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New Heart Failure Hospitalization in the Italian region of Lombardy - Epidemiological and economic impact

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1. Introduction

1.1 Heart Failure

1.1.1 Pathophysiology

According to current Heart Failure Guidelines of the European Society of Cardiology (ESC) heart failure (HF) can be defined as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures (or only at the expense of increased filling pressures). Clinically, in the guidelines HF is defined as a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an abnormality of cardiac structure or function [1]. It is important to recognize that heart failure is a clinical syndrome arising from diverse causes. Heart failure is caused by a loss of a critical quantity of functional myocardial cells after injury to the heart from a number of causes. The most common etiologies are ischemic heart disease, hypertension, and diabetes [1, 7].

Three quarters of all HF patients have preexisting hypertension, and this risk factor alone doubles the risk of developing HF compared to normotensive patients [7]. Less common, but important causes of HF in order of decreasing prevalence are cardiomyopathies, infections, toxins (e.g., alcohol, cytotoxic drugs), valvular disease, and prolonged arrhythmias.

Table A reports the classification of different etiologies of heart failure as listed in current guidelines.

Myocardial disease	**Valvular heart disease**
1. Coronary artery disease	Mitral
2. Hypertension	Aortic
3. Cardiomyopathy	Tricuspid
a. Familial	Pulmonary
i. Hypertrophic	**Pericardial disease**

ii. Dilated	Constrictive pericarditis
iii. Arrhythmogenic right ventricular cardiomyopathy	Pericardial effusion
	Endocardial disease
iv. Restrictive	Endomyocardial diseases with hypereosinophilia
v. Left ventricular non-compaction	Endomyocardial disease without hypereosinophilia
b. Acquired	Endocardial fibroelastosis
i. Myocarditis	**Congenital heart disease**
Infective	**Arrhythmia**
• Bacterial	Tachyarrhythmia
• Spirochaetal	Atrial
• Fungal	Ventricular
• Protozoal	Bradyarrhythmia
• Parasitic	Sinus node dysfunction
• Rickettsial	**Conduction disorders**
• Viral	• Atrioventricular block
Immune-mediated	**High output states**
• Tetanus toxoid, vaccines, serum sickness	• Anaemia • Sepsis
• Drugs	• Thyrotoxicosis
• Lymphocytic/giant cell myocarditis	• Paget's disease • Arteriovenous fistula
• Sarcoidosis	**Volume overload**
• Autoimmune	• Renal failure
• Eosinophilic (Churg–Strauss)	• Iatrogenic (e.g. post-operative fluid infusion)
Toxic	
• Drugs (e.g. chemotherapy, cocaine)	
• Alcohol	
• Heavy metals (copper, iron, lead)	
ii. Endocrine/nutritional	
• Phaeochromocytoma	
• Vitamin deficiency (e.g. thiamine)	
• Selenium deficiency	
• Hypophosphataemia	
• Hypocalcaemia	
iii. Pregnancy	
iv. Infiltration	
• Amyloidosis	
• Malignancy	

AV = atrioventricular; HF = heart failure

Table A. Classification of different etiologies of heart failure as listed in current guidelines [1].

The model that describes the development of heart failure is not clear yet. Heart failure may be viewed as a progressive disorder that is initiated after an index event either damages the heart muscle, with a resultant loss of functioning cardiac myocytes, or alternatively disrupts the ability of the myocardium to generate force, thereby preventing the heart from contracting normally. This index event may have an abrupt onset, as in the case of a myocardial infarction, it may have a gradual or insidious onset, as in the case hemodynamic pressure or volume overloading, or it may be hereditary, as in the case of many of the genetic cardiomyopathies. Regardless of the nature of the inciting event, the feature that is common to each of these index events is that they all, in some manner, produce a decline in pumping capacity of the heart. In most instances, patients will remain asymptomatic or minimally symptomatic following the initial decline in pumping capacity of the heart, or will develop symptoms only after the dysfunction has been present for some time. Thus, when viewed within this conceptual framework, left ventricular (LV) dysfunction is necessary but not sufficient for the development of heart failure syndrome [8].

Left ventricular dysfunction can be divided into two categories: systolic dysfunction (impaired ventricular contraction and ejection) and diastolic dysfunction (impaired relaxation and ventricular filling). Although there are many etiologies of HF, some tend to more adversely affect systolic or diastolic function, though 70% of patients with HF have systolic dysfunction compared to 30% with diastolic dysfunction [9]. In addition, most patients with systolic dysfunction also have a component of diastolic dysfunction. Whether or not a patient with HF has systolic or diastolic dysfunction depends on the ejection fraction (EF), which is defined as the amount of blood pumped from the ventricle in one heartbeat. If the EF is <40%, it is LV systolic dysfunction (commonly defined as HF with a reduced ejection fraction, HF-REF), and if it is >40%, it is diastolic dysfunction (commonly defined as HF with a preserved ejection fraction, HF-PEF). The consequence of LV dysfunction is decreased cardiac output (which is the amount of blood pumped by the heart over a given time period, CO) which in turn leads to global hypoperfusion. In addition, LV dysfunction causes an increase in the amount of blood in the ventricle and therefore an increase in both end-systolic and end-diastolic volumes. This in turn leads to an increase in LV end-diastolic pressure (LVEDP) which causes elevations in left atrial pressures which in turn lead to increases in the pressure of the capillaries in the lungs. This elevated pressure in the lungs forces fluid out of the pulmonary capillaries and leads to pulmonary congestion and the major clinical symptom of dyspnea [2].

In patients with LV dysfunction, the maladaptive changes occurring in surviving myocytes and extracellular matrix after myocardial injury lead to pathological 'remodelling' of the ventricle with dilatation and impaired contractility. What characterizes untreated systolic dysfunction is progressive worsening of these changes over time, with increasing enlargement of the left ventricle and decline in EF, even though the patient may be symptomless initially. Two mechanisms are thought to account for this progression. The first is occurrence of further events leading to additional myocyte death (e.g. recurrent myocardial infarction). The other is the systemic responses induced by the decline in systolic function, particularly neuro-humoral activation.

Two key neuro-humoral systems activated in HF are the renin–angiotensin–aldosterone system and sympathetic nervous system. In addition to causing further myocardial injury, these systemic responses have detrimental effects on the blood vessels, kidneys, muscles, bone marrow, lungs and liver, and create a pathophysiological 'vicious cycle', accounting for many of the clinical features of the HF syndrome, including myocardial electrical instability. Interruption of these two key processes is the basis of much of the effective treatment of HF [1].

1.1.2 Epidemiology and outcomes

Guidelines report that approximately 1–2% of the adult population (older than 50 years) in developed countries is affected by HF, with the prevalence rising to ≥10% among persons 70 years of age or older.

Heart failure incidence has been the objective of several studies that applied different methodologies and different disease definition. Among all, it is worth reporting the data retrieved from the Framingham study, that after following 9,405 individuals for 30 years, reported an incidence of heart failure varying from 30/10,000 person-years among men in the age range 50-59 years to 270/10,000 person-years in individuals between 80-89 years. For women the estimates varied from 20/10,000 person-years to 220/10,000 person-years in the older age group. [10].

More recently the Rotterdam epidemiological study carried out on 7,983 individuals with more than 55 years, reported a general incidence rate of 114/10,000 person-time, varying from 14/10,000 in individuals 55-59 years old to 474/10,000 in individuals older than 90 [11].

Heart failures outcomes vary greatly based on what type of etiology determined the syndrome and on what type of care is needed (e.g. hospitalization vs ambulatory).

A recent observational study conducted in 136 cardiologic wards in Europe [12] analyzed 5,118 patients with HF, of which 63% were outpatients and 37% were hospitalized for heart failure. The study outlined the different prognosis of these two different types of patients (outpatients versus inpatients) and showed that, one year after hospitalization, all-cause mortality in hospitalized patients was approximately 17% and around 7% for outpatients. In the same study, hospitalized patients had a subsequent hospitalization within one year from the first in 43.9% of cases, more than half of the time (56.4%) for heart failure.

In Italy a study was conducted with a similar design [13] which involved 61 heart centers and 5,610 patients, 67% outpatient and the remained hospitalized for HF. In this analysis, the in-hospital mortality for patients hospitalized for HF was between 6-7% and rose to 24% at one year after discharge. Also this study confirmed the different prognosis for outpatients for which, however, a mortality rate of 5.9% was observed at one year from the inclusion into the study. The incidence of re-hospitalization among patients hospitalized for HF was found to be 30.7% in half of the cases for HF. Among the most important predictors of mortality in patients hospitalized for acute heart failure were, confirming data already known in the literature, renal dysfunction, chronic obstructive pulmonary disease the bronchial and anemia.

Given the diversity of the manifestations and of the outcomes of the disease, the most recent literature has suggested to distinguish outpatients with heart failure from those with a hospitalization for HF (Hospitalized Heart failure, HHF). The rationale for this choice is that the prognosis of these two groups of patients appears to be very different [14,15]. The prognosis of outpatients, in fact, has changed dramatically, in a positive way, in the last twenty years thanks to the development of new treatments such as ACE-inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, mineralocorticoid receptor antagonists, the use of resynchronization and the of implantable defibrillators, while that of HHF patients has remained almost unchanged[15].

1.1.3 Guidelines for the pharmacological treatment

The goals of treatment in patients with established HF are to relieve symptoms and signs (e.g. oedema), prevent hospital admission, and improve survival. Although the focus of clinical trials was previously mortality, it is now recognized that preventing HF hospitalization is important for patients and healthcare systems.

Reductions in mortality and hospital admission rates both reflect the ability of effective treatments to slow or prevent progressive worsening of HF.

The relief of symptoms, improvement in quality of life, and increase in functional capacity are also of the utmost importance to patients, but they have not been the primary outcome in most trials. This is in part because they are difficult to measure and partly because some treatments previously shown to improve these outcomes also decreased survival. However, effective pharmacological therapies and Cardiac Resincronization Therapy (CRT) improve these outcomes, as well as mortality and hospitalization.

Standard therapy is based on diuretic treatment, to relieve the symptoms and signs of congestion, that is commonly used in conjunction to one of the three neurohumoral antagonists—ACE inhibitor or angiotensin receptor blocker (ARB), beta-blocker, and mineralocorticoid receptor antagonist (MRA)—that are fundamentally important in modifying the course of systolic HF and should at least be considered in every patient.

Additional treatment that have shown some benefits in HF are: ivabradine, digoxin and other digitalis glycosides, combination of hydralazine and isosorbide dinitrate, omega-3 polyunsaturated fatty acids. No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF. Diuretics are used to control sodium and water retention and relieve breathlessness and oedema as in HF-REF. Adequate treatment of hypertension and myocardial ischaemia is also considered to be important, as is control of the ventricular rate in patients with atrial fibrillation [1].

1.2 Healthcare Utilization Database use for epidemiological purpose

Healthcare utilization databases (HUD) are massive repositories of data collected in healthcare for various purposes. Such databases are maintained in hospitals, health maintenance organizations and health insurance organizations. HUD may contain medical claims for reimbursement, records of health services, medical procedures, prescriptions, and diagnoses information. It is clear that such systems may provide a valuable variety of clinical and demographic information as well as an on-going process of data collection. In general, information gathering in these databases does not initially presume and nor is planned for research purposes. Nonetheless, administrative databases may be used as a robust epidemiological research tool [16]. HUDs give the chance to answer different type of questions it is not possible to address with traditional randomized clinical trials (RCT's). RCT’s, for example, cannot provide all the necessary and sufficient information about the effectiveness and safety of drugs at the time of commercialization. On one hand the methodology

applied in the RCT's is the strength of these experiments for the interpretation of the evidence, on the other, it limits the generalizability of the data itself: RCT's have, in fact, a reduced sample size that does not represent the population affected by the disease and assess the efficacy and safety for a short time interval.

Short-term or surrogate endpoints that are often used in these studies may help to achieve the goal of marketing authorization but often do not address the issues of primary interest, such as the long-term safety, efficacy or events in real life rare adverse [17].

The increased popularity of HUDs as an epidemiological research tool is due to at least five reasons: i) the ready availability of data reduces the time and costs of research; ii) the inclusion of very large populations (e.g., beneficiaries of national healthcare service, NHS) allows discovery of even extremely rare adverse events; iii) the availability of large temporal series makes it possible to study the long-term outcomes of chronic treatments; iv) the virtually unselected nature of the target population allows for results that can be generalized to the real-world of routine clinical practice; v) the possibility of keeping track of the extent and manner in which healthcare services are prescribed by physicians and used by patients, of evaluating whether treatments succeed in preventing the outcomes they are meant to avoid, and of documenting the economic sustainability of medical interventions. All these reasons explain the enormous potential of HUDs as a tool to support decisions in public health [18].

In Italy, where the population is entirely covered by the NHS, since 10-15 years all regions are required to record every service provided by the NHS (e.g. hospital admissions, drugs prescription) to manage reimbursement to structures that provide the service.

In the region of Lombardy, more specifically, since 1997 a wide and articulated system of HUDs has been developed supporting the management of the regional health.

These databases include:

• the archive of residents receiving regional health assistance, practically the whole resident population of about ten million inhabitants, or 16% of the Italian population;

• the HUD common to all Italian regions for reimbursement of health service providers (i.e., diagnostic information about hospital discharge from public or private hospitals the so called ‘ Schede di Dimissione Ospedaliera, SDO; Emergency Room, ER; database and outpatient drug prescriptions reimbursable by the NHS);

• a single extensive recording system of health services, such as those concerning access to outpatient specialist and laboratory benefits, mental health services, emergency rooms, delivery assistance, vaccinations, among others.

All these data may be linked together by using a unique identification code. In order to preserve privacy, the Lombardy Regional Administration and Privacy Authority agreed to the systematic conversion of the patient's identification code (i.e., the tax code) into an anonymous "encrypted" code. This process prevents the possibility of identifying patients to whom health services are supplied (thus overcoming privacy barriers), while at the same time allowing recognition of each single citizen along his or her entire health track (providing data for healthcare research).

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2. Objective

As mentioned above, hospitalized heart failure is a big challenge both from a clinical and public health perspective. Additionally, although clinical and epidemiological research has paid great attention to many aspects of outpatients HF leading to a good understanding of the epidemiology, pathophysiology and pharmacology, such knowledge is not fully applicable to the field of HHF, leaving many unanswered important questions about the impact of such a condition.
The objective of this project is, through the use of Region Lombardy HUD, to attempt to provide an answer to these three questions:

- How many new heart failure hospitalizations in Region Lombardy?
  Chapter three describes the methods that were developed to quantify the epidemiological burden and impact of HHF in this region, from the identification of the proper data source to case selection and incidence and attack rates quantification.
- Determinants of new heart failure hospitalizations - Risk factors
  Chapter four evaluates the role of antihypertensive treatment in preventing HHF. More specifically it evaluates (i) the effect of adherence to antihypertensive treatment (ii) the effect of the medication at entry (iii) the effect adherence to a specific antihypertensive class, on heart failure onset on a population of new antihypertensive users.
- Consequences of new heart failure hospitalizations - Outcomes prognostic factors and economic burden and prognostic factors.
  Chapter five describes short- and long-term mortality and readmissions rate after first hospitalization for HF, short-term and long-term prognostic factors and the economic impact of HHF in Region Lombardy.

3. New heart failure Hospitalization in Lombardy: Epidemiological burden and impact

3.1 Introduction

As previously stated, the first question this project wants to address is the burden of heart failure hospitalizations in the Italian region of Lombardy. Many studies have already addressed the problem of heart failure, but only a few focused on this particular type of patients, i.e. hospitalized heart failure, who seem to have a different prognosis from those heart failure patients who never experienced hospitalization for the disease. Being one the first studies in Italy that addresses such topic through the use of administrative database, it was necessary, first of all, to select the proper data source and the proper algorithm to identify the patient population. The first question that needed to be addressed in order to proceed with case identification was regarding the proper data source. The choice was between the regional hospital discharge database (Schede di Dimissione Ospedaliera, SDO) and the Emergency Room admission database (ER). As stated in the Guidelines, HF diagnosis may be difficult especially in the early stages of the disease. Although HF symptoms bring the patient to medical attention, many of these (see table A [1]) are not specific and do not allow to discriminate between HF and other diseases. Specific symptoms of HF (eg. Paroxysmal nocturnal dyspnea, orthopnea) are less common, particularly in patients with moderate symptoms [2-5].

It may therefore happen that some of the patients admitted to the emergency room, could be registered with a diagnosis different from that of HF and diagnosed as HF only once hospitalized.

Symptoms	**Signs**
Typical	**More specific**
Breathlessness	Elevated jugular venous pressure
Orthopnoea	Hepatojugular reflux
Paroxysmal nocturnal dyspnea	Third heart sound (gallop rhythm)
Reduced exercise tolerance	Laterally displaced apical impulse
Fatigue, tiredness, increased time to recover after	Cardiac murmur

exercise	
Ankle swelling	
Less typical	**Less specific**
Nocturnal cough	Peripheral oedema (ankle, sacral, scrotal)
Wheezing	Pulmonary crepitations
Weight gain (>2 kg/week)	Reduced air entry and dullness to percussion at lung bases (pleural effusion)
Weight loss (in advanced heart failure)	Tachycardia
Bloated feeling	Irregular pulse
Loss of appetite	Tachypnoea (>16 breaths/min)
Confusion (especially in the elderly)	Hepatomegaly
Depression	Ascites
Palpitations	Tissue wasting (cachexia)
Syncope	

Table A. Symptoms and signs typical of heart failure [1]

3.2 Methods

3.2.1 Data source selection

To understand which was the proper data source, the information on the patients who were hospitalized for HF (through SDOs) were integrated with that of the same patients admitted to the emergency room (ER) shortly before (two weeks) the HF hospitalization. This way it was possible to verify which diagnosis was registered in the ER for those patients who would have been hospitalized for HF within a short period of time.

In particular, among all hospitalizations for HF in the years 2010-2011 identified for this first phase with a primary diagnosis with the ICD9 code 428.x (n. 65,929), all HF admissions of patients who had been admitted to the emergency room in the two weeks prior to hospitalization were taken into account. During these two years, and for this group of patients, there were 7,125 visits to ER (only 10.8% of admissions with ICD9 428.x). Table 1.1 (Appendix one) shows the distribution of diagnostic categories related to each of the 7,125 admissions to ER. Almost 90% of the ER admissions were recorded with a diagnosis different from that concerning the circulatory system. In fact, 45.5% of the cases reported a respiratory diagnosis, 36.2% a non-defined diseases while only

11.2% a disease of the circulatory system. These three categories (respiratory diseases, undefined and diseases of the circulatory system) were examined in detail to assess which were the ICD9 codes recorded more frequently (Tables 1.2, 1.3, 1.4). Table 1.2 shows the detail of the category "diseases of the circulatory system." Of the 801 admission to the ER with a diagnosis of circulatory disease, only half (49.0%) were recorded with a diagnosis of HF (ICD9 codes 428, 428.0, 428.1, 428.9). Out of 2,577 accesses for undefined disease, 45.2% were because of symptoms related to the respiratory system, registered with the ICD9 codes 786, 786.00, 786.09 (Table 1.3). In Table 1.4 it can be noticed that, of the 3,239 accesses for respiratory disease, 87.8% was related to lung diseases such as bronchitis, acute pulmonary edema, acute respiratory failure and other lung diseases (ICD9 codes 491, 518, 518.4, 518.81).

From these data it appears clearly that, due to the urgency of the care provided in ER, the registration of diagnosis (and therefore the information retrieved from this data source) privileges predominantly the information about the symptomatology of the patient (e.g. respiratory failure) rather than the pathology responsible for the symptomatology (e.g. congestive heart failure). The database of the ER, therefore, does not seem to be the most suitable source of information for identifying these patients.

Besides this, ER databases have reached total coverage only recently (around 2010) and, therefore, may lack some information and could not be the right means to monitor the frequency of the disease of hospitalized patients. For all these reasons, it was decided to use the SDO database to identify the incidence of HHF.

3.2.2 Case selection

Once the most appropriate source of information was identified, it was necessary to identify the most appropriate ICD9 code sets to capture the greatest number of HHF cases. Unfortunately, previous studies that have addressed the issue of heart failure, dealt with the problem in different ways.

To answer this question we have taken into account various possible scenarios.

Scenario 1 - In a recent review of Saczynski et al. [6], the authors have developed an algorithm for the identification of HHF cases through administrative data. In particular all the studies taken into account identified HHF through code 428.x alone or accompanied by other codes. The most commonly used were the following:

- 398.91 Rheumatic heart failure
- 402.01
- 402.1
- 402.91

  Hypertensive heart disease

- 404.01
- 404.03
- 404.11
- 404.13
- 404.91
- 404.93

  Hypertensive heart and chronic kidney disease

- 425 Cardiomyopathy
- 429.3 Cardiomegaly

In general, the positive predictive values (PPVs) associated with ICD-9 code 428.x alone, ranged between 84% and 100%, while those obtained by the combination with other codes varied between 77% and 79%.

From the data available in SDOs the frequency distribution of ICD9 code 428.x alone was then evaluated, together with the combination of such code with those reported above. Table 1.5 reports the distribution of code 428.x and other ICD 9 codes generally used to codify HF in the years 2010-2011: it appears clear that other codes commonly used for the definition of HHF do not particularly contribute in terms of numbers.

Scenario 2 - Another scenario could have been to consider episodes of HHF all admissions identified by the following codes:

- Code 428.x alone, in the principal diagnosis
- Codes listed in Scenario 1, in primary diagnosis, only in presence of a secondary diagnosis with ICD9 428.x

Table 1.6 shows the frequency distribution of ICD9 codes (in principal diagnosis) of this scenario with an associated code 428.x in one of the secondary diagnoses. The analysis showed that only 2.7% of hospitalizations with a 428.x code in one of the secondary diagnoses were recorded with a primary diagnosis code different from those that properly define HF in the ICD-9dictionary.

Scenario 3 - An additional scenario for the definition of HHF, could have been to use what emerged from Table 1.1. In particular, since many patients are admitted to ER in the weeks before they are hospitalized for HF and report, in the ER, a diagnosis different from HF, we evaluated to consider the following codes:

- Code 428.x alone in the principal diagnosis
- ICD9 codes 460.x-519.x (respiratory disease) and 780.x-799.x disease (not defined) in the principal diagnosis code 428.x if it were present in one of the secondary diagnoses.

Table 1.7 shows the frequency distribution of codes for diagnosis of respiratory illness and non-defined disease, used in conjunction with code 428 in secondary diagnosis. It can be observed that 25.8% of hospitalizations with a principal diagnosis of acute respiratory failure is associated with a 428.x code in one of the secondary diagnoses.

Scenario 4 - The last scenario that was taken into consideration is the identification of episodes of HHF through the use of code 127 (heart failure and shock) of the diagnosis-related group (DRG) in discharge.

In Table 1.8 it can be observed that admissions recorded with DRG code 127 report in the 92% of cases a principal diagnosis of HF.

It is interesting to see what DRG code was reported for HF admissions with an ICD9 code 428.x and a DRG different from 127. Of the 65,929 hospitalizations for HF with an ICD9 code 428.x in the period 2010-2011, 8,129 (12.3%) were associated with a different DRG 127. The details of the DRG codes used in these 8,129 hospitalizations are given in Table 1.9.

From the table it can be observed that for 40.3% of these admissions a code 124 was given (diseases cardiovascular except AMI -Acute Myocardial Infarction- with cardiac catheterization and complex diagnosis). Following the same line of reasoning, we selected all 62,492 admissions with DRG 127 for the years 2010-2011: of these, 4,692 (7.51%) were associated with a primary diagnosis other than 428.x but nonetheless concerned symptoms related to the cardiovascular system.

Summary of the selected criteria

In light of all the considerations that emerged from previous scenarios, it was decided to combine what has been described above in 3 criteria:

Criterion 1 (most specific): ICD9 codes 428.x, 402.01, 402.11 and 402.91 in principal diagnosis;

Criterion 2 (intermediate): ICD9 codes 428.x, 402.01, 402.11 and 401.91 in principal diagnosis code or DRG 127;

Criterion 3 (most sensitive) code 428.x, 402.01, 402.11, 401.91 in principal diagnosis code or DRG 127 + codes for diagnosis in symptomatic primary diagnosis (514.x, 518.4, 518.81, 785.x, 786.x) if the codes 428.x, 402.01, 402.11 401.91 are present in one of the secondary diagnosis).

The main analyses reported in this chapter were carried out applying Criterion 1 as a reference.
Appendix four reports the findings obtained from the application of criteria 2 and 3.
Figure 1.1 shows the final algorithm.

3.2.3 Cohort selection

Once the Criteria for case identification were selected, we proceeded with the identification of HHF population. Patients who, in the years 2010-2011, were beneficiaries of the Italian NHS, were resident of the Lombardy Region and hospitalized at least once with a HF diagnosis comprised the study incident cases, and the first HHF episode was denoted as index event. In this analysis Criterion 1 was selected to quantify the number of episodes. Medical records with a primary HF diagnosis (based on the aforementioned definition) at discharge were drawn from the regional hospital discharge database. Moreover, the entire HHF population (Population A) was split into two sub-populations: patients who did not experience any HHF episode in the 5 years preceding the earliest (or unique) hospitalization occurring in 2010-2011 (Population B) and patients who had already been hospitalized for HHF (Population C). Information about co-morbidities and drug prescriptions occurred during the 5-year period prior the index hospitalization was collected. The corresponding data were drawn from regional archives of hospital discharge, outpatient drug prescription, and drug prescriptions administered directly in day hospital setting, reimbursed by the NHS. Information included history of selected CV therapies, events, and procedures, and respiratory and kidney disease. In order to determine HHF incidence, only newly hospitalized HF patients (incident cases) were considered (Population B) and those who experienced multiple hospitalizations contributed only the earliest hospitalization which occurred during 2010-2011.

Population B was, thus, taken as reference. Further results concerning Population A and C are reported in Appendix four.

3.2.4 Measuring incidence and attack rates

Incidence rates of HHF were calculated dividing the number of index events occurred during the years 2010 and 2011 by the total number of person years accumulated by the source population, i.e. beneficiaries of the Italian NHS resident of Lombardy during the years 2010-2011, as recorded by the regional archive of NHS beneficiaries.

The attack rate was calculated as the total number of episodes of HHF in 2010-2011 divided by the total number of person years accumulated from the entire population at risk at the beginning of the period of interest. Contrary to what happens with incidence, in which each subject is considered only for his first event, this measure of frequency uses all the episodes in the period of interest for each subject. If two admissions of the same individual occurred at a distance of less than 28 days thus were considered as a single episode.

Rates were crude, stratified for gender and age (10-year categories), and standardized (direct standardization) with respect to the age structure of the Italian population. Findings were expressed as cases per 10,000 person-years (PYs) at risk.

The 95% confidence intervals (CIs) of the point estimates were based on the Poisson distribution.

3.2.5 Sensitivity analysis of incidence rate

Considering that all epidemiological studies suffer from some degree of measurement error, classification error or misclassification when the variables are discrete, we wanted to provide a quantitative assessment of this type of bias to better assess the uncertainty of our results. More specifically we wanted to assess how incidence rate could vary if the operational characteristics of the developed algorithm were not able to identify properly all the HHF cases. We therefore wanted to assess what would be the incidence rate of HHF assuming different level of sensitivity and specificity of our algorithm.

To evaluate the robustness of the estimates obtained through the most specific criterion of the proposed algorithm (Criterion 1), a sensitivity analysis was performed to quantify the impact of a possible misclassification of cases of HHF. According to Greenland, [7], knowing the operational

characteristics of the algorithm (SE and SP) it is possible to calculate the number of cases expected in the absence of misclassification as follows:

$$A = [Sp \cdot A^* - (1-Sp)(N-A^*)] / [SeSp - (1-Se)(1-Sp)] \quad (1)$$

Where:

A = true number of cases

A*= observed number of cases

Se = Sensitivity (Probability someone diseased is classified as diseased)

Sp = Specificity (Probability someone non-diseased is classified as non-diseased)

N = total number of individuals at the beginning of the observation

On the basis of Equation (1), we carried out two different types of sensitivity analysis: in the first we assumed that our algorithm had a specificity of 100% and we set different level of bias, assuming different levels of the sensitivity. In the second we assumed that our specificity could vary within a range of 99-100%.

Ordinary sensitivity analysis

In the first analysis, we assumed that our criterion 1 had a specificity (SP) of 100% and the stratum - specific incidence rates have been recalculated varying the sensitivity (SE = 90 %, 80 %, 70% and 60%).

Knowing the observed number of cases it was then easy to calculate the number of expected cases and the incidence rate (with 95% confidence intervals).

Monte Carlo sensitivity analysis

Ordinary or traditional sensitivity analyses, as performed and described above, estimate what the true effect measure (e.g., incidence rate) would be in light of the observed data and some hypothetical level of bias, and they provide one or more hypothetically adjusted point estimates for the effect measure of interest. While conducting ordinary sensitivity analysis is an improvement over ignoring bias, it can become difficult to summarize results as the number of parameters determining the bias increases, and it usually does not provide a full range for likely bias in the results. Ordinary sensitivity analysis can be improved through the use of Monte Carlo sensitivity

analysis, which we applied to incorporate uncertainty regarding misclassification bias (due to the potential lack of our algorithm in identifying incident cases) into the results of analyses [8,9].

In our analysis the Monte Carlo sensitivity analysis required to specify a (prior) distribution for the unknown parameters that determine misclassification to characterize their uncertainty.

In our example, it was assumed that:

- $A^* \sim Poi(T^* \lambda^*)$

λ^*= observed incidence rate (A^*/ T^*)

We assumed that Sensitivity and Specificity had a continuous uniform distribution with minimum and maximum a, b and c, d respectively:

- $Se \sim U(a,b)$
- $Sp \sim U(c,d)$

More in detail, we analyzed three Sensitivity different scenarios: 40-60% (where a=40 and b=60%), 60-80% and 80-100% with sensitivity varying within the interval 99-100% (each Se scenarios defined by respectively setting c=99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9 and 100% and d=100%).

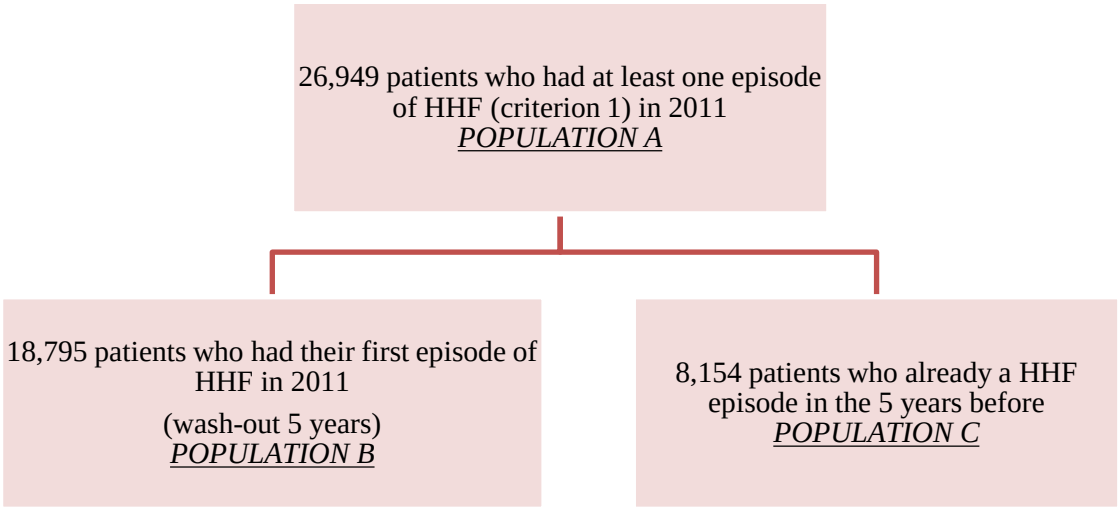
We then constructed a model to calculate the simulated data given these parameters as stated in (1). We used a Monte Carlo simulation to repeatedly re-estimate (10,000 iterations) the effect of different sensitivity and specificity level on the number of true cases generated by the algorithm. Through this procedure, we combined the priors for unknown parameters with the probability of the observed data to produce a Monte Carlo distribution for the parameter of interest.

As A is the (estimsted) true number of cases, we set our Monte Carlo simulation in order to exclude the generation of values incompatible with the meaning of this measure (e.g. negative values) imposing a constraint that, if a number < 0 was generated, the simulation should have discarded that value and repeat samlping until a number ≥ 0 was obtained [10].

Once the A distribution was calculated, we than calculated the incidence rate. To graphically represent our estimates, we selected the 2.5° and 97.5°percentile of the distribution of the incidence rate resulted from the application of the Monte Carlo procedure. It is worth highlighting that this specific methodology is valid under the assumption that the event of interest is rare [7].

Results

3.3.1 Patients characteristics



As mentioned above, we used criterion 1 to define HHF population. Baseline characteristics were define for the population enrolled in 2011. Data were initially obtained from 26,949 subjects who, during 2011, had at least one episode of HHF (Population A). Among these, 8,154 individuals had already been hospitalized within the 5-year period before the index hospitalization (Population C) while 18,795 patients did not have any HHF in the previous five years (Population B). In Table 1.10 we compared baseline characteristics of these three population of newly hospitalized patients.

The average age of hospitalized patients was 79 years (SD 11 years), and 51% of them were women. At baseline, index patients population A had a high burden of co-morbid CV and non-CV diseases including hypertension (94%), hyperlipidemia (46%), diabetes (33%), AF (28%), stroke (17%), COPD (15%), and kidney disease (20%). More than 67% of the patients were on treatment with ACE inhibitors, 60% with beta-blockers, 60% with diuretics (of whom nearly one-third were receiving aldosterone antagonists) and 43% with ARBs.

Concerning the difference between population B and C, the average age of population C was similar to that of newly hospitalized patients (population B) but, as expected, they had a worse co-morbidity and treatment profile.

3.3.2 Un-adjusted frequency

In table 1.11.a and 1.11.b are reported the absolute data emerged from the year 2010-2011.

During these two years, 69,164 heart failure hospitalizations have been registered (Criterion 1). These 69,164 hospitalizations correspond to 49,376 hospitalized patients, of which 30,463 (61.70%) had their first episode of HHF during the years 2010-2011.

3.3.3 Attack rate

In Table 1.12 are shown the age-stratum-specific attack rate per 10,000 person-years (both unadjusted and standardized as by the Italian population) and their 95% confidence interval. As expected, the attack rate were higher in man compared to women in all age-strata.
The attack rate was 0.84 (CI 95% 0.71-0.97) in younger men (0-40 years) and climbed to 614.27 (CI 95% 603.20-625.35) in patients older than eighty years. In younger women the rate was 0.48 (CI 0.38-0.58) and it reached 479.70 (CI 95% 472.96-486.44) in women with more than eighty years.
The standardized rate was calculated keeping the 2011 Italian population as reference and it was 75.10 (IC 95% 74.26-75.93) in men and 46.40 (IC 95% 45.88-46.91) in women.

3.3.4 Incidence rate

In Table 1.13 are shown the age-stratum-specific incidence rate per 10,000 person-years (both unadjusted and standardized as by the Italian population) and their 95% confidence interval.
As for attack rate the burden of this phenomenon resulted heavier in men than in women but the difference between the two genders was smaller. In the lower age-stratum men showed an incidence rate of 0.35 (IC 95% 0.29-0.41) that reaches 271.90 (IC 95% 266.36-277.44) for the upper age-stratum (>80 years). In younger women the incidence rate is 0.20 (IC 95% 0.16-0.25) that becomes 213.57 (IC 95% 210.23-216.92) in the upper stratum. Overall the standardized incidence rate was 30.81 (IC 95% 30.41-31.21) in men and 20.47 (IC 95% 20.22-20.72) in women.

3.3.5 Sensitivity analysis

Ordinary sensitivity analysis
The results of the sensitivity analysis are presented in Table 1.14 and 1.15.
Table 1.14 shows the variation of the age-specific HHF incidence rates in the male population when the sensitivity of the criterion used to identify hospitalization for HF varies. Assuming that the

specificity of our criterion remains fixed at 100%, the adjusted rates increases as the sensitivity decreases, rising from 0.39 (95% CI 0.32 to 0.45) to 0.58 (95% CI 0.49-0.68) for younger men (0-40 years), and from 302.11 (95% CI 295.96-308.26) to 453.17 (95% CI 443.94-462.39) for older men. The standardized rates increased from 34.23 (95% CI 33.80-34.67), assuming a sensitivity of 90% criterion, to 51.34 (95% CI 50.70-52.00) with a sensitivity of 60%.

Table 1.15 shows the variation of the age-specific HHF incidence rates in the female population when the sensitivity of the criterion used to identify hospitalization for HF varies. Even in this case, incidence rates increase when sensitivity decreases, passing from 0.22 (95% CI 0.17 to 0.27) to 0.33 (95% CI 0.26 to 0.41) in younger women and from 237.30 (95% CI 233.58-241.02) to 355.95 (IC 95% of 350.37-361.53) in older women. The standardized rates increased from 22.74 (95% 22.46 to 23.02) assuming a sensitivity of 90%, to 34.12 (95% CI 33.7-34.54) for a sensitivity of 60 %.

Monte Carlo sensitivity analysis

The results of the second sensitivity analysis are presented in Figure 1.2. In each of the three reported graphs it is possible to see the Monte Carlo distribution of incidence rate consequent to the different assumed levels of misclassification. As seen in the first sensitivity analysis, lower levels of sensibilities determine higher number of expected cases and, as a consequence, higher incidence rate with a broader variability. In the scenario in which we assumed sensitivity varying from 40-60% we found that range of the distribution of incidence varied from 1.47 – 57.6 to 44.8 – 65.85 (2.5° and 97.5°percentile respectively), when specificity was set at 99% or 100%. In the second scenario, with an assumed sensitivity between 60-80%, the margins of the distribution became less broad: from 0.99 - 38.72 to 33.6 – 44.10, when specificity varied from 99% to 100%. In the last scenario, sensitivity between 80-100%, the margins of the distribution became even less broad: from 0.74 - 30.1 to 26.83 – 33.14 when specificity varied from 99% to 100%.

The results of both sensitivity analyses showed, overall, that the incidence of HHF calculated by Criterion 1 can, at best, underestimate the true burden of the disease.

3.3.6 In-hospital mortality

As shown in Figure A.1.3, among all 18.795 patients who have experienced an episode of HHF in 2011, 1,329 subjects (7.1%) died (at the hospital) during the index admission. Of the 1,329 patients who died at the hospital, 50% died within the first week from the date of admission (Figure 1.4).

3.4 Discussion

This study provides estimates of the incidence of HHF in a large, well-defined population from Northern Italy in which we found that the incidence rate of newly hospitalized HF was ~3 cases every 1000 PYs.

In literature we can find several studies that address the problem of heart failure incidence. Based on the methodology applied, incident rates ranging from one to two events per 1000 PYs were reported in studies that used non-validated hospital discharge records from other European countries [11,12]. Higher incidence rates were reported in an American study, where the incidence reached a total of six events per 1000 PYs among men and women aged 45–65 years [13].

Oddly, these estimates did not differ from those reported from various studies carried out in the USA that used standardized criteria for HF ascertainment, the corresponding rates ranging from two to five events per 1000 PYs according to the Framingham criteria, [14,15] or from those reported in a European study based on Boston criteria (3–4 events per 1000 PYs) [16]. On the other hand, European studies directly capturing cases of incident HF by continuously monitoring participants for occurrence of HF during follow-up reported higher incidence rates of 17.6 and 12.5 events per 1000 PYs in men and women aged 55 years or older [17], the corresponding figures in our study being eight and seven events per 1,000 PYs, respectively.

Interpreting our data we need to consider first that inpatient data probably do not capture all cases of HF, because care is increasingly delivered in an outpatient setting. Secondly, because of privacy regulations, hospital records were not available, so HF diagnoses cannot be scrutinized and validated. A recent comprehensive study on the misclassification of claims data diagnoses, using medical record review as the gold standard, revealed that the sensitivity of claims diagnoses is often less than moderate, whereas their specificity is usually very good [18]. In particular, the specificity for congestive HF from hospital discharge records is expected to be nearly 100% because if a diagnosis is coded and recorded in the claims data it is likely that this diagnosis was made, particularly in hospital discharge summaries [19]. To verify the effect of misclassification to our estimate we ran two different types of sensitivity analysis. One ordinary analysis assumed our algorithm had a specificity of 100% and the sensitivity a point value of 60, 70, 80 or 90%. The second displayed the range of incidence rate distribution given certain range of bias. Both analyses confirmed that our estimate could, at best, underestimate the entity of the phenomenon.

To compare different results we need to take into account that differences in (i) demographic and clinical features of the investigated populations; (ii) the data source used for identifying HF cases; and (iii) criteria for heart failure ascertainment, exist across studies.

Other than for total incidence rates, our data are consistent with the increasing rates according to ascending age categories: from a few dozen hospitalized patients per 1,000 persons aged ≤40 years, to 20 (women) and 32 (men) events every 1,000 persons aged ≥80 years. In contrast, the effect of gender was moderate, i.e. a ~50% higher rate of hospitalization among men than among women. These estimates are generally similar to those reported from other population-based studies [11-17].

We found that 7% of newly hospitalized patients died during their index hospital stay. In-hospital mortality from 4% to 10% has been reported from the US ADHERE registry (Acute Decompensed Heart Failure National Registry)[20], the Canadian National Mortality Database [21], and the Italian Network on Heart Failure (IN-HF) Outcome Investigation [22]. Our results on in-hospital mortality were also similar to those reported in a recent review of studies on post-discharge adverse events among HHF patients, in which in-hospital mortality varied from 3% to 8% [23]. All these data taken together clearly indicate that, despite progress in reducing mortality of patients with chronic HF, hospitalizations for HF remain very frequent and represent a relevant clinical and economic burden for both patients and society.

3.5 References

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3.6 Appendix one

Table 1.1 Diagnostic categories of ER visits within two weeks before HF hospitalization (ICD 9 code 428.x)

YEARS 2010-2011		
DIAGNOSIS CATERGORY	**N**	**%**
CIRCULATORY SYSTEM	801	11.24
CONGENITAL ANOMALIES	3	0.04
DIGESTIVE SYSTEM	3	0.04
DISEASES OF THE BLOOD	10	0.14
ENDOCRINE METABOLIC IMMUNITY DISORDERS	126	1.77
GENITOURINARY SYSTEM	220	3.09
ILL-DEFINED CONDITION	2,577	36.17
INFECTIOUS AND PARASITIC DISEASE	7	0.10
INFLUENCING HEALTH STATUS	3	0.04
MENTAL DISORDERS	6	0.08
MUSCOSKELETAL SYSTEM	7	0.10
NEOPLASMS	2	0.03
NERVOUS SYSTEM AND SENSE ORGANS	61	0.86
POISONING	53	0.74
PREGNANCY AND CHILDBIRTH	6	0.08
RESPIRATORY SYSTEM	3,239	45.46
SKIN	1	0.01
TOTAL	7,125	

Table 1.2 - Details of ER diagnosis of circulatory system disease in patients within two weeks before HF hospitalization (ICD 9 code 428.x)

YEARS 2010-2011		
CODES ICD9	N	%
4011 – Essential benign hypertension	35	4.37
4019 – Essential unspecified hypertension	33	4.12
40211 – Benign hypertensive heart disease with heart failure	22	2.75
40290 – Unspecified hypertensive heart disease without heart failure	6	0.75
40291 – Unspecified hypertensive heart disease with heart failure	38	4.74
40411– Benign hypertensive heart and chronic kidney disease with heart failure and with chronic kidney disease stage I through stage IV, or unspecified	14	1.75
42731– Atrial fibrillation	26	3.25
428 – Heart failure	82	10.24
4280 – Congestive heart failure, unspecified	196	24.47
4281 - Left heart failure	32	4.00
4289 - Heart failure, unspecified	82	10.24
4299 - Heart disease, unspecified	5	0.62
4510 - Phlebitis and thrombophlebitis of superficial vessels of lower extremities	6	0.75
45119 - Other phlebitis and thrombophlebitis	6	0.75
4571 - Other lymphedema	33	4.12
4588 – Other specified hypotension	7	0.87
4589 – Hypotension, unspecified	25	3.12
Others	153	19.10
Total	801	100.00

Table 1.3 - Details of ER diagnosis of non-defined disease in patients within two weeks before HF hospitalization (ICD 9 code 428.x)

YEARS 2010-2011		
CODES ICD9	**N**	%
780- General symptoms	353	13.70
7802- Syncope and collapse	52	2.02
7806- Fever and other physiologic disturbances of temperature regulation	64	2.48
78079- Other malaise and fatigue	42	1.63
7823- Edema	33	1.28
7847- Epistaxis	15	0.58
7850- Tachycardia, unspecified	26	1.01
786- Symptoms involving respiratory system and other chest symptoms	953	36.98
78600- Respiratory abnormality, unspecified	27	1.05
78609- Other symptoms involving respiratory system and other chest symptoms	184	7.14
78650- Chest pain, unspecified	49	1.90
78659- Other chest pain	34	1.32
787- Symptoms involving digestive system	41	1.59
788- Symptoms involving urinary system	58	2.25
789- Other symptoms involving abdomen and pelvis	172	6.67
78900-Unspecified site of abdominal pain	24	0.93
Other	450	17.46
Total	2,577	

Table 1.4 - Details of ER diagnosis of respiratory disease in patients within two weeks before HF hospitalization (ICD 9 code 428.x)

YEARS 2010-2011		
	N	%
491 – Chronic bronchitis	330	10.19
49121 - Chronic bronchitis with (acute) exacerbation	68	2.10
4919 – Unspecified chronic bronchitis	18	0.56
518 - Other diseases of lung	1,942	59.96
5184 – Acute edema of lung, unspecified	342	10.56
51881 - Acute respiratory failure	228	7.04
51882 – Other pulmonary insufficiency, not elsewhere classified	16	0.49
51883 – Chronic respiratory failure	20	0.62
51884 – Acute and chronic respiratory failure/Acute on chronic respiratory failure	80	2.47
51889 – Other diseases of lung, not elsewhere classified	16	0.49
Other	179	5.53
Total	3,239	

Table 1.5 – Distribution of code 428.x and other ICD 9 codes generally used to codify HF

YEARS 2010-2011		
CODES ICD9	**N**	**%**
39891 - Rheumatic heart failure (congestive)	41	0.05
40201 - Malignant hypertensive heart disease with heart failure	119	0.15
40211 - Benign hypertensive heart disease with heart failure	2,139	2.78
40291 - Unspecified hypertensive heart and chronic kidney disease with heart failure and with chronic kidney disease stage I through stage IV, or unspecified	1,229	1.59
40401 - Malignant hypertensive heart and chronic kidney disease malignant with heart failure and with chronic kidney disease stage I through stage IV, or unspecified	17	0.02
40403 - Malignant hypertensive heart and chronic kidney disease malignant with heart failure and with chronic kidney disease stage V or end stage renal disease	13	0.02
40411 - Benign hypertensive heart and chronic kidney disease malignant with heart failure and with chronic kidney disease stage I through stage IV, or unspecified	213	0.28
40413 - Benign hypertensive heart and chronic kidney disease malignant with heart failure and with chronic kidney disease stage V or end stage renal disease	27	0.04
40491 - Unspecified hypertensive heart and chronic kidney disease malignant with heart failure and with chronic kidney disease stage I through stage IV, or unspecified	106	0.14
40493 - Unspecified hypertensive heart and chronic kidney disease malignant with heart failure and with chronic kidney disease stage V or end stage renal disease	18	0.02
425 – Cardiomyopathy	6,945	9.01
428 – Heart failure	65,929	85.54
4293 – Cardiomegaly	276	0.36
Total	77,072	

Table 1.6 – Distribution of principal diagnosis reporting a code listed in the Scenario 2 with a secondary diagnosis with the code ICD9 428.x

Principal diagnosis		N	%
Hypertensive heart disease	**402.01**	27	0.04
	402.11	250	0.37
	402.91	202	0.30
Hypertensive heart and chronic kidney disease	**404.01**	10	0.01
	404.03	2	0.00
	404.11	65	0.10
	404.13	7	0.01
	404.91	75	0.11
Cardiomyopathy	**425.0**	1	0.00
	425.1	15	0.02
	425.2	1	0.00
	425.4	807	1.19
	425.5	2	0.00
	425.8	32	0.05
	425.9	466	0.69
HF	**428.x**	65,929	97.08
Cardiomegaly	**429.3**	24	0.04
Total		67,915	100.00

Table 1.7 - Distribution of principal diagnosis for respiratory diseases associated with a secondary diagnosis of HF (428.x)

Principal diagnosis associated to a secondary fdiagnosis of HF			
	ICD9	**N**	%
Acute bronchitis	**466.0**	242	1.69
Bacterial pneumonia unspecified	**482.9**	921	6.44
Bronchopneumonia, organism unspecified	**485.x**	1,152	8.05
Pneumonia, organism unspecified	**486.x**	1,618	11.31
COPD with (acute) exacerbation	**491.21**	2,147	15.00
Acute respiratory failure	**518.81**	3,695	25.82
Acute and chronic respiratory failure	**518.84**	1,177	8.22
Other respiratoy diseases	**-**	2,359	16.48
Non defined diseases	**780-799**	1,000	6.99
Total		14,311	

Table 1.8 – Principal diagnosis coded with ICD9 coded of hospitalization recorded with DRG 127 (heart failure and shock)

	Hospitalizations 2010-2011
Rheumatic heart failure (congestive) (398.91)	38 (0.06%)
Hypertensive heart disease (402.x)	3,111 (4.98%)
Hypertensive heart and chronic kidney disease (404.x)	347 (0.56%)
HF (428.x)	57,800 (92.49%)
Symptoms involving cardiovascular system (785.x)	1,196 (1.91%)
Totale	62,492 (100.00%)

Table 1.9 – DRG code used in hospitalizations with a primary diagnosis of heart failure (codice 428.x)

DRG CODE different 127		N	%
103-120	Cardiovascular interventions	425	5.23
121	Malattie cardiovascolari con AMI e complicanze maggiori (vivo)	225	2.77
123	Circulatory disorders with acute myocardial infarction, expired	44	0.54
124	Circulatory Disorders Except AMI with Cardiac Catheterization with Complication/Comorbidity	3,278	40.32
468, 476, 477	Interventions not related to principal diagnosis	49	0.60
479	Other vascular procedures without complications, cormorbidities	9	0.11
515	Cardiac defibrillator implant without cardiac catheterization	1,274	15.67
518	Percutaneous cardiovascular procedures	2	0.02
525	Heart assist system implant	1	0.01
535	Cardiac defibrillator implant with cardiac catheterization	605	7.44
541	Ecmo or tracheostomy with mechanical ventilation 96+ hours	15	0.18
542	Tracheostomy with mechanical ventilation 96+ hours without major operating room procedure	20	0.25
547,549	Bypass	41	0.50
551	Pacemaker	978	12.03
553	Other vascular procedures with complications and comorbidities	58	0.71
555,557	Percutaneous cardiovascular procedure	1,105	13.59
		8,129	

Figure 1.1 - Algorithm for the definition of HHF

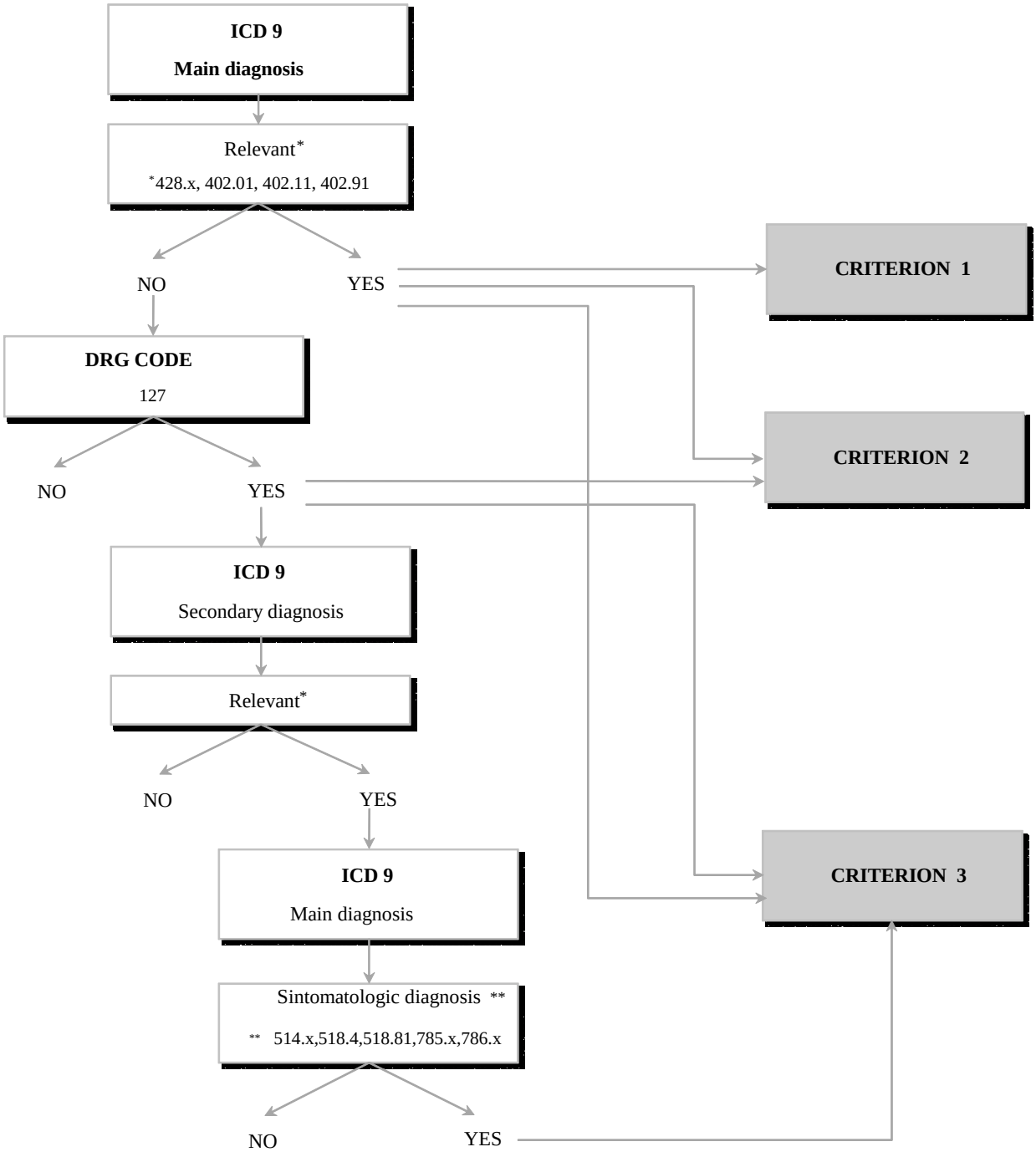
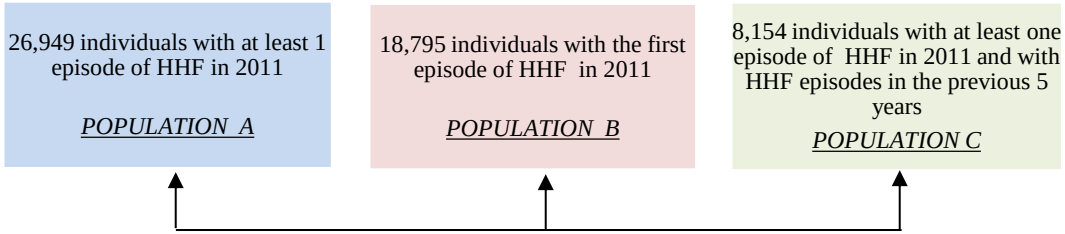


Table 1.10 – Baseline characteristics of HHF patients (criterion 1) and medical history (hospitalization and drug treatment) of five years before index date in populations A, B and C.



	Population A		Population B		Population C	
	Number /mean	Percentage /SD	Number /mean	Percentage /SD	Number /mean	Percentage /SD
Age (mean and SD)	78.93	10.38	79.04	10.55	78.67	9.99
Male	13,273	49.25	8,988	47.82	4,285	52.55
HHF hospitalization in the year before index date	3,254	12.07	-	-	3,254	39.90
HHF hospitalization in the five before index date	8,154	30.26	-	-	-	-
Any hospitalization in the year before index date	13,399	49.72	7,857	41.8	5,542	67.97
Number of hospitalization in the year before index date (mean and SD)	1.04	1.52	0.79	1.27	1.62	1.85
Number of HHF in the year before index date (mean and SD)	0.18	0.63	-	-	0.61	1.02
Medical history (5 year before index date)						
Hypertension	25,272	93.78	17,169	91.35	8,103	99.37

Hyperlipidemia	12,341	45.79	7,672	40.82	4,669	57.26
Stroke or cerebrovascular events	4,655	17.27	2,889	15.37	1,766	21.66
Peripheral Vascular Disease	354	1.31	186	0.99	168	2.06
Mitral Valve Disease	3,047	11.31	1,146	6.1	1,901	23.31
Myocardial infarction	8,826	32.75	4,535	24.13	4,291	52.62
Pacemaker	2,535	9.41	1,388	7.38	1,147	14.07
Implantable Cardioverter Defibrillator	1,008	3.74	213	1.13	795	9.75
Atrial Fibrillation	7,526	27.93	3,415	18.17	4,111	50.42
Atrial Flutter	809	3.00	357	1.9	452	5.54
Asthma	39	0.14	24	0.13	15	0.18
Bronchitis	811	3.01	333	1.77	478	5.86
COPD	4,236	15.72	2,037	10.84	2,199	26.97
Diabetes	8,965	33.27	5,532	29.43	3,433	42.1
Nephritis, Nephrotic Syndrome, and Nephrosis	5,307	19.69	2,292	12.19	3,015	36.98
Acute glomerulonephritis	11	0.04	7	0.04	4	0.05
Nephrotic syndrome	122	0.45	72	0.38	50	0.61
Chronic glomerulonephritis	63	0.23	34	0.18	29	0.36
Nephritis and nephropathy, not specified	203	0.75	94	0.5	109	1.34
Acute renal failure	1,468	5.45	688	3.66	780	9.57
Chronic kidney disease	4,321	16.03	1,730	9.2	2,591	31.78
Renal failure, unspecified	442	1.64	163	0.87	279	3.42
Renal sclerosis, unspecified	13	0.05	8	0.04	5	0.06
Disorders resulting from impaired renal function	59	0.22	34	0.18	25	0.31
Small kidney of unknown cause	12	0.04	4	0.02	8	0.1

Drug history (Five years prior index hospitalization.)						
ACE inhibitors	18,104	67.18	11,511	61.25	6,593	80.86
ARBs	11,510	42.71	7,402	39.38	4,108	50.38
Beta-Blockers	16,133	59.86	9,900	52.67	6,233	76.44
Aldosterone antagonists	8,568	31.79	3,570	18.99	4,998	61.3
Digoxin	5,493	20.38	2,680	14.26	2,813	34.5
Diuretics	16,133	59.86	9,900	52.67	6,233	76.44

Table 1.11.a – Number of hospitalizations, patients hospitalized and patients hospitalized with no history of HHF among residents in region Lombardy in the years 2010 and 2011.

CRITERION 1 428.x, 402.01,402.11,402.91 AS MAIN DIAGNOSIS		
YEARS 2010-2011	**All**	**Classified as urgent**
Hospitalizations	69,164 (100.00%)	52,026 (75.22%)
Patients hospitalized	49,376 (100.00%)	39,629 (80.26%)
Patients with no history of HHF, (as defined by Criterion 1)	30,463 (61.70%)	24,923 (50.46%)

Table 1.11.b - Number of hospitalizations, patients hospitalized and patients hospitalized with no history of HHF among residents in region Lombardy and stratified by years 2010 and 2011.

CRITERION 1 428.x, 402.01,402.11,402.91 AS MAIN DIAGNOSIS		
	YEAR 2010	**YEAR 2011**
Hospitalizations	34,336 (100.00%)	34,828 (100.00%)
Patients hospitalized	26,879 (100.00%)	26,949 (100.00%)
Patients with no history of HHF, (as defined by Criterion 1)	18,830 (70.05%)	18,795 (62.76%)

Table 1.12 – Attack rate /10,000 person-year

CRITERION 1

428.x, 402.01,402.11,402.91 AS MAIN DIAGNOSIS

Age stratum		TOTAL HOSPITALIZATIONS		URGENT HOSPITALIZATIONS*	
		Men	**Women**	**Men**	**Women**
0-40	N° of events Attack rate CI 95%	169 **0.84** 0.71-0.97	93 **0.48** 0.38-0.58	98 **0.49** 0.39-0.58	63 **0.33** 0.25-0.41
41-50	N° of events Attack rate CI 95%	623 **7.84** 7.22-8.45	184 **2.39** 2.05-2.74	397 **4.99** 4.50-5.49	134 **1.74** 1.45-2.04
51-60	N° of events Attack rate CI 95%	1,830 **29.63** 28.28-95.35	714 **11.38** 10.55-12.22	1,113 **18.02** 16.96-19.08	494 **7.87** 7.18-8.57
61-70	N° of events Attack rate CI 95%	5,420 **97.96** 95.35-100.57	2,581 **43.53** 41.85-45.21	3,603 **65.12** 62.99-67.24	1,904 **32.11** 30.67-33.55
71-80	N° of events Attack rate CI 95%	11,769 **276.80** 271.80-281.80	8,717 **147.00** 143.92-486.44	8,593 **202.10** 197.83-206.38	6,848 **115.49** 112.75-118.22
>80	N° of events Attack rate CI 95%	11,814 **614.27** 603.20-625.35	19,460 **479.70** 472.96-486.44	9,689 **503.78** 493.75-513.81	16,785 **413.76** 407.50-420.02
Standardized**	Attack rate CI 95%	**75.10** 74.26-75.93	**46.40** 45.88-46.91	**56.46** 55.73-57.19	**38.03** 37.56-38.49
Total unadjasted	Attack rate CI 95%	**66.61** 66.09-67.13		**52.26** 51.80-52.72	
Total standardized**	Attack rate CI 95%	**60.75** 60.23-61.27		**47.24** 46.78-47.70	

*In ordinary wards but classified as urgent

** For rate standardization it was used as reference the entire Italian population in 2011

Table 1.13 – Incidence rate /10,000 person-year

CRITERION 1

428.x, 402.01,402.11,402.91 AS MAIN DIAGNOSIS

Age stratum		TOTAL HOSPITALIZATIONS		URGENT HOSPITALIZATIONS*	
		Men	**Women**	**Men**	**Women**
0-40	N° of events Incidence rate CI 95%	139 **0.35** 0.29-0.41	76 **0.20** 0.16-0.25	92 **0.23** 0.19-0.28	58 **0.15** 0.11-0.19
41-50	N° of events Incidence rate CI 95%	487 **3.10** 2.83-3.38	169 **1.11** 0.94-1.28	330 **2.10** 1.88-2.33	129 **0.85** 0.70-0.99
51-60	N° of events Incidence rate CI 95%	1,365 **11.19** 10.60-11.78	556 **4.48** 4.11-4.85	896 **7.34** 6.86-7.82	401 **3.23** 2.91-3.55
61-70	N° of events Incidence rate CI 95%	3,992 **36.81** 35.66-37.95	2,028 **17.32** 16.57-18.08	2,772 **25.53** 24.58-26.48	1,539 **13.14** 12.48-13.80
71-80	N° of events Incidence rate CI 95%	8,751 **107.50** 105.25-109.75	6,889 **66.77** 65.19-68.34	6,563 **80.42** 78.47-82.36	5,505 **53.29** 51.89-54.70
>80	N° of events Incidence rate CI 95%	9,265 **271.90** 266.36-277.44	15,659 **213.57** 210.23-216.92	7,727 **225.69** 220.66-230.73	13,617 **185.20** 182.09-188.31
Standardized**	Incidence rate CI 95%	**30.81** 30.41-31.21	**20.47** 20.22-20.72	**23.85** 23.50-24.20	**17.00** 16.77-17.23
Total unadjusted	Incidence rate CI 95%	**26.77** 26.53-27.01		**21.48** 21.26-21.69	
Total standardized**	Incidence rate CI 95%	**25.64** 25.42-25.86		**20.43** 20.23-20.62	

*In ordinary wards but classified as urgent

** For rate standardization it was used as reference the entire Italian population in 2011

Table 1.14 – Variation of the age-specific HHF incidence rate at the variation of the sensitivity of the criterion used to identify patients - male population

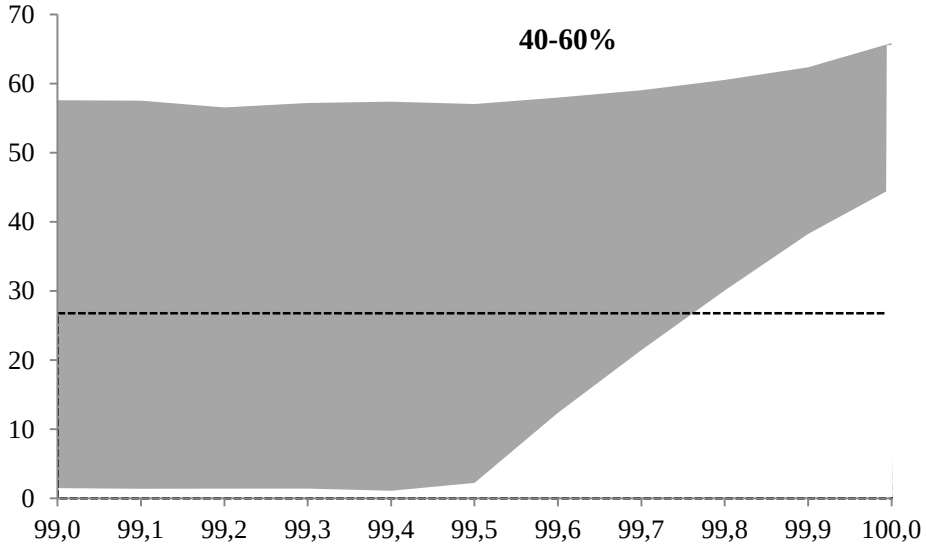
		MALE			
	SP	**1.00**	**1.00**	**1.00**	**1.00**
Age class	**SE**	**0.90**	**0.80**	**0.70**	**0.60**
0-40	**N° expected cases**	154.44	173.75	198.57	231.67
	Adjusted incidence rate	**0.39**	**0.44**	**0.50**	**0.58**
	CI 95%	0.32-0.45	0.36-0.51	0.42-0.58	0.49-0.68
41-50	**N° expected cases**	541.11	608.75	695.71	811.67
	Adjusted incidence rate	**3.44**	**3.88**	**4.43**	**5.17**
	CI 95%	3.14-3.75	3.53-4.22	4.04-4.82	4.71-4.71
51-60	**N° expected cases**	1516.67	1706.25	1950.00	2275.00
	Adjusted incidence rate	**12.43**	**13.99**	**15.99**	**18.65**
	CI 95%	11.77-13.09	13.25-14.73	15.14-16.83	17.66-19.64
61-70	**N° expected cases**	4435.56	4990.00	5702.86	6653.33
	Adjusted incidence rate	**40.90**	**46.01**	**52.59**	**61.35**
	CI 95%	39.63-42.17	44.59-47.44	50.95-54.22	59.45-63.25
71-80	**N° expected cases**	9723.33	10938.75	12501.43	14585.00
	Adjusted incidence rate	**119.44**	**134.38**	**153.57**	**179.17**
	CI 95%	116.94-121.95	131.56-137.19	150.35-156.79	175.41-182.92
>80	**N° expected cases**	10294.44	11581.25	13235.71	15441.67
	Adjusted incidence rate	**302.11**	**339.88**	**388.43**	**453.17**
	CI 95%	295.96-308.26	332.95-346.80	380.52-396.34	443.94-462.39
Standardized *	**N° expected cases**	26665.56	29998.75	34284.29	39998.33
	Adjusted incidence rate	**34.23**	**38.51**	**44.01**	**51.35**
	CI 95%	33.80-34.67	38.03-39.00	43.46-44.57	50.70-52.00

Table 1.15 - Variation of the age-specific HHF incidence rate at the variation of the sensitivity of the criterion used to identify patients - female population

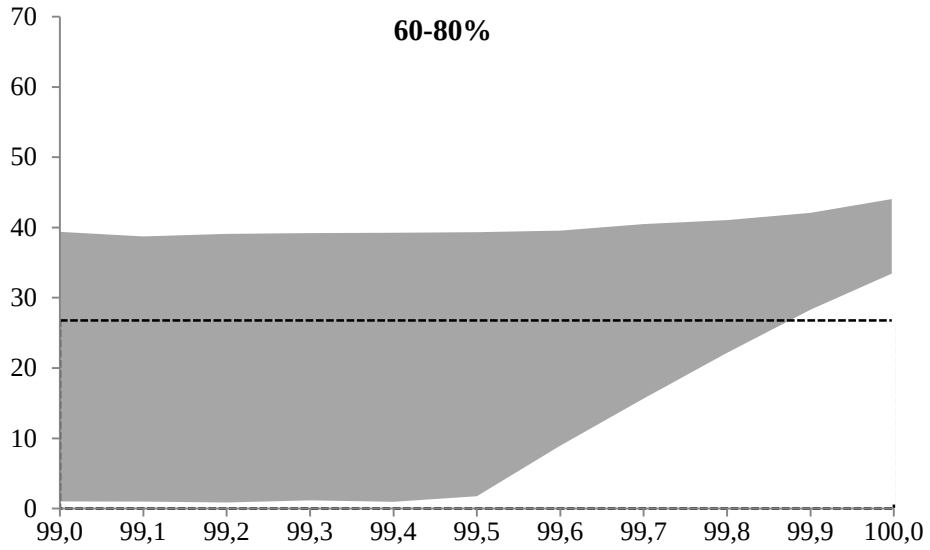
		FEMALE			
	SP	**1.00**	**1.00**	**1.00**	**1.00**
Age class	**SE**	**0.90**	**0.80**	**0.70**	**0.60**
0-40	**N° expected cases**	84.44	95.00	108.57	126.67
	Adjusted incidence rate	**0.22**	**0.25**	**0.29**	**0.33**
	CI 95%	0.17-0.27	0.19-0.31	0.22-0.35	0.26-0.41
41-50	**N° expected cases**	187.78	211.25	241.43	281.67
	Adjusted incidence rate	**1.23**	**1.39**	**1.59**	**1.85**
	CI 95%	1.05-1.42	1.18-1.6	1.35-1.82	1.57-2.13
51-60	**N° expected cases**	617.78	695.00	794.29	926.67
	Adjusted incidence rate	**4.98**	**5.60**	**6.40**	**7.47**
	CI 95%	4.56-5.39	5.13-6.07	5.87-6.93	6.85-8.09
61-70	**N° expected cases**	2253.33	2535.00	2897.14	3380.00
	Adjusted incidence rate	**19.24**	**21.65**	**24.74**	**28.87**
	CI 95%	18.41-20.08	20.71-22.59	23.67-25.82	27.61-30.12
71-80	**N° expected cases**	7654.44	8611.25	9841.43	11481.67
	Adjusted incidence rate	**74.19**	**83.46**	**95.39**	**111.28**
	CI 95%	72.44-75.94	81.49-85.43	93.13-97.64	108.66-113.91
>80	**N° expected cases**	17398.89	19573.75	22370.00	26098.33
	Adjusted incidence rate	**237.30**	**266.96**	**305.10**	**355.95**
	CI 95%	233.58-241.02	262.78-271.14	300.32-309.88	350.37-361.53
Standardized*	**N° expected cases**	28196.67	31721.25	36252.86	42295.00
	Adjusted incidence rate	**22.74**	**25.59**	**29.24**	**34.12**
	CI 95%	22.46-23.02	25.27-25.9	28.88-29.6	33.7-34.54

Figure 1.2 Range of incidence rate (Incidence rate /10,000 person-year) measures given different level of misclassification estimates. The range estimates reported are those corresponding to the 2.5° and 97.5° percentile of the distribution obtained from the Monte Carlo simulation. In each of the graph the crude incidence rate is also reported as reference (27.66/10,000 person-years).

a) Incidence rate distribution (Incidence rate /10,000 person-year) with an assumed sensitivity of the algorithm to select cases ranging from 40 to 60% and specificity from 99 to 100%. The dotted line represents the crude incidence rate (27.66/10,000 person-years).



b) Incidence rate distribution (Incidence rate /10,000 person-year) with an assumed sensitivity of the algorithm to select cases ranging from 60 to 80% and specificity from 99 to 100%. The dotted line represents the crude incidence rate (27.66/10,000 person-years).



c) Incidence rate distribution (Incidence rate /10,000 person-year) with an assumed sensitivity of the algorithm to select cases ranging from 80 to 100% and specificity from 99 to 100%. The dotted line represents the crude incidence rate (27.66/10,000 person-years).

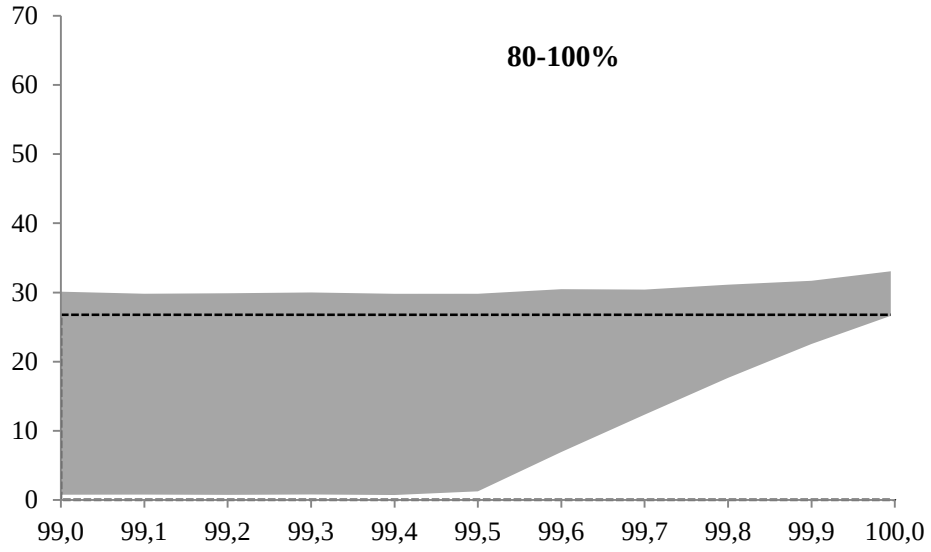
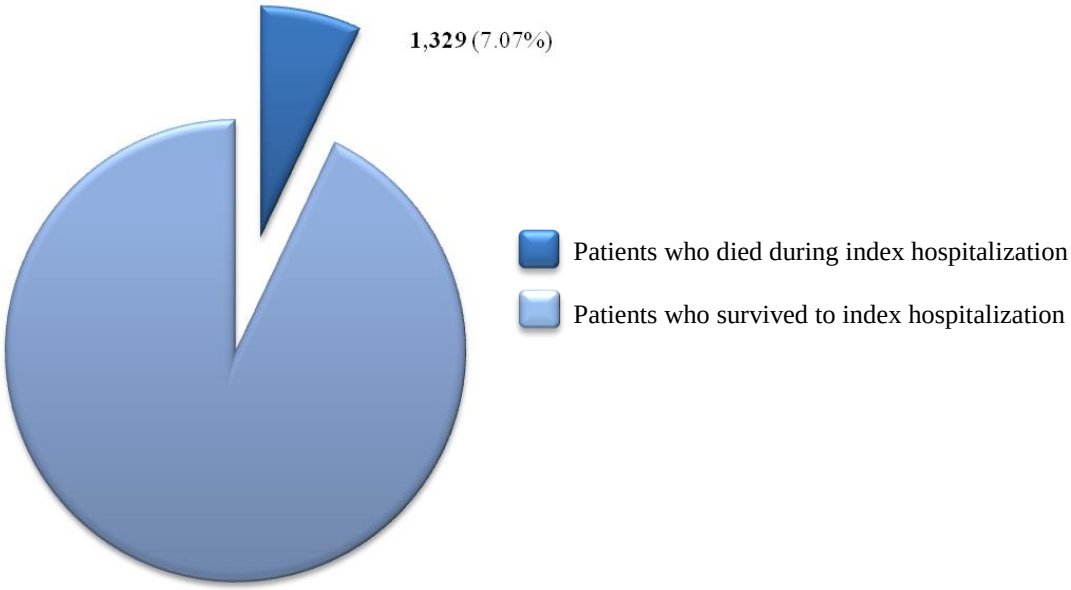


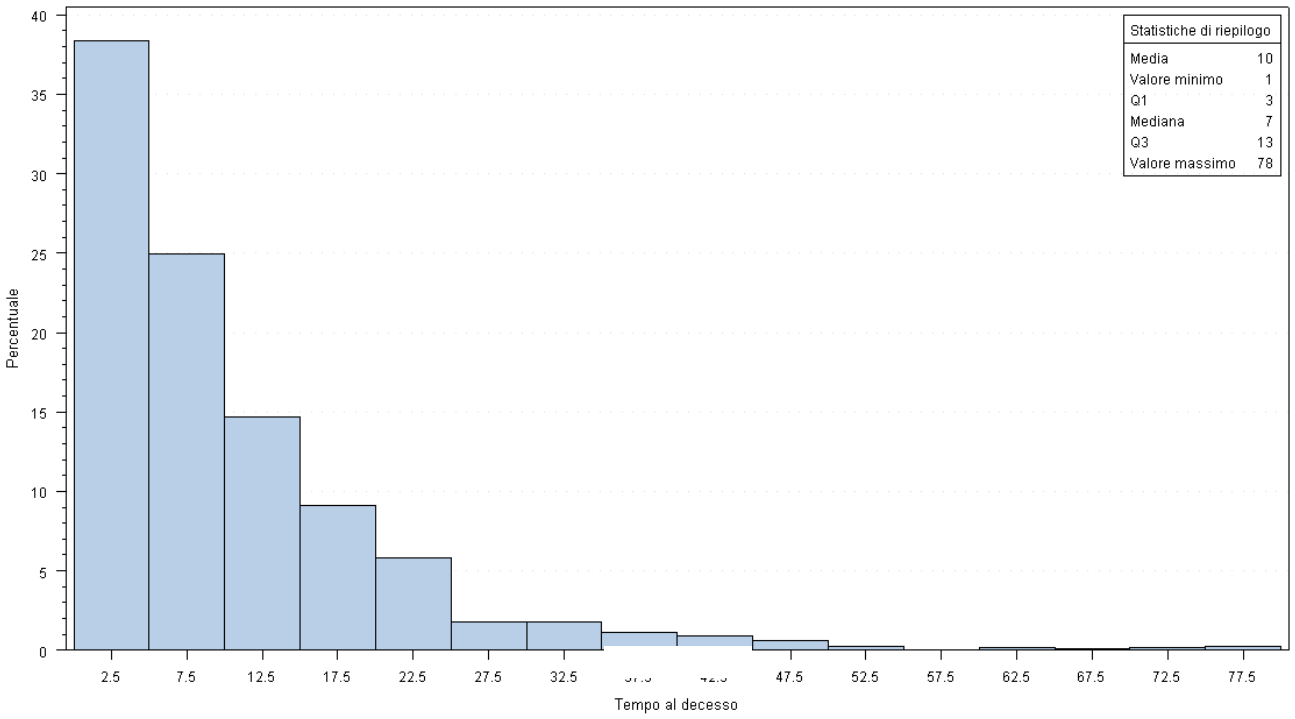
Figure 1.3 – The graphic shows the proportion of patients who died during index hospitalization. Population B



The graphics represents the proportion of patients who died during index hospitalization among all patients who had their first heart failure hospitalization.

Figure 1.4 – Distribution of time to event for patients who died during index hospitalization.

Population B



The grafic represnts the distribution of the time to event (expressen in days) for patients who were newly hospitalized for heart failure in 2011 and who died during index hospitalization.

4. Determinants of new heart failure hospitalizations- Risk factors

3. 1 Introduction

As previously mentioned, hypertension is one of the major risk factors for developing heart failure, especially in heart failure with a preserved ejection fraction (HF-PEF).

HF-PEF, in fact, seems to have a different epidemiological and aetiological profile from heart failure with a reduced ejection fraction (HF-REF), mainly because patients with HF-PEF are older, more often female and obese and are more likely to have hypertension and atrial fibrillation (AF) than those with HF-REF. [1,2]. In general, it is commonly recognized that hypertension, alone or in combination with Chronic Heart Disease (CHD), precedes the development of heart failure in the majority of both men and women [3].

Fifty years ago, before the widespread availability of effective antihypertensive drug treatment, heart failure was one of the most common complications of hypertension, accounting for 40% of deaths associated with this condition. Early data from the Framingham study demonstrated that hypertension was the major factor in the development of heart failure [4].

A 14-year follow-up of patients of the Framingham heart study showed that hypertension, alone or in combination with CHD, preceded the development of heart failure in 70% of both men and women enrolled in the study [5].

Furthermore, it has been demonstrated that the lifetime risk for heart failure doubles in subjects with blood pressure (BP) > 160/100 versus < 140/90 mmHg and that this gradient of risk is apparent in both men and women in every age decade from 40 to 70 years [6].

Hypertension is, of course, not the only factor contributing to the development of heart failure but, because of its high prevalence, carries a great population-attributable risk (PAR).

A recent study (Health, Aging, and Body Composition Study [7]) which assessed the PAR of independent risk factors for HF in a cohort of 2,934 participants without HF, confirmed the important role of hypertension in HF development: Coronary heart disease (PAR, 23.9%) and uncontrolled blood pressure (PAR 21.3% for white participants) were the two factors that carried the highest PAR.

All these data show that hypertension has a huge impact from a public health perspective, first, because its prevalence is very high throughout Europe and North America with estimates ranging from 25 up to 60% of the populations surveyed [8] and second, because demographic changes with an ageing population are causing an increase not only in the prevalence of the disease but also in the absolute number of patients diagnosed with the condition [9].

Traditionally, it has been considered that heart failure is a constellation of signs and symptoms associated with inadequate performance of the heart. However, this only focuses on one facets of the pathophysiology of the syndrome, which clearly is the result of a number of structural, functional and biological alterations that account for the progressive nature of heart failure.

Although it is well recognized that heart failure is the final stage of CVD resulting from these risk factors, the exact nature of the development process has not been fully elucidated.

A model for the progression from hypertension to heart failure has been proposed by Vasan and Levy [10] and has subsequently been modified by Himmelman (Figure A) [11].

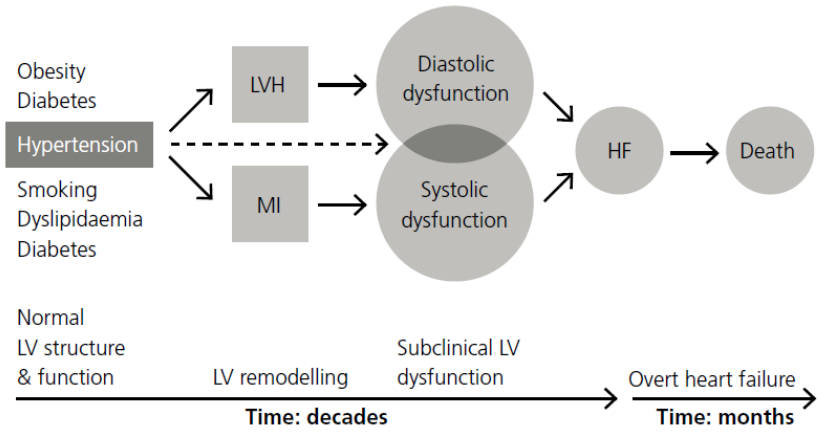


Figure A, Model for the progression from hypertension to heart failure proposed by Vasan and Levy [10] and been modified by Himmelman [11].

This model provides a single unified hypothesis that effectively links hypertension to heart failure. The model acknowledges that cardiovascular disease is a continuous and progressive disease, with a disparate timescale. In the early stages in the of progression to heart failure, the left ventricular structure and function is typically normal. However, with time, the pathologic effects of one or more cardiovascular risk factors result in the development of structural and functional changes with left ventricular hypertrophy (LVH) and myocardial infarction (MI).

The principal structural adaptation of the heart to an increased pressure load (that is the effect of hypertension) is LVH, essentially producing an increase in wall thickness at the expense of chamber volume. Compared with normotensive subjects, those with mild hypertension have a two- to three-fold higher risk for developing LVH and this risk increases with a greater severity of hypertension [12].

The development of LVH is associated with progressive degenerative changes in hypertrophied cardiac myocytes, and an abnormal accumulation of fibrillar collagen in the interstitial spaces that brings to a more severe muscle dysfunction [13]. In addition to this, hypertension is often associated with symptoms related to volume overload, reduced tissue perfusion and compensatory activation of neuro-endocrine systems, including the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), which further accelerate the progression from mild-to-moderate and severe heart failure [14].

Several studies investigating the effect of antihypertensive agents on cardiovascular disease, including heart failure, have already been published.

A meta-analysis by Law et al. evaluated the relationship between BP lowering drugs and heart failure (in both patients with or without a history of CVD) in 95 trials (of which 64 vs placebo and 31 with direct drug comparison). The meta-analysis showed that thiazide diuretics, ACE-inhibitors (ACE-i), angiotensin-receptor blockers (ARBs), and selective or vasodilatory β-blockers significantly reduced the incidence of heart failure by 24% ($p< 0.001$) on average, with no significant difference between the four classes of drugs. Calcium channel blockers (CCB) reduced heart failure by 19% when compared vs placebo but they were statistically significantly less effective in doing so compared to the other four classes of drugs (relative risk 1.22, 1.10 to 1.35; $P<0.001$) [15].

Verdecchia et al. conducted a meta-analysis of trials comparing ACE-inhibitors, ARBs, or CCBs, with diuretics, β-blockers, or placebo in hypertensive or high-risk subjects without CHF at entry.

In trials vs. placebo, the risk of CHF was reduced by 21% with ACEIs ($p=0.007$). In trials vs. diuretics/beta-blockers, no differences were found between ACEIs and comparators (OR 1.02; 95% CI 0.84-1.24), whereas CCBs were associated with an 18% higher risk of CHF (OR 1.18; 95% CI 1.00-1.39) [16].

Although different classes of drugs have been shown to be effective, adherence to treatment has not reached an optimal level yet. An Italian study conducted by GP's on 18,800 newly diagnosed hypertensive patients showed that during the first 6 months after initial diagnosis 51.4%, 40.5%, and 8.1% patients were classified as having low, intermediate, and high adherence, respectively.

This is a rather serious problem from a public health perspective, considering that, as a chronic treatment, the higher the therapy adherence, the more effective it is [17].

Non adherence is likely an important source of preventable cardiovascular morbidity and mortality. However, up until now, there have been very few large effectiveness studies assessing the relationship between adherence levels to antihypertensive medication and major cardiovascular outcomes for primary prevention of heart failure.

A Canadian study evaluated the link between antihypertensive adherence and heart failure in a cohort of hypertensive 45–85 years old patients without cardiovascular disease and newly treated with antihypertensive therapy between 1999 and 2004. The mean age was 65 years, 37% were male, 9% had diabetes, and 19% had dyslipidemia. During the 2.7 year follow-up, 4.5% had a heart failure event (1.5/100 persons-year) and HF was 11% lower in the group with a high level of adherence to antihypertensive therapy, compared with the low-adherence group (RR 0.89; 0.80–0.99) [18].

The studies described in this session were designed to estimate the effectiveness and the adherence to antihypertensive therapy in an unselected cohort with a large number of patients retrieved from the Lombardy region population.

In this cohort of patients 40–80 years old, newly treated by antihypertensive drugs and without a history of cardiovascular disease, we conducted two parallel analyses (Study 1 and 2), with the same study design, to evaluate (i) the effect of adherence to antihypertensive treatment (ii) the effect of the medication at entry and (iii) the effect adherence to a specific antihypertensive class, on heart failure onset, considering two different outcomes:

- heart failure hospitalization (study 1 A and 2 A)
- heart failure hospitalization or the first prescription of digitalis glycosides (as a proxy of chronic heart failure) (study 1 B and 2 B).

4.2 Methods

4.2.1 Data Source

Data used for this study, like those for other analyses in this work, were retrieved from the health service databases of Lombardy, an Italian region that accounts for ~16% (10 million) of the Italian population. The entire Italian population is covered by the national health service (NHS), and in

Lombardy this has been associated since 1997 with an automated system of databases to collect a variety of information, including (i) an archive of residents who receive NHS assistance (practically the whole resident population), reporting demographic and administrative data; (ii) a public and private hospital discharge database; and (iii) a database on drug prescriptions reimbursable by the NHS.

For each patient it is possible to link the information from different databases via a single identification code. In order to preserve privacy, each identification code is automatically converted to an anonymous code. The reversal of this process was prevented by deletion of the conversion table.

4.2.2 Cohort selection and follow up

Lombardy residents aged 40-80 years who were beneficiaries of the NHS represented the target population.

Of these, those who were prescribed antihypertensive drugs (in monotherapy) during 2005 were identified, the date of first prescription was considered the index date and the first class of antihypertensive the index antihypertensive.

Patients older than 80 and younger than 40 were excluded because in the years from 2003 to 2009, the hypertension guidelines did not recommend drug treatment in very elderly hypertensive individuals [19] and hypertension is much rarer at a young age with a more common involvement of secondary causes as well [20].

Drugs included all available major antihypertensive drug classes that are, diuretics (ATC C03), β-blockers (ATC C07), ACE-i (ATC C09A), ARBs (ATC C09C), and CCB (ATC C08). The two classes that work on the RAAS system (ACE+ARBs) were considered together.

To make the study population as homogeneous as possible and the data relevant to the objective of this study, four patient categories were excluded: (i) patients who started their antihypertensive treatment with more than one antihypertensive class, in order to select people who should be at the same stage of disease severity; (ii) patients who have been dispensed at least one cardiovascular drug (ATC C01, C04, C05) and patients who have been hospitalized for a CV problem (ICD9 390-459, Procedures: 35-39) within the 5 years prior the index date, in order to limit the analysis to new drug users; (iii) patients who did not reach at least one year of follow-up, to ensure at least one year of potential exposure to the drugs of interest and (iv) patients who received a prescription of digitalis glycosides during the first year of follow up.

The remaining patients represented the study cohort. Each member of the cohort accumulated person-years of follow-up from the date of first antihypertensive prescription until the earliest date among hospital admission for heart failure (study 1) and/or first prescription of digitalis glycosides (study 2), death, emigration, or end of follow up December 31, 2012.

4.2.3 Case patients and controls

Two case-control studies (A and B) were nested into the cohort of incident antihypertensive users for both studies 1 and 2. Nested case-control design is a useful alternative to cohort design when the effect of time-dependent exposure (like adherence) on rare events needs to be investigated using large databases [21]. Case patients were members of the cohort who during follow-up experienced the outcome of interest. In study 1, case patients were those who experienced a heart failure hospitalization (HHF) during follow up. HHF were identified through the hospital discharge database (principal diagnosis with ICD9 428.x, 402.01, 402.11, 402.91). In study 2, besides HHF, the outcome of interest included also the first prescription of digitalis glycosides as a proxy of chronic heart failure onset and such information was retrieved from the drugs prescription database. In study A five controls were randomly selected from the risk set for each case by matching with respect to (i) age, (ii) gender and (iii) date of entrance in the cohort. In study B, five controls were also randomly selected from the risk set for each case, but they were matched with respect to (i) antihypertensive drug at study entrance, (ii) adherence to treatment expressed as proportion of days covered and (iii) date of entrance in the cohort.

4.2.4 Assessment of treatment adherence

Adherence, i.e. the extent to which a patient takes antihypertensive medication as prescribed [22], was measured by calculating the proportion of days covered (PDC).

The PDC was assessed as the cumulative number of days during which the medication was available divided by the number of days of follow-up [23]. Patients were categorized as having very-low (PDC <25%), low (PDC 25–49%), intermediate (PDC 50–74%), and high (PDC >75%) adherence.

Besides PDC we also wanted to evaluate whether, in patients with the same adherence level, there was a difference in the probability of experiencing the outcome, based on different exposure to different type of drugs.

To achieve this objective we assessed the cumulative number of days covered by each type of antihypertensive divided by the number of days covered by any antihypertensive treatment (Proportion of Days with a Certain Antihypertensive, PDCA).
The PDCA was dichotomized, setting a threshold of PDCA <80% to identify patients with a low level of exposure to that drug class. Both cases and controls' adherence was calculated from the index date to the end of the observation period. Switch was considered as any prescription other than index class, no matter whether it was in add-on or not.

4.2.5 Covariates

In both studies 1 and 2, additional information included: (i) Charlson comorbidity index score calculated by the diagnostic information available from inpatient charts in the 5 years prior to index date [24] (ii) concomitant use of lipid-lowering, antidiabetic and antidepressant agents at baseline and other CV drugs (ATC C01) during follow up and (iii) switch to a different antihypertensive class or to combination therapy. In study B, in which cases and control were not matched by gender and age at index date, such information was also included in the model.

4.2.6 Statistical analysis

Characteristics of cases and controls were compared using the chi-square test (for type of antihypertensive drug employed at entry, concomitant users of other drugs, between class switching), its version for the trend (categories of the Charlson comorbidity index score, categories of the proportion of days covered with antihypertensive drugs) or the non-parametric test of Mann-Whitney (time of follow-up spent with antihypertensive available).
Conditional logistic regression models were fitted with the aim to estimate the odds ratio (OR), and its 95% confidence interval (CI), of the HF outcome associated with antihypertensive drug used as initial therapy and drug adherence. Adjustments were made for the aforementioned covariates.
Trend in ORs along categories of PDC was tested according to the statistical significance of the regression coefficient of the recorded variable obtained by scoring the corresponding categories. All analyses were performed using the Statistical Analysis System Software (version 9.2; SAS Institute, Cary, NC, USA). Statistical significance was set at the 0.05 level. All P-values were two-sided.

4.3 Results

The distribution of the exclusion criteria is shown in Fig.2.1. After applying the aforementioned criteria, 76,017 patients were included into the study cohort and accumulated 502,818 person-years of follow-up (on average about 6,6 years per patient).

Study 1

The cohort generated 622 cases of patients hospitalized for heart failure. As shown in table 2.1, mean age was 67, ACE-i + ARBs were by far the most common initial treatment for both case patients and controls ant there was no significant difference in PDC between the two groups. During the observation period, the two groups accumulated an average of 670 and 698 days with antihypertensive drug available (cases and controls respectively).

Compared with controls, case patients had a statistically significant worse profile of comorbidities, there were no statistically significant differences in the use of statins and antidepressants but a higher proportion of cases used antidiabetic drugs. Case patients also experienced a more frequent switch of treatment between classes of antihypertensive drugs than controls.

Study 1A, as shown in table 2.2, showed that the group with highest adherence (PDC >75%) was the one who had the lowest, and statistically significant, risk to experiment the outcome (OR 0.702, 95% CI 0.560-0.879) compared to the reference group (PDC < 25%). Low and intermediate adherence group showed a non-significant reduction in the probability of the outcome (OR 0.877 95% CI 0.666-1.155, OR 0.770 95% CI 0.581-1.021).

We then analyzed the risk reduction determined by the antihypertensive class prescribed at study entry (index antihypertensive): all the classes analyzed determined a statistically significant and similar reduction in the risk of experiencing the outcome compared to diuretics, ACE+ARB had an of OR 0.635 (95% CI 0.471-0.856), β-blockers of 0.623(95% CI 0.438-0.887) and CCB of 0.649 (95% CI 0.465-0.907) (Table 2.3).

In all analysis, a Charlson index >1, diabetes, switch of antihypertensive therapy and the use of cardiac drugs (ATC C01) during follow up, were significantly correlated to an increased risk, while statins always determined a risk reduction. We then, tried to understand if there was an interaction between adherence level and index antihypertensive on the outcome risk. To answer this question we compared high adherence groups index on ACE-i+ARBS and index on ‘other’ classes (β-blockers, CCB and Diuretics) to patients index on the ‘other’ group and with a PDC < 75%. The

analysis show that only patients who started their therapy on ACE-i+ARBs and had an adherence >75% had a significant risk reduction versus reference group.

In the second study, Study 1B (Table 2.5), we wanted to investigate if, in individuals matched for their adherence, there was any difference based on whether patients had a high (>80%) exposure to a certain antihypertensive class respect to another.

When we considered patients with a PDCA >80% for a specific class versus patients with a PDCA <80% in all classes, we always found a statistically non significant reduction of risk: ACE+ARB had an OR of 0.778 (95% CI 0.558-1.084), β-blockers of 0.969 (95% CI 0.567- 1.657), CCB of 0.843 (95% CI 0.552-1.288) and diuretics of 0.770 (95% CI 0.536-1.106), the differences among classes resulted not significant.

The outcome didn't change when all the classes were analyzed together despite ACE+ARBs (Table 2.6).

Patients who had an exposure to ACE or ARBs >80% of their days of treatment, had a non-significant risk reduction versus patients with a PDCA < 80% (OR 0.755 95% CI 0.554-1.029) as well patients in all other antihypertensive classes (OR 0.855 95% CI 0.643-1.137); differences were not significant in this case also.

Study 2

The cohort generated 878 cases of patients who were hospitalized for heart failure or who were prescribed digitalis glycosides for the first time. These cases were matched to 4,390 controls.

As in study 1, mean age was 67, ACE inhibitors + ARBs were by far the most common initial treatment for both case patients and controls and there was not significant different difference in PDC between the two groups. During follow-up, the two groups accumulated an average of 617 and 659 days with antihypertensive drug available (cases and controls respectively).

Compared with controls, case patients had a statistically significant worse profile of comorbidities, there were no statistically significant differences in the use of statins and antidepressants but a higher proportion of cases used antidiabetic drugs. Case patients also experienced a more frequent switch of treatment within and between classes of antihypertensive drugs than controls and had a significant higher use of cardiac drugs (ATC C01) during follow up (Table 2.7).

Study 2A. As shown in table 2.8, the two groups with higher adherence (50<PDC<75% and 75<PDC<100%) had a statistically significant reduction in the risk of experimenting the outcome (OR 0.719, 95% CI 0.569-0.910 and OR 0.668, 95% CI 0.549-0.812 intermediate and high adherence respectively) compared to the reference group, while low adherence group showed a non-

significant reduction in the probability of the outcome (OR 0.989 95% CI 0.666-1.155, OR 0.786 95% CI 0.581-1.244).

Concerning index antihypertensive drug, all the classes analyzed determined a significant and similar reduction in the risk of experiencing the outcome compared to diuretics, ACE+ARB had a OR 0.630 (95% CI 0.486-0.816), β-blockers of 0.588 (95% CI 0.436-0.792) and CCB of 0.671 (95% CI 0.503-0.894) (Table 2.9).

In all analysis, a Charlson index ≥ 1, diabetes, switch of antihypertensive therapy and the use of cardiac drugs (ATC C01) during follow up, were significantly correlated to an increased risk, while statins always determined a significant risk reduction.

We, then, tried to understand if there was an interaction between adherence level and index antihypertensive on the outcome risk. The analysis show that only patients who started their therapy on ACE+ARBs and had an adherence >75 had a significant risk reduction versus reference group.

The second study, Study 2B, showed again that, in patients matched for the same level of adherence, there was not difference, in terms of risk reduction, among drug classes when patients had a PDCA > 80% (β-blockers, Calcium channel blockers and Diuretics showed a not significant reduction OR 0.964 95% CI 0.642-1.449, OR 0.803 95% CI 0.548- 1.175 and OR 0.865 (95% CI 0.637-1.176 respectively). There was only one exception, the ACE+ARBs Class (OR 95% 0.736 CI 0.552-0.981), but differences among classes were not significant (Table 2.11).

The outcome didn't change when all the classes were analyzed together despite ACE+ARBs (Table 2.12).

Patients who had an exposure to ACE or ARBs >80% of their days of treatment had a significant risk reduction versus patients with a PDCA < 80% (OR 0.749 95% CI 0.574-0.978) while patients in all other antihypertensive classes had a not significant risk reduction, (OR 0.926 95% CI 0.731-1.173).

4.4 Discussion

To our knowledge, this is one of the first studies to show, in a real world setting, that patients with an adherence of at least 50% present a decrease in the risk of experiencing HHF or CHF amongst newly treated hypertensive patients for primary prevention of cardiovascular disease compared with lower adherence levels.

This study represents a confirmation about the importance of adherence to benefit of an actual prevention from cardiovascular outcomes.

It is also interesting to note that all patients with an adherence bigger than 75%, had a significant risk reduction, no matter which antihypertensive class they started with or used during follow up, and this result remained significant also when the data were adjusted by comorbidity score.

It is interesting to consider this result with the result of study 1B and 2B: when we matched patients for their adherence, our results showed that, overall, there was not a significant difference, among analyzed drug classes, on the probability of experiencing the outcome.

This fact could, again, underline the crucial role of adherence to this type of drugs, and adherence appears even more important than the drug class itself.

Another evidence that emerged from our results is that adherence level sufficient to have a significant risk reduction in the composite outcome HHF and digitalis prescription (PDC > 50%) is lower than the one needed to prevent HHF alone (PDC > 75%). This fact needs to be further investigated, but it is reasonable if we consider a digitalis prescription a less severe outcome respect to hospitalization.

The risk reduction observed in our study is similar to those reported in meta-analysis of prospectively designed overviews of randomized trials [15,25] although different methodologies were applied and different patients enrolled.

These studies carry both some strengths and some limitations.

Considering strengths: first, the investigation was based on data from a very large unselected population, which was made possible because of a cost-free health-care system for virtually all Italian citizens. Second, the drug prescription database provides highly accurate data because report of prescriptions by the pharmacies is essential for reimbursement, and filing of an incorrect report about dispensed drugs has legal consequences. Third, patients were identified from the point of the initial antihypertensive therapy, and the complete sequence of the subsequent prescriptions was available. Fourth, we were able to include patients without previous clinical evidence (drug treatment and/or hospitalization) of hypertension or CV disease so that the data should refer to the effect of antihypertensive use on new-onset of hypertension.

Among limitations: first, evaluation of treatment adherence was based on pharmacy-dispensing information.

With this method the assumption has to be made that the proportion of days covered by a prescription corresponds to the proportion of days of drug assumption, which may not be invariably the case.

Secondly, because of privacy regulations, hospital records were not available for analysis which means that diagnoses cannot be validated. However, in a previous study, we have documented that CV events diagnosed from hospital discharge data closely correspond to those of a local registry of coronary and cerebrovascular events validated according to MONICA criteria [26].

Third, this was not a randomized study, so index antihypertensive prescription could be affected by residual confounding. That is, the selection of antihypertensive drug with which starting therapy might be driven by differences of patients' characteristics, such as severity of hypertension, comorbidities, other CV risk factors, and perhaps income and educational levels.

In order to limit this type of residual confounding in studies 1B and 2B cases and controls were matched both by PDC and index antihypertensive and in all analysis data were adjusted for a number of demographic, therapeutic and clinical characteristics (such as Charlson index). It is however important to emphasize that health-care databases such as ours have a limited amount of clinical data and consequently the adjustment for measured characteristics does not entirely remove the possibility of residual confounding.

In summary, this population-based study of drug utilization patterns in a real world setting showed an association with a significant benefit linked with a good adherence to antihypertensive medication and HF in the context of primary prevention. A better adherence to pharmacological therapy is a key factor in determining the success of various therapeutic approaches. Consequently, greater attention should be paid to this aspect, which may result in improved patient outcomes. The assessment of medication adherence should be incorporated into routine clinical practice. Interventions in this area are essential so that the therapeutic benefits translate into the clinical practice.

4.5 References

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4.6 Appendix two

Figure 2.1. Flow chart of inclusion and exclusion criteria. Exclusion criteria were applied in the5 years preceding the cohort entry date.

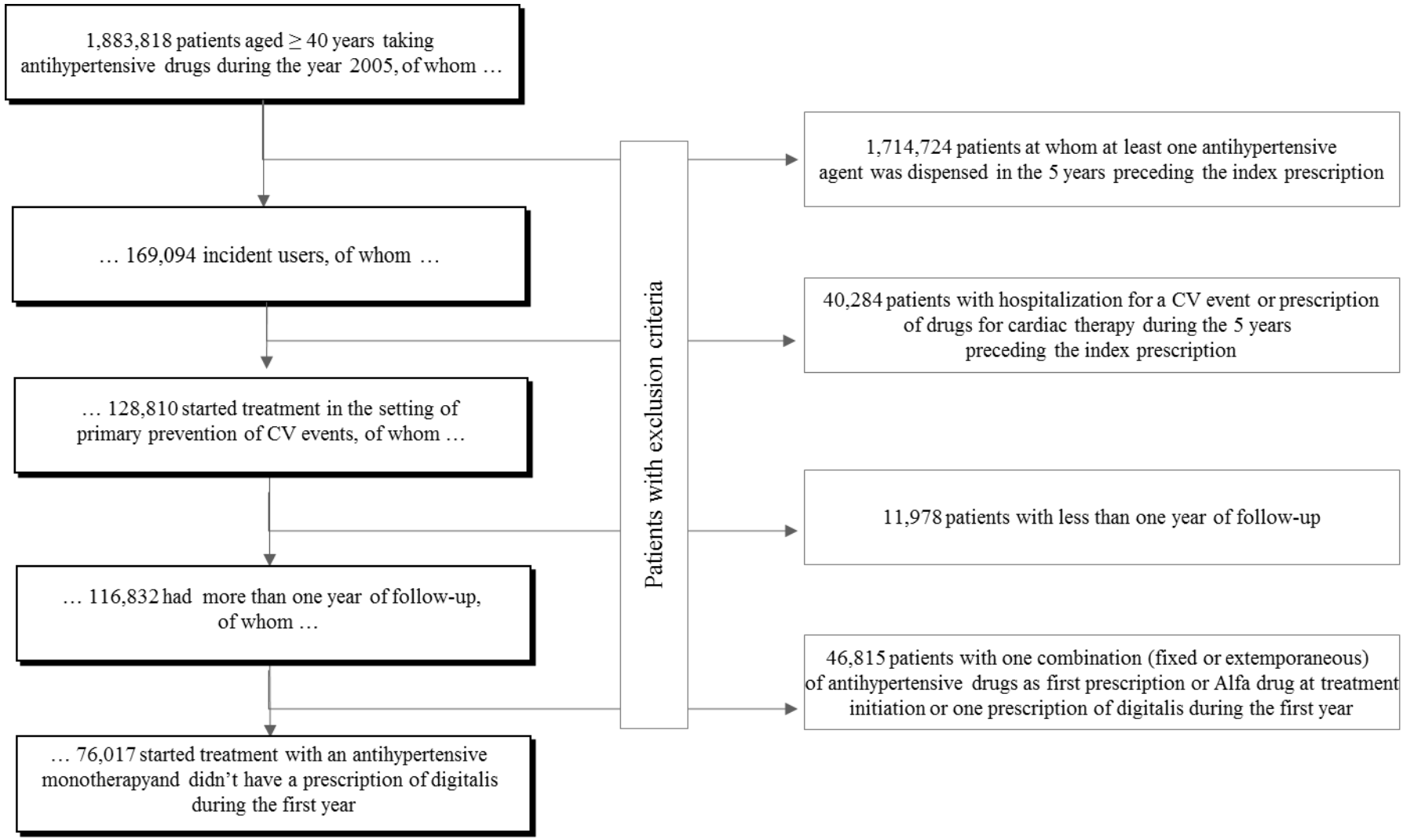

Table 2.1. Characteristics of the 622 case patients hospitalized for heart failure and of the corresponding 3,110 controls included into Study 1.

	Case patients	Controls	p-value †
Men	334 (54%)	1,670 (54%)	NP
Age at cohort entry: mean (SD)	67 (10.0)	67 (10.0)	NP
Antihypertensive drug at treatment initiation			
Diuretics	76 (12%)	237 (8%)	0.002
ACEIs + ARBs	339 (55%)	1,816 (58%)	
β-blockers	88 (14%)	469 (15%)	
CCBs	119 (19%)	588 (19%)	
Antihypertensive drug during follow-up			
Days with antihypertensive drug available: mean (SD)	670 (687)	698 (691)	0.557
Proportion of Days Covered			
0 – 25%	270 (43%)	1,283 (41%)	0.092
25 –50%	93 (15%)	405 (13%)	
50 – 75%	82 (13%)	432 (14%)	
75 – 100%	177 (29%)	990 (32%)	
Changed antihypertensive drug therapy			
Switching between classes	348 (56%)	1,423 (46%)	<0.001
Concomitant users of other drugs			
Baseline			
Lipid lowering agents	102 (16%)	608 (20%)	0.068
Antidiabetic agents	109 (18%)	337 (11%)	<0.001
Antidepressant agents	81 (13%)	456 (15%)	0.287
Follow-up			
Cardiovascular agents (C01)	55 (9%)	117 (4%)	<0.001
Charlson comorbidity index score			
0	526 (85%)	2,810 (90%)	<0.001
1	40 (6%)	130 (4%)	

≥2	56 (9%)	170 (6%)

ACEI: Angiotensin-converting enzyme inhibitor ; CCBs: Calcium channel blockers ; ARBs : Angiotensin receptor blockers

NP: no pertinent because the corresponding variable was used for case-control matching

† According to chi-square test (type of antihypertensive drug employed at entry, concomitant users of other drugs, between class switching), its version for the trend (categories of the Charlson comorbidity index score, categories of the proportion of days covered with antihypertensive drugs) or non-parametric test of Mann-Whitney (time of follow-up spent with antihypertensive available)

Table 2.2. Effect of different level of adherence to antihypertensive treatment on the risk of heart failure hospitalization. Study 1 A.

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
PDC 0-25	1	(reference)	
PDC 25-50	0.877	0.666	1.155
PDC 50-75	0.770	0.581	1.021
PDC 75-100	0.702	0.560	0.879
Charlson=1	1.464	1.003	2.137
Charlson>1	1.558	1.129	2.150
Statins	0.720	0.566	0.915
Diabetes	1.722	1.339	2.215
Depression	0.841	0.648	1.092
Switch	1.621	1.336	1.967
CV drugs (C01)	2.259	1.602	3.186

Trend's test	**P-value**
PDC	0.0015

Table 2.3. Effect of different classes of index antihypertensive on the risk of heart failure hospitalization. Study 1A.

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
Diuretics	1	(reference)	
ACE+ARB	0.635	0.471	0.856
B-Blockers	0.623	0.438	0.887
CCB	0.649	0.465	0.907
Charlson=1	1.426	0.976	2.084
Charlson>1	1.485	1.072	2.056
Statins	0.732	0.576	0.932
Diabetes	1.754	1.361	2.259
Depression	0.826	0.636	1.074
PDC 25-50	0.900	0.681	1.188
PDC 50-75	0.804	0.604	1.069
PDC 75-100	0.740	0.586	0.934
Switch	1.607	1.323	1.952
CV drugs (C01)	2.271	1.607	3.209

Table 2.4. Interaction between index antihypertensive and different level of treatment adherence on the risk of heart failure hospitalization. CCB, B-Blockers and diuretics are grouped together and defined as 'others'. Study 1-A.

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
Others PDC 00-75	1	(reference)	
ACE+ARB PDC 00-75	0.976	0.789	1.207
ACE+ARB PDC 75-100	0.673	0.520	0.870
OTHER PDC 75-100	0.992	0.719	1.370
Charlson=1	1.474	1.010	2.151
Charlson>1	1.556	1.128	2.147
Statins	0.728	0.572	0.925
Diabetes	1.751	1.360	2.253
Depression	0.843	0.650	1.095
Switch	1.536	1.275	1.851
CV drugs (C01)	2.230	1.581	3.144

Linear Hypotheses Testing Results			
Test	**Wald Chi-Square**	**DF**	**Pr > ChiSq**
PDC 75-100$_{ACE+ARB}$ = PDC 75-100$_{altro}$	4.9124	1	0.0267

Table 2.5. Effect of high exposure to each type of drug class. The proportions of days covered by a certain antihypertensive (PDCA) is the proportion of days with a certain antihypertensive divided by the number of days covered by antihypertensive treatment. Each drug class with PDCA > 80% is compared to all classes with PDCA < 80% taken together. Study 1B.

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
All PDCA 00-80	1	Reference	
ACE+ARB PDCA 80-100	0.778	0.558	1.084
B-Blockers PDCA 80-100	0.969	0.567	1.657
CCB PDCA 80-100	0.843	0.552	1.288
Diur PDCA 80-100	0.770	0.536	1.106
Age 50-70	2.662	1.867	3.794
Age >70	13.216	9.116	19.160
Males	1.564	1.277	1.915
Charlson=1	1.400	0.895	2.190
Charlson>1	2.233	1.502	3.320
Statins	0.920	0.702	1.206
Diabetes	2.203	1.641	2.959
Depression	0.829	0.616	1.117
Switch	1.680	1.322	2.134
CV drugs (C01)	2.186	1.429	3.343

Linear Hypotheses Testing Results			
Test	**Wald Chi-Square**	**DF**	**Pr > ChiSq**
$PDCA_{ACE+ARB}=PDCA_{Beta}=PDCA_{CCB}=PDCA_{Diur}$	0.7850	3	0.8530

Table 2.6. Effect of high exposure to each type of drug class. The proportions of days covered by a certain antihypertensive (PDCA) is the proportion of days with a certain antihypertensive divided by the number of days covered by antihypertensive treatment. Beta blockers, CCB and diuretics are grouped together (named as 'others') despite ACE+ARBs. Study 1-B.

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
All PDCA 00-80	1	Reference	
ACE+ARB PDCA 80-100	0.755	0.554	1.029
Others PDCA 80-100	0.855	0.643	1.137
Age 50-70	2.662	1.868	3.793
Age >70	13.197	9.104	19.129
Male	1.557	1.272	1.905
Charlson=1	1.387	0.887	2.167
Charlson>1	2.231	1.501	3.315
Statins	0.920	0.703	1.205
Diabetes	2.213	1.649	2.971
Depression	0.831	0.617	1.119
Switch	1.648	1.308	2.077
CV drugs (C01)	2.181	1.427	3.333

Linear Hypotheses Testing Results			
Test	**Wald Chi-Square**	**DF**	**Pr > ChiSq**
$PDCA_{ACE+ARB} = PDCA_{altro}$	0.4363	1	0.5089

Table 2.7. Characteristics of the 878 case patients hospitalized for heart failure or patients with a prescription of digitalis and of the corresponding 4,390 controls included into Study 2.

	Case patients	Controls	p-value †
Men	448 (51%)	2,240 (51%)	NP
Age at cohort entry: mean (SD)	67 (10.0)	67 (10.0)	NP
Antihypertensive drug at treatment initiation			
Diuretics	106 (12%)	311 (7%)	<0.001
ACEIs + ARBs	464 (53%)	2,512 (57%)	
β-blockers	134 (15%)	724 (17%)	
CCBs	174 (20%)	843 (19%)	
Antihypertensive drug during follow-up			
Days with antihypertensive drug available: mean (SD)	617 (639)	659 (649)	0.274
Proportion of Days Covered			
0 – 25%	380 (43%)	1,784 (41%)	0.007
25 –50%	136 (16%)	541 (12%)	
50 – 75%	124 (14%)	678 (15%)	
75 – 100%	238 (27%)	1,387 (32%)	
Changed antihypertensive drug therapy			
Switching between classes	479 (55%)	1,961 (45%)	<0.001
Concomitant users of other drugs			
Baseline			
Lipid lowering agents	142 (16%)	825 (19%)	0.067
Antidiabetic agents	134 (15%)	456 (10%)	<0.001
Antidepressant agents	119 (14%)	585 (13%)	0.856
Follow-up			
Cardiovascular agents (C01)	83 (9%)	141 (3%)	<0.001
Charlson comorbidity index score			
0	750 (85%)	4,011 (91%)	<0.001
1	52 (6%)	169 (4%)	

≥2		76 (9%)	210 (5%)

ACEI: Angiotensin-converting enzyme inhibitor ; CCBs: Calcium channel blockers ; ARBs : Angiotensin receptor blockers

NP: no pertinent because the corresponding variable was used for case-control matching

† According to chi-square test (type of antihypertensive drug employed at entry, concomitant users of other drugs, between class switching), its version for the trend (categories of the Charlson comorbidity index score, categories of the proportion of days covered with antihypertensive drugs) or non-parametric test of Mann-Whitney (time of follow-up spent with antihypertensive available)

Table 2.8. Effect of different level of adherence to antihypertensive treatment on the risk of heart failure hospitalization. Study 2-A.

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
PDC 0-25	1	(reference)	(reference)
PDC 25-50	0.989	0.786	1.244
PDC 50-75	0.719	0.569	0.910
PDC 75-100	0.668	0.549	0.812
Charlson=1	1.510	1.078	2.114
Charlson>1	1.861	1.404	2.466
Statins	0.783	0.639	0.960
Diabetes	1.456	1.172	1.810
Depression	0.938	0.752	1.169
Switch	1.609	1.364	1.897
CV drugs (C01)	2.797	2.094	3.736

Test del trend	**P-value**
PDC	<0.0001

Table 2.9. Effect of different classes of index antihypertensive on the risk of heart failure hospitalization. Study 2-A.

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
Diuretics	1	(reference)	
ACE+ARB	0.630	0.486	0.816
Beta blockers	0.588	0.436	0.792
CCB	0.671	0.503	0.894
Charlson=1	1.453	1.037	2.036
Charlson>1	1.761	1.326	2.340
Statins	0.795	0.648	0.976
Diabetes	1.464	1.177	1.821
Depression	0.939	0.753	1.171
PDC 25-50	1.019	0.808	1.285
PDC 50-75	0.751	0.592	0.952
PDC 75-100	0.706	0.577	0.864
Switch	1.582	1.341	1.867
CV drugs (C01)	2.844	2.124	3.807

Table 2.10. Interaction between index antihypertensive and different level of treatment adherence on the risk of heart failure hospitalization. CCB, B-Blockers and diuretics are grouped together and defined as 'others'. Study 2-A.

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
Others PDC 00-75	1	(reference)	
ACE+ARB PDC 00-75	0.944	0.792	1.125
ACE+ARB PDC 75-100	0.653	0.526	0.812
OTHER PDC 75-100	0.857	0.650	1.129
Charlson=1	1.518	1.085	2.123
Charlson>1	1.859	1.402	2.463
Statins	0.790	0.644	0.968
Diabetes	1.503	1.208	1.869
Depression	0.945	0.758	1.178
Switch	1.515	1.295	1.771
CV drugs (C01)	2.781	2.081	3.718

Linear Hypotheses Testing Results			
Test	**Wald Chi-Square**	**DF**	**Pr > ChiSq**
PDC 75-100$_{ACE+ARB}$ = PDC 75-100$_{altro}$	3.2023	1	0.0735

Table 2.11. Effect of high exposure to each type of drug class. The proportions of days covered by a certain antihypertensive (PDCA) is the proportion of days with a certain antihypertensive divided by the number of days covered by antihypertensive treatment. Each drug class with PDCA > 80% is compared to all classes with PDCA < 80% taken together. Study 2-B.

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
All PDCA 00-80	1	Reference	
ACE+ARB PDCA 80-100	0.736	0.552	0.981
B-Blockers PDCA 80-100	0.964	0.642	1.449
CCB PDCA 80-100	0.803	0.548	1.175
Diur PDCA 80-100	0.865	0.637	1.176
Age 50-70	2.642	1.977	3.529
Age >70	12.075	8.908	16.368
Males	1.414	1.198	1.669
Charlson=1	1.534	1.044	2.255
Charlson>1	1.733	1.255	2.394
Statins	1.026	0.820	1.284
Diabetes	1.794	1.388	2.318
Depression	0.865	0.678	1.103
Switch	1.607	1.316	1.962
CV drugs (C01)	3.509	2.436	5.054

Linear Hypotheses Testing Results			
Test	**Wald Chi-Square**	**DF**	**Pr > ChiSq**
$PDCA_{ACE+ARB}=PDCA_{Beta}=PDCA_{CCB}=PDCA_{Diur}$	1.7062	3	0.6356

Table 2.12. Effect of high exposure to each type of drug class. The proportions of days covered by a certain antihypertensive (PDCA) is the proportion of days with a certain antihypertensive divided by the number of days covered by antihypertensive treatment. Beta blockers, CCB and diuretics are grouped together (named as 'others') despite ACE+ARBs. Study 2-B.

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
Others PDCA 00-80	1	(reference)	
ACE+ARB PDCA 80-100	0.749	0.574	0.978
Others PDCA 80-100	0.926	0.731	1.173
Age 50-70	2.636	1.973	3.522
Age >70	12.017	8.869	16.281
Males	1.410	1.195	1.663
Charlson=1	1.528	1.039	2.245
Charlson>1	1.740	1.261	2.402
Statins	1.028	0.822	1.286
Diabetes	1.797	1.391	2.321
Depression	0.866	0.679	1.104
Switch	1.611	1.330	1.951
CV drugs (C01)	3.518	2.442	5.070

Linear Hypotheses Testing Results			
Test	**Wald Chi-Square**	**DF**	**Pr > ChiSq**
$PDCA_{ACE+ARB} = PDCA_{altro}$	1.8296	1	0.1762

5. Consequences of new heart failure hospitalizations – Outcomes, prognostic factors and economic burden

5.1 Hospitalized heart failure outcomes and prognostic factors

5.1.1 Introduction

Several studies have been performed investigating heart failure outcomes' and prognostic factors.

Due to the differences among enrolled populations (e.g. inpatients vs outpatients, new patients vs already diagnosed patients) and data sources used to investigate specific outcomes (e.g. Hospital-based registries vs administrative database), it is difficult to understand a clear trend of heart failure outcomes.

The majority of the studies consistently showed a decrease in terms of hospitalization during the last decades but confirmed the high risk of mortality and of re-hospitalization. Levy at al. analyzed the survival after heart failure onset in subjects enrolled in the Framingham Heart Study: the 30-day, 1-year, and 5-year age-adjusted mortality rates among men declined from 12, 30 and 70 % respectively, in the period from 1950 through 1969, to 11, 28 and 59 % respectively, in the period from 1990 through 1999. The corresponding rates among women were 18, 28 and 57% from 1950 through 1969 and 10, 24 and 45% for the period from 1990 through 1999. Overall, there was an improvement of 12% per decade (P=0.01 for men and P=0.02 for women) in the survival rate after heart failure onset but the mortality rate still remained considerably high [1].

Roger et al. carried out a population-based cohort study using the data from the Rochester Epidemiology Project conducted in Olmsted County, Minnesota. 4,537 Olmsted County residents with a diagnosis of heart failure (clinically validated) between 1979 and 2000 were enrolled and followed up for a mean length of 4,2 years. The incidence of heart failure did not decline during last two decades, and the survival after heart failure diagnosis was worse among men than women (relative risk, 1.33; 95% CI, 1.24-1.43) but overall improved over time (5-year age-adjusted survival, 43% in 1979-1984 vs 52% in 1996-2000, P<.001). However, men and

younger persons experienced larger survival gains, contrasting with less or no improvement for women and elderly persons [2].

The Atherosclerosis Risk in Communities cohort, a population-based study from four United States communities (from 1987 to 2002) showed a thirty-day, 1-year, and 5-year case fatalities following hospitalization for HF of 10.4%, 22%, and 42.3%, respectively [3].

In Ontario, Canada, a population-based administrative database of hospital discharge abstracts and physician health insurance claims was used to identify 419,551 incident cases of heart failure between 1997 and 2008. One-year risk-adjusted mortality decreased from 17.7% in 1997 to 16.2% in 2007 ($p = 0.02$) for outpatients, with a non-significant decrease from 35.7% in 1997 to 33.8% in 2007 ($p = 0.1$) for inpatients over the study period [4].

A Scottish administrative database highlighted that adjusted 30-day case-fatality rates, after discharge for heart failure, fell between 1986 and 2003, (adjusted OR 2003 versus 1986, 0.59 , 95% CI 0.45-0.63 in men and 0.77, 95% CI 0.67- 0.88, in women). The adjusted 1- and 5-year survival improved similarly: median survival increased from 1.33 to 2.34 years in men and from 1.32 to 1.79 years in women. In their conclusions the authors also noted that the age-adjusted prescribing rates for angiotensin-converting enzyme inhibitors, beta-blockers, and spironolactone increased from 1997 to 2003 (all $P<0.0001$ for trend) [5].

In France, Tuppin et al. through the national health insurance information system, evaluated a population of 69,958 individuals hospitalized in 2009 with a principal diagnosis of HF. The hospital mortality rate was 6.4%, with 1-month, 1-year and 2-year survival rates of 89%, 71% and 60%, respectively [6].

In Italy the GISSI group (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico) designed a multicenter, prospective, observational trial that followed a population of 5,610 HF patients for one year. Among these patients 1,855 were hospitalized for HF and 3,755 were outpatients with chronic HF (CHF). The cumulative total mortality rate at 1 year was 24% in hospitalized patients (19.2% in 797 patients newly diagnosed for HF and 27.7% in 1,058 patients who already had a hospitalization) and 5.9% in CHF. One-year hospitalization rates were 30.7% in hospitalized patients and 22.7% in CHF patients. Of all the re-hospitalizations occurred during the 1-year follow-up 23.8% were for cardiovascular reasons of which the two thirds for heart failure [7].

Similar results emerged from the ESC-HF Pilot study, a prospective, multi-center, observational survey conducted in 136 Cardiology Centers in 12 European countries. 5,118 patients were included of which 1,892 (37%) admitted for acute HF and 3,226 (63%) patients with chronic HF.

The all-cause mortality rate at 1 year was 17.4% in acute HF and 7.2% in chronic stable HF. One-year hospitalization rates were 43.9% and 31.9%, respectively, in hospitalized and chronic HF patients [8].

Even data on short-term re-hospitalization are not reassuring: in the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan) trial, 24% of patients hospitalized for HF were readmitted within 30 days of discharge despite the fact that the majority were treated with evidence-based treatments and had early post-discharge visits [9].

In a study that used Medicare administrative data to identify all fee-for-service beneficiaries admitted to a US acute care hospital for HF from 2004 to 2006 and discharged alive emerged that, among these 1,616,780 patients, 384,397 (23.8%) were readmitted to a hospital for any reason within 30 days of discharge [10].

As mentioned above the burden of HHF incidence and outcome remains still high and, although many strategies could be used to improve the quality of care, there is little knowledge on predictors of mortality and hospital readmission in the real world population, since information on this topic are mainly based on critical trial and observational studies generally conducted by cardiologists.

Numerous studies have been performed in order to identify factors associated with readmission of HF patients in order to identify patients at risk of frequent hospitalizations.

Our literature review (reported in the table below), highlighted that although a lot of predictors have been identified, not all factors have been consistently found to be predictors among different studies. Identifying outcome predictors among HF patients would help physicians to improve risk stratification and to determine the optimal post-discharge plan for preventing readmission.

Zaya et al. in their review suggested a categorization of such predictors into (1) clinical parameters; (2) serum biomarkers; (3) hemodynamic parameters; and (4) psycho-social factors [11].

Among clinical parameters are mentioned: angina [12], lower systolic blood pressure [12-18] , edema [7, 19, 20], pulmonary rales, high jugular venous pressure [12], old age [7, 12-16, 20-22], prior pacemaker implantation [12,17], atrial fibrillation [20], prolonged QT interval, elevated heart rate [23], comorbidities such as COPD [7, 13, 16, 17, 22, 29], diabetes, [13, 19-22] and depressive symptoms [12, 17], peripheral vascular disease [21,22], stroke [16,17, 21, 22], coronary heart disease [12,17], hospital length of stay [21,25,26] and previous HF hospitalization [13,15,20,21,24,27].

Among the serum biomarkers are reported: worsening renal function (expressed as lower Glomerular Filtration Ratio, GFR, or as low cystatin C) [13,22,28,30], increase in blood urea nitrogen (BUN) [15,16,18], hyponatremia [7, 14-17, 31, 32], anemia [7,12,16,17,33], B-Type Natriuretic Peptide (BNP) [34-36], cardiac troponin T [1,2,37] and uric acid (as marker of gout disease) [13].

Among the hemodynamic predictors, LVEF has been an inconsistent predictor of readmission, with some studies suggesting patients with lower LVEF were more likely to be readmitted, while others showed no difference [38-41]. Newer parameters under evaluation are: abnormal inferior vena cava diameter (> 2.0 cm), collapsibility indices measured through manual ultrasound [36] and implantable hemodynamic devices to detect intracardiac pressures, but have not entered in the general clinical practice yet [42].

Among psycho-social factors, depression has shown to increase the probability of re-hospitalization [12, 17, 43], a strong social network has been shown to reduce readmission rates in cardiac patients [44], single marital status has also been shown to be an independent correlate of readmission [45], no occupation has been independently associated to higher risk of re-hosiptalization [25], and low income was an independent predictor. Several studies have shown that there are differences in HF outcome depending on ethnic groups: [29], African Americans have a 50% higher incidence of HF compared with the general population and also have higher risk of initial and repeated hospitalization [46]. Poor follow-up was also found to be a strong predictor of HF readmission, with studies showing patients with less follow-up had a 5-fold increase in the risk of HF readmission [25].

Besides all these clinical parameters, pharmacological treatments have shown to be crucial in terms of outcome prevention [47] and, especially, low treatment adherence has been shown to be an outcome' predictors [48].

Table 1. Non-systematic literature review. Principal clinical prognostic factors of heart failure re-hospitalizations and mortality.

Title	Type of study	Patients characteristic	Wards/ Type of hospital	Country	Predictors associated to re-hospitalizations or mortality	Follow up
Aranda JM, Johnson JW, Conti JB. **Current trends in heart failure readmission rates: analysis of Medicare data.** *Clin Cardiol* 2009; 32: 47-52 [21]	Retrospective-Claims database study	28,919 pts hospitalized in 2003 with a principal discharge diagnosis code of 428 (HF) or 398.91	Medicare claims database	US	Factors associated with readmission for HF after the initial HF hospitalization included: age <65, geographic location, previous hospitalization, length of stay of initial HF hospitalization >7 days, not receiving a cardiac device implant at the time of initial HF hospitalization and history of comorbidities including diabetes, myocardial infarction, peripheral vascular disease, and stroke.	6-9 months
Barlera S, Tavazzi L, Franzosi MG, Marchioli R, Raimondi E, Masson S, Urso R, Lucci D, Nicolosi GL, Maggioni AP, Tognoni G; GISSI-HF Investigators. **Predictors of mortality in 6975 patients with chronic heart failure in the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure trial: proposal for a nomogram**. Circ Heart Fail. 2013;6:31-9. [13]	RCT	6,795 HF outatients, age >18, clinical evidence of heart failure of any cause	Cardiology and Internal medicine	Italy	Mortality was associated to: age, eGFR<60, SBP (per 1-mm Hg decrease <140 mm Hg), COPD, NYHA class III-IV, EF < 40%, Diabetes mellitus, male sex, aortic stenosis, ischemic etiology, peripheral edema, and >1 previous hospitalization for HF, Uricemia (per 1-mg/dL increase >6.9), haemoglobin decrease, BMI decrease	Median follow up 3,9 years
Belziti CA, Bagnati R, Ledesma P, Vulcano N, Fernández S**. Worsening renal function in patients admitted with acute decompensated heart failure: incidence, risk factors and prognostic implications.** Rev Esp Cardiol. 2010 Mar;63:294-302.[28]	Retrospective, Observational cohort study	200 pts, Clinical diagnosis of Heart Failure classified as ESC guidelines	Coronary Unit	Argentina	WRF was found to be independently associated to one-year mortality and readmission combined endpoint (adjusted HR = 1.65; 95% CI 1.12-2.67)	Median follow up 416 days

Cleland JG, Chiswell K, Teerlink JR, Stevens S, Fiuzat M, Givertz MM Davison BA, Mansoor GA, Ponikowski P, Voors AA, Cotter G, Metra M, Massie BM, O'Connor CM. **Predictors of postdischarge outcomes from information acquired shortly after admission for acute heart failure: a report from the Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT)Study.** Circ Heart Fail. 2014;7:76-87. [14]	Randomized-Placebo controlled	2,033 pts Hospitalized for Acute Decompensated Heart Failure	NR	19 countries	Strongest predictors of 180 days mortality: BUN, age, SBP, serum albumin and sodium.	180 days
Eastwood CA, Howlett JG, King-Shier KM, McAlister FA, Ezekowitz JA, Quan H. **Determinants of early readmission after hospitalization for heart failure.** Can J Cardiol. 2014;30(6):612-8. [73]	Prospective cohort study based on hospital discharge abstract data	18,590 patients with a primary diagnosis of HF (ICD10 I50.x) between 2002 and 2012.	Hospital discharge abstract data	Alberta, Canada	7-day all-cause readmissions were associated with history of kidney disease (adjusted odds ratio [aOR]1.28; 95% CI, 1.08-1.53), and 30-day all-cause readmissions were associated with cancer (aOR 1.31; 95% CI 1.10-1.55), pulmonary (aOR 1.14 95% CI, 1.05-1.24), liver (aOR 1.41; 95% CI 1.07-1.85), and kidney disease (1.37; 95% CI 1.24-1.52). Discharge with home care services at the time of discharge was a risk factor for readmission within 7 days (aOR, 1.26; 95% CI, 1.07-1.49) and 30 days (aOR, 1.23; 95% CI, 1.11-1.35). Discharge from a hospital with HF services was associated with lower readmission at both 7 days (aOR, 0.65; 95% CI, 0.57-0.74) and 30 days (aOR, 0.71; 95% CI, 0.65-0.77).	7 and 30 days after HF discharge

Farasat SM, Bolger DT, Shetty V, Menachery EP, Gerstenblith G, Kasper EK, Najjar SS **Effect of Beta-blocker therapy on re-hospitalization rates in women versus men with heart failure and preserved ejection fraction.** Am J Cardiol. 2010;105:229-34. [47]	Prospective cohort design	66 consecutive pts with a clinical diagnosis of HF-pEF	2 academic urban hospitals	Maryland USA	In men, HF re-hospitalizations occurred less frequently in the B-Blockers users (3 of 15 subjects, 20% p=0.29), a similar pattern was observed for all-cause re-hospitalization (33% vs 67%, respectively, p=0.33). In women, HF re-hospitalizations occurred more frequently in the B-Blockers users group (75% vs 18%, p 0.001), a similar pattern was present for all-cause re-hospitalization (86% vs 29%, p =0.001).	180 days
Felker GM, Leimberger JD, Califf RM, Cuffe MS, Massie BM, Adams KF Jr, Gheorghiade M, O'Connor CM. **Risk stratification after hospitalization for decompensated heart failure.** J Card Fail. 2004;10:460-6.[15]	RCT-Placebo Controled	949 pts hospitalized for decompensated.			Variables that predicted death at 60 days were: age, lower SBP, NYHA IV, elevated BUN, decreased sodium. Predictors of death or re-hospitalization within 60 days were: number of HF hospitalizations in the preceding 12 months, elevated BUN, low SBP, decreased Hb, and a history of percutaneous coronary intervention.	60 days
Harjola VP, Follath F, Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Hochadel M, Komajda M, Lopez-Sendon JL, Ponikowski P, Tavazzi L. **Characteristics, outcomes, and predictors of mortality at 3 months and 1 year in patients hospitalized for acute heart failure. Eur J Heart Fail**. 2010;12:239-48. [19]	Prospective European survey	Pts with a clinical diagnosis of new-onset AHF as well as those with acutely decompensated CHF (ADCHF)	Emergency area, internal medicine and cardiology	30 European countries	Variables associated to death 3 months after index discharge were: dilated cardiomyopathy, cardiomegaly, pulmonary edema and bilateral pleural effusion on the chest X-ray, normal coronary angiogram, and days spent in the intensive care unit/cardiac care unit. Variables associated to death 1 year after index discharge were : history of HF, valvular disease, hypertension, decompensated HF and hypertensive HF, peripheral pitting edema, wider QRS on ECG, left bundle branch block, preserved LVEF, and right ventricular dysfunction on echocardiogram, diabetes, anaemia, and history of CHF.	1 year

Howie-Esquivel J, Dracup K. **Effect of gender, ethnicity, pulmonary disease, and symptom stability on re-hospitalization in patients with heart failure.** Am J Cardiol. 2007 O;100:1139-44. [29]	Prospective cohort design	72 consecutive pts admitted for ADHF	Academic center	California	Variables significantly associated with rehospitalization were: gender, ethnicity, pulmonary disease, symptom stability.	90 days
Jong P, Vowinckel E, Liu PP, Gong Y, Tu JV. **Prognosis and determinants of survival in patients newly hospitalized for heart failure: a population-based study.** Arch Intern Med. 2002;162:1689-94.[22]	Retrospective population-based cohort.	**38,702** consecutive patients hospitalized for the first time for heart failure.	Population based (national ADB)	Canada	Predicotrs 30ys and 1 year mortality **:**Age, malignancies (ORs, 2.32 and 2.89 [for 30-day and 1-year mortality, respectively]; P<.001 for both), renal disease (OR, 1.97 and 2.35; P<.001 for both), dementia (ORs, 1.77 and 1.85; P<.001 for both), cerebrovascular disease (ORs, 1.57 and 1.60; P<.001 for both), rheumatologic disease (ORs, 1.32 and 1.47; P = .04 and P<.001), peripheral vascular disease (ORs, 1.17 and 1.42; P = .03 and P<.001), and previous myocardial infarction (ORs, 1.16 and 1.12; P<.001 for both). Only 1 year predictors: COPD and diabetes mellitus with chronic complications (ORs, 1.13 and 1.52; P<.001 for both).	1 year

Krumholz HM, Parent EM, Tu N, Vaccarino V, Wang Y, Radford MJ, Hennen J. **Readmission after hospitalization for congestive heart failure among Medicare beneficiaries.** *Arch Intern Med* 1997; 157: 99-104 [26]	Observational study, using Medicare administrative Files.	17,448 Medicare beneficiaries who survived their first HF hospitalization (DRG 127) between 1990, 1994.	Population based	Canada	Significant predictors of readmission included male sex (odds ratio [OR], 1.12; 95% confidence interval [CI], 1.05\x=req-\ 1.20), at least 1 prior admission within 6 months of the index admission (OR, 1.64; 95% CI, 1.53-1.77), Deyo comorbidity score of more than 1 (OR, 1.56; 95% CI, 1.45\x=req-\ 1.68), and length of stay in the index hospitalization of more than 7 days (OR, 1.32; 95% CI, 1.24-1.41).	6 months
Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. **Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model.** JAMA. 2003;290:2581-7.[16]	Retrospective community-based study	2 cohorts for a total of 4,031 newly admitted pts with a primary diagnosis of HF.	Canadian Institutes of Health Information hospital discharge. Clinical data from Hospitals	Canada	Predictors of both 30-day and 1-year mortality: age, SBP, respiratory rate, hyponatremia, and urea nitrogen concentration. Although low-hemoglobin concentration was predictive of 1-year death, it was not associated with 30-day mortality. Comorbid conditions associated with mortality included cerebrovascular disease (30-day mortality OR, 1.43; 95% CI], 1.03-1.98), chronic obstructive pulmonary disease (OR, 1.66; 95% CI, 1.22-2.27), hepatic cirrhosis (OR, 3.22; 95% CI, 1.08-9.65), dementia (OR, 2.54; 95% CI, 1.77-3.65), and cancer (OR, 1.86; 95% CI, 1.28-2.70).	30 days/ 1 year

Muzzarelli S, Leibundgut G, Maeder MT, Rickli H, Handschin R, Gutmann M, Jeker U, Buser P, Pfisterer M, Brunner-La Rocca HP. **Predictors of early readmission or death in elderly patients with heart failure.** Am Heart J 2010; 160: 308-314 [12]	Prospective randomized single-blinded multicenter trial	614 pts of the TIME-CHF trial with clinical signs or symptoms of CHF a history of HF hospitalization within the last year.	NR	Swiss and Germany	Predictors of readmission or death at 30 days were angina, lower SBP, anemia, more extensive edema, higher creatinine levels, and dry cough. At 90 days were coronary artery disease, prior pacemaker implantation, high jugular venous pressure, pulmonary rales, prior abdominal surgery, older age, and depressive symptoms.	90 days
O'Connor CM, Abraham WT, Albert NM, Clare R, Gattis Stough W, Gheorghiade M, Greenberg BH, Yancy CW, Young JB, Fonarow GC. **Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF).** Am Heart J. 2008;156:662-7. [17]	Hospital-based registry	4.402 pts hospitalized for episodes of new or worsening HF	NR	91 hospitals ascross US	Postdischarge mortality increased 22% for every 10-year increase in age. Each 10-mm Hg decrease in baseline SBP < 140 mm Hg was associated with an 18% increase in postdischarge mortality. Admission SCr was associated with postdischarge mortality, with each 1 mg/dL increase in admission SCr associated with a 32% increase in risk, up to 4 mg/dL. Admission serum sodium: every 1 mEq/L decrease up to 140 mEq/L resulted in a 3% increase in the risk of mortality. Concomitant diseases were associated with a higher risk of post-discharge mortality, including reactive airway disease, depression, and liver disease. The risk-prediction nomogram for death or rehospitalization: Admission SCr was the most important predictor of death or rehospitalization. Other factors associated to post-discharge events were: SBP, COPD, HHF within the previous 6 months, nitrates at admission, mechanical ventilation during hospitalization, admission digoxin or diuretic use, a history of cerebrovascular accident or transient ischemic attack, and liver disease. A lower risk of death or rehospitalization was associated with increasing Hb; use of an ACE inhibitor, ARB, or lipid-lowering therapy at discharge; and coronary angiography or implantable	60 and 90 days

					cardioverter defibrillator placement during hospitalization.	
O'Connor CM, Mentz RJ, Cotter G, Metra M, Cleland JG, Davison BA, Givertz MM, Mansoor GA, Ponikowski P, Teerlink JR, Voors AA, Fiuzat M, Wojdyla D, Chiswell K,Massie BM**. The PROTECT in-hospital risk model: 7-day outcome in patients hospitalized with acute heart failure and renal dysfunction**. Eur J Heart Fail. 2012 ;14:605-12. [18]	Placebo-Controlled Randomized Study	2.015 pts with a history of HF anf hospitalized for HF	NR	173 sites in North America Europe, Israel, Argentina	Composite outcome of death, worsening heart failure (WHF), or rehospitalization for HF within 7 days of the index hospital admission. The strongest predictor of the composite endpoint was higher BUN concentration. Additional predictors of a worse outcome were lower values of serum albumin, serum cholesterol, and SBP, as well as higher heart rate and respiratory rate.	7 days
Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, Ostergren J,Michelson EL, Pieper KS, Granger CB**. Predictors of mortality and morbidity in patients with chronic heart failure**. Eur Heart J. 2006 ;27:65-75. [20]	CHARM RCT (The Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity)	7,599 pts with CHF with and without left ventricular systolic dysfunction.	NR	26 countries	Predictor of the CV death or HF hospitalization: age, the model estimates a 46% increase in hazard for every 10 years of age >60. Diabetes (HR 2,03 and 1,58 insulin treated and not insulin treated respectively) EF: for EF values <45%, every 5% decrease in EF, there is a 13% increase in hazard. Previous hospitalization for HF increased the hazard by 73% if within the past 6 months, 22% otherwise. Cardiomegaly increased the hazard ratio by 35%. NYHA class III and IV increased the hazard by 32 and 54% relative to patients in class II. DBP: every 10 mmHg decrease in pressure is associated with an 11% increase in hazard. Heart rate: 8% increase in hazard for every 10 b.p.m. increase. There was a 3% increase in risk per 1 kg/m^2 decrease in body mass index (BMI) below the median value of 27.5 kg/m.2. In decreasing order of importance, bundle branch block, pulmonary crackles, dependent edema, atrial rest, dyspnoea, mitral regurgitation, and previous myocardial infarction were further	Median of 38 months

					independent and highly significant predictors of CV death and HF hospitalization. After allowing for all the aforementioned variables, there was still a gender difference with females having a 17% lower risk of CV death or HF hospitalization relative to males.	
Riegel B, Knafl GJ. **Electronically monitored medication adherence predicts hospitalization in heart failure patients.** Patient Prefer Adherence. 2013;8:1-13 [48]	Analysis of longitudinal data from a pro-spective cohort study. of a adults with HF.	Consecutive sample of 280 pts with a clinically confirmed diagnosis of chronic HF	Three outpatient settings in the north US	US	Medication adherence was the best predictor of hospitalization. Besides two dimensions of poor adherence (adherence pattern type and low percentage of prescribed doses taken), four other single factors predicted hospitalization: low hemoglobin, depressed ejection fraction, New York Heart Association class IV, and 12 or more medications taken daily.	6 months
Senni M, Gavazzi A, Oliva F, Mortara A, Urso R, Pozzoli M, Metra M, Lucci D, Gonzini L, Cirrincione V, Montagna L,Di Lenarda A, Maggioni AP, Tavazzi L; IN HF Outcome Investigators. **In-hospital and 1-year outcomes of acute heart failure patients according to presentation (de novo vs. worsening) and ejection fraction. Results from IN-HF Outcome Registry.** Int J Cardiol. 2014;17:163-9. [38]	Prospective, observational, nationwide registry	1,669 pts hospitalized for heart failure	61 Cardiolgy units	Italy	In hospital mortality was higher in patients with reduced EF but 1 year outcome are not statistically different.	In hospital and 1 year
Setoguchi S, Stevenson LW, Schneeweiss S. **Repeated hos-pitalizations predict mortality in the community population with heart failure.** *Am Heart J* 2007; 154: 260-266 [27]	Observational cohort study based on healthcare utilization database	14,374 pts who were admitted to a hospital for the first time for HF (ICD 9 428.XX)	Population -based	British Colu mbia, Canada	Mortality significantly increased after each additional HF hospitalization. Median survival times after the first, second, third, and fourth hospitalization were 2.4 (95% CI 2.3-2.5), 1.4 (95% CI 1.2-1.5), 1.0 (95% CI 0.9- 1.1), and 0.6 (95% CI 0.5-0.9) years.	

Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL, Pfeffer MA**. Influence of non-fatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure**. *Circulation* 2007; 116: 1482-1487 [24]	CHARM RCT (The Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity	7,599 pts with CHF with and without left ventricular systolic dysfunction.	NR	26 countries	The risk of death increased with each additional HF hospitalization, with a nearly 30% cumulative incremental risk associated with discharge from a second or third HF hospitalization.	
Tavazzi L, Michele Senni, Marco Metra, Marco Gorini, Giuseppe Cacciatore,Alessandra Chinaglia, Andrea Di Lenarda, Andrea Mortara, Fabrizio Oliva, Aldo P. Maggioni, on the behalf of IN-HF (Italian Network on Heart Failure) Outcome Investigators. **Multicenter Prospective Observational Study on Acute and Chronic Heart Failure One-Year Follow-up Results of IN-HF (Italian Network on Heart Failure) Outcome Registry** Circ Heart Fail 2013;6;473-481 [7]	Multicenter, nationwide, prospective observational	5,610 pts, 1,855 AHF and 3,755 outpatients with CHF	Cardiology	Italy	Factors independently associated with a higher annual mortality rate were: Older age, high serum creatinine, high blood urea nitrogen, low serum sodium, COPD, acute pulmonary edema, anemia, and symptoms of cerebral hypoperfusion.	1 year
Tsuchihashi M, Tsutsui H, Kodama K, Kasagi F, Setoguchi S, Mohr M, Kubota T, Takeshita A. **Medical and socioenvironmental predictors of hospital readmission in patients with congestive heart failure.** *Am Heart J* 2001; 142: E7 [25]	Prospective hospital registry	81 Individuals with a discharge code for CHF, validated clinically.	5 cardiology units	Japan	Five variables were identified as significant independent predictors for readmission, :poor follow-up visits OR 4.9, 95% CI 2.0-11.8, previous admission for CHF OR 3.3, 95% CI 1.8-6.1, no occupation OR 2.6, 95% CI 1.2-5.5, longer hospital stay (> 7days) (OR 3.2, 95% CI 1.2-8.5), and hypertension (OR 2.0, 95% CI 1.1-3.7).	1 year

Footnote: ADB, administrative database; ADHF, acute decompensated heart failure ; AHF, acute heart failure; BUN, blood urea nitrogen; CHF, chronic heart failure; COPD, Chronic obstructive pulmonary disease; DBP, diastolic blood pressure; EF, ejection fraction; Hb, hemoglobin; Pts, patients; SBP, systolic blood pressure; SCr, Serum Creatinine; WRF, worsening renal function.

This literature review clearly shows that the majority of the information on HF outcomes and re-hospitalization are not retrieved from population-based studies.

It is well known that subjects enrolled in clinical trials often do not represent HF patients of their broader communities, who are likely to be older, of female gender and affected by several comorbidities [22]. For example, although new hospitalized HF patients are on average 79 years old [49], most clinical trials included younger patients with a mean age of about 60-65 years [50]. Most observational studies were conducted by selected centers (e.g. cardiology units as in the Italian Network on Heart Failure Outcome Registry [7] or large hospitals which voluntarily participated to the EuroHeart Failure Survey [19]), or with no European populations such as those from the United States (e.g., the Framingham Heart Study [51] and the Cardiovascular Health Study [1]), Canada [22], and Japan [52]. Furthermore, large HF registries and databases focus on patients who have already been hospitalized for decompensated HF [53,54], thus introducing a bias due to (a) a great heterogeneity in the patients' outcomes and probably to (b) the selective better survival for those patients with favorable prognosis [55]. Accordingly, the purpose of this study was to identify short-term (30 days) and long-term (one year) prognostic factors of new HHF patients generated from a large and unselected population from the region of Lombardy. Characterization of hospitalized HF is very important for assisting clinicians in decision making and targeting treatment of high risk patients.

5.1. 2 Material and Methods

5.1.2.1 Data Source

The data used in this study were retrieved from the healthcare utilization databases of Lombardy, an Italian region that accounts for about 16% (9,704,151) of the Italian population. In Italy the population is covered by a National Health Service (NHS) and Lombardy provides an automated system of databases to collect much health care information (details on data source are reported in Chapter 1).

5.1.2.2 Cohort selection

Target population consisted of all beneficiaries of the NHS resident in Lombardy aged 50 years or more. According to the 2011 Italian Census, this population amounted to more than 3.5 million inhabitants. Of these, we identified individuals who during 2011 were hospitalized at least once with HF diagnosis. As explained in previous chapters, heart failure

diagnosis included ICD-9th codes for heart failure (428.x), and hypertensive heart failure (402.01, 402.11, and 402.91). To keep the population more homogeneous and because the objective of this study were new hospitalized HF patients, each patient contributed only with the first hospitalization occurred during 2011. Patients who already experienced at least one HF hospitalization in the ten years preceding the index admission (i.e., the first occurring hospital admission during 2011) were excluded from the analysis. Finally, since the study was aimed to identify prognostic factors of 30-day and one-year mortality/readmission after discharge for HF, patients who did not survive the index admission were also excluded. The remaining patients constituted the study cohort (Figure 5.1).

5.1.2.3 Follow up and outcomes

Each member of the cohort accumulated person-months of follow-up from the starting date (i.e. discharge from index admission), until the earliest among the dates of outcome onset (see below) or censoring, i.e. death, emigration, or end of follow-up period considered (i.e. 30-day and one-year).
Short-term (30 days after discharge) occurrence of death or hospital readmission for HF, as well as long-term (one year after discharge) occurrence of death or hospital readmission for any cause, were identified for each cohort members and defined as outcome onset.

5.1.2.4 Covariates

Covariates have been described by means of descriptive statistics. For each cohort member data included gender and age at index admission, length of stay of the index admission, pharmacological treatments dispensed within one-year before index admission (lipid-lowering, antidiabetics, antihypertensives such as angiotensin-converting-enzyme inhibitors-ACE-inhibitors, angiotensin receptor blockers-ARBs, β-blockers, mineralocorticoid receptor antagonists-MRA- and other diuretics, other antihypertensives, antiarrhythmic, antidepressants, NSAIDs and antigout preparations), hospital admissions occurred within five years before index admission (for renal dysfunction, respiratory disease, arrhythmia, coronary/aortic heart disease, cerebrovascular disease and cancer) and during follow-up (for HF, major cardiovascular events, other cardiovascular events, respiratory disease, renal failure, and other causes taken together).

5.1.2.5 Statistical analysis

Cumulative proportions of patients experiencing each outcome were separately computed by means of the Kaplan-Meier estimator. Cox's proportional hazard regression multivariable model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI), for the association between the selected covariates and time of onset of each of the outcomes of interest separately investigated. As some covariate were taken over follow-up (e.g., hospital admissions during follow-up), and because the corresponding values may vary over time, assessment of their values requires proper accounting for the varying nature of the measure. This was done by including hospital admissions during follow-up as time-dependent variables in the model. Trends in HRs were tested, when feasible, according to the statistical significance of the regression coefficient of the recoded variables obtained by scoring the corresponding categories.

5.1.3 Results

Patients' disposition is shown in Figure 3.1. The 13,171 patients included in the study cohort accumulated 137,275 and 89,279 person-months of observation depending on whether one-year mortality or one-year hospital readmission was investigated.

Median age of patients at index admission was 81 years, and 54% of them were women (Table 3.1). At baseline, HHF patients had a high burden of both cardiovascular and no cardiovascular comorbidities including hypertension, dyslipidaemia, diabetes, arrhythmia, respiratory disease, coronary heart disease, cerebrovascular disease, gout and renal dysfunction.

Within 30 days after index discharge, 4.7% of the cohort members died and and 16.3% were readmitted in hospital; of the total amount of re-hospitalizations, 26% were re-hospitalization for heart failure. Within one year, 22.6% and 57.2% of individuals respectively died and were readmitted in hospital for any cause. Among one-year-re-hospitalizations, 32% were for HF, 29% for major CV events, 47% CV events, 35% for respiratory diseases and the 22% for renal diseases (Table 3.1, Figure 3.2).

Concerning prognostic factors: a clear trend towards increasing mortality as age increases was observed for both 30-day and one-year mortality (Figure 3.3). An opposite negative trend was observed for the risk of both 30-day readmission for HF and one-year readmission for any cause. No gender effect on the considered outcomes was observed, with the exception of the significant excess of readmissions for any cause in men.

There was statistical evidence that patients on lipid-lowering drugs and ACE inhibitors, or ARBs, were at lower risk of both 30-day and one-year mortality (Figure 3.4). One-year mortality rate was also lower among users of β-blockers, other anti-hypertensive drugs and NSAIDs, while it was higher among users of diuretics, in particular of MRA, and anti-gout preparations. Figure 3.4 shows statistical evidence that patients on other antihypertensive and antiarrhythmic drugs were at higher risk of 30-day hospital readmission for HF. One-year hospitalization for any cause was higher among users of antidiabetics, diuretics, other antihypertensive, antidepressants, NSAIDs, and anti-gout preparations.

Length of stay longer than 13 days, as well as previous hospital admissions for cancer, were negative prognostic factors for all the considered outcomes (Figure 3.5). Both 30-day and one-year mortality were negatively affected by previous hospital admissions for respiratory disease and cerebrovascular disease. The risk of one-year hospital readmission for any cause was negatively affected by previous hospital admissions for renal dysfunction, respiratory disease, coronary heart disease and cerebrovascular disease.

All the considered causes of hospitalization during follow-up including cardiovascular (HF, major cardiovascular events, and other cardiovascular disease) and non-cardiovascular (respiratory disease, renal failure, and others), were negative prognostic factors for 30-day and one-year mortality (Figure 3.6).

5.1.4 Discussion

This analysis of Lombardy region patients after an initial HF hospitalization demonstrates that, despite significant advances in HF management, these patients continue to experience substantial re-hospitalization and mortality rates both within 30 days and one year the index event.

Our study has documented the high 30-day and one-year risk of mortality and hospital readmission after first admission for heart failure in unselected patients from a large population-based sample in Lombardy, Italy. We also showed a substantial heterogeneity in mortality and hospital readmission across different patients subgroups. Signs of gout (previous use of specific drugs) or cancer (previous hospitalization for) and long stay in hospital during the index admission, were negative prognostic factors for all the considered outcomes. As expected, old age negatively affected mortality, while oddly it is associated with a lower one-year readmission rate. Signs of arrhythmia (previous use of antiarrhythmic drugs) and respiratory disease (previous hospitalization for) respectively acted as negative factors for the short-term onset of readmission and mortality. It is interesting that the second

reasons for readmission (respiratory disease) in this population are diagnoses that can easily be confused with HF.

Interestingly, therapy with certain blood-pressure medicaments used for treatment of HF, such as diuretics and, in particular, MRA, was a negative prognostic factor for one-year mortality and readmission. Conversely, other blood-pressure medicaments (e.g., ACE-inhibitors, ARBs, and other antihypertensive) as well as lipid-lowering drugs, were associated with a lower one-year mortality rate. Relevant clinical comorbidities as suggested by previous hospital admissions for renal dysfunction and respiratory disease and history of major cardiovascular events, acted as negative one-year prognostic factors. Finally, experiences of hospital readmission during follow-up negatively affected both short-term and long-term mortality.

The association between advanced age and mortality in patients with HF has been observed in almost all studies aimed to identify prognostic factors [7, 12-16, 20- 22]. The same is true for comorbidities such as respiratory disease (in particular, COPD) [7,13,16, 17,22,29] or renal dysfunction [13,15,16,18,22,28,30].

As expected, the use of drugs known to be able for improving patients' outcomes, such as blockers of the renin-angiotensin system or beta-adrenergic blockers, was associated with a more favorable long-term mortality profile. This observation could be due to the favorable effect of these drugs, as demonstrated in clinical trials [47,56,57], but also to the fact that patients who can receive in the absence of contraindications or intolerance these treatments are generally less severely impaired.

This study had both strengths and limitations. Among its strengths is the fact that the study was based on data from a very large unselected population representative of the real clinical practice, which was made possible by the fact that in Italy the cost-free uniformly organized NHS covers practically all resident citizens. Moreover, patients included into the cohort were not hospitalized for heart failure in the 10-year period before the index date, making our findings relevant to patients who for the first time experienced severe clinical manifestation of heart failure. Finally, data quality of healthcare utilization databases of Lombardy has been repeatedly evaluated showing highly accurate data [58-61].

Our study, however, carries inherent limitations of a retrospective analysis of healthcare utilization database. First, the use of ICD-9 codes to identify the cause of hospitalization may lead to some misclassification. On the other hand, because of privacy regulations, hospital records were not available, so HF diagnoses cannot be scrutinized and validated. It should be considered that if a diagnosis is coded and recorded in the claims data, it is likely that this diagnosis was made, hence specificity of claims diagnoses is expected to be usually nearly

100%, particularly in hospital discharge summaries [62]. Thus, although we do not capture all HF patients of the target population, we can be reasonably certain that almost all the included patients really suffered from HF.

Second, since the Lombardy healthcare utilization database has a limited amount of clinical data, we cannot exclude that unmeasured characteristics may impact the considered outcomes, and also confound the effect of measured predictors. For example, other potentially predictors such as body mass index, biohumoral profiles, adherence to medicaments, moderate valvular heart disease and psychological factors [62] cannot be obtained from our database. Yet, we cannot distinguish heart failure patients with normal vs. reduced ejection fractions, or classify the cause of heart failure [22]. Some socio-demographic factors, such as ethnicity and socioeconomic status, were also missing in our database and hence could not be taken into account as adjusting factors.

Because of lack of data, the prognostic evaluation of a complete set of clinical and biohumoral variables able to more precisely predict the risk of death and/or hospitalization after a first admission, was not allowed in our study. However, since the database includes a set of variables available in the universe of the population of an entire region, a prognostic score based on these observations could potentially be easily, quickly and automatically generated at the hospital entry to help health care professionals dealing with HHF patients in their decision making. Further, more sophisticated clinical variables could be added during the hospital stay to further improve the prognostic accuracy.

5.2 Hospitalized heart failure economic impact

5.2.1 Introduction

Although the incidence rate seems to be decreasing, heart failure still remains a global public health problem affecting an estimated 26 million worldwide. Among the countries represented by the European Society of Cardiology (ESC), there are 15 million patients with HF [50]. Hospitalized heart failure is the leading cause of hospitalization in the United States and Europe, resulting in over 1 million admissions as a primary diagnosis and representing 1% to 2% of all hospitalizations [63].

In the USA, the annual cost of HF in 2010 is estimated to be $39.2 billion, which represents about 2% of the total US health-care budget [64]. Evaluations from different European countries indicate a similar share of HF-related costs in relation to overall health-care expenditure. [65,66].

In 2000 the UK estimated a total amount of direct cost of £716 million (almost €915 million) covered by the NHS for heart failure [67], while in 1996 in Sweden the total amount of healthcare expenditure for HF was more than €280 million [68].

This expenditure is not going to be reduced in the near future: actual epidemiological estimates tell us that HF will continue to be a substantial financial and public health concern among the aging population due to the improved survival of patients with cardiac conditions such as acute myocardial infarction and hypertension and the increasing prevalence of diabetes and obesity, two key risk factors for developing HF [69,70].

In order to better understand the amount of the direct HF expenditure covered by the NHS and the several components by which is formed, we performed an observational study based on Region Lombardy administrative database.

This study was aimed to determine the consumption of medical resources for the treatment and care of hospitalized heart failure patients and estimating the related costs from a regional health authority's perspective.

5.5.2 Material and Methods: Cohort selection and healthcare cost assessment

As in previous analyses, individuals who, in the year 2011, were beneficiaries of the Italian NHS, resident in the Lombardy Region, and hospitalized at least once with a HF diagnosis comprised the study incident cases.

Medical records with primary HF diagnosis at discharge were drawn from the regional hospital discharge database. The definition for a diagnosis for HF was based on Criterion 1 (as described in chapter 3).

Patients who had already experienced at least one HHF episode in the 5 years preceding the earliest (or unique) hospitalization occurring in 2011 were also excluded.

Incident HHF cases were denoted index events for the current study and they were used to assess the healthcare costs. In order to address NHS expenditure we only evaluated patients who survived index hospitalization.

The total cost for healthcare of each cohort member during the first year after the index hospitalization was measured from the NHS perspective using the amount that the Regional Health Authority (RHA) reimbursed health providers.

For this purpose expenses related to all hospitalizations, outpatient visits, laboratory tests and imaging evaluations, medications and drugs reimbursed by the NHS (distributed both by pharmacies or directly to patients) a year after the index admission have been taken into consideration.

Cost categories taken into account were hospitalizations for any cause, outpatient drug prescriptions, visits, procedures and diagnostic tests commonly used in the management of CV patients. General practitioner visits were not considered, because they were not recorded in the healthcare utilization databases. The hospital expenditure was measured using the information contained in the SDO which contain a variable named "value of the total amount of each hospitalization", which provides the sum of the amount of inpatient ordinary or day-hospital and the amount of hospital days over the threshold value. Specialists' outpatient visit expenditure was measured through the economic value inserted in the outpatient visits' database.

The medications considered were those for chronic diseases of the cardiovascular sphere (ATC C01, C04, C05, C06), the respiratory sphere (ATC R03), diabetes (ATC A10), hypertension (ATC C02, C03, C07, C08, C09) and hyperlipidemia (ATC C10). The prices of the drugs were taken from the tables provided by the Italian Medicine Agency.

We also wanted address another question: what would have been the NHS expenditure if patients included in the study cohort had not been hospitalized for HF?

To answer this question we selected a reference cohort suitable to be used as a comparator for the HHF cohort: reference cohort members were NHS beneficiaries matched 1:1 on gender and age at cohort entry with HHF cohort members, who did not experience hospitalization for HHF and were at risk for the outcome at the time when the matched HHF patient was discharged. Total and per capita healthcare costs (including the index

hospitalization) were measured for the all the members of both cohorts. In addition, the difference in cost for healthcare accumulated by every index event and its matched referent (excluding the index hospitalization) was calculated, and the relative difference was estimated, thus giving a measure of the excess healthcare cost due to HHF.

5.2. 3 Results

A total of 54,107 hospital admissions and 735,556 days of hospital stays were experienced by the 17,466 patients who survived the index hospitalization, this corresponds to 9,806 patients who were hospitalized at least once during the 1-year period after the index discharge.

The total direct cost for taking care of the HHF cohort members in the first year after the index discharge was €193 million (Table 3.3).

The average cost per person was €11,100, of which 4,300 euro were for the index hospitalization (39%), €5,900 for the subsequent hospitalizations (53%), and the remaining € 900 for non-hospital charges (8%) (Figure 3.7). By excluding the index hospitalization, the per capita direct cost was €6,800 and €1,400 for the HHF and the referent cohort members, respectively, the relative difference being 79.4%. The source-specific relative difference was higher for hospitalizations (83.8%) than for outpatient drug prescriptions (59.0%) and services (42.8%).

5.2.4 Discussion

Methodological strengths and weakness of this type of studies have already been mentioned in the above sessions.

It is not easy to compare different studies on heart failure expenditure: different health care organizations bring substantially different costs for the same service.

The per capita annual cost covered by the NHS during the first year after the index hospitalization that we documented , ~€11,100, is very similar to that recently reported by a Swedish study, i.e. an average annual total cost per patient of €11,900 [71].

What appears clearly is that, in order to develop cost-effective management programmes, it is important to identify the key areas in which the costs involved in treating heart failure arise.

Our results show that hospitalizations are the major source of expenditure in this type of patients. A recent review by Braunschweig et al. [72] reports that, when all costs categories are taken into consideration, in-hospital care is responsible for almost 60% of HF-related

costs in the USA. This is pretty consistent with our estimate (90%) if we think that GP's costs were not included in our evaluation.

From our results, then, we can conclude that future strategies to reduce costs in heart failure care should primarily focus on the reduction of hospitalization that represents the largest part of treatment costs and the identification of which patients are most likely to benefit from the range of interventions available.

5.3 References

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5.4 Appendix three

Figure 3.1. Flow chart of exclusion/inclusion criteria

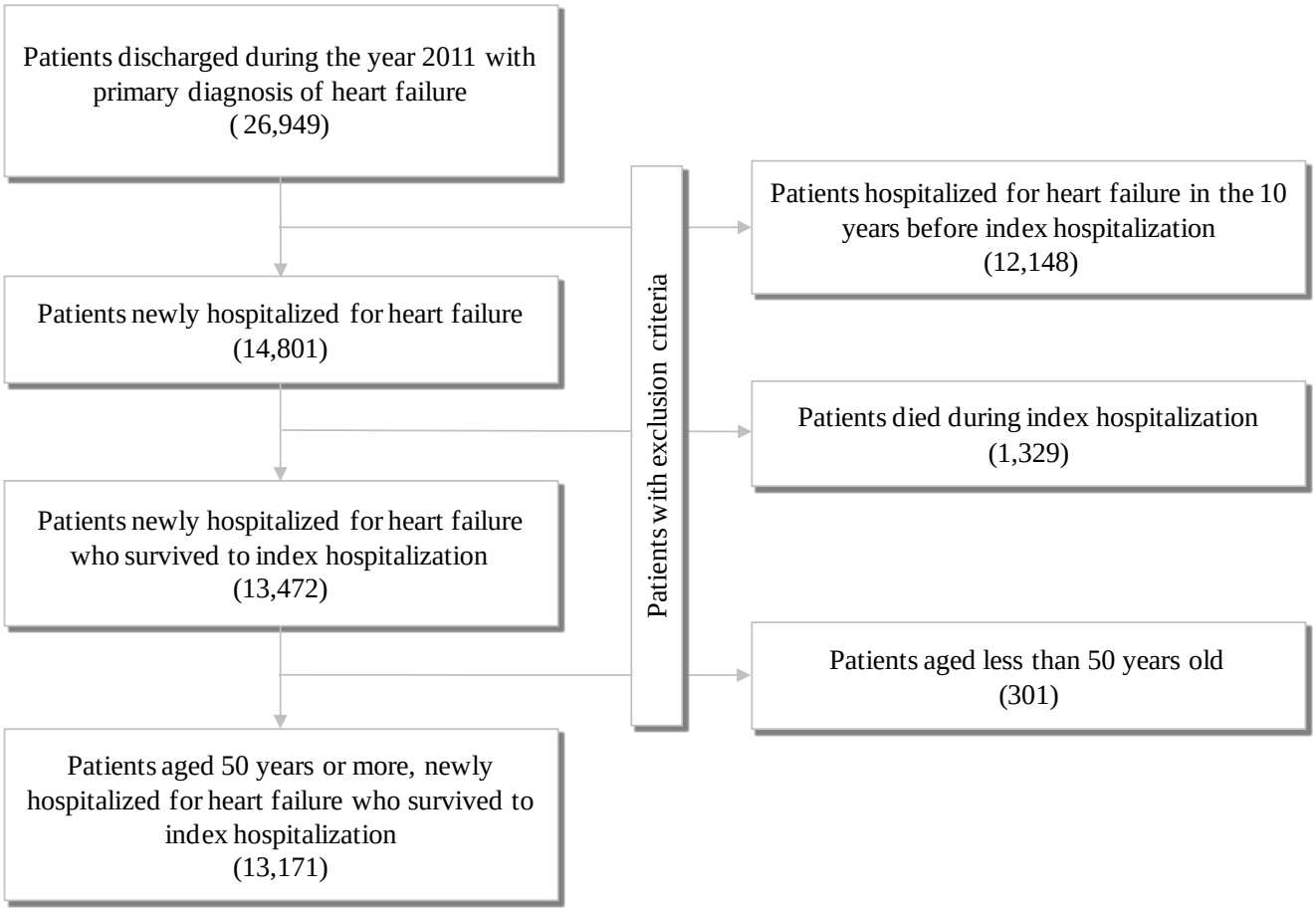


Table 3.2. Characteristics of the 13,171 new hospitalized for heart failure. Lombardy, Italy, 2011

Selected tracts	No.	%
Demographics at index admission		
Age, years, mean (SD)	79.3 (9.5)	
Age, median (IQR)	81.0 (12.0)	
Male	6,103	46.3%
Index admission		
Length of stay, days, mean (SD)	12.0 (10.3)	
Length of stay, days, median (IQR)	10.0 (7.0)	
Drugs (year before index admission)		
Lipid-lowering drugs	3,843	29.2%
Antidiabeticss	3,194	24.3%
Antihypertensives	11,157	84.7%
ACE-inhibitors or ARBs	8,739	66.4%
β-blockers	5,537	42.0%
Diuretics (except MRA)	6,334	48.1%
Mineralocorticoid antagonists (MRA)	1,163	8.8%
Other anti-hypertensives	6,458	49.0%
Antiarrhythmics	2,746	20.9%
Antidepressants	1,602	12.2%
Non-steroidal anti-inflammatory drugs (NSAIDs)	4,099	31.1%
Antigout preparations	1,843	14.0%
Hospitalizations (5 years before index admission)		
Renal dysfunction	886	6.7%
Respiratory disease	2,459	18.7%
Arrhythmia	2,441	18.5%
Coronary/aortic disease	2,081	15.8%
Cerebrovascular disease	1,787	13.6%
Cancer	1,820	13.8%
Hospitalizations during follow-up		
Readmission for any cause 30 days after index discharge	2,141	16.3%
Readmission for HF 30 days after index discharge	549	4.2%
Readmission for any cause one-year after index discharge	7,136	54.2%
HF	2,285	17.4%
CV major	2,081	15.8%

Other CV event	3,393	25.8%
Respiratory disease	2,485	18.9%
Renal failure	1,556	11.8%
Other	1,935	14.7%
Cancer	321	2.4%
Complications to certain procedures/fractures	301	2.3%
Diseases of the digestive system	286	2.2%
Procedure aftercare/adjustment device/palliative care	263	2.0%
Other	764	5.8%
Death during FU		
30 days after index discharge	621	4.7%
1 year after index discharge	2,980	22.6%

ACE-inhibitors: angiotensin-converting-enzyme inhibitors; ARBs: angiotensin receptor blockers; CV: cardiovascular

Figure 3.2. Kaplan-Meier cumulative mortality and hospital readmission within 30 days and 1 year after index discharge. Lombardy, Italy, 2011

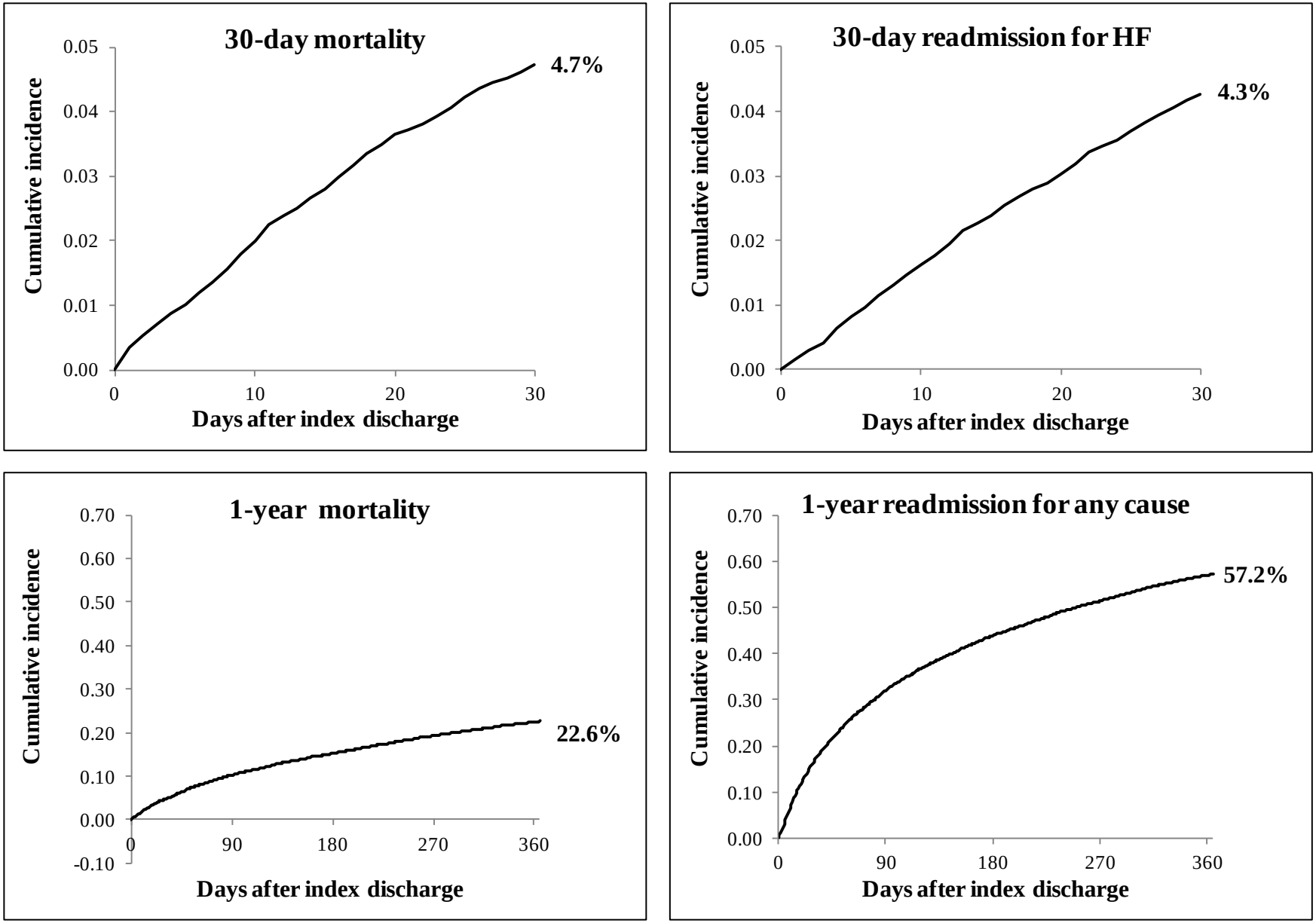
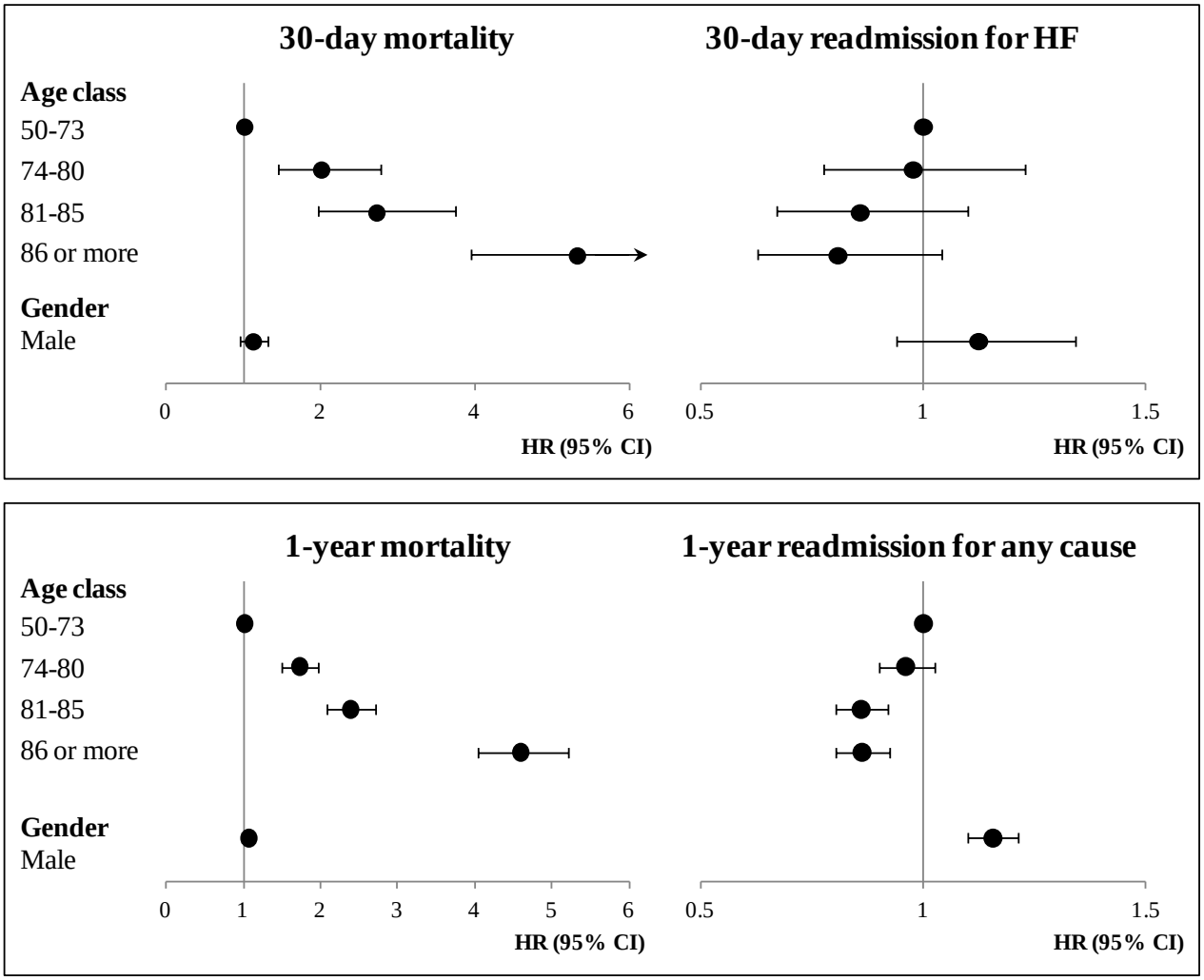
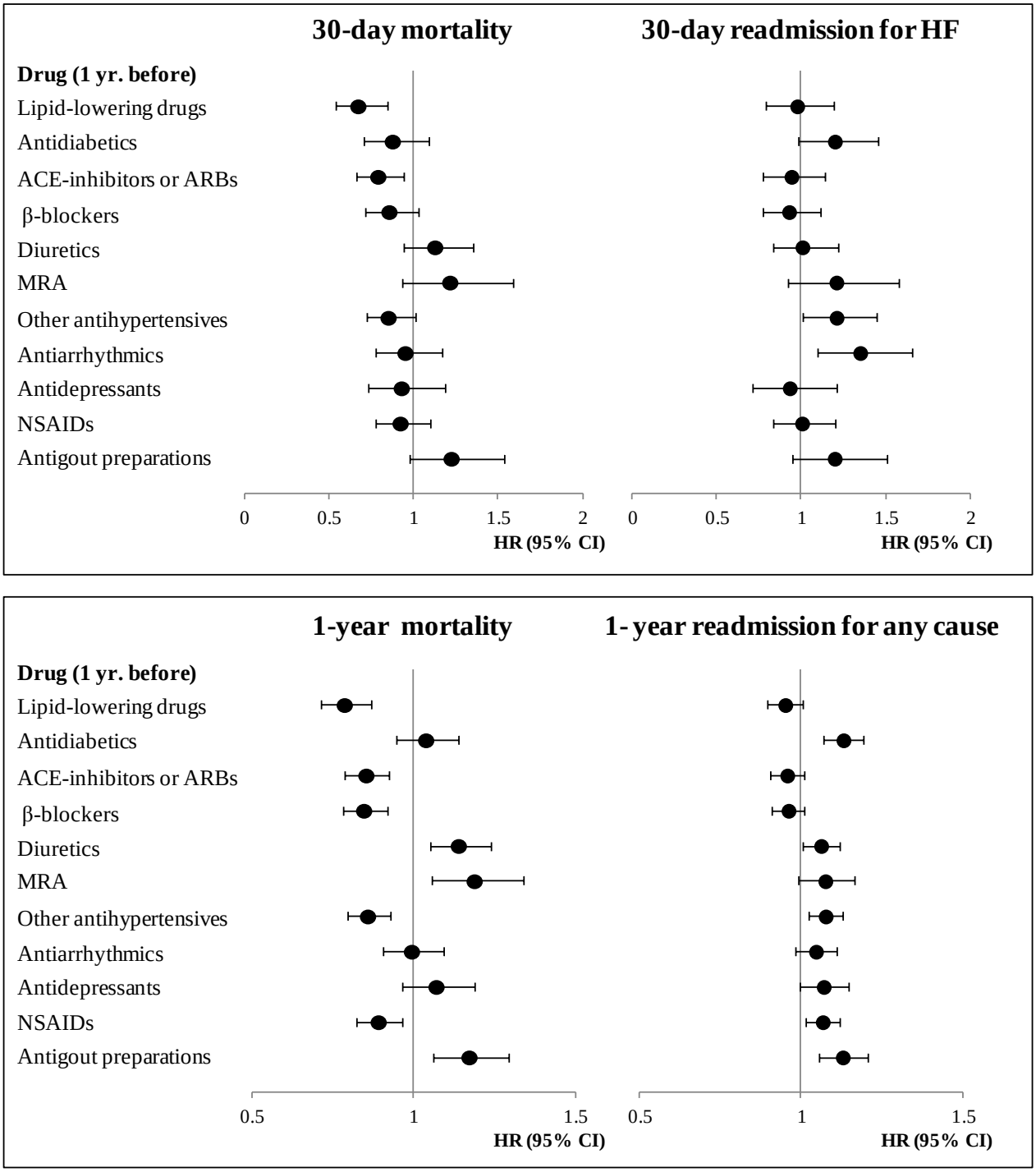


Figure 3.3 Adjusted hazard ratios (and 95% confidence intervals) of time of onset of the selected outcomes (separately investigated) associated with age classes and gender. Lombardy, Italy, 2011



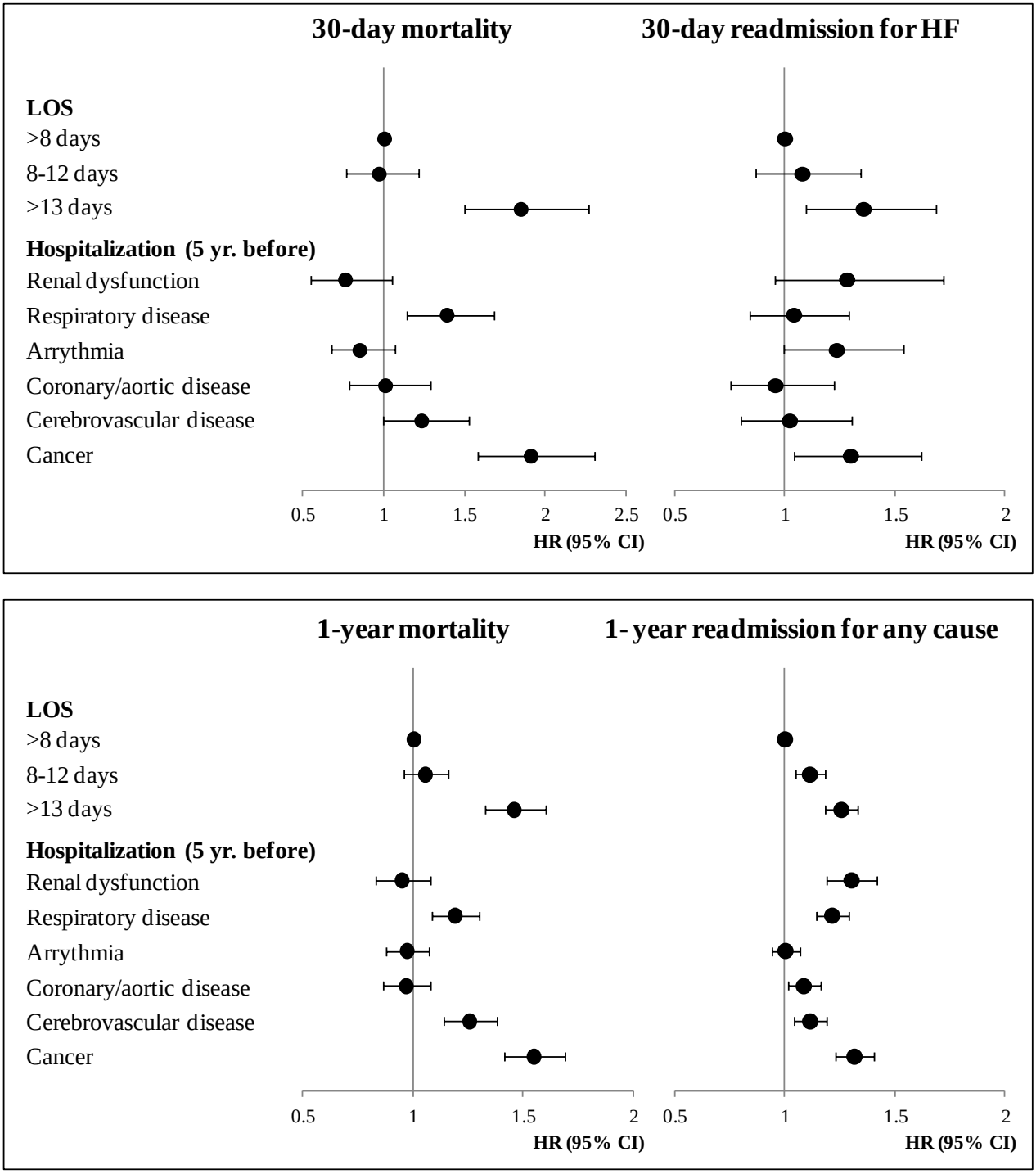
Hazard ratios were estimated with Cox proportional hazard regression multivariable model. Estimates were adjusted for all the considered covariates. Age categories were built according to quartiles

Figure 3.4 Adjusted hazard ratios (and 95% confidence intervals) of time of onset of the selected outcomes (separately investigated) associated with drugs dispensed in the one-year period before index admission. Lombardy, Italy, 2011



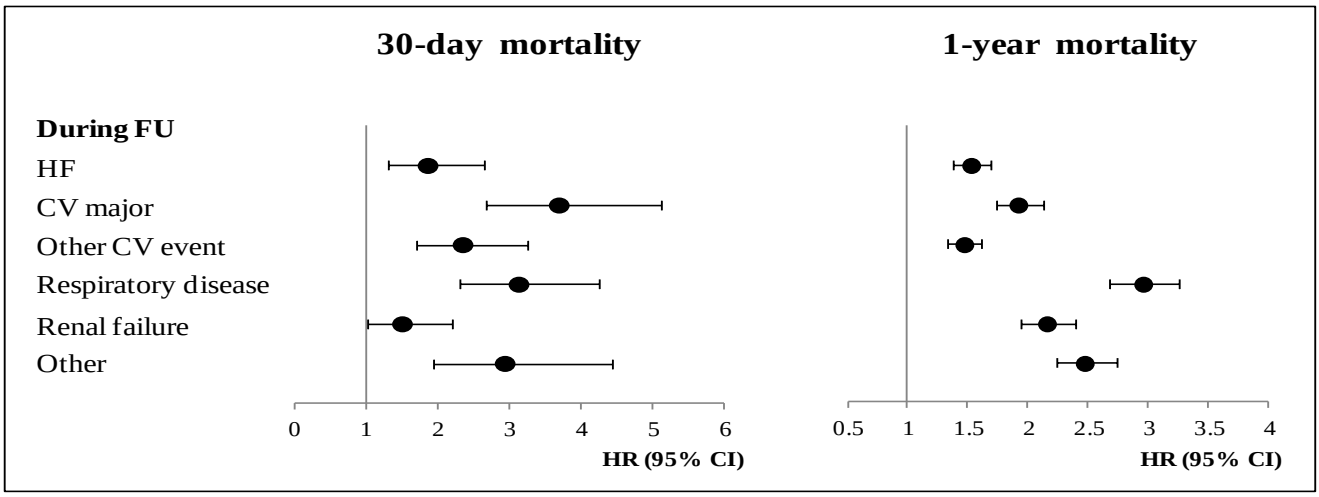
Hazard ratios were estimated with Cox proportional hazard regression multivariable model. Estimates were adjusted for all the considered covariates.

Figure 3.5 Adjusted hazard ratios (and 95% confidence intervals) of time of onset of the selected outcomes (separately investigated) associated with index admission length of stay and with hospitalizations in the 5-year period before index admission. Lombardy, Italy, 2011



Hazard ratios were estimated with Cox proportional hazard regression multivariable model. Estimates were adjusted for all the considered covariates. LOS categories were built according to tertiles. LOS: length of stay.

Figure 3.6 Adjusted hazard ratios (and 95% confidence intervals) of time of onset of 30-day and one-year mortality (separately investigated) associated with selected cause of hospitalization during follow-up. Lombardy, Italy, 2011

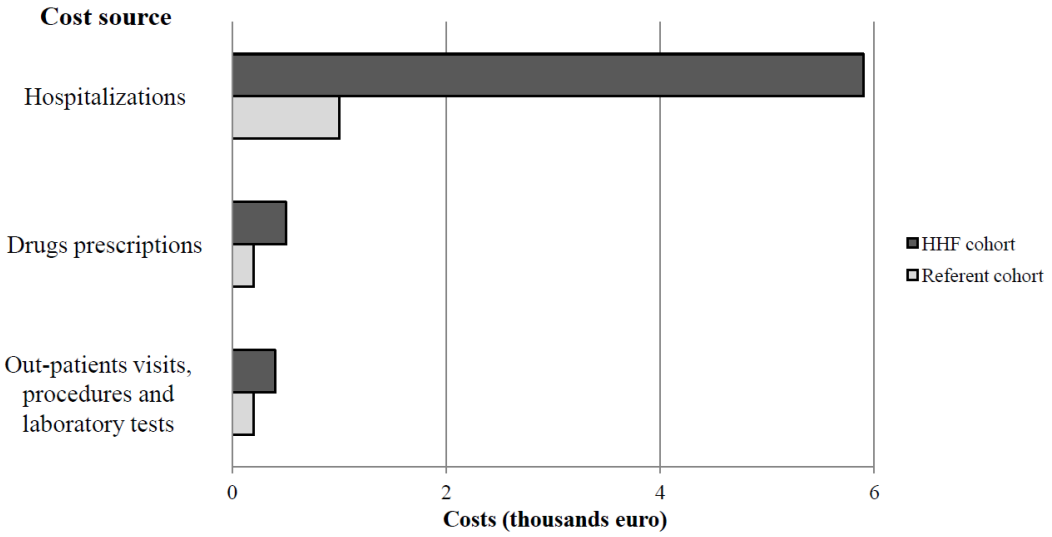


Hazard ratios were estimated with Cox proportional hazard regression multivariable model. Estimates were adjusted for all the considered covariates. CV: cardiovascular.

Table 3.3 Total and *per capita* cost sustained for health care of hospitalized heart failure and referent cohort members during the one-year period after index hospitalization, and their relative difference according to expenditure source (Lombardy, Italy, 2011).

	HHF cohort (thousands euro)		Referent cohort (thousands euro)		Relative difference
	Total	*Per capita*	Total	*Per capita*	
Inpatient cost sources					
Without index hospitalization	103,211	5.9	16,767	1.0	83.8%
With index hospitalization	177,772	10.2	-	-	
Outpatient cost sources					
Drugs	8,823	0.5	3,624	0.2	59.0%
Visits, procedures and laboratory tests	7,301	0.4	4,171	0.2	42.8%
Total					
Without index hospitalization	119,335	6.8	24,563	1.4	79.5%
With index hospitalization	193,896	11.1			

Figure 3.7 Per capita cost sustained for healthcare of hospitalized heart failure (HHF) and referent cohort members during the 1-year period after the index hospitalization (Lombardy, Italy, 2011).



Appendix four

In this appendix are reported, if different from already reported analysis, results obtained applying different criteria (Criterion 2 and 3 to different population A and C).

Table 4.1a - Number of hospitalizations, patients hospitalized and patients hospitalized with no history of HHF among residents in region Lombardy in the years 2010 and 2011.

CRITERION 2 428.x, 402.01,402.11,402.91 AS MAIN DIAGNOSIS or DRG CODE 127		
YEARS 2010-2011	**All**	**Classified as urgent**
Hospitalizations	70,707 (100.00%)	53,388 (75.51%)
Patients hospitalized	50,516 (100.00%)	40,673 (80.52%)
Patients with no history of HHF, (as defined by Criterion 2)	31,265 (61.89%)	25,652 (50.78%)

Table 4.1b - Number of hospitalizations, patients hospitalized and patients hospitalized with no history of HHF among residents in region Lombardy and stratified by years 2010 and 2011.

CRITERION 2 428.x, 402.01,402.11,402.91 AS MAIN DIAGNOSIS or DRG CODE 127		
	YEAR 2010	**YEAR 2011**
Hospitalizations	35,173 (100.00%)	35,534 (100.00%)
Patients hospitalized	27,532 (100.00%)	27,511 (100.00%)
Patients with no history of HHF, (as defined by Criterion 2)	16,475 (59.84%)	16,526 (60.10%)

Table 4.1c- Number of hospitalizations, patients hospitalized and patients hospitalized with no history of HHF among residents in region Lombardy in the years 2010 and 2011.

CRITERION 3 428.x, 402.01,402.11,402.91 AS MAIN DIAGNOSIS or DRG CODE 127 + symptomatic diagnosis (514.x, 518.4, 518.81,785.x,786.x) with an ICD9 code 428.x, 402.01,402.11,402.91 as secondary diagnosis		
YEARS 2010-2011	**All**	**Classified as urgent**
Hospitalizations	75,411 (100.00%)	57,713 (76.53%)
Patients hospitalized	53,678 (100.00%)	43,732 (81.47%)
Patients with no history of HHF, (as defined by Criterion 3)	33,446 (62.31%)	27,749 (51.70%)

Table 4.1d- Number of hospitalizations, patients hospitalized and patients hospitalized with no history of HHF among residents in region Lombardy and stratified by years 2010 and 2011.

CRITERION 3 428.x, 402.01,402.11,402.91 AS MAIN DIAGNOSIS or DRG CODE 127 + symptomatic diagnosis (514.x, 518.4, 518.81,785.x,786.x) with an ICD9 code 428.x, 402.01,402.11,402.91 as secondary diagnosis		
	YEAR 2010	**YEAR 2011**
Hospitalizations	37,407 (100.00%)	38,004 (100.00%)
Patients hospitalized	29,205 (100.00%)	29,338 (100.00%)
Patients with no history of HHF, (as defined by Criterion 3)	17,653 (60.45%)	17,722 (60.41%)

Table 4.2a - Attack rate /10,000 person-year

CRITERION 2 428.x, 402.01,402.11,402.91 AS MAIN DIAGNOSIS or DRG CODE 127					
Age stratum		**TOTAL HOSPITALIZATIONS**		**URGENT HOSPITALIZATIONS***	
		Men	**Women**	**Men**	**Women**
0-40	N° of events Attack rate CI 95%	176 **0.87** 0.74-1.00	95 **0.49** 0.39-0.59	105 **0.52** 0.42-0.62	65 **0.34** 0.26-0.42
41-50	N° of events Attack rate CI 95%	634 **7.98** 7.35-8.60	192 **2.50** 2.14-2.85	409 **5.14** 4.65-5.64	140 **1.82** 1.52-2.12
51-60	N° of events Attack rate CI 95%	1,871 **30.30** 28.92-31.67	729 **11.62** 10.78-12.46	1,147 **18.57** 17.50-19.65	508 **8.10** 7.39-8.80
61-70	N° of events Attack rate CI 95%	5,533 **100.00** 97.36-102.63	2,645 **44.61** 42.91-46.31	3,711 **67.07** 64.91-69.23	1,959 **33.04** 31.57-34.50
71-80	N° of events Attack rate CI 95%	11,977 **281.69** 276.65-286.74	8,902 **150.12** 147.01-153.24	8,777 **206.43** 202.11-210.75	7,012 **118.25** 115.48-121.02
>80	N° of events Attack rate CI 95%	12,065 **627.32** 616.13-638-52	19,967 **492.20** 485.37-499.02	9,923 **515.95** 505.80-526.10	17,240 **424.97** 418.63-431.32
Standardized**	Attack rate CI 95%	**76.61** 75.76-77.45	**47.53** 47.01-48.06	**57.84** 57.11-58.58	**39.04** 38.57-39.51
Total unadjusted	Attack rate CI 95%	**68.10** 65.57-68.62		**53.60** 53.14-54.07	
Total standardized**	Attack rate CI 95%	**62.07** 61.55-62.59		**48.44** 47.98-48.91	

*In ordinary wards but classified as urgent

** For rate standardization it was used as reference the entire Italian population in 2011

Table 4.2b - Attack rate /10,000 person-year

CRITERION 3 428.x, 402.01,402.11,402.91 AS MAIN DIAGNOSIS or DRG CODE 127 + symptomatic diagnosis (514.x, 518.4, 518.81,785.x,786.x) with an ICD9 code 428.x, 402.01,402.11,402.91 as secondary diagnosis					
Age stratum		**TOTAL HOSPITALIZATIONS**		**URGENT HOSPITALIZATIONS***	
		Men	**Women**	**Men**	**Women**
0-40	N° of events Attack rate CI 95%	186 **0.92** 0.79-1.06	98 **0.51** 0.41-0.61	115 **0.84** 0.71-0.97	67 **0.48** 0.38-0.58
41-50	N° of events Attack rate CI 95%	660 **8.30** 7.67-8.94	205 **2.66** 2.30-3.03	432 **7.84** 7.22-8.45	152 **2.39** 2.05-2.74
51-60	N° of events Attack rate CI 95%	1,962 **31.77** 30.37-33.18	776 **12.37** 11.50-13.24	1,233 **29.63** 28.28-30.99	551 **11.38** 10.55-12.22
61-70	N° of events Attack rate CI 95%	5,817 **105.13** 102.43-107.83	2,831 **47.74** 45.98-49.50	3,974 **97.96** 95.35-100.57	2,133 **43.53** 41.85-45.21
71-80	N° of events Attack rate CI 95%	12,734 **299.50** 294.29-304.70	9,527 **160.66** 157.44-163.89	9,485 **276.80** 271.80-281.80	7,608 **147.00** 143.92-150.09
>80	N° of events Attack rate CI 95%	12,952 **673.44** 661.85-658.04	21,300 **525.05** 518.00-532.11	10,767 **614.27** 603.20-625.35	18,535 **479.70** 472.96-486.44
Standardized**	Attack rate CI 95%	**81.58** 80.70-82.45	**50.76** 50.22-51.30	**75.10** 74.26-75.93	**46.40** 45.88-46.91
Total unadjasted	Attack rate CI 95%	**72.58** 72.04-73.12		**57.87** 57.38-58.35	
Total standardized**	Attack rate CI 95%	**66.17** 65.63-66.71		**60.75** 60.26-61.23	

*In ordinary wards but classified as urgent

** For rate standardization it was used as reference the entire Italian population in 2011

Table 4.3a - Incidence rate /10,000 person-year

CRITERION 2 428.x, 402.01,402.11,402.91 AS MAIN DIAGNOSIS or DRG CODE 127					
Age stratum		**TOTAL HOSPITALIZATIONS**		**URGENT HOSPITALIZATIONS***	
		Men	**Women**	**Men**	**Women**
0-40	N° of events Incidence rate CI 95%	146 **0.37** 0.31-0.43	78 **0.21** 0.16-0.25	99 **0.25** 0.20-0.30	60 **0.16** 0.12-0.20
41-50	N° of events Incidence rate CI 95%	498 **3.17** 2.89-3.45	177 **1.16** 0.99-1.33	342 **2.18** 1.95-2.41	165 **1.08** 0.92-1.25
51-60	N° of events Incidence rate CI 95%	1,402 **11.49** 10.89-12.10	569 **4.58** 4.21-4.96	927 **7.60** 7.11-8.09	414 **3.33** 3.01-3.66
61-70	N° of events Incidence rate CI 95%	4,085 **37.66** 36.51-38.82	2,076 **17.73** 16.97-18.50	2,862 **26.36** 25.40-27.33	1,584 **13.53** 12.86-14.19
71-80	N° of events Incidence rate CI 95%	8,910 **109.46** 107.19-111.73	7,035 **68.18** 66.59-69.78	6,706 **82.18** 80.21-84.14	5,637 **54.57** 53.15-56.00
>80	N° of events Incidence rate CI 95%	9,472 **278.02** 272.42-283.62	16,068 **219.18** 215.80-222.57	7,919 **231.33** 226.24-236.43	13,988 **190.27** 187.12-193.42
Standardized**	Incidence rate CI 95%	**31.48** 31.08-31.88	**20.97** 20.72-21.23	**24.46** 24.10-24.82	**17.49** 17.26-17.73
Total unadjusted	Incidence rate CI 95%	**27.39** 27.15-27.63		**22.06** 21.84-22.27	
Total standardized**	Incidence rate CI 95%	**26.23** 26.00-26.45		**20.98** 20.78-21.17	

*In ordinary wards but classified as urgent

** For rate standardization it was used as reference the entire Italian population in 2011

Table 4.3b - Incidence rate /10,000 person-year

CRITERION 3

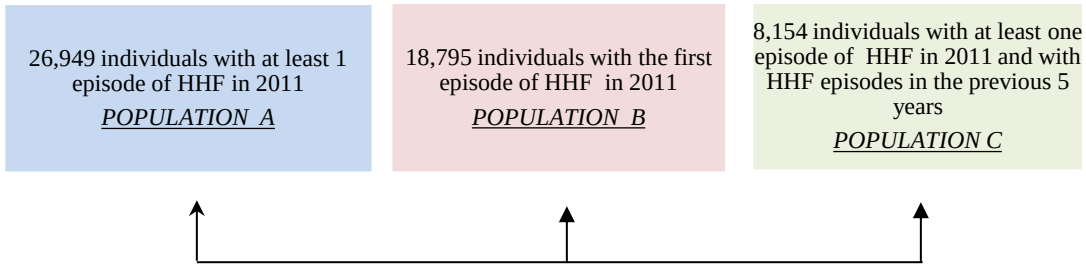
428.x, 402.01,402.11,402.91 AS MAIN DIAGNOSIS or DRG CODE 127 + symptomatic diagnosis (514.x, 518.4, 518.81,785.x,786.x) with an ICD9 code 428.x, 402.01,402.11,402.91 as secondary diagnosis

Age stratum		TOTAL HOSPITALIZATIONS		URGENT HOSPITALIZATIONS*	
		Maschi	**Femmine**	**Maschi**	**Femmine**
0-40	N° of events Incidence rate CI 95%	154 **0.39** 0.33-0.45	81 **0.21** 0.17-0.26	107 **0.27** 0.22-0.32	62 **0.16** 0.12-0.20
41-50	N° of events Incidence rate CI 95%	518 **3.30** 3.02-3.58	189 **1.24** 1.06-1.42	359 **2.29** 2.05-2.52	147 **0.97** 0.81-1.12
51-60	N° of events Incidence rate CI 95%	1,478 **12.12** 11.50-12.73	613 **4.94** 4.55-5.33	1,003 **8.22** 7.71-8.73	454 **3.66** 3.32-3.99
61-70	N° of events Incidence rate CI 95%	4,284 **41.82** 40.57-43.07	2,213 **18.90** 18.12-19.69	3,057 **28.16** 27.16-29.16	1,718 **14.67** 13.98-15.36
71-80	N° of events Incidence rate CI 95%	9,463 **116.30** 113.96-118.64	7,485 **72.52** 70.87-74.16	7,242 **88.78** 86.73-90.82	6,067 **58.75** 57.27-60.23
>80	N° of events Incidence rate CI 95%	10,119 **297.35** 291.55-303.14	17,081 **233.21** 229.71-22.59	8,538 **249.69** 244.39-254.98	14,978 **203.91** 200.65-207.18
Standardized**	Incidence rate CI 95%	**33.73** 33.31-34.14	**22.32** 22.06-22.59	**26.37** 26.00-26.74	**18.77** 18.53-19.01
Total unadjusted	Incidence rate CI 95%	**29.20** 28.95-29.45		**23.70** 23.48-23.92	
Total standardized**	Incidence rate CI 95%	**28.03** 27.80-28.25		**22.57** 22.36-22.77	

*In ordinary wards but classified as urgent

** For rate standardization it was used as reference the entire Italian population in 2011

Table 4.4 - Baseline characteristics of HHF patients (criterion 3) and medical history (hospitalization and drug treatment) of five years before index date in populations A, B and C.



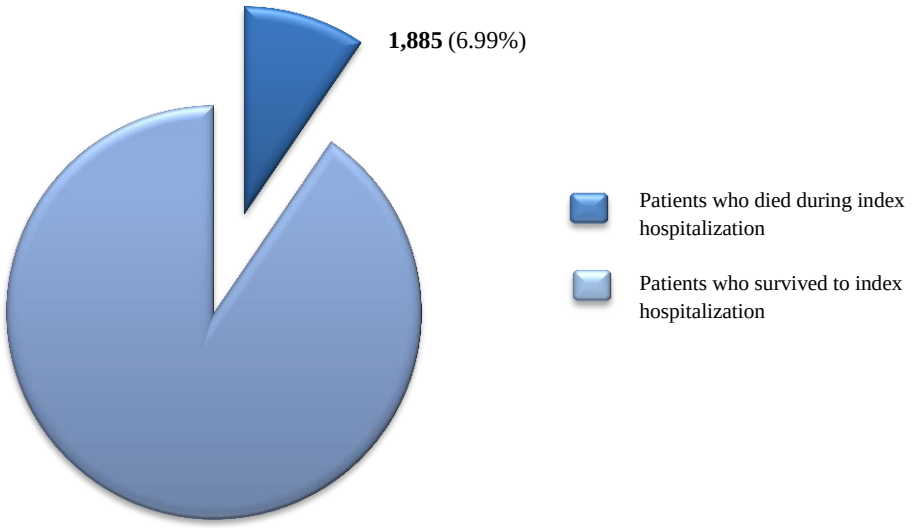
	Population A		Population B		Population C	
	Percentage /SD	Number /mean	Percentage /SD	Percentage /SD	Number /mean	Percentage /SD
Age (mean and SD)	79.00	10.39	79.03	10.63	78.93	10.02
Male	14,397	49.07	8,329	47.00	6,068	52.24
HHF hospitalization in the year before index date	5,622	19.16	-	-	5,622	48.40
HHF hospitalization in the five before index date	11,616	39.59	-	-	-	-
Any hospitalization in the year before index date	14,266	48.68	6,285	35.46	7,981	68.71
Number of hospitalization in the year before index date (mean and SD)	1.00	1.48	0.63	1.15	1.55	1.73
Number of HHF in the year before index date (mean and SD)	0.29	0.75	-	-	-	-
Medical history (5 year before index date)						
Hypertension	27,452	93.57	15,967	90.10	11,485	98.87
Hyperlipidemia	13,265	45.21	6,801	38.38	6,464	55.65
Stroke or cerebrovascular events	5,089	17.35	2,513	14.18	2,576	22.18

Peripheral Vascular Disease	394	1.34	162	0.91	232	2.00
Mitral Valve Disease	3,168	10.80	781	4.41	2,387	20.55
Myocardial infarction	9,382	31.98	3,322	18.75	6,060	52.17
Pacemaker	2,675	9.12	1,148	6.48	1,527	13.15
Implantable Cardioverter Defibrillator	1027	3.50	134	0.76	893	7.69
Atrial Fibrillation	7,942	27.07	2,539	14.33	5,403	46.51
Atrial Flutter	837	2.85	262	1.48	575	4.95
Asthma	253	0.86	119	0.67	134	1.15
Bronchitis	858	2.92	245	1.38	613	5.28
COPD	4,751	16.19	1,565	8.83	3,186	27.43
Diabetes	9,673	32.97	4,898	27.64	4,775	41.11
Nephritis, Nephrotic Syndrome, and Nephrosis	5,675	19.34	1,654	9.33	4,021	34.62
Acute glomerulonephritis	13	0.04	6	0.03	7	0.06
Nephrotic syndrome	129	0.44	53	0.30	76	0.65
Chronic glomerulonephritis	70	0.24	31	0.17	39	0.34
Nephritis and nephropathy, not specified	216	0.74	74	0.42	142	1.22
Acute renal failure	1,562	5.32	476	2.69	1,086	9.35
Chronic kidney disease	4,609	15.71	1,209	6.82	3,400	29.27
Renal failure, unspecified	457	1.56	118	0.67	339	2.92
Renal sclerosis, unspecified	14	0.05	6	0.03	8	0.07
Disorders resulting from impaired renal function	60	0.20	28	0.16	32	0.28
Small kidney of unknown cause	12	0.04	2	0.01	10	0.09
Drug history (Five years prior index hospitalization.)						
ACE inhibitors	19,579	66.74	10,446	58.94	9,133	78.62

ARBs	12,403	42.28	6,704	37.83	5,699	49.06
Beta-Blockers	17,221	58.70	8,783	49.56	8,438	72.64
Aldosterone antagonists	9,150	31.19	2,708	15.28	6,442	55.46
Digoxin	5,852	19.95	2,285	12.89	3,567	30.71
Diuretics	22,133	75.44	11,208	63.24	10,925	94.05

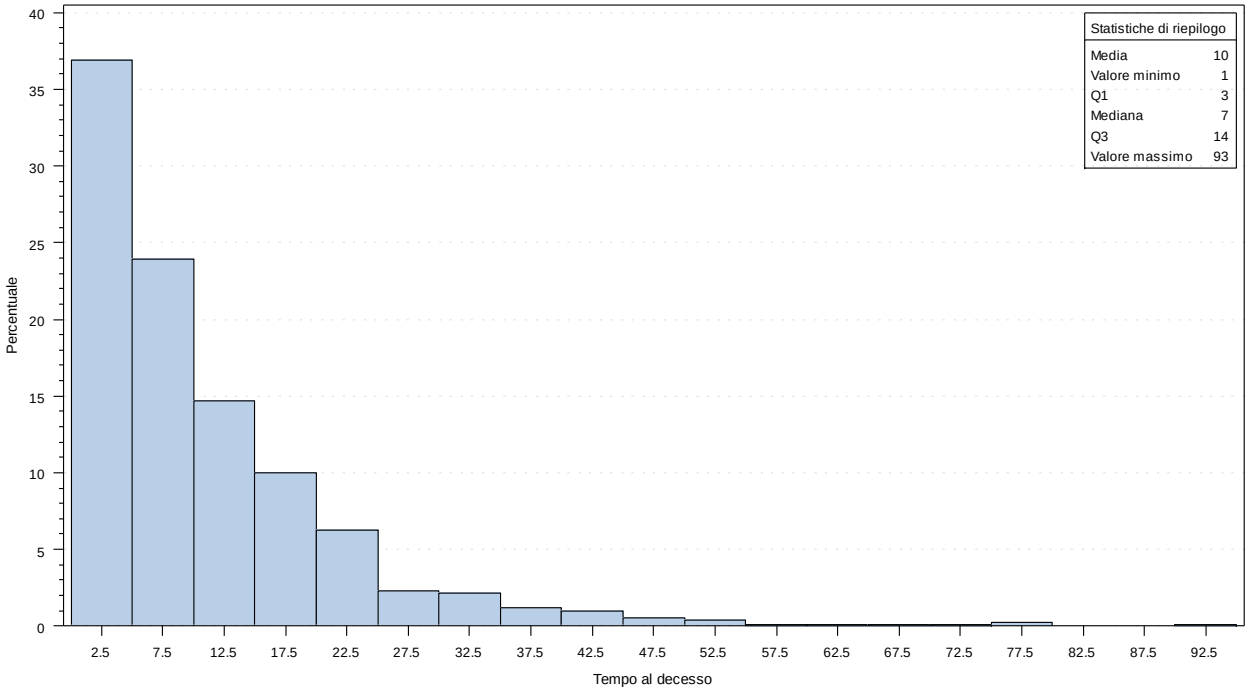
POPULATION A – CRITERION 1

Figure 4.1 - The graphic shows the proportion of patients who died during index hospitalization.



The graphics represents the proportion of patients who died during index hospitalization among all patients who had their first heart failure hospitalization.

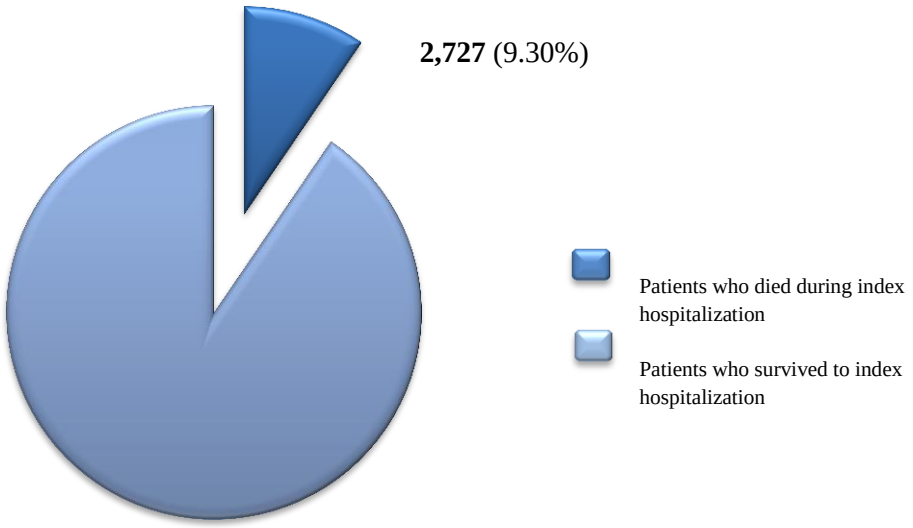
Figure 4.2 - Distribution of time to event for patients who died during index hospitalization.



The grafic represnts the distribution of the time to event (expressen in days) for patients who were newly hospitalized for heart failure in 2011 and who died during index hospitalization.

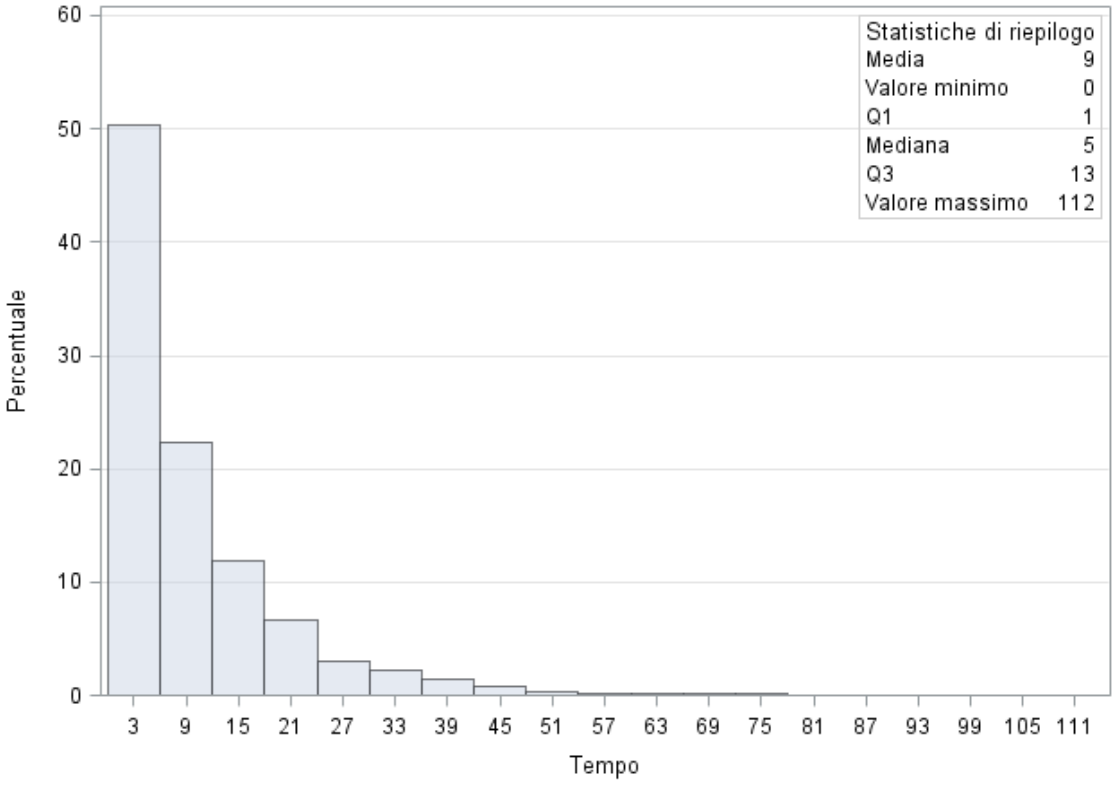
POPULATION A – CRITERION 3

Figure 4.3 - The graphic shows the proportion of patients who died during index hospitalization.



The graphics represents the proportion of patients who died during index hospitalization among all patients who had their first heart failure hospitalization.

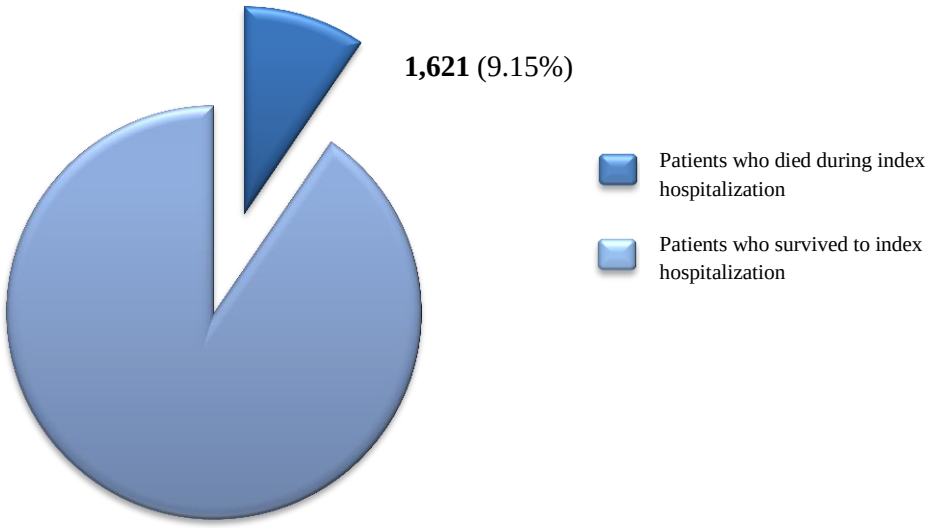
Figure 4.4 - Distribution of time to event for patients who died during index hospitalization.



The grafic represents the distribution of the time to event (expressen in days) for patients who were newly hospitalized for heart failure in 2011 and who died during index hospitalization.

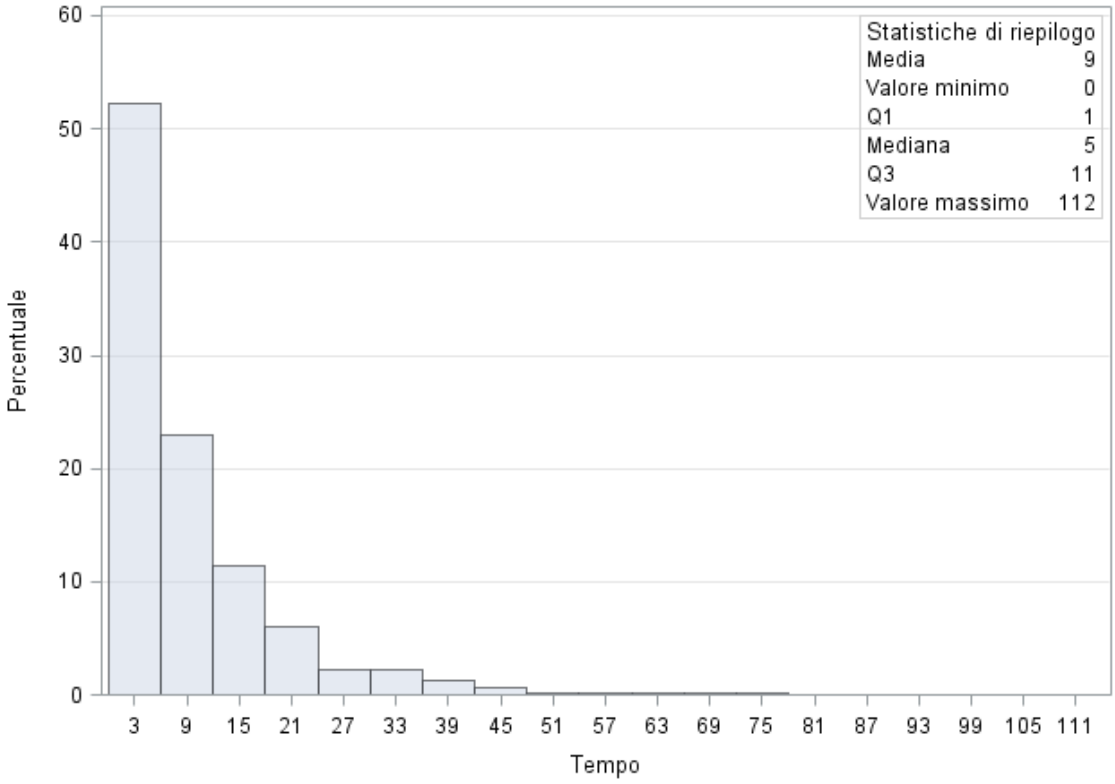
POPULATION B – CRITERION 3

Figure 4.5 - The graphic shows the proportion of patients who died during index hospitalization.



The graphics represents the proportion of patients who died during index hospitalization among all patients who had their first heart failure hospitalization.

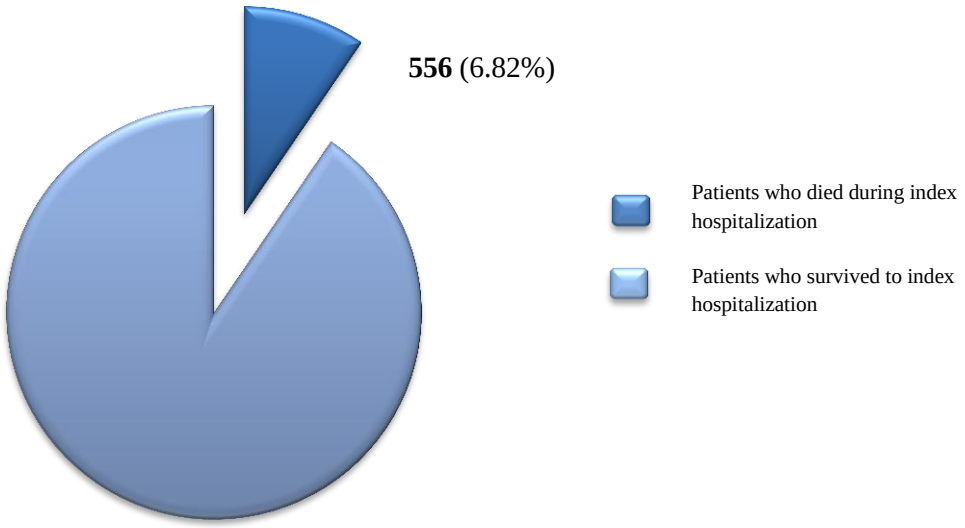
Figure 4.6– Distribution of time to event for patients who died during index hospitalization.



The grafic represnts the distribution of the time to event (expressen in days) for patients who were newly hospitalized for heart failure in 2011 and who died during index hospitalization.

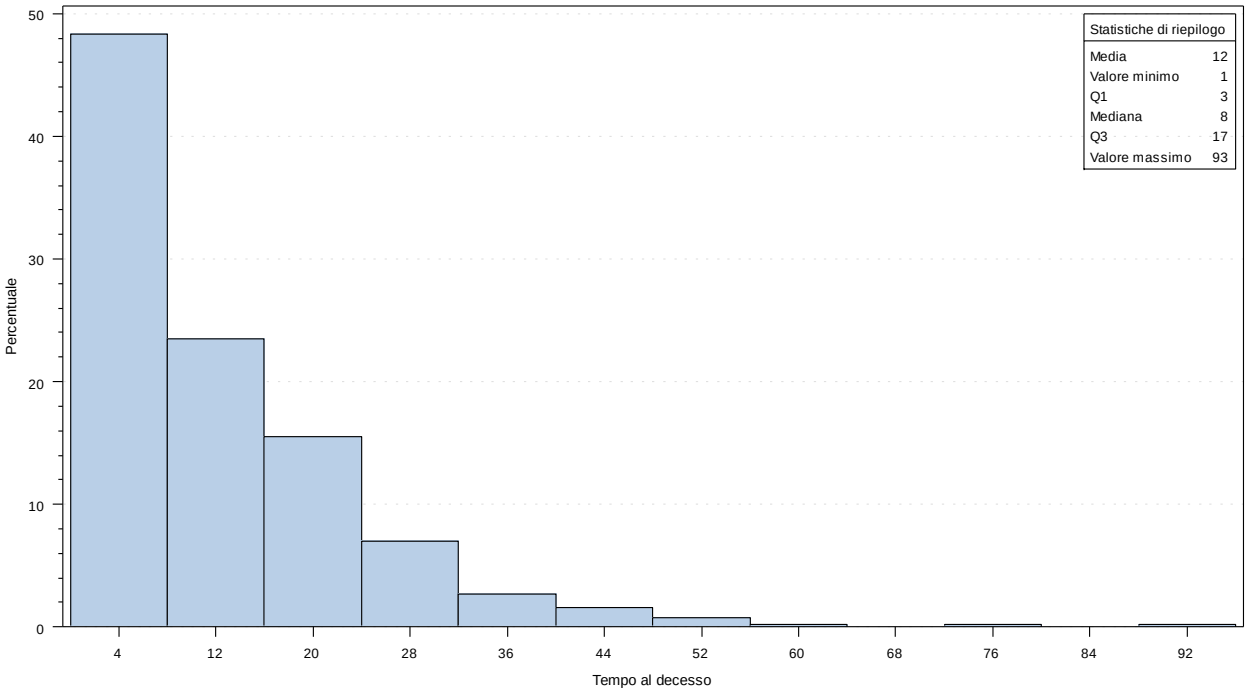
POPULATION C – CRITERION 1

Figure 4.7 - The graphic shows the proportion of patients who died during index hospitalization.



The graphics represents the proportion of patients who died during index hospitalization among all patients who had their first heart failure hospitalization.

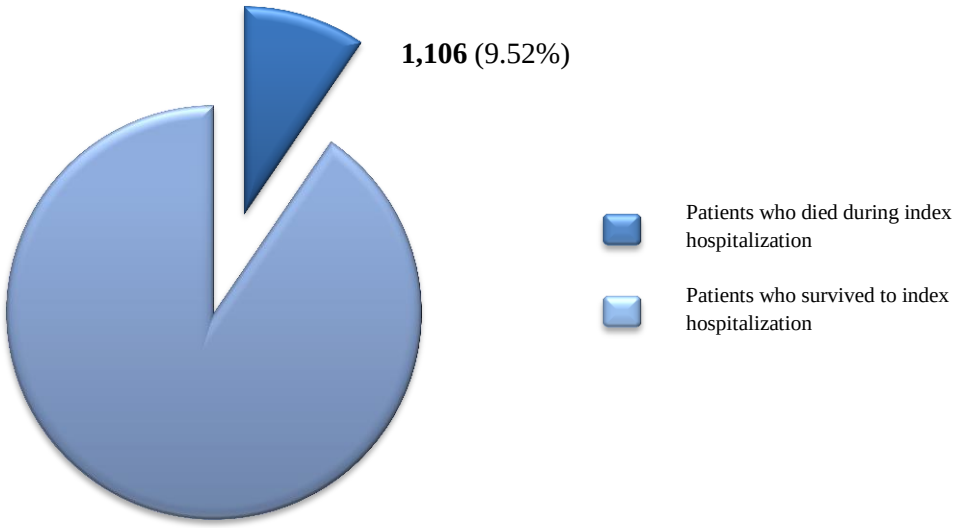
Figure 4.8 - Distribution of time to event for patients who died during index hospitalization.



The grafic represnts the distribution of the time to event (expressen in days) for patients who were newly hospitalized for heart failure in 2011 and who died during index hospitalization.

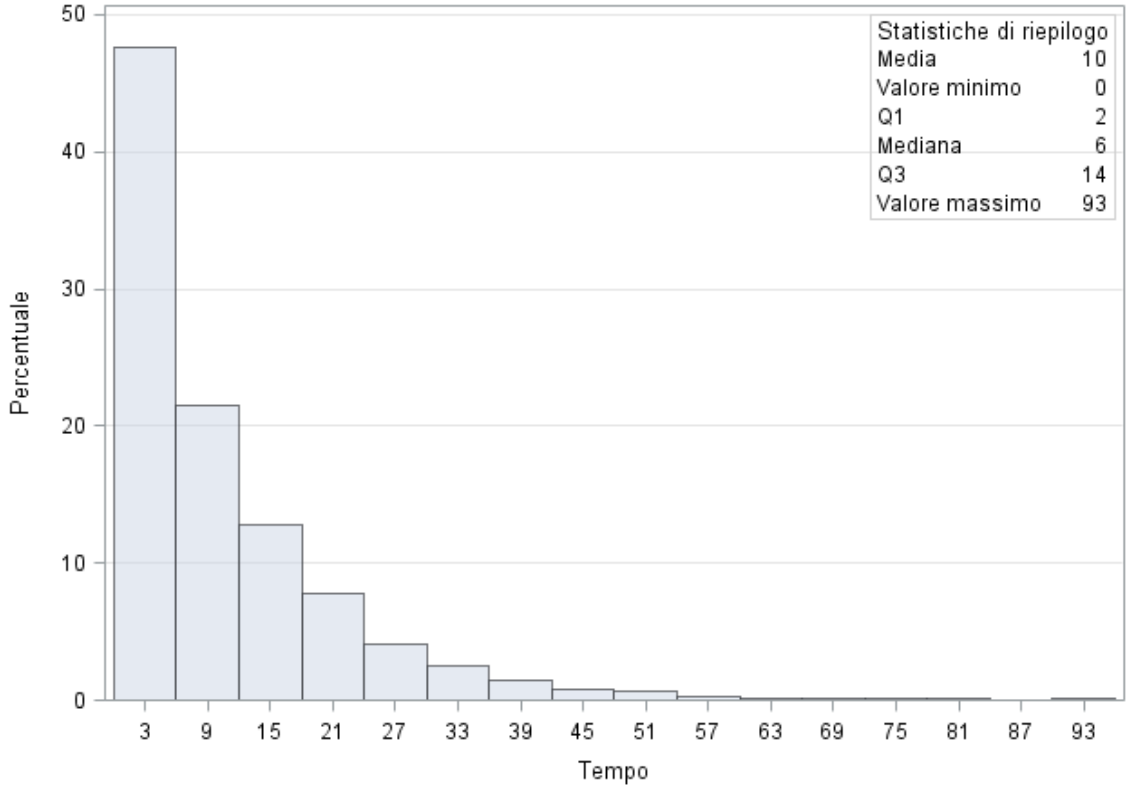
POPULATION C – CRITERION 3

Figure 4.9 - The graphic shows the proportion of patients who died during index hospitalization.



The graphics represents the proportion of patients who died during index hospitalization among all patients who had their first heart failure hospitalization.

Figure 4.10 - Distribution of time to event for patients who died during index hospitalization.



The grafic represnts the distribution of the time to event (expressen in days) for patients who were newly hospitalized for heart failure in 2011 and who died during index hospitalization.