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

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Summary

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: 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. Copyright © 2006 John Wiley & Sons, Ltd.

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Introduction

In developed countries, 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 [1]. Health economists have extensively studied the effects of such policies on drug expenditure, and a large literature on this subject is available.3

Much less is known, however, about the effect of cost containment measures on drug compliance and, as a consequence, on health outcomes. Not complying with medication, possibly because of affordability issues, can have serious consequences for health. For example, Dracup and Meleis [10] report evidence that 80% compliance to a medication regimen for hypertension lowers blood pressure to normal, whereas 50% compliance is ineffective. Shaw et al. [11] report evidence that poor adherence to drug therapy decreases the effectiveness of anti-hypertensive treatment, whereas IMS Health [12] shows that even inter-
rupting hypertensive treatment by just 7 days can increase the risk of stroke.

When a co-payment is established, patients must contribute 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, although the overall impact appears to be quite limited, with estimated price elasticities ranging from $-0.1$ to $-0.6$. Unfortunately, as pointed out by Freemantle and Bloor [13], drug reimbursement may reduce the use of both essential and non-essential drugs. Although the reduction in the use of non-essential drugs has been shown to be greater [14], the concern remains that essential medication may be affected.

Following this line of research, Atella et al. [15] investigate the role that increasing out-of-pocket expenditure can have on consumers’ attitudes to adopt strategies to contain the cost of medication. Using micro-data from two surveys, conducted in Italy and the UK, respectively, they find 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. Piette et al. [16] find 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. [17], 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, these studies are unable to study the link between compliance and health outcomes. Our goal is to fill this gap by using a unique longitudinal data set collected for an Italian province and covering the period from 1997 to 2002. Following Atella et al. [15] and Case et al. [17], our analysis is disease specific. We are able to obtain some evidence on the relationship between co-payment, compliance and health outcomes by exploiting the changes introduced by the Italian government, in January 2001, September 2001 and March 2002, to the rules regarding co-payment on drugs provided by the National Health Service (NHS) through GP prescriptions. These changes may be regarded as ‘natural experiments’ that allow us to use a difference-in-difference approach to detect statistically significant differences in the behavior of ‘high compliant’ versus ‘low compliant’ patients ‘before’ and ‘after’ the changes.

The remainder of this paper is organized as follows. The next section describes the data. The following section describes our drug-specific approach. The succeeding section discusses our indicator of compliance. The next section of the series looks at the relationship between compliance and health outcomes. The penultimate section investigates if and how health policy changes affect compliance. Final, section offers some conclusions.

### The data

Our data comes from three administrative registries maintained by the Pharmaceutical Service Department of ULSS 9, the public 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. Unfortunately, this registry contains no information on drugs dispensed during a hospitalization period. 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.

A disease-specific approach

Patients may behave differently in terms of compliance depending on the pathology they suffer from or the treatment they receive. For example, a chronic ‘asymptomatic’ pathology (such as hypertension) leads to patterns of compliance that are different from those involved in acute ‘painful’ pathologies (such as headache). Focusing on specific pathologies or specific drug treatments offers the advantage of exploring consumer decision-making in relation to specific clinical conditions and, subsequently, allowing us to derive more precise conclusions concerning the determinants of compliance and the effects of compliance on health outcomes.

In this paper we focus on patients treated with active ingredients in the ATC class C09AA, corresponding to angiotensin converting enzyme inhibitors (ACE-inhibitors). These active ingredients are the most important for the Italian NHS in terms of expenditure, accounting for about 9% of total public drug expenditure in 2003, and are mainly employed in the treatment of hypertension. According to evidence gathered by Health Search in 2003 about 80% of the prescriptions of ACE-inhibitors were issued for treating hypertension and the remaining 20% for other uses.

Hypertension is a chronic asymptomatic pathology affecting a large share of the Italian population. According to ISTAT [19], about 20% of the Italian adult population suffers of hypertension and its prevalence increases with age (37% at age 55–64, 50% at age 65–74 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 [20]. Hypertension treatment is generally long-term, and this may have important economic implications as patients receive regular 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 have serious consequences in terms of hospitalization and mortality.

Drug compliance

Drug compliance may be defined as ‘the extent to which the patient’s actual history of drug administration corresponds to the prescribed regimen’ [21, p. 332]. Thus, at the individual level, an ideal index of drug compliance would be

\[ c_{ij}^* = \frac{C_{ij}}{P_j} \]

where \( C_{ij} \) is the amount of substance (active ingredient) \( j \) consumed by patient \( i \) in a given period, \( P_j \) 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 \( P_j \) are measured in the same suitably defined unit.

Although such an indicator is in principle straightforward, the question of how to measure the numerator and the denominator has vexed many researchers. Drug consumption is typically hard to measure and most datasets only contain information on drug purchased or dispensed, whereas the actual amount of drug prescribed to a particular patient is typically unavailable. 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 [22]. Of course, ‘average dosage’ or ‘international standards’ represent an imperfect measure in the construction of an indicator of compliance, as physicians may decide to prescribe different dosages for specific patients under specific conditions.
As an alternative definition, Vermeire et al. [21] propose that ‘compliance is the extent to which a person’s behavior in terms of taking medications ... coincides with medical and health advice’. Operationally, medical advice could be approximated by international guidelines or national standards. Therefore, instead of $c_{ij}^\#$, one may work with

$$c_i = \frac{D_{ij}}{P_j}$$

where $D_{ij}$ is the amount of substance $j$ purchased by patient $i$ in a given time period and $P_j$ 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. The relationship between the measured index $c_{ij}$ and the ideal index $c_{ij}^\#$ is

$$c_i = c_i^\# \frac{D_{ij}}{C_{ij}} \frac{P_j}{P_j}$$

It is plausible to assume that $D_{ij} \geq C_{ij}$, so $c_i \geq c_i^\#$ whenever $P_j \geq P_j$. The term $P_j / P_j$ represents an important source of unobserved heterogeneity that is unlikely to be independent of a patient’s observable characteristics.

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. A DDD is not a recommended dose and may not represent a real dose. However, being a measurement unit, DDDs can be added and compared across different products. 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 may differ significantly from international standards because of both the existence of different indications for the same drug and different prescribing habits of GPs compared to international standards. As an example, Table 1 shows, for each active ingredient in the class of ACE-inhibitors, the differences between the DDDs provided by the WHO 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.

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

Calculations based on WHO [22] and OSMED [23].
advice. Consider for example the case of a patient with recorded prescriptions only for the first half of the year. Should this patient be considered ‘fully’ or ‘half’ compliant? Similarly, when the therapy is interrupted for a long period, we may wonder whether this reflects non-compliance by patients or perfect adherence to medical advice of stopping the therapy. Unfortunately, our data 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 1 year or more over the observation period.

A further problem is 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 therefore correct the doses purchased by hospitalized patients by assuming that, when hospitalized, they are treated according to the Italian ADD. We then add this amount to the doses purchased through pharmacies. The importance of this correction is larger for older patients, as hospitalization rates tend to increase with age.

**Drug compliance and health outcomes**

This section looks at the relationship between drug compliance and health outcomes. After describing our sample selection criteria, we analyze the variability of compliance across socio-demographic groups. We then consider how compliance and other socio-demographic characteristics help predict health outcomes such as hospitalization and mortality rates.

**Sample selection and descriptive statistics**

We start with all patients, born between 1910 and 1960, who were prescribed at least one drug in the ACE-inhibitor class at any time during the period 1993–2002. We restrict attention to these cohorts because they comprise the bulk of the population suffering of hypertension. Reliable data on hospitalization is only available from 1997, and so we focus on the 6-year period from 1997 to 2002. This results in an unbalanced panel of 40,168 patients and 159,959 observations. We drop patients with compliance greater than 2 (505 patients and 1827 observations dropped) because they might be outliers or cases of co-morbidity, and patients who were hospitalized for renal diseases but not for cardiovascular diseases (1270 patients and 4943 observations dropped). Although we may miss hypertensive patients who are not treated with ACE inhibitors, we are confident that we avoid selecting non-hypertensive patients. Our final sample consists of an unbalanced panel of 38,393 patients and 153,189 observations, with an average of four annual observations per patient.

Figure 1 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 close to zero until about age 55 for men and about age 60 for women. It is only after age 55 that men experience significantly 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 2 reports summary statistics of the variables in our sample by gender. We split the sample by gender and consumption pattern, with patients classified as ‘regular’ if their drug purchases are strictly positive in each year since they entered the sample, and as ‘occasional’ if their purchases are zero for at least 1 year after they entered the sample. This distinction is important given the ‘chronic’ nature of hypertension, as patients affected by this disease are supposed to be under continuous treatment.

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 pack size (28-pill package) and equal to zero for a normal pack size (14-pill package). According to our data, about 60% of regular patients purchase large packages. The share of occasional patients who purchase large packages is slightly lower (about 55%). Notice that, other things being equal, purchasing a large package means halving the time spent meeting the practitioner to get a prescription and visiting a pharmacy to cash the prescription. Variable No Enalapril is a dummy variable equal to one if a patient is treated with only one ACE-inhibitor
different from Enalapril and equal to zero otherwise. Average age of prescribing physicians is about 48 years, and over 80% of them are males. Patients whose prescription were written directly by a specialist, rather than a GP, are less than 1%. This does not mean that specialists have a marginal role in Italy, but rather that it is uncommon for a specialist to write out a prescription herself. For this reason we decided not to use this variable in our empirical analysis. Both hospitalization and mortality rates are higher for men than for women. Regular patients have higher hospitalization and mortality rates than occasional patients. This is consistent with the fact that regular patients have higher probability of being affected by cardiovascular diseases. Average compliance is slightly higher for men than for women. For regular patients average compliance is three times higher than for occasional patients. Occasional patients have positive purchases for only half of the years they are in the sample and, when they purchase, they tend to purchase less than regular patients.

Figure 2 shows the histogram of our measure of annual compliance, $\hat{c}_i$. The histogram peaks at values equal to 0.25, 0.50, 0.75, and 1. Notice that the number of patients with compliance values above 1.5 is only 1%.

As a summary of our data, the first two columns of Table 3 report the fraction of regular patients by gender and age group, while the other four columns report the sample mean and sample
standard deviation of compliance of regular patients by gender, age group and pack size (small or large). Average compliance differs little by gender. For both men and women, the relationship between age and average compliance has an inverse U-shape, reaching a maximum in the 60–69 age range. On the other hand, buying a large (28-pill) package increases a patient’s compliance considerably.

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 annual compliance in year $t$, controlling for demographic and other characteristics. To reduce the amount of unobserved heterogeneity in the data, we further select the sample by dropping patients with annual compliance below 0.1, as they may be affected by mild hypertension that could be treated simply by a healthy diet and by reducing

| Table 2. Descriptive statistics. Final sample: patients born 1910–1960 filling ACE-inhibitor prescriptions (38 393 patients and 153 189 observations) |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                                   | **Occasional**  | **Regular**     | **Occasional**  | **Regular**     |
|                                                   | **Men**         | **Women**       | **Men**         | **Women**       |
|                                                   | **Mean** | **St Dev.** | **Mean** | **St Dev.** | **Mean** | **St Dev.** | **Mean** | **St Dev.** |
| Year 1997                                          | 0.102    | 0.302           | 0.101    | 0.301           | 0.106    | 0.307           | 0.104    | 0.305           |
| Year 1998                                          | 0.139    | 0.346           | 0.138    | 0.344           | 0.124    | 0.329           | 0.124    | 0.330           |
| Year 1999                                          | 0.170    | 0.376           | 0.168    | 0.374           | 0.147    | 0.354           | 0.145    | 0.352           |
| Year 2000                                          | 0.191    | 0.393           | 0.190    | 0.392           | 0.169    | 0.375           | 0.168    | 0.374           |
| Year 2001                                          | 0.203    | 0.402           | 0.205    | 0.404           | 0.202    | 0.401           | 0.201    | 0.401           |
| Year 2002                                          | 0.195    | 0.396           | 0.199    | 0.399           | 0.252    | 0.434           | 0.257    | 0.437           |
| Age                                               | 65.7     | 11.8             | 69.3     | 12.0             | 66.3     | 11.2             | 69.9     | 11.4             |
| Age of GP                                         | 47.9     | 7.5              | 47.6     | 7.4              | 48.5     | 7.0              | 48.2     | 6.8              |
| Specialist                                        | 0.004    | 0.060           | 0.003    | 0.054           | 0.006    | 0.076           | 0.005    | 0.068           |
| No Enalapril                                      | 0.539    | 0.498           | 0.544    | 0.498           | 0.508    | 0.500           | 0.520    | 0.500           |
| More than 1 ACE-inhibitor                         | 0.039    | 0.194           | 0.036    | 0.187           | 0.042    | 0.200           | 0.033    | 0.180           |
| More than 1 card. drug                            | 0.689    | 0.463           | 0.697    | 0.460           | 0.634    | 0.482           | 0.598    | 0.490           |
| Hospital. rate for cardi. DRG                     | 0.099    | 0.299           | 0.072    | 0.259           | 0.125    | 0.330           | 0.083    | 0.277           |
| Mortality rate                                    | 0.033    | 0.179           | 0.023    | 0.148           | 0.042    | 0.201           | 0.028    | 0.165           |
| Years in the sample                               | 5.0      | 1.3              | 5.0      | 1.2              | 4.6      | 1.7              | 4.7      | 1.7              |
| Years with non-zero purchases                     | 2.3      | 1.4              | 2.3      | 1.4              | 4.6      | 1.7              | 4.7      | 1.7              |
| Compliance                                        | 0.218    | 0.334           | 0.203    | 0.322           | 0.643    | 0.354           | 0.619    | 0.342           |
| Compliance when purchasing                       | 0.468    | 0.350           | 0.451    | 0.345           | 0.643    | 0.354           | 0.619    | 0.342           |
| Observations                                      | 34 586   |                  | 44 614   |                  | 35 828   |                  | 38 161   |                  |
| Patients                                          | 7688     |                  | 9700     |                  | 10 273   |                  | 10 732   |                  |
stress factors. This further selection produces an unbalanced panel of 18,626 patients and 65,956 observations, with an average of 3.5 annual observations per patient.

The basic model for the probability of future hospitalization (Model 1) is a logit model whose covariates include cubic polynomials in age and annual compliance in the current year, indicators for using more than one ACE-inhibitor and for patients who have also been prescribed other cardiovascular drugs (multi-therapy), and a set of time dummies. The dummy for multi-therapy is included to control for confounding effects for which we do not have adequate information.\(^g\)

In addition to the basic model, we consider two specifications that include a richer set of covariates. The first (Model 2) controls for the type of ACE-inhibitor by including a dummy for consuming an ACE-inhibitor different from Enalapril. The second (Model 3) also controls for the gender and the age of the GP.\(^h\)

Table 4 presents the coefficients of the estimated models, separately for men and women. The bottom part of the table presents likelihood ratio test statistics for the joint significance of certain covariates or subsets of covariates (age, compliance, GP characteristics and calendar time).\(^i\) The intercept of the basic model corresponds to the log-odds for the baseline case, namely a person aged 55, observed in 1998, with annual compliance equal to 1, under mono-therapy and taking only one kind of ACE-inhibitor. For the baseline case, women have a slightly lower probability to be hospitalized than men. For both men and women, the effect of compliance is highly statistically significant and implies a U-shaped effect of compliance on hospitalization rates. The coefficients on the indicator for the use of more than one active ingredient and on the indicator of multi-therapy are both positive and highly significant. Notice that these dummy variables may be proxies for a patient’s poor health. The negative and significant coefficients on the dummy for the year 2002 will be discussed more thoroughly in Section 6. Hospitalization rates tend to be significantly lower for patients treated with ACE-inhibitors other than Enalapril (Model 2). Age and gender of the practitioner, instead, are only weak predictors of health outcomes (Model 3). In general, Model 2 fits the data better than Model 1, whereas Model 3 represents only a marginal improvement over Model 2.

The top panels of Figure 3 compare the hospitalization rates actually observed by gender and compliance level with the fitted probabilities from Model 2. The shaded areas are (asymptotic) two-standard error bands for the fitted probabilities. We do not show fitted probabilities for levels

<table>
<thead>
<tr>
<th>Age group</th>
<th>Share of regular patients</th>
<th>Average compliance of regular patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>40–49</td>
<td>0.505</td>
<td>0.473</td>
</tr>
<tr>
<td></td>
<td>(0.500)</td>
<td>(0.499)</td>
</tr>
<tr>
<td>50–59</td>
<td>0.573</td>
<td>0.503</td>
</tr>
<tr>
<td></td>
<td>(0.495)</td>
<td>(0.500)</td>
</tr>
<tr>
<td>60–69</td>
<td>0.568</td>
<td>0.530</td>
</tr>
<tr>
<td></td>
<td>(0.495)</td>
<td>(0.499)</td>
</tr>
<tr>
<td>70–79</td>
<td>0.597</td>
<td>0.535</td>
</tr>
<tr>
<td></td>
<td>(0.491)</td>
<td>(0.499)</td>
</tr>
<tr>
<td>80+</td>
<td>0.592</td>
<td>0.546</td>
</tr>
<tr>
<td></td>
<td>(0.492)</td>
<td>(0.498)</td>
</tr>
<tr>
<td></td>
<td>1969</td>
<td>3797</td>
</tr>
</tbody>
</table>

Average annual compliance of regular patients by age group, gender and pack size (small and large) for regular patients. For each cell we report, in order, the sample mean and standard deviation of compliance, and the cell sample size.
of compliance greater than 1.55 because the fraction of patients with annual compliance above this value is only 1%. The graphs indicate a U-shaped relationship between hospitalization and compliance, with a minimum around the value of 1 (the ‘optimal value’ of our index of compliance). For both men and women, the probability of future hospitalization for cardiovascular problems falls as current compliance moves toward the value of 1. In particular, for male patients, the probability of future hospitalization falls from about 12% when compliance is near 0.15 to 8% when compliance is close to 1. For female patients the reduction is less pronounced, but the lowest hospitalization rate again corresponds to compliance near 1.

We fitted similar logit models for the probability of future mortality, including an additional dummy variable for hospitalization for cardiac illness in the current year in order to account for the different health of the patients. As before, all models were fitted separately by gender.

Table 5 presents the estimated coefficients. The intercept of the basic model corresponds to the log-odds for the baseline case, namely a person aged 55, observed in 1998, with current compliance equal to 1, taking only one kind of ACE-inhibitor, under mono-therapy, and not hospitalized in the current year. The goodness of fit is always higher than for the hospitalization model, mainly because of the higher predictive power of age in explaining mortality. For the baseline case, the probability of death is twice as high for men than for women. As for the hospitalization model, the estimated effect of annual compliance is U-shaped. The coefficient on hospitalization in the current year is large and positive, and is slightly larger for women than for men.

The bottom panels of Figure 3 compare the mortality rates actually observed by gender and

**Table 4. Estimated coefficients of the logit model for hospitalization**

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>Age</td>
<td>−0.515**</td>
<td>−0.090</td>
<td>−0.506**</td>
</tr>
<tr>
<td>Age^2/100</td>
<td>0.893***</td>
<td>0.191</td>
<td>0.879***</td>
</tr>
<tr>
<td>Age^3/1000</td>
<td>−0.466***</td>
<td>−0.091</td>
<td>−0.461***</td>
</tr>
<tr>
<td>Compliance</td>
<td>−1.480***</td>
<td>−0.529</td>
<td>−1.369***</td>
</tr>
<tr>
<td>Compliance^2</td>
<td>0.871</td>
<td>−0.363</td>
<td>0.760</td>
</tr>
<tr>
<td>Compliance^3</td>
<td>−0.022</td>
<td>0.466</td>
<td>0.018</td>
</tr>
<tr>
<td>More than 1 ACE-inhibitor</td>
<td>0.725***</td>
<td>0.593***</td>
<td>0.579***</td>
</tr>
<tr>
<td>Multi-therapy</td>
<td>1.079***</td>
<td>1.148***</td>
<td>1.066***</td>
</tr>
<tr>
<td>No Enalapril</td>
<td>−0.315***</td>
<td>−0.272***</td>
<td>−0.331***</td>
</tr>
<tr>
<td>Female GP</td>
<td>0.040</td>
<td>0.031</td>
<td>0.008***</td>
</tr>
<tr>
<td>Age of GP</td>
<td>−0.191**</td>
<td>−0.047</td>
<td>−0.195***</td>
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<tr>
<td>Year 1999</td>
<td>−0.136*</td>
<td>−0.055</td>
<td>−0.142*</td>
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<tr>
<td>Year 2000</td>
<td>−0.236***</td>
<td>−0.097</td>
<td>−0.235***</td>
</tr>
<tr>
<td>Year 2001</td>
<td>−0.333***</td>
<td>−0.353***</td>
<td>−0.331***</td>
</tr>
<tr>
<td>Year 2002</td>
<td>−3.712***</td>
<td>−4.281***</td>
<td>−3.520***</td>
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<td>Constant</td>
<td>−6550.8</td>
<td>−5387.9</td>
<td>−6530.9</td>
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No. obs. 22 891 22 891 22 891 22 891 22 484 22 484 No Enalapril
Pseudo $R^2$ 0.0701 0.0691 0.0729 0.0711 0.0748 0.0725
Log-lik. −6550.8 −5387.9 −6530.9 −5376.2 −6373.0 −5225.8

Joint significance tests

<table>
<thead>
<tr>
<th></th>
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<th>Model 2</th>
<th>Model 3</th>
</tr>
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<td>179.88***</td>
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<td>35.56***</td>
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<td>0.0 0.0</td>
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<tr>
<td>Year</td>
<td>22.84***</td>
<td>23.44***</td>
<td>22.08***</td>
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</table>

*Significant at 10%; **Significant at 5%; ***Significant at 1%.
compliance level with the fitted probabilities from Model 2. Focusing on male patients, we estimate that increasing current compliance from 0.15 to 1 would reduce future mortality by half.

Health policy changes and compliance

The results in the previous subsection indicate that compliance helps predict future health outcomes. We now investigate the link between health policy changes and compliance. If the relationship between compliance and health outcomes may be interpreted as causal, then the existence of such link may have important implications for public policy, because it implies that health policy changes may affect health outcomes by changing the level of compliance.

Alan et al. [24, 25] and Poirier et al. [26] analyze the effect of public prescription drug programs on out-of-pocket household drug expenditure in Canada. For Italy, Atella and Rosati [27] find that the drug policy 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. All these studies 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. We try to fill this gap by exploiting the fact that our
data span three major policy changes that may be regarded as 'natural experiments', whose effects on medical compliance and health outcomes can be evaluated using a difference-in-difference (DID) specification.

The policy changes

The three policy changes are: (i) the abolition of the co-payment on drug prescriptions, on 1 January 2001 (ii) the reduction from 6 to 3 of the maximum number of packages for each prescription, on 30 September 2001, and (iii) the reintroduction of the co-payment, on 1 March 2002. Until January 2001, patients were subject to a flat charge of about 1.5 Euros on each prescription received by their physician. This prescription charge, known to Italians as the “ticket”, applied equally to all packages, irrespective of pack size, dosage or pharmaceutical form. After its abolition in January 2001, the ticket was reintroduced in March 2002 as a flat charge of 1 Euro per prescription.

The co-payment was expected to reduce both public expenditure (financial concern) and unnecessary consumption (clinical concern). Patients were exempt from the ticket either because of low income or disability, or because they suffered from specific chronic or rare pathologies diagnosed by specialists. About 93% of the adult population in our sample pays the ticket, the percentage being lower for older people. This percentage falls to zero in 2001, when the ticket was abolished.

Being a fixed amount, the ticket has an intrinsic regressive structure affecting mostly low income patients suffering from chronic conditions. From an empirical point of view, many studies confirm the role of co-payment in reducing the level of drug consumption of low income patients (see among others Freemantle and Bloor [13], Lundberg et al. [28], and Atella V, Rosati FC, Rossi

**Table 5. Estimated coefficients of the logit model for mortality**

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>Age</td>
<td>-0.215</td>
<td>-0.128</td>
<td>-0.190</td>
</tr>
<tr>
<td>Age²/100</td>
<td>0.366</td>
<td>0.200</td>
<td>0.329</td>
</tr>
<tr>
<td>Age³/10 000</td>
<td>-0.142</td>
<td>-0.038</td>
<td>-0.125</td>
</tr>
<tr>
<td>Compliance</td>
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<td>-0.287</td>
<td>-0.279</td>
</tr>
<tr>
<td>Compliance²</td>
<td>-0.039</td>
<td>-0.058</td>
<td>-0.263</td>
</tr>
<tr>
<td>Compliance³</td>
<td>0.161</td>
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</tr>
<tr>
<td>More than 1 ACE-inhibitor</td>
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<td>0.232</td>
<td>0.309***</td>
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<td>Multi-therapy</td>
<td>0.606***</td>
<td>0.537***</td>
<td>0.593***</td>
</tr>
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<td>No Enalapril</td>
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<td>-0.39***</td>
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<td>Hospitalized at t − 1</td>
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<td>0.758***</td>
<td>0.647***</td>
</tr>
<tr>
<td>Female GP</td>
<td>0.079</td>
<td>0.011</td>
<td>0.007</td>
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<td>Age of GP</td>
<td>-0.331***</td>
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<td>-0.401***</td>
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<td>Year 2000</td>
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<td>Year 2001</td>
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<td>-0.576***</td>
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<td>Year 2002</td>
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<td>-4.533***</td>
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<table>
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<tr>
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<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>0.079</td>
<td>0.011</td>
</tr>
<tr>
<td>Pseudo $R^2$</td>
<td>0.450</td>
<td>0.473</td>
<td>0.465</td>
<td>0.482</td>
<td>0.465</td>
<td>0.482</td>
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<tr>
<td>Log-likelihood</td>
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<td>423.23***</td>
<td>500.76***</td>
<td>406.80***</td>
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Joint significance tests

<table>
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<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
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<td>450.19***</td>
<td>513.13***</td>
</tr>
<tr>
<td>Compliance</td>
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<td>7.01*</td>
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<td>GP characteristics</td>
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<td>0.0</td>
</tr>
<tr>
<td>Year</td>
<td>32.30***</td>
<td>47.95***</td>
<td>32.43***</td>
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</tbody>
</table>

*Significant at 10%; **Significant at 5%; ***Significant at 1%.
Precautionary saving and health risk. Evidence from the Italian households using a time series of cross sections. *Riv Polit Econ* 2005, forthcoming. In this section, we present a simple framework that allows us to interpret such evidence from an economic point of view. For expository reasons, assume that patients choose between drugs (all products in the ACE-inhibitor class) and all other goods. As ACE-inhibitors are provided by the Italian NHS, their price is equal to the ticket. Therefore, a change in the ticket leads to a change in drug consumption, and therefore drug compliance, for each given level of consumption of the other goods.

Figure 4 shows the budget lines and the indifference curves over drugs and other goods for two types of patients — poor (BC₁) and rich (BC₂). For simplicity, we assume that drug consumption cannot exceed the recommended level corresponding to full compliance (Y = 1). For positive drug prices, poor patients would reach full compliance at the point A₃, where consumption of all other goods is equal to F₀. This point, however, need not be chosen by poor patients. In fact, if the asymptomatic nature of hypertension leads them to underestimate the long-run utility of consuming an adequate level of hypertensive drugs, then the slope of the indifference curve at A₃ may be greater than the slope of the budget line. In turn, this would lead poor patients to trade off drugs for higher quantities of other goods, moving down the budget line until reaching points like A₂ or even A₁. Atella et al. (2005) and Huttin et al. [29] present empirical evidence supporting such behavior by poor patients. On the contrary, rich patients are more likely to choose the recommended level of compliance (point E). For rich patients, the trade-off between drugs and other goods is less relevant, as their income allows purchasing the desired level of other goods without sacrificing drug consumption.

The first policy change lowers the price of ACE-inhibitors to zero, resulting in the new budget lines BC₁' for the poor and BC₂' for the rich. This enables poor patients to move to a higher level of compliance (from Y = 0.4 to Y = 1.0 in the figure), while rich patients do not change their compliance as they are already full compliants.

**The DID specification**

The model in the previous section suggests that, after the first policy change (abolition of the ticket), we should observe a higher increase in compliance for patients who were 'low compliant' at the beginning of the period relative to those who were 'high compliant'. After the second policy change (decrease in the maximum number of packages), we should observe a higher decrease in compliance for patients who were 'high compliant' at the beginning of the period relative to those who were 'low compliant'. Similarly, after the third policy change (reintroduction of the ticket), we should observe a higher decrease in compliance for patients who were 'low compliant' at the beginning of the period relative to those who were 'high compliant'.

To verify this, we divide time into four periods (period 0 corresponding to the period before the first policy change, period 1 to the period between the first and the second policy change, period 2 to the period between the second and the third policy change, and period 3 to the period after the third policy change) and consider the following model for the level of compliance Yᵢₜ of individual i in period t

\[ Y_{i_t} = \alpha_0 + \sum_{j=1}^{3} \alpha_j D_{j,t} + \beta_0 C_i + \sum_{j=1}^{3} \beta_j D_{j,t} C_i + U_{i,t}, \quad t = 0, 1, 2, 3 \]
where $D_p$ is a time dummy equal to 1 for period $j$ and to 0 otherwise, $C_j$ is equal to 1 for patients with initial compliance above a certain threshold, and $U_{it}$ is a regression error with the usual properties. According to this model, average compliance of high compliants is equal to $\mu^H = x_0 + \beta_0 + \beta_1$ in period 0 and to $\mu^H = x_0 + x_1 + \beta_0 + \beta_1$ in period $j = 1, 2, 3$, whereas average compliance of the low compliants is equal to $\mu^L = x_0$ in period 0 and to $\mu^L = x_0 + x_1$ in period $j = 1, 2, 3$. Thus, the average change in compliance after the first policy change is equal to $\Delta \mu^H = \mu^H - \mu^L = x_1$, whereas average compliance change after the second policy change is equal to $\Delta \mu^H = \mu^H = \mu^L = x_2 - x_1 + \beta_2 - \beta_1$ for the high compliants and to $\Delta \mu^L = x_2 - x_1 + \beta_2 - \beta_1$ for the low compliants. Finally, $\Delta \mu^H = \mu^H - \mu^L = x_1$ is the DID parameter for the first policy change (the difference in the average change in compliance between high compliants and low compliants from period 0 to period 1), whereas $\Delta \mu^L = \mu^L = x_2 - x_1 + \beta_2 - \beta_1$ is the DID parameter for the second policy change (the difference in the average change in compliance between high compliants and low compliants from period 1 to period 2), whereas $\beta_3 - \beta_2 = \Delta \mu^L = \mu^L = x_3 - x_2 + \beta_3 - \beta_2$ for the high compliants and to $\Delta \mu^L = x_3 - x_2 + \beta_3 - \beta_2$ for the low compliants. Finally, $\Delta \mu^H = \mu^H = \mu^L = x_1$ is the DID parameter for the third policy change (the difference in the average change in compliance between high compliants and low compliants from period 2 to period 3). The model was estimated by OLS, after dropping patients who entered the panel after January 2001 or left the panel before March 2002.

To check the robustness of our results, we considered four modification of the basic model. The first considers two different subsamples, respectively, covering the periods 2000–2002 and 1997–2002. The second adds a vector of demographic variables. The third adds a set of individual specific effects and uses the fixed-effect (within-group) estimator instead of OLS. The fourth uses different thresholds to classify patients as high compliant.

After fitting the various models separately by gender, we found no significant difference in the estimated coefficients. Thus, we simply report the results for the specification that only includes a gender dummy. Table 6 shows, for the two sub-samples (2000–2002 and 1997–2002), the OLS estimates of the model without demographic variables when patients are classified as high compliant if their initial indicator of compliance is greater or equal to 0.55. All parameters are statistically significant. In particular, the DID parameters are highly statistically significant. The negative estimate of $\beta_1$ means that, after the first policy change, low compliants increased their compliance more than high compliants. On the other hand, the negative estimate of $\beta_2 - \beta_1$ means that, after the second policy change, high compliants decreased average compliance more than low compliants. This finding reflects the fact that, in September 2001, the maximum number of packages allowed in a single prescription was lowered from 6 to 3, thereby increasing transaction costs. This affected mainly high compliants, whose mean number of packages per prescription was higher than 3 before September 2001 (it was lower than 3 for low compliants). The positive estimate of $\beta_3 - \beta_2$ means that, after the third policy change, low compliants decreased average compliance more than high compliants.

These results are robust to alternative specifications and estimation procedures. In particular, the magnitude and statistical significance of the DID parameters are unaffected by adding a vector of demographic variables or a set of individual specific effects to the basic model.

As a further robustness check, we re-estimated the model using different thresholds to classify patients as high compliants. Figure 5 presents the
estimated DID parameter for the first policy change under different values of the threshold. The DID estimates are fairly stable at around \(-25\%\) 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 who initially are high compliants have little room to further increase their level of compliance after the abolition of the ticket.

Overall, our results provide strong support for the argument that changes in compliance associated with changes in prescription charges tend to be greater for low compliant patients than for high compliant patients. Further, the fact that high compliants react to policy changes affecting the number of packages that can be prescribed, whereas low compliants mostly react to policy changes affecting co-payment, may be taken as an indicator that low compliants are low income patients whereas high compliants are high income patients.

### Speed of adjustment to policy changes

How responsive are changes in compliance to changes in the co-payment structure? To answer this question, we re-parameterize the model in the previous section to capture changes in compliance over time and estimate the resulting model at quarterly rather than annual frequency.\(^{k}\) Interacting all coefficients with quarter dummies, we are able to estimate average quarterly compliance for both high compliants and low compliants. Figure 6 reports these estimates.

It is clearly seen all three policy changes had an effect on compliance. Further, this effect was almost immediate. In particular, the abolition of the ticket in January 2001 increased the average compliance of ‘low compliant’ patients, the new equilibrium being reached within one quarter. The reintroduction of the ticket 15 months later lowered the equilibrium level, again within one quarter. However, the average level of compliance was higher than before January 2001. Because the new co-payment was below its level prior to January 2001, ‘low compliant’ patients faced a less stringent constraint than before January 2001. As predicted by our simple theoretical model, this allowed them to maintain higher levels of compliance than before.

### Policy changes and health outcomes

Our empirical analysis shows clear evidence of causality running from co-payment to compliance and from compliance to health outcomes. In order to provide a quantitative measure of the effect on...
health outcomes of changes in co-payment, we adopt a two-step procedure.

In the first step, we use Model 2, estimated in Section 6.2, to predict compliance for both high and low compliants under four policies – Policy 0 (pre 2001), Policy 1 (abolition of the ticket) Policy 2 (decrease in the number of maximum packages per prescription), and Policy 3 (reintroduction of the ticket) – all else being held constant. In the second step, we used the predicted values of compliance to feed the hospitalization and mortality models. More precisely, for each of the four policies, predicted compliance for the \( i \)th patient refers to year \( t = 2000 \) and is computed as 
\[
\bar{c}_it = E[\bar{c}_i|X_{it}],
\]
where \( \bar{c}_it \) is annual compliance at time \( t \), \( X_{it} \) is a vector of patient’s characteristics and the expected value is estimated using the model in DID specification section. Predicted hospitalization and mortality rates for the \( i \)th patient are then computed, respectively, as 
\[
E[H_{i,t+1}|\bar{c}_it = \mu(X_{it}), X_{it}] \quad \text{and} \quad E[M_{i,t+1}|\bar{c}_it = \mu(X_{it}), X_{it}, H_{it}],
\]
where \( H_{i,t+1} \) is the binary indicator of hospitalization at time \( t + 1 \), \( M_{i,t+1} \) is the binary indicator of mortality at

Table 7. Predicted compliance, hospitalization and mortality under alternative policies

<table>
<thead>
<tr>
<th>Policy</th>
<th>Compliance</th>
<th>Hospitalization</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low compliants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Policy 0</td>
<td>0.356</td>
<td>0.079</td>
<td>0.034</td>
</tr>
<tr>
<td>Policy 1</td>
<td>0.570</td>
<td>0.070</td>
<td>0.032</td>
</tr>
<tr>
<td>Policy 2</td>
<td>0.532</td>
<td>0.072</td>
<td>0.032</td>
</tr>
<tr>
<td>Policy 3</td>
<td>0.481</td>
<td>0.073</td>
<td>0.033</td>
</tr>
<tr>
<td>Policy 1–Policy 0</td>
<td>0.215</td>
<td>−0.008</td>
<td>−0.002</td>
</tr>
<tr>
<td>Policy 2–Policy 1</td>
<td>−0.038</td>
<td>0.001</td>
<td>0.000</td>
</tr>
<tr>
<td>Policy 3–Policy 2</td>
<td>−0.051</td>
<td>0.002</td>
<td>0.000</td>
</tr>
<tr>
<td>Policy 3–Policy 0</td>
<td>0.125</td>
<td>−0.005</td>
<td>−0.001</td>
</tr>
<tr>
<td><strong>High compliants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Policy 0</td>
<td>0.923</td>
<td>0.069</td>
<td>0.027</td>
</tr>
<tr>
<td>Policy 1</td>
<td>0.901</td>
<td>0.068</td>
<td>0.027</td>
</tr>
<tr>
<td>Policy 2</td>
<td>0.817</td>
<td>0.069</td>
<td>0.027</td>
</tr>
<tr>
<td>Policy 3</td>
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</tr>
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<td>Policy 1–Policy 0</td>
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<td>Policy 3–Policy 0</td>
<td>−0.134</td>
<td>0.001</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Figure 7. Predicted hospitalization and mortality rates based on compliance in \( t − 1 \) for high (H) and low (L) compliants.
time \( t + 1 \), and the expected values are computed using the estimates from Model 2 in modeling the probability of hospitalization and mortality section.

The average values of predicted outcomes (compliance, hospitalization and mortality), averaged over all units in our sample, are reported in Table 7 for each of the four policies. Notice that, for low compliants, Policy 1 implies a drop of 0.8 percentage points (from 7.9 to 7.0%) in the hospitalization rate and a drop of 0.2 percentage points (from 3.4 to 3.2%) in the mortality rate, relative to Policy 0. On the other hand, for high compliants, the differences between the two policies are not statistically significant. Overall, the predicted differences in health outcomes between Policy 3 and Policy 0 are negative and statistically significant for low compliants but not for high compliants. These effects are more clearly shown in Figure 7.

Conclusions

Our results show that compliance to anti-hypertensive drug treatment matters for health outcomes. For male patients, we estimate that the probability of future hospitalization for cardiovascular problems falls from about 12% when current compliance is near 0.15 to 8% when current compliance is close to its ‘optimal’ value of 1. For female patients the reduction is less pronounced, but the lowest hospitalization rate is still observed when current compliance is near 1. Similar conclusions hold for mortality. Focusing on male patients, we estimate that increasing current compliance from 0.15 to 1 reduces future mortality rate by half. These results are robust to different econometric specifications and to sample selection.

Changes in the co-payment structure appear to have a strong effect on the average compliance of previously low compliant patients, while leaving almost unchanged the average compliance of previously high compliant patients. Further, the fact that high compliants react to policy changes affecting the number of packages that can be prescribed, whereas low compliants mostly react to policy changes affecting co-payment, may be taken as an indicator that low compliants are low income patients and high compliants are high income patients.

The speed of adjustment appears to be extremely rapid. This is consistent with the view that policy makers should operate through changes in co-payments whenever they want to achieve rapid effects on demand. Finally, the average level of compliance of previously low compliant patients after the reintroduction of a reduced co-payment is higher than their initial level.

Our results have two important policy implications. First, although the Italian NHS spends a large amount of money on drugs, the low level of compliance observed for a substantial fraction of patients may generate negligible returns in terms of improved health outcomes. Second, as long as co-payment affects drug consumption, it will consequently affect drug compliance and therefore health outcomes. Our calculations show that, all else being constant, abolishing the prescription charge affects health outcomes for low compliants in our sample by reducing the hospitalization rate by 0.8 percentage point (from 7.9 to 7.0%) and the mortality rate by 0.2 percentage points (from 3.4 to 3.2%). This implies that the expected additional drug expenditure could be at least partly offset by the cost reduction associated with lower hospitalization and mortality rates.

Acknowledgements

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Notes

a. Main studies on the topic include Leibowitz et al. [2], Soumerai et al. [3], O’Brien [4], Harris et al. [5], Ryan and Birch [6], Hughes and McGuire [7] and Atella [8, 9].
b. ACE-inhibitors block conversion of Angiotensin I into Angiotensin II. Angiotensin II 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.

c. 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).

d. This is in contrast with the experience from other countries. According to OSMED [18] ‘contrary to what has emerged in the most recent studies of hypertension, ...., 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’.

e. 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’.

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

g. We also fitted the models separately for patients under mono- and multi-therapy obtaining very similar results.

h. Random effects versions of all three models shows little evidence of unobserved heterogeneity.

i. Statistical significance is based on asymptotic standard errors that are robust to heteroskedasticity and clustering arising from the panel structure of the data.

j. If we take into account the time costs to obtain the drug prescription from the physician and then go to the pharmacy to get the drugs dispensed, the budget constraint need not be vertical even when the ticket is zero. Accounting for these costs does not change the qualitative conclusions of our analysis.

k. The monthly frequency was not used to avoid problems of infrequency of purchase.

References


