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# Management of patients with chronic kidney disease: A French medical centre database analysis.

*Article category: epidemiology*

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## *Key messages*

- Fifty percent of all CKD patients are underscreened in general practice
- 33% of patients with CKD do not receive any nephroprotective medication
- CKD coding in electronic medical records would improve its follow-up.

Word count: 3351

## Abstract

**Objective(s):** Chronic kidney disease (CKD) is an insidious disease that requires early nephroprotective measures to delay progression to end-stage kidney disease (ESKD). The objective of this study was to describe the management of patients with CKD in primary care, including clinical and biological monitoring and prescribed treatments.

A retrospective, single-centre study was conducted on adult patients who were treated in the Maison de Neufchâtel (France) between 2012 and 2017 at least once a year. The inclusion criteria was two eGFR measurements < 60 mL/min more than 3 months apart. Two subgroups were constituted according to whether CKD was coded in the electronic medical records (EMRs).

**Results:** A total of 291 (6.7%, CI95% 5.9-7.4) patients with CKD were included. The mean eGFR was  $51.0 \pm 16.4$  mL/min. Hypertension was the most frequent health problem reported ( $n = 93$ , 32%). Nephroprotective agents were prescribed in 194 (66.7%) patients, NSAIDs in 22 (8%) patients, and PPIs in 147 (47%) patients. CKD coding in EMRs was associated with dosage of natrium (n = 34, 100%,  $p < 0.01$ ), albuminuria (n = 20, 58%,  $p < 0.01$ ), vitamin D (n = 14, 41%,  $p < 0.001$ ) and phosphorus (n = 11, 32%,  $p < 0.001$ ). Eighty-one patients (31.5%) with low eGFR without an entered code for CKD were prescribed an albuminuria dosage. Clinical monitoring could not be analysed due to poor coding.

**Conclusion:** This pilot study reinforces the hypothesis that CKD is underscreened and undermanaged. More systematic coding of medical information in EMRs and further studies on medical centre databases should improve primary care practices.

**Keywords:** renal insufficiency, chronic; primary health care; diagnostic; critical pathways; database.

## Summary (max 200 words)

Objective(s): Chronic kidney disease (CKD) is an insidious disease that requires early protective measures to delay progression to end-stage kidney disease. The aim of this study was to describe the management of patients with CKD in primary care.

A study was conducted in France by analysing the medical records of adult patients between 2012 and 2017.

Results: Of 4370 patients, 291 (6.7%) had CKD. Hypertension was the main associated medical history (32%) and was also known to be one of the main risk factors for CKD. Ninety-seven patients (33%) did not receive any medication indicated to protect the kidneys. Kidney-toxic drugs were widely prescribed, including PPIs in 47% of patients and NSAIDs in 8% of patients. Patients with a CKD note in their medical record had closer biological monitoring.

Conclusion: This pilot study reinforces the hypothesis that CKD is underscreened and undermanaged. The coding of information in primary care and further studies on these databases should improve the practice of general practice.

## Introduction

Chronic kidney disease (CKD) affects 13.4% of the world's population.<sup>1,2</sup> In 2010, 2.618 million people received renal replacement therapy (RRT) worldwide, with the incidence increasing by approximately 8% annually. Most RRT recipients are in high-income and upper-middle-income countries.<sup>3</sup> Examples of estimated annual haemodialysis costs per patient include US\$7500 in China<sup>4</sup> and US\$5000 in India<sup>5</sup> but US\$94,608 in the US<sup>6</sup> and US\$63,100 in France<sup>7</sup>, representing 0.15% of the national health insurance expenditure target.<sup>7,8</sup> By way of comparison, treatments for hypertension accounted for 1.6% of healthcare expenditure in France in 2018, and those for diabetes accounted for 3.2%.<sup>9</sup>

Recommended nephroprotective drugs have been shown to delay progression to ESKD: ACEI or ARB2 prescriptions retard CKD<sup>10</sup>, and lowering blood pressure to <130/80 mm Hg reduces future mortality risk.<sup>11</sup> The International Society of Nephrology described the main nephroprotection measures for CKD.<sup>12</sup> This implementation is part of the role of the general practitioner. An accurate description of the care is necessary to optimize this implementation. Few studies have described the outpatient management of predialysis CKD patients. They have described exposure to nephrotoxic drugs, delayed initiation of antihypertensive treatment, and unmet blood pressure goals.<sup>13,14</sup> The occurrence of iatrogenesis in the renal diseases of 100 patients seen by a nephrology consultation team in Minneapolis (USA) was 41%.<sup>15</sup> Vitamin D supplementation and vaccination coverage against pneumococcus and influenza have been described as inadequate.<sup>14</sup> Asymptomatic patients were underscreened.<sup>16</sup> The objective of this study was to confirm these data and accurately describe the management of patients with CKD in primary care.

## Method

### *Type of study*

Retrospective observational study.

### *Population*

The patients included were adults over 18 years old with CKD who were followed in general practice at the Neufchatel (Normandy) health centre and who consulted their GP at least once a year between 02/01/2012 and 06/11/2017.

### *Data collection*

The data were extracted from the medical records of the 14 general practitioners of the health centre on 06/11/2017. The database was developed in MySQL® (Structured Query Language) format and was hosted at the University Hospital of Nice. The reasons for consultation and diagnoses were coded by the doctors during their consultations using the International

Classification in Primary Care - 2nd version (ICPC-2). For variables not coded by the physician, the remaining data, including free text, were coded using an automatic coding procedure. This procedure compared the provided coding with a list of strings without regard to case or accents (derived from the reference document: ICPC-2 Medical Information Processing <sup>17</sup>) and stopped at the first match found. Data extraction was performed by the Côte d'Azur University on 06/11/2017.

### *Data analysis*

CKD was defined by two measurements of estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m<sup>2</sup> (MDRD method) at least 3 months apart, consecutive, or not. The eGFRs were performed independently of a CKD follow-up and were included in the check-ups requested by the general practitioners (GPs).

A group of patients with CKD according to the study definition was drawn and separated into two groups, depending on whether CKD was coded in the medical record history or not. The primary variable of interest was age at entry into CKD. Secondary variables were measures of nephroprotection: ACE inhibitor/ARB 2 drug prescriptions, nephrotoxic drug prescriptions, vaccination against pneumococcus and influenza, biomarker evaluation and laboratory results. The list of nephrotoxic drugs included NSAIDs, whose nephrotoxic effect is determined on the basis of many epidemiological studies with variable strengths of correlation and on pharmacological studies. <sup>18,19</sup> NSAIDs interfere with prostaglandin synthesis, which maintains eGFR and renal homeostasis, resulting in the loss of the compensatory mechanism of renal vasodilation, and causing disorders ranging from mild and transient to chronic renal disease. Other treatments defined as nephrotoxic in this study and whose prescribing was investigated included PPI, Penicillin, Allopurinol, Clopidogrel, Metformin, Cephalosporins, Fluoroquinolones, Vit D, Promestriene, Heparins, Warfarin, Carbamazepine, Sodium valproate, and Acyclovir. They were significantly less documented: they have been associated

with acute interstitial nephritis in case reports, but have been listed by the French National Authority for Health as treatments that should be reassessed for their benefit-risk balance in cases of CKD because of their probable nephrotoxicity.<sup>20</sup>

A univariate analysis of the frequency and time to initiation of nephroprotective measures was performed with RStudio version 1.3.1073 ®.

### *Quality criteria*

The STROBE grid was used to check the methodological quality criteria.

### *Ethical aspects*

This study was declared to the French National Commission for Information Technology and Civil Liberties (CNIL) and registered under n°2223855. An informative poster intended for the patients and explaining the modalities of access and rectification of the data was arranged among the member physicians.

## **Results**

There were 15,201 patients in the database, of whom 4,370 saw one of the 14 GPs at the medical centre at least once a year (figure 1) during the 4.9-year study. These 4,370 patients had an average of 0.68 creatinine measurements per year. A group of 291 patients with CKD according to the biological definition was selected, representing a prevalence of CKD of 6.7% (CI95% 5.9-7.4).

In this group with low eGFR, patients with documented and undocumented diagnoses or CKD codes were included. The mean age was  $82.6 \pm 9.2$  years, and the sex ratio of males to females was 1.97 (193 men, 98 women) (table 1). Patients had a mean of  $2.9 \pm 1.9$  creatinine determinations per year, with a mean eGFR of  $51.0 \pm 16.4$  mL/min. Patients visited their GP on average  $7.8 \pm 4.9$  times per year. The main comorbidity coded in the EMR was hypertension (n = 93, 32%, CI95% 26.6-37.3). Other antecedents are noted in figure 2.

Patients received a mean of  $4.1 \pm 0.2$  prescriptions for ACE inhibitors/ARB 2 drugs per year (for example ramipril, captopril, valsartan, or candesartan) and  $13.4 \pm 1.7$  prescriptions for nephrotoxic drugs per year. Ninety-seven patients (33.3%, CI95% 27.9-38.8) received no nephroprotective drug prescriptions during the 5-year study period, and 267 (91.8%, CI95% 88.6-95.0) received no vitamin D prescriptions. Only 11 patients (3.8%, CI95% 1.6-6.0) received a prescription for pneumococcal vaccination over the 6-year study period, and 1 patient (0.3%, CI95% 0.0-1.0) received a prescription for influenza vaccination from the medical centre.

Among the potentially nephrotoxic drugs<sup>20</sup>, PPIs were prescribed to 137 patients (47.1% CI 95% 41.3-52.8), while NSAIDs better known for their nephrotoxicity were prescribed to 22 (7.6%, CI95% [4.5-10.6]) patients. Biological monitoring results are presented in Table 1.

### **CKD group with a documented history of CKD**

In the group of patients with documented low eGFR who had an entered CKD diagnosis code, 34 had a documented history of CKD. The mean age was  $79.2 \pm 14.3$  years. The sex ratio was 1.27 (19 men, 15 women). The patients consulted their primary care physician on average  $9.1 \pm 6.1$  times per year. Patients had a mean of  $3.6 \pm 2.4$  creatinine determinations per year, with a mean eGFR of  $42.4 \pm 14.1$  mL/min.

No association was found between an entered CKD diagnosis code and the number of consultations in the medical centre, the number of prescriptions of nephroprotective drugs ( $5.2 \pm 1.7$  prescriptions per year), and the overall prescription of nephrotoxic drugs ( $13.4 \pm 12.0$  prescriptions per year). They were more likely to receive vitamin D (14/34,  $p < 0.001$ ) and to have natraemia (34/34,  $p < 0.01$ ), albuminuria (20/34,  $p < 0.01$ ), vitamin D (14/34,  $p < 0.001$ ) and phosphorus (11/34,  $p < 0.001$ ) at least once. Their eGFR was 9.8 mL/min lower ( $42.4$  mL/min,  $p < 0.01$ ) than that of the CKD group without a history of CKD.



### **CKD group without a documented history of CKD**

In the subgroup of 257 patients with low eGFR and without an entered CKD diagnosis code, the sex ratio was 2.1 (174 males, 83 females). The mean age was  $83.1 \pm 8.3$  years. There was no age difference between the subgroups with low eGFR. The patients consulted on average  $7.7 \pm 3.9$  times per year. They received a mean of  $4.6 \pm 1.7$  prescriptions for nephroprotective drugs per year and  $13.3 \pm 12.1$  prescriptions for nephrotoxic drugs. Patients had a mean of  $2.8 \pm 1.8$  creatinine determinations per year, with a mean eGFR of  $52.2 \pm 16.4$  mL/min.

### **Group without CKD but with a documented history of CKD**

Thirty-three patients with the CKD diagnosis code entered in their EMRs did not meet the inclusion criteria. This could be due to earlier legitimate coding at the start of inclusion, without new biology confirming the decreased eGFR on two measurements, or to a coding for an eGFR  $> 60$  mL/min. The mean age of patients with CKD in the medical history was  $77.9 \pm 10.8$  years compared with  $82.6 \pm 9.2$  years when only the biological definition was used for the diagnosis ( $p = 0.13$ ). Patients had a mean of  $7.7 \pm 3.9$  visits per year. They had a mean of 1.3 creatinine determinations per year, with a mean eGFR of  $56.6 \pm 16.7$  mL/min.

## **Discussion**

This pilot study describes of the follow-up of patients with CKD in primary care in France. It opens areas for reflection on the reasoning and diagnostic approach to CKD in primary care.

The prevalence of CKD in this study (291 patients, 6.7%) was half that expected from the international estimate (13.4%<sup>1,2</sup>). This seems to confirm the underscreening of CKD in ambulatory medicine. CKD is a disease that is asymptomatic for a long time and may be ignored by the physician-patient couple if neither of them actively screens for it.<sup>21</sup> This underscreening could be due to a lack of knowledge of nephroprotection measures and a fatalistic view of the evolution of CKD, making screening futile.<sup>22</sup> The annual mean reduction

in eGFR associated with physiological ageing ranges from 0.4 to 2.6 mL/min/year<sup>23</sup>: patients experiencing a rapid deterioration should be worked up for an alternative cause.

The factors associated with CKD largely overlap to a large extent with cardiovascular risk factors.<sup>12</sup> Diabetes and high blood pressure are the more common causes of CKD in adults and may take priority at the cost of renal function monitoring. Other risk factors include heart disease, obesity, a family history of CKD, inherited kidney disorders, past damage to the kidneys, and older age.<sup>24–26</sup> A more systematic creatininemia according to these risk factors would improve screening too.

Only 11.7% of patients with CKD were labelled in the medical records. This labelling seemed to show greater attention to certain clinical and biological monitoring of patients with CKD without modifying the prescriptions of nephrotoxic or nephroprotective drugs. Better labelling would allow practitioners to be more aware of CKD and to be more vigilant about the specific management of CKD in France. The French National Authority for Health made recommendations to slow patient progression of CKD. Nephrotoxic measures include controlling exposure to nephrotoxic products, including re-evaluation of the risk-benefit ratio of the nephrotoxic drugs listed in Table 1, or those with renal elimination, combating sedentary lifestyles and tobacco addiction, and encouraging dietary counselling. A blood pressure below 140 mmHg systolic and 90 mmHg diastolic should be controlled to reduce albuminuria. The treatment of choice is ACE inhibitors or ARB2. Finally, annual seasonal influenza vaccination, pneumococcal booster, HBV booster, and completion of SARS-CoV-2 vaccination are recommended in CKD patients.<sup>20</sup>

Hypertension and diabetes are the two main risk factors for CKD.<sup>6,27</sup> The EMRs included 93 (32.0%) patients with hypertension and 34 patients with CKD code, but 194 (66.7%) patients were treated with ACE/ARB2 inhibitors. We suspect that physicians were prescribing ACE/ARB2 inhibitors for hypertension or CKD without coding the reason for the prescription

in the patients' EMRs, either as a result of providers assuming they will remember disease statuses in well-known patients or as a result of refilling treatments prescribed by another specialist. This undercoding is supported by European studies where up to 45% of hypertension diagnoses could not be found in patient EMRs.<sup>28</sup>

This undercoding may be explained by the format of the study, which is an observational study, since participating doctors were not asked to change their practice or correct their incomplete EMRs. However, there is a risk that GPs will not follow clinical guidelines for conditions that have not been noted in the EMRs when opened during consultations.

This study seems to confirm the lack of prescriptions for nephroprotective drugs (n = 194, 66.7%) and vitamin D (n = 24, 8.2%). This deficiency can be explained by a lack of awareness on the subject of CKD or constraints related to the consultation itself (lack of time or cooperation from the patient)<sup>14</sup>. This may also be due to incorrectly prioritizing not adding to the numerous drugs already prescribed to patients with multiple comorbidities. Patients with type 2 diabetes have an average of 6.6 medications per day<sup>29</sup>, of which 2.7 are taken for hypertension<sup>30</sup>. Initiation of a nephroprotective prescriptions should be encouraged on the basis of its risk-benefit ratio. To improve the awareness of GPs and help them make decisions, the use of medical software equipped with alert systems proposing the initiation of nephroprotective treatment in the event of an eGFR < 60 mL/min and highlighting nephrotoxic treatments is an interesting solution to promote.

Creatininaemia (281 patients, 96.6%) and natriuria (231 patients, 79.4%) were well-assessed during renal monitoring, but these are nonspecific biomarkers also requested in the monitoring of hypertension and diabetes. Follow-up for CKD specifically, such as phosphocalcium level testing (72 patients had a calcium test, 43 patients a vitamin D test, 36

patients a phosphorus test), was significantly less prescribed, suggesting that GPs were less familiar with CKD monitoring tests.

The low level of vitamin D testing can be explained in part by the fact that it has been defunded from the French social security office since 2013, while supplementation should be standardized. There were also only a few limited indications for vitamin D supplementation at the time of the study: rickets in children, osteomalacia, osteoporosis, recurrent falls, bariatric surgery, and a kidney transplant surgery performed more than three months ago.

Proteinuria evaluation is a simple and inexpensive test to perform and is a diagnostic test in the evaluation, monitoring, and therapeutic management of CKD. Only one-third of patients were tested for proteinuria, which shows room for improvement in CKD management.

PPIs accounted for the majority of nephrotoxic prescriptions in this study (n = 137, 47%); this result is consistent with the literature.<sup>13</sup> PPIs have been associated with acute interstitial nephritis in case reports and an increased CKD in population-based studies<sup>31,32</sup>. In observational studies, PPIs are suspected to present neurological (dementia, hepatic encephalopathy), cardiovascular, digestive (*C. difficile* diarrhoea), respiratory (pneumonia) and fracture-related risks.<sup>33,34</sup> Table 1 lists drugs classified as nephrotoxic (NSAIDs) or potentially nephrotoxic according to the summaries of drug characteristics edited by industrials, mainly due to case reports of acute interstitial nephritis. Their nephrotoxicity is not clearly established, and it is difficult to conclude that prescriptions were inappropriate in the light of scientific data. However, it is important to raise the awareness of GPs regarding drugs with lesser-known nephrotoxic properties that merit precaution, especially in patients with multiple prescriptions.

Renal medication-related clinical decision support is an electronic tool that provides alerts in the case of nephrotoxic drug prescriptions in CKD patients.<sup>35</sup> Its improvement, promotion and

standardization would remind doctors of the potential nephrotoxicity of some of their prescriptions.

The study did not show any age difference between the subgroups, suggesting that there was no delay in recording the CKD once it was established. The low labelling of CKD in the records and the small size of the group with CKD in the history do not allow further extrapolation.

### **Limitations**

The database used allowed for numerous analyses, but some variables of interest could not be explored. Their addition would be interesting for future studies. Data on blood pressure measurements were not available in the database, although this is a strong marker for monitoring CKD. Referral to the nephrologist and vaccination status data were also not available. The data included regarding vaccination status were based on vaccination prescriptions during the study. The EMRs in this study show a very low prescription rate for pneumococcal, HBV, HAV, and influenza vaccinations. Vaccinations given prior to inclusion in the study or prescribed by other physicians were not documented. The almost non-existent rate of flu vaccination in our study shows a shift in the administration of flu vaccinations. Since 2019, in France, patients at risk who receive a letter from the French National Health Insurance can go directly to the pharmacist for an influenza vaccination. These patients no longer need to go through their GP. Influenza vaccination coverage exceeds the WHO target in the UK (80.5% vaccination coverage of patients over 65 years of age in 2020-21<sup>36</sup>) but remains low in France (59.9% vaccination coverage in patient over the age of 65 in 2020-21<sup>37</sup>). Unlike in England, there is no longer a vaccination reminder system for patients in France and no appointment system, which seem to be interesting procedures to standardize.

The study was monocentric and reflected the practises of 14 doctors from the same facility, which was an insufficient sample size to consider their practises representative of the practises of French GPs. This limits the extrinsic validity of our study.

## Conclusion

This pilot study reinforces existing data regarding the underscreening and undertreatment of CKD and exposure to nephrotoxins. It also suggests that better labelling of CKD in medical records could positively influence patient follow-up. This type of study could have a future role in the establishment of national epidemiological files and allow for the comparison of medical practices between different medical centres.

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### *Author approval*

All authors participated in the design of the study protocol, its implementation, follow-up, collection of results, and writing of the article, in accordance with ICMJE recommendations. All the authors declare their approval of the content of the article.

### *Data availability*

The data that support the findings of this study are available on request from the corresponding author MA. The data are not publicly available because they contain information that could compromise the medical confidentiality of the research participants.

### *Conflict of interest*

The authors declare no conflicts of interest.

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Figure 1. Flow chart of patients with CKD at Neufchatel Health Centre (2012-2017).

Figure 2. Main comorbidities noted in the medical history of 291 patients with an eGFR < 60 mL/min follow-up in general practise. N (percentage).