HEARTEN KMS – A knowledge management system targeting the management of patients with heart failure

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Abstract

The aim of this work is to present the HEARTEN Knowledge Management System, one of the core modules of the HEARTEN platform. The HEARTEN platform is an mHealth collaborative environment enabling the Heart Failure patients to self-manage the disease and remain adherent, while allowing the other ecosystem actors (healthcare professionals, caregivers, nutritionists, physical activity experts, psychologists) to monitor the patient's health progress and offer personalized, predictive and preventive disease management. The HEARTEN Knowledge Management System is a tool which provides multiple functionalities to the ecosystem actors for the assessment of the patient's condition, the estimation of the patient's adherence, the prediction of potential adverse events, the calculation of Heart Failure related scores, the extraction of statistics, the association of patient clinical and non-clinical data and the provision of alerts and suggestions. The innovation of this tool lays in the analysis of multi-parametric personal data coming from different sources, including for the first time breath and saliva biomarkers, and the use of machine learning techniques. The HEARTEN Knowledge Management System consists of nine modules. The accuracy of the KMS modules ranges from 78-95% depending on the module/functionality.

Keywords: heart failure, knowledge management system, machine learning, classification, prediction, adherence, self-management

Introduction

Heart Failure (HF) is characterized as a complex syndrome, rather than a disease, impairing the heart ventricle to fill or eject blood. It is a progressive, life threatening condition associated with high mortality rates, poor quality of file and increased direct and indirect healthcare costs. The increasing prevalence of HF in combination with the escalated costs and the above mentioned severe consequences: (i) transform HF to an epidemic in Europe and worldwide, (ii) intensify the need for effective, efficient and personalized management, (iii) necessitate the empowerment of the HF patients to be adherent to medication treatment, nutrition and physical activity suggestions provided by the experts (experts include the healthcare professional, the nutritionist, the physical activity expert and the psychologist). HF patients receive treatment suggestions related to medication, nutrition and physical activity. Lack of adherence is common, resulting to destabilizations, re-hospitalizations and adverse events including death [1].

Towards this direction, several studies focusing on HF management have been presented in the literature, either based on machine learning approaches which address (separately or in combination) early diagnosis of HF [2-18], HF subtype recognition [19-21], severity estimation [22-28], prediction of adverse events [24, 29-47], adherence estimation [48] or mHealth solutions developed for the monitoring and management the of HF patients [1].

In most of the studies the diagnosis of HF has been achieved mainly by utilizing only heart rate variability (HRV) measures [2-13], while some studies combine HRV measures with anamnestic and instrumental data [14-18]. The above mentioned data are given as input to different classifiers, such as Support Vector Machines, Classification and Regression Trees, Random Forests, etc.. The characterization of the type of HF (HF with reduced ejection fraction *vs.* HF with preserved ejection fraction) is addressed as a two class classification problem. The studies presented in the literature do not include in the datasets patients belonging to the so called “gray zone” (i.e. HF with mid-range ejection fraction) or they merge this group of patients with one of the other types of HF mentioned above [19-21]. The severity estimation is expressed either as mild, moderate, severe or in terms of New York Heart Association (NYHA) classes. The definition of the characterizations as mild, moderate and severe is differentiated between the studies depending on how the merging of the NYHA class has been performed. For example, in some studies patients with severe HF belong to NYHA class III or IV, while in some other belong to NYHA class IV only [15, 22-28]. The prediction of HF adverse events has gained the interest of researchers that developed predictive models for destabilization, re-hospitalization and mortality of HF patients. In those studies for each category of prediction, as well as between the different categories, the time frame of prediction varies from short term (one to three months) to long term (up to 5 years) [24, 29-47]. A detailed review and comparison of those studies is presented in [49].

The evolution of mHealth solutions for HF management and other chronic diseases is based on the uptake of information and communication technologies and the advent of mobile solutions. mHealth solutions allow the collection of a variety of data (lifestyle, sensor, biosensor, health-related and environmental information), the analysis of these data, the extraction of meaningful information, the transformation of the information to actionable knowledge for the HF disease. A review the available mHealth solutions, in the form of the commercial applications, research projects, or related studies is provided in [1]. According to this review, it is evident that mHealth: (i) offers personalized services for predictive, collaborative and preventive care, (ii) contributes to more accessible, better and reliable disease management, and (iii) is able to transform and improve the traditional delivery of healthcare through continuously monitoring the heart condition of the patient. However, several challenges concerning patients, healthcare professionals, payers, providers, and regulatory bodies should be addressed. The fragmented use of information in existing approaches does not allow mHealth to reveal its real potential. On the other side, the use of personal data directly from individuals can significantly support the adoption of such systems and, consequently, patient empowerment. The application of a multidisciplinary approach can contribute significantly towards the tackling of the above mentioned challenges and can maximize the impact of the mHealth solutions.

In this framework, the HEARTEN Knowledge Management System (KMS), a part of the HEARTEN platform, is a novel multi-purpose and multifunctional computational platform that is based on a variety of HF related data, among of which, are biomarkers extracted from saliva and breath biosensors, a major novelty of the proposed KMS. It enables the users to effectively assess and exploit real patient data. The HEARTEN KMS includes advanced data-driven techniques incorporated with expert-knowledge techniques towards effectively, automatically assessing the HF patient condition and risks and enhancing patient adherence. With this aim, data processing and mining approaches have been designed, tested and implemented into an integrated environment that provides multiple functionalities to the users to optimize the management of the HF patients. These functionalities cover all the patient pathways, starting from the first visit to the healthcare professional until the monitoring of the daily activities and the follow up visits and they are provided through nine different modules.

The HEARTEN KMS modules are capable to perform computational processes and support the healthcare community employing data mining techniques on a large amount of patient-specific sensor, biosensor, clinical and personal data. Through data mining/analysis techniques, the HEARTEN KMS effectively combines different types of patient data collected by other components of the HEARTEN platform and provides estimations on the patient health status (through an objective, data driven estimation of NYHA class), the risk of non-adherence, the actual adherence levels (in terms of medication, nutrition and physical activity), and the risk for adverse events. It also allows for statistical analysis, hypothesis testing and supports research. Alerts are generated when needed (*e.g.* patient deterioration, adverse event prediction, *etc.*) and sent to the relevant ecosystem actors including of course the patient himself when this is considered appropriate following a specific protocol.

The proposed KMS is evaluated on a dataset of 136 patients. The performance of each module is presented in the results section and it is compared with other existing in the literature studies which address the same problems (evaluation of HF severity, estimation of adherence profile of the patients, evaluation of treatment adherence, early prediction of adverse events etc.), either separately or in combination. Comparison confirms that the major innovations of the proposed KMS are the use of the saliva and breath biomarkers, the incorporation of several heterogeneous data, some of them recorded in a daily basis and the objective estimation of patient condition and adherence levels through machine learning techniques. In this way, the patients' daily life-status information is collected and processed, and the patient gets empowered having a central role in (self-) managing of his/her disease.

The following sections provide a short description of the HEARTEN platform, a detailed presentation of the HEARTEN KMS, information about the dataset that is utilized for the evaluation of the HEARTEN KMS, and the results that are produced from each module. Finally, a discussion section presenting a comparison of the HEARTEN KMS with relevant studies in the literature is provided.

Materials and Methods

HEARTEN Platform

HEARTEN is an integrated mHealth collaborative platform that engages all ecosystem actors: the HF patients, their caregivers, the experts. It facilitates their intercommunication and tight collaboration for effective and efficient monitoring and management of the HF patients. HEARTEN aims at improving the management of HF, empowering the patient and increasing adherence to treatment plan. HEARTEN uses sensors to record patient vital signs and activity, novel saliva and breath biosensors to monitor the status of the disease and knowledge management/machine learning techniques to evaluate the patient status based on sensor, biosensor and clinical data. Data collection is done at a home environment and a mobile application serves as the main interaction interface with the patient while the respective actors (i.e. patient, clinician, caregiver, nutritionist, physical activity expert, etc.) are informed on the patient status, progress and adherence, accordingly.

The architecture of the HEARTEN platform is depicted in Fig. 1 and includes: (i) the wearable sensors, (ii) the biosensors, (iii) the two databases (Relational database and NoSQL database), (iv) the mobile application, (v) the web application, (vi) the Cloud infrastructure, (viii) the Knowledge Management System, and (vii) the Dynamic Patient Communication Protocol (DynPCP).

In order to monitor the HF patient, different wearable sensors as well as saliva and breath biosensors are employed in the home environment. Specifically, the *wearable sensors* record the blood pressure, the heart rate and potential arrhythmias (type o arrhythmias) along with the respiratory rate, the body temperature, the body weight and other relevant features (body fat percentage, skeletal muscle percentage, body mass index, resting metabolism), etc. and the physical activity (note: the CE marked Winmedical Winpack [50] system is used). The *biosensors* measure the concentration of acetone in breath and the TNF-α and cortisol in saliva. The *Mobile Application* acts as the mean of collecting information, providing alerts, notifications and educational information to the corresponding users through usable, clean and simple to use interfaces. The *Mobile Application* is the communication tool between the HEARTEN ecosystem actors. The *Web Application* provides to the experts extended functionality for data management. The *Databases* host the heterogeneous data collected in the HEARTEN platform. More specifically, a Relational database hosts the data related to the users and a NoSQL database stores all the data retrieved from the sensors and biosensors. The *Cloud infrastructure,* supporting scalability and performance, is composed of 6 virtual machines for the KMS server, the Web Application server, the DynPCP server, the MySQL database server, the MongoDB server and the REST server. The K*nowledge Management System* analyses the multi-disciplinary data and transforms them to clinical meaningful knowledge, whereas the *Dynamic Patient Communication Protocol (DynPCP)* combines the output of KMS with patient data and produces messages, notifications, alerts to the corresponding actors of the HEARTEN platform by using the predefined patient communication protocols.

HEARTEN Knowledge Management System

The HEARTEN KMS consists of nine modules: the Score module, the Adherence risk module, the NYHA class module, the Treatment adherence module, the Event prediction module, the Association module, the Statistics module, the Monitoring-Reporting module and the KMS alerting mechanism module. Fig. 2 presents the architecture of the HEARTEN KMS, while the interaction between the modules and their activation in time is presented, through the "patient journey" (first visit to the doctor, monitoring of daily activities, follow-up visits), in Fig. 3.

Score module

Once a patient performs the first visit to the healthcare professional, demographic information, medical condition of the patient, clinical examination, lab test results and medication and the following acknowledged scores are recorded/calculated: (i) the European Heart Failure Self-care Behaviour Scale 12-item scale (EHFScBS-12) [51], which evaluates HF self-care, (ii) the Dutch Heart Failure Knowledge score (DHFKS) [52], which is related to HF knowledge in general, knowledge on HF treatment (including diet and fluid consumption), symptoms identification and occurrence, (iii) the Get With The Guidelines (GWTG) [53], which estimates the in-hospital mortality, (iv) the Seattle Heart Failure Model (SHFM) [54, 55], which predicts the 1-, 2-, and 3-year survival of HF patients, and (v) the Minnesota Living with Heart Failure [56], which provides feedback regarding the physical and emotional status of the HF patient.

Adherence risk module

The Adherence risk module provides an estimation of the adherence profile of the patient. More specifically, the module informs the experts about the expected levels of adherence in terms of medication and overall adherence (medication, nutrition and exercising). This information allows them to pay attention to this specific patient according to the expected adherence and modify the treatment plan in terms of frequency of exams, schedule of visits etc.. Furthermore, the caregiver of the patient taking into account the output of the *Adherence risk module* can adjust the frequency and the intensity of care-attention which must be provided to the patient. In order this to be achieved, the Random Forests algorithm is employed classifying the patient as low, medium or high non-adherence risk, in terms of medication and overall.

The medication adherence has been poorly studied in the past through the utilization of a machine learning approach. Son *et al.* [48] identified predictors of adherence, related to socioeconomic factors, which are used as input to Support Vector Machine classifier to classify a patient as medication adherent or not. However, the *Adherence risk module* is differentiated from the above mentioned study, since it examines the contribution of additional factors, such as the medical condition, the clinical examination, the lab measurements, as well as socio-demographic information. Furthermore, it addresses the adherence estimation as a three class problem estimating not only if the patient is adherent or not but also the level of adherence (low, medium, high).

NYHA class module

At the end of the first visit the healthcare professional has a clear view of the patient's health condition, as well as an estimation of his/her adherence profile (through the Adherence risk module), of the risk to have an adverse event (mortality) (through the *Score module*), of the emotional effect of the disease to the patient and the understanding of the patient about the HF condition (through the *Score module*). The HEARTEN KMS allows the monitoring of patients once they return home during their daily activities. More specifically, the *NYHA class module* provides an estimation of the current NYHA class of the patient.

The detection of the NYHA class (estimation of HF severity) has already been addressed as a classification problem in the literature [22-28, 49], however, the HEARTEN NYHA class module is differentiated from these studies since this model is trained and validated on data including biomarkers from saliva and breath. NYHA class detection is addressed as a three class classification problem (NYHA II, NYHA III and NYHA IV). The module runs at the end of every day taking as input not only the baseline data during the first visit but also using the everyday wearable sensor and biosensor data measurements.

Treatment adherence module

Non-adherence of HF patients to treatment suggestions (suggestions regarding medication, nutrition and physical activity exercising) has been proven a significant contributor to the presence of HF adverse events [57-61]. In order the effects of non-adherence to be avoided and the management of HF patients to be optimized, the *Treatment adherence module* evaluates if the patient is adherent or not to the suggestions provided by the experts. Based on this estimation, encouragement and motivation offered to the patient can be adjusted. The functionality of the module is depicted in Fig 4.

The *Nutrition adherence* is estimated based on information extracted from the adherence of the patient in the Mediterranean diet score [62] and on two separate questions that concern the consumption of salt and water/fluids. The score value is translated to "low", "medium" or "high" characterization, while the answers provided by the patient, through the HEARTEN mobile application, on salt and water consumption are compared with the experts recommendations. In order to combine the three different subtypes of adherence in an overall nutrition adherence estimation, specific weights on the importance of each subtype have been estimated using a multi-criteria method, namely the Analytical Hierarchy Process (AHP) [63]. AHP has been employed to a group of experts using a specific questionnaire. Based on their pairwise comparison the importance/weight of each nutrition component (i.e. Mediterranean diet, salt consumption, water consumption) has been calculated. The obtained weights of each factor are presented in Table 1, where it is clear that water and salt consumption are of upmost importance for the experts. Ordinal values (low, medium, high) are transformed to numerical values and aggregated to overall adherence score with the use of weights. Thresholds, provided by experts, are employed for the classification of the overall nutrition adherence into low, medium or high.

Table 1: Weights of each sub-type of nutrition adherence used for the calculation of the overall adherence.

Nutrition Sub-type	Weight
Mediterranean diet	0.067
Salt consumption	0.467
Water	0.467

The *Physical Activity adherence* is extracted by comparing the activity performed by the patient with the activity suggestion from the expert. It is characterized as (rules defined by the experts): (i) High: performed >80% of the suggestions of the experts, (ii) Low: performed <20% of the suggestions of the experts, (iii) Medium: performed 20-80% of the suggestions of the experts.

The *Medication adherence* is estimated by applying a classification model not only to the baseline data, as the *Adherence risk estimation module*, but also to information extracted from the wearable sensors' and biosensors' data, the output of the *Adherence risk estimation*, the *NYHA class* and the *Score module*.

The overall adherence is determined according to Table 2, where the aggregation of the different adherence types follows a transformation process similar to the nutrition case (from ordinal values to numerical; aggregation; transformation to ordinal values). Weights were derived again through the application of AHP to a group of experts.

Table 2. Overall treatment adherence characterization.

Medication adherence	Nutrition adherence	Activity adherence	Overall
Low	Low	Low	**Low**
Low	Low	Medium	**Low**
Low	Low	High	**Low**
Medium	Low	Low	**Low**
Medium	Low	Medium	**Low**
Medium	Low	High	**Low**
High	Low	Low	**Medium**
High	Low	Medium	**Medium**
High	Low	High	**Medium**
Low	Medium	Low	**Low**
Low	Medium	Medium	**Low**
Low	Medium	High	**Low**
Medium	Medium	Low	**Medium**
Medium	Medium	Medium	**Medium**
Medium	Medium	High	**Medium**
High	Medium	Low	**Medium**
High	Medium	Medium	**High**
High	Medium	High	**High**
Low	High	Low	**Medium**
Low	High	Medium	**Medium**
Low	High	High	**Medium**
Medium	High	Low	**Medium**

Medication adherence	Nutrition adherence	Activity adherence	Overall
Medium	High	Medium	**High**
Medium	High	High	**High**
High	High	Low	**High**
High	High	Medium	**High**
High	High	High	**High**

The importance/weight of each type of adherence (i.e. medication related, nutrition related, physical activity related) to the estimation of the overall adherence score is presented in Table 3, where the focus of experts (as reflected on the obtained weights) on medication and nutrition adherence is clear.

Table 3: Weights for each sub-type of the overall adherence.

Nutrition Sub-type	Weight
Medication adherence	0.455
Nutrition adherence	0.455
Activity adherence	0.091

Event prediction module

The identification of factors related to subsequent mortality or morbidity helps the experts focusing on patients who are in the need of more intense monitoring and therapy. The prediction of the event before it is manifested can therefore prove to be extremely beneficial for the patient. Existing prediction models combining different sources of information (e.g. socio-demographic, clinical examination, medical condition, lab tests, medication intake, phenotypic data, sensor data) along with machine learning techniques are presented in [24, 29-47, 49]. Recent studies have identified certain biomarkers which strongly correlate with the HF severity, progression and mortality [64-81], while the progress in analytical chemistry and biosensor development allowed their detection in saliva and breath [82-85] with prominent merits due to the easy and non-invasive sample collection. The *Event prediction module* aims to inform the experts about the possible presence of adverse events (relapses and mortality): (i) by introducing saliva and breath biomarkers into the adverse event prediction process, (ii) based on a machine learning approach (presented in the Classification – Prediction models section), (iii) taking place non – invasively (which in a future setting can be performed at home [86]), (iv) taking into account the medication adherence profile of the patient (as an outcome of the *Treatment Adherence* module).

Association module

The *Association module* provides the experts with the ability to conduct in-depth analysis and research, originated from multiple patient data. Association rules algorithm (the Apriori algorithm [87] in our case) enables the experts to extract, in a data driven way, rules (in the form of IF…THEN…) employing several patient variables. In this way, associations are examined within the recorded datasets and the experts can discover interesting interrelations and reveal new knowledge from multiple and heterogeneous data, that can reflect the relation among lifestyle, clinical condition and medication of the patients. In this sense, this module is more research oriented.

Statistics module

The *Statistics* module allows the analysis and exploitation of the great amount of the patient data for both patient monitoring and research purposes. Such analysis could not be done otherwise with commercial statistical software due to several transformations and calculations needed to derive meaningful and comparable data from the large amount of heterogeneous data collected in different type points and with different frequencies from the patients. It allows experts to find and explain dependencies which are observed frequently within the collected data. The discovered knowledge is specific for a patient under investigation, or for a group of patients. It has a dual purpose functionality: (i) monitor single patient sensor data statistics and their volatility among different day periods and types of activity as a means to support experts in the estimation of patient's status (Statistics per patient) and (ii) hypothesis testing by applying T-test on the HEARTEN database data (Group statistics), which in turn is mainly research oriented.

Monitoring-Reporting module

A summary of the patient current and future condition (presence of adverse events) is provided to the experts through the *Monitor-Reporting module* by combing the output of the rest modules.

KMS alerting mechanism module

Provides alerts/notifications to relevant ecosystem actors (i.e. doctor, patient, caregiver, nutritionist, physical activity expert, etc.) based on pre-defined alerting/notification protocols, through its integration with third party systems (DynPCP in our case). The *KMS alerting mechanism module* is activated in the case of: (i) patients' NYHA class change, (ii) score values of the patient change, (iii) an adverse event detection, (iv) low levels of medication adherence, (v) non adherence of the patient to nutrition, (vi) medium or low levels of physical activity.

Classification – Prediction models

The *NYHA class*, the *Adherence risk estimation*, the *Treatment adherence* and the *Event prediction module* utilize classification models. Given the different types of data/measurements and the large amount of features examined, a three step approach is followed in order the models to be built: (i) data cleaning, (ii) feature selection, (iii) classification. Features with more than 60% missing values, as well as features in which the distribution between the different values is larger than 80% are removed. Then, the Wrapper algorithm [88] is applied for the identification of features that can act as discriminators between the classes of the four classification problems addressed in the HEARTEN KMS modules (Table 4), in combination with the classifiers employed in the third step. The features retained for each classification problem are presented in Section 3. For the classification (third step), nine classifiers are tested [88]: (i) Random Forests, (ii) Logistic Model Trees, (iii) J48, (iv) Rotation Forest, (v) Support Vector Machines, (vi) Radial Basis Function Network, (vii) Bayesian Network, (viii) Naïve Bayes, (ix) Simple CART.

Table 4. Classification problems addressed by the HEARTEN KMS modules.

HEARTEN KMS modules	Classification problem	
NYHA class module	NYHA II *vs.* NYHA III *vs.* NYHA IV	
Adherence risk estimation module	Medication adherence risk	Low *vs.* Medium *vs.* High
	Overall adherence risk	Low *vs.* Medium *vs.* High
Treatment adherence module	Medication adherence	Low *vs.* Medium *vs.* High
Event prediction module	Event *vs.* no event	

Dataset

The following types of data were collected by the clinical center of the Universita Di Pisa (UNIPI), Italy, the Servicio Andaluz de Salud (SAS) Spain and the 2nd Department of Cardiology, University Hospital of Ioannina (UHI): (i) general information, (ii) allergies and drug side effects, (iii) medical condition, (iv) drugs (medication intake), (v) Biological data, (vi) clinical examinations, (vii) sensor data, (viii) biosensor data, (ix) score values, (x) experts' suggestions, (xi) experts' estimation regarding adherence. The information corresponding to each category of data is presented in Table 5. The involved clinical centers have submitted and received the ethical approvals from the local ethical committees, all the processes for data collection were in accordance with the fundamental ethical principles and standards and complied with relevant national, EU and international legislation, including those reflected in the Charter of Fundamental Rights of the European Union, the European Convention on Human Rights and the opinions of the European Group on Ethics in Science and New Technologies (EGE). In total 136 patients were enrolled satisfying the enrollment criteria shown in Table 6.

Table 5. Description of information collected in each category of data.

Category	Description
(i) General information	Age, Gender, Town, Country, Ethnicity, Place of birth, Education level, Employment status, Marital status, Number of Children, Caregiver, Relationship caregiver and patient, Caregiver age
(ii) Allergies and drugs side effects	Allergies presence, Drug side effects presence
(iii) Medical Condition	NYHA class, Smoking habit, Alcoholism habit, Presence or not of comorbidities: Diabetes mellitus, Hypertension, Hypotension, Dyslipedemia, Obesity, COPD, Chronic kidney disease, Coronary artery disease, Peripheral artery disease, Cerebrovascular disease, Atrial fibrillation, Prior revascularization, Prior myocardial infraction (previous Acute Myocardial Infarction), Depression, Chronic liver disease, Rheumatological disease, Oncological disease, Orthopnea, Paroxysmal nocturnal dyspnea, Dyspnea at rest, Oliguria, Fatigue, Jugular ingurgitation, Ascites, Edemas - Peripheral edemas, Pulmonary edema,

Category	Description
	Rales - Pulmonary crackles, Lethargy, Mitral regurgitations (includes cardiomegaly), Stroke / transient ischemic attack, Prior HF hospitalization within 6 months, Prior HF hospitalization but not within 6 months, Diagnosis of heart failure over 2 years ago
(iv) Drugs	Active substance, dose and frequency of intake: Diuretic medication, Digoxin medication, Aldosterone antagonistic medication, Beta-blocker medication, ACE inhibitor medication, ARBs medication, Calcium antagonistic medication, Ivabradine medication, Antiagregant agents medication, Anticoagulant agents medication, Insulin medication, Oral anti-diabetic medication, Gastro-protective-drugs medication, Statins medication, Other medication
(v) Clinical Examinations	Left bundle branch block or intraventricular delay, Right bundle branch block or intraventricular delay, Left ventricular Ejection fraction
(vi) Biological data	Height, Temperature, Systolic pressure, Diastolic pressure, Heart Rate, LDLc, HDLc, Glucose , Triglycerides, Calcium, Sodium, Potassium, Natriuretic peptides, Hemoglobin A1c, Hemoglobin, International normalized ratio, Hematocrit, White Blood Cells, SGOT, SGPT, Oxygen saturation in Capillary blood by Oximetry, Partial pressure of oxygen, Partial pressure of carbonic, Cardiac troponin I, Cardiac troponin T, Creatinine, Microalbumin in Urine, C-reactive protein (CRP), Creatine kinase in Serum or Plasma, Blood Urea Nitrogen, Urea, GFR/eGFR, Uric Acid , Iron binding capacity in Serum or Plasma, Iron in Serum or Plasma, Thyrotropin (TSH), Thyroxine (free T4), Thyroxine (free T3)
(vii) Sensor data	Time and frequency domain Heart Rate Variability features extracted from the electrocardiogram (ECG), as well as respiration rate, weight and activity related data
(viii) Biosensor data	Concentration of Tumor Necrosis Factor Alpha (TNF-α), Cortisol and Acetone (2-Propanon)
(ix) Score	European Heart Failure Self-care Behavior Scale 12-item scale, Heart Failure Knowledge score, Get with the guidelines, Seattle Heart Failure Model, Minnesota Living with Heart Failure
(x) Experts suggestions	Nutrition, Physical activity type, Physical activity duration, Physical activity frequency
(xi) Experts estimation regarding adherence	Medication adherence, Nutrition adherence, Physical activity adherence, Overall adherence

Table 6. Criteria for patient enrollment.

Criteria	Patients
I	diagnosed with HF (Framingham criteria) who have continuous symptoms with frequent recurrence
II	belonging to the functional NYHA I-IV class followed by an optimal treatment
III	recently hospitalized, (at least one in the last six months)
IV	undergone one ECG (in the last 12 months) and have HF symptoms
V	underage, with very severe HF, patients with obesity and advanced chronic kidney failure are not included

Wearable Sensor measurements processing

ECG values for each patient's sensor measurements are processed from the "PhysioNet's" HRV Toolkit [89] in order statistical measurements from QRS(RR) interval sequences to be extracted. More specifically, the following time and frequency domain features are extracted from each ECG channel: (i) the fraction of total RR intervals which are classified as normal-to-normal (NN) intervals (NN/RR), (ii) the average of all NN intervals (AVNN), (iii) the standard deviation of all NN intervals (SDNN), (iv) the standard deviation of the averages of NN intervals in all 5-minute segments of a 24-hour recording (SDANN), (v) the mean of the standard deviations of NN intervals in all 5-minute segments of a 24-hour recording (SDNNIDX), (vi) the square root of the mean of the squares of differences between adjacent NN intervals (rMSSD), (vii) the percentage of differences between adjacent NN intervals which are larger than 50ms (pNN50), (viii) the total spectral power of all NN intervals up to 0.04 Hz (TOTPWR), (ix) the total spectral power of all NN intervals up to 0.003 Hz (ULF PWR), (x) the total spectral power of all NN intervals between 0.003 and 0.04 Hz (VLF PWR), (xi) the total spectral power of all NN intervals between 0.04 and 0.15 Hz (LF PWR), (xiii) the total spectral power of all NN intervals between 0.15 and 0.4 Hz (HF PWR),(xiv) the ratio of low to high frequency power(LF/HF).

The WinMedical sensors [50], utilized in the HEARTEN platform, record the heart rate, the respiration rate, the diastolic pressure, the systolic pressure, the mean arterial pressure, the type of arrhythmias, the breath per minute, the pressure beats per minute, the body temperature, the body position and the number of steps performed. The body position is grouped in two categories: rest and activity. The max, min, mean and standard deviation values are extracted for each one of the above mentioned features and for each category of body positions, as well as the overall values. Finally, a standard weight scale measures the patient's weight, the body fat percentage, the skeletal muscle percentage and the body mass index (BMI).

After processing the sensor data, a total set of 295 features is extracted for each patient, while after the data cleaning step, 246 features are retained.

Technical implementation of HEARTEN KMS

The HEARTEN KMS was built using the JDK 1.8 API on the NetBeans development studio. The development was based on the Java Server Faces 2.2 (JSF 2.2) by using the PrimeFaces 5.3 component library. Furthermore, the RESTfull services were built using the Java API for RESTful Web Service (JSR-311) and also were supported by the Jersey RESTfull services framework. The Jackson 2.7 library for JSON data processing and parsing was also used. The Oracle GlassFish Application Server (AS) is used for the deployment of the KMS in the cloud platform. Glassfish is sponsored by Oracle® Corporation as an open source application server that hosts JAVA EE applications and provides security control, access management, resource management and data monitoring. The AS can host with enhanced security Enterprise JavaBeans, Servlets, Java Server Pages, RESTfull web services, JavaServer Faces and the Java Persistence API as its major technologies. It also provides performance, portability and scalability to all phases of application development. Concurrent users can use connection pools to handle their data that can are hosted in any database system; this is an important feature also for the KMS that provides transparency in the development and database storage.

Results

Each module of the HEARTEN KMS is tested/evaluated separately. The classification models incorporated in the NYHA class, the Adherence risk, the Treatment adherence and the Event prediction modules are evaluated using the 10-fold stratified cross validation approach. The features retained from the second step of the machine learning approach (*i.e.* the feature selection) are presented in Table 7, while the results of the classification models are presented in Table 8. To test, verify and evaluate the prediction and classification ability of the above mentioned models after their integration to the HEARTEN KMS, the input values and the results were tested against the original models.

Table 7. Features given as input to the classification model based HEARTEN KMS modules.

Module	Input	Features retained	
NYHA class estimation	Categories: (i)-(ix)	Diabetes mellitus	Depression
		Orthopnea	HDLc

Module	Input	Features retained	
		Calcium	Mean Rest Breath
		White Blood Cells	STDDEV rest pressure bpm (standard deviation of heart beats per minute in rest position)
		Cardiac troponin I	NN/RR (the fraction of total RR intervals that are classified as normal-to-normal (NN) intervals and included in the calculation of HRV statistics)
		Iron binding capacity	BMI
		Thyroxine freeT4	Cortisol
		Insulin medication	TNFa
		Acetone	NT-proBNP
Adherence risk estimation - Medication	Categories: (i)-(v), (ix)	Marital status	Prior myocardial infraction
		Dyspnea at rest	Jugular ingurgitation
		Left ventricular Ejection fraction	EHFSc-Bc-12
Adherence risk estimation - Overall	Categories: (i)-(v), (ix)	Oncological disease	Edemas Peripheral edemas
		Prior HF hospitalization (not within 6 months)	Partial pressure of carbonic
		Micro-albumin in Urine	Dutch
		Medication adherence patient (output of medication risk estimation model)	
Event prediction	Categories: (i)-(ix), Output of the Treatment adherence module	Gender	COPD
		STDDEV OVERALL STEPS (standard deviation of the overall steps performed)	MAX REST PRESSURE
		SDNNIDX (the mean of the standard deviations of NN intervals)	Cortisol
		TNFa	Acetone
		Medication adherence patient (output of the treatment adherence model)	
Treatment adherence - Medication	Categories: (vii)-(viii), Output of the NYHA class module, Output of the Adherence risk estimation module, Nutrition adherence estimation, Physical Activity adherence estimation	STDDEV OVERALL HR (standard deviation of the overall heart rate)	STDDEV OVERALL RR (standard deviation of the overall RR intervals)
		rMSSD (Square root of the mean of the squares of differences between adjacent NN intervals)	Cortisol
		TNFa	Acetone
		NYHA class	Medication adherence risk model

Table 8. Classification results of the model based HEARTEN KMS modules.

Module	Accuracy	Classifier
NYHA class estimation	95%	Random Forest
Adherence risk estimation - Medication	81%	Random Forest
Adherence risk estimation - Overall	78%	Random Forest
Event prediction	89%	Rotation Forest
Treatment adherence - Medication	85%	J48

The retained features in general were considered, by the medical experts, relevant to the decision of output of each module. A clinical explanation of the correlations-associations between the retained features and the output of each module follows.

NYHA class estimation: The Diabetes mellitus is expected to be associated with higher NYHA class and depression. Orthopnea is associated with higher NYHA class, while there is no any evidence of the correlation between HDLc and NYHA class. The relation of Calcium with NYHA class is not well established; however a study [90] associated hypercalcemia with higher NYHA class without an obvious reason. A possible explanation could be the underlying hidden association with serum proteins and vitamin D. The increase in the white blood cells value is associated with a NYHA class worsening, although the presence of very low values of white blood cells could be also be related to worse NYHA. Finally, the higher cardiac troponin value, the higher the NYHA class is.

Event prediction: The prognosis of HF in men is worst compared to women, while the presence of COPD is linked with more events. The performance of physical activity results in better prognosis. Lower values of heart rate variability are linked with the onset of an event. The high values of the two saliva and the single breath biomarkers should be correlated with more events. Finally, the more adherent the patient is, the possibility of an adverse event is reduced.

As already mentioned, it is the first time that variables related to the medical condition and lab measurements are used as predictors of medication and overall adherence. Thus, the explanation of the correlations and related associations should be further validated employing larger datasets.

Adherence risk estimation-Medication: Married patients are considered in general more adherent to medication treatment due to the support of their spouse. Dyspnea at rest and jugular ingurgitation are expected to have reverse association with medication adherence (*i.e.* a patient who is less adherent s/he would have more dyspnea at rest and jugular ingurgitation). There is no direct explanation of the association between prior myocardial infarction and left ventricular ejection fraction, so this is a correlation to be investigated. Finally, higher self-reported adherence is expected to be associated with higher medication adherence, considering also additional factors as well.

Adherence risk estimation – Overall: It is expected that decreased overall adherence results in the presence of more edemas and increased hospitalizations. A reverse association is also expected between microalbumin in urine and overall adherence. It is interesting to examine how the presence of oncological disease and the values of partial pressure of carbonic is related to overall adherence. The better knowledge about the disease (Dutch Heart Failure Knowledge score) and the low medication adherence, the greater overall adherence is expected.

Treatment adherence: A reverse association is expected to be present between, STDDEV OVERALL HR, STDDEV_OVERALL_RR, rMSSD (*i.e.* the higher the treatment adherence, the higher rMSSD values), biomarkers values (*i.e.* the higher the treatment adherence, the lower the values of biomarkers), NYHA class (*i.e.* the higher the treatment adherence, the lower NYHA class) and treatment adherence of the patient. The higher medication adherence, the higher treatment adherence should be. Moreover, usually patients who are adherent to medication are also adherent to diet and exercise.

The combination of the different types of data derives the best classification outcomes in all three relevant cases (i.e. NYHA class estimation, Event prediction, Treatment adherence-medication).

However, as different exploitation scenarios (e.g. with or without biosensors; with or without sensors, etc.) can be considered, several configurations have been tested, as it is presented in Table 9. In general, performance is quite in most of the configurations which indicates different exploitation options.

Table 9. Classification results of the model based HEARTEN KMS modules under different configuration of features.

Module	Input	Accuracy	Classifier
NYHA class	Sensor data	86%	Random Forest
	Biosensor data	75%	Random Forest
	Sensor and biosensor data	81%	Random Forest
	All (optimal features)	95%	Random Forest
Event prediction	Sensor data	78%	Radial Basis Function
	Biosensor data	81%	Logistic Model Trees
	Sensor and biosensor data	77%	Rotation Forest
	All (optimal features)	89%	Rotation Forest
Treatment adherence - Medication	Sensor data	76%	Radial Basis Function
	Biosensor data	79%	Rotation Forest
	Sensor and biosensor data	82%	Rotation Forest
	All (optimal features)	85%	J48

Discussion

We present the HEARTEN KMS, a novel system supporting HF patient management allowing for automated risk stratification, severity estimation, adverse event prediction and adherence estimation. Being a part of the HEARTEN platform the HEARTN KMS produces alert messages when needed, enabling patient empowerment. The HEARTEN KMS is evaluated on heterogeneous patient specific data including for the first time breath and saliva biomarkers. The development of the *NYHA class*, the *Adherence risk estimation*, the *Event prediction* and the *Treatment adherence* module is based on a machine learning approach comprised of data cleaning, feature selection and classification steps. Classification models are built for each of the KMS modules. Literature review reveals relevant approaches for the estimation of the severity of HF, the estimation of medication adherence and the prediction of adverse events have already been addressed as classification problem. A comparison of the proposed models with those reported in the literature is presented in Tables 10-12, respectively.

Table 10. Comparison of the HEARTEN NYHA class model with the HF severity estimation models reported in the literature.

Authors	Dataset	Classification problem	Accuracy	Classifier
Guidi *et al.* [23]	136 subjects	Mild HF *vs.* Moderate HF *vs.* Severe HF	86%	Neural networks
Guidi *et al.* [24]	136 subjects	Mild HF *vs.* Moderate HF *vs.* Severe HF	83%	Random Forests
Guidi *et al.* [30]	250 subjects	Mild HF *vs.* Moderate HF *vs.* Severe HF	81%	Random Forests
Yang *et al.* [15]	153 subjects	Healthy (NYHA I, ACC/AHA A) *vs.* HF-prone group (NYHA I, ACC/AHA B-C) *vs.* HF group (NYHA II-III, ACC/AHA C-D)	74%	Support Vector Machines
HEARTEN KMS NYHA class module	92 subjects	NYHA II *vs.* NYHA III *vs.* NYHA IV	95%	Random Forests

Table 11. Comparison of the proposed medication adherence models with those reported in the literature.

Authors	Dataset	Classification problem	Accuracy	Classifier
Son *et al.* [48]	76 subjects	Adherent *vs.* non adherent	78%	Support Vector Machines
HEARTEN KMS Medication adherence risk estimation	84 subjects	Low adherent *vs.* Medium adherent *vs.* High adherent	81%	Random Forests
HEARTEN KMS Medication treatment adherence	84 subjects	Low adherent *vs.* Medium adherent *vs.* High adherent	85%	J48

Table 12. Comparison of the HEARTEN Event prediction model with adverse event prediction models reported in the literature.

Authors	Dataset	Accuracy	Classifier
Destabilizations			
Candelieri *et al.* [31]	49 subjects	92%	Decision tree
Candelieri *et al.* [33]	49 subjects	82%	Support Vector Machines
Candelieri *et al.* [32]	49 subjects	87%	Support Vector Machines (genetic algorithm)
Guidi *et al.* [30]	136 subjects	88%	Classification and Regression Tree
Guidi *et al.* [15]	250 subjects	72%	Random Forests
Re-hospitalizations			
Zolfaghar *et al.* [34]	15,696 records	87%	Random Forests
Vedomske *et al.* [35]	1.000.000 subjects	84% (AUC)	Random Forests
Koulaouzidis *et al.* [37]	n/a	82% (AUC)	Naïve Bayes

Authors	Dataset	Accuracy	Classifier
Kang *et al.* [39]	552 subjects	59% (AUC)	J48
Tugerman *et al.* [38]	4.840 CHF patients	84%	Ensemble model with Boosted C5.0 tree and SVM
Roy *et al.* [36]	Washington State Inpatient Dataset & Heart Failure cohort data from Multi Care Health Systems	69%	Dynamic Hierarchical Classification
Shah *et al.* [29]	527 subjects	70%	Support Vector Machines
		Mortality	
Shah *et al.* [29]	527 subjects	72% (AUC)	Support Vector Machines
Fonarrow *et al.* [40]	33,046 instances (derivation cohort) & 32,229 instances (validation cohort)	12.9 (odds ratio)	Classification and Regression Tree
Bohacik *et al.* [41]	2032 subjects	78%	Alternating decision tree
Panahiazar *et al.* [43]	5044 HF subjects	1-year AUC 68.00% (baseline set) 81.00% (extended set) 2-years AUC: 70.00% (baseline set) 74.00% (extended set) 5-years AUC 61.00% (baseline set) 73.00% (extended set)	Logistic Regression
Taslimitehrani *et al.* [44]	5044 HF subjects	1-year Accuracy 91% 2-years Accuracy 83% 5-years Accuracy 81%	CPXR(Log)
Austin *et al.* [45]	EFFECT baseline (9945 HF patients) utilized 8240 & EFFECT follow up (8339 HF patients) utilized 7608	79% (AUC)	Logistic regression model (cubic smoothing splines)
Bochacik *et al.* [42]	n/a	Sensitivity 63% Specificity 66%	Fuzzy model
Ramirez *et al.* [47]	597 Chronic Heart Failure patients	Sudden Cardiac Death Sensitivity 18% Specificity 79% Pump Failure Death Sensitivity 14% Specificity 81%	C-Support Vector Machines

Authors	Dataset	Accuracy	Classifier
Subramanian *et al.* [46]	963 patients	84% (AUC)	Ensemble Logistic regression with boosting
Event *vs.* no event			
HEARTEN KMS Event prediction	95 subjects	89%	Rotation Forest

The proposed models are differentiated from those reported in the literature since: (i) they incorporate relevant clinical information from saliva and breath biomarkers, in addition to other physiological mainly data, (ii) they estimate the severity of HF in terms of NYHA II, III and IV without merging the different NYHA classes, (iii) they provide the level of patient's medication adherence, and (iv) they provide an estimation of the risk of medication (non)adherence. In addition, for the first time, an estimation of the overall adherence risk of the patient has been studied as a classification problem. It should be noted that the direct comparison of the *Event prediction* module of the HEARTEN KMS with other relevant studies reported in the literature is not feasible since the proposed module predicts the presence or not of an HF event without focusing on a specific type of event, which is the case for the relevant literature. Still, Table 12 presents this comparison.

The results reported in Table 9 indicate the prediction and classification power of the three measured biomarkers (Cortisol, TNF-α, Acetone). The future evolution of the sensing devices is expected to allow for easy, non-invasive, home collection of these measurements which in turn can make the HEARTEN KMS and the HEARTEN platform a valuable tool for HF patient (self-)management supporting adherence and providing the patients with the ability to become more active in managing their own care.

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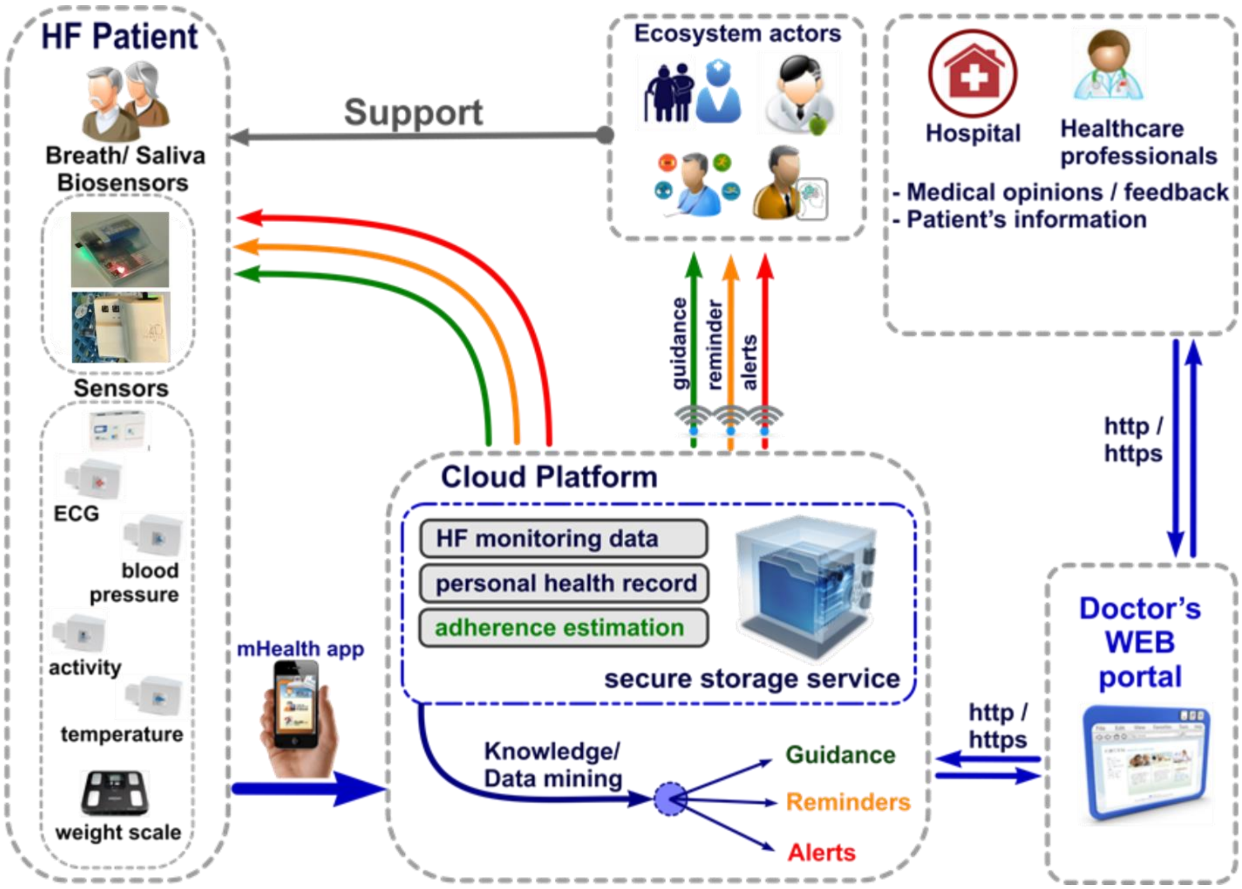

Figure 1: The HEARTEN Collaborative platform architecture.

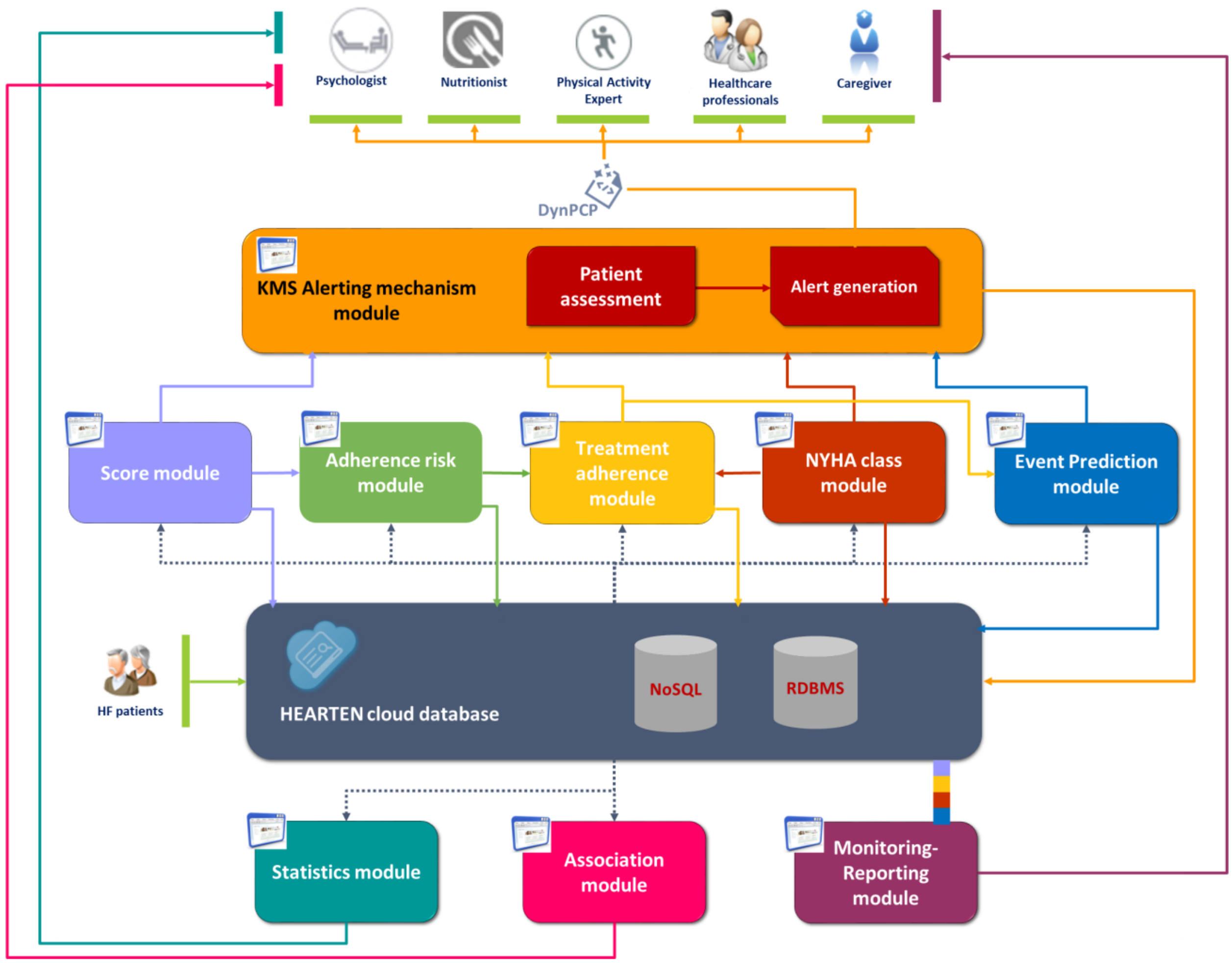

Figure 2: The HEARTEN Knowledge Management System Architecture.

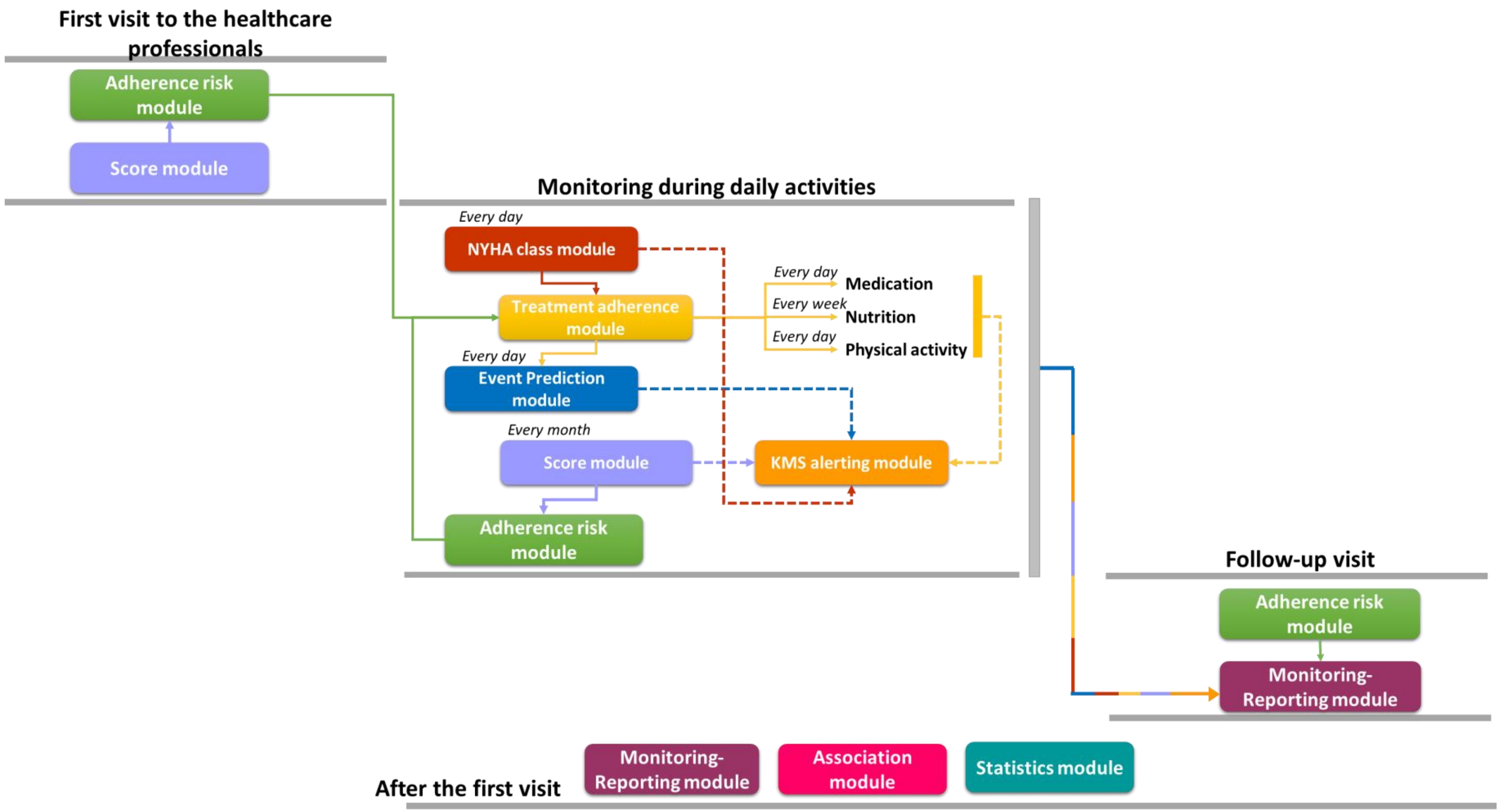

Figure 3: Interaction of HEARTEN KMS modules and timing of activation during the "patient journey".

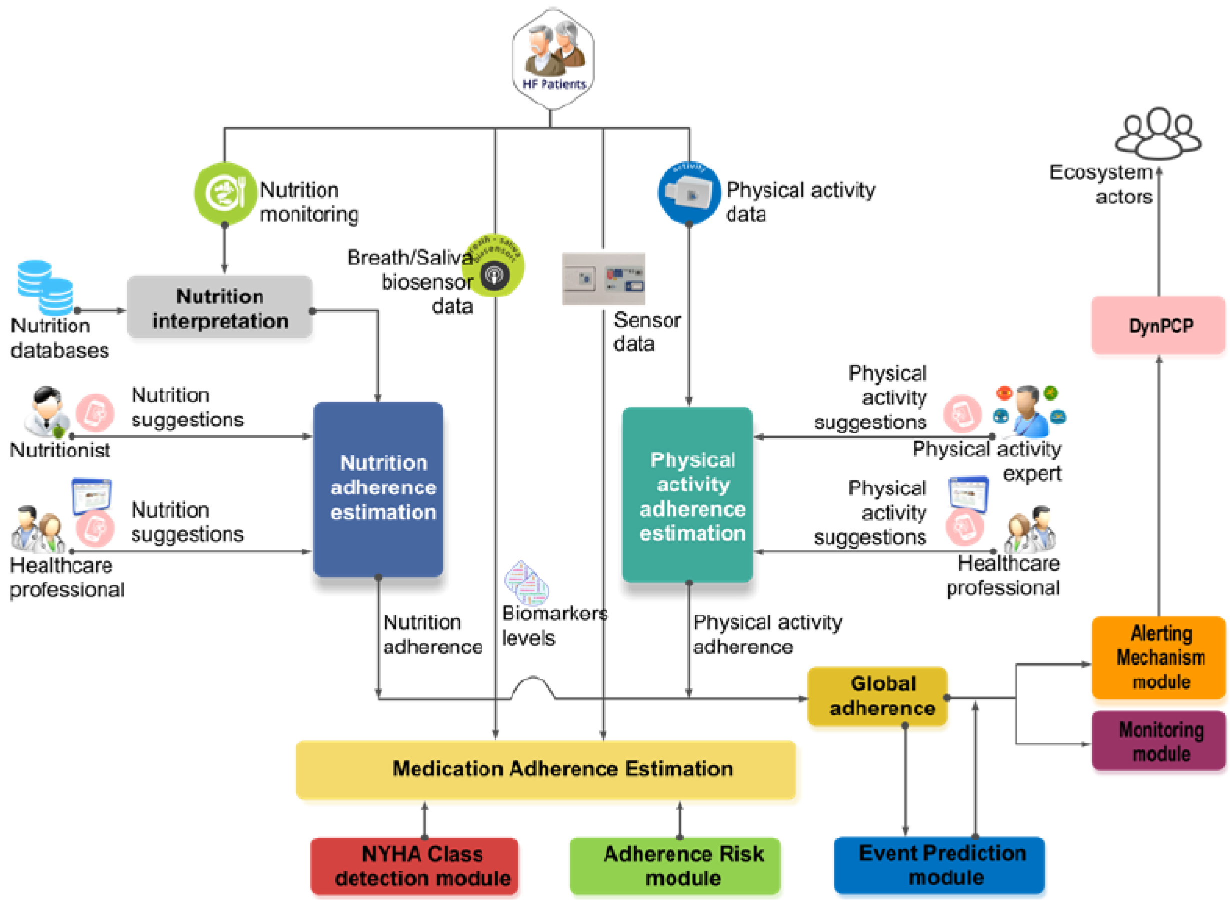

Figure 4: The Treatment adherence module functionality.