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ORIGINAL ARTICLE

Polypharmacy and medication use in patients with chronic kidney disease with and without kidney replacement therapy compared with matched controls

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ABSTRACT

Background. This study aims to examine polypharmacy (PP) prevalence in patients with chronic kidney disease (CKD) Stage G4/G5 and patients with kidney replacement therapy (KRT) compared with matched controls from the general population. Furthermore, we examine risk factors for PP and describe the most commonly dispensed medications.

Methods. Dutch health claims data were used to identify three patient groups: CKD Stage G4/G5, dialysis and kidney transplant patients. Each patient was matched to two controls based on age, sex and socio-economic status (SES) score. We differentiated between 'all medication use' and 'chronic medication use'. PP was defined at three levels: use of ≥5 medications (PP), ≥10 medications [excessive PP (EPP)] and ≥15 medications [hyper PP (HPP)].

Results. The PP prevalence for all medication use was 87, 93 and 95% in CKD Stage G4/G5, dialysis and kidney transplant patients, respectively. For chronic medication use, this was 66, 70 and 75%, respectively. PP and comorbidity prevalence were higher in patients than in controls. EPP was 42 times more common in young CKD Stage G4/G5 patients (ages 20–44 years) than in controls, while this ratio was 3.8 in patients ≥75 years. Older age (64–75 and ≥75 years) was a risk factor for PP in CKD Stage G4/G5 and kidney transplant patients. Dialysis patients ≥75 years of age had a lower risk of PP compared with their younger counterparts. Additional risk factors in all patients were low SES, diabetes mellitus, vascular disease, hospitalization and an emergency room visit. The most commonly dispensed medications were proton pump inhibitors (PPIs) and statins.

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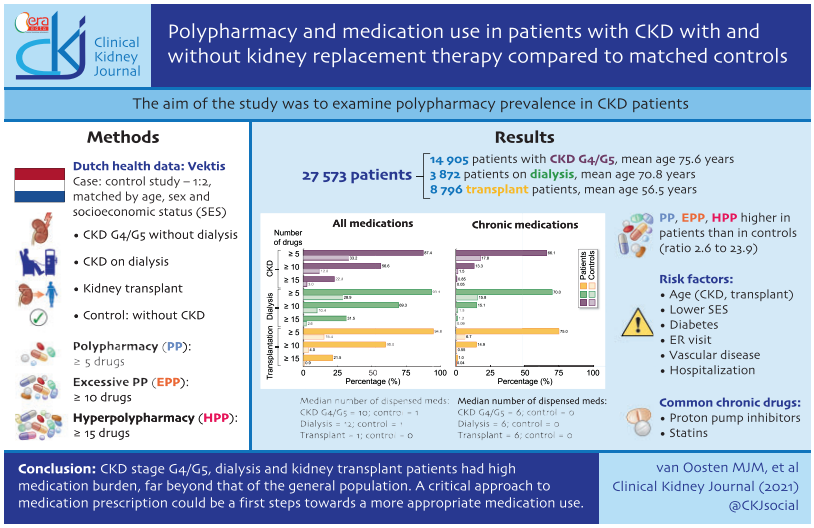
GRAPHICAL ABSTRACT



Conclusions. CKD Stage G4/G5 patients and patients on KRT have a high medication burden, far beyond that of individuals from the general population, as a result of their kidney disease and a large burden of comorbidities. A critical approach to medication prescription in general, and of specific medications like PPIs and statins (in the dialysis population), could be a first step towards more appropriate medication use.

Keywords: CKD, dialysis, health claims data, kidney transplantation, medication use, polypharmacy

INTRODUCTION

Polypharmacy (PP), defined as the concomitant use of medications by one individual, is a frequent phenomenon in clinical practice [1, 2]. Older age and multimorbidity are associated with the growing PP prevalence [2–4]. Chronic kidney disease (CKD) patients often have a large burden of comorbidities and commonly require a multitude of medications to prevent further progression of CKD, to treat its complications and to treat comorbidities [5]. This makes PP a part of their life [6–8]. PP puts patients at risk of medication-related problems, such as drug–drug interactions, suboptimal therapeutic response, a higher risk of adverse drug events and decreased medication adherence [5, 9]. Additionally, PP is associated with poorer quality of life, increased healthcare utilization with higher healthcare costs and a higher risk of morbidity and mortality [2, 10, 11]. Whether the poor outcomes associated with PP are merely a reflection of a person's poor health remain unclear. Nevertheless, findings from previously published papers suggest an association between PP and mortality, even after adjustment for measured confounders such as comorbidities [12].

The prevalence of PP varies across countries and stages of CKD [6–8, 10, 13–17]. Current studies mostly report on elderly patients, only a few studies have used nationwide data and most studies lack a comparison with the general population [6, 7, 15]. This study aims to examine PP in patients with CKD Stage G4/G5 and patients on kidney replacement therapy (KRT) compared with matched general population controls of similar age, sex and socio-economic status (SES), while making use of a national health insurance database encompassing the complete known Dutch kidney disease population. Furthermore, we aim to determine risk factors for PP and commonly dispensed medications.

MATERIALS AND METHODS

Vektis insurance claims database

We used the Vektis database, which includes virtually all Dutch citizens [18]. Vektis contains reimbursement data on all medical procedures covered by the Health Insurance Act and demographic data such as sex, year of birth, area of residence, SES (Appendix 1) and date of death [19].

All hospital procedures in The Netherlands are reimbursed via physician claims called Diagnosis–Treatment Combinations (DBCs) [20]. Vektis also includes pharmacy dispensing data on anatomical therapeutic chemical code level, the defined daily dose (DDD) and the quantity of supplied medication per year. A DDD is a technical unit that reflects the assumed average maintenance dose per day for a medication used for its main indication [21]. The annual quantity supplied for a specific medication is a product of the DDD and the number of days a medication was dispensed. Information on over-the-counter medications and medications administered during a hospital admission or dialysis treatment are missing, since the costs for the latter are covered by the hospital DBC. Since health claims databases lack clinical data, we used proxies [e.g. pharmaceutical cost groups (PCGs)], to assess the prevalence and number of chronic conditions (Appendix 1) [22, 23]. Hospitalization, intensive care unit (ICU) admission and emergency room (ER) visits were identified by specific healthcare operation codes, an element of the DBC code (Appendix 1).

Study population

We selected adults (i.e. ≥20 years) with CKD Stage G4/G5 or on KRT using 2017 healthcare claims data. Patients were divided

into three patient groups: CKD Stage G4/G5 [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2] without KRT, dialysis patients and kidney transplant patients. Patients were excluded if they switched between groups in 2017 (i.e. from CKD Stage G4/G5 to KRT and vice versa or between KRT modalities), if they died in 2017 or if matching was impossible (Figure 1).

CKD Stage G4/G5 without KRT. We selected patients with a CKD Stage G4/G5 health claim on 1 January 2017. Since primary care does not have 'disease-specific' claims comparable to DBCs, we could not identify patients solely treated in primary care.

Dialysis. Patients with a health claim for dialysis on 1 January 2017 were selected regardless of dialysis modality.

Kidney transplantation. Patients with a health claim for kidney transplantation on 1 January 2017 were selected.

Control groups. Two controls per patient, matched for age, sex and SES (per quartile) were selected, provided they had no CKD-related healthcare claim.

PP

Medications with a cumulative annual DDD ≥15 (except for antibiotic treatment) and medications with a cumulative annual DDD ≥180 were selected. The first group (DDD ≥15) was further indicated as 'all medication use', to prevent inclusion of medication dispensed for a very short period, and the second cut-off (DDD ≥180) as 'chronic medication use'.

We defined PP at three levels: concurrent use of ≥5 medications (PP), ≥10 medications [excessive PP (EPP)] and ≥15 medications [hyper PP (HPP)]. For combination medications, the individual substances could not be extracted and therefore were counted as one.

Statistical analysis

To describe baseline characteristics we used means and standard deviations (SDs) for continuous variables and frequency distributions with percentages for categorical variables. To compare baseline characteristics between patients and controls we used the chi-squared test for categorical variables and the Mann–Whitney U-test for non-normally distributed continuous variables. We calculated the PP, EPP and HPP prevalences in all patient (sub)groups and controls and expressed them as percentages. These analyses were repeated in a sensitivity analysis, including all patients who died in 2017. Ratios were calculated by dividing the PP prevalence of patients by the respective prevalence in controls. Univariate and multivariate logistic regressions were used to analyse the association between the independent variables [e.g. age, sex and diabetes mellitus (DM)] and the outcome (i.e. EPP based on chronic medication use). The EPP prevalence was low (i.e. ≤15%) and therefore the rare disease assumption for logistic regression was met [24]. For the identification of confounders, we took the criteria for confounding into account [25]. Associations were expressed as odd ratios (ORs) with 95% confidence intervals (CIs). We considered a P-value <0.05 as statistically significant. Analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics

We included 27 573 individuals: 14 905 CKD Stage G4/G5 without KRT, 3872 dialysis and 8796 transplant patients, with mean ages of 75.6, 70.8 and 56.5 years, respectively (Table 1).

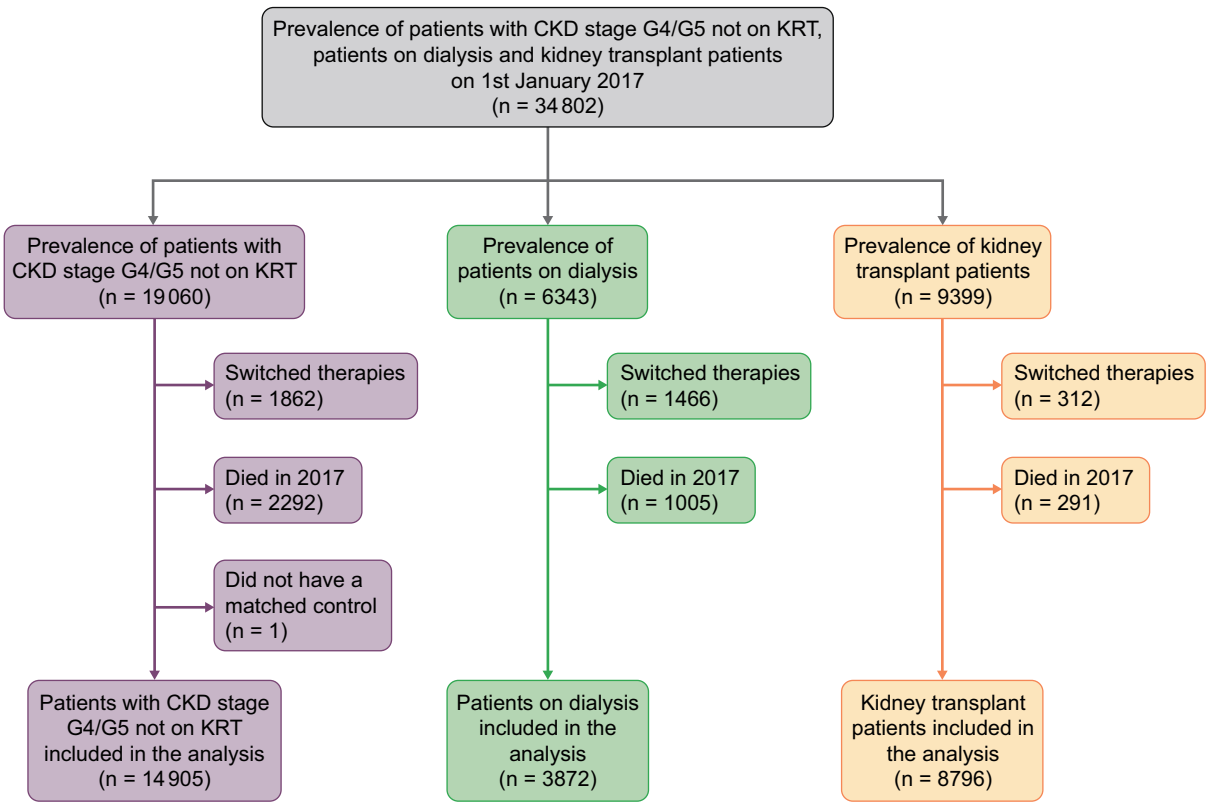


FIGURE 1: Flow chart study participants

Table 1. Baseline characteristics of CKD Stage G4/G5 without KRT, dialysis and kidney transplant patients and matched controls

	CKD			Dialysis			Kidney transplantation		
Characteristics	Patients ($n = 14\,905$)	Matched controls ($n = 29\,810$)	P-value	Patients ($n = 3872$)	Matched controls ($n = 7744$)	P-value	Patients ($n = 8796$)	Matched controls ($n = 17\,592$)	P-value
Age (years), median (25th–75th percentile)	78.0 (70.0–84.0)	78.0 (70.0–84.0)	0.99	74.0 (64.0–80.0)	74.0 (64.0–80.0)	1.00	58.0 (48.8–67.0)	58.0 (48.8–67.0)	1.00
Age (years), mean (SD)	75.6 (11.2)	75.6 (11.2)	0.99	70.8 (13.2)	70.8 (13.2)	1.00	56.5 (13.6)	56.5 (13.6)	1.00
Age (years), %									
20–44	1.8	1.8	–	4.5	4.5	–	19.6	19.6	–
45–64	12.2	12.2	–	22.5	22.5	–	48.4	48.4	–
65–74	25.0	25.0	–	25.8	25.8	–	24.6	24.6	–
≥75	61.0	61.0	1.00	47.3	47.3	1.00	7.5	7.5	1.00
Sex (male), %	52.8	52.8	1.00	58.8	58.8	1.00	59.8	59.8	1.00
SES score, median (25th–75th percentile)	−0.20 (−1.04–0.45)	−0.18 (−1.01–0.45)	0.16	−0.35 (−1.21–0.33)	−0.32 (−1.21–0.36)	0.25	−0.09 (−1.03–0.57)	−0.11 (−1.01–0.57)	0.61
Quartiles, %									
Q1	28.1	28.1	–	33.6	33.6	–	27.6	27.6	–
Q2	26.5	26.5	–	26.6	26.6	–	24.9	24.9	–
Q3	25.2	25.2	–	22.4	22.4	–	23.7	23.7	–
Q4	20.2	20.2	1.00	17.4	17.4	1.00	23.9	23.9	1.00
No. of chronic conditions, mean (SD)	1.92 (11.2)	0.68 (0.98)	<0.0001	1.86 (1.15)	0.61 (0.96)	<0.0001	1.46 (0.95)	0.33 (0.71)	<0.0001
Chronic conditions, %									
0	10.8	55.2	–	13.2	63.3	–	12.6	77.8	–
1	25.9	21.0	–	24.3	19.3	–	45.7	14.1	–
≥2	63.4	23.8	<0.0001	62.6	17.3	<0.0001	41.7	8.1	<0.0001
DM, %	35.9	11.0	<0.0001	31.1	9.8	<0.0001	28.3	5.4	<0.0001
Macrovascular disease, %	17.7	5.2	<0.0001	29.2	4.8	<0.0001	11.3	2.4	<0.0001
Coronary artery disease, %	8.7	4.3	<0.0001	13.2	4.3	<0.0001	6.0	2.5	<0.0001
Peripheral artery disease, %	8.4	2.0	<0.0001	16.9	1.8	<0.0001	4.9	0.82	<0.0001
CVA/TIA, %	2.5	1.7	<0.0001	3.6	1.5	<0.0001	1.6	0.67	<0.0001
Malignancy, %	13.7	7.4	<0.0001	16.4	6.9	<0.0001	19.2	3.6	<0.0001
Hypertension, %	88.0	35.7	<0.0001	82.7	31.7	<0.0001	86.6	17.2	<0.0001
Hospitalization, %	28.7	8.7	<0.0001	52.3	7.8	<0.0001	28.8	4.4	<0.0001
ICU admittance, %	2.6	0.78	<0.0001	8.4	0.81	<0.0001	2.5	0.35	<0.0001
ER visit, %	28.5	10.1	<0.0001	49.5	9.2	<0.0001	32.2	5.6	<0.0001

Q: quartile; CVA/TIA: cerebrovascular accident/transient ischaemic attack.

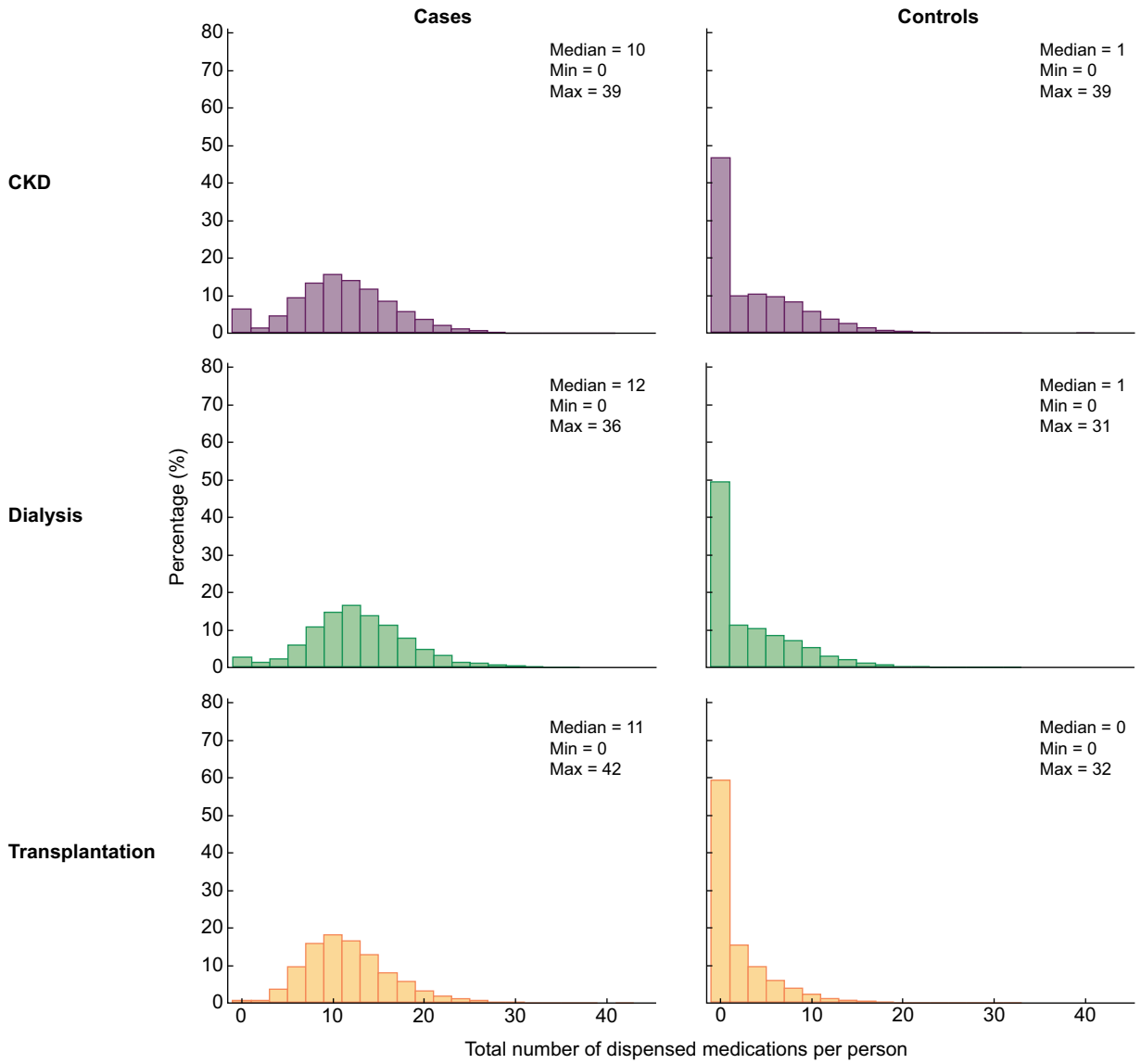


FIGURE 2: Total number of dispensed medication per percentage of CKD stage G4/G5 not on KRT patients, dialysis and kidney transplant patients versus matched controls; all medication use

Chronic comorbidity conditions were 2.9 times more prevalent in CKD Stage G4/G5 patients than in controls (1.92 versus 0.68), 3.0 times higher in dialysis patients (1.86 versus 0.61) and 4.4 times higher in transplant patients (1.46 versus 0.33). In all patient groups, the prevalence of DM, macrovascular disease and hypertension was significantly higher than in controls.

Number of dispensed medications

All medication use. The median number of dispensed medications was 10 for CKD Stage G4/G5 patients, 12 for dialysis patients and 11 for transplant patients compared with 1, 1 and 0 in controls, respectively (Figure 2).

Chronic medication use. The median number of dispensed medications was six in all patient groups, compared with zero in controls (Figure 3).

PP

Figure 4 presents the prevalence and ratio of PP in patients versus controls for 'all medication use' (left panel) and 'chronic medication use' (right panel). The results of the sensitivity analyses were consistent with the results of the main analyses (Appendix 2).

Overall

All medication use. The PP, EPP and HPP prevalences were 87.4, 56.6 and 22.8%, respectively, in patients with CKD Stage G4/G5; 93.4, 69.3 and 31.5%, respectively, in dialysis patients; and 94.8, 60.0 and 21.5%, respectively, in transplant patients (Figure 4). For all comparisons, the PP, EPP and HPP prevalences were much higher in patients than in controls, with ratios ranging from 2.6 (PP in CKD patients versus controls) to 23.9 (EPP in transplant patients versus controls).

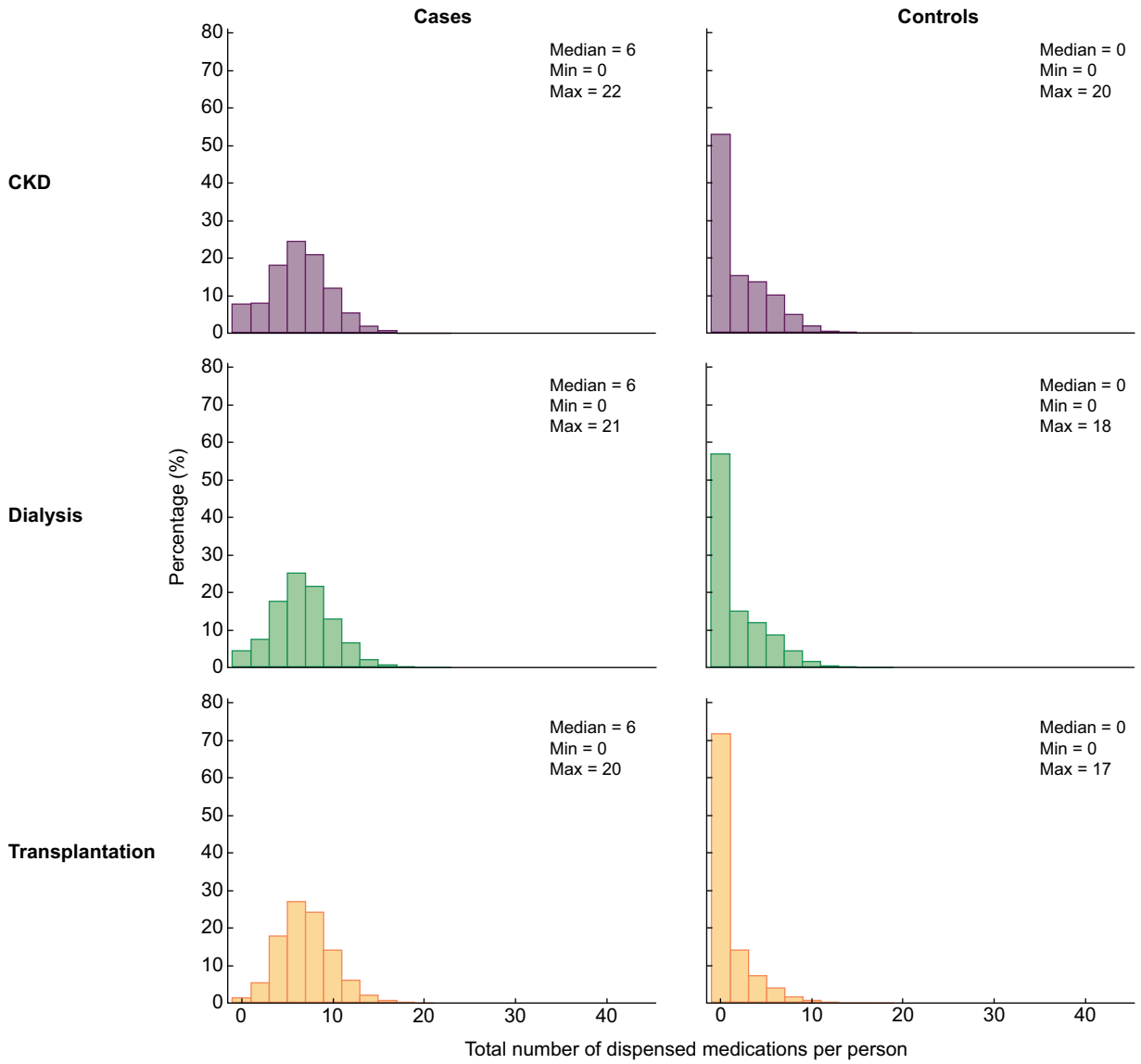


FIGURE 3: Total number of dispensed medication per percentage of CKD stage G4/G5 not on KRT patients, dialysis and kidney transplant patients versus matched controls; chronic medication use

Chronic medication use. Overall, PP based on chronic medication use was less common than PP based on all medication use (Figure 4). The PP, EPP and HPP prevalences were 66.1, 13.3 and 0.9%, respectively, in CKD Stage G4/G5 patients; 70.0, 15.1 and 1.2%, respectively, in dialysis patients; and 75.0, 14.9 and 1.0%, respectively, in transplant patients. Ratios ranged from 3.7 (PP in CKD patients) to 25.8 (EPP in transplant patients).

Patient subgroups

Tables 2 and 3 show the prevalence and ratio of PP in patients versus controls for different subgroups and for 'all' and 'chronic medication use'. Since the PP prevalence for 'all medication use' was very high and the HPP prevalence for 'chronic medication use' was very low, these results are not shown.

All medication use. In CKD Stage G4/G5 and in transplant patients, the EPP and HPP prevalences were highest in patients ≥75 years of age (CKD G4/G5: 60.0 and 24.4%; transplantation: 77.4 and 34.2%). EPP was 42.0 times more common in young CKD patients (ages 20–44 years) than in controls, and this ratio declined with age to 3.8 in patients ≥75 years (Tables 2). PP was more common in both patients and controls with chronic conditions, such as diabetes or macrovascular disease, with EP prevalence ranging from 78.1 to 89.8% in patient groups and 24.6 to 47.5% in controls. The highest PP prevalence (EPP 90.8%) was found in transplant patients with coronary artery disease.

Chronic medication use. PP was most common in CKD patients (69.4%) and dialysis patients (73.5%) ages 65–74 years and in transplant patients (85.0%) ≥75 years of age. Ratios between patient and control groups decreased with increasing age. The

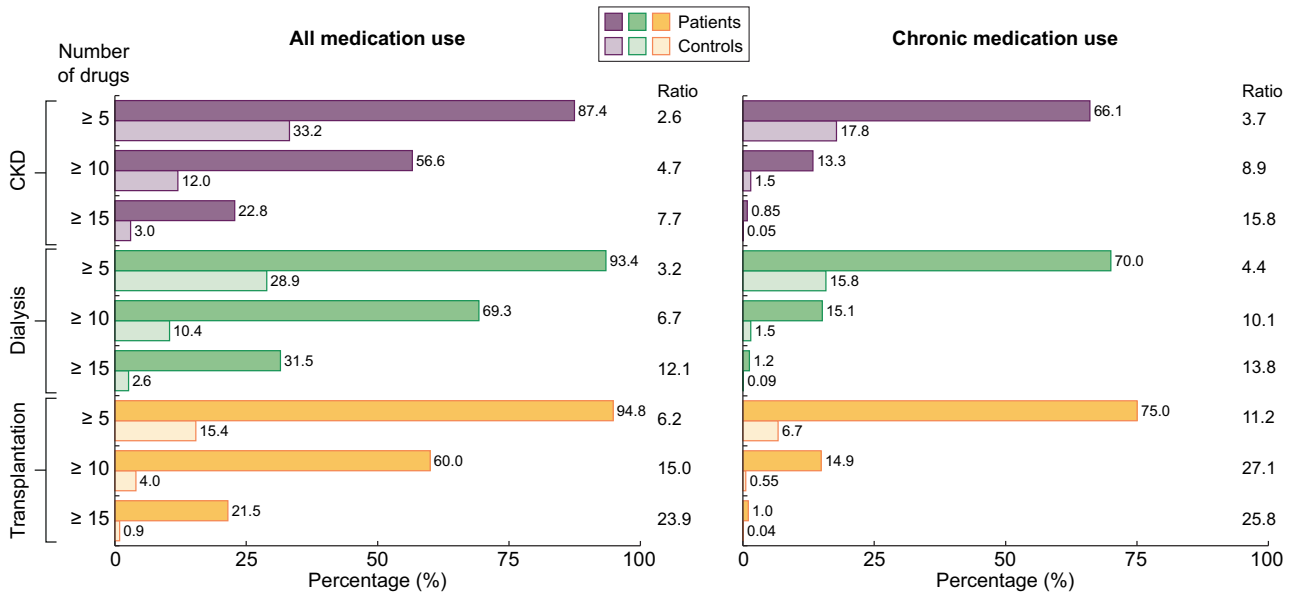


FIGURE 4: Percentage and ratio of polypharmacy of CKD stage G4/G5 without KRT, dialysis and kidney transplant patients versus matched controls for (left) all medication use and (right) chronic medication use

prevalence of PP was high in patients with chronic conditions in all patient groups (Table 3).

Risk factors for PP

Table 4 presents the unadjusted and adjusted association between patient demographics and disease-related variables and EPP (≥10 medications, 'chronic medication use'). Below we discuss the fully adjusted models if adjustment for potential confounders was possible.

CKD Stage G4/G5 without KRT. Patients ages 65–74 years [OR 1.57 (95% CI 1.33–1.85)] and ≥75 years [OR 1.24 (95% CI 1.06–1.44)] had a higher EPP risk compared with patients ages 20–64 years. In addition, an SES score in the lowest two quartiles compared with an SES score in the highest quartile [OR 1.34 (95% CI 1.17–1.55) versus OR 1.23 (95% CI 1.07–1.43)], diabetes [OR 4.98 (95% CI 4.51–5.54)] or vascular disease [OR 2.01 (95% CI 2.12–2.62)], as well as hospitalization [OR 1.35 (95% CI 1.17–1.55)] and an ER visit [OR 1.69 (95% CI 1.53–1.88)] were significantly associated with PP.

Dialysis. Patients ≥75 years of age had a lower risk of EPP [OR 0.74 (95% CI 0.59–0.91)] compared with patients ages 20–64 years. The most pronounced risk factors for EPP in dialysis patients were diabetes [OR 3.69 (95% CI 3.08–4.43)] and vascular disease [OR 2.08 (95% CI 1.72–2.51)].

Kidney transplantation. Patients ages 65–74 years [OR 3.69 (95% CI 2.89–4.71)] and ≥75 years [OR 5.88 (95% CI 4.60–7.51)] had a higher EPP risk compared with patients ages 20–64 years. In addition, being male [OR 1.19 (95% CI 1.05–1.34)], having an SES score in the lowest two quartiles compared with an SES score in the highest quartile [OR 1.34 (95% CI 1.13–1.59) versus OR 1.29 (95% CI 1.09–1.54)], diabetes [OR 5.59 (95% CI 4.91–6.36)] or vascular disease [OR 2.51 (95% CI 2.14–2.96)], hospitalization [OR 1.29 (95% CI 1.09–1.52)] and an ER visit [OR 1.76 (95% CI 1.54–2.00)] were significantly associated with EPP.

Dispensed medication classes

Table 5 shows the most commonly dispensed chronic medication. Proton pump inhibitors (PPIs) were among the most commonly dispensed medications in patients, with ≥50% of patients using a PPI versus 8–19% of controls. Also, statins were commonly dispensed (53, 51 and 40% in CKD Stage G4/G5, transplant and dialysis patients, respectively). Dispensed medication classes for all medication use are shown in Appendix 3. Of note, 3–12% of CKD patients with DM do not use antidiabetic medication, whereas 17–19% of controls with DM are diet-controlled (Appendix 3, Table A1). Furthermore, 63–75% of CKD patients with DM chronically use antidiabetic medication compared with 61–65% of controls (Table 5).

DISCUSSION

This study using Dutch health claims data demonstrates that PP is highly prevalent in CKD Stage G4/G5 patients and patients with KRT compared with the general population. Since multimorbidity is one of the driving factors of PP, we must note that chronic comorbid conditions were three to four times more prevalent in patients than in controls. In our study, PP prevalence based on 'all medication use' ranged from 87% in CKD Stage G4/G5 to 94–95% in dialysis and transplant patients. The prevalence was lower for chronic medication use. Older age was an important risk factor for PP in CKD Stage G4/G5 and transplant patients, whereas dialysis patients ≥75 years of age had a lower risk of PP compared with younger counterparts. For all patients, additional risk factors were lower SES, DM, vascular disease, hospitalization and an ER visit during the year. The PP prevalence ratio between patients and controls declined with age. The most commonly dispensed medications were PPIs and

Table 2. Percentage and ratio of PP ('all medication use') in different subgroups of CKD Stage G4/G5 without KRT patients ($n = 14\,905$), dialysis patients ($n = 3872$) and kidney transplant patients ($n = 8796$) versus matched controls ($n = 29\,810$, $n = 7744$ and $n = 17\,592$, respectively)

	All medication use																	
	CKD						Dialysis						Kidney transplantation					
	EPP ≥10 drugs			HPP ≥15 drugs			EPP ≥10 drugs			HPP ≥15 drugs			EPP ≥10 drugs			HPP ≥15 drugs		
Subgroups	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio
PP overall, %	56.6	12.0	4.7	22.8	3.0	7.6	69.3	10.4	6.7	31.5	2.6	11.9	60.0	4.0	14.9	21.5	0.90	23.9
Age (years), %																		
20–44	23.0	0.55	42.0	6.6	0.0	–	47.4	0.87	54.7	19.7	–	–	38.5	0.49	78.1	8.5	0.09	98.0
45–64	45.1	3.1	14.4	16.2	0.60	26.8	67.0	3.8	17.4	32.6	1.2	27.0	59.2	2.8	21.1	20.0	0.69	28.8
65–74	56.7	7.6	7.5	23.3	1.6	14.9	74.0	7.6	9.7	36.4	1.9	19.1	73.4	6.8	10.8	31.0	1.3	23.1
≥75	60.0	16.0	3.8	24.4	4.2	5.8	69.8	15.9	4.4	29.5	4.0	7.4	77.4	12.0	6.4	34.2	2.9	11.9
Sex, %																		
Male	56.6	11.7	4.8	21.9	2.8	7.7	69.1	9.9	7.0	31.2	2.5	12.3	59.1	3.8	15.6	19.7	0.73	26.9
Female	56.7	12.4	4.6	23.9	3.2	7.4	69.5	11.1	6.3	32.1	2.8	11.4	61.4	4.4	14.0	24.2	1.1	21.1
SES, %																		
Q1	58.4	13.7	4.2	24.7	3.7	6.7	68.7	11.9	5.8	29.4	3.2	9.3	62.4	4.4	14.0	23.3	1.1	22.2
Q2	57.6	12.1	4.8	23.7	3.0	8.0	70.8	9.9	7.2	33.5	2.9	11.7	60.9	4.5	13.5	21.5	1.1	20.0
Q3	55.4	11.2	4.9	21.8	2.8	7.9	67.6	9.4	7.2	32.6	2.3	14.1	60.1	3.7	16.4	21.6	0.67	32.1
Q4	54.5	10.6	5.1	20.4	2.5	8.2	70.3	9.7	7.3	31.6	1.8	17.8	56.3	3.4	16.5	19.4	0.76	25.4
No. of chronic conditions, %																		
0	6.2	0.63	10.0	0.62	0.08	7.9	24.0	0.55	43.5	5.3	–	–	21.3	0.21	100.6	2.7	0.04	73.9
1	31.4	11.4	2.8	6.1	1.5	4.0	53.8	10.8	5.0	14.6	1.5	9.9	47.4	6.1	7.7	9.6	0.72	13.3
≥2	75.5	46.6	1.6	33.4	13.3	2.5	84.8	45.9	1.8	43.6	13.6	3.2	85.5	37.0	2.3	40.2	9.5	4.2
DM, %	78.1	42.5	1.8	37.9	12.4	3.0	86.9	41.0	2.1	51.1	13.0	3.9	86.0	29.7	2.9	41.6	7.4	5.7
Macrovascular disease, %	79.0	47.5	1.7	39.7	15.3	2.6	84.6	45.2	1.9	48.2	14.7	3.3	89.8	36.0	2.5	49.4	7.9	6.3
Coronary artery disease, %	84.6	36.5	2.3	44.0	11.5	3.8	89.4	38.2	2.3	56.0	13.6	4.1	90.8	24.6	3.7	53.2	5.1	10.4
Peripheral artery disease, %	75.9	41.1	1.8	37.6	14.6	2.6	82.7	34.1	2.4	46.2	8.7	5.3	90.8	35.2	2.6	49.7	7.6	6.5
CVA/TIA, %	77.3	38.3	2.0	41.0	10.8	3.8	84.8	32.7	2.6	42.8	8.8	4.8	87.9	17.8	4.9	48.9	3.4	14.4
Malignancy, %	66.4	27.8	2.4	29.8	8.8	3.4	74.2	25.5	2.9	38.6	6.3	6.1	67.0	18.4	3.6	28.0	4.1	6.8
Hypertension, %	62.8	30.7	2.0	25.6	8.0	3.2	77.1	29.7	2.6	35.9	8.0	4.5	65.3	19.6	3.3	23.9	4.4	5.4
Hospitalization, %	78.2	47.1	1.7	42.9	17.1	2.5	79.2	44.4	1.8	43.0	14.5	3.0	81.8	28.2	2.9	42.6	9.5	4.5
ICU admittance, %	85.4	60.5	1.4	52.0	23.6	2.2	83.1	60.3	1.4	50.3	25.4	2.0	90.8	50.8	1.8	59.0	24.6	2.4
ER visit, %	78.5	42.6	1.8	43.5	15.1	2.9	78.4	41.1	1.9	41.3	14.8	2.8	78.0	22.8	3.4	38.5	7.5	5.1

statins, with more than half of patients using these medications.

Strengths and limitations

The main strength of this article is the use of a health claims database with almost complete national coverage of Stage G4/G5 CKD patients, by which we could study CKD Stage G4/G5 and KRT patients in the same cohort and compare them with the general population. Pharmacy dispensing data were complete and contained all medication dispensed by the pharmacy. This in contrast to other studies that used data from patient questionnaires, which heavily relies on patient memory. Another strength of pharmacy dispensing data is that they only include prescribed medication that was actually dispensed and do not cover prescribed medications that were never collected at the pharmacy. Although information on medication adherence is often missing in studies describing medication use, the regular dispensing of medication in a health claims database is an indirect yet strong indication that the medication was routinely taken.

We must consider several limitations. First, although the identification of dialysis and transplant patients is accurate using health claims data [26], we were unable to identify patients with CKD treated in primary care, being mostly elderly patients [27]. Furthermore, data on medication adherence are missing. In addition, we were unable to identify medication given during dialysis sessions. Therefore the PP levels of dialysis patients reported in this study are likely an underestimation of their actual medication burden. Finally, the estimation of chronic conditions in our study was based on proxies that are vulnerable to inaccuracy.

Prevalence of PP

The comparison of the prevalence of PP with other studies is challenging due to the substantial differences in patient selection, definition of PP and data collection. Almost all previously performed studies collected cross-sectional medication data via patient reports or medical charts. Our study is unique in that we used pharmacy dispensing data, which enabled us to monitor all dispensed medication. The availability of the annual quantity of supplied medications makes it possible to differentiate between all and chronic medication use.

The considerably higher PP prevalence based on all medication use compared with chronic medication use suggests that patients often receive short-term medication or experience medication changes. Although PP prevalence based on chronic medication use better reflects the structural medication burden, this type of medication use is not reported in other studies. Therefore we can only discuss our findings on the PP prevalence in the perspective of other studies on all medication use.

CKD Stage G4/G5 without KRT. Current literature describes PP prevalence in different stages of CKD, using different definitions of PP and mainly in elderly patients. Two studies describe PP prevalence in CKD Stage G4/G5 patients. Of these, Schmidt *et al.* [6] reported a PP prevalence of 92% (eGFR <30mL/min/1.73 m^2). Hayward *et al.* [15] describe prevalences of 91% (≥5 medications) and 43% (≥10 medications) in a group of elderly (age >65 years) patients (eGFR <20 mL/min/1.73 m^2) of different European countries. Within the subset of Dutch patients in this study, a prevalence of 91% (≥5 medications) and 43% (≥10 medications) was described. All results are comparable to our findings. Lower PP prevalence was found in patients with CKD Stages G1–G3 [6–8].

Dialysis. It is well known that dialysis patients have a high medication burden [13, 28, 29]. A pooled analysis reported that dialysis patients use 12 different medications [10, 29]. We report a median of 12 medications. A study from Saudi Arabia with 95 haemodialysis patients reported a 98% PP prevalence (>5 medications) [16], which is comparable to our PP prevalence. A Canadian study reported that 93.1% of elderly haemodialysis patients (age ≥65 years) used five or more medications [10]. No previous studies have reported on EP and HP prevalence and we are the first study in a much larger cohort of dialysis patients of all ages.

Kidney transplantation. A high pill burden is also described in transplant patients, ranging from 7 to 32 pills per day, depending on the time period after transplantation [30–32]. An Argentinean study described a mean of 7.8 different medications, while we describe a median of 10 different medications [33]. Only one Polish study reported PP prevalence in a much smaller group of 136 transplant patients as 56% (5–9 medications) and 17% (≥10 medications) [17]. We demonstrated a considerably higher PP and EP prevalence in our larger cohort of transplant patients.

Comparison with the general population. To our knowledge, this is the first study comparing the PP prevalence of CKD Stage G4/G5 patients and KRT patients with a matched control group from the general population. We demonstrate that PP prevalence is already substantially higher in young patients compared with controls, probably reflecting the high number of comorbidities in CKD patients already at a young age. The ratio of PP between patients and controls decreases with increasing age, because medication use increases more with age in the general population than it does in patients [34].

Risk factors for PP

We confirm a positive association between PP and older age in CKD Stage G4/G5 and transplant patients [6, 8, 17, 35]. The inverse association between PP and age ≥75 years in dialysis patients may suggest some reluctance to prescribe medication in the elderly dialysis patient with limited life expectancy and being at high risk for medication-related problems. We confirm that the presence of chronic conditions like DM and cardiovascular disease are risk factors for PP in all patients [6, 10, 16, 36].

Next, we described a positive association between low SES and PP for CKD Stage G4/G5 and transplant patients, in line with other studies [6, 8]. A possible explanation is that individuals with a low SES often have low health literacy and are more vulnerable to comorbid illness. Lastly, we are the first to demonstrate a positive association between PP and hospitalization or an ER visit. We hypothesize that patients with an indication for an ER visit or hospital admission likely have severe comorbid conditions or complications of their CKD for which they need additional medication prescriptions. Moreover, PP itself may be associated with hospitalization in the elderly population [37, 38], although this was not confirmed elsewhere [39].

Medication dispensing

The increased cardiovascular risk of CKD patients is reflected in the high number of medications to prevent or treat

Table 3. Percentage and ratio of PP ('chronic medication use') in different subgroups of CKD Stage G4/G5 without KRT patients ($n = 14\,905$), dialysis patients ($n = 3872$) and kidney transplant patients ($n = 8796$) versus matched controls (respectively $n = 29810$, $n = 7744$ and $n = 17\,592$)

	Chronic medication use																	
	CKD						Dialysis						Kidney transplantation					
	PP ≥5 drugs			EPP ≥10 drugs			PP ≥5 drugs			EPP ≥10 drugs			PP ≥5 drugs			EPP ≥10 drugs		
Subgroups	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio
PP overall, %	66.1	17.8	3.7	13.3	1.5	9.0	70.0	15.8	4.4	15.1	1.5	10.4	75.0	6.7	11.3	14.9	0.55	27.3
Age (years), %																		
20–44	28.1	0.7	38.5	3.3	–	–	50.9	0.9	58.7	5.2	–	–	56.2	0.52	107.6	4.5	0.03	154.0
45–64	56.5	5.3	10.6	11.8	0.58	20.5	68.6	5.8	11.8	18.6	0.80	23.1	77.0	4.6	16.8	14.7	0.39	37.9
65–74	69.4	12.6	5.5	15.9	1.1	14.1	73.5	12.8	5.7	18.5	1.0	18.4	83.1	11.9	7.0	21.3	1.0	20.9
≥75	67.7	23.0	2.9	12.9	1.8	7.0	70.6	23.6	3.0	12.6	2.2	5.8	85.0	18.8	4.5	22.4	1.4	16.4
Sex, %																		
Male, %	67.5	18.5	3.6	13.8	1.7	8.1	71.0	16.3	4.3	16.0	1.4	11.0	77.6	6.7	11.6	15.8	0.56	28.1
Female, %	64.4	17.1	3.8	12.9	1.2	10.5	68.5	15.0	4.6	13.8	1.5	9.4	71.3	6.6	10.7	13.6	0.52	26.0
SES, %																		
Q1	68.3	19.7	3.5	14.8	1.9	7.6	69.4	17.3	4.0	15.4	1.9	8.2	75.9	7.6	10.0	16.4	0.62	26.4
Q2	66.8	17.9	3.7	13.8	1.5	8.9	71.2	15.8	4.5	15.6	1.6	10.0	76.4	7.5	10.2	15.9	0.48	33.0
Q3	64.7	17.3	3.7	12.8	1.1	11.3	70.2	14.8	4.8	16.3	1.2	13.4	73.6	5.9	12.5	14.5	0.55	26.2
Q4	63.6	15.9	4.0	11.5	1.2	9.7	69.4	14.5	4.8	12.5	0.82	15.3	74.1	5.5	13.4	12.7	0.52	24.3
No. of chronic conditions, %																		
0	5.3	0.6	9.2	0.12	0.01	11.1	18.9	0.4	44.1	0.20	–	–	27.6	0.13	210.0	0.18	–	–
1	46.3	20.8	2.2	0.91	0.12	7.9	53.5	20.3	2.6	2.4	0.20	12.2	71.1	11.8	6.0	4.3	0.08	53.2
≥2	84.5	66.2	1.3	20.7	7.2	2.9	87.2	67.0	1.3	23.1	8.2	2.8	93.7	60.2	1.6	31.0	6.6	4.7
DM, %	86.2	61.8	1.4	25.6	8.3	3.1	84.3	63.5	1.3	27.6	9.6	2.9	91.8	52.0	1.8	34.2	6.1	5.6
Macrovascular disease, %	84.3	61.1	1.4	23.0	7.4	3.1	79.7	60.2	1.3	24.1	7.0	3.5	90.7	50.9	1.8	34.1	6.0	5.6
Coronary artery disease, %	87.8	51.5	1.7	25.8	6.3	4.1	88.1	49.7	1.8	31.9	8.2	3.9	93.3	39.4	2.4	38.2	3.9	9.7
Peripheral artery disease, %	83.6	52.3	1.6	22.9	7.6	3.0	74.6	50.0	1.5	20.4	2.9	7.0	90.8	52.4	1.7	34.2	8.3	4.1
CVA/TIA, %	78.7	44.8	1.8	18.3	4.2	4.3	74.6	40.7	1.8	19.6	1.8	11.1	83.0	25.4	3.3	28.4	–	–
Malignancy, %	71.8	35.0	2.1	15.2	3.7	4.1	73.2	33.7	2.2	15.3	3.7	4.1	78.4	25.3	3.1	17.0	2.1	8.2
Hypertension, %	73.2	45.9	1.6	15.1	4.0	3.8	77.6	45.5	1.7	17.5	4.4	3.9	80.8	33.5	2.4	17.0	2.9	5.8
Hospitalization, %	76.7	45.4	1.7	20.0	5.5	3.6	72.1	43.2	1.7	18.1	6.3	2.9	81.7	30.7	2.7	22.5	5.0	4.5
ICU admittance, %	77.3	52.8	1.5	16.4	8.2	2.0	69.6	54.0	1.3	22.1	9.5	2.3	79.3	55.7	1.4	28.1	9.8	2.9
ER visit, %	77.4	44.5	1.7	20.1	5.1	3.9	71.2	42.1	1.7	18.2	5.6	3.2	80.5	24.3	3.3	21.7	3.2	6.9

Table 4. Unadjusted and adjusted analysis of variables associated with PP (defined as ≥10 medications for chronic medication use[a]) in CKD Stage G4/G5 without KRT patients, dialysis patients and kidney transplant patients, using logistic regression

	CKD						Dialysis						Kidney transplantation					
	Unadjusted		Age-, sex-, SES-adjusted model		Fully adjusted model		Unadjusted		Age-, sex-, SES-adjusted model		Fully adjusted model		Unadjusted		Age-, sex-, SES-adjusted model		Fully adjusted model	
Variables	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age categories (years)																		
20–64	Ref.	–	–	–	–	–	Ref.	–	–	–	–	–	Ref.	–	–	–	–	–
65–74	1.57	1.33–1.85	NA[b]	–	NA[b]	–	1.16	0.92–1.46	NA[b]	–	NA[b]	–	3.69	2.89–4.71	NA[b]	–	NA[b]	–
≥75	1.24	1.06–1.44	NA[b]	–	NA[b]	–	0.74	0.59–0.91	NA[b]	–	NA[b]	–	5.88	4.60–7.51	NA[b]	–	NA[b]	–
Age (continuous, per 10 years)	1.01	0.96–1.05	NA[b]	–	NA[b]	–	0.96	0.90–1.03	NA[b]	–	NA[b]	–	1.51	1.44–1.59	NA[b]	–	NA[b]	–
Sex																		
Female	Ref.	–	–	–	–	–	Ref.	–	–	–	–	–	Ref.	–	–	–	–	–
Male	1.08	0.98–1.19	NA[b]	–	NA[b]	–	1.18	0.99–1.42	NA[b]	–	NA[b]	–	1.19	1.05–1.34	NA[b]	–	NA[b]	–
SES (categories)												–						
Q1	1.34	1.17–1.55	NA[b]	–	NA[b]	–	1.28	0.97–1.68	NA[b]	–	NA[b]	–	1.34	1.13–1.59	NA[b]	–	NA[b]	–
Q2	1.23	1.07–1.43	NA[b]	–	NA[b]	–	1.29	0.97–1.72	NA[b]	–	NA[b]	–	1.29	1.09–1.54	NA[b]	–	NA[b]	–
Q3	1.14	0.98–1.32	NA[b]	–	NA[b]	–	1.36	1.02–1.82	NA[b]	–	NA[b]	–	1.16	0.97–1.39	NA[b]	–	NA[b]	–
Q4	Ref.	–	–	–	–	–	Ref.	–	–	–	–	–	Ref.	–	–	–	–	–
DM	5.00	4.51–5.54	4.98	4.50–5.52	NA[b]	–	3.64	3.04–4.36	3.69	3.08–4.43	NA[b]	–	6.59	5.81–7.48	5.59	4.91–6.36	NA[b]	–
Vascular disease	2.36	2.12–2.62	2.36	2.12–2.63	2.01[c]	1.80–2.25	2.46	2.06–2.95	2.49	2.08–2.99	2.08[c]	1.72–2.51	3.64	3.14–4.22	2.86	2.45–3.33	2.51[c]	2.14–2.96
Hospitalization	2.10	1.91–2.31	2.10	1.90–2.31	1.35[d]	1.17–1.55	1.66	1.38–1.99	1.66	1.39–1.99	1.13 [d]	0.90–1.42	2.16	1.91–2.44	1.99	1.76–2.25	1.29 [d]	1.09–1.52
ICU admittance	1.29	0.98–1.69	1.28	0.98–1.69	0.64[e]	0.47–0.86	1.68	1.27–2.21	1.66	1.26–2.19	1.10 [e]	0.81–1.49	2.29	1.70–3.10	1.99	1.46–2.71	1.10 [e]	0.78–1.55
ER visit	2.12	1.92–2.33	2.11	1.92–2.33	1.69[f]	1.53–1.88	1.62	1.35–1.94	1.63	1.37–1.96	1.34 [f]	1.11–1.62	2.09	1.85–2.35	2.01	1.78–2.27	1.76 [f]	1.54–2.00

[a]The overall PP rates (for PP defined as ≥10 medications for chronic medication use) are considered rare enough to reasonably allow for the rare disease assumption for logistic regression.
[b]For this variable, no confounders could be identified considering the criteria for confounding (NA: not applicable).
[c]Model adjusted for age, sex, SES and DM.
[d]Model adjusted for age, sex, SES, DM, vascular disease and ER visits.
[e]Model adjusted for age, sex, SES, DM, vascular disease, hospitalization and ER visits.
[f]Model adjusted for age, sex, SES, DM and vascular disease.

Table 5. Percentage of most commonly dispensed medication classes of CKD Stage G4/G5 without KRT patients, dialysis patients and kidney transplant patients and matched controls: medication classes defined for chronic medication use

	Chronic medication use					
	CKD		Dialysis		Kidney transplantation	
Medication classes	Patients, % ($n = 14\,905$)	Matched controls, % ($n = 29\,810$)	Patients, % ($n = 3872$)	Matched controls, % ($n = 7744$)	Patients, % ($n = 8796$)	Matched controls, % ($n = 17\,592$)
Cardiovascular drugs						
ACE inhibitors	23.6	11.1	11.4	10.4	24.6	5.3
ARB	27.9	9.8	13.2	7.9	17.6	4.8
Beta-blockers	29.1	9.1	25.1	7.9	29.6	3.7
Calcium channel blockers	39.8	9.3	29.7	8.5	43.4	4.2
Diuretics	43.1	10.1	44.3	8.6	19.1	3.8
Statins	52.8	19.3	39.5	18.3	50.8	10.2
PPIs	51.9	19.4	65.5	16.8	54.0	8.2
Vitamin D analogues	50.6	12.5	43.4	9.9	48.5	4.7
Antithrombotic agents	45.2	19.2	50.3	17.2	29.6	7.6
Platelet aggregation inhibitors	38.8	15.3	44.6	13.9	23.9	6.2
Vitamin K antagonist	5.6	2.1	6.3	1.8	4.3	0.67
Heparin	0.27	0.14	0.44	0.10	0.47	0.06
DOAC/NOAC	1.1	1.9	0.03	1.6	1.4	0.76
Antidiabetics	25.8	6.6	19.6	6.4	21.3	3.5
Insulin	15.8	2.1	14.8	2.1	11.2	1.0
Metformin	2.2	4.7	0.03	4.8	9.2	2.6
Sulphonylurea derivative	10.3	2.9	4.5	2.5	7.1	1.5

ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; DOAC/NOAC: direct oral anticoagulant/novel oral anticoagulant.

cardiovascular conditions. Recent guidelines recommend statin prescription to CKD Stage G4/G5 patients [40]. Although (almost) all CKD Stage G4/G5 patients would be expected to fulfil the criteria for statin prescription, only half of the patients in our study used statins. Conversely, several studies question the benefit of statin therapy for dialysis patients [41–43]. Guidelines suggest that statins should not be routinely 'initiated', though they should be continued when patients already use statins when initiating dialysis treatment [44]. We suggest a critical evaluation of statin treatment in dialysis patients to reduce some of the medication burden. This also may be the case for PPIs [45]. More than 50% of CKD Stage G4/G5 and transplant patients, and even >65% of dialysis patients, used a PPI in our study. Previous studies reported PPI use of 30, 50 and 52% in haemodialysis patients and 33, 49 and 62% in CKD Stage G4/G5 patients, respectively [10, 15, 36]. The literature reports that the indication for PPI use in dialysis patients was unknown >25% of the time [46]. Since the long-term use of PPIs can have negative consequences, deprescribing of PPIs should be considered [47].

CONCLUSION

Our study demonstrates that patients with CKD Stage G4/G5 and patients on KRT have a very high medication burden, far beyond that of individuals from the general population. Important PP risk factors are age, SES, DM, vascular disease, hospitalization and an ER visit.

Medication treatment of CKD patients is a challenging balance between the benefits of pharmacotherapy for the treatment of kidney disease and comorbidities and the disadvantages of potentially inappropriate prescribing or adverse drug interaction [48]. Although physicians often check whether the prescribed medication is appropriate in their patient, it is not easy to minimize the medication burden. As directed by the Hippocratic Oath, physicians strive for optimal treatment of their patients, while avoiding those twin traps of overtreatment and therapeutic nihilism. Undertreatment has been repeatedly associated with unfavourable outcomes in dialysis patients [49]. Despite the fact that therapeutic nihilism should be avoided at all times, we propose that a critical approach to the prescription of specific medications like PPIs in all CKD patients and statins in the dialysis population could be a first step towards more appropriate medication use. Finding a proper balance between potentially beneficial medication and needless use of medications with adverse effects will remain a challenge.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The Vektis database used for this study can only be accessed by contacting Vektis (see www.vektis.nl).

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APPENDIX 1. VARIABLES BASED ON DATA OF THE VEKTIS DATABASE

SES

The SES was established by the Netherlands Institute for Social Research and is based on a person's postal code [20]. The SES score is derived from the mean income in the residential area, the percentage of people with low education and low income as well as the fraction of unemployed people in the area. The national mean SES score is 0 and ranges from −8.07 to +3.06, where a lower score indicates a lower SES and a higher score indicates a higher SES.

DM

The definition of the variable DM is based on a combination of hospital claims (DBC codes), pharmaceutical claims and health claims for primary care activities.

Definition of DM	
Diagnosis code	
Internal medicine	
313.221	DM without secondary complications
313.222	DM with secondary complications
313.223	DM chronic pump therapy
ATC code	
A10	Drugs used in diabetes
Primary care activity code	
11602	Multidisciplinary care T2DM—head tariff
13029	Diabetes medical support per year
13030	Diabetes regulation—insulin therapy
400001	Multidisciplinary care T2DM—organization and infrastructure

ATC, anatomical therapeutic chemical.

Macrovascular disease, coronary artery disease, peripheral artery disease and cerebrovascular accident (CVA)/transient ischaemic attack (TIA)

The variable macrovascular disease is a combination of the variables coronary artery disease, peripheral artery disease and CVA/TIA. The definitions of the variables coronary artery disease (= 1), peripheral artery disease (= 2) and CVA/TIA (= 3) are based on hospital claims (DBC codes).

Definition of macrovascular disease		
Diagnosis code		Variable
Cardiology		
313.101	Symptomatic ischaemic heart disease	1
313.102	Instable angina, myocardial infarction	1
313.121	CVA/TIA	3
313.123	Aneurysm	2
313.124	Atherosclerosis of the extremities/peripheral artery disease	2
313.129	Aneurysm and other arterial vascular malformations	2
Surgery		
303.403	Aneurysm thoracic aorta (including rupture)	2
303.405	Aneurysm iliac aorta	2
303.406	Aneurysm abdominal aorta, rupture	2
303.409	Vascular malformations abdomen/pelvis	2
303.410	Vascular damage upper extremity	2
303.412	Peripheral arterial occlusive disease Stage 1, arm	2
303.416	Aneurysm lower extremity	2
303.418	Peripheral arterial occlusive disease Stage 2, intermittent claudication	2
303.419	Peripheral arterial occlusive disease Stage 3, rest pain	2
303.420	Peripheral arterial occlusive disease Stage 4, gangrene	2
303.427	Crural ulcer	2
303.431	Buerger's disease	2
303.432	Diabetic foot	2
303.439	Other peripheral artery disease	2
Cardiology		

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Definition of macrovascular disease		
Diagnosis code		Variable
320.2	Thoracic pain, possible angina pectoris	1
320.3	Angina pectoris, no ischaemia detected yet	1
320.4	Angina pectoris, ischaemia detected	1
320.5	Ischaemia without angina pectoris (silent ischaemia)	1
320.7	Unstable/progressive angina pectoris	1
320.9	Acute myocardial infarction (q/non-q) anterior wall	1
320.11	Acute myocardial infarction (q/non-q) elsewhere	1
320.13	Follow-up after myocardial infarction	1
320.15	Follow-up after PTCA and/or CABG	1
320.202	Angina pectoris, stable	1
320.203	Angina pectoris, unstable	1
320.204	ST elevation myocardial infarction	1
320.205	Non ST elevation myocardial infarction	1
320.801	Follow-up after acute coronary syndrome	1
320.802	Follow-up after PTCA and/or CABG and/or ablation	1
Neurology		
330.1101	Subarachnoid haemorrhage	3
330.1102	Intracerebral haemorrhage	3
330.1103	Intracranial haemorrhage (sub/epidural)	3
330.1111	Cerebral ischaemia	3
330.1112	TIA (including amaurosis fugax)	3
Physical medicine and rehabilitation		
327.0313	CVA	3
Cardiothoracic surgery		
328.2320	Coronary artery bypass graft (CABG), venous grafts and maximum 1 arterial graft	1
328.2400	CABG (≥2 arterial grafts)	1
328.2415	CABG (1 arterial graft) + mitral valve replacement	1
328.2425	CABG (1 arterial graft) + aortic valve replacement	1
328.2470	Left ventricular plasty + CABG	1
328.2550	CABG + MVR ± tricuspid valve replacement	1
328.2555	CABG (2 arterial grafts) + MVR	1
328.2560	CABG (1 arterial graft) + AVR + MVR	1
328.2570	CABG (2 arterial grafts) + AVR	1
328.2585	CABG + hypertrophic obstructive cardiomyopathy	1
328.2630	Ventricular tachycardia + CABG	1
328.2635	Maze + CABG	1
328.2640	Ventricular septal rupture + CABG	1
328.2645	MVR + AVR + CABG	1
328.2650	MVR + CABG (2 arterial grafts)	1
328.2655	AVR + CABG + hypertrophic obstructive cardiomyopathy	1
328.2665	Aortic root + CABG	1
328.2720	Aortic dissection ± CABG	1
328.2740	Aortic ascending + CABG	1
328.2770	Aortic root + CABG + MVR	1
328.2775	Aortic dissection B/conservative	2
328.2785	Maze + CABG or AVR + MVR ± TVR	1
328.2810	Thoracoabdominal aneurysm	2
328.3210	Carotid endarterectomy	2
328.3320	Acute aortic aneurysm	2
Geriatric medicine		
335.263	CVA/TIA	3

Malignancy

The definition of the variable malignancy is based on hospital claims (DBC codes).

Definition of malignancies	
Diagnosis code	
Ophthalmology	
301.358	Tumour of the orbit
Ear Nose Throat	
302.20	Vestibular schwannoma
302.21	Malignant tumour ear
302.60	Malignant oral cavity tumour Stages 1 and 2
302.61	Malignant oral cavity tumour Stages 3 and 4
302.62	Malignant oropharyngeal tumour Stages 1 and 2
302.63	Malignant oropharyngeal tumour Stages 3 and 4
302.64	Malignant hypopharyngeal tumour Stages 1 and 2
302.65	Malignant hypopharyngeal tumour Stages 3 and 4
302.66	Malignant laryngeal tumour Stages 1 and 2
302.67	Malignant laryngeal tumour Stages 3 and 4
302.68	Malignant nasopharyngeal tumour Stages 1 and 2
302.69	Malignant nasopharyngeal tumour Stages 3 and 4
302.72	Malignant tumour salivary gland
302.84	Malignant tumour throat
302.88	Malignant skin tumour head/throat
Surgery	
303.303	Malignant neoplasm thyroid
303.306	Malignant neoplasm salivary glands
303.313	Neoplasm bronchus, lung
303.314	Neoplasm mediastinum/pleura (mesothelioma)
303.315	Malignant neoplasm oesophagus
303.318	Malignant neoplasm breast
303.319	Malignant neoplasm oesophagus/gastric cardia
303.330	Malignant neoplasm stomach
303.331	Malignant neoplasm gall bladder
303.332	Malignant neoplasm pancreas/bile ducts
303.333	Malignant neoplasm colon (excluding sigmoid/rectum)
303.334	Malignant neoplasm rectosigmoid transition zone
303.335	Malignant neoplasm rectum
303.346	Malignant neoplasm stomach, excluding gastric cardia
303.347	Peritoneal carcinomatosis caused by colorectal carcinoma without metastasis
303.348	Neoplasm liver (including metastasis)
303.349	Other malignant neoplasms abdomen
303.350	Malignant melanoma of the skin
303.352	Malignant neoplasm soft tissue
303.353	Hogdkin lymphoma, non-Hodgkin lymphoma (NHL)
303.357	Germ cell tumour
303.358	Neuroblastoma
303.359	Other oncological diagnosis
303.360	Metastasis bone
303.363	Malignant neoplasm bone (excluding metastasis)
303.367	Malignant neoplasm liver (including metastasis)
303.370	Wilms tumour
Plastic surgery	
304.35	Excision tumours with axial flap reposition, or with frozen tissue section, >5 or large malignant tumours

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Definition of malignancies	
304.509	Malignant tumour, not in functional area (FA)
304.511	Malignant tumour in FA wherefore transposition or transplantation <1%
304.513	Excision tumour wherefore transposition or transplantation in FA 1–3% or non-FA >3%, 2–5 tumours
Orthopaedic surgery	
305.1110	Metastasis in bone
305.1140	Malignant neoplasm bone
305.1150	Malignant neoplasm soft tissue
Urology	
306.40	Malignant neoplasm prostate
306.45	Malignant neoplasm prostate with lymph nodes
306.48	Malignant neoplasm prostate (orchidectomy)
306.50	Penile cancer
306.92	Penile cancer with lymph nodes
Gynaecology	
307.M11	Malignant neoplasm vulva
307.M12	Malignant neoplasm vagina
307.M13	Malignant neoplasm cervix
307.M14	Malignant neoplasm endometrium
307.M15	Malignant neoplasm myometrium
307.M16	Malignant neoplasm of ovarian/fallopian tube
307.M17	Chorionic carcinoma
307.M99	Malignant neoplasm other
Neurosurgery	
308.1810	Neurosurgical part of stereotactic radiotherapy
Dermatology	
310.14	Malignant dermatosis
Internal medicine	
313.214	Malignant neoplasm thyroid
313.264	Malignant neoplasm adrenal gland
313.291	Multiple endocrine neoplasia syndrome
313.621	Malignant neoplasm, small cell carcinoma bronchus
313.622	Malignant neoplasm, large cell carcinoma bronchus
313.623	Thymoma
313.624	Malignant neoplasm pleura
313.629	Other thoracic malignancies not further specified
313.751	Hodgkin lymphoma
313.752	NHL low grade
313.753	NHL intermediate grade/high grade
313.754	Multiple myeloma/primary amyloidosis
313.755	Monoclonal gammopathy
313.756	Acute lymphoid leukaemia
313.757	Chronic lymphoid leukaemia, Waldenström's and Hairy cell leukaemia
313.761	Acute myeloid leukaemia/Refractory anaemia with excess blasts (RAEB) in transformation
313.762	RAEB
313.771	Chronic myeloid leukaemia
313.773	Chronic myelomonocytic leukaemia
313.801	Malignant neoplasm head–throat
313.802	Malignant neoplasm central nervous system (primary)
313.811	Malignant neoplasm breast

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Definition of malignancies	
313.821	Malignant neoplasm ovarium
313.822	Malignant neoplasm cervix
313.823	Malignant neoplasm endometrium
313.831	Malignant neoplasm testicle
313.832	Malignant neoplasm prostate
313.833	Malignant neoplasm urinary tract
313.834	Malignant neoplasm kidney/Grawitz
313.839	Other malignant neoplasm in urogenital tract
313.841	Malignant neoplasm bone and articular cartilage
313.842	Malignant neoplasm skin/melanoma
313.843	Malignant neoplasm soft tissue
313.899	Malignant neoplasm not further specified
313.904	Malignant neoplasm oesophagus/gastric cardia
313.914	Malignant neoplasm stomach (excluding gastric cardia)
313.927	Malignant neoplasm colorectal
313.964	Malignant neoplasm pancreas
313.979	Other malignancies digestive tract
Gastroenterology	
318.307	Oesophagus/cardia malignancy
318.407	Stomach cancer, excluding gastric cardia cancer
318.408	Lymphoma
318.610	Colorectal cancer
731.312	Malignant neoplasm liver
313.735	Cholangiocarcinoma
313.810	Oncological treatment in case of gastrointestinal malignancy
313.906	Oncology, not gastrointestinal
Pulmonology	
322.1303	Non-small-cell lung carcinoma
322.1304	Small-cell lung carcinoma
322.1305	Mesothelioma
322.1308	Metastasis of tumour elsewhere
Neurology	
330.202	Primary malignant neoplasm intracranial
330.203	Secondary neoplasm intracranial (metastasis)
330.213	Secondary neoplasm extracranial (metastasis)
330.223	Secondary spinal neoplasm (metastasis)
330.233	Secondary neoplasm extraspinal/epidural/spine (metastasis)
330.241	Leptomeningeal malignancy
330.242	Primary leptomeningeal malignancy
330.243	Secondary leptomeningeal malignancy
330.251	Paraneoplastic condition
330.299	Other neuro-oncology
Radiotherapy	
361.101	Head and neck cancer and thyroid cancer
361.102	Gastrointestinal cancer
361.103	Lung and other intrathoracic cancer
361.104	Bone and soft tissue cancer
361.105	Breast cancer
361.106	Gynaecological cancer
361.107	Urological cancer
361.108	Tumour in central nervous system
361.109	Other malignant conditions
361.110	Haematological cancer
361.111	Unknown primary tumour
361.302	Screening of late effects of cancer treatment

Hypertension

The definition of the variable hypertension is based on a combination of hospital claims (DBC codes) and pharmaceutical claims.

Definition of hypertension	
Diagnosis code	
Internal medicine	
313.311	Hypertension
Cardiology	
320.902	Hypertension
ATC code	
C02	Antihypertensives
C03	Diuretics
C04	Peripheral vasodilators
C07	Beta-blocking agents
C08	Calcium channel blockers
C09	Agents acting on the renin–angiotensin system

Hospitalization

The definition of the variable hospitalization is based on health claims for hospital care activities that are linked to hospital claims (DBC codes). We excluded hospital care activities if the admission was related to transplantation care.

Definition of hospitalization	
Hospital activity code	
190218	Nursing day
Following care product codes were excluded	
979002140	Kidney transplantation with hospital admittance
979002141	Kidney transplantation
979002142	Living-donor kidney transplantation with hospital admittance
979002143	Living-donor kidney transplantation
979002052	Transplantation of kidney and pancreas
979002053	Transplantation of kidney and pancreas with hospital admittance
979002036	Transplantation of pancreas
979002037	Transplantation of pancreas with hospital admittance
979002136	Liver transplantation with hospital admittance
979002137	Liver transplantation
979002139	Partial liver transplantation
979002159	Care for transplantation recipient with maximum of 13 nursing days
979002160	Care for transplantation recipient with 14–28 nursing days
979002161	Care for transplantation recipient with 29–56 nursing days
979002162	Care for transplantation recipient with more than 56 nursing days
979002214	Liver transplantation or transplantation of liver and kidney with hospital admittance
979002215	Liver transplantation or transplantation of liver and kidney
979002297	Pancreas transplantation
979002299	Deceased-donor kidney transplantation with more than 28 nursing days
979002300	Deceased-donor kidney transplantation with maximum of 28 nursing days
979002302	Living-donor kidney transplantation with more than 28 nursing days
979002303	Living-donor kidney transplantation with maximum of 28 nursing days
979002305	Combined organ transplantation with more than 28 nursing days
979002306	Combined organ transplantation with maximum of 28 nursing days

ICU admission

The definition of the variable ICU admissions is based on hospital declaration codes that are linked to hospital claims (DBC codes).

Definition of ICU admission	
Hospital declaration code	
039611	Extracorporeal membrane oxygenation treatment supplement
190125	ICU treatment day supplement Group 1
190126	ICU admittance supplement Group 1—registration on first day on ICU
190127	ICU ventilator supplement Group 1
190128	ICU dialysis supplement Group 1
190129	ICU consult
190130	Interhospital critical care transport (<2 h)
190131	Interhospital critical care transport (≥2 h)
190132	Medical ICU (MICU) transport (<2 h)
190133	MICU transport (≥2 h)
190134	ICU treatment day supplement Group 2
190135	ICU admittance supplement Group 2—registration on first day on ICU
190136	ICU ventilator supplement Group 2
190137	ICU dialysis supplement Group 2
190141	ICU treatment day supplement Group 3
190142	ICU admittance supplement Group 3—registration on first day on ICU
190143	ICU ventilator supplement Group 3
190144	ICU dialysis supplement Group 3
190150	Neonatal ICU
190151	Paediatric ICU
190153	ICU treatment day—light care
190154	ICU treatment day—medium care
190155	ICU treatment day—heavy care
190156	Dialysis supplement—per ICU day
190157	ICU day—Type 1
190158	ICU day—Type 1

ER visits

The definition of the variable ER visits is based on hospital declaration codes that are linked to hospital claims (DBC codes).

Definition of ER visits	
Hospital declaration code	
190015	Emergency care contact on an emergency department
190016	Emergency care contact outside the emergency department, elsewhere in the hospital

Chronic conditions based on PCGs

Since clinical data are lacking in health claims databases, we used PCGs as a proxy to determine chronic conditions. PCGs are defined by the *Zorginstituut Nederland* (National Health Care Institute) and are used as a risk adjuster in the Dutch healthcare system [18]. Within this risk adjustment system, Dutch insurance companies receive an equalization contribution from the Healthcare Insurance Fund depending on the risk profile of the insured population. This risk profile is based on, among other things, age, gender, SES and the number of chronic conditions (PCGs), as these factors have been shown to increase the healthcare costs in subsequent years [21].

PCGs are based on the assumption that chronic conditions can be reliably identified by claims for specific prescribed drugs [18, 19]. A person is assigned to a PCG if the prescribed medication for a chronic condition is more than a certain amount during a calendar year (e.g. 180 DDD, which approximates 6 months of medication use). The validity of pharmacy claims data to identify chronic conditions has been evaluated before and has been shown to provide reliable estimates of chronic disease burden when clinical data are missing [22–24].

Chronic conditions based on PCGS

A total of 37 PCGs for the risk adjustment of 2019 (based on pharmacy data of 2017) are defined in this section [25]. We excluded the PCGs for CKD and transplantation since these overlap with the main diagnosis of our study population. Appendix 1 (Tables A1– A33) provides the chronic conditions used in this study derived from the PCGs, with the ATC codes and DDDs used for the classification of PCGs.

Defined PCGs 2019	
	Description
1	Acromegaly
2	Asthma
3	Autoimmune disorders (based on add-on)
4	Cancer I (based on add-on)
5	Cancer II (based on add-on)
6	Central nervous system disorders: multiple sclerosis
7	Central nervous system disorders: other
8	Chronic anticoagulant use
9	Chronic pain excluding opioids
10	COPD/heavy asthma
11	COPD/heavy asthma (based on add-on)
12	Crohn's disease/ulcerative colitis
13	Cystic fibrosis/pancreas enzymes
14	Depression
15	DM Type Ia, with hypertension
16	DM Type Ib, without hypertension
17	DM Type IIa, with hypertension
18	DM Type IIb, without hypertension
19	Epilepsy
20	Extreme high costs Cluster 1 (based on pharmacy claims and add-on)
21	Extreme high costs Cluster 2 (based on add-on)
22	Extreme high costs Cluster 3 (based on add-on)
23	Glaucoma
24	Growth disorders (based on add-on)
25	Heart diseases
26	HIV/AIDS
27	Hormone sensitive tumours
28	Immunoglobulin therapy (based on add-on)
29	Neuropathic pain
30	Parkinson's disease
31	Psoriasis
32	Psychosis and addiction (excluding nicotin)
33	Pulmonary (arterial) hypertension
34	Renal disorders
35	Rheumatoid arthritis
36	Thyroid disorders
37	Transplantation

Appendix Table A1. DDDs for acromegaly

ATC code	Oral
H01AX01	10 mg
H01CB02	0.7 mg
H01CB03	3 mg
H01CB05	1.2 mg

Table A2. DDDs for asthma

ATC code	Inhalation (aerosol)	Inhalation (powder)	Inhalation (solution)	Oral	Parenteral	Rectal
R03AC02	0.8 mg	0.8 mg	10 mg	–	–	–
R03AC03	2 mg	2 mg	20 mg	–	–	–
R03AC12	0.1 mg	0.1 mg	–	–	–	–
R03AC13	24 μg	24 μg	–	–	–	–
R03AK06	4 doses	2 doses	–	–	–	–
R03AK07	–	2–4 doses	–	–	–	–
R03AK08	4 doses	–	–	–	–	–
R03AK010		1 dose	–	–	–	–
R03AK011	2–4 doses		–	–	–	–
R03AK012		2 doses	–	–	–	–
R03BA01	0.8 mg	0.8 mg	1.5 mg	–	–	–
R03BA02	0.8 mg	0.8 mg	1.5 mg	–	–	–
R03BA05	0.6 mg	0.6 mg	1.5 mg	–	–	–
R03BA08	0.16 mg	–	–	–	–	–
R03BC01	40 mg	80 mg	80 mg	–	–	–
R03BC03	8 mg	–	–	–	–	–
R03CC02	–	–	–	12 mg	12	
R03DC03	–	–	–	10 mg	–	–

Restriction: only if there is no ATC code for chronic obstructive pulmonary disease (COPD)/heavy asthma or COPD/heavy asthma (based on add-on).

Table A3. DDDs for autoimmune diseases (based on add-on)

ATC code	Parental	Oral	Subcutaneous
L04AA24	27 mg	–	–
L04AA26	25 mg	–	–
L04AA29	–	10 mg	–
L04AA32	–	60 mg	–
L04AA33	5.4 mg	–	–
L04AA37	–	4 mg	–
L04AB01	7 mg	–	–
L04AB02	3.75 mg	–	–
L04AB04	2.9 mg	–	–
L04AB05	14 mg	–	–
L04AB06	1.66 mg	–	–
L04AC03	100 mg	–	–
L04AC05	540 μg	–	–
L04AC07	20 mg	–	–
L04AC08	2.7 mg	–	–
L04AC10	10 mg	–	–
L04AC11	37 mg	–	–
L04AC12	–	–	15 mg
L04AC13	2.9 mg	–	–
L04AC14	–	–	14.3 mg

Based on additional reimbursements or add-ons: expensive or orphan drugs.

Table A4. ATC codes for cancer I (based on add-on)

ATC code	Name
L01AA01	Cyclofosfamide
L01AA02	Chloorambucil
L01AA03	Melfalan
L01AA09	Bendamustine
L01AB01	Busulfan
L01AC01	Thiotepa
L01AD02	Lomustine
L01AX03	Temozolomide

(continued)

Table A4. (continued)

ATC code	Name
L01BA04	Pemetrexed
L01BB03	Tioguanine
L01BB05	Fludarabine
L01BB06	Clofarabine
L01BB07	Nelarabine
L01BC01	Cytarabine
L01BC03	Tegafur
L01BC05	Gemcitabine
L01BC06	Capecitabine
L01BC07	Azacitidine
L01BC08	Decitabine
L01BC53	Tegafur and Gimeracil and Oteracil
L01BC59	Trifluridine and Tipiracil
L01CA01	Vinblastine
L01CA02	Vincristine
L01CA04	Vinorelbine
L01CB01	Etoposide
L01CB02	Teniposide
L01CD01	Paclitaxel
L01CD02	Docetaxel
L01CD04	Cabazitaxel
L01CX01	Trabectedine
L01DB01	Doxorubicine
L01DB03	Epirubicine
L01DB06	Idarubicine
L01DB07	Mitoxantron
L01DB11	Pixantron
L01DC01	Bleomycine
L01DC03	Mitomycine
L01XA01	Cisplatine
L01XA03	Oxaliplatine
L01XB01	Procarbazine
L01XC	Avelumab
L01XC	dinutuximab Beta
L01XC02	Rituximab
L01XC03	Trastuzumab
L01XC06	Cetuximab
L01XC07	Bevacizumab

(continued)

Table A4. (continued)

ATC code	Name
L01XC08	Panitumumab
L01XC10	Ofatumumab
L01XC11	Ipilimumab
L01XC12	Brentuximab Vedotine
L01XC13	Pertuzumab
L01XC14	Trastuzumab-Emtansine
L01XC15	Obinutuzumab
L01XC17	Nivolumab
L01XC18	Pembrolizumab
L01XC19	Blinatumomab
L01XC21	Ramucirumab
L01XC22	Necitumumab
L01XC23	Elotuzumab
L01XC24	Daratumumab
L01XC26	Inotuzumab Ozogamicine
L01XC27	Olaratumab
L01XC32	Azetolizumab
L01XD05	Temoporfine
L01XE01	Imatinib
L01XE02	Gefitinib
L01XE03	Erlotinib
L01XE04	Sunitinib
L01XE05	Sorafenib
L01XE06	Dasatinib
L01XE07	Lapatinib
L01XE08	Nilotinib
L01XE09	Temsirolimus
L01XE10	Everolimus
L01XE11	Pazopanib
L01XE12	Vandetanib
L01XE13	Afatinib
L01XE14	Bosutinib
L01XE15	Vemurafenib
L01XE16	Crizotinib
L01XE17	Axitinib
L01XE18	Ruxolitinib
L01XE21	Regorafenib
L01XE23	Dabrafenib
L01XE24	Ponatinib
L01XE25	Trametinib
L01XE26	Cabozantinib
L01XE27	Ibrutinib
L01XE28	Ceritinib
L01XE29	Lenvatinib
L01XE31	Nintedanib
L01XE33	Palbociclib
L01XE35	Osimertinib
L01XE38	Cobimetinib
L01XE39	Midostaurine
L01XE42	Ribociclib
L01XX01	Amsacrine
L01XX02	Asparaginase
L01XX05	Hydroxycarbamide
L01XX11	Estramustine
L01XX14	Tretinone
L01XX17	Topotecan
L01XX19	Irinotecan
L01XX23	Mitotaan
L01XX24	Pegasparagase
L01XX25	Bexaroteen
L01XX27	Arseentrioxide
L01XX32	Bortezomib

(continued)

Table A4. (continued)

ATC code	Name
L01XX35	Anagrelide
L01XX41	Eribuline
L01XX42	Panobinostat
L01XX43	Vismodegib
L01XX44	Aflibercept
L01XX45	Carfilzomib
L01XX46	Olaparib
L01XX47	Idelalisib
L01XX50	Ixazomib
L01XX51	Talimogeen Laherparepvec
L01XX52	Venetoclax
L02BB04	Enzalutamide
L02BX03	Abirateron
L03AX16	Plerixafor
L04AX02	Thalidomide
L04AX04	Lenalidomide
L04AX06	Pomalidomide
V10XX02	Ibritumomab-Tiuxetan
V10XX03	Radium-223 Dichloride

Based on additional reimbursements or add-ons: expensive or orphan drugs. DDD not applicable; instead, the number of health claims are counted.

Table A5. ATC codes for cancer II (based on add-on)

ATC code	Name
L01AX04	Dacarbazine
L01BB02	Mercaptopurine
L01BB03	Tioguanine
L01BC02	Fluorouracil
L03AC01	Aldesleukine
V10XX04	lutetium Oxotreotide

Based on additional reimbursements or add-ons: expensive or orphan drugs. DDD not applicable; instead, the number of health claims are counted. Restriction: only if there is no ATC code for cancer I.

Table A6. DDDs for central nervous system disorders: multiple sclerosis

ATC code	Oral	Parenteral
L03AB07	–	4.3 mg
L03AB08	–	4 milIU
L03AB13	–	8.9 μg
L03AX13	–	20 μg
L04AA27	0.5 mg	–
L04AA31	14 mg	–
N07XX09	480 mg	–

milIU, million international units.

Table A7. DDDs for central nervous system disorders: other

ATC code	Oral	Parenteral
A07AA11	600 mg	–
M03BX01	50 mg	0.55 mg
M03BX02	12 mg	–
N07XX02	0.1 g	–

Restriction: only if there is no ATC code for central nervous system disorders: multiple sclerosis

Table A8. DDDs for chronic anticoagulant use

ATC-code	Oral
B01AA04	3 mg
B01AA07	5 mg
B01AE07	0.3 g
B01AF01	20 mg
B01AF02	10 mg
B01AF03	60 mg

Restriction: only if there is no ATC code for chronic obstructive pulmonary disease (COPD)/heavy asthma, COPD/heavy asthma (based on add-on), heart diseases and pulmonary (arterial) hypertension.

Table A9. DDDs for chronic pain excluding opioids

ATC-code	Oral	Rectal	Parenteral	Transdermal
M01AA01	300 mg	–	–	–
M01AB01	100 mg	100 mg	100 mg	–
M01AB05	100 mg	100 mg	100 mg	–
M01AB16	200 mg	–	–	–
M01AB55	100 mg	–	–	–
M01AC01	20 mg	20 mg	20 mg	–
M01AC06	15 mg	15 mg	15 mg	–
M01AE01	1.2 g	1.2 g	1.2 g	–
M01AE02	500 mg	500 mg	–	–
M01AE03	150 mg	150 mg	150 mg	–
M01AE11	600 mg	600 mg	–	–
M01AE17	75 mg	–	75 mg	–
M01AE52	500 mg	–	–	–
M01AH01	200 mg	–	–	–
M01AH05	60 mg	–	–	–
M01AX01	1 g	–	–	–
N01BX04	–	–	–	4 g
N06AA09	75 mg	–	75 mg	
N06AX21	60 mg	–	–	–

Restriction: only if there is no ATC code for neuropathic pain.

Table A10. DDDs for chronic obstructive pulmonary disease (COPD)/heavy asthma

ATC code	Oral	Inhalation (aerosol)	Inhalation (powder)	Inhalation (solution)	Parental	Rectal
R03AC18	–	–	150 μg	–	–	–
R03AC19	–	–	–	5 μg	–	–
R03AL01	–	6 doses	3 doses	–	–	–
R03AL02	–	6 doses	–	7.5 mL	–	–
R03AL03	–	–	1 dose	–	–	–
R03AL04	–	–	1 dose	–	–	–
R03AL05	–	–	2 doses	–	–	–
R03AL06	–	–	–	2 doses	–	–
R03AL09	–	4 doses	–	–	–	–
R03BB01	–	0.12 mg	0.12 mg	0.3 mg	–	–
R03BB04	–	–	10 μg	5 μg	–	–
R03BB05	–	–	664 μg	–	–	–
R03BB06	–	–	44 μg	–	–	–
R03BB07	–	–	55 μg	–	–	–
R03DA04	0.4 g	–	–	0.4 g	0.4 g	

Restriction: only if there is no ATC code for COPD/heavy asthma (based on add-on).

Table A11. DDDs for chronic obstructive pulmonary disease (COPD)/heavy asthma (based on add-on)

ATC code	Parental
R03DX05	16 mg
R03DX08	7.5 mg
R03DX09	3.6 mg

Based on additional reimbursements or add-ons: expensive or orphan drugs.

Table A12. DDDs for Crohn's disease/ulcerative colitis

ATC code	Oral	Rectal
A07EA04	–	100 mL
A07EA06	9 mg	1 tablet
A07EC02	1.5 g	1.5 g
A07EC03	1 g	–

Restriction: only if there is no ATC code for autoimmune diseases.

Table A13. DDDs for cystic fibrosis/pancreas enzymes

ATC code	Inhalation (powder)	Inhalation (solution)	Oral
A09AA02	–	–	4–6 tablets/capsules
J01GB01	112 mg	0.3 g	–
J01XB01	3 milIU	–	–
R05CB13	–	2.5 mg	–
R07AX30	–	–	4 tablets

milIU: million international units.

Table A14. DDDs for depression

ATC code	Oral	Parenteral
N06AA02	0.1 g	0.1 g
N06AA04	0.1 g	0.1 g
N06AA10	75 mg	30 mg
N06AA12	0.1 g	0.1 g
N06AA16	0.15 g	–
N06AA21	0.1 g	0.1 g
N06AB03	20 mg	–
N06AB04	20 mg	20 mg
N06AB05	20 mg	–
N06AB06	50 mg	–
N06AB08	0.1 g	–
N06AB10	10 mg	–
N06AF03	60 mg	–
N06AF04	10 mg	–
N06AG02	0.3 g	–
N06AX03	60 mg	–
N06AX05	0.3 g	–
N06AX11	30 mg	–
N06AX12	0.3 G[a]	–
N06AX16	0.1 g	–
N06AX22	25 mg	–
N06AX26	10 mg	–

Restriction: only if there is no ATC code for psychoses and addiction.
[a]Drugs used to quit smoking excluded.

Table A15. DDDs for DM Type I, DM Type Ia (>90 DDDs hypertension) or DM Type Ib (≤90 DDDs hypertension)

ATC code	Parenteral
A10AB01	40 IU
A10AB04	40 IU
A10AB05	40 IU
A10AB06	40 IU
A10AC01	40 IU
A10AD01	40 IU
A10AD04	40 IU
A10AD05	40 IU
A10AD06	40 IU
A10AE04	40 IU
A10AE05	40 IU
A10AE06	40 IU
A10AE54	40 IU
A10AE56	40 IU

Table A16. DDDs for DM Type II, DM Type IIa (>90 DDDs hypertension) or DM Type IIb (≤90 DDDs hypertension)

ATC code	Oral	Parenteral	Parenteral depot
A10BA02	2 g	–	–
A10BB01	10 mg	–	–
A10BB03	1.5 g	–	–

(continued)

Table A16. (continued)

ATC code	Oral	Parenteral	Parenteral depot	
A10BB09	60 mg	–	–	
A10BB12	2 mg	–	–	
A10BD02	2 tablets	–	–	
A10BD05	2 tablets	–	–	
A10BD07	2 tablets	–	–	
A10BD08	2 tablets	–	–	
A10BD10	2 tablets	–	–	
A10BD11	2 tablets	–	–	
A10BD15	2 tablets	–	–	
A10BD16	2 tablets	–	–	
A10BD20	2 tablets	–	–	
A10BF01	0.3 g	–	–	
A10BG03	30 mg	–	–	
A10BH01	0.1 g	–	–	
A10BH02	0.1 g	–	–	
A10BH03	5 mg	–	–	
A10BH05	5mg	–	–	
A10BJ01	–	15 μg	286 μg	
A10BJ02	–	1.2 mg	–	
A10BJ03	–	20 μg	–	
A10BJ05	–	0.16 mg	–	
A10BK01	10 mg	–	–	
A10BK02	200 mg	–	–	
A10BK03	17.5 mg	–	–	
A10BX02	4 mg	–	–	–

Restriction: Only if there is no ATC code for DM Type I (Ia or Ib).

Table A17. DDDs for epilepsy

ATC-code	Oral	Parenteral	Rectal
N03AA02	0.1 g	0.1 g	–
N03AA03	1.25 g	–	–
N03AB02	0.3 g	0.3 g	
N03AD01	1.25 g	–	–
N03AE01	8 mg	8 mg	–
N03AF01	1 g	–	1 g
N03AF02	1 g	–	–
N03AF03	1.4 g	–	–
N03AG01	1.5 g	1.5 g	1.5 g
N03AG04	2 g	–	–
N03AX03	0.4 g	–	–
N03AX09	0.3 g	–	–
N03AX10	2.4 g	–	–
N03AX11	0.3 g	–	–
N03AX14	1.5 g	1.5 g	–
N03AX15	0.2 g	–	–
N03AX17	1 g	–	–
N03AX18	0.3 g	0.3 g	–
N03AX21	0.9 g	–	–
NO3AX22	8 mg	–	–
NO3AX23	100 mg	100 mg	–
N05BA09	20mg	–	–

Table A18. ATC codes for extremely high costs, Cluster 1 (based on pharmacy claims and add-on)

ATC code	Name
A16AA05	Cargluminezuur
A16AB02	Imiglucerase
A16AB03	Agalsidase Alfa
A16AB04	Agalsidase Beta
A16AB10	Velaglucerase Alfa
A16AX06	Miglustat
B01AC09	Epoprostenol
B01AC21	Treprostinil
N07XX08	Tafamidis

Based on additional reimbursements or add-ons: expensive or orphan drugs. DDD not applicable; instead, the number of health claims are counted.

Table A19. ATC codes for extreme high costs, Cluster 2 (based on add-on)

ATC code	Name
A16AB05	Laronidase
L04AA25	Eculizumab

Based on additional reimbursements or add-ons: expensive or orphan drugs. DDD not applicable; instead, the number of health claims are counted.

Table A20. ATC codes for extreme high costs, Cluster 2 (based on add-on)

ATC code	Name
A16AB07	Alglucosidase Alfa
A16AB08	Galsulfase
A16AB09	Idursulfase

Based on additional reimbursements or add-ons: expensive or orphan drugs. DDD not applicable; instead, the number of health claims are counted.

Table A21. DDDs for glaucoma

ATC-code	Oral	Parenteral	Ocular
S01EA03	–	–	0.3 mL
S01EA05	–	–	0.2 mL
S01EB01	–	–	0.4/40 mL/mg
S01EC01	0.75 g	0.75 g	–
S01EC03	–	–	0.3 mL
S01EC04	–	–	0.2 mL
S01EC54	–	–	0.2 mL
S01ED01	–	–	0.2 mL
S01ED02	–	–	0.2 mL
S01ED03	–	–	0.2 mL
S01ED05	–	–	0.2 mL
S01ED51	–	–	0.1/0.2 mL
S01ED54	–	–	0.3 mL
S01EE01	–	–	0.1 mL
S01EE03	–	–	0.1 mL
S01EE04	–	–	0.1 mL
S01EE05	–	–	0.3mL

Table A22. ATC codes and DDDs for growth disorders (based on add-on)

ATC-code	Parenteral
H01AC01	2 IU
H01AC03	2 mg

Based on additional reimbursements or add-ons: expensive or orphan drugs.

Table A23. DDDs for heart diseases

ATC-code	Oral	Oral (aerosol)	Parenteral	Sublingual	Transdermal
C01AA05	0.25 mg	–	0.25 mg	–	–
C01BA01	1.2 g	–	–	–	–
C01BA03	0.4 mg	–	0.4 mg	–	–
C01BB01	–	–	3 g	–	–
C01BC03	0.3 g	–	0.3 g	–	–
C01BC04	0.2 g	–	0.2 g	–	–
C01BD01	0.2 g	–	0.2 g	–	–
C01CE02	–	–	50 mg	–	–
C01CE03	–	–	1 g	–	–
C01DA02	5 mg	2.5 mg	10 mg	2.5 mg	5 mg
C01DA08	60 mg	20 mg	10 mg	20 mg	0.1 g
C01DA14	40 mg	–	–	–	–
C01DX16	40 mg	–	–	–	–
C01EB17	10mg	–	–	–	–
C03CA01	40 mg	–	40 mg	–	–
C03CA02	1 mg	–	1 mg	–	–
C09DX04	2 tablets	–		–	–

Table A24. ATC codes and DDDs for HIV/AIDS

ATC-code	Oral	Parenteral
J05AE01	1.8 g	–
J05AE02	2.4 g	–
J05AE03	1.2 g	–
J05AE07	1.4 g	–
J05AE08	0.3 g	–
J05AE09	1 g	–
J05AE10	1.2 g	–
J05AF01	0.6 g	0.6 g
J05AF02	0.4 g	–
J05AF04	80 mg	–
J05AF05	0.3 g	–
J05AF06	0.6 g	–
J05AF07	0.245 g	–
J05AF09	0.2 g	–
J05AG01	0.4 g	–
J05AG03	0.6 g	–
J05AG04	0.4 g	–
J05AG05	25 mg	–
J05AR01	2 tablets	–
J05AR02	1 tablet	–
J05AR03	1 tablet	–
J05AR04	2 tablets	–
J05AR06	1 tablet	–
J05AR08	1 tablet	–
J05AR09	1 tablet	–
J05AR10	0.8 g	–
J05AR13	1 tablet	–

(continued)

Table A24. (continued)

ATC-code	Oral	Parenteral
J05AR14	1 tablet	–
J05AR17	1 tablet	–
J05AR18	1 tablet	–
J05AR19	1 tablet	–
J05AX07	0.18 g	
J05AX08	0.8 g	–
J05AX09	0.6 g	–
J05AX12	50 mg	–
V03AX03	150 mg	–

Table A25. DDDs for hormone-sensitive tumours

ATC-code	Oral	Parenteral	Parenteral depot	Implantation	Nasal
L02AB01	0.16 g		–	–	–
L02AB02	1 g	1 g	–	–	–
L02AE01	–	1.5 mg	–	0.11 mg	1.2 mg
L02AE02	–	1mg	0.134 mg	60 μg	–
L02AE03	–	–	–	0.129 mg	–
L02AE05	–	–	–	0.137 mg	–
L02BA01	20 mg	–	–	–	–
L02BA03	–	8.3 mg	–	–	–
L02BB01	0.75 g	–	–	–	–
L02BB02	0.3 g	–	–	–	–
L02BB03	50 mg	–	–	–	–
L02BG03	1 mg	–	–	–	–
L02BG04	2.5 mg	–	–	–	–
L02BG06	25 mg	–	–	–	–
L02BX01	–	3.6 mg	–	–	–
L02BX02	–	2.7 mg	–	–	–

Restriction: only if there is no ATC code for cancer I or cancer II.

Table A26. ATC codes for immunoglobulin therapy (based on add-on)

ATC code	Name
J06BA02	Immunoglobuline i.v.

Based on additional reimbursements or add-ons: expensive or orphan drugs. DDD not applicable; instead, the number of health claims are counted.

Table A27. DDDs for neuropathic pain

ATC-code	Oral
N03AX12	1.8 g
N03AX16	0.3 g

Table A28. DDDs for Parkinson's disease

ATC-code	Oral	Parenteral	Transdermal
N04BA02	0.6 g	–	–
N04BA03	0.45 g	–	–
N04BB01	0.2 g	–	–
N04BC01	40 mg	–	–
N04BC02	3 mg	–	–
N04BC04	6 mg	–	–
N04BC05	2.5 mg	–	–
N04BC07	–	20 mg	
N04BC09	–	–	6 mg
N04BD01	5 mg	–	–
N04BD02	1 mg	–	–
N04BD03	75 mg	–	–
N04BX01	0.45 g	–	–
N04BX02	1 g	–	–

Table A29. ATC codes and DDDs for psoriasis

ATC-code	Oral	Transdermal
D05AC01	–	1 g or mg or mL
D05AX02	–	1 g or mg or mL
D05AX03	–	1 g or mg or mL
D05AX52	–	1 g or mg or mL
D05BA02	10 mg	–
D05BB02	35 mg	–
D05BX	120 mg	–
D05BX51	120 mg	–

Restriction: only if there is no ATC code for autoimmune disorders.

Table A30. DDDs for psychosis and addiction (excluding nicotin)

ATC-code	Oral	Parenteral	Parenteral depot	Rectal	Sublingual
N05AA01	0.3 g	0.1 g		0.3 g	–
N05AB02	10 mg	–	1 mg		–
N05AB03	30 mg	10 mg	7 mg	16 mg	–
N05AC01	50 mg	20 mg	–	–	–
N05AD01	8 mg	8 mg	3.3 mg	–	–
N05AD05	0.2 g	–	–	–	–
N05AD06	10 mg	10 mg	3.3 mg	–	–
N05AE03	16 mg	–	–	–	–
N05AE05	60 mg	–	–	–	–
N05AF01	6 mg	4 mg	–	–	–
N05AF03	0.3 g	50 mg	–	–	–
N05AF05	30 mg	30 mg	15 mg	–	–
N05AG01	–	–	0.7 mg	–	–
N05AG02	4 mg	–	–	–	–
N05AG03	6 mg	–	–	–	–
N05AH02	0.3 g	0.3 g	–	–	–
N05AH03	10 mg	10 mg	10 mg	–	–
N05AH04	0.4 g	–	–	–	–
N05AL01	0.8 g	0.8 g	–	–	–
N05AX08	5 mg	–	2.7 mg	–	–
N05AX12	15 mg	15 mg	13.3 mg	–	–
N05AX13	6 mg	–	2.5 mg	–	–
N07BB01	0.2 g	–	–	–	–
N07BB03	2 g	–	–	–	–

(continued)

Table A30. (continued)

ATC-code	Oral	Parenteral	Parenteral depot	Rectal	Sublingual
N07BB04	50 mg	–	–	–	–
N07BB05	18 mg	–	–	–	–
N07BC01	–	–	–	–	8 mg
N07BC02	25 mg	25 mg	–	–	–
N07BC51	–	–	–	–	8mg

Table A31. DDDs for pulmonary (arterial) hypertension

ATC-code	Oral	Parenteral	Inhalation
B01AC11	–	50 μg	150 μg
B01AC27	1.8 mg	–	–
C02KX01	250 mg	–	–
C02KX02	7.5 mg	–	–
C02KX04	10 mg	–	–
C02KX05	4.5 mg	–	–
G04BE03	50 mg	–	–
G04BE08	10 mg	–	–

Table A32. DDDs for rheumatoid arthritis

ATC-code	Oral	Parenteral	Rectal
A07EC01	2 g		2 g
L01BA01	–	3.571 mg	–
L04AA13	20 mg		–
L04AX03	2.5 mg	3.571 mg	–
M01CB01	–	2.4 mg	–
M01CC01	0.5 g	–	–
P01BA02	0.516 g	–	–

Restriction: Only if there is no ATC code for auto-immune disorders.

Table A33. DDDs for thyroid disorders

ATC-code	Oral	Parenteral
H03AA01	0.15 mg	0.15mg
H03AA02	60 μg	60 μg
H03BA02	0.1 g	–
H03BB01	15 mg	–
H03BB02	10 mg	–

APPENDIX 2: SENSITIVITY ANALYSIS

Sensitivity analysis was performed in which the prevalence of PP was examined in case all deceased patients in 2017 were included.

		CKD		Dialysis		Kidney transplantation	
		Main analysis ($n = 14\,905$)	Sensitivity analysis ($n = 17\,198$)	Main analysis ($n = 3872$)	Sensitivity analysis ($n = 17\,198$)	Main analysis ($n = 8796$)	Sensitivity analysis ($n = 9087$)
All medication use, %							
PP	≥5 drugs	87.4	85.2	93.4	89.8	94.8	94.4
EPP	≥10 drugs	56.7	55.8	69.3	66.2	60.0	60.4
HPP	≥15 drugs	22.8	23.1	31.5	29.9	21.5	22.2
Chronic medication use							
PP	≥5 drugs	66.1	60.8	70.0	60.9	75.0	73.8
EPP	≥10 drugs	13.3	12.0	15.1	12.7	14.9	14.7
HPP	≥15 drugs	0.85	0.74	1.2	1.0	1.0	1.0

APPENDIX 3

Table A1. Percentage of most commonly prescribed dispensed medication classes of CKD stage G4/G5 not on KRT, dialysis and kidney transplant patients and matched controls; medication classes defined for all medication use

	All medication use					
	CKD		Dialysis		Kidney transplantation	
Medication classes	Patients, % ($n = 14\,905$)	Matched controls, % ($n = 29\,810$)	Patients, % ($n = 3872$)	Matched controls, % ($n = 7744$)	Patients, % ($n = 8796$)	Matched controls, % ($n = 17\,592$)
Cardiovascular drugs	–	–	–	–	–	–
ACE inhibitors	30.0	13.0	16.8	11.9	31.5	6.1
ARB	31.4	10.7	16.7	8.9	20.8	5.1
Beta-blockers	56.6	19.1	61.3	16.6	56.4	8.1
Calcium channel blockers	44.1	10.8	35.9	9.8	47.9	4.9
Diuretics	51.0	14.2	45.7	11.8	26.1	5.
Statins	61.3	22.7	48.2	21.4	63.5	12.0
PPIs	56.9	22.8	71.0	19.8	58.2	10.1
Vitamin D analogues	73.3	15.1	76.2	11.9	65.3	5.7
Antithrombotic agents	64.5	25.3	70.5	21.5	39.5	9.6
Platelet aggregation inhibitors	41.7	16.4	49.6	14.7	26.2	6.8
Vitamin K antagonist	24.2	6.7	26.9	5.0	12.3	1.5
Heparin	3.0	1.2	4.4	1.1	4.1	0.7
DOAC/NOAC	2.1	2.9	0.08	2.4	2.5	1.1
Antidiabetics	31.8	8.8	27.5	8.0	27.4	4.5
Insulin	19.9	2.6	22.0	2.6	15.2	1.3
Metformin	6.4	7.2	0.31	6.6	15.0	3.8
Sulphonureumderivate	13.2	3.6	6.8	3.1	8.8	1.8
SGLT2 inhibitors	0.09	0.05	–	0.09	0.13	0.06
DPP-4 inhibitors	2.9	0.34	1.8	0.27	1.1	0.15
GLP-1 analogues	0.28	0.06	0.10	0.14	0.14	0.11
Antibiotics	39.4	19.0	51.9	16.8	54.3	12.5
Cinacalcet	2.2	0.04	23.5	0.03	8.2	0.01
Osteoporosis prophylaxis						
Bisfosfonates	2.0	2.6	0.28	1.9	8.5	0.81
Calcium derivates	15.3	6.4	22.4	4.8	26.6	2.1
Urate-lowering therapy	25.4	1.9	17.2	1.6	14.6	0.88
Phosphate binders	12.1	0.02	78.5	0.05	3.0	0.02
Haematopoietic						
Iron[a]	14.2	1.6	4.6	1.2	7.1	0.54
EPO[a]	18.8	0.13	4.7	0.12	5.4	0.01
Opioids	8.6	3.2	13.2	2.8	6.7	1.5

[a]Intravenous iron and EPO therapy were not included in this study.

SGLT2: sodium–glucose-cotransporter 2; DPP-4: dipeptidylpeptidase-4; GLP-1: glucagon-like peptide-1; EPO: erythropoietin.

Table A2. Percentage of most commonly prescribed dispensed medication classes of CKD stage G4/G5 not on KRT, dialysis and kidney transplant patients and matched controls; medication classes defined for chronic use (complement to Table 5 in main article)

	Chronic medication use					
	CKD		Dialysis		Kidney transplantation	
Medication classes	Patients (%) ($n = 14,905$)	Matched controls (%) ($n = 29,810$)	Patients (%) ($n = 3,872$)	Matched controls (%) ($n = 7,744$)	Patients (%) ($n = 8,796$)	Matched controls (%) ($n = 17,592$)
Antidiabetics						
SGLT2 inhibitors	0.05	0.02	–	0.06	0.08	0.02
DPP-4 inhibitors	2.1	0.28	1.2	0.19	0.76	0.09
GLP-1 analogues	0.19	0.04	0.08	0.12	0.07	0.11
Antibiotics	0.40	0.17	0.80	0.19	1.4	0.10
Cinacalcet	0.98	0.02	12.7	–	4.5	–
Osteoporosis prophylaxis						
Bisfosfonates	1.4	2.1	0.08	1.5	6.2	0.65
Calcium derivates	10.7	4.8	15.2	3.6	18.2	1.5
Urate-lowering therapy	7.7	0.81	2.9	0.77	5.5	0.35
Phosphate binders	1.6	–	44.6	–	0.28	–
Hematopoietics						
Iron[a]	3.4	0.35	1.0	0.36	1.2	0.05
EPO	8.1	0.08	0.85	0.08	2.26	–
Opioids	1.7	0.58	2.0	0.52	1.2	0.34

[a]Intravenous iron and EPO therapy were not included in this study.

DOAC/NOAC: direct oral anticoagulant/novel oral anticoagulant; SGLT2: sodium-glucose-cotransporter 2; DPP-4: dipeptidylpeptidase-4; GLP-1: glucagon-like peptide-1; EPO: erythropoietin.