A Systematically Collated Library of Prescribing Safety Indicators for People With Chronic Kidney Disease

Fiona Smith ( fiona.smith@doctors.org.uk )
North Bristol NHS Trust. University of Bristol.  https://orcid.org/0000-0001-7009-5031

Samantha Hayward
North Bristol NHS Trust. University of Bristol. UK Renal Registry.

Barnaby Hole
North Bristol NHS Trust. University of Bristol. UK Renal Registry.

George Kimpton
North Bristol NHS Trust. University of Bristol.

Christine Sluman
North Bristol NHS Trust.

Penny Whiting
University of Bristol. Applied Research Collaboration West

Fergus Caskey
North Bristol NHS Trust. University of Bristol.

Research article

Keywords: chronic kidney disease, CKD primary care population, outpatient setting prescribing safety, potentially inappropriate prescribing, prescribing safety indicators

DOI: https://doi.org/10.21203/rs.3.rs-41396/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

Background

People with chronic kidney disease (CKD) have high levels of co-morbidity and polypharmacy placing them at increased risk of prescribing-related harm. Tools for assessing prescribing safety in the general population using prescribing safety indicators (PSIs) have been established. However, people with CKD pose different prescribing challenges to people without kidney disease. Therefore, PSIs designed for use in the general population may not include all PSIs relevant to a CKD population.

The aim of this study was to systematically collate a library of PSIs relevant to people with CKD.

Methods

A systematic literature search identified papers reporting PSIs. CKD-specific PSIs were extracted and categorised by Anatomical Therapeutic Chemical (ATC) classification codes. Duplicate PSIs were removed to create a final list of CKD-specific PSIs.

Results

9,852 papers were identified by the systematic literature search, of which 511 proceeded to full text screening and 196 papers were identified as reporting PSIs. Following categorisation by ATC code and duplicate removal, 841 unique PSIs formed the final set of CKD-specific PSIs. The five ATC drug classes containing the largest proportion of CKD-specific PSIs were: Cardiovascular system (26%); Nervous system (13.4%); Blood and blood forming organs (12.4%); Alimentary and metabolism (12%); and Anti-infectives for systemic use (11.3%).

Conclusion

CKD-specific PSIs could be used alone or alongside general PSIs to assess the safety and quality of prescribing within a CKD population.

Background

People with chronic kidney disease (CKD) stand to benefit from careful prescribing of medications to prevent disease progression, manage comorbidities and relieve symptoms. [1] Meanwhile they are at increased risk of prescribing-related harm as a result of incorrect dosing considering altered drug clearance or direct nephrotoxicity. Adverse drug events are common in the CKD population and interventions to optimise prescribing have shown promise. [2] However, current approaches for optimising prescribing in this patient group are limited. [1]–[3]

Prescribing safety indicators (PSIs) distinguish prescribing events that put a patient at risk of harm. [4] PSI libraries for different patient populations have been collated through expert consensus, review of
clinical guidelines, and systematic searching of published literature. One systematic approach to the identification of PSIs conducted by Spencer et al in 2012 collated 56 indicators relevant to the general primary care population. [4] Whilst such a library is applicable to a CKD population, prescribing events of unique importance to people with kidney disease may be inadequately represented when considering pharmacotherapy for this group in isolation.

The aim of this study was to use a systematic search of the published literature to produce a library of PSIs specific to outpatient prescribing for people with CKD. This library could be used alone or alongside general PSIs to assess the safety and quality of prescribing within a CKD population.

Methods

A protocol was written to collate PSIs with specific relevance to people with CKD from the published literature (PROSPERO CRD42018109113). A systematic literature search to identify papers reporting PSIs was followed by extraction of CKD-specific PSIs. Pre-defined criteria classified PSIs as CKD-specific if they were of exclusive relevance to adults (age \( \geq 18 \)) with CKD and referring to medications prescribed within the outpatient setting.

Systematic literature search

A sensitive search strategy was designed to capture all potentially relevant papers reporting PSIs. To capture PSIs from the general primary care population the search strategy used by Spencer et al. was updated to include literature published from 2012 until 2018.[4] Search terms related to three stems – clinical setting, prescribing and tool type. To reflect hospital-based delivery of advanced CKD care, a supplementary CKD-specific search was developed with revision of the clinical setting stem terms, and the addition of a stem for kidney-disease. CKD terms were chosen to capture all stages of CKD, including end-stage. This supplementary search was run from inception (1946 to 2018). Both searches were conducted in October 2018 using Medline, Embase, Pubmed, Web of Science and CINAHL. A full list of terms used in each search is available in Appendix 1 (Box 3–4; Table 2–3).

Results from the two searches were combined and duplicate results were removed. Titles and abstracts were independently screened by two of the authors (FS, GK). An inclusive approach was used, excluding only those records from non-human or paediatric work (age < 18 years) or those referring solely to prescribing in an inpatient setting. There was no selection for CKD-specific PSIs made at this stage. If a record was recommended for inclusion by one of the reviewers it progressed to full text screening.

PSI extraction and selection of CKD-specific PSIs

Full-text screening was conducted by FS. Publications reporting one or more PSI in the main text, abstract or tables of the publication were included. The details of all PSIs from the literature search were entered into a data extraction form by FS. The elements extracted are detailed in Box 1.
A two-stage process followed to identify CKD-specific PSIs. Firstly, an automated filter was developed to shortlist possible CKD-specific PSIs. The automated CKD-specific filter terms (Appendix 2: Box 5) were adapted and iteratively developed from the original search terms, through repeated comparisons between the automated process and manual review of a random sample of PSIs from the master list (BH). The final filter terms were selected once no manually included PSI was excluded by the automated process in a random sample of 100 PSIs. The output from this automated process was then divided between three authors (FS, BH, SH) who manually selected CKD-specific PSIs.

**Classification and categorisation of PSIs**

Each CKD-specific PSI was labelled with the Anatomical Therapeutic Chemical (ATC) codes of each medication listed in the prescribing statement. [5] Duplicate PSIs and those not meeting pre-specified criteria were manually removed. In order to be classified as duplicates, two PSIs had to replicate the following information: identical drug, identical level of kidney function and identical prescribing rule. If a PSI was found to contain multiple rules, with other PSIs duplicating individual rules, then only the PSI containing the most information was maintained. Following duplicate removal, it was possible to identify the proportion of PSIs defined by their ATC classification and subsequently further divide PSIs in relation to the most frequent medication classes.

**Results**

In total 9,852 papers were identified by the two searches (CKD search 5,223; general population search 4,629). Following title and abstract screening 511 papers proceeded to full text screening (CKD search = 425; general population search = 86). Of the 511 articles, 315 did not contain any PSIs. PSI extraction was performed from the remaining 196 articles, with a total of 3,464 PSIs identified. [Figure 1] The full list of
3,464 PSIs was filtered to identify 1,775 of potential relevance to people with CKD. These PSIs were reviewed by three of the authors (FS, SH, BH) with 1,231 confirmed as CKD-specific.

The CKD-specific PSIs were classified by ATC code. 371 duplicates were identified and excluded. A further 19 were deemed not to fit the pre-specified criteria after discussion between reviewing authors (6 related to inpatient prescribing and 13 were deemed not to be CKD-specific). The remaining 841 unique PSIs became the final set of CKD-specific PSIs. Examples of PSIs are demonstrated in Box 2 [full list is in Appendix 3].

CKD-specific PSIs
PSIs were found to take multiple different forms, including those that referred to single drugs (Box 2: Items 1–3), to drug classes (Item 4), and to lists of agents with particular pharmacokinetic or dynamic properties (Item 5). Some PSIs specified thresholds or ranges of kidney function (Item 1). Others referred to kidney disease non-specifically (Items 4 & 5). A variety of methods for estimating kidney function were cited, including CrCl and eGFR/GFR, though no PSI specified a method for eGFR/GFR calculation. Table 1 shows the final number of PSIs per ATC drug classification. The five ATC drug classes containing the largest proportion of CKD-specific PSIs were: Cardiovascular system (26%); Nervous system (13.4%); Blood and blood forming organs (12.4%); Alimentary and metabolism (12%); and Anti-infectives for systemic use (11.3%). Additionally, Table 1 shows the most frequent medication classes referred to in each ATC category.
Table 1
Final set of CKD-specific PSIs by ATC drug class and further subdivision to most frequently featured medication classes in each ATC category

| ATC drug class                  | CKD-specific PSIs (n, %) | Top 5 medications in the ATC drug class                                                                 | Number of CKD-specific PSIs (n, % of total 841 PSIs) |
|---------------------------------|--------------------------|----------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| Cardiovascular system           | 219 (26.0)               | Agents acting on the renin-angiotensin system                                                            | 81 (9.6)                                            |
|                                 |                          | Diuretics                                                                                               | 48 (5.7)                                            |
|                                 |                          | Lipid modifying agents                                                                                   | 44 (5.2)                                            |
|                                 |                          | Beta blocking agents                                                                                     | 14 (1.7)                                            |
|                                 |                          | Digitalis glycosides                                                                                     | 11 (1.3)                                            |
| Nervous system                  | 113 (13.4)               | Antidepressants                                                                                          | 36 (4.3)                                            |
|                                 |                          | Antiepileptics                                                                                          | 21 (2.5)                                            |
|                                 |                          | Opioids                                                                                                 | 19 (2.3)                                            |
|                                 |                          | Antipsychotics                                                                                          | 7 (0.8)                                             |
|                                 |                          | Anxiolytics                                                                                             | 6 (0.7)                                             |
| Blood and blood forming organs  | 104 (12.4)               | Direct factor Xa inhibitors                                                                             | 36 (4.3)                                            |
|                                 |                          | Direct thrombin inhibitors                                                                              | 31 (3.7)                                            |
|                                 |                          | Antithrombotic agents                                                                                    | 9 (1.1)                                             |
|                                 |                          | Heparins                                                                                               | 7 (0.8)                                             |
|                                 |                          | Other antianaemic preparations                                                                           | 7 (0.8)                                             |
| Alimentary and metabolism       | 101 (12.0)               | Sulfonylureas                                                                                           | 19 (2.3)                                            |
|                                 |                          | DPP-4 inhibitors                                                                                        | 12 (1.4)                                            |
|                                 |                          | GLP-1 analogues                                                                                         | 12 (1.4)                                            |
|                                 |                          | Biguanides                                                                                             | 10 (1.2)                                            |
|                                 |                          | SGLT2 inhibitors                                                                                        | 7 (0.8)                                             |
| Anti-infectives for systemic use| 95 (11.3)                | Other antibacterials                                                                                    | 16 (1.9)                                            |
|                                 |                          | Nucleoside and nucleotide reverse transcriptase inhibitors                                              | 13 (1.5)                                            |
|                                 |                          | Beta-lactam antibacterials, penicillins                                                                  | 7 (0.8)                                             |
| ATC drug class                                      | CKD-specific PSIs (n, %) | Top 5 medications in the ATC drug class                                      | Number of CKD-specific PSIs (n, % of total 841 PSIs) |
|---------------------------------------------------|--------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------|
|                                                   |                          | Other beta-lactam antibacterials                                            | 7 (0.8)                                             |
|                                                   |                          | Macrolides                                                                  | 7 (0.8)                                             |
| Antineoplastic and immunomodulating agents        | 81 (9.6)                 | Other anti-neoplastic agents                                                | 27 (3.2)                                            |
|                                                   |                          | Alkylating agents                                                           | 16 (1.9)                                            |
|                                                   |                          | Anti-metabolites                                                            | 14 (1.7)                                            |
|                                                   |                          | Cytotoxic antibiotics and related substances                                 | 9 (1.1)                                             |
|                                                   |                          | Plant alkaloids and other natural products                                   | 6 (0.7)                                             |
| Musculo-skeletal system                           | 68 (8.1)                 | Anti-inflammatory and anti-rheumatic products, non-steroids                  | 28 (3.3)                                            |
|                                                   |                          | Bisphosphonates                                                             | 21 (2.5)                                            |
|                                                   |                          | Antigout preparations                                                       | 14 (1.7)                                            |
|                                                   |                          | Other centrally acting agents                                               | 2 (0.2)                                             |
|                                                   |                          | Other drugs affecting bone structure and mineralisation                      | 2 (0.2)                                             |
| Antiparasitic products, insecticides and repellents| 15 (1.8)                 | Aminoquinolones                                                             | 7 (0.8)                                             |
|                                                   |                          | Biguanides                                                                  | 6 (0.7)                                             |
|                                                   |                          | Agents against leishmaniasis and trypanosomias                              | 1 (0.1)                                             |
| Genito-urinary and sex hormones                   | 14 (1.7)                 | Drugs for urinary frequency/incontinence                                      | 8 (1.0)                                             |
|                                                   |                          | Drugs for erectile dysfunction                                               | 4 (0.5)                                             |
|                                                   |                          | Other urologicals                                                            | 1 (0.1)                                             |
|                                                   |                          | Sex hormones                                                                | 1 (0.1)                                             |
| Miscellaneous                                     | 14 (1.7)                 | Miscellaneous                                                                | 14 (1.7)                                            |
| Respiratory system                                | 6 (0.7)                  | Antihistamines for systemic use                                              | 5 (0.6)                                             |
|                                                   |                          | Anticholinergics                                                            | 1 (0.1)                                             |
| ATC drug class                      | CKD-specific PSIs (n, %) | Top 5 medications in the ATC drug class | Number of CKD-specific PSIs (n, % of total 841 PSIs) |
|-----------------------------------|--------------------------|----------------------------------------|-----------------------------------------------------|
| Various                           | 6 (0.7)                  | Drugs for treatment of hyperkalemia and hyperphosphatemia | 5 (0.6)                                             |
|                                   |                          | Other renal system diagnostic radiopharmaceuticals | 1 (0.1)                                             |
| Systemic hormonal preparations    | 4 (0.5)                  | Parathyroid hormones and analogues      | 2 (0.2)                                             |
|                                   |                          | Glucocorticoids                         | 1 (0.1)                                             |
|                                   |                          | Somatostatin and analogues              | 1 (0.1)                                             |
| Sensory organs                    | 1 (0.1)                  | Antiglaucoma preparations and miotics  | 1 (0.1)                                             |
| Dermatologicals                   | 0                        | -                                      | 0                                                   |

**CKD-specific PSIs**
1. Metformin - not recommended in patients with eGFR <45 and contraindicated in patients with eGFR <30 [ATC code: A10BA]
2. Rivaroxaban - Caution in case of CrCl 15–30 ml/min - dose reduction to 15 mg/day [ATC code: B01AF]
3. Lithium - measure calcium and serum lithium levels at start of treatment; 3 monthly renal function; 6 monthly thyroid function, calcium, weight and serum lithium levels [ATC code: N05AN]
4. Drugs requiring dosage adjustment in patients with impaired kidney function and aged 65 and over: Opioids [ATC code: N02A]
5. Medicines that may accumulate and require renal function monitoring: ARBs [ATC code: C09CA]

**General PSIs [not included in CKD-specific PSI library]**
1. Prescribing a traditional oral NSAID or low-dose aspirin in patients with a history of peptic ulceration without co-prescription of gastro-protection
2. Significant drug-disease interactions in patients aged 65 and over: Congestive heart failure (systolic dysfunction) - first generation calcium channel blockers eg verapamil, diltiazem
3. Management - Associated adverse therapeutic outcome in patients aged over 65: Use of theophylline without drug level monitoring at least every 6 months - theophylline toxicity
4. Prescribing indicators for patients aged >65: Patient with OA pain interfering with daily activities has been trialled on paracetamol (acetaminophen) 2–4 g/day
5. Methotrexate prescriptions should state ‘weekly’
Box 2: PSI examples [GFR: glomerular filtration rate; CrCl: creatinine clearance, NSAID: non-steroidal anti-inflammatory drug]

[a ie what patients SHOULD be taking]

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Discussion

CKD, defined by persistently abnormal glomerular filtration rate (GFR), and/or other evidence of damage or structural abnormality, has a global prevalence approximating 13%. [6][7] The pharmacokinetic and pharmacodynamic effects of CKD and kidney replacement therapy increase the risk of drug-related harm for the CKD population, and inappropriate prescriptions are more frequent as kidney function declines. [1], [8] Direct nephrotoxicity (e.g. from aminoglycosides and non-steroidal anti-inflammatory drugs) and idiosyncratic reactions (e.g. with metformin) add further complications. [9] The need for prescribers to consider GFR is recognised in international guidance for the management of CKD. [7] Nevertheless, reported rates of GFR-inappropriate prescriptions (according to the Summary of Product Characteristics - SPCs) range between 9 and 81% for people with CKD. [1], [2]

Prescribing for people with CKD is further complicated by comorbid illness. CKD is both a cause and consequence of comorbidity, most notably microvascular, macrovascular and cardiac disease. Since CKD increases with age, acquisition of concurrent illness is frequent. People living with CKD may thus be recommended medications to manage causal conditions, coincidental co-morbidity, and complications of low-renal function – alongside agents preventative against cardiovascular disease and end stage kidney disease. Unsurprisingly, this can lead to the prescription of numerous drugs. [1], [10] The prevalence of polypharmacy – defined as the regular use of five or more medications per day – was almost 80% in a cohort of over 5000 German people with CKD. [11] Indeed, for older people with advanced CKD, the prevalence of polypharmacy is even higher (91%) and hyperpolypharmacy – defined as 10 or more medications – is common (43%). [12] Polypharmacy increases the likelihood of inappropriate prescriptions and is associated with hospitalisation and death in people with CKD. [1], [13]

Clinical support systems such as computerised alerts, manual-review and eGFR-prompts have been used to reduce inappropriate prescribing in CKD populations, and can be effective in both inpatient and outpatient settings. [2] Nevertheless, these may over-estimate prescribing errors, especially of drugs for which the benefit/risk ratio may remain high even in the setting of very low GFR – for example those acting on the renin-angiotensin axis. [7] As such, to what degree ‘inappropriate’ prescriptions for people with CKD reflect calculated benefit/risk decisions versus injudicious prescribing is unclear. Expert review of individual prescriptions are likely to be difficult and costly to apply to large populations of individuals with CKD. [2] Meanwhile, simple interventions such as eGFR prompts appear ineffective and prescribing guidance can be unclear – for example, multiple eGFR calculations are used in SPCs. [2] Better
approaches for identification of potential drug harm and targeting of interventions may exist. Harmonisation of product characteristics and GFR estimates with prescribing practice norms may help. Successful approaches to develop pharmacotherapy screening tools applicable to the elderly have been developed using systematically generated libraries of PSIs. [14], [15] This approach has advantages over guideline review alone, which although possible in defined patient groups (such as people with CKD) may fail to capture all important prescribing events. [16] The work reported here aimed to assimilate PSIs specific to people with CKD as a first-step to the generation of a prescribing-safety tool for application in this group.

A sensitive search strategy was developed, with manual extraction of 841 CKD-specific PSIs. PSIs relating to all but one ATC drug class (dermatologicals) were found, with the majority relating to cardiovascular, nervous and haematological prescribing. Drugs acting on the renin-angiotensin system, non-vitamin K oral anticoagulants, anti-diabetic medications, lipid-modifying agents, and antidepressants were particularly frequent. However, CKD-specific PSIs relating to a wide range of agents were found and the frequency of PSIs relating to particular agents should not necessarily be seen as indicative of the clinical importance of individual agents, and may simply reflect the frequency with which these agents are used, and/or general familiarity with their CKD-specific risks. [1] This library of CKD-specific PSIs is a first step towards generation of prescribing safety assessments and interventions for populations with CKD.

The main strength of this work is the use of an inclusive systematic approach before focussing on CKD-specific PSIs. This process reduces the risk of missing CKD-specific PSIs that are reported in the general literature. The main weakness is an output that requires further work before application in research or clinical settings. Removal of near-duplicate PSIs, selection of uniform dosing and GFR-estimation criteria for individual agents, appraisal in light of present evidence and supplementation with PSIs for prescribing events that did not appear is needed. Such a process will involve expert appraisal and formal approaches to consensus development beyond the scope of this work. This work focused on outpatient prescribing for individuals with CKD, so some agents well-known to present risks in kidney disease are not captured (e.g. intravenous aminoglycosides). Inpatient prescribing differs substantially from ambulatory settings, with acute illness, acute kidney injury and daily prescription review. A separate approach for collating and categorising PSIs relevant to this setting is required. A further limitation in this study is that a single author completed full text screening of articles recommended for inclusion thus posing a risk of PSIs being missed from the literature.

**Conclusion**

This study has collated a library of safety indicators relating to outpatient prescribing for people with CKD – a unique group with a higher proportion of prescribing challenges. The library generated could be used alone or alongside general PSIs to generate approaches for assessment of prescribing safety and quality for individuals and populations with CKD.

**Abbreviations**
CKD  
chronic kidney disease  
PSIs  
prescribing safety indicators  
ATC  
Anatomical Therapeutic Chemical  
GFR  
glomerular filtration rate  
SPC  
Summary of Product Characteristics

Declarations

*Ethics approval and consent to participate:* Not applicable to this research article.

*Consent for publication:* Not applicable to this research article.

*Availability of data and materials:* All data generated during this study are included in this published article (and its supplementary information files). This data can be used to assess the safety and quality of prescribing within a cohort of people with chronic kidney disease.

*Competing interests:* The authors declare that they have no competing interests.

*Funding statement:* This work was supported by Applied Research Collaboration West.

*Authors’ contributions:*  
All authors contributed to the overall development of this piece of research. FS made a substantial contribution to the conception and design of the work. She developed the systematic literature search strategy; extracted and analysed the data; and maintained the raw data set. She drafted and revised the work in preparation for publication. She is the corresponding first author. SH analysed the data, and drafted and revised the work. BH developed the automated filter which was inputted to identify CKD-specific PSIs. He also drafted and revised the work. GK assisted with initial data extraction. CS assisted with identification of CKD-specific PSIs. PW aided with development of the systematic literature search strategy. FC worked as overall supervisor for the project. All authors contributed to the final approval of the work to be published.

*Acknowledgements:* We would like to acknowledge the team at Applied Research Collaboration West who assisted with development of the systematic literature search used for this paper and thank them for their funding support.

References
[1] S. M. Laville 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., vol. 84, no. 12, pp. 2811–2823, Dec. 2018, doi: 10.1111/bcp.13738.

[2] W. H. Tesfaye, R. L. Castelino, B. C. Wimmer, and S. T. R. Zaidi, “Inappropriate prescribing in chronic kidney disease: A systematic review of prevalence, associated clinical outcomes and impact of interventions.,” Int. J. Clin. Pract., vol. 71, no. 7, Jul. 2017, doi: 10.1111/ijcp.12960.

[3] S. D. S. Fraser et al., “The burden of comorbidity in people with chronic kidney disease stage 3: a cohort study,” BMC Nephrol., vol. 16, p. 193, Dec. 2015, doi: 10.1186/s12882-015-0189-z.

[4] R. Spencer, B. Bell, A. J. Avery, G. Gookey, and S. M. Campbell, “Identification of an updated set of prescribing–safety indicators for GPs.,” Br. J. Gen. Pract., vol. 64, no. 621, pp. e181-90, Apr. 2014, doi: 10.3399/bjgp14X677806.

[5] “WHO Collaborating Centre for Drug Statistics Methodology. Structure and principles. (Last updated: 2018-02-15),” 2018. [Online]. Available: https://www.whocc.no/atc/structure_and_principles/. [Accessed: 29-Jan-2020].

[6] N. R. Hill et al., “Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis.,” PLoS One, vol. 11, no. 7, p. e0158765, 2016, doi: 10.1371/journal.pone.0158765.

[7] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, “KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease,” Off. J. Int. Soc. Nephrol. Kidney Int. Suppl., vol. 3, no. 1, pp. 1–150, 2013.

[8] T. D. Nolin, “A Synopsis of Clinical Pharmacokinetic Alterations in Advanced CKD,” Semin. Dial., vol. 28, no. 4, pp. 325–329, 2015, doi: 10.1111/sdi.12374.

[9] U. Bilge, G. Sahin, I. Unluoglu, M. Ipek, M. Durdu, and A. Keskin, “Inappropriate use of nonsteroidal anti-inflammatory drugs and other drugs in chronic kidney disease patients without renal replacement therapy.,” Ren. Fail., vol. 35, no. 6, pp. 906–910, Jul. 2013, doi: 10.3109/0886022X.2013.801272.

[10] I. M. Schmidt 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., vol. 12, no. 5, pp. 663–672, May 2019, doi: 10.1093/ckj/sfz046.

[11] N. Masnoon, S. Shakib, L. Kalisch-Ellett, and G. E. Caughey, “What is polypharmacy? A systematic review of definitions,” BMC Geriatr., vol. 17, no. 1, p. 230, Oct. 2017, doi: 10.1186/s12877-017-0621-2.

[12] S Hayward, B Hole, R Denholm, P Duncan, JE Morris, SDS Fraser, RA Payne, P Roderick, NC Chesnaye, C Wanner, C Drechsler, M Postorino, G Porto, M Szymczak, M Evans, FW Dekker, KJ Jager, FJ Caskey. International prescribing patterns and polypharmacy in older people with advanced chronic kidney disease: results from the EQUAL Study. Nephrology, Dialysis and Transplantation (in press 2020)
[13] A. Secora, G. C. Alexander, S. H. Ballew, J. Coresh, and M. E. Grams, “Kidney Function, Polypharmacy, and Potentially Inappropriate Medication Use in a Community-Based Cohort of Older Adults.,” *Drugs Aging*, vol. 35, no. 8, pp. 735–750, Aug. 2018, doi: 10.1007/s40266-018-0563-1.

[14] A. G. Society, “American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.,” *J. Am. Geriatr. Soc.*, vol. 63, no. 11, pp. 2227–2246, Nov. 2015, doi: 10.1111/jgs.13702.

[15] P. Gallagher and D. O'Mahony, “STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria.,” *Age Ageing*, vol. 37, no. 6, pp. 673–679, Nov. 2008, doi: 10.1093/ageing/afn197.

[16] K. P. J. Smits et al., “Development and initial validation of prescribing quality indicators for patients with chronic kidney disease.,” *Nephrol. Dial. Transplant*, vol. 31, no. 11, pp. 1876–1886, Nov. 2016, doi: 10.1093/ndt/gfv420.

**Figures**
Figure 1

Systematic review results and PSI extraction

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- APPENDIX3841CKDspecificPSIs.pdf
- Appendices1and2.pdf