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REVIEW

Journal of Cardiology Research

New- and Next-Generation of Telemedicine Projects and Studies in Chronic Heart Failure, with the Example of TIM-HF2 and E-Care

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Abstract

Since the beginning of the 2000's, several telemedicine projects and studies that focused on chronic heart failure have been developed with various clinical results. Numerous new and next-generation telemedicine projects have emerged in Europe over the last five years or are still under development as for computer science heart failure, especially in Europe. TIM-HF2 is the first positive prospective randomized study in regards of evidence-based medicine with positive significant clinical benefit, in terms of unplanned cardiovascular hospital admissions and all-cause deaths. The E-care telemonitoring project fits within the telemedicine 2.0 framework, based on connected objects, new Information and Communication Technologies (ICT) and Web 2.0 technologies. E-care is the first telemedicine project including Artificial Intelligence (AI). In this setting, the potential contribution of new- and next-generation telemedicine projects in terms of mortality, morbidity, and number of hospitalizations avoided is currently under study. Their impact in terms of health economics is likewise being investigated, taking into account that the economic and social benefits brought up by telemedicine solutions had previously been validated by the first-born telemedicine projects.

Keywords: *telemedicine, telemonitoring, artificial intelligence, information and communication technology, web, heart failure*

Introduction

ATo date, despite major therapeutic advances, chronic heart failure (CHF) remains serious in terms of functional or survival prognosis, with high morbidity and mortality rates [1]. In France, the number of deaths directly related to CHF is estimated at 23,000 deaths per year [2]. In this context, patients suffered from Classes III and IV New York Heart Association (NYHA) CHF, frequently present for emergency hospitalization and re-hospitalization with long hospital stays, resulting in an impaired quality of life [2]. In France, Heart Failure (HF) is responsible for more 210,000 hospitalizations per year [2], accounting for 5% of all hospitalizations.

Many of these hospitalizations could be avoided if patients took greater responsibility for their disease, were appropriately educated, and were better followed [1]. In this setting, telemedicine may be of significant help, given that it can be instrumental in optimizing CHF management, particularly by preventing emergencies such as acute HF and repeated iterative hospitalizations. Of note is that the re-hospitalization rate is 55% per year in France, which is the main evaluation end point for most telemedicine studies [3]. Likewise, telemedicine may help make it possible to better structure integrated care pathway, again with the most important evidence to be found in CHF management.

In this setting, we realized a short narrative review on the new- and next-generation of telemedicine projects and studies in CHF, with a focus on the TIM-HF2 study and the E-care project.

Since the beginning of the 2000's, several telemedicine projects and studies have been conducted in the HF field [3,4]. Most of them have investigated "*telemonitoring*" [3-5]. To the best of our knowledge, no completed projects have been published on "*teleconsultation*" and "*teleexpertise*" in the HF field, including an evaluation of the contribution of these two fields. It should be kept in mind that these projects and studies, particularly the earlier ones, more closely resembled a "*telephone follow-up*", with care providers (e.g., nurses) traveling to patient's homes, rather than the use of telemedicine as we think of it today with nonintrusive, automated, smart telemonitoring using remote sensors via modern communication technologies, *Web 2.0* tools, or even Artificial Intelligence (AI) [5].

As will be recalled, the results of telemedicine projects conducted so far in the CHF field differed from study to study, with fairly inconclusive results as far as potential clinical benefits in terms of re-hospitalization and decreased morbidity or mortality [3-5] and, in particular, the statistical significance of the results. As such, experts presently share widely divergent opinions on the actual utility of telemedicine in CHF patient management. Despite

a number of limitations, several reviews and meta-analyses have demonstrated the undeniable utility of telemedicine [3,4].

The 2016 *European Society of Cardiology* (ESC) guidelines for the diagnosis and treatment of acute and chronic HF were the first to recommend remote patient monitoring of CHF patients with a recommendation of Grade IIb and level of evidence B [6].

Over the last five years, new- and next-generation telemedicine projects and studies have emerged in the HF field, particularly in Europe [5]. Several of these projects are included in the field of "*telemedicine 2.0*", given that they all utilize new Information and Communication Technologies (ICT) as well as *Web 2.0* (tools for "e-Health 2.0") [7]. In Europe, especially in France, Italy, Spain and Germany, numerous experiments on CHF telemanagement have been conducted or are still ongoing [3-5].

Most new- and next-generation projects and studies rely on the standard connected tools for monitoring HF, such as blood pressure meters, heart rate monitors, weighing scales and pulse oximeters, which relay the collected information via Bluetooth, 3G or 4G [4,5].

Most of these projects also incorporate the following:

- Self-administered medical questionnaires or forms (symptoms and signs of HF);
- Tools for medical education, particularly disease self-appropriation, food hygiene, and physical activity (e.g. serious game);
- Tools for patient motivation (e.g. serious game);
- Tools for therapeutic (e.g. electronic pillbox) and hygiene observance;
- Tools for interaction between the patient and healthcare professionals like telephone support centers, tablets, and websites [3-5].

Thus, several projects (e.g., OSICAT, PIMS, E-Care [*for review see the reference* [5]]0/, ,8) provide questionnaires or forms regarding HF signs and symptoms such as dyspnea, palpitations, edema, and fatigue corresponding to the acronym EPOF, namely "*Essoufflement, prise de Poids, oEdèmes, and Fatigue*", as experienced by the patient. Rare project additionally includes laboratory monitoring of natriuretic peptides (e.g., PIMS) (*for review see the reference* [5]). A few projects also include ECG monitoring and even video-conferencing (e.g. TIM-HF2, E-care [*for review see the reference* [5]]).

All previously cited projects also include ICT and Web 2.0 technologies (e.g. TIM-HF2, E-care [*for review see the reference* [5]]). A few of these telemedicine projects use machine learning in order to predict patient risks of acute HF or acute CHF decompensation [8,9]. In this setting, the cloud-based software aggregates, cleans and analyzes patient data to identify patterns that may indicate potential risks and to provide predictive insights on healthcare outcomes, such as the software *MyPredi™* for the E-care project [10].

In addition, HF telemonitoring may use implantable invasive devices that send data either intermittently or continuously to the receiving physician (e.g., automatic telemonitoring). These are outside the scope of this paper [11]. In CHF, implantable telemonitoring devices for multiple parameters or cardiac hemodynamic activity monitoring have recently proven to be an effective means for preventing frequent hospitalizations.

Recently, Koehler and colleagues reported the results of the large home telemonitoring study for HF in *The Lancet, namely The Telemedical Interventional Management in Heart Failure II* (TIM-HF2) [12]. This is the first evidence-based medicine study clearly showing that remote patient management over the course of twelve months reduced the number of days lost due to unplanned cardiovascular hospital admissions, with the differences between groups being statistically significant and clinically relevant. Home telemonitoring triggered several potentially life-saving hospital admissions and overall slightly reduced the number of days patients were hospitalized due to HF. The percentage of days lost due to unplanned cardiovascular hospital admissions and all-cause deaths (primary end point) was 4.88% (95% CI 4.55-5.23) in the remote patient management group vs. 6.64% (6.19-7.13) in the standard care group (ratio 0.80, 95% CI: 0.65-1; p = 0.0460). Patients assigned to remote patient management lost a mean of 17.8 days (95% CI: 16.6-19.1) per year compared with 24.2 days (95% CI: 22.6-26) per year for patients assigned to standard care. The all-cause death rate was 7.86 (95% CI: 6.14-10.10) per 100 person years of follow-up in the remote patient management group vs. 11.34 (95% CI: 9.21-13.95) per 100 person years of follow-up in the standard care group (Hazard Ratio [HR] 0.70, 95%CI: 0.5-0.96; p = 0.0280). Cardiovascular mortality did not significantly differ between groups (HR 0.671, 95%CI: 0.45-1.01; p = 0.056).

For this TIM-HF2 care strategy, the key component was a well-structured telemedical center with physicians and HF nurses ("coordination center") available 24 hours a day and 7 days a week with the ability to act promptly according to the individual patient risk profile [12]. The actions taken by the telemedical center staff included changes in medication and admissions to the hospital as needed, in addition to educational activities. The study used a noninvasive, multi-parameter telemonitoring system installed in the patient's home, consisting of a three-channel ECG, a blood pressure monitoring device and a weight scale, by means of which the information were transferred remotely [12]. Patients received a mobile phone in order to contact the telemedical center in case of emergency. Patients were likewise followed via monthly phone interviews.

The E-care telemonitoring project, conducted in Strasbourg was developed to consolidate the positive results of telemonitoring in term of hospital readmission (one of the leading problem for CHF patient) [13,14]. E-care falls under the "*telemedicine 2.0*" category. It has been developed and designed to optimize home monitoring of CHF patients by detecting, via a telemonitoring 2.0 platform, situations having a risk of cardiac decompensation and re-hospitalization [13]. The AI of the E-care platform (*MyPredi™*) automatically generates indicators of "health status" deterioration, i.e., "warning alerts" for any chronic disease worsening, particularly CHF, that may lead to hospitalization if not treated properly. To our knowledge, this is the first project to use AI in addition to ICT.

The platform consists of connected, non-intrusive medical sensors (Figure 1), a touchscreen tablet connected to Wi–Fi, and a router or 3G/4G, making it possible to interact with the patient and provide education on treatment, diet and lifestyle [13].

The system (Figure 2) involves a server that hosts the patient's data and a secure internet portal to which the patient and hospital as well as non–hospital based healthcare professionals can connect [13].

Figure 1: *E-care's connected non-intrusive medical sensors.*

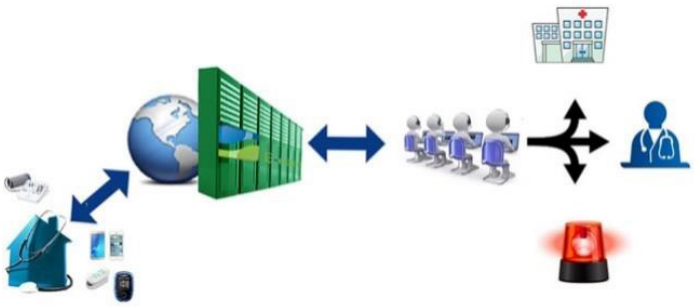

Figure 2: *E-care platform.*

E-care is based on a smart system consisting of an inference engine and medical ontology for personalized synchronous or asynchronous analysis of data that is specific to each patient with, as necessary, the sending of an AI-generated alert (*MyPredi*™) [13].

Between February 2014 and April 2015, 175 patients were included in the E-care project [14]. During this period, the E-care platform was used on a daily basis by patients and healthcare professionals, according to a defined protocol of use specific to each patient. The mean age of these patients was 72 years, and the ratio of men to women was 0.7. The patients suffered from multiple concomitant diseases, with a mean *Charlson index* (comorbidity index validated and often used for the elderly) of 4.1. The five main diseases were: CHF (in more than 60% of subjects), anemia (in more than 40% of subjects), atrial fibrillation (in 30% of subjects), type 2 diabetes (in 30% of subjects) and chronic obstructive pulmonary disease (COPD, in 30% of subjects). During the study, 1,500 measurements were taken in these 175 patients, which resulted in the E-care system generating 700 alerts for 68 patients [14]. Some 107 subjects (61.1%) had no alerts during follow-up. Follow-up data analysis of these 107 patients revealed that they exhibited no clinically significant events that might eventually have led to hospitalization. Analysis of the warning alerts showed that the E-care platform automatically and non-intrusively detected a worsening of the patient's health, particularly HF decompensation (between two to nine days), with a sensitivity, specificity, as well as positive and negative predictive values of 100%, 72%, 90% and 100%, respectively. Both the healthcare professionals and patients, even the frailest, used the E-care system without difficulty until the end of the study. For non-autonomous patients, the system was employed by a nurse in addition to his or her other assigned tasks, such as bathing and administering medication, or by family members and others close to the patient.

To date, an enhanced version of the E-care platform and *MyPredi*™ AI is scheduled to be tested in CHF patients' homes, as part of the so-called PRADO-INCADO project. PRADO is a French program to support patients returning home after hospitalization, with PRADO-INCADO specifically targeting the post-hospitalization period of HF patients [14]. Over a period of several months, 200 patients with NYHA Class II to IV HF will be followed-up by means of the PRADO organizational model developed by the national health insurance administration for HF patients (to date, n = 35). For recruitment, the project will benefit from the HF care protocol that includes cardiologists, internists, emergency physicians and geriatricians from the Strasbourg University Hospital. Here again, no draconian selection of patients will occur. Instead, patients will be gradually enrolled so that they are deemed representative of CHF subjects across France. Within this care protocol, the mean age of patients we are likely to enroll is 82 years. Both morbidity and mortality data from the 100 patients using the telemedicine solution will be compared to those of patients enrolled into the PRADO program (n = 100), as well as to those of patients eligible for neither the PRADO-INCADO project nor the PRADO program, representing the control group (n = 100). The first results are expected to be available during the first quarter of 2019.

The patients will likely originate from the greater Strasbourg area. In addition to its medical objectives, the PRADO-INCADO project also includes features having to do with cost analyses and organizational aspects concerning patient care pathways and the implementation of the solution by both patients and healthcare professionals.

The data derived from the PRADO INCADO project is to be augmented with data from the patient's environment along with the patient's profile, including prior history, medication, and adherence to treatment, diet, and lifestyle guidelines, as well as the use of the system itself. The merging of this data will likely render the telemonitoring system more effective [5,10,14]. This phase should represent an in-depth study enabling us to improve diagnosis by aided machine learning and therefore to detect abnormalities at an earlier stage.

This is in keeping with the research of Mortazavi et al. on the utility of AI in managing HF patients, and particularly the possibility afforded by AI for predicting re-hospitalization for acute HF [8].

To our opinion, these new- and next-generation of telemedicine solutions may the elements of the birth of "*Tomorrow's Medicine*"

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Funding

Grants from the Fondation de l'Avenir, the Agence Régionale de Santé du Grand-Est (ARS) and the Agence Nationale de la Recherche (ANR).

Conflicts of Interest

M. Hajjam is the scientific director of Predimed Technology. All other authors have declared that no competing interests exist.

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Rec: May 10, 2019; Acc: May 24, 2019; Pub: June 07, 2019

J Cardio Res. 2019;2(2):19
DOI: gsl.jcr.2019.000019