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Eventos cardiovasculares y renales según los estadios KDIGO de la enfermedad renal crónica en la población española: resultados de evidencia del mundo real.

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Abstract.

Objective: in Real-world analysis of thclinical profile, treatments, major adverse cardiovascular and renal events (MACE and MARE) in patients with different stages of chronic kidney disease (CKD) ~~across~~ as defined by KDIGO guidelines.

Methods: This was an observational, retrospective study using the BIG-PAC database. Adults with ≥1 measurement of estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (UACR) closest to 1st January 2018 (within up to 6 months) were included. Patients were followed for two years.

Results: From a total of 70,385 subjects analyzed, 21,127 (30.0%) had CKD based on impaired renal function or increased albuminuria. Age, prevalence of diabetes and cardiovascular disease increased as kidney function decreased, or albuminuria rose. Renin-angiotensin system inhibitors were prescribed in 47.1% to 76.4% patients classified as G3a to G5 and mildly increased albuminuria (A1), 63.2-79.6% in G1 to G5 and moderately increased albuminuria (A2), and 51.2-85.9% in G1 to G5 and severely increased albuminuria (A3). The prescription of sodium-glucose cotransporter-2 inhibitors was marginal across KDIGO categories. The incidence rates (per 1000 patient-year) of MACE ranged 102.9-245.2 in patients classified as G3a-G5 A1, 40.7-261.1 in G1-G5 A2, and 69.1-362.3 in G1-G5 A3. Incidence rates of MARE ranged 14.9-454.4 in G3a-G5 A1, 29.8-588.5 in G1-5 A2, and 11.8-637.2 in G1-5 A3. (podrian quitarse los decimales? Se ha redondeado a 1 decimal)

Conclusions: In real-world, the risk of cardiovascular and renal complications rises as kidney function declines and albuminuria worsens. Guideline-recommended therapies remain underused.

Key words: albuminuria; cardiovascular disease; chronic kidney disease; KDIGO; renal function.

Resumen.

Objetivo: Analizar el perfil clínico, tratamientos, eventos adversos cardiovasculares y renales mayores (MACE y MARE) en pacientes con enfermedad renal crónica (ERC) según los estadios KDIGO en el mundo real.

Métodos: Estudio observacional, retrospectivo utilizando la base de datos BIG-PAC. Se incluyeron adultos con ≥1 medida del filtrado glomerular estimado (FGe) y cociente albúmina/creatinina (CAC) más próximos al 1/enero/2018 (hasta 6 meses). Los pacientes fueron seguidos durante dos años.

Resultados: De los 70.385 sujetos, 21.127 (30,0%) presentaban ERC por deterioro de función renal o aumento de albuminuria. La edad y la prevalencia de diabetes y enfermedades cardiovasculares aumentaron a medida que disminuía la función renal o aumentaba la albuminuria. Se prescribieron inhibidores del sistema renina-angiotensina en 47.1-76.4% de los pacientes clasificados como G3a a G5 y albuminuria (A1) levemente aumentada, 63,2-79,6% en G1 a G5 y albuminuria moderadamente aumentada (A2), y 51,2-85,9% en G1 a G5 y albuminuria severamente aumentada (A3). La prescripción de inhibidores del cotransportador de sodio-glucosa-2 fue marginal en todas las categorías KDIGO. Las tasas de incidencia (por 1000 pacientes-año) de MACE oscilaron entre 102,9 y 245,2 en los pacientes clasificados como G3a-5 A1, 40,7-261,1 en G1-5 A2 y 69,1-362,3 en G1-5 A3. Las de MARE oscilaron entre 14,9 y 454,4 en G3a-5 A1, 29,8-588,5 en G1-5 A2 y 11,8-637,2 en G1-5 A3.

Conclusiones: En el mundo real, el riesgo de complicaciones cardiovasculares

y renales aumenta a medida que la función renal disminuye y la albuminuria empeora. Las terapias recomendadas por las guías siguen estando infrautilizadas.

Palabras clave: albuminuria; enfermedad cardiovascular; enfermedad renal crónica; KDIGO; función renal.

Introduction.

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function that have been present for at least for 3 months, and had consequences on health

CKD is classified based on etiology, estimated glomerular filtration rate (eGFR) (G1–G5 categories), and urine albumin-to-creatinine ratio (UACR) (A1–A3 categories) [1]. Different studies have analyzed the prevalence of CKD in the adult population, defined as either eGFR <60 ml/min/1.73 m^2 and/or increased UACR (≥ 30 mg/g, A2-A3), with values that range from 15 to 30% (percent??se refiere a prevalencia), according to

the study population [2-5]. CKD is associated with a marked increase in the risk of cardiovascular outcomes and renal disease progression [6-8]. As a result, the early detection of CKD appears to be mandatory to provide the best management to reduce CKD burden [9-13].

Most of the evidence on CKD population primarily relies on randomized controlled trials (RCTs), which often exclude ~~diverse~~ (???) specific types of patients and high-risk populations

that are regularly attended in real-world settings [9-13]. By contrast, real-world data (RWD)

provides relevant insights into clinical practice ~~complementing evidence from RCTs~~ [14,15]. For instance, a recent study demonstrated significant differences among diabetic with CKD patients in RCT and RWD [16]. These discrepancies, including differences in patient demographics, treatment patterns,

and data completeness, underscore the importance of integrating RWD into clinical research to better reflect real-world treatment outcomes. As a result, RWD studies are changing the landscape of clinical research by shedding light on how therapies operate outside of the controlled context of RCTs.

Unfortunately, there are only few RWD studies that have examined both cardiovascular and renal outcomes across the CKD stages as defined by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, or have addressed the analyses according to either eGFR or UACR, but not both simultaneously [6-8].

Additionally, a limited number of studies have provided a comprehensive assessment of adherence to guideline-recommended therapies in the CKD population across KDIGO stages and how prescription patterns evolve through CKD severity categories in real-world practice [17-21]. Furthermore, factors such as demographic and cultural particularities of populations and differences in healthcare practices conditioned by economic or administrative factors might have an influence on the generalizability of RWD study findings [22,23]. Therefore, collecting more RWD from diverse geographic regions and populations is essential to better understanding the global landscape of CKD and implement targeted strategies to improve CKD management, specifically by addressing the gaps identified through local analyses.

In this study, a large population database was used to gain new RWD insights into the complexities and heterogeneity of CKD care in Spain, with a particular focus on the clinical profile, guideline-recommended therapies, major adverse cardiovascular events (MACE), and major adverse renal events (MARE) outcomes across all KDIGO stages.

Methods.

We performed an observational, retrospective, and RWD-based study using the BIG-PAC database. This database includes data of 1.8 million people of primary health care centers and referral hospitals from seven Autonomous Communities of Spain. This database contains fully anonymized and dissociated secondary healthcare data and has been shown to be representative of the

Spanish population [24]. The study was approved by the Investigation Ethics Committee of Consorci Sanitari from Terrassa.

Adults should have at least one measurement of eGFR and UACR in a local laboratory close to 1st January 2018 (up to 6 months) to be included both tests measurements had to be performed within a maximum of 3 months. In addition, patients should have at least 12 months of continuous presence in the database prior to the qualifying measurement (?? It refers to the index date)of eGFR.

The index date was the date of the eGFR measurement closest to 1st January 2018 . The study population (excluding patients on dialysis [n=356] or renal transplant [n=232], was n= 70,385); these patients were staged according to KDIGO definitions based on eGFR and UACR values (model 1) [1]. Patients were followed during a 2-year period to analyze the occurrence of cardiovascular and renal outcomes. Additionally, a sensitivity analysis was performed in adults with at least two consecutive eGFR laboratory tests ≤730 days apart with values within the same CKD stage range, and at least 12 months of continuous presence in the database prior to the first qualifying eGFR. This information enhanced the reliability of CKD classification by requiring two eGFR measurements over time rather than a single value, thereby reducing the risk of misclassification due to transient eGFR fluctuations. However, this stricter criterion led to a reduction in sample size, as individuals with only one qualifying eGFR measurement were excluded. Despite this trade-off, the consistency of findings across different approaches reinforced the robustness of our results. In this case (model 2), the index date was the date of the second conclusive eGFR measure closest to 1st January 2018. The study population (n= 52,796) was staged according to KDIGO definitions based on eGFR and UACR values [1].

Baseline characteristics across KDIGO categories were determined at index date; this includes demographics, comorbidities and medications.

1. Demographics

contained age, sex, body mass index, and blood pressure. Comorbidities were searched for in all available data prior to the index date. The main baseline comorbidities included cardiovascular disease, coronary ischemic disease, heart

failure, stroke, atrial fibrillation, peripheral artery disease (PAD), and diabetes. International Classification of Diseases (ICD-9) and ICD-10 codes were considered for the diagnosis of comorbidities (https://eciemaps.mscbs.gob.es). The information about treatments was obtained from the registries for dispensing medicines, according to the Anatomical Therapeutic Chemical Classification System [25]. Treatments were prescribed according to routine practice and included renin angiotensin system inhibitors (RASi), mineralocorticoid receptor antagonists, angiotensin receptor-neprilysin inhibitors, sodium-glucose cotransporter-2 inhibitors (SGLT2i) in persons with or without diabetes, beta blockers, diuretics, calcium channel blockers, low dose aspirin, statins, and medications for the treatment of diabetes (metformin, sulfonylureas, dipeptidyl peptidase 4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), meglitinides, and insulin). Laboratory tests closest to the index date were collected and included the following UACR, eGFR, HbA1c, serum creatinine, uric acid, potassium, lipid profile and hemoglobin, .

Cardiovascular and renal events were defined as a main diagnosis during a hospital visit or during hospital admission occurring during the 2 years after the index date. Cardiovascular outcomes included myocardial infarction, stroke, heart failure, peripheral artery disease, and MACE composed of any of the following outcomes: stroke, myocardial infarction or all-cause death. Renal outcomes included hospitalization for CKD, reduction of eGFR ≥50% from baseline ~~(below a 50%???~~, dialysis, kidney transplantation, progression from A1/A2 to A3, and a composed MARE of any of the previous renal outcomes. Outcomes were calculated in the population across KDIGO categories.

Statistical analysis

Categorical variables were defined by their absolute numbers and proportions, ~~whereas~~ and the continuous variables by the mean and standard deviation. Incidence rates were presented as events (N) and rates (events per 1000 patient-years [p-y]). Follow-up was censored at the end of the observation period or death ~~end~~?? unless an event had occurred. In this study, we focused exclusively on descriptive analyses of RWD, and since no formal hypothesis

testing was performed, p-values were not calculated [26]. The data were analyzed using the statistical package SPSS v25.0 (SPSS Inc., Chicago, Illinois, USA), while R (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria) was employed to generate all data visualizations.

Results.

The total population covered 70,385 subjects, of whom 49,258 (69.4%) had normal albuminuria (A1) and renal function (stages G1 or G2) and the remaining 21,127 (30.0%) had CKD by either renal function (CKD stages >G2 or albuminuria criteria [5]. In the population of CKD patients, the mean (SD) age ranged from 72.4 (20.1) to 82.6 (9.0) years in categories G3a-5 A1, from 56.6 (11.3) to 82.3 (10.1) years in categories G1-5 A2, and from 55.7 (11.2) to 77.1 (10.7) years in categories G1-5 A3. In these KDIGO categories, the proportion of women ranged from 46.8% to 69.7%, 46.1% to 61.2% and 34.9% to 45.5%, respectively (NO entiendo lo del Rango: En cada categoría (como G3a-5 A1), están indicando varios subgrupos dentro de esa categoría, y se muestran los valores mínimo y máximo de las medias en esos subgrupos. Los valores de cada categoría están presentados en las tablas correspondientes.). Regarding comorbidities, type 2 diabetes (T2D) was present in a range from 38.2% to 46.8%, in categories G3a-5 A1, in 31.6% to 52.5% in G1-5 A2 and 53.6% to 68.0% of patients in G1-5 A3. As far as, coronary heart disease was respectively present in 8.8% to 20.3%, 4.4% to 18.4% and 6.3% to 19.4%; , and heart failure was observed in 10.7% to 27.4%, 3.1% to 31.4% and 3.4% to 32.6%, respectively. In general, an increase in age was associated with a reduction in kidney function or increased albuminuria. The proportion of women was increased n as the eGFR decreased, but there there were less women in the case of higher albuminuria. Body mass index was lower as kidney function decreased but it was higher among those patients with more albuminuria. Systolic blood pressure increased as CKD progressed up to the G3a stage and then decreased; by contrast the diastolic blood pressure decreased as renal function worsened. HbA1c increased with the magnitude of albuminuria. LDL cholesterol was lower as renal function and albuminuria worsened. The prevalence of cardiovascular diseases, and each of its

components, as well as T2D increased as renal function and albuminuria worsened (table 1, supplementary figures 1 and 2). The sensitivity analysis (model 2) showed similar results (supplementary table 1).

Regarding cardiovascular treatments, RASi were prescribed in 47.1% to 76.4%, 63.2% to 79.6%, and 51.2% to 85.9% of patients in G3a-5 A1, G1-5 A2, and G1-5 A3 of the KDIGO categories, respectively; and statins was used in n 23.5% to 56.3%, 34.2% to 56.7% and 32.6% to 60.2%, respectively. The use of RASi is increased among those patients with moderate renal dysfunction and it was decreased in advanced stages of CKD. In addition, the use of RASi was increased in patients with more albuminuria. Treatment with statins increased as renal function worsened. The prescription of SGLT2i was marginal through all KDIGO categories. The use of SGLT2i increased with albuminuria levels (table 1, supplementary figure 3). These findings were also detected in the sensitivity analysis (supplementary table 1).

The incidence of MACEs and MAREs during 2 years of follow-up. Incidence rates (per 1000 patients/year) of combined MACE variable ranged from 102.9 (es necesario poner decimales? En publicaciones previas se han mantenido. Redondeamos el texto a 1 decimal t 245.2 per 1000 in the G3a-5 A1 category, 40.7 to 261.1 in G1-5 A2, and 69.1 to 362.3 in G1-5 A3. ~~according to KDIGO classifications~~. Incidence rates for combined MARE variable ranged from 14.9 to 454.4, 29.8 to 588.5, and 11.8 to 637.2 respectively (Table 2). Both individual MACEs and MAREs incidence rates increased as renal function worsened and albuminuria rose. As shown in Figure 1, in early CKD, the risk og MACE was predominant, and the rate of Mare was more evident in advanced CKD it , but also with high risk of MACE. Mortality increased across eGFR stages, with a sharp increase in G4 and G5 (Supplementary figure 4). The presence of albuminuria increased mortality risk notably; , with A3 mortality was 1.5 to 2 times higher than withA1 in each eGFR category, even at early CKD stages.

Regarding the type of event, in absolute terms, heart failure was the most frequent event in every stage; even in G5 A1 the rate was as high as 145.12 per 1000)

(Supplementary figure 5), being worse ~~exceeding the worst-case scenario (no lo entiendo)~~ for myocardial infarction (Supplementary figure 6), stroke (Supplementary figure 7), and PAD Supplementary figure 8). Conversely, stroke had the lowest absolute rates at early CKD stages (4.81 per 1000 p-y in G1 A1) but raised steeply to 60.24 per 1000 p-y in G5 A3, surpassing myocardial infarction and PAD in later CKD stages.

Furthermore, heart failure stood out as the event that increased most ~~dramatic (means drama or quantity?~~ with rates increasing 33-fold from G1 A1 (5.27 per 1000 p-y) to G5A3 (175.81 per 1000 p-y). These numbers exceeds the relative increases seen in myocardial infarction (9.2-fold increase, from 6.48 per 1000 p-y to 59.83 per 1000 p-y), stroke (12.5-fold increase, from 4.81 per 1000 p-y to 60.24 per 1000 p-y), and PAD (10.3-fold increase, from 7.67 per 1000 p-y to 78.98 per 1000 p-y).

Regarding the risk of MARE, it increased sharply with the decline in eGFR and the increase in albuminuria. Reduction of eGFR ≥50% from baseline had the highest rates at G5 ~~(nO entiendo)~~, but hospitalization rates for CKD were high across all stages ~~wasconsistently showed the highest event rates at every stage (no lo entiendo), with G5 A1 (161.68 per 1000 p-y)~~ (Supplementary Figure 9) surpassing the peak rates observed for eGFR decline ≥50% in G1 to G4 (Supplementary Figure 10), dialysis initiation (Supplementary Figure 11), and kidney transplantation (Supplementary Figure 12). Notably, hospitalization for CKD increased ~~experienced the most dramatic rise, increasing~~ 868-fold from G1 A1 (0.28 per 1000 p-y) to G5 A3 (242.65 per 1000 p-y). These trends remained in the sensitivity analysis (Supplementary Table 2). (~~NO soy capaz de enteder este parafo y temo decir algo que no es~~

In early CKD stages (G1–G3a), all-cause mortality rates were comparable to or higher than heart failure and hospitalization for CKD. It should be emphasized the significant cardiovascular risk in patients with mild to moderate kidney dysfunction. As CKD advanced from G3b to G5 (Lo he dicho bien?, correcto), mortality continued to rise but at more moderate pace compared to the sharp acceleration of hospitalization rates, which

surpassed both mortality and heart failure in the most advanced CKD stages, particularly in those with high albuminuria (A3) (Figure 2).

Discussion.

This study was performed in a large number of patients with measurements of eGFR and UACR, as assessed by blood and urine tests collected in Healthcare Information Systems. The results shows , that patients with CKD had many comorbidities, particularly T2D and cardiovascular diseases. Even though the rates of cardiovascular and renal events were high, the use of drugs to protect cardiovascular and renal system was substantially low. In addition, although the clinical profile showed that the risk of cardiovascular and renal events worsened as renal function declined and albuminuria increased, this information did not translate into a significant improvement in the management of these patients. Furthermore, the information from patients without CKD in the same healthcare area was also collected to have information of the real impact of CKD on the clinical profile, management and cardiovascular and renal outcomes.

Our study included around 21,000 patients with CKD that were analyzed across the KDIGO categories. There were elevant differences in the clinical profile according to renal function and the degree of albuminuria . In DAPA-CKD trial ~~(Study??)~~, the mean age was 62 years, 68% T2D and 38% had cardiovascular disease [11]. In EMPA-KIDNEY and FIDELITY trials, the age was were 64 and 65 year, the percent of T2D was 97% and 100%, and cardiovascular disease was present in 27% and 46%, respectively [12,13]. It should be recognized that As a considering the inclusion and exclusion criteria of the mentioned RCTs, not all patients with CKD were represented in these studies, indicating the need for studies with RWD. In addition , although some studies have analyzed the clinical profile of patients with CKD in the real-world population [6-8], our study specifically analyzed the clinical profile, management and outcomes across KDIGO categories, including both eGFR and UACR.

In this context, our study showed that age and comorbidities increased as renal function or albuminuria worsened. Furthermore, according to the values obtained in physical examination and laboratory parameters, our data suggested that a substantial proportion of patients did not achieve the blood pressure, LDL cholesterol and HbA1c targets recommended when this study was performed [27,28]. Although there were some differences in the management ~~(en que ?)~~ according to renal function and albuminuria, the fact is that there is much room for improvement across all KDIGO categories. Importantly, in the last years, guidelines have strengthened the importance of achieving strict control of risk factors in patients with CKD due to the high/very high risk of death and cardiovascular events in this population [29-31].

Regarding cardiovascular treatments, despite the fact that the use of RASi is greater in patients with moderate renal dysfunction and with albuminuria, overall, many patients with CKD were not on RASi therapy. It should be noted that in patients with CKD the continued use of RASi is associated with cardiovascular and renal benefits , even in individuals with advanced CKD [32,33] and the discontinuation of these drugs is associated with an increased risk of subsequent death, cardiovascular complications and progression of renal renal dysfunction [34-36]. These patients, particularly those with advanced CKD, may have a higher risk of side effects, such as hyperkalemia. However, the discontinuation of RASi after hyperkalemia is associated with worsened prognosis among patients with CKD [37]. In this context, the use of novel potassium binders may facilitate the prescription and maintenance of these drugs, leading to a reduction of cardiovascular and renal complications [38].

The use of SGLT2i in our study was marginal, but it should be kept in mind that baseline data were recorded in 2018 and the first approval for indications of dapagliflozin and empagliflozin in CKD were obtained in 2021 and 2023, respectively, based on the results of the DAPA-CKD and EMPA-KIDNEY trials [11,12]. Therefore, it would be expected to observe more use of SGLT2i in the CKD population in the following years. However, recent studies have shown that these disease-modifying therapies have not yet been successfully implemented into clinical practice, mostly in patients without co-existing T2D [39]. Anyway, as the present analysis was based on data from 2018, predating the

routine incorporation of SGLT2i into standard nephroprotective therapy, further evaluation using contemporary datasets is warranted to assess their real-world impact on renal outcomes. Also, more than 40% of patients with CKD were not taking statins.

Guidelines recognize that patients with CKD have a high or very high cardiovascular risk and consequently, strict LDL cholesterol goals should be attained in this population. In this context, greater use of lipid lowering therapies, alone or in combination should be encouraged [40,41]. Our results confirm previous findings in other countries, adherence to KDIGO CKD guidelines is low globally, with significant variation among countries [20,21]. Therefore, our data showed that there are target care gaps in guideline adherence and prescription trends, and that RWD highlights opportunities for improving outcomes.

, In addition, it has to be stated that we have analyzed the data through 2 different models, using one or at least two consecutive eGFR laboratory tests. No differences were observed in trends between both models concerning patient clinical characteristics, or cardiovascular and renal outcomes occurrence across KDIGO categories. This suggests that although CKD has traditionally been defined as abnormalities of kidney structure or function, present at least for 3 months [1], when alterations in eGFR or UACR are found, the early prescription of cardiovascular and renal protective drugs should be encouraged. This is aligned with previous finding showing that single-time point assessments of UACR and eGFR can predict mortality risk, reinforcing the importance of kidney function screening [42]. In other words, just an altered value obtained in one determination of eGFR or UACR, if no acute intercurrent condition is occurring, should be sufficient to prompt a thorough evaluation of the patient's condition, consider a diagnosis of CKD and offer an early intervention with cardiovascular and renal protective therapies.

Regarding cardiovascular and renal events it should be noted that after 2 years of follow-up, the incidence rates were markedly higher in the CKD population than in those without CKD and they are increased as renal function worsened and albuminuria increased. However, even in patients without CKD according to KDIGO criteria (groups G1A1 and G2A1), any sustained decline in GFR, even within the normal range is associated with an increase in the two-year MACE and MARE

, which entails an increased vascular and renal risk. Remarkably, as kidney disease progressed, the nature of the risk changes. In the early stages of renal function impairment, cardiovascular complications were mainly responsible for heart failure and driving mortality. However, as CKD worsened, kidney-related complications became the most relevant health threat, with increase in the rate of hospitalizations surging past heart failure and even mortality, especially in those with severe albuminuria. Independently of the stage of kidney function, more albuminuria indicated a greater risk of complications. However, its effects became especially severe in the later stages of CKD, where the risk of hospitalization and death raised sharply. This pattern highlights the critical demand for early intervention to slow disease progression, reduce complications, and give patients a better chance of healthier outcomes [1]. However, heart failure was the most frequent cardiovascular event followed by PAD and hospitalization for CKD, the most common renal event. Of note, these complications may occur early in the evolution of patients with CKD. These findings are aligned with previous results by others [43-45]. These data highlight the close relationship between the heart and the kidney, namely the cardio-renal syndrome. As a result, more efforts should be made to accomplish the prompt identification of these conditions and the early initiation of appropriate treatments to delay the development of potential complications [43-45]. Previous findings have shown that a rapid decline in eGFR that indicates rapid progression of CKD is significantly associated with MACE, heart failure and myocardial infarction [46] and current guidelines are poorly adapted to end-stage kidney disease patients [47]. ~~(no se si te refieres a "rapid decline que acaba end stage kidney disese~~

Furthermore, our data reveals relevant gaps in patients care and in the management of risk factors, and missing opportunities to use evidence-based therapies. The use of drugs with proven cardiovascular and renal benefits should be encouraged, and there is a need to reduce knowledge gaps and overcome system-level barriers, as clearly indicated by the KDIGO 2024 Clinical Practice Guidelines. [1]. This recommendation should be extended across all stages of CKD, not only from the early stages to prevent the development of complications, but also in the advanced stages of CKD where the beneficial effects on cardiovascular and renal outcomes remain and are key to prevent death [48,49].

This study has some limitations. Although the retrospective design is the best to reflect performance of clinical practice, it may introduce some biases. In fact, real-world data enhance generalizability but carries risks of including confounding factors. Certainly, some data could be missing from the electronic health records. Furthermore, the retrospective designs may generate relevant hypothesis, but it cannot establish causality. However, potential biases may be mitigated due to the high number of patients included and the sensitivity analyses that confirmed these results and their consistency with previous publications. Moreover, in contrast with previous publications, our study provided a comprehensive overall description of CKD across all KDIGO categories addressing cardiovascular and renal risks, as well as gaps in the management of this population, and suggesting opportunities for improving care, making the study useful for clinicians.

In conclusion, this RWD study shows that patients with CKD are affected by many comorbidities and are at high risk for developing cardiovascular complications and renal disease progression. However, the use of cardiovascular and renal protective drugs is far from optimal in all the KDIGO categories indicative of CKD, which denotes the strong need to improve the management of these patients across the entire spectrum of the disease.

Conflict of Interests: Unai Aranda, Beatriz Palacios, Margarita Capel are AstraZeneca employees; Ignacio Hernández is an Atrys employee. Rafael Santamaría reports lecture fees from Astra-Zeneca, Boehringer-Ingelheim, Vifor CSL, Bayer; and advisory fees from Astra-Zeneca and Bayer. None related to this manuscript. Carlos Escobar has received honoraria from Almirall, Esteve, Amgen, Bayer, Boehringer, Sanofi, MSD, Mylan, Servier, Ferrer, Daiichi-Sankyo, Novartis, Pfizer, Viatris, as speaker or advisor. None related to this manuscript. Ana Cebrián declares funding to conduct clinical trials MSD and Sanofi (all to the IMIB institute); consulting fees from AstraZeneca, Bayer, Eli Lilly, MSD, Novo Nordisk and Sanofi; payment of honoraria for lectures from AstraZeneca, Bayer, Boehringer-Ingelheim, Eli Lilly, Menarini, MSD, Sanofi and Novo Nordisk. Roberto Alcázar reports lecture fees from Astra-Zeneca, Boehringer-Ingelheim, Vifor CSL, Bayer, Rubio and Fresenius Medical Care; and advisory fees from Astra-Zeneca and Bayer. None related to this manuscript. Manuel Gorostidi reports lecture fees from Astra Zeneca, and Servier, and advisory fees from Fresenius Medical Care, Boehringer Ingelheim, and Astra Zeneca (none related to the present article). This study was sponsored and financed by AstraZeneca. The rest of the authors do not have conflicts of interest.

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Table 1. Baseline characteristics by KDIGO risk category, n=70,385 subjects (model 1*).

	G1 A1	G2 A1	G3a A1	G3b A1	G4 A1	G5 A1 (no dialysis)
	35.13%	34.86%	4.96%	2.01%	0.54%	0.05%
Biodemographic data						
Age, years	52.0 (12.7)	69.25 (11.2)	77.0 (9.5)	81.0 (8.8)	82.6 (9.0)	72.4 (20.1)
Gender (female), n (%)	11614 (47.0)	12307 (50.2)	1634 (46.8)	801 (56.6)	265 (69.7)	21 (61.8)
BMI, kg/m^2	26.5 (7.2)	27.68 (6.5)	28.2 (6.2)	28.2 (6.21)	28.2 (6.5)	24.6 (7.4)
Systolic BP, mmHg	123.22 (24.0)	129.8 (22.8)	132.1 (21.6)	130.9 (21.7)	129.6 (20.9)	129.7 (9.0)
Diastolic BP, mmHg	76.51 (12.5)	75.98 (11.3)	74.2 (10.3)	71.2 (10.0)	69.7 (9.6)	74.9 (5.2)
Comorbidities						
CVD, n (%)	1916 (7.7)	4773 (19.5)	1182 (33.9)	612 (43.3)	205 (53.9)	13 (38.2)
Coronary ischemic disease, n (%)	743 (3.0)	1698 (6.9)	409 (11.7)	193 (13.6)	77 (20.3)	3 (8.8)
Heart failure, n (%)	274 (1.1)	1105 (4.5)	374 (10.7)	269 (19.0)	104 (27.4)	8 (23.5)
Stroke, n (%)	301 (1.2)	738 (3.0)	171 (4.9)	90 (6.4)	28 (7.4)	3 (8.8)
Atrial Fibrillation, n (%)	349 (1.4)	1596 (6.5)	446 (12.8)	249 (17.6)	93 (24.5)	6 (17.6)
Peripheral artery disease, n (%)	565 (2.3)	968 (3.9)	241 (6.9)	119 (8.4)	20 (5.3)	0 (0.0)
Diabetes, n (%)	4897 (19.8)	7407 (30.2)	1391 (39.8)	612 (43.3)	182 (47.9)	13 (38.2)
Type 1 diabetes, n (%)	182 (0.7)	88 (0.4)	13 (0.4)	11 (0.8)	4 (1.1)	0 (0.0)
Type 2 diabetes, n (%)	4715 (19.1)	7319 (29.8)	1378 (39.5)	601 (42.5)	178 (46.8)	13 (38.2)
No CVD nor Diabetes, n (%)	18830 (76.2)	14680 (59.8)	1536 (44.0)	509 (36.0)	101 (26.6)	15 (44.1)
CV drugs						
RAASi, n (%)	10455 (42.3)	14933 (60.9)	2668 (76.4)	1045 (73.9)	250 (65.8)	16 (47.1)
ACEi, n (%)	6268 (25.4)	7844 (32.0)	1234 (35.3)	444 (31.4)	95 (25.0)	4 (11.8)
At maximal doses, n (%)	2736 (43.7)	3366 (42.9)	555 (45.0)	200 (45.0)	44 (46.3)	4 (100.0)
ARBs, n (%)	4206 (17.0)	7117 (29.0)	1444 (41.4)	610 (43.1)	155 (40.8)	12 (35.3)
At maximal doses, n (%)	1744 (41.5)	2884 (40.5)	607 (42.0)	256 (42.0)	73 (47.1)	6 (50.0)
MRAs, n (%)	90 (0.4)	265 (1.1)	87 (2.5)	61 (4.3)	27 (7.1)	1 (2.9)
ARNI, n (%)	4 (0.0)	10 (0.0)	5 (0.1)	1 (0.1)	1 (0.3)	0 (0.0)
SGLT2i (non-T2DM), n (%)	19 (0.1)	48 (0.2)	5 (0.1)	2 (0.1)	0 (0.0)	1 (2.9)
Beta blockers, n (%)	1702 (6.9)	3738 (15.2)	828 (23.7)	418 (29.6)	128 (33.7)	4 (11.8)
Diuretics, n (%)	3233 (13.1)	8242 (33.6)	1417 (40.6)	587 (41.5)	163 (42.9)	6 (17.6)
Calcium channel blockers, n (%)	1151 (4.7)	2442 (10.0)	524 (15.0)	247 (17.5)	82 (21.6)	5 (14.7)
Low dose aspirin, n (%)	1660 (6.7)	4089 (16.7)	889 (25.5)	426 (30.1)	134 (35.3)	8 (23.5)
Statins, n (%)	8741 (35.4)	11784 (48.0)	1861 (53.3)	781 (55.2)	214 (56.3)	8 (23.5)
Diabetes medication, n (%)	4891 (19.8)	7385 (30.1)	1388 (39.8)	608 (43.0)	182 (47.9)	13 (38.2)
Metformin, n (%)	3819 (15.4)	3864 (15.7)	723 (20.7)	223 (15.8)	14 (3.7)	1 (2.9)
SU, n (%)	50 7 (2.1)	1074 (4.4)	226 (6.5)	63 (4.5)	11 (2.9)	2 (5.9)
DPP4i, n (%)	257 (1.0)	1111 (4.5)	335 (9.6)	243 (17.2)	104 (27.4)	6 (17.6)
Metiglinides, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)
GLP-1 RA, n (%)	140 (0.6)	295 (1.2)	50 (1.4)	18 (1.3)	14 (3.7)	4 (11.8)
Insulin, n (%)	1001 (4.0)	2432 (9.9)	357 (10.2)	207 (14.6)	87 (22.9)	6 (17.6)
SGLT2i (T2DM), n (%)	229 (0.9)	643 (2.6)	76 (2.2)	12 (0.8)	4 (1.1)	0 (0.0)
Biochemical parameters						
UACR, mg/g	8.8 (6.0)	10.5 (6.7)	12.6 (7.2)	14.6 (7.4)	15.0 (7.2)	10.7 (6.6)
eGFR, ml/min/1.73m^2	99.2 (4.3)	79.2 (7.9)	53.0 (4.3)	37.9 (4.2)	23.3 (4.2)	6.6 (4.5)
HbA1c, %	6.3 (1.2)	6.5 (1.0)	6.6 (1.1)	6.7 (1.1)	6.8 (1.1)	6.1 (0.9)
Creatinine, mg/dL	0.7 (0.1)	1.0 (0.2)	1.5 (0.1)	1.9 (0.2)	2.9 (0.5)	6.2 (1.2)
Uric acid, mg/dL	5.5 (1.0)	6.0 (1.1)	6.8 (1.1)	7.3 (1.2)	7.7 (1.4)	6.7 (1.4)
Potassium, mmol/L	4.9 (0.7)	5.0 (0.7)	5.1 (1.1)	5.2 (0.7)	5.3 (0.7)	5.3 (0.7)
Hemoglobin, g/dL	14.6 (1.4)	14.4 (1.4)	13.9 (1.6)	13.1 (1.7)	11.8 (1.5)	12.3 (1.6)

	G1 A2	G2 A2	G3a A2	G3b A2	G4 A2	G5 A2 (no dialysis)
	5.10%	9.13%	2.67%	1.85%	0.71%	0.05%
Biodemographic data						
Age, years	56.6 (11.3)	72.9 (10.8)	77.8 (10.1)	81.4 (9.2)	82.3 (10.1)	78.9 (16.1)
Gender (female), n (%)	1654 (46.1)	3346 (52.1)	900 (47.9)	691 (53.1)	304 (61.2)	22 (57.9)
BMI, kg/m²	29.8 (6.6)	28.9 (6.0)	28.9 (6.1)	28.4 (6.2)	28.0 (6.9)	26.4 (7.2)
Systolic BP, mmHg	130.0 (22.1)	133.2 (22.1)	133.8 (21.6)	134.4 (21.7)	133.4 (20.7)	126.6 (17.6)
Diastolic BP, mmHg	79.0 (11.2)	75.3 (10.6)	73.5 (10.1)	71.9 (9.9)	70.5 (9.4)	68.5 (9.3)
Comorbidities						
CVD, n (%)	498 (13.9)	1942 (30.2)	815 (43.4)	653 (50.2)	277 (55.7)	22 (57.9)
Coronary ischemic disease, n (%)	158 (4.4)	614 (9.6)	256 (13.6)	218 (16.7)	85 (17.1)	7 (18.4)
Heart failure, n (%)	111 (3.1)	603 (9.4)	302 (16.1)	282 (21.7)	156 (31.4)	8 (21.1)
Stroke, n (%)	84 (2.3)	306 (4.8)	106 (5.6)	98 (7.5)	30 (6.0)	3 (7.9)
Atrial Fibrillation, n (%)	131 (3.6)	751 (11.7)	365 (19.4)	269 (20.7)	127 (25.6)	10 (26.3)
Peripheral artery disease, n (%)	133 (3.7)	435 (6.8)	196 (10.4)	132 (10.1)	56 (11.3)	3 (7.9)
Diabetes, n (%)	1617 (45.0)	3152 (49.1)	986 (52.5)	680 (52.2)	268 (53.9)	12 (31.6)
Type 1 diabetes, n (%)	37 (1.0)	53 (0.8)	14 (0.7)	15 (1.2)	7 (1.4)	0 (0.0)
Type 2 diabetes, n (%)	1580 (44.0)	3099 (48.2)	972 (51.8)	665 (51.1)	261 (52.5)	12 (31.6)
No CVD nor Diabetes, n (%)	1852 (51.6)	2617 (40.7)	606 (32.3)	366 (28.1)	129 (26.0)	15 (39.5)
CV drugs						
RAASi, n (%)	2345 (65.3)	4584 (71.4)	1494 (79.6)	949 (72.9)	329 (66.2)	24 (63.2)
ACEi, n (%)	1324 (36.9)	2226 (34.7)	609 (32.4)	377 (29.0)	110 (22.1)	7 (18.4)
At maximal doses, n (%)	1087 (82.1)	1812 (81.4)	497 (81.6)	302 (80.1)	86 (78.2)	4 (57.1)
ARBs, n (%)	1030 (28.7)	2373 (36.9)	891 (47.4)	575 (44.2)	220 (44.3)	17 (44.7)
At maximal doses, n (%)	851 (82.6)	1952 (82.3)	731 (82.0)	475 (82.6)	178 (80.9)	16 (94.1)
MRAs, n (%)	30 (0.8)	129 (2.0)	72 (3.8)	51 (3.9)	18 (3.6)	2 (5.3)
ARNI, n (%)	1 (0.0)	12 (0.2)	6 (0.3)	3 (0.2)	0 (0.0)	0 (0.0)
SGLT2i (non-T2DM), n (%)	12 (0.3)	22 (0.3)	7 (0.4)	3 (0.2)	3 (0.6)	0 (0.0)
Beta blockers, n (%)	399 (11.1)	1367 (21.3)	546 (29.1)	408 (31.3)	167 (33.6)	9 (23.7)
Diuretics, n (%)	698 (19.4)	2228 (34.7)	789 (42.0)	570 (43.8)	236 (47.5)	15 (39.5)
Calcium channel blockers, n (%)	380 (10.6)	1126 (17.5)	390 (20.8)	343 (26.3)	147 (29.6)	10 (26.3)
Low dose aspirin, n (%)	489 (13.6)	1504 (23.4)	555 (29.6)	418 (32.1)	157 (31.6)	6 (15.8)
Statins, n (%)	1698 (47.3)	3425 (53.3)	1065 (56.7)	706 (54.2)	276 (55.5)	13 (34.2)
Diabetes medication, n (%)	1607 (44.8)	3138 (48.9)	982 (52.3)	676 (51.9)	268 (53.9)	12 (31.6)
Metformin, n (%)	882 (24.6)	1690 (26.3)	506 (26.9)	264 (20.3)	11 (2.2)	0 (0.0)
SU, n (%)	247 (6.9)	554 (8.6)	133 (7.1)	68 (5.2)	14 (2.8)	0 (0.0)
DPP4i, n (%)	135 (3.8)	380 (5.9)	200 (10.6)	251 (19.3)	162 (32.6)	9 (23.7)
Metiglinides, n (%)	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)
GLP-1 RA, n (%)	106 (3.0)	97 (1.5)	26 (1.4)	10 (0.8)	16 (3.2)	0 (0.0)
Insulin, n (%)	543 (15.1)	1107 (17.2)	352 (18.7)	265 (20.4)	142 (28.6)	5 (13.2)
SGLT2i (T2DM), n (%)	162 (4.5)	213 (3.3)	44 (2.3)	13 (1.0	13 (2.6)	1 2.6
Biochemical parameters						
UACR, mg/g	77.0 (56.1)	80.7 (58.0)	89.0 (63.3)	97.1 (65.8)	105.4 (70.1)	113.1 (75.1)
eGFR, ml/min/1.73m²	98.6 (4.3)	78.0 (8.1)	52.7 (4.3)	37.9 (4.2)	23.1 (4.5)	7.4 (4.9)
HbA1c, %	7.0 (1.4)	6.9 (1.2)	6.9 (1.2)	6.9 (1.1)	7.0 (1.3)	6.6 (1.3)
Creatinine, mg/dL	0.7 (0.1)	1.0 (0.2)	1.5 (0.1)	1.9 (0.2)	2.9 (0.5)	6.0 (1.2)
Uric acid, mg/dL	5.8 (1.8)	6.1 (1.0)	7.0 (2.8)	7.3 (1.2)	7.6 (1.3)	7.4 (1.2)
Potassium, mmol/L	4.9 (0.7)	5 (0.7)	5.2 (0.7)	5.2 (0.7)	5.3 (0.8)	5.1 (0.7)
Hemoglobin, g/dL	14.6 (1.5)	14.1 (1.6)	13.5 (2.0)	13.1 (2.1)	11.7 (1.4)	11.6 (1.6)

	G1 A3	G2 A3	G3a A3	G3b A3	G4 A3	G5 A3 (no dialysis)
	0.50%	1.05%	0.51%	0.49%	0.35%	0.06%
Biodemographic data						
Age, years	55.7 (11.2)	69.6 (12.6)	73.8 (10.5)	77.1 (10.7)	76.6 (12.5)	75.9 (13.8)
Gender (female), n (%)	133 (38.1)	287 (38.9)	126 (34.9)	148 (43.0)	112 (45.5)	16 (37.2)
BMI, kg/m²	30.8 (6.7)	29.8 (6.2)	29.8 (6.3)	30.3 (6.1)	28.9 (6.4)	26.3 (6.8)
Systolic BP, mmHg	132.2 (21.4)	136.4 (22.9)	135.8 (21.9)	138.3 (22.7)	133.7 (24.3)	138.1 (19.4)
Diastolic BP, mmHg	79.0 (10.8)	76.5 (11.0)	73.2 (10.1)	71.9 (10.1)	71.8 (11.2)	74.3 (9.6)
Comorbidities						
CVD, n (%)	64 (18.3)	275 (37.3)	182 (50.4)	178 (51.7)	136 (55.3)	26 (60.5)
Coronary ischemic disease, n (%)	22 (6.3)	89 (12.1)	70 (19.4)	57 (16.6)	42 (17.1)	8 (18.6)
Heart failure, n (%)	12 (3.4)	91 (12.3)	69 (19.1)	90 (26.2)	68 (27.6)	14 (32.6)
Stroke, n (%)	10 (2.9)	40 (5.4)	25 (6.9)	32 (9.3)	28 (11.4)	3 (7.0)
Atrial Fibrillation, n (%)	13 (3.7)	102 (13.8)	68 (18.8)	70 (20.3)	58 (23.6)	4 (9.3)
Peripheral artery disease, n (%)	22 (6.3)	75 (10.2)	46 (12.7)	45 (13.1)	25 (10.2)	7 (16.3)
Diabetes, n (%)	199 (57.0)	485 (65.8)	224 (62.0)	239 (69.5)	141 (57.3)	24 (55.8)
Type 1 diabetes, n (%)	12 (3.4)	8 (1.1)	4 (1.1)	5 (1.5)	6 (2.4)	0 (0.0)
Type 2 diabetes, n (%)	187 (53.6)	477 (64.7)	220 (60.9)	234 (68.0)	135 (54.9)	24 (55.8)
No CVD nor Diabetes, n (%)	143 (41.0)	211 (28.6)	89 (24.7)	73 (21.2)	64 (26.0)	11 (25.6)
CV drugs						
RAASi, n (%)	280 (80.2)	626 (84.9)	310 (85.9)	290 (84.3)	167 (67.9)	22 (51.2)
ACEi, n (%)	163 (46.7)	253 (34.3)	124 (34.3)	99 (28.8)	46 (18.7)	4 (9.3)
At maximal doses, n (%)	127 (77.9)	207 (81.8)	93 (75.0)	82 (82.8)	40 (87.0)	3 (75.0)
ARBs, n (%)	118 (33.8)	378 (51.3)	187 (51.8)	193 (56.1)	121 (49.2)	18 (41.9)
At maximal doses, n (%)	90 (76.3)	312 (82.5)	154 (82.4)	156 (80.8)	100 (82.6)	14 (77.8)
MRAs, n (%)	4 (1.1)	32 (4.3)	23 (6.4)	18 (5.2)	13 (5.3)	1 (2.3)
ARNI, n (%)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
SGLT2i (non-T2DM) , n (%)	2 (0.6)	2 (0.3)	4 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Beta blockers, n (%)	52 (14.9)	168 (22.8)	126 (34.9)	107 (31.1)	76 (30.9)	11 (25.6)
Diuretics, n (%)	76 (21.8)	285 (38.7)	154 (42.7)	182 (52.9)	130 (52.8)	17 (39.5)
Calcium channel blockers, n (%)	56 (16.0)	190 (25.8)	106 (29.4)	131 (38.1)	90 (36.6)	17 (39.5)
Low dose aspirin, n (%)	62 (17.8)	220 (29.9)	125 (34.6)	130 (37.8)	93 (37.8)	13 (30.2)
Statins, n (%)	179 (51.3)	405 (55.0)	194 (53.7)	207 (60.2)	136 (55.3)	14 (32.6)
Diabetes medication, n (%)	198 (56.7)	484 (65.7)	223 (61.8)	238 (69.2)	141 (57.3)	24 (55.8)
Metformin, n (%)	77 (22.1)	240 (32.6)	94 (26.0)	87 (25.3)	3 (1.2)	0 (0.0)
SU, n (%)	21 (6.0)	76 (10.3)	27 (7.5)	16 (4.7)	7 (2.8)	1 (2.3)
DPP4i, n (%)	18 (5.2)	53 (7.2)	57 (15.8)	89 (25.9)	84 (34.1)	7 (16.3)
Metiglinides, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GLP-1 RA, n (%)	15 (4.3)	24 (3.3)	9 (2.5)	5 (1.5)	3 (1.2)	1 (2.3)
Insulin, n (%)	114 (32.7)	231 (31.3)	112 (31.0	98 (28.5)	82 (33.3)	1 (44.2)
SGLT2i (T2DM), n (%)	24 (6.9)	33 (4.5)	15 (4.2	6 (1.7)	1 (0.4)	0 (0.0
Biochemical parameters						
UACR, mg/g	797.2 (325.0)	847.3 (372.6)	885.5 (344.5)	1040.3 (472.7)	1278.9 (589.4)	1571.0 (607.4)
eGFR, ml/min/1.73m²	98.8 (4.4)	77.3 (8.2)	52.3 (4.3)	37.6 (4.2)	22.7 (4.2)	6.8 (5.3)
HbA1c, %	7.7 (1.7)	7.4 (1.4)	7.4 (1.4)	7.3 (1.2)	7.1 (1.4)	7.2 (1.6)
Creatinine, mg/dL	0.7 (0.1)	1.0 (0.2)	1.4 (0.1)	1.9 (0.2)	2.9 (0.5)	6.1 (1.3)
Uric acid, mg/dL	6.1 (1.0)	6.5 (1.1)	7.2 (1.2)	7.2 (1.1)	7.6 (1.3)	7.6 (1.0)
Potassium, mmol/L	5.0 (0.7)	5.0 (0.7)	5.2 (0.8)	5.3 (0.8)	5.4 (0.8)	5.2 (0.7)
Hemoglobin, g/dL	14.5 (1.7)	14.1 (1.8)	13.5 (1.8)	12.8 (1.7)	11.7 (1.4)	11.7 (1.3)

ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitor; BP: blood pressure; BMI: body mass index; CAT: category; CKD: chronic kidney disease; CVD: cardiovascular disease; DPP4i: dipeptidyl peptidase-4 inhibitors; eGFR: estimated glomerular filtration rate; GLP-1 RA: glucagon-like peptide-1 receptor agonists; HbA1c: glycated hemoglobin; KDIGO: Kidney Disease: Improving Global

Outcomes; MRAs: mineralocorticoid receptor antagonists; RAASi: renin angiotensin aldosterone system inhibitors; SGLT2 i: sodium-glucose cotransporter-2 inhibitors; SU: sulphonylureas; T2DM: type 2 diabetes mellitus; UACR: urine albumin-creatinine ratio. *Adults, with one eGFR laboratory test (index date was the date of the eGFR measure meeting the criteria closest to 01/01/2018) and at least 12 months of continuous presence in the database prior to the qualifying eGFR.

Table 2. Incidence rates of complications by KDIGO risk category during 2 years of follow-up, n=70,385 subjects (model 1**).

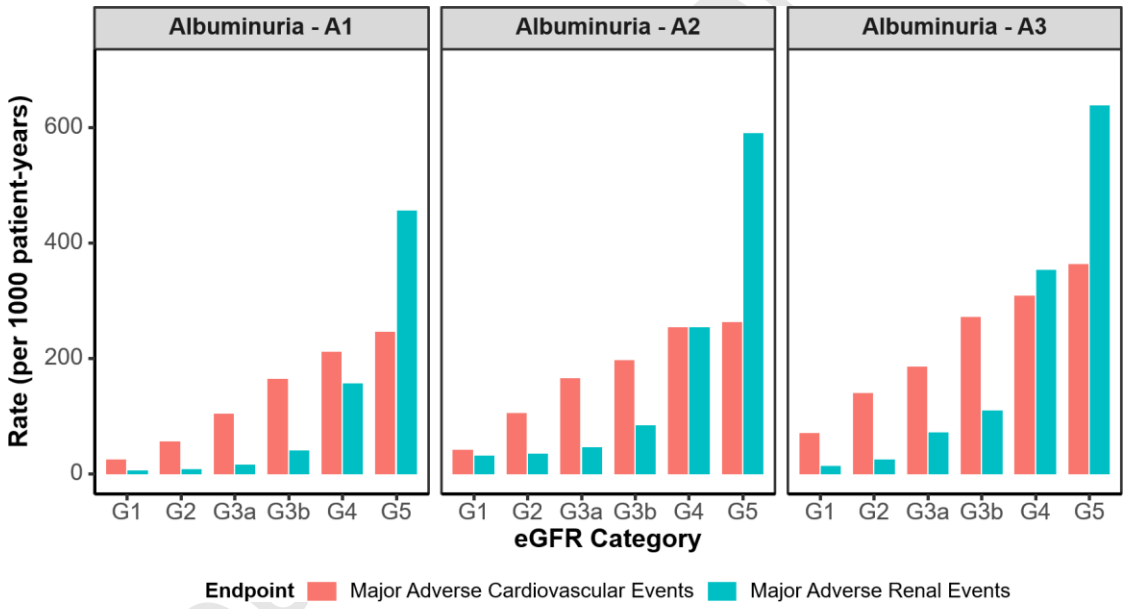
		G1 A1		G2 A1		G3a A1		G3b A1		G4 A1		G5 A1 (no dialysis)	
		35.13%		34.86%		4.96%		2.01%		0.54%		0.05%	
		N	Rates*	N	Rates*	N	Rates*	N	Rates*	N	Rates*	N	Rates*
Mortality	All-cause death	174	3.53	773	16.02	265	39.43	179	67.70	81	119.46	9	150.19
CV outcomes	Myocardial infarction	317	6.48	477	9.97	107	16.15	60	23.06	18	27.21	2	34.17
CV outcomes	Stroke	236	4.81	527	11.04	103	15.55	61	23.49	21	31.69	2	34.42
CV outcomes	Heart failure	258	5.27	1077	22.80	334	52.12	241	98.15	86	139.45	8	145.12
CV outcomes	PAD	375	7.67	698	14.66	170	25.90	72	27.95	20	30.15	3	52.87
CV outcomes	MACE	1101	22.88	2502	54.68	627	102.90	378	163.64	121	210.47	12	245.20
Renal outcomes	Hospitalization for CKD	4	0.08	16	0.33	29	4.34	57	21.96	51	81.18	8	161.68
Renal outcomes	Reduction of eGFR ≥50%	12	0.24	54	1.12	25	3.73	27	10.29	35	54.07	10	191.50
Renal outcomes	Dialysis	0	0.00	1	0.02	0	0.00	0	0.00	3	4.45	2	34.22
Renal outcomes	Kidney transplantation	1	0.02	0	0.00	0	0.00	0	0.00	1	1.47	1	17.11
Renal outcomes	Progression from A1/A2 to A3	218	4.44	274	5.71	50	7.49	21	8.01	13	19.60	1	17.04
Renal outcomes	MARE	235	4.79	336	7.01	99	14.95	100	39.10	91	155.54	18	454.36

		G1 A2		G2 A2		G3a A2		G3b A2		G4 A2		G5 A2 (no dialysis)	
		5.10%		9.13%		2.67%		1.85%		0.71%		0.05%	
		N	Rates*	N	Rates*	N	Rates*	N	Rates*	N	Rates*	N	Rates*
Mortality	All-cause death	56	7.87	434	34.99	200	56.35	219	91.48	135	160.02	11	171.17
CV outcomes	Myocardial infarction	60	8.50	180	14.73	80	23.06	59	25.14	32	39.24	3	49.96
CV outcomes	Stroke	59	8.36	237	19.46	88	25.31	74	31.73	27	33.03	3	47.14
CV outcomes	Heart failure	97	13.83	585	49.17	289	87.87	246	111.85	114	148.67	9	159.14
CV outcomes	PAD	90	12.79	338	28.03	130	37.86	81	34.77	30	36.17	4	67.72
CV outcomes	MACE	278	40.72	1162	103.43	503	164.24	399	195.32	175	252.00	13	261.06
Renal outcomes	Hospitalization for CKD	2	0.28	21	1.70	47	13.40	88	38.20	81	104.29	8	130.87
Renal outcomes	Reduction of eGFR ≥50%	5	0.70	46	3.72	14	3.96	15	6.31	62	78.80	16	317.70
Renal outcomes	Dialysis	0	0.00	1	0.08	1	0.28	2	0.84	5	5.97	2	32.26
Renal outcomes	Kidney transplantation	0	0.00	0	0.00	0	0.00	0	0.00	5	5.97	1	15.96
Renal outcomes	Progression from A1/A2 to A3	201	29.02	369	30.66	110	31.89	98	42.45	77	99.50	11	205.80
Renal outcomes	MARE	206	29.78	400	33.35	153	44.98	182	82.23	169	252.11	24	588.47

		G1 A3		G2 A3		G3a A3		G3b A3		G4 A3		G5 A3 (no dialysis)	
		0.50%		1.05%		0.51%		0.49%		0.35%		0.06%	
		N	Rates*	N	Rates*	N	Rates*	N	Rates*	N	Rates*	N	Rates*
Mortality	All-cause death	13	18.98	63	44.71	48	70.67	64	103.21	68	165.17	14	200.79
CV outcomes	Myocardial infarction	10	14.80	32	23.20	18	27.08	22	36.59	18	44.97	4	59.83
CV outcomes	Stroke	11	16.32	39	28.36	19	28.74	25	42.08	17	42.41	4	60.24
CV outcomes	Heart failure	15	22.40	75	55.99	56	88.19	75	133.21	59	156.03	11	175.81
CV outcomes	PAD	14	20.93	49	35.84	36	55.47	39	65.73	30	77.11	5	78.98
CV outcomes	MACE	44	69.07	172	138.23	107	184.73	135	270.90	101	307.50	19	362.29
Renal outcomes	Hospitalization for CKD	2	2.93	20	14.40	36	55.20	51	87.34	80	234.84	13	242.65
Renal outcomes	Reduction of eGFR ≥50%	5	7.36	15	10.72	11	16.40	11	18.00	35	91.72	19	302.94
Renal outcomes	Dialysis	1	1.46	2	1.42	1	1.48	6	9.74	20	50.62	5	76.45
Renal outcomes	Kidney transplantation	0	0.00	0	0.00	0	0.00	1	1.62	7	17.27	2	28.49
Renal outcomes	Progression from A1/A2 to A3	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Renal outcomes	MARE	8	11.85	32	23.19	45	69.97	62	108.61	106	352.10	28	637.20

CAT: category; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; KDIGO: Kidney Disease:
Improving Global Outcomes; MACE: major adverse cardiovascular events (composed of any of the following outcomes: stroke, myocardial infarction or all-cause death); MARE: major adverse renal events (composed of any of the following
renal outcomes: hospitalization for CKD, reduction of eGFR ≥50%; dialysis; kidney transplantation; progression from
A1/A2 to A3); PAD: peripheral artery disease; Per 1000 Patient-year. **Adults, with one eGFR laboratory test (index date
was the date of the eGFR measure meeting the criteria closest to 01/01/2018) and at least 12 months of continuous
presence in the database prior to the qualifying eGFR.

Figure 1: MARE and MACE rates across eGFR stages and albuminuria categories (model 1*).



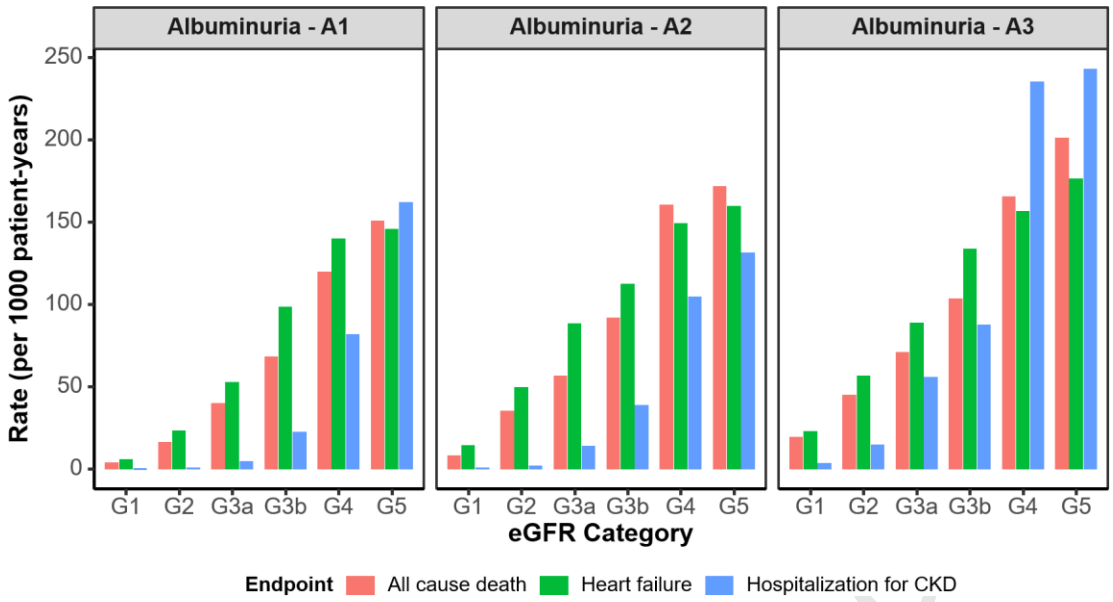
eGFR: estimated glomerular filtration rate.

MACE: major adverse cardiovascular events (composed of any of the following

outcomes: stroke, myocardial infarction or all-cause death); MARE: major adverse renal events (composed of any of the following renal outcomes: hospitalization for chronic kidney disease, reduction of eGFR ≥50%; dialysis; kidney transplantation; progression from A1/A2 to A3).

*Adults, with one eGFR laboratory test (index date was the date of the eGFR measure meeting the criteria closest to 01/01/2018) and at least 12 months of continuous presence in the database prior to the qualifying eGFR.

Figure 2: All cause deaths, Heart failure and Hospitalization for CKD rates across eGFR stages and albuminuria categories (model 1*).



CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

*Adults, with one eGFR laboratory test (index date was the date of the eGFR measure meeting the criteria closest to 01/01/2018) and at least 12 months of continuous presence in the database prior to the qualifying eGFR.