Masterproef
Katholieke Universiteit Leuven
2016
2017

Is There a Correlation Between an eGFR slope Measured over a Five-year Period and Incident Cardiovascular Events in the Following Five years Among a Flemish General Practice Population?

Dr. N. Opdeweegh, KULeuven
Promotor: Prof. M. van den Akker, Maastricht University, KULeuven
Co-Promotor: Dr. G. Van Pottelbergh, PhD, KULeuven

Table of Contents

Abstract 3

Introduction 4

Methods 6

Setting 6
Outcome 6
Statistical analysis 6

Results 7

Discussion 12

eGFR Slope and Cardiovascular Events 12
Strengths and Limitations 12
Recommendations 13

Conclusion 13

Acknowledgments 13

Addendum 14

Figures and tables with age and gender distribution of the patients in JCG 2011 14
Background information for using the Cox proportional hazards model 17
1. Testing the proportional hazards assumption 17
2. Examining influential observations (or outliers) 18
Protocol Ethical Committee 20

References 21

Abstract

Background Using INTEGO database, we examined if the estimated glomerular filtration rate (eGFR) slope over a 5-year period has a relationship with incident cardiovascular events defined as acute myocardial infarction, stroke (CVA/TIA), peripheral arterial disease and acute heart failure in the following 5 years in a Flemish general practice population.

Methods All patients aged ≥ 50 years and with at least four eGFR measurements in the period of 01/01/2006 until 31/12/2010 were extracted. The slope was calculated by the least square method (in ml/min/y) and during follow-up period (01/01/2011 until 31/12/2015) cardiovascular events were identified. The following slope categories were considered: (-1.00,1.00] (reference group), (-3.00,-1.00], (-5.00,-3.00], ≤ -5.00, (1.00,3.00] (3.00,5.00) and ≥ 5.00 ml/min/year. Cox proportional hazards model was used to assess the association between eGFR slope and incidence of cardiovascular events. Survival probability from cardiovascular events is estimated per slope category.

Results 19,567 patients had at least four eGFR measurements of which 52% was female. 12% of the ≤-5.00 slope category did a new cardiovascular event in comparison to 7.8 % of the reference group and 5.4% of the ≥5.00 slope category. Survival rates are worst in those with slope ≤ -5.00. Patients with slope of (-5.00,-3.00] and ≤-5.00 have an adjusted hazard ratio (HR) of respectively 1.37 and 1.55.

Conclusions There is a correlation between eGFR slope and incident cardiovascular events. Negative eGFR slopes of at least – 3.00 ml/min/year give a higher risk of cardiovascular events than those with stable kidney function or improved kidney function.

Introduction

Loss of kidney function due to advanced age is a normal phenomenon. Changes in glomerular filtration rate (GFR) are a consequence of hemodynamic and structural changes, including loss of renal mass (1). Current kidney function can be estimated by using the MDRD-formula (eGFR, in ml/min/1.73m^2) and is subdivided into different stages by the National Kidney Foundation (see Table 1). An eGFR persistently (≥ 3 months) dropping below 60 ml/min/1.73m^2 signifies chronic kidney disease (CKD) and is associated with a higher risk of complications. Altered pharmacokinetics and drug interactions increase drug toxicity. Metabolic and endocrine complications are common (e.g. anemia, acidosis, malnutrition, mineral disorders). Finally, hospitalization rates are higher and there is an increased risk of cardiovascular disease and death. Diabetes and hypertension are well-known risk factors for developing CKD and several guidelines (NICE, Domus Medica, SIGN) suggest that this population must be screened (2–4).

Table 1: Different stages of eGFR according to the National Kidney Foundation

Category	eGFR (ml/min/1.73m2)	Description
Stage 1	> 90	Normal or high
Stage 2	60-89	Mildly decreased
Stage 3a	45-59	Mildly to moderately decreased (CKD)
Stage 3b	30-44	Moderately to severely decreased (CKD)
Stage 4	15-29	Severely decreased (CKD)
Stage 5	<15	Kidney failure

In the Flemish part of Belgium, the prevalence of CKD is estimated 13% in males and 16% in females (5). Only a few patients with CKD will progress to end-stage renal disease, most of them will die of other conditions like cardiovascular disease. Risk factors that contribute to the development of end-stage renal disease are diabetes, high cholesterol, high LDL, hypertension and female gender (6,7). CKD is an important risk factor for developing cardiovascular events and rapid decline of kidney function is suggested to cause a higher incidence of cardiovascular events like acute myocardial infarction (AMI), heart failure, stroke (CVA/TIA) and peripheral artery disease (2,8,9). The higher cardiovascular risk in CKD is often under-recognised and undertreated in primary care (10).

Present, several studies (11–14) used the eGFR slope (ml/min/1.73m^2/year, noted as ml/min/y) which represents a more dynamic parameter in comparison to measurements taken at one point. Therefore, a distinction can be made between stable eGFR (+/- 1 ml/min/y) and variable eGFR (+/- 3 or +/-5 ml/min/y). As to cardiovascular disease and eGFR slope, two recent studies with a large study population have been conducted. Naimark et al. (13) found that eGFR changes, positive as negative, have a significant association with all-

cause mortality, cardiovascular mortality and non-cardiovascular mortality. Turin et al. investigated the association between eGFR change over 2.5 years and the risk of congestive heart failure (CHF), acute myocardial infarction and stroke (15). Risk of CHF, AMI and stroke was highest when eGFR decline was more than - 5 ml/min/y. The adjusted hazard ratios (HR) of CHF, AMI and stroke were respectively 2.57, 1.31 and 1.29. However, when adjusting for last eGFR measurement, a significant association was only seen with CHF (HR: 1.78). In Table 2 the characteristics of these studies are listed. Other studies (16–18) found similar outcomes as to cardiovascular events and mortality. Shlipak et al. (9) found that especially a rapid decline of eGFR, defined as > 3 mL/min/year, sets a higher risk for AMI, heart failure and stroke. These studies add further evidence that change in eGFR slope can give a worse cardiovascular outcome. The objective of this study is to determine if the eGFR slope over a 5-year period has a relationship with incident cardiovascular events defined as AMI, peripheral arterial disease, CVA/TIA and acute heart failure in the following 5 years in a Flemish general practice population.

Table 2: Characteristics of two studies which use the eGFR slope (in ml/min/y) to determine mortality risk (Naimark) and future risk of cardiovascular events (Turin)

	Naimark (2016) *Meta-analysis*	**Turin (2015)** *Population-based cohort study*
Study population	1.2 million *From 12 CKD and 22 other cohorts*	479 126 *Without history of cardiovascular disease*
Period eGFR measurements	3 years	4 years
Endpoints	All-cause mortality (Cardiovascular mortality and non-cardiovascular mortality)	Annual change of eGFR and incidence of congestive heart failure, acute myocardial infarction, stroke
Subgroups/ Adjustments/ Limitations	Exclusion for weight loss > 2 kg: no alteration antecedent eGFR slope and ACM Exclusion of diabetes: no meaningful difference in the risk associations	Adjustments for demographic factors, measured comorbidities, kidney function levels, proteinuria
	Adjusting for use of renin-angiotensin system-inhibiting medications in antecedent period: no meaningful difference in the risk associations	No adjustment for body mass index, blood pressure control, causes of kidney disease, smoking
	Percentages of change eGFR in comparison with slope EGFR: similar risk associations	

Methods

Setting

The present study is a retrospective data-analysis on the INTEGO databank, which incorporates epidemiological data from more than 100 general practitioners (GPs) residing in the Flemish part of Belgium. In Medidoc®, a medical software program, GPs use a coded registration system based upon validated algorithms (19). The group of patients that frequently visit the general practice in one year is called the "Jaarlijkse Contact Groep" or JCG. From this database, all patients aged ≥ 50 years with at least four eGFR measurements between 1 January 2006 and 31 December 2010 were included into the study. We split this 5-year period in 10 sub-periods of 6 months, i.e. "01/01/2006-30/06/2006", "01/07/2006-31/12/2006" and so forth. The eGFR was calculated with the MDRD equation (GFR (ml/min/1.73 m^2) = 186 × (16)−1.154 × (Age)−0.203 × (0.742 if female) × (1.212 if black)). With these measurements, we calculated the eGFR slope (ml/min/y) and divided the population into following subgroups: (-1.00,1.00] (reference group), (-3.00,-1.00], (-5.00,-3.00], ≤ -5.00, (1.00,3.00] (3.00,5.00) and ≥ 5.00 ml/min/1.73m^2 per year (ml/min/year). In the case that a patient had several creatinine values in the same semester, we took the mean value of the creatinine. Extremely high and low values of creatinine were excluded. We chose to use eGFR because it is readily available in most routine lab tests and it is the best parameter to estimate kidney function. Note that these tests were performed in different laboratories, and we took this characteristic into account (for instance, when the measure was in ml/l, we divided with 10).

Outcome

During the follow-up period, between 1 January 2011 and 31 December 2015, cardiovascular events described as incident acute myocardial infarction (AMI, ICPC-code[1]: K75 and/or K76), acute heart failure (AHF, K77), cerebrovascular event (TIA, CVA, K89; K90) and periphery arterial disease (PAD, K92) were identified. Patients with prior cardiovascular disease were not excluded. Patients who had no contact with the GP in the follow-up period were censored. We will consider following variables as potential confounders: age, female gender, diabetes (T90.02), hypertension (K85, K86), baseline kidney function and cardiovascular event in history.

Statistical analysis

All analyses were performed using R software. We analysed the slope of eGFR by using the least square method and baseline characteristics are measured on 01/01/2011 (see Table

[1] ICPC-code: International Classification of Primary Care; codes used to classify complaints and encrypt diagnoses

3). Table 4 shows the number of people with a cardiovascular (CV) event in the follow-up period, stratified to eGFR slope. Next, Cox proportional hazards model is used to evaluate the association between eGFR slope and the incidence of CV events. Before applying the Cox proportional hazards model, we need to assure if this is valid. Since the Proportional Hazards model assumption hold (see Appendix), we further calculate the hazard ratios using three different models (see Table 5).

Model 1 was the basic and adjusted for age and gender. Model 2 was more elaborate and was adjusted for age, gender, hypertension, diabetes, and CV event history. Lastly, Model 3 considered in addition one more covariate, namely the baseline kidney function, where we considered the last measurement.

Approval of the Ethical Committee of the Catholic University Leuven was requested and granted.

Results

Our target population are the patients that have been in the JCG (annual contact group) of 2011 and the total number of these patients is 151,971. Information about age and gender distribution in these groups can be found in the Appendix Figures 1-4. The number of patients aged ≥ 50 years was 58,246. Of those, 19,567 had at least four different eGFR measurements in different time periods. The mean age of this group is 66.1± 11.6 years and 52% (10,206) were women. We excluded 465 patients since we were not able to track the last time that they visited a general practitioner. An overview of the distribution of patients per category is depicted in Figure 1. Patients in the two extreme groups (≤ - 5.00 and ≥ 5.00) are more likely to be female. Patients with diabetes or hypertension are slightly more likely to be in the groups with a negative eGFR slope. Remarkable is that 69.5% of the patients in the ≤-5.00 group have a well-preserved kidney function at the first measurement. In the other groups most patients fall under category 1 and 2. In the reference group nearly half the patients are in category 2 and also stay in category 2. A rising eGFR slope gets most patients that were category 2 back into category 1. A history of CV events was more common in following groups: ≤ - 5.00 and (-5.00,-3.00].

Table 4 gives an overview of eGFR slope and CV event during follow-up. Nearly 12% of the patients in the category ≤ -5.00 and (-5.00,-3.00] had a new CV event in relation to 7.8% of the reference group. In the (3.00, 5.00) and ≥ 5.00 group, a new event occurred only in about 6 % of the patients. Figure 2 displays the results of differences in survival time between

patients belonging to any of previously defined slope groups. The event of interest is CV event and the survival time is the time in years until a person develops a CV event. The vertical ticks represent the patients that were censored. Also, an informative risk set table is added, which shows the number of patients that were under observation in the specific period. The risk table is indicative of how many people are available (or at risk) throughout this period. It appears those who have a slope ≥ 5.00 have the best survival rate; less than 10% suffered from cardiovascular event during the length of follow-up. Those patients that have a slope ((-1.00,1.00], (1.00,3.00] and (3.00,5.00)) have similar survival rates, but worse than those of ≥ 5.00. Next are the patients with slope (-3.00,-1.00], followed by (-5.00,-3.00] and the worst survival rates are those with slope ≤ -5.00. Approximately 15 % of the patients in slope category ≤ -5.00 did a CV event in comparison to the reference group, where nearly 90% did not.

Table 5 gives an overview of the hazards ratios (HR) and 95%-confidence interval per adjusted model stratified to eGFR slope. The HR of patients with a positive eGFR slope are all insignificant, where as the HR of the negative eGFR slopes are significant. The interpretation will be done for Model 2. Patients that have a slope ≤ -5.00 are 1.55 more likely to develop a CV event compared with those of (-1.00,1.00). Similar interpretations hold for the other groups as well. The adjusted HR increase with a declining negative eGFR slope, e.g. Model 2; 1.19 to 1.37 to 1.55. In other words, there is a probability of developing a CV event of respectively 54%, 58% and 61%. Adjusting for comorbidity (hypertension, diabetes and CV event in history) attenuates the HR per category, while still remaining significant for the negative eGFR slopes. Adjusting for baseline kidney function of the last measurement (Model 3) did not affect the hazard ratios of Model 2. Thereby indicating that this covariate is highly insignificant.

Table 3: Baseline characteristics of the study population on 01/01/2011

eGFR slope (in mL/min/year)	≤ - 5.00		(-5.00,-3.00]		(-3.00,-1.00]		(-1.00,1.00]		(1.00,3.00]		(3.00,5.00)		≥ 5.00	
	n=1598		*n=1433*		*n=2817*		*n=3731*		*n=3598*		*n=2765*		*n=3585*	
Age 50-59	299 (18.7%)		242 (16.9%)		481 (17.1%)		653 (17.5%)		762 (21.2%)		632 (22.9%)		959 (26.8%)	
Age 60-69	383 (24.0%)		389 (27.2%)		799 (28.4%)		1130 (30.3%)		1093 (30.4%)		917 (33.2%)		1157 (32.3%)	
Age 70-79	473 (30.0%)		447 (31.2%)		858 (30.5%)		1202 (32.2%)		1072 (29.8%)		792 (28.6%)		950 (26.5%)	
Age 80+	443 (27.8%)		355 (24.8%)		679 (24.1%)		746 (20.0%)		671 (18.7%)		424 (15.3%)		519 (14.5%)	
Female Gender	1048 (65.6%)		802 (56.0%)		1335 (47.4%)		1590 (42.6%)		1595 (44.3%)		1400 (50.6%)		2436 (68.0%)	
Diabetes	420 (26.3%)		302 (21.1%)		581 (20.6%)		699 (18.7%)		604 (16.8%)		446 (16.1%)		547 (15.3%)	
Hypertension	719 (45.0%)		601 (42.0%)		1197 (42.5%)		1491 (40.0%)		1305 (36.3%)		928 (33.6%)		1138 (31.7%)	
Baseline Kidney Function	*First*	*Last*	*First*	*Last*	*First*	*Last*	*First*	*Last*	*First*	*Last*	*First*	*Last*	*First*	*Last*
Category 1	1110 (69.5%)	590 (36.9%)	828 (57.8%)	519 (36.2%)	1270 (45.1%)	1001 (35.5%)	1378 (36.9%)	1434 (38.4%)	1175 (32.7%)	1724 (47.9%)	878 (31.8%)	1834 (66.3%)	1610 (44.9%)	3267 (91.1%)
Category 2	423 (26.5%)	604 (37.8%)	488 (34.1%)	606 (42.3%)	1236 (43.9%)	1322 (46.9%)	1941 (52.0%)	1878 (50.3%)	2074 (57.6%)	1717 (47.7%)	1713 (62.0%)	895 (32.4%)	1838 (51.3%)	310 (8.7%)
Category 3a	50 (3.1%)	214 (13.4%)	77 (5.4%)	191 (13.3%)	225 (8.0%)	325 (11.5%)	316 (8.5%)	325 (8.7%)	291 (8.1%)	132 (3.7%)	149 (5.4%)	34 (1.2%)	117 (3.3%)	6 (0.2%)
Category 3b	13 (0.8%)	127 (8.0%)	31 (2.2%)	86 (6.0%)	75 (2.7%)	129 (4.6%)	78 (2.1%)	79 (2.1%)	52 (1.5%)	22 (0.6%)	22 (0.8%)	2 (0.07%)	13 (0.4%)	1 (0.03%)
Category 4	2 (0.1%)	52 (3.3%)	9 (0.6%)	23 (1.6%)	8 (0.3%)	33 (1.2%)	15 (0.4%)	11 (0.3%)	4 (0.1%)	1 (0.03%)	3 (0.1%)	0 (0%)	4 (0.1%)	1 (0.03%)
Category 5	0 (0%)	11 (0.7%)	0 (0%)	8 (0.6%)	3 (0.1%)	7 (0.3%)	3 (0.1%)	4 (0.1%)	2 (0.1%)	2 (0.06%)	0 (0%)	0 (0%)	3 0.08%)	0 (0%)
# of patients with CV event in medical history(*)	411 (25.7%)		358 (25.0%)		628 (22.3%)		772 (20.7%)		622 (17.3%)		448 (16.2%)		459 (12.8%)	

Range: (up to and including), through]

Baseline kidney function:

- First = first eGFR measurement
- Last = last eGFR measurement

(*) Patients with following CV events in medical history: myocardial infarction (AMI, K75 and/or K76), acute heart failure (AHF, K77), cerebrovascular event (TIA, CVA, K89; K90) and periphery arterial disease (PAD, K92)

Abbreviations: CV = cardiovascular

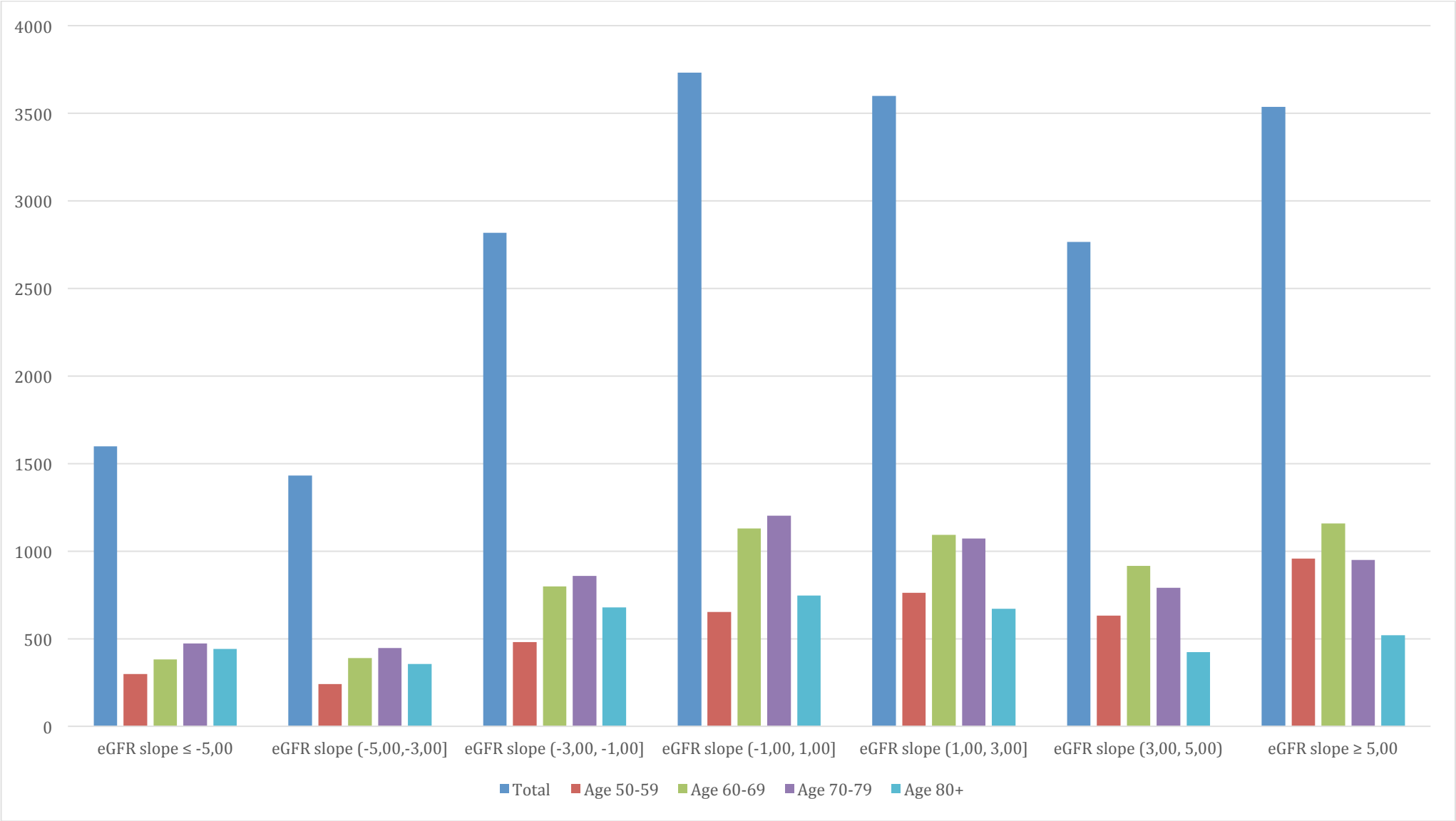

Figure 1: Overview of the number of patients per eGFR slope category. X-axis: eGFR slope category, Y-axis: number of patients.

Table 4: Number of people with a CV event and mean number of events, stratified to eGFR slope in follow-up period							
eGFR slope	**≤ - 5.00**	**(-5.00,-3.00]**	**(-3.00,-1.00]**	**(-1.00,1.00]**	**(1.00,3.00]**	**(3.00,5.00)**	**≥ 5.00**
	n=1598	*n=1433*	*n=2817*	*n=3731*	*n=3598*	*n=2765*	*n=3585*
Number of patients with CV events	*n*=192 (12.0%)	*n*=160 (11.2%)	*n*=272 (9.7%)	*n*=292 (7.8%)	*n*=249 (6.9%)	*n*=175 (6.3%)	*n*=193 (5.4%)
Mean number of CV events	225	173	302	319	278	187	216

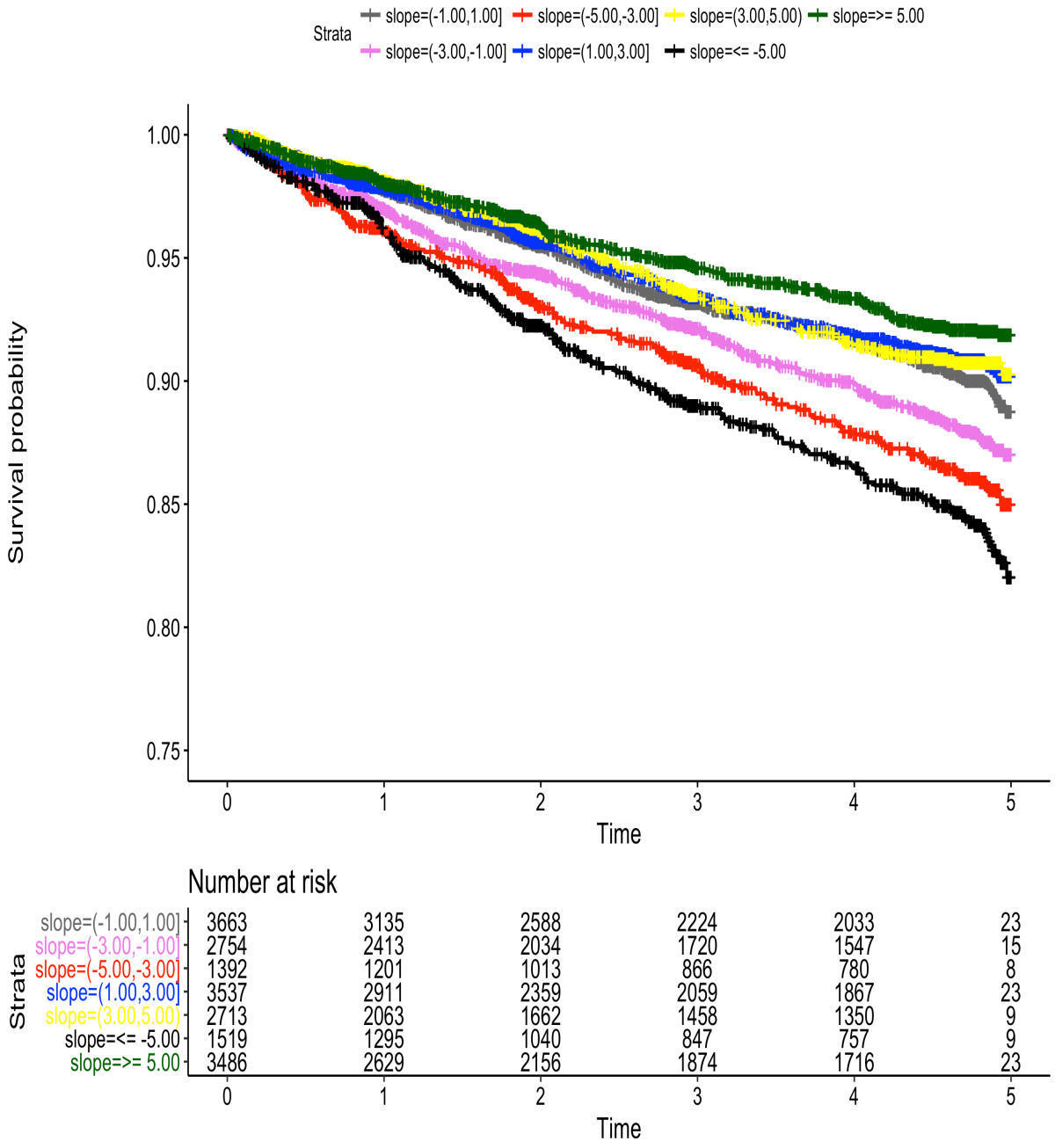

Figure 2: Estimates of survival probability in different years grouped by the "slope categories" and risk set table with number of patients at risk per year.

Table 5: Risk for an incident CV event during follow-up, hazard ratios (HR) and 95%-confidence intervals (95% CI) per eGFR slope category (in ml/min/y)

eGFR slope	≤ - 5.00	(-5.00,-3.00]	(-3.00,-1.00]	(-1.00,1.00]	(1.00,3.00]	(3.00,5.00)	≥ 5.00
HR Model1[1]	1.68 [1.40-2.02]	1.44 [1.19-1.75]	1.20 [1.02-1.42]	1.00	0.96 [0.81-1.14]	0.99 [0.82-1.19]	0.93 [0.78-1.12]
HR Model2[2]	1.55 [1.29-1.87]	1.37 [1.13-1.67]	1.19 [1.01-1.40]	1.00	0.99 [0.84-1.18]	1.02 [0.85-1.24]	1.00 [0.84-1.21]
HR Model3[3]	1.56 [1.29-1.87]	1.38 [1.13-1.67]	1.19 [1.01-1.41]	1.00	0.99 [0.84-1.17]	1.02 [0.84-1.23]	0.99 [0.82-1.21]

[1] *Adjusted for age and gender*
[2] *Adjusted for age, gender, hypertension, diabetes, and CV event history*
[3] *Adjusted for age, gender, hypertension, diabetes, CV event history and baseline kidney function (here is the last measurement)*

Discussion

eGFR Slope and Cardiovascular Events

We used a large population to examine if the eGFR slope over a 5-year period can give a subsequent worse cardiovascular outcome in the following 5 years. We found that patients with declining eGFR slope are more at risk to do a cardiovascular event than those with stable or rising eGFR slope. The survival rates of patients with eGFR slope of at least ≤ -3.00 ml/min/year are worse than the survival rates in other groups. These data suggest that eGFR slope can be prognostic for cardiovascular health.

Previous studies (6,12,13,15,16) already pointed out an increased mortality risk with declining kidney function. As to cardiovascular events, an increased risk is seen, but often is attenuated after adjustment. When we adjusted for the last eGFR measurement, no significant difference in hazard ratio was seen in contrast to the Turin study, which used a shorter time period and only three eGFR measurements. Hazards ratios for all-cause or cardiovascular mortality in these studies often had a U-shape, meaning both positive as negative eGFR slopes tend to have a higher mortality risk. We do not find this U-shape for cardiovascular events.

Strengths and Limitations

The strength of this study is that we used a large population with four eGFR measurements in different time periods, representative for the general practice. Another strong point is that we collected this data over 10 years and we made clear cut-off point on 1 January 2011, therefore using the first five years as predictor for the next five years. Other studies used a shorter time period for gaining eGFR values. There are some limitations though; we did not have any information about proteinuria, smoking and body mass index. Also there is some

variation as to the practices that are in the database; not all practices remain in it during the entire period. Further, the eGFR calculation by the MDRD equitation is insufficiently validated in the elderly population (80+). Finally, we did not calculate the variation between the eGFR measurements.

Recommendations

We think it is useful to imply the eGFR slope into the medical software program and create an alert to warn the GP when a declining eGFR of at least 3.00 ml/min/year is noticed and therefore is at risk for cardiovascular events. It contributes to the awareness of the GP more than personal intuition can do. The fact that approximately 70% of the slope category ≤ -5.00 had a normal kidney function at baseline is misleading and therefore deterioration of eGFR slope can be underestimated. Also further research is needed to see if this deterioration responds to treatment and if so, which treatments or preventive measures should be taken? Will slowing down the process of declining kidney function also diminish the incidence of cardiovascular events? For these reasons, an intervention study is needed that will assess these questions.

Conclusion

There is a correlation between eGFR slope and incident cardiovascular events. Negative eGFR slopes of at least – 3.00 ml/min/year give a higher risk of cardiovascular events than those with stable kidney function or improved kidney function.

Acknowledgments

I would like to thank Marjan van den Akker and Gijs Van Pottelbergh for their guidance. The INTEGO database was provided by Catholic University Leuven. Pavlos Mamouris did statistics on this paper.

Addendum

Figures and tables with age and gender distribution of the patients in JCG 2011

Figure 1 illustrates the age distribution of the patients in JCG 2011 and Table 1 the summary statistics. *Figure 2* illustrates the number of males and females for 2011. *Figure 3* illustrates the age distribution of these patients (≥ 50 years) in JCG 2011 and Table 2 the summary statistics. *Figure 4* depicts the number of males and females for 2011.

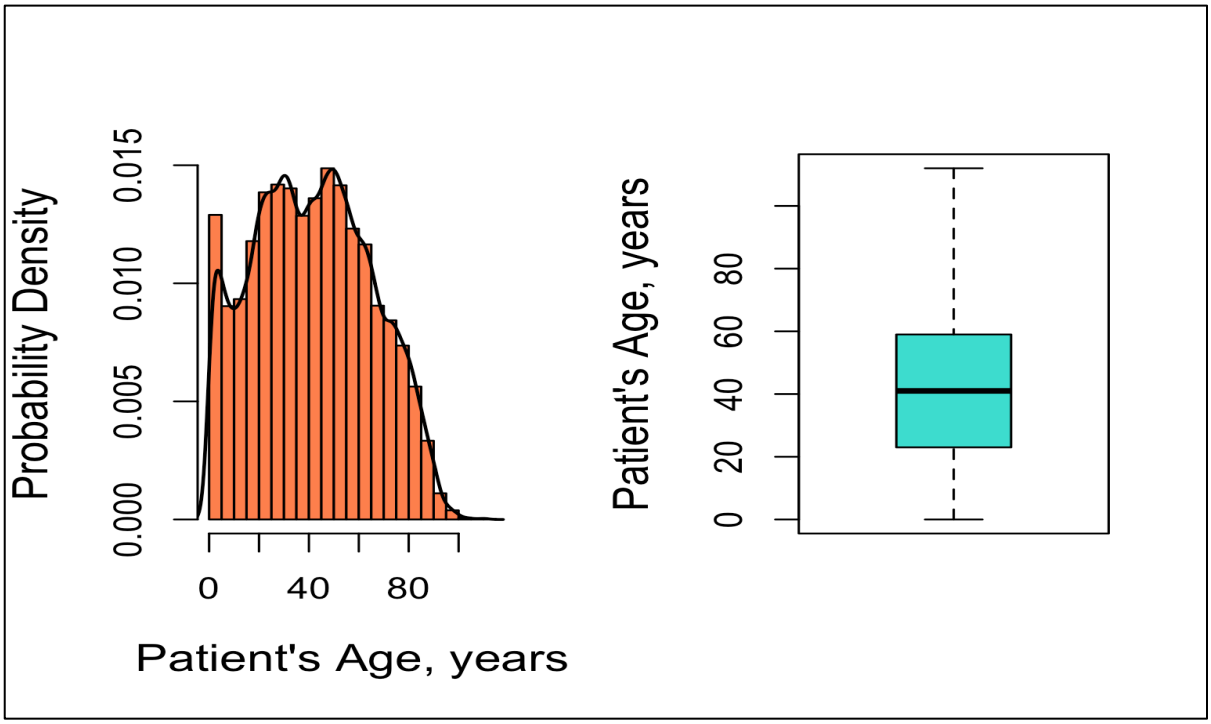

Figure 1: Age distribution of all people in JCG 2011

Table 1.1: Summary Statistics of age of all patients in JCG 2011

Statistics	Value
Mean	41.6
Standard Deviation	23.4
Median	41
Interquartile Range	36
Minimum	0
Maximum	112

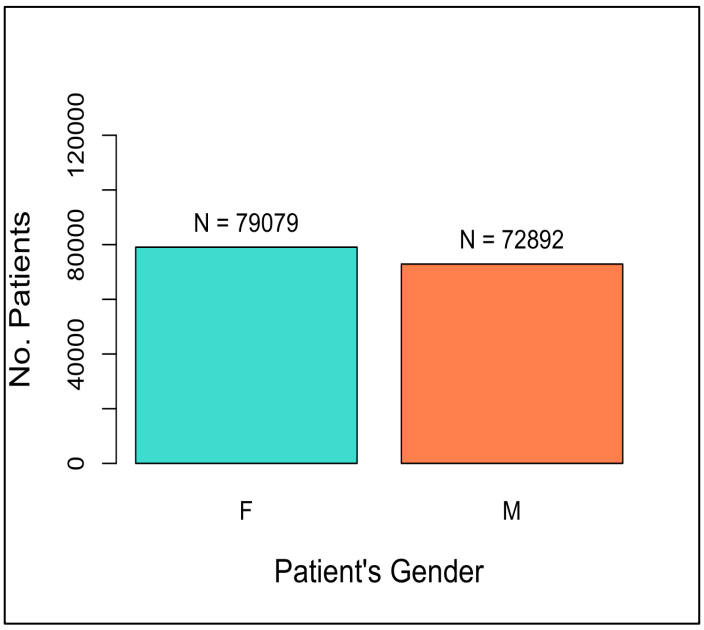

Figure 2: Gender category of all patients in JCG 2011

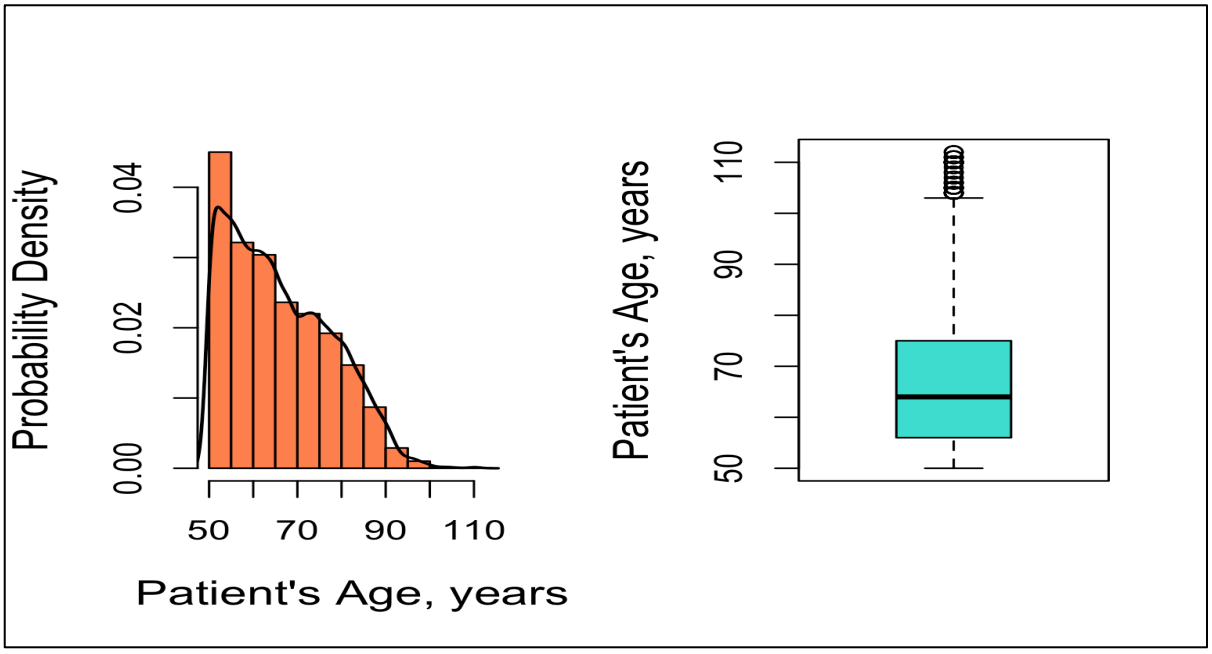

Figure 3: Age distribution of patients aged ≥ 50 years in JCG 2011

Table 1.2: Summary Statistics of age of patients aged ≥ 50 years in JCG 2011	
Statistics	**Value**
Mean	66.1
Standard Deviation	11.6
Median	64
Interquartile Range	19
Minimum	50
Maximum	112

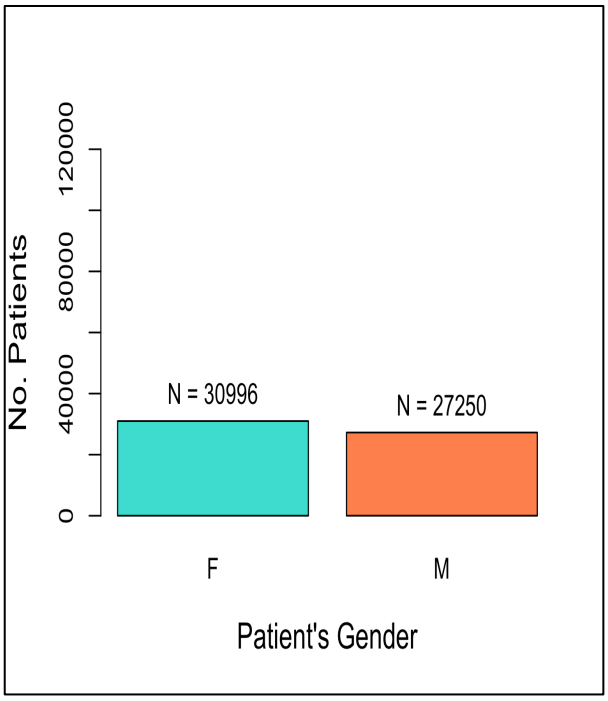

Figure 4: Age distribution of patients aged ≥ 50 years in JCG 2011

Background information for using the Cox proportional hazards model

The Cox proportional hazards model makes several assumptions. Thus, it is important to assess whether a fitted Cox regression model adequately describes the data. There are two main types of diagnostics for the Cox model:

i. Testing the proportional hazards assumption
ii. Examining influential observations (or outliers)

We will check each one of these model assumptions by using the residuals.

1. Testing the proportional hazards assumption

Table 1 describes the covariates and the variables that we are using in our final model and for this model we are checking the validity of the proportionality. The outcome variable is the time until the occurrence of an event of interest. In our case the event of interest is cardiovascular event and the survival time is the time in years until a person develops a cardiovascular event.

Table 2.1: Description of the covariates and the variables in the final Cox Model

Variables	Description
Age	Age of the patients in the baseline period[1] (>=50)
Gender	Whether the patient is a male or female
Hypertension	If a patient had hypertension before baseline
Diabetes	If a patient had diabetes before baseline
Cardiovascular Event History	If a patient had any Cardiovascular event before baseline (CVA/TIA, PAD, AHF, AMI)
Baseline kidney function	The egfr measurement the patient had before baseline
CV event	If the patient had the CV event after the baseline
Timeyear	The time in years starting at 01/01/2011 till 31/12/2015

[1]Baseline period defined as 01/01/2011

The proportional hazards (PH) assumption can be checked using statistical tests and graphical diagnostics based on the *scaled Schoenfeld residuals.* The statistical test is illustrated in Table 6 (Therneau and Grambsch, 2000). From the output below, the test is not statistically significant for each of the covariates, and the global test is also not statistically significant. Therefore, we can assume the proportional hazards.

Table 7: Formal test to check the proportional hazards assumption		
Variables	**chisq**	**p_value**
Slope_group	2.18074	0.1397
age	0.37293	0.5414
Gesl	0.00599	0.9383
hypertension	3.32448	0.0683
diabetes	3.94731	0.0469
CVeventhistory	0.28842	0.5912
Baseline_egfr	0.21076	0.6462
GLOBAL	11.10085	**0.1343**

The proportional hazard assumption is supported by a non-significant relationship between residuals and time, and refuted by a significant relationship. In principle, the *Schoenfeld residuals* are independent of time. A plot that shows a non-random pattern against time is evidence of violation of the PH assumption. Figure 6 plots these residuals against the covariates.

From the graphical inspection, there is no pattern with time. The assumption of proportional hazards appears to be supported for all the covariates.

2. Examining influential observations (or outliers)

To test influential observations or outliers, we can visualize the dfbetas, which depict the estimated changes in the coefficients divided by their standard errors. The index plots in Figure 7 show that comparing the magnitudes of the largest dfbeta values to the regression coefficients suggests that none of the observations is terribly influential individually. Thus, the outliers do not highly affect our analysis.

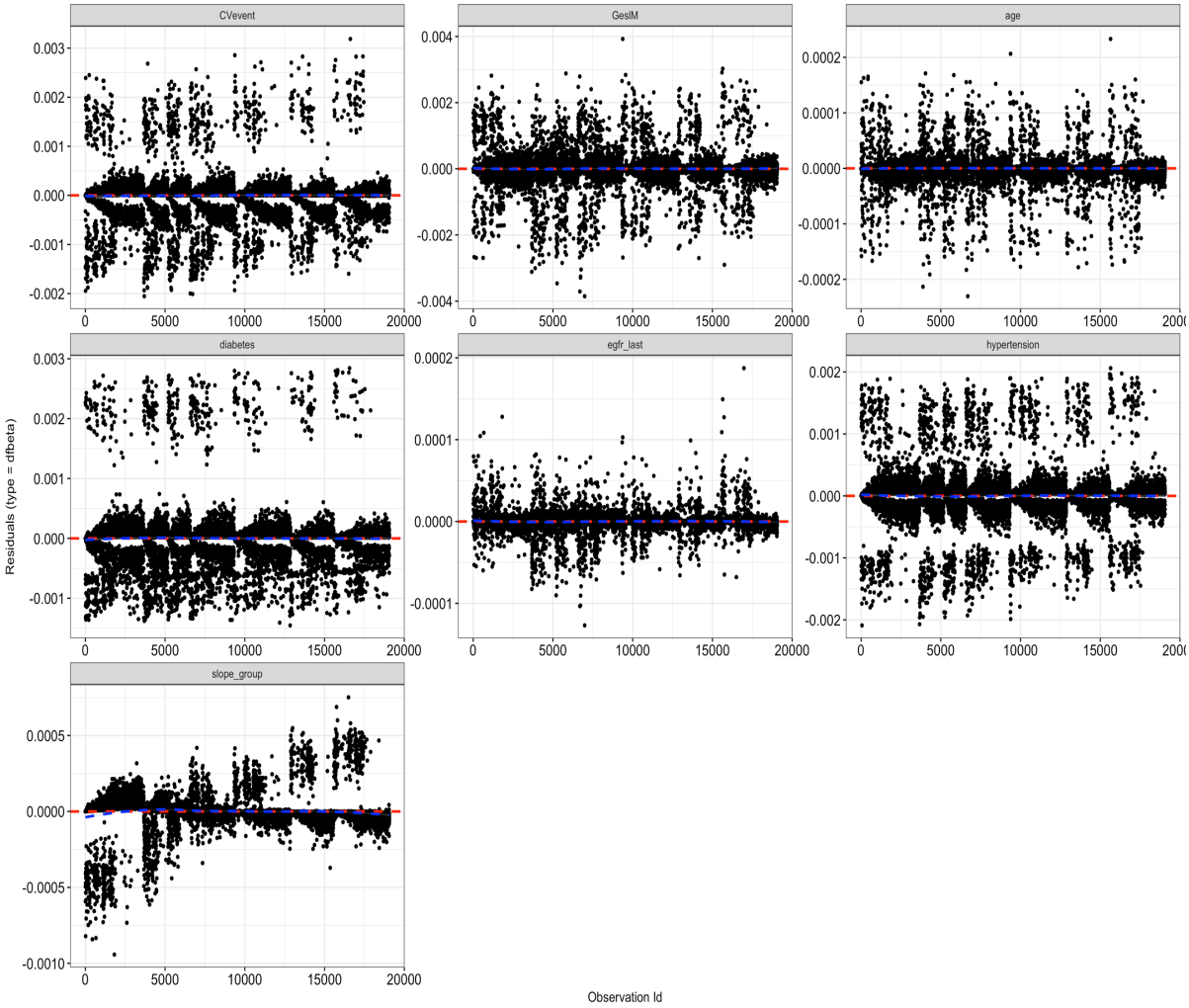

Figure 5: Plots of dfbetas to examine the influential observations

Protocol Ethical Committee

Gunstig advies van OBC 1

	Reg. nr.	Titel van de studie	Status	Beheer
	mp11647	Nierfunctieachteruitgang en cardiovasculaire morbiditeit **Student(en):** Nele Opdeweegh **Promotor:** Marjan van den Akker	Gunstig advies van OBC	

Gunstig advies van OBC

2016-03-23 17:25:29

Bekijk status geschiedenis

Student(en): Nele Opdeweegh
Promotor: Marjan van den Akker (marjan.vandenakker@med.kuleuven.be - u0067887 - Acad. Centr. voor Huisartsgeneeskunde)
Hoofdonderzoeker: Opdeweegh Nele
Faculteit: Geneeskunde
Opleiding: Master in de huisartsgeneeskunde (Leuven e.a.)
Het onderzoek is: monocentrisch
De opdrachtgever is: academisch (universiteit,...)
Het onderzoek is: Het onderzoek is uitsluitend retrospectief.

BIJKOMENDE GEGEVENS:

Achtergrond: Multimorbiditeit is de uitdaging van de 21ste eeuw. Door de toenemende vergrijzing worden deze patiënten ook meer en meer de zorg van de huisarts en dit vereist de nodige kennis. In deze masterpaper wordt de correlatie tussen nierfunctieachteruitgang en cardiovasculaire morbiditeit bekeken. Is er nood aan aangepaste richtlijnen voor patiënten met meerdere chronische/co-existerende aandoeningen? Aan de hand van de INTEGO-databank zal een analyse worden gemaakt van de beschikbare data (nierfunctie, cardiovasculaire events). Deze databank bevat epidemiologische gegevens afkomstig van huisartsen in Vlaanderen. Daarnaast worden ook de verschillende richtlijnen bekeken. Tot slot wordt in de praktijk bekeken hoe bovenstaande informatie kan toegepast worden op de patiënt.

Vraagstelling: **INTEGO databank:** retrospectieve data-analyse
Is er een correlatie tussen nierfunctieachteruitgang en cardiovasculaire events, rekening houdende met de medicatie, leeftijd en geslacht van de patiënt?
De nierfunctie zal biochemisch worden geëvalueerd op basis van creatininewaarden en eGFR. Vanaf een eGFR-waarde van minder dan 90 ml/min/1.73m2 is er sprake van lichte nierinsufficiëntie. Chronische nierinsufficiëntie wordt gedefinieerd als eGFR < 60 ml/min/1.73m2.
Er wordt nagegaan of nierfunctieachteruitgang een invloed heeft op het voorkomen van volgende cardiovasculaire events: hypertensie, hartfalen, acuut myocard infarct, TIA/CVA bij mannen en vrouwen vanaf 65 jaar.

Richtlijnen: literatuuronderzoek met zowel eerstelijnsrichtlijnen als gespecialiseerde richtlijnen
Wat staat er in de ziekte-specifieke richtlijnen inzake nierfunctieachteruitgang en cardiovasculaire events?
- Zijn er interacties?
  - Medicatie – medicatie
  - Ziekte – medicatie
  - Ziekte – ziekte
- Leidt het combineren van ziekte-specifieke richtlijnen tot conflicten in de behandeling?

Zowel richtlijnen bestemd voor eerstelijn als specialistische richtlijnen zullen bekeken worden.

Praktijk : toepassing op patiënten uit de praktijkpopulatie
Uitkomst van bovenstaande zal worden toegepast op patiënten uit de opleidingspraktijk. Alle patiënten ouder dan 65 jaar met een nierfunctiebepaling in het afgelopen jaar zullen geïncludeerd worden. Er wordt specifiek gekeken naar de groep met een eGFR waarde van minder dan 90 mL/min. In deze groep zullen we het aantal cardiovasculaire events bekijken per patiënt. Het bekijken van alle gegevens gebeurd uitsluitend op retrospectieve basis.

Methodologie: INTEGO-databank: reeds goedkeuring
Patiënten uit eigen praktijk:
- opvragen eGFR-waarden van patiënten (indien aanwezig) via labo
- bekijken cardiovasculaire events
- toetsen kennis uit deel I en deel II van de masterthesis

Referenties:

Informed consent / vragenlij...

References

1. Weinstein JR, Anderson S. THE AGING KIDNEY: PHYSIOLOGICAL CHANGES. Adv Chronic Kidney Dis [Internet]. 2010;17(4):302–7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2901622/
2. S. GA, M. CG, Dongjie F, E. MC, Chi-yuan H. Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. N Engl J Med [Internet]. 2004;351(13):1296–305. Available from: http://www.nejm.org/doi/full/10.1056/NEJMoa041031
3. Manjunath G, Tighiouart H, Coresh J, Macleod B, Salem DN, Griffith JL, et al. Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. Kidney Int. 2003;63(3):1121–9.
4. Van Pottelbergh G, Avonts M, Goossens M, Maes S, Van Heden L, Van Royen P. Chronische nierinsufficiëntie: Richtlijn voor goede medische praktijkvoering. Domus Medica. 2012;1–24.
5. Van Heden L, Maes S, Van Pottelbergh G, Bartholomeeusen S, Degryse J. Chronische nierinsufficiëntie in de Vlaamse huisartsenpraktijk. Huisarts Nu. 2008;4(37):208–12.
6. H. HT. Chronic Kidney Disease Predicts Cardiovascular Disease. N Engl J Med [Internet]. 2004;351(13):1344–6. Available from: http://www.nejm.org/doi/full/10.1056/NEJMe048211
7. Van Pottelbergh G, Bartholomeeusen S, Buntinx F, Degryse J. The evolution of renal function and the incidence of end-stage renal disease in patients aged ≥ 50 years. Nephrol Dial Transpl [Internet]. 2012;27(6):2297–303. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22102615
8. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med. 2004;351(13):1285–95.
9. Shlipak MG, Katz R, Kestenbaum B, Siscovick D, Fried L, Newman A, et al. Rapid Decline of Kidney Function Increases Cardiovascular Risk in the Elderly. J Am Soc Nephrol [Internet]. 2009;20(12):2625–30. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2794238/
10. Razavian M, Heeley EL, Perkovic V, Zoungas S, Weekes A, Patel AA, et al. Cardiovascular risk management in chronic kidney disease in general practice (the AusHEART study). Nephrol Dial Transpl. 2012;27(4):1396–402.
11. Vaes B, Beke E, Truyers C, Elli S, Buntinx F, Verbakel JY, et al. The correlation

between blood pressure and kidney function decline in older people: a registry-based cohort study. BMJ Open. 2015;5(6):e007571.

12. Van Pottelbergh G, Den Elzen WP, Degryse J, Gussekloo J. Prediction of mortality and functional decline by changes in eGFR in the very elderly: the Leiden 85-plus study. BMC Geriatr. 2013;13:61.
13. Naimark DM, Grams ME, Matsushita K, Black C, Drion I, Fox CS, et al. Past Decline Versus Current eGFR and Subsequent Mortality Risk. J Am Soc Nephrol. 2016;27(8):2456–66.
14. Turin TC, Coresh J, Tonelli M, Stevens PE, de Jong PE, Farmer CK, et al. Change in the estimated glomerular filtration rate over time and risk of all-cause mortality. Kidney Int. 2013;83(4):684–91.
15. Turin TC, Jun M, James MT, Tonelli M, Coresh J, Manns BJ, et al. Magnitude of rate of change in kidney function and future risk of cardiovascular events. Int J Cardiol [Internet]. 2016;202:657–65. Available from: http://www.sciencedirect.com/science/article/pii/S0167527315305313
16. Rifkin DE, Shlipak MG, Katz R, et al. Rapid kidney function decline and mortality risk in older adults. Arch Intern Med [Internet]. 2008;168(20):2212–8. Available from: http://dx.doi.org/10.1001/archinte.168.20.2212
17. Cheng T-YD, Wen S-F, Astor BC, Tao X, Samet JM, Wen CP. Mortality Risks for All Causes and Cardiovascular Diseases and Reduced GFR in a Middle-aged Working Population in Taiwan. Am J Kidney Dis [Internet]. 52(6):1051–60. Available from: http://dx.doi.org/10.1053/j.ajkd.2008.05.030
18. Matsushita K, Selvin E, Bash LD, Franceschini N, Astor BC, Coresh J. Change in estimated GFR associates with coronary heart disease and mortality. J Am Soc Nephrol. 2009;20(12):2617–24.
19. Truyers C, Steven E, Goderis G, Buntinx F. 20 jaar Huisartspraktijk in Vlaanderen. Acco; 2015.