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Original Article

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The evolution of renal function and the incidence of end-stage renal disease in patients aged ≥50 years

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Abstract

Background. The prevalence of chronic kidney disease (CKD) is high, especially among older patients.

Methods. In order to identify risk factors for the evolution towards end-stage renal disease (ESRD), a cohort of patients ≥50 years of age for whom at least four serum creatinine measurements were available were selected from a primary care-based database. The slope of changes in estimated glomerular filtration rate (eGFR) (using the Modification of Diet in Renal Disease formula) was calculated, and ESRD was defined as eGFR <15 mL/min. Risk factors for ESRD were analysed using Cox regression analysis.

Results. The cohort included 24 682 patients (13 305 women) with a mean age at first available measurement of 64 years. During follow-up (average 7.8 years), 212 patients (0.9%) developed ESRD. The incidence of ESRD per 10 000 person-years is low and depends on baseline eGFR (Stages 0–2: 3, Stage 3A: 13, Stage 3B: 121 and Stage 4: 765). Adjusted hazard ratios (HRs) for patients with baseline eGFR in Stage 3B or 4 depended on age (HR = 0.47 or 0.41 for patients 65–79 years and HR = 0.26 or 0.32 for patients ≥80 years compared with patients aged 50–64 years). Females (HR = 1.48) and patients with diabetes (HR = 1.20), hypertension (HR = 1.25), high total cholesterol (HR = 1.28) or high low-density lipoprotein (LDL) cholesterol (HR = 1.39) were at higher risk for ESRD.

Conclusions. Baseline eGFR, diabetes, high cholesterol, high LDL, hypertension and female gender are independent risk factors for developing ESRD. Older age at baseline predicts a lower risk.

Keywords: chronic kidney disease; end-stage renal disease; glomerular filtration rate; older patients; primary health care

Introduction

Patients with chronic kidney disease (CKD) are largely classified into five stages proposed by the US National Kidney Foundation. This classification is primarily based on the estimated glomerular filtration rate (eGFR). In this classification, patients with an eGFR <15 mL/min are classified into Stage 5 [also called end-stage renal disease (ESRD)]. According to this classification system, CKD has a high prevalence worldwide [1], and the prevalence increases dramatically [2] with advancing age. Whether the high prevalence of CKD in elderly patients is due to a true disease or to normal physiological decline of renal function with age is a topic of ongoing debate.

Despite the high prevalence of CKD, only limited numbers of the large group of patients with CKD will develop ESRD. The ERA–EDTA registry (http://www.era-edta-reg.org) reports for 2009 an incidence rate of ESRD of 201 per million for the Dutch speaking part of Belgium, 123 for the Netherlands, 108 for the UK and 146 for France. Even so, the financial burden of renal replacement therapy is considerable for society as a whole [3]. Therefore, identification of the subgroup of patients with a high risk of developing ESRD is essential. As suggested in a recent report [4], more data are needed on the evolution of CKD and the risk factors for developing ESRD before choices are made regarding the organization of special care programmes for patients with CKD with the goal of preventing ESRD. Recently, a risk score based on eGFR and proteinuria was proposed [5] based on a large cohort study.

In this article, we studied the evolution of the eGFR in a large cohort of adults seeking ambulatory primary care and elderly patients. We aimed to identify the absolute risk of developing ESRD and the role of factors such as age, gender, diabetes, hypertension, high total cholesterol and high low-density lipoprotein (LDL) on the chance of developing ESRD.

Materials and methods

Study design

Data were obtained from Intego, a Flemish general practice-based morbidity registration network based in the Department of General Practice at the Catholic University of Leuven. Currently, 90 General Practitioners (GPs), all using the medical software program Medidoc®, are collaborating in the Intego project. These GPs work in 55 practices evenly spread throughout Flanders, the northern part of Belgium. The GP's data were checked on their quality before inclusion in the database. The participating GPs receive yearly quality checks based on peer comparison

and feedback on the quality of their data. The process of this quality check was published earlier [6]. The Intego GPs prospectively and continuously register all new diagnoses together with new drug prescriptions, laboratory test results and some background information (including sex and year of birth) using computer-generated keywords linked to codes. Using specially framed extraction software, new data were collected from the computers of the participating GPs and entered into a central database. Registered data were continuously updated, accumulating a history for each patient.

Inclusion and exclusion criteria

Out of this database, we selected all patients entered between 1994 and 2008 who had at least four serum creatinine measurements and who were ≥50 years of age at the time of at least one creatinine measurement. For each of these patients, date of birth, gender, all serum creatinine measurements, diabetes and hypertension diagnoses as well as the first available measured concentration of total cholesterol and LDL cholesterol and the exact date of all these measurements were extracted.

We excluded patients with eGFR values <15 mL/min at baseline, who were already considered to have ESRD. Patients with impossible serum creatinine values were also excluded.

Creatinine measurements

The creatinine values were not measured by the same laboratory due to the design of the database, which collects data from practices all over Flanders. That is, there is no absolute certainty about the creatinine assay used. In the period between 1994 and 2008, however, almost all laboratories in Belgium used a kinetic Jaffe method without isotope dilution mass spectrometry standardization and there is a quality programme [7] for all Belgian laboratories, which diminishes the analytical differences between the different laboratories.

Ethical considerations

Before sending the data to the central database in Leuven, patient identification information was coded in each general practice using a one-way algorithm. As a result, only the registering GP was able to find out the identity of the patient to which a certain code belonged. According to the national privacy law, patients were informed about the ongoing registration through a poster on the wall in the waiting room of the registering GP. The Intego procedures were approved by the ethical review board of the Medical School of the Catholic University of Leuven (no. ML1723).

Calculations and definitions

The eGFR was calculated with the Modification of Diet in Renal Disease (MDRD) formula [8]: glomerular filtration rate (GFR) (mL/min/1.73 m^2) = $186 \times (S_{cr})^{-1.154} \times (age)^{-0.203} \times 0.742$ (if female). We used the classification system of the American Kidney Foundation to classify the patients: eGFR between 45 and 60 mL/min/1.73m^2 = Stage 3A, eGFR between 30 and 45 mL/min/1.73^2 = Stage 3B, eGFR between 15 and 30 mL/min/1.73m^2 = Stage 4 and eGFR <15 mL/min/1.73 m^2 = Stage 5. Patients with an eGFR >60 mL/min/1.73m^2 who had early signs of kidney damage (Stage 1 or 2 CKD) or no sign of kidney damage (no CKD) were analysed as one group. We defined a patient as having ESRD if his/her eGFR dropped <15 mL/min on one occasion and the mean of his/her last two measurements was still <30 mL/min. By adopting these criteria, we avoided the inclusion of patients with acute but temporary renal failure with recovery or with lab errors into the group of patients who developed ESRD. Diagnosis of hypertension and diabetes was made by the patient's GP and based on diagnostic criteria (diabetes: two measurements of fasting glucose >126 mg/dL and hypertension: two measurements of blood pressure >140/90 mmHg).

Because the criteria for hypercholesterolaemia have changed within the last 15 years, we based the diagnosis of high total cholesterol and high LDL cholesterol on the first available laboratory result. We used a cut-off value of 190 mg/dL for total cholesterol and 115 mg/dL for LDL cholesterol for diagnosis of each condition.

Statistical analyses

Subgroup analysis of the prevalence of CKD was performed for males and females and different age groups. All analyses, as well as the construction of the figures, were performed using SPSS version 16.0 software (SPSS Inc., Chicago, IL).

Results

General patient characteristics

We identified 25 254 patients who met the inclusion criteria. Of these subjects, 566 were excluded because they had one or more impossible creatinine values or were at Stage 5 CKD at baseline. Therefore, the final study cohort contained 24 682 patients. Of these patients, 13 305 were women, and the mean age at baseline was 64 years (63 for men and 64 for women). On average, 10.2 creatinine measurements (females on average 10.0 measurements and males 10.4 measurements) were available over a time period of on an average of 7.8 years. The time between first and last available creatinine measurement depends on the eGFR at baseline (mean of first two eGFR's) and age: when the eGFR at baseline >60 mL/min, the time in the cohort was 8.1 years (95% confidence interval 8.1–8.2) at age 50–64 years, 7.6 (7.5–7.7) at age 65–79 years and 5.1 (5.0–5.3) at age ≥80 years (P for trend <0.001). When the eGFR at baseline was 45–59 mL/min, the time in the cohort was 9.2 years (9.0–9.4) at age 50–64 years, 8.2 (8.1–8.3) at age 65–79 years and 5.2 (5.1–5.4) at age ≥80 years (P for trend <0.001). When the eGFR at baseline was 30–44 mL/min, the time in the cohort was 7.6 years (7.2–8.0) at age 50–64 years, 6.5 (6.3–6.7) at age 65–79 years and 4.4 (4.3–4.6) at age ≥80 years (P for trend <0.001). Finally, when the eGFR at baseline was <30 mL/min, the time in the cohort was 6.3 years (5.6–7.0) at age 50–64 years, 5.1 (4.6–5.6) at age 65–79 years and 3.2 (2.3–3.5) at age ≥80 years (P for trend <0.001). Of this cohort, 18% of the patients had diabetes, 62% had hypertension, 81% had high total cholesterol and 66% had high LDL cholesterol.

Decline in eGFR

We analysed the slope of eGFR evolution and related it to baseline GFR and age. These results are presented in Figure 1. These data show no negative trend in eGFR but, rather, follow a normal distribution (with a mean evolution for the total population of −0.06 mL/min/year). Of the study population, 15% showed a decline of 2–5 mL/min/year and 6% showed a decline >5 mL/min/year. The only exception to this normal distribution is the subgroup with patients aged 50–64 years who were classified as Stage 4 CKD at baseline. In this subgroup, there was a larger population (30%) with a decline of 2–5 mL/min/year, but this elevated percentage may be due to the limited number of patients in this subgroup ($n = 33$).

Chance of developing ESRD

For each patient, we analysed the differences between baseline classification of CKD stage, based on the mean of the first two recorded eGFRs, and the classification based on the mean of the last two eGFRs. These data are reported in Table 1. The evolution here also has two directions; some patients declined in stage and others increased in stage, but most patients were at the same stage at baseline and at the end. Patients with a mean eGFR of ≥45 mL/min/1.73m^2 at baseline had a very small chance (<0.5%) of having a mean eGFR <15 mL/min/1.73m^2 at the end, but this chance was >20% when patients were at Stage 4 CKD at

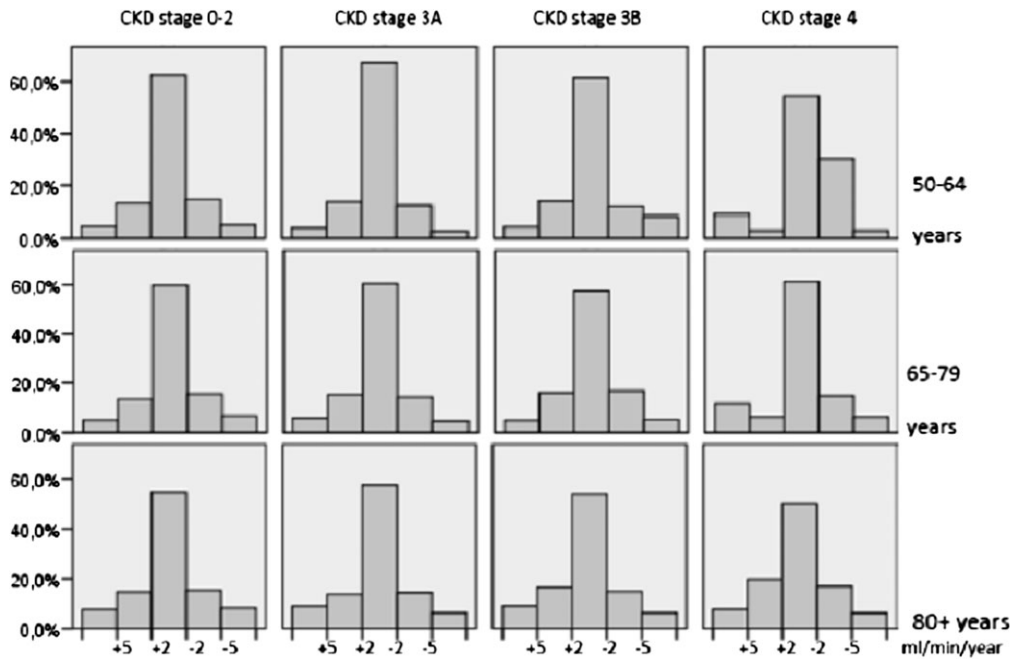

Fig. 1. Distribution of the slope of the eGFR in function of baseline eGFR and age. Horizontal axis, baseline eGFR according to stages of CKD and vertical axis, three age groups (1: 50–64 years old, 2: 65–79 years old, 3: 80+ years old). Slopes of changes in eGFR were classified into five categories (more than +5 mL/year, +2 to +5 mL/year, −2 to + 2 mL/year, −5 to −2 mL/year and less than−5 mL/year).

Table 1. Evolution of eGFR according to CKD stage[a]

Number of patients in each stage of CKD at baseline (based on the mean of the first two eGFR values)	Number of patients (%) in each stage of CKD (based on the mean of the last two eGFR readings)				
	>60 mL/min	45–60 mL/min (Stage 3A)	30–45 mL/min (Stage 3B)	15–30 mL/min (Stage 4)	<15 mL/min (Stage 5)
>60 mL/min					
Male (n =10 028)	8890 (88.7%)	870 (8.7%)	202 (2.0%)	55 (0.5%)	11 (0.1%)
Female (n = 9903)	8345 (84.3%)	1218 (12.3%)	275 (2.8%)	55 (0.6%)	10 (0.1%)
45–60 mL/min (Stage 3A)					
Male (n = 1074)	350 (32.6%)	484 (45.1%)	197 (18.3%)	39 (3.6%)	4 (0.4%)
Female (n = 2674)	994 (37.2%)	1167 (43.6%)	417 (15.6%)	85 (3.2%)	12 (0.4%)
30–45 mL/min (Stage 3B)					
Male (n = 226)	15 (6.6%)	41 (18.1%)	107 (47.3%)	51 (22.6%)	12 (5.3%)
Female (n = 614)	44 (7.2%)	148 (24.1%)	273 (44.5%)	133 (21.7%)	16 (2.6%)
15–30 mL/min (Stage 4)					
Male (n = 49)	2 (4.1%)	4 (8.2%)	6 (12.2%)	26 (53.1%)	11 (22.4%)
Female (n = 113)	3 (2.7%)	2 (1.8%)	21 (18.6%)	59 (52.2%)	28 (24.8%)
Total					
Male (n = 11 377)	9257 (81.4%)	1399 (12.3%)	512 (4.5%)	171 (1.5%)	38 (0.3%)
Female (n = 13 305)	9386 (70.5%)	2535 (19.1%)	986 (7.4%)	332 (2.5%)	66 (0.5%)

[a]Mean time between baseline and last available eGFR: 7.80 years (SD 3.90).

baseline. In total, 212 patients developed ESRD during the follow-up period. Of these 212 patients who at least once had an eGFR <15 mL/min, 166 still had an eGFR <15 mL/min when we used the last two available measurements of these patients and 46 were in Stage 4 CKD. The median time between these last two measurements was 4.0 months [interquartile range (IQR) 0.6–10.0]. The median time between the first time the patient had an eGFR< 15 and the last available eGFR was 1.38 years (IQR 0.7–5.80).

This number corresponds to 0.84% of the patients or 0.11% of the patients/year. The incidence of ESRD per 10 000 patient-years differs as a function of baseline eGFR [3/10 000 patient-years (Stage 0–2), 13/10 000 (Stage 3A), 121/10 000 (Stage 3B) and 765/10 000 (Stage 4)].

Predictors of developing ESRD

We further analysed the incidence of ESRD and related it to baseline eGFR and age (see Table 2) and as a function of gender and comorbidity (Table 3). After adjusting for comorbidity and gender (see Table 2), it is clear that, for patients with Stage 3B or 4 CKD at baseline, the risk of evolution towards ESRD decreases with increasing age [hazard ratio (HR) = 0.52 and 0.30 for patients aged

Table 2. Incidence of end-stage renal failure according to baseline eGFR class and age[a]

	Incidence of ESRD					
Baseline eGFR	Age group at baseline	Number of patients	Total years at risk	Number of patients developing ESRD	Incidence of ESRD per 100 patient-years	Adjusted HRs[b] (95% CI)
>60 mL/min						
	50–64 years	12 833	104 589	23	0.022	1
	65–79 years	6277	48 103	25	0.052	2.49 (2.41–2.57)
	80+ years	821	4125	6	0.145	4.43 (4.03–4.83)
45–60 mL/min (Stage 3A)						
	50–64 years	1185	10 855	5	0.046	1
	65–79 years	2002	16 016	27	0.169	2.78 (2.61–2.94)
	80+ years	562	2939	7	0.238	2.55 (2.15–2.95)
30–45 mL/min (Stage 3B)						
	50–64 years	109	768	12	1.56	1
	65–79 years	401	2674	30	1.13	0.70 (0.62–0.78)
	80+ years	330	1518	18	1.20	0.52 (0.43–0.61)
15–30 mL/min (Stage 4)						
	50–64 years	33	213	21	9.86	1
	65–79 years	63	326	24	7.36	0.58 (0.41–0.75)
	80+ years	66	219	13	5.94	0.30 (0.23–0.37)

[a]CI, confidence interval.
[b]Adjusted for pathology (diabetes, hypertension, high total cholesterol and high LDL cholesterol) and gender.

Table 3. Incidence of end-stage renal failure according to gender and pathology[a]

	Incidence of ESRD according to gender and pathology				
Gender	Number of patients	Total years at risk	Number of patients with ESRD	Incidence of ESRD per 100 patient-years	Adjusted HRs[b] (95% CI)
All patients	24 682	192 429	212	0.110	NA
Males	11 377	86 920	77	0.089	1
Females	13 305	105 509	135	0.128	1.48 (1.30–1.66)
Pathology	Number of patients	Total years at risk	Number of patients with ESRD	Incidence of ESRD per 100 patient-years	Adjusted hazard ratios[c] (95% CI)
None	2265	17 961	15	0.084	1
Diabetes	4322	33 279	43	0.129	1.20 (1.15–1.25)
Hypertension	9426	73 523	77	0.105	1.25 (1.22–1.28)
High total cholesterol	19 966	155 135	173	0.112	1.28 (1.26–1.30)
High LDL	16 211	125 550	155	0.123	1.39 (1.36–1.42)

[a]CI, confidence interval; NA, not available.
[b]Adjusted for pathology (diabetes, hypertension, high total cholesterol and high LDL), baseline creatinine level and age.
[c]Adjusted for baseline eGFR.

≥80 years in Stages 3B and 4, respectively, compared with patients in the same stage who were aged 50–64 years]. Besides age, female gender (HR = 1.48 compared with male gender) or diagnosed diabetes (HR = 1.20), hypertension (HR = 1.25), high total cholesterol (HR = 1.28) or high LDL cholesterol were risk factors for developing ESRD (HR between 1.20 and 1.48).

Discussion

Decline in eGFR

We found a normal distribution for the evolution of eGFR with a large group of patients who had more or less stable eGFRs over time and two smaller groups, one with an increase in eGFR and one with a decline in eGFR.

The overall rate of decline in other studies differs largely due to different study populations. Erikson *et al.* [9] (Norwegian patients, mean age of 75 years, only Stage 3 CKD) found a mean decline of 1 mL/year, whereas we found a decline in mean eGFR of 0.1 mL/min for patients in Stage 3 CKD. The MDRD study [10], on the other hand, found a mean decline in eGFR of 4 mL/year, but this study contained only patients with impaired renal function (<60 mL/min). The results from the Baltimore longitudinal study of ageing [11, 12] (healthy subjects) showed a decline of 0.3 mL/min/year in healthy normotensive subjects, whereas, we found no change in mean eGFR for patients without hypertension. For our study population as a whole, we also found that a group of 4–8% of the patients had a decline in their eGFR of >5 mL/min/year. This percentage is comparable with other population-based studies, such as that of

Eriksen *et al.* [9], who found that 6% of the patients had a decline >5 mL/year.

Chance of developing ESRD

The chance of developing ESRD when in Stage 3A is very low. Patients in Stage 3B or 4 at baseline, on the other hand, have a higher risk for developing ESRD. The incidence of ESRD we found for Stage 3A patients are comparable with those of the large cohort study of Hallan *et al.* [13]. In this study, with a mean patient age of 49 years, an incidence of ESRD of 0.04 per 100 patient-years was found, which is comparable to the 0.046 per 100 patient-years we found for the 50–64 age group. The ERA–EDTA registry reports for 2009 an incidence rate of 164 per million patients in the Flemish speaking part of Belgium aged 45–64 years, 606 for the patients aged 65–74 years and 959 for patients aged ≥75 years. When a patient is classified into Stage 3A at baseline, the chance of developing Stage 4 CKD is <4% (see Table 1), whereas approximately one-third of these patients are classified as having eGFRs >60 mL/min at the end of the follow-up period despite their earlier classification into Stage 3A. Given these data, we wondered whether the term 'moderate CKD' is correct for this group of patients.

The group of patients classified into Stage 3B at baseline, on the other hand, have a higher risk for developing ESRD (see Tables 1 and 2), but even in this case, the risk is relatively low in absolute numbers: 1.2–1.6% per year.

Predictors of developing ESRD

Younger age. We found that patients with an age of 65–79 or 80+ had a much lower risk of progression towards ESRD than patients aged 50–64 years (see Table 2). The same finding was seen in a US veteran cohort study [14]. In this cohort (97% male, 11% African American, a mean age of 73 years and mean follow-up of 3.2 years), the HRs for patients at baseline in Stages 3B and 4 were 0.59 and 0.75, respectively, for age 45–54 years and 0.10 and 0.26 for age 75–84 years.

There are two possible explanations for this important finding that higher age decreases the chance of developing ESRD over time, even starting from a similar eGFR value. Firstly, elderly patients with impaired renal function die from cardiovascular disease before they have lived long enough to develop ESRD. This theory of competition between death and ESRD is not new [14, 15]. Unfortunately, we had no mortality data in this study to analyse this mortality effect but as shown in the Result section, patients are shorter in the cohort if they are older and/or having CKD. In the survival analysis, we did corrected for these differences in drop out. There are three reasons for dropout in our study. First mortality, second change of GP and finally, no further creatinine measurements. We see no reason at all why patients with CKD are more likely to change their GP or to have fewer creatinine measurements. So indirectly, we corrected for mortality in our analyses. Another possible explanation is that the impaired renal function in elderly patients has another pathophysiological origin in most of the patients and that this 'other kind of CKD' is less likely to evolve towards ESRD than the type of CKD in younger patients.

Recently published risk scores for developing CKD [5, 16] used serum creatinine-based eGFR and proteinuria or albuminuria measurements to calculate the risk of ESRD and mortality. Given the large difference in the chance of developing ESRD in older age groups, age should be considered as a factor in these risk calculations. Age should be an important factor in the decision of whether to include a patient in a special CKD programme.

Comorbidity and female gender. The risk factors we found for developing ESRD were diagnosis of diabetes, hypertension, high total cholesterol or high LDL cholesterol. These comorbidities were already known from earlier research to be predictors of progression towards ESRD [9, 17–19]. This is logical as hypertension, diabetes and high total cholesterol and high LDL cholesterol are related to vascular damage [20], which explains the higher progression towards ESRD. Many diabetics develop on top of this a higher arteriosclerotic risk a diabetic nephropathy [21], which explains the higher chance of developing ESRD in diabetics.

We also found that female gender remains a risk factor after adjustment for other factors (see Table 3). In other studies [9, 13, 17, 18] as well as the ERA–EDTA registry, male gender was found to be a risk factor. A meta-analysis on the patient level by Jafar *et al.* [22], on the other hand, showed that female gender was a risk factor when they corrected for other baseline variables. Given the higher rate of cardiovascular mortality in men [23] and the higher rate of cardiovascular mortality in patients with CKD [5, 24], men with CKD may die more frequently before developing ESRD compared with women.

Strengths and weaknesses. We used a primary care-based registration network database to select the study cohort. It has been well documented in the past that the Intego database contains data of a representative sample of the population in Flanders [25]. On the other hand, there may be some degree of selection bias because the creatinine values were measured for clinical purposes. In addition, we selected only patients with four or more creatinine measurements, and more importantly, not all patients consult a GP. To diminish this selection bias, patients were only selected if they were ≥50 years of age because, from that age on, creatinine is often measured for routine screening. Each year, in the Intego database, on average 28311 patients >50 (year contact group) consulted their GP in the period between 1994 and 2008. Given that ~90% of the patients aged ≥50 years contacted their GP in Flanders at least once a year [6], the underlying population of the GP practices of the Intego network consists of ~31 000 patients aged ≥50 years. Therefore, using only the data from patients who had at least four serum creatinine measurements, we selected ~81% of all patients aged ≥50 years from those GPs (25 254 patients of ~31 000).

The major strengths of this study are that the study population is a large primary care population and that the

slopes of eGFR changes were calculated based on four or more serum creatinine measurements (10.2 measurements on average). In addition, two serum creatinine measurements, taken on different occasions, were always used to classify the patients by CKD stage, instead of a single measurement. In doing so, the criteria for CKD were met, and biological and analytical variance as well as the effect of acute illnesses and temporary decreases in renal function were minimized.

The study has also two major weaknesses. Although it is a well-known risk factor for the progression of CKD [18], we had no data on proteinuria/albuminuria because these were not frequently measured over the last 15 years. Secondly, we had no mortality data.

To conclude, the evolution of eGFR over time is only a negative one for a limited number of patients. Many patients have a more or less stable eGFR over time and a subgroup of patients has an increasing eGFR over time. The chance of progression to ESRD or even to Stage 4 CKD is quite low for patients who have Stage 3A CKD. Older age at baseline predicts a much lower chance of developing ESRD and should therefore be considered as a factor when predicting the risk of an individual patient for evolution towards ESRD.

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