Low adherence to loop diuretic therapy as a trigger for decompensation in chronic heart failure

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Low adherence to loop diuretic therapy as a trigger for decompensation in chronic heart failure

por

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Dissertação de candidatura ao grau de Mestre em Epidemiologia
apresentada à Faculdade de Medicina da Universidade do Porto

Orientada pela Professora Doutora Ana Azevedo

Porto, Agosto 2014

Investigação realizada no Serviço de Epidemiologia Clínica, Medicina Preditiva e Saúde Pública da Faculdade de Medicina da Universidade do Porto e no Instituto de Saúde Pública da Universidade do Porto, sob orientação da Professora Doutora Ana Azevedo.

Este trabalho foi efetuado no âmbito de um projeto financiado pela Fundação para a Ciência e a Tecnologia (PTDC/SAU-ESA/107940/2008).

Ao abrigo do Art.º 8º do Decreto-Lei nº 288/70 esta dissertação tem como base um manuscrito, submetido para publicação em revista científica, no qual colaborei na recolha, informatização e análise da informação. Fui responsável pela redação da primeira versão do manuscrito:

Low adherence to loop diuretic therapy as a trigger for decompensation in chronic heart failure.

AGRADECIMENTOS

Agradeço a todas as pessoas que, com a sua opinião, apoio e dedicação contribuíram decisivamente para a realização do 2º ciclo de estudos em Epidemiologia e para a elaboração deste trabalho: este projecto não teria sido possível sem o imprescindível apoio da minha família e dos meus amigos bem como colaboração dos meus colegas de trabalho, que das mais diversas formas permitiram que cumprisse este projeto.

À Professora Doutora Ana Azevedo devo a oportunidade de poder aplicar os conhecimentos adquiridos num projecto de investigação clínica numa área científica e num projecto particularmente estimulantes bem como a sua orientação, o rigor científico e a revisão do trabalho.

Ao Serviço de Epidemiologia Clínica, Medicina Preditiva e Saúde Pública da Faculdade de Medicina da Universidade do Porto, ao Instituto de Saúde Pública da Universidade do Porto e ao Serviço de Medicina Interna do Centro Hospitalar de São João, pelo apoio formativo e logístico na realização deste projecto.

A todas as minhas colegas que frequentaram o 2º ciclo de estudos em Epidemiologia, nomeadamente à Romana Vieira, pela amizade e companheirismo, e à Olga Laszczyńska, pela paciência e ajuda decisiva na realização do meu trabalho.

Ao meu irmão pelo exemplo.

Aos meus pais e à minha avó pelo carinho e compreensão.

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List of Abbreviations

ACC	American College of Cardiology
ACEi	Angiotensin converting enzyme inhibitor
ADHERE	Acute Decompensated Heart Failure Registry
AHA	American Heart Association
AHF	Acute Heart Failure
ARB	Angiotensin II Receptor Blocker
ARIC	Atherosclerosis Risk in Communities Study
BB	Beta-blocker
BHAT	Beta-blocker Heart Attack Trial
BNP	B-type Natriuretic Peptide
CARDIA	Coronary Artery Risk Development in Young Adults Study
CDP	Coronary drug project
CHARM	Candesartan in Heart failure - Assessment of moRtality and Morbidity
COPD	Chronic Obstructive Pulmonary Disease
DOSE	Diuretic Optimization Strategies Evaluation
EF	Ejection Fraction
FHS	Framingham Heart Study
GWTG-HF	Get With The Guidelines - Heart Failure
HF	Heart Failure
HF-PEF	Heart Failure with Preserved Ejection Fraction
HF-REF	Heart Failure with Reduced Ejection Fraction
HR	Hazard Ratio
MESA	Multi-Ethnic Study of Atherosclerosis
NCHS	National Center for Health Statistics
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NYHA	New York Heart Association
OCS	Olmsted County Study
OPTIMIZE-HF	Organized program to initiate lifesaving treatment in hospitalized patients with heart failure
OR	Odds Ratio
RAAS	Renin-Angiotensin-Aldosterone system
RR	Relative Risk
WHO	World Health Organization

1. RESUMO

Introdução: A insuficiência cardíaca (IC) está associada com morbilidade importante, redução da qualidade de vida e custos elevados realcionados funamentalmente com hospitalizações. Os objectivos do tratamento em doentes com diagnóstico estabelecido são o controlo dos sintomas, a prevenção da hospitalização e a melhoria da sobrvivência. A terapêutica diurética é necessária para o tratamento sintomático dos doentes com IC mas o papel da adesão à terapêutica na prevenção das hospitalizações não está completamente esclarecido. A aplicação de estudos observacionais podem ser muito úteis neste âmbito.

Objectivos: Quantificação do efeito da baixa adesão à terapêutica diurética como factor precipitante de descompensação de IC crónica.

Métodos: Para avaliar o efeito da baixa adesão à terapêutica foi desenhado um estudo case-time-control. Este desenho é constituído por um case-crossover de casos - doentes admitidos num hospital universitário terciário, entre Maio de 2009 e Janeiro de 2011 por IC crónica descompensada (n=325) - e um case-crossover de controlos constituído pela selecção de um grupo controlo independente - doente com IC crónica estável seguidos na consulta externa especializada em IC do mesmo hospital entre Janeiro de 2011 e Julho de 2012 (n=292). Todos os doentes incluídos estavam tratados com diurético de ansa - furosemida. A adesão foi avaliada com recurso a um questionário semi-quantitativo e classificada como baixa se o número de tomas de furosemida fosse inferior a 88% da dose semanal prescrita. Para estimar o efeito da baixa adesão foi utilizou-se regressão logística condicional. A razão entre o OR do grupo caso e o OR do grupo controlo permite estimar o OR do estudo case-time-control.

Resultado: Os casos eram mais velhos, predominantemente mulheres e apresentavam disfunção sistólica ventricular esquerda (DSVE) grave de mais frequentemente de etiologia isquémica. A prevalência de fatores de risco e comorbilidades era maior nos casos, incluindo a prevalência de hipertensão arterial, diabetes mellitus, fibrilhação auricular, doença pulmonar obstrutiva crónica e anemia, com excepção da prevalência de doença renal crónica. Os casos estavam menos frequentemente tratados com inibidores da enzima de conversão da angiotensina (IECA) ou bloqueadores-beta. A prevalência da baixa adesão era de 17% (108 doentes) nos casos e 15% (86 doentes) nos controlos. Entre os casos, a baixa adesão à terapêutica diurética estava 3 vezes aumentada e era significativamente mais provável na semana anterior à hospitalização do que 4 semanas antes (OR=3.00, 95% CI 1.09–8.25, p=0.033). Entre os controlos as diferenças reportadas relativamente à adesão eram menores e não significativas (OR=1.50, 95% CI 0.72–3.11, 0.277). O OR do estudo case-time-control para baixa adesão correspondeu a 2.00. he case-time-control OR for low adherence was 2.00. O efeito trigger da baixa adesão era mais forte entre doentes mais velhos, nas mulheres, com DSVE grave, sem factores de risco ou comorbilidades e medicados com IECA.

Conclusões: Uma taxa de adesão inferior a 88% das doses previstas de diurético de ansa em doentes com IC crónica duplica o risco de descompensação na semana seguinte. A identificação de grupos de doentes mais suceptíveis ao efeito da baixa adesão pode permitir a instituição de atempada de medidas de melhoria da adesão à terapêutica.

Low adherence to loop diuretic therapy as a trigger for decompensation in chronic heart failure

2. ABSTRACT

Introduction: Heart failure (HF) is associated with substantial morbidity, impaired quality of life and huge costs, in large part related with hospitalizations. The goals of treatment in patients with established HF are symptoms and signs relief, prevention of hospital admission and improvement in survival. Diuretics are required for the symptomatic management of HF but the role of therapy adherence in preventing hospital admissions is incompletely understood. Observational studies may be a valuable help to address these questions.

Objectives: To quantify the effect of low adherence to loop diuretic therapy as triggering factor for chronic HF decompensation.

Methods: To assess the effect of low adherence we performed a case-time-control study. It comprises a regular case-crossover of cases - patients admited at a teaching tertiary care hospital, between May 2009 and January 2011 due to decompensated chronic HF (n=325) - and a case-crossover of controls with a selection of an independent control group - stable chronic HF patients followed at the HF outpatient clinic of the same hospital between January 2011 and July 2012 (n=292). All patients included were treated with loop diuretic furosemide. Adherence was assessed by a semi-quantitative questionnaire and classified as low if less than 88% of prescribed doses were taken in the preceding week. In order to calculate these effects we have used conditional logistic regression. The ratio between the OR from the case arm study by the OR obtained in the control arm will provide the case-time-control study OR risk for acute decompensated HF if low adherence. In order to calculate these effects we have used conditional logistic regression.

Results: Case patients were older, most were women and with severe left ventricular systolic dysfunction (LVSD) from ischemic etiology. Risk factors and comorbidities prevalence was higher in cases, including arterial hypertension, diabetes mellitus, atrial fibrillation, chronic obstrutive pulmonary disease and anemia, with the exception of chronic kidney disease. Cases were less frequently treated with angiotensin converting enzyme inhibitors (ACEI) or beta-blockers. The prevalence of low adherence was 17% (108 patients) in the case arm and 15% (86 patients) in the control arm. Among cases, low adherence to diuretic therapy was 3-fold and significantly more likely in the week preceding hospitalization than 4 weeks earlier (OR=3.00, 95% CI 1.09–8.25, p=0.033). Among controls, the difference in reported adherence was smaller and non-significant (OR=1.50, 95% CI 0.72–3.11, 0.277). The case-time-control OR for low adherence was 2.00. This triggering effect was stronger among older patients, in women, with severe LVSD, without risk factors and comorbidities, and under treatment with ACEI.

Conclusions: An adherence rate below 88% dose-counts of loop diuretic in chronic HF patients doubles the risk of decompensation in the following week. The identification of patient groups in which low adherence effect is stronger may enable timely application of adherence improvement measures.

3. INTRODUCTION

Cardiovascular diseases are the number one cause of death globally: more people die annually from cardiovascular diseases than from any other cause[1]. An estimated 17.3 million people died from cardiovascular diseases in 2008, representing 30% of all global deaths[1]. Of these deaths, an estimated 7.3 million were due to coronary heart disease and 6.2 million were due to stroke[2].

Heart failure (HF) has become a leading cause of death and morbidity worldwide[2-5]. In developed countries symptomatic HF occurs in 1-2% of the adult population, 6-10% of people aged over 65 years and more than 10% of people aged over 70 years[5, 6]. HF is associated with substantial morbidity, impaired quality of life and huge costs, in large part related with hospitalizations[6].

HF can be defined as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues at normal filling pressures [5, 7]. May present acutely, with occurrence of severe symptoms and signs within 24 hours[8] but generally it is a chronic condition in which worsening of symptoms and signs can occur and may require hospitalization or more frequent recurrence to medical care (decompensation of chronic HF (CHF).

Clinically, HF is defined as a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an abnormality of cardiac structure or function[5, 7].

The diagnosis of HF, especially when relying solely on symptoms and signs (which is often the case in primary care), is difficult because there is no single diagnostic test for HF: it is largely a clinical diagnosis based on a careful history and physical examination. So, the diagnosis of HF can be difficult as many of the symptoms of HF are non-discriminating and, therefore, of limited diagnostic value[5, 8]. The clinical syndrome of HF may result from disorders of the pericardium, myocardium, endocardium, heart valves, or great vessels or from certain metabolic abnormalities, but most patients with HF have symptoms due to impaired LV myocardial function[7].

3.1 Definitions

Chronic heart failure (CHF)

A chronic heart failure (CHF) patient is usually a treated patient with previous diagnosis of HF. CHF patients are considered ‘stable’ if their symptoms and signs have remained generally unchanged for at least one month[5, 7].

Acute heart failure syndromes (AHFS)

The acute HF syndromes (AHFS) have a heterogeneous presentation that makes the development of a comprehensive classification scheme difficult (Fig. 1).

New-onset or *de novo* HF occurs in approximately 20% of all AHFS admissions when patients present for the first time with symptoms of HF. They may have no prior history of cardiovascular disease or risk factors (e.g., acute myocarditis); but more commonly, they have a background of risk factors

for HF (HF stage A according to the ACC/AHA guidelines) or pre-existing asymptomatic structural heart disease (HF stage B according to the ACC/AHA guidelines). Many of these patients develop AHFS in the setting of acute coronary syndromes (ACS).

Worsening chronic HF occurs in patients who have a history of CHF (HF stage C according to the ACC/AHA guidelines) and present with an episode of decompensation. This group accounts for the majority (approximately 80%) of patients hospitalized with AHFS. Such patients may have easily identifiable precipitants or no clear explanation for decompensation. A subgroup of these patients (10% to 15%) has advanced or end-stage HF defined as refractoriness to available therapies (ACC/AHA stage D). In these advanced HF patients, hospitalization may be triggered by severe chronic symptoms rather than by an abrupt change in clinical condition[7]. The history and physical examination allows estimation of a patient's hemodynamic status, that is, the degree of congestion ("dry" versus "wet"), as well as the adequacy of their peripheral perfusion ("warm" versus "cold") which has implications on further stratification of the patient[9].

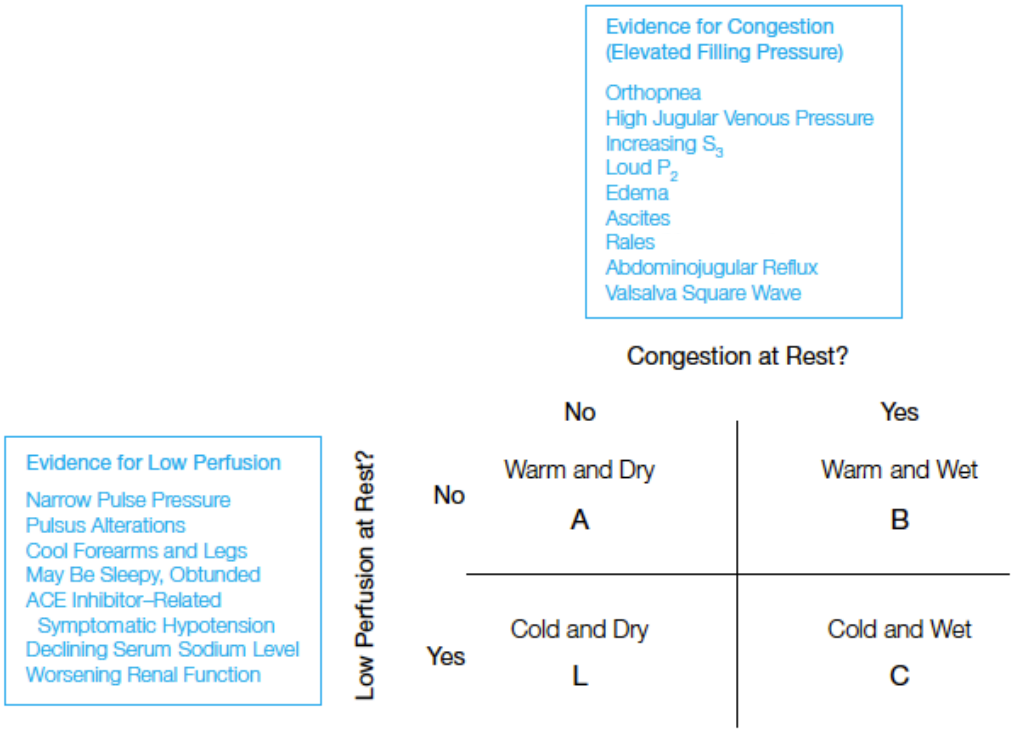


Fig. 1 – Clinical profiles of acute heart failure presentation. (*Adapted from: Nohria A, et al. JAMA. 2002;287(5):628-640*).

The main terminology used to describe HF is historical and is based on measurement of left ventricular (LV) ejection fraction (EF). Mathematically, EF is the stroke volume (which is the end-diastolic volume minus the end-systolic volume) divided by the end-diastolic volume. In patients with reduced contraction and emptying of the left ventricle (i.e. systolic dysfunction), stroke volume is maintained by an increase in end-diastolic volume (because the left ventricle dilates), i.e. the heart ejects a smaller fraction of a larger volume. The more severe the systolic dysfunction, the more the EF is reduced from normal and, generally, the greater the end-diastolic and end-systolic volumes[5, 7]. The EF is consid-

ered important in HF, not only because of its prognostic importance but also because most clinical trials selected patients based upon EF[5, 7].

Heart failure with reduced ejection fraction (HF-REF)

At least half of patients with HF have a reduced EF (HF-REF)[5, 7, 10]. The definition of HF-REF has varied, with cut-off values of left ventricular ejection fraction (LVEF) set as ≤35%, <40%, and ≤40% [5, 7, 10]. Randomized clinical trials in patients with HF have mainly enrolled patients with HF-REF with an EF ≤35% or ≤40%, and it is only in these patients that efficacious therapies have been demonstrated to date. According to HF guidelines of the European Society of Cardiology, HF-REF is defined as the clinical diagnosis of HF and EF ≤40%[5, 7].

Heart failure with preserved ejection fraction (HF-PEF)

Until the last two decades, the possibility that large numbers of patients with HF might have a normal EF was not considered. Consensus seems to be building toward use of an EF higher than 50% to designate HF-PEF classification[11]. As numerous studies have now demonstrated, HF-PEF is common suggesting it contributes significantly to the huge burden of disease caused by HF[12]. A number of recent community-based epidemiological studies of HF have suggested that 30% to 50% of cases of HF have preserved LV systolic function. The diagnosis of HF-PEF is more difficult than the diagnosis of HF-REF because it is largely one of exclusion, i.e. potential non-cardiac causes of the patient's symptoms (such as anemia or chronic lung disease) must first be excludeded[5].

It is often assumed that HF-PEF cases represent diastolic HF (DHF) [13-15]. However, careful interpretation of the data must be made because the *gold standard* for defining diastolic dysfunction is left heart catheterization and evaluation of pressure-volume curves at rest and during exercise which is not feasible as an investigative tool for the majority of patients[13]. Currently, a diagnosis of DHF is often made as a result of a patient presenting with symptoms and signs suggestive of HF in whom LV systolic dysfunction is subsequently excluded[13] which may not be the most correct assumption.

HF-PEF seems to have a different epidemiological and etiological profile from HF-REF. Patients with HF-PEF are older and more often female and obese than those with HF-REF. They are less likely to have coronary heart disease and more likely to have hypertension and atrial fibrillation (AF)[16-18].

Functional classification

Both the American College of Cardiology/American Heart Association (ACC/AHA) stages of HF and the New York Heart Association (NYHA) functional classification provide useful and complementary information about the presence and severity of HF (Fig. 2). The ACC/AHA stages of HF emphasize the development and progression of disease and can be used to describe individuals and populations, whereas the NYHA classes focus on exercise capacity and the symptomatic status of the disease[5, 7, 19].

The ACC/AHA stages of HF recognize that both risk factors and abnormalities of cardiac structure are associated with HF. Progression across HF stages is associated with reduced 5-year survival and increased plasma natriuretic peptide concentrations. Therapeutic interventions in each stage aim at modifying risk factors (stage A), treating structural heart disease (stage B), and reducing morbidity and mortality (stages C and D) should be implemented. The NYHA functional classification gauges the se-

verity of symptoms in those with structural heart disease, primarily stages C and D. It is a subjective assessment by a clinician and can change frequently over short periods of time. Although reproducibility and validity may be problematic [20], the NYHA functional classification is an independent predictor of mortality. It is widely used in clinical practice and research and for determining the eligibility of patients for certain healthcare services[7, 11].

Table 2 New York Heart Association functional classification based on severity of symptoms and physical activity

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

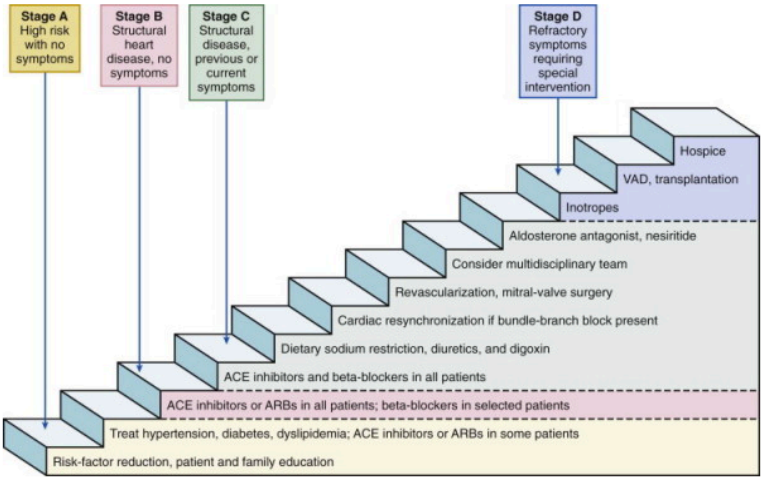


Fig. 2 – Functional classifications for HF severity evaluation: New York Heart Association (NYHA) classification and American College of Cardiology/American Heart Association (ACC/AHA) classification. (*Adapted from: McMurray JJ, et al. Eur Heart J, 2012. 33(14): p. 1787-847.[5]; Jessup M. N Engl J Med 2003; 348:2007-2018).*

3.2 Burden of disease

Prevalence

On the basis of data from NHANES 2005–2008, there is an estimated 5.7 million Americans older than 20 years that have HF and projections of crude prevalence showed that in 2010, 6.6 million Americans adults older than 18 years of age (2.8%) had HF. It is estimated that by 2030, an additional 3 million people will have HF, a 25% increase in prevalence from 2010[21, 22]. Data from the WHO suggest that the prevalence of HF differs little around the world[1].

Incidence

According to the WHO's global burden of disease report[23] of 2004, updated in 2008, the incidence of congestive HF due to rheumatic heart disease, hypertensive heart disease, ischemic heart disease or inflammatory heart diseases is, in millions, 5.7 globally, 0.5 in Africa, 0.8 in the Americas, 0.4 in Eastern Mediterranean, 1.3 in Europe and 1.4 in South-East Asia and 1.3 in Western Pacific[23].

HF incidence approaches 10 per 1000 population after 65 years of age and 75% have history of hypertension. At 40 years of age, the lifetime risk of developing HF for both men and women is 1 in 5. At 80 years of age, the remaining lifetime risk for development of new HF remains at 20% for men and women, even in the face of a much shorter life expectancy. At 40 years of age, the lifetime risk of HF occurring without antecedent myocardial infarction is 1 in 9 for men and 1 in 6 for women. The lifetime

risk for people with blood pressure 160/90 mmHg is double that of those with blood pressure 140/90 mmHg[21, 24].

The incidence differs according to ethnicity. In MESA study, African Americans had the highest risk of developing HF, followed by Hispanic, White, and Chinese Americans (4.6, 3.5, 2.4, and 1.0 per 1000 person-years, respectively). This higher risk reflected differences in the prevalence of hypertension, diabetes mellitus (DM), and socioeconomic status. African Americans had the highest proportion of incident HF not preceded by clinical MI (75%)[21, 25]. The higher HF incidence in blacks may be explained largely by the presence of higher levels of atherosclerotic risk factors[21, 26].

Data from *Kaiser Permanente* showed an increase in the incidence of HF among the elderly, with the effect being greater in men[21, 27]. In the CARDIA study, HF before 50 years of age was more common among blacks than whites. Hypertension, obesity, and systolic dysfunction are important risk factors that may be targets for prevention[21, 28]. In Olmsted County, Minnesota, the incidence of HF did not decline between 1979 and 2000[21, 29].

Mortality

The 2009 overall death rate for HF was 82.3. Any-mention death rates were 98.3 for white males, 104.5 for black males, 72.2 for white females, and 79.7 for black females. One in nine deaths has HF mentioned on the death certificate. The number of any-mention deaths from HF was approximately as high in 1995 (287 000) as it was in 2009 (275 000)[21]. In-hospital mortality seems to be improving[20].

Hospitalizations

HF is the primary diagnosis in >1 million hospitalizations annually[21]. Patients hospitalized for HF are at high risk for all-cause re-hospitalization, with a 1-month readmission rate of 25%[7]. Presently, HF is the leading cause of hospitalization among patients > 65 years of age[21]; the largest percentage of expenditures related to HF are directly attributable to hospital costs. Moreover, in addition to costs, hospitalization for acutely decompensated HF represents a sentinel prognostic event in the course of many patients with HF, with a high risk for recurrent hospitalization (e.g., 50% at 6 months) and a 1-year mortality rate of approximately 30%[30, 31].

Community studies indicate that although the incidence of HF has remained stable over time, survival has improved, leading to an increase in the prevalence of HF in the United States [29, 32, 33], which suggests that the increase in HF hospitalizations reflects, in part, the larger population of patients. Yet, little is known about the burden of hospitalization among HF patients, including the rate and cumulative number of hospitalizations per patient that occur after HF diagnosis and whether temporal changes have occurred. Studies have suggested that readmission rates are high in patients with a prior HF admission[32].

Also, little is known about the **etiology** of hospitalizations among HF patients. *Fang et al*.[34] performed an evaluation of hospitalizations from the National Hospital Discharge Survey from 1979 through 2004. They found that the proportion of hospitalizations with HF as a first-listed diagnosis remained at approximately 30% over the study period. However, there was a decline in the proportion of admissions due to coronary or other cardiovascular diseases, and an increase in the proportion

due to non-cardiovascular diseases[32]. *Curtis et al*.[35] examined hospital readmission rates among *Medicare* beneficiaries hospitalized with HF from 2001 through 2005 and found that approximately 27% of readmissions were due to HF. This analysis did not include patients without a prior HF hospitalization and only examined the first readmission, and thus cannot provide information on the total burden of hospitalizations. To date, the cause of hospitalization among community HF patients, and potential temporal changes, remain unclear[32].

Certainly, HF admission has emerged as a risk factor for hospital readmission[35]. However, despite multiple studies, no consistent **predictors** of readmission among patients with HF have emerged[35]. No studies have examined predictors of admission using incident-validated HF patients followed for a prolonged time period or used modeling techniques to account for repeated hospitalizations after HF diagnosis. As HF is a chronic disease characterized by periodic exacerbations often leading to multiple hospitalizations, analyzing only the first rehospitalization excludes information from subsequent hospitalizations[32]. In *Dunlay et. al* [32] study, independent risk factors for all cause admissions after HF diagnosis were male sex, diabetes mellitus, chronic obstructive pulmonary disease (COPD), anemia, and reduced creatinine clearance at HF diagnosis. Detection of these factors among newly diagnosed HF patients may help in identifying those at higher risk for multiple admissions and for whom more intense care is needed. The fact that most hospitalizations among HF patients are due to non-HF causes underscores the urgent need to determine whether targeting comorbidities could lead to a decrease in hospitalizations[32].

Hospitalization for HF is a growing and major public health issue. Data from HF registries have clarified the profile of patients with HF requiring hospitalization [30, 31, 36, 37]. Characteristically, such patients are elderly or near elderly, equally male or female, and typically have a history of hypertension, as well as other medical comorbidities, including chronic kidney disease, hyponatremia, hematologic abnormalities, and COPD [36, 38-40]. A relatively equal percentage of patients with acutely decompensated HF have impaired versus preserved left ventricular systolic function [41, 42].

Hospital discharges for HF were essentially unchanged from 1999 to 2009, with first-listed discharges of 975 000 and 1 094 000, respectively. In 2009, there were 3 041 000 physician office visits with a primary diagnosis of HF. In 2009, there were 668 000 emergency department visits and 293 000 outpatient department visits for HF[21, 32].

Disability

From the global burden of disease report the severity weight for HF disabling sequelae and injury is 0.24 - 0.36 and in class IV (in a scale 0-1, divided in seven classes). The impact of any disease state has to be measured not only in terms of absolute mortality rates, but the average age of those affected, its effect on quality of life and the type and cost of health-care resources it typically engenders[12]. With the notable exception of lung cancer, HF is as ‘malignant’ as many common types of cancer and is associated with a comparable number of expected life-years lost[12]. In fact, the Scottish data from Stewart *et. al* show that patients admitted to hospital with a diagnosis of cancer often survive longer than those with a diagnosis of HF[18]. As such, for both men and women, HF se-

vere enough to require hospitalization is more 'malignant' than many of the common types of cancer[12].

Comorbidities

A large proportion of readmissions for HF are associated with comorbidities that precipitate, contribute to, or complicate HF admission,[32, 43] especially in the elderly. In a recent population study, 39% of HF patients had ≥5 non-cardiac comorbidities and only 4% had HF alone[32, 44].

Quality of life

The health related quality of life (HRQOL) is reduced in HF, especially in the areas of physical functioning and vitality. Lack of improvement in HRQOL after discharge from the hospital is a powerful predictor of re-hospitalization and mortality[7, 45, 46].

Economic burden

In 1 in 9 deaths in the United States, HF is mentioned on the death certificate. The number of deaths with any mention of HF was as high in 2006 as it was in 1995[21]. Approximately 7% of all cardiovascular deaths are due to HF. In 2012, HF costs in the United States exceeded $40 billion 12. This total includes the cost of healthcare services, medications, and lost productivity. The mean cost of HF-related hospitalizations was $23,077 per patient and was higher when HF was a secondary rather than the primary diagnosis[7].

3.3 Etiology and pathophysiology

Although many conditions can lead to HF (coronary artery disease, hypertension, cardiomyopathies, valvular and congenital heart disease, arrhythmias, pericardial disease, myocarditis, pulmonary hypertension, and cardiotoxic substances— including alcohol), the predominant cause of HF in the western world is **ischemic heart disease**[8].

a) Etiology

Coronary artery disease notably increases the probability of developing HF; in 7–8 years after myocardial infarction up to 36% of patients will experience HF, especially those with left ventricular systolic dysfunction documented during admission[47].

Hypertension (systolic blood pressure over 140 mmHg, or diastolic blood pressure over 90 mmHg, or treatment with antihypertensive medication) may be the single most important modifiable risk factor for HF in the United States. Hypertensive men and women have a substantially greater risk for developing HF than normotensive men and women[7]. Elevated levels of diastolic and especially systolic blood pressure are major risk factors for the development of HF[7, 48]. The incidence of HF is greater with higher levels of blood pressure, older age, and longer duration of hypertension. Long-term treatment of both systolic and diastolic hypertension reduces the risk of HF by approximately 50% [49].

Obesity (body mass index over 30 kg/m2) **and insulin resistance** are important risk factors for the development of HF [50]. The presence of clinical diabetes markedly increases the likelihood of developing HF in patients without structural heart disease[51] and adversely affects the outcomes of patients with established HF [52].

Patients with known **atherosclerotic disease** (e.g., of the coronary, cerebral, or peripheral blood vessels) are likely to develop HF, and clinicians should seek to control vascular risk factors in such patients according to guidelines[7].

Valvular abnormalities, factors indicative of heart disease (left ventricular hypertrophy, left ventricular dilatation), a **familly history** of HF, other conventional risk factors (such as **smoking**), as well extracardiac conditions (**renal dysfunction, obstructive pulmonary disease**) all increase the risk of HF[8].

b) Pathophisiology

HF-REF is the best understood type of HF in terms of **pathophysiology**(Fig.3). The syndrome of HF arises as a consequence of an abnormality in cardiac structure, function, rhythm, or conduction[6]. HF may be viewed as a progressive disorder that is initiated after an index event either damages the heart muscle, with a resultant loss of functioning cardiac myocytes, or disruption of the ability of the myocardium to generate force, thereby preventing the heart from contracting normally[11]. The index event may have an abrupt onset, as in the case of a myocardial infarction; it may have a gradual or insidious onset, as in the case of hemodynamic pressure or volume overloading; or it may be hereditary, as in the case of many of the genetic cardiomyopathies. Regardless of the nature of the inciting event, the feature that is common to each of these index events is that they all, in some manner, produce a decline in pumping capacity of the heart. In most instances, patients will remain asymptomatic or minimally symptomatic after the initial decline in pumping capacity of the heart or will develop symptoms only after the dysfunction has been present for some time[11].

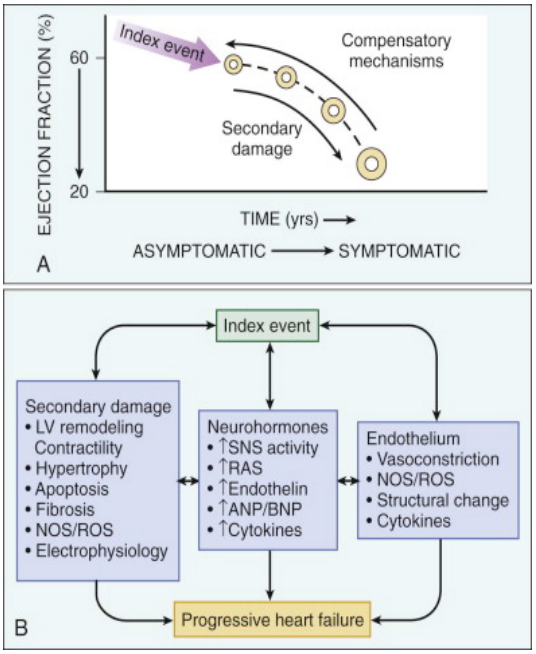


Fig. 3 – Pathophysiologic mechanisms of response to heart damage: compensatory mechanisms that become maladaptive responses. (Source: *Bonow RO, et al. Branwald's Heart Disease: a textbook of cardiovascular medicine. 9th edition. 2012*).

In response, hemodynamic and neuro-hormonal mechanisms are activated to preserve cardiac function. The decreased capacity of the left ventricle to empty during systole increases diastolic wall tension in non-injured pats of the heart. The left ventricle responds by enhancing its contraction, following the *Frank-Starling* curve. Aditionally, the sympathetic nervous system is activated, resulting in decrea-

ses inotropism and chronotropism[11]. Both compensatory mechanisms also lead to increase in internal wall stress during diastole. In response, synthesis of myofibrillar proteins is stimulated, resulting in increased wall thickness and a subsequent reduction of ventricular wall stress and dilatation, which reduces energy expenditure. An increase in diastolic wall stress in the atria suppresses the sympathetic nervous system and leads to the release of atrial natriuretic peptide. In addition, B-type natriuretic peptide (BNP) and C-type natriuretic peptide are released, respectively, by the ventricular myocardium in response to elevations of end-diastolic pressure and volume, and by endothelial cells in response to shear stress. The natriuretic peptides improve the loading conditions on the heart through their diuretic, natriuretic and vasodilator properties. In this way, a hemodynamic balance is achieved, which restores cardiac function. Long-term activation of these mechanisms, however, diminishes their favourable physiological effects and results in progressive deterioration of ventricular function. As cardiac output declines, systemic perfusion is maintained by peripheral vasoconstriction and sodium retention. Catecholamines, angiotensin II and vasopressin act to increase systemic blood pressure and expand intravascular volume, while prostaglandins and natriuretic peptides limit the pressor, antinatriuretic and antidiuretic effects of these vasoconstrictor systems. Water and salt retention result mainly from direct and indirect effects of the renin-angiotensin system on glomerular and tubular function.

Although the precise reason that patients with left ventricular dysfunction remain asymptomatic is not certain, one potential explanation is that a number of compensatory mechanisms become activated in the setting of cardiac injury or depressed cardiac output; these appear to modulate left ventricular function within a physiologic-homeostatic range, such that the functional capacity of the patient is preserved or is depressed only minimally. However, as patients transition to symptomatic HF, the sustained activation of neurohormonal and cytokine systems leads to a series of end-organ changes within the myocardium referred to collectively as left ventricule remodeling that is sufficient to lead to disease progression in HF independent of the neurohormonal status of the patient[11]. What characterizes untreated systolic dysfunction is progressive worsening of these changes over time, with increasing enlargement of the left ventricule and decline in EF, even though the patient may be asymptomatic initially[5].

The progression of left ventricular systolic dysfunction and HF syndrome, owing to “remodelling” (as a result of loss of myocytes and maladaptive changes in the surviving myocytes and extracellular matrix), probably occurs in two main ways[6]. One is as a consequence of intercurrent cardiac events (e.g., myocardial infarction), and the other as a consequence of the systemic processes activated because systolic function is reduced (e.g., neurohumoral pathways)[6].

b.1) Neurohormonal model

A growing body of experimental and clinical evidence suggests that HF progresses as a result of the overexpression of biologically active molecules that are capable of exerting deleterious effects on the heart and circulation[53]. Two key neurohormonal systems activated in HF are sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS)[5] which are responsible for **maintaining cardiac output** through increased retention of salt and water, peripheral arterial vasoconstriction, and increased contractility, and for **activation of inflammatory mediators**, which are responsible for cardiac repair and remodeling.

- Sympathetic nervous system (SNS)

The activation of the SNS is one of the most important mechanisms and occurs early in the course of HF. Activation of the SNS in HF is accompanied by a concomitant withdrawal of parasympathetic tone. Although these disturbances in autonomic control were initially attributed to loss of the inhibitory input from arterial or cardiopulmonary baroreceptor reflexes, there is increasing evidence that excitatory reflexes may also participate in the autonomic imbalance that occurs in HF[11, 54] (Fig. 4).

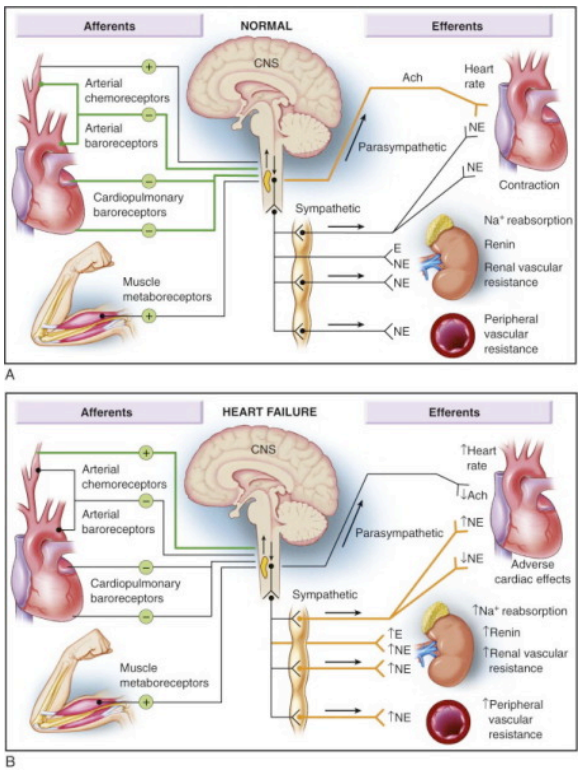


Fig. 4 – Neurohormonal model: sympathetic nervous system. (Source: *Bonow RO, et al. Branwald's Heart Disease: a textbook of cardiovascular medicine. 9th edition. 2012*).

Under **normal conditions**, inhibitory inputs from the high-pressure carotid sinus and aortic arch baroreceptors and the low-pressure cardiopulmonary mechanoreceptors are the principal inhibitors of sympathetic outflow, whereas discharge from the nonbaroreflex peripheral chemoreceptors and muscle metaboreceptors are the major excitatory inputs to sympathetic outflow. The vagal limb of the baroreceptor heart rate reflex is also responsive to arterial baroreceptor afferent inhibitory input. Healthy individuals display low sympathetic discharge at rest and have high heart rate variability. However, in **HF patients**, inhibitory input from baroreceptors and mechanoreceptors decreases and excitatory input increases, with the net result that there is a generalized increase in sympathetic nerve traffic and blunted parasympathetic nerve traffic, with a resultant loss of heart rate variability and increased peripheral vascular resistance[11, 54].

As a result of the increase in sympathetic tone, there is an increase in circulating levels of norepinephrine, a potent adrenergic neurotransmitter. The elevation of the levels of circulating norepinephrine result from a combination of increased release with reduced uptake. In patients with advanced HF, the circulating levels of norepinephrine in resting patients are two to three times those found in normal subjects. Indeed, plasma levels of norepinephrine may predict mortality in patients with HF. Whereas the normal heart usually extracts norepinephrine from the arterial blood, in patients with moderate HF, the coronary sinus norepinephrine concentration exceeds the arterial concentration, indicating increased adrenergic stimulation of the heart. However, as HF progresses, there is a significant decrease in the myocardial concentration of norepinephrine [11].

Increased sympathetic activation of the beta1-adrenergic receptor results in **increased heart rate** and **force of myocardial contraction**, with a resultant **increase in cardiac output**. In addition, the heightened activity of the adrenergic nervous system leads to stimulation of myocardial alpha1-adrenergic receptors, which elicits a **modest positive inotropic effect**, as well as **peripheral arterial vasoconstriction**. Although norepinephrine enhances both contraction and relaxation and maintains blood pressure, myocardial energy requirements are higher, which can intensify ischemia when myocardial oxygen delivery is restricted. The higher adrenergic outflow from the central nervous system may also trigger ventricular tachycardia or even sudden cardiac death, particularly in the presence of myocardial ischemia. Thus, activation of the sympathetic nervous system provides short-term support that has the potential to become maladaptive in the long term[11].

- Renin-angiotensin-aldosterone system (RAAS)

The components of the RAAS are activated comparatively later in HF. The presumptive mechanisms for RAAS activation in HF include **renal hypoperfusion**; **decreased filtered sodium reaching the macula densa in the distal tubule**; and **increased sympathetic stimulation of the kidney, leading to increased renin release from the juxtaglomerular apparatus**[11] (Fig. 5).

Renin cleaves four amino acids from circulating angiotensinogen, which is synthesized in the liver, to form the biologically inactive decapeptide angiotensin I. Angiotensin-converting enzyme (ACE) cleaves two amino acids from angiotensin I to form the biologically active octapeptide (1-8) angiotensin II. The majority (~90%) of ACE activity in the body is found in tissues; the remaining 10% of ACE activity is found in a soluble (non–membrane bound) form in the interstitium of the heart and vessel wall. The importance of tissue ACE activity in HF is suggested by the observation that ACE mRNA, ACE binding sites, and ACE activity are increased in explanted human hearts. Angiotensin II can also be synthesized through renin-independent pathways, through the enzymatic conversion of angiotensinogen to angiotensin I by kallikrein and cathepsin G and through the activation of chymase[11].

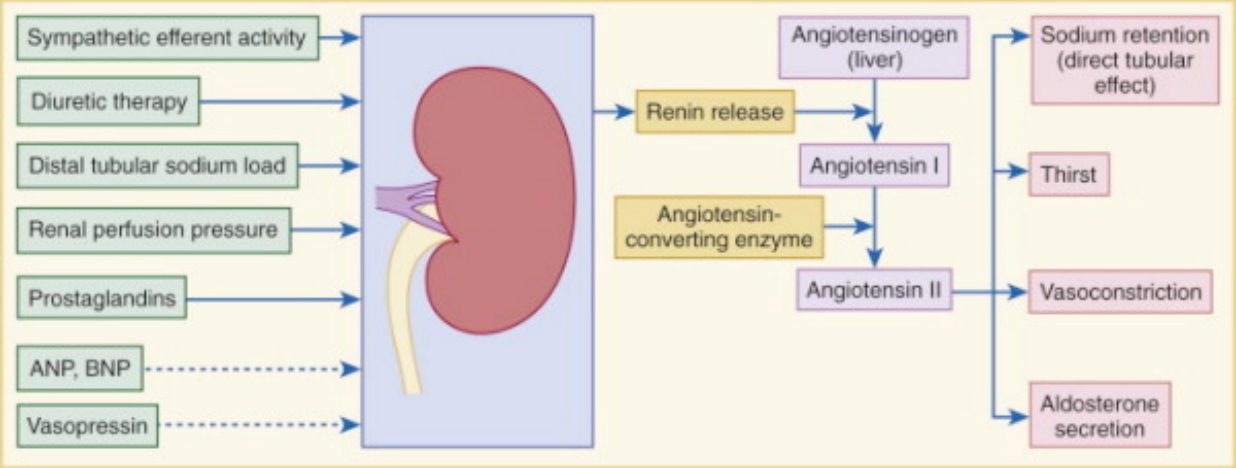


Fig. 5 – Neurohormonal model: renin-aldosterone-angiotensin system. (Source: *Bonow RO, et al. Branwald's Heart Disease: a textbook of cardiovascular medicine. 9th edition. 2012*).

Other neurohormonal pathways or neurohormones potentially involved in myocardial damage are oxidative stress, arginine vasopressin, natriuretic peptides, endothelin, neuropeptide Y, urotensin II, nitric oxide, bradykinin, adrenomodullin, apelin, adipokines and inflammatory mediators[11].

The important unifying concept that arises from the neurohormonal model is that the **overexpression of biologically active molecules contributes to disease progression by virtue of the deleterious effects these molecules exert on the heart and circulation**[11]. In addition to causing further myocardial injury, these systemic responses have detrimental effects on the blood vessels, kidneys, muscles, bone marrow, lungs, and liver, and create a pathophysiological 'vicious cycle', accounting for many of the clinical features of the HF syndrome, including myocardial electrical instability. Interruption of these two key processes is the basis of much of the effective treatment of HF[5]. The molecular, structural, and functional changes in the heart combined with these systemic processes, coupled with electrolyte imbalances, result in electrical as well as mechanical dysfunction of the heart[6, 55, 56].

b. 2) Left ventricular remodeling

Although the neurohormonal model explains many aspects of disease progression in the failing heart, there is increasing clinical evidence to suggest that our current neurohormonal models fail to completely explain disease progression in HF. That is, whereas neurohormonal antagonists stabilize HF and in some cases reverse certain aspects of the disease process, HF will progress in the overwhelming majority of patients, albeit at a slower rate. It has recently been suggested that **the process of left ventricular remodeling is directly related to future deterioration in left ventricular performance and a less favorable clinical course in patients with HF**[57]. Whereas the complex changes that occur in the heart during LV remodeling have traditionally been described in anatomic terms, the process of LV remodeling also importantly affects the biology of the cardiac myocyte, the

volume of myocyte and nonmyocyte components of the myocardium, and the geometry and architecture of the LV chamber[11].

3.4 Comorbidities

Together with the key **pathophysiological processes** in HF – left ventricular remodelling and activation of neurohormonal pathways—and **age**, comorbidity is among the main determinants of prognosis[6]. Many patients with HF have comorbidity related to the underlying cardiac problem or its cause (e.g., angina, hypertension, diabetes, smoking-related lung disease) and age (e.g., osteoarthritis), as well as a consequence of HF (e.g., arrhythmias) and its treatment (e.g., gout from diuretics)[44]. Some common comorbidities have many causes (e.g., renal dysfunction), whereas others are not fully explained (e.g., anemia, depression, disorders of breathing, and cachexia)[58-60]. The existence of many comorbidities creates the potential for drug intolerance and drug interactions and makes the management of HF very complex[44]. As more patients with HF survive longer and progress to more advanced stages, renal failure is becoming one of the most common and difficult to manage comorbidities[6].

As a common disease in the elderly, HF should not be viewed in isolation: anemia, cachexia, renal impairment, obstructive sleep apnea, COPD and diabetes mellitus are conditions frequently observed in HF patients and unfavorably affect prognosis[8, 61] (Fig. 6). The most prevalent conditions in HF patients are renal failure, described as cardio-renal syndrome (about 40%)[62], anemia (37%)[63], COPD (20-30%)[64] and depression (15-36%)[65]. Comorbidity was found to be one of the prime determinants of prognosis in a study of patients admitted with HF and contributes to the poor quality of life as perceived by HF patients[8, 61]. The complex interplay between diseases previously perceived as entities on their own is increasingly acknowledged[8, 61]. According to some population studies, more than one half of all hospitalizations were related to non-cardiovascular[21, 27].

Chronic kidney disease is common in patients with HF and coronary artery disease, and these patients have more advanced coronary atherosclerosis. Patients with renal insufficiency are less likely to be prescribed efficacious therapies, but have better outcomes if they receive these medications[62]. The term ‘cardio-renal syndrome’ refers to the complex interrelation between heart and kidneys, and denotes the decline of renal function in the setting of CHF. It originates from the observation that even minor alterations in renal function, as evidenced by reduced glomerular filtration rate and microalbuminuria, represent potent cardiovascular risk factors[64].

Anemia is a common finding in patients with chronic HF with prevalence rates between 20% and 50%. The incidence increases with NYHA functional class. It is a strong independent predictor of impaired survival: in a large study of >150,000 patients, the mortality risk was doubled in anemic HF patients[62, 66]. Also, is associated with increased morbidity and hospitalization rates. Anemia is variably reported, in part due to the lack of consensus on the definition of anemia. Anemia is also more common in women, is seen in both patients with HF-REF and HF-PE and is associated with reduced exercise capacity, impaired health related quality of life (HRQOL), and a higher risk for hospitalization[62, 66].

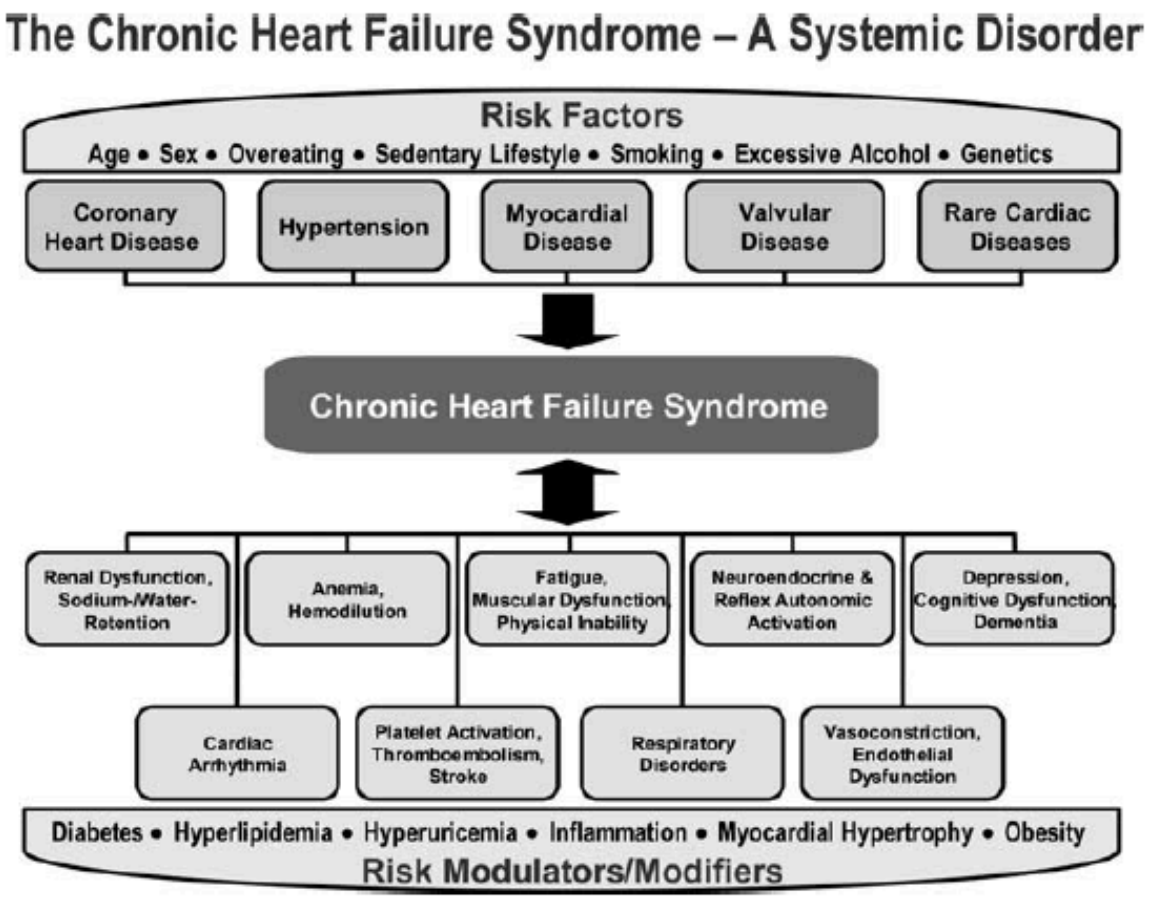


Fig. 6 – Comorbidity and its implications in heart failure: causation, exacerbation, impact in seeking care, in low adherence and masking of symptoms (Source: *Angermann CE. European Journal of Heart Failure Supplements, 2009. 8(Supplement 1): p. i5-i10.*[60])

Chronic obstructive pulmonary disease (COPD) is frequent in patients with CHF, with a prevalence ranging from 20% to 30%. Since the coexistence of both conditions has important therapeutic implications, early recognition is critical. However, COPD may be missed in patients with CHF, because dyspnea is erroneously attributed to CHF, and vice versa. Measurement of plasma natriuretic peptide levels may be useful to uncover unsuspected CHF in COPD patients. Also, HF appears to be frequently present in patients with COPD[8]. However, accurate and precise data on the prevalence of COPD in patients with HF are still lacking, and prognosis of patients with HF with concomitant COPD is largely unknown. Patients with concurrent HF and COPD may have therapeutic constraints that have not been comprehensively investigated[67].

Depression is common in patients with HF; those with depressive symptoms have lower HRQOL, poorer self-care, worse clinical outcomes, and more use of healthcare services[68]. Although it is frequently assumed that depression occurs only among hospitalized patients, a multicenter study demonstrated that even at least 3 months after a hospitalization, 63% of patients with HF reported symptoms of depression[69]. The mechanism remains unclear[69, 70]. Although remission from depression may improve cardiovascular outcomes, the most effective intervention strategy is not yet known[68].

Patients with HF are more likely than the general population to develop **atrial fibrillation** (AF). There is a direct relationship between the NYHA class and prevalence of AF in patients with HF progressing from 4% in those who are NYHA class I to 40% in those who are NYHA class IV. AF is also a strong independent risk factor for subsequent development of HF. In addition to those with HF-REF, patients with HF-PEF are also at greater risk for AF. AF can worsen symptoms in patients with HF, and, conversely, worsened HF can promote a rapid ventricular response in AF[7].

3.5 Diagnosis

HF can present suddenly, as the consequence of an acute cardiac event such as myocardial infarction; chronically, in most cases in the community to a primary-care physician, or in an acute-on-chronic fashion, when a period of worsening symptoms and signs is followed by an emergency presentation with decompensation.

Symptoms and signs

The diagnosis of HF can be difficult, especially in the early stages. The symptoms may be due to other problems, such as chronic lung disease, anemia, venous insufficiency, renal dysfunction, and hypothyroidism, or concomitant treatments, such as calcium-channel blockers or glitazones[71-73]. Symptoms that are more specific (orthopnea and paroxysmal nocturnal dyspnea) are less common, especially in patients with milder symptoms, and are, therefore, insensitive[5]. Other signs, such as raised jugular-venous pressure, cardiomegaly, and a third heart sound, are more specific but much less common and harder to detect[71-73]. Even if HF is correctly diagnosed on the basis of symptoms and signs, differentiation between preserved and reduced left-ventricular systolic function is still difficult. Consequently, the diagnosis of HF requires investigation[6].

Initial investigation

The key investigations are: echocardiography to demonstrate structural heart disease; electrocardiography (ECG) to show rhythm, rate, and conduction; chest radiography to exclude primary pulmonary disease and identify edema; blood chemistry; and hematology (Fig. 7). As well as providing diagnostic information, each investigation helps to guide treatment[5, 6]. Routine biochemical and hematological investigations are also important, partly to determine whether RAAS blockade can be initiated safely (renal function and potassium), to exclude anemia (which can mimic or aggravate HF) and other useful information[5, 6].

Natriuretic peptides

Measurement of the blood concentration of natriuretic peptides secreted by the heart can help in the diagnosis of HF especially in the acute setting[5, 6]. B-type natriuretic peptide (BNP) and N-terminal pro-BNP are more useful than the A-type natriuretic peptides[5]. Also, BNP is a well-established prognostic indicator in HF patients with a wide range of functional impairment[74].

Because the signs and symptoms of HF are so non-specific, many patients with suspected HF referred for echocardiography are not found to have an important cardiac abnormality[5, 6]. Where the availability of echocardiography is limited, an alternative approach to diagnosis is to measure the

blood concentration of a natriuretic peptide, hormones secreted in increased amounts when the heart is diseased or the load on any chamber is increased (e.g. by AF, pulmonary embolism, and some non-cardiovascular conditions, including renal failure)[5, 6]. Natriuretic peptide levels also increase with age, but may be reduced in obese patients. A normal natriuretic peptide level in an untreated patient virtually excludes significant cardiac disease[5, 6].

For patients presenting with acute onset or worsening of symptoms, the optimal exclusion *cut-off* point is 300 pg/mL for NT-proBNP and 100 pg/mL for BNP[5, 6]. For patients presenting in a non-acute way, the optimum exclusion cut-off point is 125 pg/mL for NT-proBNP and 35 pg/mL for BNP. The sensitivity and specificity of BNP and NT-proBNP for the diagnosis of HF are lower in non-acute patients[5, 6, 75-77].

Other investigations

Other tests are generally only required if the diagnosis remains unclear (e.g. if echocardiographic images are suboptimal or if an unusual cardiac cause, or a non-cardiac cause, of the patient's condition is suspected) or if further evaluation of the underlying cause of the patient's cardiac problem is indicated (e.g. perfusion imaging or angiography in suspected coronary artery disease or endomyocardial biopsy in certain infiltrating diseases of the myocardium)[5, 6].

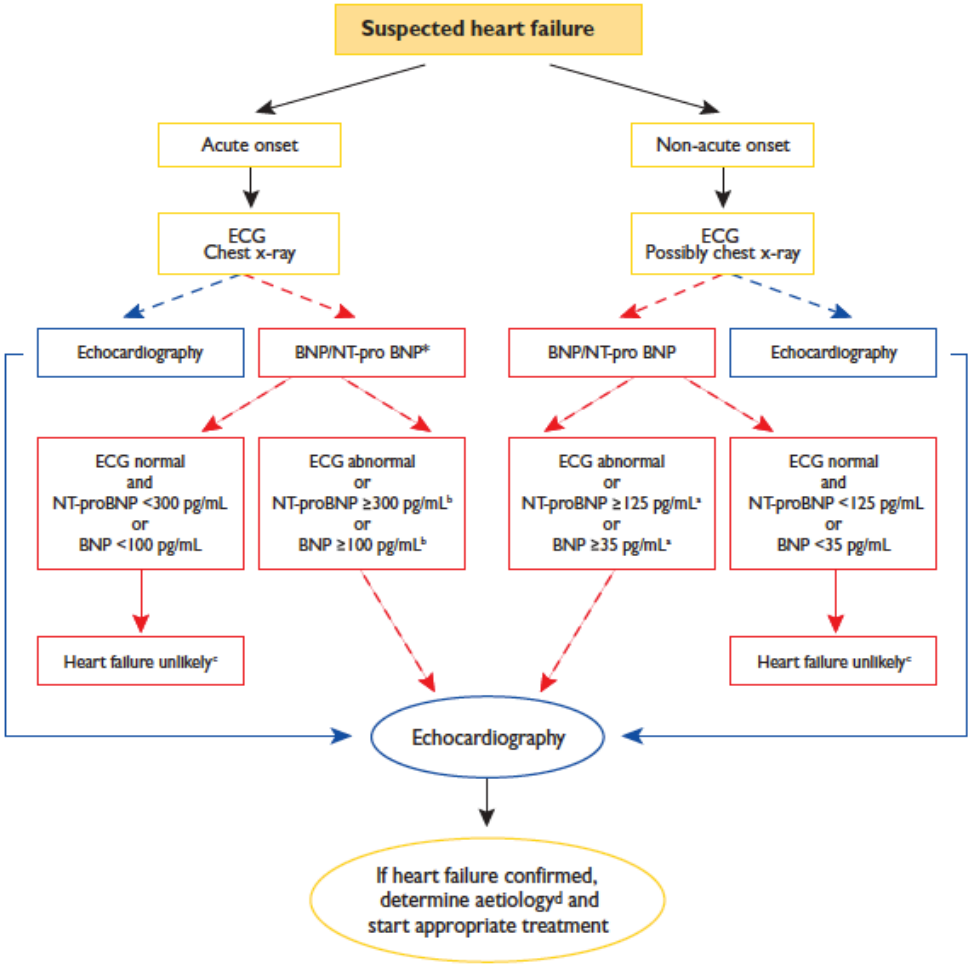


Fig. 7 – Algorithm for acute and non-acute heart failure diagnosis. (*Source: McMurray JJ, et al. Eur Heart J, 2012. 33(14): p. 1787-847.[5]).*

Algorithm

In patients presenting to hospital as an emergency with suspected HF and acute onset of symptoms, early echocardiography is recommended (and immediate echocardiography in shocked or severely hemodynamically compromised patients) (Fig. 7). If a natriuretic peptide is measured, a high exclusion cut-off point should be used. In patients presenting non-emergently in primary care, or to a hospital outpatient clinic, with slow onset of symptoms (and signs) suggestive of HF, an ECG and natriuretic peptide measurement may be used as a means of identifying patients who most need echocardiography (an echocardiogram is indicated if the natriuretic peptide level is above the exclusion threshold/ECG is abnormal). In these patients, a lower exclusion natriuretic peptide *cut-off* point should be used to prevent a 'false-negative' diagnosis of HF. Patients with a high pre-test likelihood of HF, such as those with a history of myocardial infarction, may be referred directly for echocardiography.

3.6 Prognosis

Prognosis means foreseeing, predicting, or estimating the probability or risk of future conditions. In medicine, prognosis commonly relates to the probability or risk of an individual developing a particular state of health (an outcome) over a specific time, based on his or her clinical and non-clinical profile[78]. Outcomes are often specific events, such as death or complications, but they may also be quantities, such as disease progression, (changes in) pain, or quality of life[78].

As a leading cause of death worldwide, predicting the progression of HF is important from the perspectives of facilitating patient and physician understanding of disease course and of determining the appropriate timing of the increasing number of medications and invasive interventions available to the advanced HF patient[79].

The prognosis of HF patients remains poor, even with the development of effective pharmacological and non-pharmacological interventions[8]. Although information on the natural history of a disease is relevant to illustrate its burden for health care and the society at large, prognostication in individual patients plays a crucial role in daily clinical practice[8]. After the diagnosis (and possible etiology) of HF has been established, estimation on individual patient's probability of developing clinically relevant prognostic outcomes may be done—for example, a 5-year survival probability. Such estimates are typically based on patients' characteristics, including age, comorbidity, severity and cause of HF that are known to influence prognosis. This information, together with the anticipated, preferably evidence-based, effect of possible therapeutic interventions and patient preferences, is instrumental in the decision which therapeutic measures should be taken. Importantly, this implies precise enough predictions of the future—a difficult task, the more since, apart from survival, other prognostic outcomes are of interest in HF, including hospitalizations and quality of life. The recent development of prognostic scores, enabling physicians to estimate an individual's probability of developing relevant complications as a function of the level of a limited number of prognostic factors, may be helpful.

Outcomes

The most commonly studied outcomes in HF are death and/or hospitalization. For both of these, the direct cause is often specified, e.g. due to HF, cardiovascular-related cause, or all-cause death and/or hospitalization are considered. In HF studies all-cause death/hospitalization is preferred over disease-specific cause because they do not depend on the exact ascertainment of the event's cause and also there are commonly multiple comorbidities associated that closely interplay with cardiac dysfunction and may influence and be influenced by the failing heart.

Prognosis in HF

Survival after HF diagnosis has improved over time, as shown by data from the Framingham Heart Study (FHS) [21, 80] and the Olmsted County Study (OCS) [21, 29].

In FHS, mortality rate in men after 1 year of follow-up decreased from 30% in the period 1950-1969 to 28% in the period 1990-1999, after 5 years from 70% to 59% during the same period. Similarly in women 1 and 5 years mortality rate declined from 28% to 24% and from 57% to 45% respectively, in the same period [21, 80].

In OCS, survival after HF diagnosis was worse among men than women (RR 1.33; 95% CI, 1.24-1.43) but overall improved over time (5-year age-adjusted survival, 43% in 1979-1984 vs 52% in 1996-2000, $p<0.001$)[29]. Men and younger persons experienced larger survival gains, contrasting with less or no improvement for women and elderly persons.

In the elderly, data from *Kaiser Permanente* indicate that survival after the onset of HF has also improved[21, 27]. In this study, on 5-year follow-up and adjustment for age and comorbidities, the mortality hazards decreased 33% (95% CI 14% to 48%) among men and 24% (95% CI 1% to 43%) among women[27]. However, the death rate remains high: within 1 year of follow up a third of patients die and 50% die within 5 years of diagnose[21, 29, 33].

Prognostic factors in HF

Many variables provide prognostic information, although most of this can be obtained from readily available data such as **age, etiology, NYHA class, EF, key co-morbidities** (renal dysfunction, diabetes, anemia, hyperuricemia), and **plasma natriuretic peptide concentration**[79, 81-85] (Table 1). Clearly these variables change over time, as does prognosis. Assessment of prognosis is particularly important when counselling patients about devices and surgery (including transplantation) and in planning end-of-life care with patients, their family, and caregivers[5, 61].

It is noteworthy that in order to be of importance and serve practice, prognostic determinants need not be causally related to the prognostic outcome. Age and gender, for example, are important prognostic markers in many diseases, even after adjustment for other prognostic determinants, although age *per se* may not be causally implicated, but indicates other, often immeasurable, factors that are etiologically involved[8]. Prognostic determinants in HF can be categorized in: patient characteristics and comorbidity; laboratory measurements; functional parameters and ventricular function; and interventions received[8].

Table 1 – Prognostic variables in heart failure. (*Source: McMurray JJ, et al. Eur Heart J, 2012. 33(14): p. 1787-847. [57]*).

Web Table 10: Prognostic variables in heart failure
A very large number of variables have been shown to relate to outcome in HF (and new prognostic markers are regularly identified). This table lists some of the more commonly described prognostic variables.
Demographics, history, and physical examination
Age, sex, ethnicity, NYHA class, body mass index.
Signs of congestion, increased jugular venous pressure, third heart sound, low systolic blood pressure, higher heart rate.
Diabetes mellitus, renal dysfunction, depression, COPD.
Ischaemic aetiology, history of myocardial infarction.
Routine laboratory tests
Serum sodium
Liver enzymes, bilirubin
Serum creatinine/creatinine clearance/eGFR
BUN/urea and markers of tubular injury
Serum albumin
Uric acid
Haemoglobin
Red cell distribution width
Troponin I/T
Urinary albumin creatinine ratio
Neurohormones, cytokines, and related factors[a]
Plasma renin activity
Angiotensin II
Aldosterone
Catecholamines
(Big) endothelin-1
Adrenomedullin
Natriuretic peptides[b]
Vasopressin/Co-peptin
Cytokines
sST-2
Galectin-3
Collagen markers
Electrical variables
QRS width
LV hypertrophy
Atrial fibrillation
Complex ventricular arrhythmias
Heart rate variability
Imaging variables
LV internal dimensions and fractional shortening
Cardiothoracic ratio on chest X-ray
Wall motion index (various[c])
Ejection fraction
Left atrial size
Restrictive filling pattern/short deceleration time
Right ventricular function (various[c])
Inflammation (contrast-enhanced CMR), iron content (in thalassaemia: CMR)
Amyloidosis (contrast kinetics in CMR)
Ischaemia and viability imaging, arrhythmogenic substrates
Exercise test/haemodynamic variables (rest/exercise)
VO_2
VE/VCO_2 slope
Max/peak (normal >20 mL/kg/min[d])
6-min walk distance (normal >600 m[d])
Cardiac index (normal >2.5 L/min/m^2)
LV end-diastolic pressure/pulmonary artery wedge pressure (normal <12 mmHg)

BUN = blood urea nitrogen; CMR = cardiac magenetic resonance; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HF = heart failure; LV = left ventricular; NYHA = New York Heart Association; sST-2 = soluble ST-2; VO_2 = peak oxygen consumption.
[a]This list is not intended to be comprehensive and other circulating factors may also be associated with prognosis.
[b]Various peptides including C-terminal, N-terminal, and mid-regional are predictive of outcome.
[c]Various measures/classifications can be used, and no single threshold for normal/abnormal can be given.
[d]Functional capacity varies greatly according to prior fitness, age, and sex; values given are a guideline for older (>65 years) adults.

In the general population, knowledge of **age** and **sex** can provide high accuracy in prediction of life expectancy. As progressively more severe HF develops, the predictive value of these factors declines, though female sex appears in multiple trials to be protective against HF mortality[79, 86, 87].

Impaired socioeconomic status in adulthood and childhood has consistently been shown to be a predictor of worsened outcomes[51, 88]. The impact of ethnicity on HF mortality has been more con-

flicting, with studies showing increased rates of hospitalization, along with both survival advantage and detriment in black patients[79, 89] mainly because socioeconimic status is one of its determinants.

Infiltrative and ischemic etiologies of HF are associated with worse prognosis, with one study showing 50% increased mortality for ischemic cardiomyopathy and 400% increased mortality for infiltrative cardiomyopathy as compared with idiopathic cases[90].

In the general population, increased **systolic blood pressure (BP)** and higher **body mass index (BMI)** are associated with worse outcomes and increased the risk of development of HF (approximately a 5% increase in risk for each 1-kg/m^2 increase in BMI). However, once HF has developed, higher BP and BMI are associated with decreased risk[91]. This may be due to lower BP serving as a marker of worsened HF and impaired forward flow. The state of **cardiac cachexia** is associated with significantly worsened prognosis, and multiple studies have shown improved survival in established HF patients with increased BMI, a trend that continues even into the early stages of morbid obesity. A 10% reduction in mortality for each 5-unit increase in BMI was seen in a large registry of more than 100,000 patient presentations for acute decompensated HF. The **reverse epidemiology** for weight has been noted in end-stage renal disease and metastatic cancer as well, raising the possibility of a chronic malnutrition-inflammation state heralded by these markers and associated with worsened outcomes[79, 92].

Aside from baseline characteristics of a patient, interventions also have an effect on prognosis (β-Blockers, ACE inhibitors, angiotensin receptor blockers, and aldosterone antagonists). On the contrary, **high doses of diuretics** are being correlated with worsened prognosis although the exact implications of diuretics on the prognosis its unknown[93]. Presence of positive inotropic medications has an unquestionably deleterious effect on long-term survival[79].

Device placement also changes patient prognosis, with appropriately selected patients showing a 25% to 30% relative reduction in all-cause mortality after placement of an ICD and nearly 80% of New York Heart Association (NYHA) class III and IV patients showing symptom improvement of at least 1 NYHA class after placement of cardiac resynchronization therapy (CRT) or CRT with defibrillator (CRT-D)[79, 94]. Recent clinical trials of CRT-D vs ICD in NYHA class II patients with EF less than 30% have suggested that CRT-D reduces HF hospitalizations and mortality[95].

Reduced left ventricular EF is the defining feature of systolic HF and has consistently been associated with adverse outcomes[96]. Many aspects of the echocardiogram correlate with mortality in HF, including LV end-systolic volume and stroke volume, mitral and tricuspid insufficiency, right ventricular systolic dysfunction, impaired peak early- (E) to late- (A) mitral diastolic flow ratios (E:A ratios), and impaired peak early-diastolic mitral filling velocity to peak early diastolic mitral annular velocity (E:E' ratio)[96]. The CHARM trial showed that each 10% reduction in EF was associated with a 39% increase in the risk of mortality, but this was only for EF below 45%[97].

In HF-PEF improvements in mortality have been much less impressive than those in patients with HF-REF especially because comorbidities such as diabetes and hypertension, associated with HF-PEF, are increasing globally[79].

The NYHA class has long been used as a simple, widely recognized metric of a patient's exercise capacity. Initiating one additional HF medicine has almost as favorable an effect on survival as reducing NYHA functional class by 1 category[79].

More quantitative methods of measurement include the 6-minute walk test. Having a patient walk on a treadmill using a modified Naughton protocol (1-metabolic equivalent increase in exertion with each 2-minute increment in test stage) was shown in one study to associate with a 7%increased risk of death for each 1-minute reduction in exercise capacity[98].

Impaired oxygen consumption with maximal exertion (peak VO2) correlates with worsened outcomes and has been used as a criterion for evaluation of cardiac transplantation, with current transplant candidates generally having a peak VO2 less than 12[99].

Excessive activation of the sympathetic nervous system is an important component of the development of HF. Elevated systemic catecholamine levels have been associated with worsening prognosis in HF. Markers of cardiac chamber dilation, atrial natriuretic peptide, and BNP have shown high prognostic value in HF, with the longer half-life of BNP (23 minutes vs 3-5 minutes for atrial natriuretic peptide) and dominant expression of BNP in abnormal ventricular cells as potential explanations for its wider utility[74]. An analysis from Val-HeFT showed a HR of 2.06 for morbidity and mortality with an abnormal BNP, whereas a pooled review showed a 35% increase in relative risk of death for each 100-pg/mL increment in baseline BNP. BNP has been shown to predict other important end points, including hospitalization risk in patients presenting to the emergency department and likelihood of rehospitalization based on predischarge value[100].

Common **markers of inflammation** are associated with the risk of development of HF in the general population, and levels of interleukin-6, C-reactive protein, and tumor necrosis factor α have been shown to correlate with worsened outcomes once heart failure has developed. Several proxy correlates of inflammation and stress, such as a decreased lymphocyte count or elevated leukocyte count, elevated uric acid, low cholesterol, hypoalbuminemia, and anemia, are associated
with increased risk[79].

Comorbidities are known to influence survival unfavourably in HF. In diabetes mellitus, diabetic patients on insulin, there was a doubling in risk (HR 2.03) compared with non-diabetics[84]. Anemia is present in approximately 25% of the HF, and each 1-g/dL reduction in hemoglobin has been associated with a 20% multivariate adjusted increase in risk of death[101]. In chronic renal failure, mortality worsens across the range of renal function, with 15% increased risk for every 0.5 mg/dl increase in creatinine and 7% increased risk for every 10 mL/min decrease in eGFR[51]. Patients with both HF and chronic renal failure have an extremely poor prognosis; this pathophysiological condition has been termed severe cardiorenal syndrome, in which combined cardiac and renal failure amplify progression of the individual organ pathology. In practice, not all these prognostic parameters will be known or even necessary[8]. The combination of a few independent prognostic variables may be sufficient to guide patient management. This does not imply that correction, if possible, of these prognostic determinants improves survival[79].

3.7 Management of heart failure

Major difficulties in studying HF result from its heterogeneous nature: right- vs left-sided, high vs low output, acute vs. chronic, systolic vs diastolic HF. Diastolic HF is often an exclusion diagnosis[13] and little is known about optimal treatment strategies for this population. In contrast, comprehensive guidelines exist for the treatment of systolic HF, based on robust evidence[5].

The goals of treatment in patients with established HF are to relieve symptoms and signs, prevent hospital admission, and improve survival. Although the focus of clinical trials was previously mortality, it is now recognized that preventing HF hospitalization is important for patients and healthcare systems[5, 102]. Reductions in mortality and hospital admission rates both reflect the ability of effective treatments to slow or prevent progressive worsening of HF. This is often accompanied by reverse LV remodeling and a reduction in circulating natriuretic peptide concentrations[5, 103, 104].

From several non-randomized and randomized clinical studies it seems well documented that treatment in specialized HF clinics reduces readmission frequencies and improve quality of care for HF patients[105,106]. Also, they show a reduced risk of hospital readmission and death, both in the short and long term, among patients discharged from a hospitalization index to a HF clinic, as compared with those who were discharged to the outpatient care of their usual assistant physician[106]. Care providers should be encouraged to initiate HF management programs including elements of nurse intervention and to design the clinics to meet the local needs in the best, and most feasible, way it can [105,106].

3.1.7 Pharmacologic treatment of heart failure – the role of diuretic therapy

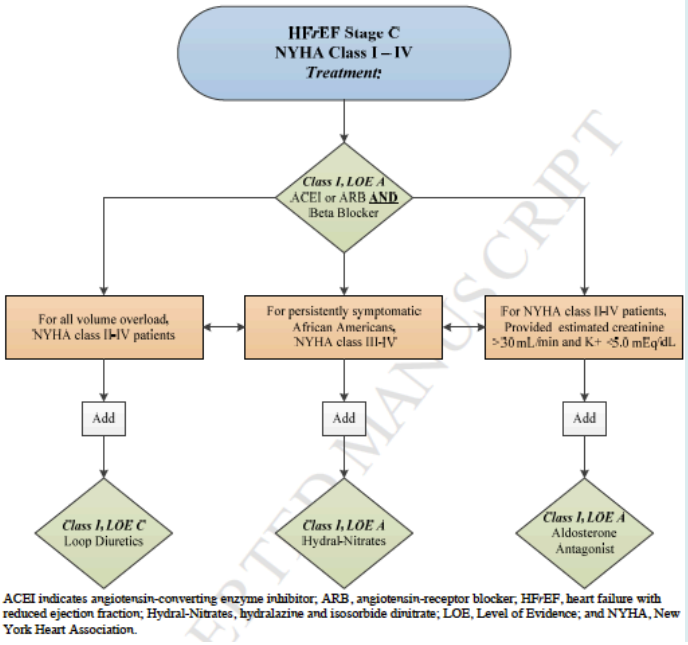
The relief of symptoms, improvement in quality of life, and increase in functional capacity are also very important to patients, but they have not been the primary outcome in most trials[5, 105]. This is in part because they are difficult to measure and partly because some treatments previously shown to improve these outcomes also decreased survival. However, effective pharmacological therapies and cardiac CRT seem to improve these outcomes, as well as mortality and hospitalization[5].

Three neurohormonal antagonists—an ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB), a beta-blocker, and a mineralocorticoid receptor antagonist —are fundamentally important in modifying the course of systolic HF and should at least be considered in every patient. They are commonly used in conjunction with a diuretic given to relieve the symptoms and signs of congestion[5, 7] (Fig. 8).

HF-PEF is increasingly recognized as a major public health problem worldwide[16]. However, trials using comparable and efficacious agents for HF-REF have generally been disappointing in showing reduction of morbidity and mortality when applied to patients with HF-PEF[7]. Thus, most of the recommended therapies for HF-PEF are directed at symptoms, especially comorbidities, and risk factors that may worsen cardiovascular disease[5, 7]. Adequate treatment of hypertension (ACEi and/or ARB are often considered as first-line agents) and myocardial ischemia (coronary artery disease is common in patients with HF-PEF) is considered to be important, as is control of the ventricular rate in patients with atrial fibrillation[5, 7, 16].

a) Diuretics

Diuretics, though not specific long-term prognostic modifiers, are cornerstone in the symptomatic management of HF[5, 7, 19, 67] as most of the symptoms of congestive HF result from excess extracellular fluid volume (Fig. 8, 9).



Pharmacological treatments indicated in potentially all patients with symptomatic (NYHA functional class II–IV) systolic heart failure

Recommendations	Class[a]	Level[b]	Ref[c]
An ACE inhibitor is recommended, in addition to a beta-blocker, for all patients with an EF ≤40% to reduce the risk of HF hospitalization and the risk of premature death.	I	A	87–91
A beta-blocker is recommended, in addition to an ACE inhibitor (or ARB if ACE inhibitor not tolerated), for all patients with an EF ≤40% to reduce the risk of HF hospitalization and the risk of premature death.	I	A	92–98
An MRA is recommended for all patients with persisting symptoms (NYHA class II–IV) and an EF ≤35%, despite treatment with an ACE inhibitor (or an ARB if an ACE inhibitor is not tolerated) and a beta-blocker, to reduce the risk of HF hospitalization and the risk of premature death.	I	A	99, 100

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; EF = ejection fraction; HF = heart failure; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

Fig. 8 – Pharmacologic treatment recommendations in heart failure with reduced ejection fraction. (*A*dapted from: Yancy CW, et al. J Am Coll Cardiol, 2013 OCT 15:62(16):e147-239[7]; McMurray JJ, et al. Eur Heart J, 2012. 33(14): p. 1787-847[5])

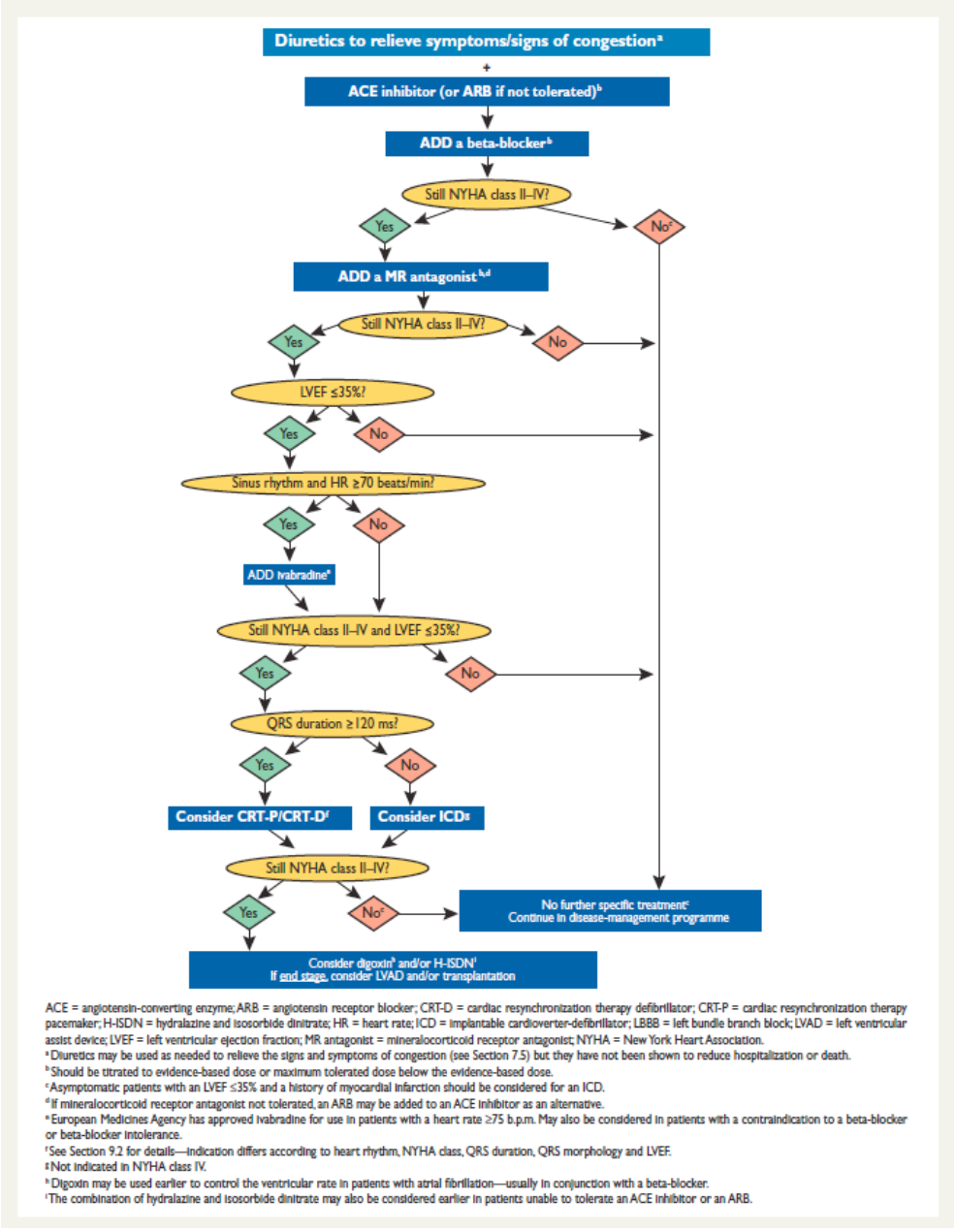
The effects of diuretics on mortality and morbidity have not been studied in patients with HF, unlike ACE inhibitors, beta-blockers, and mineralocorticoid antagonists because of recognized symptomatic benefits, a formal evaluation in randomized trials became impossible as they relieve dyspnea and edema[5, 7, 106-108] and are recommended for this reason in patients with signs and symptoms of congestion, irrespective of EF[5, 7]. However, the interpretation of symptoms and signs by patients and physicians is highly variable. Among patients with confirmed symptomatic HF, symptoms are likely to reflect true congestion but, given the high prevalence of COPD and obesity, a non-negligible proportion of dyspnea can easily lead to excessive use of diuretics[5, 7, 19, 67].

Loop diuretics produce a more intense and shorter diuresis than thiazides, which cause a more gentle and prolonged diuresis. Thiazides may be less effective in patients with reduced kidney function. Loop diuretics are usually preferred to thiazides in HF-REF although they act synergistically and the combination may be used (usually on a temporary basis) to treat resistant edema[5, 7, 19, 67].

The aim of using diuretics is to achieve and maintain euvolemia (the patient's 'dry weight') with the lowest achievable dose. This means that the dose must be adjusted, particularly after restoration of dry body weight, to avoid the risk of dehydration leading to hypotension and renal dysfunction. This may reduce cardiac output in patients with HF-PEF and often needlessly prevents the use of (or achievement of the target dose of) other disease-modifying therapies such as ACE inhibitors (or ARBs) and mineralocorticoid receptor antagonists in patients with HF-REF. Many patients can be trained to self-adjust their diuretic dose, based on monitoring of symptoms/signs of congestion and daily weight measurements[5, 7, 19, 67].

a.1) Rationale for the treatment with diuretics in HF

There is considerable evidence to show that diuretics **improve quality of life** by providing relief from symptoms of HF[14, 109, 110] (Fig. 9). In the congested patient, diuretics lower filling pressures, reduce lung water content, and are the most efficacious drugs available to relieve symptoms rapidly. Symptomatically worse patients are likely to gain the greatest improvement in quality of life from diuretic treatment[109, 110]. Diuretics are more effective in improving symptoms when compared with ACE-inhibitors. The bioavailability of the diuretic used may also influence its effects on quality of life[109, 110]. Both bumetanide and torsemide, when taken orally, have a more consistent level of absorption when compared with furosemide. Torsemide is associated with less fatigue in CHF patients when compared with furosemide[14, 109, 110].



ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; H-ISDN = hydralazine and isosorbide dinitrate; HR = heart rate; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MR antagonist = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.
[a] Diuretics may be used as needed to relieve the signs and symptoms of congestion (see Section 7.5) but they have not been shown to reduce hospitalization or death.
[b] Should be titrated to evidence-based dose or maximum tolerated dose below the evidence-based dose.
[c] Asymptomatic patients with an LVEF ≤35% and a history of myocardial infarction should be considered for an ICD.
[d] If mineralocorticoid receptor antagonist not tolerated, an ARB may be added to an ACE inhibitor as an alternative.
[e] European Medicines Agency has approved ivabradine for use in patients with a heart rate ≥75 b.p.m. May also be considered in patients with a contraindication to a beta-blocker or beta-blocker intolerance.
[f] See Section 9.2 for details—indication differs according to heart rhythm, NYHA class, QRS duration, QRS morphology and LVEF.
[g] Not indicated in NYHA class IV.
[h] Digoxin may be used earlier to control the ventricular rate in patients with atrial fibrillation—usually in conjunction with a beta-blocker.
[i] The combination of hydralazine and isosorbide dinitrate may also be considered earlier in patients unable to tolerate an ACE inhibitor or an ARB.

Fig. 9 – Pharmacologic treatment algorithm for Heart Failure. (*Source: McMurray JJ, et al. Eur Heart J, 2012. 33(14): p. 1787-847[5]*).

Withdrawal of diuretics in stable compensated patients with CHF has been shown in several studies to result in symptoms of congestion[109]. When diuretic treatment was discontinued in 41 patients with a history of HF, it was found that diuretics had to be restarted in 71% of patients after a median of 15 days, owing to worsening HF symptoms[109]. A history of hypertension, baseline furosemide dose of 40 mg/day, and a LVEF (27%) were independent predictors of diuretic re-initiation[109].

With the exception of aldosterone antagonists, diuretics **have not been studied in large-scale HF mortality endpoint** trials and this remains the major cause for uncertainty regarding their use in day-to-day clinical practice. In the meta-analysis of randomized controlled trials assessing the role of diuretics in HF, only three small placebo-controlled studies (202 participants) had reported on the effect of diuretic therapy on mortality[93, 109, 111, 112]. The most recent meta-analysis[93] included 14 trials (525 participants), 7 placebo-controlled and 7 compared diuretics against other agents such as ACE inhibitors or digoxin. **Mortality** was lower for participants treated with diuretics than with placebo, odds ratio (OR) for death 0.24, 95% confidence interval (CI) 0.07 to 0.83; p = 0.02. In patients with CHF, treatment with diuretic therapy produced a relative reduction in mortality of about 70% (absolute reduction of 8%), with wide confidence intervals, compared to placebo. If this estimate is correct, about 80 deaths could be avoided for every 1000 patients treated. However, this evidence was based on only 15 deaths out of 221 participants (6.8%). **Admission for worsening HF was reduced** in those taking diuretics in two trials (169 participants), OR 0.07 (95% CI 0.01 to 0.52; p= 0.01). Diuretic therapy compared to placebo produced a similar reduction (8% absolute risk reduction) in the risk of worsening HF. In four trials (91 participants), **diuretics improved exercise capacity** in participants with CHF with difference in means walking meters distance (WMD) - 0.72, 95% CI 0.40 to 1.04; p<0.0001. Diuretics significantly increased exercise capacity by about 28% to 33%. Importantly, the mean age of the patients in the studies was 59 years, considerably lower than the mean age of HF patients in the population, which is about 74 years. The proportion of women was higher in these trials than in other trials in HF[93].

As yet diuretic drugs have not been shown to retard the clinical deterioration or improve prognosis in patients with CHF, because adequately sized trials to address these questions have not been carried out. The common clinical impression is that diuretics do reduce mortality and retard progression of HF[93].

This evidence is not sufficient by current standards to justify widespread use of diuretics to influence clinical outcomes in CHF since diuretics were introduced without the backing of large RCTs that would now be considered essential[93]. In fact, some studies suggest that in patients with advanced systolic HF, the use of higher doses of loop diuretics is associated with significantly increased all-cause mortality: higher diuretic doses (≥160 mg) were associated with a significant increase in 1- and 2-year all cause mortality compared with the lowest loop diuretic doses (0 to 40 mg)[113].

Although it may appear obvious that patients with HF requiring higher loop diuretic doses to prevent fluid retention and control symptoms might be sicker than patients receiving lower doses, the powerful and independent association with mortality warrants further consideration[113]. The activation of RAAS, the decrease in the glomerular filtration rate, the cardiorenal syndrome and the risk of sudden death by arrhythmias are some of the reasons pointed[113].

The implications for clinical practice are that a common, simple treatment is being used without clear evidence of major benefit on important clinical outcomes. It is important to acknowledge this fact and also to stimulate interest in further clinical trials that may help us to understand both how to optimize diuretic use and to understand more about their benefits[93].

a.2) Hemodynamic and neuroendocrine effects of diuretics

The acute hemodynamic actions of diuretics reflect immediate direct or indirect vascular actions and those of diuresis and volume redistribution. Hemodynamic responses to diuretics are variable and dependent on which diuretic is used, whether the patient has acute pulmonary edema or chronic compensated HF, the degree of baseline neurohormonal activation, and presence of concomitant medications, such as ACE inhibitors[109, 114].

In **congested** patients (e.g. acute pulmonary edema), intravenous administration of furosemide results in a rapid fall in right heart filling pressures and in an improvement in symptoms before any diuresis ensues[109, 114, 115]. However, in **non-congested patients**, there is a predominant detrimental arteriolar vasoconstriction. With progressive diuresis, filling pressures continue to decline over time, whereas vascular resistance and stroke volume index tend to return to baseline. These initial adverse hemodynamic changes temporally correlate with increases in plasma norepinephrine and renin activity[116].

After **diuretic withdrawal**, patients on ACE-inhibitor and a beta-blocker had clinically stability over the preceding 3 months. Diuretic withdrawal caused significant deterioration of hemodynamic parameters and worsening of chronic HF. The fact that the patients deteriorated is evidence supporting the notion that diuretics are needed for chronic therapy. It is possible, however, that if the patients had strictly restricted their sodium intake, they could have avoided the observed deterioration[117].

The **activation of RAAS** associated with diuretic use may be a reno-protective mechanism to preserve renal function in the setting of volume depletion and reduced renal blood flow[118]. Furosemide increases circulating levels of products of the RAAS by directly causing renin release from the macula densa and as a response to intravascular volume depletion[119]. Activation of the RAAS is associated with the progression of HF[120]. Subjects with symptomatic HF have elevated aldosterone levels, which is prognostically significant in this patient population[116]. The inhibition of aldosterone with spironolactone has been shown to reduce morbidity and mortality in patients with NYHA class II-IV HF[5, 7, 121] possibly by favorable effects on heart rate variability and cardiac adrenergic tone, a reduction in cardiac fibrosis, and significant improvement in prognosis.

In **non-congested** patients, intravenous bolus of furosemide did not change plasma renin and aldosterone concentrations. Continued oral furosemide results in a significant increases in plasma renin and aldosterone levels, suggesting **late activation** of the neurohumoral axis; alternatively or in addition, it may represent a reaction to overdiuresis. Prolonged activation of the RAAS may lead to progressive salt/water retention and peripheral vasoconstriction. The noxious effects of diuretics on the neuroendocrine system, may hence persist despite ACE-inhibitor therapy and may affect prognosis adversely[109].

Volume depletion with subsequent hypotension, **decreased cardiac output**, and **worsening renal function** are common adverse effects of aggressive diuretic therapy. **Electrolyte depletion**, especially

hypokalemia and **hypomagnesemia**, can lead to **arrhythmias**. **Hypocalcemia** can lead to **secondary hypoparathyroidism**. **Hyperuricemia** associated with aggressive diuresis can lead to acute gouty flares. In addition, diuretic therapy, especially with loop diuretics, causes **adverse neurohormonal activation**. The potassium-sparing diuretic may lead to **hyperkalemia** and worsening renal failure[5, 7, 106, 109].

Diuretics should be prescribed to all patients who have evidence of, and to most patients with a prior history of, fluid retention. Diuretics should generally be combined with an ACE inhibitor, BB and MRA. Few patients with HF will be able to maintain target weight without the use of diuretics[109].

a.3) Use of diuretics

The most commonly used loop diuretic for the treatment of HF is furosemide, but some patients respond more favorably to other agents in this category (e.g., bumetanide, torsemide) because of their increased oral bioavailability[7] (Table 2).

Table 2 – Practical guidance on the use of diuretics in patients with heart failure. (Source: McMurray JJ, et al. Eur Heart J, 2012. 33(14): p. 1787-847. [57]).

Web Table 15: Practical guidance on the use of diuretics in patients with heart failure (with a reduced or preserved ejection fraction)
WHY? To relieve breathlessness and oedema in patients with symptoms and signs of congestion
IN WHOM AND WHEN? Indications Potentially all patients with symptoms and signs of congestion, irrespective of EF Should always be used in combination with an ACE inhibitor (or ARB), beta-blocker, and an MRA in patients with a reduced EF Use minimum dose necessary to maintain euvolaemia–the patient's 'dry weight' (i.e. to keep the patient free of symptoms and signs of congestion) Dose may need to be increased or decreased according to the patient's volume status; patients can be educated and trained to alter their own diuretic dose, according to need (based on symptoms, signs and weight changes–see Section 14) Contraindications Not indicated if the patient has never had symptoms or signs of congestion Known allergic reaction/other adverse reaction (drug-specific) Cautions/seek specialist advice Significant hypokalaemia (K^+ ≤3.5 mmol/L)–may be made worse by diuretic Significant renal dysfunction (creatinine >221 µmol/L [>2.5 mg/dL] or eGFR <30 mL/min/1.73 m^2)–may be made worse by diuretic or patient may not respond to diuretic (especially thiazide diuretic) Symptomatic or severe asymptomatic hypotension (systolic blood pressure <90 mmHg)–may be made worse by diuretic-induced hypovolaemia Drug interactions to look out for Combination with ACE inhibitor ARB or renin inhibitors[b]–risk of hypotension (usually not a problem) Combination with other diuretics (e.g. loop plus thiazide)–risk of hypovolaemia, hypotension, hypokalaemia, and renal impairment[a] NSAIDs[c]–may attenuate effect of diuretic
WHERE? In the community for most patients
WHICH DIURETIC AND WHAT DOSE? - *see Table 16*
HOW TO USE? Check renal function and electrolytes Start with a low dose *(see Table 16)* Adjust dose according to symptoms and signs of congestion, blood pressure, and renal function Re-check blood chemistry 1–2 weeks after initiation and after any increase in dose (urea/BUN, creatinine, K^+) When to stop up-titration, reduce dose, stop treatment–see PROBLEM SOLVING A specialist HF nurse may assist with education of the patient, follow-up (in person or by telephone), biochemical monitoring, and dose adjustment (including patient training in dose adjustment)
ADVICE TO PATIENT Explain expected benefits Symptoms improve quickly–usually within days of starting treatment Advise patients to report principal adverse effects (e.g. thirst) (avoid excessive consumption of hypotonic fluids, which can cause hyponatraemia) and dizziness/symptomatic hypotension–see PROBLEM SOLVING Advise patients to avoid NSAIDs[b] not prescribed by a physician (i.e. purchased over-the-counter)–may cause diuretic resistance and renal impairment Patient may be trained to adjust dose based on symptoms, signs, and changes in weight (if regular weighing) Dose may need to be decreased if fluid loss (e.g. due to diarrhoea/vomiting, excessive sweating)
PROBLEM SOLVING Asymptomatic low blood pressure Dose may be reduced if no symptoms or signs of congestion Symptomatic hypotension Causing dizziness/light headedness–reduce dose if no symptoms or signs of congestion Reconsider need for nitrates, CCBs,[d] and other vasodilators If these measures do not solve problem, seek specialist advice Hypokalaemia/hypomagnaesaemia Increase ACE inhibitor/ARB dose, add MRA, potassium supplements; magnesium supplements Hyponatraemia *Volume depleted:* stop thiazide or switch to loop diuretic, if possible; reduce dose/stop loop diuretics if possible; *volume overloaded:* fluid restriction; increase dose of loop diuretic; consider AVP antagonist (e.g. tolvaptan if available); i.v. inotropic support; consider ultrafiltration Hyperuricaemia/gout Consider allopurinol prophylaxis; for symptomatic gout use colchicine for pain relief; avoid NSAIDs Hypovolaemia/dehydration Assess volume status; consider diuretic dosage reduction Insufficient diuretic response/diuretic resistance Check compliance and fluid intake; increase dose of diuretic; consider switching from furosemide to bumetanide or torasemide; add MRA/increase dose of MRA; combine loop diuretic and thiazide/metolazone[e]; administer loop diuretic twice (or more times) daily or on empty stomach/consider short-term i.v. infusion of loop diuretic; consider ultrafiltration Renal impairment (rising creatinine/BUN–urea) Check for hypovolaemia/dehydration; exclude use of other nephrotoxic agents, e.g. NSAIDs, trimethoprim; withhold MRA; if using concomitant loop and thiazide diuretic stop thiazide diuretic; consider reducing dose of ACE inhibitor/ARB; consider haemofiltration/dialysis

In outpatients with HF, diuretic therapy is commonly initiated with low doses, and the dose is increased until urine output increases and weight decreases, generally by 0.5 to 1.0 kg daily. Further increases in the dose or frequency (i.e., twice-daily dosing) of diuretic administration may be required to maintain an active diuresis and sustain weight loss. The ultimate goal of diuretic treatment is to eliminate clinical evidence of fluid retention.

Diuretics are generally combined with moderate dietary sodium restriction. Once fluid retention has resolved, treatment with the diuretic should be maintained in some patients to prevent the recurrence of volume overload. Patients are commonly prescribed a fixed dose of diuretic, but the dose of these drugs frequently may need adjustment. Patients may become unresponsive to high doses of diuretic drugs if they consume large amounts of dietary sodium, are taking agents that can block the effects of diuretics (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], including cyclo-oxygenase-2 inhibitors)[122-124] or have a significant impairment of renal function or perfusion[7].

a.4) Diurectic resistance

A common problem with loop diuretics is **diuretic resistance**. This occurs through various mechanisms, the most important of which involves specific drug pharmacokinetics and physiologic adaptations within the nephron. There are two different forms of adaptive diuretic resistance. First is the **braking phenomenon**. Immediately following the first dose of a loop diuretic, there is a diminished response to subsequent doses. The mechanisms leading to braking have not been fully determined. Loop diuretics directly stimulate renin secretion from the macula densa. In addition, diuretic-induced volume loss increases the filtration fraction and stimulates efferent sympathetic nerves, which leads to enhanced NaCl reabsorption through a variety of mechanisms[5, 7, 106-108]. The second type of adaptive resistance involves longer-term use of loop diuretics. In long-term diuretic therapy, there is increased delivery of solute distal to the loop of Henle. This results in **hyperplasia and hypertrophy** of the thiazide-sensitive cells in the distal convoluted tubule and subsequent increase in distal sodium reabsorption[5, 7, 106-108].

A good measure of diuretic resistance is a low fractional excretion of sodium in patients on chronic loop diuretics[125]. Post-diuretic sodium rebound is particularly problematic in patients who do not adequately restrict dietary sodium. These patients may have adequate natriuresis but inadequate diuresis[108]. A way to overcome this **rebound phenomenon** in patients with ADHF, apart from **escalating doses**, is to give the loop diuretic as a **continuous infusion instead of a bolus**. A meta-analysis of seven randomized controlled trials comparing efficacy of continuous versus bolus intravenous infusion of furosemide found greater urine output (measured as milliliters per 24 hours) in patients given furosemide by continuous infusion[106, 126]. However, the DOSE study[127] failed to show significant differences in patients' global assessment of symptoms or in the change in renal function when diuretic therapy was administered by bolus as compared with continuous infusion or at a high dose as compared with a low dose (Fig. 10). Furthermore, meta-analysis of the existing limited studies did not confirm any significant differences in the safety and efficacy with continuous administration of loop diuretic, compared with bolus injection in patients with acute decompensated HF[11].

The **rebound effect** from chronic loop diuretics results in up-regulation of thiazide-sensitive receptors in the nephron. These cells also exhibit increased transcellular NaCl transport capacity. Under

normal circumstances, 25% of filtered sodium is reabsorbed in the loop and 5% to 10% is absorbed in the distal tubule. The added thiazide diuretic results in blockade of thiazide-sensitive electroneutral Na^+Cl^- receptors in the distal collecting duct, allowing more of the sodium presented to the distal tubule to be excreted. In addition, the longer half-life of thiazides, as compared with loop diuretics, may also help prevent diuretic rebound[128].

A significant increase in diuresis with the addition of thiazides is well documented in many studies of subjects with normal and significantly impaired renal function[129]. When thiazides and loop diuretics are combined, there is an increased risk of hypokalemia and hyponatremia[125]. Given the literature suggesting increased mortality with higher doses of loop diuretics[110], the addition of a thiazide to a low or medium dose of a loop diuretic may be preferable to maintenance of high doses of a loop diuretic alone.

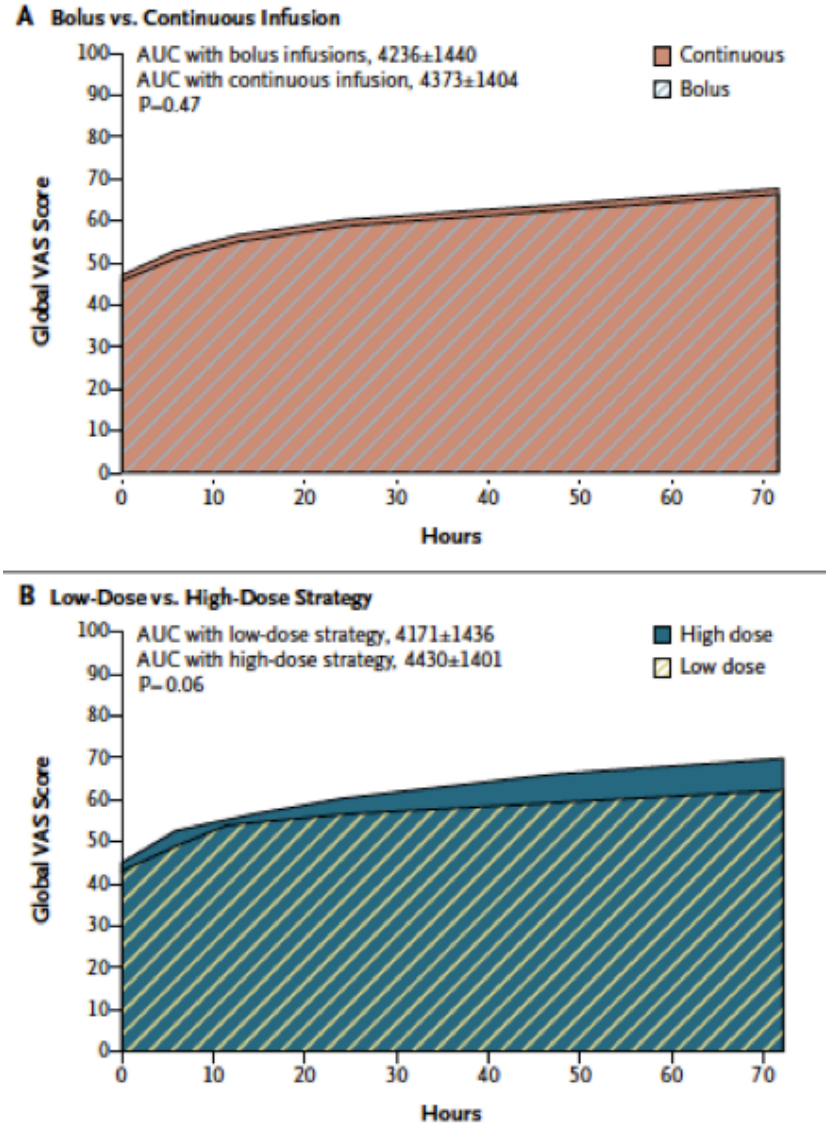


Fig. 10 – DOSE study: no differences between bolus vs. continuous infusion or between low and high doses of furosemide. (Source: Felker GM, et al. N Engl J Med, 2011. 364: p. 797-805.[123]).

3.7.2 Precipitating factors for heart failure decompensation related with pharmacologic treatment

Relapse of CHF in patients with previously stable compensated HF may be caused by deteriorating ventricular function, but several precipitating factors have been suggested[132]. The common factors that precipitate acute decompensated HF are[7]:

1. Non-adherence with medication regimen, sodium and/or fluid restriction;
2. Acute myocardial ischemia;
3. Uncorrected high blood pressure;
4. AF and other arrhythmias;
5. Recent addition of negative inotropic drugs (e.g., verapamil, nifedipine, diltiazem, BB);
6. Pulmonary embolus;
7. Initiation of drugs that increase salt retention (e.g., steroids, thiazolidinediones, NSAIDs);
8. Excessive alcohol or illicit drug use;
9. Endocrine abnormalities (e.g., diabetes mellitus, hyperthyroidism, hypothyroidism);
10. Concurrent infections (e.g., pneumonia, viral illnesses);
11. Additional acute cardiovascular disorders (e.g., valve disease endocarditis, myopericarditis, aortic dissection).

a.1) Low adherence

Adherence describes a health related behavior of a person that adheres to the recommendations of a doctor, other health care provider, or investigator in a research project. The word “adherence” aims to avoid the authoritarian associations of “compliance”, formerly used to describe this behavior[130-133], because “compliance” suggests that the patient is passively following the doctor’s orders and that the treatment plan is not based on a therapeutic alliance or contract established between the patient and the physician[134]. Both terms are imperfect and uninformative descriptions of medication-taking behavior. Unfortunately, applying these terms to patients who do not consume every medication at the desired time can stigmatize these patients in their future relationships with health care providers[133-135]. It is clear that the full benefit of the many effective medications that are available will be achieved only if patients follow prescribed treatment regimens reasonably closely.

Poor adherence limits the effectiveness of proven therapies, resulting in lost opportunities to reduce mortality and readmission rates (Fig. 11). Indeed, poor adherence accounts for up to two thirds of preventable admissions in HF and coronary artery disease[136], and is associated with mortality in patients with other chronic illnesses, including breast cancer, asthma and rheumatoid arthritis [130, 136-139].

Rates of adherence for individual patients are usually reported as the percentage of the prescribed doses of the medication actually taken by the patient over a specified period. Some investigators have further refined the definition of adherence to include data on dose taking (taking the prescribed number of pills each day) and the timing of doses (taking pills within a prescribed period)[134]. Adherence rates are typically higher among patients with acute conditions, as compared with those with

chronic conditions; persistence among patients with chronic conditions is disappointingly low, dropping most dramatically after the first six months of therapy[137-139].

The **average rates of adherence** in clinical trials can be remarkably high, owing to the attention study patients receive and to selection of the patients, yet even clinical trials report average adherence rates of only 43 to 78 percent among patients receiving treatment for chronic conditions[134, 139, 140].

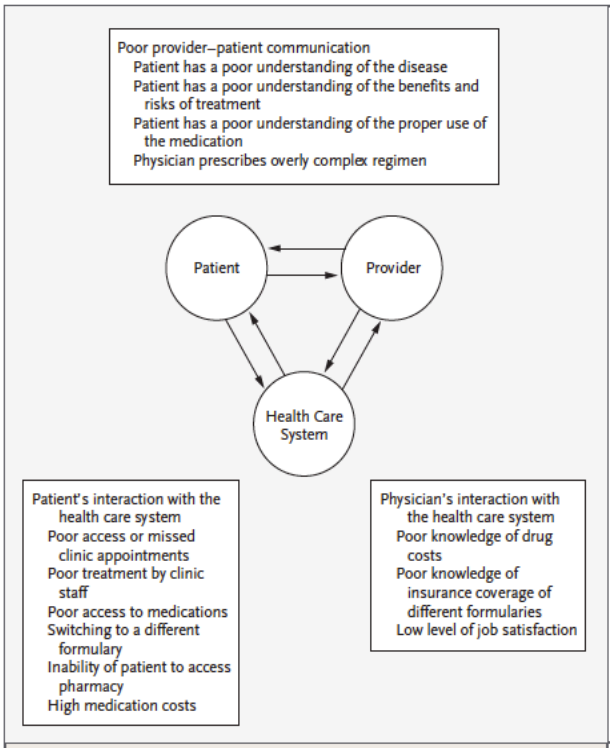


Fig. 11 – Factors that determine adherence. (*Source: Osterberg L, Blaschke T. N Engl J Med, 2005. 353: p. 487-97.*[130]).

There is **no consensual standard for what constitutes adequate adherence**. Some trials consider rates of greater than 80 percent to be acceptable, whereas others consider rates of greater than 95 percent to be mandatory for adequate adherence, particularly among patients with serious conditions. Although data on adherence are often reported as dichotomous variables (adherence vs. nonadherence), adherence can vary along a continuum from 0 to more than 100 percent, since patients sometimes take more than the prescribed amount of medication[134].

The **ability of physicians to recognize nonadherence is poo**r, and interventions to improve adherence have had mixed results. Furthermore, successful interventions generally are substantially complex and costly[134, 141, 142]. Poor adherence to medication regimens accounts for substantial worsening of disease, death, and increased health care costs in the US[134, 143].

Of all medication-related hospital admissions in the United States, 33 to 69 percent are due to poor medication adherence, with a resultant cost of approximately $100 billion a year[134]. Participants in clinical trials who do not follow medication regimens or placebo regimens have a poorer prognosis than subjects in the respective groups who do[134, 144]. Adherence to medication and placebo

regimens, therefore, both predict better outcomes, and collecting adherence data from subjects is now considered an essential part of clinical trials[134].

Research on adherence has typically focused on the barriers **patients** face in taking their medications. Common barriers to adherence are under the patient's control, so that attention to them is a necessary and important step in improving adherence. In responses to a questionnaire, typical reasons cited by patients for not taking their medications included forgetfulness (30%), other priorities (16%), decision to omit doses (11%), lack of information (9%), and emotional factors (7%); 27% of the respondents did not provide a reason for poor adherence to a regimen[134].

Physicians can contribute to patients' poor adherence by prescribing complex regimens, failing to explain the benefits and side effects of a medication adequately, not giving consideration to the patient's lifestyle or the cost of the medications, and having poor therapeutic relationships with their patients[134, 145-147].

More broadly, **health care systems** create barriers to adherence by limiting access to health care, using a restricted formulary, switching to a different formulary, and having prohibitively high costs for drugs, co-payments, or both[134, 148, 149]. An expanded view that takes into account factors under the patient's control as well as interactions between the patient and the health care provider and between the patient and the health care system are expected to have the greatest effect on improving medication adherence[134].

Important self-care behaviors capable of underlying an acute HF episode are non-adherence to salt and caloric restriction and alcohol abstinence, but also non-adherence with medications and exposure to drugs that are (relatively) contraindicated.

Non-adherence to medication and diet has repeatedly been identified as a frequent precipitating factor for admission to hospital for decompensated HF [132, 150]. This may represent an important barrier to effective treatment of CHF [132]. In fact, non-adherence to diuretic therapy may result more rapidly in increasing symptoms than that to other drug classes, whose effect is more long-term.

Moreover, when therapies are initiated in the hospital, outpatient adherence is improved as well as long-term outcomes[151-153]. Predischarge identification of patients with risk factors for nonadherence may provide opportunities to target preventable admissions through disease management plans[151].

a.2) Measurement of low adherence in HF

Assessing the degree of adherence is necessary in order to evaluate the effectiveness of prescribed treatments and to determine if the treatment is responsible for the changes in health outcomes. Variations in non-adherence prevalence rates must be cautiously interpreted as the measurement method and operational definitions vary. Adherence rates have been reported as the percentage of patients who are adherent or non-adherent, the number of patients achieving 70 –90% adherence, the percentage of full compliant days, or a particular score on a compliance/adherence scale. Regardless of

the definition used, in HF, many investigators have shown that selective adherence is common and non-adherence with some aspect of the medical regimen ranges from 5.52-64%[150, 151, 153-157].

In the GWTG-HF[151], rates of adherence with the each of the Joint Commission core measures[151] for patients with non-adherence ranged from 83% to 94%. This is higher than what was reported in the OPTIMIZE-HF registry[136, 154] from 2003 to 2004 where the adherence rates for each of the core measures ranged from 54% to 87% and the ADHERE registry[153] from 2002 to 2003 where the adherence rates ranged from 24% to 86%. Improved adherence in the GWTG-HF database may reflect more contemporary trends as well as an emerging emphasis on documentation of these measures. It is also possible that a quality improvement program like GWTG-HF may enhance evidence-based care by providing clinicians with real-time guideline reminders[151].

The best method of measuring medication adherence is by the direct method of observation. However, because this approach is rarely feasible, indirect methods such as pill count, self-report, collateral reports, clinical outcomes, prescription refills or electronic event monitoring (EEM) are usually used. Although an indirect method, EEM has high sensitivity and allows the visualization of medication taking dynamics[157]. In the study of *Wu et al*., receiver operating characteristic curves showed that adherence rates above 88% produced the optimal combination of sensitivity and specificity with respect to predicting better event-free survival [2.2 by dose count (p= 0.021) and 3.2 by dose day (p=0.002)][158].

In HF, studies of patient adherence have focused on medication use and behavioral issues such as dietary practices, exercise, daily weight measurements and smoking cessation. Adherence to the medication and dietary regimen are essential if persons with HF are to remain stable and avoid rehospitalization. Most studies of adherence have used self-report measures, a method known to underestimate non-adherence[157] and have retrospectively assessed adherence using indirect methods, typically self-report estimates, in patients readmitted to the hospital. Very few investigators have described adherence in the general HF population, but those that have differ widely. For example, results of a general HF population study found only 10% were fully adherent while 71–74% of patients in a specialized HF clinic were found to totally comply by taking all prescribed medications. In ambulatory HF patients, indirect measurements of medication adherence also varied widely, as described below[157].

Although it is challenging to compare findings from studies using different methods to evaluate medication compliance, the summary message is that adherence is an issue, and that patients find it easier to comply when medications are administered less frequently[157].

a.3) Characteristics of low adherent HF patients

In some studies the characteristics of the non-adherent HF patients were studied. In the study of *Michalsen et al*.[155] there were no significant sex or subgroup differences relating to adherence to

medical and dietary treatment. In two patients heavy alcohol intake was noted; these were both non-compliant with respect to drug treatment. The non-compliant patient group tended to be younger than the compliant group (72.2 (10.5%) *vs* 77.4 (9.7%) years) and to have a greater number of prescribed drugs (4.0 (1.5%) *vs* 3.7 (1.4%)). In the Amberdaker *et al*. study patients with non-adherence were more likely to be young, male, minority, and uninsured. In addition, non-adherent patients were more likely to have non-ischemic cardiomyopathy, lower EF, and more frequent prior HF admissions (Table 3).

Table 3 – Patient characteristics associated with low adherence. (*Source: Ambardekar AV, et al. Am Heart J, 2009. 158: p. 644-52.*[147]).

Table II. Multivariate analysis of characteristics associated with nonadherence

	Odds ratio (95% CI)	Multivariate P
Demographics		
Younger age (per each year decrease)	1.022 (1.019-1.026)	<.0001
Male gender (vs female)	1.274 (1.196-1.358)	<.0001
Nonwhite race (vs white)	1.489 (1.358-1.632)	<.0001
No health insurance (vs health insurance)	1.421 (1.236-1.633)	<.0001
Medical comorbidities		
Hypertension (vs no hypertension)	1.183 (1.078-1.298)	.0004
Chronic lung disease (vs no chronic lung disease)	1.070 (1.006-1.138)	.0322
Cigarette smoking (vs no smoking)	1.683 (1.562-1.814)	<.0001
Clinical data at presentation		
Higher weight (per each kilogram increase)	1.005 (1.003-1.007)	<.0001
Higher heart rate (per each beat/min increase)	1.005 (1.004-1.007)	<.0001
Higher blood pressure (per each mm Hg increase)	1.007 (1.006-1.008)	<.0001
Lower BUN (per each mg/dL decrease)	1.003 (1.001-1.005)	.0025
Lower left ventricular EF (per each unit decrease in left ventricular EF)	1.008 (1.006-1.010)	<.0001

Odds ratio >1.0 indicates the variable is associated with increased frequency of nonadherence.

Physical examination and laboratory findings at admission among non-adherent patients were notable for greater volume overload as evidenced by higher body weight, increased presence of jugular venous distention, rales, and edema on examination as well as higher BNP levels. Some HF prognostic variables such as blood pressure, BUN, and troponin, appeared to reflect lower disease severity in non-adherent patients, whereas other prognostic measurements such as BNP level, EF, and number of prior HF admissions were less favorable in non-adherent patients. In multivariate analysis, younger age, male gender, minority race, and lack of insurance were independently associated with non-adherence[151].

Within the population of patients with non-adherence, differences between dietary only, medication only, and both dietary and medication non-adherence were examined. Patients with medication non-adherence as a component of their non-adherence versus dietary non-adherence alone were more likely to be young, male, minority, and uninsured. This subpopulation also tended to have increased rates of non-ischemic cardiomyopathy, alcohol abuse, tobacco dependence, as well as lower EF. By contrast, diabetes and higher body mass index were more prevalent among those with dietary non-adherence. Patients with combined medication and dietary non-adherence were almost twice as likely to have had ≥2 HF admissions in the previous 6 months as well as considerably higher BNP levels[151].

a.4) Consequences of the low adherence to medications in HF patients

In the OPTIMIZE-HF[154] study non-adherence to medications, non-adherence to diet, and uncontrolled hypertension each were associated with shorter stay and lower in-hospital mortality. Patients with non-adherence to medications or diet are likely to be admitted with excessive sodium retention. These patients may more readily achieve compensation in response to salt restriction, adjustment of diuretics, and provision of medications during the inpatient hospitalization. It should be noted that patients with non-adherence to medications or diet as an admission precipitant were at high-adjusted risk of 60- to 90-day post-discharge mortality and death/re-hospitalization similar to the overall HF population.

In the GWTG-HF[151] study non-adherent patients were observed to have lower in-hospital mortality and shorter length of stay (Table 4).

Table 4 – Hospital outcomes related with low adherence. (*Source: Ambardekar AV, et al. Am Heart J, 2009. 158: p. 644-52.*[147]).

	Nonadherence	Without nonadherence	Univariate P	Adjusted odds ratio (95% CI)	Multivariate P
Mortality (%)	1.55	3.49	<.0001	0.66 (0.51-0.86)	.0017
Mean length of stay (d)	4.99	5.63	<.0001	0.94 (0.92-0.97)	<.0001
Joint Commission HF core measures (% compliance)					
Discharge instructions	82.6	81.7	.1533	1.06 (0.97-1.16)	.1725
Documentation of left ventricular EF	94.5	93.9	.0936	0.95 (0.85-1.06)	.3554
ACE or ARB for LVSD	89.9	85.0	<.0001	1.14 (0.98-1.31)	.0873
Smoking cessation counseling	91.5	90.0	.0700	1.07 (0.93-1.22)	.3680
Additional GWTG-HF quality measures (% compliance)					
β-Blocker for LVSD	91.6	89.2	.0002	1.12 (0.97-1.29)	.1271
Anticoagulation for atrial fibrillation	66.9	66.6	.8621	0.91 (0.78-1.06)	.2287
Aldosterone antagonist for LVSD	34.5	27.3	<.0001	1.14 (1.03-1.27)	.0151
Evidence-based β-blocker for LVSD	71.8	71.7	.8994	0.95 (0.84-1.06)	.3351
Hydralazine/nitrate for AA patients with LVSD	8.6	7.0	.0599	1.18 (0.91-1.52)	.2043
Discharge BP <140/90 mm Hg	70.9	75.5	<.0001	0.92 (0.85-0.99)	.0252
Lipid-lowering therapy for CAD	55.9	58.2	.0145	0.82 (0.74-0.91)	<.0001
ICD therapy for left ventricular EF <30%	35.7	41.4	<.0001	0.80 (0.69-0.93)	.0034

AA, African American.
*Adjusted for age, gender, race, insurance status, medical comorbidities, clinical data at admission, and hospital sites. Mortality multivariate analysis additionally adjusted for length of stay.

Even after adjusting for multiple variables of prognostic importance, non-adherence appeared to be independently associated with better in-hospital outcomes. Among the different subtypes of non-

adherence, patients with dietary non-adherence alone tended to have the lowest unadjusted in-hospital mortality. Non-adherent patients present with evidence of lower EF and greater volume overload, yet they have an in-hospital course characterized by a shorter length of stay and lower mortality. This suggests greater acuity of presentation but lower short-term disease severity, less difficulty in achieving stability with reinstitution of sodium restriction, fluid restriction, and/or medication, and potentially preventable admission[151].

In examining long-term outcomes, non-adherence has been associated with higher mortality and more frequent hospitalizations[136, 159]. Some poor prognostic markers among non-adherent patients including lower EF, more frequent prior admissions, and higher BNP levels. However, despite these markers, the non-adherent patients in our study had lower in-hospital mortality and shorter length of stay. The reasons why non-adherent patients had better in-hospital outcomes are unclear. Non-adherent patients were younger, had higher BP, and lower BUN levels—all markers of better prognosis in HF. It is plausible that it is easier to stabilize such patients by re-instituting sodium restriction and resuming medical therapy. This suggests that if the cycle of low adherence is broken, clinicians may be able to improve long-term outcomes in this high-risk population.

Low adherent patients were less often considered for ICD therapy, which may reflect a sense from clinicians that if patients were to become adherent with medications that improve cardiac remodeling, functional status and EF would improve obviating the need for ICD therapy[151].

In addition, patients with medication non-adherence were less likely to receive several key evidence-based medical therapies. The reasons for these differences are not clear. One possibility may be that medication non-adherence influences clinicians to be less likely to prescribe guideline-based therapies, thus potentiating a cycle of non-adherence and hospital readmission. This represents another potential area for investigation[151].

b) How to study the impact of treatment related precipitating factors

Pharmacoepidemiology explores drug efficacy or toxicity using large observational study designs. In the past few years, the number of pharmacoepidemiologic studies published in medical journals has increased, as these studies have explored drug-related questions that at times cannot be answered by performing randomized trials[160]. There are four pharmacoepidemiologic study designs that may be used to explore the association between a specific pharmacologic agent and a disease of interest: cohort studies, case-control studies, case-crossover studies, and case-time-control studies[160]. Self-matched case-only studies (such as the case-crossover or self-controlled case-series method) control by design for time-invariant confounders (measured or unmeasured), but they do not control for confounders that vary with time. A bidirectional case-crossover design can be used to adjust for exposure-time trends[161].

b.1) Case-time-control study

It has become clear by now that a major concern in studying adverse drug reactions is how to deal with transient exposures followed by a short steep increase in risk and the dependency of therapy with the severity of a disease or comorbidities, called confounding by indication.

To overcome these causes of bias a study design using only exposure histories of cases was introduced in 1991[160, 162]. Briefly, the case-crossover design is like a retrospective crossover experiment except the subjects not the investigator decide when to crossover between exposed and unexposed periods, and the exposure history is obtained only for subjects who had outcomes[162].

One version of the **case-crossover design** can be imagined as a **matched case-control design** where the controls are the same persons as the cases before the event under study occurred[162] (Fig. 12).

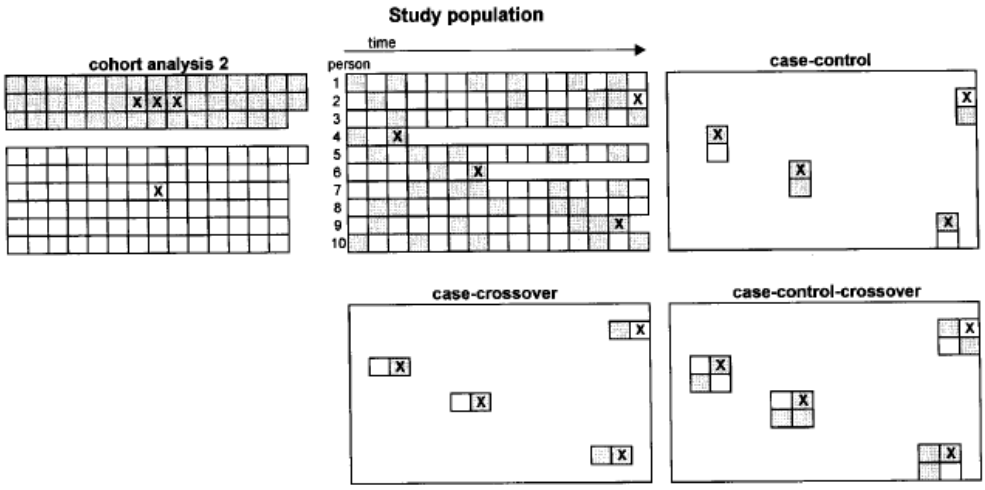


Fig. 12 – Case-crossover design. (Source: *Schneeweiss S, et al. Pharmacoepidemiol Drug Saf, 1997. 6 Suppl. 3: p. S51-S59.*[158]).

In crossover studies only persons with **'discordant'** exposure in the time windows contribute information: cases that are exposed at the time of event but unexposed in the control period or vice versa. Therefore, an efficient application of crossover designs would be an exposure that is varying over time as drug usage often is[162].

Case-crossover designs are appropriate but raise important methodological challenges, namely those related with the definition of the proper windows of exposure or the recall of past exposures – more evident when evaluating poorly educated elderly patients, or when long-term recall is intended. By using each subject experiencing the outcome (case) as his own control (the exposure observed in each case close to the occurrence of the outcome is compared with his own exposure in a previous period) in case-crossover designs, the “cases” and the “controls” are comparable in most of their known and unknown confounders overcoming most of the between-person confounding by constant characteristics. Within-person confounding by transient factors (e.g. fluctuations in disease severity, co-morbidities), however, is still possible. Temporal trends in the exposures, especially if the defined windows of exposure or the period between the windows are too long, may warrant further correction of the risk estimates. These designs allow a finer control of confounding, including confounding by chronic indication, than most other observational studies, and may be seen as an efficient variant of the matched case-control design, each case being matched with himself. The period of observation closest to the occurrence of the event corresponds to the exposure experience of the cases and previous period(s) of observation correspond(s) to the exposure among matched controls[162].

Three advantages are most noteworthy[160-162]:

1. When a researcher is dealing with a time-varying or intermittent exposure a case-crossover study is especially valuable since the **time window** of interest can be varied easily;
2. In crossover studies the same person is both case and control. This means that **cases and controls are comparable** in most of their known and unknown confounders except for intermittent exposures. This overcomes the problem of **between-person confounding** by constant characteristics. This includes confounding by chronic indication as a common cause of bias in pharmacoepidemiology;
3. In contrast to case-control studies the sometimes difficult and time consuming control sampling process is unnecessary;

There are five potential disadvantages[160-162]:

1. **Within-person confounding** by transient factors, including fluctuations in disease severity or comorbidities i.e. confounding by acute indication, is still possible;
2. Although bias in the selection of a control person is impossible because each case serves as his or her own control, it is still possible for **bias in selection of the control time window(s)**.
3. **Time trend bias** may occur if the case and control time windows are very long because there may have been changes in the usual prescribing pattern or dose of the drug of interest;
4. When the exposure is retrospectively assessed, the chance of **differential misclassification** and **measurement error of exposure** still exists;
5. Is often **impossible to study death** as an outcome since a detailed retrospective drug exposure assessment obtained by proxy interview is likely to be prone to substantial errors.

The case-time-control design is a variant of the case-crossover. It comprises, in addition to a regular case-crossover, **the selection of an independent control group**, as in a case-control study. The case-crossover analysis of the exposure history from controls (controls compared with themselves, just as cases in the case-crossover analysis) (Fig. 13) may be used to estimate the background trend in use of the drugs under study (or seasonal exposure to other precipitating factors) which is not expected to be a major concern in our study, given the relatively short period to which the evaluation of exposures refer. It may also be used to control other kinds of control-time selection bias and recall bias, and both justify the option for this design in the present investigation. The ratio of the OR from the case-crossover study by the OR obtained in this “control-crossover” analysis will provide a less biased OR estimate for the precipitating effect of the exposures under study[160-162].

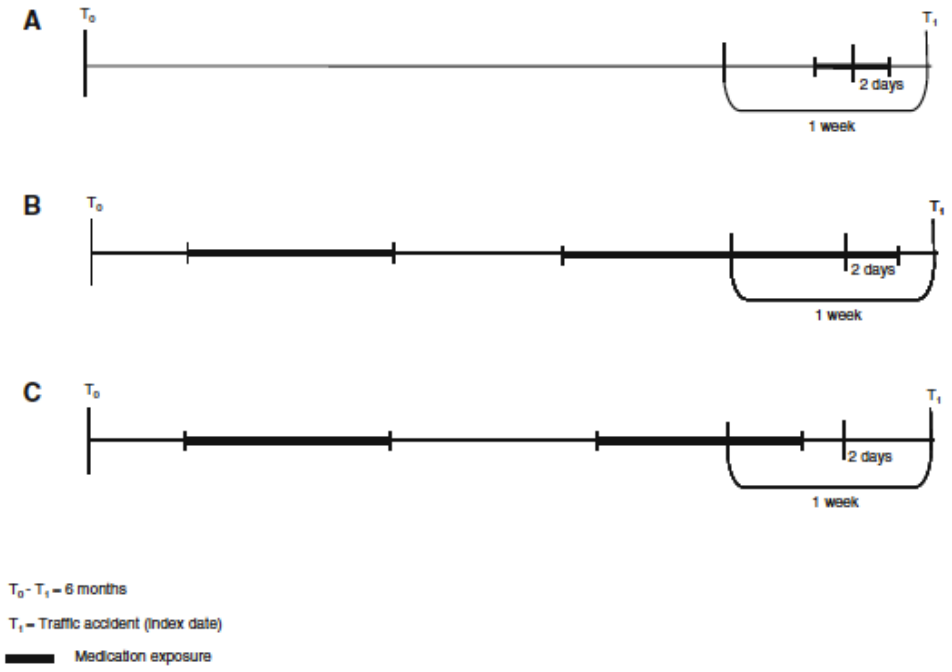


Fig. 13 – Selection of the control group and exposure time in case-crossover studies. (S*ource: Rothman KJ, Greenland S. Modern Epidemiology.Philadelphia, Pa: Lippincott; 1998.[160])*.

In the case-time-control design control are recruited at the same time as the cases. Both, cases and controls are asked for their present exposure at the time of event and at their past exposure in the control period. The rough synchronization of cases allows for an estimation of a common time trend e.g. increasing exposure over time through changes in prescribing patterns in comparison to the more general case-control-crossover design that control for individual and short-term time trends. By observing two time periods in the group of control persons, a time trend of exposure in the source population can be estimated through a trend odds ratio or control-crossover exposure odds ratio[162].

Suissa[161] showed that dividing the case-crossover exposure OR by the trend OR would produce an OR adjusted for time trend and controlled for between-person confounding[162].

Greenland[162] has shown that this adjustment cannot be universally valid: the time trend among cases could be very different from the time trend among controls and may itself be confounded by indication, introducing a new bias, larger than the original time trend bias it is aiming to adjust for. This leads to the recommendation to use case-crossover designs when there is hard to control confounding and at the same time no or a small amount of within-person confounding via a time trend (more likely, the closer the event and control periods are) and case-time-control designs are preferable if a strong time trend in cases and controls is likely[162].

4. OBJECTIVES

Low adherence to medication regimen, sodium and/or fluid reduction has been identified as a triggering factor for acute heart failure (HF) decompensation[7]. Diuretics, though not established as specific long-term prognostic modifiers, are cornerstone in HF symptomatic management. However, the impact of low adherence to therapy and its prognostic implications is undetermined yet. The impact of the triggering effect of low adherence is hard to measure since the consequences may be acute but the determinants and exposure may be variable along the time.

With our study, we aimed to quantify the effect of low adherence to loop diuretic therapy as a trigger for acute decompensation in chronic HF patients, using a case-time-control design.

5. MANUSCRIPT

Low adherence to loop diuretic therapy as a trigger for decompensation in chronic heart failure

Abstract

Introduction: Heart failure (HF) is associated with substantial morbidity, impaired quality of life and huge costs, in large part related with hospitalizations. Diuretics are required for the symptomatic management of HF but the role of therapy adherence in preventing hospital admissions is incompletely understood.

Objectives: To quantify the effect of low adherence to loop diuretic therapy as triggering factor for chronic HF decompensation.

Methods: Case-time-control design using a conditional logistic regression analysis of a case-crossover of cases – patients with acute decompensation of chronic HF and controls - patients with stable chronic HF. Adherence was assessed by a semi-quantitative questionnaire and classified as low if less than 88% of prescribed doses of furosemide were taken in the preceding week.

Results: Case patients were older, most were women and with severe left ventricular systolic dysfunction (LVSD) from ischemic etiology. Risk factors and comorbidities prevalence was higher in cases, including arterial hypertension, diabetes mellitus, atrial fibrillation, chronic obstrutive pulmonary disease and anemia, with the exception of chronic kidney disease. Cases were less frequently under angiotensin converting enzyme inhibitors (ACEI) or beta-blockers. The prevalence of low adherence was 17% (108 patients) in the case arm and 15% (86 patients) in the control arm. Among cases, low adherence to diuretic therapy was 3-fold and significantly more likely in the week preceding hospitalization than 4 weeks earlier (OR=3.00, 95% CI 1.09–8.25, p=0-033). Among controls, the difference in reported adherence was smaller and marginally significant (OR=1.50, 95% CI 0.72–3.11, 0.277). The case-time-control OR for low adherence was 2.00. This triggering effect was stronger among older patients, in women, with severe LVSD, without risk factors and comorbidities, and under treatment with ACEI.

Conclusions: An adherence rate below 88% dose-counts of loop diuretic in chronic HF patients doubles the risk of decompensation in the following week. The identification of patient groups in which low adherence effect is stronger may enable timely application of adherence improvement measures.

Keywords

Heart failure; hospitalizations; heart decompensation; diuretics; furosemide; medication adherence; case-time-control study.

Introduction

Heart failure (HF) is the primary diagnosis in >1 million hospitalizations annually and the leading cause of hospitalization among patients > 65 years of age. The number of hospitalizations has increased, but little is known about its etiology and re-hospitalization imposes a high burden on the health care system with adverse impact in long-term outcomes[1]. Patients hospitalized for HF are at high risk of re-hospitalization[2].

The acute HF syndromes have a heterogeneous presentation[2, 3]. Worsening chronic HF (CHF) occurs in patients who have a history of CHF (HF stage C according to the ACC/AHA guidelines) and present with acute or increased symptoms and signs typical of HF. This group accounts for the majority (80%) of patients hospitalized with acute HF syndromes[2, 3].

Considering the causes of decompensation, the burden attributed to effects of pharmacological exposures is unknown. Low adherence to medication and diet has repeatedly been identified as a precipitating for hospital admission due to acute decompensated HF[4, 5] in 5.5-64%[1, 5-11] of hospitalized patients mainly in observational studies which measure global adherence to treatment or registries. The effects of diuretics on mortality and morbidity have not been studied in patients with HF: a formal evaluation in randomized trials in HF hard outcomes became impossible as they are necessary for symptomatic management[2, 12-16] and recommended for this reason in patients with signs and symptoms of congestion, irrespective of ejection fraction (EF)[2, 12]. The adherence to loop diuretic therapy is particularly hard to quantify since guidelines on diuretic treatment adjustments do not exist and exposure to diuretic and the determinants of prescription are variable along time[2, 12, 17]. Low adherence to diuretic therapy may result more rapidly in increasing symptoms than to other drugs suggesting a powerful triggering effect with acute and long-term implications.

We aimed to quantify the effect of low adherence to loop diuretic therapy as triggering factor for chronic HF decompensation.

Methods

a. Study design

For the assessment of the effect of low adherence to loop diuretic therapy as a triggering factor for acute decompensation of chronic heart failure we implemented a case-time-control study [18-20]. It comprises a case-crossover of the population with acute decompensation of chronic heart failure (case arm) and a selection of an independent control group (control arm) in which the unfavourable clinical outcome is not present. The case-crossover analysis of the exposure history from controls (controls compared with themselves, just as cases in the case-crossover analysis) is used in this study

mainly to control the effect of self-report and recall bias, justifying the option for this design in our study. Also, it helps to estimate the background trend in use of the drugs under study (or seasonal exposure to other precipitating factors) which is not expected to be a major concern in our study, given the relatively short period to which the evaluation of exposures refer.

Cases for case-crossover analysis were subjects hospitalized at a teaching tertiary care hospital, between May 2009 and January 2011 due to decompensated chronic HF, defined by an increase of at least one New York Heart Association (NYHA) class in patients with chronic HF, diagnosis based on the European Society of Cardiology criteria (from EDIFICA[21, 22] cohort).

Controls for case-time-control study were stable chronic HF patients (no hospitalization due to decompensated HF in the previous 3 months) followed at the HF outpatient clinic of the same hospital between January 2011 and July 2012.

Case-time exposure was the week preceding the outcome - hospitalization, for cases, or the time of enrollment in the study, for controls. The control-time exposure was the fourth week before the index time (Fig 1) in both groups. Exposure was assessed retrospectively by self-report or for surrogates respondents whenever the patient was unable to fill the questionnaire by clinical reasons (the patient forgot, was uncooperative or presented with neurologic impairment like cognition and memory disturbances or aphasia)

Our questionnaire included semi-quantitative evaluation of adherence to furosemide in both case and control-time exposure and in the three possible periods of prescription - morning, afternoon and night (Appendix). This evaluation ranged between 9 possible classifications, in case-time in both groups and in the control-time in the cases: furosemide not prescribed in that period, all the prescriptions were taken and number of missed prescriptions - 1, 2, 3, 4, 5, 6 to 7 missings in a week. In the control-time of the control arm the classification ranged between 5 classifications: furosemide not prescribed at that period, all the prescriptions were taken and missing prescriptions - 1 to 3 missings, 4 to 6 missings and 7 missings in a week. In the cases, the self reported questionnaire was applied within the first 48 hours after hospitalization due to decompensated chronic HF. In the control arm the questionnaire was applied to patients with stable therapeutic regimen.

b. Sample

From the initial 662 eligible patients from the EDIFICA cohort, 185 were considered non-eligible because 1 had right HF, 84 were admitted with *de novo* acute HF, 77 did not have loop diuretic prescribed, 6 died before questionnaire filling and 17 were unable to fill the questionnaire by clinical reasons. Then, from 477 eligible patients, 152 were excluded because the questionnaire was not applied to 149 patients and in 3 patients there were missing data about the exposure to furosemide (Fig. 2). Thus, 325 patients were included in the case-arm. They presented a median age of 78 years, with similar gender distribution (49% were male) (Table 1). Ischemic etiology was present in 43%, 35%

had severe LVSD with a mean EF of 40%. Arterial hypertension (was the most prevalent risk factor (71%). Atrial fibrillation (AF) was the most prevalent comorbidity (50%). Only 19% had chronic obstructive pulmonary disease (COPD) documented. Renin-angiotensin-aldosterone blockade was present in 67% (53% were under angiotensin conversion enzyme inhibitors – ACEI - and 14% under angiotensin receptor blockers – ARB) and 56% were under beta-blockers (BB). The median dose of furosemide prescribed was 80 mg, 118 patients had furosemide prescribed once daily, 187 had two times daily and 20 had three times daily. The main cause to acute HF decompensation attributed by the physician was infection (37%) followed by subjective appreciation of poor adherence to treatment (27%).

The included and excluded patients from the case-arm presented similar baseline characteristics, namely age distribution, HF etiology and severity, risk factors and comorbidity prevalence and prognosis modifiers treatments. There were more man in the included (49% vs. 28%, p <0.001). Arterial hypertension was more prevalent in the excluded patients (82% vs. 71%, p=0.014). Although the median daily dose of furosemide was the same, more of the included patients were under high doses of furosemide (p=0.027). Considering the decompensation causes, assessed by the physician, infection was attributed more frequently as a decompensation cause in the excluded patients (49% vs. 37%, p=0.023). The proportion attributed to poor adherence as cause of decompensation was similar between groups (Table 1).

From the initial 343 stable outpatients during the study period, 47 patients were non-eligible because they did not have loop diuretic prescribed. From the 296 eligible patients, 4 patients were excluded, because in 2 patients the questionnaire was not applied and in 2 patients there were missing data about the exposure to furosemide. Thus, 292 patients were included in the control arm (Fig. 2).

c. Statistical analysis

Numerical variables are presented as mean (standard deviation) if normally distributed or median (interquartile range) if non-normally distributed. Categorical variables are presented as count (percent). For comparisons between groups, the chi-square test was used to compare categorical variables, a two independent-sample t test was used to compare normally distributed continuous variables, and the Mann–Whitney U test was used for continuous skewed variables.

Adherence was classified as low if less than 88% of prescribed doses were taken in the preceding week, a cut-off previously used in other studies since receiver operating characteristic curves showed that adherence rates above 88% produced the optimal combination of sensitivity and specificity with respect to predicting better event-free survival [2.2 by dose count (p=0.021) and 3.2 by dose day

(p=0.002)][23].

A conditional logistic regression[24-26] was used to quantify the risk of low adherence to loop diuretics as a trigger of acute decompensated HF. A case-time-control OR was estimated by correcting the OR from the case-arm with the OR from the control-arm.

All of the analyses were conducted using Stata 11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP) and a $p<0.05$ was considered to be statistically significant.

d. Ethics

The study protocol was according with the Declaration of Helsinki, the local ethics committee of Centro Hospitalar São João approved the study and patients gave informed consent.

Results

a. Baseline characteristics

The baseline characteristics of the study sample in each arm are shown in table 2. When comparing the patients between the two arms we found that the cases were older (78 vs. 73 years, p <0.001), with a lower proportion of male patients (49% vs. 65%, p<0.001). Patients from control arm presented more frequently with severe LVSD (35% vs. 59%, p<0.001) mainly with ischemic etiology. The prevalence of risk factors – arterial hypertension and diabetes mellitus – and comorbidities - AF, COPD and anemia - was higher in cases with the exception of the presence of chronic kidney disease (CKD), more prevalent in controls (28% vs. 35%, p <0.001). Cases were less frequently under treatment with ACEIs (53% vs. 76%, p <0.001) and BB (56% vs. 89%, p<0.001).

b. Prevalence of low adherence to loop diuretic therapy

The prevalence of low adherence to loop diuretic therapy in each exposure period, overall and stratifying by patient characteristics is shown in table 3. In the case arm, low adherence was documented in 108 patients (17%), 59 (18%) in the case-week and 49 (15%) in the control-week. In the control arm, low adherence was documented in 86 patients (15%), 46 (16%) in the case-week and 40 (14%) in the control-week. Stratifying by patient characteristics, in the case arm, the prevalence of low adherence was higher in younger patients (age < 70 years), males, with ischemic etiology and severe LVSD, without arterial hypertension, CKD, AF or anemia, without treatment with ACEI and under treatment with ARB and BB. The prevalence was similar in diabetes mellitus and COPD. In the control arm, there were some differences, since low adherence was more prevalent in

older patients, female, with non-ischemic etiology and non-severe LVSD, without diabetes mellitus and with AF. Those patterns were similar in case and control week in both arms.

c. Effect of low adherence to loop diuretic therapy

Among cases, low adherence to diuretic therapy was 3-fold and significantly more likely in the week preceding hospitalization than 4 weeks earlier (OR=3.00, 95% CI 1.09–8.25, discordant pair ratio 15/5). Among controls, the difference in reported adherence was smaller and marginally significant (OR=1.50, 95% CI 0.72–3.11, discordant pair ratio 18/12) (Table 4).

After stratifying by patient characteristics, we found that low adherence to loop diuretic therapy had a stronger effect as trigger for decompensation in older patients (3-fold) with no effect in younger patients, in females (over 4-fold) with a smaller effect in males (40%), in patients with severe LVSD (over 3-fold) and marginally in patients with non-severe LVSD (25%). The effect was higher in patients without risk factors or comorbidities: over 3-fold higher in non-diabetic patients, in patients without arterial hypertension or CKD and over 2-fold higher in patients without AF or anemia. When stratifying to prognosis modifying therapies, the effect of low adherence to loop diuretic therapy was over 3-fold higher in patients under ACEI and BB, with no effect in those not treated with ACEI but over 2-fold higher in patients not treated with BB and not treated with ARB (Table 4).

Discussion

In our case-time-control study we showed that an adherence rate below 88% dose-counts of loop diuretic in chronic HF patients doubles the risk of decompensation in the following week. ‘Adherence to’ describes a health related behavior of a person that adheres to the recommendations of a doctor, other health care provider, or investigator in a research project[27]. Low adherence to medication and diet has repeatedly been identified as a frequent precipitating factor for admission to hospital for acute HF decompensation [1, 2, 6, 28]. This may represent an important barrier to effective treatment of chronic HF[28]. Adherence rates have been reported as the percentage of patients who are adherent or non-adherent, the number of patients achieving 70 –90% adherence, the percentage of full compliant days, or a particular score on a compliance/adherence scale[1, 5-11]. Regardless of the definition used, in HF, many investigators have shown that selective adherence is common and globally low adherence with some aspect of the medical regimen ranges from 5.5-64%[1, 5-11]. In our study, we observed lower rates of low adherence to diuretic therapy, documenting higher values of mean adherence than previously reported – 92% in cases and 95% in controls. This may be due to the fact that he rates previously available are mainly from registries, in which was not determined

adherence exclusively to diuretic therapy, and to the fact that most of the patients included in our study were previously followed in our HF clinic, expected contribution to higher rates of adherence. Even though, these rates are higher than previously shown in studies on HF clinics[10].

Low adherence to therapy has been associated with higher mortality and more frequent hospitalizations [1, 5-11, 29] with high-adjusted risk of 60- to 90-day post-discharge mortality and death/re-hospitalization similar to the overall HF population[7, 23]. However, the triggering effect of low adherence to loop diuretic therapy and its contribution for acute HF decompensation is harder to define. Also, studies on its impact are lacking. The low frequency to the exposure enables the interpretation of a risk to decompensation in the presence of low adherence: the trigger effect. After estimating the OR for low adherence in cases and controls, the result of the case-time-control design may be assumed as the risk of decompensation in the following week if exposed to the trigger – low adherence to diuretic therapy.

The triggering effect was stronger among older patients, in women, with severe LVSD, without risk factors and comorbidities and under treatment with ACEI suggesting that adherence to loop diuretic therapy is very important in the more severe patients, the low adherence is documented as an exclusion cause in patients without other known important triggers and also polymedication and its adverse effects may be important for the exposure and the impact of low adherence to loop diuretic therapy. Also the effect was high in both groups of patients treated or not with BB suggesting also different patterns of adherence to other therapies for when compared with ACEI. According to previous studies[7, 23], patients with documented low adherence to therapy were associated with shorter stay, lower in-hospital mortality, more readily achieve compensation in response to salt restriction, adjustment of diuretics, and provision of medications during the inpatient hospitalization. This suggests that patients have a hypervolemic status in which institution of appropriate treatment results in fast clinical improvement implying reduced contribution to decompensation of severity of disease and presence of risk factors or comorbidities. The ability of physicians to recognize interventions to improve adherence had mixed results[30-32]. Observational studies may help to identify clinical profiles more probably related with low adherence to diuretic therapy and establish timely measures in order to improve it since.

A major concern in studying adherence to therapy is how to deal with transient exposures followed by a short steep increase in risk and the dependency of therapy with the severity of a disease or comorbidities, called confounding by indication. In order to overcome those problems, we performed a case-time-control study. The case-time-control design is a variant from a case-crossover design that is able to distinguish between continued and transient exposures as drug use often variable in time, especially if we consider patterns of adherence or exposure to drugs. Dividing the resultants OR from a case and control arm, the case-time-control will give us a less biased OR estimate for the precipitating effect of the exposures under study. In crossover studies only persons with 'discor-

dant' exposure in the time windows contribute with information: cases that are exposed at the time of event but unexposed in the control period or vice versa. Therefore, an efficient application of cross-over designs would be an exposure that is varying over time as diuretic therapy often is[29, 30]. In our study, the main objective in using this design was to control the impact of self-reported and recall bias.

There was a differential classification of exposure in the control arm, as in the control time there were only 5 options of missing doses, leading to less precise answers. To the analysis, we choose to correct those options turning them as mean missing doses, that means that every patients that answered as having missed between 1 to 3 doses in the control time week were considered has having missed 2 and those who answered as having missed between 4 to 6 doses were considered has having missed 5. After comparing the answers between the case time and the control time of the control arm, we found that the OR in the control arm is, probably, overestimated because many of the observations in the case time were distributed by the lower extremes of both intervals (missed 1 dose and 4 doses a week), something that would probably happen on the controls if those options were available. This increased the number of discordant pairs in the control arm overestimating the OR for low adherence. That means that the real difference in the risk between cases and controls is probably higher.

The main limitations of our study were the quality of self reported information and recall bias. Using the control group helped to decrease the possibility of information bias by attenuating the self-report effect. However, the recall bias remains, especially for cases, since the acute nature of the event may be a conditioning factor. Thus, differential misclassification may be present especially in the case arm. Those aspects also lead to the inclusion of a smaller number of patients since there was missing data about drug prescription. To overcome those problems, and since there is a variable exposure, prospective evaluation may be helpful in order to quantify the effect of low adherence to diuretic therapy as a triggering factor for acute HF decompensation.

Conclusions

According to our study, an adherence rate below 88% dose-counts of loop diuretic in chronic HF patients doubles the risk of decompensation in the following week.

This triggering effect was stronger among older patients, in women, with severe LVSD, without risk factors and comorbidities and under treatment with ACEI.

The identification of these profiles may enable the timely application of adherence improvement measures.

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Table 1 - Baseline characteristics of the case population and comparison between patients included and excluded in the case-crossover study.

	Eligible n = 477	Included n = 325	Excluded n = 152	*p-value*
Age (years), median (IQR)	79 (13)	78 (12)	80 (12)	0.276
Male, n (%)	201 (42)	158 (49)	43 (28)	<0.001
Ischemic etiology, n (%)	197 (41)	138 (43)	59 (39)	0.451
Severe LVSD, n (%)	160 (34)	113 (35)	47 (31)	0.532
Ejection fraction (%), mean (SD)	42 (18)	40 (17)	42 (18)	0.206
Diabetes mellitus, n (%)	203 (43)	135 (42)	68 (45)	0.528
Arterial hypertension, n (%)	355 (74)	231 (71)	124 (82)	0.014
CKD, n (%)	129 (27)	90 (28)	39 (26)	0.641
COPD, n (%)	87 (18)	60 (19)	27 (18)	0.854
AF, n (%)	233 (49)	161 (50)	72 (47)	0.659
Anemia, n (%)	224 (47)	155 (48)	69 (45)	0.639
ACEI, n (%)	243 (51)	172 (53)	71 (47)	0.206
ARB, n (%)	74 (16)	44 (14)	30 (20)	0.081
BB, n (%)	269 (56)	181 (56)	88 (58)	0.651
Furosemide dose (mg), median (IQR)	80 (40)	80 (80)	80 (40)	0.027
Decompensation cause, n (%)				
ACS	19 (4)	14 (4)	5 (3)	0.670
Infection	196 (41)	121 (37)	75 (49)	0.023
Elevated blood pressure	16 (3)	12 (4)	4 (3)	0.526
AF	78 (16)	58 (18)	20 (13)	0.435
Other rhythm disorders	10 (2)	7 (2)	3 (2)	0.834
Anemia	62 (13)	39 (12)	23 (15)	0.274
Poor adherence to treatment	126 (26)	88 (27)	38 (25)	0.889

ACEI - angiotensin conversion enzyme inhibitors; ACS - acute coronary syndrome; AF - atrial fibrillation; ARB - angiotensin receptor blockers; BB - beta-blockers; CKD - chronic kidney disease; COPD - chronic obstructive pulmonary disease; IQR - interquartile range; LVSD - left ventricular systolic dysfunction; SD - standard deviation.

Table 2 - Comparison between the patients included in the case and control arms of the case-time-control study.

	Cases n = 325	Controls n = 292	*p-value*
Age (years), median (IQR)	78 (12)	73 (19)	<0.001
Male, n (%)	158 (49)	189 (65)	<0.001
Ischemic etiology, n (%)	138 (43)	108 (37)	0.035
Severe LVSD, n (%)	113 (35)	173 (60)	<0.001
Diabetes mellitus, n (%)	135 (42)	103 (35)	0.104
Arterial hypertension, n (%)	231 (71)	187 (64)	0.062
CKD, n (%)	90 (28)	102 (35)	<0.001
COPD, n (%)	60 (19)	65 (22)	0.241
AF, n (%)	161 (50)	126 (43)	0.112
Anemia, n (%)	155 (48)	100 (34)	0.001
ACEI, n (%)	172 (53)	222 (76)	<0.001
ARB, n (%)	44 (14)	39 (13)	0.947
BB, n (%)	181 (56)	261 (89)	<0.001

ACEI - angiotensin conversion enzyme inhibitors; ACS - acute coronary syndrome; AF - atrial fibrillation; ARB - angiotensin receptor blockers; BB - beta-blockers; CKD - chronic kidney disease; COPD - chronic obstructive pulmonary disease; IQR - interquartile range; LVSD - left ventricular systolic dysfunction.

Table 3 - Prevalence of low adherence to loop diuretic therapy in each exposure period, among cases and controls, overall and stratifying by patient characteristics.

	Cases with low adherence n (%) = 108 (17)		**Controls with low adherence n (%) = 86 (15)**	
	Case week n (%)	Control week n (%)	Case week n (%)	Control week n (%)
Overall	59 (18)	49 (15)	46 (16)	40 (14)
Age (years)				
< 70	15 (24)	13 (21)	22 (13)	18 (15)
≥ 70	44 (17)	36 (14)	24 (20)	22 (13)
Gender				
Male	40 (25)	35 (22)	25 (13)	21 (11)
Female	19 (11)	14 (8)	21 (20)	19 (18)
Etiology				
Ischemic	29 (21)	27 (20)	11 (10)	5 (5)
Non-ischemic	30 (16)	22 (12)	35 (19)	35 (19)
LVSD				
Severe	29 (26)	21 (18)	26 (15)	20 (12)
Non-severe	29 (14)	28 (14)	20 (17)	20 (17)
Diabetes mellitus				
Yes	24 (18)	20 (15)	14 (14)	9 (9)
No	35 (19)	29 (15)	32 (17)	31 (16)
Arterial hypertension				
Yes	40 (17)	35 (15)	26 (14)	23 (12)
No	19 (20)	14 (15)	20 (29)	17 (16)
CKD				
Yes	10 (11)	8 (9)	12 (12)	8 (8)
No	49 (21)	41 (17)	24 (17)	24 (17)
COPD				
Yes	11 (18)	12 (20)	7 (11)	4 (6)
No	48 (18)	37 (14)	39 (17)	36 (16)
AF				
Yes	25 (16)	23 (14)	21 (17)	21 (17)
No	34 (21)	26 (16)	25 (15)	19 (11)
Anemia				
Yes	18 (12)	15 (10)	16 (16)	12 (12)
No	41 (24)	34 (20)	30 (16)	28 (15)
ACEI				
Yes	29 (17)	22 (13)	31 (14)	29 (13)
No	30 (20)	27 (18)	15 (21)	11 (16)
ARB				
Yes	11 (25)	8 (18)	10 (26)	7 (18)
No	48 (17)	41 (15)	36 (14)	33 (13)
BB				
Yes	38 (21)	29 (16)	41 (16)	34 (13)
No	21 (15)	20 (14)	5 (16)	6 (19)

ACEI - angiotensin conversion enzyme inhibitors; ACS - acute coronary syndrome; AF - atrial fibrillation; ARB - angiotensin receptor blockers; BB - beta-blockers; CKD - chronic kidney disease; CI - confidence interval; COPD - chronic obstructive pulmonary disease; LVSD - left ventricular systolic dysfunction.

Table 4 - Effect of low adherence to loop diuretic therapy as a trigger for heart failure decompensation estimated by conditional logistic regression, overall and stratifying by patient characteristics.

	Case arm			**Control arm**			**Case-time-control**
	OR	95% CI	*p*	OR	95% CI	*p*	OR
Overall	3.00	1.09-8.25	0.033	1.50	0.72-3.11	0.277	3.00 / 1.50 = 2.00
Age (years)							
< 70	3.00	0.31-28.84	0.341	3.00	0.81-11.08	0.10	3.00 / 3.00 = 1.00
≥ 70	3.00	0.97-9.30	0.057	1.00	0.40-2.52	1.00	3.00 / 1.00 = 3.00
Gender							
Male	2.25	0.69-7.31	0.177	1.57	0.61-4.05	0.350	2.25 / 1.57 = 1.43
Female	6.00	0.79-49.84	0.097	1.40	0.44-4.41	0.566	6.00 / 1.40 = 4.29
Etiology							
Ischemic	2.00	0.37-10.92	0.423	#	-	-	-
Non-ischemic	3.67	1.02-13.14	0.046	1.00	0.55-2.23	1.00	3.67 / 1.00 = 1.00
LVSD							
Severe	9.00	1.14-71.04	0.037	2.50	0.78-7.97	0.121	9.00 / 2.50 = 3.60
Non-severe	1.25	0.34-4.65	0.739	1.00	0.38-2.66	1.00	1.25 / 1.00 = 1.25
Diabetes mellitus							
Yes	3.0	0.61-14-86	0.178	3.50	0.73-16.85	0.118	3.00 / 3.50 = 0.86
No	3.0	0.81-11.08	0.099	1.10	0.47-2.59	0.827	3.00 / 1.10 = 2.73
Arterial hypertension							
Yes	2.25	0.69-7.31	0.177	1.33	0.56-3.16	0.514	2.25 / 1.33 = 1.69
No	6.00	0.72-49.84	0.097	2.00	0.50-8.00	0.327	6.00 / 2.00 = 3.00
CKD							
Yes	2.00	0.37-10.92	0.423	2.00	0.60-6.64	0.258	2.00 / 2.00 = 1.00
No	3.67	1.02-13.14	0.046	1.00	0.32-3.10	1.00	3.67 / 1.00 = 3.67
COPD							
Yes	0.67	0.11-3.99	0.657	1.25	0.59-2.67	0.565	0.67 / 1.25 = 0.54
No	6.50	1.47-28.80	0.014	#	-	-	-
AF							
Yes	1.66	0.40-6.97	0.484	1.00	0.32-3.10	1.00	1.66 / 1.00 = 1.66
No	5.00	1.10-22.82	0.038	2.00	0.75-5.33	0.166	5.00 / 2.00 = 2.50
Anemia							
Yes	2.50	0.49-12.89	0.273	2.00	0.60-6.64	0.258	2.50 / 2.00 = 1.25
No	3.33	0.92-12.11	0.067	1.25	0.49-3.17	0.638	3.33 /1.25 = 2.66
ACEI							
Yes	4.50	0.97-20.83	0.054	1.20	0.52-2.77	0.670	4.50/ 1.20 = 3.75
No	2.00	0.50-8.00	0.327	3.00	0.61-14.86	0.178	2.00 / 3.00 = 0.67
ARB							
Yes	4.00	0.45-35.79	0.215	4.00	0.45-35.79	0.215	4.00 / 4.00 = 1.00
No	2.75	0.88-8.64	0.083	1.27	0.58-2.80	0.549	2.75 / 1.27 = 2.17
BB							
Yes	5.50	1.22-24.81	0.027	1.70	0.78-3.71	0.183	5.50 / 1.70 = 3.24
No	1.33	0.29-5.96	0.706	0.50	0.05-5.51	0.571	1.33 / 0.50 = 2.66

ACEI - angiotensin conversion enzyme inhibitors; ACS - acute coronary syndrome; AF - atrial fibrillation; ARB - angiotensin receptor blockers; BB - beta-blockers; CKD - chronic kidney disease; CI - confidence interval; COPD - chronic obstructive pulmonary Disease; IQR - interquartile range; LVSD - left ventricular systolic dysfunction; OR - odds ratio.
- impossible to perform the calculation due to the absence of discordant pairs.

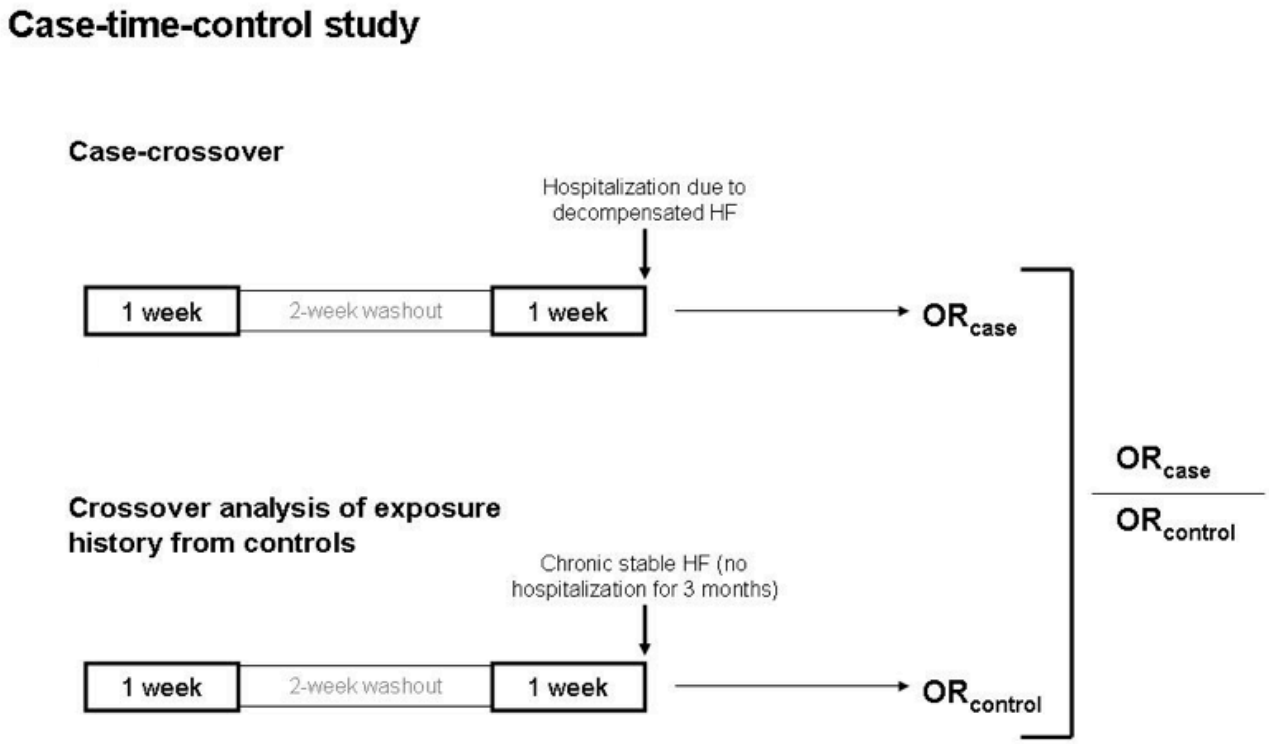

Figure 1 – Case-time-control study design: case and control case-crossover and exposure time periods considered. HF - heart failure; OR - odds ratio.

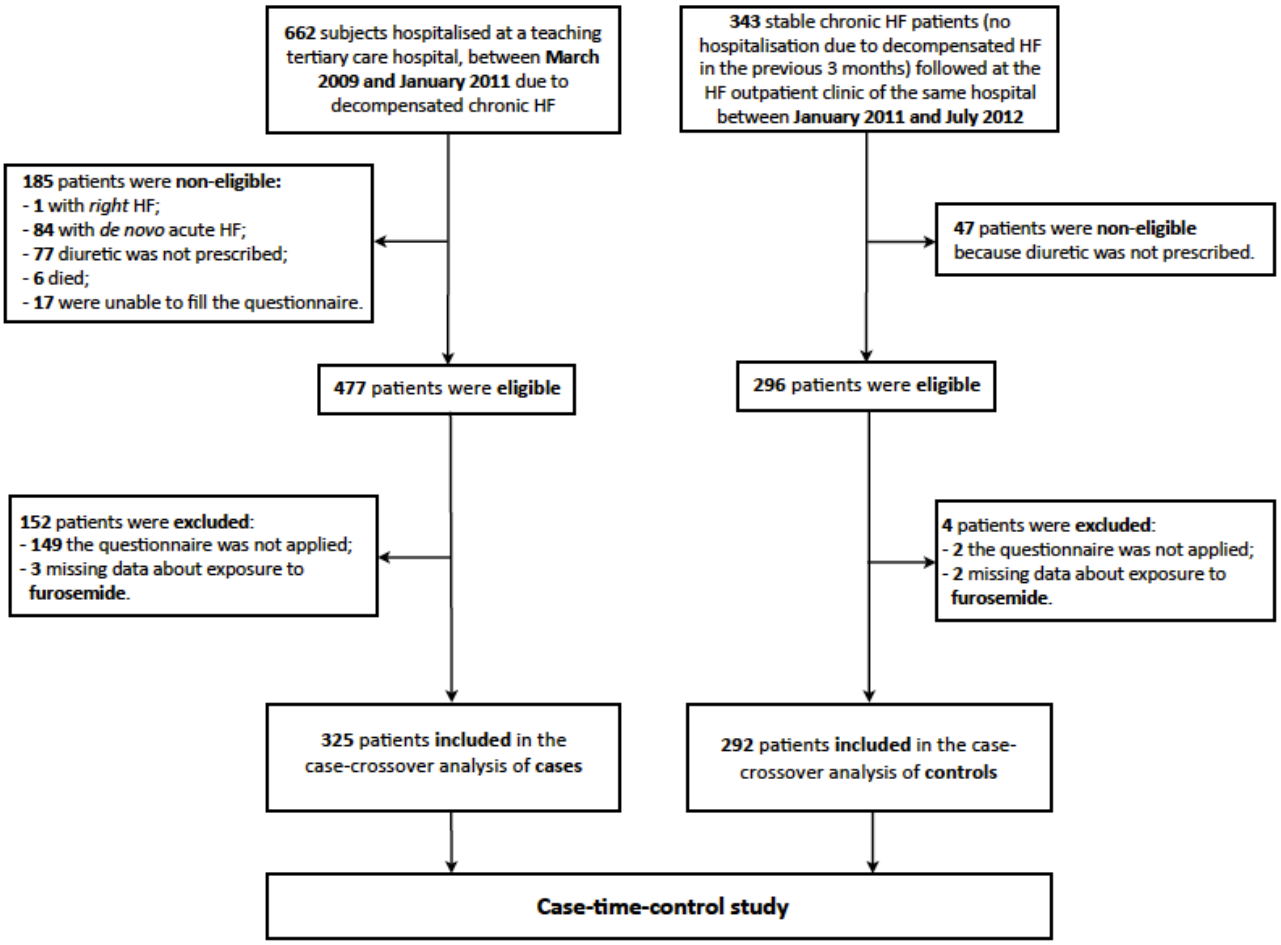

Figure 2 – Flowchart of the selection of patients included in the case and control arms of the case-time-control study. HF - heart failure.

6. CONCLUSIONS

According to our study, an adherence rate below 88% dose-counts of loop diuretic in chronic HF patients doubles the risk of decompensation in the following week.

This triggering effect was stronger among older patients, in women, with severe LVSD, without risk factors and comorbidities and under treatment with ACEI.

The identification of these profiles may enable the timely application of adherence improvement measures.

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8. APPENDIX

9. <u>Na última semana</u>, tomou os comprimidos de Lasix® da manhã todos os dias ou deixou de tomar alguma vez?

Não tem prescrito de manhã O
Tomou todos os dias O
Falhou: 1 dia O 2 dias O 3 dias O 4 dias O 5 dias O 6 dias O
Falhou todos os dias O

10. <u>Na última semana</u>, tomou os comprimidos de Lasix® da tarde todos os dias ou deixou de tomar alguma vez?

Não tem prescrito de tarde O
Tomou todos os dias O
Falhou: 1 dia O 2 dias O 3 dias O 4 dias O 5 dias O 6 dias O
Falhou todos os dias O

11. <u>Na última semana</u>, tomou os comprimidos de Lasix® da noite todos os dias ou deixou de tomar alguma vez?

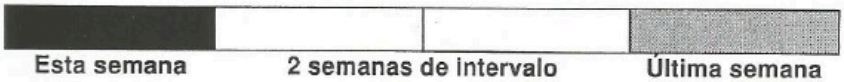
Não tem prescrito à noite O
Tomou todos os dias O
Falhou: 1 dia O 2 dias O 3 dias O 4 dias O 5 dias O 6 dias O
Falhou todos os dias O

12. Se na última semana não tomou a totalidade dos comprimidos de Lasix®, foi

Por indicação médica	O
Por iniciativa própria (decidiu não tomar)	O
Por esquecimento	O
Porque não lhos deram	O
Porque o medicamento acabou	O
Outra razão	O Qual?_____

Figure 1 – Questionnaire for the evaluation of adherence to loop diuretic therapy in the case time period of exposure (case arm).

Agora vou fazer-lhe algumas perguntas sobre uma semana que já passou há mais tempo (mostrar esquema para explicar que se ignora 2 semanas antes da última e que nos estamos a referir à anterior):



Esta semana (há 1 mês) | **2 semanas de intervalo** | **Última semana**

15. <u>Nessa semana</u>, tomou os comprimidos de Lasix® da manhã todos os dias ou deixou de tomar alguma vez?

Não tem prescrito de manhã O
Tomou todos os dias O
Falhou: 1 dia O 2 dias O 3 dias O 4 dias O 5 dias O 6 dias O
Falhou todos os dias O

16. <u>Nessa semana</u>, tomou os comprimidos de Lasix® da tarde todos os dias ou deixou de tomar alguma vez?

Não tem prescrito de tarde O
Tomou todos os dias O
Falhou: 1 dia O 2 dias O 3 dias O 4 dias O 5 dias O 6 dias O
Falhou todos os dias O

17. <u>Nessa semana</u>, tomou os comprimidos de Lasix® da noite todos os dias ou deixou de tomar alguma vez?

Não tem prescrito à noite O
Tomou todos os dias O
Falhou: 1 dia O 2 dias O 3 dias O 4 dias O 5 dias O 6 dias O
Falhou todos os dias O

18. Se nessa semana não tomou a totalidade dos comprimidos de Lasix®, foi

Por indicação médica	O
Por iniciativa própria (decidiu não tomar)	O
Por esquecimento	O
Porque não lhos deram	O
Porque o medicamento acabou	O
Outra razão	O Qual?_____

Figure 2 – Questionnaire and visual aid for evaluation of adherence to loop diuretic therapy in the control time period of exposure (case arm).

9. <u>Na última semana</u>, tomou os comprimidos de Lasix® da manhã todos os dias ou deixou de tomar alguma vez?

Não tem prescrito de manhã **O**
Tomou todos os dias **O**
Falhou: 1 dia **O** 2 dias **O** 3 dias **O** 4 dias **O** 5 dias **O** 6 dias **O**
Falhou todos os dias **O**

10. <u>Na última semana</u>, tomou os comprimidos de Lasix® da tarde todos os dias ou deixou de tomar alguma vez?

Não tem prescrito de tarde **O**
Tomou todos os dias **O**
Falhou: 1 dia **O** 2 dias **O** 3 dias **O** 4 dias **O** 5 dias **O** 6 dias **O**
Falhou todos os dias **O**

11. <u>Na última semana</u>, tomou os comprimidos de Lasix® da noite todos os dias ou deixou de tomar alguma vez?

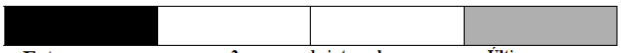
Não tem prescrito à noite **O**
Tomou todos os dias **O**
Falhou: 1 dia **O** 2 dias **O** 3 dias **O** 4 dias **O** 5 dias **O** 6 dias **O**
Falhou todos os dias **O**

12. Se na última semana não tomou a totalidade dos comprimidos de Lasix®, foi

Por indicação médica	**O**
Por iniciativa própria (decidiu não tomar)	**O**
Por esquecimento	**O**
Porque não lhos deram	**O**
Porque o medicamento acabou	**O**
Outra razão	**O** Qual?_____

Figure 3 – Questionnaire for the evaluation of adherence to loop diuretic therapy in the case time period of exposure (control arm).

Agora vou fazer-lhe algumas perguntas sobre uma semana que já passou há mais tempo (mostrar esquema para explicar que se ignora 2 semanas antes da última e que nos estamos a referir à anterior):



15. <u>Nessa semana</u>, tomou os comprimidos de Lasix® da manhã todos os dias ou deixou de tomar alguma vez?

Não tem prescrito de manhã **O**
Tomou todos os dias **O**
Falhou: 1 a 3 dias **O** 4 a 6 dias **O**
Falhou todos os dias **O**

16. <u>Nessa semana</u>, tomou os comprimidos de Lasix® da tarde todos os dias ou deixou de tomar alguma vez?

Não tem prescrito de manhã **O**
Tomou todos os dias **O**
Falhou: 1 a 3 dias **O** 4 a 6 dias **O**
Falhou todos os dias **O**

17. <u>Nessa semana</u>, tomou os comprimidos de Lasix® da noite todos os dias ou deixou de tomar alguma vez?

Não tem prescrito de manhã **O**
Tomou todos os dias **O**
Falhou: 1 a 3 dias **O** 4 a 6 dias **O**
Falhou todos os dias **O**

18. Se nessa semana não tomou a totalidade dos comprimidos de Lasix®, foi

Por indicação médica	**O**
Por iniciativa própria (decidiu não tomar)	**O**
Por esquecimento	**O**
Porque não lhos deram	**O**
Porque o medicamento acabou	**O**
Outra razão	**O** Qual?_____

Figure 4 – Questionnaire and visual aid for evaluation of adherence to loop diuretic therapy in the control time period of exposure (control arm).

2º ciclo de estudos em Epidemiologia

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Porto, Agosto 2014

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