The Stockholm CREAtinine Measurements (SCREAM) project: Fostering improvements in chronic kidney disease care

Juan Jesus Carrero & Carl Gustaf Elinder

From the 1Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; 2Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

Abstract. Carrero JJ, Elinder CG. The Stockholm CREAtinine Measurements (SCREAM) project: Fostering improvements in chronic kidney disease care. J Intern Med. 2022;291:254–268.

SCREAM (Stockholm CREAtinine Measurements project) was initiated in 2010 in collaboration with the healthcare provider of Stockholm County healthcare to quantify potential medication errors, estimate the burden of chronic kidney disease (CKD) and to illustrate the value of incorporating measures of kidney function into the medical decision process. Because most patients are unaware of their CKD and diagnoses are seldom issued, SCREAM took advantage of the commonness of serum/plasma creatinine testing, which can be used to estimate the glomerular filtration rate (eGFR) and classify the stage of CKD severity. SCREAM is periodically updated, and at present contains healthcare information of all residents in Stockholm region during 2006–2019 (about 3 million people), enriched with a broad range of laboratory measurements for those in whom creatinine or albuminuria has been measured (about 1.8 million people). This health information was linked with national administrative and quality registries via the unique personal identification number of each Swedish citizen, conforming the richest characterization in Sweden of the population’s journey through health and disease. This review discusses the context of its creation, strengths and weaknesses, key findings and plans for the future. We summarize our findings related to the burden of CKD in Sweden, its adverse health risks (such as risk of infections, cancer or dementia) and how underlying kidney function alters the risk–benefit ratio of common medications. Results have had clinical impact and demonstrate the importance of population-based research in the spectrum of clinical research to improve health.

Keywords: acute kidney injury, epidemiology, nephrology, registries, renal function

How and why was SCREAM initiated?

At the beginning of the 2010s, several publications illustrated the high prevalence of chronic kidney disease (CKD) worldwide, spurred by the development of simple creatinine-based equations to estimate glomerular filtration rate (eGFR), which allowed understanding the size and burden of this silent epidemic [1–3]. CKD, the persistent and irreversible degradation of the kidney, is nowadays acknowledged as one of the 10 most important noncommunicable diseases of the 21st century; between 10% and 15% of the adult population worldwide is living with CKD [4], a disease associated with excessive healthcare costs, disability and accounting for one tenth of all deaths [5].

Despite the uniqueness of the traditional Swedish registries, the burden of CKD in our country was largely unknown at the time. The main hindrance was the unreliability of administrative data, as most persons with CKD are not aware of their disease and are seldom diagnosed [6,7]. Two additional circumstances further called for the creation of Stockholm CREAtinine Measurements project (SCREAM):

(i) There was debate on how kidney function could best be evaluated in Swedish healthcare [8]. In 2008, a national scientific committee was assigned to evaluate methods to estimate and measure kidney function (i.e., glomerular filtration rate, GFR) and to illustrate the value of incorporating measures of kidney function into the medical decision process. Because most patients are unaware of their CKD and diagnoses are seldom issued, SCREAM took advantage of the commonness of serum/plasma creatinine testing, which can be used to estimate the glomerular filtration rate (eGFR) and classify the stage of CKD severity. SCREAM is periodically updated, and at present contains healthcare information of all residents in Stockholm region during 2006–2019 (about 3 million people), enriched with a broad range of laboratory measurements for those in whom creatinine or albuminuria has been measured (about 1.8 million people). This health information was linked with national administrative and quality registries via the unique personal identification number of each Swedish citizen, conforming the richest characterization in Sweden of the population’s journey through health and disease. This review discusses the context of its creation, strengths and weaknesses, key findings and plans for the future. We summarize our findings related to the burden of CKD in Sweden, its adverse health risks (such as risk of infections, cancer or dementia) and how underlying kidney function alters the risk–benefit ratio of common medications. Results have had clinical impact and demonstrate the importance of population-based research in the spectrum of clinical research to improve health.

Keywords: acute kidney injury, epidemiology, nephrology, registries, renal function
filtration rate, GFR). Results from this investigation supported the use of equations based on the plasma concentration of creatinine or cystatin C to calculate eGFR [9].

(ii) There was increasing concern for inappropriate drug use causing toxicity and side effects in persons with limited capacity of eliminating drug metabolites through urine [10,11]. The healthcare provider of Stockholm (i.e., Region Stockholm) developed a clinical decision support system for the prescription of drugs to patients with reduced kidney function [12]. As this support system was about to be implemented, there was a need to better understand the extent of the problem.

We saw as an opportunity the fact serum/plasma creatinine is one of the most common laboratory analyses performed in routine clinical practice. The extent of this occasional creatinine testing was unknown, but it could provide important information to size the burden of CKD in our county. We initiated in 2010 a collaborative project between Karolinska Institutet and Region Stockholm that linked health information of individuals undergoing serum/plasma creatinine tests in any form of healthcare. The “Stockholm CREATinine Measurements (SCREAM)” project since then examined areas including CKD epidemics, risk factors and health consequences of CKD, health disparities, health monitoring practices, medication errors and drug safety and effectiveness, and produced so far about 100 scientific publications. In this review, we present the information collected in the SCREAM database, its strengths and weaknesses, key findings and plans for the future.

What does SCREAM contain?

About Sweden’s health system and Swedish nationwide registries

Sweden is a Nordic country with ~10 million inhabitants that has a welfare state model with universal and tax-funded healthcare. Healthcare is fragmented into regional providers, with Region Stockholm being the largest and serving 20%–25% of Sweden’s population. All citizens of Sweden are given a unique 10-digit personal identification at birth or at entry to the country as a legal immigrant. For registry-based research, these personal identity numbers are essential because they enable easy, accurate and unambiguous individual-level linkage of the registries [13,14].

There are two main types of registries to consider:

(i) The national public authority registries are managed by the Swedish government. One example is the total population registry, which collects information on sex, date and country of birth, immigration/emigration date, civil status, kinship and date of death.

(ii) The quality registries are investigator-driven with partial government funding and are created around specific diseases. Although there are more than 200 registries and databases in Sweden, none of them allows the study of CKD at a population level.

SCREAM database

SCREAM has recently updated its content to the period 2006–2019 (previously it covered 2006–2012). It contains administrative data of all Stockholm citizens, and a rich set of laboratory measurements performed during routine clinical practice among those who had creatinine or albuminuria tested at least once.

The first component of SCREAM is the administrative health data registry of Stockholm region (Vård Analys Databasen, VAL; the Region Stockholm healthcare data warehouse) (Fig. 1). VAL contains information on all consultations in primary and specialist outpatient care, as well as hospitalizations. For each citizen, we extracted all available healthcare utilization data since 1997, which is when the International Classification of Diseases Version 10 (ICD-10) coding system was implemented. Each healthcare visit is accompanied by the date, the centre accessed and medical department, therapeutic or surgical procedures undertaken, and established diagnoses. VAL also provides demographic information including sex and date of birth, immigration to and emigration from Stockholm (which allows for censoring participants when their residency changes outside Stockholm), and municipality of residency.

The second and core component of SCREAM is a central repository of laboratory data. Three laboratory companies (Aleris, Unilabs and Karolinska) in 2018 performed the vast majority (estimated in >96%) of all clinical chemistry laboratory tests of the region. Each laboratory provider extracted a broad list of laboratory tests for all patients who had these measurements undertaken. The sole
Fig. 1 Available linkages and key information in those for the Stockholm CREATinine Measurements (SCREAM) project 2006–2019.
Table 1. Description of most relevant laboratory biomarkers extracted in the Stockholm CREAtinine Measurements (SCREAM) project covering Stockholm healthcare during 2006–2019

| Disease pathway                  | Selection of available laboratory tests                                                                 |
|----------------------------------|----------------------------------------------------------------------------------------------------------|
| Renal function                   | Creatinine, cystatin C, creatinine and iohexol clearance, uric acid                                      |
| Electrolytes/minerals            | K\(^+\), HCO\(_3^-\), Na\(^+\), Ca\(^{2+}\), PO\(_4^-\), CO\(_2\), Mg\(^+\), iron, lithium             |
| Bone mineral metabolism          | PTH, alkaline phosphatase, vitamin D                                                                     |
| Diabetes                         | HbA1c, glucose, insulin, oral glucose tolerance tests                                                   |
| Cardiology                       | Cardiac troponins, BNP, D-dimer, prothrombin time/TK                                                    |
| Rheumatoid arthritis             | ANA, RhF, ACPAs                                                                                        |
| Nutrition - anaemia              | Albumin, haemoglobin, ferritin, transferrin                                                             |
| Hormones                         | Thyroid hormones, sex hormones, LH, FSH, PSA, aldosterone, growth hormone                              |
| General markers of health        | ASAT, ALAT, ALP, gGT, GPT, GOT, haemolysis, CDT, Peth, ethanol, blood cell counts                      |
| Blood lipids                     | Cholesterol, HDL, LDL, triglycerides, apolipoproteins                                                   |
| Inflammation and infection       | CRP, fibrinogen, hepatitis A, B and C, herpes and HIV serologies                                      |
| Urine tests                      | Dipstick albuminuria/proteinuria, UACR, spot albuminuria/proteinuria, 24-hour albuminuria, electrolytes in urine |

inclusion criterion considered to enter the laboratory repository is presence of at least one creatinine or albuminuria measurement during the data extraction period (Table 1). Each laboratory test comes with the date and time of measurement (allowing the evaluation of fasting/nonfasting measurements or sequence of measurements within the day), units, method used, reference interval, source laboratory, comments from the technician (such as presence of haemolysis) and information on the department/unit that requested the analysis.

The third component of SCREAM was provided by the National Board of Health and Welfare as well as Statistics Sweden through linkage with the following quality registries of national coverage:

- The Dispensed Drug Registry, containing all pharmacy dispensations of prescribed drugs.
- The Population Registry, with monthly updated vital status and, when applicable, reported cause of death.
- The Cancer Registry, with clinical information of all biopsy-verified cancer diagnoses.
- The Birth Registry, with information on completed pregnancies and eventual complications of mother and child.
- The LISA Registry, with information on achieved education, marital and job status, taxable income and country of origin.

As a next step, we linked the data with a variety of quality registries of national coverage such as:

- The Renal Registry, with clinical information on nephrology-referred patients, including BMI, blood pressure, primary kidney disease, provision of in-hospital drugs and need of KRT.
- The cardiology registries SWEDEHEART and SWEDEHEF, with information on patients admitted to healthcare with an acute coronary syndrome or heart failure, respectively, containing clinical information such as ejection fraction, Killip class, in-hospital medications and centre practice protocols, etc.
- The Swedish Dementia Registry (SVEDEM), with information about the diagnostic workup, medical treatment and community support of patients with dementia disorders.

The personal identification number was substituted by a random identifier by Statistics Sweden, and de-identified data were made available to the researchers preserving anonymity and allowing the waiving of informed consent. There is the possibility to perform additional linkages pending approval by the ethics board and within the conditions imposed by the data owners.

We first evaluated how common creatinine testing was in our health system and hence what representativeness our extraction had [15]. In the first SCREAM dataset (period 2006–2011), out of
1,706,259 adults living in our region, SCREAM identified 1,344,197 individuals with at least one serum creatinine assessed, which corresponds to a population coverage of 66%. Our estimation of cohort coverage for the period 2006–2019 is 67%, suggesting that the rate of creatinine testing in healthcare has been rather constant over time. Some have argued that 66% coverage is a rather low representativeness. However, we reason that such coverage is higher than most screening cohorts, and that not everyone in society needs to access healthcare, particularly at young ages. When we stratified by conditions associated with creatinine testing, such as old age, we observed that SCREAM captured ~50% of all citizens in the range of 18–44 years old, >75% of citizens aged 45–64 years and >90% of all citizens aged ≥65 years old [15]. Further, as many as 98% of all individuals with a cardiovascular disease (CVD)-related diagnosis are captured in SCREAM, along with 97% of individuals with diabetes mellitus. Thus, we are confident that our observations can be extrapolated to large segments of the Stockholm population, but with some caveats: because of the intention of testing, it is plausible that participants included in SCREAM are less healthy than persons with a similar comorbidity profile who are not tested; further, citizens can access healthcare anywhere in Sweden, but only Stockholm healthcare is captured. We did observe that the coverage of SCREAM was similarly distributed throughout the 26 municipalities of the region, ranging from 62% to 72%. However, there was lower coverage in the municipalities farthest away from Stockholm city, as persons living in those areas may more easily seek care in the regions nearby (e.g., Uppsala) rather than travelling to Stockholm.

What SCREAM can and cannot do

Laboratory measurements are central to the medical decision process, particularly in CKD, where diagnoses have very low sensitivity [16]. The longitudinal collection creatinine tests in SCREAM make it ideally suitable to evaluate CKD prevalence, incidence and progression. Furthermore, clinical monitoring practices and many adverse effects of drugs are not detectable through diagnoses, often requiring laboratory data as well. For example, hyperkalaemia associated with blood pressure medication requires creatinine and potassium monitoring prior and shortly after therapy initiation to titrate dosages. Potassium elevations would only be coded with a hyperkalaemia diagnosis if severe enough to require hospitalization. However, decisions to discontinue or dose-titrate the medication would have been taken after mild/moderate potassium elevations.

There are limits and caveats when working with laboratory data, as it requires a careful assessment of the diseases being explored and the conditions around the need and frequency of laboratory testing. Laboratory-based outcomes are inherently affected by differential misclassification; the more specific a laboratory test is, the more it is linked to the conditions that require that testing. This is a truism that helps differentiate healthcare-based databases from traditional cohorts. Further, patients who are sicker are more likely to visit healthcare, and for that reason are also more likely to have repeated laboratory tests taken. Some approaches we have taken in our work to tackle this include requiring a second laboratory value or code for confirmation of an event (e.g., requiring two or more values of eGFR <60 ml/min/1.73 m² at least 90 days apart to confirm incident CKD), interpolating relative changes in biomarker analytes from the linear regression of all available tests [17], or using the established criteria for transient creatinine elevations to define acute kidney injury (AKI) [18]. At times, we have performed sensitivity analyses across specific subpopulations or patients with a similar frequency of laboratory testing [19,20], or assessed the need for clinical action (e.g., blood transfusion for gastrointestinal bleed).

Key findings of SCREAM

In this section, we discuss some of the key findings from the SCREAM database during the past 10 years.

Prevalence and recognition of CKD

Gasparini et al. [16] evaluated the prevalence of CKD and its recognition in our region. Among 1.1 million adults being tested for creatinine during 2006–2011, 6.1% were found to have eGFR <60 ml/min/1.73 m² at cohort entry. Based on conservative projections (i.e., assuming that citizens without creatinine testing were all free from CKD), we concluded that between 4.5% and 6% of the population had CKD stages 3–5 based on eGFR alone (Fig. 2). CKD stages 3–5 were more prevalent among the elderly (28% prevalence when age >75 years old), women (6.8% vs. 5.2% in men), and individuals with diabetes (17%), hypertension (17%) or CVD (31%), emphasizing the importance
of CKD as a comorbidity of the ageing population and companion of the main noncommunicable diseases. However, it was concerning that the frequency of albuminuria monitoring, consultation by nephrology care and registration of diagnoses of CKD were very low, even among subgroups with more severe disease or who have indications for referral. For instance, only 38% of diabetics and 27% of individuals with CKD were monitored for albuminuria over the following 2 years. Only 23% of individuals satisfying KDIGO criteria for referral visited a nephrologist, and only 12% of identified patients with CKD carried an ICD-10 diagnostic code. While there continues to exist the debate as to whether general screening programmes for CKD are cost-effective, our study showed that screening was already taking place and on a large scale through routine creatinine testing. The problem may lie in the integration of this information into the medical decision process. From a research perspective, our study illustrated how registry-based research, in the absence of creatinine measurements, misses about 90% of the true population with CKD [7].

Albuminuria is an underrecognized component of the CKD definition, staging and prognosis. In another SCREAM study, we identified >31,000 participants with two or more ambulatory urine albumin-to-creatinine ratio (ACR) tests, and assessed the association between changes in ACR during defined periods of 1, 2 or 3 years and the risk of end-stage kidney disease (ESKD; also known as kidney failure) [19]. Regardless of the baseline period, any increase in ACR is strongly associated with a higher risk of ESKD and any decrease in ACR is associated with reduced ESKD risk. Similar associations were found in people with and without diabetes mellitus (Fig. 3), or when adjusting for the change in eGFR during the same period. In a subsequent study, albuminuria was demonstrated to be an important predictor of adverse clinical outcomes in persons with myocardial infarction, independently of eGFR and offering

Fig. 2 Prevalence of chronic kidney disease (CKD) stages 3–5 including renal replacement therapy (RRT) by age categories in the Stockholm population during 2006–2011 (adapted from [16]).

Fig. 3 Adjusted hazard ratio (HR) of end-stage kidney disease (ESKD) associated with a fold change in urinary albumin-to-creatinine ratio (ACR) during a 2-years window in patients with and without diabetes mellitus (reproduced from [19]).
considerable improvement of risk prediction beyond conventional risk factors [21]. These data are important to inform on the need of measuring albuminuria in high-risk populations and to better interpret results of ACR monitoring at the bedside. Still, low rates of albuminuria monitoring and detection are features of all health systems globally [22].

Adverse health outcomes in persons with CKD

A low kidney function has been associated with the risk of cardiovascular events, complications of diabetes and many disorders that appear with the loss of nephrons. SCREAM provided a unique opportunity to quantify some of these risks and their interrelations, particularly rare complications that require large sample sizes to meaningfully quantify them.

Characterizing the interrelation of cardiovascular and kidney diseases. The cardiorenal syndrome, that is, the existence of a bidirectional relationship of CVD with CKD, has long been discussed and has been attributed to shared risk factors and the therapies used to manage these diseases [23,24]. While multiple studies have described the excess CVD risk in persons with CKD [25–27], there has been a paucity of studies exploring whether experiencing a CVD event increases the risk of kidney disease, which is the central hypothesis of cardiorenal syndromes type 1 and type 2. The study by Ishigami et al. [28] offered support to this pathophysiological mechanism by evaluating changes in the slope of eGFR decline among persons who experienced an incident hospitalization with heart failure, coronary heart disease or stroke. We observed that incident hospitalization with heart failure or coronary heart disease was significantly associated with a more accelerated decline in eGFR. The absolute change of this acceleration was most significant for patients with heart failure, although on the relative scale (i.e., percentage change), the acceleration of eGFR decline was similar after both events (65% and 71% increase in the rate of eGFR decline per year after incident heart failure and coronary heart disease, respectively). By contrast, incident stroke did not clearly influence the rate of kidney function decline, although a low number of identified cases may make these results less reliable. From a clinical perspective, this study illustrates the need for long-term monitoring of kidney function in patients with CVD.

The power of well-collected health information on detecting associations with rare outcomes is exemplified by the work of Vavilis et al. [29], who studied the risk of developing aortic stenosis in relation to kidney function. The study included all adult Stockholm citizens with known kidney function and without a prior diagnosis of aortic stenosis. The occurrence of aortic stenosis during follow-up was ascertained by diagnostic codes, and during a median follow-up of 5 years, only 0.5% of participants developed it. Compared with patients with normal renal function, the patients with an eGFR between 60 and 90 ml/min/1.73 m² were 14% more likely (hazard ratio [HR] 1.14; 95% CI [1.05–1.23]) to develop clinically manifested aortic stenosis, and patients with eGFR <30 ml/min/1.73 m² were 56% more likely (HR 1.56; 95% CI [1.29–1.87]) to develop it. Increased awareness of the link between these two diseases has prompted subsequent mechanistic studies delineating common culprits and resulted in practice guideline recommendations to better manage this complex population with CKD and aortic stenosis [30].

Healthcare data can also serve to inform clinical choices, such as the choice of risk stratification tools. Stroke risk scores for patients with atrial fibrillation stand out as being among the most widely adopted, with CHA2DS2-VASc or CHA2DS2-VA the most widely recommended. However, most existing stroke risk scores did not include patients with CKD or did not consider the participant’s kidney function. This creates uncertainty, as patients with CKD are both more likely to develop atrial fibrillation and stroke. De Jong et al. [31] evaluated the performance of six commonly used ischemic stroke risk scores in over 36,000 SCREAM participants with newly diagnosed atrial fibrillation and differing stages of CKD severity. After a median of 1.9 years, 3069 (8.5%) patients suffered an ischemic stroke, with risks increasing linearly with lower kidney function. In the most clinically relevant stages of CKD, predictive performance of risk scores was poor, increasing the risk of misclassification and thus of over- or undertreatment. Discrimination, particularly, was dependent on eGFR: the median c-statistic in participants with eGFR >60 ml/min/173 m² was 0.75 [range 0.68–0.78], decreasing to 0.68 [range 0.55–0.74] for participants with eGFR <30 ml/min/1.73 m². Among the six risk scores evaluated, the Modified CHADS2 score showed good performance across kidney function strata, both for discrimination (c-statistic >0.70 in all CKD stages) and
increasing, particularly for persons with eGFR 7-day and 30-day post-hypoglycaemia mortality the risk of fatal hypoglycaemia, with risks of both glycaemia. Lower kidney function also predicted trend was observed for both mild and severe hypo-
et al. [36] explored the association between HbA 1c may explain the excess AKI incidence. Yang Xu
15 ml/min/1.73 m 2. Regardless of whether the lower eGFR, with incidence rate ratios of 1.2 for eGFR 60–89 ml/min/1.73 m 2 and 5.8 for eGFR <15 ml/min/1.73 m 2 compared to those with a normal eGFR of 90–104 ml/min/1.73 m 2. This trend was observed for both mild and severe hypoglycaemia. Lower kidney function also predicted the risk of fatal hypoglycaemia, with risks of both 7-day and 30-day post-hypoglycaemia mortality increasing, particularly for persons with eGFR <15 ml/min/1.73 m 2. Regardless of whether the association between eGFR and hypoglycaemia is are causal or not, our observations emphasize the need of adequate patient monitoring. Despite guideline recommendations to assess albuminuria and eGFR at least yearly in people with type 2 diabetes, this is not done systematically in about 40% of the diabetics in our region [16].

Clinical epidemiology can be used to investigate pathophysiological mechanisms. AKI, a sudden deterioration of kidney function over days or weeks, is a not-infrequent complication of patients with diabetes and CKD, but the underlying reasons are poorly elucidated. Based on research regarding acute hyperglycaemia and AKI in the perioperative setting, we hypothesized that chronic hyperglycaemia (represented by higher levels of HbA1c) may explain the excess AKI incidence. Yang Xu et al. [36] explored the association between HbA1c and the risk of AKI in ~12,000 SCREAM adults with type 2 diabetes and CKD stages G3–G5. During a median follow-up of 2.3 years 2619 AKI events were recorded, and the models exploring both baseline and time-varying HbA1c showed a J-shape inverse association. In other words, compared with baseline HbA1c 6%–6.9%, the HR for AKI in patients with HbA1c >9% was 1.33 (95% CI [1.13–1.57]). Because AKI is common and a strong risk factor for progression of CKD and mortality, our results should be followed by interventional studies to investigate whether tighter control of hyperglycemia might reduce the risk of AKI.

Kidney disease and the risk of infections. Nephrologists caring for patients with kidney failure know well that infections are the most common and serious noncardiovascular complications. Whether kidney dysfunction at a community level has implications for the risk of infections, was unknown, and could have public health implications. Xu Hong et al. [37] showed that even small reductions in kidney function are associated with a higher risk of community-acquired infections: among >1 million SCREAM participants, we explored the risk of infections, overall and by major infection types over 12 months of follow-up. The incidence rate of infections increased with lower eGFR levels, from 74/1000 person-years for individuals with eGFR between 90 and 104 ml/min/1.73 m 2 to 419/1000 person-years for individuals with eGFR <30 ml/min/1.73 m 2. Lower respiratory tract infections, urinary tract infections and sepsis were major infections in persons with CKD (Fig. 4a). Low kidney function was also a relevant predictor of the risk of hospital-acquired infections [38]: in an evaluation of SCREAM participants admitted to hospital for an elective orthopaedic, abdominal, cardiothoracic, vascular or neurologic surgery, 5.5% of patients experienced at least one type of hospital-acquired infection (urinary tract infections, pneumonia, surgical site infections and bloodstream infections), and the odds was highest in patients with eGFR <60 ml/min/1.73 m 2 (Fig. 4b). As many of these infections are severe and may lead to fatalities [39], and considering the context of growing public health concerns about infections, both studies emphasize the need to establish effective and efficient policies for infection prevention that consider the individual’s kidney function—in society as well as in the perioperative setting.

Other outcomes associated with kidney disease. The list of adverse health outcomes associated with kidney disease expands almost every day, owing to the critical and unique role of the kidney in maintaining homeostasis, eliminating waste
products, synthesizing/metabolizing hormones. Other key works from SCREAM have documented the plausible association between eGFR and the risk of developing cancer [40], stress-related disorders [41] or dementia [42]. We also reported a higher risk of major cardiovascular events shortly after developing fractures [43] or the complications that arise as a consequence of developing secondary hyperparathyroidism [44] in persons with CKD.

**Drug safety, effectiveness and monitoring**

The loss of kidney function, even if nonpathological, alters drug metabolism and clearance [45], prolonging the half-life of drugs and metabolites and resulting in exaggeration or attenuation of drug efficacy [46]. Because of this, many clinical trials have excluded (or included in minimal proportions) patients with CKD [47], generating uncertainty as to whether these patients will benefit from, or be harmed by, such medications. It becomes clear that additional data are needed to guide prescribing strategies, which can be sought from careful analyses of routine clinical practice [48,49].

The risks of potentially inappropriate drug use by patients with CKD proved to be high. Schmidt-Mende et al. [50] evaluated the dispensation of contraindicated medications among older adults (>65 years) accessing healthcare during 2010 and with CKD stages 3–4. They evaluated a large list of both nephrotoxic medications and medications that should be avoided because of risk of adverse events. They observed that 9% of older adults with CKD stage 3 and 38% with CKD stage 4 received at least one contraindicated drug. Bosi et al. [51] expanded this work by evaluating the risk of nephrotoxic drug use by persons with eGFR <60 ml/min/1.73 m² during the more recent period 2016–2018. The situation proved to be similar or worse; during a 1-year period, 20% of patients with CKD received at least one potentially inappropriate nephrotoxic medication. Among the top nephrotoxic medications dispensed were nonsteroidal anti-inflammatory drugs, bisphosphonates, antivirals and immunosuppressant drugs. For many of these drugs, non-nephrotoxic alternatives exist that could have been prescribed instead. Notably, provider awareness of a patient’s CKD (ascertained by the presence of a diagnostic code or visit to a nephrologist) was associated with lower odds of nephrotoxic medication use (odds ratio 0.85; 95% CI [0.80–0.90]). Clearly, strategies to increase physicians’ awareness of patients’ CKD and knowledge of drug nephrotoxicity among physicians are needed to reduce inappropriate prescribing of nephrotoxic medications and prevent iatrogenic kidney injury.

Pharmacoepidemiology can be used to identify healthcare gaps in drug monitoring practices or dosing, which sets a basis for educational campaigns targeting physicians. Nilsson et al. [52] explored the adherence to the guideline...
recommendation of monitoring potassium and kidney function in patients with heart failure during the initial weeks of mineralocorticoid receptor agonists (MRA) treatment. They evaluated the presence of potassium and creatinine laboratory testing before and after MRA initiation. Although potassium and creatinine monitoring before MRA initiation was frequent, rates of postinitiation monitoring were largely inferior to what is recommended by clinical guidelines, especially among primary care centres.

Because of the inclusion/exclusion criteria of clinical trials and their strict standardized protocols for safety monitoring, rates of adverse events do not necessarily align with what is observed in the heterogeneous routine clinical practice. Trevisan et al. [53] reported a higher-than-expected 1-year incidence of hyperkalaemia (in about 20% of patients, particularly mild hyperkalaemia) in persons starting MRAs (Fig. 5b); Bandak et al. [54] described how hyperkalaemia incidence after initiation of renin-angiotensin system inhibitors (RASI) is largely dependent on eGFR (Fig. 5a). It is important to define and establish adverse event rates by CKD stage in order to evaluate the risk of adverse effects of medications cleared by the kidney: if eGFR is not accounted for, as has often been the case in preceding work, inferences about the associations between medication and outcomes will be inevitably biased.

As a next step, quantifying whether the drug-related adverse event is of clinical consequence is necessary to establish background risks and ensure a correct ascertainment of exposures. For instance, acute transient increases in creatinine right after initiation of RASI are often observed, but the clinical significance of such increases is controversial. Current clinical guidelines recommend monitoring of creatinine during the first 2 months of RASI treatment, and discontinuing if creatinine increase exceeds 30% [55]. Fu et al. [56] examined the magnitude of creatinine increase within the first 2 months of therapy among 32,000 adults initiating RASI therapy. The observations did not offer support to the recommendation to discontinue treatment when creatinine increases by 30%; instead, the risk of MACE, death or progression to ESKD increased proportional to the rise in creatinine, without any distinguishable threshold. Because subsequent reanalysis of pivotal trials found no evidence for modification of the benefit of RASI by level of creatinine increase [57,58], we speculate that the magnitude of creatinine increases may more likely be a risk marker of disease rather than a cause of adverse outcomes.
One of the main uses of pharmacoepidemiology in routinely collected healthcare data is with regard to the effectiveness and safety of medications. At the time, warfarin was the only treatment available for atrial fibrillation, with a much-discussed risk–benefit ratio for patients with CKD, due to their excess risk of both bleeding and stroke [59]. Szummer et al. [60] evaluated whether adverse clinical outcomes associated with warfarin use could be attributed to difficulties in adjusting the warfarin dose in patients with CKD. We evaluated the time-in-therapeutic range (TTR) calculated from all available international normalized ratio (INR) measurements during the first 2 years of warfarin treatment among 7738 newly diagnosed patients with atrial fibrillation. We observed that patients with eGFR <30 ml/min had worse INR control than patients with normal renal function. Furthermore, difficulties in INR control explained the adverse outcomes associated with warfarin, and optimal INR control (TTR >75%) was associated with lower risk of adverse events overall and within each CKD stratum. Other application of pharmacoepidemiology relates to the testing of drug safety/effectiveness in populations not included in pivotal trials; we could for instance expand the cardioprotective effects of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) to patients with established CVD and diabetes [61], or demonstrate the superiority of RASI over calcium channel blockers in patients with advanced CKD [62].

Postmarketing analyses of drug safety in healthcare data are also nowadays used by regulatory agencies, and especially laboratory-derived data, to confirm signals from adverse event reports. As a case example, proton pump inhibitors (PPIs, e.g., omeprazole), are one of the most commonly prescribed medications worldwide, but they have been linked to acute interstitial nephritis and hypomagnesaemia in case reports. Klatte et al. [18] reported a consistent dose-dependent association between the cumulative use of PPI (compared to the ‘non-nephrotoxic’ comparator of similar indication H2 blockers), the risk of AKI and the speed of loss of kidney function. The magnitude of relative risks was modest compared to H2 blockers (HR ranging between 1.3 and 1.4), and the absolute risk of kidney outcomes at a community level was low. However, PPIs are provided to more than 10% of the Swedish population every year, the majority without a clear indication [63]. These studies remind us to periodically reconsider the need of medications, deprescribing PPIs when they are no longer required and not initiating PPIs without a clear indication, which is also endorsed by major guidelines.

In real life, clinical decisions often revolve around whether therapies should be switched or discontinued. These questions often require more complex designs that can address immortal bias and time-varying confounding [64]. Trevisan et al. [65] employed target trial emulation methods based on cloning, censoring and weighting to evaluate the decision to stop or to continue MRA after an episode of hyperkalaemia. Although stopping MRAs is a common practice to prevent recurrent hyperkalaemia, it may have undesirable consequences as it deprives patients of their needed cardioprotection. This study showed that approximately 30% of patients who experienced hyperkalaemia shortly after initiating MRA therapy discontinued treatment in Stockholm care. Compared with continuing MRA, stopping therapy was associated with a lower 2-year risk of recurrent hyperkalaemia (HR 0.75, 95% CI [0.72–0.79]), but a higher risk of cardiovascular events and death (HR 1.10, 95% CI [1.06–1.14]). Within the limits of observational data, this study supports prolonged MRA use regardless of hyperkalaemia occurrence.

Beyond kidney disease

SCREAM is goldmine for clinical epidemiology that expands well beyond our focus on CKD [66,67]. Straightforward examples pertain to the exploration of electrolyte abnormalities [20,68–73]. Inflammation, as exemplified by high-sensitivity C-reactive protein (hsCRP), is another example; whereas RCTs were evaluating the efficacy of targeted anticytokine therapies, there was no evidence, beyond post hoc analyses from RCTs, of whether elevated hsCRP may be useful for risk stratification in secondary CVD prevention. We reported strong associations between the hsCRP of 12,905 patients with myocardial infarction and the risk of MACE, death [74], CKD progression and AKI [75]. Because of the multiple indications for hsCRP testing, the challenge in these studies was to separate ‘possibly’ monitoring tests from disease-induced ones (e.g., hsCRP ordered because of an infection).

A spirit of collaboration and the need of replication of findings. We attribute the success of this project to an open spirit of collaboration, always welcoming researchers who want to investigate their
hypotheses in SCREAM. This has proven to be an enriching experience always that helps us improve. We certainly welcome collaborative projects, and the interested researchers should feel free to contact us. We are delighted to join global initiatives to better understand factors that drive CKD and its implications for public health, such as the CKD-prognosis consortium [76–78] and the Global Burden of Disease [79–81].

Collaboration is also essential for increasing generalizability of findings. Many studies examining adverse drug events do so in just one cohort. Different prescription guidelines, formulary and cost restrictions across countries can be considered as natural experiments: if a medication is prescribed as first-line treatment for a particular condition in Sweden but second-line in the United Kingdom, replication of consistent adverse drug event relationships despite variation in prescribing practices provides greater confidence in results. Whenever the possibility has risen, collaborations with other health systems has made our work more solid and translatable [82–84].

Conclusion

Well-structured routinely collected healthcare data such as SCREAM can generate unique information to guide clinical practice through evaluation of disease burden, health trajectories and patient management decisions. SCREAM is evidencing the burden of CKD in Sweden and how the integration of information on kidney function into the medical decision process is critical in many contexts, including risk stratification, choice of medication, need of dose titration and close patient monitoring. Results have direct application to the practice and performance of our healthcare system and to the care of patients with CKD in general, but also demonstrate the importance of population-based research to improve health.

Acknowledgements

Besides those named in this review, many people have been key to this project, including Bjorn Wettermark, Olof Norin, Abdul R. Qureshi, Peter Barany, Marie Evans, Catherine M. Clase, Friedo W. Dekker, Rino Bellocco, Johan Årnlöv, Arvid Sjölander, Vivekananda Landa and Bengt Lindholm. Because of space limitations, we cannot mention all the master students, PhD students, postdocs, biostatisticians, database managers, administrators and collaborators both within and outside Karolinska Institutet. We are indebted to the patients whose life trajectories are registered in SCREAM and contribute to the advances in our field, and to the personnel at Region Stockholm and the laboratory providers who made this extraction possible. SCREAM has received funding from Region Stockholm, Swedish Research Council, US National Institute of Health, Swedish Heart and Lung Foundation, Martin Rinds Foundation and Stig and Gunborg Westman foundation. Some studies have received support from AstraZeneca, Viforpharma, Astellas, MSD, Novartis and Amgen.

Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–12.
2. Elinder CG, Barany P, Heimburger O Dosing av läkemedel bör anpassas till njurfunktionen. Lakartidningen. 2013;110:2119–20.
3. Elinder C-G, Bárány P, Heimbürger O The use of estimated glomerular filtration rate for dose adjustment of medications in the elderly. Drugs Aging. 2014;31:493–9.
4. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007;298:2038–47.
5. Collaboration GBDCKD. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395:709–33.
6. Hödlmoser S, Winkelwayer WC, Zee J, Pecois-Filho R, Pisoni RL, Port FK, et al. Sex differences in chronic kidney disease awareness among US adults, 1999 to 2018. PloS One. 2020;15:e0243431.
7. Friberg L, Gasparini A, Carrero JJ A scheme based on ICD-10 diagnoses and drug prescriptions to stage chronic kidney disease severity in healthcare administrative records. Clin Kidney J. 2018;11:254–8.
8. Hansson LO, Wadstrom J, Lipcsey M, Biglaria M, Larsson A Current Swedish renal function tests must be better. Uncertain diagnosis with routine formulas—great risk of wrong drug dosages. Lakartidningen. 2008;105:731–4.
9. Swedish Council on Health Technology Assessment. Methods to Estimate and Measure Renal Function (Glomerular Filtration Rate), A Systematic Review. Report no: 214. Swedish Council on Health Technology Assessment; 2013.
10. Odar-Cederlof I, Oskarsson P, Ohlen G, Tesfa Y, Bergendal A, Helliden A, et al. Adverse drug effect as cause of hospital admission. Common drugs are the major part according to the cross-sectional study. Lakartidningen 2008; 105:890–3.
11. SBU. Äldres läkemedelsanvändning. Hur kan den förbättras. En systematisk litteraturöversikt. SBU-rapport nr 193. Statens beredning för medicinsk utvärdering (SBU); 2009.
12 Shemeikka T, Bastholm-Rahmner P, Elinder C-G, Vég A, Törnqvist E, Cornelius B, et al. A health record integrated clinical decision support system to support prescriptions of pharmaceutical drugs in patients with reduced renal function: design, development and proof of concept. *Int J Med Inform* 2015; 84: 387-95.

13 Ludvigsson JF, Almqvist C, Bonamy A-KE, Ljung R, Michaelsén K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol* 2016; 31: 125-36.

14 Laugesen K, Ludvigsson JF, Schmidt M, Gissler M, Valdimarsdóttir UA, Lunde A, et al. Nordic health registry-based research: a review of health care systems and key registries. *Clin Epidemiol* 2021; 13: 533-54.

15 Runesson B, Gasparini A, Qureshi AR, Norin O, Evans M, Barany P, et al. The Stockholm CREAtinine Measurements (SCREAM) project: protocol overview and regional representativeness. *Clin Kidney J* 2021; 16: 119-27.

16 Gasparini A, Evans M, Coresh J, Grams ME, Norin O, Qureshi AR, et al. Prevalence and recognition of chronic kidney disease in Stockholm healthcare. *Nephrol Dial Transplant* 2021; 36: 2086-94.

17 Xu Y, Evans M, Barany P, James G, Sjölander A, Carrero JJ Factors affecting pre-end-stage kidney disease haemoglobin control and outcomes following dialysis initiation: a nationwide study. *Clin Kidney J* 2021; 14: 1780-8.

18 Klatte DCF, Gasparini A, Xu H, De Deco P, Trevisan M, Johansson ALV, et al. Association between proton pump inhibitor use and risk of progression of chronic kidney disease. *Gastroenterology* 2017; 153: 702-10.

19 Carrero JJ, Grams ME, Sood MM, Barany P, et al. Albuminuria changes are associated with subsequent risk of end-stage renal disease and mortality. *Kidney Int* 2017; 91: 244-51.

20 Nilsson E, Gasparini A, Årnlov J, Xu H, Henriksson KM, Coresh J, et al. Incidence and determinants of hyperkalaemia and hypokalaemia in a large healthcare system. *Int J Cardiol* 2017; 245: 277-84.

21 Mok Y, Ballew SH, Sang Y, Grams ME, Coresh J, Evans M, et al. Albuminuria as a predictor of cardiovascular outcomes in patients with acute myocardial infarction. *J Am Heart Assoc* 2019; 8: e010546.

22 Shin J-I, Chang AR, Grams ME, Coresh J, Ballew LH, Surapaneni A, et al. Albuminuria testing in hypertension and diabetes: an individual-participant data meta-analysis in a global consortium. *Hypertension*. 2021;78:1042-52. https://doi.org/10.1161/hypertensionaha.121.17323

23 Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, et al. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. *Eur Heart J* 2010; 31: 703-11.

24 Rangaswami J, Bhalia V, Blair JEA, Chang TI, Costa S, Lentine KL, et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation* 2019; 139: e840-78.

25 Carrero JJ, Trevisan M, Evans M, Svennberg E, Szummer K Kidney function and the risk of heart failure in patients with new-onset atrial fibrillation. *Int J Cardiol* 2020; 320: 101-5.

26 Llóman I, Szummer K, Evans M, Carrero JJ, Lund LH, Jernberg T Incidence of, associations with and prognostic impact of worsening renal function in heart failure with different ejection fraction categories. *Am J Cardiol* 2019; 124: 1575-83.

27 Carrero JJ, Trevisan M, Sood MM, Bárany P, Xu H, Evans M, et al. Incident atrial fibrillation and the risk of stroke in adults with chronic kidney disease: the Stockholm CREAtinine measurements (SCREAM) project. *Clin J Am Soc Nephrol* 2018; 13: 1314-20.

28 Ishigami J, Trevisan M, Lund LH, Jernberg T, Coresh J, Matsushita K, et al. Acceleration of kidney function decline after incident hospitalization with cardiovascular disease: the Stockholm CREAtinine Measurements (SCREAM) project. *Eur J Heart Fail* 2020; 22: 1790-9.

29 Vavilis G, Bäck M, Occhino G, Trevisan M, Bellocco R, Evans M, et al. Kidney dysfunction and the risk of developing aortic stenosis. *J Am Coll Cardiol* 2019; 73: 305-14.

30 Shroff GR, Bangalore S, Bhave NM, Chang TI, Garcia S, Mathew RO, et al. Evaluation and management of aortic stenosis in chronic kidney disease: a scientific statement from the American Heart Association. *Circulation* 2021; 143: e1088-114.

31 De Jong Y, Fu EL, Van Diepen M, Trevisan M, Szummer K, Dekker FW, et al. Validation of risk scores for ischaemic stroke in atrial fibrillation across the spectrum of kidney function. *Eur Heart J* 2021; 42: 1476-85.

32 De Boer IH Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA* 2011; 305: 2532-9.

33 Alkarian M, Zelnick LR, Hall YN, Heagerty PJ, Tuttle K, Weiss NS, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. *JAMA* 2016; 316: 602-10.

34 Perkovic V, Aggarwal R, Fiorett P, Hemmelgarn BR, Levin A, Thomas MC, et al. Management of patients with diabetes and CKD: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference.” *Kidney Int* 2016; 90: 1175-83.

35 Runesson B, Xu Y, Qureshi AR, Lindholm B, Barany P, Elinder CG, et al. Association between reduced kidney function and incident hypoglycaemia in people with diabetes: the Stockholm Creatinine Measurements (SCREAM) project. *Diabetes Obes Metab* 2020; 22: 1425-35.

36 Xu Y, Surapaneni A, Alkas J, Evans M, Shin J-Im, Selvin E, et al. Glycemic control and the risk of acute kidney injury in patients with type 2 diabetes and chronic kidney disease: parallel population-based cohort studies in U.S. and Swedish routine care. *Diabetes Care* 2020; 43: 2975-82.

37 Xu H, Gasparini A, Ishigami J, Mazyen K, Su G, Barany P, et al. eGFR and the risk of community-acquired infections. *Clin J Am Soc Nephrol* 2017; 12: 1399-408.

38 Ishigami J, Trevisan M, Xu H, Coresh J, Matsushita K, Carrero JJ Estimated GFR and hospital-acquired infections following major surgery. *Am J Kidney Dis* 2019; 73: 11-20.

39 Su G, Trevisan M, Ishigami J, Matsushita K, Stålsby Lundborg C, Carrero JJ. Short- and long-term outcomes after incident pneumonia in adults with chronic kidney disease: a time-dependent analysis from the Stockholm CREAtinine Measurement project. *Nephrol Dial Transplant* 2020; 35: 1894-900.

40 Xu H, Matsushita K, Su G, Trevisan M, Årnlov J, Barany P, et al. Estimated glomerular filtration rate and the risk of cancer. *Clin J Am Soc Nephrol* 2019; 14: 530-9.
**SCREAM and kidney disease epidemiology / J. J. Carrero and C. G. Elinder**

41 Su G, Song H, Lanke V, Liu X, Fang P, Valdimarsdóttir UA, et al. Stress related disorders and the risk of kidney disease. *Kidney Int Rep.* 2021; 6: 706-15.

42 Xu H, Garcia-Ptack S, Lindholm B, Eriksdotter M, Carrero JJ. Kidney function, kidney function decline, and the risk of dementia in older adults: a registry-based study. *Neurology.* 2021;96:e2956-65.

43 Runesson B, Trevisan M, Iseri K, Qureshi AR, Lindholm B, Barany P, et al. Fractures and their sequelae in non-diabetes dependent chronic kidney disease: the Stockholm CREAtinine Measurement project. *Nephrol Dial Transplant.* 2020; 35: 1908-15.

44 Xu Y, Evans M, Soro M, Barany P, Carrero JJ Secondary hyperparathyroidism and adverse health outcomes in adults with chronic kidney disease. *Clin Kidney J.* 2021;14:2213–20.

45 Corsonello A, Onder G, Bustacchini S, Provinciali M, Garasto S, et al. Estimating renal function to reduce the risk of adverse drug reactions. *Drug Saf.* 2012;35:47–54.

46 Dreisbach AW, Lertora JJ. The effect of chronic renal failure on drug metabolism and transport. *Expert Opin Drug Metab Toxicol.* 2008; 4: 1065-74.

47 Konstantinidis I, Nadkarni GN, Yacoub S, Saha A, Simeos P, Parikh CR, et al. Representation of patients with kidney disease in trials of cardiovascular interventions: an updated systematic review. *JAMA Intern Med.* 2016; 176: 121–4.

48 Trevisan M, Fu EL, Xu Y, Jager K, Zoccali C, Dekker FW, et al. Pharmacoepidemiology for nephrologists (part 1): concept, applications and considerations for study design. *Clin Kidney J.* 2021; 14: 1307-16.

49 Fu EL, Van Diepen M, Xu Y, Trevisan M, Dekker FW, Zoccali C, et al. Pharmacoepidemiology for nephrologists (part 2): potential biases and how to overcome them. *Clin Kidney J.* 2021; 14: 1317-26.

50 Schmidt-Mende K, Wettermark B, Andersen M, Elsevier M, Carrero J-J, Shemelkka T, et al. Prevalence of racially inappropriate medicines in older people with renal impairment – a cross-sectional register-based study in a large primary care population. *Basic Clin Pharmacol Toxicol.* 2019; 124: 256-65.

51 Bosi A, Xu Y, Gasparini A, Wettermark B, Barany P, Bellocco R, et al. Use of nephrotoxic medications in adults with chronic kidney disease in Swedish and U.S. routine care. *Clin Kidney J.* sfab210, https://doi.org/10.1093/ckj/sfab210. Published: 29 October 2021. In press.

52 Nilsson E, De Deco P, Trevisan M, Bellocco R, Lindholm B, Lund LH, et al. A real-world cohort study on the quality of potassium and creatinine monitoring during initiation of mineralocorticoid receptor antagonists in patients with heart failure. *Eur Heart J Qual Care Clin Outcomes.* 2018; 4: 267-73.

53 Trevisan M, De Deco P, Xu H, Evans M, Lindholm B, Bellocco R, et al. Incidence, predictors and clinical management of hyperkalemia in new users of mineralocorticoid receptor antagonists. *Eur J Heart Fail.* 2018; 20: 1217-26.

54 Bandak G, Sang Y, Gasparini A, Chang AR, Ballesh SH, Evans M, et al. Hyperkalemia after initiating renin-angiotensin system blockade: the Stockholm CREAtinine Measurements (SCREAM) project. *J Am Heart Assoc.* 2017;6: e005428.

55 Weir MR, Lakkis JJ, Jaar B, Rocco MV, Choi MJ, Kramer HJ, et al. Use of renin-angiotensin system blockade in advanced CKD: an NKF-KDOQI controversies report. *Am J Kidney Dis.* 2018; 72: 873-84.

56 Fu EL, Trevisan M, Clase CM, Evans M, Lindholm B, Rotmans JI, et al. Association of acute increases in plasma creatinine after renin-angiotensin blockade with subsequent outcomes. *Clin J Am Soc Nephrol.* 2019; 14: 1336-45.

57 Clase CM, Barzilay J, Gao P, Smyth A, Schmieder RE, Tobe S, et al. Acute change in glomerular filtration rate with inhibition of the renin-angiotensin system does not predict subsequent renal and cardiovascular outcomes. *Kidney Int.* 2017; 91: 683-90.

58 Ohkuma T, Jun M, Rodgers A, Cooper ME, Glassziou P, Hamet P, et al. Acute increases in serum creatinine after starting angiotensin-converting enzyme inhibitor-based therapy and effects of its continuation on major clinical outcomes in type 2 diabetes mellitus. *Hypertension.* 2019; 73: 84–91.

59 Carrero JJ, Evans M, Szummer K, Spaak J, Lindhagen L, Edors R, et al. Warfarin, kidney dysfunction, and outcomes following acute myocardial infarction in patients with atrial fibrillation. *JAMA.* 2014; 311: 919–28.

60 Szummer K, Gasparini A, Eliasson S, Årnlov J, Qureshi AR, Bárany P, et al. Time in therapeutic range and outcomes after warfarin initiation in newly diagnosed atrial fibrillation patients with renal dysfunction. *J Am Heart Assoc.* 2017;6: e004925.

61 Trevisan M, Fu EL, Szummer K, Norhammar A, Lundman P, Wanner C, et al. Glucagon-like peptide-1 receptor agonists and the risk of cardiovascular events in diabetes patients surviving an acute myocardial infarction. *Eur Heart J Cardiovasc Pharmacother.* 2021; 7: 104-11.

62 Fu EL, Clase CM, Evans M, Lindholm B, Rotmans JI, Dekker FW, et al. Comparative effectiveness of renin-angiotensin system inhibitors and calcium channel blockers in individuals with advanced CKD: a nationwide observational cohort study. *Am J Kidney Dis.* 2021; 77: 719-729.e1.

63 Ageerus L, Borgquist L, Tsson Sisid A, Wallenius V, LKostic S, Lundell L. Overdosering och ökat bruk av protonpumpshämmare. *Läkartidningen.* 2021; 118: 20220.

64 Evans M, Methven S, Gasparini A, Barany P, Birnie K, Macneill S, et al. Cinacalcet use and the risk of cardiovascular events, fractures and mortality in chronic kidney disease patients with secondary hyperparathyroidism. *Sci Rep.* 2018; 8: 2103.

65 Trevisan M, Fu EL, Xu Y, Savarese G, Dekker FW, Lund LH, et al. Stopping mineralocorticoid receptor antagonists after hyperkalemia: trial emulation in data from routine care. *Eur J Heart Fail.* 2021;23:1698–707.

66 Cui C, Sun J, Pawitan Y, Pielh F, Chen H, Ingre C, et al. Creatinine and C-reactive protein in amyotrophic lateral sclerosis, multiple sclerosis and Parkinson’s disease. *Brain Commun.* 2020; 2: fca0152.

67 Sun J, Carrero JJ, Zagai U, Evans M, Ingre C, Pawitan Y, et al. Blood biomarkers and prognosis of amyotrophic lateral sclerosis. *Eur J Neurol.* 2020; 27: 2125-33.

68 Savarese G, Xu H, Trevisan M, Dahlström U, Rossignol P, Pitt B, et al. Incidence, predictors, and outcome associations of dyskalemia in heart failure with preserved, mid-range, and reduced ejection fraction. *JACC Heart Fail.* 2019; 7: 65–76.

69 Faxén J, Xu H, Evans M, Jernberg T, Szummer K, Carrero JJ. Potassium levels and risk of in-hospital arrhythmias and mortality in patients admitted with suspected acute coronary syndrome. *Int J Cardiol.* 2019; 274: 52-58.

70 Xu H, Faxén J, Szummer K, Trevisan M, Kovesdy CP, Jernberg T, et al. Dyskalemias and adverse events associated
with discharge potassium in acute myocardial infarction. *Am Heart J.* 2018; **205**: 53–62.

71 Gasparini A, Evans M, Barany P, Xu H, Jernberg T, Ärnlöv J, et al. Plasma potassium range associated with mortality across stages of chronic kidney disease: the Stockholm CREatinine Measurements (SCREAM) project. *Nephrol Dial Transplant.* 2019; **34**: 1534–41.

72 Xu H, Evans M, Gasparini A, Szummer K, Spaak J, Ärnlöv J, et al. Outcomes associated to serum phosphate levels in patients with suspected acute coronary syndrome. *Int J Cardiol.* 2017; **245**: 20-26.

73 Janmaat CJ, Van Diepen M, Gasparini A, Evans M, Qureshi AR, Ärnlöv J, et al. Lower serum calcium is independently associated with CKD progression. *Sci Rep.* 2018; **8**: 5148.

74 Carrero JJ, Andersson Franko M, Obergfell A, Gabrielsen A, Jernberg T hsCRP level and the risk of death or recurrent cardiovascular events in patients with myocardial infarction: a healthcare-based study. *J Am Heart Assoc.* 2019; **8**: e012638.

75 Fu EL, Franko MA, Obergfell A, Dekker FW, Gabrielsen A, Jernberg T, et al. High-sensitivity C-reactive protein and the risk of chronic kidney disease progression or acute kidney injury in post-myocardial infarction patients. *Am Heart J.* 2019; **216**: 20-29.

76 Grams ME, Sang Y, Ballew SH, Matsushita K, Astor BC, Carrero JJ, et al. Evaluating glomerular filtration rate slope as a surrogate end point for ESKD in clinical trials: an individual participant meta-analysis of observational data. *J Am Soc Nephrol.* 2019; **30**: 1746-55.

77 Coresh J, Heerspan HJL, Sang Y, Matsushita K, Arnlöv J, Astor BC, et al. Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. *Lancet Diabetes Endocrinol.* 2019; **7**: 115-27.

78 Inker LA, Grams ME, Levey AS, Coresh J, Cirillo M, Collins JF, et al. Relationship of estimated GFR and albuminuria to concurrent laboratory abnormalities: an individual participant data meta-analysis in a global consortium. *Am J Kidney Dis.* 2019; **73**: 206-17.

79 Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J Am Coll Cardiol.* 2020; **76**: 2982–3021.

80 Collaborators G Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018; **392**: 1923–94.

81 Disease GBD, Injury I, Prevalence C Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018; **392**: 1789–858.

82 Bidulka P, Fu EL, Leyrat C, Kalogirou F, Mcallister KSL, Kingdon EJ, et al. Stopping renin-angiotensin system blockers after acute kidney injury and risk of adverse outcomes: parallel population-based cohort studies in English and Swedish routine care. *BMC Med.* 2020; **18**: 195.

83 Mok Y, Ballew SH, Bash LD, Bhatt DL, Boden WE, Bonaca MP, et al. International validation of the Thrombolysis In Myocardial Infarction (TIMI) risk score for secondary prevention in post-MI patients: a collaborative analysis of the Chronic Kidney Disease Prognosis Consortium and the Risk Validation Scientific Committee. *J Am Heart Assoc.* 2018; **7**: e008426.

84 Titan SM, Laureati P, Sang Y, Chang AR, Evans M, Trevisan M, et al. Bisphosphonate utilization across the spectrum of eGFR. *Arch Osteoporos.* 2020; **15**: 69.

Correspondence: Juan Jesus Carrero, Department of Medical Epidemiology and Biostatistics (MEB), Karolinska Institutet, Nobels väg 12A, Box 281, 171 77 Stockholm, Sweden. Email: juan.jesus.carrero@ki.se