Personalized drug therapy management in patients with renal impairment

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For reasons of consistency within this thesis, some terms have been standardized throughout the text. As a consequence the text may differ in this respect from the articles that have been published.

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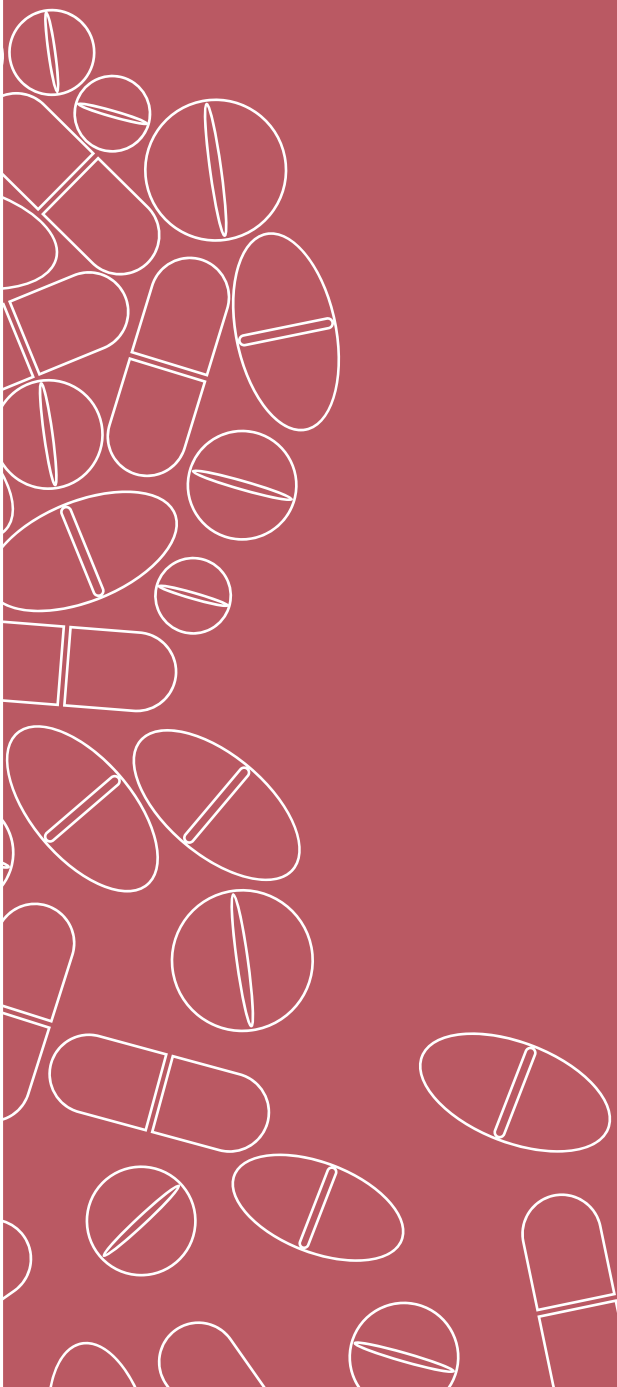
Introduction



1

Good prescribing of drugs for treatment or prevention of diseases published by the World Health Organization (WHO) involves the following six steps:[1]

1. Define the patient's problem
2. Specify the therapeutic objective
3. Verify the suitability of your P(ersonal)-drug
4. Write a prescription
5. Give information, instructions and warnings
6. Monitor (or stop?) the treatment

The P-drug in step 3 is the drug the physician has chosen to prescribe first in a specific situation, and with which he/she has become familiar.[1] The P-drug is the priority choice for a given indication and includes the dosage form, dosage schedule and duration of treatment.[1] This thesis largely focuses on patients with renal impairment. The P-drug chosen may not be suitable or needs dose adjustment in patients with renal impairment. The risk-benefit ratio in patients with renal impairment established in this step of good prescribing might be different from other patient populations without renal impairment. In addition, knowledge about the effects, both effectiveness and adverse drug reactions (ADRs), of drugs used in patients with renal impairment is limited. Therefore, if a drug is started in a patient with renal impairment, steps 5 and 6 in good prescribing of drugs will become even more important.

Personalized drug therapy management

It is generally known that the principle 'one size fits all' is not appropriate in pharmacotherapy. Personalized medicine seeks to identify the right dose of the right drug for the right patient at the right time.[2] The goal of personalized medicine is to optimize benefit and to reduce risk.[3] A well-known example of personalized medicine is the use of genotyping for the decision-making of choosing the right drug and right dose. More than a decade ago, the first area where the idea of genotyping was proposed was psychiatry.[4-6] Most psychiatric drugs are metabolized by highly polymorphic CYP2D6 and CYP2C19 enzymes.[7] Drugs which are mainly metabolized by CYP2D6 should be prescribed with caution in patients with none or few CYP2D6 enzymes, called poor metabolizers. For some drugs, for example venlafaxine, the advice is to choose another antidepressant.[8] For other drugs a relation between genotype and drug dose was found.

These findings have led to guidelines for drug dose advices.[7] Dosing advices are given categorically for poor, intermediate, extensive and ultra-rapid metabolizers. For example nortriptyline, see Table 1.1.[8]

Table 1.1 Dosing advice for nortriptyline based on genotype[8]

Genotype	Recommended daily dose of nortriptyline
Extensive metabolizer	Normal dose
Poor metabolizer	40% of normal dose
Intermediate metabolizer	60% of normal dose
Ultra rapid metabolizer	Choose an alternative or 160% of normal dose

Personalized medicine in patients with renal impairment is basically not any different. Drug dose advices are given categorically per renal function group. For example sotalol, see Table 1.2.[9]

Table 1.2 Dosing advice for sotalol based on renal function[9]

Renal function group (ml/min/1.73m^2)	Recommended daily dose of sotalol
50 - 80	Normal dose
30 - 49	Maximum of 160 mg
10 - 29	Maximum of 80 mg
< 10	No general advice

The main difference between genotype and renal function, usually expressed as glomerular filtration rate (GFR), is that GFR fluctuates over time, in some situations even within a day. In addition, the estimated GFR (eGFR) is also prone to misinterpretation of the true GFR by influencing factors, which will be discussed in this thesis.[10] In general, the genotype is measured once and is valid for a lifetime, whereas the renal function changes over time. All in all, drug dose adjustment in patients with renal impairment is also a form of personalized medicine.

Due to interindividual variation of drug response and clearance and the variation over time, personalized medicine is not a straightforward one-time only approach.[7] In addition, the way patients are informed and instructed on drug use also needs to be personalized, based on education level. In other words, clinicians seek to identify the right dose of the right drug for the right patient *over* time. It will be a challenge to identify and recognize fluctuating factors, such as renal function, timely and adjust drug therapy whenever necessary. In patients with renal impairment drug dose advices are not only about changing a drug dose, but also about discontinuation of a drug or instructions on how to detect ADRs timely. Therefore the title of this

thesis is 'Personalized drug therapy management' (PDTM) in patients with renal impairment.

Implementation of the guidelines 'Drug dose advices in renal impairment' in The Netherlands

In recent years the focus on renal function and pharmacotherapy has increased. An important contribution to this, was the Hospital Admissions Related to Medication (HARM) study, which showed that 16,000 HARMs are potentially avoidable each year in The Netherlands.[11] This finding prompted the HARM-Wrestling report, which proposed about 40 practicable recommendations to reduce the most frequently occurring and potentially avoidable HARMs.[12] About half of these recommendations concerned appropriate prescribing (e.g. adding a protective drug), a quarter concerned follow-up procedures (e.g. laboratory monitoring, such as renal function tests), and another quarter concerned communication (with the patient and other healthcare providers). Of the practical recommendations half could be supported by combining medicines with laboratory values in a computer decision support system (CDSS). Leendertse et al. showed that 10% of the HARMs were considered to be related to a medication error and renal impairment.[13] Parallel to the HARM study the Royal Dutch Association for the Advancement of Pharmacy created a handbook with drugs that need dose adjustment in patients with renal impairment or cannot be given to these patients.[9]

Approximately at the same time the Modification of Diet in Renal Disease (MDRD) formula was implemented in clinical chemistry laboratories in The Netherlands. This means that whenever a serum creatinine level is ordered, the eGFR is also reported. Reporting eGFR values in addition to serum creatinine led to a better recognition of impaired renal function and therefore it became easier to follow the guidelines for drug dose advices in renal impairment in daily clinical practice.

Some pharmacists adopted the renal drug handbook quickly and requested access to laboratory values.[14] In the beginning (the first publication of the Dutch handbook 'drug dose advices in renal impairment' was in 2008) checking the renal function in relation to the prescribed drug (dose) was performed manually. In The Netherlands the drug dose advices in renal impairment are incorporated in a national drug database (the G-standard) and from there they are available in basic pharmacotherapy-related CDSS. To use this content it is required to turn on the diagnosis 'renal impairment' in the CDSS if applicable. The next step was and still is to incorporate laboratory values, such as renal function data, into these systems and create algorithms which take into account specific individual data. Several

studies have shown that combining medication information with laboratory values in a CDSS resulted in less prescription errors.[14,15] Pharmacists were inclined at first to implement drug dose advices in renal impairment directly and straightforward. In the communication with the physicians it appeared that this approach was not appropriate.[16] The physicians were not familiar with the recommendations. Based on their clinical experience they felt that these recommendations were too rigid. Questions that physicians may ask were: "How strong is the evidence behind the advice? What is the degree of the risk when my patient gets an inappropriate drug or drug dose?". These questions ensured that the evidence behind the guidelines was further examined. It appeared that the evidence was mainly based on case reports and pharmacokinetic studies in controlled environments. The lack of population-based studies and translation of the available evidence to daily clinical practice became the domain of this thesis.

Objective and outline of the thesis

This thesis aims to give insight into the validity of the MDRD formula used in prescribing drugs in renal impairment (**Section 1**), to add new evidence to evaluate existing guidelines (**Section 2**), and to give practical approaches for handling renally excreted drugs in patients with renal impairment in daily clinical practice (**Section 3**). Overall, its objective is to contribute knowledge that facilitates personalized drug therapy management, with a particular focus on patients with renal impairment.

When studying the development of the MDRD formula it appeared that the population used, does not always reflect the population seen at the community pharmacy or in the hospital care setting. Therefore the question arose how valid the MDRD formula is in specific patient populations. First, we focused on one patient population, namely patients with Human Immunodeficiency Virus (HIV) (**Chapter 2**). This allowed us to fine-tune our selection and assessment criteria. Which aspects of a comparative study are important in a comprehensive assessment of the MDRD formula in different patient populations? The results of this systematic review about the validity of the MDRD formula in specific patient populations are presented in **Chapter 3**.

In the second part of this thesis we looked closer to the research evidence underlying the drug therapy recommendations in guidelines. We were especially interested in the frequently prescribed drugs nitrofurantoin and metformin. Both drugs are the drug of choice when, respectively urinary tract infection (UTI) in women or diabetes mellitus type 2 are diagnosed, but both drugs are also contraindicated when renal function drops below a specific level. Are patients with renal impairment

falsely withheld from a first choice drug? It appeared that the contraindication of these drugs in renal impairment was based on pharmacokinetic studies and case reports. We conducted two cohort studies. In the first study we determined whether treatment with nitrofurantoin in women with UTI and renal impairment in primary care was associated with a higher risk of ineffectiveness and/or serious ADRs than in women without renal impairment (**Chapter 4**). In the second study we determined whether treatment with metformin in patients with renal impairment was associated with a higher risk of lactic acidosis or elevated lactate levels compared to users of a non-insulin antidiabetic drug who had never used metformin (**Chapter 5**).

A specific patient population is the elderly in the hospital care setting. Guidelines in primary care exist with information about how often renal function should be measured. From our clinical experience we noticed that their renal function during hospital admission may fluctuate, even within one day, and we wondered whether this was also the case after their discharge. In the current daily clinical practice, medication histories and laboratory values are sent to the community pharmacy and general practitioner after discharge from the hospital. As it seems likely that these laboratory values will be used for drug dose advices in the following months we present a study protocol in **Chapter 6** to determine the fluctuation of the renal function after discharge from the hospital and its potential effect on appropriate prescriptions of drugs. The first results of this study are presented as well.

In the third and last part, we focused on drug therapy management in patients with renal impairment in daily clinical practice. In **Chapter 7** we show the impact of an advanced pharmacotherapy-related CDSS in identifying potential medication-related problems. This CDSS may be helpful in recognizing and optimizing PDTM. In view of the uncertainties surrounding the prescribing of drugs in patients with renal impairment we give a practical guidance in **Chapter 8** on how to cope with these uncertainties in daily clinical practice.

Finally, the results of the studies are summarized and put into a broader perspective in **Chapter 9**.

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The validity of the Modification of Diet in Renal Disease formula

Section

I

The validity of the Modification of Diet in Renal Disease formula in HIV-infected patients:

A systematic review

J Nephrol 2014; 27(1): 11-8

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2

Abstract

Rationale, aims and objectives

Renal dysfunction is highly prevalent in HIV-infected patients and may require dose adjustment of renally excreted antiretroviral drugs. The Modification of Diet in Renal Disease (MDRD)-4 formula is frequently used in daily practice to estimate patients' renal function. The aim of this systematic review was to assess the validity of the MDRD-4 formula in HIV-infected patients.

Method

A systematic search in Pubmed and EMBASE was done to identify studies which compared MDRD-4 with measured glomerular filtration rate (mGFR) in HIV-infected patients.

Results

Five studies were included, which provided data from 464 HIV-infected patients with mean mGFR ranging from 87 to 118 ml/min/1.73m^2. In all studies, results from the MDRD-4 gave an underestimation of the mGFR. Mean bias ((MDRD-4) — mGFR) ranged from -6 to -11 ml/min/1.73m^2 across studies. The accuracy expressed in terms of P_{30} ranged from 64% to 89%.

Conclusions

The MDRD-4 formula is as valid in HIV-positive as in HIV-negative patients. Because the available studies comprised mainly HIV-infected patients with mildly impaired to good renal function (GFR ≥ 60 ml/min/1.73m^2), more research is needed to validate the MDRD-4 formula in HIV-infected patients with moderate to severe renal impairment.

Introduction

Individuals infected with human immunodeficiency virus (HIV) have an increased risk of kidney disease.[1] HIV infection may result in HIV-associated nephropathy, immune complex kidney disease and acute renal failure.[2,3] These conditions are associated with progression to acquired immune deficiency syndrome (AIDS) and death.[2,4] In addition, HIV itself may influence other risk factors for kidney disease, such as abnormal lipid levels, insulin resistance and microalbuminuria.[5] A current estimate indicates a 30% prevalence of kidney dysfunction in HIV-infected patients in developed countries, defined as an estimated renal function < 90 ml/min and concomitant proteinuria. Moreover, progression to end-stage kidney disease, which may require haemodialysis, is common.[4,6,7] The high prevalence of impaired renal function in HIV-infected patients is indirectly related to the longer life expectancy in the highly active antiretroviral therapy (HAART) era.[5,8,9] Routine monitoring of patients' renal function is therefore an important component of personalized HIV care.[3]

In daily clinical practice, the Modification of Diet in Renal Disease (MDRD) formula is widely used to estimate the glomerular filtration rate (eGFR). The original 6-variable formula (serum creatinine concentration, age, sex, ethnicity, urea nitrogen and albumin concentrations), MDRD-6, was developed for a sample of ambulatory, predominantly white patients with chronic kidney disease (CKD).[10] Several years later (2000), this formula was simplified to 4 variables (serum creatinine concentration, age, sex and ethnicity), the MDRD-4.[11] The MDRD-4 formula is based on serum creatinine concentration, which is a by-product of muscle catabolism. Hence, serum creatinine is influenced by a person's muscle mass. Creatinine production is also affected by factors such as diet, gender and age. In HIV-infected patients, muscle mass may be lower and body composition may be different because of the disease itself or because of fat accumulation or redistribution due to antiretroviral treatment. Therefore, we hypothesized that the MDRD-4 formula could lead to an overestimation of the true glomerular filtration rate (GFR) in this population.[6,12–14]

As an alternative, the GFR can be measured (mGFR) directly as the renal clearance of exogenous markers such as inulin, ^{51}chromium ethylene-diamine-tetra-acetic acid (^{51}Cr-EDTA), technetium-labelled diethylene-triamine-pentacetate (^{99m}Tc-DTPA), iothalamate and iohexol. However, these markers are impractical for routine clinical use due to limited access to necessary diagnostic facilities and the high cost.[15,16]

Accurate assessment of the GFR is necessary in the treatment of HIV. First, for timely detection and management of declining renal function. Second, to adjust the

dose or change the type of antiretroviral agents and co-medications appropriately. Dose adjustments for antiretroviral drugs in renal impairment are described in international HIV treatment guidelines.[17]

The aim of this review was to assess the validity of the eGFR based on the MDRD-4 formula in HIV-infected patients.

Method

Search strategy

We performed a systematic review of published studies focused on the validity of the MDRD-4 formula in HIV-infected patients. We searched the databases Pubmed and EMBASE for relevant literature from January 2000 (when the simplified MDRD-4 formula was introduced[11]) until August 2012. We chose to limit our search strategy to the MDRD-4 formula, because this formula is the most commonly used in clinical practice.[18–20] The terms used for the overall search strategy are listed in Appendix 2.1. Titles and abstracts were reviewed independently by two authors (WE and PDS). Disagreements between the two reviewers were resolved by consensus. Subsequently, the reference lists of the selected articles were checked for additional articles.

Selection criteria

Articles were selected if they met the following criteria: (1) the study population consisted of HIV-infected patients, (2) the MDRD-4 formula was compared with a gold standard which included: ^{99m}Tc-DTPA, inulin, ^{51}Cr-EDTA, ^{125}I-iothalamate and iohexol, and (3) statistical analysis and reporting focused on bias, precision and/or accuracy (definitions are described in Table 2.1).

The MDRD-4 equations included are presented in Box 2.1.[19] Proper use of the MDRD-4 formula requires standardized serum creatinine measurements.[19]

Box 2.1 MDRD-4 equations

Standardized creatinine measurement for S_{cr} (mg/dl)
175 x standardized $S_{cr}^{-1.154}$ x $age^{-0.203}$ x 1.212 (if black) x 0.742 (if female)
Standardized creatinine measurement for S_{cr} (umol/l)
30849 x standardized $S_{cr}^{-1.154}$ x $age^{-0.203}$ x 1.212 (if black) x 0.742 (if female)
Not standardized creatinine measurement for S_{cr} (mg/dl)
186 x standardized $S_{cr}^{-1.154}$ x $age^{-0.203}$ x 1.212 (if black) x 0.742 (if female)
Not standardized creatinine measurement for S_{cr} (umol/l)
32788 x standardized $S_{cr}^{-1.154}$ x $age^{-0.203}$ x 1.212 (if black) x 0.742 (if female)

S_{cr} = serum creatinine

Table 2.1. Definitions outcome measurements

Bias		**References**
Median difference	md eGFR – mGFR	6, 24
Median percentage difference[a]	md ((eGFR – mGFR)/mGFR) x 100%	6
Mean difference	1/n x Σ (eGFR – mGFR)	34
Mean percentage difference[b]	1/n x Σ ((eGFR – mGFR)/mGFR) x 100%	44
Precision		
Inter quartile range (IQR) difference	IQR of (eGFR – mGFR)	24
IQR percentage difference[a]	IQR of (eGFR – mGFR)/mGFR x 100%	24
Limits of agreement (LOA)	Mean difference ± 1.96 SD	34, 35
Standard deviation difference (SD)	σ of all the individual differences	24, 34
Accuracy		
P_k[c]	Percentage of estimates within k% of mGFR	24
Median absolute percentage error (mAPE)	md ((|eGFR – mGFR|)/mGFR) x 100%	44
Mean absolute percentage error (MAPE)	1/n x Σ ((|eGFR – mGFR|)/mGFR) x 100%	44

[a] Preferred definition because a relative scale provides a more relevant metric.[24]
[b] In some articles the mean percentage difference was called the mean percentage error (MPE).
[c] Preferred definition of accuracy. We limited our search to P_{10}, P_{20}, P_{30} and P_{50}.
eGFR, estimated glomerular filtration rate; IQR, inter quartile range; LOA, limits of agreement; mGFR, measured glomerular filtration rate; md, median; SD, standard deviation.

After the introduction of isotope dilution mass spectrometry (IDMS)-traceable calibration of serum creatinine assays the MDRD-4 formula was re-expressed in 2007.[19]

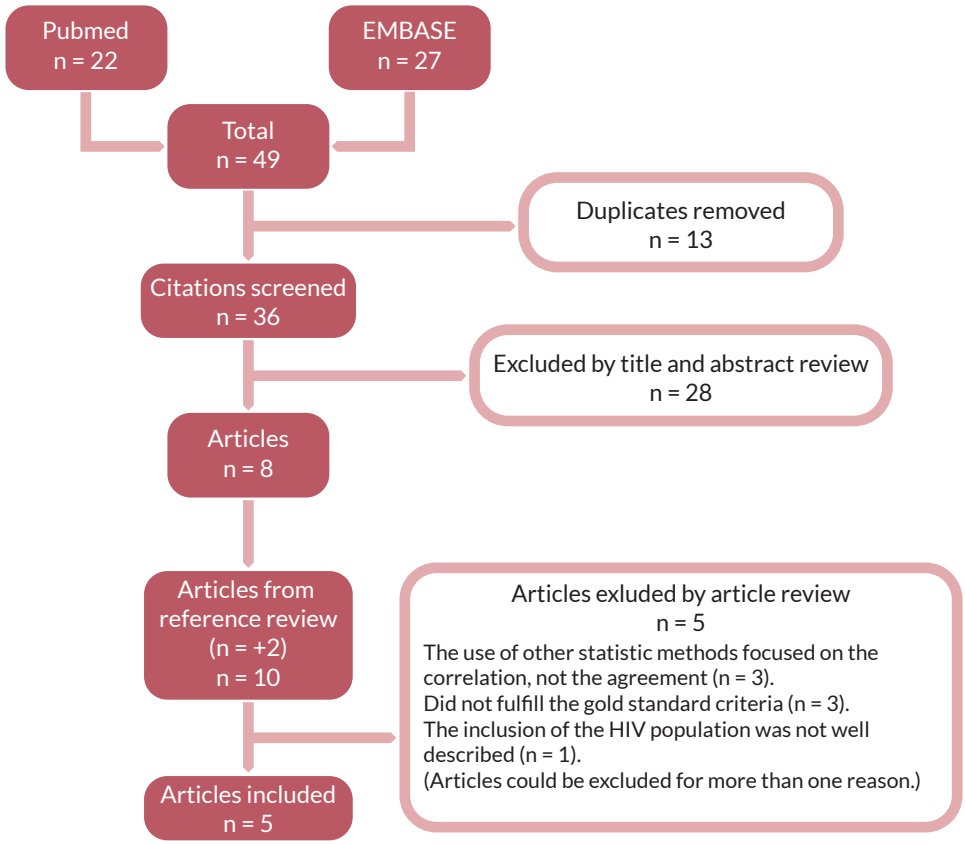
Studies were excluded if they consisted of a case report, abstract of conference, poster, if patient selection was poorly described or if an article reproduced data already published elsewhere.

Abstracted data and outcomes reported in the included articles were summarized qualitatively, paying attention to the selection of the study population (age, sex and other factors influencing the generation, clearance or measurement of creatinine[16,21]), the mean mGFR and the outcome measurements defined in Table 2.1.

Results

Figure 2.1 shows the inclusion process of studies in the review. The initial database searches identified 49 articles. Scanning for title and abstracts resulted in 8 potentially relevant articles. A further 2 potentially relevant articles were found by searching their reference lists. Of these, 5 studies fulfilled the inclusion criteria.

Figure 2.1. Results of search strategy



In Table 2.2 the most important information about these studies is summarized. They were conducted in four different countries: the United States of America, Canada, Thailand and The Netherlands. The studies were published between 2009 and 2012. The number of patients included ranged from 19 to 200.[8,22] The patient characteristics, such as age, sex and body mass index (BMI), differed among the studies. In the study of Praditpornsilpa et al. the mean age was approximately 10 years lower than in the studies of Beringer et al. and Barraclough et al.[6,14,23]

The percentage of men varied between 57% and 95%.[8,23] In the study population of Barraclough et al. the majority of patients had abnormal body composition (lipodistrophy is common in patients with HIV). This factor did not seem to influence the eGFR (data not reported).[14] The ethnicity of the study populations was also different. The study of Barraclough et al. consisted of mostly Caucasians[14],

whereas the population of Inker et al. consisted for 52% of blacks. The gold standards used were iothalamate in the studies of Beringer et al.[6] and Vrouenraets et al.[8], ^{99m}Tc-DTPA in the studies of Barraclough et al.[14] and Praditpornsilpa et al.[23] and iohexol in the study of Inker et al.[22]

Of note, the majority of patients included had mild renal impairment to normal renal function. mGFRs ranged from 23 to 175 ml/min/1.73m^2 with mean mGFRs ranging from 87 to 118 ml/min/1.73m^2.[22,23]

All five studies reported that the eGFR underestimated the mGFR. The highest underestimation was reported as a median bias of -11 ml/min/1.73m^2 in the study of Inker et al.[22] The underestimations in the study of Beringer et al., Barraclough et al. and Vrouenraets et al. were in the same range, namely -10 ml/min/1.73m^2.[6,8,14] The mean bias in the study of Praditpornsilpa et al. was reported as a mean bias of -6 ml/min/1.73m^2.[23]

The precision was presented in terms of interquartile ranges (IQR), limits of agreement (LOA) and standard deviation (SD) of the mean difference. The precision (presented as the preferred IQR percentage difference[24]) seemed better in the study by Barraclough et al.[14] (-21 to 2 ml/min/1.73m^2) than in the study by Beringer et al.[6] (-31% to 19%). The LOA in the study of Praditpornsilpa et al.[23] was very wide, namely -63 to 50 ml/min/1.73m^2, whereas the SD reported in the study of Vrouenraets et al.[8] seemed smaller, namely 17 ml/min/1.73m^2. The accuracy presented as the proportion of the eGFR values falling within a predefined percentage of the mGFR values (30% expressed as P_{30} and 50% expressed as P_{50}) ranged in 4 out of 5 studies from 80% to 89%.[8,14,22,23] Only the study of Beringer et al. reported a substantially lower P_{30} of 64%.[6] The P_{50} reported by Beringer et al. and Barraclough et al. were similar, about 100%.[6,14]

For 27 patients with renal impairment (< 60 ml/min/1.73m^2) the study of Inker et al. reported a bias, precision and accuracy of -12 ml/min/1.73m^2, 19 ml/min/1.73m^2 and 67%, respectively.[22]

Table 2.2 Patient characteristics and outcomes of the included studies

Article	Diagnosis (n = number of patients)	Sampling procedure	Age (years)
Beringer et al., 2010, United States[6]	HIV (n = 22)	HIV clinic; Inclusion criteria: age > 18, HIV, stable HIV treatment and stable kidney function over 3 months before study entry. Exclusion criteria: allergy to iodine or contrast media, anemia or pregnancy. Fluid restricted or receiving drugs known to alter excretion of creatinine. March 2007 to August 2008.	51.0 range: 41.5-60.3
Barraclough et al., 2009, Canada[14]	HIV (n = 27)	Inclusion criteria: HIV-infected adults over 18 years of age followed in the HIV clinic. Exclusion criteria: acute illness, unstable renal function (variation S_{cr} > 27 umol/l) in the previous 6 weeks, pregnancy and refusal to provide inform consent.	52 ± 9
Praditpornsilpa et al., 2012, Thailand[23]	HIV (n = 196)	Inclusion criteria: stable HIV-infected adults over 18 years of age. Exclusion criteria: acute renal failure, amputation, malnutrition (BMI < 18 kg/m^2), in a bed ridden state, with infection, edematous, gastrointestinal bleeding, heart failure or hospitalized.	43.6 ± 7.8
Vrouenraets et al., 2012, The Netherlands[8]	HIV (n = 19)	Inclusion criteria: HIV-1 infected, age ≥ 18, males or non-pregnant non-lactating females, and other criteria as part of a multinational randomized trial. Exclusion criteria: renal impairment (eGFR < 50 ml/min), concomitant therapy with nephrotoxic or investigational drugs, chronic active viral hepatitis, or other chronic liver disease and other criteria as part of a multinational randomized trial.	46 ± 8.9
Inker et al., 2012, United States[22]	HIV (n = 200)	Inclusion criteria: age > 18 years, stable on ART for at least three months, confirmed HIV status, HIV viral load and CD4 count within 6 months of recruitment. Exclusion criteria: pregnancy, allergy or contraindication for iohexol or iodine, recent acute kidney injury, cognitive or physical impairments, use of cimetidine.	48 ± 8

[a] the glomerular filtration rate was measured with one of the following gold standards: [1] (^{125}I-) iothalamate, [2] technecium-labelled diethylenetriaminepentacetate (^{99m}Tc-DTPA), [3] inulin, [4] [5] ^{51}chromium ethylenediaminetetraacetic acid (^{51}Cr-EDTA) or [5] iohexol.
[b] the population consisted of Thai ethnicity, therefore the results of the re-expressed MDRD-4 formula with Thai racial correction factor were presented.

Sex (% men)	**Influencing factors**	**Mean mGFR**[a] (ml/min/1.73m²)	**Bias** (ml/min/1.73m²)	**Precision** (ml/min/1.73m²)	**Accuracy** (%)
72.7	BMI (kg/m²) = 27.1 (21.9-30.4) African-American: 36%	111[1] range: 50.4-145	median(%): -9.56	IQR(%): -30.5 to 18.7	P_{30}: 64 P_{50}: 95
85	BMI (kg/m²) = 24.6 (21.7-26.0) Diabetes: 7% Hypertension: 26%	91[2] range: 84-114	median: -10	IQR: -21 to 2	P_{10}: 22 P_{20}: 59 P_{30}: 89 P_{50}: 100
57	BMI (kg/m²) = 22.3 ± 3.2 Diabetes: 7% Hypertension: 15%	117.7 ± 29.2[2]	mean: -6.2[b]	LOA: -62.7 to 50.4[b]	P_{30}: 84[b]
95	BMI (kg/m²) = 23.9 ± 3.0	102 ± 19[1]	mean: -10	SD: 17	P_{30}: 89
73	BMI (kg/m²) = 27 ± 6 Blacks: 52% Diabetes: 8% Hypertension: 31%	87 ± 26[5]	median: -10.9	IQR: 21.7	P_{30}: 80

ART, antiretroviral therapy; AZT, zidovudine; BMI, body mass index; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; IQR, inter quartile range; LOA, limits of agreement; mGFR, measured glomerular filtration rate; RNA, ribonucleic acid; S_{cr}, serum creatinine; SD, standard deviation; 3TC, lamivudine.

Discussion

Although the MDRD-4 formula is widely used in clinical practice to estimate the GFR in HIV-infected patients, we found few studies which had investigated the validity of the MDRD-4 formula in this specific group of patients. The five studies found reported a systematic underestimation of the GFR when using the MDRD-4 formula compared to the mGFR using gold standards (bias ranging from -6 to -11 ml/min/1.73m^2).[6,8,14,22,23] This small underestimation of the GFR is similar to that in HIV-negative adults.[5,25] It should be noted that the majority of HIV-infected patients included had mildly impaired to good renal function (GFR ≥ 60 ml/min/1.73m^2). The study of Inker et al. included 27 patients with a mGFR < 60 ml/min/1.73m^2. The underestimation reported for this subpopulation was -12 ml/min/1.73m^2.[22]

Untreated HIV infection increases energy requirements while it decreases appetite and, in more advanced stages, it limits the intake and absorption of nutrients.[26] Therefore we hypothesized beforehand that some of the HIV-infected patients would have a lower muscle mass, which should result in an overestimation of the renal function using the MDRD-4 formula.[6,12–14] However, the findings of the included studies present an underestimation. An explanation might be that the majority of the included patients had a normal BMI. The overall well-nourished HIV-infected patient population might partially be explained by the post-HAART era.[14] However, physicians should remain aware of the possibility that the eGFR can be overestimated in HIV-infected patients, for example, when there is HIV-associated wasting or a late presentation of the disease. More research is needed in this specific HIV-infected subpopulation.

In studies with black African HIV-infected patients, lower body weight (BMI < 20 kg/m^2) was represented to a greater extent.[12,15] Both studies suggested a small overestimation of the renal function using the MDRD-4 formula in these patients.[12,15] Remarkably, these latter studies found that the correction factor of 1.212 which has been included in the MDRD-4 formula for Black Americans is not applicable to the Black African population.[12,15] The study of Praditpornsilpa et al. showed that the addition of the correction factor of 1.129 for Thai ethnicity resulted in a more accurate estimation of the GFR.[23] However, this correction factor is not generalizable to other Asian ethnicities, as the correction factors for Japanese and Chinese populations are different, namely 1.23 and 0.88 respectively.[23]

The validity of the MDRD formula has also been determined in various other patient populations, with specific diseases.[27–29] For example, in liver diseases the production of creatinine is low. A low serum creatinine level leads to a higher

eGFR calculated with the MDRD formula. In patients with cirrhosis the MDRD substantially overestimated the measured renal function.[27,30] Bilo et al. found an overestimation of the renal function using the MDRD formula in patients with diabetes mellitus.[29] In patients with various types of cancers the MDRD formula was not reliable at all.[31–33] Further validation of the MDRD formula in specific patient populations is recommended, because it is widely used to personalize pharmacotherapy in renal impairment and to recognize decline in renal function.

This systematic review had several limitations. The studies were conducted in developed countries and mainly concerned patients with mildly impaired or good renal function. Since patients with a GFR < 60 ml/min/1.73m^2 were poorly represented in the studies, further research is needed to validate the MDRD-4 formula in HIV-infected patients with moderate to severe CKD.

We excluded studies which did not fulfil our criteria concerning statistical analysis. A frequently used method to compare different formulas to estimate the GFR is the correlation coefficient.[3,7] However, the most informative method to assess diagnostic tests is the Bland-Altman plot as this identifies the direction and the magnitude of the bias.[24,34,35] Apparently there is no consensus on how to present the agreement between two diagnostic tests. This is needed to interpret studies with the aim to compare diagnostic tests easily and in the same way.

Another limitation is the lack of details concerning other potentially influential factors. Many factors can influence the generation, clearance or measurement of creatinine, such as diabetes, liver disease, obesity, malnutrition, muscle wasting, amputation, hospitalization, vegetarian diet, ingestion of cooked meat, neuromuscular diseases, inflammation, ethnicity and medication (such as trimethoprim, cimetidine, some cephalosporins).[16,21] The studies included did not adequately specify to which extent these factors were present or absent in their patient population.

The results of this review do not suggest a correction factor for HIV-infected patients with normal BMI in the MDRD-4 formula. Although more evidence is needed, especially in moderate to severe renal impairment, physicians may use the MDRD-4 formula in clinical practice to personalize pharmacotherapy. The use of the MDRD-4 formula instead of the Cockcroft-Gault (CG) formula in drug dosing has been debated in general in the literature. Hudson et al. found that the MDRD estimate results in higher doses compared to the CG formula.[36] Conversely, Stevens et al. found a high concordance rate between the MDRD and CG formula compared to mGFR (determined with ^{125}I-iothalamate), namely 88% and 85%, respectively ($p < 0.001$).[37] The Food and Drug Administration now allows

manufacturers to provide drug dosing advice based on CG or MDRD formulas.[36,38] The applicability of the Chronic Kidney Disease EPIdemiology (CKD-EPI) formula is also discussed. The CKD-EPI formula exhibits more or less similar accuracy as the MDRD formula in non-HIV and HIV-infected patients for the lower ranges of the GFR (< 60 ml/min/1.73m^2) where dose adjustment usually should take place.[39–41] In the higher ranges of the GFR (≥ 60 ml/min/1.73m^2) the CKD-EPI performs better than the MDRD-4 formula.[18] Further research should include the CKD-EPI formula in addition to the MDRD formula.

In patients with renal impairment the first step is adjusting the dosage of antiretroviral agents according to international HIV treatment guidelines. For some antiretroviral agents therapeutic drug monitoring might be considered.[42] Switching to another antiretroviral drug which is not renally excreted needs to be considered in renal impairment, although possibilities may be limited in some patients, for instance, because of drug resistance. Physicians should always be aware that personalizing pharmacotherapy is a consideration between efficacy and toxicity, especially in HIV-infected patients where drug resistance is of major concern.[43]

In addition the clinical relevance of the potential inaccuracy of the eGFR in HIV-infected patients needs to be considered. The reliability of a formula depends on bias and precision. Both measurements are combined in the term 'accuracy'. The K/DOQI guidelines state that a deviation of 30% from the true GFR is acceptable. Ideally, when the accuracy is defined as P_{30} this measurement should reach 100%.[6,14] However, the included studies showed a P_{30} beneath 100%. The studies of Barraclough et al.[14] and Vrouenraets et al.[8] with a P_{30} of 89% and 89%, respectively, came nearby, but in the population of Beringer et al.[6] P_{30} was only 64%, meaning that the eGFR will deviate by more than 30% from the true GFR in almost 1/3 of cases.

An accurate eGFR is increasingly important because of the longer life-expectancy of HIV-infected patients with associated co-morbidities such as diabetes mellitus and hypertension. Although the median bias has a negative direction, the range of the precision shows that the MDRD-4 formula can also overestimate the true GFR in HIV-infected patients. This may lead to an early or late start of the management of impaired renal function, but also to incorrect dosing of antiretroviral drugs or co-medication, because the GFR may point at an incorrect category of CKD.

Based on the available information we found no indication that in good to mild impaired renal function (GFR ≥ 60 ml/min/1.73m^2) the MDRD-4 formula is less valid in HIV-positive patients compared to HIV-negative patients. Since patients with

a GFR < 60 ml/min/1.73m^2 were poorly represented by the studies, further research is needed to validate the MDRD-4 formula in HIV-infected patients with moderate to severe CKD. In selected situations, such as in patients with severe renal impairment or in patients who suffer from the HIV-wasting syndrome, measurement of the GFR with a gold standard rather than using the MDRD formula should be considered.

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Appendix 2.1 Search terms

Assessment of the renal function
Glomerular filtration rate and creatinine
Reliability
"Predictive Value of Tests"[Mesh Terms] *OR* "Reference Values"[Mesh Terms] *OR* predictive value* *OR* reference value* limitation *OR* limitations pitfalls *OR* pitfall overestimated *OR* underestimated *OR* underestimation *OR* overestimation *OR* overestimating *OR* underestimating disturbance *OR* interference "diagnostic errors"[MeSH Terms] *OR* (diagnostic AND errors) "sensitivity and specificity"[MeSH Terms] *OR* sensitivity *OR* specificity marker *OR* markers *OR* "Biological Markers"[Mesh Terms] accurate *OR* inaccurate *OR* inaccuracy *OR* accuracy
Creatinine-based formulas
(cockcroft AND gault) *OR* cockcroft-gault *OR* MDRD *OR* (modification AND diet) *OR* "kidney diseases"[MeSH Terms] *OR* (kidney AND diseases) *OR* renal disease
Date of publication
2000 – current (August 2012)
Diagnosis
Human immunodeficiency virus *OR* "HIV"[MeSH Terms] *OR* HIV

Individualizing pharmacotherapy in patients with renal impairment:

The validity of the Modification of Diet in Renal Disease formula in specific patient populations with a glomerular filtration rate below 60 ml/min. A systematic review

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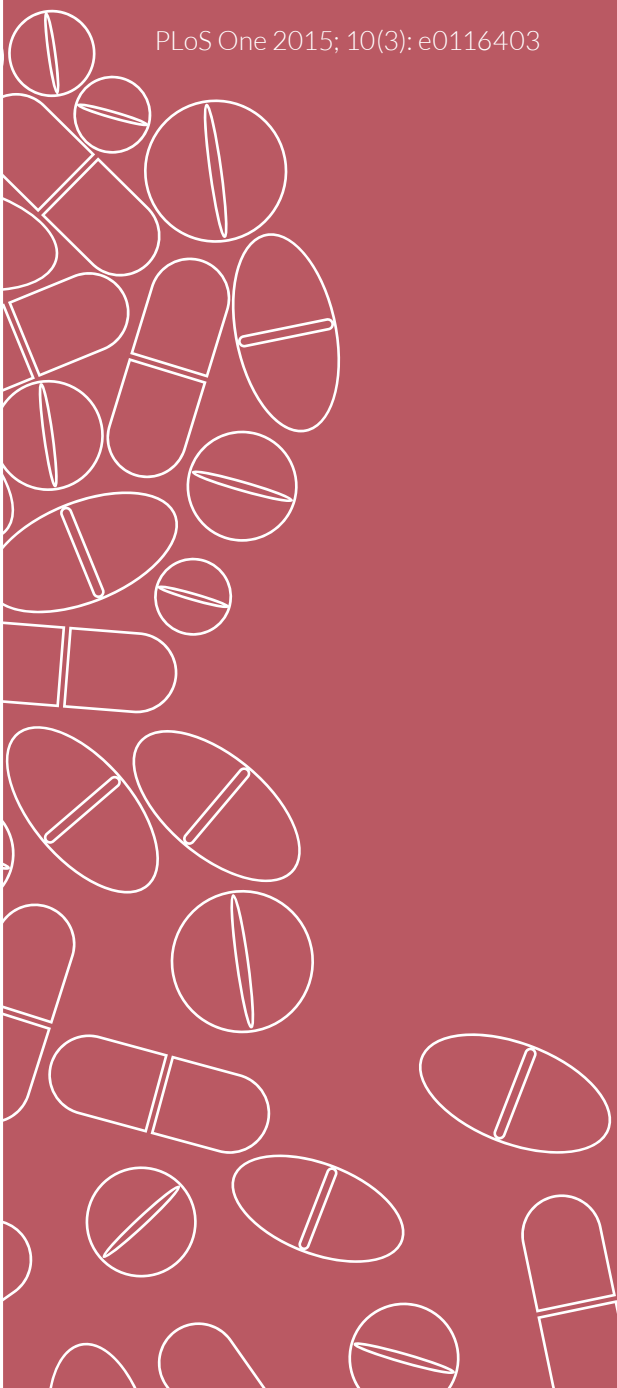

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3

Abstract

Background

The Modification of Diet in Renal Disease (MDRD) formula is widely used in clinical practice to assess the correct drug dose. This formula is based on serum creatinine levels which might be influenced by chronic diseases itself or the effects of the chronic diseases. We conducted a systematic review to determine the validity of the MDRD formula in specific patient populations with renal impairment: elderly, hospitalized and obese patients, patients with cardiovascular diseases, cancer, chronic respiratory diseases, diabetes mellitus, liver cirrhosis and human immunodeficiency virus.

Methods and findings

We searched for articles in Pubmed published from January 1999 through January 2014. Selection criteria were (1) patients with a glomerular filtration rate (GFR) < 60 ml/min(/1.73m^2), (2) MDRD formula compared with a gold standard, and (3) statistical analysis focused on bias, precision and/or accuracy. Data extraction was done by the first author and checked by a second author. A bias of 20% or less, a precision of 30% or less and an accuracy expressed as P_{30} of 80% or higher were indicators of the validity of the MDRD formula. In total we included 27 studies. The number of patients included ranged from 8 to 1831. The gold standard and measurement method used varied across the studies. For none of the specific patient populations the studies provided sufficient evidence of validity of the MDRD formula regarding the three parameters. For patients with diabetes mellitus and liver cirrhosis, hospitalized patients and elderly with moderate to severe renal impairment we concluded that the MDRD formula is not valid. Limitations of the review are the lack of considering the method of measuring serum creatinine levels and the type of gold standard used.

Conclusion

In several specific patient populations with renal impairment the use of the MDRD formula is not valid or has uncertain validity.

Introduction

Chronic kidney disease (CKD) is a common condition and affects up to 13% of the population.[1] CKD is defined as a glomerular filtration rate (GFR) < 60 ml/min/1.73m^2 or evidence of kidney damage (proteinuria, haematuria and/or abnormalities of the kidney) for at least 3 months regardless of underlying cause.[2,3] CKD is associated with adverse outcomes, such as kidney failure, cardiovascular diseases and death.[2,4,5] Since laboratories routinely report the estimated GFR (eGFR) if serum creatinine testing is ordered, the awareness of impaired renal function among physicians has increased in recent years.[6-8]

The eGFR is not only used to diagnose CKD or to monitor its course in patients with kidney disease, but also to guide decisions in pharmacotherapy. Potential uses of the eGFR in drug therapy are: (1) signal that treatment of CKD is warranted, (2) signal that a drug may be contraindicated, (3) signal that renal drug toxicity is developing, (4) signal that the risk of an adverse drug reaction or drug-drug interaction may be increased or (5) signal that a drug may be less effective. Approximately 20-30% of adverse drug reactions (ADRs) leading to hospital admission of elderly patients are related to impaired renal function.[9,10] This was mainly due to excessive doses of drugs and could have been avoided by close monitoring of renal function and adjustment of pharmacotherapy in terms of the prescribed agent(s) and/or the prescribed dosage(s).[9]

Drug dosing recommendations traditionally have used the Cockcroft and Gault (CG) formula to estimate creatinine clearance and therefore the ability of the kidney to excrete drugs.[6,11] This formula was developed in 249 adult men by using the mean 24-h urine creatinine excretion from two urine collections.[12,13] The adjustment factor for women was based on a theoretical 15% lower muscle mass.[13,14] Approximately 15 years ago a new formula was developed that provided a more accurate estimation of GFR.[15,16] The original six variable Modification of Diet in Renal Disease (MDRD) formula, MDRD-6, was developed in a sample of 1070 ambulatory, predominantly white patients with CKD.[15] The six variables were serum creatinine concentration, age, sex, ethnicity, serum urea nitrogen concentration and albumin concentration.[15] Several years later (in the year 2000), this formula was simplified to 4 variables (serum creatinine concentration, age, sex and ethnicity), MDRD-4.[16] The latter is now routinely used by many clinical laboratories worldwide.[17-20] Variability in the use of different creatinine assays among clinical laboratories led to the introduction of isotope dilution mass spectrometry (IDMS) calibration of the creatinine assays.[17,21,22] This led to the re-expression of the MDRD formulas. The MDRD formulas are presented in Box 3.1.

Box 3.1 MDRD equations

MDRD-6[15]
$170 \times S_{cr}^{-0.999} \times age^{-0.176} \times BUN^{-0.170} \times albumin^{+0.318} \times 1.180$ (if black) x 0.762 (if female)
Re-expressed after IDMS calibration[21]
$161.5 \times S_{cr}^{-0.999} \times age^{-0.176} \times BUN^{-0.170} \times albumin^{+0.318} \times 1.180$ (if black) x 0.762 (if female)
MDRD-4[16]
$186 \times S_{cr}^{-1.154} \times age^{-0.203} \times 1.212$ (if black) x 0.742 (if female)
Re-expressed after IDMS calibration[21]
$175 \times S_{cr}^{-1.154} \times age^{-0.203} \times 1.212$ (if black) x 0.742 (if female)

S_{cr} = serum creatinine (mg/dl)
BUN = blood urea nitrogen (mg/dl)
Albumin (g/dl)

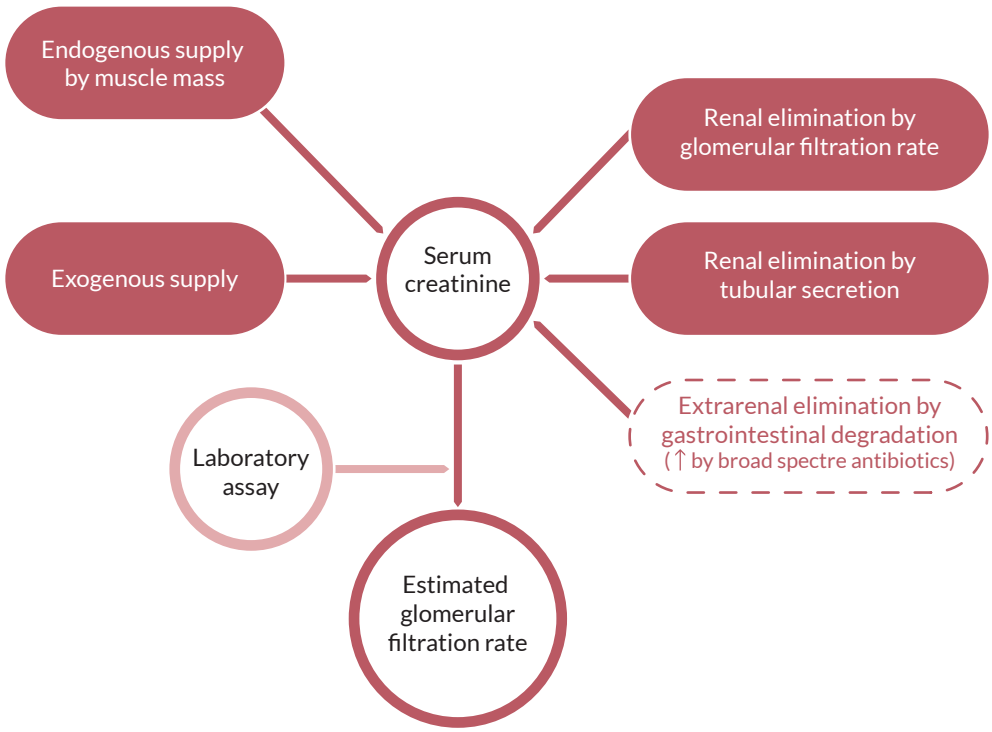
Although there is an ongoing debate on whether the MDRD formula can safely replace the CG formula in drug dosing[20,23], the MDRD formula is now widely used in clinical practice for drug dosing in various patient populations.[19,24,25] The aim of this article is to review systematically the validity and limitations of the MDRD formula in specific patient populations with a known glomerular filtration rate below 60 ml/min where adjustment of the pharmacotherapy usually should take place.

Background

The MDRD formula is an estimation of the true GFR. The true GFR is the product of the filtration rate in single nephrons and the number of nephrons in both kidneys.[4] The ideal filtration marker to determine the true GFR is freely filtered across capillary walls, unhindered by its size, charge or binding to plasma proteins and neither secreted nor reabsorbed.[4] Inulin fulfils these criteria, but is not widely used for this purpose in clinical practice, because of the necessity for intravenous infusion and the difficult chemical assay required for inulin measurement.[26] The true GFR can also be measured using other markers such as ^{51}chromium ethylene-diamine-tetra-acetic acid (^{51}Cr-EDTA), technetium-labelled diethylene-triamine-pentacetate (^{99m}Tc-DTPA), iohexol and iothalamate.[27] However, these markers are also impractical for routine clinical use due to limited access to necessary diagnostic facilities and high costs.[3,28]

Creatinine is generally considered a good filtration marker to estimate the renal function in routine clinical practice. Serum creatinine level is a function of endogenous creatinine production, exogenous creatinine supply and renal elimination (glomerular filtration and tubular secretion).[29] There is a clear inverse correlation between serum creatinine levels and the true GFR. However there are several factors which may influence serum creatinine levels without affecting GFR itself, which potentially distort the interpretation of values for clinical use (see Figure 3.1).[3,4,27,30,31]

Figure 3.1. Determinants of serum creatinine level



Endogenous creatinine production

Creatinine is formed primarily in skeletal muscles from creatine and creatine phosphate.[29] Muscle mass is the most important determinant of total body creatine content and therefore of the creatinine production.[26] Muscle mass is related to age, sex and race.[4,26,32] Although the MDRD formula corrects for age, sex and race, the formula assumes an average muscle mass. However, muscle mass can deviate across individuals in anabolic or catabolic conditions. Thus, muscle-waisting conditions, e.g. due to neuromuscular disease, chronic glucocorticoid therapy, hyperthyroidism, amputation or progressive muscular dystrophy are associated with decreased creatinine production, whereas exercise and body building are associated with increased creatinine generation.[4,26,32] In diseases with abnormally low muscle mass, serum creatinine levels will be relatively low, leading to an overestimation of the GFR, whereas the opposite will occur when the muscle mass is abnormally high.

In addition, the liver plays a major role in the biosynthesis of creatine. The rate of creatine formation and therefore the rate of creatinine production in the muscles is reduced in certain types of hepatic diseases.[33]

Exogenous creatinine supply

Dietary intake of creatinine and creatine can be either unusually high (ingestion of cooked meat, creatine supplementation) or unusually low (vegetarian diet).[4,26] This may lead to underestimation and overestimation of the GFR, respectively.

Laboratory assay of serum creatinine

Two assays are now mostly used in clinical practice to measure serum creatinine levels, namely the alkaline picrate assay (Jaffe) and the enzymatic assay. The Jaffe assay is known to have more interfering substances than the enzymatic method, which may result in a deviation of the true serum creatinine level up to 20%.[3,34] Substances which interfere with the Jaffe assay and may lead to an overestimation of serum creatinine levels include bilirubine, 5-aminolevulic acid, and high dose of lactulose. High doses of furosemide may lead to an underestimation of serum creatinine levels and cephalosporins may lead to both over- and underestimation of serum creatinine levels.[35-39] Substances which interfere with the enzymatic assay include dopamine, dobutamine, glucose and flucytosine.[26,35,36] These interferences may lead to an underestimation of serum creatinine levels and therefore an overestimation of the GFR, except for flucytosine. Flucytosine may overestimate serum creatinine levels with more than 100% and therefore underestimate the GFR.[36]

In addition to interferences of certain drugs in the creatinine assays, there are also differences in creatinine values between clinical laboratories due to differences in the creatinine assays and their calibration. Therefore an uniform creatinine measurement and an universal known calibration of the serum creatinine assays has led to the introduction of IDMS calibration.[18,40]

Creatinine secretion

Creatinine is not only excreted by glomerular filtration, but also by the renal tubules. In addition, in patients with severe renal impairment a substantial fraction of the daily creatinine production is eliminated via extrarenal routes.[26] This might lead to relatively low serum creatinine levels, leading to an overestimation of the GFR. The creatinine secretion might also be altered in situations such as trauma, prolonged immobilization and hepatic disease.[26] The etiology of these changes is unknown. Some drugs, such as cimetidine, trimethoprim and fibrates (except gemfibrozil) also alter the secretion of creatinine due to inhibition of the tubular secretion.[4,36,41] As a result serum creatinine levels will increase, independent of the GFR, and the use of serum creatinine based formulas will thus cause an underestimation of GFR. Of note, blocking creatinine secretion ensures a better reflection of the true GFR with creatinine-based formulas.[42,43]

Serum creatinine levels thus provide only a rough guide to the true GFR.[26] While the dependence of serum creatinine on muscle mass is partially accounted for in the MDRD formula (age, sex and race), various other factors influencing both production and secretion of creatinine can be present. Awareness of these limitations of creatinine-based formulas which estimate GFR is therefore necessary. In addition, variability in eGFRs also includes underlying biological intraindividual and interindividual variation of serum creatinine values ranging from 6.3% to 17%.[12,22,44]

Of note, serum creatinine levels and creatinine based formulas should only be used in patients with stable renal function. In cases of rapidly changing GFR, the actual serum creatinine levels will not reflect the GFR until steady-state has been reached.[45] A diagnosis of a low GFR must therefore rely on multiple measures of serum creatinine levels.[46]

Methods

Search strategy

We performed a systematic search in the Pubmed database for published studies about the validity of the MDRD formula in diverse patient populations. The search focused on publications between January 1999 (the introduction of the MDRD formula[15]) and January 2014. We searched for both the MDRD-4 and MDRD-6 formulas. The terms used for the overall search strategy have been listed in Appendix 3.1.

Selection criteria

We focused on studies in patients with a measured GFR (mGFR) or estimated GFR (eGFR) < 60 ml/min(/1.73m^2). Other selection criteria were: (1) MDRD formula compared with a gold standard (defined as: ^{99m}Tc-DTPA, inulin (including the analogue sinistrin[47]), ^{51}Cr-EDTA, ^{125}I- iothalamate and iohexol) and (2) statistical analysis and reporting focused on bias, precision and/or accuracy (see Table 3.1 for definitions).

We excluded case reports, abstracts, and posters. Articles which reproduced data already published elsewhere were carefully reviewed. Only if newer data added information to our review, the article was included.

Selection of patient populations

In this review we will first discuss three more general patient groups, which were inadequately represented in the development of the MDRD formula, namely (1) elderly patients, (2) hospitalized patients and (3) obese patients.

Table 3.1 Definitions outcome measurements

Bias		**References**
Median difference	md eGFR – mGFR	67, 120
Median percentage difference[a]	md ((eGFR – mGFR)/mGFR) x 100%	120
Mean difference	1/n x Σ (eGFR – mGFR)	135
Mean percentage difference[b]	1/n x Σ ((eGFR – mGFR)/mGFR) x 100%	142
Precision		
Inter quartile range (IQR) difference	IQR of (eGFR – mGFR)	67
IQR percentage difference[a]	IQR of (eGFR – mGFR)/mGFR x 100%	67
Limits of agreement (LOA)	Mean difference ± 1.96 SD	135, 136
Standard deviation difference (SD)	σ of all the individual differences	67,135
Accuracy		
P_k [c]	Percentage of estimates within k% of mGFR	67
Median absolute percentage error (mAPE)	md ((|eGFR – mGFR|)/mGFR) x 100%	142
Mean absolute percentage error (MAPE)	1/n x Σ ((|eGFR – mGFR|)/mGFR) x 100%	142

[a] Preferred definition because a relative scale provides a more relevant metric.[24]
[b] In some articles the mean percentage difference was called the mean percentage error (MPE).
[c] Preferred definition of accuracy. We limited our search to P_{10}, P_{20}, P_{30} and P_{50}.
eGFR, estimated glomerular filtration rate; IQR, inter quartile range; LOA, limits of agreement; mGFR, measured glomerular filtration rate; md, median; SD, standard deviation.

The MDRD formula was developed in a relatively young patient population (mean age: 51 ± 13 years) with CKD.[15,48] The mean body weight was 79.6 ± 16.8 kg and the mean body surface area (BSA) was 1.91 ± 0.23 m^2.[15] The body mass index (BMI) calculated from the mean weight and BSA is approximately 28 kg/m^2, so the population was not obese (> 30 kg/m^2) as a whole. Creatinine production decreases as muscle mass decreases with age or due to immobility, which is common in hospitalized patients.[49] When this results in low serum creatinine levels creatinine-based formulas may overestimate the GFR.[50] In addition, elderly, malnourished, and immobilized patients are at special risk of having depressed GFR but normal serum creatinine levels, so normal serum creatinine concentration cannot exclude significant renal impairment.[51-53] Because of these considerations we found elderly patients (≥ 65 years), hospitalized patients and obese patients (> 30 kg/m^2) of interest for further evaluation.

Second, we will discuss four common categories of chronic diseases, which are the leading cause of death in the developed world: (4) cardiovascular diseases (e.g. myocardial infarction, heart failure and stroke), (5) cancer, (6) chronic respiratory diseases (like chronic obstructed pulmonary disease (COPD) and asthma), and (7) diabetes mellitus.[54] These diseases are associated with the use of multiple drugs of

which a substantial part is renally excreted. The chronic diseases itself or the effects of the chronic diseases may alter serum creatinine levels without affecting GFR itself. In patients with chronic heart failure, a cardiovascular disease, the effective circulating volume is reduced, blood pressure is low and therefore renal perfusion pressure is reduced, leading to reduced filtration rate in viable nephrons and probably also to reduced excretion of creatinine.[55,56] The tubuli, however, are still capable of secreting creatinine actively.[55] In addition, the cornerstone in heart failure therapy are renin-angiotensin-aldosterone-system (RAAS)-inhibitors, which also may reduce glomerular filtration pressure and therefore excretion of creatinine.[56] These different mechanisms may influence serum creatinine levels. In addition, patients with heart failure are often immobile and therefore at risk for having lower serum creatinine levels.

In cancer and COPD unknown mechanisms may influence creatinine levels without affecting GFR, but reduced muscle mass and malnourishment may also be present. This latter may result in low serum creatinine levels and therefore in overestimation of the GFR. In diabetes mellitus, the choice of drugs or dosages is influenced by GFR.[57]

Finally, we searched for articles about (8) other chronic diseases in which reduced muscle mass (mainly due to immobility and malnutrition) can be present, which may render the MDRD formula less valid. Such diseases include neuromuscular diseases, rheumatoid arthritis, cystic fibrosis, human immunodeficiency virus (HIV) and liver diseases.[58-62] In certain liver diseases the production of serum creatinine is also reduced to approximately one half of the rate of patients with normal hepatic function.[58,60,63] Hyperbilirubinemia is also common among patients with liver diseases. Elevated serum bilirubine levels interfere with the Jaffe method to measure creatinine, which might lead to misleadingly low serum creatinine levels.[35,58,64]

Extraction of studies

The data and outcomes reported in the selected articles were summarized, specifically focusing on the selection of the study population, age, mean mGFR, type of creatinine assay used, type of gold standard used, mean eGFR and the outcome measures as defined in Table 3.1. Data extraction was done by the first author (WE) and checked by a second author (MW).

Description of the findings focused on:

a. number of patients included;
b. outcome measures;
c. method of measuring true GFR.[27,65]

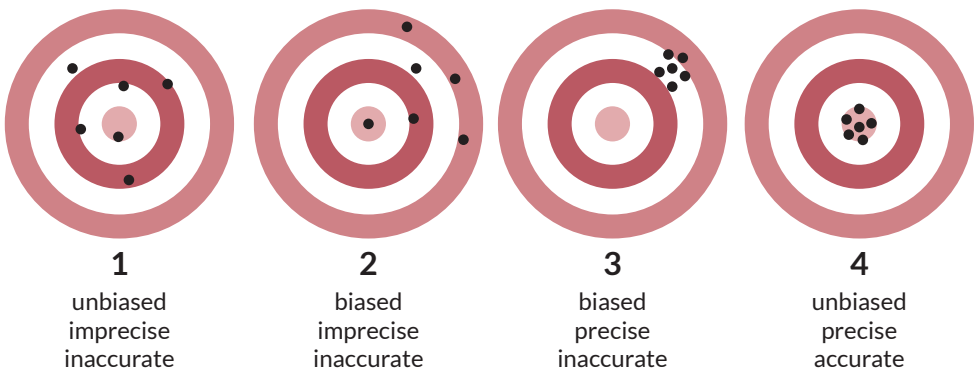
Ad (a) number of patients included

Preferably more than 100 patients should be included.[5,17] Studies with more than 100 patients included were considered of higher value in the interpretation than studies with less than 100 patients.

Ad (b) outcome measures

One of our inclusion criteria concerned the presence of outcome measures: bias, precision and accuracy. Bias represents systematic error, precision represents random error and accuracy represents both (see Figure 3.2).

Figure 3.2. Bias, precision and accuracy



In developing a model or formula, bias can to some extent be corrected by means of a correction factor. An example is the correction factor of 1.212 for Black-Americans in the MDRD formula.[15] Remaining bias refers to confounding factors for which corrections have not been included. It is not possible to completely correct for lack of precision (random error) in a model or formula. Precision is therefore an important indicator for the evaluation of the reliability of a clinical measure. Precision has been defined as the variance of the bias. The wider the variance of the bias, the higher the number that represents the precision, or in other words a wide imprecision. Accuracy is a validity indicator, which represents both precision and bias, thus systematic and random error. Accuracy is often expressed as a percentage of estimates within k% of mGFR (P_k). This outcome measure is probably most easily to interpret from a clinical perspective. For example, if P_{30} is 50%, it means that in half of the cases the

eGFR falls within ± 30% of the mGFR. Due to intraindividual and interindividual variation of serum creatinine levels and analytical variation of the measurement of serum creatinine levels and other influencing factors a P_{30} of 100% will hardly be achievable.[5,12,22] In line with other authors we considered a bias of 20% or less, a precision of 30% or less and an accuracy expressed as P_{30} of 80% or higher as indicator of sufficient validity.[14,66,67]

Ad (c) method of measuring true GFR

Several methods for true GFR measurement are available, including urinary clearance, plasma clearance or a combination of both from exogenous markers, such as ^{99m}Tc-DTPA, ^{51}Cr-EDTA, ^{125}I-iothalamate and iohexol.[68,69]

With urinary clearance, two to four 20 to 30 minutes urine collections are obtained, after administration of the exogenous marker. Urinary clearance is computed as the urine concentration of the exogenous marker multiplied by the volume of the timed urine sample, and divided by the average plasma concentration during the same time period.[27] Plasma clearance is computed from the amount of the exogenous marker administered divided by the area under the curve of plasma concentration over time. The best estimate is a two-compartment model that requires blood sampling two to three time points until 60 minutes and one to three time points from 120 minutes forward.[27]

The clearance of inulin is determined by collecting three sets of 30 minutes urinary clearance periods during a continuous intravenous infusion with 1% of inulin. Blood samples should be collected at least three times at the midpoint of the urine collections. Bladder catheterization is necessary to assure complete urine collection.[27,70] Tests containing sinistrin, an analogue of inulin and also a fructan, is frequently used as a gold standard for the measurement of GFR and therefore included in our review.[47,71]

Results and interpretation

We identified 1179 citations with the search terms listed in Appendix 3.1. In total we included 27 studies. The flow of study selection is reported in Figure 3.3. In Table 3.2 the most important information from the selected studies is summarized. The PRISMA checklist is provided as Appendix 3.2.

Figure 3.3. Flow of study selection

Elderly patients

Background

CKD is common in elderly and is associated with a high risk of cardiovascular complications.[66,69] Early recognition, intervention and management of patients with CKD by physicians has been shown to slow progression of disease and decrease complications.[72] Accurate estimate of GFR is important to detect elderly patients at risk for progressive CKD, but also in order to guide drug therapy of potentially

nephrotoxic drugs, or to adapt therapy with renally excreted drugs which is often desirable in elderly patients on polypharmacy.[73-75]

Summary of the selected articles

We included nine studies, four of which were conducted in 2013. The definition of elderly or older patients ranged from 65 to 80 years or older. The mean bias reported ranged from an underestimation of 20 ml/min/1.73m^2 in the study of Bevc et al. to an overestimation of 29% in the study of Drenth-van Maanen et al.[47,76] Interpretation of precision is more difficult. The IQR of 11 ml/min/1.73m^2 reported by Kilbride et al. is reasonable when considering persons with higher ranges of mGFR (around 60 ml/min/1.73m^2), but would be less acceptable in the lower ranges of the mGFR. The accuracy reported as P_{30} was almost 80% which implies that the variance of the bias, the precision, is too large over the total range from 7 to 60 ml/min/1.73m^2.[77] Although, four studies reported a bias within our 20% criteria[71,77,78,79], only two studies reported an accuracy above 80%, namely Stevens et al. and the subanalysis of the Kidney Disease: Improving Global Outcomes (KDIGO) CKD stage 3A in the study of Koppe et al.[71,79] In five studies (56%) the number of patients included exceeded 100.[71,76,77,79,80] Six out of nine studies described the method for measuring GFR adequately. The gold standards were reasonably performed, but only the studies of Drenth-van Maanen et al. and Froissart et al. met the number of blood samples taken over time as described above.[47,78]

Interpretation and conclusion

The nine included studies were performed reasonably. There was only one study in which the MDRD formula appeared to be valid.[79] Earlier Pottelbergh et al. conducted a systematic review with broader selection criteria and reported both over- and underestimation of the mGFR.[69] They concluded that there is no accurate creatinine-based formula to evaluate renal function in elderly patients.[69] With the more recently published studies presented here, we can confirm the conclusion that the creatinine-based MDRD formula is not valid in elderly patients.

Table 3.2 Validity of the MDRD formula in specific patient populations

Article	Study population (n = number of patients)	Mean ± SD age (years)	Mean ± SD mGFR	Gold standard
Elderly patients				
Lopes et al., 2013, Brasil[143]	n = 56 Subanalysis: mGFR < 60 ml/min/1.73m^2. Inclusion criteria: age ≥ 80 years, clinically stable, independent in activities. Exclusion criteria: to be institutionalized, unable or willing to give consent, acute infection, moderate or severe cognitive impairment, heart failure, cirrhosis, previously received dialysis, unstable COPD, previous immunosuppressive therapy within 6 months, previous chemotherapy for cancer, known HIV infection, and previously reported allergic reaction to iodine.	-*	-*	Iohexol; Blood samples were withdrawn 2, 3, 4 and 5 h after infusion.
Evans et al., 2013, Sweden[80]	n = 1831 Subanalysis: age ≥ 65 years. Inclusion criteria: patients with an iohexol measurement ≤ 30 ml/min/1.73m^2, a registered plasma creatinine on the same date, between 1999 and 2010. Exclusion criteria: renal transplants, dialysis, patients from the Lund-Malmö region.	-*	median (IQR): 15 (12-20) ml/min/1.73m^2	Iohexol; Blood samples were withdrawn at baseline and after 6-8 h or 48 h after injection for patients with eGFR between 15-30 ml/min/1.73m^2 and ≤ 15 ml/min/1.73m^2, respectively.
Koppe et al., 2013, France[71]	n = 53, KDIGO CKD stage 3A n = 68, KDIGO CKD stage 3B n = 66, KDIGO CKD stage 4-5 Inclusion criteria: age > 70 years, white (Caucasian), underwent inulin clearance for suspected or established renal dysfunction.	-*	-*	Sinistrin; Loading dose followed by continuous infusion. Urine and plasma collection (time and numbers not described).
Drenth-van Maanen et al., 2013, The Netherlands[47]	n = 16 Inclusion criteria: patients with eGFR(MDRD) ≤ 60 ml/min/1.73m^2, age ≥ 70 years, stable medical condition and cognitively able to give informed consent at acute care and outpatient geriatric ward.	82 range: 71-87	39.6 ± 14.9‡ ml/min/1.73m^2	Sinistrin; Bolus injection, blood samples were withdrawn at 10, 20, 30, 60, 90, 120, 240 and 480 min after infusion.
Kilbride et al., 2012, United Kingdom[77]	n = 234 Subanalysis: mGFR < 60 ml/min/1.73m^2. Inclusion criteria: ≥ 74 years Exclusion criteria: iodinated contrast media allergy, active malignancy, life expectancy less than 3 months, cognitive impairment, recent episode (within 3 months) of AKI, dialysis.	-*	-*	Iohexol; Bolus injection, blood samples were withdrawn at 120, 180 and 240 min.

Creatinine measurement	Mean ± SD eGFR(MDRD)	Bias	Precision	Accuracy
Jaffe	-*	Re-expressed MDRD-4 mean: 5.9 ml/min/1.73m^2	Re-expressed MDRD-4 SD: 14.1 ml/min/1.73m^2	Re-expressed MDRD-4 P_{30}: 64.3%
Enzymatic or Jaffe	-*	-*	-*	Re-expressed MDRD-4 P_{30}: 64.6%
Enzymatic	-*	Re-expressed MDRD-4‡ Stage 3A median: 2 ml/min/1.73m^2 Stage 3B median: 6.7 ml/min/1.73m^2 Stage 4-5 median: 5.95 ml/min/1.73m^2	Re-expressed MDRD-4‡ Stage 3A SD: 13.53 ml/min/1.73m^2 Stage 3B SD: 11.69 ml/min/1.73m^2 Stage 4-5 SD: 8.6 ml/min/1.73m^2	Re-expressed MDRD-4‡ Stage 3A P_{10}: 41.51%; P_{30}: 84.91% Stage 3B P_{10}: 28.99%; P_{30}: 73.91% Stage 4-5 P_{10}: 19.7%; P_{30}: 59.09%
Jaffe	MDRD-4 48.6 ± 13.8‡ ml/min/1.73m^2	MDRD-4 mean: 29.1%	MDRD-4 LOA: -16 to 34 ml/min/1.73m^2	MDRD-4 P_{30}: 62.5%
Enzymatic	-*	Re-expressed MDRD-4 median: 2.0 ml/min/1.73m^2	Re-expressed MDRD-4 IQR: 11.4 ml/min/1.73m^2	Re-expressed MDRD-4 P_{30}: 78%

Article	Study population (n = number of patients)	Mean ± SD age (years)	Mean ± SD mGFR	Gold standard
Bevc et al., 2011, Slovenia [76]	n = 266 Subanalysis: mGFR < 60 ml/min/1.73m^2. Inclusion criteria: age > 65 years, Caucasian.	-*	-*	^{51}Cr-EDTA; After single injection blood samples were withdrawn at 120, 180 and 240 min.
Stevens et al., 2007, United States[79]	n = 580 Subanalysis: age > 65 years and eGFR < 60 ml/min/1.73m^2. The results have been compiled from data from different studies.	-*	-*	Iothalamate; Withdrawing of samples was not described.
Fontsere et al., 2006, Spain[144]	n = 43 Subanalysis: age ≥ 65 years. Inclusion criteria: Caucasian adult patients with CKD stages 4-5.	-*	22.9 ± 6.8 ml/min/1.73m^2	^{51}Cr-EDTA; Withdrawing of samples was not described.
Froissart et al., 2005, France[78]	n = -* Subanalysis: age > 65 years and mGFR < 60 ml/min/1.73m^2. Exclusion criteria: renal transplant patients and age < 18 years, black patients.	-*	-*	^{51}Cr-EDTA; Collection of urine 1 h after injection and then 5 consecutive 30-min clearances. Blood was withdrawn at midpoint of each clearance period up to 300 min after injection.
Hospitalized patients				
Frank et al., 2012, Switzerland [145]	n = 69 Inclusion criteria: Caucasian patients, age > 70 years, with CKD stage 3-4 according to KDOQI guidelines of the internal medicine ward. Stable weight for 4 days. Exclusion criteria: unstable renal function in the last two weeks.	median (IQR): 80 (73-83)	median (IQR): 30.9 (22.0-43.3) ml/min	Inulin; Blood samples were withdrawn at baseline, 90, 180, 270 and 360 min.
Poggio et al., 2005, California[85]	n = 107 Inclusion criteria: patients who had mGFR performed with varying degrees of kidney dysfunction. Exclusion criteria: incomplete data, dialysis, serum creatinine level < 0.3 mg/dl (< 27 umol/l), unstable renal function.	65 ± 15	17.1 ± 17.9 ml/min/1.73m^2	Iothalamate; Bolus injection, blood samples were withdrawn at 5, 10, 15, 300, 330 and 360 min. In case of expected GFR < 30, age > 65, or creatinine level > 2.5mg/dl, a sample at 24 h was also collected.
Schuck et al., 2005, Czech Republic[86]	n = 79 Nephrology Department; Inclusion criteria: GFR < 50 ml/min/1.73m^2. Exclusion criteria: cachexia	range: 20-65	19.1 ± 10.1 ml/min/1.73m^2	Inulin; After equilibrium phase (60 min), urine collection during 60-90 min by spontaneous urination

Creatinine measurement	Mean ± SD eGFR(MDRD)	Bias	Precision	Accuracy
Jaffe	-*	MDRD-4 mean: -20.2 ml/min/1.73m^2	MDRD-4 SD: 14.9 ml/min/1.73m^2	MDRD-4 30-59 ml/min/1.73m^2 P_{30}: 77.9% 15-29 ml/min/1.73m^2 P_{30}: 56.6% < 15 ml/min/1.73m^2 P_{30}: 55.2%
-*	-*	MDRD-4 median: -1.2%	-*	MDRD-4 P_{30}: 82%
Jaffe	-*	MDRD-4 mean: -4.1 ml/min/1.73m^2	-*	-*
Jaffe	-*	MDRD-4 Male mean: 5.6% Female mean: 7.6%	MDRD-4 Male SD: 31.4% Female SD: 34.1%	-*
Jaffe	Re-expressed MDRD-4 median: 47.9 ml/min	Re-expressed MDRD-4 median: 16.3 ml/min	Re-expressed MDRD-4 IQR: 6.4 to 27.5 ml/min	-*
Jaffe	MDRD-4 23.9 ± 16.3 ml/min/1.73m^2 MDRD-6 22.5 ± 17.4 ml/min/1.73m^2	MDRD-4 median: 53% MDRD-6 median: 46%	-*	MDRD-4 MAPE: 53% P_{30}: 31% P_{50}: 49% MDRD-6 MAPE: 47% P_{30}: 36% P_{50}: 55%
Jaffe	MDRD-6 22.1 ± 8.3 ml/min/1.73m^2	MDRD-6 mean: 3.26 ml/min/1.73m^2	MDRD-6 LOA: -5.7 to 12.2 ml/min/1.73m^2	-*

Article	Study population (n = number of patients)	Mean ± SD age (years)	Mean ± SD mGFR	Gold standard
Obese patients				
Bouquegneau., 2013, Belgium[89]	n = 207 Subanalysis: mGFR < 60 ml/min/1.73m^2. Inclusion criteria: > 18 years and BMI > 30 kg/m^2. Exclusion criteria: patients treated with steroids, cimetidine or trimethoprim.	-*	36 ± 13 ml/min/1.73m^2	^{51}Cr-EDTA; After single injection blood samples were withdrawn at 120 and 240 min.
Stevens et al., 2007, United States[79]	n = 1039 Subanalysis: BMI > 30 kg/m^2 and eGFR < 60 ml/min/1.73m^2. The results have been compiled from data from different studies.	-*	-*	Iothalamate; Withdrawing of samples was not described.
Cardiovascular diseases				
Valente et al., 2014, The Netherlands[146]	n = 40 Subanalysis: mGFR < 60 ml/min/1.73m^2. Inclusion criteria: age ≥ 18 years, LVEF < 0.45, clinically stable, use of renin-angiotensin-system inhibitors. Exclusion criteria: myocardial infarction within the last 3 months, cardiac surgery or angioplasty within the last 3 months or scheduled, unstable angina pectoris, primary renal disease, prior organ transplantation, chronic use of renal function-compromising medication.	-*	-*	^{125}I-iothalamate; Constant infusion. 2 h stabilization period.
Cancer				
Craig et al., 2012, United Kingdom[147]	n = -* Subanalysis: 30 < mGFR < 59 ml/min/1.73m^2, mGFR < 30 ml/min/1.73m^2. Inclusion criteria: patients treated with chemotherapy following their mGFR, serum creatinine measured within 7 days of mGFR, serum creatinine ≥ 60 umol/l, age > 20 years. Exclusion criteria: patients with missing information, serum creatinine < 60 umol/l	-*	-*	^{51}Cr-EDTA; After single injection blood samples were withdrawn at 120 and 240 min.
Ainsworth et al., 2012, United Kingdom[106]	n = 45 Inclusion criteria: patients who had mGFR < 50 ml/min at the Department of Nuclear Medicine.	-*	-*	^{51}Cr-EDTA; Single-sample method until 2005, thereafter three-sample method.
Bolke et al., 2011, Germany[104]	n = 8 Subanalysis: mGFR ≤ 60 ml/min/1.73m^2. 8 patients with head and neck cancer presenting for combined radiochemotherapy and with known CKD stage 3-5. Exclusion criteria: high dose steroid treatment.	-*	46.8 ± 7.9‡ ml/min/1.73m^2	^{51}Cr-EDTA; Bolus injection, four blood samples between 120 and 300 min after injection.
Faluyi et al., 2011, United Kingdom[105]	n = 62 Inclusion criteria: patients with mGFR ≤ 60 ml/min with stable renal function at a Cancer Centre. Exclusion criteria: unstable renal function.	68.3 ± 11.2	-*	^{99m}Tc-DTPA; Bolus injection, blood samples withdrawn after 2 and 5 h.

Creatinine measurement	Mean ± SD eGFR(MDRD)	Bias	Precision	Accuracy
Jaffe	Re-expressed MDRD-4 36 ± 17 ml/min/1.73m^2	Re-expressed MDRD-4 mean: -0.8%	Re-expressed MDRD-4 SD: 32%	Re-expressed MDRD-4 P_{30}: 80%
-*	-*	MDRD-4 median: 4.1%	-*	MDRD-4 P_{30}: 82%
Jaffe	-*	Re-expressed MDRD-4 mean: -2 ml/min/1.73m^2	Re-expressed MDRD-4 SD: 9 ml/min/1.73m^2	-*
Jaffe	-*	Re-expressed MDRD-4 30 < mGFR < 59 mean: 15.7 ml/min/1.73m^2 mGFR < 30 mean: 7.0 ml/min/1.73m^2	-*	-*
Jaffe	-*	MDRD-4 median: 17.5%	-*	MDRD-4 median APE: 20.5%
Enzymatic	Re-expressed MDRD-4 55.2 ± 13.2‡ ml/min/1.73m^2	Re-expressed MDRD-4 median: 18.4%‡	Re-expressed MDRD-4 SD: 19.1%‡	Re-expressed MDRD-4 P_{30}: 75%‡ P_{50}: 100%‡
Enzymatic	-*	-*	-*	Re-expressed MDRD-4 P_{10}: 40.3% P_{30}: 80.6%

Article	Study population (n = number of patients)	Mean ± SD age (years)	Mean ± SD mGFR	Gold standard
Diabetes mellitus				
Iliadis et al., 2011, Greece[57]	n = 145 Inclusion criteria: consecutive type 2 diabetic outpatients with mGFR between 30-59 ml/min/1.73m^2.	71 ± 9	48.1 ± 8.1 ml/min/1.73 m^2	^{51}Cr-EDTA; Bolus injection, blood samples withdrawn after 2 and 4 h.
Rognant et al., 2011, France[148]	n = 149 Inclusion criteria: nondialyzed diabetic adult patients with mGFR < 60 ml/min/1.73m^2.	-*	36.4 ± 13 ml/min/1.73 m^2	Inulin; Continuous infusion, both blood and urine samples were withdrawn.
Fontsere et al., 2008, Spain[149]	n = 36 Subanalysis: 15 < mGFR < 59 ml/min/1.73m^2. Caucasian type 2 diabetic patients.	64 ± 8.0	31.2 ± 10.8 ml/min/1.73 m^2	^{125}I-iothalamate; Withdrawing of samples was not described.
Rigalleau et al., 2007, France[150]	n = 89 Inclusion criteria: diabetes and an eGFR < 60 ml/min/1.73m^2. Exclusion criteria: renal replacement therapy.	Normo-albuminuric 68 ± 9 Albuminuric 64 ± 12	45.6 ± 29.7 ml/min/1.73 m^2	^{51}Cr-EDTA; Bolus injection, four blood samples were withdrawn at 75, 105, 135 and 165 min and urine samples were collected at 90, 120, 150 and 180 min.
Rigalleau et al., 2005, France[110]	n = 87 Inclusion criteria: diabetic patients with mGFR < 60 ml/min/1.73m^2 Exclusion criteria: nephrotic proteinuria (> 3 g/24h), edema and dialysis.	-*	33.7 ± 14.7 ml/min/1.73 m^2	^{51}Cr-EDTA; Bolus injection, four blood samples were withdrawn at 75, 105, 135 and 165 min and urine samples were collected at 90, 120, 150 and 180 min.
Liver cirrhosis				
Mindikoglu et al., 2014, United States[115]	n = 21 Subanalysis: mGFR < 60 ml/min/1.73m^2. Inclusion criteria: cirrhosis, age ≥ 18 years. Exclusion criteria: pregnancy or breast-feeding, iothalamate or iodine allergy, not treated hepatocellular carcinoma, hyperthyroidism, inability to provide informed consent or to collect or void urine, dialysis or eGFR < 15 ml/min/1.73m^2, treatment with NSAIDs, ACE-inhibitors 1 week prior. Onset or change in diuretics 1 week prior. Acute infection, exacerbation of encephalopathy, gastrointestinal bleeding, kidney injury 1 week prior, acute cardiovascular or cerebrovascular event 3 weeks prior, and cognitive impairment.	-*	-*	Iothalamate; Blood samples were withdrawn at baseline, 5, 15, 30, 45, 60, 120, 240 and 360 min after iothalamate administration.

Creatinine measurement	Mean ± SD eGFR(MDRD)	Bias	Precision	Accuracy
Jaffe	Re-expressed MDRD-4 56 ± 13.0 ml/min/1.73m^2	Re-expressed MDRD-4 mean: 7.5 ml/min/1.73m^2	Re-expressed MDRD-4 SD: 9.5 ml/min/1.73m^2	Re-expressed MDRD-4 P_{10}: 26.3% P_{30}: 69.3%
Jaffe	-*	-*	-*	MDRD-4 P_{10}: 36.2% P_{30}: 75.3%
Jaffe	-*	MDRD-4 mean: -5.3 ml/min/1.73m^2	-*	-*
Jaffe	41.3 ± 13.1 ml/min/1.73m^2	-*	-*	MDRD-? (not mentioned) Normoalbuminuric P_{10}: 26% P_{30}: 73% P_{50}: 86% Albuminuric: P_{10}:24% P_{30}: 60% P_{50}: 79%
Jaffe	MDRD-4 38.4 ± 14.0 ml/min/1.73m^2	MDRD-4 mean: 4.7 ml/min/1.73m^2	MDRD-4 2SD: 20.6 ml/min/1.73m^2	-*
		Re-expressed MDRD-6^{a} mean: -10.4 ml/min/1.73m^2	Re-expressed MDRD-6^{a} SD: 13.65 ml/min/1.73m^2	Re-expressed MDRD-6^{a} P_{20}: 52.38% P_{30}: 61.90%
-*	-*			

Article	Study population (n = number of patients)	Mean ± SD age (years)	Mean ± SD mGFR	Gold standard
Rognant et al., 2010, France[114]	n = 45 Inclusion criteria: consecutive candidates for liver transplantation with decompensated alcoholic cirrhosis with mGFR < 60 ml/min/1.73m^2.	-*	-*	Inulin; Continuous infusion (2 to 2.5 h), collection of three to four urine samples and a blood sample midway through each collection period.
Human immunodeficiency virus				
Gagneux et al., 2013, France[126]	n = 18 Subanalysis: mGFR < 60 ml/min/1.73m^2. Inclusion criteria: age ≥ 18 years, confirmed HIV status. Exclusion criteria: pregnancy, history of allergy, thyroid dysfunction, recent AKI, and treatment by metformin, steroids, trimethoprim, or cimetidine.	-*	-*	Iohexol; Bolus injection, blood samples withdrawn after 120 and 240 min.
Inker et al., 2012, United States[127]	n = 27 Subanalysis: eGFR < 60 ml/min/1.73m^2 Inclusion criteria: age > 18 years, stable on antiretroviral therapy for at least three months, confirmed HIV status, HIV viral load and CD4 count within 6 months of recruitment. Exclusion criteria: pregnancy, allergy or contraindication for iohexol or iodine, recent AKI, cognitive or physical impairments, use of cimetidine.	-*	-*	Iohexol; Bolus injection, blood samples withdrawn after 10, 30, 120 and 240 min. For participants with serum creatinine > 1.5 mg/dl, a sample at 360 min was withdrawn.

* Not all parameters were reported in the included articles. Especially when it came to subanalysis of patients with an eGFR < 60 ml/min/1.73m^2.

‡ When individual data were available we calculated missing parameters ourselves.

≠ The MDRD-formula used was not reported. Given the time at which the study was conducted, we assume that the re-expressed MDRD-formula was used.

Hospitalized patients

Background

Reduced GFR is one of the most important complications in critically ill patients and is associated with increased morbidity and mortality in the intensive care unit (ICU) population.[81,82] In addition, acute renal failure (ARF) is also associated with high mortality.[83] Early detection of renal dysfunction and subsequent adequate treatment is therefore necessary in the hospital care setting.[84] Estimation of the GFR is also necessary for appropriate treatment of critically ill and other hospitalized patients with renally excreted drugs.[85]

Creatinine measurement	Mean ± SD eGFR(MDRD)	Bias	Precision	Accuracy
-*	-*	MDRD-4 mean: 19 ml/min/1.73m^2	MDRD-4 SD: 25 ml/min/1.73m^2	MDRD-4 P_{10}: 11% P_{30}: 40%
Enzymatic	-*	Re-expressed MDRD-4 mean: 61%	Re-expressed MDRD-4 SD: 58%	Re-expressed MDRD-4 P_{30}: 22%
-*	-*	Re-expressed MDRD-4 median: -11.9 ml/min/1.73m^2	Re-expressed MDRD-4 IQR: 19.4 ml/min/1.73m^2	Re-expressed MDRD-4 P_{30}: 66.7%

SD, standard deviation; mGFR, measured glomerular filtration rate; HIV, human immunodeficiency virus; BMI, body mass index; IQR, inter quartile range; LOA, limits of agreement; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; CKD, chronic kidney disease; KDIGO, kidney disease: improving global outcomes; KDOQI, kidney disease outcomes quality initiative; h, hour(s); min, minute(s); COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; AKI, acute kidney injury; ^{51}Cr-EDTA, ^{51}chromium ethylenediaminetetraacetic acid; ^{99m}Tc-DTPA, technetium-labelled diethylene-triaminepentacetate; NSAID, non-steroidal anti-inflammatory drug; ACE-inhibitor, angiotensin-converting-enzym inhibitor.

Summary of the selected articles

In Table 3.2 three studies are presented, which fulfilled our inclusion criteria. All three studies reported an overestimation of the true GFR, ranging from a mean bias of 3.26 ml/min/1.73m^2 in the study of Schuck et al. to a median relative bias of 53% in the study of Poggio et al.[85,86] In the study of Poggio et al. the MDRD-6 formula seemed to perform slightly better than the MDRD-4 formula with a median bias of 46%.[85] Although the bias in the study of Schuck et al. seems low, the precision exceeded our criteria of 30%.[86] Only the study of Poggio et al. reported accuracy, which appeared to be inadequate. P_{30} was 36% for the MDRD-6 formula and 31% for the MDRD-4 formula.[85] The measurement of the GFR with a gold standard was performed reasonably, although the spontaneous urination instead of

catheterization in the study of Schuck et al. is questionable.[86] The number of patients only exceeded 100 in the study of Poggio et al.[85]

Interpretation and conclusion

The MDRD formula is invalid in hospitalized patients on the internal medicine and nephrology ward. In the study of Poggio et al. selection bias was introduced, because the selection of patients was based on an individual nephrologist's perception of laboratory values not reflecting actual GFR.[85] In the other two studies the study was conducted only on the internal medicine and nephrology ward. The study population may therefore not reflect the average hospitalized patient population. In conclusion, the eGFR may largely overestimate true GFR in hospitalized patients, but the impact of this effect in different populations of hospitalized patients is still insufficiently known.

Obese patients

Background

Obesity is a well-recognized global health problem.[87] Obesity is associated with cardiovascular complications, type 2 diabetes mellitus, osteoarthritis, major depression and some cancers.[7,87] Obesity itself and its combination with these chronic diseases predispose individuals to develop CKD.[7,88] Considering the increasing number of obese patients the accuracy of the MDRD formula in obesity is of increasing importance.

Summary of the selected articles

Two articles met our selection criteria. Both studies had a study population exceeding 100 patients. One study was compiled with data from different studies, so the measurement of the GFR was not described.[79] In the study of Bouquegneau et al. the measurement of the GFR was not adequately performed.[89] In both studies the true GFR and eGFR were normalized to ml/min/1.73m^2. The bias was for both studies within our 20% criteria. The precision reported in the study of Bouquegnea et al. was slightly higher than 30%, but the accuracy was sufficient, P_{30} was 80%.[89] Stevens et al. reported also a sufficient accuracy, P_{30} of 82%.[79]

Interpretation and conclusion

We found two studies, which conducted a subanalysis about the validity of the MDRD-4 formula in obese patients (BMI > 30 kg/m^2). The performance of the MDRD-4 formula seemed valid, but the measurement of the gold standard could have been performed better. In conclusion, we were not able to draw conclusions about the validity of the MDRD formula in obese patients.

Cardiovascular diseases

Background

Numerous studies about the prognostic value of the eGFR(MDRD) in cardiovascular diseases for clinical outcomes, such as mortality, have been published.[56,90-94] In patients with end-stage heart failure, irreversibly impaired renal function precludes eligibility for heart transplantation.[95] In addition, patients with cardiovascular diseases are at risk for polypharmacy and the use of drugs that require dose adjustment in renal impairment.[96,97] Thus an accurate method to estimate GFR is essential.[98]

Summary of the selected articles

One article met our selection criteria. The mean bias of -2 ml/min/1.73m^2 with a precision of 9 ml/min/1.73m^2 were within our criteria of 20% and 30%, respectively. However, the number of patients included was low. The measurement of the true GFR was not performed with a common method, a continuous infusion of ^{125}I-iothalamate instead of a bolus injection.

Interpretation and conclusion

In conclusion, we were not able to draw conclusions about the validity of the MDRD formula in patients with heart failure (or other cardiovascular diseases).

Cancer

Background

Both cancer and its drug therapies can lead to renal impairment.[99] Renal impairment in patients with cancer is highly prevalent and has major clinical implications.[99,100] In the Belgian Renal Insufficiency and Anticancer Medication (BIRMA) study, the prevalence of renal impairment (eGFR < 90 ml/min/1.73m^2) in patients with a range of cancer diagnosis was 64%.[101] 80% of the patients treated for cancer received at least one nephrotoxic drug and/or drugs for which dosage had to be adjusted in renal impairment.[101] In our ageing societies oncologists are likely to be faced with increasing numbers of patients with both cancer and renal impairment.[102,103]

Summary of the selected articles

Four studies were selected and are presented in Table 3.2. None of these studies reported precision. Although the bias reported in the studies of Ainsworth et al. and Bolke et al. were within 20%, only the study of Faluyi et al. reported an accuracy > 80% expressed as P_{30}.[104-106] The low accuracy in the other studies implies a wide imprecision. The number of patients included in all three studies together exceeded 100. The measurement of GFR with a gold standard was not adequately performed in any of the studies. The best performed measurement of the GFR was in the

study of Bolke et al. where 4 blood samples were withdrawn over a time period of 5 hours.[104]

Interpretation and conclusion

Precision was not reported, the numbers of patients in the selected separate studies were low and only the measurement of the GFR in the study of Bolke et al. seemed robust. Yet, these studies suggest that the eGFR calculated with the MDRD formula in cancer patients with moderate to severe renal impairment may be substantially different from the mGFR for a substantial number of patients. There is no evidence that the use of the MDRD formula in drug dosing in patients with cancer and renal impairment is valid.

Chronic respiratory diseases

Background

The most frequent chronic respiratory disease is chronic obstructive pulmonary disease (COPD), which is associated with several comorbidities, such as hypertension, heart failure and diabetes.[107] Renal impairment is a significant risk factor for cardiovascular diseases for which COPD patients are at risk.[108] In addition, polypharmacy is frequent in patients with COPD.[108] An accurate estimation of the GFR seems therefore important.

Summary of the included articles

No articles met our selection criteria.

Interpretation and conclusion

When searching for articles about the validity of the MDRD formula in patients with COPD, we found some recently published articles on the prevalence of renal impairment in patients with COPD, which discussed the advantages of using creatinine-based formulas for estimating GFR rather than serum creatinine levels.[107,108] The prevalence of undiagnosed renal impairment (eGFR < 60 ml/min and normal serum creatinine levels) varied between 7% and 22%, and was higher in patients with cachexia and older age (> 64 years).[107,108] This implies that the issue of the validity of the MDRD formula in COPD patients is still far from settled. In conclusion, we were not able to draw conclusions about the validity of the MDRD formula in patients with chronic respiratory diseases and moderate to severe renal impairment.

Diabetes mellitus

Background

Diabetes mellitus is the leading cause of CKD.[109] Diabetic nephropathy affects around one-third of patients with diabetes and is the primary cause of end-stage renal disease worldwide.[57,109] Moreover, diabetic patients, especially those with impaired renal function, are at increased risk of cardiovascular events.[57,110] There is strong evidence that early detection of diabetic nephropathy leading to timely intervention improves long-term outcome.[111]

Summary of the selected articles

Several studies have been published about the validity of the MDRD-4 formula in patients with diabetes mellitus. We included five studies. The bias reported in three out of five studies were within 20%. The precision (only reported by Iliadis et al. and Rigalleau et al.) was in the same range, namely a standard deviation (SD) of approximately 10 ml/min/1.73m^2, and within our criterion of 30%.[57,110] Despite the fact that both bias and precision reported met our criteria, the accuracy was not sufficient, which implies a relatively wide imprecision throughout the mGFR range. In two out of five studies the included number of patients exceeded 100. The findings of two other studies which included nearly 90 patients were in the same range. With respect to the method for measuring GFR, the number of blood samples withdrawn in the study of Iliadis et al. (two blood samples) was probably marginal.[57] In the other four studies the method for GFR measurement was sufficient.

Interpretation and conclusion

In four studies the MDRD-4 formula overestimated the mGFR. The overestimation of the GFR might lead to higher drug doses than necessary or to a late discontinuation of, for example, metformin use and therefore to a greater risk of ADRs. Although bias pointed in the same direction in four studies, the precision (= random error), which was not adequately reported, was probably too wide, which led to low accuracy. In conclusion, the MDRD formula is not valid in patients with diabetes mellitus and renal impairment.

Other chronic diseases

From various chronic diseases of interest, we decided to present the diseases of which we could include at least two studies. These diseases were liver cirrhosis and HIV-infection.

Liver cirrhosis

Background

Renal dysfunction often accompanies later stages of chronic liver diseases and is strongly associated with increased mortality in both acute liver failure and liver cirrhosis.[58,112] Pretransplant serum creatinine level is a predictor of posttransplant mortality and posttransplant renal function.[63,113] Other risk factors to develop chronic kidney disease, such as diabetes mellitus, coronary heart disease, and hepatitis C, are common among patient with liver diseases.[113,114] It is therefore important to identify which patients with liver disease truly have renal impairment.[60]

Summary of the selected articles

Two studies were included. The mean bias ranged from -10 ml/min/1.73m^2 with the MDRD-6 formula in the study of Mindikoglu et al. to 19 ml/min/1.73m^2 with the MDRD-4 formula in the study of Rognant et al.[114,115] The corresponding imprecision expressed as SD were 14 and 25 ml/min/1.73m^2, respectively.[113,115] Both bias and imprecision were very wide for patients with a mGFR < 60 ml/min/1.73m^2. Both over- and underestimation were reported, which resulted in an accuracy expressed as P_{30} of 40% and 62%.[113,115] The number of patients in the separate studies were below 100, but the measurements of the GFR were adequately performed.

Interpretation and conclusion

The imprecision of the MDRD formula in the studies was very wide. Cholongitas et al. already reported that the MDRD overestimates the GFR to a great extent in a review in 2007.[112] The two more recently published articles confirm this conclusion. Remarkably, the study in which the MDRD-6 formula was used, reported an underestimation of the mGFR.[115] Despite the fact that only two studies met our selection criteria and per study less than 100 patients were included, the degree of over- and underestimation and precision is too large to justify the use of the MDRD formula in patients with liver cirrhosis and moderate to severe renal impairment.

Human immunodeficiency virus

Background

Individuals with HIV-infection have an increased risk of kidney disease.[116] HIV infection may result in HIV-associated nephropathy, immune complex kidney disease and ARF.[117,118] Moreover, progression to end-stage kidney disease, which may require hemodialysis, is common.[119-121] These conditions are associated with progression to acquired immune deficiency syndrome (AIDS) and death.[118,119] In addition, HIV itself may influence other risk factors for kidney disease, such as lipid levels, insulin resistance and microalbuminuria.[122] Aging, comorbidities and

the use of nephrotoxic antiretroviral drugs might lead to a higher risk for developing impaired renal function.[122-124] In addition, the use of renally excreted drugs is prevalent, therefore accurate estimation of renal function is an important component of personalized HIV care.[117,125]

Summary of the selected articles

We selected two subanalysis including only 45 patients with HIV and mGFR < 60 ml/min/1.73m^2. The imprecision reported was very wide, namely an IQR of 20 ml/min/1.73m^2 in the study of Inker et al. and a mean relative bias of 61% in the study of Gagneux et al.[126,127] This resulted in an accuracy, expressed as P_{30} of 67% and 22%, respectively.[126,127] The measurement of GFR with the gold standard iohexol was adequately performed in the study of Inker et al. and reasonably performed in the study of Gagneux et al.[126,127]

Interpretation and conclusion

We were not able to draw conclusions about the validity of the MDRD formula in patients with HIV and moderate to severe renal impairment, because of the small number of patients. The wide imprecision reported in the small subanalysis does not support the validity of the MDRD formula.

Of note, in our previously published review about the validity of the MDRD formula in HIV-infected patients we suggested that the MDRD-4 formula is as valid in HIV-positive as in HIV-negative patients.[128] The results in this review do not confirm that hypothesis for patients with moderate to severe renal impairment.

Discussion

To our knowledge this is the first systematic review, which evaluates the validity of the MDRD formula in a range of specific patient populations with moderate to severe renal impairment in a more quantitative way. We focused on studies, which compared the MDRD formula with a gold standard and which provided statistical outcome information about the degree of deviation from the true GFR. Our selection criteria were thus more stringent than previously published reviews.[3,11,129]

This review showed that the validity of the MDRD formula has not yet been tested properly in patients with cardiovascular diseases and chronic respiratory diseases. In obese patients, patients with cancer and HIV the validity of the MDRD formula has been poorly tested. The number of studies and/or the number of patients included were very low and/or the measurement of GFR was not performed adequately. Therefore the validity of the MDRD formula in these patient populations remains unclear. For patients with diabetes mellitus and liver cirrhosis, hospitalized patients

on the internal medicine and nephrology ward and elderly with moderate to severe renal impairment we concluded that the MDRD formula is not valid. A summary is given in Table 3.3.

Table 3.3 Summary of the systematic review about the validity of the MDRD formula in specific patient populations

Patient population	Validity of the MDRD formula
Elderly patients	Not valid
Hospitalized patients*	Not valid
Obese patients	Unclear
Cardiovascular diseases	Not tested
Cancer	Unclear
Chronic respiratory diseases	Not tested
Diabetes mellitus	Not valid
Liver cirrhosis	Not valid
Human immunodeficiency virus	Unclear

*The MDRD formula is not valid in patients on the internal medicine and nephrology ward. For other hospitalized patients it was not tested.

Overall, we may conclude that the application of the MDRD formula in clinical practice is not supported by available research evidence for a range of specific patient populations. The application of the MDRD formula in drug dosing may become even more difficult with the knowledge that most of these chronic diseases are present in various combinations in the individual patient, especially in elderly.[130] The variability of the eGFR in daily practice might thus be larger.

At the time this research was conducted the Chronic Kidney Disease EPIdemiology Collaboration (CKD-EPI) formulas were developed. These formulas are based on serum creatinine value, cystatine C value and a combination of both.[131,132] Overall, the CKD-EPI formula performs better than the MDRD-4 formula. However, the differences in the eGFR range < 60 ml/min/1.73m^2 are small and not clinically relevant.[17,133] In Australia, France and a few large laboratories in the United States, the eGFR is already calculated with the CKD-EPI formulas.[134] Although the CKD-EPI formulas may replace the MDRD formula, we still think that our review is of great interest. First, the limitations of the MDRD formula are due to the variable serum creatinine level. This variable still exists in the CKD-EPI formulas. Second, this review shows the importance of validating a formula in specific patient populations. Especially, populations who are at risk of having impaired renal function.

This review is not without limitations. First, we excluded studies which did not fulfill our criteria concerning statistical analysis. A frequently used method to compare

different formulas to estimate the GFR is the correlation coefficient, which has major limitations when used for this purpose.[117,121] The most informative method to assess diagnostic tests is the Bland-Altman plot, as this identifies the direction and the magnitude of the bias.[67,135,136] Secondly, the gold standards used in the presented studies were diverse. The gold standard in the development of the MDRD formula was ^{125}I-iothalamate.[15] Use of other filtration markers may introduce a systematic bias, mostly an overestimation.[4,17,44] We did not consider this variable in the interpretation of the included studies. This would have been difficult because the measurement of the GFR was often not well described and/or not adequately performed. Another limitation is the lack of taking into account the differences between the MDRD en re-expressed MDRD formulas, in other words, between IDMS calibrated creatinine measurements and uncalibrated creatinine measurements. In addition, the use of an enzymatic method or the Jaffe method also introduces variable variations in serum creatinine levels.[2,137] We did not consider such additional variables in the interpretations of the selected studies. Instead, we choose to focus on the variables explained in the method section, which in our opinion have the greatest influence on the eGFR(MDRD). Finally, we did not discuss all different patient populations. Examples of patient characteristics which may also affect the validity of the MDRD formula, but which were not reviewed here, are pregnancy and ethnicity.[138-141]

Conclusion

In summary, the use of the MDRD formula in different specific patient populations for the fine-tuning of drug therapy management is not without limitations. There is no hard evidence that the MDRD formula is valid in patients with several chronic diseases combined with renal impairment. Clinical judgment remains necessary. Instead of searching for the ideal formula for estimating GFR, we should search for practical approaches to optimize the pharmacotherapy in patients with renal impairment.

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Appendix 3.1 Search terms

Assessment of the renal function
Glomerular filtration rate and creatinine
Reliability
"Predictive Value of Tests"[Mesh Terms] *OR* "Reference Values"[Mesh Terms] *OR* predictive value* *OR* reference value* limitation *OR* limitations pitfalls *OR* pitfall overestimated *OR* underestimated *OR* underestimation *OR* overestimation *OR* overestimating *OR* underestimating disturbance *OR* interference "diagnostic errors"[MeSH Terms] *OR* (diagnostic AND errors) "sensitivity and specificity"[MeSH Terms] *OR* sensitivity *OR* specificity marker *OR* markers *OR* "Biological Markers"[Mesh Terms] accurate *OR* inaccurate *OR* inaccuracy *OR* accuracy performance
Creatinine-based formulas
(cockcroft AND gault) *OR* cockcroft-gault *OR* MDRD *OR* (modification AND diet) *OR* "kidney diseases"[MeSH Terms] *OR* (kidney AND diseases) *OR* renal disease
Date of publication
January 1999 – January 2014

Last date the search was performed: April 30th, 2014

Appendix 3.2 PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 33, titlepage
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 34
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 35-36
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 36
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 39
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 39
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	See Appendix 3.1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 39-40
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 41-43
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 41-43
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	NA

Section/topic	#	Checklist item	Reported on page #
Methods (continued)			
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 44
Protocol and registration	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 3.2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 61
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 62-63
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 63
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit: www.prisma-statement.org.

New evidence to evaluate existing guidelines

Section

II

Ineffectiveness and adverse events of nitrofurantoin in women with urinary tract infection and renal impairment in primary care

Eur J Clin Pharmacol 2013; 69: 1701-7

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4

Abstract

Purpose

To determine whether treatment with nitrofurantoin in women with urinary tract infection (UTI) and renal impairment in primary care is associated with a higher risk of ineffectiveness and/or serious adverse events than in women without renal impairment.

Methods

A cohort of 21,317 women treated with nitrofurantoin and a cohort of 7,926 women treated with trimethoprim, identified from the PHARMO Record Linkage System, were analysed. The primary outcome was ineffectiveness of treatment of nitrofurantoin defined as the start of a second antibacterial within 1 month after the start of nitrofurantoin. The secondary outcome was the occurrence of serious adverse events of nitrofurantoin leading to hospitalization within 90 days. A cohort of trimethoprim users was used to determine if the associations found for nitrofurantoin were mainly related to nitrofurantoin itself. The association between renal impairment and the risk of these outcomes were determined with Cox regression and expressed as hazard ratios (HRs).

Results

Overall, the incidence density for ineffectiveness was 5.4 per 1,000 person-days, and moderate renal impairment was not associated with ineffective treatment (HR 1.1, 95% confidence interval (CI) 0.74-1.51). The overall incidence density for adverse events was 0.02 per 1,000 person-days. In patients with renal impairment (< 50 ml/min/1.73m^2) the risk of pulmonary adverse events leading to hospitalization was significantly increased (HR 4.1, 95% CI 1.31-13.09).

Conclusions

Nitrofurantoin treatment was not associated with a higher risk of ineffectiveness in women with UTI and moderate renal impairment (30-50 ml/min/1.73m^2). However, we did find a significant association between renal impairment (< 50 ml/min/1.73m^2) and pulmonary adverse events leading to hospitalization.

Introduction

Acute uncomplicated urinary tract infection (UTI) is common in otherwise healthy, non-pregnant women of all ages. More than 30% of all women will experience at least one UTI during their lifetime.[1] Nitrofurantoin is considered a first choice for the treatment of uncomplicated UTI in different guidelines.[2–4] A recently published Cochrane review suggests that nitrofurantoin is a good choice because nitrofurantoin carries a lower risk of patients developing rash than treatment with trimethoprim-sulfamethoxazole and does not share cross-resistance with other commonly prescribed antibacterials.[1] However, there is concern about the effectiveness of nitrofurantoin in patients with renal impairment. According to the drug label, nitrofurantoin is contraindicated when the creatinine clearance is < 60 ml/min.[5,6] In patients with normal renal function nitrofurantoin is concentrated many-fold in the urine, and urine concentrations reach a much higher level than the minimum inhibitory concentration.[7] In patients with renal impairment, the excretion of nitrofurantoin is decreased, and effective antibacterial levels in the urine might not be achieved.[8–10]

Another clinical concern is that nitrofurantoin entails a greater risk of adverse events in patients with renal impairment, such as peripheral neuropathy. Serum levels of nitrofurantoin increase in these patients due to its decreased renal excretion. Evidence from clinical research to support the recommendations for its use in renal impairment is limited to pharmacokinetic studies and reports in which the duration of nitrofurantoin use was much longer than the recommended 5-10 days.[8]

Bains et al. recently conducted a retrospective observational study in 356 hospitalized patients in which the effectiveness and safety of the use of nitrofurantoin was compared between patients with an estimated glomerular filtration rate (eGFR) of ≤ 50 ml/min (renal impairment group) and those with an eGFR > 50 ml/min (control group).[11] This study showed that in hospitalized patients with an eGFR of ≤ 50 ml/min, nitrofurantoin appeared to achieve acceptable clinical recovery and was well tolerated. However, the number of patients included in this study was not sufficient to detect rare but serious adverse events. The aim of our study was therefore to determine whether ineffectiveness and the occurrence of serious adverse events during treatment with nitrofurantoin in women with uncomplicated UTI are dependent upon renal function.

Methods

Setting

An epidemiological study was conducted in a large outpatient population. Data were

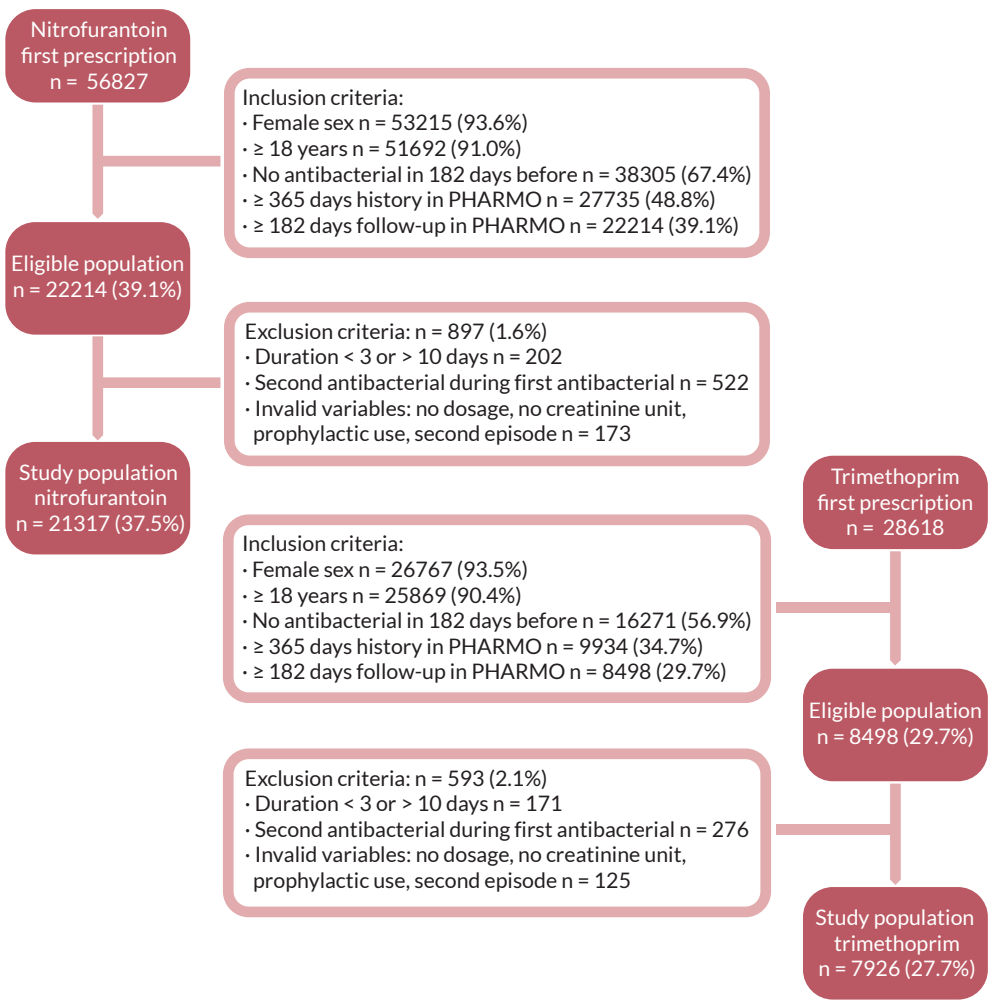
obtained from the Dutch PHARMO Record Linkage System (RLS), a database with linked drug dispensing records from community pharmacies to general practitioner data, hospitalization records and clinical laboratory data from individual patients.[12] This system includes the demographic details and complete medication history of more than three million community-dwelling residents from 1986 onwards. For this study, drug dispensing data and hospitalization data were used. The computerized drug dispensing histories contain information on the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen and the estimated duration of use. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification.[13] The hospitalization register contains data on all hospitalizations in The Netherlands, including detailed information on the primary and secondary discharge diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists and dates of hospitalization and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM). All PHARMO RLS linked research is in accordance with Dutch privacy and ethical regulations.

Study design and population

A retrospective cohort study with two cohorts was conducted with a sample of the data compiled in the PHARMO RLS. One cohort (nitrofurantoin cohort) consisted of female nitrofurantoin users with known creatinine values (measured between the day nitrofurantoine treatment was started and 1 year before the start) and without creatinine values. In this cohort the effect of renal impairment on the ineffectiveness and adverse events of nitrofurantoin was determined. The second cohort (trimethoprim cohort) consisted of female trimethoprim users with and without known creatinine values. In this cohort the effect of renal impairment on the ineffectiveness of trimethoprim was determined. We also investigated the occurrence of adverse events related to nitrofurantoin compared to the trimethoprim cohort. We hypothesized that the degree of renal impairment would not be associated with ineffectiveness and/or adverse events in patients who used trimethoprim. If associations between renal impairment and ineffectiveness and/or adverse events were to be found for nitrofurantoin users, but not for trimethoprim users, the conclusion would be that the associations found for nitrofurantoin would be mainly related to nitrofurantoin itself. Patients were eligible for inclusion when they had received a prescription for nitrofurantoin or trimethoprim between 1 January 2005 and 31 December 2010, were female and were at least 18 years of age (Figure 4.1). They should not have received any antibacterial prescription in the last half year prior to the starting date of nitrofurantoin or trimethoprim treatment. In addition,

they had to have at least 1 year of medication history prior to the starting date and 6 months of follow-up after the starting date. Patients were excluded if the duration of the nitrofurantoin or trimethoprim prescription was < 3 days or > 10 days. In The Netherlands the recommended dosage regimen of nitrofurantoin in the treatment of uncomplicated UTI is 50 mg 4 times daily or 2 times daily 100 mg for extended release preparations[14], with a recommended duration of 5 days.[3] Patients to whom a second antibacterial had been prescribed before the course of the first antibacterial had been completed, or with invalid or unclear variables were also excluded from the study (Figure 4.1).

Figure 4.1 Flowchart of the study population



Outcomes

The primary outcome was ineffectiveness of treatment of nitrofurantoin defined as the start of a second antibacterial for treatment of UTI other than nitrofurantoin within 1 month after the start of a course of nitrofurantoin treatment.

The secondary outcome was the occurrence of adverse events attributable to nitrofurantoin leading to hospitalization.[15,16] ICD-9 codes were included if serious adverse events were diagnosed during subsequent hospital admissions that occurred within 90 days after the start of nitrofurantoin treatment. These serious adverse events were classified as pulmonary reactions, allergic reactions, liver damage, blood dyscrasias or neuropathy (see Appendix 4.1).[16] Because of the features of the database we could only retrieve ICD-9 codes at discharge from the hospital. The same outcomes were determined for the trimethoprim cohort.

Renal impairment

Outcome measures were computed per renal function group based on eGFRs calculated with creatinine levels using the original 4-variable Modification of Diet in Renal Disease equation.[17] The predefined renal function groups were > 80 ml/min/1.73m^2 (no renal impairment), 50-80 ml/min/1.73m^2 (mild renal impairment), 30-49 ml/min/1.73m^2 (moderate renal impairment), 10-29 ml/min/1.73m^2 (severe renal impairment) and < 10 ml/min/1.73m^2 (end-stage renal failure), as derived from the European dosing guidelines for drugs in renal impairment.[18] Patients without creatinine values were classified as 'renal function unknown'. Data for renal function groups were pooled if the number of patients with renal impairment (< 50 ml/min/1.73m^2) were too low.

Potentially confounding factors

The following factors were studied to control for potential differences between groups in terms of predisposition to (recurrent) UTIs: age, duration of antibacterial treatment, use of blood glucose-lowering drugs (diabetes mellitus)[3], use of immunosuppressive drugs (increased susceptibility for infection)[3], sodium phosphate, magnesium citrate, potassium citrate/phosphate, citric acid or allopurinol (urolithiasis)[7], use of acetylsalicylic acid in combination with dipyridamole (stroke)[19], use of urinary antispasmodics (incontinence)[19], tamsulosin (kidney stones)[3], rivastigmine or galantamine (cognitive impairment)[19] and distigmine or carbachol (incomplete bladder emptying)[3].

Data analysis

Descriptive statistics (mean, minimum, maximum, sum) were used to describe the

frequencies and incidence density ratios in the study population. We calculated the incidence density of ineffectiveness and adverse events as the incidence per 1,000 person-days of observation. The observation period for ineffectiveness was defined as the number of days between the end date of nitrofurantoin or trimethoprim treatment and the start of a second antibacterial and was set at a maximum of 30 days. The observation period for adverse events was defined as the number of days between the end date of nitrofurantoin or trimethoprim treatment and the date of hospital admission, with a maximum of 90 days.

Table 4.1 Baseline characteristics of the study population

Baseline characteristics[a]	**Nitrofurantoin** n = 21,317 (100%)		**Trimethoprim** n = 7,926 (100%)		**p-value**[b]
Age (years)	47.8	(18-103)	49.2	(18-101)	< 0.001
18-29	5,115	(24.0)	1,843	(23.3)	
30-45	5,488	(25.7)	1,897	(23.9)	
46-64	5,610	(26.3)	2,009	(25.3)	
> 64	5,104	(23.9)	2,177	(27.5)	
Risk factors					
Diabetes	857	(4.0)	331	(4.2)	0.548
Immunosuppressive drugs	87	(0.4)	7	(0.1)	< 0.001
Urolithiasis	57	(0.3)	24	(0.3)	0.609
Stroke	144	(0.7)	58	(0.7)	0.606
Antispasmodic drugs	138	(0.6)	79	(1.0)	0.002
Kidney stones	9	(0.0)	5	(0.1)	0.468
Cognition	29	(0.1)	13	(0.2)	0.574
Incomplete bladder emptying	17	(0.1)	11	(0.1)	0.147
Duration of antibacterial treatment (days)	5.2	(3-10)	4.6	(3-10)	< 0.001
3	1,195	(5.6)	2,314	(29.2)	
4,5	17,156	(80.5)	5,012	(63.2)	
6-10	2,969	(13.9)	600	(7.6)	
eGFR (ml/min/1.73m²)	82.9	(9-200)	81.6	(7-209)	0.115
> 80 (normal renal function)	1,859	(8.7)	589	(7.4)	
50-80 (mild renal impairment)	1,842	(8.6)	597	(7.5)	
30-49 (moderate renal impairment)	166	(0.8)	74	(0.9)	
10-29 (severe renal impairment)	20	(0.1)	8	(0.1)	
< 10 (end-stage renal disease)	1	(0.0)	1	(0.0)	
Unknown	17,429	(81.8)	6,657	(84.0)	

[a] Data are presented as the mean with the range in parenthesis, or as the number of patients, with the percentage in parenthesis.
[b] The p values were calculated using t-tests for continuous variables and chi-square tests for nominal categorical variables.
eGFR: estimated glomerular filtration rate.

The strength of the associations between renal function and ineffective treatment and serious adverse events, respectively, was evaluated with multivariate Cox regression analysis and expressed as hazard ratios (HRs) with 95% confidence intervals (95% CIs). Covariates were included in the multivariate analysis if they induced a change in the crude regression coefficient of at least 10%. Data analysis was performed with IBM SPSS Statistics version 19.0 for Windows (IBM Inc., New York, NY).

Results

Of the 21,317 female nitrofurantoin users included in the study, 3,888 (18.2%) could be accommodated in predefined renal function groups because their creatinine value was known (Table 4.1). In the trimethoprim cohort, the creatinine value was known in 1,269 (16.0%) of the 7,926 female trimethoprim users included in the study. Moderate (30-49 ml/min/1.73m^2) and severe renal impairment (10-29 ml/min/1.73m^2) were observed in 166 (0.8%) and 20 (0.1%) nitrofurantoin users, respectively, and in 74 (0.9%) and 8 (0.1%) trimethoprim users, respectively. Among the risk factors for UTIs, diabetes was most prevalent in both cohorts.

Table 4.2 Association between renal impairment and ineffective antibacterial treatment

eGFR	Second antibacterial		Follow-up time	Incidence density	Crude HR	Adjusted HR [a]
(ml/min/1.73m^2)	(n)	(%)	(person-days)	(per 1000 person-days)	(95% CI)	(95% CI)
Nitrofurantoin						
> 80	291	(15.7)	49,241	5.91	1.00 reference	1.00 reference
50-80	314	(17.0)	48,068	6.53	1.10 (0.94-1.29)	0.92 (0.78-1.08)
30-49	35	(21.1)	4,191	8.35	1.41 (0.99-2.00)	1.06 (0.74-1.51)
10-29	6	(30.0)	456	13.16	2.12 (0.94-4.75)	1.57 (0.70-3.52)
< 10	0	(0)	30	NA	NA	NA
Unknown	2,431	(13.9)	46,7318	5.20	0.89 (0.78-1.00)	0.90 (0.79-1.01)
Overall	3,077	(14.4)	569,304	5.40		
Trimethoprim						
> 80	94	(16.0)	15,537	6.05	1.00 reference	1.00 reference
50-80	114	(19.1)	15,315	7.44	1.22 (0.93-1.60)	1.15 (0.87-1.51)
30-49	14	(18.9)	1,889	7.41	1.20 (0.68-2.10)	1.06 (0.60-1.88)
10-29	0	(0)	240	NA	NA	NA
< 10	0	(0)	30	NA	NA	NA
Unknown	1,092	(16.4)	174,811	6.25	1.03 (0.84-1.27)	1.03 (0.83-1.27)
Overall	1,314	(16.6)	207,822	6.32		

[a] Adjusted for age and use of blood glucose lowering drugs.
HR, hazard ratio; 95% CI, 95% confidence interval; NA, data not available.

Compared to trimethoprim users, the mean age of nitrofurantoin users was significantly lower ($p < 0.001$), the use of immunosuppressive drugs and urinary antispasmodics was significantly higher ($p < 0.001$ and $p = 0.002$, respectively) and the mean duration of antibacterial treatment was significantly longer ($p < 0.001$).

Table 4.2 shows the association between renal impairment and the risk of a second antibacterial (ineffective treatment) within 1 month after start of nitrofurantoin. Overall incidence density for ineffectiveness in nitrofurantoin users was 5.4 per 1,000 person-days. Although a trend for higher incidence densities was observed as renal function declined, renal impairment was not significantly associated with ineffective treatment. The overall incidence density for ineffectiveness in trimethoprim users was 6.3 per 1,000 person-days.

There was no significant association or trend observed between ineffective treatment and renal impairment. Table 4.3 shows the association between renal impairment and the risk of an adverse event due to nitrofurantoin leading to hospitalization. Pulmonary reactions (unspecified chest pain [n = 28], painful respiration [n = 3] and pleural effusion [n = 1]) and blood dyscrasias (haemolytic anemia [n = 1]) were observed during the 3 months of follow-up after the start of nitrofurantoin treatment. Neuropathy, allergic reactions and liver damage were not reported.

Table 4.3 Association between renal impairment and serious adverse events[a]

eGFR	Adverse event[a]		Follow-up time	Incidence density	Crude HR	Adjusted HR [b]
(ml/min/1.73m²)	(n)	(%)	(person-days)	(per 1000 person-days)	(95% CI)	(95% CI)
Nitrofurantoin						
≥ 50	13	(0.35)	332,399	0.04	1.00 reference	1.00 reference
< 50	4	(2.14)	16,618	0.24	6.14 (2.00-18.83)	4.13 (1.31-13.09)
Unknown	17	(0.10)	1,567,746	0.01	0.28 (0.14-0.57)	0.35 (0.17-0.73)
Overall	34	(0.16)	1,916,763	0.02		
Trimethoprim						
≥ 50	0	NA	106,740	NA	1.00 reference	1.00 reference
< 50	0	NA	7,470	NA	NA	NA
Unknown	8	(0.12)	598,572	0.01	NA	NA
Overall	8	(0.10)	712,782	0.01		

[a] Adverse events during subsequent hospital admissions within 90 days after the start of a course of nitrofurantoin treatment: pulmonary reactions (n = 33) and blood dyscrasias (n = 1). Adverse events after start of a course of trimethoprim treatment: pulmonary reactions (n = 8).
[b] Adjusted for age.
HR, hazard ratio; 95% CI, 95% confidence interval; NA, data not available.

Eight adverse events were observed in trimethoprim users with unknown renal function, all events were pulmonary reactions (n = 8). The overall incidence density for serious adverse events was 0.02 and 0.01 per 1,000 person-days for nitrofurantoin and trimethoprim users, respectively. The risk of an adverse event was significantly higher in nitrofurantoin users with renal impairment (< 50 ml/min/1.73m^2 [adjusted HR 4.1, 95% CI 1.31–13.09]) compared to nitrofurantoin users with good renal function (≥ 50 ml/min/1.73m^2). Due to the low incidence of adverse events in trimethoprim users, the HRs could not be calculated.

Discussion

Overall, nitrofurantoin treatment was not significantly associated with ineffectiveness in women with UTI and moderate renal impairment (30-50 ml/min/1.73m^2). However, adverse events due to nitrofurantoin use leading to hospitalization were significantly associated with renal impairment < 50 ml/min/1.73m^2.

The amount of nitrofurantoin excreted into the urine is directly related to renal function and, therefore, nitrofurantoin may be ineffective for the treatment of UTI in patients with impaired renal function.[7,9,10] A recent review reports that sufficient clinical evidence for an effect of renal impairment on the effectiveness and adverse events of nitrofurantoin is lacking.[20] In accordance, Bains et al. reported that nitrofurantoin is effective and well tolerated in hospitalized patients with renal impairment (< 50 ml/min).[11] In their study, the frequencies for starting a second antibacterial after nitrofurantoin treatment were 29% in the renal impairment group versus 22% in the group without renal impairment. In our population of outpatients these frequencies were somewhat lower, namely 22% and 16%, respectively.

In our study, no neuropathy, allergic reactions and liver damage were diagnosed during the 3 months of follow-up after the start of nitrofurantoin treatment. Pulmonary reactions were the most frequently diagnosed adverse reactions (0.16%). This observation is in agreement with the results of Holmberg et al. who also observed pulmonary reactions to be the most frequent adverse reactions associated with nitrofurantoin treatment.[16] In addition, several guidelines include a warning for pulmonary reactions due to nitrofurantoin, especially in the elderly patient.[21]

We observed lower point estimates for ineffective treatment and/or serious adverse events among patients with unknown renal function than among those with a known renal function. One possible explanation could be that patients with an unknown renal function are 'healthy survivors'.[22]

The strength of our study is that it was conducted in a very large study population

with a relative long follow-up time in general practice. However, there are a number of limitations to our study. First, the outcome second antibacterial treatment after an initial nitrofurantoin treatment may not have been sufficiently sensitive to classify ineffectiveness correctly in all cases. Although we selected only antibacterials used for UTI treatment, patients can receive those antibacterials for other reasons. Second, the registration of adverse events in the PHARMO database is limited to adverse events leading to hospitalization, which may only encompass the tip of the iceberg of all adverse events. Therefore, the occurrence of adverse events of nitrofurantoin use in relation to renal impairment may have been underestimated. A third limitation is the limited numbers of nitrofurantoin users with moderate or severe renal impairment (n = 166 and n = 20, respectively). An explanation for these small numbers could be that physicians were well aware of the contraindication for nitrofurantoin and mostly acted accordingly. The fourth limitation is that the classification of renal function groups was based on a single eGFR value of not more than 1 year old. This choice was for pragmatic reasons because clinical guidelines often recommend annual monitoring of renal function. However, variability in serum creatinine measurements ideally requires at least two creatinine measurements in a shorter period of time.[23]

In conclusion, this retrospective cohort study shows that nitrofurantoin treatment may be effective in women with UTI and renal impairment. However, we did find a significant association between renal impairment and pulmonary adverse events leading to hospitalization. Establishing the effectiveness and safety of nitrofurantoin use in women with renal impairment requires more sensitive outcome measurements.

What does this study add?

According to the drug label nitrofurantoin is contraindicated when the eGFR is < 60 ml/min because of ineffectiveness and safety problems. New evidence suggests that nitrofurantoin in patients with lower eGFRs may be both effective and safe. In our study, we found no evidence that the treatment of these women with nitrofurantoin is less effective; however, the number of adverse events leading to hospitalization was significantly increased.

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Appendix 4.1. Potentially adverse reactions of nitrofurantoin with corresponding ICD-9 codes

Type of adverse reaction[1,2]	ICD-9 code	Description of ICD-9 code
General adverse events		
Overdosing	E857	Accidental poisoning by other anti-infectives; flucytosine and nitrofurantoin derivatives
Adverse effects (in general)	E931.9	Adverse effects by other and unspecified anti-infectives; flucytosine and nitrofurantoin derivatives
Pulmonary reactions		
Common pulmonary reactions	519.9	Unspecified disease of respiratory system Respiratory Disease (chronic) NOS
Acute cellular interstitial lung disease/ pneumonia	516.33	Acute interstitial pneumonitis
Subacute interstitial pneumonia	516.30	Idiopathic interstitial pneumonia, not otherwise specified. Idiopathic fibrosing alveolitis
	516.32	Idiopathic non-specific interstitial pneumonitis
Pulmonary infiltrates and eosinophilia Eosinophilic pneumonia	518.3	Pulmonary eosinophilia
Organising pneumonia (BOOP - AFOP)	516.8	Other specified alveolar and parietoalveolar pneumonopathies Endogenous lipoid pneumonia; Interstitial pneumonia; Lymphoid interstitial pneumonia due to known underlying cause; Lymphoid interstitial pneumonia NOS; Non-specific interstitial pneumonia due to known underlying cause; Non-specific interstitial pneumonia NOS; Organizing pneumonia due to known underlying cause; Organizing pneumonia NOS
Desquamative interstitial pneumonia (DIP pattern)	516.37	Desquamative interstitial pneumonia
Pulmonary fibrosis	516.31	Idiopathic pulmonary fibrosis Cryptogenic fibrosing alveolitis
Diffuse alveolar damage (DAD): ARDS is a clinical syndrome associated with a variety of pathological findings. These include pneumonia, eosinophilic pneumonia, cryptogenic organizing pneumonia, acute fibrinous organizing pneumonia, and diffuse alveolar damage (DAD). Of these, the pathology most commonly associated with ARDS is DAD.	518.82	Other pulmonary insufficiency, not elsewhere classified Acute respiratory distress Acute respiratory insufficiency Adult respiratory distress syndrome
Acute severe pulmonary oedema/ARDS	518.4	Acute edema of lung, unspecified Acute pulmonary edema NOS; pulmonary edema postoperative

Type of adverse reaction[1,2]	ICD-9 code	Description of ICD-9 code
Pulmonary reactions (continued)		
Diffuse alveolar haemorrhage (ANCA)	786 (3)	786.3 Haemoptysis Cough with haemorrhage Pulmonary haemorrhage
Acute bronchospasm	519.11	Acute bronchospasm Bronchospasm NOS
Bronchospasm and angioedema (anaphylaxis)	517.8	Lung involvement in other diseases classified elsewhere
	995.0	Other anaphylactic reaction {Allergic shock}{Anaphylactic reaction}{Anaphylactic shock}{Anaphylaxis} NOS or due to adverse effect of correct medicinal substance properly Administered; Anaphylactoid reaction NOS
	995.1	Angioneurotic edema, not elsewhere classified Giant urticaria; Allergic angioedema
Pleural effusion	511.9	Unspecified pleural effusion Pleural effusion NOS; Pleurisy: exudative, serofibrinous, serous, with effusion NOS
Pulmonary vasculitis	417.8	Other specified diseases of pulmonary circulation: •Pulmonary:arteritis endarteritis •Rupture of pulmonary vessel •Stricture of pulmonary vessel
Peritracheal/mediastinal haemorrhage and upper airway obstruction	786.3	Haemoptysis
Skin rash, eosinophilia, and internal organs involvement including pneumonia (DRESS)	518.3	Pulmonary eosinophilia Eosinophilic asthma Löffler's syndrome Pneumonia: allergic + eosinophilic Tropical eosinophilia
Isolated acute chest pain	786.50	Unspecified chest pain
	786.52	Painful respiration. Pain: anterior chest wall, pleuritic; Pleurodynia
Acute chest pain and interstitial lung disease	786.5	Symptoms involving respiratory system and other chest symptoms 786.5 Chest pain
Allergic reactions		
Common	995.3	Allergy unspecified, not elsewhere classified Allergic reaction NOS; Hypersensitivity NOS; Idiosyncrasy NOS
	995.20	Unspecified adverse effect of unspecified drug, medicinal, and biological substance Unspecified adverse effect of unspecified medicinal substance properly administered

Type of adverse reaction[1,2]	ICD-9 code	Description of ICD-9 code
Allergic reactions (continued)		
Common (continued)	995.27	Other drug allergy Allergic reaction NEC (due) to correct medical substance properly administered; Drug allergy NOS; Drug hypersensitivity NOS; Hypersensitivity (due) to correct medical substance properly administered
	995.29	Unspecified adverse effect of other drug, medicinal, and biological substance Unspecified adverse effect of medicinal substance NEC properly administered
Anaphylactic reaction	995.0	Other anaphylactic reaction {Allergic shock}{Anaphylactic reaction}{Anaphylactic shock}{Anaphylaxis} NOS or due to adverse effect of correct medicinal substance properly administered; Anaphylactoid reaction NOS
Pruritus	698.9	Unspecified pruritic disorder Itch NOS; Pruritus NOS
Urticaria	708.0	Allergic urticaria
Angioedema	995.1	Angioneurotic edema, not elsewhere classified; Allergic angioedema
Erythema multiforme	695.1	Erythema multiforme
Fever	780.60	Fever, unspecified Chills with fever; Fever NOS; Fever of unknown origin (FUO); Hyperpyrexia NOS; Pyrexia NOS; Pyrexia of unknown origin
Liver damage		
Jaundice	782.4	Jaundice, unspecified, not of newborn Cholemia NOS; Icterus NOS
Hepatomegaly	789.1	Hepatomegaly Enlargement of liver
Blood dyscrasias		
Haemolytic anemia	283.0	Autoimmune haemolytic anemias Autoimmune haemolytic disease (cold type) (warm type); Chronic cold hemagglutinin disease; Cold agglutinin disease or hemoglobinuria; Haemolytic anemia: cold type (secondary) (symptomatic), drug-induced, wart type (secondary) (symptomatic)
	283.1	Non-autoimmune haemolytic anemias
	283.9	Acquired haemolytic anemia, unspecified Acquired haemolytic anemia NOS; Chronic idiopathic haemolytic anemia
Thrombocytopenia	287.5	Thrombocytopenia, unspecified
	287.30	Primary thrombocytopenia, unspecified Megakaryocytic hypoplasia

Type of adverse reaction[1,2]	ICD-9 code	Description of ICD-9 code
Blood dyscrasias (continued)		
Thrombocytopenia (continued)	287.39	Other primary thrombocytopenia
	287.49	Other secondary thrombocytopenia Thrombocytopenia (due to): dilutional, drugs, extracorporeal circulation of blood, massive blood transfusion, platelet alloimmunization, secondary NOS
Severe haemorrhagic diathesis	287.9	Unspecified haemorrhagic conditions Haemorrhagic diathesis (familial)
Allergic agranulocytosis	288.09	Other neutropenia Agranulocytosis; Neutropenia: immune, toxic
Neutropenia	288.03	Drug induced neutropenia
	288.00	Neutropenia, unspecified
Pancytopenia	284.1	Pancytopenia
Neuropathy		
Neuropathy	356.4	Idiopathic progressive polyneuropathy
	356.8	Other specified idiopathic peripheral neuropathy. Supranuclear paralysis
	356.9	Unspecified idiopathic peripheral neuropathy
	357.6	Polyneuropathy due to drugs
	357.9	Unspecified inflammatory and toxic neuropathies
	357.89	Other inflammatory and toxic neuropathy

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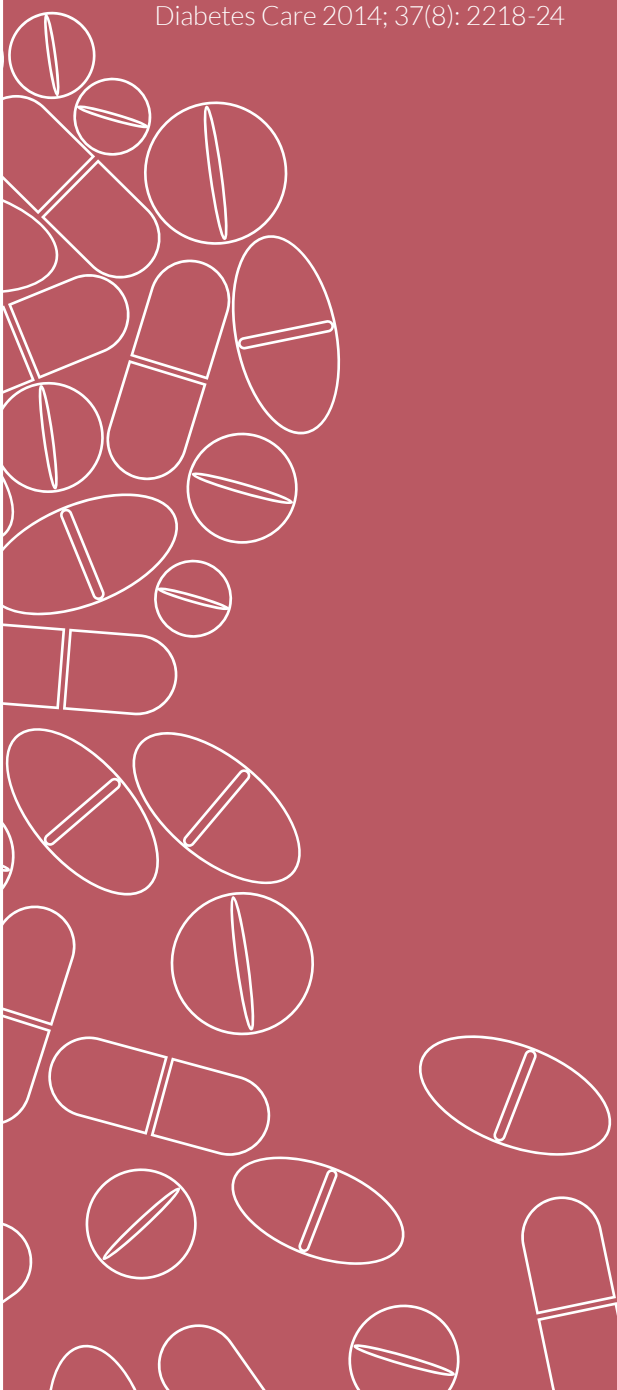
Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment:

A population-based cohort study

Diabetes Care 2014; 37(8): 2218-24



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5

Abstract

Objective

The objective of this study was to determine whether treatment with metformin in patients with renal impairment is associated with a higher risk of lactic acidosis or elevated lactate concentrations compared with users of a noninsulin antidiabetic drug (NIAD) who had never used metformin.

Research design and methods

A cohort of 223,968 metformin users and 34,571 diabetic patients who had never used metformin were identified from the Clinical Practice Research Datalink (CPRD). The primary outcome was defined as either a CPRD READ code of lactic acidosis or a record of a plasmalactate concentration > 5 mmol/l. The associations between renal impairment, dose of metformin, and the risk of lactic acidosis or elevated lactate concentrations were determined with time-dependent Cox models and expressed as hazard ratios (HRs).

Results

The crude incidence of lactic acidosis or elevated lactate concentrations in current metformin users was 7.4 per 100,000 person-years (versus 2.2 per 100,000 person-years in nonusers). Compared with nonusers, risk of lactic acidosis or elevated lactate concentrations in current metformin users was significantly associated with a renal function < 60 ml/min/1.73m^2 (adjusted HR 6.37, 95% CI 1.48-27.5). The increased risk among patients with impaired renal function was further increased in users of ≥ 730 g of metformin in the preceding year (adjusted HR 11.8, 95% CI 2.27-61.5) and in users of a recent high daily dose (> 2 g) of metformin (adjusted HR 13.0, 95% CI 2.36-72.0).

Conclusions

Our study is consistent with current recommendations that the renal function of metformin users should be adequately monitored and that the dose of metformin should be adjusted, if necessary, if renal function falls below 60 ml/min/1.73m^2.

Introduction

There is good evidence that metformin reduces the long-term incidence of macrovascular complications in type 2 diabetes mellitus, especially among overweight patients.[1-3] In contrast to alternative oral noninsulin antidiabetic drugs (NIADs) and insulin, metformin is not associated with a risk of hypoglycemia.[3-5] The most serious adverse event that has been observed during metformin use is lactic acidosis, which is characterized by an elevated blood lactate concentration (> 5 mmol/l), decreased blood pH (< 7.35) and electrolyte disturbances with an increased anion gap.[1,6-9] Estimated rates of lactic acidosis incidence during metformin use range from 1 to 47 cases per 100,000 person-years.[10,11] Reported predisposing factors include acute kidney injury, history of lactic acidosis, hypovolemia, decreased tissue perfusion or hemodynamic instability due to infection or other causes, seizure, concurrent liver disease, alcohol abuse, acute heart failure, myocardial infarction, and shock.[12-14] Although lactic acidosis during metformin use has a better prognosis than other types of severe lactic acidosis[15], reported mortality rates may be as high as 25-50%.[1,4,8] Yet metformin itself has not been linked to mortality in users developing lactic acidosis during metformin use, which perhaps reflects a primary effect of other underlying causes of the acidosis.[16]

According to current guidelines, the dose of metformin should be reviewed if the estimated glomerular filtration rate (eGFR) falls to < 45 ml/min/1.73m^2, and the drug should be stopped in patients with an eGFR < 30 ml/min/1.73m^2.[3,17,18] A decreased glomerular filtration rate may theoretically increase the risk of lactic acidosis during metformin use because metformin is eliminated unchanged by the kidneys and may therefore accumulate when kidney function becomes impaired.[3,19] However, the role of chronic renal insufficiency as a risk factor for lactic acidosis during metformin use remains controversial.

On the one hand, some authors argue that an association between high concentrations of metformin and lactic acidosis should be assumed because, for example, supratherapeutic plasma concentrations of metformin have frequently been found in patients with lactic acidosis during metformin use and because high metformin concentrations have been shown to increase plasma lactate in rats.[4,9,20] On the other hand, a contributory role of chronic renal insufficiency to lactic acidosis during metformin use was not confirmed in large epidemiological studies[12,21], and a recent study of 56 cases of severe lactic acidosis during metformin use did not find a prognostic value for blood lactate.[22]

Duong et al.[9] argue that there may be three different forms of lactic acidosis

during metformin use and that one of these is characterized by the accumulation of metformin together with acute impairment of renal function and organ decompensation, such as acute or chronic heart failure, induced by sepsis and/or dehydration. They hypothesize that this type of lactic acidosis during metformin use involves a positive feedback system comprising one or more of the following factors: vomiting and diarrhea, acute kidney injury, high doses or excessive accumulation of metformin, and acute disease states leading to tissue hypoxia. They suggest that lactic acidosis may commence with relatively small changes in hydration, kidney function, plasma concentrations of metformin, or tissue oxygenation, which then lead to positive feedback and severe lactic acidosis.

The aim of this study, therefore, was to evaluate retrospectively, in a large cohort of patients using a NIAD, whether treatment with metformin is associated with a higher risk of lactic acidosis or elevated lactate concentrations in patients with renal impairment compared with patients who had never used metformin. In addition, the risk of lactic acidosis or elevated lactate concentrations in patients with different metformin doses was evaluated.

Research design and methods

Data sources

We conducted a retrospective cohort study using the Clinical Practice Research Datalink (CPRD), previously known as the General Practice Research Database. The CPRD collates the computerized medical records of general practitioners (GPs). GPs play a key role in the U.K. health care system; they are responsible for primary health care and specialist referrals. Patients are semipermanently affiliated with a practice that centralizes the medical information from the GPs, specialist referrals, and hospitalizations. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions, and major outcomes since 1987 (www.CPRD.com).

Study population

All patients with at least one prescription for a NIAD and age > 18 years during the period of valid CPRD data collection were enrolled. For this study, data collection started in April 2004, with the introduction of the Quality and Outcomes Framework, and ended in August 2012. The first NIAD prescription after the start of data collection defined the index date. Patients with a record of any renal transplant or dialysis during the study period were excluded (n = 152 among metformin users; n = 234 among nonusers).

Exposure

Exposure to metformin and/or other NIADs was assessed in a time-dependent manner. For this purpose, total follow-up of each individual was divided into small time intervals. The length of a time interval was based on NIAD prescriptions: a time interval starts with a NIAD prescription and ends 1 day before the next NIAD prescription. If the length of a time interval exceeded 90 days, the interval was further divided into separate 90-day intervals. This approach minimizes exposure misclassification. For each time interval, the exposure to metformin was assessed as (1) current metformin use (at least one metformin prescription in the 3 months before the start of a time interval); (2) recent metformin use (a most recent metformin prescription between 3 and 6 months before the start of a time interval); (3) past metformin use (the most recent metformin prescription > 6 months before the start of a time interval); and (4) never metformin use (no metformin prescription at any time before the start of a time interval). As a consequence, a patient could move between never, current, recent, and past metformin use. A past user could become a current metformin user in the event of a new metformin prescription. Current metformin users were stratified according to their cumulative metformin exposure in the previous year (< 730 g [< 365 x 2 g] and ≥ 730 g) and their most recent prescribed daily metformin dose (≤ 2 g and > 2 g).

Renal function

For current metformin users, we evaluated the most recently recorded renal function 1 week to 1 year before the start of an interval. Renal function was evaluated by reviewing laboratory test data (eGFR(MDRD) where possible), and CPRD READ codes (stages of chronic kidney disease). In the event of multiple eGFR values on the same day, the mean value was used. CPRD READ codes were prioritized if there was a laboratory test on the same day as recording.

Outcomes

Patients were followed up from the index date to either the end of data collection, the date the patient transferred out of the practice area, the patient's death, or an event of lactic acidosis or elevated lactate concentration.

Lactic acidosis or elevated lactate concentrations were evaluated either by a CPRD READ code for lactic acidosis or by a record of plasma lactate concentration of > 5 mmol/l, whichever came first. In the event of multiple laboratory tests for lactate concentrations on the same day, the lowest value was used. In a sensitivity analysis, the highest value was used instead of the lowest value. CPRD READ codes for lactic acidosis were prioritized if there was a laboratory test on the same day as recording.

Potential confounders

The presence of risk factors for lactic acidosis during metformin use was assessed by reviewing the computerized medical records before the start of an interval. Risk factors that were considered in this study included age, sex, smoking status, body mass index (BMI), alcohol use, hemoglobin A_{1c} (HbA_{1c}), and a history of asthma/chronic obstructive pulmonary disease, chronic liver disease, heart failure, and/or sepsis.[12,23-25] We further considered a prescription in the previous 6 months for drugs that may have influenced renal function (including nonsteroidal anti-inflammatory drugs, renin-angiotensin-aldosterone-system inhibitors, loop diuretics, thiazide diuretics, beta blockers, statins, and systemic calcineurin inhibitors).

Data analysis

Cox regression analysis compared hazard rates of lactic acidosis or elevated lactate concentrations in current metformin users versus NIAD users who had never used metformin (SAS software version 9.2). Confounders were entered into the final model if they independently changed the ß-coefficient for current metformin use by at least 5%. The main association for possible interactions with any of the risk factors was tested. Current metformin users were further stratified according to renal function and metformin dose.

Results

Table 5.1 displays the baseline characteristics of NIAD users who were either current metformin users (n = 223,968) or nonusers (n = 34,571). The mean duration of follow-up was 4.3 years for metformin users and 4.9 years for nonusers. Metformin users were younger (60.1 years) than nonusers (67.8 years). No substantial difference in sex distribution was observed. The proportion of metformin users with stage 4 or 5 chronic kidney disease (eGFR < 30 ml/min/1.73m^2) was lower than that of NIAD users (0.3% and 2.8%, respectively). Heart failure was less prevalent among the metformin users compared with the nonusers (3.9% and 8.3%, respectively). Age was strongly correlated with worsening glomerular filtration rate (GFR): patients younger than 50 years old had a GFR of 96 ml/min/1.73m^2, those aged 50-64 years had a GFR of 84 ml/min/1.73m^2, patients aged 65-79 years had a GFR of 70 ml/min/1.73m^2, and the lowest GFR (59 ml/min/1.73m^2) was seen in patients aged 80 years and older (data not shown). Patients suffering from lactate acidosis or elevated lactate concentrations had a median age of 72 years (75% were older than 60 years of age).

Table 5.1 Baseline characteristics of current metformin users and nonusers among patients using NIADs

Characteristic	Current metformin users n = 223,968	(%)	Non-users n = 34,571	(%)
Follow-up time, years (mean, SD)[a]	4.3 (2.8)		4.9 (3.0)	
Female sex	105,561	(47.1)	15,007	(43.4)
Age, years (mean, SD)	60.1 (14.8)		67.8 (14.5)	
18 – 49	51,394	(22.9)	4,221	(12.2)
50 – 59	49,018	(21.9)	4,997	(14.5)
60 – 69	59,363	(26.5)	7,899	(22.8)
70 – 79	45,689	(20.4)	9,558	(27.6)
≥ 80 years	18,504	(8.3)	7,896	(22.8)
Most recent renal function (ml/min/1.73m²) in the previous year[b]				
< 30	586	(0.3)	955	(2.8)
30 – 59	29,742	(13.3)	7,436	(21.5)
≥ 60	132,344	(59.1)	14,235	(41.2)
Unknown	61,296	(27.4)	11,945	(34.6)
Smoking status				
Current smoker	45,258	(20.2)	6,848	(19.8)
Former smoker	66,485	(29.7)	9,706	(28.1)
Never smoker	111,137	(49.6)	17,387	(50.2)
Unknown	1,088	(0.5)	630	(1.8)
BMI, kg/m² (mean, SD)	31.6 (6.6)		27.6 (5.7)	
< 20.0	2,259	(1.0)	1,502	(4.3)
20.0 – 24.9	25,816	(11.5)	9,777	(28.3)
25.0 – 29.9	71,071	(31.7)	12,205	(35.3)
30.0 – 34.9	63,622	(28.4)	5,647	(16.3)
≥ 35.0	55,885	(25.0)	3,176	(9.2)
Unknown	5,315	(2.4)	2,264	(6.5)
Alcohol use				
Yes	147,319	(65.8)	20,861	(60.3)
No	64,408	(28.8)	10,363	(30.0)
Unknown	12,241	(5.5)	3,347	(9.7)
History of disease				
Asthma/COPD	36,670	(16.4)	5,309	(15.4)
Chronic liver disease	3,511	(1.6)	733	(2.1)
Heart failure	8,794	(3.9)	2,879	(8.3)
Sepsis	2,827	(1.3)	488	(1.4)
Drug use within six months with potential influence on renal function				
NSAIDs	40,147	(17.9)	5,435	(15.7)
RAAS inhibitors	91,230	(40.7)	12,151	(35.1)
Loop diuretics	21,874	(9.8)	5,468	(15.8)
Thiazide diuretics	40,538	(18.1)	5,497	(15.9)
Beta blockers	40,090	(17.9)	6,534	(18.9)
Statins	99,990	(44.6)	14,070	(40.7)
Systemic calcineurin inhibitors	316	(0.1)	255	(0.7)

Data are n (%) unless otherwise indicated.

[a] Time represents valid follow-up time for patients using metformin and control patients not using metformin.

[b] Proportion of renal function originating from READ codes: 3.6%, and 96.4% from laboratory test events.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; NIAD, noninsulin antidiabetic drug; NSAID, non-steroidal anti-inflammatory drug; RAAS, renin-angiotensin-aldosteron-system; SD, standard deviation.

Table 5.2 shows that the incidence rate of lactic acidosis or elevated lactate concentrations was 7.4 events per 100,000 person-years among current metformin users versus 2.2 events per 100,000 person-years among nonusers. Of a total of 68 events of lactic acidosis or elevated lactate concentrations, 50 (74%) originated from a READ code for lactic acidosis, whereas 18 (26%) were derived from an elevated plasma lactate concentration. Three events had both a READ record for lactic acidosis and a positive laboratory test. Current metformin users had a fourfold risk compared with NIAD users who had never used metformin, but this increase was not statistically significant (adjusted hazard ratio [AHR] 4.03, 95% CI 0.97-16.8). The risk among recent or past users of metformin also was nonsignificantly increased. None of the results were influenced by our sensitivity analysis, which used the highest value (instead of the lowest value) in the event of multiple lactate concentrations on the same day.

Table 5.2 Risk of lactic acidosis or elevated lactate concentrations in current, recent, and past metformin users compared with never users of metformin

Metformin use	Risk of lactic acidosis or elevated lactate concentrations			
	Person-years (n)	Events (n)	Age/sex adjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Never use	91,287	2	Reference	Reference
Past use	212,007	9	1.94 (0.42-8.97)	2.25 (0.48-10.5)
Recent use	40,526	2	2.25 (0.32-16.0)	2.99 (0.42-21.5)
Current use	743,151	55	3.38 (0.82-13.8)	4.03 (0.97-16.8)
Stratification of current users by most recent renal function (ml/min/1.73m²) in previous year[b]				
≥ 60	547,731	29	2.42 (0.58-10.1)	2.87 (0.67-12.3)
< 60	126,881	21	7.56 (1.77-32.2)	6.37 (1.48-27.5)
30-59 [c]	124,275	19	7.09 (1.98-27.9)	5.94 (1.55-24.7)
45-59	89,976	13	6.60 (1.49-29.2)	6.06 (1.37-27.1)
30-44	25,450	5	7.98 (1.61-39.6)	5.47 (1.05-28.5)
< 30	2,605	2	35.1 (4.90-249)	25.7 (3.57-185)
≥ 45	644,861	43	3.30 (0.79-13.8)	3.16 (0.75-13.3)
< 45	29,751	7	8.97 (1.85-43.4)	6.74 (1.34-33.8)
Unknown	68,539	5	3.33 (0.65-17.2)	4.51 (0.85-23.8)

Current metformin users are stratified by renal function.

[a] Adjusted for age, sex, body mass index, a history of heart failure, and use of renin-angiotensin-aldosterone system inhibitors and other noninsulin antidiabetic drugs/insulin in the previous 6 months. Chronic liver disease and sepsis were not included in the final model because there were too few exposed patients.

[b] Renal function records in the previous week are excluded.

[c] This substratum included 8,849 person-years, with one event that could not be subdivided further because the patients only had a READ code for Chronic Kidney Disease Stage 3 (30-59 ml/min/1.73m²).

CI, confidence interval; HR, hazard ratio.

The different strata of current metformin users (compared with NIAD users who had never used metformin) showed the following increases in the risk of lactic acidosis or

elevated lactate concentrations: (1) the risk in those with a most recent renal function < 60 ml/min/1.73m^2 was significantly higher than the risk in never users (AHR 6.37, 95% CI 1.48-27.5), whereas the risk in current users with renal function ≥ 60 ml/min/1.73m^2 (AHR 2.87, 95% CI 0.67-12.3) was not; (2) in an additional analysis, we looked at an eGFR cut-point of 45 ml/min/1.73m^2. Current metformin users with an eGFR of ≥ 45 ml/min/1.73m^2 had an AHR of lactic acidosis or elevated lactate concentrations of 3.16 (95% CI 0.75-13.3), whereas those with poorer renal function (eGFR < 45 ml/min/1.73m^2) had an AHR of 6.74 (95% CI 1.34-33.8). Among metformin users with a recorded eGFR value, 14% of all lactic acidosis or elevated lactate concentrations occurred among those with an eGFR of < 45 ml/min/1.73m^2; (3) the risk in those with a cumulative exposure to metformin of ≥ 730 g in the previous year (AHR 6.14, 95% CI 1.35-28.0) was significantly increased. This was not the case in those with an exposure < 730 g (AHR 3.69, 95% CI 0.88-15.5); (4) the risk in those with a recent prescribed daily dose of > 2 g of metformin (AHR 6.40, 95% CI 1.35-30.3) was significantly increased. This was not the case in those with a dose of ≤ 2 g of metformin (AHR 3.78, 95% CI 0.90-15.8).

When the strata in analyses 3 and 4 were substratified by renal function, the risk in metformin users with renal function < 60 ml/min/1.73m^2 consistently showed a significant increase. This was not seen in those with renal function ≥ 60 ml/min/1.73m^2 (Table 5.3). Compared with never users, there was an almost 12-fold risk in the substratum with reduced renal function and a cumulative exposure to ≥ 730 g of metformin in the preceding year (AHR 11.8, 95% CI 2.27-61.5) and a 13-fold increase in the substratum with reduced renal function and recent exposure to > 2 g of metformin/day (AHR 13.0, 95% CI 2.36-72.0).

Discussion

The risk of lactic acidosis or elevated lactate concentrations was increased sixfold in current metformin users with reduced renal function (Table 5.2). It increased further to 12- or 13-fold in substrata with high cumulative exposure to metformin in the preceding year or with recent high daily exposure to metformin (Table 5.3).

Our crude incidence rate of lactic acidosis or elevated lactate concentrations, 7.4 events per 100,000 person-years among current metformin users, corresponds well with the range of one to nine cases of lactic acidosis per 100,000 person-years of metformin use that emerged from previous studies.[7,10,12,26] Higher incidences of 47 to 57 cases per 100,000 person-years also have been reported, but this is probably due to differences in study design.[11,27] Ekström et al. assessed whether different degrees of renal function affect the safety of metformin use in a cohort study comprising

Table 5.3 Risk of lactic acidosis or elevated lactate concentrations in current metformin users stratified by cumulative exposure or recent daily exposure to metformin and further stratified by renal function

Metformin use	Risk of lactic acidosis or elevated lactate concentrations			
	Person-years (n)	Events (n)	Age/sex adjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Never use	91,287	2	Reference	Reference
Current use	743,151	55	3.38 (0.82-13.8)	4.03 (0.97-16.8)
Stratification of current users by cumulative exposure to metformin in previous year and renal function[b]				
< 730 g of metformin/year	628,644	43	3.12 (0.76-12.9)	3.69 (0.88-15.5)
Renal function ≥ 60 ml/min/1.73m^2	460,012	23	2.28 (0.54-9.65)	2.73 (0.63-11.9)
Renal function < 60 ml/min/1.73m^2	108,561	16	6.72 (1.55-29.2)	5.54 (1.26-24.4)
Unknown	60,071	4	3.03 (0.56-16.5)	4.25 (0.76-23.7)
≥ 730 g of metformin/year	114,506	12	4.78 (1.07-21.4)	6.14 (1.35-28.0)
Renal function ≥ 60 ml/min/1.73m^2	87,719	6	3.12 (0.63-15.4)	3.94 (0.78-20.0)
Renal function < 60 ml/min/1.73m^2	18,320	5	12.4 (2.42-64.1)	11.8 (2.27-61.5)
Unknown	8,468	1	5.38 (0.49-59.3)	6.96 (0.62-78.0)
Stratification of current users by most recent prescribed daily dose of metformin and renal function[b]				
≤ 2 g of metformin/day	658,391	46	3.19 (0.77-13.1)	3.78 (0.90-15.8)
Renal function ≥ 60 ml/min/1.73m^2	483,674	24	2.27 (0.54-9.58)	2.71 (0.63-11.7)
Renal function < 60 ml/min/1.73m^2	113,530	17	6.84 (1.58-29.6)	5.66 (1.29-24.8)
Unknown	61,187	5	3.73 (0.72-19.2)	5.19 (0.98-27.4)
> 2 g of metformin/day	84,759	9	4.85 (1.05-22.4)	6.40 (1.35-30.3)
Renal function ≥ 60 ml/min/1.73m^2	64,057	5	3.56 (0.69-18.4)	4.59 (0.87-24.3)
Renal function < 60 ml/min/1.73m^2	13,350	4	13.7 (2.51-74.7)	13.0 (2.36-72.0)
Unknown	7,352	0		

[a] Adjusted for age, sex, body mass index, a history of heart failure, and use of renin-angiotensin-aldosterone system inhibitors and other noninsulin antidiabetic drugs/insulin in the previous 6 months. Chronic liver disease and sepsis were not included in the final model because there were too few exposed patients.

[b] Stratification by most recent renal function in previous year. Renal function records in previous week are excluded.

CI, confidence interval; HR, hazard ratio.

more than 51,000 patients with type 2 diabetes.[21] To evaluate the occurrence of lactic acidosis, they used a composite end point that included a diagnosis of acidosis, shock, acute renal failure, and serious infections. When metformin use was compared with any other treatment, the risk of acidosis/serious infection was not significantly increased in patients with an eGFR ≤ 60 ml/min/1.73m^2.[21]

In contrast with these negative findings, we found that reduced renal function or high cumulative or daily exposure to metformin (all of which can lead to higher concentrations of metformin) were associated with an increased risk of lactic acidosis or elevated lactate concentrations. That the risk was further increased when both reduced renal function and a high intake of metformin were present is of particular

interest. This lends support to the supposition that high concentrations of metformin may increase the risk of lactic acidosis during metformin use.

A major strength of our study is that it was conducted over a long observation period in a large database representative of the U.K. population in general practice, which offers the possibility to correct for smoking and BMI. The database's information on drug exposure and diagnoses has been validated and proven to be of high quality.[12] Another strength is that we not only separately evaluated the influence of renal function and the level of metformin intake, but also did so in combination.

Like most observational studies, our study is not without limitations. First, there is the potential issue of the selection and inaccurate estimation of our outcome measure. The inclusion of patients with a lactate concentration > 5 mmol/l (26% of our cases) may have resulted in an overestimate compared with lactic acidosis during metformin use alone, since elevated lactate concentrations do not necessarily signify a diagnosis of lactic acidosis.[28] Furthermore, in a previous study of the same CPRD database (General Practice Research Database) that we used, 7 of 14 patients with a READ code of lactic acidosis were excluded after a manual review of their medical record.[12] This may have resulted in a nondifferential misclassification of the outcome, which might overestimate the incidence rates of lactic acidosis, although it is unlikely to affect the relative risk of lactic acidosis with metformin use among patients with decreased renal function. In addition, our period of observation (2004-2012) was different from the study period used by Bodmer et al. (1994-2005) and started with the year in which the so-called Quality and Outcomes Framework was introduced in the U.K.[29] The potential risk of differential underrecording among nonusers should also be considered. Because of the longstanding assumption that metformin may be linked to lactic acidosis, the lactate concentrations of metformin users may have been measured and recorded more selectively, particularly in those with reduced renal function. Nondifferential underrecording of lactic acidosis in the CPRD database may also have occurred; the presenting features of lactic acidosis are often vague[28], and GPs may not always have transferred lactic acidosis in a hospital discharge letter to their own records by means of the appropriate READ code. A counterargument against such underrecording is, of course, that lactic acidosis is a serious event that is likely to draw sufficient clinical attention. Mild elevations of lactate concentrations can be caused by a large number of pathologic conditions, ethanol, and drugs. Since we were not able to identify the exact cause of lactic acidosis, we were not able to exclude these events.

A second limitation is that we could not retrieve adequate information about all potentially relevant risk factors for lactic acidosis during metformin use. We based our classification of renal function on a READ code or a single eGFR value; we pragmatically accepted this latter value so long as it was not more than 1 year old (based on the argument that clinical guidelines often recommend annual monitoring of renal function). This may have increased the risk of including outdated information. In spite of our liberal choice, we could not retrieve renal function data for 27.4% and 34.6% of the current metformin users and nonusers, respectively (Table 5.1). Finally, we were not able to analyze the effect of acute decreases in GFR on the risk of lactic acidosis or elevated lactate concentrations.

In conclusion, our study suggests that the risk of lactic acidosis or elevated lactate concentrations is significantly increased in patients with mild to moderate renal insufficiency and that this risk is further increased in long-term heavy metformin users. Although these findings are not conclusive, they are consistent with current recommendations in the literature to adequately monitor the renal function of metformin users and to adjust the dose of metformin, if necessary, if the eGFR falls below 60 ml/min/1.73m^2.[3,17,18] This should be confirmed in future research, preferably in a study in which lactate concentrations, renal function, and metformin exposure are frequently assessed and in which all potential risk factors are accurately determined and recorded.

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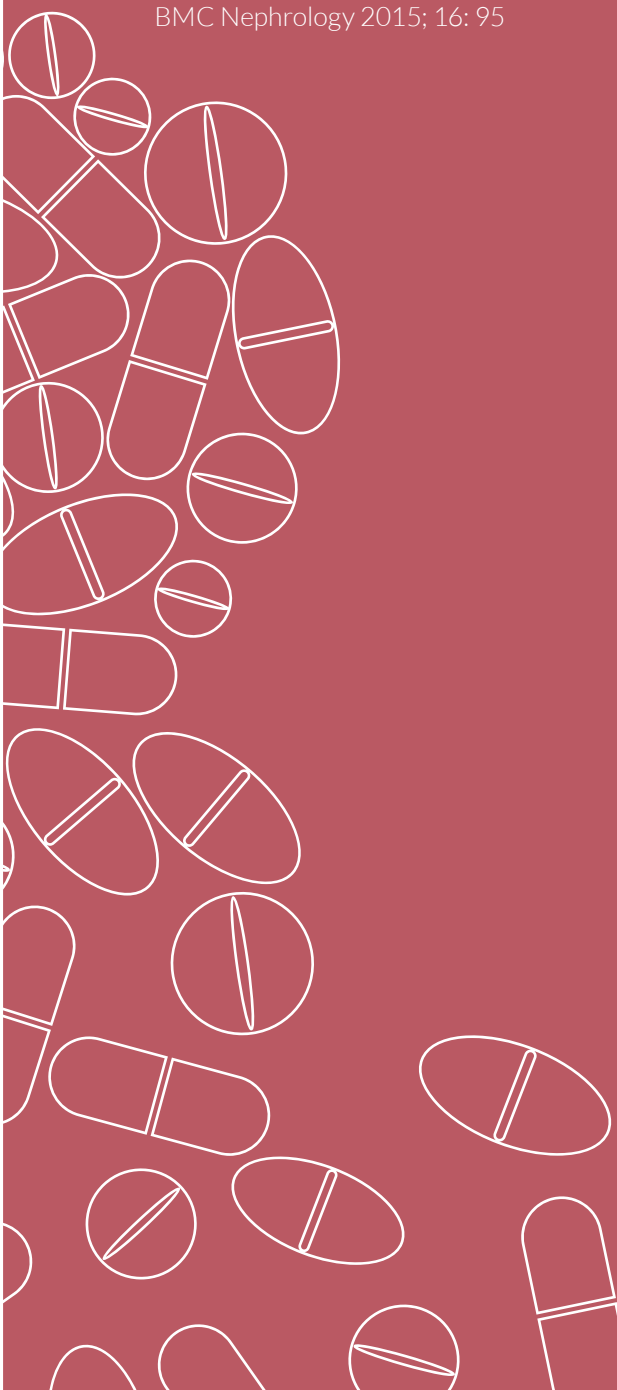
Fluctuation of the renal function after discharge from hospital and its effects on drug dosing in elderly patients:

A study protocol

BMC Nephrology 2015; 16: 95



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6

Abstract

Background

Chronic kidney disease (CKD) is associated with an increased mortality rate, risk of cardiovascular events and morbidity. Impaired renal function is common in elderly patients, and their glomerular filtration rate (GFR) should be taken into account when prescribing renally excreted drugs. In a hospital care setting the GFR may fluctuate substantially, so that the renal function group and therefore the recommended dose, can change within a few days. The magnitude and prevalence of the fluctuation of renal function in daily clinical practice and its potential effects on appropriateness of drug prescriptions after discharge from the hospital is unknown.

Methods and design

This is a prospective observational study. Patients ≥ 70 years with renal impairment (eGFR < 60 ml/min/1.73m^2) admitted to a geriatric ward are eligible to participate. Participants undergo blood sample collection to measure serum creatinine level at three time points: at discharge from hospital, 14 days, and 2 months after discharge. At these time points the actual medication of the participants is assessed and the number of incorrect prescriptions according to the Dutch guidelines in relation to their estimated renal function is measured. In addition, for a hypothetical selection of drugs, the need for drug dose adaptation in relation to renal function is measured. The outcome of interest is the percentage of patients that changes from renal function group after discharge from hospital compared to the renal function at discharge. In addition, the percentages of patients whose actual medications are incorrectly prescribed and for the hypothetical selection of drugs that would have required dose adaptation will be determined at discharge, 14 days, and 2 months after discharge. For each outcome, risk factors which may lead to increased risk for fluctuation of renal function and/or incorrect drug prescribing will also be identified and analysed.

Discussion

This study will provide data on changes in renal function in elderly patients after discharge from the hospital with a focus on the medications used. The benefits for healthcare professionals comprise of the creation, adjustment or confirmation of recommendations for the monitoring of the renal function after discharge from hospital of elderly patients.

Background

Chronic kidney disease (CKD) is associated with an increased mortality rate, as well as with an increased risk of cardiovascular events and morbidity.[1-3] Because of the longer life expectancy, due to improved treatment of chronic diseases, the prevalence of impaired renal function increases.[2-4] In addition, there is a concern about prescribing drugs, which need dose adjustment in impaired renal function, especially in the elderly who are at risk for impaired renal function.[4]

Up to one-third of the adverse drug reactions (ADRs) leading to hospital admission of elderly patients receiving outpatient care, may be related to impaired renal function.[5,6] The ADRs were serious, because they resulted in or contributed to hospital admission. The problems with ADRs, including ADRs not leading to hospital admission, due to impaired renal function might be even greater in ambulatory care. Therefore, the consideration of renal function in ambulatory care drug therapy management (DTM) should be improved.[5-7]

The estimated glomerular filtration rate (eGFR) is important in the clinical management of patients.[8] It is used for timely detection and management of declining renal function, to adjust the dosage of renally excreted drugs appropriately, and to avoid nephrotoxic drugs.[1,8,9] In The Netherlands, the eGFR is usually estimated in daily clinical practice with the Modification of Diet in Renal Disease (MDRD) formula. Dose adjustment of or refraining from renally excreted drugs commonly takes place categorically (see Table 6.1).[10]

Table 6.1 Renal function groups for drug dosing[10]

Group	Description	
1	Normal renal function	> 80
2	Mild renal impairment	50-80
3	Moderate renal impairment	30-49
4	Severe renal impairment	< 30
5	End stage renal disease (ESRD)	Requiring dialysis

In a hospital care setting a patient is closely observed and (repeated) creatinine measurements are easy to perform. Informal clinical observations suggest that the renal function may fluctuate so much that the renal function group and therefore the recommended dose, can change within a few days. A frequent scenario is that the patient is dehydrated at hospital admission with impaired renal function and during hospital admission the fluid balance is optimized and the eGFR increases.

The prevalence and the magnitude of fluctuations of the renal function after discharge from the hospital are still unknown. Since measurement of renal function is not routinely performed in the ambulatory care setting changes in renal function may remain unnoticed. It is possible that the eGFR may decrease, because of comprised fluid intake, or may increase because of the patient's further recovery. Changes of renal function may lead to a shift to another renal function group for drug dosing and thereby put patients at risk for not having optimal DTM. This may have unwanted clinical consequences, such as ADRs or insufficient effect. However, little is known about the actual prevalence of such scenarios in daily practice.

The aim of this study is to describe the changes in estimated renal function in elderly patients 14 days and 2 months after discharge from hospital compared to the value at discharge. Renal function will be classified according to the categories, which are defined in relation to DTM (see Table 6.1). In addition, incorrectly prescribed drugs in the actual medications of the patient according to the Dutch guidelines in relation to their renal function will be determined at discharge, 14 days, and 2 months after discharge from hospital. Finally, the percentage of patients in whom the fluctuation would have required another dosage regimen, if they had been taking a hypothetical selection of drugs that require dose adaptation, will be determined. For each outcome, risk factors for the fluctuation of renal function and for incorrect prescribing will be examined.

Methods and design

This study is conducted according to the Declaration of Helsinki. The study has been approved by the accredited Medical Ethical Committee of Brabant (formerly: METOPP). The Jeroen Bosch Hospital (JBZ) in 's-Hertogenbosch has provided local feasibility approval.

Study design and setting

This study is a prospective observational study and will be performed at the geriatric ward of the JBZ, which is a teaching top-clinical hospital in The Netherlands serving 800 beds.

Study population

All consecutive patients ≥ 70 years with renal impairment (eGFR < 60 ml/min/1.73m^2) calculated with the MDRD formula at admission to the geriatric ward will be asked to participate in the study. Furthermore, patients must remain community dwelling after discharge from hospital for at least 2 months. Exclusion criteria are patients with an eGFR < 10 ml/min/1.73m^2 and patients discharged for

end-of-life care.

Patients eligible for the study will be invited and informed by their geriatrician. Informed consent is obtained by the researcher. In case the patient is incapacitated the patients' legal guardian will be informed through written information and in case of participation the legal guardian will sign the informed consent. Permission to request the medication history at the community pharmacy will be asked at the same time. Patients can leave the study at any time for any reason without any consequences for their treatment.

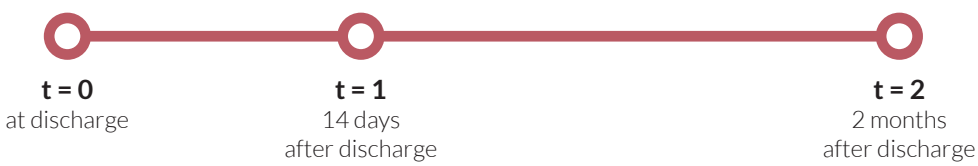
Study parameters

Primary study parameter

The main study parameter is the eGFR(MDRD). Serum creatinine level will be measured at 3 different time points (see Figure 6.1). The eGFR(MDRD) will automatically be calculated as follows:

$175 \times S_{cr}^{-1.154} \times age^{-0.203} \times 1.212$ (if black) $\times 0.742$ (if female).[11]

Figure 6.1 Several time-points during follow-up



The estimated renal function will be classified according to the categories, which are commonly applied in relation to DTM (see Table 6.1). The main endpoint is the percentages of patients in whom the eGFR improves, deteriorates and remains unchanged within 2 months after discharge compared to their eGFR at discharge.

Improvement is defined as a change to a better renal function group compared to the renal function group at discharge. Deterioration is defined as the change towards a worse renal function group compared to the renal function group at discharge. Unchanged is defined as no change in renal function group.

Secondary study parameters

At each time point the recommended dose or contraindication for each drug the patient uses will be determined in accordance with the eGFR of the patient and the Dutch guidelines for drug dose advices in renal impairment.[12] A secondary endpoint will be the percentage of patients in whom the prescribed drugs are not in accordance with the Dutch guidelines at discharge, 14 days, and 2 months after discharge from

hospital. Possible reasons for changes in the percentage of incorrect prescribed drugs at the different time points will be identified. Besides fluctuation of eGFR, other reasons could be starting a new drug not adjusted to renal function or discontinuation of a drug, which needed adjustment in renal impairment. The average number of incorrectly prescribed drugs per patient and the type of drugs most often incorrectly prescribed at the three different time points will be determined.

The top 10 most frequently prescribed drugs in the elderly outpatients (≥ 70 years) that require dose adaptation in patients with renal impairment are selected from the database of the Dutch foundation for pharmaceutical statistics (see Appendix 6.1). The recommended doses or contraindications of this hypothetical selection of drugs will be determined at each time point in relation to the renal function of the patient and subsequently compared with the recommended doses or contraindications at discharge. The endpoints will be the percentages of patients in whom a change in the medication would be needed at 14 days and at 2 months after discharge compared to changes needed in the medication at discharge.

Potential risk factors at admission and during admission which may predict fluctuation between renal function groups will be determined. These risk factors are presented in Table 6.2.

Data collection

Table 6.2 shows the detailed data collection at each time-point. When patients are admitted to the geriatric ward a blood sample is almost always routinely taken for a range of tests including serum creatinine value and C-reactive protein (CRP). Prior to discharge (max. 2 days) a blood sample will be taken to measure serum creatinine. At discharge the patients will be given two laboratory forms to collect blood samples 14 days and 2 months after discharge to measure creatinine. The patient will be reminded to go to the nearest general practitioners laboratory for blood sample collection 14 days and 2 months after discharge. Initially the blood samples were taken at the patient's nearest general practitioners laboratory. This was changed to blood sample collection at home because patients often did not show up at the laboratory.

At admission the following variables will be collected as part of usual care: age, gender, weight, length, use of non-steroidal anti-inflammatory drugs (NSAIDs) in the two weeks prior to admission, nutritional status and hydration status. The nutritional status will be defined with the Simplified Nutritional Appetite Questionnaire (SNAQ)[13] and the hydration status will be observed and judged by the physician.

Table 6.2 Data collection overview

Parameter	Time-points			
	at admission	**at discharge**	**14 days after discharge**	**2 months after discharge**
Serum creatinine level	✓	✓	✓	✓
Medication history		✓	✓	✓
Potential risk factors				
Age	✓			
Gender	✓			
Weight	✓			
Length	✓			
Incapacitated patient	✓			
Admission via emergency department or planned admission		✓		
Reason for admission (diagnosis)		✓		
C-reactive protein (CRP)	✓			
Duration of admission		✓		
Co-morbidities		✓		
Nutritional status (SNAQ-score)	✓			
Hydration status	✓			
All serum creatinine values measured during admission		✓		
Specific items in medication history:				
- NSAID use 2 weeks prior to admission	✓			
- Polypharmacy		✓		
- Use and dose of diuretics		✓		
- Use of NSAIDs		✓		
- Use of RAS-inhibitors		✓		
- Medications which influences creatinine production*		✓		

* These medications are: glucocorticosteroids, cimetidine, trimethoprim, fenofibrate (except gemfibrozil), calcitriol and alfacalcidol.[22-24]

NSAID, non-steroidal anti-inflammatory drug; RAS-inhibitor, renin-angiotensin-system-inhibitor; SNAQ, simplified nutritional appetite questionnaire.

The following parameters will be collected retrospectively per patient: all creatinine values measured during admission, admission via emergency department or a planned admission, reason for admission (diagnosis), duration of admission, co-morbidities, and medication orders during admission.

After two months the researcher will obtain the medication history (from at least 6 months prior to discharge to 2 months after discharge) of the patient from the community pharmacy.

Measurement of serum creatinine

All blood samples (heparinized plasma) will be analyzed at the Clinical Chemistry and Hematology department of JBZ. Serum creatinine levels will be measured in blood samples with the isotope dilution mass spectrometry (IDMS)-traceable Jaffe method on a Dimension Vista 1500 system (Siemens Healthcare Diagnostics).[14]

The results of the creatinine measurements will be reported to the general practitioner and/or the geriatrician as soon as the creatinine value is available. If necessary, adjustment of the medication can be made according to the Dutch guidelines by the general practitioner and/or the geriatrician. Reporting the creatinine value will not have an influence on the results. We will carefully examine the medication histories and identify changes made after reporting the creatinine value.

Statistical power estimation

This study focuses on the fluctuation of renal function in elderly patients within two months after discharge from hospital. We are both interested in the percentage patients that change from one to another renal function group, but also in the direction of these changes (improvement or deterioration).

Raosoft sample size calculator (http://www.raosoft.com/samplesize.html) was used to estimate the number of subjects required to detect a change in renal function group in 15% of the population with a 95% confidence level and a 5% margin of error. The recommended sample size is 195 subjects.

In order to detect a difference in percentage of patients in whom the change in renal function group improved or deteriorated the sample size is calculated based on the McNemar test (https://www.statstodo.com/SSizMcNemar_Pgm.php). Assuming that 5% of the patients improve and 15% of the patients deteriorate after discharge from hospital, power (1-beta) is 0.8 and probability of type I error (alpha) is 0.05, the sample size calculated is 155.

A sample size of 195 subjects should be sufficient for answering both questions in this study. Assuming that 20% of the included patients are lost to follow-up, the number of patients needed to include is 195/0.8 = 244.

Statistical analysis

For each patient data will be collected and archived in a validated data file. Errors and missing data will be monitored during data-collection, and complemented or corrected whenever possible. After completion of data-sampling, data will be checked for logical consistency (e.g. out of reach scores) and then finalized and locked. This file will be the basis for all further data analyses.

To analyse if the percentages of patients in which the renal function group improves, deteriorates and remains unchanged 14 days and 2 months after discharge from hospital compared to the renal function group at discharge are statistically significant, the McNemar-Bowker test will be used (categorical data with repeated measurements within one patient). The secondary outcome is the percentage of patients in whom the prescribed drugs are not in accordance with the Dutch guidelines. To test the differences of the concordance of the medication to Dutch guidelines at the different time points, the McNemar test will be used (binary data with repeated measurements within one patient). The same test will be used to analyse the percentage of patients in whom a change in the medication would be needed if they had been using the top 10 most frequently prescribed drugs in elderly outpatients (≥ 70 years) that require dose adaptation in patients with renal impairment. In further explorative analyses, we use various analytical methods (e.g. logistic regression analysis and nominal logistic regression analysis) to identify potential determinants of outcomes.

Discussion

DTM in patients with renal impairment is an important issue. Efforts are being taken to reduce drug therapy errors in these patients, for example by introducing clinical decision support systems.[15,16] An educational intervention providing a list of frequently used drugs and their dosing schedule already reduced the number of drug dosing errors.[17] Special attention should be paid to older patients with renal insufficiency and polypharmacy who are using high risk medications such as anticoagulants (e.g. vitamin K antagonists, direct oral anticoagulants [DOAC]), diuretics, cardiovascular agents, analgesics, and anti-diabetic agents.[18,19] All these studies and recently published guidelines for drug dose advices in renal impairment reflect on our daily clinical practice in a hospital care setting. Every time when a new eGFR is reported the correct drug or drug dose is reviewed by the hospital pharmacist. Advices may change from one day to another.

Guidelines, such as Kidney Disease: Improving Global Outcomes (KDIGO), do not offer advice about monitoring renal function after hospital discharge.[20,21] In addition, it is tempting for community pharmacists and general practitioners to rely on the latest eGFR measured in the hospital for DTM after discharge. It is uncertain how stable the eGFR is in elderly patients who have recently been admitted to the hospital. This might be especially the case when eGFR changes were frequent during hospital admission. This study is designed to address the gap in monitoring the natural course of the renal function after discharge from the hospital with attention to the medications used in the elderly. If fluctuation of the eGFR is

present at great extent this study will address whether closer monitoring of renal function and adaptation of renally excreted drugs after discharge will be needed. In addition, the benefits for healthcare professionals comprise of creation, adjustment or confirmation of recommendations for monitoring renal function after discharge from hospital of elderly patients.

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Appendix 6.1 Top 10 most frequently prescribed drugs in elderly patients

	Drug	Dose advice in renal impairment
1	furosemide	*10-30 ml/min* Starting dose as in normal renal function. If necessary, increase the dose guided by effect and indication. In case the effect is inadequate, replace furosemide by bumetanide.
2	metformin	*30-50 ml/min* Starting dose 2 x 500 mg metformin Then, increase the dose gradually to a standard maintenance dose. *10-30 ml/min* Contraindicated.
3	hydrochlorothiazide	*10-30 ml/min* Avoid hydrochlorothiazide
4	enalapril	*30-50 ml/min* Starting dose is 5 mg once daily. If necessary, increase the dose guided by clinical effect. If the prescriber is a general practitioner the maximum dose is 10 mg. If the prescriber is a specialized physician the dose may be higher. *10-30 ml/min* Starting dose is 2.5 mg once daily. If necessary, increase the dose guided by clinical effect. If the prescriber is a general practitioner the maximum dose is 5 mg. If the prescriber is a specialized physician the dose may be higher.
5	perindopril	*30-50 ml/min* If the prescriber is a general practitioner the maximum dose is 2 mg. If the prescriber is a specialized physician the dose may be higher. *10-30 ml/min* If the prescriber is a general practitioner the maximum dose is 2 mg every 48 hours. If the prescriber is a specialized physician the dose may be higher.
6	digoxin	*10-50 ml/min* After digitalization, the starting dose is 0.125 mg once daily. Then guide dose adjustment by clinical effect.
7	bumetanide	*10-30 ml/min* Starting dose as in normal renal function. If necessary, increase the dose to a maximum of 10 mg per day.
8	bisoprolol	*10-30 ml/min* Starting dose 50% of the dose as in normal renal function If necessary, increase the dose to a maximum of 10 mg per day.
9	alendronic acid	*10-30 ml/min* Use is not recommended.
10	spironolacton	*10-50 ml/min* Monitor serum potassium levels regularly.

These prescription data were obtained from the Dutch "Foundation for Pharmaceutical Statistics" (SFK) in 2012.

Addendum

First results of the study: Fluctuation of the renal function after discharge from hospital and its effects on drug dosing in elderly patients

A total of 48 patients were included. Six patients were lost to follow up; one patient went to another care setting after discharge, two patients decided to leave the study before discharge, for 1 patient we did not had a creatinine value at admission (inclusion was probably done with an older value), for 1 patient a creatinine value at discharge was missing and for 1 patient the reason was not recorded. For eleven patients we did not had a serum creatinine value 14 days and 2 months after discharge. There were several reasons: 2 patients were readmitted to the hospital, 6 patients did not go to a general practitioners laboratory for blood sample collection at both time points, 1 patient left the study, 1 patient died and 1 patient went too late for blood sample collection.

Therefore, 31 patients were eligible for analysis of which only 19 patients had both a serum creatinine value at 14 days and 2 months after discharge.

Patient characteristics are presented in Table 6.3. The mean age was 84 years and 45% was male. The mean eGFR(MDRD) at admission to the hospital was 36.7 ml/min/1.73m^2.

Table 6.3 Patient characteristics

Characteristic	Number of patients	Mean (range)/%
Age (years)	31	84 (74-98)
Sex		
Male	14	45%
Female	17	55%
eGFR at admission (ml/min/1.73m^2)		36.7 (13-59)
50-80	5	16%
30-49	17	55%
< 30	9	29%
SNAQ-score	28	1.1 (0-6)
Hydration status		
Hydrated	21	68%
Dehydrated	8	26%
Unknown	2	6%
Capacitated		
Yes	23	74%
No	7	23%
Unknown	1	3%

eGFR, estimated glomerular filtration rate; SNAQ, simplified nutritional appetite questionnaire.

Twelve out of 31 patients (39%) changed from renal function group after discharge from hospital. Table 6.4 presents the twelve patients with a change in renal function group over the three time points, at discharge, 14 days, and 2 months after discharge. The direction of the change in renal function group was in both directions, namely improvement and deterioration. Three patients showed a variable change in renal function group.

Table 6.4 Change of renal function group over three time points in patients with a change in renal function group

Patient number	Renal function group at discharge	Renal function group 14 days after discharge	Renal function group 2 months after discharge	Deterioration or improvement of renal function group after discharge
1	30-49	<30	<30	Deterioration
2	30-49	50-80	50-80	Improvement
3	<30	<30*	30-49	Improvement
4	<30	<30	Dialysis	Deterioration
5	30-49	30-49	<30	Deterioration
6	30-49	30-49	<30	Deterioration
7	30-49	<30	<30	Deterioration
8	30-49	50-80	50-80	Improvement
9	50-80	30-49	50-80	Variable
10	30-49	30-49	<30	Deterioration
11	30-49	50-80	30-49	Variable
12	30-49	50-80	30-49	Variable

* missing value: last observation carried forward.

Discussion

The number of patients in which a change occurred in renal function group is noteworthy, namely 39%. In our sample size calculation we assumed that a change of renal function group in 15% of the population would be of clinical relevance. As the first results presented, showing even a higher number of patients changing from one to another renal function group within 2 months after discharge, continuation of the study is highly recommended.

Of interest, three out of 12 patients (25%) had variable changes in renal function group. This proportion is noteworthy and further research is necessary to identify risk factors and the consequences for drug therapy management.

Drug therapy management in patients with renal impairment: a practical approach

Section

III

Comparison of a basic and advanced pharmacotherapy-related clinical decision support system in a hospital care setting in The Netherlands

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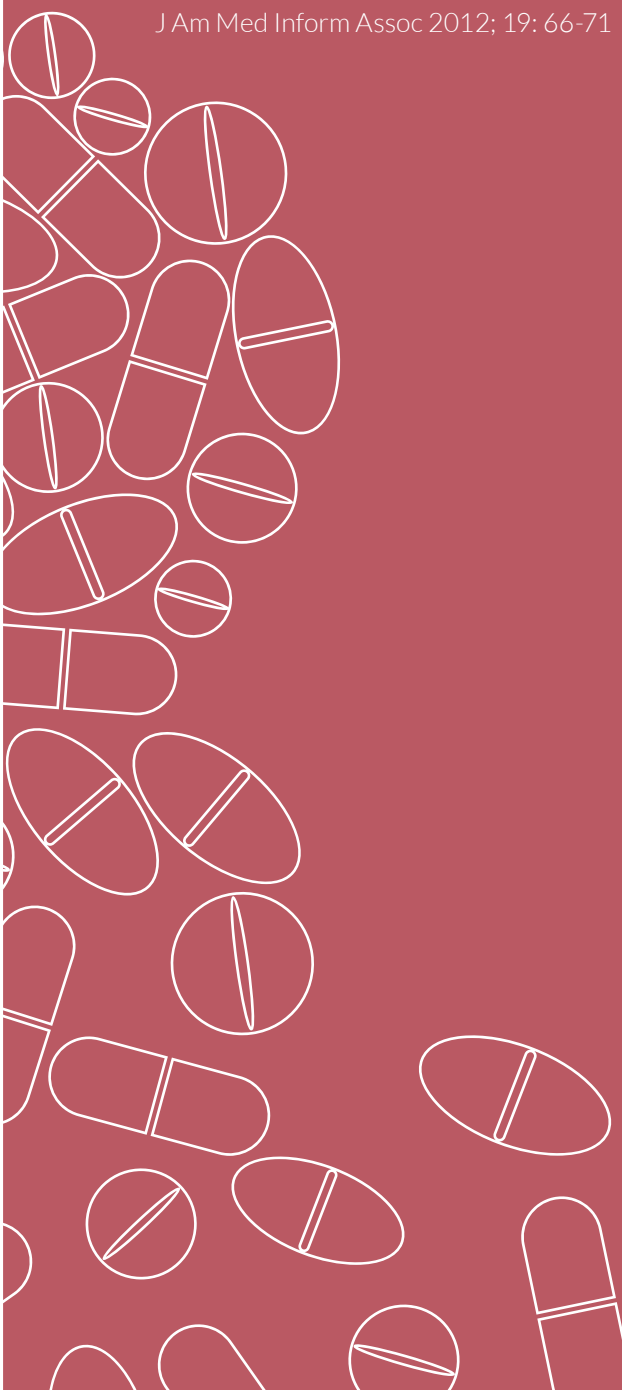

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Abstract

Objective

To compare the clinical relevance of medication alerts in a basic and in an advanced clinical decision support system (CDSS).

Design

A prospective observational study.

Materials and methods

We collected 4023 medication orders in a hospital for independent evaluation in two pharmacotherapy-related decision support systems. Only the more advanced system considered patient characteristics and laboratory test results in its algorithms. Two pharmacists assessed the clinical relevance of the medication alerts produced. The alert was considered relevant if the pharmacist would undertake action (e.g. contact the physician or the nurse). The primary analysis concerned the positive predictive value (PPV) for clinically relevant medication alerts in both systems.

Results

The PPV was significantly higher in the advanced system (5.8% versus 17.0%; $p < 0.05$). Significant differences were found in the alert categories: drug-(drug) interaction (9.9% versus 14.8%; $p < 0.05$), drug-age interaction (2.9% versus 73.3%; $p < 0.05$), and dosing guidance (5.6% versus 16.9%; $p < 0.05$). Including laboratory values and other patient characteristics resulted in a significantly higher PPV for the advanced CDSS compared to the basic medication alerts (12.2% versus 23.3%; $p < 0.05$).

Conclusion

The advanced CDSS produced a higher proportion of clinically relevant medication alerts, but the number of irrelevant alerts remained high. To improve the PPV of the advanced CDSS, the algorithms should be optimized by identifying additional risk modifiers and more data should be made electronically available to improve the performance of the algorithms. Our study illustrates and corroborates the need for cyclic testing of technical improvements in information technology in circumstances representative of daily clinical practice.

Introduction

The Hospital Admissions Related to Medication (HARM) study showed that 16,000 HARMs are potentially avoidable each year in The Netherlands.[1] This finding prompted the HARM-Wrestling report, which proposed about 40 practical recommendations to reduce the most frequently occurring and potentially avoidable HARMs.[2] About half of these recommendations concerned appropriate prescribing (e.g. adding a protective drug), a quarter concerned follow-up procedures (e.g. laboratory monitoring), and another quarter concerned communication (with the patient and other healthcare providers). Many of the recommended actions cannot be postponed until the next medication review but should be carried out as soon as a treatment is started or changed.[3] An important general recommendation was to improve, innovate, and implement information and communication technology in the pharmacotherapy process.

The currently used clinical decision support system (CDSS) in our daily hospital practice (CDSS 1, a so-called basic CDSS) has several limitations. First, it does not include specific individual patient data, such as laboratory test results, in its algorithms. Second, it cannot deal with different problems simultaneously: it assesses the clinical risk of a drug-drug interaction and that of renal insufficiency separately from each other. Another limitation concerns the complexity of clinical rules. CDSS 1 only screens drug therapies when a medication order (start, repeat, change, or stop) is entered into the system and not when other individual patient data (such as a new laboratory test result) become available. CDSS 1 generates many medication alerts which are clinically irrelevant, thereby reducing actual benefit in daily practice through alert fatigue.[4-6] All in all there is an urgent need for a more advanced pharmacotherapy-related CDSS (CDSS 2) which combines medication orders with laboratory test results and other patient characteristics and which also responds as soon as these types of data become available. Such a system should be more effective (generate more relevant alerts) and more efficient (generate fewer irrelevant alerts) compared to the current CDSS 1.

Geerts et al. have shown that in 36.7% of patients with a potential drug-drug interaction in the community pharmacy, a laboratory test is required for the assessment of the clinical relevance of the potential drug-drug interaction.[7] Other studies have shown that combining medication information with laboratory values in a CDSS results in better monitoring of adverse drug events (ADEs) in patients.[8-12]

We developed a CDSS 2 based on data from different clinical information systems. In this study we had access to inpatient medication and laboratory data. As in

other CDSS, our system generates medication alerts invoked by events ('triggers'), based on available data ('input data'), leading to a possible action ('intervention'). This application of simple or complex 'if-then' rules is comparable to the mode of operation of systems used in United States (US) hospitals.[13]

We considered it important to test CDSS 2 in direct comparison with CDSS 1 before it would be implemented, since technological improvements do not necessarily translate into improvements in clinical practice. The aim of this study was to compare the positive predictive value (PPV) for clinically relevant medication alerts in CDSS 2 with that in CDSS 1. In addition, differences between specific categories of medication alerts were explored with respect to their clinical relevance.

Background

In The Netherlands, the Royal Dutch Association for the Advancement of Pharmacy publishes a national drug database, the so-called G-standard, which is used by general practitioners, community pharmacies, and hospitals and provides digitalized safety information on all drug products registered in The Netherlands (e.g. concerning dosing, drug-drug interactions, drug duplication, drug-disease interaction, and pharmacogenetic factors).[14,15] It also presents standardized alert texts which contain information about potential adverse drug reactions and recommendations on how to respond to the alert, as well as details about clinical consequences, the underlying mechanism, and consulted references.[16] Both the basic and advanced pharmacotherapy-related CDSS investigated in this study were based on the G-standard.

The generation of specific alerts varies in different hospitals. In the Jeroen Bosch Hospital (JBZ), where this study was conducted, the physician initiates medication orders by means of a computerized physician order entry system (CPOE). If necessary, the CPOE will generate an alert for the physician, who can either take action or not. Several times each day, a pharmacist evaluates all generated medication alerts even though the physician may have already seen the alert. The pharmacist decides if further action is needed. In JBZ, the pharmacists are not allowed to cancel or change a medication order or to request for a laboratory value, but they contact the physician and advise an appropriate action.

Method

Setting

A prospective observational study was performed in the hospital pharmacy (ZANOB) of JBZ, which is a teaching top clinical hospital in The Netherlands with 800 beds.

Basic pharmacotherapy-related clinical decision support system (CDSS 1)

In 1981, Centrasys (iSOFT) was implemented in the hospital pharmacy (hereafter called system 1). The CPOE part of this system was introduced in the hospital in 2007. Up to 2011 the hospital pharmacy has used system 1 in daily practice.

System 1 is based on the G-standard and cannot cope with data from other databases, such as laboratory values. To account for the risk that reduced renal function in elderly patients may remain unnoticed, system 1 assigns the attribute 'renal impairment' to every patient above 70 years of age, regardless of their actual renal function. It is also possible to provide individual drugs in system 1 with a maximum dose of 0 mg per day. This guarantees that these drugs always generate a dose alert when prescribed, and allows the pharmacist to manually check the dose. An example is the drug methotrexate because medication errors leading to overdosing can easily occur (e.g. a high oncolytic dose given instead of a low antirheumatic one).[17]

The following clinical decision support (CDS) categories, as stated by Kuperman et al.[18], were operational in system 1: drug-allergy checking, basic dosing guidance, duplicate therapy checking, drug-drug interaction checking, drug-disease interaction checking, and drug-pregnancy checking. It should be noted that the performance of these categories depends on the availability of the input data. Medication control takes place in real-time.

The version of Centrasys used in this study was 4.31, service pack 6 with the G-standard update of July 2010.

Advanced pharmacotherapy-related clinical decision support system (CDSS 2)

Since June 2008, the hospital pharmacy has been cooperating with the software company Pharmaps to develop an advanced CDSS, known as 'Pharmaps Medicatiebewaking PLUS' (hereafter called system 2).

System 2 can handle data from different databases. Data from the clinical chemistry department and the pharmacy were available during the study period. System 2 covers all the CDS categories in system 1 except for the basic dosing guidance. In addition, it also covers the categories advanced guidance on medication-associated laboratory testing and advanced dosing guidance in relation to renal function.[18] System 2 performs all the medication surveillance covered by the G-standard (with the exception of basic dosage control) similarly to system 1, as well as additional medication surveillance (degree of renal impairment, hyperkalemia, lack of potassium, and creatinine levels and other specific recommendations of the HARM-Wrestling

report[2]). In addition, the system generates medication alerts concerning thyroid dysfunction for two drugs (amiodarone and lithium).[19] Generation of the medication alerts took place once a day (at 03:00 h). System 2 can generate medication alerts in real-time, but for practical reasons we chose to generate medication alerts once a day during this test phase.

Some aspects of medication surveillance could only be partially realized because: (1) not all patient characteristics (such as diagnosis) were electronically available and (2) the functionality of reasoning with time-frames was not yet available. For example, when a patient above 80 years of age uses a renin-angiotensin-aldosterone-system (RAAS)-inhibitor, renal function should be checked every 6 months.[2] Consequently, the CDSS should check whether renal function has been determined in the preceding 6 months and should generate an alert if this is not the case.

Pharmaps Medicatiebewaking PLUS version 3.1.2.8 was used in this study with the G-standard update of July 2010.

Data collection

During 5 randomly chosen consecutive days in July 2010, all prescribed drugs were evaluated in systems 1 and 2 on the basis of the same medication orders for all patients hospitalized in the JBZ. All medication alerts were assessed independently by two pharmacists. It was not possible to blind the pharmacists regarding the systems for practical reasons. A medication alert was considered 'relevant' when the evaluating pharmacist concluded that the physician or nurse should be contacted. An alert was considered 'irrelevant' when the evaluating pharmacist concluded that no specific action was necessary. If the two pharmacists did not agree on the same alert, a third pharmacist evaluated the medication alert for the final judgment. Our method of determining the relevance of medication alerts was similar to that of Van Doormaal et al.[20]

The 10 pharmacists involved in the study were well trained to handle basic and advanced medication alerts and consisted of one hospital pharmacist-toxicologist, two hospital pharmacists, two hospital pharmacists-clinical pharmacologists, two hospital pharmacist trainees, two pharmacists working in the hospital on a project basis and one community pharmacist. The third appraiser was a hospital pharmacist-toxicologist or hospital pharmacist trainee.

Medication alert categories

We defined categories of medication alerts in order to explore differences between systems 1 and 2 regarding the clinical relevance of the medication alerts. Classification

of the alert categories was based on the content of the signals: drug-(drug) interaction, drug-age interaction, drug duplication, drug-disease interaction, dosing guidance, and missing laboratory value. We will give an example for each category. The category drug-(drug) interaction includes medication alerts caused by the combination of two different drugs or the presence of one drug without another, for example, the absence of a laxative in opioid therapy. The category drug-age interaction includes medication alerts caused by drugs in combination with age. For example, when a non-steroidal anti-inflammatory drug (NSAID) is started and the patient is over 70 years of age a proton pump inhibitor (PPI) is recommended.[21] In system 1, age > 70 years is a proxy for the contraindication renal impairment. Medication alerts in the category drug duplication are generated by the combination of two similar drugs. The category drug-disease interaction covers medication alerts advising against particular drugs in certain conditions. For example, thiazide diuretics are contraindicated in patients with a renal function < 30 ml/min. The category dosing guidance includes all types of medication alerts with dosage advice. Medication alerts caused by a missing laboratory value belong to the category missing laboratory value.

The triggers which caused a medication alert in systems 1 and 2 were different. System 2 is capable of applying laboratory values, other patient characteristics, a combination of three or more drugs, and the absence of a drug or laboratory value in its algorithms. We checked whether each medication alert in system 2 was generated by one of the advanced properties. We defined such medication alerts as 'advanced'. The other system 2 medication alerts we defined as 'basic medication alerts'. These medication alerts were based only on medication data and the basic properties of system 2, using G-standard data.

Analysis

The proportion of all medication alerts produced which were considered clinically relevant was expressed as the PPV and was calculated separately for each system as follows:

$$\text{Positive predictive value} = \frac{\text{number of relevant medication alerts}}{(\text{number of relevant medication alerts} + \text{number of irrelevant medication alerts})}$$

Total positive predictive values (PPVs) were stratified for the different alert categories in both systems. PPVs were also calculated for each individual medication alert. Statistical tests were performed using SPSS version 16.0. The χ^2-test was used to

calculate if the difference in PPV between both systems was statistically significant. A p-value ≤ 0.05 was considered to be statistically significant.

Results

A total of 619 inpatients were included in the sample. Their mean age was 53.1 years and 45.7% were male. The total number of medication orders was 4023. The number of patients with medication orders which generated a medication alert was 438 for system 1 and 454 for system 2. The mean age of these patients was 67.2 and 67.0 years in systems 1 and 2, respectively (p = 0.60), and 51.8% and 53.5% of these patients, respectively, were male (p = 0.57).

The 4023 medication orders generated 2607 medication alerts in system 1 and 2256 in system 2. Table 7.1 shows the PPVs for all the medication alerts in both systems and for each category of medication alert.

Table 7.1 Positive predictive values for the clinical relevance of medication alerts

	System 1			System 2			
	$n_{relevant}$ *	n_{total} ‡	PPV§ (%)	$n_{relevant}$ *	n_{total} ‡	PPV§ (%)	p-value
Total of medication alerts	150	2607	5.8	384	2256	17.0	< 0.05
Alert category							
Drug-(drug) interaction[1]	82	828	9.9	172	1163	14.8	< 0.05
Drug-age interaction[2]	23	784	2.9	44	60	73.3	< 0.05
Drug duplication[3]	30	724	4.1	19	344	5.5	0.31
Drug-disease interaction[4]	0	2	0	34	139	24.5	0.42
Dosing guidance[5]	15	269	5.6	73	432	16.9	< 0.05
Missing laboratory value[6]	-	-		42	118	35.6	-◊

§ positive predictive value = $\frac{\text{number of relevant medication alerts}}{(\text{number of relevant medication alerts} + \text{number of irrelevant medication alerts})}$

* the number of clinically relevant medication alerts
‡ the total number of medication alerts
◊ the PPV could not be calculated because this category was not operational in system 1
[1] medication alerts caused by the combination of two different drugs or the combination of a drug with the absence of another drug.
[2] medication alerts caused by drugs in combination with age (in system 1, age was a proxy for the contraindication renal impairment).
[3] medication alerts caused by the combination of two similar drugs.
[4] medication alerts with the advice not to give a certain drug in certain conditions.
[5] medication alerts with a dosage advice.
[6] medication alerts caused by a missing laboratory value.

The number of relevant medication alerts increased from 150 in system 1 to 384 in system 2 for the same sample of medication orders. The difference between the PPVs of the medication alerts in system 1 and system 2 was statistically significant (5.8% versus 17.0%; $p < 0.05$). Stratification into the medication alerts categories showed statistically significant differences for the following categories: drug-(drug) interaction (9.9% versus 14.8%; $p < 0.05$), drug-age interaction (2.9% versus 73.3%; $p < 0.05$), and dosing guidance (5.6% versus 16.9%; $p < 0.05$). Remarkably, the two appraising pharmacists disagreed more often regarding the clinical relevance of medication alerts in system 2 than in system 1. The third pharmacist had to review 8.6% of the medication alerts in system 1 versus 32.9% in system 2. This difference was also statistically significant ($p < 0.05$).

PPVs were also calculated for each type of medication alert. Table 7.2 shows the top five medication alerts (occurring at least 20 times) with the highest PPVs in system 2. The highest PPV of 30.8% in system 1 was found for the medication alert 'clopidogrel + omeprazole/esomeprazole'. To improve system 2 further, it would be helpful to investigate and then adapt or eliminate frequently occurring medication alerts with the lowest PPV. Table 7.3 shows the top 10 medication alerts (occurring at least 20 times) with the lowest PPVs in system 2.

Table 7.2. The top five of medication alerts occurring at least 20 times that were generated by system 2 and had the highest positive predictive values

Alert text	$n_{relevant}$ *	n_{total} ‡	PPV§ (%)
Advice: give a proton pump inhibitor	44	60	73.3
Beware of induction or exacerbation of hyperkalemia	15	21	71.4
Clopidogrel + omeprazole/esomeprazole$^{\Delta}$	13	20	65.0
This drug requires dosage adjustment in renal impairment. Determine renal function, since the renal function is unknown in this patient.	19	55	34.5
This drug requires attention when the serum potassium level is high (> 5 mmol/l)	14	41	34.1

§ positive predictive value = $\frac{\text{number of relevant medication alerts}}{(\text{number of relevant medication alerts} + \text{number of irrelevant medication alerts})}$

* the number of clinically relevant medication alerts
‡ the total number of medication alerts
$^{\Delta}$ at the time this study was conducted, this interaction had just been noted as relevant by various (inter)national authorities. However, the effect of the combination of clopidogrel with omeprazole on cardiovascular events remains controversial.[22,23]

The impact of including laboratory values and other patient characteristics in the medication surveillance by system 2 is shown in Table 7.4. The PPV was calculated for both the basic medication alerts and the advanced medication alerts in each medication alert category. The advanced medication alerts show a significantly higher PPV than the basic medication alerts (12.2% versus 23.3%; $p < 0.05$). The

highest PPV (73.3%) was seen in the category drug-age interaction (advanced) and the lowest PPV (5.5%) in the category drug duplication (basic).

Table 7.3 The top ten of medication alerts occurring at least 20 times that were generated by system 2 and had the lowest positive predictive values

Alert text	$n_{relevant}$ *	n_{total} ‡	PPV§ (%)
Drug duplication: different strength, same mechanism of action	0	74	0.0
Selective beta-blockers + insulin	0	43	0.0
Beta-blockers + oral hypoglycemic drugs	0	25	0.0
Alpha-blocking drugs (for benign prostate hyperplasia) + beta-blockers/calcium channel blockers	0	23	0.0
Renal function: bumetanide	0	20	0.0
Renin-angiotensin-aldosterone-system (RAAS)-inhibitors + diuretics	2	120	1.7
Salicylates antithrombotic + non-steroidal anti-inflammatory drugs (NSAIDs) (other than Ibuprophen)	1	51	2.0
RAAS-inhibitors + potassium(-saving diuretics)	1	41	2.4
NSAIDs + corticosteroids	2	61	3.3
Bisphosphonates + antacids/iron/calcium	2	44	4.5

§ positive predictive value = $\frac{\text{number of relevant medication alerts}}{\text{(number of relevant medication alerts + number of irrelevant medication alerts)}}$

*the number of clinically relevant medication alerts

‡the total number of medication alerts

Table 7.4 Comparison of basic and advanced medication alerts in system 2

	Basic medication alerts			Advanced medication alerts			
	$n_{relevant}$ *	n_{total} ‡	PPV§ (%)	$n_{relevant}$ *	n_{total} ‡	PPV§ (%)	p-value
Total of medication alerts	155	1274	12.2	229	982	23.3	< 0.05
Alert category							
Drug-(drug) interaction[1]	136	930	14.6	36	233	15.5	0.75
Drug-age interaction[2]	-	-	-◊	44	60	73.3	-
Drug duplication[3]	19	344	5.5	-	-	-◊	-
Drug-disease interaction[4]	-	-	-◊	34	139	24.5	-
Dosing guidance[5]	-	-	-◊	73	432	16.9	-
Missing laboratory value[6]	-	-	-◊	42	118	35.6	-

§ positive predictive value = $\frac{\text{number of relevant medication alerts}}{\text{(number of relevant medication alerts + number of irrelevant medication alerts)}}$

*the number of clinically relevant medication alerts

‡the total number of medication alerts

◊there were no medication alerts in this category

[1]medication alerts caused by the combination of two different drugs or the combination of a drug with the absence of another drug.

[2]medication alerts caused by drugs in combination with age (in system 1, age is a proxy for the contraindication renal impairment).

[3]medication alerts caused by the combination of two similar drugs.

[4]medication alerts with the advice not to give a certain drug in certain conditions.

[5]medication alerts with a dosage advice.

[6]medication alerts caused by a missing laboratory value.

Discussion

The difference between the PPVs of systems 1 and 2 was substantial (5.8% versus 17.0%; $p < 0.05$). This shows that the clinical relevance of medication alerts was improved by including more data on patient characteristics (especially individual laboratory values) in the medication surveillance. Differences between systems 1 and 2 were mainly found in the categories drug-(drug) interaction, drug-age interaction, and dosing guidance. Regarding system 2, the advanced medication alerts showed a significantly better PPV than the basic medication alerts (12.2% versus 23.3%; $p < 0.05$). Thus, this study confirms the added value of the advanced pharmacotherapy-related CDSS for medication surveillance in a realistic sample of hospitalized patients from one hospital.

The PPVs for drug-(drug) interaction and dosage guidance in system 1 (9.9% and 5.6%, respectively) corresponded well with the results of a previous Dutch study (12% and 6%, respectively) which evaluated a system based on the G-standard.[20] In a study by Murphy et al., conducted in the US with online prospective drug-use review systems, 73.8% of the drug-drug interactions were overridden by pharmacists in a community pharmacy, giving a PPV of 26.2%.[24]

The PPVs found for individual medication alerts in systems 1 and 2 varied from 0% to 73.3%. This wide variation has also been found in some previous studies which investigated one or more specific advanced medication alerts.[25-27] Handler et al. conducted a systematic review of medication alerts based on pharmacy and laboratory data to detect ADEs such as elevated serum creatinine levels and hyperkalemia. They found PPVs ranging from 3% for hypokalemia to 50% for supratherapeutic quinidine levels.[26] Raschke et al. also found a wide variation in the PPVs for detecting ADEs (24%-97%).[27] One explanation for the broad range of PPVs is that laboratory values are often abnormal because of the onset or worsening of clinical conditions unrelated to the use of medication.[26] Another explanation is that some algorithms detect rare but immediately life-threatening ADEs, while others detect common situations with a lower potential to result in injury.[27]

This study has several limitations. First, the local user settings in both systems were different. The G-standard in system 1 had already been modified following years of experience by the hospital pharmacists. This fine-tuning had not yet taken place in system 2. Adjustment of the G-standard generally leads to a higher PPV, which implies that the contrast in the PPV between systems 1 and 2 probably would have been greater if the G-standard in system 2 had been amended. In addition, not all features of the G-standard were fully used in both systems. Second, the PPV

was chosen as the primary outcome measure for comparing systems 1 and 2. The PPV is a useful measure for the correctness and clinical relevance of the generated medication alerts but does not indicate how often relevant alerts were missing, which requires assessment of the sensitivity of the CDSS. However, this parameter requires that all truly positive alerts are recognized as such (the so-called 'gold standard'), which was not a goal of our study. One way to establish the sensitivity of a system is through the use of a set of test patients. Van der Sijs et al. and Saverno et al. calculated the sensitivity and specificity for a variety of medication alerts, including drug-drug interactions in several different CPOE and CDSS. Both groups found a wide variation in sensitivity (38%-79% and 23%-100%, respectively) and specificity (11%-84% and 83%-100%, respectively).[28,29]

The capabilities of CDSS differ between providers,[13,30] which may have influenced the generalizability of our results. However, CDSS algorithms generally rely on literature-based evidence and practice-based experience, which is accepted worldwide as the best foundation for improving clinical outcomes.[31] Therefore, the algorithms leading to medication alerts are likely very similar across countries. Consequently, we believe that the results of our study are also applicable to other CDSS.

We have identified several reasons why the PPV of system 2 may have been relatively low. First, not all information needed, such as the patient problem list (diagnosis), was electronically available. For example, the severity of the drug-drug interaction NSAIDs and RAAS-inhibitors is more important in patients with heart failure than in those with uncomplicated hypertension. A second limitation of system 2 was its inability to combine different algorithms. For example, system 2 recognized the combination of a RAAS-inhibitor and potassium(-saving diuretics) and generated a medication alert with the advice to monitor the serum potassium level. Another algorithm checked if the serum potassium level was available and within the range of 3.5-5.0 mmol/l. The first algorithm should be suppressed if the second algorithm does not generate a medication alert, because the potassium level is already monitored. Third, some of the algorithms in both systems had been incorporated to exclude any risk. For example, the alert 'drug duplication' is generated when the physician prescribes two medication orders for the same drug. Such a combination may have been ordered by accident, but may also have been intentional (e.g. two drug products to provide an unavailable dose strength). As the pharmacists in our study only contacted the physician in one out of 20 medication alerts, intentional combination appears to have occurred more often than accidental duplication.

Agreement between the two appraising pharmacists occurred less often for system 2.

The third pharmacist, who passed the final judgment, was involved significantly more often in system 2 (8.6% versus 32.9%; $p < 0.05$), probably because of the complexity of the advanced medication alerts. Laboratory values were manually searched with system 1 and so the pharmacists were familiar with advanced medication alerts, but in system 2 more and other triggers were involved in generating a medication alert. Judging a medication alert based on two drugs is easier to interpret than medication alerts based on a drug and a variable laboratory value or the addition of another drug, for example, the medication alert that a laxative should be added to an opiate. In case of piritramide 15 mg subcutaneous 4 times a day after surgery, some pharmacists will advise a laxative from day 1, whereas other pharmacists will advise a laxative only after 3 days. Therefore, interpretation of a medication alert requires particular attention when a new type of medication alert is implemented in clinical practice.

The more information is incorporated into algorithms, the more precise the generated medication alerts should be. Therefore, to better develop and optimize the algorithms, risk modifiers should be identified from evidence-based and clinical practice-based medicine. For instance, multivitamin supplements providing 25 μg of vitamin K1 have long been considered harmless for patients on warfarin. However, this view was seriously challenged by three cases of stabilized warfarin users in whom anticoagulant treatment was compromised by the initiation or cessation of a low-dosed multivitamin supplement.[32] Subsequent research showed that 25 μg of vitamin K1 daily produces subtherapeutic international normalized ratios (INRs) in users with a low vitamin K1 level.[33] In other words, vitamin K1 status is an important modifier of the risk that stabilized warfarin users are affected by dietary supplements providing a small dose of vitamin K1. Therefore, identified potentially interesting risk modifiers should be made electronically available in the database and also built into the algorithms.

The knowledge database of a CDSS should be continuously maintained by evaluating what effects medication alerts have in daily practice. The Plan-Do-Check-Act (PDCA) cycle, also known as the Deming cycle, might be helpful.[25,34] Wessels-Basten et al. improved the PPV of the lithium algorithm from 63% to 83% by using the PDCA cycle.[25] The next step to improve the PPV of system 2 is to determine why the pharmacists respond to some alerts and not to others. This could be followed by two strategies. First, if the pharmacists do not respond correctly to medication alerts, education is needed. Second, the algorithm should be fine-tuned until the PPV has improved. It is expected that the PPV of system 2 will increase when the PDCA cycle is completed.

Conclusion

The main conclusion of this study is that system 2 had a significantly higher PPV than system 1 (5.8% versus 17.0%; $p < 0.05$). The study shows that system 2 was more effective and more efficient than system 1 in carrying out medication surveillance. However, the number of irrelevant medication alerts remained relatively high.

To improve the PPV of system 2, the algorithms should be further optimized as follows: (1) by identifying risk modifiers from the existing scientific literature, (2) by making these additional risk modifiers electronically available, and (3) by cyclic testing of the effects of medication alerts in daily clinical practice (PDCA cycle).

Our study illustrates and corroborates the need to test technical improvements in information technology in circumstances representative of daily clinical practice. This type of research will contribute to further optimization of CDSS. It should also be kept in mind that maintenance of a knowledge database is a continuous process.

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Drug therapy management in patients with renal impairment:

How to use creatinine-based formulas in clinical practice

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8

Abstract

Estimated glomerular filtration rate (eGFR) is a key component in drug therapy management (DTM) in patients with renal impairment. eGFR is routinely reported by laboratories whenever a serum creatinine testing is ordered. In this paper we will discuss how to use eGFR knowing the limitations of serum creatinine-based formulas. Before starting a renally excreted drug an equally effective drug which can be used more safely in patients with renal impairment should be considered. If a renally excreted drug is needed the reliability of the eGFR should be assessed and when needed a 24-h urine creatinine clearance collection should be performed. After achieving the best approximation of the true GFR we suggest a gradually drug dose adaptation according to the renal function. A different approach for drugs with a narrow therapeutic window (NTW) is recommended compared to drugs with a broad therapeutic window. For practical purposes a therapeutic window of 5 or less was defined as a NTW and a list of NTW-drugs is presented. Considerations about the drug dose may be different at the start of the therapy or during the therapy and depending on the indication. Monitoring effectiveness and adverse drug reactions are important, especially for NTW-drugs. Dose adjustment should be based on an ongoing assessment of clinical status and risk versus the benefit of the used regimen.

In conclusion, when determining the most appropriate dosing regimen serum creatinine-based formulas should never be used naively but always in combination with clinical and pharmacological assessment of the individual patient.

Introduction

The importance of the recognition of the renal function in drug therapy management (DTM) has been well documented. Ten to thirty-two percent (in elderly patients) of adverse drug reactions (ADRs) that necessitated hospital admission were related to impaired renal function.[1,2] In the hospital care setting, patients with chronic kidney disease (CKD) are at increased risk of drug dosing errors and acute kidney injury (AKI).[3,4] Therefore, drug therapy adjustment according to renal function is of major importance to improve DTM.

The glomerular filtration rate (GFR) is widely accepted as the preferred index of kidney function and recognized as defining CKD.[5] Drug dosing recommendations traditionally have used the Cockcroft and Gault (CG) formula to estimate creatinine clearance and therefore the ability of the kidney to excrete drugs.[6] Approximately 15 years ago a new formula was developed that provided estimation of GFR (eGFR), the Modification of Diet in Renal Disease (MDRD) formula.[7] More recently the Chronic Kidney Disease EPIdemiology Collaboration (CKD-EPI) formulas for eGFR were developed.[8] Since laboratories routinely report the eGFR if serum creatinine testing is ordered, the awareness of impaired renal function and the use of eGFR in DTM among clinicians has increased in recent years.[9-11]

All the formulas have in common that they are based on serum creatinine levels. There is a clear inverse correlation between serum creatinine levels and GFR. However there are several factors which may influence serum creatinine levels and therefore eGFR without affecting true GFR itself, which potentially distorts the interpretation of these estimates for clinical use (see Figure 8.1).[12-14] Although the serum creatinine-based formulas provide a better estimation of the true GFR than serum creatinine concentrations in the general population, none have been validated in diverse patient populations.[15] Inaccuracy in eGFRs might lead either to overestimation of kidney function, leading to administration of inappropriately large doses and therefore possible toxicity, or, conversely, underestimation of kidney function, leading to subtherapeutic dosing and therefore treatment failure, and prolonged illness.[16] The effect of the possible overestimation and underestimation of true GFR is illustrated in Table 8.1 and 8.2. Table 8.1 illustrates that the inaccuracy of the eGFR may lead to a different renal function group than the renal function group to which the patient actually belongs according to the mGFR. The relative steady state drug levels that have been theoretically calculated in Table 8.2 can exceed the target level by more than 200% when relying naively on eGFR. Despite such limitations, serum creatinine-based formulas are routinely used in daily clinical

practice.[17-20] In this paper we will discuss approaches on how to use serum creatinine-based formulas in daily clinical practice in a well-informed way.

Figure 8.1. Determinants of serum creatinine level

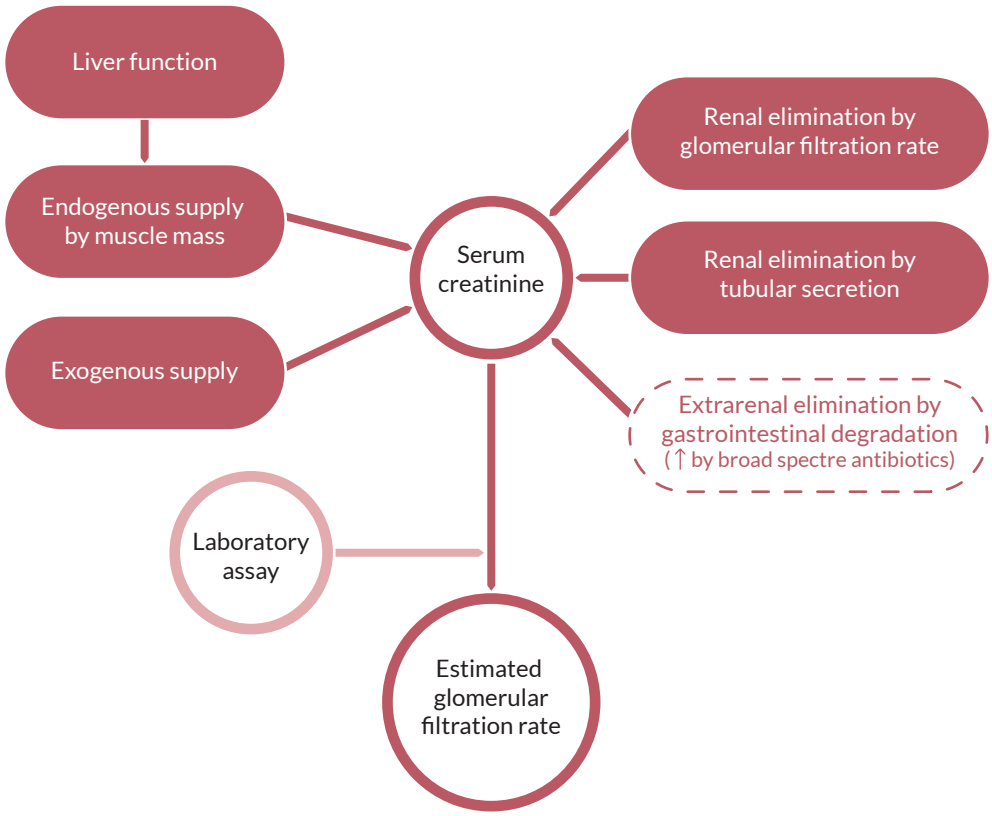

Table 8.1. The effects of the inaccuracy of the eGFR in drug dosing

mGFR (ml/min/1.73m²)	eGFR (mGFR ± 30%)* (ml/min/1.73m²)	Renal function groups for drug dosing[47] < 10	10-29	30-49	50-80	> 80
100	70-130					
60	42-78					
40	28-52					
20	14-26					

* An accuracy expressed as $P_{30\%}$ (eGFR falls within ± 30% of the mGFR) of 80% or higher has been indicated as sufficient.[25,54,55] The coloured parts in the table illustrate the effects of the inaccuracy of the eGFR (mGFR ± 30%). The eGFR may lead to a different renal function group than the renal function group to which the patient actually belongs according to the mGFR.

eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate.

Risk benefit ratio

The first question after defining the patient's health problem is, what is the therapeutic objective?[21] In general, the goal of DTM is to optimize the risk-benefit ratio and to attain an optimal therapeutic outcome.[22] In the situation of patients with renal impairment the principals for considering the risk-benefit ratio is not different from any other treatment. In a lifesaving situation, for example a treatment with antibiotics in case of sepsis, a higher dosing regimen than generally recommended for patients with renal impairment may be chosen. The risk of developing ADRs is less important in this situation than the risk to give an insufficient drug dose which may lead to untimely death. In less urgent situations, such as treating hypertension, a more conservative drug dose can be given at the start of the therapy. This drug dose can be gradually increased with monitoring effect (blood pressure) and/or ADRs. In other words: 'start low, go slow'.

The severity of the illness being treated determines if a specific ADR is accepted or not. In addition, the severity of the ADR may vary between individual patients. For patients with renal impairment the risk-benefit ratio should be taken into account when answering the following questions:

1. Can I use the eGFR reported by laboratories in DTM?
2. Is there an equally effective drug which can be used more safely in patients with renal impairment?
3. What are the chances and risks of dosing outside the therapeutic window?
   a. Considerations at start of pharmacotherapy
   b. Considerations during pharmacotherapy
4. Is it possible to monitor effectiveness and/or ADRs in order to timely intervene and/or to prevent serious situations?

How to apply eGFR in daily clinical practice

In daily clinical practice one should be aware of the limitations of creatinine-based formulas. These limitations have been described elsewhere.[15] Reported eGFR values have a degree of inaccuracy. When there are no reasons to suspect that the true GFR is substantially different from the eGFR, the laboratory value eGFR can be used without reservations.

Serum creatinine levels and therefore creatinine based-formulas should only be used in patients with stable renal function.[22] In cases of rapidly changing GFR, the serum creatinine levels will not reflect the actual GFR, until steady-state has been

reached.[23] In such situations, assessment of impaired renal function must rely on multiple measures of serum creatinine levels.[24]

In specific patients and/or clinical situations (e.g. malnourishment, low or high muscle mass, acute critical illness) where estimating equations are known to be inaccurate or clinical decision-making requires a greater accuracy than expected from eGFR, GFR should be measured.[22,25] Measurement of GFR is ideally performed with gold standards such as ^{51}chromium ethylene-diamine-tetra-acetic acid (^{51}Cr-EDTA), technetium-labelled diethylene-triamine-pentacetate (^{99m}Tc-DTPA), inulin, iohexol and iothalamate.[13] However, these markers are impractical for routine clinical use due to limited access to necessary diagnostic facilities and high cost.[26] 24-h urine creatinine clearance collection is easier to perform and might be helpful, especially in the hospital care setting. In the ambulatory care setting this method might be more inconvenient for the patient and prone to failure of collection of the entire specimen.[26,27] In any case, the endogenous creatinine clearance measured overestimates true GFR because creatinine is excreted by glomerular filtration and tubular secretion.[9] In specific patients, for example in situations where the renal function is not stable, both eGFR and 24-h urine collection are not sufficiently informative. In those situations choosing another drug or monitoring effectiveness and/or ADRs, preferably with therapeutic drug monitoring, may be appropriate (this will be discussed in the next paragraphs).

The difference between normalized (ml/min/1.73m^2) and absolute (ml/min) eGFR values should also be taken into account when someone is substantially larger or smaller than an average person, but with a normal figure (with a body surface area (BSA) of 1.73m^2). The best descriptor of body size in obese patients is still unclear.[28] The GFR increases with body size but does not increase in proportion to the total body weight.[10] Therefore, adjustment of eGFR to absolute GFR using BSA calculated based on actual body weight causes errors in the obese patients.[10,29] A recent study suggests the use of ideal body weight as the body size descriptor for GFR indexation[30], although others suggest the lean body weight.[29,31]

In summary, the reported eGFR by laboratories may not reflect the true GFR of the individual patient properly. The introduction of a 'simple' correction factor seems not possible, because the direction and degree of the deviation is not predictable.[15,32] To make it even more complex, most drug dose recommendations in patients with renal impairment are based on the CG formula, representing renal clearance of creatinine instead of eGFR. This may lead to clinically relevant problems.[33] For example when using the new thrombin inhibitors, such as dabigatran and rivaroxaban. The use

of the MDRD-4 formula instead of the CG formula, which was used in clinical trials, would result in higher doses or incorrectly judgment if patients are eligible for treatment.[34,35] Dabigatran would be recommended in a full dose for 33% of all participants when using the CG formula compared to 67% when using the MDRD-4 formula.[34] Safety has not been established using the MDRD equation, a concern since the risk of major bleeding or the development of thrombosis would be increased in patients with renal impairment.[35]

All in all, there are many uncertainties when using eGFR in DTM. In the following paragraphs we will outline possible considerations when prescribing drugs in patients with renal impairment to cope with the knowledge and uncertainties we know today.

Choice of drug

Physicians should be aware of the fact that renally excreted drugs require dose adjustment in patients with renal impairment.[1,36-38] In addition, there may not only be pharmacokinetic changes, but also pharmacodynamic changes which may differ between drugs.[37] This latter and the lack of information of drug dosing in patients with renal impairment may lead to the advice to avoid the drug (contraindication).

There are often alternatives available for patients with renal impairment. For some drug classes there are several alternatives available, for example in the drug class of statins. Only rosuvastatin is contraindicated in severe renal impairment, whereas the other statins are not.[39] If a 65-year old woman is diagnosed with diabetes mellitus type 2 with an eGFR of 35 ml/min/1.73m^2 is metformin still the first choice drug? Metformin according to the guidelines may be started in a low dose of 500 mg two times daily. The risk of metformin associated lactic acidosis increases when renal function drops below 30 ml/min/1.73m^2.[40] This risk is probably already increased in the 65-year old women, because the eGFR is near the cut-off value of 30 ml/min/1.73m^2. Furthermore, the eGFR may overestimate true GFR and the renal function may decline in the near future. It might be that gliclazide is a better choice.

In patients with renal impairment alternatives for drugs that are not renally excreted are often available. But as in every step of prescribing drugs the benefits should outweigh the risk. In some clinical situations a renally excreted drug may be necessary. Then, the drug dose becomes important, which will be discussed in the next paragraph.

Therapeutic window

The therapeutic window (TW) reflects the concentration range that provides efficacy without unacceptable toxicity. In other words, the area between the minimum

efficacious dose and the maximum tolerable dose.[41-43] The TW may also be thought of as a range of acceptable plasma levels of the drug and its active metabolite(s) in which positive therapeutic results are seen.[42] In other words presented in a formula:

$$\text{Therapeutic window (TW)} = \frac{\text{Minimum toxic plasma concentration}}{\text{Minimum effective plasma concentration}}$$

In the sequel of the definition of the TW, the question arises when is a TW called a narrow therapeutic window (NTW). Recently, Schulz et al. reported for nearly 1,000 drugs and other xenobiotics, therapeutic ('normal') and, if data were available, toxic and comatose/fatal blood-plasma concentrations.[44] The ranges reported for therapeutic and toxic blood plasma concentrations could be transformed to the presented formula above.

In Table 8.2 we illustrate the effect of overestimation and underestimation of the true GFR on the relative steady-state drug level (rC_{ss}) assuming that a rC_{ss} of 100% is reached in patients with a normal renal function of 100 ml/min/1.73m^2 and a recommended drug dose of 100 mg per day. From our clinical experience, the overestimation of the eGFR, calculated with the MDRD formula, may become as high as 50-100% in patients who are completely bedridden for a prolonged period.

Theoretically, when the TW of a drug is 2, with a minimum relative effective plasma concentration of 70% and a minimum relative toxic plasma concentration of 140%, patients may suffer from a toxic rC_{ss} (see Table 8.2). For example, when the GFR is overestimated by 25%, patients suffering from impaired renal function (< 60 ml/min/1.73m^2) will reach a rC_{ss} that exceeds 140%. If the TW is assumed to be 3 corresponding to a relative therapeutic range of 70-210%, toxic levels could also emerge easily. However, if the TW rises to 10 (70-700%, respectively), it becomes much more difficult to reach toxic levels (unless the drug level is already near the minimum toxic level).

We recommend a different approach for drugs with a NTW than for drugs with a broad therapeutic window (BTW) for drug dosing in patients with renal impairment.[22] However, definitions for NTW-drugs are lacking in the literature. We suggest that a drug with a TW of 5 or lower can be arbitrarily defined as a drug with a NTW. Table 8.3 presents examples of renally excreted drugs (or their active metabolites) with a TW of 5 or less. We used the Dutch guidelines 'Drug dose advices in renal impairment' to select drugs which need dose adjustment, are contraindicated or need therapeutic drug monitoring in renal impairment.[39]

Table 8.2. Theoretical effects of substantial overestimation of eGFR values on relative steady-state drug levels of renally cleared drugs

eGFR	Corresponding drug dose recommendation based on eGFR[a]	Assumed degree of overestimation	eGFR corrected for overestimation	Relative steady-state drug level[b]
(ml/min/1.73m²)	(mg/day)		(ml/min/1.73m²)	(%)
100	100	0%	100	100
60	100		60	167
40	50		40	125
20	25		20	125
100	100	25%	80	125
60	100		48	208
40	50		32	156
20	25		16	156
100	100	50%	67	149
60	100		40	250
40	50		27	185
20	25		13	154
100	100	100%	50	200
60	100		30	333
40	50		20	250
20	25		10	250

eGFR = estimated glomerular filtration rate.

[a] Recommended dose regimen: 100 mg if eGFR ≥ 50 ml/min/1.73m²; 50 mg if eGFR 30-49 ml/min/1.73m²; 25 mg if eGFR 10-29 ml/min/1.73m².

[b] Relative steady-state drug level (rC_{ss}) has been calculated as follows:

$$\text{Relative steady state drug level} = \frac{\text{corresponding drug dose recommendation (mg/day)}}{\text{eGFR corrected for overestimation}}$$

This formula is a simplification of the formula[56]:

$$C_{ss} = \frac{\text{Bioavailability x drug dose}}{\text{Dosing interval x drug clearance}}$$

by making the following assumptions[56]:

- The patient has a normal body surface area of 1.73m²
- The drug has a bioavailability of 1 (i.e., 100%)
- The drug has a dosing interval of 1 (i.e., once daily)
- The drug is completely renally cleared

The TW was calculated with the information summarized by Schulz et al. and supplemented with recent literature which indicates that toxic levels may be reached easily in patients with renal impairment.[39,44] It appeared that for many drugs we could not retrieve concrete TW data. Therefore, this list should be considered as a starting point, which has to be updated when new information comes available.

In addition, clinicians should also be aware when a high dose (near the maximum recommended dose) is needed of a drug without a NTW, for example amoxicilline.

Table 8.3 Renally cleared drugs with a narrow therapeutic window

Drug	Type of advice in patients with renal impairment				
	Dose adaptation	Therapeutic drug monitoring	Monitoring therapeutic effect (TE) and/or adverse drug reactions (ADR)	Therapeutic window based on Schultz et al.[44]	Other references
Analgetic and antirheumatic drugs					
Hydroxychloroquine			✓ (ADR)	5	
Antibacterial drugs					
Amikacin	✓	✓		3	37,41
Ciprofloxacin	✓		✓ (ADR)	4.6	
Gentamicin		✓		3	37,41
Tobramicin		✓		3	41
Antiepileptic drugs					
Carbamazepine		✓	✓ (ADR)	5	41,57
Oxcarbazepine	✓		✓ (TE)	4.5	
Pregabaline	✓		✓ (ADR)	5	
Primidone			✓ (TE, ADR)	5	41
Zonisamide	✓		✓ (ADR)	4	
Antiglaucoma drugs					
Acetazolamide	✓		✓ (ADR)	2.5	
Antigout drugs					
Allopurinol	✓		✓ (ADR)	4[a]	
Antimycotica					
Flucytosine	✓	✓		2.86	
Voriconazol intravenous	✓[b]			1.75	
Antiparkinsonian drugs					
Amantadine	✓		✓ (ADR)	5	
Antipsychotic drugs					
Lithium	✓	✓		3.25	37,41,57
Cardiac drugs					
Digoxin	✓	✓	✓ (TE, ADR)	5	37,41,57
Disopyramide		✓	✓ (TE)	4	
Flecainide		✓	✓ (TE)	2.5-5	41
Milrinon	✓		✓ (ADR)	2	
Gastrointestinal drugs					
Metoclopramide	✓		✓ (ADR)	4	
Various					
Memantine	✓		✓ (ADR)	3.3	
Varenicline	✓		✓ (ADR)	2.5	

[a] The therapeutic window is based on the information of the metabolite oxypurinol.

[b] Voriconazol by the intravenous route in patients with moderate to severe renal impairment is contraindicated due to the potential toxic effects of the accumulation of the solvent vehicle sulphobutyletherbetacyclo-dextrin.[58]

In the situation of bacterial meningitis, for example, patients with renal impairment are at increased risk to reach plasma concentration above the minimum toxic plasma concentration, because the minimum effective dose and therefore the plasma level is higher. A lower dose should be considered in those situations.[45]

Considerations at the start of pharmacotherapy

When a renally cleared drug is needed for a patient with renal impairment, the starting dose should be considered. The rate at which the effect of the drug must be achieved (quickly or not) is of major importance. The following questions should be asked: "What is the risk of therapeutic failure with lower doses, and what is the risk of drug toxicity with higher doses?"[45]

If the pharmacological effect is needed quickly one should consider to start with the recommended dose for patients with a normal renal function and adjust the dose depending on ADRs and/or effectiveness. In other words, consider to not adjust the drug dose to renal function. Starting with a normal dose in patients with renal impairment may be seen as a loading dose. Moreover, the half-life time of renally excreted drugs will be longer and therefore it will also take longer to reach C_{ss}. For example antibiotics, the risk when dosing too low is insufficient efficacy, but also increasing risk to develop drug resistance. For most antibiotics the ADRs are easy to observe and may be relatively mild. Therefore, starting with a normal dose is preferable.

In case it is not crucial to have a quick pharmacological effect, one should preferably start with a low dose and gradually increase the dose over time while monitoring the effectiveness of the drug and ADRs. Examples are antihypertensive drugs and statins. This is called the 'start low and go slow principle'.

Especially, for drugs with a NTW one should consider a more conservative approach.[46]

Considerations during pharmacotherapy

Drug dose recommendations concerning patients with impaired renal function are usually expressed per renal function category (50-80, 30-49, 10-29, and < 10 ml/min/1.73m^2).[39,47] Therefore recommended dose changes for most drugs are crude (e.g. halving the dose or changing from twice-a-day regimen to a once-a-day regimen).[17] One could argue that differences between eGFR and the true GFR will remain without practical consequences as long as they do not result in different renal function categories. However, the factors influencing the variance of the eGFR become more important as the eGFR approaches the nearest cut-off value for falling

into another renal function category. Then, a minor change in eGFR over time will lead to different drug dosing recommendations. It is important to keep in mind that different renal function categories to guide drug dosing are merely a derivative of a continuous function that is expressed by the following formula:

Fraction of normal dose = $1 - f_e \times (1-k_F)$

Herein, f_e is the fraction of the original dose excreted as unchanged compound (or active metabolite) in the urine, while k_F is the patient's GFR divided by 120 ml/min.[48] If one indiscriminately applies drug dose recommendations of 50% for eGFRs of 30-50 ml/min and of 25% for eGFRs of 10-30 ml/min, a minor change in eGFR from, for example, 31 to 29 ml/min will halve the drug dose. If it is assumed that the f_e for the particular drug equals 1, the formula above will yield a dose of 26% and 24% for eGFRs of 31 and 29 ml/min, respectively. Alternatively, one could decide to replace the recommended doses of half and a quarter of the full drug dose by one-third for eGFRs around 30 ml/min.[11] Following the calculation of the desired drug dose, the prescribed drug dose must be rounded off to the available strengths of the drug in question.[49]

Monitoring

Recognition of renal function as an issue to be considered when prescribing and dispensing drugs is probably more important than the precision of different estimates of renal function.[37] To overcome uncertainties, drug efficacy and safety should preferably be monitored after the start of the therapy and dose adjustment should be based on ongoing assessment of clinical status and risk versus benefit of the current regimen.[22] The Dutch guidelines for drug dosing in patients with renal impairment generally recommends therapeutic drug monitoring (TDM) and/or careful monitoring of therapeutic effects and/or ADRs for all drugs with a NTW (see Table 8.3).[39] When it is not possible to monitor effectiveness or ADRs appropriately, or when it is not possible to timely detect serious ADRs, use of a different drug should be considered.

For a number of drugs monitoring their effectiveness and/or ADRs (when feasible through TDM) is more important than dose adjustment according to current guidelines. Digoxin, for example, is a drug that is difficult to manage, particularly in elderly patients who are at high risk of decreased renal function.[50] An important limiting factor in the prediction of a digoxin dosage regimen when eGFR is < 60 ml/min, is the contribution of hepatic elimination. The latter increases when renal function decreases. This resulted in high inter-individual variation for digoxin plasma levels.[36,51] Therapeutic drug monitoring of digoxin is then indicated. Another

example is allopurinol. Treat to target serum uric acid concentrations (< 0.36 mmol/l) rather than give a dose according to renal function has been shown to be safe and effective.[52,53]

Conclusion

DTM based naively on eGFR is not without limitations. The variation in non GFR determinants of serum creatinine levels cannot be overcome with existing formulas for estimating renal function. In addition, multimorbidity and drug-drug interactions can further complicate clinical decision making.[44] The narrower the therapeutic window of a drug is, the more relevant individual patient characteristics are and the less satisfactory crude dose recommendations (such as halving the dose or doubling the dose interval) become.[17] Therefore the following considerations in DTM in patients with renal impairment should be made: (1) is the drug renally excreted? If yes, is there a safer alternative available?, (2) if not, is it possible that the eGFR substantially deviates from the true GFR? If yes, consider 24-h urine creatinine clearance collection, (3) does the BSA of the patient deviates substantially from 1.73m^2? If yes, calculate BSA and adjust eGFR to ml/min, (4) combine consideration 2 and 3 in order to achieve the best approximation of the true GFR, (5) adjust the drug dose gradually to the renal function, (6) be extra careful with drugs with a NTW and consider another starting dose depending on indication, (7) consider if it is possible to monitor effectiveness and/or ADRs with TDM and/or other measurements.

In conclusion, when determining most appropriate dosing regimen for patients with impaired renal function, the serum creatinine-based formulas should never be used naively but always in combination with clinical and pharmacological assessment of the individual patients.[46]

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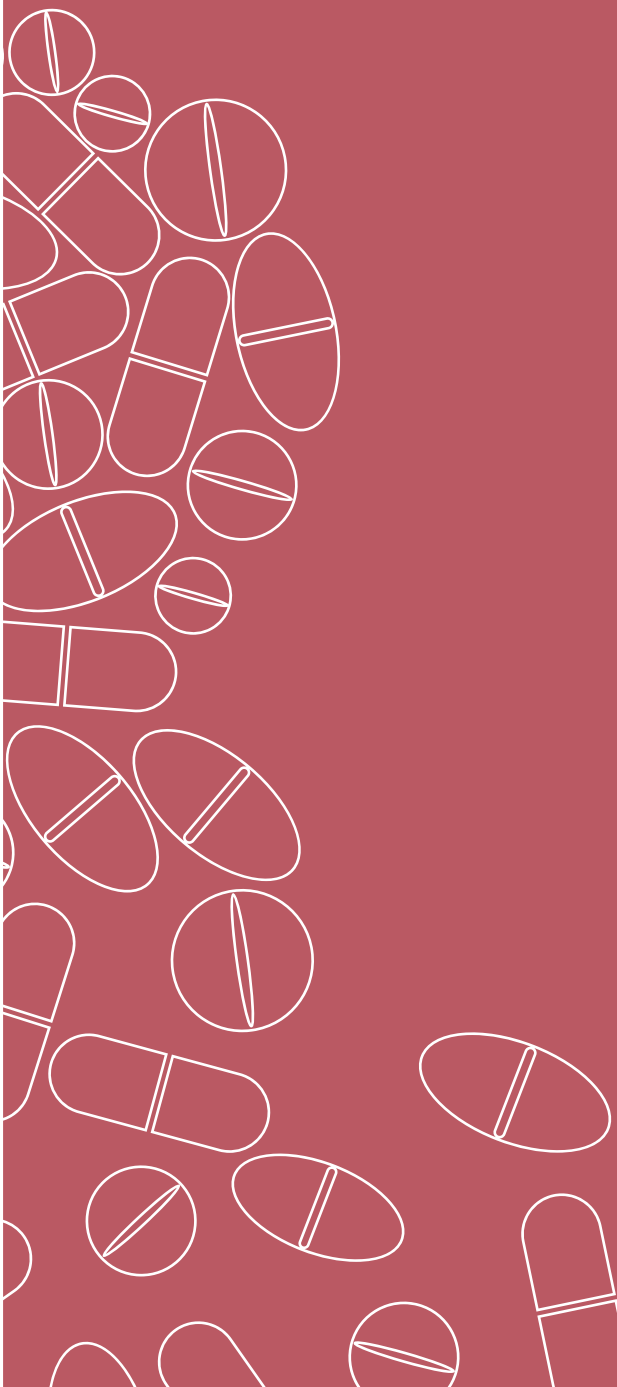
General discussion



9

Introduction

Chronic kidney disease (CKD) is a growing health problem and is associated with adverse outcomes, such as kidney failure, cardiovascular diseases and death.[1-3] In addition, patients with renal impairment have an increased risk for developing adverse drug reactions and medication-related hospital admissions.[4,5] Renal function therefore plays an important role in personalized drug therapy management (PDTM).

The estimated glomerular filtration rate (eGFR), mostly calculated with the Modification of Diet in Renal Disease (MDRD)-4 formula, is reported routinely by many clinical laboratories whenever a serum creatinine value has been ordered.[6] Computerized decision support systems (CDSS) facilitate appropriate dosing of renally cleared medications by including eGFR in its algorithms.[7] The use of CDSS has led to fewer prescribing errors in patients with renal impairment according to existing guidelines.[8,9] The implementation of guidelines in algorithms, which give an alert for an individual patient, suggests that the evidence underlying the algorithms are 'black or white'. In other words the guidelines are often implemented as a rule book, whereas it is meant to give assessment tools based on existing evidence.[10] Although it is widely understood that not every patient with a particular condition, for example patients with renal impairment, benefits from treatment adjustments that are known to work in an average population, clinicians may use guidelines as a rule book.[11] The introduction of the Dutch guidelines 'Drug dose advices in renal impairment' recommends pharmacists to actively advise another drug and/or another drug dose.[12] Although a group of experts with clinicians, both physicians and pharmacists, were involved in the development of the guidelines, the application of the guidelines in daily clinical practice encountered different perceptions between physicians and pharmacists.[13] For example, nitrofurantoin initially was contraindicated when eGFR dropped below 50 ml/min.[14] Pharmacists advised physicians to consider another drug when it was prescribed in patients with renal impairment. Physicians appeared not to be willing to do so, because they had not experienced any problems with nitrofurantoin in the past. Such differences between guidelines and clinical practice was the start of the researches presented in this thesis. To improve PDTM, it is important to understand the different perceptions and to investigate whether certain assumptions correspond with daily clinical practice.

This thesis comprises a variety of studies in which the pharmacological evidence of a part of the guidelines 'Drug dose advices in renal impairment' is examined. It starts with fundamental research about the validity of the MDRD formula. Then,

cohort studies about the risk to develop serious adverse drug reactions (ADRs), such as metformin induced lactic acidosis, are presented. In **Chapter 8** we described a practical approach to cope with the uncertainties, reported in the previous chapters, in daily clinical practice and the role which a CDSS might play. This thesis contributes to knowledge that can be used for the improvement of the role of the pharmacist in drug therapy management in patients with renal impairment.

In the general discussion three topics will be addressed from the perspective of what is already known and what is added by this thesis to improve PDTM in patients with renal impairment. These topics are:

1. Complexity of renal function in drug dosing
2. Application of the guidelines 'Drug dose advices in renal impairment'
3. Implications for clinical practice and future research

Complexity of renal function in drug dosing

Renal function

At the start (in 2009) of the studies described in this thesis, the MDRD-4 formula was used to estimate GFR. Clinical laboratories had just introduced the reporting of the eGFR calculated with the MDRD-4 formula. The advantage of this formula is that only age and serum creatinine levels are necessary to calculate eGFR. This in contrast to the Cockcroft and Gault (CG) formula wherein weight is also needed as a variable. The reporting of the eGFR by clinical laboratories stimulated pharmacists and other clinicians to give or apply drug dose advices when necessary.

As most of the drug dose advices are historically based on the older CG formula (see the next paragraph), the first question was, how valid is the MDRD formula in estimating the GFR in specific patient populations? The MDRD formula was developed in a sample of 1070 ambulatory, predominantly white patients with CKD, a mean age of 51 years, and 6% was diabetic.[15] The population was not obese and without multiple comorbidities. Patients with serious medical conditions, such as lung disease, liver disease, and heart failure (New York Heart Association class 3 and 4), were excluded.[15] In other words, how does the patient population in daily clinical practice, both in the ambulatory and hospital care setting, correspond to the patient population used to develop the MDRD formula? Are there clinical conditions in which the MDRD formula is not valid?

In **Chapter 3** we shortly reviewed the serum creatinine household. There are

numerous factors, conditions and situations that influence serum creatinine levels and thus eGFR calculated with the MDRD formula. **Chapter 2** presented a systematic review for the full range of the GFR in patients with human immunodeficiency virus (HIV). Our conclusion was that the MDRD formula was as valid in HIV-positive as in HIV-negative patients with good renal function to mild renal impairment.[16] In the meantime, from 2009 on, the Chronic Kidney Disease EPIdemiology Collaboration (CKD-EPI) formulas were developed. These formulas appeared to be more valid in the eGFR range ≥ 60 ml/min/1.73m^2. The differences in the GFR range < 60 ml/min/1.73m^2 were small and not clinically relevant.[17,18] These results reminded us that the MDRD formula was developed in patients with renal impairment and was therefore by definition not properly tested in patients with normal renal function. For our broader systematic review we therefore selected only patients with a(n) (e)GFR < 60 ml/min/1.73m^2. We conducted a systematic review to determine the validity of the MDRD formula in specific patient populations with renal impairment: elderly, hospitalized and obese patients, patients with cardiovascular diseases, cancer, chronic respiratory diseases, diabetes mellitus, liver cirrhosis and HIV. This selection was based on three general patient groups which were inadequately represented in the development of the MDRD formula, four common categories of chronic diseases, which are the leading cause of death and other chronic diseases in which reduced muscle mass can be present. In summary, the selection criteria we applied were an eGFR 60 < ml/min/1.73m^2, comparison with a gold standard, and statistical analysis focussed on bias, precision, and accuracy. We interpreted these aspects as the most important ones, because an ideal comparison was not possible. In an ideal comparison, the gold standard and the measurement of serum creatinine levels would be exactly the same as in the study about the development of the MDRD formula, namely ^{125}I-iothalamate and the kinetic alkaline picrate assay (Jaffe method), respectively.[15]

For patients with diabetes mellitus and liver cirrhosis, hospitalized patients on the internal medicine and nephrology ward and elderly with moderate to severe renal impairment we concluded that the MDRD formula is not valid.[19] The conclusion of elderly patients, and patients with liver cirrhosis was in line with existing reviews, but more robust due to less methodological limitations.[20,21] Our review also showed that the validity of the MDRD formula has not yet been tested properly or was tested poorly in patients with cardiovascular diseases and chronic respiratory diseases, obese patients, patients with cancer and HIV. In other words, the MDRD formula cannot be used naively in many patients both in the ambulatory and hospital care setting.[19]

Several reviews about the validity of the MDRD formula have been published previously.[20-23] These reviews often concerned the full range of the GFR, a diverse patient population, 24-hour urine collection as a 'gold standard', or another, to our opinion less appropriate, statistical analysis.

At the time the research for this thesis was conducted the CKD-EPI formulas were developed. These formulas are based on serum creatinine value, cystatin C value and a combination of both.[24,25] Because these formulas are also serum creatinine based, the limitations discussed for the MDRD formula are probably similar. Therefore we assume that the results of this thesis may well be sustainable, even when the newer formulas will be increasingly used in the next years.

Another limitation of the studies presented in **Chapter 2 and 3**, but also throughout the thesis, is that the classification of renal function groups was based on a single eGFR value. This choice was for pragmatic reasons because clinical guidelines often recommend annual monitoring of renal function. However, variability in serum creatinine measurements requires at least two creatinine measurements.[26] In addition, in certain clinical situations renal function may fluctuate substantially, so that the renal function group and therefore the recommended dose, can change within a few days. The magnitude of the fluctuation of the renal function in daily clinical practice and its potential effect on appropriate prescribing of medications, for example after discharge from the hospital, is unknown. **Chapter 6** presented a study design about the fluctuation of eGFR around hospital admission in the elderly. The first results suggested that in one third of the patients the renal function group changed from one category to another and therefore implies that after discharge monitoring of renal function and (further) drug dosing adjustment may be necessary within the first two months.

In summary, eGFR calculated with the MDRD formula is prone to influencing factors which may lead to a value that differs substantially from the true GFR. The MDRD formula is currently available and no alternatives are easy and forehanded and this will probably not the case in the near future. Therefore the next question is, is it possible to use the MDRD formula in drug dosing? And how should we use the MDRD formula in daily clinical practice?

Renal function and drug excretion of one drug

The ability to metabolize and eliminate drugs varies considerably between individuals.[27] The two principal organs responsible for the elimination of drugs and their metabolites from the body are the liver and the kidney.[28] In general, three processes can potentially contribute to the renal clearance of a drug: glomerular

filtration rate, tubular secretion, and tubular reabsorption.[28] The CG formula has historically been the method applied to determine drug dose regimens in patients with impaired renal function, and reflects both the glomerular filtration rate and tubular secretion.[6,22] The MDRD formula only represents the glomerular filtration rate. Therefore with the widespread automated reporting of the eGFR, calculated with the MDRD formula, the question has been raised whether eGFR can facilitate drug dosing decisions instead of the CG formula.[6] The results of available studies are contradictory, but also interpreted differently. A concordance of 80% is said to be sufficient, whereas others suggest that a difference of 15% is unacceptable. According to Spruill et al. it is not surprising that the MDRD and CG formula perform differently, because of their mathematical differences.[29] The expression of the age factor in the CG formula is linear, whereas the age factor in the MDRD formula is exponential.[29] An additional difference is the way in which the units of both formulas are expressed. The CG formula reports results in ml/min, whereas the MDRD formula reports results in ml/min/1.73m^2.[30] For patients who are substantially larger or smaller than an average person (with a body surface area of 1.73m^2) and with a normal figure the outcome of both formulas may be substantially different, and this may lead to different drug dose advices. Hudson et al. reported that the eGFR estimated with the MDRD formula resulted in higher doses compared with the CG formula.[22] Stevens et al. reported a high concordance rate between the MDRD and CG formula compared to mGFR (measured with ^{125}I-iothalamaat), namely 88% and 85%, respectively ($p < 0.001$).[6] However, the clinical relevance of the disconcordance might be high, depending on the type of drug.

In view of the foregoing, the use of the MDRD formula in drug dose advices seems less appropriate. In addition, renal dysfunction not only alters the renal excretion of unchanged drug and/or their metabolites, but it can also lead to modifications in plasma protein binding, distribution, transport and biotransformation of drug substances.[28,30] The importance of these factors for each drug will differ depending on the metabolic process affecting that drug.[30] For example, digoxin showed a great interindividual variability in the lower ranges of the eGFR (eGFR < 60 ml/min).[31,32] Although 80% of the digoxin dose is excreted unchanged in patients with normal renal function, the relative contribution of the hepatic elimination is increased in patients with renal impairment.[31] Renal impairment can also affect the pharmacodynamic (PD) action of a drug, but this has not been well studied.[28,33] For example larger doses of furosemide are needed in patients with chronic renal impairment to achieve an adequate diuretic response compared to patients with normal renal function.[28] Ideally integrated pharmacokinetic (PK)/PD studies are

needed to evaluate the necessity of drug dose adjustment in renal impairment.[28,33]

For newer drugs more attention should be paid to general pharmacokinetic principles in drug information programs.[27] In 2010 the FDA published a draft update of their guidance for industry recommending that manufacturers provide drug dose advices on the basis of the CG and MDRD or CKD-EPI formula.[33] The five major updates were [33]: (1) a PK study should be conducted in subjects with renal impairment when the drug is likely to be used in these subgroups, both for renally and non-renally excreted drugs, (2) both formulas might be used, CG and MDRD, (3) conduct studies in hemodialysis patients on dialysis, (4) study the PK of therapeutic proteins in renally impaired patients when appropriate, and (5) the results should be described in the label/product information. The intention of the FDA is a step forward, but how to cope with already existing drugs remains unclear.

In **Chapter 4 and 5** we described two cohort studies about patients with renal impairment using nitrofurantoin and metformin, respectively. Both drugs are considered to be contraindicated when renal function drops below a specific level. Nitrofurantoin and metformin are the drug of choice in urinary tract infection in women or diabetes mellitus type 2, respectively. Currently provided recommendations on drug dose are predominantly based on case reports and/or pharmacokinetic studies. The latter are often performed in healthy volunteers using a single dose, and therefore they not have to be representative for daily clinical practice. The main finding for both drugs, metformin and nitrofurantoin, was that the risk for adverse drug reactions was increased in patients with renal impairment which is in line with current recommendations.[34,35] We showed that this type of research is useful in confirming drug dose advices in a large representative population over a long period. In the metformin study we even identified that a high metformin dose in combination with renal impairment further increases the risk of lactic acidosis. The problem is that the incidence of such ADRs are rare. One unanswered question is whether there are additional risk modifiers to identify patients with a higher risk.

The database studies had several limitations. First, the outcome measures may not classify all cases correctly. In the nitrofurantoin study the outcome measurement for ineffectiveness was another antibacterial treatment used for urinary tract infection, but these antibacterials could have been used for other reasons. In the metformin study one could raise the question to which extent an elevated lactate level (> 5 mmol/l) point in the direction of lactic acidosis. Second, the registration of adverse events, diagnosis and/or laboratory values in databases is limited. In other words, the events measured in our studies might only be the tip of the iceberg. In daily clinical practice

the number of less critical events (which also may be inconvenient for the patient) might be even greater. Third, we used a single serum creatinine level to calculate eGFR or the single reported eGFR only. As we explained above, the variability in serum creatinine measurements requires at least two creatinine measurements or two reported eGFRs to assess the degree of renal impairment.[26]

In summary, cohort studies in a large database and over a long period generated new evidence to existing guidelines. In future research additional risk factors should be identified. In addition, these cohort studies showed the importance of post marketing surveillance of the behaviour of drugs in large populations of patients with renal impairment. Especially in the case of rare ADRs, such as metformin induced lactic acidosis.

Renal function and the use of multiple drugs for multiple comorbidities and/or unstable situations.

In the previous two sections we focussed on eGFR and the impact of eGFR on one specific drug. In daily clinical practice clinicians are confronted with patients with multiple comorbidities using multiple drugs. Patients with CKD frequently have comorbidities, including hypertension, diabetes, cardiovascular disease, and metabolic bone disease.[36] Polypharmacy is typical and therefore the risk of drug-drug interactions is substantial.[36]

For example, the use of an angiotensin-converting enzyme (ACE)-inhibitor as an antihypertensive drug in patients with diabetes is recommended.[37] When a patient with diabetes also has renal impairment, the risk for developing hyperkalaemia from ACE-inhibitors is approximately 5 times higher.[38] This rarely leads to severe hyperkalaemia, because the kidney is capable of adapting potassium homeostasis. However, there are situations wherein the potassium level strongly increases and leads to the discontinuation of the ACE-inhibitor, namely with the concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), potassium-sparing diuretics, or ingestion of large amounts of potassium salts.[38] In other words the combination of multiple drugs increases the risk of hyperkalaemia compared to the use of an ACE-inhibitor alone in patients with renal impairment.

Another example is the use of rivaroxaban in patients with renal impairment. Approximately two-third of the rivaroxaban is hepatically metabolized through the liver via cytochrome P450 enzymes (both CYP3A4/3A5 and CYP2J2) and one third is renally excreted unchanged via P-gp-mediated and ABCG-2 mediated secretion.[39,40] When rivaroxaban was used alone in patients with mild and moderate renal impairment the area under the curve (AUC) increased with approximately 15%.

When rivaroxaban was added to a treatment with erythromycin, a CYP3A4 and P-gp-inhibitor, the AUC of rivaroxaban increased with approximately 54% to 71% in patients with mild and moderate renal impairment, respectively, compared to rivaroxaban use alone.[39] The combined drug-drug-disease interaction resulted in a clinically relevant increase in rivaroxaban exposure.[39]

The two examples illustrate which problems may occur in patients with renal impairment when different drugs for different indications are prescribed. To avoid these problems another drug may be chosen or the drug dose may be adapted. In a stable situation renally excreted drugs can be prescribed in patients with renal impairment. However, physicians should be aware of the fact that clinical situations may change over time. For example, declining of renal function over time, change of chronic nutritional status (defined as percentage of ideal body weight), serum potassium levels and age (individual patient characteristics) are all of influence on digoxin clearance (at least in hospitalized Korean patients, but probably also in other ethnic groups).[32] Evaluating changes in patients' situations over time, for example renal function, and the effects of adjustment of drug dose regimens on the clinical outcome should be subject to future research.

It is also possible that a clinical situation changes abruptly. For example in situations, such as diuretic therapy, vomiting, and diarrhoea, it can result in true volume depletion. Patients with CKD are then more vulnerable to toxic drug effects on the kidney.[41] Such an abrupt change may even lead to developing acute kidney injury (AKI) with increased risk of mortality.[42] The best strategy is to avoid potentially nephrotoxic drugs and concomitant use of nephrotoxic drugs whenever possible.[41] In **Chapter 8** we suggest to avoid renally cleared drugs in patients with renal impairment, but that is not always possible. Choosing a drug with a broad therapeutic window may also help to reduce future problems.

In summary, multiple drugs for multiple comorbidities is common in patients with renal impairment. Drug dosing in these patients is therefore often complex.

Application of the guidelines 'Drug dose advices in renal impairment'

Clinical decision support systems

CKD is a chronic disease that is frequently associated with comorbidities, making effective treatment difficult due to the complexity of care.[43] Mistakes occurring during drug treatment are often related to an erroneous prescription, lack of time, missing information or lack of knowledge.[44] The publication of guidelines is not enough by itself to change the prescribing behaviour of clinicians in this respect. Clinical decision support systems (CDSSs) may be helpful in the implementation of guidelines, such as 'Drug dose advices in renal impairment'. CDSSs link patient characteristics with medical knowledge to generate recommendations for the clinician to improve PDTM.[45]

In **Chapter 7** we demonstrated that an advanced pharmacotherapy-related CDSS leads to more relevant alerts compared to a basic pharmacotherapy-related CDSS. The impact of adding laboratory values and other patient characteristics resulted in a significantly higher positive predictive value (PPV) for the advanced CDSS compared to the basic CDSS (23.3% versus 12.2%; $p < 0.05$).[46] However, the number of clinically irrelevant alerts remained high and continuous fine-tuning of these algorithms is necessary. Alerts related to recommendations in patients with renal impairment were not calculated separately. In our study alerts about drugs which were contraindicated in combination with a certain degree of renal impairment were classified as a 'drug-disease interaction'. If alerts contained a drug dose advice at a certain degree of renal impairment they were classified as 'dosing guidance'. The PPV for both categories increased substantially in the advanced CDSS: 24.5% versus 0% and 16.9% versus 5.6% for the category drug-disease interaction and dosing guidance, respectively.[46] We know that these increases in PPVs in the advanced CDSS were at least partly due to algorithms using renal function laboratory values.

Although the PPV was increased in the advanced CDSS, the PPV could be increased further by combining algorithms. For example, one algorithm identified the combination of a renin-angiotensin-aldosteron-system (RAAS)-inhibitor and potassium (-saving diuretics) and generated a medication alert with the recommendation to monitor the serum potassium level. Another algorithm checked if the serum potassium level was recently measured and within the range of 3.5-5.0 mmol/l. The first algorithm should be suppressed if the second algorithm does not generate a medication alert, because the potassium level is already monitored. Another step in improving a CDSS is adding more patient characteristics and

laboratory values. Seidling et al. identified potassium, leukocyte count, international normalized ratio (INR), therapeutic drug monitoring and eGFR as useful laboratory values to reduce the number of inappropriate signals. The identification of static as well as dynamic patient characteristics as modifiers is a promising strategy.[44]

In daily clinical practice alerts are often overridden by physicians and in half of the cases advices from CDSSs are ignored or not followed for several reasons.[47-49] Reasons to ignore warnings were: irrelevant, not timely, already considered before, or simply because the expected benefit of the therapy outweighs the potential risks.[44] Between physicians and pharmacists and among physicians approximately 50% agreed on the given advice or on turning the alert off because of the lack of clinical usefulness.[50,51] These results indicate that concordance in using guidelines is still lacking.

Another problem is that physicians experience the alerts as a disruption of their workflow. Reaching agreement on treatment and instructions on how to use medication often occurs before the prescription is entered into the computer.[52] Therefore current systems interrupt to correct decisions already made, rather than to assist earlier deliberations.[52] Advices in an alert vary from discourage to prescribe a certain drug to monitoring renal function in time and over time.[12] At the moment of prescription the first alert about not recommending a certain drug might be important and the physician may choose another drug. The second alert about monitoring renal function may not be important on that specific moment. The question is, is it possible to reduce the alerts at the moment of prescribing to alerts really necessary? And are physicians more prone to react on these selection of alerts? The next question is, who is responding to alerts turned off for the prescriber? To our opinion, pharmacists can play an important role here. Especially, when more prescribers are involved pharmacists have the overview of the combination of drugs for several comorbidities. Due to their education they are probably more capable of assessing the effects of a combination of drugs than physicians. In addition, pharmacists may handle specific alerts instead of the physician (see also the role of the pharmacist in PDTM described in the next section).

Many clinicians experience a CDSS as a tool to burden their work pressure. It is possible to reduce irrelevant alerts in current CDSS by using sophisticated algorithms, but these CDSSs also give more opportunities to increase the quality of PDTM. For example, an algorithm that checks if measurement of renal function is done timely. The possibilities for a CDSS are endless, but the number of alerts that can be evaluated by a clinician in daily practice is limited. In addition, daily clinical practice does not always correspond with the evidence published in guidelines.

Therefore continuous education of clinicians to improve their clinical judgment remains necessary. In the future CDSSs may also be used as a risk management tool to identify complex patients that need an integrated team-based evaluation.

In summary, CDSSs are an important element to solve some of the problems of implementing evidence into clinical practice, but not the only one.[43] Current CDSSs generate too many irrelevant alerts, but more advanced CDSSs are promising to be more effective (generate more relevant alerts) and more efficient (generate less irrelevant alerts).

Role of the pharmacist in personalized drug therapy management

In the section above we mentioned the complexity of renal function and the excretion of drugs by the kidney. With information about pharmacodynamics and pharmacokinetics of a specific drug for each degree of renal impairment drug dose advices can be achieved. It might even be possible to predict certain unstable situations and their effect on the excretion of drugs. A CDSS might be supportive in the application of all the available knowledge, including the results presented in this thesis. The next question is, how can we realize PDTM in patients with renal impairment in daily clinical practice?.

Evidence based guidelines help to make the best scientific evidence accessible for decision makers.[53] Simply making providers aware of clinical guidelines is often insufficient for inducing adherence with these clinical guidelines.[53-56] Several implementation strategies can be applied, varying from education and support of health professionals to organisational change and financial incentives. These strategies can improve healthcare delivery, although the impact is mixed and overall moderate.[53,56,57]

We started this thesis with the six steps of good prescribing of drugs (see Table 9.1).[58] The responsibility for good prescribing is entirely allocated to the prescriber in the current document of the World Health Organization (WHO). The role of pharmacists is different across countries, but in The Netherlands pharmacists are drug specialists who can play an important role in the process of good prescribing of drugs and therefore be of added value in PDTM. Due to increased numbers of guidelines and standards and the growing empowerment of patients, good prescribing of drugs cannot rely on physicians solely. The key players in this process are: the patient, the physician(s) and the pharmacist. Below we suggest the added value of pharmacists in step 3, 4 and 6 of good drug prescribing in patients with renal impairment. In The Netherlands step 5 has already been implemented very well. Giving information, instructions and warnings when a drug is dispensed for

the first time is not any different for patients with or without renal impairment. Therefore we will not discuss this particular step.

Table 9.1 Six steps in good prescribing of drugs

Step	Description	Added value of pharmacist
1	Define the patient's problem	No
2	Specify the therapeutic objective	No
3	Verify the suitability of your P(ersonal)-drug	Yes
4	Write a prescription	Yes
5	Give information, instructions and warnings	Yes
6	Monitor (or stop?) the treatment	Yes

Step 3: Verify the suitability of the personal-drug

Physicians have their personal preferred drug (P-drug) to prescribe when they suspect or diagnose a certain disease. A P-drug is based on four criteria: efficacy, safety, suitability and cost.[58] The drug of first choice applies to the general population visiting the physician. When a patient with renal impairment represents himself/herself the first choice P-drug might not be suitable. In **Chapter 8** we presented considerations when prescribing drugs in patients with renal impairment. In summary, if the P-drug is renally excreted, the first consideration should be if a safer drug for patients with renal impairment is available which is equally effective. In addition, we presented a table with renally excreted drugs with a narrow therapeutic window (NTW) for which extra attention is necessary when prescribed in patients with renal impairment. The indication and thus the rate at which the therapeutic effect has to be achieved should also be taken into account. For example, when starting an antihypertensive drug, the starting dose might be low and the dose might be increased slowly depending on the effectiveness and ADRs. For treating an infection the approach might be better the other way around. Starting with a normal dose and if necessary decrease the dose depending on clinical response and ADRs.

The added value of pharmacists in this step of good prescribing is to be a sparring partner for the physician. Awareness about the suitability or unsuitability of P-drugs in patients with renal impairment might be increased by discussing guidelines in pharmacotherapeutic consults. For example, in primary care many general practitioners and community pharmacists discuss subjects on regular basis. P-drugs or adjusted dosage of P-drugs for patients with renal impairment can be determined and specified in protocols. When a prescription reaches the pharmacy, the pharmacist evaluates the drug and drug dose prescribed with regard to the patient's renal function and, even more importantly, evaluates the prescription and

renal function in the light of the co-medication already in use by the patient. This medication review may not only lead to a change in the new prescription but also to a change in the drugs already in use.

Step 4: Write a prescription

In the era of computerized physician order entry systems, prescriptions can be read properly by the pharmacy. The added value of the pharmacist in writing the prescription itself is nihil, but the added value must be found in the application of CDSSs in the prescribing process. In the section about CDSS above we described the advantage and disadvantage and challenges in using CDSSs.

We already mentioned that pharmacists can play an important role, because pharmacists have the overview of all drugs used by the patient, also those prescribed by different physicians. The added value of pharmacists may be increased by shifting the handling of alerts from the physician to the pharmacist. For example, a 68-year old man is prescribed naproxen 500 mg twice daily by the general practitioner (GP). He also uses a selective serotonin reuptake inhibitor (SSRI) prescribed by the psychiatrist and acetylsalicylic acid by the cardiologist. The addition of a proton pump inhibitor (PPI) is recommended due to the increased risk of gastrointestinal bleeding. In The Netherlands some pharmacists already have the agreement that they can add a PPI without contacting the GP, which is defined in a protocol. These initiatives should be encouraged and expanded. In case of alerts for patients with renal impairment one could choose to show only the drugs with a NTW to the physician to improve alert fatigue. Other alerts might be handled by the pharmacist, which mainly implies that sufficient instruction and warnings are needed when the drug is dispensed. In case of doubt and when an additional clinical view of the physician is needed, the pharmacist should contact the prescriber.

Step 6: Monitor (or stop?) the treatment

Numerous studies have shown that patients with chronic conditions adhere only to 50-60% of their medications as prescribed.[59] For example, in chronic heart failure and diabetes mellitus poor adherence to medications increases hospitalization and mortality.[60,61] Patient adherence is greatest 5 days prior and 5 days post appointment with health care providers and usually tapers off significantly within 30 days.[59] Failure to identify and remediate poor adherence often results in intensified pharmacotherapy with increased doses of medication – thus increasing the overall cost of treatment, the risk of adverse effects, physician frustration, misdiagnoses, and in more extreme situations, unnecessary treatment and exacerbation of disease or even mortality.[59] Reiterative, positive reinforcement, frequent feedback and regular

follow-up are essential to ensure adequate adherence over time.[59,62] Discussing adherence to drug therapy is the first step in monitoring effectiveness and ADRs properly, both for patients with and without renal impairment. When it comes to monitoring effectiveness and/or ADRs the use of measurements, such as blood pressure, cholesterol level, therapeutic drug monitoring, serum creatinine level etc., become more important in patients with renal impairment. This is mainly due to the lack of evidence of the behaviour of a drug and therefore the prediction of the effects of a drug in patients with renal impairment seen in daily clinical practice, especially when multiple drugs are used simultaneously. In addition, the pharmacist should contact the patient more often to discuss the effectiveness and ADRs which cannot be measured. In **Chapter 8** we described the importance of monitoring and recommended to monitor effectiveness and/or ADRs with laboratory measurements whenever possible. These laboratory values may vary between monitoring renal function itself, for example after starting an ACE-inhibitor, to therapeutic drug monitoring when carbamazepine or vancomycine is started, to measuring anti-Xa activity when dabigatran is used. Traditionally, requesting a laboratory value is the task of the physician. In both our cohort studies (**Chapter 4 and 5**) the percentage of patients with unknown renal function was high. In our diabetic population this percentage was approximately 30%. An even higher number was reported by van Blijderveen et al. in a dynamic population using a diuretic, ACE-inhibitor, and/or angiotensin receptor blocker.[63] Although physicians have a positive intention to monitor biochemical parameters, this is not always achieved in clinical practice.[64] Pharmacists can play a coordinating role. Along with the evaluation with the patient about the effectiveness and/or ADRs of a drug, pharmacists may contribute to the safe, effective, and efficient use of drugs, particularly when caring for people with multiple chronic conditions where multiple clinicians are involved.[65]

Implications for clinical practice

The eGFR reported by clinical laboratories should not be used naively. The implications for clinical practice are outlined in detail in **Chapter 8**. In summary, in patients with renal impairment the drug of choice is an effective drug that is not renally excreted. If a renally excreted drug is needed the reliability of the eGFR should be assessed more carefully for drugs with a NTW. After achieving the best approximation of the true GFR, we suggest a gradually drug dose adaptation according to renal function. Monitoring effectiveness and ADRs are the key component in PDTM and should be assessed with laboratory measurements whenever possible. PDTM should be based on an ongoing assessment of clinical status outweighing the risk versus the

benefit of the used drug regimen. In **Chapter 9** we outlined the potential added value of pharmacists in coordinating the laboratory measurements and monitoring effectiveness and ADRs of drugs used in patients with renal impairment. The first step to achieve this changing role of pharmacists in PDTM is that physicians are aware of how important it is to share the eGFR value, especially in the ambulatory care setting where access to laboratory values is limited.

For some pharmacists their attitude to renal function should change as well. The eGFR value and the guidelines 'Drug dose advices in renal impairment' should not be applied strictly. Drugs with a broad therapeutic window may be dispensed without knowing renal function, except when a high dose is prescribed. For drugs with a NTW renal function should be assessed more carefully, but giving a normal dose instead of an adjusted dose on day 1 might even be more useful to achieve steady state levels more rapidly.

The first results of the study presented in **Chapter 6** confirmed that awareness of the fluctuation of the renal function after discharge from the hospital is necessary. Community pharmacies and GPs should not rely on eGFR values measured around or during hospital admission only.

Specific implications for clinical practice followed from **Chapter 4 and 5**. Although we confirmed the advices for nitrofurantoin and metformin to not give these drugs when eGFR drops below 30 ml/min/1.73m^2, additional information might be added to the existing advices in the Dutch guidelines 'Drug dose advices in renal impairment'. In line with the Medicines and Healthcare products Regulatory Agency the advice for nitrofurantoin should be: "A short course (3 to 7 days) may be used with caution in certain patients with an eGFR between 30 and 44 ml/min/1.73m^2".[66] In **Chapter 5** we found further evidence for the claim that the lower the renal function the higher the risk of lactic acidosis in metformin users. The risk was even higher when a high dose (> 2 g per day) of metformin was used. The current advice is to start with metformin 500 mg 2 times a day when renal function is between 30 and 50 ml/min/1.73m^2.[12] In daily clinical practice one should not only consider the starting dose of metformin, but also reconsider the metformin doses whenever a new eGFR value is reported, especially when eGFR drops below 60 ml/min/1.73m^2.

Implications for future research

The search for a formula 'one size fits all' to estimate GFR seems unrealistic. At least, it will take a long time to develop a formula with a better predictive value than

formulas involving serum creatinine and to validate it in diverse patient populations. Current clinical practice needs research that rather focuses on identifying variables or situations in which the currently known serum creatinine-based formulas should not be used for PDTM or used with extreme caution.

There are many studies about the potential effects on drug dose advices when using different serum creatinine-based formulas, but clinical consequences remain largely unclear.[6,22,67,68] Future research should focus on the clinical relevance of these differences in drug dose recommendations. In addition, a gradual drug dose adaptation as described in **Chapter 8** should be subject for future research as well. For example, in metformin users, does a gradual adjustment of the metformin dose in line with the decrease of renal function affects morbidity, mortality and/or risk of lactic acidosis?.

In daily clinical practice patients often have multiple morbidities and therefore use multiple drugs, especially patients with CKD. Most of the studies underlying guidelines are based on one drug in patients with a certain degree of renal impairment. Comorbidities are often excluded. The question is, how important is the factor renal function in PDTM in complex patients were multiple morbidities are present? Perhaps other factors are more of influence on the clinical effect of drugs and therefore should (also) be considered in PDTM. A broad approach on how to apply PDTM in these complex patients should be subject for future research.

Especially, in the hospital care setting it is known that eGFR may fluctuate within a day. When the eGFR points to another drug dose category, drug dose advices may also change from one day to another. What is the clinical relevance of adjusting drug doses from one day to another based on eGFR values?

In **Chapter 8** we presented a list of drugs with a NTW. Subject for future research is the clinical consequences of using this 'short-list' versus the current use of the guidelines 'Drug dose advices in renal impairment'. The added value of pharmacists in PDTM should also be investigated. This can be done by monitoring clinical effectiveness and ADRs of a specific group of drugs, for example, antibiotics.

In this thesis special attention was paid to the drugs nitrofurantoin and metformin. Other drugs which are contraindicated in patients with renal impairment might also be of interest for future research. For future research a clear definition on how to validate formulas is recommended. This should be done before a formula is implemented worldwide. It seems logical, but variables should be measured with the same method and the same gold standard should be used as in the development

study. Of interest were also the statistical methods used to analyse the validity of, in our case, the MDRD formula. The most informative method to assess diagnostic tests is the Bland-Altman plot, as this identifies the direction and the magnitude of the bias. Agreement on this aspect for future research is recommended.

Conclusion

The researches presented in this thesis showed the complexity of PDTM in patients with renal impairment. The MDRD formula that is widely used in The Netherlands in drug dosing, appeared not to be valid or the validity was unclear in specific patient populations. In addition, the results in this thesis showed that database cohort studies are useful in confirming advices published by guidelines. Despite the uncertainties of the MDRD formula and the limited evidence underlying guidelines, the fact is that the eGFR is automatically reported by clinical laboratories and the guidelines are used in daily clinical practice. In **Chapter 8** we discussed pragmatically how to use the eGFR values and the guidelines. We presented a list of drugs with a NTW that should be avoided or used with great caution in patients with renal impairment. In all cases, monitoring effectiveness and ADRs of drugs over time is an important key component in PDTM. Pharmacists may play an important role in improving PDTM by monitoring effectiveness and ADRs and coordinating the measurement of laboratory values whenever necessary. CDSS might be supportive in the application of all the available knowledge.

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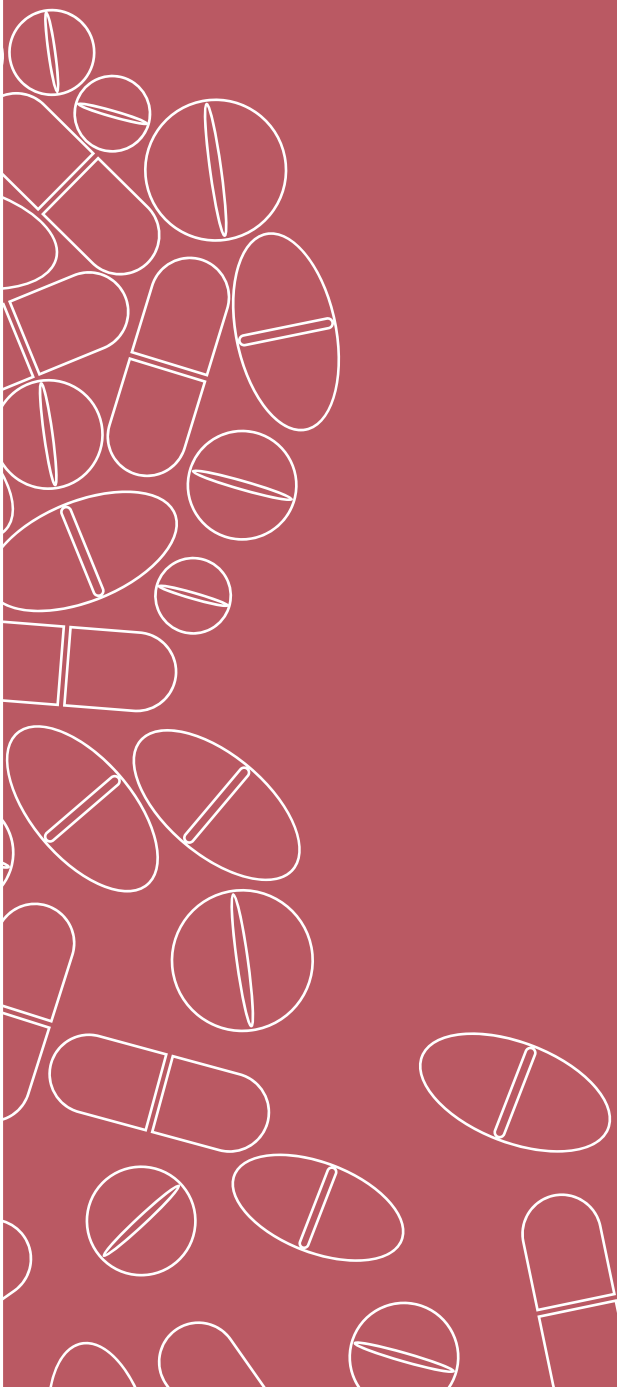
Summary



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Summary

An important challenge in the good prescribing of drugs for treatment or prevention of diseases is finding the suitable drug for the patient's problem. The risk-benefit ratio in patients with renal impairment might be different from other patient populations without renal impairment. In addition, knowledge about the clinical effects, both effectiveness and adverse drug reactions (ADRs), of drugs used in patients with renal impairment is not fully understood. Therefore, monitoring of the treatment will be even more important. As renal function fluctuates over time, the right drug and right drug dose should be reconsidered when the renal function changes substantially. Additional advices about monitoring specific variables or additional instructions for the patient to recognize ADRs timely might also be necessary. Finding the suitable drug in the right dose for the patient's problem and monitoring its effectiveness and adverse drug reactions (ADRs) over time, are defined as personalized drug therapy management (PDTM). This thesis focuses on PDTM in patients with renal impairment.

Over the past few years the focus on renal function and pharmacotherapy has increased. Studies showed that up to one third of the adverse drug reactions (ADRs) leading to hospital admission may be related to impaired renal function. After the introduction of the Modification of Diet in Renal Disease (MDRD) formula, which estimates the glomerular filtration rate (eGFR), the eGFR is reported by clinical laboratories whenever serum creatinine levels are ordered. This led to a better recognition of impaired renal function and therefore it became easier to follow the guidelines 'Drug dose advices in renal impairment' in daily clinical practice, in which drug dose advices are given categorically per renal function group. The application of these guidelines led to disagreement between pharmacists and physicians. Questions that physicians may ask were: "How strong is the evidence underlying the advice? What is the degree of the risk when my patient gets an inappropriate drug or drug dose?" These questions triggered that the evidence behind the guidelines was further examined. It appeared that the evidence was mainly based on case reports and pharmacokinetic studies in controlled environments. The lack of population-based studies and/or translation of evidence to the population seen in daily clinical practice became the domain of this thesis. This thesis aims to give insight in: (1) the validity of the MDRD formula used in prescribing drugs in renal impairment, (2) to add new evidence to evaluate existing guidelines, and (3) to give practical approaches for handling renally excreted drugs in patients with renal impairment.

The validity of the Modification of Diet in Renal Disease Formula

The MDRD formula is widely used in clinical practice to assess the correct drug dose. This formula is based on serum creatinine levels, which is a by-product of muscle catabolism. There is a clear inverse correlation between serum creatinine levels and the true GFR. However, there are several factors which may influence serum creatinine levels without affecting GFR itself, which potentially distorts the interpretation of values for clinical use. Although the serum creatinine-based formulas provide a better estimation of the true GFR than serum creatinine concentrations in the general population, these have been poorly validated in specific patient populations. Chronic diseases themselves or the effects of chronic diseases may influence serum creatinine levels. Inaccuracy in eGFRs might lead either to overestimation of renal function, leading to administration of inappropriately large doses and therefore possible toxicity, or, conversely, underestimation of renal function, leading to subtherapeutic dosing and therefore treatment failure, and prolonged illness.

Chapter 2 presents a systematic review of the validity of the MDRD formula in patients infected with human immunodeficiency virus (HIV) over the full eGFR range. Renal dysfunction is highly prevalent in HIV-infected patients and may require dose adjustment of renally excreted antiretroviral drugs. We conducted a systematic search in Pubmed and EMBASE to identify studies which compared the MDRD formula with measured glomerular filtration rate (mGFR) in HIV-infected patients. Five studies were included, which provided data from 464 HIV-infected patients. We concluded that the MDRD formula was as valid in HIV-positive as in HIV-negative patients with good renal function to mild renal impairment. More research is still needed to validate the MDRD formula in HIV-infected patients with moderate to severe renal impairment. The MDRD formula was developed in patients with chronic kidney disease (CKD) and was therefore by definition not properly tested in patients with normal renal function. For a broader systematic review in **Chapter 3** we therefore selected only patients with a(n) (e)GFR < 60 ml/min/1.73m^2. We examined the validity of the MDRD formula in the following specific patient populations: elderly, hospitalized and obese patients, patients with cardiovascular diseases, cancer, chronic respiratory diseases, diabetes mellitus, liver cirrhosis and human immunodeficiency virus (HIV). This selection was based on three general patient groups which were inadequately represented in the development of the MDRD formula, four common categories of chronic diseases, which are leading causes of death and other chronic diseases in which reduced muscle mass can be present. We searched for articles in Pubmed published from January 1999 through

January 2014. Other selection criteria we applied were a comparison of the MDRD formula with a gold standard, and statistical analysis focussed on bias, precision, and accuracy. A bias of 20% or less, a precision of 30% or less and an accuracy expressed as P_{30} of 80% or higher were indicators of the validity of the MDRD formula. In total we included 27 studies. The validity of the MDRD formula has not yet been tested properly in patients with cardiovascular diseases and chronic respiratory diseases. In obese patients, patients with cancer and HIV the validity of the MDRD formula has been insufficiently tested. For patients with diabetes mellitus and liver cirrhosis, hospitalized patients on the internal medicine and nephrology ward and elderly with moderate to severe renal impairment we concluded that the MDRD formula is not valid.

In conclusion, the use of the MDRD formula in different specific patient populations for the fine-tuning of drug therapy management is not without limitations. There is no hard evidence that the MDRD formula is valid in patients with several chronic diseases combined with renal impairment, and in some cases there is evidence that the MDRD formula is not valid.

New evidence to evaluate existing guidelines

In the second part of this thesis we looked closer to the research evidence underlying the drug treatment recommendations in guidelines. We were especially interested in the frequently prescribed drugs nitrofurantoin and metformin. Both drugs are the drug of choice when, respectively urinary tract infection (UTI) in women or diabetes mellitus type 2 are diagnosed, but both drugs are also contraindicated when renal function drops below a specific level. Are patients with renal impairment falsely withheld from a first choice drug? It became evident that the contraindication of these drugs in renal impairment was based on pharmacokinetic studies and case reports.

According to the drug label, nitrofurantoin is contraindicated when the eGFR is less than 60 ml/min, because of ineffectiveness and safety problems. In **Chapter 4** we present a cohort study in which we determined whether treatment with nitrofurantoin in women with UTI and renal impairment in primary care is associated with a higher risk of ineffectiveness and/or serious adverse events than in women without renal impairment. A cohort of 21,317 women treated with nitrofurantoin identified from the PHARMO Record Linkage System were analysed. Moderate renal impairment (30-50 ml/min/1.73m^2) was not associated with ineffective treatment, but the risk of pulmonary adverse events leading to hospitalization was significantly 4 times higher in patients with renal impairment (< 50 ml/min/1.73m^2).

For the study in **Chapter 5** about metformin we used the Clinical Practice Research Datalink (CPRD), in which the primary outcome lactic acidosis and plasma lactate levels of > 5 mmol/l could be identified. A cohort of 223,968 metformin users and 34,571 diabetic patients who had never used metformin (non-users), were identified. Compared to non-users, the risk of lactic acidosis or elevated lactate levels in current metformin users was six times higher in patient with a renal function < 60 ml/min/1.73m^2. This risk was further increased to 12 times in users with ≥ 730 g of metformin in the preceding year and in users with a recent high daily dose (> 2 g) of metformin. Our study is consistent with current recommendations that the renal function of metformin users should be adequately monitored and that the dose level of metformin should be adjusted if necessary.

Since measurement of renal function is not frequently performed in the ambulatory care setting, changes in renal function may remain unnoticed. Informal clinical observations in the hospital care setting suggest that the renal function may fluctuate so much that the renal function group and therefore the recommended dose, can change within a few days. The magnitude of the fluctuation and its potential effect on appropriate prescribing of medications, for example after discharge from the hospital, is unknown. **Chapter 6** presents a study protocol to describe these changes in eGFR in elderly patients 14 days and 2 months after discharge from hospital compared to the value at discharge. The first results showed that the proportion of patients in which a change occurred in renal function group is noteworthy, namely 39%. Further research is necessary to identify risk factors and the consequences for drug therapy management.

Both, retrospective cohort studies and prospective observational studies, are of added value for healthcare for the creation, adjustment or confirmation of recommendations for monitoring renal function and drug dose recommendations in patients with renal impairment.

Drug therapy management in patients with renal impairment in clinical practice

In the third and last section of this thesis, we focused on how the results of the previous sections can be applied in daily clinical practice. In **Chapter 7** we demonstrate that an advanced pharmacotherapy-related clinical decision support system (CDSS) may lead to more relevant alerts compared to a basic pharmacotherapy-related CDSS. The impact of adding laboratory values and other patient characteristics resulted in a significantly higher positive predictive value (PPV) for the advanced CDSS compared to the basic CDSS (23.3% versus 12.2%; $p < 0.05$). However, the number

of clinically irrelevant alerts remained high and continuous fine-tuning of these algorithms is necessary. Alerts related to recommendations in patients with renal impairment were not calculated separately, but the increase in PPV for the advanced CDSS was at least partly due to algorithms using renal function as laboratory value. In conclusion, CDSSs may be helpful in the implementation of guidelines, such as 'Drug dose advices in renal impairment'.

In view of the uncertainties surrounding the prescribing of drugs in patients with renal impairment we give practical guidance in **Chapter 8** on how to cope with these uncertainties in daily clinical practice. Before starting a renally excreted drug an equally effective drug which can be used more safely in patients with renal impairment should be considered. If a renally excreted drug is needed the reliability of the eGFR should be assessed and when necessary a 24-h urine creatinine clearance collection should be performed. After achieving the best approximation of the true GFR, we suggest a gradual drug dose adaptation according to renal function instead of using renal function groups. For drugs with a narrow therapeutic window (NTW) we recommend a more careful approach. For practical purposes a therapeutic window of 5 or less was defined as a NTW and a list of NTW-drugs is presented. Considerations about the drug dose may be different at the start of the therapy or during the therapy and depending on the indication. Considerations include the rate at which the intended therapeutic effect has to be achieved, the risk of therapeutic failure with a subtherapeutic dose, and the risk of toxicity in case the dose is too high. Monitoring effectiveness and adverse drug reactions are important, especially for NTW-drugs.

Dose adjustment of a drug, suggested by a CDSS or not, should be based on an ongoing assessment of clinical status and risk versus the benefit of the used regimen for the patient with (or without) renal impairment.

Discussion and conclusion

Finally, the results of the studies are summarized and put into a broader perspective in **Chapter 9**. Three topics are addressed: (1) complexity of renal function in drug dosing, (2) application of the guidelines 'Drug dose advices in renal impairment', and (3) implications for clinical practice and future research.

Our systematic reviews showed that the MDRD formula is not valid in diverse patient populations. Newer formulas, such as the Chronic Kidney Disease EPIdemiology Collaboration (CKD-EPI) formulas, are not expected to perform better than the MDRD formula as long as they are serum creatinine-based. The CG

formula has historically been the method applied to determine drug dose regimens in patients with renal impairment. We discussed the differences between the CG and MDRD formula and concluded that there is little evidence on the clinical relevance of the differences for most of the drugs. The fact that renal impairment not only alters the renal excretion of unchanged drug and/or their metabolites, but it can also lead to modifications in plasma protein binding, distribution, transport and biotransformation of drug substances, makes it even more complicated. Integrated pharmacokinetic/pharmacodynamic studies are needed to evaluate the necessity of drug therapy adjustment in patients with renal impairment. For older drugs cohort studies as published in this thesis might be useful to confirm current recommendations, which are mainly based on case reports and/or pharmacokinetic studies. In daily clinical practice clinicians are confronted with patients with multiple comorbidities, such as renal impairment, using multiple drugs. Therefore the best strategy is to avoid potentially nephrotoxic drugs and renally excreted drugs whenever possible.

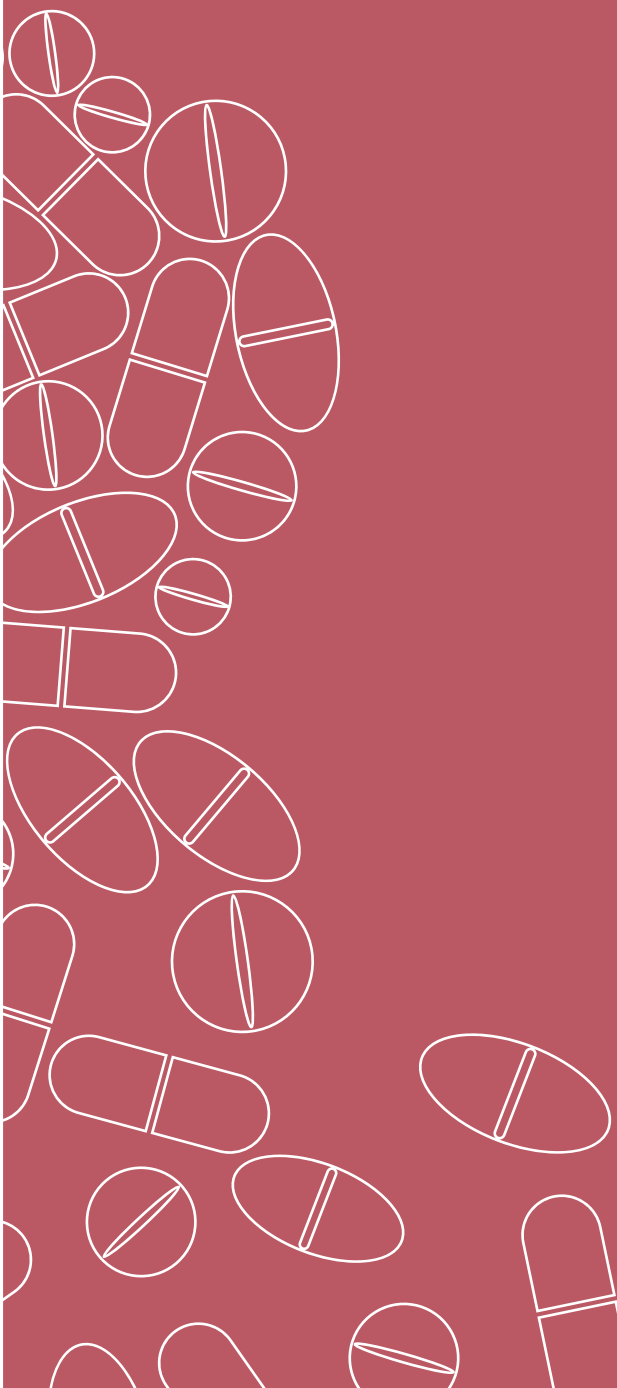
For the application of the guidelines 'Drug dose advices in renal impairment' we discussed technical support to identify patients at risk and the role of the pharmacist in PDTM. CDSSs link patient characteristics with medical knowledge to generate recommendations. In daily clinical practice alerts are often overridden by physicians and in half of the cases advices from CDSSs are ignored or not followed for several reasons. Due to increased numbers of guidelines and standards and the growing empowerment of patients, good prescribing of drugs cannot rely on physicians solely. Pharmacists can play an important role in suggesting a preferred drug in patients with renal impairment, handling specific medication alerts, coordinating measurements to assess effectiveness and/or ADRs, and evaluate effectiveness and/or ADRs by contacting the patient. Pharmacists can thus contribute to the safe, effective, and efficient use of drugs, particularly when caring for people with multiple chronic conditions where multiple clinicians are involved.

More research is needed to identify variables or situations in which the currently known serum creatinine-based formulas should not be used for drug dosing. We suggested a gradual drug dose adaptation instead of categorical. The clinical relevance of this approach is of interest for future research. A broad approach on how to apply PDTM in complex patients with renal impairment, including the added value of pharmacists described in the general discussion, should also be subject for future research.

In conclusion, the results of the studies presented in this thesis demonstrate the

complexity of PDTM in patients with renal impairment. The MDRD formula appeared not to be valid or the validity was unclear in diverse patient populations. Cohort studies appeared to be useful in confirming guidelines concerning drug therapy management in renal impairment. We discussed how serum creatinine-based formulas can be handled in daily clinical practice, despite their uncertainties. CDSSs may be supportive in the application of all the available knowledge. Pharmacists can play an important role in improving PDTM by monitoring effectiveness and/or ADRs and coordinating the measurements of laboratory values whenever necessary.

Samenvatting



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Samenvatting

Het vinden van een geschikt geneesmiddel is gegeven de diagnose van de patiënt een belangrijke uitdaging bij het voorschrijven van geneesmiddelen. De risico-batenverhouding bij een patiënt met een verminderde nierfunctie is soms anders dan bij de patiëntenpopulatie zonder verminderde nierfunctie. Bovendien is de kennis over de klinische effecten, zowel de effectiviteit als de bijwerkingen, van geneesmiddelen bij patiënten met een verminderde nierfunctie niet volledig bekend. Daarom is het monitoren van de behandeling belangrijk. De nierfunctie fluctueert in de loop van de tijd. Het juiste geneesmiddel en de juiste dosering zouden heroverwogen moeten worden zodra de nierfunctie substantieel verandert. Daarnaast zijn adviezen over het monitoren van specifieke variabelen of aanvullende instructies aan de patiënt om bijwerkingen tijdig te herkennen wenselijk. Het vinden van het juiste geneesmiddel in de juiste dosering passend bij de diagnose van de patiënt en het monitoren van het effect en de bijwerkingen in de tijd is gedefinieerd als geïndividualiseerde medicamenteuze therapie management (GMTM). Dit proefschrift gaat over GMTM bij patiënten met een verminderde nierfunctie.

In de afgelopen paar jaar is de aandacht voor farmacotherapie in relatie tot de nierfunctie gegroeid. Onderzoeken laten zien dat tot één derde van de bijwerkingen, welke hebben geleid tot een ziekenhuisopname, mogelijk waren gerelateerd aan een verminderde nierfunctie. Na de introductie van de Modification of Diet in Renal Disease (MDRD) formule, welke een schatting geeft van de glomerulaire filtratie snelheid (eGFS), rapporteren klinisch chemische laboratoria de eGFS zodra een serumkreatinine bepaling wordt aangevraagd. Dit heeft geleid tot een betere herkenning van een verminderde nierfunctie en daarmee is het ook makkelijker geworden om de richtlijnen 'Doseringsadviezen voor geneesmiddelen bij een verminderde nierfunctie' toe te passen in de dagelijkse klinische praktijk. In deze richtlijnen worden doseringsadviezen categorisch per nierfunctiegroep weergegeven. Het toepassen van deze richtlijnen leidde echter tot onenigheid tussen de apotheker en de arts. Vragen die artsen stelden waren: "Hoe sterk is het wetenschappelijk bewijs achter dit advies? Wat is de grootte van het risico wanneer mijn patiënt een onjuist geneesmiddel of een onjuiste dosering krijgt?" Deze vragen hebben geleid tot het nader bestuderen van het wetenschappelijk bewijs waarop de richtlijnen zijn gebaseerd. Het bleek dat het bewijs hoofdzakelijk bestond uit case reports en farmacokinetische studies in een gecontroleerde omgeving. Het ontbreken van onderzoeken gebaseerd op patiëntenpopulaties en/of de vertaling van de resultaten naar deze patiëntenpopulaties, welke gezien worden in de dagelijkse praktijk, is de basis van dit proefschrift. Dit proefschrift heeft als doel om inzicht te geven in: (1)

de validiteit van de MDRD formule welke wordt toegepast bij het voorschrijven van geneesmiddelen aan patiënten met een verminderde nierfunctie, (2) de meerwaarde van nieuw wetenschappelijk bewijs om bestaande richtlijnen te evalueren en (3) praktische handvaten voor het omgaan met renaal geklaarde geneesmiddelen bij patiënten met een verminderde nierfunctie.

De validiteit van de Modification of Diet in Renal Disease formule

De MDRD formule wordt wereldwijd gebruikt in de klinische praktijk om de juiste geneesmiddeldosering vast te stellen. Deze formule is gebaseerd op serumkreatinine, wat een bijproduct is van spierafbraak. Er is een duidelijke omgekeerde correlatie tussen de serumkreatinine en de ware GFS. Er zijn echter verschillende factoren welke de uitslag van de serumkreatininebepaling mogelijk kunnen beïnvloeden zonder dat het effect heeft op de GFS zelf. Dit kan potentieel leiden tot verkeerde interpretatie bij de klinische toepassing van de eGFS. Ondanks dat de formules, welke zijn gebaseerd op serumkreatininewaarden, een betere schatting geven van de werkelijke GFS dan de serumkreatininewaarde zelf in de algemene populatie, zijn deze formules onvoldoende gevalideerd in specifieke patiëntenpopulaties. Chronische ziekten zelf of de effecten daarvan zijn mogelijk van invloed op de serumkreatininewaarde. Onnauwkeurigheid in de eGFS kan mogelijk leiden tot enerzijds een overschatting van de nierfunctie, resulterend in het geven van onjuiste hoge doseringen en daarmee mogelijk toxiciteit, of anderzijds tot een onderschatting van de nierfunctie, resulterend tot subtherapeutische doseringen en daarmee mogelijk het falen van de behandeling en verlenging van de ziekteduur.

Hoofdstuk 2 presenteert een systematisch literatuuroverzicht over de validiteit van de MDRD formule in patiënten met het human immunodeficiency virus (HIV) over het hele bereik van de eGFS. Nierfunctiestoornissen komen vaak voor bij HIV-patiënten en kunnen leiden tot dosisaanpassingen van antiretrovirale geneesmiddelen welke renaal worden uitgescheiden. We voerden een systematische zoekopdracht uit in Pubmed en EMBASE naar onderzoeken waarin de MDRD formule vergeleken werd met een gemeten GFS (mGFS) in HIV-patiënten. Vijf onderzoeken werden geïncludeerd, welke data bevatten van 464 HIV-patiënten. We concludeerden dat de MDRD formule net zo valide was voor HIV-positieve als voor HIV-negatieve patiënten met een goede tot licht verminderde nierfunctie. Meer onderzoek is nodig om de MDRD formule te valideren in HIV-patiënten met matige tot ernstige verminderde nierfunctie.

De MDRD formule is ontwikkeld in patiënten met een chronische nierinsufficiëntie (CNI) en was daarmee per definitie niet getest in patiënten met een goede nierfunctie.

In **hoofdstuk 3** selecteerden we voor een bredere systematische zoekopdracht alleen patiënten met een (e)GFS < 60 ml/min/(1.73m^2). We bestudeerden de validiteit van de MDRD formule in de volgende specifieke patiëntenpopulaties: ouderen, patiënten opgenomen in een ziekenhuis, patiënten met obesitas, cardiovasculaire ziekten, kanker, chronische longziekten, diabetes mellitus, levercirrose en HIV. Deze selectie was gebaseerd op drie algemene patiëntgroepen welke onvoldoende vertegenwoordigd waren bij de ontwikkeling van de MDRD formule, vier veel voorkomende categorieën van chronische ziekten, welke wereldwijd de belangrijkste doodsoorzaken zijn, en andere chronische ziekten waarbij er sprake kan zijn van verminderde spiermassa. We zochten in Pubmed naar studies welke gepubliceerd waren vanaf januari 1999 tot januari 2014. Andere selectiecriteria waren een vergelijking van de MDRD formule met een gouden standaard en een statistische analyse gebaseerd op bias, precisie en accuraatheid. Een bias van 20% of minder, een precisie van 30% of minder en een accuraatheid uitgedrukt als P_{30} van 80% of hoger waren indicatoren voor de validiteit van de MDRD formule. In totaal includeerden we 27 studies. De validiteit van de MDRD formule bleek nog niet goed getest in patiënten met cardiovasculaire ziekten en chronische longziekten. Voor patiënten met obesitas, kanker en HIV bleek de validiteit van de MDRD formule wel getest, maar onvoldoende goed om een uitspraak te kunnen doen. Voor patiënten met diabetes mellitus en levercirrose, patiënten opgenomen op de afdeling interne geneeskunde of nefrologie en ouderen met matige tot ernstige verminderde nierfunctie concludeerden we dat de MDRD formule niet valide is.

Samenvattend, het gebruik van de MDRD formule in verschillende specifieke patiëntenpopulaties voor het verfijnen van de medicamenteuze therapie is niet zonder beperkingen. Er is geen hard wetenschappelijk bewijs dat de MDRD formule valide is in patiënten met verschillende chronische ziekten en een verminderde nierfunctie. In sommige gevallen is er bewijs dat de MDRD formule niet valide is.

Nieuw bewijs voor het evalueren van bestaande richtlijnen

In het tweede gedeelte van dit proefschrift hebben we de onderzoeken welke ten grondslag liggen aan de medicamenteuze behandeladviezen in de richtlijnen nader bekeken. We waren in het bijzonder geïnteresseerd in de frequent voorgeschreven geneesmiddelen nitrofurantoïne en metformine. Beide geneesmiddelen zijn eerste keus wanneer respectievelijk een urineweginfectie (UWI) of diabetes mellitus type 2 worden gediagnosticeerd, maar beide geneesmiddelen zijn ook gecontraïndiceerd wanneer de nierfunctie onder een bepaalde waarde komt. Krijgen patiënten met een verminderde nierfunctie onterecht een eerste keus geneesmiddel niet? Uit nader

onderzoek bleek dat het gecontraïndiceerd zijn van deze geneesmiddelen bij een verminderde nierfunctie was gebaseerd op farmacokinetische studies en case reports.

Volgens de bijsluiter is nitrofurantoïne gecontraïndiceerd wanneer de eGFS < 60 ml/min is vanwege mogelijke ineffectiviteit en veiligheidsproblemen. In **hoofdstuk 4** presenteren we een cohortstudie waarin we bekeken of de behandeling met nitrofurantoïne bij vrouwen met een UWI in de eerste lijn én een verminderde nierfunctie geassocieerd is met een hoger risico op ineffectiviteit en/of het optreden van bijwerkingen in vergelijking met vrouwen met een UWI zonder verminderde nierfunctie. Uit de PHARMO Record Linkage System was een cohort met 21.317 vrouwen, die behandeld zijn met nitrofurantoïne, geïdentificeerd en geanalyseerd. Een matige verminderde nierfunctie (30-50 ml/min/1.73m^2) was niet geassocieerd met een ineffectieve behandeling, maar het risico op pulmonaire bijwerkingen leidend tot een ziekenhuisopname was significant 4 keer hoger bij patiënten met een verminderde nierfunctie (< 50 ml/min/1.73m^2).

Voor de studie over metformine in **hoofdstuk 5** gebruikten we de Clinical Practice Research Datalink (CPRD) met als primaire uitkomstmaat lactaatacidose en plasma lactaat spiegels van > 5 mmol/l. Een cohort van 223.968 metformine gebruikers en 34.571 diabetespatiënten die nog nooit metformine hadden gebruikt (niet-gebruikers) werden geïdentificeerd. Vergeleken met niet-gebruikers was het risico op lactaatacidose of verhoogde lactaat spiegel in huidige metformine gebruikers met een nierfunctie < 60 ml/min/1.73m^2 6 keer hoger. Het risico nam verder toe tot 12 keer in gebruikers met ≥ 730 g metformine in het voorgaande jaar en in gebruikers met een recent hoge dagdosering metformine (> 2 g). De resultaten van ons onderzoek komen overeen met de huidige aanbevelingen dat de nierfunctie van metformine gebruikers adequaat moet worden gecontroleerd en dat de metformine dosering wanneer nodig moet worden aangepast.

In de ambulante zorg wordt de nierfunctie niet frequent gemeten, waardoor veranderingen onopgemerkt kunnen blijven. Informele klinische observatie in het ziekenhuis suggereerde dat de nierfunctie mogelijk in die mate kan fluctueren dat de nierfunctiegroep en daarmee de aanbevolen dosering binnen een paar dagen kan veranderen. De grootte van de fluctuatie en het potentiële effect op het juist voorschrijven van geneesmiddelen, bijvoorbeeld na ontslag, is onbekend. **Hoofdstuk 6** presenteert een studieprotocol om deze veranderingen in de eGFS bij oudere patiënten 14 dagen en 2 maanden na ontslag uit het ziekenhuis in kaart te brengen en te vergelijken met de nierfunctie bij ontslag. De eerste resultaten laten zien dat het aantal patiënten waarbij een verandering op trad in de nierfunctiegroep

noemenswaardig was, namelijk 39%. Vervolgonderzoek is nodig om risicofactoren te identificeren en uit te zoeken wat de consequenties zijn voor medicamenteuze therapie management.

Retrospectieve cohortstudies en prospectieve observationele studies zijn beiden van toegevoegde waarde voor de gezondheidszorg ten aanzien van het ontwikkelen, aanpassen of bevestigen van aanbevelingen voor de monitoring van de nierfunctie en doseringsadviezen bij patiënten met een verminderde nierfunctie.

Medicamenteuze therapie management bij patiënten met een verminderde nierfunctie in de klinische praktijk

In het derde en laatste deel van dit proefschrift, leggen we de nadruk op hoe de resultaten van de eerdere delen kunnen worden toegepast in de dagelijkse klinische praktijk. In **hoofdstuk 7** laten we zien dat een geavanceerd medicatiebewakingssysteem (MBS) mogelijk leidt tot meer relevante medicatiebewakingssignalen in vergelijking met een eenvoudig MBS. De impact van het toevoegen van laboratoriumwaarden en andere patiëntenkarakteristieken resulteerden in een significant hogere positief voorspellende waarde (PVW) voor het geavanceerde MBS in vergelijking met het eenvoudige MBS (23.3% versus 12.2%; $p < 0.05$). Echter bleef het aantal klinisch niet-relevante medicatiebewakingssignalen hoog en continue verfijning van deze algoritmen is daarom nodig. Er is geen subanalyse uitgevoerd voor de medicatiebewakingssignalen met betrekking tot aanbevelingen voor patiënten met een verminderde nierfunctie. Echter, de toename in PVW voor het geavanceerde MBS was tenminste gedeeltelijk toe te schrijven aan de algoritmen waarin de nierfunctie als laboratoriumwaarde werd gebruikt. Concluderend, MBSen kunnen ondersteunend zijn bij het implementeren van richtlijnen zoals 'Doseringsadviezen voor geneesmiddelen bij een verminderde nierfunctie'.

In het licht van de onzekerheden rondom het voorschrijven van geneesmiddelen aan patiënten met een verminderde nierfunctie geven we in **hoofdstuk 8** praktische handvaten hoe om te gaan met deze onzekerheden in de dagelijkse klinische praktijk. Voordat een renaal uitgescheiden geneesmiddel wordt gestart, dient een gelijkwaardig geneesmiddel, welke veiliger is voor patiënten met een verminderde nierfunctie, te worden overwogen. Wanneer een renaal uitgescheiden geneesmiddel toch nodig is, dient de betrouwbaarheid van de eGFS te worden vastgesteld en wanneer nodig een 24-uurs urine te worden verzameld voor de bepaling van een kreatinineklaring. Na het vaststellen van de beste schatting van de werkelijke GFS, stellen we een graduele dosisaanpassing voor op basis van de nierfunctie in plaats van het gebruik van nierfunctiegroepen. Voor geneesmiddelen met een nauwe

therapeutische breedte (NTB) wordt een voorzichtige aanpak aanbevolen. Voor praktische doeleinden was een therapeutische breedte van 5 of minder gedefinieerd als NTB en een lijst met NTB-geneesmiddelen is gepresenteerd. Overwegingen bij het bepalen van de geneesmiddeldosering is mogelijk anders aan het begin van de therapie dan tijdens de therapie en afhankelijk van de indicatie. Overwegingen bestaan uit de snelheid waarmee het beoogde therapeutische effect moet worden bereikt, de risico's van therapeutisch falen bij een te lage dosering en de risico's op toxiciteit bij een te hoge dosering. Het monitoren van effectiviteit en bijwerkingen zijn belangrijk, vooral bij NTB-geneesmiddelen.

Dosisaanpassingen van een geneesmiddel, voorgesteld door een MBS of niet, zouden gebaseerd moeten zijn op een continue beoordeling van de klinische status van de patiënt en het continu afwegen van het risico versus de baten van het gekozen behandelplan bij patiënten met (of zonder) een verminderde nierfunctie.

Discussie en conclusie

De resultaten van de onderzoeken zijn samengevat en in een breder perspectief geplaatst in **hoofdstuk 9**. Er worden drie onderwerpen behandeld: (1) de complexiteit van de nierfunctie bij het doseren van geneesmiddelen, (2) toepassing van de richtlijnen 'Doseringsadviezen voor geneesmiddelen bij een verminderde nierfunctie' en (3) gevolgen voor de klinische praktijk en toekomstig onderzoek.

Onze systematische literatuuronderzoeken lieten zien dat de MDRD formule niet valide is in diverse patiëntenpopulaties. Van nieuwere formules, zoals de Chronic Kidney Disease EPIdemiology Collaboration (CKD-EPI) formules, wordt niet verwacht dat ze beter zijn dan de MDRD formule zolang ze gebaseerd zijn op serumkreatininewaarden. Historisch gezien, is de CG formule de methode om de geneesmiddeldosering vast te stellen bij patiënten met een verminderde nierfunctie. We bediscussieerden de verschillen tussen de CG en MDRD formule en concludeerden dat er voor het merendeel van de geneesmiddelen weinig wetenschappelijk bewijs is over de klinische relevantie van de verschillen. Het feit dat een verminderde nierfunctie niet alleen de uitscheiding van geneesmiddelen en/of hun metabolieten verandert, maar ook kan leiden tot veranderingen in binding aan plasmaproteïne, distributie, transport en biotransformatie van geneesmiddelen, maakt het geheel nog complexer. Geïntegreerde farmacokinetische/farmacodynamische studies zijn nodig om het aanpassen van de medicamenteuze therapie bij patiënten met een verminderde nierfunctie te evalueren. Voor oudere geneesmiddelen kunnen cohortstudies, zoals gepresenteerd in dit proefschrift, nuttig zijn om huidige aanbevelingen, welke grotendeels gebaseerd zijn op case reports en/of farmacokinetische studies,

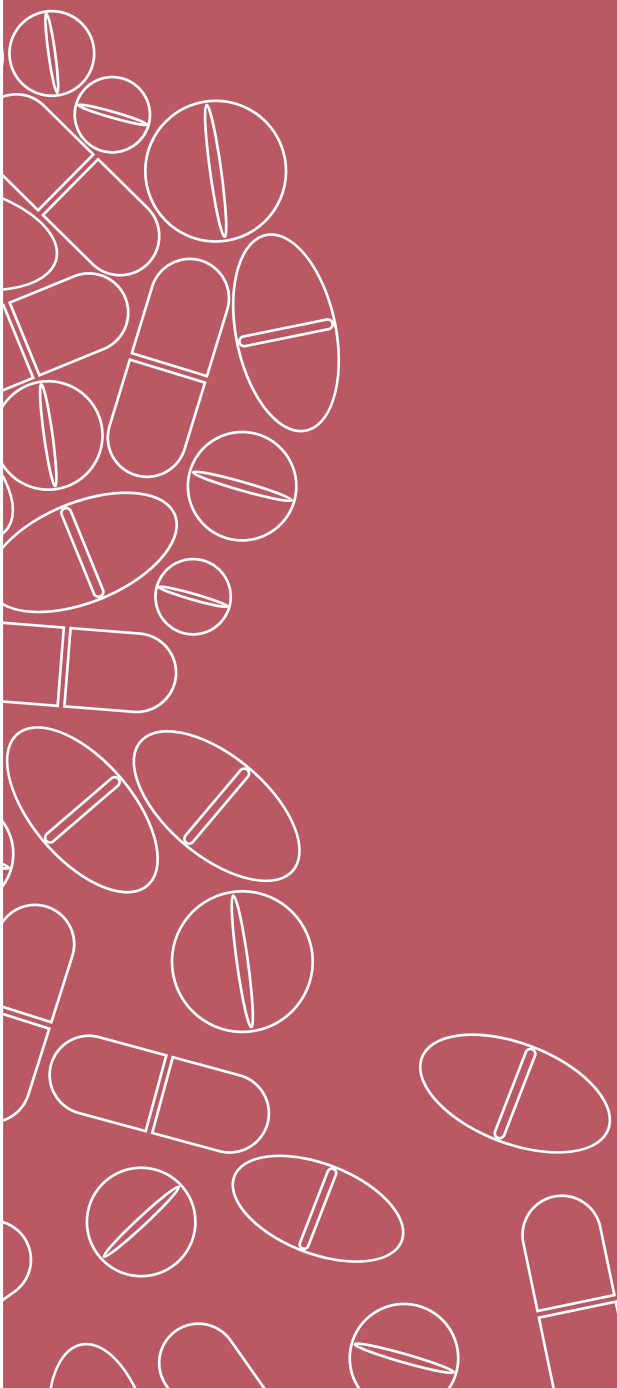
te onderbouwen. In de dagelijkse klinische praktijk worden artsen en apothekers geconfronteerd met patiënten met meerdere co-morbiditeiten, zoals een verminderde nierfunctie, en het gebruik van meerdere geneesmiddelen. De beste strategie is daarom om potentieel nefrotoxische geneesmiddelen en renaal geklaarde geneesmiddelen zoveel als mogelijk te vermijden.

Voor de toepassing van de richtlijnen 'Doseringsadviezen voor geneesmiddelen bij een verminderde nierfunctie' bediscussieerden we de mogelijkheid van technische ondersteuning om risicopatiënten te identificeren en de rol van de apotheker in GMTM. MBSen kunnen patiëntenkarakteristieken combineren met medische kennis om aanbevelingen te genereren. In de dagelijkse klinische praktijk worden deze medicatiebewakingssignalen vaak overschreven door artsen waarvan in de helft van de gevallen adviezen van MBSen worden genegeerd of niet opgevolgd om verschillende redenen. Vanwege het toenemende aantal richtlijnen en standaarden en toenemende patiëntparticipatie kan het correct voorschrijven van geneesmiddelen niet alleen bij de artsen liggen. Apothekers kunnen een belangrijke rol spelen in het adviseren van een voorkeursgeneesmiddel voor patiënten met een verminderde nierfunctie, het afhandelen van specifieke medicatiebewakingssignalen, het coördineren van bepalingen om de effectiviteit en/of bijwerkingen vast te stellen, en het evalueren van de effectiviteit en/of bijwerkingen door in gesprek te gaan met de patiënt. Apothekers kunnen dus een bijdrage leveren aan veilig, effectief en efficiënt geneesmiddelengebruik, juist wanneer het mensen met meerdere chronische ziekten betreft waar meerdere artsen bij betrokken zijn. Meer onderzoek is nodig om factoren of situaties te identificeren waarin de huidige formules gebaseerd op serumkreatinine niet gebruikt zouden moeten worden bij het doseren van geneesmiddelen bij een verminderde nierfunctie. We stelden voor om de geneesmiddeldosering gradueel aan te passen in plaats van categorisch. Een brede aanpak over hoe GMTM toe te passen bij complexe patiënten met een verminderde nierfunctie, waaronder ook de toegevoegde waarde van apothekers zoals beschreven in **hoofdstuk 9**, zou ook onderwerp moeten zijn voor toekomstig onderzoek.

Samenvattend, de resultaten van de onderzoeken gepresenteerd in dit proefschrift laten de complexiteit zien van GMTM bij patiënten met een verminderde nierfunctie. De MDRD formule bleek niet valide of de validiteit was onduidelijk in diverse patiëntenpopulaties. Cohort onderzoeken bleken toepasbaar om richtlijnen over medicamenteuze therapie management bij verminderde nierfunctie te bevestigen. We bediscussieerden hoe formules gebaseerd op serumkreatinine toch gebruikt kunnen worden in de dagelijkse klinische praktijk ondanks de onzekerheden. MBSen zouden ondersteuning kunnen bieden in het toepassen van alle beschikbare

kennis. Apothekers kunnen een belangrijke rol spelen in het verbeteren van GMTM door de effectiviteit en/of bijwerkingen van geneesmiddelen te monitoren en door bepalingen van laboratoriumwaarden te coördineren als dat nodig is.

Dankwoord



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Dankwoord

Trots is het gevoel dat overheerst nu het proefschrift af is.

Zoals elke promovendus kende ook ik mijn pieken en dalen. Na twee jaar tijd te hebben geïnvesteerd in het onderwerp 'clinical rules' switchten we naar de nierfunctie. Dit is niet een onderwerp waar mijn hart ligt. Toch won de nieuwsgierigheid naar de antwoorden op de vragen die gesteld zijn in dit proefschrift. Zonder enthousiasme van het promotieteam, interesse en steun van iedereen om me heen was dit proefschrift er niet geweest. Ik heb met veel verschillende mensen samen mogen werken, zowel wat betreft expertises als persoonlijkheden. Dit heeft mijn kennis verrijkt, maar bovenal maakten de onderlinge interacties dit promotietraject kleurrijk. Daarom een woord van dank aan iedereen die dit proefschrift mede mogelijk heeft gemaakt.

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Beste Jeroen, jij voegde je iets later bij het promotieteam toen onze wegen elkaar kruisten bij ZANOB. Enthousiast begonnen we aan het onderzoek over clinical rules. Ook jouw hart ligt niet bij fundamenteel onderzoek over validiteit van nierfunctie formules, maar door je contacten met de Universiteit Utrecht hebben we twee mooie epidemiologische onderzoeken kunnen doen, waar we allebei blij van werden. Bedankt voor je adviezen, tips en steun tijdens het traject.

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Het is des Willemijns om de mensen die me het meest na staan op eigen wijze te bedanken. Ik heb jullie lief!

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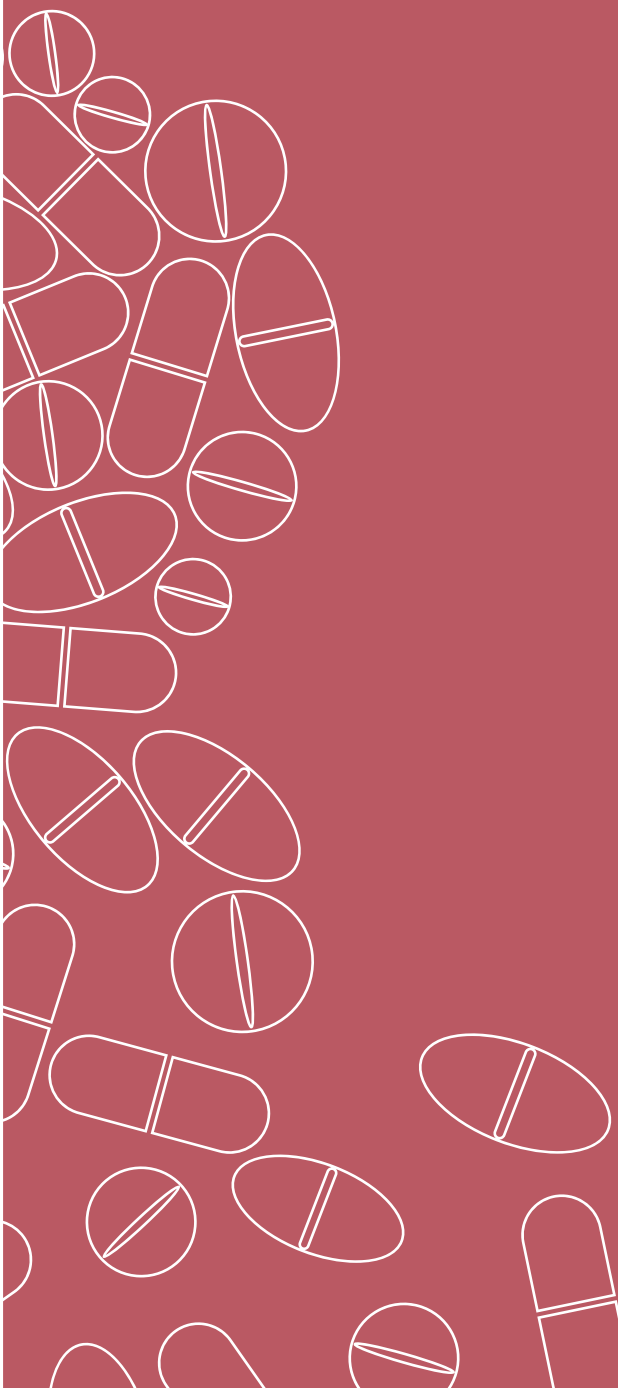

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She started to work as a pharmacist at the pharmacy of Symfora Group in Amersfoort. This was followed by voluntary work at Hermano Pedro Hospital in Antigua, Guatemala in 2004. After that she worked at the department of Clinical Pharmacy of the St. Antonius Hospital in Nieuwegein for 5 months. In April 2005 she started working as a pharmacist at ZANOB (former: Ziekenhuisapotheek Noordoost-Brabant) in 's-Hertogenbosch. In 2006 she started a traineeship to become a hospital pharmacist at the same organisation. From 2009 she combined this traineeship with the PhD research described in this thesis in affiliation with the department Scientific Institute for Quality of Healthcare (IQ healthcare), Radboud University Medical Center, Nijmegen. In December 2010 she was registered as a hospital pharmacist. After that she combined working as a hospital pharmacist at ZANOB with the PhD research at IQ healthcare. In August 2013 she travelled around the world. After that she worked as a hospital pharmacist at the hospital pharmacy of Slingeland Hospital in Doetinchem followed by working at Brocacef Ziekenhuisfarmacie in Oostrum in 2014.

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