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ORIGINAL ARTICLE

International prescribing patterns and polypharmacy in older people with advanced chronic kidney disease: results from the European Quality study

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ABSTRACT

Background. People with chronic kidney disease (CKD) are at high risk of polypharmacy. However, no previous study has investigated international prescribing patterns in this group. This article aims to examine prescribing and polypharmacy patterns among older people with advanced CKD across the countries involved in the European Quality (EQUAL) study.

Methods. The EQUAL study is an international prospective cohort study of patients ≥65 years of age with advanced CKD. Baseline demographic, clinical and medication data were analysed and reported descriptively. Polypharmacy was defined as ≥5 medications and hyperpolypharmacy as ≥10. Univariable and multivariable linear regressions were used to determine associations between country and the number of prescribed

medications. Univariable and multivariable logistic regression were used to determine associations between country and hyperpolypharmacy.

Results. Of the 1317 participants from five European countries, 91% were experiencing polypharmacy and 43% were experiencing hyperpolypharmacy. Cardiovascular medications were the most prescribed medications (mean 3.5 per person). There were international differences in prescribing, with significantly greater hyperpolypharmacy in Germany {odds ratio (OR) 2.75 [95% confidence interval (CI) 1.73–4.37]; $P < 0.001$, reference group UK}, the Netherlands [OR 1.91 (95% CI 1.32–2.76); $P = 0.001$] and Italy [OR 1.57 (95% CI 1.15–2.15); $P = 0.004$]. People in Poland experienced the least hyperpolypharmacy [OR 0.39 (95% CI 0.17–0.87); $P = 0.021$].

Conclusions. Hyperpolypharmacy is common among older people with advanced CKD, with significant international differences in the number of medications prescribed. Practice variation may represent a lack of consensus regarding appropriate prescribing for this high-risk group for whom pharmacological treatment has great potential for harm as well as benefit.

Keywords: chronic kidney disease, pharmacoepidemiology, polypharmacy, prescribing, treatment burden

ADDITIONAL CONTENT

An author video to accompany this article is available at: https://academic.oup.com/ndt/pages/author_videos.

INTRODUCTION

Polypharmacy rates are rising, particularly among older people [1]. Drivers of polypharmacy in the general population include multimorbidity, increased use of preventative medications and guidelines that focus on single diseases [2–5]. Negative consequences of polypharmacy include drug–drug interactions, adverse drug reactions, poor adherence and increased treatment burden, as well as greater medication costs [6–10].

Polypharmacy and inappropriate prescribing are common in people with all stages of chronic kidney disease (CKD), including those receiving renal replacement therapy (RRT) [11–16]. For people with advanced CKD, two key factors that influence prescribing are the high levels of comorbidity and the development and treatment of CKD-related complications, for example, renal anaemia and renal bone disease [11, 17]. Furthermore, patients with advanced CKD are particularly vulnerable to adverse drug events due to altered pharmacodynamics and pharmacokinetics.

Although polypharmacy in people with CKD has been demonstrated in a variety of countries and settings, no previous study has made international comparisons in prescribing [18–21]. International differences in healthcare systems, health beliefs, disease prevalence and clinical guidelines are some of the factors that may influence national prescribing patterns. A better understanding of international prescribing approaches could inspire transnational learning and inform further work to identify individual, local and national factors to encourage appropriate prescribing.

The aim of this article is to examine prescribing patterns and the prevalence of polypharmacy in older people with advanced CKD across the countries taking part in the European Quality (EQUAL) study.

MATERIALS AND METHODS

The EQUAL study is an international prospective cohort study that aims to determine the optimum timing of dialysis initiation for older people with advanced CKD. Eligible participants were recruited from nephrology clinics in six European countries (Germany, Italy, The Netherlands, Poland, the UK and Sweden). Inclusion criteria were age ≥65 years and an incident estimated glomerular filtration rate (eGFR) ≤20 mL/min/1.73 m^2 in the last 6 months, as estimated by the Modification of Diet in Renal Disease equation [22]. Participants were excluded if the decrease in eGFR was the result of an acute event or if they had received RRT prior to study recruitment [23]. Approval was obtained from the medical ethical committees or institutional review boards for all participating centres. Written informed consent was obtained for all eligible participants. The baseline data from the first study visit for people who were recruited from 1 March 2012 to 31 December 2017 were used in this study.

Data collection

Participants from Germany, Italy, The Netherlands, Poland and the UK were included in this analysis. Participants from Sweden were excluded, as their medication data were captured using registry linkage and thus data were only available for a limited list of medications. The remaining countries collected demographic, clinical and medication data using a case report form administered in person by a research nurse and corroborated against their medical notes. A list of the participant's current prescribed medications was recorded; 'over-the-counter' medication use and medication adherence were not captured. A weighted comorbidity score was calculated using the Charlson Comorbidity Index (CCI) [24]. Primary renal diagnosis was standardized using European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) codes [25]. In order to compare the education systems and qualifications in the included countries, the EQUAL investigators created standardized education categories.

Number of medications, medication categories and polypharmacy

The number of medications was computed as a simple count of unique preparations recorded at the first study visit. Medications were assigned to their corresponding Anatomical Therapeutic Chemical (ATC) classification codes [26]. Medication categories were created based on the first level of the ATC codes (e.g. 'cardiovascular system'). If a medication category was deemed low use, it was amalgamated into an 'other' category.

There is no universally accepted definition of polypharmacy. In the analysis, categories of polypharmacy (≥5 medications) and hyperpolypharmacy (≥10 medications) were defined. These are the most commonly used numerical definitions in the

literature [27]. Combination medications (e.g., co-amilofruse or combination inhalers) were counted as one medication rather than their separate components.

Prescribing quality indicators

A validated list of prescribing quality indicators (PQIs) that are specific to patients with CKD were used to assess prescribing quality [28, 29]. The original list of 16 PQIs was shortened to an operational list of 10 PQIs that were appropriate for our study cohort and the available data (see Supplementary data, Appendix 1 for PQI selection details). The authors of the original PQI list have previously adapted and shortened the list in a similar manner before applying it to data [29].

Statistical analyses

Descriptive statistics were used to summarize baseline demographic characteristics of study participants according to their country of residence. PQIs and specific medications were compared across countries using chi-squared and Fisher's exact tests. Univariable and multivariable linear regressions were used to determine the association between country of residence and number of prescribed medications. Univariable and multivariable logistic regressions were used to determine the association between country of residence and hyperpolypharmacy. The multivariable linear regression and multivariable logistic regression analyses adjusted for variables that were identified as confounders [30]: age, educational attainment, ethnicity, sex, eGFR, primary renal diagnosis and comorbidities. Both the multivariable analyses used robust standard errors to account for potential intragroup correlations within individual countries. All analyses were performed using Stata version 14.2 (StataCorp, College Station, TX, USA).

RESULTS

Characteristics of the study cohort

From a potential 1344 EQUAL participants, 27 lacked medication data and were excluded. The majority of the excluded patients were from The Netherlands and Germany [$n = 12$ (5.2%) and $n = 9$ (6.0%), respectively]. Of the 1317 remaining, 846 (64.2%) were male and the mean age was 76.5 years [standard deviation (SD) 6.7]. The majority were white [$n = 1262$ (95.8%)]. With regard to educational attainment, only a minority of patients had university degrees [$n = 98$ (7.4%)]. The median eGFR at the first study visit was 18.0 mL/min/1.73 m^2 [interquartile range (IQR) 16.0–19.0]. Multimorbidity was common; all participants had at least one comorbidity in addition to CKD ($n = 1293$, 24 patients had missing comorbidity data). The most frequent comorbidities were hypertension, diabetes mellitus and coronary artery disease (84.4, 42.4 and 27.3% of people, respectively). The mean body mass index was 28.5 kg/m^2 (SD 5.4). The majority of people with available smoking data were ex-smokers [$n = 558$ (42.4%)] and only 71 (5.4%) were current smokers s[moking data were unavailable for 380 people (28.9%)]. Hypertensive nephropathy was the most commonly reported primary renal diagnosis [$n = 426$ (32.4%)].

The demographic and clinical characteristics of the study cohort by country of residence are shown in Table 1. The majority (68.6%) of participants were from the UK and Italy, with only 50 (3.8%) from Poland. Participant recruitment spanned 5 years, with people from the UK, Germany and Italy recruited earlier in the study period than those in The Netherlands and Poland. Mean age and CCI were comparable across all countries. Fewer people from Germany had a diagnosis of hypertensive nephropathy (17.6%) compared with those from the other countries (mean 32.4%). People recruited from Germany also had a lower median eGFR [16.0 mL/min/1.73 m^2 (IQR 13.7–19.0)] at their first study visit than those from other countries. There was a variation in educational attainment across different countries, with participants from The Netherlands and the UK having the highest levels of education.

Prescribed medications

The mean number of prescribed medications was 9.1 (SD 3.6, range 0.0–22.0). Of the participants, 91% were experiencing polypharmacy ($n = 1194$), with 42.8% experiencing hyperpolypharmacy ($n = 564$).

Participants in Germany were prescribed the greatest number of medications per person [mean 10.4 (SD 3.8)] and people in Poland were prescribed the fewest [mean 7.2 (SD 2.8)]. For the purpose of analysis, the largest group (UK) was used as the reference group. In the multivariable analysis, people in Germany were prescribed 1.90 more medications than those in the UK [95% confidence interval (CI) 1.23–2.56, $P < 0.001$; Table 2]. People in Poland were prescribed 1.20 fewer medications than people in the UK [95% CI −2.15 to −0.24, $P = 0.029$; Table 2].

People who were recruited from Germany, The Netherlands and Italy were most likely to experience hyperpolypharmacy [odds ratio (OR) 2.75 (95% CI 1.73–4.37), $P < 0.001$; OR 1.91 (95% CI 1.32–2.76), $P = 0.001$; and OR 1.57 (95% CI 1.15–2.15), $P = 0.004$, respectively; Table 3 and Figure 1].

When the medications were categorized by ATC code, 'cardiovascular' was the most prescribed group of medications in all countries (Figure 2), with a mean of 3.5 cardiovascular medications per person (SD 1.7). Proton pump inhibitors (PPIs) were the most frequently prescribed 'non-cardiovascular' medication [$n = 612$ (46.5%)]. Of note, 41.7% ($n = 255$) of patients who were prescribed PPIs were also prescribed aspirin. Diuretics, statins, calcium channel blockers and β-blockers were each prescribed to more than half of all individuals (66.1, 60.0, 52.5 and 50.7%, respectively; Table 4). Co-prescription of multiple classes of diuretics was infrequent, with 154 patients (11.7%) prescribed two classes of diuretic and 6 patients (0.5%) prescribed three different classes. Combination medications were infrequently prescribed; formoterol and budesonide inhaler was the most commonly prescribed combination [$n = 41$ (3.1%)] followed by irbesartan–hydrochlorothiazide [$n = 10$ (0.8%)]. Iron and erythropoiesis-stimulating agents (ESAs) were prescribed to approximately a quarter of the individuals [$n = 363$ (27.6%) and $n = 334$ (25.4%), respectively]. Vitamin D supplementation in either nutritional or activated form was common [$n = 312$ (23.7%) and $n = 521$ (39.6%), respectively].

Table 1. Demographic and clinical characteristics of the study cohort

Characteristics		Germany	Italy	Netherlands	Poland	UK	Total
Study participants, *n* (% of toal cohort)		142 (10.8)	406 (30.8)	221 (16.8)	50 (3.8)	498 (37.8)	1317 (100.0)
Sex	Male, *n* (%)	82 (57.8)	267 (65.8)	153 (69.2)	35 (70.0)	309 (62.1)	846 (64.2)
Age	Years, mean (SD)	76.9 (6.4)	77.1 (6.8)	75.5 (6.4)	76.1 (7.5)	76.6 (6.8)	76.5 (6.7)
Ethnicity	White, *n* (%)	142 (100.0)	403 (99.3)	208 (94.1)	50 (100.0)	459 (92.2)	1262 (95.8)
Primary renal diagnosis	Glomerular, *n* (%)	17 (12.0)	21 (5.2)	21 (9.5)	6 (12.0)	40 (8.0)	105 (8.0)
	Tubulointerstitial, *n* (%)	9 (6.3)	31 (7.6)	14 (6.3)	3 (6.0)	48 (9.6)	105 (8.0)
	Systemic, *n* (%)	3 (2.1)	3 (0.7)	4 (1.8)	1 (2.0)	13 (2.6)	24 (1.8)
	Diabetes, *n* (%)	32 (22.5)	90 (22.2)	33 (14.9)	9 (18.0)	96 (19.3)	260 (19.7)
	Hypertension, *n* (%)	25 (17.6)	150 (37.0)	89 (40.3)	18 (36.0)	144 (28.9)	426 (32.4)
	Familial, *n* (%)	5 (3.5)	9 (2.2)	5 (2.3)	6 (12.0)	11 (2.2)	36 (2.7)
	Miscellaneous, *n* (%)	4 (2.8)	12 (3.0)	8 (3.6)	1 (2.0)	27 (5.4)	52 (4.0)
	Unknown, *n* (%)	20 (14.1)	74 (18.2)	24 (10.9)	4 (8.0)	109 (21.9)	231 (17.5)
	Missing, *n* (%)	27 (19.0)	16 (3.9)	23 (10.4)	2 (4.0)	10 (2.0)	78 (5.9)
eGFR	mL/min/ 1.73 m^2, median (IQR)	16.0 (13.7–19.0)	17.0 (15.0–19.0)	18.0 (16.0–19.0)	18.0 (17.0–20.0)	18.8 (16.6–19.9)	18.0 (16.0–19.0)
Comorbidity index	Mean (SD)	7.2 (1.7)	7.3 (1.8)	7.1 (1.8)	7.3 (2.3)	7.0 (1.8)	7.1 (1.8)
Comorbidities	Diabetes, *n* (%)	78 (54.9)	185 (45.6)	85 (38.5)	17 (34.0)	193 (38.8)	558 (42.4)
	Hypertension, *n* (%)	124 (87.3)	378 (93.1)	178 (80.5)	48 (96.0)	384 (77.1)	1112 (84.4)
	History of major vascular event, *n* (%)	53 (37.3)	158 (38.9)	102 (46.2)	28 (56.0)	152 (30.5)	493 (37.4)
	Malignancy, *n* (%)	20 (14.1)	74 (18.2)	57 (25.8)	9 (18.0)	110 (22.1)	270 (20.5)
	Missing, *n* (%)	3 (2.1)	3 (0.7)	7 (3.2)	0	11 (2.2)	24 (1.8)
Educational attainment	No education, *n* (%)	0	28 (6.9)	1 (0.5)	0	0	29 (2.2)
	Primary school, *n* (%)	9 (6.3)	112 (27.6)	29 (13.1)	10 (20.0)	158 (31.7)	318 (24.2)
	Secondary school or vocational course, *n* (%)	96 (67.6)	120 (29.6)	86 (38.9)	27 (54.0)	142 (28.5)	471 (35.8)
	University degree, *n* (%)	6 (4.2)	20 (4.9)	36 (16.3)	0	36 (7.2)	98 (7.4)
	Other, *n* (%)	13 (9.2)	0	7 (3.2)	0	0	20 (1.5)
	Missing, *n* (%)	18 (12.7)	126 (31.0)	62 (28.1)	13 (26.0)	162 (32.5)	381 (28.9)
BMI	kg/m^2, mean (SD)	30.1 (5.6)	27.4 (5.0)	28.2 (4.5)	28.0 (5.3)	29.2 (5.6)	28.5 (5.4)
Medications	Number of medications, mean (SD)	10.4 (3.8)	9.2 (3.0)	9.6 (3.8)	7.2 (2.8)	8.6 (3.7)	9.1 (3.6)
	Polypharmacy, *n* (%)	134 (94.4)	382 (94.1)	203 (91.9)	41 (82.0)	434 (87.2)	1194 (90.7)
	Hyperpolypharmacy, *n* (%)	82 (57.8)	183 (45.1)	110 (49.8)	9 (18.0)	180 (36.1)	564 (42.8)

History of major vascular event includes previous stroke, myocardial infarction, amputation due to peripheral vascular disease or heart failure; polypharmacy ≥5 medications; hyperpolypharmacy ≥10 medications. BMI, body mass index.

Table 2. International comparison of number of medications

Country (*n*)	Univariable linear regression			Multivariable linear regression[a]		
	β	P-value	95% CI	β	P-value	95% CI
UK (498)	0.00	Reference group		0.00	Reference group	
Germany (142)	1.87	<0.001	1.21–2.52	1.90	<0.001	1.23–2.56
Italy (406)	0.51	0.029	0.05–0.97	0.47	0.038	−0.03–0.92
The Netherlands (221)	1.00	<0.001	0.44–1.55	1.09	<0.001	0.56–1.62
Poland (50)	−1.41	0.007	−2.43 to −0.39	−1.20	0.014	−2.15 to −0.24

[a]Adjusted for age, ethnicity, sex, educational attainment, comorbidities (hypertension, diabetes, cerebrovascular disease, myocardial infarction, cardiac arrhythmias, lung disease and psychiatric disorders), eGFR and primary renal diagnosis.

Around a quarter of participants were prescribed sodium bicarbonate [*n* = 327 (24.8%)].

Prescriptions of different medication groups varied between countries (Figure 2). Recruits from Poland were prescribed fewer medications from the 'alimentary tract and metabolism' ATC category. In particular, fewer PPIs and activated and nutritional vitamin D supplements (10.0, 8.0 and 6.0%, respectively) were prescribed to Polish recruits compared with others (Table 4). German participants had the highest number of prescriptions for loop diuretics, angiotensin-converting enzyme inhibitors, β-blockers and sodium bicarbonate compared with people from the other countries. Tests for proportions indicate that there are differences in prescribing of all but 2 of the 20 most prescribed agents (tamsulosin and clopidogrel; Table 4).

PQIs

The proportion of people fulfilling PQIs for potentially appropriate and inappropriate prescribing is shown in Table 5 and Figure 3. PQIs that examined potentially appropriate prescribing showed that almost all people [*n* = 1243 (97.8%)] who

might benefit from antihypertensives were prescribed one. However, only half of people [$n = 176$ (48.8%)] who might benefit from phosphate binders were prescribed one; The Netherlands had the highest proportion of phosphate binder prescriptions to those who might benefit [$n = 52$ (75.4%), $P < 0.001$]. Only a small number of individuals who were prescribed phosphate binders had calcium levels that were classed as too low or too high. Of those with low calcium levels, the majority were receiving a calcium-containing binder [$n = 15$ (80%)]. Of those with high calcium levels, roughly half were receiving a non-calcium-containing binder [$n = 6$ (54.5%)].

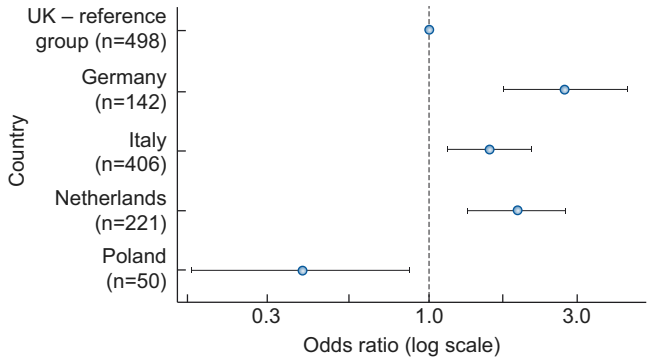

FIGURE 1: Multivariable logistic regression of hyperpolypharmacy by country.

With regard to potentially inappropriate prescribing, there were few prescriptions for dual renin–angiotensin system (RAS) blockade or non-steroidal anti-inflammatory drugs (NSAIDs) $n = 24$ (1.8%) and $n = 14$ (1.1%), respectively]. People from the UK had the greatest number of NSAID prescriptions compared with those from the other countries [$n = 11$ (2.2%), $P = 0.010$]. A minority of people were prescribed the combination of RAS inhibitors, NSAIDs and diuretics [$n = 8$ (0.6%)]. Of those with diabetes, 14 people were prescribed metformin (2.5%). Of those with high calcium levels, 22 (41.5%) were prescribed activated vitamin D, with the greatest proportion of these prescriptions observed in the German recruits [$n = 7$ (87.5%), $P = 0.004$]. Of those with haemoglobin levels $\geq$7.5 mmol/L, 66 (14.3%) were prescribed ESAs, with a greater proportion of these people residing in Germany and Italy [$n = 11$ (21.2%) and $n = 29$ (21.6%), respectively, $P = 0.006$].

DISCUSSION

In this international comparison of prescribing in older people with advanced CKD, 91% of individuals experienced polypharmacy and 43% experienced hyperpolypharmacy. The prevalence of polypharmacy is more than three times higher than that observed in people of a similar age in the general population in the UK (28% in patients $\geq$60 years of age), but consistent with that reported in the French CKD-Renal Epidemiology and

Table 3. International comparison of hyperpolypharmacy

Country (*n*)	Univariable logistic regression			Multivariable logistic regression[a]		
	OR	P-value	95% CI	OR	P-value	95% CI
UK (498)	1.00	Reference group		1.00	Reference group	
Germany (142)	2.41	<0.001	1.65–3.53	2.75	<0.001	1.73–4.37
Italy (406)	1.45	0.007	1.11–1.89	1.57	0.004	1.15–2.15
Netherlands (221)	1.75	0.001	1.27–2.41	1.91	0.001	1.32–2.76
Poland (50)	0.39	0.013	0.18–0.82	0.39	0.021	0.17–0.87

[a]Adjusted for age, ethnicity, sex, educational attainment, comorbidities (hypertension, diabetes, cerebrovascular disease, myocardial infarction, cardiac arrhythmias, lung disease and psychiatric disorders), eGFR and primary renal diagnosis.
Hyperpolypharmacy $\geq$10 medications.

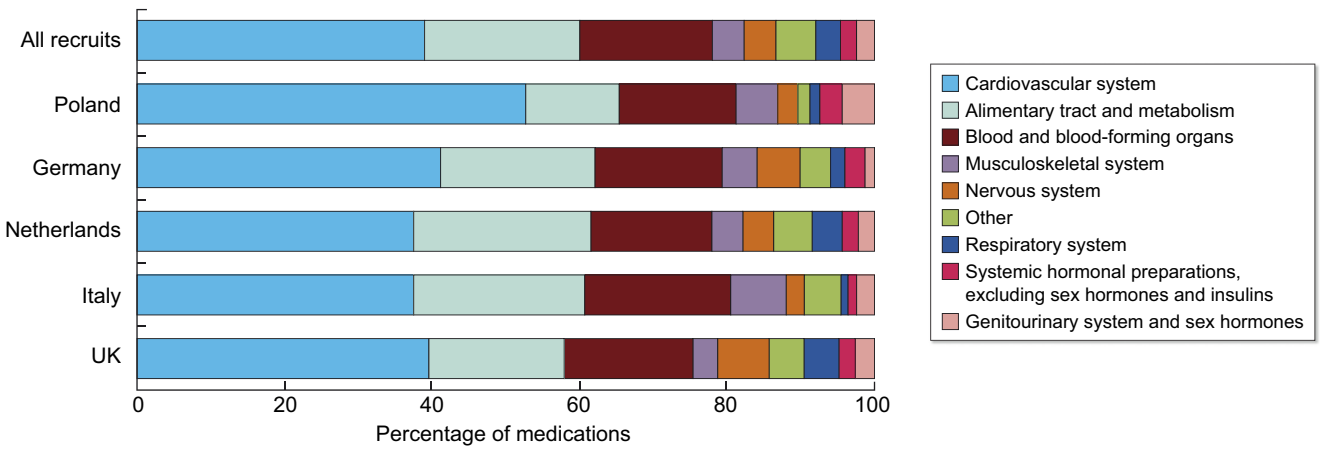

FIGURE 2: Percentage of medications in ATC categories by country.

Table 4. The top 20 prescribed medications

Medication[a]	Germany ($n=142$)	Italy ($n=406$)	Netherlands ($n=221$)	Poland ($n=50$)	UK ($n=498$)	Total ($n=1317$)	P-value
Diuretics, any	117 (82.4)	310 (76.4)	128 (57.9)	36 (72.0)	280 (56.2)	871 (66.1)	<0.001
Loop diuretics	112 (78.9)	290 (71.4)	95 (43.0)	34 (68.0)	239 (48.0)	770 (58.5)	–
Thiazide diuretics	6 (4.2)	63 (15.5)	23 (10.4)	1 (2.0)	35 (7.0)	128 (9.7)	–
Aldosterone antagonists	15 (10.6)	20 (4.9)	24 (10.9)	3 (6.0)	24 (4.8)	86 (6.5)	–
Other potassium sparing agent	1 (0.7)	0	0	0	3 (0.6)	4 (0.3)	–
Other	20 (14.1)	3 (0.7)	9 (4.1)	1 (2.0)	16 (3.2)	49 (3.7)	–
Statins	82 (57.7)	201 (49.5)	146 (66.1)	32 (64.0)	329 (66.1)	790 (60.0)	<0.001
Calcium channel blockers	78 (54.9)	205 (50.5)	116 (53.5)	37 (74.0)	256 (51.4)	692 (52.5)	0.03
β-blockers	107 (75.4)	176 (43.4)	134 (60.6)	35 (70.0)	216 (43.4)	668 (50.7)	<0.001
PPIs	47 (33.1)	253 (62.3)	108 (48.9)	5 (10.0)	199 (40.0)	612 (46.5)	<0.001
Activated vitamin D	76 (53.5)	219 (53.9)	104 (47.1)	4 (8.0)	118 (23.7)	521 (39.6)	<0.001
Aspirin	63 (44.4)	163 (40.1)	49 (22.2)	15 (30.0)	184 (36.9)	474 (36.0)	<0.001
Allopurinol	57 (40.1)	219 (53.9)	50 (22.6)	22 (44.0)	89 (17.9)	437 (33.2)	<0.001
Insulin	66 (46.5)	147 (36.2)	76 (34.4)	10 (20.0)	110 (22.1)	409 (31.1)	<0.001
Iron (intravenous or oral)	26 (18.3)	140 (34.5)	40 (18.1)	14 (28.0)	143 (28.7)	363 (27.6)	<0.001
ESAs	45 (31.7)	161 (39.7)	55 (24.9)	0	73 (14.7)	334 (25.4)	<0.001
Sodium bicarbonate	71 (50.0)	102 (25.1)	37 (16.7)	2 (4.0)	115 (23.1)	327 (24.8)	<0.001
Angiotensin receptor II blockers	39 (27.5)	105 (25.9)	76 (34.4)	2 (4.0)	105 (21.1)	327 (24.8)	<0.001
Nutritional vitamin D	75 (52.8)	82 (20.2)	122 (55.2)	3 (6.0)	30 (6.0)	312 (23.7)	<0.001
ACE inhibitors	56 (39.4)	41 (10.1)	61 (27.6)	9 (18.0)	117 (23.5)	284 (21.6)	<0.001
α-blockers (excluding tamsulosin)	14 (9.9)	81 (20.0)	22 (10.0)	16 (32.0)	146 (29.3)	279 (21.2)	<0.001
Levothyroxine	29 (20.4)	25 (6.2)	20 (9.0)	6 (12.0)	52 (10.4)	132 (10.0)	<0.001
Clopidogrel	10 (7.0)	35 (8.6)	21 (9.5)	4 (8.0)	54 (10.8)	124 (9.4)	0.636
Tamsulosin	13 (9.2)	33 (8.1)	24 (10.9)	9 (18.0)	44 (8.8)	123 (9.3)	0.207
Warfarin	1 (0.7)	34 (8.4)	0	1 (2.0)	74 (14.9)	110 (8.4)	<0.001

Values presented as *n* (%).[a]In addition, 124 people had a medication recorded which was classified as 'unknown'. ACE, angiotensin-converting enzyme.

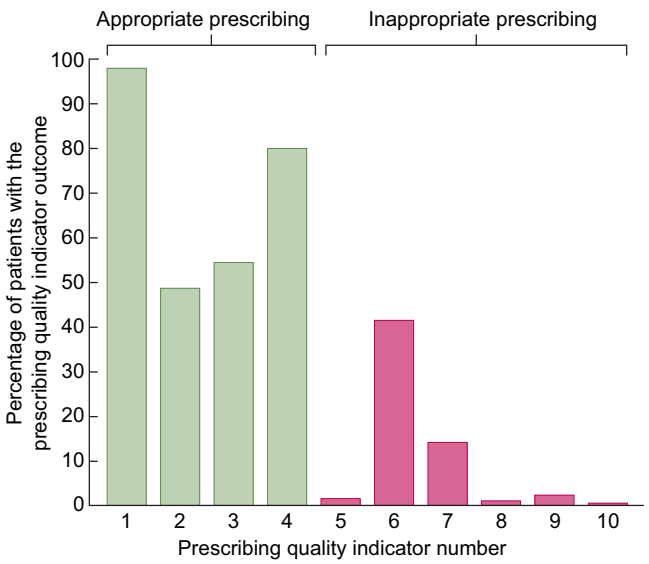

FIGURE 3: PQIs.

Information Network cohort (87% for patients with CKD Stage 4 or 5) [2, 12]. At a national level, the mean number of medications prescribed to people ≥65 years of age with an incident eGFR ≤20 mL/min/1.73 m^2 ranged between 7.2 in Poland to 10.4 in Germany, and this three-medication gap between the highest- and lowest-prescribing nations persisted after adjustment for potential clinical and sociodemographic confounders.

Prescribing patterns in the general population are known to vary by nation; e.g. the UK antihypertensive drug consumption has been reported to be two-thirds that of patients in Germany [31]. International variation in prescribing for people with CKD may largely reflect country-level factors, independent from CKD-specific influences. Whether the between-country differences are driven chiefly by prescription of medications overall or by greater and lesser use of particular drugs or drug classes is difficult to untangle. However, the high prevalence of polypharmacy and hyperpolypharmacy and the marked variation in hyperpolypharmacy between countries point towards comprehensive differences in prescribing approaches. The factors driving international variation may operate through patient and clinician behaviours or through healthcare systems.

Patient expectations and shared decision-making are linked to health and cultural beliefs and are likely to differ with country of residence [32]. Cultural attitudes towards acceptance of multiple medications may be driven by, for example, preferences for preventative care. Clinician behaviours may also differ between nations and influence the likelihood of recommending regimens with larger numbers of medications. Drivers may include tendencies for clinicians to prescribe an additional medicationversus recommending a lifestyle or other non-medicinal intervention. It is possible that there are national differences in how comfortable clinicians and patients are to share decisions regarding prescribing, whereby the number of medications prescribed may be more person-centred in some nations than others. The five included countries have diverse organizational and funding arrangements for healthcare provision, and while

Table 5. PQIs

PQI[a]	Germany	Italy	The Netherlands	Poland	UK	P-value
Potentially appropriate prescribing						
1. Patients with hypertension who are prescribed antihypertensives unless undesirable because of low diastolic blood pressure (<70 mmHg)	139 (98.6)	386 (98.0)	208 (97.2)	48 (96.0)	462 (97.9)	0.812
2. Patients with an elevated phosphate level (>1.49 mmol/L) who are prescribed a phosphate binder	21 (37.5)	50 (41.7)	52 (75.4)	0	53 (51.0)	<0.001
3. Patients treated with phosphate binders and who have an elevated calcium level (>2.54 mmol/L) who are prescribed a non-calcium-containing phosphate binder	2 (50.0)	0	2 (100.0)	0	2 (50.0)	0.636
4. Patients treated with phosphate binders and who have a low calcium level (<2.10 mmol/L) who are prescribed a calcium-containing phosphate binder	3 (75.0)	7 (77.8)	2 (66.7)	0	4 (100.0)	0.881
Potentially inappropriate prescribing						
5. Patients treated with RAS inhibitors who are prescribed at least two RAS inhibitors simultaneously (dual RAS blockade)	7 (4.9)	8 (2.0)	3 (1.4)	0	6 (1.2)	0.090
6. Patients with an elevated calcium level (>2.54 mmol/L) who are prescribed active vitamin D	7 (87.5)	8 (57.1)	3 (23.1)	0	4 (22.2)	0.004
7. Patients with a normal haemoglobin level (≥7.5 mmol/L) who are prescribed an ESA	11 (21.2)	29 (21.6)	10 (9.7)	0	16 (10.4)	0.006
8. Patients who are prescribed an NSAID	2 (1.4)	0	1 (0.5)	0	11 (2.2)	0.010
9. Patients with diabetes who are prescribed metformin	0	1 (0.5)	4 (4.7)	1 (5.9)	8 (4.1)	0.022
10. Patients who are prescribed a combination of NSAIDs, RAS inhibitors and diuretics	2 (1.4)	0	1 (0.5)	0	5 (1.0)	0.137

Values are presented as *n* (%). [a]Number and percentage of patients who meet the indicator outcome out of all of those who meet the indicator criteria. Data were missing for the following PQIs: PQI1, 3 patients; PQI2, 70 patients; PQI3 and PQI4, 43 patients, PQI6, 344 patients, PQI7, 22 patients, PQI9, 28 patients. Data were complete for PQI5, PQI8 and PQI10.

they share similar goals, there are likely to be nuances that influence prescribing patterns, such as prescription charges, implicit rationing or quality assurance measures designed to limit polypharmacy [33–36]. The interplay and communication between specialists and primary care providers may also differ at a national level; the overall responsibility for medication review and reconciliation may fall to one of these clinicians or be split between multiple clinicians.

Prescribing for patients with advanced CKD is particularly complex due to multimorbidity, altered drug kinetics and clearance and imprecise estimates of residual renal function. Because of the need for individualized prescribing, it is impossible to remark conclusively on the appropriateness of prescriptions in the study cohort at either an individual or population level [37]. The PQIs have highlighted areas of possible good and bad practice; however, some of these prescriptions may be the result of individual patient preference or specific circumstances where guidelines may not be applicable. Nevertheless, variations in the numbers and nature of medicines prescribed suggest a lack of consensus as to what the 'right' level of prescribing is for this group.

Cardiovascular drugs were the most prescribed group in this cohort, with each person prescribed an average of 3.5 cardiovascular medications. Adult prescribing data from 40 general practices in the UK demonstrated that cardiovascular medications were the most prescribed group of medications in the general population as well, with 13.5% of all adult patients prescribed three or more cardiovascular drugs [38]. The high use of cardiovascular medications in our study likely reflects the increased risk of cardiovascular events and high prevalence of cardiovascular comorbidities among individuals with CKD. Two highly prevalent drugs, PPIs (46.5% of recruits) and statins (60.0%), have both been previously identified as targets for deprescribing interventions [39–43]. It is noteworthy that, with the exception of PPIs, few of the most commonly prescribed medications could be expected to provide symptomatic benefit, with notably low levels of analgesic prescriptions. Chronic pain is a common symptom for patients with advanced CKD and is often undertreated [44, 45]. It is possible, even against the backdrop of polypharmacy, that there is both overtreatment and undertreatment at play.

The greatest strength of this study is the use of a multinational cohort of individuals who met strict inclusion criteria for age and renal function. However, only a limited number of countries were included in this international comparison, with just 50 patients from Poland. Strictly applied eligibility criteria would have helped to ensure a homogeneous group of patients. Nevertheless, older patients with eGFR ≤20 mL/min/1.73 m^2 receiving nephrology care may differ between countries in many ways, including who is eligible for a nephrology referral, whether the referral can be made directly or through a primary care provider, at what point referral is made and what care is received before that point. The variances in some baseline clinical and demographic characteristics between nations, such as the lower median eGFR observed in Germany, may indicate such differences were present. The high levels of white ethnicity, even though advanced CKD is more common in non-white people, may reflect bias in terms of included centres (from areas with smaller black and minority ethnic populations) or in terms of recruited individuals [46]. This could influence the generalizability of the findings, especially if there is an association between ethnicity and prescribing patterns. Indeed, the study focuses on older patients with advanced CKD and thus the

findings may not be applicable to younger patients or those with less severe stages of CKD.

The rigorous and protocolized approach to prospective data collection means that the medication data can be used with confidence. Unfortunately this approach did not allow capture of 'over-the-counter' medications and so may have led to an underestimate of total medication use. In addition, the cross-sectional design of the study prevents any comment on medication changes over time and may have led to short-term medications being underrepresented, which may have contributed to lower documentation of analgesics and other agents with intended symptomatic benefits. The lack of comprehensive proteinuria data led to four PQIs from the original list being excluded from our operational PQI list. Five of the PQIs required laboratory measures and the results of these tests may not have been available until after the baseline study visit. Therefore, changes to the prescriptions may have been made once the results were known, which would not have been captured due to the lack of longitudinal data available for this analysis. As such, the results for these PQIs may not truly reflect good or bad prescribing practice. Furthermore, medications were recorded by name, but not dosing regimen, so we were unable to calculate the number of tablets taken, dosing frequencies or drug doses prescribed. We were unable to comment on indications for medications or patient adherence to medication.

While, in general, rates of polypharmacy are rising [1], even though study recruitment spanned 5 years, the highest prevalence of polypharmacy was observed in patients from Germany, who were recruited earlier in the study period. The lowest prevalence of polypharmacy was observed in patients from Poland, who were recruited later. Therefore, rising polypharmacy rates during study recruitment are likely to have led to underestimation of the differences demonstrated.

CONCLUSION

This study has demonstrated both a high prevalence of polypharmacy and hyperpolypharmacy and also significant international differences in the number of medications prescribed to older patients with advanced CKD. Such variation in routine clinical prescribing suggests a lack of international consensus regarding what is 'appropriate' prescribing for older people with advanced CKD, among whom pharmacological treatment has great potential for harm as well as benefit. Further work is needed to identify the key factors that are driving these international differences in prescribing, to explore how prescribing patterns change over time and to ascertain whether and when deprescribing occurs and to determine how these changes relate to treatment burden, patient outcomes and quality of life.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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CONFLICT OF INTEREST STATEMENT

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