beta_1 + \beta_2 = \mu_2^C$ is the average compliance of the compliants in period 2, $\alpha_1 = \mu_1^{NC}$ is the average compliance of the noncompliants in period 1, $\alpha_1 + \alpha_2 = \mu_2^{NC}$ is the average compliance of the noncompliants in period 2, $\alpha_2 + \beta_2 = \Delta\mu^C$ is the average change in compliance of the compliants, $\alpha_2 = \Delta\mu^{NC}$ is the average change in compliance of the noncompliants, and $\beta_2 = \Delta\mu^C - \Delta\mu^{NC}$ is the DID coefficient (the difference in the average change between compliants and noncompliants).

The model was estimated by OLS, after dropping patients who entered the panel after January 2001 or left the panel before January 2001.

As robustness checks, we consider four modification of the base model. The first consists of adding a vector of demographic variables. The second consists of adding a set of individual specific effects and estimating using the fixed-effect (within-group) estimator. The third consists of dropping patients with no prescriptions ($Y = 0$). The fourth considers two different subsamples, one covering the period 1997–2002, the other covering the period 2000–2001.

After fitting the models separately for men and women, we find no significant difference in the estimated coefficients, and so we simply report the results for the specification that only includes a dummy variable for gender. Table 9 shows, for both sub-samples, the OLS estimates of the model, with patients classified as compliant if their indicator of compliance is greater or equal to 0.55, and excluding patients with zero compliance. All parameters have the expected sign and are statistically significant. In particular, the DID parameter is negative and highly significant. This result provides strong support for the argument that the abolition of prescription charges increase the average compliance of non-compliant patients much more than for compliant patients. As shown in Table 10, this result is robust to alternative specifications, sample selection criteria and estimation procedures.

As a further robustness check, we re-estimated the model using different thresholds to classify patients as compliant. Figure 10 presents the estimated DID parameter for different values of the threshold. The DID estimates are fairly stable at around -24% for thresholds ranging from 0.5 to 0.75. At about 0.80, we observe a noticeable increase of the estimates (in absolute terms). From 0.90 to 1.15, the negative slope becomes even steeper. Our finding that the DID parameter is higher (in absolute terms) the higher the threshold is a simple consequence of the fact that patients with a high level of compliance before the policy change have little room to further increase their level of compliance after the abolition of the ticket.

6.3 Speed of adjustment of compliance to changes in policy

How responsive are changes in compliance to changes in the co-payment structure? To answer this question, we re-parameterized the model of the previous section in order to capture changes in compliance over time and estimate the resulting model using monthly instead of annual data. By doing this, we are also able to capture the second natural experiment, in March 2002, when the ticket was reintroduced. Interacting all coefficients with monthly dummies, we are able to estimate average monthly compliance for both "compliant" and "non-compliant" patients. Figure 10 reports these estimates.

It is clearly seen that both natural experiments had an effect on compliance and that this effect was immediate. In particular, the abolition of the ticket in January 2001 increased the average compliance of "non compliant" patients, the new equilibrium being reached within one month. Its reintroduction fifteen months later reduced the equilibrium level again within one month. It is important to notice that, after March 2002, the average level of compliance is higher than before January 2001.

7 Conclusions

The main conclusion of this study is that drug compliance for anti-hypertensive drugs matters for health outcomes. According to our results, for patients under mono-therapy the probability of future hospitalization for cardiovascular problems and mortality falls by about half as current compliance moves toward its optimal value of 1. This is partly in line with the results of Dracup and Meleis (1982) who find evidence that high compliance to a medication regimen for hypertension lowers blood pressure to normal, whereas compliance below 50% is ineffective, up to a point where a low dosage produces a therapeutic effect similar to not taking a drug at all.

In particular, the probability of future hospitalization for male patients falls from about 6% when current compliance is near 0.2 to 3% when current compliance is close to 1. For female patients the reduction is less pronounced, but the lowest hospitalization rate is still observed when current compliance is near 1. For patients under multi-therapy, however, the negative relationship disappears. Similar conclusions hold for mortality. Focusing on male patients, we estimate that increasing current compliance from 0.2 to 1 reduces future mortality rate by half. As before, the effect of compliance is more marked for patients under mono-therapy compared to those on multi-therapy. These results are extremely robust to different econometric specifications and to sample selection.

Furthermore, changes in the co-payment structure appear to have a strong effect on the average level of compliance of previously non-compliant patients, while leaving almost unchanged the ave rage level of compliance of previously compliant patients. Reducing co-payments, therefore, leads to a larger fraction of patients being treated. The speed of adjustment appears to be extremely rapid. Patients (and therefore the costs for the NHS) adjust to the new regime within a month in both cases. This is consistent with the view that policy makers should operate through changes in co-payment schemes whenever they want to achieve rapid effects on demand. Finally, the average level of compliance of previously non-compliant patients after the reintroduction of the ticket is higher than before the abolition of the ticket. This suggests that a fraction of the patients experienced positive effects from a more ad equate therapeutic coverage and decided to maintain the new level of compliance even after the reintroduction of the ticket.

The policy implications of such results are quite important. First of all, although the NHS spends a large amount of money on drugs, in many cases the low level of compliance recorded for several patients within our sample may produce negligible returns in terms of improved health outcomes. This result may imposes a complete rethinking of the relationship existing between GPs and patients, with GPs that should care more about compliance profiles of their patients, possibly through a larger use of information technologies - that are still underused in Italy GP practices. The second implication that seems to emerge from our results is that in order to provide a better therapeutic coverage for all patients the drug expenditure should increase. If this remains compatible with a financial sustainable NHS still needs to be assessed. According to our results a higher compliance rate should reduce by half hospitalization rates. Although at the present our data do not allow us to quantify these benefits, we believe that there is a ample space for substitution in term of costs within the NHS. Finally, as long as co-payment affects drug consumption, it will consequently affect drug compliance and then health outcomes. This means also that, in many cases, expected saving accruing from reduction in drug expenditure could be wiped out by increasing hospital costs and social costs due increased mortality rates.

References

Anonymous (2000), Antihypertensive compliance and stroke risk. *The Pharmaceutical Journal* 265: 642.

Atella V. (1999), Drug cost containment policies in Italy: are they really effective in the long-run? The case of minimum reference price, *Health Policy*, 50: 197–218.

Atella V.(2003), Physicians prescription behavior and cost to the patients in Italy: first evidence based on focus group techniques and prescription data. In Huttin C. (ed.), *Patient Charges and Decision-Making Behaviors of Consumers and Physicians*, Amsterdam: IOS Press.

Atella V, Rosati FC. (2002), Spesa, equit e politiche sanitarie in Italia negli anni 90: quali insegnamenti per il futuro, *Politiche Sanitarie*, 3: 3–17.

Atella V., Schafheutle EI., Noyce PR., Hassell K.(2004), Affordability of medicines and patients cost reduction behaviors: empirical evidence based on SUR estimates from Italy and the United Kingdom, *Applied Health Economics and Health Policy*, forthcoming.

Case A., Le Roux I., Menendez A. (2004), Medical compliance and income-health gradients, *American Economic Association – Papers and Proceedings*, 94: 331–335.

Di Matteo R.M. (2004), Variations in patients adherence to medical recommendations. A quantitative review of 50 years of research. *Medical Care*, 42: 200–209.

Dracup KA, Meleis AI. (1982), Compliance: an interactionist approach. *Nursing Research*, 31: 31–36.

Freemantle N, Bloor K. (1996), Lessons from international experience in controlling pharmaceutical expenditure. I: influencing patients, *British Medical Journal*, 312: 1469–1471.

Harris BL, Stergachis A, Ried LD. (1990), The effect of drug co-payments on utilization and cost of pharmaceuticals in a health maintenance organization, *Medical Care*, 28: 907–917.

Hassell K, Atella V, Schafheutle E.I., Noyce PR. (2003), Cost to the patient or cost to the healthcare system? Which one matters the most for GP prescribing decisions? A UK-Italy comparison, *European Journal of Public Health*, 13: 18–23.

Houston Miller N. (1997), Compliance with treatment regimens in chronic asymptomatic diseases. *American Medical Journal*, 102(2A): 43-49.

Hughes D., McGuire A. (1995), Patient charges and the utilization of NHS prescription medicines: some estimates using a co-integration procedure, *Health Economics*, 4: 213–220.

Huttin C. (1994), The use of prescription charges, *Health Policy*, 27: 53-73.

Huttin C., Atella V., Brenner G., Hedvall M.B., Mechtler R., Noyce P., Schafheutle E. (2003), Patient survey: International hypertension results, in C. Huttin (ed.), *Patient charges and decision-making behaviors of consumers and physicians*, IOS Press.

Jacobzone S. (2000), Pharmaceutical policies in OECD countries: Reconciling social and industrial goals, OECD Labour Market and Social Policy Occasional Paper n. 40.

Jones R, Lydeard S. (1989), Prevalence of symptoms of dyspepsia in the community, *British Medical Journal*, 298: 30–32.

Leibowitz A., Manning W., Newhouse J. (1985), The demand for prescription drugs as a function of cost sharing, *Social Science and Medicine*, 21: 1063–1069.

Lundberg L., Johannesson M., Isacson D.G.L., Borgquist L. (1998), Effects of user charges on the use of prescription medicines in different socio-economic groups. *Health Policy*, 44: 123–134.

item McInnes G.T. (1999) Integrated approaches to management of hypertension: promoting treatment acceptance. *American Heart Journal*, 138: S252–S255.

O'Brien B. (1989), The effects of patient charges on the utilization of prescription medicines. *Journal of Health Economics*, 8: 109–131.

Piette J., Heisler M., Wagner T.H. (2004), Cost-related medication underuse: Do patients with chronic illnesses tell their doctors?, *Archives of Internal Medicine*, 164: 1749–1755.

Poirier, S., LeLorier, J., Pag, V.,Lacour, A. (1998), The effect of a $2 co-payment on prescription refill rates of Quebec elderly and its relationship to socio-economic status, *Canadian Pharmaceutical Journal*, 131: 30–34.

Ryan M, Birch S. (1991), Charging for health care: Evidence on the utilization of NHS prescribed medicines, *Social Science and Medicine*, 33: 681–687.

Soumerai S.B., Avorn J., Ross-Degnan D., Gortmaker S. (1987), Payment restrictions for drugs under Medicaid: Effects on therapy, cost and equity. *New England Journal of Medicine*, 317: 550-556.

Soumerai S.B., McLaughlin T.J., Ross-Degnan D., Casteris C.S., Bollini P. (1994), Effect of limiting Medicaid drug-reimbursement benefits on the use of psychotropic agents and acute mental health services by patients with schizophrenia. *New England Journal of Medicine*, 331: 650–655.

Stuart B., Grana J. (1998), Ability to pay and the decision to medicate, *Medical Care*, 36: 202-211.

Tamblyn R., Laprise R., Hanley J.A., Abrahamowicz M., Scott S., Mayo N., Hurley J., Grad R., Latimer E., Perreault R., et al. (2001), Adverse events associated with prescription drug cost-sharing among poor and elderly persons. *Journal of the American Medical Association*, 285: 421–429.

Vermeire E., Hearnshaw H., Van Royen P., Denekens J. (2001), Patient adherence to treatment: three decades of research. A comprehensive review. *Journal of Clinical Pharmacy and Therapeutics*, 26: 331–342.

Word Health Organization (WHO) Guidelines Sub-Committee, 1999.

Table 1: DDDs and PDDs by substance.

ATC code	Active ingredient	1995 WHO DDDs	Italian PDDs	Ratio DDD/PDD
C09AA01	Captopril	50	50	1
C09AA02	Enalapril	10	20	0.5
C09AA03	Lisinopril	10	20	0.5
C09AA04	Perindopril	4	4	1
C09AA05	Ramipril	2.5	5	0.5
C09AA06	Quinapril	15	15	1
C09AA07	Benazepril	7.5	10	0.75
C09AA08	Cilazapril	2.5	5	0.5
C09AA09	Fosinopril	15	15	1
C09AA10	Trandolapril	2	2	1
C09AA11	Spirapril	6	6	1
C09AA12	Delapril	30	30	1
C09AA13	Moexipril	15	15	1
C09AA15	Zofenopril	30	30	1

Table 2: PDDs per 1000 inhabitants in year 2000.

ATC code	Active ingredient	Italy*	Our sample
C09AA02	Enalapril	21.4	26.2
C09AA03	Lisinopril	7.3	3.4
C09AA04	Perindopril	4	3.5
C09AA05	Ramipril	7.4	5.7
C09AA09	Fosinopril	4.5	2.3
C09AA	ACE-inhibitors	53	46.8

* Source: OSMED, 2003

Table 3: Panel structure of the initial and the final sample.

Year	1997	1998	1999	2000	2001	2002	Total
Initial sample: Patients filling ACE-inhibitor prescriptions							
1997	17,652	17,142	16,390	15,654	14,978	14,366	96,182
1998	0	5,323	5,156	4,913	4,726	4,525	24,643
1999	0	0	5,403	5,263	5,057	4,851	20,574
2000	0	0	0	4,728	4,593	4,396	13,717
2001	0	0	0	0	5,027	4,925	9,952
2002	0	0	0	0	0	6,015	5,015
Total	17,652	22,465	26,949	30,558	34,381	38,078	170,083
Final sample: Patients born 1910–1960 filling ACE-inhibitor prescriptions							
1997	7,491	7,126	6,832	6,604	6,406	6,211	40,670
1998	0	1,715	1,592	1,515	1,460	1,415	7,697
1999	0	0	2,001	1,884	1,810	1,756	7,451
2000	0	0	0	2,040	1,947	1,875	5,862
2001	0	0	0	0	2,807	2,728	5,535
2002	0	0	0	0	0	4,285	4,285
Total	7,491	8,841	10,425	12,043	14,430	18,270	71,500

Table 4: Descriptive statistics. Final sample: Patients born 1910–1960 filling ACE-inhibitor prescriptions (20,339 patients and 71,500 observations).

Variables	Mean	St. Dev.	Min	Max
Year 1997	0.105	0.306	0	1
Year 1998	0.124	0.329	0	1
Year 1999	0.146	0.353	0	1
Year 2000	0.168	0.374	0	1
Year 2001	0.202	0.401	0	1
Year 2002	0.256	0.436	0	1
Age	68.144	11.462	37	92
Year of birth	1932	12	1910	1960
Female dummy	0.516	0.500	0	1
Large pack size	0.601	0.490	0	1
Female GP	0.168	0.374	0	1
Year of birth of GP	1952	7	1928	1968
Age of GP	48.375	6.879	34	70
Specialist	0.002	0.046	0	1
More than 1 ACE-inhibitor	0.037	0.190	0	1
Hospital. rate for cardiov. DRG	0.103	0.304	0	1
Mortality rate	0.035	0.183	0	1
Compliance	0.632	0.347	0.010	1.998

Table 5: Estimated coefficients of the linear model for annual compliance ($*$ significant at 10%; $**$ significant at 5%; $***$ P significant at 1%).

	Men	Women
Age	-0.035 *	0.015
Age^2/100	0.078 ***	-0.001
Age^3/10000	-0.051 ***	-0.010
Year 1997	0.014 **	0.013 **
Year 1998	0.000	-0.009 *
Year 1999	-0.008 *	-0.010 **
Year 2001	0.030 ***	0.023 ***
Year 2002	0.018 ***	-0.005
Large Pack size	0.125 ***	0.099 ***
Female GP	0.001	-0.017 **
Age GP	-0.001	-0.001 **
Specialist	-0.274 ***	-0.215 ***
Constant	0.557 ***	0.557 ***
No. obs.	34,639	36,861
RMSE	.345	.336

Table 6: Estimated coefficients of the logit model for hospitalization ($*$ significant at 10%; $**$ significant at 5%; $***$ significant at 1%).

	Mono-therapy		Multi-therapy	
	Men	Women	Men	Women
Compliance	-2.138 ***	-1.640 **	-1.351 ***	-1.281 ***
Compliance^2	1.225 ***	1.274 ***	0.749 ***	0.567 **
More than 1 ACE-inhibitor	0.923 ***	0.129	0.734 ***	0.582 ***
Age	-0.077	0.193	-0.663 **	-0.271
Age^2/100	0.220	-0.296	1.101 ***	0.500
Age^3/10000	-0.123	0.172	-0.565 ***	-0.261
Year 1999	-0.016	-0.340	-0.217 **	-0.007
Year 2000	-0.220	-0.058	-0.061	-0.026
Year 2001	-0.186	0.010	-0.195 **	-0.048
Year 2002	0.020	0.011	-0.299 ***	-0.298 ***
Constant	-3.965 ***	-4.112 ***	-2.546 ***	-3.107 ***
No. obs.	9,923	12,556	11,814	10,852
Pseudo ^{2}	.0407	.0219	.0296	.0273

Table 7: Estimated coefficients of the logit model for mortality ($*$ significant at 10%; $**$ significant at 5%; $***$ significant at 1%).

	Mono-therapy		Multi-therapy	
	Men	Women	Men	Women
Compliance	-2.505***	0.801	-0.088	-0.921
Compliance^2	1.469***	-0.785	-0.060	0.593
More than 1 ACE-inhibitor	0.810***	0.855**	0.396***	0.150
Age	-0.718	-0.442	0.008	0.293
Age^2/100	1.066	0.634	0.072	-0.381
Age^3/10000	-0.450	-0.232	-0.017	0.224
Hospitalized at $t-1$	0.591***	0.973***	0.745***	0.763***
Year 1999	-0.356	-0.409	-0.277**	0.029
Year 2000	-0.514**	-0.432*	-0.342**	-0.348**
Year 2001	-0.815***	-0.930***	-0.305**	-0.384**
Year 2002	-0.864***	-0.813***	-0.385***	-0.746***
Constant	-4.756***	-5.534***	-4.238***	-5.167***
No. obs.	9,923	12,556	11,814	10,852
Pseudo R^2	.139	.123	.0976	.109

Table 8: Percentage of patients paying prescription charges by age group and year.

Age group	1997	1998	1999	2000	2001	2002
41–50	0.97	0.95	0.93	0.92	0	0.75
51–60	0.98	0.95	0.93	0.93	0	0.76
61–70	0.97	0.94	0.91	0.91	0	0.75
71–80	0.93	0.90	0.88	0.88	0	0.73
80–90	0.80	0.78	0.76	0.76	0	0.63
Total	0.93	0.91	0.88	0.88	0	0.73

Table 9: Estimated OLS coefficients. Comparison across subsamples.

	Subsample 1		Subsample 2	
	Coeff.	t-ratio	Coeff.	t-ratio
$\alpha_1 = \mu_1^{NC}$	0.326	170.5	0.374	143.1
$\alpha_2 = \Delta\mu^{NC}$	0.236	59.5	0.202	50.5
$\beta_1 = \mu_1^{C} - \mu_1^{NC}$	0.560	170.1	0.489	117.0
$\beta_2 = \Delta\mu^{C} - \Delta\mu^{NC}$	-0.228	-40.6	-0.171	-29.5

Table 10: Estimated DID coefficient (β_2). Comparison across models.

Model	Coeff.	t-ratio
OLS without demographic var's	-0.228	-40.57
OLS with demographic var's	-0.228	-40.54
FE without demographic var's	-0.228	-40.44

Figure 1: Distribution of the sample by year of birth and gender.

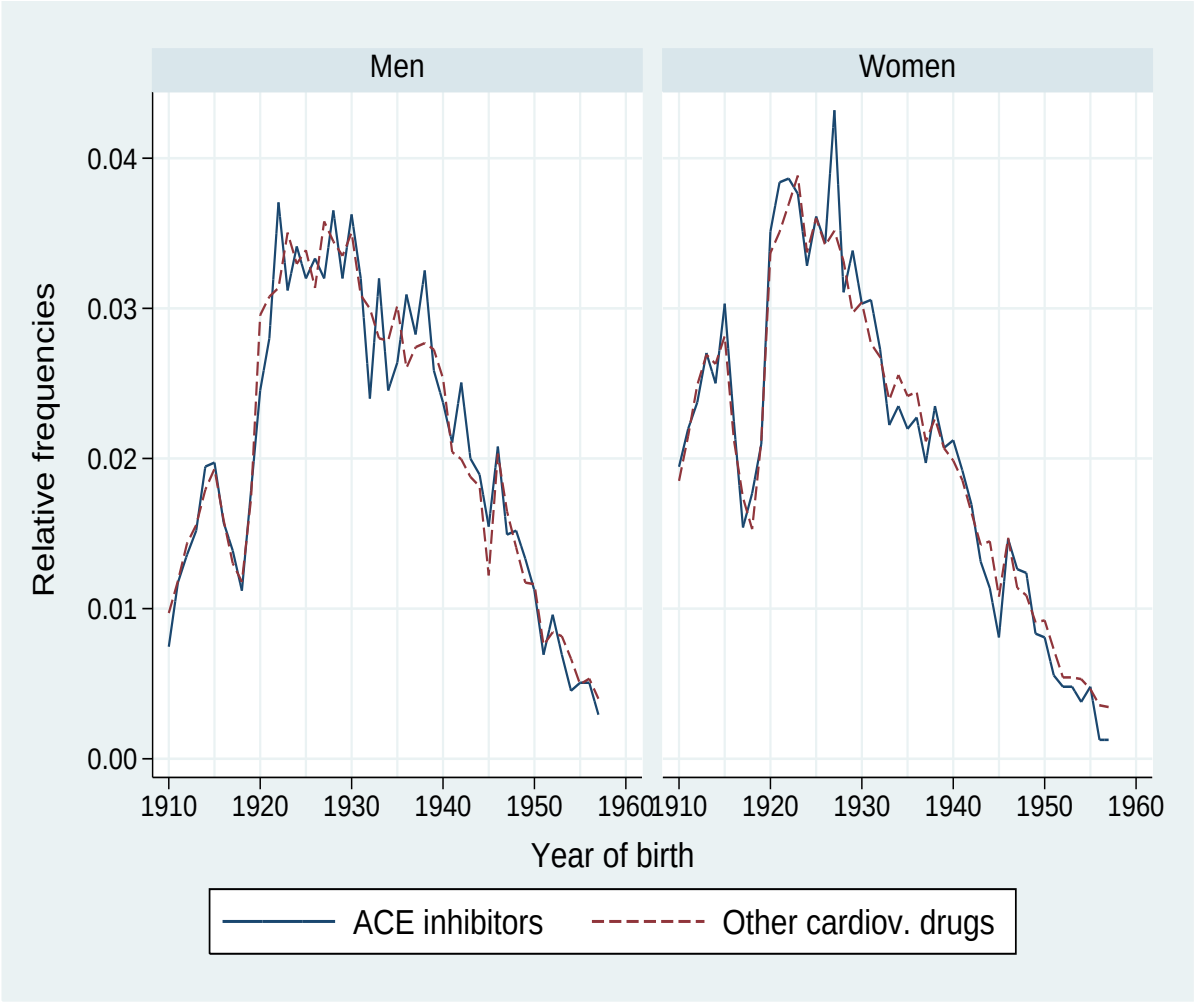

Figure 2: Hospitalization rates by age, gender and ATC class.

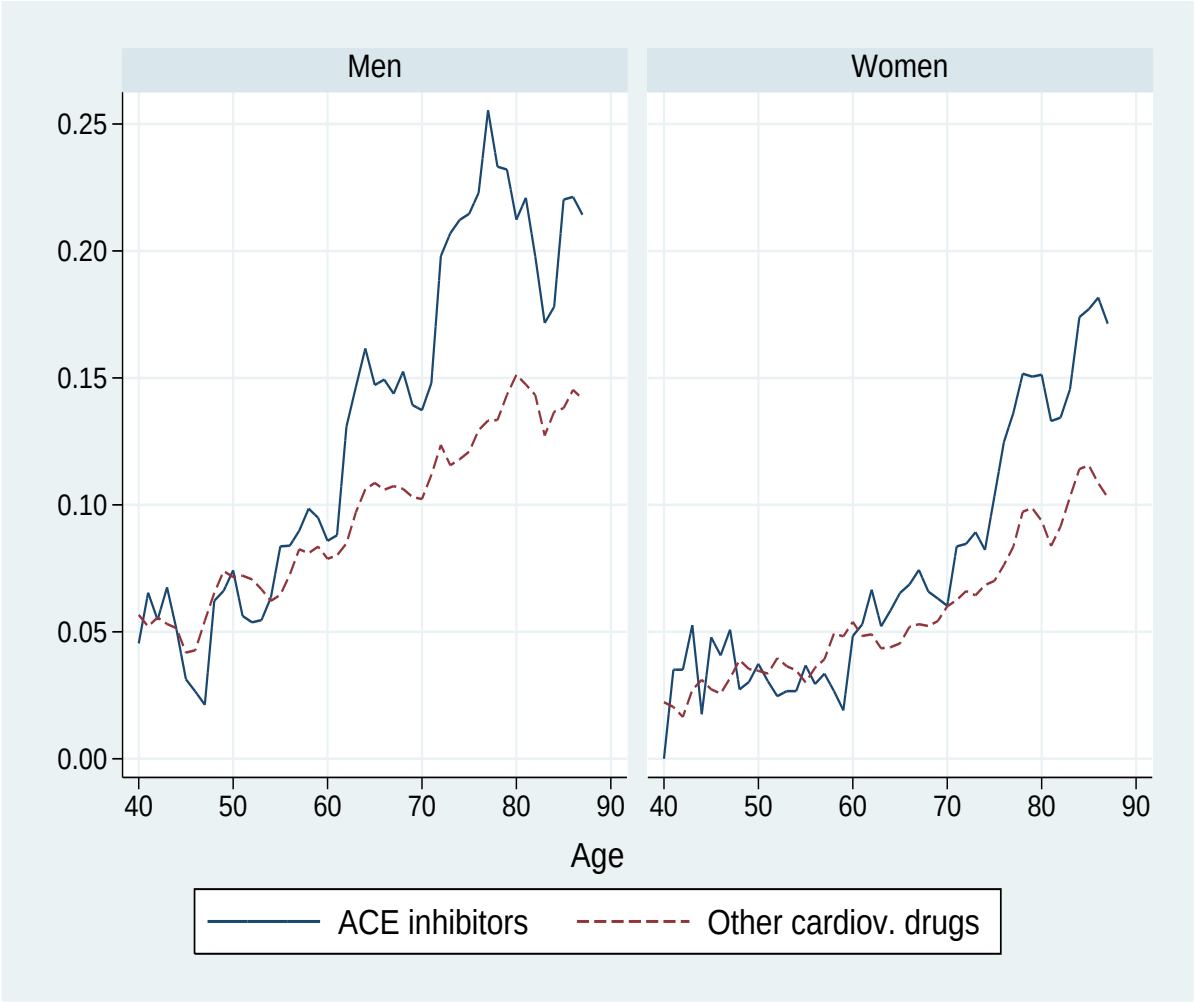

Figure 3: Mortality rates by age, gender and ATC class.

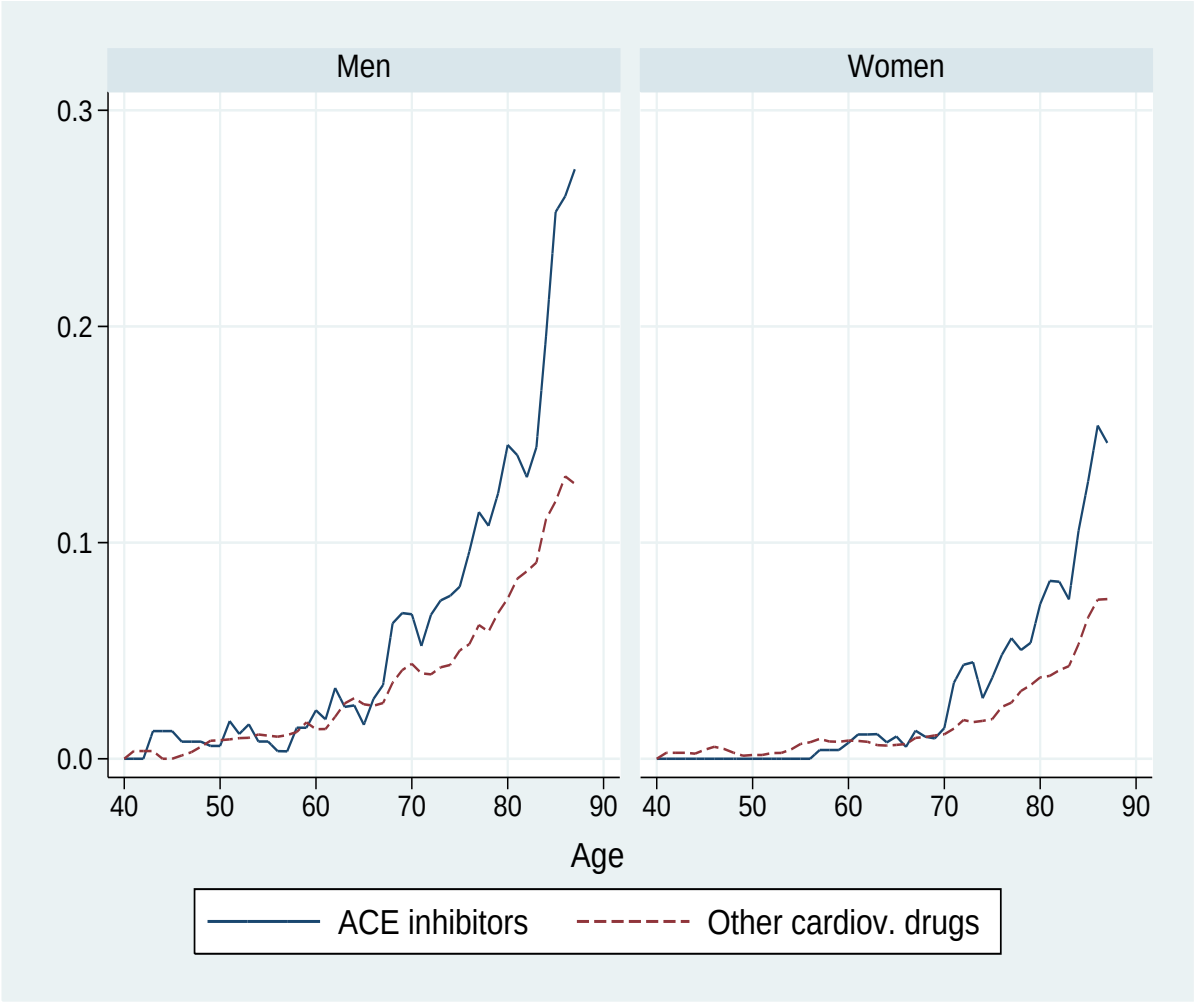

Figure 4: Distribution of compliance by active ingredient using PDD's.

Figure 5: Histogram of annual compliance.

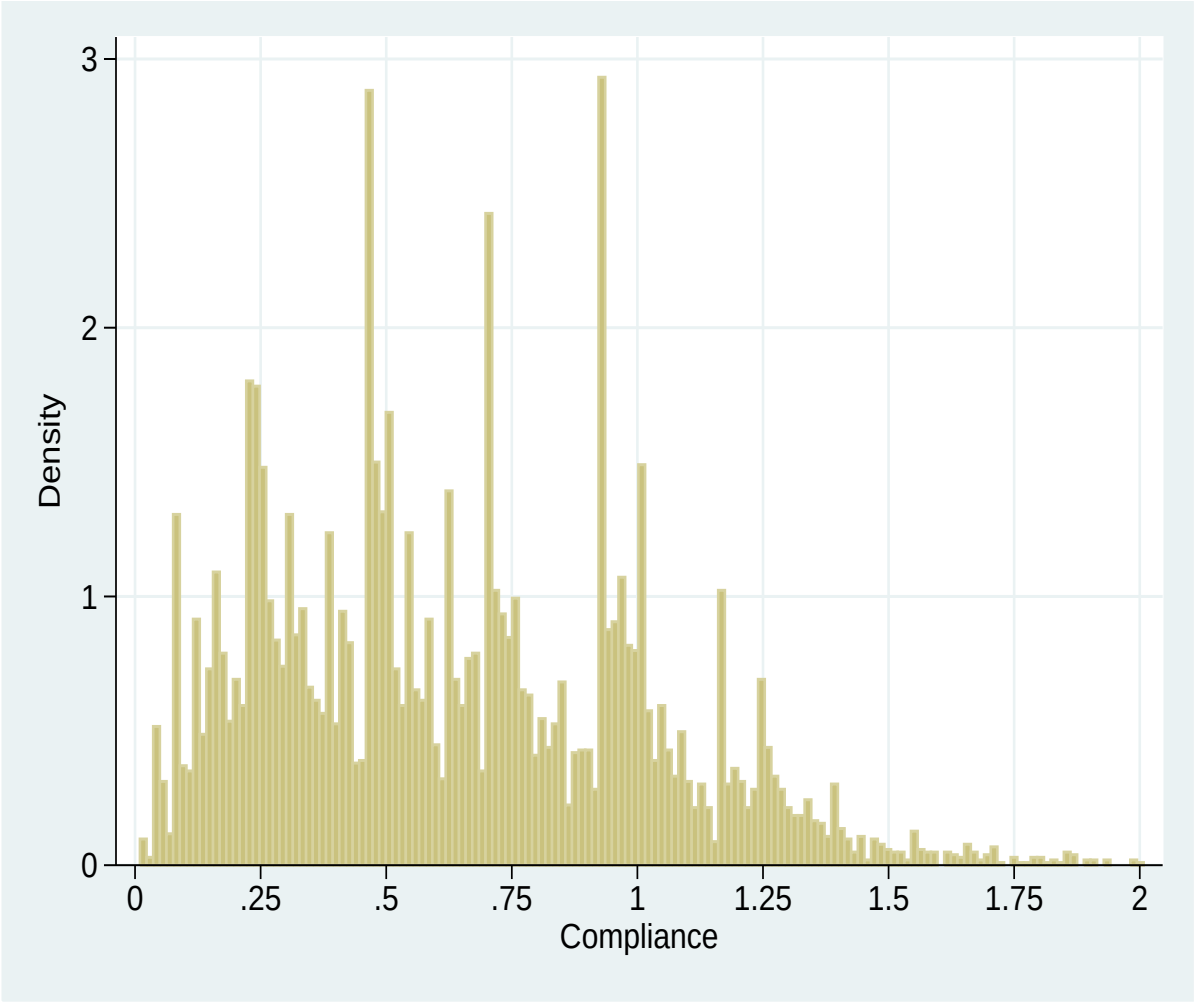

Figure 6: Average annual compliance by age and gender.

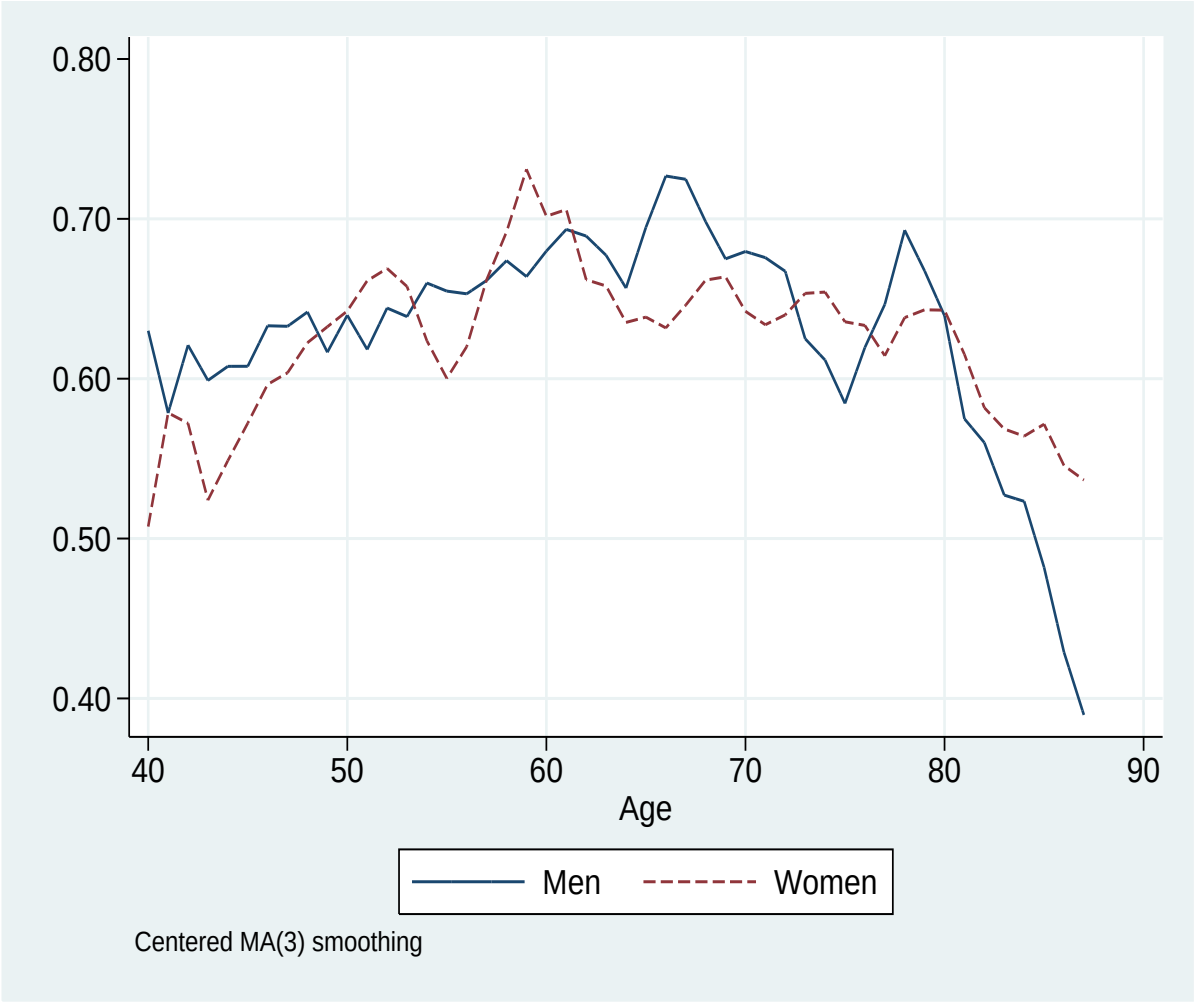

Figure 7: Observed and fitted hospitalization rates by gender and compliance level. Patients under mono-therapy.

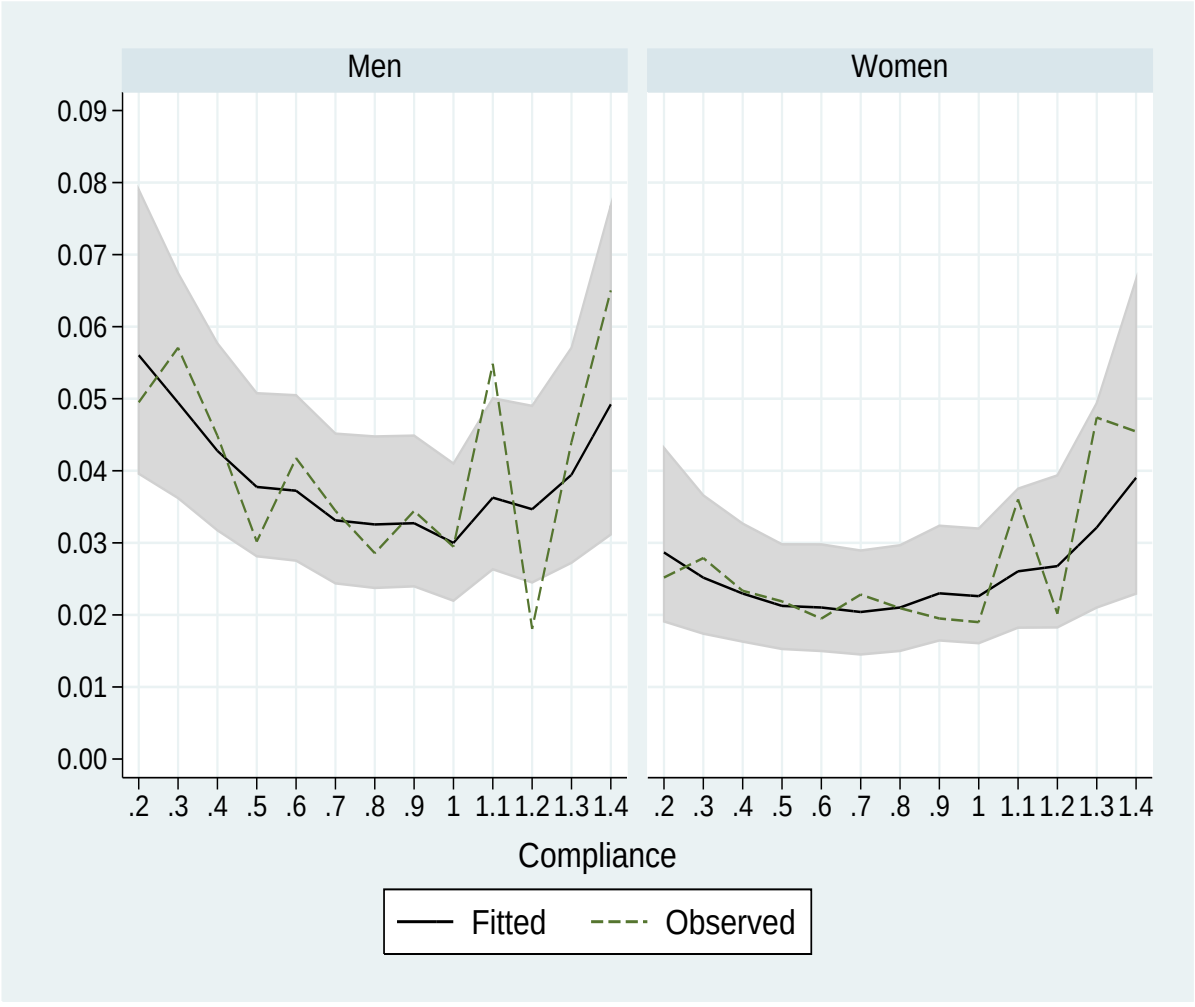

Figure 8: Observed and fitted mortality rates by gender and compliance level. Patients under mono-therapy.

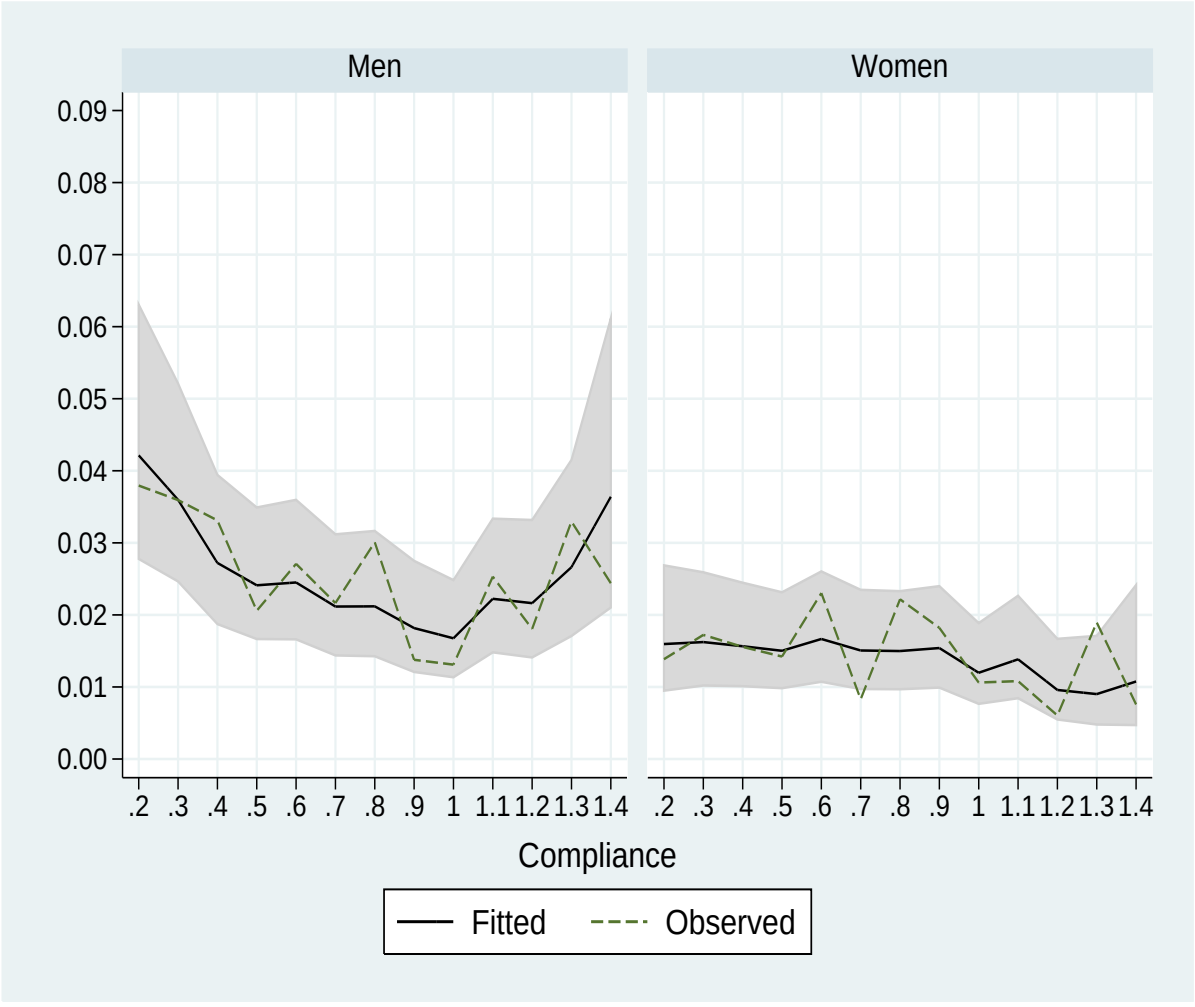

Figure 9: The effect of co-payment abolition on utility maximization for "compliant" and "non compliant" patients.

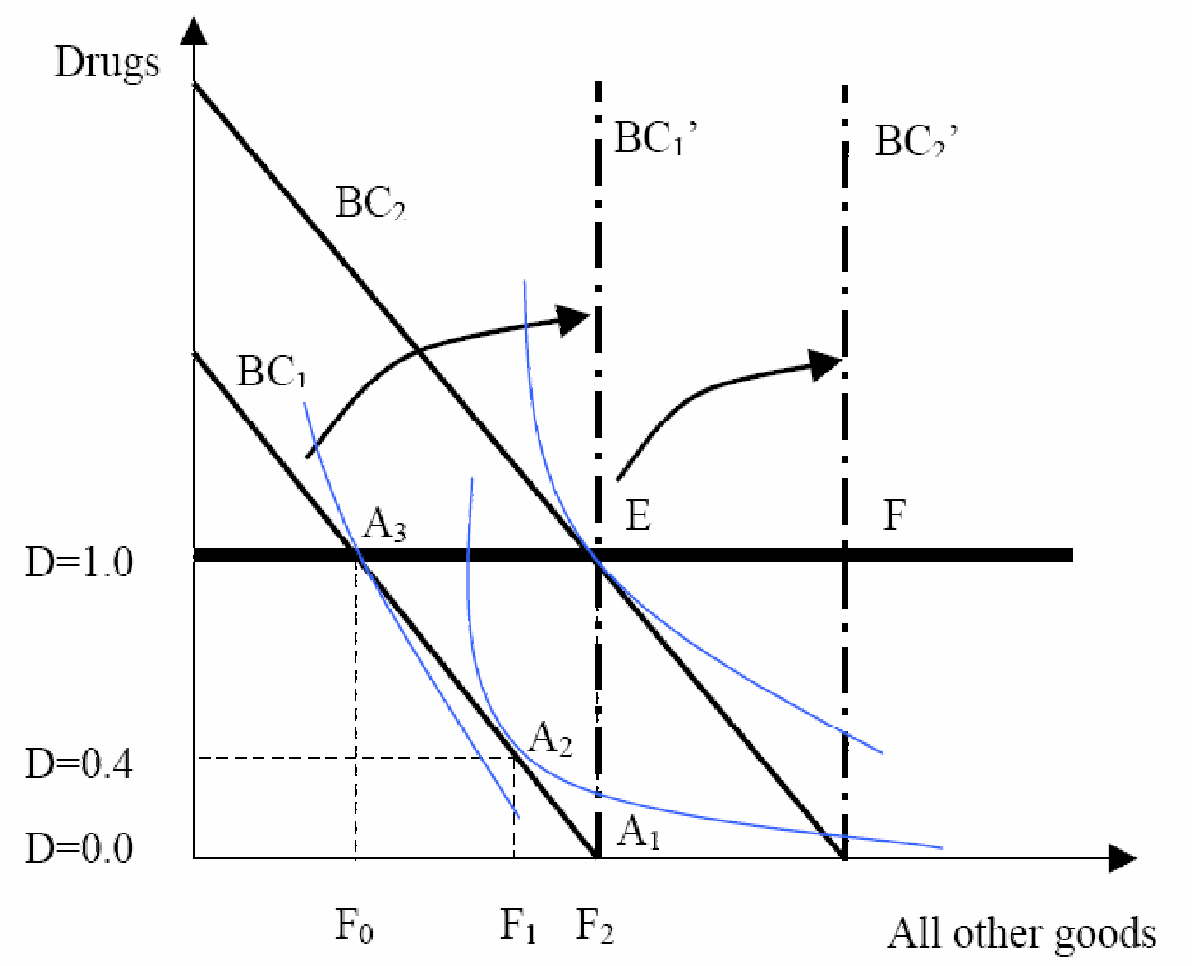

Figure 10: Estimated DID coefficient for different values of the threshold.

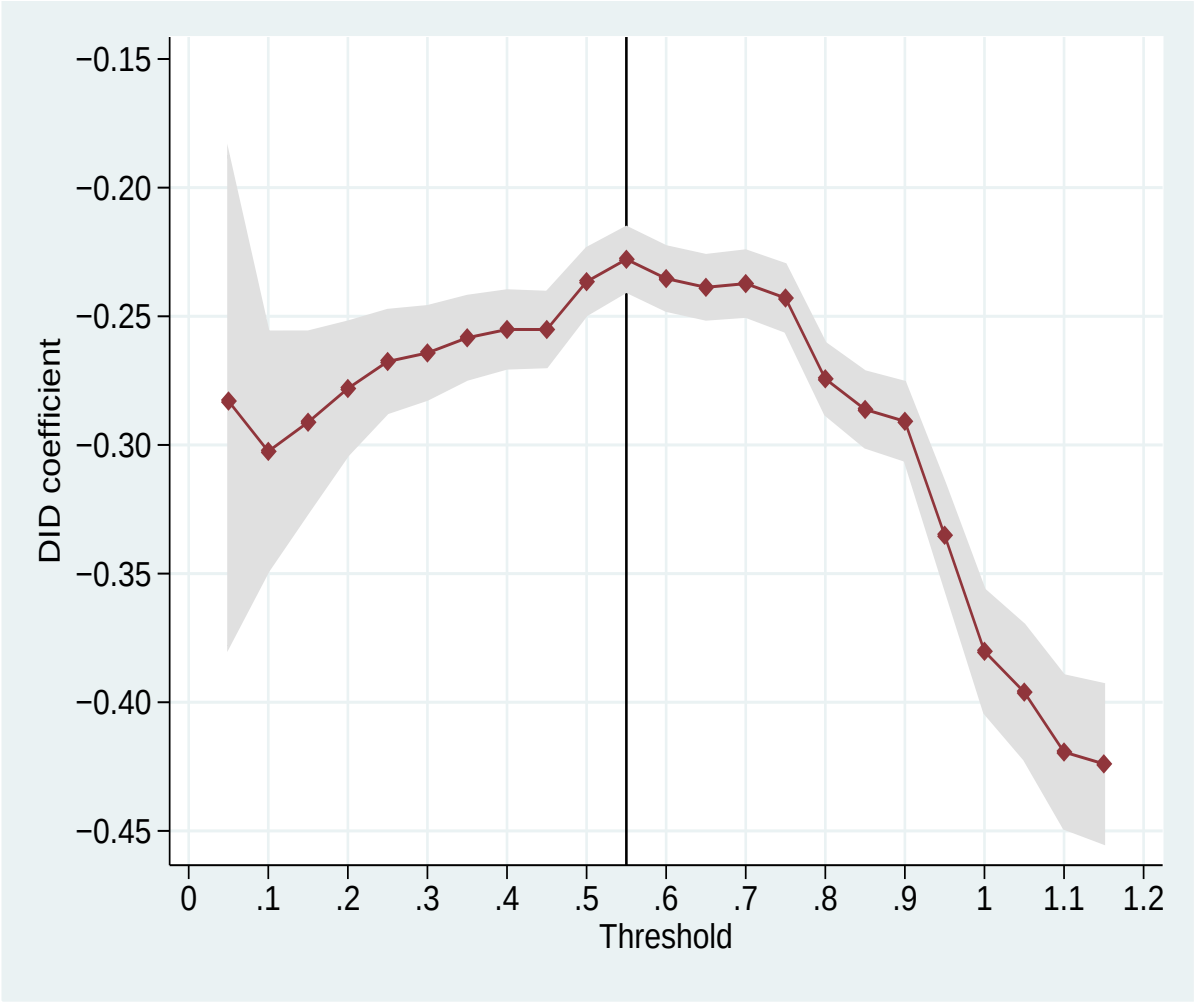

Figure 11: Average monthly compliance for compliants and noncompliants.

Appendix

Figure 12 compares the distribution of patients by year of birth in our sub-sample with the statistics provided by the National Statistical Institute (ISTAT) for the province of Treviso and Italy as a whole. The data show a higher fraction of older people in our database (for both men and women) compared to the broader picture of Italy and the Treviso province. This difference is clearly related to the age-related selection into our sample of patients suffering from the specific condition of hypertension.

Figure A.4 compares mortality rates by age and gender in our sample to the mortality rates in 1999 released by ISTAT for Italy and the province of Treviso. Considering mortality for all causes, our sample shows rates that are similar to the ones for Italy as a whole, which are somewhat higher than those reported for the province of Treviso.

Figure A.5 compares the mortality rates in our sample with those due solely to cardiac illness as released by ISTAT. Mortality rates in our sample are definitely higher. This is mainly due to the fact that, although our sample consists of people who at least once used drugs to treat cardiac diseases, we cannot distinguish mortality caused by such cardiac diseases from other causes.

Figure 12: Distribution of the sample by year of birth and gender.