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D.2.1. Domain Analysis & Use Case Definition

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CARRE Contacts

Project Coordinator:	Eleni Kaldoudi	kaldoudi@med.duth.gr
Project Manager:	Koula Zigeridou	kzygerid@alex.duth.gr

DUTH Democritus University of Thrace	Eleni Kaldoudi	kaldoudi@med.duth.gr
OU The Open University	John Domingue	john.domingue@open.ac.uk
BED: Bedfordshire University	Enjie Liu	Enjie.Liu@beds.ac.uk
VULSK: Vilnius University Hospital Santariskių Klinikos	Domantas Stundys	Domantas.Stundys@santa.lt
KTU Kaunas University of Technology	Arunas Lukosevicius	arunas.lukosevicius@ktu.lt
PIAP Industrial Research Institute for Automation & Measurements	Roman Szewczyk	rszewczyk@piap.pl

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		Comorbidities management & patient empowerment	Domantas Stundys (VULSK) Mindaugas Barysas (VULSK)
		Survey	Eleni Semertzidou (DUTH) Simos Symeonidis (DUTH) Koula Zigeridou (DUTH) Stefanos Roumeliotis (DUTH) Dimtitris Papazoglou (DUTH) Eleni Kaldoudi (DUTH)
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Executive Summary

This deliverable contains an overall domain analysis (including legal framework for medical and personal data privacy and security), the detailed methodology for use case definition and the results of the user survey for scenarios definition, as well as the definition of CARRE use cases.

About CARRE

CARRE is an EU FP7-ICT funded project with the goal to provide innovative means for the management of comorbidities (multiple co-occurring medical conditions), especially in the case of chronic cardiac and renal disease patients or persons with increased risk of such conditions.

Sources of medical and other knowledge will be semantically linked with sensor outputs to provide clinical information personalised to the individual patient, so as to be able to track the progression and interactions of comorbid conditions. Visual analytics will be employed so that patients and clinicians will be able to visualise, understand and interact with this linked knowledge and also take advantage of personalised empowerment services supported by a dedicated decision support system.

The ultimate goal is to provide the means for patients with comorbidities to take an active role in care processes, including self-care and shared decision-making, and also to support medical professionals in understanding and treating comorbidities via an integrative approach.

Terms and Definitions

The following are definitions of terms, abbreviations and acronyms used in this document.

Term	Definition
ACE – I	Angiotensin converting enzyme inhibitors
ACR	albumin to creatinine ratio
ACS	Acute coronary syndrome
AER	albumin excretion rate,
AF	Atrial fibrillation
AHF	Acute Heart Failure
AKI	Acute kidney injury
ARBs	Angiotensin II receptor blockers
Biomarker	A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention
BMI	Body mass index
BNP	Brain-type natriuretic peptide
BP	Blood pressure
bpm	Beats per minute
BW	Body Weight
CAD	Coronary artery disease
CAN	Cardiovascular Autonomic Diabetic Neuropathy
CHD	Coronary heart disease
CHF	Chronic heart failure
CI	Confidence interval
CKD	Chronic kidney disease
Comorbidity	The presence of one or more additional disorders (or diseases) co-occurring with an existing primary disease or disorder.
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CRS	Cardiorenal syndrome
CVD	Cardiovascular disease
CVP	Central venous pressure
DBP	Diastolic Blood Pressure
DM	Diabetes mellitus
DN	Diabetic nephropathy
DPWP	Data Protection Working Party
ECG	electrocardiogram
EEA	European Economic area

EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EHR	Electronic health record
EPO	Erythropoetin
ESRD	End stage renal disease
EU	European Union
FPG	Fasting Plasma Glucose
GFR	Glomerular filtration rate
GPS	Global Positioning System
HbA1c	Glycated hemoglobin
HDL	High density lipoprotein
HF	Heart failure
HR	Heart rate
ICT	Information and communications technology
IPDAS	International Patient Decision Aid Standard
LDL	Low density lipoprotein
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
NYHA	New York Heart Association
OGTT	Oral glucose tolerance test
PAD	Peripheral artery disease
PAH	Pulmonary arterial hypertension
PAR	Population attributable risk
PP	Pulse pressure
PTH	Parathormone
PWV	Pulse wave velocity
RBC	red blood cells count
Risk factor	Any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury
RQ	Research Question
RR	Relative risk
SBP	Systolic blood pressure
SCD	Sudden cardiac death
SLE	Systemic lupus erythematosus
WBC	White blood cells count
WC	Waist circumference
WHO	World Health Organisation

1. Introduction

This document is a report on the project Task 2.1. Domain analysis and use case definition.

The deliverable contains an overall domain analysis, including medical domain analysis, overview on comorbidities' management, patient`s empowerment, legal issues for medical and personal data privacy and security, results of the user survey, as well as the definition of CARRE main scenarios. The goal of the deliverable is twofold

a) To lay the background for further modelling of the cardiorenal domain. This is done mainly in Section 2. Further modelling will then be conducted as part of T.2.2 and T.2.4.

b) To lay the background for defining CARRE functional requirements. This is done mainly in Sections 3-6. User requirements will be drawn as part of T.2.2.

Section 2 gives an overview of the medical domain. In particular, Section 2.2. presents cardiorenal syndrome and its various types, giving an overview of the ones that pertain to CARRE project (i.e. Types 2, 4, and 5). Then subsection 2.3 gives a list of different factors and medical conditions related to the cardiorenal syndrome. The section starts with an approach of organizing all these factors and conditions into a hierarchy: (1) almost healthy status with presence of risk factors, (2) at least one medical condition that may lead to cardiorenal disease is diagnosed, (3) either heart of renal disease is diagnosed, (4) cardiorenal syndrome is presented, and (5) a number of other resulting/related conditions are present, including end stage renal or heart disease. This is followed by a brief presentation of each factor and condition individually, summarizing current medical evidence on prevalence and also listing common biomarkers for each factor/condition. Based on this evidence, we selected a number of the major risk factors that lead from one condition to another in the cardiorenal disease progression. These are presented in the final subsection 2.4. This subsection also includes a brief discussion on how to present a risk factor and gives a first approach towards the attributes needed to adequately describe it within CARRE project. This discussion is considered as required input to the modelling of risk factors (T.2.2), the description of medical evidence sources (T.2.3) and the CARRE scheme and ontology (T.2.4).

Section 3 provides a literature reseach on patient empowerment in comorbidities management. Section 4 presents a summary of the findings of the survey on perceptions of CARRE users; survey design and detailed responses are given in Annexes 1-3. Section 5 summarizes legal issues in terms of data privacy and security. Section 6 presents CARRE intended user groups and major use cases. Section 7 holds a reference list used for this deliverable.

2. Medical Domain Analysis

2.1. Introduction

Medical domain analysis aims to analyse the medical domain of cardio renal disease. The overview of cardiorenal syndrome types, analysis of CRS related medical conditions including co-existing diseases and characteristics or exposures of an individual that increases the likelihood of developing a cardiorenal syndrome (risk factors) and the indicators of pathogenic processes (biomarkers) leading to development and progression of cardiorenal syndrome according to current medical evidence based literature analysis is provided here. This information represents the basis of understanding for defining CARRE information model and will serve for designing the scheme and ontology during further project activities (output to T2.2, T2.3, T.6.2, and T.6.3).

2.2. Cardiorenal Syndrome Overview

Chronic heart failure and chronic renal failure are at epidemic proportions, worldwide. These patients have significantly altered cardiac, renal and all-cause outcomes [1]. Primary disorders of one of these two organs often result in secondary dysfunction or injury to the other [1,2]. Such interactions represent the

pathophysiological basis for a clinical entity called cardiorenal syndrome (CRS). Although generally defined as a condition characterized by the initiation and/or progression of renal insufficiency secondary to heart failure [3], the term CRS is also used to describe the negative effects of reduced renal function on the cardiovascular system [4]. There is no single definition that appropriately describes CRS. Prof. Claudio Ronco of San Bortolo Hospital, Vicenza, Italy defined recently the cardiorenal syndrome as a pathophysiologic disorder of the heart and kidneys whereby, acute dysfunction of one organ may induce acute or chronic dysfunction of the other [5]. Such interactions represent the pathophysiological basis for a clinical entity called cardiorenal syndrome.

Considering the complex and bi-directional relationship between the heart and the kidneys, a subdivision of CRS into 5 different subtypes seems to provide a more concise and logically correct approach. The depth of knowledge and complexity of care necessary to offer best therapy to these patients demand a multidisciplinary approach, combining the expertise of cardiology, nephrology and critical care [6].

2.2.1. CRS classification

Cardiorenal syndrome Type 1 (acute CRS) reflects an abrupt worsening of cardiac function (acute heart failure) leading to acute kidney injury (AKI). Acute kidney injury is commonly defined as an abrupt decline in renal function, over the course of hours to weeks, clinically manifesting as a reversible acute increase in nitrogen waste products measured by serum creatinine. Glomerular Filtration Rate, (GFR, measured in ml/min) which describes the flow rate of filtered fluid through the kidney, is a reliable measure for kidney function. A GFR above 90ml/min without proteinuria characterises a normal kidney function.

The mechanisms by which the onset of acute heart failure (AHF) or acutely decompensated chronic heart failure (CHF) leads to AKI are multiple and complex and vary from patient to patient [7]. The epidemiological data of CRS Type 1 shows the size of the problem. More than 1 million patients in the USA are admitted to the hospital every year with either de novo AHF or acutely decompensated CHF [8]. In these patients, chronic renal failure (CRF) is a common occurrence and predisposes them to AKI [9,10]. In CRS Type 1 the early diagnosis of AKI remains a challenge, since it is a strong predictor of mortality and hospitalization.

Cardiorenal syndrome Type 2 (chronic CRS) comprises chronic abnormalities in cardiac function (e.g. congestive CHF) causing progressive CKD. Prevalence of renal dysfunction in chronic HF has been reported to be approximately 25%, and close to 50% of patients with CHF appear to have CKD, stage 3 (GFR 30-59ml/min) or 4 (GFR 15-29ml/min) [11]. Worsening renal function in heart failure is associated with adverse outcomes and prolonged hospitalizations and even slight decreases in GFR increase significantly mortality risk in these patients [12]. Thus, an effort to preserve renal function seems of most importance in patients with CHF.

Cardiorenal syndrome Type 3 (acute renocardiac syndrome) is characterized by an abrupt and primary worsening of renal function (e.g. AKI, ischemia or glomerulonephritis) leading to acute cardiac dysfunction (e.g. HF, arrhythmia or myocardial ischemia). Type 3 CRS is less common than type 1, but this may be due to the fact that it has not been studied systematically. AKI defined by RIFLE criteria (Risk, Injury, Failure, Loss and End-stage kidney disease) [13], appears to affect close to 20% of hospitalized patients [14] and 35% of patients in intensive care units [15]. AKI can affect the heart through several pathways, whose hierarchy is not yet established and is identified as an independent, strong predictor of hospital mortality.

Cardiorenal syndrome Type 4 (chronic renocardiac syndrome) describes a state of CKD (e.g. chronic glomerular disease) contributing to decreased cardiac function, left ventricular hypertrophy (LVH), cardiac hypertrophy, diastolic dysfunction and/or increased risk of adverse cardiovascular events. Patients with CKD have between a 10 and 20-fold increased risk of cardiac death compared with age-/gender- matched control subjects without CKD [16,17]. CKD is considered a greater predictor of cardiovascular disease than diabetes mellitus [18]. Furthermore, the risk of cardiovascular death is higher than the risk of reaching end stage renal disease (ESRD) in all stages of CKD, making cardiovascular prevention a major issue in nephrology and cardiology practice.

Cardiorenal syndrome Type 5 (secondary CRS) reflects a systemic condition causing both cardiac and renal dysfunction. Sepsis, diabetes mellitus, systemic lupus erythematosus are examples of such diseases affecting both renal and cardiac function. The systematic information on type 5 CRS is limited, although there is an appreciation that as many organs fail in this setting, mortality increases.

In both chronic and acute situations, an appreciation of the interaction between heart or kidney during dysfunction of each or both has practical clinical implications [6]. CRS Type 1 and CRS Type 3 include acute

conditions (acute heart failure and acute renal failure) which need an urgent management. These patients should be admitted to hospital and treated under the supervision of specialists. CARRE Project concentrates on chronic states and outpatient services. Therefore, the further domain analysis does not scrutinise the CRS Type 1 and type 3.

In general, cardiorenal syndrome is a complex condition, with a large number of factors and conditions related to it (Figure 1). The following paragraphs of this Section 2.2 provide an overview of current evidence on types 2, 4 and 5. The following Section 2.3 then provides an overview of individual conditions related to cardiorenal syndrome.

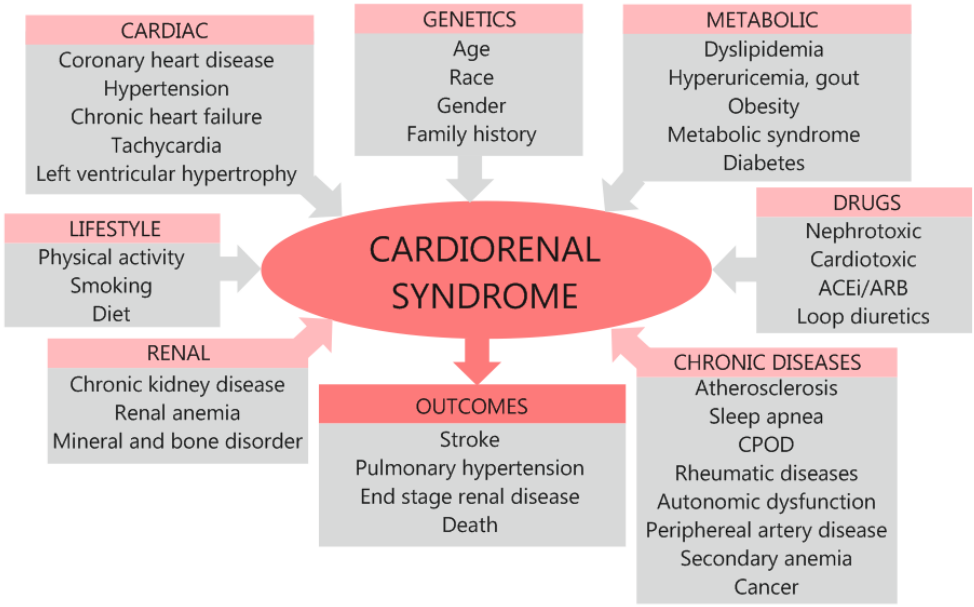


Figure 1. Overview of factors and comorbidities related to cardiorenal syndrome.

2.2.2. CardiorenalSyndromeType 2

CRS Type 2 is characterised by chronic abnormalities in myocardial function leading to worsening kidney disease. Chronic abnormalities in systolic or diastolic myocardial performance lead to alterations in neurohormone activation, renal hemodynamics, and a variety of adverse cellular processes leading to apoptosis and renal fibrosis [19].

The prevalence of renal dysfunction in patients with heart failure varies in literature. The prevalence of renal dysfunction in chronic heart failure (CHF) is approximately 25% [7]. The majority of epidemiologic information of CKD in the HF population stems from large registries such as the Acute Decompensated Heart Failure National Registry (ADHERE) [20], Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) [21], and EuroHeart Failure (EURO HF) [22,23]. Moreover, the prevalence of renal dysfunction in patients with heart failure differs according the degree of the renal dysfunction [22,24].

In patients with HF, comorbid CKD can result from intrinsic renal disease, hemodynamic abnormalities, or a combination of the two [25]. Special attention should be paid on common risk factors for CKD and HF, such as atherosclerosis, renovascular disease, hypertension, and diabetes [20].

The most common comorbidities in heart failure are hypertension, chronic pulmonary disease, arrhythmias, ischemic heart disease, obstructive sleep apnoea, renal impairment, obesity, diabetes mellitus, thromboembolism [26,27]. Any of the before mentioned comorbidities may affect prognosis of patients with HF in an unfavourable manner [20].

Available data suggest that in most cases, CHF, renal dysfunction, and anaemia represent a continuum of disease progression [28]. The incidence of arrhythmic complications increases as eGFR decreases in HF

patients [29]. If kidney dysfunction precedes the onset of AF, the measurement of kidney function may represent a relatively inexpensive and efficient way to identify individuals at higher risk for AF [30]. In patients with high-risk cardiac disease enrolled in the Multicentre Automatic Defibrillator Implantation Trial-II, a significant increase was found in the risk of sudden cardiac death with declining renal function [31]. Cardiorenal syndrome is documented as a prognosticator for cerebrovascular disease (e.g. stroke) [32]. Pulmonary hypertension is a well-recognized consequence of HF. Also, patients with CKD often have pulmonary comorbidities such as sleep apnoea that can lead to the development of pulmonary hypertension [33].

The presence of kidney dysfunction plays a detrimental role, as it is considered an adverse prognostic marker and a strong predictor of poor outcome in patients with HF [24].

2.2.3. Cardiorenal Syndrome Type 4

Cardiorenal syndrome (CRS) Type 4, or chronic renocardiac syndrome, describes a state of chronic kidney disease (CKD) leading to heart injury, disease and/or dysfunction [5]. This subtype refers to chronic abnormalities in renal function leading to cardiac disease and reflects the extreme burden of cardiovascular disease (CVD) in patients with CKD such as primary glomerular disease, hereditary nephritis, polycystic kidney disease, obstructive nephropathy, and other [34,35]. The observation that even modest reductions in renal function correlate with increased CVD morbidity and mortality has led to the recognition that CKD is an independent risk factor for CVD [36].

CRS Type 4 is a growing societal problem as the aging population, with increasing incidence of CKD, diabetes, obesity, hypertension, and other cardiovascular risks, lead to higher numbers of individuals suffering the complications of this bidirectional disorder. The rising prevalence of CKD and end-stage renal disease (ESRD) is a global medical and epidemiological problem [37]. Current estimates of CKD account for at least 13%-2% rise in a decade- of the U.S adult population (30 million patients), thus becoming a major public health problem. The European Kidney Health Alliance (EKHA) reports that approximately 10% of European citizens are affected by some degree of CKD [38].

The most common risk factors for CKD include diabetes, hypertension, cardiovascular disease, a family history of CKD, and age greater than 60 years [39]. A growing body of evidence shows that declining renal function is an independent risk factor for CVD. Patients experiencing even transient renal dysfunction have increased long-term risk for CVD [40]. Onset of CKD is associated with an increased predilection for the development of CVD-related events [41,42].The association between reduced renal function and cardiovascular risk is apparently consistent [43] at estimated glomerular filtration rates <60 ml/min. The risk for CVD increases gradually with decreasing renal function [44]. Furthermore, the risk of cardiovascular death is higher than the risk of reaching end stage renal disease in all stages of CKD, making cardiovascular prevention a major issue in nephrology and cardiology practice [45,46]. Almost half of all deaths in patients with CKD are caused by CV events, particularly congestive CHF, acute myocardial infarction and sudden cardiac death [47]. With increasing CKD levels, culminating in dialysis dependence, the association between CKD and cardiac disease follows a dose-response relationship.

2.2.4. Cardiorenal Syndrome Type 5

Cardiorenal syndrome Type 5 (secondary CRS or cardio-renal involvement in systemic conditions) is a clinical and pathophysiological entity to describe characterized by the presence of combined cardiac and renal dysfunction due to acute or chronic systemic disorders [48,7]. There is a wide spectrum of diseases that contribute to CRS Type 5, several pathophysiological mechanisms are invoked representing the response of the heart and kidney to the contributing disorder that is ongoing.

There are limited data on the incidence and determinants of CRS Type 5. In the literature, CRS Type 5 most commonly encompasses a wide spectrum of acute and chronic disorders that involve the heart and kidney [49]. The sequence of organ involvement can vary depending on the acuity and nature of the underlying disorder. The time sequence for developing CRS Type 5 depends on the underlying disease and is influenced by the underlying level of cardiac and renal function [49].

Acute systemic illnesses that can namely lead to CRS syndrome are sepsis and some more specific infectious diseases such as AIDS, malaria, hepatitis C, leptospirosis and infectious endocarditis, administration of drugs such as calcium channel blockers and heroin and cocaine intake, cancer and cancer chemotherapy, hemorrhagic shock [50]. Diabetes mellitus, amyloidosis, systemic lupus erythematosus,

rheumatoid arthritis, scleroderma and other connective tissue diseases, vasculitis, anti-phospholipid antibody syndrome, microangiopathy, thrombotic thrombocytopenic purpura, haemolytic uremic syndrome, malignant hypertension are examples of chronic diseases affecting both renal and cardiac function [23,50].

2.3. Conditions and Comorbidities

Multiple medical conditions are involved in the development and progression of CRS. Cardiac and renal axes interfere through risk factors, comorbidities, and complications. The pathogenetic interaction is demonstrated in Figure 2. One can distinguish an initial phase where the person is not yet formally diagnosed with a disease. Then, there are patients that have either heart or kidney disease. In this stage, there is an increased risk of one failing organ to lead to failure of the other, and thus lead to cardiorenal syndrome. Finally, patients with either one failing organ or with cardiorenal syndrome have an increased risk for entering end stage renal disease (ESRD, where renal function must be substituted with dialysis), and/or end stage heart failure, i.e. NYHA-IV [51]. Such patients present also an increased risk for developing a number of other complications (as shown in the bottom of the figure).

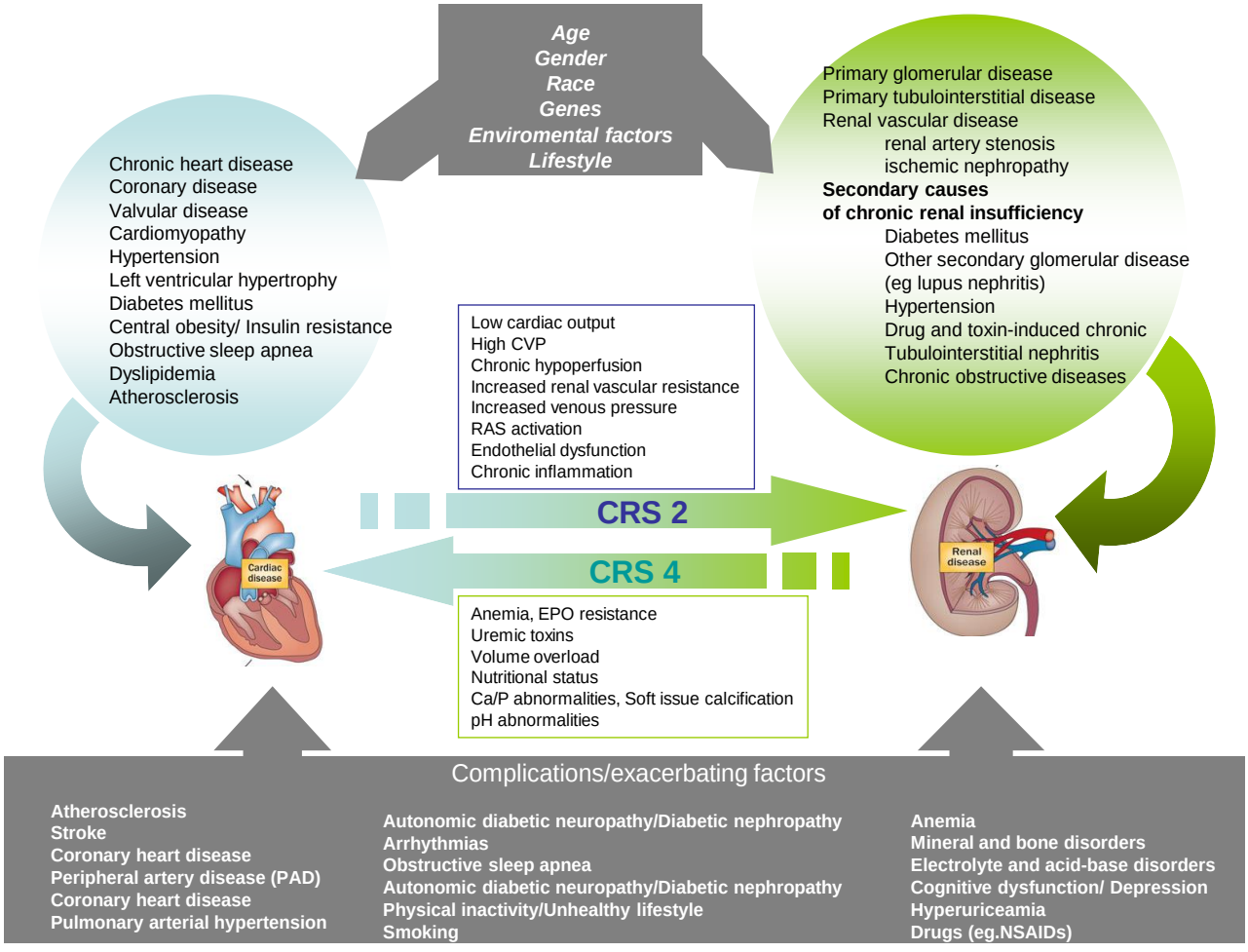


Figure 2. Overview of medical conditions involved in cardiorenal syndrome

The following paragraphs in this section present an overview of each major factor and/or condition related in any way with cardiorenal syndrome. For each one, a short description is given followed by current evidence on prevalence and its associations to other related conditions.

An important part for each condition is its quantitative characterization. This is achieved via the measurement of certain characteristic which may be used as an indicator of this medical condition - what is

called a biomarker. Thus, the short description of each factor/condition includes also a description of major related biomarkers. In CARRE we focus on biomarkers that can be easily measured at home, and involve practical and cost effective equipment, while they adequately reflect the patient's lifestyle and are of clinical importance. Some biomarkers (derived from laboratorical analysis) which cannot be easily measured at home could be obtained from patients` medical history. Thus conditions relevant to CARRE and their biomarkers are collectively listed in Table 1.

Table 1. Conditions related to cardiorenal syndrome and their biomarkers.

Group	Factors/ comorbidities	Biomarkers
Genetic	Age Race Sex Family history	Years from birth Free text Female/male Free text
Lifestyle	Physical activity	self-report, pedometers, heart rate monitors, accelerometers, indirect calorimetry, doubly-labeled water
	Smoking	Cessation, pack-year, exhaled carbon monoxide, nicotine and cotinine levels
	Diet	Daily calorie intake, dairy products, salt, etc.
Metabolic	Dyslipidemia	Lipid profile
	Hyperuricemia/gout	Serum and urine uric acid
	Obesity	bodyweight, BMI, waist circumference, body fat mass
	Diabetes	Blood glucose (fasting and 2-hours post oral glucose tolerance test), HbA1c
Cardiac	Hypertension	systolic/diastolic blood pressure
	CHF	fluid balance, ejection fraction, BNP
	Arrhytmias	heart rate, ECG
	Endothelium dysfunction	ancle-brachial index, arterial stifness
	Left ventricular hypertrophy	Myocardial mass, ECG
	Coronary heart disease	lipid profile, blood pressure, markers of endothelial dysfunction, inflammatory serum markers, LVH/LV dysfunction
Renal	CKD	creatine, GFR, ACR
	Anemia	hemoglobin
	Mineral and bone disorder	corrected calcium, phosphate, parathormone, vitamin D
Chronic diseases	Sleep apnoea	Sleep efficiency (%), fall asleep (min), hrs. slept
	COPD	Oximetry, spirometry
	Rheumatic diseases	CRP
	Autonomic dysfunction	HR variability, Ewing testing
	Atherosclerosis	lipid profile, blood pressure, markers of endothelial dysfunction, inflammatory serum markers
	Anaemia	Haemoglobin, haematocrit, ferritin, transferrin saturation
Drugs	Nephrotoxic, Cardiotoxic ACEi/ARB, Loop diuretics	

2.3.1. Gender, age, race, family history

Certain age, gender, race and family history are well established risk factors for many medical conditions, as well as CRS, and must be taken into account. For example, male gender is a risk factor for CHD. It is known that the incidence of AMI is nearly 2.5 times more frequent in male than in female, but with the increased age female patients would be affected by an increased risk of CVD because of menopause and/or comorbidity [52,53,54]. The increase in CVD risk in patients with diabetes is greater in women than in men [55]. Diabetes and a low high-density lipoprotein (HDL)-cholesterol/total cholesterol ratio operate with greater power in women. Men are at higher risk of developing ESRD, and tend to develop ESRD earlier in life, than women [56].

Systolic blood pressure and isolated systolic hypertension are major CHD risk factors at all ages and in both genders. Women are about as likely as men to develop high blood pressure during their lifetimes. However, for people younger than 45 years old, the condition affects more men than women. For people 65 years and older, high blood pressure affects more women than men [57]. Although the incidence of hypertensive complications is generally lower in women than in men. Among older adults, hypertension in women (compared to men) is both a stronger predictor of coronary risk and is more commonly seen in those with CHD. The Framingham [58] study found that the relative importance of systolic, diastolic, and pulse pressure (the difference between the systolic and diastolic blood pressures) changes with age. In patients <50 years of age, diastolic blood pressure was the strongest predictor of CHD risk; in those 50 to 59 years of age, all three blood pressure indices were comparable predictors of CHD risk, while in those ≥60 years of age, pulse pressure was the strongest predictor.

Some risk factors, such as dyslipidaemia, impaired glucose tolerance, and elevated fibrinogen have a diminished impact with advancing age, but a lower relative risk is offset by the high absolute risk in older adults. Thus, all of the major risk factors continue to be relevant in older persons. A study in the USA [59] on 3.6 million people from 2003 to 2008 showed that the prevalence of any vascular disease increased significantly with each decade of life: 2 percent in 40 to 50 year olds; 3.5 percent in 51 to 60 year olds; 7.1 percent in 61 to 70 year olds; 13 percent in 71 to 80 year olds; 22.3 percent in 81 to 90 year olds; 32.5 percent in 91 to 100 year olds. After adjusting for traditional risk factors, each additional decade of life was associated with an approximate doubling of the risk of vascular disease.

Black population develop high blood pressure more often, and at an earlier age, than whites and Hispanics do. More black women than men have high blood pressure [57]. Blacks have a considerably higher risk of ESRD partially due to hypertension and diabetes. This increased risk peaks during early adulthood and cannot be fully accounted for by racial differences in the underlying prevalence of hypertension [60]. A study by Kiberd and Clase [61] estimated the cumulative risk of ESRD among different gender- race groups. They found that the lifetime of ESRD for a 20-yr-old black woman was 7.8%; for black males, 7.3%; for white women, 1.8%; and for white males, 2.5% [60].

The importance of family history has been shown in several large cohort studies (Physician's Health Study, Women's Health Study, Reykjavik Cohort Study [62]' Framingham Offspring Study, INTERHEART Study [63], Cooper Centre Longitudinal Study [64], Danish national population database) that collectively followed over 163,000 patients, and all showed that a positive family history is associated with greater risk of developing CHD. The risk of developing CHD in the presence of a positive family history has ranged from 15 to 100% in various cohorts, with most cohorts showing a 40 to 60% increase. Family history is a significant independent risk factor for CHD, particularly among younger individuals with a family history of premature disease.

2.3.2. Smoking

Smoking is the inhalation of the smoke of burning tobacco encased in cigarettes, pipes, and cigars. A smoking habit is a physical addiction to tobacco products. Even low-level exposure to second-hand tobacco smoke has a clinically significant effect on cardiovascular disease risk [65]. Major chronic disorders associated with smoking include cardiovascular diseases, several types of cancer, and chronic obstructive pulmonary disease (lung problems). Cigarette smoking generates a cumulative oxidative stress, which may contribute to the pathogenesis of chronic diseases [66]. Tobacco kills a third to half of all people who use it, on average 15 years prematurely. Today, tobacco use causes 1 in 10 deaths among adults worldwide – more than five million people a year [67].

Globally, the weighted average adult prevalence rates estimated for the year 2010 showed that 36% of males and 7% of females were current smokers. For daily smoking, average prevalence rates among males

varied from 12% in the African Region to 42% in the Western Pacific Region. Rates among females varied from 2% in the African, South-East Asia and Eastern Mediterranean Regions to 16% in the European Region [68]. Although tobacco deaths rarely make headlines, tobacco kills one person every six seconds. Tobacco kills a third to half of all people who use it, on average 15 years prematurely. Today, tobacco use causes 1 in 10 deaths among adults worldwide – more than five million people a year [67].

Biomarkers. The pack-year is a measure of cumulative smoke exposure calculated as the mean number of cigarettes smoked daily multiplied by the numbers of years exposed to smoking. The best validated method for assessing human exposure is to ask subjects about their tobacco smoking history. Lifetime exposures can be estimated by calculating pack-years smoked (average packs smoked per day over a lifetime multiplied by number of years smoked) or cumulative tar exposure [69].

Biomarkers of exposure include any assay from a body fluid (including exhaled air) or tissue that measures a constituent or constituent metabolite of tobacco smoke. Exhaled carbon monoxide (CO), nicotine and cotinine levels are among the most useful biomarkers of exposure [70].

2.3.3. Physical activity

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. The energy expenditure can be measured in kilocalories. Physical activity in daily life can be categorized into occupational, sports, conditioning, household, or other activities [71].

Physical inactivity (lack of physical activity) has been identified as the fourth leading risk factor for global mortality (6% of deaths globally) [72]. The evidence base for protective effects of activity for women, older adults and for special populations has strengthened. Important new controlled-trial evidence has accumulated in the area of type 2 diabetes: moderate physical activity combined with weight loss, and a balanced diet can confer a 50–60% reduction in risk of developing diabetes among those already at high risk [73].

Biomarkers. Methods of assessing physical activity and related energy expenditure include self-report, pedometers, heart rate monitors, and accelerometers, as well as by more sophisticated and valid techniques such as indirect calorimetry and doubly-labeled water [74].

2.3.4. Heart failure

Heart failure (HF), often called congestive heart failure (CHF), occurs when the heart is unable to provide sufficient pump action to maintain blood flow to meet the needs of the body [75]. Common causes of heart failure include myocardial infarction and other forms of coronary artery disease, hypertension, valvular heart disease, and cardiomyopathy [76]. Clinically, HF is defined by its typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) [77]. The severity of heart failure is usually classified according to the New York Heart Association (NYHA) Functional Classification [51]. It places patients in one of four categories based on how much they are limited during physical activity (Table 2).

Table 2. NYHA Classification

Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Approximately 1–2% of the adult population in developed countries has HF, with the prevalence rising to ≥10% among persons 70 years of age or older. It is known that there are currently 6.5 million CHF patients in Europe [78]. Both the incidence and prevalence of heart failure increase steeply with age. The prevalence of heart failure is expected to rise in future as a result of an ageing population, improved survival of people with ischemic heart disease and more effective treatments for heart failure [79].

Biomarkers.

1) **Fluid balance**: Fluid overload represents a common feature and clinical condition in heart failure. Fluid overload or congestive state signs are peripheral edema, increased body weight, pulmonary edema, and elevated central venous pressure with or without a significant level of hyponatremia [80]. Bioimpedence vector analysis is effective at assessing hydration [81]. Bioimpedance spectroscopy by contrast offers the possibility to determine intra- and extracellular volume independently. This is especially important to calculate the body composition irrespectively of the fluid overload [82].
2) **Brain-type natriuretic peptide (BNP):** BNP is a 32-amino acid peptide that is synthesized within the heart ventricles and released predominantly from ventricular myocardium in response to myocyte stretch.
3) **Ejection fraction (EF):** The ejection fraction (EF) is an important measurement in determining how well the heart is pumping out blood and in diagnosing and tracking heart failure. EF is usually measured by echocardiograhy. A significant proportion of patients with heart failure happen to have a normal ventricular ejection fraction at echocardiography during examination. Previously called diastolic heart failure, it is nowadays referred to as heart failure with normal ejection fraction or HF with preserved ejection fraction [83]. A normal heart's ejection fraction may be between 55 and 70%. The more severe the systolic dysfunction, the more the EF is reduced from normal [84].

2.3.5. Coronary heart disease (CHD)

Coronary heart disease (CHD) or coronary artery disease (CAD) or ischemic heart disease (IHD) develops as a consequence of decreased blood flow to the myocardium due to coronary atherosclerosis [85]. The risk factors for CHD is hypertension, dyslipidemia, diabetes, obesity, smoking, age, gender, family history, psychosocial factors, reduced physical activity, unhealthy diet. Coronary heart disease is the cause of approximately two-thirds of cases of systolic HF [86].

There are marked variations in the epidemic of CAD among regions of the world, nations, and even between regions within a country. The age-standardized death rates from CAD are declining in many developed countries, but are increasing in developing and transitional countries, partly as a result of demographic changes, urbanization, and lifestyle changes. Nowadays about 3.8 million men and 3.4 million women worldwide die each year from CAD [87]. The number of people living with coronary heart disease (CHD) increases with age and is higher in men than in women. The American Heart Association estimates that 16.8 million American adults have ischemic heart disease, 7.9 million individuals have myocardial infarction and 9.8 million persons have angina [88]. The estimated annual incidence of heart attack (myocardial infarction) is 610.000 new attacks and 325.000 recurrent attacks annually.

Biomarkers for CHD are considered lipid profile, blood pressure, markers of endothelial dysfunction, inflammatory serum markers, presence of metabolic syndrome, LVH/LV dysfunction.

2.3.6. Hypertension

Blood pressure is a measurement of the force against the walls of the arteries as the heart pumps blood through your body. Hypertension is another term used to describe high blood pressure.

The continuous relationship between BP and CV and renal events makes the distinction between normotension and hypertension difficult when based on cut-off BP values. In practice, however, cut-off BP values are universally used, both to simplify the diagnostic approach and to facilitate the decision about treatment. Hypertension is defined as a systolic blood pressure (SBP) of 140 mm Hg or more, or a diastolic blood pressure (DBP) of 90 mm Hg or more, or taking antihypertensive medication [89,90].

More than a quarter of the world's adult population - totalling nearly one billion - had hypertension in 2000, and that this proportion will increase to 29% - 1.56 billion - by 2025. Men and women have similar overall prevalence of hypertension, and that such prevalences increase with age consistently in all world regions.

Although hypertension is more common in economically developed countries (37.3%) than in economically developing ones (22.9%), the much larger population of developing countries results in a considerably larger absolute number of individuals affected [91].

Hypertension increases the risk of HF at all ages. Data from the Framingham Heart Study [92] found that, after age 40, the lifetime risk of developing HF was twice as high in subjects with a blood pressure ≥160/100 mmHg compared to <140/90 mmHg. In another study [93] among new-onset hypertensives, the most common first major cardiovascular events were hard coronary disease (8.2%) in men and stroke (5.2%) in women. Type and incidence of first cardiovascular events varied by age and severity of hypertension at onset, with stroke predominating among older subjects with new-onset hypertension. In addition to coronary heart diseases and stroke, complications of raised blood pressure include heart failure, peripheral vascular disease, renal impairment, retinal hemorrhage and visual impairment.

Hypertension is the second leading cause of CKD (second only to diabetes) and is present in up to 80% of individuals with moderate-to-end-stage kidney disease [94]. The prevalence of hypertension is 84% in patients with stage 4–5 CKD, compared with 23% of adults without CKD [95]. Untreated or inadequately controlled hypertension is considered one of the most important risk factors for CKD progression. Among patients with CKD, the presence of hypertension increases the risk of new or recurrent cardiovascular events [86]. It is also known that hypertension increase the risk of long-term vascular complications of type 2 diabetes mellitus, including stroke, chronic kidney disease, heart disease, peripheral vascular disease, and death.

Biomarkers. According to the evidence-based guidelines for the management of high blood pressure in adults of the Seventh Joint National Committee (JNC 7) a person is considered as hypertensive if has a systolic pressure ≥140 mmHg and/or a diastolic pressure ≥90 mmHg. JNC 7 has also introduced a new classification that includes the term “prehypertension” for those with BPs ranging from 120–139 mmHg systolic and/or 80–89 mmHg diastolic [96]. This new designation, which was kept in the last published guidelines (JNC 8) is intended to identify those individuals in whom early intervention by adoption of healthy lifestyles could reduce BP, decrease the rate of progression of BP to hypertensive levels with age, or prevent hypertension entirely (Table 3) [97].

Table 3. Blood Pressure Classification according to JNC-7 and JNC-8

BLOOD PRESSURE CLASSIFICATION	SBP (mmHg)	DBP (mmHg)
NORMAL	<120	and <80
PREHYPERTENSION	120-139	or 80-89
STAGE 1 HYPERTENSION	140-159	or 90-99
STAGE 2 HYPERTENSION	≥160	or ≥100

SPB, systolic blood pressure; DPB, diastolic blood pressure

2.3.7. Arrhythmia, tachycardia, sudden cardiac death

Atrial fibrillation (AF) is the most predominant cardiac arrhythmia in elderly persons and a potent risk factor for stroke [98]. When atrial fibrillation and other arrhythmias occur, the electrical activity of the heart is disorganized, causing an irregular heartbeat.

The prevalence of AF increases with age and is accompanied by a number of comorbidities, considering that this arrythmia may frequently correlate with or result from a number of other medical conditions [99]. Estimates of the prevalence of AF in the United States ranged from ≈2.7 million to 6.1 million in 2010, and AF prevalence is expected to rise to between ≈5.6 and 12 million in 2050. The incidence of atrial fibrillation increases with age [100].

AF is a frequent cardiac arrhythmia and confers a 2- to 3-fold increased risk of ischemic stroke and mortality. In the Framingham study [101] at a mean follow-up of 14 years, 526 patients (10 percent) developed AF. AF is the most common cardiac rhythm disturbance in CKD patients; prevalence among dialysis patients is 15–20%, and it is associated with increased incidence of stroke. Renal disease and AF share several risk factors, including hypertension, diabetes mellitus, and coronary artery disease [102]. Obese participants (BMI ≥30) were significantly more likely to develop AF than those with a normal BMI (<25, adjusted HR 1.52 for men and 1.46 for women).

Tachycardia – is a heart rate of more than 100 beats per minute (BPM) in adults. Heart rate has been shown to be an independent risk factor for CVD in the general population. Two large observational studies have demonstrated increased risk of cardiac events in individuals whose resting heart rate increased over time [103,104]. More recently, in patients with resting heart rates ≥70bpm and reduced left ventricular function (either coronary artery disease or heart failure), trials of pure heart rate reduction have shown benefit. There is not enough evidence, at present, to recommend a target heart rate [86].

Arrhythmic mortality is higher among patients with renal impairment. Renal dysfunction is associated with increased rates of sudden cardiac death (SCD) [105]. In patients with high-risk cardiac disease enrolled in the Multicenter Automatic Defibrillator Implantation Trial-II [31], a significant increase was found in the risk of SCD with declining renal function (17% increase in SCD for each 10-unit reduction in eGFR in patients with ischemic LV dysfunction). In the COMPANION study [106], among patients with ischemic LV dysfunction and LV dyssynchrony, renal dysfunction was associated with a 69 % increased risk for SCD.

Biomarkers.

1) **Heart rate (HR).** Atrial fibrillation (AF) is characterized by an irregular and often rapid heartbeat.
2) **Specific ECG features**. For example, in AF sinus P wave is absent. [107,108].

2.3.8. Left ventricular hypertrophy

The clinical importance of left ventricular mass relates to identification of pathological left ventricular hypertrophy (LVH). If the left ventricle has to work too hard, its muscle hypertrophies (enlarges) and becomes thick. Because of the increased thickness, blood supply to the muscle itself may become inadequate. LVH most commonly results from the hypertension and aortic stenosis. Whether due to hypertension, coronary disease, valve disease or diabetes, LV hypertrophy is a prominent feature of evolving HF.

Data on the prevalence of LVH differs. LVH is present in 15 to 20% of the general population, is more prevalent in blacks, the elderly, the obese, and in those with hypertension [109]. The prevalence of LVH varies from 16 to 31% in individuals with GFR >30 ml/min, increasing to 60–75% prior to starting renal replacement therapy, and up to 90% of patients after the initiation of dialysis [110].

Biomarkers. Among patients with HF in the general population, antecedent evidence of LV hypertrophy is present in approximately 20% by electrocardiogram (ECG) and 60-70% by echocardiogram. Each method of demonstrating LV hypertrophy (ECG, chest film, or echocardiogram) independently predicts HF.

2.3.9. Chronic kidney disease (CKD)

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health and CKD is classified based on cause, GFR category, and albuminuria category. See CKD classification in Table 4[111].

The World Health Organization estimates that there were approximately 58 million deaths worldwide in 2005, with 35 million attributed to chronic disease [112]. The incidence of patients with end stage renal disease who need dialysis or transplantation has more than doubled in Europe and the United States during the past two decades [113]. More than 50% of deaths in CKD stage 5 cohorts are attributed to cardiovascular disease. Patients with CKD have between a 10- and 20-fold increased risk of cardiac death compared with age-/gender-matched control subjects without CKD [4].

Table 4. CKD classification			
eGFR category	***GFR (ml/min/1.73 m^2)***		
G1	≥90		
G2	60–89		
G3a	45–59		
G3b	30–44		
G4	15–29		
G5	<15		
Albuminuria category	***AER mg/24hours***	***ACR mg/mmol***	***ACR mg/g***
A1	<30	<3	<30
A2	30-300	3-30	30-300
A3	>300	>30	>300
eGFR - estimated glomerular filtration rate, AER - albumin excretion rate, ACR - albumin to creatinine ratio			

Biomarkers.

1) **Albuminuria**. Use of urinary albumin measurement as the preferred test for proteinuria detection will improve the sensitivity, quality, and consistency of approach to the early detection and management of kidney disease [114]. Albumin concentration should be reported as a ratio to urinary creatinine concentration (mg/mmol or mg/g).
2) **Urinary sediment abnormalities** as markers of kidney damage.
3) **Creatinine and glomerular filtration rate.** For most clinical circumstances, estimating GFR from serum creatinine is appropriate for diagnosis, staging, and tracking the progression of CKD [111]. Recent studies suggest that the serum level of cystatin C may be a better predictor of outcomes of cardiovascular disease than GFR estimates based on levels of serum creatinine. It is not known whether the prediction is improved because cystatin C is a better marker of GFR than levels of serum creatinine or because factors apart from GFR that affect the level of cystatin C or creatinine also are related to the risk of cardiovascular disease [115].

Criteria for CKD are listed in Table 5 [111].

Table 5.Criteria for CKD (either of the following present for >3 months)	
Markers of kidney damage (one or more)	Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol])
	Urine sediment abnormalities
	Electrolyte and other abnormalities due to tubular disorders
	Abnormalities detected by histology
	Structural abnormalities detected by imaging
	History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m2 (GFR categories G3a–G5)
eGFR - estimated glomerular filtration rate, AER - albumin excretion rate, ACR - albumin to creatinine ratio	

2.3.10. Electrolyte disorders: Hyperkalemia

Hyperkalemia is common in patients with CKD and its' frequency and severity increases with the progression of CKD [116]. Furthermore, hypekalemia can develop as a result of high dietary potassium intake, acidosis, hyperglycemia in diabetic patients, and use of certain medications such as ACEIs, ARBs, aldosterone antagonists or nonsteroidal anti-inflammatory medications. The incidence of hyperkalemia is low in patients with stage 3 CKD. However, approximately one-fourth of patients with stage 5 CKD experience a life-threatening episode of hyperkalemia that requires emergency treatment [117].

2.3.11. Acid-base disorders

In end-stage heart failure, various acid-base disorders can be discovered due to the renal loss of hydrogen ions and hydrogen ion movements into cells, the reduction of the effective circulating volume, hypoxemia and renal failure. This justifies the occurrence of metabolic alkalosis, metabolic acidosis, respiratory alkalosis, as well as respiratory acidosis alone or in combination [118]. In heart failure, the presence of acid-base imbalance associated with the activation of mechanisms that lead to salt and water retention reveals evidence concerning the pivotal role of the kidney in determining the outcome of these patients.

2.3.12. Anaemia

The World Health Organization defines anaemia as a haemoglobin concentration less 13 g/dL in men and 12g/dL in women. Available data suggest that in most cases, CHF, renal dysfunction, and anaemia represent a continuum of disease progression [28].

Anaemia is common in patients with HF, especially those with advanced stages of cardiac insufficiency, with a prevalence ranging between 4% and 55% [119]. Anaemia present in over one-third of CRS patients or the cardiorenal anaemiasyndrome can be found in one-fifth of the patients, most of whom had normocytic normochromic anaemia [27]. It is more frequent in women (a recent study of anaemia in ambulatory patients with CHF [120] reported a 64% male predominance), the elderly, and in patients with renal impairment. Anaemia in HF is associated with more symptoms, worse functional status, greater risk of HF hospitalization, and reduced survival. Anemia is a major cause of LVH and LV dilatation in ESRD [121].

Biomarkers. Haemoglobin concentration (g/dL).

2.3.13. Mineral and bone disorder

As kidney function declines, there is a progressive deterioration in mineral homeostasis, with a disruption of normal serum and tissue concentrations of phosphorus and calcium, and changes in circulating levels of hormones. These changes are considered as a systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

- abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
- abnormalities in bone turnover, mineralization, volume, linear growth, or strength
- vascular or other soft-tissue calcification [122].

Importantly, there is increasing evidence suggesting that disorders in mineral and bone metabolism are associated with increased risk for cardiovascular calcification, morbidity, and mortality [123].

Hyperphosphatemia is a major risk factor for cardiovascular disease, abnormalities of mineral metabolism and bone disease, and the progression of renal insufficiency in patients with chronic renal disease. Clinical hyperphosphatemia occurs when these phosphaturic mechanisms cannot counterbalance nephron loss. Hyperphosphatemia is associated with calcific uremic arteriolopathy and uremic cardiomyopathy, which may explain, in part, the epidemiologic connections between phosphate excess and cardiovascular disease [124,125].

In patients with chronic kidney disease there is strong association between low levels of vitamin D and cardiovascular morbidity and mortality. Vitamin D levels decrease as a result of renal progressive impairment. Progressive loss of kidney function observed in patients with CRS (mostly types 2 and 4) leads to reduced production of calcitriol (active vitamin D) and an imbalance in calcium and phosphorus levels, which are correlated with increased rates of cardiovascular events and mortality. In addition, hypocalcemia

can lead to prolonged and excessive secretion of parathyroid hormone (PTH), eventually leading to development of secondary hyperparathyroidism. These alterations entail both cardiac and renal involvement, resulting in cardio-renal syndrome [126,127].

Biomarkers. Serum ionized calcium, phosphate, PTH, vitamin D. Presently, most databases are already using the corrected calcium formula.

2.3.14. Dyslipidaemia

Dyslipidemia is the elevation of plasma cholesterol, triglycerides (TGs), or both, or a low high-density lipoprotein (HDL) level that contributes to the development of atherosclerosis.

Causes may be primary (genetic) or secondary. Secondary causes contribute to many cases of dyslipidemia in adults. The most important secondary cause in developed countries is a sedentary lifestyle with excessive dietary intake of saturated fat, cholesterol, and trans fats. Other common secondary causes include diabetes mellitus, alcohol overuse, chronic kidney disease, hypothyroidism, primary biliary cirrhosis and other cholestatic liver diseases, and drugs, such as thiazides, β-blockers, retinoids, highly active antiretroviral agents, cyclosporine, estrogen and glucocorticoids. Secondary causes of low levels of HDL cholesterol include cigarette smoking, anabolic steroids, HIV infection, and nephrotic syndrome [128].

In the Multi-Ethnic Study of Atherosclerosis (MESA) - a multicenter cohort study of 6814 persons aged 45 to 84 yrs - 29.3% of the participants had dyslipidemia, among whom lipid-lowering drug therapy was reported by 54.0%[129]. According to the National Health and Nutrition Examination Survey (NHANES 2003-2006) data an estimated 53% of U.S. adults have lipid abnormalities: 27% have high low-density lipoproteins 23% have low HDL, and 30% have high TG [130].

Biomarkers. Lipid profile: total cholesterol, triglyceridess, and HDL cholesterol, low-density lipoproteins (LDP). Lipoprotein (a) is a cholesterol-rich lipoprotein with structural similarities to LDL and is considered as a causal genetic risk factor for cardiovascular disease [131].

2.3.15. Hyperuricaemia, Gout

Hyperuricaemia is defined as a level of uric acid in the blood that is abnormally high. In humans, uric acid is the end product of purine metabolism due to the non-functioning uricase gene leading to elevated serum uric acid levels [132]. Hyperuricemia predisposes patients to both gout and nephrolithiasis.

Gout is a condition characterized by the deposition of monosodium urate crystals in the joints or soft tissue. The four phases of gout include asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout and chronic tophaceous gout [133].

The prevalence rate of asymptomatic hyperuricemia in the general population is estimated at 2-13% [134]. Gouty arthritis is the most common form of inflammatory joint disease in men older than 40 years. The National Health Survey (1983 to 1985) determined the prevalence rate of self-reported gout to be 13.6 cases per 1.000 men and 6.4 cases per 1.000 women [135]. Hyperuricaemia is common in people with CKD. Observational data had implicated that an increased uric acid in the progression of CKD is related with the adverse outcomes in people with CKD [136].

Biomarkers. Serum uric acid levels, 24 hour urinary uric acid and joint aspiration (the latter may be important in the diagnosis of acute gouty arthritis, in which uric acid crystals are found to be negatively birefringent under polarized microscopy).

2.3.16. Obesity

According to WHO overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health [137].

Worldwide, at least 2.8 million people die each year as a result of being overweight or obese. In 2008, 35% of adults aged 20+ were overweight (BMI ≥ 25 kg/m2) (34% men and 35% of women). The prevalence of overweight and obesity were highest in the WHO Regions of the Americas (62% for overweight in both sexes, and 26% for obesity) and lowest in the WHO Region for South East Asia (14% overweight in both sexes and 3% for obesity). In the WHO Region for Europe and the WHO Region for the Eastern Mediterranean and the WHO Region for the Americas over 50% of women were overweight. For all three of

these regions, roughly half of overweight women are obese (23% in Europe, 24% in the Eastern Mediterranean, 29% in the Americas). In all WHO regions women were more likely to be obese than men [138].

Obesity is associated with numerous comorbidities such as CVD, type 2 diabetes, hypertension, certain cancers, and sleep apnoea [139]. Increasing body mass index (BMI kg/m^2), even within the normal range of BMI (from 21 to 24.9), is associated with an increased risk of type 2 diabetes, hypertension, coronary heart disease, and cholelithiasis [140]. A high waist circumference (WC) is associated with an increased risk for type 2 diabetes, dyslipidaemia, hypertension, and CVD in patients with a BMI in a range between 25 and 34.9 kg/m^2 [141].

Biomarkers. Obesity is defined by body mass index (BMI) and further evaluated in terms of fat distribution via the waist–hip ratio or waist circumference (WC) and total cardiovascular risk factors. BMI is closely related to both percentage body fat and total body fat.

1) **Body Mass Index (BMI)**: BMI is a useful and widely accepted measure of overweight and obesity. It is defined as the individual's body mass divided by the square of their height – with the value universally being given in units of kg/m^2.

$$BMI = \frac{mass\ (Kg)}{[height\ (m)]^2}$$

The WHO regards a BMI of less than 18.5 as underweight while a BMI greater than 25 is considered overweight and above 30 is considered obese (Table 6):

Table 6. BMI Chart	
BMI less than 18.5	Underweight
BMI 18.5 – 24.9	Healthy weight
BMI 25.0 – 29.9	Overweight
BMI 30 or more	Obese

2) **Waist circumference (WC):** It is measured placing a tape measure around the middle, just above the hipbones. The risk goes up with a waist size that is greater than 88cm for women or greater than 102cm for men.

3) **Fat mass (Body composition):** Some authorities advocate a definition of obesity based on percentage of body fat, as follows:

Men: Percentage of body fat greater than 25%, with 21-25% being borderline
Women: Percentage of body fat great than 33%, with 31-33% being borderline

Estimation of body fat percentage from underwater weighing (or hydrostatic weighing) has long been considered to be the best method available, especially in consideration of the cost and simplicity of the equipment. There exist various anthropometric methods for estimating body fat like thicknesses of skinfolds. Advanced studies for body composition assessment include dual-energy X-ray absorptiometry (DEXA), underwater (hydrostatic) weighing, air displacement plethysmography (ADP), and bioelectrical impedance analysis (BIA) [142,143].

2.3.17. Metabolic syndrome

A cluster of risk factors for cardiovascular disease and type 2 diabetes mellitus, which occur together more often than by chance alone, have become known as the metabolic syndrome. The risk factors include raised

blood pressure, dyslipidemia (raised triglycerides and lowered high-density lipoprotein cholesterol), raised fasting glucose, and central obesity [144]. The multiplicity of prevalence data suggest that the metabolic syndrome is common worldwide, especially among older people and in certain ethnic populations [145].

It is a risk factor for coronary heart disease, as well as for diabetes,fatty liver, microalbuminuria, CKD, stroke and several cancers.

Table 7. Criteria for Clinical Diagnosis of the Metabolic Syndrome	
Measure	**Categorical Cut Points**
Elevated waist circumference	Population- and country- specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator†)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL cholesterol (drug treatment for reduced HDL cholesterol is an alternate indicator)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL

The criteria according to a Joint Interim Statement are present on Table 7. The presence of any 3 of 5 risk factors constitutes a diagnosis of metabolic syndrome [116].

Biomarkers. Waist circumference, triglycerides, HDL cholesterol, blood pressure and fasting glucose.

2.3.18. Diabetes mellitus

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels [146].

Table 8. Criteria for the diagnosis of Diabetes
A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h plasma glucose ≥200mg/dL (11.1mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).
**In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.*

It is estimated that approximately 382 million people have diabetes worldwide, while 175 million people with diabetes are undiagnosed; by 2035 this will rise to 592 million. The number of people with type 2 diabetes is increasing in every country. Diabetes caused 5.1 million deaths in 2013 and every six seconds a person dies from diabetes [147]. Estimates suggest that more than 6% of the population aged 20-79 years in EU member

states, or 30 million people, had diabetes in 2011, with 42% of diabetic adults aged less than 60 years. If left unchecked, the number of people with diabetes in EU member states will reach more than 35 million in less than 20 years. Less than 5% of adults aged 20-79 years in Belgium, Iceland, Luxembourg, Norway and Sweden have diabetes, according to the International Diabetes Federation. This contrasts with Portugal, Cyprus and Poland, where 9% or more of the population of the same age have the disease [148].

Biomarkers. For decades, the diagnosis of diabetes was based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h value in the 75-g oral glucose tolerance test (OGTT). Recently glycosylated haemoglobin A1C, with a threshold of ≥6.5% was also adopted as a criterion for type 2 diabetes mellitus. The currently used diagnostic criteria are shown in Table 8[149].

2.3.19. Respiratory Disorders and Sleep apnoea syndrome

The interaction between chronic heart failure (CHF) and concomitant respiratory disease is common and plays an important role during the management of these patients [81]. Sleep apnoea syndrome and more particularly two subtypes are often associated with CHF, both constituting multi-systemic diseases, associated with cardiovascular, respiratory and neurohormonal adverse outcomes. Obstructive sleep apnoea and central sleep apnoea often coexist with CHF as well as with each other. More specifically, the first results from collapse of normal pharynx, either complete or partial. On the other hand, the latter results from either a reduction in central respiratory drive or instability in feedback control of the central respiratory centre. Obstructive sleep apnoea constitutes risk factor for the development and the further progression of cardiovascular disease and CHF. By contrast, central sleep apnoea, may result from CHF but is associated with an increase in the risk of arrhythmias and a worse prognosis [46]. Moreover, advancing experience suggests that sleep apnoea is a frequent and often overlooked condition in CKD associated with non-dipping blood pressure, sympathetic nervous system activation, and increased CVD risk [78].

2.3.20. COPD

COPD is a preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. It is characterized by airflow limitation that is not fully reversible. Because COPD often develops in long-time smokers in middle age, patients often have a variety of other diseases related to either smoking or aging [150]. COPD is associated with important chronic comorbid diseases, including cardiovascular disease, diabetes and hypertension [151].

The available data suggest that the prevalence of physiologically defined COPD in adults aged ≥40 yrs. is 9–10% [152]. It is the fourth leading cause of chronic morbidity and mortality in the United States, and is projected to rank fifth in 2020 in burden of disease worldwide, according to a study published by the World Bank/World Health Organization.

Biomarkers. The diagnosis of COPD should be considered in any patient who has the following: symptoms of cough; sputum production; or dyspnoea; or history of exposure to risk factors for the disease.

1) **Pulse oximetry.** Arterial blood gas assessment is the preferred method to determine oxygen need because it includes acid base information. Arterial oxygen saturation as measured by pulse oximetry (SpO2) is adequate for trending.
2) **Spirometry.**The diagnosis requires spirometry; a post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ≤0.7 confirms the presence of airflow limitation that is not fully reversible.

2.3.21. Rheumatic diseases

The systemic diseases such as amyloidosis, systemic lupus erythematosus, rheumatoid arthritis, scleroderma and other connective tissue diseases, vasculitis are affecting both renal and cardiac function and leading to the development of cardiorenal syndrome (CRS) type 5 (secondary CRS). The time sequence for developing CRS type 5 depends on the underlying disease and is influenced by the underlying level of cardiac and renal function.

Amyloidosis.The amyloidoses are a group of disorders in which soluble proteins aggregate and deposit extracellularly in tissues as insoluble fibrils, causing progressive organ dysfunction [153]. The kidney is one of the most frequent sites of amyloid deposition in light chain amyloidosis, serum amyloid A type amyloidosis,

and several of the hereditary amyloidoses. Cardiac involvement is a leading cause of morbidity and mortality, especially in primary light chain amyloidosis and in both wild-type and hereditary transthyretin amyloidosis [154].

Systemic lupus erythematosus. Systemic lupus erythematosus (SLE) is a chronic autoimmune connective tissue disorder of unknown aetiology that predominantly affects women and typically has manifestations in multiple organs [155].Clinical manifestations may vary between mild arthritis and severe organ damage accompanied by fever, joint pain and fatigue. Renal involvement occurs in 40–70% of all SLE patients and pericarditis may occur in approximately 25% of SLE patients [156].

SLE is a rare disease with an estimated prevalence of 1 per 492 white adult females and it is much more common in women, with a female to male ratio approximately 9 to 1 [157,158].

Vasculitis is a group of rare diseases that have in common inflammation of blood vessels. There are many types of vasculitis. Features that vary among different forms of vasculitis and can be used for categorization include etiology, pathogenesis, type of vessel affected, type of inflammation, favoured organ distribution, clinical manifestations, genetic predispositions, and distinctive demographic characteristics (e.g., with respect to age, sex, race, ethnicity, and geographic distribution) [159]. Vasculitis can occur in conjunction with another illness, such as lupus or rheumatoid arthritis.

Arthritis is not a single disease - it is a term that covers over 100 medical conditions. It is defined as inflammation of one or more of joints. The main symptoms of arthritis are joint pain and stiffness, which typically worsen with age. The two most common types of arthritis are osteoarthritis and rheumatoid arthritis (RA) [160]. According to the CDC, an estimated 50 million U.S. adults (about 1 of 5) report having doctor-diagnosed arthritis [161]. Owing to their high prevalence, RA and renal disease often coincide. The renal toxicity of antirheumatic drugs (for example, NSAIDs or cyclosporine toxicity), secondary renal disease induced by the chronic inflammatory process (especially renal amyloidosis) and, potentially, renal manifestations of the primary disease process, however, are important differential diagnoses [162].

2.3.22. Autonomic diabetic neuropathy

Cardiovascular Autonomic Diabetic Neuropathy (CAN) is a complication of diabetes mellitus that is caused by damage of the autonomic nerve fibres that innervate the heart and blood vessels, leading to abnormalities in heart rate control and central and peripheral vascular dynamics. CAN manifests in a spectrum of subclinical and clinical presentations: it can be a reason of postural hypotension, exercise intolerance, enhanced intraoperative cardiovascular liability, increased incidence of asymptomatic ischemia, myocardial infarction, and decreased likelihood of survival after myocardial infarction in patients with diabetes mellitus. Thus, CAN is accepted as a risk marker for cardiovascular morbidity and mortality.

Poor glycaemic control in a combination with hypertension, dyslipidaemia and obesity are the most important risk factors for CAN.

There is a huge variation in cardiovascular autonomic neuropathy prevalence because of the inconsistency in the criteria used to diagnose CAN and significant differences in the study populations. CAN increases annually: the incidence of CAN is approximately 6% in patients with T1DM and 2% in patients with T2DM respectively [163,164].

Biomarkers. The main biomarkers of cardiovascular autonomic neuropathy are: heart rate (HR) (heart rate variability), blood pressure (orthostatic hypotension), 24-hour heart rate variability and blood pressure profiles. Cardiovascular autonomic reflex tests (CART), such as HR responses to deep breathing, standing and Valsalva manoeuvre, as well as blood pressure response to standing are considered as the gold standard in clinical testing for autonomic neuropathy. According to the CAN Subcommittee of the Toronto Consensus Panel statement [165], the criteria for diagnosis and staging of CAN are as follows:

– A single abnormal CART result identifies the possibility of early CAN;

– The presence of two or three abnormal test is needed for definite or confirmed CAN;

– The presence of orthostatic hypotension in addition to the CART signifies the presence of severe advanced CAN.

2.3.23. Diabetic nephropathy (DN)

Diabetic nephropathy is a clinical syndrome characterized by the following: persistent albuminuria, progressive decline in the glomerular filtration rate (GFR) and hypertension. The clinical diagnosis of DN usually depends on the detection of microalbuminuria (albumin excretion of more than 30 mg/g of creatinine in 2 out of 3 random urine samples collected in within a 6-month period). Progression of the diabetic nephropathy is divided in clinical stages depending on the duration of the disease (Table 9) [166].

Table 9. Stages of diabetic nephropathy	
Stage 1 Early hyperfunction and hypertrophy	ACR < 30 mg/g creatinine
Stage 2 Morphologic lesions without signs of clinical disease	ACR > 30 and < 300 mg/g creatinine
Stage 3 Microalbuminuria	ACR > 300 mg/g creatinine and/or persistent
	proteinuria with serum concentration of creatinine 2.0 mg/dL
Stage 4 Overt nephropathy	Serum concentration of creatinine 2.0 mg/dL with proteinuria
Stage 5 End-stage renal disease with uraemia	On dialysis

Diabetic nephropathy cases vary largely among countries; in average DN develops in 30% to 40% of patients with diabetes [167]. Approximately 20 to 30% of type 1 diabetes patients will have microalbuminuria after a mean duration of diabetes of 15 years [168]. Less than half of these patients will progress to overt nephropathy. In patients with type 2 diabetes, the incidence of microalbuminuria was 2.0% per year and the prevalence 10 years after diagnosis 25% in the U.K. Diabetic Nephropathy is one of the most significant long-term complications of diabetes mellitus, which can lead to chronic kidney disease and renal replacement therapy.

Biomarkers of DN are microalbuminuria (is earlier non-invasive marker for diabetic nephropathy), serum creatinine concentration, GFR.

2.3.24. Peripheral artery disease (PAD)

PAD manifests as insufficient tissue perfusion caused by existing atherosclerosis that may be acutely compounded by either emboli or thrombi. Risk factors for PAD include smoking, hyperlipidemia, diabetes mellitus, and hyperviscosity [169]. The prevalence rates increases with age both in men and women. Globally, 202 million people were living with peripheral artery disease in 2010 [170].

Biomarkers.

1) **Ankle Brachial Index (ABI).** ABI has been shown to be a specific and sensitive metric for the diagnosis of Peripheral Arterial Disease (PAD). The Ankle Brachial Index (ABI) is the systolic pressure at the ankle, divided by the systolic pressure at the arm.
2) **Arterial stiffness.** Arterial stiffness describes the reduced capability of an artery to expand and contract in response to pressure changes. Parameters that describe vessel stiffness include compliance and distensibility. Pulse wave velocity (PWV) is increased in stiffer arteries and, when measured over the aorta, is an independent predictor of cardiovascular morbidity and mortality.
3) **Others:** Lipid profile, smoking history, glycaemic control, weight control, blood pressure**.**

2.3.25. Atherosclerosis

Atherosclerosis is a type of arteriosclerosis - a general term for the thickening and hardening of arteries. Atherosclerosis is called the process of fatty substances, cholesterol, cellular waste products, calcium and fibrin (a clotting material in the blood) building up in the inner lining of an artery. The build-up that results is

called plaque [171]. Atherosclerosis is an inflammatory disease in which immune mechanisms interact with metabolic risk factors to initiate, propagate, and activate lesions in the arterial tree.

Major independent risk factors for the development of atherosclerosis include elevated plasma total and low-density lipoprotein cholesterol, cigarette smoking ,hypertension, diabetes mellitus, advancing age, low plasma high-density lipoprotein cholesterol, a family history of premature coronary artery disease, and psychosocial factors. Atherosclerosis presents an increased risk for cardiovascular disease such as CHD and stroke.

Biomarkers. Lipid profile, PWV, BP, CRP, fibrinogen, endothelium dysfunction, smokinghistory, glycaemic control.

2.3.26. Drugs

Cardiotoxic drugs. In some patients the occurrence of HF can be attributed to the cardiotoxic effect of a particular drug. Furthermore, as several categories of drugs may exert unfavorable hemodynamic effects, these drugs may act as a precipitating factor for a relapse in patients with previously compensated HF [172]. Drugs that usually are associated with the onset or worsening of HF are cytostatics (anthracyclines, cyclophosphamide), tricyclic antidepressants, immunomodulating drugs (interferons), anesthetics, nonsteroidal anti-inflammatory drugs, beta-adrenoceptor antagonists and antiarrhythmics [173].

Nephrotoxic drugs. Drugs cause approximately 20 percent of community-and hospital-acquired episodes of acute renal failure and the incidence of drug-induced nephrotoxicity has been increasing with the ever increasing number of drugs and with easy availability of over-the-counter medication, antibiotics, NSAIDs, angiotensin converting enzyme inhibitors (ACEI) and contrast agents are the major culprit drugs contributory to kidney damage [174].

2.3.27. Stroke

A stroke is a sudden interruption in the blood supply of the brain. Most strokes are caused by an abrupt blockage of arteries leading to the brain (ischemic stroke). Other strokes are caused by bleeding into brain tissue when a blood vessel bursts (hemorrhagic stroke). The major risk factors for stroke are similar to those for coronary heart disease, with high blood pressure and tobacco been the most significant modifiable risks. Atrial fibrillation, heart failure and heart attack are other important risk factors [175].

2.3.28. ESRD and dialysis

The final stage of chronic kidney disease is ESRD. Despite the high prevalence of chronic kidney disease , relatively few individuals with CKD progress to ESRD [176]. Optimal care of CKD patients requires accurate estimation of the risk of two competing clinical outcomes: ESRD and death. Age is the most intuitive: for a given level of kidney function, older patients are more likely to die before requiring renal replacement therapy compared with younger patients. Similarly, patients with diabetes and low levels of proteinuria have higher rates of pre-ESRD death, whereas patients with polycystic kidney disease tend to first develop ESRD [177].

The global prevalence of ESRD requiring treatment with dialysis or kidney transplantation continues to increase [178]. Since the beginning of maintenance therapy for ESRD through dialysis or transplantation, the number of patients treated for terminal kidney failure worldwide has continued to grow at a rate that is far in excess of the growth rate of the general population. By 2001, more than 1 million patients were reported worldwide to receive dialysis treatment alone, with the numbers growing at an annual global average rate of 7%.

2.4. Risk Factors

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 evidence will be

presented as a complex network of risk factors, that is pairs of conditions one related to another via a causal relationship.

The following subsections present the concept of risk factor in medicine, how this is quantified and estimated via evidence from research studies. The section concludes with a fi

2.4.1. Risk factors in medicine

In medicine risk is the probability of a negative outcome on the health of a population of subjects. 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 [179]. In general, risk factors can be:

- Environmental. It includes chemical, physical, mechanical, biological and psychosocial elements that constitute risk factors to public health.
- Demographic. Empirical findings have pointed out that age, sex, race, location, and religion all affect public health.
- Genetic. Any predisposition to conditions and habits hardcoded in the human gene.
- Behavioral – Lifestyle related. Human behaviors that are marked as "risky" and have proven to cause deterioration or provide added risk like smoking, overeating, unprotected sexual life, excessive alcohol drinking, drug abuse and sedentary lifestyle.
- Biomedical. These include 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 [180], associations between a risk factor and the associated condition include:

- 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 [181], we can present a risk factor as a triplet (Figure 3):

1) what can happen (what is the event, factor/condition/disorder 1)
2) what are the consequences (what is the resulting condition/disorder 2)
3) what is the likelihood of having these consequences when the event is present.

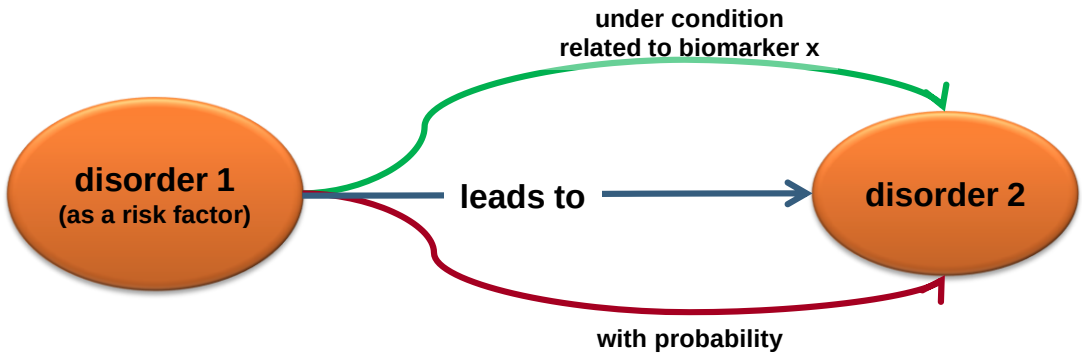


Figure 3. Schematic representation of the risk factor triplet

Furthermore, risk factors can be classified introducing a different typology [182]. Thus, depending on the ability to alter it spontaneously or by intervention two categories can be identified:

- "variable risk factor", e.g. the high blood pressure that is treated or
- "fixed marker", e.g. the date of birth or race

The multivariate nature of risk factors can be evaluated more tentatively by considering the behavior of risk in time, the response to it and metrics that can be applied to describe it. A risk factor can have a continuous presence or be recurrent with long or short intermissions. This means that given too short a period to study the effects of a risk factor, might not produce definitive or correct results. A continuous presence might have more severe consequences but an intermittent one can cause the condition to reset its status and interfere with the treatment. For example when we are considering continuous exposure to an allergenic or toxic substance the effects usually become more extreme over time but an intermittent exposure can also create the reoccurrence of specific conditions.

2.4.2. Risk Ratio and Hazard Ratio

The way to measure the likelihood requires a certain quantitative biomarker and observational studies that statistically calculate a probability. This probability is expressed as a risk ratio.

Relative risk or Risk ratio (RR) is the ratio of the **probability** of an event occurring (for example, developing a disease) in an exposed group to the probability of the event occurring in a non-exposed group.

$$RR = \frac{probability\ of\ the\ event\ when\ the\ person\ is\ exposed\ to\ a\ factor/condition}{probability\ of\ the\ event\ when\ the\ person\ is\ not\ exposed\ to\ the\ factor/condition}$$

The relative risk of developing a disease when a risk is present (as opposed when it is not present) is calculated by means of 2X2 tables (Table 10). So in a given population where

a = is the number of smokers with hypertension,

b = is the number of smokers without hypertension,

c = is the number of non-smokers with hypertension, and

d = is the number of non-smokers without hypertension

the relative risk of smokers to develop hypertension (as compared to non-smokers) is:

$$RR = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

Hence, smokers are RR times more likely to develop hypertension than non-smokers. A relative risk of 1 suggests there is no difference in risk between two groups. A relative risk >1 means that the event is more likely to occur in the study group, while a relative risk <1 means that the event is less likely to occur in the study group. Relative risks are cumulative over the entire study time period and thus are biased with respect to the time period (or endpoint) chosen.

Table 10. Risk calculation table.

	disease status	
risk	hypertension present	hypertension absent
smoker	a	b
non-smoker	c	d

Another metric of relative risk is the Hazard Ratio (HR) (e.g. [183,184]) which is most often used in clinical studies to assess the instantaneous risk at any time of a given study. So, it accounts for the reality that some subjects may drop out of the study before the event of interest happens, or that the study may end before all of the subjects experience the event (time-to-event analysis).

Hazard ratios are calculated via the survival analysis statistical method. In this method, the hazard is the slope of the survival curve,which is a measure of how rapidly subjects are dying. In the general case, this method is used to study the rate of any type of event either negative or positive (not only death). The Hazard Ratio compares two populations, the one under study (e.g. with disease or after intervention) and one control group. Survival curves for both populations are plotted and hazard is calculated. The ratio of the two hazard values is then the Hazard Ratio. There are several statistical methods for sampling the two populations, plotting the survival curves and estimating hazards.

To derive the probability a study group to experience the event before the control group, one can use the hazard ratio:

$$probability = \frac{Hazard\ Ratio}{1 + Hazard\ Ratio}$$

2.4.3. Medical evidence

Risk factors are derived from clinical studies. In the past, various evidence ranking schemes have been used, to appraise quality of evidence, based on study design and methodology utilised. Table 11 presents the grading system proposed by The Oxford Centre for Evidence-Based Medicine [185].

Table 11. OCEBM Levels of evidence (Oxford Center for Evidence-based Medicine) [185]

Level	Type of evidence for therapy/prevention, etiology/harm
1	Systematic Review (SR) of randomized trials or nested case-control studies, n-of-1 trial, or observational study with dramatic effect
2	Individual randomized trial or (exceptionally) observational study with dramatic effect
3	Non-randomized controlled cohort/follow-up study
4	Case-series, case-control studies, or historically controlled studies
5	Mechanism-based reasoning

Definitions of the study types are as follows: [186]

A systematic review (SR) is a review with a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research. It may also utilize meta-analytical methods to collate and analyze data from the studies that are included in the systematic review (meta-analysis).

Randomized controlled trial (RCT): An epidemiological experiment where eligible people are randomly allocated to two or more groups. One group receives the intervention (i.e. a new drug) while the control group(s) receive(s) inactive placebo (placebo-controlled trial) or an active comparator (comparative effectiveness trial). The researchers assess what happens to people in each group. Any difference in any of the outcomes can be attributed to the intervention.

Cohort Study A longitudinal study that follows a group of people (cohort) who are, have been, or in the future may be exposed or not exposed, or exposed in different degrees, to a factor or factors hypothesized to influence the incidence of a given disease or other outcome.

Case control study: An observational study of persons with the disease of interest (or any outcome variable) and a suitable control (comparison, reference) group of persons without the disease. The relationship of an attribute to the disease is examined by comparing the diseased and non-diseased with regard to how frequently the attribute is present or, if quantitative, the levels of the attribute, in each of the groups.

Case-series: A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment.

Evidence reported by scientific studies is used by various organizations in the field to formulate recommendations or deduce clinical practice guidelines. Sources of evidence can range from small in vitro studies or case reports to large elegant randomized clinical trials that have minimized bias to a great extent. Similarly with evidence, recommendations that are based on the evidence can be of different quality. Poor quality evidence can lead to recommendations that are not in patients' best interests; hence it is essential to assess the confidence we have in the recommendations. Several systems and approaches have been proposed for grading clinical practice guidelines. GRADE is the most widely accepted system, which has been adopted by a large number of evidence review bodies [187] and organizations including WHO [188]. It also provides free software for creating summary of findings in tables [189].

In GRADE, clinical practice guidelines are graded along two axes, in terms of the:

1. quality of evidence
   A: high
   B: moderate
   C: low
   D: very low
2. strength of recommendation
   Level 1 = strong ("we recommend")
   Level 2 = weak or discretionary ("we suggest")

2.4.4. Risk factors related to CARRE domain

The following list presents the major risk factors related to cardiorenal syndrome, as derived from the domain analysis in Sections 2.2 and 2.3.

Table 12. List of major risk factors related to cardiorenal disease

Causing factor/condition	resulting condition
Hypertension	heart failure
	renal disease
	diabetes
	cardiovascular disease
	LVH
Obesity	diabetes
	dyslipidemia
	hypertension
	renal disease
	atrial fibrillation
	cardiovascular disease
Central obesity	diabetes
	dyslipidemia
	hypertension
	cardiovascular disease
Age	peripheral vascular disease
	cerebrovascular disease
	coronary heart disease
Diabetes	heart failure

	renal disease
	cardiovascular disease
Dyslipidemia	diabetes
	cardiovascular disease
Smoking	atherosclerosis
	renal disease
	cardiovascular disease
Physical exercise	diabetes
	hypertension
	dyslipidemia
	cardiovascular disease
Alcohol abuse	hypertension
	renal disease
	cardiovascular disease
Nephrotoxic drugs	renal disease
Left ventricular hypertrophy	cardiovascular disease
Diabetic nephropathy	cardiovascular disease
Hyperkalemia	cardiac arrythmias
Family history of CVD	CVD
Menopause	CVD
Dilatatedcardiomyopahty	chronic heart failure
Acute myocardial infarction	Atrial Fibrilation
Cardiomyopahty	Ischemic heart disease
	HF
Atherosclerosis	MI
	heart failure (HF)
	peripheral vascular disease
	sudden cardiac death
Obstructive sleep apnoea	hypertension
	diabetes
	cardiovascular disease
COPD	cardiovascular disease
Anaemia	cardiovascular disease
Hyperuricaemia	cardiovascular disease
Depression	cardiovascular disease
Atrial Fibrilation	Myocardial Infarction
Chronic Kidney Disease and AF	end stage renal disease (ESRD)
AMI and CKD	death
Anemia and CKD	CVD
	death
CKD	AKI
	CVD
	PAD (peripheral arterial disease)
	hospitalization
	Cardiovascular hospitalization
	hyperkalemia

	anaemia
High protein intake (diet) in CKD	progression of CKD
Insufficient glucemic control in diabetic CKD	progression of CKD
	retinopathy
Excessive salt intake (diet) in CKD	high blood pressure
	albuminuria
	progression of CKD
Smoking in CKD	progression of CKD
Obesity in CKD	progression of CKD
	mortality
	morbitity
	Reduction in life expectancy
Lack of physical activity in CKD	progression of CKD
	progression of CVD
	mortality
	Poor QOL
Abnormalities of mineral metabolism (High serum levels of phosphorus, calcium and parathyroid hormone) in CKD	CVD
	Cardiovascular mortality
	All cause mortality
	Nonfatal cardiovascular events
Nephrotoxic drugs in CKD	progression of CKD
	AKI
Inappropriate dose adjustment of certain drugs (e.g antibiotics) in CKD	progression of CKD
	AKI
Late referral to physician in CKD	hospitalization
	mortality
ESRD (end stage renal disease)	Infectious complications
	Sudden cardiac death

2.4.5. Risk factor template

Based on the above, in order to describe a risk factor the following information should be considered and taken into account for risk factor modelling and CARRE information model/scheme/ontology in subsequent Tasks (T.2.2, T.2.4).

Risk Factor A	
source	the initial factor, condition, disorder
risk for	the resulting condition or disorder
type of association	issue_in, causes, affects, complicates
risk type	environmental, genetic, behavioral, biomedical, and demographic
fixed marker	yes or no, indicating whether we can alter/alleviate this factor or not
aggregate probability	an overall calculated probability that the source is associated with the result, as derived from and/or processed based on medical evidence

Probability X for risk factor A	
Biomarker	the specific biomarker used to measure the extend of the condition
biomarker value	the value range of the biomarker which determines the risk/hazard ratio
hazard ratio	the hazard ratio as per evidence based medicine
confidence interval	confidence interval
adjusted for	parameters for which is hazard ratio is statistically adjusted for
evidence source	pointer to evidence source, see below

Evidence source for aggregate probability X of risk factor A	
Citation	full
classification of type	see OCEBM classification in previous section
year	year of publication of the evidence
type of source	type of study producing the evidence

An example is given below:

Risk Factor: CKD as a risk factor for AKI	
source	Chronic Kidney Disease (CKD)
risk for	Acute Kidney Disease (AKI)
type of association	Predicts, Causes
risk type	Biomedical
fixed marker	No
aggregate probability	

Probability for: CKD as a risk factor for AKI		
Biomarker	Serum creatine	
biomarker value	Doubling- 2 x (baseline serum creatine) within 48hours	
odds ratio	1.66 for stage 3 CKD	20.42 for stage 4 CKD
confidence interval	1.40-1.97	17.40-23.96
adjusted for	Age, sex, race/ethnicity	
evidence source	1A (guideline KDIGO 2012)	

Evidence source for probability of: CKD as a risk factor for AKI	
Citation	Hsu CY, Ordonez JD, Chertow GM et al. The risk of acute renal failure in patients with chronic kidney disease. Kidney Int 2008; 74: 101–107.
classification of type	
year	2008
type of source	Cohort study

3. Comorbidities Management & Patient Empowerment

3.1. The concept of shared decision making

Recent research suggests that the majority (63% to 71%) of patients prefers having a say in the matters regarding their health and there seems to be a time trend for the patients to become more active in their healthcare, although it could also be attributed to the change of focus on the patients' involvement [190]. The core of patient participation in their health matters is not only following the physicians' recommendations, but also actively contributing to the decisions. Shared decision making is based on an interactional model (as opposed to the paternalistic and the informed models), defined by reference to four necessary characteristics [191] plus some additional, though very important ones [192]:

- At least both the patient and the physician are involved in the treatment decision-making process.
- The information is shared between the patient and the physician.
- Consensus must be achieved by taking steps to express treatment preferences.
- The treatment decision must be agreed upon by both the physician and the patient.
- The patient is faced with two or more treatment options with no clear best choice in terms of survival, outcome, or functionality.
- The patient's own preferences and values drive decisions.

The term shared decision-making is often mistakenly used interchangeably with *informed decision- making* – a broader term referring to patients becoming more knowledgeable about their health care and treatment decisions in general [193]. The key to the distinction of these concepts is in the aforementioned list of characteristics. Shared decision-making occurs in cases where a patient's values and preferences are the determining factors in deciding between two or more medically reasonable alternatives. Informed decision-making, on the other hand, is an effort to advance a patient's understanding of the science-base for choosing one treatment option over the other.

Shared decision making could also be understood as a continuum ranging from patient-driven decision making, through an equal partnership with care providers, to fully physician-driven decision making [194]. Shared Decision Making is a process in which clinicians and patients work together to select tests, treatments, management or support packages, based on clinical evidence and the patient's informed preferences. It involves the provision of evidence-based information about options, outcomes and uncertainties, together with decision support counselling and a system for recording and implementing patients' informed preferences. Since by definition there is no best treatment choice in cases where shared decision-making is used, the process relies on the experience and expertise of both parties to find a mutually satisfactory decision [193]. As such, the concept of shared decision making plays an important role in patient participation and empowerment.

3.2. Patient empowerment

Patient empowerment is a relatively new and rather complex concept. Definitions include but are not limited to: informing the patient, supporting the patient psychologically, building a rapport with a healthcare provider, informed choice/decision making, gatekeeping, coping, patient assertiveness, self-esteem and confidence [195]. It could be said that patient empowerment is a process that enables the patient to gain control, become initiative, solve problems and make decisions regarding their own health [196]. It is also a process dethroning doctors and getting patients up from their knees – in a way that does not leave doctors powerless, but helping people lead more proactive and fulfilling lives.

For example, VivaPort.eu personal health portal gives the patient control over their health records – it is possible to store their patient summary (and even translate it to another language, if such need arises), relevant medical documents and control who, when and how can access them; it also seeks for the patient to become engaged with self-monitoring and can display weight and heart-related history, providing perspective to the patients' current health condition.

As this concept is rather closely related to shared decision making, it could be said that this process also enables the patient to effectively and proactively participate in shared decision making.

There are tools that facilitate this process by helping the patient construct preferences and eventually make a decision - and they are called *decision aids*.

3.3. From decision aid to decision support services

Decision aid is an intervention designed specifically for the patient or a person facing health care decisions. One of the best definitions is as follows [197]: [decision aid] helps people think about choices they face, describes where and why choice exists and provides information about possible options; it helps people weight, collectively or individually, these options, foretell short, middle and long-term outcomes and their consequences, and by doing so, contribute to the construction of preferences and, eventually, making of the decisio.

Decision aids can be simple, in the form of a treatment option table, printed material, videos or more complex in the form of interactive questionnaire/tool, interactive web program [192,193,198,199]. Patient decision aids can be viewed as a means to shift from paternalist to increased patient engagement in shared decision making. Importantly, decision aids help ground but are not a replacement for direct conversation between a clinician and patient to determine the preferred course of action. A decision aid can be used both as part of the patient consultation and by the individual before or after a consultation [200]. Aids are intended to provide objective and easy to understand information about treatment options, the likely physical and emotional consequences of each option, and their potential harm and benefit. Decision aids may also include tools to assess personal values and preferences.

Decision aids is that they are designed to encourage a more deliberative “reasonable” approach to decision-making as to help minimize cognitive bias [200]. However, there exists a risk to create a decision aid with a variety of cognitive biases in it. For example, formulating an alternative in costs as opposed to benefits can change patient’s preference [201]. On the other hand, presenting two different alternatives at the same time can make decision aid less parsimonious, less comprehensive, and thus less easy to understand. Therefore framing effects, risk perception, judgment and decision making are the areas of psychology worth delving into in a creation of a decision aid.

Overall, a recent Cochrane review on the use of decision aids among people facing a treatment or screening decision found that they increase patients’ knowledge and realistic perception of outcomes, are likely to encourage decisions that are consistent with the patients’ values and improve communication between the clinician and patient, allowing greater participation in decision making [199].

The field of shared decision-making is evolving and likely will be shaped by the emergence of new technologies that change the nature of the clinical-patient encounter. For example, the use of real-time interfaces other than in-person visits may shift how decision aids are used or how shared decision-making occurs between clinician and patient [202].

3.4. Decision support intervention and decision aid design strategies and tactics

A systematic review of cancer decision support services points out three specific design strategies [203]:

- Information giving
- Enhanced participation
- Reinforcement

There are few (if any) suggestions as to which strategy is the most important, but a large number of the implementations seem to have been developed using the information giving design

The implementation methods are varied – literature lists the following categories of DSIs/DAs

Brief decision aids (answer three questions: 1. “Do I have options?”, 2. “What are the benefits and risks?”, and 3. “How can I and my HCP make a decision together that is right for me?” [204,205,206,207,208,209]

– Risk communication tools

- Patient information tools
- Booklets, audio guides
- Structured, individual and group counselling
- Patient decision boards
- Question prompt lists
- Interactive dashboards
- Decision trees, decision analysis
- Value clarification tools

There are suggestions in literature that decision analysis tools provide the most comprehensive decision support, but it seems DAs have a positive influence on both the decision-making process and decision outcome in general, regardless of the type.

3.5. Evaluating decision aids

Decision aid evaluation scale has been outlined in 2005 by the International Patient Decision Aids Standards (IPDAS). This scale aims to provide a shared evidence-informed framework with a set of criteria to enhance both the quality and effectiveness of DAs, and is widely adopted by decision aid developers worldwide.

3.6. Decision support system

A decision support system is a computer-based information system that facilitates decision-making activities. Both Sprague (1980) [210] and Keen (1980) [211] provide the following definition of a decision support system:

- A DSS is defined by the problem it addresses.
- A DSS is based both on models and analytic techniques and traditional data access and methods.
- A DSS supports the cognitive processes of individual decision makers.
- A DSS is flexible and adaptable to both the changes in the environment and the users' approach to making the decision.

Unlike the older CDSS, modern medical decision support systems should provide additional capabilities including the following [212]:

- Compatibility with both structured and free-form medical data.
- The ability to integrate information from different sources.
- The ability to understand and translate information from heterogeneous systems.
- Tolerance for sparse patient data.
- Ability to explain their decisions and recommendations.

3.7. Existing Decision Aid programs

Informed medical decisions foundation [213] has a number of DA programs in the following categories:

- Back care
- Breast cancer
- Cardiovascular disease

- Chronic Conditions
- End of life
- General health
- Mental health
- Ophthalmology
- Orthopaedic
- Prostate
- Screening and testing
- Weight loss
- Women's health

Arriba-lib: electronic library of decision aids with evidence-based modules for cardiovascular prevention, diabetes, coronary heart disease, atrial fibrillation and depression has positive associations to the decision-making process in patients and physicians. It can also be used with older age groups and patients with less formal education [214].

Ottawa Hospital Research Institute has a comprehensive list of decision aids grouped by health topics ranging from acne to weight control [215] and an online patient decision aid development e-training course [216], UK's National Health Service has a directory of Decision Aids [217] and an expert system (NHS Direct) for finding relevant Das [218], United States agency for healthcare Research and Quality under U.S. Department of Health and Human Services also has a directory of decision aids, and so on, so forth. Most of the decision aids seem to have been developed to provide information, i.e. are in a form of a booklet (e.g. this behaviour could worsen your condition, the other can do no harm, etc.) or an educational video. As CARRE decision support services mainly address treatment critiquing and planning, information retrieval and education, simplest forms of DAs will not suffice, so we should be looking towards more complex collections of various types DAs complementing a DSS.

3.8. Existing decision support system frameworks and recommendations for their development

There are quite a lot of frameworks for decision support systems mentioned in academic literature, but most of them seem to be oriented towards the health care professional. Nevertheless, there are some rather recent and intriguing developments in this particular field which also support the patients' decisions: knowledge-based OMeD system, Holmes, a Hybrid Ontological and Learning Medical System [212], Clinical Decision Support Consortium's pilot study of distributed knowledge management and clinical decision support [219]. It is not beyond the realm of reason to think that a web-based MVC real-time clinical decision support system developed by researchers at China Medical University [220] could be modified to present relevant information to the patient instead of a healthcare professional, nor is it impossible to modify vivaport.eu multilingual personal health portal to provide relevant interactive decision aids based on the personal health record stored on the site.

There have been suggestions that developers of decision-making support tools should concentrate more on the more comprehensive development process, better conveyance of information on a full range of outcome states and better presentation of outcome probabilities in a way that is understandable and interpretable by patients with different levels of health literacy [204]. Strategies to sustain relevance and quality of information content are also considered important. Also the majority of decision support services are deliberation-facilitating and tend to ignore the intuitive processes, which are also important. It has been suggested that intuitive and analytical processes may have complementary effects in patient decision support and that focusing only on supporting deliberation may limit effectiveness and negatively influence preference construction [209].

3.9. Conclusions

There doesn‘t seem to be a “silver bullet” solution to developing super-effective patient-oriented decision systems or decision aids. There are, however, evaluation tools such as IPDAS which can help ensure the overall quality of a decision aid in development, insight into human perception and decision making that can help with innovation. It also seems that the type of the decision aid is less important than expected, and even though decision analysis tools might look more effective, other researchers remind us that intuition is as important as deliberation. And even though all well-built decision aids seem to have a positive effect on both the decision-making process and decision outcome, it is important not to forget that the whole shared decision process begins with the health care professional and the patient, and both the decision-making process and the decision outcome depend on the interaction between them.

4. CARRE Survey

4.1. Introduction

The aim of the survey is to identify end-user expectations in order to give user feedback for the definition of CARRE functional requirements.

This survey targets the different types of end users

- patients with cardio renal disease and with or at risk of comorbidities and/or their carers;
- healthcare professionals of all levels, including General Practitioners, Specialized Medical Doctors, Nurses in Units and Outpatients Clinics, etc.; and
- key persons in organizations that provide managed care or health insurance, e.g. in a National Health System, private health insurance company, etc.

4.2. Aim and Research Questions

The aim of this survey is to help identify use cases and derive CARRE functional requirements. The survey was designed to capture all points of view of potential stakeholders. These can mainly be grouped into three main categories:

– the patient group (including patients, healthy individuals at risk as well as their carers), and

– the professionals, including medical experts, nursing personnel, and

– healthcare policy makers.

Research questions to investigate the patient perspective can be grouped along the following axes:

– How do patients perceive empowerment (in terms of their health condition management)? Are they willing to be empowered or prefer to be guided?

– Do patients understand their condition; are they willing to be informed about it and what information would like to have?

– Are patients willing and able to be engaged with ICT intervention that will enhance their knowledge and empower them?

– At what extend are patients willing to be monitored so that information gathered can be used to personalized empowerment and educational interventions.

Research questions to investigate the professionals' perspective can be grouped along the following axes:

– How do professionals perceive patient empowerment?

– Are professionals' willing to support and promote patient empowerment interventions?

– What would empower professionals to manage (not empower) cardiorenal patients?

Research questions to investigate the perspective of other stakeholders (e.g. policy makers) can be grouped along the following axes:

– How do other stakeholders perceive patient empowerment?

– Are they willing to support and promote patient empowerment interventions in healthcare systems?

4.3. Survey Design and Deployment

A different survey approach was chosen for each one of the target groups.

4.3.1. Patients Survey

The patients group (including healthy individuals and/or carers) was surveyed based on a questionnaire, specifically designed and validated for this purpose. The methodology for design and validation of the questionnaire is presented in detail in Annex 1 of this deliverable.

The questionnaire consisted of 5 sections:

1. Personal Information (7 questions)
2. Understanding my condition (4 questions)
3. Getting information on my condition (10 questions)
4. Empowerment or Guidance? (12 questions)
5. Technology and disease management (9 questions)

All four questions of the group on “Understanding my condition” which aim to probe patient’s perceived ability/knowledge were supplemented by additional open ended subquestions so as to have a measure of the perceived vs. real personal ability. In particular:

1. Question: I am aware of what may have caused my current condition.

   Supplement: Please list all you think that may have caused your current condition:…
2. Question: I know which symptoms I currently experience are due to my disease.

   Supplement: Please list all you know:…
3. Question: I can recognize new symptoms that may indicate disease progression

   Supplement: Please, list which ones:….
4. Question I am aware of other illnesses that may occur due to inefficient management of my current health condition.

   Supplement: Please, list all you know: …

The final questionnaire was deployed primarily in the two countries of the intended CARRE pilots in their native language. Deployment was via printed questionnaires handed out to patients in hospital waiting rooms, as well as via electronic versions of the questionnaires available on-line.

The printed questionnaires were handed out to patients in hospital waiting rooms in two different hospitals:

– General Regional Hospital of Kavala, Kavala, Greece
– Vilnius University Hospital Santariskių Klinikos, Vilnius, Lithuania

Before administering the questionnaires, in both hospitals the appropriate ethics approvals were obtained: Kavala: prot. no: 56/7.4.2014, Vilnius: prot. no 14VR-3165/2014-03-18.

The questionnaires were also made available on-line. The on-line versions were developed in the GoogleDocs web platform and are available at:

– Greek online version : https://docs.google.com/forms/d/1tf1vMukKlq46YZ6Oux_Weq5BgsI2ltStMZsI42Umb14/viewform

– Lithuanian online version : https://docs.google.com/forms/d/1ZXPAlWC3ktbvuP4IVmdnyRLE1kLOXSY9U093IsAuGMU/viewform

– English online version : https://docs.google.com/forms/d/1NG9KV6niyqG1B08cQQpEMGu9igDi0C5CLKVIxupOR00/viewform

The on-line versions of the survey were advertised via the CARRE project homepage and via the twitter and facebook project pages.

4.3.2. Healthcare Professionals Survey

Perceptions of healthcare professionals were recorded mainly by a short questionnaire. This was derived based on a focus group of healthcare professionals.

Questions focused on two main categories:

- How do professionals prefer to keep up to date with medical knowledge
- What are their perceptions about using technology in disease management

The methodology for design and validation of the questionnaire are presented in detail in Annex 2 of this deliverable.

The questionnaire was deployed mainly by DUTH and VULSK in the two countries of the intended CARRE pilots, Greece and Lithuania respectively.

4.3.3. Other Stakeholders Survey

Perceptions of policy makers were recorded via semi-structured interviews. The following outline was followed:

1) Please give us some information about the job and key responsibilities (Name, Affiliation, Position, Position Responsibilities, Years in this or at similar position).
2) Are you directly related to the field of cardiorenal disease and/or cardiorenal comorbidities? Please, explain.
3) In your opinion, what are the major problems cardiorenal patients (or people at risk of cardiorenal disease) face?
4) What are the major problems encountered today by the health professionals who deal with this disease?
5) What do you think are the most important steps for the prevention of disease?
6) Are you familiar with the term 'patient empowerment'?
7) How would you envisage empowerment of patients with cardiorenal disease (across the spectrum of patients who simply have an increased risk in those who already have heart or kidney disease, up to those with a terminal illness or other important comorbidities)? What services would you expect to make an impact? Please, elaborate.
8) If you would change something in the health system towards this direction, what would it be?
9) Would you promote a service/system empowering patients? How?
10) If yes, what would you want from such a service/system?
11) What kind of alerts or alarms would you think as important for the prevention and management of chronic cardiorenal disease and comorbidities?

4.4. Survey Results

4.4.1. Patients Survey

There were overall 389 responses by 24 April 2014. The results of these 389 first responses were analyzed and are presented in this document. It should be noted that the survey will keep running for a few more months and the accumulative results will be reported as an update to this Annex.

Basic analysis was performed by Microsoft Excel software and more advanced analysis and correlations with the IBM SPSS software. Each question was assessed first for overall performance and the results are presented in detail (per question) in Annex 1. Here **overall results are presented**, based on the percentage of respondents that agree with each statement (**sum of 'agree' and 'fully agree'**).

Overall the distribution of respondents in terms of age and sex are shown in Figure 4.

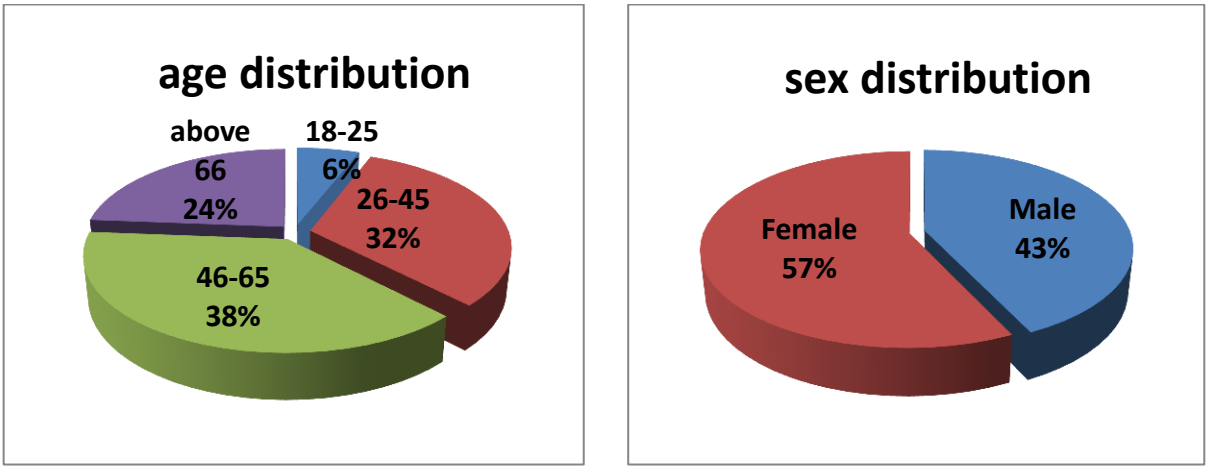


Figure 4. Age and sex distribution of the respondents.

Figure 5 shows the overall results of the category "Understanding my condition". The majority of respondents report that they are aware of what caused their condition and which symptoms can be attributed to their condition. However, less than half report that are aware of new illnesses that may occur due to inefficient management of current condition. Even less can recognize new symptoms that may indicate disease progression.

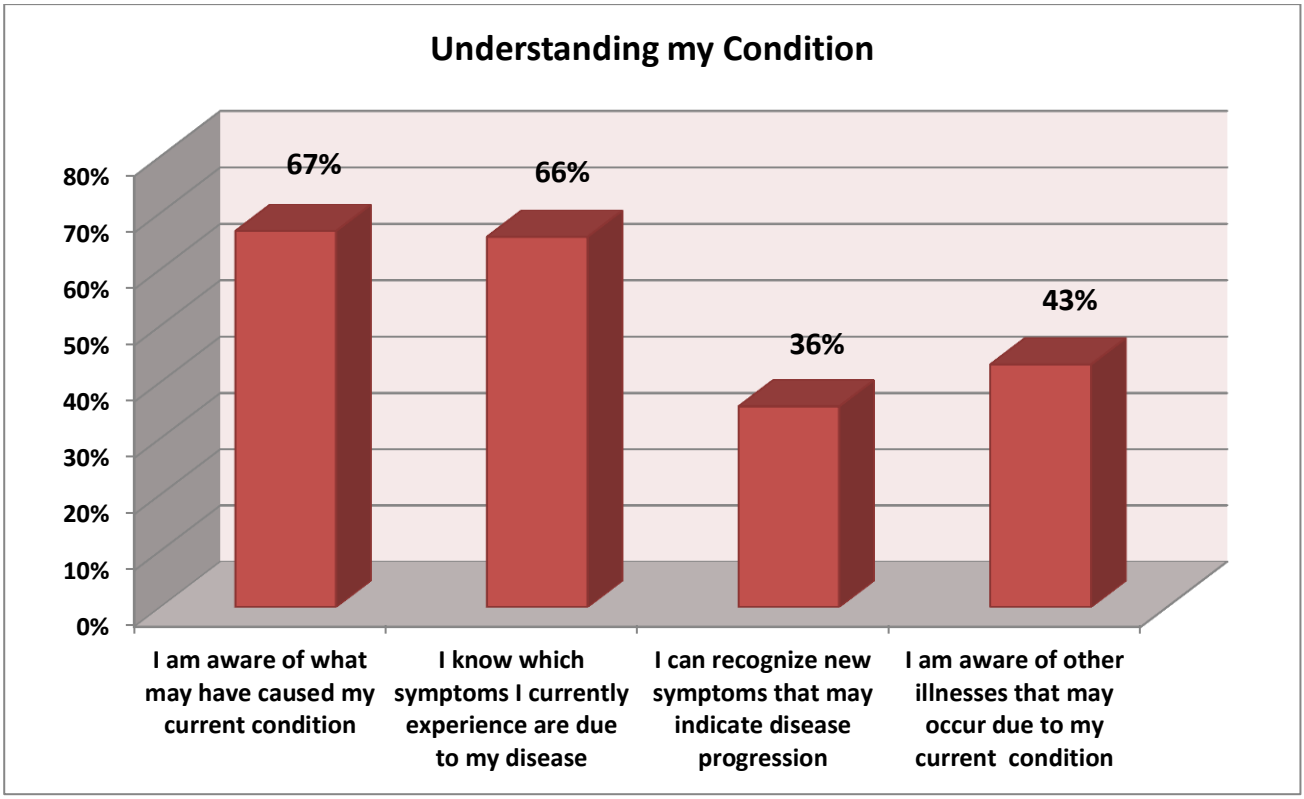
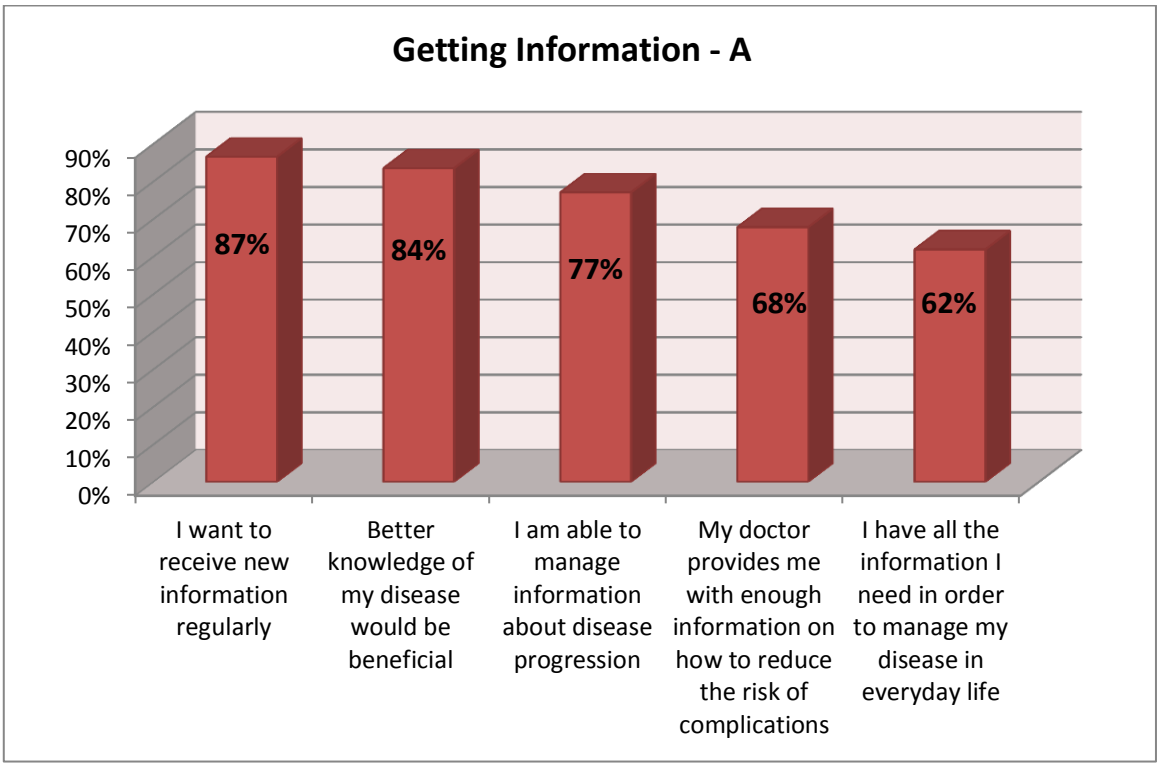


Figure 5. Overall results of the category "Understanding my condition".

Figure 6 shows the overall results of the category “Getting information on my condition”. A significant majority values information on their condition, find it easy to understand and want to receive it regularly. Also, a good majority feels able to manage information on disease progression and also feel that they have the information they need for to understand and manage their condition. However, slightly less than half feel they have information they need to understand disease progression. Also, the slightly more than half feel anxious when receiving new information about their disease.



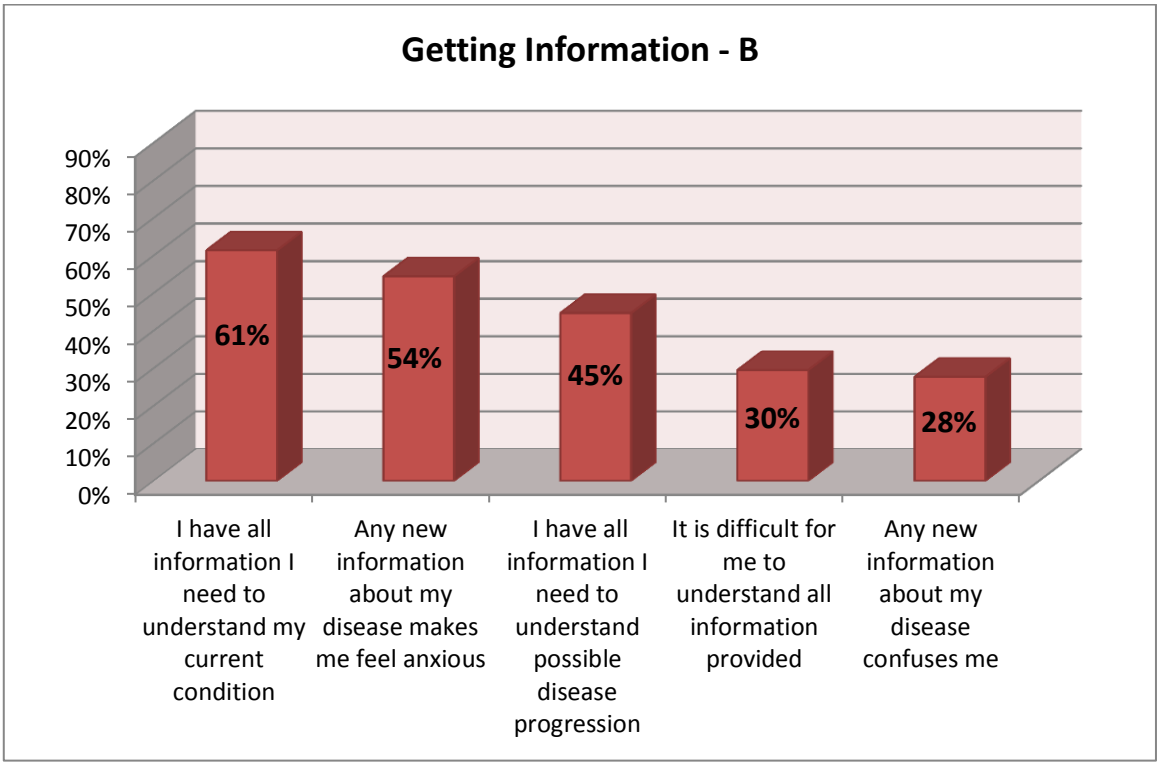
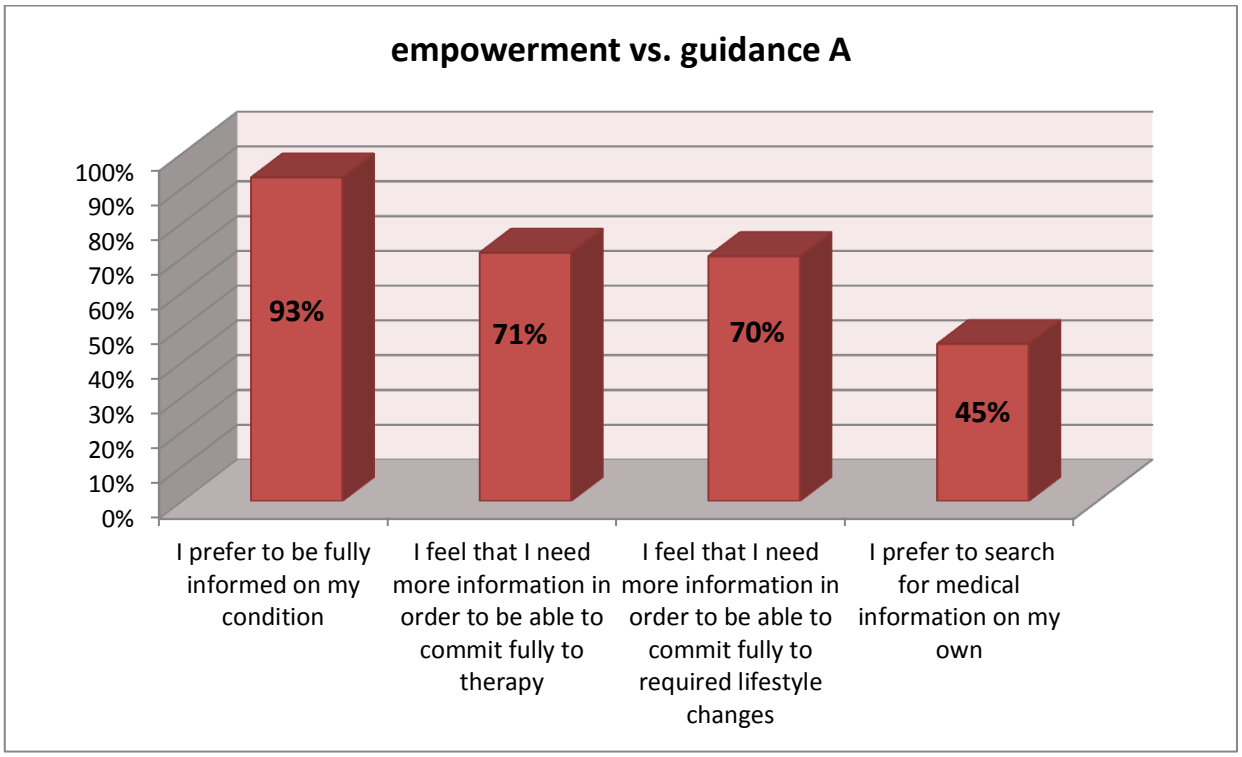


Figure 6. Overall results of the category “Getting information on my condition”.

Figure 7 shows results of the category "Empowerment vs. Guidance". The striking majority wants to be fully informed and a good majority needs more information in order to commit to therapy and lifestyle changes. Howerever, less that half prefer to search for medical information on their own. Also, the striking majority prefer to discuss their condition with their doctor, but only about half discuss it with fellow patients. About half prefer to rely only on doctor's knowledge and guidance. The majority prefers their doctor to decide on the best treatment, but when alternatives are available the majority prefers to make the final decision.



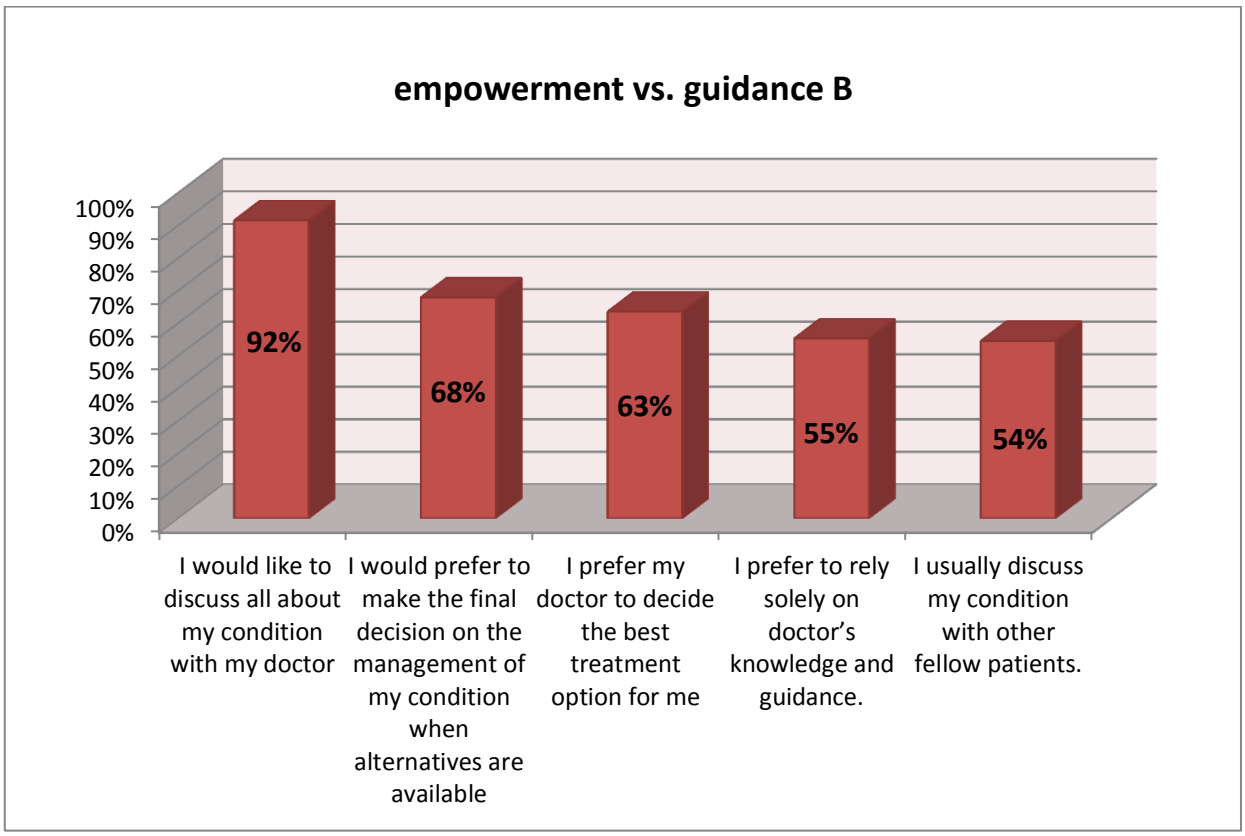


Figure 7. Overall results of selected questions in the category "Empowerment vs. Guidance"

Figure 8 shows overall results of the category "Technology and Disease Management". Only about half of respondents use the internet as a source of medical information, and even less than half feel able to recognize which internet source provides accurate medical information. However, a good majority would be willing to use applications to monitor and manage diet and physical activity, applications that provide medical alerts and a single web portal to gather and access vital information about their condition.

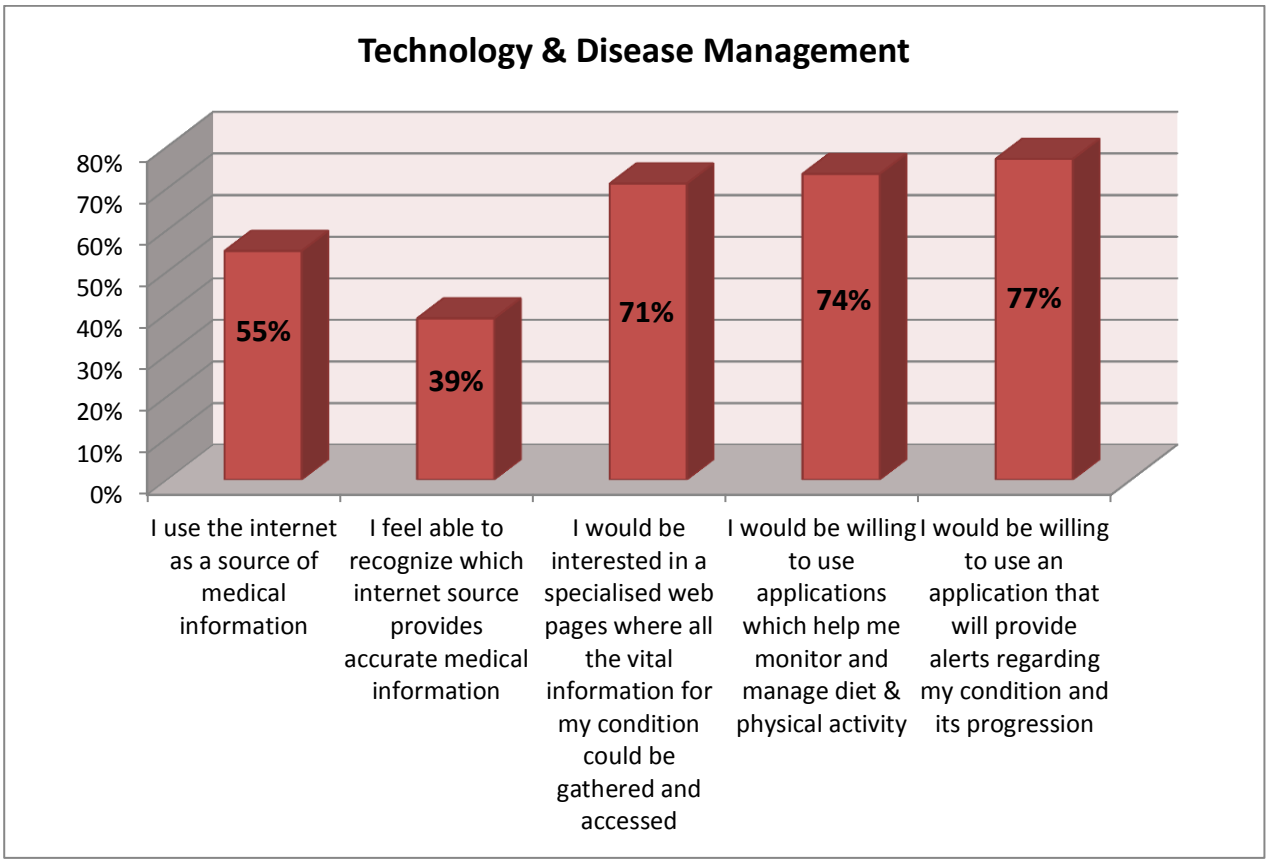


Figure 8. Overall results of selected questions in the category "Technology & Disease Management"

Further analysis based on x^2-test was performed to identify age and sex related differences in the answers. Statistically significant sex differences were found only for three statements, presented in Table 13. In particular women appeared to report higher percentages of agreement with the statement on their awareness about possible disease progression due to insufficient management of current condition. Also, women appear to be more willing to monitor their condition. However, men appear to be more confident in searching for medical information on their own.

Table 13. Significant differences across sex.

statement	female	male	$x^2(2)$	level of significance
	%	%		p<
I am aware of other illnesses that may occur due to inefficient management of my current health condition	56.8	43.8	13.053	.001
I prefer to search for medical information on my own	43.3	56.3	6.438	.05
I am willing to monitor myself and record data on my activities (e.g. weight, diet, etc.) in order to manage my condition more efficiently	56.2	43.8	11.133	.001

Statistically significant age differences were found only for 18 statements, presented in Table 14.

Table 14. Significant differences across ages.

statement	26-45	46-65	>66	$x^2(4)$	level of significance
		%	%		p<
Getting information					
I am able to manage information about possible progression of my disease.	37	40,6	22,4	9.890	0.5
Any new information about my disease confuses me.	26,2	36,4	37,4	15.300	0.1
It is difficult for me to understand all information provided.	27,7	38,4	33,9	15.896	0.1
Empowerment					
I want more information to better understand my condition and its possible progression.	35,8	42,7	21,5	18.866	0.1
I would like to know possible alternative ways of managing my condition.	35,1	42,7	22,2	13.329	0.1
I feel that I need more information in order to be able to commit fully to therapy	36,8	42,2	20	10.102	0.5
I would prefer to make the final decision on the management of my condition, when there are more than one alternative option.	39,8	41,9	18,3	23.296	.001
I prefer my doctor to decide the best treatment option for me.	27,5	40,7	31,8	21.333	.001
I prefer to rely solely on doctor's knowledge and guidance.	26,4	41,3	32,2	24.055	.001
I prefer to be fully informed on my condition	34,4	41,8	23.4	12.191	0.1
Technology and disease management					
I use the internet as a source of medical information	49	40.3	10.3	89.889	.001
I understand the health information that I find on the internet	50.6	40.3	9.1	89.230	.001
I feel able to recognize which internet source provides accurate medical information.	53.3	40.1	6.6	86.314	.001
I feel that information provided on web pages is reliable and trustworthy	48.2	41.8	10	44.886	.001
I would be interested in a specialised web pages where all the vital information for my condition could be gathered and accessed.	39.3	43.6	17.1	38.431	.001
I am willing to monitor myself and record data on my activities (e.g. weight, diet, etc.) in order to manage my condition more efficiently.	37.6	42.4	20	11.474	0.5
I would be willing to use applications which help me monitor and manage diet & physical activity.	38.8	41.4	19.8	22.046	.001
I would be willing to use an application that will provide alerts regarding my condition and its progression.	36.7	42.4	20.9	13.753	0.5

Regarding the category “Getting information”, older participants seem to feel less able to manage the information they receive about their disease. In line with this finding, they also seem to report more often confused by any new information and in turn, that it is more often difficult for them to manage the new information regarding their disease. Regarding the “empowerment” category, it seems that participants from the two younger age groups, especially those aged 46-65 years, report more often the need to have more information about their condition. For example, a higher percentage declares need for more information about their disease so as to understand their condition or to be committed to a therapy. Interestingly enough, younger participants do not seem to prefer their doctor to take solely decisions about their therapy. Instead, the older participants seem to feel well with this option. Regarding the category on technology, the older participants seem to feel unsafe with the new technology as a mean for the better management of their disease. On the contrary, significant portions of the other two groups estimate the role of new technology as being helpful for the management of their condition. Also, they seem to be willing to monitor themselves and record data on their daily activities, to use an application that would help them to manage these daily activities (eg. diet) or their physical condition, and to use an application that would provide alerts to them regarding their condition and its progression.

4.4.2. Professionals survey

The questionnaire was deployed mainly by DUTH and VULSK in the two countries of the intended CARRE pilots, Greece and Lithuania respectively by advertisement within the personnel of the affiliated hospitals.

There were overall 209 responses by 24 April 2014. Basic analysis was performed by Microsoft Excel software and more advanced analysis and correlations with the IBM SPSS software. Each question was assessed first for overall performance and the results are presented in detail (per question) in Annex 2. Here **overall results are presented**, based on the percentage of respondents that agree with each statement (**sum of ‘agree’ and ‘fully agree’**).

Overall the distribution of respondents in terms of age and sex are shown in Figure 9. It is apparent that the majority of respondents are females, and in the age group of 26-45 years old.

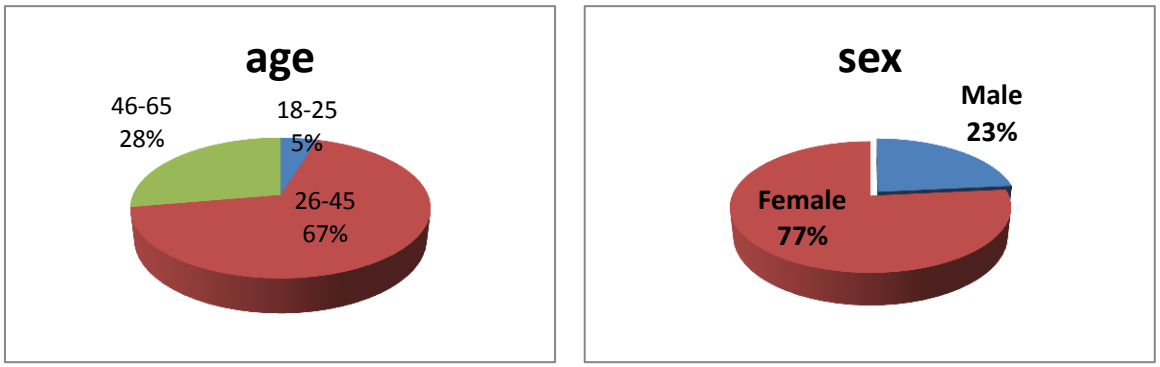


Figure 9. Age and sex distribution of respondents in the professionals’ survey.

Overall a significant majority (92%) of respondents report that they keep up to date with medical knowledge and that they feel satisfied (87.5%) with they keep up with latest developments. The sources they use to keep up to date are shown in Figure 10. Mostly internet sources (93.3%) are preferred as well as consultation with colleagues (91.9%). Medical textbooks (88%) and conferences (78.5%) follow, while authoritative evidence based medicine sources are slightly preferred over conventional scientific literature.

Responses indicate that professionals are not aware of major good or bad impact on patients condition as a result of using information they found on the internet; also, majority of professionals do not think general health information on the internet is reliable (Figure 11).

Finally a significant majority of professionals (76.6%) encourages patients to get involved in decisions about their health management; a majority believes that telemonitoring is beneficial both for the professional and the patient in disease management (Figure 12).

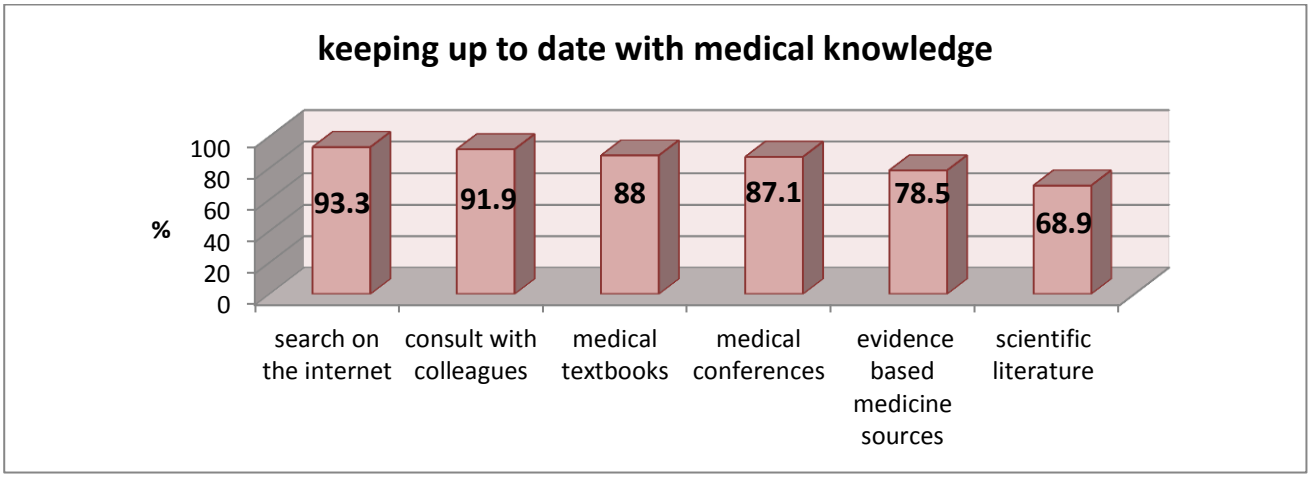


Figure 10.Sources used by professionals to keep up to date with medical knowledge

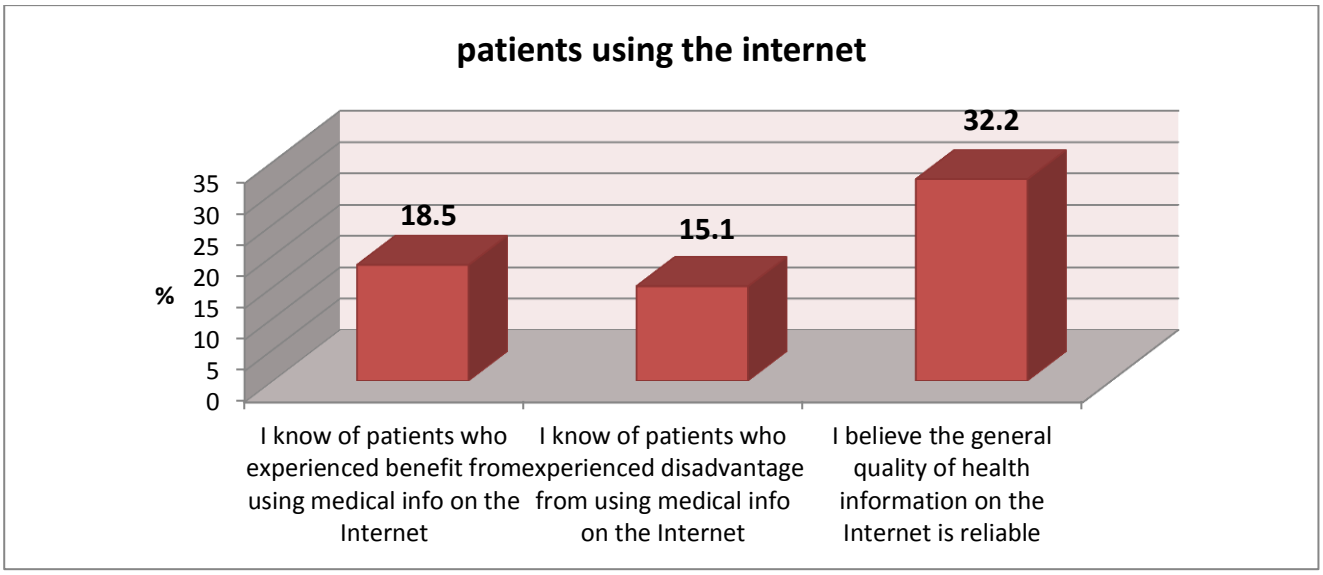


Figure 11. Professionals' perceptions on the use of internet by patients.

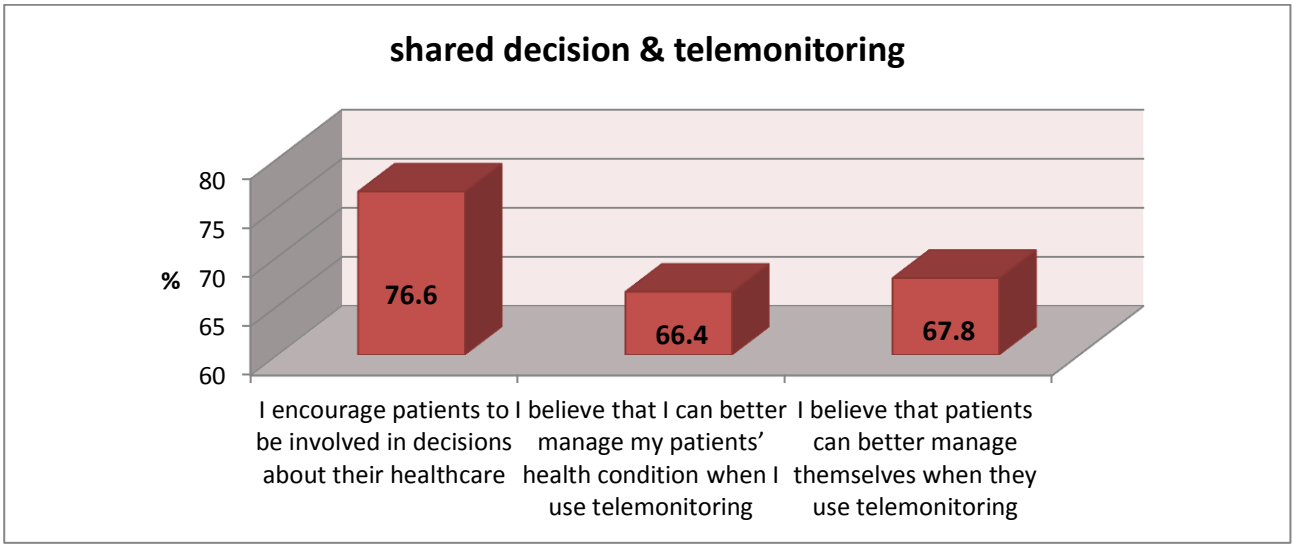


Figure 12. Professionals' perceptions on shared decision and telemonitoring

4.4.3. Other stakeholders survey

Six different interviews were conducted with various stakeholders are positions of leadership and policy making in fields related to cardiorenal disease. Summaries of these interviews are presented in Annex 3. The persons/roles interviewed are:

1) Leadership in prevention and treatment of life-style related diseases, President of European Society of Lifestyle Medicine
2) Municipality Council Member – Member of the Committee for Quality of Life
3) Head of Regional Department of Health, Prefecture
4) Director, Dialysis Center
5) Head of Cardiology Clinic, General Regional Hospital
6) Head of Nurses, Regional General University Hospital

Overall, all interviewed persons were found to be closely related either to cardiorenal disease or chronic disease management. They were familiar with patient empowerment and proponents of such services and interventions, although overall they could not report implementation of empowerment services to the desired extend. A major problem for patients was unanimously reported to be lifestyle management and increased hospital visits, often unnecessary and due to insecurity, arising from lack of proper information and support. Likewise, for doctors major problems are how to convince patients to adhere to lifestyle guidelines and how to keep them informed so that they visit hospital only when necessary, and immediately when necessary. Prevention is a major issue, and most important steps is citizen empowerment for adapting and maintain a healthy lifestyle even from childhood. Changing the healthcare paradigm from disease centered to health and prevention centered seems to be a common belief. This involves public awareness and also proper alerts of when to visit a healthcare professional.

5. Legal Issues: Data Privacy & Security

5.1. Introduction

It is well accepted that the practice of health care is extremely information intensive – clinical treatment, as well as coverage and payment, depend profoundly on robust, accurate, appropriate, and timely information – and that information is a vital component of modern health care systems. The taking of a patient's history has been a core element of the health care encounter since medical practice began, and some form of record keeping of encounters between the clinician and patient has been central to providing care, even if in ancient times the clinician relied solely on his memory to record such information. Record keeping remains a core tenet of health care, although the advent of advanced testing, genetic profiling, and the techniques of medical imaging have hugely increased the volume and detail of health information in the past decades. The fully integrated, accessible, secure, and searchable EHR is both a vehicle for much needed change in health care organization, but it also poses a significant potential threat to privacy in health care, and as a result it is important to develop specific ethical and legal frameworks for the protection of privacy in such records.

Beauchamp and Childress [221], in their textbook *Principles of biomedical ethics,* which has for many years been the touchstone of understanding medical ethics around the world, famously reduce all medical ethics into four core principles:

- **Respect for autonomy**. Health-care professionals and health care systems should respect the decision-making capacities of autonomous persons and enable individuals to make reasoned and informed choices.
- **Beneficence**. Health-care professionals and health care systems should act in a way that benefits the patient, which will require a careful balancing of benefits of treatment against the risks and costs.
- **Non-maleficence**. Health-care professionals and health care systems should not harm the patient; while accepting that avoiding any treatment may involve some form of harm, such harm should not be disproportionate to the benefits of treatment.
- **Justice**. Health-care professionals and health care systems should distribute the benefits, risks, and costs of health care fairly, so that patients in similar positions may be treated in a similar manner. If these principles are accepted as valid then it is worth considering briefly the way they are applied to a respect for privacy in EHRs.

A respect for health information privacy based in autonomy is perhaps the easiest to understand and the most closely related to common human rights concepts. The concept of autonomy is based fundamentally on the right of every competent adult to make decisions for him or herself.

Due to the relevance of data privacy and security using patient's medical data it is important to analyse the main legal documents such as European Union Directive 95/46/EC on protecting of individuals with regard to processing of personal data and on free movement of such data and the Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare. Furthermore, it is important to provide the most common concepts of data protection and privacy on an ethical point of view.

5.2. EU Directive 95/46/EC - the general EU law in the field of the protection of personal data

European Union Directive 95/46/EC on the protection of individuals with regard to processing of personal data and on the free movement of such data

Directive 95/46/EC [222] applies to the processing of personal data when delivering telemedicine services and sets the basic principles for the requirements of such data between all the actors involved in a telemedicine service. It aims at protecting individuals with regard to the processing of personal data, while achieving the free flow of personal data within European Union in the contest of internal market. It lays down obligations on data controllers and specifies the rights if data subjects.

"**Personal data**" means any information relating to an identified or identifiable natural person (the "data subject"; Art, 2 a) of Directive 95/46/EC). An identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one more factors specific to his physical, psychological, mental, economic, cultural or social identity. This includes the processing of sound and image data.

"**Processing of personal data**," means any operation or set of operations which is performed upon personal data, whether or not by automatic means, such as collection, recording, organization, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, blocking, erasure or destruction (Art. 2 b) of Directive 95/46/EC).

5.2.1. General principles for the Processing of Personal data

Use limitation principle (purpose principle): This principle (Art. 6 (1) (b) of the Directive), requires that any collection of personal data must for specific, explicit and legitimate purposes and prohibits further processing which is incompatible with the original purpose (s) of the collection.

The data quality principle: This principle in the Directive requires personal data to be relevant and not excessive for the purposes for which they are collected.

Thus, any irrelevant data must NOT be collected and if it has been collected it must be deleted (Art. 6 (1) (c)). It is also requires data to be accurate and kept up-to date.

The retention principle: This principle requires personal data kept for no longer than is necessary for the purpose for which the data were collected or further processed.

Personal data may only be processed if one of the criteria laid down in Art. 7 of the Directive applies, e.g. consent of the data subject.

Information requirements: pursuant to Arts. 10 and 11 of the Directive data controllers processing personal data must provide certain information to data subjects, such as information on the identity of the controller, on the purposes of the processing, on the recipient of the data and the existence of a right of access.

Data subject's right to access: Art. 12 of the Directive provides data subjects with the right to have access to his or her personal data, in order to check on the lawfulness, accuracy of the data and to ensure that the data are kept up-to-date.

Security related obligations: Art. 17 of the Directive impose an obligation upon data controllers to implement appropriate technical and organizational measures to protect personal data against accidental or unlawful destruction or unauthorized disclosure. The measures can be organizational or technical.

Transfers to third countries: in cases of transfer of data to countries that are not members of the EU or the European Economic Area, it may be necessary to take special precautions if the level of data protection in the third country is inconsistent with that provided by European law. Without such rules, the high standards of data protection established by the Directive would quickly be undermined, given the ease with which data can be moved around in international networks. The principle of the Directive is that personal data can only be transferred to countries outside the EU and EEA that guarantee an "adequate" level of protection. Where a non-EU country does not ensure an adequate level of protection, the Directive requires the blocking of specific transfers.

5.2.2. Special Protection for Personal data related to health

As the processing of personal data related to health is particularly sensitive, in principle, such data cannot be processed (Art. 8 of Directive 95/46/EC). The expression "data concerning health" used in Art. 8(1) must be given a wide interpretation so as to include information concerning all aspects, both physical and mental, of the health of an individual. Derogation is tolerated under very specific circumstances: limited exemptions to this prohibition principle are laid down in the Directive.

In Article 8 of the Directive a special status refers to all medical and health related information and prohibits the processing of health related data unless one of four exceptions is met:

- Explicit informed consent has been obtained from the data subject (Article 8(2)(a)); or

- Data processing is in the vital interests of the patient or of another person who is physically or legally incapable of giving consent (Article 8(2)(c)); or
- The processing of health data is required for the purposes of preventive medicine, medical diagnosis, the provision of care or treatment, or the management of health-care services AND the personal data in question are processed by a health professional (Article 8(3)); or
- There is a substantial public interest in the processing (Article 8(4)).

5.2.3. The Article 29 Data Protection Working Party

In order to help Member States interpret their duties under the Directive a data protection working party (DPWP) composed of the representatives of the national data protection authorities has been established. Its function is to advise the European Commission on the implementation of the Directive in the Member States. It is known as the Article 29 Data Protection Working Party and is referred to as the DPWP in this document [223]. The working papers of the DPWP have no binding legal authority, but because they represent the common understanding of the data protection authorities of the Member States they may be used as evidence of common best practice in any litigation. The DPWP considered in some detail the extent to which each of the four possible exemptions under Article 8 of the Directive (as listed above) could be applied in the context of an EHR: consent, vital interests, care provision, and public interest. The DPWP's deliberations on the role of privacy in EHRs is discussed below in order to provide an example of some of the issues which legal policy-makers consider when seeking to balance the competing interests in privacy of EHRs:

Consent: The DPWP did not see consent as a valid basis for processing data in an EHR. The guidance argued that because the creation of a medical record is a necessary and unavoidable consequence of care provision, a health professional may be required to process personal data in an EHR, and thus withholding of consent may be to the patient's detriment. If withholding consent could be to a patient's detriment, then such consent would not be freely given as required in Article 8(2)(a).

Vital interest: The DPWP argued that in the medical context a 'vital interest' would have to be for life- saving treatment in a context where the patient is not able to express him- or herself. Accordingly they argued that this exception could not be used for routine processing of health information in an EHR.

Health care provision: The full text of Article 8(3) requires that the personal data in question are "required" for provision of care and the personal data are processed by a health professional subject "under national law or rules established by national competent bodies to the obligation of professional secrecy or by another person also subject to an equivalent obligation of secrecy". The DPWP argued strongly against the use of this exemption to legitimate the creation of an EHR, principally because it sees an EHR as giving access to medical histories to health-care professionals who were not party to the previous treatment documented in the EHR and therefore could not have been considered by the patient when entering into the trusted relationship with the primary care. Thus the most common justification of an EHR system – that it improves the provision of health care – is not seen as sufficient by the DPWP to legitimate the collection of medical data in such a system.

Substantial public interest: The DPWP notes that since consent, vital interests, and medical care (Article 8(2)(a) and (3)), would probably not be sufficient to allow an EHR to be established, Member States should consider the possibility of adopting special regulations to safeguard privacy in EHR on the basis that an EHR is in itself a matter of public interest. Such legal provision would have to provide specific and suitable safeguards for the protection of privacy with an EHR system and would have to be duly notified with the European Commission [224].

The DPWP went on to consider what a legal framework for data protection in an EHR system as provided for under Article 8(4) might look like. The DPWP noted that if the safeguards for data privacy in an EHR are well drafted, it may be legitimate to offer an opt-out system. They argued that such an opt-out system would assume that for general health information a patient has opted-in to the system unless he or she explicitly opts-out. The DPWP suggested however, that given that an EHR will contain many different types of information such an opt-in/ opt-out system should be incremental – thus a general opt-out might apply, but a specific opt-in would be necessary for processing especially sensitive information such as information about mental health or sexually transmitted infections. The DPWP also suggested that rules should provide that a patient can prevent a particular category of medical professional seeing a particular category of his or her data. It did not say whether such suppression of data should be visible on the face of the record, but notes the value of the use of the 'sealed envelope' technique.

The DPWP also argued that the rules concerning an EHR should allow only those health-care professionals or authorized personnel of health care institutions who are presently involved in the patient's treatment to have access, and that there must be a relationship of actual and current treatment between the patient and the health-care professional wanting access to his or her EHR. They suggested that this could be well supported by modular access rights, forming categories of medical data in an EHR system to which access is limited to specific categories of health-care professionals or institutions. Thus the EHR could contain an emergency data set with relatively low access controls while highly sensitive data could be accessible only by the treating primary care physician. The DPWP recognized that patients should have access to the data held in the EHR, thus the rules for an EHR system must address issues of patient access and should consider granting access to patients so that they can add to the record themselves.

5.3. EU Directive 2011/24/EU - the application of patients' rights in cross-border healthcare

Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare.

On the basis of the assessment of the current and future extent of cross-border non-hospital care is no evidence to suggest that such care will undermine either the financial sustainability of health and social security systems overall or the organization, planning and delivery of health services. On that basis, the obstacle to free movement represented by a prior authorization requirement for such cross-border non-hospital care is not justified, and such prior authorization should therefore not be required for non-hospital care. However, Member States may have limitations on the choice of provider or other domestic planning mechanisms, which are applied domestically, including conditions, criteria of eligibility and regulatory and administrative formalities. These may also be applied to cross-border non-hospital healthcare, provided they respect internal market freedoms and any such restrictions on access to non-hospital healthcare abroad are necessary, proportionate and non-discriminatory.

Provision of cross-border healthcare does not necessary require either the patient or the professional to physically change countries, but may be provided through information and communication technologies – this is the mode of supply referred to as 'cross-border provision of services', or "E-health". This is a mode of supply of growing importance, but one, which presents specific challenges for ensuring that the different information and communication technologies of the health systems of the Member States are compatible (or "interoperable"). Widely different and incompatible formats and standards for information and communication technologies used in healthcare provision are used throughout the Community, creating both obstacles to this mode of cross-border healthcare provision and risks to health protection. It is therefore necessary to provide for Community harmonization in this area in order to achieve the interoperability of Member States' information and communication technology.

Although the Commission has been able to estimate the likely extent and nature of cross-border healthcare, data on cross-border healthcare is not sufficiently available or comparable to enable long-term assessment and management of cross-border healthcare [225]. Such data is vital to be able to monitor cross-border healthcare and its impact on health systems overall, in order to ensure that an appropriate balance is struck between free provision of health services, a high level of health protection and respecting the responsibilities of the Member States for ensuring the overall objectives of their health systems. E-health systems or services also enable the provision of cross-border care. This Directive provides for the establishment of a network of national authorities responsible for 'e-health' with the aim of improving the continuity of care and guaranteeing access to high quality healthcare. The interoperability of e-Health solutions should be achieved whilst respecting national regulations on the provision of healthcare services adopted in order to protect the patient, including legislation on Internet pharmacies, in particular national bans on mail order of prescription-only medical products to the extent that they are compatible with the case-law of the Court of Justice and Directive 97/7/EC of the European Parliament and of the Council of 20 May 1997 on the protection of consumers in respect of distance contracts and Directive 2000/31/EC of the European Parliament and of the Council of 8 June 2000 on certain legal aspects of information society services, in particular electronic commerce, in the Internal Market.

5.3.1. Article 14 of Directive 2011/24/EC – eHealth [226]

1. The Union shall support and facilitate cooperation and the exchange of information among Member States working within a voluntary network connecting national authorities responsible for eHealth designated by the Member States.
2. The objectives of the eHealth network shall be to:
   a) work towards delivering sustainable economic and social benefits of European eHealth systems and services and interoperable applications, with a view to achieving a high level of trust and security, enhancing continuity of care and ensuring access to safe and high-quality healthcare;
   b) draw up guidelines on:
      i. a non-exhaustive list of data that are to be included in patients' summaries and that can be shared between health professionals to enable continuity of care and patient safety across borders; and
      ii. effective methods for enabling the use of medical information for public health and research;
   c) support Member States in developing common identification and authentication measures to facilitate transferability of data in cross-border healthcare.

The objectives referred to in points (b) and (c) shall be pursued in due observance of the principles of data protection as set out, in particular, in Directives 95/46/EC.

5.4. Discussion

In the practice of the protection of privacy in health law, the autonomy of the patient is usually upheld by reference to concepts of consent. Thus most legislation on health records includes the requirement to seek a patient's consent before collecting, processing, or sharing health related information. Protecting the privacy and security of health information should be a high priority for all countries. However, the subject is complex and providing necessary access as well as confidentiality can be difficult in practice.

Any personal data that the controller needs to process for the purposes of his or her professional activity must meet certain levels of quality, and must comply with different principles concerning data collection and processing. The data must be collected for specified, explicit, and legitimate purposes. This principle requires that, prior to processing personal data, the controller has to define clearly and precisely the purpose(s) for which the data are to be processed. Moreover, the processing should be transparent. The data controller will, therefore, have to provide the relevant national data supervisory authority and the data subject with certain information regarding the processing, and may only process the data for the purposes for which it was collected. Thus, a doctor who may share patient identifiable data with another doctor for the purposes of treating the patient may share that same information with another healthcare professional for the purpose of conducting medical research if that purpose originally was given as one of the final uses of the data. It also would apply if this is compatible with the latter (especially if the data subject has given his or her consent to the communication) or if appropriate safeguards are met for processing personal data for medical research viewed as a scientific purpose (i.e., reasonable steps are taken to hide the true identity of a data subject). If the doctor anonymizes the personal data, there is no problem to communicate the anonymous data to a third party for scientific purposes, including medical research safe for other special rules in National Law (i.e., medical secrecy). Also, they must be processed fairly and lawfully so that if a researcher collects data in order to carry out a specified research project, he or she may not collect and process other data that are not necessary for that particular study but might be useful at some later date. The controller also must ensure the data are kept up-to-date while they are needed, and not kept longer than necessary.

Data protection law not only gives duties to data controllers, but also rights to data subjects, such as patients. Laws in EU countries grant access rights to all data subjects to data held about them, which allows them to request specific information about their own personal data; the right to ask for data to be rectified when they are incomplete or inaccurate; and, under some conditions, the right to object to the processing. On the basis of these duties, most EU countries have introduced legislation that allows patients to access their medical records and to demand a rectification of those records.

Implementing project in Lithuania and Greece, to conduct a biomedical research, firstly the approval to conduct research, except for clinical drug trials, must be issued by the Lithuanian Bioethics Committee.

Secondly, when health related personal data are going to be used for biomedical research purposes, the data may be processed only after notification of the State Data Protection Inspectorate. In this case, the State Data Protection Inspectorate must carry out a prior checking.

In order to obtain the approval to conduct biomedical research, there are main documents which must be submitted to the Ethics Committee [227]:

- Request to Grant an Approval to Conduct Biomedical Research.
- Application Form for the Biomedical Research
- Protocol of Biomedical Research and its Summary.
- Subject Information Form and Informed Consent Form.
- Form for Ethical Assessment of Biomedical Research.
- Curriculum vitae of the investigators.
- Copy of the civil responsibility insurance policy of the principal investigator and the sponsor of the biomedical research or letter of guarantee of insurance company (except studies on medical records and residual biological material).
- Scientific report of biomedical research (if any).
- License for Medical Practice of the Health Care Institution where the biomedical research will be carried out.
- Recommendation of the State Health Care Accreditation Agency under the Ministry of Health (if biomedical research involves medical device) (Information available in Lithuanian).

Following the Law on Biomedical Research, the application and documents must be examined and an approval must be issued or a reasoned refusal to grant it must be given within 45 calendar days from the registration of the documents. The approval is issued only after the payment of all the State fees.When health related personal data are going to be used for biomedical research purposes, the data may be processed only after notification of the State Data Protection Inspectorate. In this case, the State Data Protection Inspectorate must carry out a prior checking. The form for carrying out a prior checking should be submitted to the State Data Protection Inspectorate after obtaining an approval from Ethics Committee. An approval must be issued within 60 calendar days.

Informed consent is a common part of the research procedure. An informed consent can be said to have been given based upon a clear appreciation and understanding of the facts, implications, and future consequences of an action. In order to give informed consent, the individual concerned must have adequate reasoning faculties and be in possession of all relevant facts at the time consent is given. Regarding this project, there could be an opportunity and a proposition to implement an electronic informed consent through Multilingual Personal Health Portal “VivaPort” (https://vivaport.eu/), implemented by Vilnius university Hospital Santariškių Klinikos. Vivaport health portal is not only a summary of the personal health record. It is also a platform that allows patient to collect self-monitoring data (blood pressure, heart rate, weight, etc.) as well as information provided by health care institutions. In addition to this, patient using this portal could sign an electronic informed consent which could be a faster and more convenient procedure not only for patients but also and for health professionals.

5.5. Glossary

This glossary [228] was produced by the Experts Working Group on data protection and privacy and it summarizes the major concepts of data protection and privacy on an ethical point of view. It is very important to understand the concept in terms of processing patient’s medical data.

Assent is voluntary permission given by one who is under the age of consent with no legal status. (Minor) Capacity and competence to assent varies with age, cognitive development, experience of illness and country requirements. Where sensitive information from adolescents is to be collected, (i.e. about sexual behaviour, pregnancy, or use of recreational drugs) it must be carefully evaluated if parents or legal representatives should be informed. Cultural, social and ethics committee opinions will vary between Member States.

Absolutely no inducement financial or other pressures are allowed to be placed on the investigators, children

or their parents/guardians to persuade children to participate in research

Consent and assent must be voluntary and as fully informed as possible and be part of a continuous process, not just a signature on a piece of paper at the beginning of a research project. Finally, the enrolment strategies for the participants should be explained in language they can understand.

Data transfer: transmission of data or data support between information systems through any sort of media

Data privacy: Data privacy involves the right of any individuals to expect that personal information collected about them will be processed securely and will not be disseminated in any form without their written consent. Furthermore, data privacy must not be subject to "mission creep"[1].

Data protection: Data protection consists of a framework of security measures designed to guarantee that data are handled in such a manner as to ensure that they are safe from unforeseen, unintended, unwanted or malevolent use. Data protection is the technical mechanism to ensure data privacy and it concerns:

Access to data: who has the right to access each data set? How is this data accessed? Is access to the data properly logged and protected?

Conservation of the data: where, how and for how long are the data stored and archived? Are the data stored raw, anonymized, structured, or encrypted?

Accuracy: is there adequate de-multiplication and recovery of the data? Are the data properly updated when applicable and according to the study protocol? Maintained accurately? Are the data properly preserved against potential disaster (data location)?

Data protection concerns all actions deployed in order to ensure the lawful availability and integrity of the data. It also addresses the potential for intended data transfer outside legally defined boundaries that would require informed consent and that variability of national regulations for the issue be taken into account. Duration of data protection and means of irreversible data removal, if and when intended, should be clearly defined in the research protocol and in the participant information sheet.

Informed Consent: Informed consent is when it can be said with as much certainty as possible that a person has freely given consent based upon understanding as far as possible the aims, risks, benefits of the protocol and a willingness to perform research obligations. It is an agreement to do something or to allow something to happen, made with complete knowledge of all relevant facts, such as the risks involved or any available alternatives. During the informed consent process, it should be indicated who should be contacted in case of unexpected events, withdrawal or asking pertinent questions about the research. Refusal to participate should involve no penalty or loss of benefits to which the participant is otherwise entitled. Evidence of consent needs to be clear and indisputable, for example a signed paper declaration or a certified dematerialized document using specific identification processes such as opt-in or electronic certificates and signatures must be provided.

Informed Consent is a voluntary positive agreement by someone of legal age and ability who has understood the information, the implications, risks and benefits of the research and willingly agreed to participate. Participants are informed that they can withdraw at any time without having to provide a reason knowing that their withdrawal will not disadvantage their usual relationship with the investigator or the eventual benefits linked to their former participation.

Applicants should also consider how they will be able to show that the level of information was sufficient to allow the particular participants to understand the risks (i.e. to evidence not just their ‘consent’ but their ‘informed’ consent). The important aspect is that the participant needs to agree that her/his data will be used within a specific scope of research and is aware of the meaning of such use.

The informed consent should include information about how the participant’s privacy and data will be protected. (See further in this document) No personal or health record information may be taken or stored from the participant without their written informed consent

Minors, children and vulnerable persons are protected as consent must be asked, and given on their behalf by a parent/guardian or legal representative. However, consent being a continuous process in time, such consent must not be imposed indefinitely on them and must be re asked, for example for children when their reach legal majority.

[1] i.e.the expansion of a project beyond its original goal

Except in emergency cases, informed consent must be sought within sufficient time, as the patients or healthy volunteers envisaged to participate to the project may wish to think about their decisions and discuss it with others. Any pressure to participate should be avoided. Preferably, independent expert(s) should be made available for answering questions prior to signing the consent forms and consequently the beginning of the intended intervention or enrolment. The level at which this should operate is not fixed, as in so much law the issue is one of proportionality to the risks involved and the sensitivity of the data, so applicants may need to back up their judgment with the opinions of other experts in ethics and law.

International Data Transfer: Data processing that entails a data transfer outside the European Economic Area.

Personal Data: consist of information relating to an identified or identifiable person ('data Subject' or research participant); An identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical appearance, physiological, mental, economic, cultural or social identity;

Processing of personal data' ('processing') consists of any operation or set of operations which is performed on personal data, whether or not by automatic means, such as collection, recording, organisation, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, blocking, erasure or destruction;

Privacy is a fundamental part of human dignity. It is the human right to refuse interference by others in one's life: it defines the extent to which others can demand information or make choices binding another. It enables individuals to exercise control over the disclosure of their information and over decision-making by them and about them. It is a right that can be claimed by groups of individuals together. Where an individual is incapacitated, that individual's legally authorized representative can safeguard his or her privacy.

In research, therefore, respect for an individual's privacy is safeguarded through a number of mechanisms, including data protection, and informed consent/assent procedures, enabling individuals to choose whether or not to participate in a study and to see the terms under which their involvement is agreed. It is monitored by

- research ethics committees (through scrutiny of research proposals and, sometimes, on-going review),
- by the process of law,
- and most importantly, by self-protection by the individuals through their awareness of the research.

Private information can be derived from various sources and formats. It may include sensitive information like: Health-related records (e.g. patient records, biographic data , medical photographs , diet information, hospital information records, biological traits and genetic material); Criminal records or legal justice investigations and proceedings; State-related records such as tax fillings; Circulation records such as visas; residence or various geographic recordings such as GPS satellite localization recordings; bank record; financial transactions records, as well as religious beliefs, sexual orientation, ethnic identification records. Equally, it can include more general information about individuals. Usually, data are classified according to their level of importance so that users are aware of the type of data that is being collected and protected. If private (personal) data are collected, they must be stored in a secure manner and their access protected in order to avoid improper disclosure. These processes are called **data protection.**

5.5.1. Technical aspects

'Anonymisation', 'pseudonymisation' and 'identifiability': 'Anonymous' often means data which does not identify an individual; 'anonymised' means data which has been rendered anonymous; 'pseudonymised' and 'coded' means data where obvious identifiers (e.g. names and addresses) have been replaced with indirect identifiers (e.g. numbers) in the main data set and the indirect identifiers are then held with the obvious identifiers in a separate data set (known as the 'key').

However, the concept operating in European data protection law is the 'identifiability' of an individual from the data. For European data protection law to bind research on personal and sensitive personal data one must ask: is the individual identified either immediately from the data or when that data are combined with other data in the hands of another person. This combination extends only to reasonably foreseeable linkings of data. Therefore, data which is gathered anonymously without any identifiers will be outside the scope of European data protection law; data which is pseudonymised or coded will be within the scope of the law as it

is possible to reintroduce the two separate data sets and identify individuals; data which was gathered as identifiable data and then anonymized is subject to the data protection legislation when it contains identifiable data (most importantly at the point of gathering the data, requiring the disclosure by the researcher to the research participant of information including the purpose of the processing and contact details).

Authentication: A process of proving the identity of a computer or computer user. For users, it generally involves user name, password, and electronic certificates. Computers usually pass a code that identifies that they are part of a network. In keeping data privacy it is essential to ensure that the data, transactions, communications or documents (electronic or physical) are genuine. It is also important for authenticity to validate that both parties involved are who they claim they are.

6. CARRE Use Cases

This section illustrates scenarios of how intended users, i.e. patients and physicians would use the CARRE environment for managing chronic cardiorenal disease and comorbidities.

These were drawn based on the DoW and then on the survey of literature and field survey presented in previous sections. These scenarios are intended as a first preparatory phase towards functional requirement definition. The scenarios presented here will form the basis for further work which will involve all partners of the consortium and is part of Task 2.2 and will be presented in D.2.2. In particular:

- overall context diagram of the system
- formally described use cases
- overall features of the system
- functional requirements

Here, scenarios will be presented in narrative, non-technical format. Based on these scenarios, use cases will be constructed to describe interactions between the user and the system at a technical level.

6.1. User Types and Characteristics

Based on the analysis presented in previous sections, CARRE is addressed to a variety of users of the following 3 major types:

1) patients
2) healthcare professionals
3) health administration and policy makers

To the above we should also add system administrators. Each type may have a variety of categories. In particular, CARRE user groups are described below:

User Group 1: Patient 1	
ID:	P1
Title:	(Almost) healthy person at risk of heart or renal disease
Description:	This group mainly includes people with a positive family history of metabolic or cardiovascular disease and/or unhealthy lifestyle habits. The person is not considered actually a patient but rather a healthy individual with a statistically increased risk of developing a medical condition which has the potential to progress into a chronic heart or renal disease. Users in this group are not treated specifically for a CARRE related disease. However, they are aware that they are at increased risk statistically for developing one or more metabolic diseases relatively to the general population.
Major Goal:	Maintain a healthy lifestyle
Objectives:	– understand current condition as presenting risks for future disease – dietary consultation and lifestyle intervention – realize what should be monitored, how and how often – recognition of early symptoms of a related disease

User Group: Patient 2	
ID:	P2
Title:	A patient already diagnosed with a disease and/or comorbidities that are risk factors for chronic heart and/or renal disease
Description:	A patient with a disease that is a risk factor for heart or renal disease – mainly patients with metabolic disorders such as diabetes, hypertension, hyperlipidemia. The patient is under medical supervision and he is regularly monitored and treated at home.
Major Goal:	Control of the disease for progression and transition
Objectives:	– understand current condition as presenting a risk factor for major complications – dietary consultation and lifestyle intervention – educational and possibly psychological interventions – understand the nature and cause of symptoms – realize what should be monitored, how and how often – establish treatment goals – re-evaluate therapy and treatment goals in case of deterioration or new complications – recognition of a possible deregulation of the primary disease – recognition of early symptoms or signs of a possible complication – adherence to therapy – other risk factors modification – hierarchy of the most important risk factors that have to be modified and monitored

User Group: Patient 3	
ID:	P3
Title:	A patient with chronic heart or renal disease
Description:	A patient who has already been diagnosed with a chronic heart or renal disease. He usually has one or more comorbidities. He is informed that patients with chronic kidney disease constitute a group of patients at high risk for having or developing cardiovascular disease, including heart failure and vice versa.He is regularly treated and monitored.
Major Goal:	Maintenance of clinical stability / Prevention of the development of cardiorenal syndrome
Objectives:	– understand current condition as presenting a risk factor for other organ(s) involvement – recognition of early symptoms or signs of a possible complication and identify early symptoms of another other organ involvement – strict adherence to therapy – dietary consultation and lifestyle intervention (physical exercise as permitted) – creation of a self-care routine – re-evaluate therapy and treatment goals in case of deterioration or new complications – knowledge of early signs and symptoms of decompensation – recognition of life-threatening symptoms

User Group: Patient 4	
ID:	P4
Title:	Cardiorenal patient of types 2, 4 or 5
Description:	A patient with diagnosed renal and heart comorbidity, regularly treated and monitored.
Major Goal:	Prevent from progressing to end stage disease. Physicians' collaboration/coordination.
Objectives:	– understand current condition as presenting a major health problem – dietary consultation and lifestyle intervention (physical exercise if permitted) – nature and cause of symptoms – realize what should be monitored, how and how often – creation of a self-care routine – recognition of early symptoms or signs of possible complications – educational and psychological interventions – strict adherence to therapy – realize possible drug interactions or drug toxicities that may aggravate current condition – information about cross interactions between the 2 systems (heart and renal) – modification of the rest of risk factors / identification of the most important and vicious ones – knowledge of early signs and symptoms of decompensation – recognition of life-threatening symptoms – awareness of early initiation of renal dialysis

User Group: Patient 5	
ID:	P5
Title:	End stage patient
Description:	Patient at end stage renal disease (ESRD) and/or end stage heart failure (NYHA-IV)
Major Goal:	Prolong life and maintain quality of life
Objectives:	– dietary specific consultation (e.g. salt and fluid consumption) – lifestyle intervention (physical exercise if permitted) – strict adherence to therapy – recognition of early symptoms or signs of possible complications – educational and psychological interventions – recognition of life-threatening symptoms

User Group: Doctor 1	
ID:	D1
Title:	Primary healthcare physician – Family doctor
Description:	”
Major Goal:	Maintenance of clinical stability / early recognition and referral to a specialist in case of deterioration
Objectives:	– explain to patients how to monitor their own care – inform patients about what community support is available to them – suggest to patients ways they can manage their condition by reducing or removing modifiable risk factors – identify aids that can help patients with adherence to medicines – identify the barriers to self-management that patients perceive or experience – communicate with each other health care givers often (nurses, pharmacists, other doctors) – increased awareness of renal or heart function impairment in general practice patients – awareness for early detection of HF/CKD patients’ exacerbations

User Group: Doctor 2	
ID:	D2
Title:	Internist, Cardiologist, Nephrologist
Description:	”
Major Goal:	To confer an holistic and multidisciplinary therapeutic intervention programme
Objectives:	– realize the complex nature of these patients and compromised outcome – realize the necessity for cooperation/ multidisciplinary care to meet patients’ needs – identify resources and networks required to establish or maintain increase interaction between generalists and specialists – development and implementation of individualised management plans – avoidance of providing contradictory recommendations by different specialists – organize specific team function and practice systems (e.g., appointments and follow-up) to meet the needs of cardiorenal patients) – develop and implement evidence-based guidelines and support those guidelines providing education/ reminders – ensure that existing structured HF and CKD programs are aligned with recommended best practice

User Group: Nurse	
ID:	N
Title:	Nurse
Description:	”
Major Goal:	Provide specialised nursing care
Objectives:	– advanced cardiac and renal assessment skills – application of non-pharmacological strategies – encouraging patients to be actively involve in managing their own care – ability to assess functional capacity and quality of life of the patient – safely provide telephone support/advice to patients – aware of limitations and boundaries

User Group: Administration & Policy Makers	
ID:	PM
Title:	Health administration and policy makers
Description:	”
Major Goal:	Develop policies for more efficient interventions and improved outcome in patients with multisystem diseases
Objectives:	– draw on acknowledged requirements of multidisciplinary HF and CKD patients care – adapt multidisciplinary HF and CKD patients care to local needs and priorities – integrate in a more patient-oriented way of services – develop and execute programmes for public awareness and education – enhance information systems to facilitate the development of disease registries and tracking systems – monitoring of program outcomes and systems to ensure continuous quality improvement – have well-developed processes and incentives for making changes in the care delivery system when necessary

6.2. Basic Scenarios

	functional domain	use case
1.	visualization	generic model of risk factor and disease interdependence for cardiorenal disease and comorbidities
2.		personalized risk and disease progression pathways
3.		individual progress based on monitored data
4.		individual potential progression pathways
5.		comparison of personal state with current medical evidence and overall statistical views of 'similar' patients
6.		simulate personalized views of virtual patients (for treatment planning and medical education)
7.		overall statistical views of CARRE patient, in terms of health status, risk for progression, disease management
8.	monitor	biomarkers
9.		attitude via social media
10.	personalized education	educational material based on current state and risks
11.		new medical evidence available
12.	personalized planning	Diet
13.		physical activity
14.		comparison of plans with implied lifestyle, intentions, preferences (as deduced from social media)
15.	personalized alert	medical check-ups & monitoring
16.		increased risk of comorbidities
17.		increased risk of acute episodes
18.		need to change diet
19.		need to change monitoring
20.		overall change of condition (progression/regression to a new stage)
	social support	projection of current patient state to 'similar patients' in a social environment

6.3. Template for use case description

template for use case description	
ID	A unique id for referring to different use cases throughout the project.
Title	An appropriate name for the use case – a short active verb phrase e.g. RegisterForCourses
Goal	A brief description of the use case's role and purpose, that is its goal
Domain	the key functional domain of the Use Case. For CARRE project: – visualization – monitor – planning – alert – education – social support
Description	use case description
Participants	Users as defined above who participate in this use case
Special requirements	Collects all requirements on the use case, e.g. non-functional reqs, that are not considered in the use-case model, but that need to be taken care of during design or implementation.
Pre-conditions	A textual description that defines any constraints on the system at the time the use case may start.
Post-conditions	A textual description that defines any constraints on the system at the time the use case will terminate.
Flow of events	*(to be completed after discussions with all partners in T.2.2/D.2.2)* A textual description (understandable to the customer) of what the system does with regard to the use case (not how specific problems are solved by the system). – basic flow – alternate flows – unsuccessful
Validation	*(to be completed after discussions with all partners in T.2.2/D.2.2 and further refined in T.7.1/D.7.1)* Methods for validating the use case

6.4. Use cases

ID	UC_Mon_02
Title	Attitude via social media
Goal	The goal of this use case is to allow patient to understand the health effects of their lifestyle
Domain	Monitor
Description	In this use case users have a personal social media account, update frequently their status and their daily activities. An application will monitor user's health-status, lifestyle, and wellness and upload data to CARRE system which will be able to analyze user's lifestyle and medical data. Then the system will support end users with feedback supporting text with their personal daily data.
Participants	P1, P2, P3, P4
Pre-conditions	End users must have a social media account. End users must input personal information.
Post-conditions	Data export which can be used in other use case of our system

ID	UC_Vis_04
Title	Personalized risk and disease progression pathways
Goal	The goal of this use case is to allow patient to understand their disease progression
Domain	Visualization
Description	In this use case users need to upload via their monitor devices or enter manual their medical data to CARRE system. The system will analyze their medical data and sent a visualization feedback to users with their disease progression.
Participants	P1, P2, P3
Pre-conditions	End users must input personal information.
Post-conditions	

ID	UC_Vis_05
Title	Individual progress based on monitored data
Goal	The goal of this use case is to allow patient to understand their disease progression based on personal monitored data
Domain	Visualization
Description	In this use case users have personal monitor device which collects their medical and lifestyle data. Users can upload this data manual or automatic to CARRE system then the system will be able to analyze the data and sent a feedback with their disease progression.
Participants	P1, P2, P3, P4
Pre-conditions	End users must input personal information. End users need to have monitor device.
Post-conditions	

ID	UC_Vis_06
Title	Individual potential progression pathways
Goal	The goal of this use case is to allow patient to understand their disease progression if they make some changes
Domain	Visualization
Description	In this use case users insert information about their health status and possible changes in their healthcare management to CARRE system. System will be able to analyze all upload data and will send a feedback with the potential progression of their disease.
Participants	P1, P2, P3, P4
Pre-conditions	End users must input personal information.
Post-conditions	Export data which can be used in other use case of our system

ID	UC_Vis_07
Title	Comparison of personal state with current medical evidence and overall statistical views of ‘similar’ patients
Goal	The goal of this use case is to allow patient to understand their disease by comparison their personal state with current medical evidence.
Domain	Visualization
Description	In this use case users have to upload their health status to the system. System will analyze the data and be able to send a feedback with a comparison of personal state with current medical evidence or a comparison of overall statistical view of ‘similar’ patients.
Participants	P2, P3, P4, D2
Pre-conditions	End users must input personal information.
Post-conditions	

ID	UC_PE_10
Title	Educational material based on current state and risks
Goal	The goal of this use case is to inform patients about their current health status and their risks.
Domain	Personalized Education
Description	In this use case users have to insert medical data to CARRE system and then the system will analyze their data and send to them a feedback text with educational material base on the individual health state.
Participants	P1, P2, P3, P4, D1, D2
Pre-conditions	End users must input personal information.
Post-conditions	

ID	UC_PE_11
Title	New medical evidence available
Goal	The goal of this use case is to inform end users about new medical evidence available about their wises
Domain	Personalized Education
Description	In this use case users enter the health condition that they are interested in and the system will support end users with a feedback text with the latest available medical evidence.
Participants	P1, P2, P3, P4, D1, D2
Pre-conditions	
Post-conditions	

ID	UC_PP_12
Title	Diet
Goal	The goal of this use case is to allow patients to create a personal plan for their diet.
Domain	Personalized Planning
Description	In this use case user can insert data for their diet plan and CARRE system will send them a feedback of their plan.
Participants	P1, P2, P3, P4, D1, D2
Pre-conditions	Import data from previous use case • UC_Mon_01 • UC_Mon_02 End users must input personal information.
Post-conditions	A diet plan is created. Data export which can be used in other use case of our system

ID	UC_PP_13
Title	Physical Activity
Goal	The goal of this use case is to allow patients to create a personal plan for their physical activities
Domain	Personalized Planning
Description	In this use case user can insert their medical data and data for their physical activity plan and CARRE system will send them a feedback of physical activity plan according to their personal needs.
Participants	P1, P2, P3, D1, D2
Pre-conditions	Import data from previous use case • UC_Mon_01 • UC_Mon_02 End users must input personal information.
Post-conditions	A physical activity plan is created and can be saved. Data export which can be used in other use case of our system.

ID	UC_PE_14
Title	Comparison of plans with implied lifestyle, intentions, preferences (as deduced from social media)
Goal	The goal of this use case is for end users to comparison their plans with implied lifestyle, intentions and preferences as deduced from social media.
Domain	Personalized Education
Description	In this use case end users have a social account which includes personal data of their lifestyle, their intentions for their day (such as physical activities, places that they would like to visit, business meetings etc.) and their preference (such as favorite food, drinks, physical activities etc.). System will collect all the data and make a comparison between their plans and their daily life.
Participants	P1, P2, P3, P4
Pre-conditions	Import data from previous use case • UC_Mon_02 • UC_PP_12 • UC_PP_13 End users must input personal information.
Post-conditions	

ID	UC_PA_17
Title	Increased risk of acute episodes
Goal	The goal of this use case is to inform patients that are in increased risk of acute episode
Domain	Personalized Alert
Description	In this use case users insert their medical data via their monitor devices to CARRE system. The system analyzes their data and calculates the risks of their health status via medical evidence and sends an alert when it is necessary to the user.
Participants	P3, P4, D2
Pre-conditions	Import data from previous use case • UC_Mon_01 • UC_Mon_02 • UC_Vis_04 • UC_Vis_05 • UC_PP_12 • UC_PP_13 End users must input personal information.
Post-conditions	

ID	UC_PA_18
Title	Need to change diet
Goal	The goal of this use case is to inform patients to make the necessary and appropriate diet changes in order to reduce the risk of their disease
Domain	Personalized Alert
Description	In this use case the users insert their diet data to CARRE system as well as their health status. The system will be able to analyze their personal data and send an alert when diet has to change in order to reduce or prevent the risks of their disease.
Participants	P1, P2, P3, P4, D1, D2
Pre-conditions	Import data from previous use case • UC_Mon_01 • UC_Mon_02 • UC_Vis_04 • UC_Vis_06 • UC_PP_12 • UC_PP_13 End users must input personal information.
Post-conditions	

7. References

1. Iyngkaran P, et al. Cardio-renal syndrome: New Perspective in Diagnostics. SeminNephrol 2012; 32 :3-17
2. Schrier RW. Cardiorenal versus renocardiac syndrome: is there a difference? Nat ClinPractNephrol 2007; 3: 637
3. Liang KV, Williams AW, Greene EL, Redfield MM. Acute decompensated heart failure and the cardiorenal syndrome. Crit Care Med 2008; 36: S75-88
4. Ronco C, House AA, Haapio M. Cardiorenal syndrome: refining the definition of a complex symbiosis gone wrong. Intensive Care Med 2008; 34: 957-62
5. Ronco C. Cardiorenal syndromes: definition and classification. Contrib Nephrol. 2010; 164: 33-8
6. Ronco C, Maisel A. Volume overload and cardiorenal syndromes. Congest Heart Fail. 2010;16(4)(suppl 1):Si–Siv.
7. Ronco C M Haapio, Andrew A. House, Nagesh Anavekar, Rinaldo Bellom., Cardiorenal syndrome. J Am Coll Cardiol 2008; 52:1527-39
8. Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. Am Heart J. 1999;137:352-60
9. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB; OPTIMIZE-HF Investigators and Hospitals. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am CollCardiol. 2007; 50 : 768-77
10. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP; ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005;149 : 209-16
11. Hillege HL, Nitsch D, Pfeffer MA, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation 2006; 113: 671-8
12. McCullough PA. Contrast induced nephropathy. J Am Coll Cardiol 2008; 51: 1419-28
13. Kellum JA, Bellomo R, Ronco C. The concept of acute kidney injury and the RIFLE criteria. ContribNephrol. 2007;156:10-6
14. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8: R204-12
15. Bagshaw SM, George C, Dinu I, Bellomo R A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. Nephrol Dial Transplant. 2008; 23: 1203-10
16. Herzog CA. Dismal long-term survival of dialysis patients after acute myocardial infarction: an evidence-based review. Hemodial Int 2007; 11: 1-14
17. Johnson DW, Craven AM, Isbel NM. Modification of cardiovascular risk in hemodialysis patients: an evidence-based review. Hemodial Int 2007; 11: 1-14
18. Tonelli M, Muntner P, Lloyd A, Manns BJ, Klarenbach S, Pannu N, James MT, Hemmelgarn BR; Alberta Kidney Disease Network. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. Lancet. 2012;380(9844):807-14
19. McCullough PA, Ahmad A. Cardiorenal syndromes. Worlkd J Cardiol, 2011;3(1):1-9.
20. Fonarow G C; ADHERE Scientific Advisory Committee. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. Rev Cardiovasc Med. 2003;4 Suppl 7:S21-30
21. Patel K, Fonarow GC, Ekundayo OJ, Aban IB, Kilgore ML, Love TE, Kitzman DW, Gheorghiade M, Allman RM, Ahmed A. Beta-blockers in older patients with heart failure and preserved ejection fraction: Class, dosage, and outcomes. Int J Cardiol. 2014 Mar 11. pii: S0167-5273(14)00429-X.
22. Sarraf M, Masoumi A, Schrier R.W, Cardiorenal Syndrome in Acute Decompensated Heart Failure, Clin J Am Soc Nephrol, 2009,4: 2013–2026
23. Waldum B, Os I. The Cardiorenal Syndrome: What the Cardiologist Needs to Know.. Cardiology 2013;126:175–186

24. Kiernan M. S, Udelson J. E., Sarnak M., Konstam M.. Cardiorenal syndrome: Definition, prevalence, diagnosis, and pathophysiology.Feb24, 2014. UpToDate Inc

25. Sarraf M., Masoumi A., Schrier R.W. Cardiorenal versus Renocardiac Syndrome. Cardiorenal syndrome, Mechanisms, risk and treatment. Springer. 2010; p22

26. Mastromarino V, Casenghi M, Testa M, Gabriele E, Coluccia R, Rubattu S, Volpe M. Polypharmacy in Heart Failure Patients. Curr Heart Fail Rep. 2014 Feb 4. [Epub ahead of print]

27. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure, European Heart Journal (2012) 33, 1787–1847

28. Wollman Y, Schwartz D. Anemia, chronic renal disease and congestive heart failure-the cardio renal anemia syndrome: the need for cooperation between cardiologists and nephrologists. IntUrol Nephrol 2006;38:295–310.

29. Giamouzis G., Kalogeropoulos A. P., Butler J., Karayannis G., Georgiopoulou V. V., Skoularigis J., Triposkiadis F. Epidemiology and Importance of Renal Dysfunction in Heart Failure Patients. Curr Heart Fail Rep (2013) 10:411–420

30. McManus DD, Corteville DC, Shlipak MG, Whooley MA, Ix JH. Relation of kidney function and albuminuria with atrial fibrillation (from the Heart and Soul Study). Am J Cardiol. 2009 Dec 1;104(11):1551-5

31. Goldenberg I, Moss AJ, McNitt S, Zareba W, Andrews ML, Hall WJ, Greenberg H, Case RB; Multicenter Automatic Defibrillator Implantation Trial-II Investigators. Relations among renal function, risk of sudden cardiac death, and benefit of the implanted cardiac defibrillator in patients with ischemic left ventricular dysfunction.Am J Cardiol. 2006 Aug 15;98(4):485-90. Epub 2006 Jun 19

32. Jindal A, Whaley-Connell A, Sowers JR. Obesity and heart failure as a mediator of the cerebrorenal interaction. Contrib Nephrol. 2013;179:15-23. doi: 10.1159/000346718. Epub 2013 May 3

33. Abdel-Qadir H, ChughSh, LeeD.S, Improving Prognosis Estimation in Patients with Heart Failure and the Cardiorenal Syndrome. International Journal of Nephrology, Volume 2011, pp. 11.

34. Ronco C, McCullough P, Anker SD, AnandI,Aspromonte N, Bagshaw SM, Bellomo R, Berl T, Bobek I, Cruz DN, Daliento L, Davenport A, Haapio M, Hillege H, House AA, Katz N,Maisel A, Mankad S, Zanco P, Mebazaa A, Palazzuoli A, Ronco F, Shaw A, Sheinfeld G,Soni S, Vescovo G, Zamperetti N, Ponikowski P: Cardio-renal syndromes: report from theconsensus conference of the acute dialysis quality initiative. Eur Heart J 2010; 31: 703–711

35. Virzi GM, Corradi V, Panagiotou A, Gastaldon F, Cruz DN, de Cal M, Clementi M, Ronco C: ADPKD: prototype of cardiorenal syndrome type 4. Int J Nephrol 2010; 2011:490795

36. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation.2003;108:2154–2169

37. Redón J, Cea-Calvo L, Lozano JV, Fernández-Pérez C, Navarro J, Bonet A, González-Esteban J, ERIC-HTA 2003 Study Investigators: Kidney function and cardiovascular disease in the hypertensive population: the ERIC-HTA study. J Hypertens 2006; 24: 663–669.

38. Stemer G., Lemmens-Gruber R., Clinical pharmacy activities in chronic kidney disease and end-stage renal disease patients: a systematic literature review; BMC Nephrology 2011, 12:35.

39. Vassalotti JA, Stevens LA, Levey SA, Testing for Chronic Kidney Disease: A Position Statement From the National Kidney Foundation; American Journal of Kidney Diseases, Vol 50, No 2 (August), 2007: pp 169-180.

40. Mathew K, Garratt N, Holmes DR, Best PJ, Singh M, Bell MR, Barsness GW, Verghese C, Rihal S, Textor SC, Grill DE, Berger PB, Ting HH: Coronary intervention incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 2002; 105: 2259–2264.

41. Jungers P, Massy ZA, Nguyen Khoa T, Fumeron C, Labrunie M, Lacour B, Descamps- Latscha B, Man NK: Incidence and risk factors of atherosclerotic cardiovascular accidents in predialysis chronic renal failure patients: a prospective study. Nephrol Dial Transplant 1997; 12: 2597–2602.

42. Remuzzi G, Schieppati A, Ruggenenti P: Clinical practice. Nephropathy in patients with type 2 diabetes. N Engl J Med 2002; 346: 1145–1151.

43. Ronco C, Cruz DN, Ronco F: Cardiorenal syndromes. Curr Opin Crit Care 2009; 15: 384–391.

44. Ronco C, House AA, Haapio M: Cardiorenal and renocardiac syndromes: the need for a comprehensive classification and consensus. Nat Clin Pract Nephrol 2008; 4: 310–311

45. Levey AS, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasiske BL, Klag MJ, Mailloux LU, Manske CL, Meyer KB, Parfrey PS, Pfeffer MA, Wenger NK, Wilson PW, Wright JT Jr: Controlling the epidemic of cardiovascular

disease in chronic renal disease: What do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease.Am J Kidney Dis 1998; 32: 853–906

46. Shulman NB, Ford CE, Hall WD, Blaufox MD, Simon D, Langford HG, Schneider KA: Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program.The Hypertension Detection and Follow-Up Program Cooperative Group. Hypertension 1989; 13:I80–I93

47. Wali RK, Henrich WL: Chronic kidney disease: a risk factor for cardiovascular disease. CardiolClin 2005; 23: 343–362

48. McCullough P.A.. Cardiorenal Syndromes: Pathophysiology to Prevention. SAGE-Hindawi Access to Research, International Journal of Nephrology, Volume 2011, Article ID 762590, 10 pages

49. McCullough PA, Kellum JA, Mehta RL, Murray PT, Ronco C (eds): ADQI Consensus on AKI Biomarkers and Cardiorenal Syndromes. Cardiorenal Syndrome Type 5: Clinical Presentation, Pathophysiology and Management Strategies from the Eleventh Consensus Conference of the Acute Dialysis Quality Initiative (ADQI). Contrib Nephrol. Basel, Karger, 2013, vol 182, pp 174–194

50. Bagshaw SM, Cruz DN, Aspromonte N, Daliento L, Ronco F, Sheinfeld G, Anker SD, Anand I, Bellomo R, Berl T, Bobek I, Davenport A, Haapio M, Hillege H, House A, Katz N, Maisel A, Mankad S, McCullough P, Mebazaa A, Palazzuoli A, Ponikowski P, Shaw A, Soni S, Vescovo G, Zamperetti N, Zanco P, Ronco C; Acute Dialysis Quality Initiative Consensus Group. Epidemiology of cardio-renal syndromes: workgroup statements from the 7th ADQI Consensus Conference. Nephrol Dial Transplant. 2010 May;25(5):1406-16

51. American Heart Association, “Classes of Heart Failure. American Heart Association web site,” 2011, http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp

52. Carrero J.J., P. Stenvinkel, Cardiovascular Disease Risk Factors in Chronic Kidney Disease: Traditional, Nontraditional, and Uremia-related Threats; Springer-Verlag Italia 2010; 91-104.

53. Charchar FJ, Bloomer LD, Barnes TA, Cowley MJ, Nelson CP, Wang Y, Denniff M, Debiec R, Christofidou P, Nankervis S, Dominiczak AF, Bani-Mustafa A, Balmforth AJ, Hall AS, Erdmann J, Cambien F, Deloukas P, Hengstenberg C, Packard C, Schunkert H, Ouwehand WH, Ford I, Goodall AH, Jobling MA, Samani NJ, Tomaszewski M. Inheritance of coronary artery disease in men: an analysis of the role of the Y chromosome. Lancet. 2012 Mar;379(9819):915-22. Epub 2012 Feb 9

54. Janet W. Rich-Edwards, Sc.D., JoAnn E. Manson, M.D., Dr.P.H., Charles H. Hennekens. The Primary Prevention of Coronary Heart Disease in Women. N Engl J Med 1995; 332:1758-1766; June 29, 1995.

55. Douglas PS, Athena Poppas. Determinants and management of cardiovascular risk in women. Official Topic from UpToDate.

56. Iseki K., Yoshiharu Ikemiya, Kozen Kinjo, et al. Body mass index and the risk of development of end-stage renal disease in a screened cohort. Kidney International (2004) 65, 1870–1876

57. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation. 2013;127:e6–245.

58. Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, Levy D .The Framingham Heart Study. Does the relation of blood pressure to coronary heart disease risk change with aging? Circulation. 2001;103(9):1245

59. Savji N, Rockman CB, Skolnick AH, Guo Y, Adelman MA, Riles T, Berger JS Association between advanced age and vascular disease in different arterial territories: a population database of over 3.6 million subjects. J Am Coll Cardiol. 2013;61(16):1736

60. Mcclellan W. M., Flanders W. D. Risk Factors for Progressive Chronic Kidney Disease; Nephrol 14: S65–S70, 2003.

61. Kiberd BA, Clase CM: Cumulative risk for developing end-stage renal disease in the US population. J Am Soc Nephrol 13: 1635–1644, 2002.

62. Andresdottir MB, Sigurdsson G, Sigvaldason H, et al. Fifteen percent of myocardial infarctions and coronary revascularizations explained by family history unrelated to conventional risk factors. The Reykjavik Cohort Study. Eur Heart J 2002; 23:1655.

63. Rosengren A, Hawken S, Ounpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 2004; 364: 953-962

64. Bachmann JM, Willis BL, Ayers CR, et al. Association between family history and coronary heart disease death across long-term follow-up in men: the Cooper Center Longitudinal Study. Circulation 2012; 125:3092.

65. WHO Report on Global Tobacco Epidemic, 2009

66. Babizhayev M, Savel'yeva E, Moskvina S, Yegorov Y, Telomere Length is a Biomarker of Cumulative Oxidative Stress, Biologic Age, and an Independent Predictor of Survival and Therapeutic Treatment Requirement Associated With Smoking Behavior; American Journal of Therapeutics: 2011, pp e209-e226

67. WHO REPORT on the global TOBA CCO epidemic, 2008

68. WHO 2012 global progress report on implementation of the WHO Framework Convention on Tobacco Control

69. Moro L, Pedone C, Scarlata S, Malafarina V, Fimognari F, Antonelli-Incalzi R, Endothelial Dysfunction in Chronic Obstructive Pulmonary Disease; ANGIOLOGY June/July 2008, 357-364

70. Shields PG., Tobacco smoking, harm reduction, and biomarkers. J Natl Cancer Inst. 2002;**94(19):**1435-1444

71. Caspersen C. J., K. E. Powell, G. M. Christenson, Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research; Public Health Rep. 1985 Mar-Apr; 100(2): 126–131.

72. WHO, Global strategy on diet, physical activity and health, 2014 http://www.who.int/dietphysicalactivity/pa/en/

73. Bauman A.E., Updating the evidence that physical activity is good for health: an epidemiological review 2000–2003; J Sci Med Sport. 2004;7(1 Suppl):6-19

74. http://pmbcii.psy.cmu.edu/core_c/physical_activity.pdf

75. http://www.medterms.com/script/main/art.asp?articlekey=3672

76. McMurray JJ, Pfeffer MA., Heart Failure, Lancet 2005; 365(9474):1877–1889

77. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2012;33(14):1787-1847

78. *Eur Heart J Suppl* 2005;7(Suppl J):J5–J9.15

79. NICE, Chronic heart failure. NICE clinical guideline 108

80. *Congest Heart Fail.* 2010;16(4) (suppl 1):Si–Siv

81. Viswanathan G., S. Gilbert The Cardiorenal Syndrome: Making the Connection, Int. J. Nephrol 2011, Article ID 283137 10 p

82. Wabel P, Chamney P, Moissl U, Jirka T. Importance of whole-body bioimpedance spectroscopy for the management of fluid balance. *Blood Purif* 2009;27:75–80

83. Blanche C, Fumeaux T, Polikar R., Heart failure with normal ejection fraction (HFNEF): is it worth considering? *Swiss Med Wkly*. 2010;140(5-6):66-72

84. American Hearlt Association, Ejection Fraction Heart Failure Measurement, 2014https://www.heart.org/HEARTORG/Conditions/HeartFailure/SymptomsDiagnosisofHeartFailure/Ejection-Fraction-Heart-Failure-Measurement_UCM_306339_Article.jsp

85. Murphy J.G., Margaret A. Lloyd. Mayo Clinic Cardiology: Concise Textbook, 3rd Edition. Chapter 55.

86. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvänne M, Scholte op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F; European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J.* 2012;33:1635–1701

87. WHO, The global burden of disease, 2004 update, 2004 www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html

88. Lloyd-Jones D Heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation.* 2009;119:e1-e161

89. MedLinePlus, High blood Pressure, http://www.nlm.nih.gov/medlineplus/ency/article/000468.htm

90. ESH/ESC Task Force for the Management of Arterial Hypertension, 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. *J Hypertens*. 2013;10:1925-1938

91. Kearney PM1, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet.* 2005;365(9455):217-223

92. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D; Framingham Heart Study. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation.* 2002;106(24):3068

93. Lloyd-Jones DM, Leip EP, Larson MG, Vasan RS, Levy D. Novel approach to examining first cardiovascular events after hypertension onset. *Hypertension*. 2005;45(1):39.

94. Tsioufis C, Tsiachris D, Kasiakogias A, Dimitriadis K, Petras D, Goumenos D, Siamopoulos K, Stefanadis C. Preclinical cardiorenal interrelationships in essential hypertension *Cardiorenal Med* 2013;3:38–47

95. Coyne D. W., Management of Chronic Kidney Disease Comorbidities; Medscape 2011.

96. Chobanian AV1, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289(19):2560-2572

97. James PA, Oparil S2, Carter BL1, Cushman WC3, Dennison-Himmelfarb C4, Handler J5, Lackland DT6, LeFevre ML7, MacKenzie TD8, Ogedegbe O9, Smith SC Jr10, Svetkey LP11, Taler SJ12, Townsend RR13, Wright JT Jr14, Narva AS15, Ortiz E16. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 20145;311(5):507-520

98. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study JAMA. 2001;285(18):2370-2375

99. *Wu EQ, Birnbaum HG, Mareva M, Tuttle E, Castor AR, Jackman W, Ruskin J. Economic burden and co-morbidities of atrial fibrillation in a privately insured population. Curr Med Res Opin*. 2005;21(10):1693-1699

100. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2014 update: a report from the American Heart Association Circulation.2014; 129: e28-e292

101. Wang TJ, Parise H, Levy D, D'Agostino RB Sr, Wolf PA, Vasan RS, Benjamin EJ., Obesity and the risk of new-onset atrial fibrillation. JAMA 2004;292(20):2471

102. Baber U, Howard VJ, Halperin JL, Soliman EZ, Zhang X, McClellan W, Warnock DG, Muntner P. Association of chronic kidney disease with atrial fibrillation among adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Circ Arrhythm Electrophysiol. 2011;4:26-32

103. Shaper A G, G Wannamethee, P W Macfarlane, M Walker, Heart rate, ischaemic heart disease, and sudden cardiac death in middle-aged British men *Br Heart J.* 1993;70:49 – 55

104. Jouven X, Empana JP, Escolano S, Buyck JF, Tafflet M, Desnos M, Ducimetière P. Relation of heart rate at rest and long-term (>20 years) death rate in initially healthy middle-aged men. Am J Cardiol. 2009; 103 :279 – 283

105. Go AS, Yang J, Ackerson LM, Lepper K, Robbins S, Massie BM, Shlipak MG. Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure:

the Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) Study. *Circulation* 2006;113(23):2713-23

106. Saxon LA, Bristow MR, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, Feldman AM, Galle E, Ecklund F. Predictors of sudden cardiac death and appropriate shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial. Circulation 2006;114:2766–2772
107. http://www.learntheheart.com/cardiology-review/atrial-fibrillation/
108. http://ecg.utah.edu/lesson/5-2#atrial_fib
109. Cuspidi C, Sala C, Negri F, Mancia G, Morganti A; Italian Society of Hypertension. Prevalence of left-ventricular hypertrophy in hypertension: an updated review of echocardiographic studies. *J Hum Hypertens.* 2012;26:343-349
110. Tumlin JA, Costanzo MR, Chawla LS, Herzog CA, Kellum JA, McCullough PA, Ronco C. Cardiorenal syndrome type 4: insights on clinical presentation and pathophysiology from the eleventh consensus conference of the Acute Dialysis Quality Initiative (ADQI). *J Contrib Nephrol*. 2013;182:158–173
111. KDIGO. 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3:136-150
112. Levey A.S., R. Atkins, J. Coresh, E.P. Cohen, A.J. Collins, K-U Eckardt, M.E. Nahas, B. L. Jaber, M. Jadoul, A. Levin, N.R. Powe, J. Rossert, D.C. Wheeler, N. Lameire, G. Eknoyan, Chronic kidney disease as a global public health problem: Approaches and initiatives – a position statement from Kidney Disease Improving Global Outcomes; Kidney International (2007) 72, 247–259
113. Hallan S. I., K. Dahl, C. M. Oien, D. C. Grootendorst, A. Aasberg, J. Holmen, F. W. Dekke, Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey; BMJ 2006; 333.
114. CHRONIC KIDNEY DISEASE.National clinical guideline for early identification and management in adults in primary and secondary care, 2008 Royal College of Physicians of London
115. Stevens L. A., J. Coresh, T. Greene, A. S. Levey, Assessing Kidney Function — Measured and Estimated Glomerular Filtration Rate. NEJM. 354;23;2006
116. Einhorn LM, Zhan M, Hsu VD, Walker LD, Moen MF, Seliger SL, Weir MR, Fink JC. The frequency of hyperkalemia and its significance in chronic kidney disease. Arch Intern Med. 2009;169:1156-1162
117. Putcha N, Allon M. Management of hyperkalemia in dialysis patients. Semin Dial. 2007;20:431-439
118. Frangiosa A, De Santo LS, Anastasio P, De Santo NG. Acid-base balance in heart failure J Nephrol. 2006;19 Suppl 9:S115-20
119. Lang CC, Mancini DM. Non-cardiac comorbidities in chronic heart failure. Heart. 2007 Jun;93(6):665-71
120. Guralnik JM, Eisenstaedt RS, Klein HG, et al. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood*. 2004;104:2263–2268.
121. Attanasio Ph., C. Ronco, M. S. Anker, P. Ponikowski, S. D. Anker, Management of Chronic Cardiorenal Syndrome; Basel, Karger, 2010, vol 165, pp 129–139
122. KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD); OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY 2009
123. Moe S., T. Dru¨eke, J. Cunningham, W. Goodman, K. Martin, K. Olgaard, S. Ott, S. Sprague, N. Lameire, G. Eknoyan, Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO); Kidney International (2006) 69, 1945–1953
124. Kendrick J, Kestenbaum B, Chonchol M. Phosphate and cardiovascular disease. Adv Chronic Kidney Dis. 2011;18(2):113-9.
125. Gupta D, Brietzke S, Hayden MR, Kurukulasuriya LR, Sowers JR. Phosphate Metabolism in Cardiorenal Metabolic Disease. *Cardiorenal Med*. 2011;1(4):261-270.
126. Cozzolino M, Bruschetta E, Stucchi A, Ronco C, Cusi D. Role of vitamin d receptor activators in cardio-renal syndromes. *Semin Nephrol*. 2012;32(1):63-9
127. Ronco C, Cozzolino M. Mineral metabolism abnormalities and vitamin D receptor activation in cardiorenal syndromes *Heart Fail Rev*. 2012;17(2):211-20

128. http://www.merckmanuals.com/professional/endocrine_and_metabolic_disorders/lipid_disorders/dyslipidemia.html

129. Goff DC Jr, Bertoni AG, Kramer H, Bonds D, Blumenthal RS, Tsai MY, Psaty BM. Dyslipidemia prevalence, treatment, and control in the Multi-Ethnic Study of Atherosclerosis (MESA): gender, ethnicity, and coronary artery calcium. *Circulation*. 2006;113:647-656

130. Tóth PP, Potter D, Ming EE. Prevalence of lipid abnormalities in the United States: the National Health and Nutrition Examination Survey 2003-2006. *J Clin Lipidol*. 2012;6(4):325-330

131. http://www.merckmanuals.com/professional/endocrine_and_metabolic_disorders/lipid_disorders/dyslipidemia.html

132. Young Kim S., J. P. Guevara, K. Mi Kim, H. K. Choi, D. F. Heitjan, D. A. Albert, Hyperuricemia and coronary heart disease: A systematic review and meta-analysis; Arthritis Care & Research, pages 170–180, 2010.

133. Harris MD, Siegel LB, Alloway JA. Gout and hyperuricemia. *Am Fam Physician.* 1999;59(4):925-934.

134. http://emedicine.medscape.com/article/241767-overview#a0199

135. Roubenoff R. Gout and hyperuricemia. *Rheum Dis Clin North Am*. 1990;16:539–550

136. Kidney Int Suppl. 2013;3:136-150

137. http://www.who.int/topics/obesity/en/

138. http://www.who.int/gho/ncd/risk_factors/obesity_text/en/

139. Poirier P.,Thomas D. Giles,George A. Bray, Yuling Hong, Judith S. Stern, F. Xavier Pi-Sunyer, Robert H. Eckel, Obesity and Cardiovascular Disease: Pathophysiology, Evaluation, and Effect of Weight Loss. An Update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease From the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism.*Circulation. 2006; 113: 898-918*

140. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. N Engl J Med 1999; 341:427.

141. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care. 1994 Sep;17(9):961-9

142. Heyward VH. Evaluation of body composition. Current issues *Sports Med*. 1996;22(3):146-56

143. Beechy L, Galpern J, Petrone A, Das SK. Assessment tools in obesity - psychological measures, diet, activity, and body composition. *Physiol Behav*. 2012;107(1):154-71

144. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr; International Diabetes Federation Task Force on Epidemiology and Prevention; Hational Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009; 120(16):1640-1645

145. Cameron AJ, Shaw JE, Zimmet PZ. The metabolic syndrome: prevalence in worldwide populations. Endocrinol Metab Clin North Am. 2004;33:351-375

146. *Diabetes Care* 2009;32(Suppl 1): S62–S67

147. http://dx.doi.org/10.1787/9789264183896-en

148. http://www.idf.org/diabetesatlas/introduction

149. *Diabetes Care* 2012;35(Suppl 1): S11-S63

150. Rabe KF, S. Hurd, A. Anzueto, P. J. Barnes, S. A. Buist, P. Calverley, Y. Fukuchi, Ch. Jenkins, R. Rodriguez-Roisin, Ch. van Weel, J. Zielinsk, Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease; American Journal of Respiratory and Critical Care Medicine, 2007, pp. 532-555

151. Mannino D.M., D. Thorn, A. Swensen, F. Holguin, Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD; Eur Respir J 2008; 32: 962–969

152. Halbert R.J., J.L. Natoli, A. Gano, E. Badamgarav, A.S. Buist, D.M. Mannino, Global burden of COPD: systematic review and meta-analysis; Eur Respir J 2006; 28: 523–532

153. Dember L.M.. Amyloidosis - Associated Kidney Disease. Published online before print November 8, 2006, doi:10.1681/ASN.2006050460. JASN December 2006 vol. 17 no. 12 3458-3471.

154. Halwani O., Diego H Delgado. Cardiac amyloidosis: an approach to diagnosis and management. Expert Rev. Cardiovasc. Ther.8(7), 1007–1013 (2010).

155. Tsokos G.C.. Systemic Lupus Erythematosus.N Engl J Med 2011; 365:2110-2121, December 1, 2011, doi: 10.1056/NEJMra1100359

156. Bertsias G., Ricard Cervera, Dimitrios T Boumpas. EULAR Textbook on Rheumatic Diseases, 2012. Systemic Lupus Erythematosus: Pathogenesis and Clinical Features. p. 476 – 505.

157. Chakravarty, E.F., Bush, T.M., Manzi, S., Clarke, A.E. and Ward, M.M.2007. Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: Estimates obtained using hospitalization data. Arthritis & Rheumatism, 56(6): 2092–2094

158. Gurevitz SL, Snyder JA, Wessel EK, Frey J, Williamson BA. Systemic lupus erythematosus: a review of the disease and treatment options. Consult Pharm. 2013 Feb;28(2):110-21. doi: 10.4140/TCP.n.2013.110.

159. Hunder G.G. Classification of and approach to the vasculitides in adults. UpToDate

160. http://www.mayoclinic.org/diseases-conditions/arthritis/basics/definition/con-20034095

161. http://www.cdc.gov/chronicdisease/resources/publications/aag/arthritis.htm

162. *Arthritis Res Ther.* 2011;13:222

163. Vinik AI, Freeman R, Erbas T. Diabetic autonomic neuropathy. *Semin Neurol* 2003; 23: 365 372

164. Pop-Busui R, Low PA, Waberski BH, Martin CL, Albers JW, Feldman EL, Sommer C, Cleary PA, Lachin JM, Herman WH. Effects of prior intensive insulin therapy on cardiac autonomic nervous system function in type 1 diabetes mellitus: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (DCCT/ EDIC). *Circulation* 2009; 119: 2886-2893

165. Spallone V, Ziegler D, Freeman R, Bernardi L, Frontoni S, Pop-Busui R, Stevens M, Kempler P, Hilsted J, Tesfaye S, Low P, Valensi P; on behalf of the Toronto Consensus Panel on Diabetic Neuropathy*. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. *Diabetes Metab Res Rev* 2011 Jun 22.

166. Rudberg S, Osterby R. Decreasing glomerular filtration rate--an indicator of more advanced diabetic glomerulopathy in the early course of microalbuminuria in IDDM adolescents? Nephrol Dial Transplant. 1997 Jun;12(6):1149-54

167. Papale M, Di Paolo S, Magistroni R, Lamacchia O, Di Palma AM, De Mattia A, Rocchetti MT, Furci L, Pasquali S, De Cosmo S, Cignarelli M, Gesualdo L. Urine proteome analysis may allow noninvasive differential diagnosis of diabetic nephropathy. Diabetes Care. 2010 Nov;33(11):2409-15

168. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Drash AL, Ellis D, LaPorte RE, Kuller LH.Prevalence of complications in IDDM by sex and duration.Pittsburgh Epidemiology of Diabetes Complications Study II.Diabetes. 1990 Sep;39(9):1116-24

169. http://emedicine.medscape.com/article/761556-overview

170. Gerald F, R. Fowkes, Diana Rudan, Igor Rudan, et al.Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. The Lancet, Volume 382, Issue 9901, Pages 1329 - 1340, 19 October 2013.

171. http://www.heart.org/HEARTORG/Conditions/Cholesterol/WhyCholesterolMatters/Atherosclerosis_UCM_305564_Article.jsp

172. Feenstra J, Grobbee DE, Remme WJ, Stricker BH. Drug-induced heart failure. *J Am Coll Cardiol*. 1999;33(5):1152-1162

173. http://depts.washington.edu/druginfo/DTT/2007_Vol36_Files/V36N7new.pdf

174. Singh NP, Ganguli A, Prakash A. Drug-induced kidney diseases. *JAPI* 2003;51:970-979

175. http://www.who.int/cardiovascular_diseases/en/cvd_atlas_15_burden_stroke.pdf?ua=1

176. Hallan S. I., E. Ritz, S. Lydersen, S. Romundstad, K. Kvenild, S. R. Orth, Combining GFR and Albuminuria to Classify CKD Improves Prediction of ESRD; J Am Soc Nephrol 20: 1069–1077, 2009.

177. Grams M. E., J. Coresh, D. L. Segev, L. M. Kucirka, H. Tighiouart, M. J. Sarnak, Vascular Disease, ESRD, and Death: Interpreting Competing Risk Analyses; Clin J Am Soc Nephrol 7: 1606–1614, 2012

178. Clement F. M., M. T. James, R. Chin, S. W. Klarenbach, B. J. Manns, R. R. Quinn, P. Ravani, M. Tonelli, B. R. Hemmelgarn, Validation of a case definition to define chronic dialysis using outpatient administrative data; BMC Medical Research Methodology 2011, 11:25

179. Mrazek, P. B., & Haggerty, R. J. (Eds.). , 1994. Reducing risks for mental disorders: Frontiers for preventive intervention research: Summary. National Academies Press

180. National Library of Medicine (2009) Chapter 5 - Semantic Networks. UMLS Reference Manual. Bethesda, MD: U.S. National Library of Medicine, National Institutes of Health.

181. Kaplan S, The words of risk analysis, Risk Analysis, 17(4):407-417, 1997

182. Kraemer, H. C., Kazdin, A. E., Offord, D. R., Kessler, R. C., Jensen, P. S., & Kupfer, D. J. 1997. Coming to terms with the terms of risk. Archives of General Psychiatry, 54(4), 337.

183. Bull K., Spiegelhalter DJ, Tutorial in Biostatistics, - Survival Analysis in Observational Studies, Statistics in Medicine, 16:1041-1074, 1997

184. Spruance S.L., JE. Reid, MGrace, M Samore, Hazard Ratio in Clinical Trials, Antimicrob Agents Chemother. Aug 2004; 48(8): 2787–2792.

185. Oxford Centre for Evidence-based Medicine Levels of Evidence (2011) http://www.cebm.net/mod_product/design/files/CEBM-Levels-of-Evidence-2.1.pdf) Produced by J. Howick, I. Chalmers, P. Glasziou, T. Greenhalgh, C. Heneghan, A. Liberati, I. Moschetti, B. Phillips, H. Thornton, O. Goddard and M. Hodgkinson

186. Oxford Center for Evidence-based Medicine Glossary, http://www.cebm.net/?o=1116

187. http://www.gradeworkinggroup.org/society/index.htm

188. http://www.gradeworkinggroup.org/publications/index.htm

189. http://tech.cochrane.org/revman/gradepro

190. Chewning B, Bylund C, Shah B, Arora N, Gueguen J, Makoul G. Patient preferences for shared decisions: A systematic review. Patient Education & Counseling [serial online]. January 2012;86(1):9-18.

191. Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: What does it mean? (Or it takes two to tango). Soc Sci Med 1997; 44(5):681-692

192. O'Connor A, Llewellyn-Thomas H, Flood A. Modifying Unwarranted Variations In Health Care: Shared Decision Making Using Patient Decision Aids. Health Affairs [serial online]. September 2, 2004;23:63-72

193. The Shared-Decision-Making Study Group. Final report: The Practice and Impact of Shared Decision-Making. 2011. Available from: http://muskie.usm.maine.edu/Publications/PHHP/Shared-Decision-Making_Final-Report.pdf

194. Kon AA,. Difficulties in judging patient preferences for shared decision-making. J Med Ethics, 2012, 38(12):719-720.

195. Piper S. Patient empowerment: Emancipatory or technological practice?.Patient Education & Counseling [serial online]. May 2010;79(2):173-177.

196. Patient empowerment–who empowers whom?.The Lancet [serial online]. May 5, 2012, 379(9872):1677. Available from: Business Source Complete, Ipswich, MA. Accessed February 13, 2014

197. Elwyn G, Frosch D, Volandes A, Edwards A, Montori V. Investing in deliberation: a definition and classification of decision support interventions for people facing difficult health decisions. Medical Decision Making: An International Journal Of The Society For Medical Decision Making [serial online]. November 2010;30(6):701-711.

198. Measuring Shared Decision Making. A review of research evidence. A report for the Shared Decision Making programme in partnership with Capita Group Plc. 2012. Available from: http://www.rightcare.nhs.uk/wp-content/uploads/2012/12/Measuring_Shared_Decision_Making_Dec12.pdf

199. Stacey D, Légaré F, Wu J, et al. Decision aids for people facing health treatment or screening decisions. The Cochrane Database Of Systematic Reviews [serial online]. January 28, 2014;1:CD001431.

200. Sepucha et al. BMC Medical Informatics and Decision Making 2013, 13(Suppl 2):S12

201. Kahneman D. Maps of bounded rationality: Psychology for Behavioral Economics. The American Economic Review, 2003, 93(5):1449-1475

202. Final report: the practice and impact of shared decision-making [Internet]. Augusta (ME): Maine Quality Forum; 2011 Feb Available from: http://mainequalityforum.gov/SDM_Final_Report_02282011.pdf

203. Spiegle G, Al-Sukhni E, Kennedy E, et al. Patient decision aids for cancer treatment. Cancer (0008543X) [serial online]. January 2013;119(1):189-200

204. Flynn D, Ford G, Stobbart L, Rodgers H, Murtagh M, Thomson R. A review of decision support, risk communication and patient information tools for thrombolytic treatment in acute stroke: lessons for tool developers. BMC Health Services Research [serial online]. August 2013;13(1):225-237

205. Vlemmix F, Warendorf J, Nassar N, et al. Decision aids to improve informed decision-making in pregnancy care: a systematic review. BJOG: An International Journal Of Obstetrics &Gynaecology [serial online]. February 2013;120(3):257-266

206. Dugas M, Shorten A, Dubé E, Wassef M, Bujold E, Chaillet N. Decision aid tools to support women's decision making in pregnancy and birth: A systematic review and meta-analysis. Social Science & Medicine [serial online]. June 15, 2012;74(12):1968-1978

207. de Abreu M, Gafni A, Ferraz M. The Use of a Decision Board to Elicit Brazilian Patients' and Physicians' Preferences for Treatment: The Case of Lupus Nephritis. Value In Health (Elsevier Science) [serial online]. July 2, 2011;14(5):S141-S146

208. Dolan J, Veazie P, Russ A. Development and initial evaluation of a treatment decision dashboard. BMC Medical Informatics & Decision Making [serial online]. May 2013;13(1):1-9

209. de Vries M, Fagerlin A, Witteman H, Scherer L. Combining deliberation and intuition in patient decision support. Patient Education &Counseling [serial online]. May 2013;91(2):154-160

210. Sprague Jr. R.A Framework for the Development of Decision Support Systems. MIS Quarterly [serial online]. December 1980;4(4):1-26. Available from: Business Source Complete, Ipswich, MA. Accessed February 13, 2014

211. Keen, Peter G. W. Decision support systems: a research perspective. Cambridge, Mass. Center for Information Systems Research, Afred P. Sloan School of Management 1980

212. Khan A, Doucette J, Cohen R. Validation of an Ontological Medical Decision Support System for Patient Treatment Using a Repository of Patient Data: Insights into the Value of Machine Learning. ACM Transactions On Intelligent Systems & Technology [serial online]. December 2013;4(4):68-68:31

213. Informed medical decisions foundation home page, http://www.informedmedicaldecisions.org/ [accessed on February 13, 2014]

214. Hirsch O, Keller H, Krones T, Donner-Banzhoff N. Arriba-lib: association of an evidence-based electronic library of decision aids with communication and decision-making in patients and primary care physicians. International Journal Of Evidence-Based Healthcare [serial online]. March 2012;10(1):68-76

215. Ottawa Hospital Research Institute list of decision aids http://decisionaid.ohri.ca/AZlist.html[accessed on February 13, 2014]

216. Ottawa Hospital Research Institute patient decision aid development e-training course https://decisionaid.ohri.ca/eTraining/[accessed on February 13, 2014]

217. National Health Service directory of decision aids http://sdm.rightcare.nhs.uk/pda/[accessed on February 13, 2014]

218. NHS Direct web site https://www.nhsdirect.nhs.uk[accessed on February 13, 2014]

219. Dixon B, Simonaitis L, Middleton B, et al.A pilot study of distributed knowledge management and clinical decision support in the cloud. Artificial Intelligence In Medicine [serial online]. September 2013;59(1):45-53

220. Hsueh-Chun L, Hsi-Chin W, Chih-Hung C, Tsai-Chung L, Wen-Miin L, Jong-Yi Wang W. Development of a real-time clinical decision support system upon the web mvc-based architecture for prostate cancer treatment. BMC Medical Informatics & Decision Making [serial online]. January 2011;11(1):16-26

221. Beauchamp and Childress, Principles of Biomedical Ethics, 6th Edition., Oxford University Press, Incorporated, 2009

222. European Parliament And Council Directive 95/46/EC Of 24 October 1995 On The Protection Of Individuals With Regard To The Processing Of Personal Data And On The Free Movement Of Such Data (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:en:HTML)

223. Article 29 Data Protection Working Party, Opinion 5/2009 on online social networking, 01189/09/EN WP 163, Adopted on 12 June 2009 (http://ec.europa.eu/justice/policies/privacy/docs/wpdocs/2009/wp163_en.pdf)

224. Legal frameworks for eHealth", Based on the findings of the second global survey on eHealth Global Observatory for eHealth series - Volume 5, World Health Organization 2012(http://whqlibdoc.who.int/publications/2012/9789241503143_eng.pdf)

225. Proposal For A Directive Of The European Parliament And Of The Council On The Application Of Patients' Rights In Cross-Border Healthcare, European Commision, Brussels, 2.7.2008 COM(2008) 414 Final 2008/0142 (COD) (http://ec.europa.eu/health/ph_overview/co_operation/healthcare/docs/COM_en.pdf)

226. Directive 2011/24/Eu Of The European Parliament And Of The Council Of 9 March 2011 On The Application Of Patients' Rights In Cross-Border Healthcare. (http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:01:EN:HTML)

227. Lithuanian Bioethics Committee information, http://bioetika.sam.lt/

228. Data protection and privacy ethical guidelines", Experts Working Group on data protection and privacy, Chaired by: Caroline Gans-Combe, European Commision 2009 (http://ec.europa.eu/research/participants/data/ref/fp7/89827/privacy_en.pdf)

Annex 1

Patients Survey

1. Patients Survey Design

1.1. Goal

The aim of this survey is to help identify user perceptions of the major CARRE user group, namely patient (including healthy individuals at risk as well as their carers).

1.2. Outline of Survey Methodology

The survey was designed via the following approach:

- Define the goal of the survey.
- Literature review of the domain (presented in Sections 2 and 3 of this Deliverable).
- Identify research goals, i.e. specific research questions that will be addressed via the survey.
- Discuss research questions with a small number of intended survey participants, via semi-structured interviews with the aim to capture their overall response in order to identify specific survey questions.
- Compile a first draft of the questionnaire (survey instrument).
- Validate the draft questionnaire (content validation) via administering it to a group of 25 subjects
- Revise the questionnaire.
- Deploy questionnaire
- Process results

1.3. Research Questions

Overall research aims and research question topics were determined based on the area and needs of the project and following the outcomes of field survey as presented in Sections 2 & 3 of this deliverable.

Research questions to investigate the patient perspective are grouped along the following axes:

- How do patients perceive empowerment (in terms of their health condition management)? Are they willing to be empowered or prefer to be guided?
- Do patients understand their condition; are they willing to be informed about it and what information would like to have?
- Are patients willing and able to be engaged with ICT intervention that will enhance their knowledge and empower them?
- At what extend are patients willing to be monitored so that information gathered can be used to personalized empowerment and educational interventions.

1.4. Questionnaire Design & Validation

This survey aims to identify self-reported attitudes, perceived environments and behaviours. Self-reporting can be implemented by interviews, questionnaires (closed ended surveys) and diaries (semi-structured data collection on events, emotions, etc.). The most common measurement tool is a questionnaire, as it is cheap and easy to distribute and analyse, and appropriate to measure concepts (beliefs, attitudes, perceptions).

To the best of our knowledge, there no specific survey instrument available for the purposes of identifying user perceptions in the domain of cardiorenal comorbidities patient empowerement. Thus we decided to desing a new questionnaire. This took into account elements from relevelant instruments. In particular, the Questionnaire for Patient Empowerement Measurement, recently developed in the SUSTAINS FP7-ICT-

PSP-297206 project[2]. These elements where used to identify major topics which then were complemented with specific issues as raised by CARRE potential users via semi-structured interviews.

1.4.1. Semi-structured Pilot Interviews

Semi-structured interviews were conducted with 5 patients and 1 nurse in order to identify issues of concern (which then will be used to formulate survey questions). The interview was centred on the following research questions:

- how do patients perceive empowerment;
- are patients willing to be empowered or prefer to be guided;
- do patients understand their condition;
- are they willing to be informed about their condition and what information they want;
- are patients willing to engage with ICT applications;
- are patients willing to be monitored and at what extend.

Summaries of each interview are presented in the following paragraphs.

Interview #01

Subject: 51 year old male – industrial worker

Condition: Diabetes type 1. Acute onset 8 years ago, after emotional stress.

Summary of interview: Panicked at the condition onset, but then accepted his condition, mainly due to his interaction with physicians. Emphasizes personal interaction and communication with physician. Capitalizes on trusting the physician. Welcomes full control and guidance by the physician. Following therapy and diet does not seem a problem, apart from practical issues (e.g. no help in preparing the right meals). Received what he perceives as extensive and accurate information from his physicians. However, he feels that he does not understand a lot of terms, e.g. what is type I vs. type II diabetes. Uses mobile phone and occasionally the internet. Would accept remote monitoring if this means continual observation by a physician and alerts. If he could do one thing for people in his condition: would organize seminars in every part of the country for patients to attend and learn more on their condition.

Issues derived from the interview:

- paternalistic approach vs. empowerment
- self-awareness of knowledge attained
- information on medical issues
- information on practical issues
- communication with physician
- monitoring: fear, acceptance
- degree of technology uptake

Interview #02

Subject: 53 year old male, computer technician

Condition: Metabolic syndrome. Gradual deterioration 3-4 years ago, last 1,5 years on medication.

Summary of interview: Stressed over the condition, seems rather hopeless that he or his physician can manage it. Searches for information on the internet, finds is easy to understand . Would prefer to learn and be empowered via personal stories and cases, but would not engage in social media. Finds it rather difficult to follow recommended diet (change of lifestyle). Finds it necessary (but difficult) to find information on

[2] D.3.2 1.0 Questionnaire for Patient Empowerment Assessment, January 2013, SUSTAINS EC ICT-PSP-297206 project, http://www.sustainsproject.eu/publicdocuments/ Retrieved March 12, 2014

medical experts to consult about comorbidities (e.g. hepatologist for fatty liver infiltration). If he could do one thing for people in his condition: provide information on related medical specialties and experts, provide more information on understanding and micromanagement of symptoms, in general provide more information

Issues derived from the interview:

- ease of conformance to therapy and lifestyle change management (diet, physical exercise)
- awareness of comorbidities
- information on medical specialties for comorbidity management
- information on similar cases/patients
- social media engagement

Interview #03

Subject: 68 year old male

Condition: Chronic kidney disease. Onset of renal deficiency 35 years ago after ischemic stroke episode. Last 15 years on haemodialysis at medical centre.

Summary of interview: At disease onset, fear and anxiety for the condition and lack of acceptance. Values communication with physician. Searches occasionally for information, mainly via leaflets found in physician's waiting rooms and less often on the internet. However, mainly fears knowledge. He dislikes social groups and support therein. If he could do one thing for people in his condition: make sure all have regular monitoring and check-ups.

Issues derived from the interview:

- fear of the unknown
- fear of knowledge
- social support
- regular monitoring and check up

Interview #04

Subject: 70 year old female

Condition: hypertensive for 10 years, 2 last years with renal deficiency, 1 last month on haemodialysis

Summary of interview: Attributes greatly her deteriorated condition on lack of knowledge and excessive stress. She feels she lacks knowledge of her condition and the medical terms related to it, however she also feels that knowing more might be difficult to handle and stressful. If she could do one thing for people in her condition: inform them.

Issues derived from the interview:

- lack of knowledge
- fear of knowing
- stress as a contributing factor

Interview #05

Subject: 51 year male, diabetic for the last 23 years, last 4 years renal deficiency

Summary of interview: Family history of diabetes. Attributes deterioration to uncontrolled hypoglycaemic episodes. He actively searched for medical information on the internet. Would prefer if this information could be sent to him in his mobile. He tries to attend medical seminars; he considers them very helpful, but he finds medical terminology somewhat confusing and difficult to understand. If he could do one thing for people in his condition: provide better hospital treatment and more communication/interaction with the physician.

Interview #06

Subject: nurse, female, working for 29 years in internal medicine clinic, 7 last years head of nephrology clinic

Condition: not a patient, but a healthcare worker

Summary of interview: Believes that it is crucial for the patient to have continuous information. Especially on what lies ahead, what could be the progression of the condition, so that the patient does not relax and so that they adhere to therapy and lifestyle management guidelines. Adherence to diet is difficult for patients, it would be good to have a way to suggest alternative foods (of same dietary value). Patients most often are eager to learn more about their condition. However usually they do not have a complete understanding of the disease details and therapy alternatives. Patients casually ask other patients for information. If she could do one thing for people in this condition: inform patients about risk factors and lifestyle management.

Issues derived from the interview:

- information on disease progress
- information on risk factors
- information on lifestyle
- sharing experiences amongst patients

Overall issues derived collectively from all interviews:

- paternalistic approach vs. empowerment
- self-awareness of knowledge attained
- awareness of comorbidities
- information on medical condition
- information on disease progress
- information on practical issues
- information on medical specialties for comorbidity management
- information on similar cases/patients
- information on risk factors
- information on lifestyle
- fear of the unknown
- fear of knowledge
- monitoring: fear, acceptance
- communication with physician
- degree of technology uptake
- social support & social media engagement

1.4.2. Questionnaire Draft Composition

Based on the research questions as well as on the issues of concern as identified by interviews, we developed a first darft of 36 questions. These are presented below, grouped in categories corresponding to the initial research questions (RQ) of our survey.

The questions were phrased as statements, each one referring to a 5-point Likert scale[3] of: 1: fully disagree, 2: disagree, 3:neither agree or disagree, 4: agree, 5: fully agree.

[3] Likert R. (1932). "A Technique for the Measurement of Attitudes". Archives of Psychology 140: 1–55.

RQ1: Do patients understand their condition?

1. I am aware of what may have caused my current condition.
2. I know which symptoms I currently experience are due to my disease
3. I can recognize new symptoms that may indicate disease progression.
4. I am aware of other illnesses that may occur due to inefficient management of my current health condition.

RQ2: Are patients satisfied by the information provided to them?

5. I have all information I need to understand my current condition.
6. I have all the information I need in order to manage my disease in everyday life.
7. I have all information I need to understand possible disease progression.
8. My physician/nurse provides me with enough information on how to reduce the risk of future complications.
9. I believe that better knowledge of my disease would be very beneficial for better management of my condition.

RQ3: Can patients cope with information on their condition?

10. I am able to manage information about possible progression of my disease
11. Any new information about my disease makes me feel anxious
12. Any new information about my disease confuses me
13. It is difficult for me to understand all information provided
14. I want to receive new information about my condition regularly

RQ4: How do patients perceive empowerment: Are patients willing to be empowered or prefer to be guided?

15. I prefer to search for medical information on my own
16. I usually discuss my condition with other fellow patients.
17. I want more information to better understand my condition and its possible progression.
18. I want more information to better manage my condition
19. I would like to know possible alternative ways of managing my condition
20. I feel that I need more information in order to be able to commit fully to therapy
21. I feel that I need more information in order to be able to commit fully to required lifestyle changes.
22. I would prefer to make the final decision on the management of my condition, when there are more than one alternative option.
23. I prefer my doctor to decide the best treatment option for me
24. I would like to discuss treatment goals, potential implications and disease progression with my doctor
25. I prefer to rely solely on doctor's knowledge and guidance
26. I prefer to be fully informed on my condition

RQ5: Are patients willing and able to be engaged with ICT intervention that will enhance their knowledge and empower them?

27. I use the internet as a source of medical information
28. I understand the health information that I find on the internet
29. I feel able to recognize which internet source provides accurate medical information
30. I feel that information provided on authoritative internet platforms is reliable and trustworthy
31. I would be interested in a specialised internet platform where all the vital information for my condition could be gathered and accessed
32. I am willing to monitor myself and record data on my activities (e.g. weight, diet, etc.) when this is recommended to me by health care providers
33. I am willing to monitor myself and record data on my activities (e.g. weight, diet, etc.) in order to manage my condition more efficiently
34. I would be willing to use applications which help me monitor and manage diet & physical activity.
35. I would be willing to use an application that will provide alerts regarding my condition and its progression
36. I feel that my condition needs closer monitoring than currently suggested by my healthcare provider.

1.4.3. Questionnaire Validation

Major types of validity include[4]:

– Content validity: extent to which the questionnaire measures the concept of interest. Content validity can be deduced from three different sources[5]: literature, representatives of the target population and experts. Determining content validity is rather subjective, as there is no complete objective method of calculating it.

– Criterion validity: how well a score predicts an outcome. This type of validity refers to scores of an instrument and how well these predict an outcome as compared to previous instruments –

– Construct validity: how well a scale correlates with similar constructs. Construct validity is demonstrated by the ability of questionnaire to support predictions made from theoretical framework.

Each type of validity is distinct, meaning that a questionnaire can have one kind of validity but not another and can can only be validated for x patient population, under y conditions, and so forth. As the purpose of our survey is to to derive information that will help identift functional requirements for CARRE project, rather than calculate quantitatively an outcome, content validity is the most appropriate and required to be checked.

Content validity was measured by administering the questionnaire to a pilot population and asking the raters to report back on the relevance of each instrument item. For each item, three different criteria were assessed: relevance, clarity and simplicity[6]. Also, the subjects were asked to provide an overall assessment of the questionnaire in terms of its relevance, clarity of content, simplicity in terms of phrasing and experience of completing it. The questionnaire was validated separately in two different languages, Greek and Lithuanian, representing the two different population groups were the pilots of CARRE will be demonstrated. The Greek version of the questionnaire was validated by group of 26 people, while the Lithuanian version of the questionnaire was validated by a group of 25 people. The Validation Sheet (English translation) is reproduced in the end of this Annex.

To measure content validity we used the content validity ratio (CVR)[7], defined as:

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[4] Rattray J., Jones MC, Essential elements of questionnaire design and development, Journal of Clinical Nursing, 16:234-243, 2007.

[5] Burns N, Grove SK. The practice of nursingresearch conduct,critique, and utilization. 2nd ed. Philadelphia: WB Saunders Company;1993

[6] Yaghamale F., Content validity and its estimation, Journal of Medical Education, vol. 3(1), 25-27, 2003

[7] Lawshe C.H., A Quantitative approach to content validity, Personnel Psychology INC., 1975.

$$CVR = \frac{n_e - \frac{N}{2}}{\frac{N}{2}}$$

where:

n_e = number of pilot group members indicating an item (i.e. question) is "essential",

N = total number of pilot group members.

The CVR can range from a value of –1 to +1 for a particular item, with higher scores indicating greater content validity for the item. A CVR of 0 indicates that half of the pilot group members rated the item as essential. Any positive value indicates that more than half of the SMEs rated the item as essential. Items that are deemed to have too low CVR values should be deleted from the test before administration. The minimum (threshold) CVR value required for an item to be retained depends on the total number of pilot group members (one tailed test, p=0.05)[8]. Thus, in case of a pilot group of 25 subjects (either of the validation groups) this CVR threshold is 0.37.

Overall, the time to complete the Greek version was reported 9.08 ± 3.25 min, and for completed the Lithuanian version 18.32± 4.95 min.

The validation results are shown in the following graphs that present overall CVRs and also individual item CVRs for either language version of the questionnaire.

CVRs were calculated considering as essential the sum of answers corresponding to the two positive alternative answers, i.e. the sum of respondents who chose “very relevant/clear/simple” plus those who chose “relevant/clear/simple but some revision required”.

The overall rating of the Greek questionnaire is shown in Figure 13 and of the Lithuanian questionnaire in Figure 14. All categories scored well above the threshold for the Greek questionnaire. In the Lithuanian validation, “simplicity” scored under the threshold, probably indicating a not so good translation of the questions in the Lithuanian language.

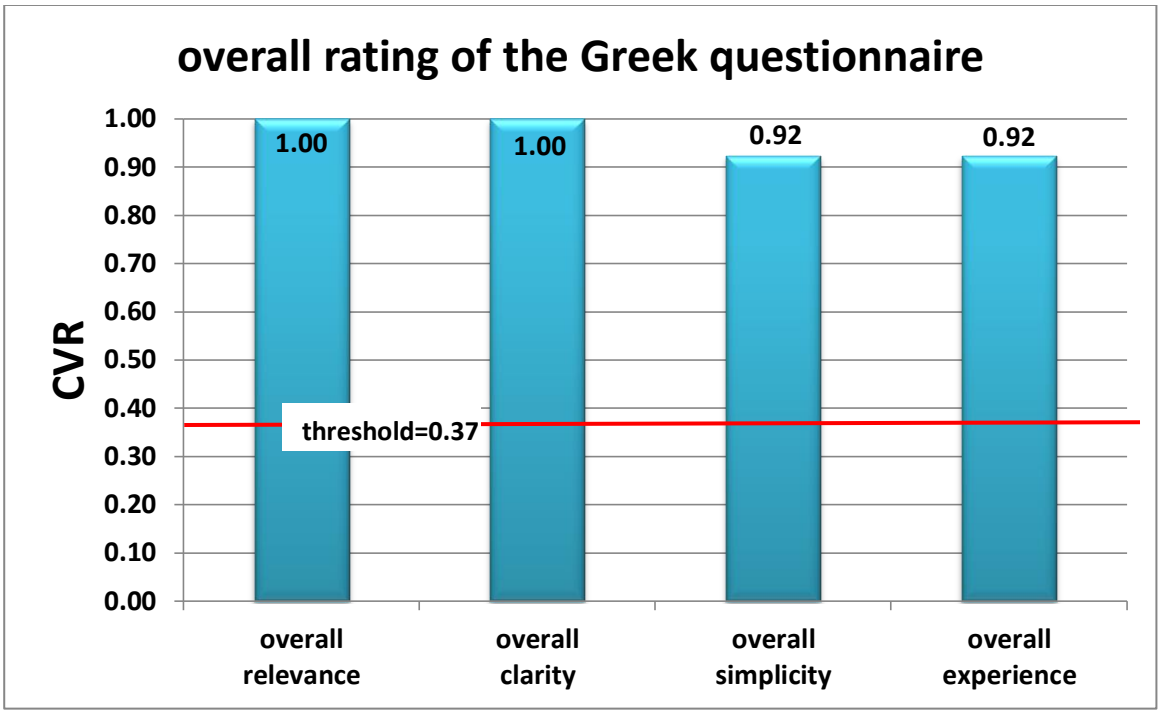


Figure 13. Overall rating of the Greek Patient Questionnaire

[8] Lawshe C.H., A Quantitative approach to content validity, Personnel Psychology INC., 1975

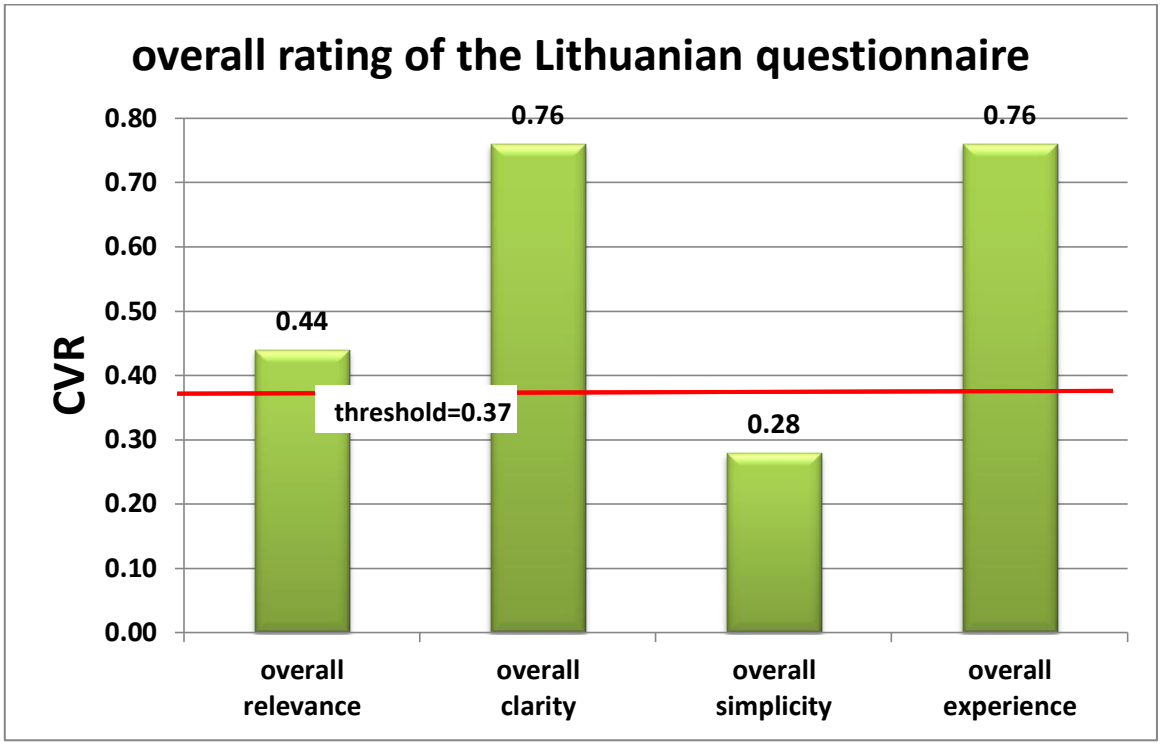


Figure 14. Overall rating of the Lithuanian Patient Questionnaire

More detailed analysis involved calculating the CVR for each individual item on the questionnaire for all three qualities measured, i.e. relevance, clarity and simplicity. Results for relevance with resperct to the aim of the survey are presented in Figure 15, for clarity of content in Figure 16, and for simplicity in terms of phrasing in Figure 17.

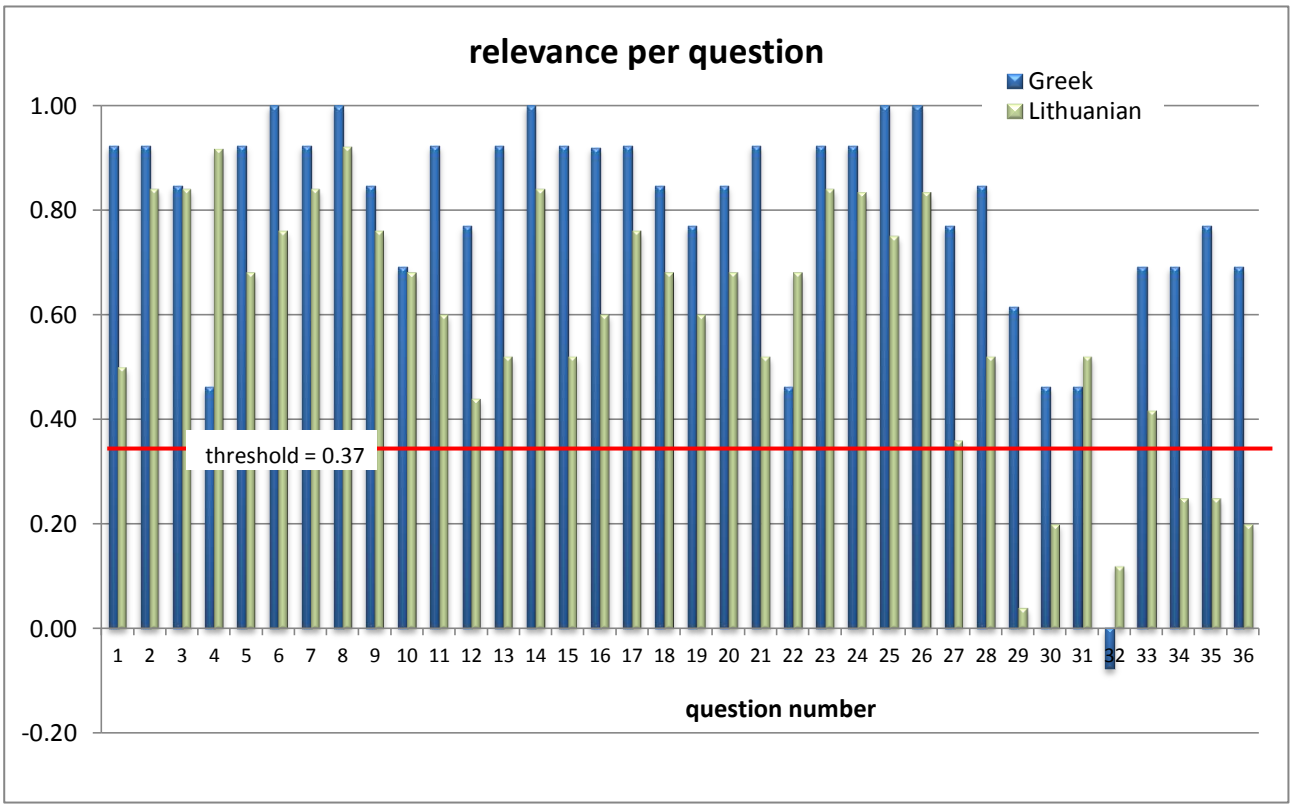


Figure 15. CVRs for relevance per question for patient questionnaire.

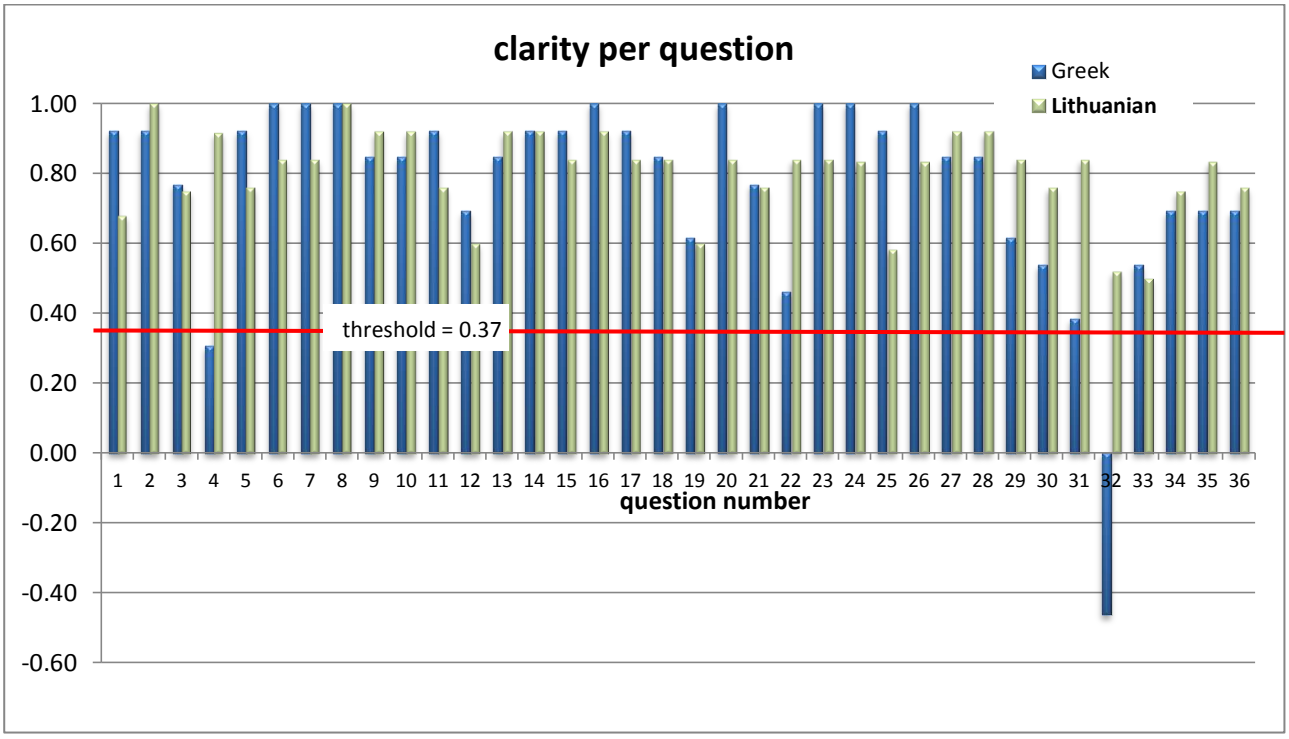


Figure 16. CVRs for clarity per question for patient questionnaire

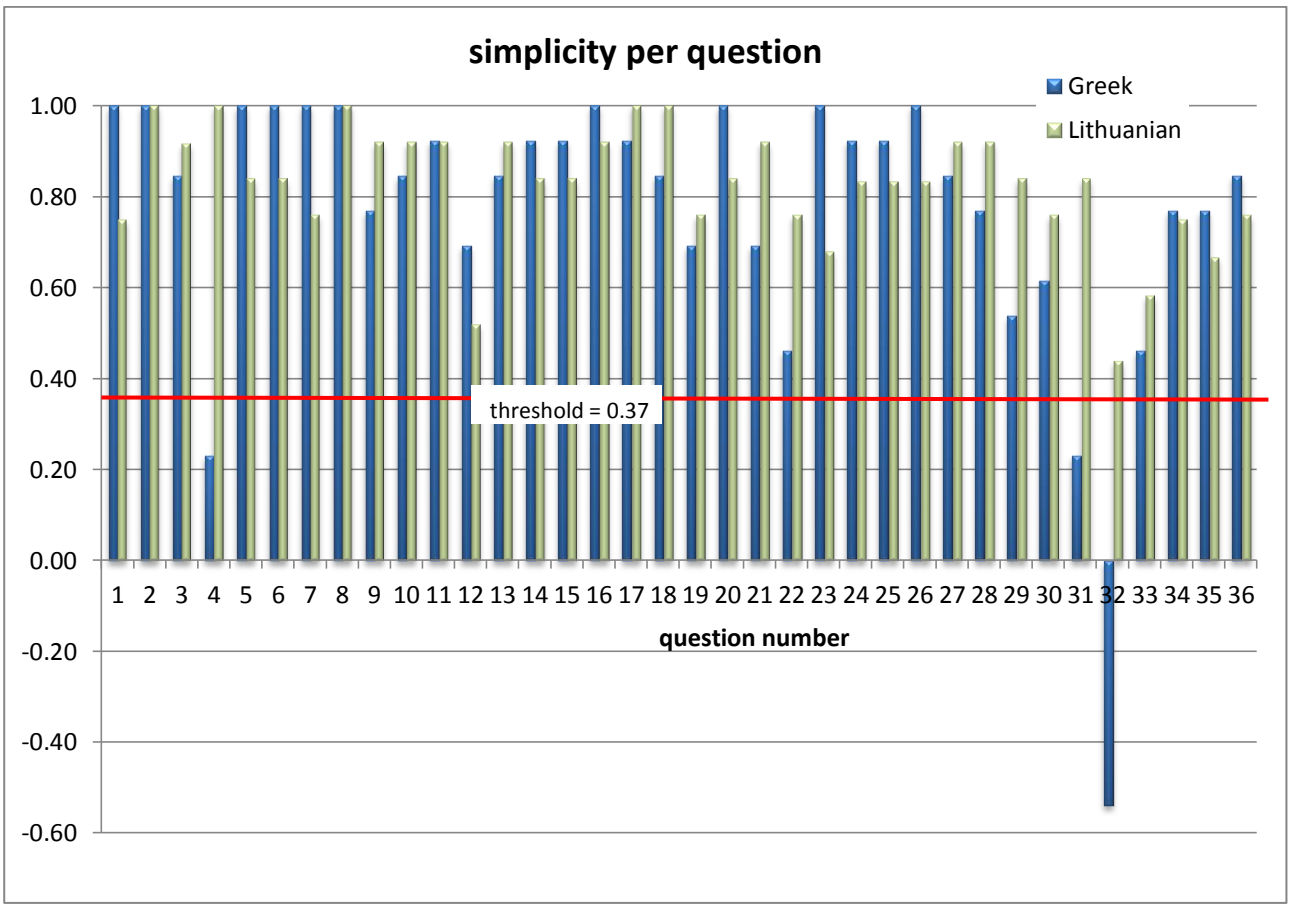


Figure 17. CVRs for clarity per question for patient questionnaire

Overall, most questions were rated above the threshold for all 3 qualities. Any exceptions of poor rating were recorded and appropriate actions were taken as presented in Table 15.

Table 15. Poorly rated questions and actions taken

Question	Rating	Actions taken
I am aware of other illnesses that may occur due to inefficient management of my current health condition	Rated just below the threshold for all 3 qualities only in the Greek	The text was rephrased in the Greek version – no changes in the Lithuanian or English version
I would be interested in a specialised internet platform where all the vital information for my condition could be gathered and accessed.	Rated below the threshold for clarity only in the Greek questionnaire	The text was rephrased.(the term “internet platform” was substituted with a more informal term “web page”)
I am willing to monitor myself and record data on my activities (e.g. weight, diet, etc.) when this is recommended to me by health care providers	Rated very poorly in all 3 qualities in both Greek and Lithuanian versions	Deleted from the final questionnaire
All questions in group “technology and disease management” apart from the one above	Rated below the threshold in relevance only in the Lithuanian questionnaire	No actions taken. This was due to the fact that in this pilot the monitoring aspect of CARRE was not efficiently explained prior to validation

Thus, the final questionnaire retained 35 of the initial questions, with 2 of them improved in terms of phrasing. In addition to these questions a section on personal information was added, including questions on age, gender, country of residence, overview of health condition and access to internet. Thus, in the final questionnaire there are It consists of 5 sections which are:

1. Personal Information (7 questions)
2. Understanding my condition (4 questions)
3. Getting information on my condition (10 questions)
4. Empowerment or Guidance? (12 questions)
5. Technology and disease management (9 questions)

All four questions of the group on “Understanding my condition” which aim to probe patient’s perceived ability/knowledge were supplemented by additional open ended subquestions so as to have a measure of the perceived vs. real personal ability. In particular:

1. Question: I am aware of what may have caused my current condition.

   Supplement: Please list all you think that may have caused your current condition
2. Question: I know which symptoms I currently experience are due to my disease.

   Supplement: Please list all you know:
3. Question: I can recognize new symptoms that may indicate disease progression

   Supplement: Please, list which ones:
4. Question I am aware of other illnesses that may occur due to inefficient management of my current health condition.

Supplement: Please, list all you know:

1.4.4. Questionnaire Deployment

The final questionnaire was deployed primarily in the two countries of the intended CARRE pilots in their native language. Deployment was via printed questionnaires handed out to patients in hospital waiting rooms, as well as via electronic versions of the questionnaires available on-line.

The printed questionnaires were handed out to patients in hospital waiting rooms in two different hospitals:

- General Regional Hospital of Kavala, Kavala, Greece
- Vilnius University Hospital Santariskių Klinikos, Vilnius, Lithuania

Before administering the questionnaires, in both hospitals the appropriate ethics approvals were obtained: Kavala: prot. no: 56/7.4.2014, Vilnius: prot. no 14VR-3165/2014-03-18.

The questionnaires were also made available on-line. The on-line versions were developed in the GoogleDocs web platform and are available at:

- Greek online version : https://docs.google.com/forms/d/1tf1vMukKlq46YZ6Oux_Weq5BgsI2ltStMZsI42Umb14/viewform
- Lithuanian online version : https://docs.google.com/forms/d/1ZXPAlWC3ktbvuP4IVmdnyRLE1kLOXSY9U093IsAuGMU/viewform
- English online version : https://docs.google.com/forms/d/1NG9KV6niyqG1B08cQQpEMGu9iqDi0C5CLKVIxupOR00/viewform

The on-line versions of the survey were advertised via the CARRE project homepage and via the twitter and facebook project pages.

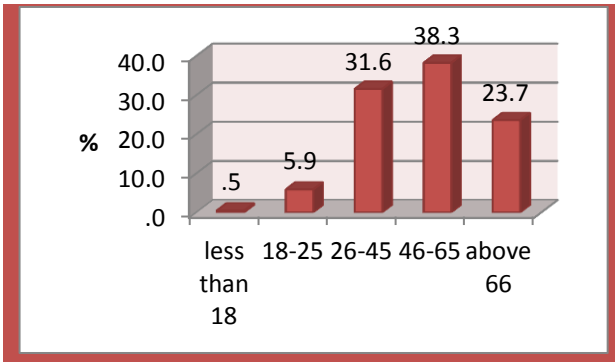
2. Survey Results and Analysis

There were overall 389 responses by 24 April 2014. The results of these 389 first responses were analyzed and are presented in this document. It should be noted that the survey will keep running for a few more months and the accumulative results will be reported as an update to this Annex.

Basic analysis was performed by Microsoft Excel software and more advanced analysis and correlations with the IBM SPSS software. The remaining of this section presents the detailed responses for each question individually. The following section presents more advanced analysis of the results.

Each question was assessed first for overall performance and the results are presented below (as %).

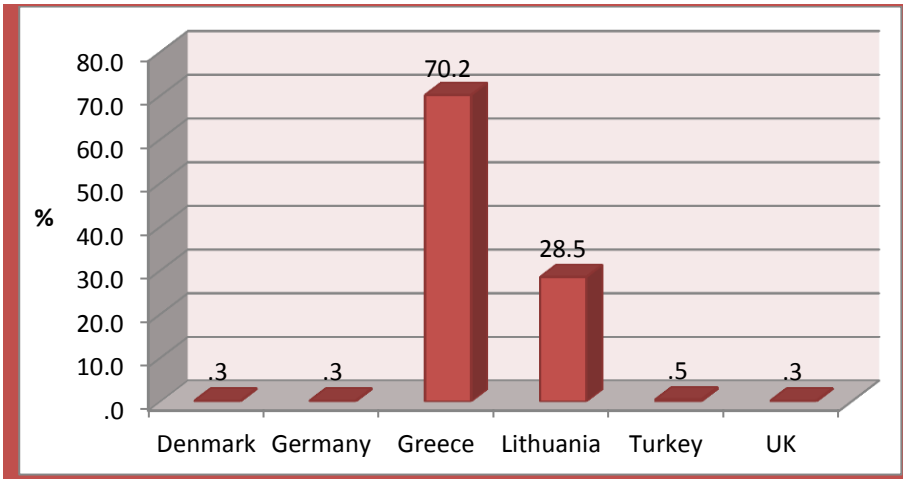
2.1. Age



		Frequency	Percent	Cumulative Percent
Age	less than 18	2	.5	.5
	18-25	23	5.9	6.4
	26-45	123	31.6	38.0
	46-65	149	38.3	76.3
	Above 66	92	23.7	100.0
	Total	389	100.0	

The majority of respondents (62) were above 46 years of age.

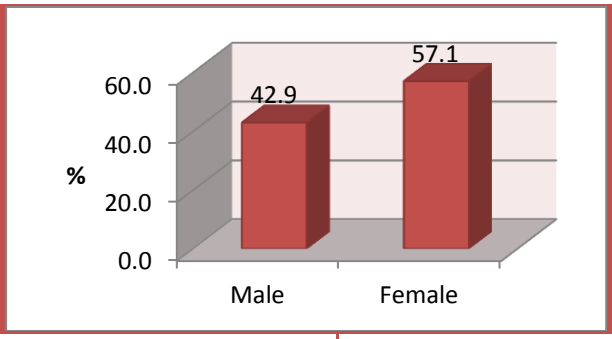
2.2. Country of Residence



		Frequency	Percent	Cumulative Percent
Country of Residence	Denmark	1	.3	.3
	Germany	1	.3	.5
	Greece	273	70.2	70.7
	Lithuania	111	28.5	99.2
	Turkey	2	.5	99.7
	UK	1	.3	100.0
	Total	389	100.0	

As expected by survey desing, the largest proportion of respondents come from the two countries of CARRE pilot demonstrations, namely Greece (70.2%) and Lithuania (28.5%).

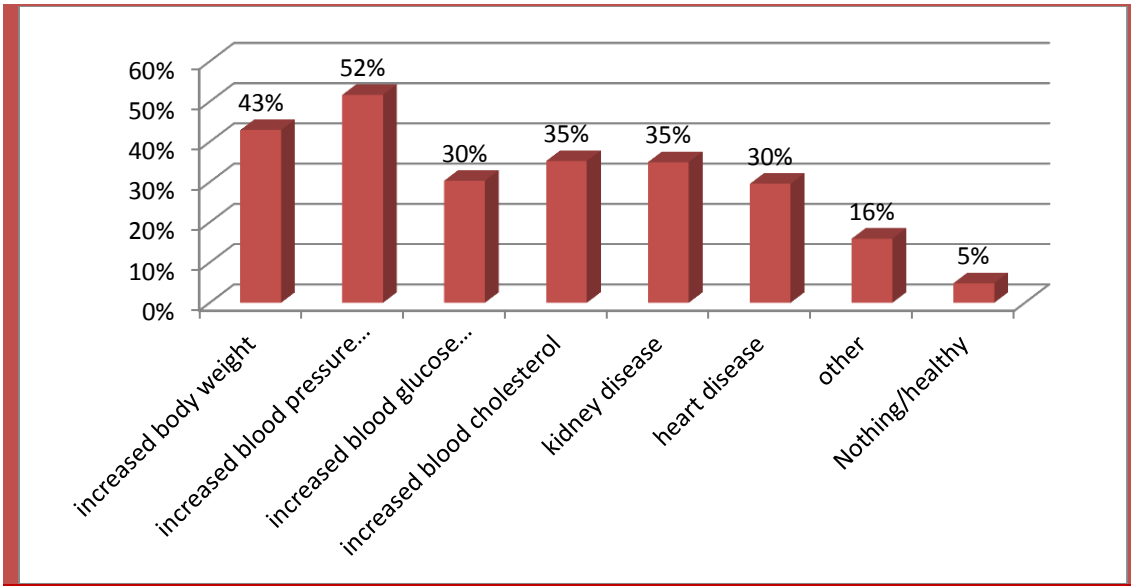
2.3. Gender



		Frequency	Percent %	Cumulative Percent
Gender	Male	167	42.9	42.9
	Female	222	57.1	100.0
	Total	389	100.0	

Almost the same percentage of men and women answered the questions in the questionnaire and indicates the sample is representative of the general population.

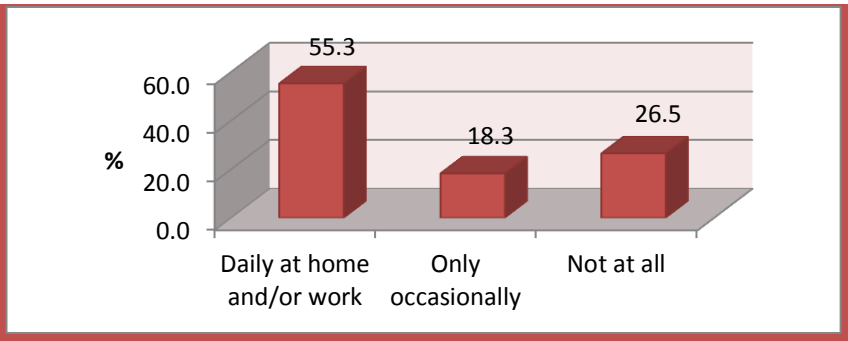
2.4. Health conditions currently being monitored or treated for



increased body weight	167	43%
increased blood pressure (hypertension)	201	52%
increased blood glucose (diabetes)	118	30%
increased blood cholesterol	137	35%
kidney disease	136	35%
heart disease	115	30%
other	62	16%
Nothing (i.e. healthy)	19	5%

The increased blood pressure (hypertension) and increased body weight were the most common conditions present in the survey participants. Also, a good number of respondents reported all other major conditions related to cardiorenal disease, thus ensuring a good representation of all patient groups in the survey.

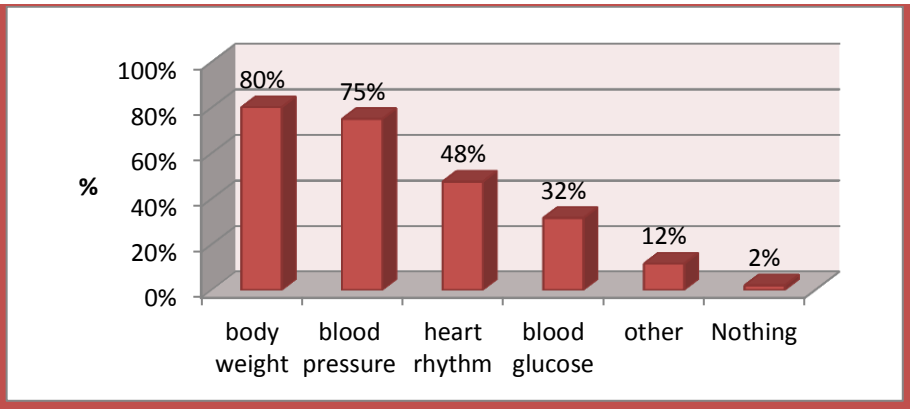
2.5. Internet access



		Frequency	Percent	Cumulative Percent
Do you have internet access?	Daily at home and/or work	215	55.3	55.3
	Only occasionally	71	18.3	73.5
	Not at all	103	26.5	100.0
	Total	389	100.0	

The majority of responders have internet access. However there is a considerable proportion (26.5%) who do not have internet access. Futher analysis is required t to show if this population has a strong correlation with age or disease stage.

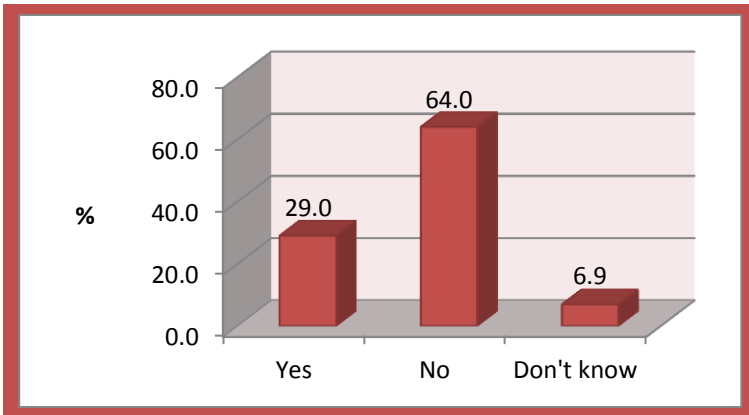
2.6. Biomarkers currently monitored



Which of the following have you monitored		
body weight	312	80%
blood pressure	292	75%
heart rhythm	185	48%
blood glucose	123	32%
other	45	12%
Nothing	8	2%

Body weight and blood pressure are the most commonly monitored biomarkers followed by heart thythm and blood glucose.

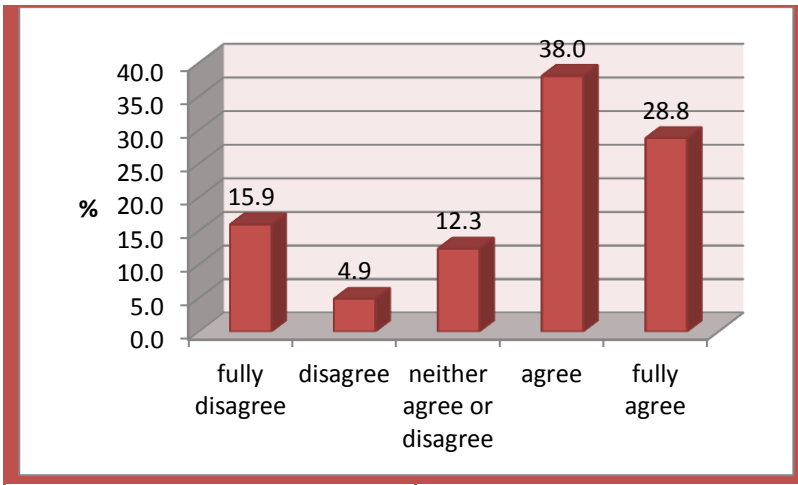
2.7. Use of telemonitoring



		Frequency	Percent	Cumulative Percent
Have you ever used telemonitoring devices?	Yes	113	29.0	29.0
	No	249	64.0	93.1
	Don't know	27	6.9	100.0
	Total	389	100.0	

The majority of respondents (64%) have not used telemonitoring services at all, while a 29% have used telemonitoring before.

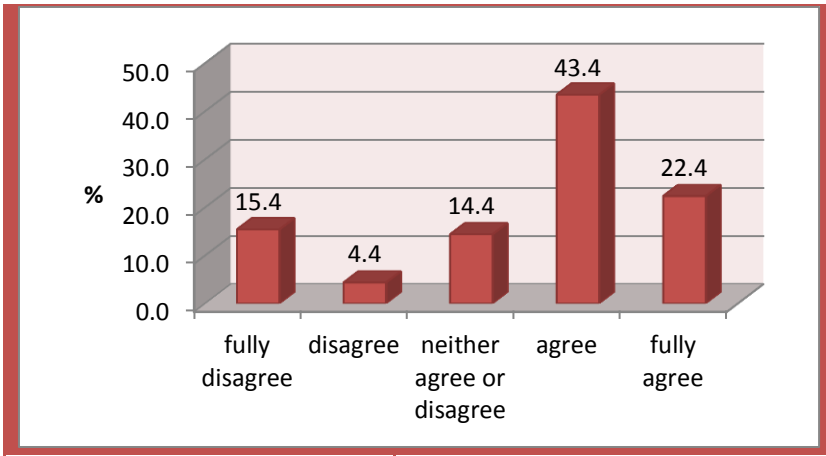
2.8. What may have caused my current condition



		Frequency	Percent	Cumulative Percent
I am aware of what may have caused my current condition.	fully disagree	62	15.9	15.9
	disagree	19	4.9	20.8
	neither agree or disagree	48	12.3	33.2
	agree	148	38.0	71.2
	fully agree	112	28.8	100.0
	Total	389	100.0	

The majority of respondents (66.8%) report that they are aware of what caused their condition. Further analysis in the subsequent section will concentrate on how this agrees with what they state as causes of their condition (as rated by a medical expert).

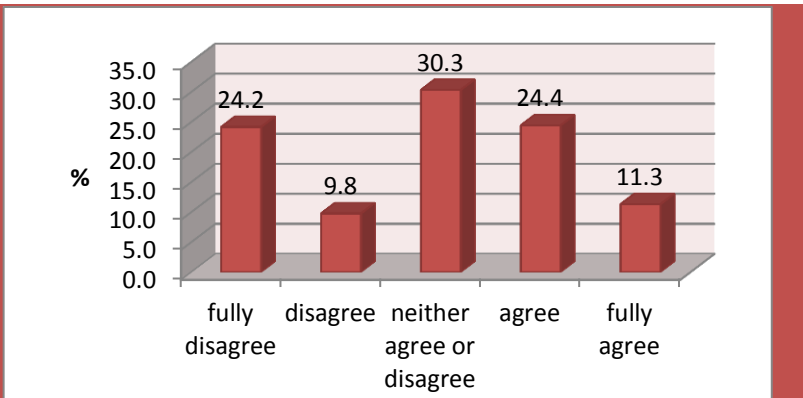
2.9. I know which symptoms I currently experience are due to my disease.



		Frequency	Percent	Cumulative Percent
I know which symptoms I currently experience are due to my disease.	fully disagree	60	15.4	15.4
	disagree	17	4.4	19.8
	neither agree or disagree	56	14.4	34.2
	agree	169	43.4	77.6
	fully agree	87	22.4	100.0
	Total	389	100.0	

The majority of respondents (65.8%) report that can identify which symptoms they currently experience are due to their disease. Further analysis in the subsequent section will concentrate on how this agrees with what they state as currently symptoms related to their disease (as rated by a medical expert).

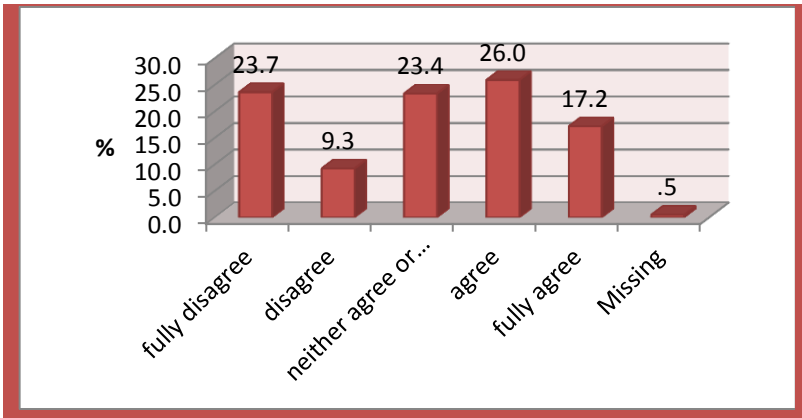
2.10. I can recognize new symptoms that may indicate disease progression.



		Frequency	Percent	Cumulative Percent
I can recognize new symptoms that may indicate disease progression.	fully disagree	94	24.2	24.2
	disagree	38	9.8	33.9
	neither agree or disagree	118	30.3	64.3
	agree	95	24.4	88.7
	fully agree	44	11.3	100.0
	Total	389	100.0	

It is interesting to note that contrary to the previous two questions where the majority of respondents showed confidence in their knowledge of their current condition, here only one third show confindence in identifying possible disease progression. Another 1/3 are not able to recognize symptoms that indicate disease progression, and the last 1/3 are unsure.

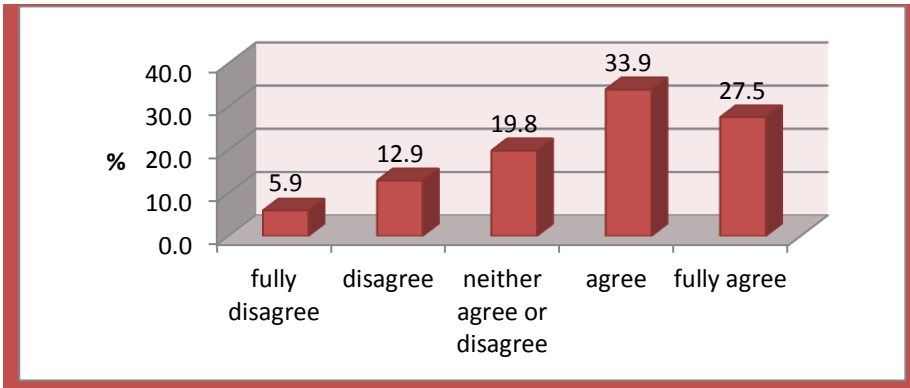
2.11. I am aware of other disease that may occur due to current condition



		Frequency	Percent	Cumulative Percent
I am aware of other illnesses that may occur due to inefficient management of my current health condition.	fully disagree	92	23.7	23.8
	disagree	36	9.3	33.1
	neither agree or disagree	91	23.4	56.6
	agree	101	26.0	82.7
	fully agree	67	17.2	100.0
	Missing	2	.5	
	Total	389	100.0	

A good number of respondents (43.2%) are aware of other illnesses that may occur due to inefficient management of their current health condition, while 1/3 report that they have no such knowledge.

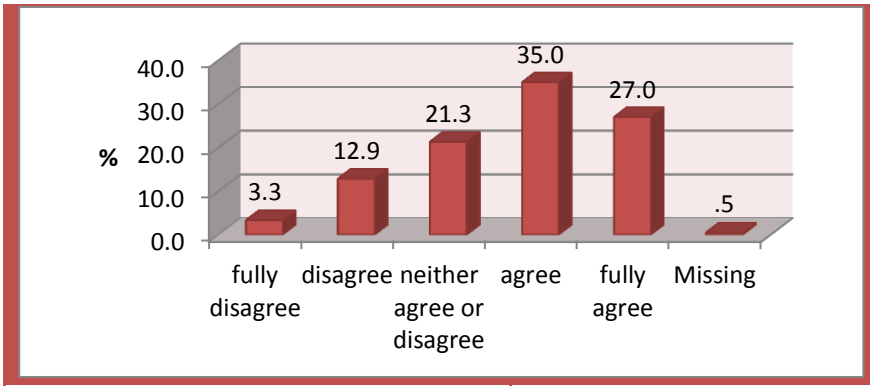
2.12. I have all information I need to understand my current condition.



		Frequency	Percent	Cumulative Percent
I have all information I need to understand possible disease progression.	fully disagree	23	5.9	5.9
	disagree	50	12.9	18.8
	neither agree or disagree	77	19.8	38.6
	agree	132	33.9	72.5
	fully agree	107	27.5	100.0
	Total	389	100.0	

The majoriy of respondents (61.4%) report that they have adequate information in order to understand possible disease progression.

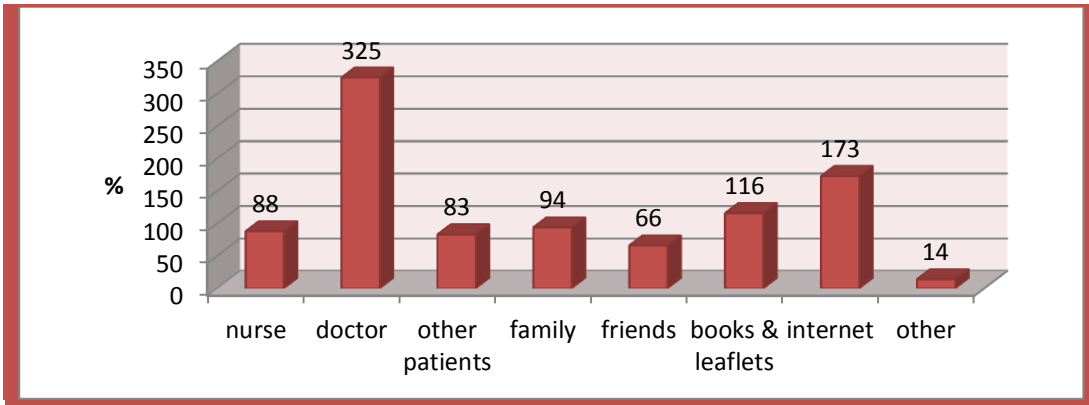
2.13. I have all the information I need in order to manage my disease in everyday life.



		Frequency	Percent	Cumulative Percent
I have all the information I need in order to manage my disease in everyday life.	fully disagree	13	3.3	3.4
	disagree	50	12.9	16.3
	neither agree or disagree	83	21.3	37.7
	agree	136	35.0	72.9
	fully agree	105	27.0	100.0
	Missing	2	.5	
	Total	389	100.0	

The majority of respondents fell that they have all information they need to manage their condition. Only 16.6% feel that they do not have such information.

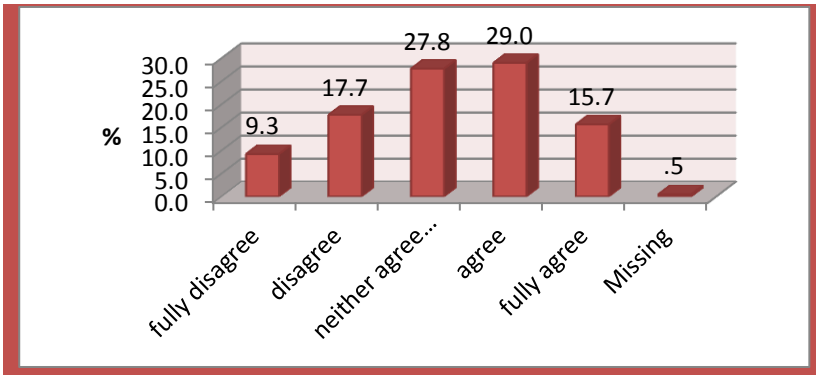
2.14. Tell us who provides this information



		frequency	percentage
Tell us who provides this information (check only the major sources of information)	nurse	88	22.6
	doctor	325	89.9
	other patients	83	21.3
	family	94	24.1
	friends	66	16.9
	books & leaflets	116	29.8
	internet	173	44.5
	other	14	3.6

The striking majority of 89.9% get information from their doctor; 2nd most used source of information is the internet, followed by books and leaflets. Family, other patients & friends are consulted at about 24-16%.

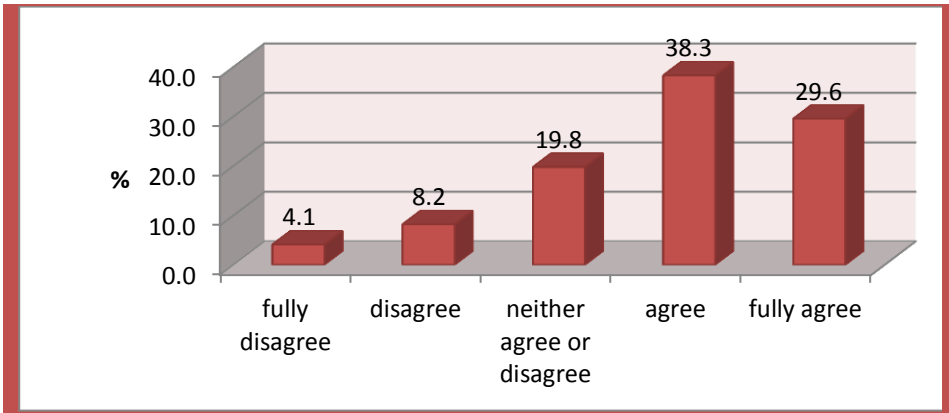
2.15. I have all information I need to understand possible disease progression.



		Frequency	Percent	Cumulative Percent
I have all information I need to understand possible disease progression.	fully disagree	36	9.3	9.3
	disagree	69	17.7	27.1
	neither agree or disagree	108	27.8	55.0
	agree	113	29.0	84.2
	fully agree	61	15.7	100.0
	Missing	2	.5	
	Total	389	100.0	

44.7% of respondents have all information they need to understand possible disease progression, 27.8% neither agree or disagree and 27% they haven't all this information. In this question were 2 missing values

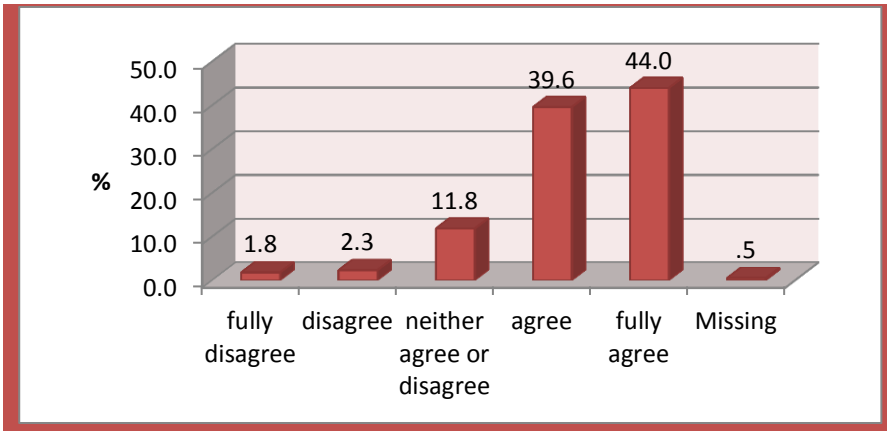
2.16. My physician provides me with information on how to reduce the risk.



		Frequency	Percent	Cumulative Percent
My physician/nurse provides me with enough information on how to reduce the risk of future complications.	fully disagree	16	4.1	4.1
	disagree	32	8.2	12.3
	neither agree or disagree	77	19.8	32.1
	agree	149	38.3	70.4
	fully agree	115	29.6	100.0
	Total	389	100.0	

67.9% responded that their healthc care professional provides necessary information on how to reduce risk of future complications.

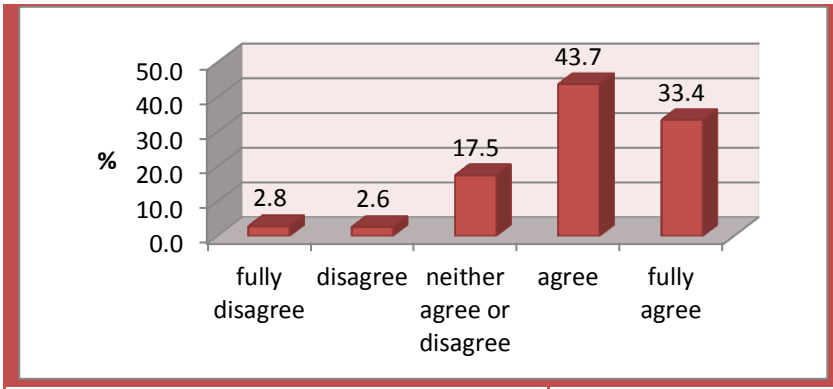
2.17. I believe that better knowledge of my disease would be beneficial.



		Frequency	Percent	Cumulative Percent
I believe that better knowledge of my disease would be very beneficial for better management of my condition.	fully disagree	7	1.8	1.8
	disagree	9	2.3	4.1
	neither agree or disagree	46	11.8	16.0
	agree	154	39.6	55.8
	fully agree	171	44.0	100.0
	Missing	2	.5	
	Total	389	100.0	

A high majority of 83.6% believe that better knowledge of their condition would be beneficial.

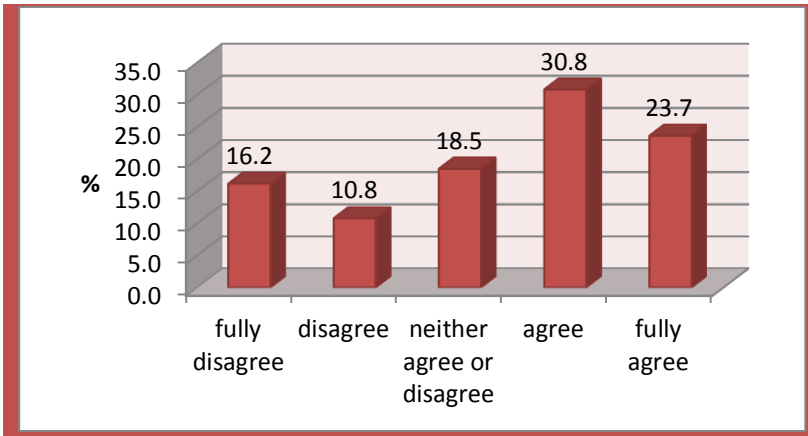
2.18. I am able to manage information about possible progression of my disease.



		Frequency	Percent	Cumulative Percent
I am able to manage information about possible progression of my disease.	fully disagree	11	2.8	2.8
	disagree	10	2.6	5.4
	neither agree or disagree	68	17.5	22.9
	agree	170	43.7	66.6
	fully agree	130	33.4	100.0
	Total	389	100.0	

Most of respondents (77.1%) feel able to manage information about progression of their disease

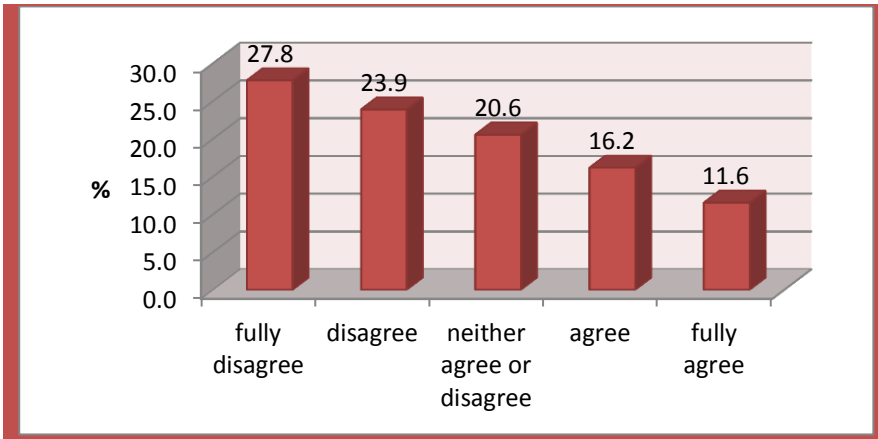
2.19. Any new information about my disease makes me feel anxious.



		Frequency	Percent	Cumulative Percent
Any new information about my disease makes me feel anxious.	fully disagree	63	16.2	16.2
	disagree	42	10.8	27.0
	neither agree or disagree	72	18.5	45.5
	agree	120	30.8	76.3
	fully agree	92	23.7	100.0
	Total	389	100.0	

More thant half of the respondents (54.5%) feel anxious about any new information about their disease, while 27% do not feel anxious about such information.

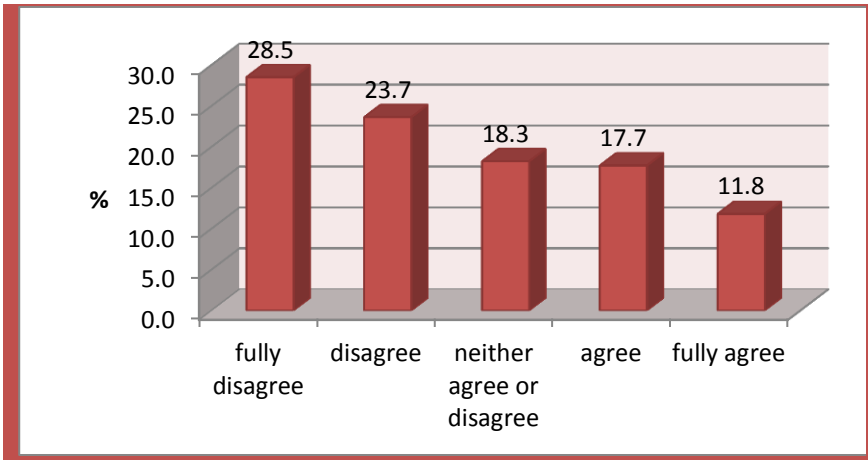
2.20. Any new information about my disease confuses me.



		Frequency	Percent	Cumulative Percent
Any new information about my disease confuses me.	fully disagree	108	27.8	27.8
	disagree	93	23.9	51.7
	neither agree or disagree	80	20.6	72.2
	agree	63	16.2	88.4
	fully agree	45	11.6	100.0
	Total	389	100.0	

51.7% do not feel confused by new information about their disease, while 27.8% feel confused.

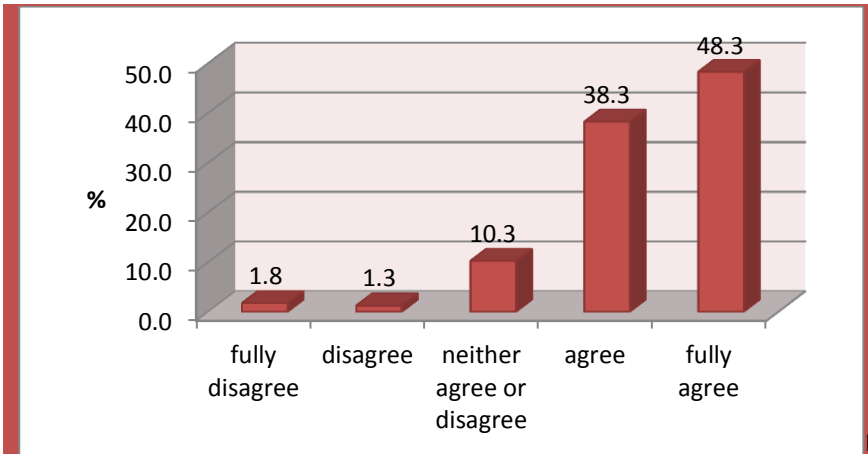
2.21. It is difficult for me to understand all information provided.



		Freqency	Percent	Cumulative Percent
It is difficult for me to understand all information provided.	fully disagree	111	28.5	28.5
	disagree	92	23.7	52.2
	neither agree or disagree	71	18.3	70.4
	agree	69	17.7	88.2
	fully agree	46	11.8	100.0
	Total	389	100.0	

52% find it easy to understand information on their condition, while 29.5% find it difficult to understand it.

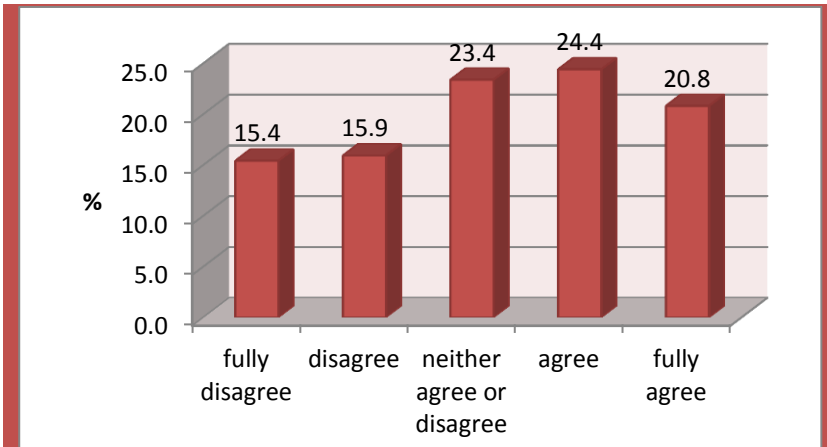
2.22. I want to receive new information about my condition regularly.



		Frequency	Percent	Cumulative Percent
I want to receive new information about my condition regularly.	fully disagree	7	1.8	1.8
	disagree	5	1.3	3.1
	neither agree or disagree	40	10.3	13.4
	agree	149	38.3	51.7
	fully agree	188	48.3	100.0
	Total	389	100.0	

Most of respondents (86.6%) want to receive new information about their condition regularly.

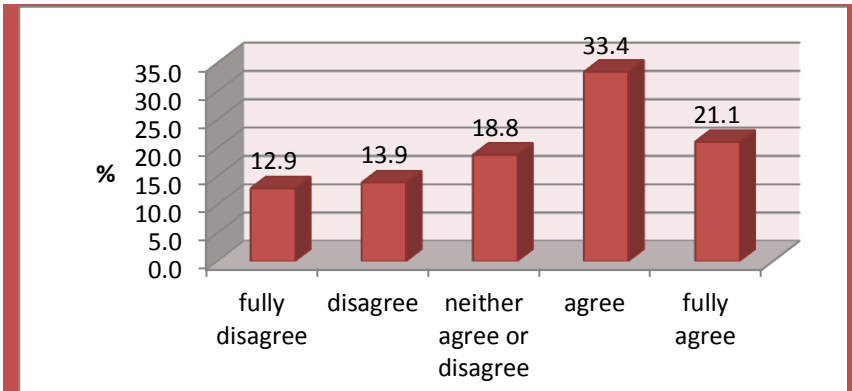
2.23. I prefer to search for medical information on my own.



		Frequency	Percent	Cumulative Percent
I prefer to search for medical information on my own.	fully disagree	60	15.4	15.4
	disagree	62	15.9	31.4
	neither agree or disagree	91	23.4	54.8
	agree	95	24.4	79.2
	fully agree	81	20.8	100.0
	Total	389	100.0	

45.2% of respondents prefer to search for medical information on their own, 31.3% disagree and 23.4% neither agree or disagree

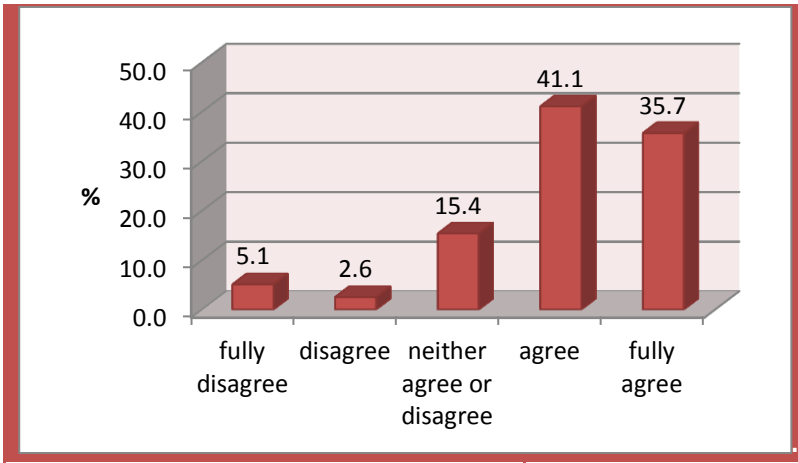
2.24. I usually discuss my condition with other fellow patients.



		Frequency	Percent	Cumulative Percent
I usually discuss my condition with other fellow patients.	fully disagree	50	12.9	12.9
	disagree	54	13.9	26.7
	neither agree or disagree	73	18.8	45.5
	agree	130	33.4	78.9
	fully agree	82	21.1	100.0
	Total	389	100.0	

54.4 % usually discuss their condition with other fellow patients.

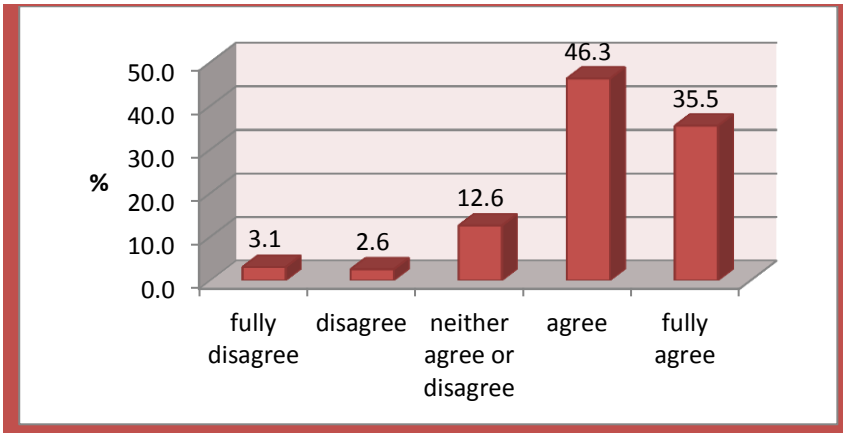
2.25. I want more information to better understand condition progression.



		Frequency	Percent	Cumulative Percent
I want more information to better understand my condition and its possible progression.	fully disagree	20	5.1	5.1
	disagree	10	2.6	7.7
	neither agree or disagree	60	15.4	23.1
	agree	160	41.1	64.3
	fully agree	139	35.7	100.0
	Total	389	100.0	

76.8% of respondents want more information to better understand their condition and its possible progression

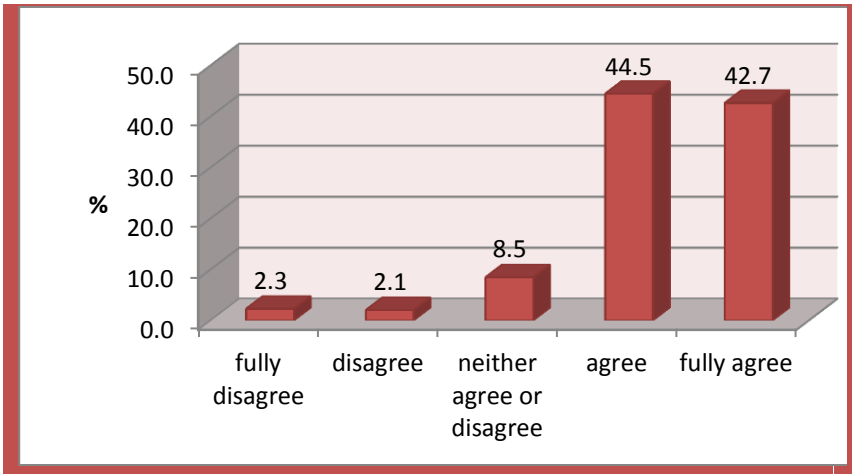
2.26. I want more information to better manage my condition.



		Frequency	Percent	Cumulative Percent
I want more information to better manage my condition.	fully disagree	12	3.1	3.1
	disagree	10	2.6	5.7
	neither agree or disagree	49	12.6	18.3
	agree	180	46.3	64.5
	fully agree	138	35.5	100.0
	Total	389	100.0	

Most of respondents (81.8%) want more information to better manage their condition

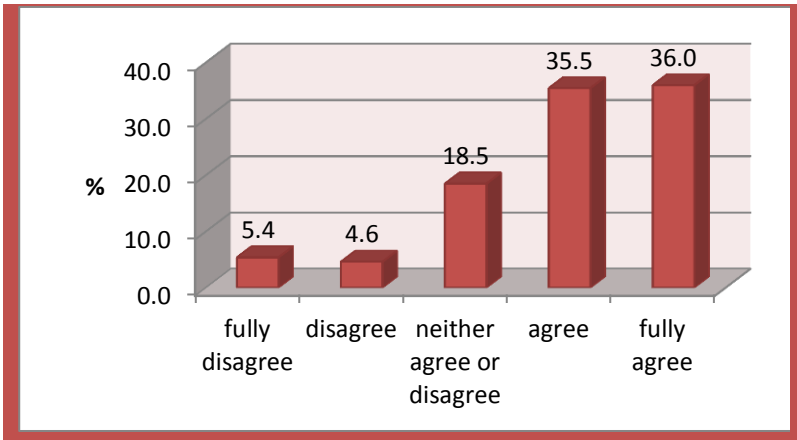
2.27. I would like to know possible alternative ways of managing my condition.



		Frequency	Percent	Cumulative Percent
I would like to know possible alternative ways of managing my condition.	fully disagree	9	2.3	2.3
	disagree	8	2.1	4.4
	neither agree or disagree	33	8.5	12.9
	agree	173	44.5	57.3
	fully agree	166	42.7	100.0
	Total	389	100.0	

87.2% would like to know possible alternative ways of managing their condition, 8.5% neither agree or disagree and 4.4% wouldn't

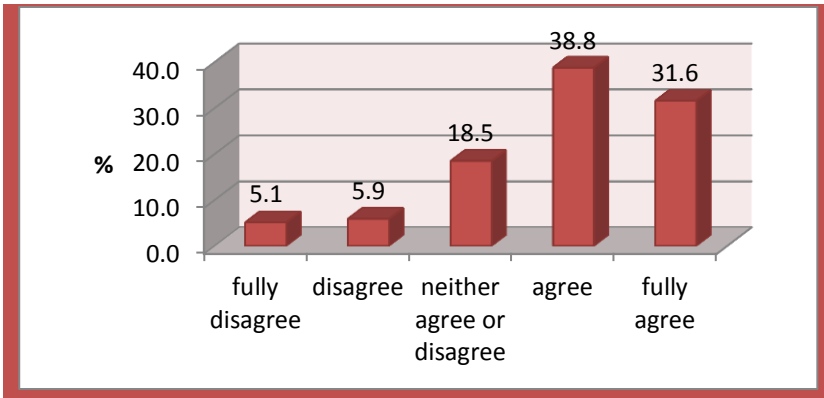
2.28. I feel that I need more information in order to be able to commit fully to therapy.



		Frequency	Percent	Cumulative Percent
I feel that I need more information in order to be able to commit fully to therapy.	fully disagree	21	5.4	5.4
	disagree	18	4.6	10.0
	neither agree or disagree	72	18.5	28.5
	agree	138	35.5	64.0
	fully agree	140	36.0	100.0
	Total	389	100.0	

Most of respondents 71.5% feel that they need more information in order to be able to commit fully to therapy

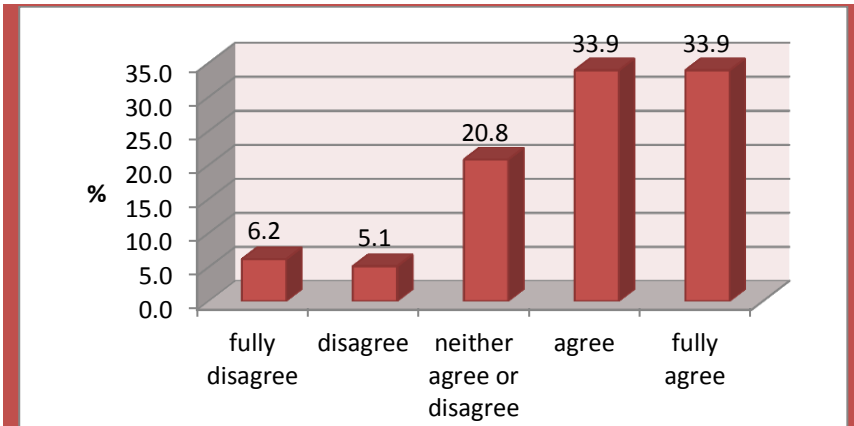
2.29. I need more information to be able to commit to required lifestyle changes.



		Frequency	Percent	Cumulative Percent
I feel that I need more information in order to be able to commit fully to required lifestyle changes.	fully disagree	20	5.1	5.1
	disagree	23	5.9	11.1
	neither agree or disagree	72	18.5	29.6
	agree	151	38.8	68.4
	fully agree	123	31.6	100.0
	Total	389	100.0	

70.4% feel that they need more information in order to be able to commit fully to required lifestyle changes.

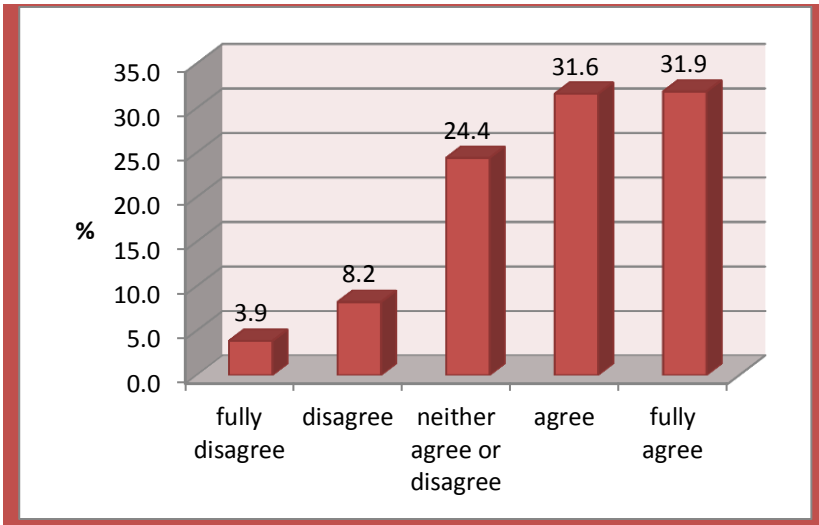
2.30. I would prefer to make the final decision, when there are alternative options.



		Frequency	Percent	Cumulative Percent
I would prefer to make the final decision on the management of my condition, when there are more than one alternative option.	fully disagree	24	6.2	6.2
	disagree	20	5.1	11.3
	neither agree or disagree	81	20.8	32.1
	agree	132	33.9	66.1
	fully agree	132	33.9	100.0
	Total	389	100.0	

67.8% of respondents would prefer to make the final decision on the management of their condition, when there are more than one alternative option

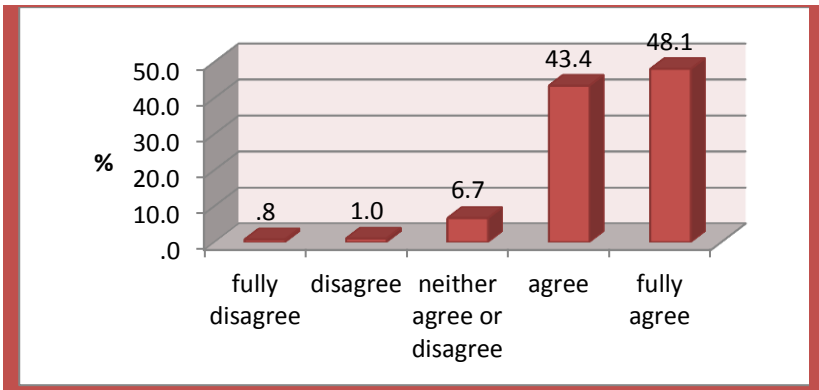
2.31. I prefer my doctor to decide the best treatment option for me.



		Frequency	Percent	Cumulative Percent
I prefer my doctor to decide the best treatment option for me.	fully disagree	15	3.9	3.9
	disagree	32	8.2	12.1
	neither agree or disagree	95	24.4	36.5
	agree	123	31.6	68.1
	fully agree	124	31.9	100.0
	Total	389	100.0	

63.5% prefer their doctor to decide the best treatment option for them

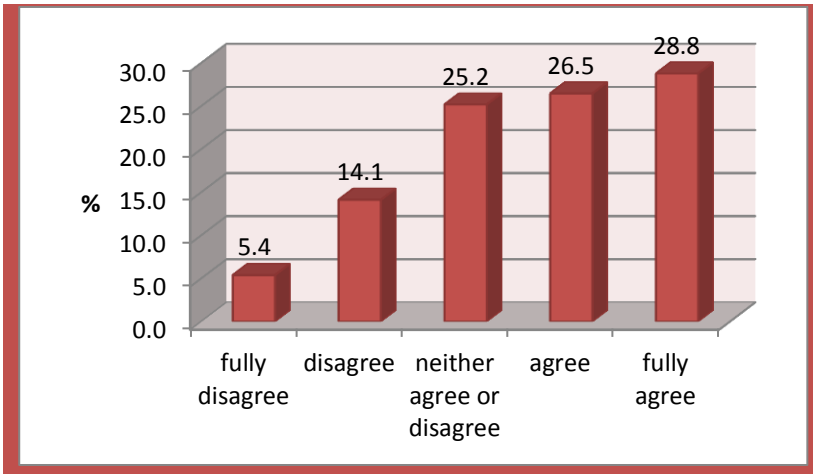
2.32. I would like to discuss treatment, implications and progression with my doctor.



		Frequency	Percent	Cumulative Percent
I would like to discuss treatment goals, potential implications and disease progression with my doctor.	fully disagree	3	.8	.8
	disagree	4	1.0	1.8
	neither agree or disagree	26	6.7	8.5
	agree	169	43.4	51.9
	fully agree	187	48.1	100.0
	Total	389	100.0	

Most of respondents (91.5%) would like to discuss treatment goals, potential implications and disease progression with their doctor

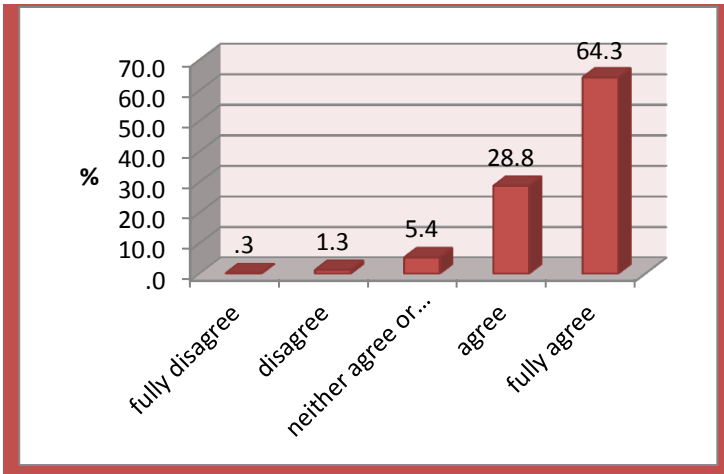
2.33. I prefer to rely solely on doctor's knowledge and guidance.



		Frequency	Percent	Cumulative Percent
I prefer to rely solely on doctor's knowledge and guidance.	fully disagree	21	5.4	5.4
	disagree	55	14.1	19.5
	neither agree or disagree	98	25.2	44.7
	agree	103	26.5	71.2
	fully agree	112	28.8	100.0
	Total	389	100.0	

About half of respondents (55.3%) prefer to rely solely on doctor's knowledge and guidance

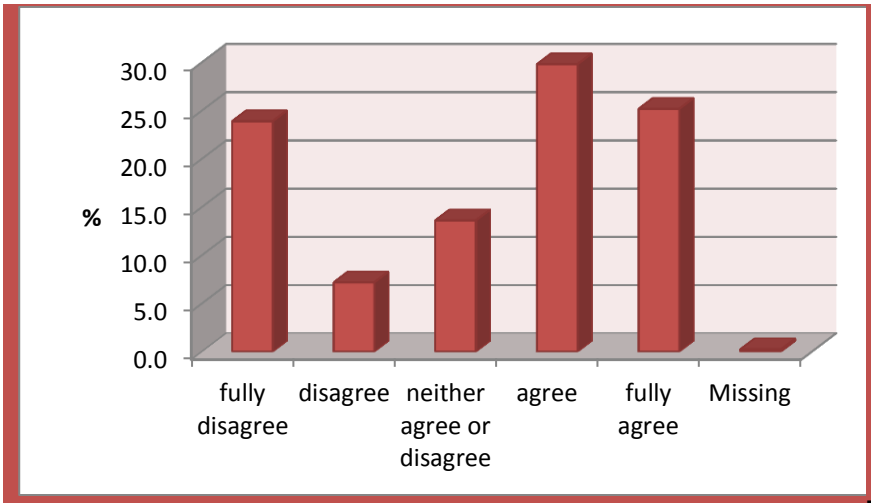
2.34. I prefer to be fully informed on my condition.



		Frequency	Percent	Cumulative Percent
I prefer to be fully informed on my condition.	fully disagree	1	.3	.3
	disagree	5	1.3	1.5
	neither agree or disagree	21	5.4	6.9
	agree	112	28.8	35.7
	fully agree	250	64.3	100.0
	Total	389	100.0	

Most of respondents (93.1%) prefer to be fully informed on my their condition

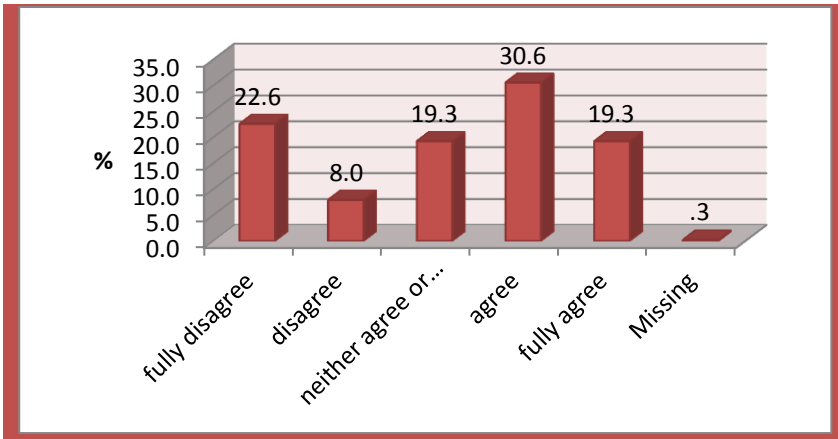
2.35. I use the internet as a source of medical information



		Frequency	Percent	Cumulative Percent
I use the internet as a source of medical information.	fully disagree	93	23.9	24.0
	disagree	28	7.2	31.2
	neither agree or disagree	53	13.6	44.8
	agree	116	29.8	74.7
	fully agree	98	25.2	100.0
	Missing	1	.3	
	Total	389	100.0	

55% of respondents use the internet as a source of medical information

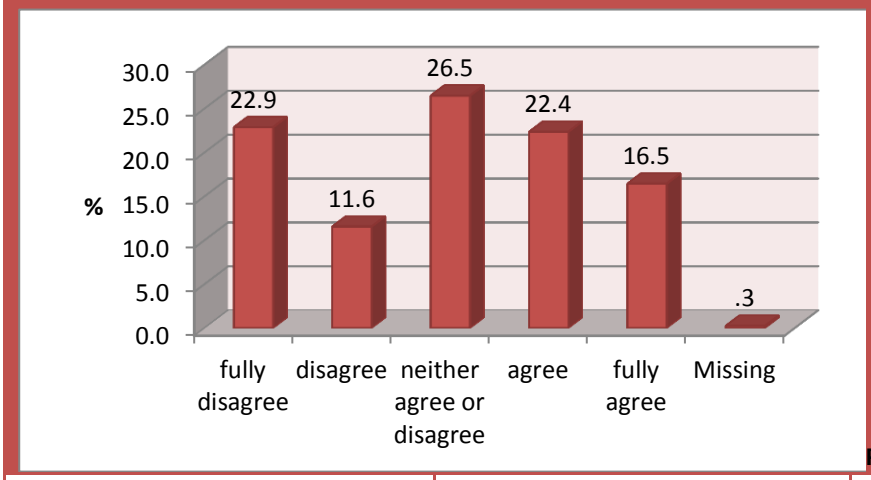
2.36. I understand the health information that I find on the internet



		Frequency	Percent	Cumulative Percent
I understand the health information that I find on the internet.	fully disagree	88	22.6	22.7
	disagree	31	8.0	30.7
	neither agree or disagree	75	19.3	50.0
	agree	119	30.6	80.7
	fully agree	75	19.3	100.0
	Missing	1	.3	
	Total	389	100.0	

Half of respondents (49.9%) understand the health information that they find on the internet

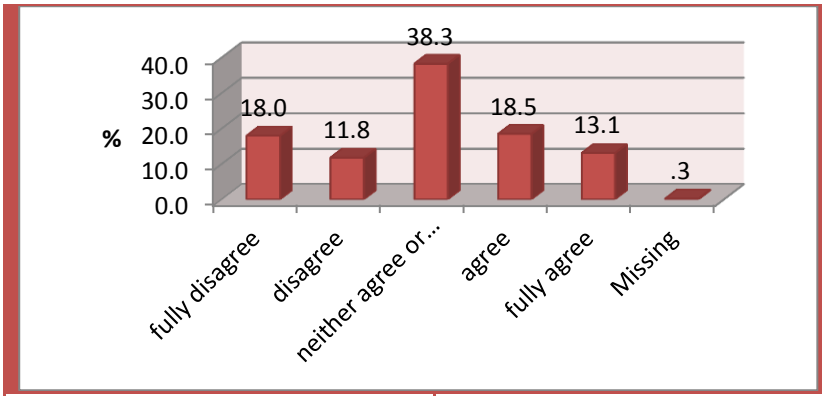
2.37. I can recognize which internet source provides accurate medical information.



		Frequency	Percent	Cumulative Percent
I feel able to recognize which internet source provides accurate medical information.	fully disagree	89	22.9	22.9
	disagree	45	11.6	34.5
	neither agree or disagree	103	26.5	61.1
	agree	87	22.4	83.5
	fully agree	64	16.5	100.0
	Missing	1	.3	
	Total	389	100.0	

38.9% feel able to recognize which internet source provides accurate medical information

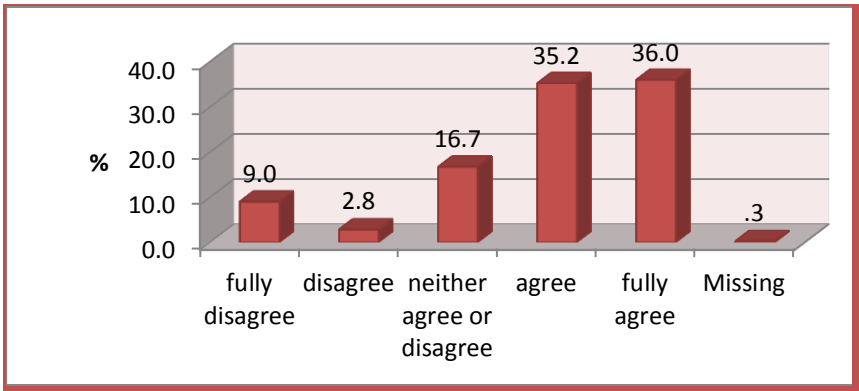
2.38. I feel that information provided on web pages is reliable and trustworthy.



		Frequency	Percent	Cumulative Percent
I feel that information provided on web pages is reliable and trustworthy.	fully disagree	70	18.0	18.0
	disagree	46	11.8	29.9
	neither agree or disagree	149	38.3	68.3
	agree	72	18.5	86.9
	fully agree	51	13.1	100.0
	Missing	1	.3	
	Total	389	100.0	

38.3% of respondents are unable to decide on the reliability of infomartion on the internet

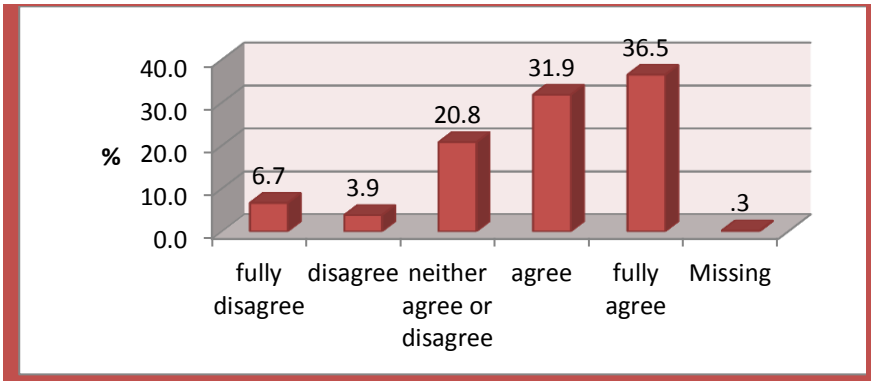
2.39. I would like a specialised portal to gather information on my condition



		Frequency	Percent	Cumulative Percent
I would be interested in a specialised web pages where all the vital information for my condition could be gathered and accessed.	fully disagree	35	9.0	9.0
	disagree	11	2.8	11.9
	neither agree or disagree	65	16.7	28.6
	agree	137	35.2	63.9
	fully agree	140	36.0	100.0
	Missing	1	.3	
	Total	389	100.0	

Most of respondents (71.2%) would be interested in a specialised web pages where all the vital information for my condition could be gathered and accessed

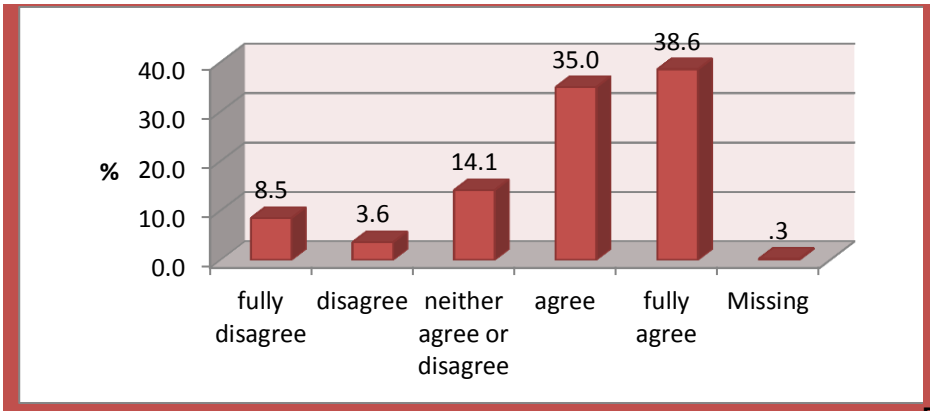
2.40. I am willing to monitor myself and record data on my activities.



		Frequency	Percent	Cumulative Percent
I am willing to monitor myself and record data on my activities (e.g. weight, diet, etc.) in order to manage my condition more efficiently.	fully disagree	26	6.7	6.7
	disagree	15	3.9	10.6
	neither agree or disagree	81	20.8	31.4
	agree	124	31.9	63.4
	fully agree	142	36.5	100.0
	Missing	1	.3	
	Total	389	100.0	

68.4% are willing to monitor themselves and record data on their activities (e.g. weight, diet, etc.) in order to manage their condition more efficiently

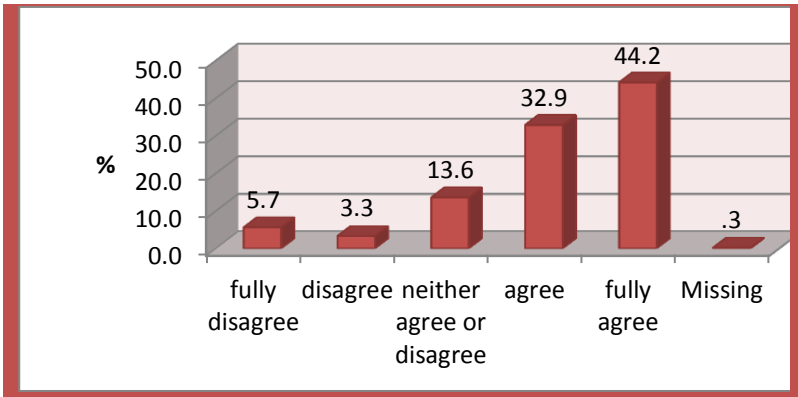
2.41. I would be willing to use applications for monitoring and planning.



		Frequency	Percent	Cumulative Percent
I would be willing to use applications which help me monitor and manage diet & physical activity.	fully disagree	33	8.5	8.5
	disagree	14	3.6	12.1
	neither agree or disagree	55	14.1	26.3
	agree	136	35.0	61.3
	fully agree	150	38.6	100.0
	Missing	1	.3	
	Total	389	100.0	

Most of respondents (73.6%) would be willing to use applications which help them monitor and manage diet & physical activit

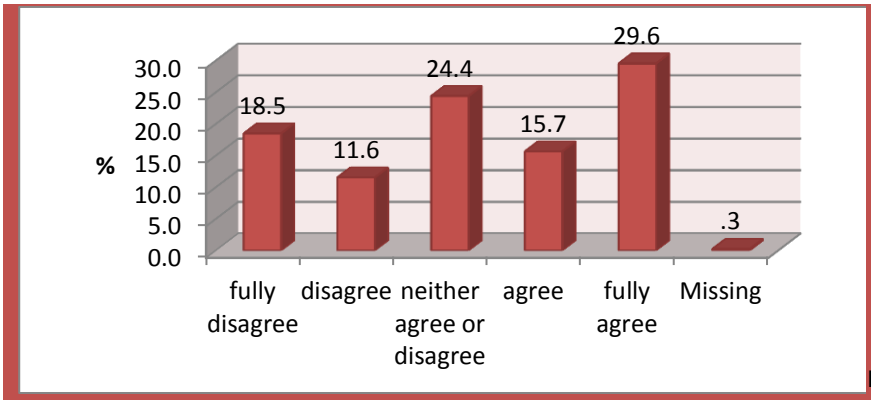
2.42. I would be willing to use an application that will provide alerts.



		Frequency	Percent	Cumulative Percent
I would be willing to use an application that will provide alerts regarding my condition and its progression.	fully disagree	22	5.7	5.7
	disagree	13	3.3	9.0
	neither agree or disagree	53	13.6	22.7
	agree	128	32.9	55.7
	fully agree	172	44.2	100.0
	Missing	1	.3	
	Total	389	100.0	

Most of respondents (77.1%) would be willing to use an application that will provide alerts regarding their condition and its progression

2.43. I feel that my condition needs closer monitoring.



		Frequency	Percent	Cumulative Percent
I feel that my condition needs closer monitoring than currently suggested by my healthcare provider.	fully disagree	72	18.5	18.6
	disagree	45	11.6	30.2
	neither agree or disagree	95	24.4	54.6
	agree	61	15.7	70.4
	fully agree	115	29.6	100.0
	Missing	1	.3	
	Total	389	100.0	

45.3% feel that their condition needs closer monitoring than currently suggested by their healthcare provider

3. Validation Sheet for Patient Questionnaire

The following questions are about how you perceive the content of the previously administered questionnaire.

This survey is conducted as part of the research project "CARRE: Personalized patient empowerment and shared decision support for cardiorenal disease and comorbidities".

The project is funded by the European Commission and aims to provide the means for patients with heart and kidney disease to take an active role in care processes, including self-care and shared decision making.

This survey aims to investigate how you perceive the previously administered CARRE Patient Survey. The results of this assessment will be used to improve the CARRE Patient Survey content.

Overall time to complete CARRE Patient Survey:	(in min)
Overall Rating of the Survey Content	
1. Relevance (with respect to the aim of survey) ☐ not relevant ☐ needs some revision ☐ relevant but some revision required ☐ very relevant	3. Simplicity in terms of phrasing ☐ not simple ☐ needs some revision ☐ simple but needs minor revision ☐ very simple
2. Clarity of content ☐ not clear ☐ needs some revision ☐ clear but needs minor revision ☐ very clear	4. Experience of completing the questionnaire ☐ not pleasant ☐ needs some improvement ☐ pleasant but needs minor improvement ☐ pleasant enough

In the following pages, for each one of the items in the CARRE Patient Survey, please state its relevance, clarity and simplicity using the following scales:

Relevance (with respect to the aim of survey)	**Clarity** of content	**Simplicity** in terms of phrasing
1 = not relevant	1 = not clear	1 = not simple
2 = needs some revision	2 = needs some revision	2 = needs some revision
3 = relevant but some revision required	3 = clear but needs minor revision	3 = simple but needs minor revision
4 = very relevant	4 = very clear	4 = very simple

Understanding my condition	relevance	clarity	simplicity
1. I am aware of what may have caused my current condition.			
2. I know which symptoms I currently experience are due to my disease.			
3. I can recognize new symptoms that may indicate disease progression.			
4. I am aware of other illnesses that may occur due to inefficient management of my current health condition.			

Getting information on my condition	relevance	clarity	simplicity
5. I have all information I need to understand my current condition.			
6. I have all the information I need in order to manage my disease in everyday life.			
7. I have all information I need to understand possible disease progression.			
8. My physician/nurse provides me with enough information on how to reduce the risk of future complications.			
9. I believe that better knowledge of my disease would be very beneficial for better management of my condition.			
10. I am able to manage information about possible progression of my disease.			
11. Any new information about my disease makes me feel anxious.			
12. Any new information about my disease confuses me.			
13. It is difficult for me to understand all information provided.			
14. I want to receive new information about my condition regularly.			

Empowerment or Guidance?	relevance	clarity	simplicity
15. I prefer to search for medical information on my own.			
16. I usually discuss my condition with other fellow patients.			
17. I want more information to better understand my condition and its possible progression.			
18. I want more information to better manage my condition.			
19. I would like to know possible alternative ways of managing my condition.			
20. I feel that I need more information in order to be able to commit fully to therapy.			
21. I feel that I need more information in order to be able to commit fully to required lifestyle changes.			
22. I would prefer to make the final decision on the management of my condition, when there are more than one alternative option.			
23. I prefer my doctor to decide the best treatment option for me.			
24. I would like to discuss treatment goals, potential implications and disease progression with my doctor.			
25. I prefer to rely solely on doctor's knowledge and guidance.			
26. I prefer to be fully informed on my condition.			

Technology and disease management	relevance	clarity	simplicity
27. I use the internet as a source of medical information			
28. I understand the health information that I find on the internet			
29. I feel able to recognize which internet source provides accurate medical information.			
30. I feel that information provided on authoritative internet platforms is reliable and trustworthy.			
31. I would be interested in a specialised internet platform where all the vital information for my condition could be gathered and accessed.			
32. I am willing to monitor myself and record data on my activities (e.g. weight, diet, etc.) when this is recommended to me by health care providers			
33. I am willing to monitor myself and record data on my activities (e.g. weight, diet, etc.) in order to manage my condition more efficiently.			
34. I would be willing to use applications which help me monitor and manage diet & physical activity.			
35. I would be willing to use an application that will provide alerts regarding my condition and its progression.			
36. I feel that my condition needs closer monitoring than currently suggested by my healthcare provider.			

Overall completeness of the survey
Please, suggest any more issues/questions the questionnaire should cover:

4. CARRE Patients Questionnaire

CARRE

Patient Survey

The following questions are about how well you understand your medical condition and how you feel about getting support to manage your condition yourself.

This survey is conducted as part of the research project "CARRE: Personalized patient empowerment and shared decision support for cardiorenal disease and comorbidities".

The project is funded by the European Commission and aims to provide the means for patients with heart and kidney disease to take an active role in care processes, including self-care and shared decision making.

This survey aims to investigate at what extend you understand your condition, whether you are willing to be informed about it and at what extend you are willing to engage with computers and technology in order to enhance your knowledge and better manage your condition.

The results of this anonymous survey will be used to guide the research and development of the CARRE project. These results, as all CARRE progress will be published promptly in the project's web site: http://www.carre-project.eu/

Please, start with giving some personal information below. The next pages have a series of statements. Please, state at which extend you agree with each statement, by marking the relevant square as follows:

1: fully disagree	2: disagree	3: neither agree or disagree	4: agree	5: fully agree

Personal Information					
Age:	☐ less than 18	☐ 18-25	☐ 26-45	☐ 46-65	☐ above 65
Country of Residence:			Gender:	☐ Female	☐ Male

Which of the following health conditions are you currently being monitored or treated for?

- ☐ increased body weight
- ☐ increased blood pressure (hypertension)
- ☐ increased blood glucose (diabetes)
- ☐ increased blood cholesterol
- ☐ kidney disease
- ☐ heart disease
- ☐ other
  please, specify if you can:

Which of the following have you monitored (or are currently monitoring) at home?

- ☐ body weight
- ☐ blood pressure
- ☐ heart rhythm
- ☐ blood glucose
- ☐ other
  please, specify if you can:

Do you have internet access?

- ☐ daily at home and/or work
- ☐ only occasionally
- ☐ not at all

Have you ever used telemonitoring devices?

- ☐ yes
- ☐ no
- ☐ don't know

Understanding my condition	**disagree**		**neutral**	**agree**	
	1	**2**	**3**	**4**	**5**
1. I am aware of what may have caused my current condition.					
Please list all you think that may have caused your current condition:					
2. I know which symptoms I currently experience are due to my disease.					
Please list all you know:					
3. I can recognize new symptoms that may indicate disease progression.					
Please, list which ones:					
4. I am aware of other illnesses that may occur due to inefficient management of my current health condition.					
Please, list all you know:					

Getting information on my condition	**disagree**		**neutral**	**agree**	
	1	**2**	**3**	**4**	**5**
5. I have all information I need to understand my current condition.					
6. I have all the information I need in order to manage my disease in everyday life.					
Tell us who provides this information(check only the major sources of information ☐ nurse ☐ family ☐ books & leaflets ☐ doctor ☐ friends ☐ internet ☐ other patients ☐ other:					
7. I have all information I need to understand possible disease progression.					
8. I can**not** recognize new symptoms that may indicate disease progression.					
9. My physician/nurse provides me with enough information on how to reduce the risk of future complications.					
10. I believe that better knowledge of my disease would be very beneficial for better management of my condition.					
11. I am able to manage information about possible progression of my disease.					
12. Any new information about my disease makes me feel anxious.					
13. Any new information about my disease confuses me.					
14. It is difficult for me to understand all information provided.					
15. I want to receive new information about my condition regularly.					

Empowerment or Guidance?	**disagree**		**neutral**	**agree**	
	1	**2**	**3**	**4**	**5**
16. I prefer to search for medical information on my own.					
17. I usually discuss my condition with other fellow patients.					
18. I want more information to better understand my					

condition and its possible progression.					
19. I do **not** feel able to manage information about possible progression of my disease.					
20. I want more information to better manage my condition.					
21. I would like to know possible alternative ways of managing my condition.					
22. I feel that I need more information in order to be able to commit fully to therapy.					
23. I feel that I need more information in order to be able to commit fully to required lifestyle changes.					
24. I would prefer to make the final decision on the management of my condition, when there are more than one alternative option.					
25. I prefer my doctor to decide the best treatment option for me.					
26. I would like to discuss treatment goals, potential implications and disease progression with my doctor.					
27. I prefer to rely solely on doctor's knowledge and guidance.					
28. I prefer to be fully informed on my condition.					
29. I feel that my condition does **not** closer monitoring than currently suggested by my healthcare provider.					
Technology and disease management	**disagree**		**neutral**	**agree**	
	1	**2**	**3**	**4**	**5**
30. I use the internet as a source of medical information					
31. I understand the health information that I find on the internet					
32. I feel able to recognize which internet source provides accurate medical information.					
33. I feel that information provided on web pages is reliable and trustworthy.					
34. I would be interested in a specialised web pages where all the vital information for my condition could be gathered and accessed.					
35. I am willing to monitor myself and record data on my activities (e.g. weight, diet, etc.) in order to manage my condition more efficiently.					
36. I do **not** feel able to recognize which internet source provides accurate medical information.					
37. I would be willing to use applications which help me monitor and manage diet & physical activity.					
38. I prefer to have limited information an my condition.					
39. I would be willing to use an application that will provide alerts regarding my condition and its progression.					
40. I feel that my condition needs closer monitoring than currently suggested by my healthcare provider.					

Annex 2

Professionals Survey

1. Survey Design

1.1. Goal

The aim of this survey is to help identify user perceptions of healthcare professionals including physicians, nurses and other healthcare professionals

1.2. Outline of Survey Methodology

The survey was designed via the following approach:

- Define the goal of the survey.
- Literature review of the domain (presented in Sections 2 and 3 of this Deliverable).
- Identify research goals, i.e. specific research questions that will be addressed via the survey.
- Discuss research questions within a focus group with the aim to capture their overall response in order to identify specific survey questions.
- Develop the questionnaire and qualitatively validate it within the focus group.
- Deploy questionnaire
- Process results

1.3. Research Questions

Research questions to investigate the professionals' perspective can be grouped along the following axes:

- How do professionals perceive patient empowerment?
- Are professionals' willing to support and promote patient empowerment interventions?
- What would empower professionals to manage (not empower) cardiorenal patients?

1.4. Questionnaire Design & Validation

Perceptions of healthcare professionals were recorded mainly by a short questionnaire. This was derived based on a focus group of healthcare professionals. The focus group was assembled by 5 physicians and 1 nurse of the University Hospital of Alexandroupoli and Regional Hospital of Kavala, Greece. In particular, there was 2 nephrology experts, 1 cardiology expert, 2 internal medicine expers and 1 nurse serving in the nephrology clinic. The group was facilitated by two researchers supervising the survey design and statistical analysis. The final questionnaire as derived by the group focused on two main categories:

- How do professionals prefer to keep up to date with medical knowledge (8 questions)
- What are their perceptions about using technology in disease management (6 questions)

2. Survey Results and Analysis

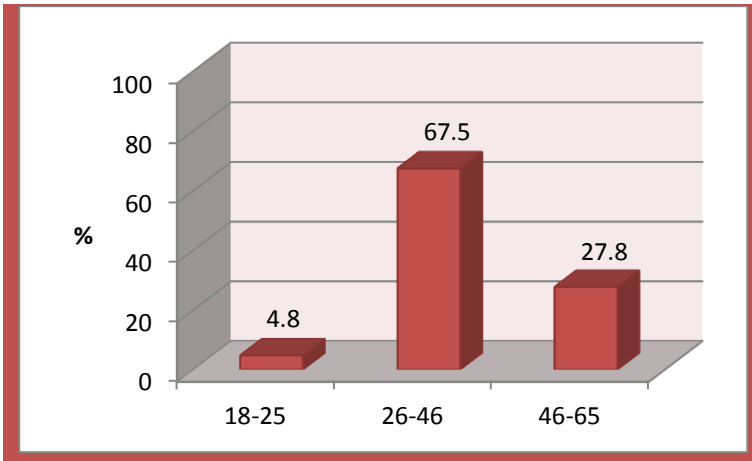
The questionnaire was deployed mainly by DUTH and VULSK in the two countries of the intended CARRE pilots, Greece and Lithuania respectively by advertisement within the personnel of the affiliated hospitals.

There were overall 209 responses by 24 April 2014. The results of these 209 first responses were analyzed and are presented in this document. It should be noted that the survey will keep running for a few more months and the accumulative results will be reported as an update to this Annex.

Basic analysis was performed by Microsoft Excel software and more advanced analysis and correlations with the IBM SPSS software. The remaining of this section presents the detailed responses for each question individually. The following section presents more advanced analysis of the results.

Each question was assessed first for overall performance and the results are presented below.

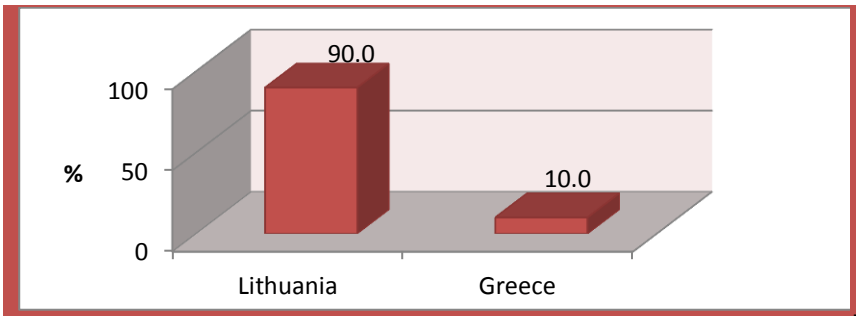
2.1. Age



		Frequency	Percent	Cumulative Percent
Age	18-25	10	4.8	4.8
	26-46	141	67.5	72.2
	46-65	58	27.8	100.0
	Total	209	100.0	

The majority of respondents were of ages 26-45.

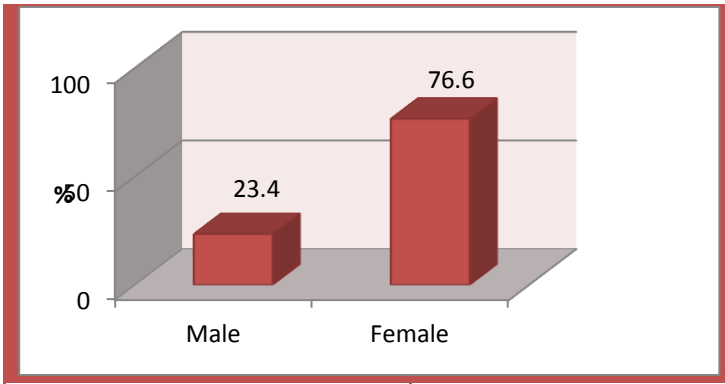
2.2. Country of Residence



		Frequency	Percent	Cumulative Percent
Country of Residence	Lithuania	188	90.0	90.0
	Greece	21	10.0	100.0
	Total	209	100.0	

The largest proportions of respondents come from Lithuania (90%). Greece proportions were only (10%). The rest EU countries did not participate in this survey as expected by the design of survey.

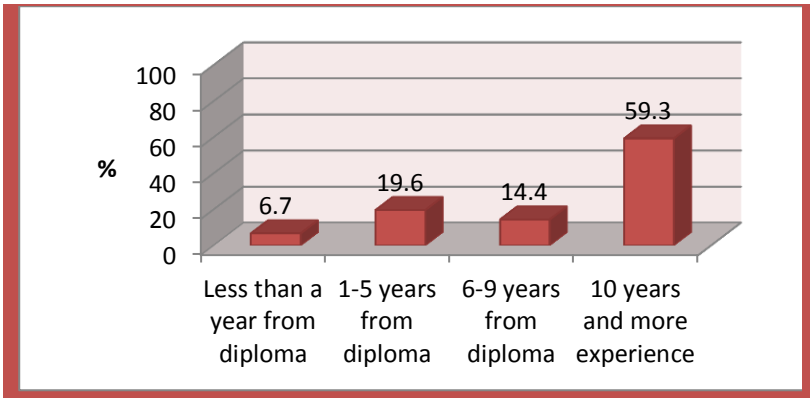
2.3. Gender



		Frequency	Percent	Cumulative Percent
Gender	Male	49	23.4	23.4
	Female	160	76.6	100.0
	Total	209	100.0	

In this survey it's obviously that we did not have a gender balance. The percentage of female answered the question in the questionnaire was higher of male.

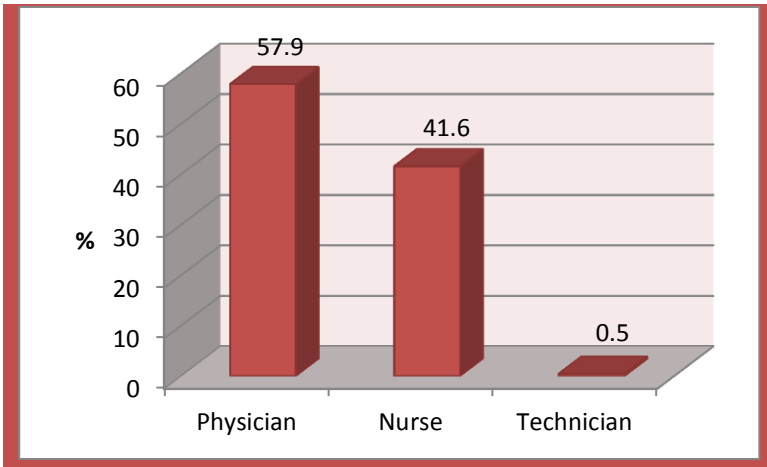
2.4. Work experience



		Frequency	Percent	Cumulative Percent
Work experience	Less than a year from diploma	14	6.7	6.7
	1-5 years from diploma	41	19.6	26.3
	6-9 years from diploma	30	14.4	40.7
	10 years and more experience	124	59.3	100.0
	Total	209	100.0	

More than half of the respondents (59.3%) report that they have 10 years and more of work an experience while ¼ report that they have 6 to 9 years from their diploma.

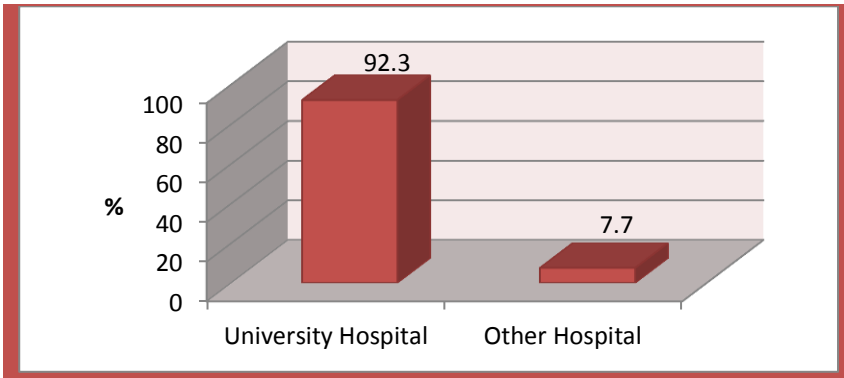
2.5. Profession



		Frequency	Percent	Cumulative Percent
Profession	Physician	121	57.9	57.9
	Nurse	87	41.6	99.5
	Technician	1	0.5	100.0
	Total	209	100.0	

More than half of respondents (57.9%) were physicians while a good number of respondents were nurses (41.6%). Only 0.5% was technician.

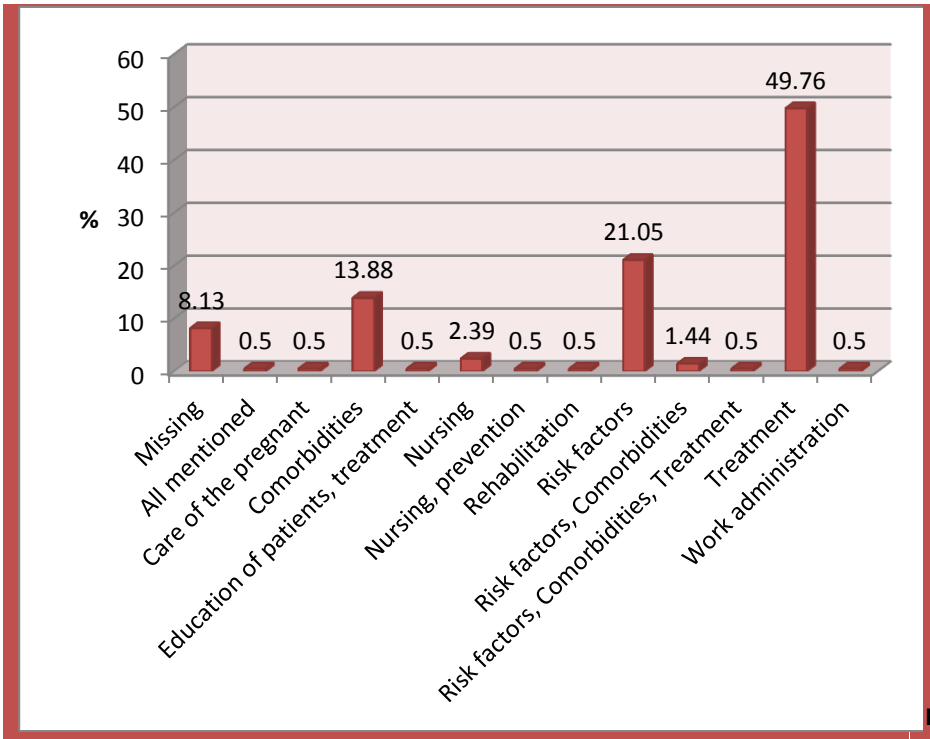
2.6. Currently working at…



		Frequency	Percent	Cumulative Percent
Currently working at	University Hospital	193	92.3	92.3
	Other Hospital	16	7.7	100.0
	Total	209	100.0	

A high majority of 92.3% were currently working at university hospital.

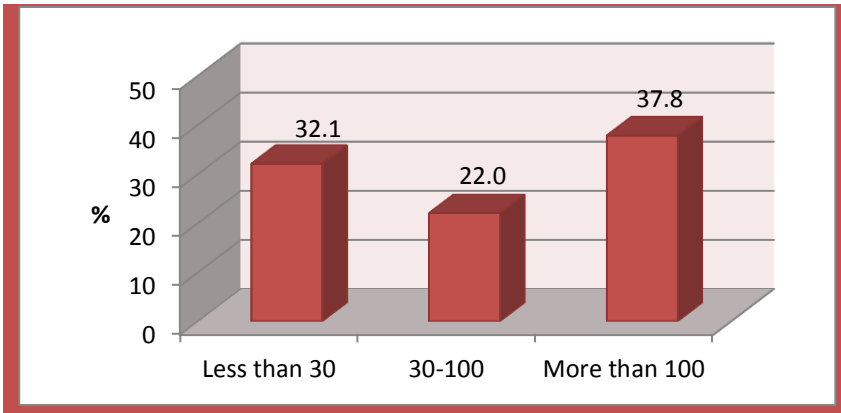
2.7. In which field would you like to get additional information?



		Frequency	Percent	Cumulative Percent
In which field would you like to get additional information	Missing	17	8.13	8.1
	All mentioned	1	0.5	8.6
	Care of the pregnant	1	0.5	9.1
	Comorbidities	29	13.88	23.0
	Education of patients, treatment	1	0.5	23.4
	Nursing	5	2.39	25.8
	Nursing, prevention	1	0.5	26.3
	Rehabilitation	1	0.5	26.8
	Risk factors	44	21.05	47.8
	Risk factors, Comorbidities	3	1.44	49.3
	Risk factors, Comorbidities, Treatment	1	0.5	49.8
	Treatment	104	49.76	99.5
	Work administration	1	0.5	100.0
	Total	209	100.0	

Almost the half of respondents (49.76%) report that they would like additional information in treatment field, while ¼ report that they want more information about risk factors.

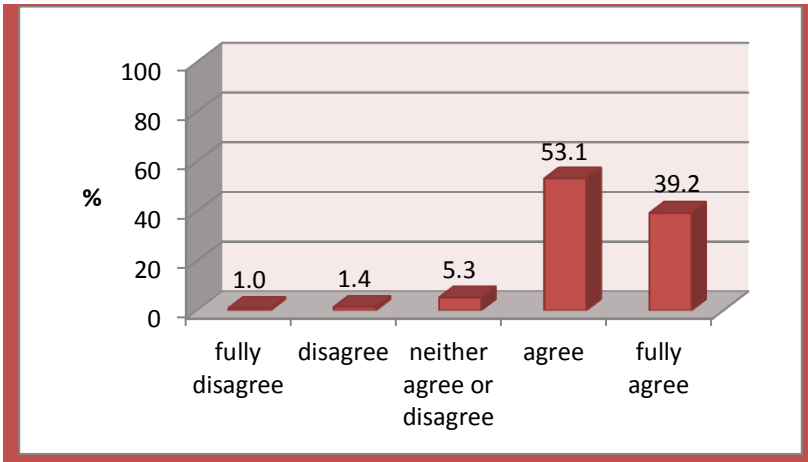
2.8. Number of cardiorenal patients treated in the last year



		Frequency	Percent	Cumulative Percent
Number of cardiorenal patients with or at risk of comorbidities treated in the last year	Less than 30	67	32.1	34.9
	30-100	46	22.0	58.9
	More than 100	79	37.8	100.0
	Total	192	91.9	
Total		209	100.0	

37.8% of respondents answered that they treated more than 100 cardiorenal patients with or at risk of comorbidities, while 32.1% reports that they treated less than 30 patients.

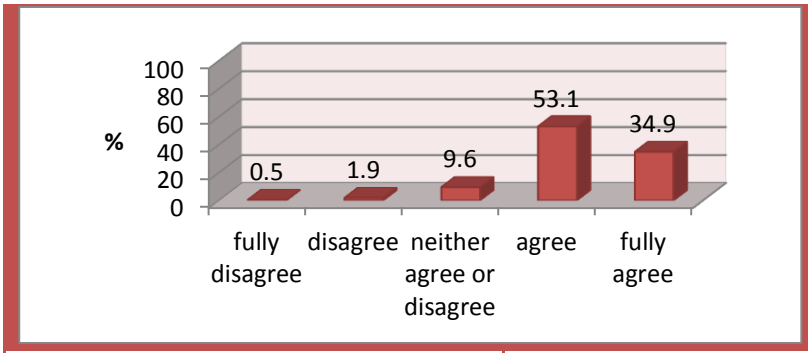
2.9. I continuously keep up to date with medical knowledge.



		Frequency	Percent	Cumulative Percent
I continuously keep up to date with medical knowledge.	fully disagree	2	1.0	1.0
	disagree	3	1.4	2.4
	neither agree or disagree	11	5.3	7.7
	agree	111	53.1	60.8
	fully agree	82	39.2	100.0
	Total	209	100.0	

A high amount of respondents (92.3%) report that they continuously keep up to date with medical knowledge.

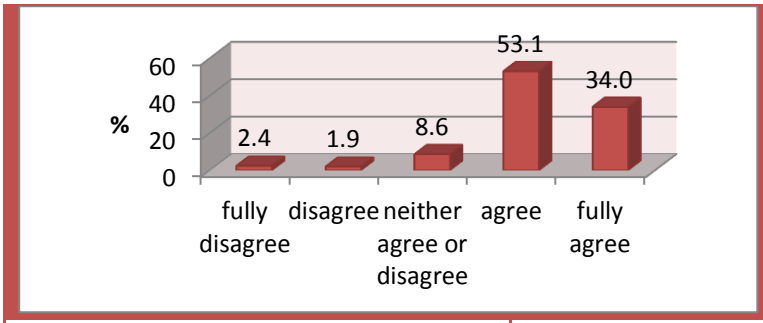
2.10. To keep up to date with medical knowledge, I use medical textbooks.



		Frequency	Percent	Cumulative Percent
To keep up to date with medical knowledge, I use medical textbooks.	fully disagree	1	0.5	.5
	disagree	4	1.9	2.4
	neither agree or disagree	20	9.6	12.0
	agree	111	53.1	65.1
	fully agree	73	34.9	100.0
	Total	209	100.0	

The majority of respondents (98%) answered that they use medical textbooks in order to keep up to date with medical knowledge.

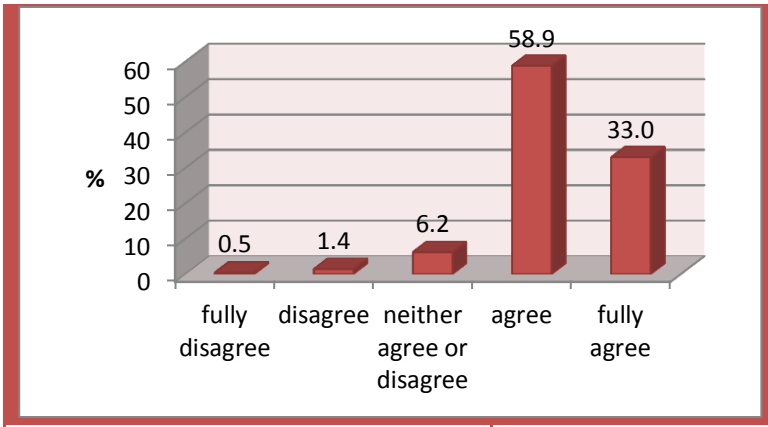
2.11. To keep up to date with medical knowledge, I attend medical conferences.



		Frequency	Percent	Cumulative Percent
To keep up to date with medical knowledge, I attend medical conferences.	fully disagree	5	2.4	2.4
	disagree	4	1.9	4.3
	neither agree or disagree	18	8.6	12.9
	agree	111	53.1	66.0
	fully agree	71	34.0	100.0
	Total	209	100.0	

A high majority of respondents (87.1%) attend medical conferences in order to keep up to date with medical Knowledge.

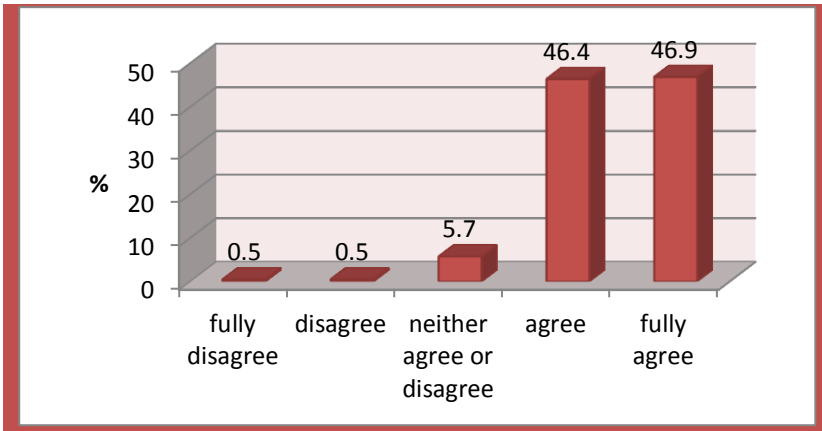
2.12. To keep up to date, I exchange experience and consult with my colleagues.



		Frequency	Percent	Cumulative Percent
To keep up to date with medical knowledge, I exchange experience and consult with my colleagues.	fully disagree	1	0.5	.5
	disagree	3	1.4	1.9
	neither agree or disagree	13	6.2	8.1
	agree	123	58.9	67.0
	fully agree	69	33.0	100.0
	Total	209	100.0	

The majority of responders (91.9%)answered that they exchange experience and consult with their colleagues in order to keep up to date with medical Knowledge.

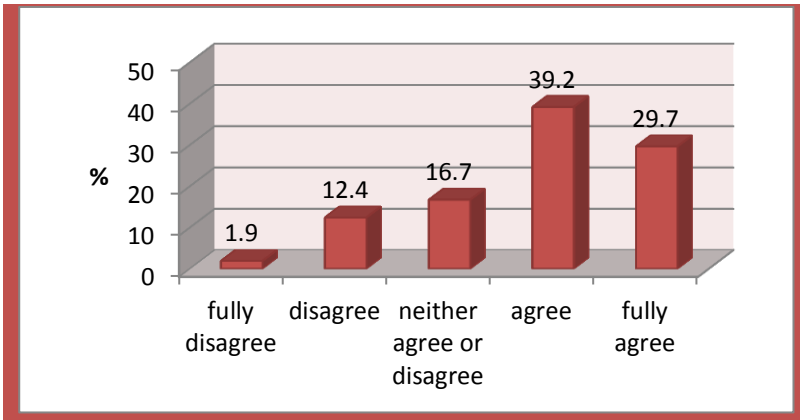
2.13. To keep up to date with medical knowledge, I search generally on the internet.



		Frequency	Percent	Cumulative Percent
To keep up to date with medical knowledge, I search generally on the internet.	fully disagree	1	0.5	.5
	disagree	1	0.5	1.0
	neither agree or disagree	12	5.7	6.7
	agree	97	46.4	53.1
	fully agree	98	46.9	100.0
	Total	209	100.0	

A high majority of respondents (83.3%) search on the internet in order to keep up to date with medical Knowledge.

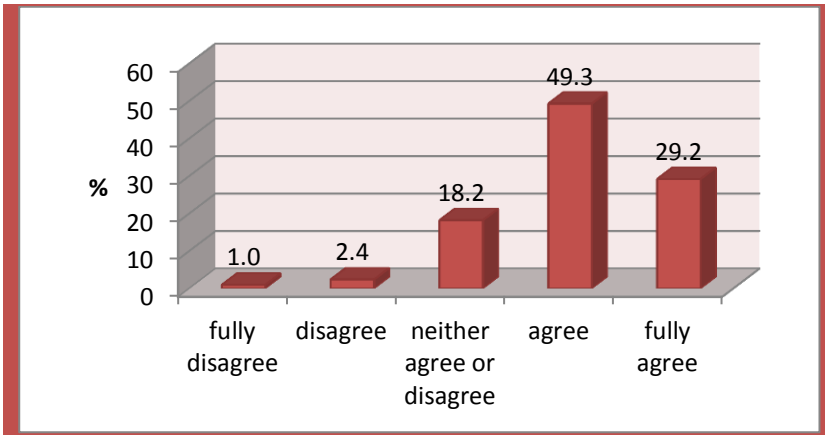
2.14. To keep up to date, I search medical scientific articles, e.g. via Pubmed.



		Frequency	Percent	Cumulative Percent
To keep up to date with medical knowledge, I search medical scientific articles, e.g. via Pubmed.	fully disagree	4	1.9	1.9
	disagree	26	12.4	14.4
	neither agree or disagree	35	16.7	31.1
	agree	82	39.2	70.3
	fully agree	62	29.7	100.0
	Total	209	100.0	

More than half of respondents (68.9%) search medical scientific articles in order to keep up to date with medical Knowledge.

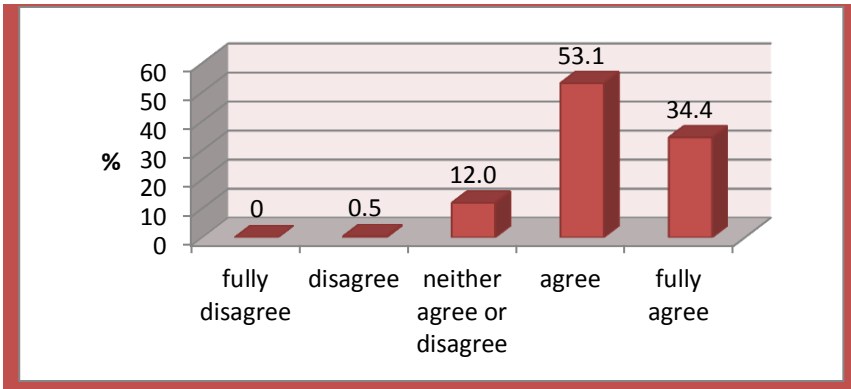
2.15. To keep up to date, I consult authoritative evidence based medicine sources.



		Frequency	Percent	Cumulative Percent
To keep up to date with medical knowledge, I consult authoritative evidence based medicine sources, e.g. Cochrane.	fully disagree	2	1.0	1.0
	disagree	5	2.4	3.3
	neither agree or disagree	38	18.2	21.5
	agree	103	49.3	70.8
	fully agree	61	29.2	100.0
	Total	209	100.0	

More than half of respondents (78.5%) consult authoritative evidence based medicine sources in order to keep up to date with medical Knowledge.

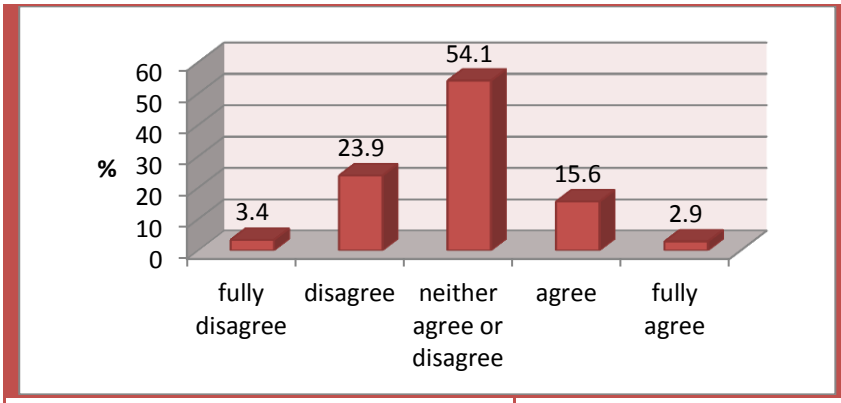
2.16. I feel very satisfied with how I keep up to date in medicine.



		Frequency	Percent	Cumulative Percent
I feel very satisfied with how I keep up to date with latest developments in medicine.	fully disagree	0	0	0
	disagree	1	0.5	.5
	neither agree or disagree	25	12.0	12.4
	agree	111	53.1	65.6
	fully agree	72	34.4	100.0
	Total	209	100.0	

Most of respondents 87.5% feel very satisfied with how I keep up to date with latest developments in medicine and 12% neither agree or disagree.

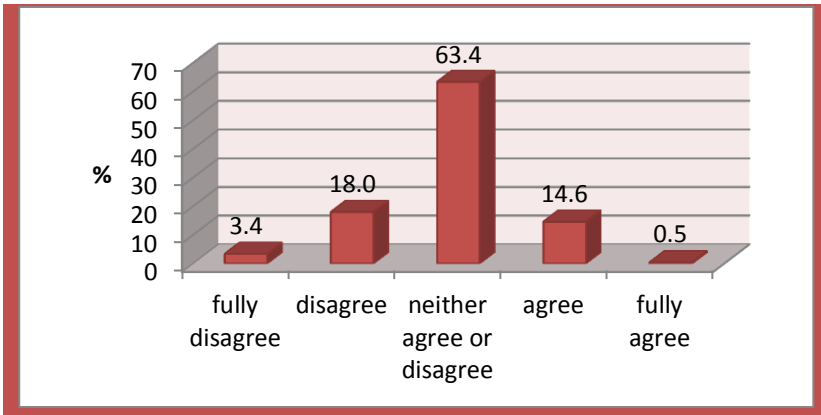
2.17. I know of patients who experienced physical benefit from the Internet.



		Frequency	Percent	Cumulative Percent
I know of patients who experienced physical benefit from taking or doing something they read about on the Internet.	fully disagree	7	3.4	3.4
	disagree	49	23.9	27.3
	neither agree or disagree	111	54.1	81.5
	agree	32	15.6	97.1
	fully agree	6	2.9	100.0
	Total	205	100.0	

Half of respondents neither agree or disagree if they know of patients who experienced physical benefit from taking or doing something they read about on the Internet, 27.3% disagree and 18.5% agree.

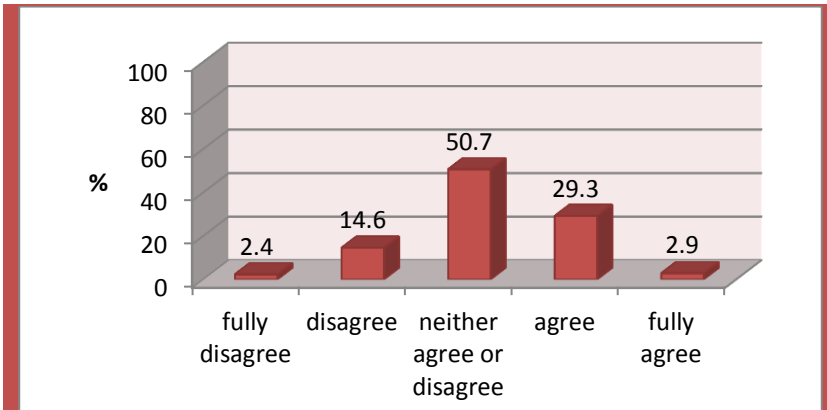
2.18. I have patients who experienced disadvantage from the Internet.



		Frequency	Percent	Cumulative Percent
I have patients who experienced dramatic physical disadvantage from taking or doing something they read about on the Internet.	fully disagree	7	3.4	3.4
	disagree	37	18.0	21.5
	neither agree or disagree	130	63.4	84.9
	agree	30	14.6	99.5
	fully agree	1	.5	100.0
	Total	205	100.0	

63.4% of respondents neither agree or disagree 21.4% disagree and 19.6% agree if they have patients who experienced dramatic physical disadvantage from taking or doing something they read about on the Internet.

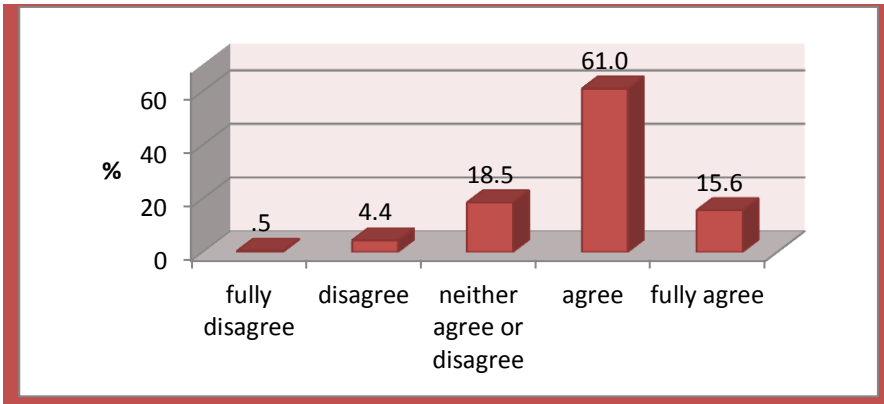
2.19. I believe the general quality of health information on the Internet is reliable.



		Frequency	Percent	Cumulative Percent
I believe the general quality of health information on the Internet is reliable.	fully disagree	5	2.4	2.4
	disagree	30	14.6	17.1
	neither agree or disagree	104	50.7	67.8
	agree	60	29.3	97.1
	fully agree	6	2.9	100.0
	Total	205	100.0	

50.7% of respondents believe the general quality of health information on the Internet is reliable, 32.2% agree and 17% disagree.

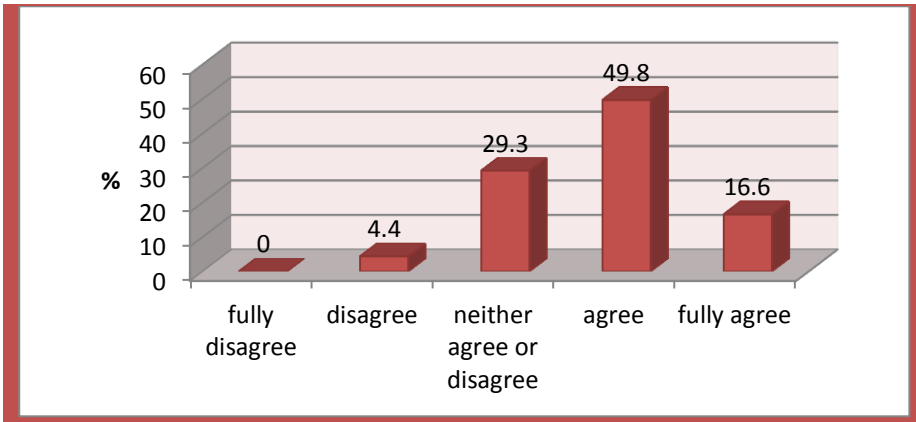
2.20. I encourage patients to be involved in the decisions about their healthcare.



		Frequency	Percent	Cumulative Percent
I encourage patients to be as much involved as they would like in the decisions about their healthcare.	fully disagree	1	.5	.5
	disagree	9	4.4	4.9
	neither agree or disagree	38	18.5	23.4
	agree	125	61.0	84.4
	fully agree	32	15.6	100.0
	Total	205	100.0	

Most of respondents 76.6% encourage patients to be as much involved as they would like in the decisions about their healthcare, 18.5% neither agree or disagree and 4.9% disagree.

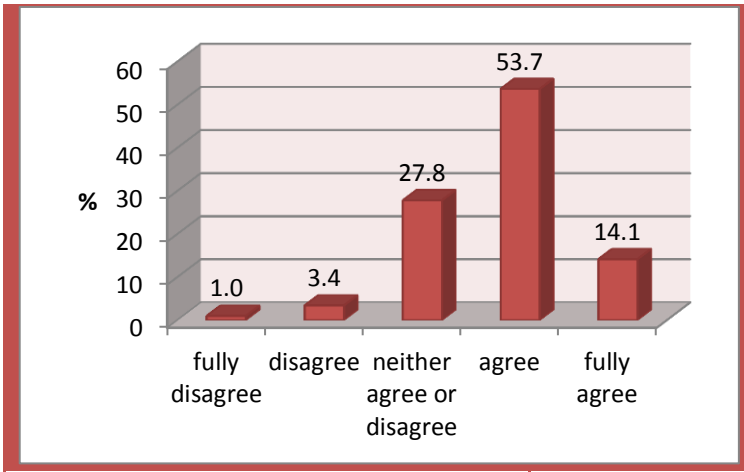
2.21. I can better manage my patients' health condition when I use telemonitoring.



		Frequency	Valid Percent	Cumulative Percent
I believe that I can better manage my patients' health condition when I use telemedicine/telemonitoring to monitor my patients.	fully disagree	0	0	0
	disagree	9	4.4	4.4
	neither agree or disagree	60	29.3	33.7
	agree	102	49.8	83.4
	fully agree	34	16.6	100.0
	Total	205	100.0	

66.4% of respondents believe that they can better manage my patients' health condition when they use telemedicine/telemonitoring to monitor my patients, 29.3% neither agree or disagree and 4.4% disagree.

2.22. Patients can better manage themselves when they use telemonitoring.



		Frequency	Percent	Cumulative Percent
I believe that patients can better manage themselves when they use personal telemedicine/telemonitoring applications.	fully disagree	2	1.0	1.0
	disagree	7	3.4	4.4
	neither agree or disagree	57	27.8	32.2
	agree	110	53.7	85.9
	fully agree	29	14.1	100.0
	Total	205	100.0	

More than a half of patients 67.8% believe that patients can better manage themselves when they use personal telemedicine/telemonitoring applications, 27.8% neither agree ore disagree and 4.4% disagree.

3. CARRE Professionals Survey

The following questions are about how well you understand your patients' medical condition and how you manage and empower them to use technology for their diseases.

This survey is conducted as part of the research project "CARRE: Personalized patient empowerment and shared decision support for cardiorenal disease and comorbidities".

The project is funded by the European Commission and aims to provide the means for patients with heart and kidney disease to take an active role in care processes, including self-care and shared decision making.

The results of this anonymous survey will be used to guide the research and development of the CARRE project. These results, as all CARRE progress will be published promptly in the project's web site: http://www.carre-project.eu/

Please, start with giving some personal information below. The next pages have a series of statements. Please, state at which extend you agree with each statement, by marking the relevant square as follows:

1: fully disagree	2: disagree	3: neither agree or disagree	4: agree	5: fully agree

Personal Information					
Age:	☐ less than 22	☐ 22-25	☐ 26-45	☐ 46-65	☐ above 65
Country of Residence:		Gender:	☐ Female	☐ Male	

Work experience

- ☐ Less than a year from diploma
- ☐ 1-5 years from diploma
- ☐ 6-9 years from diploma
- ☐ 10 years and more experience

Please indicate if you are a:

- ☐ Physician
- ☐ Nurse
- ☐ Pharmacist

Type of Institution:

- ☐ University Hospital
- ☐ Other Hospital
- ☐ Primare healthcare unit
- ☐ Private medical clinic/office

In which field would you like additional information?

- ☐ Risk factors
- ☐ Comorbidities
- ☐ Treatment
- ☐ other
  please, specify if you can:

Number of patients suffering from heart and/or kidney disease with or at risk of comorbidities treated in the last year:

- ☐ less than 30
- ☐ 30-100
- ☐ More than 100

How do doctors prefer to keep up to date with medical knowledge	**disagree**		**neutral**	**agree**	
	1	**2**	**3**	**4**	**5**
37. I continuously keep up to date with medical knowledge.					
38. In order to keep up to date with medical knowledge, I use medical textbooks.					
39. In order to keep up to date with medical knowledge, I attend medical conferences.					
40. In order to keep up to date with medical knowledge, I exchange experience and consult with my colleagues.					
41. In order to keep up to date with medical knowledge, I search generally on the internet.					

42. In order to keep up to date with medical knowledge, I search medical scientific articles, e.g. via Pubmed.					
How do doctors prefer to keep up to date with medical knowledge	**disagree**		**neutral**	**agree**	
	1	**2**	**3**	**4**	**5**
43. In order to keep up to date with medical knowledge, I use authoritative guidelines and other evidence medicine sources.					
44. I feel very satisfied with my ability to remain knowledgeable and current with the latest developments in medicine.					
Technology in empowerment and disease management	**disagree**		**neutral**	**agree**	
	1	**2**	**3**	**4**	**5**
45. I think is reliable the general quality of health information on the Internet.					
46. I encourage patients to be as much involved as they would like in the decisions about their healthcare.					
47. The use of personal telemedicine/telemonitor technology is beneficial to my patients care and management for themselves.					
48. Using telemedicine/telemonitor technology from my patients is beneficial to me in order to take care and manage them.					
49. I have patients who experienced physical benefit from taking or doing something they read about on the Internet					
50. I have patients who experienced dramatic physical disadvantage from taking or doing something they read about on the Interne					

Annex 3

Other Stakeholders Survey

1. Survey Design

Perceptions of policy makers were recorded via semi-structured interviews. The following outline was followed:

1) Please give us some information about the job and key responsibilities (Name, Affiliation, Position, Position Responsibilities, Years in this or at similar position).
2) Are you directly related to the field of cardiorenal disease and/or cardiorenal comorbidities? Please, explain.
3) In your opinion, what are the major problems cardiorenal patients (or people at risk of cardiorenal disease) face?
4) What are the major problems encountered today by the health professionals who deal with this disease?
5) What do you think are the most important steps for the prevention of disease?
6) Are you familiar with the term 'patient empowerment'?
7) How would you envisage empowerment of patients with cardiorenal disease (across the spectrum of patients who simply have an increased risk in those who already have heart or kidney disease, up to those with a terminal illness or other important comorbidities)? What services would you expect to make an impact? Please, elaborate.
8) If you would change something in the health system towards this direction, what would it be?
9) Would you promote a service/system empowering patients? How?
10) If yes, what would you want from such a service/system?
11) What kind of alerts or alarms would you think as important for the prevention and management of chronic cardiorenal disease and comorbidities?

2. Survey Results

Semi-structured interviews were conducted with the following people/roles:

1 Leadership in prevention and treatment of life-style related diseases
President of European Society of Lifestyle Medicine
Dr. Michael Sagner

2 Municipality Council Member – Member of the Committee for Quality of Life
Municipality of Alexandroupoli, Greece
Dr. Savvas Defteraios

3 Head of Regional Department of Health
Prefecture of Evros
(name available on request)

4 Director, Dialysis Center
Prefecture of Pellas, Greece
Dr. Nikolaos Zoumparidis

5 Head of Cardiology Clinic,
General Regional Hospital of Kavala, Greece
Dr. David Symeonidis

6 Head of Nurses
Regional General University Hospital of Alexandroupolis, Greece
(name available on request)

Interview #1 – Leadership in prevention and treatment of life-style related diseases

1) Information about the job and key responsibilities:
   - Name: Michael Sagner, MD
   - Affiliation: European Society of Lifestyle Medicine
   - Position: President
   - Position Responsibilities: Overseeing Research, Leadership in Prevention and Treatment of Lifestyle-related diseases
   - Years in this or at similar position 5

2) Relation to the field of cardiorenal disease and/or cardiorenal comorbidities

   I am the founder and former Chief Medical Doctor/Head of Department for Preventive Medicine and Lifestyle Medicine at the University Eppendorf.

3) Major problems cardiorenal patients face

   The major problem is managing the comorbidities and adjusting lifestyle as an essential factor to manage the diseases.

4) Major problems encountered by the health professionals who deal with this disease

   One of the major challenges is the patient adherence to lifestyle recommendations.

5) Most important steps for the prevention of disease

   They key steps are: 1) Raising awareness for the essential role of lifestyle factors in the prevention of chronic diseases. 2) Empowering patients to improve their lifestyle to sustain health and prevent diseases.

6) Familiarity with the term 'patient empowerment'

   See above

7) Vision of empowerment of patients with cardiorenal disease.

   Patient empowerment must first help raise awareness on a daily base for the importance of lifestyle factors (reminder). Then it must support patients in making the right lifestyle choices (mainly nutrition, physical activity) on a daily basis.

8) If you would change something in the health system towards this direction, what would it be?

   I absolutely think that we must go from a disease-centered system that treats symptoms to a health-centered system that treats the cause of diseases.

9) Would you promote a service/system empowering patients? How?

   Yes, we could promote it through the European Society of Lifestyle Medicine and its partners.

10) If yes, what would you want from such a service/system?
    - Easy to use

– Focus on the 'low hanging fruits' – interventions that are effective

11) What kind of alerts or alarms would you think as important for the prevention and management of chronic cardiorenal disease and comorbidities?
  – A lifestyle – centered system that monitors physical activity and nutrition
  – A biomarker – centered system that monitors risk factors

Interview #2 – Municipality Council Member – Member of the Committee for Quality of Life

1) Information about the job and key responsibilities:
  – Name: Dr. Savvas Defteraios
  – Affiliation: Municipality of Alexandroupolis, Greece
  – Position: Municipality Council Member, Member of the Committee for Quality of Life
  – Position Responsibilities: Strategic policy making and interventions for ensuring quality of life in the Municipality of Alexandroupolis. The municipality covers a population of around 80,000 and spreads to an area of 20X80 Km. The municipality is a mainly a rural area far away from metropolitan centers of the capital and other large cities of the country.
  – Years in this or at similar position: 12 years

2) Relation to the field of cardiorenal disease and/or cardiorenal comorbidities

  I am routinely involved with people with chronic disease, and cardiorenal patients, with regards to their social services support. Moreover, by profession I am a medical doctor and Assist. Prof. of Radiology, so I also am familiar with this disease on the basis of my profession.

3) Major problems cardiorenal patients face

  One of the major problems for these chronic patients is the time lost for routine visits to the hospital. More importantly, time lost because of unnessecary visits. This is due to the fact that most of these people feel unsecure (probably due to a lack of knowledge and information) and they most often decide to visit their doctor merely to check if things are Ok, that is, to have some psychological support.

4) Major problems encountered by the health professionals who deal with this disease

  The equivalent time (and cost) burden due to unnecessary patients' visits. Treating patients with this type of disease and comorbidities can be psychologically demanding. Supporting professionals with more organized and targeted continuous education and support would be good.

5) Most important steps for the prevention of disease

  Promote a healthy lifestyle for all citizens. Mainly, by informing them about what lies ahead if they do not manage to excersice and watch their diet.

6) Familiarity with the term 'patient empowerment'

  Yes.

7) Vision of empowerment for patients with cardiorenal disease.

  This is what we strive at on the Municipality Council: empower the citizen to take control of their lives. In the case of patients and especially chronic patients, I think this is much more important.

8) If you would change something in the health system towards this direction, what would it be?

Give the possibility to the patients to be able to communicate with professionals and get up to date authoritative information from their own place, i.e. via internet technologies. I think this should be the first step towards empowerment.

9) Would you promote a service/system empowering patients? How?

Definitely. Our first goal would be to incorporate such services to related Municipality Units, such as the Center for Day Care/Recreation of Elder People, where a good number of members suffer from cardiorenal related morbidities. Also, via the Social Services of every Municipality.

10) If yes, what would you want from such a service/system?

- For the patients, I would mainly see supporting access to authoritative information, stressing facts about disease progression and transition if lifestyle is not properly managed. Important functionalities would be: (a) get information on the disease (b) check if a current symptom is a reason for alert and/or visit to the doctor, (c) see what will happen when a certain condition is managed or not managed according to prescription, (d) access to ICT tools for measuring, monitoring and managing certain biomarkers, e.g. BMI and others.
- For health policy makers, it would be good to provide statistical views of the population

11) What kind of alerts or alarms would you think as important for the prevention and management of chronic cardiorenal disease and comorbidities?

see above

Interview #3 – Head of Regional Dept. of Healthcare

1) Information about the job and key responsibilities:

- Name: (available from the CARRE Coordinator)
- Affiliation: Prefecture of Evros, Greece
- Position: Head of Department of Health
- Position Responsibilities: Regional health financial management
- Years in this or at similar position: 10-11

2) Relation to the field of cardiorenal disease and/or cardiorenal comorbidities

Not directly related to chronic cardiorenal syndrome. Mainly related to end stage renal disease patients – issueing benefits for special diet. Such patients lack proper and continuous information about their condition and possible progression. Sometimes, they even have wrong information about how to manage their disease.

3) Major problems cardiorenal patients face

Increased hospitalization, which reduces quality of life for such patients. Difficulty in reaching the right service within a hospital. Often such patients are more in need of consulting rather than actually healthcare services, thus they get confused when trying to get such services within a hospital.

4) Major problems encountered by the health professionals who deal with this disease

The above increases disproportionally the cost of care and also places more burden on doctors. This could be alleviated by empowering the patient to deal personally with certain aspects of their everyday disease management.

5) Most important steps for the prevention of disease

Crucial issue. Although not in a position and expertise to suggest measures, I can certainly recognize that prevention is really crucial for the citizen and the healthcare system and the government.

6) Familiarity with the term 'patient empowerment'

Yes

7) Vision of empowerment of patients with cardiorenal disease.

Crucial issue. Although not in a position and expertise to suggest measures, I can certainly recognize that patient empowerment is really a crucial for prevention and then management and quality of life.

8) If you would change something in the health system towards this direction, what would it be?

...

9) Would you promote a service/system empowering patients? How?

Yes, within the regional healthcare system structures.

10) If yes, what would you want from such a service/system?

..

11) What kind of alerts or alarms would you think as important for the prevention and management of chronic cardiorenal disease and comorbidities?

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Interview #4 – Head of Cardiology Clinic

1) Information about the job and key responsibilities:
   - Name: Dr. Nikolaos Zoumparidis
   - Affiliation: Dialysis Center, Perfecture of Pellas
   - Position: Director
   - Position Responsibilities: Coordination, administration
   - Years in this or at similar position: 14 years

2) Relation to the field of cardiorenal disease and/or cardiorenal comorbidities

Directly related. The Center is offering renal replacement therapy in end stage renal disease patients.

3) Major problems cardiorenal patients face

ESRD patients' major problem is the increased chances of a lethal episode. Strict management of diet and therapy is required for this to be minimized. This is not often the case as they lack a continuous reminder on what they have to do and why.

4) Major problems encountered by the health professionals who deal with this disease

   Apart from financial issues, other important problems is the required psychological support of patients.

5) Most important steps for the prevention of disease

   Stratification of monitoring of related biomarkers and adherence to diet and therapy directions. This requires informing, educating and monitoring the patient during their everyday life (and not only while they visit the hospital).

6) Familiarity with the term 'patient empowerment'

   Yes.

7) Vision of empowerment of patients with cardiorenal disease.

   It is the right and necessary move to make. This will ensure that an informed patient takes conscious control of managing their everyday life and adhere to the proper lifestyle, which is crucial in the case of cardiorenal disease.

8) If you would change something in the health system towards this direction, what would it be?

   Include patient empowerment as a standard service within the healthcare system. Also, include a variety of other citizen prevention and awareness programs, including organ donation awareness.

9) Would you promote a service/system empowering patients? How?

   Certainly. Considering my personal post, I would definitely include such a service as an experimental service in our Center (even before taken up officially by the national healthcare system).

10) If yes, what would you want from such a service/system?

    I would place emphasis on informing patients of their condition, how it can worsen and what else (other symptoms and diseases) they might experience due to their current condition.

11) What kind of alerts or alarms would you think as important for the prevention and management of chronic cardiorenal disease and comorbidities?

    I would like to see reminders of what they should eat and when they should be monitored. Also, any alerts and alarms should be accompanied with the right information.

Interview #5 – Head of Cardiology Clinic

1) Information about the job and key responsibilities:
   - Name: Dr. David Symeonidis
   - Affiliation: Regional General Hospital of Kavala, Greece
   - Position: Head of Cardiology Clinic
   - Position Responsibilities: Coordination, management of clinical practice

– Years in this or at similar position: 8 years

2) Relation to the field of cardiorenal disease and/or cardiorenal comorbidities

Directly related (cardiology clinic).

3) Major problems cardiorenal patients face

The poor quality of life these chronic patients experience. This burdens also their psychological state. As disease progresses, hospital admissions increase and this further limit their normal activity. The risk of a sudden death also increases. The biggest challenge is to convince the patient to follow prescribed treatment, monitoring and diet. Also, to explain to them what disease progression and transition will bring to their everyday lives and wellbeing.

4) Major problems encountered by the health professionals who deal with this disease

The increased hospitalization rates which burdens the system and the work flow of the clinic. Also, the low rate of patient compliance with guidelines, which in turn increases the hospitalization rate.

5) Most important steps for the prevention of disease

Management of risk factors and patients compliance with guidelines. I would hope that a project such as CARRE can help in these by alerting and informing patients in a user friendly and non-intrusive way, and thus supporting them also psychologically.

6) Familiarity with the term 'patient empowerment'

Yes, I am familiar and supporter. However, I have not seen any real patient empowerment services implemented as yet.

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7) Vision of empowerment of patients with cardiorenal disease.

Inform them so that they can manage their everyday diet, monitoring and treatment more effectively.

8) If you would change something in the health system towards this direction, what would it be?

Implementation of programs for better outpatient monitoring, management and guidance of the patient and management of the disease.

9) Would you promote a service/system empowering patients? How?

Surely if it proves that really can offer to the patient and to health care system.

10) If yes, what would you want from such a service/system?

Infromation and notifications about comorbidities: deregulation of hypertension, diabetes, cardiac and renal function and activity of the individual.

11) What kind of alerts or alarms would you think as important for the prevention and management of chronic cardiorenal disease and comorbidities?

Alarms that guide the patient to seek medical advice when necessary - the timely arrival at the hospital is crucial because it is a life-threatening disease.

Interview #6 – Head of Nursing Personnel, Regional University Hospital

1) Information about the job and key responsibilities:
   - Name: (available from CARRE Coordinator on request)
   - Affiliation: Regional General University Hospital of Alexandroupolis, Greece
   - Position: Head of Nurses
   - Position Responsibilities: Coordination and management of nursing staff
   - Years in this or at similar position: 4

2) Relation to the field of cardiorenal disease and/or cardiorenal comorbidities

   Served as a nursing staff in 10 years in Cardiology Clinic and 6 years in Peritoneal Dialysis Unit.

3) Major problems cardiorenal patients face

   Frequent visits to the hospital. It is crucial for such patients to be able to communicate with their nurse/doctor so as to avoid often unnecessary visits to the hospital.

4) Major problems encountered by the health professionals who deal with this disease

   Healthcare professionals (especially nurses) should be better and fully informed with up to date information so as to be able to treat and guide patients accordingly.

5) Most important steps for the prevention of disease

   Start very early in life. Parents should be well informed and educated so as to bring up their children teaching them a healthy lifestyle, personalized to them based on family history. This is the best way to prevent diabetes, obesity and hypertension which then very often lead to cardiorenal disease. An important issue here is public awareness via media and specific targeted interventions by the National Healthcare System.

6) Familiarity with the term 'patient empowerment'

   Yes. I personally hear the term regularly in scientific conferences I attend the last years. Moreover, I can say that a good number of our nursing staff is regularly attending conferences and seminars on patient empowerment.

7) Vision of empowerment of patients with cardiorenal disease.

   Focus on information on lifestyle and disease progression. I believe that when empowered the patient feels psychologically strong. The same holds for patients' personal environment.

8) If you would change something in the health system towards this direction, what would it be?

   Introduce citizen education on healthy lifestyle very early in life.

9) Would you promote a service/system empowering patients? How?

Certainly. Moreover, I would be more than willing to get education on how to promote such a service and how to educate patients to use it.

10) If yes, what would you want from such a service/system?

Focus on supporting the patient to seek medical advice only when necessary, thus reducing cost and saving professional services for those in real need. Also, answer to health related questions, and maintain and provide information on personal medical data. Above all, such a service should be very strict to maintain personal privacy.

11) What kind of alerts or alarms would you think as important for the prevention and management of chronic cardiorenal disease and comorbidities?

Alert the healthcare professionals of a potentially life-threatening situation the patient is currently in. Calculate and project risks ratios for different patients based on their family history and lifestyle.