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 extensively studied the effects of such restrictive policies on drug expenditure, and a large literature on this subject is available[1]

Unfortunately, much less is known about the effect of these cost containment measures 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 the use of mental health services, 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. This indicates that reducing dosage below a level that produces a therapeutic effect may have similar implications 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 use 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) and Atella (1999, 2003).

cost of medication. Using micro-data from two surveys, 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 low compliant is about 47% at the top 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 for one of the 107 Italian provinces and covering the period from 1997 to 2002. 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 ACE-inhibitors, we almost certainly select those suffering from hypertension (although not all hypertensive patients). We are able to obtain some evidence on the relationship between co-payment, compliance and health outcomes 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 reintroduce the co-payment on all drugs provided by the National Health Service (NHS). By using a difference-in-difference approach, we detect statistically significant differences in the behavior of "high compliant" versus "low compliant" patients "before" and "after" the experiments.

The remainder of this paper is organized as follows. Section 2 describes the data. Section 3 describes our drug-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

The data comes from three administrative registries maintained by the Pharmaceutical Service Department of ULSS 9, the local health agency covering the southern part of the Italian province of Treviso. The first registry is the drug prescription database, which contains records of patient prescriptions, including date of dispensing, amount and Anatomical Terapeutical and Clinical Classification (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 second is the hospitalization registry, which contains records of each single hospitalization, including date of entry and dismissal, primary Diagnosis Related Groups (DRG), and cost of hospitalization. Through the anonymized personal identifiers, we were able to link patient prescription and hospitalization information to the third registry, the death and transfer registry. The resulting dataset allows us to follow individual patients through all their accesses to public health care services until they either die or leave the local health authority. Data are available from 1993 for drug prescriptions and from 1997 for hospitalizations.

Relative to survey data, these administrative data have both advantages and disadvantages. An important advantage is that they do not present problems which are typical of survey data, namely 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 they contain little information on patients' socio-economic characteristics. In particular, information on income and education is completely absent.

3 A disease-specific approach

Patients may behave differently in terms of compliance depending on the kind of pathology they suffer from or the treatment that they receive. For example, 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). Focusing on specific pathologies or on specific drug treatments 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 outcomes.

In this paper we focus on patients treated with a specific class of active ingredients: the ATC class C09AA, corresponding to the class of the Angiotensin Converting Enzyme inhibitors (ACE-inhibitors).[2] There are two reasons for doing this. First, this class of drugs is one of the most important for the Italian NHS in terms of expenditure. In year 2003, ACE inhibitors accounted for about 9% of total public drug expenditure. Second, in the Italian practice, this class of active ingredients is employed in the treatment of hypertension. In fact, according to evidence gathered from a large database collected by Health Search,[3] in 2003 about 80% of the prescriptions of ACE inhibitors (associated or not with diuretics) were issued for treating hypertension.[4]

Hypertension is a chronic asymptomatic pathology that affects a large share of the Italian population and tends to have long-term health implications. About 20% of the Italian adult population suffers of hypertension and its prevalence increases with age (37% at age 55–64, 50% at age 65–7 4 years, and 67% at age 75+). Because hypertension is an asymptomatic condition, patients do not generally feel ill because of high blood pressure. In this case, compliance with anti-hypertensives is often problematic (McInnes 1999).[5] 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

[2] ACE-inhibitors block conversion of Angiotensin I into Angiotensin II, that is a very powerful chemical which 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.

[3] Health Search is a network of Italian GPs that records information on drug prescriptions and related pathology. In 2003, the network had 320 member GPs covering 465,200 patients (for a total of 3,826,000 prescriptions).

[4] This evidence is in contrast with the experience from other countries. According to OSMED (2005, p. 13), "contrary to what has emerged in the most recent studies of hypertension, especially in the ALLHAT (2002) study, the prescription of amlodipin, doxazosin, ACE inhibitors and angiotensin II inhibitors continues to increase [in Italy]. The prescriptive behavior of Italian clinics seems to be guided mostly by the European guidelines regarding the therapy for arterial hypertension, as opposed to the American behavior whose priority is to obtain a reduction in the pressure values rather than recommend a specific pharmacological choice".

[5] There are several reasons for low compliance: 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 medications, and 5) stopping medication too soon. 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.

case, it is possible to follow patients across several years.

4 Compliance

In the context of health care, drug compliance may be defined (Di Matteo 2004) as the extent to which the patient's actual history of drug administration corresponds to the prescribed regimen. Behind this definition is the implicit assumption that medical advice is good for the patient and that rational patients should follow medical advice precisely. Thus, at the individual level, an ideal index of drug compliance would be

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

where C_{ij} is the amount of substance (active ingredient) j consumed by patient i in a given time period, P_{ij} is the amount of substance j prescribed for the same period to patient i by her physician given her health characteristics, and C_{ij} and P_{ij} are measured in the same suitably defined unit.

Although such an indicator is in principle straightforward, both the numerator and the denominator are unavailable in our data. This problem is in fact more general. Regarding the numerator, drug consumption is typically hard to measure. Most datasets only contain information on drug purchased or dispensed, which is a good proxy of consumption only under the assumption that a patient consumes all the drugs purchased or dispensed. Regarding the denominator P_{ij}, the actual drug amount prescribed to a particular patient is typically unavailable. What is generally available are only guidelines that specify the amount of active ingredients recommended for the typical or average treatment of a specific pathology. For example, guidelines for the treatment of hypertension have been published by the WHO (WHO 1999). Therefore, instead of c_{ij}^{*}, we work with

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

where D_{ij} is the amount of substance j dispensed to patient i in a given time period and $\bar{P}_j$ is the average amount of substance j that should be prescribed to a patient for the same period according to international guidelines or national standards. Of course, patients need not be treated according to international or national standards: physicians may decide to prescribe different dosages for specific patients under specific conditions. Thus, "average dosage" or "international standards" may represent an imperfect measure in the construction of an indicator of compliance.

The relationship between the measured and the ideal index of compliance is therefore

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

It is plausible to assume that $D_{ij} \geq C_{ij}$, 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.

With regard to the choice of measurement unit, the WHO adopts the Defined Daily Dose (DDD), which represents the average maintenance dose per day for a substance used in its main indication on adults.[6] Being a measurement unit, the DDD is not a recommended dose, and may not represent a real dose. Its main advantage is that 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, DDDs can be added and compared across different products.[7] In particular, it is possible to add together the DDDs of all drugs in the same broad therapeutic class or all drugs given to one or more patients. As a consequence, 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 themselves comparable and additive. We can therefore measure the compliance of a single patient without having to distinguish between active ingredients used. For the same reason, we can account for multi-therapies.

Prescription practices in individual countries can differ significantly from international standards. There are at least two reasons why these differences may occur: one is the existence of different indications for the same drug,[8] the other is different prescribing habits of GPs compared to international standards. As an example, Table 1 shows, for each active ingredients in the class of ACE-inhibitors, the differences between the DDDs provided by the WHO–according to the 1995 revision–and the average daily dosages according to the Italian drug prescription practice (for short, ADD). The main differences are for Enalapril, Lisinopril and Ramipril, for which the Italian ADDs are twice the WHO DDDs. Notice that these three substances represent more than half of total dispensing of ACE-inhibitors in Italy.

Taking the Italian ADDs as the measurement unit and the year as the time unit,[9] our index of

[6] 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.

[7] 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, such as drugs composed by "diuretics" and "ACE-inhibitors". For details on the DDD system, see the Web page of the WHO Collaborating Centre for Drug Statistics Methodology at `http://www.whocc.no/atcddd`.

[8] For example, the DDD for quinine is based on the dose used for malaria prophylaxis (1200mg) whereas in England its main indication is the treatment of leg cramps (300mg).

[9] Because of infrequency of purchase, the choice of time unit is not neutral to our measure of compliance. If the

drug compliance for unit i is

$$\bar{c}_{ij} = \frac{\sum_{t=1}^{T_i} D_{ijt}}{ADD_j \times T_i} = \frac{\bar{D}_{ij}}{ADD_j},$$

where $\sum_{t=1}^{T_i} D_{ijt}$ is total amount of doses of substance j dispensed to patient i over the T_i days for which she is observed during a year, and $\overline{D}_{ij} = T_i^{-1} \sum_{t=1}^{T_i} D_{ijt}$ is the average daily dosage of substance j dispensed to patient i during a year. Thus, our index of annual compliance is simply the ratio between the average daily purchase and the Italian average daily dose.

Since a patient may be prescribed more than one active ingredients in the class of ACE-inhibitors, compliance must be computed over all possible active ingredients dispensed 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

$$\bar{c}_i = \sum_{j=1}^{J} I_{ij}\, \bar{c}_{ij} = \frac{\sum_{j=1}^{J} I_{ij}\, \bar{D}_{ij}}{\sum_{j=1}^{J} I_{ij}\, ADD_j},$$

where I_{ij} is equal to 1 if substance j is included in patient i's therapy and is equal to zero otherwise.

Problems arise when patients undergo therapy only for certain periods, based on physician advice. Consider for example 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 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 ADD. 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.

time unit is the month or the quarter, we observe a non-negligible fraction of patients that either make no purchase or purchase large quantities. If the time unit is the year, this problem tends to be less important.

5 Compliance and health outcomes

This section looks at the relationship between compliance and health outcomes. We first analyze the determinants of compliance, and then consider how compliance and other demographic characteristics help predict health outcomes such as hospitalization and mortality rates.

5.1 Sample selection criteria

We start with all patients who were prescribed at least one drug in the ACE-inhibitor class at any time during the period 1993–2002. Because reliable data on hospitalization is only available from 1997, we focus on the 6-year period from 1997 to 2002, which result in an unbalanced panel of 43,148 patients and 170,083 observations. Given the peculiarity of the pathology under scrutiny, we restrict attention to patients born between 1910 and 1960 (2,980 patients and 10,124 observations dropped). We also drop patients with compliance 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 drop 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.

We are aware that following this approach we may miss hypertensive patients who are not treated with ACE inhibitors. However, we are highly confident that we avoid selecting non-hypertensive patients. Hence, we can safely state that the patients in our final sample may be identified as hypertensive patients.

Table 2 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 ACE-inhibitors class 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 of patients by year of birth and gender in our sample with the statistics provided by the National Statistical Institute (ISTAT) for the province of Treviso and Italy as a whole. While the distribution by year of birth and gender is quite similar for Italy and the province of Treviso, people of older cohorts are over-represented in our sample due to the fact that the prevalence of hypertension increases with age.

Figure 2 and 3 compare mortality rates by age and gender in our sample with mortality rates for all causes and for cardiac illness in 1999, as released by ISTAT for Italy and the province of Treviso. Mortality rates in our sample are similar to those for Italy as a whole, but are somewhat higher than those reported for the province of Treviso. Compared to mortality rates for cardiac illness, however, 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.

Figures 4 and 5 shows hospitalization and mortality rates by age and gender in our sample. Patients treated with ACE-inhibitors present higher hospitalization rates than those treated with other cardiovascular drugs. In either case, hospitalization rates are higher for men than for women at almost all ages. Mortality rates are very close to zero until about age 55 for men and age 60 for women. It is only after age 55 that men experience higher mortality rates than women. After age 65, patients treated with ACE inhibitors tend to have higher mortality rates than those treated with other cardiovascular drugs.

Table 3 compares average consumption of ACE-inhibitors in our sample with available national data taken from OSMED (2003). In the year 2000, average total consumption of ACE-inhibitors was 53.0 DDD per 1,000 inhabitants in Italy, while in our sample we observe a slightly lower consumption of 46.8 DDD per 1,000 inhabitants.[10] Looking inside the class of ACE-inhibitors, we observe a larger use of Enalapril in our sample compared to the Italian average (26.2 vs. 21.4 DDDs).

Table 4 reports summary statistics of the variables in our sample by sex. Variables `y1997-y2002` are dummy variables for the years from 1997 to 2002. The average age of male patients is about 66 years, while the average age of female patients is about 70 years. This reflects the higher life expectancy of women. The variable `large pack size` is a dummy variable equal to one for a large

[10] Since the OSMED data are in terms of WHO DDDs, average consumption in our sample is also measured in DDDs, not ADDs.

pack size (28-pill package) and equal to zero for a normal pack size (14-pill package). According to our data, about 60% of patients purchase large packages. Average age of prescribing physicians is about 48 years, and the vast majority of them are males. In fact, only 15.5% of male patients and 17.9% of female patients receive a prescription from a female GP. Both hospitalization rate and mortality rate are higher for men than for women. Average compliance of men is slightly higher than average compliance of women. Finally, patients whose prescription were written directly by a specialist, rather than a GP, are just 0.2%. This does not mean that specialists have a marginal role in Italy, but rather than it is uncommon for a specialist to write down directly a prescription. For this reason we decided to omit this variable.

Figure 6 shows the histograms of compliance by active ingredients for our sample. For all active ingredients, histograms peak at values equal to 0.25, 0.50, 0.75, and 1. Figure 7 shows the histogram of annual compliance $\bar{c}_i$, aggregated over active ingredients, and confirms the peaks observed for each single active ingredient in Figure 6. Notice that the number of patients with compliance values above 1.5 is only 1 percent. Figure 8 shows that the age profile of average compliance has an inverted U shape for both men and women, with no systematic difference by gender.

As a summary of our data, we fit a linear model for the mean of our indicator of compliance, separately by gender, where the covariates include a cubic polynomial in age, a linear term in the physician's age, and dummy variables for calendar year, pack size, and gender of the physician. The baseline category is a person aged 55, observed in 2000, consuming a small (14-pill) package, whose practitioner is a 50 years old male. Table 5 shows the estimated coefficients of this linear model, fitted separately by gender using OLS. Buying a large (28-pill) package increases a patient's compliance and is by far the most significant predictor of compliance. Other things being equal, purchasing a large 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. Finally, the coefficient on the year 2001 is large and positive, for reasons discussed in Section 6.

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 functions of compliance in year t, controlling for demographic and other characteristics. To reduce the amount of unobserved heterogeneity in the data, we further