The reference price system and socioeconomic differences in the use of low cost drugs - Supplement

KCE reports 126S

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
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Denmark	• **Consulted websites :** - Medicines Agency: http://www.dkma.dk - Pharmaceutical and Health Industry: http://www.talogdata.dk - Institute for rational Pharmacotherapy: http://www.irf.dk - Patients associations umbrella: http://www.danskepatienter.dk - PPRI: http://ppri.oebig.at/Downloads/Results/Denmark_PPRI_2007.pdf • **Contact with :** Miss. Elisabeth Thomsen Special adviser Danish Medicines Agency Axel Heides Gade 1 2300 Copenhagen S Denmark
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Portugal	• **Consulted websites :** - Ministry of Health: http://www.min-saude.pt/portal - Association for health information: http://www.apdis.org/index.html - National Authority for Medicines and Health Products: www.infarmed.pt/genericos - National School for Public Health: http://www.ensp.unl.pt/ensp - PPRI: http://ppri.oebig.at/Downloads/Results/Portugal_PPRI_2008.pdf • **Specialized literature :** Simoens, 2008[14]; Simoens, 2006[3]; Vogler, 2008[15] ; Espin, 2007[16]; Lopez-Casasnovas, 2000[4]; Ess, 2003[5]; Mrazek, 2002[6]; Yfantopoulos, 2008[18]; Kontozamanis, 2003[19]. • **Contact with :** Mrs Sónia Caldeira Direcção de Economia do Medicamento e Produtos de Saúde(DEMPS)/ Departamento de Avaliação Económica e de Resultados de Saúde (AER) Técnica Superior Economista Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. E-mail: sonia.caldeira@infarmed.pt
Spain	• **Consulted websites :** - Ministry of Health and Social Affairs: http://www.msps.es/en/home.htm • **Specialized literature :** Simoens, 2008[14]; Simoens, 2006[3]; Vogler, 2008[15] ; Espin, 2007[16]; Lopez-Casasnovas, 2000[4]; Ess, 2003[5]; Mrazek, 2002[6]; Yfantopoulos, 2008[18]; Kontozamanis, 2003[19]. • **Contact with :** Mr Piedad Ferré Pharmacy Counsellor General Directorate of Pharmacy Ministry of Health Spain
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New Zealand	• **Consulted websites :** - Ministry of Health: http://www.moh.govt.nz/moh.nsf - Medicines and Medical devices Safety Authority: http://www.medsafe.govt.nz/ - Health Information Service: http://www.nzhis.govt.nz/ - Pharmaceutical Management Agency: http://www.pharmac.govt.nz/ • **Specialized literature :** Simoens, 2008[14]; Simoens, 2006[3]; Vogler, 2008[15] ; Espin, 2007[16]; Lopez-Casasnovas, 2000[4]; Ess, 2003[5]; Mrazek, 2002[6]; Garattini, 2007[7].

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Australia	• **Consulted websites :** - Institute of Health and Welfare: http://www.aihw.gov.au/ - Medicare: http://www.medicareaustralia.com/ - Therapeutic goods administration: http://www.tga.gov.au/ - Government Health Information: http://www.health.act.gov.au/c/health • **Specialized literature :** Simoens, 2008[14]; Simoens, 2006[3]; Vogler, 2008[15] ; Espin, 2007[16]; Lopez-Casasnovas, 2000[4]; Ess, 2003[5]; Mrazek, 2002[6]; Garattini, 2007[7]; Healy, 2006[20].
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Germany	• **Consulted websites :** - Pharmacists Association: http://www.abda.de/ - German Bundestag: http://www.bundestag.de/ - Information System of the Federal health Monitoring (pharmaceuticals expenditure): http://www.gbe-bund.de/ • **Specialized literature :** Simoens, 2008[14]; Simoens, 2006[3]; Vogler, 2008[15] ; Espin, 2007[16]; Lopez-Casasnovas, 2000[4]; Ess, 2003[5]; Mrazek, 2002[6]. • **Contact with :** Dr Tom Stargardt Helmholtz Zentrum Munich Institute of Health Economics and Health Care Management Ingolstadter Landstr. 1 85764 Neuherberg Germany Tom.Stargardt@helmholtz-muenchen.de
Hungary	• **Consulted websites :** - Ministry of Health: www.oep.hu/gyogyszer

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Italy	• **Consulted websites :** - Ministry of Health: http://www.ministerosalute.it/ - Pharmacies association: http://www.federfarma.it/ - Pharmaceuticals Agency : http://www.agenziafarmaco.it/section8983.html • **Specialized literature :** Simoens, 2008[14]; Simoens, 2006[3]; Vogler, 2008[15] ; Espin, 2007[16]; Lopez-Casasnovas, 2000[4]; Ess, 2003[5]; Rocchi, 2004[27]; Mapelli, 2003[28]; Giuliani, 1998[29]; Mrazek, 2002[6]; Garattini, 2007[7]; Garattini, 2006[30]; Ghislandi, 2005[31]. • **Contact with :** Dott. Pietro Folino Gallo Agenzia Italiana del Farmaco - AIFA Dirigente Ufficio Coordinamento OSMED Via della Sierra Nevada, 60 00144 Roma Italy

2 COUNTRY OVERVIEW - CRITERIA DEFINING GROUPS OF DRUGS

CATEGORY 1: COUNTRIES WITH A LEVEL 1 RPS

Typically, each cluster contains at least one off-patented original drug and its generic version.

1. **Denmark** opted for a Level 1 RPS in 1993. The Danish RPS is based on the principle of chemical equivalence. This system groups together drugs that have the same active ingredient, form and strength, under standard ATC-5 classification. The number of drugs within a cluster may vary from 2 to about 15.[15] The RPS is based on generic substitution. The Danish system includes reimbursable and non-reimbursable drugs. For reimbursable drugs, the system of generic substitution is identical to the RPS. In rare cases, exemptions are allowed for patients who are not able to use the cheaper drugs for medical reasons. In this case, the physicians have to apply to the Danish Medicines Agency for exemptions.
2. **France** approved the *Tarif forfaitaire de Responsabilité* (TFR) in December 2002 (Art. 43, Law n°2002-1487, December 2002). The RPS was implemented on August 27, 2003. The TFR is not a real reference price system as it only concerns 153 generic groups.[32] It is applied when a generic version is available on the market (for all molecules of the same ATC-5 level, with the same dosage and the same packaging). Only a limited part of the generics sector is submitted to TFR, mainly the generics with a low market share.
3. **Portugal** established a RPS in 2002 which was implemented for the first time in March 2003. The RPS applies to drugs when a generic version is available on the market. It groups together drugs with the same active ingredient, pharmaceutical form, strength and route of administration.[33]
4. In **Spain**, the RPS was established by the Royal Decree 1035/99 in 1999 and implemented in December 2000. Since then, two major revisions (in 2003 and 2006) have modified drug clusters and price settings definitions. The RPS applies to drugs if at least one generic version exists (with ATC-5 level). Drugs within a cluster contain the same chemical entity (substance) with the same doses and administration route.[34] In 2001, a RPS for off-patent drugs (copies and generics) was introduced. [31]

CATEGORY 2: COUNTRIES WITH A LEVEL 2 RPS

1. **The Netherlands** bases its RPS on the criteria of therapeutically interchangeable drugs (usually at Level 2). Each reference group contains drugs that have the same therapeutic indication, similar route of administration, for the same age group and with no significant differences in clinical effects. Vogler et al. 15 point out that "The RPS is applied to all products except for products that cannot be grouped by drugs with mostly similar indications, route of administration, targeted age group and for which no clinically relevant differences in outcome apply". In The Netherlands, patented and off-patented drugs are subject to the RPS.
2. **New Zealand** introduced a Level 2 RPS in July 1993.36 Drugs are first pooled into therapeutic groups (ATC-3) and then divided into therapeutic subgroups (ATC-4). The latter implies that sub-groups contain drugs having the same or similar therapeutic effect in treating the same or similar condition, but not necessarily the same active ingredient36, 37. In New Zealand, the patent status of drugs is not taken into account. New products are reimbursed only if they join an existing subgroup.

3. In **Australia**, a Level 1 RPS started in 1990. It was applied only to drugs with associated generics available on the market. Yet, since February 1998, the RPS no longer uses Level 1 criteria and drugs within a cluster must be therapeutically exchangeable. In other words, clusters are now formed according to Level 2 criteria. These drugs are considered to have similar levels of safety and efficacy.

CATEGORY 3: COUNTRIES WITH A MULTILEVEL RPS

This third category includes countries implementing a multilevel reference price system.

1. **British Columbia** introduced a Level 1 RPS in 1994 (a Maximum Allowable Cost policy, called "Low Cost Alternative"). In 1995, the **Canadian province** started a Level 2 RPS (Reference Drug Program) for drugs that are not chemically identical but with pharmacologically and therapeutically comparable active ingredients. The RPS and Low Cost Alternative (LCA) Program were adopted to manage escalating drug costs. Five classes of drugs were included : i) histamine 2 receptor blockers, ii) non-steroidal anti-inflammatory drugs, iii) nitrates, iv) angiotensin converting enzyme inhibitors, v) dihydropyrine calcium channel blockers. The latter two categories were implemented in 1997. Patients with specific medical conditions that prevent them from taking the reference drug, or patients not responding to the generic version, can be exempted from the RPS. In this case, the physician has to request a prior authorization to grant full coverage of a drug with a price above the reference price. The Reference Drug Program does not apply to paediatric patients (18 years of age and under).
2. In **Germany**, the RPS was initially applied in 1989 for a class of drugs having the same active ingredients (generic referencing Level 1). In 1991, the RPS was extended to drugs therapeutically interchangeable (Level 2) and in 1992 to drugs used to threat some specific conditions (Level 3). Currently, inclusion criteria of drugs in different clusters can be set using the three levels. Initially, reference pricing affected all drugs, with or without patent protection. Between 1989 and 2004, patented drugs with marketing authorisation were excluded from the RPS. Since 2004, newly patented drugs may be submitted to the RPS for Level 2 or Level 3.
3. **Italy** opted for a Level 1 RPS in 2001. In 2003, the National Health System made major changes and the RPS is now based on clusters of "homogeneous groups"[27, 28]. The system can be applied at different levels depending on how homogeneous groups are defined.
4. In **Hungary**, two RPS co-exist.[15] The first RPS was implemented in 1993 and the second was introduced in 2003. The first RPS includes all drugs that have the same active ingredient, the same route of administration and the same strength (usually these drugs are bioequivalent and interchangeable, i.e. a Level 1 RPS). The second RPS is done by grouping drugs that are related but whose chemical composition may differ (Level 2). Pharmaceuticals clustered at an ATC-4 level can be further subdivided according to: a) mode of application, b) different strengths, c) duration effect, d) pharmaceuticals with approximately the same impact on the quality of life, e) proven clinical advantage and f) early identical side-effects.

3 COUNTRY OVERVIEW - CRITERIA TO DETERMINE THE REFERENCE PRICE

CATEGORY 1: COUNTRIES WITH A LEVEL 1 RPS

There is no single approach to calculate the reference price level. Instead there are multiple methods. For example:

1. In **Denmark**, the reference price is set in accordance with the least expensive equivalent generic drug available on the market amongst a group of packages of the same size or approximately of the same size. As pharmaceutical companies may change prices, market new drugs or new packages, as well as withdraw drugs or packages every 2 weeks, the reference pricing groups are updated twice a month. The reference price for each group is calculated automatically once the group has been updated.
2. In **France**, the reference price or TFR corresponds to the average price of generic drugs within the group. The reference price is fixed by the Economic Committee for Health Care Products (CEPS). The reference group is revised once a year and again after 18 months of availability on the market.
3. In **Portugal**, the reference price is the highest unitary retail price of all marketed generics in each homogeneous group. The RPS is reviewed four times a year.
4. In **Spain**, the reference price is based on the arithmetic mean of the daily treatment cost of the three cheapest drugs.[34] The Spanish reference price is very particular in the sense that it works as a maximum price for drugs included in the reference group. Galenic innovations that can prove therapeutic added value may be excluded from the reference price system during a period of five years (as stated in the RD 1338/2006). New groups are added to the system yearly, reviews may be done every two years.

CATEGORY 2: COUNTRIES WITH A LEVEL 2 RPS

In this second category of RPS), the reference price is based on the lowest drug price in the group or on the average price of all drugs within the group. More specifically:

1. In **The Netherlands,** a maximum price for drugs is fixed independently of the RPS. The Price Act (WGP) was implemented in 1996. This act determines the maximum price of a drug, by using the average price in four neighbouring countries (Belgium, Germany, France and the United Kingdom). The maximum price is reviewed twice a year. The reference price is equal to the weighted average price of all drugs (price of 1999) within the cluster. A price premium may be granted for drugs introduced after 1999 and for which the firm can prove a real therapeutic added value. The system is reviewed twice a year for the reference price and on a monthly basis for the list of drugs.
2. In **New Zealand**, the reference price level is equal to the historically lowest price in each therapeutic subgroup, regardless of patent status.[36] In addition, the Pharmaceutical Management Agency (Pharmac) may eliminate all reimbursement for a product if a substitute product is available at a lower price and if Pharmac considers that the higher priced product has no additional clinical benefit"[36]. By consequence, Pharmac uses the RPS to negotiate price cuts on new drugs that can be grouped into clusters in the RPS.
3. In **Australia,** the reimbursement level is set at the lowest drug price within each cluster. Usually, the RPS is revised annually.

CATEGORY 3: COUNTRIES WITH A MULTILEVEL RPS

In the last category, more sophisticated methods can be used to fix the reference price.

1. In **British Columbia,** the reimbursement level is based on the lowest (or the second lowest) drug price in the same related group.
2. In **Germany**, the reference price is determined by econometric methods. More specifically, a "*quasi-hedonic regression equation is applied to manufacturer price levels and the estimated coefficients are used to set relative RPS for different strengths and package sizes*".[38] Since 2004, the reference price needs to be above the lowest third of the cluster prices[1]. In principle, the reference price is reviewed annually by the national association of sickness funds.
3. In **Italy**, since the reform in 2003, the reference price is calculated as a cut-off point. Among each cluster, cost for each active ingredient is calculated per defined daily dose (DDD) and weighted by the number of packages sold in 2001(then ranked in increasing). The reference price was set at the level where jointly a) the cumulated number of DDD consumed was 60% and b) the cumulated SSN expenditure was 50% of total market. The average price of the cheapest active substance was increased by 15%, if a single active substance covered 50% of market.
4. In **Hungary**, two mechanisms exist to calculate the reference price level.
   - For ATC5 groups (Level 1), the reimbursement level is based on the drug with the lowest daily therapeutic cost (DTC) in the ATC5 groups. The reference drug must fulfil the following conditions: i) be included in the register, ii) its bioequivalence has been established, iii) has the lowest daily cost of therapy (DCT) related to gross pharmacy retail price, iv) its market share within the group reached at least 3% during the last 6 six months (of the year in question).[15]
   - For ATC4 groups, the reference price is fixed at the lowest average daily cost of therapy (ADTC). Reimbursement is equal to a specific percentage if the daily cost of treatment (DCT) does not outpace the ADTC. Otherwise, the value of the directly observed treatment (DOT) is used to calculate reimbursement as follows: ADTC*packaging/DOT.

   The RPS is revised quarterly for both systems.

[1] Roughly one third needs to be available at or below the reference price. In addition, more than 20% of prescription volume and more than 20% of revenue of a group need to be available at or below the reference price.

4 COUNTRY OVERVIEW - MEASURES FOR PHYSICIANS, PHARMACISTS AND PATIENTS

Appendix 4 is mainly based on the information published by Simoens et al. (2006)[3], Vogler et al. (2008)[15] and Espin et al. (2007)[16].

CATEGORY 1: COUNTRIES WITH A LEVEL 1 RPS

1. In **Denmark**, physicians are not directly encouraged to prescribe low cost drugs. In fact, demand for low cost drugs is mainly supported by the principle of generic substitution by pharmacists.
   - Measures for physicians: Physicians are not directly encouraged to prescribe low cost drugs (mainly generic drugs). Nevertheless, to promote INN prescribing, students in medical school are taught to prescribe by INN. Physicians receive information on their prescription behavior in the form of lists enumerating the amount and costs of prescribed drugs and official action is taken by the third-party payer if a physician's prescribing of drugs exceeds an average level.[15] The Institute for Rational Pharmacotherapy (IRF) organizes conferences and training sessions to inform physicians about rational use of drugs. Practice guidelines have also been edited by The Danish College of General Practice but physicians are free to adhere to these guidelines.
   - Measures for pharmacists**:** The principle of generic replacement by pharmacists exists since 1991. The rules of generic substitution depend of the price of the prescribed drugs.[3] Since 1997, the pharmacy must dispense a cheaper medicinal drug than the one prescribed by the doctor, unless the doctor has decided against substitution. Generic substitution is not mandatory when the price difference between the prescribed drug and the cheaper alternative is minor. In this case, the pharmacy may still have an incentive to dispense generic or low cost drugs due to the linear mark-up scheme.
   - Measures for patients: No specific campaigns aimed at patients about generic drugs or to rational use of drugs have been conducted.[3]
2. In **France**, physicians are authorized to prescribe by INN and pharmacists are encouraged to substitute a generic drug for a brand medication.
   - Measures for physicians: Since 2002, physicians are authorized to prescribe by INN. No legal obligation was attached to this measure. However, indirect financial incentives (increase in fees) were set for physicians. Indeed, physicians agreed that prescription using INN should attain at least 25% and in exchange their fees were increased.
   - Measures for pharmacists: Since 1999, generic substitution by pharmacists is allowed, unless physicians forbid it. If the physician has prescribed by INN, the pharmacist may dispense any generic drug.[3] Some financial incentives have been implemented for pharmacists to dispense generic drugs. Firstly, the pharmacist's margin was equalized between substitute generic and brand product if the substitution rate attains 35%.[3] Secondly, in 2008 the discount from the laboratories to the pharmacist was capped to 17% for generics compared to 2.5% for all brand name drugs under TFR[2].

2 Kanavos et al.(2007)[17] who conducted a pilot questionnaire survey of wholesalers and pharmacists on the discounting practises for off-patent molecules in France found that discounts of generic products vary from 20 to 70%.

- Measures for patients: Information on the existence of generic drugs was sent by the third-party payer to patients suffering from chronic illness and regularly taking an original drug. More recently, to raise their awareness of generic drugs' use, new reimbursement rules were introduced. A patient refusing generic substitution must pay the full price to the pharmacist and then ask for reimbursement to the sickness fund.

3. In **Portugal,** the government has conducted several actions to increase knowledge on generic drugs. Physicians are obliged to prescribe by INN. However, no specific policy targets were set for the prescription of generic drugs.
   - Measures for physicians: Physicians have no financial incentives to prescribe generic drugs but have the legal obligation to use the INN. They must prescribe by INN for drugs that have a generic version and also inform patients about the range of generic drugs and about the price supplement. Prescription guidelines are edited for physicians. The National Authority of Medicines and Health Products, I.P. (INFARMED) publishes and distributes among physicians the "Pharmaceuticals Generics and Reference Price System Guide" (4 times a year). An updated version is also available online on a monthly basis. Since 2007 it has also been available through Personal Digital Agenda. It contains information concerning prices and reimbursement levels of all available generics on the market.
   - Measures for pharmacists: Pharmacists can substitute an original drug for a generic version unless the physician forbids it. However, they are obliged to inform the patient about the existence of generics and their prices and to dispense the least expensive generic authorised. No financial incentives are given to the pharmacist to promote generic use.
   - Measures for patients: The government's policy is to increase patient's information on generic medicines. These campaigns were not only targeted to patients but also to the health professionals. In addition, the government has launched an advertising campaign to promote generics through television, radio and internet. Since 2006, pensioners whose income is below the national minimum wage receive an additional reimbursement of 20%**.** Since June 2009, these pensioners pay no co-payment, if they choose generic medicines.

4. In **Spain**, pharmacists can substitute a generic drug for an originator drug.
   - Measures for physicians: Prescription targets are set by each autonomous region and physicians receive feedback on their prescription behaviour. In order to improve the prescription of generic drugs, physicians can earn additional lump sums if they meet their targets but the financial incentives of this measure are very limited.3 In addition, physicians are not obliged to prescribe by INN. Nevertheless, some drug information bulletins are edited in some regions for physicians and periodic meetings are organized at the health area level to inform them about new drugs.
   - Measures for pharmacists: Pharmacists are allowed to substitute a brand drug for a generic version under the criteria of the reference price system: i) either bioavailability or ii) for narrow therapeutic margin or safety reasons as specified by Ministerial Order 2874/2007. The rules governing generic substitution by pharmacists depend on the price of the drugs. If the physician has prescribed by INN, the pharmacist must dispense the cheapest drug within the group or the brand name drugs at the reference price level (if a bio-equivalent generic version is not available). Because pharmacists receive a fixed percentage of the public price, there is no specific financial incentive to dispense cheaper drugs
   - Measures for patients: The government has conducted several actions to inform patients on generic drugs.

CATEGORY 2: COUNTRIES WITH A LEVEL 2 RPS

1. In **The Netherlands,** incentives for physicians to prescribe cheap drugs or generic drugs are limited.
   - Measures for physicians: The Government has asked (no legal obligation) physicians to prescribe by INN. In addition, physicians must inform patients about the existence of generics and their prices. In general, the impact of these measures is limited as generic substitution is voluntary. By consequence, physicians can always block substitution by prescribing by brand name rather than by INN. However, several initiatives have been undertaken to inform physicians on generic drugs.
   - Measures for pharmacists: Pharmacists are allowed to substitute generics if physicians and patients agree with it. If the physician has prescribed by INN, the pharmacist may dispense any originator or generic drugs [3]. There is no specific financial incentive for pharmacists to dispense the cheaper drugs as pharmacists receive a fixed dispensing fee per prescription.
   - Measures for patients: No campaigns to raise patient awareness on low cost drugs or generic drugs have been conducted. Since 2007 healthcare insurrers are allowed to indicate preferred multi-source (generic) medicines. Using a tender they can determine the drugs they want to reimburse (as long as they reimburse all active substances). This resulted for some drugs (e.g. statines) in price reductions of more than 90% (in 2008). Currently the most "active" insurer has a list of about 40 active substances for which he uses a preferred generic compound (Called preferential reimbursement)
2. **In New Zealand**:
   - Measures for physicians: Physicians have little direct incentives for prescribing cheap drugs or generic drugs. Measures are limited to mainly non-financial strategies. For example, some physician associations provide voluntary guidelines to their members.[36]. National guidelines to limit the prescribing of expensive drugs have been published by Pharmac.
   - Measures for pharmacists: Pharmacists are allowed to substitute a brand name drug for a generic version, unless physicians explicitly prescribe the brand drug and forbid substitution.
   - Measures for patients: No information on patient incentives was available.
3. **In Australia**:
   - Measures for physicians: To promote INN prescribing, students are taught to prescribe by INN in medical school. Pro-generic drugs campaigns to physicians, pharmacists and patients have been conducted by the Government
   - Measures for pharmacists: Pharmacists are allowed to substitute a brand drug for a generic version, unless the physician forbids it or if the patient demands an original drug.
   - Measures for patients: Pharmacy's price lists are published to raise patient awareness on low cost drugs or generic drugs.

CATEGORY 3: COUNTRIES WITH A MULTILEVEL RPS

1. In **British Columbia** the incentives to promote the use of generic and low cost drugs target only patients and their private insurers. Some private insurers modified their drug coverage to match the government policy.
   - Measures for physicians: There are no financial incentives for physicians to prescribe generic and low cost drugs. However, several information campaigns have been put into place. Through the Provincial Academic Detailing (PAD) service, participating physicians have one-on-one access to clinical pharmacists to discuss pre-determined drug topics. Academic detailing provides family physicians an opportunity to ensure that they are up to date with therapeutic issues common to their practice. Participants also receive the Prescription Pad newsletter several times a year in conjunction with the detailing sessions. The newsletter focuses on current drug therapy topics and provides physicians with evidence-based information to refer to after the session is over.
   - Measures for pharmacists: Pharmacists are allowed to substitute a brand drug for a generic version, unless the physician forbids it. They are no incentives for pharmacists to dispense generic drugs and low cost drugs.
   - Measures for patients: Patients or their private insurers have to pay the difference in price.

2. **Germany** has introduced financial incentives for physicians and allowed generic substitution by pharmacists.
   - Measures for physicians: Physicians are legally required to inform patients about any price supplement[36]. The physician price sensitivity has been reinforced by the introduction of regional budgets (in 1993) and physician budgets (in 1998). Currently, physicians surpassing their individual target[3] may be subject to individual audit on their prescribing habits. If physicians surpass their individual targets, reimbursement of the difference can be required. Physicians receive 4 times per year detailed information about individual prescription data and volume of prescription of their specialty group in the region. However, physicians are not legally required to prescribe by INN.
   - Measures for pharmacists: Since 2002, the pharmacist might dispense a cheaper drug than the one prescribed by the physician, unless the physician forbids it. If the physician has prescribed by INN, the pharmacist must dispense one of the three cheapest drugs within the group. There is no specific financial incentive for pharmacists to dispense the cheaper drugs.
   - Measures for patients: No campaigns to raise patient awareness on low cost drugs have been conducted.

3. **In Italy**, while no obligation exists, physicians prescribe by INN or use the name of the generic product. Pharmacists are allowed to substitute the cheapest equivalent drugs (generics or copies). Information campaigns have been launched to inform patients on generic drugs [15].
   - Measures for physicians: Physicians are not obliged to prescribe by INN. They may use the brand name, the INN prescription or the name of the generic drugs. However, they are obliged to inform the patient about the existence of generics and their prices[3]. Some measures at local or national level have been implemented such as: feedbacks on prescribing patterns and implementation of clinical guidelines [3, 15, 28]
   - Measures for pharmacists: Pharmacists are allowed to substitute the cheapest equivalent drugs (generics or copies)[31], unless the physician forbids it or if the patient refuses substitution. There is no specific financial measure to incite pharmacists to dispense the cheaper drugs. They receive a fixed percentage of the public price of reimbursed drugs [15,3].

3 Since 2003, physicians are informed on their individual prescription volume.

- Measures for patients: Advertising campaigns to inform patients on generic drugs have been launched by the Ministry of Health in 2002 and 2005. In addition, the Italian Medicines Agency (AIFA) has conducted pro-generic drug campaigns in 2007. Patients have access to information on the website of AIFA. A free-of-charge telephone number is available to answer questions on safety, efficacy and availability of drugs [15].

4. In **Hungary**, physicians are obliged to use accredited prescribing software and they have to inform patients about cheaper alternatives.
   - Measures for physicians: Physicians have no financial incentives to prescribe generic or cheap drugs and are not obliged to prescribe by INN. However, they are obliged to use the accredited prescribing software [4] that offers cheaper alternatives. Physicians also must inform patients about cheaper alternatives and get patient-consent to prescribe more expensive drugs. In four therapeutic groups (antacids, oral antidiabetic drugs, antihypertension drugs, cholesterin lowering drugs) daily therapeutic cost target values are determined. Those physicians who prescribe very expensive drugs in great amount are punished, namely they are obliged to take a course organised by OEP. Recently, the government started to use direct information channels (website, email, letters) to inform doctors about the market entry of generics in order to increase generic penetration.
   - Measures for pharmacists: Pharmacists are allowed to substitute the cheapest generic drugs, unless the physician forbids it. In addition, they are obliged to inform patients about the existence of generics and their prices. If the pharmacist intends to substitute a drug, he has to offer the cheapest available version of the drug for the patient. As the pharmacist margins in Hungary are a proportional share of the public price of drugs, pharmacists have no financial incentive to prescribe generic or cheap drugs.
   - Measures for patients: In the mid-1990, the government conducted several actions to inform patients on generic drugs.

4 This Accredited software has to use the database published by OEP (Országos Egészségbiztosítási Pénztár) (National Health Insurance Fund Administration) which means that the software has to operate with all the reimbursed products (no bias is allowed in terms of list of products offered by the software or in the ranking of products offered for prescription). The database contains information on the criteria of prescription (under which clinical conditions doctors are allowed to prescribe the drug; which specialists in which institutions are allowed to prescribe for which diseases). Finally, the accredited prescribing software has to offer all cheaper alternatives for physicians ranked in ascending order of unit costs; products are coloured according to their relative expense compared to the reference product.

Appendices with Chapter 3

5 ASSOCIATION OF THE RPS WITH OUTCOME MEASURES: REVIEW OF INDIVIDUAL STUDIES

Individual studies included in the 4 reviews assessed the impact of the RPS on different outcomes, including drug use, drug prices, drug expenditures for the third-party payer and for patients and patient health and health services use. Table 1 of this appendix provides an assessment of the individual studies.

ASSOCIATION OF THE RPS WITH DRUG USE

A number of studies analyzed the association of the RPS with drug use. In general, these studies are mainly descriptive, based on aggregated data and have methodological limitations to assess the direct impact of the RPS on drug use. Most of these studies conclude that the implementation of a reference price system was followed by an increase in the use of drugs priced at the reference price and by a decrease in the use of higher cost drugs within the cluster.

Giuliani et al.(1998)[29] provided empirical evidence that the introduction of a RPS stimulated the use of the reference drugs. By examining the evolution of eight therapeutic groups submitted to reference pricing in Germany during the period 1990-1996, they suggested that the implementation of a RPS was followed by a strong decline in sales (in volume) of original branded drugs. On the other hand, they also observed a shift in prescription patterns after the introduction of the RPS towards more expensive active ingredients not covered by the RPS.

Narine et al. (1999)[39] also found a positive and significant impact of the RPS on the use of reference drugs. By comparing the total number of prescriptions within the reference groups (for histamine-2 receptor antagonists, nitrates and NSAIDs) one year before and one year after the introduction in British Columbia, they found that the number of prescriptions for the reference products in all 3 therapeutic categories increased significantly after the introduction of the RPS. They also observed that the use of the cost share drugs decreased immediately after the implementation of the RPS. For example, the number of prescriptions for ranitidine decreased by 59.9% between October 1995-September 1996 and October 1994-September 1995. These results were confirmed by Narine et al. (2001)[40] who observed that "there was an immediate and pronounced shift toward the prescribing of reference products after introduction of the RPS".

Grootendorst et al.(2001)[23] drew identical conclusions by analyzing the evolution of the monthly volume of prescription of anti-anginal (nitrates, CCBs and β -blockers) dispensed to senior citizens (65 years of age and older) in British Columbia after the implementation of a RPS (from January 1997 to May 1999). According to the authors, the implementation of the RPS for nitrates drugs was directly (2 months after the introduction in October 1995) followed by an increase in the number of prescriptions for the reference standard nitrates and by a drop in the number of prescriptions for the cost share drugs (from 750 to 267 prescriptions per 100 000 senior citizens). For example, immediately after the introduction of the system the number of prescription of ISDN (a reference drug) increased by 304% (from 206 to 866 prescriptions per 100 000 senior citizens). However, the authors underlined that this increase was short-lived as the prescribing rates of the reference standard nitrates declined over time (but remained above the baseline).

Grootendorst et al.(2002)[41] who evaluated the effect of the introduction of a RPS on the consumption of nitrates, angiotensin-converting-enzyme (ACE) inhibitors and dihydropyridine calcium channel blockers (CCBS), observed a sharp change in prescribing within each of the reference drug classes after the introduction of the RPS.

According to the authors, the use of the reference standard nitrate drugs increased by 177% within 3 months after the implementation. This increase was associated with a decline of 65% in the use of the oral restricted nitrates. They found similar results for the ACE inhibitors (sharp decrease of the restricted ACE and a strong increase in the use of the unrestricted ACE inhibitors).

Marshall et al.(2002)[42] who have analyzed the effects of the RPS for Histamine-2 receptor antagonist on dispensing and reimbursement for all senior citizens of British Columbia, obtained similar results. In the 12 months after the implementation of the RPS, the monthly defined daily dose of the reference drugs (the generic cimetidine) increased by 379% and the monthly defined daily dose of the restricted drugs fell by 55%. In contrast, at medium term (between 12 months to 44 months after the introduction of the RPS), the number of DDD of restricted drugs rose but those of the reference drugs in aggregate declined (but remained above the base line).

More recently, Ubeda et al.(2007)[43] confirmed that the introduction of a RPS for antidepressant drugs in Spain was associated with an increase in the DDD consumption for antidepressant generic drugs but also with a displacement of prescription to drugs that were not included in the reference price system.

In contrast, Mabasa et al.(2006)[44] found that the introduction of a RPS had a more limited positive impact on the use of the reference drugs. They found that the adoption of a Level 3 RPS in an employer-sponsored drug plan in Canada for proton pump inhibitor (PPIs) was associated with a modest increase in utilization of the reference drugs in the 12 months after the inclusion of PPI in the Level 3 RPS.

We identified only one article that compares the effect of the implementation of a Level 1 RPS and a Level 2 on drug use. Grootendorst et al.(2005)[24] examined the effect of the implementation of a Level 1 and a Level 2 RPS on the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in British Columbia for the period of February 1993 to June 2001. They found that the impact on drug use varied according to the Level of the RPS. More specifically, the implementation of a Level 2 RPS had a more significant and positive impact on the use of reference drugs than a Level 1 reference system. For example, the use of naproxen doubled after the introduction of Level 2 RPS but the rates of the two other unrestricted NSAIDs (ibuprofen and ASA) declined after the introduction.

Additional studies have analyzed the impact of a RPS by using individual data (patients, physicians). Most of these studies indicated that the introduction of a reference price system increased the use of the reference drugs. Schneeweiss et al. (2002a)[45] analyzed the effect of the introduction in British Columbia of a reference price system for angiotensin converting enzyme (ACE) inhibitors on drug use. They found that among the patients (n= 48 355) who were receiving a cost-shared ACE inhibitor before the introduction of the RPS, 18% switched to a reference ACE inhibitor, 4% switched to another class of antihypertensive drugs and 3% stopped all treatment. In addition, they observed that i) older patients were more likely to switch to a reference drug ACE inhibitor, ii) low income patients were more likely than those with high income to switch to reference ACE inhibitor, iii) patients with high chronic disease score, congestive heart failure or diabetes stayed in general on the same cost-shared drugs after the implementation of the RPS. Schneeweiss et al. (2002c)[46] examined the impact on drug use of the introduction of a RPS for ACE inhibitors using time trend analysis. They analyzed the evolution of utilization of ACE inhibitors (covered and restricted) during the next 18 months after the introduction of the RPS. They found that the use of cost-sharing ACE inhibitors declined strongly immediately after the policy change, while the use of the covered ACE drugs increased slowly.

Schneeweiss et al. (2003)[26] drew identical conclusions, by analyzing the change in drug use after the introduction of reference pricing for dihydropyridine calcium channel blockers among patients aged 65 years or older in British Columbia (Canada). In this study, based on a cohort of patients (N=23 116), Schneeweiss et al. (2003) demonstrated that the implementation of reference pricing was directly followed by a significant reduction in consumption of the cost share drugs and a significant increase in reference drug.

Among the users of the cost share drugs CCBs (N=23 116), 9.3% switched to the reference drug (dihydropyridine) within the six months and 5.8% switched to another antihypertensive class and 3% stopped all antihypertensive drug treatment after the introduction of the RPS. The authors also demonstrated that low income patients had on average a higher probability to switch to no-cost dihydropyridine CCB (Odd ratio 1.25). In addition, low-income patients had a higher probability to stop any antihypertensive treatment after the introduction of the RPS.

More recently, Schneeweiss et al. (2006)[47] evaluated the impact of restricting coverage of 3 leading proton pump inhibitors (PPI) in British Columbia for residents aged 66 or older. They observed a significant reduction in the utilization of the restricted PPRIs after the introduction of the policy (coverage restriction for 3 proton pump inhibitors) and a significant increase in the use of the covered PPI. In addition, they estimated that 45% of all PPI users switched to the covered PPI within the 6 months after the introduction of the policy.

ASSOCIATION OF THE RPS WITH DRUG PRICES

In general, most of the studies found that the implementation of a RPS was followed by a price reduction for drugs covered by the RPS. This trend has been underlined by Ljungkvist et al. (1997)[48] for Sweden. The authors observed a sharp decrease in the price level for drugs covered by the reference price system immediately after the implementation of the system. Giuliani et al.(1998)[29], in evaluating the RPS of Germany, also noted that the prices of original branded drugs submitted to the RPS declined immediately after the introduction of the system. On the other hand, they also noted that this decrease in the average price per DDD of active ingredients covered by the RPS was partially offset by an increase in the average price per DDD of active ingredients not subject to RPS. The authors underlined that during the period 1989-1996, pharmaceutical firms have launched a number of new active ingredients at a higher price than the reference price.

Grootendorst et al. (2001)[23] found that the prices of the restricted nitrates dropped by an average of 66% (by comparison to the baseline level) just after the introduction of the RPS. Concerning the reference standard drugs, they found no evidence that the prices paid for these drugs increased after the implementation of the RPS.

Puig-Junoy (2004)[49], who provided a descriptive analysis over the period 1996-2002 of the evolution of prices for drugs covered by the RPS in Spain, found that drugs (brand, copy or generic) with a price higher than the reference price level immediately reduced their prices after the implementation of the RPS. They concluded that the effect of RPS was very "similar to maximum price regulation". They also observed that the price of drugs already on the market before the introduction of the RPS with a price equal to or lower than the reference level remained constant after the implementation of the RPS (at least during the next 10 months). At the same time, the authors noted that the implementation of the RPS was not followed by a decrease in the prices of drugs with a price initially below the reference level. Simoens et al. (2005)[2] underlined that manufacturers of original drugs have reacted in several ways to the introduction of a RPS in Belgium. Some firms have reduced prices of original drugs. For example, the price of Zestril (one original drug of lisinopril) was dropped to the price level of the generic version of lisinopril. On the other hand, some firms of original drugs have reacted to the introduction of the RPS by launching new variants of their original drugs (this is the case for Cipramil).

Andersson et al.(2006)[50] also confirmed that the introduction of a RPS in Sweden in 1993 was associated with a reduction in cost/DDD for some drugs (acetic acid derivatives and related substances, selective serotonin reuptake inihibitors, anti-gout preparations) submitted to the RPS. In particular, they used a linear segmented regression (based on volume and cost per volume) analysis to examine if a change in slope and level (intercept) of regression had occurred after the introduction of the RPS.

They concluded that the introduction of the RPS was associated with a reduced slope (acetic acid derivatives and related substances, selective serotonin reuptake inhibitors, anti-gout preparations) and a reduced level of cost/DDD (for selective serotonin reuptake inhibitors).

This negative impact of the RPS on the prices of original drugs has also been confirmed by Ubeda et al.(2007)[43]. They concluded that the implementation of a reference price had encouraged patients to use generic drugs and forced the prices of the original drugs to lower (especially at medium term). Puig-Junoy (2007)[51], who analyzed the evolution of the monthly price from January 2001 to October 2004 for the six statins covered by the RPS in Spain, observed that the introduction of the RPS "tends to decrease the price of the original relative to the price of the generics". In addition, they underlined that the price of new generic entrants after the implementation of the RPS was in all cases lower than the lowest priced generic. On the other hand, they observed that the "price of all products already on the market before the introduction of the RPS with a price equal to or lower than the reference level remained absolutely constant during the period after".

In a more recent study, based on panel regression, Brekke et al. (2009)[52] observed that the introduction of reference pricing in Norway led to an average price reduction of about 18% on brand names and 8% on generics.

In contrast to these studies which observed a reduction in the price of the drugs covered by the RPS, Narine et al. (1999)[39] and Narine et al. (2001)[40] concluded that the effects of the introduction of a RPS on the price of the original drugs (for H2 anatgonists and nitrates) were very limited. According to the authors, "few substantial changes in unit cost were observed which suggested that pricing levels, by and large were maintained".

Schneeweiss et al.(2002a)[45] concluded that the implementation of RPS for ACE inhibitors was not associated with a systematic change in drug prices per median monthly doses across substances covered by the RPS. Schneeweiss et al.(2003)[26] observed that the introduction of reference pricing for dihydropyridine calcium channel blockers (CCBs) did not produce a systematic change in drug prices across drugs (mean change -0.80 Canadian dollar per median monthly doses, SD=0.6). Schneeweiss et al.(2004)[22] also observed no significant change in per milligram price levels before and after the RPS for ACE inhibitors (all $p > 0.10$).

Grootendorst et al.(2005)[24] also found that the introduction of (Level 2) RPS had no significant effect on drug prices of original branded drugs submitted to the RPS or on drug prices of reference drugs. Only the implementation of a Level I RPS was associated with a small decrease in the prices of the restricted NSAIDs.

ASSOCIATION OF THE RPS WITH DRUG EXPENDITURES

In general, most of the studies tend to conclude that the introduction of a RPS contributed to a reduction of drugs expenditures for the third-party payer, at least in the short term. In their descriptive study of the health care system, Ljungkvist et al. (1997)[48] concluded that the savings in the drug bill for the third-party payer induced by the introduction of the reference price system was approximately equal to SEK 400 million during the first year of the introduction (in 1993).

Narine et al. (1999)[39] and Narine et al. (2001)[40] found that the British Columbia 'RPS for histamine-2 receptor anatagonist contributed to the reduction of the expenditures for the third-party payer in the first year after the introduction of this system'. Both studies underlined that the ingredient cost in all three reference groups (cost paid by the third-party payer Pharmacare) dropped from $42.0 million in the year before the introduction of reference pricing to $23.7 million the year after.

Grootendorst et al. (2001)[23] also estimated that the introduction of reference pricing for nitrates reduced third-party payer expenditures on nitrates by $14.9 million (95% CI $10.7 to $19.1 million) in the first 3.5 years after the introduction (this is equivalent to $4.2 million annually or 2% of the total amount that Pharmacare spent on drugs).

If Grootendorst et al. (2001) found that the implementation of the RPS was very effective in controlling expenditures for the third-party payer, they also noted that its impact on co-payments for patients was not so effective as they observed an increase in co-payment immediately after the RPS was implemented.

Marshall et al.(2002)[42] also concluded that the implementation of a RPS in British Columbia for common gastrointestinal drugs contributed to the reduction in provincial expenditures for these drugs. They estimated that the annualized cost saving due to the implementation of the RPS varied between $1.8 million to 3.2 million for all histamnine-2 receptor antagonists (depending on the hypothesis). On the other hand, they noted that the implementation of reference pricing increased the financial burden on senior citizens. After the introduction of a RPS for histamine-2 receptor antagonists, the total out-of-pocket expenditures incurred by senior citizens increased from less than 1% before the introduction of the RPS to 16% afterwards.

Schneeweiss et al.(2002a)[45] estimated that the cost savings to Pharmacare of the introduction of the RPS for angiotensin conveting enzyme inhibitors was $6.7 million in the first year for Pharmacare. For Schneeweiss et al.(2003)[26], the cost savings for Pharmacare of the introduction of a RPS for dihydropyridine calcium channel blockers (CCBs) were estimated to $1.67 million in the first year.

Schneeweiss et al.(2004)[22] analyzed the potential effect of RPS on four spending changes (reduced drug spending for prevalent users, reduced drug spending for incident users, increased spending for non-pharmacy health services, increased administration spending associated with the introduction of the RPS) and found a positive effect of the RPS for the provincial health insurance system in British Columbia. According to the authors, the net savings were estimated to be $5.8 million during the first year after the introduction of the RPS. More than five sixths of these savings were realized by changing drug utilization (to lower cost drugs) and only one sixth by shifting costs to patients. In contrast, Schneeweiss et al.(2004) noted that no savings were induced through drug price changes. In contrast, they underlined that the administration cost of the implementation of the RPS reached $0.42 million in the first year.

Grootendorst et al.(2005)[24] who made a distinction between the impact of a Level 1 RPS and Level 2 RPS on drug expenditures concluded that the implementation of a Level 2 was more efficient in terms of savings for the third-party payer. They estimated that a Level 1 RPS applied to the NSAIDs reduced expenditure for the third-party payer (the British Columbia Pharmacare) by about $1 million (95 percent CI: $ 0.6 to $ 1.5 million) annually against $4 million (95 percent CI : $3.6 to $ 4.4 million) for a Level 2 RPS. However, they noted that part of these savings was offset by an increase in co-payment. Total patient spending increased, respectively, by $92,000 and $ 820,000 annually after the introduction of Level 1 and Level 2.

Schneeweiss et al.(2006)[47] evaluated the economic consequences of coverage restriction for 3 leading proton pump inhibitors and estimated that the provincial health plan saved at least Can $2.9 million as in the first 6 months of the policy change. According to the authors, this decrease was entirely explained by utilization change in the use of PPI.

Lee et al.(2006) who have analyzed the impact of reference pricing on pharmaceutical expenditures for a non-OECD country found that the introduction of RPS (Level 1) in Taiwan had a significant negative impact ($p<0.05$) on the annual growth rate of pharmaceutical expenditures.

According to Brekke et al. (2009)[52] the price reduction of 18% on brand names and 8% on generics after the introduction of the RPS in Norway contributed to a cost saving of about 75 million NOK.

In contrast, Giuliani et al.(1998)[29] concluded that the introduction of the RPS in Germany was only partially effective for cost containment. Indeed, most of the savings of drugs expenditures induced by the introduction of the RPS were balanced by the fact that firms launched new active ingredients at a higher price. Ubeda et al.(2007)[43] also concluded that the reduction of the cost of many drugs covered by the RPS was offset by the displacement of prescription to new higher priced drugs not covered by the RPS.

ASSOCIATION OF THE RPS WITH HEALTH SERVICES USE AND HEALTH

A limited number of studies have assessed the impact of the implementation of a reference price system on health (mortality) and health care utilization. All of these studies are based on individual data. Most of them found no evidence of adverse effects on health and no evidence of a significant change in health care utilization after the introduction of a reference price system. This is the case for Hazlet et al.(2002)[53] who suggested that the introduction of a reference pricing policy (for an antisecretory drug) in October 1995 in British Columbia for senior citizens was not associated with a significant change in utilization of health services. Schneeweiss et al. (2002b)[54] found similar results. In particular, they found that the introduction of a reference price system for angiotensin-converting-enzyme (ACE) inhibitors for patients 65 years of age or older was not associated with changes in the rates of visits to physicians, hospitalizations, admission to long-term care facilities or mortality. In addition, the analyses of patient subgroups (low-income, chronic disease score, heart failure, renal failure) confirmed these results.

Schneeweiss et al. (2003)[26] did not observe a significant increase in physician visits in the entire cohort of patients (switchers and non-switchers) after the introduction of a reference price system for dihydropyridine calcium channel blockers among patients aged 65 years or older in British Columbia (Canada). However, they observed that switchers had an 18% increase in physician visits compared with non-switchers during the 2 months after switching but afterwards the rates of physicians visits were similar to the base line between switchers and non switchers.

Schneeweiss et al.(2006)[47] examined the clinical consequences of the introduction of a coverage restriction for 3 leading proton pump inhibitors (PPIs) for British Columbia residents aged 66 or older. They concluded that the introduction of a coverage restriction for PPIs had no significant impact on the monthly rate of hospitalization for gastrointestinal hemorrhage. They only noted a slight increase in physicians visits 3 months after the policy change (p=0.01).

Table 1: Assessment of individual studies included in the reviews

Ref	Name	Types of studies	Data	Estimation procedures	Limits
50	**Andersson et al.(2006)**	Time trend series analysis of cost, volume and cost per volume for two indicators drug groups in Sweden 1986-2002.	Based on aggregated data on deliveries of drugs to all Swedish between 1 January 1986 and December 2002; Monthly averages were calculated from quarterly observations.	Linear segmented regression analysis :analysis of changes in the level and slope of regression after the introduction of RPS.	Results of regression are not reported, limited number of observation to detect break point No unit root test (with structural break). No information on the quality of the regression. Results of robustness tests are not reported. No possibility to distinguish the effects of other measures. All conclusions should be considered with caution given the methodological flaws (purely descriptive analysis, aggregated data analysis, no adjustment for health of patient and for patient characteristics, etc).
52	**Brekke et al. (2009)(recent study not included in reviews)**	Before-after-study	Analysis based on aggregated data: monthly sales value for the 30 largest ATC groups over the period 2001 to 2004 in Norway. Time is measured in one month periods.	Panel data estimation	Little information on unit root test, heteroscedasticity, random effects versus fixed effects.
25	**Duetz et al.(2002)**	Before-after design	Based on 47 680 patients, 927 female and 2 922 male physicians. All patients (65 years or older and residents in British Columbia) who received at least 1 prescription of any ACE inhibitor between January 1995 and June 1998. Cardiologist and pulmonary specialists were excluded.	Multivariate logistic regression (multivariate adjustment for confounders)	Study limited to senior citizens in British Columbia. Difficult to generalize the results to the whole population and to the whole country.
29	**Giuliani et al.(1998)**	Time series analysis. Descriptive analysis, macro-level, no distinction between effects induced by reference pricing and by other cost containment measures.	Based on aggregated data.	Descriptive analysis. Focus on eight therapeutic groups (beta blockers, calcium antagonists, non-opiate analgesics, oral hypoglycemics, NSAIDs, expectorants, coronary dilators, systemic antibiotics). Macro-analysis of the evolution of the average prices per DDD for	All conclusions should be considered with caution given the methodological flaws (purely descriptive analysis, aggregated data analysis, no adjustment for health of patient and for patient characteristics, etc.).

				eight therapeutic groups in Germany during the 1990-1996.	
23	**Grootendorst et al.(2001)**	Before-after study	Analysis based on aggregated claims data (monthly data provided by BC Pharmacare) for the period April 1994 to May 1999. Volume of prescriptions and the units of anti-anginal drugs (nitrates, CCBs and beta-blockers) dispensed to British Columbia senior citizens (65 years of age and older). Analysis based on the number of prescriptions dispensed per 1 000 senior citizens. Descriptive analysis (trends) and extrapolation (based on a linear regression).	Extrapolation of trends from before the introduction of RPS to the period when the policy was in place.	No information over the parameters and quality of the regression used for the extrapolation. Results of robustness tests are not reported. Difficult to generalize the results to the whole population and to the whole country.
41	**Grootendorst et al.(2002)**	Before after study. Evaluation of the effect of a RPS for nitrates, angiotensin-converting-enzyme (ACE) inhibitors and dihydropyridine calcium channel blockers (CCBS).	Limited to senior citizens of British Columbia. Analysis based on individual data and assembled monthly claims data. Period : October 1995 to May 1999.	Descriptive analysis and survival models.	No information on the quality of the regression. Results of robustness tests are not reported. Only executive summary is available.
24	**Grootendorst et al.(2005)**	Before-after study of the effect of reference pricing of nonsteroidal anti-inflammatory drugs (NSAIDs).	Analysis based on aggregated claims data (monthly data provided by BC Pharmacare) over the period February 1993 to June 2001. Limited to senior citizens (65 years age or older).	Extrapolation of trends from before the introduction of RPS to the period when the policy was in place. Regression model (OLS) to test the impact of the effect of RPS on drug use and drug price. Correction for autocorrelation (Newey-west estimator).	No information on the quality of the regression. Results of robustness tests are not reported. No unit root test.
55	**Grootendorst et al.(2006)**	Examination of the impact of RPS on antihypertensive drug plan expenditures in BC and Ontario.	Based on individual data. Period 1994-2001.	Econometric approach (correction for heteroskedasticity and autocorrelation).	
53	**Hazlet et al.(2002)**	Regression analysis.	Based on individual administrative data: control cohort of 10 000 beneficiaries (random sample) and a exposed cohort of 10 000 beneficiaries who were exposed to RPS (random sample) from January 1993 to December 1997.	Longitudinal generalized regression (Poisson) with a group control.	Power analysis of sample size for each of the cohorts. Correlations and potential seasonality are discussed. Use of patient characteristics on individual level. The control cohort and the exposed cohort are not selected from the same

			Limited to British Columbia residents of 65 years or older. Limited to the drug class used in the treatment of acid peptic disease, gastric ulcer and gastroesophageal reflux disease (included histamine receptor antagonists, sucralfate and several others).		time period
[56]	**Lee et al.(2006)**	Before-after study	Based on aggregated data: monthly data for pharmaceutical expenditures from 1993 to 2006 filed by all contracted clinics, hospitals and pharmacies (BNHI).	Based on a time series analysis. Arima model.	No quality control reported. Difficult to generalize the results as it concerns a non-OECD country. Very simplistic approach.
[48]	**Ljungkvist et al. (1997)**	Time series analysis. No quality control reported.	Based on aggregated data.	Descriptive analysis of the pharmaceutical market in Sweden (organisation, cost of drugs, cost containment policy).	Limited to Sweden. All conclusions should be considered with caution given the methodological flaws (purely descriptive analysis, aggregated data analysis, no adjustment for health of patient and for patient characteristics, etc.)
[44]	**Mabasa et al.(2006)**	Before-after study design with control group.	Descriptive evidence on the evolution of the utilization of Proton Pump Inhibitors (PPIs) in an employer sponsored drug plan after the adoption of a Level 3 RPS by this employer group (6 300 members). Comparison with a control group that has not adopted this Level 3 RPS for PPIs.	Based on pharmacy claims for PPIs from June 1 2002 to May 31 2005.	No information on the patient characteristics. Difficult to generalize the results as it concerns only the employer members that have adopted this Level 3 RPS. All conclusions should be considered with caution given the methodological flaws (purely descriptive analysis, aggregated data analysis, no adjustment for health of patient and for patient characteristics, etc.)
[42]	**Marshall et al.(2002)**	Time series.	Based on aggregated data: the monthly claims data for upper gastrointestinal drugs for the period January 1993 to May 1999 (from BC Pharmacare). Prescribing volumes were converted to DDD per 100 000 senior citizens. Study limited to senior citizens (65 years age or older) in British Columbia.	Regression models to project forward trends in expenditures observed before the implementation of RPS.	Difficult to generalize the results to the whole population and to the whole country. Extrapolation of trends into the post RPS period. Descriptive analysis of the trends in DDD for drugs covered by RPS. No information over the parameter and quality of the regression used for the extrapolation. Results of robustness

					tests are not reported.
39	**Narine et al. (1999)**	Before-after study with no control group.	Based on aggregated data: total number of prescriptions (BC Pharmacare), quantity and costs within the reference group from October 1994 to September 1996. No data quality control reported. Limited to a descriptive analysis (trends analysis and evolution of market share).	Description analysis of the evolution of the numbers of prescriptions before and after (one year) the implementation of RPS in British Columbia (1995), focus on three therapeutic categories (histamine-2 receptor antagonists, nitrates and NSAIDs).	Information on the effects of RPS on the expenditures of the third-party payer is unclear. All conclusions should be considered with caution given the methodological flaws (purely descriptive analysis, aggregated data analysis, no adjustment for health of patient and for patient characteristics, etc.).
40	**Narine et al. (2001))**	Before-after study with no control group.	Based on aggregated data: total number of prescriptions (BC Pharmacare), quantity and costs within the reference group from October 1994 to September 1996.	Description analysis of the pattern of prescribing and expenditures before and after introduction of RPS in British Columbia.	No data quality control reported. Limited to a descriptive analysis (trends analysis and evolution of market share). All conclusions should be considered with caution given the methodological flaws (purely descriptive analysis, aggregated data analysis, no adjustment for health of patient and for patient characteristics, etc..
49	**Puig-Junoy (2004)**	Before-after study.	Based on aggregated data: monthly individual prices of the four top selling active ingredients (ranitidine, captopril, omeprazol, fluoxetine) covered by RPS for a period of 10 months before and 10 months after the introduction of RPS in Spain (in December 2000).	Descriptive evidence on the evolution of the price of drugs covered by the RPS in Spain and Andalusia.	Only descriptive analysis and anecdotal evidence. All conclusions should be considered with caution given the methodological flaws (purely descriptive analysis, aggregated data analysis, no adjustment for health of patient and for patient characteristics, etc.).
51	**Puig-Junoy (2007)**	Observational, retrospective interrupted times series analysis with comparison series of 46 monthly drug use and volumes of sales ratios from January 2001 to October 2004.	Based on aggregated data provided by IMS Spain. Limited to HMG-GOA reductase inhibitors (i.e. statins). Focus on the six statins available on the Spanish market with a distinction between Andalusia and the rest of Spain. Quantity has been measured as the aggregate number of prescribed units for each active ingredient.	Regression model based on a GLS estimator (correction for serial correlation, heteroskedasticity.	Only descriptive analysis and anecdotal evidence. All conclusions should be considered with caution given the methodological flaws (purely descriptive analysis, aggregated data analysis, no adjustment for health of patient and for patient characteristics, etc.).
45	**Schneeweis et al(2002a)**	Longitudinal.	Based on individual data (by linking patient characteristics and individual drug and health care utilization data and monthly claims database). Cohort of all patients	Regression analysis based on logistic models. Uses of patient characteristics.	Limited information on the parameters and quality of the regression.

			who were aged 65 years or older in 1998, who had been using any ACE inhibitor (between January 1995 and June 1998) before the implementation of a reference pricing system in British Columbia. Restricted to population who had been using any ACE inhibitor before the implementation of RPS (n=59623). Drug consumption based on the median monthly dose (MMD) dispensed.		
[54]	**Schneeweiss et al. (2002b)**	Longitudinal analysis.	Based on individual data. Cohort of all patients who were aged 65 years or older in December 1995, who received an ACE inhibitor between December 1995 and March 1996 and who were not in an long term care institution at the time of the first use of an ACE inhibitor. Distinction between switchers and non switchers patients. Poisson regression models.	Uses of patient characteristics (age, sex, income). Correction for overdispersion	Limited information on the parameters and quality of the regression.
[46]	**Schneeweiss et al. (2002c)**	Time trends analysis.	Based on individual data: all patients who were aged 65 years or older, who received an ACE inhibitor between January 1995 and June 1998. Limited to British Columbia residents.	Time trends analysis: evolution of prescription and prescription duration. Time trends of ACE inhibitor utilization as SMDs dispensed per 10 000 senior citizens were analyzed. Interrupted linear regression model with correction for autocorrelation.	Limited information on the parameters and quality of the regression.
Schneeweiss, 2003 #1202},	**Schneeweiss et al. (2003)**	Quasi experimental longitudinal study.	Based on individual data: a cohort of all patients (n=35 886 and n=23 116) who were aged 65 years or older in December 1995, who received a dihydropyridine (British Columbia Pharmacare). A subgroup (n=1 923) of switchers (from cost share drug to no cost drugs) was compared with a subgroup of patients who received only	Generalized linear models and logistic regression (correction for autocorrelation, used of a scale parameter to reduce overdispersion).	Study limited to senior citizens in British Columbia. Difficult to generalize the results to the whole population and to the whole country.

			dihydropyridine CCBs subject to cost sharing (non switchers) before and after (n=15 557). Drug consumption is based on median monthly doses.		
[22]	**Schneeweiss ett al.(2004)**	Before-after design study.	Based on aggregated data (budgetary data Limited information about data and methodology.		
[47]	**Schneeweiss et al.(2006)**	Longitudinal.	Based on segmented linear regression (correction for autocorrelation).	Time trends analysis	Limited information on the parameters and quality of the regression.
[2]	**Simoens et al. (2005)**	Time series analysis.	Based on aggregated data. Evolution of market share of generic drugs, evolution of monthly consumption of some drugs (original and generic lisinopril, cipramil, generic citalopram, sipralexa).	Descriptive evidence on the evolution of market evolution for generic drugs in Belgium between January 1998 and September 2004.	No information on the patient characteristics. Only descriptive analysis and anecdotal evidence. All conclusions should be considered with caution given the methodological flaws (purely descriptive analysis, aggregated data analysis, no adjustment for health of patient and for patient characteristics, etc.).
[43]	**Ubeda et al.(2007)**	Before-after study design.	Based on aggregated data: the prescription or drug that the Valencian autonomous government reimburses (Public administration). Data presented as DDD/1 000 inhabitants.	Descriptive evidence on the evolution of antidepressants use in primary care in the Valencian region after the introduction of a RPS for the period 2000 to 2004 (data were supplied by the Health Agency of the Valencian region). The term prescribed refers to prescription sold through pharmacies.	No information on the patient characteristics. All conclusions should be considered with caution given the methodological flaws (purely descriptive analysis, aggregated data analysis, no adjustment for health of patient and for patient characteristics, etc.).

Appendices with Chapter 4

6 RESULTS FOR 12 MOLECULES, CHOICE OF A LOW COST OR HIGH COST ORIGINAL

Patient and physician characteristics associated with the use of low cost alternatives.

A_Lanzoprazole							
Category	**Variable**	**Level**	**Total PR**	**% PR on low cost drugs**	**Odds Ratio from MV**	**(95% CI)**	**p-value**
Patients demographics	Gender	Female	6985	65.9	1.00		0.008
		Male	5620	61.2	0.94	(0.91-0.99)	
	Age group	18-44	1538	72.7	1.00		0.276
		45-64	5164	64.0	0.95	(0.88-1.02)	
		65-74	2922	59.9	1.00	(0.90-1.10)	
		75+	2981	62.8	0.99	(0.90-1.10)	
	Patient in a rest or nursing home	no	12415	63.5	1.00		0.007
		yes	190	83.2	1.23	(1.06-1.42)	
Patient Socio-Economic	Entitled to increased reimbursement	no	9403	63.7	1.00		0.841
		yes	3202	64.1	1.01	(0.95-1.06)	
	Work status	Missing	12	100	.		
		None (descendents + students)	68	82.4	1.00		0.192
		Pensioners	6723	60.6	0.81	(0.64-1.04)	
		Invalids and handicapped	1020	62.1	0.86	(0.67-1.10)	
		Registered in National Register	187	61.0	0.78	(0.58-1.05)	
		Unemployed - full time	846	71.9	0.93	(0.73-1.19)	
		Unemployed - partial time	246	67.5	0.88	(0.68-1.16)	
		Unemployed - pre-retired	307	61.9	0.88	(0.66-1.16)	
		Workers in private sector, blue collar	1117	67.9	0.90	(0.71-1.15)	
		Workers in private sector, white collar	996	68.5	0.91	(0.72-1.16)	
		Workers in public sector	563	72.5	0.96	(0.75-1.24)	
		Self-employed worker	520	66.0	0.89	(0.69-1.14)	
Choice by patient	Patient in a MM/WG (lump sum)	no	12476	63.8	1.00		0.293
		yes	129	68.2	1.08	(0.93-1.25)	
Choice by patient	Patient has a GMR	no	4704	67.0	1.00		0.015
		yes	7901	62.0	0.95	(0.91-0.99)	
Morbidity	Receiving lump sum for chronic illness	no	11497	63.9	1.00		0.902
		yes	1108	63.6	1.00	(0.92-1.07)	
GP demographics	Speciality	GP	12057	64.5	1.00		0.003
		SP	548	48.2	0.87	(0.80-0.94)	
	GP Gender	F	2387	60.8	1.00		0.091
		M	10218	64.5	1.05	(0.99-1.11)	
	GP Age Group	≤35	643	62.2	1.00		0.018
		36-45	1865	64.2	0.98	(0.89-1.07)	
		46-55	6092	67.1	0.99	(0.91-1.08)	
		55+	4005	59.0	0.92	(0.84-1.01)	
Small Area info	Groups of SS based on education	info missing	318	61.3	.		
		Q1 education	2899	63.7	1.00		0.99
		Q2 education	2867	64.6	1.01	(0.95-1.07)	
		Q3 education	2724	63.8	1.00	(0.94-1.06)	
		Q4 education	2022	62.8	0.99	(0.93-1.06)	
		Q5 education	1775	64.3	1.00	(0.93-1.08)	

MV: multivariate Model; PR: prescription ; MM/WG: medical house; GMR : Global Medical Record;

A_Glicazide							
Category	**Variable**	**Level**	**Total PR**	**% PR on low cost drugs**	**Odds Ratio from MV**	**(95% CI)**	**p-value**
Patients demographics	Gender	Female	8907	69.7	1.00		0.533
		Male	8481	69.9	1.01	(0.97-1.06)	
	Age group	18-44	186	60.2	1.00		0.864
		45-64	4297	67.5	1.02	(0.86-1.22)	
		65-74	5458	71.5	1.03	(0.85-1.25)	
		75+	7447	70.1	1.01	(0.84-1.22)	
	Patient in a rest or nursing home	no	16908	70.0	1.00		0.316
		yes	480	62.7	0.93	(0.81-1.07)	
Patient Socio-Economic	Entitled to increased reimbursement	no	11255	69.6	1.00		0.374
		yes	6133	70.2	1.02	(0.97-1.07)	
	Work status	Missing	41	97.6	.		
		Pensioners	13487	70.8	1.00		0.266
		Invalids and handicapped	950	74.9	1.05	(0.96-1.16)	
		Registered in National Register	302	65.9	0.95	(0.82-1.10)	
		Unemployed - full time	597	60.0	0.93	(0.81-1.05)	
		Unemployed - partial time	98	65.3	1.02	(0.80-1.30)	
		Unemployed - pre-retired	430	69.3	0.97	(0.84-1.13)	
		Workers in private sector, blue collar	485	56.9	0.91	(0.79-1.04)	
		Workers in private sector, white collar	491	59.9	0.92	(0.78-1.09)	
		Workers in public sector	249	81.5	1.20	(1.02-1.41)	
		Self-employed worker	258	56.6	0.99	(0.80-1.23)	
Choice by patient	Patient in a MM/WG (lump sum)	no	16821	69.8	1.00		0.511
		yes	567	70.9	0.96	(0.84-1.09)	
Choice by patient	Patient has a GMR	no	4788	55.1	1.00		≤0.001
		yes	12600	75.4	1.22	(1.16-1.29)	
Morbidity	Receiving lump sum for chronic illness	no	15523	70.2	1.00		0.243
		yes	1865	66.8	0.96	(0.89-1.03)	
GP demographics	Speciality	GP	16849	70.6	1.00		≤0.001
		SP	539	46.0	0.82	(0.74-0.91)	
	GP Gender	F	3276	69.5	1.00		0.529
		M	14112	69.9	0.98	(0.92-1.04)	
	GP Age Group	≤35	1017	67.6	1.00		0.572
		36-45	2608	68.8	0.99	(0.90-1.09)	
		46-55	6790	69.5	1.00	(0.91-1.09)	
		55+	6973	70.9	1.03	(0.94-1.12)	
Small Area info	Groups of SS based on education	info missing	500	62.6	.		
		Q1 education	4423	67.4	1.00		0.153
		Q2 education	4126	72.0	1.03	(0.97-1.09)	
		Q3 education	3598	74.5	1.06	(1.00-1.13)	
		Q4 education	2809	69.1	0.99	(0.93-1.06)	
		Q5 education	1932	64.8	0.98	(0.90-1.06)	

MV: multivariate Model; PR: prescription ; MM/WG: medical house; GMR : Global Medical Record;

C_Indapamide							
Category	**Variable**	**Level**	**Total PR**	**% PR on low cost drugs**	**Odds Ratio from MV**	**(95% CI)**	**p-value**
Patients demographics	Gender	Female	17966	61.1	1.00		≤0.001
		Male	10351	64.4	1.04	(1.02-1.07)	
	Age group	18-44	881	63.7	1.00		≤0.001
		45-64	8755	64.8	0.98	(0.92-1.05)	
		65-74	7709	63.1	0.92	(0.85-1.00)	
		75+	10972	59.6	0.88	(0.82-0.95)	
	Patient in a rest or nursing home	no	27501	62.5	1.00		0.784
		yes	816	57.0	0.99	(0.91-1.07)	
Patient Socio-Economic	Entitled to increased reimbursement	no	20008	61.7	1.00		≤0.001
		yes	8309	63.7	1.06	(1.03-1.08)	
	Work status	Missing	16	25.0	.		
		None (descendents + students)	6	16.7	1.00		0.01
		Pensioners	20063	62.1	1.74	(1.56-1.93)	
		Invalids and handicapped	1148	58.2	1.58	(1.42-1.77)	
		Registered in National Register	586	56.8	1.62	(1.42-1.85)	
		Unemployed - full time	1169	68.4	1.71	(1.54-1.91)	
		Unemployed - partial time	217	67.3	1.68	(1.45-1.96)	
		Unemployed - pre-retired	577	68.1	1.69	(1.49-1.91)	
		Workers in private sector, blue collar	1262	67.6	1.70	(1.53-1.88)	
		Workers in private sector, white collar	1520	59.3	1.62	(1.46-1.80)	
		Workers in public sector	995	59.3	1.61	(1.44-1.80)	
		Self-employed worker	758	63.9	1.82	(1.62-2.05)	
Choice by patient	Patient in a MM/WG (lump sum)	no	27795	62.1	1.00		0.019
		yes	522	75.3	1.10	(1.02-1.19)	
Choice by patient	Patient has a GMR	no	9677	52.5	1.00		≤0.001
		yes	18640	67.4	1.17	(1.14-1.20)	
Morbidity	Receiving lump sum for chronic illness	no	26251	63.0	1.00		≤0.001
		yes	2066	53.4	0.92	(0.88-0.97)	
GP demographics	Speciality	GP	27396	62.8	1.00		≤0.001
		SP	921	48.6	0.91	(0.86-0.96)	
	GP Gender	F	5210	61.6	1.00		0.911
		M	23107	62.5	1.00	(0.97-1.03)	
	GP Age Group	≤35	1752	63.2	1.00		0.145
		36-45	4208	59.1	0.97	(0.92-1.02)	
		46-55	12060	62.4	1.00	(0.95-1.05)	
		55+	10297	63.3	1.01	(0.97-1.07)	
Small Area info	Groups of SS based on education	info missing	691	68.2	.		
		Q1 education	5591	60.7	1.00		0.096
		Q2 education	6897	64.0	1.02	(0.99-1.06)	
		Q3 education	6270	62.3	1.01	(0.97-1.05)	
		Q4 education	5242	63.6	1.03	(0.99-1.06)	
		Q5 education	3626	58.6	0.97	(0.93-1.02)	

MV: multivariate Model; PR: prescription ; MM/WG: medical house; GMR : Global Medical Record;

C_Other diuretics (chlortalidone, furosemide, torasemide and spironolactone)							
Category	**Variable**	**Level**	**Total PR**	**% PR on low cost drugs**	**Odds Ratio from MV**	**(95% CI)**	**p-value**
Patients demographics	Gender	Female	28105	27.5	1.00		≤0.001
		Male	13892	24.3	0.97	(0.95-0.98)	
	Age group	18-44	1434	31.5	1.00		0.154
		45-64	10194	29.1	0.98	(0.93-1.03)	
		65-74	9022	26.4	0.96	(0.91-1.03)	
		75+	21347	24.9	0.95	(0.89-1.01)	
	Patient in a rest or nursing home	no	37526	26.2	1.00		0.017
		yes	4471	28.7	1.04	(1.01-1.08)	
Patient Socio-Economic	Entitled to increased reimbursement	no	25681	26.5	1.00		0.544
		yes	16316	26.4	0.99	(0.97-1.01)	
	Work status	Missing	56	35.7	.		
		None (descendents + students)	16	56.3	1.00		0.106
		Pensioners	31673	25.4	0.71	(0.52-0.96)	
		Invalids and handicapped	3031	30.9	0.74	(0.54-1.00)	
		Registered in National Register	670	25.5	0.70	(0.51-0.96)	
		Unemployed - full time	1390	30.8	0.74	(0.54-1.01)	
		Unemployed - partial time	245	29.8	0.72	(0.52-0.99)	
		Unemployed - pre-retired	554	32.9	0.75	(0.55-1.03)	
		Workers in private sector, blue collar	1114	28.2	0.71	(0.52-0.96)	
		Workers in private sector, white collar	1565	28.6	0.72	(0.53-0.98)	
		Workers in public sector	925	36.1	0.79	(0.58-1.07)	
		Self-employed worker	758	20.3	0.68	(0.50-0.93)	
Choice by patient	Patient in a MM/WG (lump sum)	no	41291	26.5	1.00		0.765
		yes	706	27.1	0.99	(0.94-1.05)	
Choice by patient	Patient has a GMR	no	14288	23.0	1.00		≤0.001
		yes	27709	28.2	1.05	(1.03-1.07)	
Morbidity	Receiving lump sum for chronic illness	no	33173	26.9	1.00		0.078
		yes	8824	24.7	0.98	(0.96-1.00)	
GP demographics	Speciality	GP	39994	26.6	1.00		0.73
		SP	2003	23.7	0.99	(0.96-1.03)	
	GP Gender	F	7922	24.9	1.00		0.134
		M	34075	26.8	1.02	(0.99-1.04)	
	GP Age Group	≤35	2719	26.1	1.00		0.002
		36-45	6558	24.4	0.99	(0.95-1.02)	
		46-55	18377	28.6	1.03	(0.99-1.07)	
		55+	14343	24.7	1.00	(0.96-1.03)	
Small Area info	Groups of SS based on education	info missing	1327	29.3	.		
		Q1 education	8507	31.3	1.00		≤0.001
		Q2 education	9968	26.7	0.95	(0.93-0.98)	
		Q3 education	9037	26.7	0.96	(0.93-0.98)	
		Q4 education	8210	24.1	0.93	(0.90-0.95)	
		Q5 education	4948	20.5	0.90	(0.87-0.93)	

MV: multivariate Model; PR: prescription ; MM/WG: medical house; GMR : Global Medical Record;

A_ Atenolol and Bisoprolol							
Category	**Variable**	**Level**	**Total PR**	**% PR on low cost drugs**	**Odds Ratio from MV**	**(95% CI)**	**p-value**
Patients demographics	Gender	Female	68913	52.5	1.00		0.186
		Male	41130	53.2	1.01	(1.00-1.03)	
	Age group	18-44	6360	49.1	1.00		≤0.001
		45-64	46055	53.5	1.03	(1.00-1.07)	
		65-74	28585	54.7	1.03	(0.99-1.07)	
		75+	29043	50.6	0.98	(0.94-1.02)	
	Patient in a rest or nursing home	no	108004	52.9	1.00		0.231
		yes	2039	47.4	0.97	(0.92-1.02)	
Patient Socio-Economic	Entitled to increased reimbursement	no	83978	52.1	1.00		≤0.001
		yes	26065	55.1	1.04	(1.02-1.06)	
	Work status	Missing	109	55.0	.		
		None (descendents + students)	38	47.4	1.00		0.011
		Pensioners	65248	53.0	1.03	(0.80-1.32)	
		Invalids and handicapped	5619	49.3	0.97	(0.75-1.24)	
		Registered in National Register	1730	56.8	1.04	(0.80-1.34)	
		Unemployed - full time	5456	58.2	1.06	(0.82-1.36)	
		Unemployed - partial time	1814	53.8	1.03	(0.80-1.32)	
		Unemployed - pre-retired	3143	55.6	1.04	(0.81-1.33)	
		Workers in private sector, blue collar	8519	53.9	1.03	(0.80-1.32)	
		Workers in private sector, white collar	9239	49.4	1.00	(0.78-1.29)	
		Workers in public sector	5429	50.7	1.01	(0.79-1.30)	
		Self-employed worker	3699	50.9	1.06	(0.82-1.36)	
Choice by patient	Patient in a MM/WG (lump sum)	no	108220	52.4	1.00		≤0.001
		yes	1823	73.1	1.19	(1.13-1.25)	
Choice by patient	Patient has a GMR	no	38369	45.8	1.00		≤0.001
		yes	71674	56.5	1.11	(1.09-1.13)	
Morbidity	Receiving lump sum for chronic illness	no	103901	52.9	1.00		0.288
		yes	6142	51.1	0.98	(0.95-1.01)	
GP demographics	Speciality	GP	106870	53.1	1.00		≤0.001
		SP	3173	43.3	0.94	(0.90-0.97)	
	GP Gender	F	21075	50.0	1.00		≤0.001
		M	88968	53.4	1.05	(1.03-1.07)	
	GP Age Group	≤35	6800	57.4	1.00		≤0.001
		36-45	16449	50.3	0.94	(0.91-0.97)	
		46-55	47798	53.3	0.95	(0.92-0.98)	
		55+	38996	52.4	0.94	(0.91-0.96)	
Small Area info	Groups of SS based on education	info missing	3109	52.7	.		
		Q1 education	18939	53.2	1.00		0.002
		Q2 education	24949	54.1	1.01	(0.99-1.03)	
		Q3 education	25427	54.6	1.02	(0.99-1.04)	
		Q4 education	21134	51.8	0.99	(0.97-1.02)	
		Q5 education	16485	48.8	0.97	(0.95-1.00)	

MV: multivariate Model; PR: prescription ; MM/WG: medical house; GMR : Global Medical Record;

C_other beta-bloquers (propanolol, sotalol, metroprolol, acebutol and celiprolol)							
Category	**Variable**	**Level**	**Total PR**	**% PR on low cost drugs**	**Odds Ratio from MV**	**(95% CI)**	**p-value**
Patients demographics	Gender	Female	48971	5.1	1.00		0.184
		Male	32296	5.4	1.00	(1.00-1.01)	
	Age group	18-44	7331	5.3	1.00		0.136
		45-64	30330	5.3	0.99	(0.98-1.01)	
		65-74	19937	5.7	0.99	(0.97-1.01)	
		75+	23669	4.6	0.98	(0.96-1.00)	
	Patient in a rest or nursing home	no	79155	5.2	1.00		0.971
		yes	2112	4.4	1.00	(0.98-1.02)	
Patient Socio-Economic	Entitled to increased reimbursement	no	59691	5.1	1.00		0.743
		yes	21576	5.4	1.00	(0.99-1.01)	
	Work status	Missing	119	15.1	.		
		None (descendents + students)	326	7.1	1.00		0.318
		Pensioners	48522	5.2	0.99	(0.91-1.07)	
		Invalids and handicapped	5993	5.9	1.00	(0.92-1.08)	
		Registered in National Register	1154	5.5	0.99	(0.91-1.07)	
		Unemployed - full time	4152	6.4	0.99	(0.92-1.08)	
		Unemployed - partial time	1125	7.4	1.00	(0.92-1.09)	
		Unemployed - pre-retired	2020	5.7	0.99	(0.91-1.08)	
		Workers in private sector, blue collar	5472	4.9	0.98	(0.91-1.06)	
		Workers in private sector, white collar	6458	4.0	0.97	(0.90-1.05)	
		Workers in public sector	3274	4.2	0.98	(0.90-1.06)	
		Self-employed worker	2652	4.0	0.98	(0.90-1.06)	
Choice by patient	Patient in a MM/WG (lump sum)	no	80332	5.0	1.00		≤0.001
		yes	935	19.8	1.15	(1.10-1.20)	
Choice by patient	Patient has a GMR	no	25408	4.1	1.00		0.002
		yes	55859	5.7	1.01	(1.00-1.02)	
Morbidity	Receiving lump sum for chronic illness	no	73927	5.3	1.00		0.047
		yes	7340	4.0	0.99	(0.98-1.00)	
GP demographics	Speciality	GP	77519	5.2	1.00		0.517
		SP	3748	4.6	1.00	(0.98-1.01)	
	GP Gender	F	15276	5.3	1.00		0.711
		M	65991	5.2	1.00	(0.99-1.01)	
	GP Age Group	≤35	5574	6.2	1.00		0.791
		36-45	12231	5.2	1.00	(0.98-1.01)	
		46-55	33094	5.1	0.99	(0.98-1.01)	
		55+	30368	5.1	0.99	(0.98-1.01)	
Small Area info	Groups of SS based on education	info missing	2338	5.5	.		
		Q1 education	14192	6.0	1.00		0.012
		Q2 education	20964	5.9	1.00	(0.99-1.01)	
		Q3 education	18276	5.1	0.99	(0.98-1.01)	
		Q4 education	15175	4.1	0.98	(0.97-1.00)	
		Q5 education	10322	4.5	0.99	(0.98-1.00)	

MV: multivariate Model; PR: prescription ; MM/WG: medical house; GMR : Global Medical Record;

C_Diltiazem							
Category	**Variable**	**Level**	**Total PR**	**% PR on low cost drugs**	**Odds Ratio from MV**	**(95% CI)**	**p-value**
Patients demographics	Gender	Female	17499	22.6	1.00		0.017
		Male	18497	26.1	1.03	(1.00-1.05)	
	Age group	18-44	806	28.7	1.00		≤0.001
		45-64	10573	27.7	0.98	(0.91-1.06)	
		65-74	10293	26.5	1.00	(0.91-1.09)	
		75+	14324	20.3	0.94	(0.86-1.03)	
	Patient in a rest or nursing home	no	34651	24.7	1.00		0.221
		yes	1345	17.4	0.97	(0.92-1.02)	
Patient Socio-Economic	Entitled to increased reimbursement	no	24728	25.5	1.00		0.643
		yes	11268	22.0	0.99	(0.97-1.02)	
	Work status	Missing	16	6.3	.		
		None (descendents + students)	5	0.0	1.00		0.679
		Pensioners	26052	23.0	1.35	(1.22-1.49)	
		Invalids and handicapped	2466	24.5	1.36	(1.23-1.50)	
		Registered in National Register	611	24.1	1.37	(1.21-1.55)	
		Unemployed - full time	1278	30.4	1.43	(1.28-1.59)	
		Unemployed - partial time	256	35.2	1.50	(1.26-1.78)	
		Unemployed - pre-retired	666	31.5	1.42	(1.25-1.63)	
		Workers in private sector, blue collar	1233	32.0	1.42	(1.28-1.58)	
		Workers in private sector, white collar	1368	31.1	1.40	(1.27-1.55)	
		Workers in public sector	981	30.2	1.41	(1.26-1.58)	
		Self-employed worker	1064	22.2	1.36	(1.22-1.51)	
Choice by patient	Patient in a MM/WG (lump sum)	no	35344	24.5	1.00		0.052
		yes	652	19.9	0.93	(0.87-1.00)	
Choice by patient	Patient has a GMR	no	12149	19.8	1.00		≤0.001
		yes	23847	26.8	1.09	(1.06-1.11)	
Morbidity	Receiving lump sum for chronic illness	no	31406	25.5	1.00		≤0.001
		yes	4590	17.1	0.94	(0.91-0.97)	
GP demographics	Speciality	GP	34125	24.7	1.00		0.01
		SP	1871	19.7	0.96	(0.93-0.99)	
	GP Gender	Missing	9	66.7	.		
		F	7160	24.2	1.00		0.206
		M	28827	24.5	1.02	(0.99-1.05)	
	GP Age Group	Missing	9	66.7	.		
		≤35	2412	21.3	1.00		≤0.001
		36-45	6633	30.4	1.08	(1.03-1.13)	
		46-55	14960	26.5	1.03	(0.99-1.08)	
		55+	11982	19.2	0.97	(0.93-1.01)	
Small Area info	Groups of SS based on education	info missing	1150	24.3	.		
		Q1 education	7737	24.9	1.00		0.884
		Q2 education	8318	25.3	1.00	(0.97-1.04)	
		Q3 education	7558	23.6	0.99	(0.96-1.02)	
		Q4 education	6507	24.7	1.00	(0.97-1.04)	
		Q5 education	4726	23.0	0.99	(0.95-1.03)	

MV: multivariate Model; PR: prescription ; MM/WG: medical house; GMR : Global Medical Record;

J_quinolone (roxithromycin, clarithromycin and azithromycin)							
Category	**Variable**	**Level**	**Total PR**	**% PR on low cost drugs**	**Odds Ratio from MV**	**(95% CI)**	**p-value**
Patients demographics	Gender	Female	880	56.8	1.00		0.745
		Male	535	66.0	0.99	(0.95-1.04)	
	Age group	18-44	836	76.0	1.00		0.121
		45-64	343	41.7	0.94	(0.88-1.00)	
		65-74	97	35.1	0.86	(0.74-1.01)	
		75+	139	29.5	0.94	(0.78-1.13)	
	Patient in a rest or nursing home	no	1401	60.9	1.00		0.011
		yes	14	0.0	0.71	(0.61-0.82)	
Patient Socio-Economic	Entitled to increased reimbursement	no	1219	62.9	1.00		0.32
		yes	196	43.9	0.96	(0.89-1.04)	
	Work status	Missing	2	50.0	.		
		None (descendents + students)	214	79.9	1.00		0.785
		Pensioners	288	32.3	1.04	(0.90-1.19)	
		Invalids and handicapped	51	47.1	1.03	(0.89-1.20)	
		Registered in National Register	11	72.7	1.05	(0.95-1.16)	
		Unemployed - full time	112	58.0	0.94	(0.86-1.03)	
		Unemployed - partial time	34	76.5	1.06	(0.94-1.20)	
		Unemployed - pre-retired	10	30.0	1.00	(0.74-1.35)	
		Workers in private sector, blue collar	253	72.3	1.04	(0.97-1.11)	
		Workers in private sector, white collar	307	67.8	1.01	(0.94-1.07)	
		Workers in public sector	65	46.2	1.01	(0.90-1.13)	
		Self-employed worker	68	60.3	1.01	(0.91-1.13)	
Choice by patient	Patient in a MM/WG (lump sum)	no	1408	60.2	1.00		0.69
		yes	7	71.4	1.06	(0.80-1.40)	
Choice by patient	Patient has a GMR	no	649	60.1	1.00		0.066
		yes	766	60.4	1.04	(1.00-1.09)	
Morbidity	Receiving lump sum for chronic illness	no	1365	61.1	1.00		0.356
		yes	50	38.0	0.93	(0.81-1.08)	
GP demographics	Speciality	GP	725	27.6	1.00		≤0.001
		SP	690	94.6	1.80	(1.66-1.94)	
	GP Gender	F	156	41.0	1.00		0.031
		M	1259	62.7	0.89	(0.79-0.99)	
	GP Age Group	≤35	42	4.8	1.00		≤0.001
		36-45	94	30.9	1.33	(1.13-1.56)	
		46-55	1052	73.6	1.43	(1.27-1.62)	
		55+	227	21.1	1.28	(1.12-1.46)	
Small Area info	Groups of SS based on education	info missing	240	92.9	.		
		Q1 education	202	46.5	1.00		0.013
		Q2 education	307	52.8	0.94	(0.87-1.01)	
		Q3 education	260	61.5	0.95	(0.88-1.03)	
		Q4 education	244	55.3	0.94	(0.87-1.01)	
		Q5 education	162	48.8	0.85	(0.78-0.93)	

MV: multivariate Model; PR: prescription ; MM/WG: medical house; GMR : Global Medical Record;

M_Piroxicam							
Category	**Variable**	**Level**	**Total PR**	**% PR on low cost drugs**	**Odds Ratio from MV**	**(95% CI)**	**p-value**
Patients demographics	Gender	Female	23138	20.2	1.00		≤0.001
		Male	15822	23.7	1.03	(1.02-1.05)	
	Age group	18-44	7191	25.7	1.00		0.003
		45-64	16626	22.1	0.97	(0.95-0.99)	
		65-74	7585	18.7	0.93	(0.90-0.97)	
		75+	7558	19.6	0.94	(0.91-0.98)	
	Patient in a rest or nursing home	no	38429	21.7	1.00		0.588
		yes	531	17.5	0.98	(0.89-1.07)	
Patient Socio-Economic	Entitled to increased reimbursement	no	29700	21.2	1.00		≤0.001
		yes	9260	22.9	1.04	(1.02-1.07)	
	Work status	Missing	60	30.0	.		≤0.001
		None (descendents + students)	362	24.3	1.00		
		Pensioners	17322	19.5	0.99	(0.93-1.05)	
		Invalids and handicapped	3166	23.4	0.99	(0.93-1.05)	
		Registered in National Register	577	19.1	0.96	(0.88-1.04)	
		Unemployed - full time	2479	24.1	1.00	(0.95-1.07)	
		Unemployed - partial time	1053	31.3	1.09	(1.02-1.16)	
		Unemployed - pre-retired	804	22.9	1.00	(0.93-1.07)	
		Workers in private sector, blue collar	4673	26.2	1.02	(0.97-1.08)	
		Workers in private sector, white collar	4149	20.0	0.98	(0.93-1.04)	
		Workers in public sector	2201	21.0	1.00	(0.93-1.07)	
		Self-employed worker	2114	21.6	1.04	(0.98-1.10)	
Choice by patient	Patient in a MM/WG (lump sum)	no	38572	21.4	1.00		≤0.001
		yes	388	44.1	1.21	(1.11-1.32)	
Choice by patient	Patient has a GMR	no	18173	16.5	1.00		≤0.001
		yes	20787	26.1	1.11	(1.09-1.13)	
Morbidity	Receiving lump sum for chronic illness	no	36246	21.5	1.00		0.44
		yes	2714	23.1	1.02	(0.98-1.05)	
GP demographics	Speciality	GP	36393	20.9	1.00		≤0.001
		SP	2567	32.3	1.11	(1.08-1.14)	
	GP Gender	Info missing	7	0.0	.		≤0.001
		F	6333	19.2	1.00		
		M	32620	22.1	1.06	(1.04-1.08)	
	GP Age Group	Info missing	7	0.0	.		≤0.001
		≤35	2061	23.9	1.00		
		36-45	6854	25.8	1.02	(0.98-1.05)	
		46-55	16125	22.1	0.98	(0.95-1.01)	
		55+	13913	18.8	0.96	(0.93-0.99)	
Small Area info	Groups of SS based on education	info missing	1360	21.9	.		≤0.001
		Q1 education	7865	21.9	1.00		
		Q2 education	9467	23.5	1.01	(0.99-1.03)	
		Q3 education	8458	24.2	1.02	(1.00-1.04)	
		Q4 education	6820	19.8	0.98	(0.96-1.00)	
		Q5 education	4990	15.8	0.95	(0.92-0.97)	

MV: multivariate Model; PR: prescription ; MM/WG: medical house; GMR : Global Medical Record;

N_tramadol							
Category	**Variable**	**Level**	**Total PR**	**% PR on low cost drugs**	**Odds Ratio from MV**	**(95% CI)**	**p-value**
Patients demographics	Gender	Female	48105	35.6	1.00		0.81
		Male	24144	37.0	1.00	(0.98-1.03)	
	Age group	18-44	9504	42.9	1.00		≤0.001
		45-64	26662	38.0	0.96	(0.92-0.99)	
		65-74	14512	35.7	0.93	(0.88-0.98)	
		75+	21571	30.9	0.90	(0.85-0.95)	
	Patient in a rest or nursing home	no	68213	36.5	1.00		0.413
		yes	4036	29.1	0.98	(0.94-1.03)	
Patient Socio-Economic	Entitled to increased reimbursement	no	44547	36.3	1.00		0.691
		yes	27702	35.8	1.01	(0.98-1.03)	
	Work status	Missing	134	44.8	.		
		None (descendents + students)	255	39.6	1.00		0.073
		Pensioners	38916	33.3	0.98	(0.84-1.14)	
		Invalids and handicapped	12091	37.9	0.96	(0.83-1.12)	
		Registered in National Register	1821	40.9	1.02	(0.86-1.21)	
		Unemployed - full time	4644	42.3	1.00	(0.86-1.16)	
		Unemployed - partial time	939	51.8	1.11	(0.95-1.30)	
		Unemployed - pre-retired	801	39.5	1.00	(0.84-1.19)	
		Workers in private sector, blue collar	5011	38.2	0.96	(0.83-1.12)	
		Workers in private sector, white collar	3740	39.6	0.97	(0.84-1.13)	
		Workers in public sector	1937	34.5	0.93	(0.80-1.09)	
		Self-employed worker	1960	39.0	1.01	(0.86-1.19)	
Choice by patient	Patient in a MM/WG (lump sum)	no	70748	35.7	1.00		≤0.001
		yes	1501	51.2	1.13	(1.06-1.20)	
Choice by patient	Patient has a GMR	no	27454	33.6	1.00		≤0.001
		yes	44795	37.6	1.05	(1.02-1.07)	
Morbidity	Receiving lump sum for chronic illness	no	59035	37.0	1.00		0.036
		yes	13214	31.9	0.97	(0.95-1.00)	
GP demographics	Speciality	GP	67332	35.8	1.00		0.013
		SP	4917	39.8	1.04	(1.01-1.07)	
	GP Gender	F	13629	36.3	1.00		0.347
		M	58620	36.0	1.01	(0.99-1.04)	
	GP Age Group	≤35	6037	38.1	1.00		0.006
		36-45	13078	35.9	1.01	(0.98-1.05)	
		46-55	31650	37.8	1.03	(0.99-1.07)	
		55+	21484	33.1	0.98	(0.95-1.02)	
Small Area info	Groups of SS based on education	info missing	2614	38.5	.		
		Q1 education	18264	37.8	1.00		0.031
		Q2 education	17087	36.4	0.99	(0.96-1.02)	
		Q3 education	15298	37.1	0.99	(0.96-1.03)	
		Q4 education	11529	33.2	0.96	(0.93-0.99)	
		Q5 education	7457	32.7	0.96	(0.93-1.00)	

MV: multivariate Model; PR: prescription ; MM/WG: medical house; GMR : Global Medical Record;

N_citalopram							
Category	**Variable**	**Level**	**Total PR**	**% PR on low cost drugs**	**Odds Ratio from MV**	**(95% CI)**	**p-value**
Patients demographics	Gender	Female	19982	75.2	1.00		0.046
		Male	7074	77.2	1.03	(1.00-1.07)	
	Age group	18-44	4160	79.1	1.00		0.231
		45-64	9143	75.7	0.97	(0.93-1.02)	
		65-74	4371	73.4	0.93	(0.87-1.00)	
		75+	9382	75.4	0.93	(0.87-1.00)	
	Patient in a rest or nursing home	no	24117	75.1	1.00		0.006
		yes	2939	80.9	1.07	(1.02-1.12)	
Patient Socio-Economic	Entitled to increased reimbursement	no	17878	74.1	1.00		0.004
		yes	9178	78.8	1.05	(1.02-1.09)	
	Work status	Missing	46	89.1	.		
		None (descendents + students)	162	81.5	1.00		0.297
		Pensioners	14671	74.7	0.93	(0.82-1.06)	
		Invalids and handicapped	2807	78.2	0.95	(0.84-1.07)	
		Registered in National Register	550	73.5	0.88	(0.75-1.05)	
		Unemployed - full time	1647	80.0	0.97	(0.85-1.10)	
		Unemployed - partial time	482	79.5	0.96	(0.84-1.11)	
		Unemployed - pre-retired	315	67.0	0.84	(0.70-1.01)	
		Workers in private sector, blue collar	1841	82.3	0.98	(0.87-1.11)	
		Workers in private sector, white collar	2590	76.7	0.95	(0.84-1.08)	
		Workers in public sector	1126	72.5	0.92	(0.80-1.05)	
		Self-employed worker	819	64.2	0.86	(0.74-0.99)	
Choice by patient	Patient in a MM/WG (lump sum)	no	26336	75.4	1.00		0.032
		yes	720	86.9	1.08	(1.01-1.15)	
Choice by patient	Patient has a GMR	no	10721	71.2	1.00		≤0.001
		yes	16335	78.7	1.07	(1.03-1.10)	
Morbidity	Receiving lump sum for chronic illness	no	22517	75.8	1.00		0.579
		yes	4539	75.3	0.99	(0.95-1.03)	
GP demographics	Speciality	GP	25567	76.4	1.00		≤0.001
		SP	1489	64.3	0.90	(0.85-0.95)	
	GP Gender	F	6903	78.6	1.00		0.019
		M	20153	74.8	0.96	(0.93-0.99)	
	GP Age Group	≤35	2040	77.0	1.00		≤0.001
		36-45	4406	74.8	0.97	(0.92-1.03)	
		46-55	11764	79.1	1.03	(0.98-1.08)	
		55+	8846	71.4	0.96	(0.91-1.01)	
Small Area info	Groups of SS based on education	info missing	877	71.0	.		
		Q1 education	5423	79.3	1.00		0.016
		Q2 education	6253	78.0	0.99	(0.95-1.03)	
		Q3 education	5604	75.4	0.97	(0.93-1.01)	
		Q4 education	5100	74.6	0.96	(0.92-1.00)	
		Q5 education	3799	69.9	0.93	(0.88-0.97)	

MV: multivariate Model; PR: prescription ; MM/WG: medical house; GMR : Global Medical Record;

N_acetylcysteine							
Category	**Variable**	**Level**	**Total PR**	**% PR on low cost drugs**	**Odds Ratio from MV**	**(95% CI)**	**p-value**
Patients demographics	Gender	Female	28014	44.8	1.00		0.022
		Male	29250	46.2	1.02	(1.00-1.03)	
	Age group	18-44	10279	48.2	1.00		0.01
		45-64	17842	48.0	1.01	(0.99-1.02)	
		65-74	11346	45.2	0.98	(0.95-1.02)	
		75+	17797	41.5	0.96	(0.93-0.99)	
	Patient in a rest or nursing home	no	52610	46.6	1.00		≤0.001
		yes	4654	33.0	0.91	(0.88-0.94)	
Patient Socio-Economic	Entitled to increased reimbursement	no	38667	45.9	1.00		0.011
		yes	18597	44.7	1.02	(1.01-1.04)	
	Work status	Missing	76	38.2	.		
		None (descendents + students)	893	47.0	1.00		0.039
		Pensioners	30877	43.6	1.02	(0.97-1.07)	
		Invalids and handicapped	4837	44.1	1.00	(0.95-1.04)	
		Registered in National Register	1030	48.8	1.04	(0.97-1.11)	
		Unemployed - full time	3197	51.9	1.06	(1.01-1.10)	
		Unemployed - partial time	1007	48.3	1.03	(0.98-1.08)	
		Unemployed - pre-retired	1023	48.3	1.02	(0.96-1.09)	
		Workers in private sector, blue collar	5201	48.7	1.03	(0.99-1.07)	
		Workers in private sector, white collar	4996	47.5	1.01	(0.97-1.05)	
		Workers in public sector	2221	46.6	1.00	(0.96-1.05)	
		Self-employed worker	1906	47.9	1.04	(0.99-1.09)	
Choice by patient	Patient in a MM/WG (lump sum)	no	56516	45.2	1.00		≤0.001
		yes	748	65.9	1.15	(1.09-1.21)	
Choice by patient	Patient has a GMR	no	22398	45.1	1.00		≤0.001
		yes	34866	45.7	1.03	(1.01-1.04)	
Morbidity	Receiving lump sum for chronic illness	no	47768	46.7	1.00		≤0.001
		yes	9496	39.2	0.96	(0.93-0.98)	
GP demographics	Speciality	GP	55664	45.5	1.00		0.029
		SP	1600	43.1	0.96	(0.93-1.00)	
	GP Gender	Info missing	1	0.0	.		
		F	11978	52.5	1.00		≤0.001
		M	45285	43.6	0.93	(0.92-0.95)	
	GP Age Group	Info missing	1	0.0	.		
		≤35	4682	51.4	1.00		≤0.001
		36-45	9161	48.5	1.01	(0.98-1.04)	
		46-55	25724	45.9	1.01	(0.98-1.03)	
		55+	17696	41.8	0.97	(0.95-1.00)	
Small Area info	Groups of SS based on education	info missing	2178	42.1	.		
		Q1 education	13202	42.8	1.00		≤0.001
		Q2 education	13546	44.4	1.02	(1.00-1.04)	
		Q3 education	12542	47.0	1.05	(1.03-1.07)	
		Q4 education	9648	47.1	1.05	(1.03-1.07)	
		Q5 education	6148	48.9	1.07	(1.04-1.10)	

MV: multivariate Model; PR: prescription ; MM/WG: medical house; GMR : Global Medical Record

7 PATIENTS USING THE "LEAST COSTLY" MOLECULE(S) WITHIN A CLASS OF DRUGS

7.1 PERCENTAGE OF PATIENTS

Table 1: Proton pump inhibitors (A02BC) : choice of active ingredient per patient and physician specialty (data from pharmanet sample 2008)

	All		By physician speciality			
			SP		GP	
	N patients	%	N patients	%	N patients	%
ATC Level 5						
A02BC01 omeprazole	47926	67.20	5833	63.46	42093	67.76
A02BC02 pantoprazole	12104	16.97	1915	20.83	10189	16.40
A02BC03 lanzoprazole	3426	4.80	239	2.60	3187	5.13
A02BC04 rabeprazole	1823	2.56	193	2.10	1630	2.62
A02BC05 esomeprazole	6036	8.46	1012	11.01	5024	8.09
All	71315	100.00	9192	100.00	62123	100.00

Table 2: Statins (C10AA): choice of active ingredient per patient and physician specialty (data from pharmanet sample 2008)

	All		By physician speciality			
			SP		GP	
	N patients	%	N patients	%	N patients	%
ATC Level 5						
C10AA01 simvastatin	42037	49.63	3674	48.23	38363	49.77
C10AA03 pravastatin	8486	10.02	691	9.07	7795	10.11
C10AA04 fluvastatin	1322	1.56	87	1.14	1235	1.60
C10AA05 atorvastatin	20423	24.11	2037	26.74	18386	23.85
C10AA07 rosuvastatin	12426	14.67	1128	14.81	11298	14.66
All	84694	100.00	7617	100.00	77077	100.00

Table 3: Agents acting on the renin-angiotensin system (C09): choice of active ingredient per patient and physician specialty (data from pharmanet sample 2008)

	All		By physician speciality			
			SP		GP	
	N patients	%	N patients	%	N patients	%
ATC Level 5						
C09AA01 captopril	1774	2.12	126	1.49	1648	2.19
C09AA02 enalapril	1527	1.83	131	1.55	1396	1.86
C09AA03 lisinopril	14341	17.15	1520	17.93	12821	17.06
C09AA04 perindopril	16707	19.98	2396	28.27	14311	19.04
C09AA05 ramipril	7662	9.16	1016	11.99	6646	8.84
C09AA06 quinapril	1713	2.05	145	1.71	1568	2.09
C09AA07 benazepril	3	0.00	.	.	3	0.00
C09AA08 cilazapril	249	0.30	24	0.28	225	0.30
C09AA09 fosinopril	142	0.17	17	0.20	125	0.17
C09BA02 enalapril and diuretics	587	0.70	35	0.41	552	0.73
C09BA03 lisinopril and diuretics	4496	5.38	400	4.72	4096	5.45
C09BA04 perindopril and diuretics	4256	5.09	391	4.61	3865	5.14
C09BA05 ramipril and diuretics	260	0.31	39	0.46	221	0.29
C09BA06 quinapril and diuretics	485	0.58	38	0.45	447	0.59
C09BA08 cilazapril and diuretics	83	0.10	2	0.02	81	0.11
C09BB05 ramipril and felodipine	693	0.83	33	0.39	660	0.88
C09CA01 losartan	3550	4.24	345	4.07	3205	4.26
C09CA02 eprosartan	1404	1.68	57	0.67	1347	1.79
C09CA03 valsartan	2793	3.34	210	2.48	2583	3.44
C09CA04 irbesartan	3094	3.70	265	3.13	2829	3.76
C09CA06 candesartan	2173	2.60	251	2.96	1922	2.56
C09CA07 telmisartan	1997	2.39	77	0.91	1920	2.55
C09CA08 olmesartan medoxomil	2119	2.53	153	1.81	1966	2.62
C09DA01 losartan and diuretics	2312	2.76	186	2.19	2126	2.83
C09DA02 eprosartan and diuretics	439	0.52	27	0.32	412	0.55
C09DA03 valsartan and diuretics	2194	2.62	147	1.73	2047	2.72
C09DA04 irbesartan and diuretics	2921	3.49	197	2.32	2724	3.62
C09DA06 candesartan and diuretics	1592	1.90	121	1.43	1471	1.96
C09DA07 telmisartan and diuretics	1543	1.84	65	0.77	1478	1.97
C09DA08 olmesartan medoxomil and diuretics	524	0.63	62	0.73	462	0.61
All	83633	100.00	8476	100.00	75157	100.00

Table 4: Dihydropyridine derivatives (C08CA): choice of active ingredient per patient and physician specialty (data from pharmanet sample 2008)

	All		By physician speciality			
			SP		GP	
	N patients	%	N patients	%	N patients	%
ATC Level 5						
C08CA01 amlodipine	23659	61.73	2295	63.17	21364	61.57
C08CA02 felodipine	1280	3.34	135	3.72	1145	3.30
C08CA03 isradipine	430	1.12	31	0.85	399	1.15
C08CA04 nicardipine	90	0.23	7	0.19	83	0.24
C08CA05 nifedipine	3605	9.41	320	8.81	3285	9.47
C08CA07 nisoldipine	897	2.34	93	2.56	804	2.32
C08CA08 nitrendipine	54	0.14	4	0.11	50	0.14
C08CA09 lacidipine	605	1.58	44	1.21	561	1.62
C08CA12 barnidipine	3204	8.36	334	9.19	2870	8.27
C08CA13 lercanidipine	4505	11.75	370	10.18	4135	11.92
All	38329	100.00	3633	100.00	34696	100.00

7.2 REGRESSION RESULTS

PPI						
Variable	**Level**	**N Total patients**	**% patients on the "least costly" molecule**	**Odds Ratio from MV**	**(95% CI)**	**p-value**
Patient gender	Female	41018	73.5	1.00		≤0.001
	Male	30297	70.0	0.85	(0.81-0.89)	
Patient age group	18-44	15155	74.9	1.00		≤0.001
	45-64	27341	69.5	0.78	(0.73-0.83)	
	65-74	13106	70.6	0.82	(0.74-0.92)	
	75+	15713	74.9	0.91	(0.81-1.02)	
Patient in a rest or nursing home	no	68916	71.7	1.00		≤0.001
	yes	2399	80.5	1.30	(1.12-1.51)	
Entitled to increased	no	53398	71.1	1.00		≤0.001
	yes	17917	74.8	1.14	(1.07-1.20)	
Work status	Missing	110	71.8	.		
	None (descendents + students)	801	80.5	1.00		≤0.001
	Pensioners	32308	72.2	0.70	(0.55-0.91)	
	Invalids and handicapped	6021	71.6	0.74	(0.57-0.95)	
	Registered in National Register	1364	78.4	0.97	(0.72-1.31)	
	Unemployed - full time	4852	71.2	0.73	(0.57-0.94)	
	Unemployed - partial time	1646	73.3	0.78	(0.59-1.03)	
	Unemployed - pre-retired	1265	68.9	0.73	(0.54-0.98)	
	Workers private sector, blue collar	7806	71.9	0.76	(0.59-0.97)	
	Workers private sector, white	8088	71.9	0.75	(0.59-0.96)	
	Workers in public sector	3623	67.3	0.66	(0.51-0.85)	
	Self-employed workers	3431	73.9	0.87	(0.67-1.13)	
Patient in a MM/WG (lump	no	69764	71.8	1.00		≤0.001
	yes	1551	83.4	1.99	(1.65-2.39)	
Patient has a GMR	no	30117	71.5	1.00		0.635
	yes	41198	72.3	1.01	(0.96-1.06)	
Receiving lump sum for chronic	no	62808	71.5	1.00		≤0.001
	yes	8507	75.6	1.28	(1.19-1.38)	
Physician speciality	GP	62123	72.9	1.00		≤0.001
	SP	9192	66.1	0.75	(0.71-0.79)	
Physician gender	Missing	2	50.0	.		
	F	16859	69.9	1.00		≤0.001
	M	54454	72.7	1.12	(1.06-1.19)	
Physician age group	Missing	2	50.0	.		
	≤35	7507	69.0	1.00		≤0.001
	36-45	13752	70.0	1.00	(0.92-1.08)	
	46-55	28124	73.4	1.17	(1.08-1.27)	
	55+	21930	72.5	1.11	(1.02-1.20)	
Groups of SS based on education	info missing	2615	73.1	.		
	Q1 education	14327	70.9	1.00		0.01
	Q2 education	16334	72.0	1.04	(0.98-1.12)	
	Q3 education	15222	72.1	1.06	(0.99-1.14)	
	Q4 education	12817	73.1	1.14	(1.06-1.22)	
	Q5 education	10000	71.8	1.09	(1.01-1.17)	

MV: multivariate Model; PR: prescription ; MM/WG: medical house; GMR : Global Medical Record

STATINS						
Variable	**Level**	**N Total patients**	**% patients on the "least costly" molecule**	**Odds Ratio from MV**	**(95% CI)**	**p-value**
Patient gender	Female	41530	61.9	1.00		≤0.001
	Male	43164	57.5	0.88	(0.85-0.91)	
Patient age group	18-44	3192	59.5	1.00		≤0.001
	45-64	33790	57.6	0.89	(0.80-0.99)	
	65-74	24699	59.2	0.96	(0.85-1.09)	
	75+	23013	63.2	1.10	(0.97-1.25)	
Patient in a rest or nursing	no	83372	59.5	1.00		0.035
	yes	1322	68.9	1.20	(1.01-1.42)	
Entitled to increased	no	63704	58.5	1.00		0.01
	yes	20990	63.3	1.07	(1.02-1.12)	
Work status	Missing	48	68.8	.		
	None (descendents + students)	44	52.3	1.00		≤0.001
	Pensioners	53340	60.5	1.24	(0.55-2.84)	
	Invalids and handicapped	5064	61.0	1.36	(0.60-3.10)	
	Registered in National Register	1334	64.8	1.42	(0.61-3.27)	
	Unemployed - full time	3931	62.8	1.47	(0.64-3.36)	
	Unemployed - partial time	955	60.5	1.37	(0.59-3.17)	
	Unemployed - pre-retired	2734	59.1	1.40	(0.61-3.21)	
	Workers private sector, blue collar	5045	59.1	1.36	(0.60-3.10)	
	Workers private sector, white	5262	55.7	1.22	(0.53-2.77)	
	Workers in public sector	3518	56.5	1.27	(0.55-2.89)	
	Self-employed workers	3419	48.2	0.91	(0.40-2.07)	
Patient in a MM/WG (lump	no	83426	59.4	1.00		≤0.001
	yes	1268	76.2	1.95	(1.62-2.34)	
Patient has a GMR	no	29189	58.7	1.00		0.082
	yes	55505	60.1	0.96	(0.92-1.00)	
Receiving lump sum for chronic	no	77975	59.3	1.00		0.016
	yes	6719	63.9	1.09	(1.02-1.18)	
Physician speciality	GP	77077	59.9	1.00		≤0.001
	SP	7617	57.3	0.91	(0.86-0.96)	
Physician gender	Missing	3	66.7	.		
	F	18024	62.0	1.00		0.03
	M	66667	59.0	0.95	(0.90-0.99)	
Physician age group	Missing	3	66.7	.		
	≤35	7830	62.6	1.00		≤0.001
	36-45	13564	59.9	0.91	(0.84-0.98)	
	46-55	34626	60.8	0.95	(0.89-1.03)	
	55+	28671	57.4	0.83	(0.77-0.89)	
Groups of SS based on education	info missing	2689	56.7	.		
	Q1 education	15207	63.3	1.00		≤0.001
	Q2 education	19980	59.6	0.90	(0.85-0.95)	
	Q3 education	18652	59.4	0.89	(0.84-0.95)	
	Q4 education	16011	58.6	0.88	(0.82-0.93)	
	Q5 education	12155	57.7	0.84	(0.79-0.90)	

MV: multivariate Model; PR: prescription ; MM/WG: medical house; GMR : Global Medical Record

ACE + Sartan						
Variable	**Level**	**N Total patients**	**% patients on the "least costly" molecule**	**Odds Ratio from MV**	**(95% CI)**	**p-value**
Patient gender	Female	42212	62.7	1.00		≤0.001
	Male	41421	68.8	1.36	(1.31-1.42)	
Patient age group	18-44	3961	76.0	1.00		≤0.001
	45-64	30259	65.1	0.61	(0.55-0.68)	
	65-74	21620	63.0	0.59	(0.51-0.67)	
	75+	27793	67.1	0.67	(0.59-0.77)	
Patient in a rest or nursing	no	80893	65.3	1.00		≤0.001
	yes	2740	79.6	1.98	(1.73-2.28)	
Entitled to increased	no	60568	64.7	1.00		≤0.001
	yes	23065	68.6	1.12	(1.06-1.17)	
Work status	Missing	53	81.1	.		
	None (descendents + students)	56	94.6	1.00		≤0.001
	Pensioners	53447	64.9	0.16	(0.03-0.84)	
	Invalids and handicapped	4930	71.8	0.20	(0.04-1.02)	
	Registered in National Register	1551	70.0	0.18	(0.03-0.95)	
	Unemployed - full time	3641	68.6	0.18	(0.04-0.96)	
	Unemployed - partial time	988	71.5	0.20	(0.04-1.07)	
	Unemployed - pre-retired	2113	61.7	0.15	(0.03-0.76)	
	Workers private sector, blue collar	5170	68.7	0.18	(0.03-0.92)	
	Workers private sector, white	5423	63.2	0.15	(0.03-0.76)	
	Workers in public sector	3384	65.1	0.16	(0.03-0.84)	
	Self-employed workers	2877	66.0	0.14	(0.03-0.74)	
Patient in a MM/WG (lump	no	81970	65.5	1.00		≤0.001
	yes	1663	77.6	1.72	(1.46-2.03)	
Patient has a GMR	no	30119	69.3	1.00		≤0.001
	yes	53514	63.7	0.79	(0.75-0.82)	
Receiving lump sum for chronic	no	75122	64.8	1.00		≤0.001
	yes	8511	73.6	1.35	(1.25-1.45)	
Physician speciality	GP	75157	64.8	1.00		≤0.001
	SP	8476	74.5	1.52	(1.43-1.60)	
Physician gender	Missing	2	100	.		
	F	18354	67.5	1.00		0.403
	M	65277	65.2	0.98	(0.93-1.03)	
Physician age group	Missing	2	100	.		
	≤35	8449	71.2	1.00		≤0.001
	36-45	13750	64.3	0.74	(0.68-0.80)	
	46-55	34417	65.4	0.81	(0.75-0.88)	
	55+	27015	65.1	0.79	(0.73-0.86)	
Groups of SS based on education	Missing	2592	66.1	.		
	Q1 education	16425	67.8	1.00		0.002
	Q2 education	19151	65.4	0.93	(0.88-0.99)	
	Q3 education	18105	65.0	0.93	(0.88-0.99)	
	Q4 education	15626	65.7	0.94	(0.88-1.00)	
	Q5 education	11734	64.6	0.86	(0.81-0.93)	

MV: multivariate Model; PR: prescription ; MM/WG: medical house; GMR : Global Medical Record

Dihydropyridine derivatives						
Variable	**Level**	**N Total patients**	**% patients on the "least costly" molecule**	**Odds Ratio from MV**	**(95% CI)**	**p-value**
Patient gender	Female	19945	62.4	1.00		≤0.001
	Male	18384	67.9	1.33	(1.25-1.41)	
Patient age group	18-44	1700	66.1	1.00		0.015
	45-64	11856	66.2	1.09	(0.93-1.27)	
	65-74	9767	65.3	1.04	(0.86-1.25)	
	75+	15006	63.9	0.94	(0.78-1.13)	
Patient in a rest or nursing	no	36708	64.7	1.00		≤0.001
	yes	1621	73.1	1.53	(1.30-1.81)	
Entitled to increased	no	26734	64.8	1.00		0.129
	yes	11595	65.6	1.06	(0.98-1.13)	
Work status	Missing	23	82.6	.		
	None (descendents + students)	28	50.0	1.00		0.437
	Pensioners	26037	64.4	1.56	(0.59-4.14)	
	Invalids and handicapped	2174	66.5	1.56	(0.59-4.15)	
	Registered in National Register	884	70.7	1.98	(0.73-5.34)	
	Unemployed - full time	1560	66.5	1.55	(0.58-4.14)	
	Unemployed - partial time	373	65.4	1.46	(0.53-4.01)	
	Unemployed - pre-retired	828	65.5	1.42	(0.53-3.83)	
	Workers private sector, blue collar	1987	67.3	1.65	(0.62-4.36)	
	Workers private sector, white	2040	66.1	1.52	(0.57-4.01)	
	Workers in public sector	1305	64.8	1.37	(0.51-3.65)	
	Self-employed workers	1090	65.9	1.48	(0.55-3.96)	
Patient in a MM/WG (lump	no	37609	64.8	1.00		≤0.001
	yes	720	77.9	1.83	(1.41-2.36)	
Patient has a GMR	no	14090	65.5	1.00		0.679
	yes	24239	64.8	0.99	(0.93-1.05)	
Receiving lump sum for chronic	no	33949	64.5	1.00		≤0.001
	yes	4380	69.8	1.24	(1.12-1.36)	
Physician speciality	GP	34696	64.9	1.00		0.146
	SP	3633	66.9	1.06	(0.98-1.15)	
Physician gender	Missing	2	50.0	.		
	F	8495	67.6	1.00		≤0.001
	M	29832	64.4	0.84	(0.77-0.90)	
Physician age group	Missing	2	50.0	.		
	≤35	3630	66.3	1.00		≤0.001
	36-45	6456	62.6	0.91	(0.81-1.03)	
	46-55	15185	65.7	1.11	(0.99-1.24)	
	55+	13056	65.2	1.12	(1.00-1.26)	
Groups of SS based on education	info missing	1227	67.1	.		
	Q1 education	7853	64.8	1.00		0.002
	Q2 education	8685	64.5	1.00	(0.92-1.10)	
	Q3 education	8218	62.9	0.94	(0.86-1.02)	
	Q4 education	7113	65.8	1.03	(0.94-1.13)	
	Q5 education	5233	68.3	1.15	(1.04-1.28)	

MV: multivariate Model; PR: prescription ; MM/WG: medical house; GMR : Global Medical Record

7.3 RESULTS FROM CONTRAST STATEMENT: UNEMPLOYED VERSUS EMPLOYED

PPI:

Contrast Rows Estimation and Testing Results									
Contrast	Type	Row	Estimate	Standard Error	Alpha	Confidence Limits		Wald Chi-Square	Pr > ChiSq
Unemployed vs emplyed	EXP	1	0.9958	0.0619	0.05	0.8816	1.1248	0.0046	0.9460

Statin:

Contrast Rows Estimation and Testing Results									
Contrast	Type	Row	Estimate	Standard Error	Alpha	Confidence Limits		Wald Chi-Square	Pr > ChiSq
Unemployed vs employed	EXP	1	1.2401	0.0739	0.05	1.1034	1.3939	13.0317	0.0003

ACE/sartan:

Contrast Rows Estimation and Testing Results									
Contrast	Type	Row	Estimate	Standard Error	Alpha	Confidence Limits		Wald Chi-Square	Pr > ChiSq
Unemployed vs employed	EXP	1	1.1322	0.0744	0.05	0.9953	1.2879	3.5648	0.0590

Dihydropyridine derivatives:

Contrast Rows Estimation and Testing Results									
Contrast	Type	Row	Estimate	Standard Error	Alpha	Confidence Limits		Wald Chi-Square	Pr > ChiSq
Unemployed vs emplyed	EXP	1	0.9951	0.1013	0.05	0.8150	1.2149	0.0023	0.9614

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