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Complete List of Authors:	Van den Wyngaert, Ine; KU Leuven, Department of Public Health and Primary Care Mamouris, Pavlos; Katholieke Universiteit Leuven Groep Biomedische Wetenschappen, Departement of Public Health and Primary Care Ali, Endale Alemayehu; KU Leuven, Department of Public Health and Primary Care Vaes, Bert; KU Leuven, Departement of Public Health and Primary Care; Université Catholique de Louvain (UCL), Institute of Health and Society Van Pottelbergh, Gijs; Katholieke Universiteit Leuven Groep Biomedische Wetenschappen, Departement of Public Health and Primary Care
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Impact of under-registration of chronic kidney disease on mortality and cardiovascular outcome: a time-to-event analysis

Ine Van den Wyngaert*[1], Pavlos Mamouris[1], Endale Alemayehu Ali[1], Bert Vaes[1] and Gijs Van Pottelbergh[1]

[1]Academic Centre for General Practice, Department of Public Health and Primary Care, University of Leuven, Leuven, Belgium.

*Corresponding author

E-mail: ine.vandenwyngaert@kuleuven.be

Abstract

Background and objective

Patients with impaired kidney function and increased albuminuria are at risk of developing cardiovascular disease. Previous research revealed that a substantial proportion of patients with chronic kidney disease do not get a registered diagnosis in the Electronic Health Record of the general practitioner. The aim of this study was to investigate the association between under-registration of chronic kidney disease and/with all-cause mortality and cardiovascular outcome.

Design and setting

A retrospective study in primary care.

Methods

The analyses were carried out in the INTEGO database, a general practice-based morbidity registration network in Flanders, Belgium. The study used INTEGO data from the year 2018 for all patients ≥18 years old, including 10551 patients. To assess the risk of mortality and cardiovascular disease, a time-to-event analysis was performed. Cox proportional hazard model was used to evaluate the association between under-registration and incidence of all-cause mortality and cardiovascular events with mortality as a competing risk. Subgroup analyses were performed for estimated glomerular filtration rate stages (3a, 3b, 4 and 5). Multiple imputation was done following the methodology of Mamouris et al.

Results

Mortality was higher in patients with unregistered chronic kidney disease compared to patients with registered CKD (HR 1.29, 95%-CI [1.19-1.41]). Under-registration of chronic kidney disease did not show a higher risk to develop cardiovascular disease (HR 0.92, 95%-CI [0.77-1.11]).

Conclusion

An association between under-registration and all-cause mortality could be found, although this did not appear to be the case for cardiovascular disease.

Strengths and limitations of this study

- To assess the risk of CVD and mortality, Cox-proportional hazard models were used and a competing risk analysis was performed to account for the presence of competing event (mortality).
- For the missing variables, we used multiple imputation.
- The presence of proteinuria was not taken into account in our CKD population due to the lack of data on proteinuria.
- The study used healthcare data which may underrepresent the healthy and asymptomatic that do not seek healthcare.
- Although the patient population is representative for the Flemish population, registering GPs are not representative for the GP population. It is a selected group of high quality registering practitioners which use a specific electronic health record.

Keywords: cardiovascular, chronic renal failure, mortality, survival analysis, under-registration

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Introduction

Chronic kidney disease (CKD) is a progressive condition that describes the gradual loss of kidney function over time. A reduced estimated glomerular filtration rate (eGFR) and elevated albuminuria are the two key measures in patients with CKD [1]. Multiple studies have documented suboptimal albuminuria testing in CKD patients in primary care [2, 3]. However, both reduced eGFR and the presence of albuminuria are associated with an increased risk of cardiovascular disease (CVD), hospitalisation and premature death [4-9]. The most common causes of CKD in high-income and middle-income countries are glomerulonephritis, diabetes mellitus and hypertension (the latter being also a consequence of CKD) [10-12]. The increased cardiovascular risk (CVR) in patients with CKD was therefore assumed to be the result of these underlying diseases. However, meta-analyses showed that impaired kidney function and increased albuminuria are CVR factors, independently of the presence of hypertension or diabetes mellitus [6, 13]. Kidney specific mechanisms that make significant contributions to the CVR were documented [4].

Previous research revealed that a substantial proportion of patients did not have a registered CKD diagnosis in the general practitioner's (GP) Electronic Health Record (EHR) [14, 15]. In addition, mainly patients with early-stage CKD (stage 3) remained without official diagnosis [15]. Although we know that patients with CKD are more at risk, the impact of not registering a diagnosis has not been investigated, neither on cardiovascular outcome nor on mortality [4-6].

The aim of this study was to evaluate the impact of under-registration on all-cause mortality and cardiovascular outcome in Flanders, Belgium.

Materials and Methods

Study setting and data source

This study was conducted following on from previous work [15]. In that research, the prevalence of unregistered CKD, the diagnostic delay (time between abnormal eGFR and diagnosis) and the baseline characteristics of the unregistered patient group were examined in a Belgian GP population. The same study population was used.

The analyses were carried out in the INTEGO database, a general practice-based computerised morbidity and mortality registration network in Flanders, Belgium, managed at the Department of General Practice of the University of Leuven since 1994. Data collection is regulated by an opting-out procedure. INTEGO procedures were approved by the ethical review board of the Medical School of KU Leuven (N° ML 1723) and by the Belgian Privacy Commission (no SCSZG/13/079). More than 100 GP centres applied for inclusion in this registry. Only the data of the 86 practices (representing 454 GPs) with optimal registration performance (80% coded diagnoses) were included in the database. Patient characteristics and diagnoses are encoded and classified using the International Classification of Primary Care (ICPC-2; WHO FIC Collaborating Centre). All laboratory tests performed by GPs are included in the database.

The methodology of data collection, study design, and analyses in the INTEGO registry have been previously reported [16].

Study population

Guidelines for CKD management recommend that patients should be diagnosed with CKD if the reduction in kidney function (eGFR <60 mL/ min/1.73 m^2) is present for more than three months [1, 17, 18]. All patients ≥18 years old with two consecutive eGFR laboratory measurements indicating CKD (eGFR <60 mL/min/1.73m^2) recorded >90 and ≤730 days apart during the baseline period were included. The current study used INTEGO data from the year 2018. Selected patients had at least one eGFR measurement <60 mL/min/1.73m^2 in 2018 and belonged to the GP's yearly contact group. There must be at least 12 months of continuous presence in the database prior to the first qualifying eGFR. Patients were excluded if they had a solid kidney transplant (ICD-10 Z94.0) before the date of the second qualifying eGFR (index date).

Unregistered CKD case definition

Patients with unregistered CKD were identified if they had no diagnostic CKD code for any time during the ≥12-month lookback period before the first eGFR measurement and up to 6 months post-index date. ICPC-2 codes are used more frequently in general practice than ICD-10, so we chose to

use the ICPC-2 code U99. Those with a documented U99 during this time period were considered as having registered CKD. Since the U99 code is a collective code for unspecified kidney disease - like chronic kidney disease, renal cyst - we manually checked both the code and the written diagnosis whether the code did merge with CKD. It was assumed that patients with at least one diagnostic code for CKD during the above specified time window had registered CKD.

Statistical analysis

R software (version 4.0.4) was used [19]. A descriptive analysis was performed, calculating incidences of all-cause mortality, myocardial infarction, stroke, peripheral vascular disease and heart failure among those with registered versus unregistered CKD. The follow-up period for these adverse clinical outcomes started six months after the index date until observation end date (follow-up end date or end of data coverage up to 17/07/2023, whichever came first). The variables were summarised using patient counts with percentages. The chi-square was calculated. P values less than 0.05 were considered significant. Subgroup analyses were performed for eGFR stages (3a, 3b, 4 and 5) and visualised using Kaplan-Meier curves.

To assess the risk of CVD and mortality, Cox-proportional hazard models were used. A competing risk analysis was performed to account for the presence of competing event (mortality) [20]. We estimated the hazard and sub-distribution hazard ratios (HRs and sHRs) and their 95% confidence interval (CI). P values less than 0.05 were considered significant. We adjusted for all possible confounders (age, gender, hypertension, diabetes, smoking status, hypercholesterolemia, history of CVD). We fitted the models by including and excluding covariates one-by-one (sequential method) and we did not find significant change in the estimate and significance of covariates which were already in the model after adding new covariate. We calculated the Variance Inflation Factor to check for multicollinearity [21].

Variables were chosen based on the risk factors for CVD, defined by the Framingham Heart Study [22]. Cardiovascular events were defined as myocardial infarction (ICPC-2 K75), stroke (ICPC-2 K90), peripheral vascular disease (ICPC-2 K92) and heart failure (ICPC-2 K77). Hypertension or hypercholesterolemia included patients with a diagnosis of hypertension (ICPC-2 K86) or hypercholesterolemia (ICPC-2 T93) in the EHR. Antihypertensive, lipid lowering and antidiabetic medication were defined by the ATC-codes. (Supplemental file 1) Patients with a diagnosis of diabetes type 1 or 2 in the EHR (ICPC-2 T89 and T90) and patients taking antidiabetic drugs were merged into the diabetes group. Since there was multicollinearity between total cholesterol, HDL and LDL, we chose to include total cholesterol.

For the missing variables, we used the methodology developed by Mamouris et al [23]. Concisely, in their work, they developed a 3-stage approach to impute longitudinal covariates so as complexities such as convergence and collinearity are resolved [23]. We imputed Body Mass Index (BMI), total cholesterol, systolic blood pressure (SBP) and smoking status longitudinally for years 2017-2023, thus utilising the previous and earlier information of the same patient. (Supplemental file 2) We then extracted the observed year 2018. The dataset was imputed 20 times and model analysis was performed for each imputation separately. We finally pooled the results together using Rubin's rules [24].

Results

As reported in our first research, 231 702 patients ≥18 years old were detected in the INTEGO database in 2018. (Supplemental file 3) Since the general practice didn't meet the criteria for best quality register, 40 216 patients were excluded. Among included patients, there were 10 551 patients (5.5%) with two consecutive eGFR laboratory measurements indicating chronic kidney disease (CKD) (eGFR <60 mL/min/1.73m2), recorded at least three months apart during the baseline period. Out of them, 7176 patients (68%) had no U99 at any time. The other 3375 patients (32%) had a registered diagnosis [15].

Descriptive analysis

Incidences

Incidences of all-cause mortality, myocardial infarction, stroke, peripheral vascular disease and heart failure associated with CKD diagnosis status as of index date, are being displayed in table 1.

Strata analyses

Figure 1 and 2 respectively display the differences in survival time and time to development of CVD in patients with CKD, according to the CKD stage and presence of diagnostic code in the EHR. An informative risk set table shows the number of patients who were under observation and at risk in the specific period. It appeared that registered patients in stage 3B and 4 had a much better survival rate than unregistered patients after 3 years of follow-up, namely 82.23% (registered group, stage 3B) and 72.87% (registered group, stage 4) towards 73.05% (unregistered group, stage 3B) and 59.52% (unregistered group, stage 4). (Figure 1) The same difference was documented for CKD stage 5 after 1 year of follow-up. In the registered group, 87.88% survived at that time, towards 76.09% of the unregistered patients. Only a small number of stage 5 patients were still under observation after 3 years of follow-up, making it difficult to interpret the results at that time. (Figure 1) Similar survival curves were reported in both registered and unregistered in stage 3A.

Similar to the findings for mortality, less registered patients in stage 5 developed CVD compared to unregistered stage 5 patients after 1 year of follow-up (morbidity rate 98.99% in the registered group, towards 95.65% in the unregistered group). (Figure 2) In stage 3B and 4 were the differences in morbidity rate between registered and unregistered smaller after 3 years of follow-up compared to what we documented for mortality, respectively 93.80% (registered, stage 3B and 4) compared to 93.28% (unregistered, stage 3B) and 95.24% (unregistered, stage 4). As for mortality, stage 3A showed similar results curves for unregistered and registered.

Time to event-analysis

Figure 3 and 4 respectively show the time to the occurrence of death or CVD with mortality as a competing risk. Results for analyses with and without mortality as a competing risk were similar.

All-cause mortality analysis showed that patients with unregistered CKD, male gender, age ≥65, diabetes, CKD stage 3B-5, history of CVD and (ex-)smokers had a higher chance of dying. Hypertension and hypercholesterolemia were protective factors, as was the use of antihypertensive and lipid lowering medication and BMI. The values for smoking and hypercholesterolemia were not statistically significant. The HR for total cholesterol was equal to 1.

Considering the results for CVD, only age ≥65, hypertension, antihypertensive medication, CKD stage 3B, BMI, total cholesterol and history of CVD were statistically significant. The sub-distribution hazard ratio (sHR) for unregistered CKD was <1. A history of CVD and hypercholesterolemia seemed to be protective factors for CVD, while patients with hypertension had an increased risk.

Discussion

Principal findings

This study showed that patients with a properly registered diagnosis die less quickly than unregistered ones. However, according to our results, these patients did not appear to have a lower risk to develop CVD. Besides, patients in stage 3B and 4 with a registered diagnosis had much better mortality survival rates compared to the unregistered ones. The association of under-registration and CVD was less clear in the different CKD stages.

Patients with CKD and hypercholesterolemia showed to be less associated with CVD and mortality, although the result was not statistically significant. In contrast, hypertensive CKD patients appeared to have a higher risk of CVD, but a lower risk of mortality. Patients with a history of CVD seemed to have a lower risk of new events, but a higher risk to die.

Context of the results

Under-registration appears to be associated with all-cause mortality. However, the CaReMe CKD study recently showed that the rates of cardiovascular and all-cause death were 31-49% higher in registered CKD patients than in measured CKD patients, which could not be confirmed in our study [25]. Few research has been conducted in this regard, making it difficult to compare.

The key research question of our results is what caused patients to die. Previous research showed that a reduced kidney function predicts both cardiovascular and non-cardiovascular mortality due to pulmonary disease, infection, cancer, and other causes [26-28]. The association between a reduced eGFR and the increased risk of cardiovascular events and hospitalisation was also found [9, 12, 29]. Surprisingly, the unregistered group in our study did not have a higher risk of CVD than the registered. It is unclear why no association was found. Possibly, this group died more frequently as a result of non-CVD. On the other hand, under-registration probably extends beyond renal insufficiency and also occurs with other pathologies. Mata-Casas et al. reported under-registration of diabetes mellitus in Spanish primary health care [30]. Cardiovascular diagnosis may also be under-registered, so that no association with under-registration could be found [31].

A second important question remains why the difference in mortality outcome was found between registered and unregistered patients. Is the root of the problem with the GP or the patient? Our previous research showed that there were small differences between registered and unregistered patients at baseline [15]. Hypertension was more frequently present in the registered (64.4% of the registered population) compared to the unregistered (51.7% of the unregistered population). Similar results were found for type 2 diabetes (33.1%) of the registered compared to 28.2% of the

unregistered). Small differences were also noticeable in the use of ACE-I or ARB (52.6% among the registered compared to 46.3% of the unregistered) [15]. However, these small differences do not seem to provide an adequate explanation for the difference in mortality, partly in view of the result that the unregistered group had no higher risk of CVD.

Subsequently, the follow-up of these patients should be assessed. A possible explanation for the difference in mortality between registered and unregistered groups could be that less attention was paid while prescribing and dispensing nephrotoxic (over-the-counter) medication by the GP and pharmacist, resulting in further deterioration of kidney function. There may have been less attention to the CVR factors associated with impaired renal function. In that case, we also would have expected an increase in CVD, unless, as previous described, it concerns a problem of global under-registration. On the other hand, the responsibility of the patient in the follow-up of the disease must be brought to attention. Possibly, the unregistered group contained a large proportion of patients who were not adherent to follow-up and therapy, as a result of which some did not or belatedly encountered problems. So, it is becoming increasingly important to examine these hypotheses and to involve the patient in his care and to find out what view he has in this regard [32, 33].

According to our research results, hypertension in CKD patients would be a risk factor in the development of CVD, although a protective factor in the development of all-cause mortality. Though, we know from previous research that hypertension is a risk factor for the development of CVD and premature death [34-36]. The reasons for this difference are unclear. We need to consider the effect of antihypertensive medication on this outcome, since 48% of the patients took an Angiotensin-converting-enzyme-inhibitor (ACE-I) or an Angiotensin Receptor Blocker (ARB) [15]. The beneficial effect of these drugs on cardiovascular events and all-cause mortality has been confirmed in the past [37]. Ettehad et al. described that in patients with CKD smaller risk reductions in cardiovascular events were seen as a result of antihypertensive medication than in patients without CKD [38]. However, we should also keep in mind that there may be under-registration of hypertension and SBP.

Additionally, it is surprising that hypercholesterolemia and total cholesterol do not show a higher risk on CVD and mortality, since this is a proven risk factor for CVD [22]. However, this result was not significant and may be explained by the use of lipid lowering medication, as 45% of patients were on this medication at baseline [15]. After all, Fabbian F. et al. determined that statins are an effective treatment in CKD patients, especially in the early stages of the disease [39]. A history of CVD appears to be a protective factor in the development of new CVD, of which a properly adjusted therapy can be the reason (secondary prevention) [39, 40]. In addition, we know that CKD is associated with adverse outcomes in those with existing CVD, which includes increased mortality after an acute coronary syndrome [41-43].

In our previous work, we found that the majority of patients with renal insufficiency were in stage 3, with a higher proportion registered in stage 5 (75.7% registered) compared to stage 3a (22.9% registered) [15]. However, this study showed major differences in survival rates between registered and unregistered patients in both the earlier (3B) and further stages (4 and 5) of renal failure. The importance of early detection has been described many times in the past [17, 44]. This research must therefore be a plea for early detection of CKD and registration of the diagnostic code in the EHR. A solution to detect unregistered patients can be found in an Audit-& Feedback system, since this has proven to be effective and to have added value in primary care [45, 46].

Limitations

There were some limitations to note. First, we did not take the presence of proteinuria into account in our CKD population. Mainly due to the lack of data on proteinuria, which brings us straight to the problem of under detection of proteinuria in the Flemish general practice.

Subsequently, the study used healthcare data which may underrepresent the healthy and asymptomatic that do not seek healthcare. The data of care refusers were included in the research results.

Although the patient population is representative for the Flemish population, registering GPs are not representative for the GP population. It is a selected group of high quality registering practitioners which use a specific electronic health record. This selection bias of GPs could eventually have an influence on some process parameters in the follow-up of patients [16]. In addition, data collected in a real-world setting may lack information on specific covariates and laboratory investigations. Lab results from the hospital and specialists are automatically entered into the EHR, but their diagnoses are not. We used multiple imputation to fill in the missingness (see method section).

Conclusion

An association between under-registration and all-cause mortality could be found, although this did not appear to be the case for CVD. Patients in stage 3B and 4 CKD with a registered diagnosis had much better survival rates compared to the unregistered ones. It is unclear whether better registration will lead to a better outcome, which means that the differences between the patient groups must be further mapped out.

Data availability statement: All data generated or analysed during this study are included in this published article [and its supplementary information files].

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Authors contributions: IVDW, PM, BV and GVP designed and conceptualized the study. EAA and PM performed the data analysis. IVDW drafted the manuscript. IVDW, EAA, PM, BV and GVP revised the manuscript. IVDW and GVP are the guarantors of this work. All authors read and approved the final manuscript.

Competing interests statement: None declared.

Patient and public involvement: Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

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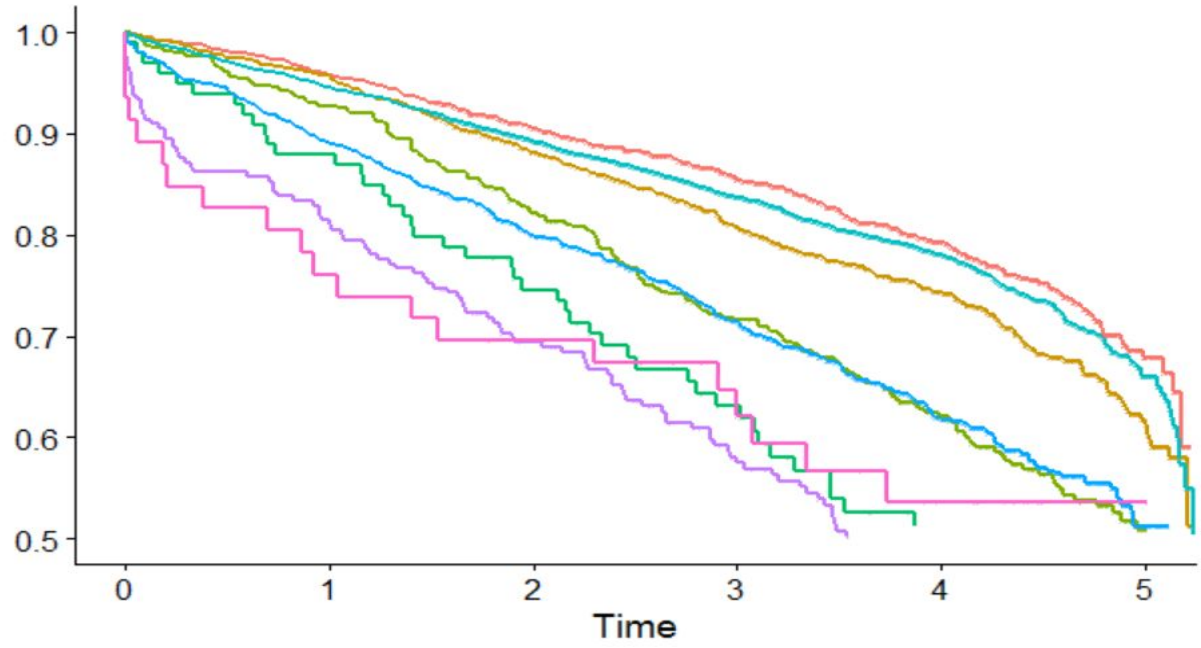
Table + table legend:

Variable	Registered CKD, n(%)	Unregistered CKD, n(%)	Total CKD, n(%)	P-value
Total patients	3375	7176	10551	
All-cause mortality, n (%)	460(13.6)	820(11.4)	1280(12.1)	0.033
Myocardial Infarction, n (%)	28(0.8)	35(0.5)	63(0.6)	0.067
Stroke, n (%)	70(2.1)	113(1.6)	183(1.7)	0.089
Peripheral Vascular Disease, n (%)	52(1.5)	82(1.1)	134(1.3)	0.004
Heart Failure, n (%)	188(5.6)	308(4.3)	496(4.7)	0.001

Table 1. Cardiovascular outcome associated with registration status.

Figures + figure legends:

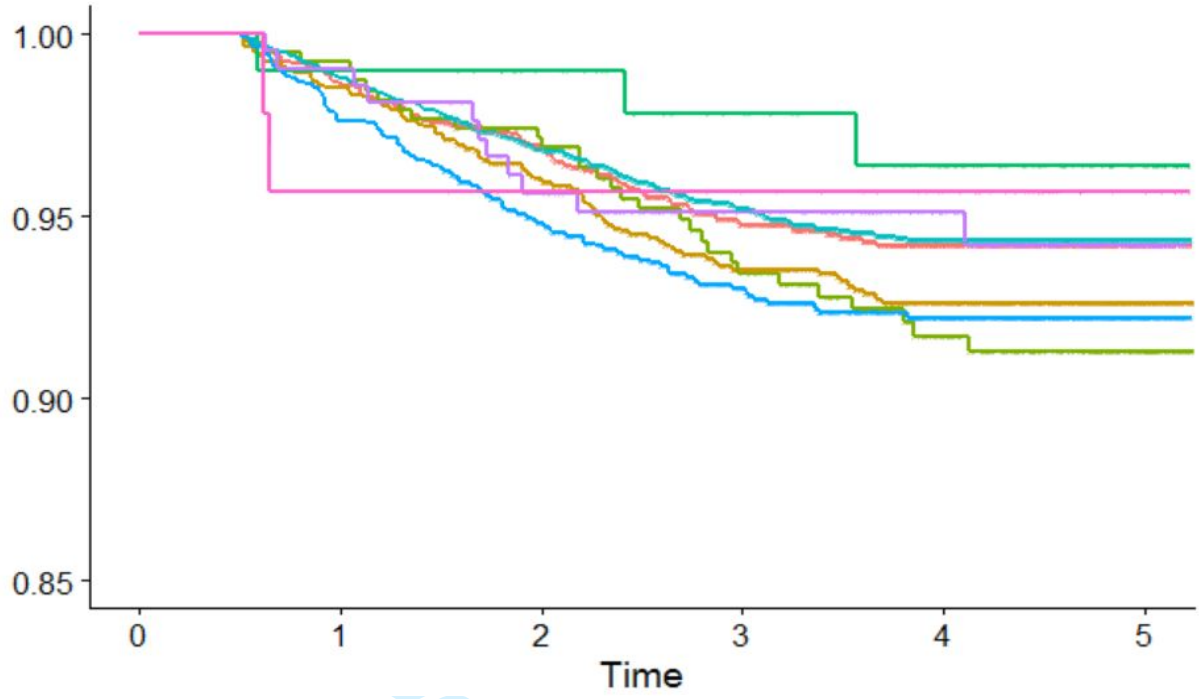


Number at risk

Registered CKD, stage 3A	1679	1608	1406	1085	640	77
Registered CKD, stage 3B	1210	1157	1021	831	585	117
Registered CKD, stage 4	387	358	308	245	170	46
Registered CKD, stage 5	99	87	70	51	33	14
Unregistered CKD, stage 3A	5699	5386	4601	3213	1604	155
Unregistered CKD, stage 3B	1221	1086	925	704	393	46
Unregistered CKD, stage 4	210	170	137	99	64	18
Unregistered CKD, stage 5	46	35	31	23	16	4
	0	1	2	3	4	5

Time (years)

Figure 1. Strata analysis for mortality. Survival probability in different years grouped by CKD stage and presence of diagnostic code. Risk set table with number of patients at risk per year.



Number at risk

Registered CKD, stage 3A	1679	1656	1500	1186	723	89
Registered CKD, stage 3B	1210	1192	1105	936	678	150
Registered CKD, stage 4	387	384	360	310	231	74
Registered CKD, stage 5	99	98	90	75	60	25
Unregistered CKD, stage 3A	5699	5631	4971	3593	1840	190
Unregistered CKD, stage 3B	1221	1192	1088	894	558	73
Unregistered CKD, stage 4	210	208	187	149	111	29
Unregistered CKD, stage 5	46	44	41	35	27	9
	0	1	2	3	4	5

Time (years)

Figure 2. Strata analysis for cardiovascular disease. Morbidity probability in different years grouped by CKD stage and presence of diagnostic code. Risk set table with number of patients at risk per year.

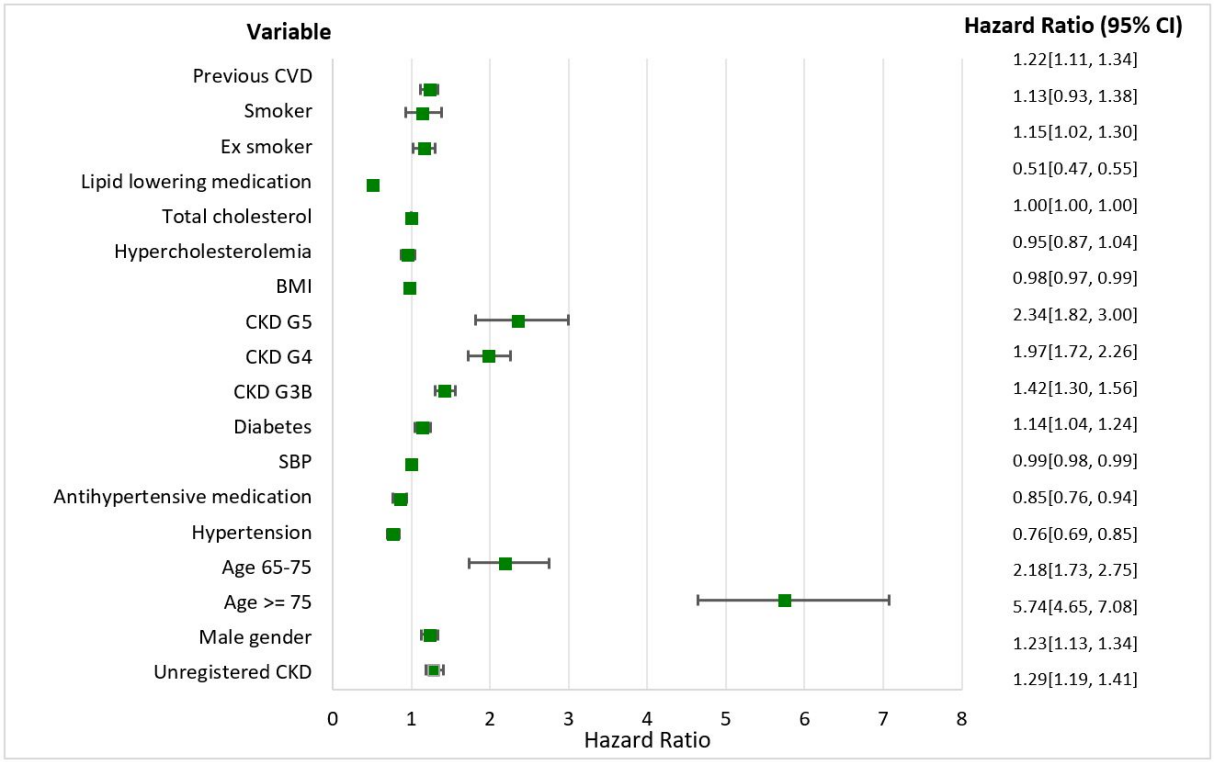


Figure 3. Mortality and time to event. HRs and the 95% confidence interval (95% CI) for different variables. Systolic blood pressure (SBP), Body Mass Index (BMI), cardiovascular disease (CVD)

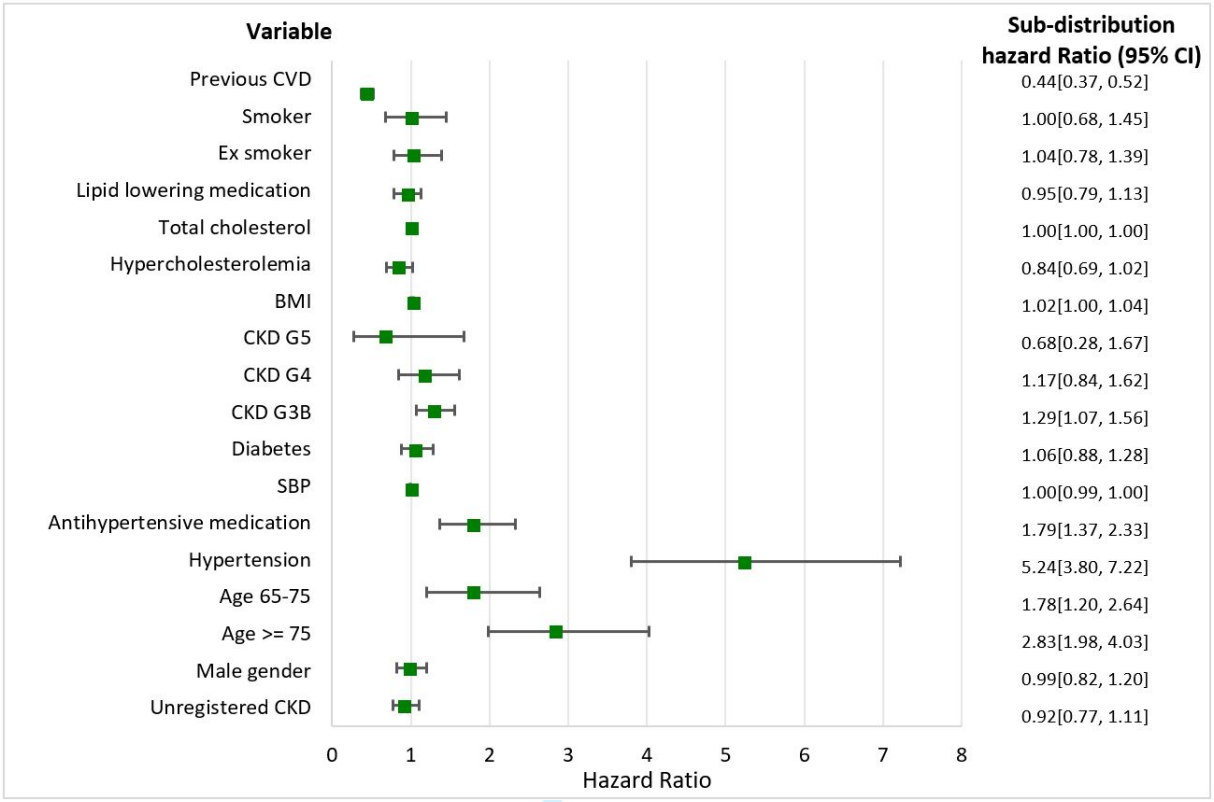
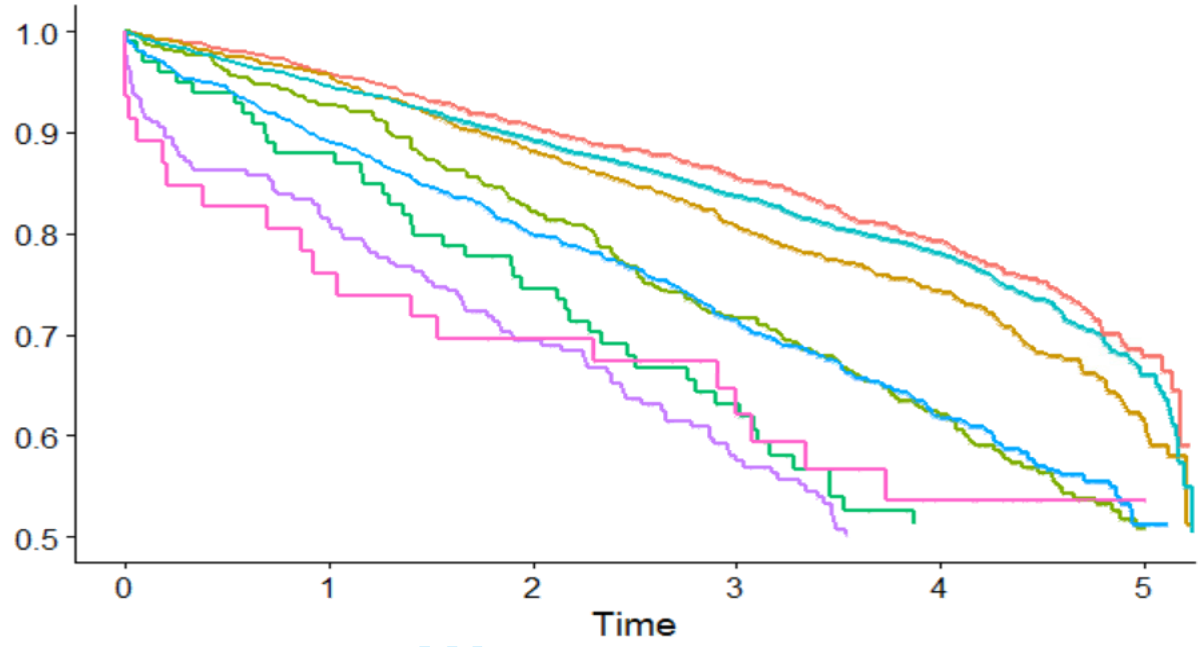


Figure 4. Cardiovascular disease with mortality as a competing risk. sHRs and the 95% confidence interval (95% CI) for different variables.

Systolic blood pressure (SBP), Body Mass Index (BMI), cardiovascular disease (CVD)



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Time (years)

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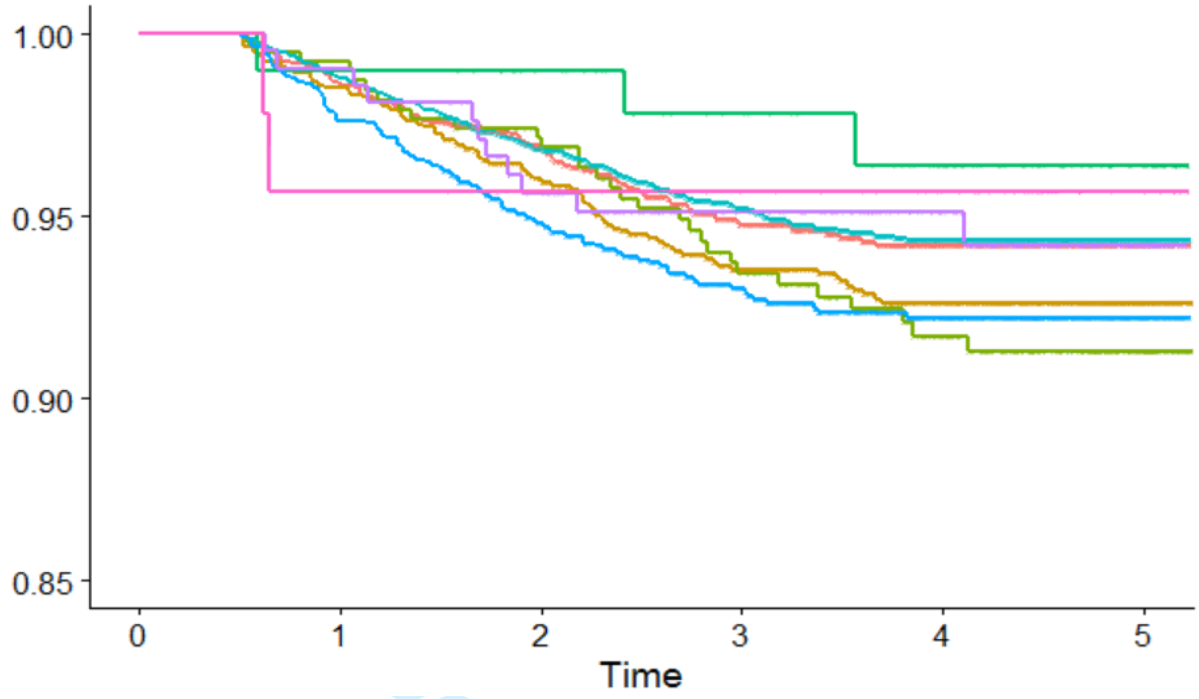

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Figure 2. Strata analysis for cardiovascular disease. Morbidity probability in different years grouped by CKD stage and presence of diagnostic code. Risk set table with number of patients at risk per year.

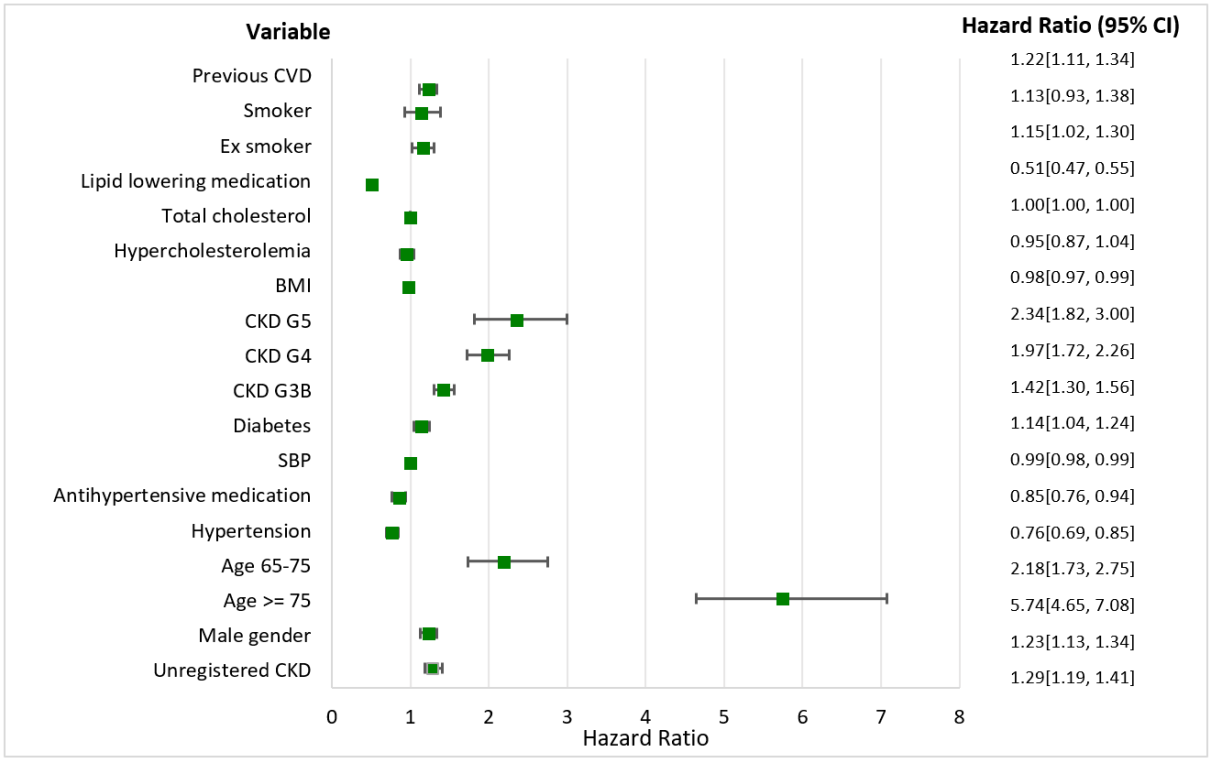


Figure 3. Mortality and time to event. HRs and the 95% confidence interval (95% CI) for different variables. Systolic blood pressure (SBP), Body Mass Index (BMI), cardiovascular disease (CVD)

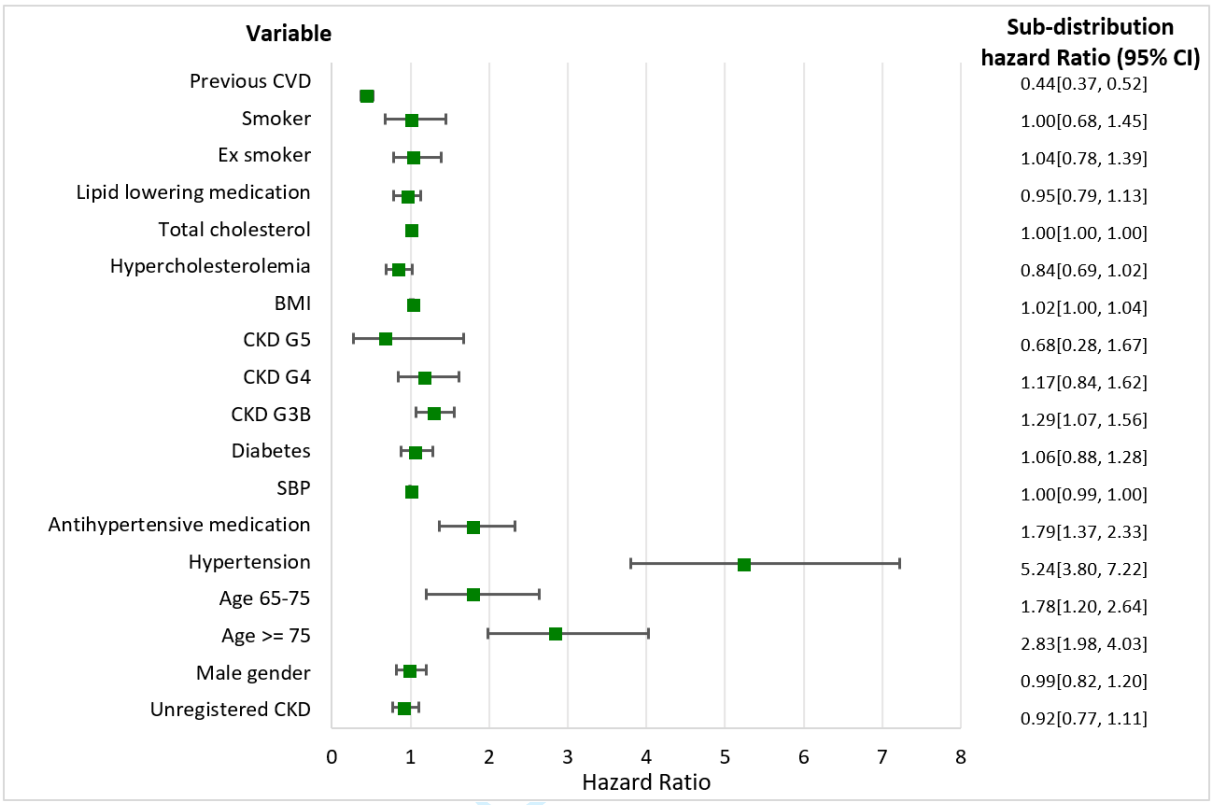


Figure 4. Cardiovascular disease with mortality as a competing risk. sHRs and the 95% confidence interval (95% CI) for different variables.
Systolic blood pressure (SBP), Body Mass Index (BMI), cardiovascular disease (CVD)

Variable	Registered CKD, n(%)	Unregistered CKD, n(%)	Total CKD, n(%)	P-value
Total patients	3375	7176	10551	
All-cause mortality, n (%)	460(13.6)	820(11.4)	1280(12.1)	0.033
Myocardial Infarction, n (%)	28(0.8)	35(0.5)	63(0.6)	0.067
Stroke, n (%)	70(2.1)	113(1.6)	183(1.7)	0.089
Peripheral Vascular Disease, n (%)	52(1.5)	82(1.1)	134(1.3)	0.004
Heart Failure, n (%)	188(5.6)	308(4.3)	496(4.7)	0.001

Table 1. Cardiovascular outcome associated with registration status.

Additional file 1: ATC codes

Antihypertensiva

- ACE inhibitors: C09A, C09B, or C10BX04, C10BX06, C10BX07, C10BX11, C10BX12, C10BX13, C10BX14, C10BX15, C10BX17, C10BX18 (combination)
- ARBs: C09C, C09D, or C10BX10, C10BX16 (combination)
- Agiotensin receptor-neprilysin inhibitor (ARNI): C09DX04
- Beta blockers: C07
- Calcium channel blockers: C08C, C08D, C08G, or C10BX03, C10BX07, C10BX09, C10BX11, C10BX14, C10BX18
- Alpha blockers, i.e., clonidine, moxonidine and methyldopa: C02AC01, C02AC05, C02AB
- Thiazide diuretics: C03A, or C10BX13
- Aldosterone receptor agonists (MRA): C03DA
- Loop diuretics: C03C

Lipid lowering medication

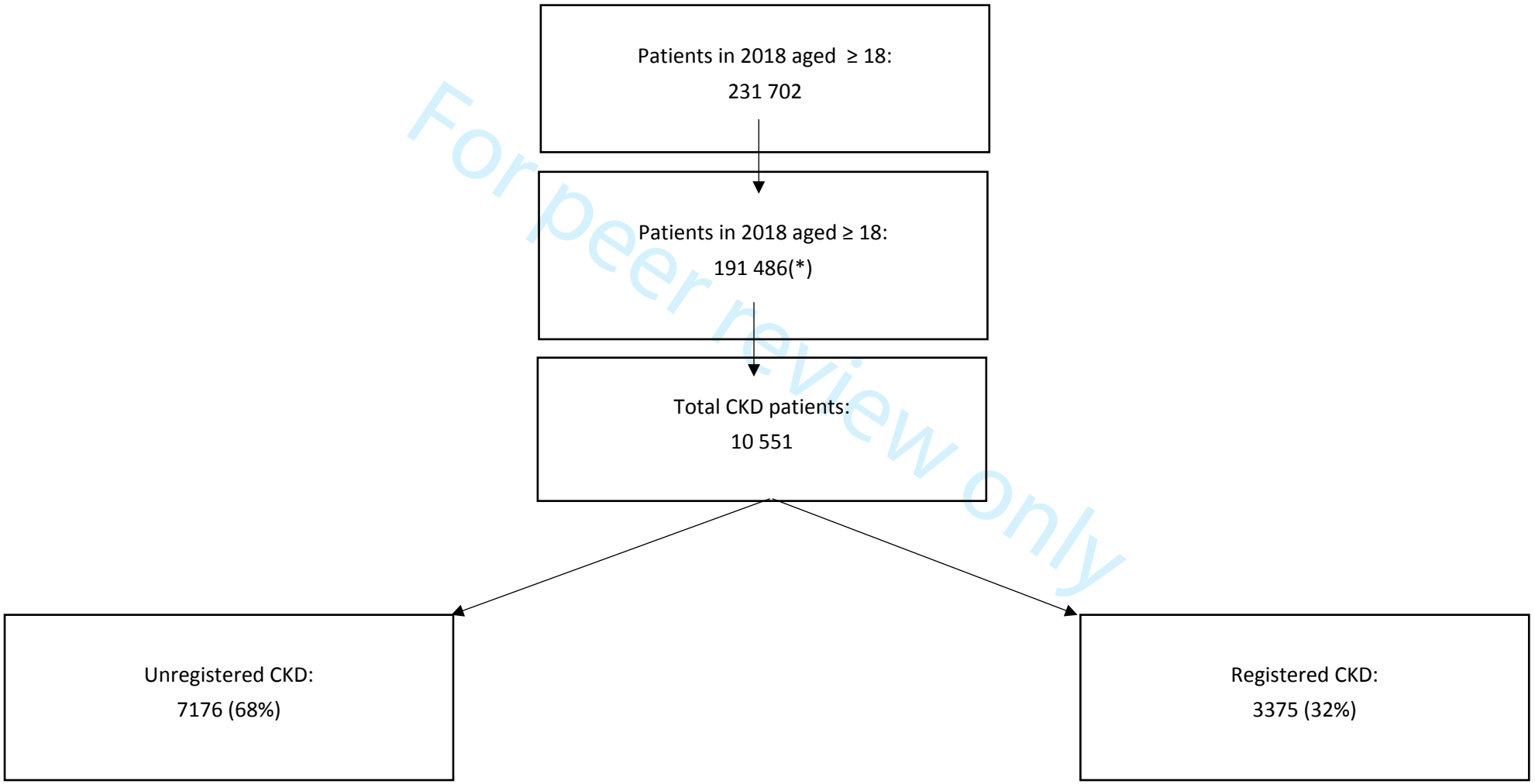
- C10

Antidiabetic drugs

- Metformin: A10BA02, or A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15, A10BD16, A10BD17, A10BD18, A10BD20, A10BD22, A10BD23, A10BD25, A10BD26 (combination)
- Sulphonylurea: A10BB, or A10BD01, A10BD02, A10BD04, A10BD06 (combination)
- Dipeptidyl peptidase 4 inhibitors (DPP-4i): A10BH, orA10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD12, A10BD13 (combination)
- Glucagon-like peptide-1 receptor agonist (GLP1-RA): A10BJ
- Insulin: A10AB, A10AC, A10AD, A10AE
- SGLT2s: A10BK01, A10BK02, A10BK03, A10BK04 or A10BD15, A10BD16, A10BD19, A10BD20, A10BD21, A10BD23, A10BD24, A10BD25 (in combination)
- Other oral anti-diabetic (OADs); Pioglitazon, acarbose, repaglinide: A10BG03, A10BF01, A10BX02, or A10BD05, A10BD06, A10BD12, A10BD14, A10BD17 (combination)

Additional file 2: Missing variables

Variable	Missingness
Total patients	10551
Smoking	75.98%
SBP	7.89%
Total Cholesterol	15.2%
BMI	55.34%



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	/
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	5-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	Additional file 2
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Association between non-registration of chronic kidney disease and mortality and cardiovascular outcome: a time-to-event analysis of retrospective primary care data

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Keywords:	Chronic renal failure < NEPHROLOGY, Mortality, CARDIOLOGY

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Association between non-registration of chronic kidney disease and mortality and cardiovascular outcome: a time-to-event analysis of retrospective primary care data

Ine Van den Wyngaert*[1], Pavlos Mamouris[1], Endale Alemayehu Ali[1], Bert Vaes[1] and Gijs Van Pottelbergh[1]

[1]Academic Centre for General Practice, Department of Public Health and Primary Care, University of Leuven, Leuven, Belgium.

*Correspondence to:
Ine Van den Wyngaert
E-mail: ine.vandenwyngaert@kuleuven.be

Keywords: cardiovascular, chronic renal failure, mortality, survival analysis, non-registration

Word count: 3188

Number of figures, tables, boxes, references: 4 figures, 1 table, 47 references

Abstract

Objective

Patients with impaired kidney function and increased albuminuria are at risk of developing cardiovascular disease. Previous research has revealed that a substantial proportion of patients with chronic kidney disease do not get a registered diagnosis in the electronic health record of the general practitioner. The aim of this study was to investigate the association between non-registration of chronic kidney disease and all-cause mortality and cardiovascular outcome.

Design and setting

A retrospective study in primary care.

Methods

The analyses were carried out in the INTEGO database, a general practice-based morbidity registration network in Flanders, Belgium. The study used INTEGO data from the year 2018 for all

patients ≥18 years old, including 10551 patients. To assess the risk of mortality and cardiovascular disease, a time-to-event analysis was performed. Cox proportional hazard model was used to evaluate the association between non-registration and incidence of all-cause mortality and cardiovascular events with mortality as a competing risk. Subgroup analyses were performed for estimated glomerular filtration rate stages (3a, 3b, 4 and 5). Multiple imputation was done following the methodology of Mamouris et al.

Results

Mortality was higher in patients with non-registered chronic kidney disease compared to patients with registered CKD (HR 1.29, 95% CI 1.19-1.41). Non-registration of chronic kidney disease was not associated with an increased risk for the development of cardiovascular disease (HR 0.92, 95% CI 0.77-1.11).

Conclusion

An association between non-registration and all-cause mortality was identified, although no such association was apparent for cardiovascular disease.

Strengths and limitations of this study

- To assess the risk of CVD and mortality, Cox-proportional hazard models were used and a competing risk analysis was performed to account for the presence of competing event (mortality).
- For the missing variables, we used multiple imputation.
- The presence of proteinuria was not taken into account in our CKD population due to the lack of data.
- The study used healthcare data, which may underrepresent the healthy and asymptomatic that do not seek healthcare.
- The participating GPs are a selected group of high quality registering practitioners that use a specific electronic health record, although the patient population is representative for the Flemish population.

INTRODUCTION

Chronic kidney disease (CKD) is a progressive condition that describes the gradual loss of kidney function over time. A reduced estimated glomerular filtration rate (eGFR) and elevated albuminuria are the two key measures in patients with CKD [1]. Multiple studies have documented suboptimal albuminuria testing in CKD patients in primary care [2, 3]. However, both reduced eGFR and the presence of albuminuria are associated with an increased risk of cardiovascular disease (CVD), hospitalisation and premature death [4-9]. The most common causes of CKD in high-income and middle-income countries are glomerulonephritis, diabetes mellitus and hypertension (the latter being also a consequence of CKD) [10-12]. The increased cardiovascular risk (CVR) in patients with CKD was therefore assumed to be the result of these underlying diseases. However, meta-analyses showed that impaired kidney function and increased albuminuria are CVR factors, independently of the presence of hypertension or diabetes mellitus [6, 13]. Kidney specific mechanisms that make significant contributions to the CVR were documented [4].

Previous research revealed that a substantial proportion of patients did not have a registered CKD diagnosis in the general practitioner's (GP) electronic health record (EHR) [14, 15]. In addition, mainly patients with early-stage CKD (stage 3) remained without official diagnosis [15]. Although we know that patients with CKD are more at risk, the impact of not registering a diagnosis has not been investigated, neither on cardiovascular outcome nor on mortality [4-6].

The aim of this study was to evaluate the impact of non-registration on all-cause mortality and cardiovascular outcome in Flanders, Belgium.

METHODS

Study setting and data source

This study was conducted following on from previous work [15]. In that research, the prevalence of non-registered CKD, the diagnostic delay (time between abnormal eGFR and diagnosis) and the baseline characteristics of the non-registered patient group were examined in a Belgian GP population. The same study population was used.

The analyses were carried out in the INTEGO database, a general practice-based computerised morbidity and mortality registration network in Flanders, Belgium, managed at the Department of General Practice of the University of Leuven since 1994. Data collection is regulated by an opting-out procedure. INTEGO procedures were approved by the ethical review board of the Medical School of KU Leuven (N° ML 1723) and by the Belgian Privacy Commission (no SCSZG/13/079). More than 100 GP centres applied for inclusion in this registry. Only the data of the 86 practices (representing 454 GPs) with optimal registration performance (80% coded diagnoses) were included in the database. Patient characteristics and diagnoses are encoded and classified using the International Classification of Primary Care (ICPC-2; WHO FIC Collaborating Centre). All laboratory tests performed by GPs are included in the database.

The methodology of data collection, study design, and analyses in the INTEGO registry have been previously reported [16].

Study population

Guidelines for CKD management recommend that patients should be diagnosed with CKD if the reduction in kidney function (eGFR <60 mL/ min/1.73 m^2) is present for more than three months [1, 17, 18]. All patients ≥18 years old with two consecutive eGFR laboratory measurements indicating CKD (eGFR <60 mL/min/1.73m^2) recorded >90 and ≤730 days apart during the baseline period were included. The current study used INTEGO data from the year 2018. Selected patients had at least one eGFR measurement <60 mL/min/1.73m^2 in 2018 and belonged to the GP's yearly contact group. There must be at least 12 months of continuous presence in the database prior to the first qualifying eGFR. Patients were excluded if they had a solid kidney transplant (ICD-10 Z94.0) before the date of the second qualifying eGFR (index date).

Non-registered CKD case definition

Patients with Non-registered CKD were identified if they had no diagnostic CKD code for any time during the ≥12-month lookback period before the first eGFR measurement and up to 6 months post-index date. ICPC-2 codes are used more frequently in general practice than ICD-10, so we chose to

use the ICPC-2 code U99. Those with a documented U99 during this time period were considered as having registered CKD. Since the U99 code is a collective code for unspecified kidney disease - like chronic kidney disease, renal cyst - we manually checked both the code and the written diagnosis whether the code did merge with CKD. It was assumed that patients with at least one diagnostic code for CKD during the above specified time window had registered CKD.

Statistical analysis

R software (version 4.0.4) was used [19]. A descriptive analysis was performed, calculating incidences of all-cause mortality, myocardial infarction, stroke, peripheral vascular disease and heart failure among those with registered versus Non-registered CKD. The follow-up period for these adverse clinical outcomes started six months after the index date until observation end date (follow-up end date or end of data coverage up to 17/07/2023, whichever came first). The variables were summarised using patient counts with percentages. The chi-square was calculated. P values less than 0.05 were considered significant. Subgroup analyses were performed for eGFR stages (3a, 3b, 4 and 5) and visualised using Kaplan-Meier curves.

To assess the risk of CVD and mortality, Cox-proportional hazard model was used. A competing risk analysis was performed to account for the presence of competing event (mortality) [20]. We estimated the hazard ratios (HRs) and derived the sub-distribution hazard ratios (sHRs) from the Fine and Gray model. Their 95% confidence interval (CI) was calculated. P values less than 0.05 were considered significant. We adjusted for all possible confounders (age, gender, hypertension, diabetes, smoking status, hypercholesterolemia, history of CVD). We fitted the models by including and excluding covariates one-by-one (sequential method) and we did not find significant change in the estimate and significance of covariates which were already in the model after adding new covariate. We calculated the Variance Inflation Factor to check for multicollinearity [21].

Variables were chosen based on the risk factors for CVD, defined by the Framingham Heart Study [22]. Cardiovascular events were defined as myocardial infarction (ICPC-2 K75), stroke (ICPC-2 K90), peripheral vascular disease (ICPC-2 K92) and heart failure (ICPC-2 K77). Hypertension or hypercholesterolemia included patients with a diagnosis of hypertension (ICPC-2 K86) or hypercholesterolemia (ICPC-2 T93) in the EHR. Antihypertensive, lipid lowering and antidiabetic medication were defined by the ATC-codes (Supplemental file 1). Patients with a diagnosis of diabetes type 1 or 2 in the EHR (ICPC-2 T89 and T90) and patients taking antidiabetic drugs were merged into the diabetes group. Since there was multicollinearity between total cholesterol, HDL and LDL, we chose to include total cholesterol.

For the missing variables, we used the methodology developed by Mamouris et al [23]. Concisely, in their work, they developed a 3-stage approach to impute longitudinal covariates so as complexities such as convergence and collinearity are resolved [23]. We imputed Body Mass Index (BMI), total cholesterol, systolic blood pressure (SBP) and smoking status longitudinally for years 2017-2023, thus utilising the previous and earlier information of the same patient (Supplemental file 2). We then extracted the observed year 2018. The dataset was imputed 20 times and model analysis was performed for each imputation separately. We finally pooled the results together using Rubin's rules [24].

Patient and public involvement

None.

RESULTS

As reported in our first research, 231 702 patients ≥18 years old were detected in the INTEGO database in 2018 (Supplemental file 3). The maximum follow-up was 3.97 years. Since the general practice didn't meet the criteria for best quality register, 40 216 patients were excluded. Among included patients, there were 10 551 patients (5.5%) with two consecutive eGFR laboratory measurements indicating chronic kidney disease (CKD) (eGFR <60 mL/min/1.73m2), recorded at least three months apart during the baseline period. Out of them, 7176 patients (68%) had no U99 at any time. The other 3375 patients (32%) had a registered diagnosis [15].

Descriptive analysis

Incidences

Incidences of all-cause mortality, myocardial infarction, stroke, peripheral vascular disease and heart failure associated with CKD diagnosis status as of index date, are being displayed in Table 1.

Variable	Registered CKD, n (%)	Non-registered CKD, n (%)	Total CKD, n (%)	P-value
Total patients	3375	7176	10551	
All-cause mortality, n (%)	460(13.6)	820(11.4)	1280(12.1)	0.033
Myocardial Infarction, n (%)	28(0.8)	35(0.5)	63(0.6)	0.067
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Heart Failure, n (%)	188(5.6)	308(4.3)	496(4.7)	0.001

Table 1. Cardiovascular outcome associated with registration status

Strata analyses

Figures 1 and 2, respectively, display the differences in survival time and time to development of CVD in patients with CKD, according to the CKD stage and presence of diagnostic code in the EHR. An informative risk set table shows the number of patients who were under observation and at risk in the specific period. It appeared that registered patients in stage 3B and 4 had a much better survival rate than non-registered patients after 3 years of follow-up, namely 82.23% (registered group, stage 3B) and 72.87% (registered group, stage 4) towards 73.05% (non-registered group, stage 3B) and 59.52% (non-registered group, stage 4) (Figure 1). The same difference was documented for CKD stage 5 after 1 year of follow-up. In the registered group, 87.88% survived at that time, towards 76.09% of the non-

registered patients. Only a small number of stage 5 patients were still under observation after 3 years of follow-up, making it difficult to interpret the results at that time (Figure 1). Similar survival curves were reported in both registered and non-registered in stage 3A.

Similar to the findings for mortality, less registered patients in stage 5 developed CVD compared to non-registered stage 5 patients after 1 year of follow-up (morbidity rate 98.99% in the registered group, towards 95.65% in the non-registered group) (Figure 2). In stage 3B and 4 were the differences in morbidity rate between registered and non-registered smaller after 3 years of follow-up compared to what we documented for mortality, respectively 93.80% (registered, stage 3B and 4) compared to 93.28% (non-registered, stage 3B) and 95.24% (non-registered, stage 4). As for mortality, stage 3A showed similar results curves for non-registered and registered.

Time to event-analysis

Figures 3 and 4, respectively, show the time to the occurrence of death or CVD with mortality as a competing risk. Results for analyses with and without mortality as a competing risk were similar.

All-cause mortality analysis showed that patients with non-registered CKD, male gender, age ≥65, diabetes, CKD stage 3B-5, history of CVD and (ex-)smokers had a higher chance of dying. Hypertension and hypercholesterolemia were protective factors, as was the use of antihypertensive and lipid lowering medication and BMI. The values for smoking and hypercholesterolemia were not statistically significant. The HR for total cholesterol was equal to 1.

Considering the results for CVD, only age ≥65, hypertension, antihypertensive medication, CKD stage 3B, BMI, total cholesterol and history of CVD were statistically significant. The sub-distribution hazard ratio (sHR) for non-registered CKD was <1. A history of CVD and hypercholesterolemia seemed to be protective factors for CVD, while patients with hypertension had an increased risk.

DISCUSSION

Principal findings

This study showed that patients with a properly registered diagnosis die less quickly than non-registered ones. However, according to our results, these patients did not appear to have a lower risk to develop CVD. Besides, patients in stage 3B and 4 with a registered diagnosis had much better mortality survival rates compared to the non-registered ones. The association of non-registration and CVD was less clear in the different CKD stages.

Patients with CKD and hypercholesterolemia showed to be less associated with CVD and mortality, although the result was not statistically significant. In contrast, hypertensive CKD patients appeared to have a higher risk of CVD, but a lower risk of mortality. Patients with a history of CVD seemed to have a lower risk of new events, but a higher risk to die.

Context of the results

Non-registration appears to be associated with all-cause mortality. However, the CaReMe CKD study recently showed that the rates of cardiovascular and all-cause death were 31-49% higher in registered CKD patients than in measured CKD patients, which could not be confirmed in our study [25]. Few research has been conducted in this regard, making it difficult to compare. We must note that non-registration may be a risk factor to mortality comparable to diabetes, but outweighed by age and stage of CKD by far. An association was found, but causality was not investigated. It is unclear whether better registration will lead to a better outcome, so this should be a topic for further research.

The key research question of our results is what caused patients to die. Previous research showed that a reduced kidney function predicts both cardiovascular and non-cardiovascular mortality due to pulmonary disease, infection, cancer, and other causes [26-28]. The association between a reduced eGFR and the increased risk of cardiovascular events and hospitalisation was also found [9, 12, 29]. Surprisingly, the non-registered group in our study did not have a higher risk of CVD than the registered. It is unclear why no association was found. Possibly, this group died more frequently as a result of non-CVD. On the other hand, non-registration probably extends beyond renal insufficiency and also occurs with other pathologies. Mata-Casas et al. reported non-registration of diabetes mellitus in Spanish primary health care [30]. Cardiovascular diagnosis may also be non-registered, so that no association with non-registration could be found [31].

A second important question remains why the difference in mortality outcome was found between registered and non-registered patients. Is the root of the problem with the GP or the patient? Our previous research showed that there were small differences between registered and non-registered

patients at baseline [15]. Hypertension was more frequently present in the registered (64.4% of the registered population) compared to the non-registered (51.7% of the non-registered population). Similar results were found for type 2 diabetes (33.1%) of the registered compared to 28.2% of the non-registered). Small differences were also noticeable in the use of ACE-I or ARB (52.6% among the registered compared to 46.3% of the non-registered) [15]. However, these small differences do not seem to provide an adequate explanation for the difference in mortality, partly in view of the result that the non-registered group had no higher risk of CVD.

Subsequently, the follow-up of these patients should be assessed. A possible explanation for the difference in mortality between registered and non-registered groups could be that less attention was paid while prescribing and dispensing nephrotoxic (over-the-counter) medication by the GP and pharmacist, resulting in further deterioration of kidney function. There may have been less attention to the CVR factors associated with impaired renal function. In that case, we also would have expected an increase in CVD, unless, as previous described, it concerns a problem of global non-registration. On the other hand, the responsibility of the patient in the follow-up of the disease must be brought to attention. Possibly, the non-registered group contained a large proportion of patients who were not adherent to follow-up and therapy, as a result of which some did not or belatedly encountered problems. So, it is becoming increasingly important to examine these hypotheses and to involve the patient in his care and to find out what view he has in this regard [32, 33]. Moreover, it seems useful to investigate why the diagnosis was not registered in the EHR. Based on these results, the problem of non-registration could be addressed.

According to our research results, hypertension in CKD patients would be a risk factor in the development of CVD, although a protective factor in the development of all-cause mortality. Though, we know from previous research that hypertension is a risk factor for the development of CVD and premature death [34-36]. The reasons for this difference are unclear. We need to consider the effect of antihypertensive medication on this outcome, since 48% of the patients took an Angiotensin-converting-enzyme-inhibitor (ACE-I) or an Angiotensin Receptor Blocker (ARB) [15]. The beneficial effect of these drugs on cardiovascular events and all-cause mortality has been confirmed in the past [37]. Ettehad et al. described that in patients with CKD smaller risk reductions in cardiovascular events were seen as a result of antihypertensive medication than in patients without CKD [38]. However, we should also keep in mind that there may be non-registration of hypertension and SBP.

Additionally, it is surprising that hypercholesterolemia and total cholesterol do not show a higher risk on CVD and mortality, since this is a proven risk factor for CVD [22, 39]. De Nicola et al. showed that the cardiovascular risk increases linearly with higher LDL in non-dialysis CKD patients [39]. However, this result was not significant and may be explained by the use of lipid lowering medication, as 45% of

patients were on this medication at baseline [15]. After all, Fabbian F. et al. determined that statins are an effective treatment in CKD patients, especially in the early stages of the disease [40]. A history of CVD appears to be a protective factor in the development of new CVD, of which a properly adjusted therapy can be the reason (secondary prevention) [40, 41]. In addition, we know that CKD is associated with adverse outcomes in those with existing CVD, which includes increased mortality after an acute coronary syndrome [42-44].

In our previous work, we found that the majority of patients with renal insufficiency were in stage 3, with a higher proportion registered in stage 5 (75.7% registered) compared to stage 3a (22.9% registered) [15]. However, this study showed major differences in survival rates between registered and non-registered patients in both the earlier (3B) and further stages (4 and 5) of renal failure. The importance of early detection has been described many times in the past [17, 45]. This research must therefore be a plea for early detection of CKD and registration of the diagnostic code in the EHR. Good mutual communication between GP and nephrologist through referral letters and clear consultation reports can contribute to this. A solution to detect non-registered patients can be found in an Audit-& Feedback system, since this has proven to be effective and to have added value in primary care [46, 47].

Limitations

There were some limitations to note. First, we did not take the presence of proteinuria into account in our CKD population. Mainly due to the lack of data on proteinuria, which brings us straight to the problem of non-detection of proteinuria in the Flemish general practice.

Subsequently, the study used healthcare data which may underrepresent the healthy and asymptomatic that do not seek healthcare. The data of care refusers were included in the research results.

Although the patient population is representative for the Flemish population, registering GPs are not representative for the GP population. It is a selected group of high quality registering practitioners that use a specific electronic health record. This selection bias of GPs could eventually have an influence on some process parameters in the follow-up of patients [16]. In addition, data collected in a real-world setting may lack information on specific covariates and laboratory investigations. Lab results from the hospital and specialists are automatically entered into the EHR, but their diagnoses are not. The large proportion of missingness is a limitation as well. We used multiple imputation to fill in this missingness (see method section).

CONCLUSION

An association between non-registration and all-cause mortality was identified, although no such association was apparent for CVD. Patients in stage 3B and 4 CKD with a registered diagnosis had much better survival rates compared with non-registered patients. It is unclear whether better registration will lead to a better outcome; the differences between these patient groups must be further mapped out.

Data availability statement: All relevant data are included in this published article (and its supplemental files), except for the data underlying Figures 1-4. As this data contains individual patient records, it can only be accessed inside a monitored analysis environment. Access to the data environment will be given to individual researchers on reasonable request.

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Contributors: IVDW, PM, BV and GVP designed and conceptualized the study. EAA and PM performed the data analysis. IVDW drafted the manuscript. IVDW, EAA, PM, BV and GVP revised the manuscript. IVDW and GVP are the guarantors of this work. All authors read and approved the final manuscript.

Competing interests: None declared.

Ethics approval: This study involves human participants. INTEGO procedures were approved by the ethical review board of the Medical School of KU Leuven (N° ML 1723) and by the Belgian Privacy Commission (no SCSZG/13/079).

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Figure titles and legends:

Figure 1. Strata analysis for mortality

Survival probability in different years grouped by CKD stage and presence of diagnostic code. Risk set table with number of patients at risk per year.

Figure 2. Strata analysis for cardiovascular disease

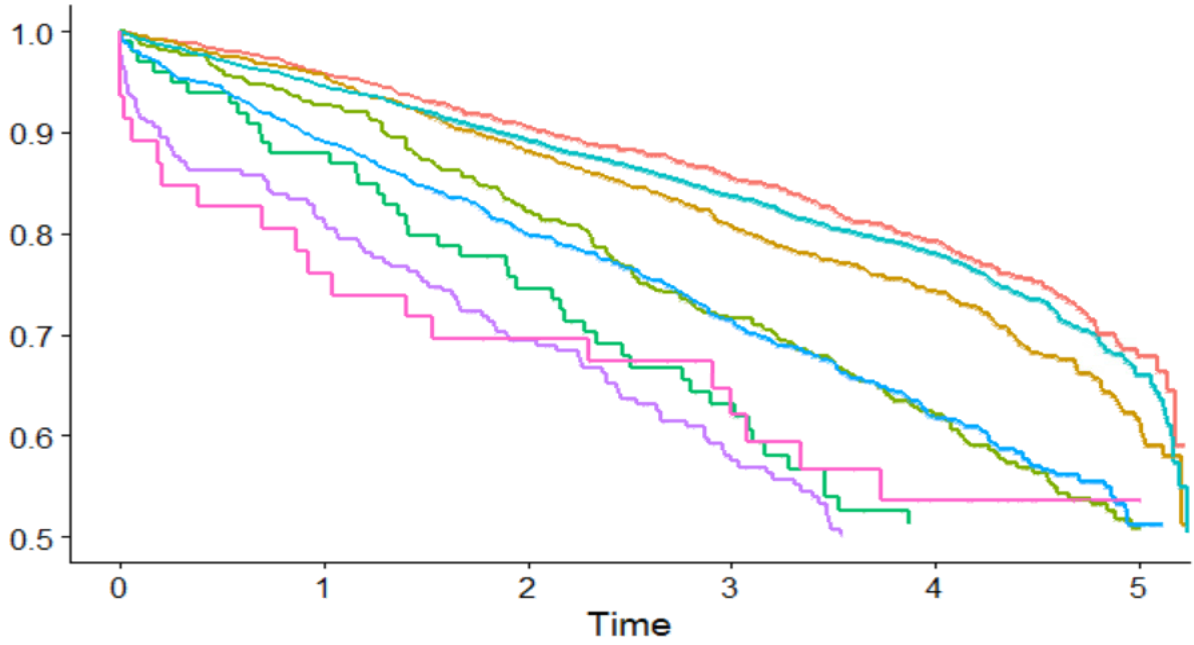
Morbidity probability in different years grouped by CKD stage and presence of diagnostic code. Risk set table with number of patients at risk per year.

Figure 3. Mortality and time to event

HRs and the 95% confidence interval (95% CI) for different variables. Systolic blood pressure (SBP), Body Mass Index (BMI), cardiovascular disease (CVD).

Figure 4. Cardiovascular disease with mortality as a competing risk

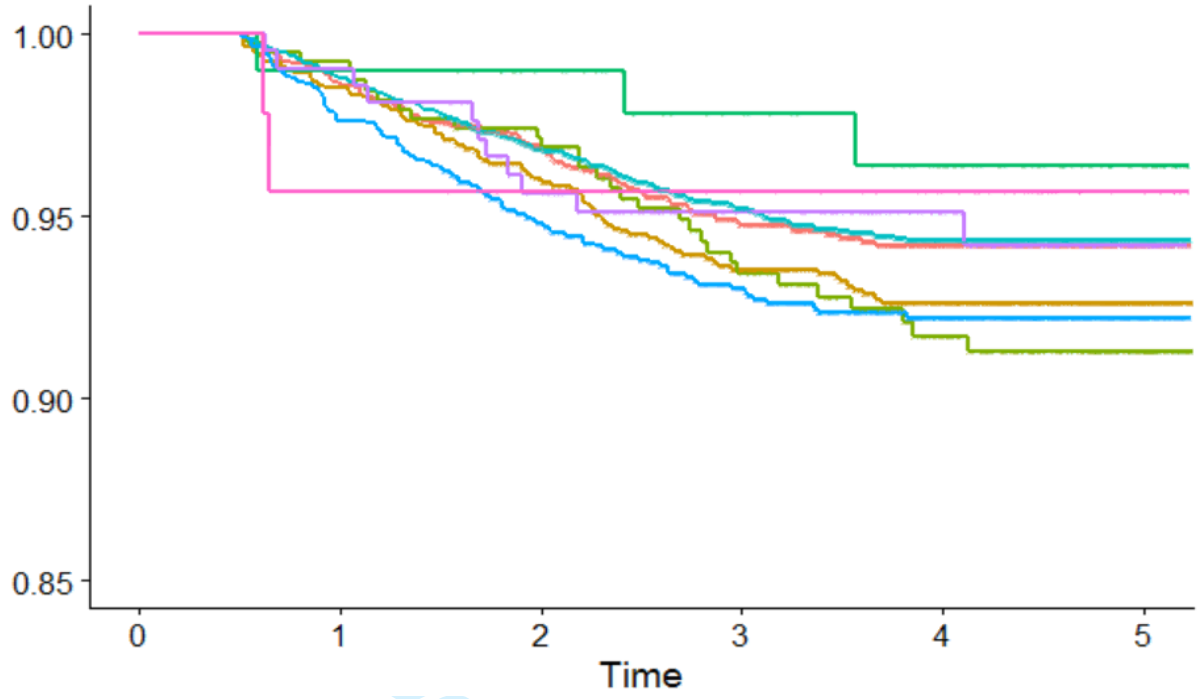
sHRs and the 95% confidence interval (95% CI) for different variables. Systolic blood pressure (SBP), Body Mass Index (BMI), cardiovascular disease (CVD).



Number at risk

Registered CKD, stage 3A	1679	1608	1406	1085	640	77
Registered CKD, stage 3B	1210	1157	1021	831	585	117
Registered CKD, stage 4	387	358	308	245	170	46
Registered CKD, stage 5	99	87	70	51	33	14
Non-registered CKD, stage 3A	5699	5386	4601	3213	1604	155
Non-registered CKD, stage 3B	1221	1086	925	704	393	46
Non-registered CKD, stage 4	210	170	137	99	64	18
Non-registered CKD, stage 5	46	35	31	23	16	4
	0	1	2	3	4	5

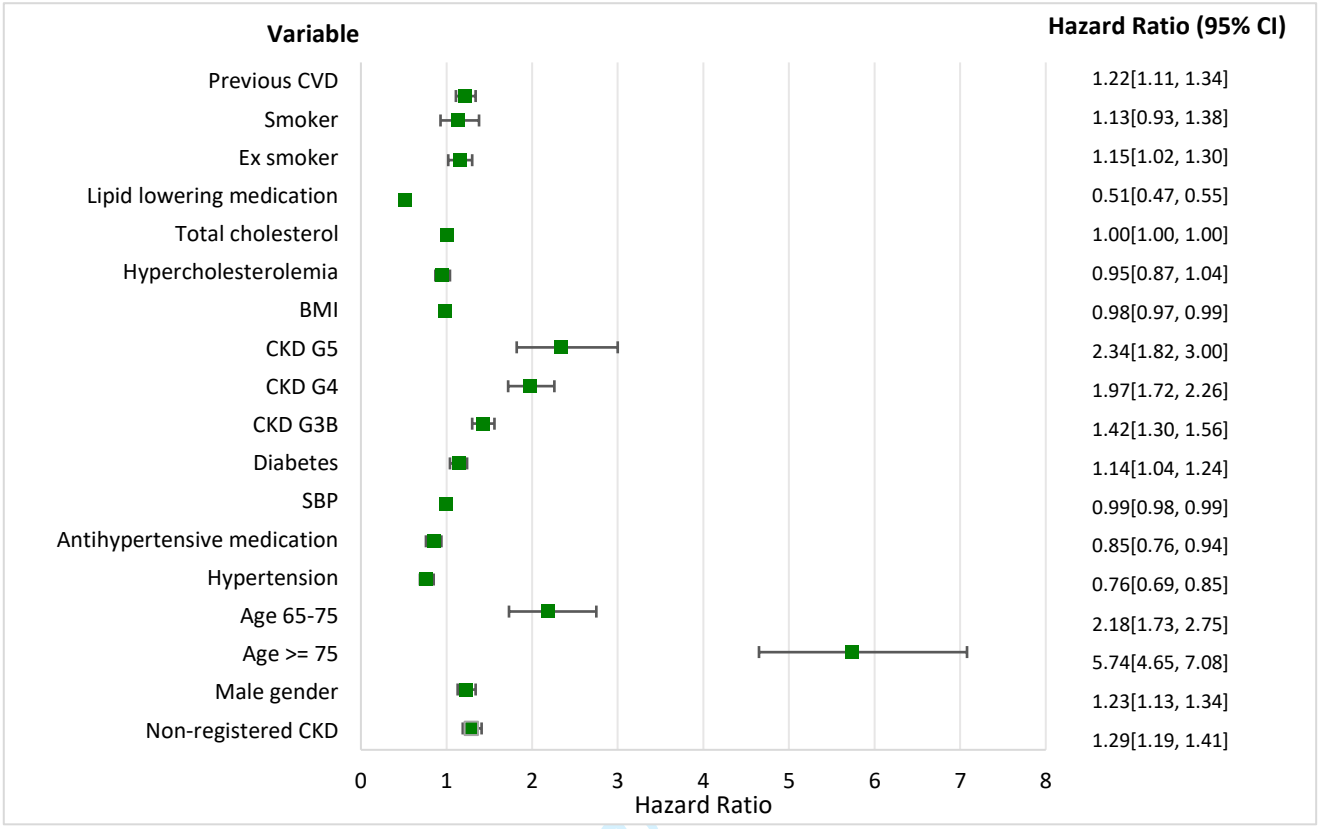
Time (years)

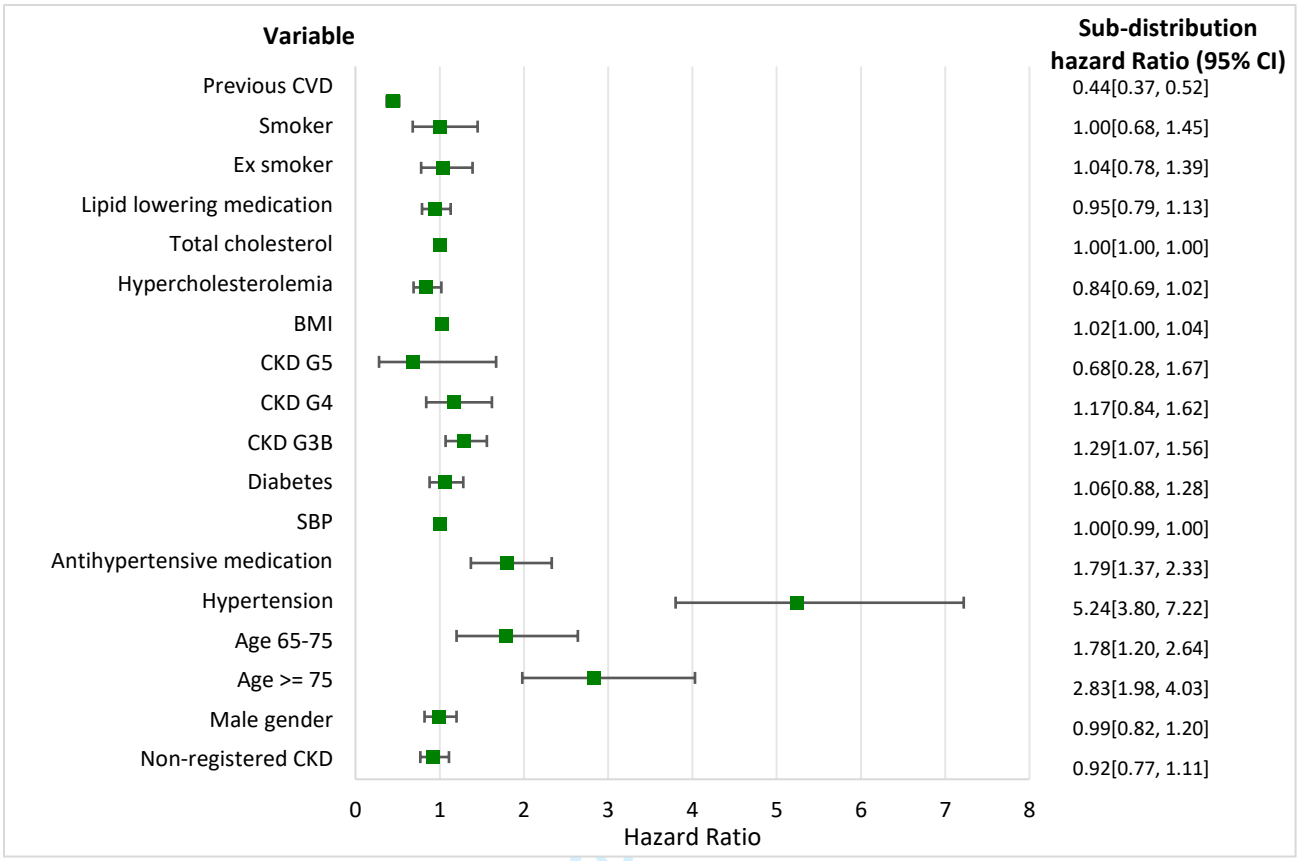


Number at risk

Registered CKD, stage 3A	1679	1656	1500	1186	723	89
Registered CKD, stage 3B	1210	1192	1105	936	678	150
Registered CKD, stage 4	387	384	360	310	231	74
Registered CKD, stage 5	99	98	90	75	60	25
Non-registered CKD, stage 3A	5699	5631	4971	3593	1840	190
Non-registered CKD, stage 3B	1221	1192	1088	894	558	73
Non-registered CKD, stage 4	210	208	187	149	111	29
Non-registered CKD, stage 5	46	44	41	35	27	9
	0	1	2	3	4	5

Time (years)


Variable
Hazard Ratio (95% CI)
Previous CVD
Smoker
Ex smoker
Lipid lowering medication
Total cholesterol
Hypercholesterolemia
BMI
CKD G5
CKD G4
CKD G3B
Diabetes
SBP
Antihypertensive medication
Hypertension
Age 65-75
Age >= 75
Male gender
Non-registered CKD
1.22[1.11, 1.34]
1.13[0.93, 1.38]
1.15[1.02, 1.30]
0.51[0.47, 0.55]
1.00[1.00, 1.00]
0.95[0.87, 1.04]
0.98[0.97, 0.99]
2.34[1.82, 3.00]
1.97[1.72, 2.26]
1.42[1.30, 1.56]
1.14[1.04, 1.24]
0.99[0.98, 0.99]
0.85[0.76, 0.94]
0.76[0.69, 0.85]
2.18[1.73, 2.75]
5.74[4.65, 7.08]
1.23[1.13, 1.34]
1.29[1.19, 1.41]
0
1
2
3
4
5
6
7
8
Hazard Ratio


Variable
Sub-distribution hazard Ratio (95% CI)
Previous CVD
0.44[0.37, 0.52]
Smoker
1.00[0.68, 1.45]
Ex smoker
1.04[0.78, 1.39]
Lipid lowering medication
0.95[0.79, 1.13]
Total cholesterol
1.00[1.00, 1.00]
Hypercholesterolemia
0.84[0.69, 1.02]
BMI
1.02[1.00, 1.04]
CKD G5
0.68[0.28, 1.67]
CKD G4
1.17[0.84, 1.62]
CKD G3B
1.29[1.07, 1.56]
Diabetes
1.06[0.88, 1.28]
SBP
1.00[0.99, 1.00]
Antihypertensive medication
1.79[1.37, 2.33]
Hypertension
5.24[3.80, 7.22]
Age 65-75
1.78[1.20, 2.64]
Age >= 75
2.83[1.98, 4.03]
Male gender
0.99[0.82, 1.20]
Non-registered CKD
0.92[0.77, 1.11]
0
1
2
3
4
5
6
7
8
Hazard Ratio

Supplemental file 1: ATC codes

Antihypertensiva

- ACE inhibitors: C09A, C09B, or C10BX04, C10BX06, C10BX07, C10BX11, C10BX12, C10BX13, C10BX14, C10BX15, C10BX17, C10BX18 (combination)
- ARBs: C09C, C09D, or C10BX10, C10BX16 (combination)
- Agiotensin receptor-neprilysin inhibitor (ARNI): C09DX04
- Beta blockers: C07
- Calcium channel blockers: C08C, C08D, C08G, or C10BX03, C10BX07, C10BX09, C10BX11, C10BX14, C10BX18
- Alpha blockers, i.e., clonidine, moxonidine and methyldopa: C02AC01, C02AC05, C02AB
- Thiazide diuretics: C03A, or C10BX13
- Aldosterone receptor agonists (MRA): C03DA
- Loop diuretics: C03C

Lipid lowering medication

- C10

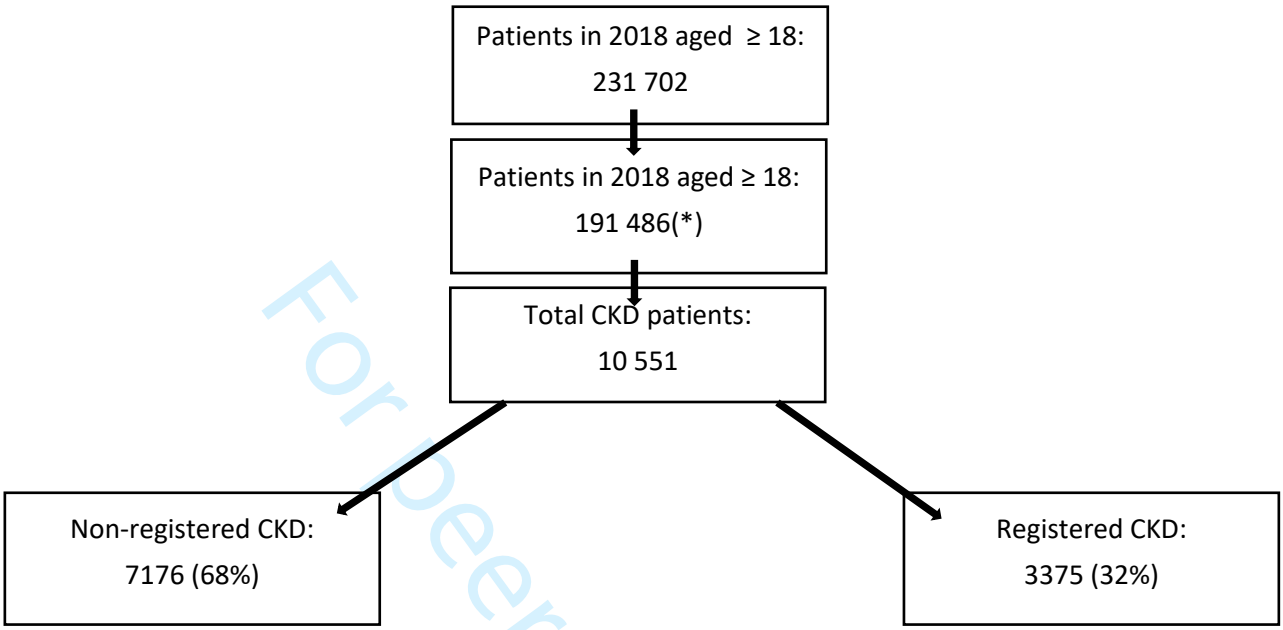
Antidiabetic drugs

- Metformin: A10BA02, or A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15, A10BD16, A10BD17, A10BD18, A10BD20, A10BD22, A10BD23, A10BD25, A10BD26 (combination)
- Sulphonylurea: A10BB, or A10BD01, A10BD02, A10BD04, A10BD06 (combination)
- Dipeptidyl peptidase 4 inhibitors (DPP-4i): A10BH, orA10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD12, A10BD13 (combination)
- Glucagon-like peptide-1 receptor agonist (GLP1-RA): A10BJ
- Insulin: A10AB, A10AC, A10AD, A10AE
- SGLT2s: A10BK01, A10BK02, A10BK03, A10BK04 or A10BD15, A10BD16, A10BD19, A10BD20, A10BD21, A10BD23, A10BD24, A10BD25 (in combination)
- Other oral anti-diabetic (OADs); Pioglitazon, acarbose, repaglinide: A10BG03, A10BF01, A10BX02, or A10BD05, A10BD06, A10BD12, A10BD14, A10BD17 (combination)

Supplemental file 2: Missing variables

Variable	Missingness
Total patients	10551
Smoking	75.98%
SBP	7.89%
Total Cholesterol	15.2%
BMI	55.34%

Supplemental file 3: Flow chart of the study population



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	/
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	5-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	Additional file 2
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.