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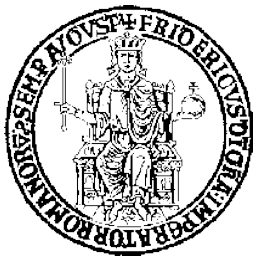

Dottorato di Ricerca in Scienza del Farmaco

XXVII Ciclo

Persistence to therapy and risk of fracture in patients treated with antiostoeporotic drugs: analysis of costs and consequences

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General Introduction

Medication non-adherence is an important public health concern, affecting health outcomes and overall health care costs. It is a widespread phenomenon and can be a barrier to safe and cost-effective use of medicines and services. The World Health Organization (WHO) define adherence as ''…the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes - corresponds with the agreed recommendations from a provider''. The failure to adherence to medication and physician prescriptions could lead to the individual not taking the prescribed drug, taking it at the wrong time or missing doses. Non-adherence can result in costly complications that are often more expensive than the medicines and worsen health outcomes.

The first study on adherence was published in 1968. Later on, several papers have been published on this topic, with the aim to develop measures of adherence, to better understand factors related to poor adherence and to promote interventions to increase adherence. However, every effort to improve adherence was almost ineffective and non-adherence to medicines remains a challenge for health care professional and scientists.

Non-adherence to treatment regimen is a prevalent problem of patients with chronic disorders. Adherence to long-term therapy for certain chronic illnesses in developed countries averages at only 50%. As the burden of chronic diseases continues to grow globally, so does the impact of non-adherence.

The WHO estimates that the cost of non-adherence to drug therapy amounts to 125 million euros per year in Europe including costs from avoidable hospitalizations, nursing home admissions, and premature deaths.

High economic costs of poor adherence to the treatment derive from an increased demand for health care, as the clinical benefits remain unfulfilled. This involves higher hospitalization costs and greater recourse to additional resources of the Health Service. The expenditures' impact is particularly important from a public health perspective, since an optimal allocation of limited available health resources is a key factor to maximize the population health level. Performing cost-effectiveness analysis by using real world data may be widely useful to support decision makers. Moreover, it would also be useful, from a third party payer, to evaluate the cost-effectiveness of increasing adherence.

Adherence is becoming a priority included in the political agenda of health care system and in the European Commission (EC), adherence has been highlighted as a priority. In 2012 was launched from EC the European Innovation Partnership on Active and Healthy Ageing (EIP-AHA) [http://ec.europa.eu/research/innovation-union/index_en.cfm?section=active-healthy-ageing.]. The EIP-AHA A1 Action Group is focused on prescription and adherence. Part of the results of this thesis have been

made available to A1 Action Group as preliminary data that might be useful for the further focused interventions.

Aim of this thesis

This thesis aims to provide more evidence on relation between poor adherence and adverse outcomes and to define reason of poor adherence, by using drug-utilization approaches using different sources of health-related automated databases. The scope of the study is also to evaluate economic impact of enhancing adherence by using *real-life* approach. The case study is population exposure to anti-osteoporotic drugs: with ageing populations, the burden of osteoporotic fractures on society will increase in the coming years and the prevention of osteoporotic fractures is therefore a major public health issue.

Chapter 1
Medication Adherence

1.1 Medication Adherence

During the last few decades, many different definitions of the process underlying the non-observance of physician's recommendations have been employed. Adherence is a relatively recent term which has replaced the notion of compliance. In the past few years, the concept of adherence has gained popularity as it implies a more reciprocal and dynamic interaction between health care providers and patients, and it recognizes the influence of medication-taking behavior [1,2].

Nowadays, the World Health Organization (WHO) definition of adherence has been universally accepted; ''…the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes - corresponds with the agreed recommendations from a provider''. This definition highlights the importance of an active involvement of the patient among with a good communication with the health professionals [3].

The first study on adherence was published in 1968 [4,5]. Later on, several papers have been published on this topic, with the aim to develop measures of adherence, to better understand factors related to poor adherence and to promote interventions to increase adherence. However, every effort to improve adherence was almost ineffective and non-adherence to medicines remains a challenge for health care professional and scientists. In developed countries non-adherence in the treatment of chronic diseases ranges from 30% to 50% and this rate is even higher in developing countries [6,7].

This degree of non-adherence results in a high number of patients that do not get the maximum benefits of medical treatment; as a consequence they experience a poor quality of life, poor health outcomes and health care costs increase [8,9].

Indeed, improvement of adherence may have a stronger effect on health outcomes than the development of new drugs [10]. Non-adherence to medical plans is a public health problem at every level of the population, but especially in older adults. Multiple chronic diseases and polypharmacy, the co-prescription of several drugs, are highly prevalent in older persons [11,12]. There is evidence that non-adherence increase with the number of chronic disease and the number of drugs. Chronic disease management requires a continuous psychological adaptation and behavioral reorganization that may lead to significant changes in respecting therapeutic indications [13].

1.2 Economic impact of non adherence to medication

Medication adherence is a growing concern to healthcare systems as nonadherence to pharmacotherapy has been associated with adverse outcomes and higher costs of care. Adherence to therapy represents a key factors necessary to gain a significant

reduction in morbidity and mortality and to optimize the use of financial resources, but this aspect is widely underestimated in clinical practice and by patients [14-18].
The World Health Organization (WHO) estimates that the cost of nonadherence to drug therapy amounts to 125 million euros per year in Europe including costs from avoidable hospitalizations, nursing home admissions, and premature deaths [3]. High economic costs of poor adherence to the treatment are caused from an increased demand for health care because the clinical benefits are unfulfilled.
This involves higher hospitalization costs and greater recourse to additional resources of the Health Service.
Several studies have suggested that patients with poor adherence to the treatment have higher costs for the health service than patients being more adherent to their treatment regimens. Furthermore, adherence to therapy is especially important for management of chronic diseases. In particular, a study by *Sokol et al.* related to four chronic conditions including diabetes, showed that a high level of adherence to therapy in diabetes is associated with lower costs related to illness and lower costs of hospitalization in patients more adherent to their treatment regimens [19].

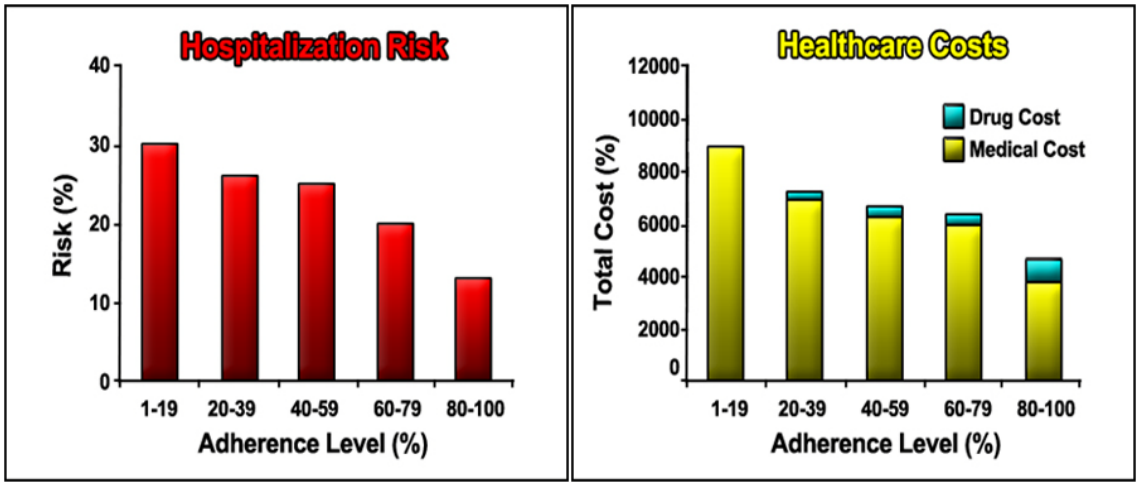

Figure 1 Adherence improbe health and reduces costs

Interesting results are reported in a recent analysis conducted by *IMS Institute for Health Care Informatics*, which estimated the economic impact of the use of inappropriate drugs in 186 countries, including Italy. The study considered six chronic diseases of high social impact such as diabetes, osteoporosis, heart failure, HIV, hyperlipidemia, hypertension, estimating at approximately $ 300 billion cost of using non-optimal drug therapies. It shows that two thirds of these costs are attributable to approximately ten million avoidable hospitalizations, equivalent to about 140 billion dollars. In particular, the issue causing highest cost was nonadherence to therapy, with a value of almost 50% of the total. This cost would amount to about € 105 billion for the 69% and it is attributable to the hospitalizations [20].

Adherence-based savings in medical costs appear to be driven primarily by reductions in hospitalization rates at higher levels of medication adherence. Hospitalization is the largest component of medical costs, so it is likely that the changes in hospitalization risk are the primary driver of the cost savings observed at higher levels of adherence.

1.3 Identifying poor adherence

At present the most common model used to assess the causes of the low adherence is the *Osterberg* model. This model evaluates the negative effects on the patient's ability to follow a medication regimen as a consequence of interactions among the patient, health care provider, and health care system (Fig.2) [14]. In this model, the level of adherence to pharmacological therapies is related to the type of relationship between the health care provider and the patient.

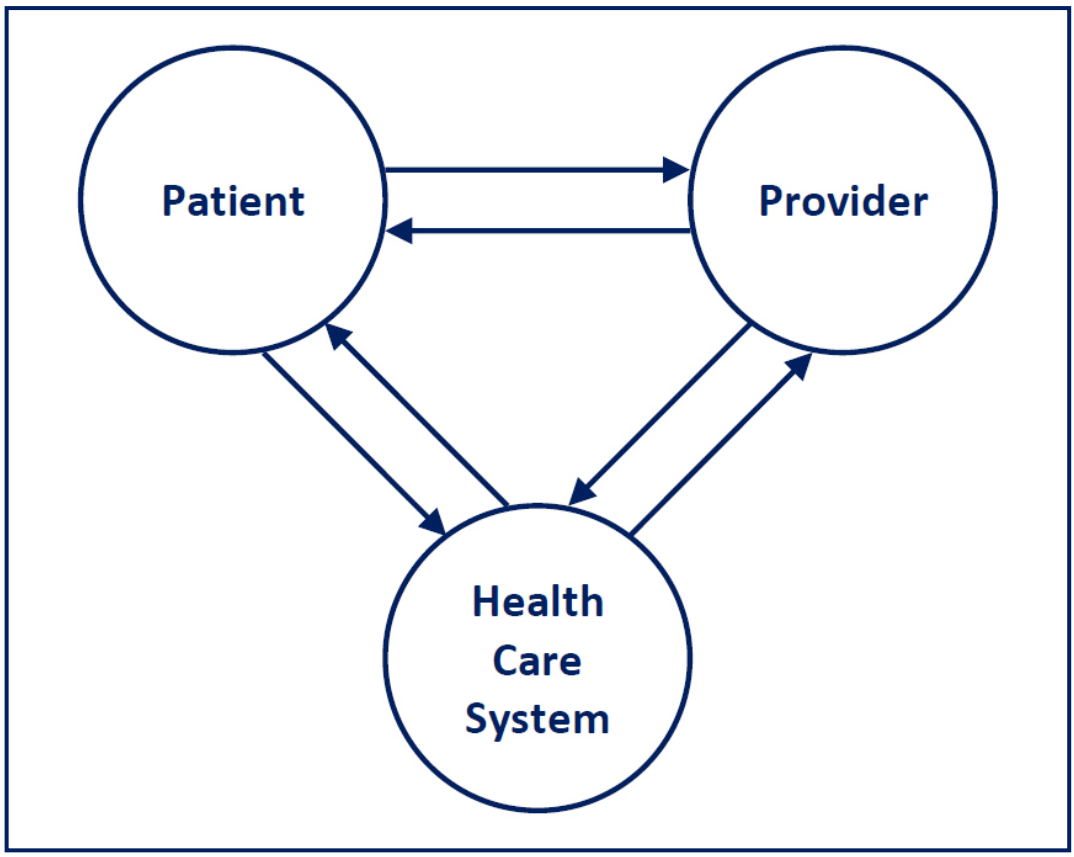

Figure 2: Barriers to adherence:the interactions among the patient, health care provider, and health care system

Variables related to how health care providers interact and communicate with their patients are key determinants of adherence and patient health outcomes [21-25]. The health care providers prescribe the medical regimen, interpret it, monitor clinical outcomes and provide feedback to patients [26]. Patients who view themselves as partners in the treatment process and who are actively engaged in the care process

have better adherence behaviour and health outcomes [27]. Warmth and empathy of the clinician emerge time and again as being central factors [28]. Whereas Physicians contribute to patients' poor adherence by prescribing complex regimens, failing to explain the benefits and side effects of a medication adequately, not giving consideration to the patient's lifestyle or the cost of the medications, and having poor therapeutic relationships with their patients [29-31]. Also, the health care delivery system has great potential to influence the adherence behaviour of patients.

The policies and procedures of the health system itself control access to, and quality of care. System variables include the availability and accessibility of services, support for education of patients, data collection and information management, provision of feedback to patients and health care providers, community supports available to patients, and the training provided to health service providers.
More broadly, health care systems create barriers to adherence by limiting access to health care, using a restricted formulary, switching to a different formulary, and having prohibitively high costs for drugs, copayments, or both [32-34].
To improve the patient's ability to follow a medication regimen, all potential barriers to adherence need to be considered. An expanded view that takes into account factors under the patient's control as well as interactions between the patient and the health care provider and between the patient and the health care system will have the greatest effect on improving medication adherence.

1.4 Determinants of patient adherence

Adherence is not only affected by patient-provider relationship and/or systemic and organizational factors associated with health care system but also the nature of condition, complexity and duration of the treatment regimen, adverse drug reactions [35-37]. According to the WHO these determinants of non-adherence can be aggregated into five dimensions [3]:

- **social and economic,**
- **health system related,**
- **therapy-related,**
- **condition-related**
- **patient related**

In Table 1 lists all the factors relating to each dimensions [38].

Table 1: Factors Reported to Affect Adherence

1.SOCIAL AND ECONOMIC DIMENSION
Limited English language proficiency
Low health literacy
Lack of family or social support network
Unstable living conditions; homelessness
Burdensome schedule
Limited access to health care facilities
Lack of health care insurance
Inability or difficult accessing pharmacy
Medication cost
Cultural and lay beliefs about illness and treatment
Elder abuse
2. HEALTH CARE SYSTEM DIMENSION
Provider-patient relationship
Provider communication skills (contributing to lack of patient knowledge or understanding of the treatment regimen)
Disparity between the health beliefs of the heath care provider and those of the patient
Lack of positive reinforcement from the health care provider
Weak capacity of the system to educate patients and provide follow-up
Lack of knowledge on adherence and of effective interventions for improving it
Patient information materials written at too high literacy level
Restricted formularies; changing medications covered on formularies
High drug costs, copayments, or both
Poor access or missed appointments
Long wait times
Lack of continuity of care
3.CONDITION-RELATED DIMENSION
Chronic conditions
Lack of symptoms
Severity of symptoms
Depression
Psychotic disorders
Mental retardation/developmental disability
4.THERAPY-RELATED DIMENSION
Complexity of medication regimen (number of daily doses; number of concurrent medications)
Treatment requires mastery of certain techniques (injections, inhalers)
Duration of therapy
Frequent changes in medication regimen
Lack of immediate benefit of therapy
Medications with social stigma attached to use
Actual or perceived unpleasant side effects
Treatment interferes with lifestyle or requires significant behavioral changes
5. PATIENT-RELATED DIMENSION
Physical Factors
Visual impairment
Hearing impairment
Cognitive impairment
Impaired mobility or dexterity
Swallowing problems
Psychological/Behavioral Factors
Knowledge about disease
Perceived risk/susceptibility to disease
Understanding reason medication is needed
Expectations or attitudes toward treatment
Perceived benefit of treatment
Confidence in ability to follow treatment regimen
Motivation
Fear of possible adverse effects
Fear of dependence
Feeling stigmatized by the disease
Frustration with health care providers
Psychosocial stress, anxiety, anger
Alcohol or substance abuse

1.5 Adherence to therapy: direct and indirect methods of measurement

The methods available for measuring adherence can be broken down into direct and indirect methods of measurement.

1.5.1 Direct methods

Direct methods of measuring adherence include:

- **Measurement of concentrations of a drug or its metabolite in blood or urine** and detection or measurement in blood of a biologic marker added to the drug formulation are examples of direct methods of measures of adherence. For instance, the serum concentration of antiepileptic drugs such as phenytoin or valproic acid will probably reflect adherence to regimens with these medications, and subtherapeutic levels will probably reflect poor adherence or suboptimal dose strengths.
- **Medication Event Monitoring System (MEMS) and electronic monitoring** which consists of a monitoring system, applied to the packages delivered to the patient. Thus, each time the package is opened and the drug is extracted the system records the time and date. This method can be effective in identifying White Coat compliers or patients who lie in order to make a good impression to the doctor. This method is still considered the golden standard for the verification of the adherence to treatment in clinical trials.

1.5.2 Indirect methods

Indirect methods of measuring adherence include:

- **Self-reports** to assess the knowledge of patient about the medications prescribed and the dosing schedule . This provide information as to whether the patient is adherent with the actual dosing schedule. Subjective assessments by interviewers can bias adherence estimates.
- **Pill counts** to be more precise counting the number of pills remaining in a patient's supply and calculating the number of pills that the patient has taken since filling the prescription is the easiest method for calculating patient medication adherence.
- **Pharmacy records based on pharmacy refills** is one of the more frequently used methods in the literature and allows of obtaining refills and the frequency with which the refills are acquired reflect different aspects of a patient's adherence behavior. This tool allows you to check the number and type of treatments withdrawn from the patient and also any interruptions occurring after the first prescription.

1.5.3 Advantages and disadvantages emerging form literature review

The collaborative group of European Innovation Partnership A1 Action Group on Active and Healthy Ageing has reviewed the international literature on all possible indicators for medication adherence assessment: self-report, therapeutic drug monitoring, pill count, electronic monitoring devices, data reviews, prescription refill records, automated refill reminders, medication event monitoring systems, pharmacy claims data and prescription claims databases, electronic pharmacy databases. In Table 2 are presented the most commonly used tools focusing on their advantages and disadvantages, with information stemming from the literature review [39].

Table 2 Adherence assessment measures in the elderly: advantages and disadvantages emerging form literature review.

Measure	Advantages	Disadvantages
Self-report	Easily understood by patients Uncomplicated to score Cost effective Allows to measure medication and behavioural adherence (no other method allows this) May focus on adherence, persistence, and discontinuation Useful screening tool in order to identify patients potentially at risk of non adherence in the future Allows discussion of reasons for nonadherence in clinical practice The evaluation may be performed also by interviewing the caregiver (proxy) thus obtaining significant and useful information for patient's management Provides user-firendly information useful both for research purpouses and for every day clinical practice	Questions may be standardized, but the test must be psychometrically sound May overestimate or understimate adherence (this can be reduced by performing the assessment as part of the clinical routine) Risk of false positive and lack of sensitivity to change due to memory recall issues (forgetfulness) and social desirability The validity of data collection may be affected by patient's cognitive deficits Enables an overall description of medication non-adherence only, compared to other methods that allows to differentiate between drugs in case of multiple pharmacy use Does not enable to differentiate among different diseases in a population (elderly) mainly characterized by plurimorbidity A self-report generic tool that assesses adherence in the elderly (crosswise diseases) considering both the complex medication regimen and behavioural suggestions is up to now not available in literature.

Measure	Advantages	Disadvantages
Medication Event Monitoring System (MEMS) and electronic monitoring devices	Allows analysis of dose-interval adherence and patterns of adherence over time	Expensive Not feasible for most clinical settings Does not suit all pharmaceutical dosage forms May underestimate adherence Vulnerable to technologic malfunction Potential positive bias by reinforcing medication intake (Hawthorne effect) Patients may alterate data by collecting the drug from the device but not taking it (e.g. by throwing it away). High participant burden (e.g. multiple visits to download data, bulky caps, pillbox use problematic) No certainty that a dose that was removed was actually consumed or administered correctly (adherence taking and timing)
Pill count	Inexpensive An overall or global measure of medication adherence	Time-consuming Inappropriate for most clinical settings Static measure, which does not reflect daily variability May overestimate adherence (if a patient is aware that a pill count is going to be conducted she/he may remove excess doses and discard them) Does not prove that medication has been swallowed Vulnerable to ‘‘pill dumping’’ Difficult to determine refill start date Assumes no medication stockpile or alternative supply No certainty that a dose that was removed was actually consumed or administered correctly (adherence taking and timing) Not suitable for medications taken on an as-needed basis

Measure	Advantages	Disadvantages
Pharmacy records based on pharmacy refills	Data are easily obtained in ‘‘closed pharmacy systems’’ Allows for population-level analyses Immune to social desirability, recall bias, and tampering Drug-drug interactions and drug-drug duplication can be monitored A short time window will accurately include drugs for continuous use	Feasible only in ‘‘closed pharmacy systems’’ Assumes that patients have a single source of medication (does not include free samples from physicians and pharmaceutical companies, or medications obtained through sharing with other family members or friends) and does not assess out of pocket medications Assumes that medication acquisition reflects adherence Studies do not always use standards method for operationalizing adherence (e.g., proprortion of days covered, medication possession ratio, medication gaps) Not useful if refills are mailed automatically or if several months’ supply is dispensed at one time Does not provide information upon timing (patients’ adherence to the prescribed timetable) Inadequate consideration of temporary nursing home care Does not include nonprescription medications lack of consensus terminology and algorithms among measures of the same concepts No certainty that a dispensed dose was actually consumed or administered correctly
Therapeutic drug monitoring	Prove the ingestion of medication Plasma concentration directly determines response May allow for detection or prevention of drug toxicity, which can lead to nonadherence May be advantageous for populations at risk for altered pharmacokinetics (e.g., patients with hepatic dysfunction, patients taking drugs that could interact)	Expensive Invasive Only useful for a limited number of medications Need of a standardized method Levels of clinical indicators may be low for other reasons than nonadherence (e.g., diet, drug interactions) Interpretation of data depends on intra- and inter-individual medication metabolism variations Vulnerable to ‘‘white coat adherence’’ Only provides a snapshot of recent adherence Static measure

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Chapter 2
Automated Databases:
sources of data for Drug Utilization Research

2.1 Automated Databases: definition and description

In drug utilization studies information on prevalence, incidence, indication, duration of treatment and medication taking behavior can be derived from different sources. A considerable amount of data on drug usage is available as part of databases with administrative, commercial or clinical purposes.

During the last decades the use of computerized databases containing medical care data has grown. These databases, called “automated databases”, are currently widely used as data sources for drug utilization studies. Administrative databases cover large sizes of population, and the data is readily available and easy to access.

Requirements of an ideal database are that all parts are easily linked by means of a patient’s unique identifier, that the records are updated on a regular basis, and that the records are verifiable and are reliable.

These source of data have been used in a substantial amount of published research [1-3]. So called automated databases have existed and been used for drug-utilization and outcome research in USA since 1980, and are primarily administrative in origin, generated by the request for payments, or claims, for clinical services and therapies. In contrast, in Europe, medical record databases have been developed for use by researchers, and similar databases have been developed in the US more recently (Figure 1). The sources of drug utilization data vary from country to country depending on the level of sophistication of record keeping, data collection, analysis and reporting and the operational considerations of the health care system. The databases may be international, national or local in scope.

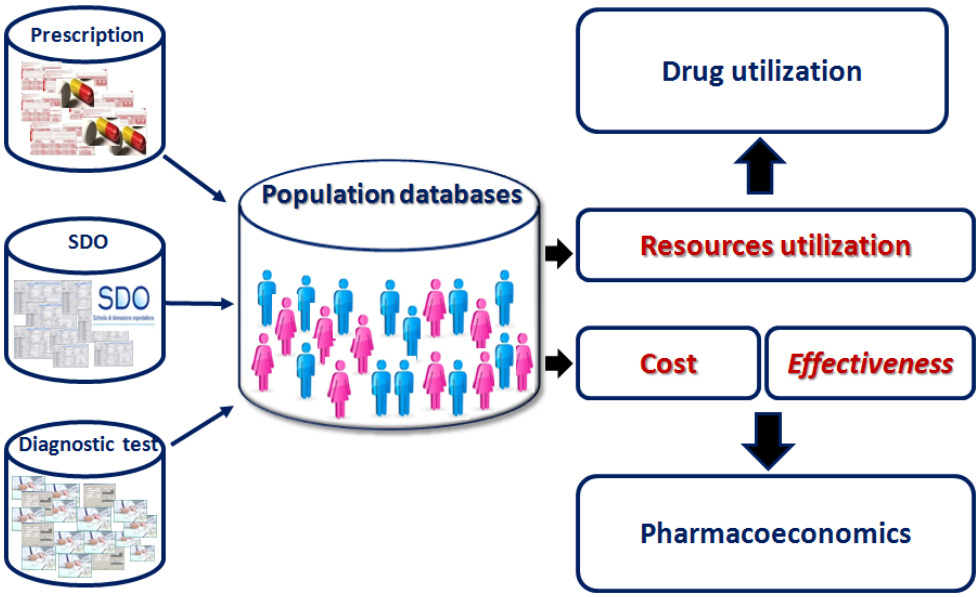

Figure 1: Population Database

2.1.1 Administrative databases

Administrative database arise from a person's use of the health-care system. When a patient goes to a pharmacy and gets a drug dispensed or if a patient goes to a hospital or to a physician for medical care, information about type of service provided and the associated cost are registered for reimbursement by National Health System/insurance. If there is a common patient identification number for both the pharmacy and the hospital discharge, these elements could be linked, and analyzed as a longitudinal medical record (Figure 2).

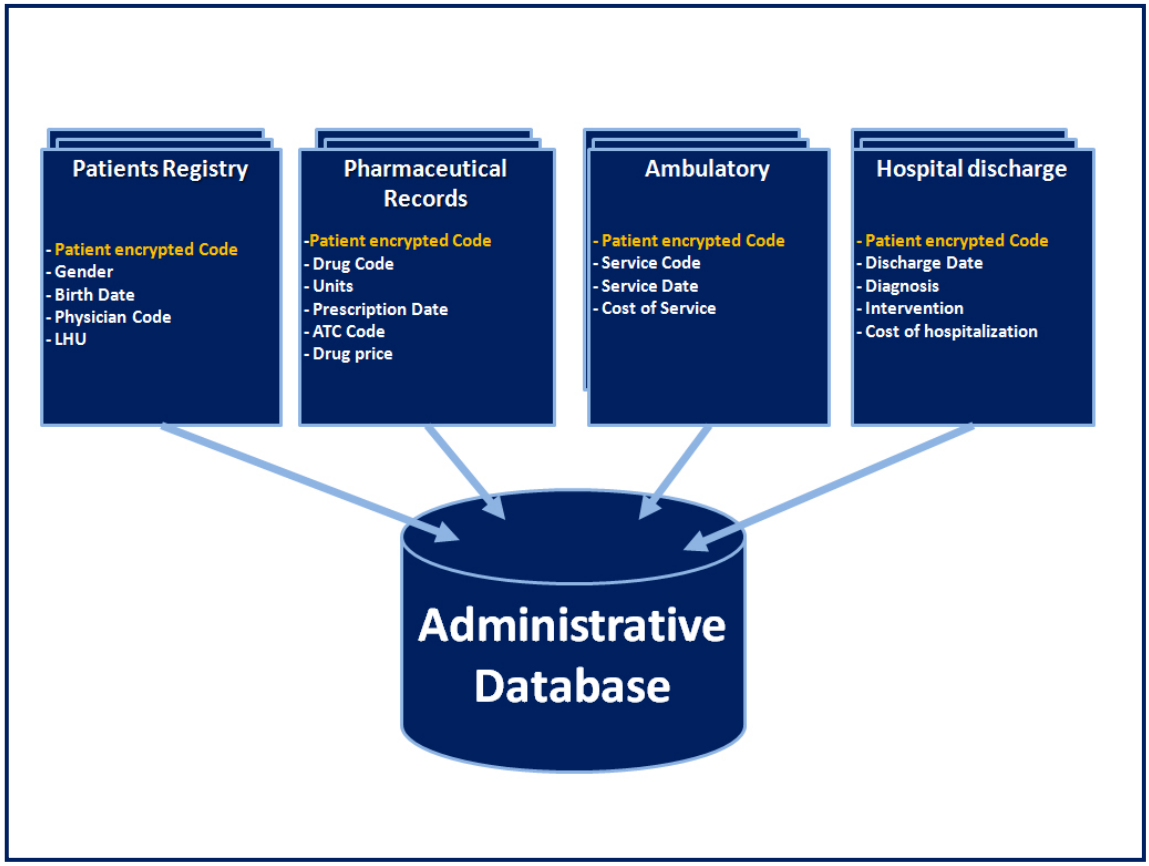

Figure 2: Administrative Database

Since drug identity and the amount of drug dispensed affect reimbursement, and because the filing of an incorrect claim about drugs dispensed is fraud, claims are often closely audited. Indeed, there have also been numerous validity checks on the drug data in claims files that showed that the drug data are of extremely high quality, that is confirming that the patient was dispensed exactly what the claim showed was dispensed, according to the pharmacy record. In fact, claims data of this type provide some of the best data on drug exposure in drug utilization research.

Example of this kind of databases used for research aim are The Odense Pharmacoepidemiologic Database (OPED) in Sweden, the Tayside Medicines

Monitoring Unit (MEMO) in Scotland and the Kaiser Permanente Medical Care Program in California [4].
Italian administrative databases are usually used with a local scope, the Local Health Authorities are the owners of the data. Recently, many research initiatives have been put in place to carry out drug utilization studies on an interregional basis.

2.1.2 Medical record databases

Data from general practitioners (GPs) records of prescriptions can be more informative about the indication for drugs prescribed, diagnoses and other health-related data, although these records are not always consistently completed.
Medical record databases are a more recent development, arising out of the increasing use of computerization in medical care. The best-known and most widely used medical record databases is the UK General Practice Research Database (GPRD) along with the newer database, The Health Improvement Network (THIN) [1]. As general practice databases, these contain primarily outpatient data. In Italy an example is the Health Search database. [5]. Medical record databases have the advantage to have a problem-linked approach. When performing a drug-utilization study using these databases, there is no need to validate the data against the actual medical record, since one is analyzing the data from the actual medical record. However, there are also unique issues one needs to be concerned about, especially the uncertain completeness of the data from other physicians and sites of care. Any given practitioner provides only a piece of the care a patient receives, and inpatient and outpatient care are unlikely to be recorded in a common medical record (Figure 3).

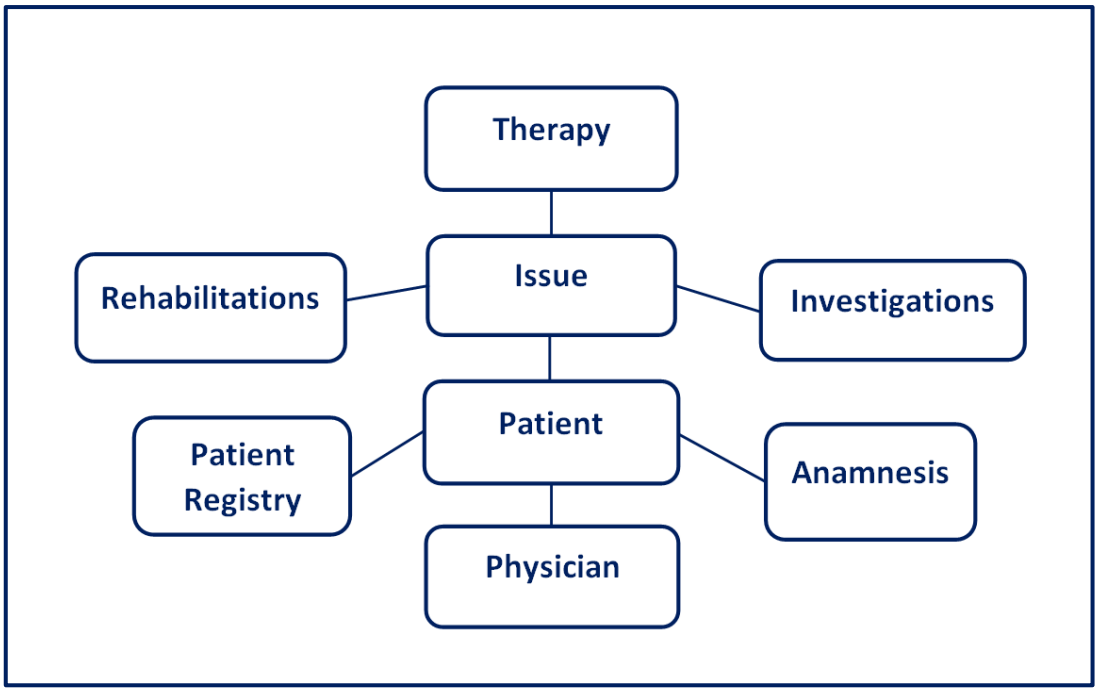

Figure 3: Medical Database: Structure and Functionally

2.1.3 Advantages

Automated databases have several important advantages. First of all their potential for providing a very large sample size. In addition, these databases are relatively inexpensive to use, especially given the available sample size, as they are by-products of existing administrative systems. Studies using these data systems do not need to incur the considerable cost of data collection, other than for those subsets of the populations for whom medical records are abstracted and/or interviews are conducted. In addition, these databases can be population-based, they can include outpatient drugs and diseases, and there is no opportunity for recall and interviewer bias, as they do not rely on patient recall or interviewers to obtain their data. Another advantage is that these databases can potentially be linked to external other electronic databases (e.g., death records, maternal-child records, police accident records), to expand the capabilities and scope of research. This requires using common identification elements (e.g., name and date of birth) and standardized semantics to allow communication across databases.

2.1.4 Limitations

The major weakness of such data systems is the uncertain validity of diagnosis data. This is especially true for administrative databases, and for outpatient data [1]. For these databases, access to medical record data for validation purposes is usually needed. This issue is less problematic for medical record databases. The addition of hospital discharge data to these resources can assist in diagnosis validity, as well [6].
In addition, such databases lack information on clinical data (e.g. blood pressure) and there are no data on smoking, alcohol, date of menopause, etc., all of which can be of great importance to selected research questions (Table.1).

Table 1: Bias and confounding in pharmacoepidemiological studies

Source of bias	Source of bias
Information bias (misclassification)	Distortion of the estimate of the association between a risk factor (e.g. use of a drug) and the occurrence of an event, due to a systematic difference in the way information concerning the measured parameter is collected for the groups being compared. Information bias may be either non-differential or differential. Non-differential misclassification may occur if there is the same probability of being misclassified for all study subjects and may lead to an underestimation of the hypothesized relationship between exposure and outcome. Differential misclassification may occur when the error rate or probability of being misclassified differs across groups of study subjects and may lead to wrong conclusions.
Selection bias	Distortion of the estimate of the association between a risk factor (e.g. use of a drug) and the occurrence of an event, resulting from the measurements made in a simple which is not representative of the population to which the results are to be extrapolated. Some examples include admission bias, diagnostic bias and survival bias.
Confounding	Systematic error resulting from the fact that a secondary variable is linked both to the exposure and the event of interest, which can wholly or partially explain their association found in an epidemiological study.

2.1.5 Specific applications

The principal aim of drug utilization research is to improve the rational use of drugs in real world setting, automated databases are used as data sources in the following research fields:

- Description of drug use patterns (statistics on drugs)
- Medication taking behavior (adherence to therapy)
- Early signals of irrational use of drugs (pharmacovigilance)
- Quality control of drug use (clinical audit)
- Economic aspects of drug use (pharmacoeconomic)
- Drug utilization studies and drug policy decisions.

Given the frequent use of automated databases as data resources for drug utilization research in the recent past, much has already learned about their appropriate role. However, care must be taken to ensure that all potential confounding factors of interest are available in the system or addressed in some other way, that diagnoses under study are chosen carefully, and that medical records can be obtained when needed to validate the diagnoses [1].

2.2 Drug utilization metrics: the ATC/DDD methodology

In 1996, World Health Organization (WHO) developed the ATC/DDD system from a European to an international standard in drug utilization studies. The main purpose of the ATC classification is as a tool for presenting drug utilization statistics and it is recommended by WHO for use in international comparisons.

The Anatomical Therapeutic Chemical (ATC) classification system divides the drugs into different groups according to the organ on which they act and according to their chemical, pharmacological and therapeutic properties. Drugs are classified in 14 main groups at five different levels (Figure 4). The fifth level identifies the chemical substance (Figure 5).

ATC I Level	DESCRIPTION
A	ALIMENTARY TRACT AND METABOLISM
B	BLOOD AND BLOOD FORMING ORGANS
C	CARDIOVASCULAR SYSTEM
D	DERMATOLOGICALS
G	GENITO URINARY SYSTEM AND SEX HORMONES
H	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINES
J	ANTIINFECTIVES FOR SYSTEMIC USE
L	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
M	MUSKOLO-SKELETAL SYSTEM
N	NERVOUS SYSTEM
P	ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS
R	RESPIRATORY SYSTEM
S	SENSORY ORGANS
V	VARIOUS

Figure 4: ATC main groups

ATC Level	DESCRIPTION
M	MUSCULO-SKELETAL SYSTEM (1st level, anatomical main group)
M05	DRUGS FOR TREATMENT OF BONE DISEASE (2nd level, therapeutic subgroup)
M05B	DRUGS AFFESTING BONE STRUCTURE AND MINERALIZATION (3rd level, pharmacological subgroup)
M05BA	BISPHOSPHONATES (4th level, chemical subgroup)
M05BA04	ALENDRONIC ACIS (5th level, chemical substance)

Figure 5: Structure of ATC code

The Defined Daily Dose (DDD) is defined as 'the assumed average maintenance dose per day for a drug used for its main indication in adults'. The DDD is a unit of measurement and does not necessarily correspond to the recommended or prescribed daily dose. The DDD is often a compromise based on a review of the available information about doses used in various countries. Drug utilization figures should ideally be presented as numbers of DDDs per 1000 inhabitants per day or, when drug use by inpatients is considered, as DDDs per 100 bed-days.

Each chemical substance has to be connected to the appropriate ATC code and DDD. The ATC/DDD system is of paramount importance to drug utilization research in order to improve quality of drug use. The DDD is a stable drug utilization metric that enables comparisons of drug consumption between healthcare systems, regions and countries and therefore makes it possible to examine trends in drug use over time and in different contexts. The European WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway, is responsible for coordinating the use of the ATC/DDD methodology (http://www.whocc.no) [7].

2.3 Definition and measurement of exposure and outcome.

Outcomes of interest in drug utilization studies can include diseases or conditions, medical procedures, laboratory tests results, or the use of particular medication, including medication adherence and persistence.

The primary exposure of interest is usually the drug exposure. It must be noted however, that diseases, conditions or procedures may also be exposures of interest. The most frequently used and the most accurate measurement of drug exposure is outpatient prescription/pharmacy records [8,9].

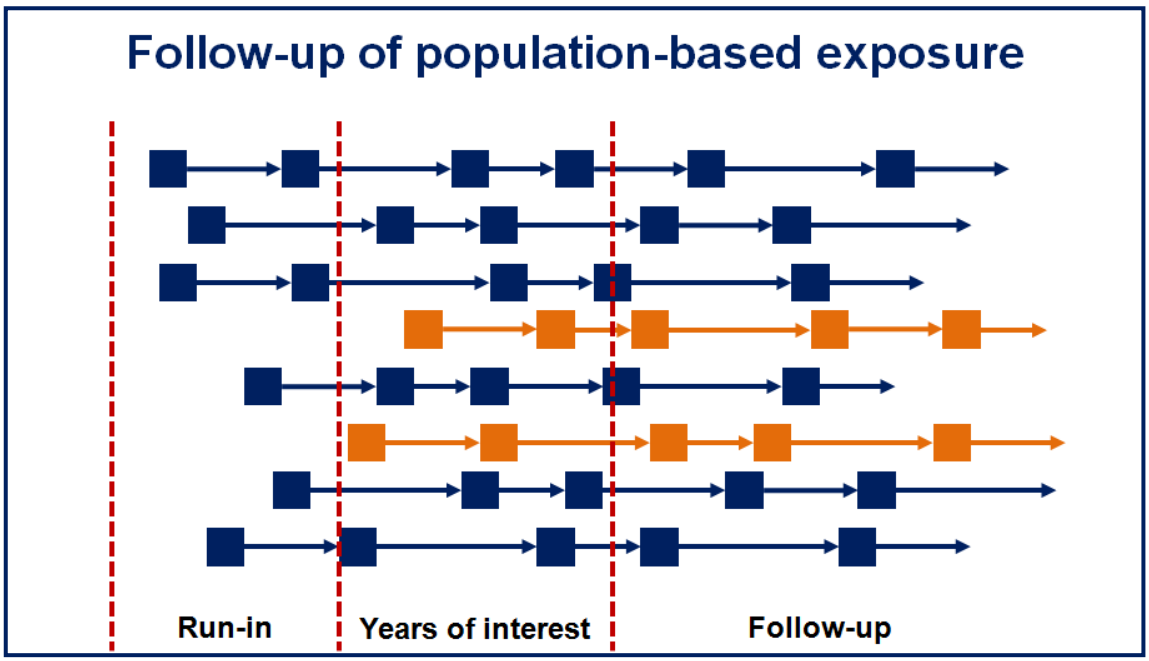

Figure 6: Waiting time distribution

2.4 Pharmacy records as tool to measure medication compliance and persistence.

Pharmacy records or pharmacy claims data offer a useful tool for assessing medication taking behavior and are particularly useful for the evaluation of drugs intended for long term therapy. In recent years, pharmacy claims databases have been used successfully to describe adherence and persistence to medication in various chronic diseases [3,10,11]. Furthermore they have been used to assess the duration and dosage of drug therapy or treatment, treatment switching, clinical and socio-demographic predictors of adherence and persistence to treatment, and the impact of medication taking behavior on clinical outcomes.

Pharmacy refill or pharmacy claims databases contain details on dispensed drugs and therefore set an upper limit for actual drug assumption. The underlying premise of measuring medication taking behavior using pharmacy refill data is that if patients do not receive timely refills from the pharmacy, they are either missing doses or not taking their medication at all. There are many different ways of assessing medication taking behavior using pharmacy records. Medication taking behaviour can be defined in terms of two distinct variables; compliance which is acting in accordance with the prescribed interval and dosage of the treatment and persistence which is continuing the treatment for the prescribed duration of time (Figure7) [10].

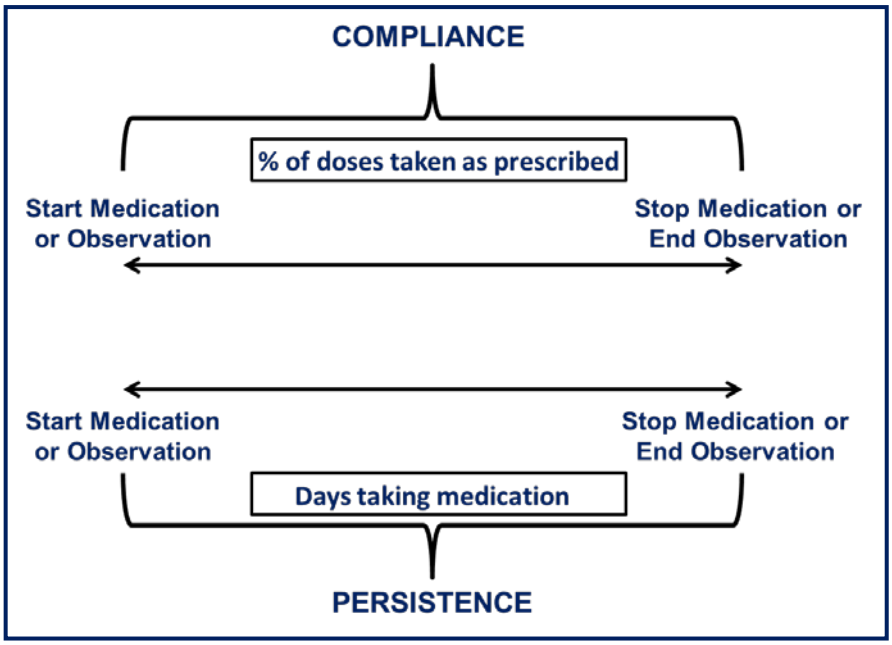

Figure 7: Definitions of compliance and persistence

2.4.1 Medication Compliance

Medication compliance refers to the act of conforming to the recommendations made by the provider with respect to timing, dosage, and frequency of medication taking. Therefore medication compliance may be defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [10].

Compliance can be calculated as both a continuous and dichotomous measure. As a continuous measure, the most common methods, as outlined and proposed by the International Society of Pharmacoeconomics and Putcomes Research (ISPOR) working group, are by way of Medication Possession Ratio (MPR) and Proportion of days covered (PDC) [11,12].

Medication Possession Ratio (MPR) is defined as the ratio of days under medication supplied to days in a time interval:

$$\textbf{MPR} = \frac{\textbf{Number of days of medication supplied within the refill interval}}{\textbf{Number of days in refill interval}}$$

Proportion of Days Covered (PDC) is defined as the number of days covered over a time interval:

$$\textbf{PDC} = \frac{\textbf{Number of days of medication covered}}{\textbf{Number of days in follow up period}}$$

The numerator of the PDC is not merely a sum of the 'days supplied' by all prescriptions filled during the period. Rather, filled prescriptions are evaluated using a set of rules to avoid double-counting covered days. Thus, the PDC is always a value between 0 and 1.

PDC differs from MPR in that it credits the patient with finishing the current fill of medication before starting the next refill. Some believe compliance can be overestimated by simply summing the days supply because patients usually refill their medication before completing the current fill.

The main limit of these methodologies is that multiple periods of non-exposure in the short term can result in the same MPR/PDC as few periods of non-exposure in the long term and duration of treatment needs to be considered [11].

These measures are often dichotomized and patients with a **PDC or MPR≥ 80% are generally classified as adherent to their treatment (< 80% non-adherent).** However unless an appropriate threshold can be justified these measures should be analyzed as continuous variables. [13]

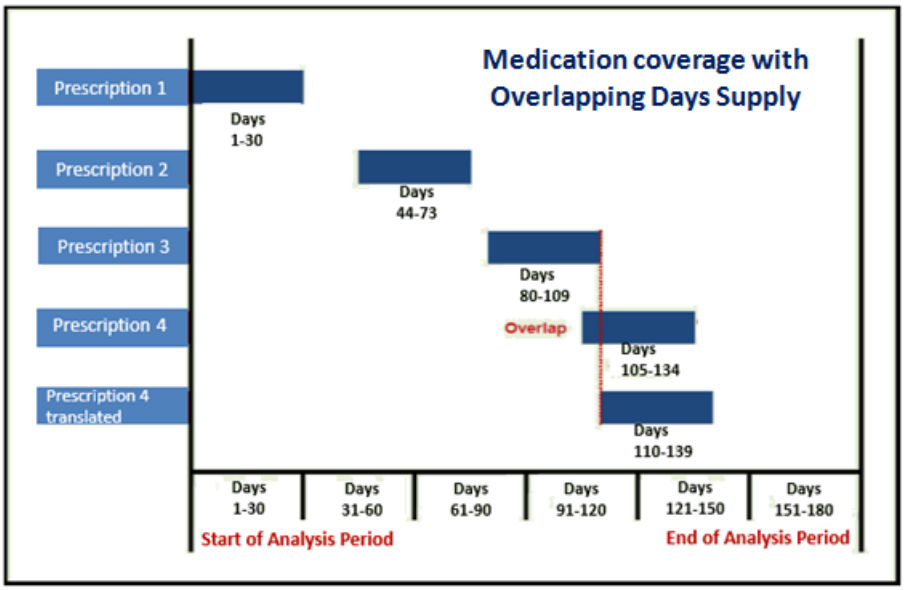

Figure 8: Compliance measure by proportion of days covered

2.4.2 Persistence

Medication persistence may be defined as "the duration of time from initiation to discontinuation of therapy" [10]. This is usually the time, measured in days, from first claim to last claim (plus the days supply of the last claim) considering the days between refills [14]. Continuing to take any amount of the medication is consistent with the definition of persistence. This definition can be operationalized in both prospective and retrospective assessments by determining the initiation of treatment, or a point in time during chronic treatment, to a point in time defined as the end of the observation period. Persistence analyses must include a prespecified limit on the number of days allowed between refills, considered the "permissible gap".

Methods for gap determination should be based on the pharmacologic properties of the drug and the treatment situation (Figure 9). By definition, persistence is reported as a continuos variable in terms of number of days for which therapy was available. Persistence may also be reported as a dichotomous variable measured at the end of a predefined time period, considering patients as being "persistent" or "nonpersistent".

The most relevant issue about this methodology is that periods of non-exposure that are shorter than the gap are not taken in account. This limitation derives from the fact that in pharmacy databases it is very difficult to estimate exactly the effective daily dose taken by the patient. In order to overcome this issue it is necessary to adjust the persistence analysis model to take into account information about the pharmacological characteristics of the drug being studied as well as the specific objectives of the study [10].

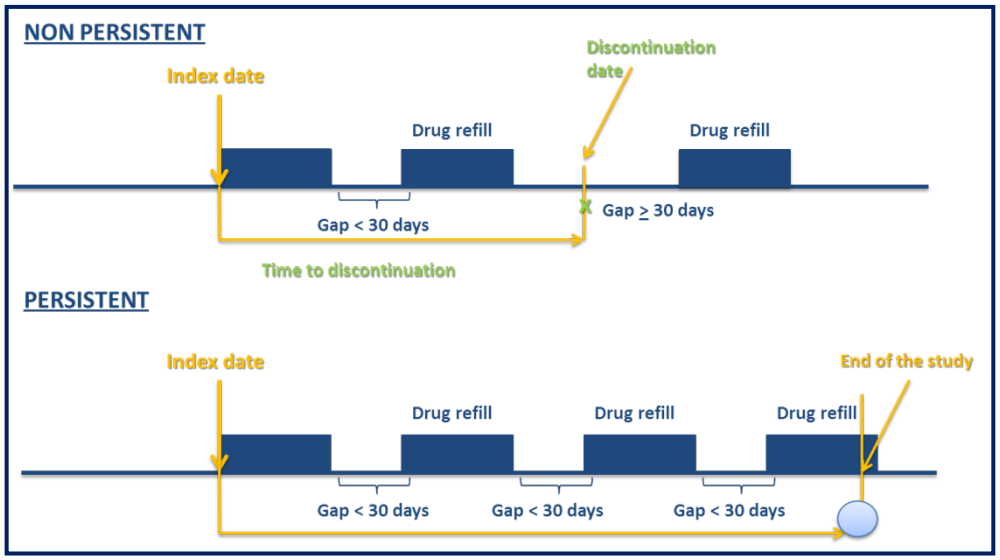

Figure 9: Methods for gap determination

2.4.3 Benefits

The benefits of using pharmacy refill records is that they are potentially immune from social desirability, recall bias and tampering and have ease of reproducibility in other settings. They represent an important tool for the indirect measurement of the levels of adherence and persistence to treatment and are easily accessible, low-cost, constantly updated, and permit a comprehensive evaluation of the entire population. They also provide an effective means of helping physicians to identify both patients with low adherence and persistence and those with a higher probability of becoming poorly adherent or interrupting or stopping therapy [15]. Other indirect measures of medication taking behavior such as patient interviews, pill counts, and clinician assessments are not practical to perform on large populations. [13]

2.4.4 Disadvantage

The major disadvantage of using pharmacy refill records is their inability to determine if the patient actually consumed the dispensed medication. The refill data must also be complete (a closed system) with patients unlikely to obtain medications from other sources not captured by the database. Measures of medication taking behavior are invalid if patients are obtaining medication in alternative ways such as free samples from physicians and pharmaceutical companies, or medications obtained through sharing with other family members [13]. Furthermore pharmacy refill or claims date does not measure out of pocket medications and may not account for treatment gaps due to hospitalization or nursing home stays.

A number of different measures and definitions of adherence and persistence have been reported in studies conducted using pharmacy databases and this makes comparison of results between studies difficult. It is also difficult to measure

medication taking behavior where mail-order is used or several months supply are dispensed at once. Patients may retain large supplies of unused medications in their homes.

Despite their limitations, the use of pharmacy refill records provides an important valid and relatively efficient method of assessing adherence and persistence in large population based research and likely to reflect medication taking behavior in the real world setting.

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Chapter 3
Economic evaluation in health care

3.1 Why is important economic evaluation in health care?

Economic considerations have gained an increasingly prominent role in the planning, management and evaluation of healthcare systems, ranging from the design mechanisms for the reimbursement of healthcare providers and the definition of arrangements aimed at improving the access to care for households, to the definition of essential packages for insurance, as well as the provision of adequate information to inform decisions on whether or not to include new medicines on hospital, state or National formularies [1-3]. Such an increased attention to the issues concerning cost and efficiency is motivated by the pervasive scarcity of resources relative to health needs and demand, driven by factors such as the HIV pandemic, the ageing of populations, the development of innovative but often expensive technologies and also by the heightened knowledge and expectations of healthcare consumers. All these forces, acting both on the demand and supply sides, have given rise to the need for sophisticated methods of quantitative analysis, including modelling of disease history and outcomes, econometric modelling for population-based resource allocation simulations, macro-level modelling of the impact of (ill-) health on wealth (and viceversa), and multi-state decision analytic models that assess the technical efficiency of health interventions [4-6].

3.2 Methods of economic evaluation

The first aim of an economic evaluation is to “identify, measure, value and compare the costs and consequences of alternatives being considered” to inform “value for money” judgments about interventions or programmes. Usually, consequences of an investment in health technologies are measured as health outcomes of the alternatives being compared, although there may be other types of consequences, such as those relating to process, considerations on social consequences of a new treatment, effects of a specific technology on the level of treatment compliance.

The four main types of full economic evaluation all approach costs in the same way, but differ in the way they approach outcomes [7]:

- **Cost-minimization analysis** is used where the consequences of two or more interventions are broadly equivalent, and so the analysis of differences between them is limited to a cost comparison. This approach is only meaningful for protocols with the same effectiveness or side effects, and is hardly applicable to heterogeneous classes of drugs like the osteoporosis drugs.
- **Cost-benefit analysis** measures both costs and benefits in monetary terms. This approach aims to demonstrate that a program will yield a net welfare gain, and ranks interventions according to the net benefit they provide. The practical

difficulties of measurement and valuing health benefits have limited the use of this type analysis in healthcare.

- **Cost-effectiveness analysis (CEA)** compares costs and outcomes espressed in a single dimension, such as a fracture avoided, BMD gained, or life-years gained. In addition, it is not possible to compare the cost-effectiveness across disease areas for example, to campare the cost-effectiveness of a statin in cardiovascular disease with a bisphosphonate in osteoporosis.
- **Cost-utility analysis (CUA)** compares costs and otcomes espressed in Quality Adjusted Life Years (QALYs). As noted above, the QALY integrates the benefits in terms of reduction in mortality and morbidity [ref]. In addition, this approach allows comparison across different health programs and diseases by using a generic unit of measure. For this reason, cost-utility is the most widely applied type of economic assessment.

There are different categories of costs that may or may not be included in an economic evaluation. It is essential to specify and justify the perspective under which the analysis is undertaken. The most common perspectives used are those of healthcare payers and society. The social perspective is the broadest, including direct and indirect medical costs, and is theoretically preferred. However, most local health care agencies recommend the use of a healthcare payer perspective in order to take into accont only those cost items falling on the third party payor's budget.

Cost-effectiveness analysis and cost-utility analysis are much more common than cost-benefit analysis when assessing the value for money of a new technology. Both these analyses are based on the concepts of incremental costs and incremental benefits of the new technology compared to the standard of care or any other alternative treatment. Hence, the output of cost-effectiveness and cost-utility analysis is an estimate of the cost per unit of effectiveness gained and of the cost per QALY gained, respectively. Such a measure, referred to as Incremental Cost-Effectiveness Ratio (ICER), is then compared to a certain acceptability threshold that is an estimate of the cost/effectiveness unity above which the technology under study cannot be funded. Such a measure can be interpreted as a proxy of the efficiency of a specific healthcare system in producing health, since it represents the cost beard to produce an additional unity of health, however that may be measured.
Obviously, in this context a central role is played by the concepts of "opportunity cost" and "incremental change" especially in publicly funded health care systems. As a matter of fact, in such situations limited resources are available to the decision maker who is responsible for allocating them among alternative uses. Choices must be made among effective health care interventions, and the decision to fund one means that others cannot be funded. The opportunity cost of funding the chosen intervention can

be seen as the health benefits that could have been derived from funding the next best alternative [8].

Threshold analysis is possible whenever a certain cost/unity of effectiveness representing the maximum willingness to pay of the system is available. So far, acceptability thresholds have been derived from past decisions of the national health authorities considering the cost/QALY gained of the services and good provided and reimbursed but national health services in several countries. However, the QALY is the only outcome measure for which some estimation of the acceptability threshold exists. Conversely, when the analysis is performed adopting another measure of health benefits, threshold analysis is still possible but the analysts has to hypothesize a threshold value based on other considerations, such as epidemiologic aspects, explicit estimations of the willingness to pay and so on.

Every time an intervention with an ICER equal to the acceptability threshold is included in the agenda of the public decision maker a QALY is forgone in some other clinical area, whereas when a treatment with an ICER lower than the threshold is introduced in clinical practice by a public decision maker, this decision frees up resources for further investments, improving the overall efficiency of the system.

However, often the cost-effectiveness is not the sole criterion for decisions concerning the allocation of healthcare resources. As a matter of fact, consideration on equity and distributive justice as well as the high innovative content of the new technology or the relevant burden of disease can justify the introduction of technologies characterized by high incremental cost effectiveness ratio. As a result, these decisions imply the loss of more than one QALY in other clinical areas and decrease the overall efficiency of the system in producing health.

The possibility of analyzing the decision problem under a wide perspective has certainly been contributing to the widespread use of cost-utility analysis as well as the increasing utilization of QALYs as a measure of health outcomes.

For these reasons, the ICER (Incremental cost effectiveness ratio), is currently the most commonly used cost-effectiveness indicator.

3.2.1 Cost-effectiveness plane

When a cost-effectiveness analysis is performed, treatments under study can be graphically represented on a cost-effectiveness plan where incremental costs are reported on the y-axis and incremental benefits are reported on x-axis. Each treatment is represented by a point on the CE plane whose coordinates are the incremental effectiveness and incremental costs with respect to the comparator, with ICER being represented by the slope of the segment joining that point with the origin of axes. An example is reported in Figure 1.

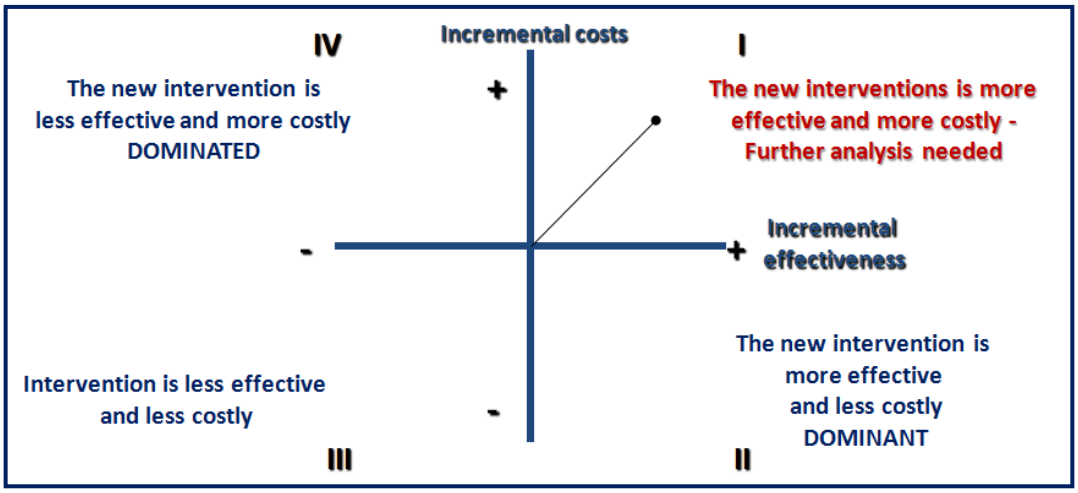

Figure 1. Example of cost-effectiveness plan.

If a treatment falls in the second quadrant it is more effective and less expensive than the comparator. Thus, it is characterized by a negative ICER, being the numerator (i.e. incremental cost) smaller than zero. In this case, if cost-effectiveness was the unique decision criterion, the new treatment should be immediately accepted without any further investigation.

The opposite situation happens when the treatment falls in the fourth quadrant. Once again, the ICER is negative but, in this case, the denominator (i.e. incremental effectiveness) is negative, while the numerator (i.e. incremental cost is still positive). A technology with this features is dominated by the comparator (i.e. the system could save money and improve health by implementing the alternative regimen), and should be immediately rejected.

Positive ICERs occur both in the first and in the third quadrant. In particular, in the third quadrant the new treatment is less effective and less expensive than the comparator (both numerator and denominator of the ratio are negative), whereas in the first quadrant the new treatment is more effective but also more expensive than the alternative regimen (both the numerator and the denominator of the ratio are positive). The treatment falling in the third quadrant should not be taken into account

for equity reasons, while treatments falling in the first quadrant require a threshold analysis in order to appraise the cost-effectiveness.

3.2.2 Limitations

The ICER approach is very intuitive and this simplicity probably justifies its widespread use. However, it exhibits some limitations that deserve mention.
A first problem arises with the interpretation of negative results. Indeed, if a negative cost per QALY is reported, without any specification of how that ratio was obtained (i.e. which incremental values were included in the ratio) it is not possible to understand if the treatment is dominant or dominated. Similar difficulties concern the interpretation of ICERs which have the same scale but fall in opposite quadrants of the cost effectiveness plane. An example is depicted in Figure 2.

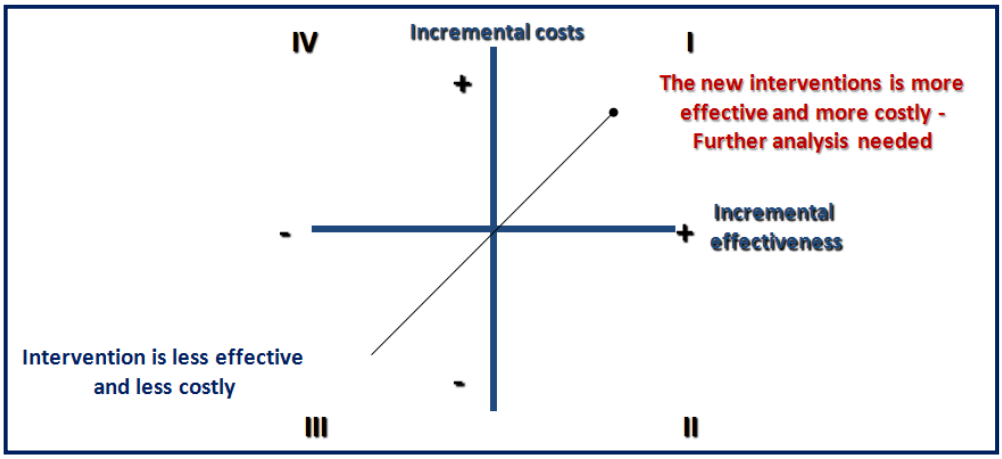

Figure 2. Difficulties in the interpretation of ICERs.

Treatments A and B in Figure 4 both report an ICER of 200£/QALY. However, treatment A produces a gain of 0.5 QALY against an incremental cost of 100£, thus its ICER should be compared to a certain cost-effectiveness acceptability threshold. Conversely, treatment B yields a saving of £100, but implies the loss of 5 QALY. Despite its ICER has same scale of that of treatment A, this treatment should not be considered. Therefore, also positive ICERs, if not correctly specified, can be misleading.

3.2.3 From ICER to Net Benefit

The net benefit approach consists in rearranging the formula of the ICER so that the increment in the effect is multiplied by the threshold:

$$NB = \lambda * \Delta E - \Delta C,$$

where λ is the considered cost-effectiveness threshold. The decision rule within the ICER framework is "if:

$$\Delta C / \Delta E < \lambda,$$

then the new treatment should be accepted". Within the net benefit approach the decision rule becomes: "if:

$$\lambda * \Delta E - \Delta C > 0,$$

then the new treatment should be accepted".

Using the net benefit approach simplifies the interpretation of results: dominated strategies have a negative NB. Dominant strategies have the highest NB. Whenever a strategy has a positive NB it is suitable to be chosen. However, if there are many options the one with the highest NB should be selected [7]. Plotting the net benefit of a strategy against threshold values we can visualize the ICER of the technology which is represented by the point in which the NB line crosses the x-axes

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Chapter 4

Results

4.1 Osteoporosis drugs in real world clinical practice : an analysis of Persistence

Abstract

The aim of our retrospective cohort study is to analyze the persistence rates in relation to antiosteoporotic drugs by using administrative databases in the Campania Region. Patients, aged≥ 40 years, were included if at least one prescription for any antiosteoporotic drugs had been filled in between January 1, 2009 and December 31, 2009. Overall, 37,594 patients were incident users of antiosteoporotic drugs.
Among them, 15,978 patients had undergone spot-therapies. A total of 2,618 (14.1%) were classified as switchers. Switching rates were highest for patients taking Alendronate 18.9 or Strontium Ranelate 15.0 and lower for patients taking Ibandronate 12.8 or Risedronate 10.8. In the overall population 33.5% of subjects were still on therapy after 6 months. At one year, persistence rates were: Ibandronate 21.6%, Risedronate 15.8%, Alendronate + Vitamin D 15.7%, Raloxifene 14.3%, Alendronate 12.6% and Strontium Ranelate 5.0%.

4.1.1 Introduction

Osteoporosis represents a huge threat to global health and national healthcare systems (1). Its treatment involves several therapeutic tools, including drugs (2) and long-term drug therapy is generally considered for chronic disorders such as osteoporosis. Patients with chronic disorders are more likely to be non adherent and/or non-persistent to treatment than those with other diseases. Adherence is currently defined as the extent to which patients take medication as prescribed by their physicians whereas persistence is the time from therapy initiation to discontinuation (3). Numerous studies have shown that inadequate persistence to prescribed therapies induces an increase in both morbidity and mortality. Lack of persistence is common among patients using oral osteoporosis treatments despite the availability of safe and efficacious therapies (4), and causes the mitigation of the therapeutic benefit and increase risk of fracture (5). Only women with higher persistence (>66%) had a larger increase in spine and hip BMD (6). A large survey of Italian osteoporotic women reported that the most common reasons for lack of persistence are: appearance of side effects, costs, inconvenient dosing, advice from other specialists, cultural and economic conditions, lack of motivation. Furthermore, the survey demonstrated that the treatment discontinuation rate varies considerably with the type of treatment (7).
Compared to epidemiological surveys, the use of administrative databases represents a significant step forward, providing a useful tool for indirect measurement of the levels of persistence (8). Administrative databases are also easily accessible and

constantly updated allowing the entire population to be evaluated. In this paper, we propose a retrospective cohort study in order to analyze the persistence to antiosteoporotic drugs in the Campania Region by using such data.

4.1.2 Materials and Methods

Data source

Data were retrieved from an administrative database of pharmacies - derived regional data regarding medication prescriptions in Campania region, Southern Italy, which has a population of about five million inhabitants. For this study, we used data collected in the years 2008-2010. The database contains all the information (i.e. drug code, dose, formulation, number of packages, date of prescription, date of dispensation) concerning outpatient drug prescriptions reimbursed by the National Health Service (NHS) and dispensed in pharmacies in the region. The database also includes demographic information (i.e. age, gender). To protect the patients' privacy, the patient code was encrypted into a unique alpha-numeric code. The reliability of this strategy as a way of producing epidemiological information has been previously documented (9). The drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system.

Study cohort

The study was designed as a retrospective cohort study. A patient selection flowchart is shown in Figure 1. Patients 40 years of age or older were included if at least one prescription for any antiosteoporotic drugs [Alendronate (ATCV:M05BA04); Alendronate + Vitamin D (ATC V M05BB03); Risedronate (ATC V M05BA07); Ibandronate (ATC V M05BA06); Raloxifene (ATC V G03XC01); Strontium Ranelate (ATC V M05BX03)] had been filled in between January 1, 2009 and December 31, 2009. The date of first prescription was considered as the index date.

Five patient categories were excluded: (i) patients who had been prescribed at least one antiosteoporotic drug within 365 days prior the index date (to ensure that the selected patients are incident users) ; (ii) patients who had been prescribed antineoplastic drugs (L01) during follow-up; (iii) patients who had not had reach at least one year of follow-up; (iv) patients who received only one prescription of antiosteoporotic drug during the follow-up; (v) patients who received a co-prescription of two different antiosteoporotic drugs on the index date.

Patients were followed from the index date until the discontinuation of antiosteoporotic therapy or until the end of the observation period (31 December 2010). For each patient, the following characteristics were assessed from the database at baseline: age, gender, co-prescription of calcium/ Vitamin D. Patients were stratified into six cohorts based on the antiosteoporotic drug prescribed (ATC V) on index date. On the basis of the first antiosteoporotic drug prescribed, patients were further classified into: (i) patients continuing the first-line drug for at least 365 days

(continuers); (ii) patients changing from the first-line to another drug (switchers); (iii) patients interrupting the first-line drug during follow up (discontinuers).

Persistence

Persistence was defined as the length of time (in days) from the date of the index prescription to the date of discontinuation therapy. Discontinuation was evaluated by using the gap method. A gap is a period during which no medication is available to the patient. A treatment period was considered discontinued if the gap between two prescriptions exceeded a period covered by drug prescribed > 30 days. Persistence was analyzed according to the type of antiosteoporotic drug. To avoid underestimating true persistence, switching of medications was allowed when establishing persistence status for all treatments combined. Switchers were considered discontinuers at the date of switch when persistence was estimated for the individual treatment types.

Statistical Analysis

Baseline characteristics of the study population were analyzed using descriptive statistics. Persistence estimates were derived using non-parametric survival analysis. Kaplan–Meier survival functions were estimated with treatment discontinuation as failure event. Discontinuation rates were assessed at 180 and 365 days. All analyses were performed using SPSS software version 17.1 for Windows (SPSS Inc, Chicago, IL, USA)

4.1.3 Results

Cohort characteristics

A total of 86,942 patients received a prescription for an antiosteoporotic drug between January 1 2009 to December 31 2009. Distribution of exclusion criteria is shown in Figure 1.

Overall, 37,594 patients were incident users of antiosteoporotic drugs. Among them, 15,978 patients had only one prescription of antiosteoporotic drug (spot therapies) . The final cohort consisted of a total of 18,515 incident users of antiosteoporotic drugs: 1,406 (7.8%) males and 17,109 (92.2%) females. The mean age [SD] of the cohort was 68.9 [10.1] years [(68.7 [10.1] females) (71.1 [10.4] males)].

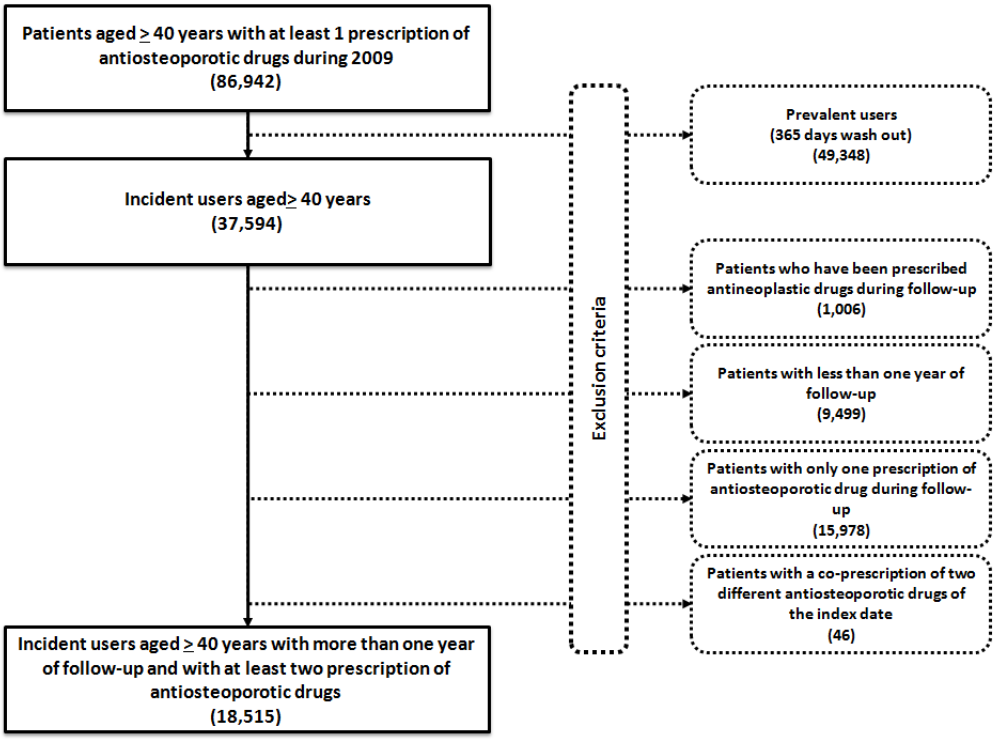

Figure 1: Patient selection flowchart

Baseline characteristics of the study population are shown in Table 1. Alendronate, alone and in association with Vitamin D (36.7%), was the most commonly prescribed drug, followed by Strontium ranelate (30.1%) Risedronate (23.6%), Ibandronate (8.5%) and Raloxifene (0.6%). Co-prescription with calcium and Vitamin D was most common for Risedronate, bimonthly, and Ibandronate (56.4%, 52.5%), respectively. On the other hand, patients starting with Strontium Ranelate were given fewer co-prescriptions of calcium and Vitamin D (40.4%). In the overall study cohort, 2,618(14.1%) were switchers. Switching rates were highest for patients taking Alendronate 437 (18.9) or Strontium Ranelate 838(15.0) and lower for patients taking Ibandronate 202 (12.8) or Risedronate 475(10.8) (Table 1).

Table 1 Baseline characteristics of the study cohort

	Alendronate N(%) 2,317 (12.5)	**Alendronate + Vit D** N(%) 4,501 (24.2)	**Ibandronate** N(%) 1,581 (8.5)	**Raloxifene** N(%) 112 (0.6)	**Strontium Ranelate** N(%) 5,605 (30.1)	**Risedronate** N(%) 4,399 (23.6)	**Total** N(%) 18,515	**P value**
Sex (F)	2,093 (90.3)	4,147 (92,1)	1,491 (94.3)	111 (99.1)	5,253 (93.7)	4,014 (91.2)	17,160 (92.2)	< 0.0001
Age (mean±SD)	68.6 ± 10.2	69.0 ± 10.1	68.6 ± 9.9	63.8 ± 10.5	69.5 ± 10.0	68.4 ± 10.2	68.9 ± 10.1	<0.0001
Switch	437 (18.9)	643 (14.3)	202 (12.8)	23 (20,5)	838 (15.0)	475 (10.8)	2,618 (14.1)	< 0.0001
Co-prescription Calcium and Vitamin D	1,123 (48.5)	853 (18.9)	830 (52.5)	35 (31.3)	2,265 (40.4)	2,479 (56.4)	7,585 (41.0)	< 0.0001

Probability of discontinuation

In the overall cohort study, persistence rates were evaluated at 180 and 365 days after initiation of treatment. In the overall population, 33.5% of subjects were still on therapy after 6 months. At one year, persistent patients were 13.9%. On the other hand, Kaplan-Meier analysis showed the details grouped by individual drugs (Figure 2). At 12 months the number of patients that remained on treatment were: Ibandronate 21.6%, Risedronate 15.8%, Alendronate + Vitamin D 15.7%, Raloxifene 14.3%, Alendronate 12.6% and Strontium Ranelate 5.0%.

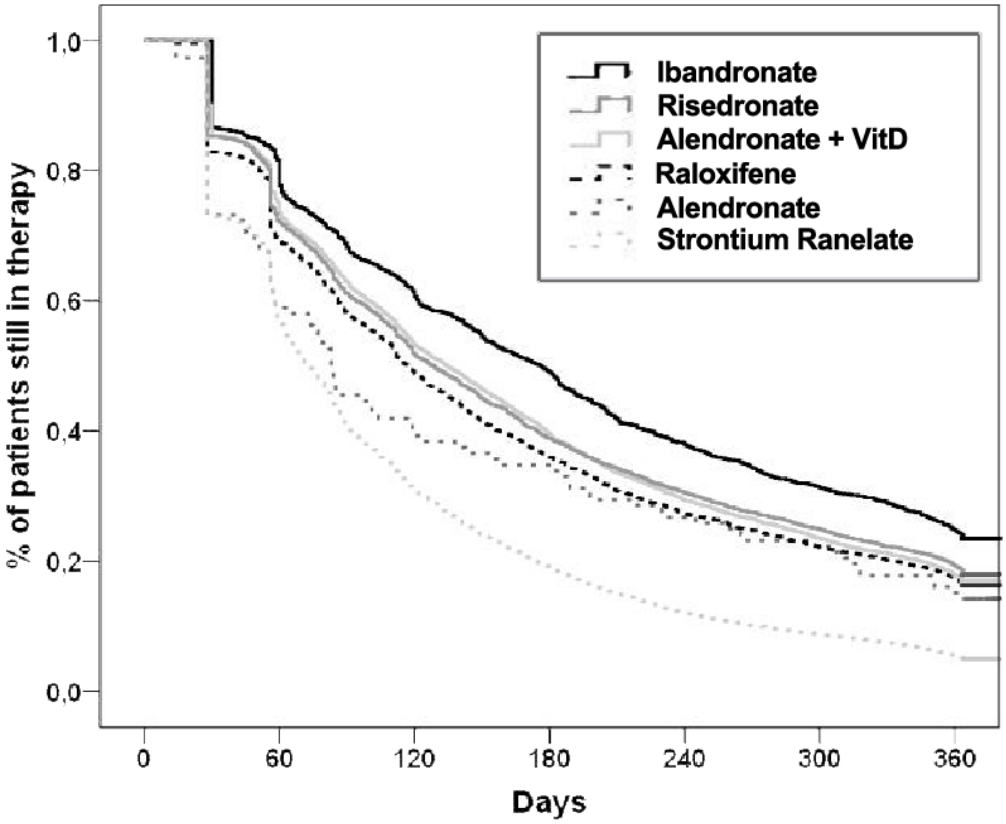

Figure 2: 12 months' persistence (%) of antiosteoporotic drugs

4.1.4 Discussion

Anti-osteoporotic drugs have fully demonstrated their efficacy in several randomized controlled trials. In clinical practice, however, anti-fracture efficacy is significantly reduced by the lack of compliance and persistence in the treatment. Medication compliance (synonym: adherence) refers to the degree or extent of conformity to the recommendations as regards day-to-day treatment by the provider with respect to the timing, dosage, and frequency. Persistence, on the other hand, is defined as the duration of time from initiation to discontinuation of therapy (3). In a large, commercially insured population, suboptimal adherence with bisphosphonate (BP) treatment was associated with increased fracture risk (4). Gallagher et al, in a study based on the data from the General Practice Research Database, showed that although use of bisphosphonates was associated with fracture risk reduction after 12 months of treatment, only 58% of the patients were treated for at least 1 year (10). In a population study Huybrechts et al. confirmed that a large proportion of patients stop treatment before a meaningful threshold (6 - 12 months) and/or have an intermittent pattern of drug use, resulting in low adherence that is associated with a 17% increase in the fracture rate, a 37% increase in the risk of all-cause hospitalization; and higher average monthly costs for all medical services combined (11). In patients with hip fractures too, the twelve-month mean medication possession ratio was 67%, while the rate of persistence was 41% (12). Siris et al. confirmed in a systematic review that low compliance and persistence rates for osteoporosis therapies in the real-life setting result in increased rates of fragility fractures (13). A recent systematic review focused on adherence to bisphosphonates showed a 46% increased fracture risk in non-compliant patients versus compliant patients(5). Our data showed that the persistence to therapy is significantly worse than reported in literature. Indeed we found that 70% of the entire sample had discontinued the treatment six months after initiation of therapy. At one year, only 13.9% of the subjects were still on treatment. The most important determinant of both persistence and compliance to treatment is the type of drug and the dose regimen. Kothawala P. et al conducted a systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis and found that adherence is enhanced with weekly dosing compared with daily dosing (14). An International Osteoporosis Foundation survey found that women considered most of the disadvantages of oral BP therapy to be related to inconvenient dosing regimens and concerns about possible adverse events, in particular those at the gastrointestinal level, which are minimized by complex administration procedures (15). A change in dosing frequency would have a positive effect upon adherence to therapy. In our cohort we found a significant difference in persistence according to whether drugs were drugs administered daily, weekly or monthly. The worst persistence with treatment was found in patients treated with strontium ranelate - 5% in one year. The

best persistence rate found at one year has been found for Ibandronate (21.6%) which has a monthly regimen. This result is considerably lower than that reported in literature and far below the threshold of clinical efficacy of an antiosteoporotic drug. The ability to proactively identify patients who are likely to become non-adherent may offer significant advantages for personalizing prescribing choices and adherence-related interventions. In our study patients changing from the first-line to another drug (switchers) were 14.1%. Switching rates were highest for patients taking Alendronate 18.9 or Strontium Ranelate 15.0 and lower for patients taking Ibandronate 12.8 or Risedronate 10.8. The high frequency of switch therapy in patients treated with ranelate may be due to its daily administration, while the low persistence with alendronate may be due to gastrointestinal side effects. An improvement action of osteoporosis management should include the employment of drugs with less frequent dosing, thus obtaining both an increase in rate of persistence and a reduction in side-effect. Recently, particular interest has been focused on the use of administrative databases as a tool for indirect measurement of the levels of persistence. Baio et al. (8) suggest the use of drug administrative databases to monitor adherence to osteoporosis treatment. They also propose a multifaceted approach, which includes the Triad Model (suggested by the World Health Organization) which involves patients, physicians and healthcare administrations. The integration of these strategies may have a widespread and economically sustainable impact on low adherence, and could improve treatment effectiveness and clinical outcomes in a real-life scenario. The limitations of our study are mainly related to the use of administrative databases as data source. Indeed, although these databases allow the inclusion of a large number of patients in real world conditions, they do not include important clinical findings that could influence persistence.

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4.2 Rates and reasons for lack of persistence with anti-osteoporotic drugs: analysis of the Campania region database

Abstract

Subjects with chronic diseases are more likely to be non-persistent to pharmacological treatment. Lack of persistence is common among subjects using oral anti-osteoporotic drugs, and leads to increased risk of fragility fracture. The aim of our retrospective study is to analyze the rates and reasons for discontinuation of anti-osteoporotic drugs in the Campania Region. Subjects aged over 40 years were included if they had received at least one prescription for any anti-osteoporotic drugs. Data were obtained from an administrative database of regional data on outpatient drug prescriptions reimbursed by the National Health Service. Patients were followed until the discontinuation of anti-osteoporotic therapy or until the end of the observation period. A total of 30,048 were incident users of anti-osteoporotic drugs: 28,317 (94.2%) females. The mean age of the cohort was 69.0±10.0 years. Weekly bisphosphonates (51.1%) were the most commonly prescribed drugs. In the overall population, persistence rates were 34.8% after 6 months and 13.4% at one year. A multivariate Cox proportional hazard analysis showed that daily regimen (HR 1.9) treatments remained at higher risk of early discontinuation compared to weekly regimen therapies. Our data showed that the persistence to osteoporosis therapy is significantly worse than reported in literature.

4.2.1 Introduction

Osteoporosis is a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increased risk of minimal trauma fractures [1]. Fragility fractures are underestimated and this is often due to the underdiagnosis of osteoporosis in patients at higher risk, resulting in the undertreatment of this condition and consequently in an additional risk of fractures [2]. Osteoporosis treatment involves several therapeutic options, including long-term drug therapy [3]. Osteoporotic patients, like those suffering from other chronic disorders, are more likely to be non-adherent and/or non-persistent to pharmacological treatment. In 2008, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Work Group defined compliance or adherence as “the extent to which patients take medication as prescribed by their physicians”, whereas persistence is the time from treatment initiation to discontinuation [4]. It was demonstrated that in osteoporotic patients, only women with higher persistence (>66%) had a larger increase in bone mineral density (BMD) at lumbar spine and hip [5], while low compliance and low persistence rates for anti-osteoporotic drugs lead to increased rates of fragility fractures [6]. A

systematic review showed a 46% increase of fracture risk in noncompliant patients to bisphosphonates treatment [7]. Our previous data showed that persistence to anti-osteoporotic drugs is significantly worse in Southern Italy population than the one reported in world literature, with the 70% of the subjects that discontinued their treatment 6 months after the initiation, and only the 13.9% of them are still on treatment at 1 year [8]. The most common reasons for discontinuation from anti-osteoporotic medication had been identified as side effects, costs, inconvenient dosing, advice from other specialists, socioeconomic conditions, and lack of motivation [9].

The aim of our study is to analyze, in a large population of Campania region, the rates and the risk factors for discontinuation of anti-osteoporotic drugs.

4.2.2 Materials and methods

Data sources and patient selection

Data were retrieved from an administrative database of pharmacies-derived regional data regarding medication prescriptions in Campania region, Southern Italy, which has a population of about six million inhabitants. For this study, we used data collected in the years 2009-2011. The database contains all the information concerning outpatient drug prescriptions reimbursed by the National Health Service (NHS) and dispensed in pharmacies of the entire Campania region.

The database also includes demographic information (i.e. age, gender). To protect the patients' privacy, the patient code was encrypted into a unique alpha-numeric code. The reliability of this strategy as a way of producing epidemiological information has been previously documented [8]. The drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system.

The study was designed as a retrospective cohort study. Subjects 40 years of age or older were included if at least one prescription for any anti-osteoporotic drug had been filled in between July 1, 2009 and June 30, 2010. The date of first prescription was considered as the index date. Criteria for patients' selection have been described in a previous paper [8]. Patients were followed from the index date until the discontinuation of anti-osteoporotic therapy or until the end of the observation period (June 30, 2011). For each patient, the following characteristics were assessed from the database at baseline: age, gender, co-prescription of calcium/vitamin D and switch. Patients were stratified into five cohorts based on dosing regimen treatment at the index date. Persistence was defined as the length of time in days from the date of the index prescription to the date of discontinuation therapy. Discontinuation was evaluated by using the gap method. A gap is a period during which no medication is available to the patient. A treatment period was considered discontinued if the gap between two prescriptions exceeded a period covered by drug prescribed > 30 days. Persistence was analyzed according to the type of dosing regimen. To avoid

underestimating true persistence, switching of medications was allowed when establishing persistence status for all treatments combined.

Statistical Analysis

Baseline characteristics of the study population were analyzed using descriptive statistics. Persistence esteems over time were derived using Kaplan–Meier survival analysis considering treatment discontinuation as failure event and comparing differences using Log-rank test (4 degrees of freedom).

A multivariate Cox proportional hazard analysis was used to identify the association of dosing regimen and other variables with persistence with the initial medication. The patients who initiated with weekly bisphosphonates (BPs) regimen were used as the reference group. Statistical significance was defined at an α level of 0.05 with a hazard ratio higher than 1 indicating a relative increase in the risk of early discontinuation.

All analyses were performed using SPSS software version 17.1 for Windows (SPSS Inc, Chicago, IL, USA

Sensitivity analyses

Sensitivity analyses were carried out for the measurement of persistence by extending the refill gap from the 30 days baseline analysis to 45 and 60 days. Sensitivity analyses were also performed using two alternative definitions of persistence, excluding or including patients who were switchers.

4.2.3 Results

In the study period, in Campania region, subjects with at least one prescription (of any drug) and aged over 40 years in our database were 1,690,192. Among these subjects, 30,048 (1.78%) were incident users of anti-osteoporotic drugs: 1,731 (5.8%) males and 28,317 (94.2%) females. The mean age (SD) of the cohort was 69.0 (10.0) years. Baseline characteristics of the study population are shown in table 1. Weekly BPs (51.1%), were the most commonly prescribed drugs, followed by strontium ranelate (SR) (30.2%), monthly BPs (17.5%), raloxifene (R) (0.7%) and daily BPs (0.4%). Co-prescription with calcium and vitamin D was most common for monthly BPs (61%). On the other hand, patients starting with daily BPs and weekly BPs had fewer co-prescriptions of calcium and vitamin D (35.8% and 39.8% respectively). In the overall study cohort, 1,532 (5.1%) were switchers. Switching rates were higher for patients taking daily BPs (21.6%) and lower for patients taking monthly BPs and weekly BPs (6.8% and 4.2% respectively).

Table 1. Baseline characteristics of the study population (*N*=30,048)

	Daily BP *n (%)*	**Weekly BP** *n (%)*	**Montly BP** *n (%)*	**Raloxifene** *n (%)*	**S. Ranelate** *n (%)*	**Total**
	134 (0.4%)	**15,354 (51.1%)**	**5,273 (17.5%)**	**198 (0.7%)**	**9,089 (30.2%)**	
Sex (female) *n* (%)	117 (87.31%)	14,319 (93.26%)	5,000 (94.82%)	194 (97.98%)	8,687 (95.58%)	28,317 (94.2%)
Age (mean ±SD)	69.73±10.16	69.16±10.01	68.28±10.07	63.58±9.81	69.37±9.89	69.0±10.0
Switcher n (%)	29 (21.64%)	639 (4.16%)	359 (6.81%)	8 (4.04%)	497 (5.47%)	1,532 (5.1%)
Calcium – Vitamin D intake n (%)	48 (35.82%)	6,115 (39.83%)	3,217 (61.01%)	65 (32.83%)	4,264 (46.91%)	13,709 (46.2%)

Table 2 summarizes cohort data at 90, 180, 270 and 365 days after initiation of treatment. In the overall population, 13.4% of subjects were still on therapy after one year. Persistence was higher when the refill gap period was increased: at 45 or 60 days persistence was 19.8% vs. 13.4% (≤30 days) and 23.8% vs. 13.4% (≤30 days), respectively, after 1 year.

Table 2 . Persistence over time with oral osteoporosis treatments (switching allowed).

Time point	**Total cohort (*N* =30,048)**	
	Patients on therapy (%)	95% CI
3 months	59.2	58.6 – 59.8
6 months	34.8	34.2 – 35.4
9 months	22.3	21.9 – 22.7
1 year	13.4	13.0 – 13.8

Table 3 shows that inclusion or exclusion of switchers had minimal influence on the observed persistence; the rates differ by < 3%, independently from any definition of refill gap duration.

Table 3 . Sensitivity analysis on 1 year persistence with regard to prescription gap and treatment switch.

Prescription refill gap	**Total cohort (*N* =30,048)**	
	Switchers* defined as non-persistent, n (%)	Switchers defined as persistent, n (%)
30 days	3,667 (12.2%)	4,025 (13.4%)
45 days	5,396 (18.0%)	5,960 (19.8%)
60 days	6,455 (21.5%)	7,156 (23.8%)

*Switching of oral dosing regimen
Switching of individual drugs within the same regimen (changers) was not considered as non-persistence

Kaplan-Meier analysis showed the details grouped by individual regimen (Figure 1). At 12 months the percentage of patients that remained on treatment was, in decreasing order: 17.2% for monthly BPs; 14.7% for weekly BPs; 8.1% for R; 5.4% for SR; 5.2% for daily BPs .

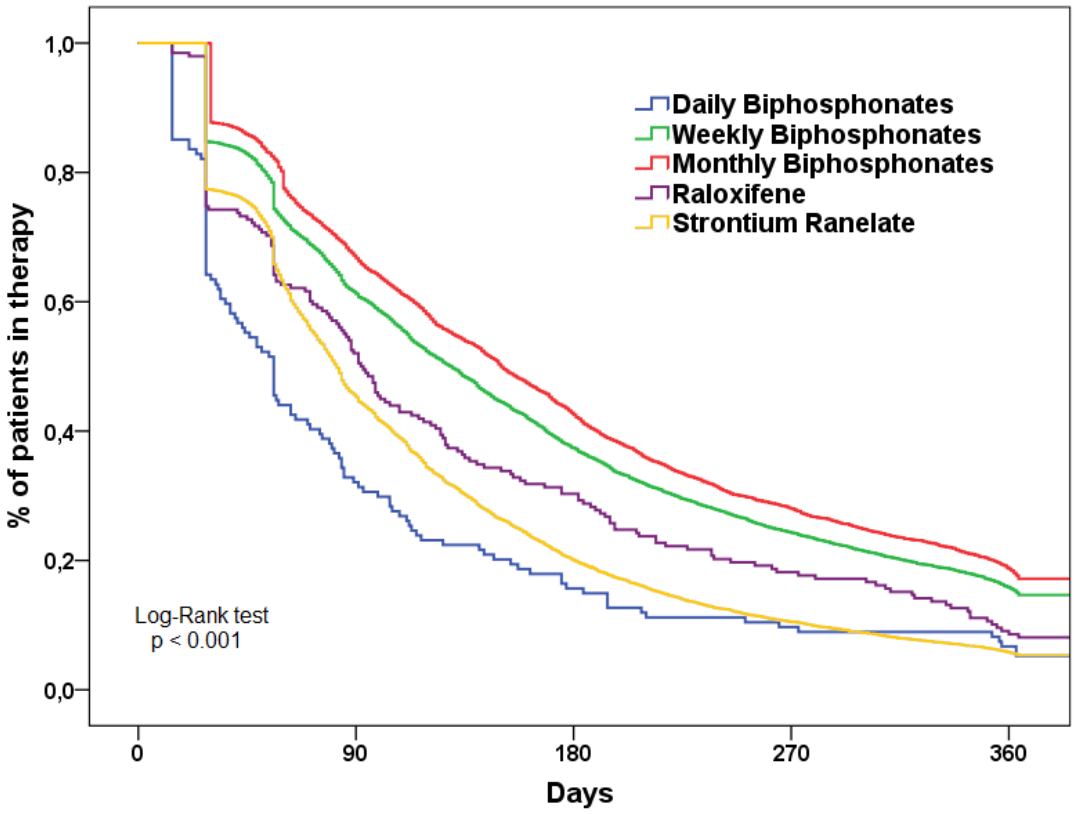

Figure 1. One year persistence (%) with antiosteoporotic drugs.

A multivariate Cox proportional hazard analysis was estimated to identify variables that were significantly associated with non-persistence. The final estimated model is presented in table 4. Patients receiving daily BPs regimen and SR were at a higher risk of early discontinuation (HR 1.98 and 1.6, respectively) compared to patients in treatment with weekly BPs regimen. Moreover, patients treated with monthly BPs regimen had a lower risk of early discontinuation (HR 0.9) compared to patients in treatment with weekly BPs regimen. In our cohort, male gender was associated with a 11% higher risk of discontinuation compared to female gender (HR 0.89). Patients who started treatment with a co-prescription with calcium and vitamin D had a lower risk of early discontinuation (HR 0.72).

Table 4 . Determinants of non-persistence (multivariate Cox hazard model)

Covariates	**HR**	***p* value**	**95% *CI***	
Sex				
Female	0.890	<0.001	0.844	0.937
Dosing regimen				
Daily BPs dosing regimen	1.983	<0.001	1.626	2.420
Montly dosing regimen	0.929	<0.001	0.896	0.963
Strontium Ranelate	1.614	<0.001	1.568	1.660
Raloxifene	1.289	0.001	1.110	1.497
Calcium – Vitamin D intake				
yes	0.717	<0.001	0.699	0.736

4.2.4 Discussion

Campania is a region of Southern Italy which has a total population of 5,834,056 [10], of which 1,690,192 (29%) are those aged over 40 years who are taking at least one drug, according to drug prescription database that includes all outpatient drug prescriptions reimbursed by the National Health Service (NHS), and 1.78% of these are taking an anti-osteoporotic drug. In this cohort of patients, our data showed that the persistence to osteoporosis therapy is significantly worse than that reported in literature [11], but similar to a previous paper that considered a smaller population of the same region (not including population referring to the first Local Health District of Naples ASLNA1) in the year 2009 [8]. Although anti-osteoporotic drugs demonstrated to be effective, in clinical practice, anti-fracture effectiveness is significantly reduced by the high rate of discontinuation [12]. Siris et al. emphasized the importance of good treatment compliance and persistence with osteoporosis therapies in order to achieve a significant therapeutic benefit in terms of reduced rates of fragility fractures [13].

Gallagher et al., analysing the United Kingdom General Practice Research Database, reported that only 41.7% of patients were still on treatment at one year, resulting in a reduction of hip fractures rate (-22%) [14]. In particular, in our cohort, only 34.8% and 13.4% of the patients continued anti-osteoporotic treatment at 6 months and at one year respectively, after initiation of therapy, and this being a demonstration of a doubling of discontinuation rates compared to previous studies [12]. The most important risk factors of the lack of persistence to treatment seem to be the type of drug and the dose regimen. In 2007, a meta-analysis suggested that both compliance and persistence to drug therapy for osteoporosis were enhanced with weekly dosing compared with daily dosing regimen [15]. In our study, we reported a lower persistence rate in subjects treated with daily BPs or SR (5% in 1 year) than in subjects treated with monthly BPs (21.6%), that showed, in our cohort, the best persistence at 1 year. The most common circumstances when patients and/or physicians consider changing medication are side effects and safety concerns, uncomfortable dosing, perception of ineffectiveness, and cost of drugs [9]. In our study, switching rates were higher for patients taking daily BPs or SR and lower for patients taking weekly BPs, highlighting the prominent role of side effects and inconvenient dosing regimens. In our cohort, male gender was associated with a higher risk of discontinuation compared to female gender (HR 0.89), that is much less than that reported in a previous study in Italian hip fracture patients [16]. Although there is little persistence with calcium and vitamin D supplementation alone, when it is combined with other anti-osteoporotic drugs, it positively influences the persistence rate [17]. Our study confirms that patients who received a co-prescription with calcium and vitamin D had a lower risk of early discontinuation (HR 0.72). The limitation of our study is due to the use of administrative database, which does not allow us to analyze potential clinical factors that negatively affect the persistence rates, including side effects, no perceived benefits, misinformation given by the physician, and lack of motivation. Our findings suggest that the prescription of drugs with less frequent dosing regimen represents the keystone of the therapeutic strategy to obtain an optimal persistence to anti-osteoporotic drugs.

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4.3 Assessment and potential determinants of compliance and persistence to anti-osteoporosis therapy in Italy

Abstract

Objectives: To analyze adherence to anti-osteoporosis drugs(AODs) and to assess the influence of patient-related and drug-related factors. **Study Design:** Observational, retrospective study. **Methods:** Data on prescriptions for AODs from 2007 through 2008 were retrieved from the administrative databases of10 Italian local health units. Key measurements included compliance and persistence at 1 year. Multivariate regression analyses were performed to estimate adjusted risk ratios for compliance less than 80% and adjusted hazard ratios for no persistence. **Results**: Of 40,004 new patients (89.9% women, mean age 69.8 years), 84.0% were treated with bisphosphonates and 74.6% of administration regimens were weekly. Overall, 75.1% of patients had suboptimal levels of compliance and 84.7% were not persistent; almost one-third had only 1 prescription. In regression analyses, younger age, change of drug, and concomitant corticosteroid therapy were significantly associated to compliance and persistence in both genders. In women, weekly and monthly regimens reduced the risk for poor compliance (sex-adjusted relative risks 0.729 [0.697-0.762], 0.846 [0.817-0.876], respectively) and no persistence (sex-adjusted hazard ratios 0.591 [0.541-0.646], 0.508 [0.461-0.560], respectively) compared with a daily regimen. **Conclusions:** In our study, 75% of subjects had discontinuous treatment and inadequatedrug supply. Age and frequency of administration were strongly associated with adherence. Improvement is urgently needed, and occasional prescriptions represent the main target.

4.3.1 Introduction

Osteoporosis has become a clinical and public health concern because osteoporotic fractures are one of the most common causes of disability and reduced quality of life, and an important contributor to medical costs in many regions of the world [1]. Several medications are currently available for the prevention and treatment of osteoporosis [2]. However, the effectiveness observed in trials may not be applicable to daily practice, where 50% to 80% of patients discontinue bisphosphonate use in the first year of therapy [3,4]. Moreover, noncompliance with bisphosphonates has also been reported to be a frequent issue, with rates varying from 35% to 65% of medication possession ratio [4].

The full benefits of medications for osteoporosis cannot be reached if compliance is low: poorly compliant patients have a greater risk of fractures than patients who adhere to their prescribed therapy [5], resulting in higher healthcare use and costs [6].

The aim of this study was to investigate compliance and persistence with antiosteoporosis drugs (AODs) in a sample of new users and to assess the influence of potential determinants.

4.3.2 Methods

Data Source

Data used for this retrospective pharmacoepidemiological study were retrieved from the health service databases of the Local Health Units (LHUs) —provincial-level divisions

of the Regional Health Authority—of Bergamo (Lombardy Region, Northern Italy), Avezzano-Sulmona, Chieti, Lanciano-Vasto, Teramo (Abruzzo Region, Southern Italy), Avellino, Benevento, Caserta, Napoli Nord, Salerno (Campania Region, Southern Italy), with a total population of about 5.5 million people, entirely covered by the National Health Service (NHS).

Prescription data contain dispensed drug name (commercial and international common denomination), Anatomical Therapeutic Chemical (ATC) classification category, dose, number of packs, and date of dispensation. We used the demographic database to retrieve demographic information about patient (gender and age).

In compliance with Italian law on privacy, Health Authorities converted patient personal codes to anonymous codes.

Data Selection

AIFA, which is the Italian Medicines Agency and national authority responsible for drug regulation in Italy, has approved 3 bisphosphonates (alendronate, ibandronate, and risedronate) and 4 other drugs (raloxifene, teriparatide, strontium ranelate, and parathyroid hormone) for the treatment of osteoporosis. Oral bisphosphonates are available for daily (alendronate, risedronate), weekly (alendronate, risedronate), or monthly (ibandronate, risedronate) dosing. The Italian government grants reimbursement for AODs in cases of osteoporosis diagnosed by computerized bone mineralometry (T score less than –4, or less than –3 in high-risk patients), previous vertebral fractures, or chronic therapy with corticosteroids in subjects older than age 50 years.

Patients were included in this analysis if they received a prescription of AODs between January 1 and December 31, 2007. A retrospective analysis covering the period from January to December 2006 was performed to identify new users, excluding subjects who had been prescribed any osteoporosis treatment during the 12-month period prior to the index prescription. The first claim for an AOD during the study period was considered the patient's index date. We also obtained information about any prescription of corticosteroidsduring the period of 2006 to 2008 . Each patient was followed up prospectively for 1 year. Subjects were classified into treatment groups based on the study drug first received.

Outcome measures

To evaluate treatment compliance and persistence in our cohort, according to International Society for Pharmacoeconomics and Outcomes Research (ISPOR) definitions [7-9], the length time with drug available for each refilled prescription was calculated using specific Defined Daily Doses (DDDs) [10]. Switching products was not considered an interruption.

Compliance (adherence) was measured as medication possession ratio (MPR), calculated as the total number of days of drug supplied in the observation period divided by the total number of days in the observation period (365), calculated as a percentage. Optimal compliance with therapy was defined by MPR of at least 80%.

Persistence was quantified by the number of days covered by drug from initiation to discontinuation of therapy . Discontinuation occurred when the period between the end of the coverage of a prescription and the date of the refill was longer than the permissible gap of 30 days [11, 12]. Patients with at least 1 discontinuation episode were considered nonpersistent, even if they subsequently restarted treatment. A sensitivity analysis was performed in order to determine the influence of the duration of the permissible gap on the results.

Statistical analysis

MPR was described by mean values and by distribution of patients across MPR classes. Persistence rates were evaluated using Kaplan–Meier survival analysis. Heterogeneity tests across groups were undertaken using the unpaired student's *t* test or a 1-way analysis of variance (ANOVA) for continuous variables, and χ^2 test for categorical measures, as appropriate. The impact of some sociodemographic and clinical variables on MPR was estimated using multivariate. Poisson regression analysis (dependent variable: MPR <80%). As persistence can change over time, we use a Cox proportional hazards model (dependent variable: nonpersistence). Both regression analyses were adjusted for LHUs. All analyses were performed using SPSS 19.0 (SPSS Inc, an IBM Company , Chicago, Illinois).

4.3.3 Results

We identified 40,004 new users of AODs in 2007: 35,956 women (89.9%, mean age [standard deviation] 69.8 years [11.2]), 4048 men (mean age [SD] 69.6 years [13.9]). Of those, 1792 subjects were 50 years or older and on chronic corticosteroid therapy: 1403 women (3.9%) and 389 men (9.6%). Characteristics of prescriptions are reported in Table 1. Alendronic acid was the most commonly prescribed drug (with or without colecalciferol, 45.8% women and 53.2% men), followed by risedronic acid and strontium ranelate. Antiosteoporosis therapy was mainly administered weekly (97.2% of all prescriptions of only alendronic acid and 96.6% of all prescriptions of risedronic acid). Generics were used by 6.1% of both women and men. The switch to another drug was more frequent than the change of administration regimen (10.0% vs 6.3%).

Table 1. Patients With Prescriptions of Antiosteoporosis Therapy: Characteristics of Prescriptions

	Women	Men	Total
Antiosteoporosis Drugs, n (%)			
Alendronic acid	10,728 (29.8)	1486 (36.7)	12,214 (30.5)
Alendronic acid + cholecalciferol	5754 (16.0)	667 (16.5)	6421 (16.1)
Risedronic acid	11,054 (30.7)	1209 (29.9)	12,263 (30.7)
Ibandronic acid	2511 (7.0)	193 (4.8)	2704 (6.8)
Strontium ranelate	5281 (14.7)	442 (10.9)	5723 (14.3)
Raloxifene	492 (1.4)	37 (0.9)	529 (1.3)
Teriparatide	122 (0.3)	14 (0.3)	136 (0.3)
Parathyroid hormone	14 (0.0)	0 (0.0)	14 (0.0)
Generics	2183 (6.1)	247 (6.1)	2430 (6.1)
Daily administration	6499 (18.1)	835 (20.6)	7334 (18.3)
Weekly administration	26,946 (74.9)	3020 (74.6)	29,966 (74.9)
Monthly administration	2511 (7.0)	193 (4.8)	2704 (6.8)
Changes			
Change of drug	3726 (10.4)	288 (7.1)	4014 (10.0)
Change of frequency of administration	2290 (6.4)	222 (5.5)	2512 (6.3)

Compliance is reported in Table 2. Although suboptimal in 75.1% of our total sample, compliance was better for women.

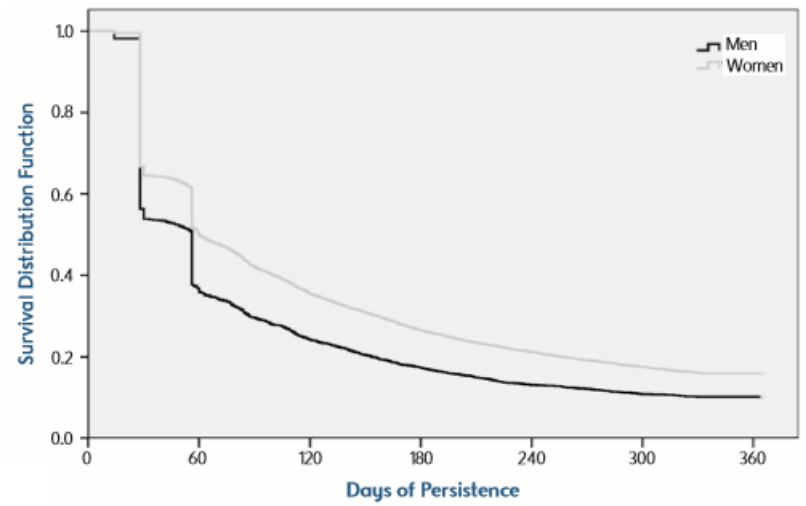
Table 2. Compliance With Antiosteoporosis Therapy

	Women	Men	Total
Compliance			
MPR, mean ± SD	47.84 ± 36.61	34.79 ± 34.15	46.52 ± 36.58
MPR classes, n (%)			
<50%	20,261 (56.3)	2943 (72.7)	23,204 (58.0)
50-80%	6410 (17.8)	447 (11.0)	6857 (17.1)
≥80%	9285 (25.8)	658 (16.3)	9943 (24.9)

MPR indicates medication possession ratio; SD, standard deviation.

More than 70% of subjects had already interrupted their treatment after 6 months (Figure).

Figure. Kaplan-Meier Curve Proportion of Patients Who Interrupted the Antiosteoporosis Therapy



At 1 year, persistent women and men were 15.9% and 10.1%, respectively. In these groups, mean compliance was about 100%. Of the nonpersistent population, females (87.7%) and males (92.8%) had suboptimal compliance; about one-third of nonpersistent women and half of nonpersistent men had only 1 prescription in the study period (Table 3). Excluding these subjects, mean MPR levels were 64.3% in women and 58.1% in men. On the other hand, 46.2% and 29.2% of nonpersistent women and men, respectively, showed at least 1 prescription after the interruption (Table 3). The sensitivity analysis with a permissible gap of 60 days showed a persistence rate of 40.5%.

Table 3. Persistence to Antiosteoporosis Therapy

	Women	Men	Total
Persistence			
Persistent patients, n (%)	5711 (15.9)	408 (10.1)	6119 (15.3)
Patients with MPR ≥80%, n (%)	5578 (97.7)	396 (97.1)	5974 (97.6)
Nonpersistence			
Nonpersistent patients, n (%)	30,245 (84.1)	3640 (89.9)	33,885 (84.7)
Days of persistence, mean ± SD	83.63 ± 74.35	67.44 ± 63.21	81.89 ± 73.40
MPR, mean ± SD	37.68 ± 30.27	27.28 ± 26.87	36.56 ± 30.10
MPR classes, n (%)			
<50%	20,261 (67.0)	2943 (80.9)	23,204 (68.5)
50-80%	6277 (20.8)	435 (12.0)	6712 (19.8)
≥80%	3707 (12.3)	262 (7.2)	3969 (11.7)
Patients with 1 prescription, n (%)	10,738 (35.5)	1934 (53.1)	12,672 (37.4)
Patients who restarted therapy, n (%)	13,988 (46.2)	1063 (29.2)	15,051 (44.4)

MPR indicates medication possession ratio; SD, standard deviation.

Table 4 reports adjusted risk ratios for suboptimal compliance and shows that female subjects younger than 50 years and those 75 years or older were at higher risk of suboptimal compliance, while weekly or monthly administrations (women only), change of drug or of frequency of administration, and concomitant use of

corticosteroids were associated with a lower risk of noncompliance. Similar patterns can be seen in the adjusted hazard ratios for nonpersistence (Table 4).

Table 4. Adjusted Risk Ratios for Compliance <80% and Adjusted Hazard Ratios for Nonpersistence

	Compliance <80%				Nonpersistence			
	Women		Men		Women		Men	
	aRR	CI	aRR	CI	aHR	CI	aHR	CI
Age <50 years[a]	1.127	(1.099-1.157)	1.044	(1.005-1.085)	1.312	(1.234-1.394)	1.252	(1.109-1.415)
Age ≥75 years[a]	1.053	(1.040-1.066)	1.008	(0.981-1.037)	1.125	(1.099-1.152)	0.996	(0.929-1.067)
Use of any bisphosphonate[b]	0.998	(0.964-1.034)	1.187	(1.103-1.278)	1.234	(1.134-1.362)	0.790	(0.667-0.936)
Use of generics	0.992	(0.963-1.021)	0.926	(0.861-0.996)	0.965	(0.918-1.014)	0.917	(0.795-1.058)
Weekly administration[c]	0.729	(0.697-0.762)	1.047	(0.955-1.149)	0.591	(0.541-0.646)	0.905	(0.780-1.049)
Monthly administration[c]	0.846	(0.817-0.876)	1.066	(0.992-1.145)	0.508	(0.461-0.560)	0.900	(0.732-1.107)
Change of drug	0.900	(0.871-0.930)	0.900	(0.819-0.989)	0.902	(0.875-0.949)	0.845	(0.715-0.999)
Change of frequency of administration	1.003	(0.963-1.044)	0.888	(0.791-0.996)	0.959	(0.900-1.023)	0.750	(0.616-0.914)
Use of corticosteroids	0.900	(0.866-0.936)	0.870	(0.816-0.928)	0.841	(0.791-0.893)	0.713	(0.634-0.802)

Both regression analyses were adjusted for LHU (Local Health Unit)
aHR indicates adjusted hazard ratio; aRR, adjusted risk ratio; CI, confidence interval.
[a]Age 50-74 years as reference.
[b]Versus other anti-osteoporosis drugs.
[c]Daily administration as reference.

4.3.4 Discussion

Osteoporotic fractures represent one of the most common causes of disability and are associated with enormous healthcare expenditure. Although several specific therapies are available, accumulating evidence suggests that these agents are underused in clinical practice [13]. Moreover, even in subjects undergoing therapy, the management of osteoporosis is difficult because of poor compliance [5].

Several studies showed that a significant proportion of female patients stopped their treatment within 6 months of initiation and more than half did so within 1 year [4, 14]. In addition, observational studies, although showing wide variations, reported high rates of suboptimal adherence [15, 18]. McCombs and colleagues reported a mean MPR of 68%, 1-year persistence rates of 24.2%, and mean lengths of persistence of 170 days for bisphosphonates[19]. Downey and colleagues observed a 12-month prevalence of optimally compliant patients (MPR ≥80%) of less than 60%, with persistence rates of 20% [15].

Results of previous studies are not always directly comparable to ours due to a number of methodological differences such as the population selected, the definition of compliance and persistence, the duration of follow-up, analytical techniques used, and differences in settings (populations, practices, and healthcare systems)[20].

Nonetheless, our findings are consistent with data from other studies, highlighting the widespread problem of poor adherence to antiosteoporosis therapy. In our study mean MPR was less than 50%; the optimal compliance rate was 25%; and proportion of persistent subjects was about 15%. These values are mainly the consequence of the high percentage of subjects with only the first prescriptions (almost 1 out of 3 patients with only 1 prescription in the observed year), a finding particularly relevant in the

male cohort (48%) and in younger subjects (53% among subjects <50 years).Evaluation of the adherence in patients with at least 2 prescriptions showed significantly higher values (mean MPR was 64.3% in women and 58.1% in men).

As AODs are characterized by side effects (gastrointestinal, musculoskeletal, neurological) and transient symptoms that adversely affect the quality of life of the patient, the properties of these drugs may be responsible, at least in part, for the observed large proportion of users with only 1 prescription[21].

The simple distinction between compliant subjects and those exhibiting suboptimal compliance, as well as that between persistent and nonpersistent subjects, provides only a rough description of patient attitude toward drug use, and is strongly influenced by the choice of analysis parameters (an analysis performed with a permissible gap of 60 days showed a persistence rate of 40.5%). In fact, among nonpersistent subjects, 12% had the medication available for more than 80% of the time, thus becoming part of the compliant group despite the presence of occasional therapeutic gaps. Therefore, the proportion of subjects with a discontinuous treatment and insufficient drug supply during 1 year decreased to 75% of the total cohort. These are the patients who may derive a lower-than-expected benefit from therapy.

Indeed, it should be noted that non-persistence, as defined in this and other studies, is not necessarily equivalent to permanent treatment discontinuation, as patients may lapse and then resume treatment after a 'drug holiday' of variable duration. Actually, most publications that have examined persistence to osteoporosis pharmacotherapy have considered only the initial treatment episode. However, an underreported finding is that many patients who discontinue pharmacotherapy return to treatment after a variable gap, a percentage ranging between 30% and 50% of nonpersistent subjects [22, 23].

In our study , 46% of nonpersistent women and 29% of nonpersistent men showed at least 1 prescription after the first gap. It is possible that these drug-free intervals could have been avoided through closer monitoring of these subjects by their physician.

Previous studies were all conducted using female cohorts, and thus compliance and persistence data in men are scant. In a retrospective chart-review study of male veterans, Hansen and colleagues observed optimal compliance in 59% of patients[24].

Our study adds data showing that compliance and persistence rates in men were lower than those estimated in women, mainly due to a greater proportion of subjects with only 1 prescription. In men, as reported in the literature, osteoporosis is a prevalent problem that is under-recognized and undertreated, and morbidity and mortality following a fracture are also greater than they are for women [25]. From this perspective, the observed low levels of adherence have even more clinically relevant implications, requiring more attention by physicians, especially in this population.

A few studies have investigated factors influencing nonadherence, identifying side effects, age, and therapeutic regimen as main determinants [11, 26- 29].

In our regression analyses, age was a major determinant of poor adherence and non-persistence, as both younger age and older age increased risk, probably due to a reduced perception of adverse outcome from osteoporosis [30, 31] (which has low prevalence in people under age 50 years) and to the increased comorbidity and concomitant treatments at older ages (which may lead practitioners and patients to favour other therapies) [31, 32].

A major perceived problem with oral bisphosphonates is the inconvenience of the regimen, and the association between complex drug regimens and compliance is well established [33]. Several studies showed that less frequent dosing regimens significantly improved levels of both compliance and persistence [34- 37]. This was confirmed in our female sample, supporting a great possibility of improvement from new formulations with delayed administration frequency.

In our analyses, the presence of a therapy change has been shown to reduce the risk of non-adherence and non-persistence. This evidence may suggest the switch as an indicator of further attention by the physician (to counteract the onset of adverse effects or to meet the patient's needs), but we should consider that switching to another brand may result in the accumulation of drug units that are not used, which can lead to skewed levels of compliance.

Data about patients who were prescribed bisphosphonates because of chronic corticosteroid therapy are scarce. A study by Curtis and colleagues evaluated persistence and compliance to bisphosphonates at 2 years among corticosteroid users and reported a mean MPR of 73% [38]. In our study, compliance levels within corticosteroid therapy were poor (mean MPR 56.4%), although higher than those of other patients (mean MPR 46.1%) and in regression analyses, the use of corticosteroids significantly reduced risk of suboptimal compliance and of non-persistence. It is likely that these patients are more aware of the risk of fractures and the importance of anti-osteoporosis therapy.

The results of our study should be considered within the context of the study's limitations, mainly related to the use of administrative registry as a data source. Although this database allows access to information on a large number of patients gathered in real-world conditions and repeated dispensing over regular intervals is a good proxy for actual compliance and persistence to treatment, pharmacy claims do not guarantee the real consumption of medications, nor do they reflect the actual timing or manner of use. In addition, the administrative database does not capture drugs taken during hospitalization and use of over-the-counter calcium and supplements including vitamin D, so we did not cover all anti-osteoporosis interventions. Moreover, data on many important clinical variables that may influence compliance and persistence are not available.

On the other hand, the absence of exclusion criteria specific for age, pathology , or concomitant treatment allowed us to evaluate the AOD utilization profile of an unselected population in the general practice setting. The enrollment of both gender into the study provided information about prescriptive patterns and adherence and persistence to therapy also in the male population. In addiction, we extended our observation to all medications recommended for osteoporosis treatment by Italian guidelines.

Overall, our data underscore the urgent need to improve the use of antiosteoporosis drugs, and suggest some priorities for intervention to improve compliance and persistence. First, both patients and doctors should be more aware that, after the decision to start a pharmacologic therapy, this cannot be interrupted; and that a scheduled, close follow-up is crucial, at least during the initial months of therapy, to reduce drop-out rate after the first prescription. Second, indications to minimize side effects should be offered to the patients whenever these drugs are prescribed. The risk/benefit ratio for younger and older patients should also be expressed. Finally, weekly or monthly regimens should be the preferential choice. The results of such improvement strategies could be easily monitored using the administrative databases, as showed by the current study.

4.3.5 Conclusions

This study confirms that compliance and persistence to antiosteoporosis drugs is suboptimal in everyday practice, with short periods of persistence and lengthy gaps in therapy, and with 75% of treated patients probably getting no benefit or only partial benefit from therapy. To address these issues, a strategy to detect first prescriptions without any refill should be implemented (such as automated alerts close to the end of drug availability after a prescription is filled), along with adequately planned follow-up to monitor treatment effectiveness and compliance, and selection of a drug regimen that can help patients be more compliant with therapy. This is an example of how administrative databases, when available, can be used to monitor drug use and to identify the areas in which improvement is needed to increase compliance and persistence to therapy.

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4.4 Gender differences in medication taking behaviour: a case of osteoporosis

Abstract

The aim of this study is to perform gender specific analysis regarding the persistence to antiosteoporotic drugs by using administrative databases. Patients 60 years of age or older were included if at least one prescription for any antiosteoporotic drugs had been filled in between January 1, 2006 and December 31, 2006. The final cohort consisted of a total of 7,867 patients (87.2% women). The mean patient age for both genders at the index date was 74.5 years. The crude analysis of long-term gender persistence showed a significant difference between women and men users: the relative number of persistence patients after 1 year was 66.4% in men and 44.7% in women. The Kaplan Meier plots of time to persistence start to differ for men vs women approximately 60 days after treatment start.

4.4.1 Introduction

Osteporosis is mostly defined as the disease of women, because the prevalence and fracture rates are much higher in postmenopausal women than in older men. The prevalence of osteoporosis in Europe was estimated to be 27.6 million (22.1 million of women and 5.5 million of men) in 2010 [1].

In recent years, however, there has been increasing recognition that male osteoporosis also represents an important burden as a common cause of morbidity, mortality and health care expenditure [2-4]. Also, men are more likely than women to have osteoporosis that is undiagnosed and undertreated [5-6].

Moreover, bone fracture are important factors of high mortality and morbidity rates in osteoporotic patients. Lack of persistence is common among subjects using oral anti-osteoporotic drugs, and leads to increased risk of fragility fracture [7-9]. The aim of this study is to perform gender specific analysis regarding the persistence to antiosteoporotic drugs.

4.4.2 Materials and methods

We conducted a retrospective cohort study using administrative data from four local health authorities in the Abruzzo Region (Central Italy), which comprise about 900,000 inhabitants (68% of the overall regional population).

Data sources

The data used for this study were obtained from outpatient drug prescriptions, hospital discharges and ambulatory care records collected from January 1, 2005 to December 31, 2008 (study period). Briefly, outpatient drug prescriptions include all information about prescribed drugs reimbursed by the NHS (i.e. drug code, dose,

formulation, number of packages, date of prescription). Drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Hospital discharges collect information on primary diagnosis, up to five secondary diagnoses, performed medical or surgical procedures, date and ward of admission and discharge and in-hospital death. All diagnoses and procedures are codified according to the International Classification of Disease, 9th Revision (ICD-9-CM). This database includes the patients' personal identification number, procedure codes, date of prescription and costs.

All data sources were matched by record-linkage analysis through a unique personal identification code that is encrypted to protect the patient's privacy and linked to the civil registry in order to collect demographic information (i.e. age, gender, date of death or emigration) of all residents covered by the NHS. The reliability of this strategy to produce clinical-epidemiological information has been previously documented. Because this automated system is anonymous, neither ethical committee approval nor informed consent was required for the present study.

Study cohort

The study was designed as a retrospective study cohort. Patients 60 years of age or older were included if at least one prescription for any antiosteoporotic drugs [Alendronate (ATCV:M05BA04); Alendronate + Vitamin D (ATC V M05BB03); Risedronate (ATC V M05BA07); Ibandronate (ATC V M05BA06); Raloxifene (ATC V G03XC01); Strontium Ranelate (ATC V M05BX03) and Teriparatide (ATC V H05AA02)] had been filled in between January 1, 2006 and December 31, 2006. The date of first prescription was considered as the index date.

Three patient categories were excluded:

- patients who had been prescribed antineoplastic drugs (L01) during follow-up;
- patients with a medical claim for malignant bone cancer as a reason for hospitalization (ICD-9: 170 e 198.5) or pathological fracture (ICD-9: 733.1);
- patients who had not reached at least one year of follow-up and medical history.

Patients were followed from the index date until the discontinuation of antiosteoporotic therapy or until the end of the observation period (31 December 2008). For each patient, additional data elements available in the database include the following characteristics at the index date: age, gender, co-prescription of calcium/ Vitamin D, dosing regimen treatment, previous treatments, previous fractures, diagnostic tests and fractures.

Persistence

Persistence was defined as the length of time (in days) from the date of the index prescription to the date of discontinuation therapy. Discontinuation was evaluated by using the gap method. A gap is a period during which no medication is available to the

patient. A treatment period was considered discontinued if the gap between two prescriptions exceeded a period covered by drug prescribed > 30 days. Persistence was analyzed according to the type of dosing regimen. To avoid underestimating true persistence, switching of medications was allowed when establishing persistence status for all treatments combined. Switchers were considered discontinuers at the date of switch when persistence was estimated for the individual treatment types.

Statistical Analysis

Baseline characteristics of the study population were analyzed using descriptive statistics: quantitative variables were described by means and standard deviations while categorical variables were described by counts and percentages. Chi-square was used to examine the differences in proportion of persistence between males and females.

Persistence estimates over time (discontinuation rates were assessed at 365 days) were derived using Kaplan–Meier survival analysis, stratifying for gender, considering treatment discontinuation as failure event and comparing differences using Log-rank test (1 degree of freedom).

All analyses were performed using SPSS software version 17.1 for Windows (SPSS Inc, Chicago, IL, USA).

4.4.3 Results

Cohort characteristics

The final cohort consisted of a total of 7,867 patients, aged 60 or older, identified through records of filled prescriptions for an antiosteoporotic drug between January 1, 2006 to December 31, 2006 and satisfied the inclusion/exclusion criteria. Baseline characteristics of the study population according to gender are shown in Table 1. The majority of patients were women (87.2%), and 3.9% had a history of an osteoporotic fracture.

Males and females were similar in mean age. The mean patient age for both genders at the index date was 74.5 years with 27.3% of the patients between 60 an 70 years of age, 46.1% of the patients between 70 and 80 years of age and 26.6% of patients≥ 80 years of age.

The most common index prescription for the all population was weekly bisphosphonate (90.2% of the population), followed by daily bisphosphonate (4.4% of the population), strontium ranelate (2.5% of the population), raloxifene (1.7% of the population), monthly bisphosphonate (0.9% of the population) and teriparatide (0.4% of the population).

There was no significant differences in previous treatment and prevalent fractures occurred one year before the index prescription histology between males and females (p = 0.665 and p = 0.760 respectively). Regarding concomitant medications,

approximately 19.4 % of the all patients used calcium and vitamin D besides osteoporosis medication (12.8% for males and 20.3% for females).
About one-fifth of all subjects had experienced with spot therapy, but men were more likely than women to have a spot therapy experience (45.4% vs. 14.5%, p < 0.001).
Approximately 6% of all included patients switched between the included medications outside dosing regimen but differences in switching patterns were analyzed between males and females: males had significantly more occurrences (18.9% vs 4.4%, p < 0.001).

Table 1. Baseline characteristics of the study population (N= 7,862)

	Male n (%) 1,009 (12.8)	Female n (%) 6,858 (87.2)	Total n (%) 7,867	*p* value
Age (mean ±SD)	74.6 ± 7.7	74.5 ± 7.7	74.5 ± 7.7	
Age groups				0,57
60-69 years	268 (26.6)	1,877 (27.4)	2,145 (27.3)	
70-79 years	474 (47.0)	3,156 (46.0)	3,630 (46,1)	
≥ 80 years	267 (26.5)	1,825 (26.6)	2,092 (26.6)	
Initial drug[a]				< .0001
Daily bisphosphonate	116 (11.5)	229 (3.3)	345 (4.4)	
Weekly bisphosphonate	871 (86.3)	6,223 (90.7)	7,094 (90.2)	
Montly bisphosphonate	<0.1 (<0.1)	67 (1.0)	67 (0.9)	
Raloxifene	7 (0-7)	123 (1.8)	130 (1.7)	
Strontium ranelate	15 (1.5)	184 (2.7)	199 (2.5)	
Teriparatide	<0.1 (<0.1)	32 (0.5)	32 (0.4)	
Previous treatment	723 (71.7)	4,959 (72.3)	5,682 (72.2)	0,46
Prevalent fractures[b]	38 (3.8)	272 (4.0)	310 (3.9)	0,53
Calcium - VitD intake	129 (12.8)	1,394 (20.3)	1,523 (19.4)	< .0001
Spot therapy	458 (45.4)	997 (14.5)	1,455 (18.5)	< .0001
Switcher	191 (18.9)	305 (4.4)	496 (6.3)	< .0001
Previous comorbidity				0.006
None	222 (22.0)	1,864 (27.2)	2,086 (26.5)	
1	397 (39.3)	2,586 (37.7)	2,983 (37.9)	
2	261 (25.9)	1,613 (23.5)	1,874 (23.8)	
≥ 3	129 (12.8)	795 (11.6)	924 (11.7)	
Test	707 (70.1)	5,395 (78.7)	6,102 (77.6)	< .0001
Fracture	40 (4.0)	366 (5.3)	406 (5.2)	0.066

[a] Initial dosing regimen is calculated by each patient irrespective of switching

[b] 1 year before the index prescription

Persistence

The estimated Kaplan–Meier life table, with cumulative persistence rates (prescription refill gap ≤ 30 days) for the total population and gender-specific rates, are presented in Table 2. For the full cohort, persistence was 47.5 % (95 % CI, 46.3–48.7 %) after 1 year. Median time on treatment (time at which cumulative persistence rate is equal to 50 %) was 250 days.

Table 2. Persistence over time with oral osteoporosis treatments (switching allowed)

Time point	Total cohort (*N* = 7,867)		Women (*N* = 6,858)		Men (*N* = 1,009)	
	Patients on therapy (%)	95% CI	Patients on therapy (%)	95% CI	Patients on therapy (%)	95% CI
3 months	67.8	66.8-68.8	66.5	65.3-67.7	76.5	73.9-79.0
6 months	54.8	53.6-56.0	52.6	51.4-53.8	69.8	67.0-72.5
9 months	49.3	48.1-50.5	46.7	45.6-47.9	67.1	64.1-70.0
12 months	47.5	46.3 - 48.7	44.7	43.5 - 45.9	66.4	63.4 - 69.2

Kaplan–Meier plots of the gender-specific data are shown in Fig. 1. The crude analysis of long-term gender persistence showed a significant difference between women and men users (log-rank test, $p < 0.001$): the relative number of persistence patients after 1 year was 66.4% in men and 44.7% in women. The Kaplan Meier plots of time to persistence start to differ for men vs women approximately 60 days after treatment start (Fig.1).

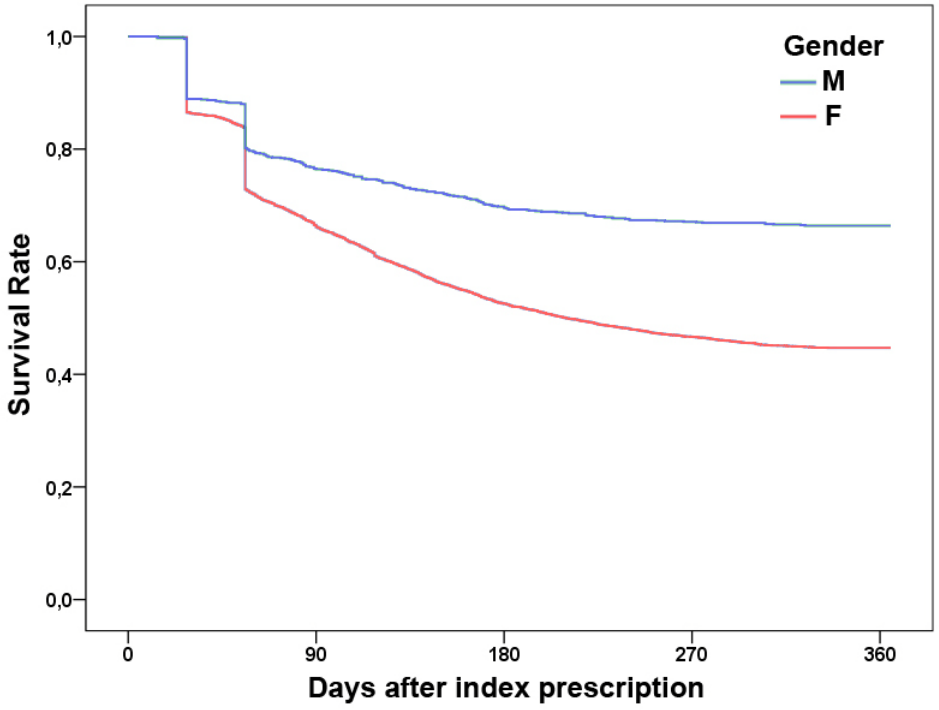

Figure 1: 1 year Kaplan–Meier survival curves showing the differences in outcomes

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4.5 Persistence to therapy and the associated risk of fractures with antiosteoporotic drugs

Abstract

The aim of this study was to investigate the determinants of non-persistence and impact of persistence on the risk of fractures by using administrative databases. The final cohort consisted of a total of 7,862 patients, aged ≥60 years, identified through records of filled prescriptions for an antiosteoporotic drug between January 1, 2006 to December 31, 2006.

Kaplan – Meier analysis showed that 3,733 patients (47.5%) were persistent with antiosteoporotic drugs after 1 year. An adjusted analysis showed that there is a big difference in persistence between women and men: women are more likely to be non-persistent than men (HR:1.94). Switcher patients were more likely to be non-persistent (HR:1.22). Persistence with antiosteoporotic drugs is a significant predictor of incurring a fracture. In the logistic regression analysis adjusted for potential confounders odds of fracture were significantly lower for persistent patients (OR:0.79).

4.5.1 Introduction

Osteoporosis is a chronic progressive disease characterized by low bone mass and deterioration of bone structure, leading to an increate risk of fractures. It is a major public health problem, affecting hundreds of millions of people worldwide [1-2].

The primary aim of pharmaceutical therapy is to reduce the risk of osteoporotic fractures. However, long-term adherence to therapy is requie for optimal therapeutic benefit for patients with osteoporosis. Poor adherence is considered to be one primary reason for suboptimal clinical benefit [3-6]. Several studies have shown that adherence to treatment of osteoporosis is poor, resulting in suboptimal real-world treatment effectiveness [7-14].

The aim of this study was to investigate the determinants of non-persistence and impact of persistence on the risk of fractures.

4.5.2 Materials and Methods

We conducted a retrospective cohort study using administrative data from four local health authorities in the Abruzzo Region (Central Italy), which comprise about 900,000 inhabitants (68% of the overall regional population).

Data sources

The data used for this study were obtained from outpatient drug prescriptions, hospital discharges and ambulatory care records collected from January 1, 2005 to December 31, 2008 (study period). Briefly, outpatient drug prescriptions include all information about prescribed drugs reimbursed by the NHS (i.e. drug code, dose,

formulation, number of packages, date of prescription). Drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Hospital discharges collect information on primary diagnosis, up to five secondary diagnoses, performed medical or surgical procedures, date and ward of admission and discharge and in-hospital death. All diagnoses and procedures are codified according to the International Classification of Disease, 9th Revision (ICD-9-CM). This database includes the patients' personal identification number, procedure codes, date of prescription and costs.

All data sources were matched by record-linkage analysis through a unique personal identification code that is encrypted to protect the patient's privacy and linked to the civil registry in order to collect demographic information (i.e. age, gender, date of death or emigration) of all residents covered by the NHS. The reliability of this strategy to produce clinical-epidemiological information has been previously documented. Because this automated system is anonymous, neither ethical committee approval nor informed consent was required for the present study.

Study cohort

The study was designed as a retrospective study cohort. Patients 60 years of age or older were included if at least one prescription for any antiosteoporotic drugs [Alendronate (ATCV:M05BA04); Alendronate + Vitamin D (ATC V M05BB03); Risedronate (ATC V M05BA07); Ibandronate (ATC V M05BA06); Raloxifene (ATC V G03XC01); Strontium Ranelate (ATC V M05BX03) and Teriparatide (ATC V H05AA02)] had been filled in between January 1, 2006 and December 31, 2006. The date of first prescription was considered as the index date.

Three patient categories were excluded:

- patients who had been prescribed antineoplastic drugs (L01) during follow-up;
- patients with a medical claim for malignant bone cancer as a reason for hospitalization (ICD-9: 170 e 198.5) or pathological fracture (ICD-9: 733.1);
- patients who had not reached at least one year of follow-up and medical history.

Patients were followed from the index date until the discontinuation of antiosteoporotic therapy or until the end of the observation period (31 December 2008).

Covariates

For each patient, additional data elements available in the database include the following characteristics at the index date: gender, age, dosing regimen, previous treatments, previous fractures, co-prescription of calcium/ Vitamin D, Spot therapy, Swither, Comorbidity, diagnostic tests and fractures.

Comorbidity

Information on patients comorbidity were adapted to Age Adjusted Charlson Comorbidity Index (ACCI) scores which were calculated for each patient by taking into

account all comorbidity conditions present at the index date with additional points added for age.

Diagnostic tests

Study patients were classified as exposed or not exposed to diagnostic tests related to the bone fracture on the basis of the presence or absence of at least one prescription during the study period. Diagnostic tests were classified into: 1st level laboratory tests- ERA (code: 90.82.5), CBC (code: 90.62.2), fractionated serum proteins (code: 90.38.4), calcemia (code: 90.11.4), phosporemia (90.24.5), total alkaline phosphatase (code: 90.23.5), creatininemia (code: 90.16.3); 2nd level laboratory tests- ionized calcium (code: 90.11.6), TSH (code: 90.42.1), PHT (code: 90.35.5), 25OH-VitD (code: 90.44.6), cortisol (code: 90.15.3), immunofixation (code:90.69.2), anti-gliadin, anti-endomysium, anti-transglutamise antibodies (code: 90.48.06, 90.49.5, 90.49.7, 90.52.2, 90.53.6), transaminase (code: 90.09.2, 90.04.5), urinary electrophoresis proteins (code:90.39.1), neoformation turnover (code: 90.24.1, 90.35.4, 90.37.7), resorption turnover (code: 90.16.7, 90.28.2, 90.36.6); 1st level instrumental tests- back X-ray (code: 87.23), umbocacral X-ray (code: 87.24), spine X-ray (code: 87.29), densiometry (code: 88.99.2, 88.99.3, 88.99.5); 2nd level instrumental tests – spine MRI (code: 88.93, 88.93.1), Spine CT scan (code: 88.38.1, 88.38.2).

Fracture

Study patients were classified as exposed or not exposed to bone fracture on the basis of the presence or absence of at least one hospitalization event with primary or secondary diagnosis of osteoporotic fracture during follow-up. Hospitalizations were selected based on discharge diagnosis, present on the National Hospitalization Database (SDO), of probable osteoporotic fracture according to the International Statistical Classification of Disease and Related Health Problems 9th Revision (ICD-9) during follow-up: ICD-9 codes 820.0 to 820.1 (femoral neck fractures), 820.2 to 820.3 (per-trochanteric femoral fractures), 820.8,820.9, 821.1,821.2,821.3 (other femoral fractures), 812 (humeral fractures), 824 (ankle fractures), 813 (forearm/wrist fractures) 823 (proximal tibia/fibula), 805, 806 (vertebral fractures) 807.0, 807.1 (rib), 808 (pelvis).

Outcome measures

The primary outcome of this study was persistence at one year. Persistence was defined as the length of time (in days) from the date of the index prescription to the date of discontinuation therapy. Discontinuation was evaluated by using the gap method. A gap is a period during which no medication is available to the patient. For the analysis of persistence, a treatment period was considered discontinued if the refill gap between two prescriptions exceeded a period covered by drug prescribed > 30 days. Persistence was analyzed according to the type of dosing regimen. To avoid underestimating true persistence, switching of medications was allowed when establishing persistence status for all treatments combined.

In order to investigate the impact of persistence with antiosteoporotic drugs on the risk of fractures, the secondary outcome of this study was hospitalized osteoporotic fractures based on ICD-9 codes related osteoporotic fracture.

Statistical Analysis

Demographic and clinical characteristics of the study population were examined using standard statistical methods: continuous variables were described by means and standard deviations while categorical variables were described by absolute and relative frequencies.

Persistence esteems over time were derived using Kaplan–Meier survival analysis considering treatment discontinuation as failure event and comparing differences using Log-rank test (4 degrees of freedom).The determinants of non-persistence, that showed an association with a $p \leq 0.25$ in the univariate Cox regression analysis, were also considered as covariates in the multivariable Cox regression.

A logistic regression model was performed to assess the relationship between persistence with antiosteoporotic drugs and odds of fracture; univariate and multivariate models were performed; in the multivariate model were entered all potential confunders (gender, age group, previous fractures, persistence at one year and ACCI) that were significant at the $p \leq 0.25$ in the univariate model.

All analyses were performed using SPSS software version 17.1 for Windows (SPSS Inc, Chicago, IL, USA).

Sensitivity analyses

Sensitivity analyses were performed for the occurrence of fracture.We considered fractures that occurred in the first three months after the index date as previous fractures and did not consider recurrent fractures after the first one.

Additional sensitivity analyses were carried out for the measurement of persistence by extending the refill gap from the 30 day baseline analysis to 45 and 60 days.

4.5.3 Results

Baseline characteristics and study cohort

The final cohort consisted of a total of 7,862 patients, aged 60 or older, identified through records of filled prescriptions for an antiosteoporotic drug between January 1, 2006 to December 31, 2006 and satisfied the inclusion/exclusion criteria. Baseline characteristics of the study population are shown in Table 1. The majority of patients were women (87.2%). The mean patient age at the index date was 74.5 years with 27.3% of the patients between 60 an 70 years of age, 46.1% of the patients between 70 and 79 years of age and 26.6% of patients ≥ 80 years of age.

The most common index prescription for the all population was weekly bisphosphonate (90.2% of the population), followed by daily bisphosphonate (4.4% of the population), strontium ranelate (2.5% of the population), raloxifene (1.7% of the population), monthly bisphosphonate (0.9% of the population) and teriparatide (0.4%

of the population). About 4.4% of patients had fractures that occurred before the index date. Regarding coprescription of calcium and Vitamine D approximately 19.4 % of the all patients used calcium and vitamin D besides osteoporosis medication. About one-fifth of all subjects had experienced with spot therapy and approximately 6% of all included patients switched between the included medications. Patients were dichotomized into three escalating ACCI groups: 0, 1-3 and ≥ 5. In total, Zero score (0) was found in 91.6%, Mild score (1-4) was found in 1.3% and Severe score (≥ 5) in 7.1%. At last, 77.6% of patients was exposed to diagnostic tests related to the bone fracture.

Table1. Baseline characteristics of the included patients (*N* = 7,862).

Patients analysed (*N* = 7,862)	
Female Sex, *n* (%)	6,856 (87.2)
Age (mean ±SD)	74.53 ± 7.66
Age groups *n* (%)	
60-69 years	2,145 (27.3)
70-79 years	3,628 (46.1)
≥80 years	2,089 (26.6)
Dosing regimen[a]	
Daily bisphosphonates	7,090 (90.2)
Weekly bisphosphonates	345 (4.4)
Montly bisphosphonates	67 (0.9)
Raloxifene	130 (1.7)
Strontium ranelate	198 (2.5)
Teriparatide	32 (0.4)
Previous treatment, *n* (%)	5,681 (72.3)
Previous fractures, *n* (%)	342 (4.4)
Co-prescription of Calcium/Vit D, *n* (%)	1,523 (19.4)
Spot therapy, *n* (%)	1,452 (18.5)
Switcher, *n* (%)	496 (6.3)
ACCI, *n* (%)	
Zero Score [0]	7,200 (91.6)
Mild Score [1-4]	100 (1.3)
Severe Score [≥ 5]	562 (7.1)
Tests, *n* (%)	6,102 (77.6)
Fractures, *n* (%)	374 (4.8)

[a] Initial dosing regimen is calculated by each patient irrespective of switching

Persistence

Kaplan – Meier analysis showed that 3733 patients (47.5%) were persistent with antiosteoporotic drugs after 1 year when prescription refill gap ≤ 30 days. Persistence was higher when the refill gap period was increased. Adopting 45 or 60 days as refill gap, Kaplan-Meier curves show persistence rates of 4,793 (61.0%) and 5,363 (68.2%) respectively after 1 year (Fig.1).

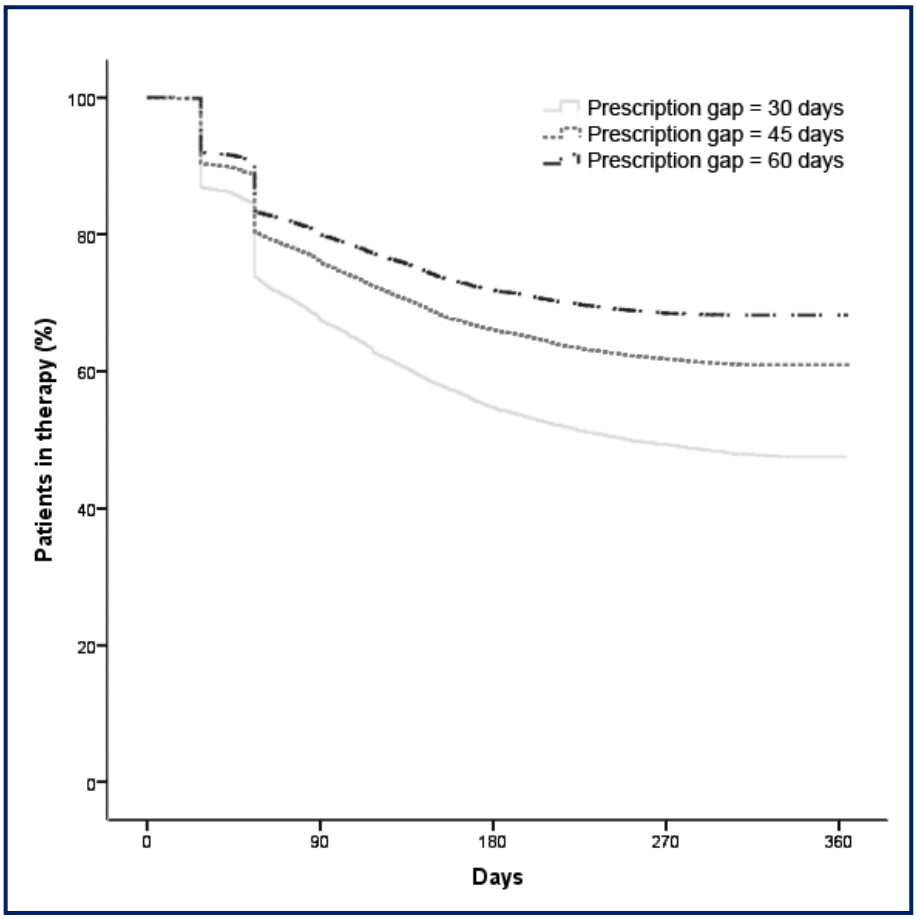

Fig. 1. Overall persistence patients treated with osteoporosis drugs therapy.

Determinants of non-persistence to antiosteoporotic drugs

Determinants of non-persistence are shown in Table 2. An adjusted analysis showed that there is a big difference in persistence between women and men: women are more likely to be non-persistent than men [HR, 1.94, (95% CI, 1.73-2.18)]. No significant difference was found between a weekly and a daily dosing regimen [HR, 1.04, (95% CI, 0.89-1.21)]. Switcher patients were more likely to be non-persistent [HR, 1.22, (95% CI, 1.07-1.39)]. No significant difference was found to ACCI groups.

Table 2. Determinants of non-persistence of osteoporosis medications (*N* = 7,862).

Characteristics	365 days persistence (%)	**Unadjusted HR** (95% CI)	*p*-value	**Adjusted HR** (95% CI)	*p*-value
Gender					
Male	66.5	Reference			
Female	44.7	1.88 (1.68-2.10)	< 0.001	1.94 (1.73-2.18)	< 0.001
Dosing regimen					
Daily bisphosphonates	50.1	0.95 (0.82-1.11)	0.547	1.04 (0.89-1.21)	0.666
Weekly bisphosphonates	46.6	Reference			
Montly bisphosphonates	58.2	0.74 (0.51-1.07)	0.108	0.99 (0.68-1.44)	0.985
Strontium Ranelate	63.1	0.64 (0.51-0.80)	< 0.001	0.72 (0.57-0.91)	0.007
Raloxifene	54.6	0.82 (0.63-1.06)	0.122	0.76 (0.59-0.99)	0.041
Teriparatide	59.4	0.68 (0.39-1.16)	0.158	0.61 (0.35-1.04)	0.071
Switcher					
No	47.5	Reference			
Yes	47.2	1.02 (0.90-1.15)	0.812	1.22 (1.07-1.39)	0.002
Previous treatment					
No	61.9	Reference			
Yes	42.0	1.71 (1.58-1.84)	< 0.001	1.68 (1.55-1.82)	< 0.001
ACCI					
Zero score [0]	47.2	Reference			
Mild score [1-4]	44.0	1.08 (0.83-1.40)	0.560	1.12 (0.86-1.46)	0.395
Severe score [≥5]	51.2	0.90 (0.80-1.02)	0.106	0.96 (0.85-1.09)	0.534

Influence of persistence on fracture risk

For the analysis of the impact of persistence and other factors on the risk of fracture, persistence with antiosteoporotic drugs is a significant predictor of incurring a fracture. In the logistic regression analysis adjusted for potential confounders odds of fracture were significantly lower for persistent patients [OR, 0.79, (95% CI, 0.63-0.97)]. Older patients were more likely to incur a fracture than younger [70-79: OR, 1.52, (95% CI, 1.13-2.06); ≥ 80: OR, 2.49, (95% CI, 1.83-3.39)]. The odds of fracture were significantly higher for patients with previous fractures in comparison with those without previous fractures [OR, 1.70, (95% CI, 1.12-2.59)] (Table 3.).

Table 3. Logistic regression model: impact of persistence and other factors on the risk fracture.

Characteristics	**Unadjusted OR** (95% CI)	*p*-value	**Adjusted OR** (95% CI)	*p*-value
Gender				
Male	Reference			
Female	1.31 (0.93-1.85)	0.119	1.28 (0.91-1.82)	0.159
Age				
60-69	Reference			
70-79	1.54 (1.14 -2.06)	0.005	1.52 (1.13-2.06)	0.006
≥80	2.56 (1.89 -3.45)	< 0.001	2.49 (1.83-3.39)	< 0.001
Previous fractures				
No	Reference			
Yes	1.71 (1.58-1.84)	< 0.01	1.70 (1.12-2.59)	0.013
Persistence				
No	Reference			
Yes	0.78 (0.63-0.97)	0.022	0.79 (0.63-0.97)	0.026
ACCI				
Zero score [0]	Reference			
Mild score [1-4]	0.86 (0.32-2.36)	0.772	1.35 (0.49-3.78)	0.562
Severe score [≥5]	1.50 (1.06-2.12)	0.022	1.33 (0.94-1.90)	0.112

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4.6 Cost analysis of osteoporosis in real word clinical practice

Abstract

The aim of this study is to analyze healthcare costs of osteoporosis and to build a economic model cost-effectiveness of pharmacological intervents based on real world data. The cost analysis was conducted taking each healthcare service into account, i.e. drug therapy, diagnostic tests and hospitalization admissions, during the study period. A hypothetical scenario based on the real-life available evidence was constructed.The mean level of adherence to populate the hypothetical scenario of "full adherence" was set at MPR $\geq$ 80 % .

The model built by adding a step value, constrained by a normal random variable, to the real-word adherence of each subject so that the subject shifted to the hypotetical scenario of *full adherence*, in order to quantify the clinical outcome (number of fractures) achievable in the hypotetical scenario.

Cost-effectiveness of full adherence compared to real world adherence was expressed in terms of Incremental Cost effectiveness Ratio (ICER) and the number of fractures avoided was set as an effectiveness unit of measure. The mean annual healthcare cost per fracture avoided was € 247.44, of which medical treatments and diagnostic tests accounted for € 103.60 (41.9%) and € 143.84 (58.1%), respectively. The mean annual helathcare cost per fractured patient was € 1,044.85, of which medical treatments, diagnostic tests and hospitalizations for osteoporotic fracture accounted for € 88.73 (8.5%), € 169.48 (16.2%) and € 786.65 (75.3%), respectively.

4.6.1 Introduction

Adherence to medications is poor and suboptimal in many chronic diseases. Nonadherence can reduce treatment effectiveness and can negatively affect healthcare costs and thus the treatments' cost-effectiveness.

Adherence in the setting of osteoporosis has been shown to be just as problematic, if not worse, than that in other chronic diseases [1-4].

Economic evaluations based on modelling are commonly used to compare alternative treatment strategies in osteoporosis, to support decision-makers and to inform treatment guidelines [5-7].

Decision models can be used to forecast the results of clinical trials which usually provide a short follow up. These usually represent the bases for economic evaluations. Moreover, if adequately designed, decision making models allow taking uncertainty around parameters into accont, and to account for the lack of compliance that can be observed in clinical practice.

When first and second order uncertainty are fully explored andreliable real world data are used to popultate the model, then generalizable results can be obtained and the information produced can be considered relevant even to different jurisdictions.
Given this backdrop, the aim of this study is to analyze healthcare costs of osteoporosis though an economic model to compute the cost-effectiveness of pharmacological regimens based on real world data.

4.6.2 Matherial and Methods

Data source

The data of the analysed subjects were drawn from the administrative databases of four Local Health Authorities in the Abruzzo Region (Central Italy), which comprise about 900,000 inhabitants (68% of the overall regional population). Database contain information about outpatient drug prescriptions, hospital discharges and ambulatory care records collected from January 1, 2005 to December 31, 2008 (study period). Briefly, outpatient drug prescriptions include all information about prescribed drugs reimbursed by the NHS (i.e. drug code, dose, formulation, number of packages, date of prescription, drugs cost). Hospital discharges collect information on primary diagnosis, up to five secondary diagnoses, performed medical or surgical procedures, date and ward of admission and discharge and in-hospital death. All diagnoses and procedures are codified according to the International Classification of Disease, 9th Revision (ICD-9-CM). This database includes the patients' personal identification number, procedure codes, date of prescription and costs. All data sources were matched by record-linkage analysis through a unique personal identification code that is encrypted to protect the patient's privacy and linked to the civil registry in order to collect demographic information (i.e. age, gender, date of death or emigration) of all residents covered by the NHS. The reliability of this strategy to produce clinical-epidemiological information has been previously documented. Because this automated system is anonymous, neither ethical committee approval nor informed consent was required for the present study.

Patient included

Patients 60 years of age or older were included if at least one prescription for any antiosteoporotic drugs had been filled in between January 1, 2006 and December 31, 2006. The date of first prescription was considered as the index date.

Osteoporotic Fracture

The patients included in the analysis were classified as exposed or not exposed to osteoporotic fracture on the basis of the presence or absence of at least one hospitalization event with primary or secondary diagnosis of osteoporotic fracture during the follow-up. Hospitalizations were selected based on discharge diagnosis, reported on the National Hospitalization Database (SDO), of probable osteoporotic fracture according to the International Statistical Classification of Disease and Related

Health Problems 9th Revision (ICD-9) during the follow-up. The following ICD-9 codes were considered relevant to the current analysis: 820.0 to 820.1 (femoral neck fractures), 820.2 to 820.3 (per-trochanteric femoral fractures), 820.8, 820.9, 821.1,821.2, 821.3 (other femoral fractures), 812 (humeral fractures), 824 (ankle fractures), 813 (forearm/wrist fractures) 823 (proximal tibia/fibula), 805, 806 (vertebral fractures) 807.0, 807.1 (rib), 808 (pelvis).

Adherence to therapy

For each group, exposed or not to osteoporotic fracture, compliance with antiosteoporotic drugs was calculated. Compliance was quantified by the Medication Possession Ratio (MPR), which has become a standard method of evaluating drug compliance and is defined as the number of prescribed therapy units (daily doses) divided by the number of assumed for prescription periods that extended beyond the end of the study period. Patients were considered compliant if their MPR was $\geq$ 80%. This value is commonly used as a cutoff point when evaluating compliance.

Healthcare costs and resources use

The cost analysis was conducted taking into account each healthcare good or service - drug therapy, diagnostic tests and hospitalization admissions – consumed by the patient during the study period. Healthcare resources where quantified under the NHS perspective. More in detail:

- drug cost has been calculated based on the amount of money the health system reimbursed to providers of care;
- diagnostic test cost has been calculated basing on the national tariff for outpatient services:
- hospitalization cost was obtained from National Hospitalization Database (SDO)

The mean annual healthcare cost per patient in the follow-up was also calculated.

Model Structure

Data source was represented by the evidence emerging from the studies described above which showed poor adherence to antiosteoporotic drugs and the relationship between persistence with antiosteoporotic drugs and risk of fracture (OR 0.79) .

Based on the real-life evidence available a hypothetical scenario was construcred.

The average level of adherence to achieve the hypothetical scenario of “full adherence” was estimated at MPR $\geq$ 80 % .

The model was built by adding a step value, constrained by a normal random variable, to the real-word adherence of each subject so that the subject shifted to the hypotetical scenario of *full adherence* , in order to quantify the clinical outcome (number of fractures avoided) in the hypotetical scenario.

Cost-effectiveness was expressed in terms of Incremental Cost effectiveness Ratio (ICER). This indicator is calculated as the ratio between the incremental costs and the incremental efficacy of the strategy under study compared to its alternative. The

indicator was calculated both in the hypothetical scenario of “full adherence” and at baseline (“real word adherence”) .
The chosen measure of effectiveness was the number of fractures avoided.

$$\text{ICER} = \frac{\text{Healthcare Costs “full adherence” – Healthcare Costs “real world adherence”}}{\text{N. fractures “full adherence” – N. fractures “real world adherence}}$$

4.6.3 Results

Overall, 7,862 patients were prevalent users of antiosteoporotic drugs: 7,456 patients (94.8%) was not exposed to osteoporotic fracture and 406 patients (5.2%) was exposed to osteoporotic fracture during the follow-up (Figure 1).

Adherence to therapy

Based on the calculated Medication Possesion Ratio (MPR), adherence to therapy with antiosteoporotic drugs after 1 year was 34.7% in fractured patients and 34.4% in not fractured patients (Figure 1).

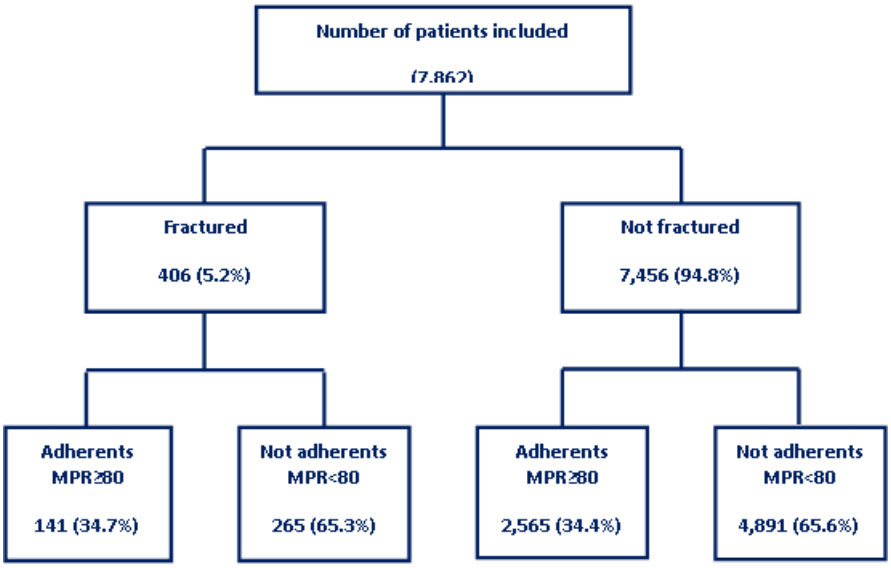

Figure 1: Flow chart selection

Cost of healthcare services

The mean annual healthcare cost per patient not fractued was € 247.44, of which € 103.60 (41.9%) was for drug treatments and € 143.84 (58.1%) for diagnostic tests.
The mean cost of drug treatments increased from € 54.57 in non adherent patients (MPR<80) to € 197.09 in adherent patients, while the cost of diagnostic testing ranged from € 106.50 in non adherent patients to € 215.04 in adherent patients. Consequently, the mean annual healthcare cost per not fractured patient increased from € 161.08 in non adherent patients to € 412.13 in adherent patients.

The mean annual helathcare cost per fractured patient was € 1,044.85, of which € 88.73 (8.5%) was for drug treatments, € 169.48 (16.2%) for diagnostic tests and € 786.65 (75.3%) for hospitalizations for osteoporotic fracture.

The mean cost of drug treatments increased from € 69.15 in non adherent patients (MPR<80) to € 125.52 in adherent patients, while the cost of diagnostic testing ranged from € 63.92 in adherent patients to € 225.64 in non adherent patients. Consequently, the mean annual healthcare cost per patient fractured increased from € 1,003.69 in adherent patients to € 1,066.75 in non adherent patients.In conclusion, costs for fractured patients resulted to be about four times greater than those of not fractured patients.

Table 3 – Total healthcare costs in osteoporotic patients, exposed and not exposed to osteoporotic fracure

	Drug treatments	Diagnostic tests	Hospitalisations for fracture	Total
Not fractured				
Adherents (MPR >80%)				
N. patients	2,565	2,565	2,565	2,565
Mean cost (€)	197.09	215.04	0	412.13
Total cost (€)	505,539.97	551,575.61	0	1,057,115.58
Non adherents (MPR <80%)				
N. patients	4,891	4,891	4,891	4,891
Mean cost (€)	54.57	106.50	0	161.08
Total cost (€)	266,921.55	520,904.80	0	787,826.35
Total				
N. patients	7,456	7,456	7,456	7,456
Mean cost (€)	**103.60**	**143.84**	**0**	**247.44**
Total cost (€)	772,461.52	1,072,480.41	0	1,844,941.93
Fractured				
Adherents (MPR >80%)				
N. patients	141	141	141	141
Mean cost (€)	125.52	63.92	786.65	1,003.69
Total cost (€)	17,698.14	9,012.30	110,917.65	141,520.53
Non adherents (MPR <80%)				
N. patients	265	265	265	265
Mean cost (€)	69.15	225.64	786.65	1,066.75
Total cost (€)	18,324.62	59,795.00	208,462.25	282,687.46
Total				
N. patients	406	406	406	406
Mean cost (€)	**88.73**	**169.48**	**786.65**	**1,044.85**
Total cost (€)	36,022.76	68,807.30	319,379.90	424,207.99

Cost effectiveness analysis

The economic model showing simulating the improved outcome of real world patients if they achieved full adherence, showed that the average cost of medical treatments in case of optimal adherence per patient/year would increase (from € 88.73 in Real word adherence to € 125.52 in full adherence).

Before this rising costs per year of drug therapy, the clinical outcome , expressed in terms of number of fractures, would decreases by 65%. In this scenario, also the total yearly costs related hospitalizations would decrease (from € 319,379 in real word adherence to € 110,917 in full adherence) .

The ICER , expressed in terms of cost/fracture avoided equals € 821 (Figure 2). This value indicates the cost that the NHS should support each fracture avoided.

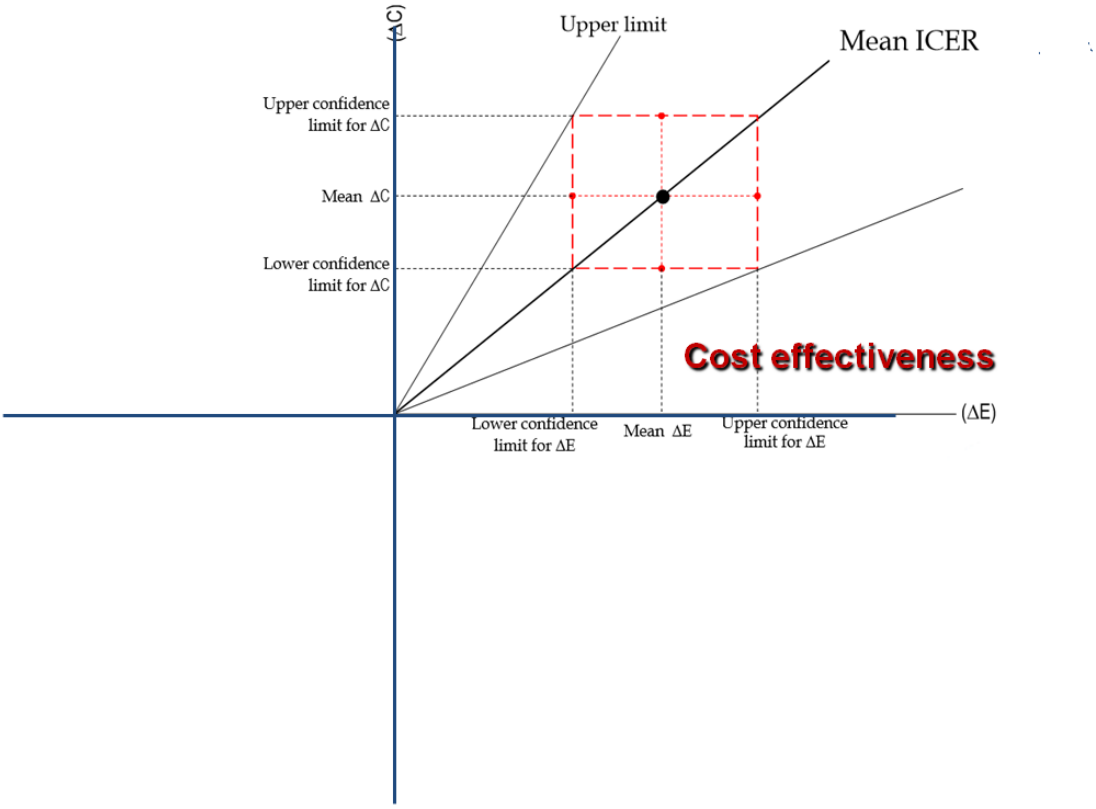

Figure 2: Incremental Cost Effectiveness Ratio

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General Discussion

Health-related automated databases are crucial systems to evaluate cost-effectiveness of intervention in a real world scenario. They are an innovative tool to assess adherence in large population and to evaluate cost-effectiveness of enhancing medication adherence.
Up to now very few studies have been carried out by using real world data to evaluate cost effectiveness of intervention. The research as described in this thesis therefore was conducted in a large unselected population reflecting the patients' treatment in the real-life setting and focused on pharmacoeconomic evaluation of improve adherence to treatment.

Main findings

The results showed sub optimal level of persistence. Our findings showed a lower level of adherence to antiosteoporotic drugs, persistence to therapy at 1 year was only 47.5%, than in other countries. [1]. This could be explained by the fact that interventions to improve adherence to treatment in chronic diseases have been running for a long time in those countries, while in Italy action to improve adherence are still at a pilot stage. Recently the Italian medicine agency (AIFA) proposed a National Adherence Implementation Plan converging Scientific, Political and Economic efforts to apply system actions with effective clinical/economic impact.
The results showed that drug regimen is one of the strong predictors of non-adherence. Patients receiving daily BP and Strontium Ranelate were at a higher risk of early discontinuation, HR: 1.98 and HR: 1.6 respectively, compared to patients in treatment with weekly BPs regimen. Moreover, patients treated with monthly BPs regimen had a lower risk of early discontinuation (HR: 0.9) compared to patients in treatment with weekly BPs regimen. This is in line with evidence reported in the WHO (need for action) complexity and duration of the treatment regimen. Gender influences adherence to therapy and this is an issue that could be taken in strong consideration in tailor intervention to improve adherence. The analysis of gender persistence after 1 year showed a significant difference between women and men, 44.7% and 66.4% respectively. Another aspect is comorbidity this highlighted that an approach centered on comorbidity/multimorbidity, could be more pertinent, in particular when address health issues concerning older people. About health care costs the results showed that the mean annual healthcare cost was € 247.44 per patient not fractued and € 1,044.85 per fractured patient. At last, the ICER , expressed in terms of cost/fracture avoided equals € 821. This value indicates the cost that the NHS should support each fracture avoided.

Strengths and weakness

The relevance of our study is strengthened by the size of our sample and the ability to draw information from a real-world setting. Indeed, it is well known that findings from randomized clinical trials (RCTs) are not always representative of clinical practice especially to evaluate compliance. Observational studies such as the present report allow to explore the health outcomes of patients in routine care outside the limits of an RCT. Nevertheless, we acknowledge that a number of potential limitations might have influenced our results. The presence of unrecognized confounders could lead to overestimate the magnitude of the association between exposure and outcome as compared with the results of RCTs. In particular, our findings may be subject to confounding by indication due to the lack of randomization. Our dataset does not include information about the duration and severity of osteoporosis, clinical information (i.e. smoking and BMI). However, we attempted to limit the influence on the study outcomes by adjusting for age, gender, ACCI, presence/absence of previous fracture, previous treatment. Despite this limitation our findings are in line with findings from other studies highlighted [1,2].

Needs to share data for cross-national comparison

Little is known about cross-national comparison (CNC) on adherence to medication and factors associated with non-adherence. Drug utilization studies have applied different methods to various data types to describe adherence to medication. Comparison of results of these studies is difficult owing to differences in the methods applied, data sources used and population groups selected [3]. Combining and sharing data across different European settings applying a uniform method of assessment could be useful, in order to increase sample size, to perform long-term studies and to share common strategies at EU level.

Future perspective for economic evaluation by using real world data

This thesis has highlighted how important can be real-world data to build economic models. Classic approaches are based on results from clinic trials, which can be of little use in taking informed decisions while planning health policies, although they still represent the most validated and robust methodology.

Conclusion

This thesis demonstrated the potential of the use of existing data sources to evaluate appropriateness of drug use. Drugs cost money to buy, but if we use them in an appropriate way we can also save costs in other areas. In particular enhancing adherence to medication may lead to reductions in the number of patients requiring hospitalization. This research only explored cost effectiveness of improve adherence in

drug use for osteoporosis, but clearly many different pattern of drugs for chronic conditions could be assessed in a similar way.

Future perspective

The data highlight the need for additional research. Findings of the present study may be a basis for future studies aimed at implementing health policies and educational efforts to improve medication adherence. Identification of interventions providing prescribing guidance. Identification of tools to support the delivery of effective medication reviews with rationalization of prescribing needs and effective communication of outcomes to patients and all actors involved in providing care. Enhancement of pharmacist role [4]. Action Group A1 of the European Innovation Partnership on Active and Healthy Ageing will develop these interventions, focusing on pilot initiatives and activities, as well as collaborative work and synergies across European partners, in order to both reduce disability and increment active life expectancy by improving prescribing quality and adherence to drug treatment [5].

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Appendix A: List of Antiosteoporotic drugs

List of antiosteoporotic drugs according to ATC classification (V level ATC codes) included in the studies. The list is based on drugs used in outpatient setting and reimbursed by NHS, available on the Italian market at the data of the study.

ATC V Code	Drug	Package Quantity	Administration/Regimen
G03XC01	Raloxifene	14 pill -60 mg 28 pill – 60 mg	Daily Daily
H05AA02	Teriparatide	1 pen – 28 doses 20mcg/80 µl	Daily
M05BA04	Alendronate	14 pill – 10 mg 4 pill – 70 mg	Daily Weekly
M05BA06	Ibandronate	1 pill – 150 mg	Monthly
M05BA07	Risendronate	28 pill – 5 mg 4 pill – 35 mg 2 pill – 75 mg	Daily Weekly Monthly
M05BB03	Alendronate+Vit D	4 pill – 70 mg	Weekly
M05BX 03	Stronzium Ranelate	28 bags – 2g	Daily

Appendix B: Hospitalizations for osteoporotic fracture

The ICD-9 is an acronym for "International Statistical Classification of Disease and Related Health Problems 9th Revision". This ninth edition is a publication form the World Health Organization comprising a set of codes that are used worldwide to classify diseases and injuries. The following table shows the list of ICD-9 codes that identify patient with hospitalization for osteoporotic fracture.

ICD-9 Codes	Description
805	Fracture of vertebral column without mention of spinal cord injury
805.0x	Cervical, closed
805.1x	Cervical, open
805.2	Dorsal [thoracic], closed
805.3	Dorsal [thoracic], open
805.4	Lumbar, closed
805.5	Lumbar, open
805.6	Sacrum and coccyx, closed
805.7	Sacrum and coccyx, open
805.8	Unspecified, closed
805.9	Unspecified, open
806	Fracture of vertebral column with spinal cord injury
807.0	Rib(s), closed
807.1	Rib(s), open
808	Fracture of pelvis
812	Fracture of humerus
812.0x	Upper end, closed
812.1x	Upper end, open
812.2x	Shaft or unspecified part, closed
812.3x	Shaft or unspecified part, open
812.4x	Lower end, closed
812.5x	Lower end, open
813	Fractures of radius and ulna
813.0x	Upper end, closed
813.1x	Upper end, open
813.2x	Shaft, closed
813.3x	Shaft, open
813.4x	Lower end, closed
813.5x	Lower end, open
813.8x	Unspecified part, closed
813.9x	Unspecified part, open
820	Fracture of neck of femur
820.0x	Transcervical fracture, closed
820.1x	Transcervical fracture, open
820.2x	Pertrochanteric fracture, closed
820.3	Pertrochanteric fracture, open
820.8	Unspecified part of neck of femur, closed
820.9	Unspecified part of neck of femur, open
821	Fractures of other and unspecified parts of femur
821.0x	Shaft or unspecified part, closed
821.1x	Shaft or unspecified part, open
821.2x	Lower end, closed
821.3x	Lower end, open
824x	Fracture of ankle

Appendix C: Diagnostic tests

Patients were classified as exposed or not exposed to diagnostic tests related to the osteoporotic fracture. Diagnostic test are classified into:

- 1st and 2nd level Laboratory Tests;
- 1st and 2nd level Instrumental Tests.

Laboratory Test Level	Test code	Description
1st	90.11.4	Calcemia
	90.16.3	Creatininemia
	90.23.5	Total alkaline phosphatase
	90.24.5	Phosphoremia
	90.38.4	Fractionated serum proteins
	90.62.2	CBC
	90.82.5	ERA
2nd	90.04.5 90.09.2	Transaminase
	90.11.6	Ionized calcium
	90.15.3	Cortisol
	90.16.7 90.28.2 90.36.6	Resorption turnover
	90.24.1 90.35.4 90.37.7	Neoformation turnover
	90.35.5	PTH
	90.39.1	Urinary electrophoresis proteins
	90.42.1	TSH
	90.44.6	25OH-VitD
	90.48.06 90.49.5 90.49.7 90.52.2 90.53.6	Anti-gliadin, anti-endomysium, anti-tranglutaminase antibodies
	90.69.2	Immunofixation

Instrumental Test Level	Test code	Description
1st	87.23	Back X-ray
	87.24	Umbocacral X-ray
	87.29	Spine X-ray
	88.99.2 88.99.3 88.99.5	Densitometry
2nd	88.38.1 88.38.2	Spine CT scan
	88.93 88.93.1	Spine MRI

Appendix D: Charlson Comorbidity Index (CCI)

The comorbidity index developed by Charlson et al. is a validated method of classifying comorbidity to predict short- and long-term mortality from medical records. It replaces direct measures of the severity of an illness, which require a prospective data collection. The Charlson index assigns weights for a number of major conditions present among secondary diagnoses. The index score is the total of assigned weights, and represent a measure of the burden of comorbid disease.

This index is a weighted measure that incorporates 19 different medical categories and each weighted according to its potential to impact on mortality. Those with a relative risk below 1.5 were assigned a weight of 1; conditions with a risk of 1.5 to <2.5 a weight of 2; conditions with a risk of 2.5 to <3.5 a weight of 3; and metastatic tumors and AIDS were assigned a weight of 6. The final score was calculated for each patient by taking into account all comorbid conditions present when the index was applied.

In the following table is reported the list of scored comorbidities with their relative weight in the scoring system and the ICD-9 codes.

Comorbid condition	ICD-9 codes	Weight
Ischemic heart disease	410, 410.1, 410.2, 410.3, 410.4, 410.5, 410.6, 410.7, 410.8, 410.9, 412	1
Congestive heart failure	398.91, 402.01, 402.11,402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4, 425.5, 425.7, 425.8, 425.9, 428.0, 428.1, 428.9	1
Peripheral vascular disease	093.0, 437.3, 440.0, 440.1, 440.2, 440.3, 440.8, 440.9, 441.0, 441.1, 441.2, 441.3, 441.4, 441.5, 441.6, 441.7, 441.9, 443.1, 443.8, 443.9, 557.1, 557.9, V43.4	1
Cerebrovascular disease	362.34, 430, 431, 432, 432.0, 432.1, 432.9, 433, 433.0, 433.1, 433.2, 433.3, 433.8, 433.9, 434, 434.0, 434.1, 434.9, 435, 435.0, 435.1, 435.2, 435.3, 435.8, 435.9, 436, 437, 437.0, 437.1, 437.2, 437.3, 437.4, 437.5, 437.6, 437.7, 437.8, 437.9, 438, 438.0, 438.1, 438.2, 438.3, 438.4, 438.5, 438.8, 438.9	1
Dementia	290.0, 290.1, 290.2, 290.3, 290.4, 290.8, 290.9, 291.0, 291.1, 291.2, 291.3, 291.4, 291.5, 291.8, 291.9, 294.1, 331.2	1
Chronic pulmonary disease	416.8, 416.9, 490, 491, 491.0, 491.1, 491.2, 491.8, 491.9, 492.0, 492.8, 493.0, 493.1, 493.2, 493.9, 494.0, 494.1, 495.0, 495.1, 495.2, 495.3, 495.4, 495.5, 495.6, 495.7, 495.8, 495.9, 496, 500, 501, 502, 503, 504, 505, 506.4, 508.1, 508.8	1
Rheumatologic disease	446.5, 710.0, 710.1, 710.2, 710.3, 710.4, 714.0, 714.1, 714.2, 714.8, 725	1
Peptic ulcer disease	531.0, 531.1, 531.2, 531.3, 531.4, 531.5, 531.6, 531.7, 531.9, 532.0, 532.1, 532.2, 532.3, 532.4, 532.5, 532.6, 532.7, 532.9, 533.0, 533.1, 533.2, 533.3, 533.4, 533.5, 533.6, 533.7, 533.9, 534.0, 534.3, 534.4, 534.5, 534.6, 534.7, 534.9	1
Mild liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570, 571.0, 571.1, 571.2, 571.3, 571.4, 571.5, 571.6, 571.8, 571.9, 573.3, 573.4, 573.8, 573.9, V42.7	1
Diabetes mild to moderate	250.0, 250.1, 250.2, 250.3, 250.8, 250.9	1

Comorbid condition	ICD-9 codes	Weight
Diabetes with chronic complications	250.4, 250.5, 250.6, 250.7	2
Hemiplegia or paraplegia	334.1, 342.0, 342.1, 342.8, 342.9, 343.0, 343.1, 343.2, 343.3, 343.4, 343.8, 343.9, 344.0, 344.1, 344.2, 344.3, 344.4, 344.5, 344.6, 344.9	2
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.0, 582.1, 582.2, 582.4, 582.8, 582.9, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 585, 586, 588.0, V42.0, V45.1, V56.0, V56.1, V56.2, V56.3, V56.8	2
Any malignancy, including lymphoma and leukemia	140.0, 140.1, 140.3, 140.4, 140.5, 140.6, 140.8, 140.9, 141.0, 141.1, 141.2, 141.3, 141.4, 141.5, 141.6, 141.8, 141.9, 142.0, 142.1, 142.2, 142.8, 142.9, 143.0, 143.1, 143.8, 143.9, 144.0, 144.1, 144.8, 144.9, 145.0, 145.1, 145.2, 145.3, 145.4, 145.5, 145.6, 145.8, 145.9, 146.0, 146.1, 146.2, 146.3, 146.4, 146.5, 146.6, 146.7, 146.8, 146.9, 147.0, 147.1, 147.2, 147.3, 147.8, 147.9, 148.0, 148.1, 148.2, 148.3, 148.8, 148.9, 149.0, 149.1, 149.8, 149.9, 150.0, 150.1, 150.2, 150.3, 150.4, 150.5, 150.8, 150.9, 151.0, 151.1, 151.2, 151.3, 151.4, 151.5, 151.6, 151.8, 151.9, 152.0, 152.1, 152.2, 152.3, 152.8, 152.9, 153.0, 153.1, 153.2, 153.3, 153.5, 153.6, 153.7, 153.8, 153.9, 154.0, 154.1, 154.2, 154.3, 154.8, 155.0, 155.1, 155.2, 156.0, 156.1, 156.2, 156.8, 156.9, 157.0, 157.1, 157.2, 157.3, 157.4, 157.8, 157.9, 158.0, 158.8, 158.9, 159.0, 159.1, 159.8, 159.9, 160.0, 160.1, 160.2, 160.3, 160.4, 160.5, 160.8, 160.9, 161.0, 161.1, 161.2, 161.3, 161.8, 161.9, 162.0, 162.2, 162.3, 162.4, 162.5, 162.8, 162.9, 163.0, 163.1, 163.8, 163.9, 164.0, 164.1, 164.2, 164.3, 164.8, 164.9, 165.0, 165.8, 165.9, 170.0, 170.1, 170.2, 170.3, 170.4, 170.5, 170.6, 170.8, 171.0, 171.2, 171.3, 171.4, 171.5, 171.6, 171.7, 171.8, 171.9, 172.0, 172.1, 172.2, 172.3, 172.4, 172.5, 172.6, 172.7, 172.8, 172.9, 174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9, 175.0, 175.9, 176.0, 176.1, 176.2, 176.3, 176.4, 176.5, 176.8, 176.9, 180.0, 180.1, 180.8, 180.9, 182.0, 182.1, 182.8, 183.0, 183.2, 183.3, 183.4, 183.5, 183.8, 183.9, 184.0, 184.1, 184.2, 184.3, 184.4, 184.8, 184.9, 186.0, 186.9, 187.1, 187.2, 187.3, 187.4, 187.5, 187.6, 187.7, 187.8, 187.9, 188.0, 188.1, 188.2, 188.3, 188.4, 188.5, 188.6, 188.7, 188.8, 188.9, 189.0, 189.1, 189.2, 189.3, 189.4, 189.8, 189.9, 190.0, 190.1, 190.2, 190.3, 190.4, 190.5, 190.6, 190.7, 190.8, 190.9, 191.0, 200.0, 200.1, 200.2, 200.8, 201.0, 201.1, 201.2, 201.4, 201.5, 201.6, 201.7, 201.9, 202.0, 202.1, 202.2, 202.3, 202.4, 202.5, 202.6, 202.8, 202.9, 203.0, 203.1, 204.0, 204.1, 204.2, 204.8, 204.9, 205.0, 205.1, 205.2, 205.3, 205.8, 205.9, 206.0, 206.1, 206.2, 206.8, 206.9, 207.0, 207.1, 207.2, 207.8, 208.0, 208.1, 208.2, 208.8, 208.9, 238.6	2
Moderate or severe liver disease	456.0, 456.1, 456.2, 572.2, 572.3, 572.4, 572.8	3
Metastatic solid tumor	196.0, 196.1, 196.2, 196.3, 196.5, 196.6, 196.8, 196.9, 197.0, 197.1, 197.2, 197.3, 197.4, 197.5, 197.6, 197.7, 197.8, 198.0, 198.1, 198.2, 198.3, 198.4, 198.5, 198.6, 198.7, 198.8, 199.0, 199.1	6
AIDS	0.42	6

Age also was determined to be a significant contributing factor for overall survival and was subsequently incorporated into the Charlson comorbidity score to create a single index accounting for both age and medical comorbidity, the Age-Adjusted Charlson Comorbidity Index (ACCI). This modification to the Charlson index included the age of patient as a correction variable of the final score. For each decade after 40 years, a point is added: 1 point for age group 41-50 years, 2 points for age group 51-60 years, 3 points for 61-70 years and 4 points for 71 years or older.
The table below shows the points added to the score according to the age group of belonging.

Scoring Age:

Age groups	Points
< 40 years	0
41 – 50 years	1
51 – 60 years	2
61 – 70 years	3
71 – 80 years	4

The overall score represents the weighted summation of their medical conditions with a high score representing a higher medical comorbidity. Patients were dichotomized into three groups by ACCI score: low score (0-1), mild score (2-3), severe score (≥4).

Appendix E: Statistical Methods

In many studies the variable of direct interest is the length of time that elapses before some event occurs. This event may be death, or death due to a particular disease, and for these reason the analysis of such data is often referred as *survival analysis*.
Survival times are then data that measure follow-up time from a defined starting point to the occurrence of a given event, for example the time from the beginning to the end of a remission period or the time from the diagnosis of a disease to death or, as in this study, the time from treatment of antiosteoporotic drugs initiation (index date) to discontinuation of therapy.
A survival time is described as censored when there is a follow-up time but the event has not yet occurred or is not known to have occurred. Then, such survival times are termed censored, to indicate that the period of observation was cut off before the event of interest occurred.
Standard statistical techniques cannot usually be applied to survival data because the underlying distribution is rarely normal and the data are often 'censored'.
In analyzing survival data, two functions that are dependent on time are of particular interest:

- the *survival function* S(t) that is defined as the probability of surviving at least to time t;
- the *hazard function* h(t) that is the conditional probability of dying at time t having survived to that time.

The graph of S(t) against t is called the *survival curve*.

Kaplan Meier Method

The Kaplan-Meier method can be used to estimate the survival curve from the observed survival times without the assumption of an underlying probability distribution: from a set of observed survival times (including censored times) in a sample of individuals, it is possible to estimate the proportion of people who would survive a given length of time under the same circumstances. The Kaplan-Meier method allows a table and a graph to be produced; these are referred to as the life table and survival curve respectively.
To determine the Kaplan–Meier estimate of a survival function, a series of time intervals is formed. Each of these intervals is constructed to be such that one observed death is contained in the interval, and the time of this death is taken to occur at the start of the interval. A plot of the Kaplan–Meier estimate of the survival function (Figure 1) is then a step function, in which the estimated survival probabilities are constant between adjacent death times and only decrease at each death.

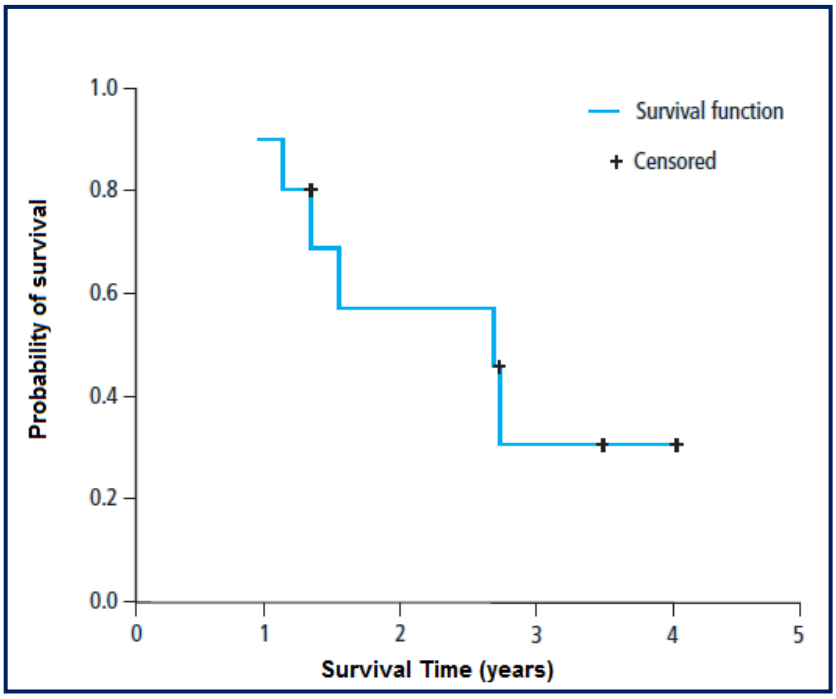

Figure 1. Kaplan-Meier estimate of the survival function

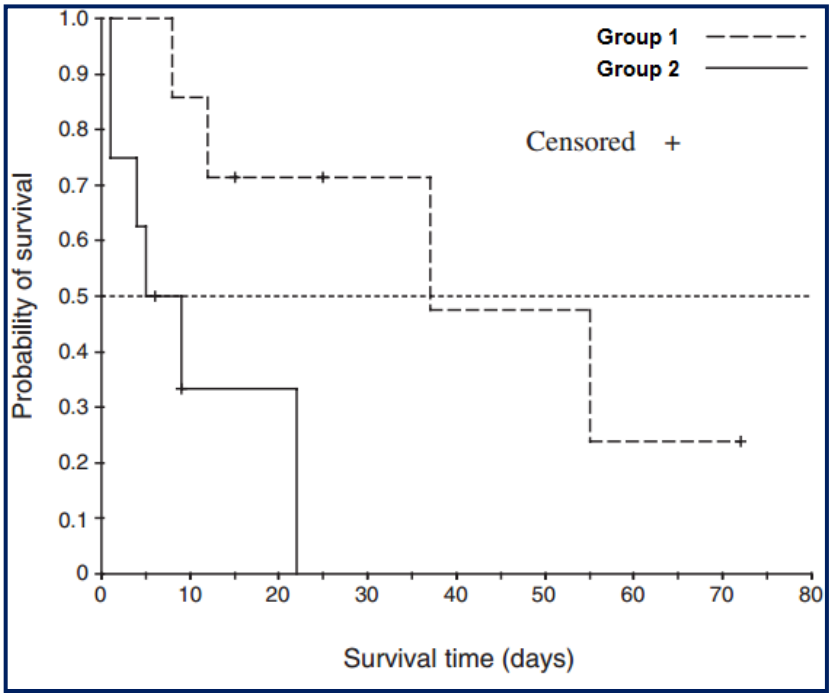

Figure 2. Survival curves for two different groups

An important part of survival analysis is to produce a plot of the survival curves for each group of interest (for example, persistent and non-persistent group). However, the comparison of the survival curves of groups (Figure 2) should be based on a formal non-parametric statistical test called the *log-rank test* and not upon visual impressions. The log-rank test is used to test the null hypothesis that there is no difference between the population survival curves (i.e. the probability of an event occurring at any time point is the same for each population).

The log rank test is used to test whether there is a difference between the survival times of different groups but it cannot be used to explore (and adjust for) the effects of other explanatory variables to be taken into account. Adjustment for variables that are known to affect survival may improve the precision with which we can estimate the treatment effect.

Cox's proportional hazards model

The Cox model is a well recognized statistical technique for analyzing survival data. It is based on a modeling approach to the analysis of survival data. The purpose of the model introduced by Cox is to simultaneously explore the effects of several variables on survival. It is also known as *proportional hazards regression analysis*.

Cox's proportional hazard model is analogous to a multiple regression model and enables the difference between survival times of particular groups of patients to be tested while allowing for other factors. In this model, the response (dependent) variable is the "hazard". The hazard is the probability of dying (or experiencing the event in question) given that patients have survived up to a given point in time, or the risk for death at that moment.

A Cox model must be fitted using an appropriate computer program (such as SAS, STATA or SPSS). The final model from a Cox regression analysis will yield an equation for the hazard as a function of several explanatory variables.

Interpreting the Cox model involves examining the coefficients for each explanatory variable. A positive regression coefficient for an explanatory variable means that the hazard (risk of death) is higher, and thus the prognosis worse. Conversely, a negative regression coefficient implies a better prognosis for patients with higher values of that variable. The *p*-values indicate if the difference between different groups is or not statistically significant and if the 95% confidence interval for the hazard ratio includes 1, it suggests no difference in survival.

Cox regression is considered a semi parametric procedure because the baseline hazard function, $h_0(t)$, (and the probability distribution of the survival times) does not have to be specified. Because the hazard function is not restricted to a specific form, the semi-parametric model has considerable flexibility and is widely used.