International prescribing patterns and polypharmacy in older people with advanced chronic kidney disease: results from the EQUAL Study

S Hayward[1,2,3], B Hole[1,2,3], R Denholm[2], P Duncan[2], JE Morris[4], SDS Fraser[4], RA Payne[2], P Roderick[4], NC Chesnaye[5], C Wanner[6], C Drechsler[6], M Postorino[7], G Porto[7], M Szymczak[8], M Evans[9], FW Dekker[10], KJ Jager[5] ,FJ Caskey[2,3] on behalf of the EQUAL Study investigators

1. UK Renal Registry, Southmead Hospital, Bristol, United Kingdom

2. Bristol Medical School, University of Bristol, United Kingdom

3. Dept of Nephrology, Southmead Hospital, North Bristol Trust, United Kingdom

4. Faculty of Medicine, University of Southampton, United Kingdom

5. ERA-EDTA Registry, Dept of Medical Informatics, Amsterdam University Medical Center, University of Amsterdam, Amsterdam Public Health research institute, Amsterdam, The Netherlands

6. Dept of Medicine, Division of Nephrology, University Hospital of Würzburg, Würzburg, Germany

7. Clinical Epidemiology and Pathophysiology of Renal Diseases and Hypertension, CNR-IFC, Reggio Calabria, Italy

8. Dept of Nephrology and Transplantation Medicine, Wroclaw Medical University, Wroclaw, Poland

9. Dept of Clinical Sciences Intervention and Technology, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

10. Dept of Clinical Epidemiology, Leiden University Medical Center, The Netherlands

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 paper aims to examine prescribing and polypharmacy patterns amongst older people with advanced CKD across the countries involved in the European Quality Study (EQUAL).

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

Results: Of the 1317 participants from 5 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 (OR 2.75, 95% CI 1.73-4.37, p<0.001, reference group United Kingdom), 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 amongst 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, polypharmacy, prescribing, pharmacoepidemiology, treatment burden.

Introduction

Polypharmacy rates are rising, particularly amongst older people.[1] Drivers for polypharmacy in the general population include multimorbidity, increased use of preventative medications, and guidelines which focus on single diseases.[2–5] Negative consequences of polypharmacy include drug-drug interactions, adverse drug reactions, poor adherence and increased treatment burden, alongside 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 which 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 trans-national learning and inform further work to identify individual, local and national factors to encourage appropriate prescribing.

The aim of this paper 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 Study (EQUAL).

Materials and methods

The EQUAL study is an international prospective cohort study which 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, United Kingdom (UK) and Sweden). Inclusion criteria were age ≥65 years old and an incident estimated glomerular filtration rate (eGFR) ≤20ml/min/1.73m^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 1st March 2012 to 31st 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 so 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 standardised using European Renal Association – European Dialysis and Transplant Association codes.[25] In order to compare the education systems and qualifications in the included countries, the EQUAL investigators created standardised 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 their corresponding Anatomical-Therapeutic-Chemical (ATC) classification codes.[26] Medication categories were created based upon the first level of the ATC codes (for example, '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 descriptive 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 (for example, 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) which 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 which were appropriate for our study cohort and the available data (see 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 summarise baseline demographic characteristics of study participants according to country of residence. PQIs and specific medications were compared across countries using Chi squared and Fisher's exact tests. Univariable and multivariable linear regression were used to determine the association between country of residence and number of prescribed medications. Univariable and multivariable logistic regression were used to determine the association between country of residence and hyperpolypharmacy. The multivariable linear regression and multivariable logistic regression analyses adjusted for variables which were identified as confounders[30]: age, educational attainment, ethnicity, sex, eGFR, primary renal diagnosis and co-morbidities. 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.

Results

Characteristics of the study cohort

From a potential 1,344 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 1,317 remaining, 846 (64.2%) were male and the mean age was 76.5 years (standard deviation (SD) 6.7). The majority were white (n=1,262, 95.8%). With regards to educational attainment, only a minority of patients had university degrees (n=98, 7.4%). The median eGFR at the first study visit was 18.0mL/min/1.73m^2 (inter-quartile range (IQR) 16.0-19.0). Multimorbidity was common; all participants had at least one comorbidity in addition to CKD (n=1,293, 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 (BMI) was 28.5kg/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, (smoking data was 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 to those from the other countries (mean 32.4%). People recruited from Germany also had a lower median eGFR (16.0 mL/min/1.73m^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). Ninety one percent of participants were experiencing polypharmacy (n=1,194), 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) were used as the reference group. In the multivariable analysis, people in Germany were prescribed 1.90 more medications than those in the UK (95% 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- -0.24, p=0.029, table 2).

People who were recruited from Germany, the Netherlands and Italy were most likely to experience hyperpolypharmacy (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 categorised by ATC code, 'cardiovascular' were found to be 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 beta blockers were each prescribed to over 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 2 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 irebesartan-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). 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, 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 (ACE) inhibitors, beta blockers and sodium bicarbonate compared to people from the other countries. Tests for proportions indicate that there are differences in prescribing of all but two of the 20 most prescribed agents (tamsulosin and clopidogrel, table 4).

Prescribing quality indicators

The proportion of people fulfilling PQIs for potentially appropriate and inappropriate prescribing are shown in table 5 and figure 3. PQIs which 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 which were classed as too low or too high. Out of those with low calcium levels, the majority were receiving a calcium containing binder (n=15, 80%). Out of those with high calcium levels, roughly half were receiving a non-calcium containing binder (n=6, 54.5%).

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 to 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%). Out of those with diabetes, 14 people were prescribed metformin (2.5%). Out of those with high calcium levels, 22 people (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). Out of those with haemoglobin

levels ≥7.5 mmol/L 66 people (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 over three-times higher than that observed in people of a similar age in the general population in England (28% in patients aged 60 years or above), but consistent with that reported in the French CKD-REIN cohort (87% for patients with CKD stage 4 or 5).[2,12] At a national level, the mean number of medications prescribed to people aged 65 years and over with an incident eGFR of less than 20mL/min/1.73m^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 socio-demographic confounders.

Prescribing patterns in the general population are known to vary by nation; for example, 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, for example, by 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 medication, compared with 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 organisational and funding arrangements for health care provision and whilst they share similar goals, there are likely to be nuances which 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 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. On account of the need for individualised 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, variation in the numbers and nature of medicines prescribed suggests 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 Scotland 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 is likely to reflect the increased risk of cardiovascular events and high prevalence of cardiovascular comorbidities amongst individuals with CKD. Two highly prevalent drugs, PPIs (46.5% of recruits) and statins (60.0%), have both been previously identified as targets for de-prescribing 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 prescription. 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 under treatment 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 will have helped to ensure a homogeneous group of patients. Nevertheless, older patients with eGFR ≤20mL/min/1.73m^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 generalisability 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 so the findings may not be applicable to younger patients or those with less severe stages of CKD.

The rigorous and protocolised 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 number of tablets taken, dosing frequencies or drug doses prescribed. We were unable to comment on indications for medications or patient adherence to medication.

Whilst in general, rates of polypharmacy are rising,[1] even though study recruitment spanned five 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 under-estimation 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, amongst 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.

Acknowledgements

We would like to thank all the patients and health professionals participating in the EQUAL study. A full list of acknowledgements of health professionals is included in appendix 2. Funding was received from the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), the Swedish Medical Association, the Stockholm County Council ALF and CIMED, Njurfonden (Sweden), the Italian Society of Nephrology (SIN-Reni), the Dutch Kidney Foundation (SB 142), the Young Investigators grant in Germany, and the National Institute for Health Research (NIHR) in the United Kingdom.

References

1. Guthrie, B., Makubate, B., Hernandez-Santiago, V. & Dreischulte, T. The rising tide of polypharmacy and drug-drug interactions: Population database analysis 1995-2010. *BMC Med.* **13**, (2015).
2. Slater, N., White, S., Venables, R. & Frisher, M. Factors associated with polypharmacy in primary care: A cross-sectional analysis of data from the English Longitudinal Study of Ageing (ELSA). *BMJ Open* **8**, (2018).
3. Payne, R. A. The epidemiology of polypharmacy. *Clin. Med.* **16**, 465–469 (2016).
4. Wauters, M. *et al.* Polypharmacy in a Belgian cohort of community-dwelling oldest old (80+). *Acta Clin. Belgica Int. J. Clin. Lab. Med.* **71**, 158–166 (2016).
5. 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. Pharmacoepidemiol. Drug Saf.* **3**, (2014).
6. Schuler, J. *et al.* Polypharmacy and inappropriate prescribing in elderly internal-medicine patients in Austria. *Wien. Klin. Wochenschr.* **120**, 733–741 (2008).
7. Frazier, S. . . Health Outcomes and Polypharmacy in Elderly Individuals. An integrated literature review. *J. Gerontol. Nurs.* **31**, 4–12 (2005).
8. Incalzi, Raffaele Antonelli, Corsonello, Andrea, Pedone, Claudio, Corica, Francesco, Carbonin, P. Depression and drug utilization in an elderly population. *Ther. Clin. Risk Manag.* **1**, 55–60 (2005).
9. Henderson, J. A., Buchwald, D. & Manson, S. M. Relationship of medication use to health-related quality of life among a group of older American Indians. *J. Appl. Gerontol.* **25**, (2006).
10. Hughes, C. M. Medication non-adherence in the elderly: how big is the problem? *Drugs Aging* **21**, 793–811 (2004).
11. Fraser, S. D. S. *et al.* The burden of Comorbidity in people with chronic kidney disease stage 3: A cohort study. *BMC Nephrol.* **16**, (2015).
12. Laville, S. M. *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.* **84**, 2811–2823 (2018).
13. Mehrotra, R. *et al.* Pill Burden, Adherence, Hyperphosphatemia, and Quality of Life in Maintenance Dialysis Patients. *Clin. J. Am. Soc. Nephrol.* **4**, 1089–1096 (2009).
14. Secora, A., Alexander, G. C., Ballew, S. H., Coresh, J. & Grams, M. E. Kidney Function, Polypharmacy, and Potentially Inappropriate Medication Use in a Community-Based Cohort of Older Adults. *Drugs and Aging* **35**, 735–750 (2018).
15. Battistella, M., Jandoc, R., Ng, J. Y., McArthur, E. & Garg, A. X. A Province-wide, Cross-sectional Study of Demographics and Medication Use of Patients in Hemodialysis Units Across Ontario. *Can. J. Kidney Heal. Dis.* **5**, 205435811876083 (2018).
16. Chakraborty, S. *et al.* Prescribing patterns of medicines in chronic kidney disease patients on maintenance hemodialysis. *Indian J. Pharmacol.* **48**, 586 (2016).
17. Tonelli, M. *et al.* Comorbidity as a driver of adverse outcomes in people with chronic kidney disease. *Kidney Int.* **88**, 859–866 (2015).
18. Tesfaye, W. H., Castelino, R. L., Wimmer, B. C. & Zaidi, S. T. R. Inappropriate prescribing in chronic kidney disease: A systematic review of prevalence, associated clinical outcomes and impact of interventions. *International Journal of Clinical Practice* **71**, (2017).

19. Dörks, M., Herget-Rosenthal, S., Schmiemann, G. & Hoffmann, F. Polypharmacy and Renal Failure in Nursing Home Residents: Results of the Inappropriate Medication in Patients with Renal Insufficiency in Nursing Homes (IMREN) Study. *Drugs and Aging* **33**, 45–51 (2016).

20. Njeri, L. W., Ogallo, W. O., Nyamu, D. G., Opanga, S. A. & Birichi, A. R. Medication-related problems among adult chronic kidney disease patients in a sub-Saharan tertiary hospital. *Int. J. Clin. Pharm.* **40**, 1217–1224 (2018).

21. Fasipe, O. J., Akhideno, P. E., Nwaiwu, O. & Adelosoye, A. A. Assessment of prescribed medications and pattern of distribution for potential drug-drug interactions among chronic kidney disease patients attending the nephrology clinic of lagos university teaching hospital in sub-saharan West Africa. *Clin. Pharmacol. Adv. Appl.* **9**, 125–132 (2017).

22. Levey, A. S. *et al.* Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann. Intern. Med.* **145**, 247–254 (2006).

23. Jager, K. J. *et al.* The EQUAL study: A European study in chronic kidney disease stage 4 patients. *Nephrology Dialysis Transplantation* **27**, (2012).

24. Charlson, M. E., Pompei, P., Ales, K. L. & MacKenzie, C. R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* **40**, 373–83 (1987).

25. Venkat-Raman, G. *et al.* New primary renal diagnosis codes for the ERA-EDTA. *Nephrol. Dial. Transplant.* **27**, 4414–4419 (2012).

26. *WHO collaborating centre for drug statistics methodology, ATC classification index with DDDs, 2019. Oslo, Norway 2018.*

27. Masnoon, N., Shakib, S., Kalisch-Ellett, L. & Caughey, G. E. What is polypharmacy? A systematic review of definitions. *BMC Geriatrics* **17**, (2017).

28. Smits, K. P. J. *et al.* Development and initial validation of prescribing quality indicators for patients with chronic kidney disease. *Nephrol. Dial. Transplant.* **31**, 1876–1886 (2016).

29. Smits, K. P. *et al.* Prescribing quality in secondary care patients with different stages of chronic kidney disease: a retrospective study in the Netherlands. *BMJ Open* **9**, e025784 (2019).

30. Jager, K. J., Zoccali, C., MacLeod, A. & Dekker, F. W. Confounding: What it is and how to deal with it. *Kidney Int.* **73**, 256–260 (2008).

31. OECD Health statistics 2017. (2017).

32. Vaughn, Lisa. Jacquez, Farrah. Baker, R. Cultural health attributions, beliefs, and practices: Effects on healthcare and medical education. *open Med. Educ. J.* **2**, 64–74 (2009).

33. McIntosh, J. *et al.* A case study of polypharmacy management in nine European countries: Implications for change management and implementation. *PLoS One* **13**, (2018).

34. Mair, Alpana. Fernandez-Llimos, Fernando. Alonso, Albert. Harrison, Cathy. Hurding, Simon. Kempen, Thomas. Kinnear, Moira. Michael, Nils. McIntosh, Jennifer. Wilson, M. *Polypharmacy management by 2030: a patient safety challenge*. (2017).

35. Scheunemann, L. & White, D. The ethics and reality of rationing in medicine. *Chest* **140**, 1625–1632 (2011).

36. Cylus, Jonathan. Papanicolas, I. An analysis of perceived access to health care in Europe: How universal is universal coverage? *Health Policy (New. York).* **119**, 1133–1144 (2015).

37. Aronson, J. Polypharmacy, appropriate and inappropriate. *Br. J. Gen. Pract.* **56**, 484–485 (2006).

38. Appleton, S. C., Abel, G. A. & Payne, R. A. Cardiovascular polypharmacy is not associated with unplanned hospitalisation: Evidence from a retrospective cohort study. *BMC Fam. Pract.* **15**, (2014).

39. Messow, C. M. & Isles, C. Meta-analysis of statins in chronic kidney disease: Who benefits? *QJM* **110**, 493–500 (2017).

40. Freedberg, D. E., Kim, L. S. & Yang, Y. X. The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association. *Gastroenterology* **152**, 706–715 (2017).

41. Fick, D. M. *et al.* American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J. Am. Geriatr. Soc.* **67**, 674–694 (2019).

42. McIntyre, C., McQuillan, R., Bell, C. & Battistella, M. Targeted Deprescribing in an Outpatient Hemodialysis Unit: A Quality Improvement Study to Decrease Polypharmacy. *Am. J. Kidney Dis.* **70**, 611–618 (2017).

43. Triantafylidis, L. K., Hawley, C. E., Perry, L. P. & Paik, J. M. The Role of Deprescribing in Older Adults with Chronic Kidney Disease. *Drugs and Aging* (2018). doi:10.1007/s40266-018-0593-8

44. Davison, S. N. Chronic pain in end-stage renal disease. *Adv. Chronic Kidney Dis.* **12**, 326–34 (2005).

45. Nagar, V. R., Birthi, P., Salles, S. & Sloan, P. A. Opioid use in chronic pain patients with chronic kidney disease: A systematic review. *Pain Medicine (United States)* **18**, 1416–1449 (2017).

46. Wilkinson, Emma. Brettle, Alison. Waqar, Muhammad. Randhawa, G. Inequalities and outcomes: end stage kidney disease in ethnic minorities. *BMC Nephrol.* **20**, 234 (2019).

Table 1. Demographic and clinical characteristics of the study cohort							
		Germany	**Italy**	**Netherlands**	**Poland**	**UK**	**Total**
Study participants	n (% of total 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	Mean years (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)
	Tubulo-interstitial, 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	Median eGFR ml/min/1.73m^2 (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 CCI (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	Mean kg/m^2 (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	Mean number of medications (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)

Abbreviations: *SD* standard deviation; *eGFR* estimated glomerular filtration rate; *IQR i*nterquartile range; *CCI* Charlson Co-morbidity Index*; BMI* body mass index. *Definitions: history of major vascular event* - previous stroke, myocardial infarction, amputation due to peripheral vascular disease, or heart failure; *polypharmacy* ≥ 5 medications; *hyperpolypharmacy* ≥ 10 medications.

Table 2. International comparison of number of medications						
	Univariable linear regression			Multivariable linear regression*		
Country (n)	**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
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 - -0.39	-1.20	0.014	-2.15 - -0.24
*Adjusted for age, ethnicity, sex, educational attainment, co-morbidities (hypertension, diabetes, cerebrovascular disease, myocardial infarction, cardiac arrhythmias, lung disease and psychiatric disorders), eGFR and primary renal diagnosis.						

Table 3. International comparison of hyperpolypharmacy						
	Univariable logistic regression			Multivariable logistic regression*		
Country (n)	**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
*Adjusted for age, ethnicity, sex, educational attainment, co-morbidities (hypertension, diabetes, cerebrovascular disease, myocardial infarction, cardiac arrhythmias, lung disease and psychiatric disorders), eGFR and primary renal diagnosis. *Definitions: hyperpolypharmacy* ≥ 10 medications.						

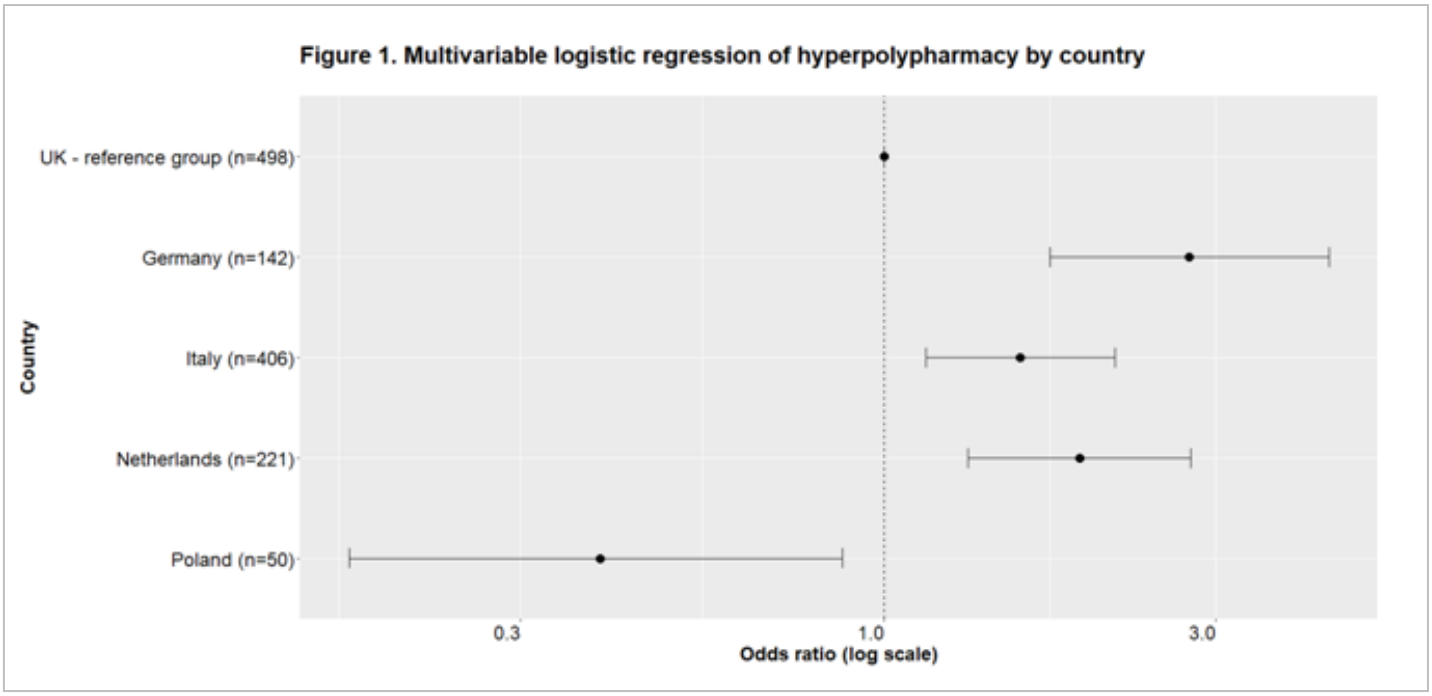
Figure 1. Multivariable logistic regression of hyperpolypharmacy by country
UK - reference group (n=498)
Germany (n=142)
Italy (n=406)
Netherlands (n=221)
Poland (n=50)
Country
0.3
1.0
3.0
Odds ratio (log scale)

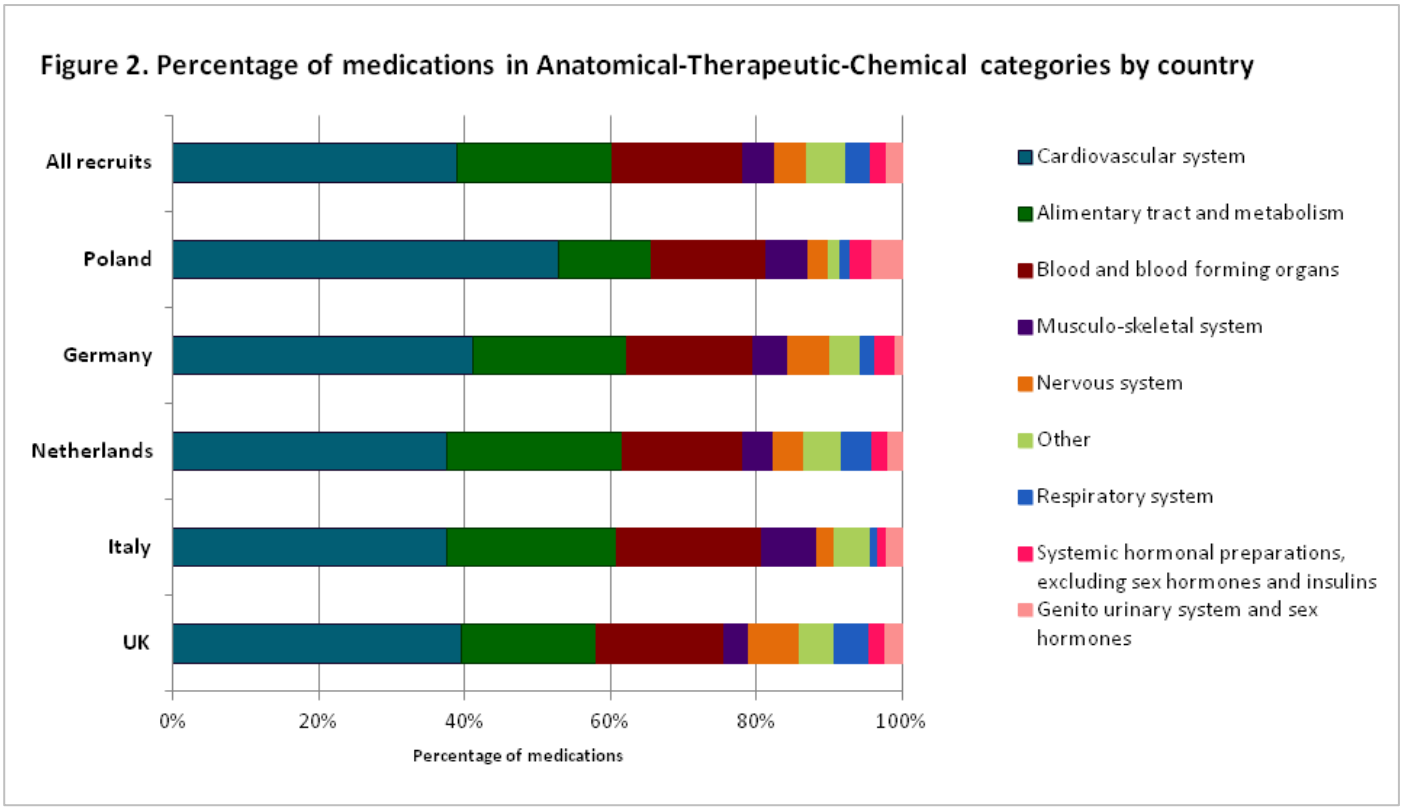
Figure 2. Percentage of medications in Anatomical-Therapeutic-Chemical categories by country
All recruits
Poland
Germany
Netherlands
Italy
UK
0%
20%
40%
60%
80%
100%
Percentage of medications
Cardiovascular system
Alimentary tract and metabolism
Blood and blood forming organs
Musculo-skeletal system
Nervous system
Other
Respiratory system
Systemic hormonal preparations, excluding sex hormones and insulins
Genito urinary system and sex hormones

Table 4. The top 20 prescribed medications

Medication* **(n, %)**	**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
Beta blockers	107 (75.4)	176 (43.4)	134 (60.6)	35 (70.0)	216 (43.4)	668 (50.7)	<0.001
Proton pump inhibitors	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
Erythropoiesis stimulating agents	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
Alpha 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

**In addition, 124 people had a medication recorded which was classified as 'unknown'.*

Abbreviations: ACE inhibitors Angiotensin-converting enzyme inhibitors

Table 5. Prescribing quality indicators						
PQI n, (%)*	**Germany**	**Italy**	**Netherlands**	**Poland**	**UK**	**P value**
Potentially appropriate prescribing						
1. Patients with hypertension that are prescribed antihypertensives unless undesirable because of low diastolic blood pressure (<70 mm Hg)	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) that 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 with an elevated calcium level (>2.54 mmol/L) that 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 with a low calcium level (<2.10 mmol/L) that 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 that 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) that 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) that are prescribed an ESA	11 (21.2)	29 (21.6)	10 (9.7)	0	16 (10.4)	0.006
8. Patients that are prescribed an NSAID	2 (1.4)	0	1 (0.5)	0	11 (2.2)	0.010
9. Patients with diabetes that are prescribed metformin	0	1 (0.5)	4 (4.7)	1 (5.9)	8 (4.1)	0.022
10. Patients that are prescribed a combination of NSAIDs, RAS inhibitors and diuretics	2 (1.4)	0	1 (0.5)	0	5 (1.0)	0.137

*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.

Abbreviations: RAS – Renin-angiotensin system; *NSAID* Non steroidal anti-inflammatory drugs; *ESA* Erythropoiesis stimulating agents.

Figure 3. Prescribing quality indicators