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ASSESSING HEALTHCARE PATHWAYS

BY MEANS ADMINISTRATIVE DATA

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To my husband

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Abstract

The burden of a condition, illness or risk factor on the population is a fundamental issue in Public Health and evaluating this burden appears to be necessary to improve health systems and policies, and to help decision makers for a better allocation of public resources. Several measures used to quantify the burden of disease can also be used to assess and quantify the impact of a healthcare intervention. In particular, the population attributable fraction allows to determine the number of disease's cases that would be avoided or prevented if a particular risk factor was removed. Clinical Pathways are composed by several evidence-based healthcare intervention and are considered both as tool for patients' care and as a way to describe the structure of a care process that is worldwide used to make care processes transparent and to improve the efficiency and quality of health care. However, the real impact of these pathways on several clinical outcomes, in particular in outpatient settings, is a little explored field. If we consider the subject's adherence to recommendations contained in Clinical Pathways as a 'gold standard' of healthcare to avoid adverse clinical events/complications, the condition of 'non-adherence' represents a risk factor that could be controlled and limited, if not even removed.

The aim of this thesis is to assess the impact of healthcare interventions for specific health conditions, from the Public Health point of view, in terms of (i) size of the problem, (ii) process of care and (iii) association between process and outcomes. To this purpose, this thesis is composed of four parts that lead to explore the main issue of this work and to understand how we can measure the impact of some healthcare interventions on subjects affected by several chronic conditions.

In the first part of this thesis, an introduction to the concept of *Burden of Disease* is provided, with a summary of several measures commonly used in different research settings for its evaluation. This concept can be applied also to the healthcare intervention assessment, as described in Chapter 2.

The second part describes *Clinical Pathways* (CPs) and their use in the healthcare. This part also introduces an Italian project aimed to assess the impact of several pathways on patients' clinical outcomes. In this project, outpatient CPs are used to compare different Regional Health Systems from the point of view of the accountability: in this way, each Regional System will be made responsible for both (i) the quality of healthcare deliver (with process-of-care indicators assessment) and (ii) the clinical results following the health services provided (with the outcome indicators evaluation).

Finally, a new assessment proposed by this project in order to identify the process indicators that are associated with the outcomes is explained.

Then, the third part explains some methodological aspects I learned about in these years, from data sources (large administrative databases) to study designs and statistical analysis used for retrospective observational studies, up to deepening the population attributable fraction measure and its different applications. This last measure, usually used to assess the burden of a disease/risk factor on the population, is used in this thesis to quantify the proportion of outcomes that can be avoided if all subjects would not be exposed to a risk factor, such as an inappropriate drug prescription or a 'non-adherent' behavior.

The last part reports three studies conducted during my PhD course that, from different points of view, explore the concept of the impact of healthcare interventions in different clinical contexts. In the first study, we evaluated the population attributable fraction of several concomitant drugs' use on a specific clinical outcome. In this context, the population attributable fraction calculated indicates the number of outcomes that could be prevented with more careful prescription patterns. The second study reports methods and main findings of the validation study of the approach proposed for Italian monitoring process-of-care project. In particular, the implications of this approach are discussed. The third study (work in progress) applies the concept of population attributable fraction to the approach used in the previous study. In this work, we consider the condition of 'non-adherence' to the CP as a risk factor for disease-specific outcomes and the population attributable fraction that represents the number of cases that could be avoided if all subjects would be adherent, to some extent, to that CP.

Part I

Introduction

Chapter 1

Measuring the *burden of disease* in Public Health

The impact (burden) of a condition, illness or risk factor on the population is a fundamental issue in Public Health and evaluating this burden appears to be necessary to improve health systems and policies. In health literature, the composite impact of the number of cases and the cases' severity (and the associated economic impacts) is frequently referred to the *Burden of Disease* (BOD) concept. In general, the BOD is composed by an evaluation of the epidemiologic data describing the illness and a subsequent analysis of health effects in terms of their impact on public health and society (1,2). It emerges from the literature that BOD analysis is crucial to (i) define healthcare and research priorities, (ii) identify disadvantaged groups, (iii) provide comparative measures, and (iv) evaluate and plan health interventions and programs (3), for supporting decision makers in allocation of available resources.

Since 1991, the World Bank and the World Health Organization (WHO) have translated the Burden of Disease concept into the "Global Burden of Disease Study", with the aim of quantifying the impact of premature mortality and disability caused by the main pathologies or groups of diseases. To achieve this goal, 107 medical conditions and 10 risk factors were studied in eight different regions of the world, stratifying the population by age and sex (4).The main results that emerged from this study [Figure 1] show how the epochal changes that have affected the world in the past 20 years (from 1990 to 2010) also have repercussions on the health of the population. In general, there is a decrease in the incidence of infectious diseases and an increase in the incidence of chronic-degenerative diseases. In particular, life expectancy has grown globally, but above all life expectancy in health has increased, i.e. the years of life without disability. Fortunately, there has been a reduction in the risk situations related to infectious diseases of childhood, with a consequent improvement in health in the lower age group. Finally, the projection for 2030 indicates the near explosion of psychiatric diseases in an almost epidemic form.

The assessment of the BOD is composed by two main steps (1,2). The first consist in the assessment of available epidemiological data to accurately estimate the number of disease cases and evaluate the strength and weakness of this data, with particular attention to possible sources of bias that may influence the results. The second step is formed by the analysis of disease's effects in terms of impact

on health and society, by (i) evaluating symptoms (frequency and duration) in sick individuals, (ii) identifying the degree of disability that affects the ill subjects and (iii) quantifying the loss of work productivity associated with a disease condition.

Optimally, the BOD measures should have certain characteristics to ensure their usefulness (3). First, a useful measure of the effectiveness of public health interventions could detect either an absolute or a relative change in health status over time, such as mortality rate which can be expressed as raw (absolute sense) or as a percentage (relative sense). Second, a key concept for the adequacy of a measure is validity, the extent to which the indicator measures what it should measure. Third, the population health measure should be sensitive to major health policy changes. Fourth, the measure should be reliable, stable over time and equivalent across settings.

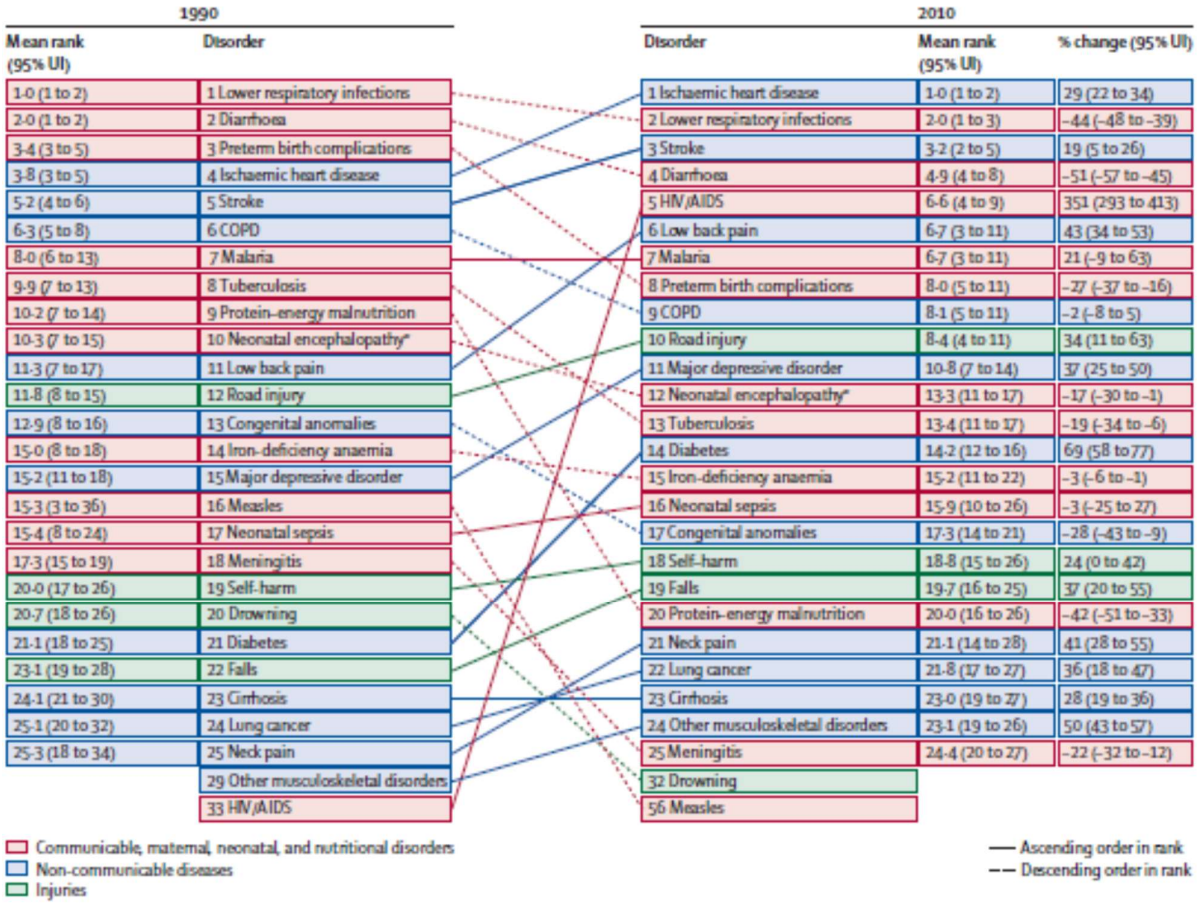


Figure 1. Global disability-adjusted life year ranks with 95% UI for the top 25 causes in 1990 and 2010, and the percentage change with 95% UIs between 1990 and 2010. Adapted from Murray et al. (2012)
*UI=uncertainty interval. COPD=chronic obstructive pulmonary disease. *Includes birth asphyxia/trauma.*

The BOD measures can be classified into three categories: (i) the ‘primary measures', such as prevalence, incidence and mortality, are measures that depict the severity of the illness; (ii) the so-called 'composite measures’, other than a combination of the ‘primary measures'; and (iii) the economic and monetary measures.

Through this thesis, I focus the attention on those measures of our interest, namely the category of measures that can be used to assess frequency and severity of a disease. In particular, measures of disease frequency are used to describe how common an illness (or other health event) is, with reference to the size of the population (the population at risk) and to a measure of time. There are two main measures of disease frequency: prevalence and incidence.

The severity of a disease can be assess using measures of (i) mortality and morbidity, (ii) years of life lost due to death, (iii) years lived with disability, and (iv) attributable fraction.

Prevalence

Prevalence measures the proportion of individuals in a defined population that have a disease or other health condition/outcome of interest at a specified point in time (point prevalence) or during a specified period of time (interval or period prevalence) (5). It is usually expressed as a fraction, a percentage, or as the number of cases per 10,000 or 100,000 people.

Prevalence is a useful measure for quantifying the burden of disease in a population at a given point in time, but it is not a useful measure for establishing the determinants of disease in a population. Calculating prevalence of various conditions across different geographical areas or amongst different sub-groups of the population and then examining prevalence of other potential risk factors can be of particular use when planning health services.

Incidence

In contrast to prevalence, incidence is a measure of the number of new cases of a disease (or other health condition/outcome of interest) that develops in a population at risk during a specified time period. Since this quantity includes all individuals who become cases over the entire interval, it is sometimes referred to as the cumulative incidence proportion. To be “at risk” can mean that an individual has previously been unaffected by the disease, or that susceptibility has been regained after previously contracting the disease and recovering (5).

The incidence risk assumes that the entire population at risk at the beginning of the study period has been followed for the specified time period for the development of the outcome under investigation.

However, in some study participants may be lost during follow-up (for migration, death, refusal to continue the study). To account for these variations during follow up, a more precise measure can be calculated, the incidence rate. Incidence rates also measure the frequency of new cases of disease in a population. However, incidence rates take into account the sum of the time that each person remained under observation and at risk of developing the outcome under investigation.

Mortality and morbidity rates

Mortality rate, or death rate, is a measure of the number of deaths (in general, or due to a specific cause) in a particular population, scaled to the size of that population, per unit of time. Mortality rate is typically expressed in units of deaths per 1,000 individuals per year.

Morbidity rate (from Latin *morbidus*, meaning 'sick, unhealthy') indicates a diseased state, disability, or poor health due to any cause. The term is used to refer to non-fatal outcomes, as hospitalization rates, and includes the evaluation of disability degree.

Population attributable fraction

The population attributable fraction (PAF) quantifies the contribution of a risk factor to a disease or a death (6). PAF is the proportional reduction in population disease or mortality that would occur if exposure to a risk factor were reduced to an alternative ideal exposure scenario (eg. no tobacco use). As a result, PAFs for individual risk factors often overlap and add up to more than 100 percent. For a specific description of this particular measure, see Chapter 7.

Chapter 2

The impact of healthcare interventions

In public health, in addition to assessing the burden of a disease or condition, the evaluation of the impact of health interventions is also important to measure both the appropriateness of care provided and the performance of healthcare system. This aspect is implemented in the analysis of the process following the taking charge of the patient with an illness, conducted with specific indicators that evaluate the diagnostic, therapeutic and care procedures to which the patients are subjected during their care plan. This framework makes the evaluation of the adherence to guidelines possible, measuring the gap between the expected process and the observed therapeutic path.

The identification of process indicators can be facilitated by the scientific literature, which, especially for the main diseases (both chronic and non-chronic ones), offers a large number of evidence-based guidelines. The implementation of such guidelines at patient level defines the clinical pathway (CP) of a subject.

2.1 Definition of Clinical Pathways

Some evidence suggests that the creation of guidelines is inadequate (7–9) as passive dissemination alone rarely results in changes in practice (10,11). Estimates across the healthcare environment suggest that 30–40% of patients do not receive treatments with proven effectiveness (12). One promising method of minimizing this gap is the implementation of clinical pathways (13).

Clinical Pathways (CPs) represent the application of evidence-based guidelines related to a clinical condition, in a specific organizational context of a health authority, considering the resources available. CPs are local models that, based on the more recent guidelines and in relation to the available resources, allow the analysis of differences between an expected situation and the one observed to improve quality. They are also tools that allow healthcare companies to outline the best path that is possible, within their own organizations, for a specific clinical problem (14).

Therefore, the identification and development of CPs is becoming increasingly important as an instrument aimed at assessing continuity of care and implementing guidelines, to ensure a stable and complete action of take charge of the patient.

As stated by Degeling et al. (15), a clinical pathway represents a method to achieve a result. A pathway is a tool for empowering clinicians to strike a balance between the clinical and resource dimensions of care and between the requirements of both clinical autonomy and transparent accountability. The team's perspective is essential. Pathways provide a basis for re-establishing "responsible autonomy" as the primary organising principle of clinical work. If multidisciplinary teams, including both clinicians and managers, do not work together on the re-organisation of healthcare, all parties will continue to be driven by the distrust and related crises of confidence that pervade the field (15).

CPs have been implemented in a wide range of healthcare systems, mainly to improve the efficiency of hospital care while maintaining or improving quality. The first systematic use of CPs took place in 1985 at the New England Medical Center in Boston (USA), after the introduction of Diagnosis Related Groups (DRGs) in 1983 (16). To each DRG a reference length-of-stay (LOS) and a budget are typically assigned. CPs, as a method for monitoring processes and processing time, were introduced for reducing LOS and managing costs. In the late 1990's, more than 80% of US hospitals used some pathways (17), while CPs were introduced in the early 1990's in the UK (16,18). CPs, or integrated care pathways as they are called in the UK, are considered to be tools for designing care processes, improving clinical governance and the quality of clinical care, and ensuring that delivered care is based on the latest research (19–21). From the late 1990's, CPs have been disseminated all over the world (16) and nowadays are used worldwide as a tool used to structure/design and improve care processes within the patient-centered care concept (22,23).

Although they have been in use for more than 30 years, there is still uncertainty about the issue of CPs, in particular concerning their definition, their actual use, their knowledge and diffusion, the methods used for their development and implementation and their effects on outcomes (clinical and otherwise) (24).

Recently, 17 different nouns have been found to that describe the concept of CP (20), the most frequently used are *clinical pathway*, *critical pathway*, *integrated care pathway*, and *care map* (25,26). A literature review found more than 80 different definitions of CPs in Medline literature, published between 2000 and 2003, which differ from one another according to the purpose and scope of application for which they were developed (26).

Some evidence exists to support the use of CPs to change behaviour and improve quality of care (8,9,27–29). A Cochrane systematic review on the use of CPs in hospitals indicates that CPs reduce in-hospital complications and improve documentation (30).

Today (and in this thesis), we refer to the definition of CP contained in the "*Piano Nazionale per il Governo delle Liste d'Attesa*" (PNGLA) 2012-2014, which characterizes the CP as: "A pre-defined, articulated and coordinated sequence of services provided to patients, at in/out-hospital/territorial level, which involves the integrated participation of various specialists and professionals (in addition to the patient himself), in order to achieve the most appropriate diagnosis and therapy for a specific pathological situation" (31).

Thus, CPs consist in the set of activities provided by different healthcare professionals to answer the patient's demand, from the diagnosis to the problem solution or to the end of life. For some pathologies, the network of services to be activated is limited to a single hospital organizational structure with little interdependence with other operating units or hospitals. For example, for subjects affected by Non-Hodgkin lymphoma the operative unit of Hematology provides most of the diagnostic and therapeutic services. On the other hand, other clinical conditions, as COPD or oncological diseases, refer to many services between hospital and territory.
It can be said that the objective of a CP is the condition of health/the health problem of the patient, and that it is the sum of heterogeneous health and welfare processes (prevention, diagnosis, treatment and follow-up) of different nature regarding a professional, organizational and logistic point of view. Furthermore, CPs can be evaluated, in its entirety or in specific sub-processes, with respect to effectiveness, efficiency and equity (possibility to intercept the entire population of patients affected by the same need for health protection). Clinical pathways and the concept of clinical governance shared a common aspect: the definition of behavior and expected standards in patient's management is found both in the literature about the implementation of clinical governance strategies and in that focused on CPs (32).

2.2 How to design a Clinical Pathway

The realization of a CP consists of four phases that refer to the known (plan, do, check, act): analysis, re-organization, change management, monitoring (33,34).
Phase 1: context analysis.
This step provides the recognition of the "in-use methods" of taking charge of a specific disease/health condition and it is carried out using both qualitative and quantitative methods of

analysis. Qualitative analyses are aimed to understand the current management of the patient within the organizational structures of one or more healthcare companies (35). Quantitative investigations are conducted retrospectively and are intended to (i) intercept the population carrying a specific health-care need; and (ii) record the consumption of services provided in the past. The analysis is performed using the administrative flows contained in the operating systems of healthcare companies.

Phase 2: re-organization of care processes.

Following the first phase, some phenomena that require interventions of various kind (professional, organizational, economic) usually emerge. The issue that characterizes this phase concern the reference standards with regard to which the existing reality can be monitored. These standards are usually found in professional guidelines or studies *ad hoc*. This second phase usually produces a document, shared with all the actors involved, which defines the objects of change that the CP proposes and the subjects with responsibility for the expected results.

Phase 3: change management.

Once the areas of change have been defined, it starts a management phase that, using the resources available in the healthcare company, is able to achieve the objectives defined in the previous phase. At this point it is very important to appropriately select tools to support the desired change.

Phase 4: change monitoring.

In the last phase, it is opportune to evaluate (quantitatively) the results achieved by redesign and monitor CPs over time, with the aim of analyzing the benefits associated with the implementation of the pathway. The time necessary for the assessment of performances and tools adopted depends on (i) the content of the objects of change, and (ii) the time for the change management tools to be effective. The mechanisms used to evaluate the CP should be as routine as possible, to easily ensure subsequent checks.

2.3 Territorial Clinical Pathways: the problem of chronicity

It is opportune to focus the attention on some aspects that characterize the territorial services (36):

• they focus on prevention and self-directed medicine;

• they support permanent patient care;

• they highlighted the importance of integration between health action and social/health welfare.

Today, initiatives that promote preventive care in a broader sense appear more and more numerous: in addition to traditional primary and secondary prevention activities, the efforts of local health services are focusing on those ideas that can slow down the disease evolution process or can preserve

patients' health conditions. Moreover, new models of care that enhance the continuity of relationship between patients and health services have been implemented. These models of care have developed from three emerged phenomena in today's society: (i) the aging of population, with consequent increase in chronic diseases; (ii) the evolution of diagnostic technologies, with the possibility of early diagnosis compared to pathologies with a high social impact; and (iii) the transfer of services previously provided in hospital to the territorial setting, based on assessments of organizational appropriateness, technological progress and the pushes of cost containment. These situations are associated with the evidence that for some health needs, the evolution of the disease is accompanied by the worsening of socio-environmental fragility conditions; then, this aspect generates the necessity to integrate health and social interventions.

Developing CPs seems to be more complicated in territorial than in hospital settings, in particular regarding the four phases above described. First of all, there are not standardized methodologies to intercept the patients' cohorts and specific algorithms should be created to query administrative databases for estimating the population affected by a disease or a specific health condition (37). Another critical aspect about territorial CPs is related to their contents. In fact, territorial CPs largely concern chronic pathologies. The WHO defines chronic diseases as *noncommunicable diseases (NCDs)*, or *diseases of long duration and generally slow progression* (38). Therefore, these are long-period pathologies with a necessary constant monitoring, to avoid their exacerbation and subsequent hospitalization. In this context, a multidisciplinary approach between primary and non-primary care professionals is more than ever necessary.

Chronic diseases, as hypertension or diabetes, that in the past were almost completely managed by hospitals, currently are managed by territorial services. In order to support this transfer process of care setting, first organizational models of services dedicated to chronic pathologies were born. In particular, territorial services must face with two new situations: (i) the *new chronic*, or new chronic conditions induced by the innovation of knowledge and technology, these are diseases, such as some tumors, which, thanks to new diagnostic and therapeutic solutions, have turned from acute - with high mortality - into chronic diseases with high survival rates; and (ii) the *high complexity chronicity*, i.e. chronic diseases that require constant interchange between hospital and territory as they can have acute events in the chronic course of the disease. These diseases therefore require specialized skills and high cost resources in addition to the traditional monitoring and follow-up functions of territorial services. These health issues ask health systems important questions regarding the roles/projects of integration between hospital and territory.

2.4 Italian experiences of Clinical Pathways

A recent research was carried out by FIASO (Federazione Italiana Aziende Sanitarie e Ospedaliere) and the Politecnico di Milano's School of Management in 2014 to evaluate the spread and the characteristics of CPs in Italy (39). This research involves several health facilities located in 14 Italian Regions: 26 Local Health Units, 14 hospitals, 2 Institutes for Treatment and Research e 1 Regional Emergency Management Structure. A total of 338 CPs were identified, involving mainly 25 clinical areas: oncology, cardiology, neurology, endocrinology (of which thyroid diseases account for 16%, while the remaining 74% refers to CPs about diabetes), and the respiratory system (Figure 2). The regions with the greatest number of pathways are Lombardy (129 CPs), Emilia Romagna (67), Tuscany (40) and Lazio (26).

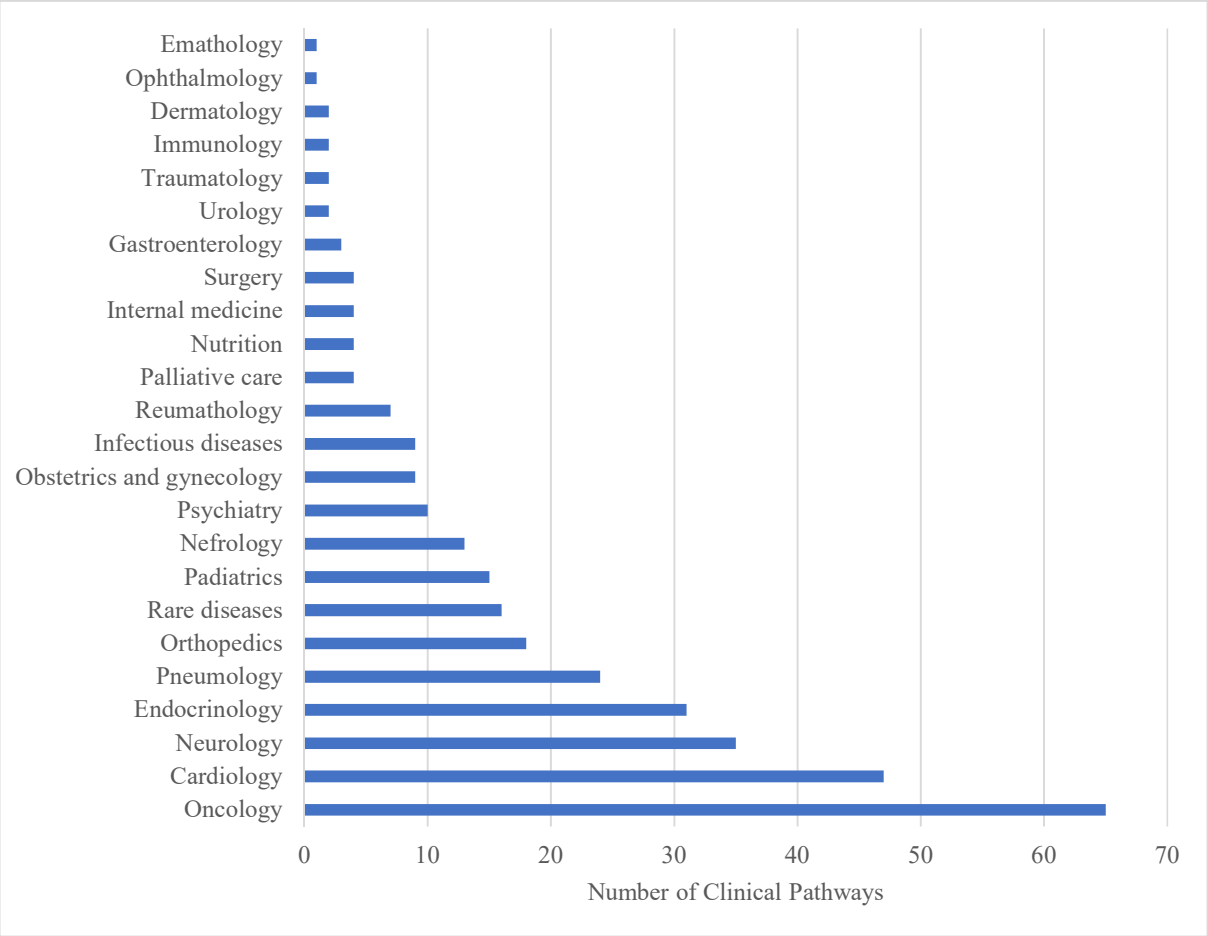


Figure 2. CPs clinical areas in Italy. Adapted from FIASO report.

Considering the patients involved by a single pathway, 51% of CPs is aimed at almost all patients with the specific disease, 21% covers 50-75% of the total number of ill patients, while only 20% of CPs can be defined as "almost experimental" as it addresses a small part of the patients' need.

Within the considered sample, most of the CPs are defined at individual facility level (52%) or at most by groups of facilities (34%), which collaborate to define common diagnostic-therapeutic pathways. CP application involves almost in all cases the hospital component, which provides services related to the paths in 41% of cases while 52% of the CPs is integrated between hospital and territory. Only in few cases, the application of CPs is limited to a single Operating Unit (2%) or only to the territory services (5%).

In general, this research showed a consistency between the point of application of pathways and the professionals involved in the supply of services: hospital staff is constantly involved, given the greater application of CPs in hospitals, but the shift of CPs towards the territory leads to a more balanced involvement of all the figures. Specifically, the 176 pathways that involve both hospital and territory mean the collaboration of hospital staff (93%), outpatient specialists in the area (88%), General Practitioners (GPs, 85%) and other social welfare organizations (37%). The pathways applied at the facility level always involve the hospital staff but only to a lesser extent specialists, GPs and other local organizations. On the other hand, territorial CPs always expect the presence of GPs, and the presence of the outpatient specialists is very significant (63%).

Chapter 3

Objective

The aim of this thesis is to assess the impact of specific health conditions, in terms of (i) size of the problem, (ii) process of care, and (iii) association between process and outcomes.

In order to reach this goal, I analyzed the measure of attributable fraction as a technique to evaluate the impact of a condition or a risk factor on the population, and its application in different study settings. I then went further into the topic of clinical pathways (CP) as a tool to evaluate the impact of health interventions and, more specifically, the Italian project of analysis and evaluation of these pathways. Finally, I applied both methodologies (attributable fraction and CP assessment) to evaluate the overall impact of health interventions on the population.

Part II

Clinical pathways and basic levels of care

Chapter 4

Clinical Pathways: an Italian project

The assessment of health services, both hospital and territorial, is one of the most critical dimensions of quality assessment in the health care, as it should combine (i) the need for health of the population, (ii) the quality of care processes, and (iii) the need for effectiveness, efficiency and resources' proper use. For this purpose, the concept of Basic Levels of Care (in Italian "Livelli Essenziali di Assistenza", LEA) was introduced in 2001 in Italy. They represent the set of services that the National Health Service (NHS) is required to provide to all citizens, free of charge or on payment of a fee, in order to ensure uniform conditions throughout the country (40). The Basic Levels of Care, therefore, allow to guarantee a homogeneous health service to all citizens in terms of amount and quality of services and to identify the correct supply of health services.

The Agreement between Government, Regions and Autonomous Provinces of Trento and Bolzano of 10th July 2014, concerning the Health Pact for years 2014-2016, underlines the need for the Ministry of Health "to implement an adequate evaluation system of the quality of care and of the assistance uniformity in the national territory in order to continuously monitor the effectiveness and efficiency of the services […]". The same Agreement provides for the updating of the decree dated 12th December 2001, about the "Guarantee system for health care monitoring ", and for approval of the health care monitoring methodology.

In compliance with the indications just mentioned, the Health Planning Directorate General of the Ministry of Health described the purpose, structure and application methods of the national New Guarantee System (NGS). It is defined as a descriptive system created with the purpose of evaluation, monitoring and assessment of the health care provided by public and private organizations in all the regions, including the regions with special status, and the autonomous provinces of Trento and Bolzano. The NGS is made up of a set of indicators related to the three macro-levels of care (collective prevention and public health, territorial care, hospital care) and provides for the monitoring and evaluation of Clinical Pathways (CP) for specific health conditions.

4.1 Healthcare assessment: major issues

Randomized controlled clinical trials (RCTs) are considered as the most reliable method for generating evidence on the efficacy of medical interventions, first of all in clinical pharmacology

setting. For some decades, however, the scientific community believes that RCTs are not adequate in decision-making because they cannot capture the impact of care in the current clinical practice. The distance between the evidence generated in a controlled but artificial environment, typical of the RCTs, and their actual impact in the so-called real world can be explained by same factors: (i) the complexity of the therapeutic regimens; (ii) the demographic and clinical heterogeneity of patients; (iii) the prolongation of many therapies over time; and (iv) the often-questionable adherence of prescribers to clinical guidelines, as well as that of patients to physician's recommendations.

The typical approach to healthcare assessment is the so-called service-based approach that consider the single service provider under surveillance. This approach is based on providers' comparison with a performance evaluation, in order to identify the best practices on which to base the system growth and improvement. The performances evaluation and comparison among services dedicated to the same category of services represent a useful tool for governance of local health system. To assess properly the complex healthcare provision system a periodic revision and a validation of benchmarks and basic standards are needed. This evaluation system is also fundamental for innovation processes implementation and allows for best clinical practice detection and for performance comparison among healthcare units. Nevertheless, the performance evaluation considering the activity of a service provider as independent by other providers' activity is not completely acceptable, even if this evaluation can be intrinsically useful to the decision process.

In the process of quality of care assessment, the two approaches now outlined (RCTs and the service-based approach) should be considered necessary but not sufficient to meet the information needs of institutional stakeholders. They are both necessary because (i) solid evidence of efficacy and safety must be provided for the registration of a new therapeutic device, and in this case RCTs do not find valid alternatives, and (ii) for the accreditation and evaluation of a healthcare provider, the NHS must necessarily ascertain its quality by measuring its structural and process characteristics. At the same time, they both are not sufficient because (i) RCTs are not able to predict the impact of therapeutic interventions on clinical practice, and (ii) the attention of the NHS must be directed not only to providers' quality but also to the citizen-beneficiary of the NHS, evaluating the appropriateness of the whole clinical pathway, its usefulness (for the patient) and sustainability (for the NHS).

4.2 A real-world based approach

A new approach is necessary to overcome and solve the issues discussed above. This approach should be centered on the patient, his/her clinical history and his/her health and social needs. Indeed, the

health of each subject that benefices of NHS depends not only from a single device or therapeutic action, nor from services offered by individual accredited providers, but it is the result of the whole pathway that involves the patient as a carrier of (complex) needs. This pathway needs a close integration between health and social services. All these aspects inspire an innovative, real-world based approach that could be able to harmonize the evaluation of medical interventions and health care, and to fill the knowledge gaps of institutional stakeholders (as the Ministry of Health, Regional Health Directorates, Italian Drug Agency).

The evaluation of clinical pathways in the real world is characterized by three main aspects. First of all, it is certainly not an alternative to both the evaluation of medical interventions through RCTs and the evaluation of service-centered care, rather it can be considered a complementary approach. Furthermore, it is patient-centered and implies the analysis of all patients' contacts with NHS' services (that represents the CP). Finally, it is a versatile approach because (i) it can be adapted both to the evaluation of a single treatment, as well as of the whole CP, (ii) it can be used to assess both the appropriateness of the process, as well as the impact of the CP on clinical outcomes, and (iii) it is implicitly oriented to the economic sustainability of the system.

These characteristics suggest that the present approach can be suitably included in three different contexts:

- in the clinical research framework, as it implies that the observation unit is represented by the individual subject, assessing the effectiveness and safety of a treatment. By analogy with the evaluation of medical interventions, this approach is aimed at providing further knowledge (i) on expected effects of a therapeutic treatment used in clinical practice, and (ii) on the most appropriate diagnostic, therapeutic and clinical pathway to be prescribed to a patient with specific personal and clinical features;
- in public health setting, as a government tool that can be used to combine citizens' health and the sustainability of the system. By analogy with the evaluation of health care, the approach is thus aimed at providing the decision maker with sufficient elements (about care systems' organization, the reimbursement of a therapeutic treatment, or a new and innovative reimbursement system) able to reduce the uncertainty inside every decision;
- in real-world evidence (RWE) area, because it is able to produce "credible" evidence on the best way to treat patients in the future, from patients' past experiences of healthcare received and clinical results observed in the real world. To provide RWE it is necessary to have data taken from the real-world data (RWD). Therefore, considering the complexity of new drugs and new therapeutic

strategies, as well as their high costs, the RWE is one of the fundamental key points for a proper governance, with the conduct of a valid clinical research, of course.

4.3 The Italian experience

The Italian project related to monitoring and evaluation of CPs and Basic Levels of Care is inserted in this more general and overall context.

The evaluation of CPs at Regional and National level is carried out in terms of appropriateness, clinical outcome, equity and economic impact. The general aim of this Italian project is to compare the different care models for some chronic and acute diseases in order to identify the best strategy in terms of effectiveness, cost-effectiveness and economic sustainability. Therefore, this project wants to highlight the gap between what is observed in the real world and what would be expected from clinical guidelines.

The evaluation is carried out on two levels that are different but connected to each other:

- the patient level, in terms of (i) needs/health demand measure (i.e., estimate of the prevalence or identification of cohorts of subjects who are affected by a specific chronic disease), and (ii) classification of patients affected by a condition/illness according to severity and other determinants of resource consumption;
- the healthcare intervention, in relation to (i) the measure of the treatment process, (ii) the measure of outcomes of a specific CP, and (iii) the estimation of costs for the health system.

Specifically, the project involves the development of shared indicators to be used in healthcare monitoring and assessing at Regional and National level, within the provisions of the NGS. Furthermore, a methodological platform for the calculation of these indicators and for the design of studies aimed at generating scientific evidence to support the public health policies will be provided to all Regions involved.

To this end, a work group was set up at the Italian Ministry of Health, which developed and tested a methodology for monitoring and evaluating CPs that can be applicable at National and Regional level in the context of health assessment and planning activities.

The identified methodology allows to:

- estimate the total number of patients affected by the disease of interest (prevalence rate);

- estimate the total number of new patients taken in charge annually for the disease of interest (incidence rate);
- evaluate the CP of prevalent or incident subjects with reference to the level of care (prevention, territorial or hospital setting);
- identify suitable process measures (process indicators) of those CPs;
- define outcomes of interest for the NHS that are experienced by diseased patients, and identify suitable outcome measures (outcome indicators);
- estimate resources consumption of CPs, in terms of both already-defined tariffs (DRG) and real costs;
- evaluate effectiveness and the efficiency of considered CPs, i.e. the impact of the adherence to a determine CP towards the risk to develop a clinical outcome;
- compare CPs observed for the same disease/health need in terms of effectiveness, quality and efficiency;
- draw-up meta-analytical estimates and assessments at National level, from single Region risk estimates.

The same sequence of health interventions can be ensured by different organizational models according to the demographic, social and welfare situation in which the interventions have to be applied; therefore, in the evaluation of the PDTA the chosen indicators are independent from the organizational model, measuring the expected effects in terms of type of services, timing and clinical outcomes. Comparing the values of the indicators obtained through different organizational models represents an important source of information to identify the best organizational choices.

Process and outcome indicators should be measurable and applicable among all the Regions involved in the project and must not have any political connotation. Then, it is not properly correct to make comparisons among Regions in terms of reached clinical outcomes, because a bias called "ecological fallacy" can incur (41). In fact, clinical outcomes used (as specified below) may depend on factors that could hardly be controlled and standardized, because they may differ according to the Region or to Regional policies (in particular regarding adopted procedures or encoding). Nevertheless, the identification of outcomes is useful to verify that adherence to a process explains part of the outcomes that are also observed in the Regions.

For each selected CP, the Italian working group developed and updated a protocol containing population selection criteria, definition of indicators (about process, outcome and association between

process and outcome), data sources, and how to account for clinical conditions' severity. The operating protocol was therefore evaluated by scientific societies and professional associations as the Federation of Italian Clinical-Scientific Societies (FISM) and the Physicians and Dentists Professional Order's National Federation (FNOMCeO).

Chapter 5

Diseases and definitions

As first application of this methodology, diseases with a high impact on the population and on healthcare are considered. These are: (i) chronic obstructive pulmonary disease (COPD), (ii) diabetes, (iii) heart failure (HF), (iv) breast cancer in women, and (v) colon cancer. For these clinical conditions, scientific evidence supports the application of CPs and provide specific indicators and related reference values. In this thesis, clinical pathways of diabetes and HF will be assessed, as mentioned in a previous chapter.

Some definitions used in the study protocol for each disease are described below.

Cohort of prevalent subjects

It is the cohort of subjects that have the disease in the inclusion period. These subjects are identified if included at least in one of the considered HCU databases, in the recruitment year.

Cohort of incidence subjects

It is the cohort of subject with a new onset of the considered disease in the inclusion period. These subjects are identified if they are (i) included at least in one of the considered HCU databases in the recruitment year, and at the same time (ii) not included in any HCU databases in the previous three years.

Process indicator

This is a measure of the appropriateness of the process of care, in relation with the reference standard defined by clinical guidelines for the specific disease. This indicator allows the identification of critical points in the CP, providing early indications for the development of care process improvement interventions and information about the quality of system performance (i.e. in terms of timing of the intervention). Process indicators are less influenced by differences in clinical complexity if compared with outcome ones.

Outcome indicator

It measures the clinical outcome of one or more healthcare interventions that can be included in the CP. Differences in clinical complexity, habits and lifestyle may influence this indicator. Therefore,

these aspects should be addressed both in the computation phase, through adequate risk-adjustment techniques, and in the interpretation of results obtained.

Association between process and outcome

This evaluation allows to validate the relation between the compliance to a process (for example, the adherence to a drug treatment) and the outcome observed (for example, the mortality rate), using adequate statistical models for clinical practice assessment. Clinical evidences, indeed, derives from populations and clinical settings that are usually far away from those in a real CP. This aspect represents the start point for the definition and the application of a CP in the real world of health care. Analysis of the association process-outcome in the Italian socio-demographic and healthcare setting can provide useful information for both restructuring monitoring criteria and indicators and defining clinical guidelines for new CPs.

Comorbidity assessment

The assessment of clinical complexity is usually carried out through indexes that can predict clinical outcomes, such as mortality or hospital re-admissions, in the short and medium term. These indexes weight hospital admissions and/or some drugs prescriptions that can be related to patients' co-morbid condition. In scientific literature, most diagnosis-based comorbidity scores have been developed from hospital-based surveys that reviewed inpatients' medical records, and only later they were adapted for use with large administrative data (42–52). For the purpose of this thesis, two different indexes are used: the well-known Charlson Comorbidity Index (CCI) (42) and the Multisource Comorbidity Score (MCS) (53).

The CCI is a method of predicting mortality by classifying or weighting comorbid conditions (comorbidities) that has been widely utilized by health researchers to measure burden of disease and case mix (42). Since the publication of Charlson et al.'s original article in 1987, the index has been validated for its ability to predict mortality in various disease subgroups (52) and can be adapted also in order to predict resources' utilization and costs of chronic diseases (54).

The MCS was generated according to the methodology used to build the Charlson index, the Chronic Disease Score (CDS), and other similar indexes, but with some peculiarities: (1) it uses the full range of information available about hospital admissions and drug prescriptions (not only one data source such as CCI and CDS); (2) it considers two outcomes (deaths and hospitalizations); and (3) it is built

on 1the Italian population using Italian administrative health data. This last aspect can explain the best predictive performance of MCS compared to other comorbidity indexes (53).

In CPs evaluation, this new index can have a double utility. On one hand, it can be used for the risk-adjustment of both outcome indicators and the association between process and outcome assessment. On the other hand, if appropriately used, it can be used to compare the clinical complexity among different population groups, i.e., it can provide the prevalence rate of individuals with an index value higher of a given threshold).

Part III

Methods

Chapter 6

Data sources

6.1 Large administrative databases

Although randomized clinical trials provide important information on drugs' efficacy and safety, results obtained from these studies cannot be generalized to the whole population, as already illustrated in the previous chapter (55).

Indeed, these studies are based on highly selected samples and enrolled a limited number of individuals, who often under-represent patients more vulnerable. Furthermore, most clinical studies are conducted in hospitals, usually prestigious ones, in which patients are subjected to strictly controlled dietary and behavioral regimes and they are not free to manage their habits (food, lifestyles, etc.) according to its own choice. These characteristics make these study contexts very distant from the real clinical practice. Therefore, despite the results from randomized clinical trials are sufficient to approve the placing on the market of a drug, they cannot answer the most important questions that doctors and patients daily have to deal with (56). Another factor to consider is the fact that adherence to pharmacological treatment in clinical practice is much lower than that obtained in an experimental context (57–61).

For these reasons subjects' observation should continue even after the marketing of the drug (62).

In this regard, in the last decade healthcare databases (DB) have been widely used for pharmacoepidemiologic studies (63). These databases can be classified into two broad categories: those that collect information for administrative purposes (administrative DBs) and those that are used by physicians to record clinical information about their patients' health (DB of general practitioners or clinical DB). Through the information available from administrative DBs, such as personal data, hospital admissions and pharmaceutical prescriptions, several studies providing important results about drugs' safety and efficacy profile have been conducted. One of the main characteristics of these DBs, the possibility of reflecting the real clinical practice for large and not selected populations, makes them very popular. Indeed, this is an aspect that certainly overcomes one of the main limitations of randomized clinical trials (64).

Despite the numerous advantages that administrative DBs led in pharmacoepidemiologic studies, some critical issues mainly related to the incompleteness of important clinical information (i.e., diagnostic tests results, Body Mass Index or information related to patients' lifestyle, as smoking habits and alcohol consumption) have emerged (65,66).

The lack of such information represents one of the main barriers to resolve because (i) it can be the cause of an incorrect measurement of variables of interest (measurement error) which can lead to incorrect classification of individuals based on drug's exposure or disease status (misclassification); (ii) it can make the confounding control difficult (particularly for unmeasured confounding). On the other hand, despite general practitioners' DBs are richer in information about patients' clinical profile and lifestyle, they are often poor in information about outpatient visits and hospital admissions (67,68).

Therefore, in order to be able to answer comprehensively to different pharmacoepidemiologic questions, it would be appropriate to integrate the information coming from each DB and to correct the distortions resulting from the aforementioned limitations through adequate strategies.

6.2 Italian healthcare utilization databases

All Italian citizens have equal access to health care services as part of the NHS. Information systems of HCU databases exist within each of the 20 Italian regions to collect a variety of information, at least including: 1) an archive of residents who receive NHS assistance (the whole resident population), reporting demographic and administrative data, other than the dates in which the individual started (because he/she was born or immigrated) or stopped (because he/she died or emigrated) the condition of NHS beneficiary; 2) a database about hospital discharge records including information about primary diagnosis, co-existing conditions and performed procedures; 3) a drug prescription database providing information on all community drugs reimbursed by the NHS; 4) a database for outpatient visits, including visits in specialist ambulatories and diagnostic laboratories accredited from the NHS; 5) a database about co-payment exception for diagnosed chronic disease.

All these sources of health data focus on the single performance (discharge, visit, pharmaceutical prescription) and can be interconnected so as to be able to follow the patient through the different contacts to the health facilities. Currently this interconnection is possible in all Italian regions, using a unique identification code within each region. In order to preserve privacy, identification codes were automatically converted into anonymous codes, and the inverse process was prevented by deletion of the conversion table.

6.3 Classifications

All information about primary diagnosis, co-existing conditions and performed procedures (included in hospital discharge records) are coded according to the International Classification of Diseases, 9th revision - Clinical Modification (ICD-9 CM) classification system, developed by WHO. It is a classification of diseases, injuries, surgical interventions, diagnostic and therapeutic procedures. In the national protocol, and also in this thesis, the presence of an asterisk (*) after a part of a code indicates that all sub-categories are considered.

All information about drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system, also developed by WHO, that is a systematic classification of drugs through their active substances.

For outpatient visits, reference is made to the National Outpatient Specialist Nomenclator (annex 4 to the DPCM "Definition and updating of the essential levels of assistance", Gazzetta Ufficiale General Series n.65 of 18-3-2017 - Ordinary Supplement No. 15).

Chapter 7

The Population Attributable Fraction

In epidemiologic studies, the strength of association between risk factors and an outcome are often reported as relative risk (RR) or odds ratio (OR). These measures do not, however, consider the importance of the risk factor at the population level, as its prevalence is not considered. Population Attributable Fraction (PAF), also known as Attributable Risk (AR), is the integrated measure that takes into account both the strength of association between the risk factor and the outcome and the prevalence of the risk factor in the population. Therefore, PAF is a statistical concept that can be used to quantify the impact of exposure to different risk factors on mortality or morbidity at the population level. PAF assesses the proportion of outcome in a population attributable to an exposure to one or several risk factors, or likewise, the proportion of outcome that could be avoided if the current exposure distribution was replaced by a hypothetical, presumably preferable exposure distribution.

The basic idea of PAF is to estimate the proportion of outcome in a given population that would theoretically not have occurred if none of the individuals had been exposed to the risk factor. Since its introduction (69), PAF has gradually become more widely used and the estimation of PAF has been applied in different settings and study designs. Originally, PAF was formulated for a single dichotomous risk factor (69) and was later extended for multiple, polytomous or continuous risk factors (70–72). Initially, PAF estimates do not accounted for confounding factors and were thus generally biased (69,70,73). Later, different statistical strategies for the adjustment of potential confounding factors in the estimation of PAF, mainly stratification and modeling, have been developed (71,74,75). There is a large body of literature on formulas for the estimation of PAF in case-control, cross-sectional studies, and in cohort studies with a fixed follow-up time (71,75), as well as in cohort studies with censored time-to-event data, which properly consider the follow-up time (76–78).

7.1 Review of the literature: definition of PAF

Once it has been established that there is a causal association between a risk factor and an outcome, we may wish to ascertain what proportion of the outcome is due to the exposure to the risk factor. Let us consider a binary outcome variable D and a dichotomous risk factor E. Let us denote D for the presence of the outcome ($\overline{D}$ for the absence), and E for the presence of exposure to the risk factor ($\overline{E}$

for the absence of exposure). Then, let $P(E)$ and $P(D)$ denote the exposure prevalence and the outcome occurrence within the entire population, respectively. Lastly, let $R_E = P(D \mid E)$ and $R_{\bar{E}} = P(D \mid \bar{E})$ represent the outcome occurrence in the exposed and unexposed individuals, and $RR = R_E/R_{\bar{E}}$ the relative risk between the exposed and unexposed individuals. At this point, the proportion of the outcome occurring among exposed subjects, which is in excess compared to those unexposed, can be calculated by dividing the risk difference between the exposed and the unexposed subjects by the risk in the exposed ones:

$$AF = \frac{P(D|E) - P(D \mid \bar{E})}{P(D|E)} = \frac{R_E - R_{\bar{E}}}{R_E} = \frac{(RR-1)}{RR} \qquad (7.1)$$

This quantity is here referred to as the Attributable Fraction (AF), i.e. the proportion of the outcome among the exposed subjects that could be attributable to the given exposure. In the literature, it has also been referred to as attributable risk (73), attributable risk percent (79) and etiologic fraction (70). Miettinen distinguished between etiologic fraction "attributable to" or "related to" a given risk factor depending on whether all or just some confounding by extraneous factors was under control. Greenland and Robins (80) further distinguished between etiologic fraction and excess fraction: depending on whether a case is defined as a case for which the exposure played an etiologic role, thus making it occur earlier, or a case that would not have occurred if exposure had never occurred. The definitions behind the algebraic formulations may thus affect the estimates obtained.

The AF can be generalized to the total population of exposed and unexposed individuals in order to quantify the importance of the exposure at the population level. The total outcome occurrence within the whole population is given by $P(D)$ and the excess outcome occurrence among the exposed individuals in the whole population by $P(D) - P(D|\bar{E})$. Then, the proportion of outcome occurring among both exposed and unexposed subjects that could be attributable to a given exposure can be calculated as

$$PAF = \frac{P(D) - P(D \mid \bar{E})}{P(D|E)} \qquad (7.2)$$

Since $P(D) = (E)R_E + (1 - P(E))R_{\bar{E}}$, if $P(D)$ in formula (7.2) is substituted with this formulation and the nominator and denominator are divided by $R_{\bar{E}}$, the formula (7.2) can also be expressed as

$$PAF = \frac{P(E)(RR-1)}{1+P(E)(RR-1)} \qquad (7.3)$$

This quantity is here referred to as the Population Attributable Fraction (PAF) and it was first presented in the literature by Levin (69) in 1953. Currently, the most often used is formula (2.2) and was given by MacMahon and Pugh in 1970 (73).

Similarly, as there are several formulations and definitions for PAF, depending on which aspect of the measure has been emphasized, there are also several names for it (81–83). The terms most often used for this measure are attributable risk (84) and population attributable risk (73). Since the quantity itself is not a risk but a proportion, terms which include words such as "proportion", "fraction", or "percentage" have been used. Popular terms within this setting include: attributable proportion (69), attributable fraction (85), population attributable fraction (86), etiologic fraction (70), excess fraction (80), attributable risk percentage (87), and population attributable risk percent (79). The fact that some of these terms, such as attributable risk, attributable fraction and attributable risk percent have also been used to refer to attributable fraction only among exposed individuals (2.1), and that some authors have used more than one term for the same measure shows the ambiguity in used terminology. Whereas AF restricts its attention to the exposed cases and only depends on the strength of the association between risk factor and outcome through RR, PAF focuses on the entire population and depends on the prevalence of the exposure to a risk factor. Thus, a risk factor with a moderate RR but a high prevalence can play a significant role in promoting the outcome within the population. Hence, whereas RR and odds ratio (OR) are mainly used to establish an association between a risk factor and an outcome, PAF can be used to measure the potential benefit of an intervention, indicating the outcome proportion that could be avoided if it were possible to remove the exposure to the risk factor from the population. As mentioned before, in the definition of PAF a causal relationship between risk factor and outcome is assumed and the exposure itself is assumed to have a harmful effect on the outcome. Thus, in case of a dichotomous risk factor, the outcome occurrence is assumed to be greatest in the exposed group and $RR > 1$. In that case, the PAF varies within [0,1] and it is usually expressed as a percentage. However, if the exposure was protective, the outcome occurrence would be greatest in the unexposed group and RR < 1. In this case, the PAF would become negative.

7.2 PAF generalization: to account for confounding

The basic formulas for PAF presented so far, (7.2) and (7.3), only include one dichotomous risk factor. However, in a more realistic situation, there are risk factors with several levels of exposure or, again, several risk factors. Miettinen in 1974 was the first to generalize the formula (7.3) from a dichotomous setting to a multifactorial setting with several polytomous risk factors (70). Another generalization, developed by Walter in 1976 (71) and based on Levin's formula (7.3), has been often referred to:

$$PAF = \frac{\sum_{s=1}^{S} P(E_s)(RR_s - 1)}{1 + \sum_{s=1}^{S} P(E_s)(RR_s - 1)} \qquad (7.4)$$

where s =1,..., S denotes the exposure levels, i.e. all the different combinations of the risk factor values, $P(E_s)$ indicates the prevalence of the sth exposure level among those with a positive outcome and RR_s is the relative risk at the sth exposure level in comparison with the reference level.

However, all these formulas do not adjust for confounding factors, and therefore PAF resulting estimates are called crude or unadjusted and are generally biased. Thus, to obtain reliable PAF estimates, these formulas need to be generalized and adjusted for potential confounding.

The two most popular strategies for estimating the adjusted PAF based on stratification are the Mantel-Haenszel approach and the weighted-sum approach. The Mantel-Haenszel approach, proposed by Kuritz and Landis (88,89) and Greenland (80), is based on estimating a common adjusted RR in cross-sectional studies (or OR in case-control studies) for all adjustment levels (j) and plugging in this estimate together with the prevalence of exposure among those levels. The weighted-sum approach, suggested by Walter in 1976 (71) and later studied by Whittemore (90,91), is based on weighting the stratum-specific PAF estimates, so that

$$PAF = \sum_{j=1}^{J} w_j PAF_j \qquad (7.5)$$

where w_j is the stratum-specific weight based on the proportion of outcome at the jth level. Comprehensive overviews of point and variance estimation of PAF based on these methods, as well as on other stratification-based adjustment methods and their limitations have been given in the literature (6,75,92,81).

Despite the usefulness of stratification-based adjustment methods in the estimation of PAF, as the number of adjustment and exposure levels increases, computations become burdensome to perform and obtaining a reasonable number of subjects for all strata could be difficult to guarantee (93). Furthermore, stratification requires that both risk and confounding factors should be categorical, which may result in loss of information. To avoid these problems, regression models have been developed: they allow flexible and efficient estimation of the adjusted PAF, as several categorical or continuous risk/confounding factors can be included in the models (with or without their interactions, allowing also for the analysis of potential effect modification). Furthermore, regression models yield maximum likelihood estimators that have favorable asymptotic properties.

7.3 PAF model-based estimation in epidemiological studies

Despite the confusion regarding formulas, definitions and names of PAF, the use of this measure has gradually increased, and its estimation has been studied in different epidemiological designs as cross-sectional, case-control, and cohort.

In the estimation of PAF, the risk factors are assumed to precede and be causally related to the outcome. The concept and application of PAF can thus be considered more realistic in cohort studies and less realistic in cross-sectional studies. Traditionally, however, PAF has been most often estimated from cross-sectional and case-control studies (6,75,92) and less from cohort studies, where issues such as length of follow-up and censoring arise.

In cross-sectional studies, a study population is selected in an unrestricted manner so that sampling is independent of disease and exposure status. After this selection, the outcome status and exposure to a risk factor are ascertained simultaneously, and the prevalence of the outcome according to the exposure status is compared (94). Thus, all quantities in the basic formula (7.1) are estimable. For a dichotomous exposure, a crude (unadjusted) estimate of PAF can be obtained as

$$PAF = \frac{n_1 m_0 - n_0 m_1}{n_0 + m_0} \qquad (7.6)$$

where n_0 and n_1, respectively, denote the numbers of unexposed and exposed diseased subjects ($n_0 + n_1 = n$) and m_0 and m_1 the numbers of unexposed and exposed disease-free subjects ($m_0 + m_1 = m$). A variance estimate can be obtained from the delta-method (95) by considering the full (unrestricted) multinomial model, in which all four quantities n_0, n_1, m_0 and m_1 come from a common multinomial distribution with index $n + m$, considered as fixed (exposure and disease

status are random) (71). As cross sectional studies involve no follow-up, diseased individuals will be prevalent rather than incident cases so that PAF estimates will represent the proportion of prevalent disease cases that can be attributed to exposure. In this context, interpretation of PAF will require special care to assess whether current rather than previous exposure is relevant to disease occurrence or whether exposure has a prognostic role on disease survival (75).

In case-control studies, groups of cases and non-cases (i.e. controls) are compared. Cases and controls are sampled independently of their exposure status from the entire source population, with respect to a current or previous exposure to a risk factor. In case–control studies, formula (7.3) should be consider in order to estimate $P(E)$ from the proportion exposed in the controls, making the rare-disease assumption, and use odds ratio estimates rather than rate ratio or relative risk estimates. Thus, the following PAF point estimate can be obtained

$$PAF = \frac{n_1 m_0 - n_0 m_1}{m_0 n} \qquad (7.7)$$

where n_0 and n_1, respectively, denote the numbers of unexposed and exposed cases ($n_0 + n_1 = n$) and m_0 and m_1 the numbers of unexposed and exposed controls ($m_0 + m_1 = m$). Also in case-control studies, variance estimates can be obtained from applying the delta-method (95) and considering the appropriate distributions for quantities n_1 and m_1, namely independent binomial distributions with respective indexes n and m considered as fixed (exposure is random conditional on disease status) (71).

In cohort studies, the exposure to a risk factor is known at the beginning of the follow-up and the population at risk of developing the outcome is followed for a given time period. During or after this period, new cases are identified, and their incidence is compared, according to the exposure status. In this setting, PAF is defined as the proportion of outcome that occur and that could be avoided during a certain follow-up time (T) if it was possible to change some risk factor values to specific target values. The follow-up time (T) is defines as the time from baseline (t = 0) to the time of the event of interest or censoring, whichever comes first. If death is the outcome of interest, PAF is the proportion of mortality that could hypothetically be avoided during a time interval (0; t] if its risk factors were modified (78). On the other hand, if the outcome of interest is represented by the disease incidence, PAF is the proportion of disease cases that could hypothetically be avoided during a time interval (0; t] if its risk factors were modified. In this case, the occurrence of death before contracting the disease of interest causes selection in the population during follow-up (96). Thus, if risk factors related to

disease's incidence are also related to mortality, their modification could affect both the risk of the disease and the risk of death. Therefore, censoring due to death needs to be taken into account in the definition of PAF for disease incidence (97).

Three different approaches for estimating PAF and its confidence interval from cohort studies have been proposed. In the first approach, only the occurrence of the event of interest is observed ignoring the timing of the event, i.e. event outcomes are treated as binary (75). In this case, the only difference with cross-sectional studies is that the outcome is not observed simultaneously with the risk factors but after a fixed follow-up time, and thus the logistic model used for the estimation of PAF and its confidence interval in cross-sectional studies can be applied. In this approach, however, information may be lost and reliable estimates can be obtained only in case of no censoring during follow-up. In the second approach, event or censoring time are observed but the effect of the hypothetical risk factor modification to the low-risk level is estimated at the instantaneous time point t (76,77). This estimate describes the proportion of events that could be prevented by changing the risk factor level in a small time interval $[t; t + \Delta t]$, where $\Delta t \rightarrow 0$. Usually, however, it is more useful to demonstrate the effect of the risk factor modification during a longer time interval $(0; t]$ as it is done in the third, most recently suggested, approach (76–78,96). For example, in case of an outcome, such as death, that is inevitable in time and can only be delayed, it would be useful to calculate PAF estimates for time intervals of different length in order to demonstrate the long-term effect of a risk factor modification (78). When the outcome is disease occurrence, potential censoring due to death needs to be considered and the impact of censoring on results can be observed in a longer follow-up (96). Furthermore, due to the inevitability of death, the PAF in both cases will eventually approach zero as time goes to infinity and thus become meaningless. This aspect points up the importance of specifying a definite time interval. Despite its importance, the last approach shows some difficulties in computation. To overcome these issues, Laaksonen et al. assumed proportional hazards models with a piecewise constant baseline hazard functions for death and disease occurrence for the estimation of PAF for a time interval $(0; t]$ (97).

Chapter 8

Study designs and statistical analysis

In this chapter, a brief description of study designs and statistical analysis adopted and performed in this thesis is provided.

8.1 Cohort study design

The cohort study design is a commonly used epidemiologic study design. This study design is used to assess the incidence of a disease and to evaluate the relationship between a certain exposure and the outcome of interest, in particular when the exposure is rare. This design implies the selection of a study population sample (a cohort) with common defined characteristic and disease-free at study entry. Then, subjects included in the cohort are followed for a certain time period. During this time frame, the outcome occurrence is assessed. The end of follow-up period is usually defined as the earliest occurrence between outcome, death, migration, end of data availability (98,99). The question of interest should be clear and correctly formulated, considering the nature of (i) the outcome/measure of disease occurrence, (ii) the nature of the exposure and (iii) the variables of interest (100).

The choice of the cohort depends on the hypothesis under investigation. Two groups of subjects are selected, namely "exposed" and "unexposed" to a certain risk factor, usually a disease risk factor, and the incidence of the disease is compared between the two groups. The exposed could be compared with a group of unexposed subjects (e.g. smoker vs non-smokers) or with a group of subjects with a different exposure level (e.g. heavy smokers vs light smokers). Exposed and unexposed groups should have various common characteristics, for example about factors that could be associated with the outcome of interest, but different patterns of the exposure under study.

Exposure could be evaluated as time independent or time dependent factor. In the first case, exposure is defined without considering its variability during a time interval and it is usually measured at cohort entry. In the second case, exposure is measured during follow-up at different time point to allow the assessment of exposure modification during follow-up. Indeed, if exposure changes over time, the use of time fixed exposure may introduce bias in the association estimate (101).
Cohort studies design allows to assess both multiple outcomes after a single exposure and rare exposures. Then, these studies could assess the temporal relationship between exposure and disease

onset. However, cohort studies are not the more suitable design if there are rare outcomes or events which take a long time to develop. The problem could be overcome with the selection of a study population composed by a highly exposed subjects.

8.2 New-users design

In a new-user design, patients who start the drug therapy of interest in the study are selected and subjects who have already received that treatment in previous years are excluded from the study (102,103).

There are several advantages related to the new user design. First, it could eliminate the immortal time bias, because time-on-study starts at the beginning of the therapy (102,104). Consequently, the selection of new users may reduce bias that can be introduced if prevalent users are considered in the analysis. Such biases are due to modification of disease risk factors during drug treatment and to the fact that prevalent users may be less susceptible to the onset of the event and could be more adherent to drug therapy compared to new-users (104). Second, new-user design could identify effects that occur shortly after the start of the therapy compared to studies that include prevalent users (104).

On the other hand, a new-user design can have some limitations. First, the limited time of observation could reduce the possibility to assess a decreasing in the disease's risk. Second, differences in how to define incident users can lead to different estimates. Third, in new-user design studies the analysis is focused on patients at the initial stage of the therapy or with a lower disease severity, reducing the power in terms of results generalizability to the entire population setting. Finally, a restriction to incident users could reduce the sample size of the study and therefore the precision of the final estimates (104). To that end, large HCU databases may be useful to identify new users (105) or a multicenter study could be necessary to reach a sufficient number of interesting events (104).

8.3 Meta-analysis

Meta-analysis is a quantitative, formal, epidemiological study design used to systematically assess previous research studies to derive conclusions about a specific body of research (106). Meta-analysis is conducted to assess the strength of evidence present on a disease and treatment. Aims of a meta-analysis are (i) to determine whether an effect exists and (ii) to determine whether the effect is positive or negative and, ideally, to obtain a single summary estimate of the effect. This process allows obtaining (i) conclusive results from potentially contrasting evidence derived from individual studies and (ii) more precise point estimates with an increased statistical power compared with the individual studies, which could be characterized by a small sample size, for example. Furthermore, results of a

meta-analysis can answer questions not posed by the individual studies, settle controversies arising from apparently conflicting studies, and generate new hypotheses. In particular, the heterogeneity assessment is crucial in the development of new hypotheses.

A thorough and disciplined literature search characterized a meta-analysis. According to the PRISMA/MOOSE statement, an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes and study design (PICOS) should be provided (107,108). It is important to obtain all relevant studies, as not to obtained biased results. Published papers and abstracts are usually identified by a computerized literature search of electronic databases. The choice of studies to be included in meta-analysis is based on inclusion criteria that should be defined at early stage of study protocol development. Also the rationale for these criteria should be clearly stated. If there is more than one hypothesis to be tested, separate selection criteria should be defined for each hypothesis.

From the considered studies, information about general characteristics (author, year, source of publication, information about the populations and related features), research design, treatment, effect size and the related measures of variability, controlled variables or adjustments need to be collected. Once this information is collected, it is possible to calculate the pooled estimate of the effect sizes obtained from the individual studies that could be risk ratios, odds ratios, or risk differences for event data, differences in means for continuous data, or hazard ratios for survival time data. Heterogeneity analysis, sensitivity analysis, and evaluation of publication bias are further methods used in post hoc analysis.

All methods used should allow for the weighting of studies. The concept of weighting reflects the value of the evidence of any single study. Usually, studies are weighted according to the inverse of their variance (109). Therefore, smaller studies usually contribute less to the estimates of overall effect.

The main decisions to take when conducting a meta-analysis is whether to use a fixed-effects or a random-effects model. A fixed-effects model assumes that the effect expected from each study is the same and the only source of variation in observed outcomes is that occurring within the study. Consequently, it is assumed that the models are homogeneous: there are no differences in the underlying study population, no differences in subject selection criteria, and treatments are applied the same way (110). Fixed-effect methods used for dichotomous data include most often the Mantel-Haenzel method (111) and the Peto method (112).

Random-effects models have an underlying assumption that a distribution of effects exists, resulting in heterogeneity among study results, known as τ^2. Consequently, as software has improved, random-effects models that require greater computing power have become more frequently conducted. This is desirable because the strong assumption that the effect of interest is the same in all studies is frequently untenable. Moreover, the fixed effects model is not appropriate when statistical heterogeneity (τ^2) is present in the results of studies in the meta-analysis. In the random-effects model, studies are weighted with the inverse of their variance and the heterogeneity parameter. Therefore, it is usually a more conservative approach with wider confidence intervals than the fixed-effects model where the studies are weighted only with the inverse of their variance. The most commonly used random-effects method is the DerSimonian and Laird method (113). Furthermore, it is suggested that comparing the fixed-effects and random-effect models developed as this process can yield insights to the data (114).

A meta-analysis allows to examine sources of heterogeneity among studies and to understand whether and how to generalize the results. It is important to distinguish between different sources of heterogeneity. Variability in the participants, interventions, and outcomes studied has been described as clinical diversity, and variability in study design and risk of bias has been described as methodological diversity (115). When the observed intervention effects varying by more than the differences expected among studies that would be attributable to random error alone, we talk about statistical heterogeneity. It is composed by the variability in the intervention effects evaluated among different studies and it is a consequence of clinical or methodological diversity (or both) among the studies. Statistical heterogeneity is usually simply referred to as “heterogeneity”.

Variation among *k* trials is usually assessed using Cochran's *Q* statistic and the corresponding chi-squared (χ^2) test of heterogeneity with *k*-1 degrees of freedom, but it has relatively poor power to detect heterogeneity among small numbers of trials (116,117). However, heterogeneity of results among trials is better quantified using the inconsistency index I^2, which describes the percentage of total variation across studies (118). Uncertainty intervals for I^2 (dependent on *Q* and *k*) are calculated using the method described by Higgins and Thompson (119). Negative values of I^2 are put equal to zero, consequently I^2 lies between 0 and 100%. A value >75% may be considered substantial heterogeneity. This statistic is less influenced by the number of trials compared with other methods used to estimate the heterogeneity and provides a logical and readily interpretable measure, but it still can be unstable when only a few studies are combined (120).

In a meta-analysis, a critical issue is about the papers that may have been missed. There is good reason to be concerned about this potential loss because studies with significant and positive results are more likely to be published than studies with non-significant or "negative" results. Therefore, it is important to examine the results of each meta-analysis in order to evidence publication bias. Several methods have been developed to provide an assessment of publication bias. Among those, the most commonly used is the funnel plot. The funnel plot provides a graphical evaluation of the potential for bias and was developed by Light and Pillemer (121) and discussed in detail by Egger and colleagues (122,123). A funnel plot is a scatterplot of treatment effect against a measure of study size. If publication bias is not present, the plot is expected to have a symmetric inverted funnel shape.

In this thesis, the meta-analytical approach is used in two different settings. In the first study [see Chapter 9], this approach is used to systematically assess research study results about the relation between concomitant use of certain drugs and bleeding events. In the second study [see Chapter 10], we used a meta-analytical method to obtain a pooled estimate from several Italian Regions' specific risk estimates. In this second case, this approach allowed to consider each Region as a single study, and to evaluate each Region results' as study results to be meta-analyzed.

All analyses in this thesis were performed using the Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC, USA), RevMan Version 5.1 (Nordic Cochrane Center) and the R package "metaphor" (R Foundation for Statistical Computing, Vienna, Austria) (124). Statistical significance was set at the 0.05 level. All p-values were two-sided.

Part IV

Applications

Chapter 9

Bleeding events attributable to concurrent use of warfarin and other medications in high-risk elderly: Meta-analysis and Italian population-based investigation

Published in European Journal of Clinical Pharmacology (125)

9.1 Introduction

Atrial fibrillation (AF) is a common disease, with a 1-in-4 lifetime risk after age 40 years (126) , and is associated with a 3- to 5-fold increased risk of stroke (127,128). Given that aging per se is an additional strong risk factor for stroke (129), prophylaxis with anticoagulation therapy is especially important for reducing AF-related ischemic stroke in elderly patients.

Warfarin is widely used for the prevention and treatment of thromboembolic events in patients with mechanical heart valves (130) and venous thromboembolism (131), and it has shown to reduce the risk of stroke by 60% to 70% (132), but its use involves a substantial risk of over-anticoagulation and bleeding (133,134). Despite the approval of novel oral anticoagulants within the past several years (135–138), warfarin continues to be commonly used in routine care, so that its safety, primarily risk of bleeding, is still at present-day of concern.

Warfarin has a narrow therapeutic index, therefore slight increases in plasma concentration due to the pharmacokinetic interactions with both other drugs and food may increase its risk of bleeding (139). In addition, there is the possibility of a pharmacodynamics interaction with some drugs that may increase *per se* the risk of bleeding (140). Hence, several factors, in particular older age and polypharmacy, may increase the risk of over-anticoagulation and bleeding during warfarin therapy (141,142). Many drugs, including antibiotics, non-steroidal anti-inflammatory drugs, certain drugs affecting the central nervous system, and platelet aggregation inhibitors, have been reported to interact with warfarin (139).

The specific aim of this study is to estimate the proportion of bleedings attributable to concurrent use of warfarin and other drugs compared to use of warfarin alone. With this purpose, we summarized evidence from published observational studies to obtain estimates of the relative risks of bleeding

associated with concurrent use of warfarin and other medications compared to use of warfarin alone. A population-based investigation in a cohort of Italian cardiopathic elderly patients was carried out to estimate the prevalence of warfarin users at whom selected medications were prescribed concomitantly with warfarin. Finally, we estimated the population attributable fraction, i.e., the proportion of bleedings attributable to the concomitant use of warfarin and other drugs. The more general aim of this paper is to show capability of a simple and inexpensive approach for measuring the impact of the prescriptive inappropriateness on drug adverse outcomes at the population level, so to provide relevant policy measures for establishing public health priority.

The paper is a part of an Italian project promoted by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) which supported the Italian Group for Appropriate Drug prescription in the Elderly (I-GrADE).

9.2 Methods

Summarizing evidence

A meta-analysis was performed according to the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines (108). A MEDLINE and EMBASE search of the literature was conducted to identify studies investigating the risk of bleeding associated to concurrent use of warfarin and other medications, compared to warfarin use alone. Observational studies published from January 1995 up to the end of December 2015 were identified using the following keywords: ("warfarin") AND ("drug interactions" OR "drug" AND "interactions") OR "drug interactions" OR ("drug" AND "interaction") OR "drug interaction" AND ("haemorrhage" OR "bleeding" AND "risk"). Search was limited to studies published in English or Italian. Completeness was verified comparing our search with that of general reviews and meta-analyses published on this issue (139,143–147).

All the titles and abstracts were accurately screened to exclude those not compliant to our inclusion criteria. Studies were included if based on either cohort or case-control design when: (a) concurrent use of warfarin and potentially interacting medications was the exposure of interest and warfarin use alone the reference; (b) the outcome of interest was bleeding as a whole or specific subtypes of bleeding; (c) crude or adjusted estimates of the association of exposure and outcome (that is, relative risk (*RR*), odds ratio, hazard, and the corresponding 95% confidence interval (*CI*)) were reported. Papers that did not report original findings (i.e., systematic review and meta-analysis) and risk estimates (e.g., letters and case report), and randomized controlled trials were excluded. When data

were published more than once, the most recent and complete publication was considered. Two readers (RIC and FR) independently determined the eligibility of each article for inclusion. Discrepancies between readers were resolved in conference.

For each included study, we extracted details on study design, publication year, country, number of cases and their age, exposure definition (concurrent therapy and time window between concomitant use of drugs and bleeding), *RR* (or other association measures) and the corresponding 95% CI, adjustment and stratification variables.

The summary *RR* for concurrent use of warfarin and potentially interacting medications as compared with use of warfarin alone (reference therapy) and bleeding risk was estimated using both the fixed-effects model and the random-effects model proposed by DerSimonian & Laird (113). Pooled estimates were calculated when at least three papers reported specific drug combination of interest. When a significant heterogeneity was found, the results from the random-effects model were presented. Heterogeneity between study-specific estimates was tested using chi-square statistics and measured with the I^2 statistics (a measure of the percentage variation across the studies caused by heterogeneity) (118). Publication bias was evaluated through funnel plot analysis and the Egger's test (122).

The analyses and the correspondent graphical visualizations were conducted by using RevMan Version 5.1 (Nordic Cochrane Center) and the R package "metafor" (R Foundation for Statistical Computing, Vienna, Austria) (124).

Warfarin and concomitant drugs use

The data used for the present study were retrieved from the health service databases of five Italian healthcare territorial units participating to the I-GrADE project, i.e., three Regions (Lazio, Lombardy and Tuscany) and two Local Health Units (Caserta and Treviso). About 21 million of beneficiaries residing in these areas, accounting for nearly 35% of the whole Italian population, were recorded in the corresponding databases.

The National Health Service (NHS) covers the entire Italian population by providing universal and free of charge coverage for most healthcare services. This program is administered by an automated system of databases including demographic and administrative data of NHS beneficiaries, and information on their use of healthcare services. The latter include, between others, outpatient drug

prescriptions reimbursable by the NHS coded according to the Anatomical Therapeutic Chemical (ATC) classification system.

Individuals who were resident in one of the five participating Italian healthcare territorial units, aged 65 years or older, and hospitalized for cardiovascular (CV) events (ICD-9 code: 390-459) from January 1, 2007 to June 30, 2011 were identified. The first CV hospital admission during this period was defined index hospitalization. Patients who survived to the index hospitalization and who received at least one prescription of warfarin (ATC code: B01AA03) within one year from the discharge of index hospitalization were included in the study cohort. Given that all included subjects had been admitted to a hospital during the last year for serious CV before inclusion in the study, we assumed cohort members as a frail population at high bleeding risk.

For each cohort member data included gender, age, CV diseases diagnosed at index hospitalization and selected co-medications (i.e., blood pressure- and lipid-lowering agents, antidiabetic drugs, platelet inhibitors, antiarrhythmic drugs, proton-pump inhibitors, antidepressants and thyroid hormones) dispensed within the one-year period before the index hospitalization. The Charlson comorbidity index score (54) was also calculated. Use of warfarin within the first year from the discharge of index hospitalization was also recorded.

Each cohort member accumulated person-years of follow-up from starting (i.e., the date of first prescription of warfarin), until censoring (i.e., death, emigration, or 365 days after starting). The use of other medications potentially able to interact with warfarin in increasing the risk of bleeding according to the above described meta-analysis, was assessed during follow-up. These comprised: certain antibiotics (i.e., cotrimoxazole (J01EE01), macrolides (J01FA) and quinolones (J01M)), Selective Serotonin Reuptake Inhibitors (SSRIs; N06AB), Non-Steroidal Anti-Inflammatory Drugs (NSAIDs; M01A), platelet aggregation inhibitors (B01AC), amiodarone (C01BD01), lipid-lowering agents (C10) and thyroid hormones (H03).

The duration of the period covered by a prescription was calculated by dividing the total amount of the drug prescribed for the corresponding defined daily dose. Concomitant use was defined as at least one-day of overlap between warfarin and another medication. The prevalence of concurrent users was calculated as the proportion of cohort members who experienced concurrent use of warfarin and other medications among warfarin users as a whole.

Estimating population attributable fraction

The Population Attributable Fraction (PAF) is an epidemiological measure used to estimate the impact of exposure to a risk factor on the occurrence of a particular disease at the population level combining information on the exposure-outcome association as well as on the exposure prevalence in the target population (6). In the current investigation, the meta-analytic summary *RR* of bleeding associated with concurrent use of warfarin and potentially interacting medications versus use of warfarin alone and the prevalence p of concurrent users in the Italian population aged 65 years or older who experienced a CV event (population of interest) were combined as (148)

$$\text{PAF} = (p(RR-1))/(1+p(RR-1))$$

The variance of PAF was estimated using the delta method (149) and corresponding 95% CI was then calculated.

Statistical significance was set at the 0.05 level for all analyses.

9.3 Results

Meta-analysis

Based on title and abstract we identified 2,353 papers (Figure 9.6.1). We excluded 2,293 of them from the abstract and 44 papers were further excluded because they did not satisfy the inclusion criteria. Of the remaining 16 studies complying the inclusion criteria, another one was added from reference lists of reviews and meta-analysis, so that 17 original papers were considered in this meta-analysis (150–167). Concurrent use of warfarin and cotrimoxazole (153,155,160,161,165,166), macrolides (160,161,166), quinolones (153,155,159,166), SSRIs (151,154,158–161,165,167), NSAIDs (150,154,159,160,165), platelet aggregation inhibitors (154,156,160,161,163,165), amiodarone (160,163,164), lipid-lowering agents (152,157,163) and thyroid hormones (160,162,163) was investigated from the included studies (Supplementary material_1).

Figure 9.6.2 reports study-specific and summary RRs of bleeding associated with concurrent use of warfarin and potentially interacting medications. Compared with use of warfarin alone, concomitant use of cotrimoxazole, amiodarone, quinolones, macrolides, platelet aggregation inhibitors, SSRIs, NSAIDs and lipid-lowering agents respectively increased the bleeding risk of 171% (149% to 194%), 103% (10% to 276%), 92% (49% to 148%), 89% (46% to 145%), 60% (41% to 81%), 45% (21% to 75%), 45% (17% to 80%) and 21% (5% to 39%), respectively. There was no evidence that concomitant use of thyroid hormones and warfarin increase the risk of bleeding with respect to

warfarin alone. Between-study heterogeneity was almost always significant and numerically relevant. With the exception of studies investigating the concurrent use of warfarin and SSRI, no evidence of publication bias was observed for the other investigated relationships (Supplementary material_2).

Target population

Among the 1,097,840 elderly hospitalized for CV disease during the considered period and who survived to the index hospitalization, 140,801 (13%) received at least one prescription of warfarin within one year after index discharge and were then included into the study cohort.

Table 9.5.1 provides the baseline characteristics of warfarin users. At the index hospitalization, cohort members had mean age of about 77 years, 52% of them were men, and 44% had diagnosis of arrhythmia (the remaining suffering of heart failure, ischemic disease or stroke). Most cohort members were treated with blood-pressure lowering agents (mainly diuretics, angiotensin converting enzyme inhibitors and β-blockers), and more than one third of the investigated population was treated with proton-pump inhibitors, while the use of platelet aggregation inhibitors, lipid-lowering agents, antiarrhythmics (mainly amiodarone), antidiabetics, antidepressants (mainly SSRIs) and thyroid hormones was less frequent. Very few patients already experienced bleeding events. Almost 16% of cohort members did not have chronic comorbidities, while more than 60% of them had Charlson comorbidity index ≥2.

Prevalence of concomitant users and population attributable fraction

Prevalence of concomitant users and PAF estimates are showed in Figure 9.6.3. Overall, 32% of bleeding events that occurred in our target population are expected to be attributable to concurrent use of warfarin and certain antibiotics: quinolones (PAF: 20.5%, 16.7% to 25.1%), macrolides (8.8%; 95% CI: 7.5% to 10.3%) and cotrimoxazole (3.0%, 2.5% to 3.6%). Another 58% of bleeding events could be attributable to concurrent use of platelet aggregation inhibitors (14.2%, 12.3% to 15.8%), amiodarone (21.0%, 1.0% to 41.0%), NSAIDs (10.2%, 1.0% to 20.0%), SSRIs (5.8%, 4.5% to 7.6%) and lipid-lowering agents (7.7%, 0% to 18.2%).

9.4 Discussion

The present study provides further evidence that concurrent use of warfarin and certain antibiotics (cotrimoxazole, macrolides and quinolones), SSRIs, platelet inhibitors, NSAIDs, lipid-lowering agents and amiodarone increases the risk of bleeding. The latter was not trivial because among concomitant users, the risk excess ranges from 21% (lipid-lowering agents) to 171% (cotrimoxazole)

higher compared to patients on warfarin monotherapy. As novel and original message, we estimate that in our target population of high-risk old people, more than half of bleeding events occurred among warfarin users would be attributable to the interactions under study.

Adverse Event Reports (AER) databases are useful tools for identifying potential drug adverse event associations (168). Although they provide answers in a timely and cost-effective fashion and reflect the realities of clinical practice, it should be considered that analyses from AER data cannot be used to infer the comparative strength of causality but rather to generate hypotheses of potential adverse reactions (169–171). Real-world evidence from observational studies should be preferred if the aim is to study suspected associations, taking into account that they should be designed to approximate randomized experiments as closely as possible (172).

Since severe haemorrhages among patients under treatment with warfarin are of clinical and public health concern (173–176), and because ranking risk factors according to their impact on outcome onset at population level has implications for policy makers, we measured the fraction of clinically relevant bleedings which occurred among warfarin users that might be attributable to concurrent use of warfarin with other medications. Our approach is based on a simple rationale. Firstly, we conducted a meta-analysis of published studies for summarizing relative risks associated with concomitant use of warfarin and other medicaments. It should be emphasized that our meta-analysis supplies evidence on the strength of the exposure-outcome association, the corresponding estimates indicating how much a single combination is able to increase the outcome risk. However, a given drug combination, although characterized by a potential high risk, could have a little impact at the population level when it is rarely prescribed. On the contrary, combinations with a potential low risk but often prescribed could impact generating several adverse outcomes. For this reason, in a second step we performed a real-world study, which used routinely collected population-based drug prescription data, for estimating exposure prevalence. For example, lipid lowering agents are more prescribed than cotrimoxazole. Therefore, we observed that lipid lowering agents had a much higher impact than cotrimoxazole if concomitantly prescribed with warfarin, even though this combination is associated with a lower risk of bleeding than the combination warfarin-cotrimoxazole. However, the latter observation cannot be generalized to every target population depending on physician's behaviour.

The present study has several strengths. To our best knowledge, this is the most extensive recognition of medications causing bleedings if concurrently used with warfarin. The investigation was based on a very large unselected population, likely representative of the Italian target population. The target

population was well defined since it is restricted to warfarin users who were aged over 65 years and were discharged for CV disease. Data on drug use were comprehensive and highly accurate since pharmacists are required to record all dispensed prescriptions in charge to the NHS in order to obtain reimbursement. Incorrect reports about the dispensed drugs have legal consequences (63).

However, the validity of our findings might be questioned on the basis of possible weakness of the main assumptions underlying the approach. The first assumption is that the observed associations are causal. Available evidence from clinical trials and possible mechanisms underlying the drug-drug interactions considered in this study appears to support this assumption. Because of the common antithrombotic action of anticoagulant and platelet inhibitors, concurrent use of these medicaments is expected of increasing the bleeding risk with respect to monotherapy, as consistently confirmed from a meta-analysis of randomized trials (177). Antibiotics act by disrupting intestinal flora that synthesizes vitamin K_2 (155) and inhibiting Cytochrome p450 isozymes, which metabolize warfarin (178). Mechanisms for SSRIs include direct platelet effects, such as the antagonism of serotonin transporters, thereby impairing platelet aggregation (179), depletion of platelet serotonin levels (180–184), and reduction in platelet count (185). NSAIDs have a well-known antiplatelet effect, can affect the serum levels of warfarin by inhibiting Cytochrome p450 and can cause gastric erosion thereby further increasing the risk of GI bleeding in patients treated with warfarin (150). Also amiodarone inhibits the hepatic metabolism of warfarin via Cytochrome p450 (164). Lipid-lowering agents have antiplatelet and other anti-thrombotic properties that would tend to promote bleeding (152).

The second assumption is that relative risk estimations are unbiased. Since primary studies included into the meta-analysis were observational investigations, we cannot exclude the possibility that confounding by indication might in part explain our relative risk estimations. For example, patients under dual therapy might be more frail, and perhaps more susceptible to bleeding, than patients on warfarin alone. Combining prescription data from Italy with bleeding relative risk data from completely different populations (none of the cohorts listed in the supplementary table came from Italy) may be arguable. This is especially true against the background that Italy exhibits relative poor INR-monitoring performance as measured by Time in Therapeutic Range (TTR) compared to other European and especially Scandinavian countries (174,186,187). The bleeding risk in the present Italian population may actually be higher than indicated in the studies based on other populations due to poorer follow-up in Italy. In addition, the definition of outcome varied from study to study and the populations included into the primary studies were heterogeneous. The strength of evidence was reduced for some of the drug classes considered because of high statistical heterogeneity. This was

the case of quinolones, NSAIDs and SSRIs showing considerable variation across the studies caused by heterogeneity of 87%, 78% and 71% respectively. We can speculate that a part of heterogeneity might be explained by differences in the quality of clinical follow-up (187). Finally, there was evidence of publication bias for the concurrent use of warfarin and SSRI. Notwithstanding these limitations, our meta-analysis includes published information on the issue and consequently provides the most accurate estimates of bleeding risk associated with combined exposure to warfarin and other medicaments.

The third assumption is that concomitant warfarin prescription data, are unbiased. Validity of our estimates is based on the assumption that drugs dispensed by pharmacies correspond to drug consumption, which may not be the case (66). It should be mentioned that this type of bias necessarily leads to an underestimation of attributable fractions.

In conclusion, this study provides an estimate of the percentage of bleeding events in warfarin users attributable to the concomitant use of other medications. It should be however emphasized that some of these drugs appear to be essential for the treatment/prevention of CV conditions. As a consequence, other than a reduction of bleeding risk, an increased risk of other serious complications is expected by avoiding their use. A comprehensive risk-benefit assessment in the individual case is therefore advised before to take any clinical decision. Concomitant use of warfarin and these drugs could be acceptable in some cases, provided that proper INR-monitoring and warfarin dose adjustments are performed. Findings of this study should help both physicians, for taking care of and monitoring elderly people already on treatment with warfarin by taking into account the trade-off between benefits and potential risks of bleeding, and health authorities to promoting good clinical practice.

9.5 Tables

Table 9.5.1. Baseline characteristics of the included 140,801 cohort members. I-GrADE project, Italy, 2007-2012.

	Warfarin users (n = 140,801)
Age (years): mean (SD)	76.8 (6.3)
Male	73,076 (51.9%)
Main diagnosis at index hospitalization	
Arrhythmia	61,953 (44.0%)
Heart Failure	32,620 (23.2%)
Ischemic disease	25,075 (17.8%)
Stroke	21,153 (15.0%)
Previous use of selected drugs [(a)]	
Blood pressure-lowering agents	120,450 (85.5%)
Diuretics	65,070 (46.2%)
Angiotensin-converting-enzyme inhibitor	62,843 (44.6%)
Beta-blockers	53,359 (37.9%)
Calcium-channel-blockers	45,656 (32.4%)
Angiotensin receptor blockers	42,175 (29.9%)
Platelet inhibitors	51,052 (36.2%)
Lipid-lowering agents	40,084 (28.4%)
Antiarrhythmic medicaments	26,602 (18.8%)
Amiodarone	17,004 (12.0%)
Antidiabetic agents	21,195 (15.0%)
Proton-pump inhibitors	54,152 (38.4%)
Antidepressants	18,432 (13.0%)
SSRIs	14,239 (10.1%)
Thyroid hormones	7,324 (5.2%)
Previous bleeding events [(a)]	4,056 (2.8%)
Charlson comorbidity index [(a)]	
0	22,408 (15.9%)
1	33,220 (23.6%)
≥ 2	85,173 (60.5%)

[(a)] One year before the admission date of index hospitalization

Abbreviations: SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors

9.6 Figures

Figure 9.6.1. Flow-chart of study's selection for the meta-analysis, according to MOOSE Guidelines

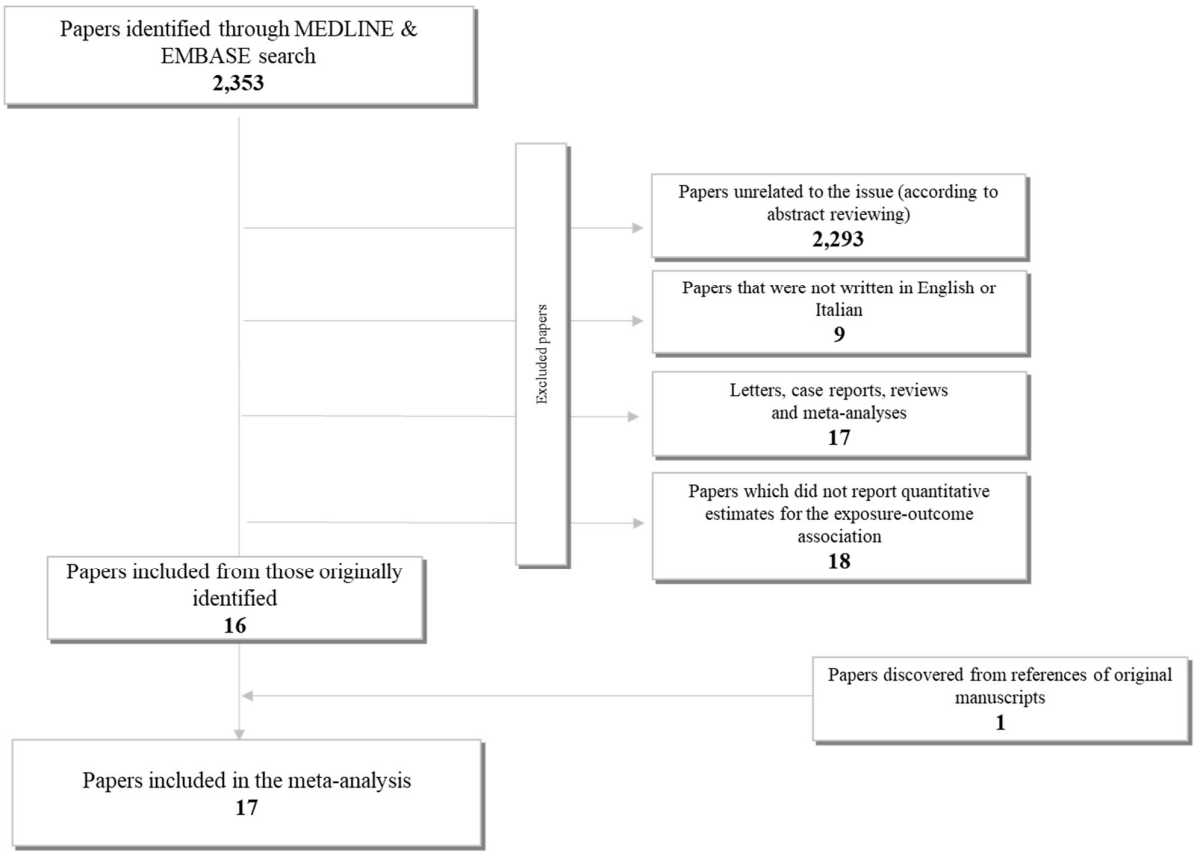
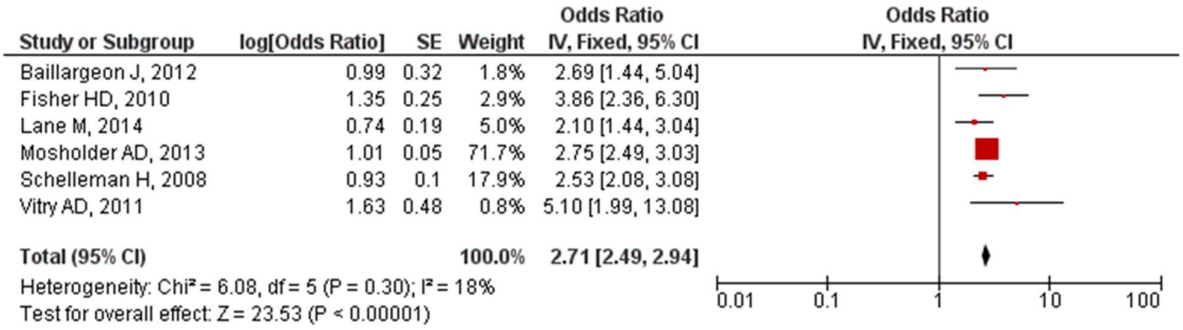
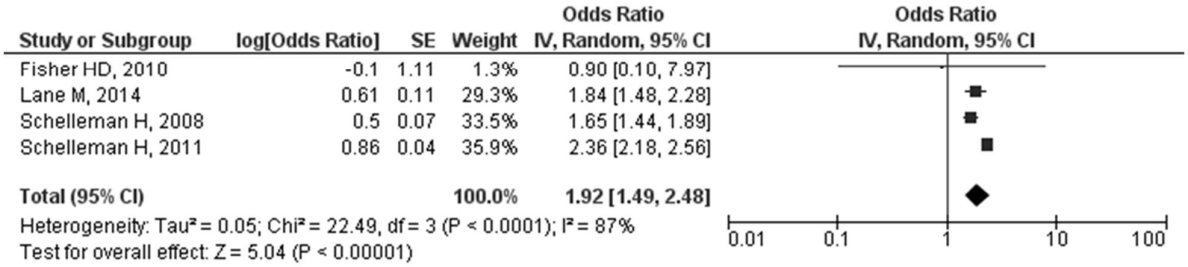


Figure 9.6.2. Study-specific and summary relative risk estimates of bleeding associated with concurrent use of warfarin and selected medicaments vs. use of warfarin alone.

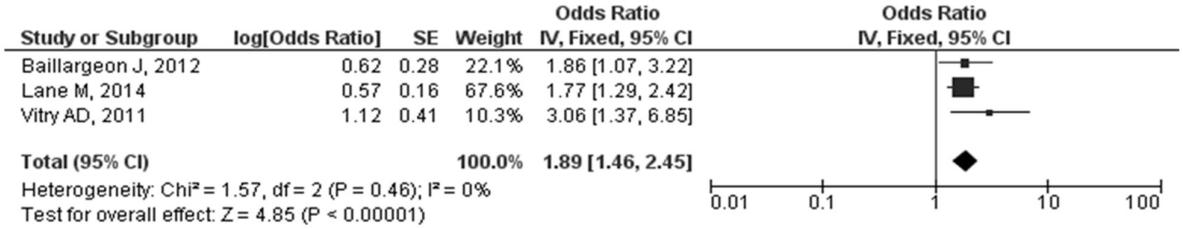
Warfarin + Cotrimoxazole



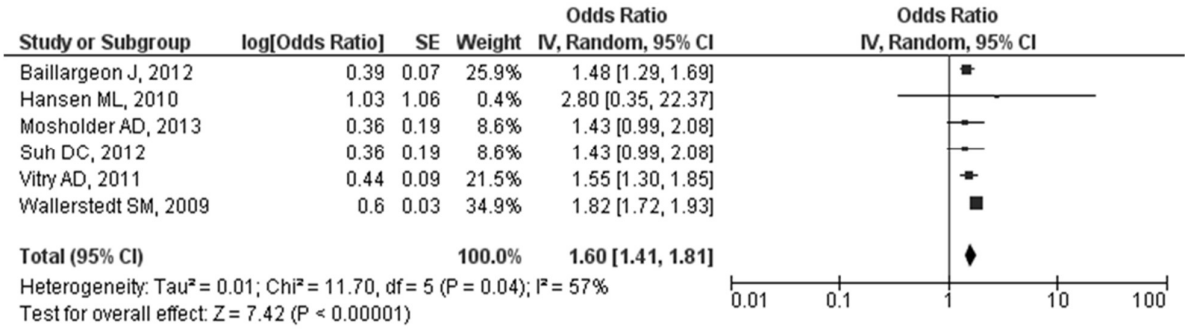
Warfarin + Quinolones



Warfarin + Macrolides



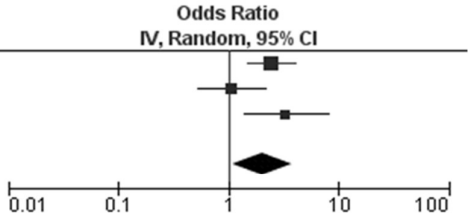
Warfarin + Platelet aggregation inhibitors



Warfarin + Amiodarone

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Lam J, 2013	0.9	0.25	41.6%	2.46 [1.51, 4.01]
Suh DC, 2012	0.07	0.36	32.4%	1.07 [0.53, 2.17]
Vitry AD, 2011	1.2	0.45	26.1%	3.32 [1.37, 8.02]
Total (95% CI)			**100.0%**	**2.03 [1.10, 3.76]**

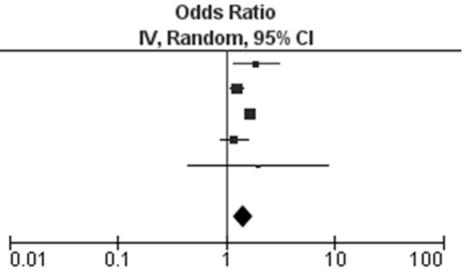
Heterogeneity: Tau² = 0.17; Chi² = 4.91, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 2.27 (P = 0.02)



Warfarin + NSAIDs

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Battistella M, 2005	0.64	0.25	12.5%	1.90 [1.16, 3.10]
Mosholder AD, 2013	0.22	0.07	30.8%	1.25 [1.09, 1.43]
Schelleman H, 2011	0.52	0.04	33.6%	1.68 [1.56, 1.82]
Vitry AD, 2011	0.17	0.15	21.2%	1.19 [0.88, 1.59]
Wallerstedt SM, 2009	0.68	0.76	2.0%	1.97 [0.45, 8.75]
Total (95% CI)			**100.0%**	**1.45 [1.17, 1.80]**

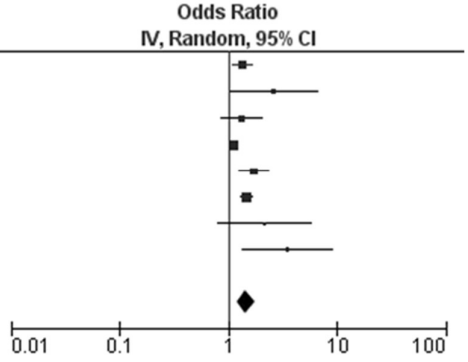
Heterogeneity: Tau² = 0.03; Chi² = 17.85, df = 4 (P = 0.001); I² = 78%
Test for overall effect: Z = 3.38 (P = 0.0007)



Warfarin + SSRI

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Baillargeon J, 2012	0.29	0.11	18.9%	1.34 [1.08, 1.66]
Cochran KA, 2011	0.96	0.47	3.5%	2.61 [1.04, 6.56]
Kurdyak PA, 2005	0.29	0.22	10.6%	1.34 [0.87, 2.06]
Mosholder AD, 2013	0.1	0.05	23.7%	1.11 [1.00, 1.22]
Quinn GR, 2014	0.55	0.16	14.6%	1.73 [1.27, 2.37]
Schelleman H, 2011	0.38	0.07	22.3%	1.46 [1.27, 1.68]
Vitry AD, 2011	0.77	0.5	3.1%	2.16 [0.81, 5.75]
Wallerstedt SM, 2009	1.25	0.48	3.3%	3.49 [1.36, 8.94]
Total (95% CI)			**100.0%**	**1.45 [1.21, 1.75]**

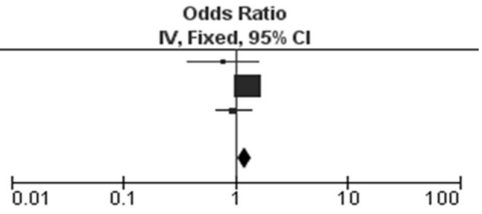
Heterogeneity: Tau² = 0.03; Chi² = 23.75, df = 7 (P = 0.001); I² = 71%
Test for overall effect: Z = 3.97 (P < 0.0001)

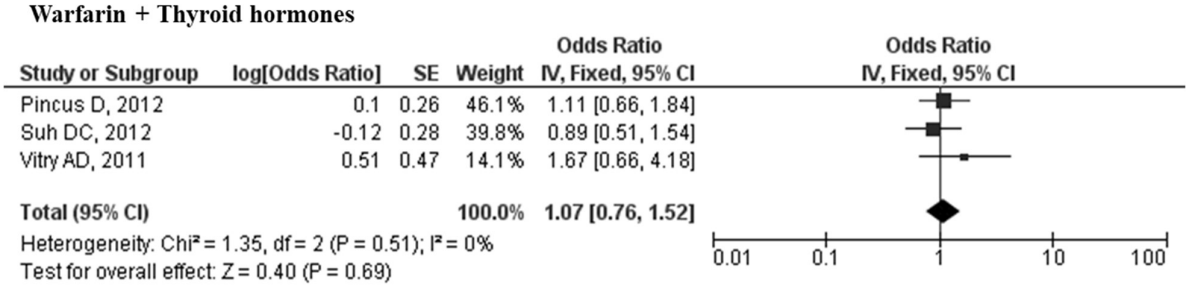


Warfarin + Lipid-lowering agents

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Douketis JD, 2007	-0.26	0.37	3.8%	0.77 [0.37, 1.59]
Schelleman H, 2010	0.25	0.08	81.7%	1.28 [1.10, 1.50]
Suh DC, 2012	-0.04	0.19	14.5%	0.96 [0.66, 1.39]
Total (95% CI)			**100.0%**	**1.21 [1.05, 1.39]**

Heterogeneity: Chi² = 3.51, df = 2 (P = 0.17); I² = 43%
Test for overall effect: Z = 2.61 (P = 0.009)

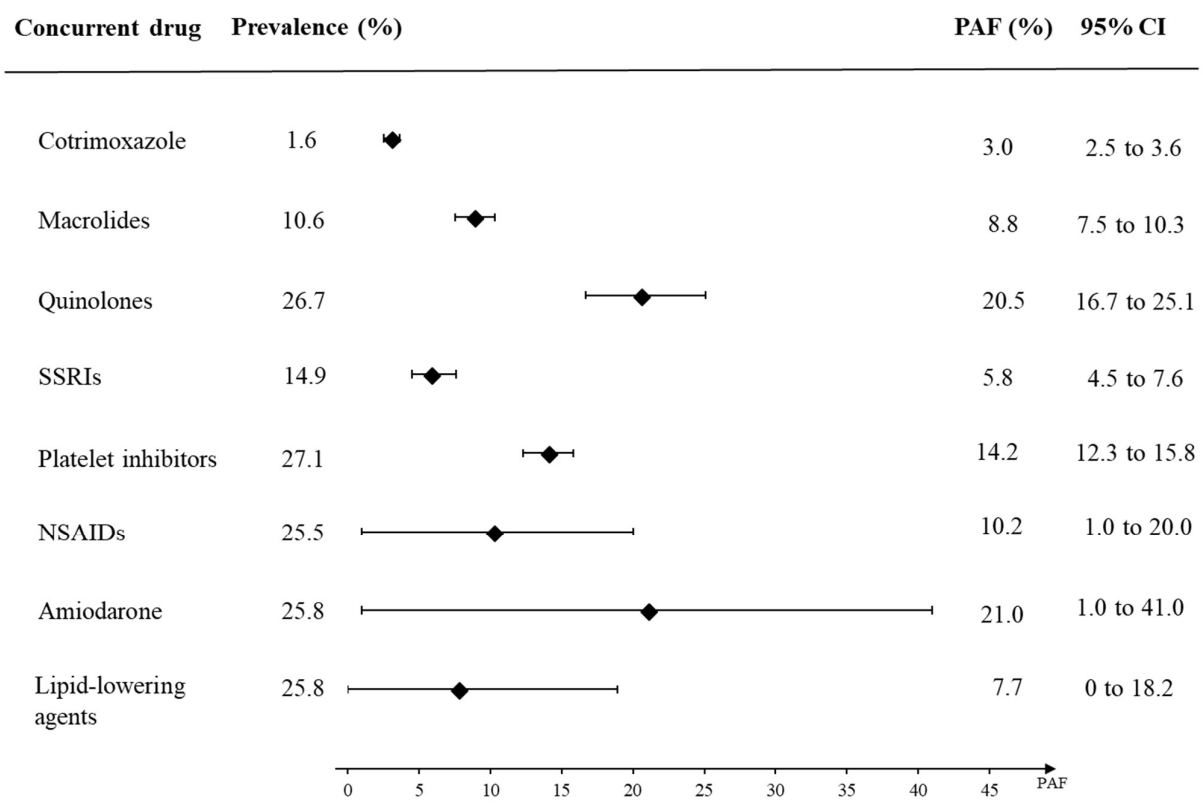




Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, that is, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with corresponding 95% CIs; p-values are from testing for heterogeneity between study-specific estimates; where p-values are <0.05, summary relative risk estimates are obtained by random effect model.

Abbreviations: SE, standard error; CI, confidence interval; SSRI, selective serotonin reuptake inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs.

Figure 9.6.3. Prevalence of concurrent users of warfarin and selected medicaments among warfarin users and corresponding population attributable fractions. I-GrADE project, Italy, 2007-2012



Squares represent population attributable fraction estimates; horizontal lines represent 95% CIs.

Abbreviation: PAF, population attributable fraction; CI, confidence interval; SSRI, selective serotonin reuptake inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs.

9.7 Supplementary material

9.7.1 Supplementary material_1

Characteristics of published studies investigating bleeding risk on concurrent users of warfarin and other medications

First author, publication year, country	Study design	Age	Outcome definition	No. cases	Concurrent therapy	Time window between concomitant use and bleeding	Reported RR (95% CI)	Controlled variables/ notes
Battistella, 2005, Canada (150)	Case-control	Over 65	Upper GI bleeding	24 22 25 17	NSAIDs Celecoxib Rofecoxib Ocular antibiotics	90 days	1.9 (1.4 to 3.7) 1.7 (1.2 to 3.6) 2.4 (1.7 to 3.6) 0.9 (0.7 to 1.3)	Age, gender, potential interacting medications, prior GI bleed, comorbidities, use of other gastrotoxic medications and antiulcer agents.
Kurdyak, 2005, Canada (151)	Case-control nested	Over 65	Upper GI bleeding	41 95 10 49 105 15	Fluoxetine/fluvoxamine Other SSRIs Secondary TCAs Fluoxetine/fluvoxamine Other SSRIs Secondary TCAs	90 days 180 days	1.2 (0.8 to 1.7) 1.1 (0.9 to 1.4) 0.7 (0.4 to 1.4) 1.2 (0.9 to 1.6) 1.0 (0.8 to 1.3) 1.0 (0.6 to 1.7)	Previous hospitalization for upper GI bleeding, medication associated with upper GI bleeding (NSAIDs, aspirin, glucocorticoids, PPI), CYP2C9 inhibitors and inducers, diabetes and medical comorbidity.
Douketis, 2007, Canada (152)	Case-control nested	Over 66	Upper GI or intracranial bleeding	NR	Statin	180 days	0.77 (0.46 to 1.30)	Number of drugs used in the past year, history of upper GI bleeding or intracranial bleeding, residency in a long-term care facility at cohort entry, number of different drugs prescribed in the year before the index bleed.

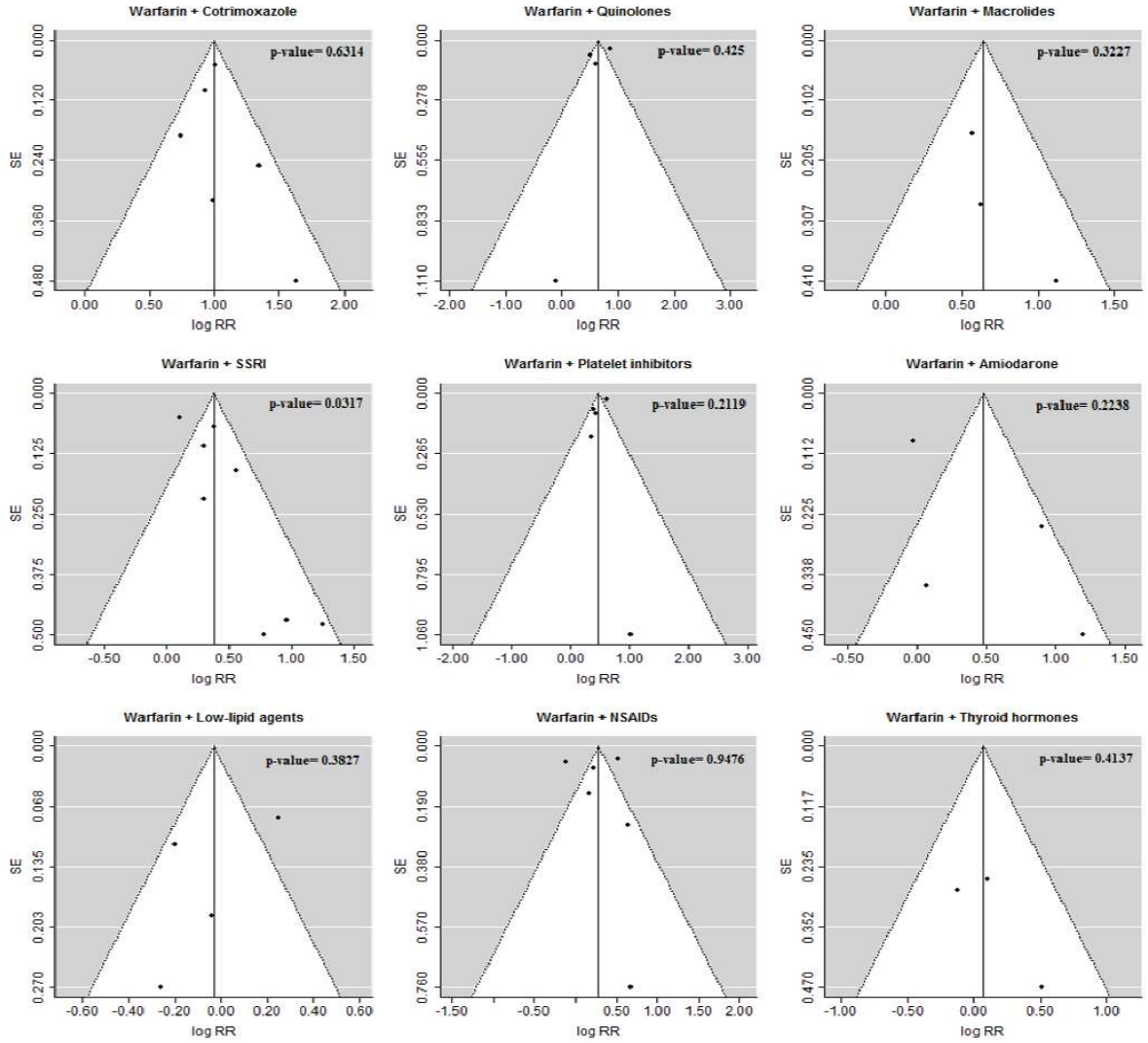
Schelleman, 2008, USA (153)	Case-control nested	Over 18	GI bleeding	150 214 21 75 35 104 112 1,940 166 2,830 850	Ciprofloxacin Levofloxacin Gatifloxacin Cotrimoxazole Fluconazole Cephalexin Amoxicillin PPI Metronidazole Paracetamol Prednisone	6-10 days 30 days	1.62 (1.31 to 1.99) 1.55 (1.30 to 1.86) 2.84 (1.79 to 4.49) 2.54 (2.08 to 3.10) 1.89 (1.35 to 2.64) 1.38 (1.10 to 1.73) 1.28 (1.03 to 1.58) 1.65 (1.57 to 1.73) 3.23 (2.76 to 3.78) 1.49 (1.42 to 1.55) 1.93 (1.80 to 2.07)	Age, gender, race, state, prior GI bleed, chronic renal disease, liver disease, use of concomitant drugs potentially associated with bleeding.
Wallerstedt, 2009, Sweden (154)	Cohort	55-80	Bleeding event	9 2 1 1	SSRI NSAIDs Aspirin Glucosamine	Concomitant	3.49 (1.37 to 8.91) 1.97 (0.44 to 8.74) 2.79 (0.35 to 22.21) 8.90 (1.10 to 71.94)	Age, gender, use of concomitant drugs potentially associated with bleeding.
Fischer, 2010, Canada (155)	Case-control nested	Over 65	Upper GI bleeding	25 30 31 11 5 10	Cotrimoxazole Amoxicillin or ampicillin Ciprofloxacin Nitrofurantoin Norfloxacin Ocular antibiotics	14 days	3.84 (2.33 to 6.33) 1.37 (0.92 to 2.05) 1.94 (1.28 to 2.95) 1.40 (0.71 to 2.75) 0.38 (0.12 to 1.26) 0.99 (0.50 to 1.93)	Age, gender, history of UGI haemorrhage, history of cirrhosis and alcoholism, number of prescription drugs within 1 year of the index date, long-term care status, other antibiotics of interest, and other concomitant drug use.
Hansen, 2010, Denmark (156)	Cohort	Over 30	Bleeding event	1,209 69	Aspirin Clopidogrel	90 days	1.83 (1.72 to 1.96) 3.08 (2.32 to 3.91)	Age, gender, comorbidities, concomitant medical treatment.
Schelleman, 2010, USA (157)	Case-control nested	Over 18	GI bleeding	67 16 277 499 113	Gemfibrozil Fluvastatin Simvastatin Atorvastatin Pravastatin	30 days	1.96 (1.19 to 3.24) 1.45 (0.68 to 3.09) 1.33 (1.00 to 1.78) 1.29 (1.04 to 1.61) 0.66 (0.38 to 1.14)	Age, gender, race, state, prior GI bleed, diabetes, number of prior warfarin prescriptions filled in the index date.
Cochran , 2011, Chicago (158)	Case-control	Over 18	Bleeding event	22 14	Antidepressants SSRI	6 months	2.0 (0.9 to 4.5) 2.6 (1.0 to 6.4)	-

Schelleman, 2011, USA (159)	Case-control	Over 18	GI bleeding	162 146 114 258 316 77 122 20 3,189 721 818 3,300	Citalopram Escitalopram Fluoxetine Paroxetine Sertraline Venlafaxine Amitriptyline Nortriptyline Paracetamol NSAIDs Levofloxacin PPI	29 days	1.73 (1.25 to 2.38) 1.19 (0.82 to 1.71) 1.63 (1.11 to 2.38) 1.64 (1.27 to 2.12) 1.18 (0.90 to 1.56) 1.43 (0.88 to 2.31) 1.47 (1.02 to 2.11) 1.45 (0.68 to 3.12) 1.55 (1.49 to 1.61) 1.68 (1.55 to 1.81) 2.36 (2.20 to 2.54) 1.48 (1.42 to 1.54)	Age, gender, index date, race, number of prior warfarin prescriptions filled on the index date, nursing home, use of concomitant drugs potentially associated with bleeding, dementia, liver disease, prior gastrointestinal bleed, renal disease.
Vitry, 2011, Australia (160)	Cohort	Over 65	Bleeding event	32 6 6 50 28 5 69 27 6 4 7	Antibiotics Macrolides Cotrimoxazole Low-dose aspirin Clopidogrel Amiodarone NSAIDs Celecoxib Tramadol SSRI Thyroid hormones	7 days 28 days	2.34 (1.55 to 3.54) 3.07 (1.37 to 6.90) 5.08 (2.00 to 12.88) 1.44 (1.00 to 2.07) 2.23 (1.48 to 3.36) 3.33 (1.38 to 8.00) 1.19 (0.90 to 1.59) 1.07 (0.69 to 1.68) 2.37 (0.93 to 6.01) 2.17 (0.81 to 5.78) 1.66 (0.66 to 4.16)	Age, gender, socio-economic index, number of co-morbidities, number of prescribers, number of different pharmacies used, previous bleeding related hospitalisations during the 1-year period before first warfarin prescription, number of different medicines prescribed during the study period, residential status and if bleeding occurred in the first 2weeks of warfarin initiation.
Baillargeon, 2012, Texas (161)	Case-control nested	Over 65	Bleeding event	17 17 24 40 22 31 36 156 70 27 49	Antibiotic agent Azole Antifungals Macrolides Quinolones Cotrimoxazole Penicillins Cephalosporins SSRI Corticosteroid SNRI Platelet inhibitors	15 days	2.37 (1.75 to 3.22) 1.86 (1.08 to 2.31) 1.86 (1.08 to 3.21) 1.69 (1.09 to 2.62) 2.70 (1.46 to 5.05) 1.92 (1.21 to 2.07) 2.45 (1.52 to 3.95) 1.34 (1.08 to 1.67) 2.30 (1.64 to 3.21) 1.17 (0.73 to 1.90) 1.43 (1.00 to 2.07)	Age, gender, indication for warfarin use, event month, ethnicity, all drug groups, comorbidity index, having stayed in a nursing home in the 90 days before event/index date.

Pincus. 2012, Canada (162)	Case-control nested	Over 66	Bleeding event	10,532	Levothyroxine	30 days	1.11 (0.67 to 1.86)	Age, gender, previous hospitalization with haemorrhage, income quintile, residence in a long-term care facility, history of atrial fibrillation or chronic kidney disease, number of drugs prescribed in the past year.
Suh, 2012, USA (163)	Case-control nested	Over 18	Bleeding event	164 141 95 32 93 42 117 168 226 273	Analgesics Anti-infectives Platelet inhibitors Anticoagulants Antidepressants Antiarrhythmics Thyroid hormones GI drugs Antihypertensives drugs Lipid-lowering agents	30 days	1.33 (1.07 to 2.24) 1.76 (1.39 to 2.13) 1.56 (1.18 to 1.68) 1.91 (1.20 to 2.14) 1.28 (0.97 to 1.55) 1.07 (0.74 to 3.04) 0.89 (0.70 to 2.07) 1.18 (0.98 to 1.06) 0.87 (0.71 to 1.19) 0.96 (0.78 to 1.65)	Age, gender, warfarin daily dose, days of warfarin exposure, previous hospitalizations or emergency room visits, number of outpatient visits, $CHADS_2$ score, specific comorbidities (stroke, cardiovascular disease, hypertension, anaemia, diabetes and GI disorders).
Lam, 2013, Canada (164)	Cohort	Over 65	Bleeding event	50	Amiodarone	30 days	2.45 (1.49 to 4.02)	Age, gender, year of cohort entry, high-dimensional propensity score.
Mosholder, 2013, UK (165)	Cohort	Over 65	Bleeding event	63 66 1,747 NR NR NR	Cotrimoxazole Ampicillin Oseltamivir Platelet inhibitors NSAIDs SSRI	7 days 14 days	3.07 (2.76 to 3.49) 1.89 (1.29 to 2.59) 1.47 (1.06 to 2.02) 1.48 (1.29 to 1.72) 1.24 (1.08 to 1.43) 1.11 (1.00 to 1.22)	Age, gender, geographical region, income subsidy, recent hospitalization, concomitant drugs potentially associated with bleeding, comorbid medical conditions including those that could affect bleeding (liver disease, cystitis, ulcer diverticulosis).
Lane, 2014, USA (166)	Cohort	Over 65	Bleeding event	14 30 11 33 2 5 3 11 34	Cotrimoxazole Ciprofloxacin Levofloxacin Azithromycin Clarithromycin Metronidazole Fluconazole Clindamycin Cephalexin	Concomitant	2.09 (1.45 to 3.02) 1.87 (1.42 to 2.50) 1.77 (1.22 to 2.55) 1.64 (1.16 to 2.33) 2.40 (1.16 to 4.94) 1.63 (0.61 to 4.39) 2.11 (0.60 to 7.34) 0.58 (0.31 to 1.09) 0.70 (0.48 to 1.04)	Age, gender, race, comorbid diagnosis, indication for anticoagulation, co-prescription of other medications known to interact with warfarin.
Quinn, 2014, California (167)	Cohort	Over 18	Major bleeding event	43 11	SSRI TCA	Concomitant	1.41 (1.04 to 1.92) 0.82 (0.56 to 1.46)	Age, gender, ATRIA bleeding risk score, time in INR range ≥3.0.

Abbreviations: No. cases, number of bleeding events; RR, relative risk; CI, confidence interval; GI, gastro-intestinal; NSAIDs, non-steroidal anti-inflammatory drugs; COX-2s, cyclooxygenase-2 inhibitors; PPI, proton-pump inhibitors; SSRI, selective serotonin reuptake inhibitors; UGI, upper gastro-intestinal; SNRI, serotonin norepinephrine reuptake inhibitors; $CHADS_2$, Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus, prior Stroke 2 or transient ischemic attack, or thromboembolism; NR, not reported; ATRIA, AnTicoagulation and Risk factors In Atrial fibrillation; INR, international normalized ratio.

9.7.2 Supplementary material_2



Funnel plots representing publication bias of published studies investigating bleeding risk on concurrent users of warfarin and other medications

Abbreviations: SE, standard error; RR, relative risk.

Chapter 10

Effectiveness of adherence to recommended clinical examinations of diabetics in preventing diabetes-related hospitalizations

Submitted to International Journal for Quality in Health Care (188)

10.1 Introduction

Evidence exists that microvascular and cardiovascular complications may be appreciably reduced in patients with type 2 diabetes when multifactorial, intensive lifestyle modifications are implemented (189). Accordingly, evidence-based clinical practice guidelines (CPGs) have been published (190–192), with specific recommendations for managing patients with type 2 diabetes. Nevertheless, studies investigating the success of guidelines on the management of diabetes have shown that treatment goals are often not met in 'real-life' practice, and implementation of strategies for protecting the onset of complications in patients with type 2 diabetes remains suboptimal (193–195).

Several initiatives have been implemented for monitoring the quality of care for patients with diabetes in 'real-life' practice, while controlling costs (196–200). The Diabetes Quality Improvement Project (DQIP), which was designed to influence the care of patients with diabetes from United States (201), developed a set of indicators for monitoring care quality. Among these, the so-called accountability indicators consisting in verifying the percentage of diabetics who regularly receive clinical evaluations (e.g., glycaemic and lipid profiles, kidney functioning and dilated eye exams) are focused to compare health systems and plans or providers (197). Although improvements in the process of diabetes care have been documented though these indicators, their effectiveness is largely untested (202–204), making evaluation essential.

According to the Italian Constitution, responsibility for guaranteeing citizens' health is shared by the Central Government and every of the 21 administrative units (19 regions and 2 autonomous provinces), so justifying the need of the first for comparing quality of care supplied by the latter. Accordingly, a system of assessment for integrated care pathways across different levels for specific

clinical conditions is on developing by a National expert working group of the Italian Health Ministry. In developing the system of indicators, particular attention was taken to what was actually measurable by, and comparable between, the Italian regions.

Taking inspiration by the above-mentioned DQIP accountability indicators, the working group developed a set of process indicators for quality of diabetes care. Because a better process profile, as measured by these indicators, not necessarily translate into better outcomes, a study for validating the set of indicators through their relationship with measurable clinical outcomes was designed. The current paper reports methods and main findings of the validation study and discusses the implications of monitoring the process of diabetes care and, more in general, of the proposed approach.

10.2 Methods

Data sources

This study is based on computerized healthcare utilization (HCU) databases from three Italian regions (Lombardy, Emilia-Romagna and Lazio). Overall, these data covered almost 20 million beneficiaries of the Italian NHS, nearly one third of the entire Italian population.

All Italian citizens have equal access to health care services as part of the NHS. Information systems of healthcare utilization databases exist within each of the 20 Italian regions to collect a variety of information, at least including: 1) an archive of residents who receive NHS assistance (the whole resident population), reporting demographic and administrative data, other than the dates in which the individual started (because he/she was born or immigrated) or stopped (because he/she died or emigrated) the condition of NHS beneficiary; 2) a database on hospital discharge records including information about primary diagnosis, co-existing conditions and performed procedures (coded according to the ICD-9 CM classification system); 3) a drug prescription database providing information on all community drugs reimbursed by the NHS (coded according to the Anatomical Therapeutic Chemical (ATC) classification system); 4) a database on outpatient visits, including visits in specialist ambulatories and diagnostic laboratories accredited from the NHS; 5) a database on co-payment exception for diagnosed chronic disease, including diabetes. As a unique identification code was used for all databases within each region, their record linkage allowed searching out the complete care pathway of beneficiaries of NHS. In order to preserve privacy, identification codes were

automatically converted into anonymous codes, and the inverse process was prevented by deletion of the conversion table.

Harmonization and data processing

Although databases did not substantially differ across all regions for several aspects, a data harmonization was performed, thus allowing that data extraction processes targeted the same semantic concepts, and analyses to be performed under a common data model. Anonymized data were extracted and processed locally by using a common Statistical Analysis System (SAS) program which was developed by one of ours according to protocol previously approved by the Italian Health Ministry working group.

Diagnostic and therapeutic codes used in the current study for drawing records and fields from databases are reported in Table S1.

Capturing "prevalent" and "incident" diabetics

Beneficiaries of the NHS who in the index year (i.e., in 2014) had aged 18 years or older and were resident in three Italian regions (Lombardy, Emilia-Romagna and Lazio) formed target population. With the aim of ensuring enough time back for capturing diabetics, subjects were excluded if they were recorded as beneficiaries of the regional NHS after the year 2011.

Subjects belonging to the target population were considered affected by diabetes whether they leaved 'footprints' of diabetes through supplied services from the NHS. Accordingly, prevalent diabetics were subjects who in the last two years prior the index one (i.e., from 2012 until and including the index year) had at least two prescriptions of antidiabetic agents in two distinct dates over 365 days, and/or at least one hospital admission with primary or secondary diagnosis of diabetes. In addition, subjects who in the year 2014 took advantage on co-payment exemption for diabetes were also considered prevalent diabetics.

Subjects belonging to the target population were patients newly taken in care for diabetes whether they for the first time during the index year leaved 'footprints' of diabetes through supplied services from the NHS. According to this definition, incident diabetics were the portion of prevalent ones who in the last three years prior the index one (i.e., from 2011 until and excluding the index year) did not

experience any antidiabetic prescription, hospital admission with primary or secondary diagnosis of diabetes, and co-payment exemption for diabetes.

Prevalence and incidence rates of diabetes were calculated for the target population of each participant region and for the whole population of all the regions taken together. Rates were standardised (direct method) according to gender and twenty-year intervals of age of the Italian population. Between-region differences in prevalence and incidence rates were evaluated by testing the null hypothesis of homogeneity according to Esteve et al. (205).

Incident cohort features and follow-up

In order to have enough time to appreciate the effect of adherence to recommendations on the selected outcomes (see below), subjects detected as incident diabetics during 2010 were included in the study cohort: in other words, the clock was bring back four years with respect to the above reported time interval used for detecting incident diabetics. Patients entered into the cohort at the date when the first 'footprint' of diabetes was leaved, i.e., when the second antidiabetic prescription or the first hospital admission was experienced, or the co-payment exception was released during the index year, whatever occurred firstly.

Baseline characteristics of cohort members (i.e., those recorded at the date of cohort entry or during the previous three years) included gender, age, drug therapies and comorbidities. Drug therapies included antiplatelet, digitalis glycosides, organic nitrates, antiarrhythmics, blood pressure- and lipid-lowering agents, antidepressants, non-steroidal anti-inflammatory drugs, anti-gout agents and drugs for chronic obstructive pulmonary disease. Comorbidities were measured through previous hospitalizations for cancer, heart failure, and ischaemic heart, cerebrovascular, respiratory and kidney disease. In addition, the so-called Multisource Comorbidity Score, a new comorbidity index obtained from both inpatients diagnostic information and outpatients drug prescriptions, and recently validated using data from the here considered Italian regions (53), was considered.

Cohort members accumulated person-years of follow-up starting from the date of cohort entry until the occurrence of one of the following events, whichever came first: the study outcome (hospital admission for selected diagnoses, see below), death, emigration, or end-point of follow-up, i.e., December 31, 2015.

Adherence to recommendations

Outpatient visits, including assessments of glycated haemoglobin, lipid profile (total and HDL cholesterol and triglycerides), urine albumin excretion, serum creatinine and dilated eye exams dispensed to cohort members during follow-up were identified. A patient was considered adherent to recommendations whether he/she every year was submitted to at least two glycated haemoglobin assays, and at least one of the other evaluations (191,206).

Other than for each individual recommendation, the cumulative number of recommendations was calculated. A score of increasing adherence was developed by categorizing each cohort member according whether almost none (0 or 1), just some (2 or 3) or almost all (4 or 5) recommendations were followed in a given year.

Outcome

A composite outcome was developed to take into account complications of diabetes potentially avoidable. A cohort member was considered to experience the outcome whether during follow-up at least one hospital admission occurred with primary or secondary diagnosis, or correlated procedures, of: (i) brief-term diabetes complications, (ii) uncontrolled diabetes, (iii) long-term vascular outcomes, and (iv) no traumatic lower limb amputation (ICD-9 CM codes used for capturing outcomes are reported in Supplementary material_1). The date of first hospitalization with one of these diagnoses was considered as the date of outcome onset.

Association between adherence and outcome

We used the following two-stage procedure (207) for generating pooled meta-analytic estimates of adherence-outcome association.

In the first stage, a Cox proportional hazard regression model was fitted within each participant region for separately estimating the hazard ratio (HR) and its 95% confidence interval (CI), for the association between adherence to each recommendation taken individually, as well as to the total adherence score, and the risk of experiencing the outcome. Adjustments were made for above listed covariates. As adherence may change over time, assessment of its effect requires consideration of its varying nature. A time-dependent covariate was built by considering the adherence to recommendations experienced during the one-year period before each risk set forms itself up, i.e., by the patient who the outcome occur at a given moment of the follow-up (case) and the cohort members

who until then have not experienced it, having accumulated the same observation period of the case. In this way, the brief-term effect of adherence on the outcome onset (close adherence) was investigated. However, as more careful and frequent evaluations might be requested because of worsening clinical profile, we realized that a paradoxical positive adherence–outcome association might be observed by considering adherence so close to the outcome. To account for such a bias, which can be considered as a form of protopathic bias (208), a time-dependent adherence delayed of one year with respect to the close adherence was also considered (delayed adherence).

In the second stage, we summarized the original estimates by using a random-effect model. The latter assumes that the true relationship between adherence and outcome could vary between regions that is, the region-specific effect estimates are assumed a random sample of the corresponding relevant distribution, and the combined estimates the mean effect of this distribution. The approach proposed by DerSimonian and Laird was used for estimating such an effect (113). Heterogeneity of estimates between regions was tested by Cochran's Q test and measured with the I^2 statistics (the proportion of between-region variability due to heterogeneity) (118).

For all hypotheses tested, 2-tailed p-values less than 0.05 or, in an equivalent manner, 95% CI of HR that does not contain the value expected under the null hypothesis was considered significant.

Ethical issues

The Ethical Committee of the University of Milano-Bicocca evaluated the protocol and established that the study (i) to be exempt from informed consent (according to General Authorization for the Processing of Personal Data for Scientific Research Purposes Issued by the Italian Privacy Authority on December 15, 2016; http://www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/docweb/5805552) (ii) provides sufficient guarantees of anonymizing individual records, and (iii) was designed according to quality standards of good practice of observational research based on secondary data.

10.3 Results

Prevalence and incidence of diabetic subjects

Table 10.5.1 shows that, among the nearly 16 million NHS beneficiaries forming the whole target population, 1,139,043 and 76,490 subjects respectively met our algorithm for capturing prevalent and incident diabetics in the year 2014, being the corresponding standardised rates 6.7 diabetics every

100 persons and 4.5 new diabetics every 1,000 person-year. There was evidence that prevalence and incidence standardised rates significantly differed between regions, being higher rates observed for the population from Lazio.

Baseline characteristics of the cohort of 77,285 diabetics newly taken in care during 2010 are shown in Table 10.5.2. Although beneficiaries from Lazio showed lower values of the Multisource Comorbidity Score, they were at higher prevalence of patients under treatment with almost all the considered drugs.

Adherence to recommendations

During the first year after diagnosis, newly taken in care diabetics (incident cases) had in general little adherence to the considered recommendations, being only 16% of them submitted to dilated eye exam, little bit more than 30% to glycated haemoglobin and urine albumin excretion evaluations, and more than half to lipid profile and serum creatinine assays (Table 10.5.3). It is noteworthy that 20% and 44% of newly taken in care diabetics respectively adhered to almost all (4 or 5) or almost none (0 or 1) recommendations. Again, there was evidence that diabetics from Lazio had lower adherence than those from Lombardy and Emilia-Romagna ($p < 0.001$).

Outcome

During follow-up, cohort members accumulated 322,645 person-years of observation and experienced 875 hospital admissions for brief-term diabetes complications (incidence rate, 2.4 cases every 1,000 PY), 4,372 uncontrolled diabetes (12.0 every 1,000 PY), 18,319 long-term vascular outcomes (55.7 every 1,000 PY), and 262 no traumatic lower limb amputation (0.7 every 1,000 PY). The first occurring hospital admission for one of these causes (i.e., the composite outcome of interest) happened for 20,363 cohort members with incidence rate of 63.1 cases every 1,000 PY.

Association between adherence and outcome

Forrest plots for the adherence-outcome relationship within each participant region, as well as for summarizing national data, are shown in Figure 10.6.1. In some cases, the protective action of adherence to recommendations was better highlighted by the delayed adherence, than by near one (i.e., by considering exposure to recommendations in the period brought back of one year with respect to the closer one). This was dramatically evident for patients who closely adhered to serum creatinine who were at 50% higher outcome risk than no-adherent patients. Conversely, delayed adherence to serum creatinine, but also to glycated haemoglobin, was significantly associated with reduced

outcome risk. There was no clear evidence that close and delayed adherences generated different estimates for the remaining recommendations. In addition, although usually significant (with the exception of dilated eye exam), adherence to each individual recommendation was weakly associated with the outcome, being summarized risks of adherent diabetics reduced of around 10% or less with respect to no adherent ones. It is noteworthy that there was never evidence of between regions heterogeneity of the estimated delayed adherence-outcome associations.

Figure 10.6.2 reports the trend in HRs according to increasing level of delayed adherence within each participant region, as well as for summarizing national data. A clear trend towards decreasing outcome risk as the total adherence score increases was observed for all regions, albeit with between-region differences. According to summarized estimates, compared to diabetics who adhered to none or almost none recommendation, significant risk reductions of 16% (95% CI, 6% to 24%) and 20% (7% to 28%) were observed for those who adhered to just some (2 or 3) and almost all (4 or 5) recommendations, respectively.

10.4 Discussion

The present study confirms previous observations that guidelines for the management of diabetes are often not met in the 'real-life' practice (197), even in the Italian setting (200). In addition, evidence of regional variations in the management of diabetes within the same country (209–211), was confirmed from our study. The new important finding, however, is that diabetics who regularly received almost all the recommended clinical evaluations (i.e., assessments of glycated haemoglobin, lipid profile, urine albumin excretion and serum creatinine and dilated eye exams) had a 20% reduction of the risk of hospitalization for selected outcomes compared to patients who received none, or almost none evaluation. Assuming that these estimates are unbiased, the proportion of complication of diabetes attributable to suboptimal adherence to recommendations was of 9.8%, i.e., nearly 1,990 of the 20,363 hospital admissions occurred among cohort members could have been avoided if all they had adhered to the considered recommendations (212). This finding is very important for reaching a consensus in how to measure and compare the quality of care of diabetics, to develop process improvements, and to reduce practice heterogeneity (200).

Our results suggest that not only patients, but also the health care system could benefit of improving management of diabetics (213). In fact, an annual cost of around 60 Euros is expected from the NHS perspective for performing the considered evaluations. To put this cost along some perspective, recent

estimates indicate average annual costs for diagnosed diabetes ranging from 3,110 € in Spain (214) until 8,308 € in USA (215). In addition it has been reported that annual hospital costs for people with diabetes experiencing major CV complications, are between four and ten times the average per capita health expenditure in a given country (216) (i.e., 2,713 € for Italy in the year 2014 according to the World Bank data (217)).

Our study was designed under the auspices of the Italian Health Ministry with the aim to obtain a simple tool for appreciating regional variations in the management of patients with diabetes. This implies the availability of good quality data useful for (i) capturing prevalent diabetics; (ii) identifying those who are newly taken in care; (iii) characterizing they as far as possible for their features; (iv) outlining their use of recommended clinical services; and (v) identifying those who experience relevant clinical outcomes. This was made possible because in Italy, an automated system of databases providing information on essential healthcare, including those for diabetes care, was available in each of the 19 regions for the management of the public funded healthcare system virtually involving all citizens. Because of constraints limiting the free movement of electronic health data even within the same country (218), a two-stage procedure allowing for local data processing and subsequent pooling aggregate data, was adopted. Admitting comparability in data quality, guarantees of privacy respect and estimates accuracy are provided by the procedure (219). Accordingly, the illustrated design is ongoing to be applied to other relevant chronic diseases including heart failure, chronic obstructive pulmonary disease, breast and colorectal cancer, among others.

Existing figures pertaining to general adult population showed prevalence rates ranging from 6% (England) to 8% (USA) (220,221), and incidence rates ranging from 2 cases every 1,000 PY (Ireland) to 7 cases every 1,000 PY (USA) (220,222). We found prevalence and incidence rates respectively being 7% and 5 cases of every 1,000 PY, therefore within the expected range according to the worldwide figures.

Routine laboratory tests of glycosylated haemoglobin, lipid profile, serum creatinine and urinary albumin are recommended for patients with diabetes (191,206). Consistently with other reports (223), some of which refer to the Italian setting (224,225), we found a wide gap between guidelines-driven recommendations and their clinical application. In fact, we observed that only 34% of the included incident diabetics controlled at least twice glycosylated haemoglobin, while only 20% of them

adhered to all, or almost all, the recommended controls within the first year after they were taken in care. This finding is of particular concern given that nearly one-fifth of participants had a history of major CV outcomes and three out five of them had comorbidities related to increasing mortality risk. Much has been written on the concept of "clinical inertia", that is the finding that medication changes are not made in a prompt manner (226,227)). However, as clinical action cannot be taken whether laboratory tests that have not been completed, delays in patients' presenting for laboratory testing represent one more barrier to timely care (206).

Few and inconsistent evidence is available regarding the generally assumed relationship between adherence to recommendations and patient outcomes (228–233). Inconsistency is likely due to serious difficulties inherent systematic uncertainty of observational evaluations. For example, in our application we found that adherence to recommendations in a given year, particularly to serum creatinine and glycosylated haemoglobin evaluations, was associated with increased risk of outcome. We suspect that protopathic bias might explain this paradoxical finding. In fact, the symptomatic onset of diabetic complications in the outpatients setting (unobserved true outcome) may have led to changing therapeutic regimen and then to increasing clinical evaluations for monitoring its effect. In these conditions, a paradoxical positive association between exposure and detected outcome (hospital admission) could be observed (208). To address this possibility, a one-year delayed lag-time period preceding the detected outcome was applied. As suspected, by this stratagem following the considered recommendations were found to exert a protective action on the outcome onset.

We found that rather than with each individual recommendation, the cumulative number of followed recommendations predicted the outcome onset, that is, the higher is its value, the better the protective action on diabetes related hospitalizations. Among the possible explanations for this finding, the more reasonable is that the speed of diabetes progression might be reduced by structured care of which regular control might be a proxy.

Limitations of the study should be taken into account for correctly interpreting our results. One, as individuals aged less than 18 years were excluded from the considered target population, patients affected by, and taken in care for type 2 diabetes mellitus should have been mainly captured. Nevertheless, we cannot exclude that some patients with type 1 diabetes may have been included. This however, does not modify our main conclusion that diabetics, both type 1 and type 2, should benefit of more careful adherence to recommendations. Two, information about health service

outpatient facilities supplied by private organizations are not available from our databases. For example, we suspect that, particularly for some regions, a portion of eye exams are performed in private clinics. Three, the length of follow-up might be insufficient to appreciate the effect of disease progression on clinical outcome. It is possible that the protective action of regular control found in our study faded after a longer follow-up period, so that only a general trend, rather than a reliable estimate of the strength of association, may be appreciate from our study. Four, adherence to pharmacological therapy (i.e. to antidiabetic agents) was not taken into account in our analysis. However, antidiabetic agents available in the Italian market at the time of our patients' follow-up have shown only modest beneficial effects on macrovascular complications (234–237), which are the main cause of hospital admission among those considered for building the composite outcome. In addition, not all diabetics need drug therapy since some of them achieve glycaemic control with diet and exercise alone. Finally, because patients with frequent controls are expected to have different clinical characteristics than those with less intensive examinations, our results could be affected by confounding by indication. That is, the reduction in diabetes-related hospitalization associated with better adherence to recommendations might have been generated by uncontrolled factors, accompanying but different from a better adherence. For example, less frequent controls might had been requested for patients who reached good glycaemic target. However, as the latter are at lower baseline risk of experiencing the outcome, the protective action of regular controls is expected to be higher than that observed in our study. Of course, this does not entirely eliminate the problem of confounding, one aspect of which is that because adherence may be a surrogate for overall health-seeking behaviour, patients more adherent might also have more regularly followed healthy lifestyle advices, more effectively treated or dealt with diabetes more frequently as out- rather than in-hospital. Further evidence is thus urgently needed to confirm the protective role of adherence to recommendations among diabetics.

In the meantime, because benefits for patients and health care system are expected from improving adherence to guidelines-driven recommendations, tight control of diabetics through regular clinical examinations must to be considered the cornerstone of national guidance, national audits, and quality improvement incentives schemes.

10.5 Tables

Table 10.5.1. Diabetes prevalence (patients who in the index year and/or in the previous 2 years leaved 'footprints' of disease presence) and incidence (newly taken in care patients) among beneficiaries of the National Health Service (NHS) of three Italian regions

	Lombardy	Emilia-Romagna	Lazio	Total
NHS beneficiaries aged 18 years or older	8,277,623	3,734,707	4,902,165	16,914,495
All known diabetics (prevalent) [#]	516,547	256,670	365,826	1,139,043
Prevalence rate (every 100 persons)				
Crude	6.2	6.9	7.5	6.7
Standardized	6.2	6.6	7.7	6.7
Newly taken in care diabetics (incident) [§]	37,462	15,904	23,124	76,490
Incidence rate (every 1,000 PY)				
Crude	4.5	4.3	4.7	4.5
Standardized	4.4	4.1	4.8	4.5

[#] Subjects were considered prevalent cases of diabetes whether in the current year and/or in the previous two years had at least (i) two prescriptions of antidiabetic drugs in two distinct dates, and/or (ii) a hospital admission with primary or secondary diagnosis of diabetes; and/or those who in the current year (iii) took advantage on exemption to pay health service for diabetes

[§] Subjects were considered incident cases of diabetes whether in the current year had at least (i) two prescriptions of antidiabetic drugs in two distinct dates, and/or (ii) a hospital admission with primary or secondary diagnosis of diabetes; and/or those who in the current year (iii) obtained for the first time the exemption to pay health service for diabetes; among these patients, those who in the three years before current had at least a prescription of antidiabetic drugs and/or a hospital admission with primary or secondary diagnosis of diabetes; and/or those who already had the exemption for diabetes, were excluded

Table 10.5.2. Baseline characteristics of diabetics newly taken in care (incident cases) in three Italian regions

	Lombardy	Emilia-Romagna	Lazio	Total
Male gender	18,987 (54.5%)	9,225 (53.4%)	12,353 (49.1%)	40,565 (52.5%)
Age (years)				
18-30	547 (1.6%)	314 (1.8%)	760 (3.0%)	1,621 (2.1%)
31-50	5,472 (15.7%)	2,778 (16.1%)	4,313 (17.2%)	12,563 (16.3%)
51-70	17,759 (50.9%)	7,654 (44.3%)	12,063 (48.0%)	37,476 (48.5%)
70-90	10,624 (30.5%)	6,210 (36.0%)	7,755 (30.8%)	24,589 (31.8%)
>90	460 (1.3%)	317 (1.8%)	259 (1.0%)	1,036 (1.3%)
Medications †				
Antiplatelet	10,005 (28.7%)	4,386 (25.4%)	8,297 (33.0%)	22,688 (29.4%)
Digitalis glycosides	1,265 (3.6%)	453 (2.6%)	1,052 (4.2%)	2,770 (3.6%)
Organic nitrates	2,267 (6.5%)	653 (3.8%)	1,641 (6.5%)	4,561 (5.9%)
Antiarrhythmics	1,099 (3.2%)	272 (1.6%)	856 (3.4%)	2,227 (2.9%)
Blood-pressure lowering agents	20,651 (59.2%)	7,837 (45.4%)	16,072 (63.9%)	44,560 (57.7%)
Lipid lowering agents	7,113 (20.4%)	3,490 (20.2%)	7,730 (30.7%)	18,333 (23.7%)
Antidepressants	3,456 (9.9%)	1,889 (10.9%)	3,089 (12.3%)	8,434 (10.9%)
NSAIDs	10,417 (29.9%)	4,295 (24.9%)	12,870 (51.2%)	27,582 (35.7%)
Anti-gout drugs	2,457 (7.1%)	1,147 (6.6%)	1,761 (7.0%)	5,365 (6.9%)
Drugs for COPD	4,254 (12.2%)	2,057 (11.9%)	5,310 (21.1%)	11,621 (15.0%)
Comorbidities #				
Cancer	3,474 (10.0%)	1,801 (10.4%)	2,258 (9.0%)	7,533 (9.7%)
Ischemic heart disease	2,788 (8.0%)	1,426 (8.3%)	1,625 (6.5%)	5,839 (7.6%)
Cerebrovascular disease	1,984 (5.7%)	1,138 (6.6%)	1,313 (5.2%)	4,435 (5.7%)
Heart failure	1,551 (4.5%)	1,063 (6.2%)	933 (3.7%)	3,547 (4.6%)
Respiratory disease	3,195 (9.2%)	1,888 (10.9%)	1,997 (7.9%)	7,080 (9.2%)
Kidney disease	938 (2.7%)	601 (3.5%)	574 (2.3%)	2,113 (2.7%)
Multisource comorbidity score				
0	21,859 (62.7%)	10,022 (58.0%)	12,783 (50.8%)	44,664 (57.8%)
1	5,933 (17.0%)	3,476 (20.2%)	6,683 (26.6%)	16,092 (20.8%)
2	3,630 (10.4%)	1,926 (11.2%)	3,176 (12.6%)	8,732 (11.3%)
3	1,367 (3.9%)	758 (4.4%)	1,230 (4.9%)	3,355 (4.3%)
4	2,073 (6.0%)	1,091 (6.3%)	1,278 (5.1%)	4,442 (5.7%)

NSAIDs: Non-steroidal anti-inflammatory drugs; COPD: chronic obstructive pulmonary disease

† According to drug dispensed in the 3 years before the current

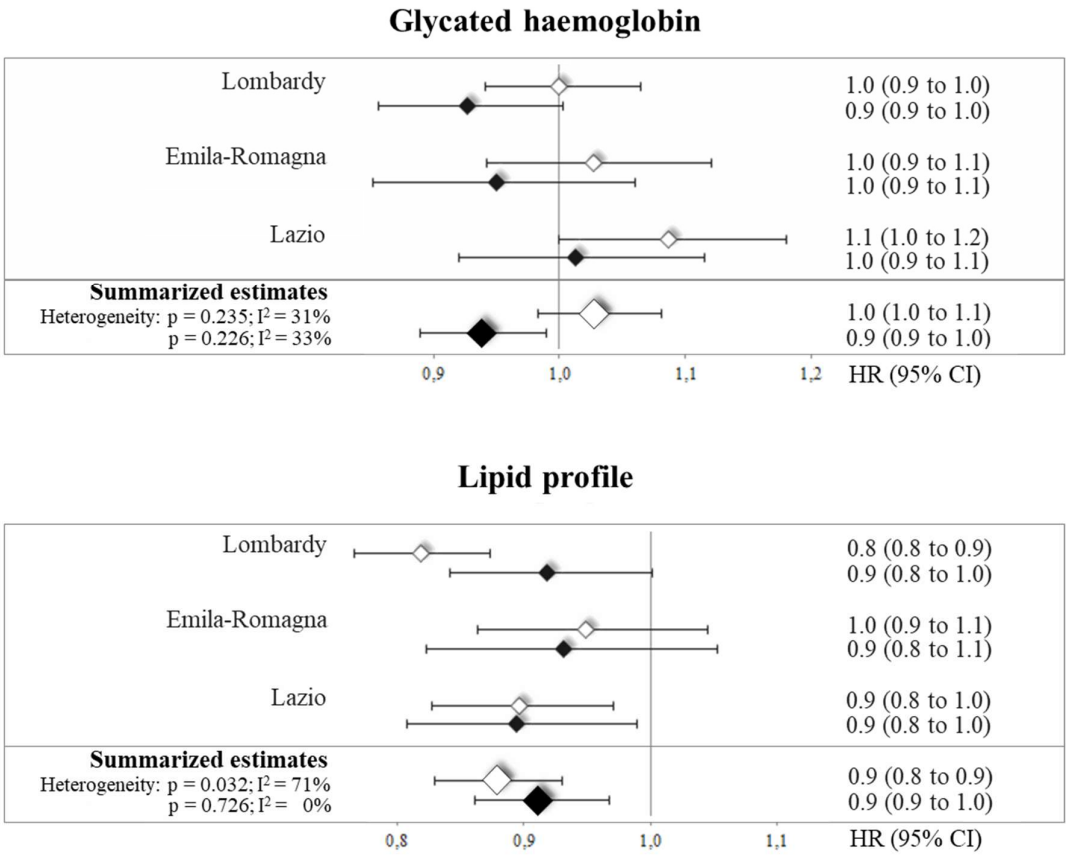
According to hospital admission in the 3 years before the current

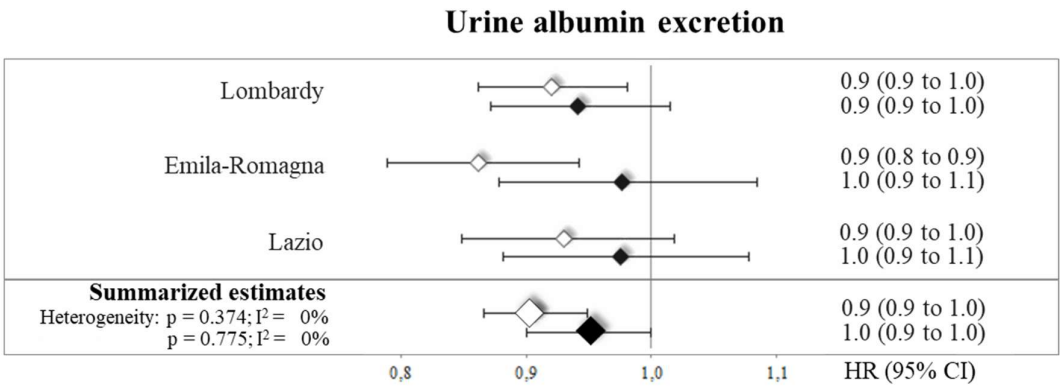
Table 10.5.3. Diabetics newly taken in care (incident cases) who during the first year after diagnosis adhered to selected recommendations in three Italian regions

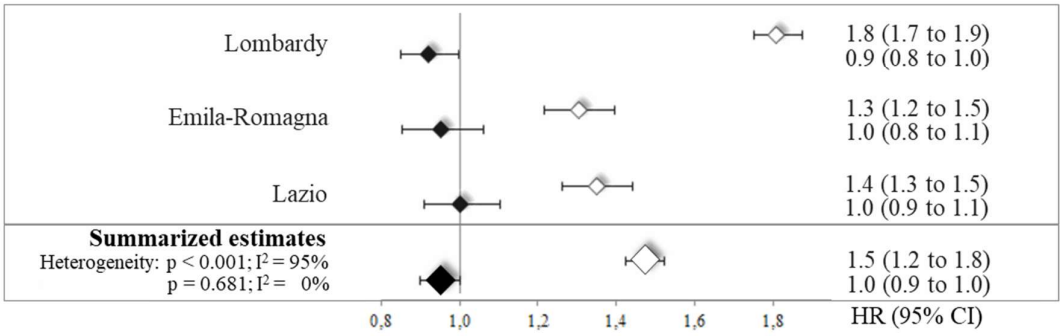
	Lombardy	Emilia-Romagna	Lazio	Total
Individual recommendations				
Glycated haemoglobin	13,881 (39.8%)	6,349 (36.8%)	5,997 (23.8%)	26,227 (33.9%)
Lipid profile	19,297 (55.4%)	9,365 (54.2%)	11,575 (46.0%)	40,237 (52.1%)
Urine albumin excretion	11,976 (34.4%)	6,565 (38.0%)	4,841 (19.3%)	23,382 (30.3%)
Serum creatinine	21,176 (60.7%)	11,000 (63.7%)	14,314 (56.9%)	46,490 (60.2%)
Dilated eye exam	4,204 (12.1%)	3,888 (22.5%)	3,936 (15.7%)	12,028 (15.6%)
Categories of cumulative number of recommendations				
0 or 1	14,015 (40.2%)	6,702 (38.8%)	13,249 (52.7%)	33,966 (44.0%)
2 or 3	13,350 (38.3%)	6,108 (35.4%)	8,309 (33.0%)	27,767 (35.9%)
4 or 5	7,497 (21.5%)	4,463 (25.8%)	3,592 (14.3%)	15,552 (20.1%)

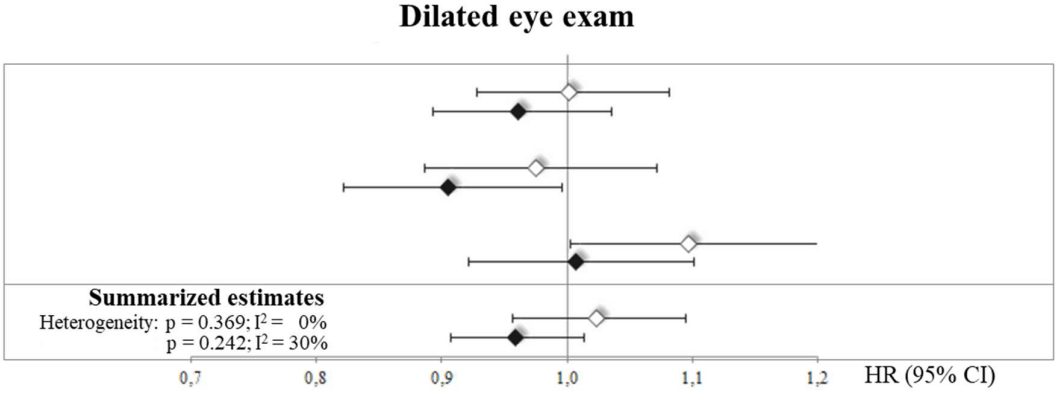
10.6 Figures

Figure 10.6.1. Forest plots of region-specific (smaller diamonds) and summarized (larger diamonds) hazard ratios (HR) for the association between time-dependent close (black diamonds) and delayed (white diamonds) adherence to selected recommendations, and the risk of hospital admission for selected causes, including brief-term diabetes complications, uncontrolled diabetes, long-term vascular outcomes, and no traumatic lower limb amputation



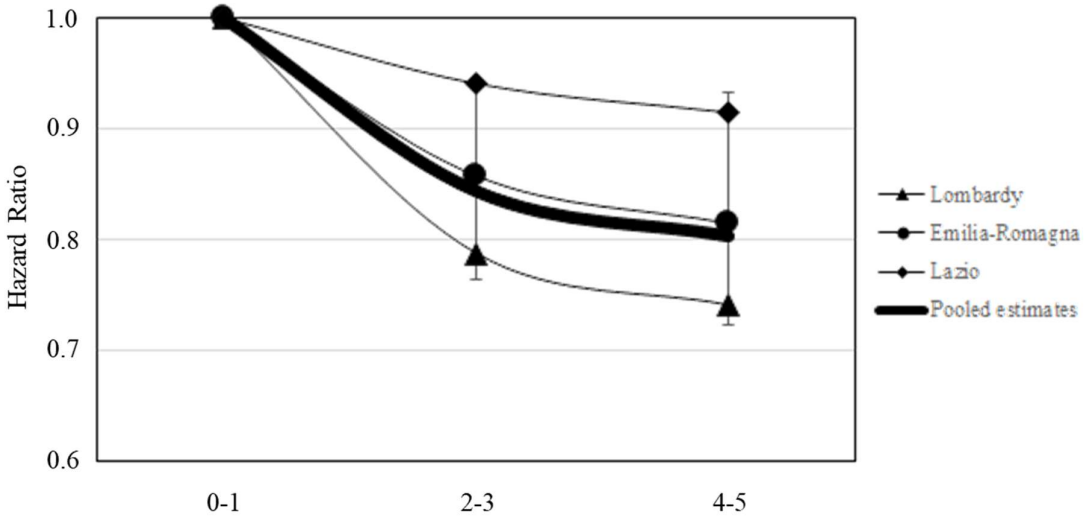






Adherence to recommendations experienced during the one-year period before each risk set (close adherence) and delayed of one year with respect to the close adherence (delayed adherence) are considered. HR, and 95% confidence intervals (represented by horizontal lines), were estimated by fitting a Cox proportional hazard model. Estimates were adjusted for gender, age and selected medications and comorbidities (please see covariates listed in Table 10.5.2). Random effects model was used for summarized estimates. P-values and I^2 testing and measuring for heterogeneity between region estimates are reported

Figure 10.6.2. Trends in region-specific and summarized hazard ratios (HR) for the association between categories of total adherence to recommendations and the risk of hospital admission for selected causes, including brief-term diabetes complications, uncontrolled diabetes, long-term vascular outcomes, and no traumatic lower limb amputation



HR were estimated by fitting a Cox proportional hazard model. Estimates were adjusted for gender, age and selected medications and comorbidities (please see covariates listed in Table 10.5.2). Random effects model was used for summarized estimates. Vertical lines represent 95% confidence intervals of summarized HR.

10.7 Supplementary material

Supplementary material_1

ICD-9 codes

Description		ICD9-CM codes
Case identification		
Diabetes mellitus		250.*, 648.0
Outcomes		
Brief-term diabetes complications		250.3*, 250.8*, 251.0, 251.1, 251.2, 962.3
Long-term diabetes complications		250.4*-250.9*
	Heart failure	428.*, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93
	Myocardial infarction	410.*, 411.0, 412, V45.81, V45.82
	Cerebrovascular disease	430.*-438.*
	Arrhythmia	426.*, 427.0-427.4, 427.6*, 427.8*, 427.9, 37.8* (procedure code)
	Peripheral vascular disease	250.7*, 440.2*, 440.3*, 443, 444
	Lower limb complications	681.1*, 682.6, 682.7, 707.1, 711.9*, 713.5, 730.0*, 730.1*, 730.2*, 730.3*, 785.4
	Operations on vessels of heart	36.0*-36.3*, 36.9, 88.5* (procedure codes)
Uncontrolled diabetes		250.02, 250.12, 250.22, 250.32
No traumatic lower limb amputation		84.10-84.19 (procedure codes)
Covariates		
Cancer		140-239.*
Ischemic heart disease		410-414.*
Cerebrovascular disease		430-438.*
Heart failure		428.*, 402.01, 402.11 e 402.91
Respiratory disease		460-519.*
Kidney disease		584-586.*

ATC codes

Drugs	ATC codes
Antidiabetic agents	A10
Antiplatelet	B01A
Digitalis glycosides	C01AA
Organic nitrates	C01DA
Antiarrhythmics	C01B
Blood-pressure lowering agents	C02, C03, C07, C08, C09
Lipid lowering agents	C10
Antidepressants	N06A
NSAIDs	M01A
Anti-gout drugs	M04
Drugs for COPD	R03

Chapter 11

Effectiveness of adherence to recommended clinical examinations and therapy in subjects with heart failure: A real-world study from Italian health claims

Work in progress

11.1 Introduction

Heart failure (HF) is a complex clinical syndrome that affects more than 23 million people worldwide (238). Its prevalence is between 1% and 3% in adult population of high-income countries, but it increases up to 30% among older people (239,240). In fact, HF is a major public health issue and the leading cause of hospitalizations in subjects aged over 65 years (241,242), being associated with increasing healthcare costs in Europe and a high burden of mortality and morbidity (243).

According to the Italian Constitution, responsibility for guaranteeing citizens' health is shared by the Central Government and every of the 21 administrative units (19 regions and 2 autonomous provinces), so justifying the need of the first for comparing quality of care supplied by the latter. Accordingly, a system of assessment for integrated care pathways across different levels for specific clinical conditions is on developing by a National expert working group of the Italian Health Ministry. In developing the system of indicators, particular attention was taken to what was actually measurable by, and comparable between, the Italian regions.

Several standard, guideline-based, process-of-care performance measures have been developed and implemented in the last years, that provide a mechanism through which the quality of HF care can be measured and improved (244). The selection of appropriate process measures for use in quality improvement, public profiling or financial incentives is quite important, with potential implications for patients' outcomes, the healthcare system and the administrative burden (245). Studies have been conducted on inpatient HF performance measures, and some process-of-care measures were associated with post-discharge clinical outcomes (246–249). Only few studies examine the relationships between adherence to several current and emerging outpatient HF process measures and clinical outcomes (247,250–252). However, to date, no studies explore the impact of outpatient recommendations' adherence profiles on clinical outcomes for these patients.

Given these gaps in the literature, we conducted a population-based cohort study in the Lombardy region of Italy, to evaluate the association between the adherence to defined process-of-care indicators and selected outcomes for HF outpatient subjects. Moreover, a second aim of this study is to assess the impact of indicators' adherence profiles in terms of outcomes that could be avoided.

11.2 Methods

Data sources

This study is based on computerized healthcare utilization (HCU) databases from the Italian Lombardy Region, that covered almost 10 million beneficiaries of the Italian NHS. As reported in a previous study (188), the Regional information system of healthcare utilization databases collects a variety of information including: *(i)* an archive of residents who receive NHS assistance (the whole resident population), reporting demographic and administrative data, other than the dates in which the individual started (because he/she was born or immigrated) or stopped (because he/she died or emigrated) the condition of NHS beneficiary; *(ii)* a database on hospital discharge records including information about primary diagnosis, co-existing conditions and performed procedures (coded according to the ICD-9 CM classification system); *(iii)* a drug prescription database providing information on all community drugs reimbursed by the NHS (coded according to the Anatomical Therapeutic Chemical (ATC) classification system); *(iv)* a database on outpatient visits, including visits in specialist ambulatories and diagnostic laboratories accredited from the NHS. A unique identification code was used and, in order to preserve privacy, identification codes were automatically converted into anonymous codes, and the inverse process was prevented by deletion of the conversion table.

Diagnostic and therapeutic codes used in the current study are reported in Supplementary material_1.

Cohort selection and follow-up

Beneficiaries of the NHS who in 2007 (index year) had aged 50 years or older and were resident in Lombardy Region formed target population. With the aim of ensuring enough time back for capturing subjects with HF, these were excluded if they were recorded as beneficiaries of the regional NHS after the year 2004.

Subjects belonging to the target population were considered affected by HF whether they had at least one hospitalization with a primary diagnosis of HF with a date of discharge between 1st January and 31st December 2007 (prevalent subjects). In case of multiple hospitalizations, the first one during the index year will be consider as the index hospitalization. Subjects who died during the index hospitalization were excluded from the study. Incident cases were the portion of prevalent ones who

did not experience any hospital admission with diagnosis of HF and/or with the DRG code (Diagnosis-Related Group) of HF and shock in the last three years prior the index one.

A user-only design was adopted (102,103): among incident cases of heart failure, only those with at least one prescription of angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB) or beta-blockers within 90 days from the index hospitalization discharge date were considered for the analysis. Therefore, the most recent prescription date between the first prescription of ACE inhibitors/ARB and the first prescription of beta-blockers was considered as the index date.

Baseline characteristics of cohort included gender, age, drug therapies and comorbidities. Drug therapies included antidiabetic drugs, antiplatelet, digitalis glycosides, organic nitrates, other blood pressure- and lipid-lowering agents, antidepressants, non-steroidal anti-inflammatory drugs, anti-gout agents and drugs for chronic obstructive pulmonary disease. Comorbidities were measured through previous hospitalizations for cancer, diabetes, ischaemic heart, cerebrovascular, respiratory and kidney disease. In addition, the so-called Multisource Comorbidity Score (MCS), a new comorbidity index obtained from both inpatients diagnostic information and outpatients drug prescriptions, and recently validated using data from the here considered Italian regions (53), was considered.

Cohort members accumulated person-years of follow-up starting from the index date until the occurrence of one of the following events, whichever came first: the study outcomes (emergency hospital admission for HF and death), emigration, or end-point of follow-up, i.e., December 31, 2012.

Adherence to recommendations

Outpatient visits, including echocardiogram execution, and drug dispensation of ACE inhibitors/ARB and beta-blockers during follow-up were identified. A patient was considered adherent to recommendations whether he/she every year was submitted to at least one echocardiogram (253) and had a *proportion of days covered* (PDC) by ACE inhibitors/ARB and beta-blockers ≥ 75% (254–256).

Other than for each individual recommendation, a classification describing the adherence profile of each subject was developed and cohort members were categorized in three groups: non-adherent to any recommendations (Score_0), adherent to at least one of the two drugs recommendations (Score_1) and adherent to at least one of the two drugs recommendations and to echocardiogram one (Score_2).

The adherence to recommendations was calculated in the first year after the index date.

Outcome

Two outcomes were considered to take into account complications of HF potentially avoidable: (i) all-cause mortality; (ii) a new emergency hospitalization occurred with primary diagnosis of HF (ICD-9 CM codes used for capturing outcomes are reported in Table S1). Both outcomes were calculated through the whole follow-up.

Association between adherence and outcome and population attributable fraction

To assess the impact of recommendation's adherence on defined outcomes, analysis was performed in three steps.

In the first step, adherence to recommendations was considered during the first year period after the index date and therefore final cohort was composed by subjects with at least 365 days of follow-up. A propensity score (PS) matching design was used to ensure that patients classified according to their adherence with recommendations had similar baseline features (257). Two strategies were used for calculating the PS. Conventional logit regression considering the dichotomous exposure to an individual recommendation as the outcome of interest, was initially fitted. Logit regression was extended to the setting of three levels overall adherence index as the outcome of interest. In both the settings, the outcome was modelled as a function of the above reported covariates (please see Additional measurements section) and balanced cohorts were then built by using 1:1 (adherence vs. no adherence) and 1:1:1 (increasing levels of overall adherence index) nearest neighbour matching algorithm (258).

Then, a Cox proportional hazard regression model was fitted for estimating the hazard ratio (HR) and its 95% confidence interval (CI), for the association between adherence to each recommendation taken individually, as well as to adherence group, and the risk of experiencing the outcomes. In particular, mortality risk was assessed starting from the second year after the index date until the end of follow-up period, while emergency re-hospitalization risk was calculated only during the second year of follow up. A Poisson model was also fitted to evaluate the impact of the adherence on the number of re-hospitalizations during the second year in terms of incidence rate ratio (IRR) and its 95% CI.

In the second analysis, the Population Attributable Fraction (PAF) was used to assess the impact of process' adherence to outcomes in terms of cases that would not have occurred if all subjects were adherent to drug recommendations or to drug and echocardiogram recommendations (Score_1 and Score_2). A SAS macro was applied, following the approach proposed by Laaksonen et al (96) for

PAF estimation in cohort studies. Both mortality and new emergency hospitalizations were used as outcome of interest in the whole follow up.

For all hypotheses tested, p-value less than 0.05 was considered significant.

11.3 Results

Adherence to recommendations and outcome

Baseline characteristics of the cohort of 9,178 subjects hospitalized for HF during 2007 are shown in Table 11.6.1. Among these subjects, those who had at least 365 days of follow-up were 8,207.

During the first year after diagnosis, newly taken in care heart failure subjects (incident cases) had similar adherence to recommendation related to drug assumption (69.9% and 67.3% for ACEi/ARB and beta-blockers assumption, respectively) but a low adherence to outpatient visits, being only 31.9% of them submitted to echocardiogram (Table 11.6.2). It is noteworthy that about 60% of newly taken in care HF subjects adhered to at least one drug recommendation. In calculating the total adherence score, 260 subjects were not included in any of the defined groups, therefore they were not considered in the subsequent analysis.

During follow-up, cohort members accumulated 40,028 person-years of observation and experienced 3,242 deaths (incidence rate, 80.9 cases every 1,000 PY), and 32,953 person-years experiencing 2,768 new emergency admissions whit a primary diagnosis of HF (incidence rate, 83.9 cases every 1,000 PY).

Association between adherence and outcome

Forrest plots for the adherence-outcome relationship are shown in Figure 11.7.1 and Figure 11.7.2. Adherence to recommendations related to drugs assumption is associated with a significant mortality risk reduction (23% (95% CI, 16% to 33%) and 32% (26% to 38%) for ACEi/ARB and beta-blockers assumption, respectively), but no association is observed with emergency re-hospitalization risk. Adherence to echocardiogram recommendation seemed to be not related with both outcomes. Compared to subjects who were non-adherent to any recommendation, a significant mortality risk reduction of 24% (17% to 31%) and 44% (36% to 52%) were observed for those who adhered to at least one drugs' recommendation (Score_1 group) and to at least one drug and echocardiogram recommendations (Score_2 group), respectively. A decreased risk of emergency re-hospitalization is also observed in subjects who adhered to at least one drug recommendation (Score_1 group), while the adherence to at least one drug and echocardiogram recommendations (Score_2 group) is not associated with a significant risk reduction.

In Figure 11.7.3 results from Poisson model are shown. There is a significant reduction in IRR for emergency re-hospitalizations of 22% (7% to 34%) in subjects adhered to at least one drug recommendation (Score_1 group), but no association is shown in subjects belonging to Score_2 group.

Figure 11.7.4 shows the impact of being adherent to recommendations on deaths and of emergency re-hospitalization for HF, using the PAF estimate. About 2 deaths and emergency re-hospitalizations cases out of 100 could be avoided if all no-adherent subjects were adherent to at least one drug recommendation (Score_1 group). Whether all no-adherent subjects were adherent to at least one drug and echocardiogram recommendations (Score_2 group), a mean of 6 and 5 (out of 100) deaths and emergency re-hospitalizations cases, respectively, could be prevented.

Figure 11.7.5 reports a decreased trend in PAF for death cases according to follow-up time (intervals of 365 days), starting from the second year after the index date. This trend started from about 12 and 4 cases of death that could be prevented in the first year until about 2 and 1 cases in the last year of follow-up, whether all subjects in Score_0 group were in both Score_2 and Score_1 groups, respectively.

11.4 Discussion

This study shows that the adherence to one or more recommendation can lead to a decreased risk of clinical outcomes in HF subjects. A non-adherence profile to recommendations could be considered as the non-adherence to a specific clinical pathway (CP) and, therefore, could represent a risk factor for developing the outcome. Results from this study show the impact of the adherence to specific recommendations on the outcome in terms of PAF, that represent the proportion of cases that could be prevented by eliminating the risk factor (a non-adherent behavior). We considered the adherence to the specific recommendations either taken individually and categorized in a total score of adherence. For the creation of score's classes, we taken in consideration two main aspects. The first is about subjects with a previous hospitalization for HF that in the follow-up are only subjected to echocardiographic examination and do not use drugs. These subjects were excluded from our analysis (and do not fall into any of the score categories) because it is difficult to clinically justify such a behavior, and they are certainly different patients compared to all other cohort subjects. The second aspect concerned the recommendation about drug assumption. As indicated by clinical guidelines, not all subjects should undergo double hypotensive therapy (ACEi/ARB and beta-blockers) (244). Therefore, in the construction of the score we took this issue into consideration, indicating that the condition was satisfied if subjects took at least one of the two recommended drugs.

However, this study shows a lower adherence rate of outpatient subjects with HF to drugs' assumption recommendations then that reported from other studies. In fact, about 70% and 67% of Lombard subjects with HF are adherent to ACE inhibitors/ARB therapy and to beta-blockers, respectively. Fonarow et al (247), reported an adherence rate of about 80% and 86% for ACE inhibitors/ARB and beta-blockers, respectively, while a study of Wu et al (251) showed an adherence rate of 88.8% for ACE inhibitors/ARB. Both studies measured the adherence to ACE inhibitors/ARB indicator in subjects with left ventricular ejection fraction (LVEF) lower than 40%.

Moreover, in our study, the adherence measured using both the three singles indicators (echocardiogram, ACE inhibitors/ARB and beta-blockers therapy) and the adherence score calculated in the first year after index date is related to a low mortality risk in HF subjects with a follow-up of at least 365 days. In particular, adherence to ACE inhibitors/ARB therapy shows a decreased mortality risk comparable with that reported by Wu et al (251). Fonarow et al (247), also found that adherence to both ACE inhibitors/ARB and beta-blockers was associated with a low mortality risk of OR 0.51 (95% CI, 0.42 to 0.63) and 0.45 (0.34 to 0.59), respectively. In his study, Wu consider the documentation about left ventricular (LV) function as a process-of-care indicator for outpatient care, as recommended by clinical guidelines (244). In our study, we can consider the indicator of echocardiogram execution as a proxy of LV assessment, because during an echocardiogram this particular assessment is always conducted, even if we do not know any result of this procedure. However, we found no association between the adherence to echocardiogram indicator and the mortality risk, as reported also by Wu et al (251).

In our study, we explored the emergency re-hospitalization for HF as the second outcome of interest. In particular, we considered this outcome as an acute event that can occur early after the follow-up beginning, mostly in subjects that have a non-adherent profile to recommendations. For this reason, as we calculated the adherence to recommendations in the first year after the index date, this outcome is assessed only in the second year of follow-up. Under this condition, we found that the adherence to drugs' recommendations (at least one between ACEi/ARB or beta-blockers assumption) is positively associated with a risk reduction of being re-hospitalized for HF. At the same time, for subjects with the adherence profile just mentioned, we found a significative reduction in the IRR for emergency-re-hospitalization, evaluated with the Poisson model.

Furthermore, to quantitively evaluate the contribution of the adherence to recommendations to the outcomes, we estimated the PAF. To date, PAF has been one of the most applied measures for estimating the association between cardiovascular risk factors and clinical outcomes, allowing policy makers to anticipate the potential impact of preventive strategies targeting certain risk factors (259–

262). But there are no studies that measure the impact of following a CP on clinical outcomes, in particular in outpatient subjects.

From our study, we can observe that the PAF for mortality is higher in the first years of follow-up considered, and tent to decrease with time. This means that there is a higher risk of experiencing an outcome in the first years after an acute event, that can be kept under control by assuming a specific drug therapy. In fact, we observed that if non-adherent subjects become adherents to drugs' recommendations (at least one between ACEi/ARB or beta-blockers assumption), this change can lead to a higher number of avoidable cases. This number is even greater if subjects were adherent to both drugs' and echocardiogram recommendations. At the same time, this result can be interpreted as a survival curve, where subjects that had a longer free-outcome survival are those that more difficultly will experience the outcome itself. However, data from our analysis show that the adherence in the first year is sub-optimal and thus it is necessary to support patients on their clinical path, in order to make them aware of the importance of care to be followed.

This study has several limitations that should be taken into account for correctly interpreting our results. First of all, information about health service outpatient facilities supplied by private organizations are not available from our databases. For example, we can suspect that a portion of echocardiograms, the indicator to which less patients were adherent, is performed in private clinics. Second, it should be remembered that the recommendation about ACEi/ARB assumption is indicated for subjects with reduced LVEF (244). In the present study, a stratification of subjects according to LVEF was not carried out as this data was not available. Finally, validity of our estimates is based on the assumption that drugs dispensed by pharmacies correspond to drug consumption, which may not be the case (66). It should be mentioned that this type of bias necessarily leads to an underestimation of attributable fractions.

Conclusions

This study is among the first ones that demonstrate a significant association between the adherence to HF process measure, calculated with ACEi/ARB, beta-blockers and echocardiogram, and the overall survival and the emergency re-hospitalization for HF. In particular, this is the first study that explore the impact of this adherence in terms of PAF, i.e., the proportion of outcomes that could be prevented if all HF subjects were to some extent adherent to clinical recommendations. Further evidence is thus needed to confirm the protective role of adherence to recommendations among HF subjects.

11.5 Tables

Table 11.5.1. Baseline characteristics of study cohort, according to MCS class.

	MCS_1 (N = 3,067)	MCS_2 (N = 3,305)	MCS_3_4_5 (N = 2,806)	Combined (N = 9,178)
Male gender	1,684 (54.9)	1,769 (53.5)	1,624 (57.9)	5,077 (55.3)
Age (years)				
50-59	457 (14.9)	217 (6.6)	136 (4.85)	810 (8.8)
60-69	783 (25.5)	629 (19.0)	554 (19.74)	1,966 (21.4)
70-79	1,091 (35.6)	1,333 (40.3)	1,240 (44.1)	3,664 (39.9)
80-89	664 (21.6)	1,003 (30.4)	788 (28.08)	2,455 (25.8)
>90	72 (2.4)	123 (3.7)	88 (3.1)	283 (3.1)
Medications †				
Antidiabetic	364 (11.9)	847 (25.6)	1,153 (41.1)	2,364 (25.8)
Antiplatelet	1,046 (34.1)	2,612 (79.0)	2,403 (85.6)	6,061 (66.0)
Digitalis glycosides	54 (1.8)	700 (21.2)	550 (19.6)	1,304 (14.2)
Organic nitrates	126 (4.1)	1,211 (36.6)	1,273 (45.4)	2,610 (28.4)
Antiarrhythmics	170 (5.5)	632 (19.1)	668 (23.8)	1,470 (16.0)
Other Blood-pressure lowering agents	1,197 (39.0)	2,598 (78.6)	2,376 (84.7)	6,171 (67.2)
Lipid lowering agents	537 (17.5)	1,248 (37.8)	1,320 (47.0)	3,105 (33.8)
Antidepressants	218 (7.1)	346 (10.5)	477 (17.0)	1,041 (11.3)
NSAIDs	989 (32.2)	1,335 (40.4)	1,194 (42.6)	3,518 (38.3)
Anti-gout drugs	95 (3.1)	472 (14.3)	909 (32.4)	1,476 (16.1)
Drugs for COPD	265 (8.6)	582 (17.6)	798 (28.4)	1,645 (17.9)
Comorbidities #				
Cancer	71 (2.3)	106 (3.2)	625 (22.3)	802 (8.7)
Diabetes	79 (2.6)	317 (9.6)	883 (31.5)	1,279 (13.9)
Ischemic heart disease	159 (5.2)	692 (20.9)	1,221 (43.5)	2,072 (22.6)
Cerebrovascular disease	32 (1.0)	150 (4.5)	656 (23.4)	838 (9.1)
Respiratory disease	112 (3.6)	309 (9.4)	772 (27.5)	1,193 (13.0)
Kidney disease	4 (0.1)	34 (1.0)	494 (17.6)	532 (5.8)

Abbreviations: MCS, Multisource Comorbidity Score; NSAID, Non-steroidal anti-inflammatory drugs; COPD, chronic obstructive pulmonary disease

† According to drug dispensed in the 3 years before 2007

According to hospital admissions in the 3 years before 2007

Table 11.5.2. Cohort subjects with at least 365 days of follow-up who, during the first year after index date, adhered to selected recommendations in Lombardy Region

	Cases (8,207)	
	N	%
Echocardiogram	2,618	31.9
ACEi/ARB assumption†	5,739	69.9
Beta-blockers assumption#	5,521	67.3
Total adherence score		
Score_0	843	10.6
Score_1	4,746	59.7
Score_2	2,358	29.7

Subjects non-adherents to any recommendations belong to Score_0 group, those adherents to at least one of the two drugs' recommendations belong to Score_1 group and those adherents to at least one of the two drugs' and to echocardiogram recommendations belong to Score_2).

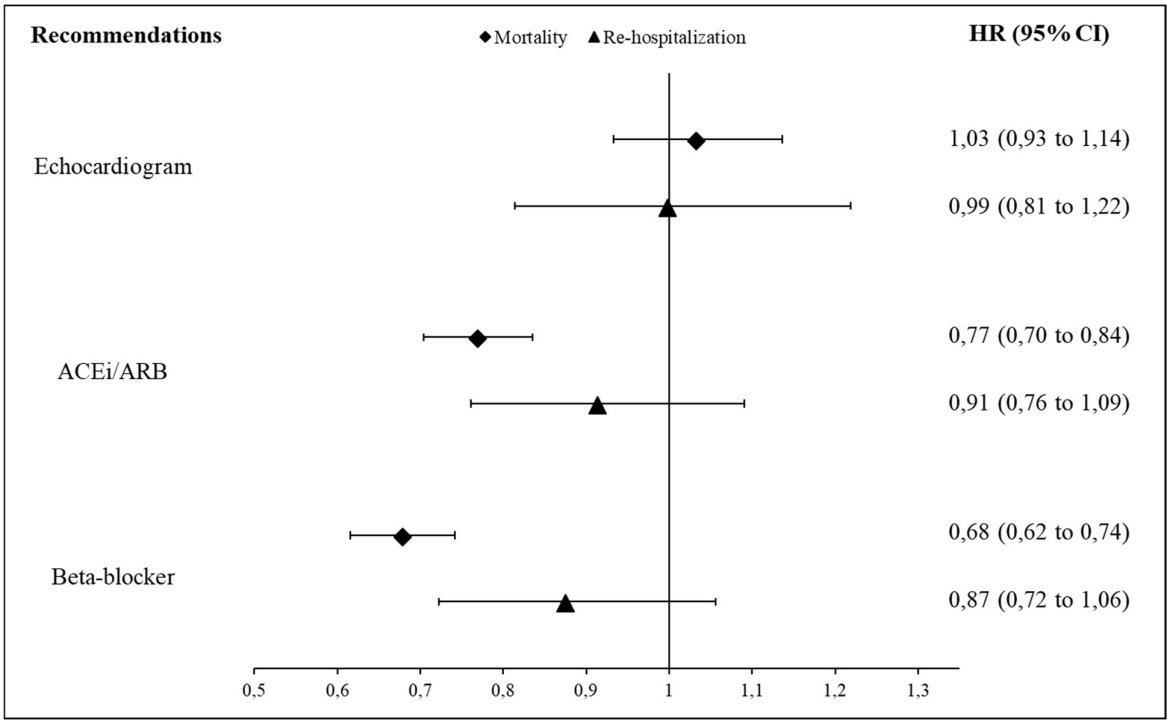
Abbreviations: ACEi, Angiotensin Converting Enzyme inhibitors; ARB, Angiotensin Receptor Blockers

† Considered among subjects who received a prescription of ACEi/ARB within 3 months from the index date

Considered among subjects who received a prescription of beta-blockers within 3 months from the index date

11.6 Figures

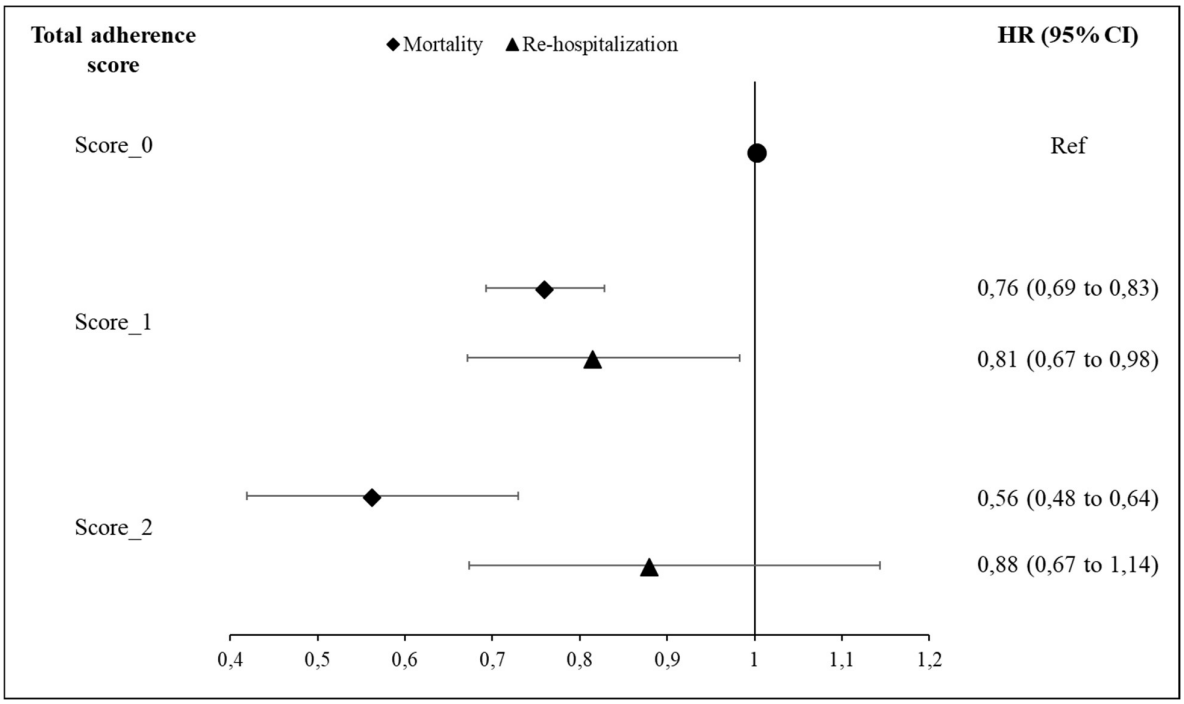
Figure 11.6.1. Forest plots of hazard ratios (HR) for the association between first-year adherence to selected recommendations and the risk of death and emergency hospital re-admission for HF



Adherence to recommendations is considered during the first-year period after index date, mortality risk is considered during the whole follow-up period while the re-hospitalization risk is calculated in the second year after the index hospitalization. HR, and 95% confidence intervals (represented by horizontal lines), were estimated by fitting a Cox proportional hazard model. Subjects were matched using propensity score method according to baseline covariates.

Abbreviations: HR, hazard ratio; ACEi, Angiotensin Converting Enzyme inhibitors; ARB, angiotensin receptor blockers.

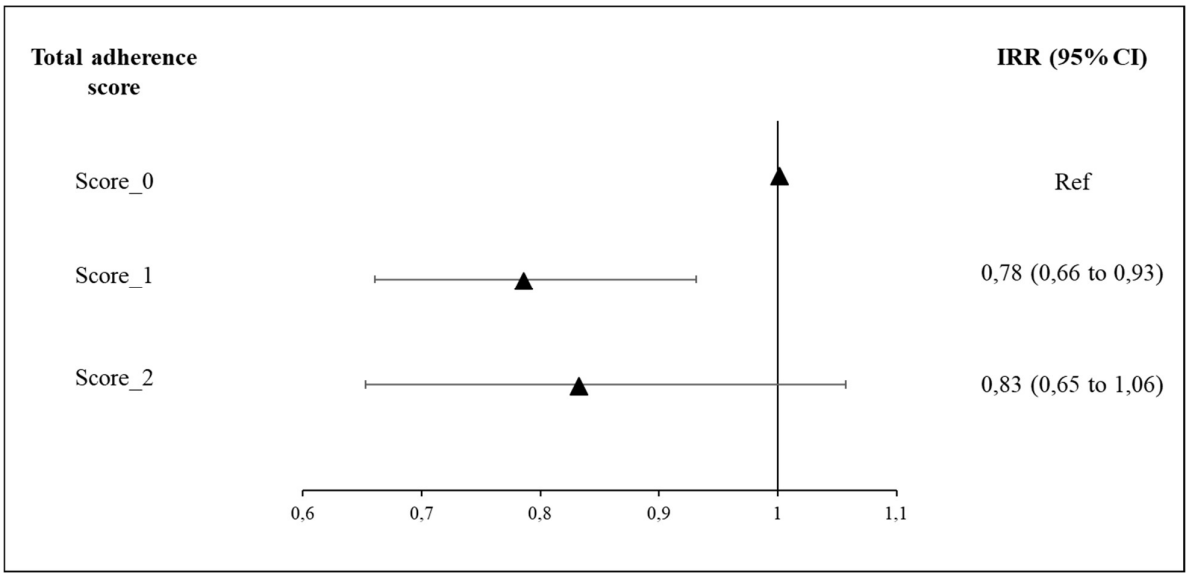
Figure 11.6.2. Forest plots of hazard ratios (HR) for the association between total adherence score and the risk of death and emergency hospital re-admission for HF



Adherence to recommendations is considered during the first-year period after index date, mortality risk is considered during the whole follow-up period while the re-hospitalization risk is calculated in the second year after the index hospitalization. HR, and 95% confidence intervals (represented by horizontal lines), were estimated by fitting a Cox proportional hazard model. Subjects were matched using propensity score method according to baseline covariates. Subjects non-adherents to any recommendations belong to Score_0 group, those adherents to at least one of the two drugs' recommendations belong to Score_1 group and those adherents to at least one of the two drugs' and to echocardiogram recommendations belong to Score_2).

Abbreviations: HR, hazard ratio; CI, confidence interval.

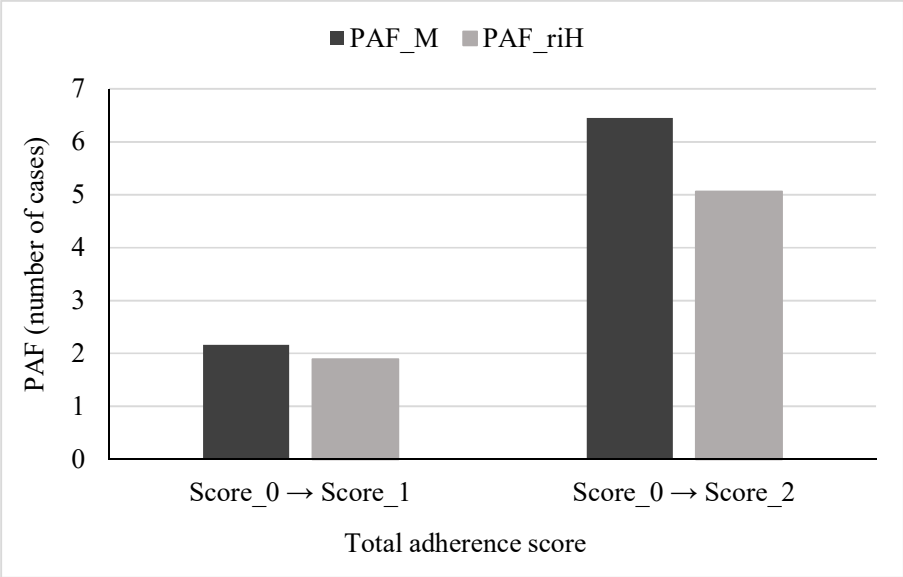
Figure 11.6.3. Forest plots of incidence rate ratios (IRR) for the association between total adherence score and the number of emergency re-hospitalizations for HF



Adherence to recommendations is considered during the first-year period after index date and the number of emergency re-hospitalizations for HF is calculated in the second year after the index date. IRR, and 95% confidence intervals (represented by horizontal lines), were estimated by fitting a Poisson model. Subjects were matched using propensity score method according to baseline covariates. Subjects non-adherents to any recommendations belong to Score_0 group, those adherents to at least one of the two drugs' recommendations belong to Score_1 group and those adherents to at least one of the two drugs' and to echocardiogram recommendations belong to Score_2).

Abbreviations: IRR, incidence rate ratio; CI, confidence interval.

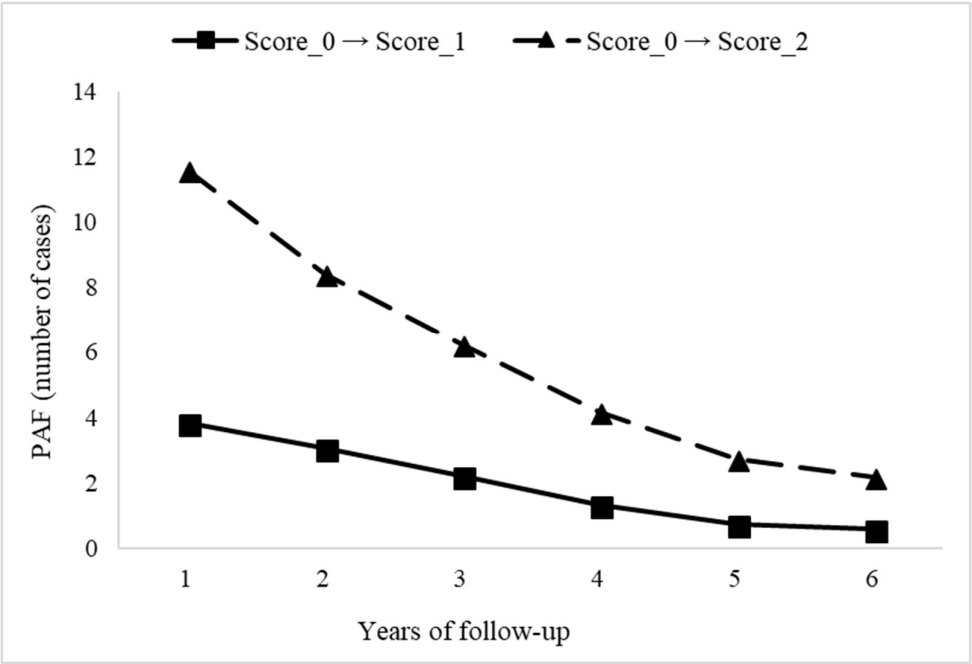
Figure 11.6.4. PAF for deaths (PAF_M) and for emergency re-hospitalizations (PAF_riH)



PAF represents the number of outcome cases (deaths or emergency re-hospitalizations) that could be prevented if all subjects in Score_0 group (non-adherents to any recommendation) would be in Score_1 group (adherents to at least one of the two drugs' recommendations) or Score_2 group (adherents to at least one of the two drugs' and to echocardiogram recommendations). Adherence to recommendations is considered during the first-year period after index date, PAF for death is considered during the whole follow-up period while the PAF for emergency re-hospitalization is calculated in the second year after the index hospitalization. PAF estimates were adjusted for gender, age and selected medications and comorbidities (please see covariates listed in Table 11.5.1).

Abbreviations: PAF, population attributable fraction; PAF_M, population attributable fraction for death; PAF_riH, population attributable fraction for emergency re-hospitalization.

Figure 11.6.5. PAF trend for death according to follow-up time



PAF represents the number of outcome cases (deaths) that could be prevented if all subjects in Score_0 group (non-adherents to any recommendation) would be in Score_1 group (adherents to at least one of the two drugs' recommendations) or Score_2 group (adherents to at least one of the two drugs' and to echocardiogram recommendations). Adherence to recommendations is considered during the first-year period after index date, PAF is considered during the whole follow-up period, starting from the second year after the index hospitalization. PAF estimates were adjusted for gender, age and selected medications and comorbidities (please see covariates listed in Table 11.5.1).

Abbreviations: PAF, population attributable fraction.

11.7 Supplementary material

Supplementary material_1

ICD-9 codes

Description		ICD9-CM codes
Case identification and outcome		
Heart failure		428.*, 402.01, 402.11 e 402.91
Covariates		
Cancer		140-239.*
Diabetes		250.*
Ischemic heart disease		410-414.*
Cerebrovascular disease		430-438.*
Respiratory disease		460-519.*
Kidney disease		584-586.*

ATC codes

Drugs	ATC codes
ACE inhibitors/ARB	C09
Beta-blockers	C07
Antidiabetic agents	A10
Antiplatelet	B01A
Digitalis glycosides	C01AA
Organic nitrates	C01DA
Antiarrhythmics	C01B
Other blood-pressure lowering agents	C02, C03, C08
Lipid lowering agents	C10
Antidepressants	N06A
NSAIDs	M01A
Anti-gout drugs	M04
Drugs for COPD	R03

Part V

Final Considerations

The burden of a condition, illness or risk factor on the population is a fundamental issue in Public Health and it can be applied also to healthcare interventions. Therefore, the aim of this thesis was to assess the impact of healthcare interventions for chronic health conditions, from the Public Health point of view. The measure of population attributable fraction can be used for this evaluation and can easily be adapted to different settings and study designs.

If we consider an inappropriate prescription as a risk factor for adverse outcomes (I Study), the population attributable fraction indicates the proportion of outcomes (for example, bleeding events) that could be avoided with careful prescription patterns that consider all patients' comorbidities and indicators of pharmacological blood distribution.

Clinical Pathways (CPs) are considered as an evidence-based tool for patients' care, that can be standardize and used to compare different Health Systems from the point of view of efficiency and quantity of care (II Study). Specific process indicators were used to assess subjects' adherence profile and a better profile could be translate into better outcomes for diabetic subjects. Because benefits for patients and health care system are expected from improving adherence to guidelines-driven recommendations, tight control of diabetics through regular clinical examinations must to be considered the cornerstone of national guidance, national audits, and quality improvement incentives schemes.

As a condition of 'non-adherence' to a CP can be considered as a risk factor from a Public Health point of view, the population attributable fraction methodology can be applied to the CPs assessment (III Study). Mortality and emergency re-hospitalization are the outcomes considered for subjects with heart failure and also in this case a better process profile can translate into better outcomes. In particular, population attributable fraction estimates the proportion of both outcomes that could be avoided if all subjects would be adherent, to some extent, to clinical recommendations.

From this thesis, we can drown two main conclusions.

The first one concerns the efficacy of CPs analysis in the evaluation, in the real-world practice, of the association between the adherence to a specific recommended treatment and clinical outcomes. CPs, in fact, are evidence-based tools used to plan patients' care but their efficacy on patients' outcomes is difficult to assess, in particular in outpatient setting, because many variables can bias the estimates. The II and the III study evaluated CP assessment efficacy in determine which recommendation is more associate with the outcome under study. This approach, using large administrative databases, can lead to re-design the considered CPs, in order to change the strength of those recommendations

not associated with the outcome of interest. However, further studies are needed to continue the exploration of this issue.

The second conclusion concerns the use of population attributable fraction as a measure to determine the impact of healthcare interventions on clinical outcomes. In clinical research, in fact, we are used to think about the strength of the association between two variables (usually a risk factor and an outcome) in terms of risk ratio, that specify the difference risk between two groups. By contrast, the use of population attributable fraction is not so common in clinical setting, but it is useful to understand the real impact of a healthcare intervention because it provides the number of outcomes that could be avoided if the risk factor would be eliminated. As we have demonstrated, this measure fits adequately in different settings and it should be used more frequently to help policy makers and health authorities in promoting good clinical practice.

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