Investigating new approaches to improve Heart Failure management

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Promotor: Professor Annie Robert

A ma famille,

Le baobab s'élève par ses racines
Vous êtes le socle sur lequel ma vie s'enracine
Aucun hommage ne saurait rivaliser avec tant d'amour et de sacrifices
Mais j'espère que vous verrez en ce travail le couronnement de votre édifice

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Dans l'adversité et la douleur
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Dans la joie et le bonheur
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Près de toi désormais, ma vie elle, suivra son cours
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Peer-reviewed publications

Sawadogo K, Ambroise J, Vercauteren S, Vanhalewyn M, Castadot M, Col J, Robert A. Development of a Potentially Individualized Algorithm to Detect Heart Failure Events through Home Telemonitoring. Br J Med Med Res 2017;19(1): 1-14.

Sawadogo K, Ambroise J, Vercauteren S, Castadot M, Col J, Robert A. Télésurveillance médicale couplée au pronostic clinique des patients atteints d'insuffisance cardiaque, Bruxelles, Belgique. Rev Epidémiol Sante Publique 2016;64(4):S231.

Sawadogo K, Ambroise J, Vercauteren S, Castadot M, Vanhalewyn M, Col J, Robert A. Interaction between the Kansas City Cardiomyopathy Questionnaire and the Pocock's clinical score in predicting heart failure outcomes. Qual Life Res 2016;25:1245–1255.

Sawadogo K, Ambroise J, Vercauteren S, Castadot M, Vanhalewyn M, Col J, Robert A. Characterization of daily weight, blood pressure and pulse rate using home telemonitoring in patients with heart failure. Trop Med Int Health 2015;20(1):252.

De Schryver N, Marchandise S, Scavée C, **Sawadogo K**, Robert, A, le Polain de Waroux JB. Predictors of Heart Failure in Pacemaker Receivers with Permanent and Complete Atrioventricular Block: Lessons from a Single Center Registry. Acta cardiol 2013;68(5):539-539.

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International communications

7ème Congrès International d'Epidémiologie ADELF-EPITER : Poster. **Sawadogo K**, Ambroise J, Vercauteren S, Castadot M, Vanhalewyn M, Col J, Robert A. Interprétation du Télémonitoring en fonction du pronostic clinique des patients insuffisants cardiaques.

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Journée Doctorale de l'IRSS – UCL (2016) : Oral Presentation. **Sawadogo K**, Ambroise J, Vercauteren S, Castadot M, Vanhalewyn M, Col J, Robert A. Interpreting Home Telemonitoring according to the clinical prognosis of Heart Failure patients.

Journée des Doctorants de l'Ecole Doctorale - Ecole de Santé Publique – ULB (2014) : Oral Presentation. **Sawadogo K**, Ambroise J, Vercauteren S, Castadot M, Vanhalewyn M, Col J, Robert A. Six-Month Tele-Trends of Daily Heart Rate, Blood Pressure and Weight to Predict Cardiac Events (Prospective BELGIUM-HF Registry).

2nd IREC PhD Day – UCL (2014): Poster. **Sawadogo K,** Ambroise J, Vercauteren S, Castadot M, Vanhalewyn M, Col J, Robert A. Six-Month Tele-Trends of Daily Heart Rate, Blood Pressure and Weight to Predict Cardiac Events (Prospective BELGIUM-HF Registry)

List of abbreviations

ACE: Angiotensin-Converting– Enzyme

ARB: Angiotensin Receptor Blockers

BELGIUM-HF: Better Efficacy in Lowering events by General practitioner's Intervention Using remote Monitoring in Heart Failure

BNP: B-type Natriuretic Peptide

CAD: Coronary Artery Disease

CCE: Cardiac Composite Endpoint

CHFQ: Chronic Heart Failure Questionnaire

CRT: Cardiac Resynchronization Therapy

ECG: Electrocardiogram

EF: Ejection Fraction

ESC: European Society of Cardiology

GFR: Glomerular Filtration Rate

GPs: General Practitioners

HF: Heart Failure

HFmrEF: Heart Failure with mid-range Ejection Fraction

HFpEF: Heart Failure with preserved Ejection Fraction

HFrEF: Heart Failure with reduced Ejection Fraction

HIV/AIDS: Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome

HRQoL: Health Related Quality of Life

HTM: Home Telemonitoring

IC: insuffisance cardiaque

ICD: Implantable Cardioverter Defibrillator

IDI: Integrated Discrimination Improvement

KCCQ: Kansas City Cardiomyopathy Questionnaire

LVAD: Left Ventricular Assist Device

LVEF: Left Ventricular Ejection Fraction

MACD: Moving Average Convergence Divergence

MAGGIC: Meta-Analysis Global Group in Chronic Heart Failure

MI: Myocardial Infarction

MLHFQ: Minnesota Living with Heart Failure Questionnaire

NPV: negative predictive value

NRI: Net Reclassification Improvement

NT-proBNP: N-terminal pro-B type Natriuretic Peptide.

NYHA: New York Heart Association

PPV: positive predictive value

QoL: Quality of Life

SD: standard deviation

SDS: signal-derived-statistics

sMDRD: simplified Modification of Diet in Renal Disease

STS: Structured Telephone Support

WHO: World Health Organization

Summary

Background. Despite significant advances in therapeutic methods over the decades, HF remains today a major public health problem with a significant economic burden. The present thesis was conducted in order to investigate new alternatives to improve HF prognosis and reduce its economic burden.

Objectives. To build in a first step, a new more efficient alert triggering system for early detection of HF deterioration based on Home telemonitoring principle. To assess in a second step, the complementary between quality-of-life health status measures and traditional health status measures of morbidity and mortality in defining HF prognosis.

Methods. We used data from the BELGIUM-HF project, a prospective registry of HF outpatients. Patients completed 6-month blind daily body weight, blood pressure and pulse measurements, recorded as signal data and used to build a signal score. A clinical score was computed based on the Meta-Analysis Global Group in Chronic HF (MAGGIC) formula. A score combining signal and MAGGIC score was derived. A quality-of-life score was computed using the Kansas City Cardiomyopathy Questionnaire (KCCQ). The predictive performance of these scores was assessed according to the occurrence of a cardiac composite endpoint (CCE) of death or medical emergency with or without hospitalization.

Results. The signal score included body weight's variability on 3 consecutive days, body weight's increase on 3 and 7 consecutive days, pulse's variability on 3 and 7 consecutive days, diastolic blood pressure's mean on 3 consecutive days, differential pressure's variability on 3 consecutive days. It had ability in predicting CCE. The score combining the signal score with the MAGGIC clinical score improved CCE prediction with 92% sensitivity and 77% specificity for a 25% cut-off point. Furthermore, for HF patients with a low MAGGIC score, the KCCQ score allowed to further identify a subgroup at high risk of CCE.

Conclusions. We identified two convincing and conclusive alternatives to improve HF prognosis. First, we built a new more efficient stand-alone alert triggering system for early detection and early preventive therapeutic intervention of HF deterioration which performed better than the previous systems. Second, we showed that quality-of-life health status measures and traditional health status measures of morbidity and mortality can complement each other to well-define HF prognosis.

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Chapter 1

Introduction

1.1. Definition of Heart Failure

Descriptions of Heart Failure (HF) exist from ancient Egypt, Greece and India.[1] The foxglove was already used as heart disease medicine in Roman times.[1] However, it took until 1628 and the description of circulation by William Harvey to have a good understanding of this pathologic condition.[1] Several definitions of HF were proposed since then but, because discrimination between normal and failing heart still cannot be achieved by a single measurement, no definition of HF is universally accepted.[2] The recent definition proposed by the European Society of Cardiology (ESC) is as follows: "*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*."[3] HF is a most common complication of coronary artery disease. However, other abnormalities such as those of the valves, pericardium, endocardium, heart rhythm and conduction can also cause HF or most often a combination of these abnormalities.[3] [4][4]

1.2. Terminology

Different terminologies are used for HF depending on the measurement of the left ventricular ejection fraction (LVEF). Indeed, among HF patients, there are those with normal LVEF [considered as LVEF ≥ 50%; HF with preserved EF (HFpEF)] and those with reduced LVEF

[considered as LVEF < 40%; HF with reduced EF (HFrEF)]. An LVEF of 40 to 49% represents a gray area which is now defined as HF with mid-range EF (HFmrEF).[3,5] Between these three groups, there is a difference according to patients' demographic profile, underlying aetiologies, and response to therapies. Therefore, it is necessary to differentiate them.[6] Most clinical trials after 1990 included patients with HFrEF and therefore, the effectiveness of therapies in reducing morbidity and mortality has been shown only in these patients.[3]

In HFrEF, several compensatory mechanisms and adaptive changes explaining the progression of this pathologic condition have been identified. The progression of the disease can be slowed by an interruption of this cascade allowing reducing the clinical events.[7] Contrariwise, no unifying paradigm can explain the progression of the disease in HFpEF. Indeed, a more complex and heterogeneous pathophysiology has been suggested for HFpEF in recent studies. This heterogeneous pathophysiology involves a multitude of mechanisms affecting not only the heart but also lungs, skeletal muscles and kidneys. Therefore, HFpEF is a systemic disorder which should be treated by multidisciplinary teams.[8]

1.3. Epidemiology

HF is a major public health problem which affects about 26 million adults worldwide including 15 million in Europe, leading sometimes to consider it as a global pandemic.[9] A comparison can be made with the 32 million[10] and the 35 million[11] living respectively with cancer and Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) worldwide. The prevalence of HF is difficult to interpret due to various definitions. But, in developed countries, it is approximately 1-2% of the adult population, rising to more than 10% among people older than 70 years.[12,13] (Figure 1)

Among HF patients, up to 50% have an HFpEF and this proportion has increased over time.[5] The epidemiological profile of these patients seems different from that of HFrEF patients. Indeed, compared to HFrEF, patients with HFpEF are older, predominantly women, usually have a history of hypertension and atrial fibrillation and less frequently have a history of myocardial infarction.[14,15] Patients with HFmrEF have intermediate characteristics between those of patients with HFrEF and HFpEF, but still need to be well defined by further studies.[16]

In Belgium, HF prevalence's statistics are missing but an extrapolation based on United States data allows estimating that more than 200,000 (1.8%) Belgians are suffering from HF.[17] (Figure 1) In addition, each year, 15,643 new HF patients are diagnosed.[18]

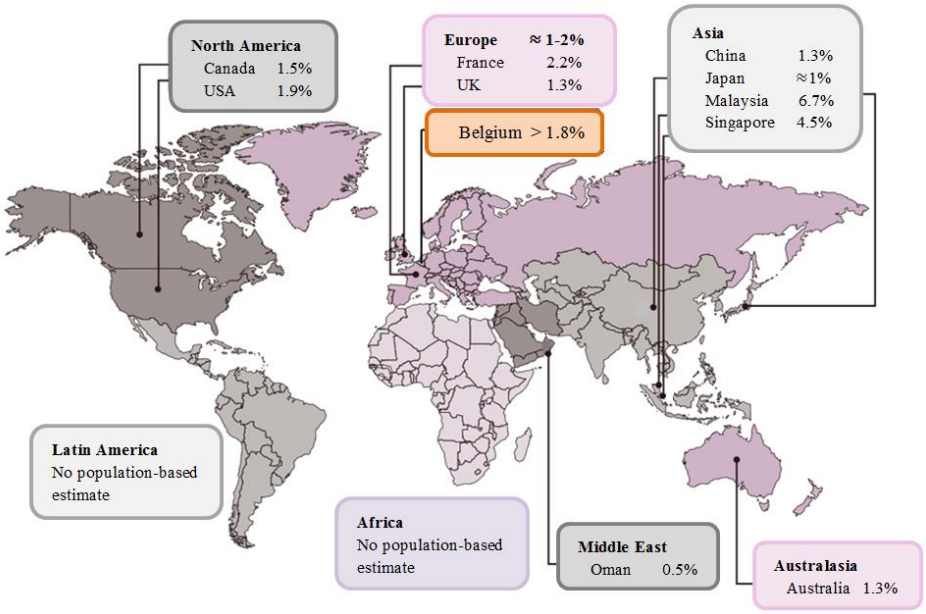


Figure 1. Proportion of the population living with heart failure in some countries across the globe. Adapted from *Ponikowski P. et al. ESC Heart Failure 2014;1:8*.[17,19]

1.4. Economic burden

The economic burden of HF is significant. Indeed, HF accounts for about 1-3% of total healthcare expenditure in North America,[20] Western Europe[21] and Latin America.[22] In 2012, HF treatment costs in Belgium were about €868.79 million accounting for 1.99% of the total health expenditure.[23] More than 60% of these costs were related to hospitalizations and the cost of medication accounted for only 6%.[24] (Figure 2)

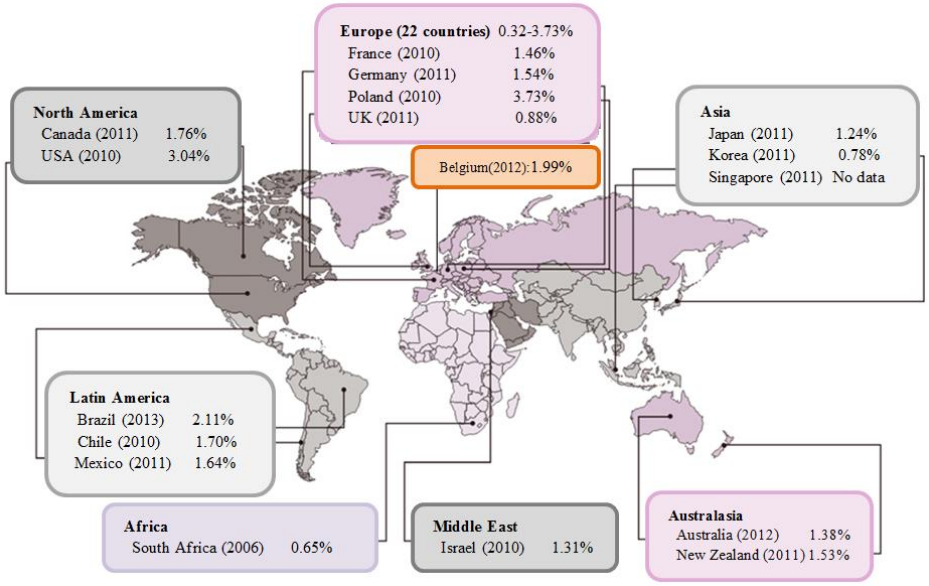


Figure 2. Proportion of hospital admissions with heart failure as the primary diagnosis compared to total hospital admissions in some countries across the globe. Adapted from *Ponikowski P. et al. ESC Heart Failure 2014;1:9*.[19,23]

1.5. Pathophysiology

Knowledge about the pathophysiology of HF remains limited and that of left ventricular systolic dysfunction is best understood. It is from studies of myocardial infarction that most of this knowledge was acquired.[25] The pathophysiology of HF is very complex and several nested compensatory mechanisms and adaptive changes are used to explain the progression of this pathologic condition. No single model can fully explain these pathophysiologic mechanisms.[26] (Figure 3)

Ventricular dysfunction follows death or dysfunction of myocytes and longstanding pressure or volume overload[27] leading to a reduction in cardiac output following an impaired contractility or relaxation.[28] Reduction in cardiac output and under-perfusion of systemic organs lead to the activation of compensatory mechanisms.[28]

There is first a hemodynamic compensatory mechanism. Two adaptive responses are observed through this mechanism. On the one hand, the reduction in cardiac output leads to a global hypoperfusion. The response to the drop in stroke volume is an increase in end-diastolic volume and pressure. This, according to the Frank-Starling law, will restore cardiac output. If sustained in the long-term, this adaptive response becomes deleterious and leads to changes in the form and function of the ventricle, a phenomenon known as ventricular remodeling. The electrical conduction and ventricular function are then affected and ultimately lead to the development of HF.[27,29,30] On the other hand, the increase in left ventricle end-diastolic pressure results in an increase in left atrial pressure, then in an increase in the pressure of the capillaries in the lungs leading to a pulmonary congestion.[29] There are currently two theories for explaining the genesis of congestion. Firstly, an exogenous fluid accumulation and, secondly, an endogenous fluid shift from venous body reservoirs.[31] The first best known theory explains that congestion occurs as a result of sodium and water retention which is gradual over several days or weeks and is accompanied by an exogenous fluid accumulation, an increase in body weight and effective circulatory volume, with prominent renal dysfunction.[30,31] The second theory has been recently proposed and it explains congestion as a consequence of endogenous fluid shift, which occurs rapidly (hours) and is accompanied by an increase in sympathetic outflow causing vasoconstriction in venous capacitance vessels and leading to a shift of volume from venous blood reservoir into the systemic circulation. This does not lead to an exogenous fluid retention or to a body weight gain.[30-32]

There is also a neurohormonal compensatory mechanism. Indeed, myocardial stress induced by the reduction in cardiac output, activates various neurohormonal pathways to offset the vascular congestion and hypoperfusion caused by ventricular dysfunction.[30] The sympathetic system is activated, leading to the release of norardrenaline (norepinephrine) which helps thereby increasing contractility, heart rate and vasoconstriction. This is helpful in the short-term; however, in a long-term, this can worsen HF prognosis.[28,30] . This system is desirable in the short-term but when prolonged, it may worsen ventricular dysfunction.[28,30]

Other compensatory mechanisms are also involved such as immune and inflammatory changes, oxidative stress, cytokine system activation, increased activation of vasodilatory molecules including atrial and brain natriuretic peptides. Moreover, genetic background, sex, age and environment may influence these compensatory mechanisms.[26,30]

With regard to the pathophysiology of HF, it seems relevant to remotely monitor HF patients' body weight, blood pressure and pulse rate.

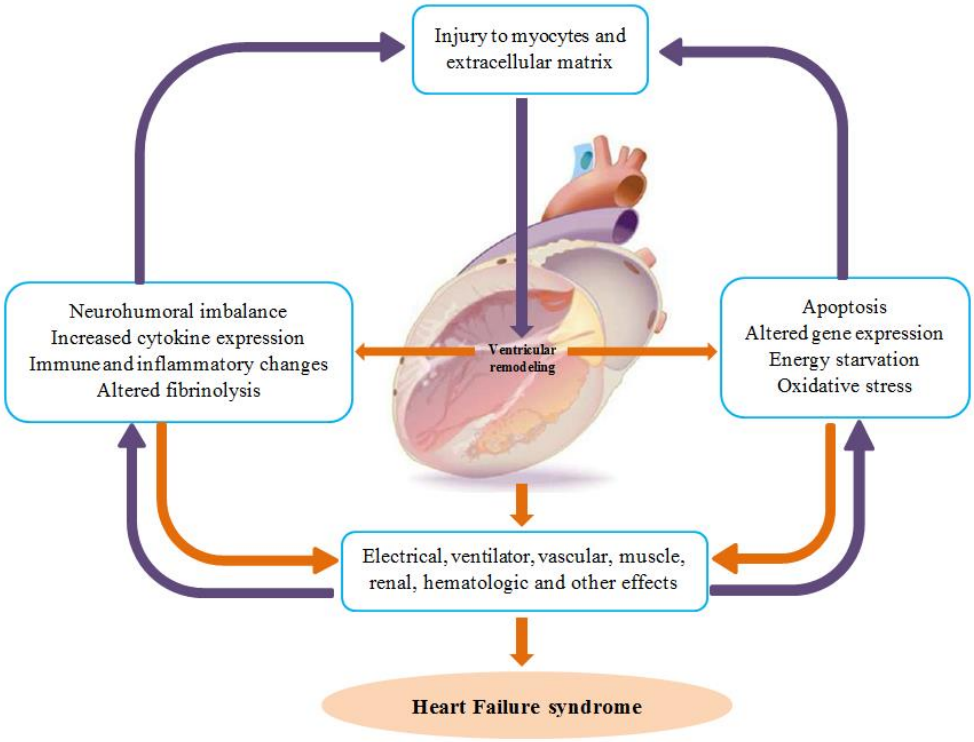


Figure 3. Pathophysiology of Heart Failure. Adapted from *McMurray J.J. N Engl J Med 2010;362(3):229*.[13]

1.6. Diagnosis

When a cardiac failure occurs, the patient and/or physician are usually alerted by signs and symptoms, reflecting most often fluid retention (pulmonary congestion and/or peripheral oedema) and less often, reduction in cardiac output with peripheral hypoperfusion; for example, symptoms such as, breathlessness, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema and signs such as low systolic blood pressure, bi-basal rales, an audible third heart sound, elevated jugular venous distension, hepatojugular reflux, hepatomegaly, ascites, peripheral edema.[25,28,31] The New York Heart Association (NYHA) functional classification is commonly used to describe the degree of the limitation of the patient ordinary activities by the typical symptoms of HF.[25] However, these symptoms and signs have an unsatisfactory sensitivity and specificity in the diagnosis of HF. Therefore, in the diagnostic algorithm (Figure 4), the diagnosis of HF must be further confirmed by appropriate additional

investigations such as electrocardiogram (ECG), chest X-ray, laboratory assessment (with specific biomarkers) and echocardiography.[25,31]

Symptoms and signs can be used to assess a patient's response to treatment and stability over time. Indeed, persistence of symptoms despite treatment reflects an inadequate treatment which should be readjusted. Likewise, worsening of symptoms places the patient at risk of urgent hospital admission or death and requires early therapeutic intervention.[3]

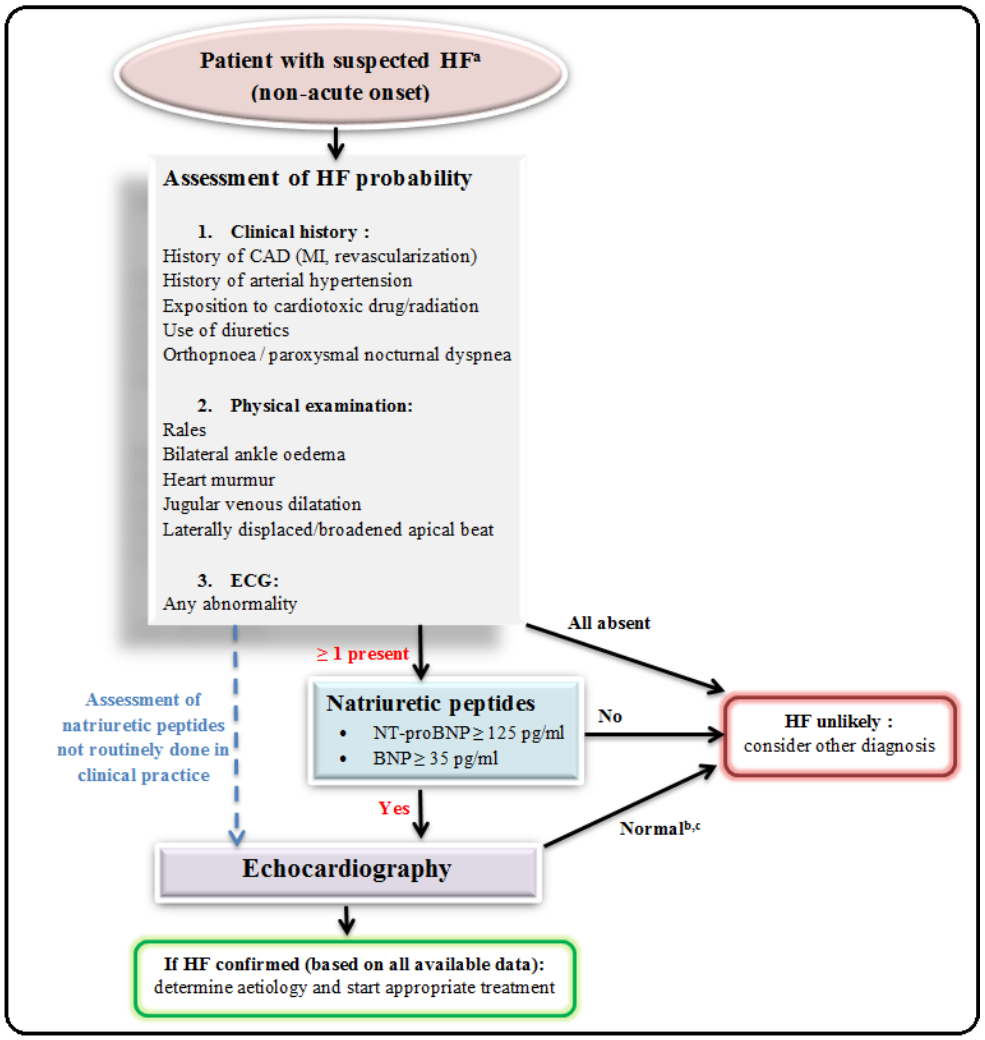


Figure 4. Diagnostic algorithm for a diagnosis of heart failure of non-acute onset. Adapted from *Ponikowski P. et al. ESC Eur Heart J 2016;37(27):2141*.[3]

BNP = B-type natriuretic peptide; CAD = coronary artery disease; HF = heart failure; MI = myocardial infarction; NT-proBNP = N-terminal pro-B type natriuretic peptide.

[a]Patient reporting symptoms typical of HF.

[b]Normal ventricular and atrial volumes and function.

[c]Consider other causes of elevated natriuretic peptides.

1.7. Treatment

HF treatment aims to improve the clinical status, the functional capacity and the quality of life of patients, thereby, preventing hospital admission and reducing mortality. HF treatment includes both lifestyle modification as well as medical therapies and depends on the type of HF.[3,29] For HFrEF, treatment may be pharmacologic and/or non-pharmacologic. Pharmacologic management includes several drugs whose roles are to prevent the deleterious effects of compensatory mechanisms activated in response to cardiac failure. Angiotensin-converting– enzyme (ACE) inhibitors and angiotensin-receptor blockers lead to peripheral vasodilatation by decreasing afterload. They also affect left ventricular hypertrophy, remodeling, and renal blood flow. Aldosterone antagonists neutralize the effects of aldosterone. Diuretics decrease preload. Digoxin increases contractility. Inotropes increase myocardial contractility. Beta-blockers slow the heart rate, decrease blood pressure, and have a direct beneficial effect on the myocardium, enhancing reverse remodeling. Alpha-blockers can cause vasodilatation. Vasodilators decrease afterload. Nesiritide decreases preload and afterload. Non-pharmacologic management includes cardiac resynchronization therapy (CRT) which aims to improve ventricular efficiency by simultaneously pacing both ventricles. Lifestyle modification includes physical exercises which aim to improve peripheral blood flow and skeletal-muscle physiology.[3,29,33] (Figure 5)

No therapy has been shown to improve outcome in patients with HFpEF or HFmrEF. For these patients, the current therapy aims to reduce volume overload (when present), to treat cardiovascular and non-cardiovascular co-morbidities and to develop additional strategies to reduce symptoms and improve well-being.[3,5] But, the recent findings in HFpEF pathophysiology open the way for new therapeutic targets.[8]

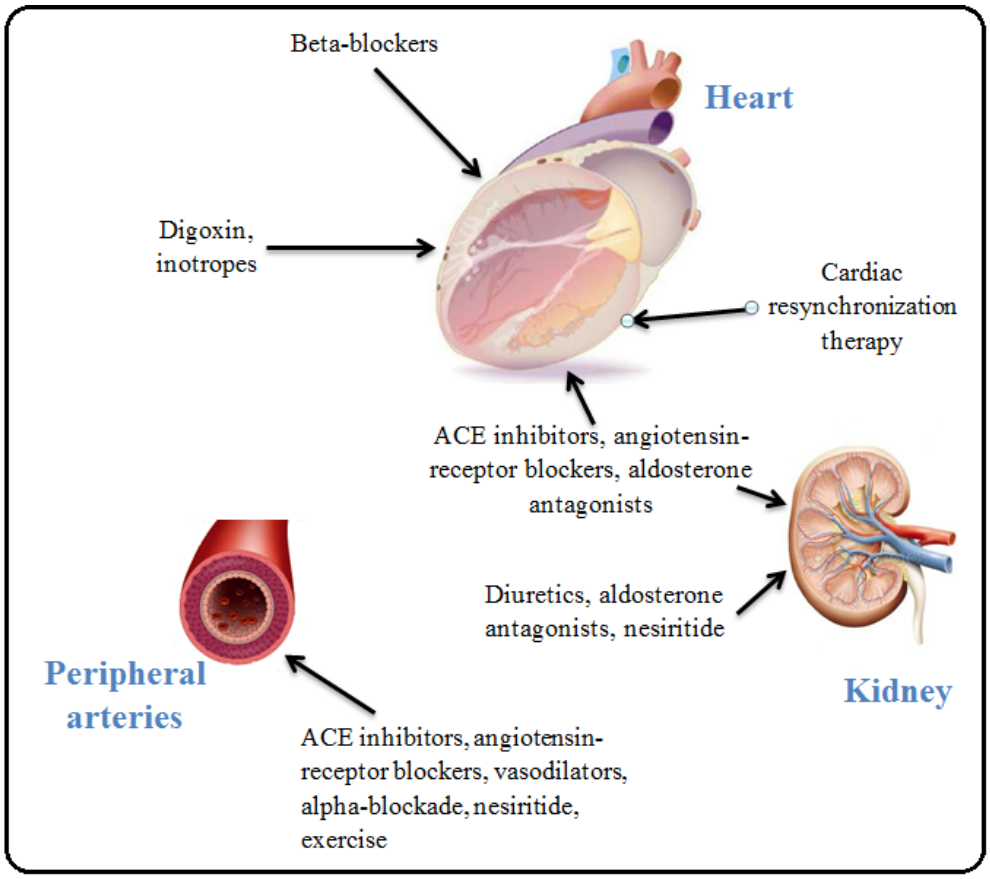


Figure 5. Primary targets of treatment in heart failure. Adapted from *Jessup M. et al. N Engl J Med 2003;348(20):2010.*[33]

1.8. Management of Heart Failure in Belgium

The management of HF in Belgium is carried out by general practitioners (GPs), office-based cardiologists or internists and hospitals. It differs according to the category of HF patients. GPs constitute most of the time, the primary care for HF patients.[24] Indeed, 70% of them admitted to diagnose and manage HF alone in patients with NYHA class II-III against 25% cardiologists and 5% internists or geriatricians. This proportion decreased to 40% in patients with NYHA class IV.[34] They usually rely on ECG and X-rays to confirm the diagnosis and sometimes the patient is referred for an echocardiography. This last test as well as stress test and cardiac catheterization are most often requested by cardiologists.[24]

Asymptomatic chronic HF is often an incidental finding in the course of a concomitant condition or during screening of other diseases for which an echocardiography is often performed. Therefore, for these asymptomatic patients, the cardiologist, inside or outside the hospital is the first one involved in the diagnosis.[24] If the patient is not hospitalized, a treatment is proposed by the cardiologist. This treatment will be initiated by him or by the GP who will have to follow the evolution and to readjust the treatment if necessary. If the patient

is hospitalized at the time of the diagnosis, the treatment is initiated by the cardiologist and continued care will be assured by the GP.[24]

Symptomatic HF is most often clinically suspected by the GP in the presence of severe symptoms. He/her can then confirm the diagnosis by means of laboratory tests, ECG, chest X-rays and echocardiograms. If the GP performs examinations not carried out by the specialists he/her can then confirm the diagnosis without their advice and therefore initiates the treatment by itself. However, most of the GPs ask for an echocardiography. For these symptomatic patients, the treatment can be initiated by the GP alone or with the advice of a specialist. In case of a bad clinical course, the GP refers the patient to a specialist for further examination and treatment adjustment.[24]

Patients with acute HF are often referred by their GPs to the hospital emergency where they are evaluated and treated.[24]

In Belgium, despite efforts to set up HF programs coordinated by multidisciplinary teams (composed of cardiologists, GPs, nurses, pharmacists, physiotherapists, dieticians, social workers, surgeons, psychologists and so on),[35] a study showed that less than 30% of responding hospitals had one.[36]

Chapter 2

Rationale of the study

Age-adjusted cardiovascular disease-related mortality has declined by about two-thirds in developed countries during the past half-century except for HF.[37] HF management has evolved over the decades and can be divided into several eras. The "Non-pharmacologic Era" was prior to 1980's. At that time, HF management was focused on lifestyle changes such as bed rest, inactivity and fluid restrictions, as well as on digitalis and diuretics which represented the mainstay of treatment.[38] The "Pharmacologic Era" began in 1980's with the publication of the Vasodilator Heart Failure Trial (V-HeFT) which showed that the combination of nitrates and hydralazine had some benefit for HF patients.[38-40] From there, the "Pharmacologic Era" continued over the decades with the progressive understanding of HF pathophysiology. Thus, in the 1990's, ACE inhibitors, beta-blockers and spironolactone have shown their ability to alter the natural history of HF progression.[41-43] Then, in the 2000's, Angiotensin Receptor Blockers (ARB) were introduced in the management of HF.[44] Beside pharmacologic progress, a new era in HF management began in the 2000's. It was "Device Era" also known as "Electrophysiologic Intervention" of HF. At this time, left ventricular assist device (LVAD), implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) have been shown to reduce mortality in HF.[45-48] However, despite these therapeutic advances, HF prognosis remains very bad with a still high mortality. Indeed, half of the patients die within four years after the diagnosis of HF and more than half in the year when the diagnosis is severe HF.[49] In Belgium, among the 15,643 new HF patients diagnosed each year, one in four patients die in the same year of diagnosis.[18]

The first observation was that such therapeutic measures, what effective they might be, could be beneficial only in the context of a therapeutic strategy that fully involves the patient in his / her own care. Indeed, lack of compliance with medications and lifestyle recommendations were among the primary reasons behind the high rate of HF events.[50] So, it turned out that education at discharge was a vital component for improving outcomes in HF and a strong focus on education of patients and their families was required.[51] Moreover, various studies have suggested that guidelines combined with expert advices represented an effective way of providing tailored management. However, there were a significant number of patients to be treated according to the recommendations. Thus, while patients might have contact with specialists during admission to hospital and at outpatient follow up, most care would be delivered in the community and led by GPs.[52] At the same time, the development of community based nurse specialists has proved to be beneficial by facilitating a community based multidisciplinary approach.[53] Despite this, the treatment of patients with HF remained suboptimal. A number of barriers to improve HF management have been identified by GPs including uncertainty about diagnosis, lack of awareness of relevant research evidence, lack of diagnostic resources such as echocardiography, and lack of access to specialist advice.[54] To deal with this, it was suggested to build special HF clinics led by nurses and doctors to verify diagnosis, optimize treatment, and improve information and education for patients and family members.[55] HF clinics have provided an optimal management of HF thereby, improving HF prognosis but they could not absorb the ever-increasing number of HF patients.

Thus, despite the evolving understanding of HF pathophysiology and substantial progress in the management of HF during these eras, HF remains today a major public health problem. HF is currently the leading cause of hospitalization in people older than 65 years and a diagnosis of HF is associated with a still high early post-discharge mortality and readmission rate.[56,57] In Western Europe, one in four patients is readmitted to hospital within 12 weeks of hospital discharge.[58] In a prospective observational cohort study conducted in 2 Belgian hospitals, 18.3 % of patients died or were readmitted to hospital within 3 months of hospital discharge.[59] With the aging population and the improvement of post-infarction survival in Belgium as in all developed countries, this trend is expected to continue with an increasing impact on the costs of health care.[18] Given the significant burden of HF on health care, it is necessary to develop new management strategies that may decrease morbidity, mortality, along with the substantial health care expenditures related to this disease.

In the recent years, there has been the emergence of new pharmacologic therapies. The latest promising drugs that have been approved to treat HF were the combination of Angiotensin-Neprilysin inhibitors. In addition, some of the newer agents in testing offer promising results.[56,60] Although it is recognized that pharmacologic therapies have substantly improved survival in patients enrolled in trials, evidences of improved prognosis in longitudinal studies are few and restricted to hospitalized patients.[61] Recurrent hospitalizations are usually the result of poor adherence to drug therapy, inadequate drug therapy, changes in diet or inadequate patient support.[57] Up to two-thirds of hospital admissions might be prevented by

improved management.[62] The aim of the present work was to investigate new strategies to improve HF management.

One promising alternative to this end could be the use of telemedicine or telehealth services. With the technological advances in the acquisition, storage and transmission of bio signals, the wider availability of low-cost, user-friendly equipment, there is an increasing interest in using telemedicine applications to monitor HF patients remotely. The American Heart Association has recently published recommendations for the implementation of telemedicine in cardiovascular and stroke care.[63] Is it the beginning of a new era in the management of HF? Telemedicine, a term initiated in the 1970's meaning literally "healing at a distance" consists of using information and communication technologies to improve patient outcomes by increasing access to medical care and information.[64] Telemedicine can be asynchronous involving pre-recorded data exchange between two or more persons at different times, or synchronous implying that those concerned are simultaneously connected for an immediate exchange of information.[65] In developed countries, most of the telemedicine services are focused on diagnosis and clinical management.[66] Biometric measurement devices are increasingly used to remotely monitor and manage patients with acute or chronic diseases. Some predict that telemedicine will profoundly transform the supply of health care in developed countries by shifting health care services from hospitals and clinics to households.[67]

Telemedicine for HF patients can take the form of structured telephone support (STS), non-invasive monitoring with home-based portable technology or remote invasive hemodynamic monitoring.[68,69] Meta-analyzes have shown that STS programs in HF could reduce rehospitalizations of about 25% but had no significant impact on mortality.[70,71] But these results have been challenged by the Tele-HF study in which STS provided no significant benefit over usual care in reducing rehospitalizations or deaths.[72] In this study, 14% of patients never used the system and 45% did not adhere to it, showing a failure of voice-interactive technology and the service by which it was delivered rather than a failure of the concept of STS.[69,72] Beyond telephone calls, patient monitoring can be achieved by non-invasive home telemonitoring (HTM) of physiological data with detectable changes such as body weight, blood pressure or pulse rate allowing early detection of HF deterioration.[63,69] Meta-analyzes have suggested that HTM could reduce mortality by 17% to 47% and hospitalizations by 7% to 48% during 6 to 12 months of follow-up in HF outpatients.[63,73,74] However, three major multicenter randomized controlled trials in HF failed to demonstrate superiority of HTM protocols over usual care.[4,72,75] But, as in TIM-HF trial, patients' adherence to the HTM system was highly satisfactory with 81% of patients completing more than 70% of daily transmissions.[4] Remote invasive monitoring can be used to improve home-based monitoring. It can take the form of implantable devices already used for other indications such as permanent pacemakers, ICD or CRT, or implantable hemodynamic sensors and monitors specially designed, able to measure intracardiac pressures.[63,69] A pulmonary artery sensor, the CardioMEMS device was examined in the CHAMPION trial and reduced HF hospitalizations by 30% among patients in NYHA class III with a HF hospitalization in the previous 12 months.[76] This device is now approved by the US Food and

Drug Administration in reducing HF hospitalizations.[63] However, further studies of implantable hemodynamic monitoring devices are still needed to reproduce and validate these findings.[63,68]

From the above data, it seems reasonable to postulate that HTM can be a useful tool to keep HF patients out of the hospital and improve their prognosis. However, there remain unresolved issues. Firstly, HTM can it be beneficial to all HF patients? Most studies have shown that patients with a recent HF hospitalization were more likely to benefit from this technology. Secondly, which clinical parameters should be monitored and how often? HF is a complex syndrome and the mechanism of its decompensation remains unclear. So, we cannot be limited to a single clinical parameter to guide management. Thirdly, how the recorded data should they be processed? Telemonitoring generates a huge volume of data and a visual analysis of crude data accumulating in a central database is unmanageable. Fourthly, who receives the data, who takes action and how? This issue may raise the responsibility of health professionals with respect to data processing and could represent a barrier to the effective implementation of HTM in the absence of legal and regulatory framework.[63,69]

To confer HTM technology with superiority over usual care in reducing HF readmissions and deaths, we considered to develop a new more efficient alert triggering system based on HTM principle. It will be an individualized non-invasive automated and autonomous alert triggering system for early detection and early preventive therapeutic intervention of HF deterioration. To ensure that our system will be more efficient, we proposed alternatives to some of the unresolved issues that still restrict the use of HTM in the management of HF patients. First, we considered that the prerequisite to confer HTM with a potential superiority over previous approaches would rely on formulations of monitored parameters characteristics that are associated with HF events. In the literature, there was no description on how the signals varied, nor how they were processed for changes assessment, how were defined thresholds and were assessed their predictive value of triggering an alert or an intervention. Thus, it was not clear how the monitoring contributed to the interventions, how it really predicted the events and finally yielded somewhat unreliable conclusions. To counter this, signal trend processing in relation to events was part of our study. Second, to avoid workload imposed by the visual analysis of transmitted data, we then built a dynamic algorithm-related-event through which, transmitted measurements could be daily automatically compared to preset limits for triggering an alert. Third, to have a potentially individualized alert triggering system, we took into account the baseline clinical risk of each patient as estimated by the clinical score developed by the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC).[77] Fourth, we built a fully autonomous system, not involving an exchange of information between patients and health professionals and therefore, not implying the responsibility of the latter.

A second possible alternative to improve HF management could be to supplement traditional measures of clinical effectiveness in HF patients such as reduction in mortality and hospitalizations by other health status measures. Despite the World Health Organization

(WHO) definition of health as "*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*" since 1948,[78] health as long been measured narrowly and in the negative.[79] With the aging of the population resulting from demographic shift, the management of quality of life in life-restricting diseases has become needful. Thus, the concept of quality of life (QoL) in health was introduced from the 1980's.[80] QoL is a complex concept that encompasses physical, psychological and social domains of health.[81] There is no universally accepted definition of QoL. The WHO defined QoL as "*an individual's perception of his/her position in life within the context of culture and value systems in which he/she lives and in relation to his/her objectives, expectations, standards and concerns goals*".[82] In a broad sense, QoL concept extends to all factors relating directly and indirectly to health status. It reflects the mental and physical well-being of a person in his everyday life.[83] Because many valued aspects of life such as income, freedom, quality of the environment are not generally considered to be related to health, some proposed to use the term "health related quality of life" (HRQoL).[83] HRQoL assessments are designed to characterize an individual patient's quality of life from his/her own subjective perspective.[84] HRQoL measures *illness* experience as opposed to the *disease*.[83] It describes the patient's reality, his/her personal point of view as opposed to the reality defined by professional medical knowledge.[85] HRQoL measurements aim to assess the impact of diseases on patients' quality of life and how they face and cope with these situations. Thus, HRQoL assessment provides an important source of information in addition to clinical and biological tests.[83,86] Instruments used to measure quality of life must be valid (measuring what is supposed to measure), reliable (giving the same measurement if repeated in stable patients), sensitive (reflecting clinically meaningful differences in quality of life across the broad spectrum of the clinical conditions) and responsive (detecting changes when the patients' conditions change).[84,87]

Instruments designed to measure HRQoL are generally categorized as generic or specific. Generic instruments are general health measures encompassing a wide range of constructs and applicable to patients with different conditions and diseases. Because of their global nature, these generic instruments are not always able to detect major problem experienced by patients with specific disorders such as HF.[88,89] Disease-specific instruments contrariwise, measure the problems and HRQoL related to a specific disease or disorder.[90] These specific instruments better appreciate issues that are relevant to patients and have been shown to be more responsive to changes in QoL occurring over a given time period and to be more sensitive in discriminating the range of impairment in QoL.[91] Beyond its effects on mortality, HF is often accompanied by restricted physical activity and severe complaints in several areas of quality of life.[92] It is a chronic condition with no hope of recovery which affects quality of life more profoundly than many other chronic diseases.[93] For most patients living with chronic progressive disease, maintaining a good quality of life is as important as survival.[94] Therefore, the two main goals in HF management are to prevent further disease progression (mortality, hospitalizations and deterioration of left ventricular function) and to alleviate patients suffering. Using a HRQoL disease-specific instrument is necessary to quantify this latter treatment goal.[95] Seven disease-specific instruments to measure HRQoL in patient with HF have been identified in a systematic review.[88] Among them, the Kansas City

Cardiomyopathy Questionnaire (KCCQ) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ) were the most highly rated by experts, closely followed by the Chronic Heart Failure Questionnaire (CHFQ). They are the three most commonly used disease-specific measures for HF patients.[96] The KCCQ, published in June 2000 is the most recently developed of the three recommended instruments.[95] The authors described it as "*a valid, reliable and responsive health status measure for patients with congestive HF and may serve as a clinically meaningful outcome in cardiovascular research, patient management and quality assessment*".[95] Despite its short lifespan, the KCCQ has quickly become quite popular and received the best ratings for validity, sensitivity to change and interpretability.[88] Indeed, it was found to reflect clinical changes in HF patients most accurately.[97] Moreover, compared to the MLHFQ, correlation coefficients for social, functional and physical areas are higher and a more precise correlation with survival has been established with the KCCQ.[98,99] For a long time in the past, HF studies outcomes were focused on reducing hospitalizations and mortality. But nowadays, HRQoL is increasingly incorporated as an outcome measure in clinical trials.[100-103] However, despite the availability of validated HF HRQoL instruments and their frequent use in randomized trials, clinical management as well as research efforts do not yet sufficiently focus on this aspect. A good universal understanding of QoL in clinical practice is not yet reached.[98,104] Recommendations to incorporate HF HRQoL assessments in evidenced-based guidelines have failed so far. Lack of easy to administer questionnaires, difficulty to translate a HRQoL score into concrete management implications[99] and scarce motivation of health professionals have been identified as the most relevant obstacles.[96,105] Likewise, the current prognostic models in HF are fundamentally limited because they focused on survival and rehospitalization and still fail to include measures of HRQoL. In that, they incorrectly presume that all survival represents a favorable outcome despite the evidence that many patients would prefer a better QoL at the expense of its quantity.[94,106-108] But what is the degree of concordance between instruments for measuring HRQoL and traditional instruments for measuring morbidity and mortality in HF? Are these instruments correlated? What can be the additional predictive value of HRQoL measures in assessing HF patients' prognosis?

As already mentioned, HF is a complex syndrome with a still incompletely understood pathophysiology. Therefore, its appropriate management cannot be limited to the use of a few biomarkers. Moreover, measurement of HRQoL promotes patient's active participation in his/her own care. We hypothesized that if these two types of health measurement instruments in HF were complementary, their combination could then represent a possible alternative to well-define HF prognosis. Among the traditional prognostic models in HF, the most valid and the most generalizable one is the clinical risk score developed by the MAGGIC group.[77] So, in a second step in the present work, we assessed the relationship between the MAGGIC clinical score and the KCCQ score as well as their added prognostic value.

Chapter 3

Objectives and methods

3.1. Objectives

3.1.1. General objective

The general objective of the present work was to develop new management strategies in order to improve the prognosis of HF patients.

3.1.2. Specific objectives

To achieve this general objective, two specific objectives have been formulated. In a first time, we proposed to build a new individualized non-invasive automated and autonomous alert triggering system for early detection and early preventive therapeutic intervention of HF deterioration. This specific objective was reached in three steps. Firstly, by identifying the characteristics in the dynamic (daily changes) of the monitored parameters (body weight, blood pressure, pulse rate) that can be predictive of HF events. Secondly, by building a potentially individualized dynamic prediction score using both the previously identified characteristics and the MAGGIC clinical score. Finally, by defining the normal limits of the dynamic prediction score to optimally set predefined thresholds for alerts triggering.

In a second time, we proposed to assess the complementarity between quality-of-life health status measures and traditional health status measures of morbidity and mortality in defining HF prognosis. To achieve this specific objective, we assessed the relationship between the KCCQ score and the MAGGIC score as well as their additive prognostic value in a first step.

Then, in a second step, we analyzed the prognostic significance of changes in quality-of-life score (KCCQ).

3.2. Methods

Methods are described in detail in each publication presented in Chapter 4. In this section we briefly described the overall structure of the methodology.

3.2.1. Study design

We used data from the **Better Efficacy in Lowering events by General practitioner's Intervention Using remote Monitoring in Heart Failure (BELGIUM-HF)** project which was designed in 2007 and implemented in 2008-2010 in Brussels and South of Belgium. It was a prospective registry of HF outpatients followed by their GPs but identified from the records of 16 cardiology centres coordinated by "Clinique Saint-Jean" in Brussels. For each identified patients, his/her GP was contacted for the study. If the GP agreed, the patient was followed up to 6 months by his/her GP. An informed consent was obtained from each study participant. The protocol was approved by Ethical Committees of each centre and all studies were conducted in accordance with the principles of the Declaration of Helsinki, and the European directive 2001/20/EC.

3.2.2. Study patients

Patients were enrolled by general practitioners, outside of clinical settings. They were eligible to be included in the study if they met all the following criteria: they had a left ventricular systolic dysfunction defined as a LVEF < 40% documented by echocardiography, contrast ventriculography or radionuclide angio-scintigraphy within 6 months prior to the inclusion, they had been hospitalized within the past 6 months for mild to severe HF defined as NYHA Class II to IV, clearly documented by the cardiologist's report, they had received loop diuretics (furosemide, bumetanide, torasemide) within 2 weeks prior to screening and inclusion, and they were older than 18 years.

Patients were excluded if they met any of the following criteria: patients awaiting cardiac surgery or who underwent myocardial revascularization within the preceding 3 months, patients treated by or considered candidates for chronic hemodialysis procedures, patients whose cognitive aptitudes were impaired.

Besides the study patients, 38 healthy volunteers stratified into 6 groups according to age and gender were also recruited. They were enrolled on the basis of the unique condition of not having HF and were not necessarily free of any disease.

3.2.3. Study outcomes

As already stated, the major issue in HF is the persistence of still high early post-discharge readmission rates. Indeed, reducing readmission rates in HF could concomitantly reduce its economic burden and improve quality of care. Therefore, the outcome of interest in HF is

readmission rather than mortality. But these are two competitive outcomes because a patient who died has no longer a risk to be readmitted to hospital. Furthermore, urgent visits to a specialist, even without hospitalization also increase the costs of care. Accordingly, we considered in the present study, a cardiac composite endpoint (CCE) including the occurrence of death or medical emergency with or without hospitalization. With such a combined endpoint, the most important event to consider is usually the one which occurs first.
The clinical course of patients was thus assessed with respect to the occurrence during 6-months of follow-up of a CCE. Events were classified as cardiac or non-cardiac events due to co-morbidities. Only cardiac events were considered as endpoints and were further classified as worsening HF, arrhythmias, hypo/hypertension, and elective hospitalization.

3.2.4. Data collection

3.2.4.1. Signal data

3.2.4.1.1. Signal acquisition

Each patient received a VitalCare® portable vital sign platform including a Stabil-O-Graph electronic tensiometer and a balance TC 100 (Vitalsys NV-SA, Brussels, Belgium), as well as a mobile phone (Belgacom, NV-SA, Brussels, Belgium). Using these home-based bluetooth-coded medical devices, patients performed daily measurements of body weight, blood pressure and pulse rate for up to six months. The recording of all these measures in a patient was described as the "patient signal". An illustration is given on Figure 6 which shows the daily changes in body weight, blood pressure and pulse rate for a study patient during his follow-up between January 25th and March 21th.

The 38 healthy volunteers also performed the same measurements for up to three months.

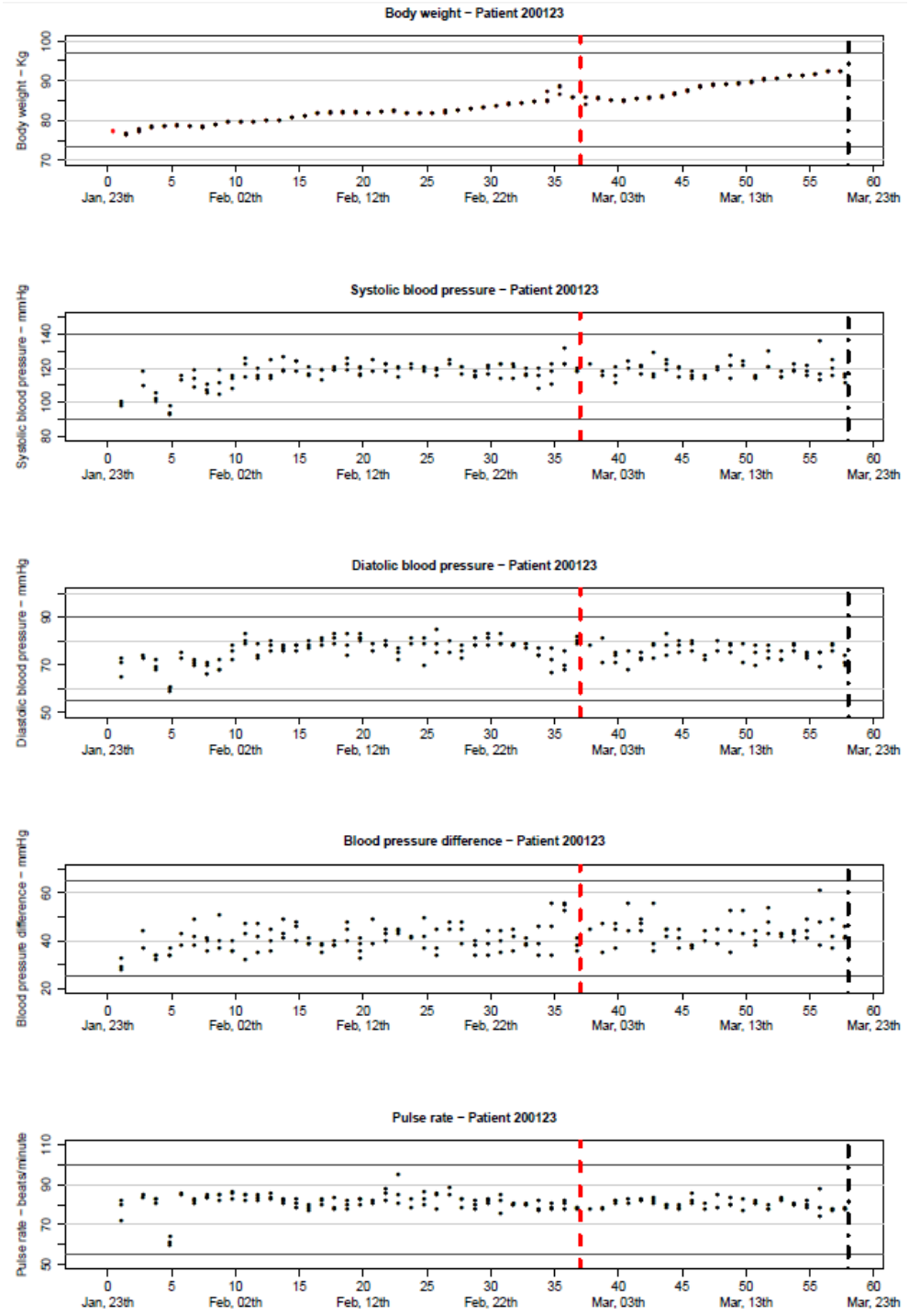


Figure 6. Illustration of a patient signal

3.2.4.1.2. Quality control of the acquired signal

3.2.4.1.2.1. Detection and control of the signal artefacts

When the acquisition period was closed for all patients, signal trends were visually examined for inter-days variations. Rare but unambiguous artefacts were identified on body weight measures, but not in blood pressure nor in pulse rate. They were identified as abrupt and transient drops of several kilos arising either from the inappropriate use of the scale or from technical deficiencies and were groups into two sorts of anomalies. The first kind of anomaly was a body weight's measurement a j-day much lower than the body weight's measurements on the previous (j-3, j-2, j-1) or the following (j+1, j+2, j+3) days. The second kind of anomaly was a series of body weight's measurements on consecutive days (j, j+1,…j+k) that were much lower than the body weight's measurements on the previous (j-1, j-2, j-3) and the following (j+k+1, j+k+2, j+k+3) days, resulting in a drop of the body weight's signal trend described as a "tray". An illustration of these two kinds of anomalies is given on Figure 7.

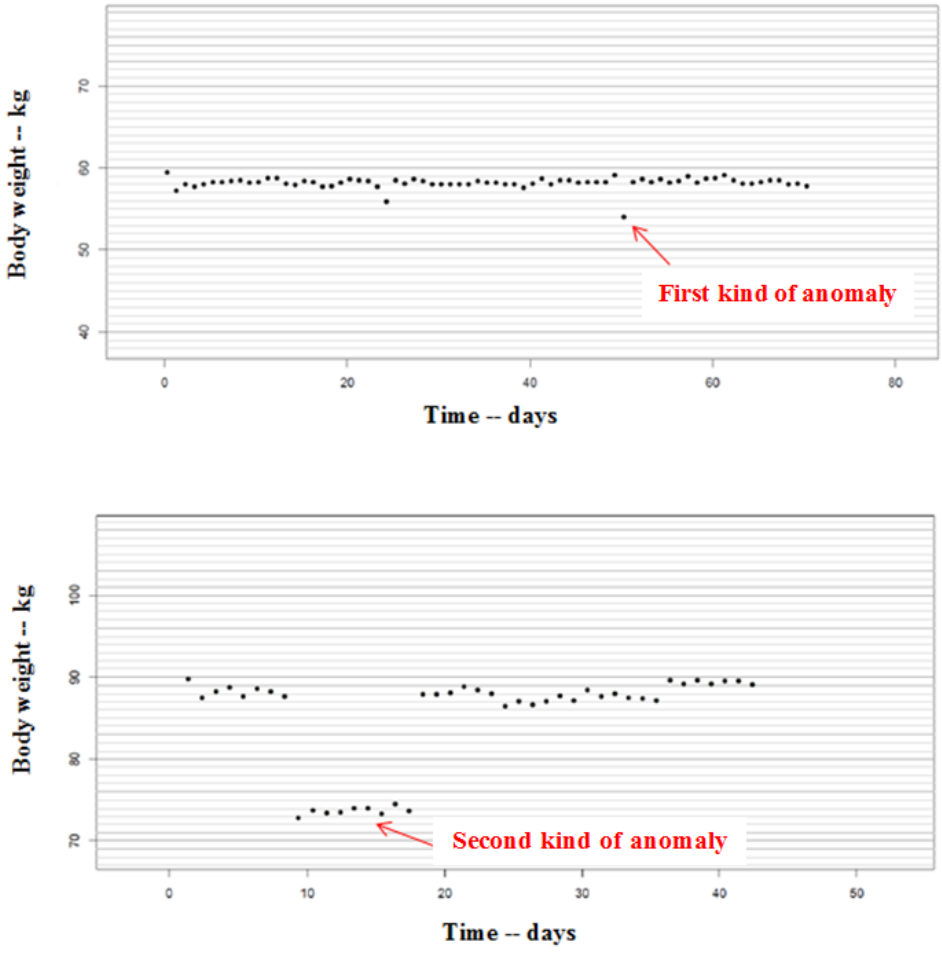


Figure 7. The two kinds of anomalies on body weight trends

An outlier detection algorithm was developed to remove or correct such aberrant body weight data. Several decisions rules were considered.

We first used a simplified rule adapted from Dendale et al. which consisted of triggering an alert when the difference between the body weight a j-day and the body weight at 0-day (that is baseline value) was higher than 2 kg.[109] With this rule, a large number of alerts were generated and all anomalies were not detected.

A second decision rule was based on Zhang et al. which involved calculating the difference between the body weight a j-day and the moving average body weight computed using the body weight's values of the previous 3 days ($weight_{j-3}$, $weight_{j-2}$, $weight_{j-1}$). An alert was generated when this difference exceeded 1.36 kg (3 lbs).[110] This method produced a smaller number of anomalies than the method adapted from Dendale et al. Nevertheless the number of detected anomalies remained high and such decision was unable to detect the second kind of anomalies.

We therefore used a third decision rule which combined the two previous decision rules to detect both kinds of anomalies at the same time. With this decision rule, the first kind of anomalies was detected as with the first decision rule. Nevertheless, a fixed threshold of 3 kg (called threshold 1) rather than 2 kg was selected to reduce the number of detected anomalies. The second kind of anomalies was detected in a first time as with the second decision rule, but also adapted to reduce the number of detected anomalies by using threshold 1 (3 kg) instead of the threshold of 1.36 kg. In a second time, if a drop was detected, the difference between the body weight on j-day and the body weight on j-day +1 was compared to a fixed threshold of 2 kg (threshold 2) to determine if it was the beginning of a second kind of anomaly. This procedure was repeated iteratively until the end of the second kind of anomaly if so. However, this decision rule had also some limitations. Indeed, for patients whose body weight signal was very steady, the method failed to identify all anomalies. Contrariwise, the method identified too many anomalies for patients whose body weight signal was highly variable.

We then decided in a four decision rule, to replace the two fixed thresholds used previously by new thresholds based on a variability operator. Threshold 1 was thus set to 3*SD ($weight_{j-3}$, $weight_{j-2}$, $weight_{j-1}$) and threshold 2 was set to 2*SD ($weight_{j-3}$, $weight_{j-2}$, $weight_{j-1}$). But with this decision rule, we had the opposite effect. For patients whose body weight signal was very steady, the method identified too many anomalies. Contrariwise, the method failed to identify all anomalies for patients whose body weight signal was highly variable.

Finally, as fixed and variable thresholds produced opposite effects, we combined them in a last decision rule. So, a robust threshold was set to 2.5 kg + 1.5*SD ($weight_{j-3}$, $weight_{j-2}$, $weight_{j-1}$). This last decision method corrected the above problems.

The two kinds of anomalies were treated differently. For the first kind of anomalies, the unique dropout body weight value has been deleted. For the second kind of anomalies, a corrective factor was added to all body weight's values in the "tray". This corrective factor was equal to the difference between the mean of the body weight computed using the body weight's values during the consecutive days of the anomaly ($weight_j$, $weight_{j+1}$,…,$weight_{j+k}$)

and the mean of the body weight computed using the body weight's values during the 3 days preceding the anomaly ($weight_{j-3}$, $weight_{j-2}$, $weight_{j-1}$). Additionally to the correction of the two kinds of anomalies, we also deleted for each patient, the body weight value measured the first day because this measurement was frequently very different from the following measures. It was found that this first measurement was carried out at the time of the equipment delivery, out of standard conditions.

Through this quality control of the acquired signal, the validity of the recorded data was increased.

3.2.4.1.2.2. Within-patients' variation control

From a set of triplicate measurements that the first 12 patients agreed to perform, inter-measurements variability coefficients were 3.9% for systolic blood pressure, 5.1% for diastolic blood pressure, 4.1 % for pulse rate and 0.2% for body weight.

3.2.4.2. Clinical data

A medical history was obtained from each patient at baseline providing information on personal history, cardiovascular risk factors and concomitant treatment.

A clinical evaluation of each patient was also performed at baseline and at the consecutive follow-up visits 1 after 3 months and 2 after 6 months.

A functional evaluation has been done at baseline and at each consecutive follow-up visit 1 (3 months) and 2 (6 months) using both the NYHA classification summarized in Table 1[111] and a six-minutes' walk test.

Table 1. Classification of the New York Heart Association

Class I	Patients with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II	Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III	Patients with marked limitation of activity; they are comfortable only at rest.
Class IV	Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

The six-minutes' walk test was optional but strongly recommended and performed in accordance with the GP or the cardiologist. This test was performed according to the guidelines of the American Thoracic Society at baseline and at each consecutive follow-up visit.

Laboratory tests were also performed at baseline and at each consecutive follow-up visit. They included hematological (hemoglobin), chemical (glucose, creatinine, sodium, potassium,

cholesterol, troponin) and hormonal (B-Type natriuretic peptide and/or NT-pro B-Type natriuretic peptide) assays. Patients' renal function was assessed trough glomerular filtration rate (GFR), the best overall index of renal function. GFR was estimated from the simplified Modification of Diet in Renal Disease (sMDRD) equation according to the following formula[112] and a renal dysfunction was defined as a GFR_{sMDRD} < 60 ml/min/1.73m^2:

$$Male: GFR_{sMDRD}\ (\text{ml/min}/1.73m^2) = 186.3 * (serum\ creatinine)^{-1.154} * (age)^{-0.203}$$

$$Female: GFR_{sMDRD}\ (\text{ml/min}/1.73m^2) * 0.742$$

Moreover, a resting 12-head ECG was also performed at baseline and at each consecutive follow-up visit.

Likewise, a 2D-echocardiography as well as a Doppler examination were performed at baseline and at the second follow-up visit, 6 months after entry. Although this second evaluation was optional, it was strongly recommended and performed with approval of the GP or the cardiologist.

3.2.4.3. Quality-of-life questionnaire

A quality-of-life assessment was performed at baseline and at each consecutive follow-up visit 1 (3 months) and 2 (6 months) using the Kansas City Cardiomyopathy Questionnaire (KCCQ). The KCCQ is a valid, reliable and responsive self-administrated questionnaire developed to better describe HRQoL in HF patients. It includes 23 items aggregated into 15 questions and measured on a Likert scale with 5 to 7 response choices. The KCCQ quantifies several domains of HF patients' health status. Physical limitation is quantified by questions 1a-f, symptoms (frequency, severity and stability) by questions 2 to 9, self-efficacy by questions 10 and 11, quality of life by questions 12, 13 and 14 and social limitation by questions 15a-d. For all these 5 subscales, scores are standardized on a 0 to 100 scale with lower scores indicating poor health status. Physical limitation and symptoms subscales are aggregated into a clinical summary score. Except for self-efficacy, all the 5 subscales are aggregated into an overall summary score. Using a valid Belgian French version of the KCCQ, we computed a quality-of-life score for each patient. A copy is given in appendice 1.[95]

3.2.5. Construction of a signal score

From the complete signal of daily measurements of each patient, we computed a series of signal-derived statistics that were included in a generalized linear model to build a signal score. These included standard deviation and slope of body weight, mean and standard deviation of systolic blood pressure, mean and standard deviation of diastolic blood pressure,

mean and standard deviation of differential blood pressure and mean and standard deviation of pulse rate, computed on 3-days, 5-days and 7-days' time windows.

3.2.6. Construction of a clinical score

The clinical prognosis of HF is highly variable from one patient to another. Several risk models for patients with HF have already been developed. [113-117] However, most of them were developed from a small database in a single cohort of HF patients and restricted to patients with HFrEF, thereby limiting their generalizability to other HF populations. The Seattle Heart Failure Model was the most common but its robustness, applicability and generalizability are limited.[113] To overcome the limitations of the previous risk models and build a valid prognostic model in HF patients, the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) established in 2013 a valid, generalizable and easy-to-use clinical risk score of mortality in HF patients based on a large meta-analysis.[77]

We aimed to build an alert triggering system which would incorporate the patient's baseline clinical risk. In this respect, we needed a valid prognostic model in HF patients. Developing a clinical risk model from our database was possible. But, as with several previous risk models, it would have been limited in its generalizability to other HF populations. So, for our alert triggering system to be easily implemented in clinical practice, we decided to use the valid MAGGIC clinical score.

The MAGGIC score was developed through a large meta-analysis including 39,372 HF patients' individual data, both with reduced and preserved LVEF from six randomized controlled trials and 24 cohort studies. The mean age of patients was 68 ± 12 years and 65% were men. There were as many patients with a history of myocardial infarction as with a history of hypertension, for a proportion of 43%. In addition, 23% and 21% of patients had a history of diabetes and atrial fibrillation respectively. NYHA class III or IV were found in 42% of patients. Mean LVEF was 35 ± 14% and HFrEF was found in 75.3% of patients while HFpEF (defined as LVEF ≥ 40%) was found in 24.7%. Regarding the management of HF, 82% of patients were receiving a diuretic, 67% an ACE-inhibitor or ARB and 34% a beta-blocker. This study also confirmed the phenotype of patients with HFpEF which were older, predominantly women, with most often a history of hypertension than HFrEF patients. Furthermore, HFrEF were most often treated with an ACE-inhibitor (75 vs 44%), a beta-blocker (39 vs 33%) and a spironolactone (24 vs 16%) compared to those with HFpEF. The primary outcome was death from any cause. During a median follow-up of 2.5 years, it was recorded in 40.2% of patients (23.4% in patients with HFpEF and 26.3% in patients with HFrEF).[15]

By including the 31 baseline variables available in a Poisson regression model, the authors identified 13 independent predictors defining the MAGGIC clinical score according to the following formula [77]:

$$
\begin{aligned}
MAGGIC\ score = \\
&+ 0.143 * \left(\frac{\text{age}}{10}\right) + 0.109 * male - 0.035 * \\
&\quad body\ mass\ index(up\ to\ 30\,\tfrac{kg}{m^2}) \\
&+ 0.147 * smoker - 0.126 * \left(\frac{systolic\ blood\ pressure}{10}\right) \\
&+ 0.352 * diabetes + 0.343 * NYHA\ III + 0.521 * NYHA\ IV \\
&- 0.542 * \left(\frac{ejection\ fraction\ (up\ to\ 40\%)}{5}\right) \\
&+ 0.206 * chronic\ obstructive\ pulmonary\ disease \\
&+ 0.173 * HF\ duration + 0.038 * \left(\frac{creatinine(up\ to\ 350\ \mu mol/l)}{10}\right) \\
&- 0.274 * beta\ blocker \\
&- 0.096 * angiotensine\ converting\ enzyme\ inhibitor \\
&\quad or\ angiotensin\ receptor\ blocker \\
&+ 0.039 * \left(\frac{age}{10}\right) * \left(\frac{ejection\ fraction}{5}\right) \\
&+ 0.012 * \left(\frac{systolic\ blood\ pressure}{10}\right) * \left(\frac{ejection\ fraction}{5}\right)
\end{aligned}
$$

It turns out that the risk of death increases on average by 15% every 10 years in HF patients. It also increases by 12% for men, by 16% for current smokers, by 42% if they suffer in addition from diabetes, by 41% and 68% respectively for HF patients with NYHA class III and class IV compared to HF patients with NYHA class II, by 23% if they suffer in addition from chronic obstructive pulmonary disease, by 19% if HF duration exceeds 18 months, by 4% with each increase of 10 µmol/l in creatinine up to 350 µmom/l. By contrast, the risk of death in HF patients decreases on average by 42% with each 5% increase in LVEF but only up to 40%. Indeed, no further trend in prognosis was found above 40% of LVEF. The risk of death also decreases by 4% with each 1 kg/m^2 increase in body mass index up to 30 kg/m^2, by 12% with each 10 mmHg increase in systolic blood pressure, by 9% for patients treated with an ACE-inhibitor/ARB, by 24% for patients treated with a beta-blocker.[77]
Moreover, the effect of age on mortality depends on LVEF. Indeed, each simultaneous 10 years increase in age and 5% increase in ejection fraction leads to a further 4% increase in mortality above the risk of these variables considered independently. This means that the positive effect of an increase in LVEF decreases with the aging of patients. In the same way, the effect of systolic blood pressure on mortality also depends on LVEF. Each simultaneous 10 mmHg increase in systolic blood pressure and 5% increase in ejection fraction leads to a further 1.2% increase in mortality above the risk of these variables considered independently. This means that the positive effect of an increase in LVEF decreases as a patient's systolic blood pressure increases.[77]

In addition, authors also performed separate risk models for patients with HFrEF (LVEF < 40%) and patients with HFpEF (LVEF ≥ 40%). It appears that the influence on mortality in both subgroups is similar for most predictors. Nevertheless, two exceptions were found. On

the one hand, for age whose effect on mortality is more pronounced in patients with HFpEF compared to patients with HFrEF. On the other hand, for systolic blood pressure whose positive effect on mortality is less pronounced in patients with HFpEF compared to patients with HFrEF. This finding is consistent with the two interactions incorporated in the overall model of the MAGGIC score.[77]

Using the MAGGIC score formula, we computed a clinical score for each patient in our study. The model-derived clinical MAGGIC score was defined as the 0-100 rescaling of the estimated regression line and the higher the score, the worse the patient's prognosis.

3.2.7. Construction of a combined score

The MAGGIC score has a unique value while the signal score is dynamic with a value which is updated every day. So, the MAGGIC score can be seen as a baseline risk score whereas the signal score can be used as a short-term predictive score. Accordingly, we combined these two scores using a logistic model to build a new dynamic combined score for the prediction of HF events.

3.2.8. Definition of the normal ranges of the combined score

The combined score formula was applied to the 38 healthy volunteers in order to establish its normal range of values.

3.2.9. Definition of a diagnostic strategy

In order to implement a diagnostic strategy with the BELGIUM-HF system, we assessed the positive predictive value (PPV) and the negative predictive value (NPV) of various cut-offs for triggering an alert according to various a priori HF events prevalence's rates.

$$PPV = \frac{\text{Prior} * \text{Sensitivity}}{[\text{Prior} * \text{Sensitivity} + (1 - \text{Prior}) * (1 - \text{Specificity})]}$$

$$NPV = \frac{(1 - \text{Prior}) * \text{Specificity}}{[(1 - \text{Prior}) * \text{Specificity} + (1 - \text{Sensitivity}) * \text{Prior}]}$$

3.2.10. Relationship between the MAGGIC score and the KCCQ score

The MAGGIC score is a measure of HF patients' health status from clinical and biological indicators' perspective, whereas the KCCQ score is a measure of HF patients' health status from their own perspective. Therefore, we assessed the relationship between both measures of HF patients' health status. Thus, the baseline MAGGIC score and the baseline KCCQ score as well as their interaction were introduced in a logistic model to assess their predictive power of a HF event during 6 months of follow-up.

3.2.11. Interpreting clinical changes in KCCQ scores

Changes in KCCQ scores were analyzed between baseline and 3-months' follow-up in a first time, and between baseline and 6-months' follow-up in a second time. The prognostic significance of these changes in KCCQ scores was assessed by comparing the incidence of cardiac events in patients who experienced deterioration in KCCQ scores with that of patients who experienced improvement in KCCQ scores during these periods.

3.2.12. Data analyses

Data were processed and analyzed with codes in R. The significance level was set to 0.05 and all tests were two-sided.

3.3. Workflow

To achieve the general objective of the present thesis, we divided the workflow into four questions (Figure 8). The first question will address the ability of the signal score, the MAGGIC score and the combined score to predict HF events. The second question will assess the complementarity between the MAGGIC score and the KCCQ score in predicting HF events. The third question will analyze changes in patients' KCCQ score during follow-up. To attempt to complete the workflow, the signal score could also be considered to predict a deterioration in quality of life in a fourth question.

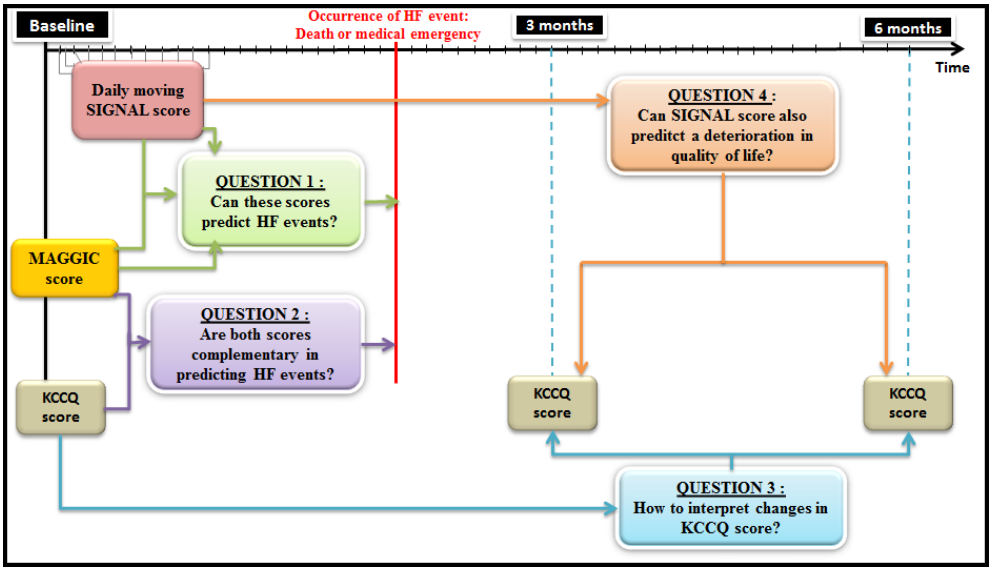


Figure 8. General workflow

Chapter 4

Results

4.1. Description of patients and events

From January 2008 to December 2010, 288 patients were assessed for eligibility. However, 117 were not included because of exclusion criteria or refusal. The remaining 171 patients were enrolled but a further 25 patients failed to start home measurements because of various reasons (procedural mismatches). Monitoring was initiated in 146 patients. In addition to the patients, 38 healthy volunteers stratified into 6 groups according to age and gender also performed HTM measurements. (Figure 9)

Furthermore, among the 171 patients who signed the informed consent form, a total of 143 patients filled out the KCCQ at baseline. They were only 75 patients and only 60 patients to fill out the KCCQ respectively at the 3-months and the 6-months follow-up visits. (Figure 9)

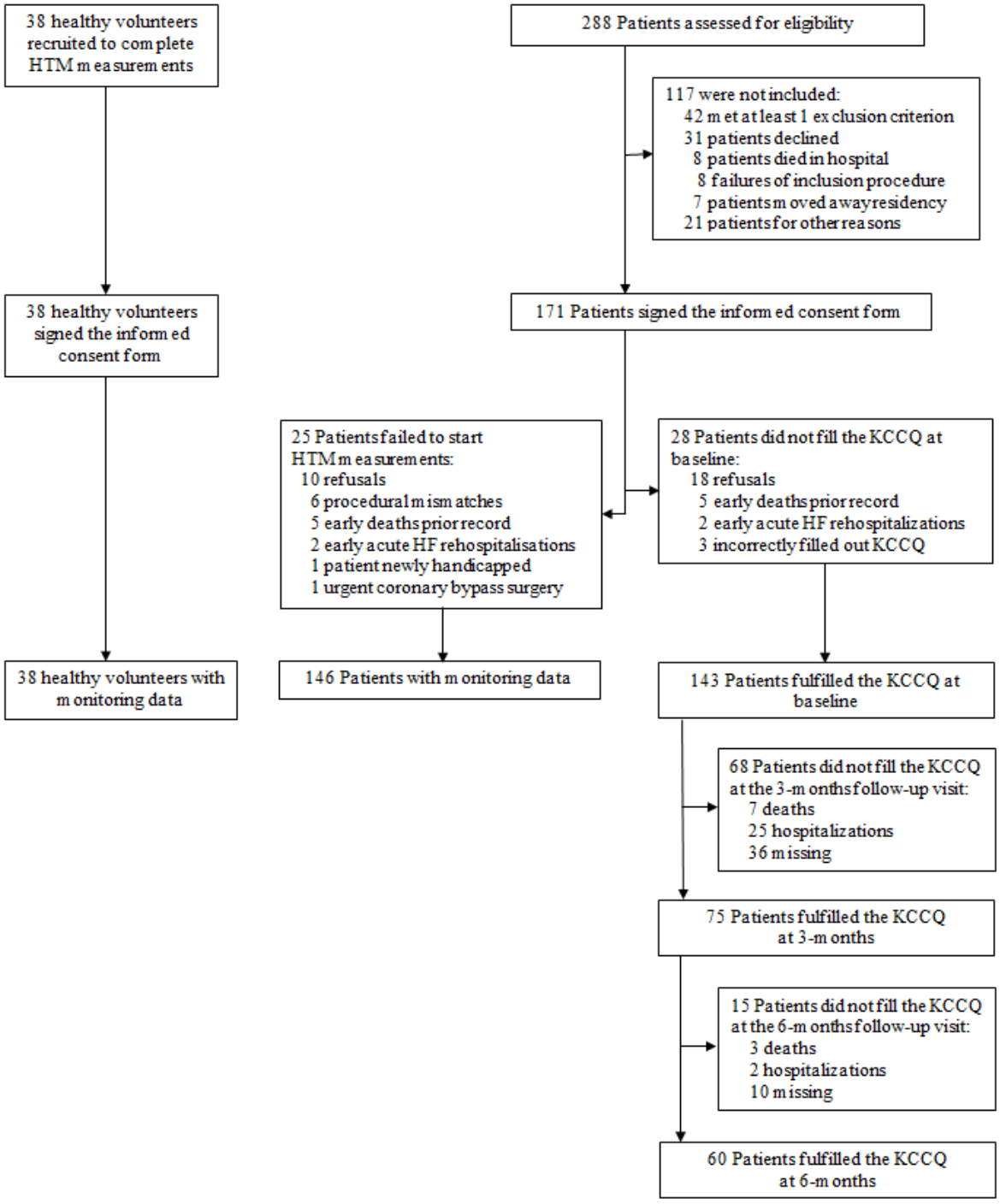


Figure 9. Flowchart

The baseline characteristics of the 25 patients who failed to start HTM measurements were compared to the 146 patients who completed the monitoring. All the variables were similar in both subgroups as illustrated in Table 2. The 25 patients lacking monitoring seemed to have more frequently a history of diabetes and ischemic heart disease compared to monitored patients but the difference was not statistically significant. (Table 2) The same observation was made when considering only the 10 patients for whom the reason for not having completed HTM measurements was refusal. (Table 3) So, patients who failed to start HTM measurements did not appear to be sicker than those who completed HTM measurements.

Table 2. Baseline characteristics of patients according to the achievement of monitoring

	All patients	Monitoring		P value*
		Yes	No	
	n = 171	n = 146	n = 25	
Clinical data				
Age – years	70 ± 12	68 ± 12	71 ± 10	0.22
Male – no (%)	125 (73.0)	108 (74.0)	17 (68.0)	0.53
Body mass index – kg/m^2	27.2 ± 4.9	27.0 ± 4.8	28.8 ± 5.5	0.09
SBP– mmHg	117 ± 18	116 ± 19	120 ± 13	0.31
DBP – mmHg	71 ± 13	71 ± 13	73 ± 13	0.48
Pulse – beat per minute	79 ± 17	78 ± 17	82 ± 18	0.28
NYHA III-IV – no (%)	100 (58.5)	84 (57.5)	16 (64.0)	0.60
Risk factors				
Hypercholesterolemia – no (%)	88 (51.5)	74 (50.7)	14 (56.0)	0.75
Hypertension – no (%)	98 (57.3)	82 (56.2)	16 (64.0)	0.52
Diabetes – no (%)	59 (34.5)	46 (31.6)	13 (52.0)	0.09
Smoker – no (%)	36 (21.1)	31 (21.2)	5 (20.0)	0.80
Medical history				
Ischemic heart disease – no (%)	106 (61.9)	86 (58.9)	20 (80.0)	0.07
COPD – no (%)	26 (15.2)	24 (16.4)	2 (8.0)	0.45
Biological data				
NTerminal-ProBNP– pg/ml	3896 (1998-6890)	3813 (1854-6894)	4882 (3105-6595)	0.45
GFR – ml/min/1.73m^2	57 ± 21	57 ± 20	54 ± 19	0.49
LVEF –%	28 ± 7	28 ± 7	27 ± 6	0.55
Concomitant treatment				
ACE-inhibitor/ARB –no (%)	161 (94.2)	138 (94.5)	23 (96.0)	0.64
Beta-blocker – no (%)	139 (81.2)	117 (80.1)	22 (88.0)	0.42
Aldosterone antagonist –no (%)	114 (66.7)	99 (66.8)	15 (60.0)	0.73
MAGGIC score – %	34 ± 15	33 ± 14	39 ± 16	0.71

SBP: systolic blood pressure; DBP: diastolic blood pressure; NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; BNP: brain natriuretic peptide; GFR: glomerular filtration rate estimated from sMDRD equation[112]; LVEF: left ventricular ejection fraction; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; Plus minus data are Mean ± SD

***For continuous variables, Student t-test if normal distribution with equal variance and Wilcoxon rank sum test if not. For discrete variables, Chi-square test**

Table 3. Baseline characteristics of patients who refused to complete the monitoring

	Patients with monitoring data n = 146	Patients who refused monitoring n = 10	P value*
Clinical data			
Age – years	71 (59 – 79)	71 (66 – 76)	0.87
Male – no (%)	108 (74.0)	7 (70.0)	0.73
Body mass index – kg/m^2	26 (24 – 29)	29 (26 – 33)	0.19
SBP – mmHg	114 (105 – 129)	125 (108 – 133)	0.27
DBP – mmHg	70 (60 – 80)	72 (62 – 88)	0.37
Pulse – beat per minute	75 (68 – 85)	78 (70 – 80)	0.76
NYHA class III-IV – no (%)	84 (57.5)	5 (50.0)	0.53
Risk factors			
Hypercholesterolemia – no (%)	74 (50.7)	5 (50.0)	0.75
Hypertension – no (%)	82 (56.2)	5 (50.0)	0.75
Diabetes – no (%)	46 (31.6)	6 (60.0)	0.09
Smoker – no (%)	31 (21.2)	2 (20.0)	0.90
Medical history			
Ischemic heart disease – no (%)	86 (58.9)	7 (70.0)	0.09
COPD – no (%)	24 (16.4)	1 (10.0)	0.90
Biological data			
NTerminal-Pro BNP – pg/ml	3813 (1854-6894)	4225 (3050-6590)	0.49
GFR – ml/min/1.73m^2	57 (41 – 73)	55 (40 – 71)	0.47
LVEF –%	28 (23 -33)	27 (20 – 35)	0.91
Concomitant treatment			
ACE-inhibitor/ARB – no (%)	138 (94.5)	9 (90.0)	0.98
Beta-blocker – no (%)	117 (80.1)	8 (80.0)	0.99
Aldosterone antagonist –no (%)	99 (66.8)	6 (60.0)	0.73
MAGGIC score – %	34 (25 – 45)	31 (22 – 45)	0.74

SBP: systolic blood pressure; DBP: diastolic blood pressure; NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; BNP: brain natriuretic peptide; GFR: glomerular filtration rate estimated from sMDRD equation[112]; LVEF: left ventricular ejection fraction; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; Continuous data are Median (Percentile 25 – Percentile 75)

***Mann Whitney test for continuous variables and Fisher test for discrete variables**

The baseline clinical characteristics of the 146 patients who completed HTM measurements are reported in Table 4 with differentiation according to the occurrence or not of a cardiac event. Mean age of patients was 68 ± 12 years. 54 % of patients were more than 70 years old and 73 % were men. NYHA symptoms of class III or IV were found in 57 %. At baseline, patients who experienced a cardiac event were older, had a poor functional status according to NYHA, had higher values of BNP and more frequently had renal failure than those who did not experienced a cardiac event. (Table 4)

Table 4. Baseline characteristics of patients

	All patients	Death or medical emergency (with hospitalization or not)	
		Yes	No
	n = 146	n = 61	n = 85
Clinical data			
Age – years	68 ± 12	71 ± 11	66 ± 13
Male – no (%)	108 (74.0)	46 (75.4)	62 (72.9)
Body mass index – kg/m^2	27.0 ± 4.8	26.9 ± 3.7	27.0 ± 5.5
Systolic blood pressure – mmHg	116 ± 19	115 ± 19	117 ± 18
Diastolic blood pressure – mmHg	71 ± 13	69 ± 14	72 ± 17
NYHA class III-IV – no (%)	84 (57.5)	41 (67.2)	43 (50.6)
Risk factors			
Hypercholesterolemia – no (%)	74 (50.7)	34 (55.7)	40 (47.1)
Hypertension – no (%)	82 (56.2)	31 (50.8)	51 (60.0)
Diabetes – no (%)	46 (31.6)	22 (36.1)	24 (28.2)
Smoker within past 12 months – no (%)	31 (21.2)	10 (16.4)	21 (24.7)
Six-Minute Walk Test –Median (IQR)	290 (200-380)	219 (160-311)	300 (238-420)
Biological data*			
Brain natriuretic peptide – pg/ml	741.3 (3.2)	853.9 (3.2)	621.0 (3.2)
Glucose – mg/dl	107.2 (1.3)	109.2 (1.4)	105.7 (1.3)
Cholesterol – mg/dl	147.9 (1.3)	137.1 (1.3)	156.9 (1.4)
LDL cholesterol – mg/dl	79.4 (1.5)	70.5 (1.5)	84.0 (1.6)
Creatinine – mg/dl	1.45 (1.44)	1.48 (1.48)	1.34 (1.35)
Left ventricular ejection fraction – %	28 ± 7	28 ± 8	28 ± 7
Renal failure[¶] – no (%)	11 (7.5)	7 (11.5)	4 (4.7)
COPD – no (%)	24 (16.4)	11 (18.0)	13 (15.3)

Plus minus data are mean ± SD; IQR: interquartile range; NYHA: New York Heart Association; LDL: Low Density Lipoprotein; COPD: Chronic Obstructive Pulmonary Disease

***Data are geometric means (SD); [¶]Renal failure = GFR < 60 ml/min/1.73 m^2**

More details on patients' medical history and concomitant treatment at baseline were given in Table 5. Coronary disease was the most common medical history which was reported in 86 (59%) patients and most often as a myocardial infarction (41%). The management of patients was quite optimal with more than 80% of them receiving in addition to the diuretic, a beta blocker or an ACE inhibitor/ARB.

Table 5. Patients' medical history and concomitant treatment at baseline

	All patients	Death or medical emergency (with hospitalization or not)	
		Yes	No
	n = 146	n = 61	n = 85
Medical history			
Previous coronary disease – no (%)	86 (58.9)	36 (59.0)	50 (58.8)
Previous myocardial infarction – no (%)	60 (41.1)	25 (41.0)	35 (41.2)
Previous cerebrovascular accident – no (%)	12 (8.2)	5 (8.2)	7 (8.2)
Previous toxic cardiomyopathy – no (%)	13 (8.9)	5 (8.2)	8 (9.4)
Valvulopathy – no (%)	11 (7.5)	7 (11.7)	4 (4.9)
Previous percutaneous coronary intervention – no (%)	47 (32.2)	21 (34.4)	26 (30.6)
Previous coronary artery bypass graft surgery – no (%)	36 (24.7)	16 (26.2)	20 (23.5)
Previous implanted ICD or CRT – no (%)	38 (26.0)	19 (31.1)	19(22.4)
Concomitant treatment			
Aspirin – no (%)	96 (65.8)	38 (62.3)	58 (68.2)
Clopidogrel – no (%)	35 (24.0)	14 (23.0)	21 (24.7)
Beta blocker – no (%)	117 (80.1)	49 (80.3)	68 (80.0)
ACE /ARB – no (%)	138 (94.5)	58 (95.1)	80 (94.1)
Loop diuretics – no (%)	146 (100)	61 (100)	85 (100)
Aldosterone antagonist – no (%)	99 (67.8)	38 (62.3)	61 (71.8)
Nitrate – no (%)	26 (17.8)	14 (23.0)	12 (14.1)
Antiarrhythmic – no (%)	49 (33.6)	26 (44.1)	23 (27.7)
Statin – no (%)	88 (60.3)	38 (62.3)	50 (58.8)
Digoxin – no (%)	17 (11.6)	6 (9.8)	11 (12.9)
Calcium antagonist – no (%)	6 (4.1)	2 (3.3)	4 (4.7)
Nonsteroidal anti-inflammatory – no (%)	3 (2.1)	2 (3.3)	1 (1.2)
CRT – no (%)	9 (6.2)	5 (8.5)	4 (4.8)
ICD – no (%)	7 (4.8)	2 (3.3)	5 (6.1)
Erythropoietin – no (%)	3(2.1)	2 (3.3)	1 (1.2)
Antidepressive – no (%)	28 (19.2)	15 (24.6)	13 (15.3)

The baseline clinical characteristics of the 38 healthy volunteers who also completed HTM measurements are reported in Table 6. They were not free of any disease because 2 (5%), 8 (21%), 4 (11%) and 7 (18%) healthy volunteers had respectively a medical history of diabetes, hypertension, hypercholesterolemia and renal failure. Moreover, almost all of them received a treatment for a cardiovascular condition other than HF. (Table 6)

Table 6. Baseline characteristics of healthy volunteers

	Healthy volunteers n = 38	**Patients n = 146**
Clinical data		
Age – years	61 ± 12	68 ± 12
Male – no (%)	22 (57.9)	108 (74.0)
Body mass index – kg/m^2	26.7 ± 3.4	27.0 ± 4.8
Systolic blood pressure – mmHg	136 ± 14	116 ± 19
Diastolic blood pressure – mmHg	82 ± 11	71 ± 13
Pulse – beat per minute	74 ± 15	78 ± 17
Risk factors		
Hypercholesterolemia – no (%)	4 (10.5)	74 (50.7)
Hypertension – no (%)	8 (21.1)	82 (56.2)
Diabetes – no (%)	2 (5.3)	46 (31.6)
Smoker within past 12 months – no (%)	4 (10.5)	31 (21.2)
Biological data*		
Glucose – mg/dl	95.0 (2.3)	107.2 (1.3)
Cholesterol – mg/dl	145.9 (3.2)	147.9 (1.3)
Hemoglobin – g/dl	14.0 ± 1.3	13.1 ± 1.9
GFR – ml/min/1.73m^2	56 ± 19	57 ± 21
Renal failure[¶] – no (%)	7 (18.4)	11 (7.5)
Concomitant treatment		
ACE-inhibitor/ARB– no (%)	7 (18.4)	138 (94.5)
Beta-blocker – no (%)	11 (28.9)	117 (80.1)
Aldosterone antagonist– no (%)	2 (5.3)	99 (66.8)
Calcium antagonist – no (%)	3 (7.9)	6 (4.1)
Statin – no (%)	8 (21.1)	88 (60.3)
Aspirin – no (%)	6 (15.8)	96 (65.8)

GFR: glomerular filtration rate estimated from sMDRD equation[112]; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; Plus minus data are Mean ± SD

[¶]Renal failure = GFR < 60 ml/min/1.73 m^2

All events occurring during follow-up are reported in Table 7. Out of the 146 monitored patients, 61 (42%) experienced cardiac events and 55 (38%) remained free of any events, whereas non-cardiac events were reported in 30 patients (20%). Twelve patients died (8%), 10 of them from HF (7%) and two from cancer. As a whole, 111 cardiac events occurred: 10 deaths and 101 medical emergencies with or without hospitalization. Among these cardiac events, a majority of 82 (74%) events were identified as worsening HF, and 19 (17%) events were attributed to arrhythmias or hypo / hypertension. Out of the 111 cardiac events, 96 occurred during signal acquisition: 3 deaths and 93 medical emergencies with or without hospitalization, which were recorded in 61 distinct patients. Among these 61 patients, 35 patients experienced at least two cardiac events. (Figure 10) Among the 61 cardiac events which occurred first, 59 were medical emergencies with or without hospitalization and only two deaths occurred as the first event.

Table 7. Occurrence of events during follow-up

	Death	Medical emergency with or without hospitalization	Total
	n	n	n
All patients (n = 171)	20		
Non-monitored patients (n = 25)	8		
Monitored patients (n = 146)	12	155	167
Cardiac events (All)	10	101	111
Heart Failure	10	72	82
Arrhythmias	0	15	15
Hyper/Hypotension	0	4	4
Elective cardiac hospitalizations	-	10	10
Non-cardiac events (All)	2	54	56
Pulmonary	0	20	20
Renal failure	0	6	6
Cerebral accident	0	2	2
Traum/Orthopedic surgery	0	7	7
Other	2	19	21

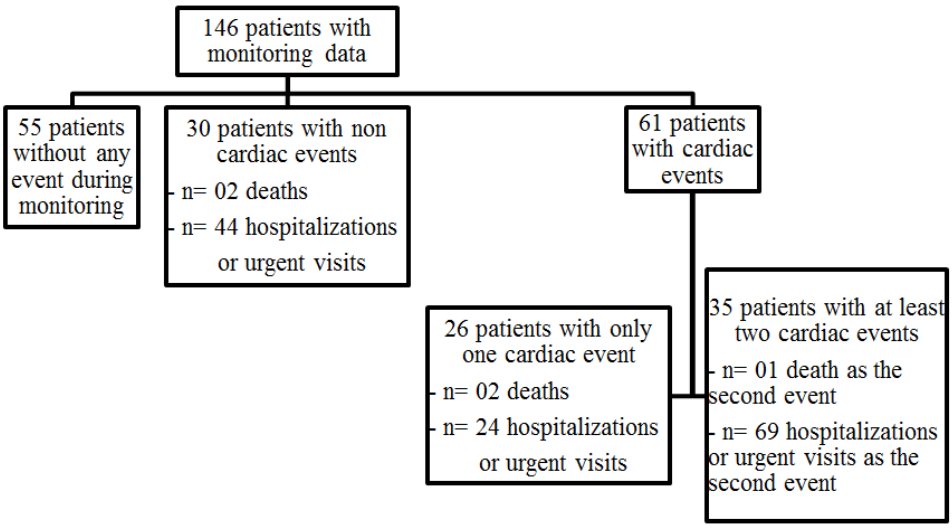
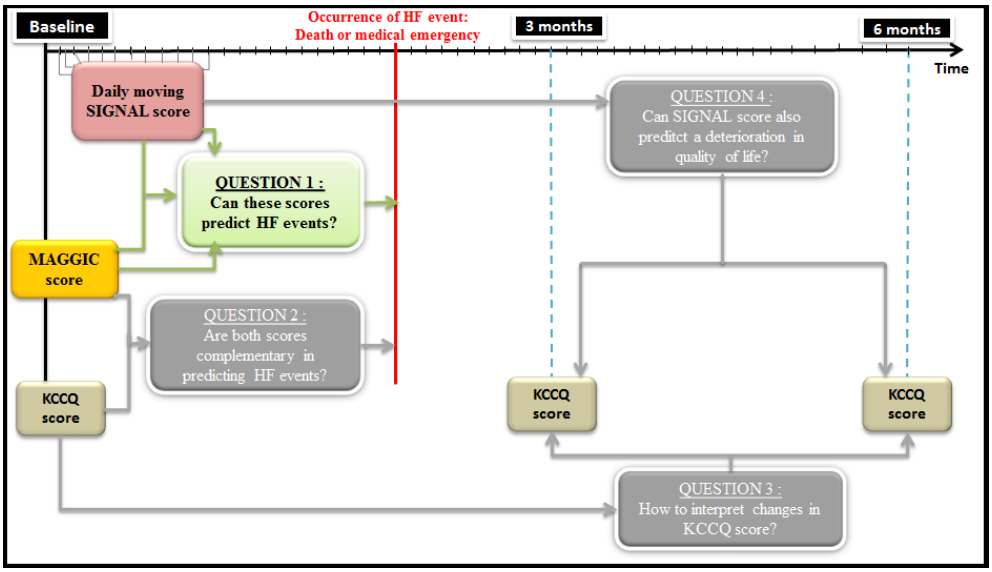


Figure 10. Flow of events during 6-months signal acquisition

We will now consider developing a new more efficient alert triggering system for early detection and early preventive therapeutic intervention of HF deterioration. This could be achieved through question 1 of our general workflow which will address the ability of the signal score, the MAGGIC score and the combined score to predict HF events.



Progression in the workflow

4.2. Publication 1

Development of a Potentially Individualized Algorithm to Detect Heart Failure Events through Home Telemonitoring

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Résumé

Objectifs. La télésurveillance médicale à domicile représente une alternative encourageante dans la réduction des réhospitalisations chez les patients insuffisants cardiaques. L'objectif de cette étude était dans un premier temps, d'identifier les caractéristiques des paramètres télésurveillés qui sont prédictifs des évènements cardiaques. Dans un second temps, il s'agissait de construire un score de prédiction en combinant les caractéristiques précédemment identifiées au pronostic clinique des patients.

Méthodes. Les patients ont complété à l'aveugle pendant 6 mois, des mesures quotidiennes de poids, de pression artérielle et de pouls. Un évènement cardiaque composite (CCE) incluant la survenue d'un décès, d'une hospitalisation ou d'une visite urgente chez le médecin a été considéré. Une série de statistiques dérivées du signal (SDS) ont été calculées sur des fenêtres de temps de 3, 5 et 7 jours. Un score signal de prédiction d'un CCE a été développé en incluant les SDS dans un premier modèle de régression logistique utilisant un sous-ensemble des données de signal (« *Training* ») et sa précision a été évaluée sur un autre sous-ensemble de données (« *Testing* »). Un score clinique a été calculé sur base de la formule du groupe *Meta-Analysis Global Group in Chronic Heart Failure.* Ces deux scores ont été combinés à travers un second modèle logistique. Ces trois scores (signal, clinique et combiné) ont été comparés à l'aide de courbes ROC.

Résultats. La télésurveillance à domicile a été complétée par 146 patients au total et 96 CCE sont survenus chez 61 patients en 6 mois. Le score signal combinait 7 SDS incluant la variabilité du poids sur 3 jours consécutifs, l'augmentation progressive du poids sur 3 et sur 7 jours consécutifs, la variabilité du pouls sur 3 et sur 7 jours consécutifs, la moyenne de la pression artérielle diastolique sur 3 jours consécutifs et la variabilité de la pression artérielle différentielle sur 3 jours consécutifs. Le score signal prédisait l'occurrence d'un CCE (sous-ensemble *Training* : AUC = 0.796, P < 0.001 ; sous-ensemble *Testing* : AUC = 0.830, P < 0.001). Le second modèle logistique a résulté en un score combiné ayant amélioré la prédiction d'un CCE (sous-ensemble *Training* : AUC = 0.830, P < 0.001 ; sous-ensemble *Testing* : AUC = 0.891, P < 0.001) avec une sensibilité de 92% et une spécificité de 77% pour un cut-off à 25%.

Conclusions. Les données de signal et les données cliniques se complètent dans la prédiction du risque chez les patients insuffisants cardiaques.

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Development of a Potentially Individualized Algorithm to Detect Heart Failure Events through Home Telemonitoring

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Authors' contributions

This work was carried out in collaboration between all authors. Author KS performed data analysis and drafted the manuscript. Author JA took part in data analysis and in drafting the paper. Authors SV, MV, MC, JC and AR participated in the design and the study protocol implementation. Author JC also contributed to writing the paper. Author AR also supervised the study. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Home telemonitoring represents a promising approach to reduce heart failure (HF) patients' hospital readmissions. The aim of the study was, in a first step, to identify the monitored parameters' characteristics that are predictive of HF events. In a second step, it was to build a prediction score by combining both the identified characteristics and the patients' clinical prognosis.
Methods: Patients completed 6-month blind daily body weight, blood pressure and pulse

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measurements. A cardiac composite endpoint (CCE) of death, hospitalization or urgent visit was considered. A series of signal-derived statistics (SDS) were computed on 3, 5 and 7 days' time windows. A signal score for CCE prediction was built by including SDS in a first logistic model using a subset of signal set (training) and its accuracy was assessed in another subset (testing). A clinical score was computed using the Meta-Analysis Global Group in Chronic Heart Failure formula. Both scores were combined using a second logistic model. We compared the three scores using ROC curves.

Results: Monitoring was completed by 146 patients and 96 CCE occurred in 61 patients. The first logistic model resulted in a signal score which combined 7 SDS including body weight's variability on 3 consecutive days, body weight's increase on 3 and 7 consecutive days, pulse's variability on 3 and 7 consecutive days, diastolic blood pressure's mean on 3 consecutive days, differential pressure's variability on 3 consecutive days. The signal score had ability in predicting CCE occurrence (training set: AUC= 0.796, $P < .001$; testing set: AUC=0.830, $P < .001$). The second logistic model resulted in a combined score that improved CCE prediction (training set: AUC= 0.830, $P < .001$; testing set: AUC= 0.891, $P < .001$) with 92% sensitivity and 77% specificity.

Conclusions: Signal data and clinical data provide additive information to risk prediction.

Keywords: Heart failure; telemonitoring; hospital admission; prediction.

1. INTRODUCTION

Heart failure (HF) is the leading cause of hospitalization in people older than 65 years [1]. These patients then frequently experience repeated hospitalizations or urgent visits to a medical specialist or even death. In Western Europe, hospital readmission rate reached 24% within 12 weeks of HF discharge [2]. These events should be predicted. Several studies [3-5] suggested to remotely monitor clinical parameters with detectable changes such as body weight, blood pressure or pulse rate, for early detection of HF events. However, the clinical efficacy of technology-assisted remote home telemonitoring (HTM) remains debated [6]. The European Society of Cardiology (ESC) recommends that a patient with a body weight increase of 2 kg or more in 3 days, alerts a healthcare professional for early pharmacological intervention [7]. This standard rule has been assessed in the WISH trial which showed no reduction of death or HF-related hospitalizations in the HTM group [3]. Two major multicenter randomised controlled trials (RCTs) assessed other published simple decisions rules (body weight > 3 lbs in 1 day or > 5 lbs in 3 days) and failed to demonstrate superiority of HTM protocols over usual care [8,9]. Even the recent BEAT-HF trial, one of the largest RCTs of remote HTM in an HF population showed no significant effect of HTM in reducing hospital readmission rate [4]. However, meta-analyzes which include these RCTs continue to suggest a significant effect of HTM in reducing HF-related events [5,10]. The main constraint is that there is no consensus on the threshold of change in these clinical parameters, or on the corresponding time window that should lead to trigger an alert. To improve the diagnostic power of HTM algorithms in detecting HF events, the characterization of clinical parameters' changes that are associated with HF events is a prerequisite. Subsequently, the development of a potentially individualized algorithm could provide a better performance in predicting HF events [11]. The aim of the present study, part of the Better Efficacy in Lowering events by General practitioner's Intervention Using remote Monitoring in Heart Failure (BELGIUM-HF) project was to find a better measurement through HTM parameters to better predict HF events. It was in a first step, to identify characteristics in the dynamic (daily changes) of the monitored parameters (body weight, blood pressure, pulse rate) that are predictive of HF events. In a second step, it was to build a potentially individualized prediction score using both the identified characteristics and the patients' clinical prognosis as estimated by the clinical score developed by the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) [12].

2. METHODS

2.1 Patients

The study design has been partly described previously [13]. In brief, general practitioners (GPs) were invited to prospectively register their HF outpatients. Patients were eligible if they were hospitalized for HF in the preceding 6 months, had a left ventricular ejection fraction <40% and required daily loop diuretics within the 2 weeks before inclusion. An informed consent was obtained from each patient and the study

protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

2.2 Study Outcomes

The predictive performance of HTM was developed with respect to the occurrence during 6-months of follow-up of a cardiac composite endpoint (CCE). CCE was defined as death or hospitalization or a non-scheduled call from the patient leading to an urgent visit of the physician and resulting in a medical intervention such as a change in diuretics doses. Events were classified as cardiac or non-cardiac events due to co-morbidities. Death was assumed being cardiac unless an immediate non-cardiovascular cause was clearly documented.

2.3 Signal Acquisition

HF is accompanied by several changes induced by various mechanisms including an activation of neuro-humoral reflexes resulting in detectable changes in water retention which may precede the clinical deterioration [14]. An increased global sympathetic activity also accompanies HF producing detectable changes in heart rate, rhythm, systemic and pulmonary pressures [14]. Therefore, it seemed relevant to remotely monitor patients' body weight, blood pressure and pulse rate.

In this study, we used an automatic non-invasive monitoring with home-based portable technology. Patients were provided with Bluetooth-coded sphygmomanometers and scales (Vitalsys Inc) and dedicated mobile phones (Belgacom Inc). The equipment was hiding all results of daily measurements of blood pressure, pulse and body weight. An auditory signal informed patient when data were transmitted. No additional messages were programmed. A nurse-technician visited each patient, installed the material in an adequate space and taught him the procedure. He instructed the patient to make measurements each morning after having emptied the bladder and before breakfast. He also called the patient when more than 2 days elapsed without measurements and provided home assistance. Data were stored in real time at the Monitoring Data Centre (Touring Inc, Brussels). GPs were not involved in the telemonitoring procedure itself, nor were they aware of the accumulated data.

2.4 Signal Analysis and Construction of a Signal Score

A complete signal of daily monitored parameters was available for patients who completed the study. Such a patient signal is illustrated on Fig. 1 for daily body weight's measurements.

Each dot represents the patient daily body weight's measurement during his follow-up between January 25th and March 21th. That patient was hospitalized on February 29th (vertical dotted line) and he died on March 21th (vertical dotdash line).

From the complete signal of each patient, a series of signal-derived statistics (SDS) were computed on a short 3 days' time window [15,16] and a long 7 days' time window [17] as previously used in literature, as well as on a middle 5 days' time window. These SDS included means and standard deviations of all monitored parameters, computed based on their 3, 5 or 7

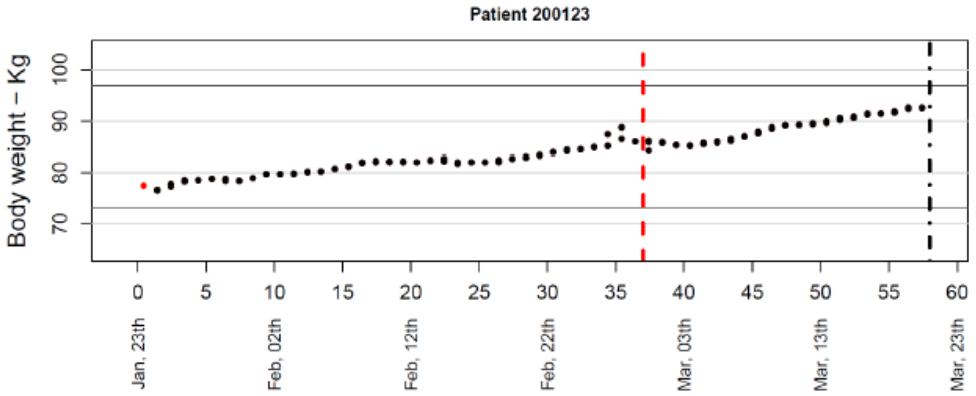

Fig. 1. Example of the body weight signal of a patient

consecutive values preceding each time-point. In addition, we computed a body weight's slope corresponding to the slope of the linear regression of body weight against measure date using the 3, 5 or 7 consecutive values of body weight preceding each time-point.

A mathematical model for CCE prediction was built in a subset of signal set (training) and its accuracy was assessed in another subset of signal set (testing). Considering that both training and testing sets had to include positive (i.e. a time-point with a CCE) and negative (i.e. a time-point without CCE) cases, the following procedure was applied to build these two sets. In the training set, the positive cases were included as the first event for patients with at least one CCE while the negative cases were included as a randomly selected time-point for patients without CEE. In the testing set, the positive cases were included as the second event for patients with at least two CCE while the negative cases were included as a randomly selected time-point for patients without CEE. These two sets were mutually exclusive and the same SDS were computed in both sets.

In a first step, all SDS from the training set were compared between positive and negative cases using Student t-test. In a second step, a signal score was built by including SDS in a first logistic regression with CCE as the outcome variable coded 1 if a CCE occurred and 0 otherwise. We used the log odds ratio as the signal score. Considering the large number of candidates covariates (p = 30 SDS) compared to the moderate number of observations (n=146), the coefficients of the logistic regression models were estimated using the Least Absolute Shrinkage and Selection Operator (LASSO) method in order to avoid overfitting problem. In such dataset where the number of covariate is high compared to the number of observations, LASSO enable indeed to alleviate overfitting problem and to improve the overall prediction [18].

The selection of the variables was based on the predictive performance of the model, as recommended in such method [19]. The L_1-norm penalty λ of the LASSO logistic regression model was indeed selected to maximize its predictive performance which was estimated using a leave-one-out cross validation in the training set. In this method, the model is developed on all the training set but one unit and a prediction is made for that single unit. This procedure is repeated for all units of the training set that is 146 times in our study. The L_1-norm penalty λ was selected based on a 0.25 increment on a scale from 0.5 to 15, meaning a total number of 59 values considered for λ.

The predictive performance of the selected model was then computed on the testing set.

2.5 Computation of the Clinical MAGGIC Score

To build a potentially individualized prediction algorithm by combining HTM parameters to patients' clinical prognosis, we required a valid prognostic model in HF patients. The MAGGIC group established a valid risk score of mortality in patients with HF as following [12]:

$$
\begin{aligned}
MAGGIC\ score = \\
&+ 0.143 * \left(\frac{age}{10}\right) + 0.109 * male - 0.035 * body\ mass\ index \\
&+ 0.147 * smoker - 0.126 * \left(\frac{systolic\ blood\ pressure}{10}\right) \\
&+ 0.352 * diabetes + 0.343 * NYHA\ III + 0.521 * NYHA\ IV \\
&- 0.542 * \left(\frac{ejection\ fraction}{5}\right) \\
&+ 0.206 * chronic\ obstructive\ pulmonary\ disease \\
&+ 0.173 * HF\ duration + 0.038 * \left(\frac{creatinine}{10}\right) - 0.274 * beta\ blocker \\
&- 0.096 * angiotensine\ converting\ enzyme\ inhibitor \\
&\qquad or\ angiotensin\ receptor\ blocker \\
&+ 0.039 * \left(\frac{age}{10}\right) * \left(\frac{ejection\ fraction}{5}\right) \\
&+ 0.012 * \left(\frac{systolic\ blood\ pressure}{10}\right) * \left(\frac{ejection\ fraction}{5}\right)
\end{aligned}
$$

This MAGGIC score has a 0-100 scale and the highest the score, the highest the risk. Using this formula we computed a clinical score.

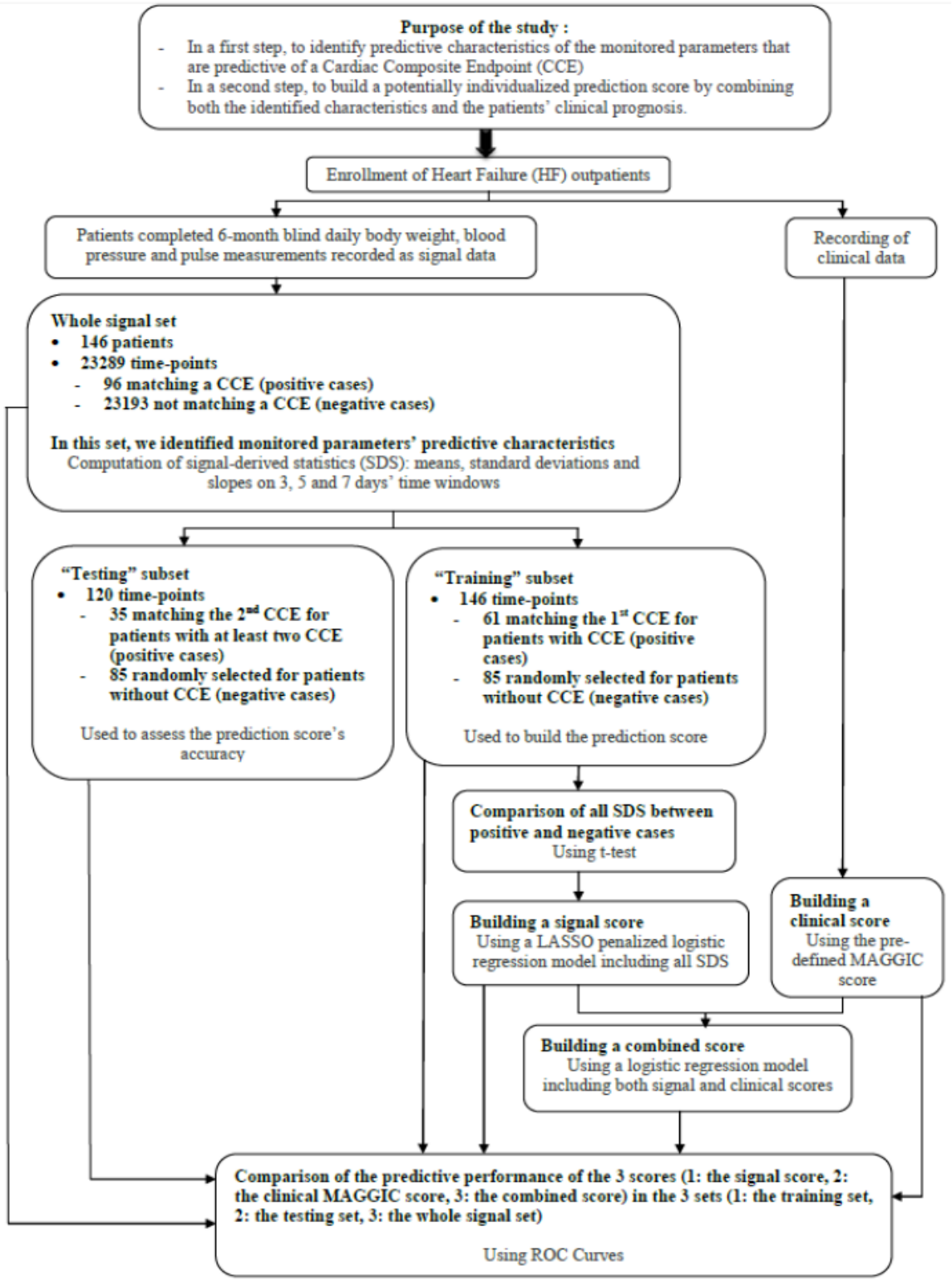

Fig. 2. Workflow of methodology

2.6 Computation of a Combined Clinical-signal Score

The MAGGIC score is a cross-sectional assessment of risk whereas the signal score is a dynamic event detector. So the former can be used as a baseline risk score and the latter as a short-term predictive score. In a second logistic model, we combined these two scores to estimate a new dynamic score for predicting a CCE within the next day. The outcome in this model was the occurrence of a CCE (coded 1 if a CCE occurred and 0 otherwise) and the covariates included the signal and the MAGGIC scores. The training set was used to build this combined score and its accuracy was assessed in the independent testing set.

2.7 Predictive Performance Comparison

ROC curves were used to assess the diagnostic value of the three scores (1: The signal score, 2: The MAGGIC score, 3: The combined score) in both the training and the testing sets. Being aware of the special correlation structure of data, the performance of scores was still assessed on the whole signal time-points in all patients. Whereas the training and the testing sets included both, one selected time-point for each patient, the whole signal included all time-points with corresponding SDS in all patients. So for the whole signal, positive cases were all time-points matching an event and negative cases were all time-points not matching an event. The signal score built in the training set was also assessed in the whole set. The MAGGIC score and the combined score were also computed in the whole set.

All statistical analyses were performed using R version 3.0.3. A workflow is shown in Fig. 2.

3. RESULTS

3.1 Baseline Characteristics

From January 2008 to December 2010, 288 patients were assessed for eligibility. However, 117 were not included because of exclusion criteria or refusal. The remaining 171 patients were enrolled but a further 25 patients failed to start home measurements because of various reasons (procedural mismatches). Monitoring was initiated in 146 patients.

The 25 patients lacking monitoring were compared to monitored patients at the starting point of HTM. They were similar for all variables but BNP neuropeptides level that was higher in non-monitored patients (P =.03) (Tables 1 and 2).

Table 1. Clinical characteristics of patients used to compute the MAGGIC score

	All patients	Monitoring		*P* Value[b]
		Yes	No	
	n=171	n=146	n=25	
Age --years	70.0 ± 12.0	68.2 ± 12.3	71.4 ± 9.8	.22
Left ventricular ejection fraction -- %	27.6 (7.0)	27.7 (7.1)	26.8 (6.3)	.55
NYHA class III-IV –no (%)	100 (58.5)	84 (57.5)	16 (64.0)	.60
Creatinine[a] – mg/dl	1.44 (1.45)	1.45 (1.44)	1.35 (1.44)	.49
Diabetes -- no (%)	59 (34.5)	46 (31.6)	13 (52.0)	.07
Beta blocker -- no (%)	139 (81.2)	117 (80.1)	22 (88.0)	.42
Systolic blood pressure --mmHg	117 ± 18	116 ± 19	120 ±13	.31
Body Mass Index -- kg/m^2	27.2 ± 4.9	27.0 ± 4.8	28.8 ± 5.5	.09
Time since diagnosis -- months	38 ± 44	36 ± 45	48 ± 55	.08
Smoker within past 12 months – no (%)	36 (21.1)	31 (21.2)	5 (20.0)	.80
COPD -- no (%)	26 (15.2)	24 (16.4)	2 (8.0)	.45
Men -- no (%)	125 (73.0)	108 (74.0)	17 (68.0)	.53
ACE or Sartan – no (%)	161(94.2)	138 (94.5)	23(96.0)	.64
MAGGIC score -- %				
Mean ± SD	34 ± 15	33 ± 14	39 ± 16	.71
Median (Percentile 25 – Percentile 75)	34 (24 – 45)	34 (25 – 45)	32 (21 -44)	
Minimum - Maximum	0 - 73	0 - 73	0 - 72	

[a]Data are geometric means (SD); [b]For continuous variables, Student t-test if normal distribution with equal variance and Wilcoxon rank sum test if not. For discrete variables, Chi-square test

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Table 2. Clinical characteristics not included in the MAGGIC score

Variables	All patients	Monitoring		*P* Value[c]
		Yes	No	
	n=171	n=146	n=25	
Body weight -- kg	77.9 ± 16.8	77.1 ± 16.3	82.8 ± 19.6	.12
Diastolic blood pressure -- mm Hg	71± 13	71 ± 13	73 ± 13	.48
Pulse -- beat per minute	79 ± 17	78 ± 17	82 ± 18	.28
Cardiovascular Risk Factors				
Hypertension -- no (%)	98 (57.3)	82 (56.2)	16 (64.0)	.52
Diabetes -- no (%)	59 (34.5)	46 (31.6)	13 (52.0)	.07
Hyperlipidemia -- no (%)	88 (57.3)	74 (50.6)	14 (56.0)	.67
Medical History				
Ischemic Heart Disease -- no (%)	106 (61.9)	86 (58.9)	20 (80.0)	.07
Alcohol Excess -- no (%)	14 (8.2)	13 (8.9)	1 (4.0)	.70
Investigations				
GFR[a] -- ml /min/ 1.73m^2	57 ± 21	57 ± 20	54 ± 19	.49
BNP[b]-- pg/mL	814	781	1230	.03
IQR	(339; 1846)	(291; 1754)	(283; 4470)	
NTerminal-Pro BNP[c] -- pg/mL	3896	3813	4882	.45
IQR	(1998; 6890)	(1854; 6894)	(3105; 6595)	
Concomitant Treatment				
Loop Diuretics -- no (%)	169 (98.8)	145 (99.3)	24(96.0)	.27
Aldosterone Antagonist -- no (%)	114 (66.7)	99 (66.8)	15 (60.0)	.49

[a]GFR = Glomerular Filtration Rate estimated from sMDRD equation[19]; [b]BNP = Brain Natriuretic Peptide, median and IQR, inter-quartile ranges; [c]For continuous variables, Student t-test if normal distribution with equal variance and Wilcoxon rank sum test if not. For discrete variables, Chi-square test

3.2 Study Outcomes

Out of the 146 monitored patients, 61 (42%) experienced a CCE during the 6-months signal acquisition. Among them, 35 (57%) experienced at least two CCE. As a whole, 96 CCE occurred during signal acquisition: 3 deaths, 93 hospitalizations or urgent visits (Fig. 3).

3.3 Signal Score

All the SDS computed on the complete signal data are shown in Table 3.

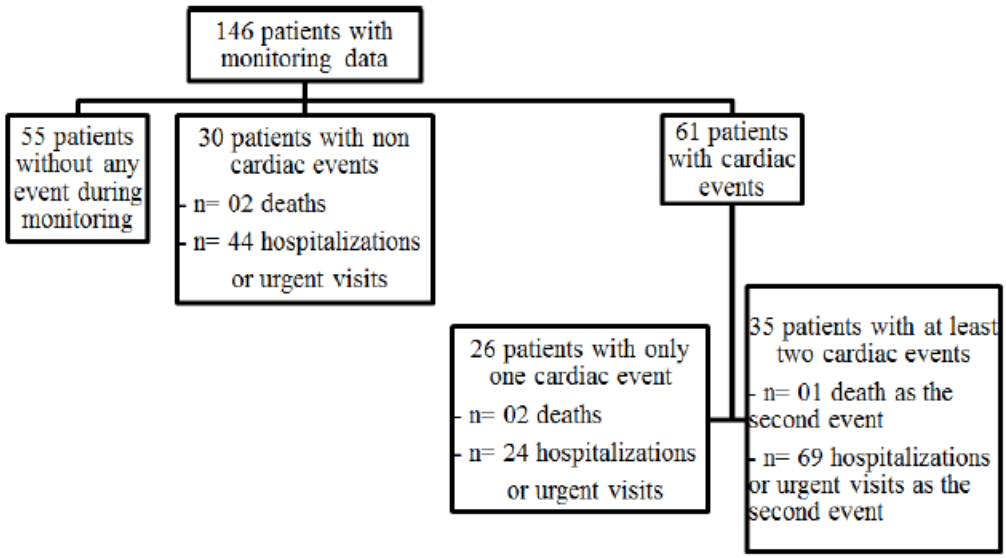

Fig. 3. Flow of events during signal acquisition

The training set included signal data during 7 days before the first event in the 61 patients experiencing at least one CCE and before a random time-point in the remaining 85 patients who did not experience a CCE, thereby including all monitored patients. The testing set included signal data during 7 days before the second event in the 35 patients experiencing at least two CCE and before another random time-point in 85 patients, thereby including 120 of the 146 monitored patients.

Comparison of SDS in the training set showed that, pressures and pulse rates were alike between patients with or without CCE. But, body weight's slope and body weight's standard deviation in the 3-, 5-, and 7-days preceding the CCE were higher in patients with CCE (Table 3).

All SDS listed in Table 3 were candidate covariates introduced in the LASSO regression to build the signal score. The impact of the L_1-norm penalty λ of the LASSO logistic regression on the coefficients of the model is shown in Fig. 4. While a complex model including the 30 initial candidate covariates was obtained when a 0 penalty was applied, most regression coefficients were sharply shrinked to 0 with increasing value of λ. With an optimal value of 3.5 for λ, the model included the seven following SDS in the signal score:

$$
\begin{aligned}
Signal\ score = \\
&+3.713 * Slope\ (body\ weight\ over\ 7\ consecutive\ days) \\
&+0.944 * SD\ (body\ weight\ during\ 3\ consecutive\ days) \\
&+0.804 * Slope\ (body\ weight\ over\ 3\ consecutive\ days) \\
&+0.034 * SD\ (pulse\ rate\ during\ 7\ consecutive\ days) \\
&+0.017 * SD\ (pulse\ rate\ during\ 3\ consecutive\ days) \\
&-0.020 * Mean\ (diastolic\ blood\ pressure\ during\ 3\ consecutive\ days) \\
&-0.049 * SD\ (differential\ blood\ pressure\ during\ 3\ consecutive\ days)
\end{aligned}
$$

A higher signal score was observed in a patient with an increase of body weight's variability on 3 consecutive days, or a sustained body weight's increase on 3 or 7 consecutive days, or an increased of pulse rate's variability on 3 or 7 consecutive days, or a decrease in mean diastolic blood pressure on 3 consecutive days, or a narrow differential blood pressure on 3 consecutive days. A sustained body weight's increase on 7 consecutive days was the most important feature given its highest coefficient.

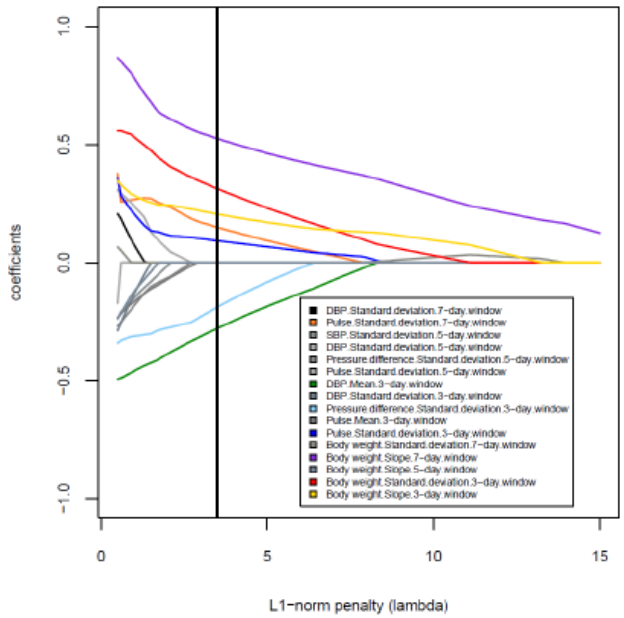

Fig. 4. Impact of the L1-norm penalty λ of the LASSO logistic regression model on the coefficients

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Table 3. Signal-Derived-Statistics in the 3-day, 5-day and 7-day window preceding a cardiac composite endpoint or a random time-point in patients without event, using training set

Signal derived statistics	3- day window			5- day window			7- day window		
	Yes	No	*P*- value	Yes	No	*P*- value	Yes	No	*P*- value
	n =61	n = 85		n =61	n = 85		n =61	n = 85	
Body weight SD[a] -- Kg	0.58 ± 0.46	0.41 ± 0.28	.009	0.67 ± 0.47	0.53 ± 0.32	.04	0.75 ± 0.46	0.55 ± 0.30	.002
Body weight slope – Kg/day	0.43 ± 0.29	0.29 ± 0.21	.002	0.31 ± 0.30	0.20 ± 0.18	.01	0.26 ± 0.23	0.13 ± 0.12	< .001
SBP[b] mean -- mmHg	123 ± 23	128 ± 22	.26	124 ± 22	127 ± 21	.32	123 ± 22	127 ± 21	.24
SBP[b] SD[a] -- mmHg	6.3 ± 4.5	6.6 ± 4.9	.65	7.1 ± 3.5	7.0 ± 4.0	.84	7.6 ± 3.8	7.1 ± 3.0	.41
DBP[c] mean --mmHg	74 ± 15	77 ± 15	.28	74 ± 14	76 ± 14	.38	73 ± 14	76 ± 14	.28
DBP[c] SD[a] -- mmHg	5.0 ± 3.6	5.3 ± 3.8	.60	5.9 ± 3.0	5.7 ± 3.2	.67	6.1 ± 2.8	5.8 ± 2.8	.54
BP[d] difference mean--mmHg	49 ± 13	51 ± 13	.48	50 ± 13	51 ± 14	.50	49 ± 12	51 ± 14	.44
BP[d] difference SD[a] -- mmHg	5.1 ± 3.4	6.0 ± 4.2	.21	6.1 ± 3.0	6.2 ± 3.4	.75	6.3 ± 2.8	6.4 ± 3.4	.87
PR[e] mean --ppm	79 ± 16	77 ± 14	.55	79 ± 16	77 ± 14	.50	78 ± 16	77 ± 14	.53
PR[e] SD[a] --ppm	6.4 ± 6.9	5.0 ± 4.8	.18	6.7 ± 5.9	5.4 ± 4.0	.11	6.8 ± 5.3	5.3 ± 3.7	.052

Data are mean ± SD; [a]SD= Standard Deviation; [b]SBP=Systolic Blood Pressure; [c]DBP=Diastolic Blood Pressure; [d]BP= Blood Pressure; [e]PR= Pulse Rate; To calculate the body weight's SD on a 3-days window for each patient, we computed standard deviation using the 3 consecutive values of body weight preceding the patient specific time-point. We then averaged these values by subgroups of patients with and without CCE

Table 4. Sensitivity and Specificity of BELGIUM-HF dynamic algorithms as compared with other literature's rules, assessed in the testing set

	Belgium-HF			Standard "rules- of-thumb"		TEMA-HF1 trial rules*
	Clinical score	Dynamic algorithms				
	MAGGIC score (cut-off = 40%)	Signal score: (cut-off = 20%)	Combined score: MAGGIC score + Signal score (cut-off = 25%)	3 lbs in 1 day	5 lbs in 3 days	Body weight ± 2kg from discharge or SBP[a] outside 90-140 mmHg or PR[b] outside 50-90/min
Sensitivity (%)	86	60	92	5	10	79
Specificity (%)	29	78	77	96	98	31
Youden index	0.15	0.38	0.69	0.01	0.08	0.10

[a]SBP = Systolic Blood Pressure; [b]PR= Pulse rate

The coefficients' paths identify the covariates to contribute to the prediction model. For the optimal value of λ (3.5), achieved by leave-one-out cross validation, the model include 7 SDS.

The signal risk score predicted CCE in the training set (AUC= 0.796), in the testing set (AUC= 0.830) and in the whole signal time-points of all patients (AUC=0.749, all $P < .001$, Fig. 5).

Prediction of CCE with the combined score was superior to each separate score in the training set (left panel), in the testing set (central panel), and in the whole signal (right panel).

3.4 MAGGIC Score

The MAGGIC score was predictive of CCE in the training set (AUC= 0.663), in the testing set (AUC=0.748) and in the complete set (AUC=0.649) ($P < .001$, Fig. 5).

3.5 Combined MAGGIC and Signal Scores

The second logistic model resulted in the following new combined score (P < .001 and P = 0.004 for statistical tests on the coefficients of signal and MAGGIC scores respectively).

$$Combined\ score = \\ + 0.781 \\ + 1.478 * Signal\ score \\ + 1.031 * MAGGIC\ score$$

Prediction of CCE with the combined score was superior to each separate score in the training set (AUC=0.830), in the testing set (AUC=0.891), and when using the whole signal (AUC=0.781) with all $P < .001$ (Fig. 5), meaning that clinical data and signal data brought additive information to risk prediction. This is also illustrated in Fig. 6, in 5 individual patients. The MAGGIC score is a single value per patient estimated at baseline. The signal score is a daily value. Patient C with a low MAGGIC score had no event. Patients A, B, D and E with high MAGGIC score experienced each one, at least one event, all at high values of the signal score. The combined score is also a daily value. These 5 patients had similar median signal scores. But, when combining the signal score with the MAGGIC score, patients A and E with a high MAGGIC score, had a high combined score; patients B and D with a medium MAGGIC score, had a medium combined score; patient C with a low MAGGIC score, had a low combined score. This allows for an individualization of HTM.

The MAGGIC score is a single value per patient (left panel). The signal score is a daily value. A box plot represents all score values of a single patient (central and right panels). Squares indicate the score value of a patient, the day he experienced an event. Combining the MAGGIC score with the signal score induces a high increase (patients A and E), an intermediate increase (patients B and D) or a decrease (patient C) in daily values, allowing the individualization of monitoring. Cut-off can be set to trigger alerts as 25% for the combined score in this example.

3.6 Comparison of the Combined Score's Diagnostic Accuracy with Simple Rules

Using some cut-off (40%, 20% and 25% respectively for MAGGIC, signal and combined scores), we assessed sensitivity and specificity of each of the three scores. Alarms can be set at other cut-off values, according to the targeted positive predictive value. The MAGGIC score had a high sensitivity but a low specificity whereas the signal score had a high specificity but a low sensitivity in the testing set. Combining the two scores allowed having a more effective diagnostic method with a good sensitivity (92%) and a good specificity (77%) (Table 4). Running standard "rules-of-thumb" (RoTs) showed a low sensitivity of 5% for a loss of 3 lbs in 1 day and of 10% for a loss of 5 lbs in 3 days. The rules applied in TEMA-HF1 trial [20] achieved a sensitivity of 79% but with only 31% of specificity (Table 4).

4. DISCUSSION

BELGIUM-HF study was designed to identify in a first step, the characteristics in the daily changes of the monitored parameters (body weight, blood pressure, pulse rate) that are predictive of HF-related events. It turned out that body weight's variability on a short 3-days' time window, as previously described in other studies [15,16] was predictive of a cardiac event. But in addition, we found that a sustained body weight's increase over a longer time window of 7 consecutive days significantly increased the predictive value of the signal score. A pulse rate's variability on a 7-days' time window, a decrease in mean diastolic blood pressure on a 3-days' time window and a narrow differential blood pressure on a 3-days' time window also contributed to a better performance of the signal score. This signal score, combined in a second step with the

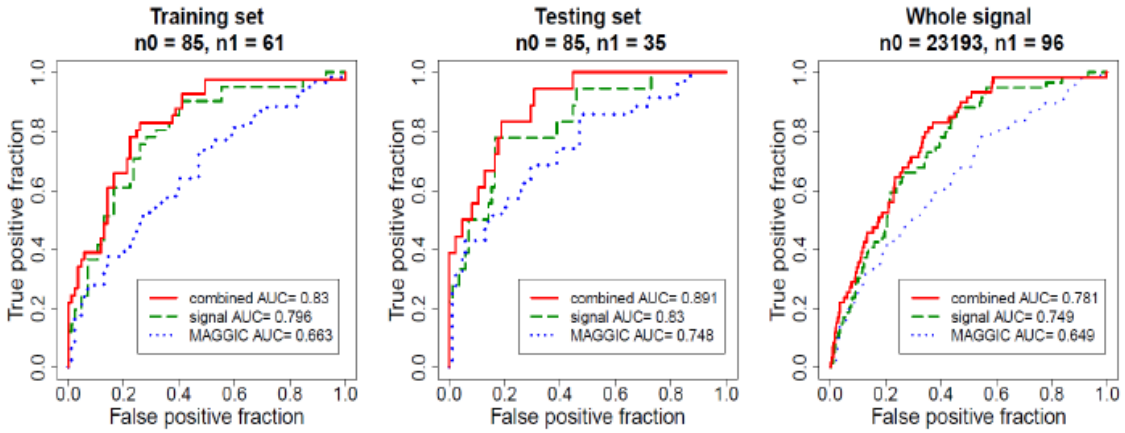

Fig. 5. ROC curves of the various scores for the cardiac composite endpoint (CCE)

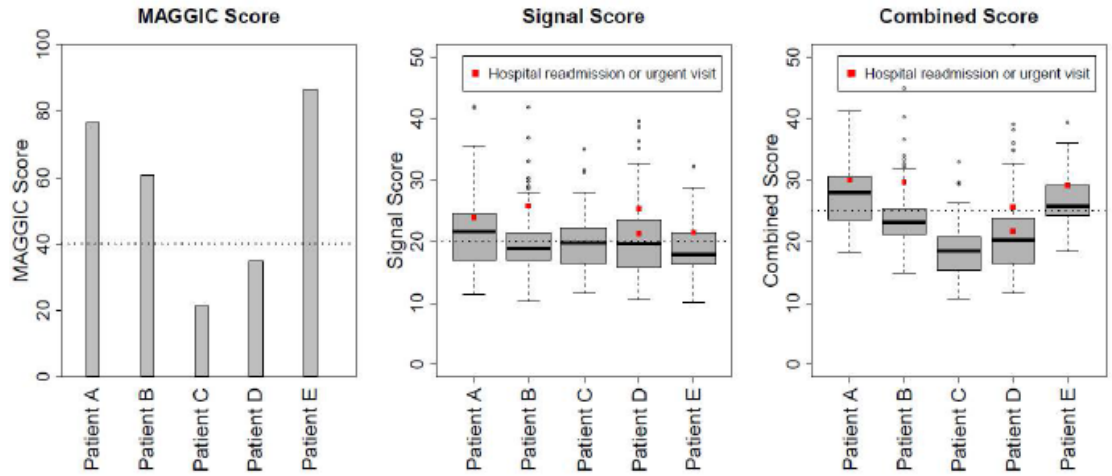

Fig. 6. Illustration of each of the three scores in 5 individual patients

MAGGIC clinical score resulted ultimately in an efficient individualized dynamic algorithm whose predictive value was higher, whatever the cutoff, as demonstrated by ROC curves.

Combining HTM with MAGGIC score provides two main advantages. Firstly, we showed that this combination better predicted HF events than previously developed algorithms. Secondly, patients at high risk of re-hospitalization or sudden death appear to benefit more from HTM programs compared to patients with stable HF [21]. Combining HTM with MAGGIC score could well help to identify the subgroup of patients for whom this technology would be most beneficial.

Because of major differences in data collections and events definitions, indirect comparisons of our results with published algorithms are hazardous, but direct comparisons with simple rules, notably the RoTs >3 lbs in 1 day or >5 lbs in 3 days can be made using BELGIUM-HF data. These two RoTs showed a high specificity (respectively 96% and 98%) but a low sensitivity (respectively 5% and 10%) for detecting events. This was also observed in Zhang [15] and in Ledwidge [17] datasets. Moreover, in BELGIUM-HF dataset, the rules of predetermined limits of changes in body weight, pulse rate or systolic blood pressure as proposed in TEMA-HF1 trial [20], achieved a 79% sensitivity but only a 31% specificity. Compared to these rules, our dynamic algorithm (92% sensitivity and 77% specificity) resulted in a high increase in specificity with an increase in sensitivity. Therefore, dynamic algorithms seem to have advantages over simple RoTs in detecting HF events. In the Ledwige dataset, a 7-days moving average algorithm of

body weight and its variability significantly improved the detection of HF events with a high sensitivity of 82% [17]. However, this sensitivity may have artificially increased because, as authors pointed out, the body weight trend itself served to comfort the diagnosis of worsening HF in 54% of patients. Our individualized dynamic algorithm also improved the detection of HF events (92% sensitivity) ensuring a valid measure of sensitivity.

There are some limitations to the present study and the small sample size is the main one. Likewise, to include negative cases in the training and testing sets, we randomly selected time-points. This could hamper the accuracy of the model specificity. Furthermore, even if signal windows used in the testing set were different from signal windows used in the training set, we cannot avoid a correlation between these two data sets because patients were the same in both sets. However, the testing set is equivalent to the training set for using the model derived in the training set. Finally, body weight gain does not occur in all patients before a HF-related event [22]. Indeed, the pathophysiology of acute decompensated HF is complex and the mechanism of this decompensation remains unclear. Whilst in some cases it is due to volume expansion, half of patients did not experience an increase in total body weight [23]. An alternative hypothesis proposed by Fallick et al. is that an autonomically mediated shift between total extracellular fluid volume and effective circulating blood volume explains the development of congestion in many patients with decompensated HF [22]. This new approach assigns sympathetic activation of the venous capacitance vessels in the setting of left ventricular dysfunction as the major driving source of elevated filling pressures [22]. Changing our thinking to incorporate strategies that target fluid shifts as well as fluid gain may bring acute and chronic benefits [23]. Remote monitoring of other clinical parameters (blood pressure, heart rate) in addition to body weight, and more, the combination with MAGGIC clinical score in our study improved the predictive value of HTM. In the future, HTM could further combine devices designed to monitor right heart hemodynamic capacity to deal with the complex pathophysiology of HF.

Nevertheless, there are several arguments proving the quality of our study. Firstly, the BELGIUM-HF dataset was made of a blind storage of automated physiological measurements and a separate inventory of factual clinical events. This design authorized unbiased descriptions of the signal trends prior to an event's occurrence. Secondly, by considering the monitored parameters' characteristics that are associated with HF events, we allowed a valid measure of the sensitivity of our prediction algorithm. Thirdly, we combined the signal score with the MAGGIC score, to build an individualized dynamic algorithm whose predictive power on HF events seems more efficient.

5. CONCLUSION

In conclusion, the BELGIUM-HF study identified a new individualized dynamic algorithm which appears to be the best approach to predict HF instability that led to major factual clinical events. Combining HTM with MAGGIC score showed that signal data and clinical data provide additive information to risk prediction in HF patients. HTM technology to predict HF events should include patients' clinical prognosis. However, further studies would be needed to confirm these findings.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail. 2001;3(3):315-22.
2. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al. The EuroHeart Failure survey programme- A survey on the quality of care among patients with heart failure in Europe. Part 1: Patient characteristics and diagnosis. Eur Heart J. 2003;24(5):442-63.
3. Lynga P, Persson H, Hagg-Martinell A, Hagglund E, Hagerman I, Langius-Eklof A, et al. Weight monitoring in patients with severe heart failure (WISH). A randomized controlled trial. Eur J Heart Fail. 2012; 14(4):438-44.
4. Ong MK, Romano PS, Edgington S, Aronow HU, Auerbach AD, Black JT, et al. Effectiveness of remote patient monitoring after Discharge of hospitalized patients with heart failure: The better effectiveness

after Transition-Heart Failure (BEAT-HF) randomized clinical trial. JAMA Intern Med. 2016;176(3):310-8.

5. Inglis SC, Clark RA, Dierckx R, Prieto-Merino D, Cleland JG. Structured telephone support or non-invasive telemonitoring for patients with heart failure. Cochrane Database Syst Rev. 2015;10:CD007228.
6. Anker SD, Koehler F, Abraham WT. Telemedicine and remote management of patients with heart failure. Lancet. 2011;378(9792):731-9.
7. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008;29(19):2388-442.
8. Chaudhry SI, Mattera JA, Curtis JP, Spertus JA, Herrin J, Lin Z, et al. Telemonitoring in patients with heart failure. N Engl J Med. 2010;363(24): 2301-9.
9. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Bohm M, et al. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: The telemedical interventional monitoring in heart failure study. Circulation. 2011;123(17): 1873-80.
10. Pandor A, Thokala P, Gomersall T, Baalbaki H, Stevens JW, Wang J, et al. Home telemonitoring or structured telephone support programmes after recent discharge in patients with heart failure: Systematic review and economic evaluation. Health Technol Assess. 2013; 17(32):1-207, v-vi.
11. McDonald K, Wilkinson M, Ledwidge M. Role of monitoring devices in preventing heart failure admissions. Curr Heart Fail Rep. 2015;12(4):269-75.
12. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Kober L, Squire IB, et al. Predicting survival in heart failure: A risk score based on 39 372 patients from 30 studies. Eur Heart J. 2013;34(19):1404-13.
13. Sawadogo K, Ambroise J, Vercauteren S, Castadot M, Vanhalewyn M, Col J, et al. Interaction between the Kansas City cardiomyopathy questionnaire and the Pocock's clinical score in predicting heart failure outcomes. Qual Life Res. 2016; 25(5):1245-55.
14. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med. 1999;341(8):577-85.
15. Zhang J, Goode KM, Cuddihy PE, Cleland JG, Investigators T-H. Predicting hospitalization due to worsening heart failure using daily weight measurement: Analysis of the Trans-European Network-Home-Care Management System (TEN-HMS) study. Eur J Heart Fail. 2009;11(4): 420-7.
16. Chaudhry SI, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. Circulation. 2007; 116(14):1549-54.
17. Ledwidge MT, O'Hanlon R, Lalor L, Travers B, Edwards N, Kelly D, et al. Can individualized weight monitoring using the HeartPhone algorithm improve sensitivity for clinical deterioration of heart failure? Eur J Heart Fail. 2013;15(4):447-55.
18. Pavlou M, Ambler G, Seaman SR, Guttmann O, Elliott P, King M, et al. How to develop a more accurate risk prediction model when there are few events. BMJ. 2015;351:h3868.
19. Vittinghoff E. Regression methods in biostatistics: Linear, logistic, survival, and repeated measures models. 2nd ed. New York: Springer; 2012.
20. Dendale P, De Keulenaer G, Troisfontaines P, Weytjens C, Mullens W, Elegeert I, et al. Effect of a telemonitoring-facilitated collaboration between general practitioner and heart failure clinic on mortality and rehospitalization rates in severe heart failure: The TEMA-HF 1 (TElemonitoring in the MAnagement of Heart Failure) study. Eur J Heart Fail. 2012;14(3):333-40.
21. Kitsiou S, Pare G, Jaana M. Effects of home telemonitoring interventions on patients with chronic heart failure: An

overview of systematic reviews. J Med Internet Res. 2015;17(3):e63.

22. Fallick C, Sobotka PA, Dunlap ME. Sympathetically mediated changes in capacitance: Redistribution of the venous reservoir as a cause of decompensation. Circ Heart Fail. 2011;4(5):669-75.

23. Burchell AE, Sobotka PA, Hart EC, Nightingale AK, Dunlap ME. Chemohypersensitivity and autonomic modulation of venous capacitance in the pathophysiology of acute decompensated heart failure. Curr Heart Fail Rep. 2013; 10(2):139-46.

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4.2.2. Illustration of the BELGIUM-HF alert triggering system

The principle of BELGIUM-HF automated and autonomous alert triggering system is shown in Figure 11. The measurements of the daily monitored clinical parameters (body weight, blood pressure and pulse rate) are automatically transmitted to the patient's mobile phone. The transmitted data are analyzed using 4 pre-installed successive applications. Application 1 allows recording the data transmitted on a day j. Application 2 then allows a quality control of the data transmitted on this day. Application 3 is used to plot the dynamic daily signal of each measured parameter. Application 4 finally computes the value of the prediction score on day j. If this value reaches the predefined threshold, an alert is triggered on day j, otherwise no alert is triggered on that day. This process is repeated daily with new transmitted data.

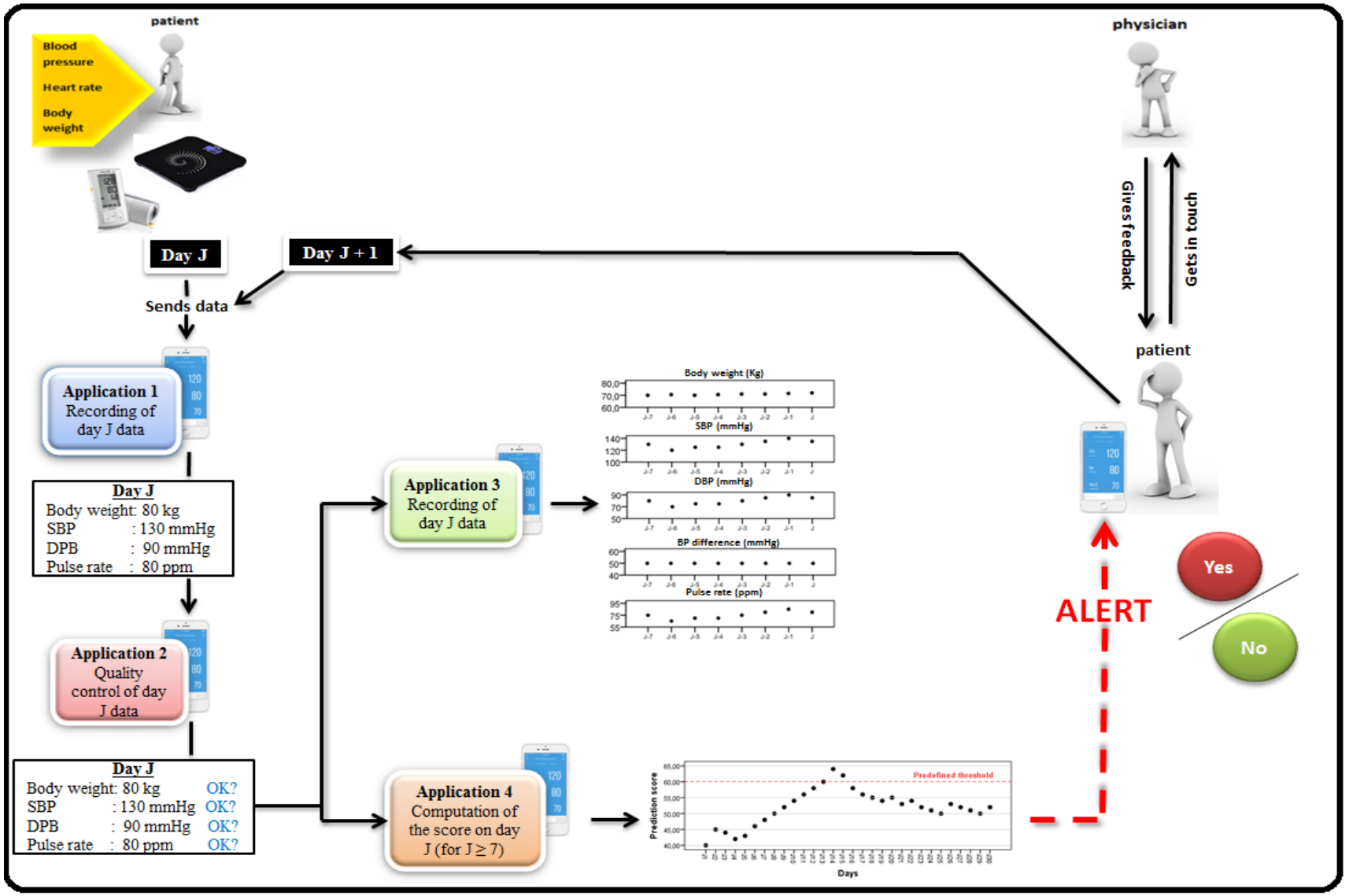


Figure 11. Principle of the BELGIUM-HF automated and autonomous alert triggering system

4.2.3. Summary of the methodology in Publication 1

A workflow of the methodology implemented in Publication 1 is given in Figure 12.

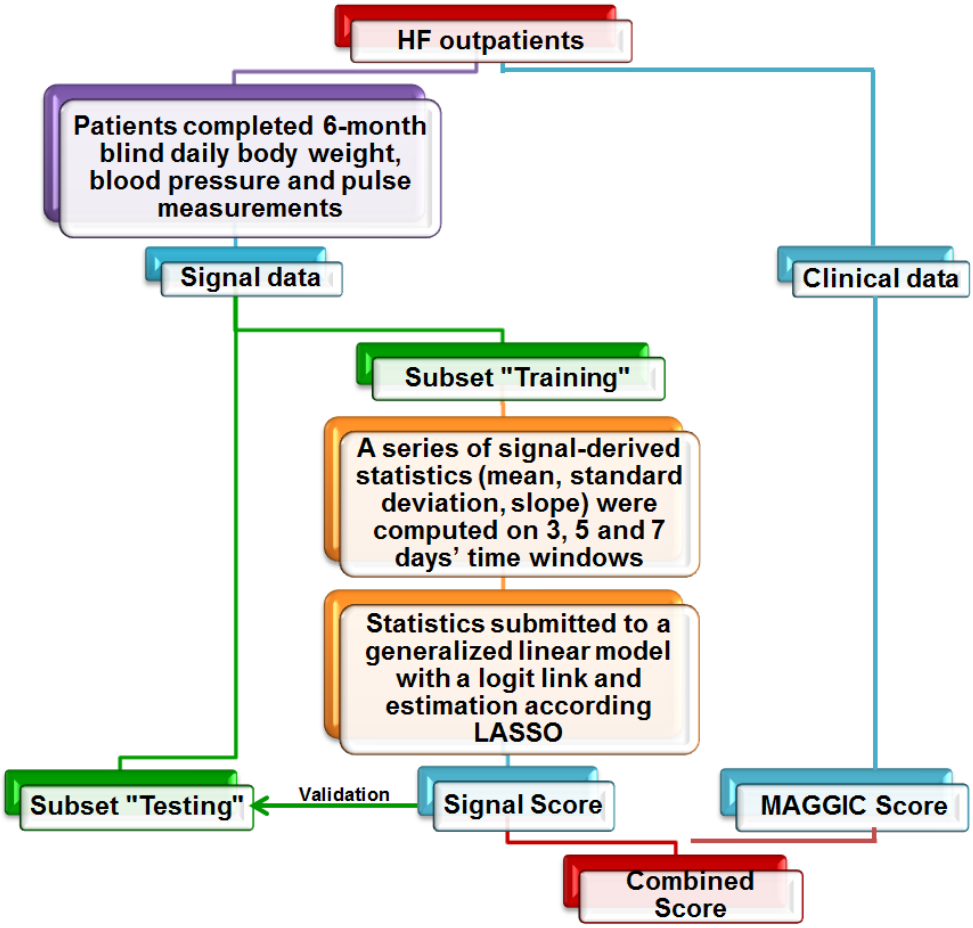


Figure 12. Workflow of methodology

Figures 13a and 13b illustrate more clearly the development and the validation of the signal score through two subsets of data ("Training and "Testing"). Signal score was built on the training set and validated on the testing set in order to avoid overfitting problem. The training set included all signal data during the 7 days preceding the first event (n = 61) and all signal data during the 7 days preceding a randomly selected time-point for patients without CCE during signal acquisition (n = 85). The testing set included all signal data during the 7 days preceding the second event for patients with at least two CCE (n = 35) and all signal data during the 7 days preceding another randomly selected time-point for patients without CCE during signal acquisition (n = 85). A series of signal-derived-statistics (mean, standard deviation and slope for body weight) were computed using the 3, 5 and 7 consecutive values

of body weight, blood pressure and pulse rate preceding each time-point. A mathematical model for CCE prediction was then built using these signal-derived-statistics in the training set and its accuracy was assessed in the testing set.

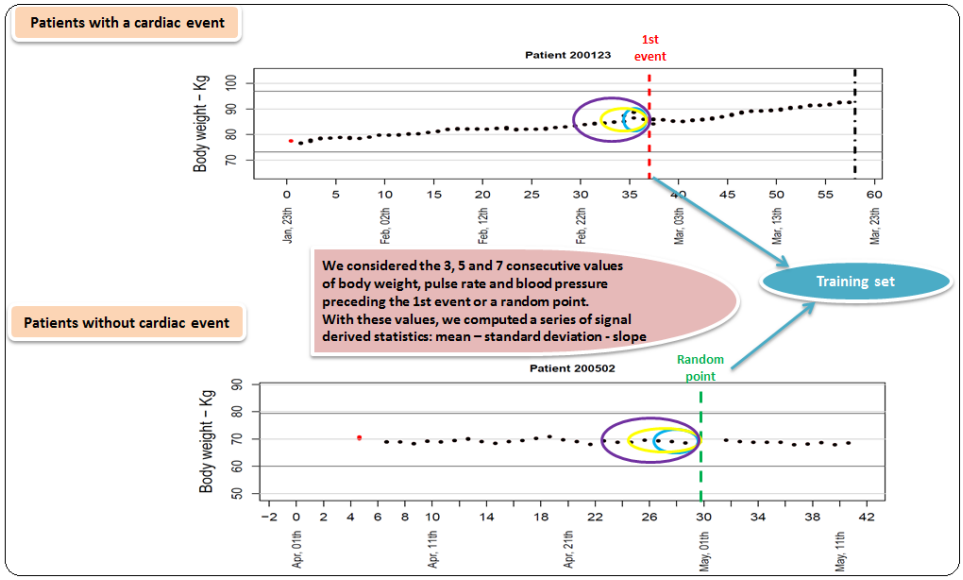


Figure 13a. Illustration of the development of the signal score

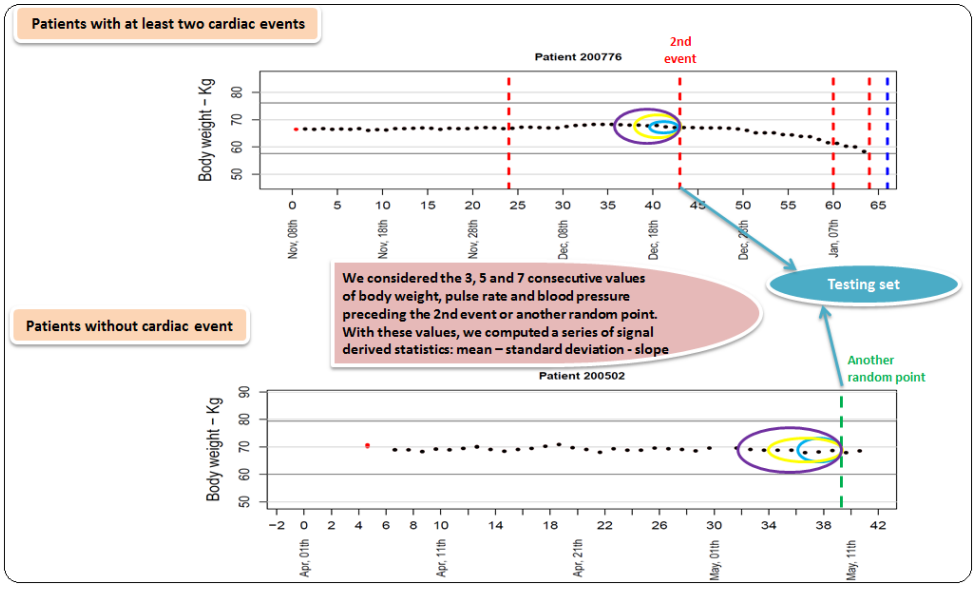


Figure 13b. Illustration of the validation of the signal score

4.2.4. Additional results to Publication 1

The overall net reclassification improvement (NRI) was equal to 0.04. The event NRI was equal to 0.21 showing that the combined score improved the detection of patients with CCE. The non-event NRI however was equal to –0.17 showing that the combined score unfortunately also increased risk estimates for patients without CCE. (Table 8)

Using instead the integrated discrimination improvement (IDI) measure, we found that the event IDI was equal to 5.81 indicating that the risk predicted by the combined score was higher on average than that predicted by the signal score in patients with CCE. However, the non-event IDI was equal to –3.86 showing that the risk predicted by the combined score was also higher on average than that predicted by the signal score in patients without CCE. In all patients, the overall absolute IDI was equal to 1.95 yielding a relative IDI of 0.11 and showing that the combined score increased discrimination by 11% compared to signal score.

Table 8. Reclassification among patients who experienced a cardiac composite endpoint (CCE) and those who did not experience a CCE during follow-up

Signal score	**Combined score**			
Frequency	< 21%	21-42%	> 42%	Total
Patients who experienced a CCE				
< 21%	2	0	1	3
21-42%	0	9	12	21
> 42%	0	0	37	37
Total	2	9	50	61
Patients who did not experience a CCE				
< 21%	3	10	0	13
21-42%	4	43	10	57
> 42%	0	1	14	15
Total	7	54	24	85

A TRIPOD checklist for prediction model development is given in appendice 2.

4.2.5. Illustration of the contribution of the BELGIUM-HF algorithm

With reference to Figure 14, the combined score outperformed each of the two scores (signal and MAGGIC) separately whatever the cutoff in the two subsets. The 95% confidence intervals on the area under the curve (AUC) were [0.801 ; 0.844], [0.793 ; 0.798], and [0.632 ; 0.694] respectively for combined, signal and MAGGIC scores in the training set.

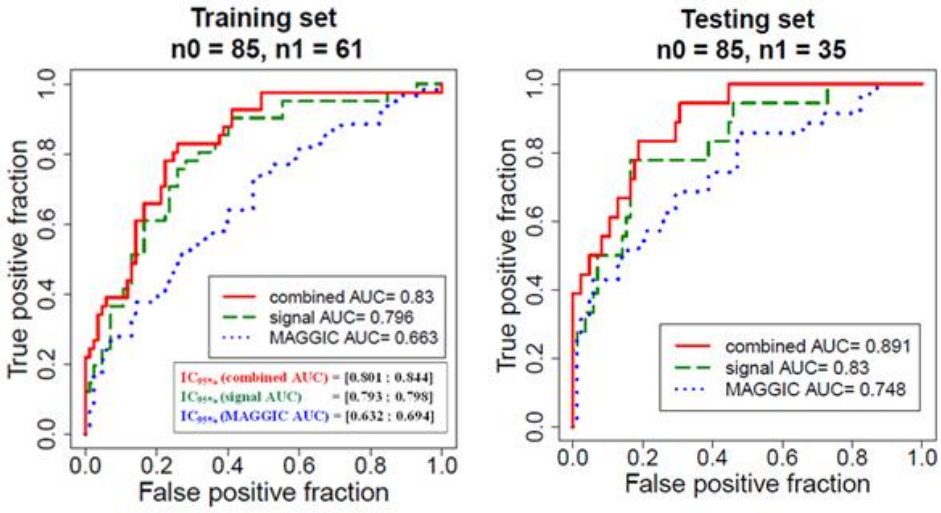


Figure 14. Comparison of the three scores using ROC curves

Taking an example with 5 individual patients, Figure 15 also illustrated the added value of the combined score. On the left panel is shown the MAGGIC score which is a single value per patient estimated at baseline. In this example, patients A and E had high MAGGIC scores whereas patient C had a low MAGGIC score. On the central panel is shown the signal score which is a dynamic value updated every day. A boxplot represents each patient's all signal scores values. The combined score is also a dynamic daily value. The signal scores values of these patients were similar. Combining the signal score with the MAGGIC score resulted in a high increase for patients A and E with a high baseline risk and a decrease for patients C with a low baseline risk. A cut-off defined on the combined score rather than on the signal score would be more efficient because triggering an alert would then be proportional to the baseline risk of each patient.

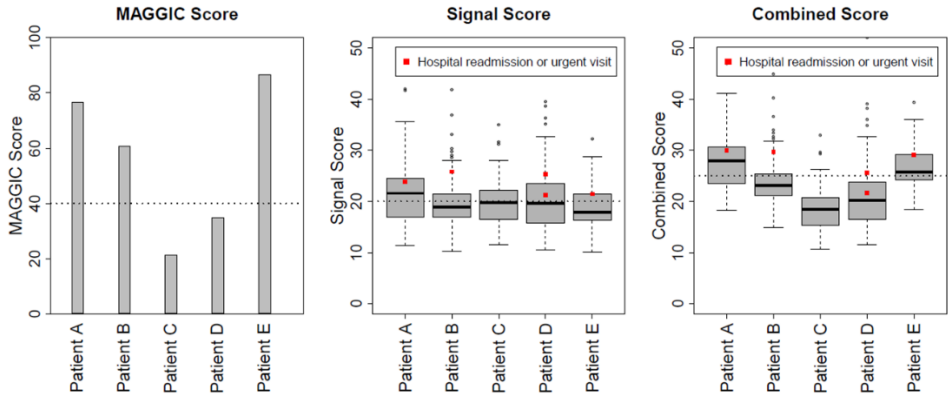


Figure 15. Illustration of the contribution of the combined score in 5 individual patients

Regarding the compliance with the system, 92% of the monitored data have been properly recorded. The remaining 8% did not match missing data but corresponded to periods during which patients had been admitted to hospital and were therefore no longer able to perform daily measurements of the monitored parameters.

4.3. Normal ranges of the combined prediction score

The combined score was applied to the 38 healthy volunteers stratified into 6 groups according to their age and gender. Tables 9a, 9b and 9c summarize the distribution of each of the variables included in the combined score among these 38 volunteers. All the 7 variables included in the signal score showed significant variability in these healthy volunteers except for the mean diastolic blood pressure on 3 consecutive days. The score combining the signal score to the MAGGIC score also showed a significant variability among these volunteers. This is well illustrated in Figure 16.

Table 9a. Distribution of variables included in the combined score in healthy volunteers aged under 60 years

	< 60 years									
	Body weight 7 days slope (kg/day)	Body weight 3 days SD (kg)	Body weight 3 days slope (kg/day)	Pulse rate 7 days SD (ppm)	Pulse rate 3 days SD (ppm)	DBP 3 days mean (mmHg)	BP difference 3 days SD (mmHg)	SIGNAL Score (%)	MAGGIC Score (%)	COMBINED Score (%)
Male										
1	0.1 ± 0.1	0.6 ± 0.4	0.4 ± 0.3	4.9 ± 2.2	4.2 ± 3.0	94 ± 7	6 ± 4	16 ± 4	15	13 ± 4
2	0.1 ± 0.1	0.3 ± 0.2	0.2 ± 0.2	5.2 ± 2.6	4.9 ± 3.4	96 ± 4	9 ± 4	12 ± 3	19	10 ± 3
3	0.2 ± 0.2	0.5 ± 0.3	0.3 ± 0.3	7.4 ± 4.9	6.4 ± 6.1	96 ± 5	13 ± 11	15 ± 5	18	13 ± 5
4	0.1 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	3.5 ± 1.0	3.4 ± 1.6	87 ± 5	5 ± 3	12 ± 2	23	10 ± 2
5	0.1 ± 0.1	0.5 ± 0.2	0.3 ± 0.2	6.1 ± 2.1	5.4 ± 2.9	86 ± 5	12 ± 8	13 ± 4	18	11 ± 4
6	0.1 ± 0.1	0.4 ± 0.2	0.3 ± 0.2	7.8 ± 3.3	7.5 ± 4.4	93 ± 4	7 ± 4	14 ± 4	21	12 ± 4
7	0.1 ± 0.1	0.4 ± 0.2	0.3 ± 0.2	5.6 ± 2.0	4.9 ± 3.0	74 ± 5	8 ± 6	16 ± 4	0	11 ± 4
8	0.2 ± 0.1	0.5 ± 0.3	0.3 ± 0.3	5.8 ± 2.4	4.8 ± 3.4	99 ± 5	6 ± 3	15 ± 4	11	12 ± 4
9	0.1 ± 0.1	0.5 ± 0.4	0.3 ± 0.4	8.1 ± 2.8	8.6 ± 4.2	79 ± 5	9 ± 7	17 ± 5	1	12 ± 5
10	0.2 ± 0.1	0.3 ± 0.2	0.3 ± 0.2	5.3 ± 1.1	4.8 ± 2.2	83 ± 2	5 ± 3	17 ± 4	16	15 ± 4
Female										
11	0.1 ± 0.1	0.3 ± 0.2	0.2 ± 0.2	4.5 ± 2.6	3.9 ± 2.9	64 ± 3	6 ± 3	16 ± 3	13	12 ± 3
12	0.1 ± 0.2	0.5 ± 0.3	0.4 ± 0.	8.5 ± 2.8	7.3 ± 4.4	80 ± 3	5 ± 3	19 ± 5	12	15 ± 5
13	0.1 ± 0.1	0.4 ± 0.2	0.3 ± 0.2	5.5 ± 2.3	5.1 ± 3.4	66 ± 4	3 ± 2	19 ± 4	3	14 ± 4
14	0.2 ± 0.3	0.6 ± 0.3	0.3 ± 0.3	5.9 ± 2.1	5.2 ± 2.0	84 ± 5	6 ± 3	17 ± 5	13	13 ± 5
15	0.1 ± 0.1	0.4 ± 0.3	0.3 ± 0.3	5.0 ± 2.2	4.1 ± 2.8	64 ± 4	7 ± 4	18 ± 5	8	14 ± 5
16	0.2 ± 0.5	0.5 ± 0.4	0.3 ± 0.3	7.2 ± 2.5	6.6 ± 4.4	89 ± 4	7 ± 5	17 ± 9	3	12 ± 9

Data are mean ± standard deviation; DBP: diastolic blood pressure; BP: blood pressure

Table 9b. Distribution of variables included in the combined score in healthy volunteers aged [60 ; 70[years

	[60 ; 70 [years																														
	Body weight 7 days slope (kg/day)			**Body weight 3 days SD (kg)**			**Body weight 3 days slope (kg/day)**			**Pulse rate 7 days SD (ppm)**			**Pulse rate 3 days SD (ppm)**			**DBP 3 days mean (mmHg)**			**BP difference 3 days SD (mmHg)**			**SIGNAL Score (%)**			**MAGGIC Score (%)**	**COMBINED Score (%)**		
Male																															
17	0.1	±	0.1	0.4	±	0.3	0.3	±	0.3	10.1	±	5.1	9.2	±	6.9	99	±	5	9	±	5	15	±	5	24	13	±	4
18	0.2	±	0.1	0.5	±	0.3	0.3	±	0.3	4.2	±	1.5	3.6	±	1.8	90	±	3	5	±	3	16	±	4	31	16	±	4
19	0.2	±	0.1	0.5	±	0.3	0.3	±	0.3	3.3	±	1.2	3.0	±	1.8	94	±	6	8	±	3	14	±	5	24	13	±	5
20	0.1	±	0.1	0.3	±	0.2	0.3	±	0.2	3.4	±	1.1	3.1	±	1.8	77	±	4	6	±	3	15	±	2	18	13	±	2
21	0.1	±	0.1	0.4	±	0.2	0.3	±	0.2	3.1	±	1.5	2.6	±	2.0	97	±	4	4	±	2	14	±	3	32	14	±	3
22	0.1	±	0.1	0.3	±	0.2	0.2	±	0.2	3.9	±	2.3	3.2	±	2.4	74	±	5	4	±	2	16	±	3	28	15	±	3
Female																															
23	0.1	±	0.1	0.3	±	0.2	0.3	±	0.2	8.7	±	3.9	7.9	±	5.5	75	±	3	6	±	4	17	±	4	28	16	±	4
24	0.1	±	0.1	0.3	±	1.2	0.2	±	0.2	3.4	±	2.1	3.1	±	2.9	66	±	3	7	±	4	15	±	3	16	12	±	3
25	0.1	±	0.1	0.3	±	0.3	0.2	±	0.2	4.3	±	1.7	3.7	±	2.4	84	±	3	6	±	4	13	±	4	38	14	±	4
26	0.1	±	0.1	0.3	±	0.2	0.2	±	0.2	5.0	±	2.0	3.9	±	2.9	81	±	5	5	±	3	14	±	3	40	15	±	3
27	0.1	±	0.1	0.2	±	0.1	0.2	±	0.1	7.9	±	1.8	6.9	±	3.4	92	±	4	6	±	4	12	±	3	35	12	±	3
28	0.1	±	0.1	0.3	±	0.2	0.2	±	0.2	5.9	±	2.7	5.3	±	3.9	81	±	4	6	±	4	14	±	3	27	13	±	3

Data are mean ± standard deviation; DBP: diastolic blood pressure; BP: blood pressure

Table 9c. Distribution of variables included in the combined score in healthy volunteers aged 70 years or older

	≥ 70 years																														
	Body weight 7 days slope (kg/day)			Body weight 3 days SD (kg)			Body weight 3 days slope (kg/day)			Pulse rate 7 days SD (ppm)			Pulse rate 3 days SD (ppm)			DBP 3 days mean (mmHg)			BP difference 3 days SD (mmHg)			SIGNAL Score (%)			MAGGIC Score (%)	COMBINED Score (%)				
Male																															
29	0.1	±	0.1	0.3	±	0.3	0.2	±	0.3	5.9	±	1.4	5.2	±	3.0	83	±	5	4	±	3	15	±	5	37	16	±	5
30	0.1	±	0.1	0.3	±	0.3	0.2	±	0.3	2.6	±	0.8	2.1	±	1.3	78	±	2	6	±	3	15	±	6	26	14	±	6
31	0.1	±	0.1	0.4	±	0.3	0.3	±	0.2	3.0	±	1.5	2.4	±	1.6	73	±	2	5	±	2	16	±	4	36	17	±	4
32	0.1	±	0.1	0.4	±	0.3	0.2	±	0.2	3.7	±	1.4	3.1	±	2.2	85	±	3	5	±	3	14	±	3	34	14	±	3
33	0.1	±	0.1	0.3	±	0.1	0.2	±	0.2	6.1	±	3.0	5.0	±	4.1	87	±	3	7	±	4	13	±	3	44	15	±	3
34	0.1	±	0.1	0.3	±	0.2	0.2	±	0.2	2.2	±	0.8	1.8	±	1.0	72	±	4	5	±	2	16	±	4	39	17	±	4
Female																															
35	0.1	±	0.1	0.3	±	0.2	0.2	±	0.2	4.2	±	1.2	3.8	±	2.1	78	±	3	5	±	3	15	±	4	29	15	±	3
36	0.1	±	0.1	0.4	±	0.3	0.3	±	0.3	4.8	±	1.2	4.3	±	2.1	74	±	2	5	±	3	16	±	4	34	16	±	4
37	0.1	±	0.1	0.3	±	0.3	0.2	±	0.2	3.2	±	1.1	2.4	±	1.6	65	±	3	5	±	3	16	±	3	43	17	±	3
38	0.1	±	0.1	0.3	±	0.3	0.2	±	0.3	2.0	±	1.0	2.0	±	1.4	69	±	3	6	±	3	16	±	4	36	16	±	4

Data are mean ± standard deviation; DBP: diastolic blood pressure; BP: blood pressure

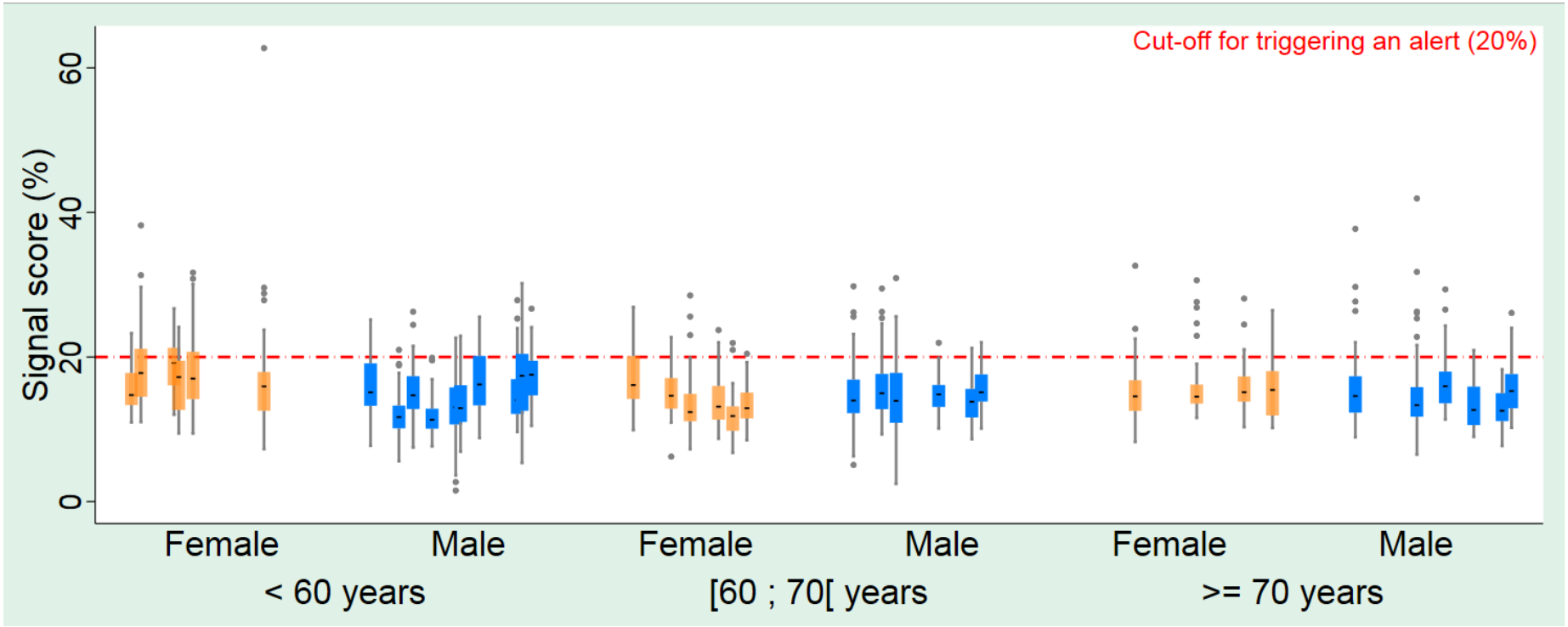


Figure 16. Distribution of the signal score in 38 healthy volunteers

Selection of healthy volunteers was based on the absence of HF. They therefore had a good clinical prognosis according to the MAGGIC score. Indeed, they had almost all a MAGGIC score below 40%. Contrariwise, most HF patients had a MAGGIC score above 40% whether or not they experienced a cardiac event during follow-up. This explains the high sensitivity (86%) but the poor specificity (29%) when using the 40% cut-off for the MAGGIC score. (Figure 17a)

The 20% cut-off for the signal score resulted in a few number of alerts in healthy volunteers compared to HF patients. Indeed, this cut-off produced, 58 (60.4%), 5102 (22.0%) and 262 (11.8%) alerts in HF patients with cardiac events, in HF patients without cardiac events and in healthy volunteers respectively. (Figure 17b and Table 10)

The number of produced alerts in healthy volunteers was even smaller when using the 25% cut-off of the combined score. With this cut-off, 88 (91.7%), 5334 (23.0%) and 34 (1.5%) alerts were produced in HF patients with cardiac events, in HF patients without cardiac events and in healthy volunteers respectively. (Figure 17c and Table 10)

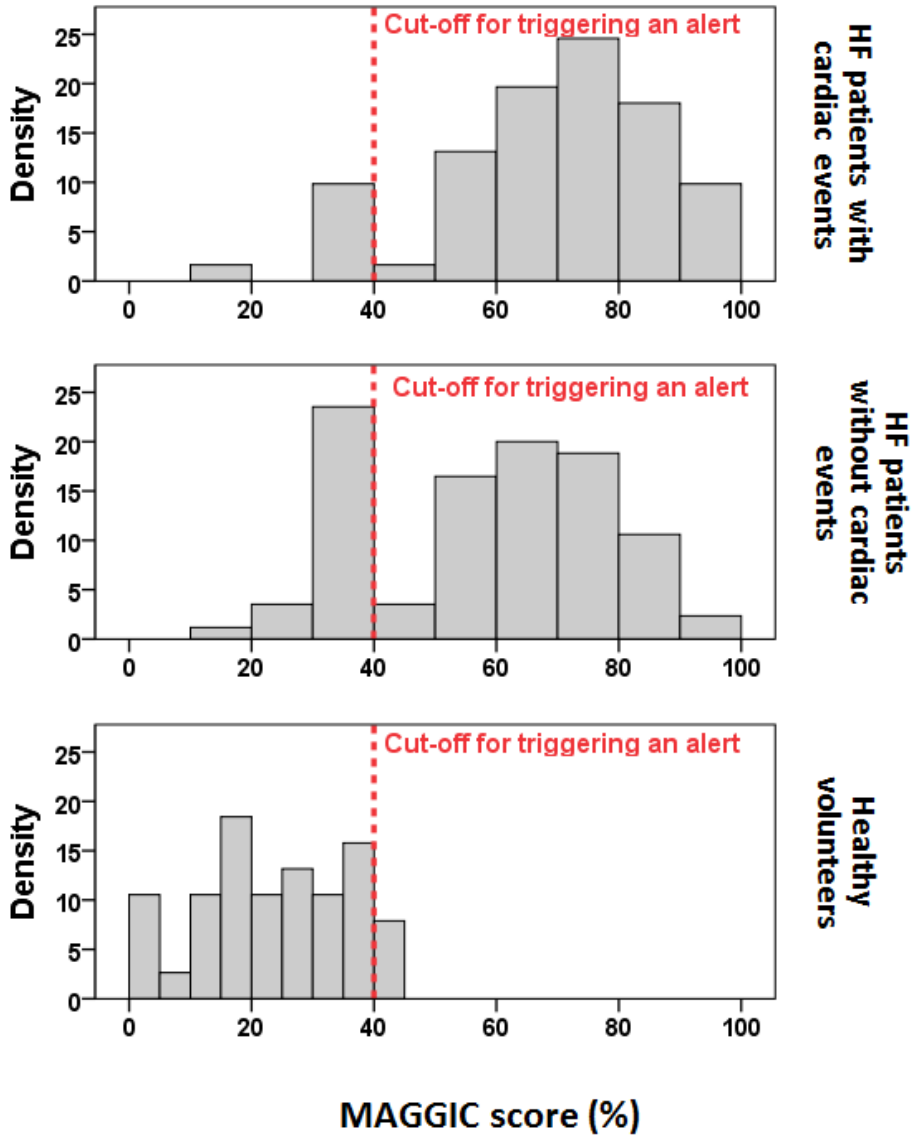


Figure 17a. Distribution of the MAGGIC score in HF patients and healthy volunteers

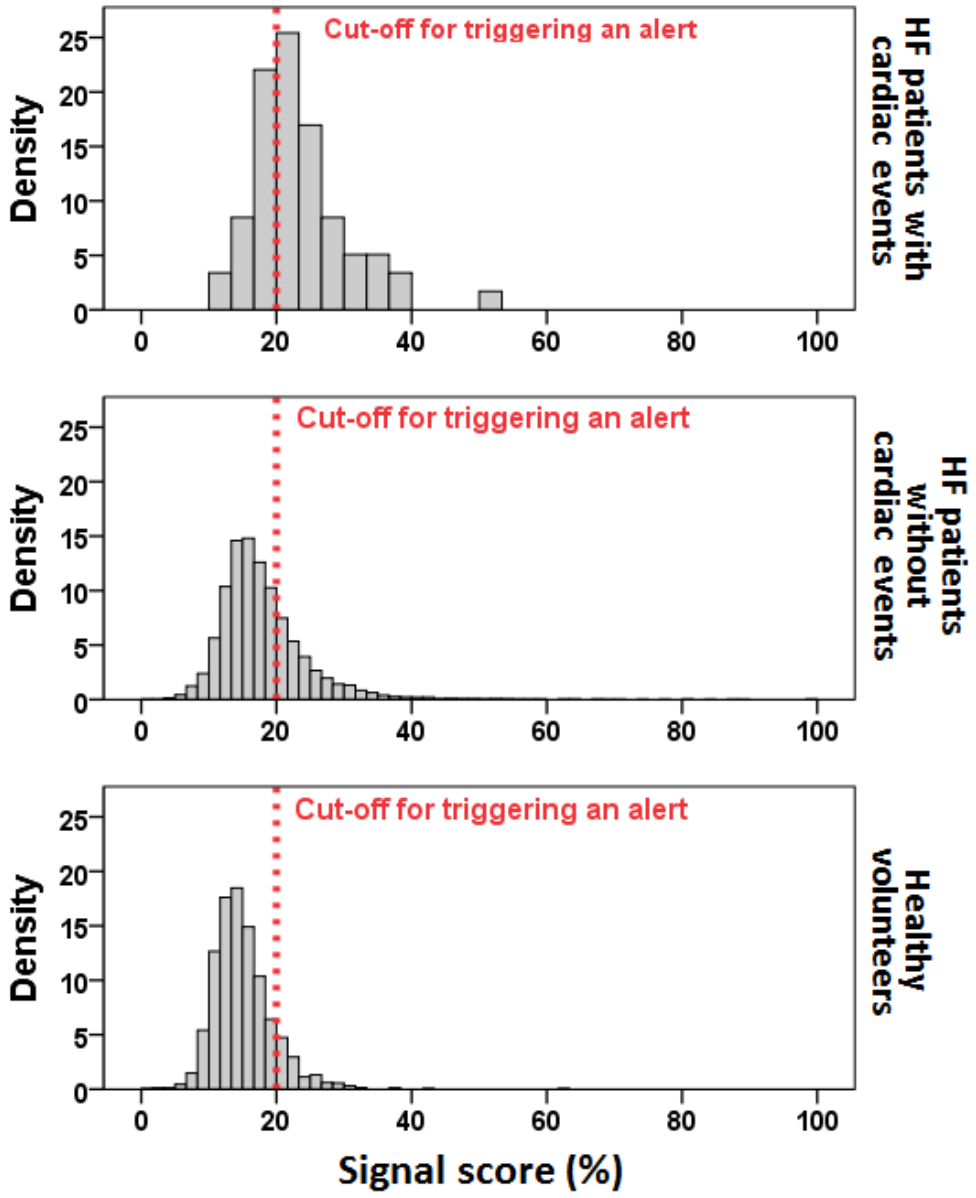


Figure 17b. Distribution of the signal score in HF patients and healthy volunteers

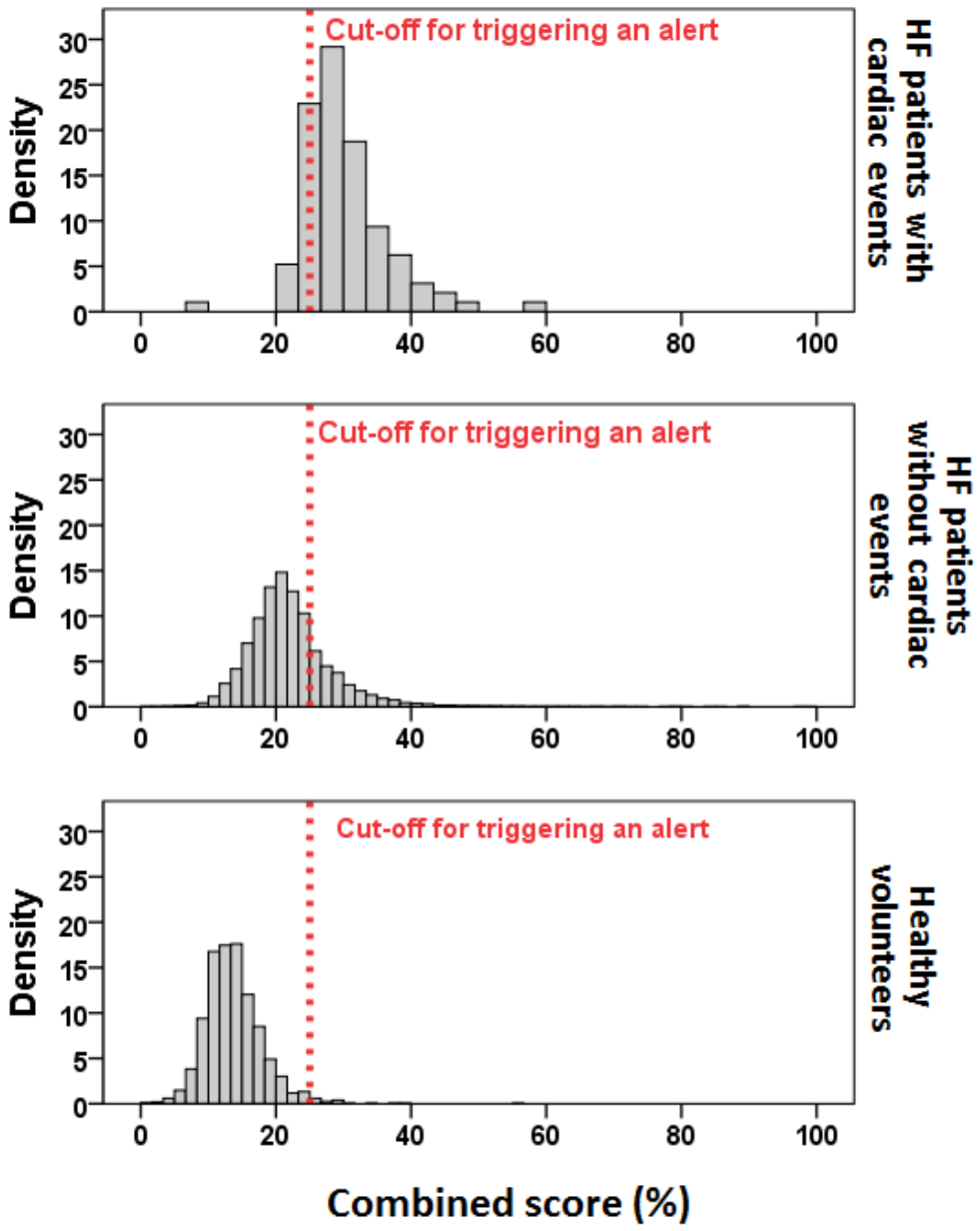


Figure 17c. Distribution of the combined score in HF patients and healthy volunteers

Table 10. Number of alerts according to the selected cut-off in patients and healthy volunteers

	Signal score (cut-off = 20%)	Combined score (cut-off = 25%)
Heart failure patients (n = 146)		
Total number of values	23289	23289
True positives values - - no (%)	58 (0.2)	88 (0.4)
False positives values - - no (%)	5102 (21.9)	5334 (22.9)
True negatives values - - no (%)	18091 (77.7)	17859 (76.7)
False negatives values - - no (%)	38 (0.2)	8 (0.03)
Healthy volunteers (n = 38)		
Total number of values	2225	2225
Alerts - - no (%)	262 (11.8)	34 (1.5)

We then assessed the diagnostic performance of various cut-offs of the combined score for triggering an alert and the resulting predictive values according to some a priori prevalence's rates of HF events. These results are summarized in Table 11.

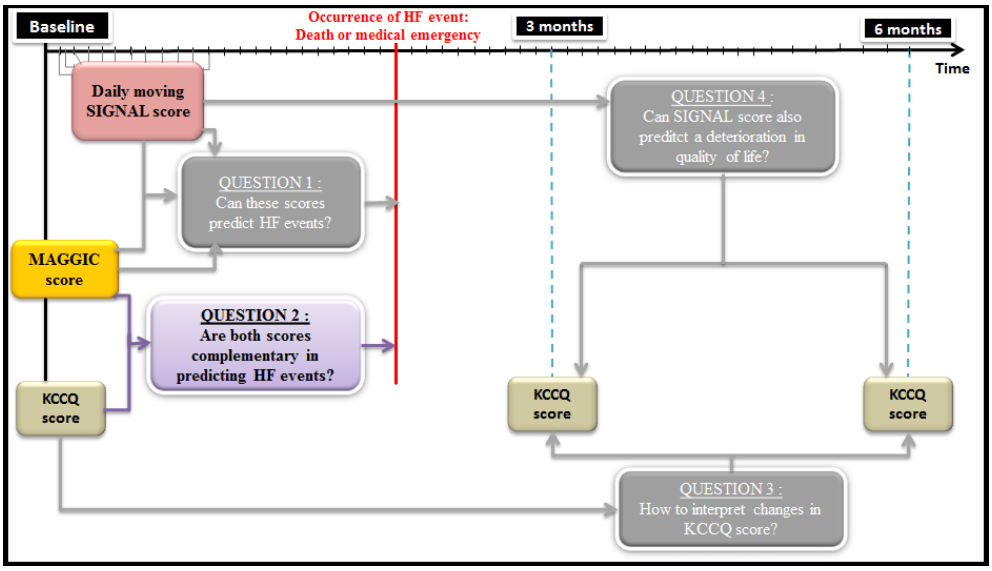
Table 11. Diagnostic performance of various cut-offs of the combined score for triggering an alert with resulting predictive values

Cut-off for triggering an alert (%)	Sensitivity (%)	Specificity (%)	Alerts in healthy volunteers (%)	Prior (%)	PPV (%)	NPV (%)
15	99	9	32.5	5	5	99
				20	21	97
				42*	44	93
				50	52	90
20	99	39	7.0	5	8	99
				20	29	99
				42*	54	98
				50	62	98
25	92	77	1.5	5	17	99
				20	50	97
				42*	74	93
				50	80	91
30	42	91	0.3	5	20	97
				20	54	86
				42*	77	68
				50	82	61
35	19	96	0.2	5	20	96
				20	54	83
				42*	77	62
				50	83	54

PPV : positive predictive value ; NPV : negative predictive value
***Prevalence of HF events in our study**

The selected 25% cut-off of the combined score resulted in the best positive (74%) and negative (93%) predictive values for the observed HF events' prevalence of 42%. This cut-off also resulted in the best positive and negative predictive values for HF events' prevalence between 20 and 50%. But, when HF events' prevalence is very low around 5%, the best positive and negative predictive values are achieved with a higher cut-off of 30%. A too low cut-off for triggering an alert generates a high number of alerts in healthy volunteers. (Table 11)

We have just built a new more efficient alert triggering system for early detection and early preventive therapeutic intervention of HF deterioration. In the next step, we will assess the complementarity between quality-of-life health status measures and traditional health status measures of morbidity and mortality in defining HF prognosis. This will be achieved through question 2 of our general workflow by assessing the relationship between the MAGGIC score and the KCCQ score in predicting HF events.



Progression in workflow

4.4. Publication 2

Interaction between the Kansas City Cardiomyopathy Questionnaire and the Pocock's clinical score in predicting heart failure outcomes

Kiswendsida Sawadogo[1], Jérôme Ambroise[1], Steven Vercauteren[2], Marc Castadot[2], Michel Vanhalewyn[3], Jacques Col[2], Annie Robert[1].

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Qual Life Res 2016;25:1245–1255.

Résumé

Objectifs. L'insuffisance cardiaque (IC) est un syndrome clinique complexe. Sa prise en charge appropriée devrait par conséquent combiner plusieurs outils de mesure de la santé. Nous avons évalué dans cette étude, la relation entre le score établi par le *Kansas City Cardiomyopathy Questionnaire* (KCCQ) et le score clinique établi par le groupe *Meta-Analysis Global Group in Chronic Heart Failure* (MAGGIC).

Méthodes. Nous avons réalisé un registre prospectif de patients IC suivis en ambulatoire par leurs médecins généralistes. Le critère de jugement principal était la survenue d'un décès ou d'une hospitalisation durant les 6 mois de suivi. Un modèle de régression multivarié a été effectué incluant le score KCCQ, le score MAGGIC ainsi que leur interaction.

Résultats. De janvier 2008 à décembre 2010, 143 patients ont été enrôlés. L'âge moyen des patients était de 68 ans et 74% étaient de sexe masculin. Le score KCCQ et le score MAGGIC étaient inversement corrélés ($r = -0.24$, $p = 0.026$). Au total, 61 (42.7%) événements sont survenus. Il y avait une proportion importante d'événements (77.8%) chez les patients avec un score MAGGIC > 50%, quel que soit la valeur du score KCCQ. Lorsque le score KCCQ était ≤ 50%, il y avait une faible augmentation de risque à mesure que le score MAGGIC augmentait (OR= 2.0, $IC_{95\%}$ = 0.6 to 6.6). Cependant, lorsque le score KCCQ était compris entre 50 et 75 ou > 75%, il y avait une augmentation importante de risque à mesure que le score MAGGIC augmentait (OR= 6.9, $IC_{95\%}$ = 1.2 to 38.9) et (OR= 7.4, $IC_{95\%}$ = 0.8 to 69.7) respectivement.

Conclusions. Les patients avec un score MAGGIC élevé sont déjà à risque élevé de décès ou d'hospitalisation. Pour les patients avec un faible score MAGGIC, le score KCCQ permet encore d'identifier un sous-groupe à risque élevé de développer ces événements cardiaques.

4.4.1. Presentation of Publication 2

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Interaction between the Kansas City Cardiomyopathy Questionnaire and the Pocock's clinical score in predicting heart failure outcomes

Kiswendsida Sawadogo[1] · Jérôme Ambroise[1] · Steven Vercauteren[2] · Marc Castadot[2] · Michel Vanhalewyn[3] · Jacques Col[2] · Annie Robert[1]

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Abstract

Purpose Heart failure (HF) is a complex syndrome. Its appropriate management should combine several health measurements. We assessed the relationship between the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Pocock's clinical score.

Methods We conducted a prospective registry of HF outpatients. The main outcome was occurrence of death or hospitalization during a 6-month follow-up. A multivariate logistic regression was performed, including the KCCQ overall summary score, the Pocock's clinical score and their interaction in the model.

Results From January 2008 to December 2010, 143 patients were involved. Mean age of patients was 68 years, and 74 % were men. KCCQ's overall summary score and Pocock's clinical score were inversely correlated ($r = -0.24$, $p = 0.026$). A total of 61 (42.7 %) events occurred. There was a high proportion of events (77.8 %) in patients with a Pocock's clinical score >50 %, whatever the KCCQ score value. When the KCCQ score was ≤50 %, there was a low increase in risk as the Pocock's clinical score increased (OR 2.0 [0.6; 6.6]). However, when the KCCQ score was between 50 and 75 or ≥75 %, there was a high increase in risk as the Pocock's clinical score increased (OR 6.9 [1.2; 38.9] and OR 7.4 [0.8; 69.7], respectively).

Conclusions Patients with a high Pocock's clinical score are at a high risk of death or hospitalization. For patients with a low Pocock's clinical score, the KCCQ score can identify those at risk of these events.

Keywords Heart failure · Kansas City Cardiomyopathy Questionnaire · Quality of life

Introduction

Heart failure (HF) is the leading cause of hospitalization in patients older than 65 years [1] with readmission rates over 40 % within the 6 months following a hospital discharge [2]. The prognosis of HF is very bad, making it a major public health problem. About half of the patients die within the 4 years following the diagnosis of HF and more than half in the year if the HF is severe [3]. Therefore, well-determining HF prognosis is important and requires an approach that cannot be limited to the use of a few biomarkers. Other health measurements such as quality-of-life indicators are useful. The Kansas City Cardiomyopathy Questionnaire (KCCQ) has been developed to quantify the health status of patients with congestive HF. It is a valid, reliable, self-administered, 23-item questionnaire that quantifies physical limitations, symptoms, self-efficacy, social interference and quality of life on a 0–100 % scale [4]. Subsequent studies have validated the KCCQ and further demonstrated that a decrease in KCCQ is associated with a poorer prognosis of hard outcome endpoints in HF

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patients [5, 6]. Heart failure's prognosis in individual patients is highly variable. Assessing the prognosis of each patient based on his/her own overall risk score is useful for an appropriate management. Risk models for patients with HF exist [7, 8]. Most were developed in a single cohort of patients, and there is therefore a need to assess their generalizability. The Meta-analysis Global Group in Chronic HF (MAGGIC) includes individual data on 39,372 patients with HF [9]. In this large study, Pocock and his group established a generalizable, easy-to-use clinical score on a 0–100 % scale that increases as the risk of mortality increases [9]. The Pocock's clinical score is comprised of observed factors and patient characteristics, while the KCCQ is self-reported by patients. These two instruments do not appear to overlap. If both of these instruments have prognostic value in HF, then one can expect a negative correlation between them, despite the fact that each questions differing aspects of the disease in patients. Using a prospective registry of HF outpatients followed by general practitioners outside of clinical settings (part of the Better Efficacy in Lowering events by General practitioner's Intervention Using remote Monitoring in Heart Failure—BELGIUM-HF study, a remote home telemonitoring study in HF in which patients completed a six-month blind daily weight, blood pressure and pulse measurements), we assessed the relationship between the KCCQ and the Pocock's clinical score [9], and their additive prognostic value.

Materials and methods

Study design

The BELGIUM-HF study was designed in 2007 and implemented in 2008–2010 in Brussels and southern Belgium. It was a prospective registry of HF outpatients followed by their general practitioners (GP) but identified from the records of 16 cardiology centers. The protocol was approved by the ethical committee of each of the 16 centers, and an informed consent form was signed by each of the participants. For each identified patient, his/her GP was contacted for the study. If the GP agreed, the patient was followed for up to 6 months by his/her GP.

Study patients

Patients were enrolled by their general practitioners in a non-institutional environment. They were eligible if they were hospitalized for HF in the preceding 6 months, had a left ventricular ejection fraction (LVEF) <40 % and required daily loop diuretics within the preceding 2 weeks of inclusion. Excluded patients were patients <18 years of age, patients awaiting cardiac surgery or who underwent myocardial revascularization within the preceding 3 months, patients treated by or considered for chronic hemodialysis procedures and patients whose cognitive aptitudes were impaired.

Data collection

Clinical and biological data were collected at baseline. Patients also fulfilled the KCCQ and performed the Six-Minute Walk Test.

Health status assessment

The New York Heart Association (NYHA) classification was used to assess patients' cardiovascular status. The NYHA class is a four-level scale assigning a functional class (from I to IV) based on physical limitations caused by cardiac symptoms. NYHA class I is defined as cardiac disease but no symptoms and no limitation in ordinary physical activity. NYHA class II describes mild symptoms and slight limitation during ordinary activity. NYHA class III is defined as an inability to perform a physical activity without symptoms. NYHA class IV describes severe limitation with symptoms even while at rest [10].

Patients enrolled in the study completed the KCCQ at baseline. The KCCQ is a 23-item, self-administered questionnaire that encompasses several domains including physical limitation, symptoms (frequency, severity and recent changes), self-efficacy, social interference and quality of life for patients with congestive HF [4]. An overall summary score is then computed by combining these individual scores. This summary score ranges from 0 to 100 %, and the higher the score, the better the quality of life [4]. The questionnaire's validity, reliability and responsiveness to clinical change have previously been established [11, 12]. In previous studies, the overall summary score was divided into four categories that were associated with an increased risk of mortality and hospitalization for patients with decreasing scores: 0 to <24 % (*worst*); 25–49 % (*poor*); 50–74 % (*fair*); and 75–100 % (*good*) [13, 14].

Pocock's clinical score

The Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) includes individual data on 39,372 patients with HF, both reduced and preserved left ventricular ejection fraction (EF), from 24 cohort studies and six clinical trials [9]. It established a generalizable, easy-to-use risk score of mortality in patients with HF using Poisson regression models [9]. Authors identified 13 variables as significant independent predictors of mortality in the

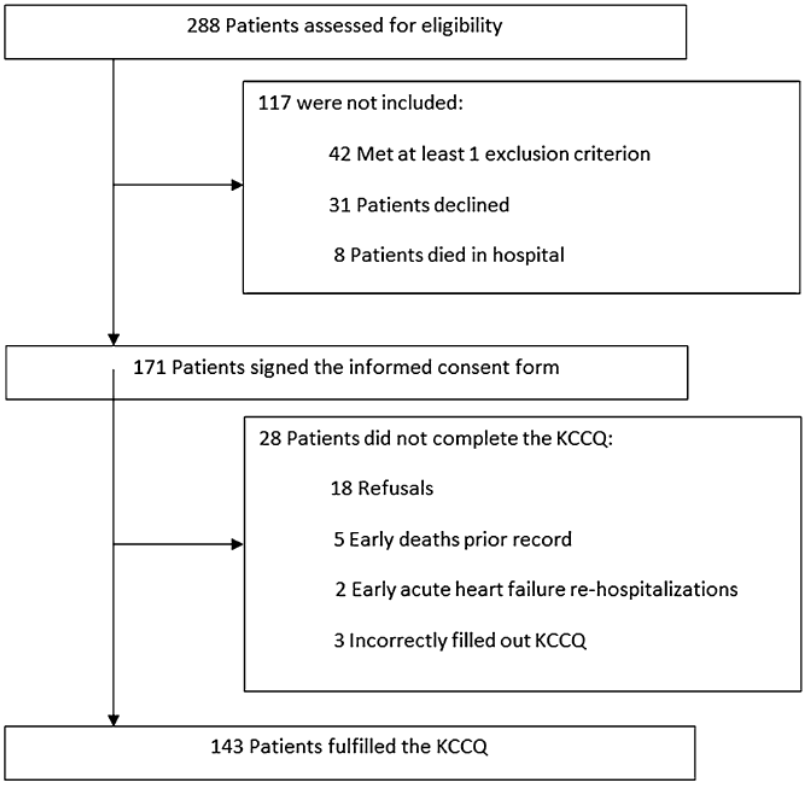

Fig. 1 Flowchart. Out of 288 patients assessed for eligibility, 143 fulfilled the Kansas City Cardiomyopathy Questionnaire

following order: age, low LVEF, New York Heart Association (NYHA) class, serum creatinine, diabetes, absence of a prescribed beta-blocker, low systolic blood pressure, low body mass, time since diagnosis, current smoker, chronic obstructive pulmonary disease, male gender and absence of a prescribed angiotensin-converting-enzyme inhibitor or angiotensin-receptor blockers [9]. The model-derived clinical score was defined as the 0–100 rescaling of the estimated regression line, with a zero score corresponding to the lowest possible risk of a patient. Using this model, we computed a risk score of each patient of the BELGIUM-HF study.

The Six-Minute Walk Test

The Six-Minute Walk Test is a practical simple test. It requires a 100-ft hallway but no exercise equipment or advanced training for technicians [15]. This test measures the distance that a patient can quickly walk on a flat, hard surface during a period of 6 min. "It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood neuromuscular units and muscle metabolism" [15]. Good correlations have been reported between the Six-Minute Walk Test and cardiopulmonary testing. In some clinical situations, the Six-Minute Walk Test provides information that may be a better index of the patient's ability to perform daily activities than is peak oxygen uptake, i.e., the 6-min walking distance correlates better with measures of quality of life [16]. The test was performed according to the guidelines of the American Thoracic Society at baseline, and the total distance walked during the test was considered.

Study outcome

The main outcome was death or hospitalization within 6 months. Both events were equally weighted to define the outcome as a dummy variable coding for any of these two events.

Statistical analyses

Patients' characteristics are presented as mean with standard deviation (SD) or median with quartiles for continuous variables and as number and proportion for discrete variables. Variables with a lognormal distribution are listed as geometric mean (SD). Pearson correlation was used to

Table 1 Baseline characteristics of patients

	All patients $n = 143$	Death or hospital readmission	
		Yes $n = 61$	No $n = 82$
Clinical data			
Age—years	68 ± 12	71 ± 11	66 ± 13
Male—no (%)	106 (74.1)	46 (75.4)	62 (75.6)
Body mass index (kg/m^2)	27.0 ± 4.8	26.9 ± 3.7	27.0 ± 5.5
Systolic blood pressure (mmHg)	113 ± 26	112 ± 20	114 ± 29
Diastolic blood pressure (mmHg)	69 ± 17	67 ± 14	70 ± 19
NYHA class III–IV—no (%)	83 (58.0)	41 (67.2)	43 (52.4)
Risk factors			
Hypercholesterolemia—no (%)	74 (51.7)	34 (55.7)	40 (48.8)
Hypertension—no (%)	82 (57.3)	31 (50.8)	51 (62.2)
Diabetes—no (%)	47 (32.9)	22 (36.1)	25 (30.5)
Smoker within past 12 months—no (%)	37 (25.9)	12 (19.7)	25 (30.5)
Six-Minute Walk Test—median (IQR)	290 (200–380)	219 (160–311)	300 (238–420)
Biological data[a]			
Brain natriuretic peptide (pg/ml)	741.3 (3.2)	853.9 (3.2)	621.0 (3.2)
Glucose (mg/dl)	107.2 (1.3)	109.2 (1.4)	105.7 (1.3)
Cholesterol (mg/dl)	147.9 (1.3)	137.1 (1.3)	156.9 (1.4)
LDL cholesterol (mg/dl)	79.4 (1.5)	70.5 (1.5)	84.0 (1.6)
Creatinine (mg/dl)	1.44 (1.45)	1.48 (1.48)	1.34 (1.35)
Left ventricular ejection fraction (%)	28 ± 7	28 ± 8	28 ± 7
Renal failure—no (%)	11 (7.7)	7 (11.5)	4 (4.9)
Chronic obstructive pulmonary disease—no (%)	22 (15.4)	11 (18.0)	11 (13.4)

Plus minus data are mean ± SD

NYHA New York Heart Association, *LDL* low-density lipoprotein

[a] Data are geometric means (SD)

assess the correlation between KCCQ subscales and the NYHA class or the total walked distance at the Six-Minute Walk Test. Trends across KCCQ overall summary score categories were analyzed using Cochran–Armitage trend test for categorical variables and Spearman's rank correlation for continuous variables. Pearson correlation was used to assess the correlation between KCCQ scores and the Pocock's clinical score [9]. A multivariate logistic regression was performed, including the KCCQ overall summary score and the Pocock's clinical score that were encoded into dummy variables and their interaction in the model. The significance level was set to 0.05, and all tests were two-sided. Statistical analyses were performed using SPSS 22.

Results

From January 2008 to December 2010, 288 patients were eligible for study entry. However, 117 were not included because of exclusion criteria or refusal. Among the remaining 171 patients, another 28 patients did not complete the KCCQ for various reasons (Fig. 1). A total of 143 patients filled out the KCCQ at baseline. Because this study is a part of the BELGIUM-HF study, a remote home telemonitoring study in HF, patients had regular contacts with their GPs, so no hospitalization or death was lost to follow-up.

The baseline clinical characteristics of patients are reported in Table 1. Mean age of patients was 68 years, with 54 % aged >70 years, and 74 % men. New York Heart Association symptoms of class III or IV were found in 58 %.

Figure 2 shows the distribution of the KCCQ's subscales and summary scores. At baseline, patients' symptoms were stabilized and they had a positive perception of self-efficacy. Nearly half of them had a KCCQ's overall summary score of at least 50 at baseline.

The difference between the cumulative KCCQ's overall summary score distribution of patients who experienced an HF outcome and those who did not experience an event

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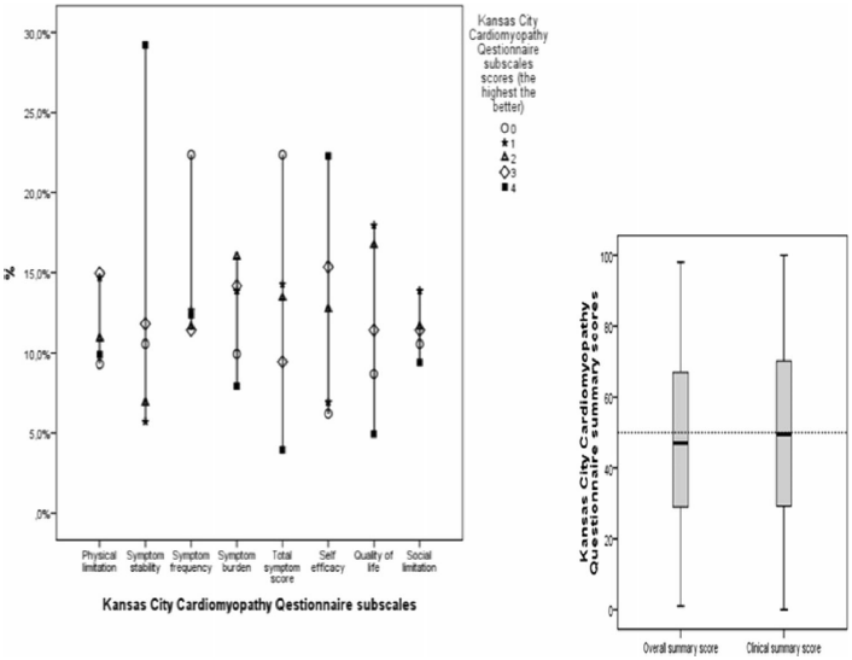

Fig. 2 Distribution of Kansas City Cardiomyopathy Questionnaire subscales and summary scores in patients with heart failure. At baseline, most of the patients had symptoms remission and felt self-efficacy. Nearly half of the patients had an overall summary score of at least 50 %

Table 2 Baseline variables identified by Pocock with trends across the Kansas City Cardiomyopathy Questionnaire's (KCCQ)

	All patients $n = 143$	KCCQ overall summary score categories				
		Worst (<25) $n = 32$	Poor (25–49) $n = 45$	Fair (50–74) $n = 39$	Good (75–100) $n = 27$	Trend test p value
Age—years	68 ± 12	67 ± 13	71 ± 12	67 ± 13	67 ± 11	0.57
Left ventricular ejection fraction (%)	28 ± 7	28 ± 7	27 ± 6	27 ± 8	29 ± 8	0.40
NYHA class III–IV—no (%)	83 (58.0)	24 (75.0)	35 (77.8)	18 (46.2)	6 (22.2)	<0.001
Creatinine[a] (mg/dl)	1.44 (1.45)	1.30 (1.44)	1.50 (1.4)	1.45 (1.44)	1.30 (1.44)	0.49
Diabetes—no (%)	46 (32.2)	11 (34.4)	9 (20.0)	17 (43.6)	9 (33.3)	0.45
Beta-blocker—no (%)	114 (79.7)	30 (93.8)	34 (75.6)	29 (74.4)	21 (77.8)	0.13
Systolic blood pressure (mmHg)	113 ± 26	116 ± 20	115 ± 23	110 ± 32	107 ± 27	0.12
Body mass index (kg/m^2)	27.0 ± 4.8	28.4 ± 5.9	26.2 ± 5.4	26.7 ± 4.3	27.0 ± 3.4	0.92
Time since diagnosis (months)	38 ± 44	41 ± 45	41 ± 37	44 ± 55	23 ± 35	0.09
Smoker within past 12 months—no (%)	36 (25.2)	11 (34.4)	9 (20.0)	7 (17.9)	9 (33.3)	0.80
COPD—no (%)	22 (15.4)	9 (28.1)	8 (17.8)	4 (10.3)	1 (3.7)	0.008
Male—no (%)	106 (74.1)	23 (71.9)	32 (71.1)	28 (71.8)	23 (85.2)	0.29
ACEor Sartan—no (%)	135 (94.4)	27 (84.4)	44 (97.8)	38 (97.4)	26 (96.3)	0.07
Pocock's clinical score	34 ± 15	38 ± 16	36 ± 14	34 ± 16	31 ± 14	0.04

Plus minus data are mean ± SD

COPD chronic obstructive pulmonary disease, *ACE* angiotensin-converting-enzyme inhibitor

[a] Data are geometric means (SD)

Table 3 Patients' other characteristics

	All patients $n = 143$	KCCQ overall summary score categories				
		Worst (<25) $n = 32$	Poor (25–49) $n = 45$	Fair (50–74) $n = 39$	Good (75–100) $n = 27$	Trend test p value
Clinical data						
Diastolic blood pressure (mmHg)	69 ± 17	72 ± 14	68 ± 14	68 ± 21	67 ± 18	0.32
Pulse rate—beats per minute	78 ± 18	81 ± 16	78 ± 16	78 ± 21	76 ± 19	0.09
Sinusal rhythm—no (%)	109 (76.2)	23 (71.9)	35 (77.8)	29 (74.4)	22 (81.5)	0.04
Pulmonary rhoncus—no (%)	47 (32.9)	14 (43.8)	18 (40.0)	8 (20.5)	7 (25.9)	<0.001
Jugular distension—no (%)	36 (25.2)	13 (40.6)	16 (35.6)	6 (15.4)	1 (3.7)	0.003
Peripheral edema—no (%)	52 (36.4)	15 (46.9)	24 (53.3)	7 (17.9)	6 (22.2)	
Six-Minute Walk Test distance (m)	298 ± 130	258 ± 138	280 ± 149	311 ± 127	334 ± 105	0.04
Biological data[a]						
Brain natriuretic peptide (pg/ml)	741.3 (3.2)	977.2 (2.9)	630.9 (3.6)	660.7 (2.6)	676.1 (3.4)	0.29
Glucose (mg/dl)	107.2 (1.3)	107.2 (1.3)	100.0 (1.2)	109.6 (1.4)	114.8 (1.5)	0.51
Troponin (µg/l)	0.034 (2.6)	0.032(0.347)	0.030 (2.820)	0.033 (1.995)	0.047 (2.754)	0.47

Plus minus data are mean ± SD

[a] Data are geometric means (SD)

Table 4 Correlations between KCCQ subscales and NYHA class or Six-Minute Walk Test

	NYHA	p value	Walk distance	p value
Kansas City Cardiomyopathy Questionnaire subscales				
Physical limitation	−0.46	<0.001	0.18	0.04
Symptom stability	−0.08	0.02	0.33	0.01
Symptom frequency	−0.43	<0.001	0.31	0.01
Symptom burden	−0.40	<0.001	0.26	0.04
Total symptom score	−0.43	<0.001	0.30	0.02
Self-efficacy	−0.14	0.09	0.18	0.16
Quality of life	−0.33	<0.001	0.27	0.03
Social limitation	−0.39	<0.001	0.24	0.07
Overall summary score	−0.44	<0.001	0.27	0.03
Clinical summary score	−0.46	<0.001	0.25	0.04

was not Gaussian along the continuous level of the KCCQ score. Indeed, the two curves were not sigmoids, and the difference was larger for KCCQ scores around 25 %. Consequently, the KCCQ score could not be considered as a continuous scale, and it was more relevant to considering a four-point scale (quartiles) than a hundred-point scale (Online Resource 1).

Table 2 summarizes the 13 Pocock's independent predictors of mortality in patients with HF and their relationship with the previously described categories of the KCCQ's overall summary score [9]. Only 18.9 % of patients reported a good KCCQ's overall summary score at baseline (≥75 %). A worst KCCQ's overall summary score (≤25 %) was found in 22.4 % of patients. The proportion of patients with the most severe symptoms on NYHA classification increased as the KCCQ's overall summary score decreased (trend $p < 0.001$). The same observation was made for the proportion of patients with a chronic obstructive pulmonary disease (trend $p = 0.008$). Such variables are measures of physical capacities that are expected to be correlated with tools measuring perceived health such as the KCCQ. In contrast, other variables such as creatininemia and the use or not of beta-blockers are not expected to reflect a perceived health. When taking into account all of the 13 variables to compute Pocock's clinical score, it was observed that the mean Pocock's clinical score increased as the KCCQ's overall summary score decreased (trend $p = 0.04$). KCCQ's overall summary score was inversely correlated with the Pocock's clinical risk score ($r = -0.24$, $p = 0.026$).

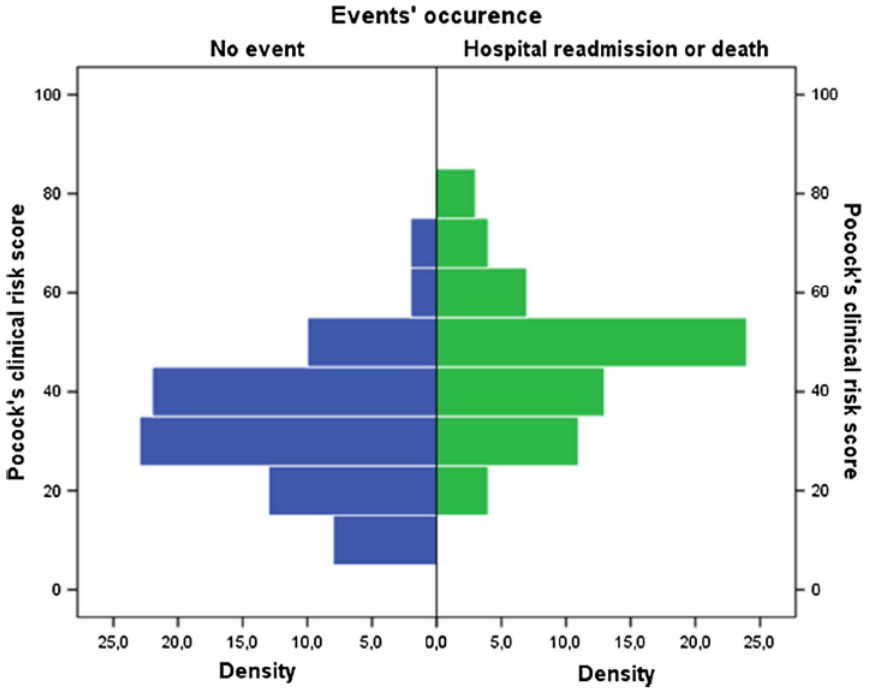

Fig. 3 Histogram of Pocock's clinical score according to event occurrence. Patients who experienced an event had the highest Pocock's clinical scores at baseline

Other patient characteristics such as the proportion of patients in sinus rhythm (trend $p = 0.04$) and the mean walk distance at the Six-Minute Walk Test (trend $p = 0.04$) decreased with the KCCQ's overall summary score (Table 3). Mean diastolic blood pressure (trend $p = 0.32$), mean pulse rate (trend $p = 0.09$), the proportion of patients with pulmonary rhoncus (trend $p < 0.001$) and those with peripheral edema (trend $p = 0.003$) increased as the KCCQ's overall summary score decreased (Table 3). We also observed that brain natriuretic peptide levels were the highest in patients with a low KCCQ's overall summary score (Table 3).

When looking at the correlation between each of the KCCQ subscales and the NYHA class, we found all significant negative correlations except for the self-efficacy subscale ($p = 0.09$), showing low KCCQ values in patients from high NYHA classes. In addition, the walk distance for the Six-Minute Walk Test was positively correlated with all KCCQ subscales except the self-efficacy subscale ($p = 0.16$), similarly showing low walk distances in patients with lower KCCQ values, who are also the frailest patients (Table 4).

During the 6 months of follow-up, 10 (7.0 %) patients died. In addition, 51 (35.7 %) were reported hospitalized, resulting in 42.7 % of patients presenting an event during the 6 months following study start. Patients who experienced an event were older and had more severe symptoms on NYHA classification (Table 1). They also had higher levels of brain natriuretic peptide and a smaller mean walk distance at the Six-Minute Walk Test (Table 1).

Patients who experienced an event had a higher Pocock's clinical score at baseline as illustrated in Fig. 3.

Almost all patients with a high Pocock's clinical score (≥50 %) experienced an event regardless of the KCCQ's overall summary score. For patients with a medium (25–50 %) or a low (≤25 %) Pocock's clinical score, we observed a morbi-mortality gradient according to the KCCQ's overall summary score. Indeed, the number of events observed in these patients increased as their KCCQ's overall summary score worsened (Fig. 4).

Using multivariate logistic regression, the estimated equation for the KCCQ overall summary score and the Pocock's clinical score was the following:

$$\begin{aligned}\text{Logit}(p) = &-2.303 + 1.996 \times \text{Pocock}_{25-50\,\%} + 1.514 \\ &\times \text{KCCQ}_{\leq 50\,\%} + 0.693 \times \text{KCCQ}_{50-75\,\%} \\ &- 1.304 \times \text{Pocock}_{25-50\,\%} \times \text{KCCQ}_{\leq 50\,\%} \\ &- 0.059 \times \text{Pocock}_{25-50\%} \times \text{KCCQ}_{50-75\,\%}\end{aligned}$$

A significant interaction was found between the KCCQ overall summary score and the Pocock's clinical score. This interaction is illustrated in Table 5. There was a high proportion of events (14/18 = 77.8 %) in patients with a high (>50 %) Pocock's clinical score, whatever the KCCQ

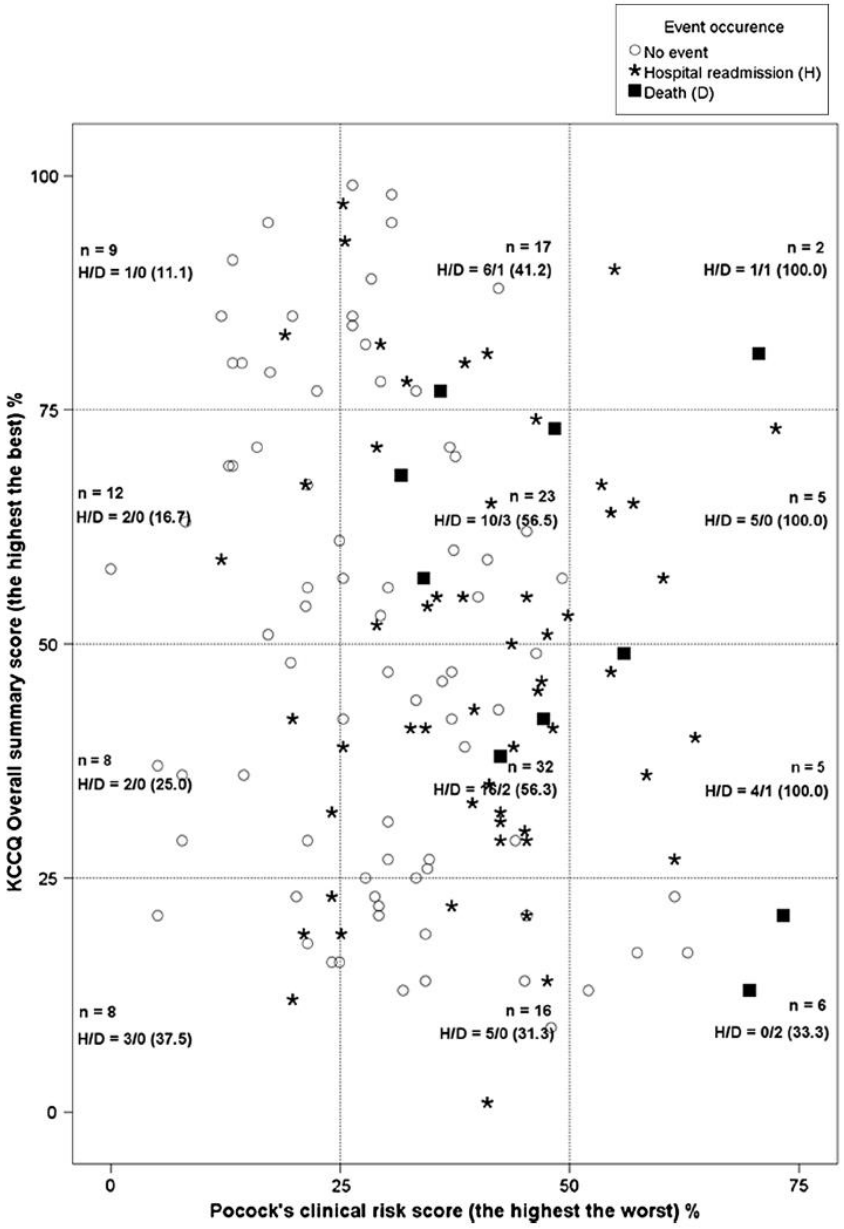

Fig. 4 Kansas City Cardiomyopathy Questionnaire's overall summary score and Pocock's clinical score according to event occurrence. Patients with a significantly affected Pocock's clinical score (>50 %) have almost all experienced an event. For patients with a slightly affected Pocock's clinical sore (≤50 %) at baseline, we observed a morbi-mortality gradient according to the KCCQ overall summary score. Indeed, the proportion of events in these patients increased as their KCCQ overall summary score worsened

score value. When the KCCQ score was ≤50 % (top panel), there was a low increase in risk as the Pocock's clinical score increased (OR 2.00, 95 % CI 0.60–6.62). But when the KCCQ score was between 50 and 75 % (middle panel) or ≥75 % (lower panel), there was a high increase in risk as the Pocock's clinical score increased (OR 6.94, 95 % CI 1.24–38.86, and OR 7.36, 95 % CI 0.78–69.70, respectively).

Comparing the KCCQ subscales mean scores with respect to the occurrence of death or hospital admission in the subgroup of patients with a medium or a low Pocock's clinical score, we observed that patients who experienced an event had lower mean scores for each of these ten subscales. The difference between mean scores was about 3 for all subscales except for self-efficacy, where it reached 10 (Online Resource 2).

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Table 5 Multivariate logistic regression: predictive value of Pocock's clinical score and Kansas City Cardiomyopathy Questionnaire's overall summary score

	n	Events *n* (%)	OR	IC[a] 95 % (OR)
KCCQ overall summary score: high risk (≤50 %)				
Pocock's clinical score: high risk (≥50 %)	11	7 (63.6)	Not computed[b]	
Pocock's clinical score: medium risk (25–50 %)	48	23 (47.9)	2.00	[0.60; 6.62]
Pocock's clinical score: low risk (≤25 %)	16	5 (31.3)	1	
KCCQ overall summary score: medium risk (50–75 %)				
Pocock's clinical score: high risk (≥50 %)	5	5 (100.0)	Not computed[b]	
Pocock's clinical score: medium risk (25–50 %)	23	13 (56.5)	6.94	[1.24; 38.86]
Pocock's clinical score: low risk (≤25 %)	12	2 (16.7)	1	
KCCQ overall summary score: low risk (≥75 %)				
Pocock's clinical score: high risk (≥50 %)	2	2 (100.0)	Not computed[b]	
Pocock's clinical score: medium risk (25–50 %)	17	7 (41.2)	7.36	[0.78; 69.70]
Pocock's clinical score: low risk (≤25 %)	9	1 (11.1)	1	

OR odds ratio

[a] 95 % confidence interval

[b] Because of 64–100 % events

Discussion

The purpose of this study was to assess the relationship and the additive prognostic value of the KCCQ, a validated measurement tool for patient-perceived health status in congestive HF, and the Pocock's clinical score of mortality in HF patients. We found an inverse correlation between the KCCQ's overall summary score and the Pocock's clinical score. This indicates that patients with a significantly affected Pocock's clinical score also tend to have a poorer quality of life. When Pocock's clinical score is high (>50 %), there is no additional prognostic value of KCCQ's overall summary score for hospital admission or death within 6 months. However, when Pocock's clinical score is medium (25–50 %) or low (≤25 %), KCCQ's overall summary score has a significant prognostic value. Therefore, these two instruments are complementary ways to assess the progression of HF.

Pocock's clinical score has an interesting prognostic value in that patients with a high Pocock's clinical score almost all experienced an event.

As already established [4], we reported a negative correlation between KCCQ and NYHA class and a positive correlation between KCCQ and walk distance at the Six-Minute Walk Test. Nonetheless, we observed that the KCCQ's self-efficacy subscale was not significantly correlated with the NYHA class or to the walk distance at the Six-Minute Walk Test, in contrast to the other nine subscales of the KCCQ. This reflects the fact that most KCCQ subscales and the NYHA classification assess the patient's physical limitations. For the KCCQ subscales, this limitation is based on the patient's perspective, and for the NYHA classification, it is based on the physician's perspective [17, 18]. In contrast, the self-efficacy subscale assesses a very subjective aspect related to the knowledge of the patient about his/her HF. This is consistent with the findings of a recent study conducted to reconceptualize KCCQ subscales and to advance its use, more than 10 years after its publication [19].

We further observed that patients who experienced an event had the lowest mean scores for all KCCQ's subscales. The difference between these mean scores was the highest for the self-efficacy subscale. Thus, the KCCQ's self-efficacy subscale does not seem consistent with the other KCCQ's subscales, but it evaluates an important health status, i.e., patient autonomy, and requires thorough assessment.

Our study has limitations, and the small sample size is the main one. Nevertheless, despite our small number of patients, there are several arguments proving the quality of our data base. Firstly, as we have just discussed, patients were recruited by their general practitioners in a non-institutional environment. Such a sample is smaller, but it is more representative of patients with HF in their daily life, outside of hospitals. In this respect, it is original and deserves special attention. Secondly, with a small sample, we observed 42.7 % of events at 6 months, which is consistent with the 40 % [2] reported in the literature. Thirdly, we found consistent correlations between all the KCCQ subscales and the NYHA class and walk distance at Six-Minute Walk test, as already established. Finally, we found the prognostic value of the Pocock's clinical score. All these give a power to generalize our findings.

In conclusion, patients with a high Pocock's clinical score are at a high risk of death or hospitalization during a 6-month follow-up and the KCCQ does not add prognostic

value. For patients with a low Pocock's clinical score, the KCCQ score allows for further characterization of a still high risk group. That information might lead to targeting therapies interventions to mitigate that group's risk of death or hospitalization. These two instruments are therefore complementary in assessing health in its globality for HF patients. KCCQ may therefore represent a different approach in HF management.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Dickstein, K., Cohen-Solal, A., Filippatos, G., McMurray, J. J., Ponikowski, P., Poole-Wilson, P. A., et al. (2008). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *European Heart Journal, 29*(19), 2388–2442.
2. Krumholz, H. M., Parent, E. M., Tu, N., Vaccarino, V., Wang, Y., Radford, M. J., et al. (1997). Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Archives of Internal Medicine, 157*(1), 99–104.
3. Swedberg, K., Cleland, J., Dargie, H., Drexler, H., Follath, F., Komajda, M., et al. (2005). Guidelines for the diagnosis and treatment of chronic heart failure: Executive summary (update 2005): The task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology. *European Heart Journal, 26*(11), 1115–1140.
4. Green, C. P., Porter, C. B., Bresnahan, D. R., & Spertus, J. A. (2000). Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: A new health status measure for heart failure. *Journal of the American College of Cardiology, 35*(5), 1245–1255.
5. Network of Nurses of G-H, & Di Giulio, P. (2014). Should patients perception of health status be integrated in the prognostic assessment of heart failure patients? A prospective study. *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation, 23*(1), 49–56.
6. Joseph, S. M., Novak, E., Arnold, S. V., Jones, P. G., Khattak, H., Platts, A. E., et al. (2013). Comparable performance of the Kansas City Cardiomyopathy Questionnaire in patients with heart failure with preserved and reduced ejection fraction. *Circulation Heart Failure, 6*(6), 1139–1146.
7. Levy, W. C., Mozaffarian, D., Linker, D. T., Sutradhar, S. C., Anker, S. D., Cropp, A. B., et al. (2006). The Seattle Heart Failure Model: Prediction of survival in heart failure. *Circulation, 113*(11), 1424–1433.
8. Pocock, S. J., Wang, D., Pfeffer, M. A., Yusuf, S., McMurray, J. J., Swedberg, K. B., et al. (2006). Predictors of mortality and morbidity in patients with chronic heart failure. *European Heart Journal, 27*(1), 65–75.
9. Pocock, S. J., Ariti, C. A., McMurray, J. J., Maggioni, A., Kober, L., Squire, I. B., et al. (2013). Predicting survival in heart failure: A risk score based on 39 372 patients from 30 studies. *European Heart Journal, 34*(19), 1404–1413.
10. Criteria Committee of the New York Heart Association. (1994). *Nomenclature and criteria for diagnosis of diseases of the heart and great vessels* (9th ed.). Boston: Little Brown.
11. Eurich, D. T., Johnson, J. A., Reid, K. J., & Spertus, J. A. (2006). Assessing responsiveness of generic and specific health related quality of life measures in heart failure. *Health and Quality of Life Outcomes, 4*, 89.
12. Spertus, J., Peterson, E., Conard, M. W., Heidenreich, P. A., Krumholz, H. M., Jones, P., et al. (2005). Monitoring clinical changes in patients with heart failure: A comparison of methods. *American Heart Journal, 150*(4), 707–715.
13. Heidenreich, P. A., Spertus, J. A., Jones, P. G., Weintraub, W. S., Rumsfeld, J. S., Rathore, S. S., et al. (2006). Health status identifies heart failure outpatients at risk for hospitalization or death. *Journal of the American College of Cardiology, 47*(4), 752–756.

14. Chan, P. S., Soto, G., Jones, P. G., Nallamothu, B. K., Zhang, Z., Weintraub, W. S., et al. (2009). Patient health status and costs in heart failure: Insights from the eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS). *Circulation, 119*(3), 398–407.
15. Laboratories A.T.S.Co.P.Sf.C.P.F. (2002). ATS statement: Guidelines for the six-minute walk test. *American Journal of Respiratory and Critical Care Medicine, 166*(1), 111–117.
16. Guyatt, G. H., Thompson, P. J., Berman, L. B., Sullivan, M. J., Townsend, M., Jones, N. L., et al. (1985). How should we measure function in patients with chronic heart and lung disease? *Journal of Chronic Diseases, 38*(6), 517–524.
17. Spertus, J. A. (2008). Evolving applications for patient-centered health status measures. *Circulation, 118*(20), 2103–2110.
18. Raphael, C., Briscoe, C., Davies, J., Ian Whinnett, Z., Manisty, C., Sutton, R., et al. (2007). Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. *Heart, 93*(4), 476–482.
19. Masterson Creber, R., Polomano, R., Farrar, J., & Riegel, B. (2012). Psychometric properties of the Kansas City Cardiomyopathy Questionnaire (KCCQ). *European Journal of Cardiovascular Nursing: Journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology, 11*(2), 197–206.

4.4.2. Illustration of the complementarity between the KCCQ score and the MAGGIC score

Figure 18 illustrates the inverse relation between the KCCQ score and the MAGGIC score suggesting that patients with a bad clinical prognosis also tended to have a poor quality of life. It also shows that patients with a poor clinical prognosis (MAGGIC score > 50%) were already at high risk of HF events. Among patients with a better clinical prognosis (MAGGIC score ≤ 25%), those with a poor quality of life (KCCQ score < 25%) are still at high risk of HF events.

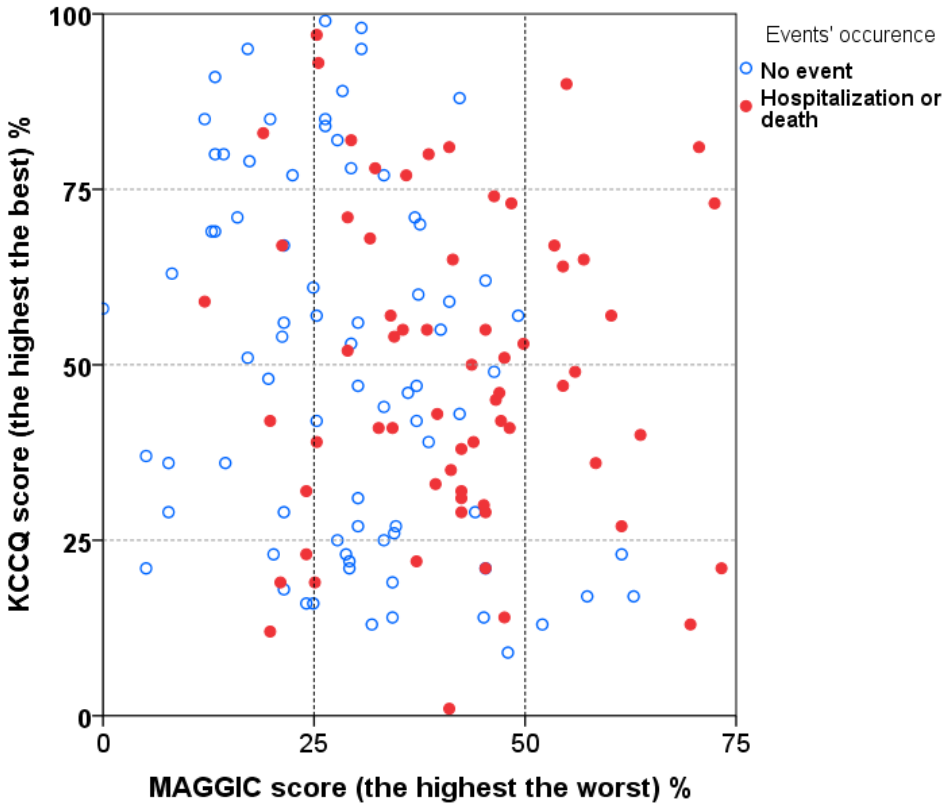
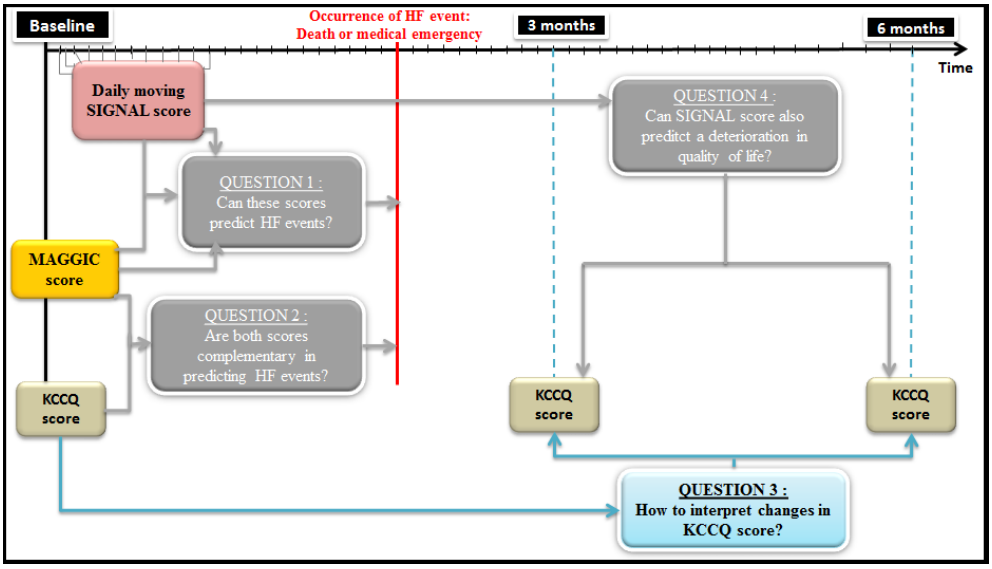


Figure 18. Relationship between the KCCQ score and the MAGGIC score

We just showed that quality-of-life health status measures and traditional health status measures of morbidity and mortality can complement each other to well-define HF prognosis. For further insight into these findings, we will consider in the following step, changes in quality-of-life score (KCCQ) as an outcome. This will be achieved through question 3 of our general workflow.



Progression in workflow

4.5. Changes in patients' quality of life during follow-up

A total of 143 patients filled out the KCCQ at baseline. They were only 75 to fill it at the follow-up visit 1 after 3 months and only 60 to fill it at the follow-up visit 2 after 6 months.

Table 11 summarizes the patients' QoL scores within each subscale of the KCCQ during follow-up. Patients' mean QoL scores appeared to have improved during the course of the study but with significant variability.

Table 11. Changes in patients' quality of life during follow-up.*

	Baseline n = 143	3-months follow-up n = 75	6-months follow-up n = 60
KCCQ summary scores			
Physical limitation	50.8 ± 29.5	59.1 ± 26.4	58.3 ± 27.9
Symptom stability	67.5 ± 35.0	58.3 ± 22.3	55.8 ± 25.4
Symptom frequency	52.3 ± 28.1	73.0 ± 23.4	68.9 ± 26.5
Symptom burden	57.3 ± 27.3	74.9 ± 21.4	70.3 ± 25.7
Total symptom score	54.8 ± 26.6	73.9 ± 21.3	69.6 ± 25.2
Self-efficacy	62.9 ± 29.0	77.5 ± 23.0	80.2 ± 22.3
Quality of life	46.2 ± 25.4	62.9 ± 26.8	58.6 ± 29.6
Social limitation	47.3 ± 30.9	55.4 ± 34.7	57.3 ± 33.2
Clinical summary score	51.7 ± 26.2	65.3 ± 22.6	63.4 ± 23.7
Overall summary score	48.5 ± 24.3	61.1 ± 24.6	59.5 ± 25.4

***Plus-minus values are means ± standard deviations**
KCCQ: Kansas City Cardiomyopathy Questionnaire

Table 12 shows the within-patients' variation of the KCCQ score during follow-up among the remaining 60 patients with KCCQ data at 6-months of follow-up. For most subscales of the KCCQ, mean QoL scores have increased between baseline and 3-months follow-up visit and they decreased slightly thereafter between 3-months and 6-months follow-up visits. The same observation was made for the overall summary score.

Table 12. Within-patients' variation of the Kansas City Cardiomyopathy Questionnaire score during follow-up.*

	Patients who fulfilled the questionnaire at baseline n = 143		
		Remaining at 3-months n = 75	
			Remaining at 6-months n = 60
	Baseline	3-months	6-months
Kansas City Cardiomyopathy Questionnaire overall summary score			
Physical limitation	50.5 ± 27.1	58.6 ± 27.3	58.3 ± 27.9
Symptom stability	68.8 ± 35.2	58.8 ± 21.1	55.8 ± 25.4
Symptom frequency	50.8 ± 28.2	74.3 ± 22.7	68.9 ± 26.5
Symptom burden	54.4 ± 26.3	74.7 ± 22.0	70.3 ± 25.7
Total symptom score	52.6 ± 25.9	74.5 ± 21.2	69.6 ± 25.2
Self-efficacy	65.8 ± 29.7	77.7 ± 22.7	80.2 ± 22.3
Quality of life	45.1 ± 26.5	63.2 ± 24.8	58.6 ± 29.6
Social limitation	49.6 ± 30.1	56.6 ± 34.9	57.3 ± 33.2
Clinical summary score	50.3 ± 24.6	65.4 ± 23.1	63.4 ± 23.7
Overall summary score	48.2 ± 23.2	61.5 ± 24.5	59.5 ± 25.4

***Plus-minus values are means ± standard deviations**

Moreover, at baseline, there were more patients in the worst QoL categories (worst and poor). But over the course of the study, most patients have shifted to the best QoL categories (fair and good). (Table 13) This observation is better illustrated in Figure 19.

Nevertheless, we noted that 25 (33.3%) patients and 22 (36.7%) patients experienced deterioration in QoL at 3 and 6-months of follow-up respectively (patients below the diagonals in Figure 19). Patients in this subgroup also experienced more cardiac events than those who experienced improvement in QoL at the same time (36% vs 20% and 77% vs 18% respectively at 3-months and 6-months of follow-up).

Furthermore, 7 (9.3%) patients and 4 (6.7%) patients experienced deterioration of more than 25% of their QoL at 3 and 6-months of follow-up respectively (patients below the red dashed lines in Figure 19). In this subgroup of patients, the proportion of cardiac events was much higher. Indeed, 43% of these patients experienced a cardiac event at 3-months of follow-up while all of these patients experienced a cardiac event at 6-months of follow-up.

Table 13. Changes within the Kansas City Cardiomyopathy Questionnaire's categories during follow-up.*

	Worst (< 25)	Poor (25 – 49)	Fair (50 – 74)	Good (75 – 100)
Baseline (n = 143)	32 (22.4)	45 (31.5)	39 (27.3)	27 (18.9)
3-month follow-up (n = 75)	6 (8.0)	22 (29.3)	20 (26.7)	27 (36.0)
6 months follow-up (n = 60)	7 (11.7)	16 (26.7)	18 (30.0)	19 (31.7)

***Data are no (%)**

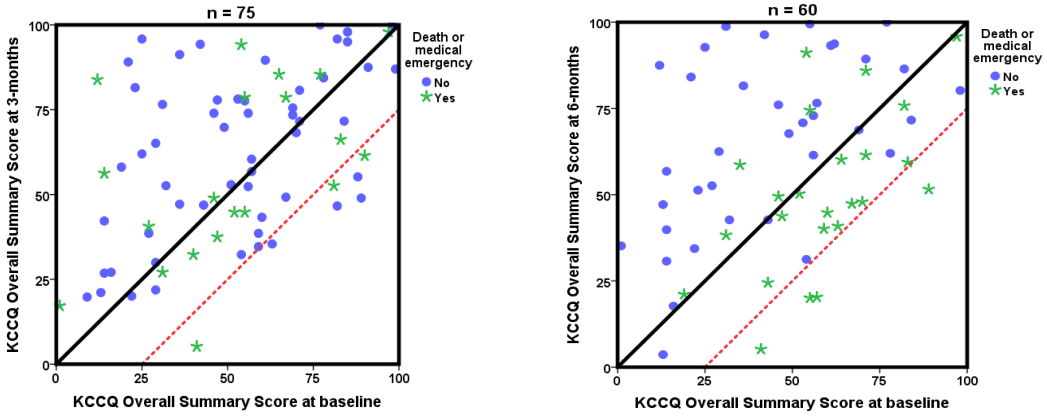


Figure 19. Square-diagonal graphs of changes in KCCQ overall summary score after 3 and 6 months of follow-up

Chapter 5

Discussion

The aim of the present thesis was to develop new management strategies to reduce mortality and hospital readmission rates in HF patients. HTM represents a useful tool to this end. Thus, in a first step, we proposed solutions to some of the unresolved issues that still limit the use of HTM in the management of HF patients. In this attempt, we first identified in publication 1, characteristics in the daily changes of the clinical monitored parameters (body weight, blood pressure, pulse rate) that are predictive of HF-related events. It turned out that a patient would trigger an early alert to prevent a HF-related event, as much as his body weight increases over 3 to 7 consecutive days; or if he/her has a significant body weight variation over 3 consecutive days; or if he/her has a significant pulse rate variation over 3 to 7 consecutive days; or if he/her has a decrease in the mean of 3 consecutive days' diastolic blood pressure; or if he/her has a narrow differential blood pressure during 3 consecutive days. We then combined these HF-related events' predictors identified from the monitored parameters with the clinical MAGGIC score. We decided to use the valid MAGGIC clinical score instead of developing a clinical risk model from our database in order to build a system that will be easily generalizable. Indeed, our HF population was similar to that of the MAGGIC study in that, in both HF populations mean age was 68 years, most of them were men, about 40% of them had a history of myocardial infarction and HF events occurred in about 40% of cases. But they differed in that mean LVEF was lower in our study (28 ± 7% vs 35 ± 14%). This is because the MAGGIC study did not include only patients with HFrEF as

in our study but also patients with HFpEF. HFrEF was nevertheless found in 75% of patients in the MAGGIC study. These two HF populations also differed in that patients in our study were sicker (NYHA class III or IV: 57% vs 42%) and more treated (ACE/ARB: 93% vs 67%; beta-blocker: 80% vs 34%) than the MAGGIC study's population. However, these variables are included in the MAGGIC score formula. So, the risk for a patient is adjusted according to these variables. Therefore, using the MAGGIC score in our HF population was quite appropriate and more beneficial.

Combining the predictors identified from the monitored parameters with the MAGGIC score resulted in a new HF events' dynamic prediction algorithm with which the triggering of alerts would be proportional to the patients' baseline clinical risk. So with our algorithm, an alert will be triggered faster for a patient with a poor baseline clinical score while the algorithm will be more lenient with a patient whose baseline clinical score is good. The predictive performance of this new algorithm was higher (whatever the cutoff) than that of an algorithm only based on remotely monitored parameters. This new algorithm was applied to healthy volunteers in order to establish the normal range of values and to ensure that the system will not generate a lot of false positives. Healthy volunteers were not free of any disease because many of them had a medical history of diabetes, hypertension, hypercholesterolemia or renal failure. No difference was found for the signal score according to age or gender in healthy volunteers. The 20% cut-off for the signal score resulted in a few number of alerts in healthy volunteers (12%) compared to HF patients with cardiac events (60%). The difference was more apparent with the 25% cut-off for the combined score which produced only 1.5% alerts in healthy volunteers and up to 92% alerts in HF patients with cardiac events. The 25% cut-off for the combined score thus appears to be a good cut-off for triggering alerts.
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The normal range of values could be used anyway to optimally set predefined thresholds for alerts triggering. Therefore, this new algorithm can be easily implemented to build an individualized non-invasive automated and autonomous alert triggering system for early detection and early preventive therapeutic intervention of HF deterioration. This new system will be more efficient in several points.

First, our prediction algorithm only includes the characteristics of the remotely monitored parameters that are really related to HF events. This aspect was not considered in previous studies which relied on predefined thresholds to trigger alerts and it was not clear how the daily changes in monitored parameters really predicted HF events. Taking this aspect into account, we have improved the predictive performance of our algorithm which has thus outperformed the traditional "rules-of-thumb" and the rule applied in TEMA-HF1 trial.[109]

Second, our system will not monitor the only body weight parameter as in the WISH[118] and Tele-HF[72] trials which failed to demonstrate superiority of HTM protocols over usual care. As in the TEN-HMS[119], the TIM-HF[120], the TEMA-HF1[109] and the BEAT-HF[75] trials, our system also takes into account in addition to the body weight, the blood pressure and the pulse rate.

HF is a complex syndrome usually accompanied by several comorbidities and as some authors have already pointed out, its appropriate management cannot be limited to a single clinical parameter.[109,110,120] Moreover, HF deterioration can occur without an increase in body weight in half of patients.[121] A pathophysiological hypothesis increasingly supports that HF deterioration is consecutive to an endogenous fluid shift from venous body reservoirs rather than an exogenous fluid accumulation and does not lead to an exogenous fluid retention or to a body weight gain.[31] As such, consideration should be given to measuring more than body weight in HTM interventions.[122] Monitoring blood pressure and pulse rate allows to early detect complications such as atrial fibrillation or hyper- or hypotension which can quickly lead to hospitalization or death.[109]

Third, our prediction algorithm is a dynamic one. The prediction score is a daily value, computed each day by including the new values of the monitored parameters. The preset fixed limits of body weight changes like those of the "rules-of-thumb" (body weight gain over 3 lbs in 1 day or 5 lbs in 3 days) have been found to be inappropriate in predicting worsening HF in Zhang[110] and Ledwidge datasets.[123] HF patients may have considerable daily fluctuations in body weight due to life style readjustment and therefore, short-term changes in body weight do not appear to be related to HF deterioration.[110,123,124] To address this problem, the body weight of the first monitoring day was used as the reference body weight in the TEMA-HF1 trial.[109] However, during a 6-months follow-up, body weight variations exceeding the predetermined threshold of 2 kg used in this study may occur without these variations being necessarily linked to an accumulation of fluid, therefore accounting for the low specificity of the TEMA-HF1 rule. Accordingly, moving long-term variations algorithms as our prediction algorithm or that of Zhang[110] and Ledwidge[123], performed better than fixed limits of short-term body weight changes in detecting HF deterioration. Moreover, in the BEAT-HF trial, an alert was triggered for a body weight gain occurring over a longer time window (weekly gain > 6 lbs) but HTM interventions did not reduce 180-day readmissions. Some authors pointed out that absolute changes in body weight do not seem very sensitive in detecting impending decompensation and that more gradual body weight gain may be more valuable in detecting HF deterioration. The BELGIUM-HF prediction algorithm analyzes the body weight slope up to 7 consecutive days thereby allowing tracking cumulative subtle body weight gain on 7 consecutive days. This feature is also the most important one of our prediction score given its highest coefficient. A time window longer than 7 days would it be more efficient in predicting HF events? Chaudhry[125] and colleagues have shown that body weight gain begins 30 days prior to clinical deterioration of HF but that this increase was more pronounced 1 week before hospitalization for HF. Using a 30-days' time window would not be an appropriate management strategy because it would take at least 30 days to trigger an alert. A patient monitoring system is expected to trigger an alert within a reasonable time window. Zhang[110] and colleagues have assessed the performance of a moving average convergence divergence algorithm (MACD) in predicting hospitalization for worsening HF in the 14 days prior to the hospitalization. This MACD outperformed the simple RoT algorithms (body weight gain > 3 lbs in 1 day or > 5 lbs in 3 days) and was very specific (89.4%) but not very

sensitive (20.4%). We also assessed the performance of the BELGIUM-HF system in predicting HF events on a 14-days' time window and it did not bring any added value compared to the 7-days' time window. Therefore, the 7-days' time window seems to be the most appropriate time window for an optimal monitoring of HF patients.

Fourth, BELGIUM-HF algorithm was built to be implemented in an automated non-invasive alert triggering system. Another issue about the use of HTM in the management of HF patients is whether to use an invasive or a non-invasive strategy. A meta-analysis on effective technologies for non-invasive remote monitoring in HF identified the four following specific technologies: videophone, interactive voice response, STS and HTM.[122] Videophone's effectiveness was assessed in only one study which found no differences in all-cause mortality compared to usual care.[126] Interactive voice response technology was investigated in only two studies in this meta-analysis which found no benefit of this technology over usual care.[127] These findings were consistent with those of a larger randomized controlled trial, the Tele-HF trial.[72] Furthermore, few patients in Tele-HF trial complied with the system; 14% of patients never used the system and 45% did not adhere to it, reflecting a failure of voice-interactive technology.[69,72] Among non-invasive remote monitoring technologies, STS and HTM are the most used and both were found to be significantly better than usual care in reducing deaths and HF-related hospitalizations.[122,128] A meta-analysis comparing the main forms of non-invasive remote monitoring technologies in HF showed that when these specific technologies were ranked according to their effectiveness to reduce deaths and readmissions in HF patients, HTM was always ranked first.[128] Moreover, STS technology requires a case manager to conduct follow-up calls to patients and it has been reported that for a case manager who provide follow-up calls for 50 patients, HTM technology allows to manage 200-300 patients in the same time.[129] However, by being potentially able to electronically monitor several physiological data at once, HTM technology can generate a huge volume of data. Therefore, a visual examination of all these data is not practical.[69] By integrating an algorithm which will automatically compute each day a prediction score using the values of the monitored data, the BELGIUM-HF system as with similar systems (TEMA-HF1, BEAT-HF) will exempt from this workload. Automatic HTM systems also promote patients' adherence as in TIM-HF trial with 81% of patients completing more than 70% of daily transmissions.[4] In our study, adherence to the system was 100% because the 8% of non-transmitted data did not match missing data but corresponded to periods during which patients had been admitted to hospital and were therefore no longer able to perform daily measurements of the monitored parameters. Furthermore, HTM enables patients to be actively involved in their own condition management through frequent self-monitoring.[130,131] This, in addition to the fact that HTM uses electronic devices that are already part of the patients' daily lives (smartphones, tablets) increases patients' adherence to this technology and their compliance with treatment.[69,132] Invasive monitoring through implantable hemodynamic monitors could enhance home-based monitoring by providing more accurate ant robust data to identify patients at high risk of decompensation.[63,133] Indeed, it has been shown that the first detectable change preceding the worsening of decompensation is an increase in filling pressure which can occur 20 days

before, followed by changes in autonomic adaptation and intrathoracic impedance and finally weight gain and the onset of symptoms occurring only a few days before.[56,134] Based on this observation, several studies have been conducted using a variety of implantable hemodynamic monitors to measure changes in cardiac filling pressures in HF outpatients including COMPASS-HF, HOMEOSTASIS and most recently the CHAMPION-trials.[76,135,136] The safety and the efficacy of the CardioMEMS device, the most-well studied pulmonary artery sensor was examined in the CHAMPION-trial which demonstrated a 30% decrease in HF-related hospitalizations over a 6-months' time period in patients using this device.[76] This device is now approved by the US Food and Drug Administration for NYHA class III HF patients with a HF hospitalization in the previous 12 months in order to decrease readmissions.[56,63] However, further studies are still needed to assess the efficacy and cost-effectiveness of the CardioMEMS device as well as to identify factor that may influence the use of invasive remote monitoring devices.[63] Furthermore, a health care provider is required to review and interpret transmitted data. This could be an obstacle to a real impact of this device.[56] In overall, invasive monitoring strategies could allow to monitor more accurate and robust parameters in the prediction of HF deterioration than non-invasive monitoring strategies which nevertheless contribute to improve patients' compliance with treatment by making them central partners in their own management. A combination of these two home monitoring strategies could be considered in future studies.

Fifth, BELGIUM-HF alert triggering system was built to be a stand-alone system. This system was developed on the basis of HTM principle but it differs from HTM technologies in their strictest definition in that it does not involve an exchange of data between patients and health care providers. Alerts will be sent to the patient's mobile phone who will then have to get in touch with his/her doctor which one will be able to readjust his/her treatment. HTM technology in its classical form could raise on the one hand the issue of the responsibility of the healthcare professional who receives and must respond to the alerts that will be triggered and on the other hand, the issue of the security of the transmitted data.[63] With BELGIUM-HF system, healthcare professionals will not be responsible for alerts triggered and in addition, patient privacy and confidentiality will be easily guaranteed.
Sixth, BELGIUM-HF system is an individualized alert triggering system which integrates the baseline MAGGIC clinical score of each patient. There is evidence suggesting that patients at high risk of readmission or death appear to benefit more from HTM technology.[69,137] With BELGIUM-HF system, the triggering of alerts would be proportional to the patients' baseline clinical risk.

Seventh, a quality control of the transmitted data is performed with the BELGIUM-HF system. During the 6-month period of signal recording, transmitted data were neither viewed nor analyzed. If there was a problem with the equipment, assistance was provided by Touring Secours. But when the acquisition period was closed, signal trends were visually examined and rare but unambiguous artefacts were identified only on body weight measures. These artefacts consisted of abrupt and transient drops of several kilos arising either from technical

deficiencies of the scale or from its use by a third party. Being able to detect these artefacts is very important because these are incidents that cannot be prevented. In this respect, an artefact detection algorithm has been developed and incorporated into the BELGIUM-HF system to automatically check and correct the signal data.

In the light of the above, the new BELGIUM-HF individualized non-invasive automated and stand-alone alert triggering system outperforms previous HTM systems in several points and could significantly enhance the effectiveness of HTM technologies in reducing HF-related hospitalizations and deaths.

The BELGIUM-HF stand-alone system could thus be used in a new management strategy of HF patients which would allow early prevention of HF-related readmissions within 24 hours. Indeed, even though we considered a composite endpoint of death or medical emergency with or without hospitalization, only two deaths occurred as the first event among the 96 events which occurred during signal acquisition. The BELGIUM-HF system therefore detects more specifically HF-related readmissions. Furthermore, the system assesses the risk of readmission on a daily basis and therefore a preventive therapeutic intervention could be performed within 24 hours. Two different approaches can be considered with the BELGIUM-HF system for the management of HF patients.

The first approach could use the positive predictive value. In this case, a single cut-off for triggering an alert should be set. The 25% cut-off of the combined score resulted in a good positive predictive value (74%) with a good negative predictive value (93%) meaning that if an alert is triggered, the patient has a 74% probability to be readmitted to hospital without an early preventive therapeutic intervention. However, positive predictive value depends on prevalence. Indeed, the previous positive and negative predictive values were achieved with the observed HF events' prevalence of 42% in our study. When considering various cut-offs and various a priori prevalence's rates of HF events, the 25% cut-off of the combined score still provide the best positive and negative predictive values for HF events' prevalence between 20 and 50%. But for low HF events' prevalence (around 5%), the cut-off should be set to a higher value of 30% to achieve the best positive and negative predictive values. Moreover, rather than using the single value of the cut-off, we can consider a strategy using three risk gradients through three ranges of values and translated into three color gradients. Let's take the example for a cut-off set at 25% to trigger an alert. Each day, it could be considered that for a combined score < 20%, the patient would be in the green zone and no action would be required. But if the combined score is between 20 and 24%, the patient would be in the orange zone and should closely monitor his/her diet and be fully compliant with treatment. Finally, if the combined score is ≥ 25%, the patient would be in the red zone. In this case, an alert is triggered and the patient should get in touch with his/her GP for an early preventive therapeutic intervention. This strategy could allow a more active participation of the patient in his/her own care.

In a second approach, the cut-off for triggering an alert could be set according to the patient's perception of his/her own health rather than using a single cut-off for all patients. In this regard, for a patient feeling bad (KCCQ score < 25%) a lower cut-off could be set for faster triggering of alert while for a patient feeling good (KCCQ score ≥ 75%) a higher cut-off will be set for a later triggering of alert. Finally, for a patient whose KCCQ score is between 25 and 74%, an optimal cut-off could be used.

In a second step to improve HF prognosis, we considered supplementing traditional health status measures of morbidity and mortality with quality-of-life health status measures to better define the prognosis of HF patients. To that end, we assessed in Publication 2, the relationship between the MAGGIC clinical score and the KCCQ score, as well as their additive prognostic value. The MAGGIC score is a valid, robust, applicable and generalizable easy to use risk score for mortality in patients with HF of both reduced and preserved ejection fraction. The higher the MAGGIC score, the worst the patient's prognosis.[77] The KCCQ is a valid, reliable, sensitive and responsive quality-of-life status measure for HF patients. It also appears to be a valid measure of health status in both HFrEF and HFpEF patients.[138] A KCCQ score can be computed and the lower this score, the worst the patient's quality of life.[95] Firstly, we found an expected inverse correlation between these two scores indicating that HF patients at high risk of mortality also tend to have a poorer quality of life. Secondly, we found that when the MAGGIC score is high, HF patients are already at high risk of death or hospitalization and the KCCQ score has no added prognostic value. However, when the MAGGIC score is low, the KCCQ score allows to further identify a subgroup at high risk of death or hospitalization. Therefore, these two types of health measurement instruments are complementary in assessing health in its globality in HF patients. We also assessed the prognostic value of changes in KCCQ scores over time. We found in this respect that patients who experienced deterioration in QoL at 3 and 6-months of follow-up also experienced more cardiac events than those who experienced improvement in QoL at the same time.

KCCQ can thus provide an important source of information in addition to the MAGGIC clinical score, useful and even necessary for a better management of HF patients. It may therefore provide a different approach in HF management. The concept of perceived health is as important as clinical scores in predicting HF events. It's another way for assessing risk in HF patients that should be considered. Considering our findings, KCCQ could be used together with the MAGGIC score into a new management strategy of HF patients organized into two steps. In a first step, the practitioner will consider the MAGGIC score. If the MAGGIC score is poor (> 50%) ie for patients going wrong, he/her no longer needs to consider the KCCQ score because for these patients, whatever the perception they have about their own health status, they have a very high risk of experiencing a HF event and a preventive therapeutic intervention should be performed early. If the MAGGIC score is favorable (≤ 50%) ie for patients doing well, the practitioner will then have to consider the

KCCQ score in a second step to identify those who have in addition a poor (< 25%) KCCQ score ie patients feeling bad. Indeed, these patients who doing well but who feel bad have also a very high risk of experiencing a HF event and a preventive therapeutic intervention must also be performed.

HF is a complex syndrome and its appropriate management cannot be limited to the single use of traditional health status measures such as the MAGGIC score. Self-perceived health status measures such as the KCCQ score are useful and even necessary because biological and physiological data, symptoms, functional status and health perceptions all impact the individual's overall quality of life.[139] Moreover, HF is a chronic condition and for most patients living with chronic disease, treatment goal has shifted from disease cure to maintaining and improving HRQoL.[139,140] Indeed, patients are increasingly placing an emphasis on their health status and HRQoL instruments may provide an important, systematic approach of obtaining QoL data that cannot be obtained from other measures such laboratory data or imaging.[141,142] There is an increasing need to improve the patient-centeredness of health care and taking into account patients' perception of their health status could be a useful approach to this end. HF management can be adjusted according to patients' adherence to optimal medical therapy but also according to their understanding of their symptoms.[142] Over the past two decades, there has been a growing interest on health perceived measures and an evolution of HRQoL concept.[139,143] Prior to HRQoL measurements, clinicians-assessed measures such as NYHA class had been primarily used to assess HF patients' functional status. However, HRQoL have proven to be more reproducible than clinician-assessed measures and even than more objective tests such as measures of ejection fraction or valve gradients.[142,144,145] Using HRQoL can help to better assess patients' health status because physicians may underestimate the impact of symptoms on patients' physical and social function.[142] Hence, HRQoL has become an important endpoint for clinical trials in HF.[146] Nevertheless, only 16% of modern cardiovascular clinical trials have included a HRQoL measurement.[147] Despite the evidence of the added value of HRQoL measurements in the assessment of HF patients' health, their use in routine clinical practice is still awaited.[142] However, as with our study, HRQoL assessments have shown their ability to discriminate HF patients at high risk for traditional outcomes. Being able to use them to identify HF patients who deserve more attention, more intensive therapy is therefore fully justified and the importance of incorporating them into clinical practice has been recently highlighted.[148,149] The KCCQ is now the most widely used HF HRQoL measurement and it has been found to be a significant predictor of mortality, hospitalization and change in health.[99,150,151] But for KCCQ to be adopted into routine practice there are still challenges ahead.

First, acceptance of KCCQ by patients and clinicians and its implementation into clinical workflow is a fundamental prerequisite.[142,149] A lengthy questionnaire to fill might not meet patient adherence and clinicians are limited by a time constraint. The respondent and administrative burden of the KCCQ has been addressed recently. The first full version of the KCCQ, the KCCQ-23 could be self-administrated under 10 min.[142,152] Recently, a short version of the KCCQ, the KCCQ-12 which maintains the psychometric properties of the full

KCCQ has been developed and validated.[152] KCCQ-12 retained strong correlations with the original scales, high reliability and high responsiveness. It also had comparable properties with the full KCCQ in terms of prognosis and interpretability but with the main advantage that this short-form KCCQ-12 requires only 2 to 3 min to be self-administered.[152] Therefore, the burden of filling the KCCQ should no longer act as a barrier to its use into clinical care which now depends on a real commitment of patients and clinicians.[142]

Second, HRQoL instrument easy to interpret are necessary for a use in clinical setting. It is necessary that the instrument can explicitly determine what differences in scores are clinically meaningful.[153] The predictive validity of KCCQ was assessed in several studies which showed that the KCCQ could clearly define whether a patient has a large, moderate or small clinical deterioration.[142] In the same way, we have shown that among HF patients with a good MAGGIC clinical score, those with poor KCCQ scores were at higher risk of death or hospital readmission. But it has not yet been well described, whether clinicians or patients understand the KCCQ score and find it useful in the clinical setting.[142] We observed for example that about one-third of patients experienced a loss in QoL after 3 and 6 months of follow-up. But the use of a poor-worst KCCQ score in routine care and its translation into a well-tailored therapeutic intervention is not immediately evident.[105]

Third, to promote the integration of KCCQ into clinical practice, its use should first be facilitated.[142,149] The recent development in recording electronic health data through mobile telecommunications tools represents a real opportunity for this purpose. A mobile application could be developed to facilitate on the one hand the filling of the questionnaire and on the other hand, to facilitate computation and interpretation of the KCCQ score.[142,149]
Furthermore, it has been recently shown that a high KCCQ score assessed before hospital discharge was significantly associated with low HF 30-day readmission rate and it contributed to significantly improve readmission prediction reliability when combined with other clinical components most of which being included in the MAGGIC score (age, gender, beta blocker, ACE/ARB, ejection fraction).[154] HF is still one of the most common diagnoses associated with 30-day readmission[155] and these results also support the need to combine the KCCQ score with the MAGGIC score to better define HF prognosis.

The added value of the KCCQ in the prognosis of HF seems therefore undeniable. Moreover, its combination with the MAGGIC score would allow assessing health in a global perspective for HF patients. Results from our study further strengthen the validity of the use of KCCQ as a tool for monitoring patients in routine clinical care. Such a health status scale should no longer be used as a surrogate but as a highly meaningful outcome of care.

The limitations of the present project are discussed in details in each publication. In general, the small sample size was one of these limitations. Patients were however recruited from their GPs and such a sample is more representative of HF patients in their daily life. Another

limitation was that, as in most studies on HF, we included only patients with reduced ejection fraction. This may limit the generalization of our findings to all HF patients. The problem with HFpEF is that its identification remains difficult because it is a systemic disorder with a heterogeneous pathophysiology affecting not only the heart but also other organs.[8] We also had the constraint of being able to compare our algorithm with those of other studies, hence the need to use the same HFrEF patients' population as these studies. However, one in two HF patients has a preserved ejection fraction and this proportion is increasing over time.[5] So, HFpEF patients should be involved in future studies. Another limitation was related to the lack of patient compliance in filling the KCCQ. Following the baseline assessment of the KCCQ, very few patients fulfilled the KCCQ during the subsequent follow-up visits 1 (3 months) and 2 (6 months). That did not allow us to assess the relevance of a change in KCCQ score as an outcome for HF patients. It also emphasizes that to achieve an effective use of KCCQ in routine care, patients and clinicians' awareness will be previously required. Nevertheless, several arguments related to the strength of this project have been identified. They were discussed in details in each publication and attest the originality and the robustness of our findings.

Chapter 6

Conclusions and perspectives

6.1. Conclusions

"*The very essence of cardiovascular practice is the early detection of heart failure*". This assertion of Sir Thomas Lewis in 1933 is still relevant today and still imposes a major challenge to clinicians and researchers. Indeed, HF is a major public health problem and an early detection of HF deterioration could allow a preventive therapeutic intervention resulting in a reduction in HF outcomes and its economic burden. The present thesis considered two alternatives to this end. In a first step, by coming up with solutions to some of the unresolved issues that still limit the use of HTM in the management of HF patients, we built a new individualized non-invasive automated and autonomous alert triggering system for early detection and early preventive therapeutic intervention of HF deterioration. This new BELGIUM-HF system appears to be more efficient than the previous HTM systems for HF patients. HF management has evolved over the decades through several eras. Considering the constant progress in HTM technologies as well as the increasingly promising results of their use in the management of HF patients, it can be considered that a new era, "the HTM era" could begin in HF management. In this regard, the BELGIUM-HF system would be a leading tool. In a second step, we showed the complementarity between the MAGGIC score (an instrument for assessing mortality in HF patients) and the KCCQ score (an instrument for assessing QoL in HF patients) in predicting HF outcomes. Health should no longer only be measured narrowly and in the negative through traditional measures of morbidity and mortality in HF. HF is a chronic condition and living with a good quality of life is an important goal for most patients living with chronic disease. Moreover, HF is a complex

syndrome with a still incompletely understood pathophysiology and as we have shown, supplementing the MAGGIC score with the KCCQ score allows to well-define the prognosis of HF patients. Despite evidence of the added value of the KCCQ in predicting HF outcomes, its use in routine clinical practice is still awaited. The present thesis serves to also emphasize that it is time to integrate KCCQ into daily practice.

6.2. Perspectives

HF remains today a major public health problem with still high post-discharge mortality and readmission rates. These events are usually the result of poor adherence to drug therapy, bad lifestyle habits or inadequate drug therapy. An appropriate management of these patients is therefore necessary to improve their prognosis. But how could this be done? The present thesis identified in a first step a new more efficient system to help monitor HF patients at home between two scheduled visits. In a second step, it proposed to assess HF patients' health in a global perspective by integrating the KCCQ into routine care. However, further studies should be conducted to validate our findings.

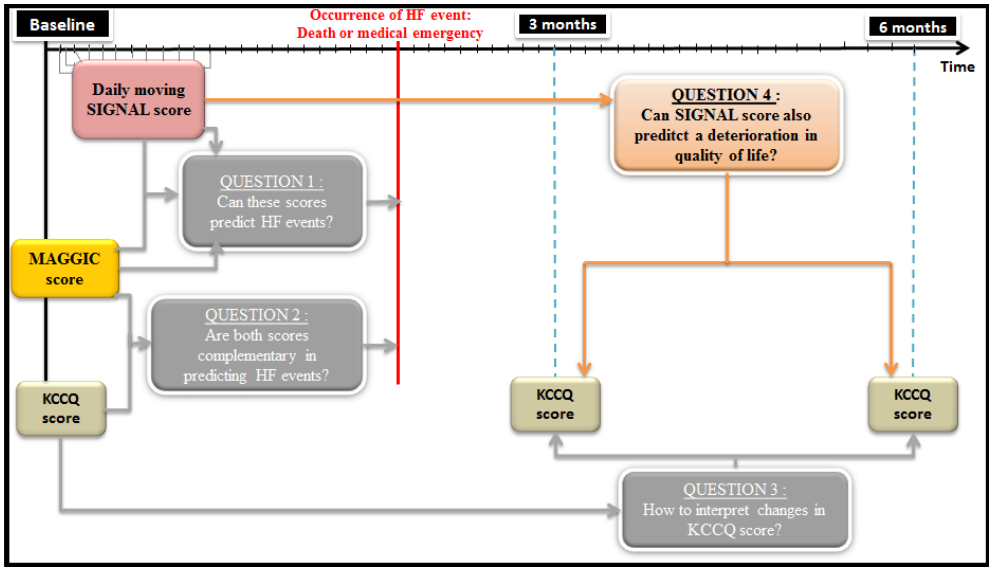
First, the performance of regression models used in diagnostic and prognostic prediction research is generally better on the data set on which the model has been constructed (derivation set) compared to the performance of the same model on new data (validation set)[156,157], especially in small data sets.[158,159] To address this, several approaches have been suggested to estimate a model's optimism[156], such as bootstrap resampling, crossvalidation, and split-sampling techniques. In our study, we used a split-sampling technique by building the BELGIUM-HF algorithm in a subset (training) and then assessing its accuracy in another subset (testing). These techniques are internal validation techniques, because the performance is estimated using patients from the model's derivation set only.[156] However, for relatively small data sets, internal validation of prediction models by these techniques may not be sufficient and indicative for the model's performance in future patients. External validation is essential before implementing prediction models in clinical practice.[160] Therefore, as we applied the "rules-of-thumb" and the rule of TEMA-HF1 study[109] to BELGIUM-HF patients, BELGIUM-HF algorithm could also easily be applied to other HF patients to ensure external validation.

Second, the BELGIUM-HF system needs to be validated in a prospective clinical study conducted to assess the efficacy of BELGIUM-HF system in reducing HF outcomes. This study should compare a HF management strategy using the BELGIUM-HF system to usual care. A cost-effectiveness analysis should also be considered in this study. Based on the results of this prospective clinical study, a large randomized control trial could then be conducted to definitely prove the efficacy of BELGIUM-HF system in reducing HF outcomes.

Third, prior to the use of KCCQ in routine care, more research is needed to better define how to use changes in KCCQ score to maximize its interpretation and usefulness and to assess the efficacy of a strategy including KCCQ into routine care compared with usual routine care.

Increasing education of patients, clinicians and policy makers is also necessary to recognize the importance of measuring and integrating KCCQ into daily practice.

Fourth, by suggesting that health should now be measured in a global perspective for HF patients, the BELGIUM-HF system could be considered for predicting deterioration in HF patients' quality of life. Question 4 of our workflow could then be achieved.



References

1. Davis RC, Hobbs FD, Lip GY. ABC of heart failure. History and epidemiology. BMJ 2000;320:39-42.
2. Denolin H, Kuhn H, Krayenbuehl HP, Loogen F, Reale A. The definition of heart failure. Eur Heart J 1983;4:445-8.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force M. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.
4. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Bohm M, Boll H, Baumann G, Honold M, Koehler K, Gelbrich G, Kirwan BA, Anker SD, Telemedical Interventional Monitoring in Heart Failure I. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the telemedical interventional monitoring in heart failure study. Circulation 2011;123:1873-80.
5. Redfield MM. Heart Failure with Preserved Ejection Fraction. N Engl J Med 2016;375:1868-77.
6. Butler J, Fonarow GC, Zile MR, Lam CS, Roessig L, Schelbert EB, Shah SJ, Ahmed A, Bonow RO, Cleland JG, Cody RJ, Chioncel O, Collins SP, Dunnmon P, Filippatos G, Lefkowitz MP, Marti CN, McMurray JJ, Misselwitz F, Nodari S, O'Connor C, Pfeffer MA, Pieske B, Pitt B, Rosano G, Sabbah HN, Senni M, Solomon SD, Stockbridge N, Teerlink JR, Georgiopoulou VV, Gheorghiade M. Developing therapies for heart failure with preserved ejection fraction: current state and future directions. JACC Heart Fail 2014;2:97-112.
7. Fang JC. Heart Failure With Preserved Ejection Fraction: A Kidney Disorder? Circulation 2016;134:435-7.
8. Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, Paulus WJ. Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction: A Multiorgan Roadmap. Circulation 2016;134:73-90.
9. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CS, Sato N, Shah AN, Gheorghiade M. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 2014;63:1123-33.
10. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
11. Fettig J, Swaminathan M, Murrill CS, Kaplan JE. Global epidemiology of HIV. Infect Dis Clin North Am 2014;28:323-37.
12. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart 2007;93:1137-46.

13. McMurray JJ. Clinical practice. Systolic heart failure. N Engl J Med 2010;362:228-38.
14. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251-9.
15. Meta-analysis Global Group in Chronic Heart F. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur Heart J 2012;33:1750-7.
16. Lam CS, Solomon SD. The middle child in heart failure: heart failure with mid-range ejection fraction (40-50%). Eur J Heart Fail 2014;16:1049-55.
17. INAMI. L'usage efficient des médicaments en ambulatoire dans l'insuffisance cardiaque. Rapport du Jury. Bruxelles 2008.
18. Devroey D, Van Casteren V. The incidence and first-year mortality of heart failure in Belgium: a 2-year nationwide prospective registration. Int J Clin Pract 2010;64:330-5.
19. Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, Jaarsma T, Krum H, Rastogi V, Rohde LE, Samal UC, Shimokawa H, Siswanto BB, Sliwa K, Filippatos G. Heart failure: preventing disease and death worldwide. ESC Heart Failure 2014;1:4-25.
20. Writing Group M, Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Roger VL, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J, American Heart Association Statistics C, Stroke Statistics S. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation 2010;121:e46-e215.
21. Neumann T, Biermann J, Erbel R, Neumann A, Wasem J, Ertl G, Dietz R. Heart failure: the commonest reason for hospital admission in Germany: medical and economic perspectives. Dtsch Arztebl Int 2009;106:269-75.
22. Bocchi EA, Braga FG, Ferreira SM, Rohde LE, Oliveira WA, Almeida DR, Moreira Mda C, Bestetti RB, Bordignon S, Azevedo C, Tinoco EM, Rocha RM, Issa VS, Ferraz A, Cruz F, Guimaraes GV, Montera Vdos S, Albuquerque DC, Bacal F, Souza GE, Rossi Neto JM, Clausell NO, Martins SM, Siciliano A, Souza Neto JD, Moreira LF, Teixeira RA, Moura LZ, Beck-da-Silva L, Rassi S, Azeka E, Horowitz E, Ramires F, Simoes MV, Castro RB, Salemi VM, Villacorta Junior H, Vila JH, Simoes R, Albanesi F, Montera MW, Sociedasde Brasileira de C. [III Brazilian Guidelines on Chronic Heart Failure]. Arq Bras Cardiol 2009;93:3-70.
23. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. Int J Cardiol 2014;171:368-76.
24. Cosyns B, Claeys M. Management of heart failure in Belgium. Eur J Heart Fail 2001;3:509-12.
25. McMurray JJ, Komajda M, Anker S, Gardner R. Heart failure: epidemiology, pathophysiology and diagnosis. In: Camm AJ, Lüscher TF, Serruys PW, eds. The ESC Textbook of Cardiovascular Medicine: Malden: Blackwell Publishing; 2006:685-719.

26. Mann DL. Mechanisms and models in heart failure: A combinatorial approach. Circulation 1999;100:999-1008.
27. Kotzé A, Howell SJ. Heart failure: pathophysiology, risk assessment, community management and anaesthesia. Contin Educ Anaesth Crit Care Pain 2008;8:161-6.
28. Brake R, Jones ID. Chronic heart failure part 1: pathophysiology, signs and symptoms. Nurs Stand 2017;31:54-63.
29. Kemp CD, Conte JV. The pathophysiology of heart failure. Cardiovasc Pathol 2012;21:365-71.
30. Sanchez-Marteles M, Rubio Gracia J, Gimenez Lopez I. Pathophysiology of acute heart failure: a world to know. Rev Clin Esp 2016;216:38-46.
31. Ponikowski P, Jankowska EA. Pathogenesis and clinical presentation of acute heart failure. Rev Esp Cardiol (Engl Ed) 2015;68:331-7.
32. Fallick C, Sobotka PA, Dunlap ME. Sympathetically mediated changes in capacitance: redistribution of the venous reservoir as a cause of decompensation. Circ Heart Fail 2011;4:669-75.
33. Jessup M, Brozena S. Heart failure. N Engl J Med 2003;348:2007-18.
34. Edep ME, Shah NB, Tateo IM, Massie BM. Differences between primary care physicians and cardiologists in management of congestive heart failure: relation to practice guidelines. J Am Coll Cardiol 1997;30:518-26.
35. Nellessen E. Application des trajets de soins à l'insuffisance cardiaque. Vaisseaux, Coeur, Poumons Numéro spécial 2009.
36. Claes N, Jacobs N, Vijgen J. Impact of heart failure on hospital activity and healthcare costs in Belgium. J Med Econ 2008;11:71-9.
37. Muller-Werdan U, Stockl G, Werdan K. Advances in the management of heart failure: the role of ivabradine. Vasc Health Risk Manag 2016;12:453-70.
38. Sahasranam KV. Heart failure management - Evolution over the ages. BMH Med J 2017;4:17-22.
39. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med 1986;314:1547-52.
40. Sacks CA, Jarcho JA, Curfman GD. Paradigm shifts in heart-failure therapy--a timeline. N Engl J Med 2014;371:989-91.
41. Investigators S, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.
42. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996;334:1349-55.
43. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709-17.

44. Cohn JN, Tognoni G, Valsartan Heart Failure Trial I. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667-75.
45. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Ascheim DD, Tierney AR, Levitan RG, Watson JT, Meier P, Ronan NS, Shapiro PA, Lazar RM, Miller LW, Gupta L, Frazier OH, Desvigne-Nickens P, Oz MC, Poirier VL, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure Study G. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001;345:1435-43.
46. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH, Sudden Cardiac Death in Heart Failure Trial I. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-37.
47. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM, Comparison of Medical Therapy P, Defibrillation in Heart Failure I. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-50.
48. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA, 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W, Investigators M-CT. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329-38.
49. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Levy S, Linde C, Lopez-Sendon JL, Nieminen MS, Pierard L, Remme WJ, Task Force for the D, Treatment of Chronic Heart Failure of the European Society of C. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:1115-40.
50. Evangelista L, Doering LV, Dracup K, Westlake C, Hamilton M, Fonarow GC. Compliance behaviors of elderly patients with advanced heart failure. J Cardiovasc Nurs 2003;18:197-206; quiz 7-8.
51. Paul S. Hospital discharge education for patients with heart failure: what really works and what is the evidence? Crit Care Nurse 2008;28:66-82.
52. Leslie SJ, McKee SP, Imray EA, Denvir MA. Management of chronic heart failure: perceived needs of general practitioners in light of the new general medical services contract. Postgrad Med J 2005;81:321-6.
53. Blue L, Lang E, McMurray JJ, Davie AP, McDonagh TA, Murdoch DR, Petrie MC, Connolly E, Norrie J, Round CE, Ford I, Morrison CE. Randomised controlled trial of specialist nurse intervention in heart failure. BMJ 2001;323:715-8.

54. Fuat A, Hungin AP, Murphy JJ. Barriers to accurate diagnosis and effective management of heart failure in primary care: qualitative study. BMJ 2003;326:196.
55. Dahlstrom U. Heart failure clinics: organization, development, and experiences. Curr Opin Cardiol 2001;16:174-9.
56. Chaudhry SP, Stewart GC. New pharmacological and technological management strategies in heart failure. Vasc Health Risk Manag 2017;13:111-21.
57. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail 2001;3:315-22.
58. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, van Gilst WH, Widimsky J, Freemantle N, Eastaugh J, Mason J, Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of C. The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J 2003;24:442-63.
59. De Sutter J, Pardaens S, Audenaert T, Weytjens C, Kerckhove BV, Willems RA, De Laet N, Van Camp G. Clinical characteristics and short-term outcome of patients admitted with heart failure in Belgium: results from the BIO-HF registry. Acta Cardiol 2015;70:375-85.
60. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Investigators P-H, Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.
61. MacIntyre K, Capewell S, Stewart S, Chalmers JW, Boyd J, Finlayson A, Redpath A, Pell JP, McMurray JJ. Evidence of improving prognosis in heart failure: trends in case fatality in 66 547 patients hospitalized between 1986 and 1995. Circulation 2000;102:1126-31.
62. Heart Failure Society of A, Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, Katz SD, Klapholz M, Moser DK, Rogers JG, Starling RC, Stevenson WG, Tang WH, Teerlink JR, Walsh MN. HFSA 2010 Comprehensive Heart Failure Practice Guideline. J Card Fail 2010;16:e1-194.
63. Schwamm LH, Chumbler N, Brown E, Fonarow GC, Berube D, Nystrom K, Suter R, Zavala M, Polsky D, Radhakrishnan K, Lacktman N, Horton K, Malcarney MB, Halamka J, Tiner AC, American Heart Association Advocacy Coordinating C. Recommendations for the Implementation of Telehealth in Cardiovascular and Stroke Care: A Policy Statement From the American Heart Association. Circulation 2017;135:e24-e44.
64. Strehle EM, Shabde N. One hundred years of telemedicine: does this new technology have a place in paediatrics? Arch Dis Child 2006;91:956-9.
65. Rao B, Lombardi A, 2nd. Telemedicine: current status in developed and developing countries. J Drugs Dermatol 2009;8:371-5.
66. Craig J, Patterson V. Introduction to the practice of telemedicine. J Telemed Telecare 2005;11:3-9.
67. Heinzelmann PJ, Lugn NE, Kvedar JC. Telemedicine in the future. J Telemed Telecare 2005;11:384-90.

68. Moayedi Y, Ross HJ. Advances in heart failure: a review of biomarkers, emerging pharmacological therapies, durable mechanical support and telemonitoring. Clin Sci (Lond) 2017;131:553-66.
69. Dierckx R, Pellicori P, Cleland JG, Clark AL. Telemonitoring in heart failure: Big Brother watching over you. Heart Fail Rev 2015;20:107-16.
70. Clark RA, Inglis SC, McAlister FA, Cleland JG, Stewart S. Telemonitoring or structured telephone support programmes for patients with chronic heart failure: systematic review and meta-analysis. BMJ 2007;334:942.
71. Inglis SC, Clark RA, McAlister FA, Ball J, Lewinter C, Cullington D, Stewart S, Cleland JG. Structured telephone support or telemonitoring programmes for patients with chronic heart failure. Cochrane Database Syst Rev 2010:CD007228.
72. Chaudhry SI, Mattera JA, Curtis JP, Spertus JA, Herrin J, Lin Z, Phillips CO, Hodshon BV, Cooper LS, Krumholz HM. Telemonitoring in patients with heart failure. N Engl J Med 2010;363:2301-9.
73. Giamouzis G, Mastrogiannis D, Koutrakis K, Karayannis G, Parisis C, Rountas C, Adreanides E, Dafoulas GE, Stafylas PC, Skoularigis J, Giacomelli S, Olivari Z, Triposkiadis F. Telemonitoring in chronic heart failure: a systematic review. Cardiol Res Pract 2012;2012:410820.
74. Kashem A, Droogan MT, Santamore WP, Wald JW, Marble JF, Cross RC, Bove AA. Web-based Internet telemedicine management of patients with heart failure. Telemed J E Health 2006;12:439-47.
75. Ong MK, Romano PS, Edgington S, Aronow HU, Auerbach AD, Black JT, De Marco T, Escarce JJ, Evangelista LS, Hanna B, Ganiats TG, Greenberg BH, Greenfield S, Kaplan SH, Kimchi A, Liu H, Lombardo D, Mangione CM, Sadeghi B, Sadeghi B, Sarrafzadeh M, Tong K, Fonarow GC, Better Effectiveness After Transition-Heart Failure Research G. Effectiveness of Remote Patient Monitoring After Discharge of Hospitalized Patients With Heart Failure: The Better Effectiveness After Transition -- Heart Failure (BEAT-HF) Randomized Clinical Trial. JAMA Intern Med 2016;176:310-8.
76. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS, Group CTS. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 2011;377:658-66.
77. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Kober L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN, Meta-Analysis Global Group in Chronic Heart F. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J 2013;34:1404-13.
78. World Health Organization. Official Records of the World Health Organization. Vol 2. Geneva, Switzerland : World Health Organization; 1948.
79. Centers for Disease Control and Prevention. Measuring Healthy Days. Atlanta, Georgia: CDC; 2000.
80. Konstam V, Salem D, Pouleur H, Kostis J, Gorkin L, Shumaker S, Mottard I, Woods P, Konstam MA, Yusuf S. Baseline quality of life as a predictor of mortality and

hospitalization in 5,025 patients with congestive heart failure. SOLVD Investigations. Studies of Left Ventricular Dysfunction Investigators. Am J Cardiol 1996;78:890-5.
81. Testa MA, Simonson DC. Assessment of quality-of-life outcomes. N Engl J Med 1996;334:835-40.
82. Study protocol for the World Health Organization project to develop a Quality of Life assessment instrument (WHOQOL). Qual Life Res 1993;2:153-9.
83. Guyatt GH. Measurement of health-related quality of life in heart failure. J Am Coll Cardiol 1993;22:185A-91A.
84. Coelho R, Ramos S, Prata J, Bettencourt P, Ferreira A, Cerqueira-Gomes M. Heart failure and health related quality of life. Clin Pract Epidemiol Ment Health 2005;1:19.
85. Siegrist J, Junge A. Measuring the social dimension of subjective health in chronic illness. Psychother Psychosom 1990;54:90-8.
86. Alla F, Briancon S, Guillemin F, Juilliere Y, Mertes PM, Villemot JP, Zannad F, Investigators E. Self-rating of quality of life provides additional prognostic information in heart failure. Insights into the EPICAL study. Eur J Heart Fail 2002;4:337-43.
87. Swenson JR, Clinch JJ. Assessment of quality of life in patients with cardiac disease: the role of psychosomatic medicine. J Psychosom Res 2000;48:405-15.
88. Garin O, Herdman M, Vilagut G, Ferrer M, Ribera A, Rajmil L, Valderas JM, Guillemin F, Revicki D, Alonso J. Assessing health-related quality of life in patients with heart failure: a systematic, standardized comparison of available measures. Heart Fail Rev 2014;19:359-67.
89. Morgan K, McGee H, Shelley E. Quality of life assessment in heart failure interventions: a 10-year (1996-2005) review. Eur J Cardiovasc Prev Rehabil 2007;14:589-607.
90. Bennett SJ, Oldridge NB, Eckert GJ, Embree JL, Browning S, Hou N, Chui M, Deer M, Murray MD. Comparison of quality of life measures in heart failure. Nurs Res 2003;52:207-16.
91. Wiebe S, Guyatt G, Weaver B, Matijevic S, Sidwell C. Comparative responsiveness of generic and specific quality-of-life instruments. J Clin Epidemiol 2003;56:52-60.
92. Wielenga RP, Coats AJ, Mosterd WL, Huisveld IA. The role of exercise training in chronic heart failure. Heart 1997;78:431-6.
93. Jaarsma T, Johansson P, Agren S, Stromberg A. Quality of life and symptoms of depression in advanced heart failure patients and their partners. Curr Opin Support Palliat Care 2010;4:233-7.
94. Lewis EF, Johnson PA, Johnson W, Collins C, Griffin L, Stevenson LW. Preferences for quality of life or survival expressed by patients with heart failure. J Heart Lung Transplant 2001;20:1016-24.
95. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35:1245-55.

96. Garin O, Ferrer M, Pont A, Rue M, Kotzeva A, Wiklund I, Van Ganse E, Alonso J. Disease-specific health-related quality of life questionnaires for heart failure: a systematic review with meta-analyses. Qual Life Res 2009;18:71-85.
97. Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P, McCullough PA, Pina I, Tooley J, Weintraub WS, Rumsfeld JS, Cardiovascular Outcomes Research C. Monitoring clinical changes in patients with heart failure: a comparison of methods. Am Heart J 2005;150:707-15.
98. Nieminen MS, Dickstein K, Fonseca C, Serrano JM, Parissis J, Fedele F, Wikstrom G, Agostoni P, Atar S, Baholli L, Brito D, Colet JC, Edes I, Gomez Mesa JE, Gorjup V, Garza EH, Gonzalez Juanatey JR, Karanovic N, Karavidas A, Katsytadze I, Kivikko M, Matskeplishvili S, Merkely B, Morandi F, Novoa A, Oliva F, Ostadal P, Pereira-Barretto A, Pollesello P, Rudiger A, Schwinger RH, Wieser M, Yavelov I, Zymlinski R. The patient perspective: Quality of life in advanced heart failure with frequent hospitalisations. Int J Cardiol 2015;191:256-64.
99. Parissis JT, Nikolaou M, Farmakis D, Paraskevaidis IA, Bistola V, Venetsanou K, Katsaras D, Filippatos G, Kremastinos DT. Self-assessment of health status is associated with inflammatory activation and predicts long-term outcomes in chronic heart failure. Eur J Heart Fail 2009;11:163-9.
100. Altenberger J, Parissis JT, Ulmer H, Poelzl G, LevoRep I. Rationale and design of the multicentre randomized trial investigating the efficacy and safety of pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep study). Eur J Heart Fail 2010;12:186-92.
101. de Vries AE, de Jong RM, van der Wal MH, Jaarsma T, van Dijk RB, Hillege HL. The value of INnovative ICT guided disease management combined with Telemonitoring in OUtpatient clinics for Chronic Heart failure patients. Design and methodology of the IN TOUCH study: a multicenter randomised trial. BMC Health Serv Res 2011;11:167.
102. Ghali JK, Tam SW, Ferdinand KC, Lindenfeld J, Sabolinski ML, Taylor AL, Worcel M, Curry CL, Cohn JN, Investigators AH. Effects of ACE inhibitors or beta-blockers in patients treated with the fixed-dose combination of isosorbide dinitrate/hydralazine in the African-American Heart Failure Trial. Am J Cardiovasc Drugs 2007;7:373-80.
103. Mark DB, Knight JD, Velazquez EJ, Howlett JG, Spertus JA, Djokovic LT, Harding TM, Rankin GR, Drew LA, Szygula-Jurkiewicz B, Adlbrecht C, Anstrom KJ, Surgical Treatment for Ischemic Heart Failure Trial I. Quality of life and economic outcomes with surgical ventricular reconstruction in ischemic heart failure: results from the Surgical Treatment for Ischemic Heart Failure trial. Am Heart J 2009;157:837-44, 44 e1-3.
104. Sauser K, Spertus JA, Pierchala L, Davis E, Pang PS. Quality of life assessment for acute heart failure patients from emergency department presentation through 30 days after discharge: a pilot study with the Kansas City Cardiomyopathy Questionnaire. J Card Fail 2014;20:18-22.
105. Network of Nurses of GISSI-HF. Di Giulio P. Should patients perception of health status be integrated in the prognostic assessment of heart failure patients? A prospective study. Qual Life Res 2014;23:49-56.

106. Allen LA, Gheorghiade M, Reid KJ, Dunlay SM, Chan PS, Hauptman PJ, Zannad F, Konstam MA, Spertus JA. Identifying patients hospitalized with heart failure at risk for unfavorable future quality of life. Circ Cardiovasc Qual Outcomes 2011;4:389-98.
107. Stevenson LW, Hellkamp AS, Leier CV, Sopko G, Koelling T, Warnica JW, Abraham WT, Kasper EK, Rogers JG, Califf RM, Schramm EE, O'Connor CM. Changing preferences for survival after hospitalization with advanced heart failure. J Am Coll Cardiol 2008;52:1702-8.
108. Stewart GC, Brooks K, Pratibhu PP, Tsang SW, Semigran MJ, Smith CM, Saniuk C, Camuso JM, Fang JC, Mudge GH, Couper GS, Baughman KL, Stevenson LW. Thresholds of physical activity and life expectancy for patients considering destination ventricular assist devices. J Heart Lung Transplant 2009;28:863-9.
109. Dendale P, De Keulenaer G, Troisfontaines P, Weytjens C, Mullens W, Elegeert I, Ector B, Houbrechts M, Willekens K, Hansen D. Effect of a telemonitoring-facilitated collaboration between general practitioner and heart failure clinic on mortality and rehospitalization rates in severe heart failure: the TEMA-HF 1 (TElemonitoring in the MAnagement of Heart Failure) study. Eur J Heart Fail 2012;14:333-40.
110. Zhang J, Goode KM, Cuddihy PE, Cleland JG, Investigators T-H. Predicting hospitalization due to worsening heart failure using daily weight measurement: analysis of the Trans-European Network-Home-Care Management System (TEN-HMS) study. Eur J Heart Fail 2009;11:420-7.
111. New York Heart Association Criteria Committee. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, Numéro 567 ;Numéro 1994: Little Brown; 1994.
112. Smilde TD, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction. Circulation 2006;114:1572-80.
113. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole-Wilson PA, Mann DL, Packer M. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation 2006;113:1424-33.
114. O'Connor CM, Hasselblad V, Mehta RH, Tasissa G, Califf RM, Fiuzat M, Rogers JG, Leier CV, Stevenson LW. Triage after hospitalization with advanced heart failure: the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) risk model and discharge score. J Am Coll Cardiol 2010;55:872-8.
115. O'Connor CM, Whellan DJ, Wojdyla D, Leifer E, Clare RM, Ellis SJ, Fine LJ, Fleg JL, Zannad F, Keteyian SJ, Kitzman DW, Kraus WE, Rendall D, Pina IL, Cooper LS, Fiuzat M, Lee KL. Factors related to morbidity and mortality in patients with chronic heart failure with systolic dysfunction: the HF-ACTION predictive risk score model. Circ Heart Fail 2012;5:63-71.

116. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, Ostergren J, Michelson EL, Pieper KS, Granger CB. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J 2006;27:65-75.
117. Senni M, Parrella P, De Maria R, Cottini C, Bohm M, Ponikowski P, Filippatos G, Tribouilloy C, Di Lenarda A, Oliva F, Pulignano G, Cicoira M, Nodari S, Porcu M, Cioffi G, Gabrielli D, Parodi O, Ferrazzi P, Gavazzi A. Predicting heart failure outcome from cardiac and comorbid conditions: the 3C-HF score. Int J Cardiol 2013;163:206-11.
118. Lynga P, Persson H, Hagg-Martinell A, Hagglund E, Hagerman I, Langius-Eklof A, Rosenqvist M. Weight monitoring in patients with severe heart failure (WISH). A randomized controlled trial. Eur J Heart Fail 2012;14:438-44.
119. Cleland JG, Louis AA, Rigby AS, Janssens U, Balk AH, Investigators T-H. Noninvasive home telemonitoring for patients with heart failure at high risk of recurrent admission and death: the Trans-European Network-Home-Care Management System (TEN-HMS) study. J Am Coll Cardiol 2005;45:1654-64.
120. Abraham WT, Compton S, Haas G, Foreman B, Canby RC, Fishel R, McRae S, Toledo GB, Sarkar S, Hettrick DA, Investigators FS. Intrathoracic impedance vs daily weight monitoring for predicting worsening heart failure events: results of the Fluid Accumulation Status Trial (FAST). Congest Heart Fail 2011;17:51-5.
121. Burchell AE, Sobotka PA, Hart EC, Nightingale AK, Dunlap ME. Chemohypersensitivity and autonomic modulation of venous capacitance in the pathophysiology of acute decompensated heart failure. Curr Heart Fail Rep 2013;10:139-46.
122. Conway A, Inglis SC, Clark RA. Effective technologies for noninvasive remote monitoring in heart failure. Telemed J E Health 2014;20:531-8.
123. Ledwidge MT, O'Hanlon R, Lalor L, Travers B, Edwards N, Kelly D, Voon V, McDonald KM. Can individualized weight monitoring using the HeartPhone algorithm improve sensitivity for clinical deterioration of heart failure? Eur J Heart Fail 2013;15:447-55.
124. Cuba Gyllensten I, Bonomi AG, Goode KM, Reiter H, Habetha J, Amft O, Cleland JG. Early Indication of Decompensated Heart Failure in Patients on Home-Telemonitoring: A Comparison of Prediction Algorithms Based on Daily Weight and Noninvasive Transthoracic Bio-impedance. JMIR Med Inform 2016;4:e3.
125. Chaudhry SI, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. Circulation 2007;116:1549-54.
126. Wakefield BJ, Ward MM, Holman JE, Ray A, Scherubel M, Burns TL, Kienzle MG, Rosenthal GE. Evaluation of home telehealth following hospitalization for heart failure: a randomized trial. Telemed J E Health 2008;14:753-61.
127. Capomolla S, Pinna GD, La Rovere MT, Maestri R, Ceresa M, Ferrari M. Heart failure case disease management program : A pilot study of home telemonitoring versus usual care. Eur Heart J Suppl 2004;6:F91-F8.
128. Kotb A, Cameron C, Hsieh S, Wells G. Comparative effectiveness of different forms of telemedicine for individuals with heart failure (HF): a systematic review and network meta-analysis. PLoS One 2015;10:e0118681.

129. Anker SD, Koehler F, Abraham WT. Telemedicine and remote management of patients with heart failure. Lancet 2011;378:731-9.
130. Dierckx R, Houben R, Goethals M, Verstreken S, Bartunek J, Saeys R, De Proft M, Boel E, Vanderheyden M. Integration of remote monitoring of device diagnostic parameters into a multidisciplinary heart failure management program. Int J Cardiol 2014;172:606-7.
131. Mabote T, Wong K, Cleland JG. The utility of novel non-invasive technologies for remote hemodynamic monitoring in chronic heart failure. Expert Rev Cardiovasc Ther 2014;12:923-8.
132. Albert NM. A systematic review of transitional-care strategies to reduce rehospitalization in patients with heart failure. Heart Lung 2016;45:100-13.
133. Sousa C, Leite S, Lagido R, Ferreira L, Silva-Cardoso J, Maciel MJ. Telemonitoring in heart failure: a state-of-the-art review. Rev Port Cardiol 2014;33:229-39.
134. Adamson PB. Pathophysiology of the transition from chronic compensated and acute decompensated heart failure: new insights from continuous monitoring devices. Curr Heart Fail Rep 2009;6:287-92.
135. Bourge RC, Abraham WT, Adamson PB, Aaron MF, Aranda JM, Jr., Magalski A, Zile MR, Smith AL, Smart FW, O'Shaughnessy MA, Jessup ML, Sparks B, Naftel DL, Stevenson LW, Group C-HS. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure: the COMPASS-HF study. J Am Coll Cardiol 2008;51:1073-9.
136. Ritzema J, Troughton R, Melton I, Crozier I, Doughty R, Krum H, Walton A, Adamson P, Kar S, Shah PK, Richards M, Eigler NL, Whiting JS, Haas GJ, Heywood JT, Frampton CM, Abraham WT, Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients Study G. Physician-directed patient self-management of left atrial pressure in advanced chronic heart failure. Circulation 2010;121:1086-95.
137. Kitsiou S, Pare G, Jaana M. Effects of home telemonitoring interventions on patients with chronic heart failure: an overview of systematic reviews. J Med Internet Res 2015;17:e63.
138. Joseph SM, Novak E, Arnold SV, Jones PG, Khattak H, Platts AE, Davila-Roman VG, Mann DL, Spertus JA. Comparable performance of the Kansas City Cardiomyopathy Questionnaire in patients with heart failure with preserved and reduced ejection fraction. Circ Heart Fail 2013;6:1139-46.
139. Tucker R, Quinn JR, Chen DG, Chen L. Kansas City Cardiomyopathy Questionnaire Administered to Hospitalized Patients With Heart Failure. J Nurs Meas 2016;24:245-57.
140. Chen HY, Baumgardner DJ, Rice JP. Health-related quality of life among adults with multiple chronic conditions in the United States, Behavioral Risk Factor Surveillance System, 2007. Prev Chronic Dis 2011;8:A09.
141. Heo S, Lennie TA, Okoli C, Moser DK. Quality of life in patients with heart failure: ask the patients. Heart Lung 2009;38:100-8.
142. Kelkar AA, Spertus J, Pang P, Pierson RF, Cody RJ, Pina IL, Hernandez A, Butler J. Utility of Patient-Reported Outcome Instruments in Heart Failure. JACC Heart Fail 2016;4:165-75.

143. Dreyer RP, Jones PG, Kutty S, Spertus JA. Quantifying clinical change: discrepancies between patients' and providers' perspectives. Qual Life Res 2016;25:2213-20.
144. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. Circulation 1981;64:1227-34.
145. Raphael C, Briscoe C, Davies J, Ian Whinnett Z, Manisty C, Sutton R, Mayet J, Francis DP. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. Heart 2007;93:476-82.
146. Anker SD, Agewall S, Borggrefe M, Calvert M, Jaime Caro J, Cowie MR, Ford I, Paty JA, Riley JP, Swedberg K, Tavazzi L, Wiklund I, Kirchhof P. The importance of patient-reported outcomes: a call for their comprehensive integration in cardiovascular clinical trials. Eur Heart J 2014;35:2001-9.
147. Rahimi K, Malhotra A, Banning AP, Jenkinson C. Outcome selection and role of patient reported outcomes in contemporary cardiovascular trials: systematic review. BMJ 2010;341:c5707.
148. Psotka MA, von Maltzahn R, Anatchkova M, Agodoa I, Chau D, Malik FI, Patrick DL, Spertus JA, Wiklund I, Teerlink JR. Patient-Reported Outcomes in Chronic Heart Failure: Applicability for Regulatory Approval. JACC Heart Fail 2016;4:791-804.
149. Sepehrvand N, Ezekowitz JA. How to Do More With Less. Circ Cardiovasc Qual Outcomes 2015;8:460-2.
150. Eurich DT, Johnson JA, Reid KJ, Spertus JA. Assessing responsiveness of generic and specific health related quality of life measures in heart failure. Health Qual Life Outcomes 2006;4:89.
151. Farkas J, Pahor M, Zaletel-Kragelj L. Self-rated health in different social classes of Slovenian adult population: nationwide cross-sectional study. Int J Public Health 2011;56:45-54.
152. Spertus JA, Jones PG. Development and Validation of a Short Version of the Kansas City Cardiomyopathy Questionnaire. Circ Cardiovasc Qual Outcomes 2015;8:469-76.
153. Deshpande PR, Rajan S, Sudeepthi BL, Abdul Nazir CP. Patient-reported outcomes: A new era in clinical research. Perspect Clin Res 2011;2:137-44.
154. Dai S, Manoucheri M, Gui J, Zhu X, Malhotra D, Li S, D'Souza J, Virkram F, Chada A, Jiang H. Kansas City Cardiomyopathy Questionnaire Utility in Prediction of 30-Day Readmission Rate in Patients with Chronic Heart Failure. Cardiol Res Pract 2016;2016:4571201.
155. Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI, Barreto-Filho JA, Kim N, Bernheim SM, Suter LG, Drye EE, Krumholz HM. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. JAMA 2013;309:355-63.
156. Harrell FE, Jr., Lee KL, Matchar DB, Reichert TA. Regression models for prognostic prediction: advantages, problems, and suggested solutions. Cancer Treat Rep 1985;69:1071-77.

157. Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. Ann Intern Med 1999;130:515-24.
158. Steyerberg EW, Eijkemans MJ, Habbema JD. Stepwise selection in small data sets: a simulation study of bias in logistic regression analysis. J Clin Epidemiol 1999;52:935-42.
159. Steyerberg EW, Eijkemans MJ, Harrell FE, Jr., Habbema JD. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. Stat Med 2000;19:1059-79.
160. Bleeker SE, Moll HA, Steyerberg EW, Donders AR, Derksen-Lubsen G, Grobbee DE, Moons KG. External validation is necessary in prediction research: a clinical example. J Clin Epidemiol 2003;56:826-32.

Appendices

Appendice 1: Belgian French version of the Kansas City Cardiomyopathy Questionnaire

Questionnaire sur l'insuffisance cardiaque (Kansas City)

Ce questionnaire concerne votre **insuffisance cardiaque** et les effets qu'elle peut avoir sur votre vie de tous les jours. Veuillez lire et compléter les questions suivantes. Il n'y a pas de bonnes ou mauvaises réponses. Choisissez simplement la réponse qui correspond le mieux à votre cas.

1. L'**insuffisance cardiaque** affecte différentes personnes de différentes manières. Certains souffrent d'essoufflements, tandis que d'autres ressentent de la fatigue. Veuillez indiquer dans quelle mesure votre **insuffisance cardiaque** (par exemple, essoufflement ou fatigue) vous a limité(e) dans votre capacité à faire les activités suivantes au cours des 2 dernières semaines.

Cochez (**X**) une seule case par ligne

Activité	**Extrêmement** limité(e)	**Nettement** limité(e)	**Moyennement** limité(e)	**Un peu** limité(e)	**Pas du tout** limité(e)	**Limité(e) pour d'autres raisons ou n'ai pas fait cette activité**
Vous habiller	☐	☐	☐	☐	☐	☐
Prendre une douche/un bain	☐	☐	☐	☐	☐	☐
Marcher environ 100 mètres sur terrain plat	☐	☐	☐	☐	☐	☐
Faire du jardinage, le ménage, ou porter les courses	☐	☐	☐	☐	☐	☐
Monter une volée d'escalier	☐	☐	☐	☐	☐	☐
Faire du jogging ou vous dépêcher (comme pour ne pas manquer un bus)	☐	☐	☐	☐	☐	☐

2. Par rapport à il y a 2 semaines, vos symptômes d'**insuffisance cardiaque** (par exemple, essoufflement, fatigue ou gonflement des chevilles) ont-ils changé ?

Ceux-ci :

Se sont fortement aggravés	Se sont un peu aggravés	N'ont pas changé	Se sont un peu améliorés	Se sont fortement améliorés	Pas de symptôme ces 2 dernières semaines
☐	☐	☐	☐	☐	☐

KCCQ – Belgium/French

3. Ces 2 dernières semaines, combien de fois vous êtes-vous réveillé(e), le matin, avec les chevilles, les jambes ou les pieds **gonflés** ?

Tous les matins	Au moins 3 fois par semaine mais pas tous les jours	1 à 2 fois par semaine	Moins d'une fois par semaine	Pas une fois ces 2 dernières semaines
☐	☐	☐	☐	☐

4. Ces 2 dernières semaines, dans quelle mesure avez-vous été gêné(e) par le **gonflement** de vos pieds, chevilles ou jambes ?

   Ce gonflement a été :

Extrêmement gênant	**Nettement** gênant	**Moyennement** gênant	**Un peu** gênant	**Pas du tout** gênant	**Pas de gonflement**
☐	☐	☐	☐	☐	☐

5. Ces 2 dernières semaines, en moyenne, combien de fois la **fatigue** a-t-elle limité votre capacité à faire ce que vous vouliez ?

Tout le temps	Plusieurs fois par jour	Au moins une fois par jour	Au moins 3 fois par semaine mais pas tous les jours	1 à 2 fois par semaine	Moins d'une fois par semaine	Pas une fois ces 2 dernières semaines
☐	☐	☐	☐	☐	☐	☐

6. Ces 2 dernières semaines, dans quelle mesure la **fatigue** vous a-t-elle gêné(e) ?

   Cette fatigue a été :

Extrêmement gênante	**Nettement** gênante	**Moyennement** gênante	**Un peu** gênante	**Pas du tout** gênante	**Pas de fatigue**
☐	☐	☐	☐	☐	☐

7. Ces 2 dernières semaines, en moyenne, combien de fois un **essoufflement** a-t-il limité votre capacité à faire ce que vous vouliez ?

Tout le temps	Plusieurs fois par jour	Au moins une fois par jour	Au moins 3 fois par semaine mais pas tous les jours	1 à 2 fois par semaine	Moins d'une fois par semaine	Pas une fois ces 2 dernières semaines
☐	☐	☐	☐	☐	☐	☐

KCCQ – Belgium/French

8. Ces 2 dernières semaines, dans quelle mesure votre **essoufflement** vous a-t-il gêné(e) ?

Cet essoufflement a été :

Extrêmement gênant	**Nettement** gênant	**Moyennement** gênant	**Un peu** gênant	**Pas du tout** gênant	**Pas d'essoufflement**
☐	☐	☐	☐	☐	☐

9. Ces 2 dernières semaines, en moyenne, combien de fois avez-vous dû dormir assis(e) dans un fauteuil ou soutenu(e) par au moins 3 oreillers à cause de problèmes d'**essoufflement** ?

Toutes les nuits	Au moins 3 fois par semaine mais pas toutes les nuits	1 à 2 fois par semaine	Moins d'une fois par semaine	Pas une fois ces 2 dernières semaines
☐	☐	☐	☐	☐

10. Les symptômes d'**insuffisance cardiaque** peuvent s'aggraver pour diverses raisons. Dans quelle mesure êtes-vous sûr(e) de savoir quoi faire ou qui appeler si votre **insuffisance cardiaque** s'aggrave ?

Pas du tout sûr(e)	**Pas très** sûr(e)	**Assez** sûr(e)	**Presque** sûr(e)	**Tout à fait** sûr(e)
☐	☐	☐	☐	☐

11. Dans quelle mesure comprenez-vous ce que vous pouvez faire pour éviter que les symptômes liés à **votre insuffisance cardiaque s'aggravent** (par exemple, vous peser régulièrement, suivre un régime pauvre en sel, etc.) ?

Je ne comprends pas du tout	Je ne comprends pas très bien	Je comprends assez bien	Je comprends plutôt bien	Je comprends très bien
☐	☐	☐	☐	☐

12. Ces 2 dernières semaines, dans quelle mesure votre **insuffisance cardiaque** vous a-t-elle empêché(e) de profiter de la vie ?

Enormément	**Beaucoup**	**Moyennement**	**Un peu**	**Pas du tout**
☐	☐	☐	☐	☐

13. Si vous deviez passer le reste de votre vie dans votre état actuel d'**insuffisance cardiaque**, quel serait votre sentiment à ce sujet ?

Pas du tout satisfait(e)	Plutôt insatisfait(e)	Assez satisfait(e)	Plutôt satisfait(e)	Tout à fait satisfait(e)
☐	☐	☐	☐	☐

14. Ces 2 dernières semaines, vous êtes vous senti(e) découragé(e) ou déprimé(e) à cause de votre **insuffisance cardiaque** ?

Tout le temps	**La plupart du temps**	**De temps en temps**	**Rarement**	**Jamais**
☐	☐	☐	☐	☐

15. Dans quelle mesure votre **insuffisance cardiaque** affecte-t-elle votre mode de vie ? Merci de bien vouloir indiquer comment votre **insuffisance cardiaque** a pu limiter votre participation aux activités suivantes, au cours des 2 dernières semaines.

Cochez (**X**) une seule case par ligne

Activité	**Extrêmement** limité(e)	**Nettement** limité(e)	**Moyennement** limité(e)	**Un peu** limité(e)	**Pas du tout** limité(e)	**Limité(e) pour d'autres raisons ou n'ai pas fait cette activité**
Loisirs et hobbies	☐	☐	☐	☐	☐	☐
Activités professionnelles ou tâches ménagères	☐	☐	☐	☐	☐	☐
Rendre visite à des parents ou à des amis	☐	☐	☐	☐	☐	☐
Relations intimes ou sexuelles	☐	☐	☐	☐	☐	☐

Appendice 2: TRIPOD statement

Section/Topic		Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	1-2
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	2
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	2
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	2
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	2
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	2
	5b	Describe eligibility criteria for participants.	2
	5c	Give details of treatments received, if relevant.	NA
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	3
	6b	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	3-4
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	3
Sample size	8	Explain how the study size was arrived at.	-
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	NA
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	4
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	4
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	4
Risk groups	11	Provide details on how risk groups were created, if done.	NA
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	6
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	7
Model development	14a	Specify the number of participants and outcome events in each analysis.	7
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	9
Model specification	15a	Present the full prediction model to allow predictions for individuals (all regression coefficients, and model intercept or baseline survival at a given time point).	8 & 10
	15b	Explain how to the use the prediction model.	8 & 10
Model performance	16	Report performance measures (with CIs) for the prediction model.	11
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	12
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	10-11
Implications	20	Discuss the potential clinical use of the model and implications for future research.	11-12
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	NA
Funding	22	Give the source of funding and the role of the funders for the present study.	-