Potentially inappropriate prescribing in people with chronic kidney disease: cross-sectional analysis of a large population cohort

Accepted Manuscript

British Journal of General Practice

Potentially inappropriate prescribing in people with chronic kidney disease: cross-sectional analysis of a large population cohort

MacRae, Clare; Mercer, Stewart; Guthrie, Bruce

DOI: https://doi.org/10.3399/BJGP.2020.0871

To access the most recent version of this article, please click the DOI URL in the line above.

Received 21 November 2020
Revised 18 November 2020
Accepted 23 November 2020

Potentially inappropriate prescribing in people with chronic kidney disease: cross-sectional analysis of a large population cohort

Authors

Dr Clare MacRae MBChB, BSc, MRCGP, DFSRH, MAcadMEd, DCH, GP and Clinical Teacher, University of Edinburgh, Edinburgh, UK.

Professor Stewart Mercer MBChB, MSc, PhD, MRCGP, FRCGP, FRSPE, FFPHM, Professor of Primary Care and Multimorbidity, University of Edinburgh, Edinburgh, UK.

Professor Bruce Guthrie, BA, MSc, PhD, MRCP, FRCGP, Professor of primary care medicine, University of Edinburgh, Edinburgh, UK.

Corresponding author

Professor Bruce Guthrie, BA, MSc, PhD, MRCP, FRCGP, Professor of primary care medicine, University of Edinburgh, Edinburgh, UK.

Word count

2568

Keywords

Chronic kidney disease (CKD), renal impairment, potentially inappropriate prescribing, epidemiology, general practice

Abstract

Background: Many drugs should be avoided or require dose-adjustment in chronic kidney disease (CKD). Previous estimates of potentially inappropriate prescribing rates have been based on data on a limited number of drugs and mainly in secondary care settings.

Aim: To determine the prevalence of contraindicated and potentially inappropriate primary care prescribing in a complete population of people with known CKD.

Design and Setting: Cross-sectional study of prescribing patterns in a complete geographical population of people with CKD defined using laboratory data.

Method: Drugs were organised by British National Formulary advice. Contraindicated (CI) drugs: “avoid”. Potentially high risk (PHR) drugs: “avoid if possible”. Dose inappropriate (DI) drugs: dose exceeded recommended maximums. CKD was defined as eGFR≤60 ml/min/1.73m2 for >three months.

Results: 28,489 people with CKD were included in analysis, of whom 70.0% had CKD 3a, 22.4% CKD 3b, 5.9% CKD 4, and 1.5% CKD 5. 3.9% (95%CI 3.7-4.1) of people with CKD stages 3a-5 were prescribed one or more CI drug, 24.3% (95%CI 23.8-24.8) PHR drug, and 15.2% (95% CI 14.8-15.62) DI drug. CI drugs differed in prevalence by CKD stage, and were most commonly

Conclusion: Potentially inappropriate prescribing is common at all stages of CKD. Development and evaluation of interventions to improve prescribing safety in this high-risk population are needed.

Word count: 260

How this fits in

General practitioners (GPs) are at the frontline in identification and management of chronic kidney disease (CKD), and in the United Kingdom (UK) almost all long-term prescribing and medication reviews occur in the primary care setting making this a key target for interventions to improve prescribing safety in CKD. Several studies refer to potentially inappropriate prescribing in secondary care, while little is known about the prevalence of potentially inappropriate prescribing in CKD for a wide range of drugs in primary care.

Our study finds that potentially inappropriate prescribing in primary care is common at all stages of CKD and existing recommendations for prescribing in renal impairment are often non-specific and relatively unhelpful to clinicians. There is a need to improve understanding of the benefit-harm balance of prescribing in renal impairment and to develop interventions to improve prescribing safety.

Introduction

Chronic kidney disease (CKD) is as an abnormality in kidney structure or function, present for more than three months, defined by cause, glomerular filtration rate (GFR), and albuminuria category.[1, 2] The Global Burden of Disease study estimates worldwide prevalence of all stage age-standardised CKD at 8.7%,[3] making it a significant public health problem. CKD encompasses a heterogeneous group of disorders[4] of varying severity and rate of progression.[5] While the proportion of individuals with CKD who develop end stage renal dysfunction (ESRD) and require renal replacement therapy (RRT) or transplantation is small,[6] CKD is an important risk factor for cardiovascular disease (CVD) and all-cause mortality,[6, 7] and significantly drives healthcare costs.[1, 7-9] Good clinical care, including the adjustment of medications according to renal function, and avoiding medications that increase the risk of adverse outcomes, can slow progression and reduce morbidity.[1, 10] General practitioners (GPs) are at the frontline in early identification and management of CKD.[9] In the United Kingdom (UK), for example, almost all long-term prescribing and medication reviews occur in the primary care setting,[11, 12] making primary care a key target for interventions to improve prescribing safety in CKD.

CKD prevalence rises sharply with increasing age, and comorbidity and polypharmacy are therefore common in people with CKD.[4, 13] Clinical management is often complicated by multiple physicians being simultaneously involved in patient care.[14] Adverse drug reactions (ADRs) are unintended, harmful events attributed to the use of medicines.[15] Individuals with CKD are at

terms of morbidity, mortality and additional loss of kidney function with accelerated progression to ESRD.[17]

Most studies to date have focused on potentially inappropriate prescribing in all adults with CKD in secondary care with fewer studies examining community prescribing of a wide range of drugs.[18-21] The aim of this study was to examine the prevalence of potentially inappropriate prescribing in a population cohort of people with CKD.

Methods

The overall design was a retrospective, population-based analysis of all residents of two Scottish health boards aged ≥18 years with laboratory confirmed CKD. Health care in Scotland is provided free at the point of use by the National Health Service, with required registration with a single general practice which provides primary medical care, acts as a gatekeeper to secondary care, and prescribes virtually all community-dispensed medicines including those recommended by specialists (who only prescribe highly specialist drugs such as cancer chemotherapy and some biologics). Linkage between datasets was performed at a patient level using the Community Health Index (CHI) number, the National Health Service Scotland unique patient identifier. Linked data used in analysis included demography, laboratory data to define CKD, and community dispensed prescriptions. Every dispensed prescription was provided with 100% allocation of prescriptions to individuals. Data were provided by the University of Dundee Health Informatics Centre (HIC).[22] HIC Standard Operational Procedures (SOPs) have been approved

analysis was performed using anonymised data held in the ISO270001 and NHS Scotland accredited HIC Safe Haven.

CKD status and stage were determined using laboratory calculated estimated glomerular filtration rate (eGFR) values calculated by the hospital laboratory carrying out the creatinine measurement using isotope dilution mass spectrometry standardised creatinine values, traceable to NIST SRM 914 reference material, using the abbreviated the Modification of Diet in Renal Disease (MDRD) equation.[23] A cross-sectional cohort of permanently registered residents with CKD was defined on 31st March 2018, using the most recent eGFR values. CKD was defined as most recent eGFR <60ml/min/1.73m^2 and a previous eGFR <60 more than 84 days previously and no intervening eGFR values ≥60. CKD stage was defined as Stage 3a ('mild') for eGFR 45-59 ml/min/1.73m^2, CKD Stage 3b ('moderate') for eGFR 30-44 ml/min/1.73m^2, CKD Stage 4 ('severe') for eGFR 15-29 ml/min/1.73m^2, and CKD Stage 5 ('end stage renal disease' (ESRD)) for eGFR <15 ml/min/1.73m^2. Categorisation into mild, moderate, severe, and end-stage groupings was done to allow application of BNF prescribing standards, because the majority of British National Formulary (BNF – the standard UK prescribing reference used by clinicians) "renal impairment" warnings referred to these terms rather than eGFR.

All drugs with a renal impairment warning in the BNF 78 September 2019 – March 2020[24] were identified, and warnings were categorised into three groups (Figure 1). Contra-indicated (CI) drugs were those where the warning explicitly stated to "avoid" the drug at particular levels of renal function. Potentially high risk (PHR) drugs were those where the warning stated "avoid if

We analysed the prevalence of current prescription of all included drugs in people with CKD 3a or worse within the total population calculated according to National Records of Scotland 2018 mid-year population estimates,[25] stratified by CKD status, and 95 % confidence intervals (CI) were calculated. Statistical analyses were undertaken using SPSS version version 22 (IBM Corp., Armonk, N.Y., USA).

Results

There were 28,489 individuals, aged 18 years and older, with known CKD based in most recent laboratory evaluation and registered with a GP in the region on 31st March 2018 (Table 1), representing 4.4% of the total population of 644,080 people.[25] Between 1st January 2006 and 31st March 2018, 488,268 adults aged ≥18 years had one or more eGFR values reported. 27,931 of those had only one eGFR and so could not be evaluated, leaving 460,337 people had two or more eGFR values and could be evaluated for CKD. Of this group, 84% of people aged 65-74 years old, and 90% of ≥75 years were evaluable. 19,977 (70.0% of all people with CKD) had CKD 3a, 6383 (22.4%) CKD 3b, 1693 (5.9%) CKD 4, and 436 (1.5%) CKD 5. Mean age was similar throughout CKD cohorts, ranging from 72.25 years (SD 14.4) in stage 5 to 79.38 years (10.9) in stage 3b. Female sex was more common in all CKD stages except CKD5. People with CKD across all stages were most commonly in the 2nd and 3rd quintile for Scottish Index of Multiple Deprivation (SIMD) (1 being least and 5 being most deprived) (Table 1).

There were 670 drugs with a 'renal impairment' warning in the BNF, of which 226 (33.8%) were

recommendations for 43 (6.4%) PHR drugs, and dose reduction recommendations for 35 (5.3%) DI drugs. The majority of CI advice was specific to CKD stages 4 and 5.

3.9% (95%CI 3.7-4.1) of people with CKD stages 3a-5 were prescribed one or more CI drug, 24.3% (95%CI 23.8-24.8) a PHR drug, and 15.2% (95% CI 14.8-15.62) a DI drug (Table 2). CI drugs were least commonly prescribed throughout all CKD stages and were least common in CKD stage 3a associated with fewer CI restrictions being placed on drug use in this stage of CKD (Figure 2). In absolute terms, PHR drug prescriptions were most common in all stages of CKD, followed by DI drug prescriptions, with prescriptions in both groups most common in CKD stage 3a.

Prevalence of contra-indicated (CI) prescribing by CKD stage

Prevalence rates for CI prescribing differed substantially depending on CKD stage. Prescribing rates in all CKD stages was low (3.9%, 95%CI 3.7-4.1). The lowest prevalence in stage 3a (0.5%, 95%CI 0.4–0.6), and the most common prescription in this group was oxytetracycline (0.2%, 95%CI 0.1–0.3) (Table 2, Figure 3, Table S7). Prescribing rates rose to 4.5% (95%CI 4.0–5.0) in stage 3b, with nitrofurantoin prescribing accounting for 3.7% (95%CI 3.2–4.2) of this figure (Table 2). The majority of BNF CI recommendations related to CKD stage 4 or worse (Figure 1) and people with CKD stage 4 had the highest prevalence of CI prescribing (36.0%, 95%CI 33.7–38.2). The most commonly prescribed CI drugs in CKD stages 4 and 5 were aspirin (19.1%, 95%CI 17.2–21.0) and 13.1% (95%CI 9.9-16.2) respectively (Table 2, Figure 3, Table S7). Prescribing rates were similar between sexes, most common in the 85 and over age group, and similar throughout all SIMD quintiles (Table 3).

Prevalence of potentially high risk (PHR) drugs

All stages of CKD had similar prevalence rates for PHR prescribing. Lowest prevalence was seen in CKD stage 4 (19.4%, 95%CI 17.6-21.3), and highest in CKD stage 3a (25.1%, 95%CI 24.5–25.7) (Table 2 and Figure 3). Co-codamol was the most commonly prescribed PHR drug in CKD stages 3a (11.3%, 95%CI 10.9-11.8), 3b (9.6%, 95%CI 8.8–10.4), and 4 (6.9%, 95%CI 5.6–8.2). Oxycodone was the most frequently prescribed PHR drug in CKD stage 5 (6.2%, 95%CI 4.5–7.9). The most commonly prescribed non-steroidal anti-inflammatory drug (NSAID) was naproxen with prescribing prevalence of 3.49% (95%CI 3.24–3.75) in stage 3a, 1.3% (95%CI 1.0–1.6) in stage

were most common in the 45 – 64 age group and were similar throughout all SIMD quintiles (Table 3).

Prevalence of dose known to be inappropriate (DI) drugs

Excessive dosing was least common in CKD stage 3a at 13.4% (95%CI 12.9–13.8) and most common in CKD stage 4 (26.4%, 95%CI 24.3–28.6) (Table 2, Figure 3, Table S9). Ramipril was the most commonly prescribed DI drug in stage 3a (13.4%, 95%CI 12.9–13.8), and 3b (7.9%, 95%CI 7.2–8.6). Simvastatin was the most frequently prescribed in CKD stage 4 (10.0%, 95%CI 8.5–11.4) and was not seen in earlier stages of CKD due to dose instructions being specific to CKD stage 4 and worse. Ranitidine was the most commonly prescribed DI drug in CKD stage 5 (6.6%, 95%CI 4.3–9.0). Prescribing rates were significantly higher in males compared with females, most common in the 65 – 74 age group, and similar throughout all SIMD quintiles (Table 3).

Discussion

Summary

In this large primary care-based study, potentially inappropriate prescribing was widespread at all stages of CKD. CI drugs represented the least common potentially inappropriate drug prescribing to people with all stages of CKD, and there was substantial variation in prescribing rates by CKD stage with most of this prescribing being seen in CKD stages 4 and 5. PHR drugs were the most commonly prescribed drugs throughout all stages of CKD showing much less variation between CKD stages. DI drugs were commonly seen in all stages of CKD, showing highest prescribing prevalence in CKD stage 4.

Strengths and limitations

Strengths of the analysis include systematic analysis of primary care potentially inappropriate prescribing for people with known CKD within a population cohort with ascertainment of CKD using laboratory data and measurement of dispensed prescribing. Limitations include the absence of clinical details such as coexisting comorbidities, and physical parameters such as blood pressure readings and urinalysis findings, which would have allowed better evaluation of the appropriateness of prescribing and address the difficult decisions faced by GPs when weighing up risks and benefits of prescribing. Inclusion of prescribing site and individual physician prescribing practices would provide relevant information to support the development of interventions to improve prescribing safety, however data for these areas were not available

taken using routine data is difficult. For the DI drugs, we therefore only report prescribing where we can be certain that the dose was inappropriate based on the strength dispensed. In addition to this, the prevalence of CKD is based on the laboratory information available to the clinician, and so there will be people within the population who remain undiagnosed. Therefore, prescribing rates in this study are conservative and the prevalence of potentially inappropriate prescribing will be worse than reported. However, very high proportions of older people had at least two eGFR values, so we do not expect under ascertainment to be too serious given that CKD prevalence is most common in this group. Finally, reflecting ambiguity in the evidence, renal impairment warnings in the BNF are frequently non-specific meaning we could not reliably measure the appropriateness of prescribing for the majority of the drugs with any renal warning. However, this finding that clinicians are commonly expected to use clinical judgement in the face of minimal evidence is an important one in its own right.

Comparison with existing literature

Several studies refer to potentially inappropriate prescribing in secondary care,[26-28] while few studies examine primary care prescribing. A recent primary care based study by Wood et al reported prescribing outside recommendations in 2.0 – 39.9% in a sample of eight drugs.[18] Angiotensin-converting enzyme (ACEi) inhibitors, simvastatin, thiazides, NSAIDS and metformin were commonly prescribed, drugs that were also commonly seen in our study population. Byrne et al examined nine high-risk prescribing combinations, demonstrating significant variation in potentially inappropriate prescribing practice between individual GP prescribers and found that

and NSAIDS. One serum creatinine measurement identified the CKD cohort and the study found prevalence of inappropriate prescribing of 42.5% and 58.1% for CKD stages 3 and 4 respectively. The higher prevalence likely reflects the use of a one-year look-back period for prescribing compared to 84 days in this study. A North American primary care study looked at the number and proportion of adults with CKD stages 3 and 4 who were prescribed at least one NSAID or another relatively contraindicated medication.[20] This study examined prescribing over a 2-year period and found that 46.6% were prescribed a relatively contra-indicated drug, and 34.0% an NSAID during the study period. Hull et al performed a cross-sectional survey of 12,011 patients with CKD in a population in England with CKD examining NSAID prescribing rates by ethnicity, and found that prescribing rates decreased with increasing CKD stage in people of all ethnicities,[29] a finding that was also found in our study. Prescribing of specific drugs were seen in our study and across other similar observational studies, indicating the strength of this evidence base and the applicability of our study findings to clinical decision making and health policy. Study design amongst existing literature is highly heterogenous making it difficult make identify direct comparison and clear conclusions, however it is clear that potentially inappropriate prescribing in the primary care setting is a significant problem.

Implications for research and/or practice

Many drugs were prescribed outside BNF renal prescribing recommendations, but some of this prescribing is recommended in other clinical guidance. Notably, the BNF recommends avoiding aspirin in severe renal impairment (for the purposes of this study interpreted as CKD stages 4

decisions to weigh up the risk to benefit ratio in individuals.[30] High-risk prescribing can be appropriate if the benefits outweigh the potential harm of omitting a drug,[31] so the correct indicator for these prescribing rates is unlikely to be zero. Additional pharmacoepidemiology studies in the context of CKD are needed to provide a stronger evidence base.

Research is needed to better understand processes associated with prescribing and improve existing mechanisms for making prescribing safer, including acute and repeat prescribing practices, and exploring analgesic use in palliative care. Evaluation of prescribing practices between GP practices would also provide useful information on which to base a complex intervention. A UK primary-care based study showed that a combination of professional education, clinician prompts, and financial incentives significantly reduced the rate of high-risk prescribing of NSAIDS and antiplatelet medications, supporting use of complex interventions to reduce high-risk prescribing.[31] At present, Scottish GP electronic medical records prescribing systems do not trigger point-of-care alerts to clinicians based on the presence renal impairment. Alerts based on renal function might improve prescribing safety, and this is an important area for evaluation in future research. Decisions to stop medications can be patient dependent, with some patients preferring to accept the risks of harm from certain medicines particularly those that improved quality of life in the context of informed discussions where patients are exerting choice over treatment. Increasing the time available for GPs and pharmacists to engage with medication reviews might be related to improving the use of medications for example reducing potentially inappropriate prescribing without a clear indication.[32]

impairment, and to develop and evaluate interventions to improve prescribing safety in this population.

Table 1. Study and population characteristics

		Any CKD N=28,489 (4.4% of 644,080)	CKD 3a (eGFR 45-59) N=19,977	CKD 3b (eGFR 30-44) N=6,383	CKD 4 (eGFR 15-29) N=1,693	CKD 5 (eGFR <15) N=436
Age						
	Mean, years (SD)	74.79 (12.34)	73.09 (12.2)	79.38 (10.9)	78.18 (13.0)	72.25 (14.4)
	18 – 24	21 (0.1)	14 (0.1)	5 (0.1)	2 (0.1)	0 (0)
	25 – 34	152 (0.5)	115 (0.6)	18 (0.3)	10 (0.6)	9 (2.1)
	35 – 44	369 (1.3)	284 (1.4)	38 (0.6)	33 (1.9)	14 (3.2)
	45 – 54	1367 (4.8)	1157 (5.8)	125 (2.0)	51 (3.0)	34 (7.8)
	55 – 64	3285 (11.5)	2755 (13.8)	348 (5.5)	126 (7.4)	56 (12.8)
	65 – 74	7509 (26.4)	5859 (29.3)	1240 (19.4)	308 (18.2)	102 (23.4)
	75 – 84	9478 (33.3)	6386 (32.0)	2399 (37.6)	558 (33.0)	135 (31.0)
	85 and over	6308 (22.1)	3407 (17.1)	2210 (34.6)	605 (35.7)	86 (19.7)
Sex						
	Female, number (%)	17768 (62.3)	12487 (62.5)	4085 (64.0)	985 (58.2)	211 (48.4)

Socioeconomic Status by SIMD					
Quintile, number (%)					
1	4981 (17.5)	3456 (17.3)	1125 (17.6)	313 (18.5)	87 (20.0)
2	6288 (22.0)	4312 (21.6)	1442 (22.6)	418 (24.7)	116 (26.6)
3	6025 (21.1)	4197 (21.0)	1398 (21.9)	341 (20.1)	89 (20.4)
4	5453 (19.1)	3806 (19.1)	1215 (19.0)	348 (20.6)	84 (19.3)
5	4996 (17.5)	3659 (18.3)	1047 (16.4)	237 (14.0)	52 (11.9)

Figure 1. Drug inclusion chart

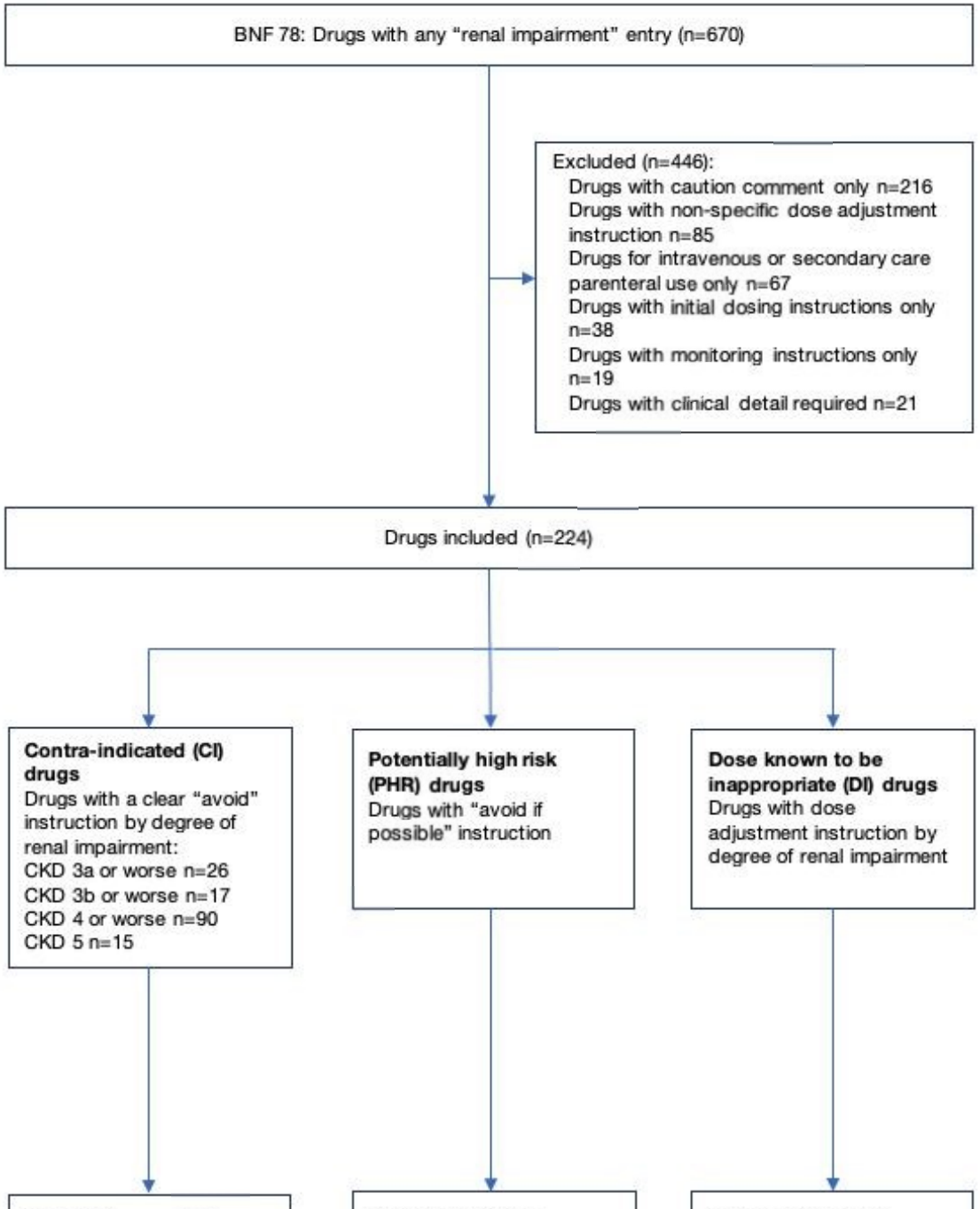


Table 2. Prevalence of potentially inappropriate prescribing by CKD stage

Drug Group	% of people in receipt of a prescription (95% confidence interval)				
	All CKD	**CKD3a**	**CKD3b**	**CKD4**	**CKD5**
	N=28,489	**N=19,977**	**N=6,383**	**N=1,693**	**N=436**
CI drugs					
One or more drug	3.9 (3.7-4.1)	0.5 (0.4–0.6)	4.5 (4.0–5.0)	36.0 (33.7–38.2)	25.5 (21.5–29.5)
Most common drugs		Oxytetracycline 0.2 (0.1–0.3)	Nitrofurantoin 3.7 (3.2–4.2)	Aspirin 19.1 (17.2–21.0)	Aspirin 13.1 (9.9-16.2)
		Acetazolamide 0.06 (0.02-0.10)	Leflunomide 2.3 (1.1–3.6)	Thiazide 5.7 (4.6–6.9)	Lercanidipine 2.3 (0.9–3.7)
		Calcitriol 0.05 (0.02–0.08)	Oxytetracycline 1.1 (0.3–1.9)	Spironolactone 4.4 (3.4–5.4)	Metformin 1.8 (0.6–3.1)
					Ropinirole 1.8 (0.0-3.1)
PHR drugs					
One or more drug	24.3 (23.8-24.8)	25.1 (24.5–25.7)	23.6 (22.5-24.6)	19.4 (17.6-21.3)	21.1 (17.3-24.9)
Most common drugs		Co-codamol 11.3 (10.9-11.8)	Co-codamol 9.6 (8.8–10.4)	Co-codamol 6.9 (5.6–8.2)	Oxycodone 6.2 (4.5–7.9)
		Tramadol 6.2 (5.9–6.6)	Tramadol 6.2 (5.6–6.8)	Oxycodone 6.2 (4.5–7.9)	Morphine 6.0 (3.2–8.7)
		Naproxen 3.49 (3.24–3.75)	Oxycodone 4.8 (4.0–5.6)	Tramadol 5.3 (4.2–6.4)	Co-codamol 5.3 (3.1–7.5)

DI drugs					
One or more drug	15.2 (14.8-15.62)	13.4 (12.9–13.8)	17.7 (16.4–18.3)	26.4 (24.3–28.6)	17.9 (14.4–21.8)
Most common drugs		Ramipril 8.3 (7.9–8.6)	Ramipril 7.9 (7.2–8.6)	Simvastatin 10.0 (8.5–11.4)	Ranitidine 6.6 (4.3–9.0)
		Atorvastatin 2.8 (2.6–3.1)	Ranitidine 4.4 (3.9-4.9)	Ranitidine 5.1 (4.0–6.1)	Simvastatin 6.4 (4.1–8.7)
		Sitagliptin 1.5 (1.4–1.7)	Atorvastatin 2.9 (2.5–3.3)	Ramipril 4.3 (3.3–5.3)	Ramipril 4.3 (3.3–5.3)

Table 3. Prevalence of potentially inappropriate prescribing by sex, age, and socioeconomic status

			% of people in receipt of a prescription (95% confidence interval)		
			CI drugs	PHR drugs	DI drugs
Sex					
	Female	N=17768	4.4 (3.0 – 5.8)	5.7 (4.3 – 7.1)	14.3 (13.0 – 15.5)
	Male	N=10721	4.2 (2.4 – 6.0)	4.6 (2.8 – 6.4)	22.1 (20.7 – 23.6)
Age					
	18 – 24	N=21	0	0	0

25 – 34	N=152	3.3 (0 – 18.7)	12.5 (0 – 26.5)	7.2 (0 – 22.0)
35 – 44	N=369	2.4 (0 – 12.4)	8.4 (0 – 17.8)	11.9 (5.8 – 18.1)
45 – 54	N=1376	2.8 (0 – 8.0)	9.4 (4.6 – 14.2)	15.4 (10.9 – 19.9)
55 – 64	N=3285	2.5 (0 – 5.9)	9.8 (6.8 – 12.4)	17.3 (14.4 – 20.1)
65 – 74	N=7509	3.6 (1.4– 5.8)	7.0 (4.9 - 9.1)	20.3 (18.6 – 22.2)
75 – 84	N=9478	4.4 (2.5 – 6.3)	3.8 (1.9 – 5.7)	19.3 (17.7 – 20.9)
85 and over	N=6308	6.4 (4.1 – 8.7)	1.9 (0 – 4.4)	11.4 (9.2 – 13.6)
Socioeconomic status by SIMD Quintile				
1	N=4981	4.6 (1.9 – 7.2)	5.4 (2.8 – 8.1)	18.9 (16.7 – 21.1)
2	N=6288	4.3 (1.9 – 6.7)	5.1 (2.8 – 7.4)	18.3 (16.3 – 20.3)
3	N=6025	4.5 (2.1 – 6.9)	5.9 (3.5 – 8.3)	17.1 (15.0 – 19.2)
4	N=5453	4.8 (2.3 – 7.3)	4.9 (2.4 – 7.4)	16.3 (14.1 – 18.6)
5	N=4995	3.2 (0.5 – 5.8)	5.0 (2.4 – 7.7)	15.7 (13.4 – 10.1)

Figure 2. Prevalence of potentially inappropriate prescribing by drug group and CKD stage

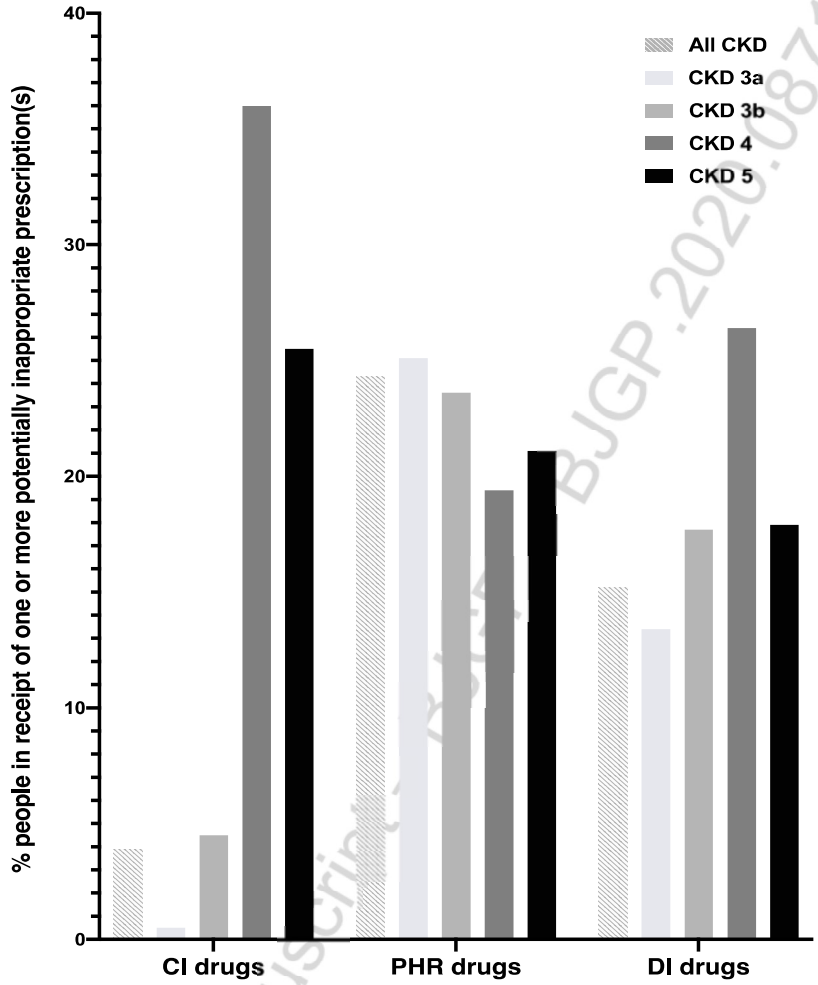
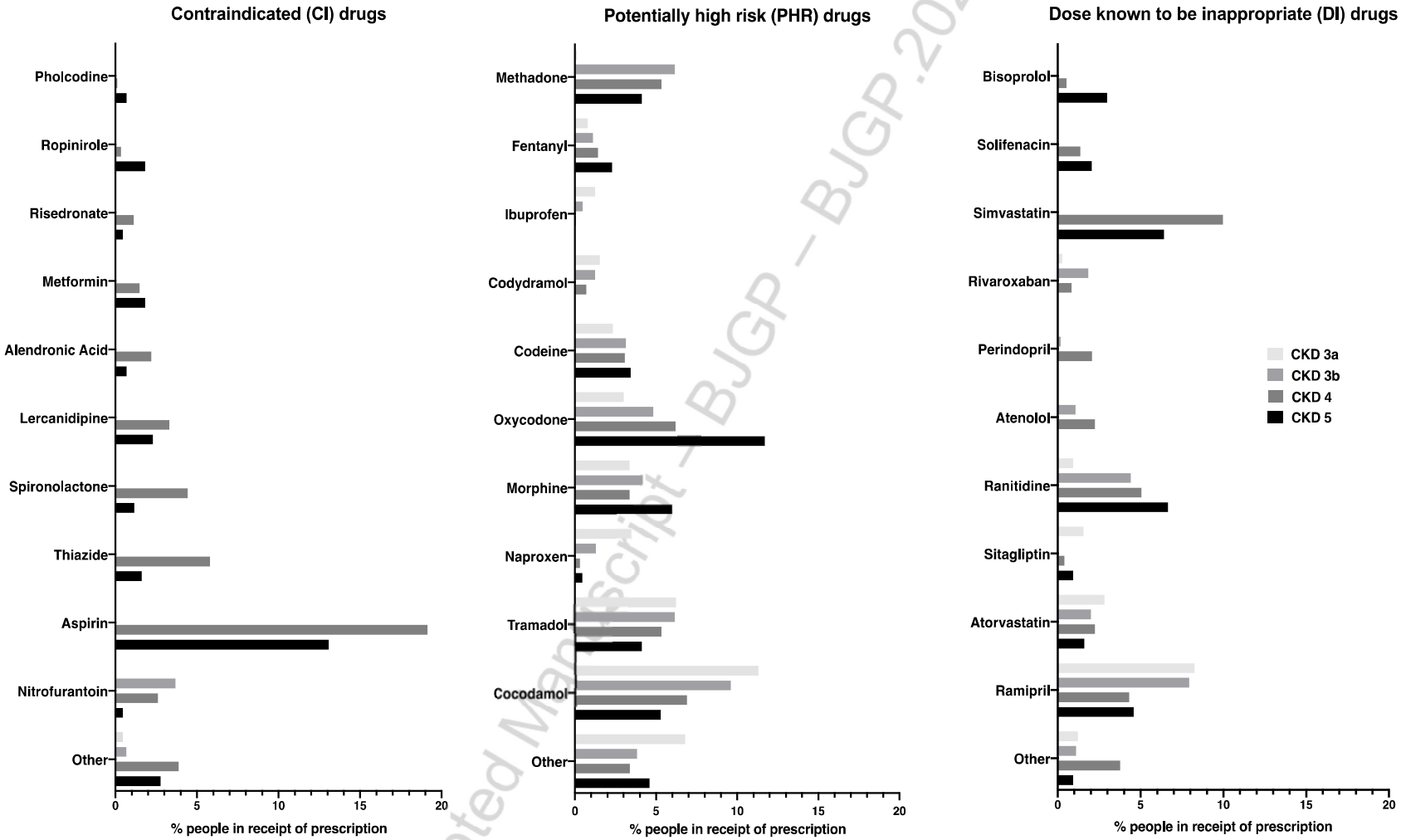


Figure 3. Prevalence of potentially inappropriate prescribing by **drugs within drug group**



References

1. Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International Supplements 2013;3:1–150. Available at https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf (accessed 18 September 2020).
2. Manski-Nankervis J-AE, Thuraisingam S, Sluggett JK, et al. Prescribing for people with type 2 diabetes and renal impairment in Australian general practice: A national cross sectional study. Prim Care Diabetes. 2019;13(2):113-21. DOI: 10.1016/j.pcd.2018.09.001.
3. Bikbov B, Purcell CA, Levey AS, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395(10225):709-33. DOI: 10.1016/S0140-6736(20)30045-3.
4. Levey AS, Coresh J. Chronic kidney disease. Lancet. 2012;379(9811):165-80. DOI: 10.1016/S0140-6736(11)60178-5.
5. Brück K, Jager KJ, Zoccali C, et al. Different rates of progression and mortality in patients with chronic kidney disease at outpatient nephrology clinics across Europe. Kidney Int. 2018;93(6):1432-41. DOI: 10.1016/j.kint.2018.01.008.
6. Webster AC, Nagler EV, Morton RL, Masson P. Chronic Kidney Disease. Lancet. 2017;389(10075):1238-52. DOI: 10.1016/S0140-6736(16)32064-5.
7. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. Lancet. 2013;382(9888): 260-72. DOI: 10.1016/S0140-6736(13)60687-X.
8. Zhang L, Wang F, Wang L, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. Lancet. 2012;379(9818):815-22. DOI: 10.1016/S0140-6736(12)60033-6.
9. Allen AS, Forman JP, Orav EJ, et al. Primary care management of chronic kidney disease. Journal of general internal medicine. 2011;26(4):386. DOI: 10.1007/s11606-010-1523-6.
10. Doody HK, Peterson GM, Watson D, Castelino RL. Retrospective evaluation of potentially inappropriate prescribing in hospitalized patients with renal impairment. Curr Med Res Opin. 2015;31(3):525-35. DOI: 10.1185/03007995.2015.1010036.
11. Wallis KA, Elley CR, Moyes S, Kerse N. Safer Prescribing and Care for the Elderly

13. Levey AS, Inker LA, Coresh J. Chronic kidney disease in older people.(Report). JAMA. 2015;314(6):557. DOI: 10.1001/jama.2015.6753.
14. Quintana-Bárcena P, Lord A, Lizotte A, et al. Development and validation of criteria for classifying severity of drug-related problems in chronic kidney disease: A community pharmacy perspective. Am J Health Syst Pharm. 2015;72(21): 1876. DOI: 10.2146/ajhp140765.
15. Coleman JJ, Pontefract SK. Adverse drug reactions. Clin Med (Lond). 2016;16(5):481, 481. DOI: 10.7861/clinmedicine.16-5-481.
16. Parameswaran Nair N, Chalmers L, Connolly M, et al. Prediction of Hospitalization due to Adverse Drug Reactions in Elderly Community-Dwelling Patients (The PADR-EC Score). PLoS One. 2016;11(10). DOI: 10.1371/journal.pone.0165757.
17. Paola R, Giuseppe R, Richard G, et al. Chronic kidney disease. Nat Rev Dis Primers. 2017;3(1). DOI: 10.1038/nrdp.2017.88.
18. Wood S, Petty D, Glidewell L, Raynor DT. Application of prescribing recommendations in older people with reduced kidney function: a cross-sectional study in general practice. BJGP, 2018;68(670):e378. DOI: 10.3399/bjgp18X695993.
19. Byrne CJ, Cahir C, Curran C, Bennett K. High-risk prescribing in an Irish primary care population: trends and variation. Br J Clin Pharmacol. 2017;83(12):2821-30. DOI: 10.1111/bcp.13373.
20. Guirguis-Blake J, Keppel GA, Holmes J, et al. Prescription of high-risk medications among patients with chronic kidney disease: a cross-sectional study from the Washington, Wyoming, Alaska, Montana and Idaho region Practice and Research Network. J Fam Pract. 2018;35(5):589. DOI: 10.1093/fampra/cmy001.
21. Schmidt-Mende K, Wettermark B, Andersen M, et al. Prevalence of renally inappropriate medicines in older people with renal impairment — A cross-sectional register-based study in a large primary care population. Basic Clin Pharmacol Toxicol. 2019;124(3):256-65. DOI: 10.1111/bcpt.13127.
22. Health Informatics Centre (HIC) - Trusted Research Centre. University of Dundee Trusted Research Environment. Available at https://wwwdundeeacuk/hic/ (accessed 6 June 2020)

25. National Records of Scotland. Mid-Year Population Estimates 2018. Available at https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/population/population-estimates/mid-year-population-estimates/mid-2018 (accessed 29 August 2020).
26. Tesfaye WH, Peterson GM, Castelino RL, et al. Medication-Related Factors and Hospital Readmission in Older Adults with Chronic Kidney Disease. J Clin Med. 2019;8(3). DOI: 10.3390/jcm8030395.
27. Sommer J, Seeling A, Rupprecht H. Adverse Drug Events in Patients with Chronic Kidney Disease Associated with Multiple Drug Interactions and Polypharmacy. Drugs Aging. 2020;37(5):359. DOI: 10.1007/s40266-020-00747-0.
28. Jones SA, Bhandari S. The prevalence of potentially inappropriate medication prescribing in elderly patients with chronic kidney disease. Postgrad Med J. 2013;89(1051):247. DOI: 10.1136/postgradmedj-2012-130889.
29. Hull S, Mathur R, Dreyer G, Yaqoob MM. Evaluating ethnic differences in the prescription of NSAIDs for chronic kidney disease: a cross-sectional survey of patients in general practice. Br J Gen Pract. 2014;64(624):e448-e55. DOI: 10.3399/bjgp14x680557.
30. Schmidt-Mende K, Hasselström J, Wettermark B, Andersen M, Bastholm-Rahmner P. General practitioners' and nurses' views on medication reviews and potentially inappropriate medicines in elderly patients - a qualitative study of reports by educating pharmacists. Scand J Prim Health Care. 2018;36(3): 329-41. DOI: 10.1080/02813432.2018.1487458.
31. Dreischulte T, Donnan P, Grant A, et al. Safer Prescribing — A Trial of Education, Informatics, and Financial Incentives. NEJM, 2016;374(11):1053-64. DOI: 10.1056/NEJMsa1508955
32. Duncan P, Cabral C, McCahon D, Guthrie B, Ridd MJ. Efficiency versus thoroughness in medication review. BJGP. 2018;69(680),e190-198. DOI: https://doi.org/10.3399/bjgp19X701321.