Chronic Kidney Disease as an Important Co-morbid Condition in Coronary Heart Disease Patients

Chronische Nierenerkrankung als bedeutender Risikofaktor bei Patienten mit koronarer Herzkrankheit

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1. Summary

In patients with established coronary heart disease (CHD) the adequate control of the modifiable "traditional" cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, achieving or maintaining normal body weight by regular physical activity and smoking cessation is of major importance to improve prognosis. This comprises to reduce the risk of disease progression, future vascular events, the development of congestive (ischemic) heart failure and ultimately to prolong survival. Guideline recommendations for secondary CHD prevention include specific treatment targets for blood pressure, lipid levels, and markers of glucose metabolism for both younger and older patients. Chronic kidney disease (CKD) has been identified as a "non-traditional" risk factor for worse outcome in CHD patients, as it is associated with a markedly increased risk for subsequent CV events and mortality.

The current thesis project addresses the quality of CHD prevention in a recent German sample of CHD patients with an emphasis on the group of older patients. Particularly, the role of CKD as an important co-morbid condition in CHD will be highlighted across CHD patients in Europe and detailed information on CKD awareness from the perspective of patients but also their treating physicians will be analyzed. The specific objectives are to investigate (a) the quality of care in a recent sample of German CHD patients and to investigate variation of risk factor control between younger and elder patients (≤70 versus >70 years). Also, (b) to analyze the prevalence of CKD across Europe in stable CHD patients in the outpatient setting as well as during a hospital stay for CHD. Finally, (c) to investigate the level of awareness of CKD in German CHD patients and their treating physicians.

Data from the European-wide EUROASPIRE IV (European Action on Secondary and Primary Prevention by Intervention to Reduce Events) study were used that include data on 7998 CHD patients in the ambulatory setting (study visit) as well as during a hospital stay for CHD (index). The German EUROASPIRE IV study center in Würzburg recruited 536 patients in 2012-2013. Risk factor control in the German subset was compared against the current recommendations of the European Society of

Cardiology (ESC) as adopted by the German Society of Cardiology (Deutsche Gesellschaft für Kardiologie, DGK). CKD was described following international nephrology guidelines by stages of glomerular filtration rate (eGFR) and albuminuria. German patients were asked in an additional *kidney specific module* whether they have ever been told by a physician about renal impairment. The fact that CKD or acute kidney injury (AKI) was mentioned in prominent parts of the hospital discharge letter as well as correct ICD-coding of CKD or AKI served as a proxy for physician's awareness of CKD.

We found that a majority of German CHD patients was treated with drug therapies for secondary prevention recommended by current ESC guidelines including e.g. β-blockers, anti-platelets and statins. However, treatment targets for blood pressure and LDL-cholesterol levels were not achieved in many patients (45% and 53%, respectively) and glycemic control in diabetic CHD patients with HbA1-levels <7% was insufficient (61%). A minority of patients reported on current smoking (10%), but unhealthy life-styles such as overweight/obesity were frequent (85% and 37%, respectively). Patterns of care differed between younger and older CHD patients while older patients were less likely to receive the recommended medical CHD-therapy, were more likely to have uncontrolled blood pressure and also to be diabetic. However, a greater proportion of diabetic patients >70 years was achieving the HbA1c target, and less elder patients were current smokers or were obese. About 17% of patients on average had overt CKD (eGFR< 60 ml/min/1.73m^2) in the entire European sample at the study visit, and an additional 10% had albuminuria despite preserved eGFR. These numbers showed considerable variation among countries. Impaired kidney function was observed in every fifth patient admitted for CHD in the entire European dataset of the EUROASPIRE IV study. Similar numbers were found for impaired kidney function in the German EUROASPIRE IV subset. Of those CHD patients with CKD at the study visit, only a third were aware of their renal impairment. A minority of these patients was being seen by nephrologists, however, with a higher likelihood of CKD awareness and specialist care in more advanced stages of CKD. About a third of patients admitted for CHD showed either CKD or AKI during the hospital

stay, but the discharge letter mentioned chronic or acute kidney disease only in every fifth of these patients. In contrast, correct ICD coding of CKD or AKI was more complete, but still suboptimal.

In summary, quality of secondary prevention in German CHD patients indicates considerably room for improvement, with life-style modifications may become an even greater factor in prevention campaigns than medical treatment into certain target ranges. Preventive therapies should also consider different needs in older individuals acknowledging physical and mental potential, other comorbidities and drug-interactions with co-medication. CKD is common in CHD patients, not only in the elderly. Since CHD and CKD affect each other and impact on worse prognosis of each other, raising the awareness of CKD among patients and physicians and considering CKD in medical therapy may improve prognosis and slow disease progression of CHD as well as CKD.

2. Zusammenfassung

Bei Patienten mit koronarer Herzkrankheit (KHK) ist die Behandlung der „klassischen“ kardiovaskulären Risikofaktoren wie Bluthochdruck, Hypercholesterinämie, Diabetes, regelmäßige körperliche Bewegung und ein normales Körpergewicht sowie der Nikotinverzicht von endscheidender Bedeutung, um die Prognose der Patienten zu verbessern. Dies beinhaltet eine Verminderung des Risikos für ein Fortschreiten der KHK, zukünftige kardiale bzw. kardiovaskuläre Ereignisse, der Entwicklung einer symptomatischen Herzinsuffizienz und letztlich die Reduktion des Mortalitätsrisikos. Klinische Leitlinien empfehlen in der Sekundärprävention für KHK spezifische Behandlungsziele für Bluthochdruck, Hypercholesterinämie und Diabetes, sowohl für jüngere als auch für ältere Patienten. Die chronische Niereninsuffizienz (NI) stellt einen sogenannten „nicht-klassischen“ Risikofaktor für eine schlechtere Prognose bei KHK-Patienten dar und ist assoziiert mit einem deutlich erhöhten Risiko für eine Progression der KHK und kardiovaskuläre Mortalität.

Die vorgelegte Arbeit widmet sich der Qualität der Sekundärprävention an kürzlich erhobenen Daten von KHK Patienten mit einem Schwerpunkt auf der Gruppe der Patienten mit fortgeschrittenem Alter. Außerdem wird die Rolle der chronischen Nierenerkrankung als bedeutender Risiko-Faktor bei Patienten mit koronarer Herzkrankheit in Europa sowie detaillierte Informationen bezüglich des Bewusstseins („Awareness“) hinsichtlich der Nierenerkrankung von Seiten der Patienten, aber auch aus der Sicht der behandelnden Ärzte untersucht. Die Studienziele im Speziellen beinhalten (a) die Umsetzung der KHK-Leitlinien in einem deutschen Kollektiv von Patienten inklusive der Unterschiede in der Versorgung zwischen Jüngeren und älteren Patienten (≤70 versus >70 Jahre). Zudem (b) wird die Prävalenz der NI in stabilen ambulanten Verhältnissen und ebenso während eines Krankenhausaufenthaltes aufgrund eines KHK-Ereignisses in 24 Europäischen Ländern inklusive Deutschland untersucht. Schließlich (c) wird am deutschen Studienzentrum das Bewusstsein („Awareness“) für Nierenerkrankungen sowohl bei den Patienten als auch den behandelnden Ärzten analysiert.

Es wurden die Daten der europaweiten EUROASPIRE IV (European Action on Secondary and Primary Prevention by Intervention to Reduce Events) Studie verwendet, für die zwischen 2012 und 2013 insgesamt 7998 KHK Patienten rekrutiert wurden. Sie enthält Informationen aus einem ambulanten Studienbesuch und aus einem Krankenhausaufenthalt aufgrund eines KHK-Ereignisses (Index). In den 536 Patienten, die am deutschen EUROASPIRE IV Studienzentrum in Würzburg eingeschlossen wurden, wurde die Qualität der Risikofaktorkontrolle nach den Empfehlungen der Europäischen Gesellschaft für Kardiologie (European Society of Cardiology, ESC) bzw. der Deutschen Gesellschaft für Kardiologie (DGK) untersucht. Chronische NI wurde anhand von international empfohlen Nephrologie-Leitlinien in Stadien eingeteilt anhand von glomerulärer Filtrationsrate (eGFR) und Albuminurie. Am deutschen EUROASPIRE IV Studienzentrum wurden die Patienten zudem in einem zusätzlichen „Nieren-spezifischen Modul" befragt, ob sie jemals von einem Arzt hinsichtlich einer Nierenerkrankung aufgeklärt wurden. Um das Bewusstsein für Nierenerkrankungen bei Ärzten einzuschätzen, wurde untersucht, ob akute oder chronische Nierenfunktionseinschränkungen im Arztbrief des Index-Aufenthaltes erwähnt wurden, und ob Nierenerkrankungen adäquat ICD-codiert waren.

Die Analysen ergaben, dass die Mehrheit der deutschen KHK-Patienten mit den empfohlenen Präparaten β-Blocker, Aspirin und Statinen behandelt werden, allerdings wurden die Ziel-/ Grenzwerte für Blutdruck und Cholesterin oftmals nicht erreicht (in 45% bzw. 53% der Patienten), ebenso wie die Blutzuckerkontrolle bei diabetischen Patienten (39%). Nur wenige Patienten waren aktive Raucher (10%), aber viele waren übergewichtig (85%) oder adipös (37%). Ältere Patienten erhielten etwas seltener die empfohlenen Präparate und waren häufiger hypertensiv oder Diabetiker. Allerdings zeigten sich diabetische Patienten älter als 70 Jahre besser kontrolliert und ältere Patienten waren seltener Raucher oder übergewichtig. Im Durchschnitt hatten 17% der KHK Patienten – mit großer Variation innerhalb der teilnehmenden Staaten – im EUROASPIRE JV Gesamtkollektiv eine chronische NI (eGFR <60 ml/min/1.73m²) und zusätzliche 10% hatten Albuminurie bei weitgehend erhaltener eGFR. Eine eingeschränkte Nierenfunktion zeigte sich auch in jedem fünften Patienten bei Krankenhausaufnahme

für das Index Ereignis im EUROASPIRE IV Gesamtkollektiv. Ähnliche Zahlen hinsichtlich der Nierenfunktionseinschränkungen fanden sich auch im deutschen Studienkollektiv. Von denjenigen Patienten des deutschen Studienzentrums bei denen eine chronische NI vorlag, gab nur ein Drittel an, von ihrer Nierenfunktionseinschränkung zu wissen. Nur sehr wenige von diesen Patienten wurden von einem Nephrologen behandelt, wobei Patienten mit fortgeschrittener NI sich sowohl häufiger ihrer NI bewusst waren als auch von Spezialisten behandelt wurden. Im Index-Krankenhausaufenthalt hatte ein Drittel der Patienten wenigstens einen Hinweis auf eine entweder chronisch oder akut eingeschränkte Nierenfunktion. Lediglich in einem Fünftel dieser Patienten war diese Diagnose allerdings im Entlassungsbrief erwähnt, während die Codierung nach Entlassung zwar vollständiger, aber immer noch lückenhaft war.

Die Qualität der Sekundärprävention in deutschen KHK-Patienten lässt weiterhin beträchtlichen Raum für Verbesserung. Hierbei erscheinen die Veränderung im Lebensstil weitaus zielführender zu sein als die medikamentöse Therapie in definierte Zielbereiche. Die medizinische Therapie und die Herangehensweise an Verhaltensänderungen muss insbesondere bei älteren Patienten an die besondere Bedürfnisse dieser Patientengruppe angepasst werden, beispielsweise deren eingeschränkte körperliche und kognitive Leistungsfähigkeit, die Komorbiditäten und mögliche Medikamenten-Interaktionen. Chronische NI ist häufig bei KHK Patienten anzutreffen, nicht nur bei älteren Studienteilnehmern. KHK und chronische NI beeinflussen sich und die Prognose des jeweils anderen gegenseitig, sodass eine Steigerung des Bewusstseins für Nierenerkrankungen sowohl bei Patienten als auch bei Ärzten, und die Anpassung der Behandlungsstrategie womöglich zu einer Verbesserung der Prognose und zur Verlangsamung des Fortschreitens beider Erkrankungen, KHK und NI führen.

3. Introduction

3.1. Secondary prevention in coronary heart disease

Patients with established coronary heart disease (CHD) are at high risk of disease progression including recurrent vascular events, hospitalizations and mortality[1]. A robust body of evidence is available and clinical guidelines have been published by national and international societies including the European Society of Cardiology (ESC) on how to improve prognosis regarding prolonged survival and reducing the risk of disease progression, vascular events and the development of ischemic congestive heart failure in this high-risk population[2]. Therapeutic strategies target at various components of the disease to stabilize existing plaques, reduce the risk of thrombotic events on vulnerable areas of the endothelium, to reduce the tone of the sympathetic nervous system and to overall reduce the progression of the underlying arteriosclerosis. Herein, the "traditional" cardiovascular (CV) risk factors include (a) blood pressure and hypertension, (b) lipids, particularly low density lipoprotein – cholesterol (LDL-C) levels and dyslipidemia, (c) glucose metabolism and diabetes mellitus, (d) nicotine and smoking, (e) male gender, and (f) a positive family history of vascular events[2].

Medical therapy of secondary prevention in CHD consists of three major drug classes: platelet inhibition e.g. by acetyl-salicylic acid (ASS), β-blockade, and lipid control, in particular the use of statins, to lower LDL-C levels. For the "traditional" CV risk factors, therapeutic targets have been proposed, e.g. LDL-C below 1.8 mmol/L (70 mg/dl) and 2.5 mmol/L (100 mg/dl), respectively, blood pressure generally below 140/90 mmHg, with modified targets for certain subgroups of patients (elderly patients or those with diabetes), and adequate glycemic control (HbA1c <7%) in patients with diabetes[2]. While these medical treatments rely on the prescriptions of a physician, another major aspect of the therapeutic strategy in secondary CHD prevention is based on factors that are predominantly in the responsibility of the patient, mainly life style factors. These are to quit smoking, to regularly being physically active with about 30 minutes moderately to vigorous intense exercise training 3 times per week and to maintain a

healthy diet, low of salt and (unsaturated and saturated) fat, and rich of fruit, vegetables and fish, which also has been referred as the Mediterranean diet[2, 3]. Not only that life style changes impact on lowering blood pressure and LDL-C levels, regular physical activity and healthy diet also lead to maintaining normal body weight, i.e. a body mass index (BMI) of <25 kg/m², or to reducing body weight in overweight (BMI 25-30 kg/m²) or obese (BMI <30 kg/m²) patients. Overweight/obesity, unhealthy diet and limited physical activity are responsible for an increased risk for the development of glucose dysregulation including impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and overt diabetes mellitus type 2, which further increase the risk of CHD progression, CHD events and mortality[2, 4]. Herein, undetected diabetes in CHD patients particularly impacts on long term prognosis of CHD including disease progression and mortality[5].

Although clinical practice guidelines for secondary prevention in patients with CHD get promoted among physicians and are easily accessible, previous studies show limited implementation of appropriate preventive measures in daily clinical practice[6, 7]. Over the last decade the prescription rates of platelet-inhibitors, β-blockers and statins are increasing and the vast majority of CHD patients receive the recommended drug classes. However, treatment targets of blood-pressure, LDL-C levels and glycemic control in diabetic patients are frequently not achieved[6, 7]. While smoking rates overall are decreasing in the Western world, a trend towards more smokers particularly in younger individuals[8] including those with established CHD[7] can be observed. Furthermore, beneficial life-style modifications are far from optimal, especially more CHD patients are overweight or obese, and are diabetic, which might be related to and also caused by each other[6, 7]. Details of these secular trends and their underlying reasons in particular why life-style modifications show only little improvement, yet even worsening of patient behavior need to be understood and focused on in future studies. It appears that the improvements of medical CHD therapy over the last years are counteracted by inadequate life-style changes[9]. These observations in CHD patients reflect behavior patterns which are evident in the underlying general population, mainly in the developed but also in the developing world. Since this is not the main aspect of

the current thesis, only some aspects will be discussed in a brief and very general overview: individuals in their regular daily activities at the work place and at home are physically relatively inactive and present with inadequate eating habits, i.e. a high intake of calories and salt. Genetically, among others a shift in the uric acid metabolism, i.e. the reduced activity of uricase leading to elevated uric acid levels, might be involved[10]. This genetic change improved survival chances of hominids as it impacts on the pathophysiology of energy storage in fatty tissue, which enabled the human race to move from the jungle (with unlimited supply of fruit and carbohydrates) to the savanna and even colder areas, where food and energy is much less and irregularly accessible. Therefore, nowadays, the genetic variation that guaranteed survival during evolution causes problems in a time in which food is overwhelmingly available, i.e. overweight/obesity and hypertension[10]. Another aspect can be approached by psychology: Why do individuals e.g. with CVD and myocardial infarction, frequently continue smoking and refrain from being physically active and stay overweight and obese, although the benefits of normal weight and quitting smoking are being discussed by their treating physician and are also introduced in campaigns to the general population. It seems that taking pills, but staying at a high underlying risk of the disease without changing own regular behavior, is much easier than modification of life style patterns. This phenomenon, which includes depression, cognitive impairment but also personal behavior[11], needs to be understood in much more detail that it can be targeted in future interventions in CHD.

The European Society of Cardiology (ESC) initiated the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) program in 1995 to investigate quality of care in secondary CHD prevention across Europe [12]. In regularly conducted cross-sectional surveys, identical standardized methodology is being used to collect data on risk factor control and behavior in the participating countries. In each country, patients of one geographical area (>0.5 million inhabitants) are being recruited from at least one hospital providing interventional cardiology and cardiac surgery and one hospital offering care for AMI and myocardial ischemia. While nine countries participated in EUROASPIRE I (1995-1996)[13], the number increased to 15 in EUROASPIRE II (1999-2000)[14] and 22 in

EUROASPIRE III (2006-2007)[15]. The current EUROASPIRE IV survey was a cooperation of the ESC with the European Association for Cardiovascular Prevention and Rehabilitation (EACPR) and enrolled patients of 24 European countries between 2012 and 2013[16]. The study also focused for the first time on the detection of dysglycemia and diabetes[17] by incorporating elements of the Euro Heart Survey of Diabetes and the Heart[18].

The German Society of Cardiology generally follows the recommendations of the ESC and publishes German adaptions of the ESC guidelines in the format of comments and "Pocket-Leitlinien"[19]. Similar trends in terms of quality of care in secondary CHD prevention as well as in changes over time were observed in the German subset of EUROASPIRE I to III (1995 to 2007), which was conducted in the region of Münster: while the recommended medical therapy was increasingly prescribed, treatment targets for LDL-C and blood pressure were frequently not met[20]. Overall, the rate of current smokers was unchanged, but numbers for overweight and obesity as well as for diabetes were rising[20]. To further investigate the success of national campaigns to promote healthy life style, smoking cessation and the risk of CV disease but also education of physicians, it is of particular interest to continue to observe current practice of clinical care for CHD patients as well as to investigate patient's behavior and life-style.

3.2. The elderly patient with coronary heart disease

Life-expectancy in Western countries including Germany is continuously rising[21, 22] and the group of older patients with CV-risk factors and established CHD as well as with CKD will constitute a major challenge for physicians and the community[21]. Due to improved health care, e.g. early diagnosis of myocardial ischemia, catheter interventions such as percutaneous coronary intervention (PCI) and stent implantation, better techniques in coronary artery bypass grafting (CABG) surgery, and a wide spectrum of medication for secondary prevention, patients are more likely to survive cardiac events that would have led to death a few decades ago. Furthermore, changes in CHD treatment, but also public education

and population wide policies can achieve substantial reductions in CVD mortality as it has been shown over the last decades in Scotland[23]. Contributions to these observations can be estimated by epidemiological methods, i.e. the IMPACT model, by which about 40% of the decline in mortality rates could be explained by improved treatment (including also secondary prevention), and another 40% by reductions in risk factors such as blood pressure, total cholesterol and smoking on a population level[24]. However, variations were observed across social groups according to socioeconomic status and also were some of these beneficial changes counteracted by increases in obesity and diabetes[24]. Recent analyses from nine European countries also predicted significant reductions in CHD mortality rates by 2020 and highlighted the need for policy and health campaigns to promote healthy diet and lifestyle among the population to reduce the burden of CVD and CV mortality[25].

Despite these beneficial secular trends due to improved primary and secondary CHD prevention, the group of elderly patients with severe coronary atherosclerosis and a number of comorbid conditions, including diabetes and hypertension will be growing substantially in the future[21]. Moreover, during lifetime atherosclerosis may manifest also as cerebrovascular disease with a high risk of stroke, or as peripheral artery disease (PAD) with the risk of ischemia and ulcerations and subsequent hospitalizations for radiologic and surgical interventions, including amputations. Cardiac ischemia, despite timely and effective treatment, causes a variety of processes in the myocardium, including demarcation of the scar, organization of the scar-surrounding areas and morphology of the left ventricle and the entire heart, which has been referred as cardiac remodeling[26]. These processes frequently result in the development of congestive (ischemic) heart failure (CHF), including symptoms such as fatigue, dyspnea and edema[27] and are associated with a extremely high risk of hospital admissions and mortality[22, 28].

Prevention of the development of CVD and CHD should therefore be the primary goal of health policy and medical therapy[21, 29, 30], to reduce the societal burden of individuals suffering from CHD and its long term consequences such as CHF, which are particularly evident in older patients. The optimal

strategy, however, for secondary CHD prevention in the elderly is widely discussed, as the evidence for secondary CHD prevention in older patients is much less conclusive as compared to younger individuals[31, 32]. Clinical care in older patients has to consider on one hand treatment targets that have been shown to reduce adverse outcomes, such as tight targets levels for blood pressure and lipids, but also a *per se* lower level of physical activity, accumulations of other co-morbid conditions and drug-interactions in this multi-morbid population[21, 33]. The medical need on one hand and the reluctance from potential side effects may preclude many physicians to prescribe recommended therapy also in the elderly.

Only very few studies investigated differences in CHD risk factor control stratified by age groups, but found that in general older patients are less likely to receive treatment according to guideline recommendations[20, 34, 35]. Therefore, investigation of differences in management patterns among older CHD patients in a recent sample is important to understand the reasons for potential variations and to guide future research to overcome potential obstacles in applying adequate CHD treatment to the vulnerable group of elder individuals.

3.3. Chronic kidney disease as non-traditional risk factor for CHD

Beside from the traditional risk factors for CHD such as hypertension, dyslipidemia, diabetes, etc. a number of other conditions have been described that are related to the development and the prognosis of CHD. These non-traditional risk factors include e.g. homocysteine, Lp(a), anemia and chronic kidney disease (CKD)[2, 30] and may be related to an increased risk for worse prognosis. The phenomenon, that even if traditional risk factors are well controlled, the risk for worse CVD outcome is still much elevated when compared to healthy individuals and varies considerably among patients with CVD, indicates that other factors, including non-traditional risk factors as described above, but also environmental factors, metabolomics and genetic variations might contribute to CVD occurrence and its progression, which is frequently described as “residual risk”[36]. CKD and CHD share similar pathogenetic pathways such as

arterio-/atherosclerosis and chronic inflammation[37, 38]. It has been shown that CKD is an important risk modifier in CHD[39], associated with CHD progression[40, 41], worsening of heart failure[42], and an increased risk of hospitalization and mortality[40, 43].

Population-based studies indicate that CKD is common in the Western world with prevalence rates of 3% to 26% [44, 45], depending on the country, the population studied and the method by which kidney function was determined. Importantly, the prevalence of CKD is substantially higher in older individuals[45]. There is an ongoing debate whether a decline in kidney function with increasing age should be considered as normal or as a result of a variety of comorbid conditions, and thus as an expression of "unsuccessful aging"[46, 47]. Recent data from the German DEGS study[48] showed a considerably low rate of CKD of 2.3% in all participants (18-79 years old), a higher rate of CKD in older individuals (13%), and also a significant proportion of 12% of subjects (up to >25% in older individuals) with albuminuria.

CKD is associated with an aggravated risk for mortality and morbidity when compared to the healthy population[49] while CKD is generally defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m². In recent years, the role of albuminuria in addition to reduced eGFR has been investigated in much more detail. A large pooled analysis of several studies reported that a lower eGFR is associated with a more than doubled risk of all-cause and CV mortality in patients without significant proteinuria. On the other hand, those patients with largely preserved eGFR, but significant levels of albuminuria, experienced an up to 3.7 fold higher risk for death (CV death 4.8 fold) when compared to patients without albuminuria [50]. The important role of albuminuria in addition to eGFR is reflected by the current classification proposed by the international Kidney Disease Improving Global Outcomes (KDIGO) group, according to CKD-G and CKD-A stages[37] (see figure 1).

Patients with CKD in general are frequently older and are more likely to present with several comorbid conditions such as diabetes, vascular disease and in those with established CHD, a longer duration of CHD and more severe coronary atherosclerosis[38].

Figure 1: CKD – classification according eGFR and albuminuria

		Albuminuria (ACR)		
CKD-stage	$eGFR_{CKD-EPI}$ (ml/min/1.73m²)	**A1** (< 30 mg/g)	**A2** (30 – 300 mg/g)	**A3** (> 300 mg/g)
G1	≥ 90			
G2	60 – 89			
G3a	45 – 59			
G3b	30 – 44			
G4	15 – 29			
G5	< 15			

Legend: CKD stages by eGFR category (CKD-G) and level of albuminuria (CKD-A) as suggested by KDIGO; colors indicate low risk (green), moderately increased risk (yellow), high risk (orange), very high risk (red) for worse prognosis [37]

While CKD aggravates the prognosis of CHD in considerably stable condition as described above, kidney dysfunction also disposes the patient to complications and a worse clinical course in hospital stays of various causes [51, 52], including admissions for CHD[40, 53-55]. In heart surgery, e.g. in CABG, the role of CKD is reflected by the fact that it is an important component in assessing the patient's operative risk by EuroSCORE 2 [56]. The score also includes other patient characteristics such as age, gender, chronic pulmonary disease, cerebrovascular disease or PAD, neurological dysfunction, and previous cardiac surgery. Not only in CABG surgery, but also after AMI and PCI, CKD is a major risk factor for the development of acute kidney injury (AKI)[57-59]. It should be noticed that acute cardiac events, e.g. due to CHD, can directly affect renal function, e.g. by low cardiac-output in AMI, thus leading to AKI[60]. AKI is defined as an acute deterioration of kidney function indicated by retention of soluble factors, e.g. serum creatinine (SCr) or urea, and/or drop in urine volume. It is increasingly acknowledged that even slight changes in SCr, i.e. a rise of >0.3 mg/dl, are associated with important early and long-term

consequences[59, 60]. Patients experiencing AKI are at increased risk for the development and progression of CKD, progression of CHD, and impaired outcomes in CHD[60-62]. The health economic relevance of kidney dysfunction, acknowledging multi-morbidity of patients and risk for complications, is also reflected by the fact that adequate ICD-10 coding of CKD and AKI impacts on hospital reimbursement[63].

Despite the relevance of impaired kidney function in CHD patients, comparable data on the proportion of CKD in CHD patients are sparse[64, 65]. A comprehensive assessment of the prevalence of CKD in European CHD patients, using identical methodology of data collection and measurement of parameters of kidney function (serum creatinine [SCr] and albuminuria) in all participating countries, in the outpatient setting as well as during hospital stays for CHD is needed. Herein, detailed description of the characteristics of CHD patients with kidney dysfunction will allow easier identification of these high risk individuals in clinical practice.

3.4. Specialist Care for CKD

As described in section 3.3., CHD patients with CKD represent a multi-morbid and vulnerable population. Therapeutic management should thus be adapted accordingly and renal specialists, e.g. nephrologists, should be involved. Key components of medical care in CKD in general should consider adequate hydration, avoidance of nephro-toxic drugs, dose adjustments of medication according to kidney function, the use of nephro-protective drugs, e.g. ACE-inhibitors and AT1-receptor antagonists[37], and certain targets for e.g. blood pressure control[2, 66-68]. It is a crucial component of nephrology care to estimate the individual patient's risk for disease progression[69] to better decide on respective treatment goals and to educate the patient accordingly. It has been shown that early referral to nephrology and specialist care for impaired kidney function is associated with tighter blood pressure control and a reduced risk for CKD progression[70, 71]. Furthermore, data suggest that early referral is related to a reduced risk of CHD events and mortality[70, 72], also once renal replacement therapy by hemodialysis is

initiated[73]. Adequate information of CKD patients in preferably long-term pre-dialysis care and on chronic hemodialysis treatment, respectively, is also related to a greater satisfaction of patient needs from the perspective of the patient[74] and with improved quality of life[75, 76]. However, the latter might be mediated by better education of the patient regarding the choice of renal replacement therapy (hemodialysis, peritoneal dialysis) and timely placement of the vascular access[77].

To the best of our knowledge, data on the proportion of CHD patients with CKD who are referred to specialty kidney care, including nephrologists, as well as how many of these patients are being seen and treated by renal specialists are currently not available for Germany.

3.5. Awareness of CKD among patients and physicians

As described above, CKD is common and represents an important condition, but considerably few individuals (<5% - 30%) are aware of the disease in population based studies[78, 79], CKD cohorts[80, 81] and in CHD patients[65]. National campaigns and public education programs e.g. in the UK and the US have been launched, but significant improvements in the level of CKD awareness could not be observed in those individuals with CKD in general population studies[82-86] and also in the general population[86]. Patient education and patient's awareness of a certain disease has been shown to be related to better adherence to medication[87, 88] and improved achievement of treatment targets[86, 89], yet, with varying results among populations studied[90]. Also in CKD, evidence on the impact of CKD awareness from the perspective of the patient related to risk factor control and improved outcomes are conflicting: a study of the National Health and Nutrition Examination Survey (NHANES) of the US showed that in patients with CKD a higher level of patients' knowledge of impaired kidney function was not related to improved achievement of treatment targets or adequate blood pressure[86]. On the other hand, in patients of the prospective cohort study CHOICE also from the US indicated a reduced risk of mortality in patients on dialysis with adequate knowledge about their disease, treatment targets and dietary advice when

compared to less educated patients[91]. Recent results of an interventional study in CKD patients not on dialysis are encouraging, that focused education of the primary care physician (PCP) and the patient including his relatives can indeed improve risk-factor control and also slow the progression rate of CKD[92]. It seems intuitive that a patient feels more confident if he is aware of a certain condition and is informed and educated accordingly about the treatment options. On the other hand, he might also be frightened by the information on the diagnosis and the disease's prognosis [93], which may aggravate depressive mood, since depression is a common comorbidity in CHD[94] as well as in CKD[95].

The education of the patient and the level of awareness of certain diseases are directly dependent on the patient-physician interaction[96, 97] and thus dependent on the level of awareness of the disease among physicians[93, 98]. Consequently, the role of CKD as an important diagnosis is widely discussed in the medical literature, but needs to be judged by the physician as important enough that it should be discussed with the patient. Information on kidney function is routinely visible to physicians, as since the introduction of SCr-based equations, eGFR is increasingly displayed on the laboratory report routinely with every SCr measurement worldwide[99, 100]. Similar to the outpatient setting, kidney dysfunction and/or episodes of AKI during hospital stays need to be recognized by the treating physician and judged as relevant to be reported in the discharge letter, which is the primary source of information transfer to the ambulatory setting.

Evidence is sparse regarding the perception of kidney disease in routine care of patients with CHD, from the perspective of patients in stable conditions as well as of physicians in the hospital setting. Describing the level of CKD awareness and the determinants among patients and physicians will help to identify potential targets on how to improve CKD awareness, which may positively impact on adherence to therapy, risk factor control and ultimately to clinical prognosis of patients.

4. Aims and hypotheses

The current project investigates the role of CKD in secondary CHD prevention from various perspectives. The specific objectives corresponding to three manuscripts are as follows.

Aim 1

To report on current quality of CHD care in the German sample of the EUROASPIRE IV study with an emphasis on potential variations in risk factor control between younger and older patients, who are also more likely to suffer from several comorbid conditions, including CKD.

We hypothesize fairly adequate medical treatment, but limited achievement of treatment targets and insufficient life-style and behavior of patients. We also hypothesize that treatment and behavior patterns will vary between younger and elder patients, and that a greater proportion of CKD in older individuals will be observed.

Aim 2

To investigate the prevalence and characteristics of CKD in the entire setting of the multinational EUROASPIRE IV study of 24 European countries. This includes impaired kidney function during a hospital stay for CHD, in stable conditions in the ambulatory setting and also changes in kidney function between both.

We hypothesize CKD to be a common comorbid condition in CHD patients with considerable variation among countries. Determinants of impaired kidney function will largely consist of traditional CV risk factors, but potentially also specific factors such as urgency of the CHD event and type of treatment for CHD may indicate significant and meaningful associations.

Aim 3

To analyze the proportion of CHD patients referred to specialist kidney care (e.g., nephrology), and particularly the level of CKD awareness and its determinants in the German sample of the EUROASPIRE IV study. Analysis of CKD awareness includes (1) the perspective of the patient in the ambulatory setting including specialist (nephrology) care for CKD, (2) the perspective of the treating physician in a hospital stay for CHD (as evidenced by the fact that altered kidney function is being mentioned in prominent parts of the discharge letter), (3) the adequacy of ICD-coding during the hospital stay for CHD.

We hypothesize that the majority of patients and physicians to be unaware of kidney disease, yet higher awareness in those with more severe CKD. In contrast, ICD-coding is likely to be more complete as it is relevant for case-payment.

5. Methods

5.1. Study population – the EUROASPIRE IV study

The ESC initiated the fourth survey of the EUROASPIRE program to not only study the current quality of CV risk factor control in CHD patients and to investigate secular trends by comparing the results to the previous surveys. But also for the first time in EUROASPIRE, detailed data on the prevalence of the important comorbid conditions diabetes and CKD were collected. The EUROASPIRE IV study was carried out in 2012-2013 and included 78 recruiting centers of 24 countries and enrolled a total of 7998 patients with CHD[16]. All hospitals of one geographical area (>0.5 million people) per country were identified, including at least one hospital providing interventional cardiology and cardiac surgery and at least one additional hospital offering care for AMI and myocardial ischemia. At least two recruiting centers per country were selected by considering an approximately equal chance for any patient of the geographical area fulfilling the inclusion criteria (see below) to be treated in these hospitals and to be included in the study sample. Within each country, a total of 400 patients was suggested to be included, which allowed to estimate prevalences with a precision of at least 5% and with a confidence of 95%.

Of note, it was recommended by the EUROASPIRE IV study protocol that the same geographical area and recruiting centers that participated in previous EUROASPIRE surveys should be selected. However, due to retirement of the national coordinator Prof. U. Keil, the German study center moved from Münster (EUROASPIRE I, II and III) to Würzburg (EUROASPIRE IV) with the national coordinators Prof. P. Heuschmann, Prof. S. Störk.

Patients with CHD were included if they were between 18 and 79 yrs of age and were admitted to the recruiting hospitals due to a coronary event (index) six months to three years prior to the anticipated study visit. These included CABG surgery, PCI, AMI, or myocardial ischemia, the latter two receiving conservative therapy without intervention. The latest event during the hospital stay was used for index-

classification. After identification through the hospitals' digital information systems, subjects were consecutively (starting from 6 months since the hospital stay and going backwards in time) invited to attend the EUROASPIRE IV study visit.

5.2. Data collection

Study visit

Information on medical history, medication, knowledge of risk factors, their targets of treatment, life-style and behavior including diet, body weight, physical activity, smoking were assessed by personal interviews. In self-administered questionnaires, data on adherence to medication, anxiety and depression (Hospital Anxiety and Depression Scale [HADS]), health status (EQ 5D), quality of life (HeartQoL), and physical activity (International Physical Activity Questionnaire [IPAQ]) were collected. The following physical measurements and examinations were performed according to standardized EUROASPIRE IV manuals: blood pressure was measured up to four times in a resting sitting position using the Omron M5-I automatic digital sphygmomanometer. Weight and height were measured with SECA scale model 701 and SECA measuring stick model 220, respectively. Waist circumference was assessed by a metal measuring tape. Breath carbon monoxide (CO) in exhaled air was measured with Smokerlyser (Bedfont Scientific, Model Micro+). Serum and EDTA-blood samples were drawn, in a preferably fasting state, processed immediately and stored at -80°C on site. After completion of recruitment, samples were shipped to the central EUROASPIRE IV laboratory (Laboratory of Analytical Biochemistry, National Public Health Institute, Helsinki, Finland) where SCr, lipid levels (total cholesterol, LDL-cholesterol [LDL-C], HDL-cholesterol [HDL-C], triglycerides) and HbA1c were measured. As requested by the EUROASPIRE IV protocol, urinary albumin/creatinine ratio (ACR) was measured locally at each study center. Fasting plasma glucose (FPG) in the venous EDTA blood sample was measured on-site using the HemoCue, model Glucose 201+ device. Non-diabetic participants fasting for at least 10 hours were destined to

undergo oral glucose tolerance testing (OGTT): following the FPG measurement, patients were asked to drink 75g of glucose in 200 ml of plain water. Two hours later, a second blood venous draw with a EDTA-tube was performed and plasma glucose was measured.

Retrospective chart review

Study participants also consented in retrospective chart review of their index-hospitalization to obtain detailed information on the CHD event that had led to admission at the recruiting hospitals 6-36 months prior to the study visit (see above). This included data on the urgency of the CHD event (elective, urgent, emergency), therapy (conservative, PCI/stent, CABG), comorbidities and CV risk factors, measurements (e.g. weight, blood pressure) and laboratory data of clinical routine (e.g., lipids, HbA1c, and SCr at hospital admission and ACR at any day during the hospital stay). Furthermore, information from the discharge letter was extracted including CV risk factors, measurements and performed procedures and also those that had been recommended to be performed in the outpatient setting after discharge.

Central data management

All data were collected on paper-based case report forms (CRF) and entered manually into web-based CRFs using unique identification numbers provided by the EUROASPIRE IV data management center EURObservationalResearch Programme (Nice, France). Data were centrally checked for completeness and plausibility. Respective queries were sent to each study center for clarification. On request to the EUROASPIRE IV steering committee, a copy of the country specific datasets was sent to the National Coordinators. The dataset for the current thesis project, including definition of risk factors and comorbid conditions, was prepared in close cooperation with the EUROASPIRE IV study director, Prof. K. Kotseva, and the support of the EUROASPIRE IV data management center (S. Authier). This was

particularly done to apply identical definitions of variables in the entire EUROASPIRE IV dataset (see study aim 2), as they were used and published in the analyses for the main EUROASPIRE IV manuscript[16].

5.3. The German EUROASPIRE IV study center

Study population

At the German study center, participants were recruited from the University Hospital Würzburg, Department of Medicine I (Director Prof. G. Ertl), and the Department of Cardiovascular Surgery (Director Prof. R. Leyh). The Department of Medicine at the Klinik Kitzinger Land (Dr. W. Karmann) served as the "external" recruiting center. Subjects eligible for EUROASPIRE IV received up to three postal invitation letters and study procedures were performed at the joint survey unit of the Comprehensive Heart Failure Center (CHFC) and the Institute for Clinical Epidemiology and Biometry (ICE-B) of the University of Würzburg. It offers about 170 m² of space and includes dedicated rooms for check-in/waiting area, physical measurements, echocardiography/ultrasound examination, physical examination, data-management and laboratory facilities for collection, on-site processing and storage (-80°C) of biomaterials.

Data collection

Invited subjects were informed about the purpose, the risks and potential benefits of the EUROASPIRE IV study by physicians or an epidemiologist and all participants provided written informed consent. In addition to the previously described contents of the core EUROASPIRE IV protocol, center specific modules were implemented, e.g. echocardiography, carotid ultrasound measurement, or a screening instrument for impaired cognition (Montreal – Cognitive Assessment [MoCA]). We also collected additional serum, EDTA and urine samples which were stored long-term at -80°C at the local biobank of the CHFC and the interdisciplinary bank of biomaterials and data (ibdw) for future analysis of

biomarkers of the German participants only. Moreover, further details during the index hospital stay were collected from the hospital record, the hospital's laboratory system and the discharge letter. Herein, the CHFC DataWarehouse was utilized for data extraction for patients admitted to the University Hospital Würzburg[101]. In principle, all routine clinical data can be accessed through the CHFC DataWarehouse, while pseudonymized data handling and gate-keepers assure adherence to German data-protection laws.

For the current project, a *kidney specific module* was implemented at the German study center a few weeks after enrollment started and thus data were missing in 11.6%. It included questions regarding patient's awareness of CKD (*"Have you ever been told by a doctor/health care provider that your kidney function is impaired, e.g. not as good as it would be expected?"*), the recommendation to seek professional advice from a kidney specialist (*"Have you ever been told by a doctor/health care provider that you should be seen by a specialist to have your kidney function checked?"*) and whether or not a patient had been seen by a kidney specialist (*"Have you ever been seen by a specialist to have your kidney function checked and/or treated?"*). Furthermore, additional information on kidney function during the index hospital stay (SCr at hospital discharge, acute kidney injury (AKI), renal replacement therapy, CKD or AKI reported in the discharge letter, ICD-10 coding for CKD and AKI, OPS-codes for dialysis treatment) were collected.

Data management

Data of these extended modules at our study center were collected on pseudonymized paper-based CRFs or handled and stored digitally. After plausibility checks and verification of data, the extended module data were merged to the German EUROASPIRE IV dataset by employing the EUROASPIRE IV specific patient-ID and center-ID, as well as a locally used national-ID to identify individual participants.

Ethics and data protection

The EUROASPIRE IV study at the German study center was approved by the ethics committee of the Medical Faculty of the University of Würzburg (Vote 58/12). Recruitment strategy including identification of eligible participants and contact by postal letters as well as data handling within the study was approved by the data protection officers at the University Hospital Würzburg and the University of Würzburg (DS-117.605-15/12).

5.4. Definitions

We used the most recent definition of CKD according to KDIGO[37]. Estimated glomerular filtration rate (eGFR) was calculated based on SCr using the CKD-EPI formula[102] and the following CKD-G stages were classified: CKD-G1 eGFR ≥90 ml/min/1.73m², CKD-G2 eGFR 60 to <90 ml/min/1.73m², CKD-G3a eGFR 45 to <60 ml/min/1.73m², CKD-G3b eGFR 30 to <45 ml/min/1.73m², CKD-G4 eGFR 15 to <30 ml/min/1.73m², CKD-G5 eGFR <15 ml/min/1.73m². Urinary albumin/creatinine ratio was used to define CKD-A strata: CKD-A1 ACR <30 mg/g; CKD-A2 ACR 30 to <300 mg/g; CKD-A3 ACR ≥300 mg/g (*see figure 1*). Acute kidney injury (AKI) was also defined according to KDIGO[60] as an increase in SCr of ≥0.3 mg/dl within 48 hours or SCr-increase of 1.5-1.99x baseline SCr within 7 days (AKI stage 1), SCr-increase of 2.0-2.9x baseline SCr (stage 2) and SCr-increase ≥3.0x baseline or SCr >4 mg/dl or dialysis (stage 3).

Cardiovascular risk factors at the study visit were defined as follows: overweight (BMI ≥25 kg/m²), obesity (BMI ≥30 kg/m²), abdominal overweight (waist circumference in females ≥80cm, in males ≥94cm) and central obesity (waist circumference in females ≥88cm, in males ≥102cm)[103]; smoking either self-reported or CO-values of >10ppm in exhaled air if self-reported smoking was denied[104]. Dyslipidemia was described as LDL-cholesterol ≥2.5 mmol/l (≥100 mg/dl) and also as LDL-cholesterol ≥1.8 mmol/l (≥70 mg/dl)[2]. Hypertension followed suggestions of the ESC as blood pressure ≥140/90 mmHg, and ≥140/80

mmHg in patients with diabetes[16]. Diabetes was self-reported and adequate glycemic control in diabetic patients was defined as HbA1c <7.0%[2].

Covariates of the index hospital stay included the urgency of the index event (elective, acute [>24 hours], emergency [<24 hours] intervention/procedure), heart failure (according to case history or echocardiographic findings of cardiac dysfunction at admission) and CV-risk factors known at admission or reported in the discharge letter (hypertension, dyslipidemia, diabetes, smoking). Obesity was defined as BMI ≥30 kg/m² at admission or explicitly stated in the discharge letter.

Further details of variables and definitions used in the manuscripts are provided in the respective results sections (*see Manuscript 1 "EUROASPIRE IV – main results in Germany", Manuscript 2 "CKD in 24 European Countries in EUROASPIRE IV", Manuscript 3 "CKD awareness in the German EUROASPIRE IV study").*

5.5. Statistical methods

Statistical analyses were performed with SAS 9.3 (SAS Institute Inc., Cary, NC, USA). Two-sided p-values <0.05 were considered as statistically significant. Data are presented as numbers of observations (proportions, %), mean ± standard deviation (SD), median (inter-quartile range [IQR]), dependent on normal distribution of continuous variables. Normal distribution was tested with the Kolmogorov-Smirnov test and by investigating histogram plots. Differences across groups (e.g. CKD vs. no CKD) were tested by student's t-test/ANOVA, Wilcoxon rank-sum test/Kruskal-Wallis-test and χ^2/Fisher's exact test, as appropriate. To compare prevalences of CKD across countries in the entire EUROASPIRE IV dataset (*see Manuscript 2 "CKD in 24 European Countries in EUROASPIRE IV"*), data were age-standardized following the 2013 European Standard Population[105] by applying the weights in each age-stratum as displayed in the appendix (*see Age-standardization (European Standard Population 2013)).* Determinants

of CKD and CKD awareness were analyzed by logistic regression and results are displayed as Odds Ratio (OR) with respective 95% confidence interval (CI). To account for country-specific effects on the relationship of CKD to the various co-variates in these, the participating country was included as random intercept in multilevel multivariate logistic regression modelling (*see Manuscript 2 "CKD in 24 European Countries in EUROASPIRE IV"*). Analyses were performed on a complete-case dataset. Since data of the *kidney specific module* was missing in n=62 (11.6%) of patients, we tested the robustness of the multivariate models on a dataset with imputed missing data, using five imputations derived from the Markov Chain Monte Carlo method (SAS `proc mi`) (*see Manuscript 3 "CKD awareness in the German EUROASPIRE IV study"*).

6. Results

6.1. Manuscript 1 "EUROASPIRE IV – main results in Germany"

Wagner M, Gelbrich, G., Kircher, J., Kotseva, K., Wood, D., Morbach, C., Leyh, R., Ertl, G., Karmann, W., Stork, S. and Heuschmann, P. U.: *Secondary Prevention in Younger vs. Older Coronary Heart Disease Patients-Insights from the German Subset of the EUROASPIRE IV Survey,* International Journal of Behavioral Medicine (2017), epub ahead of print[106]; doi: 10.1007/s12529-017-9691-y; copyright © 2017. Reprinted by permission of Springer US to include the final accepted manuscript.

6.1.1. Summary

The study sample consisted of all n=536 CHD patients that were enrolled in the EUROASPIRE IV study at the German study center between August 2012 and March 2013 Median age was 68.7 years and 82% of the participants were male, with 2.8 years median duration of CHD. Medical therapy recommended in secondary CHD prevention consists of platelet-inhibition, β-blockade and lipid lowering drugs, which were prescribed in the German sample in 89%, 83% and 85% of the patients, respectively. Treatment targets for LDL-C are <2.5 mmol/l (<100 mg/dl) and according to most recent recommendations <1.8 mmol/l (<70 mg/dl)[2] and were achieved in 47% and 11% of the enrolled patients, respectively. 55% had adequate blood pressure control, while we applied the definition according to the German Society of Cardiology[67], with slightly different cut-offs in subgroups as compared to ESC suggestions (blood pressure ≥140/90mmHg; diabetes ≥140/85 mmHg, elderly patients >80 yrs ≥150/90 mmHg, CKD ≥130/90 mmHg). Dysglycemia, (i.e. diabetes or impaired fasting glucose/impaired glucose tolerance) was reported by 146 patients (27%), in which adequate glycemic control (HbA1c <7%) was observed in 61%. The majority of the patients were overweight (85%), 37% were obese and 10% were current smokers.

Older patients (≥70 years) as compared to younger patients (<70 years) were less likely to receive the recommended medical CHD-therapy of platelet-inhibition (84% vs. 93%, p<0.001) and β-blockade

(79% vs. 87%, p=0.02) and to have inadequate blood pressure control (50% vs.40%, p=0.02). No differences were observed for the prescription of lipid lowering drugs (86%% vs. 84%, p=0.7) and the control of lipid - levels (LDL-C <2.5 mmol/l: 51% vs. 45%, p=0.1); LDL-C <1.8 mmol/l: 12% vs. 9%, p=0.3). No statistically significant differences were found for the proportion of diabetes (30% vs. 26%, p=0.4), but we observed a trend towards a greater proportion of elderly diabetic patients achieving the recommended HbA1c target (68% vs. 55%, p=0.1). Moreover, smoking was less common in older patients (2.6% vs. 17%, p<0.001) as well as obesity (31% vs. 41%, p=0.01).

In the total cohort, 25% had overt CKD (i.e. eGFR <60 ml/min/1.73m²), while 42% of older patients had CKD as compared to 12% in younger subjects (p<0.001). This was also reflected by lower values of eGFR (median 64 ml/min/1.73m² [IQR 51 to 76] vs. 81 [70 to 92], p<0.001) and a greater amount of albuminuria (ACR 6.8 mg/g [2.6 to 19.9] vs. 3.2 [0.7 to 11.8], p<0.001).

6.1.2. Manuscript 1, as accepted for publication

Secondary Prevention in Younger vs. Older Coronary Heart Disease Patients

– Insights from the German subset of the EUROASPIRE IV Survey

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Abstract

Background: Evidence is limited on implementation of secondary prevention guidelines for coronary heart disease (CHD) in clinical practice and variations between younger and elder patients. We investigated the control of cardiovascular risk factors in German patients with CHD enrolled in the European-wide EUROASPIRE IV survey, stratified by younger (18-69 yrs) and older (70-79 yrs) age groups.

Methods: Eligible subjects were identified via the hospitals' patient information system and invited to attend a study-visit 6 mo to 3 yrs after hospitalization for CHD (myocardial infarction, ischemia, angioplasty/stent, coronary bypass grafting). Information on life-style and medication was collected by interview.

Results: 536 patients were recruited in 2012/13 (median age 69 years [IQR 62 – 74yrs], 18% female, 44% ≥70 years of age, median time between index hospitalization and study visit 1.8 [1.1 – 2.5] years). Proportion of CHD patients receiving recommended drug therapy was 89% for platelet-inhibitors (younger vs. older patients 93% vs 84%, p <0.01), 83% for statins (83% vs. 85%, p=0.9), and 83% for beta-blockers (87% vs. 79%, p=0.02). Uncontrolled blood pressure was observed in 45% (40% vs. 50%, p=0.02), LDL-cholesterol levels > 2.5 mmol/l in 53% (56% vs. 49%, p=0.1) and HbA1c levels >7% in diabetic patients in 39% (45% vs. 32%, p=0.1). 85% were overweight (86% vs. 85%, p=0.8), 37% were obese (41% vs 31%, p=0.01) and 10% reported current smoking (17% vs 3%, p<0.01).

Conclusions: Although most CHD patients received the drug classes recommended by guidelines, treatment goals were frequently not achieved. Elderly subjects had a less favorable pattern, which may reflect multi-morbidity and weaker identification with treatment targets. National CHD prevention strategies should not only focus on enhancing lifestyle modifications and reaching treatment targets, but also on highlighting the different needs in older individuals.

Key-words

coronary heart disease, secondary prevention, risk-factors, elderly, EUROASPIRE survey

Background

The main purpose of medical treatment in patients with coronary heart disease (CHD) is to adequately control the risk factors of disease progression, such as hypertension, dyslipidemia, diabetes, overweight/obesity, and smoking, and to aim for an overall healthy lifestyle [1]. However, previous studies showed that implementation of guideline recommendations for appropriate preventive measures in daily clinical practice remains suboptimal [2,3].

The European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) surveys – a multinational initiative of the European Society of Cardiology (ESC) – addressed guideline implementation in clinical practice in CHD patients in three previous phases since 1995 [4-6]. In the current EUROASPIRE IV survey, 7998 patients with CHD aged 18 to 79 years from 24 European countries were examined between 2012 and 2013 [3]. The main results indicated insufficient control of established risk factors, albeit the majority of patients is now treated with anti-platelet drugs, statins and beta-blockers. Many CHD patients also still smoke, and the prevalence of low physical activity as well as of overweight/obesity is increasing. However, considerable variability of risk factors and secondary prevention therapy was observed between participating European countries [3].

Due to the gain in life expectancy in Western countries [7] the absolute number of older patients with CV risk factors and established CHD will increase in the next decades. The optimal strategy for secondary CHD prevention in the elderly is widely discussed, as evidence is much less conclusive as compared to younger individuals [8,9]. Therapeutic care in the elderly has to consider on one hand treatment targets that have been shown to reduce adverse outcomes, such as tight targets levels for blood pressure and lipids, but also a *per se* lower level of physical activity, accumulations of other co-morbid conditions and drug-interactions and polypharmacy in this multi-morbid population [10,7]. Only few studies reported on differences in CHD risk factor control between younger and elder patients [11-13].

Therefore, we report the main results of quality of CHD care in secondary prevention at the German study center of the EUROASPIRE IV survey. We apply current updated guideline recommendations by the ESC [1] and the German Society of Cardiology [14], and analyze potential variations in risk factor control between younger (<70 years) and older (70 to 79 years) patients.

Methods

Patient population

The principle results including the methodology of the "hospital-arm" of the entire EUROASPIRE IV survey have been published previously [3]. Patients between 18 and 79 yrs of age with CHD were invited to attend a study visit if they had been admitted due to a coronary event (coronary artery bypass grafting [CABG], percutaneous coronary intervention [PCI], acute myocardial infarction [MI], or myocardial ischemia, the latter two receiving conservative therapy without intervention) in the 6-36 months prior to the anticipated study visit. The latest event during the hospital stay was used for index classification. At the German study center, participants were recruited from the Dept. of Medicine I, the Dept. of Cardiovascular Surgery, University Hospital Würzburg and the Dept. of Medicine, Klinik Kitzinger Land. Eligible subjects were identified through the hospitals' medical records and consecutively invited by up to three postal letters.

Data collection

At the study visit, detailed information on medical history, medication, life-style and behavior were collected, and measurements (e.g. blood pressure, weight, height, carbon monoxide [CO] in exhaled air, oral glucose tolerance testing [OGTT], blood draw, preferably in participants fasting) were performed according to EUROASPIRE IV standards [3]. Study participants also consented in retrospective chart review of their index-hospitalization to obtain information on the index event, risk factors, medication and clinical measurements.

Data management

Management regarding data requested by the EUROASPIRE IV protocol was provided by the EURObservationalResearch Programme (Nice, France). These data were entered into web-based case report forms (CRF) using unique identification numbers. After data had been centrally checked for completeness and plausibility, a copy of the German data was sent to our study center, where it was connected to an electronic database that includes additional local data, which were collected on pseudonymized paper-based CRFs.

Ethics

All patients provided written informed consent to take part in the study. The study was approved by the ethics committee of the Medical Faculty, University of Würzburg (Vote 58/12) and by the data protection officer of the University of Würzburg and the University Hospital Würzburg.

Definitions

We stratified patients into younger (<70 years) and older (≥70 years) age groups, which was near the median age in our sample and provided roughly equal sample sizes of the age-groups. Uncontrolled blood pressure, regardless of hypertensive treatment, was defined as suggested by the German Society of Cardiology [15] as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Cut-off values differed for patients with self-reported diabetes (systolic ≥140 mmHg, diastolic ≥85 mmHg), patients >80 years (systolic ≥150 mmHg, diastolic ≥90 mmHg), and patients with chronic kidney disease (albumin/creatinine ratio ≥300 mg/g) (systolic ≥130 mmHg, diastolic ≥90 mmHg).

Dyslipidemia was described as LDL-cholesterol ≥2.5 mmol/l (≥100 mg/dl) and also as LDL-cholesterol ≥1.8 mmol/l (≥70 mg/dl) [1]. Classification of overweight (body mass index [BMI] ≥25 kg/m²) and obesity (≥30 kg/m²) were based on weight and height, abdominal overweight (female ≥80 cm/ male ≥94 cm) and central obesity (female ≥88 cm/ male ≥102 cm) on waist circumference [16]. CO values of >10 ppm in exhaled air were suggestive of current smoking even if self-reported smoking was denied [17]. Adequate glycemic control in diabetic patients was defined as HbA1c <7.0% [1].

Statistical Methods

Analyses were performed using SPSS 21 (IBM Corporation, NY, USA) and SAS 9.3 (SAS Institute Inc., Cary, NC, USA). Two-sided p-values <0.05 were considered statistically significant. Data are reported as proportions (%) and median (inter-quartile range, IQR). Data were compared according to categories of age at the study visit ($</\geq$ 70 years) using Wilcoxon rank sum test and χ^2-test or Fisher's exact-test, as appropriate.

Results

Patient Population

Between August 2012 and March 2013, a total of n=1380 persons were invited, of which n=536 were recruited (response rate 38.8%). At the study visit, median age of the participants was 68.7 years; 234 patients were between 70 and 79 years (43.7%) and thus considered older patients; younger patients (n=302 [56.3%]) were predominantly aged between 60 and 69 years (n=197 [36.8%]), while 86 (16%) were between 50 and 59 years and 19 (3.5%) were younger than 50 years. Overall, 82.3% were male and median time since index hospitalization was 1.8 years (**table 1**). The index event was CABG in 15.5%, PCI/stent in 69.0%, acute MI (without subsequent intervention by PCI/stent or CABG) in 5.2% and myocardial ischemia in 10.3% of the patients. The index event was the primary diagnosis of CHD in every third individual. Median duration of CHD was 2.8 years, while older patients (70-79 yrs) presented with longer CHD history (3.4 vs. 2.6 yrs, $p<0.01$). Primary care in regards to CHD by a cardiologist was reported of 67.2% of participants (69.9% younger vs. 63.7% older patients, $p=0.13$).

A platelet inhibiting agent was prescribed in 89% of the patients (**table 2**). Patients of older age received platelet inhibitors less often (83.8% vs. 93.1%, $p<0.001$), but were more often on anticoagulation therapy (7.3% vs 2.7%, $p=0.01$). Similar numbers were observed for beta-blocker therapy, i.e. 83.4% of all patients, 79.1% in older vs. 86.8% in younger patients ($p=0.02$). No difference between age groups was evident for the use of lipid-lowering treatment in general (total 84.7%) or statin therapy in particular (total 83.2%). All three substance classes primarily recommended for CHD (i.e. platelet inhibitor, beta-blocker, statin) were prescribed in 65.5% of patients, 72.5% younger vs. 56.4% in older patients ($p<0.001$).

Overweight/Obesity and Smoking

Overweight was self-reported by 44.4% of the participants (**table 1**), but 85.3% were overweight and 36.7% were obese based on BMI categories. Older patients were less likely to be obese as compared to younger individuals (30.7% vs. 41.2%, $p=0.01$). Ten percent reported to be active smokers, with 2.6% older patients vs. 16.6% younger patients ($p<0.001$). An additional eight self-reporting non-smokers

(1.7%) had CO-levels >10ppm, i..e indicative for smoking. These were mainly younger individuals (2.8% vs. 0.4%, p=0.07).

Blood Pressure

Hypertension was self-reported by 72.2% (**table 1**), with no differences between age groups. Yet, 95.7% were treated with at least one anti-hypertensive drug (beta-blocker, any diuretic, ACE/ARB inhibition, calcium-channel blocker, others). Median blood pressure differed between older and younger patients (140/79 mmHg vs. 131/81 mmHg, p<0.01). About 45% of all patients were not within the recommended blood pressure targets (**table 3 panel A**), with similar numbers in patients with self-reported hypertension and those treated with at least one anti-hypertensive drug. Patients of older age were more likely to be hypertensive (about 50% vs. 40%, p<0.05).

Dyslipidemia

Hyperlipidemia was reported by 60.8% of participants (**table 1**). Median fasting total cholesterol was 4.46 mmol/l (172 mg/dl) and LDL-cholesterol levels were 2.54 mmol/l (98 mg/dl). Cholesterol levels were slightly higher in younger patients as compared to older patients (p<0.05). About half of all patients had the recommended LDL-levels <2.5 mmol/l (~100 mg/dl) (**table 3, panel B**), with no major differences between age groups or between patients with self-reported hyperlipidemia or on any lipid-lowering drug. By contrast, only very few patients (about 10%) reached LDL-levels of <1.8 mmol/l (<70 mg/dl).

Diabetes mellitus

Every fourth patient reported on diabetes mellitus (1.1% type 1 and 24.1% type 2) and 2% had an impaired fasting glucose (IFG)/impaired glucose tolerance (IGT), with no significant differences between age groups (**table 1**). Of diabetic patients, 54.1% were treated with oral anti-glycemic drugs alone, 9.6% received insulin alone, and 21.9% were on combined treatment (**table 2**). While 21 patients (14.4%) with self-reported glucose dysregulation (diabetes of IFG/IGT) were not treated with any anti-diabetic medication, four patients (0.8%) were treated with these drugs, but did not report on diabetes or IFG/IGT. In patients with dysglycemia, median HbA1c level was 6.7%, with no significant differences between age

groups (**table 3, panel C**). 60% of patients with dysglycemia had adequate glycemic control, while 53% of younger patients revealed HbA1c levels <7% under their antidiabetic treatment, as compared to 69% of older individuals (p=0.06).

Discussion

The current report on secondary prevention for CHD within the German arm of the EUROASPIRE IV survey shows that a majority of CHD patients was treated with the recommended basic drug therapy containing beta-blockers, platelet inhibitors, and statins. Treatment targets for blood pressure and LDL-cholesterol levels were not achieved in many patients and glycemic control in diabetic CHD patients with HbA1 levels below 7% was insufficient. We observed a trend towards smoking cessation, but unhealthy lifestyles indicated by overweight/obesity were still frequent. Patterns of therapeutic care differed between younger CHD patients and patients older than 70 years. Generally, older CHD patients were less likely to receive the recommended pharmacological therapy, exhibited inadequate blood pressure control more often, and were more likely to be diabetic. Nevertheless, a greater proportion of diabetic patients was achieving the HbA1c target, and less elder patients were current smokers or were obese.

Representing a global burden, CHD is one of the major causes of mortality, responsible for 15.6 million deaths worldwide [18]. Due to improved health care, mortality rates as well as absolute numbers of death of CHD are decreasing in Europe over the past 10 years, whereas a rise in hospital admissions can be observed [19-21]. Preventive care measures not only impact on the risk of morbidity and mortality in patients with established heart disease, but also reduce the risk of developing vascular disease in high risk populations [22,23]. Patients are increasingly aware of the benefits of a healthy lifestyle, as are providers regarding treatment targets over the last decade. Yet, translation of guideline recommendations in clinical practice remains insufficient [2].

Guideline recommendations for secondary CHD prevention also apply to patients of older age [22,1,24], but achievement of certain goals may be limited due to conflicting recommendations of various specialties as these patients frequently present with not only one, but multiple conditions [25,12].

Unhealthy life-styles, smoking and overweight/obesity

The secular trends observed across Europe regarding unhealthy lifestyle in general, and obesity and smoking in particular among younger patients, was also evident in the current EUROASPIRE IV survey, however, with a wide variation of treatment and behavior patterns. For example, the prevalence of smoking ranged from 7% in Finland to 28% in Cyprus [3]. The prevalence determined for Germany, i.e. about 10% smokers, is promising since it is lower than in previous surveys (16-18%); however, about 17% of younger CHD patients were identified as current smokers [13]. In general, these data seem to point towards a subtle national trend towards smoking cessation in the German CHD population [26]. Overweight and obesity represent a major burden in the "Western world". It is remarkable that even across very different European communities in EUROASPIRE IV the vast majority of about 75 to 85% of CHD patients are classified as overweight (BMI >25 kg/m²). Considerable variability was observed regarding obesity (i.e. BMI >30 kg/m²) with 26% in Serbia and 49% in Slovenia [3]. In Germany, 85% were overweight and 37% were obese, with higher rates in younger patients, which is overall comparable to trends described for EUROASPIRE I-III [13] and consistent with trends reported previously [27]. The latter study also reported on a lower level of physical activity in older adults, potentially because of frailty, dizziness due to hypotension and fear of falls. On the other hand, it has been shown, that even limited but regular physical activity reduces the risk for CV events even in the elderly [28].

Medical treatment in secondary CHD-prevention

Overall, the vast majority of patients in the EUROASPIRE IV study was being treated with the recommended cardio-protective drug therapy, i.e. platelet inhibitor, beta-blocker, and statin. The German estimates are comparable with the European average [3]. Prescription patterns varied in older vs. younger patients: those older than 70 years were less likely to receive beta-blocker and also platelet inhibitors, however, a greater proportion of anticoagulation therapy was observed in these patients. The latter was related to a greater proportion of older patients with atrial fibrillation. Only about half of older patients received all recommended drug classes simultaneously, while this number was about 70% in younger patients.

It is well known that prescription patterns and adherence to guideline recommendations vary in older patients [29]. These frequently multi-morbid patients present with multiple medications ("polypharmacy"), and medical therapy and adherence might be limited by contraindications and side effects [30,31]. This dilemma of medical need and potential side effects might stop many physicians from prescribing drug classes of secondary CVD-prevention as recommended by guidelines. Further, cognitive impairment of the elderly is highly prevalent in older subjects with vascular disease and might impede such efforts [32]. However, adequate CHD-specific pharmacotherapy has been associated with improved outcomes also in older CHD patients. Hence, efforts should be made to prescribe such regimens also in the elderly patient [11,33,34]. However, it may take some time to educate physicians that even the elderly benefit from the same secondary prevention therapy that has been developed through clinical trials that were mainly performed on younger individuals.

Blood pressure control and hypertension

Recently, the definition of hypertension and the recommended blood pressure targets were modified and adapted by International and National Societies [15,35]. Generally, blood pressure values of greater than 140/90 mmHg are considered "hypertensive", while even higher values are acceptable for the elderly (150/90 mmHg) to acknowledge comorbid conditions and the risk of hypotension, dizziness, and falls. Therefore, applying the "old" blood pressure target of 130/80 mmHg classified only 29% of German patients (European average 33%) as being within the recommended range [3]. According to updated recommendations, 55% of German CHD patients were within the suggested blood pressure range. *Vice versa*, 45% in the entire German EUROASPIRE IV sample were not treated adequately, in fact even 50% of patients older than 70 years. It will be interesting to see how the data of the recently published SPRINT trial may change guideline recommendations; in non-diabetic patients with increased CV risk, a blood pressure target as low as 120 mmHg reduced CV events and mortality, in the entire group as well as in the elderly [36].

Compared to the previous EUROASPIRE surveys, there might be a positive trend over the last decade for more patients being on treatment targets [13]. However, there is considerable variation about valid estimates on the prevalence of uncontrolled hypertension in Germany. Recent data from the DEGS survey suggest that about 80% of subjects in a nationwide representative sample of adults present with controlled blood pressure of <140/90 mmHg. A similar proportion was observed in patients with self-reported stroke or CHD [37] . A European survey (including Germany) on general practitioners, internists and cardiologists also report on comparable numbers between 50-60% of patients being treated within the recommended range [38]. Encouraging results have been reported of seven German population based studies, which indicate lower blood pressure levels and a much better control of hypertensive patients in recent years [39].

Lipid control and dyslipidemia

Although eight to nine out of ten German patients in EUROASPIRE IV were treated with lipid lowering drugs, mainly statins, only one out of ten reached LDL-cholesterol levels <70 mg/dl, and 60% were below 100 mg/dl. Treating dyslipidemia is a cornerstone of CHD care as it reduces mortality in secondary [40] and primary CHD prevention [41]. Statin treatment is also similarly effective in the elderly as compared to younger individuals [42]. Better translation from guideline recommendations into clinical practice is reflected by increasing numbers of patients on lipid-lowering drugs over the last decade [2,13], with now about 80-90% of patients across Europe being on statins [3]. We did not find any evidence that treatment patterns vary between younger and older individuals, neither in prescription rates of lipid-lowering agents, nor in accomplishing treatment goals. The importance of tightly controlling LDL-levels was further highlighted by lowering the target to <70 mg/dl by the ESC for all CHD patients in 2013 [1]. Therefore, starting in 2012, EUROASPIRE IV was not able to address this updated recommendation. How national and international campaigns are effective to establishing this strict target level in clinical practice, how it translates in improved outcomes, but also how safe these measures are, is a still open debate and needs to be investigated in future studies. Herein it should be noted, that follow-up LDL-measurement and treating

patients to a defined LDL-target has been questioned recently in clinical practice guidelines [43,44], because of sparse evidence that this approach is associated with improved outcomes.

Dysglycemia and diabetes mellitus

Disturbances in glucose metabolism and particularly type 2 diabetes are frequently a consequence of obesity, unhealthy diet and limited physical activity. Diabetes further increases the risk for CV complications and progression of CHD [1] and should thus be detected early-on and treated consequently. In the German sample of EUROASPIRE IV, 25% reported diabetes (European average: 27%), an estimate that is as high as never before in German CHD patients enrolled in previous phases of EUROASPIRE [13]. It is known that the prevalence of diabetes is growing in both the developed and developing world, paralleling the rise in obesity rates [45,46]. In Germany, increasing rates may slow in recent years in the general population, with a fairly stable prevalence of about 9% [47].

Glycemic control in diabetic patients with CHD is a key component of secondary prevention and HbA1c levels of <7% are generally recommended [48,1]. We found that only 60% of diabetic CHD patients were within the target range. Moreover, younger patients were even less likely to be adequately treated for dysglycemia, with more than 50% with HbA1c greater than 7%. This is of particular interest, as the benefits of tight glycemic control outweigh the harms (e.g. hypoglycemic episodes) in younger patients, whereas less strict treatment targets have been proposed for the elderly (i.e. HbA1c >7.5% or >8.0%) [49,48] to reflect multimorbidity and the risk of adverse events [50,51].

Limitations

The current study has limitations that deserve mentioning. First, our findings were derived from participants of the area of Würzburg and are therefore not generalizable to all CHD patients in Germany. Second, our study sample might even not be representative for all patients admitted for CHD at the recruiting centers, as only 38.8% of invited subjects agreed to participate. Due to data protection regulations, analysis of reasons for non-participation is limited: eligible patients who did not participate in EUROASPIRE IV were more likely to be female and of slightly younger age. Third, it is not possible to

unrestrictedly compare our current results of EUROASPIRE IV to the findings of the previous EUROASPIRE surveys I to III in Germany, as the study center and the source population moved from Münster to Würzburg [13]. Thus, secular trends across the German EUROASPIRE phases have to be interpreted with caution. Finally, as EUROASPIRE IV did not include patients older than 79 years at the index event, we are unable to make any assumptions on patients aged 80 years or older, a subgroup that is likely to increase in the next decades due to a longer life-expectancy and rising survival rates of CVD events.

Conclusions

Most CHD patients in Germany received the recommended medication for secondary prevention, but treatment targets were not achieved in many patients and patterns varied in the elderly. While the prevalence of smoking was considerably low, overweight/obesity and limited physical activity, particularly in younger individuals are alarming. Modification of life-styles may become an even greater factor in prevention campaigns than medical treatment into certain target ranges, but should also consider different needs in older individuals.

List of abbreviations

BMI	Body mass index
CABG	coronary artery bypass grafting
CHD	coronary heart disease
CO	Carbon monoxide
CRF	case report form
CV	cardiovascular
EUROASPIRE	European Action on Secondary and Primary Prevention by Intervention to Reduce Events
ESC	European Society of Cardiology
IQR	inter-quartile range
LDL	low density lipoprotein
MI	myocardial infarction
OGTT	oral glucose tolerance test
PCI	percutaneous coronary intervention

Declarations

Ethics approval and consent to participate

All patients provided written informed consent to take part in the study. The study was approved by the ethics committee of the Medical Faculty, University of Würzburg (Vote 58/12) and by the data protection officer of the University of Würzburg and the University Hospital Würzburg. (see above, section methods)

Consent for publication

Not applicable

Availability of data and materials

The datasets generated during and/or analysed during the current study are property of the European Society of Cardiology and are not publicly available.

Competing Interests

GG reports grants from University Göttingen within the FIND-AF-randomized trial (FIND-AF-randomized is supported by an unrestricted grant to the University Göttingen from Boehringer-Ingelheim), grants from University Göttingen within DZHK analysis projects (the DZHK is funded by a BMBF grant), personal fees from Charité - Universitätsmedizin Berlin within the TIM-HF-II trial for data safety and monitoring board membership (TIM-HF-II is supported by a BMBF grant to the Charité), grants from University Hospital Würzburg within the MOOD-HF trial for biometry and steering committee membership (MOOD-HF is supported by a BMBF grant and an unrestricted grant to the University Hospital Würzburg from Lundbeck), grants from the Rehabilitation Center Roter Hügel Bayreuth (trial sponsor) for biometry in the CaRitaS trial, outside the submitted work.

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Authors contributions

All authors contributed to the conception of the study and MW, GG, JK, KK, DW, StS, PUH contributed to study design. All authors contributed to data acquisition and MW, GG, KK contributed to data analysis. MW, GG, KK, CM, StS, PUH contributed to data interpretation. MW, GG, CM, StS and PUH drafted and all other authors critically revised the manuscript and all authors gave final gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Tables

Table 1: Characteristics of study participants by age group

	Total N=536	**age <70 yrs** n=302	**age ≥70 yrs** n=234	**p-value**
Age, yrs	68.7 (61.6-74.2)	62.1 (57.5-66.0)	75.2 (72.8-77.5)	<0.001
Male gender	441 (82.3)	253 (83.8)	188 (80.3)	0.30
Coronary heart disease				
Self-reported				
- CABG ever	140 (26.1)	66 (21.9)	74 (31.6)	0.01
- PCI/Stent ever	418 (80.0)	242 (80.1)	176 (75.2)	0.17
- acute myocardial infarction ever	212 (39.6)	129 (42.7)	83 (35.5)	0.09
Duration of CHD, yrs	2.8 (1.9-9.0)	2.6 (1.8-5.2)	3.4 (2.2-14.5)	<0.001
Index-event [1]				0.08
- CABG	83 (15.5)	36 (11.9)	47 (20.1)	
- PCI/Stent	370 (69.0)	218 (72.2)	152 (65.0)	
- acute MI	28 (5.2)	17 (5.6)	11 (4.7)	
- myocardial ischemia	55 (10.3)	31 (10.3)	24 (10.3)	
Index-event as primary diagnosis of CHD	181 (33.8)	100 (33.1)	81 (34.6)	0.91
Time between index-event and study-visit, yrs	1.8 (1.1-2.5)	1.7 (1.1-2.4)	1.9 (1.1-2.5)	0.24
Co-morbidities				
Self-reported heart failure	79 (14.8)	40 (13.3)	39 (16.7)	0.27
Self-reported stroke/TIA	55 (10.3)	25 (8.3)	30 (12.8)	0.09
Self-reported peripheral artery disease	47 (8.8)	23 (7.6)	24 (10.3)	0.28
Self-reported hypertension	387 (72.2)	217 (71.9)	170 (72.7)	0.94
Blood pressure, mmHg				
- systolic	136 (124-149)	131 (121-148)	140 (129-151)	<0.001
- diastolic	80 (73-87)	81 (75-88)	79 (72-86)	0.005
Self-reported hyperlipidemia	326 (60.8)	197 (65.2)	129 (55.1)	0.06
Cholesterol (total), mmol/l	4.46 (3.95-5.16)	4.50 (3.98-5.27)	4.44 (3.79-5.06)	0.04
LDL-Cholesterol, mmol/l	2.54 (2.06-3.09)	2.59 (2.19-3.17)	2.49 (1.98-3.01)	0.03
HDL-Cholesterol, mmol/l	1.16 (0.99-1.36)	1.14 (0.99-1.34)	1.16 (0.99-1.37)	0.53
Self-reported overweight	238 (44.4)	150 (49.7)	88 (37.6)	0.005
BMI, kg/m²	28.6 (26.3-31.2)	29.0 (26.4-31.5)	28.2 (26.1-30.5)	0.04
- overweight [2]	454 (85.3)	258 (85.7)	196 (84.9)	0.78
- obesity	195 (36.7)	124 (41.2)	71 (30.7)	0.01
Waist, cm	103	104	103	0.33

	(96-111)	(96-112)	(94-110)	
- Abdominal overweight [3]	448 (84.7)	254 (84.7)	194 (84.7)	0.98
- Central obesity	333 (63.0)	187 (62.3)	146 (63.8)	0.74
Self-reported smoking	56 (10.4)	50 (16.6)	6 (2.6)	<0.001
CO, ppm	2 (2-3)	3 (2-3)	2 (2-3)	<0.001
- Smoker	*10 (6-16)*	*11 (6-17)*	*8 (2-10)*	*0.11*
- Non-Smoker	*2 (2-3)*	*2 (2-3)*	*2 (2-3)*	*0.03*
Self-reported dysglycemia	146 (27.2)	78 (26.1)	68 (29.7)	0.36
Of those				
- Diabetes	*135 (25.2)*	*74 (24.5)*	*61 (26.1)*	*0.67*
- IFG/IGT	*11 (2.1)*	*4 (1.3)*	*7 (3.0)*	*0.18*

Legend: displayed are proportions n (%) and median (IQR), analyses restricted to patients without missing values in respective variables; abbreviations: CHD, coronary heart disease; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; MI, myocardial infarction; TIA, transient ischemic attack; IFG, impaired fasting glucose; IGT, impaired glucose tolerance

[1] reason for hospitalization that qualified for participation in EUROASPIRE IV (latest during hospital stay); acute MI and myocardial ischemia classified as events that were treated conservatively, without PCI or CABG

[2] Overweight: BMI ≥25 kg/m²), obesity: BMI ≥30 kg/m²

[3] Abdominal overweight: waist circumference ≥80 cm (female), ≥94 cm (male); central obesity: waist circumference ≥88 cm (female), ≥102 cm (male)

Table 2: Medication at study visit by age group

	Total N=536	**age <70 yrs** n=302	**age ≥70 yrs** n=234	**p-value**
Platelet inhibitors	477 (89.0)	281 (93.1)	196 (83.8)	<0.001
Of these				
- aspirin only	*363 (67.7)*	*207 (68.5)*	*156 (66.7)*	*0.001*
- clopidogrel/others only	*16 (3.0)*	*8 (2.7)*	*8 (3.4)*	
- both Aspirin and Clopidogrel/others	*98 (18.3)*	*66 (21.9)*	*32 (13.7)*	
Beta-Blocker	447 (83.4)	262 (86.8)	185 (79.1)	0.02
ACE-inhibitor/ARB	438 (81.7)	240 (79.5)	198 (84.6)	0.13
Calcium channel inhibitors	121 (22.6)	66 (21.9)	55 (23.5)	0.65
Diuretics [1]	242 (45.2)	110 (36.4)	132 (56.4)	<0.001
Other antihypertensive therapy [2]	19 (3.5)	9 (3.0)	10 (4.3)	0.42
Any antihypertensive agent [3]	513 (95.7)	286 (94.7)	227 (97.0)	0.19
Lipid-lowering drugs [4]	454 (84.7)	254 (84.1)	200 (85.5)	0.66
Of these				
- Statins	*446 (83.2)*	*251 (83.1)*	*195 (83.3)*	*0.95*
Diabetes medication [5]				0.21
- insulin	14 (9.6)	4 (5.1)	10 (14.7)	
- oral anti-glycemic drug	79 (54.1)	43 (55.1)	36 (52.9)	
- insulin and oral anti-glycemic drug	32 (21.9)	20 (25.6)	12 (17.7)	

Legend: displayed are proportions n (%), analyses restricted to patients without missing values in respective variables; abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker

[1] Diuretics including e.g. thiazides, loop-diuretics, aldosterone antagonists

[2] Other anthypertensives including e.g. alpha2-receptor agonists, alpha1-receptor blocker, direct renin-inhibitors

[3] Beta-blockers, ACE-inhibitor/ARB, Ca-channel inhibitors, diuretics, other antihypertensive agent

[4] Including statins, fibrates, nicotinic acids, resins, omega-3 fatty acids

[5] in pts with self-reported dysglycemia

Table 3: Control of risk factors: hypertension, dyslipidemia and diabetes at study visit by age group

	Total	age <70 yrs	age ≥70 yrs	p-value
A) uncontrolled blood pressure [1]				
- all pts.	239 (44.7)	121 (40.2)	118 (50.4)	0.02
- pts with self-reported hypertension	202 (52.3)	101 (46.8)	101 (59.4)	0.01
- pts. with antihypertensive therapy	227 (44.3)	112 (49.3)	115 (50.7)	0.01
B) Dyslipidemia				
LDL cholesterol ≥2.5 mmol/l (≥ ~100 mg/dl)				
- all pts.	266 (52.7)	158 (55.6)	108 (48.9)	0.13
- pts with self-reported hyperlipidemia	186 (61.6)	115 (62.8)	71 (59.7)	0.58
- pts. with lipid-lowering therapy	205 (47.9)	122 (51.1)	89 (43.9))	0.14
LDL cholesterol ≥1.8 mmol/l (≥70 mg/dl)				
- all pts.	451 (89.3)	257 (90.5)	194 (87.8)	0.33
- pts with self-reported hyperlipidemia	282 (93.4)	172 (94.0)	110 (92.4)	0.60
- pts. with lipid-lowering therapy	376 (87.9)	213 (89.2)	163 (86.2)	0.37
C) Glycemic control				
All patients				
- HbA1c, %	5.7 (5.5-6.2)	5.7 (5.4-6.2)	5.8 (5.6-6.2)	0.002
- Proportion of pts with HbA1c >7%	63 (11.9)	39 (13.0)	24 (10.4)	0.35
Pts with self-reported dysglycemia				
- HbA1c, %	6.7 (6.2-7.6)	6.8 (6.2-7.8)	6.6 (6.1-7.3)	0.12
- Proportion of pts with HbA1c >7%	57 (39.6)	36 (46.8)	21 (31.3)	0.06
Pts. with self-reported dysglycemia or treated with any diabetes medication				
- HbA1c, %	6.7 (6.2-7.6)	6.8 (6.2-7.8)	6.6 (6.1-7.4)	0.21
- Proportion of pts with HbA1c >7%	59 (39.1)	36 (45.0)	23 (32.4)	0.11

Legend: displayed are proportions n (%), analyses restricted to patients without missing values in respective variables;

[1] uncontrolled blood pressure: systolic RR ≥ 140 mmHg or diastolic RR ≥90 mmHg; patients with self-reported diabetes: systolic RR ≥ 140 mmHg or diastolic RR ≥85 mmHg; patients > 80 yrs systolic RR ≥ 150 mmHg or diastolic RR ≥90 mmHg; patients with proteinuria (ACR ≥300 mg/g) systolic RR ≥ 130 mmHg or diastolic RR ≥90 mmHg

6.2. Manuscript 2 "CKD in 24 European Countries in EUROASPIRE IV"

Wagner, M., Wanner, C., Kotseva, K., Wood, D., De Bacquer, D., Ryden, L., Stork, S. and Heuschmann, P. U. on behalf of the EUROASPIRE IV investigators: *Prevalence of chronic kidney disease and its determinants in coronary heart disease patients in 24 European countries: Insights from the EUROASPIRE IV survey of the European Society of Cardiology.* European Journal of Preventive Cardiology 24(11), pp. 1168-1180[107]; doi: 10.1177/2047487317708891; copyright © 2017 by the European Society of Cardiology. Reprinted by permission of SAGE Publications, Ltd.

6.2.1. Summary

For this part of the project, we analyzed data of 7998 subjects of 24 European countries enrolled in EUROASPIRE IV. At the study visit in considerably stable condition, median eGFR was 78 [66 to 91] ml/min/1.73m², median ACR was 6.4 (7.7 to 19.5) mg/g and 17% had CKD as defined as eGFR <60 ml/min/1.73m². However, we observed wide variation of CKD among countries with a range of age standardized prevalence rates from 13% in Spain to 26% in Slovenia. Further 9% of EUROASPIRE IV participants had largely preserved eGFR (i.e. ≥60 ml/min/1.73m²) but significant albuminuria (i.e. CKD stages G1A3, G2A2, G2A3) and were thus at risk for CKD progression[50]. Multivariate, multilevel logistic regression analysis resulted in older age (OR 1.11 per year [95% CI 1.10 to 1.12]), female gender (OR 2.0 [1.7 to 2.3]), diabetes (OR 1.3 [1.1 to 1.5]), obesity (OR 1.3 [1.1 to 1.4]), previous CABG (OR 1.5 [1.3 to 1.7]) and a history of CHF (OR 1.7 [1.4 to 2.1]) as independent determinants of CKD at the study visit.

Data collection from medical records of the index hospital stay for CHD included SCr values at hospital admission. In 18% of the patients, impaired kidney function (i.e. eGFR <60 ml/min/1.73m²) was observed. We used the conservative term *impaired kidney function*, as we cannot claim stable condition at hospital admission, which would be required for description of *chronic kidney disease*, because clinical circumstances due to CHD events can acutely affect kidney function, e.g. AKI (see discussion 7.3 Chronic kidney disease in CHD patients). Median eGFR was 80 (65 to 93) ml/min/1.73m², and in the vast majority

of subjects (99%) data on albuminuria (ACR) was missing. Prevalence rates of impaired kidney function varied substantially among countries, ranging from 7.5% in Finland to 38% in the UK. Older age (OR 1.10 [1.09 to 1.11]), female gender (OR 1.9 [1.6 to 2.3]), diabetes (OR 1.4 [1.2 to 1.6]), hypertension (OR 1.4 [1.1 to 1.8]), CABG (OR 1.5 [1.2 to 2.0] or AMI (OR 1.2 [1.0 to 1.5]) prior to the index hospital stay, and a history of CHF (OR 1.4 [1.1 to 1.6]) emerged as independent risk factors for impaired kidney function from logistic regression modelling.

In 6857 patients (86% of the total sample), eGFR values at both the index hospital stay and the study visit were available, enabling the calculation of the change in eGFR:

$$\Delta eGFR = eGFR_{index\ hospital\ stay} - eGFR_{study\ visit}$$

Median ΔeGFR was +1.8 (-7.1 to +9.7) ml/min/1.73m². Kidney function improved (ΔeGFR > +5ml/min/1.73m²) in 39%, remained stable (-5 ≤ ΔeGFR ≤ +5ml/min/1.73m²) in 31%, and declined (ΔeGFR < -5 ml/min/1.73m²) in 30% of the patients. Independent determinants in multilevel, multivariate linear regression of a positive ΔeGFR (i.e. improved kidney function between the index hospital stay and the study visit) included older age (β-coefficient +0.44 [95% CI +0.40 to +0.47]), female gender (+0.9 [+0.2 to +1.7]), a longer time between the index-hospital stay and the study visit (+1.8 [+1.1 to +2.5]), the index event representing an emergency (+1.3 [+0.3 to +2.3]), a history of CHF (+0.9 [+0.3 to +1.6]) and a higher eGFR at hospital admission (+0.40 [0.38 to 0.42]).

6.2.2. Manuscript 2, as published

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Prevalence of chronic kidney disease and its determinants in coronary heart disease patients in 24 European countries: Insights from the EUROASPIRE IV survey of the European Society of Cardiology

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Abstract

Aims: Chronic kidney disease (CKD) is associated with the development and progression of coronary heart disease (CHD), in addition to classic cardiovascular risk factors. We analysed the prevalence of CKD in CHD patients from 24 European countries in the ambulatory setting and in a preceding hospital stay for CHD (index).

Methods and results: A total of 7998 EUROASPIRE IV participants (median 65 years of age, 76% male) attended a study visit 6–36 months after the index hospitalisation. CKD was classified according to stages of estimated glomerular filtration rate (eGFR) and albuminuria (urinary albumin/creatinine ratio). In stable CHD conditions (study visit), 17.3% had CKD (eGFR <60 mL/min/1.73 m^2) with variation among participating countries (range 13.1–26.4%). A further 12% presented with preserved eGFR but significant albuminuria. During the hospital stay due to a coronary event, impaired kidney function was observed in 17.6% (range 7.5–38.2%). Risk factors for impaired kidney function included older age, female gender, classic cardiovascular (CV) risk factors, details of CHD history and congestive heart failure (multivariate regression). Of all patients, 38.9% had declined, 31.3% were stable and 29.8% had improved kidney function between hospital discharge and the study visit, dependent on age, gender, CV risk factors, CHD history and cardiac dysfunction (multivariate regression).

Conclusions: Every fifth CHD patient had CKD, while every tenth exhibited albuminuria as the sole indicator of kidney damage. These subjects are at increased risk of progression of CKD and CHD complications. After hospital stays due to CHD, there is potential of recovery of kidney function, but our findings underline the importance of identifying patients who are at high risk of developing CKD in order to counteract disease progression.

Keywords

Chronic kidney disease, prevalence, coronary heart disease, EUROASPIRE survey, secondary prevention

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Introduction

Patients with coronary heart disease (CHD) are at high risk of subsequent cardiovascular (CV) events.[1] Even if clinical practice guideline recommendations are followed in secondary prevention, including modification of lifestyle and behaviour by quitting smoking, counteracting overweight/obesity and increasing physical activity, and by adequate control of blood pressure, low-density lipoprotein (LDL)-cholesterol and hyperglycaemia,[2] there is a residual risk of morbidity and mortality among such patients. Over the last decades, evidence has accumulated that chronic kidney disease (CKD), an important risk modifier in CHD[3] associated with CHD progression,[4,5] worsening of heart failure[6] and an increased risk of hospitalisation and mortality,[4,7] may be a link to the remaining risk. Both CHD and CKD share similar pathogenetic pathways such as arteriosclerosis/atherosclerosis and chronic inflammation.[8,9]

CKD itself is common in the Western world and is associated with an aggravated risk of mortality and morbidity when compared to the healthy population.[10–12] CKD disposes the patient to complications and a worse clinical course in hospital stays of various causes, including admissions for CHD.[13] On the other hand, acute cardiac events can directly affect renal function, leading to acute kidney injury (AKI), which itself is an important risk factor of both the development and progression of CKD,[14] the progression of CHD and impaired outcomes in CHD.[15] Despite these prognostic implications, comprehensive data on the contemporary prevalence of CKD in CHD patients across Europe are lacking, as well as data on impairments in kidney function during hospitalisation for CHD.

The present study investigated the prevalence and characteristics of CKD in stable CHD patients using data from the EUROASPIRE IV study in 24 European countries. Current nephrology (Kidney Disease: Improving Global Outcomes [KDIGO]) recommendations for CKD classification were applied,[8] and variations of CKD rates among participating countries were investigated. Moreover, the proportion of impaired kidney function at a hospital stay due to CHD is reported, together with changes in kidney function between the hospital stay and the study visit at least 6 months after hospital discharge.

Methods

Patient population

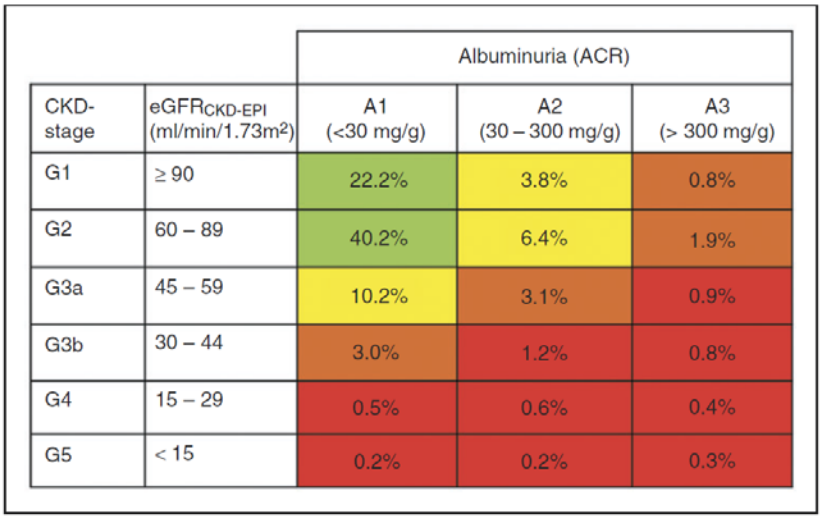
The study design and methodology of the fourth European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE IV) survey have been published previously.[16] Between 2012 and 2013, 7998 patients (aged 18–80 years) from 24 European countries attended a study visit 6–36 months after a hospital stay (index) due to CHD (coronary artery bypass grafting [CABG], percutaneous coronary intervention [PCI], acute myocardial infarction [MI] without further intervention such as PCI/stent or CABG or myocardial ischaemia) (Supplementary Figure S1). Within each country, a geographical area (>0.5 million people) was selected, with at least one hospital offering interventional cardiology and cardiac surgery and one or more acute hospitals admitting patients with MI and myocardial ischaemia. Within these centres, all hospitalised patients meeting the inclusion criteria were identified from the hospital's patient management systems and invited to participate in the study. EUROASPIRE IV addressed lifestyle changes and control of classic CV risk factors in clinical practice in CHD patients.[16] The study also focused on previously undetected diabetes and dysglycaemia,[17] as well as on renal impairment. Local ethics committees approved the study in each country and all patients provided written informed consent.

Data collection

Detailed data were collected at the study visit regarding all aspects of secondary prevention, including medical history, medication, behaviour and control of risk factors; these also included standardised measurements of blood pressure, weight, height and carbon monoxide (CO) in exhaled air.[16] Blood samples were drawn in a fasting state, processed immediately and stored at −80°C on site. After completion of recruitment, samples were shipped to the central EUROASPIRE IV laboratory (Laboratory of Analytical Biochemistry, National Public Health Institute, Helsinki, Finland), where serum creatinine (SCr), lipid levels and HbA1c were measured. SCr analysis was performed in a clinical chemistry analyser (Abbott Laboratories, Abbott Park, IL, USA) and determined enzymatically using commercial reagents from Sentinel (Milan, Italy) (coefficient of variation 1.1 ± 0.1%, systematic error (bias) 0.4 ± 1.0%). The urinary albumin/creatinine ratio (ACR) was measured locally at each study centre as requested by the EUROASPIRE IV protocol. Study participants also consented to a retrospective chart review of the index hospital stay in order to obtain information on the index event, risk factors, medications and clinical measurements, including SCr at admission (i.e. the first measurement in the patient record) and ACR (Supplementary Figure S1).

Definitions

Kidney function was classified according to KDIGO (Figure 1), while CKD glomerular filtration rate



CKD-stage	$eGFR_{CKD-EPI}$ (ml/min/1.73m²)	Albuminuria (ACR) A1 (<30 mg/g)	A2 (30 – 300 mg/g)	A3 (> 300 mg/g)
G1	≥ 90	22.2%	3.8%	0.8%
G2	60 – 89	40.2%	6.4%	1.9%
G3a	45 – 59	10.2%	3.1%	0.9%
G3b	30 – 44	3.0%	1.2%	0.8%
G4	15 – 29	0.5%	0.6%	0.4%
G5	< 15	0.2%	0.2%	0.3%

Figure 1. Prevalence of CKD stages at the EUROASPIRE IV study visit; age standardised to the 2013 European standard population[18]; colours indicate low risk (green), moderately increased risk (yellow), high risk (orange) and very high risk (red) for worse prognosis according to Kidney Disease: Improving Global Outcomes (KDIGO).[8]
ACR: urinary albumin/creatinine ratio; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

(CKD-G) stages were defined by applying the CKD-Epidemiology Collaboration (CKD-EPI) equation in order to calculate the estimated glomerular filtration rate ($eGFR_{study\ visit}$ and $eGFR_{index}$).[8] ACR measurements were used to define CKD albuminuria (CKD-A) stages; due to missing data of 99% of participants for ACR in the medical records, CKD-A stages could not be assessed for the hospital stay. CKD was also categorised as eGFR <60 vs ≥60 mL/min/1.73 m². Changes in kidney function (ΔeGFR) between the index hospital stay and the study visit were calculated as $eGFR_{index} - eGFR_{study\ visit}$ and categorised as declined (ΔeGFR <−5 mL/min/1.73 m²), stable (ΔeGFR −5 to +5 mL/min/1.73 m²) and improved (ΔeGFR >+5 mL/min/1.73 m²) kidney function.

CV risk factors at the study visit comprised hypertension (blood pressure ≥140/90 mmHg, or ≥140/80 mmHg in patients with diabetes), diabetes (self-reported), dyslipidaemia (LDL-cholesterol ≥2.5 mmol/L), obesity (body mass index [BMI] ≥30 kg/m²) and smoking (self-reported or CO in exhaled air >10 ppm).[16] Covariates of the index hospital stay included the urgency of the index event (elective, acute [>24 hours] or emergency [<24 hours] intervention/procedure), heart failure (according to case history or echocardiographic findings of cardiac dysfunction at admission) and CV risk factors known at admission or reported in the discharge letter (hypertension, dyslipidaemia, diabetes and/or smoking). Obesity was defined as BMI ≥ 30 kg/m² at admission or explicitly stated in the discharge letter.

Statistical methods

Data are reported as proportions and medians (interquartile ranges [IQRs]). Data were compared according to respective categories (i.e. CKD and change in eGFR) using Wilcoxon rank-sum tests, Kruskal–Wallis tests and χ^2 tests/Fisher's exact tests, as appropriate. Proportions of CKD across participating countries were age standardised using the 2013 European standard population.[18] Determinants of CKD at the study visit and impaired kidney function during the index hospital stay were analysed by multivariate, multilevel logistic regression (including covariates that were significant in univariate analyses) using a backwards selection procedure and considering the participating country as a random intercept. Changes in eGFR between the index hospital stay and the study visit were investigated by multivariate, multilevel linear regression. In all of the multivariate models, no evidence for co-linearity between explanatory variables was evident, as tested for by variance inflation factors being >10. Analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC, USA). Two-sided p-values <0.05 were considered statistically significant.

Results

Prevalence of CKD in stable CHD patients (study visit)

Of the total of 7998 CHD patients in EUROASPIRE IV, SCr measurements were available in 7508 (93.9%)

participants, who were slightly older (64.7 vs. 63.0 years, $p = 0.004$), more likely to be male (75.9% vs. 71.6%, $p = 0.03$) and with PCI/stent as the index event (54.5% vs. 46.3%, $p < 0.001$) as compared to subjects without SCr data. Median $SCr_{study\ visit}$ was 0.96 mg/dL (IQR 0.84–1.09 mg/dL), referring to a median $eGFR_{study\ visit}$ of 78.3 mL/min/1.73 m^2 (IQR 65.5–91.1 mL/min/1.73 m^2). Urinary measurements were missing in 1822 patients (22.8%), and the median $ACR_{study\ visit}$ was 6.44 mg/g (IQR 2.65–19.47 mg/g).

In apparently stable conditions at the study visit, 1294 patients (17.3%) presented with eGFR < 60 mL/min/1.73 m^2, with considerable variation among participating countries (age-standardised prevalence rates from 13.1% in Spain to 26.4% in Slovenia; Supplementary Table S1). In age-standardised data according to KDIGO classification (Figure 1; crude data in Supplementary Figure S2), a further 12.9% of CHD patients presented with either major albuminuria (i.e. stages G1A3 0.8% and G2A3 1.9%) or moderately elevated albuminuria (i.e. stages G1A2 3.8% and G2A2 6.4%), despite a largely preserved eGFR (i.e. ≥60 mL/min/1.73 m^2).

Patients with CKD were significantly older, more likely to be female, with a longer history of CHD including CABG and PCI/stenting, and to present with a higher prevalence of classic CV risk factors and heart failure at the study visit (Table 1). In multivariate modelling, older age, female gender, prior CABG, history of congestive heart failure (CHF), diabetes and obesity were independently associated with the risk of CKD (Table 2).

Prevalence of impaired kidney function during a hospital stay due to CHD (index)

Data on SCr_{index} at hospital admission of the index CHD event were available in 92.3% ($n = 7380$) patients. Subjects without SCr data reported a slightly longer duration of CHD prior to the index event (2.5 vs. 1.7 years, $p = 0.02$), but did not differ from subjects with SCr_{index} data regarding age, gender or the classification of the index event (all $p > 0.2$). The median $eGFR_{index}$ was 79.7 mL/min/1.73 m^2 (IQR 65.0–92.8 mL/min/1.73 m^2) and the median SCr_{index} was 0.95 mg/dL (IQR 0.81–1.11 mg/dL). Impaired kidney function (i.e. $eGFR_{index}$ < 60 mL/min/1.73 m^2) was observed in 1266 patients (17.6%, age-standardised prevalence 16.9%). Among participating countries, age-standardised prevalences ranged from 7.5% in Finland to 38.2% in the UK (Supplementary Table S2). Missing data on ACR (99%) precluded classification according to CKD-A stages. The eGFR categories were as follows: ≥90 mL/min/1.73 m^2 30.9% (age standardised 26.1%), 60–89 mL/min/1.73 m^2 51.5% (age standardised 42.2%); 45–59 mL/min/1.73 m^2 12.2% (age standardised 11.2%), 30–44 mL/min/1.73 m^2 4.2% (age standardised 4.2%), 15–29 mL/min/1.73 m^2 0.9% (age standardised 1.1%) and <15 mL/min/1.73 m^2 0.3% (age standardised 0.4%).

Patients with impaired kidney function at hospital admission presented with a longer duration of CHD and it was less likely that the index event was the primary diagnosis of CHD as compared to subjects with normal kidney function (Table 3). The index event as the cause for hospital admission was more likely to be CABG and also planned as an elective intervention/surgery in renal patients. From multivariate modelling (Table 4), older age, female gender, history of CABG and MI prior to the index event and history of CHF, along with diabetes and hypertension, were independent determinants of impaired kidney function at hospital admission.

Changes in kidney function between hospital stay (index) and study visit

A total of 6857 patients (85.7%) had SCr values at both the index hospital stay and the study visit, thereby permitting a calculation of the change in eGFR (ΔeGFR). Those with missing data were slightly younger (64.0 vs. 64.7 years, $p = 0.02$) and with a longer duration of CHD (2.7 vs. 2.5 years, $p = 0.02$) than with SCr data available at both occasions. Median ΔeGFR was +1.8 mL/min/1.73 m^2 (IQR −7.1 to +9.7 mL/min/1.73 m^2). Kidney function improved (ΔeGFR >+5 mL/min/1.73 m^2) in 2666 (38.9%), remained stable (−5 ≤ ΔeGFR ≤ +5 mL/min/1.73 m^2) in 2146 (31.3%) and declined (ΔeGFR < −5 mL/min/1.73 m^2) in 2054 (29.8%) patients (Supplementary Table S3).

In multivariate linear regression modelling (Table 5), a positive ΔeGFR (i.e. improved kidney function between the index hospital stay and the study visit) was independently associated with older age, female gender, a longer time between the index hospital stay and the study visit, an index event representing a non-elective CHD procedure (particularly emergency events), a history of heart failure and better kidney function (i.e. higher eGFR) at hospital admission (see Supplementary Table S4 for patient characteristics at the index event according to changes in kidney function).

Discussion

The main finding in this large trans-European survey of patients with stable CHD is that approximately 17% of the patients have CKD with eGFR < 60 mL/min/1.73 m^2. In addition, 12% were at increased risk of CKD progression, as indicated by significant

Table 1. Patient characteristics at the study visit by chronic kidney disease (estimated glomerular filtration rate by CKD-EPI) .

Characteristic	eGFR $\geq$ 60 mL/min/1.73 m^2, n = 6202 (82.7%)	eGFR < 60 mL/min/1.73 m^2, n = 1294 (17.3%)	p-value
Age (years)	63.2 (56.5–69.8)	72.1 (66.0–76.1)	<0.001
Male gender	4894 (78.9%)	797 (61.6%)	<0.001
CHD history			
Duration of CHD	2.4 (1.5–5.5)	3.1 (1.7–10.7)	<0.001
CHD history			
– CABG	1270 (20.6%)	399 (31.1%)	<0.001
– PCI/stent	4106 (66.5%)	793 (61.6%)	<0.001
– Acute MI	2735 (44.3%)	595 (46.3%)	0.20
History of heart failure	505 (8.2%)	194 (17.2%)	<0.001
Classic CV risk factors			
BMI (kg/m^2)	28.6 (25.9–31.6)	29.1 (26.1–32.2)	0.002
Overweight[a]	5045 (81.6%)	1073 (83.4%)	0.12
Obesity[a]	2298 (37.2%)	526 (40.9%)	0.01
Blood pressure			
Systolic	132.5 (121–146)	135 (122–149)	0.002
Diastolic	79 (72–86)	77 (70–85)	<0.001
Hypertension			
JES4 ($\geq$130/80)	4148 (67.0%)	877 (67.9%)	0.54
JES5 ($\geq$140/90, 140/80 if diabetic)	2632 (42.5%)	604 (46.8%)	0.005
LDL-cholesterol (mmol/L)	2.39 (1.92–3.08)	2.34 (1.88–3.07)	0.11
Hyperlipidaemia			
LDL $\geq$ 2.5 mmol/L (100 mg/dL)	2712 (45.1%)	525 (42.3%)	0.07
LDL $\geq$ 1.8 mmol/L (70 mg/dL)	4888 (81.3%)	991 (79.8%)	0.22
Diabetes[b]	1561 (25.2%)	442 (34.2%)	<0.001
Smoking[c]	1082 (17.5%)	130 (10.1%)	<0.001
Chronic kidney disease			
SCr (mg/dl)	0.93 (0.81–1.04)	1.31 (1.16–1.50)	<0.001
eGFR$_{CKD-EPI}$ (mL/min/1.73 m^2)	83.1 (72.2–93.1)	50.5 (42.9–55.7)	<0.001
ACR (mg/g)	6.2 (2.7–15.9)	13.3 (3.8–52.2)	<0.001

Data are proportions n (%) or medians (interquartile ranges); p-values of Wilcoxon rank-sum tests or χ^2 tests.
[a]Overweight BMI $\geq$ 25 kg/m^2, obesity BMI $\geq$ 30 kg/m^2.
[b]Self-reported.
[c]Self-reported or carbon monoxide in exhaled air >10 ppm.
BMI: body mass index; CHD: coronary heart disease; CABG: coronary artery bypass graft; CV: cardiovascular; LDL: low-density lipoprotein; PCI: percutaneous coronary intervention; MI: myocardial infarction; JES: Joint European Societies; eGFR: estimated glomerular filtration rate; SCr: serum creatinine; ACR: urinary albumin creatinine ratio

albuminuria despite preserved eGFR. Age-standardised prevalences of CKD varied considerably between different countries. In addition to classic CV risk factors, a longer CHD duration and a history of CHF were independently associated with the risk of CKD. Impaired kidney function (i.e. chronic and/or acute reduction of eGFR) was common and indeed observed in approximately every fifth patient admitted for CHD. Dependent on the characteristics of the index CHD event, there was a substantial potential for recovery, but also for further decline of kidney function after hospital discharge.

Prevalence of CKD in stable CHD conditions at the EUROASPIRE IV study visit

While CKD patients are at high risk of the development and progression of CHD,[9,19] CKD is also an important risk factor for a worse clinical course in secondary CHD prevention.[4,6] Reduced eGFR, as well as

Table 2. Determinants of chronic kidney disease at the study visit.

	Univariate		Multivariate[a]	
Determinant	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Age (per year)	1.12 (1.11–1.13)	<0.001	1.11 (1.10–1.12)	<0.001
Gender (female vs. male)	2.36 (2.06–2.70)	<0.001	1.95 (1.68–2.26)	<0.001
CHD duration (per year)	1.04 (1.03–1.05)	<0.001	1.01 (0.99–1.02)[b]	0.12
CABG ever	1.73 (1.50–2.00)	<0.001	1.47 (1.26–1.73)	<0.001
PCI/stent ever	0.80 (0.70–0.92)	0.002	0.93 (0.79–1.10)[b]	0.39
MI ever	1.09 (0.96–1.25)	0.17	1.12 (0.96–1.30)[b]	0.14
History of CHF	2.15 (1.77–2.62)	<0.001	1.67 (1.35–2.07)	<0.001
CV risk factors				
Diabetes[c]	1.54 (1.34–1.77)	<0.001	1.27 (1.09–1.47)	0.004
Hyperlipidaemia[d]	0.86 (0.75–0.99)	0.035	0.86 (0.74–1.01)[b]	0.06
Hypertension[e]	1.18 (1.04–1.35)	0.012	0.91 (0.78–1.05)[b]	0.18
Smoking[f]	0.53 (0.43–0.65)	<0.001	1.09 (0.86–1.38)[b]	0.48
Obesity[g]	1.16 (1.02–1.32)	0.027	1.24 (1.07–1.43)	0.006

Data are odds ratios (95% CIs) of multilevel (country) logistic regression, outcome: $eGFR_{study\ visit} < 60\,mL/min/1.73\,m^2$.
[a]Multivariate model, backwards selection ($p > 0.05$); order of exclusion: (1) smoking; (2) PCI/stent ever; (3) acute MI ever; (4) CHD duration; (5) hypertension; (6) hyperlipidaemia;
[b]Odds ratio (95% CI) of covariates before being removed from the model.
[c]Self-reported.
[d]LDL-cholesterol ≥ 2.5 mmol/L.
[e]Blood pressure ≥ 140/90 mmHg, ≥140/80 mmHg in patients with self-reported diabetes (JES5).
[f]Self-reported or carbon monoxide in exhaled air >10 ppm.
[g]Body mass index ≥30 kg/m^2.
CHD: coronary heart disease; CI: confidence interval; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; MI: myocardial infarction; CHF: congestive heart failure; JES: Joint European Societies

albuminuria/proteinuria, impact on the risk of CVD and CV events in CHD patients,[20,21] but also in the general population.[10] The important role of albuminuria, in addition to reductions of eGFR, is reflected by the current KDIGO classification according to CKD-G and CKD-A stages.[8] Reports indicate that a lower eGFR is associated with a more than doubled risk of all-cause and CV mortality in those without significant proteinuria, yet those with largely preserved eGFR, but significant levels of albuminuria, experience an up to 3.7-fold higher risk of death (CV death 4.8-fold) when compared to patients without albuminuria.[10] As verified by the present survey, ACR is rarely measured in the clinical routine, and this particular group is frequently underdiagnosed, despite being at risk for progression of CKD[8] and for progression of CHD with limited evidence.[22,23] We found approximately 12% of stable CHD patients to have largely preserved eGFR, but significant albuminuria. Unfortunately, it was impossible to address their risk for progression of CKD and CHD due to the lack of a second study visit.

The prevalences of CKD, usually defined as CKD stage 3a and higher (i.e. $eGFR < 60\,mL/min/1.73\,m^2$),[8] in a variety of settings, including population-based cohorts, are reported to be between 6% and 26%.[24] Yet, robust data on the proportion of CHD patients with CKD are limited.[25–27] Rigorous and standardised assessment of renal parameters in stable CHD patients across a broad variety of European countries is a major strength of the current EUROASPIRE IV study. The overall prevalence of CKD stages 3a and higher (i.e. $eGFR < 60\,mL/min/1.73\,m^2$) in the ambulatory and thus considerably stable setting was 17%, with wide variation between participating countries: low rates of approximately 13–14% were found in Finland, France, Ireland and Spain, and higher rates of up to 23–26% were found in Bosnia Herzegovina, Cyprus, Czech Republic and Slovenia. These differences might, on the one hand, be explained by variations in the study population due to a wide spectrum of recruitment success,[16] but may also reflect true variations in prevalence rates.[10,24]

The risk of CKD at the EUROASPIRE IV study visit was associated with older age, obesity, diabetes and female gender. The latter unexpected relationship might be due to under-representation and therefore potentially selective recruitment of female CHD patients in CHD studies per se,[28] and needs confirmation in future studies. CKD was more common in patients with a history of CABG, which might reflect

Table 3. Patient characteristics during the index hospital stay by impaired kidney function (eGFR < 60 mL/min/1.73 m^2).

Characteristic	eGFR ≥ 60 mL/min/1.73 m^2, $n = 6081$ (82.4%)	eGFR < 60 mL/min/1.73 m^2, $n = 1299$ (17.6%)	p-value
Age (index)	61.7 (54.9–68.3)	70.2 (64.0–74.3)	<0.001
Male gender	4771 (78.5%)	823 (63.4%)	<0.001
Index event			0.002
– CABG	749 (12.3%)	206 (15.9%)	
– PCI/stent	3335 (54.8%)	652 (50.2%)	
– MI	1372 (22.6%)	307 (23.6%)	
– Myocardial ischaemia	625 (10.3%)	134 (10.3%)	
Details of CHD event during index hospital stay			
Urgency			0.004
Elective	1214 (20.1%)	305 (23.6%)	
Acute/urgent	3264 (54.1%)	697 (54.0%)	
Emergency (<24 hours)	1557 (25.8%)	289 (22.4%)	
AMI, any	3183 (50.8%)	635 (49.2%)	0.02
NSTEMI	*1186 (37.3%)*	*202 (31.8%)*	*0.02*
STEMI	*627 (19.7%)*	*127 (20.0%)*	
Unclear/missing	*1370 (43.0%)*	*306 (48.2%)*	
Therapy (max.)			<0.001
Conservative (no intervention)	1997 (32.8%)	441 (34.0%)	
PCI/stent	3334 (54.8%)	652 (50.2%)	
CABG	750 (12.3%)	206 (15.9%)	
CHD history			
Index event as the primary diagnosis of CHD	3804 (62.9%)	706 (55.0%)	<0.001
In those with history of CHD			
Duration of CHD	*3.7 (0.8–10.7)*	*7.5 (1.4–14.8)*	*<0.001*
CABG (prior to index)	*322 (14.4%)*	*140 (24.2%)*	*<0.001*
PCI/stent (prior to index)	*1197 (53.4%)*	*265 (46.0%)*	*0.002*
MI (prior to index)	*1463 (65.8%)*	*388 (68.3%)*	*0.26*
History of heart failure[a]	2591 (48.6%)	716 (60.0%)	<0.001
Classic cardiovascular risk factors (index)			
Diabetes[b]	1540 (27.0%)	462 (37.8%)	<0.001
Hypertension[b]	4484 (76.8%)	1135 (89.3%)	<0.001
Hyperlipidaemia[b]	4188 (74.7%)	917 (77.7%)	0.03
Smoking[b]	1689 (31.0%)	196 (17.4%)	<0.001
Obesity[c]	1822 (35.8%)	433 (39.3%)	0.03
Kidney function			
SCr at admission[d] (mg/dL)	0.90 (0.80–1.03)	1.32 (1.19–1.51)	<0.001
eGFR at admission (mL/min/1.73 m^2)	84.8 (73.1–95.2)	51.2 (43.0–56.2)	<0.001

Data are proportions n (%) or medians (interquartile ranges); p-values of Wilcoxon rank-sum tests or χ^2 tests.
[a]Known at hospital admission or echocardiographic findings of cardiac dysfunction.
[b]Known at hospital admission or stated in discharge letter.
[c]Body mass index ≥30 kg/m^2 at hospital admission or stated in discharge letter.
[d]First measurement in patient record.
CHD: coronary heart disease; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; MI: myocardial infarction; AMI: acute myocardial infarction; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; SCr: serum creatinine; eGFR: estimated glomerular filtration rate.

Table 4. Determinants of impaired kidney function at the index hospital stay.

	Univariate		Multivariate[a]	
Determinant	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Age (index) (per year)	1.11 (1.10–1.12)	<0.001	1.10 (1.09–1.11)	<0.001
Gender (female vs. male)	2.36 (2.06–2.70)	<0.001	1.93 (1.64–2.27)	<0.001
Index event (vs. CABG)				
- CABG	Reference	–	Reference	–
- PCI/stent	0.63 (0.53–0.76)	<0.001	0.85 (0.68–1.05)	0.13
- Acute MI	0.73 (0.59–0.90)	0.004	1.02 (0.79–1.31)	0.88
- Myocardial ischaemia	0.74 (0.57–0.95)	0.018	0.67 (0.49–0.92)	0.013
Urgency (vs. elective)				
Elective	Reference	–	–	–
Acute/urgent	0.90 (0.76–1.08)	0.25	0.92 (0.71–1.21)[b]	0.55
Emergency	0.80 (0.65–0.97)	0.027	0.95 (0.73–1.23)[b]	0.68
Therapy (max.) (vs. conservative)				
Conservative (no intervention)	Reference	–	–[c]	
PCI/stent	0.87 (0.75–1.00)	0.052		
CABG	1.37 (1.12–1.67)	0.003		
Any MI during index hospital stay (regardless of index)	0.91 (0.80–1.04)	0.146	1.04 (0.77–1.42)[b]	0.79
Index as primary CHD event	0.78 (0.68–0.89)	<0.001	1.03 (0.73–1.44)[b]	0.88
CHD duration prior to index (per year)	1.03 (1.02–1.04)	<0.001	1.01 (0.99–1.02)[b]	0.25
CABG (prior to index)	1.89 (1.51–2.37)	<0.001	1.54 (1.16–2.03)	0.004
PCI/stent (prior to index)	1.01 (0.86–1.19)	0.907	0.91 (0.73–1.14)[b]	0.41
MI (prior to index)	1.19 (1.03–1.37)	0.023	1.24 (1.04–1.47)	0.017
CHF[d]	1.53 (1.33–1.78)	<0.001	1.35 (1.14–1.58)	0.001
CV risk factors (index)				
Diabetes (index)[e]	1.58 (1.37–1.81)	<0.001	1.40 (1.19–1.64)	<0.001
Hyperlipidaemia[e]	1.17 (0.99–1.38)	0.058	0.99 (0.80–1.24)[b]	0.97
Hypertension[e]	2.30 (1.89–2.80)	<0.001	1.44 (1.14–1.81)	0.003
Smoking[e]	0.54 (045–0.64)	<0.001	0.88 (0.71–1.08)[b]	0.22
Obesity[f]	1.16 (1.01–1.34)	0.043	1.03 (0.86–1.24)[b]	0.74

Data are odds ratios (95% CIs) of multilevel (country) logistic regression, outcome: $eGFR_{index}$ <60 mL/min/1.73 m^2.

[a]Multivariate model, backwards selection ($p > 0.05$); order of exclusion: (1) index therapy; (2) hyperlipidaemia; (3) index as primary CHD event; (4) acute MI during index hospital stay (regardless of index classification); (5) obesity; (6) PCI prior to index; (7) urgency of index event; (8) CHD duration prior to index; (9) smoking.

[b]Odds ratio (95% CI) of covariates before being removed from the model.

[c]Variable excluded from multivariate modelling due to violation of convergence criterion.

[d]Known at hospital admission or echocardiographic findings of cardiac dysfunction.

[e]Known at hospital admission or stated in discharge letter.

[f]Body mass index ≥30 kg/m^2 at hospital admission or stated in discharge letter.

CHD: coronary heart disease; CI: confidence interval; CV: cardiovascular; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; MI: myocardial infarction; CHD: congestive heart failure; SCr: serum creatinine; eGFR: estimated glomerular filtration.

a longer and more severe course of CHD. Cardiac surgery may also be causal of CKD because of potential episodes of AKI during cardiopulmonary bypass.[29,30] CKD was also related to symptomatic CHF, which might reflect a two-way relationship and has been described as 'cardio-renal syndrome'; while cardiac dysfunction causes impaired kidney function (e.g. via reduced renal perfusion and several pathways including hormone activation), conversely, CKD itself can further aggravate CHD, particularly in established heart failure.[31,32]

Impaired kidney function in a hospital stay due to CHD

Impaired kidney function has been identified as an important risk factor for complications during and worse outcome after hospital stays of various

Table 5. Determinants of changes in kidney function between index hospital stay and the study visit.

Determinant	Univariate		Multivariate[a]	
	β-coefficient (95% CI)	*p*-value	β-coefficient (95% CI)	*p*-value
Age (index) (per year)	0.03 (0.00–0.07)	0.043	0.44 (0.40–0.47)	<0.001
Gender (female vs. male)	−0.59 (−1.34 to 0.15)	0.12	0.93 (0.21–1.65)	0.011
Time between index event and study visit (per log[year])	1.45 (0.72–2.18)	<0.001	1.80 (1.09–2.51)	0.011
Index event (vs. CABG)				
– CABG	Reference	–	Reference	–
– PCI/stent	1.12 (0.11–2.14)	0.03	1.01 (−1.22 to 3.41)	0.35
– AMI	0.32 (−0.86 to 1.49)	0.56	1.74 (−0.02 to 3.51)	0.05
– Myocardial ischaemia	0.01 (−1.40 to 1.41)	0.99	1.21 (−0.66 to 3.08)[b]	0.20
Urgency (vs. elective)				
Elective	Reference	–	Reference	–
Acute/urgent	0.42 (−0.53 to 1.37)	0.39	0.24 (−0.68 to 1.16)	0.61
Emergency	2.09 (1.04–3.14)	<0.001	1.32 (0.32–2.33)	0.01
Therapy (max.) (vs. conservative)				
Conservative (no intervention)	Reference	–	–	–
PCI/stent	0.91 (0.15–1.66)	0.019	−0.11 (−1.06 to 0.85)	0.83
CABG	−0.20 (−1.31 to 0.91)	0.72	−1.56 (−3.24 to 0.13)[b]	0.07
Index as primary CHD event	0.28 (−0.38 to 0.94)	0.40	−0.18 (−0.87 to 0.50)[b]	0.60
CHD duration prior to index (per log[year])	−0.21 (−0.54 to 0.11)	0.20	−0.09 (−0.43 to 0.25)[b]	0.60
CABG (prior to index or index event)	−0.49 (−1.33 to 0.34)	0.25	0.60 (−0.22 to 1.43)[b]	0.15
PCI/stent (prior to index or index event)	0.87 (0.18–1.56)	0.014	0.01 (−1.96 to 1.97)[b]	0.99
MI (prior to index or index event)	−0.49 (−1.14 to 0.16)	0.14	0.01 (−1.21 to 1.22)[b]	0.99
CHF[c]	0.25 (−0.49 to 1.00)	0.50	0.90 (0.24–1.57)	0.008
CV risk factors (index)				
Diabetes[d]	−1.03 (−1.76 to −0.31)	0.005	−0.16 (−1.30 to 0.98)[b]	0.78
Hyperlipidaemia[d]	−0.27 (−1.07 to 0.53)	0.51	0.22 (−1.16 to 1.60)[b]	0.75
Hypertension[d]	−0.50 (−1.32 to 0.32)	0.23	0.37 (−0.43 to 1.16)[b]	0.36
Smoking[d]	0.56 (−0.19 to 1.31)	0.14	−0.10 (−1.62 to 1.42)[b]	0.89
Obesity[e]	−1.00 (−1.73 to −0.26)	0.008	0.03 (−1.18 to 1.24)[b]	0.96
Kidney function (index)				
eGFR (per mL/min/1.73 m^2)[f]	0.28 (0.27–0.30)	<0.001	0.40 (0.38–0.42)	<0.001

Data are β-coefficients (95% CIs) of multilevel (country) linear regression, outcome: ΔeGFR ($eGFR_{index} - eGFR_{study\ visit}$).
[a]Multivariate model, backwards selection ($p > 0.05$); order of exclusion: (1) PCI prior to or during index; (2) smoking; (3) obesity; (4) AMI prior to or during index; (5) diabetes; (6) hyperlipidaemia; (7) CHD duration prior to index; (8) index as primary CHD event; (9) index event; (10) hypertension; (11) therapy (max.) during index; (12) CABG prior to or during index.
[b]β-coefficient (95% CI) of covariates before being removed from the model.
[c]Known at hospital admission or echocardiographic findings of cardiac dysfunction.
[d]Known at hospital admission or stated in discharge letter.
[e]Body mass index ≥30 kg/m^2 at hospital admission or stated in discharge letter.
[f]Based on first SCr measurement in patient record.
CHD: coronary heart disease; CV: cardiovascular; CI: confidence interval; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; MI: myocardial infarction; AMI: acute myocardial infarction; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; CHF: congestive heart failure; SCr: serum creatinine; eGFR: estimated glomerular filtration rate.

causes,[33,34] including CHD.[4,30,35] CKD patients frequently present with multiple comorbidities (older age, diabetes, vascular disease, etc.) and with CHD with a longer duration of CHD and potentially more severe coronary atherosclerosis.[9] For those undergoing CABG, CKD impacts on preoperative risk status according to EUROSCORE 2 assessment.[36] Moreover, this is a major determinant of post-operative AKI,[29] as well as in acute MI and after coronary interventions.[37,38] It is increasingly acknowledged that even

a slight deterioration of kidney function, reflected by a rise of SCr levels of 0.3 mg/dL, is associated with important early and long-term outcomes.[14,29]

EUROASPIRE IV collected the first recorded SCr measurement during the index event. Kidney function at hospital admission may be prone to variation due to acute clinical events; in particular, patients with acute coronary syndrome and MI may present with symptoms of acute heart failure (e.g. low cardiac output), which may result in episodes of AKI. In addition, CABG and contrast application during PCI may cause impairments in kidney function. Therefore we report on impaired kidney function during the hospital stay rather than CKD, as we cannot claim a chronic and stable condition in all patients. Approximately 17% of the patients had impaired kidney function, however, with major variations between countries (from 10% to >30%). Although this might at least partly reflect varying recruitment strategies,[16] it would be of great interest and importance to investigate whether these differences reflect true variations at the patient level across European countries, or whether hospital admission and transfer strategies between different healthcare systems or variations in CHD treatment and care are responsible for these dramatic prevalence differences. Older age, female gender, diabetes and hypertension were independently related to impaired kidney function at hospital admission, as were also previous CABG or MI and a history of CHF. This reflects a more severe course of CHD and the specific relationship of the 'cardio-renal syndrome'.[31] Apart from female gender, which needs further investigation (see above), these determinants describe CHD patients with CKD as individuals with a multitude of comorbidities.

Changes of kidney function after a hospital stay due to CHD

There are few data available on the course of CKD in the ambulatory setting after a hospital stay due to CHD.[30,39–41] In situations of 'true' CKD that is already present prior to the hospital stay, it is unlikely that major improvements in kidney function can be achieved. The aim of care must then focus on reducing the decline in kidney function by renin-angiotensin-aldosterone-system (RAAS) blockade, avoidance of nephrotoxic agents and strict control of classic CV risk factors.[8] In contrast, those CHD patients with an episode of AKI during the hospital stay but without major pre-existing CKD have a great potential for improvements or complete recovery of kidney function. However, even those patients with markers of kidney function in the normal range after AKI remain at risk for the development of CKD, whereas other patients are at risk for non-recovery of AKI and either experience a rapid decline in kidney function or remain dependent on renal replacement therapy.[14]

In EUROASPIRE IV, we report on the proportions of those with declined, stable and improved kidney function, but due to the limitations discussed below (data on episodes of AKI during the index hospital stay not being captured in the dataset, as well as data on kidney function at hospital discharge, varying methods of SCr measurement at index hospital stay, confounding by medical treatment, lifestyle changes, etc., between index hospital stay and EUROASPIRE IV study visit), our results should be interpreted with caution as purely descriptive and hypothesis generating. Patients with better kidney function at hospital admission were more likely to present with improved kidney function at the study visit, as well as female patients and those with a longer duration between the index event and the study visit. Those patients in whom the index event was classified as non-elective had a greater chance of recovery of kidney function as compared to those with elective procedures. This might be explained by the fact that CKD patients undergo elective procedures mostly in stable conditions and thus there might be no reason for meaningful improvements of kidney function thereafter. Yet, older patients and those with CHF also recovered kidney function, which may initially seem counterintuitive. This may, however, be an expression of greater awareness and more intense physician care after hospital discharge.

Strengths and limitations

The EUROASPIRE IV dataset contains high-quality prospectively collected data of the study visit, including standardised measurements of the risk factors of a large sample of CHD patients across 24 European countries and is thus a unique source for describing CKD and its associated factors, particularly as there were few missing data on ACR as well as on SCr. However, there are limitations. First, the prevalence rates cannot be considered as representative of the participating countries due to the selection processes of the centres, the recruitment success within the countries and the fact that only those patients who survived long enough after the index hospital stay could be enrolled in EUROASPIRE IV. Therefore, it is possible that the study participants may represent a considerably 'healthier' CHD population, as 'sicker' CHD patients may have died early, may not have been able to attend the study visit due to medical/physical circumstances or may have opted not to participate in a study dedicated to the quality of secondary prevention in CHD.[16] Second, the validity of retrospectively collected data of hospital records in 78 of the centres might be limited due to variation in SCr measurement methods in routine patient care and the

non-standardised description of risk factors and completeness at admission and in discharge letters. In addition, ACR was not routinely measured in European hospitals for analysing the level of proteinuria and variations among countries. Third, we were not able to address all of the factors related to changes in eGFR between discharge of the index hospital stay, including episodes of AKI, fluid management, kidney function at hospital discharge, medical care (e.g. the use of angiotensin-converting enzyme inhibitors and diuretics) and patient compliance/behaviour in the ambulatory setting. Detailed analysis of these factors would be beyond the scope of this manuscript, and we therefore included only determinants in our models that were available during the hospital stay describing their prognostic value regarding changes in kidney function. Finally, the robust and consistent association of female gender with impaired kidney function at the study visit as well as during the index hospital stay needs to be interpreted with caution. As discussed above, underrepresentation and selective recruitment of women might have influenced the results.

Conclusion

The EUROASPIRE IV dataset provides a comprehensive, up-to-date view of kidney function in CHD patients across Europe. In CHD patients with stable conditions, every forth to fifth patient has CKD, including those with preserved eGFR but significant albuminuria. As CKD is common in hospital stays for CHD, routine albuminuria measurement might be useful for determining the entire risk spectrum of CKD, including AKI. The present findings underline the importance of identifying patients who are at high risk of developing CKD in order to counteract such progression.

Author contribution

All authors (MW, CW, KK, DW, DDB, LR, SS and PUH) contributed to the conception or design of the work. All authors contributed to the acquisition, analysis or interpretation of data for the work. MW, CW, KK, SS and PUH drafted the manuscript. All authors critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work, ensuring integrity and accuracy.

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Declaration of conflicting interests

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6.2.3. Supplementary materials, as published

Supplementary data

Figure s1: Study design EUROASPIRE IV

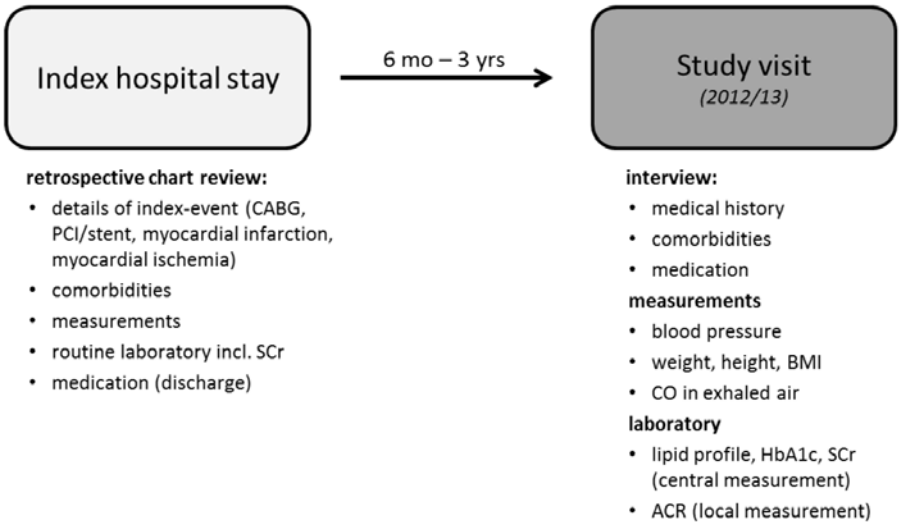

*Figure s2: KDIGO stages **at study visit** (crude data)*

		Albuminuria (ACR)			Total
CKD-stage	$eGFR_{CKD-EPI}$ (ml/min/1.73m²)	**A1** (< 30 mg/g)	**A2** (30 – 300 mg/g)	**A3** (> 300 mg/g)	
G1	≥ 90	1319 23.3%	210 3.7%	33 0.6%	1562 27.5%
G2	60 – 89	2601 45.8%	433 7.6%	101 1.8%	3135 55.3%
G3a	45 – 59	500 8.8%	176 3.1%	30 0.5%	706 12.4%
G3b	30 – 44	127 2.2%	52 0.9%	24 0.4%	203 3.6%
G4	15 – 29	22 0.4%	18 0.3%	12 0.2%	52 0.9%
G5	< 15	3 0.1%	2 0.1%	11 0.2%	16 0.3%

Legend: CKD stages according to KDIGO (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group; KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease; Kidney inter., Suppl. (3) 1-150); colors indicate low risk (green), moderately increased risk (yellow), high risk (orange), very high risk (red) for worse prognosis

*Table s1: Proportions of patients with CKD ($eGFR_{CKDEPI}$ <60 ml/min/1.73m²) among countries at the **study visit***

	Proportion of patients with CKD n (% within country)	**Age-adjusted proportions of patients with CKD** (Standard European Population)
Belgium	**67 (19.9%)**	**18.5%**
Bosnia Herzegovina	**20 (16.7%)**	**25.9%**
Bulgaria	**21 (18.0%)**	**19.0%**
Croatia	**70 (15.8%)**	**16.3%**
Cyprus	**11 (15.9%)**	**23.4%**
Czech Republic	**105 (21.6%)**	**25.2%**
Finland	**68 (14.8%)**	**14.4%**
France	**53 (14.8%)**	**13.7%**
Germany	**107 (20.2%)**	**20.1%**
Greece	**6 (12.5%)**	**20.6%**
Ireland	**19 (9.6%)**	**14.5%**
Latvia	**49 (16.9%)**	**18.0%**
Lithuania	**83 (18.3%)**	**17.7%**
Netherlands	**73 (16.9%)**	**20.1%**
Poland	**64 (17.0%)**	**18.4%**
Romania	**99 (19.2%)**	**18.3%**
Russian Federation	**79 (19.0%)**	**21.8%**
Serbia	**69 (18.0%)**	**19.3%**
Slovenia	**57 (23.4%)**	**26.4%**
Spain	**19 (11.1%)**	**13.1%**
Sweden	**60 (17.4%)**	**19.6%**
Turkey	**19 (8.4%)**	**21.8%**
Ukraine	**26 (10.9%)**	**15.0%**
United Kingdom	**50 (20.9%)**	**19.6%**

*Table s2: Proportions of patients with impaired kidney function ($eGFR_{CKDEPI}$ <60 ml/min/1.73m²) among countries during the **index hospital stay***

	Proportion of patients with impaired kidney function n (% within country)	**Age-adjusted proportion of patients with impaired kidney function** (Standard European Population)
Belgium	**76 (24.1%)**	**21.4%**
Bosnia Herzegovina	**47 (18.6%)**	**22.8%**
Bulgaria	**35 (29.2%)**	**32.4%**
Croatia	**112 (27.1%)**	**26.3%**
Cyprus	**13 (14.9%)**	**17.6%**
Czech Republic	**113 (24.0%)**	**22.3%**
Finland	**36 (8.2%)**	**7.5%**
France	**42 (11.4%)**	**13.1%**
Germany	**91 (17.1%)**	**14.1%**
Greece	**6 (15.0%)**	**27.8%**
Ireland	**9 (4.6%)**	**9.3%**
Latvia	**47 (19.3%)**	**19.6%**
Lithuania	**83 (18.1%)**	**19.1%**
Netherlands	**46 (10.4%)**	**10.2%**
Poland	**60 (16.8%)**	**15.9%**
Romania	**87 (17.6%)**	**16.1%**
Russian Federation	**88 (23.5%)**	**31.0%**
Serbia	**70 (20.1%)**	**19.0%**
Slovenia	**42 (17.4%)**	**18.3%**
Spain	**25 (15.2%)**	**20.2%**
Sweden	**48 (14.1%)**	**18.3%**
Turkey	**22 (10.0%)**	**20.0%**
Ukraine	**51 (20.7%)**	**21.6%**
United Kingdom	**50 (23.8%)**	**38.2%**

Table s3: *changes in kidney function between the index hospital stay and the EA4 study visit among participating countries*

	Declined ΔeGFR < -5 ml/min/1.73m²		**Stable** ΔeGFR ≥ -5 – ≤+5 ml/min/1.73m²		**Improved** ΔeGFR > +5 ml/min/1.73m²	
	crude	Age-standardized	crude	Age-standardized	crude	Age-standardized
Belgium	113 (37.1%)	37.3%	93 (30.5%)	31.0%	99 (32.5%)	47.5%
Bosnia Herzegovina	29 (34.1%)	40.3%	23 (27.1%)	27.7%	33 (38.8%)	43.1%
Bulgaria	63 (53.9%)	60.3%	40 (34.2%)	31.8%	14 (12.0%)	20.8%
Croatia	255 (65.2%)	70.1%	94 (24.0%)	22.0%	42 (10.7%)	12.3%
Cyprus	17 (25.4%)	30.9%	22 (32.8%)	42.5%	28 (41.8%)	46.2%
Czech Republic	188 (40.5%)	51.3%	131 (28.2%)	30.0%	145 (31.3%)	30.9%
Finland	35 (8.0%)	8.3%	165 (37.8%)	45.9%	236 (54.1%)	61.0%
France	91 (26.2%)	30.7%	114 (32.9%)	33.4%	142 (40.9%)	43.7%
Germany	86 (16.8%)	15.4%	82 (16.0%)	17.2%	345 (67.3%)	77.8%
Greece	14 (36.8%)	53.7%	14 (36.8%)	49.3%	10 (26.3%)	42.3%
Ireland	21 (10.9%)	14.7%	58 (30.1%)	38.9%	114 (59.1%)	56.5%
Latvia	73 (30.5%)	29.1%	84 (35.2%)	35.7%	82 (34.3%)	40.6%
Lithuania	93 (22.4%)	21.3%	129 (31.1%)	30.8%	193 (46.5%)	52.6%
Netherlands	39 (10.5%)	22.4%	125 (33.5%)	30.6%	209 (56.0%)	57.6%
Poland	126 (35.5%)	42.1%	127 (35.8%)	37.4%	102 (28.7%)	36.9%
Romania	130 (27.4%)	30.6%	133 (28.1%)	26.1%	211 (44.5%)	45.6%
Russian Federation	150 (41.3%)	55.1%	143 (39.4%)	37.3%	70 (19.3%)	22.9%
Serbia	132 (39.3%)	39.9%	99 (29.5%)	28.5%	105 (31.3%)	31.6%
Slovenia	46 (19.2%)	26.5%	86 (35.8%)	40.4%	108 (45.0%)	48.0%
Spain	66 (41.3%)	52.8%	59 (36.9%)	34.5%	35 (21.9%)	22.7%
Sweden	50 (15.4%)	19.7%	130 (40.0%)	43.7%	145 (44.6%)	42.8%
Turkey	58 (27.6%)	28.0%	79 (37.6%)	39.4%	73 (34.8%)	39.7%
Ukraine	108 (50.7%)	52.8%	56 (26.3%)	29.4%	49 (23.0%)	32.3%
United Kingdom	62 (31.3%)	34.8%	60 (30.3%)	36.2%	76 (38.4%)	36.6%

*Table s4: Patient characteristics **at index event** according to changes in kidney function between index-hospital stay and EA4-study visit*

	Declined kidney function ΔeGFR < -5 ml/min/1.73m² n=2054 (29.8%)	**Stable kidney function** ΔeGFR ≥ -5 to ≤+5 ml/min/1.73m² n=2146 (31.3%)	**Improved kidney function** ΔeGFR > +5 ml/min/1.73m² n=2666 (38.9%)	**p-value**
Age (index)	62.7 (55.7; 69.2)	63.2 (56.6; 69.8)	63.7 (56.8; 70.7)	0.007
Gender, male	1507 (73.7%)	1672 (77.9%)	2034 (76.3%)	0.006
Time between index event and study visit (yrs)	1.3 (0.9; 1.8)	1.3 (0.9; 1.9)	1.4 (1.0; 2.0)	<0.001
Index event				<0.001
- CABG	251 (12.3%)	270 (12.6%)	338 (12.7%)	
- PCI/stent	1039 (50.8%)	1180 (55.0%)	1536 (57.6%)	
- MI	527 (25.8%)	464 (21.6%)	544 (20.4%)	
- myocardial ischemia	228 (11.2%)	232 (10.8%)	248 (9.3%)	
Urgency				<0.001
Elective	463 (22.8%)	513 (24.0%)	409 (15.5%)	
Acute/urgent	1110 (54.6%)	1116 (52.3%)	1435 (54.3%)	
Emergency	460 (22.6%)	505 (23.7%)	801 (30.3%)	
AMI, any	1042 (51.3%)	1025 (48.0%)	1485 (56.1%)	<0.001
NSTEMI	*352 (33.8%)*	*358 (34.9%)*	*600 (40.4%)*	*<0.001*
STEMI	*165 (15.8%)*	*203 (19.8%)*	*342 (23.0%)*	
Unclear/missing	*525 (50.4%)*	*464 (45.3%)*	*543 (36.6%)*	
Therapy (max.)				<0.001
Conservative (no intervention)	755 (36.9%)	696 (32.4%)	792 (29.7%)	
PCI/stent	1039 (50.8%)	1180 (55.0%)	1535 (57.6%)	
CABG	251 (12.3%)	270 (12.6%)	339 (12.72%)	
Index event as the primary diagnosis of CHD	1242 (61.3%)	1298 (60.9%)	1661 (62.5%)	0.463
Duration of CHD prior to index event if not primary diagnosis	3.8 (0.9; 11.1)	5.1 (1.0; 11.8)	4.5 (0.7; 12.3)	0.090
CABG (prior to index or index event)	355 (17.5%)	391 (18.3%)	515 (19.4%)	0.252
PCI/stent (prior to index or index event)	1191 (58.8%)	1345 (62.9%)	1732 (65.0%)	<0.001
MI (prior to index or index event)	953 (46.9%)	922 (43.2%)	1085 (40.8%)	<0.001
History of heart failure[a]	1011 (54.2%)	915 (48.7%)	1171 (50.4%)	0.002
Classic cardiovascular risk factors (index)				
Diabetes[b]	628 (32.2%)	532 (26.5%)	679 (27.3%)	<0.001
Hypertension	1609 (80.9%)	1636 (79.2%)	1973 (77.1%)	0.002
Hyperlipidemia	1428 (75.6%)	1499 (75.6%)	1825 (74.6%)	0.684
Smoking	529 (29.3%)	534 (28.0%)	709 (29.6%)	0.475
Overweight/obesity[c]	666 (38.7%)	601 (33.8%)	755 (33.9%)	0.002
Kidney function/ chronic kidney disease				
SCr at admission[d]	1.10 (0.98; 1.23)	0.93 (0.80; 1.10)	0.87 (0.76; 1.00)	<0.001
eGFR at admission	68.0 (57.0; 78.3)	82.4 (67.1; 94.2)	88.0 (75.3; 97.5)	<0.001
CKD-stage at admission[e]				<0.001
- stage G1	148 (7.2%)	765 (35.7%)	1192 (44.7%)	
- stage G2	1257 (61.5%)	1065 (49.6%)	1251 (46.9%)	
- stage G3a	463 (22.6%)	207 (9.7%)	162 (6.1%)	
- stage G3b	143 (7.0%)	79 (3.7%)	53 (2.0%)	
- stage G4	33 (1.6%)	17 (0.8%)	8 (0.3%)	

- stage G5	1 (0.1%)	13 (0.6%)	0	

Legend: data are proportions n(%) or median (interquartile range); p-value of Kruskal-Wallis-test or χ^2-test; abbreviations: CHD, coronary heart disease; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; MI, myocardial infarction; AMI, acute myocardial infarction; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; SCr, serum creatinine; eGFR, estimated glomerular filtration rate

[a] known at hospital admission or echocardiographic findings of cardiac dysfunction

[b] known at hospital admission or stated in discharge letter

[c] BMI ≥30 kg/m² at hospital admission or stated in discharge letter

[d] First measurement in patient record

[e] CKD-G stages according to KDIGO: G1 eGFR ≥90 ml/min/1.73m²; G2 60-89 ml/min/1.73m²; G3a 45-59 ml/min/1.73m²; G3b 30-44 ml/min/1.73m²; G4 15-29 ml/min/1.73m², G5 <15 ml/min/1.73m²

6.3.Manuscript 3 "CKD awareness in the German EUROASPIRE IV study"

Wagner, M., Wanner, C., Schich, M., Kotseva, K., Wood, D., Hartmann, K., Fette, G., Rucker, V., Oezkur, M., Stork, S. and Heuschmann, P. U.: *Patient's and physician's awareness of kidney disease in coronary heart disease patients - a cross-sectional analysis of the German subset of the EUROASPIRE IV survey.* BMC Nephrology 18(1): 321[108]; doi: 10.1186/s12882-017-0730-3; copyright © 2017. *[Open Access} – this article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).*

6.3.1. Summary

Data of the *kidney specific module* were used to analyze CKD awareness among patients and their treating physicians in the German EUROASPIRE IV sample (n=536). For this project we defined CKD as CKD-G1A3, G2A2, G2A3 and all G3a-stages and higher, thus including those patients with albuminuria but preserved eGFR which are at high risk for CKD progression[50]. With a median eGFR of 74 (60 to 85) ml/min/1.73m² and a median ACR of 4.9 (1.3 to 15.8) mg/g, 185 patients (35%) were classified as having CKD at the study visit. Of these subjects, 34% reported that they had been told about CKD, 15% were referred and 13% had been seen by a renal specialist. Determinants of a higher chance of CKD awareness based on multivariate regression included more severe kidney disease, i.e. lower levels of eGFR (OR 0.94 [0.92 to 0.96]), obesity (OR 2.0 [1.1 to 3.6]), a history of CHF (OR 2.0 [1.0 to 4.0]) and the fact that kidney dysfunction was mentioned in a recent hospital discharge letter (OR 5.5 [2.4 to 12.9]).

Collection of all SCr values which were measured during the entire hospital stay of the index event allowed detailed analysis of the clinical course of kidney function including episodes of AKI. At hospital admission and at discharge 18% had eGFR <60 ml/min/1.73m², while also 18% experienced any episode of AKI. Any impairment of kidney function, either acute or chronic was observed in 32% of the patients. Yet, of those with kidney dysfunction, i.e. either CKD or AKI, impaired kidney function was reported in prominent parts of the discharge letter in 21%. Related factors of reporting kidney disease in the

discharge letter were more severe renal impairment (eGFR per 1 ml/min/1.73m² OR 0.92 [0.89 to 0.94]), higher stages of AKI (stage 2/3 OR 93 [10 to 848]) and it was less likely to be reported if the index event represented the primary diagnosis of CHD (OR 0.4 [0.1 to 1.0]). Relevant ICD-10 diagnoses regarding kidney disease were coded for 72% of those individuals with either AKI or CKD during the index hospital stay. These included codes for any CKD (N18, N19, I12.0, I13) in 63% and AKI (N17) in 5% of these patients. Coding was more complete in more severe AKI stages (100% in stage 2, 75% of stage 3) and CKD stages (77% stage G3a, 95% stage G3b, 100% stage G4, 100% stage G5).

It has to be mentioned that Dr. Martin Schich completed his medical doctoral thesis[109], by employing parts of the data of the *kidney specific module*. Although he also analyzed CKD awareness in the German EUROASPIRE IV sample, the analyses and results presented in the manuscript and the current thesis, respectively vary and are much more detailed. The main differences were as follows: Dr. Schich used the more conservative definition of CKD, i.e. eGFR < 60 ml/min/1.73m², while we also included those patients with preserved eGFR but albuminuria, i.e. those with high risk for CKD and CKD progression. For the manuscript and the thesis, we also performed a variety of multivariate analyses of CKD awareness, from the patient's as well as from the treating physician's perspective to analyze important determinants, including sensitivity analyses and imputation of missing variables. Furthermore, we investigated the ICD codes for any kind of kidney impairment during the hospital stay, to understand CKD as an important comorbid condition in CHD also from the perspective of reimbursement for the hospital.

6.3.2. Manuscript 3, as published

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RESEARCH ARTICLE Open Access

Patient's and physician's awareness of kidney disease in coronary heart disease patients – a cross-sectional analysis of the German subset of the EUROASPIRE IV survey

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Abstract

Background: Chronic kidney disease (CKD) is a common comorbid condition in coronary heart disease (CHD). CKD predisposes the patient to acute kidney injury (AKI) during hospitalization. Data on awareness of kidney dysfunction among CHD patients and their treating physicians are lacking. In the current cross-sectional analysis of the German EUROASPIRE IV sample we aimed to investigate the physician's awareness of kidney disease of patients hospitalized for CHD and also the patient's awareness of CKD in a study visit following hospital discharge.

Methods: All serum creatinine (SCr) values measured during the hospital stay were used to describe impaired kidney function ($eGFR_{CKD\text{-}EPI}$ < 60 ml/min/1.73m^2) at admission, discharge and episodes of AKI (KDIGO definition). Information extracted from hospital discharge letters and correct ICD coding for kidney disease was studied as a surrogate of physician's awareness of kidney disease. All patients were interrogated 0.5 to 3 years after hospital discharge, whether they had ever been told about kidney disease by a physician.

Results: Of the 536 patients, 32% had evidence for acute or chronic kidney disease during the index hospital stay. Either condition was mentioned in the discharge letter in 22%, and 72% were correctly coded according to ICD-10. At the study visit in the outpatient setting 35% had impaired kidney function. Of 158 patients with kidney disease, 54 (34%) were aware of CKD. Determinants of patient's awareness were severity of CKD (OR_{eGFR} 0.94; 95%CI 0.92–0.96), obesity (OR 1.97; 1.07–3.64), history of heart failure (OR 1.99; 1.00–3.97), and mentioning of kidney disease in the index event's hospital discharge letter (OR 5.51; 2.35–12.9).

Conclusions: Although CKD is frequent in CHD, only one third of patients is aware of this condition. Patient's awareness was associated with kidney disease being mentioned in the hospital discharge letter. Future studies should examine how raising physician's awareness for kidney dysfunction may improve patient's awareness of CKD.

Keywords: Coronary heart disease, Chronic kidney disease, Patients' awareness, Physicians' awareness, ICD-coding of CKD, EUROASPIRE survey

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Background

Chronic kidney disease (CKD) has been identified as a common and important risk factor in patients with coronary heart disease (CHD) [1–4]. Patients with CKD represent a multi-morbid population [5] which is at risk for various complications, e.g. episodes of acute kidney injury (AKI), in hospital stays of various causes, including CHD [6]. CKD and AKI impact independently on morbidity and mortality, even if classic cardiovascular risk factors, such as hypertension, diabetes, and dyslipidemia are controlled [7–10]. The health economic relevance of kidney disease, acknowledging multi-morbidity of patients and risk for complications, is also reflected by the fact that adequate ICD-10 coding for CKD and AKI impacts on reimbursement [11].

Early referral to nephrology or specialist care for impaired kidney function is associated with a reduced risk of CHD events, CKD progression, and mortality [12]. To decide on treatment goals and educate the patient, nephrology care suggests determining the risk of an individual patient for disease progression [13]. The awareness of CKD in the general population and in CKD cohorts is limited [14, 15]. It is suggested that well-informed patients aware of their disease may show better adherence to medication and may easier achieve treatment targets [16, 17].

In CHD, many patients and physicians know about of the importance of classic cardiovascular (CV) risk factors, treatment targets, and lifestyle advice such as smoking cessation, diet, or physical activity [18, 19]. However, implementation of guideline recommendations into daily practice is still far from optimal [20]. Evidence is sparse regarding the perception of kidney disease in patients with CHD [21], both from the perspective of patients as of physicians. Herein, to report on important inhospital events including e.g. chronic and/or acute deterioration of kidney function in discharge letters is important to transfer information from the hospital to the ambulatory setting.

In the current study, we analyzed (a) how chronic and/or acutely impaired kidney function is reported in the discharge letter after hospitalization for CHD and (b) the completeness of ICD coding for CKD and AKI as reflection the physician's awareness of kidney disease. We also describe the level of CKD awareness in CHD patients in the ambulatory setting following hospital discharge.

Methods

Patient population and study setting

We used data of the German sample ($n = 536$) of the EUROASPIRE IV survey [20]. The EUROpean Action on Secondary and Primary Prevention by Intervention to Reduce Events surveys are a multinational initiative of the European Society of Cardiology and the European Association for Cardiovascular Prevention and Rehabilitation to assess quality of secondary prevention in CHD patients across Europe [19]. The study design of the EUROASPIRE IV "hospital-arm" has been reported previously [20]. Briefly, for each participating country, a geographical region with > 0.5 million people was selected in which at least one hospital offering interventional cardiology and cardiac surgery and one or more acute hospitals admitting patients with MI and myocardial ischemia. All patients hospitalized for acute or elective treatment of CHD (coronary artery bypass grafting [CABG], percutaneous coronary intervention [PCI], acute myocardial infarction, or myocardial ischemia) were identified from the hospital's patient management systems and invited to participate in the study. This "index" CHD-event could represent the primary diagnosis of CHD as well as any subsequent episode in previously established CHD. Subjects were eligible if they were 18–79 years old and the study visit took place between 6 and 36 months after the index hospital stay. All participants provided written informed consent. At the German study center, patients were recruited from the University Hospital Wuerzburg (Dept. of Medicine I and Department for Thoracic and Cardiovascular Surgery) and the Klinik Kitzinger Land (Dept. of Medicine). The study protocol and data-handling at the German study center were approved by the Ethics Committee of the Medical Faculty of the University of Würzburg (Vote 58/12) and the data protection officers of the University Hospital and the University of Würzburg (DS-117.605-15/12).

Data collection

Information on the CHD event, risk factors, clinical measurements and laboratory values (e.g. SCr at hospital admission) were obtained by retrospective review of index hospitalization charts. During the study visit, details of CHD history (e.g. MI, CABG, PCI/stent) and information on co-morbid conditions, medication, lifestyle and behavior were collected in personal interviews, and standardized examinations were performed according to the EUROASPIRE IV protocol, including blood pressure, weight, height, carbon monoxide (CO) in exhaled air [22]. Serum creatinine (SCr), lipid profile and HbA1c were analyzed centrally from fasting blood samples at the National Public Health Institute, Helsinki, Finland. In addition, urinary albumin/creatinine ratio (ACR) was measured locally.

In addition to the core EUROASPIRE IV protocol, we implemented a *kidney module* at the German study center a few weeks after the start of enrollment, thus respective information was missing in $n = 62$ (11.6%) individuals. Additional information relating to kidney function during the index hospitalization, i.e. details of CKD or AKI, including dialysis requirement, reported in the discharge letter, was collected by chart review. For all German patients we were able to retrospectively

collect laboratory data on SCr at hospital discharge and the maximum value of SCr during the hospital stay. For patients admitted to the University Hospital Würzburg ($n = 498$) the Data Warehouse of the Comprehensive Heart Failure Center [23] was utilized, e.g. for extraction of SCr values, ICD-10 codes for CKD and AKI, and OPS-codes for dialysis treatment. At the study visit, we collected data on the patient's awareness of CKD and specialist care during personal interviews. It included the following questions: "Have you ever been told by a doctor/health care provider that your kidney function is impaired, e.g. not as good as it would be expected?"; "Have you ever been told by a doctor/health care provider that you should be seen by a specialist to have your kidney function checked?"; "Have you ever been seen by a specialist to have your kidney function checked and/or treated?".

Presence of CKD

Kidney function was categorized into CKD-G and CKD-A stages based on estimated glomerular filtration rate ($eGFR_{CKD\text{-}EPI}$) and ACR according to KDIGO (Kidney Disease: Improving Global Outcomes) [24] (Fig. 1). Due to 95.5% missing data on ACR in the hospital records, impaired kidney function during the hospital stay was described as $eGFR_{CKD\text{-}EPI} < 60$ ml/min/1.73m^2 at hospital admission or at discharge or any episode of AKI. AKI during the index hospital stay was defined as SCr increase of ≥ 0.3 mg/dl within 48 h or SCr increase of 1.5–1.99× baseline SCr within 7 days (KDIGO AKI stage 1), SCr-increase of 2.0–2.9× baseline SCr (stage 2) and SCr-increase ≥ 3.0× baseline or SCr > 4 mg/dl or dialysis (stage 3) [25]. A binary variable CKD at the study visit was defined as all CKD-G stages G3a and higher and CKD stages G1A3, G2A2, G2A3 (i.e., largely preserved GFR but significant albuminuria).

Outcome (awareness)

The fact that CKD or AKI was explicitly stated in prominent parts in the discharge letter (diagnoses and/or summary) and the completeness of ICD coding (i.e., correct coding of CKD [ICD-10 codes N18, N19, I12.0, I13) and/or AKI [ICD-10 code N17]) was used to operationalize *physician's awareness of kidney disease.*

Patients' awareness of CKD was defined as positive response to the first question of the kidney module: "Have you ever been told by a doctor/health care provider that your kidney function is impaired, e.g. not as good as it would be expected?".

Covariates

During the index hospital stay the following risk factors were defined: history of heart failure (according to case history or echocardiographic findings of cardiac dysfunction at admission); cardiovascular risk factors known at admission or reported in the discharge letter as hypertension, dyslipidemia, diabetes, smoking and obesity (BMI ≥ 30 kg/m^2 at admission or explicitly stated in the discharge letter). Definitions of risk factors at the study visit were as follows: hypertension (blood pressure ≥ 140/90 mmHg, ≥ 140/85 mmHg in diabetes, ≥ 150/90 mmHg in patients > 80 yrs., ≥130/90 mmHg in patients with CKD [26]), diabetes (self-reported

		Albuminuria (ACR)			Total
CKD-stage	$eGFR_{CKD\text{-}EPI}$ (ml/min/1.73m²)	**A1** (< 30 mg/g)	**A2** (30 – 300 mg/g)	**A3** (> 300 mg/g)	
G1	≥ 90	79 15.2%	9 1.7%	2 0.4%	90 17.3%
G2	60 – 89	257 49.4%	36 6.9%	10 1.9%	303 58.3%
G3a	45 – 59	76 14.6%	17 3.3%	3 0.6%	96 18.5%
G3b	30 – 44	15 2.9%	5 1.0%	2 0.4%	22 4.2%
G4	15 – 29	3 0.6%	2 0.4%	3 0.6%	8 1.5%
G5	< 15	0	0	1 0.2%	1 0.2%
total		430 82.7%	69 13.3%	21 4.0%	520 100%

Fig. 1 Stages of CKD according to eGFR and albuminuria following KDIGO classification; displayed are number of patients (%) within each category. The color code indicates risk category according to KDIGO [24]: green "low risk", yellow "moderate risk", orange "high risk" and red "very high risk"

diabetes or impaired fasting glucose or impaired glucose tolerance), dyslipidemia (LDL cholesterol ≥2.5 mmol/L), obesity (body mass index [BMI] ≥30 kg/m^2) and smoking (self-reported, or CO in exhaled air >10 ppm [20]).

Statistical methods

Data are reported as proportions and median (interquartile range, IQR) and were compared across categories of interest (i.e. impaired kidney function during hospital stay, CKD at study visit) using Wilcoxon rank-sum test, Kruskal-Wallis test and χ^2 test/Fisher's exact test, as appropriate. The trend of patient's awareness, referral to specialist and visit at the specialist across CKD-G stages was analyzed by Cochran-Mantel-Haenszel test. Determinants of *patients' awareness of CKD* (i.e. positive response to the first question of the kidney module: "Have you ever been told by a doctor/health care provider that your kidney function is impaired, e.g. not as good as it would be expected?") and the fact that CKD or AKI were mentioned in the hospital discharge letter (*physician's awareness of kidney disease)* in all participants were investigated by univariable and multivariable logistic regression, using backwards selection including variables statistically significant in univariate analysis. Results are displayed as odds ratio (OR) with respective 95% confidence intervals (CI). Analyses were performed on a complete case dataset, i.e. $n = 474$ with data on the *kidney module*. We tested the robustness of the multivariable models on a dataset with imputed missing data, using five imputations derived from the Markov Chain Monte Carlo method (SAS proc. mi). We also performed sensitivity analyses in which eGFR <50 ml/min/1.73 m^2 was used rather than <60 ml/min/1.73m^2 to increase the confidence in the patient suffering from true kidney disease by excluding patients with only a minor variation in SCr that made their eGFR values being slightly below 60 ml/min/1.73m^2. Analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). Two-sided p-values <0.05 were considered statistically significant.

Results

Prevalence of impaired kidney function during the (index) hospital stay

A total of 536 German patients were enrolled in EURO-ASPIRE IV (median age at the index hospital stay 67 years, 82% male). Median SCr at hospital admission for the index CHD event (i.e. first measurement in patient record) was 0.9 (IQR 0.8; 1.1) mg/dl, reflecting an $eGFR_{admission}$ of 81.1 (66.2; 93.3) ml/min/1.73m^2 and 94 patients (17.6%) had eGFR <60 ml/min/1.73 m^2. At hospital discharge (i.e. last measurement in patient record), median SCr was 1.0 (0.8; 1.1) mg/dl, median $eGFR_{discharge}$ was 78.7 (64.1; 91.4) ml/min and 100 (18.1%) patients had eGFR <60 ml/min/1.73m^2. AKI was observed in 94 (18.1%) subjects. Most AKI episodes represented a slight increase of SCr (AKI stage 1: 89.4%), while a rise in SCr of not more than exactly 0.3 mg/dl was observed in 16 patients. Two events were of AKI stage 2 (2.1%) and 8 (8.5%) were of stage 3, of which 3 had to be treated by acute hemodialysis. Any impairment in kidney function during the hospital stay (either eGFR <60 ml/min/1.73m^2 at admission, or at discharge or AKI) was observed in 172 patients (32.2%). Patients with impaired kidney function were older, more often had a history of heart failure, had a longer duration of CHD, and were more likely to receive CABG during the hospital stay. The hospital stay was on average also longer in CKD patients as compared to patients without renal impairment (Table 1). No differences in classic CV risk factors were observed. In the sensitivity analysis applying the lower eGFR cut-off, we found 38 (7.1%) subjects with eGFR <50 ml/min/1.73m^2 at hospital admission, $n = 46$ (8.7%) at hospital discharge and any impairment of kidney function during the hospital stay in $n = 119$ (22.3%) patients. We did not find any meaningful differences in the patient characteristics as compared to results using the eGFR 60 ml/min/1.73m^2 cut-off (detailed data not shown).

Physician's awareness of kidney disease during the (index) hospital stay

Of the 474 patients in whom data on the *kidney module* were available (see Methods), CKD and/or AKI were reported in prominent sections of the hospital discharge letter in 37 (7.8%) of all patients and in 32 (21.5%) of patients with impaired kidney function. While older age, length of hospital stay, diabetes and obesity lost their association in multivariable modeling, worse kidney function at hospital discharge (OR_{eGFR} 0.92 [95% CI 0.89; 0.94]) and more severe episodes of AKI (OR 93 [10; 848]) remained independently related to *physician's awareness of kidney disease*. Moreover, in patients in whom the index event was the primary diagnosis of CHD, it was less likely (OR 0.38 [0.14; 1.00]) that impaired kidney function was mentioned in the discharge letter (Table 2). In sensitivity analyses, these findings were similar when imputing the missing values (data not shown).

Of patients admitted to the University Hospital Würzburg ($n = 498$) that had CKD or experienced AKI during the index hospital stay ($n = 162$), relevant ICD codes were applied to 117 (72.2%) patients after discharge. Correct coding was particularly observed in those patients with more severe stages of AKI (100% in stage 2, 75% in stage 3) and CKD (76.9% in stage G3a, 95.2% in G3b, 100% in G4 and 100% in G5).

Table 1 Patient's characteristics during the EUROASPIRE IV index hospital stay by impaired kidney function

	Normal kidney function n = 362 (67.8%)	Impaired kidney function n = 172 (32.2%)	p-value
Age, years	64.0 (58.5; 70.4)	72.0 (65.7; 75.1)	<0.001
Male sex	301 (83.2%)	139 (80.8%)	0.51
Length of hospital stay (days)	3 (1; 7)	8 (3; 11)	<0.001
Details of CHD event during index hospital stay			
AMI, any	128 (35.5%)	75 (43.6%)	0.07
NSTEMI	53 (41.4%)	33 (44.0%)	0.26
STEMI	60 (46.9%)	28 (37.3%)	
Unclear/missing	15 (11.7%)	14 (18.7%)	
Therapy (max.)			<0.001
Conservative (no intervention)	54 (14.9%)	29 (16.9%)	
PCI/stent	279 (77.1%)	88 (51.2%)	
CABG	29 (8.0%)	55 (32.0%)	
CHD history			
Index event as the primary diagnosis of CHD	162 (44.8%)	64 (37.2%)	0.10
In those with h/o CHD			
Duration of CHD, yrs.	1.4 (0.4; 9.0)	5.9 (0.6; 16.3)	<0.01
CABG (prior to index)	35 (17.5%)	21 (19.4%)	0.67
PCI/stent (prior to index)	101 (50.5%)	55 (50.9%)	0.94
MI (prior to index)	125 (62.5%)	65 (60.2%)	0.69
History of heart failure[a]	117 (32.7%)	82 (48.0%)	<0.001
Classic cardiovascular risk factors			
Diabetes[b]	98 (27.2%)	51 (30.2%)	0.47
Hypertension[b]	299 (84.2%)	142 (86.6%)	0.48
Hyperlipidemia[b]	237 (67.1%)	112 (70.0%)	0.52
Smoking[b]	76 (22.8%)	28 (18.9%)	0.33
Obesity[c]	145 (41.1%)	75 (47.5%)	0.18
Kidney function			
SCr at admission[d], mg/dl	0.9 (0.8; 1.0)	1.2 (0.9; 1.3)	<0.001
eGFR at admission, ml/min/1.73m^2	86.3 (74.9; 96.3)	59.2 (51.3; 80.5)	<0.001
SCr at discharge[e], mg/dl	0.9 (0.8; 1.0)	1.2 (1.0; 1.4)	<0.001
eGFR at discharge, ml/min/1.73m^2	85.2 (74.6; 93.8)	57.5 (49.0; 73.8)	<0.001

Data are n (%), median (inter quartile range), analyses restricted to patients without missing values in respective variables
Abbreviations: CHD coronary heart disease, *CABG* coronary artery bypass grafting, *PCI* percutaneous coronary intervention, *MI* myocardial infarction, *AMI* acute myocardial infarction, *STEMI* ST-elevation myocardial infarction, *NSTEMI* non-ST-elevation myocardial infarction, *SCr* serum creatinine, *eGFR* estimated glomerular filtration rate
[a]Known at hospital admission or echocardiographic findings of cardiac dysfunction
[b]Known at hospital admission or stated in discharge letter
[c]Body mass index ≥30 kg/m^2 at hospital admission or stated in discharge letter
[d]First measurement in patient record
[e]Last measurement in patient record

Prevalence of chronic kidney disease at the study visit

The study visit was performed on average 1.8 years (1.1; 2.5) after the index hospital stay. At the study visit, 530 of the 536 German patients had SCr values available, with a median of 1.0 (0.9; 1.2) mg/dl reflecting an eGFR of 74.1 (60.0; 85.3) ml/min/1.73 m^2. ACR was measured in 526 subjects (98.1%), with a median of 4.9 (1.3; 15.8) mg/g. One patient was on chronic hemodialysis treatment (started already prior to the index-hospital stay). According to KDIGO classification of CKD (Fig. 1), 127 (24.4%) individuals had eGFR <60 ml/min/1.73m^2 and another 48 subjects (9.2%) had largely preserved eGFR but significant albuminuria (i.e. stages G1A3, G2A2, G2A3). Patients with CKD were more likely to be older, with a longer duration of CHD and a history of CABG, heart failure and peripheral artery disease

Table 2 Determinants of physician's awareness of kidney disease[a] at the EUROASPIRE IV index hospital stay (logistic regression)

	Univariable		Multivariable[b]	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Patient's age (index) [per year]	1.06 (1.01; 1.11)	<0.01	0.98 (0.92;1.04)	0.56
Patient's sex [male vs. female]	1.10 (0.44; 2.72)	0.84	–	–
Length of hospital stay [log(d)]	1.58 (1.15; 2.18)	<0.01	1.25 (0.83; 1.89)	0.29
Therapy (max.) [vs. no intervention)]		0.10	–	–
PCI/stent vs. conservative				
CABG vs. conservative	0.49 (0.21; 1.12)			
	1.07 (0.39; 2.96)			
AMI during hospital stay	1.49 (0.76; 2.94)	0.24	–	–
Index hospital stay as primary CHD event [yes vs. no]	0.32 (0.14; 0.75)	<0.01	0.38 (0.14; 1.00)	0.05
History of CHF[c]	1.12 (0.56; 2.21)	0.76	–	–
Cardiovascular risk factors				
Diabetes[d] (index)	2.57 (1.30; 5.07)	<0.01	1.85 (0.77; 4.44)	0.17
Hypertension[d] (index)	2.12 (0.63; 7.09)	0.22	–	–
Hyperlipidemia[d] (index)	2.21 (0.95; 5.17)	0.07	–	–
Smoking (index)[d]	0.35 (0.10; 1.16)	0.08	–	–
Obesity[e] (index)	2.23 (1.11; 4.48)	0.02	1.34 (0.58; 3.11)	0.49
Kidney function				
eGFR at discharge [per ml/min/1.73m^2]	0.93 (0.91; 0.95)	<0.001	0.92 (0.89; 0.94)	<0.001
AKI-stages [vs.no AKI][f]		<0.001		<0.001
Stage 1 [vs. no AKI]	1.51 (0.59; 3.85)		0.38 (0.12; 1.22)	
Stage 2/3 [vs. no AKI]	54.7 (10.8; 277.7)		92.7 (10.1; 847.9)	

Data are odds ratio (OR) with respective 95% confidence interval (CI) and p-value
Abbreviations: CHD coronary heart disease, *CABG* coronary artery bypass grafting, *PCI* percutaneous coronary intervention, *eGFR* estimated glomerular filtration rate, *AKI* acute kidney injury, *CKD* chronic kidney disease
[a]CKD and or AKI explicitly mentioned (diagnoses, summary) in the discharge letter of the index hospital stay; analyses based on $n = 474$ patients in whom data on the *kidney module* were available (see Methods)
[b]Multivariable model of backward selection, included are variables with significant ($p < 0.05$) association in univariable analysis; p for exclusion 0.05; non-significant associations displayed italic with OR (95% CI) and *p*-value when variable left the model. Order of exclusion: (1) age; (2) obesity; (3) length of hospital stay; (4) diabetes
[c]Known at hospital admission or echocardiographic findings of cardiac dysfunction
[d]Known at hospital admission or stated in discharge letter
[e]Body mass index ≥30 kg/m^2 at hospital admission or stated in discharge letter
[f]SCr increase of ≥0.3 mg/dl within 48 h or SCr-increase of 1.5–1.99× baseline SCr within 7 days (stage 1), SCr-increase of 2.0–2.9× baseline SCr (stage 2) and SCr-increase ≥3.0× baseline or SCr >4 mg/dl or dialysis (stage 3)

(Table 3). Classic risk factors such as hypertension, diabetes, dyslipidemia and overweight/obesity were also more common in subjects with impaired kidney function, whereas smoking was less prevalent in CKD patients. Primary care regarding CHD was reported to be provided by a cardiologist in 111 (60%) patients with CKD, which on average also had spent a shorter time in education. In those patients, impaired kidney function was reported more frequently in the discharge letter of the index hospital stay. The sensitivity analysis using the eGFR <50 ml/min/1.73m^2 cut-off identified 65 patients (12.3%). Again, the differences in patient characteristics between of those subjects with more advanced CKD as compared to those with normal kidney function were overall very similar (detailed data not shown) to the results derived from the results presented above (Table 3).

Patients' awareness of chronic kidney disease at the study visit

Data on patient awareness were part of the *kidney module* at the German study center and were thus available in $n = 474$ participants (see Methods). Of those 158 subjects with CKD, 54 (34.2%) patients reported that they had been told about chronic kidney disease, 23 (14.6%) were referred to a renal specialist and 21 (13.3%) had been seen by a specialist. Even in those without overt renal dysfunction at the study visit, 19 (5.5%) reported to be aware of impaired kidney function, 11 (3.2%) were referred and 12 (3.5%) were seen by a specialist. Overall, greater proportions of awareness, referral or specialist care were observed in more advanced stages of kidney disease (p for trend <0.01), however, based on a limited number of observations (Table 4). Accordingly, reduced

Table 3 Patient characteristics at the EUROASPIRE IV study visit by chronic kidney disease[a]

	normal kidney function $n = 345$ (65.1%)	chronic kidney disease $n = 185$ (34.9%)	*p*-value
Age, yrs	65.4 (59.6; 72.2)	73.4 (66.5; 77.0)	<0.001
Male gender	291 (84.4%)	145 (78.4%)	0.09
Total year in education, yrs	12 (11; 15)	11 (11; 14)	<0.001
Education level (higher vs. lower levels[b])	72 (20.9%)	27 (14.6%)	0.08
History of CHD			
Duration of CHD	2.7 (1.9; 6.4)	3.4 (2.0; 12.9)	<0.01
CHD history			
- CABG	77 (22.3%)	59 (31.9%)	0.02
- PCI/stent	278 (78.6%)	138 (74.6%)	0.12
- AMI	131 (38.0%)	49 (42.7%)	0.30
History of heart failure	40 (11.6%)	38 (20.7%)	<0.01
History of stroke	33 (9.8%)	22 (11.9%)	0.45
History of peripheral artery disease	18 (5.2%)	29 (15.7%)	<0.001
Classic CV risk factors			
BMI [kg/m^2]	28.0 (25.9; 30.7)	29.5 (27.0; 32.8)	<0.001
Overweight (BMI ≥25)	281 (82.2%)	168 (91.3%)	<0.01
Obesity (BMI ≥30)	105 (30.7%)	86 (46.7%)	<0.001
Blood pressure			
Systolic	133 (122; 148)	138 (128; 152)	<0.01
Diastolic	80 (73; 87)	81 (73; 88)	0.67
Hypertension[c]	142 (41.2%)	96 (52.2%)	0.02
LDL-cholesterol (mmol/l)	2.59 (2.16; 3.14)	2.43 (1.98; 2.98)	0.02
Hyperlipidemia			
LDL cholesterol ≥2.5 mmol/l	188 (56.1%)	77 (45.6%)	0.03
LDL cholesterol ≥1.8 mmol/l	307 (91.6%)	143 (84.6%)	0.02
Diabetes[d]	70 (20.5%)	75 (41.4%)	<0.001
Smoking[e]	49 (14.2%)	14 (7.6%)	0.02
Chronic kidney disease			
$SCr_{study\text{-}visit}$ (mg/dl)	1.0 (0.8; 1.0)	1.2 (1.1; 1.4)	<0.001
$eGFR_{CKD\text{-}EPI}$ (ml/min/1.73m^2)	81.0 (71.2; 90.4)	53.9 (46.6; 62.6)	<0.001
$ACR_{study\text{-}visit}$ (mg/g)	2.9 (0; 7.4)	20.4 (5.0; 78.5)	<0.001
Information on impaired kidney function in a discharge letter of a hospital stay due to CHD[f]	6 (1.9%)	31 (19.0%)	<0.001

Data are n(%), median (inter quartile range), analyses restricted to patients without missing values in respective variables
Abbreviations: CHD coronary heart disease, *CABG* coronary artery bypass grafting, *PCI* percutaneous coronary intervention, *AMI* acute myocardial infarction, *BMI* body mass index, *LDL* low density lipoprotein, *SCr* serum creatinine, *eGFR* estimated glomerular filtration rate, *ACR* urinary albumin/creatinine ratio
[a]CKD (stages CKD-G3 and higher, G2A2, G2A3, G1A3) vs. normal kidney function (G1A1, G1A2, G2A1)
[b]Higher (intermediate between secondary level and university [e.g. technical training], College/University completed, post graduate degree) vs. lower levels of education
[c]As recommended by the German Society of Cardiology as blood pressure ≥ 140/90 mmHg, ≥140/80 mmHg in patients with diabetes, ≥140/85 mmHg in diabetes, ≥150/90 mmHg in patients >80 years, ≥130/90 mmHg in patients with CKD
[d]Self-reported diabetes or impaired fasting glucose/impaired glucose tolerance
[e]Self-reported or CO >10 ppm
[f]EUROASPIRE IV index hospital stay

kidney function (OR_{eGFR} 0.94 [0.92; 0.96]) was also related to an increased level of *patient's awareness of CKD* in multivariable logistic regression, aside from a history of heart failure (OR 1.99 [1.00; 3.97]), obesity (OR 1.97 [1.07; 3.64]), and the fact that renal impairment was reported in the index discharge letter (OR 5.51 [2.35; 12.9]) (Table 5). Similar results emerged from analyses of the imputed dataset.

Table 4 Patient's awareness of CKD at the EUROASPIRE IV study visit and specialist care by stages of CKD

	CKD G stages at EUROASPIRE IV study visit[a]							
	G1		G2		G3a (*n* = 83)	G3b (*n* = 18)	G4 (*n* = 7)	G5 (*n* = 1)
	All patients (*n* = 84)	Patients with impaired kidney function[b] (*n* = 1)	All patients (*n* = 275)	Patients with impaired kidney function[b] (*n* = 47)				
Ever been told by a doctor about impaired kidney function	2 (2.4%)	0	24 (8.7%)	7 (14.9%)	33 (39.8%)	7 (38.9%)	6 (85.7%)	1 (100%)
Recommendation to seek professional advice/referred to kidney specialist[c]	1 (1.2%)	0	12 (4.4%)	2 (4.3%)	11 (13.3%)	5 (27.8%)	4 (57.1%)	1 (100%)
Seen by a kidney specialist[c]	1 (1.2%)	0	13 (4.7%)	2 (4.3%)	9 (10.8%)	4 (22.2%)	5 (71.4%)	1 (100%)

Data are n (% proportions within each category) based on a total of *n* = 474 patients in whom data on the kidney module were available (see Methods).
P-value for comparison across all categories
Abbreviations: CKD chronic kidney disease
[a]CKD G stages according to KDIGO based on $eGFR_{CKD\text{-}EPI}$; G1 eGFR ≥90 ml/min/1.73m^2; G2 60–89, G3a 45–59, G3b 30–44; G4 15–29, G5 < 15 or renal replacement therapy
[b]Definition based on $eGFR_{CKD\text{-}EPI}$ and urinary albumin/creatinine (ACR) ratio; KDIGO-stages G1A1, G1A2 and G2A1 considered as normal kidney function, whereas G1A3, G2A2, G2A3 and more severe G-stages are considered as chronic kidney disease (CKD) (see Methods)
[c]Specialist care, e.g. by nephrology, urology

Discussion

In our population of German CHD patients enrolled in EUROASPIRE IV, about one third of patients in considerably stable conditions at the study visit had CKD, but only a third of those reported that they had been told about renal impairment. A substantial proportion of patients experienced AKI (18%) during a hospital stay for CHD and/or was discharged with compromised kidney function (18%). Yet, the discharge letter of these patients prominently mentioned chronic or acute kidney disease only in 20%. In contrast, correct ICD coding of CKD or AKI, which is relevant for reimbursement, was more complete but still suboptimal.

Awareness of CKD among CHD patients with kidney disease

Although CKD is common and associated with worse prognosis, only a small proportion of patients (<5–30%) are aware of their disease in population-based studies [14, 27], CKD cohorts [15, 28] and in CHD patients [21]. Despite public education programs e.g. in the US or the UK, only little improvement in CKD awareness could be observed [17, 29]. Early diagnosis is needed to inform patients about their disease and initiate appropriate treatment [30]. Patient education should be expected to improve adherence to medication and treatment targets [16, 31], but data in CKD are conflicting. Patients on renal replacement therapy (RRT) with adequate knowledge about their disease and treatment targets including dietary restrictions have a lower mortality risk when compared to less educated patients [32]. In contrast, in earlier stages of CKD, achievement of treatment targets for adequate blood pressure control was not significantly associated with the level of patient's awareness of CKD [17]. Yet, recent data are encouraging that focused education of the primary care physician (PCP) and the patient including his relatives can indeed improve risk factor control and also slow the progression rate of CKD [33]. As directly from the patent's perspective, it seems intuitive that one feels more confident if he is aware of a certain condition and is informed and educated accordingly about the treatment options. On the other hand, he might also be frightened by the information on the diagnosis and the disease's prognosis [31], which may aggravate depressive mood, since depression is a common comorbidity in CHD [34] as well as in CKD [35]. Specialist care, e.g. provided by a nephrologist, may help to adequately inform patients about their individual risk for CKD progression [13], and thus help individualizing the therapeutic strategy and treatment targets. It has been shown that (early) referral to nephrology care can slow CKD progression and is associated with reduced mortality risk once RRT is initiated [36, 37].

In our sample of stable CHD patients, we found 24% with CKD (i.e., applying the commonly used cut-off of eGFR <60 ml/min/1.73m^2), which is nearly 10-times higher than in recent numbers of the German general population [38]. Another 10% of our sample had albuminuria with preserved eGFR representing those at risk for CKD progression [24, 39]. Of those with CKD, only about a third were aware of their disease and only a minority was being seen by nephrologists, however, with higher likelihood of CKD awareness and specialist care in more severe stages of CKD. The latter observation, however, is based on very few data in the respective categories and need to be interpreted with caution. We could not find significant associations with CKD awareness with the level of education, gender, or diabetic status. Yet, a history of heart failure was related to a higher level of CKD awareness, independently of the severity of CKD. This might be explained by frequent appointments

Table 5 Determinants of patient's awareness of CKD[a] at the EUROASPIRE IV study visit (logistic regression)

	Univariable		Multivariable[b]	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age, [/yr]	1.05 (1.02; 1.08)	<0.01	*0.97 (0.93; 1.01)*	*0.18*
Male gender [vs. female]	0.59 (0.33; 1.07)	0.08	–	
Education				
Total years [/log(yr)]	0.65 (0.28; 1.50)	0.32	–	
Higher vs. lower levels[c]	0.57 (0.27; 1.20)	0.14	–	
Information on impaired kidney function in a discharge letter of a hospital stay due to CHD[d]	15.8 (7.45; 33.7)	<0.001	5.51 (2.35; 12.9)	<0.001
Primary care for CHD provided by cardiologist [vs. non-cardiologist]	0.88 (0.52; 1.48)	0.62	–	–
History of CHD				
CHD duration [/log(yr)]	1.30 (1.01; 1.66)	0.04	*0.89 (0.64; 1.23)*	*0.47*
CABG ever	1.52 (0.88; 2.63)	0.13	–	–
History of heart failure	2.43 (1.36; 4.34)	<0.01	1.99 (1.00; 3.97)	0.05
History of peripheral artery disease	2.19 (1.07; 4.48)	0.03	*0.83 (0.31; 2.19)*	*0.71*
Diabetes[e]	1.23 (0.71; 2.13)	0.45	–	
Smoking[f]	0.81 (0.37; 1.78)	0.60	–	
Dyslipidemia[g]	1.37 (0.80; 2.34)	0.25	–	
Obesity[h]	1.93 (1.16; 3.21)	0.01	1.97 (1.07; 3.64)	0.03
$eGFR_{CKD\_EPI}$ at study visit [/ml/min/1.73m^2]	0.93 (0.91; 0.95)	<0.001	0.94 (0.92; 0.96)	<0.001
ACR at study visit [/ log(mg/g)]	1.09 (1.01; 1.17)	0.02	*0.99 (0.91; 1.08)*	*0.88*

Data are odds ratio (OR) with respective 95% confidence interval (CI) and p-value

Abbreviations: CHD coronary heart disease, *CABG* coronary artery bypass grafting, *PAD* peripheral artery disease, *eGFR* estimated glomerular filtration rate according to CKD-EPI formula, *AKI* acute kidney injury, *CKD* chronic kidney disease

[a]positive response to "Have you ever been told by a doctor/health care provider that your kidney function is impaired, e.g. not as good as it would be expected?"; analyses based on *n* = 474 patients in whom data on the *kidney module* were available (see Methods)

[b]Multivariable model of backward selection, included are variables with significant ($p < 0.05$) association in univariable analysis; p for exclusion 0.05; non-significant associations displayed italic with OR (95% CI) and *p*-value when variable left the model. Order of exclusion: (1) ACR; (2) history of PAD; (3) duration of CHD; (4) age

[c]Higher (intermediate between secondary level and university [e.g. technical training], College/University completed, post graduate degree) vs. lower levels of education

[d]EUROASPIRE IV index hospital stay

[e]Self-reported diabetes or impaired fasting glucose/impaired glucose tolerance

[f]Self-reported or CO >10 ppm

[g]LDL-cholesterol ≥2.5 mmol/L

[h]Body mass index ≥30 kg/m^2

specifically for heart failure and potentially also for cardio-renal syndrome [40] at the cardiologist and the PCP, with an increased likelihood of impaired kidney function being detected, mentioned and discussed during such appointments. Furthermore, we found that patients were more likely to know about impaired kidney function if either CKD or AKI was mentioned in a recent discharge letter. Both factors underline the relationship of patient information as being directly dependent on the physician's awareness, information and education [41].

Physician's awareness of kidney disease during a hospital-stay for CHD

Patients with kidney disease are also at a higher risk for complications in hospital stays for CHD and impaired prognosis after discharge [42, 43]. Causes for affected kidney function are multifactorial, including acutely reduced renal perfusion in myocardial infarction, nephrotoxic contrast application during catheter interventions, but also in elective CABG surgery [25]. These AKI episodes, which might be only temporary changes in kidney function of milder degree (e.g., a rise in SCr by 0.3 mg/dl in AKI stage 1 [25]) are associated with an increased risk for cardiovascular events, cardiac dysfunction, heart failure progression, and risk of hospitalization and death [44].

In general, markers of kidney function at hospital admission and during the early phase of a hospital stay are more likely to be influenced by AKI, whereas kidney function might be improved and stabilized at hospital discharge. While in the core protocol of EUROASPIRE IV only SCr values at hospital admission were collected, at the German study center, we used all SCr

measurements during the index hospital stay, thus enabling detailed analysis of the course of kidney function including AKI episodes. Of note, even if all methods were considered (e.g. urinary dip-stick, 24 h urine collection, ACR or total protein/creatinine ratio), in more than half of the patients no measure of proteinuria was available. Therefore, estimating the entire spectrum of kidney disease including proteinuria was impossible.

We found that during the index hospital stay, about 18% of patients experienced AKI, while most episodes were of stage 1, but more severe stages including those needing hemodialysis were observed. Only a very small number of patients had a rise of SCr of exactly 0.3 mg/dl that did not further increase in subsequent laboratory measurements. Also about 18% were found for impaired kidney function at hospital admission and at hospital discharge, respectively. Yet, one third of all patients was detected as having any impairment of kidney function either acute and/or chronic, respectively.

Since the introduction of equations based on SCr to estimating GFR, eGFR is increasingly displayed on routine laboratory reports with every SCr measurement [45], including the recruiting German EUROASPIRE IV centers. Therefore, information on kidney function is routinely visible to the treating physician. Moreover, the role of CKD and AKI as an important comorbid condition is widely discussed in the medical literature. The rationale for using mentioning of CKD or AKI in prominent parts of the hospital discharge letter as a proxy for *physician's awareness of impaired kidney function* was as follows: First, even slight changes in SCr need to be recognized by the physician as AKI, an important acute complication during the hospital stay. Second, either CKD or AKI reflect important risk factors for both CHD and CKD progression. Since the discharge letter represents the most important document of information transfer from the hospital to the ambulatory setting, the treating physician needs to judge kidney dysfunction as important enough to be clearly reported the discharge letter. In clinical routine in Germany, particularly the first part (diagnoses) and the end of the document (summary and medication) are predominantly being read by PCPs due to time constraints.

We found that the discharge letter reported only one fifth of patients with impaired kidney function (acute or chronic). While comorbid conditions, CHD history or the procedure itself were unrelated to *physician's awareness*, it was reassuring that higher stages of CKD or AKI increased chances for kidney dysfunction being reported in the discharge letter. Importantly, in patients in whom the index event was the primary diagnosis of CHD, impaired renal function was frequently not reported in the discharge letter. In particular in these patients, comprehensive description of traditional and non-traditional CV risk factors is needed for establishing an individualized treatment concept for optimal secondary CHD prevention [46]. The discharge letter not only addresses the PCP, but also constitutes an important source for information to the patient himself, supporting self-empowerment, self-management and self-monitoring. Since reporting CKD or AKI in the discharge letter relates to patients' awareness of CKD, raising the *physician's awareness of kidney disease* may ultimately lead to better informed patients.

Completeness of ICD-coding for kidney disease in patients with CHD

In 2003/2004, the German Diagnosis Related Group (G-DRG) system replaced the cost-based reimbursement of hospital stays employing ICD diagnoses, procedures, and comorbidities [11]. For each case, coding usually gets completed a few days after discharge, commonly with the help of expert coding assistants. As AKI and CKD increase the amount of reimbursement, adequate coding is highly relevant for the hospital. In our study, CKD and AKI were correctly coded for the majority of patients, in particular in those with advanced stages. However, there were still patients in whom adequate coding of renal function would have increased monetary benefits for the hospital.

Strengths and limitations

The unique setting of the EUROASPIRE IV study including the *kidney module* at the German study center allows a comprehensive view on CKD awareness among CHD patients and their treating physicians, however, limitations need to be mentioned. First, the study-sample cannot be claimed as representative neither for CHD patients in Germany nor for those admitted for CHD at the recruiting hospitals due to the selection process of centers and the recruitment success [20]. Second, CKD at the EUROASPIRE IV study visit was classified based on a single measurement of SCr and ACR, while usually two independent measurements for adequate assessment of CKD are desired [24]. However, study participants were in apparently stable condition at the time of recruitment. In contrast, as also discussed above, during the index hospital stay, kidney function at admission as well as at discharge might be influenced by acute clinical circumstances, e.g. acute kidney injury at admission or the (prolonged) convalescence of kidney function after AKI. Third, any SCr-based estimation of GFR has limitations, and mild to moderately impaired kidney function may be better described by equations based on Cystatin C [47], which unfortunately was not available. However, we chose the SCr-based CKD-EPI formula as it outperforms the MDRD formula in particular in GFR between 60 and 90 ml/min/1.73m^2 [48]. Fourth, the patient's knowledge of having been told

about CKD may by influenced by multiple factors, including the setting of a study visit, therefore recall bias may apply. In addition, particularly in older subjects, a slight deterioration of kidney function might be considered as normal, age-related decline in GFR. Fifth, the number of variables tested in logistic regression analyses may be considered as too high, thus finding and missing associations by chance and limited power is surely possible. Finally, the substantial discrepancy between correct ICD-coding and presence of impaired kidney function in the discharge letter might be explained the fact that the discharge letter is predominantly prepared by junior physicians and may not reflect awareness by the more senior physician involved in care decisions, whereas the coding is supported by professional coders who may detect comorbid conditions that may have not been in the primary focus of the patient's therapeutic care.

Conclusion

In patients with CHD, mild to moderate CKD is a common comorbidity, but only few patients are aware of their renal dysfunction. Furthermore, in only a limited number of patients, renal impairment is being reported in hospital discharge letters, whereas the majority of subjects appears correctly ICD-coded. Stringent reporting of CKD and AKI may improve information transfer to care givers in the outpatient setting. How this may further lead to better informed patients, higher attainment of treatment targets, and improved management of both CKD and CHD should be focus of future studies.

Abbreviations

ACR: Albumin / creatinine ratio; AKI: Acute kidney injury; AMI: Acute myocardial infarction; BMI: Body mass index; CABG: Coronary artery bypass grafting; CHD: Coronary heart disease; CHF: Congestive heart failure; CI: Confidence interval; CKD: Chronic kidney disease; CKD-EPI: Chronic kidney disease epidemiology collaboration; CVD: Cardiovascular disease; eGFR: Estimated glomerular filtration rate; ESC: European Society of Cardiology; HDL-C: High density lipoprotein cholesterol; IQR: Inter-quartile range; KDIGO: Kidney disease – improving global outcomes; LDL-C: low density lipoprotein cholesterol; OR: Odds ratio; PCI: Percutaneous coronary intervention; SCr: Serum creatinine; SD: Standard deviation

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Availability of data and materials

The datasets generated during and/or analysed during the current study are property of the European Society of Cardiology and are not publicly available.

Authors' contributions

All authors contributed to the conception of the study and MW, CW, MS, StS, PUH contributed to study design. MW, MS, KK, DW, GF, MO, StS, PUH contributed to data acquisition and MW, MS, KH, VR contributed to data analysis, and MW, MS, CW, KK, MO, StS, PUH contributed to data interpretation. MW, MS, CW, StS and PUH drafted and all other authors critically revised the manuscript and all authors gave final gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Ethics approval and consent to participate

All patients provided written informed consent to take part in the study. The study was approved by the ethics committee of the Medical Faculty, University of Würzburg (Vote 58/12) and by the data protection officer of the University of Würzburg and the University Hospital Würzburg (DS-117.605-15/12). (see above, Methods section).

Consent for publication

Not applicable.

Competing interests

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7. Discussion

In the current thesis project we addressed the role of CKD in patients with established CHD from various perspectives. First, we investigated the quality of care in the German sample of the EUROASPIRE IV with an emphasis of the differences between younger and older individuals, as the elderly represent a vulnerable patient population with several comorbid conditions, including CKD. Second, we analyzed the prevalence of CKD and its determinants among all 24 participating countries in the EUORASPIRE IV survey in stable conditions at the study visit, but also during a hospital stay due to CHD. Finally, data of the *kidney specific module* in the German sample allowed detailed insights into the level of CKD awareness among CHD patients and their treating physicians as well as the proportion of CHD patients referred to and seen by nephrologist physicians.

Our results show that a majority of German CHD patients was treated with the recommended basic drug therapy containing β-blockers, anti-platelets and statins. Treatment targets for blood pressure and LDL-cholesterol levels were not achieved in many patients and glycemic control in diabetic CHD patients with HbA1-levels below 7% was insufficient. A fairly small proportion of patients reported active smoking, but unhealthy life-style habits including overweight/obesity were frequent. Patterns of risk factor control differed between younger CHD patients and patients older than 70 yrs. Generally, older patients were less likely to receive the recommended medical CHD-therapy, to have inadequate blood pressure control, and were more likely to be diabetic. But a greater proportion of diabetic patients was achieving the HbA1c target, and less elder patients were current smokers or were obese.

Across all 24 participating countries in EUROASPIRE IV, we found that about 17% of patients with CHD had overt CKD with eGFR < 60 ml/min/1.73m² in stable condition at the EUROASPIRE IV study visit. In addition, 9% were at increased risk for CKD progression as indicated by significant albuminuria despite preserved eGFR. Age standardized prevalence rates of CKD varied considerably between different countries. Besides traditional CV risk factors, a longer CHD duration and a history of CHF were

independently associated with the risk of CKD. During the hospital stay for CHD (index) impaired kidney function, i.e. chronic and/or acute reduction of eGFR, was common and indeed observed in about every fifth admitted patient. Dependent on characteristics of the index CHD event there was a substantial potential for recovery, but also for further decline of kidney function after hospital discharge.

Analysis of data of the *kidney specific module* in the German EUROASPIRE IV subset, we found about a third of patients at the study visit that had CKD, but only a third of those reported that they had been told about renal impairment. A minority of these patients was being seen by nephrologists, however, with a higher likelihood of CKD awareness and specialist care in those with worse kidney function. During the index hospital stay for CHD, a substantial proportion of patients experienced AKI (18%) and/or was discharged with compromised kidney function (18%). Yet, the discharge letter of these patients prominently mentioned chronic or acute kidney disease only in every fifth of these patients. In contrast, correct ICD coding of CKD or AKI, which is relevant for reimbursement, was more complete but still suboptimal.

In the following sections we will highlight the findings of the current thesis project in the context of the published literature regarding (1) quality of care in secondary CHD prevention, including medical treatment, blood pressure, dyslipidemia, glucose metabolism and diabetes and also unhealthy life styles such as smoking and overweight/obesity, (2) variations of risk factor patterns, medical therapy and behavior in elderly patients with CHD, (3) the prevalence of CKD in CHD patients across Europe, in the clinical course at hospital admission for CHD events, in the ambulatory setting after hospital discharge and changes in kidney function in between, and finally (4) the level of CKD awareness of patients and their treating physicians, as indicated by either acute or chronic impairments in kidney function in the discharge letter but also by correct ICD-coding.

7.1. Quality of secondary CHD prevention in Germany

CHD represents a global burden as one of the major causes of mortality and is responsible for 15.6 million deaths worldwide[110]. Absolute numbers of death due to CHD as well as mortality rates are decreasing in Europe over the past 10 years, whereas a rise in hospital admissions can be observed[22, 111, 112]. Preventive care measures aim to improve the prognosis of patients with established heart disease, in terms of prolonged survival and reducing the risk of disease progression, vascular events and the development of ischemic congestive heart failure[2]. Furthermore, life-style modification and adequate risk factor control also reduce the risk of developing vascular disease in high risk populations[30, 113]. Patients are increasingly aware of the benefits of healthy lifestyle, and also are providers regarding treatment targets over the last decade[114-116], yet, translation of guideline recommendations in clinical practice is insufficient[7].

Medical treatment and blood pressure

We found that the vast majority of patients were treated with the recommended cardio-protective drug therapy, i.e. platelet-inhibitors, β-blockers and statins, which was very similar to the European average[16]. However, only about a third of patients in Germany as well as throughout Europe were below the blood pressure target of 130/80 mmHg applicable during the study recruitment (2012-2013). Recently, the definition of hypertension was modified and a raised blood pressure target of 140/90 mmHg in general was adapted by International and National Societies[67, 68], yet, exemptions for diabetic patients, elderly and patients with CKD apply. Even then, still 45% in the entire German EUROASPIRE IV sample were not treated adequately. In this matter, it will be interesting how the data of the recently published SPRINT trial will further influence international guideline recommendations; in non-diabetic patients with increased CV risk, a blood pressure target as low as 120 mmHg lead to reduced CV events and mortality, in the entire group as well as in the elderly[117]. As the first major medical society, the American Heart Association and the American College of Cardiology defined elevated blood pressure at

values >120/80 mmHg, stage 1 hypertension 130-139/80-90 mmHg and >140/90 mmHg as stage 2 hypertension, with the consequence that millions of Americans became hypertensive due to the new definition[118]. The decision of updating the cut-off for hypertension has caused major discussions throughout the world, mainly about the transfer of findings derived from optimally controlled settings of clinical trials to the "real world" of daily clinical practice, but also that different methods of blood pressure measurement result in sometimes dramatically different blood pressure values[119]. The latter was surely evident in the SPRINT trial, in which an automated office based blood pressure (AOBP) measurement device was used (5 min resting, followed by automated blood pressure measurements), that is rarely used in daily clinical practice[120]. It should be noted that the beneficial effect of intensive blood pressure lowering was also evident in patients with CKD[121], but side effects on kidney function, namely AKI and hyperkalemia, both leading to hospital admissions were also observed in the group with the lower blood pressure target[122]. These mechanisms on kidney function and hard clinical outcomes in CKD patients as well as in the general population need to be understood in further studies. Of note, the KDIGO group is currently working on updates of hypertension guidelines in nephrology, incorporating the results of the SPRINT trial.

Considering secondary prevention in CHD patients, the German EUROASPIRE data suggest a trend towards more CHD patients being treated on-target over the last decade[20]. However, only few valid data on the prevalence of uncontrolled hypertension in Germany have been published. Recent data from the DEGS survey suggest that about 80% of subjects in a nationwide representative sample of adults present with controlled blood pressure of <140/90 mmHg[123]. A similar proportion was observed in patients with self-reported stroke or CHD[123]. A European survey (including Germany) on general practitioners, internists and cardiologists also reported on comparable numbers between 50-60% of patients being treated within the recommended range[124]. A very recent article reported on a pooled analysis of seven German population based studies which suggested lower blood pressure levels in general and a fairly better control in hypertensive patients[125].

Why patients treated for hypertension might not be within the recommended blood pressure target may be caused by multiple reasons, including those in the responsibility of the physician and others mainly patient related. Since the blood pressure targets vary between societies and also between specialties and frequently various target ranges were defined for specific subgroups of patients even in one clinical practice guideline, physicians may be confused and not sure what target might be applicable to the patient[126]. The doctor may also opt that a specific recommended target does not apply to the individual patient, due to whatever reasons, including comorbid conditions[126], side-effects or potentially limited life-expectancy[126, 127]. Therefore, even if hypertensive medication has been prescribed, the drug combination or the individual drug's doses might not be enough to lower blood pressure under the recommended level, but this might be due to a specific decision process of the treating physician. On the other hand, in the setting that the therapy would indeed be sufficient for adequate blood pressure control, the prescribed medication needs to be regularly taken by the patient. The impact of adherence to medical therapy and patient's compliance on risk factor control is widely debated[128] and is certainly influenced by the fact that a raised blood pressure by itself does not directly hurt or makes anyone feel uncomfortable. In fact, taking the pills may lead to hypotension, including orthostatic dysregulation, dizziness and fatigue, which may lead to unreliable medication intake. Adherence to therapy is associated with patient's awareness of the long-term consequences of hypertension and is therefore dependent on adequate education also by the care-giver. However, socio-economic status, communication barriers and the patient's intrinsic motivation affect this interaction and are related to adherence to therapy[128]. The consequences of non-adherence on morbidity and mortality but also for the economy are well known in CVD, including hypertensive medication, antiplatelet-therapy and lipid-lowering drugs[129, 130].

Dyslipidemia

It is certainly a major improvement in CHD-care to treat dyslipidemia as it has been shown to reduce mortality in primary[131] and secondary CHD prevention[132]. The translation of the evidence in clinical practice is reflected by increasing numbers of patients being on lipid-lowering drugs over the last decade[7, 20] with now about 80-90% of patients across Europe being on statins[16]. The importance of tightly controlling LDL-levels was further highlighted by recommendations of the ESC to lower the LDL-C target to <70 mg/dl for all CHD patients in 2013[2]. Therefore, starting in 2012, EUROASPIRE IV was not able to address this updated recommendation. Although about 90% of patients in the German EUROASPIRE IV sample were treated with lipid lowering drugs, mainly statins (European average 86%), only 10% reached the tight target of LDL-C <70 mg/dl and 60% were below 100 mg/dl (European average 19%, and 59%, respectively). How national and international campaigns are effective to establish this strict target level in clinical practice, how it translates in improved outcomes, but also how safe these measures are, needs to be investigated in future studies. Herein it should be noted, that follow-up LDL-measurements and treating patients to a defined LDL-target has been questioned recently in clinical practice guidelines of the American College of Cardiology[133] and KDIGO[134], because of sparse evidence that this approach is associated with improved outcomes.

Glucose metabolism and diabetes

Disturbances in glucose metabolism and diabetes further increase the risk for CV-complications and progression of CHD[2] and should thus be detected early-on and treated consequently. In the German sample of EUROASPIRE IV, 25% reported on diabetes (European average: 27%), an estimate that is as high as never before in German CHD patients enrolled in previous phases of EUROASPIRE[20]. It is known that the prevalence of diabetes is growing in the developed (and developing) world, simultaneously to the rise in obesity rates[135, 136]. In Germany, increasing rates may slow in recent years in the general population, with a fairly stable prevalence of about 9%[137]. Glycemic control in diabetic patients with CHD

is a key component of secondary prevention and HbA1c-levels of <7% are generally recommended[2, 4]. We found that only 60% of diabetic CHD patients were within the target range, which is slightly better than the European average of 52%.

Unhealthy life-styles

The secular trend in Europe regarding unhealthy lifestyle in general, obesity, and smoking, in particular among younger patients, was also observed in the current EUROASPIRE IV survey, however, with a wide variation of smoking and obesity patterns between participating countries[16]. It was remarkable, that even across very different European communities in EUROASPIRE IV the vast majority of 82% of CHD patients was classified as being overweight, while 37% were obese[16]. In Germany, 85% were overweight and 37% were obese, with higher rates in younger patients, which is overall comparable to the trend described for EUROASPIRE I-III[20]. The German result of about 10% smokers is lower as compared to the European average of 16%[16]. The number is also promising as it is also lower than in the previous surveys (16-18%), but still about 17% of younger CHD patients were current smokers[20]. Our findings support the observed national trend towards slight smoking cessation in the German general population[138].

A detailed analysis by Kotseva et al. found in the entire EUROASPIRE IV study that the benefits of improvements of medical therapy in CHD patients over the last decade were somewhat antagonized by inadequate life-style, in particular persistent smoking, insufficient physical activity and increasing rates of overweight and obesity[9].

7.2. Variations of CHD care among the elderly

Guideline recommendations for secondary CHD prevention also apply to patients of older age, although the evidence is less robust as compared to younger individuals[2, 139, 140]. However, achievement

of certain goals in the elderly may be limited due to conflicting recommendations of various specialties because these patients frequently present with not only one, but multiple conditions[35, 141].

Regarding the primarily recommended drug classes for secondary CHD prevention, we found that patients older than 70 years were less likely to receive β-blocker and also anti-platelet-therapy. No differences were observed for the proportion of patients being on lipid lowering drugs and statins. It is well known that prescription patterns and adherence to guideline recommendations vary in older patients[142]. These frequently multi-morbid patients present with multiple medications ("polypharmacy"), and medical therapy and adherence might be limited by contraindications and also side effects[143, 144]. However, adequate CHD-specific pharmacotherapy has been shown to be associated with improved outcomes in older CHD patients and should thus be prescribed in elderly patients also[34, 145-147]. The dilemma of medical need and potential side effects might restrain physicians to prescribe medication as recommended by guidelines. Their efforts, however, may be countered by cognitive impairment which is highly prevalent in the elderly, particularly in subjects with CVD[148] and affects adherence to medication and prescribed therapy.

As mentioned, higher blood pressure values are acceptable for the elderly (150/90 mmHg) to acknowledge comorbid conditions and the risk of hypotension, dizziness and falls[67]. Yet, even when these adjusted blood pressure targets were applied, about half of the patients were hypertensive. The fact that older patients were less likely to achieve the recommended blood pressure target was in line with the current European average[16] and also with the trend on previous data from German EUROASPIRE studies[20].

In contrast, we did not find any differences between younger and older individuals in accomplishing LDL-C treatment goals which and suggests improved lipid lowering treatment in the elderly as compared to previous data[20]. In our analyses we could also support the evidence that older patients are less likely to be obese and also less likely to be current smokers as compared to younger individuals[149]. These

observations suggest that older patients despite an accumulation of multiple CV risk factors, may present with improved behavior and an overall "healthier" life-style. It could also be the consequence of more intense therapeutic support which is also underpinned by the fact that older patients with diabetes were more likely to have HbA1c levels <7.0%. *Vice versa* younger patients were less likely to be adequately treated for dysglycemia, which is of particular interest, as the benefits of tight glycemic control outweigh the harms (e.g. hypoglycemic episodes) in younger patients. Of note, less strict treatment targets have been discussed for the elderly (i.e. HbA1c >7.5% or >8.0%)[4, 150] to reflect multimorbidity and the risk of adverse events[151, 152].

In these matters it should be noted that generally older patients are less physically active as compared to younger individuals, potentially because of frailty, dizziness due to hypotension, hypoglycemia, arthritis and the fear of falls[149]. But on the other hand it has been shown that even limited but regular physical activity can reduce the risk for CV events even in the elderly[153]. We did not study the level of physical activity in the current thesis project in detail as it is subject of a different thesis project of our group.

Although the evidence for effective secondary CV prevention is mainly based on studies that were performed in "younger" individuals, the vast majority of findings is also applicable to the elderly although this group presents with specific characteristics such as frailty, impaired cognition, multi-morbidity and a variety of drug-interactions. It may take some time to educate physicians that the large group of older CHD patients does also benefit from the recommended therapy.

7.3. Chronic kidney disease in CHD patients

In the high-risk population of CHD patients, individuals frequently have a variety of traditional CV risk factors, but may also present with other factors that have been shown to be relevant for prognosis.

These non-traditional factors may be independently related to and even causal for an increased risk for CHD, e.g. Lp(a)[154], or a consequence of chronic inflammation caused by atherosclerosis and CHD, e.g. anemia[155]. CKD is common in CHD and both share identical pathology, such as atherosclerosis, similar traditional CV risk factors and both influence the prognosis of each other[38]. That is, patients with CKD are at high risk for the development and progression of CHD[38, 156], and also CKD impacts on a worse clinical course and CV events in CHD patients[40, 42, 157, 158].

Prevalence of CKD in stable CHD conditions at the EUROASPIRE IV study visit

Data on the prevalence of overt CKD, usually defined as CKD-G stage 3a and higher (i.e. eGFR <60 ml/min/1.73m²)[37], in CHD patients is limited [64, 65, 159]. Rigorous and standardized assessment of renal parameters in CHD patients visit across a broad variety of European countries is a major strength of the current EUROASPIRE IV study. The overall prevalence of CKD (i.e. eGFR <60 ml/min/1.73m²) in the ambulatory, thus considerably stable setting, was 17%, with a wide variation from 13% to 26% between participating countries. These differences might be explained by variations in the study population due to a wide spectrum of recruitment success and potentially also selection bias of enrolled patients[16]; but these numbers may also reflect true variations in prevalence rates[44, 50]. Furthermore, we found about 10% of patients that presented with largely preserved eGFR but with significant albuminuria. As mentioned previously, these patients are at high risk for the development of overt CKD and its progression[37, 160, 161]. As ACR, or any other measure to determine albuminuria/proteinuria is rarely measured in clinical routine, this particular group is frequently underdiagnosed. In the EUROASPIRE IV study, SCr and ACR data at the study visit were very complete, thus, enabling a comprehensive evaluation of kidney function. Unfortunately, however, it was impossible to address the risk for progression of CKD and CHD in relation to CKD, both with impaired eGFR and preserved eGFR and with or without albuminuria/proteinuria, due to the lack of a second study visit.

The results of the multivariable analyses indicated that patients with CKD were more likely to be of older age, to be obese and to have diabetes, thus supporting the evidence that CKD frequently represents a population in which a multitude of classic CV risk factors accumulate. It was however unexpected that female gender was strongly and independently associated with CKD, a finding that certainly needs to be confirmed in further studies. It is possible that female CHD patients in the German EUROASPIRE IV sample were underrepresented (18% women, 82% men), which is a commonly observed phenomenon in CHD research[162]. This might on one hand be explained by a higher prevalence of CHD and a greater risk of CV events in men[2], but on the other hand gender specific differences in multiple pathways may be involved, which are not fully understood to date: These may include sex specific pattern of atherosclerosis and vascular dysfunction, CV risk and psychosocial factors, symptoms of CV events affecting accurate and timely diagnosis and also treatment success and outcomes of acute coronary syndromes[162]. Therefore, the recruited female individuals may not be representative for all female CHD patients that were eligible to participate in EUROASPIRE IV. Recruited women may also not reflect a similar risk profile as in male patients, i.e. potentially only relatively more female patients (as compared to male subjects) with a considerably sicker health status agreed to be studied in EUROASPIRE IV, whereas healthier female patients opted to not participate. Analyses of factors that were related to study participation were limited due to data protection laws.

CKD was also more common in patients with a history of CABG, which on one hand indicates a longer and more severe course of CHD. Cardiac surgery on the other hand may be considered as to be causal of CKD because of potential episodes of acute kidney injury (AKI) during cardiopulmonary bypass[55, 59]. Finally, CKD was also related to symptomatic CHF which can reflect a two-way relationship that has been described as “cardio-renal syndrome”: while cardiac dysfunction causes impaired kidney function e.g. via reduced renal perfusion and several pathways including hormone activation, *vice versa* CKD itself can further aggravate CHD in particular in established heart failure[163-165].

Impaired kidney function in a hospital stay due to CHD

Impaired kidney function itself, but also CKD as an indicator of multi-morbid patients is a strong risk factor for complications during and worse outcome after hospital stays of various causes, including CHD[40, 51, 52, 54, 55]. Herein, patients with CKD are at increased risk for the development of AKI after CABG surgery, AMI and after coronary interventions [57-59].

In EUROASPIRE IV, data on the first SCr measurement in the patient record of the index-event was collected. Kidney function at hospital admission may be prone to variation due to acute clinical events: in particular, patients with acute coronary syndrome and MI may present with symptoms of acute heart failure (e.g. low cardiac output), which may result in episodes of AKI. Also CABG and contrast application during PCI can cause impairments in kidney function. In our analyses on the entire EUROASPIRE IV dataset, about every fifth EUROASPIRE IV patient had impaired kidney function at hospital admission for the index CHD event. We found major variations between countries, with low numbers of less than 10% in Finland and more than 30% in the UK. This might be caused by varying recruitment strategies and success among countries[16]. But it would also be of great interest and importance to investigate whether these differences reflect true variations at the patient level across European countries or if hospital admission and transfer strategies between different health care systems or variations in CHD treatment and care are responsible for the dramatic prevalence differences.

Similar to the findings at the study visit, independent determinants of impaired kidney function during the hospital stay for the index CHD event comprised older age, female gender and traditional CV risk factors such as diabetes and hypertension. Furthermore, a history of CABG and/or acute MI and of CHF before the index hospital stay were related to impaired kidney function, which overall reflect a more severe course of CHD and the specific relationship of the "cardio-renal-syndrome"[163]. Apart from female gender, which needs further investigation (see above) these determinants describe CHD patients with CKD as individuals with a multitude of comorbidities.

Changes of kidney function after a hospital stay due to CHD

There are only few data available on the course of CKD in the ambulatory setting after a hospital stay due to CHD[55, 62, 166, 167]. The prognosis naturally depends on the kidney function in stable condition prior to the index CHD event, the details of the event itself, including urgency and therapy applied. In situations of "true" CKD, already present prior to the hospital stay, it is unlikely that major improvements in kidney function can be achieved after a hospital stay for CHD. The aim of care must then focus on reducing the decline in kidney function by RAAS blockade, avoidance of nephrotoxic agents and strict control of classic CV risk factors[37]. In contrast, those CHD patients without major pre-existing CKD but with an episode of AKI during the hospital stay, either caused by cardiac dysfunction in AMI, by contrast application in PCI, or after cardiopulmonary bypass during CABG, have a great potential for improvements or complete recovery of kidney function. However, even those patients with markers of kidney function in the normal range after AKI remain at risk for the development of CKD, whereas other patients are at risk for non-recovery of AKI and either experience rapid decline in kidney function or remain dependent on renal replacement therapy[60].

As mentioned previously, in EUROASPIRE IV only data on SCr at hospital admission were available. Neither data on AKI during the hospital stay nor details on kidney function at hospital discharge were collected. At discharge, kidney function is thought to be in more stable condition as compared to admission. Renal function may still be affected by AKI, but most patients should be in improved health status and acute renal and cardiac impairments are likely to be resolved. Furthermore, as verified by the present survey, ACR is rarely measured in clinical routine and practically no data on albuminuria/proteinuria were collected to assess the entire risk spectrum and the clinical course of kidney function during and after the index hospital stay.

In all European CHD patients of EUROASPIRE IV, we found that patients with better kidney function at hospital admission were more likely to present with improved kidney function at the study visit, also

female patients and those with longer duration between the index event and the study visit. Those patients in whom the index event was classified as non-elective had a greater chance of recovery of kidney function as compared to those with elective procedures. This might be explained by the fact that CKD patients undergo elective procedures mostly in stable conditions and thus there might be no reason for meaningful improvements of kidney function thereafter as mentioned. Yet, older patients and those with CHF also recovered kidney function, which may seem counterintuitive on first sight. This may, however, be an expression for a higher awareness and more intense physician care after hospital discharge.

7.4. Awareness of CKD in CHD patients and their treating physicians

The data of the *kidney specific module* that we collected for the German EUROASPIRE IV subset allowed a comprehensive view on kidney function and the level of awareness among these CHD patients. We found a slightly higher prevalence of CKD (24% with eGFR <60 ml/min/1.73m² and further 10% with preserved eGFR but significant albuminuria), as compared to the average in the entire EUROASPIRE IV sample. Yet, the number of CKD in the German CHD sample of EUROASPIRE IV is about ten times higher when compared to most recent DEGS data from the German general population[48], which indicates that CHD patients in general are at high risk for CKD, but also describe CHD patients as a population with a multitude of comorbid conditions, and thus at increased risk for worse outcome, including CHD progression and mortality. Consequently, particularly CHD patients should be screened for impaired kidney function and if evident, then patients should also be referred to nephrology care.

Awareness of CKD and specialist care among CHD patients with kidney disease

Of those German EUROASPIRE IV patients with CKD, only about a third reported that they had ever been told by a physician regarding impaired kidney function. It was reassuring that those patients with

more severe stages of CKD were more likely to be aware of renal impairment. But still a substantial proportion was not aware, although eGFR was as low as <30 ml/min/1.73m². These data, however, need further confirmation, since our findings are based on a very limited sample size. We could not find significant associations of CKD awareness with the level of education, gender, or diabetic status. Yet, a history of heart failure was related to a higher level of CKD awareness, independently of the severity of CKD. This might be explained by frequent appointments specifically for heart failure and potentially also for cardio-renal syndrome[164] at the cardiologist and the PCP, with an increased likelihood of impaired kidney function being detected, mentioned and discussed during such appointments. We also found that patients were more likely to know about impaired kidney function if any renal impairment was mentioned in a recent hospital discharge letter. On one hand this observation reflects information transfer from the hospital to the PCP, the primary addressee of the discharge letter, which then can be discussed with the patient. But it also suggests that patients themselves may read these documents and reflect the contents and the discharge letter represents thus an important source for information to the patient himself, supporting self-empowerment, self-management and self-monitoring. Anyhow, our results underline the relationship of patient information as being directly dependent on the physician's awareness, information and education[96].

Of the CHD patients with kidney disease, only very few more than every tenth patient was seen by a renal specialist, while patients with more severe stages of CKD were more likely to being cared of by a nephrologist. But still more than a third was not referred to or being treated by a specialist, although eGFR was <30 ml/min/1.73m². Again, these dramatic numbers are based on limited sample size and need to be confirmed. In the setting of advanced CKD, it is of major importance to enhance the interaction of PCP, cardiologists, and nephrologists to monitor kidney function and to adequately adjust medical therapy and diet[37]. Furthermore, to assess the patient's individual risk for CKD progression[69], and thus help individualizing the therapeutic strategy including management of the choice of renal replacement therapy (hemodialysis, peritoneal dialysis), planning and placing dialysis access, and

(preemptive, living-donor) kidney transplantation. Based on multiple reports, (early) referral to nephrology care can slow CKD progression and is associated with reduced mortality risk once RRT is initiated[71, 73].

Physician's awareness of CKD during a hospital-stay for CHD

Analysis of all SCr values that were measured during the index hospital stay allowed a more detailed view on the course of kidney function in the German EUROASPIRE IV patients. Unfortunately, ACR or any other measure of albuminuria or proteinuria (e.g. urinary dip-stick, 24-hour urine collection, or total protein/creatinine ratio), was missing in too many patients, thus prohibiting further analysis. We found that about two out of ten patients had either impaired kidney function, i.e. eGFR <60 ml/min/1.73m² at hospital admission, which is likely to be affected by acute renal dysfunction as discussed above, or at discharge, which is more likely to reflect more stable condition. However, another 18% of patients experienced any AKI episode, which were mostly only slight increments of SCr (AKI stage 1), but more severe stages including those needing hemodialysis treatment were observed. Altogether, one third of all patients experienced any impairment of kidney function, either AKI or impaired kidney function at admission or at hospital discharge.

We used the fact that CKD or AKI was mentioned in prominent parts of the hospital discharge letter as a proxy for physician's awareness of impaired kidney function because of various reasons. Since the introduction of equations based on SCr to estimating GFR, eGFR is increasingly displayed on routine laboratory reports with every SCr measurement[99], including the recruiting German EUROASPIRE IV centers. Therefore, information on kidney function is routinely visible to the treating physician. Moreover, the role of CKD and AKI as an important comorbid condition that impacts on complications during hospital stays and impaired prognosis after discharge[51, 54, 168] is widely discussed in the medical literature. Therefore, even slight changes in SCr, i.e. AKI stage 1[60] need to be recognized by the physician as AKI, and interpreted as an important complication. Subsequently, since the discharge letter represents

the most important document of information transfer from the hospital to the ambulatory setting, the treating physician needs to judge kidney dysfunction as important enough to be clearly reported the discharge letter. In clinical routine in Germany, particularly the first part (diagnoses) and the end of the document (summary and medication) are predominantly being read by PCPs due to time constraints.

We found that of those patients that presented with any kind of kidney dysfunction during the index hospital stay, either acute or chronic, in only one fifth CKD or AKI was mentioned in the hospital discharge letter, which we interpreted as a limited level of physician's awareness of impaired kidney function. Other patient related comorbid conditions such as CHD history, or the procedure for the CHD event itself were unrelated to physician's awareness. It was reassuring that higher stages of CKD or AKI increased the chance for kidney dysfunction being reported in the discharge letter. Importantly, in patients in whom the index event was the primary diagnosis of CHD, impaired renal function was frequently not reported in the discharge letter. In particular in these patients, comprehensive description of traditional and non-traditional CV risk factors is needed for establishing an individualized treatment concept for optimal secondary CHD prevention[2]

Completeness of ICD-coding for kidney disease in patients with CHD

In 2003/2004, the German Diagnosis Related Group (G-DRG) system replaced the cost-based reimbursement of hospital stays employing ICD diagnoses, procedures, and comorbidities[63]. For each case, coding usually gets completed a few days after discharge, commonly with the help of expert coding assistants. As AKI and CKD increase the amount of reimbursement, adequate coding is highly relevant for the hospital. In our study, CKD and AKI were correctly coded for the majority of patients, in particular in those with advanced stages. However, there were still patients in whom adequate coding of renal function would have increased monetary benefits for the hospital.

The discrepancy between the observations that CKD or AKI was mentioned in the discharge letter of very few patients with kidney disease during the index hospital stay, whereas the majority of these patients are correctly coded, is striking and to the best of our knowledge, has never been reported in the German setting before. A possible explanation is that in the overwhelming clinical duties of doctors in daily clinical routine, including organizing a high number of new admissions and discharges from the ward, mild stages of CKD and AKI might frequently not be recognized and judged as important events and comorbidities. A few days after discharge, in a considerably protected atmosphere of the coding-rounds, the expert assistants may point the physicians to elevated levels of SCr which then may or may not get approved as correct diagnoses for CKD or AKI by the physicians. It is in the direct financial interest of the hospital that these relevant diagnosis that impact on the DRG of each case are coded as completely and correctly as possible, since it results in the amount of reimbursement for each case.

7.5. Strengths and Limitations

The EUROASPIRE IV study is a unique source to describe the quality of CHD care in considerably stable conditions in the ambulatory setting (study visit) as well as during a hospital stay for CHD (index hospital stay). The dataset allows comparison across all participating European countries due to prospectively collected data and standardized measurements at the study visit, as well as identical procedures for retrospective data collection of the patient's hospital record. Variation of blood levels (e.g. cholesterol, HbA1c, SCr) dependent on collection, handling and measurement of biomaterials is markedly reduced by standardized processing of biomaterials and central measurement of blood markers. Consequently, data on SCr were very complete, and only very few data were missing for ACR, which was measured locally at each study center, but requested by the EUROASPIRE IV protocol and standardized description of spot urine collection was provided. Moreover, the *kidney specific module* at

the German study center enables a comprehensive view on specialist care for CKD, and awareness of CKD among CHD patients and their treating physicians.

However, limitations need to be mentioned. First, the study sample of EUROASPIRE IV cannot be claimed as representative neither for CHD patients in the respective countries nor for those admitted for CHD at the recruiting hospitals in each country due to the selection process of centers and the recruitment success[16], which also applies to the German subset. Our findings derived from participants of the Würzburg-region are thus not generalizable to all CHD patients in Germany and may not even be representative for all CHD patients admitted for CHD at the University Hospital Würzburg or the Klinik Kitzinger Land, as only 38.8% of invited subjects agreed to participate. Due to data protection regulations, analysis of reasons for non-participation is limited: eligible patients who did not participate in EUROASPIRE IV were more likely to be female and of slightly younger age. In the entire cohort, subjects not recruited were also more likely to be female, but no difference in age could be found[16].

Second, it is not possible to unrestrictedly compare our current results of EUROASPIRE IV to the findings of the previous EUROASPIRE surveys I – III in Germany, as the study center and the source population has changed from Münster to Würzburg[20]. Thus, secular trends over the past years have to be interpreted with caution. The region of Münster comprises 2.57 million inhabitants, with 372 inhabitants per km². In contrast, Würzburg represents a more rural region in Lower Franconia with a total of 1.3 million inhabitants (152 inhabitants per km²). Participants of EUROASPIRE IV were older as compared to EUROASPIRE I- III (68.9 years vs. 58.6/59.5/60.0 years) and also with a longer time between index-event and study visit (1.8 years vs. 1.3/1.5/1.1 years).

Third, EUROASPIRE IV excluded patients older than 79 years at the index event. Therefore we are unfortunately not able to make any assumptions on the group of “very old” CHD patients, 80 years or older. Research on these individuals is of particular interest as due to growing life expectancy in general

and improved health care which leads to rising survival rates of CHD events, this group will enlarge significantly in the next decades.

Fourth, CKD was classified based on a single measurement of SCr and ACR at the study visit, while usually two independent measurements for adequate assessment of CKD are desired[37]. However, study participants were in apparently stable condition at the time of recruitment as they were not hospitalized or invited to the study visit because of any acute clinical reason. Also, any SCr-based estimation of GFR has limitations, and mild to moderately impaired kidney function may be better described by equations based on Cystatin C[169], which unfortunately was not available. But we chose the SCr-based CKD-EPI formula as it outperforms the MDRD formula in particular in GFR between 60 and 90 ml/min/1.73m² [102].

Fifth, the quality of retrospectively collected data of the index hospital stay across 78 centers in 24 European countries is prone to be influenced by substantial variation, although standardized procedures and CRFs have been provided. Therefore, the validity these data might be limited due to non-standardized description of risk factors and completeness at admission and in discharge letters in routine clinical care across Europe. Furthermore, measurement methods (e.g. for SCr, urinary creatinine, albumin) vary and ACR was not routinely measured in the participating hospitals to analyze the level of proteinuria during the index hospital stay.

Sixth, when we investigated the changes of eGFR between the index hospital stay and the study visit in the entire EUROASPIRE IV sample, we were not able to address all possible related factors, such as episodes of AKI, kidney function at hospital discharge, and medical care and patient compliance/behavior in the ambulatory setting. Some of these limitations were overcome by the German *kidney specific module*, e.g. episodes of AKI, kidney function at hospital discharge). Other data, e.g. on medical care and patient compliance/behavior between the index hospital stay and the study visit were collected, but detailed analysis of these factors would be beyond the scope of this project. We

therefore included only determinants in our models that were available during the hospital stay describing their prognostic value regarding changes in kidney function.

Finally, while the sample size of the entire EUROASPIRE IV dataset allows sufficient statistical power for detailed regression analysis with a large number of explanatory variables, the number of observations in the German sample is limited from a statistical perspective. Therefore, any assumptions on results based on small sample sizes, e.g. the number of patients being referred and seen by renal specialists, need to be interpreted with caution and need to be confirmed by independent studies. Moreover the number of variables tested in regression analyses on the German dataset may be considered as too high, thus finding and missing associations by chance and limited power is surely possible.

8. Conclusions

The results of the current thesis project indicate that based on very recent data of the EUROASPIRE IV study, most patients with CHD in Germany receive the recommended medication for secondary prevention but targets for specific risk factors, including blood pressure, diabetes and LDL-Cholesterol were not achieved in many patients. While the prevalence of smoking was considerably low, overweight/obesity and limited physical activity, particularly in younger individuals are alarming. Modification of life-styles may become an even greater factor in prevention campaigns than medical treatment into certain target ranges. The number and compilation of risk factors, including CKD, as well as treatment patterns and achievement of recommended targets vary in the elderly. These individuals represent a vulnerable group in which the therapeutic strategy of secondary CHD prevention must consider different needs, physical and mental potential, other comorbidities and drug-interactions with co-medication.

We were able to analyze the proportion of CKD in the entire European setting of the EUROASPIRE IV study and found that every forth to fifth patient in stable condition has CKD including those with preserved eGFR but significant albuminuria, however, with a wide variation across participating countries. Chronic and/or acute kidney dysfunction is also very common in patients admitted for CHD events, but the lack of routine albuminuria measurement precluded determination of the entire risk spectrum of kidney dysfunction. In the German data we observed that kidney dysfunction was not mentioned in the hospital discharge letter in many patients with renal impairment whereas ICD-coding was more complete. Raising the level of physician's awareness of kidney disease in the hospital as well as in the ambulatory setting, including routine measurement of albuminuria/ proteinuria will help to identify those patients with CKD and those at risk to develop CKD, which represents an important risk factor for the prognosis of CHD. Enhancing the information transfer of renal impairment from the hospital to the ambulatory setting may also help to recognize CKD as an important aspect in CHD care, to

adjust therapeutic strategy and treatment targets which are likely to improve management and prognosis of both CKD and CHD.

Information on kidney (dys-)function should also be discussed with the patient to raise the level of CKD awareness among patients. Only a minority of patients with CKD in the German EUROASPIRE IV setting reported that they had ever been told by a physician regarding impaired kidney function. Raising the physician's awareness of kidney disease may ultimately lead to better informed patients which then may be more confident in the medical therapy and suggested treatment, may improve adherence to medication and following recommendations for improving life-style and behavior.

9. References

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10. Appendix

10.1. Abbreviations

ACR	albumin / creatinine ratio
AKI	acute kidney injury
AMI	acute myocardial infarction
BMI	body mass index
CABG	coronary artery bypass grafting
CHD	coronary heart disease
CHF	Congestive heart failure
CHFC	Comprehensive Heart Failure Center Würzburg
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease epidemiology collaboration
CVD	cardiovascular disease
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
FPG	fasting plasma glucose
ICE-B	Institute for Clinical Epidemiology and Biometry, University of Würzburg
IQR	inter-quartile range
HDL-C	high density lipoprotein cholesterol
KDIGO	Kidney Disease – Improving Global Outcomes
LDL-C	low density lipoprotein cholesterol
OGTT	oral glucose tolerance testing
OR	Odds Ratio
PAD	peripheral artery disease
PCI	percutaneous coronary intervention
SCr	serum creatinine
SD	standard deviation

10.2. Age-standardization (European Standard Population 2013)

Weights of the various age strata for age-standardization according to the European Standard Population 2013 as suggested by the European Commission[105].

Age group (years)	Standard population
0	1 000
1 – 4	4 000
5 – 9	5 500
10 – 14	5 500
15 – 19	5 500
20 – 24	6 000
25 – 29	6 000
30 – 34	6 500
35 – 39	7 000
40 – 44	7 000
45 – 49	7 000
50 – 54	7 000
55 – 59	6 500
60 – 64	6 000
65 – 69	5 500
70 – 74	5 000
75 – 79	4 000
80 – 84	2 500
85 – 89	1 500
90 – 94	800
95+	200
total	**100 000**

10.3. Description of contributions

This paragraph aims to describe the role of all researchers that were co-authoring the three manuscripts included in the current thesis. The official form of the statement of individual author contributions can be found below (Statement of individual author contributions)

The European wide EUROASPIRE IV study and the core protocol were designed and methods were developed mainly by Prof. Kornelia Kotseva (KK) and Prof. David Wood (DW) with the help of Prof. Lars Rydén (LR) and Prof. Dirk DeBacquer (DDB). The execution of the EUROASPIRE IV study in Germany and the German study centers (Würzburg and Kitzingen) was realized by the German National EUROASPIRE IV Coordinators Prof. Peter U. Heuschmann (PUH) and Prof. Stefan Störk (StS). Prof. Georg Ertl (GE), Director Dept. of Medicine I, University Hospital Würzburg, Prof. Rainer Leyh (RL), Director Dept. of Cardiovascular Surgery, University Hospital Würzburg, and Dr. Wolfgang Karmann (WK), Director Dept. of Medicine, Klinik Kitzinger Land permitted recruitment of patients of the three recruiting hospitals.

Dr. Martin Wagner (MW) was responsible for organization of the EUROASPIRE IV study and data collection at the German center with the help of Julia Kircher (JK) and Dr. Martin Schich (MS). MW primarily designed the studies and the analysis plan for all three manuscripts included in the thesis. He also designed and implemented the *kidney specific module* at the German study center with the help of Prof. Christoph Wanner (CW) and MS. As described in section *6.3. Manuscript 3 "CKD awareness in the German EUROASPIRE IV study"*, MS completed his medical doctoral thesis while working on study aim 3 and also used data of the *kidney specific module*. Georg Fette (GF) helped with data collection by utilizing the CHFC Datawarehouse. Katrin Hartmann (KH) helped with data management. MW primarily performed all statistical analyses and created all figures included in the manuscripts with the help of Prof. Götz Gelbrich (GG) and Viktoria Rücker (VR). The findings were primarily interpreted by MW and also by PUH, StS, CW, MS, Dr. Caroline Morbach (CM), Dr. Mehmet Oezkur (MO), KK, DDB, LR and all other co-authors of the respective manuscripts. MW wrote all three manuscripts including introduction,

materials and methods, results and discussions. All co-authors reviewed the respective manuscripts, revised and commented critically.

10.4. Statement of individual author contributions

"Dissertation Based on Several Published Manuscripts"

Statement of individual author contributions and of legal second publication rights

Publication: Wagner M, Gelbrich G, Kircher J, Kotseva K, Wood D, Morbach C, Leyh R, Ertl G, Karmann W, Störk S, Heuschmann PU: *"Secondary Prevention in Younger vs. Older Coronary Heart Disease Patients – Insights from the German subset of the EUROASPIRE IV Survey"*; International Journal of Behavioral Medicine (2017), epub ahead of print							
Participated in	**Author Initials,** Responsibility decreasing from left to right						
Study Design Methods Development	KK	DW	PUH	StS	MW	JK	
Data Collection	MW	JK	PUH	StS	GE	RL	WK
Data Analysis and Interpretation	MW	PUH	StS	GG	CM	MO	
Manuscript Writing							
Writing of Introduction	MW	PUH	StS	CM	KK		
Writing of Materials and Methods	MW	PUH	StS	CM	KK		
Writing of Discussion	MW	PUH	StS	CM	KK		
Writing of First Draft	MW	PUH	StS	CM	KK		

Publication: Wagner M, Wanner C, Kotseva K, Wood D, De Bacquer D, Rydén L, Störk S, Heuschmann PU: *"Prevalence of chronic kidney disease and its determinants in coronary heart disease patients in 24 European countries: Insights from the EUROASPIRE IV survey of the European Society of Cardiology"*; European Journal of Preventive Cardiology (2017), 24(11):1168-1180							
Participated in	**Author Initials,** Responsibility decreasing from left to right						
Study Design Methods Development	MW	CW	PUH	KK	StS	DW	
Data Collection	KK	DW	MW	PUH	StS		
Data Analysis and Interpretation	MW	PUH	CW	KK	DDB		
Manuscript Writing							

Writing of Introduction	MW	PUH	CW	LR	KK	StS	
Writing of Materials and Methods	MW	PUH	CW	LR	KK	StS	DDB
Writing of Discussion	MW	PUH	CW	LR	KK	StS	
Writing of First Draft	MW	PUH	CW	LR	KK	StS	

Publication: Wagner M, Wanner C, Schich M, Kotseva K, Wood D, Hartmann K, Fette G, Rücker V, Oezkur M, Störk S, Heuschmann PU: *"Patient's and Physician's Awareness of Kidney Disease in Coronary Heart Disease Patients – a cross-sectional Analysis of the German Subset of the EUROASPIRE IV Survey";* BMC Nephrology (2017), 18(1): 321							
Participated in	**Author Initials,** Responsibility decreasing from left to right						
Study Design Methods Development	MW	CW	PUH	StS	KK	DW	
Data Collection	MW	MS	PUH	StS	GF	KK	
Data Analysis and Interpretation	MW	KH	VR	CW	PUH	StS	MO
Manuscript Writing							
Writing of Introduction	MW	PUH	CW	StS			
Writing of Materials and Methods	MW	PUH	CW	StS			
Writing of Discussion	MW	PUH	CW	StS			
Writing of First Draft	MW	PUH	CW	StS			

The doctoral researcher confirms that he has obtained permission from both the publishers and the co-authors for legal second publication.

The doctoral researcher and the primary supervisor confirm the correctness of the above mentioned assessment.

Dr. Martin Wagner Würzburg

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Doctoral Researcher's Name Date Place Signature

Prof. Dr. Peter Heuschmann Würzburg

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Primary Supervisor's Name Date Place Signature

10.5. Statement of individual author contributions to figures

"Dissertation Based on Several Published Manuscripts"

Statement of individual author contributions to figures/tables/chapters included in the manuscripts

Publication: Wagner M, Gelbrich G, Kircher J, Kotseva K, Wood D, Morbach C, Leyh R, Ertl G, Karmann W, Störk S, Heuschmann PU: *"Secondary Prevention in Younger vs. Older Coronary Heart Disease Patients – Insights from the German subset of the EUROASPIRE IV Survey"*; International Journal of Behavioral Medicine (2017), epub ahead of print	
Figure	**Author Initials,** Responsibility decreasing from left to right
No figure included	

Publication: Wagner M, Wanner C, Kotseva K, Wood D, De Bacquer D, Rydén L, Störk S, Heuschmann PU: *"Prevalence of chronic kidney disease and its determinants in coronary heart disease patients in 24 European countries: Insights from the EUROASPIRE IV survey of the European Society of Cardiology"*; European Journal of Preventive Cardiology (2017), 24(11):1168-1180					
Figure	**Author Initials,** Responsibility decreasing from left to right				
1	MW	CW	PUH	StS	KK
s1	MW	CW	PUH	StS	KK
s2	MW	CW	PUH	StS	KK

Explanations: figures s1, s2 in supplementary data

Publication: Wagner M, Wanner C, Schich M, Kotseva K, Wood D, Hartmann K, Fette G, Rücker V, Oezkur M, Störk S, Heuschmann PU: *"Patient's and Physician's Awareness of Kidney Disease in Coronary Heart Disease Patients – a cross-sectional Analysis of the German Subset of the EUROASPIRE IV Survey";* BMC Nephrology (2017), 18(1): 321					
Figure	**Author Initials,** Responsibility decreasing from left to right				
1	MW	CW	PUH	StS	KK

I also confirm my primary supervisor's acceptance.

Dr. Martin Wagner Würzburg

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Doctoral Researcher's Name Date Place Signature

10.6. Acknowledgements

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11. Curriculum Vitae

01/2017 – present	Nephrologist, Medical Co-Director (since 2018), Dialysis Center Fulda, KfH-Kuratorium für Dialyse und Nierentransplantation
01/2016 – present	Adjunct Faculty (Nephrology), Dept. of Medicine I, Div. of Nephrology, University Hospital Würzburg
07/2009 – present	Adjunct Instructor (Medicine), Tufts University, School of Medicine, Boston, Massachusetts, USA
01/2012 – 12/2017	Lecturer, Institute for Clinical Epidemiology and Biometry, University of Würzburg
02/2013 – 02/2017	PhD-fellowship "Clinical Science", Graduate School of Life Sciences, University of Würzburg
06/2013	Board Certification "Internal Medicine / Nephrology" ("Facharzt")
07/2009 – 12/2015	Residency/Fellowship in Internal Medicine, Dept. of Medicine I, Div. of Nephrology, University Hospital Würzburg
08/2009	Degree Master of Science "Clinical Research", Sackler School of Biomedical Sciences, Tufts University, Boston, Massachusetts, USA
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11/2005	Doctoral thesis "magna cum laude" (degree of Dr. med.), University of Würzburg, Dept. of Medicine, Div. of Nephrology
07/2004 – 06/2007	Residency in Internal Medicine, Dept. of Medicine I, Div. of Nephrology and Cardiology, University Hospital Würzburg
07/2004	Graduation in Medicine ("Approbation")
01/2003 – 06/2004	Internship ("Arzt im Praktikum") in Internal Medicine, Dept. of Medicine I, Div. of Nephrology, University Hospital Würzburg
11/2002	Final examination in Medicine
1995 – 2002	Medical School, Universities of Würzburg and Kiel

Würzburg, _____

12. Affidavit

I hereby confirm that my thesis entitled ***Chronic Kidney Disease as an Important Co-morbid Condition in Coronary Heart Disease Patients*** is the result of my own work. I did not receive any help or support from commercial consultants. All sources and/or materials applied are listed and specified in the thesis.

Furthermore, I confirm that this thesis has not yet been submitted as part of another examination process neither in identical nor in similar form.

Würzburg, _____

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Dissertation ***Chronische Nierenerkrankung als bedeutender Risikofaktor bei Patienten mit koronarer Herzkrankheit*** eigenständig, d.h. insbesondere selbständig und ohne Hilfe eines kommerziellen Promotionsberaters, angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

Ich erkläre außerdem, dass die Dissertation weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

Würzburg, _____

Danksagung

An dieser Stelle bedanke ich mich herzlich für die Unterstützung von verschiedenen Seiten, die die Fertigstellung dieser Arbeit ermöglicht haben.

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