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ORIGINAL ARTICLE

# Patterns of medication use and the burden of polypharmacy in patients with chronic kidney disease: the German Chronic Kidney Disease study

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## ABSTRACT

**Background.** Patients with chronic kidney disease (CKD) bear a substantial burden of comorbidities leading to the prescription of multiple drugs and a risk of polypharmacy. However, data on medication use in this population are scarce.

**Methods.** A total of 5217 adults with an estimated glomerular filtration rate (eGFR) between 30 and 60 mL/min/1.73 $m^2$ or an eGFR $\geq$60 mL/min/1.73$m^2$ and overt proteinuria (>500 mg/day) were studied. Self-reported data on current medication use were assessed at baseline (2010–12) and after 4 years of follow-up (FU). Prevalence and risk factors associated with polypharmacy (defined as the regular use of five or more drugs per day) as well as initiation or termination of polypharmacy were evaluated using multivariable logistic regression.

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**Results.** The prevalence of polypharmacy at baseline and FU was almost 80%, ranging from 62% in patients with CKD Stage G1 to 86% in those with CKD Stage G3b. The median number of different medications taken per day was eight (range 0–27). β-blockers, angiotensin-converting enzyme inhibitors and statins were most frequently used. Increasing CKD G stage, age and body mass index, diabetes mellitus, cardiovascular disease and a history of smoking were significantly associated with both the prevalence of polypharmacy and its maintenance during FU. Diabetes mellitus was also significantly associated with the initiation of polypharmacy [odds ratio (OR) 2.46, (95% confidence interval 1.36–4.45); P = 0.003].

**Conclusions.** Medication burden in CKD patients is high. Further research appears warranted to address the implications of polypharmacy, risks of drug interactions and strategies for risk reduction in this vulnerable patient population.

**Keywords:** chronic kidney disease, GCKD study, medication use, polypharmacy, prescription patterns

## INTRODUCTION

Chronic kidney disease (CKD) represents a global public health burden with increasing prevalence worldwide. Studies estimate that 23–36% of people ≥64 years of age have CKD [1, 2]. Patients with CKD suffer from a high number of comorbidities, including underlying diseases and consequences of impaired kidney function, such as hypertension, diabetes, cardiovascular disease (CVD), CKD-related bone and mineral disease and anaemia [3, 4]. This in turn leads to the need for multiple medications to mitigate symptoms and progression of the consequences and comorbidities associated with CKD.

Polypharmacy, usually defined as the regular intake of five or more medications per day, is of growing importance in ageing populations [5, 6]. Combination of prescription- and over-the-counter (OTC) drugs increases the probability of adverse drug reactions and interactions, which are leading causes of hospitalization and death [7–9]. Alterations in pharmacodynamic and pharmacokinetic parameters in patients with renal insufficiency further complicate the situation [10]. The simultaneous need for multiple medications and appropriate dosing considerations make pharmacological treatment of patients with CKD and its related comorbidities challenging [10, 11]. In fact, uncertainties and increased risks of adverse drug reactions and interactions may prompt some to withhold specific therapies due to the fear of adverse effects [12–14]. In addition, since CKD patients are frequently underrepresented in large outcome trials, the risk–benefit ratio for many pharmacological interventions is less certain in the presence of CKD [15].

Despite the recognized challenging circumstances of pharmacotherapy in CKD patients, surprisingly little is known about current practice patterns, the prevalence of polypharmacy and predisposing factors. In order to address this knowledge gap, we analysed medication data of patients enrolled into the German CKD (GCKD) study, a prospective observational cohort study of patients with moderately severe CKD.

## MATERIALS AND METHODS

### Study population and design

The GCKD study is a prospective observational study of 5217 patients 18–74 years of age under routine care by nephrologists. The study design was previously described in detail [4]. Patient enrolment was based on an estimated glomerular filtration rate (eGFR) of 30–60 mL/min/1.73 m$^2$ or an eGFR >60 mL/min/1.73 m$^2$ in the presence of 'overt' albuminuria/proteinuria (albuminuria >300 mg/g creatinine or proteinuria >500 mg/g creatinine). Exclusion criteria were defined as non-Caucasian ethnicity, active malignancies, previous transplantations, New York Heart Association heart failure stage IV and legal attendance. Patients who gave written informed consent were enrolled across nine study centres in Germany. The study was approved by the local ethics committees and registered in the national registry for clinical studies [German Clinical Trials Register (DRKS) 00003971].

### Data collection and baseline variables

Baseline assessment included physical examination, measurements of body weight and height, heart rate, single-lead electrocardiogram and resting blood pressure. Trained and certified personnel applied standardized questionnaires to collect information on co-morbidities, lifestyle, sociodemographic factors and symptoms of heart failure and gout status. Blood samples were obtained at baseline and at each follow-up (FU) visit every 2 years. Kidney function was categorized according to the Kidney Disease: Improving Global Outcomes clinical practice guideline [16], based on eGFR using the Chronic Kidney Disease Epidemiology Collaboration formula [17] and urinary albumin:urinary creatinine ratio (<30, 30–<300 and ≥300 mg/g).

Smoking status was defined as never, former and current smoker. Education level was categorized as ≤9, 10 and ≥10 years of schooling. The absence or presence of diabetes mellitus was defined as haemoglobin A1c ≥6.5% or use of antidiabetic medication. Anaemia was defined as haemoglobin <12 g/dL (females) and <13 g/dL (males). According to the Guidelines of the European Society of Hypertension and the European Society of Cardiology, hypertension was coded if systolic blood pressure was ≥140 mmHg or diastolic blood pressure was ≥ 90 mmHg or if the patient was on antihypertensive medication. Body mass index (BMI) was defined as weight (kg)/height(m)$^2$ and further classified into overweight (BMI≥25–< 30 kg/m$^2$) or obese (BMI ≥ 30 kg/m$^2$). Patients with total serum cholesterol levels ≥200 mg/dL or low-density lipoprotein cholesterol >100 mg/dL and triglycerides >150 mg/dL or patients who were taking lipid-lowering drugs were considered dyslipidaemic [18].

### Measures and definitions

Medication intake including the use of prescribed drugs as well as OTC medication was assessed as a patient-reported item. The start of a new medication was taken into account at each FU visit; the reported medication intake was validated using the individual medical record. All substances were classified using the Anatomical Therapeutics Chemical (ATC) Classification System of the World Health Organization. If drugs combined two or more pharmacologically active substances, then ATC codes for each individual substance were abstracted. Polypharmacy was defined as the daily use of five or more active substances, including the intake of non-oral and OTC medications [5]. Initiation or

termination of polypharmacy as previously described by Abolhassani *et al.* [19] served as grouping variables classifying the use of multiple medications into two groups in relation to time: initiation (no polypharmacy at baseline but at FU) and termination (polypharmacy at baseline but not at FU).

### Statistical analysis

Data are described using means ± standard deviations (SDs) for continuous variables and frequency distributions with percentages for categorical variables. Univariable and multivariable logistic regression were used to analyse the relationship of polypharmacy with a number of variables, including CKD stage, age, sex, education, BMI, smoking status, diabetes mellitus, hypertension and dyslipidaemia. Thus we accounted for demographic factors as well as the most common comorbidities as confounding factors. Associations between polypharmacy and these variables are expressed in terms of odds ratios (ORs) with 95% confidence intervals (CIs), as obtained from the coefficient estimates of the logistic regression models. P-values $<0.05$ were considered significant. Calculations were carried out using Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, NC, USA).

## RESULTS

### Cohort characteristics, comorbidities and medication prescriptions

Patient characteristics are presented in Table 1. The majority of patients had CKD Stage G3a [$n=1717$ (33.3%)] or G3b [$n=1865$ (36.1%)]. Hypertension, diabetes, CVD and dyslipidaemia were the most frequent comorbid conditions showing an increase in prevalence with lower eGFR. The median number of different medications per day was 8 (7 at FU), whereas the range of daily intake in the whole cohort varied between 0 and 27 individual substances (Figure 1). Antihypertensives and lipid-lowering drugs were the most frequently used medication classes, followed by diuretics, platelet aggregation inhibitors and urate-lowering therapy. Overall, β-blockers and angiotensin-converting enzyme (ACE) inhibitors were the most frequently administered drug classes. The use of at least one antihypertensive agent significantly reduced blood pressure (Supplementary data, Table S4). Prescription rates of different medication classes (Table 1 and Supplementary data, Figure S1) increased with advanced stages of CKD, with the exception of ACE inhibitors (60% in CKD Stage G1 versus 47.7% in CKD Stage G4/5). As shown in Figure 2, the most commonly prescribed individual substances were simvastatin (38.4%), ramipril (31.7%) and acetylsalicylic acid (32.6%), followed by allopurinol (31%), torasemide (28.3%) and hydrochlorothiazide (26.6%). Only 11% of patients received vitamin K antagonists and 13% received psychopharmacological treatment (Supplementary data, Table S3). Furthermore, patients reported a substantial amount of OTC medication intake. The most commonly used drugs in this group were vitamins (D and B), as well as magnesium and calcium supplements. Thirty-one percent of patients received vitamin D supplements; supplementary iron was taken by 5% and folic acid by 2% of the study participants. Intake of reported homeopathic agents was relatively small, varying between 3% and 5% in different CKD stages.

### Polypharmacy at baseline

The prevalence of polypharmacy in our cohort was high. At baseline, almost 80% of patients received polypharmacy and 20% were prescribed >10 different medications per day (Figure 1). An increase of drug prescription rates was observed with lower eGFR (Table 1): 62% of patients with CKD Stage G1 received polypharmacy, whereas this number rose to 92% for patients with CKD Stage G4/5.

In univariate logistic regression analysis, a stage of lower GFR was associated with greater odds to receive polypharmacy. In addition, patients who received polypharmacy were older, had a higher BMI, were less educated and were more likely to have a history of smoking (Table 2).

In multivariate logistic regression, male sex was associated with reduced odds of receiving polypharmacy [OR 0.71 (95% CI 0.60–0.84); $P<0.0001$]. Comorbid conditions such as diabetes mellitus [OR 3.58 (95% CI 2.83–4.52); $P<0.0001$], CVD [OR 3.21 (95% CI 2.37–4.35); $P<0.0001$], hypertension [OR 6.02 (95% CI 4.56–8.52); $P<0.0001$] and dyslipidaemia [OR 1.36 (95% CI 1.01–1.86); $P=0.0494$] were significantly and positively associated with polypharmacy.

### Change of polypharmacy patterns during FU

Medication data of 3128 patients were available for longitudinal analysis comparing baseline and FU results. Sample characteristics at FU were similar compared with baseline data (Supplementary data, Table S2). During the 4-year period, the overall prevalence of polypharmacy decreased slightly from 80% (2515/3128) at baseline to 76% (2389/3128) at FU. In 13% of patients who received five or more medications at baseline, polypharmacy was not present at FU. In contrast, in 33% of 604 patients who received fewer than five medications at baseline, polypharmacy had been initiated during FU (Table 3).

Univariate logistic regression analysis identified diabetes mellitus, increased BMI and a lower GFR stage to be significantly associated with initiation of polypharmacy (Supplementary data, Table S1). After adjustment for confounders, comorbid diabetes mellitus remained a significant risk factor to initiate polypharmacy in CKD patients (OR 2.46, $P=0.003$).

In addition, older age, higher BMI as well as lower eGFR and prevalent comorbid conditions such as diabetes, CVD or a history of smoking were significantly associated with lower odds of terminating polypharmacy (see Table 3).

## DISCUSSION

### Main findings

This study documents a heavy burden of polypharmacy in patients with moderate CKD; 8 of 10 participants of the GCKD study cohort were exposed to polypharmacy and 2 of 10 took >10 different substances per day. Older age, higher BMI and CKD stage as well as comorbid CVD, diabetes, hypertension and dyslipidaemia significantly increased the odds of receiving polypharmacy. In addition, a history of smoking and a lower level of education were identified as risk factors for exposure to polypharmacy.

### Comparison with other reports

Most studies investigating polypharmacy have so far been conducted in cohorts of older adults without CKD, or at least not enriched for CKD. In such studies, prevalence rates of

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**Table 1. Sample characteristics, comorbidities and medications by eGFR categories at baseline (n=5217).**

| Clinical characteristics | eGFR categories (ml/min/1.73$^2$) | | | | |
|---|---|---|---|---|---|
| | ≥ 90, CKD stage G1 (n=233) | 60-89, CKD stage G2 (n=883) | 45-59, CKD stage G3a (n=1717) | 30-44, CKD stage G3b (n=1865) | <30, CKD stage G4/5 (n=461) |
| UACR categories (mg/g), n (%) | | | | | |
| < 30 | 33 (14.2) | 440 (49.8) | 962 (56.0) | 855 (45.8) | 155 (33.6) |
| 30-299 | 78 (33.5) | 214 (24.2) | 435 (25.3) | 592 (31.7) | 145 (31.5) |
| ≥ 300 | 122 (52.4) | 216 (24.5) | 289 (16.8) | 397 (21.3) | 155 (33.6) |
| Age, years; Mean (SD) | 41.8 (±12.9) | 55.6 (±12.6) | 61.3 (±10.4) | 62.6 (±10.6) | 63.5 (±10.1) |
| Sex, n (%) | | | | | |
| Male | 120 (51.5) | 480 (54.4) | 1064 (62.0) | 1147 (61.5) | 288 (62.5) |
| Female | 114 (48.9) | 403 (45.6) | 653 (38.0) | 718 (38.5) | 173 (37.5) |
| BMI, kg/m$^2$; Mean (SD) | 28.5 (±6.8) | 29.3 (±6.0) | 29.8 (±5.8) | 30.1 (±5.9) | 30.4 (±6.2) |
| Comorbidities, n (%) | | | | | |
| Diabetes mellitus | 50 (21.5) | 249 (28.2) | 607 (35.4) | 722 (38.7) | 209 (45.3) |
| Heart failure | 11 (4.7) | 133 (15.1) | 296 (17.2) | 367 (19.7) | 109 (23.6) |
| Hypertension | 217 (93.1) | 816 (92.4) | 1645 (95.8) | 1833 (98.3) | 458 (99.3) |
| Coronary heart disease[a] | 8 (3.4) | 114 (12.9) | 342 (19.9) | 433 (23.2) | 130 (28.2) |
| Cerebrovascular disease[b] | 5 (2.1) | 74 (8.4) | 145 (8.4) | 221 (11.8) | 60 (13.0) |
| Peripheral vascular disease | 6 (2.6) | 60 (6.8) | 147 (8.6) | 212 (11.4) | 62 (13.4) |
| Cardiovascular disease (CVD)[c] | 11 (4.7) | 132 (14.9) | 297 (17.3) | 414 (22.2) | 119 (25.8) |
| Dyslipidemia | 210 (90.1) | 835 (94.6) | 1631 (95.0) | 1776 (95.2) | 443 (96.1) |
| Anemia | 20 (8.6) | 60 (6.8) | 122 (7.1) | 198 (10.6) | 78 (16.9) |
| Gout | 18 (7.7) | 160 (18.1) | 400 (23.3) | 518 (27.8) | 164 (35.6) |
| Smoking status, n (%) | | | | | |
| current smoker | 82 (35.2) | 163 (18.5) | 240 (14.0) | 269 (14.4) | 67 (14.5) |
| former smoker | 67 (28.8) | 346 (39.2) | 763 (44.4) | 816 (43.8) | 231 (50.1) |
| never smoker | 84 (36.1) | 371 (42.0) | 709 (41.3) | 775 (41.6) | 161 (34.9) |
| Educational level, years; n (%) | | | | | |
| ≤ 9 | 72 (30.9) | 396 (44.8) | 885 (51.5) | 1110 (59.5) | 290 (62.9) |
| 10 | 74 (31.8) | 280 (31.7) | 521 (30.3) | 458 (24.6) | 107 (23.2) |
| >10 | 79 (33.9) | 185 (21.0) | 275 (16.0) | 266 (14.3) | 57 (12.4) |
| Polypharmacy[d], n (%) | | | | | |
| Yes | 144 (61.8) | 649 (73.5) | 1364 (79.4) | 1599 (85.7) | 422 (91.5) |
| No | 89 (38.2) | 234 (26.5) | 353 (20.6) | 266 (14.3) | 39 (8.5) |
| Medication, n (%)-most commonly prescribed classes- | | | | | |
| Beta blockers | 44 (18.9) | 404 (45.8) | 925 (53.9) | 1147 (61.5) | 308 (66.8) |
| HMG-CoA-reductase inhibitors | 78 (33.5) | 341 (38.6) | 829 (48.3) | 943 (50.6) | 263 (57.0) |
| ACE inhibitors | 141 (60.5) | 385 (43.6) | 818 (47.6) | 878 (47.1) | 220 (47.7) |
| Angiotensin II receptor blockers | 92 (39.5) | 347 (39.3) | 686 (40.0) | 813 (43.6) | 214 (46.4) |
| Diuretics (loop) | 34 (14.6) | 243 (27.5) | 549 (32.0) | 880 (47.2) | 282 (61.2) |
| Ca channel blockers, dihydropyridine | 43 (18.5) | 258 (29.2) | 636 (37.0) | 793 (42.5) | 228 (49.5) |
| Platelet aggregation inhibitors | 26 (11.2) | 253 (28.7) | 623 (36.3) | 691 (37.1) | 191 (41.4) |
| Urate-lowering therapy | 23 (9.9) | 176 (19.9) | 513 (29.9) | 742 (39.8) | 234 (50.8) |
| Vitamin D analogues | 66 (28.3) | 236 (26.7) | 449 (26.2) | 640 (34.3) | 213 (46.2) |
| PPI | 53 (22.7) | 236 (26.7) | 458 (26.7) | 528 (28.3) | 150 (32.5) |
| Diuretics (thiazides) | 44 (18.9) | 209 (23.7) | 465 (27.1) | 519 (27.8) | 137 (29.7) |
| Thyroid hormones | 37 (15.9) | 178 (20.2) | 381 (22.2) | 393 (21.1) | 98 (21.3) |
| OTC medication, n (%)-most frequently used- | | | | | |
| Vitamines | 77 (33.0) | 293 (33.2) | 551 (32.1) | 731 (39.2) | 230 (49.9) |
| Magnesium | 19 (8.2) | 124 (14.0) | 223 (13.0) | 264 (14.2) | 59 (12.8) |
| Calcium | 42 (18.0) | 139 (15.7) | 192 (11.2) | 207 (11.1) | 55 (11.9) |
| Dietary supplement | 18 (7.7) | 88 (10.0) | 145 (8.4) | 132 (7.1) | 28 (6.1) |
| Homeopathic agents | 12 (5.2) | 33 (3.7) | 64 (3.7) | 50 (2.7) | 21 (4.6) |

eGFR data on 58 patients were missing and those were excluded.

[a]Coronary heart disease is defined as a history of myocardial infarcion, bypass surgery or percutaneous transluminal coronary angioplasty.

[b]CVD is defined as cardiac valve replacement, aortic aneurysm or coronary heart disease.

[c]Cerebrovascular disease is defined as a history of carotic surgery or intervention or stroke.

[d]Polypharmacy is defined as intake of five or more medications per day, OTC medication included.

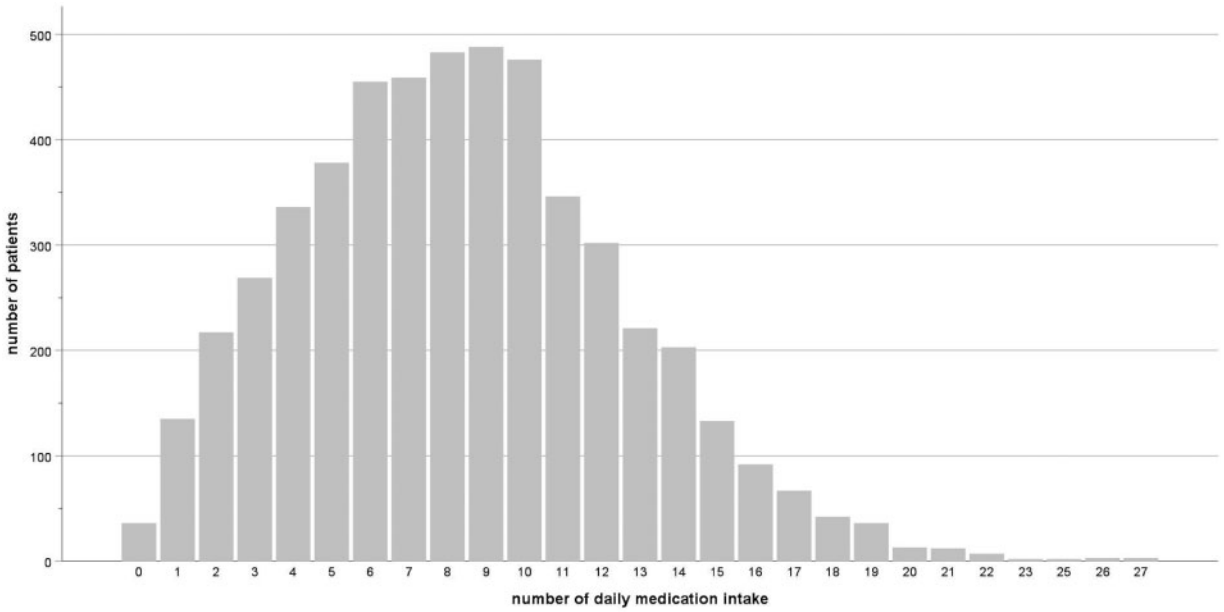


**FIGURE 1:** Total number of medication intakes (prescribed and OTC) per patient at baseline (2010–12) ($N = 5217$).

polypharmacy between 41% and 60%, and thus markedly <80% as in our study, have been reported in different settings and age groups [20–22]. Many treatment considerations for the geriatric population are also applicable to the CKD setting [23]; older adults as well as CKD patients suffer from multiple comorbid diseases with high rates of cardiovascular events triggering strategies for secondary prevention. Thus the very high medication burden in our study population could reflect a particularly high number of comorbidities. In line with this assumption, almost two-thirds of the 12 most commonly used drugs in our study were related to treatment of cardiovascular and cardiometabolic co-morbid conditions. A recent study published by Laville *et al.* [24] showed a similar medication burden in the French Chronic Kidney Disease-Renal Epidemiology and Information Network cohort study.

## Appropriateness of medication

The prescription pattern observed in our study presumably reflects the dilemma between evidence-based treatment recommendations for single disease entities or comorbidities and the overall feasibility, appropriateness and benefit of pharmacotherapy, which probably tend to plateau with an increasing number of prescriptions. In fact, it is likely that the observed treatment regimens are still below strict implementation of guidelines. Despite the high burden of CVD in CKD, the use of cardioprotective medications in kidney disease patients has been reported as lower than in non-CKD patients [3, 13, 25]. In a study of 619 CKD patients conducted in 2005 prior to the Study of Heart and Renal Protection [26], Bailie *et al.* [27] showed that 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors were only received by 16% of patients and ACE inhibitors were prescribed to 44% of CKD patients. These findings are contrasted by our results, since almost 50% of the GCKD study participants received an HMG-CoA reductase inhibitor as well as an ACE inhibitor at baseline, suggesting that the prescription paradigm might have changed over time. However, ACE inhibitor prescriptions decreased with higher CKD stage, which might be due to the fear of hyperkalaemia or because patients had experienced it. According to the most recent guideline for lipid management, 88% of patients who participated in the GCKD study would fulfil criteria for statin prescription [28]. Recent studies also suggested an additional benefit of dual treatment with ezetimibe with decreasing GFR [26, 29]. Implementation of this evidence would further increase medication load and polypharmacy prevalence. Similar considerations hold true for antihypertensive agents. Although blood pressure was reasonably controlled in the overall cohort, only slightly >50% of patients had an office blood pressure <140/90 mmHg [30]. These measurements were obtained during a single office visit and may have been affected by the 'white-coat' effect. On the other hand, this population also shows a high prevalence of masked uncontrolled hypertension [31]. Nonetheless, our findings suggest that according to current guidelines, a substantial proportion of patients would require more intense blood pressure–lowering therapy, which in at least some patients would presumably require the prescription of additional antihypertensives and thus a further increase in medication load. In addition, we have previously shown that a high proportion of patients in the GCKD study cohort had hyperuricaemia despite treatment. Implementing a target of <6 mg/dL would further increase the medication burden [32].

In contrast, there is clear evidence that the use of multiple medications correlates with several negative health outcomes, including higher health care costs, severe adverse drug reactions and medication non-adherence [33]. However, it is still not clear whether the higher risk of receiving inappropriate medication with an increasing number of medications or the number of medications *per se* associates with these outcomes [33]. Laville *et al.* [24] found that exposure to polypharmacy significantly increased the odds of receiving at least one inappropriate medication. In addition, O'Hare *et al.* [34] recently showed that older patients with CKD were less likely to benefit from medications to prevent end-stage renal disease than younger patients. We are not aware of any studies that have tested the benefits and risks of strategies limiting the exposure to polypharmacy in patients who already have CKD, but our findings suggest that such approaches deserve to be tested.

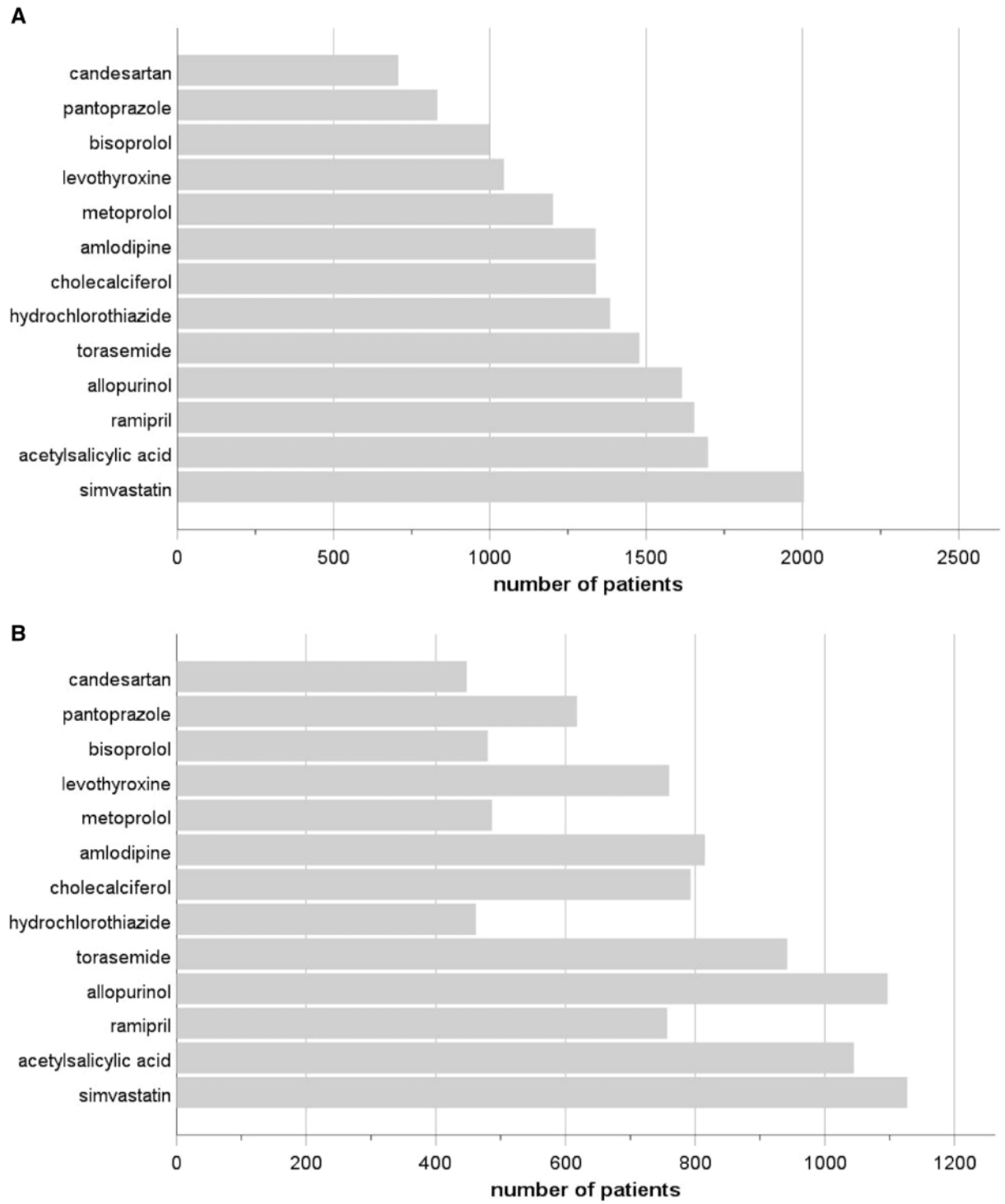


**FIGURE 2:** Most commonly prescribed individual drugs at (**A**) baseline (2010–12, N = 5217) and (**B**) after FU (2014–16, N = 3128).

We observed a frequent use of proton pump inhibitors (PPIs). Explanations for this may include the high number of study participants on antiplatelet drugs and the increasing risk for gastrointestinal bleeding with more advanced CKD stages, the high hospitalization rates in this study population (with PPIs possibly started during hospitalization and then not discontinued) as well as the high proportion with a metabolic syndrome, which increases the risk for gastroesophageal reflux disease [35]. Gastrointestinal symptoms related to reduced kidney function may also play a role. Given the emerging evidence for an association between PPI use and the development as well as the progression of CKD [36–38], avoiding long-term PPI use may potentially improve outcomes.

## Risk factors for polypharmacy

Our analyses revealed that older age, higher BMI and a history of smoking were significantly associated with exposure to more

**Table 2. Bivariate and multivariate analysis of factors associated with polypharmacy[a] in patients with CKD at baseline (*N* = 5217)**

| Clinical characteristics | Bivariate analysis, OR (95% CI) | P-value | Multivariate analysis, OR (95% CI) | P-value |
|---|---|---|---|---|
| eGFR categories (mL/min/1.73 m$^2$) | | <0.0001 | | <0.0001 |
| ≥90 | Ref. | | Ref. | |
| ≥60–<90 | 1.71 (1.27–2.32) | | 1.15 (0.81–1.63) | |
| ≥45–<60 | 2.39 (1.79–3.19) | | 1.18 (0.84–1.65) | |
| ≥30–<45 | 3.72 (2.77–4.99) | | 1.56 (1.11–2.21) | |
| <30 | 6.69 (4.39–10.19) | | 2.36 (1.48–3.77) | |
| Sex, *n* (%) | | <0.1091 | | <0.0001 |
| Male | 1.12 (0.97–1.29) | | 0.71 (0.60–0.84) | |
| Female | Ref. | | Ref. | |
| Age group (years) | | <0.0001 | | <0.0001 |
| <50 | Ref. | | Ref. | |
| ≥50–<60 | 2.02 (1.66–2.46) | | 1.25 (1.0–1.57) | |
| ≥60–<70 | 3.53 (2.94–4.24) | | 1.62 (1.30–2.02) | |
| ≥70–<80 | 5.35 (4.29–6.67) | | 2.21 (1.70–2.88) | |
| BMI (kg/m$^2$) | | <0.0001 | | <0.0001 |
| ≤25 | Ref. | | Ref. | |
| >25–<30 | 1.61 (1.37–1.9) | | 1.13 (0.93–1.36) | |
| ≥30 | 4.48 (3.71–5.42) | | 2.21 (1.79–2.75) | |
| Diabetes mellitus | | <0.0001 | | <0.0001 |
| Yes | 6.50 (5.24–8.07) | | 3.58 (2.83–4.52) | |
| No | Ref. | | Ref. | |
| Hypertension | | <0.0001 | | <0.0001 |
| Yes | 9.96 (7.30–13.57) | | 6.02 (4.26–8.51) | |
| No | Ref. | | Ref. | |
| CVD[b] | | <0.0001 | | <0.0001 |
| Yes | 4.99 (3.75–6.64) | | 3.21 (2.37–4.35) | |
| No | Ref. | | Ref. | |
| Dyslipidaemia | | <0.0001 | | 0.0494 |
| Yes | 2.0 (1.55–2.6) | | 1.36 (1.00–1.86) | |
| No | Ref. | | Ref. | |
| Gout | | <0.0001 | | 0.0076 |
| Yes | 2.15 (1.78–2.60) | | 1.38 (1.11–1.71) | |
| No | Ref. | | Ref. | |
| Smoking status | | <0.0001 | | 0.0002 |
| Never smoker | Ref. | | Ref. | |
| Former smoker | 1.76 (1.51–2.06) | | 1.46 (1.22–1.75) | |
| Current smoker | 0.99 (0.82–1.2) | | 1.15 (0.92–1.43) | |
| Education level (years) | | <0.0001 | | 0.0042 |
| ≤9 | Ref. | | Ref. | |
| 10 | 0.56 (0.47– 0.66) | | 0.89 (0.74–1.07) | |
| >10 | 0.34 (0.28–0.41) | | 0.68 (0.55–0.84) | |

[a]Polypharmacy is defined as intake of five or more medications per day, OTC medication included.
[b]CVD is defined as cardiac valve replacement, aortic aneurysm or coronary heart disease.

than five medications per day as well as the risk to maintain polypharmacy over the observation period of 4 years. Similar associations as well as lower odds for polypharmacy in men have previously been observed in the general and the elderly population [19, 39, 40].

Maintaining polypharmacy over time was associated with lower GFR, comorbid CVD and a history of smoking. Patients with a lower level of education were at greater risk of receiving polypharmacy. Such an association has also previously been reported in a non-CKD population in Sweden [41] and might be related to higher health risks of a lower socio-economic status. Our results show that diabetes mellitus is a prominent risk factor for the initiation of polypharmacy over time. This goes along with studies in the general population showing that diabetes, a higher BMI, hypertension and dyslipidaemia are associated with polypharmacy in patients with normal renal function [19, 21, 42].

## Limitations and strengths

Our study has several limitations. First, a certain recall bias might have occurred since participants may tend to report only the 'most important' medications rather than the total number. We attempted to reduce this bias through validation of medical records. Second, despite the fact that direct patient interviews allow more accurate assessment than the use of administrative data, we could not always clearly distinguish whether a medication was taken based on a prescription or obtained OTC. Third, since certain drugs belong to more than one medication class, the classification might not have been perfectly in line with the

**Table 3. Multivariate analysis of factors associated with initiation and termination of polypharmacy[a] in patients with CKD between baseline (2010–12) and FU (2014–16)**

| Clinical characteristics | Initiation ($n = 202$), OR (95% CI) | P-value | Termination ($n = 321$), OR (95% CI) | P-value |
|---|---|---|---|---|
| eGFR categories (mL/min/1.73 m$^2$) | | 0.0621 | | <0.0001 |
| ≥90 | Ref. | | Ref. | |
| ≥60–<90 | 1.28 (0.57–2.89) | | 0.79 (0.45–1.39) | |
| ≥45–<60 | 1.54 (0.7–3.41) | | 0.54 (0.31–0.94) | |
| ≥30–<45 | 2.47 (1.09–5.58) | | 0.36 (0.20–0.64) | |
| <30 | 1.99 (0.65–6.1) | | 0.32 (0.15–0.68) | |
| Sex | | 0.0941 | | 0.0815 |
| Male | 0.72 (0.49–1.06) | | 1.27 (0.97–1.66) | |
| Female | Ref. | | Ref. | |
| Age group (years) | | 0.7600 | | <0.0001 |
| <50 | Ref. | | Ref. | |
| ≥50–<60 | 1.28 (0.79–2.09) | | 1.52 (1.04–2.22) | |
| ≥60–<70 | 1.1 (0.67–1.81) | | 1.08 (0.75–1.57) | |
| ≥70–<80 | 1.25 (0.67–2.33) | | 0.54 (0.35–0.86) | |
| BMI (kg/m$^2$) | | 0.1021 | | <0.0001 |
| ≤25 | Ref. | | Ref. | |
| >25–<30 | 1.15 (0.76–1.76) | | 0.86 (0.63–1.18) | |
| >30 | 1.72 (1.04–2.87) | | 0.43 (0.31–0.61) | |
| Diabetes mellitus | | 0.003 | | <0.0001 |
| Yes | 2.46 (1.36–4.45) | | 0.32 (0.23–0.45) | |
| No | Ref. | | Ref. | |
| Hypertension | | 0.2274 | | 0.0856 |
| Yes | 1.47 (0.79–2.77) | | 0.54 (0.27–1.09) | |
| No | Ref. | | Ref. | |
| CVD[b] | | 0.504 | | 0.0019 |
| Yes | 1.3 (0.60–2.82) | | 0.53 (0.35–0.79) | |
| No | Ref. | | Ref. | |
| Dyslipidaemia | | 0.3466 | | 0.2757 |
| Yes | 1.37 (0.71–2.61) | | 0.74 (0.42–1.28) | |
| No | Ref. | | Ref. | |
| Gout | | 0.2362 | | 0.0629 |
| Yes | 1.43 (0.87–2.35) | | 0.69 (0.49–0.96) | |
| No | Ref. | | Ref. | |
| Smoking status | | 0.1214 | | 0.0006 |
| Never smoker | Ref. | | Ref. | |
| Former smoker | 1.39 (0.92–2.10) | | 0.68 (0.52–0.9) | |
| Current smoker | 1.58 (0.96–2.6) | | 0.49 (0.32–0.74) | |
| Education level (years) | | 0.6948 | | 0.3544 |
| ≤9 | Ref. | | Ref. | |
| 10 | 1.29 (0.83–1.99) | | 1.09 (0.81–1.46) | |
| >10 | 1.06 (0.67–1.68) | | 1.28 (0.91–1.8) | |

Results are described as ORs as obtained from multivariable logistic regression analysis (95% CI).
[a]Polypharmacy is defined as intake of five or more medications per day, OTC medication included.
[b]CVD is defined as cardiac valve replacement, aortic aneurysm or coronary heart disease.
Initiation is no polypharmacy at baseline, but at FU-4. Termination is polypharmacy at baseline, no polypharmacy at FU-4.

reasons for use. Fourth, in the absence of a control group of patients without CKD, we cannot determine to which extent medication patterns are related to CKD or the comorbidities observed in our cohort. Fifth, all our patients were under nephrological care, so our findings may not be generalizable to a larger group of CKD patients not receiving specialist care. Finally, conclusions about adherence to the reported medication cannot be drawn. Significant strengths of our study include its large sample size and the fact that all patients were studied in a system of 'free' health care, based on mandatory insurance, thus reducing the influence of differences in access to health care. The use of in-person data collection performed by trained study personnel presumably helped to directly assess all medications that the patient was aware of, irrespective of whether it was prescribed by different physicians and including non-prescribed medications.

## CONCLUSIONS

In summary, our data highlight that CKD patients are prone to polypharmacy, indicating a need for future research to address the implications of polypharmacy and the lack of evidence for pharmacological interventions in this population. Despite a clinical rationale for the use of most, if not all, individual drugs prescribed, the risk:benefit ratio for the entirety of all prescribed drugs in one individual may need to be considered in the context

of the disadvantages of polypharmacy. Drug prioritization strategies could potentially be helpful to optimize pharmacological intervention [43]. Implementation of interprofessional and patient-personalized tools to guide a deprescribing process in kidney disease patients such as the Screening Tool to Alert to Right Treatment (START)/Screening Tool for Older Persons' Prescriptions (STOPP) criteria, the PRISCUS (latin for 'time-honored') and Fit for the Aged (FORTA) scores or electronic alert systems [44–47] may help to better balance the benefits and risks of pharmacological treatment in this vulnerable population.

## SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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## AUTHORS' CONTRIBUTIONS

I.M.S., S.H., S.T., G.S., T.D., U.T.S., A.K., J.F., J.T.K., R.K. and K.U.E. made contributions to the concept and design of the study. B.B. and J.N. cleaned and provided the routine data. U.T.S. helped with medication coding. J.N., M.S., B.B. and I.M.S. analysed the data. I.M.S. and K.U.E. wrote the first draft of the manuscript, which was subsequently reviewed and approved by all the authors.

## CONFLICT OF INTEREST STATEMENT

The authors have declared no conflicts of interest pertinent to this work.

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