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Universidad del País Vasco — Euskal Herriko Unibertsitatea

PREDICTION OF HEART FAILURE DECOMPENSATIONS USING ARTIFICIAL INTELLIGENCE - MACHINE LEARNING TECHNIQUES

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For my parents

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"Medicine is a science of uncertainty and an art of probability."

- Sir William Osler-

INDEX

PUBLICATIONS RELATED TO THIS PhD THESIS

N. Larburu, A. Artetxe, V. Escolar, A. Lozano, and J. Kerexeta, "Artificial Intelligence to Prevent Mobile Heart Failure Patients Decompensation in Real Time: Monitoring-Based Predictive Model.," *Mob. Inf. Syst.*, no. 1546210, p. 11, 2018.

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ABBREVIATIONS

AI	Artificial Intelligence
AIC	Akaike Information Criterion
AF	Atrial Fibrillation
ANP	Atrial Natriuretic Peptides
APRN(s)	Advanced Practice Registered Nurses
ARIMA	Auto Regressive Integrated Moving Average
AUC	Area Under Curve
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
BUH	Basurto University Hospital
CCHP	Centre for Connected Health Policy
CFS	Correlation-based Feature Selection
CHF	Chronic Heart Failure
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CRM	Customer Relationship Management
CRT	Cardiac Resynchronisation Therapy
CT	Computed Tomography
DBP	Diastolic Blood Pressure
DCN	Data Collection Notebook
DHF	Decompensated Heart Failure
DM	Diabetes Mellitus
DNN	Deep Neural Network
DRG	Diagnosis Related Groups
DT	Decision Tree

EHFScBS	European Heart Failure Self-Care Behaviour Scale
EHR	Electronic Health Record
ER	Emergency Room
FA/pt-y	False Alerts per patient per year
FDA	Food and Drug Association
GFR	Glomerular Filtration Rate
GP	General Practitioner
HF	Heart Failure
HFU	Heart Failure Unit(s)
HR	Heart Rate
ICD	Implantable Cardioverter Defibrillator
ICER	Incremental Cost Effectiveness Ratio
ICT	Information and Communication Technologies
IHO	Integrated Healthcare Organisations
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MA	Moving Average
MACD	Moving Average Convergence Divergence
MDRD	Modification of Diet in Renal Disease
ML	Machine Learning
MLP	Multilayer Perceptron
MRI	Magnetic Resonance Imaging
NB	Naïve Bayes
NO	Nitric Oxide
NO2	Nitrogen Dioxide
NOX	Nitrogen Oxides
NSAIDs	Nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
QALY	Quality-Adjusted Life Years

QoL	Quality of Life
O2Sat	Oxygen Saturation
O3	Tropospheric Ozone
PM10	Particulate Matter 10
RCT	Randomised Clinical Trial(s)
RF	Random Forest
ROC	Receiver Operating Characteristic
RPT	Remote Patient Telemonitoring
SBP	Systolic Blood Pressure
Se	Sensitivity
SMD	Standardised Mean Difference
SMOTE	Synthetic Minority Oversampling Technique
SO2	Sulphur Dioxide
SVM	Support Vector Machine
T2DM	Type 2 Diabetes Mellitus
U4H	United 4 Health
WHO	World Health Organization

I. INTRODUCTION

1.1. What is heart failure?

Heart failure (HF) is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.

The current definition of HF restricts itself to stages at which clinical symptoms are apparent. Before clinical symptoms become apparent, patients can present with asymptomatic structural or functional cardiac abnormalities [systolic or diastolic left ventricular (LV) dysfunction], which are precursors of HF. Recognition of these precursors is important because they are related to poor outcomes, and starting treatment at the precursor stage may reduce mortality in patients with asymptomatic systolic LV dysfunction [1].

1.2. Epidemiology of heart failure

Heart failure is a major concern in public health. Its total impact is increased by its high incidence and prevalence and its unfavourable medium-term prognosis. In addition, HF leads to huge health care resource consumption: it is the first cause of hospitalisation in persons aged 65 years or older and represents 3% of all hospital admissions and 2.5% of health care costs in our country.

Over the last 30 years, improvements in treatments and their implementation have improved survival and modestly reduced the hospitalisation rate in patients with HF, although the outcome often remains unsatisfactory.

Only 2 population-based studies of the **prevalence of HF** have been conducted in Spain: the PRICE (Prevalencia de Insuficiencia Cardiaca en España [Heart Failure Prevalence Study in Spain]) study and the EPISERVE (Insuficiencia cardiaca en consultas ambulatorias: comorbilidades y actuaciones diagnóstico-terapéuticas por diferentes especialistas [Heart failure in outpatients: comorbidities and management by different specialists]) study.

According to PRICE study, in the developed world this disease affects approximately 2% of the adult population, a prevalence that increases exponentially with age. The prevalence is lower than 1% in the population aged less than 50 years but doubles with each decade and exceeds 8% in persons aged more than 75 years. By age, the prevalence of HF was 1.3% at age 45 to 54 years, 5.5% at 55 to 64 years, 8% at 65 to 75 years, and 16.1% at >75 years. These numbers are similar in men and women [2].

The EPISERVE study wanted to investigate the clinical characteristics of heart failure in outpatients and its diagnostic and therapeutic management. The prevalence of heart failure was 2% in primary care, 17% in cardiology and 12% in internal medicine. Hypertension or coronary disease was the cause in more than 80% of cases and the prevalence of comorbidities was high [3].

However, other studies carried out in Europe and the United States demonstrate lower rates of HF. According to one study developed in USA and published in 2009 [4], the prevalence of validated Chronic Heart Failure (CHF) was 2.2% (95% confidence interval [CI], 1.6%-2.8%) and it increased with age groups: from 0.7% for those aged 45 to 8.4% for those aged 75 years or older. Another English study [5] demonstrated a prevalence of 1.5% in their population with a steeply increase with age, reaching over 1% per annum in those aged 85 years or over, but very uncommon in those aged less than 55 years. These differences may be due to methodological limitations and lack of data from appropriately designed studies in our country.

According to the ESC, the 12-month **hospitalisation rates** are 44% for hospitalised patients and 32% for stable/ambulatory HF patients. [6].

In Spain there is a single study that analyses the behaviour of heart failure hospitalisations, published by Fernández Gassó et al [7], and it determines that between 2003 and 2013, there was a sustained increase in standardized rates of hospitalisation for HF, which affected persons 75 years and was associated with a rise in comorbidity.

Registries from other countries show a reduction of the HF hospitalisations rate over the last years. One study in U.S. [8] demonstrated a relative 26.9% decrease from 2001 to 2009 (p-for-trend<0.001). Two studies outside of the U.S. have evaluated HF hospitalisation trends since 2000. In Canada [9] the overall age-standardised HF rate (including hospitalisations, outpatient clinic and emergency department visits) decreased by 25.1% from 1999 to 2007. In New Zealand [10] the HF hospitalisation rate decreased by 28.6% for men and 31.2% for women until 2008. Reasons for the decline in HF hospitalisation rate are likely multi-factorial. One possibility is that control of risk factors leading to HF have improved over time. Incidence of ischemic heart disease has also decreased over the past decade with parallel increases in the use of neurohumoral treatment, antiplatelets and statins. Another contributor to the decline in HF hospitalisation rate may be due to shifting of location of HF care from hospitals or emergency department to outpatient settings.

The natural history of HF is punctuated by decompensations that usually require hospitalisation and tend to follow a bimodal pattern, with more frequent peaks after diagnosis (30% of readmissions in HF) and in the final stage of the disease (50% of readmissions) [2].

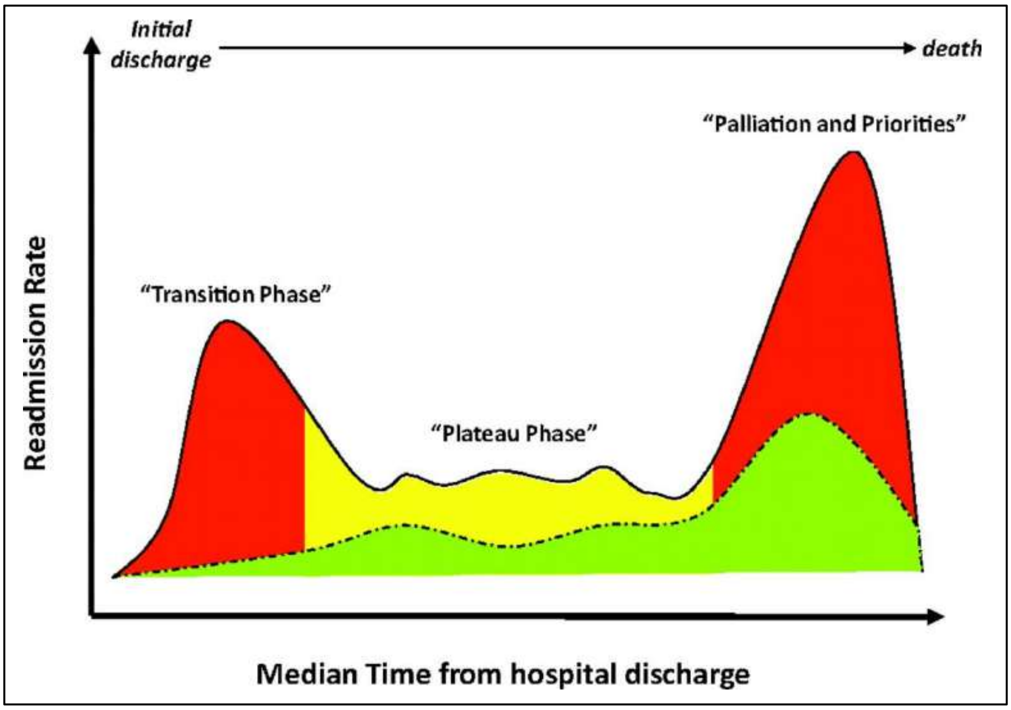


Figure 1. *Three-phase terrain of lifetime readmission risk after heart failure hospitalisation. Figure from Desai et Stevenson. The shaded red areas depict periods of highest risk for readmission immediately following discharge and just before death; the shaded yellow area reflects the lower risk plateau phase; and the shaded green reflects the assumed baseline of unavoidable readmissions.*

Discharge from a heart failure hospitalisation is followed by a readmission within 30 days in 25% of cases. Recurrent heart failure and related cardiovascular conditions account for only about half of readmissions in patients with heart failure, whereas other comorbid conditions account for the rest [11].

The most common precipitating factor in the study carried out by Formiga et al [12] was an infectious disease, mostly of the upper respiratory tract, followed by arrhythmias, anaemia, and high blood pressure. Infections have been found to be highly prevalent in other studies and their impact on the HF patient is noticeable in cold climates. The deleterious effect on hemodynamic posed by supraventricular arrhythmias occurring in a failing heart is a well-known predictor of adverse outcome. A less common factor was the inadequate use of harmful drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), which render HF patients prone to fluid retention, especially when there is concomitant diuretic use. It is noteworthy that a small proportion of patients developed acute HF after emotional stress.

Taken together, preventable precipitating factors account for 30–60% of the causes of acute HF, depending on whether only patient and physician behaviour-related factors (such as non-compliance, dietary transgression, withdrawal of HF drugs, use of harmful drugs) are considered, or if concomitant diseases potentially amenable to better control (hypertension, arrhythmias, ischemic heart disease) are also included.

Early post discharge readmissions are strongly linked to the quality of inpatient care. Although they may be partly due to incomplete patient stabilisation, they are frequently caused by poor discharge coordination and failure to ensure good quality post discharge care [13].

In efforts to identify opportunities to improve quality of care, several interventions have been developed to lower readmission rates after HF hospitalisation, including a tight control of comorbid diseases, improved hospital and post discharge care, post discharge planning, home-based follow-up, patient-centred educational programmes and the use of supportive tools such as HF clinics or multidisciplinary support teams. Nevertheless, readmission rates for heart failure have not changed in recent years. Readmitting approximately a quarter of patients after HF hospitalisation within 30 days is not likely to represent optimal care for patients and suggests that there is substantial room and a clear opportunity for improvement that might be achieved through enhancing the quality of inpatient care or through improved transitions from the inpatient to the outpatient environments [12].

The ESC-HF pilot study demonstrated that 12-month all-cause **mortality rates** for hospitalised and stable/ambulatory HF patients were 17% and 7%, respectively. In all patients with HF, most deaths are due to cardiovascular causes, mainly sudden death and worsening HF [6].

According to the Spanish National Statistics Institute, diseases of the circulatory system remained the first cause of death in 2018, followed by tumours and by diseases of the respiratory system. In more detail, among circulatory diseases, ischaemic heart diseases, cerebrovascular diseases and heart failure were once again the first, second and third place in the number of deaths [13].

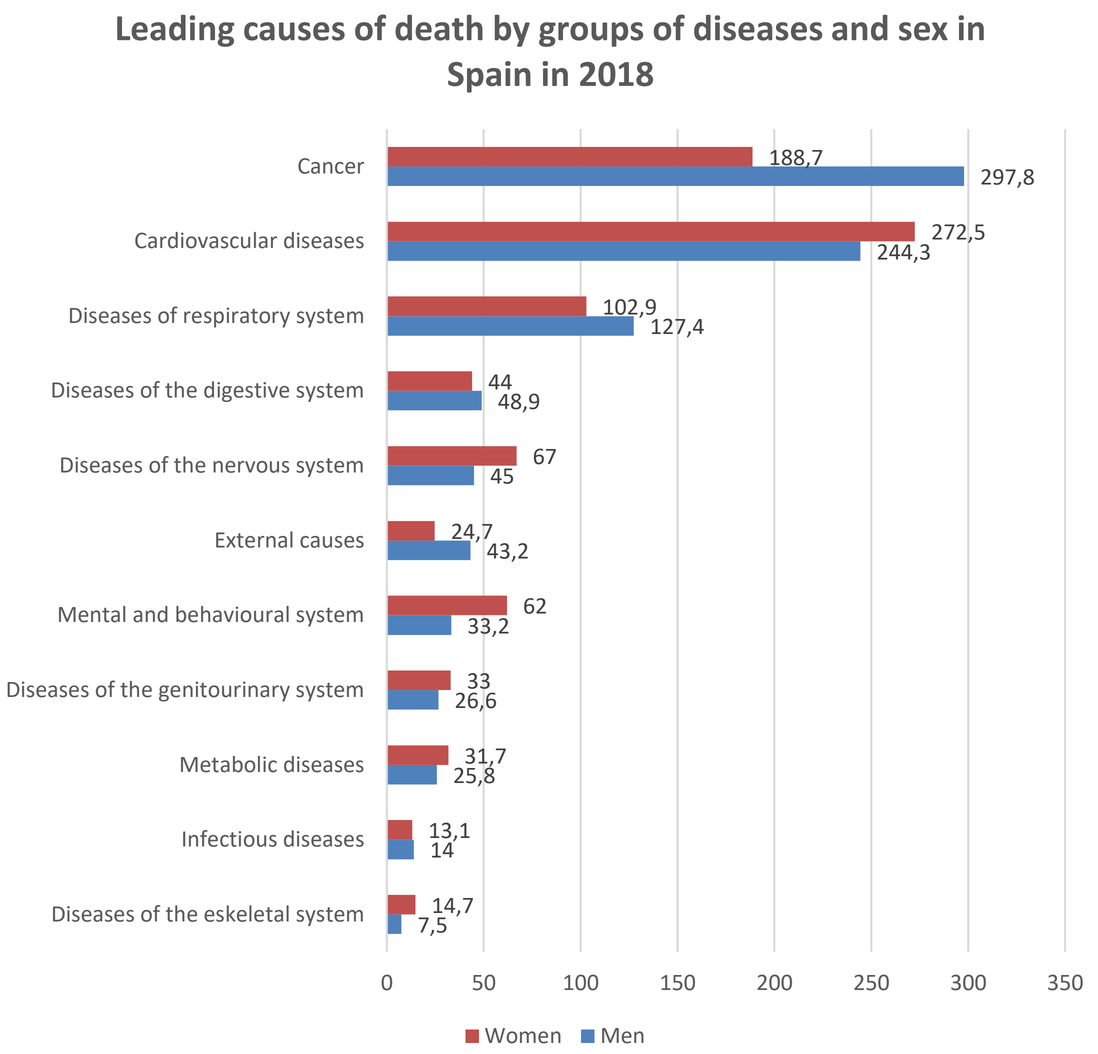


***Figure 2**. Leading causes of death by groups of diseases (per 100.000 inhabitants) and sex in Spain in 2018. From Spanish National Statistics Institute* [13].

The **treatment costs of heart failure** are relatively high. It has been estimated that in western industrialised countries, between 1–2% of total annual health care expenditure is related to the care of patients with heart failure. In heart failure, costs are driven mainly by hospital admission charges and are relatively constant between health care systems as a proportion, representing 67–75% of the total cost of treating a patient. There is also a positive correlation between the cost of heart failure treatment for an individual and the severity of their disease. The relation is non-linear and rises almost exponentially as the New York Heart Association (NYHA) class of heart failure goes up. [14]. At present, drug therapy represents only a small proportion of the component costs of HF (10%). Given the high prevalence of HF in the community, drug therapy, however, represents a substantial source of healthcare expenditure. The non-medical costs of CHF are difficult to estimate. These costs include those of lost earnings, sickness benefits, hospital transportation and social welfare support [15].

In Spain, one recent study has evaluated the medical and non-medical costs of chronic heart failure [16]. The estimated total cost for the 1-year follow-up ranged from € 12995 to € 18220, depending on the scenario chosen. The largest cost item was informal caregiving (59.1%-69.8% of the total cost), followed by health care costs (26.7%- 37.4%), and professional care (3.5%). Of the total health care costs, the largest item corresponded to hospital costs, followed by medication. Total costs differed significantly between patients in functional class II and those in classes III or IV.

Good disease control to delay its progression to more advanced stages would help to reduce readmissions and would favour patient autonomy, thus resulting in a more positive perception of health status and resource savings.

1.3. Telemedicine in heart failure

Telemedicine, a term coined in the 1970s, which literally means “healing at a distance”, signifies the use of information and communication technologies (ICT) to improve patient outcomes by increasing access to care and medical information. Recognizing that there is no one definitive definition of telemedicine, the World Health Organization (WHO) has adopted the following broad description: “The delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities” [17].

The many definitions highlight that telemedicine is an open and constantly evolving science, as it incorporates new advancements in technology and responds and adapts to the changing health needs and contexts of societies.

Interest in telemedicine as a way of providing care has been stimulated by the rising costs of hospital treatment, rapid advances in technology, and the wider availability of low-cost, patient-friendly equipment. Remote patient telemonitoring (RPT) allows the evaluation of patients' vital signs and provides diagnostic information that can be transmitted to health professionals. It has the potential to involve patients more in their own care, assist the titration of medications, improve compliance, and help providers identify early signs of worsening heart failure and its precipitating factors. Home telemonitoring also may assist with care at home or early discharge planning, thereby reducing admissions, hospital days, and rates of mortality [18].

According to the Centre for Connected Health Policy (CCHP), there are four categories for telehealth use today. These are:

1. Live videoconferencing. Also known as synchronous video, live videoconferencing is a live, two-way interaction between a person and a healthcare provider using audio-visual telecommunications technology. This kind of telehealth is often used to treat common illnesses, to determine if a patient should proceed to an emergency room, or to provide psychotherapy sessions.

2. Store-and-forward or asynchronous video. Store-and-forward is the transmission of recorded health history through an electronic communications system to a healthcare provider who uses the information to treat the patient outside of real time. This method is often used in rural areas between a primary care practitioner or nurse practitioner who would like to consult with a specialist in another location.

3. Remote patient telemonitoring (RPT). RPT is the collection of personal health and medical data from a patient or resident in one location that is then transferred electronically to a nurse, caregiver, or physician in a different location for monitoring purposes. RPT is already being used to a great extent in order to monitor the vital health statistics of patients with chronic diseases.

4. Mobile health or mHealth. It uses mobile communications devices, such as smartphones and tablet computers, and hundreds of software applications for these devices, which can assist patients in common illnesses and support healthcare.

In the HF care process focused on transitions of care, there are potential advantages of using telemedicine. Firstly, it allows remote monitoring of biological markers and/or symptoms to enable the early detection and monitoring of decompensation and other clinical events that would otherwise lead to readmission; secondly, it establishes a channel of communication with patients from their home to conduct structured follow-up after discharge, whether by telephone calls or videoconference [19].

Thus, the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic HF recommend for the first time "remote patient monitoring" of HF patients with a recommendation of grade IIb, Level of Evidence B [1].

The number of patients using telemedicine is increasing and it is expected that it will continue growing in the next years. In fact, telemedicine can provide care to a big number of patients who otherwise could not be controlled due to their limitations to go to the medical appointments.

Earlier reviews of multidisciplinary programmes for chronic heart failure have been unable to make definitive conclusions about the value of remote monitoring strategies given the paucity of relevant studies and patient numbers at the time of these analyses. However, several studies with relatively large numbers of patients have been published recently, permitting a more detailed analysis [20].

Overall, they have shown positive results in improving survival, reducing hospital admissions, and improving quality of life [21] [22] [23]; however, some large randomized controlled trials have shown neutral results [24] [25]. These differences may be due to different methodological approaches, inclusion and exclusion criterion and the type of telemedicine used. There may be also differences in the staff and the care process developed in each hospital.

The Cochrane review carried out by Inglis et al included 25 studies evaluating telemonitoring with structured telephone support (total of 9222 participants) and 18 studies using non-invasive telemonitoring (total of 3860 participants). Both strategies reduced all-cause mortality (Structured telephone support RR 0.87, 95% CI 0.77 to 0.98; non-invasive telemonitoring RR 0.80, CI 95% 0.68 to 0.94) and heart failure-related hospitalisations (Structured telephone support RR 0.85, 95% CI 0.77 to 0.93; non-invasive telemonitoring RR 0.80, CI 95% 0.68 to 0.94). Neither structured telephone support nor telemonitoring demonstrated effectiveness in reducing the risk of all-cause hospitalisations (structured telephone support: RR 0.95, 95% CI 0.90 to 1.00; non-invasive telemonitoring: RR 0.71, 95% CI 0.60 to 0.83). 9 of 11 structured telephone support studies and 5 of 11 telemonitoring studies reported significant improvements in health-related quality of life [26].

The systematic review of Knox et al included 26 studies with 7066 participants and investigated the effectiveness of telemedicine in health-related quality of life (QoL). Studies had to report a quantitative measure for mental, physical or overall QoL in order to be included. Telemedicine was not significantly more effective than usual care on mental and physical QoL (standardised mean difference (SMD) 0.03, (95% confidence interval (CI) 0.05–0.12), and SMD 0.24, (95% CI 0.08–0.56), respectively) [27].

Osteba, the Basque Office for Health Technology Assessment which objective is to promote the appropriate use of health technologies in terms of safety, effectiveness, accessibility and equity, providing necessary information for decision-making, elaborated a review about clinical effectiveness and cost-effectiveness of non-invasive telemonitoring on patients with heart failure. The evidence of the effect of telemonitoring on mortality came from the meta-analysis carried out on 21 Randomised Clinical Trials (RCTs) with a total of 5,755 patients with HF, where a statistically significant reduction of 20% was observed in terms of the relative risk of mortality (RR 0.80; 95 % CI: 0.70 to 0.91). The risk of hospitalisations related to HF decreased by 30% with telemonitoring interventions in comparison to usual care (RR 0,70; 95 % CI: 0.60 to 0.82; nine studies; 2,246 patients). Non-invasive telemonitoring had no significant effect on the risk of all-cause hospitalisations (RR 0.96; 95% CI: 0.60 to 1.02; nine studies; 5,347 patients). Remote monitoring had a positive and significant effect on the overall quality of life when compared to standard care (SMD 0.34; 95 % CI: 0.05 to 0.63; p=0.02) [28].

BEAT-HF is a recently published study which objective was to evaluate the effectiveness of a care transition intervention using remote patient monitoring in reducing 180-day all-cause readmissions among a broad population of older adults hospitalised with HF. Among 1437 participants, the median age was 73 years. Overall, 46.2% were female. The intervention and usual care groups did not differ significantly in readmissions for any cause 180 days after discharge, which occurred in 50.8% (363 of 715) and 49.2% (355 of 722) of patients, respectively (adjusted hazard ratio, 1.03; 95% CI, 0.88-1.20; P = .74). In secondary analyses, there were no significant differences in 30-day readmission or 180-day mortality, but there was a significant difference in 180-day quality of life between the intervention and usual care groups. No adverse events were reported [29].

Miller et al studied the long-term cost-effectiveness of disease management in systolic heart failure. Over their lifetimes, patients experienced a lifespan extension of 51 days. Combined discounted lifetime programme and medical costs were $4850 higher in the disease management group than the control group, but the programme had a favourable long-term discounted cost-effectiveness of $43,650/QALY (quality-adjusted life years), suggesting that disease management of heart failure patients can be cost-effective over the long term [30].

Klersy et al performed a meta-analysis of 21 RCTs (5715 patients) in order to assess the cost-effectiveness and the cost utility of remote patient monitoring when compared with the usual care approach. They concluded that remote patient monitoring was associated with a significantly lower number of hospitalisations for HF [incidence rate ratio (IRR): 0.77, 95% CI 0.65–0.91, P < 0.001] and for any cause (IRR: 0.87, 95% CI: 0.79–0.96), while long stay was not different. Moreover, the former was the “dominant” technology over existing standard care with lower costs and a QALYs gain of 0.06 [31].

Lastly, the study leaded by Thokala concluded that telemonitoring was the most cost-effective strategy in their scenario. Compared with usual care, RPT had an estimated incremental cost effectiveness ratio (ICER) of £11 873/QALY, whereas structured telephone support HH had an ICER of £228 035/QALY [32].

Overall, cost-effectiveness analyses suggest that home RPT is an optimal strategy in most scenarios, but there is considerable uncertainty in relation to clear descriptions of the interventions and robust estimation of costs.

In Spain, there have been several experiences with the use of telemedicine in the field of HF.

A clinical study assessed a platform for telemonitoring and the promotion of self-care in the HFU of Hospital Universitario Germans Trias i Pujol. A prospective intervention study with before/after comparison design of an interactive telemedicine platform in HF patients, randomized 1:1 into two groups was carried out: A) Motiva System with educational videos, motivational messages, and questionnaires, and B) Motiva System + self-monitoring of blood pressure, heart rate, and weight. Hospitalisations were compared over 12 months prior to and post study inclusion. There were 92 patients included (71% male; 66.3 +/- 11.5 years; 71% ischemic aetiology) with a mean follow-up of 11.8 months (interquartile range, 8.6-12). Hospitalisations for HF decreased by 67.8% (P = 0.010) and for other cardiac causes by 57.6% (P = 0.028). The number of days in hospital for HF decreased by 73.3% (P = 0.036), without statistically significant differences between groups, and for other cardiac causes by 82.9% (P = 0.008). The perception of quality of life improved significantly both for the generic scale (P < 0.001) and for the HF specific questionnaire (P = 0.005) [33].

In this setting, in the Hospital del Mar HF programme (Barcelona), a telemedicine platform was developed (telemonitoring and teleintervention with videoconference) for the follow-up of patients with HF deemed at high-risk at the time of discharge. The efficacy of this platform was subsequently assessed in a randomized clinical trial. In this study, 178 patients with HF were randomized to either structured follow-up based on face-to-face encounters (control group, 97 patients) or delivering health care using telemedicine (81 patients). Telemedicine included daily signs and symptoms based on telemonitoring and structured follow-up by means of video or audio-conference. The median age of the patients was 77 years, 41% were female, and 25% were frail patients. The trial showed a significant relative reduction of 61% for admissions due to HF and 45% for health care costs in favour of the group followed-up with telemedicine [34].

All in all, there remains a need for strategies to improve heart-failure outcomes, and the global findings indicate the importance of a thorough evaluation of disease-management strategies before their widespread adoption [24].

1.4. State of the art of Machine learning

1.4.1. What is Machine Learning?

Machine learning (ML) is a field of computer science that utilises artificial intelligence (AI) to learn relationships or patterns from the data without the need to define them a priori [35]. It arises at the intersection of statistics, which seeks to learn relationships from data, and computer science, with its emphasis on efficient computing algorithms. The roots of AI date back over 80 years from concepts laid out by Alan Turing, Warren McCulloch and Walter Pitts.

It is very hard or even impossible for humans to derive useful information from the massive amounts of data that have been collected and stored in the healthcare field, that is why machine learning is widely used nowadays to analyse these data and help diagnosing diseases as it reduces diagnosing time and increases the accuracy and efficiency. It is also very useful in follow-up, prognostic stratification, assessment of relapses and hospital readmissions.

The way that ML algorithms work is that they detect hidden patterns in the input dataset and build models. Then, they can make accurate predictions for new datasets that are entirely new for the algorithms. This way the machine becomes more intelligent through learning; so, it can identify patterns that are very hard or impossible for humans to detect by themselves. ML algorithms and techniques can operate with large datasets and make decisions and predictions. Figure 3 [36] represents a simplified representation of how machine learning works.

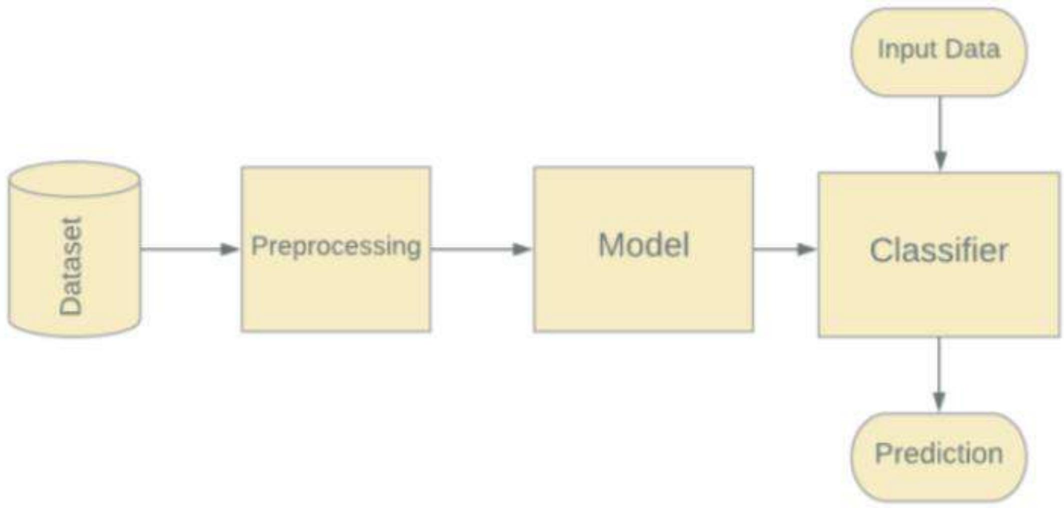


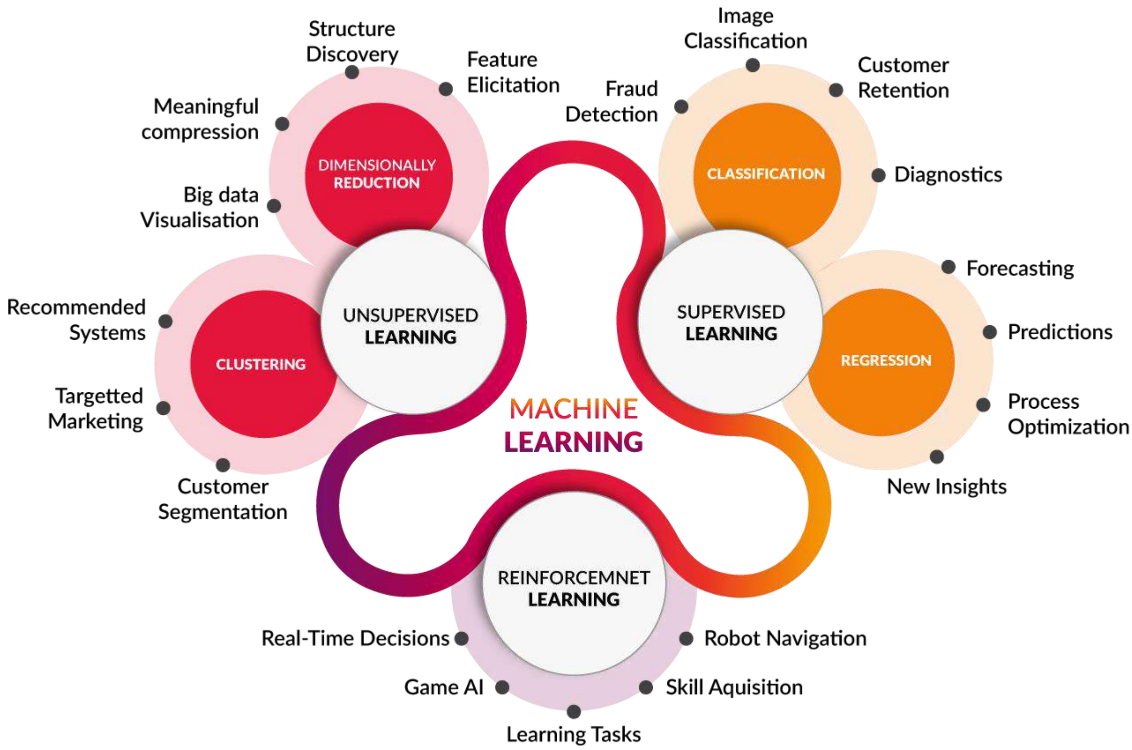
***Figure 3**. Machine Learning Simplified Representation. Adapted from al-Janabi et al* [36].

In this figure, the dataset, which in our case can be an electronic health record (EHR), is pre-processed first. The pre-processing phase is crucial as it cures the dataset and prepares it to be used by the machine learning algorithm. The model consists of a single algorithm, or it can contain multiple algorithms working together in a hybrid approach. The output of the model is a classifier; this is where the intelligence is, and this is what will make the prediction. If the classifier receives input data, it can predict without any human interruption.

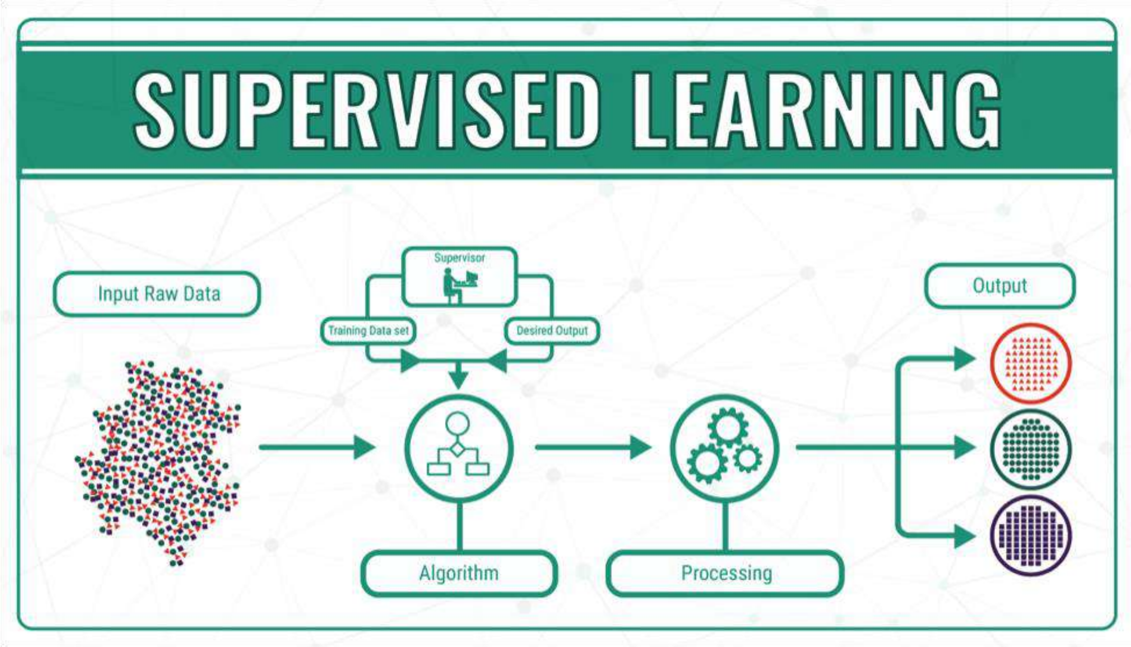
The performance and accuracy of the predictive model is not only affected by the algorithms used, but also by the quality of the dataset and the pre-processing techniques. **Pre-processing** refers to the steps applied to the dataset before applying the machine learning algorithms to the dataset. The pre-processing stage is very important because it prepares the dataset and puts it in a form that the algorithm understands and can process it. Datasets can have errors, missing data, redundancies, noise, and many other problems which cause the data to be unsuitable to be used by the machine learning algorithm directly. Another factor is the size of the dataset. Some datasets have many attributes that make it harder for the algorithm to analyse it, discover patterns, or make accurate predictions. Such problems can be solved by analysing the dataset and using the suitable data pre-processing techniques. Data pre-processing steps includes: data cleaning, data transformation, missing values imputation, data normalization and harmonisations if needed (this happens when the data comes from heterogeneous resources), feature selection, and other steps depending on the nature of the dataset [37].

1.4.2. Types of Classifiers

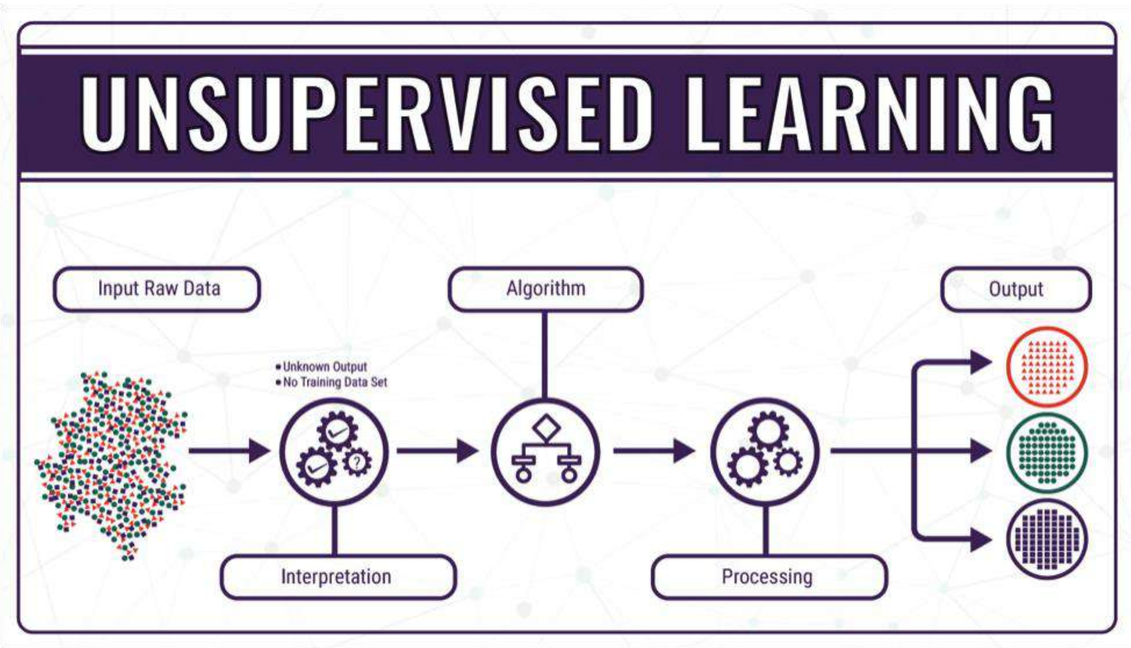
The types of learning used by computers are subclassified in three main categories: supervised learning, unsupervised learning and reinforcement learning.



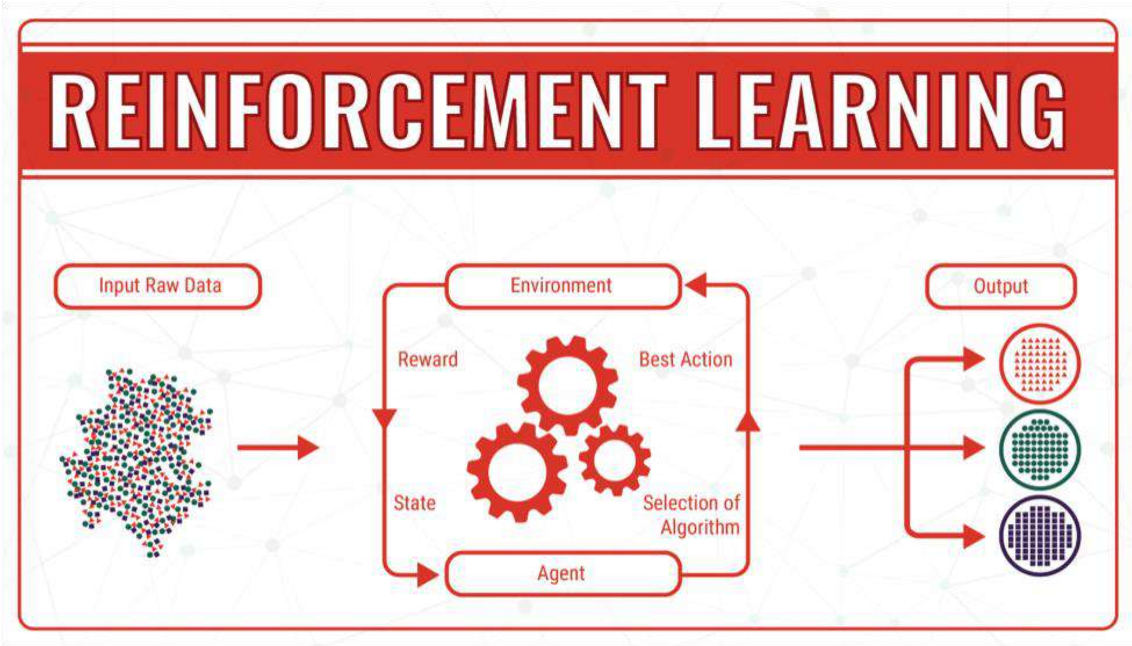
Supervised learning techniques are undoubtedly the most widely used methods in ML and those with the best results. These procedures rely on a dataset from which the response variable to be predicted (e.g., diagnosis, parameter, segmentation) is determined through the correct labelling of examples. An example of the supervised learning technique is classification and regression [38].



In contrast, in **unsupervised learning**, there are no outputs to predict. Instead, we try to find naturally occurring patterns or groupings within the data. This is inherently a more challenging task to judge and often the value of such groups learned through unsupervised learning is evaluated by its performance in subsequent supervised learning tasks [39].



Reinforcement learning. This technique is in the middle of supervised and unsupervised learning, where the model improves its performance as it interacts with the environment. Hence, learn how to correct its mistakes. It ought to get the correct result through examination and trying out different possibilities [40].



The most common type of learning is the supervised learning technique, especially **the classification technique.** It performs predictions for future cases based on a previous dataset. Here we present a brief definition of the most widely used classification techniques for heart disease prediction [36].

Naive Bayes (NB): Naive Bayes classifier belongs to a family of probabilistic classifiers based on Naive Bayes theorem. It assumes sturdy independence between the features, and this is the essential part of how this classifier makes predictions. It is easy to build, and it usually performs well which makes it suitable for the medical science field [38].

$$\underbrace{P(c \mid x)}_{\text{Posterior Probability}} = \frac{\overbrace{P(x \mid c)}^{\text{Likelihood}}\,\overbrace{P(c)}^{\text{Class Prior Probability}}}{\underbrace{P(x)}_{\text{Predictor Prior Probability}}}$$

$$P(c \mid \mathrm{X}) = P(x_1 \mid c) \times P(x_2 \mid c) \times \cdots \times P(x_n \mid c) \times P(c)$$

Artificial neural network (ANN): This algorithm was developed to imitate the neurons in the human brain. It consists of some nodes or neurons that are connected, and the output of one node is the input of another. Each node receives multiple inputs, but the output is only one value. The Multi-Layer Perceptron (MLP) is a widely used type of ANN, and it consists of an input layer, hidden layers, and an output layer. A different number of neurons are assigned to each layer under different conditions [38].

While the roots of AI date back over 80 years, it was not until 2012 that the subtype of deep learning was widely accepted as a viable form of AI [41]. A deep learning neural network (DNN) consists of digitized inputs, such as an image or speech, which proceed through multiple hidden layers of connected 'neurons' that progressively detect features, and ultimately provides an output. A key differentiating feature of deep learning compared with other subtypes of AI is its autodidactic quality; the neural network is not designed by humans, but rather the number of layers is determined by the data itself. The neural net interpretation is typically compared with physicians' assessments using a plot of true-positive versus false-positive rates, known as a receiver operating characteristic (ROC), for which the area under the curve (AUC) is used to express the level of accuracy [42].

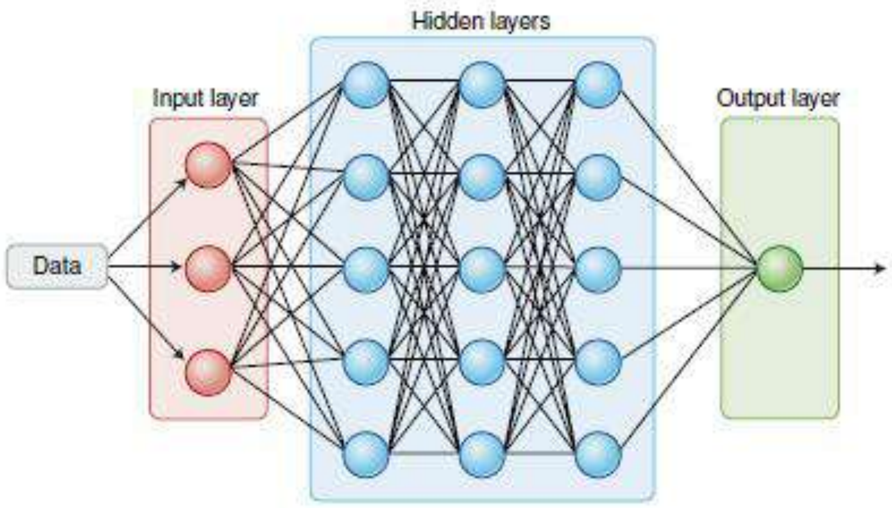


Figure 4*: A deep neural network, simplified. Credit: Debbie Maizels/Springer Nature* [42]

Decision tree (DT): This algorithm has a tree-like structure or flowchart-like structure. It consists of branches, leaves, nodes and a root node. The internal nodes contain the attributes while the branches represent the result of each test on each node. DT is widely used for classification purposes because it does not need much knowledge in the field or setting the parameters for it to work [6].

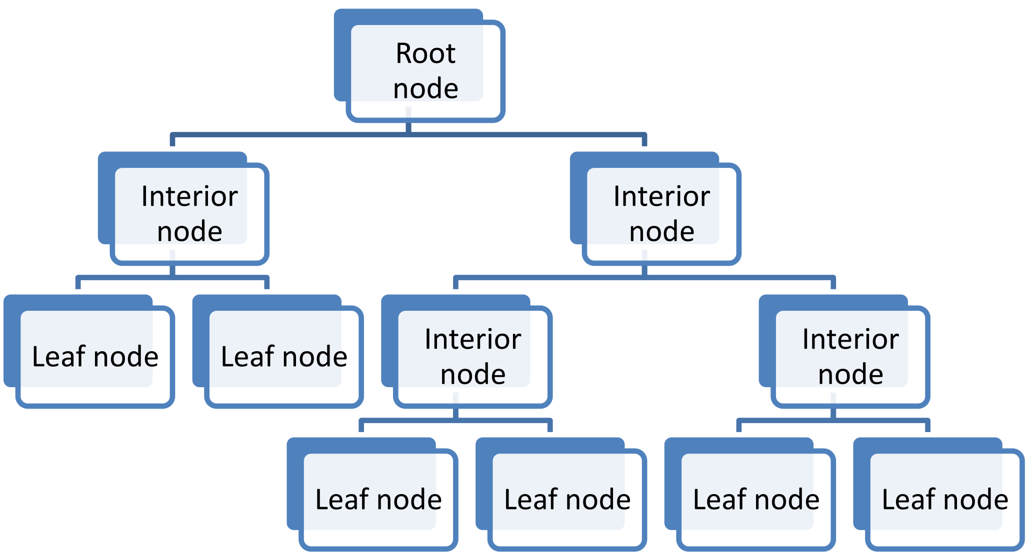


Figure 5*. Example of a decision tree model.*

Random Forest (RF) is an ensemble classifier consisting of multiple decision trees trained using randomly selected feature subspaces. This method builds multiple decision trees at training phase. Each tree gives a prediction (votes) and the class having most votes over all the trees of the forest will be selected (majority voting).

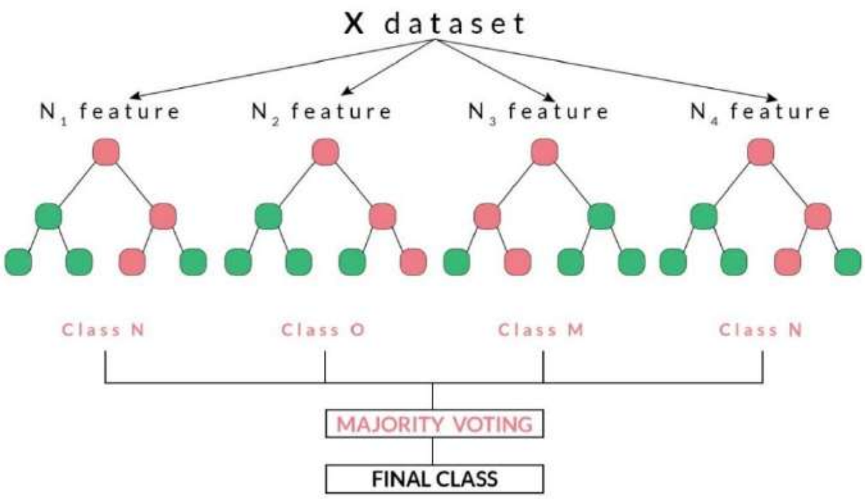


Figure 6. *Example of a random forest model.*

K nearest neighbor (KNN): This algorithm predicts the class of a new instance based on the most votes by its closest neighbors. It uses Euclidean distance to calculate the distance of an attribute from its neighbours.

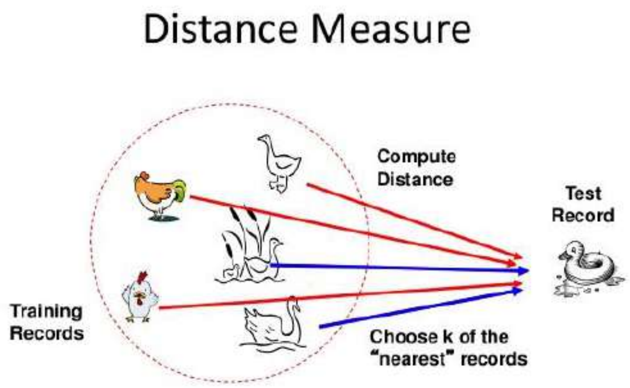


Figure 7. *Example of a K-nearest neighbor model.*

Support vector machine (SVM): This algorithm has a useful classification accuracy. It is defined as a finite-dimensional vector space which consists of a dimension for every feature/attribute of an object (figure 8).

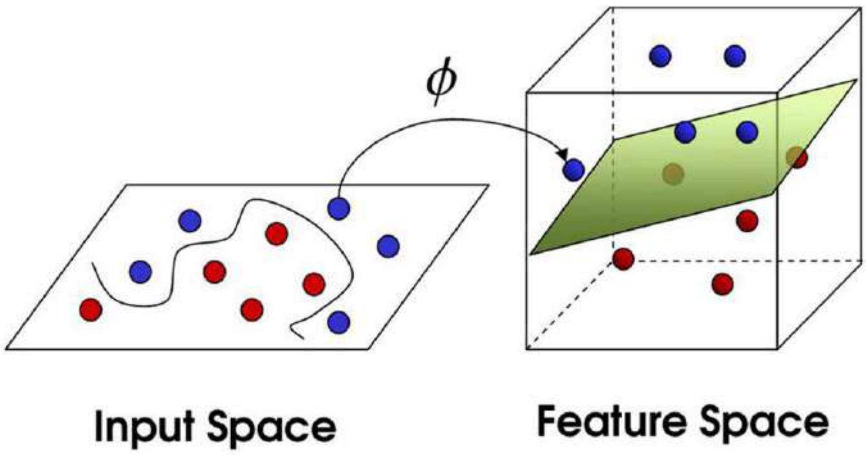


***Figure 8**. Principles of support vector machine operation. Adapted Nashif et al* [43].

Genetic algorithm: It is an evolutionary algorithm that is built based on Darwin's theory of evolution. It imitates methods in nature such as mutation, crossover, and natural selection. One of the mostly used advantages of the genetic algorithm is its usage to initialize weights of the neural network model. That is why its use alongside ANN is witnessed in many researches to produce a hybrid prediction model.

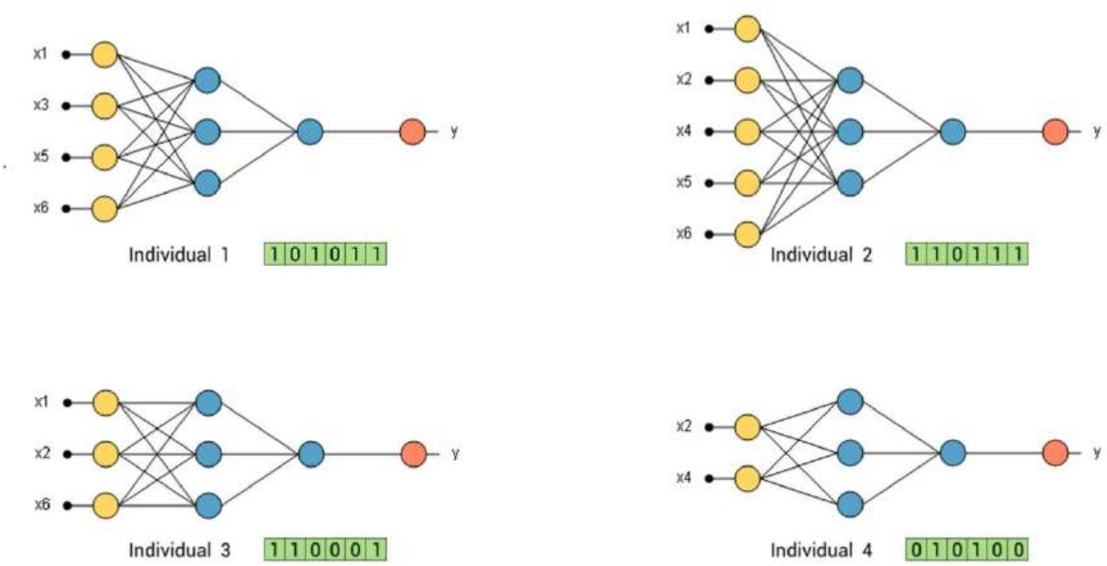


***Figure 9**. Example of a genetic algorithm model.*

<u>Ensemble learning</u>: This method combines multiple classifiers into one model to increase the accuracy. There are three types of Ensemble learning method. The first type is Bagging, which is aggregating classifiers of the similar kind by voting technique. Boosting is the second type, which is like bagging, yet the new model is affected by previous models results. Stacking is the third type, which means aggregating machine learning classifiers for various kinds to produce one model [38].

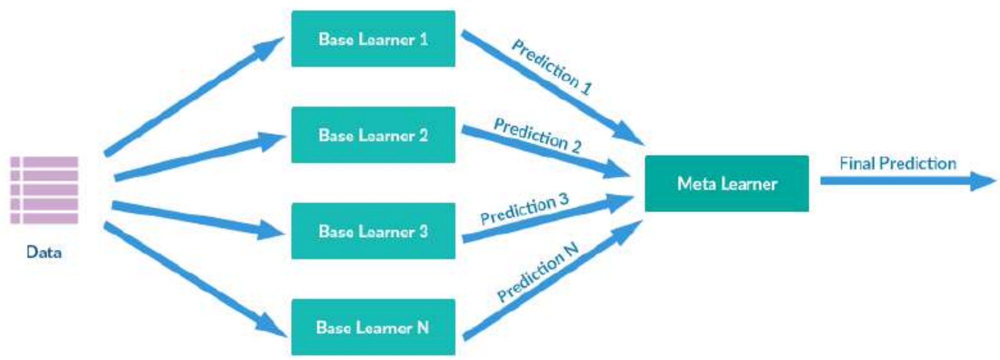


***Figure 10**. Example of an ensemble learning model.*

1.4.3. Construction of a machine learning model

The construction of a ML model does not simply involve the application of a learning algorithm to a database, but is a whole process which usually includes the steps shown in figure 11 [38].

The first stages are common to conventional statistics; raw data are converted into information with structured data (pre-processed), and an initial database is constructed (step 1). From this database, a descriptive and exploratory analysis is performed to identify and select the most significant variables; these variables will be directly applied to the ML algorithms (step 2).

The next stage, now specific to ML techniques, is the division of the dataset into 2 or 3 subsets—training, (validation), and testing— (step 3 of figure 11). The training set is the dataset used to adjust the various ML algorithms selected (step 4). A wide range of classification and regression algorithms is available (see above). In theory, no algorithm is better than another; its ability to make a good adjustment will depend on the characteristics of the data (e.g., number of variables, linearity, normality, missing values, and continuous or categorical variables). Once the adjustment has been made, the validation data subset is used to evaluate the quality of the model (step 5). To do this, the aim is to maximize the metric of greatest interest in our case, such as area under the ROC curve, precision, sensitivity, and accuracy. It is common for this training validation process to be repeated several times while randomizing both subsets, which is known as k-fold cross validation. The objective is to optimize the internal parameters of the algorithm used, evaluate the robustness of the model, and determine whether the model is sub-adjusting or over-adjusting the data, trying to find a balance between the 2 scenarios.

Once the final model has been constructed, the test data subset is used to verify that the final ML model behaves as expected with data that has not been used for its construction or validation (step 6). If this result differs from that obtained in the validation set, the dataset used for training is probably insufficient and should be expanded if a reliable estimator is needed before its generalized use (step 7).

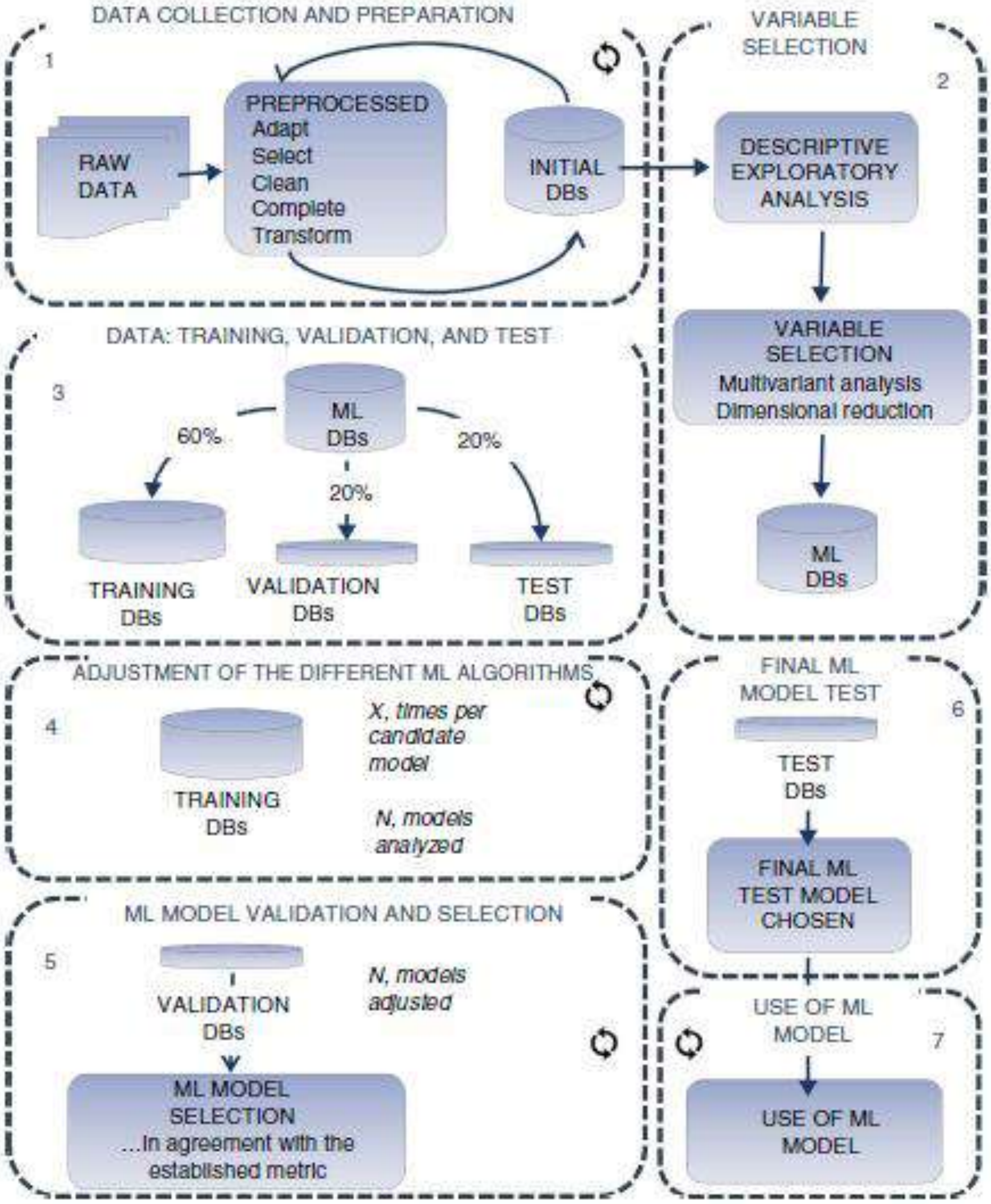


Figure 11. *Application methodology of a machine learning model. DB, database; ML, machine learning* [38].

1.4.4. Artificial Intelligence in Medicine

The use of AI, and the deep-learning subtype in particular, has been enabled using labelled big data, along with markedly enhanced computing power and cloud storage, across all sectors. In medicine, this is beginning to have an impact at three levels: for clinicians, predominantly via rapid and accurate interpretation; for health systems, by improving workflow and the potential for reducing medical errors; and for patients, by enabling them to process their own data to promote health.

Artificial Intelligence for clinicians

A growing amount of literature has accumulated showing the usefulness of machine learning methods in medical image analysis for the detection of anatomical structures, segmentation, computer aided detection and computer aided diagnosis [44].

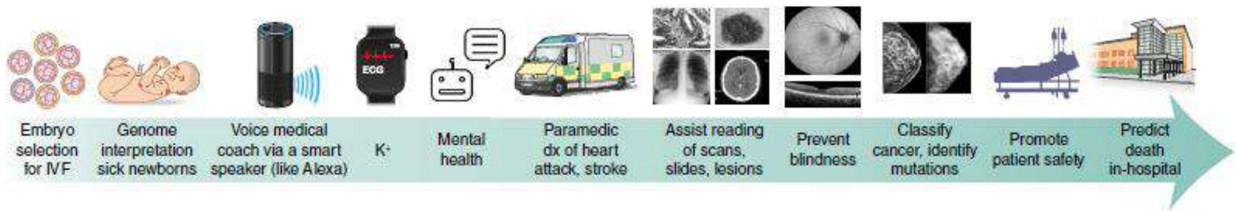


Figure 12. *Examples of AI applications across the human lifespan. dx, diagnosis; IVF, in vitro fertilization K+, potassium blood level* [42]

Previous work by Shen et al. [45] and Miotto et al. [46] have reviewed the use of deep learning techniques in various medical domains such as translational bioinformatics, medical informatics including electronic health records, genomics, public health and mobile data from sensor-equipped smart phones and wearable devices. Together, these studies have simultaneously highlighted the role of deep learning algorithms in achieving diverse medical insights in diagnosis of diseases like cancers, drug design, 3D brain reconstruction, tissue classification, organ segmentation, human behaviour monitoring and infectious disease epidemics, but also the need for the improvement of the current deep learning models.

Datasets are collected mostly by the healthcare professionals at hospitals and healthcare facilities or at times by digital devices. These include patient demographics, medical history, patient examinations, laboratory results, and diagnosis and procedure codes.

Different kinds of data sets have been used for heart failure diagnosis (Fig. 13). These include clinical findings, characteristics of heart and electronic hospital records [47].

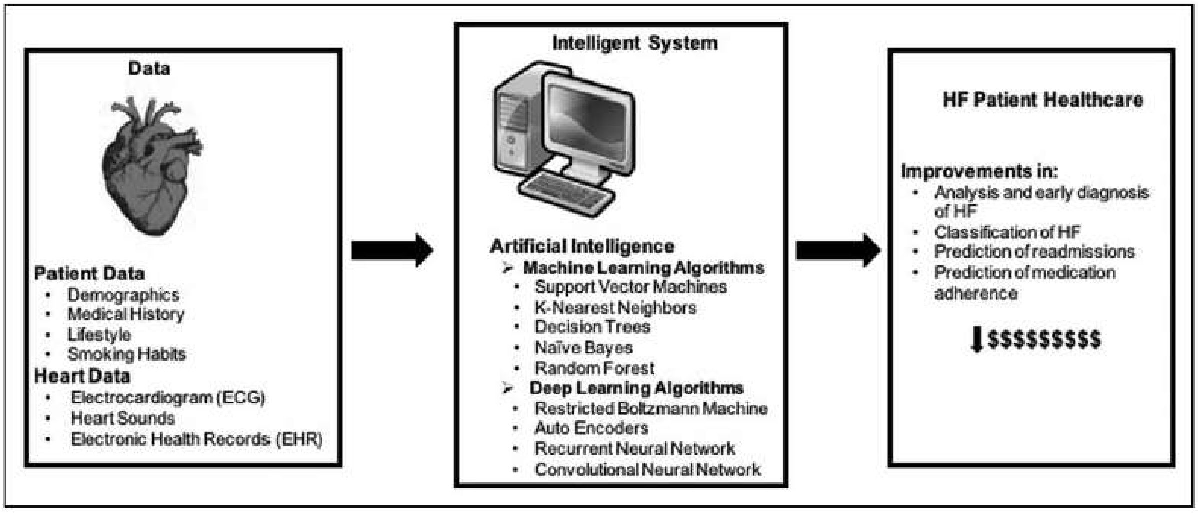


Figure 13. *Patient datasets and machine learning techniques used in heart failure for diagnosis, classification, predicting readmissions and medication adherence to improve heart failure patient healthcare* [47]

Yang et al. [48] developed a system for the detection of heart failure based on clinical features that include blood test results, heart rate variability, echocardiography, ECG, chest radiography, 6-minute walk test and a physical test. In their study, the participating individuals were divided into three classes, namely, healthy (no cardiac dysfunction), heart failure-prone (asymptomatic stages of cardiac dysfunction) and heart failure (symptomatic stages of cardiac dysfunction). They used a machine learning method, the support vector machine (SVM) for the classification into three classes and achieved an overall accuracy of 74.44%.

In a deep learning model, built on a dataset of 40 patients, Gharehchopogh et al. [49] used age, sex, blood pressure and smoking habits as variables and achieved an area under the receiver operating characteristic (AUC) curve of 0.95 for heart failure classification. Furthermore, their model, which was based on neural networks achieved a precision of 95% with the false positive proportion of 9%.

Wu et al. [50] evaluated heart failure prediction based on electronic health record data of 6 months. The health data used in this study constituted of demographic, health behaviour, use of healthcare, clinical diagnosis, clinical measures, laboratory data and prescriptions. In their study, heart failure could be predicted more than 6 months before the clinical diagnosis, with an AUC of 0.76, using logistic regression and boosting.

The use of too many variables in machine learning increases the complexity of the system and creates problems such as over-fitting. To overcome this, investigators have used other methods such as rough sets and linear regression to reduce the number of attributes within the dataset. Son et al. [51] used a machine learning method of decision trees that utilises rough sets and linear regression models by conducting 10-fold cross validation in a dataset that contained 72 laboratory findings. The rough set method (accuracy 97.5%, sensitivity 97.2% and specificity 97.7%) outperformed the regression method (accuracy 88.7%, sensitivity 90.1% and specificity 87.5%) in discriminating heart failure patients from those with dyspnoea. Although previous studies have used a binary output variable, in which the prediction would be either the presence or absence of heart failure, Aljaaf et al. [52] proposed a multilevel risk assessment method for heart failure based on a dataset composed of clinical features that included chest pain type, chest pain location, blood pressure, cholesterol level, smoking habits, family history of coronary artery disease and exercise features. The authors added obesity and physical activity as additional features to improve the performance. Their study used C4.5 decision tree classifier (a machine learning algorithm used for classification) with a 10-fold cross validation to classify every test instance into one of the following classes: 1, no risk; 2, low risk; 3, moderate risk; 4, high risk; 5, extremely high risk for heart failure.

Their system outperformed the previous best machine learning systems and yielded an accuracy of 86.5%, sensitivity of 86.5% and specificity of 95.5%.

An innovative diagnostic system was developed by Zheng et al. [53] who built a model for heart failure diagnosis based on heart sound characteristics and cardiac reserve features. The authors applied various algorithms such as least square SVM, artificial neural network and hidden Markov models on the data consisting of 152 patients. The least square SVM classifier gave the best performance as depicted by 95.39% accuracy, 96.59% sensitivity and 93.75% specificity for the detection of heart failure. However, as heart sound characteristics are influenced by many confounders, the labelling of heart sound data was a limitation, which affected the overall performance of their diagnostic system.

Lastly, Choi et al. [54] investigated the use of temporal relations among events in electronic health records to predict heart failure. The dataset used for their study had 3884 incident heart failure cases and 28903 controls. The recurrent neural networks outperformed the classical machine learning algorithms for detection of incident heart failure and achieved an AUC of 0.78 and 0.88 for 12-month and 18-month observational window, respectively.

Artificial intelligence and health systems

Hospital care has the largest expenditure (about two-thirds) among the total cost of heart failure treatment [55]. Therefore, unsurprisingly previous studies have evaluated different machine learning methods for the prediction of hospital readmissions. Being able to predict key outcomes could, theoretically, make the use of health care resources more efficient and precise. For example, if an algorithm could be used to estimate the risk of a patient's hospital readmission that would otherwise be undetectable given the usual clinical criteria for discharge, steps could be taken to avert discharge and attune resources to the underlying issues.

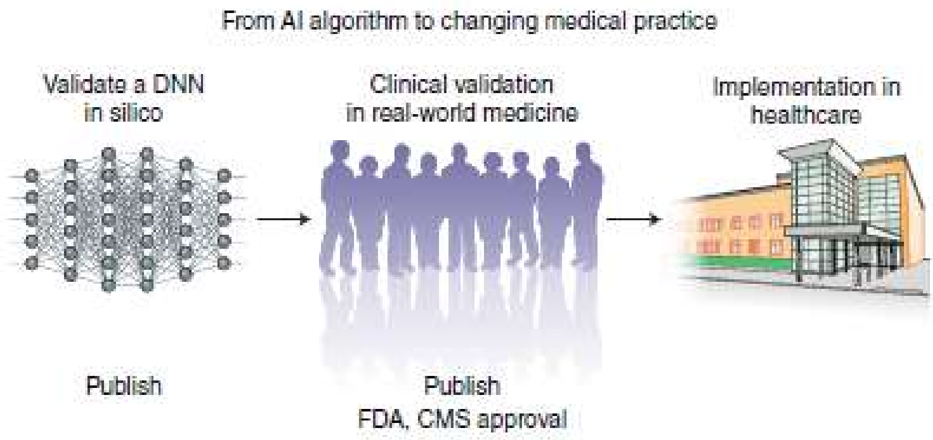


Figure 14. *Call for due process of AI studies in medicine* [42]

In several telemedicine studies developed in diverse pathologies, such as Chronic Obstructive Pulmonary Disease [56] and preeclampsia [57], predictive models have been successfully applied. Hear Failure, however, is a less explored field and fewer studies that create predictive models to determine whether a patient will be readmitted within 30 days after discharge have been published. Most of these predicting models make use of baseline information of patients, such as age, sex or left ventricular ejection fraction, but haemodynamic parameters (i.e. heart rate or blood pressure) which could be crucial for detecting and preventing an ambulatory patient admission, are missing.

Telemonitoring data obtained from heart failure patients is, therefore, an easy and obvious target for researchers. Koulaouzidis et al. [58] built a system to predict hospital readmissions for heart failure patients using telemonitored physiological data. Their dataset contained information for left ventricular ejection fraction, NYHA class, comorbidities, blood pressure and medications. The authors used an analysis of vectors and signals to predict a score of readmissions in their study. The best predictive performance gave an AUC of 0.82 with 8-day telemonitoring data. Kang et al. [59] used a J48 decision tree to build a prediction model for heart failure readmissions using the 'Outcome and Assessment Information Set-C' dataset of 552 telemonitored patients. From the decision tree technique, the presence of skin tissues, patient's living situation, patient's overall health status, severe pain experiences, frequency of activity limited pain and total number of anticipated therapy visits were identified as the risk predictors for rehospitalisation. Mortazavi et al. [60] demonstrated the effectiveness of advanced machine learning algorithms over the traditional linear regression methods in a set of 472 telemonitoring variables to predict heart failure readmissions. Other authors have used a metaheuristic approach to machine learning modelling. Zheng et al. [61] developed models for hospital readmissions using metaheuristics, which included age, sex, length of stay, admission acuity, comorbidity index score and readmission risk. They obtained the best accuracy of 78.4 with 97.3% sensitivity. Bayati et al. [62] constructed a predictive model for readmission for heart failure and studied how its predictions can be used to perform patient specific interventions. Such analyses are expected to be of immense value in situations wherever it is not economically feasible to provide all programmes to all patients. More recently, Baechle et al. [63] proposed Latent Topic Ensemble Learning, which uses an ensemble of topic-specific models to leverage data from different hospitals. This innovative method contrasts with historical approaches that use local data to build the model, and the latter performs poorly whenever supplied with test data from different hospitals. Compared with baseline methods, Latent Topic Ensemble Learning significantly outperformed the best performing baseline methods for cost reduction because of hospital readmission.

Artificial intelligence and patients

The work for developing deep-learning algorithms to enable the public to take their healthcare into their own hands has lagged behind that for clinicians and health systems, but there are a few such algorithms that have been FDA-cleared or are in late stage clinical development. In late 2017, a smartwatch algorithm was FDA-cleared to detect atrial fibrillation, and subsequently in 2018 Apple received FDA approval for their algorithm used with the Apple Watch Series 4. The photoplethysmography and accelerometer sensors on the watch learn the user's heart rate at rest and with physical activity, and when there is a significant deviation from expected, the user is given a haptic warning to record an ECG via the watch, which is then interpreted by an algorithm. There are legitimate concerns that the widescale use of such an algorithm, particularly in the low-risk, young population who wear Apple watches, will lead to a substantial number of false-positive atrial fibrillation diagnoses and prompt unnecessary medical evaluations. In contrast, the deep learning of the ECG pattern on the smartwatch, which can accurately detect whether there is high potassium in the blood, may provide usefulness for patients with kidney disease. This concept of a 'bloodless' blood potassium level reading via a smartwatch algorithm embodies the prospect of an algorithm able to provide information that was not previously obtainable or discernible without the technology. Eventually, when all of an individual's data and the corpus of medical literature can be incorporated, a holistic, prevention approach would be possible [42].

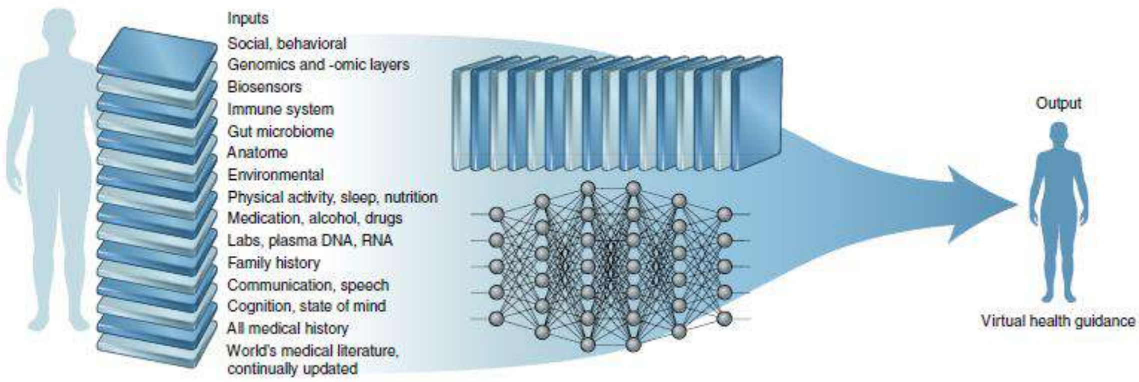


Figure 15. *The virtual medical coach model with multi-modal data inputs and algorithms to provide individualized guidance* [42]

Limitations and challenges

The main characteristic of AI in terms of ML models is that learning is based on the identification of patterns in datasets. This philosophy is simultaneously a strong point, because computers are extremely efficient and precise at finding such patterns when they exist, and a limitation, for several reasons. First, because the amount of data required to obtain an accurate model can be substantial. This can be a problem in medicine, where the implementation of automatic data collection systems is just beginning, such systems must meet established legal and ethical criteria, and some rare diseases inevitably have few studies. It is worth noting that all the potential of the health data used to support clinical professionals and patients is not often sufficiently exploited. Other times the exploited clinical data, in the form of, for example predictive models to identify patients at high risk, is not applied in a real setting to support clinicians and patients [64]. Beyond this issue, much work is needed to strive for medical research that provides a true representative cross-section of the population [65].

In addition, even with algorithms with good results for a dataset, ML models suffer from an inability to correctly detect and classify cases that they have not previously seen. Along these lines, the reliability and quality of the data source are essential for an algorithm to be realistic and correct.

Another important limitation is the opacity and interpretability of the ML models, particularly the DL models [66]. These techniques are used as ''black boxes'', which are fed inputs to obtain an output, namely a prediction. Thus, ML offers us answers in the form of predictions, but not a biological explanation. This opaqueness has led to both demands for explainability, such as the European Union's General Data Protection Regulation requirement for transparency—deconvolution of an algorithm's black box—before an algorithm can be used for patient care.

There is also considerable debate about using AUC as the key performance metric, since it ignores actual probability values and may be particularly misleading in regard to the sensitivity and specificity values that are of clinical interest [67]

There are more obstacles and pitfalls and some of these obstacles relate to pragmatic issues relevant to the medical industry, including reimbursement and liability [39]. An overriding issue for the future of AI in medicine rests with how well privacy and security of data can be assured. New models of health data ownership with rights to the individual, use of highly secure data platforms, and governmental legislation are needed to counter the looming security issues that will otherwise hold up or ruin the chances for progress in AI for medicine [68].

Future considerations

Bringing AI to medicine is just beginning. There has been remarkably little prospective validation for tasks that machines could perform good enough to help clinicians or predict clinical outcomes that would be useful for health systems, and even less for patient-centred algorithms. The field is certainly high on promise and relatively low on data and proof. The risk of faulty algorithms is exponentially higher than that of a single doctor–patient interaction, yet the reward for reducing errors, inefficiencies, and cost is substantial. Accordingly, systematic debugging, audit, extensive simulation, and validation, along with prospective scrutiny, are required when an AI algorithm is unleashed in clinical practice.

With these caveats, it is also important to have reasonable expectations for how AI will ultimately be incorporated. It seems that medicine will unlikely ever surpass Level 3 of autonomy (figure 16), a conditional automation, for which humans will indeed be required for oversight of algorithmic interpretation of images and data. The goal is for synergy, offsetting functions that machines do best combined with those that are best suited for clinicians.

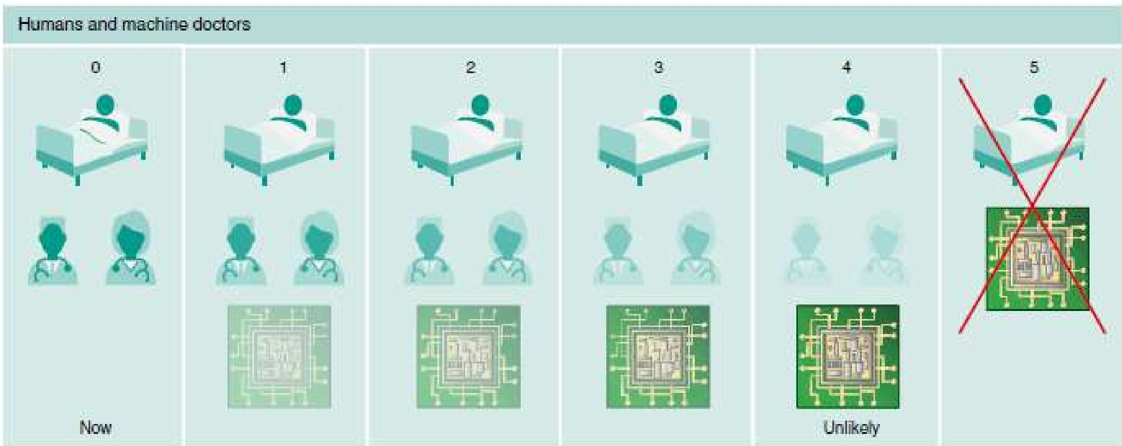


Figure 16. *Levels of autonomy of AI in medicine* [42]

1.5. Organisation of the Basque Health Service

1.5.1. Osakidetza: Basque Health Service

The setting is the Basque Public Health System (with a reference population of 2.2 million inhabitants), which has health policies predominantly funded by taxes and operates on principles of universality, free access and financial fairness. Essentially, everyone is entitled to the same level of care no matter how much money they have. Its primary care is particularly praised, with specialized general practitioners (GP) acting as the gatekeepers to the health system.

Osakidetza (Servicio Vasco de Salud/Basque Health System) is the public healthcare system of the Basque Country, a region located in the north of Spain. Osakidetza was created by the Health Department of the Basque Government in 1983. All the public hospitals and primary care of the Basque Region are under this organization. The Basque Health System includes 14 hospitals, more than 100 primary care clinics organised through four different geographical areas.

Osakidetza is promoting new ways of facing aging and chronic illnesses and has recently incorporated a telehealth service for patients living with chronic Heart Failure (CHF). The aim of this service is to support and improve quality of health through rising levels of self-management and achieve equal or better good clinical outcomes. It gives patients a central role in the management of congestive heart failure, to adjust the choice and dosage of medications, promoting compliance to treatment, and allows healthcare professionals to follow up patients' health status more closely and facilitate early symptom detection. Patients transmit their parameters daily and the telemonitoring devices send the data to the gateway in the patient's home. This transmits the data to the Heart Failure Unit, where a cardiologist or a nurse dedicated to heart failure verify the parameters and the alarms by a phone call to the patient. The Organizational Model includes Hospital, Primary Care an e-Health Centre:

- ✓ Integrated sanitary organisations, which involve Primary care teams and specialised care hospital.
- ✓ OSAREAN (Multichannel Communication Service between the patient and the health service).

- ✓ Telecare services that provide logistics support.

CHF telehealth has provided telemonitoring services to more than 350 patients from our hospital. Currently there are 70 patients activated in the program.

1.5.2. Basurto University Hospital (BUH)

Basurto University Hospital is the public health centre situated in Bilbao, capital of Biscay (Spain). It has 614 beds for hospitalisation and is the third most frequented hospital in the Basque Country. Its area of influence is approximately 350 000 inhabitants, being the reference centre for patients with decompensated heart failure in the area of Bilbao.

1.5.3. Basque Population

Life expectancy in the Basque Country is gradually increasing in both men (79.5 years) and women (86.4 years). Accordingly, the number of people with chronic illnesses is increasing, as is the complexity of their conditions. It has been estimated that more than 40% of over-64-year-olds in the population have some type of chronic illness and that this figure is likely to double by 2040.

Over recent years, the number of people requiring hospital admission has steadily risen. By broad diagnostic groups, the leading causes of morbidity were circulatory, digestive and respiratory system diseases in men, while admissions in women tended to be related to pregnancy or circulatory and digestive system diseases. Specifically, the most common diagnoses on discharge were heart failure (2.5%) and chronic bronchitis (2.3%).

Regarding mortality, the number of deaths has continued to grow over the last decade (increasing by 10% from 2001-2011), due to the ageing of the population. According to the Basque Mortality

Register, in recent years, cancer followed by cardiovascular disease were the leading causes of mortality, respectively accounting for 32% and 29% of all deaths; while in the case of women, cardiovascular diseases outranked cancer [69].

1.5.4. Health plans

In order to face the challenge of managing disease chronicity, wide consensus exists to orient health organizations towards a patient-centred continuum-of-care approach through integrated health interventions.

The Department of Health of the Basque Government launched in 2010 the "Strategy to tackle the challenge of chronicity in the Basque Country" (J.F. Orueta et al. 2013), which aimed to re-orient the health system towards an integrated care model and, therefore, towards a patient- centred approach. [70].

Moreover, this department has developed the "Health Policy for the Basque Country 2013-2020: Health, the people's right, everyone's responsibility". It has been a dynamic process, open to input and active involvement of experienced technical and healthcare professionals. This health plan targets over 2 million people, and its final objective is to improve the health and well-being of all this population.

Below, there are the principles underlying the 2013-2020 Basque Health Plan [69]:

- ✓ Universality: Universal access to high-quality healthcare services, health protection and promotion, and illness prevention for everyone who lives in the Basque Country.
- ✓ Solidarity:
    - High-quality health provision for all everyone regardless of their economic means.
    - The establishment of systems in the health sector for accountability to society.
    - Co-responsibility of institutions and the population in relation to their mutual responsibility concerning health determinants and health-related behaviours.

- ✓ Equity:
    - Lack of systematic and potentially avoidable differences in health and illness between population groups defined in social, economic, demographic or geographic terms. The achievement of equity in health implies that everyone has the same opportunity to reach their full health potential, regardless of their social circumstances (social position, gender, place of residence, type of work, income, level of education and country of origin).
    - Emphasis on increasing equity in access to, use of and quality of care received from health services at all levels.
    - Support for healthcare equity as part of a commitment to social justice.
- ✓ Quality of health services:
    - An endeavour to humanise care in the services provided to the population.
    - Coordination between care levels.
    - Collaborative approaches at the micro level, local networks of organisations with healthcare and social responsibilities; and at the strategic level, corporate social responsibility.
    - Promotion of research aiming to improve population health and guide the provision of health services. Development and innovation, fostering knowledge sharing between professionals.
    - Efficiency in care processes, combined with clinical safety as a key element.
- ✓ Civic engagement:
    - Participation of organisations of civil society in setting and implementing the health agenda.
    - Promotion of self-help and personal responsibility.
- ✓ Sustainability:
    - Greater efficiency of the sector using integrated care and public health models.
    - Coordination between care levels and of social services with other sectors.

All in all, it pretends the improvement of care for patients with chronic heart failure through enhancing continuity of care and coordination between all levels of care.

1.5.5. Heart failure in our area

The number of hospitalisations due to worsening heart failure has increased in a gradual and sustained way in the last years. In fact, improvements in treatments of acute coronary syndromes and their implementation have improved survival of ischemic heart disease and, therefore, increase the number of patients with heart failure. Moreover, new treatments for HF have increased survival of these patients and, thus, the possibility of hospital admission. Population ageing is another contributing factor to the increase of incidence and prevalence of HF.

In BUH, most hospital admissions due to worsening heart failure are in the cardiology service, being the second one Internal Medicine (Table 1).

During 2018, 1196 hospital admissions due to HF took place in the cardiology service and 557 in Internal medicine. Mortality, mean stay and percentage of women are higher in patients admitted to Internal Medicine service. This may be since these patients are older, with more advanced stages of the disease and with more comorbidities. Mean stays are 6.7 and 8.07 days respectively.

In that year, 30 days readmission rate of patients with decompensated heart failure in the cardiology service was 12.43%. 94.3% of the hospital admissions came from the emergency department while the rest were programmed hospital admissions.

	2019 (until 31st July)	**2018**	**2017**	**2016**	**2015**	**2014**	**2013**
HF hospital admissions							
Cardiology	504	1196	1197	900	922	789	794
Internal Medicine	311	557	412	306	127	139	151
Mean stay (days)							
Cardiology	6.61	6.7	6.61	6.87	6.25	4.76	7.08
Internal Medicine	7.78	8.07	7.78	8.05	7.63	15.00	7.25
Deaths (%)							
Cardiology	6.05	5.10	6.02	8.11	4.1	4.6	4.2
Internal	8.10	10.36	11.22	8.82	13.4	11.5	9.9

Medicine							
30 days readmission in cardiology	13.28	12.43	13.82	16.88 (*)	14.19 (*)	15.48 (*)	19.83 (*)
Mean age							
Cardiology	78.91	76.25	75.52	71.40	80	80	79
Internal Medicine	83.03	83.27	85.68	79.97	84	84	83
Men (%)							
Cardiology	54.56	54.01	52.88	58.45	53.00	53.20	52.3
Internal Medicine	51.77	47.04	43.20	44.66	39.40	38.80	45.7

Table 1*. Distribution and characteristics of hospital admissions due to worsening HF in BUH.*
(*) Includes Cardiology and Internal Medicine.

All things considered, heart failure has an increasing incidence in our health area, with a high hospital admission rate, fundamentally due to a high and growing complexity of our patients and a lack of structures that facilitate early recognition of heart failure decompensations.

In order to estimate the cost of hospital admissions, the diagnosis-related group (DRG) classification system was developed in the early 1980s. It is a system to classify hospital cases into one of the existing groups and its original objective was to develop a classification system that identified the "products" that the patient received. Actually, prospective payment rates based on DRGs have been established as the basis of Medicare's hospital reimbursement system.

The cost for each DRG depends on the hospital where the admission takes place. For the BUH, for example, the mean cost varies from 3500 to 7500 euros, depending on the assigned DRG.

1.5.6. Heart Failure Unit in Basurto University Hospital

Heart Failure Unit in Basurto University Hospital was stablished in 2013. Previously, there was only a specific HF consultation, but it could not be considered a unit. In 2017 this unit was given the accreditation of "Specialized heart failure unit" inside the SEC-Excellence Heart Failure Project.

The HFU is formed by 3 cardiologists (1 with a full-time contract and the other two with a partial contract) and 2 nurses (one reference nurse in the hospitalisation area and one nurse dedicated to the management of the alarms generated in telemonitoring and education and titrations of treatments of outpatients). We have also the collaboration of other staff (cardiologists in the ward and Coronary Unit), as well as advanced practice registered nurses (APRNs) or nurse care managers who coordinate patient care and provide primary and specialty health care, and a call centre ("Consejo Sanitario").

APRNs care for patients as well as interacting with the public, often serving as a liaison between the doctor and the families of patients. Their advanced training means they have great levels of knowledge, manifesting in greater decision-making ability and expertise in areas such as diagnosis and assessment, planning and implementation, evaluation of healthcare and record-keeping. In our area, they depend on primary care services but collaborate with the HF unit. They are our best option for the follow-up and treatment of our patients because not only do they administer treatments at home, but also do an integrated assessment of the patients, follow-up, education, self-care encouragement, patients' empowerment and develop personalized activities. Moreover, they have a high availability and usually can go to the patients' home the same day.

Osakidetza has also a call centre run by nurses that works 24 hours 365 days per year. It is a reference point used by patients who ask for recommendations for usual health problems that do not require a face-to-face sanitary intervention. They answer common doubts and offer actuation rules depending on the symptoms. Furthermore, they make the follow-up of patients with chronic illnesses and collaborate in health prevention and promotion programmes.

The specific attention of our patients is based on the "Plan de Intervención Integrada a la población con insuficiencia cardiaca (PIP)" [71]. The main objective of this project is to improve the prognostic and quality of life of patients with HF, as well as reduce the number of hospital admissions thanks to the coordinated participation of the different care levels and promotion of patients' empowerment. This document explains the different care paths of the medical assistance of these patients and includes actuations in Primary Care, specialised units and hospitalisation.

1.6. Protocol for care assistance of patients admitted to hospital due to decompensated heart failure

Here is a summary of the protocol for care assistance of patients admitted to hospital due to decompensated heart failure (Figure 17).

Hospitalisation:

- Clinical evaluation and medical intervention: diagnostic confirmation, aetiology and clinical stabilisation. Discharge report must include final diagnosis, comorbidities and risks, aetiology of the decompensation, physical examination, complementary investigations (labs, radiology, etcetera), course while in hospital, interventions, discharge plan (medications, follow-up instructions for patients including possibility of self-adjustment of diuretics), referrals and appointments.
- Reference nurse in the hospitalisation area. The in-hospital period is an ideal time to provide education about heart failure, its monitoring and management. This way, the nurse provides patients and their families verbal information supported by written material (Annex 1). The main objectives are care coordination and getting the maximal independence and autonomy of the patients and their caregivers. The nurse completes the education process with some scales (see later) and completes a nurse report that will guide the patient in the corresponding assistance path.

- Barthel scale (annex 2) [72] [73]. The main aim of the Barthel Index of Activities of Daily Living is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason. Total possible scores range from 0 – 100, with lower scores indicating increased disability.
- European Heart Failure Self-Care Behaviour Scale (EHFScBS) (annex 3) [74] [75] is a 12-item, self-administered questionnaire that covers items concerning self-care behaviour of patients with heart failure. Face-validity and concurrent validity was established with a Cronbachs' alpha of 0.81.
- Gijon scale of social and familiar evaluation (annex 4) [76]. This scale has five items (family situation, economic situation, housing, relationships and social support) and a range score between 5 and 25, in which low scores identify older people who live with their family, have good contacts and participate in community activities. In contrast, high scores identify older people who live alone, have social poor support and little participation with community activities. The cutting line is 16 points and it denotes social risk. The intraclass correlation coefficient (inter-observer reliability) of this scale is 0.957 and the Cronbach alfa coefficient is 0.4467, which denotes moderate to low consistency. All in all, this scale is as a measuring instrument that detects risk situations and social problems with good reliability and acceptable validity.

Post-discharge follow-up:

An early follow-up after discharge is essential for an optimal transition between the acute phase and long-term follow-up in the outpatients' clinic.

- Continuity of care at discharge with nursing. This is a brief nursing report that specifies the patient's pathology, activities carried out at hospital and general recommendations on discharge.

– Phone call 72 hours after discharge: a call centre in Bilbao makes a phone call to the patient 72 hours after hospital discharge. It consists of 7 predefined questions that try to detect early heart failure decompensations, make good care transitions between hospital and general practitioners, review doubts with medications, check the treatment and detect problems with the prescribed drugs (Annex 5). The generated questionnaires are reviewed by the nurse of the HFU and, if specific actuations are required, the cardiologist is informed and acts accordingly. An interventional study carried out by Cordero et al [77] which included 430 patients evaluated the effectivity of a structured phone call protocol made 72 hours after hospital discharge. The analysis showed that patients who received this structured phone call had a lower re-admission rate (10%) and a lower 30 days HF-related readmission risk (adjusted OR = 0.54; CI 95%= 0.28-0.92; P = 0.02) and all causes readmission risk (adjusted OR = 0.49; CI 95%= 0.3-0.81; P <0.01).

– Early visit with nursing: it takes place 7-10 days after discharge and the main objective is continuing with the educational process initiated during hospitalisation. They centre in 3 spheres: maintenance (diet, exercise, and treatment intake), monitoring (to detect and prevent decompensations) and self-care.

General follow-up (GP and Cardiologist)

- Medical appointment with the general practitioner to continue the follow-up (global assessment, treatment review and education).
- Medical appointment with the cardiologist 1 month after discharge. In certain cases (young patients, severe ventricular dysfunction, intensive care unit admissions with mechanical ventilation and / or inotrope drugs), the follow-up will be in the specialized HF unit.

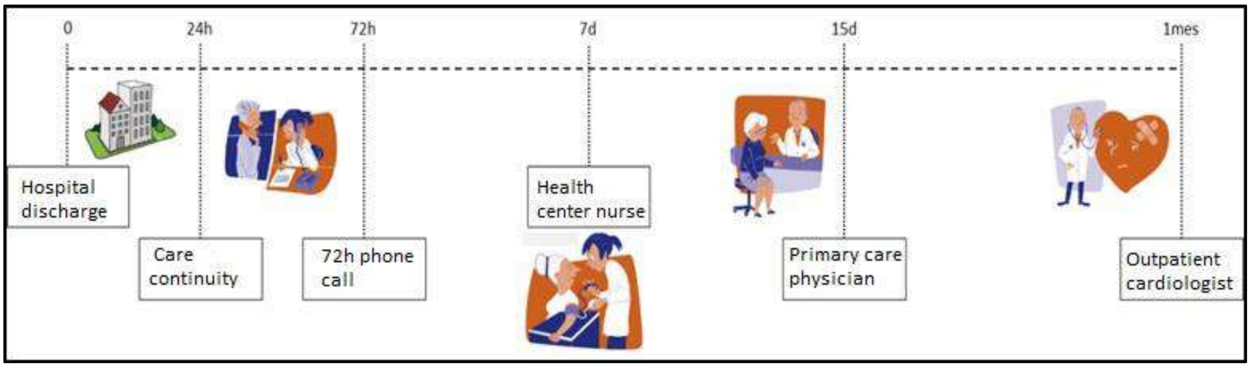


Figure 17. *Follow-up after hospital discharge due to decompensation of heart failure.*

1.7. Protocol for the attention to telemonitored patients

In 2014 and inside the European project "United 4 Health" (U4H) [78], BUH started a new programme of home telemonitoring. The main aim of this study was to roll-out an integrated intervention using telemonitoring in HF patients and exploit innovative telemedicine solutions in the treatment of patients with heart failure.

U4H project focused on finding ways to maximise new technology, such as telehealth solutions, to help improve healthcare, access to care, self-management and resource utilization. In addition to sharing the learning associated with designing and adopting innovative health and care service models, the project's core philosophy was that the telehealth solutions should provide value for citizens, health care providers and payers by improving access to services, reducing costs (medical appointments, fewer emergency admissions to hospital) and increasing care quality; thereby delivering more personalised tailored care with easier involvement of family and caregivers.

Patients with HF receive remote monitoring of their HF conditions. Thus, patients at home use the devices provided to measure their heart rate, pulse-oximetry and weight. The devices collect the data and send to the gateway wirelessly. In the first phase of the study, an operator of the Call Centre of Osakidetza-Basque Health System (Consejo Sanitario) checked the data collected by the patients. The personnel acted according to a protocol based on the severity of the alarm, and in addition, during working hours, the cardiologist of the HF unit was available to answer questions and make possible treatment adjustments. In some studies, non-healthcare personnel oversee the review of patient's measurements. However, the fact that the follow-up of the patients is carried out by nurses with knowledge in HF provides an important added value when performing education and resolution of doubts about hygienic-dietary measures and treatment. Patients' follow-up by a nursing call centre has been used with success in other projects developed by the Osakidetza, such as TELBIL [79][80] and telEPOC [81].

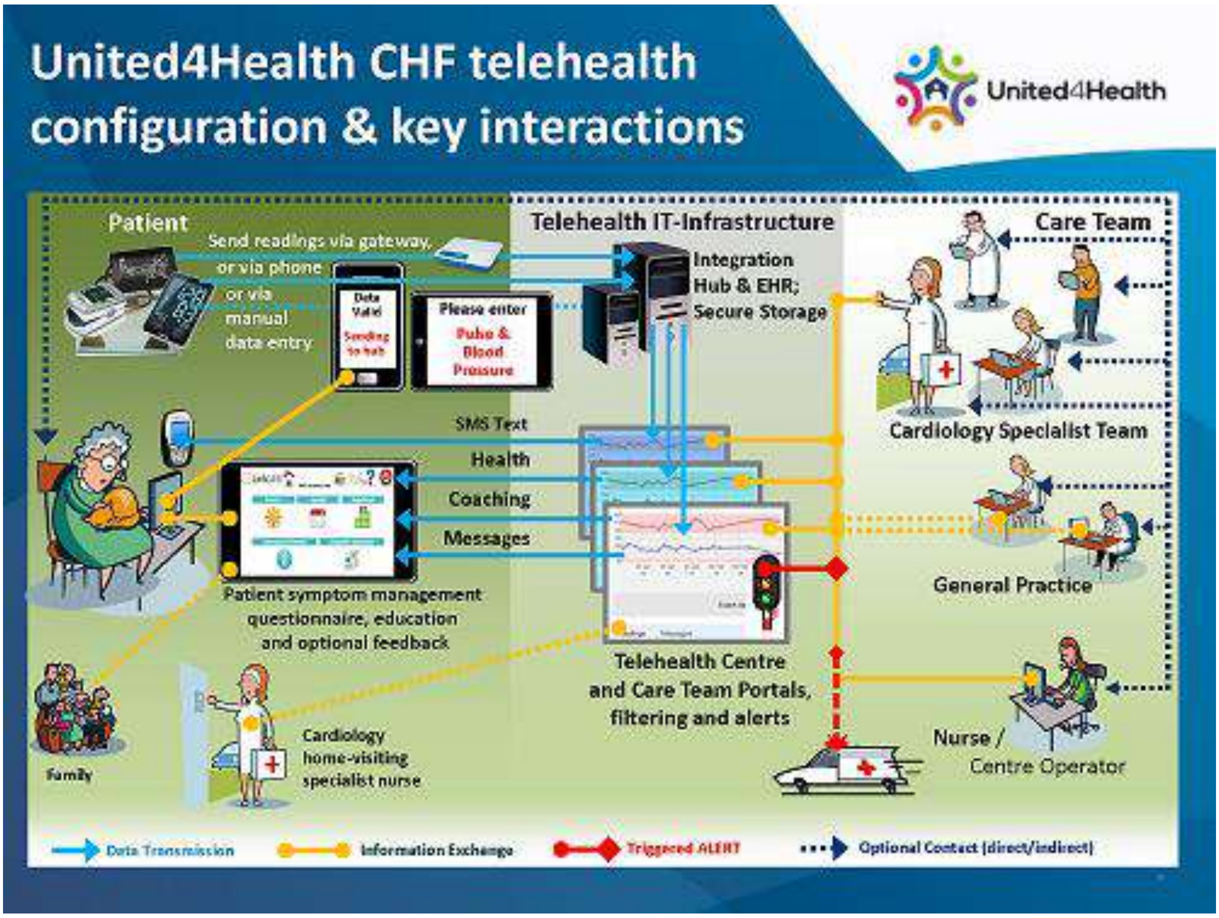


***Figure 18**. Telehealth service model for remote monitoring of HF.*

Actually, and with the growth of the HFU, a nurse dedicated to HF and/or a clinician checks these data from Monday to Friday (08.00 – 15.00h). This has been an important step forward as it allows for a much more personalised follow-up of patients, with the possibility of face-to-face consultations with both the nurse and the unit doctor. Recently, telemonitored patients have a telephone number attended by personnel from the HF unit, which allows them to quickly and efficiently resolve doubts that patients may have regarding their state of health and treatment, and which could otherwise lead to visits to the emergency department.

If the patient sends the transmission out of this schedule or the data are collected on holiday days or during the weekend, the call centre is responsible for checking them. This way, the actuation over alarms that require immediate attention in guaranteed, independently of the day of the week or the hour.

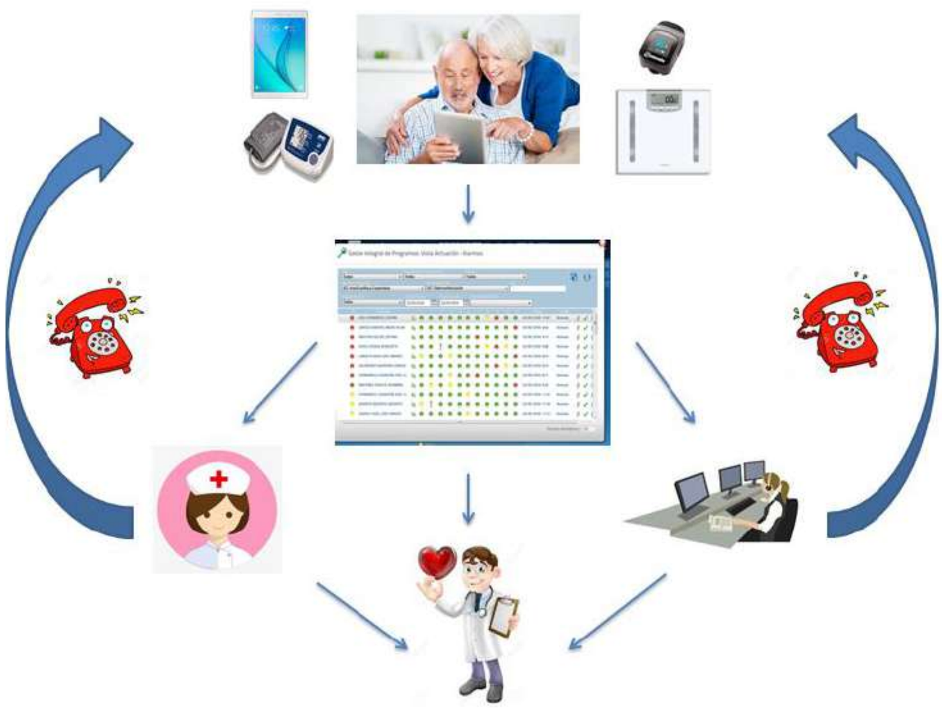


***Figure 19**. Current actuation protocol.*

In the case of clinical parameters exceed the normal range, the system's software detects the alert situations for the clinician to manage and, if required, take any necessary action. Should a decompensation be detected, the cardiologist can: 1. Adjust the dose of oral diuretics (the clinician informs the patient or relatives and prescribes the drug in the electronic service), 2. Activate APRNs to evaluate the patient and administer intravenous diuretics at home, 3. Derive the patients to the Day Hospital to administer intravenous drugs, 4. Schedule a hospital admission, 5. Derive the patient to his/her GP, 6. Send an ambulance.

The protocol indicates that the severe alarms must be considered first.

The final objective of this project was to allow patients with HF to manage their disease to adjust the choice and dose of medicines, promote treatment compliance, help professionals to detect early signs of deterioration and thus contribute to the sustainability of the health system.

Patients' recruitment usually takes place at hospital. A nurse dedicated to HF visits patients hospitalised in cardiology ward due to decompensated heart failure and carries out 2 main activities. Firstly, he develops an education process: explanation to the patient and family or caregiver the illness, its main symptoms, causes of decompensations, importance of treatment and general recommendations, allowing patient's empowerment. Secondly, he explains the telehealth programme and gives specific information (Annexes 6 and 7). If the patient is interested, the nurse shows the devices and how to use them. In fact, we have the same devices at hospital that are given to the patients at home, so a few tests are done to verify that the patient, family or caregiver understands the devices and knows how to use them. Should these requirements be fulfilled, documentation about HF and the programme are given, as well as the informed consent and the adherence agreement. A notification about the inclusion in this programme should appear in the discharge report.

Soon after discharge, the enterprise that gives technical support to this programme proceeds to the installations of the telemonitoring devices at the patient's home and he/she is included in the computer programme.

Initially, the programme used for the management of the data was the Customer Relationship Management (CRM) system (Annex 8) but it has been replaced by Osabide Global, the computing platform used by Osakidetza (Basque Health System) (Annex 9).

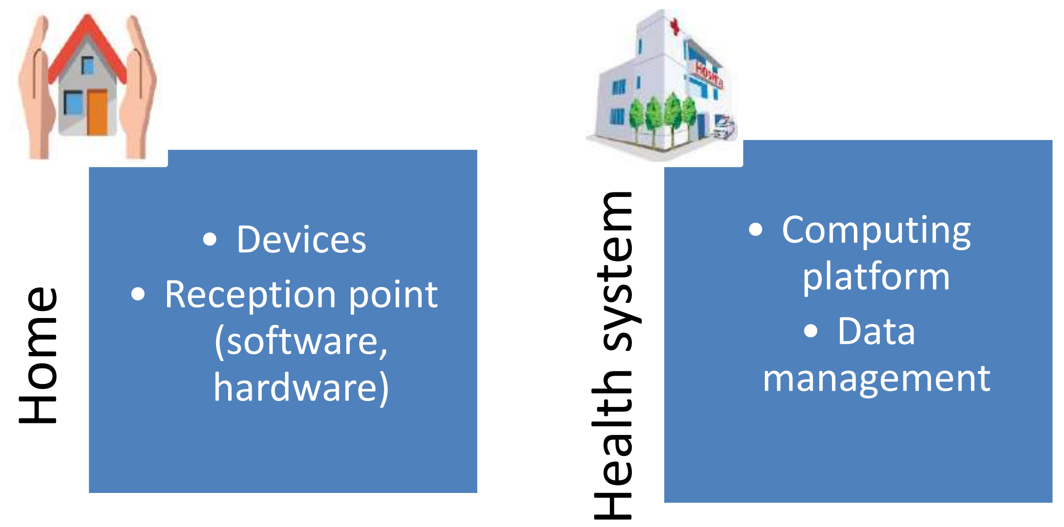


Figure 20. *Technological infrastructure for the development of telehealth.*

The current system includes a tablet (reception point) and accessory devices (tensiometer, pulsioximeter and digital scale) with a Bluetooth connection (figure 21).

***Figure 21**. Current devices.*

All the devices are mobile, and it allows patients to go on holidays or to other relatives' home and bring the system with them to continue with the monitoring.

Patients measure their blood pressure, oxygen saturation, heart rate and weigh daily and transmit all the data using the tablet. They also complete a simple questionnaire about their health status (see 3.4 Protocol for telemonitored patients).

In order to facilitate patient's follow-up, alarms with pre-established thresholds for each parameter (systolic blood pressure, diastolic blood pressure, heart rate and oxygen saturation) are installed. That is, if the digit exceeds or does not reach the maximum or minimum threshold, an alarm is generated (Annex 9). All alarms are customizable. There are also specific alarms for the questionnaire. For each incorrect question that the patient answers, one point is added. It should be outlined that weight alarms are generated by tendency rules. That is to say that one abnormal digit does not generate an alarm because it requires that the rise or descent in the weight will be maintained.

The frequency of the transmissions is variable and stablished by the cardiologist of the unit. At present, we recommend daily transmissions because the eventual detection of a decompensation improves. However, at the beginning of the study, transmissions were scarcer (1-3 days per week). Nevertheless, patients or relatives can send "extra" transmissions if they feel it appropriate (extreme numbers, malaise…) or are said to do that by the clinicians.

The follow-up (distance, face-to-face, phone calls) made by the doctor, nurse or call centre is registered in the computerised clinical history in a specific section ("HF evolution").

All in all, telemonitoring helps to improve global care of the patient with HF because it involves a team compound by cardiologists, nurses and general practitioners.

II. HYPOTHESIS AND OBJECTIVES

2.1. Why do this study

As explained before, telemonitoring started in our hospital with the participation in United 4 Health study [78]. The main aim of this project was to roll-out an integrated intervention using telemonitoring in HF patients to detect and respond to the organisational barriers and changes that occur when scaling up a pilot study. It also aimed to exploit and roll-out innovative telemedicine solutions previously validated as part of the European Renewing Health project in the treatment of patient with heart failure, allowing patients to manage their disease to adjust the choice and dose of medicines, promote treatment compliance, help professionals to detect early signs of deterioration and thus contribute to the sustainability of the health system.

Previous works in BUH have demonstrated the usefulness of structured protocols in the follow-up of patients after hospital discharge [77] and the reduction of rehospitalisations in telemonitored patients with HF compared with a control group [82]. In this last work, 100 telemonitored patients were analysed. After 1 year of follow-up, there was a 25% reduction in hospital admissions (n=35 in the intervention group -IG- vs 47 in the control group -CG-), a clinically relevant but not statistically significant difference (p 0.380). In this interval there were 7 deaths in the IG and 19 in the CG; this means a lower mortality in the IG 7.07% vs 19.39%, a significant decrease with p 0.009.

Nevertheless, efforts to develop a deterministic understanding of rehospitalisation have been difficult, as no specific patient or hospital factors have been shown to consistently predict 30-day readmission after hospitalisation for HF. A systematic review of 112 studies describing the association between traditional patient characteristics and readmission after hospitalisation for HF found that demographic characteristics, comorbid conditions, and markers of HF severity such as left ventricular ejection fraction and New York Heart Association class were associated with readmission in only a minority of cases [83]. Although higher levels of admission cardiac troponin and B-type natriuretic peptide were associated with readmission risk, these cardiac biomarkers were measured in fewer than one in six of the included studies. These results may relate to the fact that examined covariates have generally not included common conditions and syndromes found in the elderly. Social factors have also not been conclusively related to short-term readmission despite increased attention to this topic in recent years. This may be because the relationship between social factors and readmission is complex.

Taking all these facts into account, the HFU of BUH is developing new projects to improve the assistance care of patients with HF. Up to know, we were using telemonitoring with a codification system that generated alarms depending on the received values (see "Applied alerts for ambulatory patients admission" in section 3.4.1). However, these simple rules generated large number of false alerts being, hence, not trustworthy. The final aims of this work are: (i) asses the benefits of RPT (confirm the results of preliminary studies which suggested a trend in the reduction of hospital admissions and mortality), (ii) detect which parameters measured by telemonitoring best predict HF decompensations [64] and (iii) create predictive models [84] that will reduce false alerts and detect early decompensations that otherwise will lead to hospital admissions. So, we pretend that this model will (i) be generally applicable in HF patients, (ii) improve the clinical practice by developing an accurate system that detects the risk of decompensation, (iii) allow professionals to maintain an efficient and personalized support and follow-up of patient, and (iv), as explain before, reduce HF patients admission and readmission rate, which have a high economic impact.

In addition, we want to assess the impact of environmental factors on heart failure decompensations [85]. Up to now, several investigations about the impact of environmental factors in public health are already published, concluding that exposure to particulate matter (PM) air pollution contributes to cardiovascular morbidity and mortality [86] [87] and that urban air pollution and climate change are environmental risk factors of respiratory diseases [88] [89]. However, few studies in the field of HF have been carried out and none of them have determined the impact of a set of several environmental factors on HF decompensations, being the field where our work is focused on.

2.2. Work hypothesis

Our hypotheses are the following:

- Telemonitoring can support clinicians in their daily practice by enabling the supervision of ambulatory patients in real time.
- Machine learning applied to data collected from telemonitored patients can improve current clinical practice, reducing simple false alerts, and optimize clinicians time and reduce costs.

2.3. Objectives

Our main objectives are 1) to assess the benefits of RPT and 2) implement machine learning techniques using RTP to improve these results and determine the risk of decompensation of a HF patient in real time.

To achieve these goals, we will develop the following phases:

Asses the benefits of RPT

- Compare the number of HF-related hospitalisations during the study follow-up period in the intervention group (IG) with a control group (CG) in order to assess whether RPT achieves a reduction in HF-related hospitalisations.
- Compare mortality in the IG with a CG to assess whether follow up via RPT leads to a reduction in mortality.
- Describe the adherence to telemonitoring during the follow-up.
- Evaluate the association between the frequency of transmissions and HF decompensations that require hospital admissions.

- Evaluate patients' satisfaction with telemedicine.

Improve the results obtained with RPT using ML techniques:

- Determine which features or parameters measured by telemonitoring best predict a HF decompensation.

- Present predictive models to assess the risk of heart failure decompensations in real time using a telemedicine system.

- Calculate the impact of several environmental factors on HF decompensations.

III. METHODS

3.1. Study type

We carried out an interventional, controlled and non-randomised study, with a follow-up of 46 months (from May 2014 to February 2018) to assess the usefulness of RPT. Data were obtained retrospectively.

Data obtained in this first phase were used to train the predictive models and validate them through machine learning techniques.

3.2. Population and sample

Study population: the study included patients with decompensated heart failure that either had a recent hospital admission or were managed as an out-patient in our area of reference. The study period covers from May 2014 to February 2018 (46 months). Those patients who were admitted several times due to worsening heart failure during the study period were assessed as candidates in the first episode, which was considered the "index" admission, and the subsequent episodes as re-admissions. Inclusion and exclusion criterion are described below:

Inclusion criterion

- Age of at least 18 years.
- Diagnosis of heart failure confirmed by a cardiologist.
- Recent decompensation that required diuretic adjustment (both oral and intravenous).
- Capable of using telemonitoring technology.

Exclusion criterion

- Severe concomitant disease.

- Associated comorbidity with life-expectancy inferior to 1 year.
- Dementia or moderate to severe cognitive impairment.
- Inability to use the required technology or lack of disposition of relatives or caregivers to do the transmissions.
- Patients out of Bilbao-Basurto health organisation area.

In the study, patients were divided into two groups depending on whether they were incorporated into the RPT programme or not:

- RPT or intervention group (IG): patients with the ability to use RPT devices themselves or with the help of a caregiver, who accepted and consented to participate in the RPT programme and had the devices installed at home.
- Control group (CG): selected by drawing a random sample from the list of patients who met the inclusion criteria and did not participate in the RPT programme. The inclusion period is the same as for the RPT group.

The reasons why patients were not telemonitored were mainly personal or logistical. Some patients were not offered the possibility of telemonitoring or, if offered, rejected because they did not want to participate in the programme, had difficulty handling the devices or did not have the necessary family support, or belonged to another healthcare organization. It should be highlighted that at the beginning of the present study the hospital only had landline devices, so patients that did not had landline or expend long periods of time out of their usual homes were not included.

3.3. Study variables

Variable definition:

- Decompensated heart failure (DHF) is a sudden or progressive worsening of the signs and symptoms of heart failure, which typically includes difficulty breathing (dyspnoea), leg or feet swelling, and fatigue.
- Hospitalisation or hospital admission refers to placing in medical care in a hospital.
    - The emergency hospitalisation is a type of hospitalisation usually following an access to the Emergency Department and at the appearance of an acute health problem which requires medical and diagnostic-therapeutic cares which cannot be delayed.
    - The programmed admission is a type of hospitalisation for pathologies which do not require emergency procedures and therefore can be scheduled. Usually, they follow an examination which recommends that the patient should be hospitalised to continue with medical care.
- Hospital emergency stay: spell of care in the emergency department of a hospital where the patient is admitted for diagnosis and/or treatment but does not require hospital admission, being the length of stay in this department variable.
- Hospital admissions or emergency stays are classified into HF-related or non-HF related. This classification is done by a cardiologist after the review of the discharge report.
- Predictive modelling is a process that uses data mining and probability to forecast outcomes. Each model is made up of several predictors, which are variables that are likely to influence future results. Once data has been collected for relevant predictors, a statistical model is formulated.

3.3.1. Main result variables

The first step to predict the risk of decompensation is to telemonitor ambulatory patients. In order to know if this intervention is effective, we assessed the mean number of HF-related hospitalisations per patient in both groups involved in the study (IG and CG). We also calculated the crude and time-adjusted mortality in both groups. Another variable that we considered useful as a measure of the effectiveness of the intervention was the duration of readmissions (days of hospital stay) due to decompensated HF. Moreover, we assessed the relationship between transmission rate and detection of decompensations, as well as patient satisfaction included in the RPT group.

In the second part, we analysed these data together with the alerts used in the clinical practice of our hospital (see section 3.4) to evaluate the parameters that best predict decompensations in our group of telemonitored patients (using sensitivity and false alerts values). We also applied machine learning techniques to create predictive models in order to improve the results obtained so far. It is important to highlight that current medical practice uses sensitive alerts, that although they detect most of the decompensations due to their high sensitivity, they also have too many false alerts, being not trustworthy. Therefore, the main goal of this part of the study was the reduction of these false alerts.

Finally, we completed the analysis with environmental data (air components and meteorological parameters) to see if these variables influence HF decompensations.

3.3.2. Secondary variables

Baseline characteristics of the study population are collected at the inclusion in the telemonitoring programme.

- **Demographic characteristics**: gender (male, female), year of birth, toxic habits (non-smoker, current smoker, ex-smoker), origin (in-patient, out-patient)

- **Biological parameters**: heart rate (bpm), oxygen saturation (%), systolic blood pressure -SBP- (mm Hg), diastolic blood pressure -DBP- (mm Hg), weight (kg), height (cm), body mass index -BMI- (kg/m2)
- **Clinical questionnaire**: Well-being, current medication, new medication, diet and exercise, ankle state, walks, shortness of breath, bronchial secretions.
- **Blood analysis**: urea (mg/dl), creatinine (mg/dl), sodium (mEq/l), potassium (mEq/L), haemoglobin (g/dl).
- **Cardiomyopathy**: left ventricular ejection fraction -LVEF- (%), year of diagnosis of the cardiopathy, type of cardiopathy (ischemic, valvular heart disease, hypertensive, idiopathic, others), rhythm (sinus rhythm, atrial fibrillation), implanted device (yes/no and type: peacemaker, cardiac resynchronisation therapy -CRT-, implanted cardioverter defibrillator -ICD-)
- **Comorbidities**: peripheral vascular disease, cerebrovascular disease, Chronic obstructive pulmonary disease (COPD) and need of home oxygen supply, Diabetes Mellitus (DM), chronic kidney disease (CKD).
- **Indexes**: Barthel Index of Activities of Daily Living, Gijon scale of social and familiar evaluation, European Heart Failure Self-care Behaviour Scale (EHFScBS).
- **Heart failure decompensations** during the follow-up: number of HF decompensations treated with oral diuretic adjustments, intravenous diuretics, subcutaneous furosemide, or attended at hospital (emergency department or hospital admission) and duration of hospital admission if it occurred.

Environmental Data. This second sort of data is separated in two types of information:

- **Weather information**

Attribute	Unit
Air temperature	ºC
Humidity	%
Precipitation	mm=l/m^2

Irradiation	w/m^2

***Table 2**. List of attributes of the weather dataset and their unit.*

- **Air quality information**

Attribute	Unit
Carbon monoxide	µg/m3
Nitric oxide (NO)	µg/m3
Nitrogen Dioxide (NO2)	µg/m3
Nitrogen Oxides (NOX)	µg/m3
Tropospheric Ozone (O3)	µg/m3
Sulphur dioxide (SO2)	µg/m3
Particulate Matter 10 (PM10)	µg/m3
Benzene	µg/m3
Orthoxylene	µg/m3
Toluene	µg/m3

***Table 3**. List of attributes of the air quality dataset and their unit.*

Variables common to both groups are:

- **Follow-up time**: the duration of the study is 46 months. Follow-up time is considered until patients complete the study period, leave the RPT or die. In the case of patients who do not participate in the RPT, the follow-up ends the 28th February 2018 or when the patient dies.
- **Cause of end of follow-up**: Reason for end of follow-up (end of study, death, lack of adaptation to the study). If death, reason of it (HF-related, non-HF, sudden death, unknown).

Exclusive variables of the RPT group: number of transmissions made, satisfaction scales.

3.4. Protocol for telemonitored patients

In addition to the explanation in the section 1.7, the protocol for telemonitored patients include the following:

Patients transmit, via the devices installed at home, the following parameters: SBP, DBP, HR, O2sat and weight. They also send a questionnaire about the state of their health that consists of 8 questions (Table 4). In the current devices all the parameters are entered automatically (in the previous ones some parameters were entered automatically or manually).

Questions	Answers
Comparing with the previous 3 days, I feel:	Better/Worse/Same
Does my medication feel good?	Yes/no
In the last 3 days, have I taken any medication without the supervision of my doctor?	Yes/no
Am I following the diet and exercise recommendations given by my doctor and nurse?	Yes/no
In the last days, my ankles are:	Better/Worse/Same
Can I go for a walk like the days before?	Yes/no
Do I have a feeling of shortness of breath when I lie in bed?	Yes/no
Do I notice that I have started coughing or having phlegm?	Yes/no

Table 4. *Health questionnaire.*

3.4.1. Applied Alerts for Ambulatory Patients Admission

To capture the instances that will be used for the classifiers, the alerts used in current medical practice are the starting point. This section presents the different types of alerts that are used in our medical practice and their performance to select the optimal ones to be applied in our study.

- **Generic Alerts**

The following section describes the alerts implemented in our hospital. They are differentiated into “yellow” and “red” alerts, being these last ones more restrictive, and therefore, more critical.

- Simple Rules: The following tables present the generic rules and the alerts' thresholds based on each parameter individually. Anyway, these thresholds can be modified individually by the clinicians depending on the patients' characteristics. For example, if a patient's O2Sat values are always lower than 90, but the patient is stable, the O2Sat alerts are adapted. This study uses the adapted alerts.

Parameter to study	Threshold number	Type of alert
SBP	85 - 95	Yellow
	150 -180	Yellow
	<85	Red
	>180	Red
DPB	50 - 60	Yellow
	100 - 110	Yellow
	<50	Red
	>110	Red
HR	50 - 55	Yellow
	90 - 110	Yellow
	<50	Red
	>110	Red
O2Sat	90 - 94	Yellow
	<90	Red

Table 5. *Generic rules of each parameter individually.*

- Weight tendency: Besides simple rules, the programme also checks the tendency of weight values in order to trigger an alarm (Table 6).

Parameter to study	Time period	Minimum (kg)	Maximum (kg)	Type of Alert
Weight change	5 days	1	2	Yellow
	3 days	1	2.5	Red
	5 days	2	2.5	Red

***Table 6**: Weight Alerts.*

- Questionnaire: The programme creates alarms based on the answers from the questionnaire: if one or more answers are "worse", the questionnaire alert triggers (see table 4).

3.5. Data acquisition

Clinical data (baseline and demographic characteristics) come from computerised clinical histories and were collected by two cardiologists and two nurses of the HFU at the inclusion in the telemonitoring programme. Blood test parameters were gathered from the first blood test available. Patients' admissions (emergency admissions, hospital admissions and home care interventions due to HF decompensations) were collected from computerised clinical histories once the study was closed. Ambulatory patient monitored data (blood pressure, heart rate, O2 saturation, weight and questionnaire) come from the computing programme and are provided by the computer experts. All data are kept in a computerised database in the Basurto university hospital.

The Basque Agency of Meteorology (Euskalmet) enables the possibility to access weather data recorded since 2003, from the Open Data Euskadi website (Basque Government, 2009). This information is collected every ten minutes by each station of Euskalmet distributed in the Basque Country. Among all the different stations distributed in the three provinces of the Basque Country, for this study the data from the one located in Deusto (Bilbao) was selected since it is the closest one to the patients of the study.

The Open Data Euskadi website recovers information about the air quality (Basque Government, 2017).

3.6. Statistical analysis

The sample is described for all variables by summary measures after checking for normality when adequate. First, a descriptive analysis for continuous variables is done and these variables are expressed as mean (standard deviation [SD]) or median [interquartile range], according to whether distribution is normal or not) while categorical variables are expressed as percentages. Baseline characteristics between groups are compared with chi-square test for categorical variables and Student t test / analysis of variance (ANOVA) for continuous variables. In variables with no normal distributions or no homogeneous variances, a nonparametric test (Kruskal-Wallis or Mann-Whitney) is used. Univariate and multivariate analysis is performed using logistic regression (backward stepwise method) and survival analysis is done through Cox proportional hazards regression (backward stepwise method). Level of significance is set in 5% and confidence intervals are calculated at 95%.

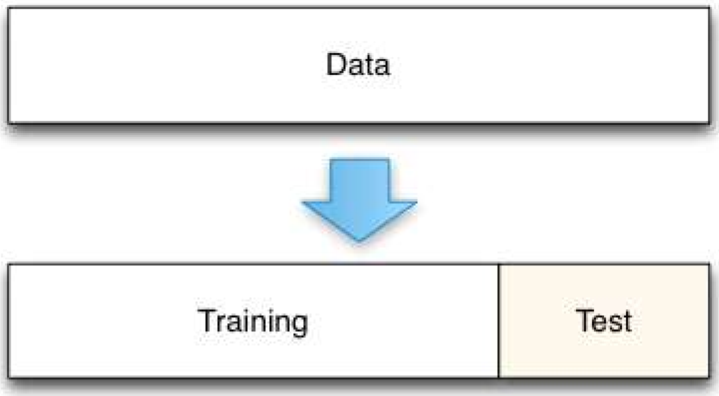
Data are analysed with SPSS (Statistical Package for Social Sciences) programme of IBM for Windows v23, R Statistics v3.6.2 and STATA v14.2. I also benefited from the collaboration of Vicomtech, an applied research centre located in San Sebastian and specialised in Advanced Interaction technologies, Computer Vision, Data Analytics, Computer Graphics and Language Technologies.

3.6.1. Usage of artificial intelligence (machine learning techniques) to determine which parameters measured by telemonitoring best predict a HF decompensation and create predictive models.

The methodology applied for the generation of the predictive models is presented [64]: (i) training and testing dataset construction, (ii) application of alerts implemented in current clinical setting, (iii) selection of the alerts for the study, (iv) generation of the dataset to apply the machine learning classifiers, and (v) the application and comparison of different classifiers.

1. Splitting Training and Testing Datasets

To build and test a predictive model, the clinical data is divided in training and testing datasets. The training dataset is used to develop the model, and once it is finished, the resulting model is tested with the testing dataset. This way, the overfitting is prevented, and it is possible to check whether the created model will generalise well.



2. Application of alerts implemented in current clinical setting

To capture the instances that will be used for the classifiers, the alerts used in current medical practice are the starting point (see section 3.4.1). This way, the resulting dataset is more balanced, since the number of monitoring data that leads into decompensation is very limited. Here are the different types of alerts used in our study and their performance to select the optimal ones.

- Generic Alerts: simple rules (SBP, DBP, HR, O2Sat), weight tendency and questionnaire (well-being, medication, diet and exercise, symptoms of congestion).

- Implemented Alerts based on Moving Average (MA). Weight associated alerts have been improved, and hence, tendency rules for weight have been substituted for a more advanced method, based on moving average. Moving Average Convergence Divergence (MACD) algorithm calculates the difference between the average value taken from two windows and generates an alert when this difference exceeds a pre-specified threshold.

3. Selection of Alerts for Instances Generation.

To obtain the right dataset of instances, the best combination of alerts is sought. First, a filter is applied to discard the days in which HF decompensations have not happened. Once the alerts are selected, when at least one of these alerts is triggered, the patient data of that day is used to build the dataset for machine learning model building.

4. Generation of the dataset to apply the machine learning classifiers

The applied attributes come from (i) the telemonitoring dataset, (ii) the baseline dataset and (iii) the readmission dataset.

- Telemonitoring dataset: the value of SBP, DBP, HR, O2Sat attributes, and, in the case of the weight, the values of the MA algorithm.

- ✓ The number of consecutive alerts for each type of alert: Yellow alerts (the number of yellow alerts that have been triggered in the previous consecutive days related to SBP, DBP, HR and O2Sat -4 attributes-), red alerts (the number of red alerts that have been triggered in the previous consecutive days related to SBP, DBP, HR and O2Sat -4 attributes-), MA (the number of alerts that have been triggered in the previous consecutive days for the MA algorithm -1 attribute-)

✓ Questionnaires: The answers of the 8 questions of the questionnaire (8 attributes)

- Baseline dataset (Baseline information of the patients)

- Decompensations dataset (1 attribute): HF decompensations include those episodes treated at home (oral treatment adjustment, administration of iv diuretic or sc furosemide pumps), hospital admissions and emergency visits in that interval.

5. Applied Machine Learning Classifiers

After applying the filters mentioned in the previous section, the following classifiers are used:

- Naïve Bayes: Naive Bayes methods follow the "naive" assumption that the components of the feature vectors are statistically independent. On one hand, the Gaussian Naive Bayes assumes that the likelihood follows a Gaussian distribution, where the mean and standard deviation of each feature is estimated from the sample. On the other hand, the Bernoulli Naive Bayes assumes Bernoulli's distribution in the parameters.

- Decision Trees (DT) are built by recursive partitioning of the data space using a quantitative criterion followed by a pruning process to reduce overfitting. Tree leaves correspond to the probabilistic assignment of data samples to classes. At each node, the algorithm selects the feature that best splits the samples according to the normalized information gain.

- Random Forest is an ensemble classifier consisting of multiple decision trees trained using randomly selected feature subspaces. This method builds multiple decision trees at training phase. A pruning process is applied to reduce both tree complexity and training data overfitting. Each tree gives a prediction (votes) and the class having most votes over all the trees of the forest will be selected (majority voting).

- Support Vector Machines (SVM) look for the set of support vectors that allow to build the optimal discriminating surface in the sense of providing the greatest margin between classes.

- Neural Network. Multilayer Perceptron (MLP) is a neural network that consists of at least three layers of nodes, namely: (i) an input layer, ii) one or more hidden layers and iii) an output layer. The input layer consists of a set of neurons that represents input features. The hidden layer transforms the outputs of the input layer by means of nonlinear activation functions. The output layer collects the values of the hidden layer and builds the output value.

- Class balancing. In this work, like in many other supervised classification problems, imbalanced class distribution leads to important performance evaluation issues and problems to achieve desired results. The underlying problem with imbalanced datasets is that classification algorithms are often biased towards the majority class and hence, there is a higher misclassification rate of the minority class instances. Although there are several methods that can be used to tackle the class imbalance problem, we have followed an oversampling approach. We have used the Synthetic Minority Oversampling Technique (SMOTE).

VALIDATION METHOD

Once the model has been created (in the training set) and tested (in the testing set), it is validated how it works in the real world.

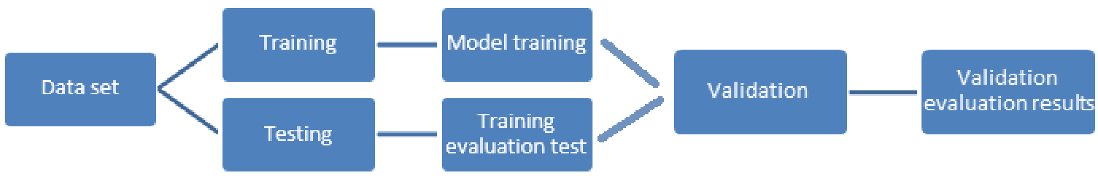


Figure 22. *Sequence of creating a model through artificial intelligence – machine learning techniques.*

Although there are many ways to assess the generalization ability of a machine learning model, such as cross-validation, time-series can be problematic for such validation techniques, as there is an ordered timeline factor to be considered. Henceforth, we use cross validation on a rolling basis [36], as it is explained in Figure 23.

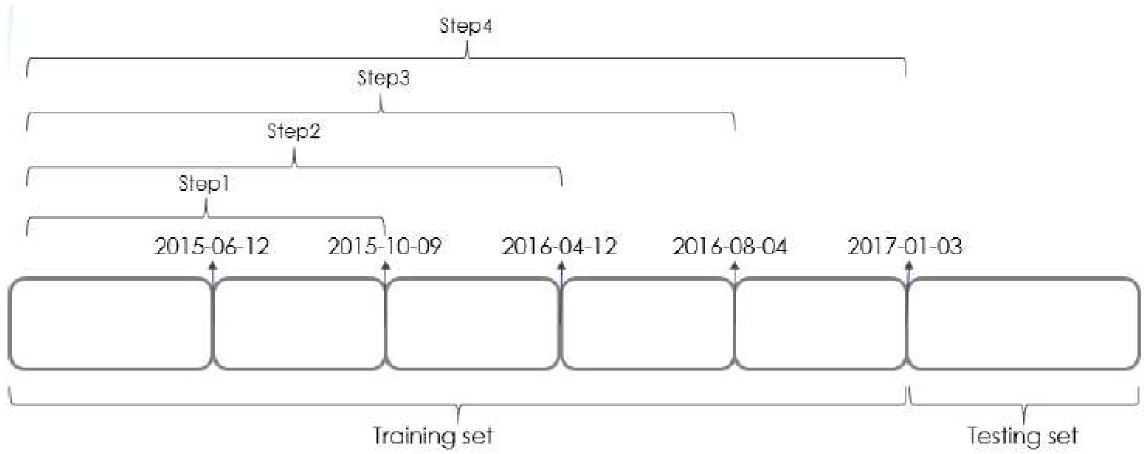


Figure 23. *Cross Validation on a Rolling basis applied in the study.*

The training set is separated in the five sets shown in the Figure 23. Each set corresponds to a period (dates are written on the top) with a pre-specified number of decompensations. The splits are not exactly equitable, since all the predecessors of a decompensation must fit within the same block. In Step 1, the classifier is trained in the first block and tested in the next block getting the score for Step 1. Following, in Step 2, the classifier is trained in Step 1, and tested in the new one, getting the score for Step 2. Repeating the same with Step 3 and Step 4 we get four scores. It is supposed that the first step is the more unstable, as there is less data to train the classifiers, but, while the training set increase, it is believed that the results will become stable, and the score will converge to its real testing value.

The score value used to test the classifiers is the Area Under the ROC Curve (AUC), a measure that evaluates the balance between sensitivity and specificity and that gets an accurate estimation even in moderately imbalanced datasets, which is our case. The AUC value is used to check how well the classifiers perform, and consequently select the best one. To test the global predictive model, we use Se and FA/pt-y which are the ones used in the literature.

CLASSIFIERS COMPARISON

There are many methods of Machine Learning in literature, but some get better results in certain datasets. This is the reason why we study the predictive capacity of some (7) of these contrasted Machine Learning methods to determine which method is the best suited to our database.

In Figure 24, the AUC values of each classifier are illustrated for each of the steps defined in the rolling cross validation method. The points are the mean of the AUCs achieved in each case, with its standard deviation drawn with whiskers. High standard deviation value indicates that the classifier is less generalizable, while low standard deviation hints a stable classifier.

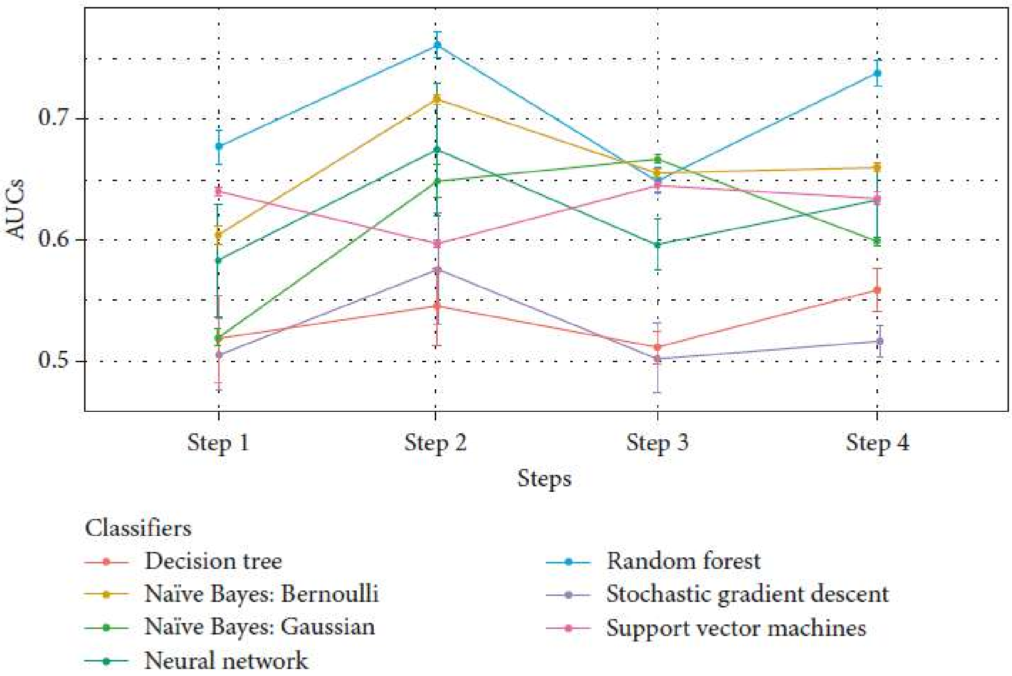


Figure 24*: AUC values of the classifiers (colours) depending on the steps (axis x)*

It is expected that the AUCs values converge as the number of steps grow, although with the available dataset there is a trend of significative improvement in the second step, and a worsening trend in the third one. However, Figure 24 clearly shows that the best classifiers are Naïve Bayes (NB) with Bernoulli method and the Random Forest (RF). NB classifier has lower AUC value than RF, but the standard derivation is almost negligible, and the trend throw the steps is more stable.

Hence, it is expected that its performance will not vary significantly over time with new data. RF gets the best scores, but it is unstable and it has high standard derivations. Henceforth, NB with Bernoulli method and RF classifiers are selected to validate the models. Decision Tree and SGD classifiers give the lowest results. The other three classifiers (NB with Gaussian distribution, SVM and MLP classifiers) perform better, but not as good as the selected two.

Thus, we will use NB with Bernoulli method and RF classifiers to create predictive models that improve the results so far obtained, preserving the capacity for detect decompensations of ambulatory patients but significantly reducing the false alerts.

3.6.2. Impact of environmental factors on HF decompensations

This study makes use of two different sets of data: one related to the number of hospital admissions, and the other one related to the environmental factors to determine whether they have an impact on HF related decompensations [85].

Hospital Admissions

In this section, we use hospital admissions to study HF decompensations. Therefore, the first dataset compiles the daily hospitalisations related to HF in the public hospital OSI Bilbao-Basurto (Osakidetza), located in the Basque Country (Spain). The usable admissions dataset is from January of 2012 to August of 2017. It should be noted that in this section the study time has been extended since computerized data is available since 2012 and we believe that a greater “n” and follow-up will provide more reliable results. A total number of 8338 hospitalisations of 5343 different patients are available in this dataset, with a mean of 4.02 admissions per day.

We have relied on discharge coding, being HF in the principal position (highest degree of accuracy), withdrawing cases with codes related to respiratory infections.

Environmental Data

This environmental dataset is separated in weather information and air quality information. This information was selected due to their demonstrated impact on HF decompensations in previous studies ([90] Burnett et al., 1997; [91] Das et al., 2014; [92] Levin et al., 2018; [93] Morris et al., 1995; [94] Stewart et al., 2002).

- Weather

The Basque Agency of Meteorology (Euskalmet) enables the possibility to access weather data recorded since 2003, from the Open Data Euskadi website ([95] Basque Government, 2009). This information is collected every ten minutes by each station of Euskalmet distributed in Euskadi. We selected the station located in Deusto (Bilbao) since it is the closest one to our reference area (2 km from the station to the OSI Bilbao-Basurto Hospital. Location of the meteorological station is high 3m, longitude -2.96º, latitude 43.3º).

The pre-processing of this dataset consisted in three steps.

First, the selection of the attributes for obtaining a complete dataset was done, since not all the variables were measured in all the years between 2012 and 2017 (some of them started to be measured later). In order to obtain a complete dataset, only the attributes measured in those years were considered. Thus, the parameters of air temperature, humidity, precipitation, and irradiation are the ones used for this experiment.

Second, each parameter was grouped per day (data was recorded every 10 minutes), calculating their mean value. In addition, as the literature suggests ([91] Das et al., 2014), in case of temperature, the minimum and maximum values for each day were also added to the dataset.

Finally, an imputation of missing values (0.33% of the data) was done, which may be caused by technical problems in the station. The imputation by Structural Model & Kalman Smoothing was used for this, as it is the one that best performs for time series with a strong seasonality ([96] Moritz and Bartz-Beielstein, 2017). In summary, the dataset corresponding to weather consists of humidity (%), precipitation (l/m2), irradiation (w/m2), mean temperature (°C), minimum temperature (°C), and maximum temperature (°C).

- Air Quality

The Open Data Euskadi website also gives the opportunity to recover information about the air quality ([97] Basque Government, 2017).

For the pre-processing part of this dataset, the missing values that corresponded to an 11% of the data were imputed using the same method as for the previous dataset, the imputation by Structural Model & Kalman Smoothing ([96] Moritz and Bartz-Beielstein, 2017).

Grouping

Each attribute of the study was grouped by weeks: on the one hand, admissions related data is grouped by the total number of admissions in each week. On the other hand, the mean, maximum, minimum and the standard deviation of each week are used to group the environmental attributes.

Once the data was grouped by weeks, two different studies were done: (i) a univariate regression to determine whether the admissions may influence future hospitalisations prediction, and (ii) a multivariate regression to determine the impact of environmental factors on admission rates.

Univariate Regression

In order to study the effect of admissions in future hospitalisations rate, first time series decomposition is performed to later choose the best Auto Regressive Integrated Moving Average (ARIMA) model.

- Decomposition

The hospitalisation rate may vary on time depending on several factors. In order to determine how these variations behave, a decomposition process was conducted. This is a mathematical procedure which transforms a time series into three components, each of them depicting one of the underlying categories of patterns ([98] Jebb and Tay, 2017).

- Univariate ARIMA

Once the decomposition was done, the hospitalisations dataset was analysed as time series to determine the impact of admissions on following week's hospitalisations. For that, the ARIMA model was implemented.

ARIMA stands for auto-regressive integrated moving average and it is a class of statistical models for analysing and forecasting time series data ([99] Brownlee, 2017).

Multivariate Regression

The next step was to analyse the regression taking also into account the environmental information. First of all, we calculated the correlations between all environmental factors and admission rates. This way we could select the most significant factors for the experiment. Following, the multivariate ARIMA was implemented to determine their impact all together.

- Selection of Attributes

As mentioned before, the variables were grouped by weeks. The correlation was estimated using the non-parametric test of Kendall, which measures the strength of dependence between two numeric variables ([100] Rui and Vera, 2017) and it is one of the most used tests for this type of non-parametric data. In addition, this analysis was done relating all the attributes with the number of admissions of the following week.

Note that, since the mean, maximum and minimum values of the environmental factors were closely related, only the one with the highest correlation was considered per attribute.

- Multivariate ARIMA

After the study of the univariate ARIMA and the selection of the most correlated environmental attributes, a multivariate ARIMA model was carried out.

For that, first we employed all attributes and tested the Akaike Information Criterion (AIC) value (this criterion states that the one that presents the minimum AIC value is considered the optimal ([101] Akaike, 1974)). If the p-value of an attribute was too high, this value was discarded, and the AIC value was checked again. If the value improved (AIC decreased), we kept that value out of our model. Otherwise we put it back. This process was done iteratively until AIC did not decrease anymore.

3.7. Ethical and Legal Issues

Ethical approval for the study was gained from the ethical committee of investigation of our hospital (Annex 11). The project was developed following the World Medical Association Declaration of Helsinki in 1964 about the recommendations guiding medical doctors in biomedical research involving human subjects and its later reviews by the World Medical Assembly in Tokyo, Japan in 1975, in Venice, Italy in 1983, and in Hong Kong in 1989. The project also followed the order SCO/256/2007, 5th of February, that stablishes the principles and guidelines for Good Clinical Practices and the Convention about human rights and biomedicine, conducted in Oviedo 4th April 1997 and the following updates.

The investigators of this study declare that all clinical data from people participating in the project are separated from the personal identification data, thus guaranteeing the anonymity of the patient, as specified in the Spanish Personal Data Protection Law (15/1999 Organic Law of 13th December), Royal Decree 1720/2007 of 21st December approving the Development Regulation of the Organic Law 15/1999 to Law 41/2002 of 14th November (regulatory law of patient autonomy and rights and obligations regarding information and clinical documentation) as well as Law 3/2001 of 28th May (regulatory law of informed consent and patients' medical records), Law 3/2005 of 7th March, of modification of Law 3/2011 and Decree 29/2009 of 5th February which regulates access to electronic health records.

Clinical data of the patients have been collected by the researcher in the Data Collection Notebook (DCN) specific to the study. Each DCN is encrypted, protecting the patient's identity. Only the research team and the health authorities, which have the duty to keep confidential, have access to all the data collected for the study. Only information that cannot be identified can be transmitted to third parties. If information is transmitted to countries outside the European Union, they must comply at least the applicable requirements to data protection in Europe. Once the study is finished, the data collected for research purposes will be anonymised for future use.

IV. RESULTS

4.1. Population included in the study

In the intervention group 245 patients were enrolled from May 2014 until February 2018. Of these 245 patients, five of them were excluded because they did not perform any transmission (consent revocation, no device installation) or death in the first 30 days of follow-up. So, for the present study, the dataset contains a cohort of **240 HF patients**. There is an average follow-up of 13.44 ± 8.65 months. Note that the follow-up is not homogeneous in this group of patients, since the time they have been in the telemonitoring programme has been different, depending on the clinical evolution.

Below we show the origin of the patients included in the IG, as well as the causes of their departure from the programme.

Baseline Characteristics	Percentage (n)
Origin	
In-patient	89.58% (215)
Out-patient	10.42% (25)
Cause of end of follow-up	
Death	21.23% (38)
Clinical stability	72.07% (129)
Patient's wish	1.12% (2)
Clinical impairment	4.46% (8)
Difficulties with technology	1.12% (2)

Table 7*. Origin of the patients included in the IG, as well as the cause of their departure from the programme.*

The control group is formed by **315 patients** randomly selected from the database that includes all patients who have presented a HF admission in Cardiology or Internal Medicine in our hospital in that period. The end of follow-up is determined by the patient's death or the end of the study period (February 28, 2018). The average follow-up in this group is 21.63 ± 14.58 months.

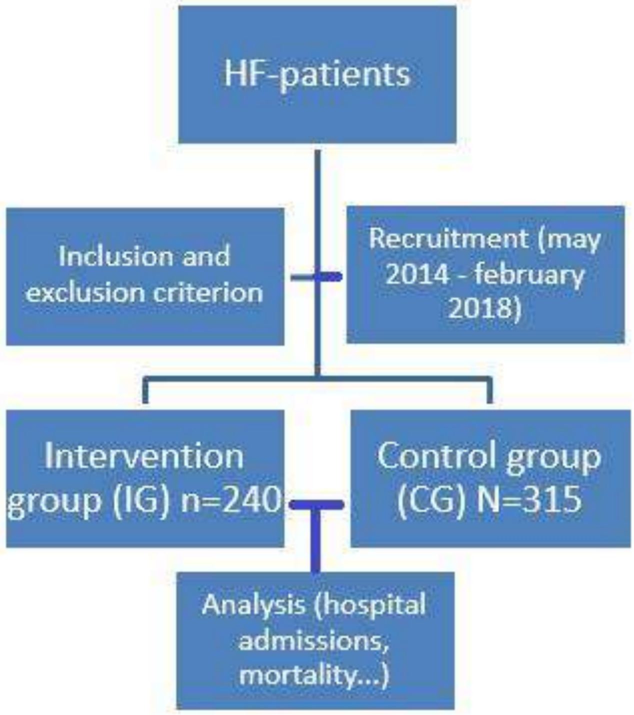


***Figure 25**. General design of the study*

4.1.1. Descriptive analysis of the study population: initial comparison of groups

Table 8 describes the baseline characteristics of the study population. 60.8% of the patients of the IG group are men, with a mean age of 76.34 years (SD 11.35). The number of years of evolution of HF is 5.8 (SD 7.04), the most frequent cardiopathy is ischemic, with a mean LVEF of 42.26% (SD 15.17) and the presence of comorbidities is high, being the most frequent chronic type 2 diabetes mellitus (T2DM), kidney disease and COPD.

If we are talking about the CG, 51.1% of the patients are men, with a mean age of 80.97 years (SD 9.79). The number of years of evolution of HF is 3.65 (SD 1.89), the most frequent cardiopathies are ischemic and hypertensive (with a similar distribution), with a mean LVEF of 51.54% (SD 14.43) and the presence of comorbidities is quite high.

Baseline Characteristics	Intervention group	Control group	p
Age	76.34 (11.35)	80.97 (9.79)	<0.001
<65	16.87% (40)	8.57% (27)	
65-75	19.75% (47)	12.06% (38)	
>75	63.38% (153)	79.37% (250)	
Sex	60.8% men (146)	51.1% men (161)	0.025
Height	161.93 (9.88)	160.1 (9.41)	0.781
Weight	72.44 (15.93)	72.17 (15.81)	0.848
Body mass index (BMI)	27.63 (5.59)	28.13 (5.34)	0.321
Smoker			0.683
Current	12.5% (30)	11.8% (37)	
Never	57.5% (138)	59.2% (186)	
Ex-smoker	30% (72)	29% (92)	
Cardiopathy			
LVEF (%)	42.26 (15.17)	51.54 (14.43)	<0.001
Normal (>55%)	24.70% (60)	57.78% (182)	
Mild disfunction	18.93% (45)	12.39% (39)	
Moderate disfunction	25.51% (61)	15.23% (48)	
Severe disfunction	30.86% (74)	14.60% (46)	
Number of years with HF	5.8 (2.24)	3.65 (1.89)	<0.001
Type of cardiopathy			<0.001
Ischemic	33.1% (79)	29.5% (95)	
Valvular	19.2% (46)	21.9% (69)	
Hypertensive	13% (31)	28.4% (90)	
Idiopathic	19.6% (47)	5.6% (17)	
Others	15.1% (37)	14.6% (44)	
Rhythm			0.0789
Sinus rhythm	37.2% (89)	35.9% (113)	
Atrial fibrillation or atrial flutter	62.8% (151)	64.1% (202)	
Device			<0.001
No	74.9% (180)	86% (271)	
Pacemaker	11.7% (28)	11.5% (36)	

ICD	4.2% (10)	1.9% (6)	
CRT	2.9% (7)	0.3% (1)	
ICD-CRT	6.3% (15)	0.3% (1)	
Comorbidities			
Peripheral vascular disease	11.7% (28)	10.5% (33)	0.683
Cerebrovascular disease	18.3% (44)	21.6% (68)	0.393
Chronic obstructive pulmonary disease (COPD)	30.4% (73)	24.8% (78)	0.149
Need of home oxygen supply	2.9% (7)	1% (3)	0.110
Diabetes mellitus	40.8% (98)	28.9% (91)	0.004
Chronic kidney disease (CKD)	37.5% (90)	27.6% (87)	0.017
Blood analysis			
Urea (mg/dl)	73.00 (36.92)	64.61 (38.79)	0.010
Creatinine (mg/dl)	1.29 (0.50)	1.31 (0.73)	0.756
Sodium (mEq/l)	140.10 (4.09)	138.12 (5.40)	<0.001
Potassium (g/dl)	4.26 (0.74)	4.36 (0.61)	0.097
Haemoglobin (g/dl)	12.50 (1.92)	12.32 (2.28)	0.345
Scales *			
Barthel	83.29 (14.16)	68.92 (27.23)	<0.001
Gijón	7.39 (2.33)	7.62 (2.31)	0.401
European Heart Failure Self-care Behaviour Scale (EHFScBS)	27.91 (8.64)	28.74 (9.79)	0.555

***Table 8**. Baseline characteristics of the study population. * Barthel Scale: 214 patients in IG, 151 in CG; Gijón Scale: 210 patients in IG; 115 patients in CG; EHFScBS Scale: 195 patients in IG, 50 in CG.*

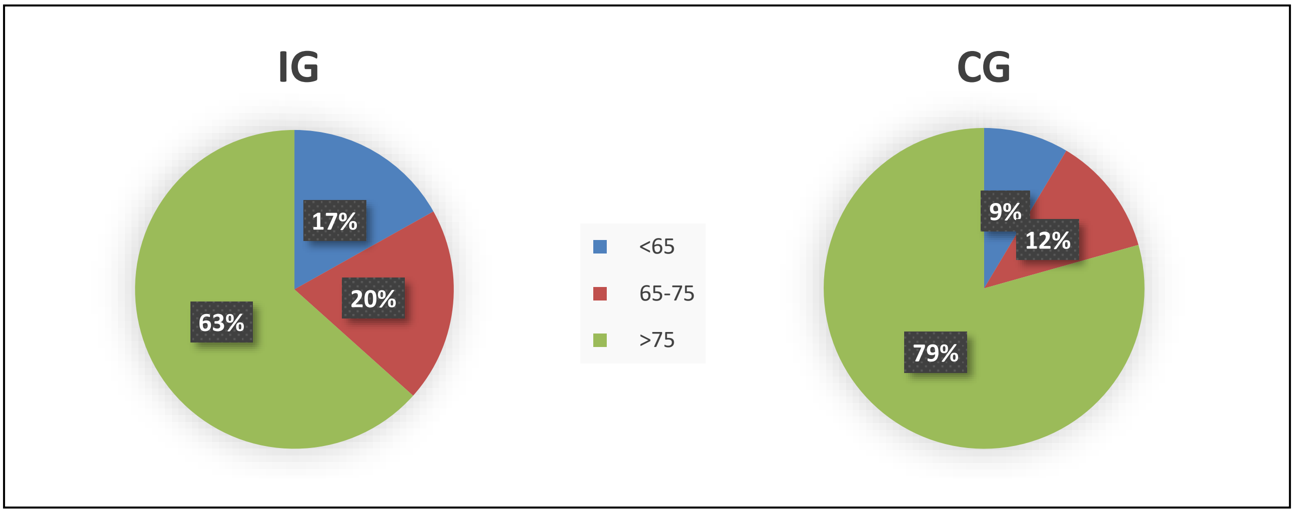


Figure 26. *Age distribution of the population sample (intervention group and control group)*

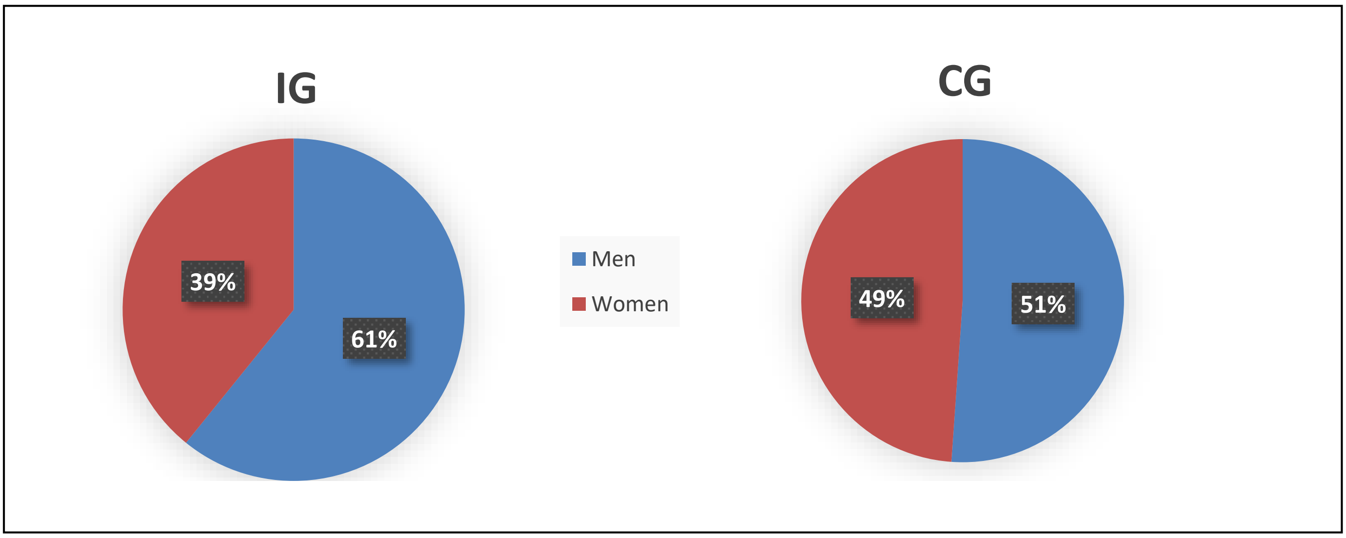


Figure 27*. Sex distribution of the population sample.*

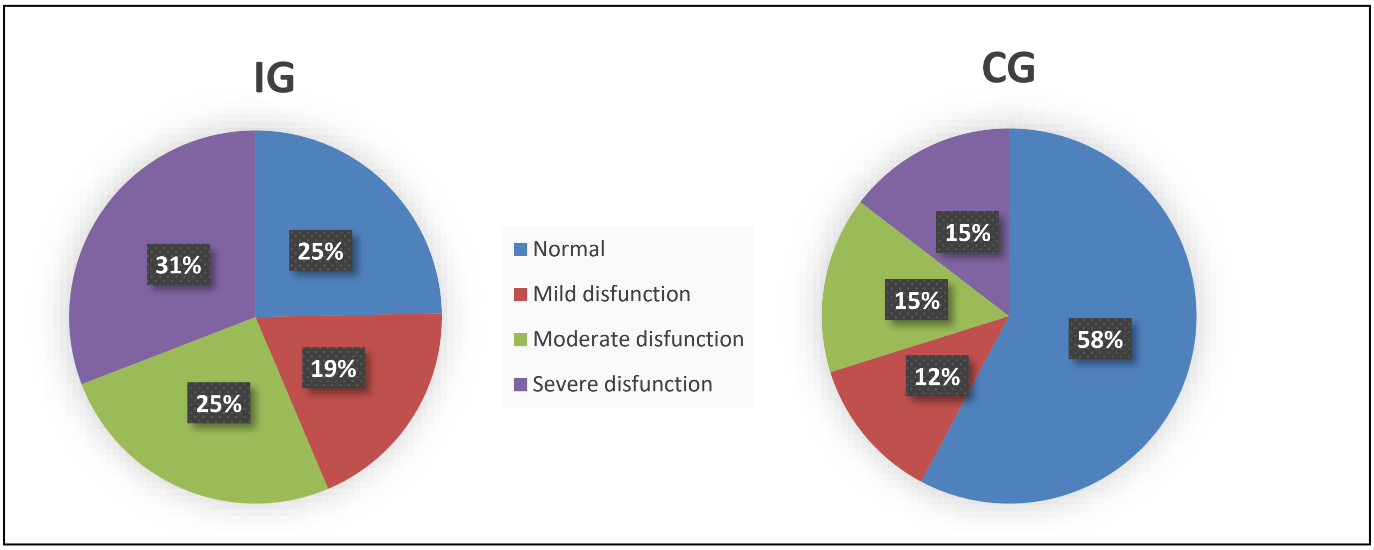


Figure 28. *LVEF distribution of the population sample.*

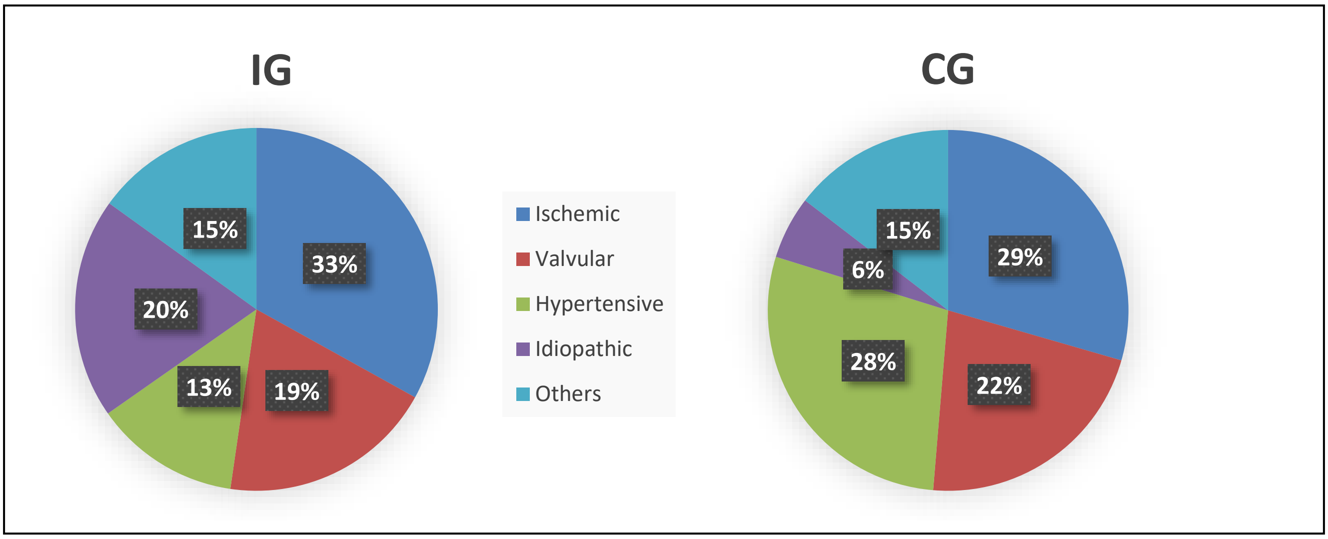


Figure 29. *Type of cardiopathy of the population sample.*

The profile of the patient admitted due to worsening HF in the cardiology service of our hospital is reflected in this study. Gender distribution indicates that most women have normal or mildly depressed LVEF, along with non-ischemic aetiology. Conversely, men have depressed LVEF associated with ischemic aetiology. Because HF is the final stage of most heart diseases, they are elderly patients with associated comorbidities, on average patients had 2.35 (SD 1.19) comorbidities excluding HF, leading to a mild to moderate degree of dependency.

Type of cardiopathy	Sex	
	Man (%)	Woman (%)
Ischemic	45.9%	12.9%
Valvular	13.0%	29.0%
Hypertensive	8.2%	20.4%
Idiopathic	21.9%	16.1%
Others	11.0%	21.6%
	100%	100%

***Table 9**. Contingency table with the distribution of the type of cardiopathy according to sex in IG.*

LVEF (%)	Sex	
	Man (%)	Woman (%)
Normal	13.7%	42.6%
Mild disfunction	16.4%	22.3%
Moderate disfunction	30.8%	17%
Severe disfunction	39.1%	18.1%
	100%	100%

***Table 10**. Contingency table with the distribution of LVEF according to sex in IG.*

During the 46 months of follow-up, 179 patients were discharged from the telemonitoring programme (the reasons were death, clinical stability, patient's wish, clinical impairment, difficulties with technology – see table 7-) while 66 continue at the end of this study.

There are some differences between the populations in each group that are worth discussing.

Age: The mean age of the IG is 76.34 (SD 11.35) vs 80.97 (SD 9.79) of the CG, p=0.001, implying that the IG is significantly younger.

LVEF: The mean LVEF in the IG is 42.26 (SD 15.17) vs 51.54 (SD 14.43) in the CG, p=0.001. If we group according to the classification indicated in HF guidelines, 75.30% of the patients of the IG have reduced FEVI, compared to 42.22% of the CG.

Years of evolution since the first episode of HF: There are significant differences in the evolution time of heart disease: the mean years of evolution of HF in the IG is 5.8 (SD 2.24) vs 3.65 (SD 1.89) in the CG (p <0.001).

Comorbidities: The number of comorbidities is high in both groups, although it is higher in the IG. In this group there is a higher prevalence of COPD patients (30.4% vs 24.8%, p=0.149), as well as T2DM (40.8% vs 28.9% with p=0.004) and CKD (37.5% vs 27.6% with p=0.017).

Scales: The IG has a mean Barthel scale value of 83.29 (SD 14.16) versus 68.92 (SD 27.23), this difference being statistically significant and implying that the CG has less autonomy or a greater degree of dependence. It should be noted that the Barthel scale is recorded in 89.17% of patients in the RPT group, but only in 48.71% of patients in the CG. There are no differences in the degree of self-care assessed by the EHFScBS scale or in the result of the Gijón scale.

4.1.2. Population recruitment to the telemonitoring programme

At the beginning of the study, the incorporation of patients into the programme was slow (we remind the reader that it started within the U4H project). After this initial period, the inclusion criteria became more flexible, so the number of patients grew significantly. Similarly, stable patients were discharged from the programme (without episodes of decompensation in recent months and with acquisition of knowledge about self-care).

The following figure shows the number of incorporations and discharges during the follow-up.

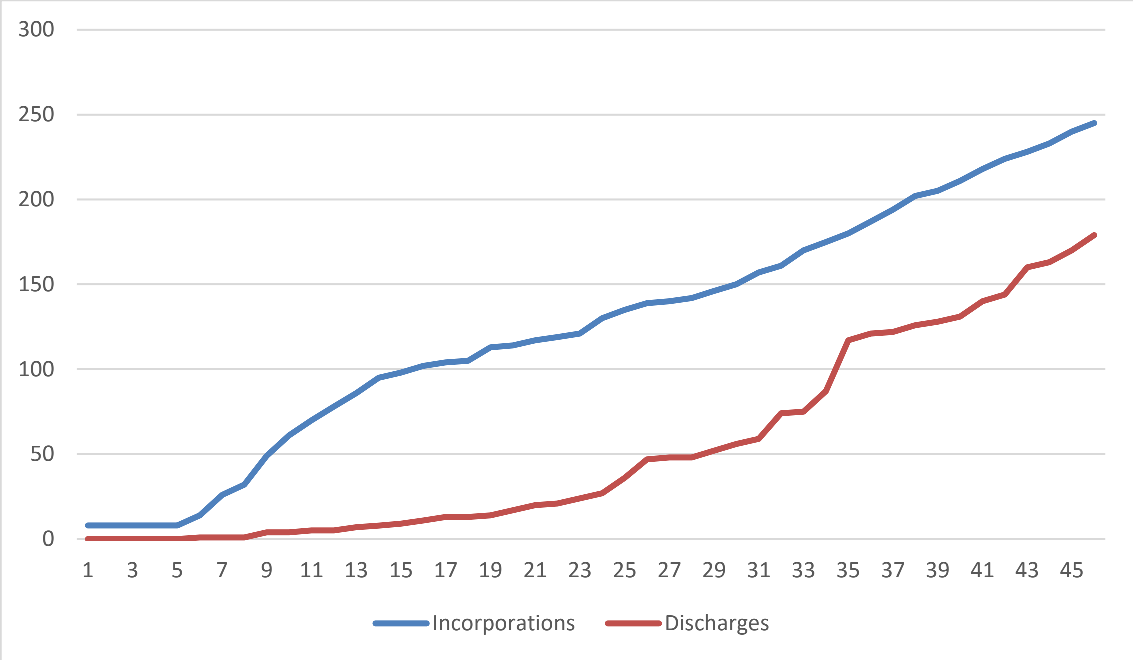


Figure 30*. Number of incorporations and discharges in the telemonitoring programme during the follow-up.*

4.2. Descriptive analysis of HF decompensations in the IG

During the 46 months of follow-up, a total of 527 heart failure decompensations in 148 different patients were detected. Of these, 347 were managed at home (253 with oral diuretic adjustment, 79 with intravenous treatment and 15 with subcutaneous furosemide pumps [102] [103]). There were 146 hospital admissions (131 in Basurto hospital and 15 in Santa Marina -chronic patients' hospital of our health area-. Of these decompensations, 18 were programmed). In addition, there were 34 emergency visits that did not require hospital admission (resolution of the decompensation with the intravenous treatment administered in this department) (25 in Basurto hospital and 9 in Santa Marina).

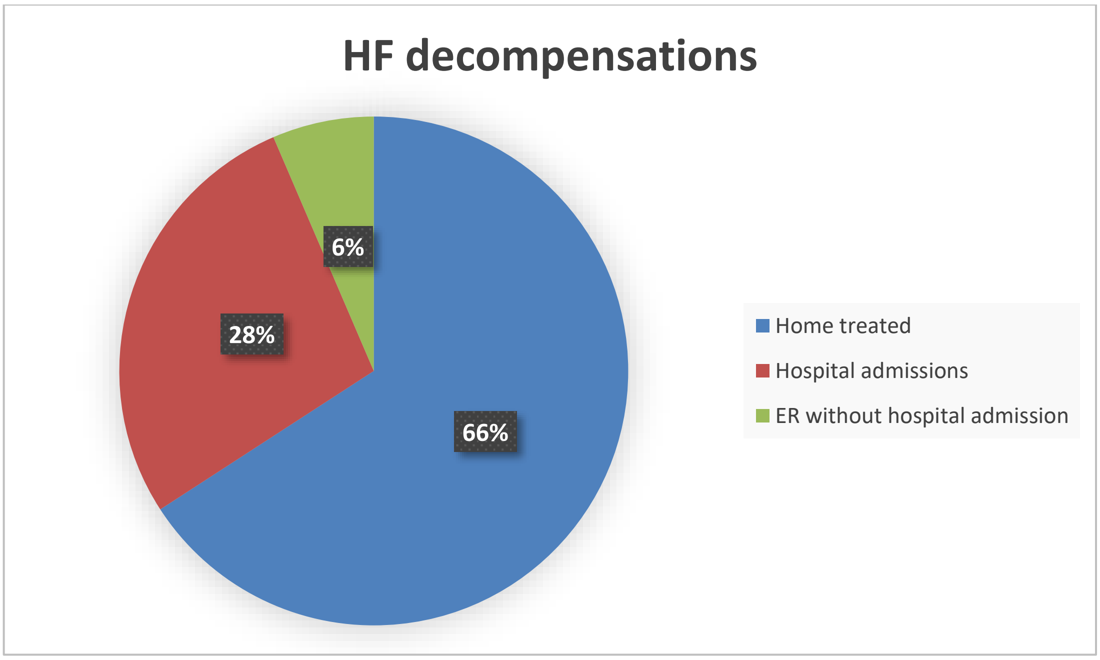


Figure 31. *Distribution of detected HF decompensations.*

	Hospitalisations	ER without hospitalisation	Decompensations treated at home
2014 (8 months)	12	3	18
2015	41	12	93
2016	50	10	83
2017	38	8	127
2018 (2 months)	5	1	26
Total	146	34	347

Table 11. *Distribution of HF detected decompensations*

The mean duration of decompensations was 6.47 days (SD 4.80) (table 12, figure 32)

Type of decompensation	Duration days, mean (SD)
Global	6.47 (4.80)
Treated at home	6.62 (4.22)
Emergency without hospital admission	0.86 (0.43)
Hospital admission	4.91 (5.61)

Table 12. *Mean duration in days of HF decompensations depending on the type of treatment received.*

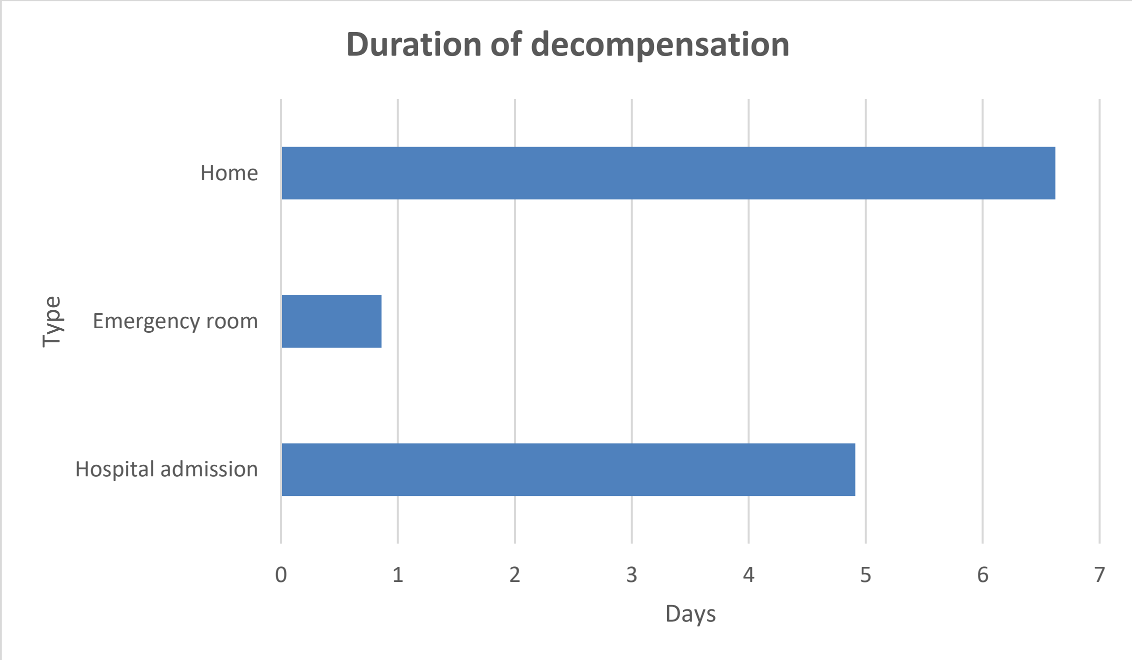


Figure 32. *Representation of the duration (in days) of HF decompensations according to the type of treatment received.*

Most of the decompensations detected through RPT were satisfactorily treated at home (65.85%). In these cases, oral diuretic treatment was adjusted, and the episode resolved in 72.9% of cases, while intravenous (iv) diuretic was needed due to resistance of the condition on 79 occasions (22.8% of cases). Subcutaneous furosemide perfusion pumps were placed in 15 cases (4.3%) because of the impossibility of puncture of peripheral intravenous lines and/or reappearance of symptoms when the diuretic was administered orally.

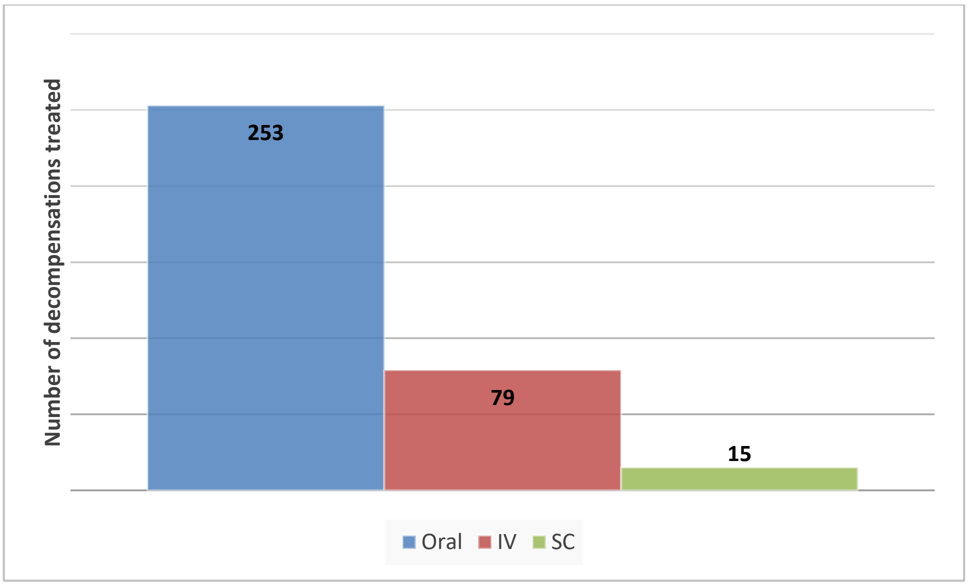


Figure 33*. Number of decompensations treated at home in the IG according to the treatment received.*

As can be seen in the following figure, the use of the intravenous line has undergone a gradual increase throughout the follow-up.

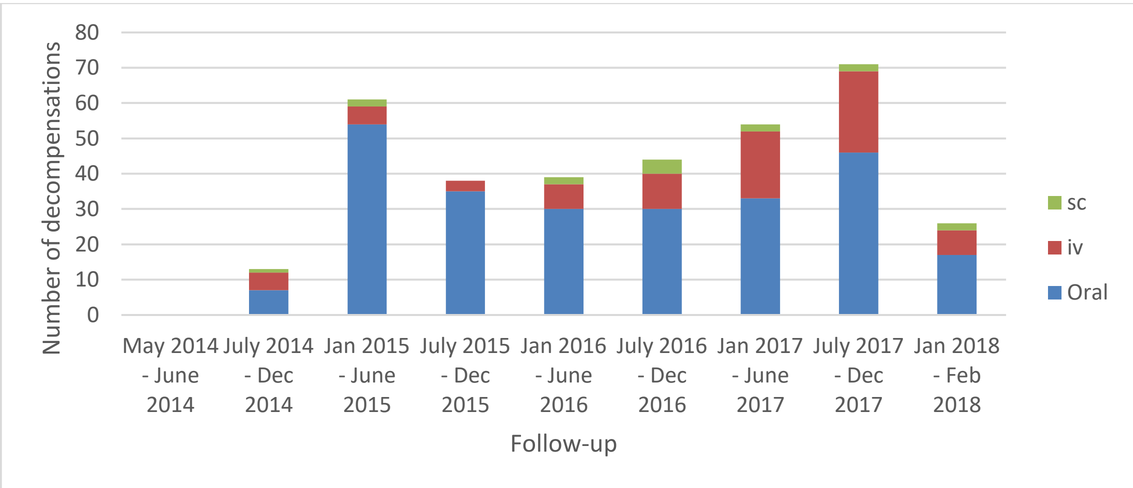


Figure 34*. Comparative of number of decompensations treated at home with oral, iv and sc diuretics*

If we focus on hospital admissions due to worsening HF, 70% of telemonitored patients did not have any hospital admission. Of those who were admitted to hospital, the majority (14.17%) had only one admission during follow-up.

4.3. Evaluation of the usefulness of RPT / Results of telemonitoring study

In order to know if this intervention is effective, we analysed:

- Number of HF-related hospitalisations per patient in both groups, including the duration of readmissions (days of hospital stay).
- The all-cause and HF-related mortality in both groups involved in the study.
- Adherence to telemonitoring and relationship between transmission rate and detection of decompensations in the IG.
- Patients' satisfaction included in the IG.

4.3.1. Comparison of HF-related hospital admissions during the follow-up in both groups.

During the 46 months of follow-up, there were 146 hospital admissions in 72 different patients in IG. The hospital re-admission rate at 30 days was 6.2% and 14.6% at 90 days; the average stay of the re-admissions by HF in this group was of 4.91 days (DE 5.61). During the whole follow-up, 70% of the telemonitored patients did not present any hospital admissions due to HF.

Likewise, there were 156 HF-related hospital admissions in 92 different patients in the CG group. The hospital readmission percentage at 30 days was 5.7% and 12.4% at 90 days; the average in-hospital stay was of 3.48 days (SD 7.88). 70.79% of the patients did not present any HR-related hospital admission.

	Intervention group		Control group	
Hospital admissions per patient	**Number of patients**	**Percentage**	**Number of patients**	**Percentage**
0	168	70.00	223	70.79
1	34	14.17	46	14.60
2	16	6.67	29	9.21
3	13	5.42	10	3.17
4	6	2.50	5	1.59
5	2	0.82	2	0.63
6	0	0.00	0	0
7	1	0.42	0	0
Total	**240**	**100**	**315**	**100**

Table 13*. Number of hospital admissions in the IG and in CG during follow-up.*

Figure 35 shows the number of times each patient was admitted to hospital due to worsening HF, being the distribution similar in both groups. It should be noted that in both groups there were several patients who had 3 or more admissions.

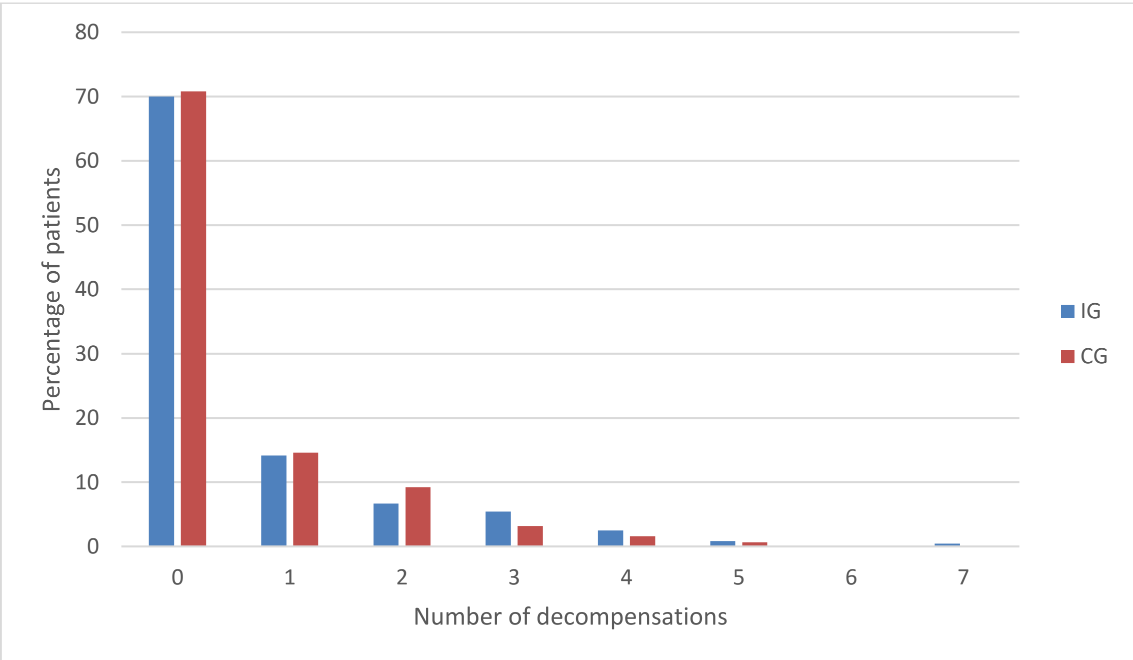


Figure 35*. Distribution of HF-related hospital admissions between groups*

	Any hospital admission		
	0	1 or more	Total
IG	168 70.00%	72 30.00%	240 100%
CG	223 70.79%	92 29.21%	315 100%
Total	391 70.45%	164 29.55%	555 100%

***Table 14**. Distribution of hospital admissions in both comparison groups.*

	IG	CG	Total
Incidence rate	0.024	0.018	0.020

***Table 15.** Incidence rate of HF-related hospital admissions in both groups*

	Point estimate	95% Confidence Interval
Inc. rate difference	0.007	-0.0003 to 0.0133
Inc. rate ratio	1.376	0.9966 to 1.8937

***Table 16**. Incidence rate difference and ratio in both groups*

There are no significant differences in the number of HF-related hospital admissions (30% in IG vs 29.21% in CG with p-value = 0.839), being the incidence rate 0.024 hospital admissions/patient-month in IG and 0.018 in CG.

The mean time until the 1st hospital admission is also similar between groups (27.51 months in IG vs 28.61 months in CG)

	Number of subjects	Restricted mean	Standard Error	95% Confidence Interval
IG	240	27.51	1.27	25.02 to 29.99
CG	315	28.61	0.98	26.69 to 30.54

***Table 17**. Time (in months) until first hospital admission in both groups.*

Univariate analysis

An analysis of the variables associated with HF-related hospital admissions was made. It shows that the female sex seems a protective factor (HR -0.310, p=0.05), while the presence of KCD and the number of years of evolution of heart disease are factors significantly associated with re-admissions (HR 0.559, p<0.001 and HR 0.0824, p = 0.001 respectively).

Variable	HR	p-value
Age	0.009	0.204
Sex	-0.310	0.050
Weight	-0.001	0.764
LVEF	0.003	0.945
Creat	0.296	0.002
KCD	0.559	<0.001
Years of evolution	0.082	0.001

Table 18*. Univariate analysis of the variables associated to HF-related hospitalisation in the entire sample.*

As explained before, sex is a factor related with HF-related hospital admissions, being female a protective factor.

Sex	Events observed	Events expected
Man	102	89.67
Woman	62	74.33
Total	164	164

Table 19*. Log-rank test for equality of survivors' functions (p=0.05)*

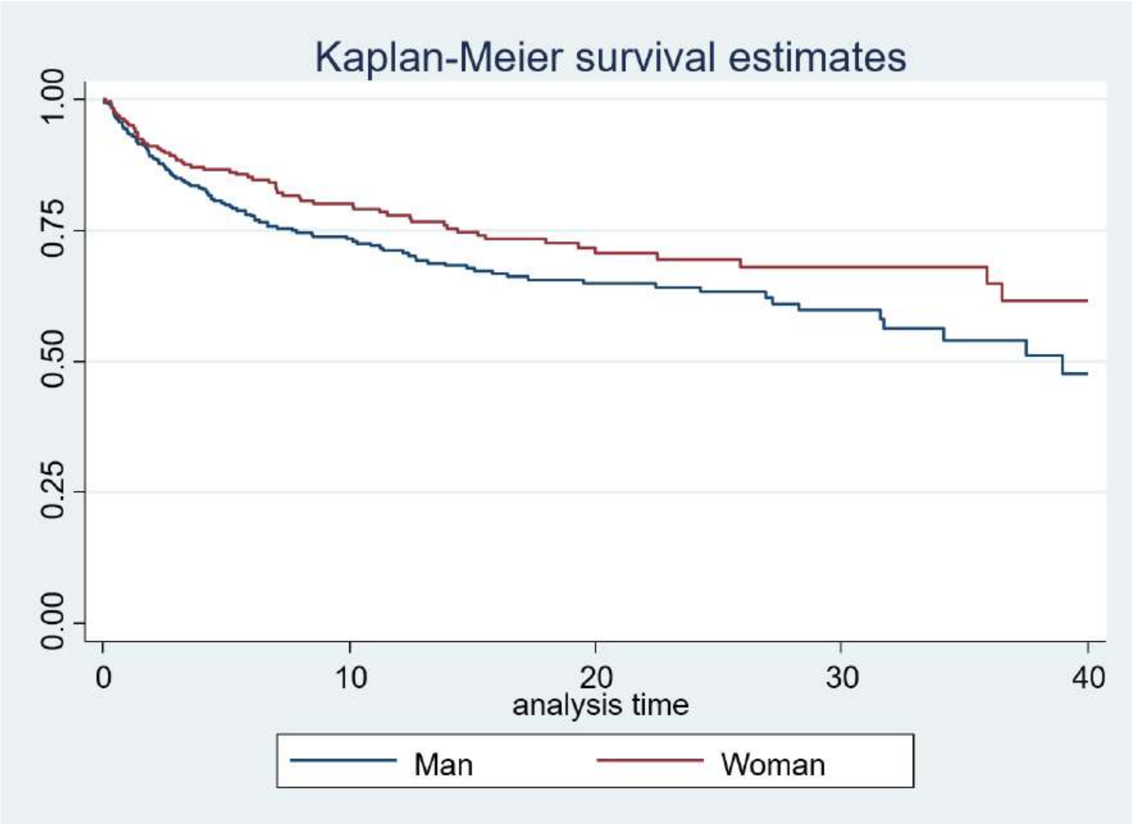


***Figure 36**. Survival curve to HF-related first hospital readmission according to sex. Survival analysis is performed using Kaplan Meier analysis (p=0.05).*

We can see that HF decompensations occurred more commonly in men. It should be highlighted that the distribution between the 2 groups is asymmetrical: in men the median is not in the centre of the box and the whiskers are longer, indicating heterogeneity of variances between the two groups.

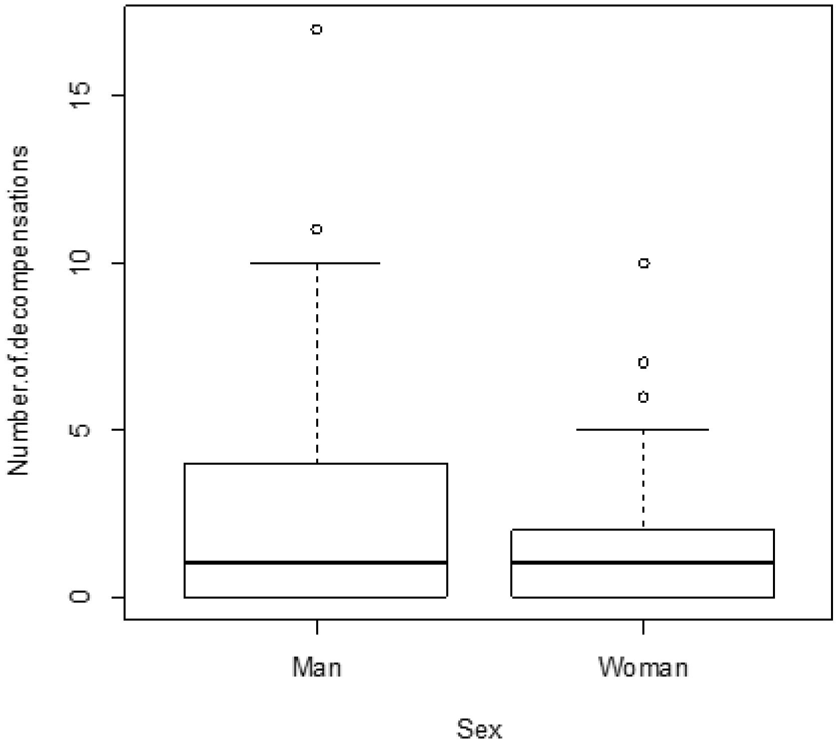


Figure 37*. Distribution of HF decompensations in men and women.*

The following figure shows the mean values of the variable "Number of decompensations" for the different levels of the sex factor (male/female), with confidence intervals for each mean. As in the previous representation, it can be observed that the number of decompensations was higher among men.

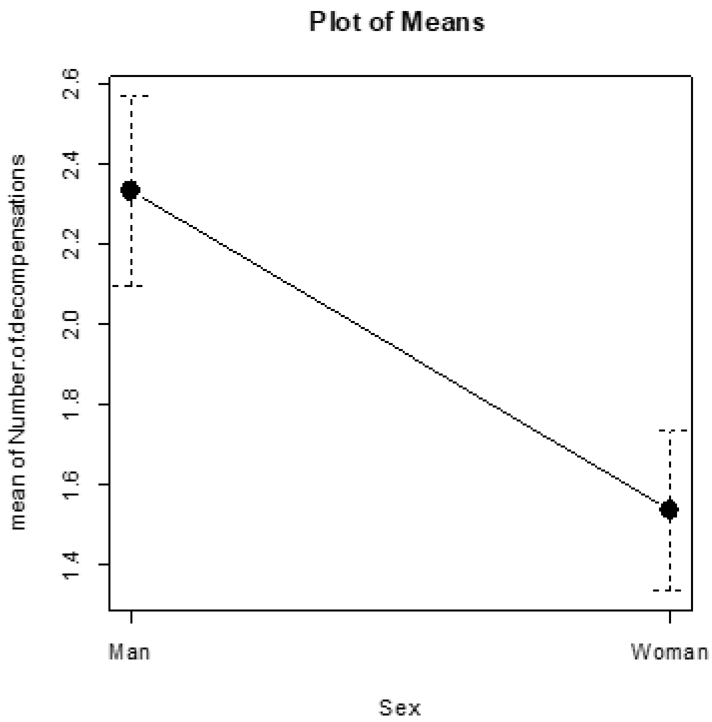


Figure 38*. Mean of number of HF-related decompensations for men and women.*

The type of heart disease the patient has is also related to hospitalisations. Below is a comparison of the decompensations suffered according to the type of heart disease. The following table shows that the cardiopathy with the highest risk of decompensation in our group is ischemic, followed by valvular and hypertensive, with a statistical significance of p= 0.024. Ischemic heart disease also has earlier mortality (early separation of Kaplan-Meier survival curves).

Type of cardiopathy	Events observed	Events expected
Ischemic	59	46.20
Valvular	32	33.54
HTA	31	37.39
Idiopathic	19	19.70
Other	23	27.18
Total	164	164

Table 20*. Comparison of the decompensations suffered according to the type of heart disease.*

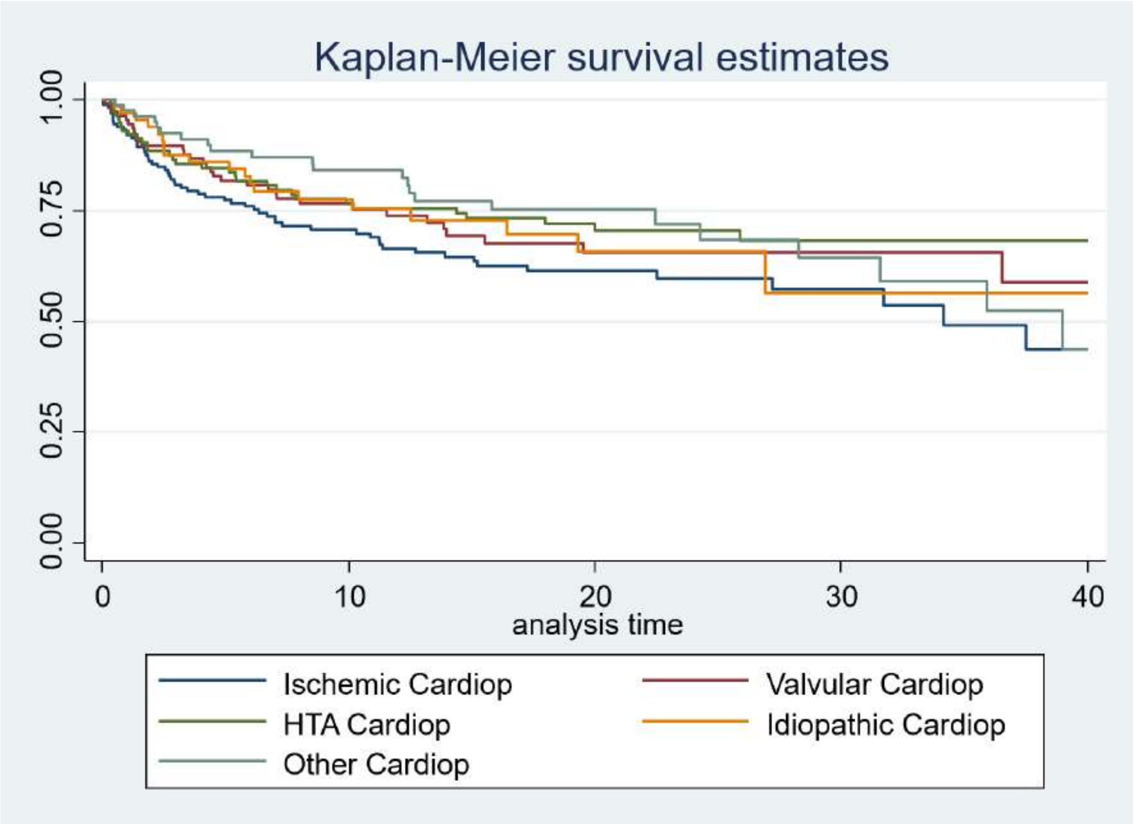


Figure 39*. Survival curve to HF-related first hospital readmission according to type of cardiopathy. Survival analysis is performed using Kaplan Meier analysis (p= 0.024)*

Tobacco is not associated to heart failure decompensations in our study.

There are no significant differences in our group between the HF decompensations and the history of cerebrovascular disease, type 2 DM, COPD, peripheral vascular disease and atrial fibrillation/flutter.

Multivariate analysis

We used multivariate analysis to build different models to see if there are any interactions with the variables that modify or confuse the results obtained above.

The best two models are:

	Hazard Ratio	Standard error	p-value	95% Confidence Interval
IG	1.032	0.175	0.851	0.740 to 1.440
Sex (woman)	0.724	0.118	0.047	0.527 to 0.996
Age	1.013	0.008	0.083	0.998 to 1.028
CKD	1.574	0.263	0.007	1.134 to 2.184
Evolution of HF (years)	1.081	0.270	0.002	1.030 to 1.136

Table 21. *Adjusted model (number 3) using Cox regression and Brelow method*

	Hazard Ratio	Standard error	p-value	95% Confidence Interval
IG	1.006	0.166	0.973	0.727 to 1.390
CKD	1.689	0.271	0.001	1.232 to 2.314
Evolution of HF (years)	1.080	0.257	0.001	1.031 to 1.132

Table 22. *Adjusted model (number 5) using Cox regression and Brelow method*

And they have been selected according the results of "aic" and "bic" (smallest values):

	Model 1	Model 2	Model 3	Model 4	Model 5
IG	1.038	1.041	1.032	0.983	1.006
Sex	0.801	0.738	0.724	0.774	---
Tobacco **Non-smoker** **Ex-smoker** **Current smoker**	 1 1.205 1.245	---	---	---	---
Age	1.015	1.013	1.01	---	----
Creat	1.136	1.145	---	---	---
KCD	1.429	1.427	1.574	1.668	1.689
Evolution of HF (years)	1.080	1.082	1.081	1.076	1.080
aic	1900.812	1902.117	**1900.96**	1901.554	1902.062
bic	1935.291	1928.02	1922.546	1918.823	**1915.014**

Table 23. *Multivariate analysis of the variables associated to HF- related hospital admissions*

According to these tables, and once corrected by confusing variables, the results remain unchanged, meaning that HF-related hospitalisations are similar between the two comparison groups (HR 1.006 in model 3 with p=0.973 and HR 1.039 in model 5 with p=0.983).

Due to the competitive risk between the patient's death and the possibility of re-admission, a survival analysis was performed using the Kaplan Meyer curve.

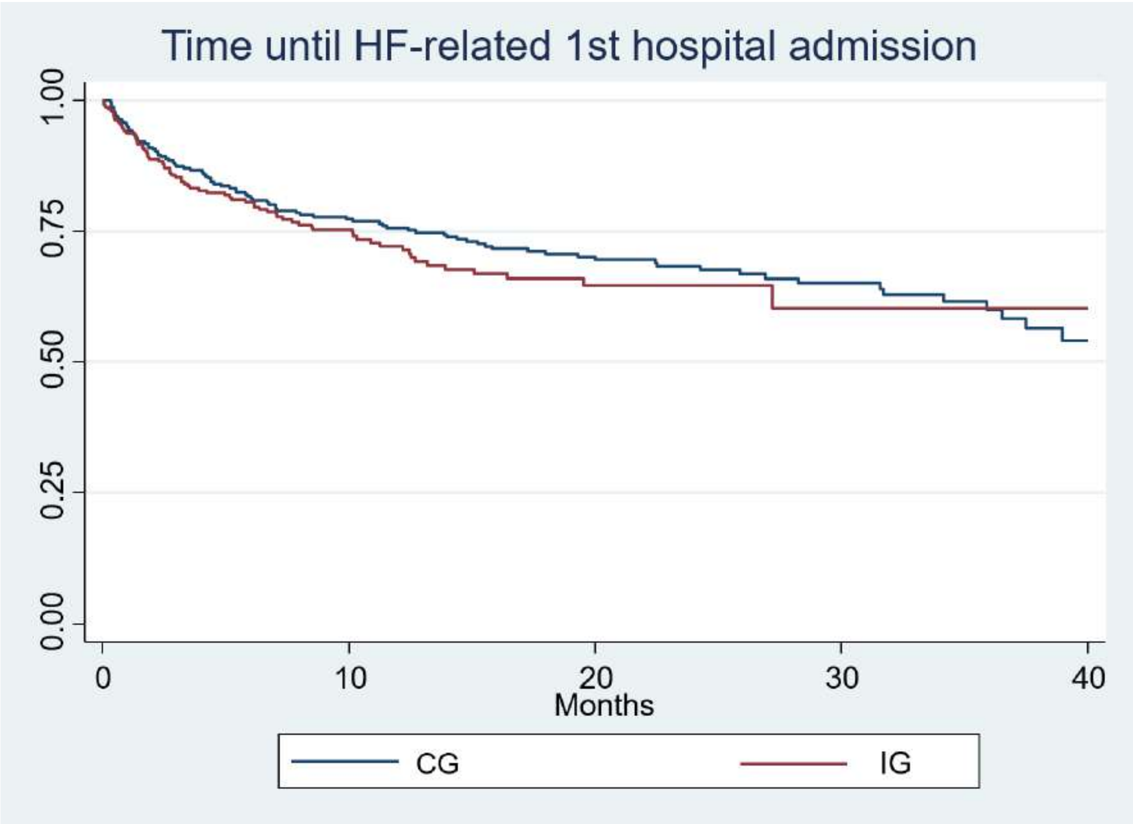


Figure 40. *Survival curve to first HF-related hospital readmission. Survival analysis is performed between the IG and the CG using Kaplan Meier analysis.*

4.3.2. Comparison of all-cause and HF-related mortality between the intervention and control group.

After a follow-up of 46 months there have been 47 deaths in the IG and 176 in the CG. This means a lower mortality in the IG (19.58% vs 55.87%), a significant decrease with $p < 0.001$.

Group	Deaths	Time until death (days)	Incidence rate	Number of patients
IG	47 (19.58%)	308.6	0.152	240
CG	176 (55.87%)	546.2	0.322	315
Total	223 (40.18%)	854.8	0.260	555

Table 23. *Comparison of mortality between groups.*

Figures 41 and 42 show the evolution of mortality on a Kaplan Meyer curve.

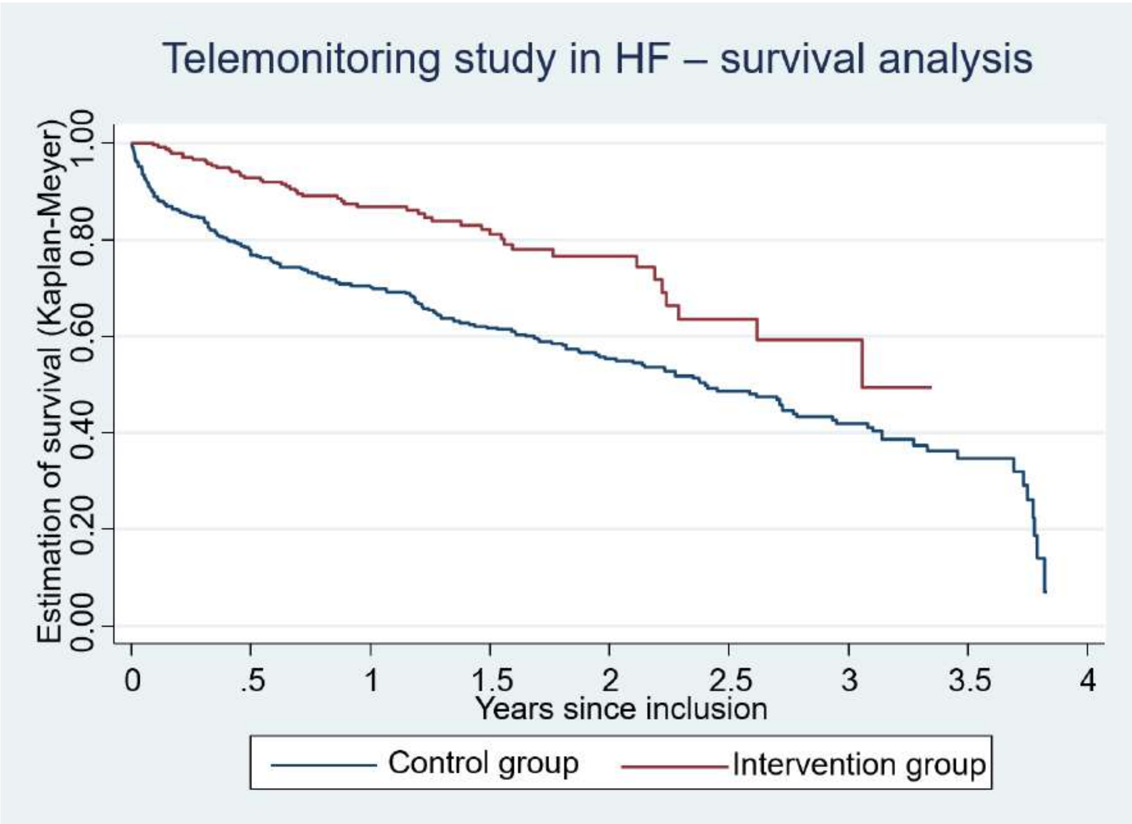


Figure 41. *Survival curve to death for 46 months. Survival analysis is performed between the IG and CG using Kaplan Meier analysis (Log Rank test, p<0.001).*

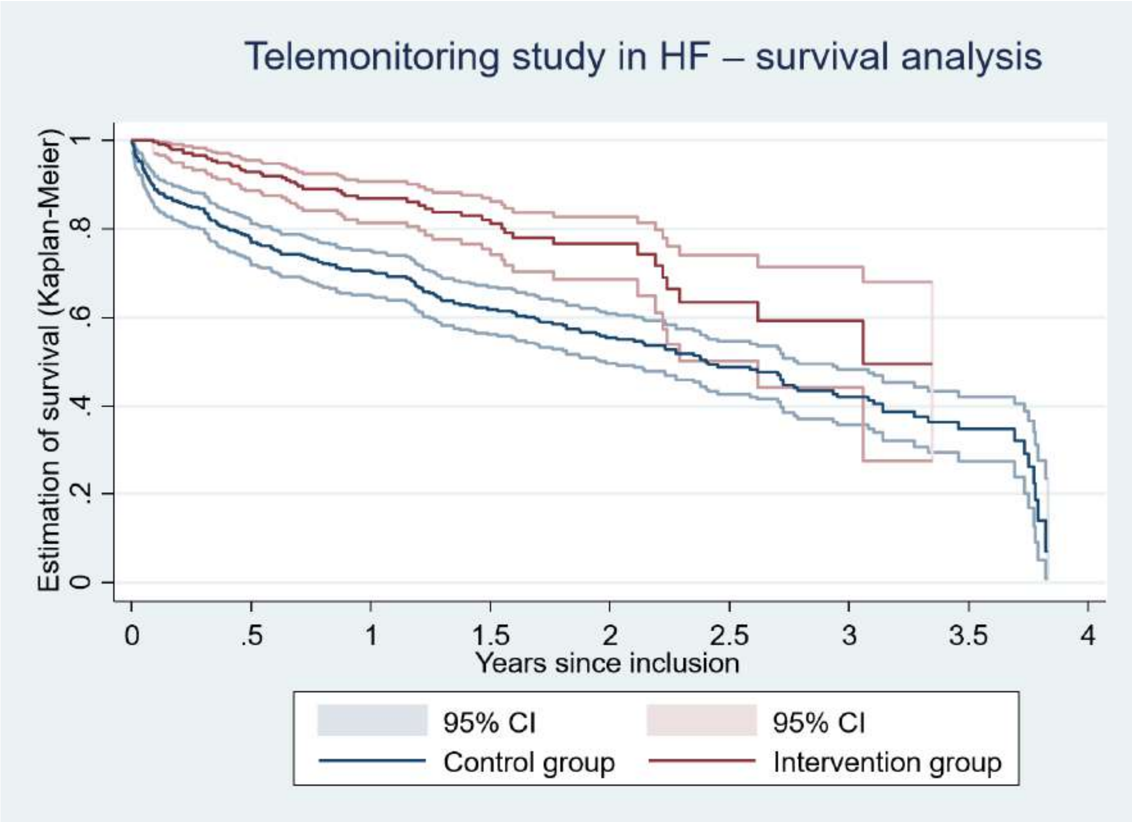


***Figure 42**. Survival curve to death for 46 months with 95% confidence intervals. Survival analysis is performed between the IG and CG using Kaplan Meier analysis (Log Rank test, p<0.001)*

The cause of death, however, is quite similar. Thus, 46.81% of deaths in the IG and 50% in the CG are due to progression of HF.

Group	Deaths	HF-related deaths	Non-HF deaths	Unknown (Sudden death)
IG	47	22	21	4 (4)
CG	176	88	67	21 (4)
Total	223	110	88	25 (8)

IG (n=240); CG (n=315)

***Table 24**. Distribution of causes of death in patients who died during follow-up in each group.*

Description of characteristics of deceased patients

A total of 223 patients died, 47 in the IG (21.08%) and 176 in the CG (78.92%).

The characteristics of deceased patients are as follows: 57.2% were men, with an average age of 82.43 (SD 8.97) years. 41.10% were smokers or ex-smokers. The mean LVEF was 46.27 (SD 19.91); 69.07% had AF and 19.07% carried an implantable device. Regarding comorbidities, 31.35% had T2DM and 37.71% had CKD.

Multivariate analysis

Table 25 shows the multivariate analysis for all-cause mortality (Cox regression - Breslow method for ties). This shows that belonging to the IG decreases the risk of death from all causes (HR 0.48; 95% CI 0.333 - 0.672; p<0.001). The covariables that significantly influence this analysis are age (HR 1.04; 95% CI 1.029 - 1.064; p <0.001), LVEF (HR 0.98, 95% CI 0.975-0.994, p 0.02) and CKD (HR 1.55, 95% CI 1.170 - 2.066, p 0.002).

Variables	HR	Standard error	CI 95%	P
IG	0.47	0.08	0.333 – 0.672	<0.001
Age	1.04	0.09	1.029 – 1.064	<0.001
LVEF	0.98	0.004	0.975 – 0.994	0.002
CKD	1.55	0.22	1.170 – 2.066	0.002

***Table 25**. Multivariate analysis for all-cause mortality throughout the sample (HR: Instant risk throughout the follow-up).*

4.3.3. Adherence to telemonitoring

We have a dataset with 1.408.397 transmissions (media 5868.32 transmissions per patient, SD 3938.41)

Adherence to the RPT programme was high. Of the 240 patients included, 109 (45.42%) transmitted between 75 and 100% of the days. Only a minority (7 patients, 2.92% of the total) performed less than 25% of the required transmissions.

Ratio	Frequency	Percentage	Cumulative
0-24% days of transmission	7	2.92	2.92
25-49% days of transmission	62	25.83	28.75
50-74% days of transmission	62	25.83	54.58
75-100% days of transmission	109	45.42	100
Total	240	100	

Table 26*. Number of transmissions in the IG during follow-up.*

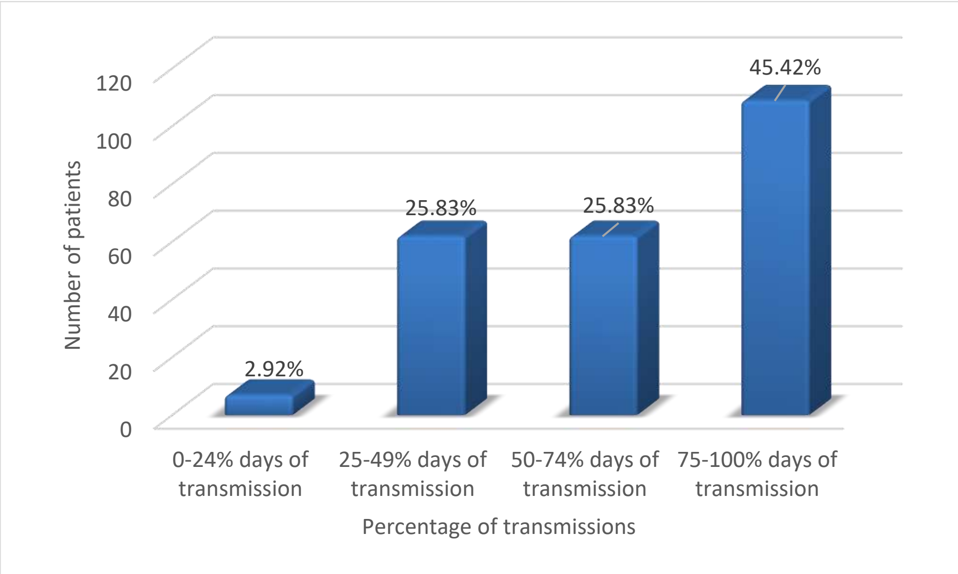


Figure 41*. Percentage of transmissions from telemonitored patients.*

During the 46 months of follow-up, only 4 patients voluntarily left the programme: 2 elderly patients who had problems using technological devices and 2 other young patients who were unable to adapt to the routine of taking measurements. The time from their inclusion in the study to their last measurement was 20, 48, 216 and 281 days.

4.3.4. Association between the frequency of transmissions and HF decompensations that require hospital admissions

Below is a table that specifies the number of HR-related hospital admissions and the frequency of transmissions made.

		Hospital admissions per patient								
		0	1	2	3	4	5	6	7	**Total**
Frequency of trans missions	0-24%	6 85.71%	0 0%	0 0%	1 14.29%	0 0%	0 0%	0 0 %	0 0%	7 100 %
	25-49%	45 72.58%	6 9.68%	3 4.84%	4 6.45%	3 4.84%	1 1.61%	0 0 %	0 0%	62 100 %
	50-74%	45 72.58%	8 12.90%	5 8.06%	2 3.23%	2 3.23%	0 0%	0 0 %	0 0%	62 100 %
	75-100%	72 66.06%	20 18.35%	8 7.34%	6 5.50%	1 0.92%	1 0.92%	0 0 %	1 0.92%	109 100 %
Total		168 70%	34 14.17%	16 6.67%	13 5.42%	6 2.50%	2 0.83%	0 0 %	1 0.42%	

Table 27. *Average hospital admissions in telemonitored patients according to the frequency of transmissions*

Table 28 shows the relationship between the number of admissions and the transmissions made, with no significant differences between groups.

Hospital admissions		**Odds Ratio**	**Standard error**	**p**	**95% CI**
Frequency of trans missions	25-49%	2.26	2.53	0.464	0.25 to 20.24
	50-74%	2.26	2.53	0.464	0.25 to 20.24
	75-100%	3.08	3.38	0.306	0.36 to 26.57

***Table 28**. Relationship between HF hospitalisations and the number of transmissions made by telemonitoring (comparison with transmission frequency of 0-24%)*

The number of days spent in hospital was not statistically significant in relation to the number of transmissions carried out (correlation factor r= 0.078 with p=0.226).

4.3.5. Evaluation of the patients' perception - Satisfaction survey

A satisfaction survey of the telemonitoring service of our hospital was developed. In this study, 37 randomly selected patients in the IG took part and the results were obtained by personnel from outside the programme (Care4Chronics) through telephone interviews performed between 29th October and 13th November 2018.

Regarding the socio-demographic characteristics of the users who participated in the programme and who carried out the interview, 62% were men with an average age of 71 years. However, it should be noted that almost half of them were over 80 years old.

Age	**<50**	**50-65**	**65-80**	**>80**
% of interviewed	2.7	10.8	37.9	48.6

70.3% of the interviews were conducted with patients using the programme, while 29.7% of the interviews were answered by relatives/caregivers (due to poor functional status of the patient).

100% of those interviewed rated the professionalism of the team as good or very good, as well as the quality of the care received. In general, women had a more favorable opinion than men. By age, the best scores were found in the user group of 65 years of age or older. It should be mentioned that the best overall assessment of care was given by the caregivers who answered to the survey because the patient was not in good health.

Patients reported that RPT had a positive impact on self-confidence, allowing them to develop a better routine of self-management and adherence to treatment. Most patients or caregivers saw the RPT as a tool that helped them in managing their chronic illness and in their relationship with healthcare professionals but preferred it to be complementary to traditional face-to-face care.

4.4. Improvement of the results obtained with RPT using machine learning algorithms.

In this part, we analysed the data obtained in the previous section (4.3) along with the alerts used in the clinical practice of our hospital (see section 3.4) to evaluate the parameters that best predict HF decompensations in our group of telemonitored patients. For this purpose, we use sensitivity and false alerts values.

We also applied machine learning techniques to create predictive models in order to improve the results obtained so far, reducing false alerts.

Finally, we completed the analysis with environmental data (air components and meteorological parameters) to see if these variables influence HF decompensations.

V. DISCUSSION

5.1. Evaluation of the usefulness of telemonitoring

5.1.1. Hospital admissions

During the 46 months of follow-up, no statistically significant differences were found in the rate of hospital readmission between the IG (146 hospital admissions in 72 patients - incidence rate 0.024) and the CG (156 hospital admissions in 92 different patients -incidence rate 0.018-). The readmission rate at 30 and 90 days was similar between both groups, as well as the days of hospital stay.

Note that the HF-related readmission rate in 30 and 90 days has been lower than in other studies [105]. HF-Inpatient care at the BUH is performed according to the PIP IC [106], and includes assessment by the hospital nurse with education in self-care and knowledge of the disease, completion of the 72-hour call by the call centre and early control in primary care and outpatient cardiology. This could justify the fact that the number of admissions in both groups was lower than initially expected.

There are several reasons that may have influenced that the decrease in the number of HF-related hospital admissions was not greater.

Patients in the IG had more years of disease evolution (5.8 vs 3.65, p<0.001), associated with a significantly lower mean LVEF (42.26 vs 51.54, p<0.001) and greater need for CRT type devices (6.3% vs 0.5%, p<0.001), which ''a priori'' implies that they start from a more deteriorated baseline situation. The distribution of the type of cardiopathy is also different, with a predominance of ischemic, idiopathic and valvular cardiopathy in the IG, while in the CG the prevalence of hypertensive cardiopathy stands out.

The number of comorbidities is high in both groups, although there is a higher prevalence of COPD patients in the RPT group (30.4% vs 24.8%, p=0.149), as well as T2DM (40.8% vs 28.9%, p=0.04) and CKD (37.5% vs 27.6%, p=0.017). Of special importance is the presence of chronic renal disease as it has been shown to be the co-morbidity that most influences the prognosis and evolution of HF [107].

In terms of age, the mean age of the IG is 4.5 years younger than that of the CG (76.34 vs 80.97, $p<0.001$). However, despite what one might initially think, in the multivariate analysis age was not associated with either readmission or mortality, probably because younger patients have more severe heart disease and predominance of depressed LVEF.

In addition, we must consider the power of telemonitoring to detect early decompensations, to treat them at home, and if the outcome is not appropriate, manage an early hospital admission.

Finally, there is the competitive risk between death and hospitalisation. We have already seen in the previous section (4.3.2) that mortality is significantly lower in the IG, which makes the probability of admission to this group higher.

Despite the control provided by telemonitoring, there are patients who have continued to present decompensations, and patients who died during follow-up presenting the most hospital admissions. This indicates that in patients with advanced refractory HF who are in the final stage of the disease, RPT is probably not sufficient and that other forms of care, such as palliative care, should be encouraged [108].

It is important to keep in mind that RPT alone does not improve health outcomes in patients with HF. It is adequate monitoring, correct interpretation, and actions taken based on the data received that have the potential to improve these outcomes. Therefore, the key to the success of these programmes is not so much the RPT technology itself, but the coordination of care required by the health system for the proper follow-up of these patients [109]. It is essential to have a well-organized structure around the patient that allows for a combination of non-presential follow-up with the possibility of treating decompensations without hospital admission and coordination with primary care. Likewise, as the study has progressed, improvements have been incorporated in patient follow-up, alarm management, and alternatives to hospitalisation for the treatment of decompensations. In this regard, the use of the intravenous line has undergone a gradual increase throughout the follow-up. This is due to the structural improvement of the unit that has allowed to contact the advanced practice registered nurses for the administration of intravenous diuretic at home, as well as the better resolution of certain decompensations with this treatment, allowing to shorten the duration of this therapy if we compare it with the oral administration.

5.1.2. Mortality

Mortality rates in the IG of our study are lower than some population-based studies [110] [111] and this better prognosis is probably based on the higher level of compliance with therapeutic guidelines (above all, by up-titrating beta-blockers, ACEi, ARA, ARNI and ARM), educational interventions with stimuli to promote self-care, and the multidisciplinary approach; all aspects which have received special attention in our population.

We have also seen a statistically significant reduction in mortality in the IG (19.58% vs. 55.87% in the CG, $p<0.001$). This reduction in mortality was also seen in other studies [112] and several hypotheses have been put forward: direct benefit of RPT in the medical care received by the patient; improvement of patient self-care related to RPT; willingness to use RPT as a marker for those patients predisposed to self-management of their disease and the health resources offered to them. In previous studies, RPT was associated with increased therapeutic compliance [113], drug titration [114], and adherence to non-pharmacological recommendations [115].

Although there was not a significant decrease in related HF hospitalisations, the fact that decompensations were detected early may indicate a lower severity of decompensations in the RPT group, which may have contributed to the decrease in mortality. This is an important point, since in a recently published study the decrease in readmissions was accompanied by an increase in mortality [116], which demonstrates that when assessing the efficacy of an intervention plan, we must set objectives that indicate that we have really improved patient care. Focusing solely on reducing readmissions can lead us to deny hospitalisation to patients who really need it, thereby increasing the risk of mortality.

Another significant finding of our study is the considerable percentage of deaths from non-cardiovascular causes (44.68% of the total in RPT patients) that could be explained by several factors [110]: high patient comorbidity, optimal drug and non-drug treatment in a specialized unit, the greater access these units afford to patients with HF decompensations, or administration of intravenous treatments in outpatient contexts in initial phases of decompensation.

5.1.3. Prognostication

Although the study is not designed to determine what baseline characteristics or comorbidities are associated with an increased risk of heart failure decompensation, we have detected that there are several variables associated with HF-related hospital admissions.

Our study shows that the female sex seems a protective factor (HR -0.310, p 0.05), while the presence of KCD and the number of years of evolution of heart disease are factors that are significantly associated with re-admissions (HR 0.559, p<0.001 and HR 0.0824, p 0.001 respectively). The type of heart disease the patient has is also related to hospitalisations. The cardiopathy with the highest risk of decompensation in our group is ischemic, followed by valvular and hypertensive, with a statistical significance of p=0.024. Ischemic heart disease also has earlier mortality.

These results are similar to those described in the literature. The Framingham study, as way of illustration, showed that women have less hospital admissions and a better median survival (twice as good as men) [117].

The cardiopathy with the highest risk of decompensation in our group is ischemic. This finding is described in other registries [118], in which chronic HF of ischemic aetiology carries a greater risk of morbidity and mortality than that of a nonischaemic aetiology. It may be due to the fact that acute ischemic cardiomyopathy is a rapidly progressive disorder in which most subjects do not have significant improvements in LVEF during the first 6 months of follow-up [119]. Exceptions to this rule are infiltrative causes of myocardial disease, such as amyloidosis and haemochromatosis [118].

An increasing time of evolution of heart failure is an independent risk factor for all-cause mortality and HF hospitalisation [121]. In general, patients with advanced heart disease have a greater deterioration of LVEF along with organic involvement secondary to HF, all associated with a lower effect of the established treatment.

The last factor associated with an increased risk of heart failure decompensation in our study is chronic renal disease. Renal impairment is often associated with HF due to renal hypoperfusion, and the use of diuretics, ACE inhibitors, angiotensin receptor antagonist, and the other concomitant medications. Serum creatinine concentration, which is often quoted as a barometer of renal impairment, is actually a poor indicator of renal function. An estimation of the glomerular filtration rate (GFR) is better for the accurate assessment of renal function [120], and the Modification of Diet in Renal Disease (MDRD) equations have been validated in patients with CHF. A GFR below 60 mL/min/m2 is associated with complications of renal disease. Moreover, a reduced GFR is independently predictive of all-cause mortality [121].

However, there are over 300 prognostic markers described in patients with HF [122]. In fact, many variables have prognostic power in HF, but the markers vary in their success for predicting outcome because of the heterogeneous nature of HF and the populations in which the variables were studied. Many of the described variables are inter-related and although they may be strong univariate markers of prognosis, they can be competitively removed in any multivariate model.

5.1.4. Adherence to telemonitoring

In our work there was a high rate of participation and transmission among patients who agreed to participate. This high transmission rate (45.42% of patients have transmitted between 75 and 100% of the days and 71.25% between 50 and 100%) may be due to (1) performance expectancy (improvements in HF management and peace of mind), (2) effort expectancy (ease of use and technical issues), (3) facilitating conditions (availability of technical support and adherence calls), (4) social influence (support from family, friends, and trusted clinicians), and (5) habit (degree to which taking readings became automatic) [123]. We believe that the education provided by the nurse during hospitalisation is fundamental, as he reports on the importance of home parameter monitoring at a particularly vulnerable time for the patient, and the subsequent monitoring from the HF unit in which the patient is regularly contacted by telephone.

This high rate of participation and transmission among patients who agreed to participate contrasts with those obtained in Kao's study [112], in which only 23.9% of the patients who had the devices installed used them and with Warre's work, in which average adherence rates declined significantly over time [123]. Indeed, the main problems described by the RPT studies are the low adherence rate, difficulty in the use of the technologies and lack of patient involvement.

Our group of patients is significantly older (76.34 years, SD 11.35) than that studied in other trials (67.3 years (SD 9.6) in the Bekelman et al. study [124] and 72 years (interquartile range 62-83) in the Kenealy et al. study [125]. However, it is noteworthy that there has been great acceptance of the technology. It is essential to design simple, user-friendly devices for elderly patients so that most of them can take measurements autonomously or with supervision.

5.1.5. Association between frequency of transmissions and HF-related hospital admissions.

Around 70% of telemonitored patients did not have HF-related hospital admissions during follow-up.

It could be expected that patients who have made fewer transmissions have had more hospital admissions as HF-related decompensations could not be detected by telemonitoring due to the low number of transmissions. However, our work does not demonstrate differences between the number of HF-related hospital admissions according to the transmissions made by telemonitoring in that period.

This may be due to the fact that patients who have made fewer transmissions are the most stable (patients are allowed to make fewer weekly transmissions and are also given permission so that if they go on short holiday periods, they do not wear the devices and do not transmit those days). Moreover, the follow-up period in stable patients is usually shorter since they have not had decompensations or if had, they have learned to detect and treat them at home. Thus, this type of patients has been discharged earlier from the telemonitoring programme.

As in the previous case, patients with more transmissions have not had less hospital admissions (one might think that a high number of transmissions would detect more decompensations that could be treated on an outpatient basis). In this case, the patients with the highest number of transmissions are those who are most unstable and with the highest congestion data, so they are not allowed to make fewer transmissions and when a decompensation is detected, usually home treatment is not sufficient and they end up in hospital. In the same way, the follow-up in telemonitoring is usually longer.

In addition, we must bear in mind that there are patients who have a relatively short follow-up (equal to or less than 6 months). This is either because they have died in this period or they have been stable and therefore have been discharged from the programme. These two circumstances also make it difficult to analyse the results.

It should be noted that at the beginning of the programme the number of transmissions could be reduced to 3 per week for those patients who were stable, without recent decompensations and with parameters within the range. Over time, however, we preferred patients to transmit daily or almost daily in an attempt to detect decompensations earlier should they occur.

5.1.6. Satisfaction

Assessment of patient satisfaction was not an objective of the study. However, 37 patients were surveyed by telephone to assess the impact of telemedicine on quality of life. The conclusion was that the patients have considered the RPT programme as a tool that can help them in the control of their chronic disease and in the relationship with health professionals. Our experience shows that there is an important relationship between patient satisfaction and adherence to RPT. In previous studies, such as the one published by Lusignan et al., patients were also highly satisfied with telemonitoring [126].

5.2. Improvement of the results obtained with RPT using ML techniques

5.2.1. Predictors of worsening heart failure

Up to now, efforts to develop a deterministic understanding of rehospitalisation have been difficult, as no specific patient or hospital factors have been shown to consistently predict HF decompensations and/or HF-related hospital readmissions.

There are multiple studies that describe the association between patient characteristics, analytical parameters and hemodynamic measures with readmissions after hospitalisation for HF. These studies have not found factors directly and repeatedly associated to HF decompensations and it may be because these parameters are not measured in all studies and also to the fact that examined covariates have generally not included common conditions and syndromes found in HF patients. These findings confirm the fact that the relationship between baseline characteristics and clinical factors with readmission is complex [83] [127] [128] [129].

This variability and multiplicity of parameters has served as the basis for this study, with the aim of seeking a combination of non-invasive, simple parameters that allow us to identify early decompensation of heart failure, to treat them early and avoid, as far as possible, hospital admissions.

Here we present which parameters measured by telemonitoring best predict HF decompensations in our hospital:

- Between the haemodynamic parameters, the weight variations (1 kg increase in 3 days or 3 kg in 5 days) and desaturation below 90% in pulse oximetry are good predictors of HF decompensation according to Se and FA/pt-y values.
- Regarding to the questionnaire, "worse" answers in questions (“Comparing with the previous 3 days, I feel… “) and 5 (“In the last days my ankles are…”) are very good predictors of decompensation. Questions 6 (“Can I go for a walk like the days before?”) and 7 (“Do I have a feeling of shortness of breath when I lie in bed?”) also have good predictive

values, but less than questions 1 and 5. The other questions cannot be considered as alerts, because of their low/null prediction capacity.

These results obtained in our centre are consistent with the published bibliography, although these studies do not specify the values of sensitivity, specificity and false positives and negatives. Neither the usefulness of the combination of these parameters nor their predictive value for the detection of HF decompensations are evaluated in the same study.

Our study determines that weight variations (1 kg increase in 3 days or 3 kg in 5 days) are associated to HF decompensations. This fact is confirmed by the study of Chaudhry et al [130]. It showed that clinically important increases in body weight begin at least 1 week before hospitalisation for heart failure. Moreover, during this time period, the risk of heart failure hospitalisation increases in a monotonic fashion with increasing amounts of weight gain. In contrast, weight gain was not observed before hospitalisation for causes other than heart failure.

In addition, improvements have been made in the calculation of weight variations using different mathematical methods. After representing all the results of the MA algorithm and applying the Youden index [104], the optimal Se and FA/pt-y values are similar to the results of the already alert implemented weight alert. But based on the literature [131][132][133], this latest one is best.

Changes in weight, especially over short periods of time, can be good indicators of volemic worsening. Many studies, however, are controversial on this subject, indicating that little or no weight gain is observed before an episode of decompensation or that a modest weight loss is observed after clinical compensation of an acute HF episode. In many cases, decompensation may occur not due to the build-up of fluid, but by water redistribution from the periphery to the lungs by neurohumoral and inflammatory acute activation, leading to cardiac and vascular alterations that promote reduced venous capacitance and increased peripheral arterial resistance [134].

Desaturation below 90% in pulse oximetry is another good predictor of HF decompensation according to our study. Similar results were obtained by Masip et al [135]. Their study shows the utility of baseline SpO2 as a complementary tool to establish the diagnosis and severity of acute or decompensated heart failure. The finding of a baseline SpO2 lower than 93 may be considered a threshold to this diagnosis and a warning to clinicians about this complication. The lower the SpO2 value, the higher the probability and severity of HF. The main advantage of SpO2 lies in the fact that is non-invasive, it can be monitored continuously, and it is not affected by interobserver or intraobserver variability.

Patient self-assessments are also useful in predicting mortality and hospitalisation. In fact, strong correlations have been observed between scores and functional class and the number of heart failure decompensation that require hospitalisations: worse self-assigned scores are associated with increased hospitalisation rates, worse quality of life, and decreased survival [136] [135] [137].

5.2.2. Predictive models

As explained before, in clinical practice, the diagnosis of HF based on a single observation is challenging. Although on average patients gain weight prior to HF hospitalisation, only a minority of patients (20%) have substantial weight gain, weight fails to predict accurately hospitalisation, and monitoring based on weight alone has proven ineffective. Heart rhythm and electrical disturbances only directly or indirectly describe a portion of early indicators of decompensation. Moreover, a single threshold in a continuous broadly distributed biological measure predisposes to inaccuracy. In addition, one-half to two-thirds of decompensations have potentially avertable precipitants which may be incompletely captured in current models: medication/diet non-adherence, socio-economic factors, infection and pulmonary processes, worsening renal function, hypertension, and ischaemia. Any test predicting decompensation will appear inaccurate if an alternative condition with different pathophysiology is misattributed (such as COPD exacerbation) [138].

Thus, the use of a multi-parameter-based evaluation of symptoms and signs of congestion is probably the best contemporary strategy. Recent studies have shown that the application of machine learning techniques may have the potential to improve heart failure outcomes and management, including cost savings by improving existing diagnostic and treatment support systems.

Therefore, we used machine learning techniques to improve the accuracy of our alarms and to detect which combination of parameters measured by telemonitoring best predict HF decompensations, avoiding false negative alerts.

At present, there is little evidence what combination of biometric measurements and questionnaires of self-reported symptoms is most effective in predicting deterioration of heart failure. Besides the combination, thresholds for these measurements are also less well studied. It stands to reason that when set too wide, then there is a high risk that the patient is decompensated before an alert trigger is generated whereas thresholds which are set too tightly could lead to many 'false' alert triggers. In fact, reducing avoidable telehealth alerts could vastly improve the efficiency and sustainability of telehealth programmes for HF management [139].

Current medical practice uses sensitive alerts (they detect most of the decompensations due to their high sensitivity), but they also have too many false alerts. Therefore, the main goal of this study is to improve this imbalance, reducing these false alerts. All in all, this work has shown an improvement from current alerts system implemented in the hospital. The system reduces the number of false alerts notably, from 28.64 FA/pt-y of the current medical practice to even 7.8 FA/pt-y for the "red" group, which is denoted as the most restrictive group. This last result is achieved with the predictive model built by applying NB with Bernoulli to the combination of telemonitoring alerts and questionnaire alerts (testing set) (R2: Weight + Ankle + well-being plus the yellow alerts of SBP, DBP, O2Sat and HR). However, as expected, the application of machine learning techniques entails a decrement on sensitivity values. The results obtained in this study for the "red" group is Se=0.47, while the alerts used in the current medical practice applied to the same testing dataset achieve Se=0.76. Despite this Se worsening, it is notorious that the FA/pt-y has much higher decrement, with which we conclude that this new predictive model improves the current medical practice. Moreover, when comparing the obtained results with the state of the art, the Se values are similar or better to these studies that do not consider transthoracic impedance [140] [131].

Table 40 presents the results of different studies that determine whether a monitored HF patient will have a decompensation, usually implementing alerts. Based on the literature studies, we could consider the number of false alerts per patient per year (FA/pt-y) as de facto standard to determine the number of false positives. However, as shown in Table 40, some of the studies present the specificity value.

Study	Data type	Dataset	Results
Zhang et al [132]	Weight	135 patients, 1964 monitoring days	Se = 20.4 – 58.3% Sp = 54.1 – 89.4%
Gyllensten et al [131]	Weight	91 patients, 10 months	Se = 13 – 20 % Sp = 90 – 91%
	Non-invasive transthoracic bio-impedance		Se = 13% Sp = 91%
Adamson et al [141]	Blood pressure	274 patients	Se = 83.1% FA = 4.1/pt-y
Abraham et al [140]	Intrathoracic impedance	156 patients, 537 ± 312 days	Se = 76.4% FA = 1.9/pt-y
	Weight		Se = 21% FA = 4.3/pt-y
Ledwidge et al [133]	Weight	87 patients, 23.9 ± 12 weeks	Se = 21- 82% Sp = 68 – 86%
Gilliam et al [142]	Multivariate	201 patients	Se = 41% FA = 2/pt-y

***Table 40**. Summary of decompensation detection studies*

On average, models designed to predict the combined outcome of death or hospitalisation, or of hospitalisation only, have a poorer discriminative ability than those designed to predict death. This may be because hospitalisation is genuinely more difficult to predict than death (perhaps because the decision about who to admit to the hospital is much more dependent on health care supply) or because there has been less focus on this type of outcome (as evidenced by the smaller number of published reports) [143]. Irrespective of the underlying causes of such differences, we believe that efforts are needed to increase the performance of such models in the future to make them clinically more useful.

As a matter of fact, we pretend that our model will (i) be generally applicable in HF patients, (ii) improve the clinical practice by developing an accurate system that detects the risk of decompensation, (iii) allow professionals to maintain an efficient and personalized support and follow-up of patient, and (iv) reduce HF patients admission and readmission rate, which have a high economic impact.

Hospital admissions are the main cost component of HF for health systems. Additionally, and not less important, the days of hospital stay due to decompensated HF have a deleterious impact on the prognosis of the illness itself, as well as on the psycho-emotional well-being of the patients, their relatives and/or care givers. Finally, together with prognostic and economic aspects, among others, the social repercussion of episodes of HF (sick leave, dependency, etc.) must be considered.

Finally, we must stress that heart failure is a very complex disease with multiple factors, and its predictiveness is complex. Nevertheless, larger amount of data and the registration of all type of decompensations is key to improve the current model.

5.2.3. Environmental factors

In this study, the impact of previous HF decompensations and different environmental factors on hospital admissions due to worsening HF is studied. For that, a regression model for time series was built, and the external attributes that most affect the number of hospitalisations were tested. The attribute with most impact on the number of admissions is a previous HF admission. It also has a cyclical distribution with a similar pattern repeated every year: the period with most decompensations is the cold one and this number depends on the number of admissions in the previous weeks. Regarding the external attributes that most affect the number of hospitalisations, air temperature is concluded to be the most significant environmental factor (negative correlation), although some other attributes, such as precipitation, are also relevant. So, a significant winter peak in HF-related hospitalisations has been identified. These population-based findings are in accord with the results of other studies examining this topic [90] [91] [94] which found a similar seasonal variation in discharges.

The hemodynamic stresses and neurohumoral activation that accompany a reduction in temperature may exacerbate HF, induce myocardial ischemia and precipitate arrhythmias which in turn could further increase the risk of HF decompensation. Other mechanisms could also underly the seasonal variation in HF-related morbidity and mortality. Respiratory infections, especially those related to influenza, are more frequent in winter and could precipitate HF [94] so a significant percentage of HF hospitalisations could be accounted for by this seasonal increment in respiratory diseases.

Moreover, this analysis shows a consistent association between increasing levels of some ambient pollutants, such as SO2 (precursor of acid rain) and NOX air (major air pollutant formed by combustion systems and motor vehicles).

These results contrast to those obtained by Burnet [90] and Morris [93], in which concentrations of carbon monoxide in big cities of the USA and Canada displayed the strongest and most consistent association with hospitalisation rates among the pollutants. This association was independent of season, temperature, and other major gaseous pollutants. Nevertheless, it is possible that the observed association represented the impact of some other, unmeasured pollutant or group of pollutants covarying in time with carbon monoxide.

However, the climate in Bilbao, the environmental aspects and the socio-economic conditions are different to those described in other cities included in this kind of studies. Bilbao has an oceanic climate, the rain rate is high, and traffic is restricted to certain areas of the city, so the dispersion of pollutants is higher and that may explain the distribution and effect on health of air pollutants.

In fact, carbon monoxide exposure leads to elevations in the systolic blood pressure and, to a lesser extent, the heart rate and respiratory quotient, altering the ability of haemoglobin to transport oxygen to a degree enough to induce cardiac disease. Nitrogen oxides (NOX) and sulphur dioxide (SO2) are other important ambient air pollutants. NOX exposure increases the risk of respiratory tract infections through the pollutant's interaction with the immune system. Sulphur dioxide (SO2) contributes to respiratory symptoms in both healthy patients and those with underlying pulmonary disease. An alternative mechanism for the induction of congestive heart failure by air pollutants involves direct myocardial toxicity. Moreover, direct toxicities of these pollutants to the heart are very well demonstrated (Mustafic et al 2012) [144]) as for the brain more recently, increasing risk of stroke (Hadley et al, 2018) [145].

These data support the warning issued by the World Health Organization (WHO): air pollution is responsible for about seven million deaths a year in the world, 2.5 million of which correspond to heart diseases (25%), and 1.4 million to stroke (24%). In this regard, there are several Spanish studies indicating that 93% of the Spanish population breathes air that exceeds the limits considered dangerous to health.

All in all, our analysis of data demonstrates the impact of pollutant agents and the seasonality of hospital admissions for HF. Our findings have potentially important management implications. First, increased vigilance in winter is important in patients with HF in order to detect and correct decompensation at an early stage. Second, pneumococcal and influenza immunization should be encouraged, not just to avoid these infections, but also for their potential role in winter exacerbations of HF. Finally, this study warns about new effects of these pollutants and opens the way for a more exhaustive study of these parameters and how to improve the quality of our environment.

VI. CONCLUSIONS

The conclusions of this study are:

1. Telemonitoring has not shown a statistically significant reduction in the number of HF-related hospital admissions in the IG compared to the CG.
2. With the limitations of this study, we have observed a statistically significant reduction in mortality in the IG with a considerable percentage of deaths from non-cardiovascular causes.
3. Men and ischemic cardiomyopathy have the highest risk of decompensation and hospitalisation in our study.
4. We have observed a high rate of participation and transmission among patients in the IG.
5. In our group there are no differences between the number of HF-related hospital admissions according to the transmissions made by telemonitoring.
6. The patients have considered the RPT programme as a tool that can help them in the control of their chronic disease and in the relationship with health professionals.
7. Significant weight increases, desaturation below 90%, perception of clinical worsening, including development of oedema, worsening of functional class and orthopnoea are good predictors of heart failure decompensation.
8. Machine learning techniques have improved the current alerts system implemented in our hospital. The system reduces the number of false alerts notably although it entails a decrement on sensitivity values.
9. The best results are achieved with the predictive model built by applying NB with Bernoulli to the combination of telemonitoring alerts and questionnaire alerts (R2: Weight + Ankle + well-being plus the yellow alerts of SBP, DBP, O2Sat and HR).
10. The attribute with most impact on the number of admissions is a previous HF admission. Regarding the external attributes, air temperature is the most significant environmental factor (negative correlation) in our study, although some other attributes, such as precipitation, are also relevant.
11. This work also shows a consistent association between increasing levels SO2 and NOX air and HF hospitalisations.

VII. LIMITATIONS

Our study has several limitations:

1. Data from the CG have been collected retrospectively.
2. There are basal differences between the groups; if the sample size had been greater, the groups could have been more homogeneous.
3. The protocol of action of RPT is being adapted and is not rigid, so there is variability between professionals and over time.
4. As the clinical data used in the study is from Caucasian patients, the model may perform differently in different settings, such as in non-Caucasian population.
5. Heart failure is a very complex disease with multiple factors, and its predictiveness is complex.
6. Datasets can have errors, missing data, redundancies, noise, and many other problems which cause the data to be unsuitable to be used by the machine learning algorithm directly.
7. The amount of data required to obtain an accurate model is substantial, so larger amount of data and the registration of all type of decompensations is key to improve the current model.
8. Even with algorithms with good results for a dataset, ML models suffer from an inability to correctly detect and classify cases that they have not previously seen. Thus, the reliability and quality of the data source are essential for an algorithm to be realistic and correct.
9. There are patients that did not monitor regularly. Consequently, we only have 79.52% decompensations with 3 or more measurements during the previous week. The rest did not have even 3 measurements, and hence, they were not predictable.
10. The non-random nature of the study may have introduced selection biases even though attempts were made to minimise them in the analysis phase by controlling for possible confounding variables.
11. ML offers answers in the form of predictions, but not a biological explanation.
12. Regarding the impact of environmental factors in HF decompensations, these results may not be applicable to other regions with different climates, as temperature variations and rain rate differ from our study. Another limitation is that this is an observational study and

despite statistical adjustments, a causal and definite relationship between seasonality, environmental pollutants and hospital admissions for HF cannot be determined. Furthermore, we have relied on discharge coding, which has high accuracy in the principal position but is lower in secondary positions. As differentiating an exacerbation of respiratory disease, respiratory infection and decompensated HF is clinically difficult, particularly in the elderly, miscoding of pulmonary infection as HF may be as likely as HF miscoded as pulmonary infection.

VIII. FINAL CONSIDERATIONS

Up to now medicine has been remarkably conservative. Beyond the reluctance and resistance of physicians to change, the life science industry and government regulatory agencies have not developed at the expected speed. At present, however, this situation is changing because medicine is starting to embrace and leverage the progress of the digital era. In fact, a radical change is necessary to take medicine and health care where it needs to go, where it can go. In this aspect, doctors need to evolve, not just to survive but to thrive in the world of digital medicine.

The emerge of powerful tools to digitize human beings with full support of well-organised structures creates an opportunity to change the face of how health is delivered. This is about to innovative technologies that make for precise medicine, the avoidance of vast waste, the reduction of medical and medication errors, and a fresh individual-centric approach.

At present, indeed, medical care is largely shaped by guidelines, which are indexed to a population rather than an individual. And the evidence from clinical research is derived from populations that frequently do not translate to the real world of persons.

This behaviour may be about to change: in the era of computerised medicine, an individualised approach is mandatory: each human being needs to be seen and treated with utter respect for his or her individuality, creating valuable knowledge that can markedly improve the quality of a life. In this area, collaboration between academic centres has greatly improved with the need for "big science", bringing together multidisciplinary expertise to accomplish ambitious projects.

What is fascinating here is the paradox that our contemporary capacity to understand an individual relies on network science – the more data that can be captured and processed, the sharper the definition of a particular individual. Massive polling of the data from individuals creates a positive feedback loop, such as the overabundant data becomes more valuable and defined ‐ transforming the extensive data to real information and knowledge that can ultimately be used to improve the health of individuals. The enhancement of health in a large number of individuals is the precursor to an upgrade in population health.

If we focus on HF, we hope the future holds the development of an effective, universally applicable risk stratification model utilizing the numerous predictors of readmission that have been identified.

Perhaps better risk models will allow providers to better tailor comprehensive HF management programmes, therapies, follow-up, and allocation of resources according to the needs of each individual patient and thus lead to reduced re-hospitalisation of patients with chronic HF.

Thus, the digital revolution and artificial intelligence in particular, can do more than enhance diagnoses and treatments. It can also save doctors from doing unnecessary tasks, allowing them to spend more time connecting with their patients, enhancing humanity. Maybe this would permit us to use the future to bring back the past: to restore the care in health care by giving both the gift of time to clinicians and empowerment to patients (for those who want it). This will allow the possibility of more time providing thorough, intimate, and meaningful care for our patients, as no machine can.

What matters now is not the new capabilities we have, but how we turn those capabilities, both technical and social, into opportunities. A new path in history has been charted. Let's take the digital world's profound ability to influence and apply it to our health.

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X. ANNEXES

10.1. Educational material about heart failure for patients


¡HAY QUE APRENDER A LEER LAS ETIQUETAS!
Sodio por porción
1300mg
460mg
310mg
650mg
260mg
Sodium 480mg 20%
Nutrition Facts
BAJOS EN SAL LOS QUE TIENEN MENOS DEL 5% DE LO RECOMENDADO POR DÍA
ALTOS EN SAL LOS QUE TIENEN MAS DEL 15% DE LA CANTIDAD RECOMENDADA POR DÍA.
ALTO CONTENIDO EN SAL SÍ TIENEN MÁS DE 250mg de SODIO POR PORCIÓN


Cuanto más elaborada es la comida contiene más Sodio/Sal!!
SALMON FRESCO 56 mgr Sodio
SALMON EMPAQUETADO 272 mgr Sodio
PEPINILLO NATURAL 2 mgr Sodio
PEPINILLOS ENLATADOS 395 mgr Sodio
TOMATE NATURAL 4 mgr Sodio
SALSA TOMATE CASERA 40 mgr Sodio
TOMATE NATURAL EN LATADA 200 mgr Sodio
TOMATE COCINADO 600 mgr Sodio


¿Cómo puedo prevenir la INSUFICIENCIA CARDIACA?
BEBA UNA CANTIDAD DE LIQUIDOS REGULAR
ENTRE 1 LITRO Y LITRO y MEDIO DE LIQUIDO CADA DÍA
-MEDIO LITRO MÁS DE LIQUIDOS EL DÍA QUE SUDE PORQUE HACE CALOR, TIENE FIEBRE O SI TIENE DIARREA-
ACUERDESE QUE LA FRUTA, LECHE, SOPAS SE CONSIDERAN LIQUIDOS
250ml
250ml
250ml
250ml
1 – 1½ LITRO POR DIA
SI COMIENZA A RETENER LIQUIDOS
(SUBE DE PESO O COMIENZAN LOS SINTOMAS DE ALERTA)
EVITE COMER CON SAL Y NO BEBA DEMASIADO LIQUIDO


¿Cómo puedo prevenir la INSUFICIENCIA CARDIACA?
- NO REALICE ESFUERZOS QUE LE PROVOQUEN FATIGA.
EVITE LAS TEMPERATURAS EXTREMAS.
NO SALGA A HORAS DEL DIA CALUROSAS O FRIAS.
NO SE AUTOMEDIQUE
HAY MEDICACIONES – COMO LOS ANTIINFLAMATORIOS-
(MEDICACIONES PARA EL DOLOR DE HUESOS O BRONQUITIS)
QUE PUEDEN RETENER LIQUIDOS
Consulte con su centro de salud sí tiene dudas sobre el ejercicio que puedee realizar o si necesita medicación


¿Cómo puedo prevenir la INSUFICIENCIA CARDIACA?
LA MEJOR FORMA DE RECONOCER QUE SE ESTAN RETENIENDO LIQUIDOS ES PESANDOSE TODOS LOS DIAS.
COMPARE LO QUE PESA CADA DÍA (A LA MISMA HORA Y PESO)
SÍ RETIENE LIQUIDOS – SUBIRÁ DE PESO
SUBIDAS DE MEDIO KILO EN UN DÍA O DE 200 GR PERO VARIOS DIAS SEGUIDOS SIN HABER COMIDO MÁS, LE PUEDEN AVISAR ANTES QUE APAREZCA LA FATIGA.
RECUERDE SU PESO SIN RETENCIÓN DE LIQUIDOS
SI SUBE DE PESO DE FORMA BRUSCA O PROGRESIVAMENTE:
- QUITE TODA LA SAL DE LA COMIDA Y NO BEBA MAS DE 1 LITRO DE LIQUIDO AL DÍA.
- REVISE QUE TOMA CORRECTAMENTE LA MEDICACIÓN INDICADA.
- ASEGURESE QUE NO TOMA PASTILLAS NUEVAS (EFERVESCENTES/ANTIINFLAMATORIOS).
- PIDA CITA EN SU CENTRO DE SALUD PARA CONSULTAR.


¿QUE TENGO QUE HACER AL VOLVER A CASA?
HAY QUE TOMAR LAS PASTILLAS
COMO LE INDIQUEMOS AL ALTA DEL HOSPITAL
- ASEGURESE DE QUE LO HA ENTENDIDO BIEN
- PIDA AYUDA O PREGUNTE ANTES DE DEJAR EL HOSPITAL
SI LE RESULTA COMPLICADO SEGUIR EL TRATAMIENTO
PIDA AYUDA
EN EL CENTRO DE SALUD, FARMACIA, A UN FAMILIAR, UTILICE UN PASTILLERO….
SI AL LLEGAR A CASA, LA MEDICACION NO LE SIENTA BIEN
CONSULTE EN SU CENTRO DE SALUD, NO LA DEJE SIN PREGUNTAR


¿QUE TENGO QUE HACER AL VOLVER A CASA?
COMIENCE A MOVERSE POCO A POCO
LOS PRIMEROS DÍAS POR CASA REALICE PASEOS Y EJERCICIOS QUE NO LE PROVOQUEN FATIGA.
CUANDO SE SIENTA BIEN - SALGA A LA CALLE EVITANDO CUESTAS Y HORAS DE CALOR O FRIO.
EL EJERCICIO QUE NO LE PROVOCA FATIGA ES BUENO PARA SU CORAZÓN
DESCANSE AL MENOS 8 HORAS
PERO EVITE PERMANECER EN LA CAMA
Y LAS SITUACIONES ESTRESANTES
REALICE COMIDAS SANAS: SIN GRASA Y SIN SAL
SI TIENE SOBREPESO:
TIENE QUE COMER MENOS, MAS SANO Y PASEAR MAS.


SI TIENE OTRAS ENFERMEDADES COMO:
DIABETES, TENSION ALTA , SOBREPESO O BRONQUITIS
DEBE CUIDARLAS PARA MEJORAR LA INSUFICIENCIA CARDIACA
UNA DIABETES BIEN CONTROLADA AYUDA A SU CORAZÓN
RECUERDE LO IMPORTANTE QUE ES ADELGAZAR, HACER EJERCICIO, UNA BUENA ALIMENTACIÓN Y SEGUIRLAS INDICACIONES/CONTROLES
UNA TENSIÓN ARTERIAL CONTROLADA AYUDA A SU CORAZÓN
RECUERDE LO IMPORTANTE QUE ES COMER CON MINIMA SAL, TOMAR LA MEDICACION COMO LE HAN INDICADO, EVITAR EL ALCOHOL Y HACER EJERCICIO
REDUCIR EL SOBREPESO AYUDARA A SU CORAZÓN
SI SUFRE DE BRONQUIOS TOME LOS INHALADORES COMO LE HAN INDICADO


Si se toma la tensión en su domicilio ¿cómo hacerlo?
- Después de haber estado, al menos, 5 minutos en reposo. Un periodo más prolongado si ha hecho ejercicio.
- Siéntese cómodo y relajado
* Los pies apoyados en el suelo. Sin cruzar las piernas.
* La espalda en el respaldo de la silla.
- El brazo al nivel del corazón, sin ropa que comprima y apoyado.
- Con la vejiga vacía (sin ganas de orinar)
- Tómese la tensión en dos ocasiones. Separadas en 2-5 min.
- Apunte las cifras para mostrarlas en su centro de salud junto a la fecha y la hora.
Compruebe calibración regularmente.
Tamaño manguito adecuado.
- Evite hablar durante la toma.
- No fume, ni tome café en los 30 minutos previos.
- Sin comida copiosa o alcohol en la hora previa.
- Sin tener dolor o ansiedad.
AUNQUE LA TENSIÓN ESTE BIEN DEBE ACUDIR A LOS CONTROLES PERIODICOS


LA VACUNACION ANTIGRIPAL
PROTEGE A LAS PERSONAS CON INSUFICIENCIA CARDIACA
SIGA LAS RECOMENDACIONES SOBRE VACUNACION DE SU CENTRO DE SALUD.
EN EPOCA DE GRIPE Y CATARROS: REDUZCA EL CONTAGIO
- LAVANDOSE LAS MANOS.
- EVITE CONTACTO DIRECTO CON PERSONAS ENFERMAS
SI COMIENZA CON SINTOMAS GRIPALES:
NO ABANDONE LA MEDICACION HABITUAL
CONSULTE EN SU CENTRO DE SALUD COMO ACTUAR
-PERO NO SE AUTOMEDIQUE-

10.2. Barthel Scale

Activity	Patient's situation	Score
Feeding	- Independent (food provided within reach)	10
	- Needs help cutting, spreading butter, etc.	5
	- Unable	0
Bathing	- Independent (or in shower)	5
	- Dependent	0
Dressing	- Independent (including buttons, zips, laces, etc.)	10
	- Needs help, but can do about half unaided	5
	- Dependent	0
Grooming	- Independent face/hair/teeth/shaving (implements provided)	5
	- Needs help with personal care	0
Bowels	- Continent	10
	- Occasional accident (once/week)	5
	- Incontinent (or needs to be given enemata)	0
Bladder	- Continent (for over 7 days)	10
	- Occasional accident (max. once per 24 hours)	5
	- Incontinent, or catheterized and unable to manage	0
Toilet use	- Independent (on and off, dressing, wiping)	10
	- Needs some help, but can do something alone	5
	- Dependent	0
Transfer	- Independent	15
	- Minor help (verbal or physical)	10
	- Major help (one or two people, physical), can sit	5
	- Unable – no sitting balance	0
Mobility	- Independent (but may use any aid, e.g., stick)	15
	- Walks with help of one person (verbal or physical)	10
	- Wheelchair independent, including corners, etc.	5
	- Immobile	0
Stairs	- Independent up and down	10
	- Needs help (verbal, physical, carrying aid)	5
	- Unable	0

Maximum score: 100 points (90 if wheelchair)

Score	Dependency grade
< 20	Total
20-35	Severe
40-55	Moderate
≥ 60	Mild
100	Independent

10.3. European Heart Failure Self-Care Behaviour Scale (EHFScBS)

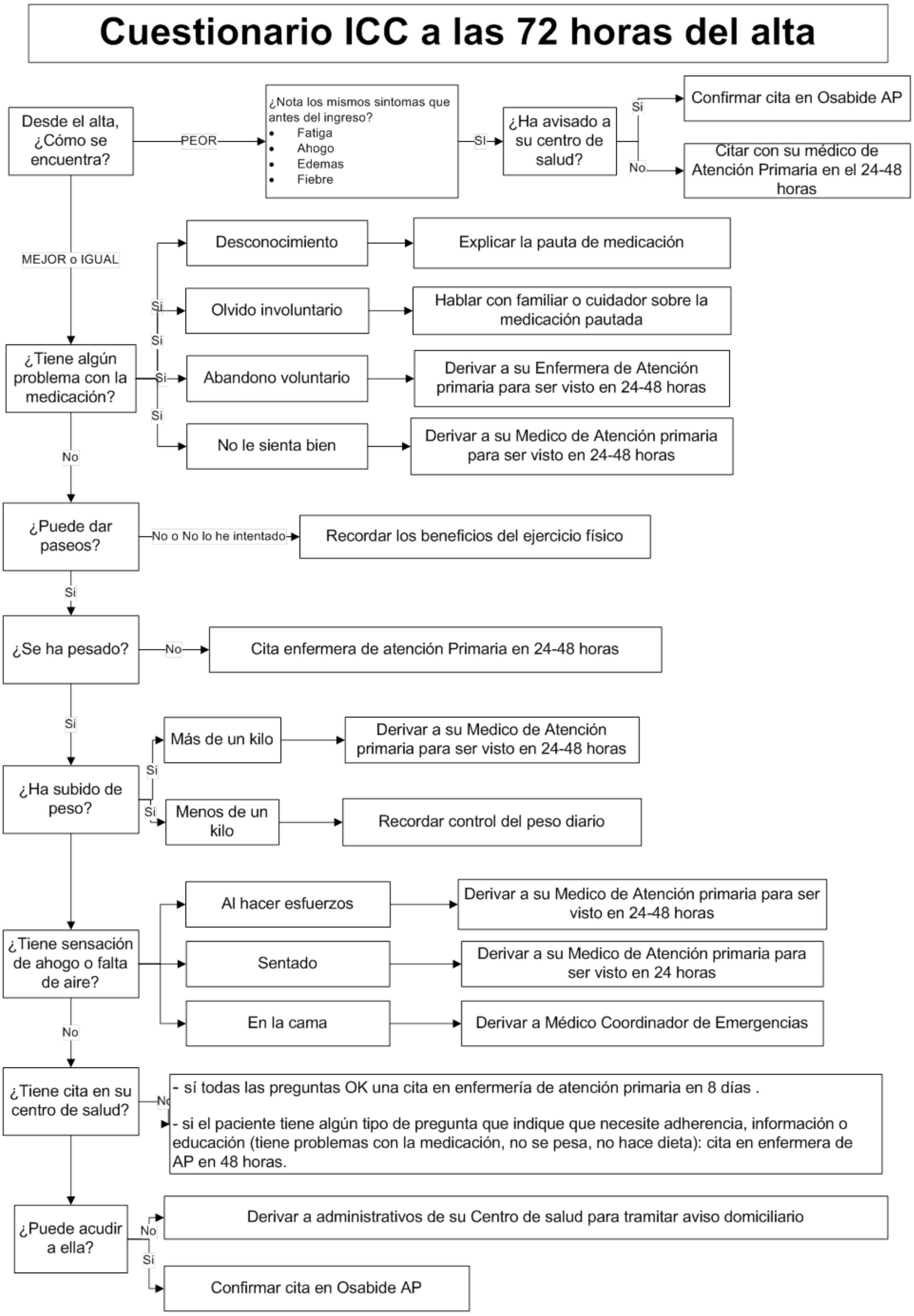
	Always	Usually	Sometimes	Hardly ever	Never
I weigh myself every day	1	2	3	4	5
In case of dyspnoea/shortness of breath, I take it easy	1	2	3	4	5
If my shortness of breath increases, I contact my doctor or nurse	1	2	3	4	5
If my feet/legs become more swollen than usual, I contact my doctor or nurse	1	2	3	4	5
If I gain 2 kg in 1 week, I contact my doctor or nurse	1	2	3	4	5
I limit the amount of fluids I drink (not more than 1.5–2 l/day)	1	2	3	4	5
I take a rest during the day	1	2	3	4	5
If I experience increasing fatigue, I alert my doctor	1	2	3	4	5
I eat a low salt diet	1	2	3	4	5
I take my medication as prescribed	1	2	3	4	5
I get a flu shot every year	1	2	3	4	5
I exercise regularly	1	2	3	4	5

Self-care level: Total score:

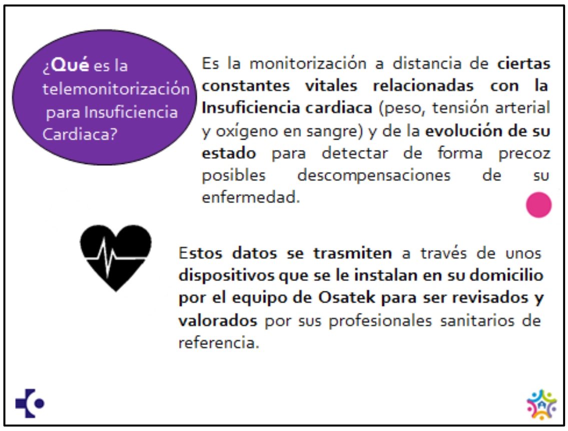
10.4. Gijon scale of social and familiar evaluation

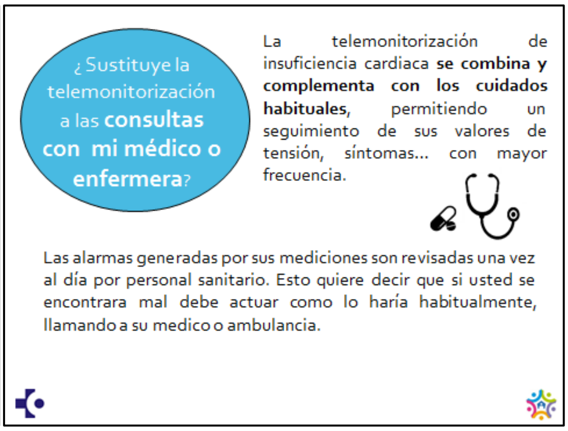
Family conditions	
He/she lives with the family, without physical/mental dependence	1
He/she lives with his/her spouse and they are of similar age	2
He/she lives with his/her spouse but has some grade of dependency	3
He/she lives alone and has sons/daughters who live near	4
He/she lives alone and does not have any son or daughter or the live far away	5
Economic situation	
>1.5 fold the minimum salary	1
From the minimum salary to 1.5-fold the minimum salary	2
From the minimum salary to the minimum pension	3
Minimum pension	4
Without incomes or incomes inferior to the minimum pension	5
Housing	
Adequate to necessities	1
Architectural barriers at home or in the entrance hall (steps, toilets, narrow doors…)	2
Humidity, lack of cleanliness, inadequate equipment (without complete toilet, warm water, heating…)	3
Lack of lift or telephone	4
Inadequate housing (shack, ruins, without minimum equipment…)	5
Social contacts	
Adequate relationships with family and neighbours	1
Relationships only with family and neighbours	2
Relationships only with family or neighbours	3
He/she does not leave home but receives visits	4
He/she does not leave home nor receive visits	5
Assistance from the social network	
With familiar o neighbouring assistance	1
Social volunteering	2
Without assistance	3
He/she is waiting for entry to a retirement home	4
He/she has permanent care	5
Total score	

10.5. 72 hours post-discharge questionnaire



10.6. Information about telemonitoring given to the patient





¿Cuáles son los posibles **riesgos** y **molestias** de la telemonitorización?

En caso de recibir un dato no esperado (pudiera tratarse de una dato correcto o de un error en la transmisión) se le indicará que realice una nueva medición para corroborar la información. Existe la posibilidad de que estas llamadas o la repetición ocasional de las mediciones **le provoque ansiedad, intranquilidad o que le resulte muy pesado.**

Podría suceder que tengamos **datos que de otra forma no se conocerían** o que los datos se evalúen de forma inadecuada, lo que podría **generar procedimientos que no se realizarían en ausencia de telemonitorización.**

¿Qué implica **participar en este estudio**?

Para participar deberá **seguir la rutina de transmisión de datos y cuestionarios utilizando el equipo de telemonitorización** según las pautas definidas sus profesionales sanitarios de referencia

Se le instalará en su hogar un kit de telemonitorización que consta de:

- Pulsioxímetro
- Tensiómetro
- Báscula digital
- Base receptora de señales

¿Qué pasará **cuando este estudio acabe**?

El **equipo responsable del proyecto se pondrá en contacto con usted** para retirarle el equipo de telemonitorización.

Se le pedirá que conteste un **cuestionario sobre su satisfacción** con respecto a la utilización de los dispositivos.

Se analizarán los resultados y se valorará si es usted un posible candidato a beneficiarse en un futuro de este tipo de intervenciones y **su médico de referencia decidirá la mejor manera de seguir tratando su condición**

¿Tiene algún **coste** para mi?

La **instalación y utilización de los dispositivos** es gratuita

La **transmisión de las medidas** se hace mediante su línea telefónica sin coste adicional alguno.

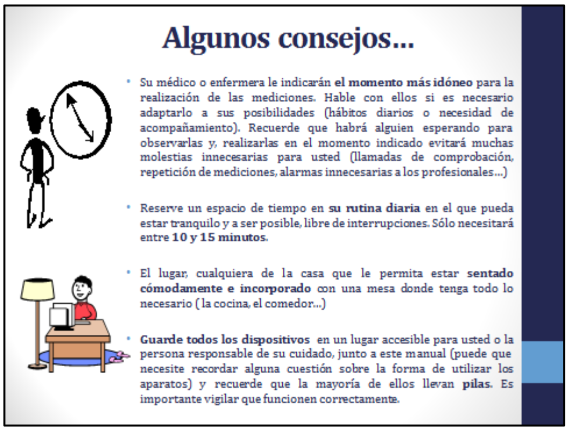
El **gasto de electricidad** es de aproximadamente 10 céntimos al mes.

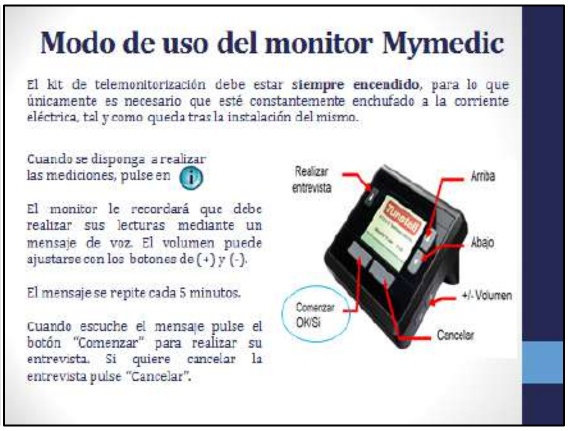
Cualquier otra acción que se pueda desencadenar durante el estudio no acarrearán ningún coste para usted.

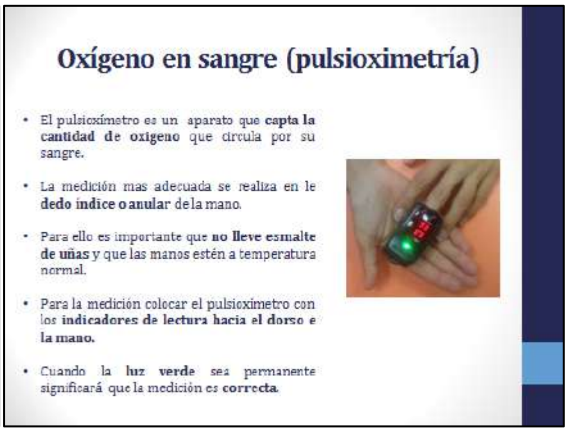
Si tienes **cualquier otra duda sobre la telemonitorización de Insuficiencia Cardiaca,** no dudes en consultar a:

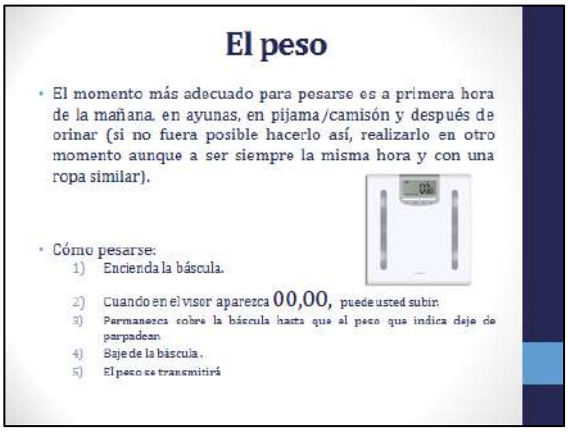
Unidad Insuficiencia Cardiaca
626 648 020

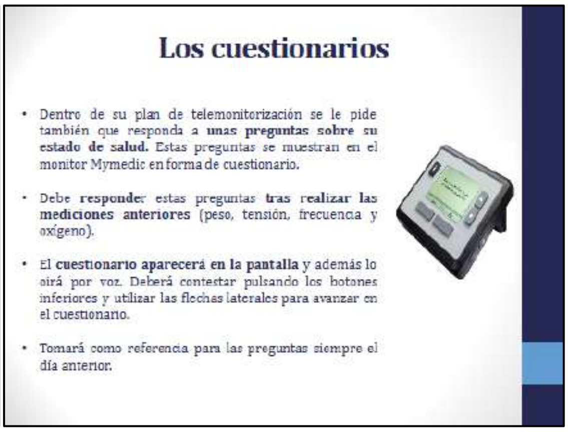
10.7. Information about how to use the telemonitoring devices.

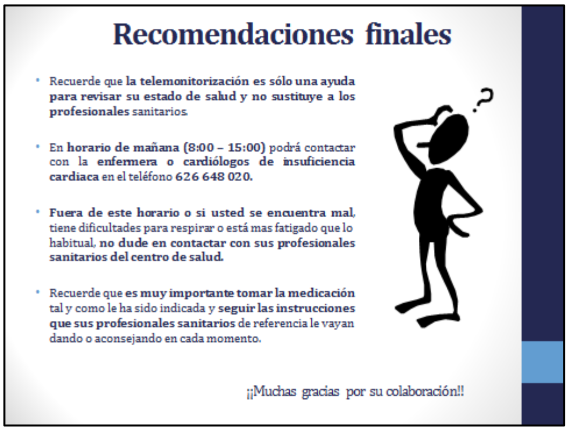




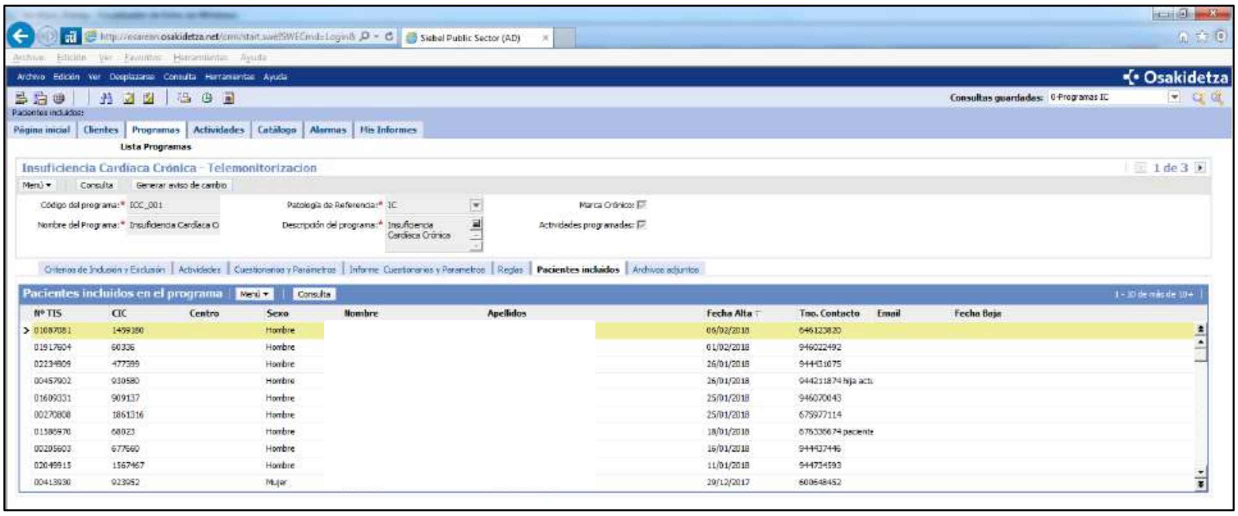


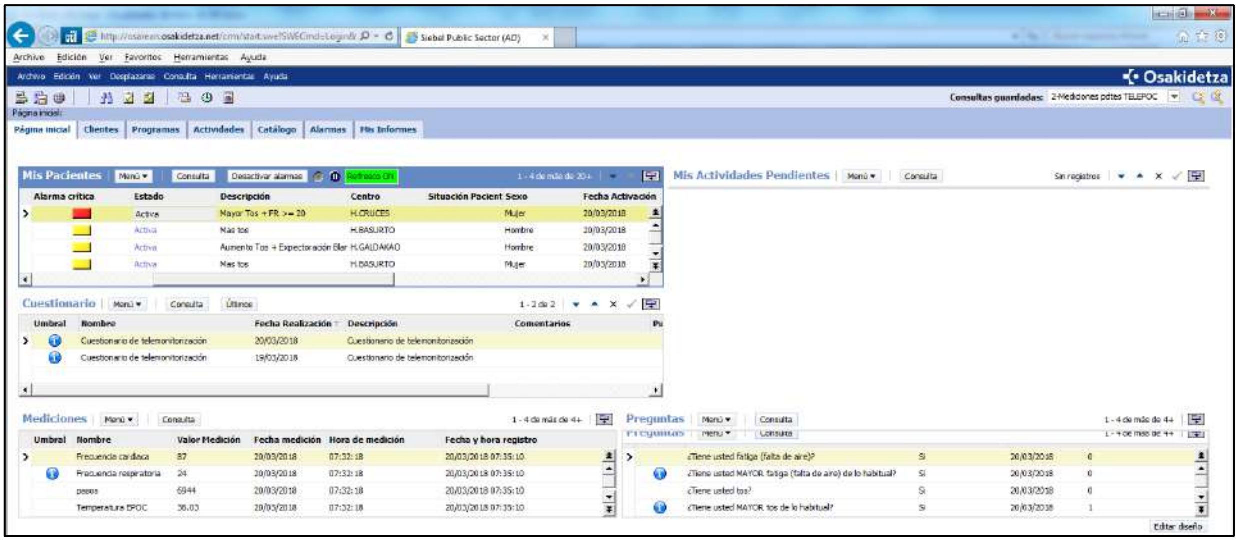

El peso
• El momento más adecuado para pesarse es a primera hora de la mañana, en ayunas, en pijama/camisón y después de orinar (si no fuera posible hacerlo así, realizarlo en otro momento aunque a ser siempre la misma hora y con una ropa similar).
• Cómo pesarse:
1) Encienda la báscula.
2) Cuando en el visor aparezca 00,00, puede usted subir.
3) Permanezca sobre la báscula hasta que el peso que indica deje de parpadear.
4) Baje de la báscula.
5) El peso se transmitirá

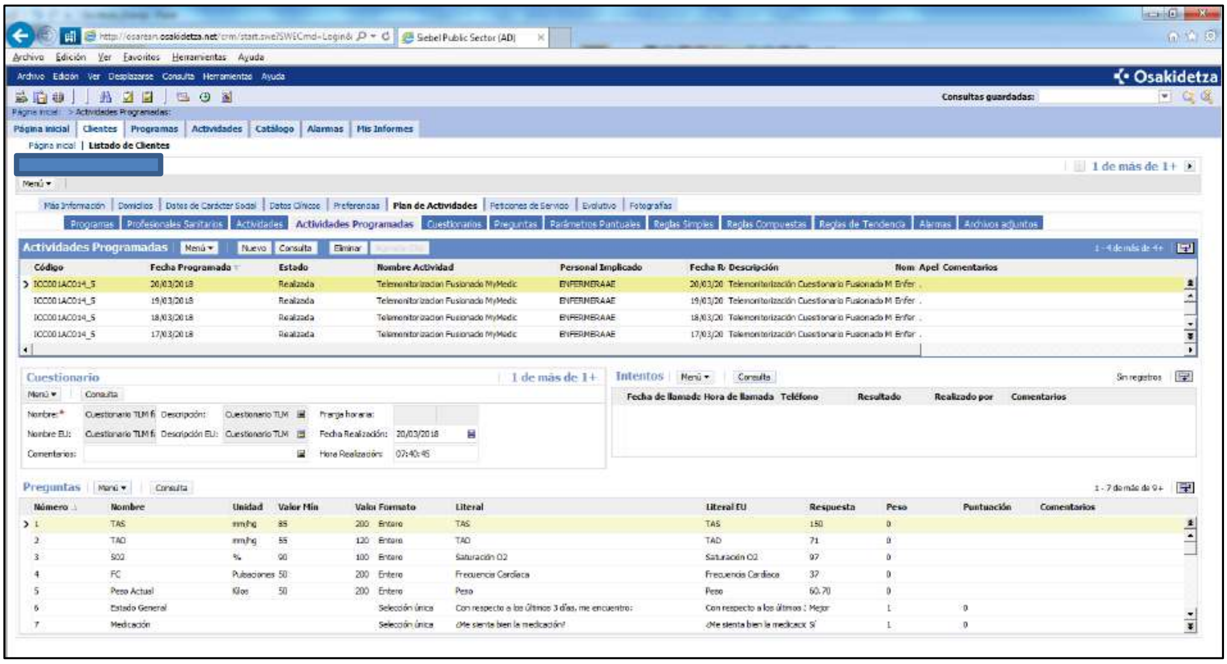

Los cuestionarios
• Dentro de su plan de telemonitorización se le pide también que responda a unas preguntas sobre su estado de salud. Estas preguntas se muestran en el monitor Mymedic en forma de cuestionario.
• Debe responder estas preguntas tras realizar las mediciones anteriores (peso, tensión, frecuencia y oxígeno).
• El cuestionario aparecerá en la pantalla y además lo oirá por voz. Deberá contestar pulsando los botones inferiores y utilizar las flechas laterales para avanzar en el cuestionario.
• Tomará como referencia para las preguntas siempre el día anterior.


Recomendaciones finales
• Recuerde que la telemonitorización es sólo una ayuda para revisar su estado de salud y no sustituye a los profesionales sanitarios.
• En horario de mañana (8:00 – 15:00) podrá contactar con la enfermera o cardiólogos de insuficiencia cardiaca en el teléfono 626 648 020.
• Fuera de este horario o si usted se encuentra mal, tiene dificultades para respirar o está mas fatigado que lo habitual, no dude en contactar con sus profesionales sanitarios del centro de salud.
• Recuerde que es muy importante tomar la medicación tal y como le ha sido indicada y seguir las instrucciones que sus profesionales sanitarios de referencia le vayan dando o aconsejando en cada momento.
¡¡Muchas gracias por su colaboración!!

10.8. Initial computing programme (CRM) for the follow-up of telemonitored patients.



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Página inicial | Listado de Clientes
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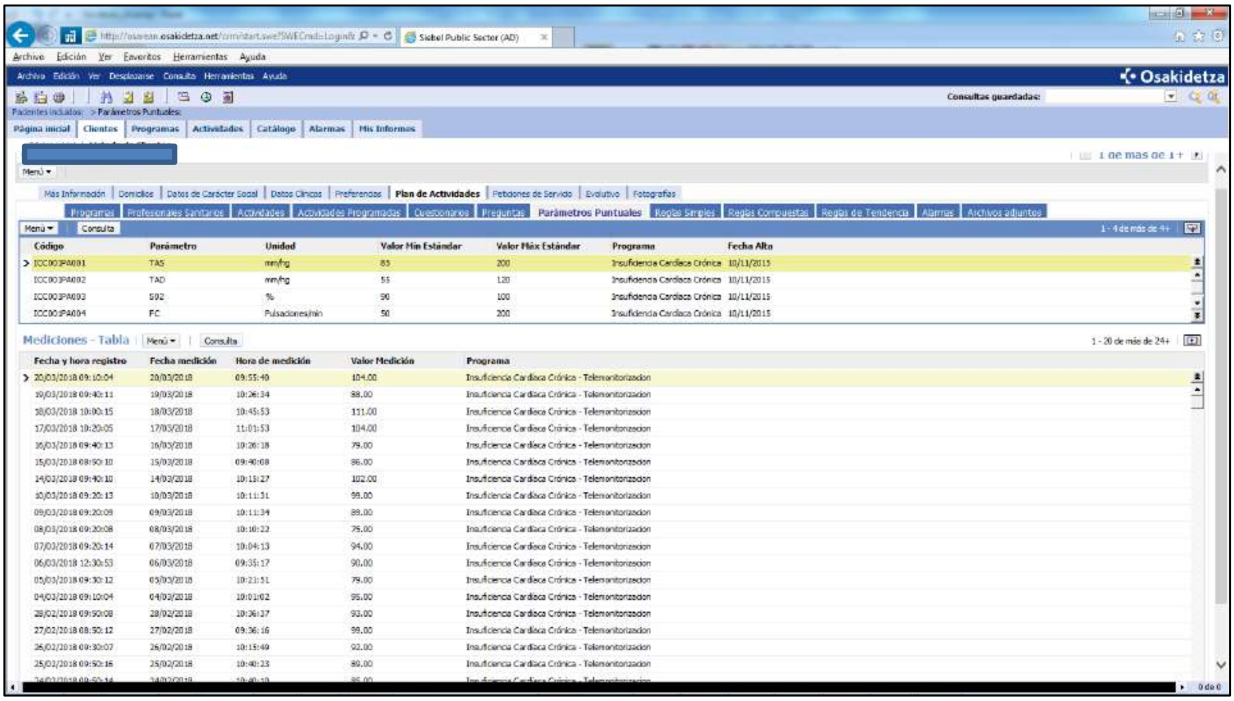
Programas Profesionales Sanitarios Actividades Actividades Programadas Cuestionarios Preguntas Parámetros Puntuales Reglas Simples Reglas Compuestas Reglas de Tendencia Alarmas Archivos adjuntos
Actividades Programadas
Código Fecha Programada Estado Nombre Actividad Personal Implicado Fecha R. Descripción Nom Apel Comentarios
Cuestionario
Intentos
Fecha de llamada Hora de llamada Teléfono Resultado Realizado por Comentarios
Preguntas
Número Nombre Unidad Valor Min Valor Formato Literal Literal EU Respuesta Peso Puntuación Comentarios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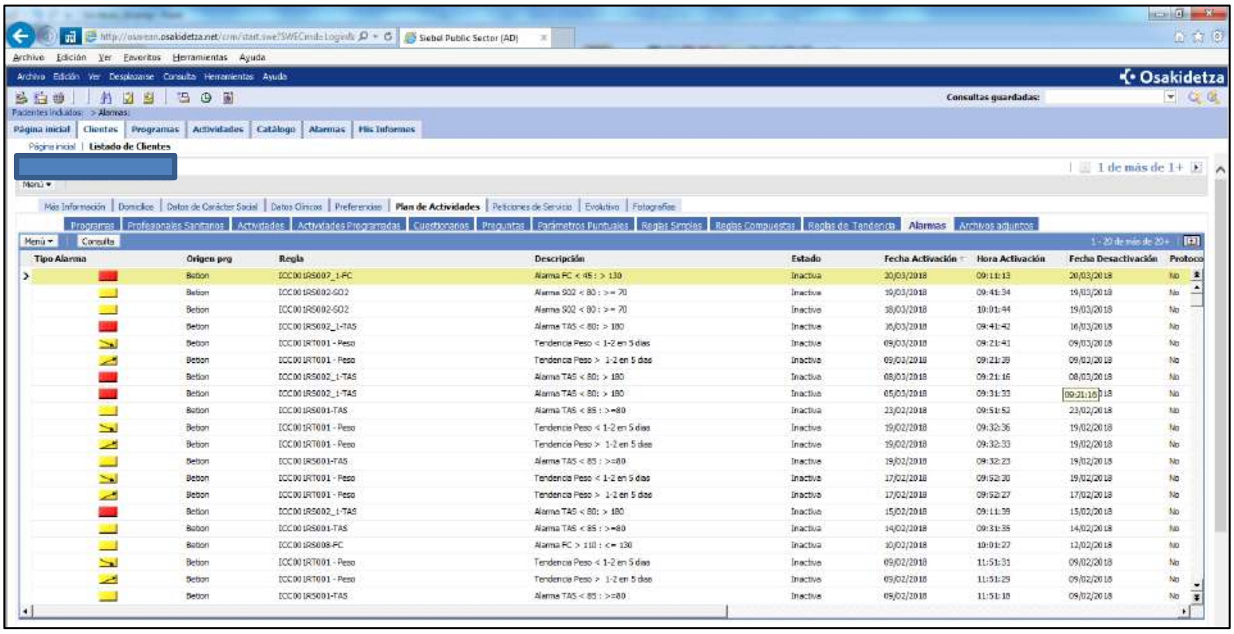
Fecha y hora registro Fecha medición Hora de medición Valor Medición Programa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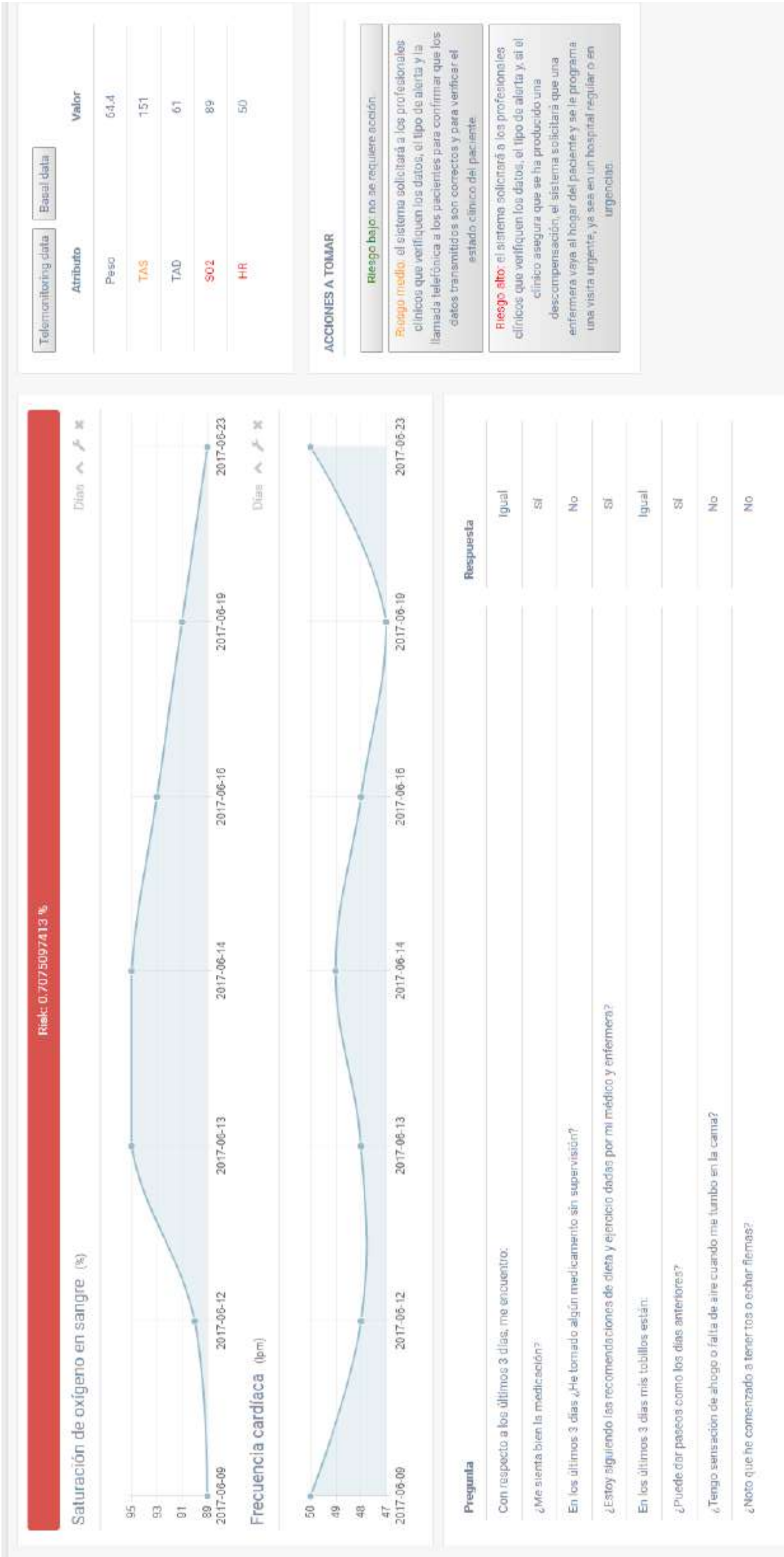
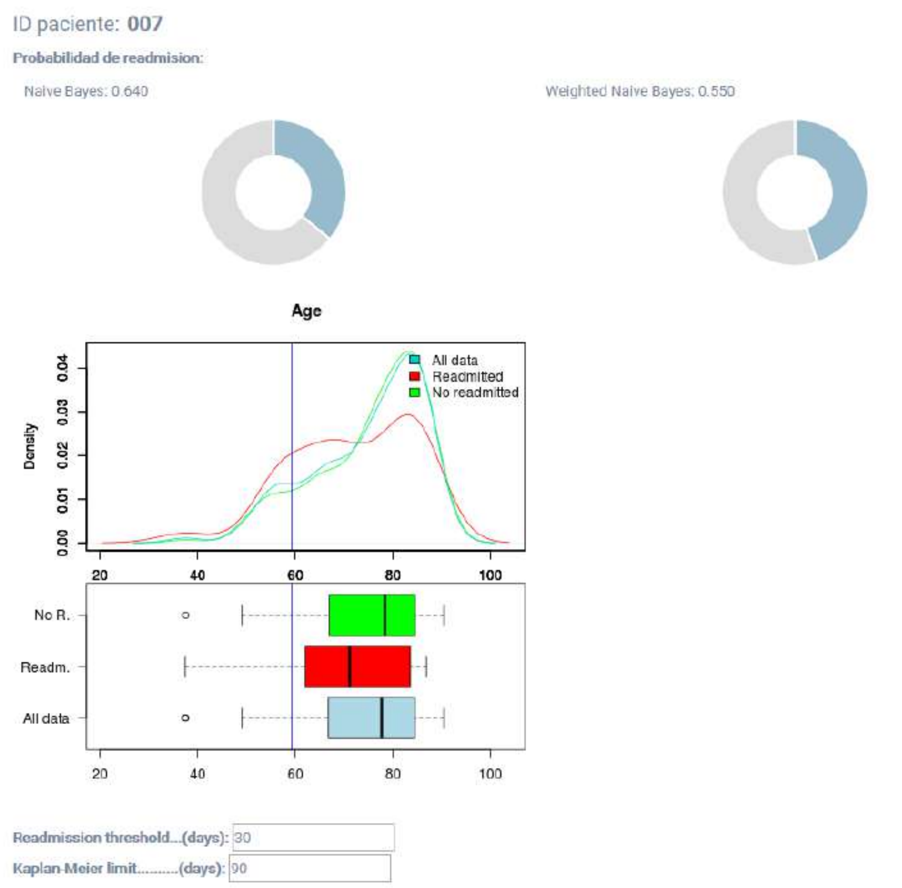
Plan de Actividades
Alarmas
Tipo Alarma
Origen prg
Regla
Descripción
Estado
Fecha Activación
Hora Activación
Fecha Desactivación

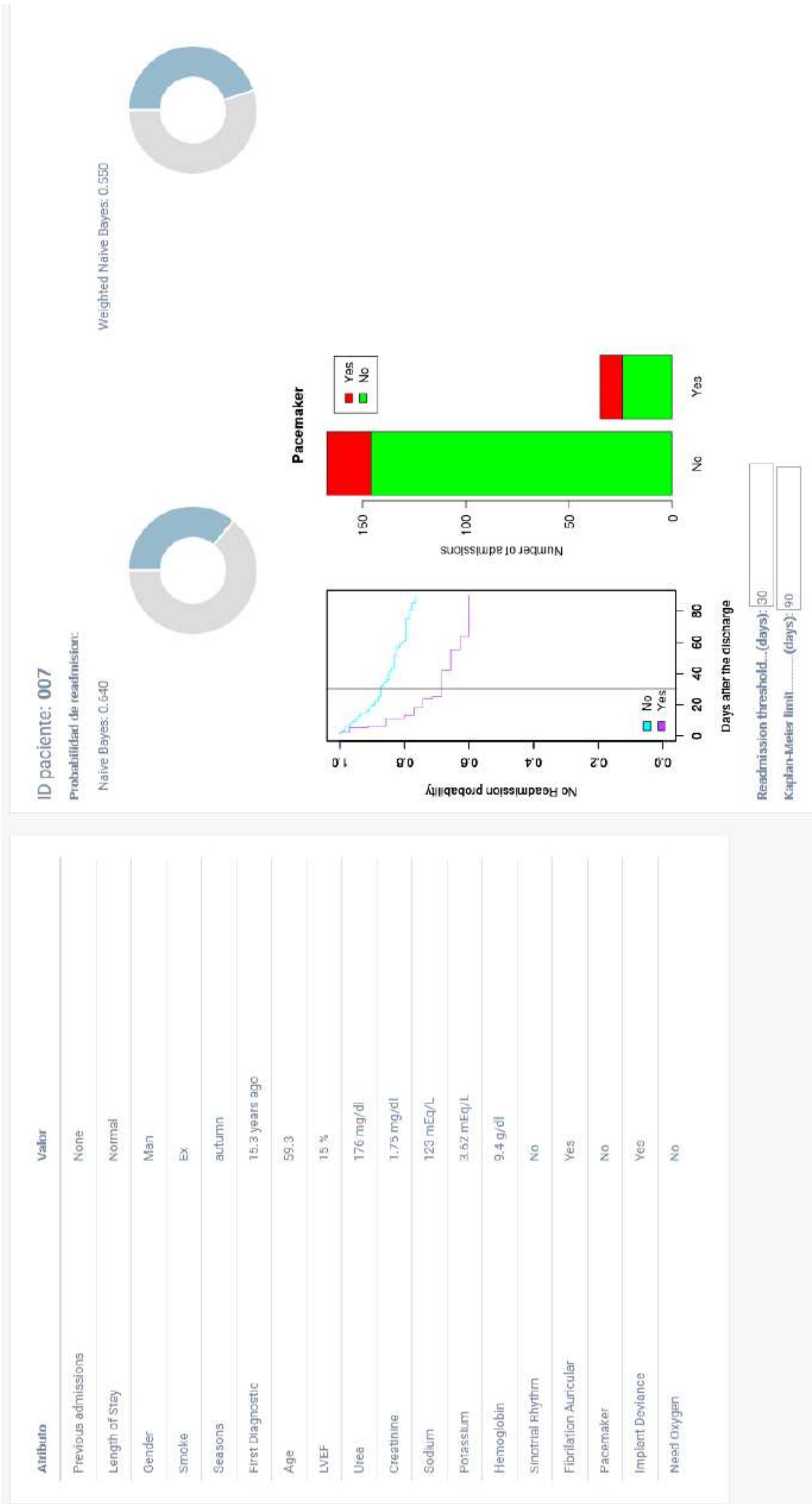
10.9. Actual computing programme for the follow-up of telemonitored patients.

10.10. Developed predictive models



Atributo	Valor
Previous admissions	None
Length of Stay	Normal
Gender	Man
Smoke	Ex
Seasons	autumn
First Diagnostic	15.3 years ago
Age	59.3
LVEF	15 %
Urea	176 mg/dl
Creatinine	1.75 mg/dl
Sodium	123 mEq/L
Potassium	3.62 mEq/L
Hemoglobin	9.4 g/dl
Sinotrial Rhythm	No
Fibrilation Auricular	Yes
Pacemaker	No
Implant Deviance	Yes
Need Oxygen	No




ID paciente: 007
Probabilidad de readmisión:
Naive Bayes: 0.640
Weighted Naive Bayes: 0.550
Pacemaker
Yes
No
Number of admissions
No Readmission probability
Days after the discharge
Readmission threshold...(days): 30
Kaplan-Meier limit..........(days): 90
Atributo
Valor
Previous admissions None
Length of Stay Normal
Gender Man
Smoke Ex
Seasons autumn
First Diagnostic 15.3 years ago
Age 59.3
LVEF 15 %
Urea 176 mg/dl
Creatinine 1.75 mg/dl
Sodium 123 mEq/L
Potassium 3.62 mEq/L
Hemoglobin 9.4 g/dl
Sinotrial Rhythm No
Fibrilation Auricular Yes
Pacemaker No
Implant Deviance Yes
Need Oxygen No

10.11. Favourable report from the Clinical Research Ethics Committee of the Basque Country

CEIC E
Euskadiko Ikerketa Klinikoetarako Batzorde Etikoa
Comité Ético de Investigación Clínica de Euskadi

EUSKO JAURLARITZA
GOBIERNO VASCO
OSASUN SAILA
DEPARTAMENTO DE SALUD

INFORME DEL COMITE ETICO DE INVESTIGACION CLINICA DE EUSKADI (CEIC-E)

Dra. Iciar Alfonso Farnós como Secretaria del CEIC de la Comunidad Autónoma de País Vasco (CEIC-E)

CERTIFICA

Que este Comité, de acuerdo a la ley 14/2007 de Investigación Biomédica, Principios éticos de la declaración de Helsinki y resto de principios éticos aplicables, ha evaluado el estudio titulado **UNIversal solutions in TElemedicine Deployment for European HEALTH care Estudio United4Health,** Código Interno: PI2014007

Versión del Protocolo: Versión 2
Versión de la HIP: GENERAL / Versión 2 (15/11/2013)

Y que este Comité reunido el día 29/01/2014 (recogido en acta 02/2014) ha decidido emitir **informe favorable** a la realización de dicho estudio por los siguientes Investigadores:

- Nekane Murga Eizagaechevarria *(Cardiología) Hospital Universitario Basurto*
- Mª Isabel Romo Soler *Comarca Bilbao*

Lo que firmo en Vitoria, a 6 de febrero de 2014

Fdo:

EUSKO JAURLARITZA
GOBIERNO VASCO
OSASUN SAILA
DEPARTAMENTO DE SALUD

21 FEB 2014

Euskadiko Ikerketa Klinikoetarako Batzorde Etikoa
Comité Ético de Investigación Clínica de Euskadi (CEIC-E)

Dra. Iciar Alfonso Farnós
Secretaria del CEIC de la Comunidad Autónoma del País Vasco (CEIC-E)

Bilbao, 23 de noviembre de 2018

Estimada Dra. ESCOLAR:

Le comunicamos que en la reunión del Comité Ético de Investigación Clínica (CEIC) celebrada el día 17 de noviembre de 2018 y analizada la documentación presentada en relación al estudio titulado:

Sistema de monitorización y guiado Inteligente para pacientes con iNsuficiencia CARdíaca. Estudio INCAR

Se emite:

INFORME FAVORABLE

NUEVA INVESTIGADORA COLABORADORA

Dra VANESA ESCOLAR PEREZ,
HOSPITAL UNIVERSITARIO BASURTO. OSI BILBAO BASURTO.
SERVICIO DE CARDIOLOGIA

Fdo.: Dr. Antonio Escobar Martinez
SECRETARIO
CEIC OSI BILBAO BASURTO