Clinical Kidney Journal, 2023, vol. 16, no. 10, 1580–1586

https://doi.org/10.1093/ckj/sfad079
Advance Access Publication Date: 10 April 2023
CKJ Review

CKJ REVIEW

Pharmacokinetic relevance of glomerular hyperfiltration for drug dosing

Carmine Zoccali [1,2,3], Francesca Mallamaci[4] and Raffaele De Caterina[5,6]

[1]Renal Research Institute, New York, NY, USA, [2]Institute of Molecular Biology and Genetics (Biogem), Ariano Irpino, Italy, [3]Associazione Ipertensione Nefrologia Trapianto Renal (IPNET), c/o Nefrologia, Grande Ospedale Metropolitano, Reggio Calabria, Italy, [4]Nefrologia and CNR Unit, Grande Ospedale Metropolitano Reggio Calabria, Italy, [5]Chair of Cardiology, University of Pisa, Pisa, Italy and [6]Cardiology Division, Pisa University Hospital, Pisa, Italy

Correspondence to: Carmine Zoccali; E-mail: carmine.zoccali@icloud.com

ABSTRACT

In chronic kidney disease (CKD) patients, hypofiltration may lead to the accumulation of drugs that are cleared mainly by the kidney and, vice versa, hyperfiltration may cause augmented renal excretion of the same drugs. In this review we mainly focus on the issue of whether hyperfiltration significantly impacts the renal clearance of drugs and whether the same alteration may demand an up-titration of the doses applied in clinical practice. About half of severely ill, septic patients and patients with burns show glomerular hyperfiltration and this may lead to enhanced removal of drugs such as hydrophilic antibiotics and a higher risk of antibiotic treatment failure. In general, hyperfiltering obese individuals show higher absolute drug clearances than non-obese control subjects, but this depends on the body size descriptor adopted to adjust for fat excess. Several mechanisms influence pharmacokinetics in type 2 diabetes, including renal hyperfiltration, reduced tubular reabsorption and augmented tubular excretion. However, no consistent pharmacokinetic alteration has been identified in hyperfiltering obese subjects and type 2 diabetics. Non-vitamin K antagonist oral anticoagulants (NOACs) have exhibited lower plasma concentrations in hyperfiltering patients in some studies in patients with atrial fibrillation, but a recent systematic review failed to document any excess risk for stroke and systemic embolism in these patients. Hyperfiltration is common among severely ill patients in intensive care units and drug levels should be measured whenever possible in these high-risk patients to prevent underdosing and treatment failure. Hyperfiltration is also common in patients with obesity or type 2 diabetes, but no consistent pharmacokinetic alteration has been described in these patients. No NOAC dose adjustment is indicated in patients with atrial fibrillation being treated with these drugs.

Keywords: GFR, glomerular hyperfiltration, intensive care, pharmacokinetics, sepsis

Chronic kidney disease (CKD) is a condition characterized by renal dysfunction, i.e. alterations in the glomerular filtration rate (GFR) ranging from hypofiltration to hyperfiltration and/or evidence of renal damage as manifested by proteinuria and/or alterations in the urine sediment and/or in renal imaging [1]. Hyperfiltration is an alteration that has received increased attention in nephrology [2]. A low nephron number at birth or a nephron loss due to renal diseases incites a compensatory GFR increase in existing nephrons (hyperfiltration at the single nephron level), which maintains the global GFR. On the other hand, in the early phases of obesity and diabetes there can be a global increase in the GFR attributable to a primary increase in

Received: 5.1.2023; *Editorial decision:* 23.3.2023

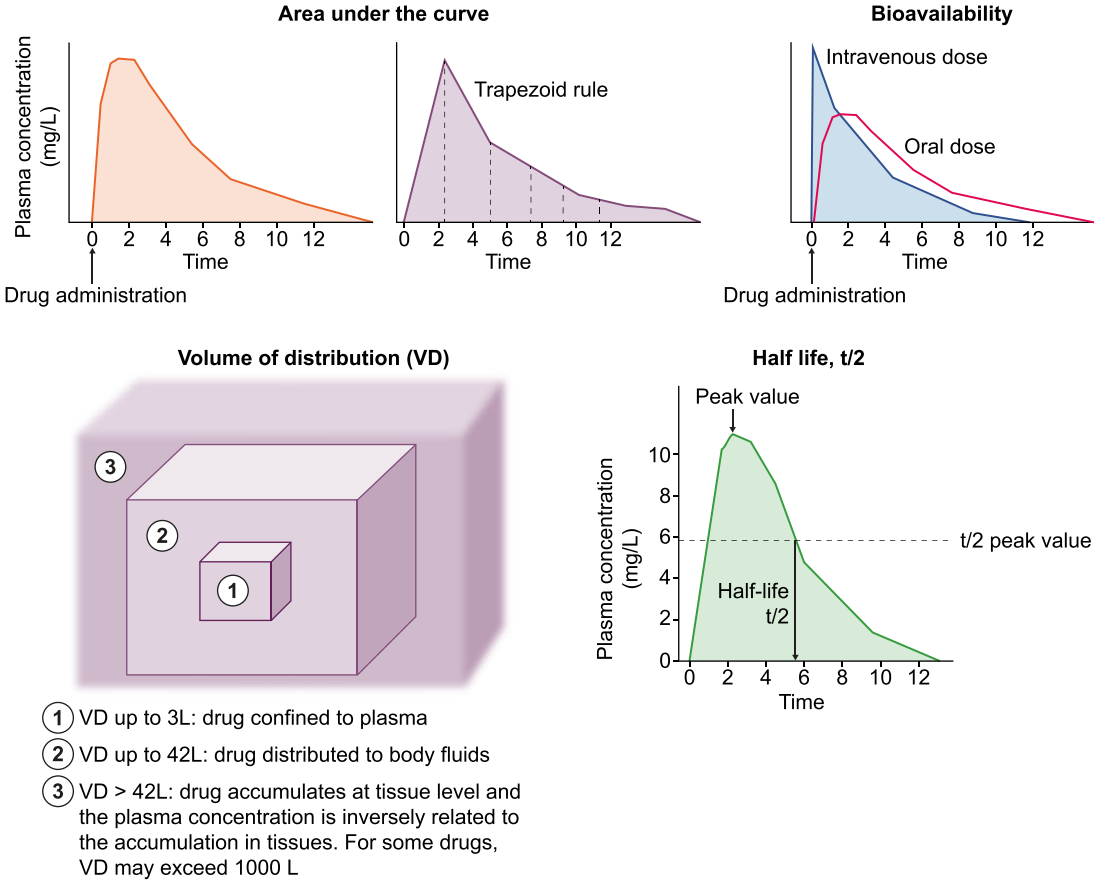

Figure 1: Standard pharmacokinetic parameters. The area under the curve, bioavailability, volume of distribution and half-life. The figure is commented into detail in the text.

the reabsorption of sodium and glucose in the proximal tubule [3]. In this review we use the term hyperfiltration in reference to 'global hyperfiltration'.

In CKD patients, hypofiltration may lead to the accumulation of drugs that are cleared mainly by the kidney and, vice versa, hyperfiltration may cause augmented renal excretion of drugs. Because the pharmacokinetic relevance of decreased GFR is well established and extensively covered in worldwide manuals like *UpToDate* [4] and *Goodman & Gilman's: The Pharmacological Basis of Therapeutics* [5], herein we will mainly focus on the issue of whether hyperfiltration impacts significantly on the renal clearance of drugs and whether the same alteration may demand an up-titration of the doses applied in clinical practice.

PHARMACOKINETICS STUDIES IN CKD PATIENTS

Clinical pharmacology is a relatively new science, and pharmacokinetic studies were started only in the 1960s [6]. Early on, renal function emerged as critical among factors impacting the plasma concentration of drugs mainly excreted via the renal route. Initial studies in patients with CKD built upon the linear relationship between the drug elimination rate constant and creatinine clearance. Based on this relationship, individual drug elimination parameters were estimated in these patients. Simple nomograms were constructed to estimate the elimination rate fraction, i.e. the elimination rate of a given drug as a fraction of its normal elimination rate constant [7]. These nomograms allowed the adaptation of drug dosage to the individual patient. More sophisticated approaches applying non-linear models are now used to refine the pharmacokinetics of drugs that undergo extensive tubular secretion, a pathophysiological context where non-linearity in drug handling is expected [7]. The application of pharmacokinetic studies in patients with renal dysfunction lagged for many years. Until 2007 the US Food and Drug Administration (FDA) did not demand pharmacokinetic studies in patients with kidney diseases, and for this reason, 43% of applications for the registration of new drugs made between 2002 and 2007 did not include pharmacokinetic studies in patients with CKD [8].

Comprehensive evaluations of the pharmacokinetic characteristics of drugs to adjust drug doses for CKD patients are now increasingly made by the industry. To assist proper applications of pharmacokinetic principles, the European Medicines Agency (EMA) and the FDA issued specific guidelines on the study of the pharmacokinetic profile of drugs in patients with CKD, including recommendations on how to assess the adequacy of the linear model for describing the elimination of drugs [7].

Pharmacokinetic studies estimate various parameters [9] (Fig. 1). The area under the curve (AUC) is the integral value of the concentration of a drug in plasma as a function of time. In practical terms, the drug concentration is measured at discrete time points and the trapezoidal rule estimates the AUC. This parameter is proportional to the decrease in total clearance (see below)

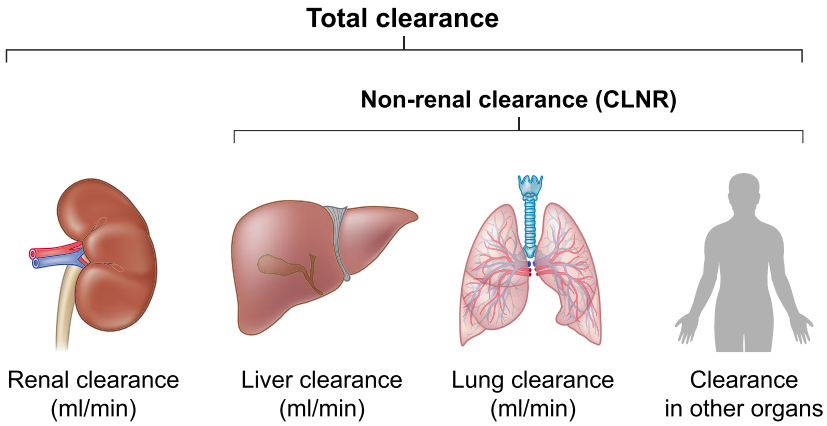

Figure 2: Total clearance and non-renal clearance (see main text).

and, as such, it defines the exposure to the drug after a single dose. In general, the greater the overall drug exposure for a certain dose, the greater the risk of adverse drug reactions. Absolute bioavailability is the fraction of the drug that attains systemic circulation, and it is estimated by comparing the AUC of a given dose (oral, subcutaneous, transrectal or transdermic) with the AUC attained after rapid intravenous injection. Practically, oral bioavailability depends on gastrointestinal absorption and first-pass elimination in the liver. For other routes of administration, it depends on specific characteristics of the same routes. The volume of distribution (*Vd*) is a theoretical rather than a real volume. It relates the plasma concentration of the drug to the total amount of the same drug in the whole organism. It is expressed as litres per kilogram of body weight and it mainly depends on the distribution and binding of the drug to extravascular tissues compared with plasma proteins. If the *Vd* is ≈3 L, the drug is largely confined to the plasma compartment (e.g. a drug with strong binding to albumin). If it is >42 L (the total body water of a person with a weight of 70 kg), the drug is also distributed to tissues. Some drugs have very high distribution volumes of ≥1000 L. In such cases, the drug is mainly sequestered at the tissue level and has a very low plasma concentration (Fig. 1). In other words, the higher the *Vd*, the lower the plasma concentration, and vice versa. The elimination $t_{½}$ is the time required for the plasma concentration to halve, and it is estimated by measuring the rate of decrease of a given drug in a series of at least three measurements after the peak value (Fig. 1). Total clearance (Fig. 2), the parameter that most closely describes drug elimination, is the blood volume cleared of a drug, measured in litres per hour or millilitres per minute. This parameter is the sum of the clearance of individual organs, the kidney and the liver. For some drugs, clearance may also occur via the lung [10] or the skin [11]. Clearance may be active (e.g. drug metabolism or active secretion) or passive, like glomerular filtration. As for renal clearance, this is generally measured by the rate of excretion of the drug in urine and the simultaneous changes in the drug plasma concentration. Non-renal clearance is the sum of the hepatic clearance and the clearance in other tissues and organs (Fig. 2).

A drug not supported by adequate pharmacokinetics analyses in CKD patients is prudently labelled by the drug company producing it as 'non-indicated' for these patients. This is the case for metformin, an antidiabetic medication that was not used in patients with a GFR <30 ml/min/1.73 m^2. However, based on new studies, current European Best Practice guidelines [12] indicate that metformin at a lower dosage can be safely administered to patients with severely impaired renal function. Similarly, some studies suggest that the novel-acting oral anticoagulant (NOAC) apixaban, which was previously contraindicated in severe CKD, can be used at a reduced dosage in stage 5G CKD patients on regular dialysis treatment, a possibility endorsed by the FDA [13]. However, a recent network meta-analysis showed that apixaban at low doses is ineffective for thromboembolism prevention in dialysis patients with atrial fibrillation [14] and new trials are needed for the benefit:risk profile of apixaban in these patients.

Pharmacokinetic studies in the CKD population are generally conducted in patients with decreased GFR, while there is almost inexistent information on the possible influence of high GFR (hyperfiltration) on drug dosage. In theory, hyperfiltration can increase the renal clearance of drugs handled by the kidney and may therefore demand an up-titration of the dosage of the same drugs. To deal with this issue, we preliminarily discuss the definition and the health implications of glomerular hyperfiltration to review then-available studies focusing on drug dosing in patients with hyperfiltration.

WHAT IS HYPERFILTRATION?

The GFR is the undisputed standard for measuring renal function. The global GFR can be seen as the sum of all single-nephron GFRs. Single-nephron GFR increases mainly as a compensatory mechanism in response to nephron loss and therefore single-nephron hyperfiltration is often associated with global hypofiltration rather than with hyperfiltration [3].

Glomerular hyperfiltration denotes a situation where the global GFR is above a given threshold [3]. Obesity, diabetes and hypertension are well-known risk factors for hyperfiltration [2]. However, there is no formally established threshold for defining this alteration. In a meta-analysis in 2015, where the GFR was estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, thresholds ranging from 91 to 175 ml/min/1.73 m^2 were adopted [15]. Most studies failed to include a reference or normal population and only a few considered the relationship between the GFR and the risk of

adverse clinical outcomes. In the same meta-analysis, the association between the GFR and the risk of cardiovascular death was U-shaped, with a risk increase at low and high eGFR levels [16]. In men, an eGFR of 120 ml/min/1.73 m^2 entailed an independent 70% risk increase for death compared with the reference GFR value (95 ml/min/1.73 m^2). Thus, at least from a prognostic point of view, a high eGFR (>120 ml/min/1.73 m^2) is unquestionably an unfavourable prognostic sign. Even though there is no gold standard threshold for the diagnosis of hyperfiltration, ≈40–50% of individuals in the general population and in high-risk cohorts had a GFR (CKD-EPI formula) >95 ml/min/1.73 m^2, which is the reference value adopted in the meta-analysis we discussed before [16]. Overall, the problem of defining a hyperfiltration threshold to apply in drug dosing remains a research priority because the prevalence of obesity, a condition frequently associated with hyperfiltration and atrial fibrillation as well, is >40% in the adult population in the USA and >20% in Europe. As to the estimate of the GFR, the error in the high-normal GFR range by the CKD-EPI formula is substantially less than that by the Modification of Diet in Renal Disease (MDRD) equation [17], which is, in turn, more reliable than the creatinine clearance [18]. It is important to note that the CKD-EPI and MDRD formulas calculate the GFR standardised for body surface area (BSA) in ml/min/1.73 m^2. However, the renal clearance of drugs is proportional to individual GFR (expressed as ml/min) and not BSA-standardised GFR. Thus the BSA standardisation is inappropriate in patients with BSAs different than the standard (1.73 m^2), like obese individuals. To individualise the GFR for drug dosing, the FDA recommends multiplying the standardised GFR by the individual's BSA and dividing by 1.73 [19]. Non-invasive methods for direct measurement of true GFR at the point of care are being developed, and their application may, in the future, refine drug dosing [20].

HYPERFILTRATION AND DRUG DOSING

Whether hyperfiltration and the resulting higher drug excretion may in some cases lead to drug underdosing is a problem scarcely investigated. An otherwise rich and well-written review on clinical pharmacokinetics in kidney disease [21] did not report any information on this issue, which is also overlooked in most clinical pharmacology textbooks. Yet it is well established that hyperfiltration may cause suboptimal plasma concentrations of drugs in some conditions.

Severely ill patients

In severely ill, septic patients in intensive care units (ICUs), systemic inflammation and massive cytokines release cause vasodilation, increased cardiac output and renal blood flow, and the resulting glomerular hyperfiltration may lead to enhanced removal of drugs [22, 23]. Consequently, drug exposure, the AUC, is lower in hyperfiltering than in normofiltering patients (Fig. 3). Hydrophilic antibiotics (e.g. aminoglycosides, β-lactams, glycopeptides and colistin) often attain suboptimal plasma concentrations because their distribution volume is expanded and because they are removed at an enhanced rate in hyperfiltering, critically ill patients [22]. Patients with extensive burns are a special category among critically ill patients. Renal hyperfiltration and high non-renal clearance (CLNR)—i.e. enhanced metabolism in the liver and/or elimination via the biliary system, non-enzymatic degradation and direct loss via the exudating burned tissue [24]—are frequently observed in these patients. In these patients, CLNR increases during the

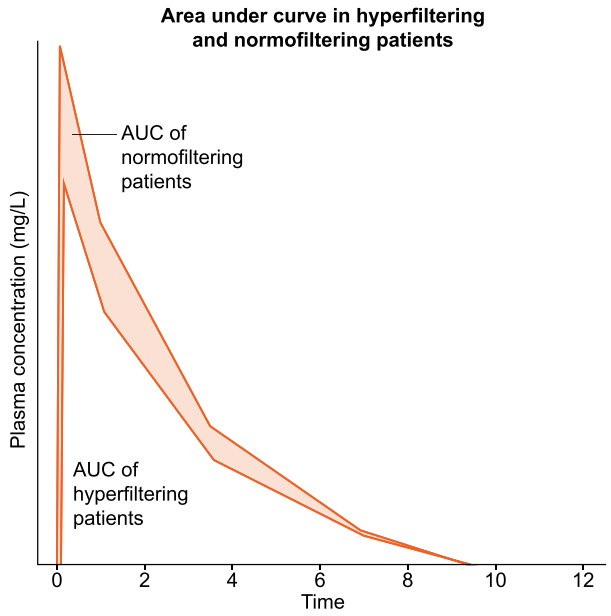

Figure 3: Area under the curve in hyperfiltering and normofiltering patients.

hypermetabolic phase [23] and ethanol clearance, an indicator of the oxidative capacity of the liver, is double that observed in healthy individuals [25]. Hyperfiltration affects most patients with major burns. In a series of 128 patients with major burns [26], hyperfiltration as measured by 24-hour creatinine clearance (CrCl >130 ml/min/1.73 m^2) was present in 52% of patients. Hyperfiltering patients had a median CrCl of 144 ml/min/1.73 m^2 and this alteration was associated with more antibiotic treatment failures (27.3%) compared with non-hyperfiltering patients (12.9%). In another series of 100 patients with major burns [27] where creatinine clearance was estimated by the Cockcroft–Gault equation (CG-eCrCl), hyperfiltration (eCrCl ≥130 ml/min) at study entry was present in the majority (64%) of patients. Subthreshold and undetectable trough concentrations of imipenem, meropenem, piperacillin and cefepime concentrations were common among hyperfiltering patients and were strongly associated with eCrCl [27]. However, at variance with the study by Claus *et al.* [26], no association was found between hyperfiltration and treatment failure in this study. Clearly, larger studies are needed to assess whether hyperfiltration impacts the response to antibiotic treatment in patients with major burns.

Obese patients and patients with type 2 diabetes

For most drugs, the liver is the main organ of clearance. Obesity is frequently associated with non-alcoholic fatty liver, an alteration that may alter hepatic blood flow [28], thereby reducing the clearance of drugs in the liver. On the other hand, renal hyperfiltration—an alteration favouring accelerated removal of drugs—is present in the majority (≈50%) of patients with early type 2 diabetes, and the same alteration is also common among obese subjects [29]. Molecules with weak or moderate lipophilicity (e.g. lithium) have predictable pharmacokinetics because these drugs are distributed mainly in lean tissues, and their dosage should be based on the ideal body weight (IBW). However, other drugs with weak or moderate lipophilicity (e.g. some antibacterial and anticancer drugs) are partly distributed

in adipose tissues, and their dosage is based on IBW plus a percentage of the patient's excess body weight [30]. For markedly lipophilic drugs (e.g. some β-blockers), the degree of lipophilicity is only loosely related to their distribution in fat/lean tissue in obese individuals.

Drug clearance in obesity should be calculated by making an allowance for excess fat mass. However, there is no single valid method to relate drug clearance to the severity of obesity. Factoring for lean body weight (LBW) is plausible, as the major drug-clearing organs (the liver and kidneys) are parts of LBW [31]. In general, obese individuals show higher absolute drug clearances than non-obese control subjects and drug clearance does not increase linearly with total body weight, while drug clearance and LBW are directly related [31]. For this reason, some recommend LBW [32] as the ideal body-size descriptor to adjust for the impact of body composition on drug clearance. However, in other analyses [33], no body-size metric explained more than ≈20% of the total interindividual pharmacokinetic variability for any drug. Thus there is no accepted body size descriptor to characterize drug clearance in the obese population. Until now no drug treatment failures associated with hyperfiltration in obese patients have been described.

As for type 2 diabetes, several factors may influence the pharmacokinetics of drugs in these patients. These factors include altered intestinal absorption, reduced gastric emptying, subcutaneous adipose tissue and muscle blood flow changes, altered biotransformation and renal excretion encompassing renal hyperfiltration, reduced tubular reabsorption and augmented tubular excretion [34]. However, no consistent pharmacokinetic alteration has been identified in hyperfiltering type 2 diabetics [34].

THE CASE OF NOACs

It is well known that the use of NOACs—i.e. dabigatran, apixaban, edoxaban and rivaroxaban—in patients with CKD demands caution because these drugs are variably metabolized by the kidney [35]. The problem of renal function in patients with NOACs is not limited to the risk of overdosing in patients with reduced GFR, but extends to the risk of underdosing in hyperfiltering patients, a problem amplified by the use the CG equation [36], which is still the equation recommended by the 2018 version of the European Heart Rhythm Association Practical Guide on NOACs [37] and by major scientific European [38] and North American [39] cardiology associations. The CG equation is inherently limited because it is based on serum creatinine measurements, which are uncalibrated to the international isotopic dilution mass spectroscopy (IDMS) creatinine standard and may overestimate IDMS-calibrated creatinine by 10–20% [40]. As discussed, the standard CKD-EPI equation is the best-validated equation and in theory it would appear preferable to the CG equation for application in clinical practice and in studies aimed at identifying the GFR threshold, minimizing the risk of NOAC underdosing in hyperfiltering patients with atrial fibrillation. However, in the landmark trials that tested NOACs [41, 42, 43], this equation was not applied and therefore major cardiology societies continue to endorse the use of the CG equation.

There is evidence that NOACs, when administered at appropriately reduced doses, generally confer similar protective effects against cardioembolism and a lower risk of major bleeding compared with vitamin K antagonists (VKAs) in stage G3 CKD patients (eGFR 30–60 ml/min/1.73 m^2) and the FDA has produced recommendations for dosing down NOACs to an eGFR of 15 ml/min/1.73 m^2 (and for apixaban for eGFR <15 ml/min/1.73 m^2) [44]. On the other hand, a signal for a possibly decreased efficacy of edoxaban in patients with higher renal clearance levels was first reported in a subanalysis of the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 trial [41]. Similar findings were derived from subanalyses of other trials with apixaban [42] and with rivaroxaban [43]. Recently, Huqi *et al.* [45] conducted a systematic review of studies that assessed the efficacy of NOACs in patients with high-normal and high eCrCl. In a combined analysis of the four major trials that compared NOACs versus warfarin, a significant interaction was registered between treatment (NOACs versus warfarin) and the eCrCl for the risk of ischaemic stroke or systemic embolism ($P = .005$) and death ($P = .009$). The risk for these events by treatment favoured warfarin at high eCrCl levels, thereby *prima facie* supporting the contention that hyperfiltration may lead to NOACs underdosing in hyperfiltrators. Counterintuitively, no interaction between treatment and the CG-eCrCl for haemorrhagic complications emerged in these analyses. Overall, in this systematic review, the high eCrCl did not significantly impact plasma levels of NOACs or the efficacy of these drugs as compared with VKAs. The therapeutic window of NOACs is large and includes drug levels typically seen in renal hyperfiltrators [45]. Further studies are needed to definitively establish whether higher renal [45] excretion of NOACs in renal hyperfiltrators impacts NOAC efficacy. But now, the up-titration of NOAC dosages in renal hyperfiltrators is unjustified [46].

In conclusion, hyperfiltration is common among severely ill patients in ICUs and drug levels should be measured whenever possible in these high-risk patients to prevent underdosing and treatment failure. Hyperfiltration is also common in patients with obesity or type 2 diabetes, but no consistent pharmacokinetic alteration has been described in these patients. No NOAC dose adjustment is indicated in patients with atrial fibrillation being treated with these drugs.

FUNDING

None declared.

AUTHORS' CONTRIBUTIONS

Carmine Zoccali conceived the review and laid a writing plan. Francesca Mallamaci and Raffaele De Caterina wrote the parts assigned to them. Carmine Zoccali finally prepared a version combining the three parts. This version was finally approved by the other authors.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

C.Z. is a Fresenius Medical Care (FMC) Europe consultant and received a fee for lecturing at FMC Israel. C.Z. and F.M. are members of the *CKJ* editorial board. R.D.C. reports grants from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb–Pfizer alliance, Daiichi-Sankyo, Menarini, Roche, Novartis, Sanofi, Merck, Portola, AstraZeneca, Amgen and Guidotti, all outside the submitted work.

REFERENCES

1. Kidney Disease: Improving Global Outcomes CKD Work Group. Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013;**3**:1–150.
2. Cortinovis M, Perico N, Ruggenenti P *et al*. Glomerular hyperfiltration. *Nat Rev Nephrol* 2022;**18**:435–51. https://www.nature.com/articles/s41581-022-00559-y
3. Zoccali C, Mallamaci F. The overdriven glomerulus as a cardiovascular risk factor. *Kidney Int* 2018;**93**:13–5. https://linkinghub.elsevier.com/retrieve/pii/S0085253817307342
4. Rochon PA. Drug prescribing for older adults - UpToDate 2022. https://www.uptodate.com/contents/drug-prescribing-for-older-adults?search=drug%20dosing&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
5. Brunton L, Knollmann B. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 14th ed. New York: McGraw Hill, 2023. https://www.mhprofessional.com/goodman-and-gilman-s-the-pharmacological-basis-of-therapeutics-14th-edition-9781264258079-usa
6. Matzke GR, Aronoff GR, Atkinson AJ *et al*. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2011;**80**:1122–37. https://linkinghub.elsevier.com/retrieve/pii/S0085253815549843
7. Pradhan S, Wright DFB, Duffull SB. Evaluation of designs for renal drug studies based on the European Medicines Agency and Food and Drug Administration guidelines for drugs that are predominantly secreted. *Br J Clin Pharmacol* 2021;**87**:1401–10. https://onlinelibrary.wiley.com/doi/10.1111/bcp.14536
8. Zhang Y, Zhang L, Abraham S *et al*. Assessment of the impact of renal impairment on systemic exposure of new molecular entities: evaluation of recent new drug applications. *Clin Pharmacol Ther* 2009;**85**:305–11. http://doi.wiley.com/10.1038/clpt.2008.208
9. Grogan S, Preuss CV. *Pharmacokinetics*. Treasure Island, FL: StatPearls, 2023. https://www.ncbi.nlm.nih.gov/books/NBK557744/
10. Olsson B, Bondesson E, Borgström L *et al*. Pulmonary drug metabolism, clearance, and absorption. In: Smyth HDC Hickey AJ, eds. *Controlled Pulmonary Drug Delivery*. New York: Springer, 2011. http://link.springer.com/10.1007/978-1-4419-9745-6_2
11. Maciel Tabosa MA, Hoppel M, Bunge AL *et al*. Predicting topical drug clearance from the skin. *Drug Deliv Transl Res* 2021;**11**:729–40. https://link.springer.com/10.1007/s13346-020-00864-8
12. Guideline Development Group,Bilo H, Coentrao L *et al*. Clinical practice guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). *Nephrol Dial Transplant* 2015;**30**(Suppl 2):ii1–142. https://academic.oup.com/ndt/article-lookup/doi/10.1093/ndt/gfv100
13. Hylek EM. Apixaban for end-stage kidney disease. *Circulation* 2018;**138**:1534–6. https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.118.036449
14. Kuno T, Takagi H, Ando T *et al*. Oral anticoagulation for patients with atrial fibrillation on long-term dialysis. *J Am Coll Cardiol* 2020;**75**:273–85. https://linkinghub.elsevier.com/retrieve/pii/S0735109719384906
15. Cachat F, Combescure C, Cauderay M *et al*. A systematic review of glomerular hyperfiltration assessment and definition in the medical literature. *Clin J Am Soc Nephrol* 2015;**10**:382–9. https://cjasn.asnjournals.org/lookup/doi/10.2215/CJN.03080314
16. Nitsch D, Grams M, Sang Y *et al*. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. *BMJ* 2013;**346**:f324. https://www.bmj.com/lookup/doi/10.1136/bmj.f324
17. Levey AS, Stevens LA, Schmid CH *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604. http://annals.org/article.aspx?doi=10.7326/0003-4819-150-9-200905050-00006
18. Levey AS, Bosch JP, Lewis JB *et al*. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999;**130**:461–70. http://www.ncbi.nlm.nih.gov/pubmed/10075613
19. U.S. Food and Drug Administration. Pharmacokinetics in patients with impaired renal function – study design, data analysis, and impact on dosing and labeling. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-renal-function-study-design-data-analysis-and-impact-dosing-and
20. Bilbao-Meseguer I, Rodríguez-Gascón A, Barrasa H *et al*. Augmented renal clearance in critically ill patients: a systematic review. *Clin Pharmacokinet* 2018;**57**:1107–21. http://link.springer.com/10.1007/s40262-018-0636-7
21. Lea-Henry TN, Carland JE, Stocker SL *et al*. Clinical pharmacokinetics in kidney disease. *Clin J Am Soc Nephrol* 2018;**13**:1085–95. https://cjasn.asnjournals.org/lookup/doi/10.2215/CJN.00340118
22. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit Care Med* 2009;**37**:840–51. http://journals.lww.com/00003246-200903000-00006
23. Udy AA, Jarrett P, Stuart J *et al*. Determining the mechanisms underlying augmented renal drug clearance in the critically ill: use of exogenous marker compounds. *Crit Care* 2014;**18**:657. http://ccforum.biomedcentral.com/articles/10.1186/s13054-014-0657-z
24. Udy AA, Roberts JA, Lipman J *et al*. The effects of major burn related pathophysiological changes on the pharmacokinetics and pharmacodynamics of drug use: an appraisal utilizing antibiotics. *Adv Drug Deliv Rev* 2018;**123**:65–74. https://linkinghub.elsevier.com/retrieve/pii/S0169409X17302004
25. Zdolsek HJ, Sjöberg F, Lisander B *et al*. The effect of hypermetabolism induced by burn trauma on the ethanol-oxidizing capacity of the liver. *Crit Care Med* 1999;**27**:2622–5. http://journals.lww.com/00003246-199912000-00003
26. Claus BOM, Hoste EA, Colpaert K *et al*. Augmented renal clearance is a common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy. *J Crit Care* 2013;**28**:695–700. https://linkinghub.elsevier.com/retrieve/pii/S0883944113000646
27. Huttner A, von Dach E, Renzoni A *et al*. Augmented renal clearance, low β-lactam concentrations and clinical outcomes in the critically ill: an observational prospective cohort study. *Int J Antimicrob Agents* 2015;**45**:385–92. https://doi.org/10.1016/j.ijantimicag.2014.12.017
28. Ijaz S, Yang W, Winslet MC *et al*. Impairment of hepatic microcirculation in fatty liver. *Microcirculation* 2003;**10**:447–56. http://doi.wiley.com/10.1080/mic.10.6.447.456

29. Helal I, Fick-Brosnahan GM, Reed-Gitomer B *et al*. Glomerular hyperfiltration: definitions, mechanisms and clinical implications. *Nat Rev Nephrol* 2012;**8**:293–300. http://www.ncbi.nlm.nih.gov/pubmed/22349487
30. Cheymol G. Effects of obesity on pharmacokinetics implications for drug therapy. *Clin Pharmacokinet* 2000;**39**:215–31. http://www.ncbi.nlm.nih.gov/pubmed/11020136
31. Han PY, Duffull SB, Kirkpatrick CMJ *et al*. Dosing in obesity: a simple solution to a big problem. *Clin Pharmacol Ther* 2007;**82**:505–8. http://doi.wiley.com/10.1038/sj.clpt.6100381
32. Janmahasatian S, Duffull SB, Ash S *et al*. Quantification of lean bodyweight. *Clin Pharmacokinet* 2005;**44**:1051–65. http://link.springer.com/10.2165/00003088-200544100-00004
33. Mathijssen R, Sparreboom A. Influence of lean body weight on anticancer drug clearance. *Clin Pharmacol Ther* 2009;**85**:23. http://doi.wiley.com/10.1038/sj.clpt.6100511
34. Dostalek M, Akhlaghi F, Puzanovova M. Effect of diabetes mellitus on pharmacokinetic and pharmacodynamic properties of drugs. *Clin Pharmacokinet* 2012;**51**:481–99. http://link.springer.com/10.2165/11631900-000000000-00000
35. Harel Z, Sholzberg M, Shah PS *et al*. Comparisons between novel oral anticoagulants and vitamin K antagonists in patients with CKD. *J Am Soc Nephrol* 2014;**25**:431–42. https://jasn.asnjournals.org/lookup/doi/10.1681/ASN.2013040361
36. Cemin R, Foco L, Zoccali C *et al*. Should we continue assessing glomerular filtration rate with the Cockroft-Gault formula in NOAC-treated patients? The magnitude of the problem. *J Clin Med* 2020;**9**:1893. http://www.ncbi.nlm.nih.gov/pubmed/32560421
37. Steffel J, Verhamme P, Potpara TS *et al*. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;**39**:1330–93. https://academic.oup.com/eurheartj/article/39/16/1330/4942493
38. Kirchhof P, Benussi S, Kotecha D *et al*. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–962. https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehw210
39. January CT, Wann LS, Calkins H *et al*. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol* 2019;**74**:104–32. https://linkinghub.elsevier.com/retrieve/pii/S0735109719302098
40. Pai MP. Estimating the glomerular filtration rate in obese adult patients for drug dosing. *Adv Chronic Kidney Dis* 2010;**17**:e53–62. https://linkinghub.elsevier.com/retrieve/pii/S154855951000087X
41. Bohula EA, Giugliano RP, Ruff CT *et al*. Impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 Trial. *Circulation* 2016;**134**:24–36. https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.116.022361
42. Hijazi Z, Hohnloser SH, Andersson U *et al*. Efficacy and safety of apixaban compared with warfarin in patients with atrial fibrillation in relation to renal function over time. *JAMA Cardiol* 2016;**1**:451–60. http://cardiology.jamanetwork.com/article.aspx?doi=10.1001/jamacardio.2016.1170
43. Lindner SM, Fordyce CB, Hellkamp AS *et al*. Treatment consistency across levels of baseline renal function with rivaroxaban or warfarin. *Circulation* 2017;**135**:1001–3. https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.116.024666
44. Aursulesei V, Costache II. Anticoagulation in chronic kidney disease: from guidelines to clinical practice. *Clin Cardiol* 2019;**42**:774–82. http://www.ncbi.nlm.nih.gov/pubmed/31102275
45. Huqi A, Zoccali C, Giugliano RP *et al*. The non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients with high-normal renal function – a systematic review. *Vasc Pharmacol* 2022;**147**:107123. https://linkinghub.elsevier.com/retrieve/pii/S1537189122001720
46. Huqi A, Zoccali C, Giugliano RP *et al*. Safety of non-vitamin K antagonist oral anticoagulants: concerns in patients with atrial fibrillation and glomerular hyperfiltration? *Eur Heart J* 2023;**44**:322–5. http://www.ncbi.nlm.nih.gov/pubmed/35983667