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Heart failure in France: chronic heart failure therapeutic management and risk of cardiac decompensation in real-life setting

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THESE

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Discipline Pharmacoépidémiologie
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par Pauline BOSCO

L'INSUFFISANCE CARDIAQUE EN FRANCE

Etude de la prise en charge thérapeutique et du risque de
décompensation en vie réelle

-

HEART FAILURE IN FRANCE

*Chronic heart failure therapeutic management and risk of cardiac
decompensation in real-life setting*

Sous la direction de **Nicholas Moore**
Et la co-direction de **Sebastian Schneeweiss**

Présentée et soutenue publiquement le 13 Décembre 2019

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ABSTRACT

In France, around one million persons would be affected by heart failure (HF); there are nearly 70 000 deaths related to HF and more than 150 000 hospitalizations despite a well defined treatment management. These numbers should increase in the next years due in particular to the ageing of the population.

The objective of this work was to study the use of the pharmacological treatments indicated in HF (beta-blocker, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonist, diuretics, digoxin, ivabradine) in real-world setting and to identify the clinical or pharmacological predictors associated with a new episode of cardiac decompensation.

A first work has enabled to estimate the accuracy of French claims databases in identifying HF patients.

A second study estimated that 17 to 37% HF patients were not exposed to any HF treatment in the year following an incident HF hospitalization.

The third and fourth parts of this thesis showed that almost one fourth of HF patients was rehospitalized within the 2 years following a first hospitalization. The main clinical predictors of rehospitalization were age, high blood pressure, atrial fibrillation and diabetes. The association found between bivalent iron use and HF rehospitalization underlines the importance of the risk related to anemia or iron deficiency in the occurrence of a cardiac exacerbation episode.

These results allow to reconsider the treatment management of HF patients and highlight the need to reinforce the surveillance of patients with a highest risk of cardiac exacerbation.

Key words

Pharmacoepidemiology; Heart Failure; Claims database; Cardiac decompensation

Title

Heart failure in France: chronic heart failure therapeutic management and risk of cardiac decompensation in real-life setting

RÉSUMÉ

En France, environ un million de personnes seraient touchées par l'insuffisance cardiaque (IC) ; on recense près de 70 000 décès liés à l'IC, et plus de 150 000 hospitalisations et cela, malgré une prise en charge thérapeutique bien codifiée. Ces chiffres devraient s'accroître dans les années futures du fait notamment du vieillissement de la population.

L'objectif de ce travail était d'étudier l'utilisation des traitements pharmacologiques indiqués dans le traitement de l'IC (beta bloquant, inhibiteur de l'enzyme de conversion, anti-aldostérone, antagoniste des récepteurs à l'angiotensine II, diurétiques, digoxine, ivabradine) en situation réelle de soin, et d'identifier les facteurs cliniques ou pharmacologiques associés à la survenue d'un épisode de décompensation cardiaque.

Un premier travail a permis de mesurer la fiabilité des bases de données médico-administratives françaises pour identifier des patients IC.

Une deuxième étude a permis d'estimer que 17 à 37% de patients IC n'étaient exposés à aucun traitement de l'IC dans l'année suivant une première hospitalisation pour IC.

Les troisième et quatrième parties de cette thèse ont mis en évidence qu'environ un quart des patients IC étaient réhospitalisés dans les 2 ans suivant une première hospitalisation.

Les principaux facteurs cliniques prédictifs de cette réhospitalisation étaient l'âge, l'hypertension artérielle, la fibrillation auriculaire et le diabète. L'association retrouvée entre l'utilisation de fer bivalent et la réhospitalisation pour IC, souligne l'importance du risque lié à la présence d'une anémie ou d'une déficience en fer dans la survenue d'un épisode de décompensation cardiaque.

Ces résultats permettent de reconsidérer la prise en charge thérapeutique chez les patients IC et mettent en avant la nécessité de renforcer la surveillance des patients les plus à risque de décompenser leur IC.

Mots clés

Pharmacoépidémiologie ; Insuffisance Cardiaque ; base de données medico-administrative; décompensation cardiaque

Titre

L'insuffisance cardiaque en France : étude de la prise en charge thérapeutique et du risque de décompensation en vie réelle

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ABBREVIATIONS

| | |
|-------------------------|---|
| ACEI | Angiotensin-converting enzyme |
| ARB | Angiotensin receptor blockers |
| ATC | Anatomical Therapeutic Chemical |
| ARNI | Angiotensin receptor neprilysin inhibitor |
| BB | Beta-blocker |
| (N-T pro-) BNP | (N-Terminal pro-) B type Natriuretic Peptide |
| CCAM | <i>Classification Commune des Actes Médicaux</i> (French medical classification for clinical procedures) |
| CRT | Cardiac Resynchronization Therapy |
| ECG | Electrocardiogram |
| EGB | <i>Echantillon généraliste des bénéficiaires</i> |
| EMA | European Medicines Agency |
| ESC | European Society of Cardiology |
| HF | Heart Failure |
| HF_rEF | Heart Failure with reduced Ejection Fraction |
| HF_mEF | Heart Failure with moderate Ejection Fraction |
| HF_pEF | Heart Failure with preserved Ejection Fraction |
| HR | Hazard Ratio |
| ICD | Implantable cardioverter defibrillator |
| ICD-10 | International Classification of Disease, 10th revision |
| IV | Intravenous |
| LVAD | Left ventricular assist device |
| LVEF | Left Ventricular Ejection Fraction |
| LTD | Long-Term Disease (List of major chronic diseases with full insurance cover of all claims related to disease) |
| MRA | Antimineralocorticoid |
| MSA | <i>Mutualité Sociale Agricole</i> |
| NABM | <i>Nomenclature des Actes de Biologie Médicale</i> |
| NYHA | New York Heart Association |
| OR | Odds Ratio |
| PMSI | <i>Programme de Médicalisation des Systèmes d'information</i> |
| RCT | Randomized Clinical Trial |
| RR | Risk Ratio |
| RSI | <i>Régime Social des Indépendants</i> |
| TTE | Transthoracic Echocardiography |
| SNDS | <i>Système National des données de Santé</i> (National healthcare insurance system database) |
| 95%CI | 95% Confidence Interval |

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1. CONTEXT

1.1. Diagnosis and clinical aspects

According to the European Society of Cardiology (ESC), Heart Failure (HF) is defined as a complex clinical syndrome caused by structural or functional impairment of ventricular filling or ejection of blood and resulting in a reduced cardiac output and/ or elevated intracardiac pressures at rest or during stress [1–3]. Many causes conspire to induce HF including coronary artery disease, which is the most common cause, hypertension, diabetes, previous viral infection, alcohol abuse, chemotherapy and ‘idiopathic’ dilated cardiomyopathy (Table 1).

Table 1. Etiologies of HF from 2016 European Society of Cardiology recommendations

| DISEASED MYOCARDIUM | | |
|--|------------------------------------|--|
| Ischaemic heart disease | Myocardial scar | |
| | Myocardial stunning/hibernation | |
| | Epicardial coronary artery disease | |
| | Abnormal coronary microcirculation | |
| | Endothelial dysfunction | |
| Toxic damage | Recreational substance abuse | Alcohol, cocaine, amphetamine, anabolic steroids. |
| | Heavy metals | Copper, iron, lead, cobalt. |
| | Medications | Cytostatic drugs (e.g. anthracyclines), immunomodulating drugs (e.g. interferons monoclonal antibodies such as trastuzumab, cetuximab), antidepressant drugs, antiarrhythmics, non-steroidal anti-inflammatory drugs, anaesthetics. |
| | Radiation | |
| Immune-mediated and inflammatory damage | Related to infection | Bacteria, spirochaetes, fungi, protozoa, parasites (Chagas disease), rickettsiae, viruses (HIV/AIDS). |
| | Not related to infection | Lymphocytic/giant cell myocarditis, autoimmune diseases (e.g. Graves' disease, rheumatoid arthritis, connective tissue disorders, mainly systemic lupus erythematosus), hypersensitivity and eosinophilic myocarditis (Churg–Strauss). |
| Infiltration | Related to malignancy | Direct infiltrations and metastases. |
| | Not related to malignancy | Amyloidosis, sarcoidosis, haemochromatosis (iron), glycogen storage diseases (e.g. Pompe disease), lysosomal storage diseases (e.g. Fabry disease). |
| Metabolic derangements | Hormonal | Thyroid diseases, parathyroid diseases, acromegaly, GH deficiency, hypercortisolaemia, Conn's disease, Addison disease, diabetes, metabolic syndrome, pheochromocytoma, pathologies related to pregnancy and peripartum. |
| | Nutritional | Deficiencies in thiamine, L-carnitine, selenium, iron, phosphates, calcium, complex malnutrition (e.g. malignancy, AIDS, anorexia nervosa), obesity. |
| Genetic abnormalities | Diverse forms | HCM, DCM, LV non-compaction, ARVC, restrictive cardiomyopathy (for details see respective expert documents), muscular dystrophies and laminopathies. |
| ABNORMAL LOADING CONDITIONS | | |
| Hypertension | | |
| Valve and myocardium structural defects | Acquired | Mitral, aortic, tricuspid and pulmonary valve diseases. |
| | Congenital | Atrial and ventricular septum defects and others (for details see a respective expert document). |
| Pericardial and endomyocardial pathologies | Pericardial | Constrictive pericarditis Pericardial effusion |
| | Endomyocardial | HES, EMF, endocardial fibroelastosis. |
| High output states | | Severe anaemia, sepsis, thyrotoxicosis, Paget's disease, arteriovenous fistula, pregnancy. |
| Volume overload | | Renal failure, iatrogenic fluid overload. |
| ARRHYTHMIAS | | |
| Tachyarrhythmias | | Atrial, ventricular arrhythmias. |
| Bradyarrhythmias | | Sinus node dysfunctions, conduction disorders. |

ARVC = arrhythmogenic right ventricular cardiomyopathy; DCM = dilated cardiomyopathy; EMF = endomyocardial fibrosis; GH = growth hormone; HCM = hypertrophic cardiomyopathy; HES = hypereosinophilic syndrome; HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome; LV = left ventricular.

The current definition of HF is limited to stages at which typical clinical symptoms (dyspnea, fatigue) or signs (tachycardia, laterally displaced/broadened apical beat, orthopnoea, rales or crackles, pleural effusion, jugular venous dilatation, peripheral oedema or hepatomegalia) are apparent.

For patients presenting symptoms or signs for the first time the probability of HF should first be evaluated based on the patient's prior clinical history physical examination and resting ECG [1–3]. If at least one element is abnormal, plasma cardiac natriuretic peptides should be measured but this is not routinely done in clinical practice. A transthoracic echocardiography (TTE) remains the method of choice for establishing HF diagnosis. It provides immediate information on chamber volumes, ventricular systolic and diastolic function, wall thickness, valve function and pulmonary hypertension. A Left Ventricular Ejection Fraction (LVEF) of less than 40% confirms the diagnosis of HF with reduced Ejection Fraction (HFrEF) which was previously referred as “systolic” HF. Otherwise, HF is defined as HF with mid-range ejection fraction (HFmEF) when LVEF ranges from 40 to 49%, and as HF with preserved Ejection Fraction (HFpEF or previously referred as “diastolic” HF) when LVEF is equal to or above to 50%. These diagnoses need nevertheless to be supported by objective evidence of other cardiac functional and structural alterations underlying HF at rest or during exercise.

Differentiation between HFpEF and HFrEF patients is important given that it implies different underlying aetiologies, demographic, co-morbidities, and response to therapies [1–3].

Prevalence of HFpEF is higher in people older than 75 years and it most often concerns women with history of obesity and smoking [4, 5]. Patients with HFpEF are more likely to have cardiovascular comorbidities (such as hypertension, diabetes, atrial fibrillation, valvular disease) and non-cardiovascular comorbidities (such as renal failure, anaemia, chronic pulmonary disease, hypothyroidism, cancer, peptic ulcer and psychiatric disorders [6]. The most common causes of HFpEF are hypertensive heart disease and hypertrophic cardiomyopathy [7, 8].

In contrast, HFrEF patients are younger and mostly male. The most common causes of HFrEF are ischemic heart disease and dilated cardiomyopathy [7, 8]. Hyperlipidemia, sustained ventricular tachycardia or ventricular fibrillation, and left bundle branch block are more common in patients with HFrEF [5, 7, 8].

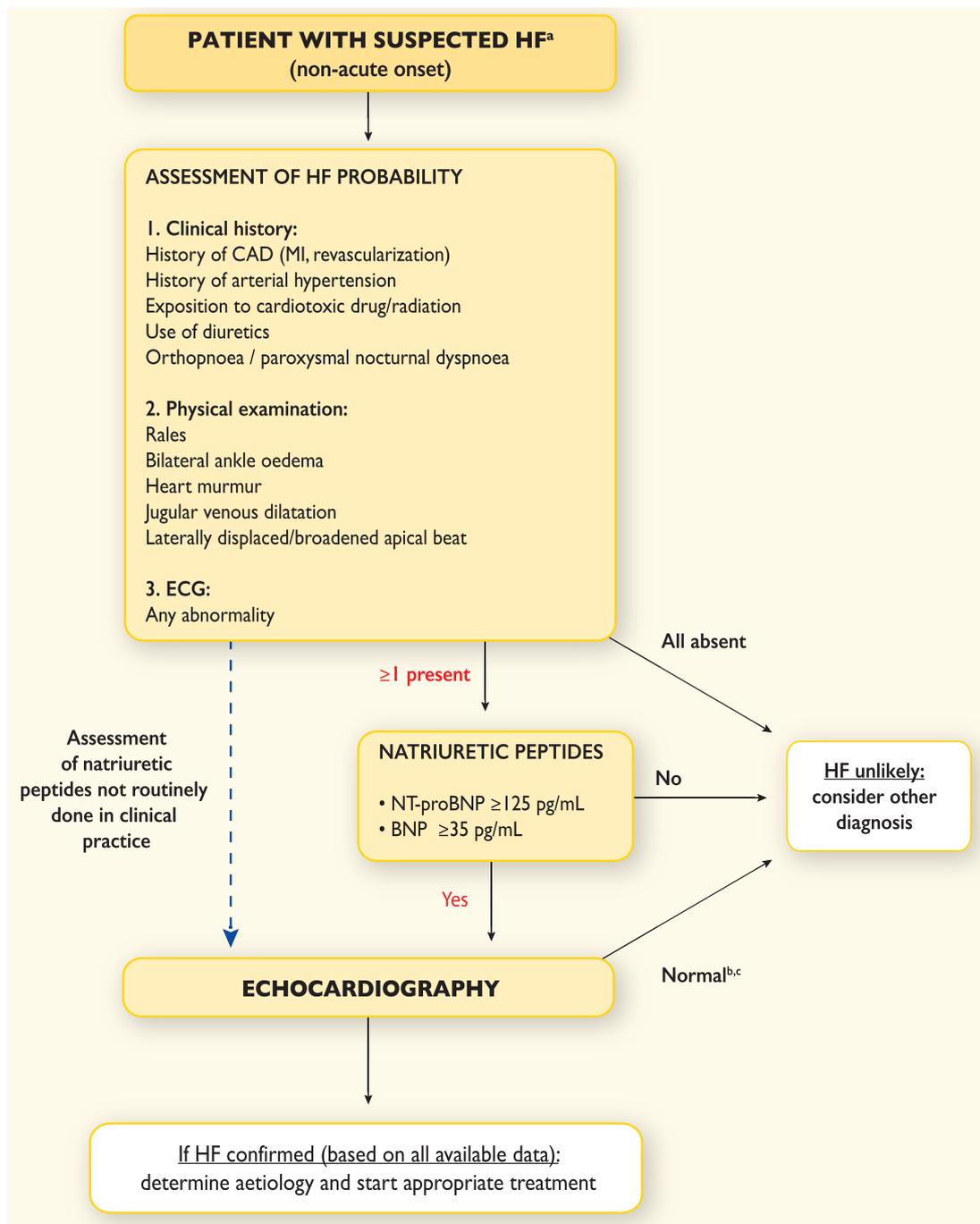


Figure 1. Diagnosis algorithm for a diagnosis of heart failure of non-acute onset, from 2016 European Society of Cardiology recommendations.

BNP=B-type Natriuretic Peptide; CAD=coronary Artery Disease; HF=Heart Failure; MI=Myocardial Infarction; NT-proBNP=N-Terminal pro-B type Natriuretic Peptide

^aPatient reporting symptoms typical of HF. ^bNormal ventricular and atrial volumes and function. ^cConsider other causes of elevated natriuretic peptides.

A grey area exists for patients without HFrEF or HFpEF. Patients with HFmrEF are recently considered as a distinct group of patients who most probably have primarily mild systolic dysfunction, but with features of diastolic dysfunction [3]. Characteristics of HFmrEF patients are generally intermediate between those of HFrEF and HFpEF patients: a high prevalence

of comorbidities as in HFpEF (i.e. hypertension, diabetes, atrial fibrillation, chronic pulmonary and kidney disease); and a high prevalence of coronary artery disease as in HFrEF, particularly in males and older patients [6]. However, this category is still subject to debate. Some authors consider that HFmEF patients do not have a unique pattern of symptoms or pathophysiology which distinguish them from patients with a preserved or a reduced EF [9] . According to them, the range of values for HFmEF patients is so narrow that delineation of the subgroup is inconsistent with the accuracy and reproducibility of the methods routinely used to assess systolic function in clinical practice. Furthermore, consistent evidence across several classes of drugs now indicates that treatments that are effective in reducing the risk of major adverse clinical outcomes in patients with an LVEF of 40% or lower are also beneficial in those with an LVEF of 41% to 50%.

1.2. Epidemiology

1.2.1. General Data on HF

HF affects from 1 to 2 % of the adult population in developed countries, up to 10% or more in people over 70 year of age [10]. In France, its prevalence was estimated in 2008 to be at 2.3% of the adult population and it reached 15.1% among people over 85 years of age [11]. The incidence of HF has substantially declined over the last decade no doubt due to the successful and significant advances in treatment strategies and improvement of primary prevention although the impact on the survival and the hospitalization remains unsatisfactory. The prevalence tends thus to increase with the ageing of the population and in the absence of apparent change in mortality [6, 12].

HF has a poor prognosis: around 30% of HF patients die in the year following a first hospitalization for HF and nearly 50% die within 5 years of diagnosis [13–15]. Despite recent inpatient care improvements leading to a reduction of in-hospital mortality and length of stay [16], re-admission within 30 days after an initial hospitalization concerns one in four patients [15, 17].

HF is also challenging by its considerable financial burden. Iterative hospitalizations contribute to increase the financial burden of the disease, which represents in Europe approximately 2% of the total health-care budget [13, 18] and in France, around €2.5 billions of the healthcare expenditure supported by the National Health Insurance System in 2013 [19].

1.2.2. Specific data on HFrEF and HFpEF

Patients with HFrEF or HFpEF represent respectively half of HF patients but these data vary depending on the definition used for HFpEF and HFrEF [6]. In the past two decades, the proportion of individuals with HFpEF increased from 38% to 54% of all the cases with HF and this proportion was considered to increase progressively with aging of the population and with the increase of the prevalence of patients with hypertension, obesity and diabetes[4]. In contrast, the proportion of patients with HFrEF is relatively stable and even tends to decrease. By 2020, HFpEF will be dominant in driving the overall HF; its expected relative prevalence will exceed 65% (8 % of persons older than 65 years of age) and that HFrEF will be 31 % [20].

Patients with HFpEF apparently have a lower risk of mortality than patients with HFrEF. However, data concerning morbidity are heterogeneous: some studies suggest a slightly higher risk in HFpEF patients while others demonstrate no difference in risk [21].

1.3. Management of heart failure

1.3.1. Main pharmacological treatment

The goals of pharmacological treatment in patients with established HF are to relieve symptoms and signs, prevent hospital admission, and improve survival.

Diuretics

Diuretics currently indicated in HF in France are loop (furosemide and bumetanide), thiazide (hydrochlorothiazide) and potassium-sparing diuretics, the latter being also called aldosterone receptor antagonists (aldosterone and spironolactone) (Figure 2).

Loop diuretics are very powerful diuretics, also used in hypertension management, which act by inhibition of the $\text{Na}^+ \text{-K}^+ / 2\text{Cl}^-$ co-transporter in the thick ascending limb of nephron loop. Inhibition of this pump can lead to a significant increase in the distal tubular concentration of sodium and therefore to a reduction of water reabsorption in the collecting duct. These mechanisms lead to both diuresis and natriuresis. These drugs also induce renal synthesis of prostaglandins, which contributes to their renal action including the increase in renal blood flow and redistribution of renal cortical blood flow. Extensively bound to plasma proteins (96%), these drugs are not filtered by the glomeruli and must be secreted in the proximal tubular to reach their target site. They undergo very little hepatic metabolism. With a quick onset of action, these short-acting drugs are used preferably in the morning (in order to avoid untimely nocturnal rising to urinate). Furosemide and bumetanide are two loop diuretics marketed in France. They may be administered orally or intravenously, but due to the low bioavailability of the furosemide, its intravenous (IV) dose must be doubled when it is administered orally (20 mg furosemide IV = 40 mg furosemide *per os* = 0,5 mg bumetanide IV = 0,5 mg bumetanide *per os*).

Thiazide diuretics are less efficacious than loop diuretics in producing diuresis and natriuresis. They act by inhibition of the $\text{Na}^+ / \text{Cl}^-$ transporter in the distal tubule. Their mechanism depends on renal prostaglandin production. These drugs are mainly used in hypertension management. Only hydrochlorothiazide has an indication in HF: it can be used in addition to loop diuretics to potentiate their effect. Hydrochlorothiazide is not hepatically metabolized but is eliminated rapidly by the kidney. It crosses the placental but not the blood-brain barrier and is excreted in breast milk.

The increased sodium delivery induced by loop and thiazide diuretics in the distal segment of the distal tubule will stimulate the aldosterone-sensitive sodium pump to increase sodium reabsorption in exchange for potassium and hydrogen ion. The increased loss of potassium and hydrogen ions can lead respectively to hypokalaemia and metabolic alkalosis. Part of the loss of potassium and hydrogen ion by loop and thiazide diuretics results from activation of the renin-angiotensin-aldosterone system that occurs because of reduced blood volume and arterial pressure. These diuretics as any diuretics may also cause hypotensive episodes and acute gout.

Aldosterone receptor antagonists or antimineralocorticoids (MRA) include spironolactone, also indicated in essential hypertension, and eplerenone. Unlike the loop and thiazide diuretics, these drugs do not produce hypokalaemia. They act by antagonizing the actions of aldosterone(s) at the distal segment of the distal tubule. This causes more sodium (and water) to pass into the collecting duct and be excreted in the urine. By inhibiting aldosterone-sensitive sodium reabsorption, less potassium and hydrogen ion are exchanged for sodium by this transporter and therefore less potassium and hydrogen are lost to the urine. MRA have a bioavailability of 70% and a hepatic metabolism. MRA side effects are the same than the ones common to other diuretics, but include also hyperkalaemia and for the non-specific aldosterone receptor antagonist (i.e. spironolactone) hormonal side effects such as gynecomastia.

The effects of loop and thiazide diuretics on mortality and morbidity have not been studied in Randomized Clinical Trials (RCTs). According to a Cochrane meta-analysis, these diuretics appear to reduce the risk of death and worsening HF in patients with chronic HF when compared with placebo, and to improve exercise capacity when compared with an active control [22, 23]. MRAs showed their efficacy in RCTs in term of mortality and HF hospitalization for patients with HFrEF and LVEF $\leq 35\%$ who remained symptomatic despite adequate treatment [24, 25].

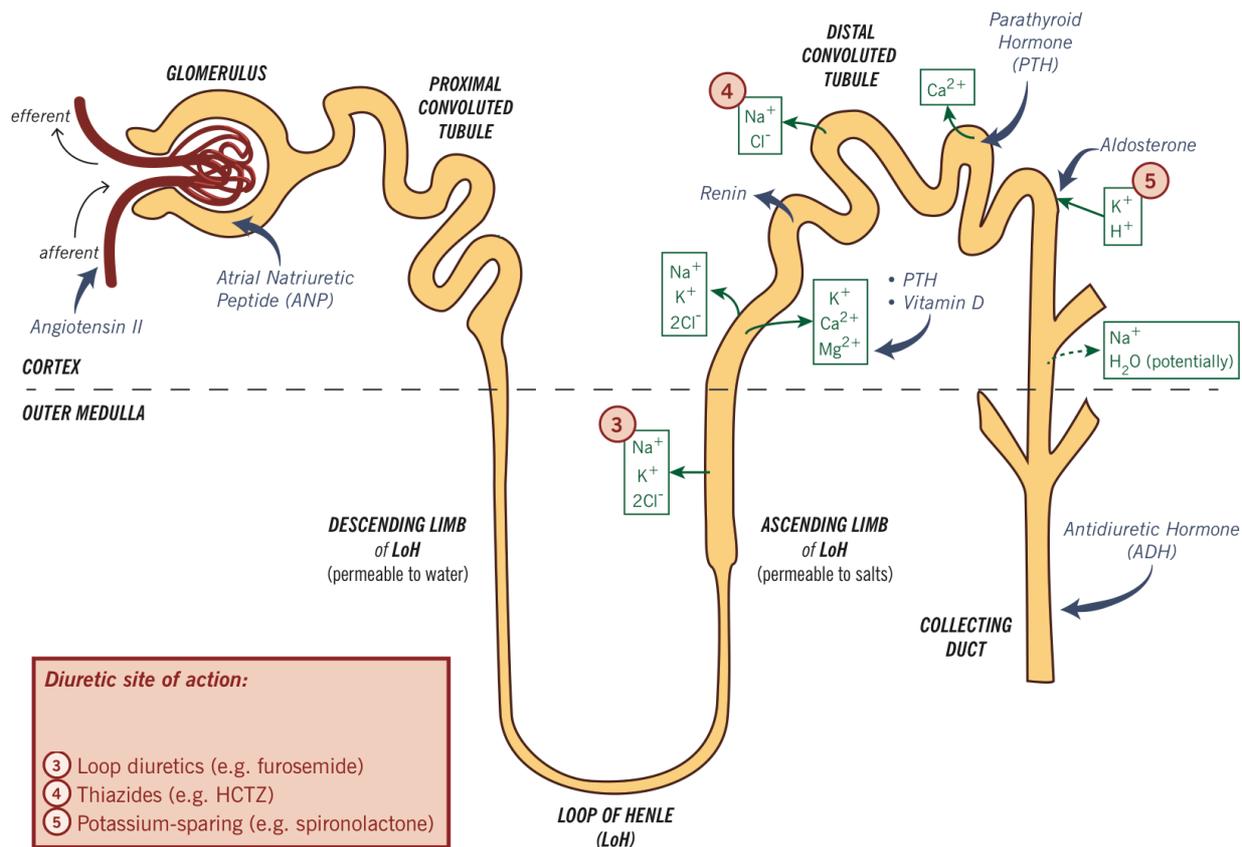


Figure 2. Mechanism of action of diuretics used in HF treatment

Beta-blockers (BB)

Four BBs have an indication in HF treatment in France: carvedilol, bisoprolol, metoprolol and nebivolol. These drugs are competitive beta-adrenoceptors antagonists, which block the binding of norepinephrine and epinephrine to these receptors. This inhibits normal sympathetic effects that act through these receptors.

The first generation BBs were non-selective, meaning that they blocked both beta-1 (β_1) and beta-2 (β_2) adrenoceptors. Second generation BBs are more cardioselective in the sense that they are relatively selective (i.e. can be lost at higher drug dose) for β_1 adrenoceptors (bisoprolol, metoprolol, nebivolol). Finally, the third generation BBs are drugs that also possess vasodilator actions through blockade of vascular alpha-adrenoceptors (carvedilol). Their efficacy in HF treatment seems to be closely linked with a decrease of cardiac output and consequently of blood pressure, and with a decrease of the deleterious cardiac remodeling induced by catecholamines.

BB pharmacokinetics are related in part to their lipid solubility. Some drugs are very lipid soluble molecules (carvedilol, metoprolol, nebivolol) while other are hydrosoluble or with an intermediate solubility (bisoprolol). Thus, carvedilol has a 25% bioavailability, high hepatic first pass metabolism and hepatic excretion. Bisoprolol has a high bioavailability (90%), 50% hepatic metabolism to an inactive metabolite and renal excretion.

BB side effects are not frequent and mostly concern bradycardia, arterial hypotension, vasoconstriction of extremities, bronchial hyperactivity in particular in asthmatic patients or hypoglycaemia in diabetic patients.

RCTs have shown that BBs reduce mortality and morbidity in symptomatic patients with HFrEF, despite adequate treatment [26–31] but they have not been tested in congested or decompensated patients. BBs should be initiated in clinically stable patients at a low dose and gradually up-titrated to the maximum tolerated dose [3]. They should be considered for rate control in patients with HFrEF and atrial fibrillation, especially in those with high rate, since no benefit on mortality hospital admissions has been reported for BBs in these patients [32].

Angiotensin-converting enzyme inhibitors (ACEI)

ACEI indicated in HF in France are: captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril and ramipril. These drugs produce vasodilation by inhibiting the formation of the vasoconstrictor angiotensin II, formed out of angiotensinogen in angiotensin I and then in angiotensin II by the consecutive actions of renin and ACE.

Most of these drugs are inactive prodrugs metabolized to an active metabolite by hepatic hydrolysis. Excretion is renal for all of the drugs except for fosinopril (50% renal - 50% hepatic) and ramipril (50% renal – 50% biliary).

ACEI also break down bradykinin (a vasodilator substance), which can contribute to their vasodilator action. The increase in bradykinin is also responsible for troublesome side effects such as dry cough and angioedema.

In RCTs, ACEIs have been shown to reduce mortality and morbidity in patients with HFrEF [33–37]. They are recommended unless contraindicated or not tolerated in all symptomatic patients.

Angiotensin receptor blockers (ARB)

ARBs indicated in HF in France are: candesartan, losartan and valsartan. These drugs are receptor antagonists that block type 1 angiotensin II receptors on blood vessels and other tissues such as the heart. These receptors are coupled to the Gq-protein and IP3 signal transduction pathway that stimulates vascular smooth muscle contraction.

Because ARBs do not inhibit ACE, they do not cause an increase in bradykinin, which contributes to the vasodilation produced by ACEI and also some of the side effects of ACEI (cough and angioedema).

In RCTs, candesartan has been shown to reduce cardiovascular mortality [38] and valsartan showed an effect on hospitalization for HF (but not on all-cause hospitalizations) in patients with HFrEF receiving background ACEIs [39].

Digoxin

Digoxin is a cardiac glycoside. It is a potent inhibitor of cellular Na⁺/K⁺-ATPase, which increases contractility of the heart (inotropy). By mechanisms that are not fully understood, digoxin has a parasympathomimetic action reducing sinoatrial firing rate (negative chronotropy) and conduction velocity of and slows electrical impulses through the atrioventricular node (negative dromotropy).

Digoxin is present predominantly as unbound to plasma proteins, which explains its quick onset of action. It is mainly stored in muscle tissue and has a large distribution volume (5 L/kg). The hepatic metabolism of digoxin is insignificant and its excretion is essentially renal in the non-metabolized form. This is the reason why haemodialysis is inefficient in case of drug intoxication induced by its relatively narrow therapeutic safety window. Excessive plasma concentrations can lead to arrhythmias, which may be life threatening.

Ivabradine

In France, ivabradine is indicated in the treatment of symptomatic stable angina but its indication was extended to HF treatment in February 2012. Ivabradine lowers heart rate by selectively inhibiting *If* channels in the heart in a concentration-dependent manner without affecting any other cardiac ionic channels (including calcium or potassium). The *If* currents are located in the sinoatrial node and are the site of all cardiac pacemaker activity.

Ivabradine binds by entering and attaching to a site on the channel pore from the intracellular side and disrupts I_f ion current flow, which prolongs diastolic depolarization, lowering heart rate. Ivabradine therefore lowers the pacemaker firing rate, consequently lowering heart rate and reducing myocardial oxygen demand.

Ivabradine's oral bioavailability is about 40%. It is bound at 70% to plasma proteins. It is extensively metabolized by oxidation in the gut and liver in active metabolites, which are equally excreted in feces and urine.

The principal side effects of ivabradine are phosphenes and less frequently, severe bradycardia.

In RCTs, ivabradine reduced the combined endpoint of mortality or hospitalization for HF in patients with symptomatic HFrEF or LVEF $\leq 35\%$, in sinus rhythm and with a heart rate ≥ 70 beats per minute (bpm) who had been hospitalized for HF within the previous 12 months, receiving treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose), an ACEI (or ARB) and an MRA [40]. The European Medicines Agency (EMA) approved ivabradine for use in Europe in patients with HFrEF with LVEF $\leq 35\%$ and in sinus rhythm with a resting heart rate ≥ 75 bpm, because in this group ivabradine conferred a survival benefit based on a retrospective subgroup analysis requested by the EMA [41].

Hydralazine and isosorbide dinitrate

Hydralazine is not marketed in France but in the United States only for self-identified black patients. Its precise mechanism of action is not fully understood. It apparently lowers blood pressure by exerting a peripheral vasodilating effect through a direct relaxation of vascular smooth muscle. In patients with HF, hydralazine decreases systemic vascular resistance and increases cardiac output.

Hydralazine is rapidly and extensively absorbed (up to 90%) from the gastrointestinal tract and undergoes extensive first-pass metabolism by genetic polymorphic acetylation, which is responsible for a threefold range of oral bioavailability. After the drug reaches the systemic circulation, it is combined with endogenous aldehydes and ketones, to form hydrazone metabolites. Hydralazine undergoes extensive hepatic metabolism; it is excreted mainly in the form of metabolites in the urine.

In a RCT, hydralazine showed a reduction of mortality and HF hospitalizations in self-identified black patients (defined as being of African descent) with HFrEF and NYHA Classes III–IV, in addition of conventional therapy [42]. This explains why hydralazine is used only in this specific population in United States.

Angiotensin receptor neprilysin inhibitor (ARNI)

ARNI is a new therapeutic class of agents acting on the renin-angiotensin-aldosterone and the neutral endopeptidase systems. The first in class is LCZ696, which is a molecule that combines the moieties of valsartan and sacubitril (neprilysin inhibitor) in a single substance. By inhibiting neprilysin, the degradation of natriuretic peptides, bradykinin and other peptides is slowed. High circulating A- and B-type natriuretic peptides exert physiologic effects countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodelling.

In comparison to the ACE inhibitor enalapril, sacubitril/valsartan appears as more efficacious in reduction the occurrence cardiovascular death or hospitalisation for HF by 20% and of all-cause mortality by 16% [43] with a comparable safety and tolerability profile [44].

This drug has been launched on the French market in May 2016.

1.3.2. Implantable devices and surgical procedures

Implantable devices are an important treatment option for some patients with HF who may be at risk of irregular heart rhythm or an abnormal muscle contraction that cannot be controlled with medications. Several types of devices are currently available: the implantable cardioverter defibrillator, the cardiac resynchronization therapy and the left ventricular assist device.

The **Implantable Cardioverter Defibrillator** (ICD) is a device implanted in the pectoral region, which can detect and automatically terminate atrial and ventricular tachyarrhythmias.

The **Cardiac Resynchronization Therapy** (CRT) or biventricular pacing is a modality of cardiac pacing used in patients with left ventricular systolic dysfunction and dyssynchronous ventricular activation that provides simultaneous or nearly simultaneous electrical activation of the left and right ventricles via stimulation of the left and right ventricles (biventricular

pacing) or left ventricle alone. This is performed by either a CRT-pacemaker or by a combined CRT-implantable cardioverter-defibrillator.

The **Left ventricular assist device (LVAD)** is a battery-operated, mechanical pump-like device that's surgically implanted. It helps maintain the pumping ability of a heart that can't effectively work on its own while waiting for a possible heart transplantation.

Heart surgery isn't frequently used to treat heart failure. It's only recommended in well-selected HF patients with specific cardiac impairments such as obstruction of coronary arteries, ischemic mitral incompetence or left ventricular aneurysm.

Finally, having a **heart transplant** is one of the last forms of treatment available to patients with heart failure. Generally it is only considered when all other forms of appropriate treatment have been tried and failed.

1.3.3. Guidelines on the HF management

Therapeutic patient education

According to the World Health Organization, the therapeutic patient education should be systematically included in the management of patients with chronic diseases. Therapeutic patient education is complementary to drug treatment and it provides the patient with useful information and skills to control his/her disease effectively [45, 46]. It includes information on:

- HF and its symptoms so patient can recognize signs of decompensation;
- HF medications (name, dose, side effects), contraindicated medications and the risks of self-medicating;
- Dietary recommendations (sodium intake limited to a maximum of 6 grams per day);
- Combating sedentary lifestyle;
- Interest in biological monitoring, vaccination, and fighting against cardiovascular risk factors (smoking, etc.).

Patient education is an important component in heart failure care but educational therapeutic interventions still require further optimization. Despite the fact that many patients received education and perceived information about heart failure as important, they had low levels of knowledge and lacked a clear understanding of why they had developed heart failure, how it was defined and what relevant self-care behavior should be performed [46].

Pharmacological management of patients with HFrEF

For patients with HFrEF, the pharmacological management is essentially based on the use of neuro-hormonal antagonists (BBs, ACEI and MRAs) unless contraindication or bad tolerance. They are commonly used in conjunction with a diuretic given to relieve the symptoms and signs of congestion (2,3,22) .

A BB and an ACE inhibitor should both be started as soon as possible after diagnosis of HFrEF (Figures 3 and 4). An ARB should be used as an alternative to ACEI for patients who do not tolerate these drugs, or for patients with persisting symptoms despite treatment with an ACE inhibitor and a BB and unable to tolerate a MRA. A MRA is recommended in all symptomatic HFrEF patients despite an adequately conducted treatment (ACEI or ARB, and BB) with a LVEF $\leq 35\%$. Eplerenone must be preferred to spironolactone in patients with recent myocardial infarction [47]. Since 2016, the European Society of Cardiology recommends to use ARB to replace ACEI, when HFrEF patients remain symptomatic despite appropriate treatment. To date, the French guidelines have not been updated to integrate this recommendation.

If despite these treatments, patient has resistant symptoms, digoxin may be proposed. According to European Society of Cardiology guidelines, ivabradine may also be considered as an alternative to digoxin in patients in sinus rhythm with an EF $\leq 35\%$, a heart rate remaining ≥ 70 b.p.m., and persisting symptoms or in patients who do not tolerate BB [2, 3].

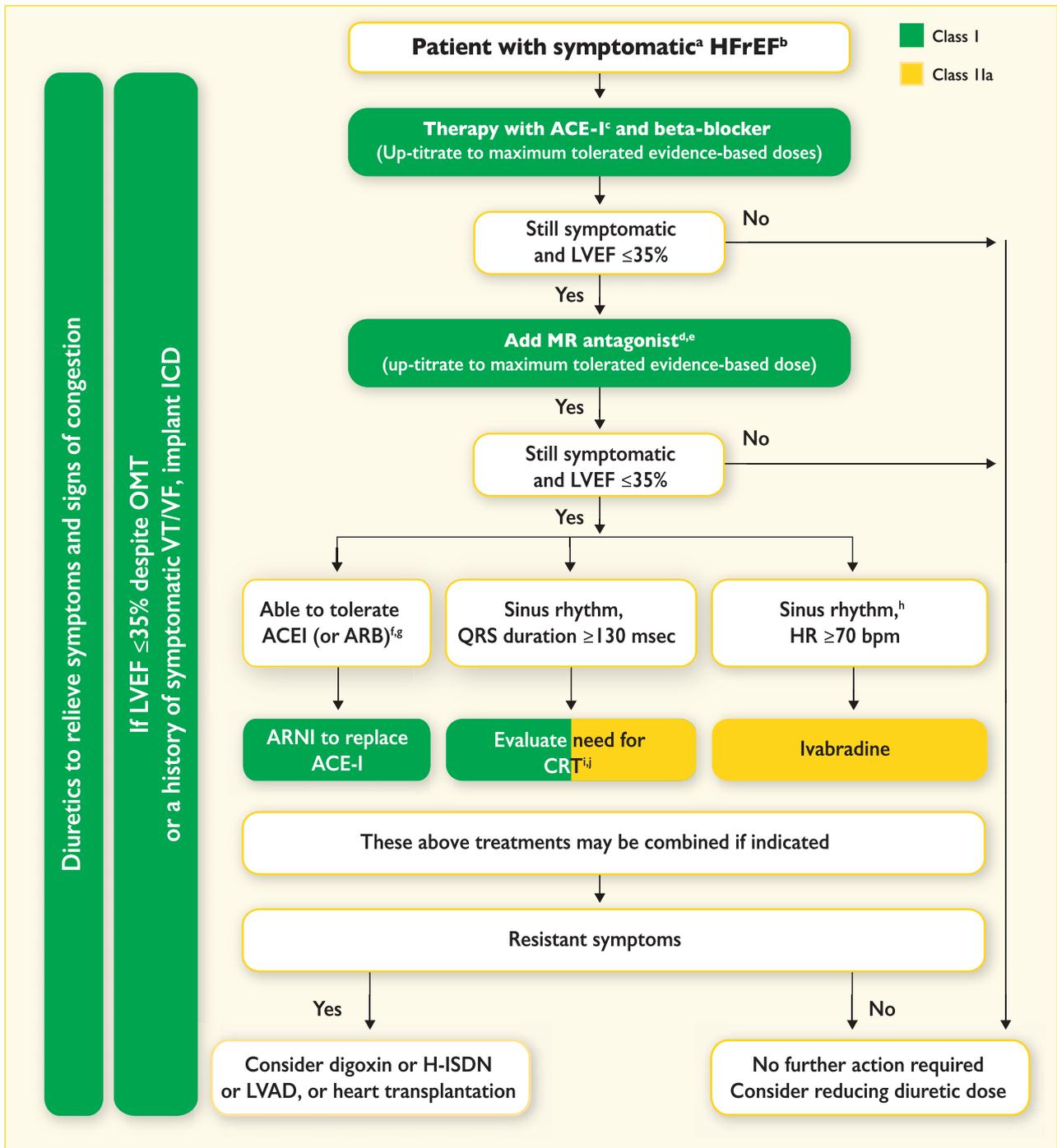


Figure 3. Therapeutic algorithm for a patient with a symptomatic heart failure with reduced ejection fraction from 2016 European Society of Cardiology guidelines

HFrEF=Heart Failure with reduced Ejection Fraction; LVEF=Left Ventricular Ejection Fraction; ACEI=Angiotensin Converting Enzym Inhibitor; BB=Beta-Blockers; ARB=Angiotensin II Receptor Blockers

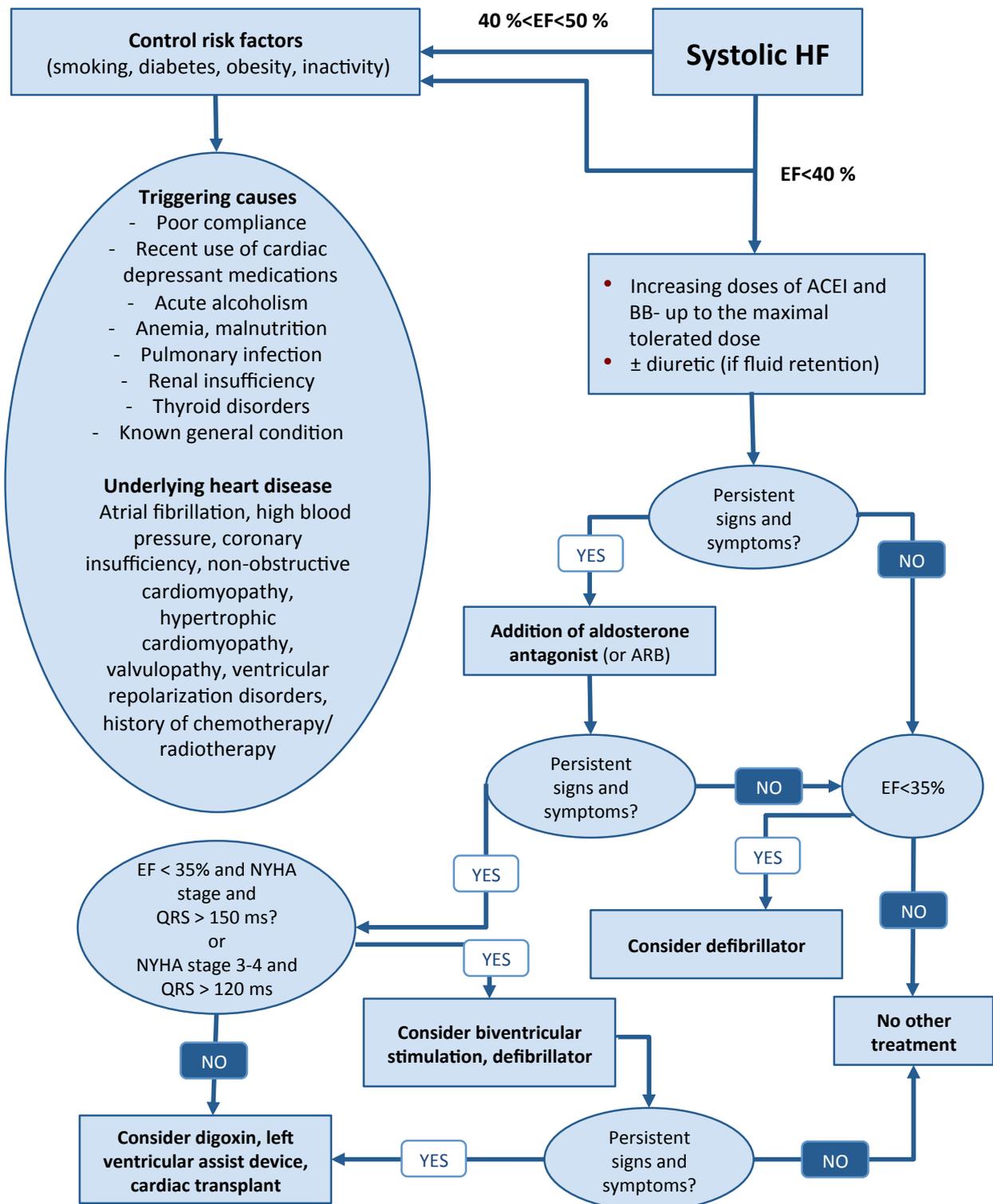


Figure 4. Therapeutic algorithm for a patient with systolic heart failure, adapted from the 2014 French guidelines (*Haute Autorité de Santé, "Guide du Parcours de soin -Insuffisance Cardiaque", Juin 2014*).

HF=Heart Failure; EF=Ejection Fraction; ACEI=Angiotensin Converting Enzym Inhibitor; BB=Beta-Blockers; ARB=Angiotensine II Receptor Blockers

Pharmacological management of patients with HFpEF

No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HFpEF. Diuretics are used to control sodium and water retention and relieve breathlessness and oedema as in HFrEF. 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. Two very small studies have shown that the heart rate-limiting calcium-channel blocker (CCB) verapamil may improve exercise capacity and symptoms in these patients. Rate-limiting CCBs may also be useful for ventricular rate control in patients with atrial fibrillation and in the treatment of hypertension and myocardial ischaemia (which is not the case in patients with HFrEF where their negative inotropic action can be dangerous). BBs may also be used to control the ventricular rate in patients with HFPEF and atrial fibrillation.

Indication for implantable devices

Advanced HF represents a stage of the disease where patients' symptoms are resistant to therapy and they remain very limited and at risk of lethal ventricular arrhythmia [2, 3]. In patients who meet the appropriate criteria, device therapy may offer substantial benefit.

ICD (Implantable Cardioverter Defibrillator) is recommended in patients with symptomatic HF and an EF $\leq 35\%$ despite ≥ 3 months of treatment with optimal pharmacological therapy, who are expected to survive for >1 year with good functional status, to reduce the risk of sudden death in HF patients who have had severe ventricular dysrhythmia

CRT (Cardiac Resynchronization Therapy) is primarily aimed at patients with advanced HF (NYHA functional Class III and ambulatory Class IV) who have a EF $\leq 35\%$ who are in sinus rhythm, and have a QRS duration above 120 ms.

1.4. Application of pharmacoepidemiology in HF

1.4.1. Definition of pharmacoepidemiology

Pharmacoepidemiology is the study of pharmacological effect of medication and of their utilization in real world clinical practice. Just as the term implies, pharmacoepidemiology combines clinical pharmacology with epidemiology [48]. Pharmacology is the study of the effects of medications in people. It includes pharmacokinetics and pharmacodynamics of a patient to predict the drug effect on a patient. Epidemiology is the study of the distribution and determinants of diseases in populations. By combining the interest of pharmacology and epidemiology, a pharmacoepidemiologist applies epidemiology principles to study the effects of medications in human populations.

Pharmacoepidemiology therefore focused on the use and on the undesired and beneficial effects of medications after they have been launched on the market, to promote their appropriate use and thus improve public health. This discipline involves studies on drug use patterns (i.e. pattern of drug prescribing, the appropriateness of use, medication adherence and persistence patterns, and the identification of predictors for medication use) and drug effects (i.e. effectiveness or adverse effects). Assessing medication use in real world practice is all the most important given the differences observed between the target population (population for which the medication is intended) and the reached population after marketing (population who really uses the medication). In real world clinical practice, patients who use the medication are more numerous, older, sicker, more treated with higher dose and with other drugs than in clinical trials.

Pharmacoepidemiology studies are thus essential to supplement clinical trial data. They benefit from the methodology developed in general epidemiology (i.e. cohort study, case-control studies) and may further develop them for applications of methodologies unique to pharmacoepidemiology.

1.4.2. Data sources

Large health care databases are often used to address research questions within pharmacoepidemiology. These databases can generally be divided into two types; the medical records databases and the administrative claims databases [49]. In general, data in medical records databases are recorded as part of the process of clinical outpatient care, while administrative databases record information as a by-product of financial transactions.

Because administrative databases are derived from pharmacy billing records, they reflect with high reliability patients' drugs consumption. They include complete healthcare data from several consecutive years, making them an excellent resource for the study of large, demographically diverse multicenter cohorts at a fraction of the time and costs of other conventional data sources [50]. However, they do not contain information on potentially important confounding variables such as smoking status, alcohol use and body mass index contrary to medical records databases.

In France, the nationwide healthcare insurance system database is the SNDS (*Système National des Données de Santé*), which covers 98.8% of the French population [51]. Most of the subjects (76% of inhabitants in France in 2015) are insured under the general scheme, which mainly covers salaried employees of the private sector and their dependents. The remaining individuals are insured under other minor schemes representing specific populations such as civil servants and students, liberal professions and their dependents, farmers and agricultural workers. It provides pseudonymized information on all reimbursed medical and paramedical encounters, drugs claims, hospital admissions and procedures - except for psychiatric hospitals and rehabilitation centers which are only available in the SNDS database -, registration for Long Term Disease (LTD) and date of death. All these data are linked to create a longitudinal record of outpatient health encounters, hospital diagnoses and drug dispensing. Hospital and LTD diagnoses are coded according to the International Classification of Disease – 10th revision (ICD-10) and medications are identified according to their Anatomical and Therapeutic Classification (ATC). The EGB database (*Echantillon Généraliste de Bénéficiaires*) is a representative permanent 1/97th sample of the SNDS, using a unique national pseudonymised identifier. It contains the same data as in the SNDS except data from psychiatric hospitals and rehabilitation centers. It was an interesting alternative to SNDS for studying diseases with high prevalence or with frequent outcomes since the delay to access its data were significantly shorter than for the full SNDS.

1.4.3. Data on HF treatment in real-life setting

Thanks to the successful and significant advances in treatment strategies and improvement of primary prevention, the management of HF has considerably improved over the last decade, leading to a reduction of HF incidence. However, the morbidity-mortality is still high among HF patients [6, 12], suggesting that HF medications that have proven to be effective

in clinical randomized trial, do not always have optimal utilization in a real-world setting. Pharmacoepidemiology studies are thus legitimate to better investigate HF treatments in order to understand how and for whom these treatments are really used. Several pharmacoepidemiology studies have already been conducted on HF medications to assess in real-world setting how these drugs are used and what are their effects. A non-exhaustive review of these studies has been published in the *Journal of Pharmacology Research*¹.

Drug use

In pharmacoepidemiology studies, drug use may be assessed by two parameters: adherence, which refers to whether a patient takes a prescribed medication according to schedule and persistence, which indicates whether a patient stays on therapy or the time from initiation to discontinuation of therapy [52].

According to the literature, persistence to HF treatment was estimated as high with treatment dosages below recommended dosages [53–55]. However, most of these observational studies have described the HF treatment persistence on patients who initiated their treatment just after a HF hospitalization [56–61] and not in patients who initiated therapy as outpatients.

Treatment adherence has been reported as not optimal, as with many other chronic treatment. Two large reviews focused on this issue. DiMatteo reviewed articles published within a 50 year-period of research (1948–1998), and showed that 79.4% (95%CI: 77.4%; 81.4%) of patients with chronic HF are adherent to their treatment(s), and that they were more adherent to their pharmacological prescriptions than to lifestyle modifications (i.e. health behavior, appointment-keeping and diet) [62]. The review of van der Walet al. included more recent articles (1988–2003) and assessed the extent to which a persons' behavior (in terms of taking medication, following diet or executing life style changes) coincides with the clinical prescription (i.e. compliance) [63]. The estimated compliance rates varied considerably from 10% to 99% although most studies described compliance rates of approximately 70%. In both of these reviews, authors pointed out that medication adherence estimates were greatly variable, as its appraisal was affected by different definitions and measures of adherence, which have evolved over the years.

¹ Salvo F, Bezin J, **Bosco-Levy P**, et al. Pharmacological treatments of cardiovascular diseases: Evidence from real-life studies. *Pharmacol Res.* 2017 Apr 118:43-52

Effects

Most of the recent comparative effectiveness studies of HF treatments, focused on head-to-head comparisons between the effects of the different drugs of a single pharmacological class.

The protective effect of BBs on mortality or hospitalization has been confirmed in real-life in CHF patients, regardless of whether ejection fraction (EF) was preserved (EF \geq 50%: Hazard Ratio, HR 0.68, 95%CI 0.52; 0.94) or reduced (EF $<$ 50%, HR 0.52, 95%CI 0.41; 0.69) [64]. Evidence suggests that there is no substantial difference in term of all-cause mortality and/or hospitalization among the individual BBs [65–67]; moreover, there is no difference between BBs listed in guidelines of HF (carvedilol, metoprolol, and bisoprolol), and the non-listed ones (atenolol, propranolol, and timolol) [68]. A head-to-head study, that compared metoprolol and carvedilol, showed that patients with HF of ischemic origin (mainly HF_rEF) had a better survival on metoprolol (HR 0.54, 95%CI 0.43; 0.66), whereas patients with other HF types had better survival when treated with carvedilol (HR 0.85, 95%CI 0.78; 0.91) [69].

The effectiveness of the different ACE-Is seems globally comparable [70, 71] and no difference was found either among the different ARBs [74]. One study by Pilote et al. suggested a better profile of ramipril in comparison to enalapril or captopril in terms of mortality [72]; their results were also consistent when using fixed-exposure model (enalapril vs. ramipril: HR 1.36, 95%CI 1.30; 1.41; captopril vs. ramipril: HR 1.61, 95%CI 1.50; 1.74) and time-dependent model (enalapril vs. ramipril: HR 1.10, 95%CI 1.04; 1.16; captopril vs. ramipril: HR 1.13 95%CI 1.01; 1.26).

The benefits of spironolactone (the most frequently used MRA) in real-life use seem to be lower outside the clinical trial setting; recent studies suggested that spironolactone does not reduce all-cause mortality [73, 74], especially in patients with not advanced HF (NYHA class I–II) [74]. A study on real life tolerability of spironolactone confirmed an extremely high risk of severe hyperkalemia (HR 3.46, 95%CI 1.97; 6.06) but did not show any significant association with acute kidney injury (HR 0.66, 95%CI 0.42; 1.05) [76]. Data from a clinical trial of eplerenone are promising [75], and its mineralocorticoid receptor selectivity should offers major advantages comparing to spironolactone in term of frequency of potential adverse events such as sexual side effects [76]. However, no real-life data on eplerenone are currently available.

Recent evidence supports the idea that digoxin is useful to reduce symptoms of HF, but did not influence hard outcomes such as mortality. A systematic review and meta-analysis of randomized clinical trials and observational studies indicated that digoxin led to a small but significant reduction in all cause hospital admission (risk ratio, RR 0.92, 95%CI 0.89; 0.95), and to lower rates of admissions related to cardiovascular disease and heart failure. This study suggests that the neutral effect on mortality comes from studies with a lower risk of biases [77].

1.5. Research hypothesis and objectives

As previously reported, HF is a significant public health burden as a result of the important morbidity-mortality that it causes and the substantial costs that it generates. It appeared that this situation persists despite the development in the last 35 years of effective treatment. This raises questions as to the actual management of HF in clinical practice, which may affect the apparent efficacy of the pharmacological treatment observed in clinical trials. Most of pharmacoepidemiology studies that we reviewed showed effectiveness of pharmacological treatment broadly comparable with efficacy reported by clinical trials. This implies that other real-life parameters may influence HF management and its prognosis. These parameters need to be identified and studied to help health care decision makers to develop public health measures that will optimize the management of HF patients.

The general objective of this work was thus to study, the pharmacological management of chronic HF and the risk of developing cardiac decompensation – whether induced or not by medications – among HF patients in France in real world.

We considered that an appropriate approach to address this objective was to use the representative permanent 1/97th sample (EGB) of the French nationwide claim database, the SNDS, which contain the overall information on reimbursed healthcare consumption for HF patients.

A **first step** was to find a method to identify HF patients in the database and then validate it to ensure an accurate identification of our source population and the corresponding outcome. Because data related to out-patient diagnoses are not available in the database and treatments used for HF are not specific to the disease, we considered that it would be more relevant to use in-patient discharge diagnoses to identify HF patients. We thus conducted a validation study to estimate the diagnostic performance of the HF discharge codes from the French hospital discharge diagnoses database (PMSI) by combining data from electronic health records and those of the PMSI.

A **second step** was to quantify the proportion of HF patients treated with each of the main treatments indicated in chronic HF after a first HF hospitalization, and to describe their use pattern in the first year following this incident hospitalization in real world setting. This step was essential to get a precise idea of the number of HF patients who were really concerned

with these treatments in the early stage of the disease and to understand if the modalities of use of these treatments over time may explain the dilution of their expected effectiveness. We thus conducted a cohort study to describe the treatment initiation patterns and the subsequent treatment changes among HF patients, in the first year following an incident hospitalization for HF in real-world setting, using the random permanent sample of the French nationwide claim database, the EGB.

Third and fourth steps were to identify the predictors of cardiac decompensation after a first HF hospitalization, whether they were inherent to the patient characteristics or related to extrinsic factors such as pharmacological treatments. These steps were crucial to understand what are the factors among those identified, which could be managed by specialists from the onset of the disease, to decrease cardiac decompensation and thus HF mortality. To meet this objective, we conducted two studies using EGB data:

1. The first study was a cohort study aiming to identify the early and long-term clinical predictors of cardiac decompensation, managed either in hospital or at home in the 2 years following a first HF hospitalization;
2. The second study was a nested case-control study, which sought to identify the main drugs potentially responsible for HF readmission within the 2 years following a first HF hospitalization.

Results of these studies have been reported in 4 scientific articles submitted to peer-reviewed international journals. The 4 articles are presented in the present thesis: two articles have been accepted for publication, 1 article has been submitted and 1 manuscript is ready for submission. These findings have also been presented at national and international symposiums. These oral and poster presentations are listed in Appendice 1. Simultaneously, two non-exhaustive literature reviews have been published in an international journal and in the chapter of the ESC textbook.

2. VALIDATION OF HOSPITAL DISCHARGE DIAGNOSIS CODES RELATED TO HEART FAILURE

2.1. Rational and methodological considerations

When pharmacoepidemiology studies are conducted in claim databases, study population and outcomes should be accurately identified and selected to avoid any misleading results. Errors in these parameters lead to distorted estimates of effect and to underpowered or biased tests [78]. In the French nationwide claims database (SNDS or EGB), diagnoses from hospital discharge, outpatient consultation or LTD, medical procedures, treatments or care pathway may be used to this end, but only if they are specifically related to the study disease. When it comes to identify HF patients, only the use of diagnosis codes seems appropriate. To date, there is no treatment, medical procedure or care pathway specific of HF. For instance, medications that HF patients receive are also indicated for underlying diseases such as hypertension or ischemic heart disease.

Diagnosis codes that may be used for identification of HF patients are however limited to those of hospitalization discharge diagnoses and LTD, since outpatient consultation diagnoses are not available in the SNDS database. The ICD-10 diagnosis codes related to HF are the codes I50.x.

Before using hospital discharge coding for disease identification, it is necessary to understand how the French hospital discharge diagnoses database (PMSI) is organized [79]. In this database, three fields may be populated: the primary diagnosis, the linked diagnosis and the associated diagnosis. Primary diagnosis is the health problem that motivated the admission to the hospital. It is determined at hospital discharge. For patients hospitalized successively in several medical units, the primary diagnosis of the hospitalization, as well as all medical unit primary diagnoses, are generally taken into account to define the occurrence of an outcome in a pharmacoepidemiology study. A linked diagnosis can exist only if the primary diagnosis is a care procedure with a code Z of the ICD-10 classification (e.g. chemotherapy session) for a chronic or LTD disease. It indicates the disease at the origin of the care procedure. As primary diagnosis, linked diagnosis is taken into account to define the occurrence of an outcome in a pharmacoepidemiology study. Associated diagnoses are specified if they represent specific healthcare resources. They are mainly underlying chronic diseases. Associated diagnoses can be used to define chronic diseases but are generally not taken into account to define the occurrence of an outcome (many being false positives for the studied outcome).

LTD database also contains diagnosis codes but only for the so-called “exonerated” long-term diseases. It includes severe or chronic diseases, which require a long-term treatment or expensive therapeutic strategies and for which patients may benefit from copayment exempt status for all medical procedures and services related to these diseases. It concerns one of the 30 listed diseases (i.e. stroke, HF, diabetes) or an off-list chronic disease which requires an expensive treatment for more than 6 months (i.e. Paget’s disease) or multiple diseases resulting in a disabling condition and which requires long-term treatment for more than 6 months (i.e. generalized osteoarthritis with walking disorders and urinary incontinence) [80]. In pharmacoepidemiology studies, LTD codes are mostly used to define comorbidities but not the occurrence of an outcome. They can be used to identify a study population but in addition to a specific treatment or medical procedure.

To refine the selection of HF subjects, we thought to develop an algorithm for HF identification associating the HF discharge diagnosis codes to codes related to echocardiography or BNP. However, the identification of echocardiography was not systematically coded during a cardiology visit, as the levels of reimbursement may be similar for a visit with or without echocardiography and BNP could not be identified when they were performed in a public hospital, as they are not reimbursed individually. We thus only focus on HF diagnosis codes available either through discharge hospital summary or LTD for the identification of HF patients.

The best approach to assess viability and reliability of a coding is thus to compare data from hospital discharge summary to clinical data of patients’ medical record referring to the same hospital stay. Multiple studies were conducted on this issue in several countries [81–86], but none had yet been done in France.

2.2. Objective

The objective of this work, which was conducted in two university hospitals (Bordeaux and Paris), was to assess the diagnostic accuracy of the HF ICD-10 codes I50.x, by comparing discharge diagnostic codes to medical diagnoses registered in patient medical records. This study also provided all information necessary to accurately identify HF patients for future studies in the SNDS using hospital discharge coding.

Results of this study have been published in 2018 in *Pharmacoepidemiology and Drug Safety*.

2.3. Article

2.3.1. Reference

Bosco-Lévy P, Duret S, Picard F, Dos Santos P, Puymirat E, Gilleron V, Blin P, Chatellier G, Looten V, Moore N. *Diagnostic accuracy of the International Classification of Diseases, Tenth Revision, codes of heart failure in an administrative database. Pharmacoepidemiol Drug Saf. 2019 Feb;28(2):194-200.*

2.3.2. Abstract

Purpose: Heart failure (HF) is a common, serious and still poorly known illness, which might benefit from studies in claims databases. However, to provide reliable estimates, HF patients must be adequately identified. This validation study aimed to estimate the diagnostic accuracy of the ICD10 codes I50.x, heart failure, in the French hospital discharge diagnoses database.

Methods: This study was performed in two university hospitals, comparing recorded discharge diagnoses and electronic health records (EHR). Patients with discharge ICD10 codes I50.x were randomly selected. Their EHR were reviewed to classify HF diagnosis as definite, potential or miscoded based on the European Society of Cardiology diagnostic criteria, from which the codes' positive predictive value (PPV) was computed.

To estimate sensitivity, patients with an EHR HF diagnosis were identified, and the presence of the I50.x codes was sought for in the hospital discharge database.

Results: Two hundred possible cases of HF were selected from the hospital discharge database and 229 patients with a HF diagnosis were identified from the EHR. The PPV of I50.x codes was 60.5% (95 %CI 53.7 to 67.3%) for definite HF and 88.0% (95%CI 83.5 to 92.5) for definite/potential HF. The sensitivity of I50.x codes was 64.2% (95%CI 58.0 to 70.4%). PPV results were similar in both hospitals; sensitivity depended on the source of EHR: departments of cardiology had a higher sensitivity than non-specialized wards.

Conclusions: Diagnosis codes I50.x in discharge summary databases accurately identify patients with HF but fail to capture some of them.

Diagnostic accuracy of the *International Classification of Diseases, Tenth Revision*, codes of heart failure in an administrative database

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Abstract

Purpose: Heart failure (HF) is a common, serious, and still poorly known illness, which might benefit from studies in claims databases. However, to provide reliable estimates, HF patients must be adequately identified. This validation study aimed to estimate the diagnostic accuracy of the *International Classification of Diseases, Tenth Revision* (ICD-10) codes I50.x, heart failure, in the French hospital discharge diagnoses database.

Methods: This study was performed in two university hospitals, comparing recorded discharge diagnoses and electronic health records (EHRs). Patients with discharge ICD-10 codes I50.x were randomly selected. Their EHRs were reviewed to classify HF diagnosis as definite, potential, or miscoded based on the European Society of Cardiology diagnostic criteria, from which the codes' positive predictive value (PPV) was computed. To estimate sensitivity, patients with an EHR HF diagnosis were identified, and the presence of the I50.x codes was sought for in the hospital discharge database.

Results: Two hundred possible cases of HF were selected from the hospital discharge database, and 229 patients with an HF diagnosis were identified from the EHR. The PPV of I50.x codes was 60.5% (95% CI, 53.7%-67.3%) for definite HF and 88.0% (95% CI, 83.5%-92.5%) for definite/potential HF. The sensitivity of I50.x codes was 64.2% (95% CI, 58.0%-70.4%). PPV results were similar in both hospitals; sensitivity depended on the source of EHR: Departments of cardiology had a higher sensitivity than had nonspecialized wards.

Conclusions: Diagnosis codes I50.x in discharge summary databases accurately identify patients with HF but fail to capture some of them.

KEYWORDS

accuracy, heart failure, ICD-10, pharmacoepidemiology, positive predictive value, sensitivity, validation study

1 | INTRODUCTION

Heart failure (HF) is a serious and increasingly common illness worldwide. HF is described as a syndromic disease consisting of a

constellation of unspecific symptoms (lower-limb oedema, dyspnoea, or tachycardia) and is caused by various aetiologies leading in all cases to cardiac dysfunction.^{1,2} HF affects from 1% to 2% of the adult population in developed countries, up to 10% or more in people over

70 years of age.³ In France, its prevalence was estimated in 2008 to be at 2.3% of the adult population, and it reached 15.1% among people over 85 years of age.⁴ HF has a poor prognosis: A quarter of HF patients are rehospitalized within 30 days after an initial hospitalization, and nearly 50% of HF patients die within 5 years of diagnosis.^{5,6} Iterative hospitalizations contribute to increase the financial burden of the disease, which represents in Europe approximately 2% of the total health care budget.^{5,7} The incidence of HF declined substantially over the last decade no doubt due to the successful and significant advances in treatment strategies and improvement of primary prevention, but this contrasts with no apparent change in mortality.⁸ A better understanding of the management of HF patients in real life and their compliance to the various treatments strategies may help to explain the persistence of high mortality rate.

Claims databases have become excellent resources for the study of diseases and outcomes in real life since they provide large, demographically diverse, multicentre cohorts at a fraction of the time and cost of other conventional data sources.⁹ In France, the SNDS (*Système National des Données de Santé*) contains complete health care data for over 99% the French population.¹⁰ Its 1/97th sample, the EGB (*Echantillon Généraliste de Bénéficiaires*), provides a representative and unselected sample of the whole population. These databases are commonly used to study disease epidemiology, drug utilization, and comparative effectiveness, including for HF.^{11,12} Diseases may be identified using *International Classification of Diseases, Tenth Revision (ICD-10)* codes from the national hospital discharge database (*Programme de médicalisation des systèmes d'information [PMSI]*), included in the SNDS. However, the validity and reliability of this coding need to be verified against clinical diagnostic data, which has not yet been done in France.

As a consequence, we did a validation study, the objective of which was to assess the diagnostic accuracy of the HF ICD-10 codes I50.x in SNDS, by comparing discharge diagnostic codes to medical diagnoses registered in patient medical records.

2 | METHOD

2.1 | Study design and data source

This validation study compared data from the French hospital discharge database PMSI, to medical records. PMSI contains administrative and medical data on all hospital admissions in any private or public health care institutions in France. Hospitalization diagnoses are coded in ICD-10 as principal diagnosis or secondary diagnoses; medical, surgical, and other procedures are also included, as are expensive medications for instance. They can be obtained separately for each hospital.

Medical records include, for each patient, hospital discharge summaries and the results of biological, radiographic, or echocardiographic examinations performed during the hospital stay. These records are available through the hospital electronic medical records system, or from clinical data warehouses.^{13,14}

Two cohorts of patients were selected: one from PMSI, on the ICD-10 discharge codes I50.x, which was compared with the electronic health record (EHR) to calculate the code's positive predictive value

KEY POINTS

- This study assessed the diagnostic accuracy of the discharge heart failure ICD-10 codes I50.x, in the French National Healthcare Database.
- The positive predictive value of these codes was around 90%, thereby ensuring a reliable identification of patients with a diagnosis of heart failure.
- However, the sensitivity remained modest; these codes need to be implemented in a heart failure algorithm to measure disease incidence accurately.

(PPV); a second cohort was identified from the discharge diagnosis of HF, and the corresponding ICD-10 codes in PMSI were examined to measure the codes' sensitivity.

2.2 | Study populations

Patients were over 40 years of age, hospitalized between 1 January and 31 December 2014 in two large French academic hospital centres, in Bordeaux (CHU de Bordeaux, CHUB) and in Paris (Hopital Européen Georges Pompidou, HEGP).

2.2.1 | Selection and classification of patients from the PMSI population

The PMSI population included a random selection of patients from each hospital, identified by the presence of an ICD-10 hospital discharge code I50.x in any diagnosis position (I50.0 Congestive HF; I50.1 Left ventricular failure; I50.9 HF, unspecified).

For each patient, PMSI records were then linked to the corresponding EHR, using the patient individual identity number and the date of the hospital stay. If a subject had multiple hospital stays with I50.x discharge codes in the studied year, only the first visit was considered in the analysis. Two experienced physicians reviewed patients' EHR in order to classify them as definite HF, potential HF, or miscoded, using the European Society of Cardiology (ESC) definition as gold standard.¹ A patient was considered as having a definite HF if, in addition to the presence of an HF diagnosis or an equivalent term established and validated by independent cardiologists (Appendix S1), other more "objective" diagnostic criteria were found in the EHR. "Objective" diagnostic criteria included structural or functional cardiac abnormalities detected on echocardiography as defined by the ESC and/or a brain natriuretic peptide (BNP) elevation over 400 pg/mL. The patients with only an HF term with no other "objective" diagnostic criteria were classified as potential. In the cases where a patient had hospital discharge codes of HF in secondary diagnosis position with no HF term mentioned in the corresponding EHR, the review board also looked at hospital discharge summaries of prior admissions within the previous 12 months to identify the presence of an HF term. Otherwise, patients with hospital discharge codes of HF and with no HF diagnosis in the corresponding EHR were defined as miscoded.

For the determination of PPV, patients were considered as true positives if HF diagnosis was definite or potential and as false-positive cases if they were miscoded.

2.2.2 | Selection and coding of patients from the EHR population

The EHR population, used to determine sensitivity of hospital coding, included patients with a medical diagnosis or history of HF. At the HEGP in Paris, patients were randomly selected using a full-text search of HF terms (Appendix S1) through the I2B2 data warehouse.^{13,14} Two independent physicians then reviewed their EHR. In CHUB, patients were selected by the hospital cardiologists from their department database's active patient lists. For each included HF patient, EHRs were then linked to the corresponding hospital discharge ICD-10 codes using the patient individual identity number and the date of the hospital stay. If a subject had multiple hospital discharge summaries in the studied year, only the first visit was considered in the analysis. To measure sensitivity, patients were considered as true positive if at least one I50.x discharge code was found in any diagnosis position for the corresponding hospital stay. Otherwise, patients were defined as false negatives for the code. An independent expert committee of cardiologists reviewed each hospital discharge summary to achieve consensus.

2.3 | Statistical methods

Patients' characteristics were described according to the data source from which patients were identified.

Diagnostic accuracy of the hospital discharge codes I50.x was estimated by the calculation of positive predictive value (PPV) sensitivity (Se) and their corresponding 95% confidence intervals (95% CI). The formulae for PPV and Se were, respectively,

$$\text{PPV} = \text{TP}/(\text{TP} + \text{FP}),$$

$$\text{Se} = \text{TP}/(\text{TP} + \text{FN}),$$

where TP and FP are true and false positives, respectively, and FN is false negative. The number of subjects needed to estimate a Se value or a PPV of at least 85% with an accuracy of 5% and an α risk of 5% was 204 patients for each cohort.

Analyses were performed by SAS software version 9.4 (SAS Institute Inc; Cary, North Carolina).

2.4 | Sensitivity analysis

As quality of ICD coding might change over time and might depend on the hospital departments involved in coding, two sensitivity analyses were performed. A first analysis was conducted to assess spatial variability of coding quality by estimating the PPV of the I50.x codes among the cardiology, internal medicine, and geriatric medicine departments known to manage a higher number of HF patients than the other departments. A second analysis was conducted to assess temporal variability of coding quality by comparing the PPV of the

I50.x codes among patients selected in 2009 from the PMSI, to that of patients selected in 2014.

3 | RESULTS

3.1 | Description of the study populations

Overall, we identified 200 possible HF cases with a discharge summary code I50.x in the PMSI population and 229 patients with an HF diagnosis from the EHR (Figure 1). Several differences were found in patient characteristics between the two datasets particularly concerning mean age and some cardiovascular co-morbidities (Table 1). For each population, patient characteristics were also described stratified by the hospital centre (Appendix S2).

3.2 | PPV of the HF discharge codes I50.x

Among the 200 patients from the PMSI population, the HF code was indicated as main diagnosis code in 36.5% and as secondary code in 63.5% (Table 2). From their EHR information, 121 (60.5%) were classified as having a definite HF, 55 (27.5%) as having a potential HF, and 24 (12.0%) as having a miscoded diagnosis of HF. The PPV of the HF discharge codes I50.x was thus 60.5% (95% CI, 53.7%-67.3%) when the HF diagnosis was definite and 88.0% (95% CI, 83.5%-92.5%) when the HF diagnosis was definite or potential. The PPV of the HF discharge codes I50.x was higher when the code was the main diagnosis for both definite HF (69.9%; 95% CI, 59.3%-80.4%) and definite/potential HF (95.9%; 95% CI, 88.5%-99.1%).

3.3 | Sensitivity of the HF discharge codes I50.x

Among the 229 HF patients from the EHR population, 64.2% (95% CI, 58.0%-70.4%) had a code I50.x in the corresponding hospital discharge summary. Among the 82 HF patients with no code I50.x in the corresponding hospital discharge summary, 68% had a code related to an underlying cardiac disease. The most frequent cardiac codes were those related to ischaemic heart disease (48.7%; ICD-10 codes I20.x-I25.x), to dilated cardiomyopathy (31.7%; ICD-10 code I42.0), to atrial fibrillation (25.6%; ICD-10 codes I48.x), to valvular disease (15.9%; ICD-10 codes I05.x-I08.x, I34.x-I37.x), or to another cardiac rhythm disorder (11.0%; ICD-10 codes I44.x, I47.x, I49.x). Four patients were common to both PMSI and EHR populations: one in Bordeaux and three in Paris.

3.4 | Sensitivity analyses

To assess spatial variability of coding quality, PPV was estimated within the predefined hospital departments (Table 3). As patients could have been admitted to different care units during their hospital stay, only the care units that reported I50.x codes in the corresponding discharge summary were considered in the analysis. The review of EHR gave a PPV of 87% in Bordeaux and a PPV of 89% in Paris. By department, PPV was 90.7% in cardiology, 90% in internal medicine, 80% in geriatric medicine, and 88% for the other departments. To assess temporal variability of

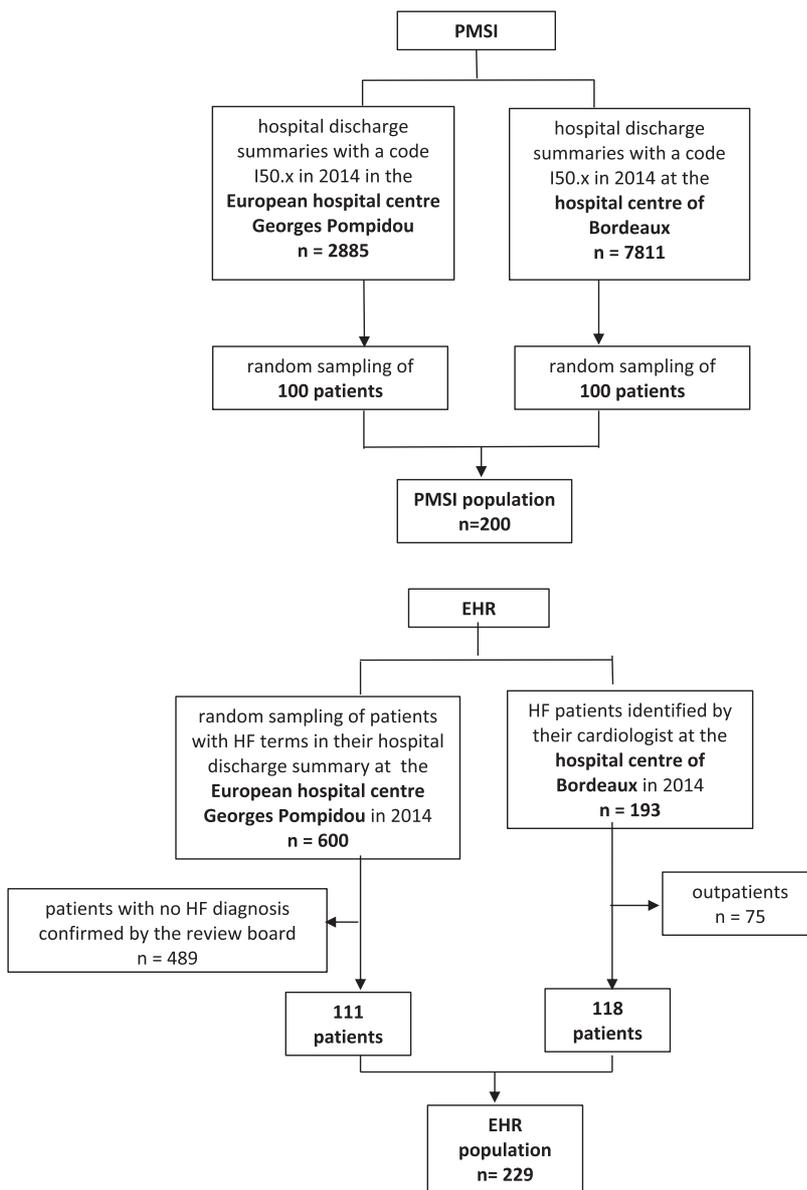


FIGURE 1 Flow chart of the two study cohorts identified in two hospital centres from the French hospital discharge database, the PMSI (*Programme de médicalisation des systèmes d'information*) or from the electronic health records (EHRs)

coding quality, 200 patients who were hospitalized in 2009 with I50.x codes at discharge were included. Among them, 149 (74.5%) had a potential or definite HF according to their EHR.

4 | DISCUSSION

This present study examined the diagnostic accuracy of the HF ICD-10 codes I50.x in France, by comparing HF discharge diagnostic codes with HF medical diagnoses registered in the patients' EHR. It suggests that the I50.x codes are accurate enough to identify HF patients, but failed to capture the exhaustiveness of HF inpatients. To our knowledge, no validation study of the I50.x codes has been undertaken and published so far in France.

In the present study, the PPV of the I50.x codes was globally satisfactory: 88% of the I50.x patients were classified as having a definite or potential HF according to the ESC definition. The validity of the

codes I50.x was markedly higher when the codes were specified as main diagnosis and higher in patients treated in internal medicine and cardiology compared with geriatrics. This finding was consistent with studies in other settings, for which the PPV varied from 76 to 93%.¹⁵⁻²⁰ As expected, the highest values were found in studies which focused on specific populations where prevalence of HF may be higher, such as patients with acute myocardial infarction,²¹ or patients from emergency departments.¹⁵ The present study also found a tendency to increasing PPV over time. This could reflect the progressive improvement of coding in France stimulated by a national quality control drive with regular coding audits and the publication of clear diagnostic criteria by professional bodies (ESC).

The present study reported a rather modest sensitivity (64.2%). This proportion may even be slightly overestimated as an important part of HF patients (51.5%) was identified by cardiologists, who have greater experience in coding cardiac diseases than other physicians. One explanation may be the use by clinicians of codes related to an

TABLE 1 Patients' characteristics at baseline in the ICD-10 population or the population identified from the electronic health records (EHR)

| | PMSI n = 200 | EHR n = 229 |
|-----------------------------------|-----------------|----------------|
| Sociodemographic characteristics | | |
| Age, y (±SD) | 76.8 (±13.4) | 69.1 (±11.5) |
| Female, n (%) | 90 (45.0) | 66 (28.8) |
| Inclusion site | | |
| CHU de Bordeaux | 100 | 118 |
| Hopital Européen Georges Pompidou | 100 | 111 |
| Co-morbidities | | |
| Cardiovascular | | |
| Arterial hypertension | 105 (52.5) | 113 (49.3) |
| Ischaemic heart disease | 70 (35.0) | 122 (53.3) |
| Atrial fibrillation | 64 (32.0) | 83 (36.2) |
| Valvular disease | 47 (23.5) | 70 (30.6) |
| Dilated cardiomyopathy | 27 (13.5) | 67 (29.3) |
| Hypertrophic cardiomyopathy | 8 (4.0) | 7 (3.1) |
| Hypertensive heart disease | 10 (5.0) | 5 (2.2) |
| Dyslipidaemia | 50 (25.0) | 97 (42.4) |
| Diabetes | 39 (19.5) | 55 (24.0) |
| Noncardiovascular | | |
| Chronic kidney disease | 53 (26.5) | 49 (21.4) |
| Tumour | 31 (15.5) | 23 (10.0) |
| Respiratory insufficiency | 30 (15.0) | 5 (2.2) |
| COPD | 14 (7.0) | 22 (9.6) |
| Peripheral artery disease | 10 (5.0) | 19 (8.3) |
| Thyroid disease | 9 (4.5) | 13 (5.7) |
| Biological parameters | | |
| Type B natriuretic peptide, n (%) | | |
| 100-400 pg/mL | NA | 63 (27.5) |
| >400 pg/mL | NA | 69 (30.1) |
| Echocardiography | | |
| LVEF < 50%, n (%) | NA | 149 (65.1) |

Abbreviations: BNP, type B natriuretic peptide; COPD, chronic obstructive pulmonary disease; HNT, arterial hypertension; LVEF, left ventricular ejection fraction; NA, non-available.

underlying cause of HF such as ischaemic heart disease, dilated cardiomyopathy, atrial fibrillation, or valvular disease instead of specific HF codes. This may also reflect coding practice: An HF might not be coded by clinicians for patients with stable HF that did not require specific treatment during the hospitalization. The variability of

TABLE 2 Positive predictive value (PPV) of the codes I50.x and its corresponding 95% confidence interval (95% CI) according to the code position and the HF diagnosis classification, in patients from the ICD-10 population (n = 200)

| I50.x code position | Definite HF | | | Definite/Potential HF | | |
|-------------------------------|-------------|------|-----------|-----------------------|------|-----------|
| | n | PPV | 95% CI | n | PPV | 95% CI |
| Main diagnosis (n = 73) | 51 | 69.9 | 59.3-80.4 | 70 | 95.9 | 88.5-99.1 |
| Secondary diagnosis (n = 127) | 70 | 55.1 | 46.5-63.8 | 106 | 83.5 | 77.0-89.9 |
| Any field (n = 200) | 121 | 60.5 | 53.7-67.3 | 176 | 88.0 | 83.5-92.5 |

Abbreviations: 95% CI, 95% confidence interval; HF, heart failure; PPV, positive predictive value.

TABLE 3 Positive predictive value (PPV) of the codes I50.x and its corresponding 95% confidence interval (95% CI) estimated according to the hospital department responsible for coding and to the coding year, in patients from the ICD-10 population

| | n | PPV | 95% CI |
|-----------------------------------|-----|------|-----------|
| Hospital centre | | | |
| CHU de Bordeaux | 87 | 87.0 | 80.4-93.6 |
| Hopital Européen Georges Pompidou | 89 | 89.0 | 81.1-94.4 |
| Coding hospital department | | | |
| Cardiology (n = 108) | 98 | 90.7 | 85.3-96.2 |
| Geriatric medicine (n = 10) | 8 | 80.0 | 44.4-97.5 |
| Internal medicine (n = 21) | 17 | 90.0 | 58.1-94.6 |
| Other departments (n = 83) | 73 | 88.0 | 81.0-95.0 |
| Coding year | | | |
| 2009 (n = 200) | 149 | 74.5 | 68.5-80.5 |
| 2014 (n = 200) | 176 | 88.0 | 83.5-92.5 |

Abbreviations: HF, heart failure; PPV, positive predictive value; 95% CI, 95% confidence interval.

sensitivity estimates for HF coding in the literature ranged from 29% to 86%.¹⁵⁻²⁰ The considerable heterogeneity of PPV and sensitivity across these studies may be related to the choice of the study population, the predefined HF algorithm, the clinical settings, and the reference standards used, making international extrapolations difficult. Most of these studies were conducted on general hospitalized populations, but one of them was limited to a selected population of elderly people in whom HF is more prevalent.¹⁵ All of these studies validated administrative coding data using medical record reviews, but some of them, in conjunction with chart reviews, applied specific standardized criteria such as Framingham¹⁵ or ESC criteria.^{17,18} Finally, the number and the type of the codes combined in the HF algorithms varied according to the studies even though the common ICD-10 codes in all studies was I50.x.

The low sensitivity of the ICD-10 codes I50.x renders inappropriate the sole use of these codes in epidemiological studies examining incidence or prevalence of the disease. On the other hand, high PPV is desirable when studying comparative effectiveness of drugs in a given indication.

4.1 | Study strengths and weaknesses

Among the strengths is that HF diagnosis in EHR was confirmed based on the benchmark diagnosis criteria of the ESC by two experienced

physicians, which can certify the reliability of the established diagnosis. Our analyses included a large representative sample of patients, randomly selected in two major French university hospitals. The 1-year study period allowed to reduce seasonal variations observed in prevalence of HF rehospitalizations,^{22,23} which may have influenced PPV estimates. For each HF patient identified from either PMSI or EHR, only one hospital stay was considered, to avoid coding redundancy for the same patient, which may overestimate PPV estimates. Lastly, our sensitivity analyses provided a detailed overview on spatial and temporal variability of coding quality.

There are also some weaknesses: The study focused on estimating PPV and Se of the I50.x codes, but did not attempt to evaluate the specificity and the negative predictive value (NPV). Specificity and NPV could not be calculated in the present study because data were sampled from the codes and the diagnosis of interest. The choice of the diagnostic accuracy parameters is crucial and mainly depends on the study objective and thus the study design. For instance, a high PPV allows a reliable identification of patients with a diagnostic of interest in a cohort allowing to minimize misclassification bias, but it cannot stand alone to estimate disease incidence. However, a high value of Se can redress this issue by providing accurate estimates of the disease incidence. This study also focused on only one set of codes intended to identify HF, while other studies included a larger selection of codes also related to the underlying disease.^{21,24} We chose the codes I50.x because they correspond precisely to the HF definition, irrespective of the HF aetiology. The custodians of the national SNDS database have suggested an HF identification algorithm,²⁵ which might be an interesting addition for the diagnosis, but its performance was not yet validated. Finally, coding performance was assessed in two major university hospitals, but coding may be different in smaller hospitals, or in private clinics. This may not affect PPV and association studies, but might degrade sensitivity. This would warrant further studies in these secondary information centres and the diffusion of coding guidelines for the use of the diagnostic codes. These putative local variations may be mitigated by the ongoing effort by the national hospital association ATIH, the health care insurance system, and the regional health authorities to harmonize coding across the country, using instruction manuals for coding, by hiring professional coding assistants and by regular audits of the codes in randomly chosen hospitalizations.

5 | CONCLUSION

The hospital discharge summary ICD-10 codes I50.x were reliable to identify cases of HF but did not identify them exhaustively. The effects of high PPV and middling sensitivity will vary according to the use and objectives of pharmacoepidemiological studies in national databases.

ETHICS STATEMENT

This study was declared to the data protection officer of the French Data Protection Authority (*Commission nationale de l'informatique et des libertés* [CNIL]) and was approved by the local research ethics committee of each hospital centre.

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CONFLICT OF INTEREST

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2.4. Discussion of main results

To date, this study is the first in France to assess the diagnostic accuracy of the HF hospitalization discharge codes by comparing recorded discharge diagnoses and electronic health records. Results confirm that the use of the hospitalization discharge codes I50.x allow to identify not exhaustively but with sufficient accuracy HF hospitalized patients. The high Positive Predictive Value (PPV) estimated for the codes I50.x was consistent with studies in other settings [81–86]. This suggests that these codes may be used for identification of HF patients, irrespective of the database considered. One explanation of this high estimate is that HF is characterized by a constellation of symptoms, which taken individually are not specific of the disease, but taken together, are sufficient to accurately diagnose HF. As reported in a previous study, most HF patients present with more than one of these symptoms when they get hospitalized [87]. Furthermore, HF diagnosis is often confirmed by paraclinical exams such as BNP or echocardiography, performed during the hospitalization stay, which should not lead to a coding different from that used for HF. Our study also reported a modest value of sensitivity which may be explained by the fact that clinicians have coded for underlying cardiovascular disease responsible for HF rather than for HF. One reason of this coding may be that a specific treatment has been initiated during hospitalization to manage these diseases in addition to the standard HF treatment (i.e. anticoagulant in atrial fibrillation, or platelet aggregation for ischemic heart disease).

One of the main limitations of this study was that coding performance was assessed in two major university hospitals. Coding may be different in smaller hospitals, or in private clinics. This may not affect PPV and association studies, but might degrade sensitivity. These putative local variations may be mitigated by the ongoing effort by the national hospital association (ATIH), the healthcare insurance system and the regional health authorities to harmonize coding across the country, using instruction manuals for coding, by hiring professional coding assistants, and by regular audits of the codes in randomly chosen hospitalizations. Another limitation was that this validation study did not allow us to distinguish between HFpEF and HFrEF patients. Indeed, at the time when the study was carried out, codes specific to HFpEF or HFrEF and results of the echocardiography were not available in the PMSI database.

Since March 1st, 2019, ATIH has decided to introduce new codes that would characterize the left ventricular EF:

1. I50.00 or I50.10 for HF with LVEF \geq 50%;
2. I50.01 or I50.11 for HF with LVEF $<$ 50% and \geq 40%;
3. I50.02 or I50.12 for HF with LVEF $<$ 40%;
4. I50.09 or I50.19 for HF with unspecified LVEF.

It will therefore be necessary to carry out further validation studies in the future to assess the performance of these new codes. For studies undertaken before 2019 in the SNDS database, it will also be essential to identify what proxies could be used to distinguish between HFpEF and HFrEF patients. Finally, the current coding methods for HF in the PMSI database are not sufficient to certify the chronic or acute nature of HF. According to the ATIH's guidelines, primary diagnosis is the health problem that motivates the admission in the hospital and that determines the hospital discharge, and associated diagnoses include all underlying (chronic or not) health conditions, which have required medical care during the hospitalization stay. Acute HF is thus mostly coded as primary diagnosis, but it can also be coded sometimes as associated diagnosis. For instance, if a patient presents with an acute heart failure caused by a pulmonary infection, the primary diagnosis will be "pneumonia" and HF will be indicated as associated diagnosis. This issue must be properly taken into account in further research.

2.5. Conclusion

The French nationwide claim database satisfies many criteria required for the assessment of the therapeutic management of HF and its risk of cardiac decompensation in real-life setting. Data of the SNDS or its representative sample, the EGB, are available for a long period of time: data collection started from 2005-2006 and will continue for a period of maximum 20 years. These databases are used to conduct longitudinal studies as it permits tracing back patients' care paths and use of care in both hospital and office-based care environments over a long period. Although the procedure of data access is complex, it remains more economic and faster than for field studies.

One limitation of these databases concerns the reliability and validity of the data they contain. Results of this study, which was the first in France to assess the diagnostic accuracy of the HF hospitalization discharge codes, confirmed that data from the French hospitalization discharge summary database are sufficiently accurate to identify HF patients or HF outcome in the context of this thesis. However, other features should be used in addition to this coding to ensure a better characterization of HF (chronic or acute, with preserved or reduced EF). PPV of HF coding being very consistent with that of studies performed in other countries, this allows consideration of the replication of this work at international level.

This first study confirmed that it is possible to identify with adequate accuracy the source population and the outcomes of interest that will be studied in our further research. Primarily, it was about describing the use patterns of treatment used in HF in real world. This was the secondary objective of this thesis.

3. HEART FAILURE TREATMENT USE IN REAL WORLD

3.1. Rational and methodological considerations

Modalities of chronic HF management have considerably expanded these last 35 years. These involve multiple levels of action: an improving primary prevention based on a multi-disciplinary approach involving general practitioner, cardiologist, physiotherapist, nurse or dietician, a highly codified pharmacological treatment in case of HFrEF and surgical therapeutic options.

Current pharmacological treatments have clearly shown important benefits in terms of morbidity and mortality in chronic HF, but their appropriate use remains indispensable to expect benefit. Persistence and adherence are two parameters commonly used in pharmacoepidemiology studies to assess how treatments are used in clinical practice. Previous studies have reported non-optimal adherence to HF treatment but with estimates which varied widely according to the method applied [62, 63] and persistence was estimated as high with treatment dosages below recommended dosages [53–55]. These studies considered only patients who initiated the studied treatment at discharge from a HF hospitalization but not patients who initiated therapy as outpatients. However, HF is a chronic disease, which rapidly evolves and thus implies constant adjustment of HF treatments over time. Adherence and persistence are thus two parameters difficult to handle for assessing in a representative way, how HF treatments are used in clinical practice in the overall population of HF patients.

Instead of focusing on HF treatment adherence or persistence, we thus decided to study the treatment initiation patterns and the subsequent treatment changes among HF patients after an initial hospitalization for HF.

3.2. Objective

To our knowledge, only one study has dealt with this subject with the same approach as ours using US medical and pharmacy claims data from the Truven Health MarketScan database [59]. Prior to initiating this work, no study has been carried out on this topic in France. The objective of this work was thus to describe the treatment initiation patterns and the subsequent treatment changes among HF patients, in the first year following an incident hospitalization for HF, in a real-world setting, using data from the random sample of the French nationwide claims database, the EGB.

Results of this study have been accepted for publication in the *European Journal of Clinical Pharmacology*.

3.3. Article

3.3.1. Reference

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3.3.2. Abstract

Background: Although the efficacy and safety of existing therapies of heart failure (HF) have been demonstrated in clinical trials in the last 35 years, little is known about the treatment patterns of HF in clinical practice, especially in France.

Objectives: To describe the treatment initiation patterns and the subsequent treatment changes among HF patients, in the first year following an incident hospitalisation for HF, in a French real-world setting.

Methods: A cohort of patients aged 40 years old and older, with an incident hospitalisation for HF between January 1, 2008 and December 31, 2013, was identified in the EGB, the 1/97th permanent random sample of the French nationwide claims database. All patients who died during the index hospitalization or with a period of at least 3 consecutive months with no healthcare dispensing recorded were excluded. All included patients were followed one year. HF drugs of interest were: beta blockers (BB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), aldosterone antagonists (AA), diuretics, digoxin or ivabradine. Drug exposure was assessed quarterly using a Proportion of Days Covered $\geq 66\%$ (≥ 60 days out of the 90 days of the quarter covered by the treatment of interest), by considering HF drugs individually or in combination. Drug changes were assessed between each quarter over the first year of follow-up.

Results: Between 2008 and 2013, 7,387 patients from EGB were included. The mean age at baseline was 77.7 years (± 12.0 years) and 51.6% were women. During the follow-up, 24.4% of patients died and around 20% were not exposed to any HF treatment. From the 1st quarter to the end of follow-up, 48.3% to 43.2% of patients had diuretics, around one third had BB or

ACEI, around 9% had ARB or AA, 6% had digoxin and 2% had ivabradine. The main change occurred between the first and the second quarter and concerned 53.1% of the initially untreated patients; by the second quarter, 22.2% had initiated a BB/ACEI/ARB combination, 13% a diuretic alone, 7.4% a BB and 4.9% a BB/ACEI/ARB/AA combination.

Conclusion: This study provides precious information on treatment patterns after an initial hospital admission for heart failure at a time when new treatments for heart failure are emerging.

Pharmacological treatment patterns in heart failure: a population based cohort study

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ABSTRACT

Background: Although the efficacy and safety of existing therapies of heart failure (HF) have been demonstrated in clinical trials, little is known about the treatment patterns in clinical practice, especially in France.

Objectives: To describe the treatment initiation patterns and the subsequent treatment changes among HF patients, in the first year following an incident hospitalisation for HF, in a French real-world setting.

Methods: A cohort of patients aged ≥ 40 years, with an incident hospitalisation for HF between 01/01/2008 and 31/12/2013, was identified in the 1/97th permanent random sample of the French nationwide claims database and followed 1 year. HF drug exposure - beta blockers (BB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), aldosterone antagonists (AA), diuretics, digoxin or ivabradine- was assessed quarterly using a Proportion of Days Covered $\geq 66\%$ (≥ 60 days out of the 90 days of the quarter), by considering HF drugs individually or in combination. Drug changes were assessed between each quarter.

Results: Between 2008 and 2013, 7,387 patients were included. Their mean age was 77.7 years (± 12.0 years) and 51.6% were women. During the follow-up, 24.4% died, 20% were not exposed to any HF treatment, 48.3% to 43.2% had diuretics, one third had BB or ACEI, 9% had ARB or AA, 6% had digoxin and 2% had ivabradine. The main change occurred between the first and the second quarter for 53.1% of the initially untreated patients.

Conclusion: This study provides valuable information on treatment patterns after an initial hospitalization for HF.

INTRODUCTION

Heart Failure (HF) represents a major health problem, especially in the aging populations of developed countries. It affects from 1 to 2 % of the adult population, up to 10% or more in people over 70 years of age [1]. In France, its prevalence was estimated in 2008 to be 2.3% of the adult population and it reached 15.1% among people over 85 year of age [2] its mortality is estimated at nearly 50% within 5 years of diagnosis [3–5]. It is also associated with a high economic burden with, in 2013, an estimated health expenditure of around 2% of the European total health-care budget [3, 4] and around €2.5 billions of the healthcare expenditure supported by the French National Health Insurance System [6].

HF is generally divided into two main types, heart failure with reduced ejection fraction (HFrEF), which mainly affects younger patients and patients with myocardial mass reduction (e.g. because of previous myocardial infarction or with idiopathic cardiomyopathy) and heart failure with preserved ejection fraction (HFpEF), which mainly affects elderly. Current guidelines clearly define the pharmacological management of HFrEF patients. For these patients, the European Society of Cardiology (ESC) recommends, as first-line treatment, the use of neuro-hormonal antagonists (cardioselective Beta Blockers (BB); angiotensin-converting enzyme inhibitors (ACEI); angiotensin receptor blockers (ARBs)) with a diuretic to relieve retention symptoms [7, 8]. An aldosterone antagonists (AA) may be added to the previous combination of treatment if patients have persisting symptoms. Finally, digoxin and ivabradine may be proposed if patients fail to respond. To date, no pharmacological treatment has demonstrated efficacy for the treatment of HF with preserved ejection fraction (HFpEF): calcium-channel blocker (CCB) and some HFrEF treatments are still used in HFpEF patients without any recommendation [7, 8].

The efficacy of existing therapies for HFrEF has been demonstrated in clinical trials, as was their safety with over 35 years' experience. However, little is known about the actual treatment patterns of HF in clinical practice in France. Observational studies have described

the treatment initiated just after a HF hospitalization [9, 10], but none studied the changes in treatment after initiation.

The objective of this study was thus to describe the treatment initiation patterns and the subsequent treatment changes among HF patients, in the first year following an incident hospitalization for HF, in a French real-world setting.

METHOD

Study design and data source

This is a cohort study using data from the EGB database (*Echantillon Généraliste de Bénéficiaires*), a representative permanent 1/97th sample of the national healthcare data system in France, SNDS (*Système National des Données de Santé*), which covers 99% of the French population from birth to death [11]. Complete data before 2011 are available for subjects covered by the main scheme, covering salaried employees and their dependents, i.e., 76% of the French population. For each insured person, SNDS provides pseudonymized information on all reimbursed medical and paramedical encounters, drugs claims, hospital admissions and procedures except for psychiatric hospitals and rehabilitation centres, registration for Long Term Disease (LTD) and date of death. Hospital diagnoses are coded according to the International Classification of Disease 10th edition (ICD-10) and the quality of this coding is ensured by regular internal and external audits [12]. The quality of hospital coding for HF has been verified (13). Death is recorded in CepiDC., the national death registry. These three databases are linked so that it is possible to create a longitudinal record for each patient in the linked databases [11].

Study population

We included in the cohort all patients aged over 40, covered by the main health insurance system, with an incident hospitalization for HF between January 1, 2008 and December 31, 2013. An incident HF hospitalization was defined as a first hospitalization with a discharge code I50.x of the ICD-10 in any diagnostic position, with no LTD registration or hospital admission for HF in the 2 previous years. The date of the incident HF hospitalization discharge was defined as the index date. Patients were required to have a pre-index period of 1 year and at least 1 year of follow-up after the index date (excluding deaths). We excluded all patients who died during the index hospitalization or who had a period of at least 3 consecutive months with no healthcare dispensing recorded (i.e. patients who were probably

institutionalized, for whom healthcare use data is not available in the database). Patients were followed for 1 year after index date or until death if it occurred before.

Study variables

Baseline patient characteristics at index date included age and gender. Comorbidities were defined using disease identification algorithms developed by the custodians of the French national healthcare system which includes disease-specific treatments, diagnosis ICD-10 codes of hospital discharge summaries and LTD registrations [13] identified during the year before index period. Characteristics of the index hospitalization included length of stay and procedures performed during the stay. Drug treatment at index date was identified for the following treatment classes: cardioselective BB, ACEI, ARB, AA, digoxin, ivabradine, diuretics (loop or thiazide diuretics) and calcium channel blockers (CCB). Drug treatment during the follow-up was identified for the same classes except for CCB since they are not included in current guidelines of HF with preserved Ejection Fraction (HFpEF) and they are not specific treatment for HF. Drug exposure was assessed quarterly in the first year of follow-up using the Proportion of Days Covered (PDC) by each drug. We defined PDC as the number of days covered by all drug dispensings in a given quarter, divided by the total number of days in the quarter (90 days). Each drug dispensing covered a period of 30 or 90 days according to the number of tablets dispensed. If a patient had a $PDC \geq 66.6\%$ (i.e. exposure to a medication at least 60 days over a quarter), then this patient was considered as exposed to the treatment in the entire quarter. We included the duration of hospitalizations during the studied quarter in the calculation of the coverage period if patient was already exposed to the medication on the first day of this hospitalization (Supplementary Figure 1). The exposure of patients who died during the quarter was not assessed in the considered quarter. Patients were grouped based on the medications to which they were exposed during that quarter and according to the different lines of HFpEF treatment proposed by the ESC guidelines. We thus considered the following combinations:

- No HFrEF treatment;
- Diuretics alone;
- BB alone;
- BB/ACEI/ARB (*i.e.* BB+ACEI or BB+ARB or ACEI or ARB or ACEI+ARB or BB+ACEI+ARB);
- BB/ACEI/ARB/AA (*i.e.* BB+ACEI+AA or BB+ARB+AA or ACEI+AA or ARB+AA or ACEI+AA+ARB+ or BB+AA or AA alone)
- Any combination with digoxin or ivabradine.

Diuretics were not included in combination treatments (except when considered alone) since they are given mainly for management of symptoms. Patient who died or who had a device treatment such as implantable cardioverter defibrillator (ICD)/cardiac resynchronization therapy (CRT) during the quarter were also identified.

Statistical Analyses

Main analysis

We performed descriptive analyses where categorical variables were described in number and percent, and quantitative variable in mean and standard deviation (SD) or median and interquartile range (IQR). As the information on ejection fraction was not available in our database, we used the age as a proxy for the type of HF and we thus categorized our analyses by age (40-65 years, ≥ 75 years). Patients under 65 years are more likely to have HFrEF [14], whereas patients over 75 years are known to be more likely to have HFpEF [15, 16]. We used a Sankey diagram to illustrate the drug modifications over the first year of follow-up.

Sensitivity analysis

We also performed a sensitivity analysis that consisted in varying the threshold of the PDC from 50% to 80%.

RESULTS

Among the 10,919 patients identified in the EGB who had an incident hospitalization for HF between 2008 and 2013, 7,387 met the inclusion criteria (Figure 1).

Baseline characteristics

Characteristics of the study population at baseline and description of the index hospitalisation are reported in Table 1. Patients had a mean age of 77.7 years (± 12.0 years); 68.5% were over 75 years old and 15.5% were under 65. Proportions were relatively well distributed in the whole cohort between males (48.4%) and females (51.6%), but the proportion of women tended to be higher in patients over 75 years old (59.1%) than in patients under 65 (33.4%). The most frequent cardiovascular conditions were high blood pressure (HBP; 86.3%), atrial fibrillation (40.5%) and ischemic heart disease (33.7%). About one fourth of patients had diabetes (27.8%) or a chronic respiratory disease (28.1%) and 14.4% had chronic renal failure. The proportion of patients with HBP or chronic renal failure tended to be higher in patients above 75, while the proportion of patients with ischemic heart disease or chronic respiratory disease tended to be higher in those under 65. Within the 12 months pre-index period, patients had a median of 12 (IQR [8.0;18.0]) outpatient consultations: patients over 75 years old had a median of 13.0 (IQR [8.0;19.0]) while patients under 65 years old had a median of 9.0 (IQR [5.0;15.0]) office visits. During this 12-month period, almost all patients visited a general practitioner but only around 30% of them visited a cardiologist. The median number of previous hospitalizations was 2.0 (IQR [1.0;3.0]) and the median number of distinct medications dispensed within the pre-index period was 17.0 (IQR [12.0;22.0]). The median duration of the index hospitalization was 8.0 days (IQR [4.0;14.0]). For 15% of patients, a measure of plasma BNP or an echocardiography was performed during the stay. Three quarter of patients returned home after hospitalisation discharge.

HF treatment

Overall, 10.9% died during the first quarter after initial hospital discharge and 24.4% during the year of follow-up. Within the 90 days following the hospital discharge, 71.9% of patients

received at least one dispensing of a diuretic, 42.2% at least one of BB, 40.8% at least one of ACEI, 12.9% at least one of ARB, 14.4% at least one of AA, 10.1% at least one of digoxin and 2.6% at least one of ivabradine (Table 2). The proportion of patients with at least one dispensing of BB, ACEI, AA, or ivabradine tended to be higher in younger patients and the proportion of patients with at least one dispensing of diuretics, ARB or digoxin tended to be higher in older patients. A quarter of the patients had at least one dispensing of CCB, and particularly dihydropyridines, whatever their age.

When exposure was assessed quarterly by the individual PDC for each medication, the proportions of patients increased between the 1st and the 2nd quarter for each medication and then slightly decreased from the 2nd quarter to the end of follow-up: from 48.3% to 43.2% of patients had diuretics, around one third had BB or ACEI, around 9% had ARB or AA, 6% had digoxin and 2% had ivabradine. When stratified by age, the proportion of patients receiving BB, ACEI, AA, or ivabradine tended to be higher in younger patients while the proportion of patients receiving diuretics, ARB or digoxin tended to be higher in older patients for each quarter. When assessed in the 5585 (75.6%) patients who did not die during the follow-up, the distribution of patients covered by each HF drugs was broadly constant over quarters (Supplementary Figure 2).

When HF medications were grouped by combination, their dispensing increased slightly between the 1st and 2nd quarters but remained broadly constant over the three remaining quarters: around 30% of patients had a combination involving BB/ACEI/ARB, around 10% were treated with either BB or diuretics alone, around 7% had a combination of BB/ACEI/ARB/AA or any combination with digoxin or ivabradine (Table 3). When stratified by age, proportions of patients with BB/ACEI/ARB or BB/ACEI/ARB/AA tended to be higher in younger patients. In the 1st quarter, 37.1 % of patients were not exposed to any HF treatment. This concerned around 16-18% of patients in the following quarters, and mostly younger patients. Use of implantable device was limited with less than 1% of patients concerned in each quarter.

HF treatment changes

Treatment changes during follow-up are summarized in Figure 2. The main changes occurred between the first and the second quarter and concerned 53.1% of patients who were initially not exposed to any HFrEF drug. By the second quarter, 22.2% of the 2,741 initially untreated patients initiated a BB/ACEI/ARB combination, 13% a diuretic, 7.4% a BB and 4.9% a BB/ACEI/ARB/AA combination, but 38.1% remained untreated (see supplementary Table 1). By the third and fourth quarters, respectively 12.4% and 10.2% of untreated patients initiated a BB/ACEI/ARB combination. It is interesting to note that for each quarter, between 6 and 7% of the patients previously treated with BB/ACEI/ARB became untreated. Between the second and the fourth quarter of follow-up, the majority of the patients remained treated with the same treatment: this concerned approximately 60-70% of patients on diuretics, 70% of patients on BB, 75% of patients on BB/ACEI/ARB/AA, and 80% of patients on BB/ACEI/ARB.

Sensitivity analysis

For a PDC > 50%, a less restrictive definition of the drug exposure, 12.2 to 22.9% of patients were identified as untreated and 63.4 to 69.1% were identified as treated for each quarter (Supplementary Table 2). For a PDC > 80% - a threshold traditionally used to assess adherence, 23.9 to 63.6% of patients were identified as untreated and 25.5 to 56.6% were identified as treated for each quarter.

DISCUSSION

Using data from a representative nationwide claim database, this study gives valuable information on the pharmacological management of HF patients in France, over the year following a first hospitalization for HF in a real world setting. Between 17% and 37% of patients, mostly under 65, were not exposed to any HFrEF treatment in the year following hospital discharge. For patients treated with HFrEF treatment, the most frequent treatment used was the combination BB/ACE/ARB, especially in younger patients. The majority of patients remained treated during the first year of follow-up with the same treatment initiated within the 90 days following initial hospital discharge.

Our study population characteristics at hospital discharge were consistent with those of other studies [10, 17, 18]. Stratification according to age – due to the lack of data for EF – provided groups of patients whose characteristics were broadly similar to those of the HFrEF/HFpEF patients. As reported by another study focusing on HFpEF patient characteristics, patients over 75 years old were more likely to have cardiovascular comorbidities such as hypertension, atrial fibrillation and valvular disease and non-cardiovascular comorbidities such as renal failure [19]. However, contrary to existing data, patients over 75 years old did not have more diabetes, psychiatric disorders or chronic respiratory disease than younger patients [19]. As reported by other studies focusing on HFrEF patient characteristics, patients under 65 years old were more likely to be male and to have cardiovascular comorbidities such as ischemic heart disease and dilated cardiomyopathy [14, 20]. This may also justify the relatively high rates of diabetes and chronic respiratory disease (markers of overweight and chronic smoking), both associated with ischemic heart disease, a major provider of HRrEF [21].

As previously reported, 37.1% of patients were not exposed to any HFrEF treatment in the first quarter following hospital discharge. This may concern HFpEF patients for whom there is no recommended therapy, but the similar distribution of untreated patients between age

groups does not support this hypothesis. Age is only a proxy of the HF_rEF/HF_pEF status and this variable might thus not distinguish accurately between HF_rEF and HF_pEF. Pharmacologically untreated patients may be New York Heart Association Classification (NYHA) class I patients who may benefit from strict application of dietary rules only. The NYHA class is not available in our database making identification of these patients difficult. In the second quarter of follow-up, 53.1% of the initially untreated patients were treated with a HF_rEF medication, but 16.3% remained still pharmacologically untreated at the end of the follow-up. These results are in line with other studies which found a proportion of untreated patients varying between 29% and 41.8% [22, 23]. The most likely is that these patients with a first episode of heart failure were initially treated with dietary restriction, especially salt-free diet. It is if this diet failed to control heart failure symptoms that they were put on a medicinal treatment we could identify.

For each HF medication, the percentages of patients treated at hospital discharge were lower than those reported in other studies [17, 18, 24, 25], but patients included in these studies were prevalent HF hospitalized patients. In our study, most treated patients had diuretics, BB or ACEI. The proportion of patients using ivabradine after hospitalization was small, but this may be explained by the later emergence of clinical trial data regarding ivabradine [26]. The high use of CCBs mainly represented by dihydropyridines reflects the use of these medications essentially for HBP treatment. The proportion of patients having an ARB was lower than expected (expected to be similar to that of patients treated with ACEI), but this might be explained by the fact that our study included a relatively healthier, newly diagnosed population. Our results appeared to be consistent with those reported by two other studies that also included incident HF patients [10, 23]. Prescribers may prefer to start with ACEI, and switch to ARB in the case of poor tolerability of the ACEI (e.g., cough)

Treatment changes were mostly observed during the first quarter among the 53.1% of untreated patients who became treated in the following quarter. This suggests a delay of around 3 months in HF treatment initiation after a first HF hospitalization discharge.

Interestingly, a non-negligible proportion of patients treated with the combination of BB/ACEI/ARB (7-8%) had a treatment de-escalation for each quarter throughout the study period. It is however difficult to know if this is related to a medically justified reason (i.e., patients with mild HF symptoms, effective non-pharmacological treatment, patients who did not tolerate treatment or with severe comorbidities) or not (i.e. patients with poor treatment adherence). To our knowledge, only one recent study offers consistent data on HF treatment changes, but the measure of exposure was not assessed in the same way than ours, leading to results that are difficult to compare [23].

Our study presents several limitations. These mainly concern those common to most healthcare databases, namely the assumption that treatment dispensing equates intake, but these databases have been frequently used and validated for the assessment of medication-taking behavior [27, 28]. Furthermore, some useful information for characterizing HF patients was lacking in our database. This concerns for instance the ejection fraction, useful to distinguish between HF_rEF and HF_pEF patients (although we used age as a proxy to counter this limit), the results of the BNP done during the stay which would have help to characterise the type of heart failure more accurately, the NYHA class necessary to assess HF severity, or the reason for office visits, important to identify better the onset of HF. Another limitation is that we used incident HF hospitalizations to identify and include our study population. Our results can thus not be extrapolated to prevalent HF outpatients. This however concerns but a minority of patients since HF tends to rapidly worsen and inevitably results in hospitalization. The specified threshold of PDC used to measure drug exposure (66%) may be discussed since it does not correspond to the common 80% threshold recommended to assess adherence in pharmacoepidemiology studies [28]. Our threshold seems however more appropriate to assess exposure to a chronic treatment quarterly in a real world setting. A threshold of 66.6% (i.e. at least 60 days) is less restrictive than a threshold of 80% - as reported in the sensitivity analysis - when drug exposure is assessed quarterly.

This study has also several important strengths. First, it relies on a high quality database, the EGB, which contains a population representative of the French national population and which thus provides reliable estimates of drug utilization in real world conditions [11]. The ICD-10 codes applied to select our study population have been previously validated and provide good diagnostic performance (PPV: 88.0%).[29] Finally, our exposure measure allows a complete assessment of the HF drug utilization in real world setting, taking into account both dispensing and coverage of a drug over a considered quarter.

In conclusion, this study provides possibly valuable information on treatment patterns after an initial hospital admission for heart failure, as a baseline for the study of the medicinal interventions and the risk of re-hospitalisation or death from heart failure, at a time when new treatments for heart failure are emerging.

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ETHICS STATEMENT

This study was done in a pseudonymized database, not requiring patient consent. It was reviewed by INSERM internal processes, which did not oppose it. INSERM CIC1401 at that time had permanent access to the 1/97 sample of SNDS, pending INSERM approval.

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CONFLICTS OF INTEREST

Dr P. Bosco-Lévy, C Favary, J Jové, R Lassalle, C Droz-Perroteau have nothing to disclose.

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AUTHOR CONTRIBUTION

P Bosco-Lévy, N Moore, C Droz-Perroteau contributed in designing and supervising the study. C Favary, J Jove and R Lassalle performed the analyses. All authors discussed the results. P Bosco-Lévy, wrote the manuscript and all authors reviewed it.

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Table 1. Description of patient baseline and index hospitalization characteristics

| | [40;65 [years n = 1,147 | ≥75 years n = 5,059 | Cohort n = 7,387 |
|---|-------------------------------------|--------------------------------|-----------------------------|
| Demographic characteristics | | | |
| Mean age (± SD) at index date (in years) | 56.1(6.5) | 84.5 (5.8) | 77.7 (12.0) |
| Sex female, n (%) | 383 (33.4) | 2,991 (59.1) | 3,813 (51.6) |
| Comorbidities, n (%) | | | |
| High blood pressure | 857 (74.7) | 4,498 (88.9) | 6,372 (86.3) |
| Ischemic heart disease | 454 (39.6) | 1,558 (30.8) | 2,488 (33.7) |
| Cardiac rhythm disorders | 204 (17.8) | 1,012 (20.0) | 1,438 (19.5) |
| Valvulopathy | 179 (15.6) | 928 (18.3) | 1,317 (17.8) |
| Atrial fibrillation | 285 (24.8) | 2,268 (44.8) | 2,994 (40.5) |
| Dilated cardiomyopathy | 230 (20.1) | 272 (5.4) | 644 (8.7) |
| Dyslipidemia | 456 (39.8) | 2035 (40.2) | 3112 (42.1) |
| Peripheral vascular disease | 118 (10.3) | 358 (7.1) | 598 (8.1) |
| Stroke | 73 (6.4) | 465 (9.2) | 634 (8.6) |
| Other cardio-neurovascular conditions | 429 (37.4) | 1,785 (35.3) | 2,683 (36.3) |
| Diabetes | 335 (29.2) | 1,288 (25.5) | 2,055 (27.8) |
| Chronic respiratory disease (asthma or COPD) | 336 (29.3) | 1348 (26.6) | 2076 (28.1) |
| Sleep apnea | 93 (8.1) | 164 (3.2) | 349 (4.7) |
| Cancer | 115 (10.0) | 686 (13.6) | 971 (13.1) |
| Chronic renal failure | 126 (11.0) | 771 (15.2) | 1,061 (14.4) |
| Pancreatic and liver disease | 119 (10.4) | 143 (2.8) | 331 (4.5) |
| Inflammatory disease | 30 (2.6) | 120 (2.4) | 182 (2.5) |
| Dementia | 7 (0.6) | 617 (12.2) | 644 (8.7) |
| Parkinson's disease | 8 (0.7) | 166 (3.3) | 185 (2.5) |
| Epilepsy | 28 (2.4) | 69 (1.4) | 122 (1.7) |
| Psychiatric disease | 145 (12.6) | 605 (12.0) | 874 (11.8) |
| Within the 12 months of pre-index period | | | |
| Median number (± SD) of office visit per patient | 9.0 [5.0;15.0] | 13.0 [8.0;19.0] | 12.0 [8.0;18.0] |
| ≥ 1 visit at the general practitioner, n (%) | 1,084 (94.5) | 4,920 (97.3) | 7,138 (96.6) |
| ≥ 1visit at the cardiologist, n (%) | 280 (24.4) | 1,497 (29.6) | 2,150 (29.1) |
| Median number [IQR] of hospitalizations per patient | 2.0 [1.0;3.0] | 2.0 [1.0;3.0] | 2.0 [1.0;3.0] |
| Median number [IQR] of distinct medications (level 3 of the ATC code) | 15.0 [9.0;20.0] | 17.0 [13.0;22.0] | 17.0 [12.0;22.0] |
| During index hospitalization | | | |
| Median [IQR] length of stay | 7.0 [3.0;11.0] | 8.0 [5.0;14.0] | 8.0 [4.0;14.0] |
| ≥ 1 medical procedure performed during the stay, n (%) | | | |
| BNP dosage | 164 (14.3) | 796 (15.7) | 1,140 (15.4) |
| Echocardiography | 265 (23.1) | 612 (12.1) | 1,100 (14.9) |
| Cardiac implantable devices | 25 (2.2) | 28 (0.6) | 61 (0.8) |
| Cardiac rehabilitation | 18 (1.6) | 28 (0.6) | 62 (0.8) |
| Heart transplant | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Type of hospitalization discharge, n (%) | | | |
| Home | 887 (77.3) | 3,749 (74.1) | 5,546 (75.1) |
| Internal or interinstitutional transfer | 259 (22.6) | 1,308 (25.9) | 1,838 (24.9) |
| Unknown | 1 (0.1) | 2 (0.0) | 3 (0.0) |

SD: Standard Deviation; COPD: Chronic Obstructive Pulmonary Disease; IQR: Interquartile Range; BNP: Brain Natriuretic Peptide

Table 2. Description of the HF medications use at hospitalization discharge and during the 4 quarters following the index date

| | [40;65 [years n = 1,147 | ≥75 years n = 5,059 | Cohort n = 7,387 |
|--|-------------------------------------|--------------------------------|-----------------------------|
| ≥ 1 dispensing in the 90 days after hospital discharge, n (%) | 1016 (88.6) | 4353 (86.0) | 6415 (86.8) |
| Diuretics* | 727 (63.4) | 3,723 (73.6) | 5,310 (71.9) |
| Loop | 663 (57.8) | 3,505 (69.3) | 4,958 (67.1) |
| Thiazide | 106 (9.2) | 455 (9.0) | 694 (9.4) |
| BB | 642 (56.0) | 1,913 (37.8) | 3,121 (42.2) |
| ACEI | 661 (57.6) | 1,796 (35.5) | 3,015 (40.8) |
| ARB | 116 (10.1) | 670 (13.2) | 956 (12.9) |
| AA | 256 (22.3) | 586 (11.6) | 1,061 (14.4) |
| Digoxin | 81 (7.1) | 555 (11.0) | 743 (10.1) |
| Ivabradine | 56 (4.9) | 87 (1.7) | 193 (2.6) |
| CCB* | 255 (22.2) | 1,269 (25.1) | 1,822 (24.7) |
| Dihydropiridines | 199 (17.3) | 1,045 (20.7) | 1,486 (20.1) |
| Verapamil | 35 (3.1) | 107 (2.1) | 177 (2.4) |
| Diltiazem | 29 (2.5) | 122 (2.4) | 179 (2.4) |
| Others | 2 (0.2) | 14 (0.3) | 20 (0.3) |
| Proportion of days covered ≥ 66.6% | | | |
| <u>During 1st quarter</u> | | | |
| Diuretics | 422 (36.8) | 1,929 (38.1) | 2,811 (38.1) |
| BB | 374 (32.6) | 1,019 (20.1) | 1,711 (23.2) |
| ACEI | 396 (34.5) | 962 (19.0) | 1,692 (22.9) |
| ARB | 68 (5.9) | 327 (6.5) | 484 (6.6) |
| AA | 141 (12.3) | 252 (5.0) | 498 (6.7) |
| Digoxin | 34 (3.0) | 226 (4.5) | 309 (4.2) |
| Ivabradine | 28 (2.4) | 42 (0.8) | 87 (1.2) |
| <u>During 2nd quarter</u> | | | |
| Diuretics | 515 (44.9) | 2,453 (48.5) | 3,568 (48.3) |
| BB | 496 (43.2) | 1,317 (26.0) | 2,248 (30.4) |
| ACEI | 503 (43.9) | 1,246 (24.6) | 2,166 (29.3) |
| ARB | 93 (8.1) | 460 (9.1) | 679 (9.2) |
| AA | 182 (15.9) | 352 (7.0) | 675 (9.1) |
| Digoxin | 53 (4.6) | 330 (6.5) | 446 (6.0) |
| Ivabradine | 45 (3.9) | 48 (0.9) | 122 (1.7) |
| <u>During 3rd quarter</u> | | | |
| Diuretics | 493 (43.0) | 2,313 (45.7) | 3,398 (46.0) |
| BB | 495 (43.2) | 1,249 (24.7) | 2,167 (29.3) |
| ACEI | 497 (43.3) | 1,205 (23.8) | 2,100 (28.4) |
| ARB | 102 (8.9) | 445 (8.8) | 674 (9.1) |
| AA | 180 (15.7) | 330 (6.5) | 646 (8.7) |
| Digoxin | 47 (4.1) | 294 (5.8) | 391 (5.3) |
| Ivabradine | 41 (3.6) | 42 (0.8) | 114 (1.5) |
| <u>During 4th quarter</u> | | | |
| Diuretics | 462 (40.3) | 2,183 (43.2) | 3,190 (43.2) |
| BB | 487 (42.5) | 1,184 (23.4) | 2,075 (28.1) |
| ACEI | 476 (41.5) | 1,119 (22.1) | 1,972 (26.7) |
| ARB | 104 (9.1) | 426 (8.4) | 660 (8.9) |
| AA | 170 (14.8) | 303 (6.0) | 609 (8.2) |
| Digoxin | 45 (3.9) | 298 (5.9) | 394 (5.3) |
| Ivabradine | 51 (4.4) | 44 (0.9) | 125 (1.7) |

BB: Beta Blockers; ACEI: Angiotensin-Converting Enzyme Inhibitors ; ARB: Angiotensin Receptor Blockers ; AA: aldosterone antagonists; CCB: Calcium Channel Blockers

*A patient may have several medications

Table 3. Description of the HF treatment during the 4 quarters following the index date: medications are grouped according to the different guideline-recommended combinations.

| | [40;65 [years n = 1,147 | ≥75 years n = 5,059 | Cohort n = 7,387 |
|--|-------------------------------------|--------------------------------|-----------------------------|
| During the 1st quarter after index hospital discharge, n (%) | | | |
| Death | 53 (4.6) | 663 (13.1) | 802 (10.9) |
| Survivors | 1,094 (95.4) | 4,396 (86.9) | 6,585 (89.1) |
| No HF _r EF treatment | 418 (36.4) | 1,885 (37.3) | 2,741 (37.1) |
| HF _r EF treatment | 676 (58.9) | 2,511 (49.6) | 3,844 (52.0) |
| Diuretics alone | 82 (7.1) | 546 (10.8) | 720 (9.7) |
| BB alone | 71 (6.2) | 407 (8.0) | 561 (7.6) |
| BB/ACEI/ARB | 334 (29.1) | 1,075 (21.2) | 1,731 (23.4) |
| BB/ACEI/ARB/AA | 127 (11.1) | 215 (4.2) | 436 (5.9) |
| Any combination with digoxine or ivabradine | 62 (5.4) | 268 (5.3) | 396 (5.4) |
| Implantable device | 30 (2.6) | 21 (0.4) | 76 (1.0) |
| During the 2nd quarter after index hospital discharge, n (%) | | | |
| Death | 29 (2.5) | 365 (7.0) | 443 (6.0) |
| Survivors | 1,065 (92.9) | 4,031 (79.7) | 6,142 (83.1) |
| No HF _r EF treatment | 244 (21.3) | 882 (17.4) | 1,348 (18.2) |
| HF _r EF treatment | 821 (71.6) | 3,149 (62.2) | 4,794 (64.9) |
| Diuretics alone | 70 (6.1) | 639 (12.6) | 816 (11.0) |
| BB alone | 99 (8.6) | 467 (9.2) | 672 (9.1) |
| BB/ACEI/ARB | 406 (35.4) | 1,365 (27.0) | 2,174 (29.4) |
| BB/ACEI/ARB/AA | 149 (13.0) | 300 (6.0) | 565 (7.6) |
| Any combination with digoxine or ivabradine | 97 (8.5) | 378 (7.5) | 567 (7.7) |
| Implantable device | 13 (1.1) | 8 (0.2) | 33 (0.4) |
| During the 3rd quarter after index hospital discharge, n (%) | | | |
| Death | 29 (2.5) | 247 (4.9) | 306 (4.1) |
| Survivors | 1,036 (90.3) | 3,784 (74.8) | 5,836 (79.0) |
| No HF _r EF treatment | 223 (19.4) | 801 (15.8) | 1,229 (16.6) |
| HF _r EF treatment | 813 (71.0) | 2,983 (59.0) | 4,607 (62.4) |
| Diuretics alone | 55 (4.8) | 590 (11.7) | 749 (10.1) |
| BB alone | 90 (7.8) | 456 (9.0) | 663 (9.0) |
| BB/ACEI/ARB | 423 (36.9) | 1,319 (26.1) | 2,137 (28.9) |
| BB/ACEI/ARB/AA | 157 (13.7) | 282 (5.6) | 553 (7.5) |
| Any combination with digoxine or ivabradine | 88 (7.7) | 336 (6.6) | 505 (6.8) |
| Implantable device | 10 (0.9) | 5 (0.1) | 19 (0.3) |
| During the 4th quarter after index hospital discharge, n (%) | | | |
| Death | 23 (2.0) | 197 (3.9) | 251 (3.4) |
| Survivors | 1,013 (88.3) | 3,587 (70.9) | 5,585 (75.6) |
| No HF _r EF treatment | 227 (19.8) | 767 (15.2) | 1,201 (16.3) |
| HF _r EF treatment | 786 (68.5) | 2,820 (55.7) | 4,384 (59.3) |
| Diuretics alone | 51 (4.4) | 557 (11.0) | 710 (9.6) |
| BB alone | 89 (7.8) | 425 (8.4) | 616 (8.3) |
| BB/ACEI/ARB | 411 (35.8) | 1,239 (24.5) | 2,027 (27.4) |
| BB/ACEI/ARB/AA | 140 (12.3) | 257 (5.1) | 513 (7.0) |
| Any combination with digoxine or ivabradine | 95 (8.3) | 342 (6.8) | 518 (7.0) |
| Implantable device | 3 (0.3) | 5 (0.1) | 11 (0.1) |

BB: Beta Blockers; ACEI: Angiotensin-Converting Enzyme Inhibitors ; ARB: Angiotensin Receptor Blockers ; AA: aldosterone antagonists; CCB: Calcium Channel Blockers

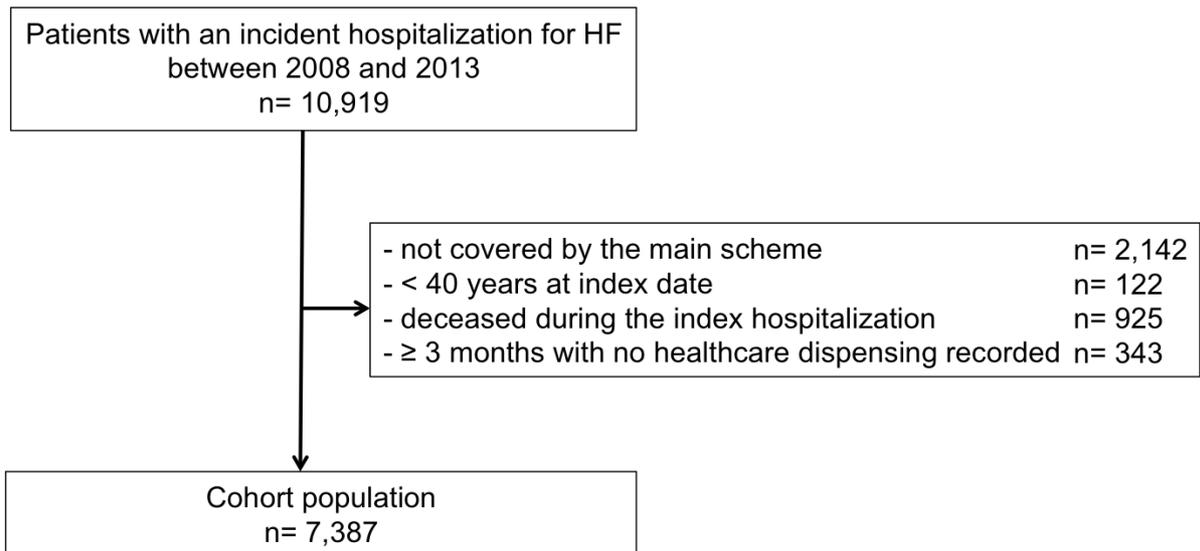


Figure 1. Study flow-chart

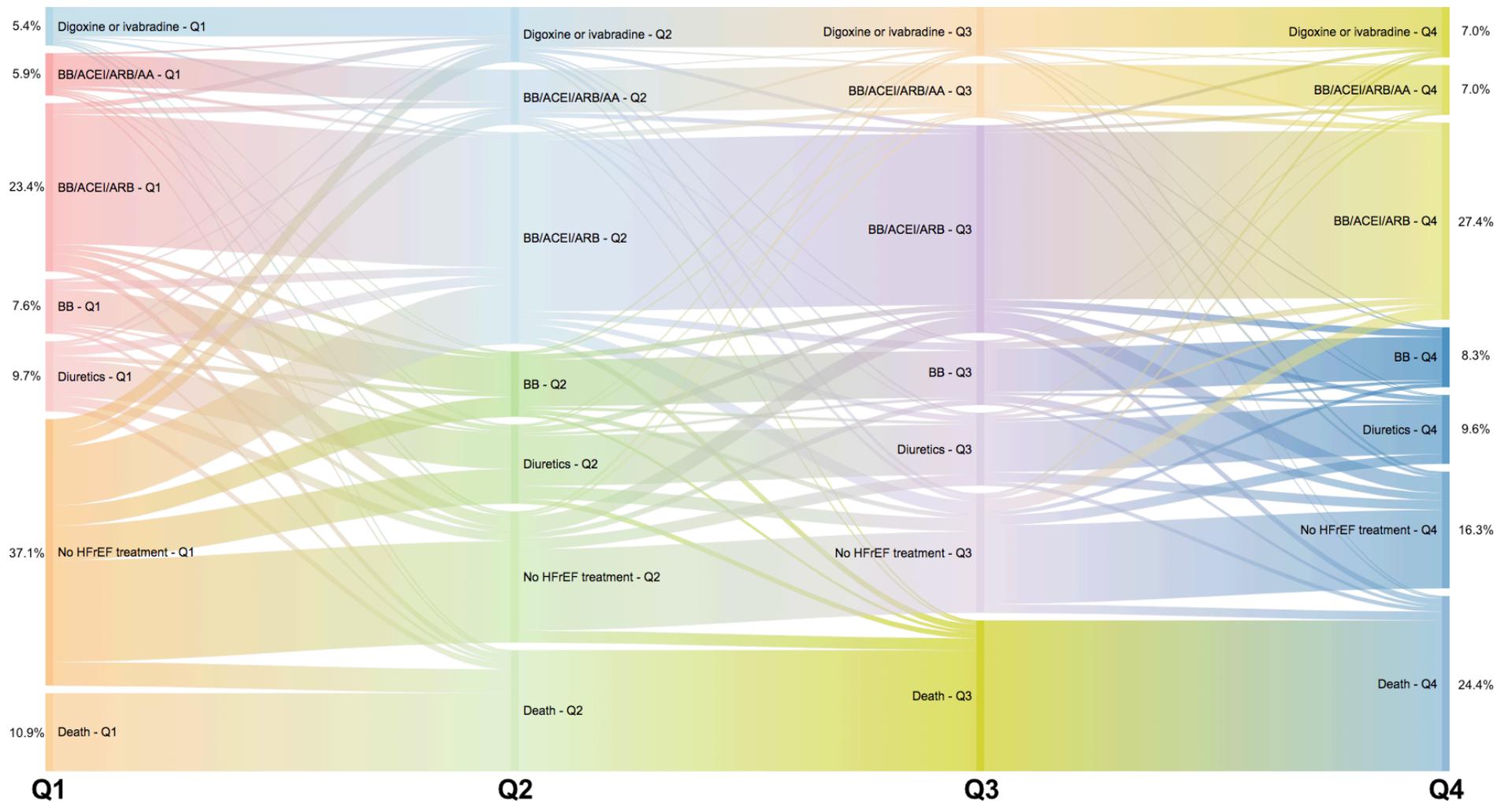
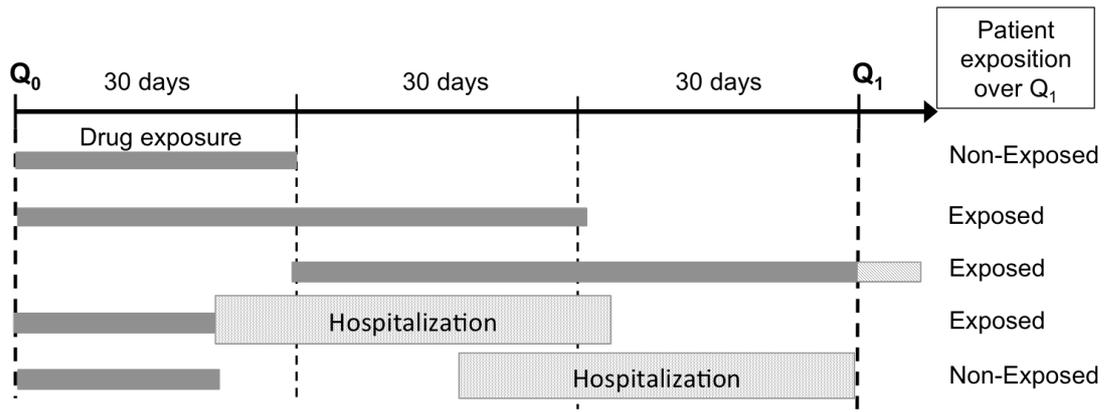
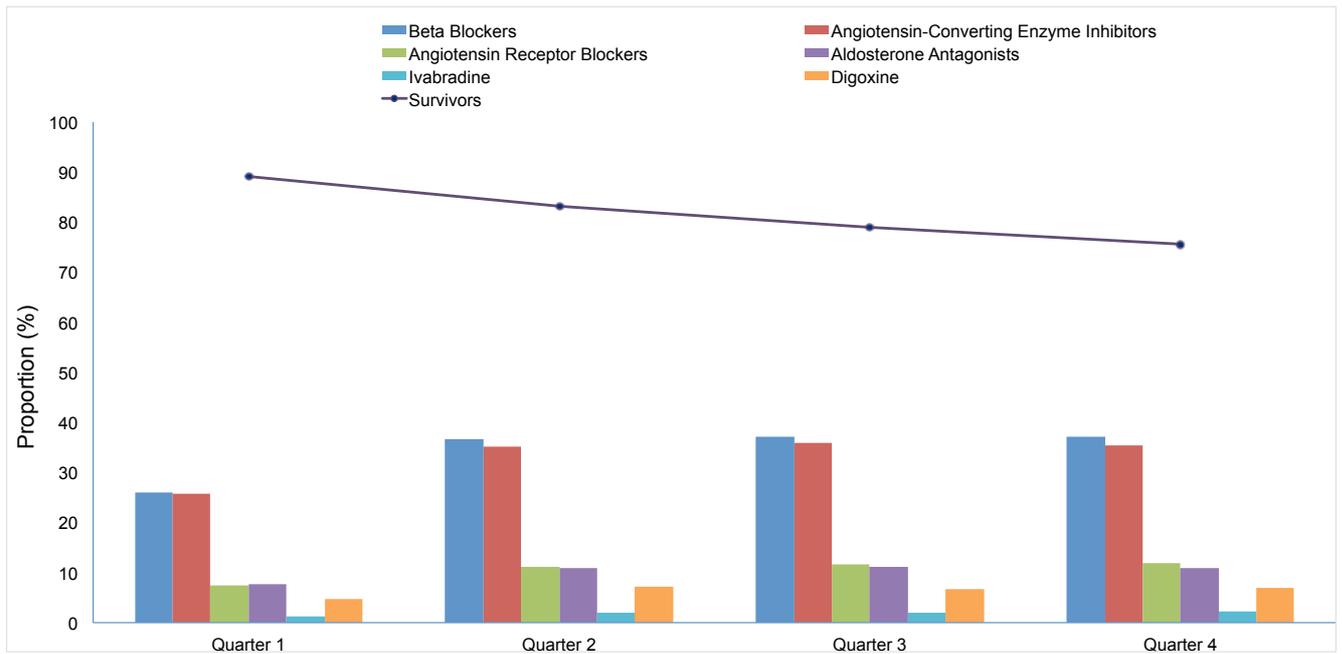


Figure 2. Sankey diagram representing modification of Heart Failure treatment over the 4 quarters of the follow-up (Q: quarter; BB: Beta Blockers; ACEI: Angiotensin-Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blockers ; AA: aldosterone antagonists;.



Supplementary Figure 1. Description of the method used to assess patient exposition to each medication of interest by quarter (Q)



Supplementary Figure 2. Distribution of the medications indicated in the treatment of Heart Failure, among patients who did not die during the follow up, when the exposure was measured by quarter.

Supplementary Table 1. HF treatment changes for each quarters of the follow-up

| Period | Initial medication | Targeted medication | [40;65 years n = 1147 | ≥75 years n = 5059 | Cohort n = 7387 |
|---|---------------------------|------------------------|----------------------------|-----------------------|---------------------|
| From quarters 1^s to 2 | | | | | |
| | No HFrEF treatment | | 418 (36.4) | 1,885 (37.3) | 2,741 (37.1) |
| | | Diuretics | 28 (2.4) | 288 (5.7) | 357 (4.8) |
| | | BB | 41 (3.6) | 133 (2.6) | 204 (2.8) |
| | | BB/ACEI/ARB | 92 (8.0) | 396 (7.8) | 608 (8.2) |
| | | BB/ACEI/ARB/AA | 32 (2.8) | 78 (1.5) | 135 (1.8) |
| | | Digoxine or ivabradine | 19 (1.7) | 113 (2.2) | 151 (2.0) |
| | | No HFrEF treatment | 188 (16.4) | 678 (13.4) | 1043 (14.1) |
| | | Death | 18 (1.6) | 199 (3.9) | 243 (3.3) |
| | Diuretics | | 82 (7.1) | 546 (10.8) | 720 (9.7) |
| | | Diuretics | 37 (3.2) | 287 (5.7) | 370 (5.0) |
| | | BB | 8 (0.7) | 33 (0.7) | 47 (0.6) |
| | | BB/ACEI/ARB | 13 (1.1) | 68 (1.3) | 94 (1.3) |
| | | BB/ACEI/ARB/AA | 3 (0.3) | 17 (0.3) | 24 (0.3) |
| | | Digoxine or ivabradine | 5 (0.4) | 21 (0.4) | 29 (0.4) |
| | | No HFrEF treatment | 13 (1.1) | 66 (1.3) | 95 (1.3) |
| | | Death | 3 (0.3) | 54 (1.1) | 61 (0.8) |
| | BB | | 71 (6.2) | 407 (8.0) | 561 (7.6) |
| | | Diuretics | 1 (0.1) | 16 (0.3) | 19 (0.3) |
| | | BB | 39 (3.4) | 257 (5.1) | 352 (4.8) |
| | | BB/ACEI/ARB | 18 (1.6) | 51 (1.0) | 84 (1.1) |
| | | BB/ACEI/ARB/AA | 3 (0.3) | 9 (0.2) | 17 (0.2) |
| | | Digoxine or ivabradine | 1 (0.1) | 8 (0.2) | 10 (0.1) |
| | | No HFrEF treatment | 8 (0.7) | 38 (0.8) | 49 (0.7) |
| | | Death | 1 (0.1) | 28 (0.6) | 30 (0.4) |
| | BB/ACEI/ARB | | 334 (29.1) | 1,075 (21.2) | 1,731 (23.4) |
| | | Diuretics | 1 (0.1) | 36 (0.7) | 52 (0.7) |
| | | BB | 7 (0.6) | 31 (0.6) | 49 (0.7) |
| | | BB/ACEI/ARB | 265 (23.1) | 826 (16.3) | 1333 (18.0) |
| | | BB/ACEI/ARB/AA | 17 (1.5) | 30 (0.6) | 59 (0.8) |
| | | Digoxine or ivabradine | 16 (1.4) | 28 (0.6) | 56 (0.8) |
| | | No HFrEF treatment | 25 (2.2) | 73 (1.4) | 116 (1.6) |
| | | Death | 3 (0.3) | 51 (1.0) | 66 (0.9) |

| | | | | |
|--|------------------------|-------------------|-------------------|---------------------|
| BB/ACEI/ARB/AA | | 127 (11.1) | 215 (4.2) | 436 (5.9) |
| | Diuretics | 1 (0.1) | 7 (0.1) | 10 (0.1) |
| | BB | 3 (0.3) | 6 (0.1) | 10 (0.1) |
| | BB/ACEI/ARB | 14 (1.2) | 13 (0.2) | 33 (0.4) |
| | BB/ACEI/ARB/AA | 93 (8.1) | 160 (3.1) | 323 (4.4) |
| | Digoxine or ivabradine | 7 (0.6) | 5 (0.1) | 19 (0.3) |
| | No HFrEF treatment | 5 (0.4) | 10 (0.2) | 21 (0.3) |
| | Death | 4 (0.3) | 14 (0.2) | 20 (0.2) |
| Digoxine or ivabradin | | 62 (5.4) | 268 (5.3) | 396 (5.4) |
| | Diuretics | 2 (0.2) | 5 (0.1) | 8 (0.1) |
| | BB | 1 (0.1) | 7 (0.1) | 10 (0.1) |
| | BB/ACEI/ARB | 4 (0.3) | 11 (0.2) | 22 (0.3) |
| | BB/ACEI/ARB/AA | 1 (0.1) | 6 (0.1) | 7 (0.1) |
| | Digoxine or ivabradine | 49 (4.3) | 203 (4.0) | 302 (4.1) |
| | No HFrEF treatment | 5 (0.4) | 17 (0.3) | 24 (0.3) |
| | Death | 0 (0.0) | 19 (0.4) | 23 (0.3) |
| Death | Death | 53 (4.6) | 663 (13.1) | 802 (10.9) |
| <u>From quarters 2 to 3^d</u> | | | | |
| No HFrEF treatment | | 244 (21.3) | 882 (17.4) | 1,348 (18.2) |
| | Diuretics | 13 (1.1) | 81 (1.64) | 114 (1.5) |
| | BB | 14 (1.2) | 34 (0.7) | 56 (0.8) |
| | BB/ACEI/ARB | 35 (3.1) | 100 (2.0) | 167 (2.3) |
| | BB/ACEI/ARB/AA | 6 (0.5) | 15 (0.3) | 25 (0.3) |
| | Digoxine or ivabradine | 2 (0.2) | 23 (0.5) | 29 (0.4) |
| | No HFrEF treatment | 163 (14.2) | 526 (10.4) | 836 (11.3) |
| | Death | 11 (1.0) | 103 (2.0) | 121 (1.6) |
| Diuretics | | 70 (6.1) | 639 (12.6) | 816 (11.0) |
| | Diuretics | 36 (3.1) | 413 (8.2) | 516 (7.0) |
| | BB | 3 (0.3) | 16 (0.3) | 26 (0.4) |
| | BB/ACEI/ARB | 8 (0.7) | 44 (0.9) | 63 (0.9) |
| | BB/ACEI/ARB/AA | 3 (0.3) | 10 (0.2) | 13 (0.2) |
| | Digoxine or ivabradine | 2 (0.2) | 12 (0.2) | 15 (0.2) |
| | No HFrEF treatment | 12 (1.0) | 100 (2.0) | 131 (1.8) |
| | Death | 6 (0.5) | 44 (0.9) | 52 (0.7) |

| | | | | |
|-------------------------------|------------------------|-------------------|---------------------|---------------------|
| BB | | 99 (8.6) | 467 (9.2) | 672 (9.1) |
| | Diuretics | 2 (0.2) | 21 (0.4) | 28 (0.3) |
| | BB | 61 (5.3) | 339 (6.7) | 479 (6.5) |
| | BB/ACEI/ARB | 18 (1.6) | 34 (0.7) | 60 (0.8) |
| | BB/ACEI/ARB/AA | 5 (0.4) | 8 (0.2) | 14 (0.2) |
| | Digoxine or ivabradine | 1 (0.1) | 11 (0.2) | 16 (0.2) |
| | No HFrEF treatment | 10 (0.9) | 30 (0.6) | 47 (0.6) |
| | Death | 2 (0.2) | 24 (0.5) | 28 (0.4) |
| BB/ACEI/ARB | | 406 (35.4) | 1,365 (27.0) | 2,174 (29.4) |
| | Diuretics | 2 (0.2) | 50 (1.0) | 57 (0.8) |
| | BB | 9 (0.8) | 46 (0.9) | 73 (1.0) |
| | BB/ACEI/ARB | 346 (30.2) | 1088 (21.5) | 1761 (23.8) |
| | BB/ACEI/ARB/AA | 16 (1.2) | 25 (0.5) | 55 (0.7) |
| | Digoxine or ivabradine | 4 (0.3) | 18 (0.4) | 25 (0.3) |
| | No HFrEF treatment | 23 (2.0) | 88 (1.7) | 136 (1.8) |
| | Death | 6 (0.5) | 50 (1.0) | 67 (0.9) |
| BB/ACEI/ARB/AA | | 149 (13.0) | 300 (5.9) | 565 (7.6) |
| | Diuretics | 1 (0.1) | 8 (0.2) | 11 (0.1) |
| | BB | 1 (0.1) | 9 (0.2) | 12 (0.2) |
| | BB/ACEI/ARB | 12 (1.0) | 24 (0.5) | 46 (0.6) |
| | BB/ACEI/ARB/AA | 123 (10.7) | 219 (4.3) | 434 (5.9) |
| | Digoxine or ivabradine | 2 (0.2) | 4 (0.1) | 7 (0.1) |
| | No HFrEF treatment | 8 (0.7) | 24 (0.5) | 38 (0.5) |
| | Death | 2 (0.2) | 12 (0.2) | 17 (0.2) |
| Digoxine or ivabradine | | 97 (8.5) | 378 (7.5) | 567 (7.7) |
| | Diuretics | 1 (0.1) | 17 (0.3) | 23 (0.3) |
| | BB | 2 (0.2) | 12 (0.2) | 17 (0.2) |
| | BB/ACEI/ARB | 4 (0.3) | 29 (0.6) | 40 (0.5) |
| | BB/ACEI/ARB/AA | 4 (0.3) | 5 (0.1) | 12 (0.1) |
| | Digoxine or ivabradine | 77 (6.7) | 268 (5.3) | 413 (5.6) |
| | No HFrEF treatment | 7 (0.6) | 33 (0.7) | 41 (0.6) |
| | Death | 2 (0.2) | 14 (0.3) | 21 (0.3) |
| Death | Death | 82 (7.1) | 1028 (20.3) | 1245 (16.9) |

From quarters 3 to 4^h

| | | | | |
|---------------------------|------------------------|-------------------|---------------------|---------------------|
| No HFrEF treatment | | 223 (19.4) | 801 (15.8) | 1,229 (16.6) |
| | Diuretics | 11 (1.0) | 76 (1.5) | 101 (1.4) |
| | BB | 8 (0.7) | 31 (0.6) | 42 (0.6) |
| | BB/ACEI/ARB | 28 (2.4) | 77 (1.5) | 125 (1.7) |
| | BB/ACEI/ARB/AA | 5 (0.4) | 18 (0.4) | 31 (0.4) |
| | Digoxine or ivabradine | 6 (0.5) | 23 (0.5) | 33 (0.4) |
| | No HFrEF treatment | 157 (13.7) | 507 (10.0) | 808 (10.9) |
| | Death | 8 (0.7) | 69 (1.4) | 89 (1.2) |
| Diuretics | | 55 (4.8) | 590 (11.7) | 749 (10.1) |
| | Diuretics | 35 (3.1) | 407 (8.0) | 515 (7.0) |
| | BB | 3 (0.3) | 22 (0.4) | 31 (0.4) |
| | BB/ACEI/ARB | 2 (0.2) | 29 (0.6) | 36 (0.5) |
| | BB/ACEI/ARB/AA | 2 (0.2) | 8 (0.2) | 12 (0.2) |
| | Digoxine or ivabradine | 1 (0.1) | 14 (0.3) | 17 (0.2) |
| | No HFrEF treatment | 9 (0.8) | 80 (1.6) | 97 (1.3) |
| | Death | 3 (0.3) | 30 (0.6) | 41 (0.6) |
| BB | | 90 (7.8) | 456 (9.0) | 663 (9.0) |
| | Diuretics | 1 (0.1) | 23 (0.5) | 28 (0.4) |
| | BB | 63 (5.5) | 312 (6.2) | 446 (6.0) |
| | BB/ACEI/ARB | 11 (1.0) | 39 (0.8) | 64 (0.9) |
| | BB/ACEI/ARB/AA | 1 (0.1) | 6 (0.1) | 10 (0.1) |
| | Digoxine or ivabradine | 2 (0.2) | 6 (0.1) | 10 (0.1) |
| | No HFrEF treatment | 11 (1.0) | 47 (0.9) | 76 (1.0) |
| | Death | 1 (0.1) | 23 (0.5) | 29 (0.4) |
| BB/ACEI/ARB | | 423 (36.9) | 1,319 (26.1) | 2,137 (28.9) |
| | Diuretics | 3 (0.3) | 36 (0.7) | 48 (0.6) |
| | BB | 13 (1.1) | 42 (0.8) | 73 (1.0) |
| | BB/ACEI/ARB | 351 (30.6) | 1043 (20.6) | 1720 (23.3) |
| | BB/ACEI/ARB/AA | 6 (0.5) | 22 (0.4) | 37 (0.5) |
| | Digoxine or ivabradine | 5 (0.4) | 25 (0.5) | 36 (0.5) |
| | No HFrEF treatment | 39 (3.4) | 96 (1.9) | 159 (2.2) |
| | Death | 6 (0.5) | 55 (1.1) | 64 (0.9) |
| BB/ACEI/ARB/AA | | 157 (13.7) | 282 (5.6) | 553 (7.5) |
| | Diuretics | 1 (0.1) | 9 (0.2) | 12 (0.2) |

| | | | | |
|-------------------------------|------------------------|-----------------|------------------|------------------|
| | BB | 2 (0.2) | 10 (0.2) | 14 (0.2) |
| | BB/ACEI/ARB | 15 (1.3) | 33 (0.7) | 57 (0.8) |
| | BB/ACEI/ARB/AA | 125 (10.9) | 200 (4.0) | 416 (5.6) |
| | Digoxine or ivabradine | 3 (0.3) | 5 (0.1) | 8 (0.1) |
| | No HFrEF treatment | 8 (0.7) | 15 (0.3) | 31 (0.4) |
| | Death | 3 (0.3) | 10 (0.2) | 15 (0.2) |
| Digoxine or ivabradine | | 88 (7.7) | 336 (6.6) | 505 (6.8) |
| | Diuretics | 0 (0.0) | 6 (0.1) | 6 (0.1) |
| | BB | 0 (0.0) | 8 (0.2) | 10 (0.1) |
| | BB/ACEI/ARB | 4 (0.3) | 18 (0.4) | 25 (0.3) |
| | BB/ACEI/ARB/AA | 1 (0.1) | 3 (0.1) | 7 (0.1) |
| | Digoxine or ivabradine | 78 (6.8) | 269 (5.3) | 414 (5.6) |
| | No HFrEF treatment | 3 (0.3) | 22 (0.4) | 30 (0.4) |
| | Death | 2 (0.2) | 10 (0.2) | 13 (0.2) |
| Death | Death | 111 (9.7) | 1275 (25.2) | 1551 (21.0) |

Supplementary Table 2. Sensitivity analyses where HF treatment exposure was assessed quarterly using the Proportion of Days Covered (PDC) varying from 50% to 80%

| | PDC ≥ 50% | | | PDC ≥ 80% | | |
|---|-----------------------------|------------------------|---------------------|-----------------------------|------------------------|---------------------|
| | [40;65 years n = 1,147 | ≥75 years n = 5,059 | Cohort n = 7,387 | [40;65 years n = 1,147 | ≥75 years n = 5,059 | Cohort n = 7,387 |
| During the 1st quarter after index hospital discharge | | | | | | |
| No HFrEF treatment, n (%) | 266 (23.2) | 1,144 (22.6) | 1,689 (22.9) | 755 (65.8) | 3,179 (62.8) | 4,699 (63.6) |
| HFrEF treatment, n (%) | 828 (72.2) | 3,252 (64.3) | 4,896 (66.3) | 339 (29.6) | 1,217 (24.1) | 1,886 (25.5) |
| Diuretics alone | 78 (6.8) | 654 (12.9) | 843 (11.4) | 48 (4.2) | 309 (6.1) | 409 (5.5) |
| BB alone | 91 (7.9) | 502 (9.9) | 689 (9.3) | 45 (3.9) | 210 (4.2) | 301 (4.1) |
| BB/ACEI/ARB | 399 (34.8) | 1,413 (27.9) | 2,198 (29.8) | 166 (14.5) | 509 (10.1) | 832 (11.3) |
| BB/ACEI/ARB/AA | 169 (14.7) | 297 (5.9) | 595 (8.1) | 57 (5.0) | 90 (1.8) | 188 (2.5) |
| Any combination with digoxine or ivabradine | 91 (7.9) | 386 (7.6) | 571 (7.7) | 23 (2.0) | 99 (2.0) | 156 (2.1) |
| During the 2nd quarter after index hospital discharge | | | | | | |
| No HFrEF treatment, n (%) | 190 (16.6) | 668 (13.2) | 1036 (14.0) | 345 (30.1) | 1,304 (25.8) | 1,962 (26.6) |
| HFrEF treatment, n (%) | 875 (76.3) | 3,363 (66.5) | 5,106 (69.1) | 720 (62.8) | 2,727 (53.9) | 4,180 (56.6) |
| Diuretics alone | 74 (6.5) | 642 (12.7) | 823 (11.1) | 66 (5.8) | 578 (11.4) | 749 (10.1) |
| BB alone | 97 (8.5) | 479 (9.5) | 676 (9.2) | 95 (8.3) | 432 (8.5) | 626 (8.5) |
| BB/ACEI/ARB | 433 (37.8) | 1,459 (28.8) | 2,323 (31.4) | 356 (31.0) | 1,194 (23.6) | 1,908 (25.8) |
| BB/ACEI/ARB/AA | 166 (14.5) | 343 (6.8) | 636 (8.6) | 121 (10.5) | 232 (4.6) | 453 (6.1) |
| Any combination with digoxine or ivabradine | 105 (9.2) | 440 (8.7) | 648 (8.8) | 82 (7.1) | 291 (5.8) | 444 (6.0) |
| During the 3rd quarter after index hospital discharge | | | | | | |
| No HFrEF treatment, n (%) | 174 (15.2) | 596 (11.8) | 936 (12.7) | 320 (27.9) | 1182 (23.4) | 1804 (24.4) |
| HFrEF treatment, n (%) | 862 (75.2) | 3,188 (63.0) | 4,900 (66.3) | 716 (62.4) | 2602 (51.4) | 4032 (54.6) |
| Diuretics alone | 58 (5.1) | 609 (12.0) | 767 (10.4) | 56 (4.9) | 520 (10.3) | 676 (9.2) |
| BB alone | 96 (8.4) | 458 (9.1) | 669 (9.1) | 87 (7.6) | 422 (8.3) | 624 (8.4) |
| BB/ACEI/ARB | 434 (37.8) | 1,402 (27.7) | 2,253 (30.5) | 372 (32.4) | 1157 (22.9) | 1870 (25.3) |
| BB/ACEI/ARB/AA | 171 (14.9) | 333 (6.6) | 627 (8.5) | 127 (11.1) | 230 (4.5) | 444 (6.0) |
| Any combination with digoxine or ivabradine | 103 (9.0) | 386 (7.6) | 584 (7.9) | 74 (6.5) | 273 (5.4) | 418 (5.7) |
| During the 4th quarter after index hospital discharge | | | | | | |
| No HFrEF treatment, n (%) | 183 (16.0) | 561 (11.1) | 902 (12.2) | 334 (29.1) | 1131 (22.4) | 1765 (23.9) |
| HFrEF treatment, n (%) | 830 (72.4) | 3,026 (59.8) | 4,683 (63.4) | 679 (59.2) | 2456 (48.5) | 3820 (51.7) |
| Diuretics alone | 53 (4.6) | 582 (11.5) | 735 (9.9) | 47 (4.1) | 522 (10.3) | 668 (9.0) |
| BB alone | 87 (7.6) | 443 (8.8) | 631 (8.5) | 90 (7.8) | 381 (7.5) | 567 (7.7) |
| BB/ACEI/ARB | 437 (38.1) | 1,310 (25.9) | 2,156 (29.2) | 347 (30.3) | 1076 (21.3) | 1753 (23.7) |
| BB/ACEI/ARB/AA | 152 (13.3) | 301 (5.9) | 583 (7.9) | 119 (10.4) | 206 (4.1) | 418 (5.7) |
| Any combination with digoxine or ivabradine | 101 (8.8) | 390 (7.7) | 578 (7.8) | 76 (6.6) | 271 (5.4) | 414 (5.6) |

BB: Beta Blockers; ACEI: Angiotensin-Converting Enzyme Inhibitors ; ARB: Angiotensin Receptor Blockers ; AA: aldosterone antagonists; CCB: Calcium Channel Blockers

3.4. Discussion of main results

This study showed that a substantial proportion of HF patients were not exposed to any HFrEF treatment in the first year following hospital discharge for HF and that most of the initially untreated patients initiated treatment after a delay of around 3 months. These results are consistent with existing data [54]. These findings also suggest that studies on treatment adherence [62, 63] or persistence [53–55] may have reported overestimated estimates as they focused only on patients who initiated treatment at discharge but not on patients who initiated therapy as outpatients, within the first 3 months after discharge hospitalization for instance.

In view of the chronic nature and activity of HF, we have made the choice of assessing quarterly treatment exposure to describe as accurately as possible the constant adjustment of HF medications over time. This study provides thus a dynamic description of the HF treatment use, which was lacking so far, but does not allow to draw conclusions regarding untreated patients. The absence of treatment may be considered as a sub-optimal adherence, but it may be also related to a medically justified reason (i.e., patients with mild HF symptoms, effective non-pharmacological treatment, patients who did not tolerate treatment or with severe comorbidities).

One important limitation of this study is the non-availability of some relevant data in the EGB database, such as the ejection fraction, useful to distinguish between HFrEF and HFpEF patients, the NYHA class necessary to assess HF severity, or the reason for office visits, important to identify better the onset of HF or the reason of treatment non-adherence. This is important to consider since it may impact the generalizability of the results.

3.5. Conclusion

Findings of this study support the idea that HF patients do not use HF treatments optimally after an initial HF hospitalization. This sub-optimal use of HF treatment could be one factor explaining why these treatments have a limited impact in clinical practice and HF morbidity and mortality continue to be significant.

After having carried out a study describing the pharmacological treatment patterns of HF patients in France in clinical practice, we have decided to focus on identifying the risk

factors - pharmacological and non-pharmacological of cardiac decompensation in real world setting. This was the third objective of this thesis.

4. CLINICAL PREDICTORS OF HEART FAILURE DECOMPENSATION

4.1. Rationale

Despite the successful and significant advances in treatment strategies and improvement of primary prevention the risk of post-discharge mortality and rehospitalisation remains high. The development of prognostic models is essential to identify the determinants of the course and outcome of patients with HF. Prognostic characteristics identified through these models allow to establish high-risk profile for HF patients from the outset of the disease and to identify possible therapeutic targets.

Identification of predictors associated with all cause mortality is useful to assess the prognostic of the disease, which appear to be worse than for many cancers with an estimated 50% of HF patients dying within 5 years of the diagnosis [14]. However, assessment of all-cause mortality alone does not allow discernment of risk related to the comorbidity vs. risk associated with HF itself. HF patients are elderly patients with multiple age-related comorbidities and each comorbidity may impart a mortality risk. These elderly patients may thus die either of the disease itself, related cardiovascular causes or age-associated non-cardiovascular causes. According to literature, cardiovascular deaths constitute the majority of deaths – including mostly sudden death and heart failure death -, but non-cardiovascular deaths still constitute between 30 and 50% of deaths [88, 89].

Another approach to better understanding the mechanisms underlying the poor prognosis of HF patients is thus to assess the predictors of cardiac decompensation, which manifests itself by a HF worsening leading to a HF readmission in serious cases or managed at home by the administration of high-ceiling diuretics. One important consideration when assessing predictors of cardiac decompensation is to take into account competing events such as death. A competing event is defined as an event that precludes the event of interest from occurring or fundamentally changes its probability. It can lead to a bias in the estimates by informative censoring [90].

We thus decided to study the predictors of cardiac decompensation, managed in hospital or at home, among HF patients after an initial hospitalization for HF and taking into account the competing risk of death.

4.2. Research hypothesis and objectives

Several studies have already focused on identifying predictors of HF readmission with different settings and varying periods of follow-up, but to date and to our knowledge, none has taken into account competing risk of death in the analyses and none has studied cardiac decompensation as we considered it. The objective of this work was thus to describe the probability of repeat HF decompensation within the 2 years following a first hospitalization for HF, and to identify associated risk factors taking into account the competing risk of death in a real-world setting, using data from the random sample of the French nationwide claims database, the EGB.

Results of this study have been submitted to *Journal of Cardiovascular Pharmacology and Therapeutics*.

4.3. Article

4.3.1. Reference

Bosco-Lévy P, Favary C, Jové J, Lassalle R, Moore N, Droz-Perroteau C. Predictors of heart failure decompensation: a population based cohort study. Submitted to J. Cardiovasc. Pharmacol. Ther., October 2019.

4.3.2. Abstract

Aims: After a first hospitalization for Heart Failure (HF), patients are at high risk of experiencing repeat cardiac decompensation. Existing information on the predictors of HF readmission need to be updated, and predictors derived from ambulatory HF treatment, of which little is known. The aim of this study is to describe the probability of repeat HF decompensation within the 2 years following a first hospitalization for HF, and to identify associated risk factors.

Methods: All patients aged ≥ 40 years with an incident HF hospitalization between 2008 and 2013, were identified in the 1/97th permanent random sample of the French nationwide claims database and followed 2 years. Outcomes were readmission for HF or ambulatory treatment for Acute Heart Failure (AHF) (initiation or increase of high ceiling diuretics). The Cumulative Incidence Function method was used to estimate the probability of each event, taking into account a competing risk of death.

Results: At 2 years, 21.0% of HF patients had been re-hospitalized and 29.9% received ambulatory AHF treatment. The risk of readmission or ambulatory AHF

treatment significantly increased with age (Hazard Ratio, HR: 1.29 / 1.54 respectively), high blood pressure (HR: 1.42 / 1.58), atrial fibrillation (HR: 1.27 / 1.19), and diabetes (HR: 1.26 / 1.21).

Conclusion: These results will contribute to a better management of patients, and prevention of repeat hospital admission in patients with a first hospital admission for heart failure.

Predictors of heart failure decompensation: a population based cohort study

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Keywords: Heart Failure; cardiac decompensation; Heart failure readmission; ambulatory Heart Failure treatment; claims database

Word count of the text: 2882 words

ABSTRACT

Background: After a first hospitalization for Heart Failure (HF), patients are at high risk of experiencing repeat cardiac decompensation. Existing information on the predictors of HF readmission need to be updated, and predictors derived from ambulatory HF treatment, of which little is known.

Aims: The aim of this study is to describe the probability of repeat HF decompensation within the 2 years following a first hospitalization for HF, and to identify associated risk factors.

Methods: All patients aged ≥ 40 years with an incident HF hospitalization between 2008 and 2013, were identified in the 1/97th permanent random sample of the French nationwide claims database and followed 2 years. Outcomes were readmission for HF or ambulatory treatment for Acute Heart Failure (AHF) (initiation or increase of high ceiling diuretics). The Cumulative Incidence Function method was used to estimate the probability of each event, taking into account a competing risk of death.

Results: At 2 years, 21.0% of HF patients had been re-hospitalized and 29.9% received ambulatory AHF treatment. The risk of readmission or ambulatory AHF treatment significantly increased with age (Hazard Ratio, HR: 1.29 / 1.54 respectively), high blood pressure (HR: 1.42 / 1.58), atrial fibrillation (HR: 1.27 / 1.19), and diabetes (HR: 1.26 / 1.21).

Conclusion: These results will contribute to a better management of patients, and prevention of repeat hospital admission in patients with a first hospital admission for heart failure.

Word count of the abstract: 231/250 words

INTRODUCTION

The successful and significant advances in treatment strategies and improvement of primary prevention has led to a substantial decline of Heart Failure (HF) incidence over the last decade (1). However, HF patients remain at very high risk of hospitalization and/or death (2,3). Approximately 17–27% of patients are re-hospitalized for any reason within 30 days, and up to 50% are readmitted by 6 months (4–6). Around one third of these hospitalizations are caused by acute decompensated HF (7–10), for which inpatient treatment involves the management of the cause of decompensation and the administration of an intravenous diuretic to effectively reduce the systemic and pulmonary congestion (11,12). In-hospital mortality ranges from 4% to 7% (13), but the real problem starts when a patient is discharged from the hospital and enters the most vulnerable post-discharge phase: just during the first 90 days after hospital discharge 10–15% of patients die (14). When HF patients experience volume overload without meeting hospitalization criteria, they can be treated in ambulatory with diuretics and the adequate treatment of the underlying cause of decompensation (15). Outpatient use of diuretic then reflects an exacerbation of the disease.

One possible solution for physicians to identify high-risk patients, and better customize effective interventions, would be to identify the early and long-term predictors of cardiac decompensation. Numerous studies have been conducted to identify factors associated with AHF readmission (7–9) but to our knowledge none has focused on factors associated with outpatient initiation/increase use of diuretics so far.

Moreover, to study the HF decompensation end-point, competing events as death need to be taken into account to ensure that estimates will not be biased by informative censoring (16).

The aim of this study is thus to describe the probability of HF decompensation leading to an HF readmission or increased ambulatory care and to identify the associated risk factors,

within the 2 years following a first hospitalization for HF, taking into account competing risk of death and, data from the French nationwide healthcare database.

METHOD

Study design and data source

This cohort study was conducted using data from the *Echantillon Généraliste de Bénéficiaires* (EGB) database, a representative permanent 1/97th sample of the national healthcare data system in France, *Système National des Données de Santé* (SNDS) which covers 99% of the French population from birth to death (17). Complete data before 2011 are available only for subjects covered by the main insurance plan, covering salaried employees and their dependents, i.e., 76% of the French population. For each insured person, SNDS provides pseudonymized information on all reimbursed medical and paramedical encounters, drugs claims, hospital admissions and procedures (except for psychiatric hospitals and rehabilitation centers), registration for Long Term Diseases (LTD) dispensing from copayment, and date of death, but not its cause. Hospital diagnoses are coded according to the International Classification of Disease 10th edition (ICD-10) and the quality of this coding is ensured by regular internal and external audits (18). The quality of hospital coding for HF has been verified. (19)

Study population

We included in the cohort all patients aged over 40, covered by the main health insurance plan, with a first hospitalization for HF between January 1, 2008 and December 31, 2013. An incident HF hospitalization was defined as a first hospitalization with a discharge code I50.x of the ICD-10 in any diagnostic position, with no LTD registration or hospital admission for HF in the 2 previous years. The date of the incident HF hospitalization discharge was defined as the index date. Patients were required to have a pre-index period of 1 year and at least 2 year of follow-up after the index date (excluding deaths). We excluded all patients who died

during the index hospitalization. Patients were followed for 2 years after index date or until death or outcome whichever came first.

Outcomes of interest

The outcome measures assessed over 2 years after index hospitalization were HF readmission and ambulatory Acute Heart Failure (AHF) treatment. HF readmission was defined as any hospitalization of more than 24 hours with a diagnosis of AHF identified based on the algorithm developed by the custodians of the French national healthcare system (20), which includes the validated ICD-10 discharge code I50.x (Predictive Positive Value: 88.0%) (3). Ambulatory AHF treatment included outpatient initiation or increase of loop diuretic (i.e. furosemide ATC code C03CA01 or bumetanide ATC code C03CA02). Initiation of loop diuretic was defined as a new dispensing of loop diuretic in patients who have not received any loop diuretic within the 3 months following the index date. Increase in loop diuretic was defined as a dispensing of loop diuretic with an equivalent to furosemide dose (20 mg furosemide intravenous = 40 mg furosemide *per os* = 0,5 mg bumetanide intravenous = 0,5 mg bumetanide *per os*) (21) that was strictly greater than 40 mg per day and higher than the daily dose of the initial loop diuretic treatment initiated within the 91 days after index hospitalization.

Predictors

Potential predictors were selected based on review of the literature, clinical relevance, and availability (7–9). These included demographic characteristics at index date, length of stay in the index hospitalization, and other potential candidate variables selected during the year before the index hospitalization such as preexisting comorbid conditions, number of hospitalizations, number of office visits to the general practitioner or the cardiologist and

number of distinct medications based on ATC level 3. We did not consider echocardiography or BNP performed within the year preceding index hospitalization as potential predictors, since their coding is not reliable. Indeed, echocardiography is not systematically coded during a cardiology visit, as the levels of reimbursement may be similar for a visit with or without echocardiography, and BNP could not be identified when it is performed in a public hospital, as it is not reimbursed individually.

Statistical Analyses

Main analysis

We performed descriptive analyses where categorical variables were described in number and percent, and quantitative variable in mean and standard deviation (SD) or median and interquartile range (IQR). The cumulative probability of having each event was estimated using the Cumulative Incidence Function (CIF) method, which incorporates competing risks of death from any cause (22). The CIF method is the sum of the conditional probabilities of having the outcome given that individual is alive in each interval of the follow-up period. CIF estimates were presented as percentage with 95% confidence intervals (95% CI). A Fine and Gray model was then used to assess the predictors of HF readmission and ambulatory HF treatment at 2 years after index hospitalization, accounting for the competing risk of death. For the outcome ambulatory AHF treatment, the original date of the model was shifted to 91 days after the index hospitalization discharge to avoid the immortal time bias (23) induced by the definition of the outcome. The variables were introduced in a multivariate model if their significance was <0.25 in univariate analysis and if they fulfilled the hypothesis of linearity and the hypothesis about the probabilities of risk. Variables were then retained in the multivariate model if they were significantly associated with the outcome after adjusting for

age, sex and cardiovascular comorbidities. Results are presented as Hazard Ratios (HR) with 95% CI.

Sensitivity analysis

In order to distinguish the early risk factors from late onset risk factors, we performed similarly a predictive model for each outcome at 6 months after index hospitalization.

RESULTS

Among the 10,915 patients identified in the EGB who had an incident hospitalization for HF between 2008 and 2013, 7,708 met the inclusion criteria (Figure 1).

Baseline characteristics

Characteristics of the study population at baseline and description of the index hospitalization are reported in Table 1. Patients had a mean age of 77.9 years (\pm 12.1 years), with slightly fewer males (47.9%) than females (52.1%). The most frequent cardiovascular conditions were: high blood pressure (HBP; 84.7%), atrial fibrillation (40.2%) and ischemic heart disease (33.3%). About one fourth of patients had diabetes (27.3%) or a chronic respiratory disease (27.8%) and 14.3% had chronic renal failure. Within the 12 months pre-index period, patients had a median of 12 (IQR [7.0; 18.0]) outpatient consultations, especially at the general practitioner. The median number of previous hospitalizations was 2.0 (IQR [1.0; 3.0]) and the median number of distinct medications dispensed within the pre-index period was 17.0 (IQR [12.0; 22.0]). The median duration of the index hospitalization was 8.0 days (IQR [4.0; 14.0]). For 15% of patients, a measure of plasma BNP or an echocardiography was performed during the stay. Three quarter of patients returned home after hospitalization discharge.

Outcomes

The cumulative incidence of HF readmission rose from a minimum of 11.6% (95%CI 10.9; 12.3) at 6 months after index hospitalization to a maximum of 21.0% (CI95% 20.1; 22.0) in the 2nd year (Figure 2 and Supplementary Table 1). The cumulative incidence of ambulatory AHF treatment was 8.9% (95%CI 8.3; 9.6) at 6 months after index hospitalization and reached 29.9% (95%CI 28.8; 30.9) in the 2nd year.

Predictors of outcomes

The association with each risk factor is presented in Table 2 for each outcome. The risk for HF readmission or ambulatory AHF treatment significantly increased with age for [65; 75[and ≥ 75 years (HRs vs. [40; 65[years : 1.38 and 1.54; 1.29 and 1.39 respectively for each outcome), High blood pressure (HBP) (HRs: 1.42 and 1.54 respectively), atrial fibrillation (HRs: 1.27 and 1.19 respectively), diabetes (HRs: 1.26 and 1.21 respectively) and other cardio-neurovascular conditions (HRs: 1.14 and 1.15 respectively). Ischemic heart disease, dilated cardiomyopathy, valvulopathy and chronic renal failure increased significantly HF readmission risk only (HRs: 1.15, 1.23, 1.30 and 1.31 respectively). For the number of distinct medications there was a significant increased risk only for ambulatory AHF treatment for]12; 17],]17; 22] and >22 medications (HRs vs. ≤ 12 : 1.16, 1.33, 1.50 respectively) and hospitalization for AHF within the 3 months following the index date (HR: 1.55). Stroke was associated with decreased risk for both HF readmission and ambulatory AHF treatment (HRs: 0.72 and 0.77 respectively), cancer and dementia were associated with decreased risk for HF readmission (HR: 0.72 and 0.73 respectively) and length of stay in the index hospitalization of more than 14 days was inversely associated with ambulatory AHF treatment (HR vs. ≤ 7 days: 0.88).

Sensitivity analysis

Most of the risk factors associated with HF readmission at 2 years after index hospitalization were similarly associated after 6 months. HBP, atrial fibrillation, ischemic heart disease and dilated cardiomyopathy, other cardio-neurovascular conditions, valvulopathy and chronic renal failure were associated with increased risk of HF readmission (HRs: 1.34, 1.26, 1.22, 1.42, 1.16, 1.47, 1.56 respectively) while cancer and stroke were associated with decreased risk of HF readmission (HRs: 0.72 and 0.71 respectively) (Table 3). By comparison with the

2-year analysis, HBP, previous hospitalization for AHF within the 3 months following the index date and >22 medications dispensed within the previous 12 months were associated with increased risk of ambulatory AHF treatment (HRs: 1.52, 2.03 and HRs vs. ≤ 12 medications: 1.53 respectively. Being female also had a protective effect on the risk of ambulatory AHF treatment (HR: 0.85).

DISCUSSION

This population-based cohort study has shown that 21% of HF patients were readmitted for HF and 29.9% had ambulatory AHF treatment within 2 years after index hospitalization, taking into account competing risk of death. Moreover, increasing age, and the presence of HBP, diabetes and atrial fibrillation were independently associated with these 2 outcomes.

Patient characteristics

Patients included in this study were old (mean age of 77.9 years), more likely to be female and had multiple comorbidities. Patients included after HF admission as in our study, tend to have a worse clinical profile compared to ambulatory patients included in randomized clinical trials (24–27). This is not surprising since study populations in clinical trials are more homogeneous than in real life setting and some fragile and at-risk specific populations are often not included in these trials (i.e. pregnant women, elderly patients or with renal or liver impairment and short life expectancy). Nevertheless, characteristics of our patients were consistent with those of HF patients after HF admission in observational studies conducted in France (28–30) or in other countries (31–33).

Outcomes

In comparison with literature, our estimates of long-term outcomes were mostly lower (11.6% at 6 months to 21.0% at 2 years after index hospitalization). Existing results concerning HF readmission vary depending on the setting the study setting and the duration of follow-up: at 6 months, HF readmission was 23% to 32% (9), it rose to 35% at 1-year follow-up (34) and reached 36% to 48% at 2-year follow-up (35). The difference observed between our results and those in the literature could be explained by the competing risk statistical approach that we applied. The classic Kaplan-Meier method consistently overestimates the cumulative incidence of the outcome compared to CIF, and the magnitude of the overestimation is all the greater that the number of the competing event is particularly important (36), as is the case for

death in HF (37). Results on the ambulatory AHF treatment cannot be compared to the literature since no study has been carried out on these outcomes to date. Our results showed that HF readmission increased during the 8 first months and was then exceeded by ambulatory AHF treatment.

Factors associated with outcomes

Our study has shown that age, HBP, atrial fibrillation, ischemic heart disease, valvulopathy, dilated cardiomyopathy and chronic renal failure had a positive, although modest, effect on HF readmission. These results are consistent with those of previous studies, within the same order of magnitude (7–9). The factors associated with increased risk of ambulatory AHF were globally the same as those associated with increased risk of HF readmission except for ischemic heart disease, dilated cardiomyopathy, valvulopathy and chronic renal failure for ambulatory AHF treatment. When the number of distinct medications dispensed within the previous 12 months was strictly over 12, the risk of ambulatory AHF treatment increased modestly. Finally, the length of stay of index hospitalization more than 14 days vs. less than 7 days and previous hospitalization for AHF within the 3 months following the index date reduced the risk of ambulatory AHF treatment. The lack of other studies with this outcome does not allow us to compare these results.

Interestingly, cancer, dementia and stroke appeared to be associated with decreased risk of HF readmission. Another study also found that cerebrovascular disease was associated with a lower rate of HF readmission (38). Other infrequently reported that cancer and dementia consistently increased the risk of readmission but these risks were assessed within 6 months following index hospitalization (9). Ambulatory AHF treatment was also inversely associated with stroke. These results may be explained by the fact that these patients benefit from a closer long-term monitoring because of the severity of their disease, which ensures a better

control of their HF. Another reason would be that signs of cardiac decompensation are misdiagnosed in these patients because of the disability associated with the disease (hemiplegia and aphasia in stroke or confusion in dementia). It could thus be relevant to systematically exclude or study separately these patients in future observational studies as in clinical trials.

Limitations

Our study presents several limitations. First, some useful information for characterizing HF patients was lacking in our database. This concerns for instance the ejection fraction (EF), useful to distinguish between HF with reduced EF and HF with preserved EF, the NYHA class necessary to assess HF severity, or the reason for office visits, important to identify better the onset of HF. The lack of data about EF should however not impact our results since the prognosis in term of readmission and mortality is not quite different between these two subgroups of patients (39). Because they were also not available in the database, some important potential risk factors such as serum biomarkers (hemoglobin, sodium serum level, BNP dosage or renal clearance) or psychosocial parameters (marital status, work status or relational environment) were not included in our model. Biological variables were however not relevant predictors in our study, since our objective was to assess the long-term predictors within 2-year follow-up and these parameters were too susceptible to vary between the moment where the dosage was performed and the outcome.

Strengths

This study has also several important strengths. It relies on a high quality database, the EGB, which contains a population representative of the French national population and which thus provides reliable estimates of drug utilization in real world conditions (17). Moreover, the risk of HF misdiagnosis inherent in any administrative database was minimized by using previously validated ICD-10 codes with a good diagnostic performance (PPV: 88.0%) to

select our study population (19). Finally, the sensitivity analysis performed at 6 months after index hospitalization strengthened the findings of the main analysis. It confirmed that most of risk factors identified for each outcomes within the 2 years after index hospitalization, were also early risk factors.

Conclusion

This study confirmed the high rate of HF readmission occurring within the 2 years following an index hospitalization. Results are however less alarming than expected when death is considered as competing event. This study highlights also relevant early and long-term risk factors of HF decompensation managed either in hospital or at home, helping specialists to develop a complete risk profile for HF patients after a first HF hospitalization in order to better customize effective interventions.

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CONFLICTS OF INTEREST

Dr P. Bosco-Lévy, C Favary, J Jové, R Lassalle, C Droz-Perroteau have nothing to disclose.

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AUTHORS' CONTRIBUTION

P Bosco-Lévy, N Moore and C Droz-Perroteau contributed in designing and supervising the study. R Lassalle J. Jové and C. Favary performed the analyses. All authors discussed the results. P Bosco-Lévy wrote the manuscript in consultation with all authors.

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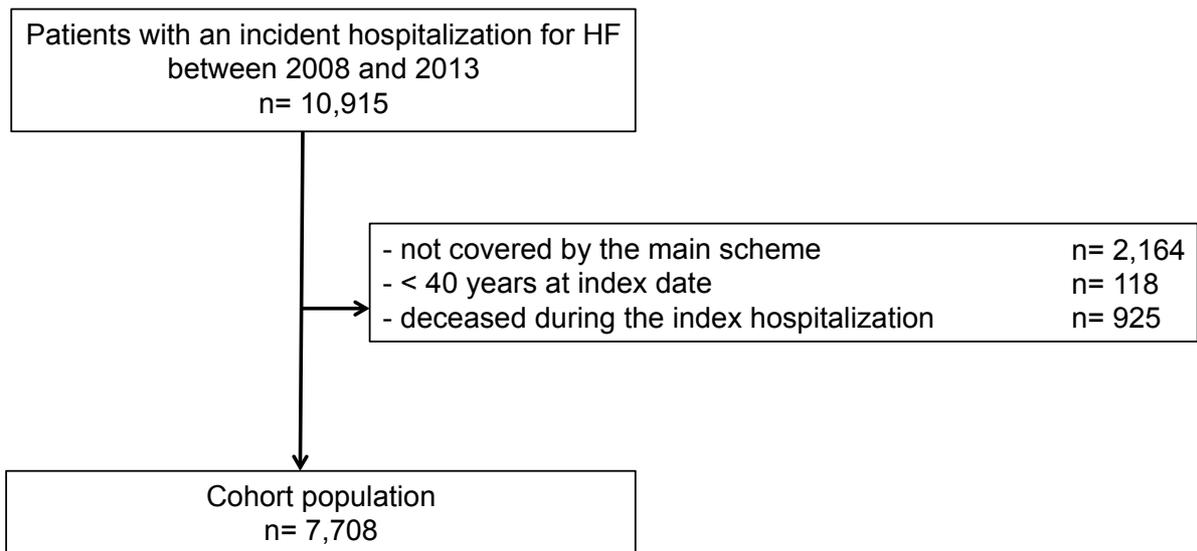


Figure 1. Study flow-chart

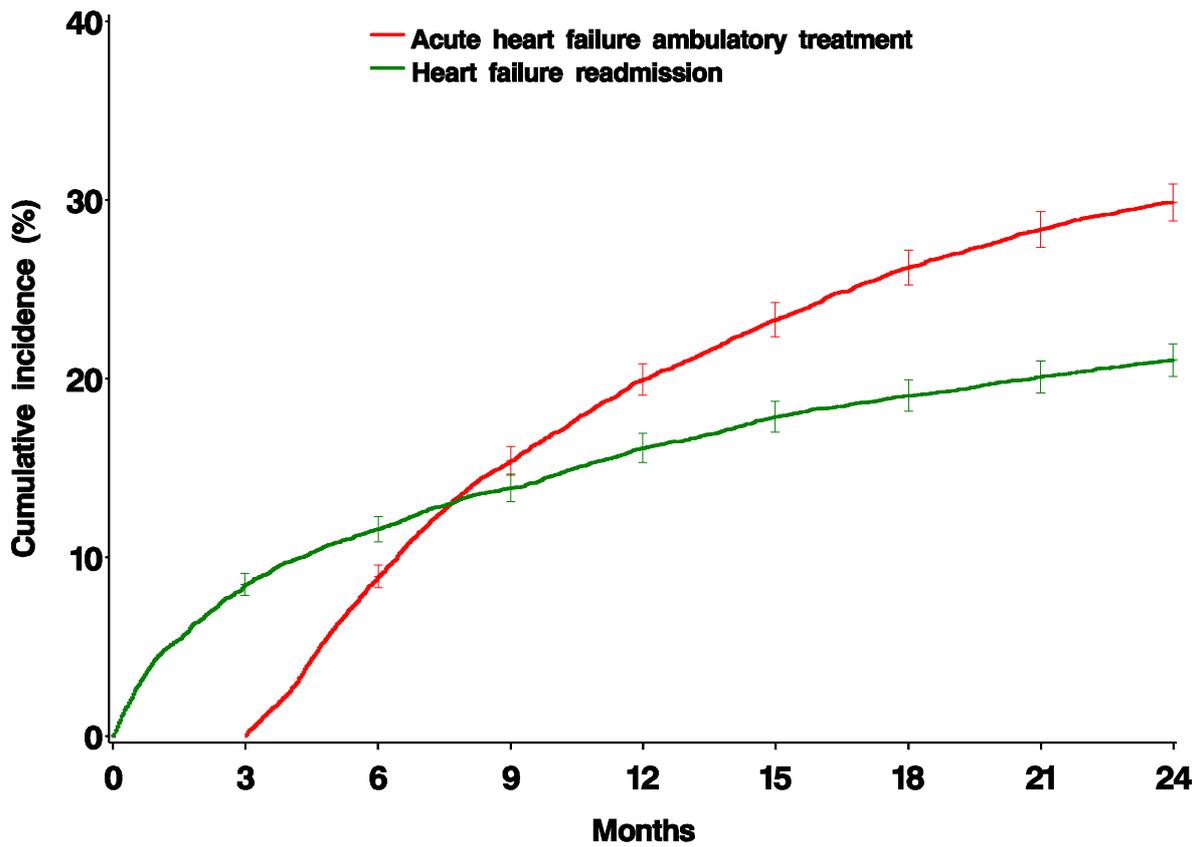


Figure 2. Graphic representation of the probability of Heart Failure (HF) readmission and ambulatory Acute Heart Failure (AHF) treatment within 2 years after the index hospitalization for HF, taking into account competing risk of death (Fine and Gray method). For the outcome ambulatory AHF treatment, the original date of the model was shifted to 91 days after the index hospitalization discharge to avoid the immortal time bias induced by the definition of the outcome.

Table 1. Description of patient baseline and index hospitalization characteristics

| | Cohort n = 7,708 |
|---|-----------------------------|
| Demographic characteristics | |
| Mean age (\pm SD) at index date (in years) | 77.9 (12.1) |
| Sex female, n (%) | 4,016 (52.1) |
| Comorbidities, n (%) | |
| High blood pressure | 6,532 (84.7) |
| Ischemic heart disease | 2,564 (33.3) |
| Cardiac rhythm disorders | 1,485 (19.3) |
| Valvulopathy | 1,351 (17.5) |
| Atrial fibrillation | 3,100 (40.2) |
| Dilated cardiomyopathy | 666 (8.6) |
| Dyslipidemia | 3175 (41.2) |
| Peripheral vascular disease | 614 (8.0) |
| Stroke | 668 (8.7) |
| Other cardio-neurovascular conditions | 2,774 (36.0) |
| Diabetes | 2,106 (27.3) |
| Chronic respiratory disease (asthma or COPD) | 2,145 (27.8) |
| Sleep apnea | 354 (4.6) |
| Cancer | 993 (12.9) |
| Chronic renal failure | 1,106 (14.3) |
| Pancreatic and liver disease | 340 (4.4) |
| Inflammatory disease | 191 (2.5) |
| Dementia | 725 (9.4) |
| Parkinson's disease | 193 (2.5) |
| Epilepsy | 130 (1.7) |
| Psychiatric disease | 938 (12.2) |
| Within the 12 months of pre-index period | |
| Median number [IQR] of office visit per patient at the general practitioner | 12.0 [7.0;18.0] |
| at the cardiologist | 10.0 [6.0;15.0] |
| | 0.0 [0.0;1.0] |
| Median number [IQR] of hospitalizations per patient | 2.0 [1.0;3.0] |
| Median number [IQR] of distinct medications (level 3 of the ATC code) | 17.0 [12.0;22.0] |
| During index hospitalization | |
| Median [IQR] length of stay | 8.0 [4.0;14.0] |
| ≥ 1 medical procedure performed during the stay, n (%) | |
| BNP dosage | 1,164 (15.1) |
| Echocardiography | 1,133 (14.7) |
| Cardiac implantable devices | 63 (0.8) |
| Cardiac rehabilitation | 64 (0.8) |
| Heart transplant | 0 (0.0) |
| Type of hospitalization discharge, n (%) | |
| Home | 5,743 (74.5) |
| Internal or inter-institutional transfer | 1,962 (25.5) |
| Unknown | 3 (0.0) |

Tableau 2. Risk factors associated with Heart Failure (HF) readmission or ambulatory Acute Heart Failure (AHF) treatment in the 2 years following the index HF hospitalization discharge in multivariate analysis considering death as competing risk after and adjustment on age, sex and cardiovascular comorbidities.

| | HF readmission | | Ambulatory AHF treatment | |
|--|-------------------|---------|--------------------------|---------|
| | HR (IC 95%) | p | HR (IC 95%) | p |
| Multivariate model | | | | |
| Age, years | | <0.0001 | | <0.0001 |
| [65; 75[vs. [40; 65[| 1.38 (1.14; 1.68) | | 1.29 (1.10; 1.51) | |
| ≥75 vs. [40; 65[| 1.54 (1.30; 1.82) | | 1.39 (1.22; 1.59) | |
| Sex | | 0.07 | | 0.08 |
| Female vs. Male | 0.91 (0.82; 1.01) | | 0.93 (0.85; 1.01) | |
| High blood pressure | | <0.0001 | | <0.0001 |
| Yes vs. No | 1.42 (1.20; 1.68) | | 1.54 (1.32; 1.79) | |
| Atrial fibrillation | | <0.0001 | | <0.0001 |
| Yes vs. No | 1.27 (1.15; 1.40) | | 1.19 (1.09; 1.30) | |
| Ischemic heart disease | | 0.01 | | 0.88 |
| Yes vs. No | 1.15 (1.03; 1.28) | | 0.99 (0.91; 1.09) | |
| Dilated cardiomyopathy | | 0.02 | | |
| Yes vs. No | 1.23 (1.03; 1.45) | | | |
| Cardiac rhythm disorders | | 0.25 | | 0.28 |
| Yes vs. No | 1.07 (0.95; 1.21) | | 1.06 (0.96; 1.17) | |
| Other cardio-neurovascular conditions | | 0.01 | | 0.002 |
| Yes vs. No | 1.14 (1.03; 1.27) | | 1.15 (1.05; 1.26) | |
| Diabetes | | <0.0001 | | <0.0001 |
| Yes vs. No | 1.26 (1.13; 1.40) | | 1.21 (1.10; 1.32) | |
| Valvulopathy | | <0.0001 | | 0.33 |
| Yes vs. No | 1.30 (1.15; 1.47) | | 1.05 (0.95; 1.18) | |
| Chronic renal failure | | 0.0001 | | |
| Yes vs. No | 1.31 (1.15; 1.50) | | | |
| Cancer | | 0.0001 | | |
| Yes vs. No | 0.72 (0.61; 0.85) | | | |
| Dementia | | 0.001 | | |
| Yes vs. No | 0.72 (0.60; 0.89) | | | |
| Stroke | | 0.001 | | 0.002 |
| Yes vs. No | 0.72 (0.59; 0.87) | | 0.77 (0.66; 0.91) | |
| Number of distinct medications delivered within the previous 12 months | | | | <0.0001 |
|]12; 17] vs. ≤12 | | | 1.16 (1.02; 1.31) | |
|]17; 22] vs ≤12 | | | 1.33 (1.17; 1.51) | |

| | HF readmission | | Ambulatory AHF treatment | |
|--|----------------|---|--------------------------|---------|
| | HR (IC 95%) | p | HR (IC 95%) | p |
| >22 vs. ≤12 | | | 1.50 (1.32; 1.70) | |
| Hospitalization for AHF within the 3 months following the index date | | - | | <0.0001 |
| Yes vs. No | - | | 1.55 (1.35; 1.78) | |
| Number of hospitalizations within the previous 12 months | | | | <0.0001 |
| >3 vs. ≤ 3 | | | 0.77 (0.68; 0.88) | |
| LoS in the index hospitalization (days) | | | | 0.02 |
|]7; 14] vs. ≤ 7 | | | 1.04 (0.95; 1.15) | |
| >14 vs. ≤ 7 | | | 0.88 (0.79; 0.98) | |

Tableau 3. Risk factors associated with Heart Failure (HF) readmission or ambulatory Acute Heart Failure (AHF) treatment in the 6 months following the index HF hospitalization discharge in multivariate analysis considering death as competing risk after and adjustment on sex and cardiovascular comorbidities.

| | HF readmission | | Ambulatory AHF treatment | |
|--|-------------------|---------|--------------------------|---------|
| | HR (IC 95%) | p | HR (IC 95%) | p |
| Multivariate model | | | | |
| Sex | | 0.13 | | 0.04 |
| Female vs. Male | 0.90 (0.78; 1.03) | | 0.85 (0.72; 0.99) | |
| High blood pressure | | 0.01 | | 0.002 |
| Yes vs. No | 1.34 (1.08; 1.65) | | 1.52 (1.17; 1.99) | |
| Atrial fibrillation | | 0.001 | | |
| Yes vs. No | 1.26 (1.10; 1.44) | | | |
| Ischemic heart disease | | 0.007 | | 0.64 |
| Yes vs. No | 1.22 (1.05; 1.40) | | 1.04 (0.88; 1.22) | |
| Dilated cardiomyopathy | | 0.001 | | 0.78 |
| Yes vs. No | 1.42 (1.15; 1.75) | | 0.96 (0.73; 1.26) | |
| Cardiac rhythm disorders | | 0.07 | | |
| Yes vs. No | 1.16 (0.99; 1.36) | | | |
| Other cardio-neurovascular conditions | | 0.04 | | |
| Yes vs. No | 1.16 (1.01; 1.34) | | | |
| Valvulopathy | | <0.0001 | | |
| Yes vs. No | 1.47 (1.25; 1.71) | | | |
| Chronic renal failure | | <0.0001 | | |
| Yes vs. No | 1.56 (1.32; 1.84) | | | |
| Cancer | | 0.004 | | |
| Yes vs. No | 0.72 (0.58; 0.90) | | | |
| Stroke | | 0.009 | | |
| Yes vs. No | 0.71 (0.55; 0.92) | | | |
| Hospitalization for AHF within the 3 months following the index date | | - | | <0.0001 |
| Yes vs. No | - | | 2.03 (1.65; 2.51) | |
| Number of distinct medications delivered within the previous 12 months | | | | 0.001 |
|]12; 17] vs. ≤12 | | | 1.17 (0.94; 1.47) | |
|]17; 22] vs ≤12 | | | 1.20 (0.95; 1.50) | |
| >22 vs. ≤12 | | | 1.53 (1.23; 1.90) | |

Supplementary Table 1. Probabilities of Heart Failure (HF) readmission and ambulatory Acute Heart Failure (AHF) treatment within 2 years after HF hospital discharge (index date), taking into account competing risk of death (Fine and Gray method). For the outcome ambulatory AHF treatment, the original date of the model was shifted to 91 days after the index hospitalization discharge to avoid the immortal time bias induced by the definition of the outcome.

| | Index date | M3 | M6 | M9 | M12 | M15 | M18 | M21 | M24 |
|---|------------|----------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| HF readmission | | | | | | | | | |
| Number of patients at risk | 7,708 | 6,335 | 5,747 | 5,326 | 4,967 | 4,674 | 4,406 | 4,197 | 3,998 |
| Number of patients with the outcome | 0 | 652 | 891 | 1,069 | 1,241 | 1,376 | 1,467 | 1,548 | 1,621 |
| Number of patients with the competing event (death) | 0 | 721 | 1070 | 1313 | 1500 | 1658 | 1835 | 1963 | 2089 |
| Cumulative probability, % [IC 95 %] | 0.0 | 8.5 [7.9; 9.1] | 11.6 [10.9; 12.3] | 13.9 [13.1; 14.7] | 16.1 [15.3; 16.9] | 17.9 [17.0; 18.7] | 19.0 [18.2; 19.9] | 20.1 [19.2; 21.0] | 21.0 [20.1; 22.0] |
| Ambulatory AHF treatment | | | | | | | | | |
| Number of patients at risk | 7,708 | 6906 | 5,788 | 5,041 | 4,504 | 4,094 | 3,722 | 3,444 | 3,223 |
| Number of patients with the outcome | - | 0 | 687 | 1,186 | 1,537 | 1,795 | 2,020 | 2,185 | 2,301 |
| Number of patients with the competing event (death) | - | 802 | 1,233 | 1,481 | 1,667 | 1,819 | 1,966 | 2,079 | 2,184 |
| Cumulative probability, % [IC 95 %] | - | 0 | 8.9 [8.3; 9.6] | 15.4 [14.6; 16.2] | 19.9 [19.1; 20.8] | 23.3 [22.4; 24.2] | 26.2 [25.2; 27.2] | 28.4 [27.3; 29.4] | 29.9 [28.8; 30.9] |

AHF: Acute Heart Failure ; HF : Heart Failure

Discussion of main results

This study confirms that the rate of HF readmission remains high after an initial HF hospitalization in comparison with findings of previous studies, even when death is considering as competing event. Around one in five HF patient has a repeat HF hospitalization within the 2 years following a first admission.

The original aspect of this work was to study the ambulatory management of cardiac decompensation by identifying variations in loop diuretic use over time. These diuretic variations were identified among numerous patients since almost 1 in 3 patients initiated a diuretic or had an increase in diuretic dose within the 2 years following a first admission for HF. One limitation in assessing this outcome was that the chronologies spanning the HF readmission and the changes related to diuretic use were not taken into account. The initiation or the increase of diuretic may indeed have led to an HF readmission or have been result form a previous HF hospitalization. One way to address this issue would have been to develop a combined outcome including both events (HF readmission and ambulatory AHF treatment), but the shift of the original date for the survival analysis of the outcome ambulatory AHF treatment – to avoid the immortal time bias induced by the definition of the outcome – did not make this option possible.

Results of this study also allow to determine a profile of HF patients at risk to be readmitted for HF or receiving ambulatory AHF treatment after HF hospitalization discharge. Patients with increasing age, HBP, diabetes or atrial fibrillation are thus more at risk to have a repeat HF hospitalization or to receive ambulatory AHF treatment than the ones who do not present with these characteristics. These clinical characteristics have the advantage of being stable over time (contrary to biological variables) and therefore are appropriate factors for early as long term prognostic.

4.4. Conclusion

This study highlighted the main clinical predictors responsible for cardiac decompensation in early and long term in HF patients. Specific care dedicated to these conditions would undoubtedly improve HF prognostic. However, these clinical risk factors should not be considered independently of other potential extrinsic risk factors such as drug use. This issue was addressed in the last study of this thesis.

5. PHARMACOLOGICAL PREDICTORS OF HEART FAILURE DECOMPENSATION

5.1. Rationale

As previously mentioned, one major issue related to HF is the iterative hospitalizations it generates, and the magnitude of the costs associated. We previously highlighted that some clinical characteristics of HF patients may influence the risk of HF readmission, but other extrinsic risk factors such as drug use may also decompensate HF and precipitate a new hospital admission.

Patients with HF often have a high medication burden for several reasons. First, HF forms the end-stage of different cardiovascular diseases and their predisposing risk factors and patients need drug treatment not only for heart failure itself but also for cardiovascular related conditions. Moreover HF patients are elderly and present with a number of unrelated, non-cardiovascular diseases, which further increase the number of pharmaceutical substances with which they are treated. It has been reported that 40% of patients with HF had > 5 non cardiac comorbidities [122]. Polypharmacy is a common issue in HF patients; in USA, patients take on average 6.8 prescription medications per day, resulting in 10.1 doses a day [123]. Polypharmacy may be deleterious for HF patients in particular because of direct myocardial toxicity related to the drug itself or adverse drug-drug interactions. Drugs may directly cause or exacerbate HF by negative inotropic, lusitropic, or chronotropic effects, by exacerbating hypertension or by delivering a high sodium load. Drug-drug interactions may also increase the risk of cardiac exacerbation by limiting the beneficial effects of HF medications. A previous study found that patients taking at least 2 prescription medications had a 13% risk of an adverse drug-drug interaction, which increased to 38% for 4 medications and 82% with ≥ 7 medications [124].

A non-exhaustive review published in the *ESC Textbook of Cardiovascular Medicine*² has referenced, based on published data, the main non-cardiovascular drugs responsible for cardiac decompensation and has detailed their mechanism of action.

² **Bosco- Levy P**, Bezin J, Salvo F, and Moore N, « Cardiovascular effects of non-cardiovascular drugs » in *The ESC Textbook of Cardiovascular Medicine*, Oxford, Oxford University Press, 2019, pp. 61-66.

5.2. Review of the literature

Non- cardiac drugs may cause or exacerbate heart failure by various mechanisms: (a) by causing heart damage known to be involved in the onset of heart failure (valvular heart disease, ischaemic heart disease, or cardiac rhythm disorder); (b) by affecting cardiac contractility either directly by cytotoxicity or by negative inotropic and lusitropic effects; or (c) by increasing systemic vascular resistance either by exacerbating hypertension or by delivering a high sodium load. A relevant list of non-cardiac medications leading to heart failure precipitation or exacerbation has been established by the American Heart Association based on a review of multiple studies (case reports, case series, meta- analysis, prospective and observational trials). This list (published in *Circulation* in 2016 [125]) includes medications such as non-steroidal anti-inflammatory drugs (NSAIDs), antidiabetic drugs, cancer chemotherapy, anti- infective medications, antiepileptic and rheumatologic agents.

Some drugs may cause heart failure by direct myocardial toxicity, for instance, several anticancer medications [125]. Anthracyclines such as doxorubicin or daunorubicin, a class of cytotoxic agents much used in haematological and solid organ tumours, induce cellular damage in myocytes, leading to a dilated or a restrictive cardiomyopathy. The damage seems to be irreversible, cumulative, and related to the lifetime total dose of the drug received, which may limit their use as cancer chemotherapy.

Cyclophosphamide and ifosfamide are both alkylating agents with a mechanism of cardiac injury that has not been precisely elucidated. They require hepatic activation to their active metabolite phosphoramidate mustard. Preclinical studies suggest that this active phosphoramidate mustard causes increased free radical formation in cardiac tissue, leading to cell dysfunction or death. The onset of heart failure is acute, occurring within 1–10 days of treatment, and it usually resolves after drug discontinuation. Several targeted therapies such as trastuzumab, bevacizumab, lapatinib, sorafenib, or sunitinib induce significant cardiac dysfunction in some patients. The biological mechanism of cardiotoxicity is not clear but is presumably related to cellular pathways within cardiomyocytes on which they operate, such as epidermal growth factor receptor 2 or vascular endothelial growth factor- A ligand.

There is no clear relation to dose, and heart failure is often reversible after drug discontinuation [125].

Occasional cases of cardiotoxicity including new-onset and worsening heart failure have been reported with itraconazole, but no causality has been established. On the basis of animal and clinical pharmacology studies, itraconazole may exert negative inotropic effects; however, the precise mechanism is not known. On the basis of these data, the United States Food and Drug Administration recommends avoiding itraconazole in patients with a history of heart failure for onychomycosis and to consider itraconazole only in cases of life-threatening fungal infections

Several cases of new-onset dilated cardiomyopathy with subsequent heart failure have also been reported with amphotericin B [125].

In clozapine users, myocarditis and cardiomyopathy are rare but potentially fatal. Clozapine-induced myocarditis typically occurs in the first 8 weeks of therapy and is not related to dose. It may be a result of an immunoglobulin E-mediated hypersensitivity reaction, but other potential mechanisms including elevations in catecholamine levels, blockade of calcium-dependent ion channels, and increased production of inflammatory mediators have been proposed [125].

Finally, based on post-marketing data, tumour necrosis factor-alpha inhibitors such as infliximab, etanercept, and adalimumab, which play a major role in the management of patients with rheumatoid arthritis and Crohn's disease, have been associated with new onset or worsening of heart failure. However, a recent systematic review found controversial results. The 2015 American College of Rheumatology report recommends the use of these treatments in patients with heart failure only if there are no other reasonable treatment options and if the heart failure is in a compensated state [125].

Beyond a direct impact on the cardiomyocyte, heart failure may be induced or more often worsened by drugs acting peripherally, on vascular contractility, or causing volume overload by interfering with the renal excretion of sodium. This is especially the case for NSAIDs, which have been associated with an increased risk of cardiac decompensation ever since they were first marketed [126]

Their anti-inflammatory effect is related to inhibition of cyclooxygenase isoenzymes COX-1 and COX-2. NSAIDs do not appear to cause new occurrence of heart failure, but their use is strongly correlated with relapse of heart failure [125]. NSAIDs increase systemic resistance through sodium and water retention via the inhibition of renal COX-2. Recently, a large observational European study found that the risk of admission for heart failure was increased for at least nine NSAIDs: diclofenac, ibuprofen, indomethacin, ketorolac, naproxen, nimesulide, piroxicam, etoricoxib, and rofecoxib, irrespective of COX-2 selectivity. The magnitude of the association varied according to the drug and the dose [127]. In contrast, the recent PRECISION trial investigating cardiovascular safety of naproxen, ibuprofen, and celecoxib in over 20,000 patients found the selective COX-2 inhibitor to be somewhat superior to the two non-selective NSAIDs [128]. Current recommendations of the American Heart Association and European Society of Cardiology suggest avoiding this class of drugs in patients with heart failure [3, 102].

Antidiabetic medications, such as thiazolidinediones and dipeptidyl peptidase-4 inhibitors have been involved in controversies about their role in causing exacerbation of or new-onset heart failure. Thiazolidinediones such as rosiglitazone and pioglitazone are peroxisome proliferator-activator receptor gamma agonists that modulate the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism in adipose tissue, muscle, and liver. Studies strongly suggest that thiazolidinediones exacerbate existing and increase the risk for new-onset heart failure by increasing sodium reabsorption in the distal nephron [125]. American and European guidelines [3] recommend avoiding thiazolidinedione use in patients with heart failure, and the marketing of these drugs is now restricted to certain countries. Rosiglitazone has been removed from the European market because it was associated with increased rates of myocardial infarction and pioglitazone has been withdrawn from the French market because of a suspected association with bladder cancer [3, 129]. The antidiabetic effect of dipeptidyl peptidase-4 inhibitors is due to a reversible binding to the dipeptidyl peptidase-4 enzyme which prevents the degradation of endogenously released incretin hormones, glucose-dependent insulinotropic polypeptide, and glucagon-like peptide-1. This leads to an increase of insulin release and a decrease of glucagon level. Excess heart failure admissions have been observed with saxagliptin and

sitagliptin, but a possible class effect has been suggested by a meta- analysis although the underlying mechanism is not well understood [125].

5.3. Research hypothesis and objectives

The drugs listed here above are now known to be at risk of cardiac decompensation, but there is still a lack of data concerning the quantification of their risks. The review of these drugs may also not be exhaustive, and other drugs potentially associated with AHF readmission would required to be identified in order to adapt their use in HF patients.

The aim of this study is thus to identify, in real world setting, the known or to date unknown drugs potentially associated with a HF readmission among incident hospitalized HF patients, using a representative sample of the French nationwide healthcare database, the EGB (*Echantillon Généralise de Bénéficiaires*).

The manuscript summarizing the main findings of this study is currently ready for submission and it will be proposed soon to an international peer reviewed journal

5.4. Article

5.4.1. Reference

Bosco-Lévy P, Favary C, Jové J, Lassalle R, Moore N, Droz-Perroteau C. Drugs associated with heart failure readmission: a nested case-control study

5.4.2. Abstract

Background: Because of their age and their underlying conditions, HF patients are likely to be exposed to multiple drugs, which can cause cardiac decompensation. The drugs potentially associated with AHF readmission would required to be identified in order to adapt their use in these patients.

Objectives: To identify, in real world setting, the known or to date unknown drugs potentially associated with a HF readmission among incident hospitalized HF patients.

Methods: A nested case-control study was conducted using a representative sample of the French healthcare nationwide database, the Echantillon Généraliste de

Bénéficiaires (EGB). Cases and controls were identified from a cohort of patients with an incident HF hospitalization between January 1, 2008 and September 31, 2013. Cases were all patients presenting with an incident readmission for AHF during the 2 years of follow-up and controls were randomly selected from the risk set and matched to a given case on age, sex and inclusion date. The risk of AHF readmission was studied for each medication dispensed during the recent (i.e. 60 to 30 days before readmission) or current (i.e. 30 to 7 days preceding readmission) exposure period using conditional logistic regression model.

Results: From the 6052 patients of the cohort, 694 patients with an incident hospitalization for AHF after the initial HF hospitalization were matched to 1 930 controls. Only the recent use of bivalent iron and soft paraffin and fat products were associated with a higher risk of AHF readmission (Odds Ratios [95% Confidence Interval]: 1.71 [1.05-2.80] and 2.02 [1.23-3.34] respectively).

Conclusion: The associations found suggest that some comorbidity has an important prognostic role on the risk of AHF readmission rather than the use of certain drugs may worsen HF.

Drugs associated with heart failure readmission: a nested case-control study

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Keywords: Heart Failure, readmission, drugs at risk, pharmacoepidemiology, nested case control, claims database

Word count of the text: words

ABSTRACT

Background: Because of their age and their underlying conditions, HF patients are likely to be exposed to multiple drugs, which can cause cardiac decompensation. The drugs potentially associated with AHF readmission would required to be identified in order to adapt their use in these patients.

Objectives: To identify, in real world setting, the known or to date unknown drugs potentially associated with a HF readmission among incident hospitalized HF patients.

Methods: A nested case-control study was conducted using a representative sample of the French healthcare nationwide database, the *Echantillon Généraliste de Bénéficiaires* (EGB). Cases and controls were identified from a cohort of patients with an incident HF hospitalization between January 1, 2008 and September 31, 2013. Cases were all patients presenting with an incident readmission for AHF during the 2 years of follow-up and controls were randomly selected from the risk set and matched to a given case on age, sex and inclusion date. The risk of AHF readmission was studied for each medication dispensed during the recent (i.e. 60 to 30 days before readmission) or current (i.e. 30 to 7 days preceding readmission) exposure period using conditional logistic regression model.

Results: From the 6052 patients of the cohort, 694 patients with an incident hospitalization for AHF after the initial HF hospitalization were matched to 1 930 controls. Only the recent use of bivalent iron and soft paraffin and fat products were associated with a higher risk of AHF readmission (Odds Ratios [95% Confidence Interval]: 1.71 [1.05-2.80] and 2.02 [1.23-3.34] respectively).

Conclusion: The associations found suggest that some comorbidity has an important prognostic role on the risk of AHF readmission rather than the use of certain drugs may worsen HF.

Word count of the abstract: 280

INTRODUCTION

Heart Failure (HF) is a major public health issue because of the iterative hospitalization it generates and the magnitude of the associated costs. One in four patients is readmitted within 30 days after an initial hospitalization (1,2) and iterative hospitalizations contribute to increase the financial burden of the disease, which is approximately 2% of the total health-care budget in Europe (3,4) and in France, around €2.5 billions of the healthcare expenditure supported by the National Health Insurance System in 2013 (5). Part of these hospitalizations may be induced by non-cardiovascular drugs, which may cause or exacerbate HF either by direct myocardial toxicity related to drug use or by adverse drug-drug interactions that may limit the beneficial effects of HF medications. Many of these drugs have been referenced by the American College of Cardiology and the American Heart Association Class of Recommendation and Level of Evidence, in order to establish recommendations on their use, encompassing the estimated magnitude and certainty of benefit of a clinical action in proportion to risk (6).

In HF, the use of multiple drugs is common; HF patients need drug treatment not only for heart failure itself but also for cardiovascular underlying conditions. Moreover, HF patients are elderly and present with a number of unrelated, non-cardiovascular comorbidities (7), which further increase the number of pharmaceutical substances with which they are treated. According to Masoudi et al., HF patients take on average 6.8 prescription medications per day, resulting in 10.1 doses a day (8). As the number of prescription medications increases, so does the potential for adverse drug events and drug-drug interactions. For instance, Goldberg et al found that patients taking at least 2 prescription medications had a 13% risk of an adverse drug-drug interaction, which increased to 38% for 4 medications and 82% with ≥ 7 medications (9).

Although some drugs are known to be at risk of cardiac decompensation, there is still a lack of data concerning the quantification of these risks in the French population. The list of these drugs may also not be exhaustive, and other drugs potentially associated with AHF readmission would required to be identified in order to adapt their use in HF patients.

The aim of this study is thus to identify, in real world setting, the known or to date unknown drugs potentially associated with a HF readmission among incident hospitalized HF patients, using a representative sample of the French nationwide healthcare database, the EGB (*Echantillon Généralise de Bénéficiaires*).

METHOD

Study design and data source

A nested case-control study was conducted using data from the *Echantillon Généraliste de Bénéficiaires* (EGB) database, a representative permanent 1/97th sample of the national healthcare data system in France, *Système National des Données de Santé* (SNDS) which covers 99% of the French population from birth to death (10). Complete data before 2011 are available only for subjects covered by the main insurance plan, covering salaried employees and their dependents, i.e., 76% of the French population. For each insured person, SNDS provides pseudonymized information on all reimbursed medical and paramedical encounters, drugs claims, hospital admissions and procedures (except for psychiatric hospitals and rehabilitation centers), registration for Long Term Diseases (LTD) dispensing from copayment, and date of death, but not its cause. Hospital diagnoses are coded according to the International Classification of Disease 10th edition (ICD-10) and the quality of this coding is ensured by regular internal and external audits (11). The quality of hospital coding for HF has been verified. (12)

Study population

The study population consisted of a cohort of patients aged over 40, covered by the main health insurance plan, with a first hospitalization for HF whose discharge date was identified between January 1, 2008 and September 31, 2013. An incident HF hospitalization was defined as a first hospitalization with a discharge code I50.x of the ICD-10 in any diagnostic position, with no LTD registration or hospital admission for HF in the 2 previous years. Patients were required to have a pre-index period of 1 year and at least 2 year of follow-up after the index date (excluding deaths). We excluded all patients who died during the index hospitalization or within the 90 days following discharge hospitalization, who were

readmitted for Acute HF (AHF) within the 90 days following discharge hospitalization or who had a period of at least 90 days with no healthcare dispensing recorded. The 90th day following the incident HF hospitalization discharge was defined as the inclusion date. Patients were followed for 2 years after inclusion date or until death or outcome whichever came first.

Case-control selection

Cases were all patients of the cohort with an incident readmission for AHF during the 2 years of follow-up. Diagnosis of AHF was identified based on the algorithm developed by the custodians of the French national healthcare system (13) which includes the validated ICD-10 discharge code I50.x (12). For each case, we used the entry date of AHF readmission to define the index date. Up to 6 controls were randomly selected from the risk set after matching on age (± 5 years), sex and inclusion date (± 7 days). All controls were alive and had no previous AHF readmission when they were selected from the risk set to be matched to a given case. The date of matching defined the index date for controls. To ensure that all drugs dispensing could be identified within the 60-day window preceding index date, we restricted all analyses to cases and matched controls, who did not have any hospitalization within the 60 days preceding the index date.

Exposure assessment

The exposure of interest was all medications reimbursed within the 60 days preceding index date. Patients were considered exposed to one given medication (identified using ATC codes level 4) if they receive at least one dispensing of this medication during the following drug exposure periods: within the 7 days preceding index date (index date excluded), between 7 and 30 days before index date (i.e. current exposure) or between 30 and 60 days before index date (i.e. recent exposure). The 7-day drug exposure period preceding index date was used to

identify associations between medication and AHF readmission potentially biased by reverse causality. This bias occurs when the reason of drug initiation is influenced by early signs or symptoms of AHF. Consequently, a time lag period of 7 days between index date and drug exposure period was incorporated in the definition of the current exposure period to minimize this bias (14).

Confounding factors

Potential confounding factors were selected within the 1-year period of history before inclusion or at inclusion date (i.e. age, Charlson Comorbidity Index score adapted to the SNDS database (15), cardiac comorbidities not included in the Charlson Comorbidity Index Score, number of previous hospitalizations, number of previous office visits to the general practitioner or the cardiologist and number of distinct previously dispensed medications based on ATC level 3), between inclusion date and the day preceding drug exposure period (i.e. exposure to HF medications and the medication of interest), and during the drug exposure period (all dispensed medications with the exception of the medication of interest). Exposure to HF medications and to the medication of interest was assessed using the *Medication Possession Ratio* (MPR) measured between inclusion date and the day preceding drug exposure period (i.e. number of days covered by all dispensing of a given drug divided by the number of days between inclusion date and the day preceding drug exposure period). MPR was considered in 4 classes: 0%,]0; 40%],]40; 80%] and]80; 100%].

Statistical Analyses

We performed descriptive analyses where categorical variables were described in number and percent, and quantitative variable in mean and standard deviation (SD) or median and interquartile range (IQR). We used absolute standardized differences to examine covariate

balance between cases and matched controls. In studies with large sample sizes, statistically significant differences are often not meaningful; the absolute standardized difference is not influenced by sample size. A standardized difference of 0.1 (10%) is commonly used to denote meaningful imbalance between groups (16). Associations between a given medication and AHF readmission were estimated using conditional logistic regression model. For each drug exposure period, medications were first selected if they had significance <0.25 in univariate analysis. Association to AHF readmission was assessed for each pre-selected medication after adjustment on potential confounders. Results are presented as Odd Ratios (OR) with corresponding 95% confidence intervals (95% CI).

RESULTS

A total of 6 052 patients were included in the cohort (Figure 1). The cohort was followed for a mean of 1.66 years (SD 0.62 years). Overall, 694 patients with an incident hospitalization for AHF after the initial HF hospitalization and without any hospitalization within the 60 days preceding index date were matched to 1 930 controls. Among the cases, the median duration before AHF readmission was 8 months after inclusion date (IQR [3.3; 14.4]).

Characteristics of these cases and matched controls are reported in Table 1. Cases were on average 80.7 (SD 9.7) years old at index date, were predominantly female (52.2%) and had an average Charlson Comorbidity Index score of 7.1 (SD 2.1). The most frequent cardiac comorbidities not included in the Charlson Comorbidity Index score among cases were: high blood pressure (96.8%), atrial fibrillation (49.3%) and dyslipidemia (47.3%). Within the 12 months pre-index period, cases had a median of 14 (IQR [9.0; 19.0]) outpatient consultations, especially at the general practitioner. The median number of previous hospitalizations was 2.0 (IQR [1.0; 3.0]) and the mean number of distinct medications dispensed within the pre-index period was 19.5 (SD 6.4). Matched controls had very similar characteristics to those of the cases.

Drugs potentially associated with AHF readmission are presented in Table 2 according to the drug exposure period considered and after adjustment on potential confounders. HF subjects were more likely to be readmitted for AHF if they had a current exposure to selective to bivalent iron (OR 2.02, 95%CI [1.23-3.34]) or to soft paraffin and fat products although the low limit of the 95%CI is very close to 1 (OR 1.71, 95%CI [1.05-2.80]). No significant other association was found for the drugs identified in the recent exposure period or during the 7 days before index date.

DISCUSSION

This nested case-control study showed that the current use in real life setting of bivalent iron and soft paraffin and fat products were associated with an increased risk of AHF readmission.

To our knowledge, no other study has examined the association between the recent or current use of drugs with the risk of AHF readmission. The American College of Cardiology and the American Heart Association Class of Recommendation and Level of Evidence have referenced a list of drugs that may cause or exacerbate heart failure based on data from case reports, case series, package inserts, meta-analyses, and prospective and observational trials (6). However, the drugs referenced by this report did not emerged as significantly associated with AHF readmission in our study. This might be explained by a lack of power related to the database used, the EGB which is only a sample of the overall French nationwide database. Another reason may be that these drugs are avoided in HF patients because the risk related to their use is currently well known by prescribers.

Among drugs currently used before AHF readmission, bivalent iron and soft paraffin and fat products appeared to be significantly associated with an increased risk of AHF readmission. After comparison with published data, it appears that the association found between bivalent iron exposure and the risk of AHF readmission reflects rather the prognostic role of underlying comorbidities in AHF readmission such as anemia or iron deficiency, than the consequence of the use of the medications indicated to treat these conditions. Indeed, both anemia and iron deficiency are known to be associated with a decrease in effort capacity and quality of life, as well as a rise in hospital admission frequency (17). Several studies showed clinical benefits of iron therapy, resulting in increasing haemoglobin concentration, but also in improving the functioning of non-haematopoietic tissues, such as skeletal muscles (18). The

latest HF Guidelines (2016) have even recommended routine evaluation of iron deficiency in patients with HF and ferric carboxymaltose therapy

However, we cannot rule out the possibility that our findings reflect the possible involvement of bivalent iron in unfavorable drug interactions with medications that influence cardiovascular functions.

The association found between soft paraffin and fat products and AHF readmission seems to be serendipitous, since these products has no specific therapeutic effect or use. As for bivalent iron, these products may also be related to an underlying comorbidity, which remains to be identified.

This study presents several limitations. First, this study suffers from a lack of power due to the database used. Although EGB contains a population representative of the French national population and is commonly used for pharmacoepidemiology studies (10), its size is limited to assess the effect of each medication on the risk of AHF readmission. Only the strongest associations could be identified. Because of the size of the population, it was not possible to study the associations by stratifying on the dispensed daily doses of a considered medication or on the age, which would have help to distinguish between HF with reduced ejection fraction and HF with preserved fraction, information that was not available in our database. Besides the ejection fraction, other valuable information was lacking in our database. This concerns for instance the results of the BNP performed during the stay, which would have help to characterise the type of heart failure more accurately, the NYHA class necessary to assess HF severity, or the reason for office visits, important to identify better the onset of cardiac exacerbation.

This study also presents some strength. The methodology applied namely the nested case-control approach, provides robust estimates. Compared with a full cohort approach using a

survival analysis with time dependent variables, the nested case-control analysis is computationally more efficient (19) while producing odds ratios that are unbiased estimators of incidence rate ratios with little or no loss in precision (20). Because the database used contains prerecorded information on dispensations, the possibility of recall bias was eliminated. Moreover, controls presented with similar characteristics to cases allowing overcoming selection bias. The matching of the controls on age, sex and index date and the adjustment on relevant comorbidities through the Charlson index comorbidity score also helped to limit confusion bias.

Conclusion

This study did not confirm that the use of certain drugs may worsen HF, but it reinforced the fact that some comorbidity has an important prognostic role on the risk of AHF readmission. Further specific studies are required to deepen these findings.

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ETHICS STATEMENT

This study was done in a pseudonymized database, not requiring patient consent. It was reviewed by INSERM internal processes, which did not oppose it. INSERM CIC1401 at that time had permanent access to the 1/97 sample of SNDS, pending INSERM declaration.

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CONFLICTS OF INTEREST

Dr P. Bosco-Lévy, C Favary, J Jové, R Lassalle, C Droz-Perroteau have nothing to disclose.

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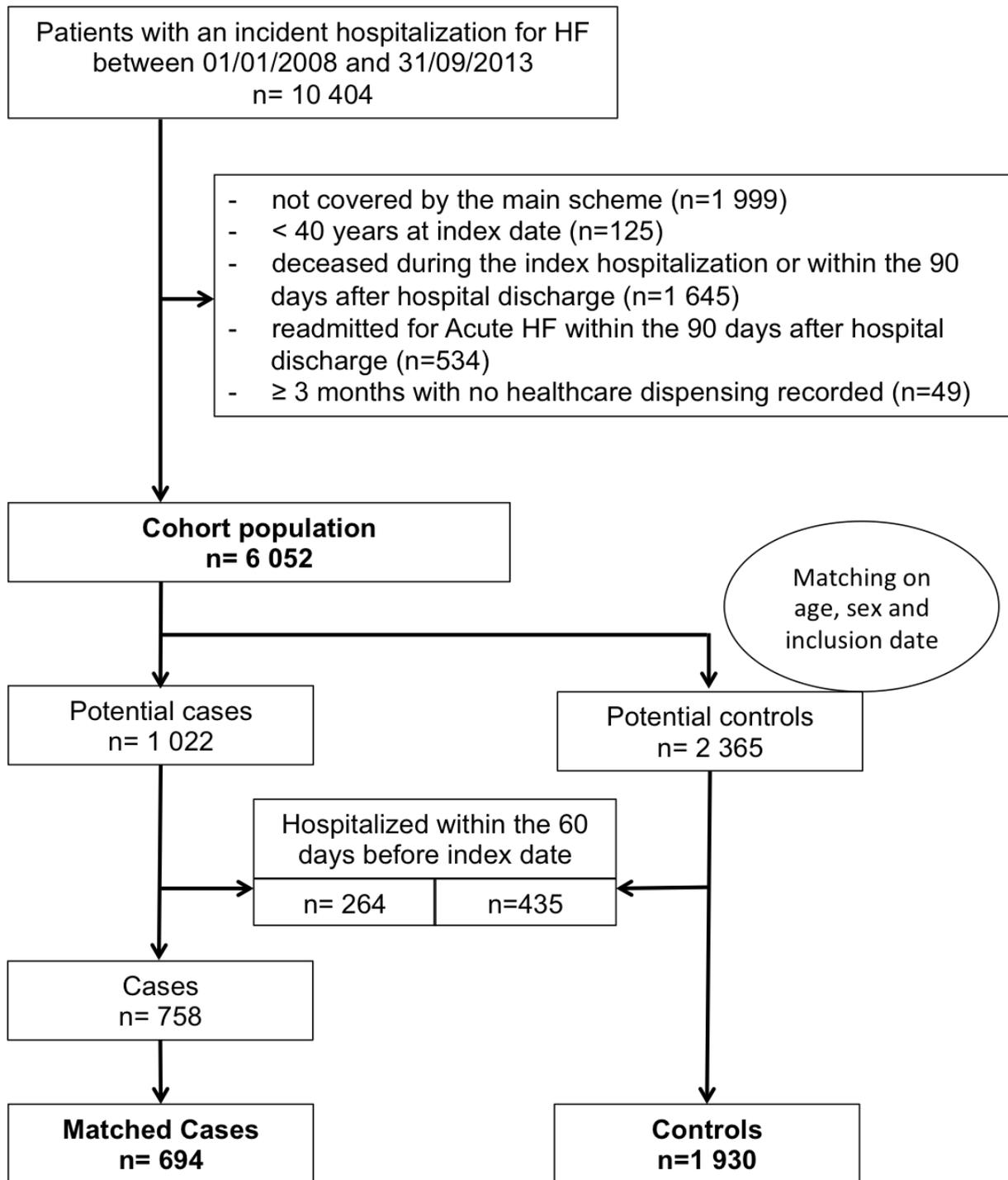


Figure 1 Study flow-chart

Table 1. Baseline description of cases and matched controls

| | Cases n=694 | Controls n=1930 | Standardized differences |
|---|------------------------|----------------------------|-------------------------------------|
| Demographic characteristics* | | | |
| Mean (SD) age at index date (years) | 80.7 (9.7) | 80.7 (5.9) | 0.001 |
| Sex female, n (%) | 362 (52.2) | 1095 (52.2) | 0 |
| Charlson Comorbidity Index score*, n (%) | | | |
| [2-3] | 9 (1.3) | 17 (1.3) | 0.042 |
| [4-5] | 113 (16.3) | 302 (17.4) | |
| [6-7] | 342 (49.3) | 939 (47.3) | |
| >7 | 230 (33.1) | 672 (33.9) | |
| Cardiac comorbidities not included in the Charlson Comorbidity Index score*, n (%) | | | |
| High blood pressure | 672 (96.8) | 1800 (92.7) | 0.185 |
| Dyslipidemia | 328 (47.3) | 953 (49.5) | -0.046 |
| Atrial fibrillation | 342 (49.3) | 807 (41.4) | 0.159 |
| Cardiac rhythm disorders | 152 (21.9) | 411 (21.5) | 0.009 |
| Valvulopathy | 152 (21.9) | 341 (17.2) | 0.118 |
| Dilated cardiomyopathy | 68 (9.8) | 150 (9.0) | 0.026 |
| Other cardio-neurovascular conditions | 298 (42.9) | 689 (37.0) | 0.122 |
| Within the 12 months of pre-index period* | | | |
| Median number [IQR] of office visit per patient | | | |
| at the general practitioner | 12.0 [8.0;17.0] | 11.0 [7.0;16.0] | 0.152 |
| at the cardiologist | 0.0 [0.0;1.0] | 0.0 [0.0;1.0] | 0.062 |
| Median number [IQR] of hospitalizations per patient | 2.0 [1.0;3.0] | 2.0 [1.0;3.0] | 0.093 |
| Mean number (SD) of distinct medications (level 3 of the ATC code) | 19.5 (6.4) | 18.3 (4.1) | 0.224 |

* For controls, means, standard deviations, medians, interquartile ranges and percentages were weighted by the inverse number of controls matched to each case.

§ Charlson Comorbidity Index Score adapted to the of French nationwide healthcare database SNDS and including 17 categories of comorbidity

Table 1. Association between drugs use and heart failure readmission according to the different drug exposure windows

| | 7 days of drug exposure | | 7-30 days of drug exposure (Current exposure) | | 30-60 days of drug exposure (Recent exposure) | |
|---|--------------------------|---------|---|---------|---|---------|
| | Adjusted OR* [IC 95%] | p-value | Adjusted OR* [IC 95%] | p-value | Adjusted OR* [IC 95%] | p-value |
| A02BC - Proton-pump inhibitors | 0.83 [0.59-1.47] | 0.76 | - | - | - | - |
| N02BE - Anilides | 1.26 [0.86-1.86] | 0.23 | 1.15 [0.89-1.50] | 0.29 | 1.17 [0.91-1.50] | 0.23 |
| A12BA - Potassium | 1.43 [0.87-2.34] | 0.15 | 0.97 [0.68-1.39] | 0.87 | 1.08 [0.76-1.54] | 0.66 |
| C10AA - HMG CoA reductase inhibitors | - | - | 0.71 [0.50-1.00] | 0.05 | - | - |
| B01AA - Vitamin K antagonists | - | - | 1.27 [0.93-1.75] | 0.14 | 0.95 [0.70-1.29] | 0.76 |
| C01BD - Antiarrhythmics, class III | - | - | 0.91 [0.60-1.37] | 0.64 | 1.18 [0.80-1.75] | 0.39 |
| M04AA - Inhibitors uric acid production | - | - | 1.30 [0.81-2.08] | 0.27 | 1.18 [0.71-1.96] | 0.52 |
| C01DA - Organic nitrates | - | - | 0.90 [0.55-1.49] | 0.69 | 1.46 [0.96-2.21] | 0.07 |
| N05CF - Benzodiazepine related drugs | - | - | 1.26 [0.86-1.86] | 0.23 | 0.94 [0.62-1.43] | 0.77 |
| N06AB - Selective serotonin reuptake inhibitors | - | - | 1.53 [0.95-2.46] | 0.08 | - | - |
| R03AK - Adrenergics with corticosteroids or other drugs | - | - | 1.18 [0.73-1.91] | 0.49 | - | - |
| H02AB - Glucocorticoids | - | - | 1.25 [0.76-2.04] | 0.38 | 1.51 [0.97-2.37] | 0.07 |
| B03AA - Bivalent iron, oral preparations | - | - | 2.02 [1.23-3.34] | 0.006 | - | - |
| D02AC - Soft paraffin and fat products | - | - | 1.71 [1.05-2.80] | 0.03 | 1.14 [0.71-1.83] | 0.58 |
| R03BB - Anticholinergics | - | - | 1.15 [0.64-2.06] | 0.63 | 0.74 [0.40-1.35] | 0.33 |
| B01AC - Platelet aggregation inhibitors excl. heparin | - | - | - | - | 0.88 [0.64-1.21] | 0.43 |
| A06AD - Osmotically acting laxatives | - | - | - | - | 1.31 [0.91-1.88] | 0.14 |
| G04CA - Alpha-adrenoreceptor antagonists** | - | - | - | - | 1.61 [0.81-3.21] | 0.17 |
| M02AA - anti-inflammatory non-steroids for topical use | - | - | - | - | 1.27 [0.84-1.92] | 0.25 |
| N02AX - Other opioids | - | - | - | - | 1.20 [0.78-1.84] | 0.41 |
| A10BB - Sulfonylureas | - | - | - | - | 1.09 [0.60-1.97] | 0.78 |
| R03AC - Selective beta-2-adrenoreceptor agonists | - | - | - | - | 0.93 [0.58-1.51] | 0.78 |
| A10AE - Insulins and analogues for injection, long-acting | - | - | - | - | 1.49 [0.82-2.71] | 0.19 |

* Adjusted on age, the Charlson Comorbidity Index Score, cardiac comorbidities not included in the Charlson Comorbidity Index Score, number of previous hospitalizations, number of previous office visits to the general practitioner or the cardiologist and number of distinct previously dispensed medications, medications dispensed during the exposure period with a frequency >5% (apart from the medication of interest), *Medication Possessio Ratio* of heart failure medications and the medication of interest calculated between inclusion date and the day preceding drug exposure period.

** in men only

5.5. Discussion

The main finding of this article was that bivalent iron use dispensed to treat anemia or iron deficiency was significantly associated with a higher risk of AHF readmission. This result confirmed those of previous studies [138, 139].

However, this did not bring to light any new or already known associations between the current or recent use of medications and AHF readmission. This is mainly explained by the lack of power of the study due to the size of the database we used. The overall French nationwide database, the SNDS, would have been more appropriate than its 1/97th sample for this study but the complexity and the time required to obtain data have not enabled the use of this database as part of this thesis.

The reason for choosing a nested case control study as study design for our study was that it offered the possibility to study the association with AHF readmission for multiple medications and for various drug exposure periods. The purpose of this approach was to identify drugs potentially at risk of cardiac decompensation, but these findings would have required strengthening by other studies. For instance, self-controlled case series could be considered to study specifically the effect of a transient exposure to a given medication.

6. GENERAL CONCLUSION AND PERSPECTIVES

The efficacy of the medications used in HF has been shown in many clinical trials in the last 30 years. However the persistence of a high rate of mortality and morbidity in HF patients raise questions about the optimization of HF patients care in real world setting.

At the initiation of this thesis, few data was published to understand the therapeutic management and the risk of cardiac decompensation in real-life setting. We have thus conducted several studies, for which the results may help to address the remaining questions concerning HF patient characteristics and provide insights to improve their care management. The significant methodological challenge of this work was to use data of the French healthcare administrative database, which constitutes a valuable tool for the description of healthcare consumption in HF patients but for which clinical data is sorely lacking.

After validating the accuracy of the codes to use for identifying HF patients in the EGB database, we made the choice to include all patients with a HF diagnosis coded either as main or secondary diagnosis for each of the studies conducted as part of this thesis. We are aware that this choice is arguable; we could have included only patients with HF diagnosis coded as main diagnosis to ensure a better sensitivity for our study population, but we deemed this definition too restrictive. We based our choice on the fact that, in theory, the HF diagnosis is coded as secondary diagnosis only if it produces an “increase in care and in use of resources in comparison with the initial comorbidity” [142]. Whatever the position of the diagnosis coding, HF patients should thus have received specific care for their condition during their hospital stay.

We showed, in the second part of this work, that between 17% and 37% of HF patients were not exposed to any HF_rEF treatment in the year following hospital discharge. This significant proportion of HF patients may represent patients who benefit only from strict application of dietary rules, or patients who were hospitalized as part of their HF check and who secondarily received a treatment. This may explain why half of these untreated patients became treated within the 3 months following hospital discharge. These findings show that it would thus be preferable to

assess persistence or adherence to HF treatments a few months after hospital discharge rather than immediately after hospital discharge.

The third part of our work confirmed that slightly less than one quarter of HF patients had repeat hospitalizations within the 2 years following an incident HF hospitalization and that the main clinical predictors of readmission were age, high blood pressure, atrial fibrillation and diabetes. This proportion is high, although less alarming than those found in published studies [104, 120, 121], particularly because of the methodology applied, which takes into account the competing risk of death. These results reinforce the idea that HF patients, and especially those with a highest risk profile, need a regular medical surveillance. Monitoring of HF patients needs to be multifaceted with intensive patient education, optimisation of the therapeutic regimen and ongoing surveillance. But to date there is no clear guidelines on what factors should be monitored, and how frequently these factors should be reported. The potential for home monitoring such as home visitation, telemedicine or external or implantable devices, is substantial to improve the management of HF patients. Some of these monitoring devices have already been demonstrated to improve health status and reduce HF hospitalizations [143]. Further studies are nevertheless required to determine what place these monitoring methods would occupy within the HF treatment strategy.

Finally, although our last study did not highlight any significant associations between medication use and AHF readmission, it underlines the importance of the management of certain medical conditions such as anemia or iron deficiency to prevent repeat hospitalizations. Nonetheless, these findings appear to justify the carrying out of further studies with greater power using larger databases such as the SNDS to complete the investigation of drugs potentially at risk of cardiac decompensation in HF patients. Although expensive and time-consuming, linkage of healthcare consumption data from SNDS with clinical data from a prospective cohort or from a HF registry such as FRESH (FRENch Survey on Heart Failure) could provide interesting alternatives to compensate for the lack of clinical data of the SNDS.

Despite these limits, this work provides valuable primary findings on chronic HF therapeutic management and risk of cardiac decompensation in real-life setting, which may serve as a basis for further pharmacoepidemiology studies. For instance, with the recent marketing of the HF drug Entresto[®], new studies will be required to assess its benefit and safety in real conditions of use.

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APPENDICES

Appendices 1. Publications and communications linked to the thesis

Publications

Salvo F, Bezin J, **Bosco-Levy P**, et al. Pharmacological treatments of cardiovascular diseases: Evidence from real-life studies. *Pharmacol Res.* 2017 Apr 118:43-52.

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Appendice 2. Other publications and communications

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