Original Article

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

Manon J. M. van Oosten¹, Susan J. J. Logtenberg², Marc H. Hemmelder³,⁴, Martijn J. H. Leegte⁵, Henk J. G. Bilo⁶,⁷,⁸, Kitty J. Jager¹ and Vianda S. Stel¹

¹Department of Medical Informatics, Amsterdam UMC, University of Amsterdam, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands, ²Department of Internal Medicine, Diakonessenhuis, Utrecht, The Netherlands, ³Division of Nephrology, Department of Internal Medicine, Maastricht University Medical Center, The Netherlands, ⁴Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, The Netherlands, ⁵Dutch Renal Registry, Nefrovisie Foundation, Utrecht, The Netherlands, ⁶Diabetes Research Center and Department of Epidemiology and Statistics, Isala Hospital, Zwolle, The Netherlands, ⁷Department of Internal Medicine, University Medical Center, Groningen, The Netherlands and ⁸Faculty of Medicine, Groningen University, Groningen, The Netherlands

Correspondence to: Manon J. M. van Oosten; E-mail: m.j.m.vanoosten@amsterdamumc.nl

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. 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)].

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.

Received: 17.2.2021; Editorial decision: 20.4.2021

© The Author(s) 2021. Published by Oxford University Press on behalf of ERA-EDTA.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
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. >20years) 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 m²] 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, 3,872 dialysis and 8,796 transplant patients, with mean ages of 75.6, 70.8 and 56.5 years, respectively (Table 1).
Table 1. Baseline characteristics of CKD Stage G4/G5 without KRT, dialysis and kidney transplant patients and matched controls

| Characteristics                                      | CKD Patients (n = 14,905) | Matched controls (n = 29,810) | P-value | CKD Patients (n = 3,872) | Matched controls (n = 7,744) | P-value | CKD Patients (n = 8,796) | 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                           | <0.0001 | 13.2                     | 63.3                           | <0.0001 | 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                       | 0.7                            | <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.
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).
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
Table 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
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 EPP.

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 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.

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.
| Subgroups | 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 |
| 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 | 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 | 6.70 | 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 | 4.4 | 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 | 0.06 | 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 | 16.3 | 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 |
| Macrovacular 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 | 27.5 | 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 |
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 = 3,872) and kidney transplant patients (n = 8,796) versus matched controls (respectively n = 29,810, n = 7,744 and n = 17,592)

| Subgroups                  | CKD Patients | Matched controls | Ratio | Dialysis Patients | Matched controls | Ratio | Kidney transplantation Patients | Matched controls | Ratio |
|----------------------------|--------------|------------------|-------|-------------------|------------------|-------|---------------------------------|------------------|-------|
| PP overall, %              | 66.1         | 17.8             | 3.7   | 13.3              | 1.5              | 9.0   | 70.0                            | 15.8             | 4.4   |
| Age (years), %             |              |                  |       |                   |                  |       |                                 |                  |       |
| 20–44                      | 28.1         | 0.7              | 38.5  | 3.3               | –                | –     | 50.9                            | 0.9              | 58.7  |
| 45–64                      | 56.5         | 5.3              | 10.6  | 11.8              | 0.58             | 20.5  | 68.6                            | 5.8              | 11.8  |
| 65–74                      | 69.4         | 12.6             | 5.5   | 15.9              | 1.1              | 14.1  | 73.5                            | 12.8             | 5.7   |
| ≥75                        | 67.7         | 23.0             | 2.9   | 12.9              | 1.8              | 7.0   | 70.6                            | 23.6             | 3.0   |
| Sex, %                     |              |                  |       |                   |                  |       |                                 |                  |       |
| Male, %                    | 67.5         | 18.5             | 3.6   | 13.8              | 1.2              | 10.5  | 68.5                            | 15.0             | 4.6   |
| Female, %                  | 64.4         | 17.1             | 3.8   | 12.9              | 1.2              | 10.5  | 68.8                            | 15.0             | 4.6   |
| SES, %                     |              |                  |       |                   |                  |       |                                 |                  |       |
| Q1                         | 68.3         | 19.7             | 3.5   | 14.8              | 1.9              | 7.6   | 69.4                            | 17.3             | 4.0   |
| Q2                         | 66.8         | 17.9             | 3.7   | 13.8              | 1.5              | 8.9   | 71.2                            | 15.8             | 4.5   |
| Q3                         | 64.7         | 17.3             | 3.7   | 12.8              | 1.1              | 11.3  | 70.2                            | 14.8             | 4.8   |
| Q4                         | 63.6         | 15.9             | 4.0   | 11.5              | 1.2              | 9.7   | 69.4                            | 14.5             | 4.8   |
| No. of chronic conditions, %|              |                  |       |                   |                  |       |                                 |                  |       |
| 0                          | 5.3          | 0.6              | 9.2   | 0.12              | 0.01             | 11.1  | 18.9                            | 0.4              | 44.1  |
| 1                          | 46.3         | 20.8             | 2.2   | 0.91              | 0.12             | 7.9   | 53.5                            | 20.3             | 2.6   |
| ≥2                         | 84.5         | 66.2             | 1.3   | 20.7              | 7.2              | 2.9   | 87.2                            | 67.0             | 1.3   |
| DM, %                      | 86.2         | 61.8             | 1.4   | 25.6              | 8.3              | 3.1   | 84.3                            | 63.5             | 1.3   |
| Macrovascular disease, %    | 84.3         | 61.1             | 1.4   | 23.0              | 7.4              | 3.1   | 79.7                            | 60.2             | 1.3   |
| Coronary artery disease, %  | 87.8         | 51.5             | 1.7   | 25.8              | 6.3              | 4.1   | 88.1                            | 49.7             | 1.8   |
| Peripheral artery disease, %| 83.6         | 52.3             | 1.6   | 22.9              | 7.6              | 3.0   | 74.6                            | 50.0             | 1.5   |
| CVA/TIA, %                 | 78.7         | 44.8             | 1.8   | 18.3              | 4.2              | 4.3   | 74.6                            | 40.7             | 1.8   |
| Malignancy, %              | 71.8         | 35.0             | 2.1   | 15.2              | 3.7              | 4.1   | 73.2                            | 33.7             | 2.2   |
| Hypertension, %            | 73.2         | 45.9             | 1.6   | 15.1              | 4.0              | 3.8   | 77.6                            | 45.5             | 1.7   |
| Hospitalization, %         | 76.7         | 45.4             | 1.7   | 20.0              | 5.5              | 3.6   | 72.1                            | 43.2             | 1.7   |
| ICU admittance, %          | 77.3         | 52.8             | 1.5   | 16.4              | 8.2              | 2.0   | 69.6                            | 54.0             | 1.3   |
| ER visit, %                | 77.4         | 44.5             | 1.7   | 20.1              | 5.1              | 3.9   | 71.2                            | 42.1             | 1.7   |
Table 4. Unadjusted and adjusted analysis of variables associated with PP (defined as ≥10 medications for chronic medication use)1 in CKD Stage G4/G5 without KRT patients, dialysis patients and kidney transplant patients, using logistic regression

| Variables                        | CKD | Dialysis | Kidney transplantation |
|----------------------------------|-----|----------|------------------------|
|                                  | Unadjusted | Age-, sex-, SES-adjusted model | Fully adjusted model |
|                                  | Unadjusted | Age-, sex-, SES-adjusted model | Fully adjusted model |
|                                  | 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                            |     |          |                        |
|                                  |     |          |                        |
| 65–74                            |     |          |                        |
|                                  |     |          |                        |
| ≥75                              |     |          |                        |
|                                  |     |          |                        |
| Age (continuous, per 10 years)   |     |          |                        |
|                                  |     |          |                        |
| Sex                              |     |          |                        |
| Female                           | 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 |
| Male                             |     |          |                        |
|                                  |     |          |                        |
| 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                               |     |          |                        |
|                                  |     |          |                        |
| 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 1.72–2.51 | 3.67 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 1.35–1.88 | 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 |

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.

For this variable, no confounders could be identified considering the criteria for confounding (NA: not applicable).

Model adjusted for age, sex, SES and DM.

Model adjusted for age, sex, SES, DM, vascular disease and ER visits.

Model adjusted for age, sex, SES, DM, vascular disease, hospitalization and ER visits.

Model adjusted for age, sex, SES, DM and vascular disease.
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.

FUNDING

This work is financed by a grant from the Dutch Kidney Foundation.

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).

REFERENCES

1. Fincke BG, Snyder K, Cantillon C et al. Three complementary definitions of polypharmacy: methods, application and
comparison of findings in a large prescription database. *Pharmacopsiemiol Drug Saf* 2005; 14: 121–128

2. Payne RA. The epidemiology of polypharmacy. *Clin Med (Lond)* 2016; 16: 465–469

3. Morin L, Johnell K, Laroche ML et al. The epidemiology of polypharmacy in older adults: register-based prospective cohort study. *Clin Epidemiol* 2018; 10: 289–298

4. Fano V. Estimating the prevalence and the determinants of polypharmacy using data from a health administrative database: a comparison of results obtained employing different algorithms. *Adv Pharmacopsiemiol Drug Saf* 2014; 3: 151

5. Mason NA, Bakus JL. Strategies for reducing polypharmacy and other medication-related problems in chronic kidney disease. *Semin Dial* 2010; 23: 55–61

6. Schmidt IM, Hübner S, Nadal J et al. Patterns of medication use and the burden of polypharmacy in patients with chronic kidney disease: the German Chronic Kidney Disease study. *Clin Kidney J* 2019; 12: 663–672

7. Laville SM, Metzger M, Stengel B et al. Evaluation of the adequacy of drug prescriptions in patients with chronic kidney disease: results from the CKD-REIN cohort. *Br J Clin Pharmacol* 2018; 84: 2811–2823

8. Fraser SDS, Roderick PJ, May CR et al. The burden of comorbidity in people with chronic kidney disease stage 3: a cohort study. *BMC Nephrol* 2015; 16: 193

9. Mason NA. Polypharmacy and medication-related complications in the chronic kidney disease patient. *Curr Opin Nephrol Hypertens* 2011; 20: 492–497

10. Battistella M, Jandoc R, Ng JY et al. A province-wide, cross-sectional study of demographics and medication use of patients in hemodialysis units across Ontario. *Can J Kidney Health Dis* 2018; 5: 2004358118760832

11. Park HY, Ryu HN, Shim MK et al. Prescribed drugs and polypharmacy in healthcare service users in South Korea: an analysis based on National Health Insurance Claims data. *Int J Clin Pharmacol Ther* 2016; 54: 369–377

12. Leelakanok N, Holcombe AL, Lund BC et al. Association between polypharmacy and death: a systematic review and meta-analysis. *J Am Pharm Assoc* 2017; 57: 729–738.e10

13. Parker K, Nikam M, Jayanti A, Mitra S. Medication burden in CKD-5D: impact of dialysis modality and setting. *Clin Kidney J* 2014; 7: 557–561

14. St Peter WL. Management of polypharmacy in dialysis patients. *Semin Dial* 2015; 28: 427–432

15. Hayward S, Hole B, Denholm R et al. International prescribing patterns and polypharmacy in older people with advanced chronic kidney disease: results from the European Quality study. *Nephrol Dial Transplant* 2020; 36: 503–511

16. Alshamrani M, Almalki A, Qureshi M et al. Polypharmacy and medication-related problems in hemodialysis patients: a call for deprescribing. *Pharmacy (Basel)* 2018; 6: 76

17. Wozniak I, Kolonko A, Chudek J et al. Influence of polypharmacy on the quality of life in stable kidney transplant recipients. *Transplant Proc* 2018; 50: 1896–1899

18. Vektis. Vektis - Inzichten op maat. www.vektis.nl (3 March 2020, date last accessed)

19. de Boo A. Vektis - information center for health care services. TSG 2011; 89: 358–359

20. Westerdijk M, Zuurbier J, Ludwig M, Prins S. Defining care products to finance health care in the Netherlands. *Eur J Health Econ* 2012; 13: 203–221

21. World Health Organization. *Defined Daily Dose. Definition and General Considerations*. Geneva: World Health Organization. 2021. [https://www.who.int/tools/atc-ddd-toolkit/about-ddd](https://www.who.int/tools/atc-ddd-toolkit/about-ddd)

22. Lamers LM. Pharmacy costs groups: a risk-adjuster for capitation payments based on the use of prescribed drugs. *Med Care* 1999; 37: 824–830

23. Lamers LM, van Vliet RJ. The Pharmacy-based Cost Group model: validating and adjusting the classification of medications for chronic conditions to the Dutch situation. *Health Policy* 2004; 68: 113–121

24. Greenland S, Thomas DC. On the need for the rare disease assumption in case-control studies. *Am J Epidemiol* 1982; 116: 547–553

25. Jager KJ, Zoccali C, Macleod A et al. Con founding: what it is and how to deal with it. *Kidney Int* 2008; 73: 256–260

26. Mohnen SM, van Oosten MJM, Los J et al. Healthcare costs of patients on different renal replacement modalities – analysis of Dutch health insurance claims data. *PloS One* 2019; 14: e0220800

27. van Oosten MJM, Brohet RM, Logtenberg SJ et al. The validity of Dutch health claims data for identifying patients with chronic kidney disease: a hospital-based study in the Netherlands. *Clin Kidney J* 2021; 14: 1586–1593

28. Chiu YW, Teitelbaum I, Misra M et al. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. *Clin J Am Soc Nephrol* 2009; 4: 1089–1096

29. Manley HJ, Cannella CA, Baille GR et al. Medication-related problems in ambulatory hemodialysis patients: a pooled analysis. *Am J Kidney Dis* 2005; 46: 669–680

30. Hardinger KL, Hutcherson T, Preston D et al. Influence of pill burden and drug cost on renal function after transplantation. *Pharmacotherapy* 2012; 32: 427–432

31. Adhikari UR, Taraphder A, Hazra A et al. Pill burden does not influence compliance with oral medication in recipients of renal transplant. *Indian J Pharmacol* 2016; 48: 21–25

32. Low JK, Crawford K, Manias E et al. Quantifying the medication burden of kidney transplant recipients in the first year post-transplantation. *Int J Clin Pharm* 2018; 40: 1242–1249

33. Bril F, Castro V, Centurion IG et al. A systematic approach to assess the burden of drug interactions in adult kidney transplant patients. *Curr Drug Saf* 2016; 11: 156–163

34. Cadogan CA, Ryan C, Hughes CM. Appropriate polypharmacy and medicine safety: when many is not too many. *Drug Saf* 2016; 39: 109–116

35. Schuler J, Dückelmann C, Beindl W et al. Polypharmacy and inappropriate prescribing in elderly internal medicine patients in Austria. *Wien Klin Wochenschr* 2008; 120: 733–741

36. Manley HJ, Garvin CG, Drayer DK et al. Medication prescribing patterns in ambulatory haemodialysis patients: comparisons of USRDS to a large not-for-profit dialysis provider. *Nephrol Dial Transplant* 2004; 19: 1842–1848

37. Parker K, Wong J. Is polypharmacy an increasing burden in chronic kidney disease? The German experience. *Clin Kidney J* 2019; 12: 659–662

38. Fried TR, O’Leary J, Towle V et al. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. *J Am Geriatr Soc* 2014; 62: 2261–2272

39. Payne RA, Abel GA, Avery AJ et al. Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. *Br J Clin Pharmacol* 2014; 77: 1073–1082
40. NHG-Richtlijnen. Chronische nierschade. https://richtlijnen.nhg.org/standaarden/chronische-nierschade

41. Wanner C, Krane V, März W et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005; 353: 238–248

42. Baigent C, Landray MJ, Reith C et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011; 377: 2181–2192

43. Fellström BC, Jardine AG, Schmieder RE et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009; 360: 1395–1407

44. Wanner C, Tonelli M, Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. KDIGO clinical practice guideline for lipid management in CKD: summary of recommendation statements and clinical approach to the patient. Kidney Int 2014; 85: 1303–1309

45. Desbuissons G, Mercadal L. Use of proton pump inhibitors in dialysis patients: a double-edged sword. J Nephrol 2021; 34: 661–672

46. McIntyre C, McQuillan R, Bell C et al. Targeted deprescribing in an outpatient hemodialysis unit: a quality improvement study to decrease polyparmacy. Am J Kidney Dis 2017; 70: 611–618

47. Triantafylidis LK, Hawley CE, Perry LP et al. The role of deprescribing in older adults with chronic kidney disease. Drugs Aging 2018; 35: 973–984

48. MacRae CE, Mercer S, Guthrie B. Potentially inappropriate prescribing in people with chronic kidney disease: cross-sectional analysis of a large population cohort. Br J Gen Pract 2020; 71: e483–e490

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

(continued)
(continued)

### 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

| Diagnosis code | Variable |
|----------------|----------|
| 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

| Diagnosis code | Variable |
|----------------|----------|
| 327.0313       | CVA | 3 |

### Cardiothoracic surgery

| Diagnosis code | Variable |
|----------------|----------|
| 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

| Diagnosis code | Variable |
|----------------|----------|
| 335.263        | CVA/TIA | 3 |

### Malignancy

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

**Definition of malignancies**

| Diagnosis code | Description |
|----------------|-------------|
| 301.358        | Tumour of the orbit |
| 301.368        | Vestibular schwannoma |
| 301.369        | Malignant tumour ear |
| 301.370        | Malignant oral cavity tumour Stages 1 and 2 |
| 301.371        | Malignant oral cavity tumour Stages 3 and 4 |
| 301.372        | Malignant oropharyngeal tumour Stages 1 and 2 |
| 301.373        | Malignant oropharyngeal tumour Stages 3 and 4 |
| 301.374        | Malignant laryngeal tumour Stages 1 and 2 |
| 301.375        | Malignant laryngeal tumour Stages 3 and 4 |
| 301.376        | Malignant nasopharyngeal tumour Stages 1 and 2 |
| 301.377        | Malignant nasopharyngeal tumour Stages 3 and 4 |
| 301.378        | Malignant tumour salivary gland |
| 301.379        | Malignant tumour throat |
| 301.380        | Malignant skin tumour head/throat |
| 301.381        | Cancer of the skin surface head/throat |
| 301.382        | Malignant neoplasm larynx/gastric cardia |
| 301.383        | Malignant neoplasm oesophagus/gastric cardia |
| 301.384        | Malignant neoplasm stomach |
| 301.385        | Malignant neoplasm gall bladder |
| 301.386        | Malignant neoplasm pancreas/bile ducts |
| 301.387        | Malignant neoplasm colon (excluding sigmoid/rectum) |
| 301.388        | Malignant neoplasm rectosigmoid transition zone |
| 301.389        | Malignant neoplasm rectum |
| 301.390        | Malignant neoplasm stomach, excluding gastric cardia |
| 301.391        | Peritoneal carcinomatosis caused by colorectal carcinoma without metastasis |
| 301.392        | Neoplasm liver (including metastasis) |
| 301.393        | Other malignant neoplasms abdomen |
| 301.394        | Malignant melanoma of the skin |
| 301.395        | Malignant neoplasm soft tissue |
| 301.396        | Hodgkin lymphoma, non-Hodgkin lymphoma (NHL) |
| 301.397        | Germ cell tumour |
| 301.398        | Neuroblastoma |
| 301.399        | Other oncological diagnosis |
| 301.400        | Metastasis bone |
| 301.401        | Malignant neoplasm bone (excluding metastasis) |
| 301.402        | Malignant neoplasm liver (including metastasis) |
| 301.403        | Wilms tumour |

**Plastic surgery**

| Diagnosis code | Description |
|----------------|-------------|
| 304.35         | Excision tumours with axial flap reposition, or with frozen tissue section, >5 or large malignant tumours |

(continued)
| Code     | Condition                                                                 |
|----------|---------------------------------------------------------------------------|
| 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 |
| 304.515 | Orthopaedic surgery                                                        |
| 305.1110| Metastasis in bone                                                         |
| 305.1140| Malignant neoplasm bone                                                   |
| 305.1150| Malignant neoplasm soft tissue                                             |
| 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                                             |
| 307.11  | Malignant neoplasm vulva                                                   |
| 307.12  | Malignant neoplasm vagina                                                  |
| 307.14  | Malignant neoplasm cervix                                                  |
| 307.15  | Malignant neoplasm endometrium                                            |
| 307.16  | Malignant neoplasm of ovarian/fallopian tube                              |
| 307.17  | Chorionic carcinoma                                                        |
| 307.99  | Malignant neoplasm other                                                   |
| 308.1810| Neurosurgical part of stereotactic radiotherapy                           |
| 310.14  | Malignant dermatosis                                                       |
| 312.14  | Malignant neoplasm thyroid                                                 |
| 312.264 | Malignant neoplasm adrenal gland                                           |
| 312.291 | 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 gammapathosis                                                   |
| 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                                                  |
| 313.821 | Malignant neoplasm ovariurn                                                |
| 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                                         |
| 313.906 | Oncology, not gastrointestinal malignancy                                  |
| 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                                                   |
| 731.735 | Cholangiocarcinoma                                                         |
| 313.810 | Oncological treatment in case of gastrointestinal malignancy              |
| 313.906 | Oncology, not gastrointestinal malignancy                                  |
| 322.1303| Non-small-cell lung carcinoma                                              |
| 322.1304| Small-cell lung carcinoma                                                  |
| 322.1305| Mesothelioma                                                              |
| 322.1308| Metastasis of tumour elsewhere                                             |
| 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                                                       |
| 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

### 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

(continued)
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 | Description                                      |
|---------------------------|--------------------------------------------------|
| 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.

#### Appendix Table A1. DDDs for acromegaly

| ATC code | Oral |
|----------|------|
| H01AX01  | 10 mg|
| H01CB02  | 0.7 mg|
| H01CB03  | 3 mg |
| H01CB05  | 1.2 mg|
| 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               | –                   | –                     | –    | –          | –      |
| R03AK09  | –                     | –                   | –                     | –    | –          | –      |
| R03AK10  | –                     | 1 dose              | –                     | –    | –          | –      |
| R03AK11  | 2-4 doses             | –                   | –                     | –    | –          | –      |
| R03AK12  | –                     | 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 1 (based on add-on)

| ATC code | Name               |
|----------|--------------------|
| L01AA01  | Cyclofosfamide     |
| L01AA02  | Chloomambucil      |
| L01AA03  | Melafan            |
| 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  | Neralabine         |
| L01BC01  | Cytarabine         |
| L01BC03  | Tegafur            |
| L01BC05  | Gemicitabine       |
| L01BC06  | Capecitabine       |
| L01BC07  | Azacitidine        |
| L01BC08  | Decitabine         |
| L01BC09  | Trifluridine and Tipiracil |
| L01CA01  | Vinblastine        |
| L01CA02  | Vincristine        |
| L01CA04  | Vinorelbine        |
| L01CB01  | Etoposide          |
| L01CB02  | Teniposide         |
| L01CD01  | Paclitaxel         |
| L01CD02  | Docetaxel          |
| L01CD04  | Cisplatin          |
| L01CD05  | Mitoxantrone       |
| L01CB07  | Mitoxantrone       |
| L01CD11  | Cisplatin          |
| L01CD01  | Bleomycine         |
| L01CD03  | Mitomycin          |
| L01XA01  | Cisplatin          |
| L01XA03  | Oxaliplatin        |
| L01XBO1  | Procarbazine       |
| L01XC    | Avelumab           |
| L01XC    | dinutuximab Beta   |
| L01XC02  | Rituximab          |
| L01XC03  | Trastuzumab        |
| L01XC06  | Cetuximab          |
| L01XC07  | Bevacizumab        |

(continued)
| ATC code | Name                        | ATC code | Name                        |
|----------|-----------------------------|----------|-----------------------------|
| L01XC08  | Panitumumab                 | L01XX35 | Anagrelide                  |
| L01XC10  | Ofatumumab                  | L01XX41 | Erlubine                    |
| L01XC11  | Iplimumab                   | L01XX42 | Panobinostat                |
| L01XC12  | Brentuximab Vedotin         | L01XX43 | Vismodegib                  |
| L01XC13  | Pertuzumab                  | L01XX44 | Affibercept                 |
| L01XC14  | Trastuzumab-Emtansine       | L01XX45 | Carboplatin                 |
| L01XC15  | Obinutuzumab                | L01XX46 | Olparib                     |
| L01XC17  | Nivolumab                   | L01XX47 | Idelalisib                  |
| L01XC18  | Pembrolizumab               | L01XX50 | Ixazomib                    |
| L01XC19  | Blinatumomab                | L01XX51 | Talimogene Laherparepvec    |
| L01XC21  | Ramucirumab                 | L01XX52 | Venetoclax                  |
| L01XC22  | Necitumumab                 | L02BB04 | Enzalutamide                |
| L01XC23  | Elotuzumab                  | L02BX03 | Abirateron                  |
| L01XC24  | Daratumumab                 | L03AX16 | Plerixafor                   |
| L01XC26  | Inotuzumab Oxogamicine      | L04AX02 | Thalidomide                 |
| L01XC27  | Olaratumab                  | L04AX04 | Lenalidomide                |
| L01XC32  | Azetilizumab                | L04AX06 | Pomalidomide                |
| L01XE01  | Imatinib                    | V10XX02 | Ibritumomab-Tiuxetan        |
| L01XE02  | Gefitinib                   | V10XX03 | Radium-223 Dichloride       |
| 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  | Dalrafenib                  |          |                             |
| 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  | Hydroxyurea Carboxamide     |          |                             |
| L01XX11  | Estramustine                |          |                             |
| L01XX14  | Tretinone                   |          |                             |
| L01XX17  | Topotecan                   |          |                             |
| L01XX19  | Irinotecan                  |          |                             |
| L01XX23  | Mitotane                    |          |                             |
| L01XX24  | Pegasparagase               |          |                             |
| L01XX25  | Bexarotene                  |          |                             |
| L01XX27  | Arseentrioxide              |          |                             |
| L01XX32  | Bortezomib                  |          |                             |

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

| ATC code | Name                        |
|----------|-----------------------------|
| L01AX04  | Dacarbazine                 |
| L01BB02  | Mercaptopurine              |
| L01BB03  | Tioguanine                  |
| L01BC02  | Fluouracil                  |
| 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.

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 | –         |

millIU, 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      | \_          |
| M01AD01   | 1.2 g    | 1.2 g  | 1.2 g      | \_          |
| M01AD02   | 500 mg   | 500 mg | \_         | \_          |
| M01AD03   | 150 mg   | 150 mg | 150 mg     | \_          |
| M01AE11   | 600 mg   | 600 mg | \_         | \_          |
| M01AE17   | 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) | Parenteral | Rectal |
|----------|------|----------------------|---------------------|-----------------------|------------|--------|
| R03AC18  | –    | 150 μg               | –                   | –                     | \_         | \_     |
| R03AC19  | –    | \_                   | 5 μg                | –                     | \_         | \_     |
| R03AL01  | 6 doses | 3 doses               | –                   | –                     | \_         | \_     |
| R03AL02  | 6 doses | \_                   | 7.5 mL              | –                     | \_         | \_     |
| R03AL03  | \_   | \_                   | \_                  | \_                    | \_         | \_     |
| R03AL04  | \_   | 1 dose               | –                   | –                     | \_         | \_     |
| R03AL05  | \_   | \_                   | \_                  | \_                    | \_         | \_     |
| R03AL06  | \_   | \_                   | \_                  | \_                    | \_         | \_     |
| R03AL09  | 4 doses | \_                   | \_                  | \_                    | \_         | \_     |
| R03BB01  | 0.12 mg | 0.12 mg               | 0.3 mg              | –                     | \_         | \_     |
| R03BB04  | \_   | 10 μg                | 5 μg                | \_                    | \_         | \_     |
| R03BB05  | \_   | \_                   | \_                  | \_                    | \_         | \_     |
| R03BB06  | \_   | \_                   | \_                  | \_                    | \_         | \_     |
| R03BB07  | \_   | \_                   | \_                  | \_                    | \_         | \_     |
| 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 | Parenteral | Parenteral |
|----------|------------|------------|
| 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 millU             | \_                   | \_   |
| R05CB13  | \_                  | 2.5 mg               | \_   |
| R07AX30  | \_                  | \_                   | 4 tablets |

millU: million international units.
Table A14. DDDs for depression

| ATC code  | Oral   | Parenteral | 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 | –          | –          |
| N06AB03   | 20 mg  | –          | –          |
| N06AB04   | 20 mg  | 20 mg      | –          |
| N06AB05   | 20 mg  | –          | –          |
| N06AB06   | 50 mg  | –          | –          |
| N06AB08   | 0.1 g  | –          | –          |
| N06AB10   | 10 mg  | –          | –          |
| N06AB03   | 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.

^aDrugs 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 | Parenteral | Parenteral | 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. (continued)

| ATC code  | Oral   | Parenteral | 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   | 5 mg    | –          | –          | –                |
| 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 (la or lb).

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  | –          | –      |
| N03AX22   | 8 mg   | –          | –      |
| N03AX23   | 100 mg | 100 mg     | –      |
| N05BA09   | 20 mg  | –          | –      |

(continued)
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 |
| S01EE01  | –    | –          | 0.3 mL |
| S01EE03  | –    | –          | 0.1 mL |
| S01EE04  | –    | –          | 0.1 mL |
| S01EE05  | –    | –          | 0.3 mL |

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 (aerosol) | Parenteral | Sublingual | Transdermal |
|----------|----------------|------------|------------|-------------|
| C01AA05  | 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        | –          | –           |
| C01DA08  | 5 mg           | 2.5 mg     | 10 mg      | 2.5 mg      | 5 mg       |
| C01DA14  | 40 mg          | –          | –          | –           |
| C01DX16  | 40 mg          | –          | –          | –           |
| C01EB17  | 10 mg          | –          | –          | –           |
| 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 | Implantation | Nasal |
|----------|------|------------|--------------|-------|
| L02AB01  | 0.16 g | – | – | – |
| L02AB02  | 1 g | 1 g | – | – |
| L02AE01  | – | 1.5 mg | 0.11 mg | 1.2 mg |
| L02AE02  | – | 1 mg | 0.134 mg | 0.129 mg |
| L02AE03  | – | – | – | 0.137 mg |
| L02AE05  | – | – | – | – |
| L02BA01  | 20 mg | – | – | – |
| L02BA02  | – | 8.3 mg | – | – |
| L02BB01  | 0.75 g | – | – | – |
| L02BB02  | 0.3 g | – | – | – |
| L02BG01  | 50 mg | – | – | – |
| L02BG02  | 1 mg | – | – | – |
| L02BG03  | – | 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 | 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)
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.

### Table A30. (continued)

| ATC-code | Oral | Parenteral depot | Rectal | Sublingual |
|----------|------|------------------|--------|------------|
| N07BB04  | 50 mg | -                | -      | -          |
| N07BB05  | 18 mg | -                | -      | -          |
| N07BC01  | -    | -                | -      | 8 mg       |
| N07BC02  | 25 mg | 25 mg            | -      | -          |
| N07BCS1  | -    | -                | -      | 8 mg       |

### Table A31. DDDs for pulmonary (arterial) hypertension

| ATC-code | Oral | Parenteral | Inhalation |
|----------|------|------------|------------|
| B01AC11  | -    | 50 µg      | 150 µg     |
| B01AC27  | 1.8 mg | -          |            |
| C02XX01  | 250 mg | -          |            |
| C02XX02  | 7.5 mg | -          |            |
| C02XX04  | 10 mg | -          |            |
| C02XX05  | 4.5 mg | -          |            |
| G04BE03  | 50 mg | -          |            |
| G04BE08  | 10 mg | -          |            |

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

### 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| -       | -      |

### Table A33. DDDs for thyroid disorders

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

### Polypharmacy and medication use in patients with CKD

| | CKD | Dialysis | Kidney transplantation |
|-----------------|-----------------|-----------------|-----------------|
| | Main analysis (n = 14 905) | Sensitivity analysis (n = 17 198) | Main analysis (n = 3 872) | Sensitivity analysis (n = 17 198) | Main analysis (n = 8 796) | Sensitivity analysis (n = 9 087) |
| 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 |
### 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

| Medication classes                  | All medication use | CKD Patients, % (n = 14 905) | Matched controls, % (n = 29 810) | Dialysis Patients, % (n = 3872) | Matched controls, % (n = 7744) | Kidney transplantation 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                            | 5.0                               |                                   |
| 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                               |                                   |
| Sulphonyluremderivate              | 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           |                    |                               |                                   |                                 |                                 |                                    |                                   |
| Bisphosphonates                    | 2.0                | 2.6                           | 0.28                             | 1.9                             | 8.5                             | 0.81                              |                                   |
| Calcium derivatives                | 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*                              | 14.2               | 1.6                           | 4.6                              | 1.2                             | 7.1                             | 0.54                              |                                   |
| EPO*                               | 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                               |                                   |

*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)

| Medication classes          | Chronic medication use | CKD Patients (%) | Matched controls (%) | Dialysis Patients (%) | Matched controls (%) | Kidney transplantation Patients (%) | Matched controls (%) |
|-----------------------------|------------------------|------------------|----------------------|-----------------------|----------------------|-------------------------------------|----------------------|
|                             |                        | 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                 | 0.08                                | 0.02                 |
| DPP-4 inhibitors            | 2.1                    | 0.28             | 1.2                  | 0.19                  | 0.76                 | 0.76                                | 0.09                 |
| GLP-1 analogues             | 0.19                   | 0.04             | 0.08                 | 0.12                  | 0.07                 | 0.07                                | 0.11                 |
| Antibiotics                 | 0.40                   | 0.17             | 0.80                 | 0.19                  | 1.4                  | 1.4                                 | 0.10                 |
| Cinacalcet                  | 0.98                   | 0.02             | 12.7                 | –                     | 4.5                  | –                                   |                      |
| Osteoporosis prophylaxis    |                        |                  |                      |                        |                      |                                     |                      |
| Bisphosphonates             | 1.4                    | 2.1              | 0.08                 | 1.5                   | 6.2                  | 6.2                                 | 0.65                 |
| Calcium derivates           | 10.7                   | 4.8              | 15.2                 | 3.6                   | 18.2                 | 18.2                                | 1.5                  |
| Urate-lowering therapy      | 7.7                    | 0.81             | 2.9                  | 0.77                  | 5.5                  | 5.5                                 | 0.35                 |
| Phosphate binders           | 1.6                    | –                | 44.6                 | –                     | 0.28                 | –                                   |                      |
| Hematopoietics              |                        |                  |                      |                        |                      |                                     |                      |
| Irona                       | 3.4                    | 0.35             | 1.0                  | 0.36                  | 1.2                  | 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                  | 1.2                                 | 0.34                 |

aIntravenous 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.