

Understanding International Variations in Kidney Failure Incidence and Initiation of Replacement Therapy



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Introduction: Incidence of kidney replacement therapy (KRT) varies widely across countries. Its relations to individual characteristics, nephrology practices for slowing chronic kidney disease (CKD) progression, and KRT access remain unclear.

Methods: We investigated intercountry differences in kidney failure (KF) rate, defined by a sustained estimated glomerular filtration rate (eGFR) <15 ml/min per 1.73 m², and separately in KRT incidence, before and after adjusting for risk factors and blood pressure (BP) control or renin-angiotensin-aldosterone system inhibitor (RAASi) prescription practices in the CKD Outcomes and Practice Patterns Study (CKDopps) cohort study.

Results: Among 7381 patients with CKD stage 3 to 4 at enrollment, 1297 progressed to KF and 947 initiated KRT over a 3-year follow-up period. Compared to the United States, demographic-adjusted and eGFR-adjusted hazard ratios (HRs) (HRs, 95% confidence intervals [CI]) for a sustained low eGFR were 0.77 (95% CI, 0.57–1.02) in Brazil, 0.90 (95% CI, 0.75–1.08) in France, and 1.03 (95% CI, 0.86–1.03) in Germany. Further adjustment for comorbidities, albuminuria, systolic BP, and RAASi prescription did not substantially change these HRs. In contrast, compared with the United States, the fully-adjusted HR for KRT remained significantly lower in Brazil (0.55, 95% CI 0.39–0.79), higher in Germany (95% CI, 1.36, 1.09–1.69), and similar in France (95% CI, 1.07, 0.81–1.39).

Conclusion: Individual risk factors for CKD progression in nephrology patients appeared to explain most intercountry variations in KF but not KRT incidence. This suggests a prominent role for differences in practices related to KRT initiation or access, but not those for slowing disease progression. This study also shows that using KRT as a KF surrogate may bias estimates of associations with CKD progression risk factors.

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KEYWORDS: chronic kidney disease; epidemiology; international comparisons; kidney failure; kidney replacement therapy; risk factors

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Although about 4 million people with KF are treated with dialysis or live with a kidney transplant worldwide, it has been estimated that the number of patients in need of KRT is at least twice as high.^{1,2}

Macroeconomic factors (such as gross domestic product per capita, percentage of gross domestic product spent on health care, or dialysis facility reimbursement rate) largely drive the wide intercountry variations in the incidence of KRT reported by national registries³ and in KRT access.^{4–8} Nevertheless, we recently highlighted a significant gap in KRT incidence that is not explained by variations in the prevalence of CKD, even in high-income countries where access to KRT is not restricted. This finding suggests that differences in patient risk factors or in clinical practices for slowing CKD progression or initiating dialysis may play a role.⁹

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Few health data systems can capture information on patients with KF, defined by a sustained low glomerular filtration rate (<15 ml/min per 1.73 m²) over at least 4 weeks, not treated with dialysis or transplantation.^{10,11} The effect of individual characteristics and nephrology practices on kidney protection or dialysis initiation may nevertheless be approached through international comparisons of CKD cohorts, particularly those that include large populations of patients with advanced CKD. Brück *et al.*¹² first showed variations in the annual eGFR decline among European cohorts, which ranged from 0.8 to 2.4 ml/min per 1.73 m² on average after adjustment for demographics, baseline eGFR, primary kidney disease, comorbidities, and smoking. A second study from the international Network of CKD cohorts¹³ also showed a wide range in the time to halving of eGFR across cohorts over 3 continents, from 26 to 114 per 1000 person-years, after standardization by age, sex, and baseline eGFR. These cohorts may, however, have been hampered by differences in design, notably the study populations (general practice or nephrology patients, from any facility type or limited to university hospitals) and data collection (based on a research protocol or routine care data). These studies have not investigated the potential effect on kidney outcomes of achieving guideline treatment targets for slowing CKD progression,¹⁴⁻¹⁶ despite large variations between countries in BP control and RAASi use.¹⁷⁻¹⁹

The CKDopps is a prospective cohort study of patients with moderate and advanced CKD recruited from national samples of nephrology clinics in Brazil, Germany, France, and the United States.²⁰ To investigate the effect of patient risk factors and clinical practices intended to slow CKD progression on international variations in kidney outcomes, we assessed the magnitude of intercountry differences in the risks of sustained low eGFR and separately of KRT, before and after adjustment for these factors.

METHODS

Participants

We studied patients with nondialysis-CKD stages 3 to 5 enrolled in the CKDopps between 2012 and 2017 from Brazil, France, Germany, and the United States. In each country, a national list of nephrology clinics, stratified by geographic region and clinic characteristics (size and public vs. private), was assembled to serve as a sampling frame for selecting nationally representative samples. Each clinic developed a census to identify all eligible patients who were at least 18 years of age, had eGFR <60 ml/min per 1.73 m² at the time of screening, and no prior chronic dialysis or kidney transplant.

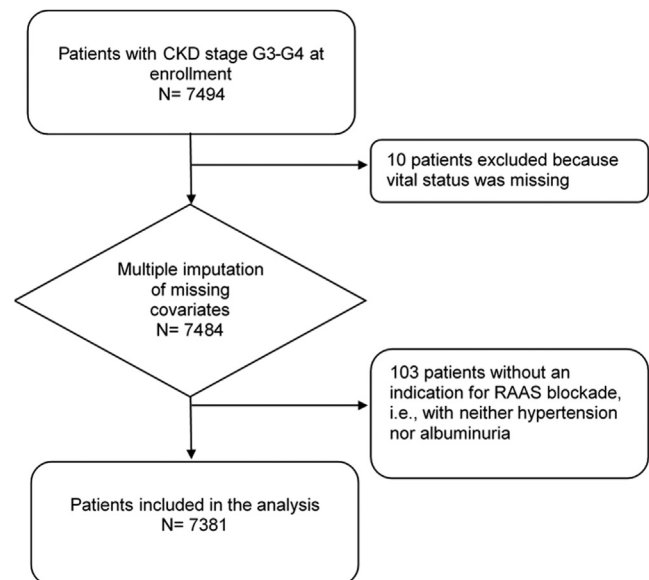


Figure 1. Flowchart of the study cohort. CKD, chronic kidney disease; RAAS, renin-angiotensin-aldosterone system.

Census patients who met eligibility criteria were approached for study participation. Further details of the study protocol have been published elsewhere.²⁰ The analysis presented here focused on 7381 patients with CKD stages 3 and 4 at baseline and an indication for treatment by RAAS blockade (i.e., for hypertension or albuminuria, Figure 1). All patients signed informed consent as required by national and local ethics committee regulations.

Data Collection

CKDopps collected data with a common protocol in all participating countries. Clinical research associates or study nurses ensured study sites' protocol adherence and the quality of data collection. Baseline data were collected from medical records. These included demographics, comorbidities, outpatient BP, height, and weight, and laboratory measurements. No clinical data were collected beyond those performed as part of usual care because the aim is to evaluate typical practices in nephrology clinics. One exception was laboratory measurements in France, where a standard set of tests including serum creatinine and spot albuminuria were requested annually.²¹ Prescriptions of RAASi, including angiotensin conversion enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors, and aldosterone receptor antagonists, were recorded along with all other prescribed medications. Patients were classified with hypertension if so reported in the medical record or if they were prescribed antihypertensive medications; with diabetes if so reported in the medical record or if they were prescribed glucose-lowering medication or had HbA1c $\geq 6.5\%$ or fasting glucose ≥ 7.0 mmol/l

or a random glucose ≥ 11.0 mmol/l at baseline. eGFR was calculated with the CKD-epidemiology collaboration equation,²² and coefficient for Black race was used in Brazil, France, and the United States. Because ethnicity information was not collected in Germany, the related coefficient was not used in this country. Albuminuria or proteinuria, measured from spot or 24-hour urine samples, was used to assign patients to albuminuria (or proteinuria) categories as defined in the Kidney Disease: Improving Global Outcomes 2012 guidelines as follows: A1 (normal or mildly increased), A2 (moderately increased), A3 (severely increased or nephrotic range).¹⁴ When spot or 24-hour urine values were not available, dipstick values were used for grading albuminuria by including no or trace proteinuria, 1+, 2+, and $\geq 3+$, in albuminuria categories A1, A2, and A3, respectively.

Outcomes

KRT was systematically reported, and time-to-event was ascertained from study enrollment to start of maintenance dialysis or preemptive kidney transplantation. The onset of KF, defined by an eGFR < 15 ml/min per 1.73 m² sustained over at least 4 weeks,¹⁰ was ascertained from routine eGFR measurements. The event was considered “sustained” when KRT was initiated at any time following the initial event, or when a confirmatory eGFR less than 15 ml/min per 1.73 m², or death occurred more than 4 weeks after the initial event. Of 1646 patients with an eGFR value < 15 ml/min per 1.73 m², 61% to 84%, depending on the country, met at least 1 of the above endpoints (Supplementary Table S1). We used statistical modeling to estimate event risk, taking into account both the uncertainty of its onset and timing (see statistical analyses) and the differences in eGFR assessment frequency across countries. Patients were censored at pre-KRT death, or the last recorded visit, or at 36 months to take into account intercountry differences in the duration of follow-up.

Statistical Analyses

Descriptive statistics are used to report baseline patient characteristics by country. To deal with missing data (Supplementary Table S2), we performed multiple imputation (Proc MI, SAS version 9.4, SAS Institute Inc., Cary, NC) with the fully conditional specification method²³ and combined analysis through 20 complete datasets according to Rubin and Schencker's rules.²⁴ Crude and adjusted HRs for KRT and their 95% CI were estimated with proportional hazard models. We assumed a Weibull distribution of the baseline hazard function, which has been shown to fit survival models well.^{25,26} To estimate HRs (95% CI) of sustained low eGFR while accounting for interval-censoring and the probability of meeting the 15 eGFR threshold between

the last eGFR measurement above 15 ml/min per 1.73 m² and the end of follow-up, we used illness-death models for interval-censored data, also assuming Weibull distribution (SmoothHazard package in R, 3.6.2, R Core Team, Vienna, Austria).²⁷⁻²⁹ In these three-state models, sustained eGFR < 15 ml/min per 1.73 m² is the transient state, and KRT, the absorbing state (Supplementary Figure S1). These are Markov models,³⁰ which rely on the assumption that transition intensities from one state to another are independent of the time spent in the current state, an assumption shown to be reasonable in a previous study.³¹ These 2 events share a number of associated factors, which may help to avoid bias arising from unobserved eGFR events.²⁷ Because HRs for KRT derived from these models are split into “before” and “after” the onset of sustained eGFR < 15 ml/min per 1.73 m² (each of the 2 sets of HRs corresponding to a distinct transition rate, Supplementary Figure S1), we do not report them. We checked the proportional hazard assumption for covariates with plots of $-\log(-\log\{S\{t\}\})$ against $\log(t)$. Models were adjusted for the following: (i) age in 5 categories (< 50 , 50–59, 60–69, 70–79, ≥ 80 years), sex, ethnicity (Black vs. Other), and baseline eGFR; (ii) Kidney Disease: Improving Global Outcomes albuminuria categories, body mass index, diabetes, cardiovascular comorbidities, malignancy, in addition to variables in model 1; and (iii) systolic BP and RAASi prescription, in addition to variables in model 2. We conducted subgroup analyses by age (< 70 or ≥ 70 years), sex, and according to diabetes, heart failure, and RAASi prescription status. We performed 3 sensitivity analyses. First, because our models assumed the risk associated with covariates to be the average across countries, we repeated our analyses with sequential exclusion of 1 country at a time from the models. Second, to test the robustness of our findings, we fitted a parametric (Weibull distribution) proportional hazard model to model the risk of sustained eGFR < 15 . Third, because Black ethnicity significantly differed across countries and may confound the association with KRT incidence,^{32,33} we assessed intercountry variations restricted to non-Black patients.

RESULTS

Patient Characteristics at Baseline

We studied a total of 7381 patients with CKD stage 3 and 4 at baseline and an indication for RAASi prescription, either hypertension or proteinuria (Figure 1, Table 1). Participating patients from Brazil ($n = 747$) were the youngest (median age 67 years), had the lowest prevalence of albuminuria (52%), and the lowest mean systolic BP (133 mm Hg). Those from France ($n = 2786$) were recruited at higher

Table 1. Patient characteristics at baseline, by country

Patient characteristics	Country			
	Brazil (n = 747)	France (n = 2786)	Germany (n = 2539)	United States (n = 1309)
Age (yr)	67.0 (58.0–77.0)	69.0 (60.0–77.0)	75.0 (67.0–80.0)	71.0 (62.0–78.0)
Men	53.8	65.7	56.8	51.6
Black	26.2	2.5	NA	19.7
CKD stage				
3a	10.2	16.0	6.7	8.3
3b	27.3	39.8	16.0	26.4
4	62.5	44.2	77.3	65.2
Estimated GFR (ml/min/1.73 m ²)	28.9 (10.2)	32.9 (10.8)	26.4 (9.4)	28.3 (10.2)
Albuminuria category ^{c,d}				
Normal or mildly increased	48.0	26.2	35.0	33.3
Moderately increased	21.0	32.7	31.8	22.2
Severely increased	20.8	33.5	21.8	30.3
Nephrotic range	10.2	7.6	11.4	14.2
Primary nephropathy				
Diabetes	32.3	20.6	30.2	33.5
Hypertension/large vessel disease	30.0	28.5	34.6	33.2
Glomerulonephritis	7.9	17.5	8.1	7.2
Interstitial nephritis/pyelo-nephritis	8.4	11.9	5.9	4.0
Polycystic kidney disease	2.9	5.7	3.1	2.4
Other	4.0	10.3	16.1	10.6
Unknown	14.5	5.4	1.9	9.2
BMI (kg/m ²), mean (SD) ^b	27.8 (5.4)	28.8 (5.9)	29.2 (5.7)	31.6 (7.1)
Systolic BP (mm Hg) ^b	132.5 (19.5)	142.4 (20.3)	136.6 (21.5)	136.4 (20.6)
Diastolic BP (mm Hg) ^b	78.9 (11.0)	78.2 (12.2)	75.7 (11.4)	73.0 (11.6)
History of hypertension ^{a,e}	96.7	92.6	96.5	97.2
Antihypertensive prescription ^b	95.8	94.7	95.3	95.3
RAAS inhibitor use ^b	72.4	78.5	79.4	55.2
History of diabetes ^f	49.7	43.7	47.3	58.6
Glucose-lowering prescription ^b	30.6	36.5	31.1	37.2
Coronary heart disease ^g	23.2	25.1	29.3	31.5
Heart failure ^g	17.5	13.0	13.2	16.1
Cerebrovascular disease ^g	10.8	11.9	10.1	12.1
Peripheral vascular disease ^g	23.6	17.1	18.8	16.0
Other cardiovascular diseases ^g	15.1	27.0	21.6	20.2
Cancer other than skin ^g	9.4	21.4	13.8	16.5

ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; GFR, glomerular filtration rate; IQR, interquartile range; NA, not available; PCR, protein-to-creatinine ratio; PER, protein excretion rate; RAAS, renin-angiotensin-aldosterone system.

^a1 to 5% missing data.

^b7 to 13% missing data.

^c29% missing data. For percentage of missing data by country, see [Supplementary Table 1](#).

^dDefinition of albuminuria categories:

Normal or mildly increased: ACR <30 mg/g, PCR <150 mg/g, AER <30 mg/day, PER <150 mg/day, Dipstick none or trace Moderately increased: ACR 30–300 mg/g, PCR 150–500 mg/g, AER 30–300 mg/day, PER 150–500 mg/day, Dipstick 1+ Severely increased: ACR 300–2000 mg/g, PCR 500–3000 mg/g, AER 300–2000 mg/day, PER 500–3000 mg/day, Dipstick 2+ Nephrotic range: ACR >2000 mg/g, PCR >3000 mg/g, AER >2000 mg/day, PER >3000 mg/day, Dipstick 3+ or more

^ePatients were classified with hypertension if so reported in the medical record, or if they were prescribed antihypertensive medications.

^fPatients were classified with diabetes if so reported in the medical record, or if they were prescribed glucose-lowering medication, or had HbA1c ≥ 6.5% or fasting glucose ≥ 7.0 mmol/l or a random glucose ≥ 11.0 mmol/l.

Categorical variables are presented as percentages. Continuous variables are presented as means (SD) or medians (IQR).

mean eGFR level (33 ml/min per 1.73 m²), had the highest prevalence of albuminuria (64%), and the highest mean systolic BP (142 mm Hg). Patients from Germany (n = 2539) were the oldest (median age 75 years) and had the lowest mean eGFR level (26 ml/min per 1.73 m²). Those from the United States (n = 1309) had the highest mean body mass index (32 kg/m²) and diabetes prevalence (59%), and were least likely to be prescribed RAASi (55%).

Incidence of Kidney Events by Country

Median follow-up ranged from 2.2 years in the United States to 3.0 years in France and Germany ([Table 2](#)). A total of 947 patients initiated KRT over this period, and 638 died before KRT. Crude incidence of KRT ranged from 3.2 per 100 person-years in Brazil to 8.0 in Germany, and the pre-KRT death rate from 1.6 to 4.8 per 100 person-years. Median eGFR within 30 days before KRT initiation was higher in Brazil (13.9 ml/min per

1.73 m²) and the United States (11.4 ml/min per 1.73 m²) than in Germany (10.1 ml/min per 1.73 m²) or France (9.5 ml/min per 1.73 m²), overall and across subgroups defined by sex, ethnicity, or history of heart failure (Supplementary Table S3). Data on eGFR at KRT initiation were missing more often in the former than the latter countries. The percentage of patients starting KRT with unobserved sustained low eGFR was also higher in Brazil and the United States than in the European countries, and the interval between the last measured eGFR and KRT initiation longer—2.3 months in the former versus 0.6 to 0.7 in the latter countries (Supplementary Figure S2). Of note, routine eGFR measurements were mostly, but not exclusively, based on isotope dilution mass spectrometry-traceable creatinine assays in France, Brazil, and the United States (Supplementary Table S4), information on assay type was not collected in Germany.

The mean annual number of eGFR measurements per patient over the period ranged from 1.7 to 2.7 across countries; it was higher at higher CKD stages (Supplementary Figure S3). In all, 1297 (18%) patients reached a sustained eGFR <15 ml/min per 1.73 m², ranging from 9% in Brazil to 24% in Germany. The interval between the last eGFR measurement and the end of follow-up also varied across countries. In patients who either died before KRT or were censored, it was 2 months in France and Germany, 4 months in the United States, and 12 months in Brazil (Supplementary Figure S2).

Adjusted HRs for Kidney Events According to Country

We used illness-death models to estimate HR of sustained low eGFR, while taking into account the uncertainty of the time to event between 2 eGFR measurements (interval-censoring) and between the last eGFR measurement and the onset of KRT, death, or end of follow-up. After adjusting for patient characteristics and comorbidities, there were no large or statistically significant differences in the hazard of sustained low eGFR across countries and minimal changes with further adjustment for systolic BP and RAASi prescription (Table 3). These results were consistent across subgroups of age, sex, diabetes or heart failure status, and RAASi prescription (Figure 2).

In contrast, the crude HR for KRT was significantly lower in Brazil and higher in Germany than in the United States, and remained virtually unchanged after adjusting for covariates: 0.55 (95% CI, 0.39–0.76) and 1.37 (95% CI, 1.11–1.69), respectively (Table 3). The crude HR for KRT was significantly lower in France than in the United States, but was attenuated after adjustment for age, sex, and baseline eGFR with minimal changes after further adjustment for other

covariates. Subgroup analyses showed that the excess risk of KRT in Germany compared with the United States was stronger in men than women, in patients older than 70 years, and in those with versus without diabetes or heart failure (Figure 2, Supplementary Table S5). The lower risk of KRT in Brazil than elsewhere was consistent in all subgroups, except among patients with heart failure. Of note, the HRs associated with study covariates were mostly consistent between kidney outcomes, except those for men or patients with diabetes or heart failure. These categories appeared to be more strongly associated with KRT than with a sustained low eGFR (Supplementary Table S6).

Sensitivity analyses with sequential exclusion of one country at a time provided results that were essentially unchanged (Supplementary Table S7), as did analysis restricted to non-Black patients (Supplementary Table S8). When time to a sustained low eGFR was modeled with a standard parametric proportional hazard model, follow-up duration was significantly shorter than in the illness-death model for Brazil and the United States, because of their less frequent eGFR measurements. Nonetheless, all HRs remained nonsignificant (Table 4).

DISCUSSION

This study, based on patients recruited from nephrology clinics in Brazil, France, Germany, and the United States, 4 countries with diverse population profiles, clinical practices, and health systems, showed modest intercountry variations in CKD progression to KF, as defined by a sustained low eGFR, after adjustment for known risk factors for progression. These same risk factors, however, failed to explain the variations in KRT incidence in the different countries. BP control and RAASi prescription contributed little to these variations after controlling for kidney markers. These findings provide new insights into the sources of country variations in KRT incidence attributable to patient profiles and CKD management.

Enhancing our understanding of the sources of international variations in KRT incidence unrelated to KRT practices, that is, those related to individual characteristics or clinical practices of kidney protection, is difficult. The most relevant design should compare the risks of KF between countries, based on the consensus definition of a sustained eGFR <15 ml/min per 1.73 m² over at least 4 weeks.^{10,34} Nonetheless, the challenges in using eGFR to assess kidney outcomes in observational studies are increasingly recognized, especially when values are based on routine laboratory data.³⁵ Strategies to mitigate misclassification of events have been proposed,³⁶ but there is no definitive

Table 2. Incidence of kidney outcomes and competing death, by country

Events	Country				Total
	Brazil (n = 747)	France (n = 2786)	Germany (n = 2539)	United States (n = 1309)	(N = 7381)
KRT					
n events (%)	49 (7)	328 (12)	439 (17)	131 (10)	947 (13)
Follow-up (yr), median (IQR)	2.3 (1.8–3.0)	3.0 (3.0–3.0)	3.0 (2.6–3.0)	2.2 (0.9–3.0)	3.0 (2.6–6.0)
Crude incidence per 100 PY (95% CI)	3.2 (2.3–4.1)	4.3 (3.9–4.8)	8.0 (7.2–8.7)	5.8 (4.8–6.9)	5.6 (5.3–4.6)
Estimated GFR (ml/min/1.73 m ²) within 30 days of KRT, median (IQR) ^a	13.9 (10.2–18.5)	10.0 (7.3–13.2)	10.4 (8.0–13.5)	11.4 (8.2–13.5)	10.1 (7.5–13.7)
Pre-KRT death					
n events (%)	24 (3%)	255 (9%)	265 (10%)	94 (7%)	638 (9%)
Follow-up (yr), median (IQR)	2.3 (1.8–3.0)	3.0 (3.0–3.0)	3.0 (2.6–3.0)	2.2 (0.9–3.0)	3.0 (2.6–6.0)
Crude incidence per 100 PY (95% CI)	1.6 (0.9–2.2)	3.4 (3.0–3.8)	4.8 (4.2–5.4)	4.2 (3.3–5.0)	3.8 (3.5–4.1)
Sustained eGFR <15 ml/min/1.73 m ² , n (%)	65 (9%)	473 (17%)	602 (24%)	157 (12%)	1297 (18%)
Patients with unobserved sustained eGFR <15 among those who started KRT, n (%)	26 (53%)	64 (20%)	120 (27%)	57 (44%)	267 (28%)
Patients who did not start KRT during follow-up among those with sustained eGFR <15, n (%)	42 (65%)	209 (44%)	283 (47%)	83 (53%)	617 (48%)

eGFR, estimated glomerular filtration rate; IQR, interquartile range; KRT, kidney replacement therapy; PY, person-year.

^aData available for 41%, 73%, 60%, and 44% of the patients who initiated KRT in, respectively, Brazil, France, Germany, and the United States.

Kidney replacement therapy numbers on the second row of the table 2 equal the number of sustained low eGFR (11th row) minus that of patients who did not initiate kidney replacement therapy (last row), plus the number who initiated kidney replacement therapy with unobserved low eGFR (second last row)—e.g., for France, 328 = 473–209+64.

guidance in ascertaining eGFR-based outcomes (single vs. sustained low eGFR) or appropriate statistical methods. In particular, evaluation of routine eGFR-based outcomes is hampered by intermittent measurements.^{37,38} In this context, time-to-event, that is, the exact time when eGFR meets the 15 ml/min per 1.73 m² threshold, is unknown, and patient status between the last eGFR measurement and the last follow-up visit is uncertain. By right-censoring follow-up at patients' last eGFR measurement, standard survival analyses may substantially overestimate the risk of eGFR <15 ml/min per 1.73 m².^{27,28} Thus, as with KRT, which may poorly reflect variation in burden of KF because of differences in practices of treatment initiation, comparing eGFR-based event has its own caveats: intermittent assessment, unequal practices of surveillance, and, eventually, sparse data. To enhance the understanding of international variations in KF incidence, we proposed a model-based intercountry comparison of eGFR events in CKDopps, using illness-death model which simultaneously takes into account the interval-censoring of events and the uncertainty of occurrence of a sustained eGFR <15 ml/min per 1.73 m² before KRT, death, or end of follow-up.

We observed a very similar pattern in crude HR estimates for a sustained low eGFR and for KRT; the HR was lower in Brazil and France and higher in Germany than in the United States. The magnitude of these differences between countries, however, was weaker for a sustained low eGFR than for KRT, especially after adjustment for patient profiles and kidney markers. The variations we found in the risk of KF are difficult to compare directly with those of previous international studies, due to their differences from ours in terms of

both participating countries and reported eGFR-based outcomes. The study most similar to ours is that from international Network of CKD cohorts,¹³ which showed highly heterogeneous incidence rates of both KRT and time to halving of eGFR across CKD cohorts from Australia, Canada, India, Japan, Korea, the United Kingdom, the United States, and Uruguay. In that study, adjusting for demographics and a number of individual-level laboratory markers serving as proxies for health status and health care quality did not substantially attenuate the differences, thereby indicating the influence of other factors potentially related to study setting. The European CKD Burden Consortium¹² used a joint model to compare mean annual eGFR changes and mortality risks of 9 cohorts from Belgium, Cyprus, Italy, Spain, and the United Kingdom. Its similar failure to explain country variations in eGFR decline by risk factors for CKD progression led the authors to suggest that selection criteria influenced the results. Nevertheless, beyond differences in participating countries and cohort profiles, the lack of a standardized protocol may also have contributed to discrepancies in findings between these 2 studies and ours.

Registry or census data have consistently indicated much higher crude KRT incidence in the United States than in Brazil or France; in the 2020 United States Renal Data System Annual Report, these were 395 per million population versus 218 and 169, respectively.³ Although KRT incidence among patients recruited from nephrology clinics cannot be compared with that in the general population, it is worth noting that CKDopps patients enrolled in Brazil and France were also at lower risk for KRT than those in the United States. The protocol-driven higher eGFR at enrollment

Table 3. Crude and adjusted hazard ratios of kidney outcomes, by country

Kidney outcomes/countries	Crude	Model 1	Model 2	Model 3
Sustained eGFR <15 ml/min/1.73 m ²				
Brazil	0.78 (0.59–1.04)	0.77 (0.57–1.02)	0.87 (0.64–1.17)	0.88 (0.65–1.19)
France	0.62 (0.52–0.74)	0.90 (0.75–1.08)	0.96 (0.79–1.16)	0.92 (0.75–1.13)
Germany	1.17 (0.99–1.38)	1.03 (0.86–1.23)	1.09 (0.90–1.33)	1.12 (0.92–1.37)
United States	Reference	Reference	Reference	Reference
Kidney replacement therapy				
Brazil	0.55 (0.39–0.76)	0.48 (0.34–0.66)	0.55 (0.39–0.76)	0.55 (0.39–0.76)
France	0.71 (0.58–0.87)	0.98 (0.79–1.21)	1.07 (0.81–1.39)	1.01 (0.82–1.25)
Germany	1.33 (1.09–1.61)	1.19 (0.97–1.47)	1.36 (1.09–1.69)	1.37 (1.11–1.69)
United States	Reference	Reference	Reference	Reference

eGFR, estimated glomerular filtration rate.

Time to sustained estimated glomerular filtration rate <15 ml/min/1.73 m² was modeled with illness-death models for interval-censored data. These models take into account uncertainty for time-to-event (between 2 estimated glomerular filtration rate measurements) and uncertainty about whether patients reached the event between the last estimated glomerular filtration rate measurement and the last follow-up. Time to kidney replacement therapy was modeled with parametric proportional hazard models. Both outcome models were adjusted for 1) age, sex, ethnicity, and baseline estimated glomerular filtration rate; 2) variables in model 1 + Kidney Disease: Improving Global Outcomes albuminuria categories, body mass index, diabetes, cardiovascular comorbidities, malignancy; and 3) variables in model 2 + baseline systolic blood pressure and renin-angiotensin-aldosterone system inhibitor prescription.

mostly explained the lower risk in the French cohort. On the other hand, the lower risk of KRT incidence observed in Brazil cannot be explained by the study protocol or the patients' risk of CKD progression, namely, lower systolic BP, or higher use of RAASi. In addition, neither a higher mortality rate⁹ nor a late dialysis start³⁹ justified the lower incidence, as eGFR in those who initiated dialysis was higher than that of American patients. It is plausible that a group of Brazilian patients either died before starting KRT or did not start despite a low eGFR due to limited KRT access, or faced logistical challenges in the transition between advanced CKD and KRT that can delay dialysis initiation despite timely referral to nephrology care. Our analysis likely captures a combination of patients who had a timely start of KRT and others who did not start KRT during the observation period for the various reasons enumerated above.

In Germany, where KRT incidence in the general population is close to that in France,⁴⁰ CKDopps uncovered a risk of KRT among nephrology patients 37% higher than in the United States, with older age and less albuminuria having net offsetting effects. This excess risk did not appear to be related to earlier dialysis start, because eGFR at initiation was slightly lower among German patients. These findings may indicate faster CKD progression in German patients, broader access to KRT in the study population, or possibly discretionary choice to start dialysis earlier.⁴¹ These latter explanations are supported by subgroup analyses showing substantially higher KRT incidence in the elderly and in patients with comorbidities in Germany than in the United States.

Major strengths of this study include the representativeness of national samples from nephrology clinics in countries with diverse patient profiles and

nephrology practices, a population with mainly advanced CKD and a high rate of KF events, the use of a common protocol, and individual-level data collection of both risk factors and measures to slow CKD progression.

This study also has limitations. First, the selection of patients under nephrology care does not allow our findings to be generalized to a broader population of patients with CKD under the care of other specialists or by primary care physicians. Practice patterns, health care system policies, and access to care were not integrated into the analysis of the intercountry differences in KRT incidence, and therefore our findings and interpretations are limited and may differ at the population level. Second, despite using a standard protocol, methods used to identify KRT and death events differed somewhat between countries. Ascertainment relied only on clinic records in Brazil and the United States, whereas record linkage was also used with the national KRT and death registries in France, and the Network of German Kidney Centers registry in Germany. Underestimation of these events in Brazil and the United States cannot be fully ruled out, although the similarity of HR estimates for the 2 reported kidney outcomes suggests that it would be minimal. Third, covariates in this study were modeled based on a single time-point (baseline), and data on systolic BP relied on routinely reported measurements that may have increased measurement errors and thus weakened its association with kidney outcomes. The associations for these covariates were, however, all as expected, particularly the excess kidney risk associated with higher systolic BP. Fourth, we used routine laboratory creatinine values to estimate GFR, and it was not possible to ensure that all were measured with isotope dilution mass spectrometry-traceable assays,

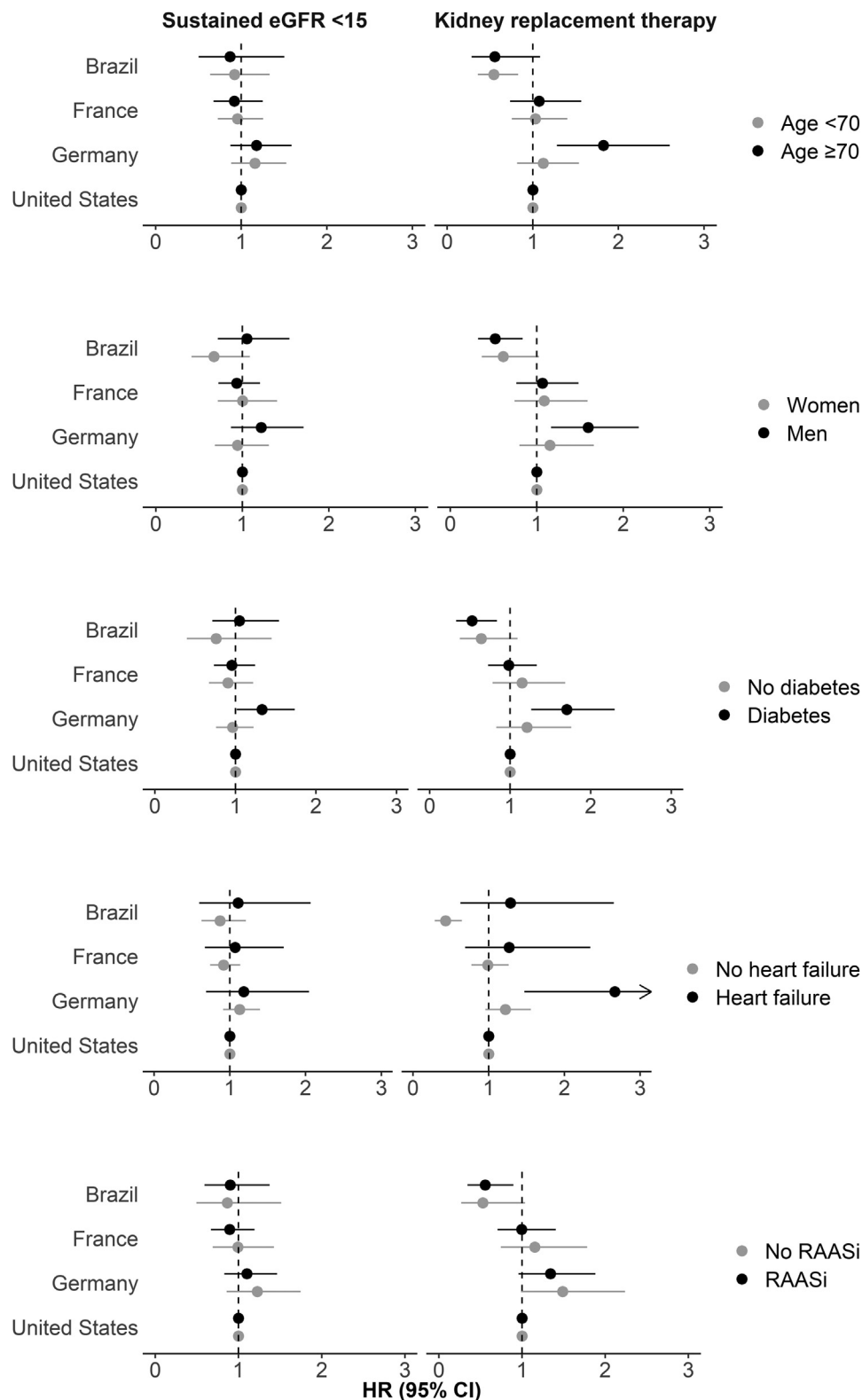


Figure 2. Fully adjusted hazard ratios for kidney outcomes according to country, and by subgroups of age, sex, diabetes status, heart failure, and RAASi prescription. The United States is used as the reference. Time to sustained eGFR <15 ml/min/1.73 m² was modeled with illness-death models for interval-censored data. These models take into account uncertainty for time-to-event between 2 eGFR measurements and between the last eGFR measurement and the end of follow-up. Time to KRT was modeled with parametric proportional hazard models. Both models were adjusted for age, sex, ethnicity, and baseline eGFR, albuminuria categories, body mass index, diabetes, cardiovascular comorbidities, malignancy, baseline systolic blood pressure, and RAAS inhibitor prescription. eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy; RAASi, renin-angiotensin-aldosterone system inhibitor.

Table 4. Adjusted hazard ratios for a sustained eGFR <15 ml/min/1.73 m² by country, by an alternative model specification

Kidney outcome/countries	Illness-death model for interval-censored data (main analysis)			Proportional hazard model for time to sustained eGFR <15 (censored at the last eGFR measurement)		
	n events	F/u (mo)	HR (95% CI)	n events	F/u (mo)	HR (95% CI)
Sustained eGFR <15						
Brazil	65	2.3 (1.8–3.0)	0.88 (0.65–1.19)	65	0.5 (0.0–1.4)	1.04 (0.77–1.42)
France	473	3.0 (3.0–3.0)	0.92 (0.75–1.13)	473	3.0 (2.9–3.0)	0.83 (0.68–1.03)
Germany	602	3.0 (2.6–3.0)	1.12 (0.92–1.37)	602	3.0 (1.3–3.0)	1.00 (0.82–1.22)
United States	157	2.2 (0.9–3.0)	Reference	157	0.9 (0.0–2.0)	Reference

CI, confidence interval; eGFR, estimated glomerular filtration rate; f/u, follow-up; HR, hazard ratio.

Both models were adjusted for age, sex, ethnicity, and baseline eGFR, Kidney Disease: Improving Global Outcomes albuminuria categories, body mass index, diabetes, cardiovascular comorbidities, malignancy, baseline systolic blood pressure, and renin-angiotensin-aldosterone system inhibitor prescription.

despite the wide availability of these tests across participating sites over the study period. Other than creatinine, Jaffe-interfering chromogens, however, have much less effect at high than low creatinine levels as those of study participants, so that bias due to creatinine measurement errors, if any, would have minimal effect on our findings. Fifth, the number of routine eGFR measurements per patient-year was lower in Brazil and in the United States than in France and Germany, which may explain their higher number of KRT initiations with unobserved eGFR <15 ml/min per 1.73 m² and without nearby eGFR data. Nevertheless, this limitation was mitigated by the use of illness-death models for interval-censored data, as suggested by our sensitivity analysis with a standard proportional hazard model. Finally, our models assume that the excess risk of events associated with covariates is equivalent to the mean risk estimate across countries. In support of this assumption, the sensitivity analysis with sequential exclusion of one country at a time shows that our results are robust and not over-influenced by a particular country.

Implications of these findings are 2-fold. First, caution is necessary when using KRT as a surrogate for KF in the study of the risk factors for CKD progression, because it may result in underestimating or overestimating associations, as observed in this study for sex, diabetes, heart failure, and RAASi prescription. On the other hand, using routine eGFR measurements to diagnose KF may raise other methodological issues, such as interval censoring, which would require appropriate statistical analyses. Second, in this study, the factors that most completely explained the international variations in kidney outcomes were eGFR and albuminuria; other factors had a much smaller effect. This highlights the importance of regular albuminuria monitoring, which has been shown to be far from optimal, even among patients under nephrology care.¹⁹ Moreover, in the CKDopps population of nephrology patients, most of whom have an indication for RAASi use, better BP control and RAASi prescription appeared to have little effect on country variations in the risks of both KRT and sustained low eGFR. The European CKD Burden Consortium study also observed

this result.¹² Although surprising on first consideration, this does not mean that these measures play no role in country-level variations. Rather, once country differences in risk factors for CKD progression (primarily baseline eGFR and albuminuria) are taken into account, adjustment for BP control and RAASi adds little, because their “effect” on progression to KF is mediated by these factors.

In conclusion, our study shows that country differences in risk factors for CKD progression may explain variations in the risk of a sustained low eGFR, but not in that of KRT for some countries. These findings indicate that differences in clinical practices during the transition period from KF to KRT may substantially influence the timing of dialysis initiation even among patients referred to nephrology care—an observation that merits further investigation.

APPENDIX

List of CKDopps Investigators

CKDopps Steering Committee and Country Investigators

Antonio Lopes, Roberto Pecoits-Filho (Brazil); Christian Combe, Christian Jacquelinet, Ziad Massy, Bénédicte Stengel (France); Johannes Duttlinger, Danilo Fliser, Gerhard Lonnemann, Helmut Reichel (Germany); Takashi Wada, Kunihiro Yamagata (Japan); Ron Pisoni, Bruce Robinson (United States).

Additional CKDopps Research Group

Antonio A Lopes, Roberto Pecoits-Filho (Brazil); Natalia Alencar de Pinho, Christian Combe, Elodie Speyer, Bénédicte Stengel (France); Kunihiro Yamagata (Japan); Christos Argyropoulos, Rupesh Raina, Bruce M Robinson (United States).

DISCLOSURE

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and Kyowa Hakko Kirin; additional commercial support was provided by AstraZeneca, FMC Asia-Pacific Ltd., FMC Canada Ltd., Janssen, Keryx, MEDICE Arzneimittel Putter, Proteon, and Vifor Fresenius Medical Care Renal Pharma. All support is provided without restrictions on publications, all grants are made to Arbor Research Collaborative for Health and not to these authors. HR reports having consultancy agreements with Amgen and Vifor; and reports receiving honoraria from Vifor. BMR has received consultancy fees or travel reimbursement since 2019 from AstraZeneca, GlaxoSmithKline (GSK), Kyowa Kirin Co., and Monogram Health, all paid directly to his institution of employment. RP-F reports having consultancy agreements with Bayer, Akebia, Astra Zeneca, GSK; reports receiving research funding from Fresenius Medical Care; reports receiving honoraria from Bayer, Astra Zeneca, Lilly, Boehringer; reports participation on a Data Safety Monitoring Board or Advisory Board for Bayer, Akebia, Astra Zeneca, GSK. BS reports receiving support for the CKD-Renal Epidemiology and Information Network cohort, which contributes data for CKDopps, through a public-private partnership with funding from Fresenius Medical Care and GSK since 2012 and Vifor France since 2018, Sanofi-Genzyme from 2012 to 2015, Baxter and Merck Sharp & Dohme-Chibret (MSD France) from 2012 to 2017, Amgen from 2012 to 2020, Lilly France from 2013 to 2018, Otsuka Pharmaceutical from 2015 to 2020, and AstraZeneca from 2018 to 2021. CC reports the same support as BS. He further reports honoraria from Amgen, Fresenius, and GSK for congress symposia. All the other authors declared no competing interests.

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The CKDopps Steering Committee and Country Investigators from Brazil, France, Germany, Japan, and the United States (see <https://www.dopps.org/OurStudies/ChronicKidneyDiseaseCKDopps.aspx> for individual names) provided oversight for the CKDopps study and guidance on research and publications. We thank Jo Ann Cahn for the English editing, and Julie Boucquemont and Marie Metzger for their feedback on the statistical analysis.

Part of this study was presented at the ASN's Kidney Week, November 4-7 2021, San Diego, United States; and at the 58th ERA-EDTA's Congress, June 5-8 2021, Berlin, Germany.

SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

Figure S1. Graphical representation of the study's illness-death model.

Figure S2. Distribution of the interval from the last eGFR assessment to the end of follow-up according to KRT status, by country.

Figure S3. Distribution of the frequency of eGFR assessments according to CKD stage at baseline, and by country.

Table S1. Number of patients assessed for a sustained eGFR <15 ml/min/1.73 m², by country.

Table S2. Percentage of missing data for baseline characteristics, by country.

Table S3. Estimated glomerular filtration rate within 30 days of kidney replacement therapy initiation, by country.

Table S4. Availability of isotope dilution mass spectrometry-traceable creatinine assays, by country.

Table S5. Adjusted hazard ratios for kidney outcomes according to country, by subgroup.

Table S6. Adjusted hazard ratios for kidney outcomes according to patient characteristics, systolic blood pressure, and RAASi prescription.

Table S7. Adjusted hazard ratios of kidney outcomes according to country, with sequential exclusion of 1 country at a time.

Table S8. Adjusted hazard ratios of kidney outcomes according to country, overall and in non-Black patients.

STROBE Statement.

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