Personalized Patient Empowerment and Shared Decision Support for Cardiorenal Disease and Comorbidities

Eleni Kaldoudi

1 School of Medicine, Democritus University of Thrace, 68100 Alexandroupoli, Greece
kaldoudi@med.duth.gr

Abstract. The Chronic heart and kidney disease are serious and common amongst the world population. They often appear simultaneously and they can cause each other, while they share a multitude of underlying risk conditions, such as obesity, diabetes, and hypertension. To help tackle cardiorenal disease, the European Commission funded the CARRE interdisciplinary research consortium to compile a variety of personalized alerting, planning and educational services so that patients and professionals alike are empowered and can make shared informed decisions. CARRE project uses commonly available personal sensors, such as activity trackers, scales and personal health records, to collect information about the person, which is then projected against current medical knowledge to produce a personalized risk prediction model. This paper presents an overview of the project outcomes including breakthroughs in sensor technology, semantic technologies, visual analytics, and decision support services.

1 Introduction

Comorbidity refers to the presence of one or more disorders in addition to a primary disease or disorder (either independently, or as a consequence of the primary condition or otherwise related) [1]. Approximately half of all patients with chronic conditions, even in a nonelderly population, have comorbidities [2].

In view of the high degree of comorbidity, single-disease management does not appear promising as a strategy to care for such patients. But as only a few overall management guidelines exist, comorbidities frustrate providers and patients. So, most patients see individual providers, increasing the risk of fragmented care and negative outcomes. Comorbidity makes even more cumbersome self-care and treatment adherence. Patients need a significant amount of time to self-manage comorbidities and to conduct their own risk-benefit analyses. There is also recent evidence that comorbidity influences the relationship between self-efficacy and self-care maintenance [3]. Common to all studies of comorbidity management approaches is the realization that educational and otherwise empowering interventions as well as shared decision support might improve patient and caregiver well-being and lead to a better management of the overall condition [4].
Research with the CARRE project [5] addresses this need following a “first understand, then conquer, then decide” approach that first fosters understanding of the complex interdependent nature of the comorbid condition in general and as specialized for the specific patient; then calculates informed estimations for disease progression and comorbidity trajectories and compiles a variety of personalized alerting, planning and educational services so that patients (and professionals) are empowered, and can, eventually, make shared informed decisions.

In specific, the CARRE project developed a novel technological infrastructure for visual and quantitative understanding of disease progression pathways and comorbidities trajectories and their dynamics, enriched with up-to-date medical evidence and personalized for the individual patient.

The core of CARRE effort lies in semantic interlinking various sources of up-to-date medical evidence with personal patient data, in order to create a personalized model of the disease and comorbidities progression pathways. Visual presentations of this personalized model form the basis for patient empowerment services. Finally, the personalized model of comorbidities will be used for shared decision support services targeting personalized education, complex risk calculation for disease & comorbidities progression, alerts for adverse events of multiple treatments and personalized planning.

In order to achieve the above objectives, CARRE consortium is driven by two partners from the medical domain, namely the School of Medicine at Democritus University of Thrace (Greece), and the Vilnius University Hospital Santariskiu Klinikos (Lithuania), both with a proven experience in medical research in cardiorenal disease and comorbidities as well as with a long record of developing and deploying informatics interventions in the real healthcare setting. The core semantic model and interlinking is performed by the Knowledge Media Institute, the Open University (UK) a leading expert in semantic technologies, while The Centre for Computer Graphics and Visualisation, University of Bedfordshire (UK) undertakes the work on visual analytics and cloud computing – both partners also contribute their long experience in semantic information extraction from unstructured data sources and web service oriented architectures. The Biomedical Engineering Institute, Kaunas University of Technology (Lithuania), contributes research in personal sensors and sensor networks for cardiorenal disease and tackles the integration of personalized sensor data. Finally, the Industrial Research Institute for Automation and Measurements (Poland) brings in the required expertise on decision support systems and on systems security.

This paper gives an overview of the rational that drives the CARRE project, presents major outcomes and discusses expected impact.

2 Rationale and Motivation

CARRE addresses the specific medical domain of cardiorenal disease and comorbidities as this is a very common, life threatening and costly condition and because it also presents a number of challenges and opportunities for the demonstration of CARRE outcomes. Cardiorenal syndrome is the condition characterized by simultaneous kidney and heart failure while the primarily failing organ may be either the heart or the
kidney. Very often the dysfunction occurs when the failing organ precipitates the failure of the other.

Chronic kidney disease (CKD) is defined according to the presence or absence of kidney damage and level of kidney function. Most patients with CKD (over 50 million individuals worldwide) succumb to cardiovascular events, while each year over 1 million develop end-stage renal failure, which requires costly treatment and unaffordable renal replacement therapy by chronic dialysis or renal transplantation [6]. Chronic kidney disease patients are not of concern solely because a few will progress to end-stage renal disease, but mainly because they carry a greatly enhanced risk of premature death from cardiovascular events. About 30% of all deaths worldwide and 10% of all healthy life lost to disease are due cardiovascular disease alone [7]. It is now well documented that the presence of chronic kidney disease significantly increases the risk of a cardiovascular event in both diabetes and hypertension, and in the last decade it has been as well appreciated that CKD alone is a strong risk factor for cardiovascular disease [2,8,9]. Most patients (86%) with advanced CKD have at least one comorbidity and most patients with CKD have interrelated comorbidities with shared risk factors, including hypertension, atherosclerosis, diabetes, and lipid disorders that can worsen renal and cardiovascular outcomes [10].

Kidney disease is not rare – some 9-16% of the population presents evidence of renal dysfunction [11]. Moreover, recent studies show that the high prevalence of a perceived CKD in the elderly population is likely to reflect the underlying high prevalence of overt and subclinical atherosclerosis and cardiovascular disease [12]. This leads to the conclusion that CKD is a reflection of diffuse and age-related cardiac and kidney damage that may not warrant the label of disease but certainly justifies attention with reduction of lifelong cardiovascular risks and careful evaluation and treatment.

Major risk factors for CKD include [13]: (1) Susceptibility factors: genetic or familial predisposition, racial factors, as well as low birth weight and infant malnutrition; male and elderly also appear to be more susceptible. (2) Initiation factors: hypertension, diabetes, hyperlipidemia, obesity, metabolic syndrome, smoking, infections (scabies, H-pyrol, hepatitis C, HIV, etc.), inflammatory disease (IBD, psoriasis, periodontitis, any “-itis”). (3) Progression factors: non-modifiable factors (including genetics, race, age, and sex) and modifiable progression factors, including systemic hypertension, proteinuria, obesity, dyslipidemia, cigarette smoking, regular and heavy (more than two drinks daily) consumption of alcohol, consumption of analgesics, and non-steroidal anti-inflammatory agents.

Hypertension, or high blood pressure, was a primary or contributing cause of death for 348,000 Americans in 2008, or nearly 1,000 deaths a day [14]. About 68 million American adults (i.e. 1 in every 3) have high blood pressure [15]. Hypertension is often the cause of accelerated progression of cardiovascular and kidney disease. The prevalence of hypertension is 84% in patients with stage 4–5 CKD, compared with 23% of adults without CKD [16]. Taking into account the high prevalence of hypertension even in early stages of kidney disease, regular blood pressure monitoring and appropriate management, often involving both nephrologists and cardiologists, is of crucial importance.

Chronic heart failure (CHF) is now recognized as a major and escalating public health problem. The costs of this condition, both in economic and personal terms, are
considerable. Approximately 1–2% of the adult population in developed countries has CHF, with the prevalence rising to ≥10% among persons 70 years of age or older [17]. Healthcare expenditure on CHF in developed countries consumes 1-2% of the total health care budget [18]. CHF is responsible for more hospitalizations than all forms of cancer combined and is the leading cause of hospitalization in patients older than 65 years of age [19]. Coronary artery disease is the cause of approximately two-thirds of cases of systolic heart failure, although hypertension and diabetes are probable contributing factors in many cases. There are many other causes of systolic CHF, which include previous viral infection, alcohol abuse, chemotherapy, and ‘idiopathic’ dilated cardiomyopathy. CHF still represents a major cause of cardiac mortality and morbidity with a clear need for better home.

Diabetes is also a well-established risk factor of both cardiovascular and renal disease. Many diabetic patients in the long run develop clinically significant nephropathy, the kidney being affected by progressive sclerosis and proteinuria. Diabetes accounts for 44% of all new cases of kidney failure in 2008. It also remains the leading cause of non-traumatic lower-extremity amputations and blindness among adults aged 20–74 years [20]. The rise of diabetes within the economically privileged countries over the past decade has become so significant that it has been termed an epidemic. According to data the 2011 National Diabetes Fact Sheet from the Centres for Disease Control and Prevention, USA, over 25.8 million children and adults have diabetes (8.3% of the population) [20]. Affecting over 8% of the US population, diabetes costs the nation almost $100 billion annually and can cause severe complications in individuals, including cardiovascular disease, neuropathy and retinopathy [21]. Despite of all the tremendous progress being made in the management of diabetes and its complications (e.g. various public health initiatives striving for wider monitoring of daily blood sugar, regular foot and eye exams, etc.) diabetes remains the 7th leading cause of death in US.

One of the most important aspects of cardiorenal disease and comorbidities diagnosis and treatment is early detection and aggressive management of underlying causes. Preventing progression to end stage renal and cardiac deficiency may improve quality of life and help save health care costs. Prevention of the disease includes: lifestyle modification (controlling obesity, diabetes and hypertension), public-health education for reduction of excessive bodyweight, regular exercise, and dietary approaches, control of hypertension, dietary protein restriction and blood-pressure control, proteinuria management, dyslipidemia management and smoking cessation. Delaying disease progression is crucial and must include patient education and aggressive treatment and management of CKD and its comorbidities [8,9]. However, effective implementation of such strategies will only come when both the general public and the renal patients and healthcare professionals work together towards public awareness and lifestyle management on a personal basis.

3 CARRE Approach

CARRE targets personalized patient empowerment and decision support in cardio renal disease and comorbidities. The overall concept lies on aggregating data on the
person and meshing these with current medical evidence to produce a variety of empowerment services (Fig. 1). The following paragraphs provide our approach towards addressing each one of the key terms in the CARRE target. The overall CARRE architecture and technological approach is subsequently presented.

![Diagram](image)

**Fig. 1.** The overall CARRE approach to personalized patient empowerment. Ubiquitously available quantified-self personal data are interlinked with rigorous state-of-the-art medical evidence to deliver a variety of personalized empowerment services to support cardiorenal disease prevention and management via self-management, education and mindchange.

### 3.1 Disease and Comorbidities

When addressing disease in the presence of comorbidities, each different medical condition the patient presents should not be viewed independently, but a “patient as a whole” view approach should be followed [4]. This places an emphasis on dealing successfully with all associations, interactions, co-dependencies, implications, adverse events, etc. that occur between different conditions co-presenting at the same patient at the same time, as well as between the different treatment regimens these conditions involve.

A recent thorough treatment of this issue [22] suggests that one way to improve care is to cross reference evidence and guidelines for each condition with guidelines on comorbidities. As it has already been argued in literature [22], simple cross referencing of existing medical evidence and guidelines for all possible combinations of conditions would quickly make it unreadable and thus inefficient. Thus, in CARRE we follow a personalized and semantically enriched approach to create dynamic cross referencing of semantically related evidence data.
From the overview of the medical domain presented in the previous section it is evident that cardiorenal disease and comorbidities is a complex domain. Related conditions do not have a single cause, but evidence suggests that there are multiple causal chains. In order to capture this in CARRE, current medical evidence is presented as a complex network of risk factors, that is, pairs of conditions one related to another via a causal relationship.

3.2 The Patient’s Perspective

Taking into account the patient dimension requires knowledge of two different aspects: (a) an adequate view of physiological status at all times, including biomedical signals carrying information on medical conditions as well as more general physiological activity and status; and (b) an understanding of other aspects of the patient perspective.

The physiological status of the patient at all times, including biomedical signals carrying information on medical conditions as well as more general physiological activity and status, is a rather profound technological outcome nowadays. Personal data from sensors that form the quantified self and are now described as a new asset class with the potential to transform health care and global public health [23]. CARRE involves the recording of a variety of telemetry signals from personal wearable, portable and mobile sensors that record and transmit signals relevant to cardiorenal disease and comorbidities. An adequate variety of such sensors is included: wireless sensors for monitoring body weight and composition, physical activity, vital heart signs, blood pressure and blood glucose. Other aspects of the patient perspective, including aspirations, mood, preferences, lifestyle, intentions, specific planning, etc. are a very important part of patient disposition. CARRE deploys semantic information extraction to capture such personal aspects of patient disposition via the patient’s presence in online social media. Alternatively, and in cases where such on-line presence is inadequate to yield meaningful information, such personal perspective is captured by information provided by the patient via the CARRE portal.

3.3 Empowerment Services

Patient empowerment is about designing and delivering health and social care services in a way that they are inclusive and enable citizens to take control of their health care needs. Patient empowerment puts the patient at the heart of services. According to the European Network for Patient Empowerment [24] an empowered activated patient: understands their health condition and its effect on their body; feels able to participate in decision-making with their healthcare professionals; feels able to make informed choices about treatment; understands the need to make necessary changes to their lifestyle for managing their condition; is able to challenge and ask questions of the healthcare professionals providing their care; takes responsibility for their health and actively seeks care only when necessary; and actively seeks out, evaluates and makes use of information.

CARRE directly address this basic requirement for the patient to understand their
condition, its potential progression, its inter-relationships with (potential) comorbidities, respective implications of lifestyle, treatments, etc. This is primarily achieved via a visual analytics approach which takes into account the CARRE model and its personalization via the instantiation for each patient. Patient empowerment services aim to enable the patient to have an overall view of his/her own health status and lifestyle and a clear (visual) understanding of potential disease progression and interaction with comorbidities.

Empowerment via visual analytics addresses the medical professional as well, providing different views that will enable the medical expert to have an overall visual understanding of the potential disease interactions and progression pathways in the cardiorenal disease and comorbidities area; this is be a dynamic visualization, driven by new medical knowledge as this is harvested from the related sources.

3.4 Decision Support

Traditionally, medical decision support systems can be generally viewed [25] as either (a) the so-called ‘strong’ artificial intelligence systems whose behavior is at some level indistinguishable from humans; or (b) an alternative approach that looks at human cognition and decides how it can be supported in complex or difficult situations, something like a form of ‘cognitive prosthesis’ that will support the human in a task.

The CARRE approach for decision support follows the ‘cognitive aid’ line. Most importantly, as the patient is the focus of the CARRE project, our approach for decision making mainly targets to support the patient in making informed decisions for their active health management. CARRE decision support services thus mainly address treatment critiquing and planning, information retrieval and education.

Such services are based on the real-time data/model driven coupling of the personalized/instantiated CARRE model with relevant medical evidence as well as with relevant on-line educational resources. These include: (a) personalized risk assessment for cardiorenal disease comorbidities; and/or risk assessment of cardiorenal disease based on other comorbidities; risk assessment of disease and comorbidities progression; (b) lifestyle management; (c) alerts & planning for medical check-ups and monitoring; and (d) patient education and related to cardiorenal disease and potential comorbidities.

Similarly, CARRE decision support services target the medical professional. Here the decision support services address overall professional continuous education and updating on new relevant evidence as well as patient specific support for decision making. Specifically, CARRE services to the medical professional include: (a) alerts for increased risk of comorbidities and/or potential for acute disease episodes for a particular patient; (b) decision support as to when and how a particular patient should change monitoring protocol; and (c) medical expert updates on scientific literature, personalized to the medical expert (e.g. based on expertise) and more importantly personalized to the patient in question (based on patient disease condition and calculated risks for progression and/or comorbidities).
3.5 CARRE Service Environment

An overview of the CARRE service environment is shown in Fig. 2. Key to personalized services are two types of data: personal private data on health status and public data on medical knowledge. Personal private data are aggregated from a variety of sources and stored in a private repository and include:

- Personal private data are aggregated from a variety of sources and stored in a private repository and include:
  - Medical evidence aggregation
  - Evidence based medical literature
  - Educational resources
  - Social media
  - Personal health information
  - Quantified self

Fig. 2. Overview of the CARRE service environment. Personal data aggregators feed information on the quantified self to a private repository. Medical evidence aggregators create a public evidence repository. Information from the two repositories is interlinked to provide rich visual analytics and decision support services.

Sensor data: Data collected from personal sensors developed by 3rd party sensor devices manufacturers. These data include measurements on weight, blood pressure, physical activity etc. These data reside in the cloud, as provided by 3rd party providers. These data are collected, stored and managed under the responsibility of the patient. Access to such data is via secure channels and requires user (patient) authorization.

Medical data: Data on medical history as stored in third party personal health record (PHR) systems. The patient is responsible to input and maintain these data using a 3rd party PHR system. Access to these data is via secure channels and requires user (patient) authorization.

Web social and lifestyle related data: These data include any interaction of the user with 3rd party web-based social systems, including the patient’s web browser. Examples of such data are patient’s browser history, patient’s web searches and any input in widely used social media. Access to these data is via secure channels and requires user
(patient) authorization.

On the other hand, public data on medical knowledge are aggregated from on line authoritative sources, are available via an open public repository and include:

**Medical literature:** These data include scientific publications that are the commonly accepted sources of medical evidence. Normally these publications reside in the web repositories of individual scientific journals and can be reached via dedicated scientific indexing services available on the web, the main one considered here being PubMed. These data can be accessed via public application programming interfaces (APIs).

**Educational resources:** This includes educational items on medical issues addressed to patients. Such data reside on third party web repositories (e.g. MedlinePlus, Wikipedia) and can be accessed via public APIs.

Private and public data are generated and consumed by a number of different CARRE services; these include:

**Risk factor description system.** Service and respective user application for entering risk factor descriptions (risk elements, evidence etc.). Data entry is via a browser based application and the service produces automatically the appropriate RDF triples, to be stored in the public repository.

**Risk association data mining.** This service provides data mining methods to discover relevant risk associations in published medical evidence literature, as indexed in PubMed. The service presents results to the medical expert who is thus assisted into entering new (or updating existing) risk factor descriptions into the system.

**Educational resources aggregation and annotation system.** This service allows the annotation of educational resources by medical experts. This leads to the generation of appropriate RDF triples of educational resource metadata, to be stored into the public RDF repository.

**Sensor data aggregation.** This includes a collection of services that support the personal sensor data aggregation, such as: authentication with 3rd party data sources, pulling data from manufacturers’ data cloud, subscription to pub/sub services, and transformation of data into RDF.

**Personal health record (PHR) data aggregation.** This mechanism implements the collection of relevant health information from personal health record systems, namely demographic data, diagnoses, and medication summary). The service allows automatic harvesting from an existing PHR or, alternatively, manual data entry by the patient (if a PHR is not used by the patient). Additionally, the service transforms acquired data into the appropriate RDF triples to be stored into the private RDF repository.

**Personal medical data manual entry system.** This refers to the browser-based application that will allow end-users to manually enter personal health information. It is meant to be used complementary to the PHR data aggregation service (described above) in cases where a PHR system is not used by the patient.

**Personal lifestyle data aggregation.** This service provides patient lifestyle infor-
mation as deduced from information generated by the patient’s in web presence (e.g. Google searches, Twitter). The service also transforms information into the appropriate RDF triples to be stored in the private RDF repository.

**Semantic enrichment.** This service is part of data aggregation and concerns both public and personal data. It aims at automatically transforming data from different formats into CARRE RDF statements, confroming with the CARRE ontology.

**Content delivery for CARRE visualisation and decision support.** This concerns the layer placed on top of the CARRE RDF repositories and serves the requests coming from the middleware components. It is comprised of a set of RESTful methods to serve CARRE-related requests. Typically, these requests are encoded in a web-friendly format such as JSON.

**Access control & personalised content delivery.** An access control mechanism is deployed on top of the RDF repositories to ensure the secure delivery of data to and from the middleware components. Furthermore, this access control service will be responsible for the personalisation of the delivered content, i.e. an end-user request sent to/from the application space will be processed accordingly here.

**Personal data analytics.** This service analyses all personal data collected through APIs, compares these with generic medical evidence data on risk factors and creates the personalised risk model for each patient.

**Comorbidity model visualisation.** This service creates the visualisation of the generic and personalised risk model and also integrates the visual output of the decision support service.

CARRE services use and interlink private and public data to create a variety of output which includes:

**Generic visualization of risk factors.** This illustrates graphically the CARRE comorbidity model. It is accessible by both authenticated and guest users and can be used to present an overview (e.g. including all risk elements) or present a detailed risk association with all relevant data.

**Personalized visualization of risk factors.** This includes an interactive graphical user interface and provides the set of pictograms (graphics), text and other visual components. One of the features of all visualization components are scalability and adaptability in order to allow easy configuration of presented elements (interface) on tablets or standard monitor display.

**Personalized alerts.** This is the outcome of the decision support service (DSS). A basic feature of DSS is the timely identification of new health risks for the patient and creation of the respective alerts. Hence the DSS provides the variables for the visualization object on how to present a given piece of information using various techniques – for example presentation of comorbidity risk level. DSS informs the patient about medical check-ups, monitoring, increased risk of disease progression and transition, the need to change diet etc.

**Display of (links to) relevant educational resources.** This refers to information
indexed and provided through linking mechanisms by CARRE. The targets of the above links are web-based repositories with educational data. The links are provided complementarily to medical terminology in order to assist end-users to understand the CARRE-produced knowledge.

4 Major Outcomes

Major project outcomes include research and technological development towards data aggregation, semantic data and knowledge representation and linking, visual analytics and decision support services. Also, the work is supported by a conceptual model of empowerment services as a cognitive process and best practices for preserving privacy by design in personal eHealth systems. CARRE project breakthroughs are all provided freely as open source software via the project web site: https://www.carre-project.eu/innovation/breakthroughs/.

4.1 A Conceptual Model of Patient Empowerment as a Cognitive Process

Patient empowerment has emerged as a new paradigm to improve medical outcomes through self-directed behavior change. Rappaport [26] defined empowerment as “a process, a mechanism by which people, organizations, and communities gain mastery over their affairs”. In health science, patient empowerment is understood as an enabling process or outcome [27,28] by which patients are encouraged to autonomous self-regulation, self-management and self-efficacy in order to achieve maximum health and wellness [29]. Empowerment can therefore be described as a process where the purpose of an educational intervention is to increase patients’ ability to think critically and act autonomously; while it can also be viewed as an outcome when an enhanced sense of self-efficacy occurs as a result of the process [30]. Reviews of the field reveal three basic dimensions of patient empowerment: education, engagement, and control [31,32]. Although there is a clear distinction between these three dimensions, often empowerment interventions include all three dimensions in their goal and, eventually, in their design. This has obvious implications for the methodology and tools that will be used to evaluate the specific intervention.

Following the overall approach of cognitive psychology, we propose to treat patient empowerment in terms of three levels of increasing complexity and importance [33]: awareness, participation and control (Fig. 3). The most basic level refers to the complex task of health awareness and corresponds to the educational dimension described above. Treating this as personal awareness of one’s own health rather than the process of formal education underscores the fact that the patient should clearly understand the implications of the information provided and is able to act upon it. We can identify three sub-levels of increasing complexity [34]: information gathering (i.e. simple facts), knowledge (i.e. information with a purpose), and understanding (i.e. conscious knowledge, achievement of explanation and grasp of reasonableness). At a second level, empowerment strives to achieve patient’s engagement in the health care process. Here we should emphasize active and proactive participation in managing the disease
and its treatment and in preventing disease progression and transition. Successful patient’s participation can be achieved only when the patient is health aware. However, this is not the only prerequisite. The patient additionally needs emotional strength, a suitable, supportive physical environment, an enabling framework and last but not least an accurate feedback about the progress of his/her disease and disease management in order to be able to re-adjust participation. The final level of empowerment is about achieving control which includes the abilities of decision making and mind changing. Decision making refers to a collaborative process where patient and healthcare professionals discuss and interact to reach a shared decision. On the other hand, control of action involves internal cognitive processes – what we refer to as mind changing; that is the capacity to modify one’s own mental states like beliefs or intentions.

**Fig. 3.** Patient empowerment modelled as a cognitive process. There are three distinct levels of increasing complexity and importance: awareness, engagement and control. Each level presents its own contributing factors.

CARRE aims to create a set of empowerment interventions that address all level of the proposed empowerment model. In particular:

– provide visual and quantitative model of disease progression pathways and comorbidities trajectories, based on current medical evidence (awareness: information aggregation and knowledge);
– personalize the risk model to each individual based on his personal medical data and real-time sensor measurement to support disease status awareness (awareness: understanding);
– use the personalized model in conjunction with real time monitoring to create a set of alarms to enable patient engagement (engagement: enabling framework); and
– provide advanced decision support services and mind change interventions based on the real-time coupling of medical evidence, personal health status and intentions and beliefs, as deduced from social web data mining (control).

4.2 Representing Medical Evidence on Risk Factors: the CARRE ontology

The core of CARRE functionality revolves around the concept of comorbidity, and in particular comorbidities in the case of cardiorenal syndrome. From the overview of the medical domain presented in earlier sections, it is evident that cardiorenal disease and comorbidities is a complex domain. Related conditions do not have a single cause, but medical evidence suggests that there are multiple causal chains. Existing algorithms for risk prediction for, e.g., cardiovascular risk, include the Framingham equation [35], the Joint British Societies (JBS) formula [36] and the ASSIGN score [37]. These only take account of a limited set of risk factors and possible outcomes, as these have been produced by specific clinical studies – thus can be limited in application. In order to capture this complexity, CARRE developed a conceptual model and ontology [38] to generically describe the concept of risk factor and then use this to create a structured open repository of current medical evidence on risk factors for the cardiorenal disease.

In medicine risk is the probability of a negative outcome on the health of a population. The agents responsible for that risk are called risk factors when they aggravate a situation and are being used to predict up to a degree the occurrence of a condition or deterioration of a patient’s health dividing the population into high and low risk groups [39]. In general, risk factors can be: environmental (e.g. chemical, physical, mechanical, biological and psychosocial elements that constitute risk factors to public health); demographic (e.g. age, sex, race, location, occupation); genetic; behavioral and lifestyle related (e.g. smoking, overeating, unprotected sexual life, excessive alcohol drinking, drug abuse and sedentary lifestyle); and biomedical (i.e. conditions present in a patient that can influence his/her health by creating or affecting other conditions).

The relation between the two conditions, initial and resulting may not always be proven causation. Following UMLS Semantic Network [40], associations between a risk factor and the associated condition include:

– is an issue in: the risk factor is a point of discussion for a condition
– affects: the risk factor produces a direct effect on the condition
– causes: the risk factor brings about the condition
– complicates: the risk factor causes another (risk) factor to become more complex (recursive).

The existence of a risk factor isn’t a determinant of consequence but the degree of its influence can be statistically calculated. Extending work on general risk analysis [41], we can present a risk factor as a triplet: (1) what can happen; what is the existing
event, factor/condition/disorder; (2) what are the consequences: what is the resulting condition/disorder; and (3) what is the likelihood of having these consequences when the event is present. The way to measure the likelihood requires a certain quantitative biomarker or other measurable quantity and observational studies that statistically calculate a probability. This probability is expressed as a risk ratio. Based on this description, primary concepts and their relationships are identified in the paragraphs below and shown schematically in Fig. 4.

Fig. 4. Basic concepts and their relationships in the CARRE medical risk factor model as described by the CARRE risk factor conceptual model and ontology

The association of one risk element as the risk source with another risk element which is the negative outcome under certain conditions is a ‘risk association’. Note that a source risk element can be associated to a target risk element with more than one risk association. This association is a rather complex one and is characterized by a number of other concepts: the association type (causal or other); the risk ratio value and type (relative risk, odds ratio, etc.); the observable condition; and the evidence source. For the association to occur, certain circumstances should exist. These prerequisite circumstances relate directly to the existence of the risk agent (source risk target) and/or its severity, and/or any other specific conditions. These are reported via certain ‘observables’, that is, variables that can be measured or otherwise ascertained (e.g. biomarkers, biometric variables, biological signals and other non-biological factors e.g. environmental). The circumstances thus are ascertained via an explicit logical expression that involves observables; this logical expression is termed ‘observables condition’. Finally, risk associations in medicine are determined from clinical studies as reported in evidence based medical literature. Thus, each association is directly related to an ‘evidence source’ which is a specific scientific publication.

This analysis is captured in the formal CARRE ontology developed in OWL/XML CARRE ontology and published in the NCBO Bioportal, (at
CARRE ontology links to a number of relevant external standardized vocabularies, namely: ICD-10 [42] and SNOMED-CT [43] (for diseases), FOAF and HL7 (for demographics), UMLS [44] (for genetic, environmental and behavioural concepts), W3C ontologies for time, time zone and geography, CMO and LOINC (for measurements), and QUDT [45] and UO [46] (for units of measurement).

4.3 Risk Factor Description System and Repository

In order to enable the open and seamless use and reuse of these described medical risk factors, we have developed an on-line web based system for their description. Also, the resulting risk factor descriptions are available as Linked Data, in the Resource Description Framework (RDF) format [47], via an open access RDF repository. The system has been designed based on the concept of microservices [48] architecture and is implemented in HTML5 and JavaScript using the AngularJS framework [49]. The application follows a graph data model and the data scheme is described by the CARRE risk factor ontology.

Medical experts used the ontology and system to identify and describe 96 different risk factors. The descriptions resulted in 253 respective associations. There were 53 involved risk elements, corresponding to a total of 90 different observables. The evidence sources used were 60 scientific publications. The risk factor identification methodology (summarized in Fig. 5) involves systematic literature search by medical
experts to point out the latest highest evidence level scientific publications on risk factors in cardiorenal disease and comorbidities. The resulting risk factor repository is updated continually and is freely available from the project web site. A typical screenshot of the system in Fig. 6 shows the textual description of a risk factor along with the abstract of the evidence source as in PubMed and some alternative graphical views of the risk factor network.

Fig. 6. Typical screenshots of the web based risk factor description system. The main screen shows the description of a risk evidence while the screens at the bottom and right show different graphical representations supported to depict views of the complex risk factor network.

4.4 Personal Data Aggregation

Based on the risk factor analysis, useful self-monitoring parameters include: body weight, fat, fluid balance, blood pressure, pulse wave velocity and arterial stiffness parameters, arrhythmias, glucose level in blood, physical activity. CARRE project has selected and tested a large number of representative personal sensors available in the market [50] and developed software aggregators to harvest data from vendor clouds via their provided APIs. Aggregators involve where needed novel work on advanced signal processing, for example; automatic analysis of electrocardiograms for the detection of atrial fibrillation episode [51]; processing of electrocardiographic and impedance plethysmographic signals acquired using modified body composition scales for the calculation of pulse arrival time, which is directly related to arterial stiffness [52]; a photoplethysmography based method for automatic detection of premature ventricular contractions [53].
CARRE project innovation involves also the development of new personal sensors, namely a wristwatch type multisensory system for continuous monitoring of physiological and biomechanical parameters and a weight scale for intermittent body composition and cardiovascular parameters monitoring.

Another aggregator developed within the project aims to extract patient intentions from web searches [54]. This aggregator emphasizes privacy by design to preserve patients’ discretion.

### 4.5 Visual Analytics

Visual analytics techniques are essential to handle complex information in a complex world. Visualization techniques offer means for exploratory navigation, which are useful when the user does not have clearly defined objectives (as opposed to searching). As graph structures are common in many application domains a variety of different graph visualization approaches have been developed [55]. Such approaches offer means to interactively navigate, analyze and gain understanding of the structure and relationships within the data, for example in semantic databases and semantically described social networks [56]. CARRE employs visual analytics to help medical professionals to better understand the individual patient’s disease development and help patients to understand their own disease development, which in turn assists them to adhere to the self-management plan.

The role of visual analytics is to visualize health data, risk factor data and the integrated visual analysis of health data and risk factor data. CARRE provides web-based components for interactive health data visualization and risk analysis, including healthline and parallel coordinates for fitness and biomarker data, node-link diagram, chord diagram and sankey diagram for risk factor data visual analysis and a preliminary experiment on personalized risk visualization and disease progression simulation [57]. A healthline is a special form of timeline to visualize multiple variables of continuous fitness statistics and biomedical markers which may cover a long period and in CARRE it is used to display personal sensor data. These healthlines can be studied visually for correlations via the technique of parallel coordinates [58], an approach for visualizing multiple quantitative variables using multiple axes which are placed parallel to each other in the most common case.

The core knowledge base of risk factor evidence is visualized by a number of different techniques. These data are essentially a graph whose nodes are risk elements with multiple attributes attached, such as risk element type and observables, while each directed edge represents a risk factor directed from the source to the target risk element, described by a number of attributes, such as the observable condition and information on the likelihood. As such, a traditional risk factor data visualization is a node-link diagram [59] with force-directed layout algorithms [60] to allow for dynamic and interactive graphs. To support visual information disambiguation for graphs with large numbers of nodes, we also implement the visualization of the chord diagram [61]. The benefits of the chord diagram are that all the nodes are arranged on a circle and the edges from one node are grouped and bundled, which reduces the hairball problems which occur in the node-link diagram. A comparative example of the node-link and chord visualizations of the risk factor network in cardiorenal disease as
in current evidence is shown in Fig. 7. These visualizations of the risk factor evidence data are also interlinked and parametrized on the basis of the personal medical data to show the personalized risk network for each patient. A number of filters can also be applied by the patient to project different evolutions of the personal health risk network when changes in the personal variables occur; this allows for a visualization of expected health outcomes linked to specific lifestyle and personal biometrics changes (Fig. 8).

Fig. 7. Node-link visualization of the risk factor evidence data for the cardiorenal disease (left) and the corresponding cord diagram (right). Both visualizations are interactive and display related information and attributes on hovering the mouse over various visualization elements.

Fig. 8. On the left, the node-link visualization of the personalized risk factor network for a 70 year old female with a weight of 94Kg and height 160cm (which corresponds to a body mass index above 36) and hypertension. On the right, the visualization of the risk factor network for the same individual after reducing the body weight to achieve a normal value body mass index. The visualization changes interactively as the patient slides bars that correspond to any of the parameters that can be altered via lifestyle management and adherence to therapy.
4.6 Evaluation

The CARRE service is currently being evaluated via a randomized control trial the impact of the CARRE intervention to (a) health literacy, (b) patient empowerment, (c) quality of life and (d) health condition (including risk reduction and prevention, disease progression, reduction in necessary medication, and lifestyle improvement). The clinical investigational study will produce the first results after 6 months of clinical investigation in a total of 80 patients at two different pilot sites in two different EU countries. The clinical investigation is planned to extend beyond the duration of the project so as to be able to draw statistically significant solutions after longer study periods.

5 Discussion

CARRE aims at strengthening the cardiorenal patient, mainly by reinforcing the patient understanding of the disease and its comorbidities complex interdependencies as they are personalized to the specific patient. CARRE thus implements the “patients getting up off their knees” mandate of current patient empowerment initiatives [62]. By improving the patient’s ability to understand and manage his/her own complex disease in the presence of comorbidities, patients can better negotiate with different teams of health professionals and navigate the complexities of health systems for comorbid management; literature suggest that this is crucial to achieving better health outcomes [63].

Studies in the mid-1990s based upon firm-level data from thousands of companies suggest that there is a significant payoff from information technology (IT) investments [64]. These results suggest that investing in IT is on average a positive return on investment activity, but the benefits of IT investments are difficult to measure and risk factors can significantly impact the actual ROI realized. Social return on investment is a method for measuring values that are not traditionally reflected in financial statements, including social, economic and environmental factors, which can identify how effectively an organization uses its capital and other resources to create value for the community [65]. While a traditional cost-benefit analysis is used to compare different investments or projects, social return on investment is used more to evaluate the general progress of certain developments, showing both the financial and social impact of the corporation. The issue of value creation by eHealth systems has been explored in several EU-funded projects. An initial consolidated attempt was undertaken by the European eHealth IMPACT study [66]. The study concluded that identifying the economic and financial benefits of eHealth needs to take into consideration the overall operational context within which these applications and services lie. More importantly, it indicated the need to go beyond non-financial elements, by considering issues such as change management and organizational adaptation within the healthcare delivery organization for developing a specific eHealth system or application.

CARRE puts the citizen on the center. Empowerment is implemented with an interactive graph that shows the particular risks customized for each individual based on their status as derived from their personal medical data and also from personal mobile
sensors, such as activity meters, scales and blood pressure or glucose monitors. The graph can be used to plan best lifestyle changing regimes to lower risks, improve odds for disease progression and delay disease deterioration. CARRE also offers a range of intuitive alerts to help patients or people at risk of chronic heart or kidney disease to apply efficient self-monitoring and take educated decisions on their lifestyle and health management. The project also empowers the medical expert. CARRE has developed a novel system to describe current medical evidence on risk factors in a comprehensive and intuitive way, including concise tabular and interactive graphical views. New evidence on risk factors can be incorporated in this dynamic reference database via a simple to use interface and following a transparent rigorous peer review process. Additionally, experts can use the personalized patient models to explain complex health conditions to the patients and collaborate towards informed co-design of personalized care plans.

CARRE research outcomes include a number of scientific and technological innovations, all provided as open access technologies from the project site: a novel risk factor ontology; a medical risk factor database and respective management system with web user access and open APIs; aggregators for personal medical sensors, personal health records, educational resources, and scientific literature; new sensors and signal processing algorithms: wrist watch activity meter and body composition scale; advanced visual analytics for exploring complex risk factor trajectories; decision support engine and personalized services; patient empowerment cognitive model; a privacy-by-design approach for personal eHealth applications; and standards deployment. Overall, CARRE is designed to steer the active involvement of patients and health authorities in the management of comorbidities. CARRE service brings evidence based medicine to the patient via an intuitive interactive interface. This enables the patient to understand their health risks and set their own personalized lifestyle goals in order to reduce risks and prevent health deterioration and disease progression.

Acknowledgements

CARRE project presented in this paper is the result of a highly collaborative work of six different European research teams under the leadership of Prof. E. Kaldoudi (Democritus University of Thrace, Greece), Prof. J. Domingue (Open University, UK), Dr. E. Liu (University of Bedfordshire, UK), Dr. D. Stundys (Vilnius University Hospital Santariskiu Klinikos, Lithuania), Prof. A. Lukosevicius (Kaunas University of Technology, Lithuania) and Prof. R. Szewczyk (Industrial Research Institute for Automation and Measurements, Poland). The project is funded by European Commission under the FP7-ICT grant no. 611140.

References

14. CDC: Awareness and Treatment of Uncontrolled Hypertension Among Adults. MMWR 61 (2012) 703–709
15. CDC: Prevalence, Treatment, and Control of Hypertension. MMWR 60 (2011) 103–8
36. JBS3 Board: Joint British Societies’ Consensus Recommendations for the Prevention of Cardiovascular Disease (JBS3). Heart 100S2 (2014), i11–i67

45. QUDT: Quantity, Unit, Dimension and Type Ontologies, http://qudt.org/ (last visited on May 15, 2016)
49. Google; AngularJS framework https://angularjs.org/ (last visited on May 15, 2016)