# DRUG DOSING IN PATIENTS WITH RENAL IMPAIRMENT

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## Abstract

Inappropriate prescribing (IP) is common in patients with poor renal function in hospital and in outpatient settings. The extent of IP among patients with impaired renal function varies between countries and medical specialities. The aim of this study was to assess the prevalence of IP in a 400-bed acute care hospital and to identify drug classes which are inappropriately prescribed.

This study was divided into three main stages. The initial stage was a comparison of medication dosing regimens for chronic kidney disease in medication information sources (British National Formulary [BNF], The Renal Drug Handbook [RDH], UpToDate® [UTD]), which was followed by the development of a medication dosage adjustment guideline for the hospital. The third stage of the study was a retrospective descriptive study that included patients 18 years and older admitted to East Tallinn Central Hospital (ETCH), in Estonia, for more than 24 hours with documented estimated glomerular filtration rates (eGFR) less than 60 ml/min/1.73m$^2$. Patients were selected using stratified random sampling. Medication data and eGFR was collected from electronic health records.

The level of agreement for medication dosage adjustments according to renal function between the three sources was less than 50% (46.5%, 44.1%, and 39.6% for BNF, RDH, and UTD, respectively) from 202 recommendations for 71 medications. The guideline developed for the hospital consisted of 54 medications. For the assessment of IP, the study included 399 patients (63% female; 37% male) with an average age of 79 (range 42-99) years. At least one inappropriate prescription was present for 236 (59.1%) patients and 90 patients (38.1%) received ≥3 inappropriately prescribed medications.

The prevalence of IP according to eGFR was 32.0% (n=790) with 15% of the prescriptions (n=115) contraindicated in patients with renal impairment. Anticoagulants (n=261, 43.6%) were the most inappropriately prescribed class of medication followed by analgesics (n=85, 33.9%) and antihyperglycemic agents (n=55, 39.6%). Male gender, diabetes, venous thromboembolism, acute kidney injury, length of hospitalisation and surgery performed during hospitalisation were considered to be predictors of IP.

The results of the study provide insight for prescribing in patients with renal impairment in hospital settings. IP was a frequent problem among patients with impaired renal function at ETCH. Patients with renal impairment could benefit from a medication dosage adjustment guideline.

**Keywords:**

Inappropriate prescribing; medication information; guideline; renal function estimation; renal dosage adjustment; patient safety

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# List of Abbreviations

| | |
|---|---|
| absGFR | Absolute glomerular filtration rate |
| ABW | Actual body weight |
| ACEi | Angiotensin-converting enzyme inhibitors |
| ADEs | Adverse drug events |
| adjBW | Adjusted body weight |
| AF | Atrial fibrillation |
| AKI | Acute kidney injury |
| ARBs | Angiotensin II receptor blockers |
| BMI | Body mass index |
| BNF | British National Formulary |
| BSA | Body surface area |
| CDSS | Clinical decision support system |
| CG | Cockcroft-Gault |
| CI | Confidence interval |
| CKD | Chronic kidney disease |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CPOE | Computerised physician order entry |
| CrCl | Creatinine clearance |
| Cys | Cystatin C |
| DOACs | Direct oral anticoagulants |
| eCrCl | Estimated creatinine clearance |
| eGFR | Estimated glomerular filtration rate |
| EMA | European Medicines Agency |

| | |
|---|---|
| ETCH | East Tallinn Central Hospital |
| FDA | Food and Drug Administration |
| GFR | Glomerular filtration rate |
| IBW | Ideal body weight |
| ICD-10 | International Statistical Classification of Diseases and Related Health Problems 10$^{th}$ Revision |
| ICU | Intensive care unit |
| IQR | Interquartile range |
| IP | Inappropriate prescribing |
| IT | Informational technology |
| HF | Heart failure |
| KDIGO | Kidney Disease: Improving Global Outcomes |
| LBW | Lean body weight |
| LOS | Length of hospital stay |
| LMWH | Low molecular weight heparin |
| mCrCl | Measured creatinine clearance |
| MDRD | Modification of Diet in Renal Disease Study |
| mGFR | Measured glomerular filtration rate |
| MI | Myocardial infarction |
| NSAIDs | Nonsteroidal anti-inflammatory drugs |
| OR | Odds ratio |
| RDH | The Renal Drug Handbook |
| SCr | Serum creatinine |
| SD | Standard deviation |
| SPC | Summary of product characteristics |

| | |
|---|---|
| TBW | Total body weight |
| TMREC | Tallinn Medical Research Ethics Committee |
| UK | United Kingdom |
| USA | United States of America |
| UTD | UpToDate® |
| VTE | Venous thromboembolism |
| WHO | World Health Organization |

# Chapter 1

# Introduction

## 1.1 Background

With an ageing population the increase in the incidence of chronic conditions and in polypharmacotherapy is common. Age, comorbidities, and polypharmacotherapy are considered as risk factors for inappropriate prescribing (IP) including IP in patients with decreased renal function. Reasons why the extent of IP is high in patients with decreased renal function are due to the difference in the renal function estimation equations used; the effect of underlying factors, such as obesity, on renal function assessment; and discordance between medication information sources.

## 1.2 Inappropriate Prescribing

In 2017 the World Health Organization (WHO) published the third Global Patient Safety Challenge with a focus on medication safety, including IP (WHO, 2017). The report stressed the importance of avoiding medication errors and supporting standardisation of procedures for appropriate prescribing in high-risk situations, such as in the hospital setting or for the elderly, in order to improve patient outcome (WHO, 2017).

For the elderly validated and standardised criteria, such as Beers List, have been developed to guide medication management, but for the patients with renal impairment no such validated criteria exist (AGS Beers Criteria® Update Expert Panel, 2019). There are guidelines which suggest avoiding or adjusting dosages of certain medications, but none are solely supported by nephrology societies or kidney disease associations in Europe and in the United States of America (USA) (Ashley and Dunleavey, 2018; Joint Formulary Committee, 2018).

In the context of impaired renal function IP can be defined as misuse of medication including inappropriately high dosages in relation to renal function, incorrect frequency and/or duration of treatment, use of contraindicated medication (O'Connor et al, 2012; Doody et al, 2015).

The extent of IP among patients with impaired renal function varies depending on the country, type of facility (e.g. inpatient setting, ambulatory care, elderly care) and medical specialty (e.g. general medicine, surgery) (Salomon et al, 2003; Yap et al, 2005; Nielsen et al, 2014; Doody et al, 2015; Tesfaye et al, 2017). IP has been reported to be highest in hospitalised patients with chronic kidney disease (CKD) with an incidence ranging from 9 to 81% (Long et al, 2004; Liu et al, 2012; Prajapati and Ganguly, 2013; Doody et al, 2015; Holm et al, 2015; Saad et al, 2019). In the community and elderly care settings the extent of IP is lower, between 16-52%, but varies extensively from one setting and country to another (Long et al, 2004; Breton et al, 2011; Gheewala et al, 2014; Khanal et al, 2015).

The reason behind significant differences in the prevalence of IP could be due to inconsistencies between dosage adjustment guidelines with some guidelines relying on the instructions present in the summary of product characteristics (SPC), whereas other guidelines, such as The Renal Drug Handbook (RDH), uses clinical experience of the physicians and research papers published after the medication is launched into the market (Khanal et al, 2014; Doody et al, 2015). Another reason for IP could be lack of quantitative information about medication dosage adjustments making it difficult to adjust dosages properly and/or compare the extent of IP with other studies (Khanal et

al, 2014). Suggestions, such as ‘reduce dose’ or ‘increase dosing interval’ can be misleading to healthcare professionals and result in IP (Vidal et al, 2005).

Correct classification and diagnosis of renal impairment is another challenge when adjusting medication dosages. Different equations for estimating renal function exist and this can lead to classification of patients with varying severities (i.e. mild, moderate, severe) of renal impairment (Khanal et al, 2014). An unclearly defined recommendation, such as ‘use with caution in severe renal impairment’ is subjective and cannot give any conclusive instructions for prescribing.

Polypharmacotherapy, advanced age, and number of comorbidities are considered as potential causes for IP. Recently admission to hospital was described to independently increase the risk for IP (Chang et al, 2015; Doody et al, 2015; Khanal et al, 2015; Pérez et al, 2018).

### 1.2.1 Polypharmacotherapy

Polypharmacotherapy is one of the most reported causes for IP. Use of more than 5 medications concomitantly has been described to increase the risk of IP among patients with impaired renal function (Breton et al, 2011; Chang et al, 2015, Doody et al, 2015; Saleem and Masood, 2016). The more medications a patient takes the higher the prevalence of potential IP. The association is even stronger when renal function decreases as more recommendations and restrictions for dosage adjustment exist in severe renal impairment group (Chang et al, 2015). In a study by Kang and Hong, polypharmacotherapy was shown to contribute to renal impairment (Odds ratio (OR) = 1.572, 95% confidence interval (CI) = 1.492 to 1.656) and excessive polypharmacotherapy, defined as usage of more than 10 medications, showed even

greater increase in renal impairment (OR=2.069, 95% CI=1.876 to 2.283) (Kang and Hong, 2019).

### 1.2.2 Advanced Age

With increasing age of the population, that often goes together with polypharmacotherapy, risk of IP rises notably (Liu et al, 2012; Khanal et al, 2015; Kang and Hong, 2019). Although age and polypharmacotherapy independently increase the incidence of IP, one is often a reason for the other. Elderly are more prone to IP due to age-related changes in the kidneys (Hanlon et al, 2011; Khanal et al, 2015). Decrease in renal function is common in older adults and is overlooked as a normal physiological change but can still affect pharmacokinetics and pharmacodynamics of medications and lead to IP and toxicity (Doody et al, 2015; Khanal et al, 2015).

### 1.2.3 Multimorbidity

Having several chronic conditions, including CKD, puts patients at increased risk of potential IP. Several studies have shown correlation between the extent of IP and the number of comorbidities (Chang et al, 2015; Khanal et al, 2015; Saleem and Masood, 2016). The most common comorbidities reported among patients with impaired renal function associated with increased IP are reported to be diabetes and heart failure (HF), which can lead to further decline in renal function (Chang et al, 2015). HF and diabetes are also diseases with significant medication burden to the patient, several of which dosages need to be adjusted to account for decreased renal function (Clark et al, 2019; House et al, 2019; Roux-Marson et al, 2020).

### 1.2.4 Hospitalisation

In a recent study Pérez et al concluded that admission to hospital was an independent risk factor for IP among elderly (Pérez et al, 2018). Elderly patients who were hospitalised were more likely to be exposed to IP after admission compared to IP before admission. The reason whether IP was increased due to illness triggering admission or due to further medical interventions while hospitalised is unknown (Pérez et al, 2018). In view of current research, a study by Pérez et al adds another important aspect to the risk factors leading to IP. Apart from patient's age, comorbidities and polypharmacotherapy playing a role in IP, hospitalisation can increase the possibility of IP.

### 1.2.5 Options to Decrease Inappropriate Prescribing

IP in patients with impaired renal function is known to have an impact on patient outcomes in terms of increased rate of adverse drug events (ADEs), length of hospital stay (LOS), and mortality (Hug et al, 2009; Baum and Harder, 2010; Breton et al, 2011; Tesfaye et al, 2017; Arias Pou et al, 2019). Studies report the implementation of solutions to overcome the problem of IP (Baum and Harder, 2010; Awdishu et al, 2016; Al Raiisi et al, 2019; Arias Pou et al, 2019; Saad et al, 2019).

It has been reported that implementing clinical decision support systems (CDSS) to hospital electronic systems decreases IP (Chertow et al, 2001; Tawadrous et al, 2011; Awdishu et al, 2016; Arias Pou et al, 2019). CDSS beneficial effects have been thought to be due to the impact of real-time recommendations as most of the prescribing takes place at patients' bedside (Such Díaz et al, 2013; Awdishu et al, 2016; Elkhadragy et al, 2019). Some studies have stressed the issue of system alert fatigue and rejection of

dosage adjustment recommendation by prescriber as a limitation of CDSS (Such Días et al, 2013; Kane-Gill and Kellum, 2015; Awdishu et al, 2016). To overcome some of the CDSS limitations a recent study by Elkhadragy et al suggested that CDSS should have more tailored approach that distinguishes between renally eliminated medications and nephrotoxic medications to improve clinical practice and significantly reduce IP among patients with decreased renal function (Elkhadragy et al, 2019).

Clinical pharmacist intervention has shown to have the greatest impact on dosage adjustments in patients with decreased renal function. Clinical pharmacists attending ward rounds, where the majority of prescribing takes place, and having direct contact with the prescriber instead of impersonalised recommendation from the CDSS, shows the best results in decreasing IP (Viktil and Blix, 2008; Hassan et al, 2009; Cabello-Muriel et al, 2014; Holm et al, 2015). A study by Joosten and colleagues showed that clinical pharmacist intervention decreased risks for ADEs from 38% to 6% (Joosten et al, 2013). Al Raiisi et al conclude that there is still lack of well-conducted randomised control trials to show the positive contribution of the clinical pharmacist in a multidisciplinary team caring for patients with chronic illnesses (Al Raiisi et al, 2019). But evidence shows some positive impacts on clinical, humanistic, and economical outcomes of the clinical pharmacist intervention in the care of CKD patients (Al Raiisi et al, 2019).

Other options for medication optimisation and dosage adjustment also exist. The United Kingdom (UK) National Health Service recommends implementing in-house guidelines at the hospitals for medication management in acute kidney injury (AKI)[1]. Studies

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[1]UK Renal Registry. Guidelines for Medicine Optimisation in Patients with Acute Kideny Injury [Internet]. Think Kidneys; 2018 [cited 2020 Mar 25]. Available from: https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2016/07/Medicines-optimisation-toolkit-for-AKI-MAY17.pdf.

propose consulting nephrologists on the ward or carrying out physician educational programs as an option to decrease IP in patients with renal impairment (Baum and Harder, 2010; Saad et al, 2019).

## 1.3 Importance of Correct Drug Dosing in Renal Impairment

Decreased renal function and IP have both been associated with worse outcomes among hospitalised patients. Increased risks of ADEs, increased mortality, higher costs and effect on the quality of life have been listed as frequent adverse events related to decreased renal function (Cherthow et al, 2005; Hassan et al, 2009; Cox et al, 2013; Tesfaye et al, 2017).

Cox et al showed that 13% of the patients who had AKI or were recovering from AKI had ADEs, the percentage was higher for potential ADEs (17%) (Cox et al, 2013). The most frequently reported ADE was worsening of AKI, potential ADEs were mainly related to IP – failure to adjust medication dosages according to renal function or use of nephrotoxic medications (Cox et al, 2013). Cox and colleagues stressed that two thirds of the ADEs could have been prevented by proper dosage adjustment of medications (Cox et al, 2013). Similar results were described by Hug and colleagues, reporting that almost all of the serious and life-threatening ADEs were preventable with antimicrobials, pain medications and cardiovascular medications being the main medication classes involved in ADEs (Hug et al, 2009).

ADEs have been shown to contribute to longer LOS in patients with decreased renal function (Hug et al, 2009; Cox et al, 2013). ADEs and decreased creatinine clearance (CrCl) independently increase LOS, in patients with both ADEs and decreased CrCl LOS

doubles, being 5.28 extra days compared to 2.21 extra days at the hospital in patients with just decreased renal function (Hug et al, 2009). Other studies have found similar increases in hospitalisation periods, from 1.9 up to 8.2 additional days in hospital due to ADEs and decreased renal function (Bates et al, 1997; Classen et al, 1997; Bates et al, 2001).

Increased mortality is one of the biggest concerns with kidney disease. It has been reported that all-cause mortality is 5.5 times higher with decreased CrCl compared to patients without decreased CrCl (Levy et al, 1996). A slight increase in serum creatinine (SCr) (AKI Stage 1, SCr ≥ 26.2 µmol/L) increases long-term mortality post cardiac surgery with a potential association between AKI and increased risk of myocardial infarction (MI) (Hansen et al, 2013). Hansen at al also stated that increased five-year mortality correlated with worsening severity of AKI (Hansen et al, 2013). Other studies have reported AKI and CKD as being risk factors for cardiovascular adverse events, especially HF, and increased mortality (Go et al, 2004; Thompson et al, 2015; Go et al, 2018). Decreased renal function is also related to subsequent HF admissions (Go et al, 2018).

A recent study looking into causes of death in patients with decreased renal function showed an increase in cardiovascular related deaths with a higher proportion of deaths caused by HF and valvular disease with declining estimated glomerular filtration rate (eGFR) (Thompson et al, 2015). Lower eGFR was associated with an increased mortality by diabetes complications and infections, but with a smaller proportion of cancer-related deaths (Thompson et al, 2015).

Late diagnosis and not acknowledging decreased renal function, presence of ADEs, IP, and prolonged LOS can increase the overall cost per patient during hospitalisation (Bates

et al, 2001; Cherthow et al, 2005; Hassan et al, 2009; Tesfaye et al, 2017). Correct estimation of renal function helps in choosing the correct dosing of medications especially in renal impairment.

## 1.4 Renal Function Estimates

A widely used parameter to estimate renal function is SCr, which in many circumstances is unreliable and not the best marker of renal function in patients who are acutely ill with unstable SCr. There are new parameters in sight including low-molecular-weight proteins, such as cystatin C (Cys), and other proteins that are produced in response to tissue injury, but until these are not validated in different population groups their reliability is debatable (Cox, 2018; Hart and Anderson, 2018; Peters et al, 2018; Barreto et al, 2019; Stefani et al, 2019).

For years the gold standard for estimating renal function was CrCl by using the Cockcroft-Gault equation (CG) (Cockcroft and Gault, 1976). Until the mid-nineties recommendations by the Food and Drug Administration (FDA) were clear that CG was the equation to be used to estimate renal function when conducting clinical trials for new medications. With new equations – Modification of Diet in Renal Disease Study (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) – to estimate glomerular filtration rate (GFR) becoming available at the beginning of 2000s the accuracy of CG was questioned (Levey et al, 1999; Levey et al, 2009).

MDRD and CKD-EPI formulae are more practical and easier to use in clinical practice as they do not require knowledge of patient's weight. Both formulae are proven to be more accurate in evaluating renal function than estimated creatinine clearance (eCrCl) by CG

(Levey et al, 1999; Levey et al, 2009). In 2013 Kidney Disease: Improving Global Outcomes (KDIGO) organisation stated that eGFR equations (MDRD, CKD-EPI, or any future eGFR formula) should be used to estimate renal function for the purpose of diagnosing and classifying CKD (KDIGO CKD Work Group, 2013). MDRD and CKD-EPI formulae are the new gold standards to estimate GFR in everyday clinical practice and accepted to be used in dosage adjustment studies by KDIGO, FDA, and European Medicines Agency (EMA)[2] (Huang et al, 2009; Matzke et al, 2011).

### 1.4.1 Cockcroft-Gault Equation

The most commonly used marker to assess renal function is SCr measurement from the blood. The most accurate measure of renal function is the 24-hour urine collection test used in pharmacokinetic studies, but because it is time consuming and logistically difficult, it is rarely used in clinical practice (Dowling et al, 2013).

Since the mid-seventies a urine-free estimation of CrCl – CG equation – is available. The equation uses patient's gender, age, weight, and SCr to calculate CrCl. CG may not be the ideal method to use in the laboratory as patient's weight is often not documented in electronic health records[3].

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[2]European Medicines Agency. Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function [Internet]. European Medicines Agency; 2016 [cited 2020 Mar 25]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-pharmacokinetics-medicinal-products-patients-decreased-renal-function_en.pdf.

[3]Radiometer Medical ApS. History of GFR and practical issues related to implementation [Internet]. Radiometer Medical ApS; c2018 [cited 2020 Mar 25]. Available from: https://acutecaretesting.org/en/articles/history-of-gfr-and-practical-issues-related-to-implementation.

With new possibilities becoming available to estimate GFR it has been debated whether SCr is the best marker for renal function (Fan et al, 2015; Hart and Anderson, 2018; Barreto et al, 2019). CG equation is highly dependent on weight and muscle mass and for people with decreased or increased muscle mass, such as frail, elderly and obese patients, SCr might not be the most reliable marker to estimate renal function (Bouquegneau et al, 2016; Hart and Anderson, 2018). CG equation incorporates weight into the calculation for CrCl which allows for a more personalised approach. Recent studies have shown that using ideal body weight (IBW) or adjusted body weight (adjBW) instead of actual body weight (ABW) will give more accurate eCrCl results (Bouquegneau et al, 2016; Hart and Anderson, 2018). There is not enough evidence that these body weight modifications give more precise results[4].

eCrCl calculation by CG is known to slightly overestimate renal function when compared to measured glomerular filtration rate (mGFR), which is due to the fact that creatinine is filtered and secreted in the nephron tubules (Bauer, 2005; Stefani et al, 2019). Overestimation of renal function is seen in overweight patients when ABW is used for CrCl calculations and could be of importance for patients who have borderline renal function and are placed into less severe categories of renal function which leads to different recommendations for dosage adjustments (Michels et al, 2010; Hart and Anderson, 2018; Stefani et al, 2019).

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[4]National Institute of Diabetes and Digestive and Kidney Diseases. CKD and Drug Dosing: Information for Providers [Internet]. National Institute of Diabetes and Digestive and Kidney Diseases; 2015 [cited 2020 Mar 25]. Available from: https://www. niddk.nih.gov/health-information/professionals/advanced-search/ckd-drug-dosing-providers#approach.

CG equation is still the main formula used in clinical trials involving patients with decreased renal function regardless of the weight estimation used. The FDA and EMA allow dosage adjustment studies to be conducted using eGFR formulae[2,5]. Without long-term multi-centre studies in diverse populations with newer formulae, for the purpose of medication dosing, CG should remain the one to be used for dosage adjustments especially for the elderly, acutely ill, and overweight patients, and for the older medications only tested using CG formula (Cox, 2018).

### 1.4.2 Chronic Kidney Disease Epidemiology Collaboration Equation

CKD-EPI is a newer formula that incorporates gender, age, race, and SCr and gives an estimation of GFR (Levey et al, 2009). It is accurate in estimating GFR and has been recommended by KDIGO to be used together with MDRD equation for staging and diagnosing CKD. Evidence of CKD-EPI for use for medication dosing purposes is still inconclusive (KDIGO CKD Work Group, 2013; Chew-Harris et al, 2015; Eppenga et al, 2016; Andrade et al, 2018).

Studies show that on average patient eGFR correlates well with eCrCl and could be one option to adjust medication dosages, although no formal recommendations by FDA, EMA, or KDIGO are published to support this practice (Michels et al, 2010; Khanal et al,

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[2]European Medicines Agency. Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function [Internet]. European Medicines Agency; 2016 [cited 2020 Mar 25]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-pharmacokinetics-medicinal-products-patients-decreased-renal-function_en.pdf.

[5]Food and Drug Administration. Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling [Internet]. Food and Drug Administration; 2010 [cited 2020 Mar 25]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-renal-function-study-design-data-analysis-and-impact-dosing-and.

2017). It is still debated whether CKD-EPI is precise enough to be used in patient populations, such as elderly, critically ill, or in patients at extremes of body weight; or suitable for all the medications on the market such as direct oral anticoagulants (DOACs) (Bouquegneau et al, 2016; Hart and Anderson, 2018; Lee et al, 2019).

eGFR is allowed to vary to some extent from mGFR (Table 1.1). The same acceptability for accuracy also stands for eCrCl, allowing the estimation to be within 30% of the actual measured creatinine clearance (mCrCl) (Eppenga et al, 2016). Estimation can lead to under- or over-dosing and with some eGFR results a great fluctuation in dosage recommendations can be seen (Eppenga et al, 2016).

**Table 1.1 Effects of the inaccuracy of the eGFR in medication dosing. (Adopted from: Eppenga WL, Kramers C, Derijks HJ, Wensing M, Wetzels JF, De Smet PA. Drug therapy management in patients with renal impairment: how to use creatinine-based formulas in clinical practice. Eur J Clin Pharmacol. 2016;72(12):1433-9).**

| | | Renal function groups for drug dosing[44] | | | | |
|---|---|---|---|---|---|---|
| **mGFR (ml/min/1.73m$^2$)** | **eGFR (mGFR ± 30%)*** | **< 10** | **10-30** | **30-50** | **50-80** | **> 80** |
| 100 | 70-130 | | | | | |
| 60 | 42-78 | | | | | |
| 40 | 28-52 | | | | | |
| 20 | 14-26 | | | | | |

**An accuracy expressed as P30% (eGFR falls within + 30% of the mGFR) of 80% or higher has been indicated as sufficient.*

In certain eGFR range the patient can fall into 3 different dosing categories despite what the actual GFR is (Eppenga et al, 2016). The inaccuracy of eCrCl or eGFR increases with increasing GFR and could be as much as half or double of the actual GFR (Michels et al, 2010; Stefani et al, 2019).

A margin of error of 30% allowed for formulae to estimate actual GFR, it is questionable whether it is important from the point of dosage adjustment recommendations for values of eCrCl and eGFR to be equal (Eppenga et al, 2016; Stefani et al, 2019). Patients who participated in the development of CKD-EPI equation on average had absolute glomerular filtration rate (absGFR) 10% higher than the eGFR normalised to body surface area (BSA) (Levey et al, 2009). This leads to another issue of whether absGFR or normalised eGFR should be used.

### 1.4.3 Absolute Glomerular Filtration Rate

absGFR (ml/min) is recommended to be used for dosage adjustments by EMA and is used to give recommendations in RDH[2] (Ashley and Dunleavey, 2018). Hospital laboratories report eGFR normalised to BSA (ml/min/1.73m$^2$) which works for the average patient with average weight and height. If the patient's BSA, for any reason, is significantly bigger or smaller than 1.73m$^2$, then the normalised eGFR result should be taken with caution (Bouquegneau et al, 2016; Hart and Anderson, 2018).

A growing number of studies are trying to prove that there is no statistically significant difference between different estimations of renal function for the average population as the estimations are all relatively accurate and the differences might not be clinically important in terms of patient outcome (Eppenga et al, 2016; Khanal et al, 2017).

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[2]European Medicines Agency. Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function [Internet]. European Medicines Agency; 2016 [cited 2020 Mar 25]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-pharmacokinetics-medicinal-products-patients-decreased-renal-function_en.pdf.

Considering the lack of well-designed long-term studies, SCr based equations should be approached with caution and always used together with clinical judgment and personalised approach (Eppenga et al, 2016).

### 1.4.4 Newer Markers to Estimate Renal Function

Concerns about the accuracy of SCr based equations for estimation of renal function have led to the development of more reliable markers (Kashani et al, 2017; Rysz et al, 2017; Barreto et al, 2019). Cys has been proposed to be one of the markers to estimate renal function better as it does not depend on the muscle mass or dietary protein intake (Stevens et al, 2008; Tangri et al, 2011).

Recent studies have shown that using Cys alone might not give the most accurate result as it can be affected by inflammation, weight and height of the patient, and also its non-renal elimination (Rule et al, 2006; Stevens et al, 2009). The greatest precision accuracy is seen when using Cys and SCr together to reduce the effect of non-GFR determinants of each marker alone (Stevens et al, 2008; Fan et al, 2015). CKD-EPI equation that considers both, SCr and Cys, has shown good performance in estimating renal function in the average population and also in the elderly (Fan et al, 2015; da Silva Selistre et al, 2019). Variations exist between SCr and Cys based equations for medication dosing purposes and whether Cys alone or together with SCr is applicable for dosage adjustments is yet to be determined (Peters et al, 2018; Barreto et al, 2019).

### 1.4.5 Estimating Renal Function in Obese Patients

In obese patients the choice of equation to estimate renal function is more important. eCrCl is usually calculated using ABW which is known to overestimate GFR in obese

population with a body mass index (BMI) greater than 30. Increase in BMI and total body weight (TBW) is not linearly correlated to GFR, hence the use of ABW overestimates mGFR (Pai, 2010). Some researchers suggest using IBW or lean body weight (LBW) instead of ABW as these could better estimate the increase in muscle mass in relation to TBW in obese patients (Demirovic et al, 2009; Lemoine et al, 2014). In another study Bouquegneau et al showed that use of adjBW values incorporated into the CG formula had the least bias compared to use of mGFR and was the most accurate to estimate GFR (Bouquegneau et al, 2016).

GFR formulae normalised to BSA tend to underestimate mGFR in the obese population. It has been suggested that removing normalisation for BSA improves accuracy of CKD-EPI equation in obese patients (Chew-Harris et al, 2015; Bouquegneau et al, 2016; Hart and Anderson, 2018). De-indexation of eGFR formulae has also been recommended by FDA and EMA for patients at extremes of body weight who were not included in the cohort to develop these formulae[2,5].

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[2]European Medicines Agency. Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function [Internet]. European Medicines Agency; 2016 [cited 2020 Mar 25]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-pharmacokinetics-medicinal-products-patients-decreased-renal-function_en.pdf.

[5]Food and Drug Administration. Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling [Internet]. Food and Drug Administration; 2010 [cited 2020 Mar 25]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-renal-function-study-design-data-analysis-and-impact-dosing-and.

### 1.4.6 Estimating Renal Function in Elderly

The elderly are a heterogenous population with underlying factors, such as age, comorbidities, body weight, that need to be considered when estimating renal function. CG formula underestimates mCrCl and mGFR in the elderly regardless of body weight estimate (e.g. TBW, indexed or de-indexed to BSA) used (Pequignot et al, 2009; Flamant et al, 2012; Dowling et al, 2013). According to the majority of the studies conducted in elderly MDRD equation overestimates mGFR and is the least reliable when eGFR rises above 60 ml/min/1.73m$^2$ (Pequignot et al, 2009; Dowling et al, 2013; Kilbride et al, 2013). All CKD-EPI formulae (SCr, Cys, and SCr-Cys) tend to overestimate mGFR. CKD-EPI incorporating SCr and Cys shows the best accuracy, whereas CKD-EPI with SCr alone seems to have the lowest bias according to Koppe et al and could be the first choice to estimate GFR if measurement of Cys is not available (Koppe et al, 2013; Werner et al, 2017).

There is not enough evidence to make a decision regarding which marker or equation is best to assess renal function in older patients, but the least biased and most accurate estimation is using SCr and Cys together in one of the eGFR formulae (e.g. CKD-EPI) (Lopes et al, 2013; Werner et al, 2017). Hart and Anderson suggest using more than one method to assess renal function and to be extremely cautious when applying these estimates in dosage adjustments for elderly (Hart and Anderson, 2018).

## 1.5 Medication Dosage Adjustment Guidelines

In the SPC, guidance for dosing for patients with decreased renal function is provided, but oftentimes information is limited and inconclusive, and misleads the prescriber

without more detailed background knowledge about dosage adjustments in certain patient populations.

Guidelines have been developed to overcome limitations of SPC and to provide more precise guidance for prescribers[2] (Khanal et al, 2014). The most widely used information sources in Europe and USA for medication dosing purposes are British National Formulary (BNF), RDH, Drug Prescribing in Renal Failure, UpToDate® (UTD) and Micromedex®. Guidelines from these sources have their limitations and the user must be aware of, for example, which renal function estimation equation was used in the specific guideline. Recommendations are inconsistent and vary extensively between different guidelines (Khanal et al, 2014; O'Shaughnessy et al, 2017).

In the context of the current study focus is made on the three commonly used medication information sources by the pharmacists and physicians at East Tallinn Central Hospital (ETCH), a 400-bed acute care hospital in the capital of Estonia, where this study was conducted.

### 1.5.1 British National Formulary

The BNF compiles information about medications into one easy-to-use source that can be used at the patient's bedside. Although focusing on the products available in the UK the BNF is used by the pharmacists in Estonia as an excellent source of medication information. In the BNF suggestions on how to adjust dosages in patients with renal

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[2]European Medicines Agency. Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function [Internet]. European Medicines Agency; 2016 [cited 2020 Mar 25]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-pharmacokinetics-medicinal-products-patients-decreased-renal-function_en.pdf.

impairment often follow recommendations in the SPC with a difference that BNF uses MDRD equation normalised to BSA to guide dosage adjustment for majority of the medications if not stated otherwise (Joint Formulary Committee, 2018).

Incorporating the IBW in the CG formula is only suggested for dosage adjustments of toxic drugs and for patients at extremes of body weight (BMI <18,5 or ≥30), for the latter an absGFR is also given as an option. In the elderly the BNF states that SCr might not be the ideal marker to estimate renal function due to underlying problems, such as decreased body mass, and recommends to always assume at least mild renal impairment in older adults (Joint Formulary Committee, 2018).

### 1.5.2 The Renal Drug Handbook

The RDH focuses on providing information regarding medication dosing in renal impairment and for patients on dialysis. Information in the RDH is gathered from a wide range of resources and also from the clinical experience of the editorial board of the UK Renal Pharmacy Group. More patient-centred and practical approaches rather than theoretical knowledge make recommendations in the handbook unique (Ashley and Dunleavey, 2018).

Recommendations for dosage adjustments in the RDH are given based on CG formula. According to the authors eGFR based on MDRD could be used for patients of average weight for dosage adjustments as there is good correlation between CG and MDRD formulae. Normalised eGFR should not be used in patients at extremes of body weight nor for medications with narrow therapeutic indices, an absGFR should be calculated for them using the patient's actual BSA. RDH, similarly to BNF, recommends that when

prescribing for elderly mild renal impairment should be assumed at all times (Ashley and Dunleavey, 2018).

### 1.5.3 UpToDate®

UTD provides medication information using monographs from Lexicomp® – an online medication information source. Database is mostly USA oriented and might not always have complete information about medications used in Europe, despite that it provides the most up to date information and data from most recent literature. Recommendations for dosage adjustments in renal impairment are combined from SPC, other published guidelines and recent publications[6].

UTD does not prefer one renal function estimate to another. Each medication monograph usually contains information which estimate or equation (e.g. eCrCl, eGFR) is suggested to be used to guide dosage adjustment.

## 1.6 Current Practice at the Study Setting

There are many informational technology (IT) solutions available in the healthcare system in Estonia[7]. All health records are electronic and accessible to physicians, in different hospitals across the country, and also to the patients themselves. Outpatients' electronic prescribing with integrated medication interaction checker and alert system takes up more than 99% of all the prescriptions, but inpatient prescribing is still mostly

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[6]UpToDate®. Drugs & Drug Interactions [Internet]. UpToDate, Inc; c2020 [cited 2020 Mar 25]. Available from: https://www.uptodate.com/home/drugs-drug-interaction.

[7]Tervise ja Heaolu Infosüsteemide Keskus (TEHIK). Teenused ja projektid [Internet]. TEHIK [cited 2020 May 18]. Available from: http://www.tehik.ee/tervis/teenused-ja-projektid/

done on paper. Despite all the advancements with regards to IT solutions in healthcare, there is still no computerised physician order entry (CPOE) or CDSS in place in the majority of the hospitals in Estonia. When prescribing, physicians need to rely on their clinical judgment, consult another physician, and/or look up information from SPC or from other available sources.

There are no studies conducted in Estonia that describe common medication information sources used by physicians to search information about medication dosing and administration. Physicians tend to rely on their own knowledge or consult product SPC for additional information. Even though all the physicians in ETCH have access to abundant medication information sources such as UTD, Micromedex®, AusDI by MedicalDirector, to name a few, these seem to be used less frequently.

There is only one clinical pharmacist, mostly working at the intensive care unit (ICU), to provide medication information to the hospital. There is no in-house guideline in place for the management of CKD and AKI patients nor there is a guideline for proper dosage adjustments of medications in renal impairment to guide physicians in their decisions.

Considering all the above, this study aimed to enlighten current practice in medication management of patients with impaired renal function at ETCH.

## 1.7 Aim and Objectives

The aim of the study is to describe medication usage in patients with decreased renal function in the inpatient units in ETCH in Estonia.

The objectives are:

To assess prevalence of IP in patients with decreased renal function.

To identify the most common drug classes which are inappropriately prescribed in patients with decreased renal function.

To look for any correlation between potential risk factors leading to IP among patients with decreased renal function.

# Chapter 2

# Methodology

## 2.1 Overview

The study was divided into 5 stages (i) comparison of medication information sources (ii) development of medication dosage adjustment guideline (iii) setting up a 'Data collection form' (iv) validation of the 'Data collection form' by a multi-disciplinary expert panel and testing feasibility of the form (v) patient data collection from electronic health records.

## 2.2 Study Setting

The study was conducted in ETCH in Tallinn, Estonia. ETCH is a 400-bed tertiary care teaching hospital located in the capital of Estonia and is the 3rd biggest hospital in Estonia primarily treating adult patients. There are 7 clinics at ETCH – Diagnostic Clinic, Clinic of Internal Medicine, Eye Clinic, Women`s Clinic, Surgery Clinic, Clinic of Medical Rehabilitation and Long-Term Nursing Clinic.

## 2.3 Ethics Approval and Permission for Study

Permission to conduct the study was sought and granted by the ETCH Research Committee and ETCH Quality Assurance Committee. Ethics approval from Estonia was granted by the Tallinn Medical Research Ethics Committee (TMREC). Ethics approval from Malta was granted by University of Malta Research Ethics Committee (Appendix 1).

## 2.4 Comparison of Medication Information Sources

Three sources (i.e. BNF, RDH and UTD) were used to compare recommendations for medication dosages adjustment according to renal function[6] (Joint Formulary Committee, 2018; Ashley and Dunleavey, 2018) (Appendix 3). The SPC was consulted if the previous three sources did not give conclusive information. Level of agreement between sources was assessed.

## 2.5 Development of Medication Dosage Adjustment Guideline

Medication dosage adjustment guideline was developed based on the information in BNF, RDH and UTD, and on the results of the comparison of these 3 sources (Appendix 4). In addition, SPC and recent literature were consulted to provide comprehensive recommendations. Validation of the guideline by clinical pharmacists and physicians was performed. The medication dosage adjustment guideline was used to compare medication dosages and renal function with the criteria in the developed guideline.

## 2.6 Development of the 'Data collection form'

The 'Data collection form' was divided into two parts (Appendix 2). The first part of the form included patient demographical data: gender, age, height, weight, comorbidities, LOS, ward, and interventions (e.g. surgery) made during hospitalisation. The second part of the 'Data collection form' included laboratory parameters and information about medication: SCr; eGFR; medication name, dosage, frequency, and route of

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[6]UpToDate®. Drugs & Drug Interactions [Internet]. UpToDate, Inc; c2020 [cited 2020 Mar 25]. Available from: https://www.uptodate.com/home/drugs-drug-interaction.

administration. Patients' gender, age, weight and height were collected to allow calculation of CrCl according to the CG equation and absGFR using patient's BSA.

Information about comorbidities and interventions made during hospitalisation were included to the 'Data collection form' to show possible correlation between decreased renal function and comorbidities, other diagnoses at discharge and/or interventions made during hospitalisation. The ward of hospitalisation was included to assess extent of IP between different medical specialities and wards.

## 2.7 Validation of the 'Data collection form'

An expert panel consisting of 3 physicians (infectious disease physician, internal medicine physician, and intensive care physician) and 3 pharmacists (1 drug safety pharmacist and 2 clinical pharmacists) validated the 'Data collection form'. The 'Data collection form' was delivered to the members of the expert panel via email together with a brief overview of the study and instructions on how to carry out the validation. Participants were free to comment on the 'Data collection form'. Written feedback of the 'Data collection form' was received within a week after sending the email.

Feedback received from the expert panel was analysed by the researcher and 'Data collection form' was edited accordingly.

Suggested changes to be made consisted of inclusion (e.g. diagnoses, route of administration of medication) and/or exclusion (e.g. allergies, ADEs) of certain parameters; clarification of some parameters and how these will be collected (e.g. age and date of birth); updates in the data collection protocol.

## 2.8 Data Collection

Data collection was carried out over a period of 6 months using electronic health records and performing chart reviews. Patient demographics, medications and laboratory parameters were recorded.

### 2.8.1 Period of Data Collection

Data collection was carried out after approval from TMREC was granted between July 2019 and December 2019. Patients included in the study had to be admitted to the ETCH the previous year, between 1st January 2018 and 31st December 2018. If the patient was discharged from the hospital after 31st December 2018, data concerning the medication was collected only until 31st December 2018.

### 2.8.2 Sampling Design

The study sample was selected using stratified random sampling method from the group of patients admitted to the ETCH during 2018. Patients were divided into 6 groups according to ward or clinic they were in. The wards and clinics were:

1) internal medicine ward
2) cardiology and endocrinology ward
3) neurology ward
4) gastroenterology ward
5) rehabilitation clinic
6) surgery clinic

After initial stratification a sample size was determined using following equation:

$$n = \frac{z^2 \times \hat{p}(1-\hat{p})}{\varepsilon^2}$$

where n is the sample size, z is the z-score, p̂ is the population proportion, ε is the margin of error.

Margin of error of 5% and confidence interval of 95% (giving the z-score of 1.96) were chosen to calculate the sample size. As exact number of patients with impaired renal function eligible for the study was unknown, population proportion of 0.5 was set. A sample size of at least 385 patients was necessary. A final sample of 399 patients was selected.

Study sample was selected randomly from the strata sets. Final sample was formed taking into account inclusion and exclusion criteria (Figure 2.1).

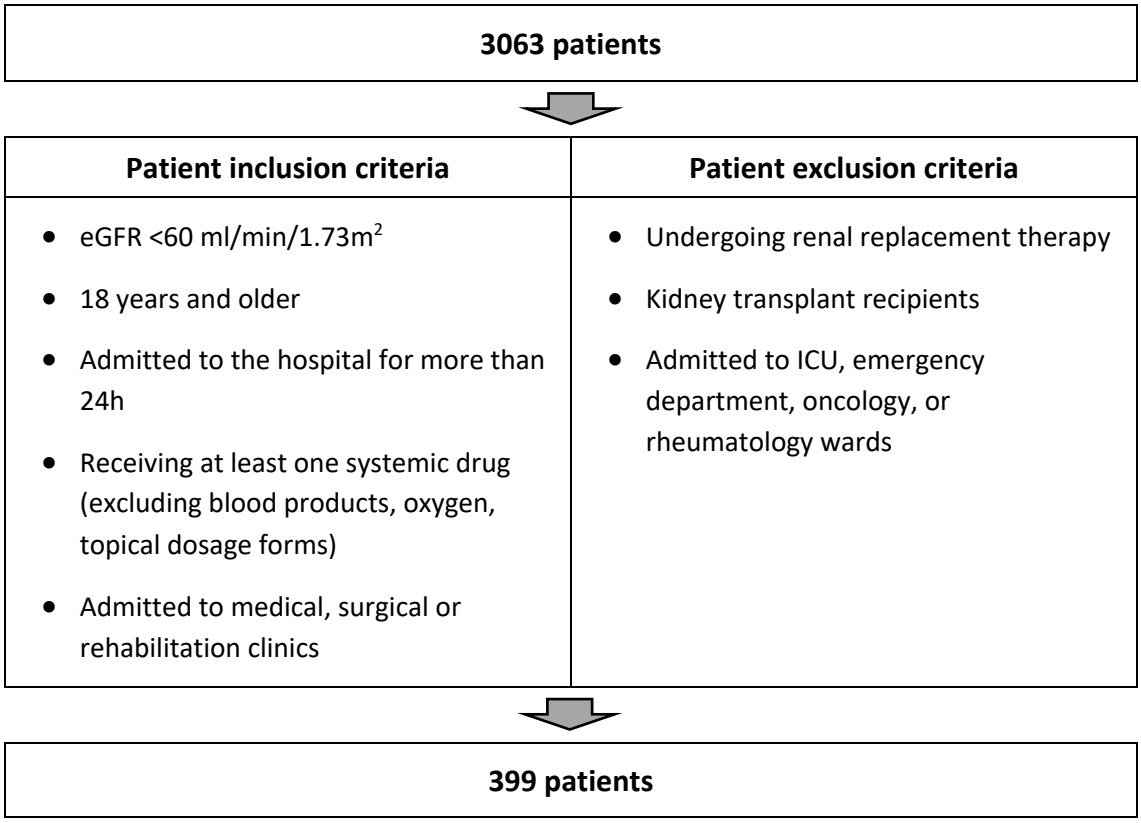


**Figure 2.1 Sample size and inclusion/exclusion criteria (N=399)**

### 2.8.3 Medical Chart Access

Patient demographics, results of the laboratory analyses and data of medications used were drawn from the electronic health records. eHealth system for ETCH was used to access patients' health records. Access to the records was granted by the board of ETCH using the research approval number. All the information was directly inputted from the eHealth system to the Epidata Software.

EpiData Software is an electronic data entry, and documentation, system with error detection features (e.g. double entry verification, backup and encryption options). The 'Data collection form' was transferred to Epidata Software and features to check entered data and alerts of errors were set up to minimise mistakes during data input.

When accessing patients' records a list of the patients' identification numbers and medical record numbers was delivered to the researcher in an encrypted form to maintain anonymity. During data entry, patients were coded according to the order of entering the study. Each patient was assigned a unique code. The key for the codes was protected with a password (only known to a principal investigator) and kept in the internal server of ETCH. Data entry to the software was performed using unique patient codes, thus keeping data anonymous and only traceable with the key for the codes.

### 2.8.4 Patients' Chart Review

The 'Data collection form' was filled in according to the protocol. Information about demographics were collected once, laboratory results and data about medication use were collected daily, or according to eGFR results, throughout the hospitalisation period. The maximum data collection period regardless of the LOS was 1 month. If a

patient was admitted to the hospital more than once during the study period only data related to the first admission was considered.

#### 2.8.4.1 Demographic Data

Diagnoses were documented using International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes[8]. All codes, except codes with V, W, X, Y and Z, were recorded, excluded codes reflect external causes of morbidity and mortality and/or other factors influencing health status which are not relevant for this research. Patient's diagnostic codes were documented in 3 separate categories: main diagnosis, complications of main diagnosis and comorbidities.

Admission and discharge dates were recorded together with the withdrawal date from the study. Patients were withdrawn from the study if eGFR rose above 60 ml/min/1.73m$^2$ or on the day of their last eGFR measurement below 60 ml/min/1.73m$^2$. If eGFR was less than 60 ml/min/1.73m$^2$ additional reasons for withdrawal (discharged, transferred to another ward, transferred to ICU, or death) were documented. If a patient was transferred to another hospital with eGFR <60 ml/min/1.73m$^2$ it was documented as the patient was discharged.

#### 2.8.4.2 Laboratory Parameters and Medications

Patients' haematocrit value was recorded on the day of the first eGFR reading <60 ml/min/1.73m$^2$ to exclude dehydration and volume depletion as a cause of increased

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[8]World Health Organization (WHO). International Statistical Classification of Diseases and Related Health Problems 10th Revision [Internet]. WHO; c2020 [cited 2020 Apr 18]. Available from: https:// www.who.int/classifications/icd/icdonlineversions/en/.

SCr and decreased eGFR. If a patient underwent surgery and/or was administered contrast media, dates of the interventions were recorded as both of these can affect SCr and eGFR and be one of the causes for AKI.

Data about the medications used were generally collected on the same day when eGFR results were taken. The generic name of the drug, dosage, frequency and route of administration were recorded. In case of intravenous drug administration total 24-hour dosage and volume of the medication were recorded. All systemic drugs taken by the patient were recorded, excluding blood products, oxygen, and topical dosage forms (including eyedrops). If intravenous fluids, contrast media, and/or parenteral nutrition were administered and documented in patients' electronic health records, these products were considered and were recorded.

## 2.9 Analysis

Data analysis was carried out using R statistical software[9]. Results for descriptive parameters were expressed as mean, median or proportion with standard deviation (SD), range, interquartile range (IQR), or with 95% CI. Statistical analysis to compare means of IP between 3 different renal function estimates was performed using chi-squared test. Statistical significance was reported with the 95% CI at $p<0.05$. Predictors of IP were assessed using univariate and multivariate logistic regression models. The dependent variable in logistic regression models was inappropriate prescribing. At prescription level the independent variables were LOS, number of prescriptions, route

[9]The R Foundation. R: A language and environment for statistical computing. Version 3.6.3 [software]. 2020 Feb 29 [cited 2020 May 21]. Available from: https://www.r-project.org.

of administration and eGFR category for univariable analysis and for multivariable analysis LOS and number of prescriptions were excluded. At patient level the independent variables were age, gender, BMI, LOS, surgery, contrast media administration, Charlson comorbidity index, AKI, atrial fibrillation (AF), diabetes, HF, hypertension, MI, and venous thromboembolism (VTE) for univariable analysis; and gender, LOS, surgery, contrast media administration, AKI, diabetes, and VTE for multivariable analysis. OR between dependent and independent variables was reported with 95% CI. In all analyses a *p* value less than 0.05 was considered to be statistically significant.

# Chapter 3

# Results

## 3.1 Results Overview

The comparison of three medication information sources showed differences in recommendations for dosage adjustments in renal impairment. Based on the information in the sources a guideline was developed for ETCH to assess medication dosage adjustment of the study population. The study included 399 patients from inpatient wards at ETCH with decreased renal function defined as eGFR less than 60 ml/min/1.73m$^2$. Medication dosage adjustments were assessed according to eGFR, absGFR and eCrCl. Prevalence of IP varied across different renal function estimates with certain medications showing significantly different rate of IP between estimates. The most common drug classes that were inappropriately prescribed were anticoagulants and analgesics. Association between IP and age, gender, comorbidities and interventions performed during hospitalisation were evaluated.

## 3.2 Comparison of Three Medication Information Sources

Table 3.1 is an example of recommendations for dosage adjustment in three different sources (i.e. BNF, RDH and UTD). Seventy-one medications were analysed, and recommendations documented (Appendix 3). There were similar recommendations for dosage adjustments in three sources, but a number of differences were identified as well. BNF, RDH and UTD also use different renal function estimates and this was not always comparable.

Morphine dosage adjustment recommendations in three sources are illustrated in Table 3.1. RDH gives quantitative recommendation for the prescriber shown as percentage of regular dosage. BNF and UTD both provide qualitative recommendations, but the suggestions are distinct.

**Table 3.1 Morphine dosage adjustment recommendations in three sources**

| | **British National Formulary (BNF)** ml/min/1.73m$^2$ | | | **Renal Drug Handbook (RDH)** ml/min | | | **UpToDate (UTD)** ml/min / ml/min/1.73m$^2$ | | | **Comments** |
|---|---|---|---|---|---|---|---|---|---|---|
| | **eGFR 30-59** | **eGFR 10-29** | **eGFR <10** | **GFR 20-50** | **GFR 10-20** | **GFR <10** | **(e)GFR/CrCl 30-59** | **(e)GFR/CrCl 10-29** | **(e)GFR/CrCl <10** | |
| **Morphine** | Avoid or reduce dose | Avoid or reduce dose | Avoid or reduce dose | 75% | 50% | 25% | no adjustment - caution* | no adjustment - caution* | no adjustment - caution* | *caution - consider reducing dose |

Table 3.2 illustrates the level of agreement between sources with a total number of 202 recommendations for 71 medications. Overall agreement between the 3 sources was less than 50% (46.5%, 44.1%, and 39.6%) of the recommendations suggesting the same dosage adjustment. Recommendations were considered consistent between sources if the dosage, the frequency, and/or other qualitative recommendations were the same. There was more disagreement between sources than agreement with regards to dosage adjustments (47.0%, 45.0%, and 48.0%, respectively). Around 10% of the total number of recommendations could not be compared due to lack of data.

BNF and RDH (94 of 202, 46.5%) show higher level of agreement in recommendations compared to UTD (89 and 80 of 202, respectively). The highest number of agreements for BNF compared to RDH and UTD (37 and 32 medications, respectively) were in the eGFR 30-50 ml/min/1.73m$^2$ category, followed by the eGFR <10 ml/min/1.73m$^2$

category (32 and 31 medications, respectively). For RDH and UTD the level of agreement between sources was highest in the most severe renal impairment category (29 of 71 medications, 40.8%).

**Table 3.2 The level of agreement of dosage adjustments between three sources (N=202)**

| | BNF vs RDH, n (%) | BNF vs UTD, n (%) | RDH vs UTD, n (%) |
|---|---|---|---|
| **Number of consistent recommendations** | 94 (46.5) | 89 (44.1) | 80 (39.6) |
| eGFR 30-50 ml/min/1.73m$^2$ * | 37 (52.1) | 32 (45.1) | 28 (39.4) |
| eGFR 10-29 ml/min/1.73m$^2$ * | 25 (35.2) | 26 (36.6) | 23 (32.4) |
| eGFR <10 ml/min/1.73m$^2$ * | 32 (45.1) | 31 (43.7) | 29 (40.8) |
| **Number of inconsistent recommendations** | 95 (47.0) | 91 (45.0) | 97 (48.0) |
| eGFR 30-50 ml/min/1.73m$^2$ * | 26 (36.6) | 28 (39.4) | 31 (43.7) |
| eGFR 10-29 ml/min/1.73m$^2$ * | 38 (53.5) | 34 (47.9) | 36 (50.7) |
| eGFR <10 ml/min/1.73m$^2$ * | 31 (43.7) | 29 (40.8) | 30 (42.3) |
| **Number of recommendations which could not be compared (e.g. data not available)** | 13 (6.4) | 22 (10.9) | 25 (12.4) |

*Proportion expressed as a percentage of medications compared between medication information sources (n=71).

The eGFR category of 10-29 ml/min/1.73m$^2$ had the least consistency in recommendations and highest disagreement rate throughout all 3 sources. When comparing BNF and RDH, 53.5% (38 of 71) of the medications had discrepancies with regards to dosage adjustments.

For four medications (cefazolin, ampicillin/sulbactam, sultamicillin and trimetazidine) recommendations were only available in one of the sources (UTD and for sultamicillin in SPC), thus it was not possible to make comparison.

## 3.3 Development of Medication Dosage Adjustment Guideline for East Tallinn Central Hospital

In order to compare medication dosages of the study population a guideline for medication dosage adjustments was developed. Comparison of three medication information sources (i.e. BNF, RDH, UTD) revealed significant discrepancies in recommendations and showed that one source is not enough to make conclusions about correct dosing. A guideline was put together for ETCH mainly based on the three above mentioned sources. Product SPC and/or recent literature were consulted if a conclusive recommendation was not possible to make based on the three sources. The list of study medications included in the guideline were available in the hospital formulary.

The developed guideline consisted of 54 hospital formulary medications (Appendix 4). The main medication classes in the guideline were antimicrobials, analgesics, cardiovascular agents (including anticoagulants) and antihyperglycemic agents.

## 3.4 Validation Results of Expert Panel

The 'Data collection form' validation expert panel included 3 physicians and 3 pharmacists. Physicians in the expert panel suggested to record haematocrit values to separate patients with possible dehydration from the ones with true renal insufficiency, and to document diagnosis of AKI and CKD on admission if applicable. Pharmacists suggested changes in documenting medication information, such as inclusion of route of administration and to omit duration of treatment. Recommendation to limit data collection to 1 month (i.e. maximum 31 days) was proposed by a clinical pharmacist in the expert panel. Physicians and pharmacists agreed that it was important to document all the patient's diagnoses instead of just selected comorbidities related to CKD. Options

on how to record the diagnoses were discussed and decision to use discharge diagnoses divided into 3 categories was made.

## 3.5 Selection of Patient Sample

During 2018 a total of 11479 patients were admitted to the ETCH inpatient wards which were included in the study. More than quarter (26.7%, n=3063) of the total number of patients had eGFR less than 60 ml/min/1.73m$^2$ (Figure 3.1).

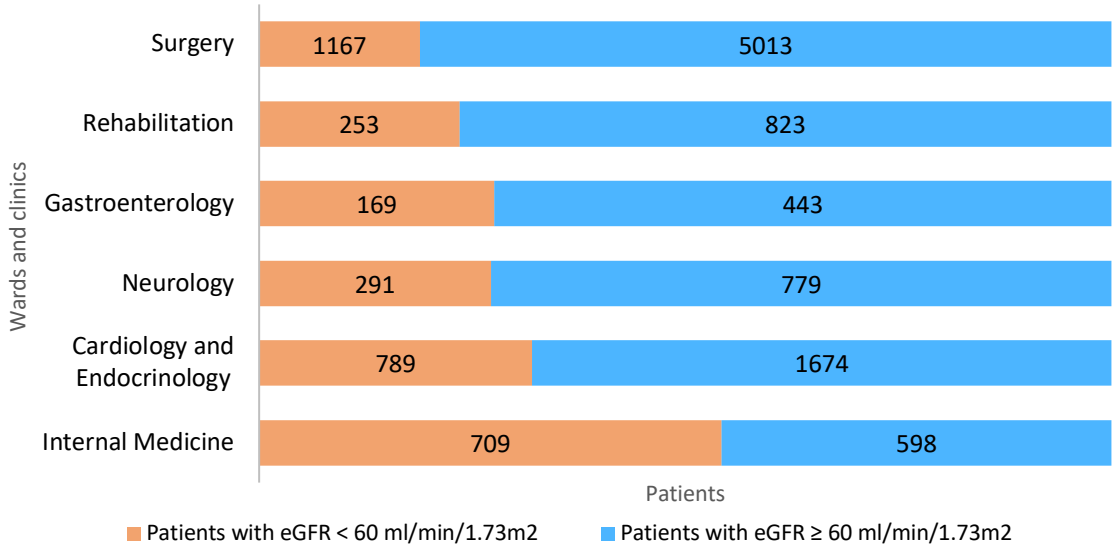



**Figure 3.1 Renal function profile of patients in different wards (N=11479)**

In most wards and clinics patients with decreased renal function (eGFR <60 ml/min/1.73m$^2$) constituted around 25% (range 18.9%-32.0%) of the total number of patients admitted. In the internal medicine ward the proportion of patients with eGFR less than 60 ml/min/1.73m$^2$ was twice as high as in the rest of the wards, being 54.3% (709 of 1307) of all the admitted patients in the ward.

Study sample was selected from 3063 patients who had eGFR less than 60 ml/min/1.73m$^2$. After inclusion and exclusion criteria was applied a final sample of 399 patients was identified (Figure 3.2). Final sample accounts for more than one tenth (13.2%, n=399) of the number of patients admitted throughout 2018 with eGFR <60 ml/min/1.73m$^2$.

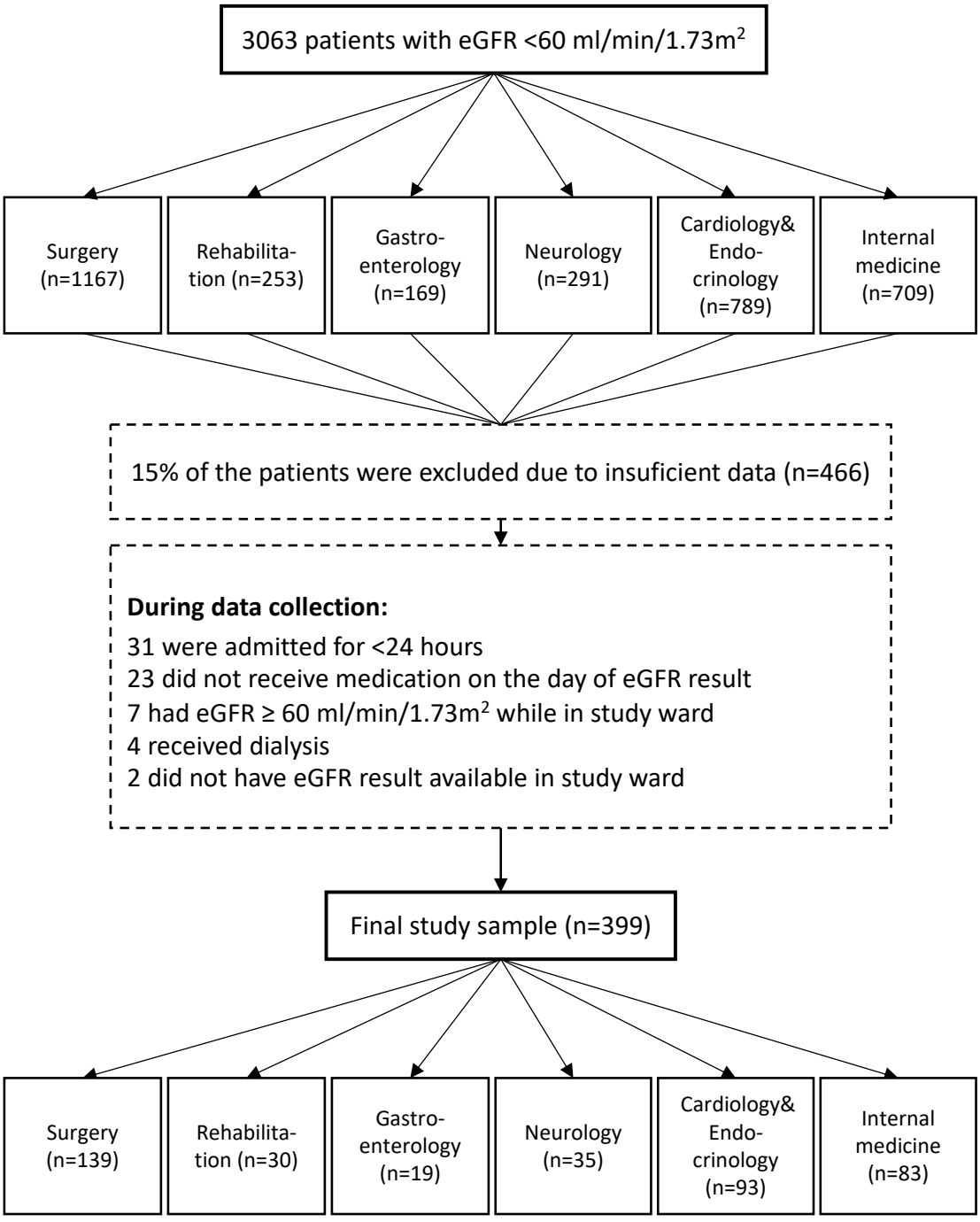



**Figure 3.2 Study sample (N=399)**

## 3.6 Demographics of the Study Population

Demographics and clinical characteristics of the 399 studied patients are summarised in Table 3.3. There were more female (n=250) than male (n=149) in the study population with 88% of the patients being over 65 years of age. Slightly more than one third (37.7%, n=126) of the patients (n=334) who had weight and height documented in their health records were obese (BMI≥30), the percentage was higher in female (42.8%, n=89) than in male (29.4%, n=37). Mean BSA was 1.9$m^2$ (95% CI=1.9 to 1.9), higher in male (2.1 $m^2$) and lower in female (1.8 $m^2$).

The mean Charlson comorbidity index across study population, and for male, was 5 (IQR 3), indicating 21% estimated 10-year survival. On average in women age-adjusted Charlson index was 6 (IQR 3), indicating 2% estimated 10-year survival. Most common comorbidities according to ICD-10 are presented in Table 3.4. Five most common comorbidities were similar between gender with an exception of chronic ischemic heart disease (I25) in men and type 2 diabetes (E11) in women. Majority (75.2%, n=300) of the patients had hypertension, and 37.1% (n=148) and 35.1% (n=140) had HF and/or AF, respectively. Part of the Charlson index is diagnosis of CKD, which was recorded in 94 patients (23.6%). Seventy-two (18.0%) patients had or developed AKI (a rise in SCr by ≥26.5 µmol/l) during hospitalisation, but only 19 (27.5%) of them had it appropriately documented in their health records. Four patients with CKD diagnosis also developed AKI with CKD. From the number of patients 286 (71.7%) patients did not have kidney disease of any type recorded in their health records even though all the patients had eGFR <60 ml/min/1.73$m^2$.

**Table 3.3 Patient demographics (N=399)**

| Characteristic | Value (% [95% CI]) |
|---|---|
| Mean age (years) | 79.0 [41.9 … 98.8, IQR 13.9] |
| Patients over 65 years | 351 (88.0% [84.8 … 91.2]) |
| **Physical measures (n=334)** | |
| BMI | 29.2 [28.5 … 29.8] |
| BMI ≥ 30 | 126 (37.7% [32.5 … 42.9]) |
| BMI < 18.5 | 4 (1.2% [0.03 … 2.4]) |
| **Hospitalisation** | |
| Mean length of hospitalisation (days) | 6.0 [1.0 … 31.0, IQR 6.0] |
| Surgery performed | 66 (16.5% [12.9 … 20.2]) |
| Administration of contrast media | 84 (21.1% [17.1 … 25.1]) |
| **Reason for withdrawal** | |
| eGFR > 60 ml/min | 93 (23.3% [19.2 … 27.5]) |
| Discharged | 222 (55.6% [50.8 … 60.5]) |
| Moved to another ward | 65 (16.3% [12.7 … 19.9]) |
| Moved to ICU | 3 (0.8% [0.0 … 1.6]) |
| Deceased | 16 (4.0% [2.1 … 5.9]) |
| **Diagnoses** | |
| Charlson comorbidity index | 5.0 [1.0 … 15.0, IQR 3.0] |
| Hypertension | 300 (75.2% [70.9 … 79.4]) |
| Atrial fibrillation | 140 (35.1% [30.4 … 39.8]) |
| Heart failure | 148 (37.1% [32.4 … 41.8]) |
| Myocardial infarction | 37 (9.3% [6.4 … 12.1]) |
| Diabetes | 105 (26.3% [22.0 … 30.6]) |
| Acute kidney injury | 72 (18.0% [14.3 … 21.8]) |
| Developed AKI during hospitalisation* | 59 (14.8% [11.3 … 18.3]) |
| Uncoded AKI during hospitalisation (n=72)* | 53 (73.6% [63.4 … 83.8]) |
| Chronic kidney disease | 94 (23.6% [19.4 … 27.7]) |
| Unspecified renal failure coded in records | 2 (0.5% [0.0 … 1.2]) |
| **Prescribing** | |
| Median medication per day | 8.0 [1.0 … 26.0, IQR 6.0] |
| Patients with inappropriate prescribing | 236 (59.1% [54.3 … 64.0]) |
| 1 inappropriate prescription (n=236) | 90 (38.1% [31.9 … 44.3]) |
| 2 inappropriate prescriptions (n=236) | 56 (23.7% [18.3 … 29.2]) |
| ≥3 inappropriate prescriptions (n=236) | 90 (38.1% [31.9 … 44.3]) |

*Development of AKI defined as increase in SCr by ≥ 26.5 µmol/l based on the recorded SCr values.

Prevalence of IP by patients was 59.1% (n=236) of whom 53 patients (22.5%) received at least one contraindicated medication. Out of all the patients 22.6% (n=90) had three or more inappropriately prescribed medications during hospitalisation.

Renal function of 93 patients normalised (eGFR >60 ml/min/1.73m$^2$) during hospitalisation. More than half of the patients (55.6%, n=222) were discharged with eGFR <60 ml/min/1.73m$^2$, 65 were transferred to another ward, 3 (all female) were transferred to ICU, and 16 patients died during hospitalisation.

**Table 3.4 Most common comorbidities (N=399)**

| ICD-10 Code | Diagnosis | Count (%) |
|---|---|---|
| I11 | Hypertensive heart disease | 193 (48.4%) |
| I48 | Atrial fibrillation and flutter | 130 (32.6%) |
| I50 | Heart failure | 103 (25.8%) |
| E11 | Type 2 diabetes mellitus | 98 (24.6%) |
| N18 | Chronic kidney disease | 91 (22.8%) |

Differences can be seen in the patient demographics between different specialities (i.e. internal medicine, surgery, rehabilitation) (Appendix 5). Patients in the rehabilitation clinic were older (80.3 years, IQR 11.1), with a higher BMI (31.1 [95% CI=29.0 to 33.2]) and greater proportion of patients with BMI ≥30, and had longer LOS (11.0 days, IQR 4.8) compared to patients in surgery (5.0 days, IQR 5.0) and internal medicine (6.0 days, IQR 6.0) clinics. Surgical patients were younger (77.6 years, IQR 15.1) with fewer comorbidities (Charlson index 5, IQR 2), on average received fewer medications (6, IQR 5.0) and had shorter LOS (5 days, IQR 5.0), but none of the findings were statistically significant compared to the patients in rehabilitation and internal medicine clinics. In the internal medicine and rehabilitation clinics patients received more medications

(n=9) per day compared to surgery (n=6). In all three wards around half of the patients had at least one inappropriately prescribed medication (60.4%, 46.7%, and 59.7%, respectively) and roughly 20% had three or more inappropriately prescribed medications. Hypertensive heart disease, with or without HF; atrial fibrillation and flutter; and diabetes were among the most common comorbidities in all three clinics with surgery having the lowest proportion of patients with those comorbidities. Fifteen patients in the surgery clinic developed AKI during hospitalisation and almost all (13 of 15) did not have AKI documented in their health records. Documentation rate of AKI was higher in internal medicine clinic, but 69.6% (39 of 56) of the patients did not have AKI properly documented. CKD was recorded in one third (30.9%, n=71) of patients in internal medicine clinic while the percentages were 12.9% (n=18) and 16.7% (n=5) in surgery and rehabilitation clinics, respectively.

## 3.7 Inappropriate Prescribing

A total of 9382 prescriptions of 399 patients were analysed. Out of all the prescriptions 2467 (26.3%) prescriptions were of the medications that need dosage adjustment and were included in the renal dosage adjustment guideline developed for ETCH (Appendix 4). Table 3.5 illustrates the extent of IP form total number of prescriptions and from prescriptions of the medications that need dosage adjustment. For absGFR and eCrCl there were less prescriptions (n=1947) added into the comparison due to incomplete medical records (i.e. absence of weight and height) and therefore inability to calculate absGFR and eCrCl.

**Table 3.5 Inappropriate prescribing**

| | Number of prescriptions | According to eGFR, % (n) | According to absGFR, % (n) | According to eCrCl, % (n) |
|---|---|---|---|---|
| IP from the total number of prescriptions | 9382 | 8.4% (790) | 6.1% (568) | 6.3% (597) |
| IP from the prescriptions needing dosage adjustment | 2467 | 32.0% (790) | 29.2% (568)* | 30.6% (596)* |

*Percentage calculated from the number of prescriptions available for absGFR and eCrCl (n=1947).

Figure 3.3 illustrates the classification of correct and inappropriate prescriptions between renal function categories. The highest proportion (457 of 790 prescriptions, 57.8%) of inappropriate prescriptions were placed into eGFR category >30 ml/min/1.73m$^2$, followed by eGFR 10-30 ml/min/1.73m$^2$ with 38.9% (307 of 790 prescriptions) and only minority, 3.3% (26 of 790 prescriptions), in the most severe renal function category of eGFR <10 ml/min/1.73m$^2$. In the latter the prevalence of IP among the eGFR category was 45.6% (26 prescriptions of 57).

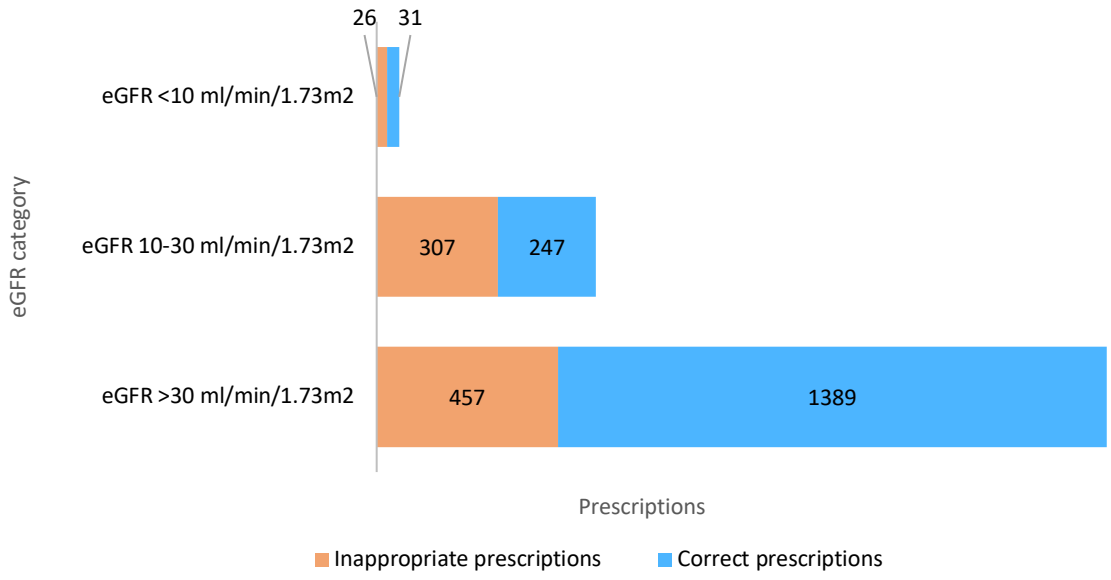
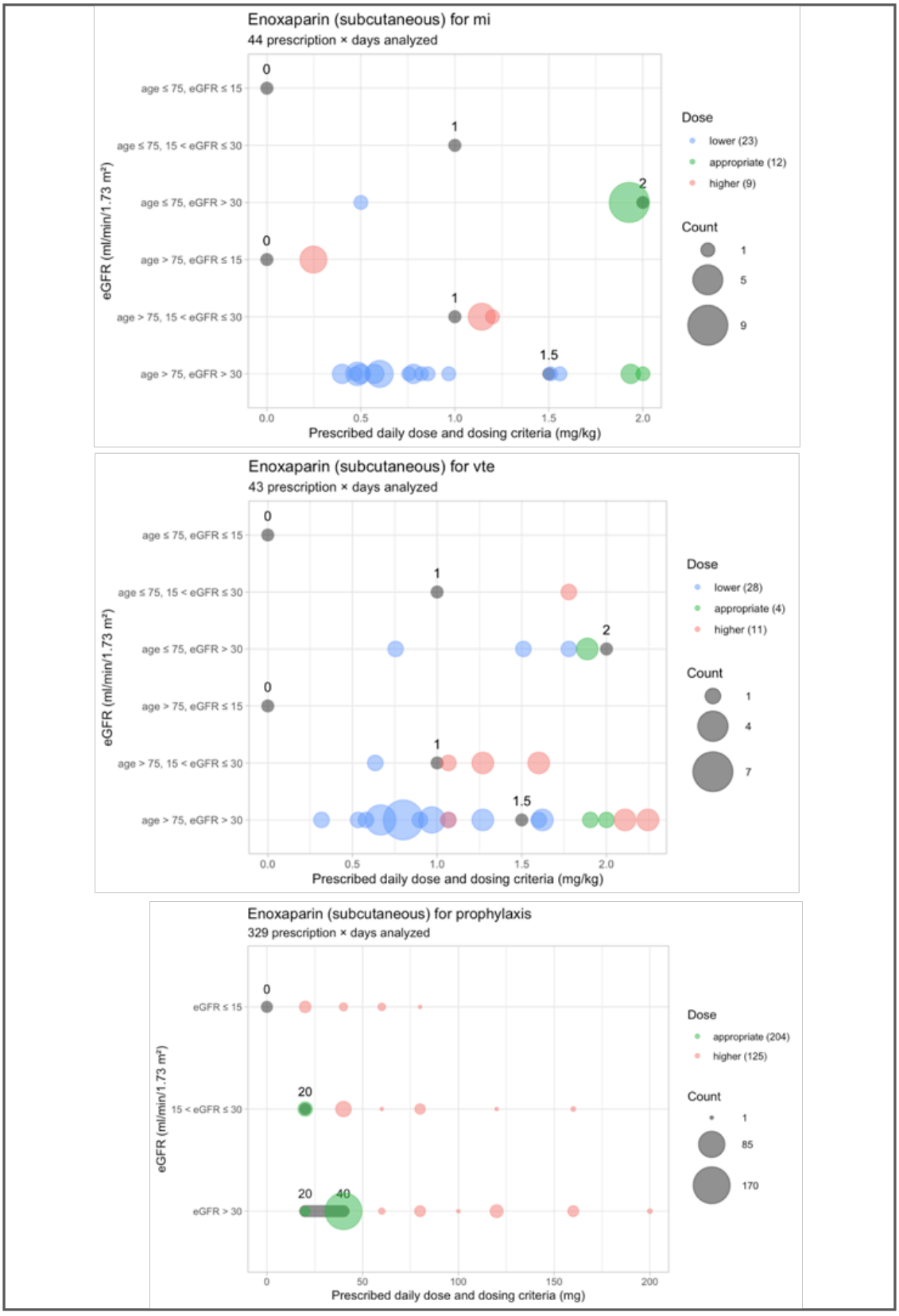



**Figure 3.3 Inappropriate prescriptions by renal function category (N=2467)**

Similar results were observed for the severe renal impairment category of eGFR 10-30 ml/min/1.73m$^2$ with 55.4% of IP (307 prescriptions of 554). For eGFR above 30 ml/min/1.73m$^2$ the prevalence of IP within the category was lower (24.8%, 457 prescriptions of 1846). Classification of inappropriate prescriptions of each medication between three eGFR categories can be found in Appendix 6.

Out of 54 medications included in the guideline 41 (75.9%) medications had discrepancies in prescribing (Appendix 7). Enoxaparin (n=453) was the most prescribed medication included in the guideline, followed by ampicillin/sulbactam (n=213), rosuvastatin (n=197), spironolactone (n=149), and ramipril (n=145). All the named medications, excluding spironolactone, were also inappropriately prescribed in this study. The highest IP values according to eGFR were detected for oseltamivir (100%), pethidine (92.6%), metoclopramide (93.3%), tranexamic acid (87.5%), and dexketoprofen (73.6%); according to absGFR for oseltamivir (100%), metoclopramide (92.5%), sultamicillin (88.9%), tranexamic acid (87.5%), and dexketoprofen (70.2%); according to eCrCl for oseltamivir (100%), trimethoprim/sulfamethoxazole (100%), metoclopramide (92.5%), sultamicillin (88.9%), and tranexamic acid (87.5%); excluding medications with only 1 prescription and showing IP.

IP can be further subdivided into dosage too low, dosage too high, or contraindicated use of medication. The classification of IP by medication can be found in Appendix 8. Higher than recommended dosage was the main contributor for IP, whereas antimicrobials and anticoagulants are the main medication classes presenting a high proportion of IP derived from too low dosage. An example of IP and dosing patterns of enoxaparin is illustrated in Figure 3.4. Dosing patterns for the rest of the medications can be found in Appendix 9.




Grey – recommended dosage for renal impairment

**Figure 3.4 Enoxaparin dosing patterns for myocardial infarction (n=44), venous thromboembolism (n=43) and for thromboprophylaxis (n=329) according to eGFR.**

IP varies between different specialities across all three renal function estimates used (Table 3.6). The highest proportion of IP according to all three renal function estimates can be seen in urology ward (52.8%, 44.7%, and 44.7% according to eGFR, absGFR, and eCrCl, respectively) followed by orthopaedics and internal medicine. Urology and orthopaedics both yielded IP rates above 30%. Rest of the wards had a prevalence of IP similar or lower than the average IP for the whole hospital.

**Table 3.6 Inappropriate prescribing in different wards (N=2467)**

| **Ward** | **Rx** (for absGFR and eCrCl) | **IP according to eGFR, % (n)** | **IP according to absGFR*, % (n)** | **IP according to eCrCl*, % (n)** |
|---|---|---|---|---|
| Internal medicine | 792 (487) | 36.1% (286) | 33.9% (165) | 32.9% (160) |
| Cardiology | 684 (600) | 27.0% (185) | 25.5% (153) | 27.5% (165) |
| Surgery | 310 (270) | 33.9% (105) | 27.8% (75) | 31.1% (84) |
| Neurology | 162 (93) | 23.5% (38) | 25.8% (24) | 25.8% (24) |
| Orthopaedics | 146 (138) | 35.6% (52) | 33.3% (46) | 39.9% (55) |
| Urology | 123 | 52.8% (65) | 44.7% (55) | 44.7% (55) |
| Rehabilitation I | 110 (107) | 29.1% (32) | 29.0% (31) | 31.8% (34) |
| Gastroenterology | 57 (49) | 14.0% (8) | 12.2% (6) | 20.4% (10) |
| Rehabilitation II | 46 (43) | 17.4% (8) | 9.3% (4) | 11.6% (5) |
| Endocrinology | 34 | 32.4% (11) | 26.5% (9) | 11.8% (4) |
| Spinal surgery | 3 (3) | 0.0% (0) | 0.0% (0) | 0.0% (0) |

Rx – number of prescriptions
*Percentage calculated from the total number of prescriptions available for absGFR and eCrCl.

Classification of IP according to eGFR in different wards is illustrated in Table 3.7. As expected, and shown in the medication-based classification of IP, inappropriate prescribing was mostly derived from using higher than recommended dosages.

**Table 3.7 Classification of inappropriate prescribing in different wards according to eGFR (N=2467)**

| Ward | Rx, n | Inappropriate Rx, n (%) | Dose too low, n (%) | Dose too high, n (%) | Contraindicated Rx, n (%) |
|---|---|---|---|---|---|
| Internal medicine | 792 | 286 (36.1% [32.8 … 39.5]) | 53 (6.7% [5.0 … 8.4]) | 233 (29.4% [26.2 … 32.6]) | 32 (4.0% [2.7 … 5.4]) |
| Cardiology | 684 | 185 (27.0% [23.7 … 30.4]) | 60 (8.8% [6.7 … 10.9]) | 125 (18.3% [15.4 … 21.2]) | 14 (2.0% [1.0 … 3.1]) |
| Surgery | 310 | 105 (33.9% [28.6 … 39.1]) | 31 (10.0% [6.7 … 13.3]) | 74 (23.9% [19.1 … 28.6]) | 17 (5.5% [2.9 … 8.0]) |
| Neurology | 162 | 38 (23.5% [16.9 … 30.0]) | 5 (3.1% [0.4 … 5.7]) | 33 (20.4% [14.2 … 26.6]) | 5 (3.1% [0.4 … 5.7]) |
| Orthopaedics | 146 | 52 (35.6% [27.8 … 43.4]) | 14 (9.6% [4.8 … 14.4]) | 38 (26.0% [18.9 … 33.1]) | 15 (10.3% [5.3 … 15.2]) |
| Urology | 123 | 65 (52.8% [44.0 … 61.7]) | 10 (8.1% [3.3 … 13.0]) | 55 (44.7% [35.9 … 53.5]) | 18 (14.6% [8.4 … 20.9]) |
| Rehabilitation I | 110 | 32 (29.1% [20.6 … 37.6]) | 7 (6.4% [1.8 … 10.9]) | 25 (22.7% [14.9 … 30.6]) | 6 (5.5% [1.2 … 9.7]) |
| Gastro-enterology | 57 | 8 (14.0% [5.0 … 23.1]) | 3 (5.3% [0.0 … 11.1]) | 5 (8.8% [1.4 … 16.1]) | 0 (0.0%) |
| Rehabilitation II | 46 | 8 (17.4% [6.4 … 28.3]) | 2 (4.3% [0.0 … 10.2]) | 6 (13.0% [3.3 … 22.8]) | 2 (4.3% [0.0 … 10.2]) |
| Endocrinology | 34 | 11 (32.4% [16.6 … 48.1]) | 1 (2.9% [0.0 … 8.6]) | 10 (29.4% [14.1 … 44.7]) | 6 (17.6% [4.8 … 30.5]) |
| Spinal surgery | 3 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

Rx – prescriptions

### 3.7.1 Inappropriate Prescribing of Anticoagulants

Out of all the prescriptions that needed dosage adjustment according to renal function 24.2% (n=598) were made for anticoagulants (Table 3.8). Enoxaparin accounted for the majority (75.8%, n=453) of prescriptions for anticoagulants and almost every second prescription, according to all three renal function estimates, was inappropriately prescribed. The prevalence of IP was highest according to eGFR (47.2%, n=214). Rivaroxaban showed a statistically significant difference ($\chi^2$=6.6, $p$=0.04) in the extent of IP between three renal function estimates. Overall, the prevalence of IP of anticoagulants was higher than the average IP for all the medications.

**Table 3.8 Inappropriate prescribing of anticoagulants (N=598)**

| **Medication** | **Rx** (for absGFR and eCrCl) | **IP according to eGFR, n (%)** | **IP according to absGFR*, n (%)** | **IP according to eCrCl*, n (%)** |
|---|---|---|---|---|
| Apixaban | 59 (55) | 29 (49.2%) | 29 (52.7%) | 29 (52.7%) |
| Enoxaparin | 453 (330) | 214 (47.2%) | 140 (42.4%) | 145 (43.9%) |
| Rivaroxaban | 74 (65) | 14 (18.9%) | 25 (38.5%) | 18 (27.7%) |
| Dabigatran | 12 (11) | 4 (33.3%) | 4 (36.4%) | 4 (36.4%) |
| **Total** | **598 (461)** | **261 (43.6%)** | **198 (43.0%)** | **196 (42.5%)** |

Rx – number of prescriptions
*Percentage calculated from the total number of prescriptions available for absGFR and eCrCl.

### 3.7.2 Inappropriate Prescribing of Antimicrobials

Out of all the prescriptions that needed dosage adjustment according to renal function 24.3% (n=599) were made for antimicrobials and antifungals. Table 3.9 illustrates IP among this class of medications. On average, IP was around 25% across all renal function estimate groups, which is less than the average IP for all the medications. If oseltamivir

was classified as antimicrobial, IP throughout all renal function estimates would rise about 5% (32.1%, 28.8%, and 30.1% for eGFR, absGFR, and eCrCl, respectively). Even though the prescription rate of oseltamivir was not high (36 for eGFR, 28 for absGFR and eCrCl), the prevalence of IP was 100% through all three estimates used. As shown in Table 3.9, IP is not consistent across all medications, some antimicrobials, such as, cefazolin, amoxicillin/clavulanic acid, sultamicillin, trimethoprim/sulfamethoxazole, and ertapenem, were more often inappropriately prescribed than others.

**Table 3.9 Inappropriate prescribing of antimicrobials and antifungals (N=599)**

| **Medication** | **Rx** (for absGFR and eCrCl) | **IP according to eGFR, n (%)** | **IP according to absGFR*, n (%)** | **IP according to eCrCl*, n (%)** |
|---|---|---|---|---|
| Amoxicillin/ Clavulanic acid | 101 (63) | 46 (45.5%) | 28 (44.4%) | 35 (55.6%) |
| Ampicillin/ Sulbactam | 213 (154) | 56 (26.3%) | 34 (22.1%) | 30 (19.5%) |
| Cefazolin | 23 (20) | 23 (100.0%) | 20 (100.0%) | 20 (100.0%) |
| Cefotaxime | 45 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Cefoxitin | 2 | 2 (100.0%) | 2 (100.0%) | 2 (100.0%) |
| Ceftazidime | 1 (0) | 1 (100.0%) | 0 (0.0%) | 0 (0.0%) |
| Cefuroxime | 76 (52) | 11 (14.5%) | 7 (13.5%) | 7 (13.5%) |
| Ciprofloxacin | 58 (46) | 8 (13.8%) | 2 (4.3%) | 2 (4.3%) |
| Clarithromycin | 26 (14) | 4 (15.4%) | 0 (0.0%) | 0 (0.0%) |
| Ertapenem | 7 (4) | 4 (57.1%) | 2 (50.0%) | 2 (50.0%) |
| Fluconazole | 7 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Nitrofurantoin | 1 | 0 (0.0%) | 0 (0.0%) | 1 (100.0%) |
| Piperacillin/ Tazobactam | 19 (18) | 1 (5.3%) | 1 (5.6%) | 1 (5.6%) |
| Sultamicillin | 13 (9) | 8 (61.5%) | 8 (88.9%) | 8 (88.9%) |
| Trimethoprim/ Sulfamethoxazole | 7 (5) | 4 (57.1%) | 3 (60.0%) | 5 (100.0%) |
| **Total** | **599 (440)** | **168 (28.0%)** | **107 (24.3%)** | **113 (25.7%)** |

Rx – number of prescriptions
*Percentage calculated from the total number of prescriptions available for absGFR and eCrCl.

### 3.7.3 Inappropriate Prescribing of Analgesics

Out of all the prescriptions that needed dosage adjustment 10.2% (n=251) were made for acute and chronic pain medications (Table 3.10). Ibuprofen, dexketoprofen, and pethidine had the highest IP rates across all three renal function estimates. The latter yielded an IP of 92.6% (n=25) according to eGFR, which is due to the recommendation suggesting avoiding pethidine in patients with eGFR <60 ml/min/1.73m$^2$ and, if possible, in general for the treatment of acute pain. The difference in the extent of IP of pethidine was statistically significant ($\chi^2$=9.0, *p*=0.01) between three renal function estimates. Prevalence of IP was highest according to eGFR, overall, almost every third analgesic was inappropriately prescribed. The rate of IP for analgesics was comparable to average IP of all the medications.

**Table 3.10 Inappropriate prescribing of analgesics (N=251)**

| **Medication** | **Rx** (for absGFR and eCrCl) | **IP according to eGFR, n (%)** | **IP according to absGFR*, n (%)** | **IP according to eCrCl*, n (%)** |
|---|---|---|---|---|
| Codeine | 38 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Dexketoprofen | 53 (47) | 39 (73.6%) | 33 (70.2%) | 34 (72.3%) |
| Diclofenac | 3 (1) | 1 (33.3%) | 1 (100.0%) | 1 (100.0%) |
| Etoricoxib | 32 (30) | 9 (28.1%) | 9 (30.0%) | 11 (36.7%) |
| Gabapentin | 11 | 4 (36.4%) | 4 (36.4%) | 5 (45.5%) |
| Ibuprofen | 8 | 5 (62.5%) | 3 (37.5%) | 4 (50.0%) |
| Morphine | 11 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Naproxen | 1 | 1 (100.0%) | 0 (0.0%) | 1 (100.0%) |
| Pethidine | 27 (24) | 25 (92.6%) | 14 (58.3%) | 15 (62.5%) |
| Pregabalin | 6 (6) | 0 / 6 (0.0%) | 0 / 6 (0.0%) | 0 / 6 (0.0%) |
| Tramadol | 61 (55) | 1 (1.6%) | 0 (0.0%) | 0 (0.0%) |
| **Total** | **251 (232)** | **85 (33.9%)** | **64 (27.6%)** | **71 (30.6%)** |

Rx – number of prescriptions
*Percentage calculated from the total number of prescriptions available for absGFR and eCrCl.

### 3.7.4 Inappropriate Prescribing of Antihyperglycemic Agents

Among antihyperglycemic agents metformin was the most inappropriately prescribed medication found in 73.4% (n=102) of all the prescriptions in this class (Table 3.11). The overall prevalence of IP of antihyperglycemic agents exceeded the average IP (39.6% and 32.0% according to eGFR, respectively). More than every third metformin prescription was inappropriate, glimepiride and sitagliptin yielding even higher prevalence of IP according to eGFR (44.4% and 46.2%, respectively). Difference in the extent of IP of sitagliptin was significant ($\chi^2$=10.3, *p*=0.006) between renal function estimates.

**Table 3.11 Inappropriate prescribing of antihyperglycemic agents (N=139)**

| **Medication** | **Rx** (for absGFR and eCrCl) | **IP according to eGFR, n (%)** | **IP according to absGFR*, n (%)** | **IP according to eCrCl*, n (%)** |
|---|---|---|---|---|
| Gliclazide | 6 (3) | 1 (16.7%) | 1 (33.3%) | 0 (0.0%) |
| Glimepiride | 18 (14) | 8 (44.4%) | 5 (35.7%) | 5 (35.7%) |
| Metformin | 102 (85) | 40 (39.2%) | 27 (31.8%) | 33 (38.8%) |
| Sitagliptin | 13 (9) | 6 (46.2%) | 0 (0.0%) | 0 (0.0%) |
| **Total** | **139 (111)** | **55 (39.6%)** | **33 (29.7%)** | **38 (34.2%)** |

Rx – number of prescriptions
*Percentage calculated from the total number of prescriptions available for absGFR and eCrCl.

### 3.7.5 Inappropriate Prescribing of Cardiovascular Agents

Out of all the prescriptions that needed dosage adjustment 28.7% (n=707) were made for cardiovascular agents, and related agents to treat or prevent cardiovascular complications (e.g. statins) (Table 3.12). Ramipril, rosuvastatin and spironolactone were the most prescribed medications in this class (145, 197, and 149 prescriptions,

respectively). Prevalence of IP among cardiovascular agents was notably lower than the average IP of all the medications, though some medications, such as, bisoprolol and trimetazidine, had above average rate of IP.

**Table 3.12 Inappropriate prescribing of cardiovascular agents (N=707)**

| **Medication** | **Rx** (for absGFR and eCrCl) | **IP according to eGFR, n (%)** | **IP according to absGFR*, n (%)** | **IP according to eCrCl*, n (%)** |
|---|---|---|---|---|
| Bisoprolol | 20 (4) | 4 (20.0%) | 2 (50.0%) | 2 (50.0%) |
| Digoxin | 46 (32) | 5 (10.9%) | 3 (9.4%) | 6 (18.8%) |
| Hydrochlorothiazide | 56 (55) | 8 (14.3%) | 8 (14.5%) | 9 (16.4%) |
| Indapamide | 44 (43) | 14 (31.8%) | 11 (25.6%) | 11 (25.6%) |
| Pentoxifylline | 13 | 1 (7.7%) | 1 (7.7%) | 1 (7.7%) |
| Ramipril | 145 (103) | 47 (32.4%) | 25 (24.3%) | 26 (25.2%) |
| Ranolazine | 1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Rosuvastatin | 197 (188) | 38 (19.3%) | 28 (14.9%) | 35 (18.6%) |
| Simvastatin | 25 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Spironolactone | 149 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Trimetazidine | 11 (10) | 5 (45.5%) | 3 (30.0%) | 4 (40.0%) |
| **Total** | **707 (623)** | **122 (17.3%)** | **81 (13.0%)** | **94 (15.1%)** |

Rx – number of prescriptions
*Percentage calculated from the total number of prescriptions available for absGFR and eCrCl.

Another 2 medications yielding high IP rates were metoclopramide and tranexamic acid. Prevalence of IP of metoclopramide was 93.3% (n=56) according to eGFR and 92.5% (n=49) according to absGFR and eCrCl, and of tranexamic acid 87.5% (n=7) across all three renal function estimates.

### 3.7.6 Prescribing Contraindicated Medications

Use of contraindicated medications was detected in 115 (4.7% [95% CI=3.8 to 5.5]), 75 (3.9% [95% CI=3.0 to 4.7]), and 74 (3.8% [95% CI=3.0 to 4.7]) prescriptions according to

eGFR, absGFR and eCrCl, respectively. In total 12 out of 54 medications which were included in the guideline had at least 1 contraindicated prescription (Table 3.13). Most common medications which use was contraindicated according to eGFR were analgesics (dexketoprofen [n=11] and pethidine [n=25]), enoxaparin (n=35), indapamide (n=13), glimepiride (n=8), and hydrochlorothiazide (n=8). Enoxaparin ($p$=0.04) and pethidine ($p$=0.01) showed statistically significant difference in contraindication rates between 3 renal function estimates.

**Table 3.13 Contraindicated medications across three renal function estimates**

| **Medication** | **Rx** (for absGFR and eCrCl) | **CI according to eGFR, n (%)** | **CI according to absGFR, n (%)** | **CI according to eCrCl, n (%)** | **Test** |
|---|---|---|---|---|---|
| Enoxaparin | 453 (330) | 35 (7.7% [5.3 … 10.2]) | 21 (6.4% [3.7 … 9.0]) | 11 (3.3% [1.4 … 5.3]) | $\chi^2$ (2) = 6.6, $p$ = 0.04* |
| Hydrochloro-thiazide | 56 (55) | 8 (14.3% [5.1 … 23.5]) | 8 (14.5% [5.2 … 23.9]) | 9 (16.4% [6.6 … 26.1]) | $\chi^2$ (2) = 0.1, $p$ = 0.9 |
| Dexketoprofen | 53 (47) | 11 (20.8% [9.8 … 31.7]) | 5 (10.6% [1.8 … 19.5]) | 7 (14.9% [4.7 … 25.1]) | $\chi^2$ (2) = 2.0, $p$ = 0.4 |
| Indapamide | 44 (43) | 13 (29.5% [16.1 … 43.0]) | 11 (25.6% [12.5 … 38.6]) | 11 (25.6% [12.5 … 38.6]) | $\chi^2$ (2) = 0.2, $p$ = 0.9 |
| Oseltamivir | 36 (28) | 1 (2.8% [0.0 … 8.1]) | 0 (0.0%) | 0 (0.0%) | $\chi^2$ (2) = 1.6, $p$ = 0.5 |
| Etoricoxib | 32 (30) | 9 (28.1% [12.5 … 43.7]) | 9 (30.0% [13.6 … 46.4]) | 11 (36.7% [19.4 … 53.9]) | $\chi^2$ (2) = 0.6, $p$ = 0.8 |
| Pethidine | 27 (24) | 25 (92.6% [82.7 … 100.0]) | 14 (58.3% [38.6 … 78.1]) | 15 (62.5% [43.1 … 81.9]) | $\chi^2$ (2) = 9.0, $p$ = 0.01* |
| Glimepiride | 18 (14) | 8 (44.4% [21.5 … 67.4]) | 5 (35.7% [10.6 … 60.8]) | 5 (35.7% [10.6 … 60.8]) | $\chi^2$ (2) = 0.4, $p$ = 0.8 |
| Ibuprofen | 8 | 3 (37.5% [4.0 … 71.0]) | 1 (12.5% [0.0 … 35.4]) | 2 (25.0% [0.0 … 55.0]) | $\chi^2$ (2) = 1.3, $p$ = 0.5 |
| Diclofenac | 3 (1) | 1 (33.3% [0.0 … 86.7]) | 1 (100.0%) | 1 (100.0%) | $\chi^2$ (2) = 2.2, $p$ = 0.3 |
| Naproxen | 1 | 1 (100.0%) | 0 (0.0%) | 1 (100.0%) | $\chi^2$ (2) = 3.0, $p$ = 0.2 |
| Nitrofurantoin | 1 | 0 (0.0%) | 0 (0.0%) | 1 (100.0%) | $\chi^2$ (2) = 3.0, $p$ = 0.2 |

Rx – number of prescriptions; CI – contraindication
*Statistically significant difference ($p$<0.05)

Proportionally the highest number of contraindicated prescriptions from the medications that need dosage adjustment according to eGFR were recorded in endocrinology (6 of 34, 17.6%) and urology (18 of 123, 14.6%) wards (Table 3.7). In urology the main contraindicated medications were analgesics (e.g. ibuprofen, pethidine) and in endocrinology all six contraindicated prescriptions were for enoxaparin.

## 3.8 Changes in Dosing Between Three Renal Function Estimation Equations

By only taking into consideration different equations for dosage adjustments, 1947 prescriptions could be compared in relation to eGFR, absGFR and eCrCl. eGFR was used as the reference to compare dosages. If absGFR had been used instead of eGFR for those 54 medications in the medication adjustment guideline, 1.0% (n=19, 95% CI=0.5 to 1.4) of the dosages should have been decreased even further, 11.9% (n=231, 95% CI=10.4 to 13.3) should have been increased, and the rest (87.1%, n=1697, 95% CI=85.7 to 88.6) would have stayed the same. Medications with the greatest proportion allowed to be used in higher dosage according to absGFR were rosuvastatin, spironolactone, ramipril, metformin, rivaroxaban, and also some antimicrobials (Appendix 10).

If eCrCl had been used instead of eGFR, 6.4% (n=125, 95% CI=5.3 to 7.5) of the dosages would have needed further reduction in dosage, 9.2% (n=179, 95% CI=7.9 to 10.5) should have been increased, and 84.4% (n=1643, 95% CI=82.8 to 86.0) would not have changed. Medications with the highest proportion of further need for dosage reduction according to eCrCl were digoxin, metformin, rivaroxaban, and cefazolin; and of which increase in dosage would have been allowed were rosuvastatin, metoclopramide, dabigatran, pethidine, and ampicillin/sulbactam (Appendix 11).

Based on these findings it can be seen that absGFR tends to allow higher dosages to be used compared to eCrCl, but the difference is not significant. eCrCl on the other hand classifies more prescriptions needing further decrease in dosage compared to absGFR. Overall, for both equations, the level of agreement with eGFR was slightly below 90%.

## 3.9 Factors Contributing to Inappropriate Prescribing

Associations between IP and several parameters at patient and prescription level suggested to contribute to IP were assessed using univariable and multivariable logistic regression model.

Figure 3.5 illustrates that intravenous (OR=2.17, 95% CI=1.76 to 2.68) and subcutaneous (OR=3.23, 95% CI=2.56 to 4.09) medications have higher odds to be prescribed inappropriately than oral medications. The odds for IP were almost 4 times greater in eGFR category 10-30 ml/min/1.73m$^2$ (OR=3.77, 95% CI=3.08 to 4.63) and 2 times higher in eGFR <10 ml/min/1.73m$^2$ (OR=2.34, 95% CI=1.35 to 4.04). Other predictors of IP at prescription level were thought to be LOS and number of prescriptions. Longer hospitalisation (OR=1.01, 95% CI=0.97 to 1.05, *p*=0.453) and number of prescriptions (OR=1.00, 95% CI=0.98 to 1.03, *p*=0.783) were not associated with an occurrence of IP in univariable analysis.

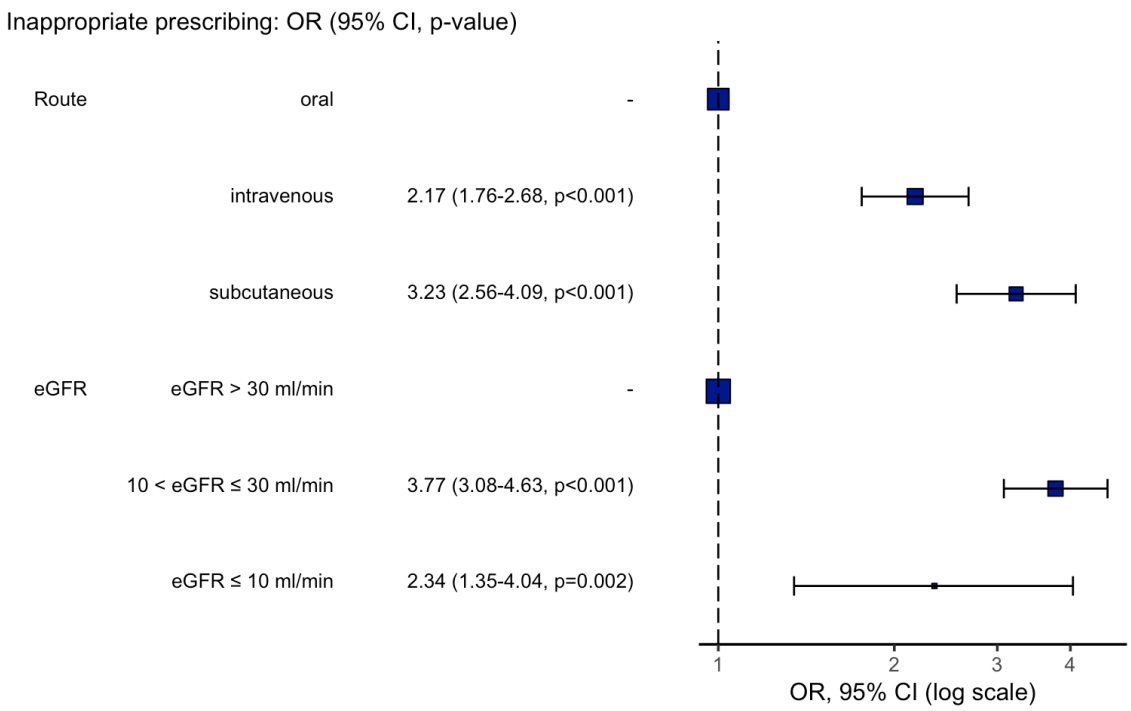



**Figure 3.5 Predictors of inappropriate prescribing at prescription level (N=2467).**

When looking at the predictors of IP at patient level on Figure 3.6 gender seems to have an effect on the occurrence of IP, as females have 40% lower odds for IP (OR=0.59, 95% CI=0.37 to 0.94) compared to males. Medications showing significant differences in the extent of IP between genders were rosuvastatin, metformin, amoxicillin/clavulanic acid, hydrochlorothiazide, and dabigatran.

Longer LOS (OR=1.06, 95% CI=1.01 to 1.12) and surgery during hospitalisation (OR=1.83, 95% CI=1.02 to 3.33) were both considered to contribute to increased odds for IP. Significantly higher IP rate ($p$<0.001) among patients undergoing surgery was seen for enoxaparin.

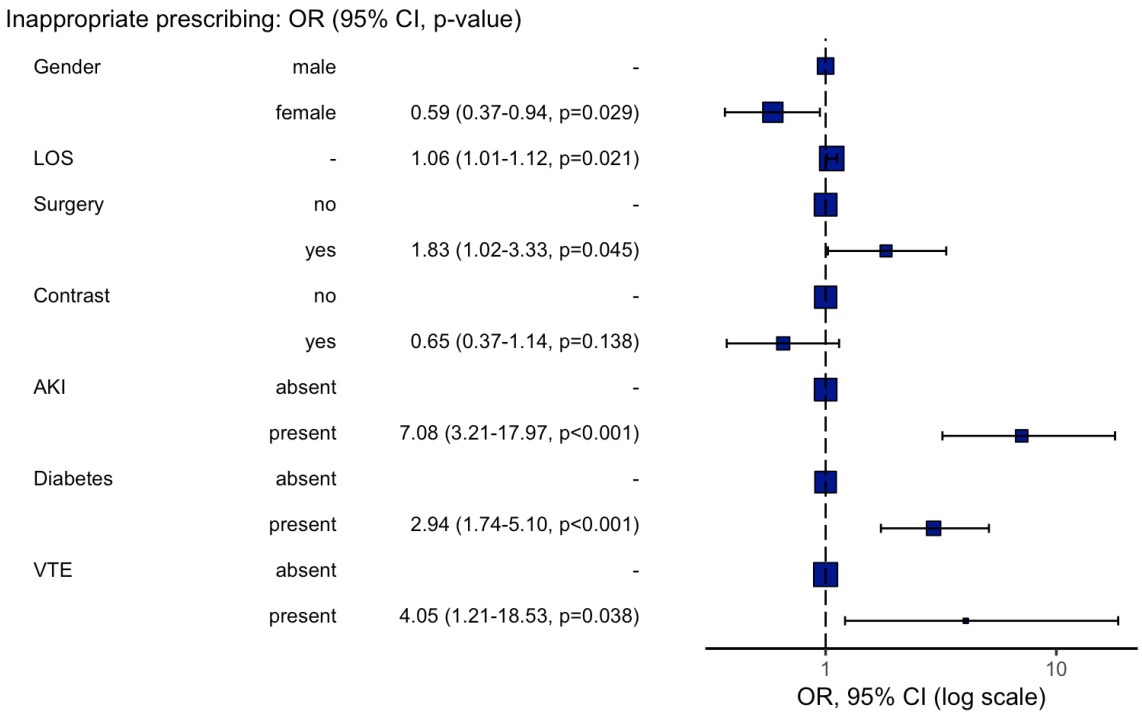



**Figure 3.6 Predictors of inappropriate prescribing at patient level (N=399).**

Patients' comorbidities, such as AKI, diabetes mellitus, and VTE were all associated with greater odds for IP. Presence of AKI (both documented and undocumented) was the strongest predictor of IP (OR=7.08, 95% CI=3.21 to 17.97) with enoxaparin, rosuvastatin, indapamide, and etoricoxib showing significant differences ($p$<0.001) in the extent of IP between patients with and without AKI. VTE together with IP was present in 17 patients with enoxaparin being the major contributor for the IP among these patients. Enoxaparin yielded 90.2% (55 of 61 prescriptions) IP rate which was statistically significant ($p$<0.001) compared to the patients without VTE (40.6%, 159 of 392 prescriptions). Among patients with diabetes significantly higher ($p$<0.05) IP rates were detected for ramipril and dexketoprofen.

Patient's BMI (OR=1.00, 95% CI=0.96 to 1.03, $p$=0.793) and age (OR=1.00, 95% CI=0.98 to1.02, $p$=0.884) did not show association with IP using univariable logistic regression

model. Contrast media administration did not contribute to the occurrence of IP (OR=0.65, 95% CI=0.37 to 1.14, *p*=0.138), although known to be a predictor of AKI. Other comorbidities namely AF, HF, hypertension, and MI were not associated with greater odds for IP in multivariable logistic regression model, but hypertension (OR=1.69, 95% CI=1.07 to 2.67, *p*=0.025), AF (OR=1.61, 95% CI=1.05 to 2.47, *p*=0.030) and HF (OR=1.85, 95% CI=1.21 to 2.84, *p*=0.005) were all independently associated with the occurrence of IP. Charlson comorbidity index was associated with IP in univariable analysis (OR=1.17, 95% CI=1.06 to 1.30, *p*=0.002) (Appendix 12).

# Chapter 4

# Discussion

Renal dosage adjustment of medications is a topic that has been discussed on many levels. Which formula to use for dosage adjustments, to what extent these have to be done for certain medications and what is the benefit of adjustments is still debatable. With an ageing population that has several comorbid conditions, including CKD, the problem of decreased renal function and its effect on patient outcomes cannot be overlooked. It is evident that patients with decreased renal function are more at risk for having ADEs leading to longer hospitalisation (Chertow et al, 2005). Furthermore, it is described that poor renal function causes increase in mortality and higher costs in healthcare (Chertow et al, 2005). Risk of ADEs and worsening of renal function should be minimised as these are strongly associated with higher mortality (Chertow et al, 2005; Hassan et al, 2010). Studies have shown high prevalence of IP in healthcare settings despite the availability of dosing guidelines (Hassan et al, 2009; Nielsen et al, 2014; Drenth-van Maanen et al, 2015). Presence of clinical pharmacist in the ward and CDSS seem to have a greater impact on improving acceptance rates of dosage adjustments (Cabello-Muriel et al, 2014; Arias Pou et al, 2019). This led to the conduct of current study – to have a closer look into the current practice with regards to renal dosage adjustment in ETCH. The retrospective study design allowed to observe everyday practice at ETCH, to identify the most common medication classes that were inappropriately prescribed and to develop a medication dosage adjustment guideline to improve appropriate prescribing of renally eliminated medications.

To develop a medication dosage adjustment guideline for ETCH it would have been inappropriate to just take one of the guidelines already available and implement it at ETCH. Every hospital, or other clinical setting, has its own specific needs and differences

in clinical practice that have to be taken into account when implementing new processes and guidelines.

There are a number of studies showing discrepancies between different guidelines, furthermore these guidelines generally only give recommendations for CKD patients and not for patients with AKI (Vidal et al, 2005; Khanal et al, 2014; O'Shaughnessy et al, 2017). AKI and other conditions with unstable SCr may need different approaches for dosage adjustments. In order to develop a guideline suitable for ETCH different medication information sources were analysed. BNF, RDH and UTD were chosen as these are the most common sources used by the physicians in different hospitals. Comparison of BNF, RDH, and UTD showed 45% of discordance between medication information sources when comparing 71 medications and 202 recommendations. These results are in agreement with other published studies also showing low level of agreement between sources, though none of the studies compared these 3 sources (Khanal et al, 2014; O'Shaughnessy et al, 2017).

Similarly to a study by O'Shaughnessy and colleagues most discordances were reported in the eGFR category of 10-30 ml/min/1.73m$^2$ (O'Shaughnessy et al, 2017). With moderate renal impairment defined as eGFR 30-50 ml/min/1.73m$^2$, many medications do not need any dosage adjustment which as a result provides a higher level of agreement between medication information sources. Frequently medications are contraindicated in patients in the lowest eGFR category (<10 ml/min/1.73m$^2$) or lacking dosage adjustment studies, which again gives a higher level of agreement due to fewer possibilities for recommendations.

There are reasons why eGFR 10-30 ml/min/1.73m$^2$ group has the most versatile recommendations. It can be seen that in the guidelines different eGFR values are often used for dosing in severe renal impairment (eGFR <30 ml/min/1.73m$^2$). Same dosing can be recommended for different eGFR ranges when comparing sources and as a result place the medication into different category for dosage adjustment.

Another reason for the high number of discrepancies in the severe renal impairment category might be the primary reference used to provide recommendations. Some guidelines mostly refer to the recommendations in the SPC (e.g. BNF) to guide dosage adjustments, which is a logical and ethical choice from a clinical perspective (Joint Formulary Committee, 2018). Other sources (e.g. RDH, UTD) are more innovative and combine recent literature and clinical experience in the recommendations, which could be of benefit in terms of patient outcomes, but these can be substantially different from the ones in the SPC[6] (Ashley and Dunleavey, 2018). It is up to the physician to decide which source of information to use, as these more innovative guidelines might not have strong evidence from large randomised control studies. Using these sources physicians are put under pressure to take full responsibility on the accuracy of dosage adjustment.

Another reason for the high number of discrepancies is the use of qualitative terms when referring to a decline in renal function. 'Moderate renal impairment' or 'Severe renal impairment' can be interpreted differently, especially if there is no explanation provided. Severe impairment in one guideline may refer to eGFR less than 10 ml/min/1.73m$^2$ and in another eGFR less than 30 ml/min/1.73m$^2$, but it can also refer

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[6]UpToDate®. Drugs & Drug Interactions [Internet]. UpToDate, Inc; c2020 [cited 2020 Mar 25]. Available from: https://www.uptodate.com/home/drugs-drug-interaction.

to a range, such as eGFR 15-30 ml/min/1.73m$^2$, which again makes it difficult to evaluate the level of agreement between sources.

In the current study a high number of disagreements between sources can also be due to the evaluation process of recommendations. For instance, for sitagliptin BNF and UTD state 50mg once daily for eGFR 30-45 ml/min/1.73m$^2$, RDH suggests the same dosage, but up to eGFR 50 ml/min/1.73m$^2$. These recommendations are not the same, thus were considered different and marked as disagreement between sources. Another example of disagreement was suggestion 'avoid or reduce dose' in one source and if the other one only stated 'avoid', these were considered inconsistent. In clinical practice a more cautious dosing for sitagliptin with eGFR 45-50 might not have a significant impact on patients' outcome, as other parameters are also used to guide dosing in diabetes patients (Goodchild and Chowdhury, 2017).

Regardless of eGFR category the way recommendations are presented has a great impact when drawing comparisons between sources. The most convenient are quantitative recommendations with precise dosage adjustments, either exact numeric dosage or frequency of administration. Another option is to express dosage adjustments as percentages of normal dosages, which could be useful for medications with a wide dosing range for different clinical conditions, but this approach assumes that the prescriber is aware of the normal maximum dosages for each condition and patient population (e.g. pregabalin). This adds another step to dosage adjustment making it more error-prone and likely to result in no adjustment at all. The least informative are qualitative recommendations, such as 'reduce dose', which, for the physicians, is the most complicated to follow (Vidal et al, 2005).

When analysing dosage adjustments, it is important to consider different renal function estimates used. BNF uses eGFR according to MDRD equation which is well-proven to overestimate renal function in elderly population and in patients at extremes of body weight due to its normalisation to BSA (Pequignot et al, 2009; Dowling et al, 2013; Kilbride et al, 2013). It is also reported that MDRD equation is the least accurate when GFR rises over 60 ml/min/1.73m$^2$. RDH uses CG equation and eCrCl to guide adjustments and in UTD renal function estimates vary between medication monographs. When simply comparing dosage recommendations different equations might not be of great importance, but in clinical practice correct interpretation of renal function is crucial.

Comparison of medication information sources was a stepping stone to developing dosage adjustment guideline for ETCH. From the comparison it can be seen that there were a number of discrepancies between chosen sources, and in order to develop a reliable guideline for the hospital, in addition to these sources, SPC and recently published literature were consulted to provide the most accurate and up to date recommendations. The main focus in the developed guideline was made on providing comprehensive and clear recommendations for dosage adjustments of medications in the hospital formulary. Recommendations of preferred renal function estimates and approaches to dosage adjustments in specific patient populations are provided. Implementation of in-house guideline makes dosage adjustment information readily available to all physicians and can help improve appropriate prescribing.

In the current study the extent of IP for all the patients was lower than in similar studies due to inclusion/exclusion criteria (Holm et al, 2015; Saad et al, 2019). Patients from the ICU, emergency department, oncology, and rheumatology were excluded, which could

have underestimated the prevalence of IP and underestimated the extent of IP of certain medication classes, such as antimicrobials. Depending on which renal function estimates are used affects the extent of IP and makes it intricate to compare between studies. In the following paragraphs all the proportions of IP are expressed according to eGFR (using CKD-EPI equation) if not stated otherwise. By definition IP should include all inappropriate dosages, but it might not always be clearly stated in all the studies. In the current study both higher and lower than recommended dosages were included in the analysis, as both are equally important in terms of treatment and side effects.

The extent of IP can vary extensively between ambulatory or acute care, and also between medical specialty (Gheewala et al, 2014; Doody et al, 2015; Holm et al, 2015; Khanal et al, 2015; Saad et al, 2019). Medication use profile of each specialty is the key to understanding the risk of IP. Surgery could be considered as high-risk speciality for IP because antimicrobials, anticoagulants and analgesics, which are the main treatment options in surgery clinic, are the most often inappropriately prescribed medication classes. This hypothesis was mostly true, with orthopaedics (35.6%, n=52) and general surgery (33.9%, n=105) both achieving higher than average IP rate, and with urology yielding the highest prevalence of IP (52.8%, n=65). Nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, and the antiemetic, metoclopramide, were the most inappropriately prescribed medications in all 3 wards. Male gender and surgery performed during hospitalisation are predictors of IP which could be the reason why the prevalence of IP was high in urology ward compared to the rest. A poor background knowledge of dosage adjustments by physicians cannot be excluded. In urology and orthopaedics wards half of the medications (7 of 13 and 6 of 11, respectively) reached IP rate of 100%, which together with the overall high IP rate could indicate that the

physicians in named wards are not aware of the need for dosage adjustment of certain medications. Another reason for high IP rate could be the absence of an internal medicine physician or nephrologist to attend the ward. The 100% IP rate in surgery ward is more promising including 5 out of 18 medications. Orthopaedics and urology were also wards with the highest proportion of contraindicated prescriptions mostly for analgesics, most commonly pethidine. Usage of pethidine in ETCH as analgesic was everyday practice in 2018, although in decreased renal function its use is contraindicated due to accumulation of neurotoxic metabolite.

Medication usage profile in internal medicine clinic varied without any distinct medication class being the most prevalent. In general, IP rate in internal medicine clinic was lower than in surgery, around 25% (range 14-36.1%), with the highest IP rate in internal medicine ward. High prevalence of IP could be due to the greatest number of inappropriate prescriptions (n=792), and complex patient profiles, but also due to lack of knowledge of recommendations for dosage adjustment of certain medications. This could have been why oseltamivir, metoclopramide and tranexamic acid all reached almost 100% IP rate. Usage of contraindicated medications was only 4% with the main contributor being enoxaparin, which classification as inappropriate prescription is discussed below. Very low proportion of contraindicated prescriptions could be one of the markers showing that physicians are generally aware of the need for dosage adjustment and the risks of not adjusting dosages, but the absence of clear recommendations has an impact on the extent of IP.

Appropriate dosages of certain medications can sometimes be questioned. Antimicrobials, for instance, are one class of medications where dosage adjustment at

the initiation of treatment is not recommended. Loading dosage should mostly be administered despite renal function and depending on patient's condition further higher dosages of antimicrobials may be warranted (Ashley and Dunleavey, 2018; Eyler and Shvets, 2019). Risk-benefit ratio of longer than recommended higher dosages should be evaluated in each separate case.

The IP rate for antimicrobials in the current study should be taken with caution as antimicrobial dosing is often guided by minimum inhibitory concentration and susceptibility and because of the retrospective study design it was not possible to know the exact reasoning behind decisions over antimicrobial treatment (Eyler and Shvets, 2019). It was also not possible to separate loading and maintenance dosages of antibiotics or to account for the day of the switch of antibiotic therapy. Administration of loading dosages seemed to be missing and reduction in dosage was made straight away. These issues could have contributed to the overestimation of the rate of IP in view of loading dosages, and to the underestimation in the context of switching from one antimicrobial to another, which on the day of the switch were administered in lower dosages per day.

Both too high and too low dosages were considered inappropriate but knowing the clinical scenario would have helped to distinguish between clinically significant and insignificant IP. For instance, cefazolin had an IP rate of 100% and all the prescriptions were considered to be lower than recommended dosages. Knowing that cefazolin is mostly used for perioperative antimicrobial prophylaxis, and the duration of treatment is short, could have led to possible mis-documentation of the dosages throughout hospitalisation due to patient's medications only being recorded on the days of the eGFR

value less than 60 ml/min/1.73m$^2$. Nevertheless, too low dosage of antimicrobials could lead to treatment failure, antimicrobial resistance, and increase in side effects, whereas too high dosage causes accumulation, toxicity, and increases probability of side effects (Eyler and Shvets, 2019). Thus, both are equally important when assessing IP and cannot be excluded from the evaluation of the extent of IP.

Low molecular weight heparin (LMWH), enoxaparin, is another example where clinical judgement can overrule the dosage adjustment recommendations according to renal function. In this study enoxaparin had the highest number of IP prescriptions with an overall IP rate of 47.2% (n=214). In the context of enoxaparin proper documentation of diagnosis plays an important role in the evaluation of IP and might have been one of the main factors leading to high extent of IP. If diagnosis indicating treatment dosage (e.g. VTE, MI) was missing from patient's records, it was classified as patient should have received a prophylaxis dosage, which as a result gives falsely high IP rate. Another reason could have been rounding of the dosage to the nearest available prefilled syringe size, which are available with a 20mg step (e.g. 20mg, 40mg, 60mg), and with a weight-based dosing using ABW this could have further affected the appropriate dosing and lead to IP.

High extent of IP of oseltamivir could partially be explained by the same documentation of diagnosis phenomena. If influenza was not documented in the records for patients receiving oseltamivir, then prescription of oseltamivir was classified as prophylaxis treatment and could have contributed to the high extent of IP. Only 8 prescriptions out of 36 were affected by incomplete documentation and the effect on overall IP might be considered marginal.

Analgesics is another class of medications which use is problematic. Package inserts for NSAIDs warn about the risk of possible renal damage and suggest using with caution or avoiding completely. Medication information sources also provide distinct recommendations. SPC of dexketoprofen states that the use in moderate to severe renal impairment (eGFR <60 ml/min/1.73m$^2$) is contraindicated, whereas BNF and RDH are less stringent and allow use with eGFR above 30 ml/min/1.73m$^2$ in decreased dosage[10] (Joint Formulary Committee, 2018; Ashley and Dunleavey, 2018). In the current study recommendations from the BNF and RDH were adopted relying on the clinical practice and safety information pointed out by these sources. Adoption of recommendations from BNF and RDH should have notably lowered the extent of IP, but despite more lenient recommendations the extent of IP was high (73.6%). It seemed that a more cautious approach was taken with intravenous than oral dexketoprofen, although intravenous administration of medications was considered to be a predictor of IP in this study.

Metformin, first line option for the treatment of diabetes mellitus, is another complex medication in terms of IP. SPC of metformin prohibits use with GFR below 30 ml/min, but recommendation in the guideline developed for ETCH is more lenient allowing treatment with maximum 500mg till GFR 10 ml/min[11]. All the patients who received metformin with a GFR below 30 ml/min had it prescribed in higher dosage than 500mg, thus still contributing to the IP analysis, but not contraindicated. Despite the wide use

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[10]MENARINI INTERNATIONAL O.L.S.A. SPC of dexketoprofen [Internet]. MENARINI INTERNATIONAL O.L.S.A; 2018 [cited 2020 May 20]. Available from: https://www.medicines.org.uk/emc/product/159/smpc.

[11]Wockhardt UK Ltd. SPC of metformin [Internet]. Wockhardt UK Ltd; 2017 [cited 2020 May 20]. Available from: https://www.medicines.org.uk/emc/product/2415/smpc.

of metformin, and being the gold standard for diabetes care, 39.2% (n=40) of the prescriptions were inappropriately prescribed. It is not clear why the extent of IP was high, but it might be that potential ADEs of metformin are not considered important, benefit outweighs the risk in multimorbid patients, and/or lack of knowledge about the dosage range with specific GFR values.

Other studies have reported high prevalence of IP among angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) (Cabello-Muriel et al, 2014; Roux-Marson et al, 2020). Only medication from those classes included in this study was ramipril due to being the only medication out of ACEi and ARBs (in the hospital formulary) that had clear recommendations for dosage adjustment. For instance, dosage for initiation of perindopril is stated in different guidelines (BNF, RDH, UTD), but maximum allowed dosage is not stated, thus it was not feasible to include perindopril in the study as it was not possible to distinguish between starting and maintenance dosages. Only ACEi in the study, ramipril, had an average IP rate (32.4%), but as ACEi and ARBs are also known for their renoprotective effect and potential to increase life-expectancy in HF patients the risk of worsening renal function can sometimes be overlooked by the greater benefit of continuing therapy (Molnar et al, 2014; Brar et al, 2018; Clark et al, 2019).

One of the objectives of the research was to assess prevalence of IP using three different renal function estimation equations (i.e. eGFR, absGFR, eCrCl). The idea behind using three estimates instead of one was to evaluate if there were significant differences in IP between equations in this study populations. Secondary outcome based on the

evaluation was to determine which renal function estimation approach should be used for medication dosage adjustments at ETCH.

At ETCH, CKD-EPI equation is used for the assessment of renal function and the value provided with each SCr result. Due to the fact that eGFR result by CKD-EPI is readily available for the physicians it is also the value used for dosage adjustment of medications. Although CG formula is the gold standard formula for dosage adjustments, newer formulae (e.g. MDRD, CKD-EPI equations) have started to replace CG, but the reliability of eGFR performance with regards to dosage adjustments is not clear.

The use of eGFR for specific patient populations (e.g. elderly, critically ill, patients at extremes of body weight) is questionable, because taking into account just gender, age and SCr is not enough to estimate renal function for dosage adjustments (Dowling et al, 2013; Bouquegneau et al, 2016; Hart and Anderson, 2018). Comparing different renal function estimates, performing series of SCr analysis, or using another marker (e.g. Cys) to estimate renal function might be a reasonable alternative to creatinine-based eGFR. In view of the current study eGFR, absGFR and eCrCl were used to compare medication dosages between equations. Around 85% of the dosage recommendations were similar between three equations supporting the idea of using eGFR instead of eCrCl for dosage adjustments. It has to be kept in mind that even though the overall level of agreement was good, the proportions between higher and lower dosages between equations were notably different for some medications (e.g. rivaroxaban). Other studies have also reported that sole use of one estimation equation for all the patients, and all the medications, is misleading (Bouquegneau et al, 2016; Hart and Anderson, 2018).

DOACs are one class of medications that require use of CG formula and eCrCl for dosage adjustments due to possibility of under- or overdosing leading to life-threatening side effects, such as thromboembolism or bleeding, when using eGFR formulae (Chan et al, 2016; Lee et al, 2019). Medications with narrow therapeutic indices (e.g. digoxin) also possess high risk for ADEs, thus eCrCl with therapeutic drug monitoring, if applicable, should be preferred instead of eGFR (Ashley and Dunleavey, 2018; Joint Formulary Committee, 2018).

Elderly patients are another example where sole use of eGFR can lead to wrong estimation of renal function due to decreased muscle mass, hence present with falsely low SCr values that might not represent the true renal clearance. In elderly, a comparison of two renal function estimates should be performed at all times when newer markers, such as Cys, are not available (Hart and Anderson, 2018). Adding another contributor, such as obesity, makes the estimation even more complicated. In view of the current study, including mostly elderly patients of whom one third were obese, caution must be taken when assessing SCr levels and interpreting eGFR values. For patients at extremes of body weight the use of de-indexation of eGFR formulae (i.e. absGFR) has been proposed to account for the possible underestimation when normalised eGFR formulae are used (Chew-Harris et al, 2015; Bouquegneau et al, 2016; Hart and Anderson, 2018). With regards to IP, absGFR provided the lowest prevalence of IP among three estimates used in this study and showed a trend towards bolder approach in prescribing, which might not always be appropriate (e.g. anticoagulants) (Chan et al, 2016; Lee et al, 2019).

From the practical side the use of three renal function estimates in everyday clinical practice in the same healthcare facility might not be feasible. Taking into account the study population and medication usage profile in the study wards it seems reasonable to propose implementation of eGFR and eCrCl for the assessment of renal function for dosage adjustments. Values of eGFR can be independently used most of the times, but in the elderly, or in patients at extremes of body weight, a comparison of two equations should be performed and decision of dosage adjustment made accordingly (Hart and Anderson, 2018). To account for the increase, or decrease, in LBW when using eCrCl adjBW, instead of TBW, should be used as this has been shown to correlate the best with mGFR (Bouquegneau et al, 2016). Implementation of Cys measurements into the clinical practice at ETCH should be the goal for the future to provide better care for the patients with decreased renal function (Werner et al, 2017; da Silva Selistre et al, 2019).

Inclusion and exclusion criteria specified that in order to be included in the study patients had to be 18 years or older and have at least one recording of eGFR <60 ml/min/1.73m$^2$. The criteria did not mandate presence of CKD or AKI, thus it gave an opportunity to analyse a wide range of patients with different clinical profiles. Despite this, the mean age of study population was 79 years (IQR 13.9) with 50% of the patients being between 65 and 93 years. In the context of the results the focus is on the IP in the elderly patients with decreased renal function, as 88% of the study population was over 65 years. It is well known that the prevalence of IP increases with age due to physiological changes in the kidneys, high burden of comorbidities, and polypharmacotherapy (Chang et al, 2015; Doody et al, 2015; Khanal et al, 2015; Kang and Hong, 2019). A mean Charlson index of 5 (IQR 3) and average 8 medications per day (IQR 6) could indicate a higher prevalence of IP among this study population.

Other studies have shown correlation between age and the extent of IP – with increasing age the possibility of having one or more inappropriate prescription rises (Liu et al, 2012; Doody et al, 2015; Khanal et al, 2015). This study did not find any correlation between advanced age and IP which could be due to the study population being primarily elderly and analysis, in the view of comorbidities and polypharmacotherapy, between different age groups was not possible.

Gender correlates with IP showing higher odds for IP in males. The data is conflicting with regards to gender being a predictor of IP and in a recent study an opposite association was drawn where they showed that females had higher risk of IP (Breton et al, 2011; Pérez et al, 2018). There is no clear explanation why male gender should be a risk factor for IP in the current study, but it could be related to underlying comorbidities leading to decreased renal function (e.g. heart failure), and also due to higher incidence of AKI and CKD in males in this study population.

The number of comorbidities and also certain diseases have been associated with increased rate of IP (Chang et al, 2015; Khanal et al, 2015; Saleem and Masood, 2016). Charlson comorbidity index was an independent predictor of IP in univariable analysis but did not show significance in the multivariable analysis. Even though these findings are in line with other studies, the accuracy of Charlson comorbidity index in the current study is questionable mainly due to poor documentation of comorbidities in health records. It was out of scope of this study to evaluate correct documentation of diagnoses, but a trend towards not recording all the diagnoses in certain specialities or by some physicians was present. Not acknowledging and documenting patients' underlying comorbidities could have led to estimation of a lower number of

comorbidities and lower Charlson indices among study population, and therefore influence the association between the prevalence of IP and the number of comorbidities.

One of the most common risk factors for CKD and end-stage renal disease is diabetes which due to its pathophysiology can eventually lead to diabetic nephropathy and renal failure (National Kidney Foundation, 2012; Alicic et al, 2017). Diabetes has been associated with increased risk for IP and also associated with polypharmacotherapy in the elderly (Manley et al, 2003; Khanal et al, 2015, Roux-Marson et al, 2020). Findings of this study support the association showing that the presence of diabetes was a predictor of IP increasing the odds 3 times. Kidney disease related to diabetes often remains under-recognised, together with some antihyperglycemic medications (e.g. metformin) being primarily renally eliminated and requiring dosage adjustments for renal function, these could be the main causes of higher prevalence of IP in patients with diabetes (Alicic et al, 2017).

Owing to strong association between IP and diabetes a hypothesis whether obesity could affect IP was tested. Obesity (BMI greater than 30) is known to be a major risk factor for diabetes and cardiovascular diseases (Riaz et al, 2018). Higher BMI itself did not contribute to IP in this study, but despite non-significant association with IP weight must be considered when assessing renal function. eGFR formulae are normalised to BSA and eCrCl incorporates weight into the calculation which in obese patients can lead to misinterpretation of patient's actual renal function and ultimately increase the risk for IP (Bouquegneau et al, 2016).

VTE was strongly associated with occurrence of IP. VTE is often a complication of a surgery but also a complication of CKD which is known to increase the risk of IP (Daneschvar et al, 2008). In patients with VTE the evaluation of IP is complicated. Higher than recommended dosages of anticoagulants could lead to fatal bleeding, but on the other hand using reduced dosages recommended for patients with renal impairment could cause a fatal thrombus. Findings from the RIETE Registry support the use of full normally prescribed dosage of anticoagulants (i.e. LMWH) despite renal function (Monreal et al, 2006; Trujillo-Santos et al, 2013). Enoxaparin was the biggest contributor for IP in patients with VTE in this study and when considering the risk-benefit ratio of higher compared to lower dosages of anticoagulants the association between VTE and IP should be acknowledged, but in clinical practices dosages should not be changed only according to renal function.

Decrease in renal function, both chronic and acute, is associated with higher incidence of IP (Saleem and Masood, 2016; Yang et al, 2016). AKI, either documented or undocumented in health records, was shown to be the greatest predictor of IP. When renal function declines the risks for IP increase, but a more concerning issue in the current study, and also possible cause for a high IP rate among AKI patients, was the documentation of AKI. AKI diagnosis was beyond the scope of this study, but the baseline characteristics showed that 73.6% of the patients with AKI did not have AKI documented despite the drop in eGFR value suggesting at least mild AKI. The findings are in accordance with a study by Wilson et al suggesting that more than half of the AKI diagnoses are inappropriately documented (Wilson et al, 2013). The high extent of undocumented, and probably unrecognised, AKI could have been one of the main causes for AKI being a strong predictor of the occurrence of IP. Better acknowledgement

and documentation of AKI could be one of the options to decrease the extent of IP and also to improve patient outcomes namely decrease mortality and LOS (Chertow et al, 2005; Wilson et al, 2013).

Multivariable analysis failed to show significance in the odds between cardiovascular diseases and IP. Significance was detected in univariable analysis for hypertension, HF, and AF showing to be independent risk factors for IP. These findings are in line with other studies reporting association between IP and cardiovascular diseases (Khanal et al, 2015; Saleem and Masood, 2016). The nature and treatment of HF and hypertension explain that both could be associated with decreased renal function in the long term, thus increase the risk for IP (Clark et al, 2019; House et al, 2019).

Interventions in the hospital, such as surgery and contrast media administration, could be considered as risk factors for IP in patients with already decreased renal function because both are known to increase the risk of AKI (Biteker et al, 2014; van der Molen et al, 2018). Contrast media administration which in the past was associated with higher incidences of contrast induced nephropathy was not a significant risk factor among study population (van der Molen et al, 2018). On the other hand, patients undergoing surgery were considered to have higher odds for IP. Risk factors for perioperative AKI are advanced age, diabetes, male gender and decline in renal function, which were also predictors of IP in the current study (Park et al, 2019). Increased odds for IP in patients undergoing surgery could be due to the overall higher prevalence of IP in surgery clinic. It is not clear whether surgical inappropriate prescriptions are caused by high rate of undocumented AKI (86.7%) or the lack of knowledge with regards to dosage adjustments by the physicians.

In addition to comorbidities and surgery, longer hospitalisation (7 days compared to 5 days) was shown to be a predictor of IP. Other studies have shown conflicting results, but it could be hypothesised that the longer patient is hospitalised the higher the number of prescriptions and the higher the probability for IP (Chertow et al, 2005; Drenth-van Maanen et al, 2015; Saleem and Masood, 2016). IP and decline in renal function during hospitalisation being risk factors for prolonged LOS and increased mortality have been previously documented (Chertow et al, 2005; Cox et al, 2013).

At prescription level IP was associated with route of administration and renal function category (eGFR <10 ml/min/1.73m$^2$, 10-30 ml/min/1.73m$^2$ and >30 ml/min/1.73m$^2$). Higher odds for IP for subcutaneous medications were largely due to the high prevalence of IP for enoxaparin. Antimicrobials and analgesics could have contributed to the two-fold increase in odds for IP for intravenous medications compared to oral medications.

Decline in renal function has been associated with increased risk of IP which could also be seen from the correlation between AKI and IP at patient level. Almost four times higher odds of IP in eGFR category 10-30 ml/min/1.73m$^2$ at prescription level were observed. Owing to inconsistencies in recommendations between medication information sources greater odds for IP were expected. The comparison of three medication information sources also showed the highest number of discordances in renal function category of 10-30 ml/min/1.73m$^2$. Failing to provide clear recommendations to physicians could be a risk factor leading to IP.

Polypharmacotherapy is reported to be the main contributor for IP (Breton et al, 2011; Chang et al, 2015, Doody et al, 2015; Saleem and Masood, 2016). Due to large differences in the number of daily medications at prescription level this association was

not established in current study. Association between polypharmacotherapy and IP at patient level might have been significant, but due to the format of data collection and documentation associations between polypharmacotherapy and IP could not be determined.

## 4.1 Recommendations for Clinical Practice Improvement

This study showed that IP is a common issue in most wards throughout ETCH. Implementation of medication dosage adjustment guideline would help to decrease the prevalence of IP and improve patient safety. Implementation of a paper-based guideline is a step closer to improving appropriate prescribing but is not an ideal solution as it requires constant alertness by physicians to be able to detect and acknowledge medications needing dosage adjustment. Implementation of a CPOE system – within it a CDSS and a consultation option with a clinical pharmacist – would be the goal to improve medication and patient safety in patients with decreased renal function (Awdishu et al, 2016; Al Raiisi et al, 2019; Arias Pou et al, 2019; Elkhadragy et al, 2019). CPOE system would allow real-time analysis of prescriptions, give continuous feedback of IP across the whole hospital, and would enable to detect and solve discrepancies faster.

## 4.2 Limitations of the Study

This was a retrospective observational study, thus it was not possible for the researcher to clarify information or understand the exact reasoning behind dosage adjustments. Due to retrospective study design there could have been higher selection and information bias.

Study population was relatively small and gathered from selected wards. This does not allow extrapolation of the results to a wider population. In addition, patients from the ICU, emergency department, oncology, and rheumatology were excluded due to complexity of patient profiles where dosage adjustment according to renal function is not always the main priority, dosages for certain conditions differ from regular use (e.g. oncology), or due to high turnover of patients (e.g. emergency department).

Only renal function was taken into account to assess IP, but there could have been other underlying factors (e.g. previous illness, poor clinical condition), or usage of different medication information sources other than the ones used in this study, contributing to no adjustment of medication dosages. This could have led to wrong estimation of the prevalence of IP.

Medication use and SCr were only documented on days when eGFR was below 60 ml/min/1.73m$^2$, meaning that if the laboratory results came back later in the evening the dosage adjustment could have happened the day after and might have not been recorded. But this is unlikely because most of the laboratory results are run early in the morning with the exception of emergency patient cases. eGFR results reflect the change in renal function over several days on which medications might not have been recorded. As the medications were recorded on specific days of the hospitalisation, the appropriateness of the loading and maintenance dosages of antibiotics were not assessed and this could have led to misinterpretation of the extent of IP.

Study was limited to the medications available in the hospital formulary, which could have caused underestimation of the prevalence of IP.

Weight and height were not always documented in health records, which may have caused wrong estimation of the proportion of obese patients relative to the overall study population.

Comorbidities were not always documented in discharge notes, thus were not included in the analysis, which may have led to underestimation of comorbidities and affected the association between IP and Charlson comorbidity index.

Due to inconsistent documentation of diagnoses, it was not possible to assess the presence of AKI or CKD diagnosis on admission.

## 4.3 Recommendations for Research

As this study gave information about the current situation at the hospital, a post-guideline implementation study should be conducted to assess the impact of medication dosage adjustment guideline on clinical practice. Other outcome measures namely ADEs and mortality in terms of dosage adjustment should be considered in future research. Conducting the study in other wards that were excluded from this study would give a better overview of IP in the whole hospital. Transferring the guideline to the hospital CPOE system in the future and evaluating the impact of real-life recommendations while prescribing would be another step further. An interventional study comparing the effect of more individualised approaches by clinical pharmacists instead of a fixed guideline should also be undertaken.

## 4.4 Conclusion

This study has provided knowledge of the current situation of prescribing in patients with renal impairment in a hospital setting in Estonia. There were no previous studies of that extent conducted in Estonia assessing the prevalence of IP and describing medication usage in patients with renal impairment. It is evident that acknowledgement of impaired renal function could be improved, and inappropriate prescribing and correct dosage adjustments are common issues in spite of all available medication information sources. Anticoagulants and analgesics were the most frequently inappropriately prescribed medications at ETCH with clinical speciality and comorbidities affecting the extent of IP.

Inappropriate prescribing in patients with renal impairment is an ongoing problem that needs to be addressed. Acknowledging the problem and being aware of the possible predictors of IP together with clear and consistent recommendations available for physicians could help improve patient outcomes.

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# Appendix 1

# Permission to conduct the study and ethics approvals

KINNITATUD
AS Ida-Tallinna Keskhaigla
juhatuse 15.08.2011.a. otsusega

**Lisa 2. Komisjoni otsus**

**AS Ida -Tallinna Keskhaigla**

**Uurimistööde hindamise komisjoni otsus nr 1.1-19/19-19-1**

| | |
|---|---|
| **Uurija nimi** | Kairi Marlen Antoniak |
| **Uurija e-mail** | kairimarlen.antoniak@itk.ee |
| **Uurija telefon** | 5284262 |
| **Asutus, mida uurija esindab** (üliõpilastel ka eriala ja taotletav kraad) | ITK proviisor<br>Malta Ülikool koostöös Illinois Ülikooliga Chicagos, kliiniline farmaatsia, Pharm.D. |
| **Kaasuurija(d)** | Juhendaja: Janis Vella Szijj, janis.vella@um.edu.mt |
| **Uurimistöö teema** " Ravimikasutus langenud neerufunktsiooniga patsientidel" | |
| **Planeeritav uurimuse läbiviimise koht:** | Ida-Tallinna Keskhaigla |
| **Planeeritav uurimuse läbiviimise aeg:** | juuli - detsember 2019 |

**Uurimistöö taotluse vaatas läbi komisjon koosseisus:**

Helen Trelin

Katti Kõrve

Liisa Kuhi

Marika Tammaru

**Komisjon kaasas hinnangu andmise protsessi konsultandi (nimi, ametikoht):**

Kristo Kaul- infoturbejuht

Mari-Liis Rehepapp- teadusosakonna spetsialist

**Komisjon otsustas**

☐ **Anda luba uuringu läbiviimiseks Ida-Tallinna Keskhaiglas**

☒ **Anda luba uuringu läbiviimiseks Ida-Tallinna Keskhaiglas pärast meditsiinieetika komitee kooskõlastuse esitamist**

☐ **Mitte anda luba uuringu läbiviimiseks Ida-Tallinna Keskhaiglas**

**Loast keeldumise põhjus/märkused:**

**Kas uuringu läbiviimiseks on vajalik kasutada ITK arhiivmaterjale?**

☒ **Ei**
☐ **Jah;** ☐ **elektroonilisi andmebaase** ☐ **paberarhiivi**

| |
|---|
| **Kas arhiivimaterjaliga töötades on vajalik ligipääs isikustatud andmetele**<br>☒ **Ei**<br>☐ **Jah** |
| **Tulemustest ülevaate andmise vorm:** |
| **Komisjoni esimehe allkiri** Marika Tammaru  \| **Kuupäev**<br>29.04.2019 |

| |
|---|
| Loa korral, mille jõustumise tingimuseks on eetikakomitee kooskõlastuse esitamine:<br>☒ Eetikakomitee kooskõlastus esitatud |
| Komisjoni esimehe allkiri  \| Kuupäev<br>18.06.2019 |

KINNITATUD
AS Ida-Tallinna Keskhaigla
juhatuse 15.08.2011.a. otsusega

**Appendix 2. Commission Decision**

**AS Ida -Tallinna Keskhaigla**

**Research Commission Decision no 1.1-19/19-19-1**

| | |
|---|---|
| **Principal Investigator** | Kairi Marlen Antoniak |
| **Email of Investigator** | kairimarlen.antoniak@ik.ee |
| **Phone of Investigator** | 5284262 |
| **Institution** (if student, specialty and qualification) | ETCH pharmacist<br>University of Malta in collaboration with University of Illinois in Chicago, Clinical Pharmacy, Pharm.D. |
| **Co-Investigator(s)** | Supervisor: Janis Vella Szijj,<br>janis.vella@um.edu.mt |
| **Title of Research project:** Drug dosing in patients with renal impairment | |
| **Research Setting:** | East Tallinn Central Hospital (ETCH) |
| **Research Period:** | July – December 2019 |

**Research request form was evaluated by the Commission:**

Helen Trelin

Katti Kõrve

Liisa Kuhi

Marika Tammaru

**Commission included following person(s) to the decision-making process (name, position):**

Kristo Kaul – Head of Information Security

Mari-Liis Rehepapp – Research unit assistant

**Commission Decision**

☐ **Permission granted for conducting a research in East Tallinn Central hospital**

☒ **Permission granted for conducting a research in East Tallinn Central hospital after approval from Ethics Committee**

☐ **Permission not granted for conducting a research in East Tallinn Central hospital**

**Explanation of rejecting research project:**

| |
|---|
| **Is there a need to use documents from ETCH archives?**<br>☒ **No**<br>☐ **Yes;** ☐ **electronic databases** ☐ **documents on paper**<br>**Is there a need to access personal data while working with documents from archives?**<br>☒ **No**<br>☐ **Yes** |
| **Form for giving overview of the results:** |

| | |
|---|---|
| **Head of Commission Signature** Marika Tammaru | **Date**<br>29.04.2019 |

| |
|---|
| To be filled in case the requirement for permission was ethics committee approval:<br><br>☒ Ethics Committee approval submitted |

| | |
|---|---|
| Head of Commission Signature | Date<br>18.06.2019 |

**Tallinna Meditsiiniuuringute Eetikakomitee**

**Otsus nr 2820**

Tallinna Meditsiiniuuringute Eetikakomitee (TMEK) koosseisus: Adik Levin, Anne Kull, Avo-Rein Tereping, Ingrid Peek, Jaanus Kerge, Jaak Põlluste, Kadi Lubi, Kaire Innos, Kristi Rüütel, Marje Liibek, Vahur Valvere, arutas oma koosolekul 13. juunil 2019 ja otsustas lugeda kooskõlastatuks uuringuprojekti **„Ravimikasutus langenud neerufunktsiooniga patsientidel“**, mille vastutav uurija on **Kairi Marlen Antoniak, MSc Pharm** (AS Ida-Tallinna Keskhaigla). Isikuandmete kaitse seaduse § 6 lõige 4 alusel antakse luba andmesubjektide nõusolekuta isikuandmete töötlemiseks (töödeldavate isikuandmete kirjeldus on toodud lisas 1).

Taotlus nr 2031, TMEK koosoleku protokoll nr 241.
Kooskõlastus väljastatud 18.06.2019.

Kristi Rüütel
TMEK esimees
/allkirjastatud digitaalselt/

Marje Liibek
TMEK sekretär
/allkirjastatud digitaalselt/

Tallinna Meditsiiniuuringute Eetikakomitee
Tervise Arengu Instituut, Hiiu 42, 11619 Tallinn
tel 659 3924
eetikakomitee@tai.ee
www.tai.ee

**Tallinn Medical Research Ethics Committee**

**APPROVAL No 2820**

Tallinn Medical Research Ethics Committee (TMREC) on the staff of Kristi Rüütel, Jaak Põlluste, Marje Liibek, Vahur Valvere, Adik Levin, Jaanus Kerge, Kaire Innos, Kadi Lubi, Ingrid Peek

has discussed in the meeting on **13 June 2019**

and **DECIDED**

**TO CONSIDER AS HARMONIZED WITH ETHICS COMMITTEE**

the research project **"Drug dosing in patients with renal impairment"**, principal investigator **Kairi Marlen Antoniak** (East Tallinn Central Hospital).

Application No 2031, minutes of the TMREC No 241.
Approval 2820 delivered June 18, 2019.

Initial decision was in Estonian and signed digitally by Kristi Rüütel (Chairman of TMREC) and Marje Liibek (Secretary of TMREC)

Marje Liibek
Secretary of TMREC

12.07.2019

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Ref No: **FRECMDS_1819_090**

Wednesday 4th December 2019

Mr Kairi Marlen Antoniak
Ristiku 34-13,
10320,
Tallinn,
Estonia.

Dear Mr Kairi Marlen Antoniak,

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

**Drug dosing in patients with renal impairment**

The Faculty Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Professor Pierre Mallia
Chairman
Research Ethics Committee

# Appendix 2

# Data Collection Form

Data Collection Form

| **Patient code** | |
|---|---|
| **Gender** | |
| **Date of Birth** | |
| **Age** | |
| **Weight** (kg) | |
| **Height** (cm) | |
| **Ward** (1-internal; 2-cardiology; 3-neurology; 4-gastrology; 5- endocrinology; 6-rehabilitation I; 7-rehabilitation II; 8-surgery; 9-orthopedics; 10-spinal surgery; 11-urology) | |
| **Date of admission** | |
| **Date of discharge** | |
| **Date patient withdrawn from the study** | |
| **Reason for withdrawal** (1-eGFR >60; 2-other) | |
| **If <u>other</u>, indicate:** 1-discharged; 2-transferred to other (non-ICU) ward; 3-transferred to ICU; 4-death | |
| **Main diagnosis** | |
| **Complications of main diagnosis** | |
| **Comorbidities** | |
| **AKI on admission** | |
| **CKD on admission** | |
| **Hematocrit** | |
| **Interventions made during hospitalisation** (1-surgery; 2-contrast agent administration; 3-both) | |
| **Date of intervention** | |

Data Collection Form

| **Patient code** | |
|---|---|
| **Date of eGFR measurement** | |
| **eGFR (ml/min/1.73m$^2$)** | |
| **SCr** | |
| **Number of medications** | |
| **Name of Medication** | |
| **Dose of Medication** | |
| **Frequency of Medication** | |
| **Route of administration** | |

# Appendix 3

# Renal dosage adjustment recommendations in British National Formulary, The Renal Drug Handbook and UpToDate®

| | Medication | Route | Unit | GFR/CrCl >60 | | British National Formulary (BNF) ml/min/1.73m² eGFR 30-59 | | eGFR 10-29 | | eGFR <10 | | Renal Drug Handbook (RDH) ml/min GFR 30-59 | | GFR 10-29 | | GFR <10 | | UpToDate (UTD) ml/min / ml/min/1.73m² (e)GFR / CrCl 30-59 | | (e)GFR / CrCl 10-29 | | (e)GFR / CrCl <10 | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ANTIDIABETICS | **Gliclazide** | PO | mg | **40-160** | **x1-2** | caution | | caution | | avoid* | | <50 caution (start 20-40mg x1)§ | | | | | | no adj. | | no adj. | | **X** | | §crcl<40ml/min contraindicated by manufacturer<br>*if sever impairment (=<30ml/min) |
| | **Glimepiride** | PO | mg | **1-6** | **x1** | caution | | caution | | avoid* | | normal dose | | 10-20 start 1mgx1 | | start 1mgx1 | | normal dose (start 1mgx1) | | normal dose (start 1mgx1) | | eGFR <15 | | *if sever impairment (=<30ml/min) |
| | | | | | | | | | | | | | | | | | | | | | | **X** | | |
| | **Metformin** | PO | mg | max 2g* | | max 2g | | | | | | 45-59 - max 2g | | 10-45 | | | | eGFR 45-60 - max 2g | | | | | | *BNF<br>‘UTD<br>§initiating Tx: 50% of normal dose (250mg) (max 1g)<br>during Tx: <50% (max 1g) |
| | | | | max 2,5g‘ | | | | | | | | | | 30-44 - max 1g | | | | eGFR 30-45 - max 1g | | | | | | |
| | | | | **500** | **x3** | **normal** | | **X** | | **X** | | **25-50%** | | **25%** | | **X** | | | | **X** | | **X** | | |
| | **Sitagliptin** | PO | | eGFR >45 | | 30-45 | | <30 | | | | 30-50 | | <30 | | | | eGFR 30-45 | | eGFR <30 | | | | |
| | | | mg | **100** | **x1** | **50** | **x1** | **25** | **x1** | | | **50** | **x1** | **25** | **x1** | | | **50** | **x1** | **25** | **x1** | | | |
| ANTIMI | **Amoxicillin/ clavulanate** | PO | | 375-625 | x2-3 | | | | | | | no adj.* | | | | | | | | CrCl - avoid 1g tbl | | CrCl - avoid 1g tbl | | *Doses in renal impairment are taken from personal experience<br>§N/A |
| | | | mg | **1000** | **x2** | | | **375-625** | **x2** | **375-625** | **x1** | | | | | | | | | **375-625** | **x2** | **375-625** | **x1** | |
| | | IV | | | | | | LD 1200mg | | LD 1200mg | | | | LD 1,2g* | | LD 1,2g (alternative 600mgx3)* | | § | | | | | | |
| | | | mg | **1200** | **x3** | | | **600** | **x2** | **600** | **x1** | | | **1,2** | **x2** | **1,2** | **x2** | | | | | | | |
| | **Ampicillin/ sulbactam** | IV | g | | | § | | | | | | § | | | | | | CrCl (ml/min/ 1.73m2)* | | 15-29 | | 5-14 | | §N/A<br>*UNASYN SPC same doses; CrCl <5ml/ min - 1,5-3g q48h |
| | | | | **3** | **x3-4** | | | | | | | | | | | | | | | **1,5-3** | **x2** | **1,5-3** | **x1** | |
| | **Cefazolin** | IV | g | | | § | | | | | | § | | | | | | CrCl 35-54* | | CrCl 11-34 | | <10 | | §N/A<br>*Zepilen SPC same doses<br>1) surgical prophy.: 3g if >120kg |
| | | | | **2** | **x3-4** | | | | | | | | | | | | | **2** | **x3** | **50%** | **x2** | **50%** | **q18-24** | |
| | **Cefotaxime** | IV | g | max 12g/d | | | | | | <5 - LD 1g | | | | | | <5 | | | | | | **normal dose** | **q24** | |
| | | | | **1-2** | **x2-4** | | | | | **50%** | | | | | | **50%** | | | | | | **50%** | | |
| | **Cefoxitin** | IV | g | max 12g/d | | CrCl 30-50 - comp. UTI | | CrCl | | avoid* | | § | | | | | | CrCl 30-50 - LD 1-2g | | LD 1-2g | | CrCl 5-9 - LD 1-2g | | *no information in SPC<br>§N/A |
| | | | | **1-2** | **x4-6** | **2** | **x2-3** | **2** | **x1-2** | | | | | | | | | **1-2** | **x2-3** | **1-2** | **x1-2** | **0,5-1** | **x1-2** | |
| | | | | | | | | | | | | | | | | | | | | | | <5 - LD 1-2g | | |
| | | | | | | | | | | | | | | | | | | | | | | **0,5-1** | **q24-48** | |
| ANTI | **Ceftazidime** | IV | g | | | CrCl 31-50 - LD 1g* | | CrCl 16-30 LD 1g | | CrCl 6-15 - LD 1g | | 31-50 | | 16-30 | | 6-15 | | CrCl 31-50 | | 16-30 | | <15 | | *BNF refers to SPC (Ceftazidime MIP SPC) - in severe infections increase single dose by 50% or increase dosing interval<br>1) ARC (CrCl ≥130 mL/min/1.73m2): 2g q6h or LD 2g + 10g/24h |
| | | | | **(1)-2** | **x3** | **1** | **x2** | **1** | **x1** | **0,5** | **x1** | **1-2** | **x2** | **1-2** | **x1** | **0,5-1** | **x1** | **1-2** | **x2** | **1-2** | **x1** | **0,5-1** | **x1** | |
| | | | | | | | | | | <5 - LD 1g | | | | | | <5 | | | | | | | | |
| | | | | | | | | | | **0,5** | **q48** | | | | | **0,5-1** | **q48** | | | | | | | |
| | **Cefuroxime** | PO | mg | **250-500** | **x2** | § | | | | | | no adj. | | | | | | CrCl | | **250-500** | **x1** | **250-500** | **q48** | §no information |
| | | IV | g | | | | | 10-20 | | <10 | | | | 10-20 | | <10 | | CrCl | | 10-20 | | <10 | | |
| | | | | **0,75-1,5** | **x3-4** | | | **0,75** | **x2** | **0,75** | **x1** | | | **0,75-1,5** | **x2** | **0,75-1,5** | **x1** | | | **0,75-1,5** | **x2** | **0,75-1,5** | **x1** | |

| | Medication | Route | Unit | GFR/CrCl >60 | | British National Formulary (BNF) ml/min/1.73m² eGFR 30-59 | | eGFR 10-29 | | eGFR <10 | | Renal Drug Handbook (RDH) ml/min GFR 30-59 | | GFR 10-29 | | GFR <10 | | UpToDate (UTD) ml/min / ml/min/1.73m² (e)GFR / CrCl 30-59 | | (e)GFR / CrCl 10-29 | | (e)GFR / CrCl <10 | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CROBIALS | **Ciprofloxacin** | PO | mg | | | | | | | | | | | | | § | | CrCl 30-50 | | CrCl 5-29 | | | | *alternative dose for IV/PO<br>§100% dose may be given for short periods under exceptional circumstances |
| | | | | **500-750** | **x2** | **250-500** | **x2** | **250-500** | **x1** | **250-500** | **x1** | | | **50-100%** | | **50%** | | **250-500** | **x2** | **250-500** | **q18** | | | |
| | | IV | mg | | | LD 200mg | | LD 200mg | | LD 200mg | | | | | | § | | 10-50* | | CrCl 5-29 | | <10* | | |
| | | | | **400** | **x2-3** | **200-400** | **x2** | **200-400** | **x1** | **200-400** | **x1** | | | **50-100%** | | **50%** | | **50-75%** | **x2** | **200-400** | **q18 -24** | **50%** | **x2** | |
| | **Claritromycin** | PO | mg | **500-1000** | **x1** | | | avoid ER formula | | avoid ER formula | | no adj. § | | | | | | CrCl* | | | | | | *for ER and IR reduce 50%<br>§ER formula N/A<br>¶IV formula N/A<br>1)50% = 250mg x1 or 250mg x2 |
| | | | | **250-500** | **x2** | | | **50%** | | **50%** | | | | | | | | | | **50%** | | **50%** | | |
| | | IV | mg | **500** | **x2** | | | **50%** | | **50%** | | | | **250-500** | **x2** | **250-500** | **x2** | ¶ | | | | | | |
| | **Ertapenem** | IV | g | 1 | **x1** | | | **500** | **x1** | **500** | **x1** | | | **500-1000** | **x1** | **500** | **x1** | eGFR | | **500** | **x1** | **500** | **x1** | |
| | **Fluconazole** | PO /IV | mg | | | <50 - normal LD | | | | | | <50* | | 10-20 | | <10 | | CrCl <50 - normal LD* | | | | | | *No dose adjustment is required for single dose therapy<br>1)LD 800mg (12 mg/kg) on day 1, then 400mg (6 mg/kg) once daily; weight based dosing IF <50 kg or >90 kg (UTD) |
| | | | | **100-400** | **x1** | **50%** | **x1** | **50%** | **x1** | **50%** | **x1** | **50-100%** | **x1** | **50-100%** | **x1** | **50%** | **x1** | **50%** | **x1** | **50%** | **x1** | **50%** | **x1** | |
| | **Nitrofurantoin** | PO | mg | | | <45 - avoid* | | | | | | 45-60 - caution' | | <45* | | | | GFR/CrCl | | CrCl <30§ | | | | *30-44 - only for 3-7 days for unc. lower UTI by multidrug resistant pathogens<br>'increased risk of Tx failure +side effects<br>§avoid in elderly >65y<br>UTD-for uncomplicated UTI |
| | | | | **50-100** | **x4** | | | | | | | | | **X** | | **X** | | | | | | | | |
| | **Oseltamivir** | PO | mg | | | | | | | avoid | | | | same as BNF or:* | | Tx - 30mg once or:* | | | | | | | | *based on clinical experience and good tolerability |
| | | Px | | **75** | **x1** | **30** | **x1** | **30** | **q48** | | | | | **75** | **q48** | **30** | **1d + 7d** | **30** | **x1** | **30** | **q48** | | | |
| | | Tx | | **75** | **x2** | **30** | **x2** | **30** | **x1** | | | | | **75** | **x1** | **75** | **once** | **30** | **x2** | **30** | **x1** | | | |
| | **Piperacillin/ tazobactam** | IV | g | | | 20-40 | | <20 | | | | 20-40 | | <20 | | | | 20-40* | | <20 | | | | *CrCl >100 - prefer extended infusion<br>1) ARC (CrCl ≥130 mL/min/1.73m2): LD 4,5g + 18g/24h (CrCl 130 to <170) OR 22.5g/24h (CrCl ≥170) |
| | | | | **4,5** | **x3-4** | **4,5** | **x3** | **4,5** | **x2** | **4,5** | **x2** | **4,5** | **x3** | **4,5** | **x2** | **4,5** | **x2** | **4,5** | **x3** | **4,5** | **x2** | **4,5** | **x2** | |
| | | ext. inf | | **4,5 (4h)** | **x3(4)** | | | | | | | | | | | | | **4,5** | **x2-3** | **4,5** | **x2** | **4,5** | **x2** | |
| | **Sulfamethoxazole/ trimethoprim** | PO /IV | mg | | | | | 15-30 | | <15 - avoid | | | | | | only if HD available | | GFR 10-50 - LD 960mg* | | | | <10 - avoid - LD 960mg | | *same doses as BNF or alternative. mg/kg dosing for IV based on trimethoprim component |
| | | | | **960** | **x2** | | | **50%** | | | | | | **50%** | | **50%** | | **480** | **x2** | **480** | **x2** | **480** | **x1** | |
| | | IV | | | | | | | | | | | | | | | | **4-5 mg/kg** | **x2** | **4-5 mg/kg** | **x2** | **2,5-5 mg/kg** | **x1** | |
| | **Sultamicillin** | PO | mg | | | § | | | | | | § | | | | | | § | | 20-30* | | <20* | | §N/A<br>*ampicillin SPC |
| | | | | **375 (750)** | **x3(2)** | | | | | | | | | | | | | | | **66%** | | **50%** | **x2** | |
| | **Apixaban** | PO | mg | | | | | CrCl 15-29 - normal | | | | | | 15-30 - normal | | <15 - x | | | | CrCl<30(25) - avoid* | | | | *no info available (excluded from clinical trials) - Total hip arthroplasty or total knee arthroplasty (CrCl <30); DVT, PE Tx, indef. AC for VTE recurrence<br>'only some experts recommend |
| | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | CrCl 15-29 (AF only) | | | | | | 15-30 (AF only) | | <15 (AF only) | | | | CrCl 15-29 (AF only)' | | | | |
| | | | | | | | | Cr >133 + >80y +/- <60kg (AF only) | | CrCl <15 | | | | | | | | | | Cr >133 + >80y +/- <60kg (AF only) | | CrCl <15 - ok, no recom. (AF only) | | |
| | | | | **2,5-10** | **x2** | | | **2,5** | **x2** | **X** | | | | **2,5** | **x2** | **2,5** | **x2** | | | **2,5** | **x2** | | | |

| | Medication | Route | Unit | GFR/CrCl >60 | | British National Formulary (BNF) ml/min/1.73m² eGFR 30-59 | | eGFR 10-29 | | eGFR <10 | | Renal Drug Handbook (RDH) ml/min GFR 30-59 | | GFR 10-29 | | GFR <10 | | UpToDate (UTD) ml/min / ml/min/1.73m² (e)GFR / CrCl 30-59 | | (e)GFR / CrCl 10-29 | | (e)GFR / CrCl <10 | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CARDIOVASCULAR A | **Atenolol** | PO | mg | | | >35 | | 15-35 - max | | <15 (or 50mg q48) | | no adj. | | | | | | eGFR >35 | | 15-35 - max | | <15 (or 50mg q48) | | |
| | | | | **25-100** | **x1** | **normal dose** | | **50** | **x1** | **25** | **x1** | | | | | | | **normal dose** | | **50** | **x1** | **25** | **x1** | |
| | **Bisoprolol** | PO | mg | | | | | <20 - max | | | | no adj. | | | | | | CrCl <40 - caution* | | | | | | *start 2,5mg |
| | | | | **5-20** | **x1** | | | **10** | **x1** | | | | | | | | | | | | | | | |
| | **Candesartan** | PO | mg | **2-32** | **x1** | | | | | <15 - caution* | | | | <20 - start 2mg | | | | no adj.' | | | | | | *start 4mg; 'eGFR<30 - AUC doubled |
| | **Dabigatran** | PO | mg | >50 | | CrCl 30-50 (VTE profyl) | | avoid | | avoid | | 30-50 (VTE profyl) | | avoid | | avoid | | CrCl <50 + P-gp inh (Tx+profyl) - avoid; (VTE profyl) | | CrCl <30 (Tx DVT/PE) - avoid* | | avoid | | *not studied<br>1) CrCl - actual BW was used.<br>2) Some experts consider contraindicated with severe renal impairment for AF (CrCl ≤30);<br>3) Geriatric patients ≥65 years: Avoid with CrCl <30 due to lack of efficacy and safety evidence. (UTD) |
| | | | | **75-220** | **x1** | **150** | **x1** | | | | | **150** | **x1** | | | | | **150** | **x1** | | | | | |
| | | | | | | CrCl 30-50 (Tx+profyl DVT/PE/AF) | | avoid | | avoid | | AF - normal | | 15-30 AF (if CYP450 inh-avoid) | | <15 - avoid | | CrCl 30-50 AF (+elderly) - may consider dose adj | | CrCl 15-30 AF (if P-gp inh - avoid) | | <15 - avoid | | |
| | | | | **110-150** | **x2** | **110-150** | **x2** | | | | | | | **75** | **x2** | | | | | **75** | **x2** | | | |
| | **Digoxin** | PO | mcg | **62,5-250** | | reduce dose + TDM* | | reduce dose + TDM* | | reduce dose + TDM* | | 20-50 | | 10-20* | | <10* | | CrCl 10-50 (dose 25-75%)' | | MD dose 25-75%' | | MD dose 10-25%' | | *TDM - 6-8h after dose (or before next dose (in 24h))<br>'reduction in LD (PO/IV) may not be necessary (Vd may be increased in AKI)<br>§use nomogram (CrCl + lean BW or height)<br>1) Elderly: max 125mcg for AF and HF |
| | | IV | mcg | **750-1000** | | | | | | | | **125-250** | **x1** | **125-250** | **x1** | **62,5** | **q24-48** | **62,5** | **q24-36** | **62,5** | **q24-36** | **62,5** | **q48** | |
| | | | | | | | | | | | | | | | | | | CrCl 30-80 (HF only)§ | | HF only§ | | HF only§ | | |
| | | | | | | | | | | | | | | | | | | **125** | **x1** | **125** | **q48** | **125** | **q48** | |
| | **Enoxaparin** | IV/SC | | | | | | CrCl 15-30 | | CrCl <15 - avoid' | | | | 15-30 | | <15 - avoid' | | | | CrCl <30 | | | | *bolus doses differ > check enoxap. GL<br>'only for dialysis pt<br>1) Tx dose: Monitor anti-Xa for all degrees of renal impairment (trough and peak)<br>2) Doses may differ for obesity |
| | | | mg | **20-40** | **x1** | | | **20** | **x1** | | | | | **20** | **x1** | | | | | **30** | **x1** | **30** | **x1** | |
| | | | mg | **40-100** | **x2** | | | VTE/STEMI/ ACS Tx* | | | | | | Tx* | | | | | | VTE/STEMI/ ACS Tx* | | | | |
| | | | mg/kg | **0,75-1** | **x2** | | | **1** | **x1** | | | | | **1** | **x1** | | | | | **1** | **x1** | **1** | **x1** | |
| | **Enalapril** | PO | mg | | | | | <30 - start 2,5mg | | | | | | <20 - start 2,5mg | | | | GFR 10-50 | | CrCl <30 - start 2,5mg | | GFR <10 | | *Initial dose of 0.625 mg, may repeat in 1 hour if inadequate response, then 1.25 mg every 6 hours (UWhealth) |
| | | | | **2,5-40** | **x1** | | | | | | | | | | | | | **50-100%** | | | | **25%** | | |
| | **Eptifibatide** | IV | mcg/kg | **180** | **x1** | 30-50 - normal bolus | | avoid | | avoid | | 30-50 - normal bolus | | normal bolus | | normal bolus | | CrCl <50* | | | | | | *CrCl - actual BW should be used<br>CrCl <50 - max 7,5 mg/h |
| | | | mcg/kg/min | **2** | | **1** | | avoid | | avoid | | **1** | | **1** | | **1** | | **1** | | **1** | | **1** | | |
| | **Hydrochlorothiazide** | PO | mg | **25-200** | | | | avoid | | avoid | | § | | | | | | CrCl | | usually ineffective* | | avoid | | §N/A<br>*only together with loop diuretics |
| | **Indapamide** | PO | mg | | | | | avoid | | avoid | | no adj. | | | | caution§ | | GFR 10-50 - max | | max | | max | | §stop if pre-ex renal imp aggravated |

| | Medication | Route | Unit | GFR/CrCl >60 | | British National Formulary (BNF) ml/min/1.73m² eGFR 30-59 | | eGFR 10-29 | | eGFR <10 | | Renal Drug Handbook (RDH) ml/min GFR 30-59 | | GFR 10-29 | | GFR <10 | | UpToDate (UTD) ml/min / ml/min/1.73m² (e)GFR / CrCl 30-59 | | (e)GFR / CrCl 10-29 | | (e)GFR / CrCl <10 | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AGENTS | | | | **1,5-2,5** | x1 | | | | | | | | | | | | | **2,5** | **x1** | **2,5** | **x1** | **2,5** | **x1** | |
| | **Pentoxifylline** | PO | mg | **600** | **x1-2** | | | | | | | | | | | | | CrCl 10-50* | | | | | | *or CrCl <30 - 400mgx1; >30 - no adj.<br>§consider switching 600mg to 400x1-2 |
| | | | | **400** | **x2-3** | | | **50-70%** | | **50-70%** | | | | **400** | **x1-2** | **400** | **x1-2** | **400** | **x1-2** | **400** | **1-2** | **400** | **x1** | |
| | **Perindopril** | | | | | | | | | | | | | | | | | | | | | | | |
| | | PO | mg | **2-8** | **x1** | start 2mg | | 15-30 - start 2mg q48 | | | | start 2mg | | 15-30 - start 2mg | | <15 - start 2mg* | | | | CrCl <30 - not rec. - 15-30 - 2mg q48 | | | | *Normal doses have been used in CKD 5 |
| | | | | **2,5-10** | **x1** | start 2,5mg | | 15-30 - start 2,5mg q48 | | | | start 2,5mg | | 15-30 - start 2,5mg | | <15 - start 2,5mg q48h* | | | | | | | | |
| | **Ramipril** | PO | mg | | | max | | max* | | max* | | | | <20 - start 1,25mg' | | | | CrCl <40* | | | | | | *initial 1,25mg (max 5mg/d)<br>'Normal doses have been used in CKD 5 |
| | | | | **1,25-10** | **x1** | **5** | | **5** | | **5** | | | | | | | | **25%** | | | | | | |
| | **Ranolazine** | PO | mg | **375-750** | **x2** | 30-80 - caution | | avoid | | avoid | | 30-50 - caution* | | Avoid or reduce dose | | Avoid or reduce dose | | § | | | | | | *increased risk of side effects (inc AKI)<br>§D/C if AKI develops |
| | **Rivaroxaban** | PO | mg | | | | | CrCl 15-49 and 20mg (Tx+profyl DVT/PE)* | | <15 - avoid | | | | 15-50 (Tx+profyl DVT/PE)' | | <15 - avoid | | | | CrCl <30 (Tx DVT/PE) - avoid | | avoid | | *reduce dose if risk of bleeding outweighs the risk of recurrent deep-vein thrombosis or pulmonary embolism<br>'GFR15-29 - use with caution<br>§CrCl <30 were excluded; PCI+AF-avoid<br>¶PCI+AF - 10mg with clopidogrel<br>1) CrCl - actual BW was used (33-209kg) |
| | | | | **10-20** | **x1** | | | **15** | **x1** | | | | | **15-20** | **x1** | | | | | | | | | |
| | | | | **2,5** | **x2** | | | CrCl <30 (ACS) - avoid | | | | | | | | | | | | CrCl <30 (ACS) - avoid | | CrCl <15 (CAD, PAD) - avoid | | |
| | | | | | | | | CrCl 15-49 (AF) | | <15 - avoid | | | | 15-50 (AF)' | | <15 - avoid | | ¶ | | CrCl 15-49 (AF)§ | | <15 - avoid | | |
| | | | | **20** | **x1** | | | **15** | **x1** | | | | | **15** | **x1** | | | | | | **15** | **x1** | | |
| | **Rosuvastatin** | PO | mg | | | max | | <30 - avoid | | avoid | | max | | max | | max | | eGFR | | max | | max | | |
| | | | | **5-40** | **x1** | **20** | **x1** | | | | | **20** | **x1** | **10** | **x1** | **10** | **x1** | | | | **10** | **x1** | **10** | **x1** | |
| | **Simvastatin** | PO | mg | **10-80** | **x1** | | | caution if >10mg | | caution if >10mg | | | | | | caution if >10mg (max 40mg) | | | | | | severe imp. - caution (start 5mg) | | |
| | **Spironolactone** | PO | mg | | | | | | | avoid* | | 20-50 | | 10-20 | | avoid | | eGFR 30-50 -start12,5 (HF)' | | HF only | | HF only | | *Avoid in acute renal insufficiency or severe impairment<br>'may double the dose every 4 weeks if K+ and SCr ok |
| | | | | **25-400** | | | | | | | | **50%** | | **50%** | | | | **25** | **x1** | **X** | | **X** | | |
| | **Tranexamic acid** | | | | | SCr 120-249* | | SCr 250-500* | | SCr >500* | | 20-50 | | 10-20 | | | | SCr 120-249 | | SCr 250-500 | | SCr >500 | | *SPC<br>§general doses N/A (only cardiac surgery)<br>1) ALL **mg/kg** |
| | | PO | mg | **1000-1500** | **x2-3** | **15** | **x2** | **15** | **x1** | **7,5** | **x1** | **25** | **x2** | **25** | **x1-2** | **12,5** | **x1** | **15** | **x2** | **15** | **x1** | **15** | **q48** | |
| | | IV | mg | **500-1000** | **x3-4** | **10** | **x2** | **10** | **x1** | **5** | **x1** | **10** | **x2** | **10** | **x1** | **5** | **x1** | § | | | | | | |
| | **Trimethazidine** | PO (ER tbl) | mg | **35** | **x2** | § | | | | | | § | | | | | | **35** | **x1** | **X** | | **X** | | SPC - CrCl |
| | **Codeine** | PO | mg | | | Avoid or reduce dose | | Avoid or reduce dose | | Avoid or reduce dose | | no adj. | | 10-20* | | | | GFR 10-50 | | | | | | *may be increased<br>1) SPC same as UTD |
| | | | | **30-60** | **x4** | | | | | | | | | **30** | **x6** | **30** | **x4** | **75%** | | **75%** | | **50%** | | |

| | Medication | Route | Unit | GFR/CrCl >60 | | British National Formulary (BNF) ml/min/1.73m² eGFR 30-59 | | eGFR 10-29 | | eGFR <10 | | Renal Drug Handbook (RDH) ml/min GFR 30-59 | | GFR 10-29 | | GFR <10 | | UpToDate (UTD) ml/min / ml/min/1.73m² (e)GFR / CrCl 30-59 | | (e)GFR / CrCl 10-29 | | (e)GFR / CrCl <10 | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NEUROLOGICAL AGENTS | **Dexketoprofen** | PO | mg | | | caution - initial max | | avoid* | | avoid* | | caution | | 10-20 avoid if possible | | | | § | | | | | | *avoid in moderate to severe imp.<br>'only if dialysis<br>§N/A; Elderly: Max: 50mg/d (unless well tolerated) |
| | | | | **25** | **x3** | **25** | **x2** | | | | | | | | | **X'** | | | | | | | | |
| | **Diclofenac** | PO (IR tbl) | mg | **75-150** | | avoid if possible | | avoid if possible | | avoid | | no adj. | | avoid if possible | | **X*** | | eGFR <60 - caution§ | | avoid | | avoid | | *only if dialysis<br>§Avoid use in patients with intercurrent disease that increases risk of AK |
| | **Etoricoxib** | PO | mg | **30-120** | **x1** | avoid if possible | | avoid | | avoid | | <50 avoid if possible | | avoid if possible | | **X*** | | ¶ | | | | | | *only if dialysis ¶N/A<br>§Avoid use in patients with intercurrent disease that increases risk of AK |
| | **Fentanyl** | IV | mcg | **50-3500** | **x1** | Avoid or reduce dose | | Avoid or reduce dose | | Avoid or reduce dose | | GFR <50* | | | | | | CrCl <50 - caution | | | | | | *Titrate to response; Renal impairment irrelevant for short surgery<br>§caution - consider reducing dose |
| | | | mcg/kg/h | **3-10** | | | | | | | | **75%** | | **75%** | | **50%** | | | | | | | | |
| | **Gabapentin** | PO | mg | | | CrCl 50-79 | | | | | | 15-60 - start low | | | | | | CrCl 50-79 - no adj' | | | | | | *150mg daily dose to be given as 300mg in 3 divided doses on alternate days<br>'max doses for all CrCl as BNF<br>§max 600 mg/day in 2 divided doses<br>1)CrCl <15: further dose reductions may be required in proportion to CrCl |
| | | | | | | **200-600** | **x3** | | | | | | | | | | | | | | | | | |
| | | | | | | CrCl 30-49 | | 15-29* | | <15* | | | | | | <15* | | CrCl 30-49 | | 15-29§ | | <15 | | |
| | | | | **300-1200** | **x3** | **100-300** | **x3** | **50-200** | **x3** | **50-100** | **x3** | | | | | **50** | **x3** | **50%** | | **75%** | | **90%** | | |
| | **Ibuprofen** | PO | mg | **200-400** | **x3** | caution | | caution | | avoid* | | <50 avoid if possible | | avoid if possible | | **X'** | | eGFR - caution§ | | avoid | | avoid | | *avoid in severe impairment<br>'only if dialysis<br>§Avoid use in patients with intercurrent disease that increases risk of AKI |
| | **Memantine** | PO | mg | | | 30-49* | | 5-29 | | <5 - avoid | | 30-50* | | | | | | CrCl 30-49 - start 5mg* | | CrCl 5-29' | | | | *if well tolerated after at least 7 days can be increased in steps to 20mg/d<br>'start 5mg x1 for 1 week |
| | | | | **5-20 (60)** | **x1** | **10** | **x1** | **10** | **x1** | | | **10** | **x1** | **10** | **x1** | **10** | **x1** | | | **5** | **x2** | | | |
| | **Morphine** | PO | mg | **5-…** | | Avoid or reduce dose | | Avoid or reduce dose | | Avoid or reduce dose | | 20-50 | | 10-20 | | | | no adj. - caution | | | | | | *caution - consider reducing dose |
| | | IV | mg | **1-…** | | | | | | | | **75%** | | **50%** | | **25%** | | | | | | | | |
| | **Naproxen** | PO | mg | **(250)-500** | **x2-(3)** | avoid if possible | | avoid | | avoid | | avoid if possible | | avoid if possible | | **X*** | | eGFR <60 - caution§ | | avoid | | avoid | | *only if dialysis<br>§Avoid use in patients with intercurrent disease that increases risk of AKI |
| | **Pethidine** | IV | mg | **25-50** | **q4** | Avoid or reduce dose | | Avoid or reduce dose | | Avoid or reduce dose | | | | 10-20 | | avoid if possible | | avoid (as analgesic) | | avoid (as analgesic) | | avoid (as analgesic) | | |
| | | | | | | | | | | | | | | **75%** | **q6** | **50%** | **q8** | | | | | | | |
| | **Pramipexole** | PO | mg | IR tbl | | 20-50 - max | | <20 - max | | | | 20-50 - max | | <20 - max | | | | CrCl 30-50 (start 0,125x2) | | 15-29 (start 0,125x1) | | <15 - avoid | | salt form dosing |
| | | | | **0,125-1,5** | **x2** | **2,25** | | **1,57** | **x1** | **1,57** | **x1** | **2,25** | | **1,57** | **x1** | **1,57** | **x1** | **0,75** | **x3** | **1,5** | **x1** | | | |
| | **Pregabalin** | PO | mg | | | start 75mg/d - max | | 15-30 - start 25-50mg/d - max | | <15 - start 25mg - max | | start 75mg/d | | 15-30-start 25-50mg/d | | <15 - start 25mg/d | | CrCl - start 75mg/d - max* | | CrCl 15-30 - start 25-50mg/d - max* | | <15 - start 25mg - max* | | *max dose depends on the normal daily dose |
| | | | | **50-200** | **x3** | **150** | **x2** | **75** | **x2** | **75** | **x1** | | | | | | | **150** | **x2** | **75** | **x2** | **75** | **x1** | |
| | **Risperidone** | PO | mg | | | | | | | | | <50 | | | | | | caution - start 0,5x2 | | start 0,5x2 | | start 0,5x2 | | |
| | | | | **0,5-4** | | **50%** | | **50%** | | **50%** | | **50%** | | **50%** | | **50%** | | | | | | | | |

| | Medication | Route | Unit | GFR/CrCl >60 | | British National Formulary (BNF) ml/min/1.73m² eGFR 30-59 | | eGFR 10-29 | | eGFR <10 | | Renal Drug Handbook (RDH) ml/min GFR 30-59 | | GFR 10-29 | | GFR <10 | | UpToDate (UTD) ml/min / ml/min/1.73m² (e)GFR / CrCl 30-59 | | (e)GFR / CrCl 10-29 | | (e)GFR / CrCl <10 | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Topiramate** | PO | mg | | | <70 - caution | | | | | | | | <20* | | * | | eGFR <70* | | * | | * | | *Initial max > titrate to response |
| | | | | **25-250** | **x2** | **50%** | | | | | | | | **50%** | | **50%** | | **50%** | | **50%** | | **50%** | | |
| | **Tramadol** | PO | mg | **50-400** | **24h** | Avoid or reduce dose | | Avoid or reduce dose | | Avoid or reduce dose | | | | 10-20* | | * | | | | ER - avoid; IR - max | | ER - avoid; IR - max | | *Initial max > titrate as tolerated |
| | | IV | mg | **50-600** | **24h** | | | | | | | | | **50-100** | **x3** | **50** | **x3** | | | **100** | **x2** | **100** | **x2** | |
| | **Venlafaxine** | PO | mg | ER tbl | | caution | | | | | | | | | | | | CrCl 30-89 | | max | | max | | |
| | | | | **37,5-375** | **x1** | | | **50%** | | **50%** | | | | **50%** | | **50%** | | **50-75%** | | **50%** | | **50%** | | |
| **VARIA** | **Allopurinol** | PO | mg | | | | | max | | max | | 20-50 - max | | 10-20 - max | | max (or 100mg q48) | | * | | max' | | | | *Initial: <1.5 mg per unit of eGFR + follow manufacturers SPC 'doses >300mg can be used with proper monitoring |
| | | | | **100-300** | **x1-3** | **normal dose** | | **100** | | **<100** | | **200-300** | | **100-200** | | **100** | | | | **300** | | | | |
| | **Metoclopramide** | PO /IV | mg | | | | | | | avoid if possible* | | no adj. | | | | | | CrCl <40 - initial IV § | | | | | | *avoid in severe impairment §PO: Diabetic gastroparesis: CrCl ≤60mL/min: 5mg x4 (max: 20 mg/day) |
| | | | | **10** | **x3** | | | | | | | | | | | | | **50%** | | **50%** | | **50%** | | |
| | **MgSO4** | IV | g | | | Avoid or reduce dose | | Avoid or reduce dose | | Avoid or reduce dose | | * | | | | | | HypoMg' | | | | | | *N/A 'Renal dysfunction max 20g/48h (eclampsia - UK SPC for all) |
| | | | | **1,2-12** | | | | | | | | | | | | | | **50%** | | | | | | |

X–contraindicated; PO–oral; IV–intravenous; Tx–treatment; Px–prophylaxis; LD–loading dose; N/A–not available; UTI–urinary tract infection; ARC–augmented renal clearance; ER–extended release; IR–immediate release; HD–haemodialysis; DVT–deep vein thrombosis; PE–pulmonary embolism; AC–anticoagulants; AUC–area under curve; P-gp–P-glycoprotein; Vd–volume of distribution; MD–maintenance dose; TDM–therapeutic drug monitoring; STEMI–ST-elevation myocardial infarction; ACS–acute coronary syndrome; PCI–percutaneous coronary intervention; D/C–discontinue

# Appendix 4

# Renal dosage adjustment guideline for East Tallinn Central Hospital

Renal dose adjustment guideline for ETCH

| | Route | Normal dose | GFR 30-50 | GFR 10-30 | GFR <10 | Comments |
|---|---|---|---|---|---|---|
| **ANTIHYPERGLYCEMIC AGENTS** | | | | | | |
| **Gliclazide** | PO | **40-160mg x1-2** | **20-160mg x1-2** | **X** | **X** | |
| **Glimepiride** | PO | **1-6mg x1** | **normal dose** | **X** | **X** | |
| **Metformin** | PO | **500-850mg x3**<br>**1000mg x2** | eGFR 30-44 - max§<br>**500mg x2** | avoid if possible - max 25% of the normal dose<br>**500mg x1** | **X** | Max: 2.5g<br>§initiating Tx: 50% of normal dose (250mg) (max 1g); during Tx: <50% (max 1g) |
| **Sitagliptin** | PO | **25-100mg x1** | eGFR 30-45<br>**25-50mg x1** | eGFR <30<br>**25mg x1** | **25mg x1** | |
| **ANTI-INFECTIVES** | | | | | | |
| **Amoxicillin/ clavulanate** | PO<br>IV | **375-625 x2-3**<br>**1000mg x2**<br>**1200mg x3** | **normal dose**<br>**normal dose**<br>**normal dose** | avoid 1g tbl<br>**375-625mg x2**<br>may consider 1.2gx2<br>**600mg x2** | avoid 1g tbl<br>**375-625mg x1**<br>may consider 1.2gx1<br>**600mg x1** | Use CrCl for IV dosing |
| **Ampicillin/ sulbactam** | IV | **1.5-3g x3-4** | **normal dose** | CrCl 15-29<br>**1.5-3g x2** | CrCl 5-14<br>**1.5-3g x1** | Use CrCl<br>CrCl <5ml/min - 1,5-3g q48h |
| **Cefazolin** | IV | **2g x3-4** | CrCl 35-54<br>**2g x3** | CrCl 11-34<br>**2g x2** | **1-(2)g x1** | surgical prophy.: 3g if >120kg |
| **Cefotaxime** | IV | **1-2g x2-4** | **normal dose** | **normal dose** | GFR <5<br>**1-2g x1** | Max: 12g/day |
| **Cefoxitin** | IV | **1-2g x4-6** | **1-2g x2-3** | **1-2g x1-2** | **X** | Max: 12g/day<br>Use CrCl |
| **Ceftazidime** | IV | **(1)-2g x3** | **(1)-2g x2** | CrCl 16-30<br>**(1)-2g x1** | CrCl 6-15<br>**(0.5)-1g x1**<br><5<br>**(0.5)-1g q48** | 1g dosing only for UTI<br>In severe infections increase single dose by 50% or increase dosing interval<br>1) ARC (CrCl ≥130 mL/min/1.73m2): 2g q6h or LD 2g + 10g/24h |
| **Cefuroxime** | PO<br>IV | **250-500mg x2** | **normal dose** | **250-500mg x1**<br>GFR 10-20 | **250-500mg q48** | |

| | Route | Normal dose | GFR 30-50 | GFR 10-30 | GFR <10 | Comments |
|---|---|---|---|---|---|---|
| | | **0.75-1.5g x3-4** | **normal dose** | **0.75-1.5g x2** | **0.75-1.5g x1** | |
| **Ciprofloxacin** | PO | **500-750mg x2** | **250-500mg x2** | **250-500mg x1** | **250-500mg x1** | |
| | IV | **400mg x2-3** | **(200)-400mg x2** | **(200)-400mg x1** | **200-400mg x1** | |
| **Claritromycin** | PO | **500-1000mg x1** | **normal dose** | avoid ER formula | avoid ER formula | |
| | | **250-500mg x2** | **normal dose** | **250mg x1-2** | **250mg x1-2** | |
| | IV | **500mg x2** | **normal dose** | **250mg x2** | **250mg x2** | |
| **Ertapenem** | IV | **1g x1** | **normal dose** | **500mg x1** | **500mg x1** | |
| **Fluconazole** | PO/IV | **50-400mg x1** | **50-100mg x1** | **50-200mg x1** | **50-200mg x1** | No dose adjustment is required for single dose therapy<br>1)IV LD 800mg (12 mg/kg) on day 1, then 400mg (6 mg/kg) once daily; weight based dosing IF <50 kg or >90 kg |
| **Nitrofurantoin** | PO | | GFR 45-70 - caution' | GFR <45*§ | | 'Risk of Tx failure + side effects<br>*30-44 - only for 3-7 days for unc. lower UTI by multidrug resistant pathogens<br>§avoid in elderly >65y |
| | | **50-100mg x3-4** | **25-50mg x3-4** | **X** | **X** | |
| **Oseltamivir** | PO | | | | | |
| | Proph. | **75mg x1** | **30mg x1** | **30mg q48** | **X** | |
| | Tx | **75mg x2** | **30mg x2** | **30mg x1** | **X** | |
| **Piperacillin/ tazobactam** | IV | | GFR 20-40* | GFR <20 | | *CrCl >100 - prefer extended infusion<br>1) ARC (CrCl ≥130 mL/min/1.73m2): LD 4,5g + 18g/24h (CrCl 130 to <170) OR 22.5g/24h (CrCl ≥170) |
| | | **4.5g x3-4** | **4.5g x3** | **4.5g x2** | **4.5g x2** | |
| | ext. inf | **4.5g(4h) x3(4)** | **4.5g x2-3** | **4.5g x2** | **4.5g x2** | |
| **Sulfamethoxazole/ trimethoprim** | PO | **960mg x2** | **480mg x2** | **480mg x2** | GFR <10 - avoid if possible OR **480mg x1** | Alternative dosing by mg/kg for IV based on TMP component |
| | IV | **960mg x2** | **normal dose** | **480mg x2** | **GFR <15 - avoid** | |
| **Sultamicillin** | PO | | | | <20 | |
| | | **375(750) x3(2)** | **normal dose** | **375mg x2** | **375mg x1-2** | |
| **CARDIOVASCULAR AGENTS** | | | | | | |
| | PO | Tx/P DVT/PE | | CrCl 15-29 | CrCl <15 | |
| | | **2.5-10mg x2** | **normal dose** | **normal dose** | **X** | |

| | Route | Normal dose | GFR 30-50 | GFR 10-30 | GFR <10 | Comments |
|---|---|---|---|---|---|---|
| **Apixaban** | | AF<br>**2.5-5mg x2** | **normal dose** | CrCl 15-29<br>SCr >133 + >80y +/- <60kg<br>**2.5mg x2** | CrCl <15<br>**X** | Always use CrCl |
| **Bisoprolol** | PO | **5-20mg x1** | **normal dose** | caution*<br>**5-10mg x1** | caution*<br>**5-10mg x1** | *start 2,5mg |
| **Dabigatran** | PO | VTE prophylaxis<br>**75-220mg x1**<br>AF, Tx/P DVT/PE<br>**110-150mg x2** | **75-150mg x1**<br>AF+elderly - may consider dose adj.<br>**110-150mg x2** | **X**<br>**X** | **X**<br>**X** | 1) CrCl - actual BW was used.<br>2) Some experts consider contraindicated with severe renal impairment for AF (CrCl ≤30);<br>3) Geriatric patients ≥65 years: Avoid with CrCl <30 due to lack of efficacy and safety evidence.<br>4) IF CrCl <50 + P-gp inh - avoid for Tx and prophylaxis |
| **Digoxin** | PO | **62.5-250mg** | **62.5-125mg x1** | **62.5-125mg x1** | **62.5mg x1** | TDM - 6-8h after dose (or before next dose (in 24h))<br>Reduction in LD (PO/IV) may not be necessary (Vd may be increased in AKI)<br>Use nomogram (CrCl + lean BW or height)<br>1) Elderly: max 125mcg for AF and HF |
| **Enoxaparin** | IV/SC<br>Tx<br>Tx | VTE prophylaxis<br>**20-40mg x1**<br>**18-74y: 1mg/kg x2**<br>**75y>: 0.75mg/kg x2** | **normal dose**<br>**normal dose**<br>**normal dose** | CrCl 15-30<br>**20mg x1**<br>**1mg/kg x1**<br>**1mg/kg x1** | CrCl <15<br>**X**<br>**X**<br>**X** | 1) Tx dose: Monitor anti-Xa for all degrees of renal impairment (trough and peak)<br>2) Doses may differ for obesity |
| **Hydrochlorothiazide** | PO | **25-200mg** | **normal dose** | **X*** | **X** | *only together with loop diuretics |
| **Indapamide** | PO | **1.5-2.5mg x1** | **normal dose** | **X** | **X** | |
| **Pentoxifylline** | PO | **600mg x1-2**<br>**400mg x2-3** | **normal dose***<br>**normal dose** | **600 x1**<br>**400 x1-2** | **600 x1**<br>**400 x1-2** | *consider switching 600mg to 400x1-2 |
| **Ramipril** | PO | **1.25-10mg x1** | **1.25-5mg x1** | **1.25-5mg x1** | **1.25-5mg x1** | If GFR <30 initial 1,25mg (max 5mg/d)<br>Normal doses have been used in CKD 5 |

| | Route | Normal dose | GFR 30-50 | GFR 10-30 | GFR <10 | Comments |
|---|---|---|---|---|---|---|
| **Ranolazine** | PO | **375-750mg x2** | **normal dose**- titrate slow | **X** | **X** | Increased risk of side effects (inc AKI) |
| **Rivaroxaban** | PO | Tx/P DVT/PE<br>**10mg x1**<br>**15mg x2**<br>**20mg x1**<br>AF<br>**20mg x1** | CrCl 15-49 and 20mg*<br>**normal dose**<br>**normal dose** | **normal dose**<br>CrCl 15-49 (AF)'§<br>**15mg x1** | CrCl <15<br>**X**<br>CrCl <15<br>**X** | *reduce dose if risk of bleeding outweighs the risk of recurrent deep-vein thrombosis or pulmonary embolism<br>'GFR15-29 - use with caution<br>§CrCl <30 were excluded; PCI+AF-avoid<br>1) CrCl - actual BW was used (33-209kg) |
| **Rosuvastatin** | PO | **5-40mg x1** | **5-20mg x1** | **5-10mg x1** | **5-10mg x1** | |
| **Simvastatin** | PO | **10-80mg x1** | **normal dose** | **10-40mg x1** | **10-40mg x1** | |
| **Spironolactone** | PO | **12.5-200mg x1-2** | **12.5-100mg x1-2** | **1.25-5mg x1-2** | **X** | |
| **Tranexamic acid** | PO<br>IV | **1000-1500mg x1-3**<br>**500-1000mg x1-3** | SCr 120-249<br>**15mg/kg x1-2**<br>**10mg/kg x1-2** | SCr 250-500<br>**15mg/kg x1**<br>**10mg/kg x1** | SCr >500<br>**7,5mg/kg x1**<br>**5mg/kg x1** | Use actual bodyweight |
| **Trimethazidine** | PO | **35mg x2** | **35mg x1** | **X** | **X** | Extended release formula<br>Dose according to CrCl |
| **NEUROLOGICAL AGENTS** | | | | | | |
| **Codeine** | PO | **30-60mg x1-4** | **30-60mg x1-3** | **30-60mg x1-3** | **30-60mg x1-2** | |
| **Dexketoprofen** | PO | **12.5-25mg x1-3** | caution - initial max<br>**12.5-25mg x1-2** | **X** | **X*** | *only if dialysis<br>1) Elderly: Max: 50mg/d (unless well tolerated |
| **Diclofenac** | PO | **50-100mg x1-3** | **X** | **X** | **X*** | *only if dialysis<br>Avoid use in patients with intercurrent disease that increases risk of AKI<br>Immediate release formula |
| **Etoricoxib** | PO | **30-120mg x1** | **normal dose** | **X** | **X*** | *only if dialysis<br>Avoid use in patients with intercurrent disease that increases risk of AKI |
| **Gabapentin** | PO | **300-1200mg x1-3** | **100-300mg x1-3** | CrCl 15-29*<br>**50-200mg x1-3** | CrCl <15*<br>**50-100mg x1-3** | *150mg daily dose to be given as 300mg in 3 divided doses on alternate days<br>1)CrCl <15: further dose reductions may be required in proportion to CrCl |

| | Route | Normal dose | GFR 30-50 | GFR 10-30 | GFR <10 | Comments |
|---|---|---|---|---|---|---|
| **Ibuprofen** | PO | **200-400mg x1-3** | **X** | **X** | **X*** | *only if dialysis<br>Avoid use in patients with intercurrent disease that increases risk of AKI |
| **Memantine** | PO | **5-20(60)mg x1** | CrCl 30-50*<br>**5-20mg x1** | CrCl 5-30<br>**5-10mg x1** | CrCl <5<br>**X** | *if well tolerated after at least 7 days can be increased in steps to 20mg/d |
| **Morphine** | PO<br>IV | **5-60mg x1-6**<br>**1-15 mg x1-6** | GFR 15-50<br>**5-45mg x1-6**<br>**1-11mg x1-6** | GFR 15-30<br>**5-45mg x1-6**<br>**1-11mg x1-6** | GFR <15<br>**5-30mg x1-6**<br>**1-7,5mg x1-6** | |
| **Naproxen** | PO | **(250)-500mg x2-(3)** | **X** | **X** | **X*** | *only if dialysis<br>Avoid use in patients with intercurrent disease that increases risk of AKI |
| **Pethidine** | IV | **25-50mg x1-6** | avoid (as analgesic) | avoid (as analgesic) | avoid (as analgesic) | |
| **Pramipexole** | PO | **0.125-1.5mg x3** | CrCl 20-50 (start 0,125mgx2)<br>**0.125-1.125mg x2** | CrCl <20 (start 0,125mgx1)<br>**0.125-1.5 x1** | **0.125-1.5mg x1** | Immediate release formula |
| **Pregabalin** | PO | **50-200mg x2-3** | start 75mg/d*<br>**50-150mg x1-2** | CrCl 15-30 - start 25-50mg/d*<br>**75mg x1-2** | CrCl <15 - start 25mg*<br>**75mg x1** | *max dose depends on the normal daily dose |
| **Risperidone** | PO | **0.5-4mg** | **0.5-2mg x1** | **0.5-2mg x1** | **0.5-2mg x1** | |
| **Topiramate** | PO | **25-250mg x1-2** | eGFR <70*<br>**12.5-125mg x1-2** | **12.5-125mg x1-2** | **12.5-125mg x1-2** | *Initial max > titrate to response |
| **Tramadol** | PO<br>IV | **50-100mg x1-4**<br>**50-100mg x1-6** | **normal dose** | ER - avoid*<br>**50-100mg x1-3** | ER - avoid*<br>**50mg x1-3** | *Initial max > titrate as tolerated |
| **Venlafaxine** | PO | **37.5-375mg x1** | **normal dose** | **37.5-187.5mg x1** | **37.5-187.5mg x1** | Extended release formula |
| | | | **VARIA** | | | |
| **Allopurinol** | PO | **100-300mg x1-3** | caution*<br>**normal dose** | 10-20<br>**100-200mg x1** | **100mg x1** | *Initial: <1.5 mg per unit of eGFR + follow manufacturers SPC |
| **Metoclopramide** | PO/IV | **10mg x1-3** | GFR 15-60; max 500mcg/kg day<br>**5mg x1-3** | GFR <15;max 500mcg/kg day<br>**5mg x1-2** | **5mg x1-2** | PO: Diabetic gastroparesis: CrCl ≤60mL/min: 5mg x4 (max: 20 mg/day) |

*X–contraindicated; PO–oral; IV–intravenous; Tx–treatment; UTI–urinary tract infection; ARC–augmented renal clearance; LD–loading dose; TDM–therapeutic drug monitoring; P-gp–P-glycoprotein; Vd–volume of distribution

# Appendix 5

# Patient demographics by clinics

| Characteristic | Internal medicine clinic (% [95% CI]) (n=230) | Surgery clinic (% [95% CI]) (n=139) | Rehabilitation clinic (% [95% CI]) (n=30) |
|---|---|---|---|
| Mean age (years) | 79.7 [46.6 … 98.7, IQR 13.5] | 77.6 [41.9 … 98.5, IQR 15.1] | 80.3 [54.4 … 95.4, IQR 11.1] |
| Patients over 65 years | 209 (90.9% [87.1 … 94.6]) | 116 (83.5% [77.3 … 89.6]) | 26 (86.7% [74.5 … 98.8]) |
| **Physical measures** | n=175 (76.1%) | n=131 (94.2%) | n=28 (93.3%) |
| BMI | 29.0 [28.0 … 30.0] | 28.9 [27.8 … 30.1] | 31.1 [29.0 … 33.2] |
| BMI ≥ 30 | 63 / 175 (36.0% [28.9 … 43.1]) | 46 / 131 (35.1% [26.9 … 43.3]) | 17 / 28 (60.7% [42.6 … 78.8]) |
| BMI < 18.5 | 1 / 175 (0.6% [0.0 … 1.7]) | 3 / 131 (2.3% [0.0 … 4.9]) | 0 / 28 (0.0%) |
| BSA | 1.9 [1.9 … 2.0] | 1.9 [1.9 … 1.9] | 1.9 [1.8 … 2.0] |
| **Hospitalisation** | | | |
| Mean length of hospitalisation (days) | 6.0 [1.0 … 30.0, IQR 6.0] | 5.0 [1.0 … 31.0, IQR 5.0] | 11.0 [6.0 … 27.0, IQR 4.8] |
| Surgery performed | 2 (0.9% [0.0 … 2.1]) | 59 (42.4% [34.2 … 50.7]) | 5 (16.7% [3.3 … 30.0]) |
| Administration of contrast media | 63 (27.4% [21.6 … 33.2]) | 21 (15.1% [9.2 … 21.1]) | 0 (0.0%) |
| **Reason for withdrawal** | | | |
| eGFR > 60 ml/min | 54 (23.5% [18.0 … 29.0]) | 36 (25.9% [18.6 … 33.2]) | 3 (10.0% [0.0 … 20.7]) |
| discharged | 126 (54.8% [48.4 … 61.2]) | 75 (54.0% [45.7 … 62.2]) | 21 (70.0% [53.6 … 86.4]) |
| moved to another ward | 37 (16.1% [11.3 … 20.8]) | 22 (15.8% [9.8 … 21.9]) | 6 (20.0% [5.7 … 34.3]) |
| moved to ICU | 2 (0.9% [0.0 … 2.1]) | 1 (0.7% [0.0 … 2.1]) | 0 (0.0%) |
| deceased | 11 (4.8% [2.0 … 7.5]) | 5 (3.6% [0.5 … 6.7]) | 0 (0.0%) |
| **Diagnoses** | | | |
| Charlson comorbidity index | 6.0 [1.0 … 15.0, IQR 3.0] | 5.0 [1.0 … 10.0, IQR 2.0] | 6.0 [2.0 … 10.0, IQR 3.0] |
| Hypertension | 180 (78.3% [72.9 … 83.6]) | 95 (68.3% [60.6 … 76.1]) | 25 (83.3% [70.0 … 96.7]) |

| Characteristic | Internal medicine clinic (% [95% CI]) (n=230) | Surgery clinic (% [95% CI]) (n=139) | Rehabilitation clinic (% [95% CI]) (n=30) |
|---|---|---|---|
| Atrial fibrillation | 105 (45.7% [39.2 … 52.1]) | 27 (19.4% [12.8 … 26.0]) | 8 (26.7% [10.8 … 42.5]) |
| Heart failure | 107 (46.5% [40.1 … 53.0]) | 30 (21.6% [14.7 … 28.4]) | 11 (36.7% [19.4 … 53.9]) |
| Myocardial infarction | 31 (13.5% [9.1 … 17.9]) | 4 (2.9% [0.1 … 5.7]) | 2 (6.7% [0.0 … 15.6]) |
| Diabetes | 63 (27.4% [21.6 … 33.2]) | 32 (23.0% [16.0 … 30.0]) | 10 (33.3% [16.5 … 50.2]) |
| Acute kidney injury | 56 (24.3% [18.8 … 29.9]) | 15 (10.8% [5.6 … 15.9]) | 1 (3.3% [0.0 … 9.8]) |
| Developed AKI during hospitalisation* | 45 (19.6% [14.4 … 24.7]) | 13 (9.4% [4.5 … 14.2]) | 1 (3.3% [0.0 … 9.8]) |
| Uncoded AKI during hospitalisation* | 39 / 56 (69.6% [57.6 … 81.7]) | 13 / 15 (86.7% [69.5 … 100.0]) | 1 / 1 (100.0%) |
| Chronic kidney disease | 71 (30.9% [24.9 … 36.8]) | 18 (12.9% [7.4 … 18.5]) | 5 (16.7% [3.3 … 30.0]) |
| Unspecified renal failure coded in records | 2 (0.9% [0.0 … 2.1]) | 0 (0.0%) | 0 (0.0%) |
| **Prescribing** | | | |
| Median medication per day | 9.0 [1.0 … 26.0, IQR 6.0] | 6.0 [1.0 … 18.0, IQR 5.0] | 9.0 [1.0 … 16.0, IQR 4.0] |
| Inappropriate prescribing by patient | 139 (60.4% [54.1 … 66.8]) | 83 (59.7% [51.6 … 67.9]) | 14 (46.7% [28.8 … 64.5]) |
| 1 inappropriate prescription | 43 / 139 (30.9% [23.3 … 38.6]) | 39 / 83 (47.0% [36.3 … 57.7]) | 8 / 14 (57.1% [31.2 … 83.1]) |
| 2 inappropriate prescriptions | 35 / 139 (25.2% [18.0 … 32.4]) | 21 / 83 (25.3% [15.9 … 34.7]) | 0 / 14 (0.0%) |
| ≥3 inappropriate prescriptions | 61 / 139 (43.9% [35.6 … 52.1]) | 23 / 83 (27.7% [18.1 … 37.3]) | 6 / 14 (42.9% [16.9 … 68.8]) |
| Contraindicated prescriptions by patient | 19 (8.3% [4.7 … 11.8]) | 29 (20.9% [14.1 … 27.6]) | 5 (16.7% [3.3 … 30.0]) |
| 1 contraindicated prescription | 7 / 19 (36.8% [15.2 … 58.5]) | 21 / 29 (72.4% [56.1 … 88.7]) | 4 / 5 (80.0% [44.9 … 100.0]) |
| 2 contraindicated prescriptions | 4 / 19 (21.1% [2.7 … 39.4]) | 5 / 29 (17.2% [3.5 … 31.0]) | 0 / 5 (0.0%) |
| ≥ 3 contraindicated prescriptions | 8 / 19 (42.1% [19.9 … 64.3]) | 3 / 29 (10.3% [0.0 … 21.4]) | 1 / 5 (20.0% [0.0 … 55.1]) |

*Development of AKI defined as increase in SCr by ≥ 26.5 µmol/l based on the recorded SCr values.

# Appendix 6

# Classification of inappropriate prescribing by medication according to estimated glomerular filtration rate category

| Medication | Prescriptions, n | eGFR ≤ 10 ml/min, n (%) | eGFR 10 - 30 ml/min, n (%) | eGFR > 30 ml/min, n (%) | Test |
|---|---|---|---|---|---|
| Enoxaparin | 453 | 10 / 10 (100.0%) | 85 / 110 (77.3%) | 119 / 333 (35.7%) | $\chi^2$ (2) = 68.7, $p$ < 0.001* |
| Ampicillin/Sulbactam | 213 | 4 / 4 (100.0%) | 32 / 68 (47.1%) | 20 / 141 (14.2%) | $\chi^2$ (2) = 37.0, $p$ < 0.001* |
| Rosuvastatin | 197 | 3 / 6 (50.0%) | 28 / 32 (87.5%) | 7 / 159 (4.4%) | $\chi^2$ (2) = 121.9, $p$ < 0.001* |
| Ramipril | 145 | 1 / 2 (50.0%) | 26 / 55 (47.3%) | 20 / 88 (22.7%) | $\chi^2$ (2) = 9.6, $p$ = 0.008* |
| Metformin | 102 | 0 / 0 (0.0%) | 10 / 10 (100.0%) | 30 / 92 (32.6%) | |
| Amoxicillin/Clavulanic acid | 101 | 3 / 5 (60.0%) | 16 / 22 (72.7%) | 27 / 74 (36.5%) | $\chi^2$ (2) = 9.4, $p$ = 0.009* |
| Cefuroxime | 76 | 0 / 0 (0.0%) | 2 / 26 (7.7%) | 9 / 50 (18.0%) | |
| Rivaroxaban | 74 | 0 / 0 (0.0%) | 0 / 6 (0.0%) | 14 / 68 (20.6%) | |
| Tramadol | 61 | 1 / 6 (16.7%) | 0 / 10 (0.0%) | 0 / 45 (0.0%) | $\chi^2$ (2) = 9.3, $p$ = 0.009* |
| Metoclopramide | 60 | 3 / 3 (100.0%) | 15 / 19 (78.9%) | 38 / 38 (100.0%) | $\chi^2$ (2) = 9.2, $p$ = 0.01* |
| Apixaban | 59 | 0 / 0 (0.0%) | 1 / 4 (25.0%) | 28 / 55 (50.9%) | |
| Ciprofloxacin | 58 | 0 / 7 (0.0%) | 5 / 12 (41.7%) | 3 / 39 (7.7%) | $\chi^2$ (2) = 10.2, $p$ = 0.006* |
| Hydrochlorothiazide | 56 | 0 / 0 (0.0%) | 8 / 8 (100.0%) | 0 / 48 (0.0%) | |
| Dexketoprofen | 53 | 0 / 0 (0.0%) | 11 / 11 (100.0%) | 28 / 42 (66.7%) | |
| Digoxin | 46 | 0 / 1 (0.0%) | 0 / 5 (0.0%) | 5 / 40 (12.5%) | |
| Indapamide | 44 | 0 / 0 (0.0%) | 13 / 13 (100.0%) | 1 / 31 (3.2%) | |
| Oseltamivir | 36 | 1 / 1 (100.0%) | 13 / 13 (100.0%) | 22 / 22 (100.0%) | |
| Etoricoxib | 32 | 0 / 0 (0.0%) | 9 / 9 (100.0%) | 0 / 23 (0.0%) | |
| Pethidine | 27 | 0 / 0 (0.0%) | 2 / 2 (100.0%) | 23 / 25 (92.0%) | |
| Clarithromycin | 26 | 0 / 0 (0.0%) | 3 / 5 (60.0%) | 1 / 21 (4.8%) | |
| Cefazolin | 23 | 0 / 0 (0.0%) | 0 / 0 (0.0%) | 23 / 23 (100.0%) | |

| Medication | Prescriptions, n | eGFR ≤ 10 ml/min, n (%) | eGFR 10 - 30 ml/min, n (%) | eGFR > 30 ml/min, n (%) | Test |
|---|---|---|---|---|---|
| Bisoprolol | 20 | 0 / 0 (0.0%) | 3 / 9 (33.3%) | 1 / 11 (9.1%) | |
| Piperacillin/Tazobactam | 19 | 0 / 4 (0.0%) | 0 / 0 (0.0%) | 1 / 15 (6.7%) | |
| Glimepiride | 18 | 0 / 0 (0.0%) | 8 / 8 (100.0%) | 0 / 10 (0.0%) | |
| Pentoxifylline | 13 | 0 / 0 (0.0%) | 0 / 0 (0.0%) | 1 / 13 (7.7%) | |
| Sitagliptin | 13 | 0 / 0 (0.0%) | 2 / 2 (100.0%) | 4 / 11 (36.4%) | |
| Sultamicillin | 13 | 0 / 1 (0.0%) | 1 / 4 (25.0%) | 7 / 8 (87.5%) | $\chi^2$ (2) = 6.1, $p$ = 0.05* |
| Dabigatran | 12 | 0 / 0 (0.0%) | 0 / 0 (0.0%) | 4 / 12 (33.3%) | |
| Gabapentin | 11 | 0 / 0 (0.0%) | 3 / 3 (100.0%) | 1 / 8 (12.5%) | |
| Trimetazidine | 11 | 0 / 0 (0.0%) | 0 / 0 (0.0%) | 5 / 11 (45.5%) | |
| Ibuprofen | 8 | 0 / 0 (0.0%) | 0 / 0 (0.0%) | 5 / 8 (62.5%) | |
| Tranexamic acid | 8 | 0 / 0 (0.0%) | 4 / 4 (100.0%) | 3 / 4 (75.0%) | |
| Trimethoprim/ Sulfamethoxazole | 7 | 0 / 0 (0.0%) | 2 / 3 (66.7%) | 2 / 4 (50.0%) | |
| Ertapenem | 7 | 0 / 0 (0.0%) | 4 / 5 (80.0%) | 0 / 2 (0.0%) | |
| Gliclazide | 6 | 0 / 0 (0.0%) | 0 / 0 (0.0%) | 1 / 6 (16.7%) | |
| Diclofenac | 3 | 0 / 0 (0.0%) | 0 / 0 (0.0%) | 1 / 3 (33.3%) | |
| Cefoxitin | 2 | 0 / 0 (0.0%) | 0 / 0 (0.0%) | 2 / 2 (100.0%) | |
| Ceftazidime | 1 | 0 / 0 (0.0%) | 1 / 1 (100.0%) | 0 / 0 (0.0%) | |
| Naproxen | 1 | 0 / 0 (0.0%) | 0 / 0 (0.0%) | 1 / 1 (100.0%) | |

# Appendix 7

# Inappropriate prescribing by medication across three renal function estimates

| Medication | Prescriptions§, n | eGFR, n (%) | absGFR, n (%) | eCrCl, n (%) | Test |
|---|---|---|---|---|---|
| Enoxaparin | 453 (330) | 214 (47.2% [42.6 … 51.8]) | 140 (42.4% [37.1 … 47.8]) | 145 (43.9% [38.6 … 49.3]) | $\chi^2$ (2) = 1.9, $p$ = 0.4 |
| Ampicillin/Sulbactam | 213 (154) | 56 (26.3% [20.4 … 32.2]) | 34 (22.1% [15.5 … 28.6]) | 30 (19.5% [13.2 … 25.7]) | $\chi^2$ (2) = 2.5, $p$ = 0.3 |
| Rosuvastatin | 197 (188) | 38 (19.3% [13.8 … 24.8]) | 28 (14.9% [9.8 … 20.0]) | 35 (18.6% [13.1 … 24.2]) | $\chi^2$ (2) = 1.5, $p$ = 0.5 |
| Ramipril | 145 (103) | 47 (32.4% [24.8 … 40.0]) | 25 (24.3% [16.0 … 32.6]) | 26 (25.2% [16.9 … 33.6]) | $\chi^2$ (2) = 2.5, $p$ = 0.3 |
| Metformin | 102 (85) | 40 (39.2% [29.7 … 48.7]) | 27 (31.8% [21.9 … 41.7]) | 33 (38.8% [28.5 … 49.2]) | $\chi^2$ (2) = 1.3, $p$ = 0.5 |
| Amoxicillin/clavulanic acid | 101 (63) | 46 (45.5% [35.8 … 55.3]) | 28 (44.4% [32.2 … 56.7]) | 35 (55.6% [43.3 … 67.8]) | $\chi^2$ (2) = 2.0, $p$ = 0.4 |
| Cefuroxime | 76 (52) | 11 (14.5% [6.6 … 22.4]) | 7 (13.5% [4.2 … 22.7]) | 7 (13.5% [4.2 … 22.7]) | |
| Rivaroxaban | 74 (65) | 14 (18.9% [10.0 … 27.8]) | 25 (38.5% [26.6 … 50.3]) | 18 (27.7% [16.8 … 38.6]) | $\chi^2$ (2) = 6.6, $p$ = 0.04* |
| Tramadol | 61 (55) | 1 (1.6% [0.0 … 4.8]) | 0 (0.0%) | 0 (0.0%) | $\chi^2$ (2) = 1.8, $p$ = 0.4 |
| Metoclopramide | 60 (53) | 56 (93.3% [87.0 … 99.6]) | 49 (92.5% [85.3 … 99.6]) | 49 (92.5% [85.3 … 99.6]) | |
| Apixaban | 59 (55) | 29 (49.2% [36.4 … 61.9]) | 29 (52.7% [39.5 … 65.9]) | 29 (52.7% [39.5 … 65.9]) | $\chi^2$ (2) = 0.2, $p$ = 0.9 |
| Ciprofloxacin | 58 (46) | 8 (13.8% [4.9 … 22.7]) | 2 (4.3% [0.0 … 10.2]) | 2 (4.3% [0.0 … 10.2]) | $\chi^2$ (2) = 4.3, $p$ = 0.1 |
| Hydrochlorothiazide | 56 (55) | 8 (14.3% [5.1 … 23.5]) | 8 (14.5% [5.2 … 23.9]) | 9 (16.4% [6.6 … 26.1]) | $\chi^2$ (2) = 0.1, $p$ = 0.9 |
| Dexketoprofen | 53 (47) | 39 (73.6% [61.7 … 85.5]) | 33 (70.2% [57.1 … 83.3]) | 34 (72.3% [59.6 … 85.1]) | $\chi^2$ (2) = 0.1, $p$ = 0.9 |
| Digoxin | 46 (32) | 5 (10.9% [1.9 … 19.9]) | 3 (9.4% [0.0 … 19.5]) | 6 (18.8% [5.2 … 32.3]) | $\chi^2$ (2) = 1.5, $p$ = 0.5 |
| Indapamide | 44 (43) | 14 (31.8% [18.1 … 45.6]) | 11 (25.6% [12.5 … 38.6]) | 11 (25.6% [12.5 … 38.6]) | $\chi^2$ (2) = 0.6, $p$ = 0.8 |
| Oseltamivir | 36 (28) | 36 (100.0%) | 28 (100.0%) | 28 (100.0%) | |
| Etoricoxib | 32 (30) | 9 (28.1% [12.5 … 43.7]) | 9 (30.0% [13.6 … 46.4]) | 11 (36.7% [19.4 … 53.9]) | $\chi^2$ (2) = 0.6, $p$ = 0.8 |
| Pethidine | 27 (24) | 25 (92.6% [82.7 … 100.0]) | 14 (58.3% [38.6 … 78.1]) | 15 (62.5% [43.1 … 81.9]) | $\chi^2$ (2) = 9.0, $p$ = 0.01* |
| Clarithromycin | 26 (14) | 4 (15.4% [1.5 … 29.3]) | 0 (0.0%) | 0 (0.0%) | $\chi^2$ (2) = 4.7, $p$ = 0.1 |
| Cefazolin | 23 (20) | 23 (100.0%) | 20 (100.0%) | 20 (100.0%) | |
| Bisoprolol | 20 (4) | 4 (20.0% [2.5 … 37.5]) | 2 (50.0% [1.0 … 99.0]) | 2 (50.0% [1.0 … 99.0]) | $\chi^2$ (2) = 2.5, $p$ = 0.3 |

| Medication | Prescriptions§, n | eGFR, n (%) | absGFR, n (%) | eCrCl, n (%) | Test |
|---|---|---|---|---|---|
| Piperacillin/Tazobactam | 19 (18) | 1 (5.3% [0.0 … 15.3]) | 1 (5.6% [0.0 … 16.1]) | 1 (5.6% [0.0 … 16.1]) | |
| Glimepiride | 18 (14) | 8 (44.4% [21.5 … 67.4]) | 5 (35.7% [10.6 … 60.8]) | 5 (35.7% [10.6 … 60.8]) | $\chi^2$ (2) = 0.4, $p$ = 0.8 |
| Pentoxifylline | 13 | 1 (7.7% [0.0 … 22.2]) | 1 (7.7% [0.0 … 22.2]) | 1 (7.7% [0.0 … 22.2]) | |
| Sitagliptin | 13 (9) | 6 (46.2% [19.1 … 73.3]) | 0 (0.0%) | 0 (0.0%) | $\chi^2$ (2) = 10.3, $p$ = 0.006* |
| Sultamicillin | 13 (9) | 8 (61.5% [35.1 … 88.0]) | 8 (88.9% [68.4 … 100.0]) | 8 (88.9% [68.4 … 100.0]) | $\chi^2$ (2) = 3.2, $p$ = 0.2 |
| Dabigatran | 12 (11) | 4 (33.3% [6.7 … 60.0]) | 4 (36.4% [7.9 … 64.8]) | 4 (36.4% [7.9 … 64.8]) | |
| Gabapentin | 11 | 4 (36.4% [7.9 … 64.8]) | 4 (36.4% [7.9 … 64.8]) | 5 (45.5% [16.0 … 74.9]) | $\chi^2$ (2) = 0.3, $p$ = 0.9 |
| Trimetazidine | 11 (10) | 5 (45.5% [16.0 … 74.9]) | 3 (30.0% [1.6 … 58.4]) | 4 (40.0% [9.6 … 70.4]) | $\chi^2$ (2) = 0.5, $p$ = 0.8 |
| Ibuprofen | 8 | 5 (62.5% [29.0 … 96.0]) | 3 (37.5% [4.0 … 71.0]) | 4 (50.0% [15.4 … 84.6]) | $\chi^2$ (2) = 1.0, $p$ = 0.6 |
| Tranexamic acid | 8 | 7 (87.5% [64.6 … 100.0]) | 7 (87.5% [64.6 … 100.0]) | 7 (87.5% [64.6 … 100.0]) | |
| Trimethoprim/ Sulfamethoxazole | 7 (5) | 4 (57.1% [20.5 … 93.8]) | 3 (60.0% [17.1 … 100.0]) | 5 (100.0%) | $\chi^2$ (2) = 3.0, $p$ = 0.2 |
| Ertapenem | 7 (4) | 4 (57.1% [20.5 … 93.8]) | 2 (50.0% [1.0 … 99.0]) | 2 (50.0% [1.0 … 99.0]) | |
| Gliclazide | 6 (3) | 1 (16.7% [0.0 … 46.5]) | 1 (33.3% [0.0 … 86.7]) | 0 (0.0%) | $\chi^2$ (2) = 1.2, $p$ = 0.5 |
| Pregabalin | 6 | 0 (0.0%) | 1 (16.7% [0.0 … 46.5]) | 0 (0.0%) | $\chi^2$ (2) = 2.1, $p$ = 0.3 |
| Diclofenac | 3 (1) | 1 (33.3% [0.0 … 86.7]) | 1 (100.0%) | 1 (100.0%) | $\chi^2$ (2) = 2.2, $p$ = 0.3 |
| Cefoxitin | 2 | 2 (100.0%) | 2 (100.0%) | 2 (100.0%) | |
| Ceftazidime | 1 (0) | 1 (100.0%) | 0 (0.0%) | 0 (0.0%) | |
| Naproxen | 1 | 1 (100.0%) | 0 (0.0%) | 1 (100.0%) | $\chi^2$ (2) = 3.0, $p$ = 0.2 |
| Nitrofurantoin | 1 | 0 (0.0%) | 0 (0.0%) | 1 (100.0%) | $\chi^2$ (2) = 3.0, $p$ = 0.2 |

eGFR – estimated glomerular filtration rate; absGFR – absolute glomerular filtration rate; eCrCl – estimated creatinine clearance
*statistically significant difference ($p$<0.05)
§number in the brackets refers to the number of prescriptions available for absGFR and eCrCl

# Appendix 8

# Classification of inappropriate prescribing by medication according to estimated glomerular filtration rate

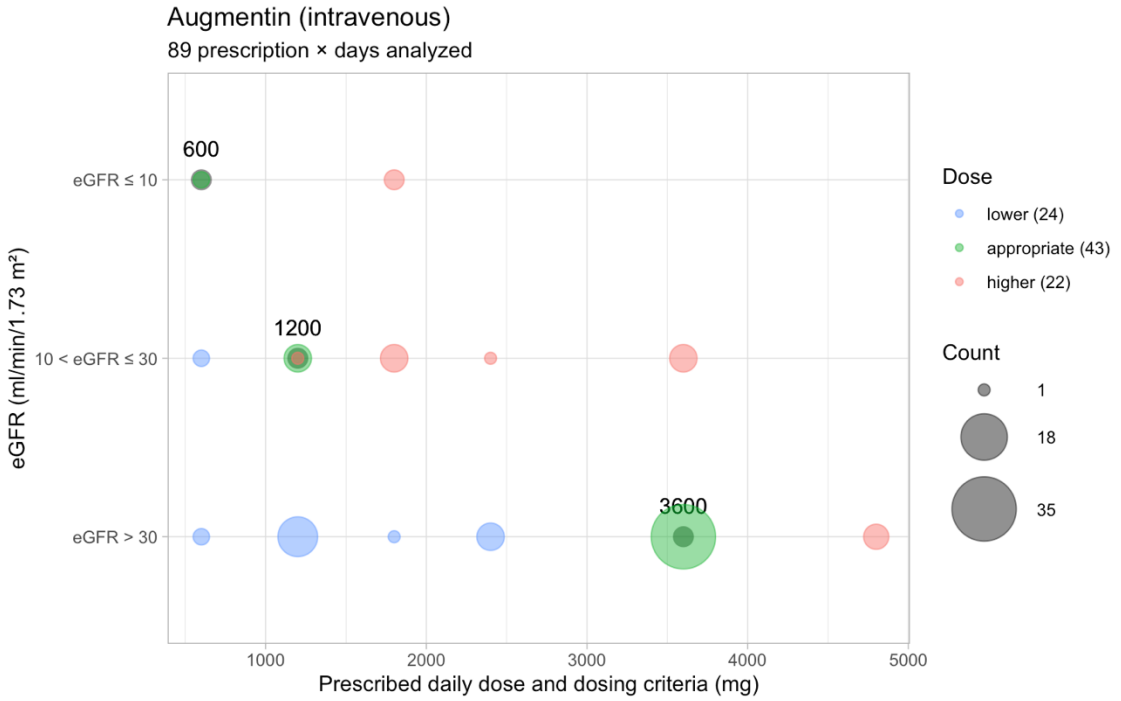
| Medication | Prescriptions, n | Inappropriate prescriptions, n (%) | Dose too low, n (%) | Dose too high, n (%) | Contraindicated prescriptions, n (%) |
|---|---|---|---|---|---|
| Enoxaparin | 453 | 214 (47.2% [42.6 … 51.8]) | 51 (11.3% [8.3 … 14.2]) | 163 (36.0% [31.6 … 40.4]) | 35 (7.7% [5.3 … 10.2]) |
| Ampicillin/Sulbactam | 213 | 56 (26.3% [20.4 … 32.2]) | 23 (10.8% [6.6 … 15.0]) | 33 (15.5% [10.6 … 20.4]) | 0 (0.0%) |
| Rosuvastatin | 197 | 38 (19.3% [13.8 … 24.8]) | 0 (0.0%) | 38 (19.3% [13.8 … 24.8]) | 0 (0.0%) |
| Spironolactone | 149 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Ramipril | 145 | 47 (32.4% [24.8 … 40.0]) | 0 (0.0%) | 47 (32.4% [24.8 … 40.0]) | 0 (0.0%) |
| Metformin | 102 | 40 (39.2% [29.7 … 48.7]) | 0 (0.0%) | 40 (39.2% [29.7 … 48.7]) | 0 (0.0%) |
| Amoxicillin/Clavulanic acid | 101 | 46 (45.5% [35.8 … 55.3]) | 24 (23.8% [15.5 … 32.1]) | 22 (21.8% [13.7 … 29.8]) | 0 (0.0%) |
| Cefuroxime | 76 | 11 (14.5% [6.6 … 22.4]) | 7 (9.2% [2.7 … 15.7]) | 4 (5.3% [0.2 … 10.3]) | 0 (0.0%) |
| Rivaroxaban | 74 | 14 (18.9% [10.0 … 27.8]) | 12 (16.2% [7.8 … 24.6]) | 2 (2.7% [0.0 … 6.4]) | 0 (0.0%) |
| Allopurinol | 61 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Tramadol | 61 | 1 (1.6% [0.0 … 4.8]) | 0 (0.0%) | 1 (1.6% [0.0 … 4.8]) | 0 (0.0%) |
| Metoclopramide | 60 | 56 (93.3% [87.0 … 99.6]) | 1 (1.7% [0.0 … 4.9]) | 55 (91.7% [84.7 … 98.7]) | 0 (0.0%) |
| Apixaban | 59 | 29 (49.2% [36.4 … 61.9]) | 28 (47.5% [34.7 … 60.2]) | 1 (1.7% [0.0 … 5.0]) | 0 (0.0%) |
| Ciprofloxacin | 58 | 8 (13.8% [4.9 … 22.7]) | 0 (0.0%) | 8 (13.8% [4.9 … 22.7]) | 0 (0.0%) |
| Hydrochlorothiazide | 56 | 8 (14.3% [5.1 … 23.5]) | 0 (0.0%) | 8 (14.3% [5.1 … 23.5]) | 8 (14.3% [5.1 … 23.5]) |
| Dexketoprofen | 53 | 39 (73.6% [61.7 … 85.5]) | 0 (0.0%) | 39 (73.6% [61.7 … 85.5]) | 11 (20.8% [9.8 … 31.7]) |
| Digoxin | 46 | 5 (10.9% [1.9 … 19.9]) | 0 (0.0%) | 5 (10.9% [1.9 … 19.9]) | 0 (0.0%) |
| Cefotaxime | 45 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Indapamide | 44 | 14 (31.8% [18.1 … 45.6]) | 0 (0.0%) | 14 (31.8% [18.1 … 45.6]) | 13 (29.5% [16.1 … 43.0]) |
| Codeine | 38 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Oseltamivir | 36 | 36 (100.0%) | 0 (0.0%) | 36 (100.0%) | 1 (2.8% [0.0 … 8.1]) |

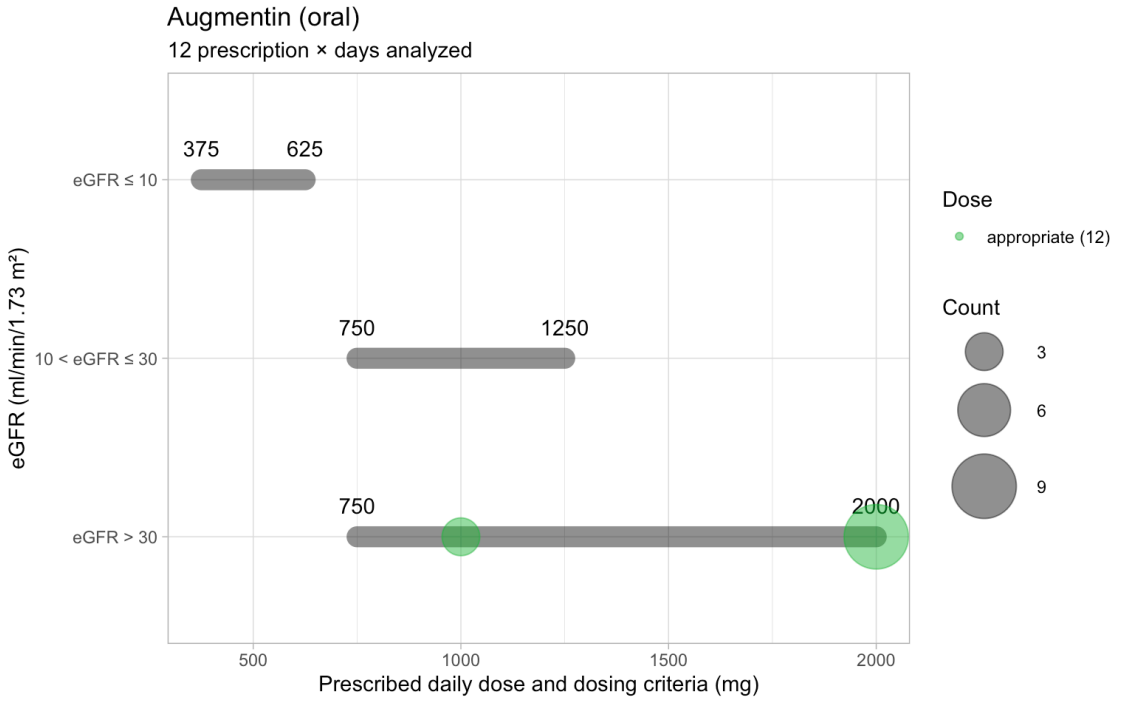
| Medication | Prescriptions, n | Inappropriate prescriptions, n (%) | Dose too low, n (%) | Dose too high, n (%) | Contraindicated prescriptions, n (%) |
|---|---|---|---|---|---|
| Etoricoxib | 32 | 9 (28.1% [12.5 … 43.7]) | 0 (0.0%) | 9 (28.1% [12.5 … 43.7]) | 9 (28.1% [12.5 … 43.7]) |
| Pethidine | 27 | 25 (92.6% [82.7 … 100.0]) | 0 (0.0%) | 25 (92.6% [82.7 … 100.0]) | 25 (92.6% [82.7 … 100.0]) |
| Clarithromycin | 26 | 4 (15.4% [1.5 … 29.3]) | 1 (3.8% [0.0 … 11.2]) | 3 (11.5% [0.0 … 23.8]) | 0 (0.0%) |
| Simvastatin | 25 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Cefazolin | 23 | 23 (100.0%) | 23 (100.0%) | 0 (0.0%) | 0 (0.0%) |
| Bisoprolol | 20 | 4 (20.0% [2.5 … 37.5]) | 4 (20.0% [2.5 … 37.5]) | 0 (0.0%) | 0 (0.0%) |
| Piperacillin/Tazobactam | 19 | 1 (5.3% [0.0 … 15.3]) | 1 (5.3% [0.0 … 15.3]) | 0 (0.0%) | 0 (0.0%) |
| Glimepiride | 18 | 8 (44.4% [21.5 … 67.4]) | 0 (0.0%) | 8 (44.4% [21.5 … 67.4]) | 8 (44.4% [21.5 … 67.4]) |
| Pentoxifylline | 13 | 1 (7.7% [0.0 … 22.2]) | 1 (7.7% [0.0 … 22.2]) | 0 (0.0%) | 0 (0.0%) |
| Sitagliptin | 13 | 6 (46.2% [19.1 … 73.3]) | 0 (0.0%) | 6 (46.2% [19.1 … 73.3]) | 0 (0.0%) |
| Sultamicillin | 13 | 8 (61.5% [35.1 … 88.0]) | 3 (23.1% [0.2 … 46.0]) | 5 (38.5% [12.0 … 64.9]) | 0 (0.0%) |
| Dabigatran | 12 | 4 (33.3% [6.7 … 60.0]) | 3 (25.0% [0.5 … 49.5]) | 1 (8.3% [0.0 … 24.0]) | 0 (0.0%) |
| Gabapentin | 11 | 4 (36.4% [7.9 … 64.8]) | 0 (0.0%) | 4 (36.4% [7.9 … 64.8]) | 0 (0.0%) |
| Morphine | 11 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Trimetazidine | 11 | 5 (45.5% [16.0 … 74.9]) | 0 (0.0%) | 5 (45.5% [16.0 … 74.9]) | 0 (0.0%) |
| Ibuprofen | 8 | 5 (62.5% [29.0 … 96.0]) | 0 (0.0%) | 5 (62.5% [29.0 … 96.0]) | 3 (37.5% [4.0 … 71.0]) |
| Tranexamic acid | 8 | 7 (87.5% [64.6 … 100.0]) | 0 (0.0%) | 7 (87.5% [64.6 … 100.0]) | 0 (0.0%) |
| Trimethoprim/ Sulfamethoxazole | 7 | 4 (57.1% [20.5 … 93.8]) | 1 (14.3% [0.0 … 40.2]) | 3 (42.9% [6.2 … 79.5]) | 0 (0.0%) |
| Ertapenem | 7 | 4 (57.1% [20.5 … 93.8]) | 0 (0.0%) | 4 (57.1% [20.5 … 93.8]) | 0 (0.0%) |
| Fluconazole | 7 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

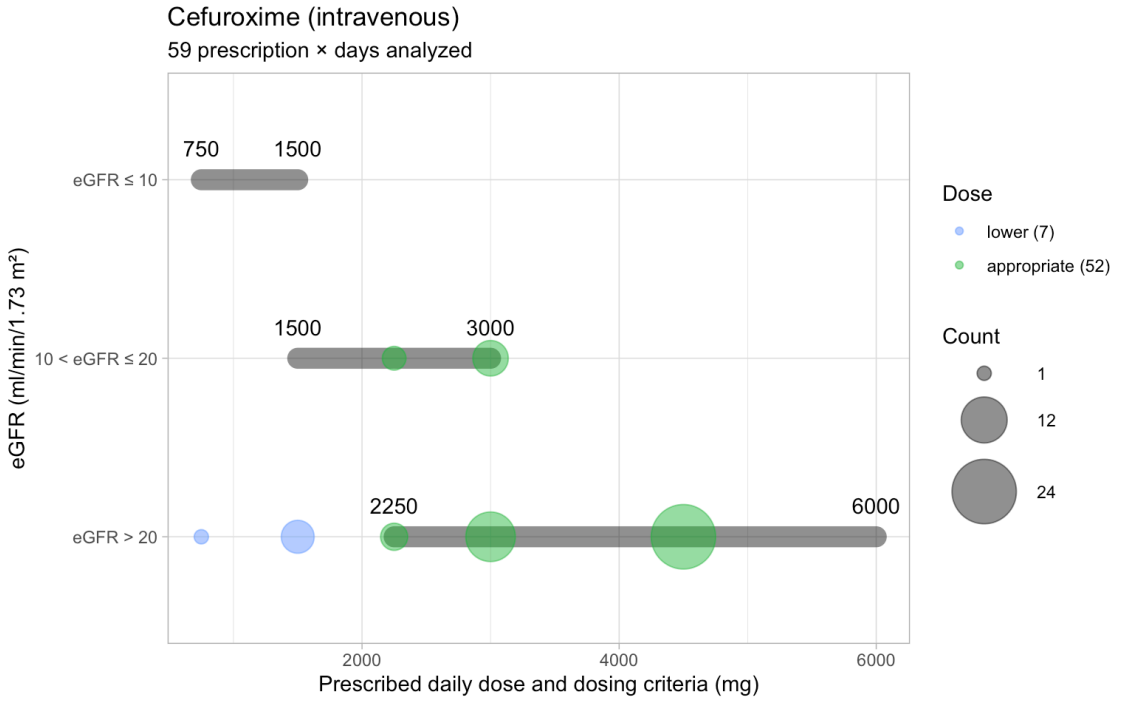
| Medication | Prescriptions, n | Inappropriate prescriptions, n (%) | Dose too low, n (%) | Dose too high, n (%) | Contraindicated prescriptions, n (%) |
|---|---|---|---|---|---|
| Gliclazide | 6 | 1 (16.7% [0.0 … 46.5]) | 1 (16.7% [0.0 … 46.5]) | 0 (0.0%) | 0 (0.0%) |
| Pregabalin | 6 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Risperidone | 4 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Diclofenac | 3 | 1 (33.3% [0.0 … 86.7]) | 0 (0.0%) | 1 (33.3% [0.0 … 86.7]) | 1 (33.3% [0.0 … 86.7]) |
| Cefoxitin | 2 | 2 (100.0%) | 2 (100.0%) | 0 (0.0%) | 0 (0.0%) |
| Ceftazidime | 1 | 1 (100.0%) | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |
| Memantine | 1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Naproxen | 1 | 1 (100.0%) | 0 (0.0%) | 1 (100.0%) | 1 (100.0%) |
| Nitrofurantoin | 1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Pramipexole | 1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Ranolazine | 1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Topiramate | 1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Venlafaxine | 1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

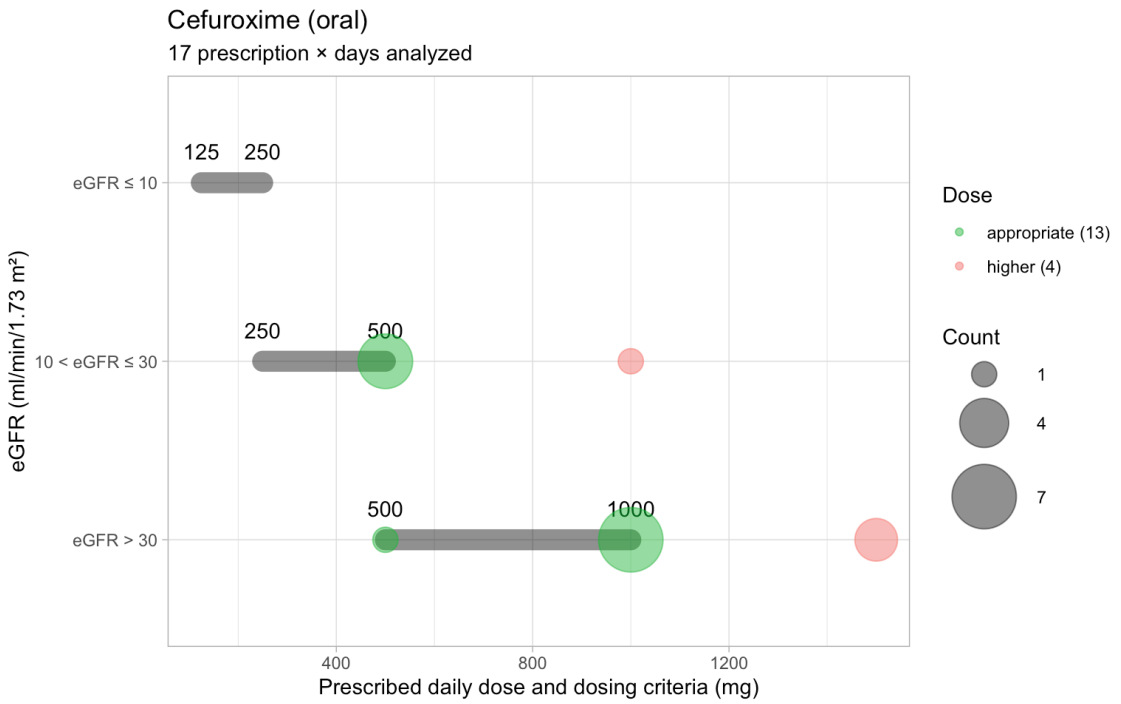
# Appendix 9

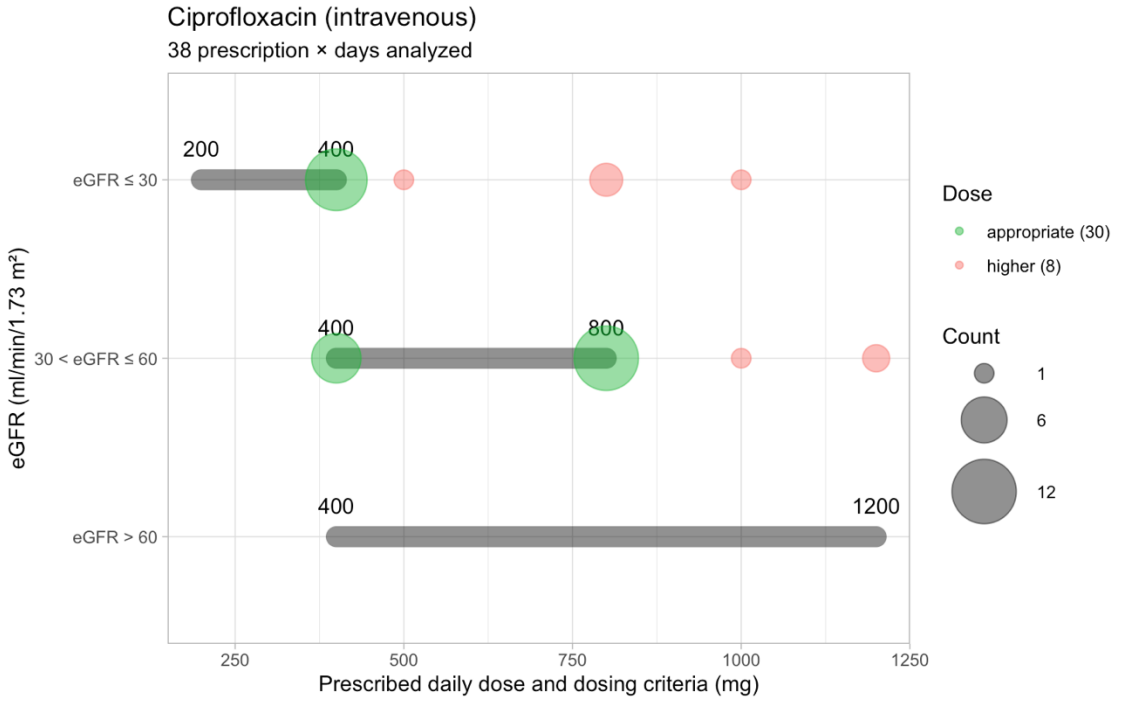
# Dosing patterns of medications with at least five inappropriate prescriptions

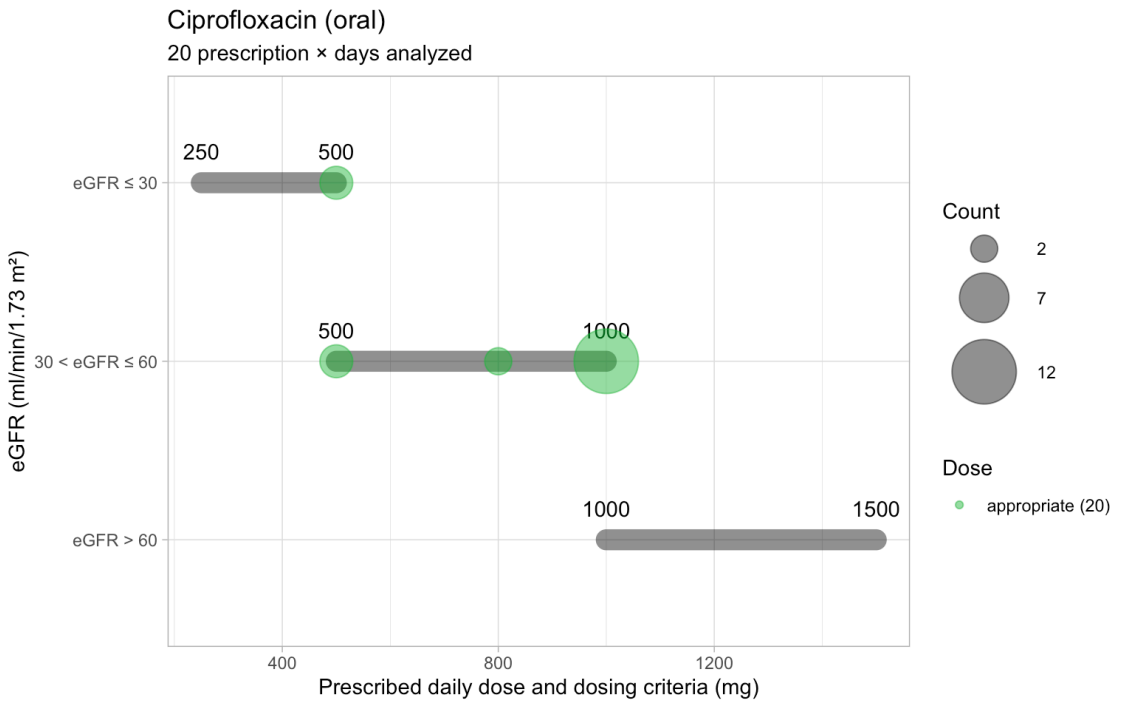

Augmentin (intravenous)
89 prescription × days analyzed
600
1200
3600
eGFR ≤ 10
10 < eGFR ≤ 30
eGFR > 30
eGFR (ml/min/1.73 m²)
1000
2000
3000
4000
5000
Prescribed daily dose and dosing criteria (mg)
Dose
lower (24)
appropriate (43)
higher (22)
Count
1
18
35

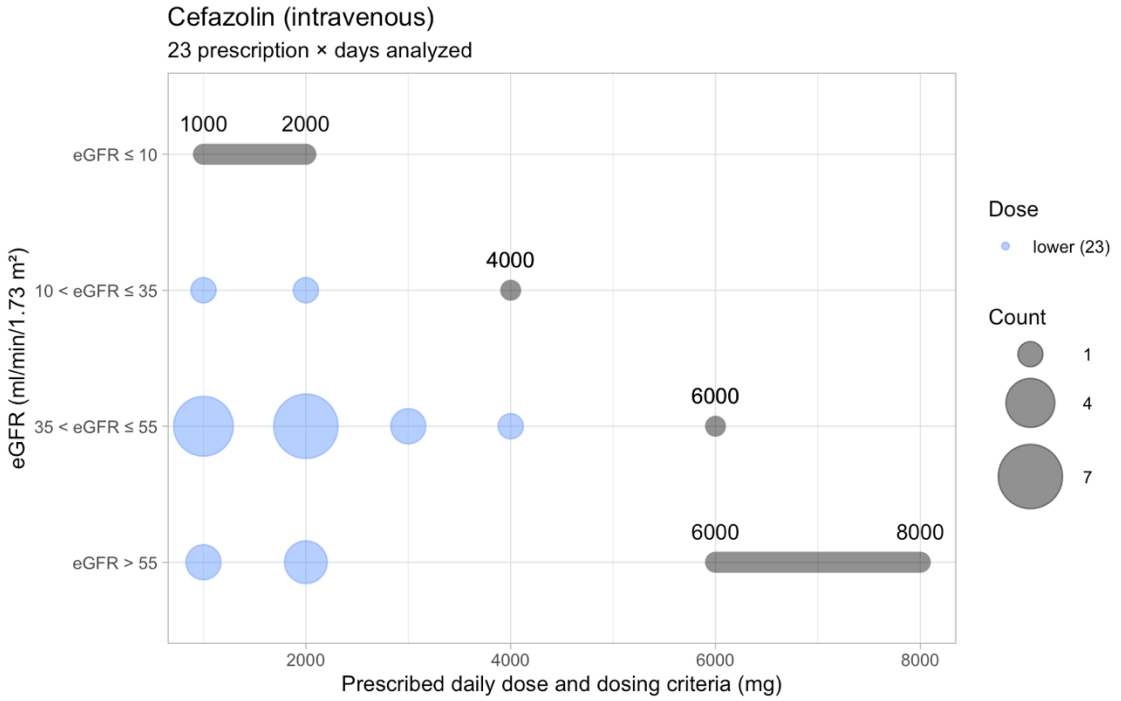

Augmentin (oral)
12 prescription × days analyzed
375
625
750
1250
750
2000
eGFR ≤ 10
10 < eGFR ≤ 30
eGFR > 30
eGFR (ml/min/1.73 m²)
500
1000
1500
2000
Prescribed daily dose and dosing criteria (mg)
Dose
appropriate (12)
Count
3
6
9

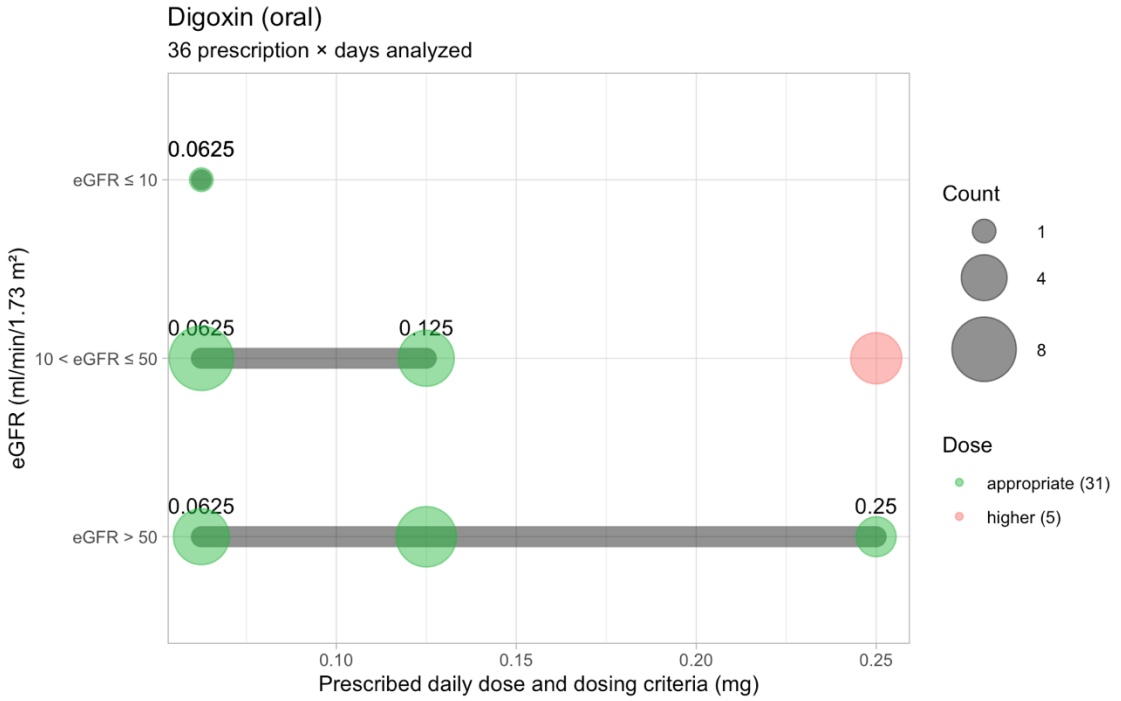

Cefuroxime (intravenous)
59 prescription × days analyzed
750
1500
1500
3000
2250
6000
eGFR ≤ 10
10 < eGFR ≤ 20
eGFR > 20
eGFR (ml/min/1.73 m²)
2000
4000
6000
Prescribed daily dose and dosing criteria (mg)
Dose
lower (7)
appropriate (52)
Count
1
12
24

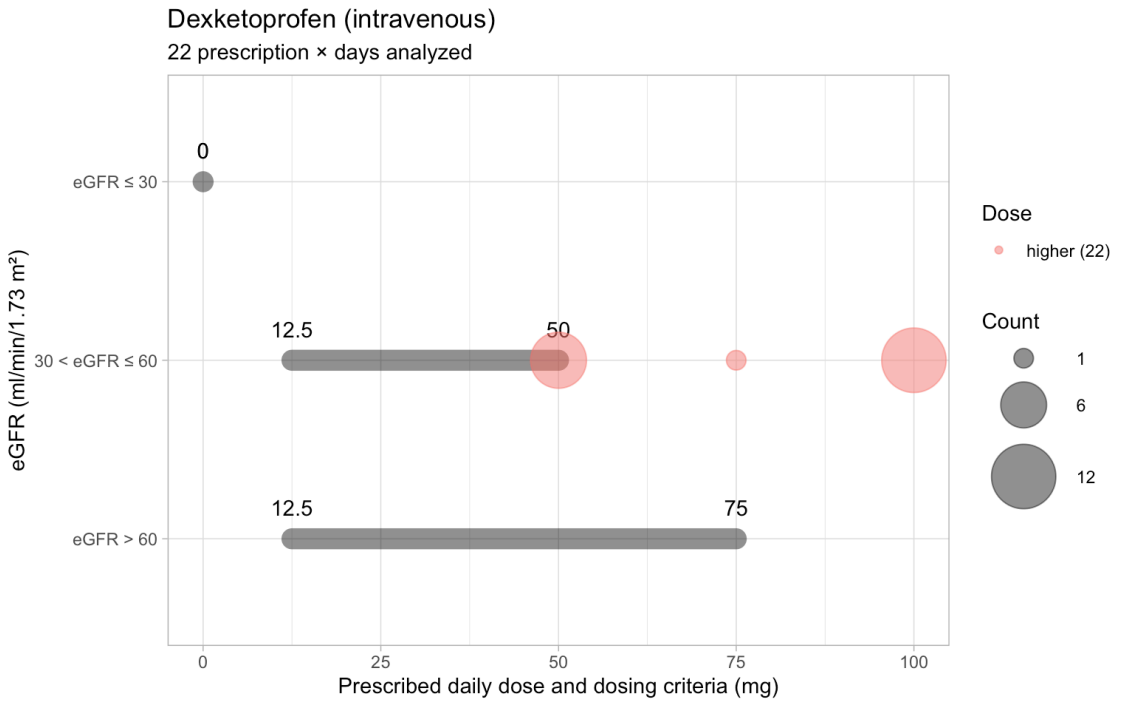

Cefuroxime (oral)
17 prescription × days analyzed
125
250
250
500
500
1000
eGFR ≤ 10
10 < eGFR ≤ 30
eGFR > 30
eGFR (ml/min/1.73 m²)
400
800
1200
Prescribed daily dose and dosing criteria (mg)
Dose
appropriate (13)
higher (4)
Count
1
4
7

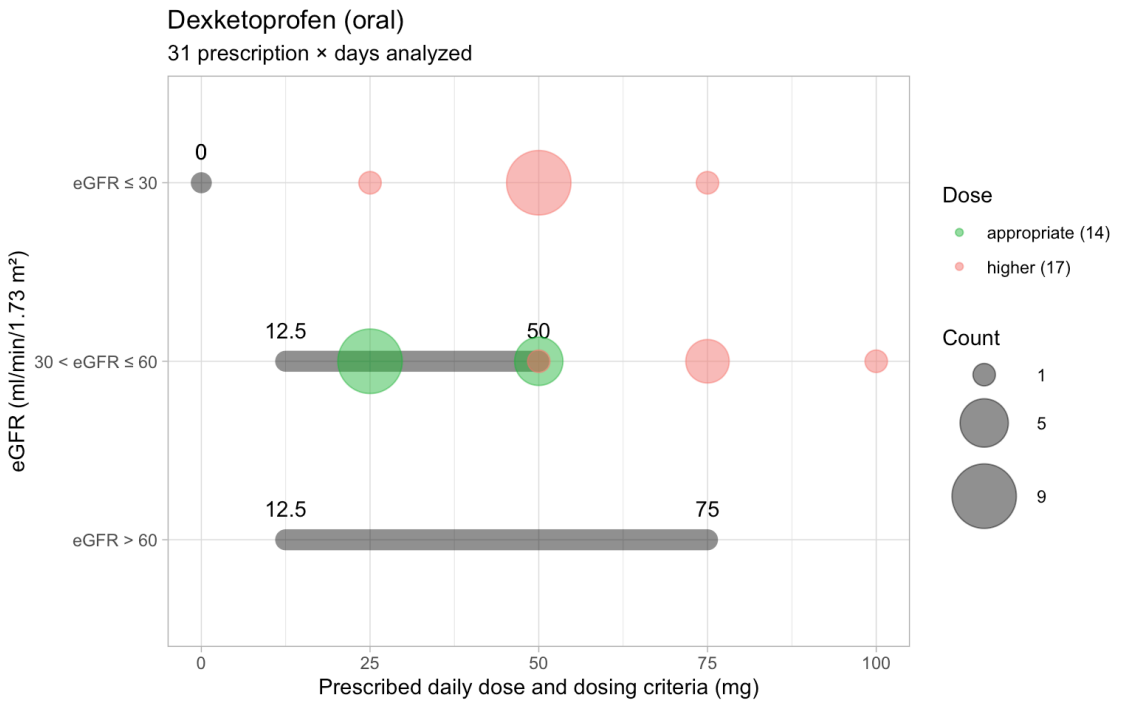

Ciprofloxacin (intravenous)
38 prescription × days analyzed
200
400
400
800
400
1200
eGFR ≤ 30
30 < eGFR ≤ 60
eGFR > 60
eGFR (ml/min/1.73 m²)
250
500
750
1000
1250
Prescribed daily dose and dosing criteria (mg)
Dose
appropriate (30)
higher (8)
Count
1
6
12

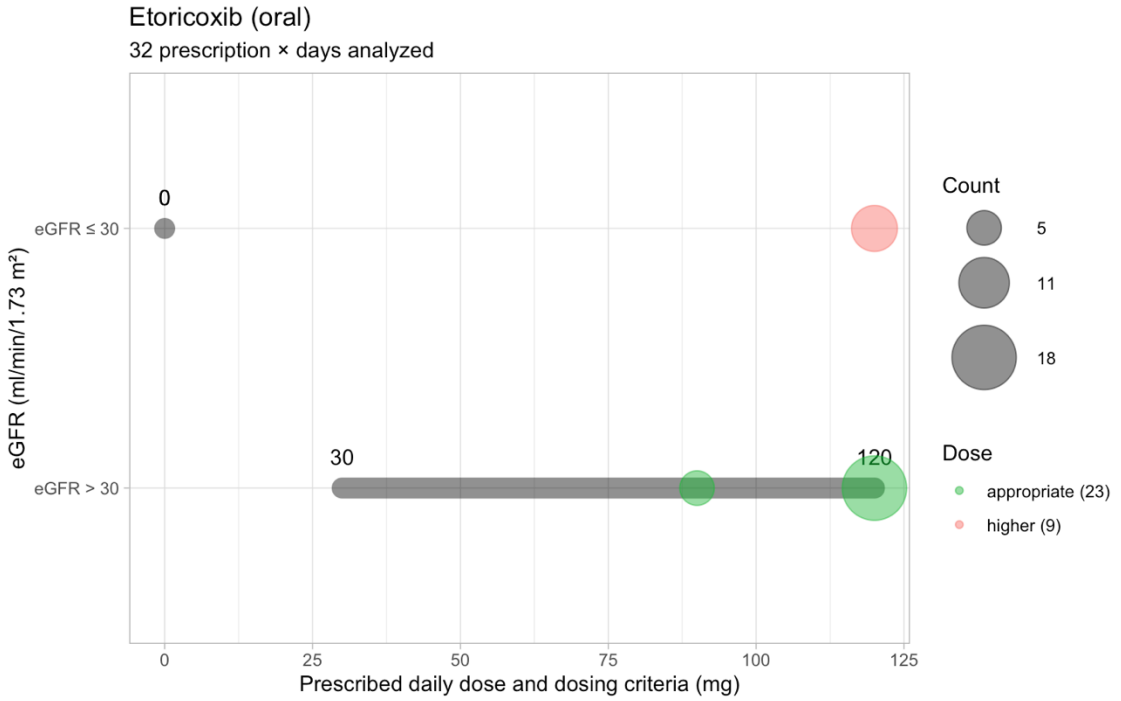

Ciprofloxacin (oral)
20 prescription × days analyzed
250
500
500
1000
1000
1500
eGFR ≤ 30
30 < eGFR ≤ 60
eGFR > 60
eGFR (ml/min/1.73 m²)
400
800
1200
Prescribed daily dose and dosing criteria (mg)
Count
2
7
12
Dose
appropriate (20)

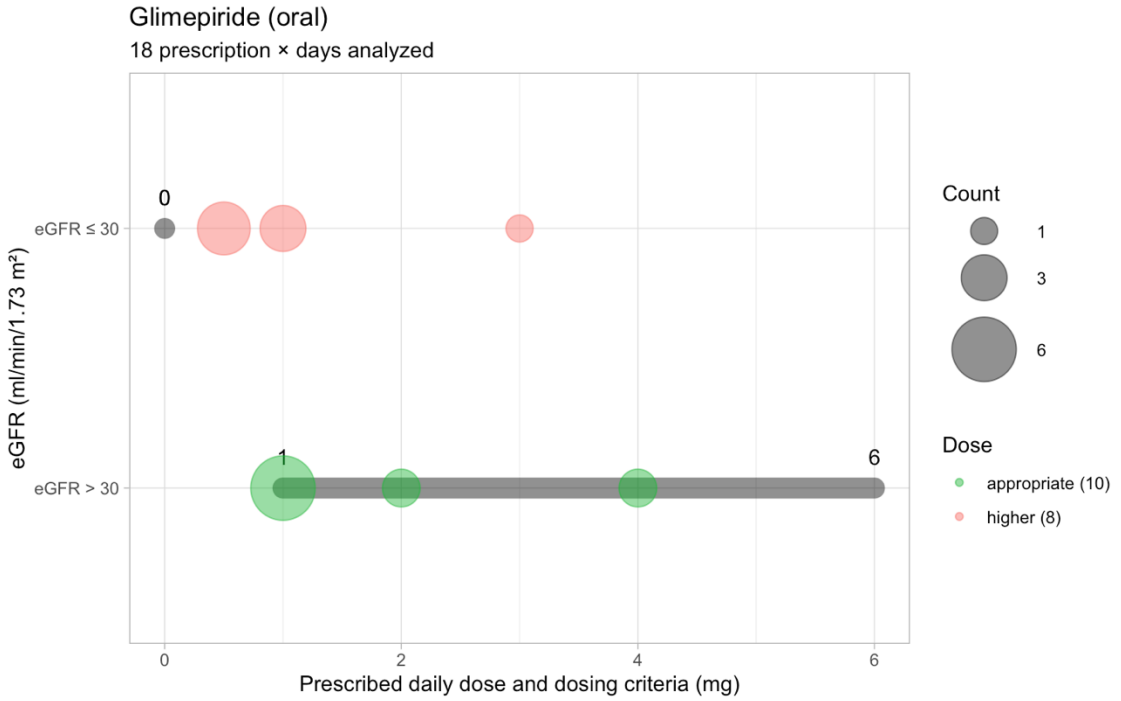

Cefazolin (intravenous)
23 prescription × days analyzed
1000
2000
4000
6000
6000
8000
eGFR ≤ 10
10 < eGFR ≤ 35
35 < eGFR ≤ 55
eGFR > 55
eGFR (ml/min/1.73 m²)
2000
4000
6000
8000
Prescribed daily dose and dosing criteria (mg)
Dose
lower (23)
Count
1
4
7

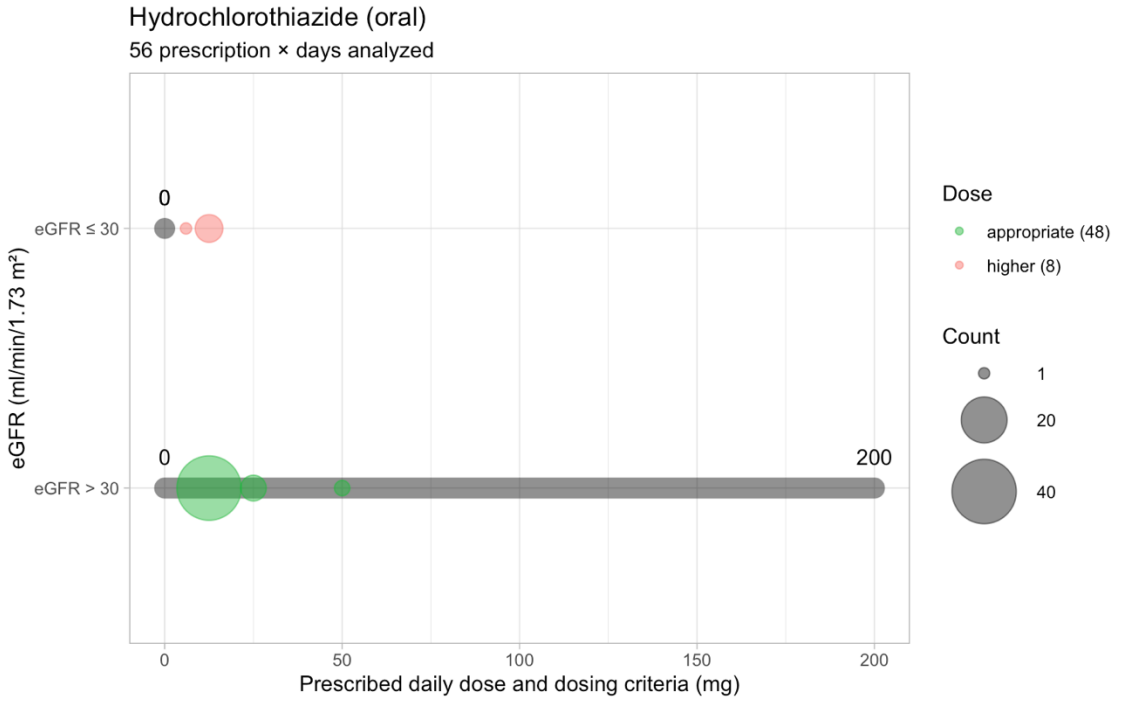

Digoxin (oral)
36 prescription × days analyzed
0.0625
0.0625
0.125
0.0625
0.25
eGFR ≤ 10
10 < eGFR ≤ 50
eGFR > 50
eGFR (ml/min/1.73 m²)
0.10
0.15
0.20
0.25
Prescribed daily dose and dosing criteria (mg)
Count
1
4
8
Dose
appropriate (31)
higher (5)

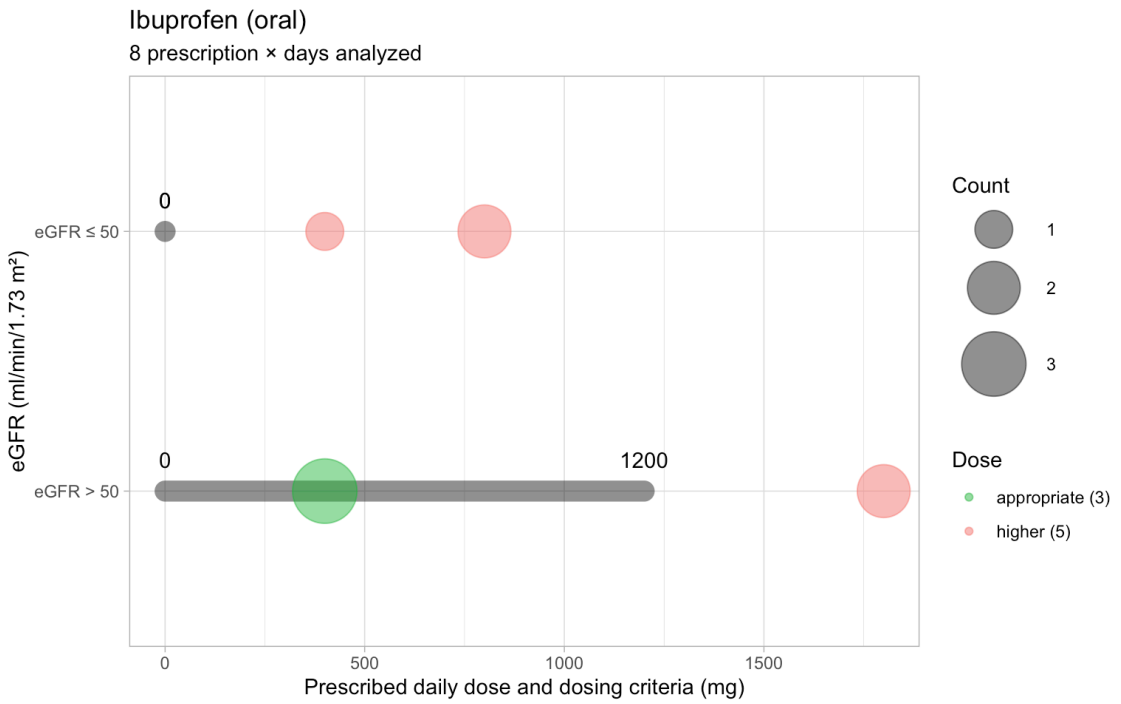

Dexketoprofen (intravenous)
22 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 30
30 < eGFR ≤ 60
eGFR > 60
0
12.5
50
12.5
75
0
25
50
75
100
Prescribed daily dose and dosing criteria (mg)
Dose
higher (22)
Count
1
6
12

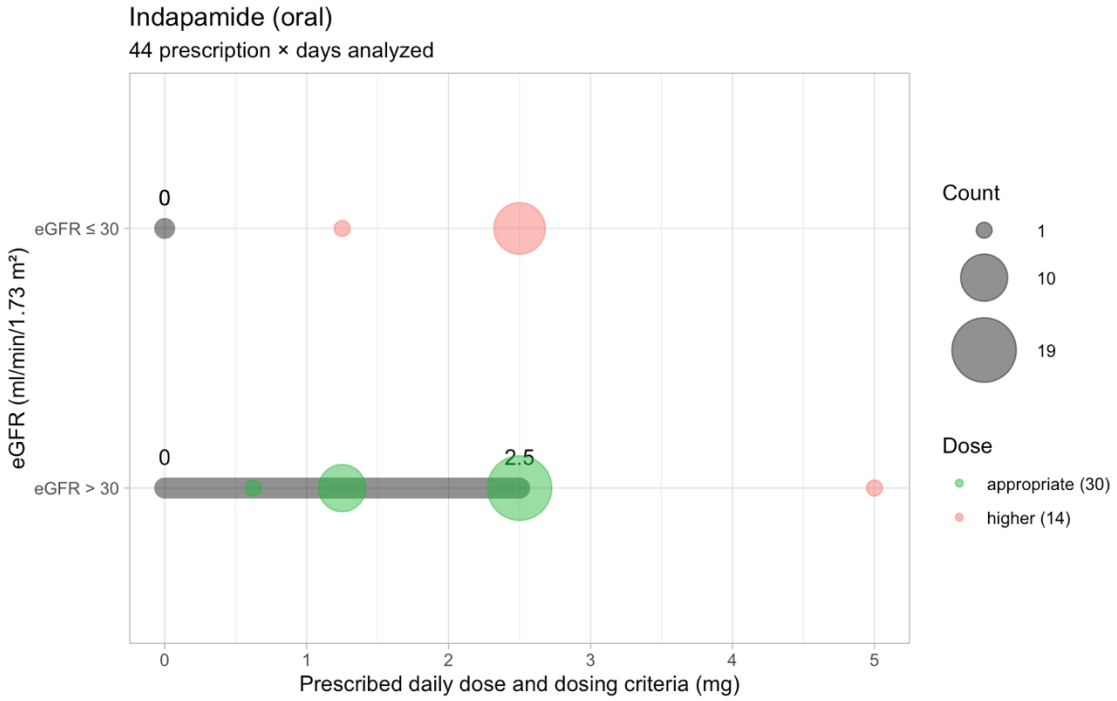

Dexketoprofen (oral)
31 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 30
30 < eGFR ≤ 60
eGFR > 60
0
12.5
50
12.5
75
0
25
50
75
100
Prescribed daily dose and dosing criteria (mg)
Dose
appropriate (14)
higher (17)
Count
1
5
9

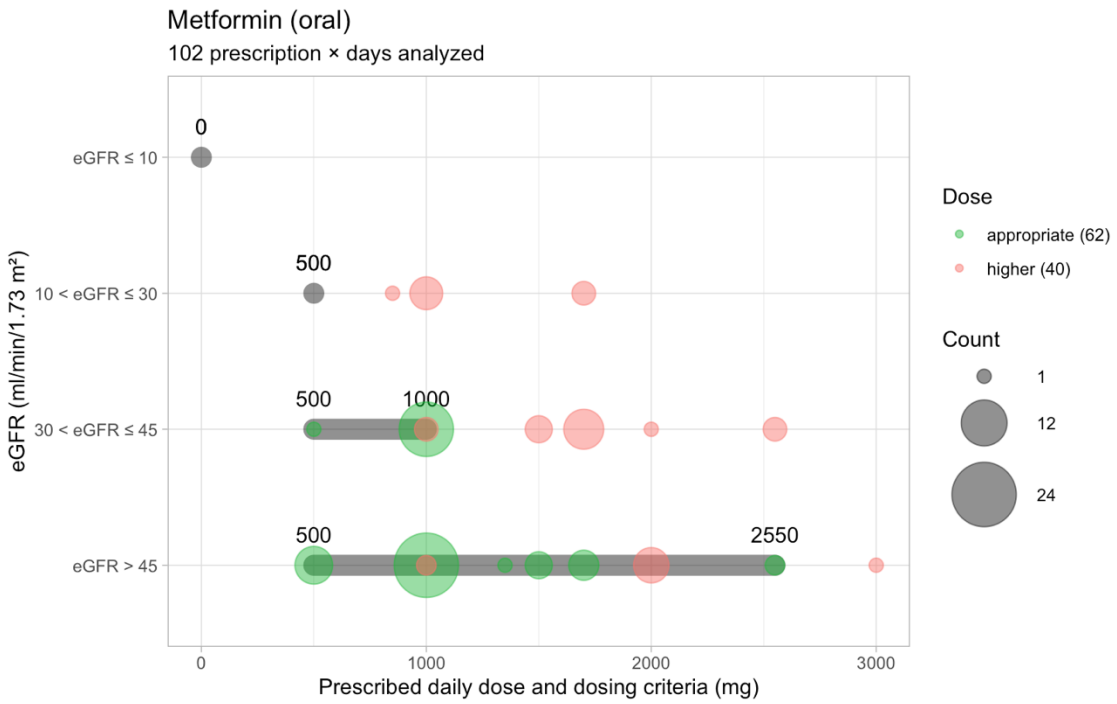

Etoricoxib (oral)
32 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 30
eGFR > 30
0
30
120
0
25
50
75
100
125
Prescribed daily dose and dosing criteria (mg)
Count
5
11
18
Dose
appropriate (23)
higher (9)

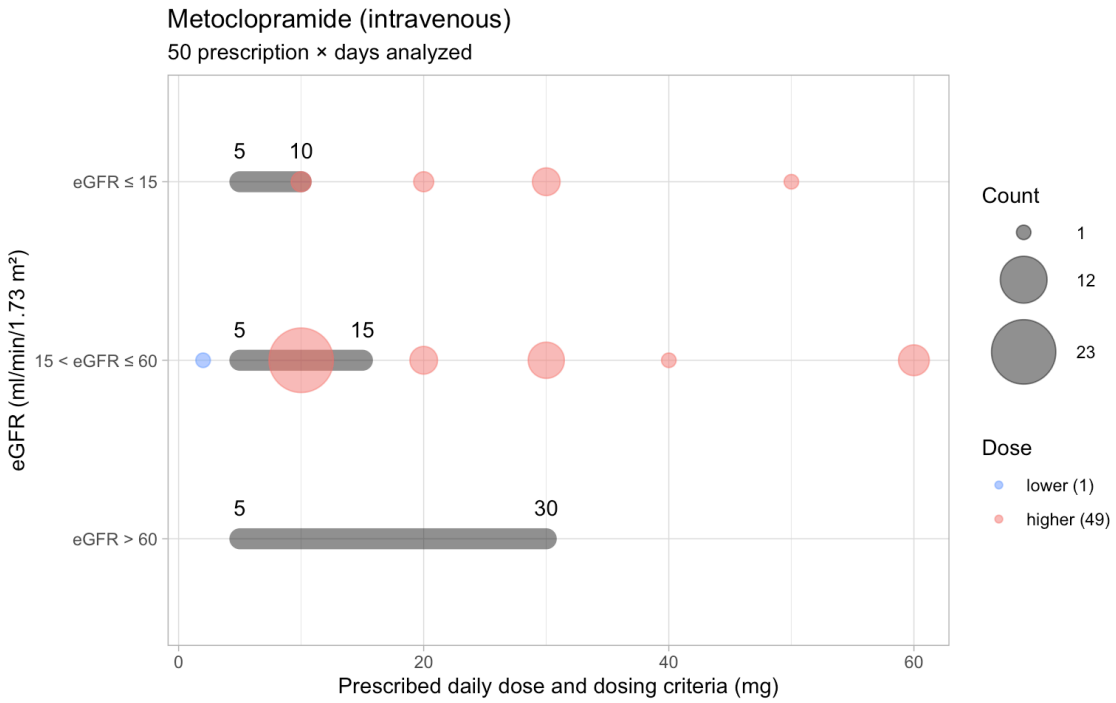

Glimepiride (oral)
18 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 30
eGFR > 30
0
1
6
0
2
4
6
Prescribed daily dose and dosing criteria (mg)
Count
1
3
6
Dose
appropriate (10)
higher (8)

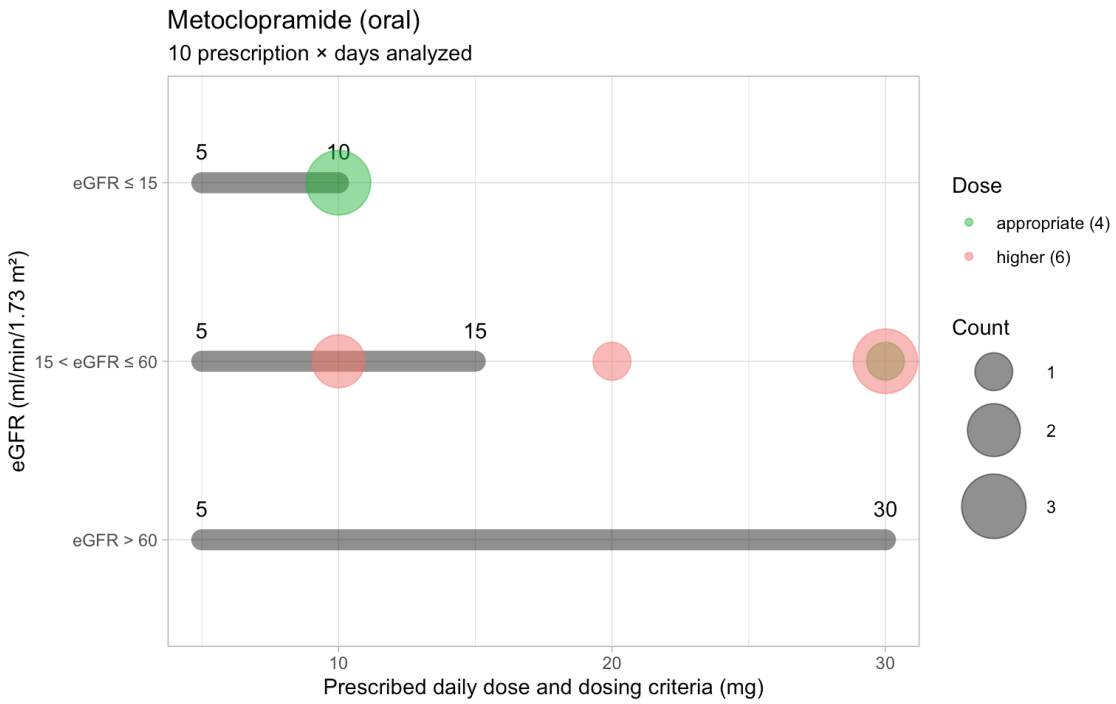

Hydrochlorothiazide (oral)
56 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 30
eGFR > 30
0
0
200
0
50
100
150
200
Prescribed daily dose and dosing criteria (mg)
Dose
appropriate (48)
higher (8)
Count
1
20
40

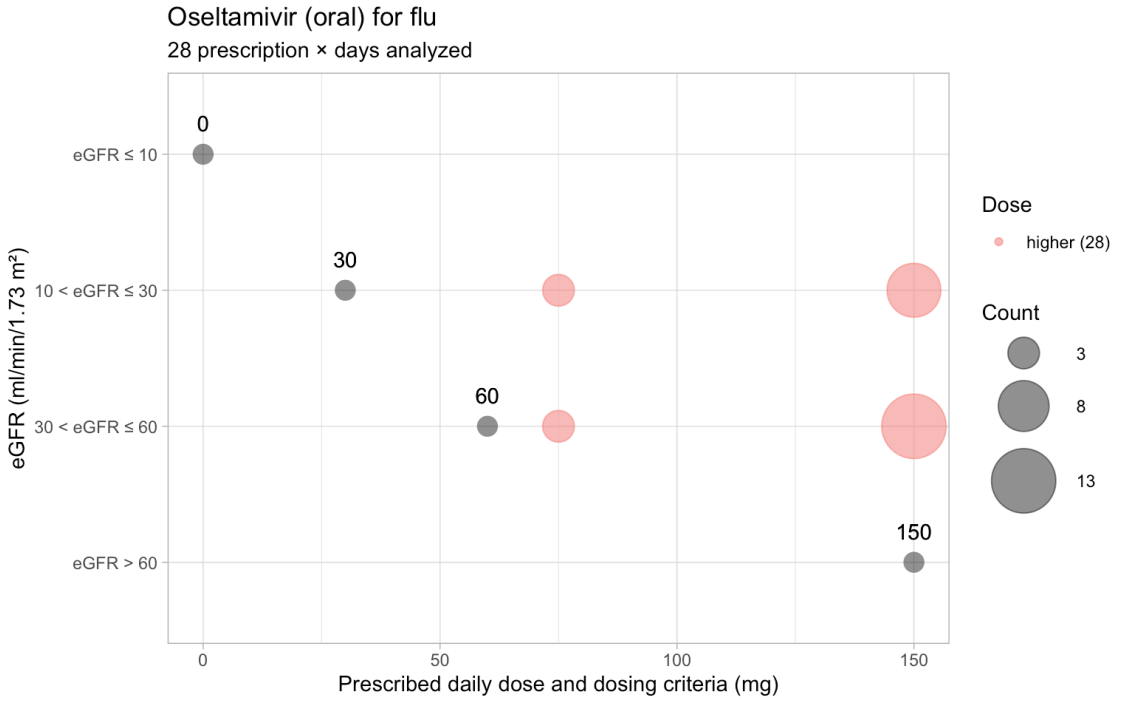

Ibuprofen (oral)
8 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 50
eGFR > 50
0
0
1200
0
500
1000
1500
Prescribed daily dose and dosing criteria (mg)
Count
1
2
3
Dose
appropriate (3)
higher (5)

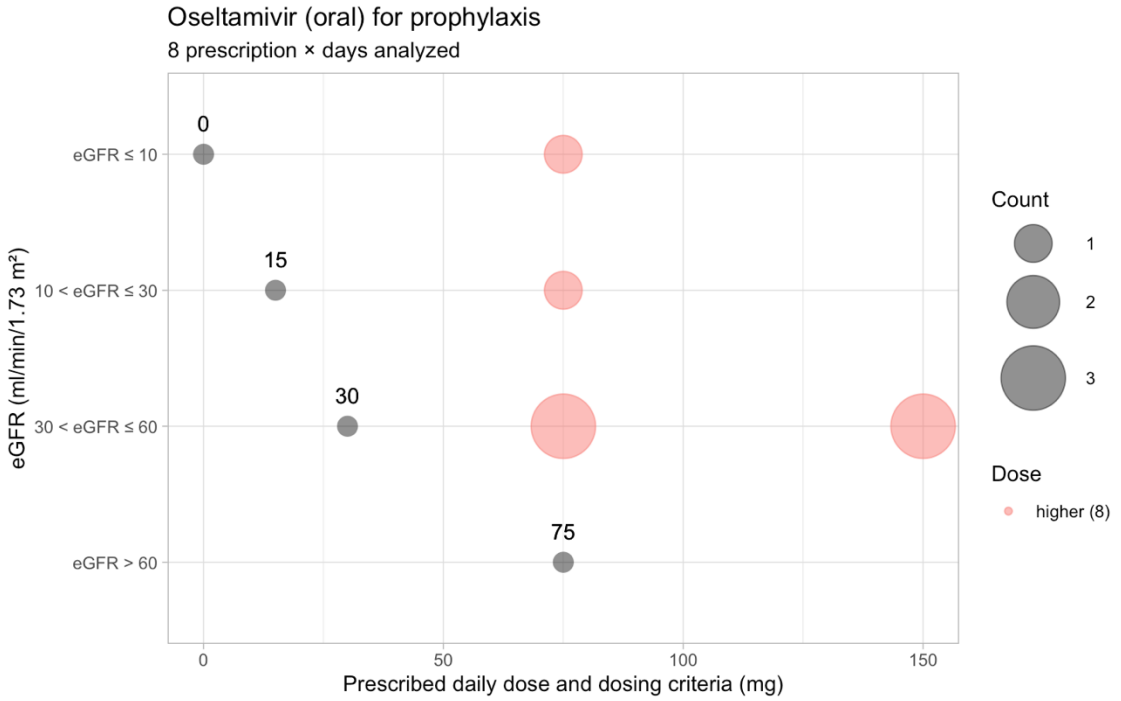

Indapamide (oral)
44 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 30
eGFR > 30
0
0
2.5
0
1
2
3
4
5
Prescribed daily dose and dosing criteria (mg)
Count
1
10
19
Dose
appropriate (30)
higher (14)

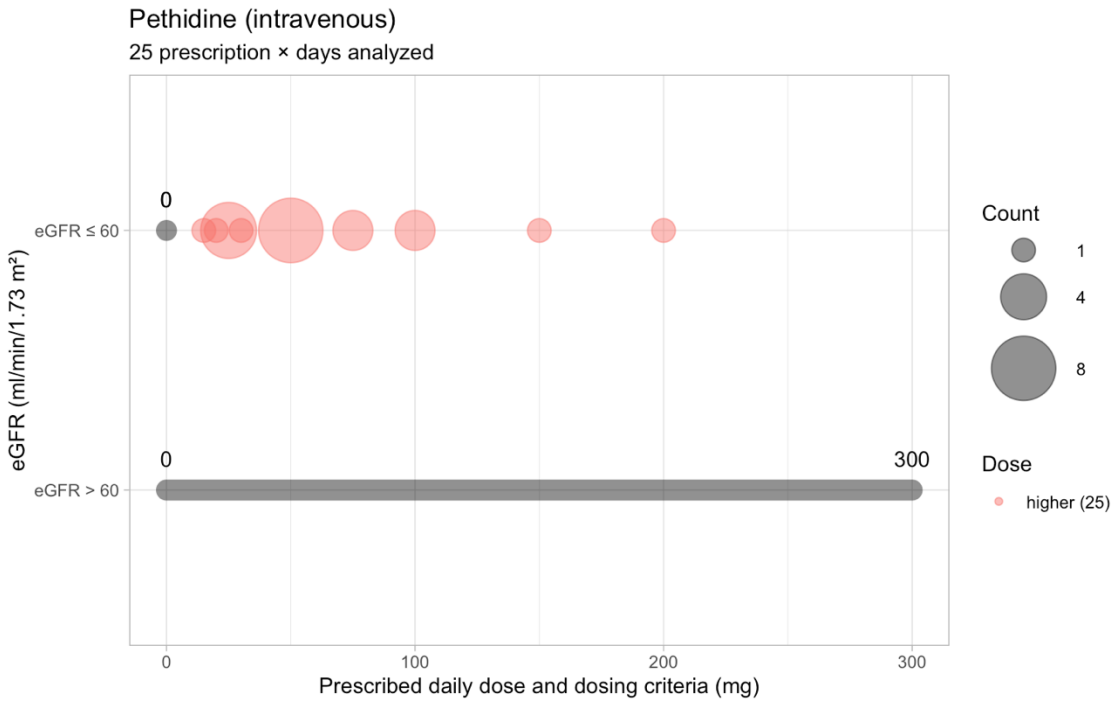

Metformin (oral)
102 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 10
10 < eGFR ≤ 30
30 < eGFR ≤ 45
eGFR > 45
0
500
500
1000
500
2550
0
1000
2000
3000
Prescribed daily dose and dosing criteria (mg)
Dose
appropriate (62)
higher (40)
Count
1
12
24

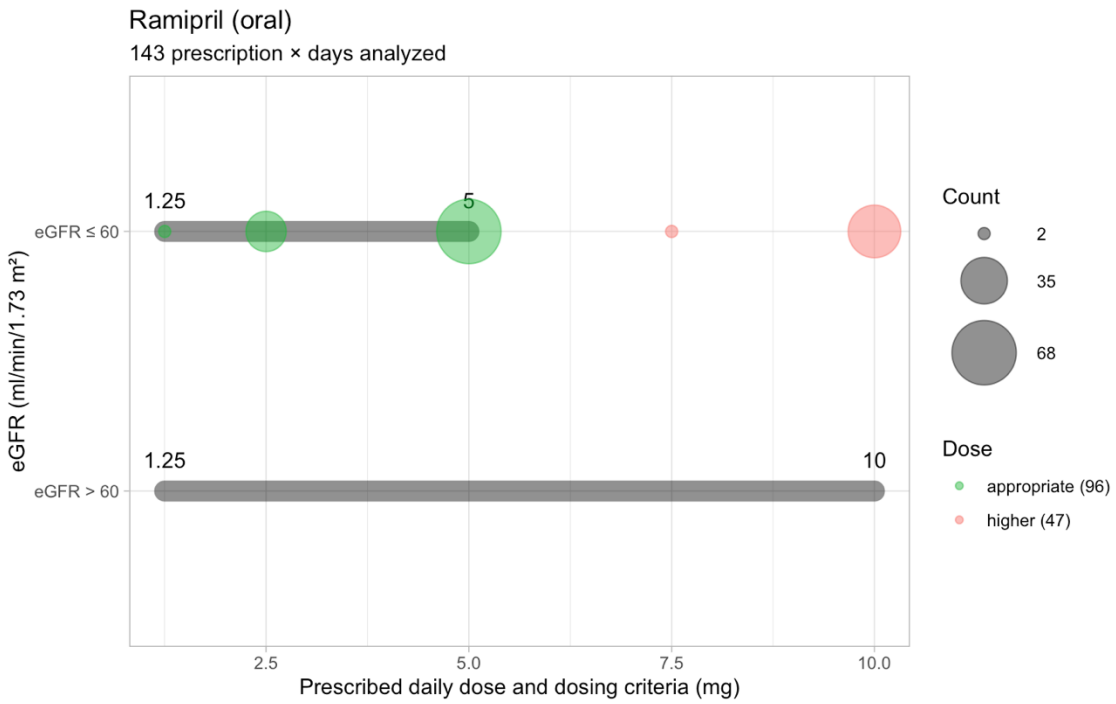

Metoclopramide (intravenous)
50 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 15
15 < eGFR ≤ 60
eGFR > 60
5
10
5
15
5
30
0
20
40
60
Prescribed daily dose and dosing criteria (mg)
Count
1
12
23
Dose
lower (1)
higher (49)

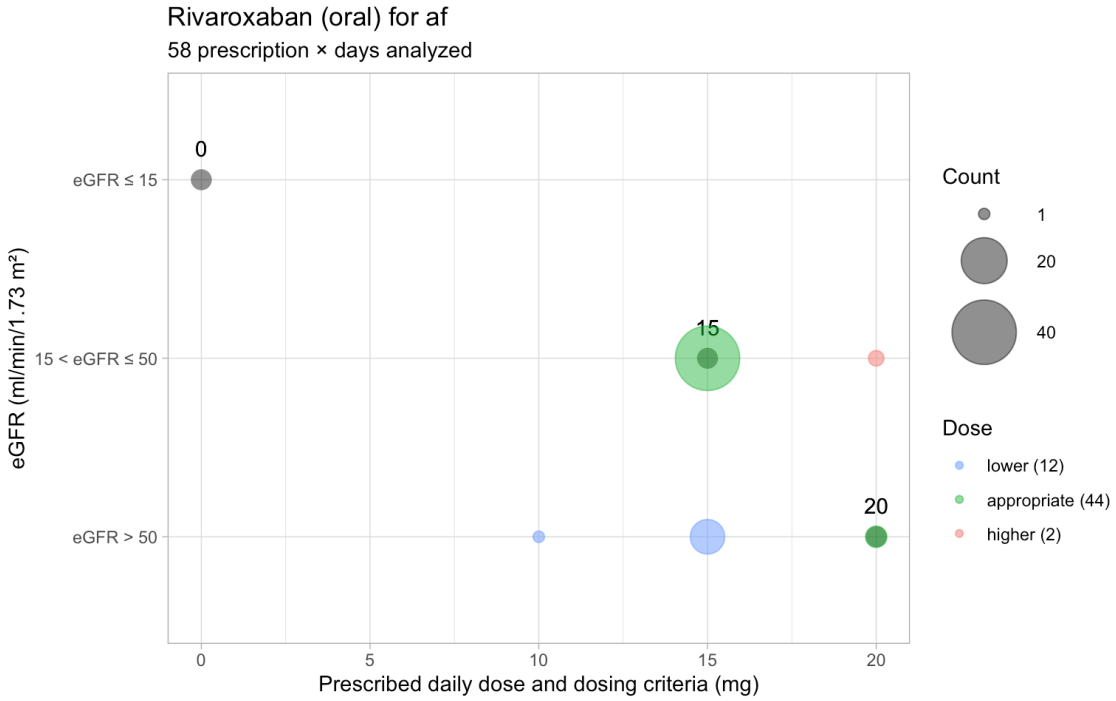

Metoclopramide (oral)
10 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 15
15 < eGFR ≤ 60
eGFR > 60
5
10
5
15
5
30
10
20
30
Prescribed daily dose and dosing criteria (mg)
Dose
appropriate (4)
higher (6)
Count
1
2
3

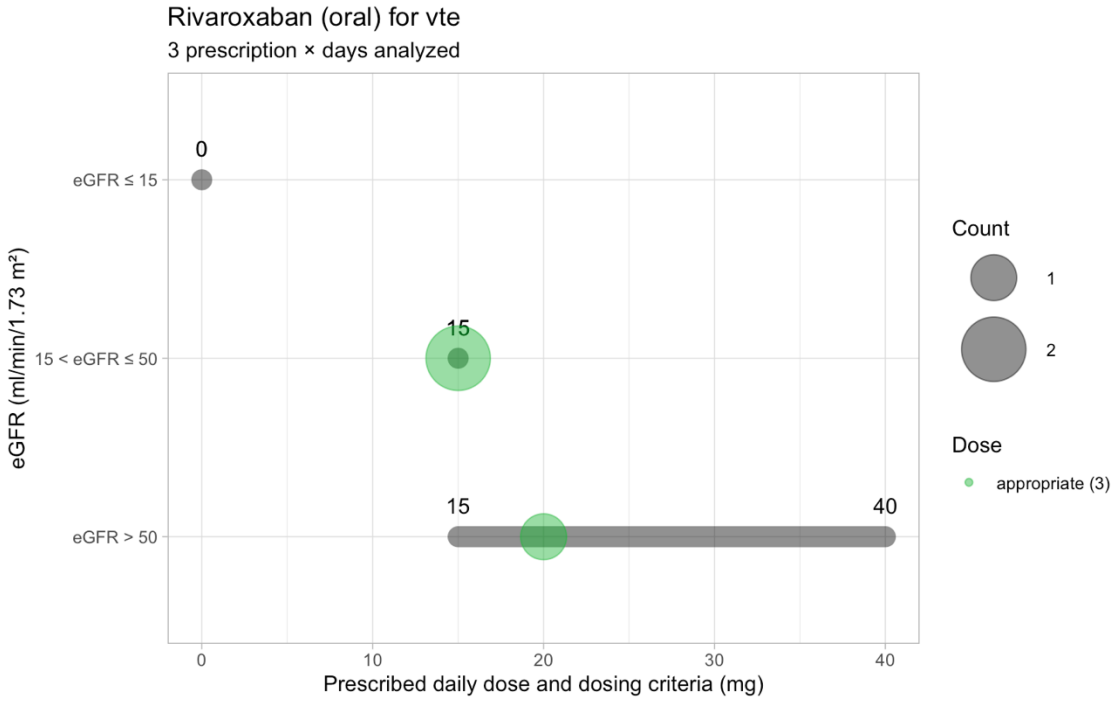

Oseltamivir (oral) for flu
28 prescription × days analyzed
eGFR ≤ 10
10 < eGFR ≤ 30
30 < eGFR ≤ 60
eGFR > 60
eGFR (ml/min/1.73 m²)
0
30
60
150
0
50
100
150
Prescribed daily dose and dosing criteria (mg)
Dose
higher (28)
Count
3
8
13

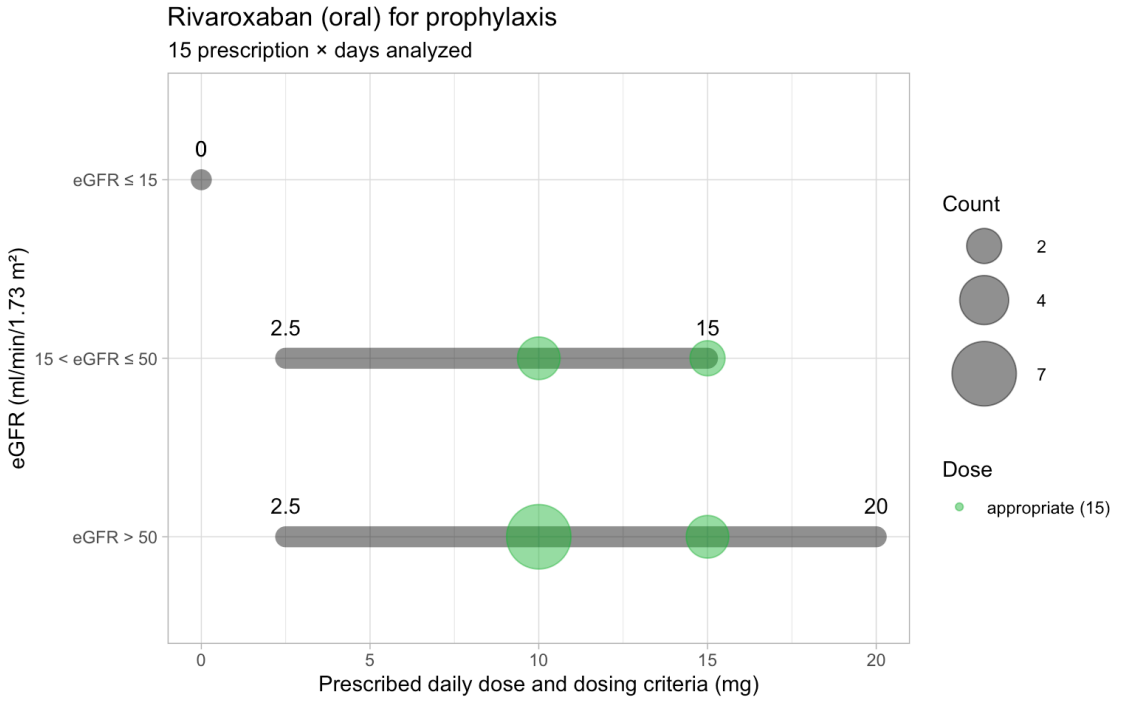

Oseltamivir (oral) for prophylaxis
8 prescription × days analyzed
eGFR ≤ 10
10 < eGFR ≤ 30
30 < eGFR ≤ 60
eGFR > 60
eGFR (ml/min/1.73 m²)
0
15
30
75
0
50
100
150
Prescribed daily dose and dosing criteria (mg)
Count
1
2
3
Dose
higher (8)

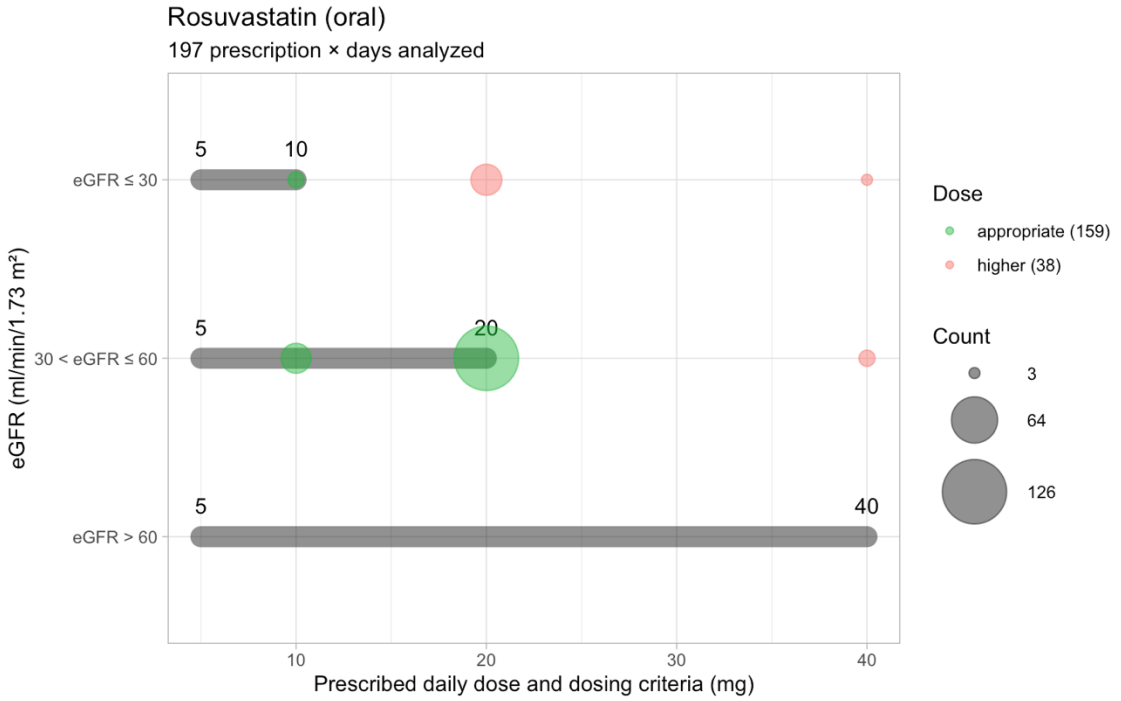

Pethidine (intravenous)
25 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 60
eGFR > 60
0
0
300
0
100
200
300
Prescribed daily dose and dosing criteria (mg)
Count
1
4
8
Dose
higher (25)

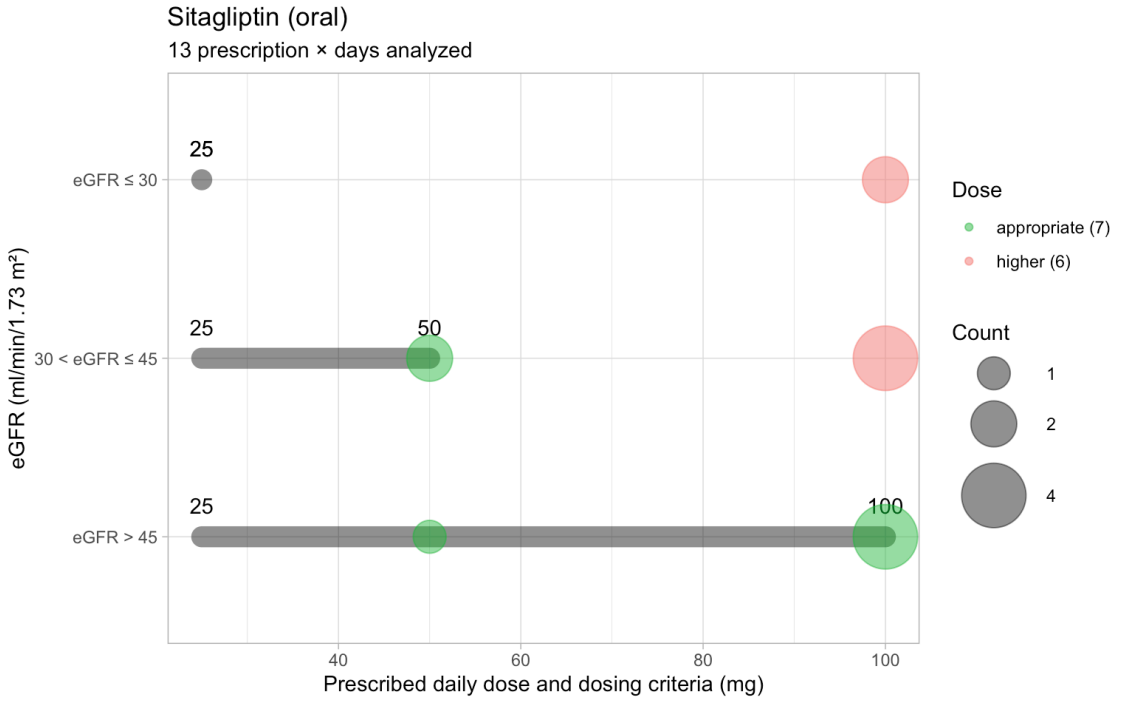

Ramipril (oral)
143 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 60
eGFR > 60
1.25
5
1.25
10
2.5
5.0
7.5
10.0
Prescribed daily dose and dosing criteria (mg)
Count
2
35
68
Dose
appropriate (96)
higher (47)

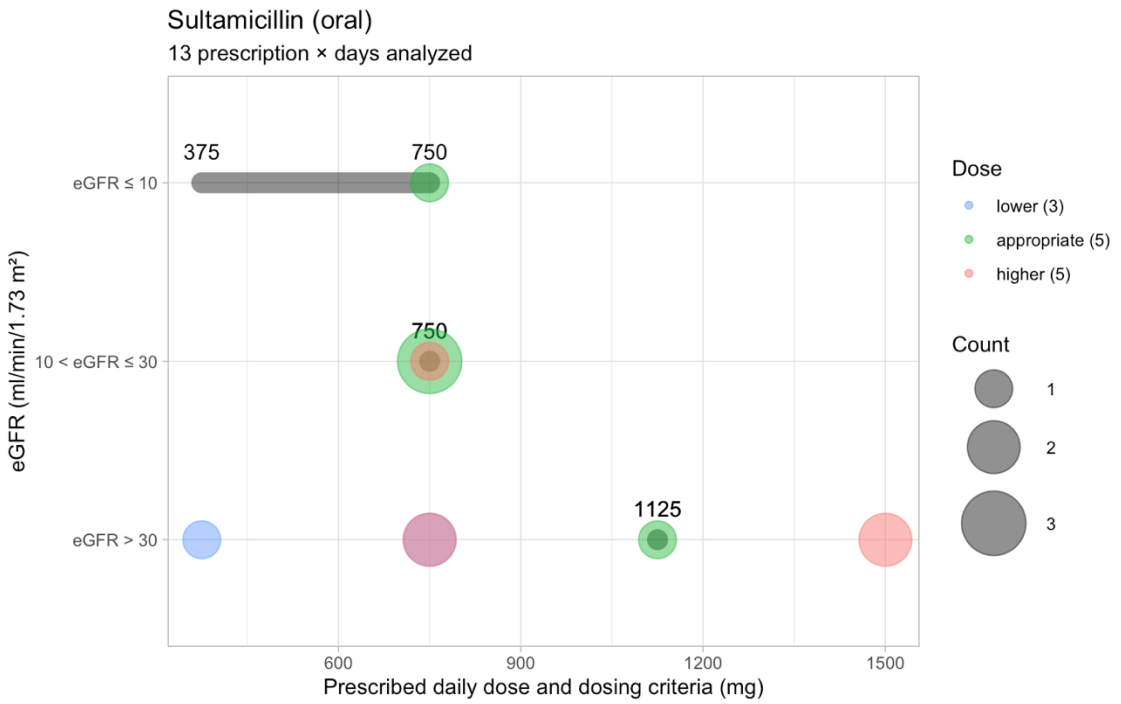

Rivaroxaban (oral) for af
58 prescription × days analyzed
eGFR ≤ 15
15 < eGFR ≤ 50
eGFR > 50
eGFR (ml/min/1.73 m²)
0
15
20
0
5
10
15
20
Prescribed daily dose and dosing criteria (mg)
Count
1
20
40
Dose
lower (12)
appropriate (44)
higher (2)

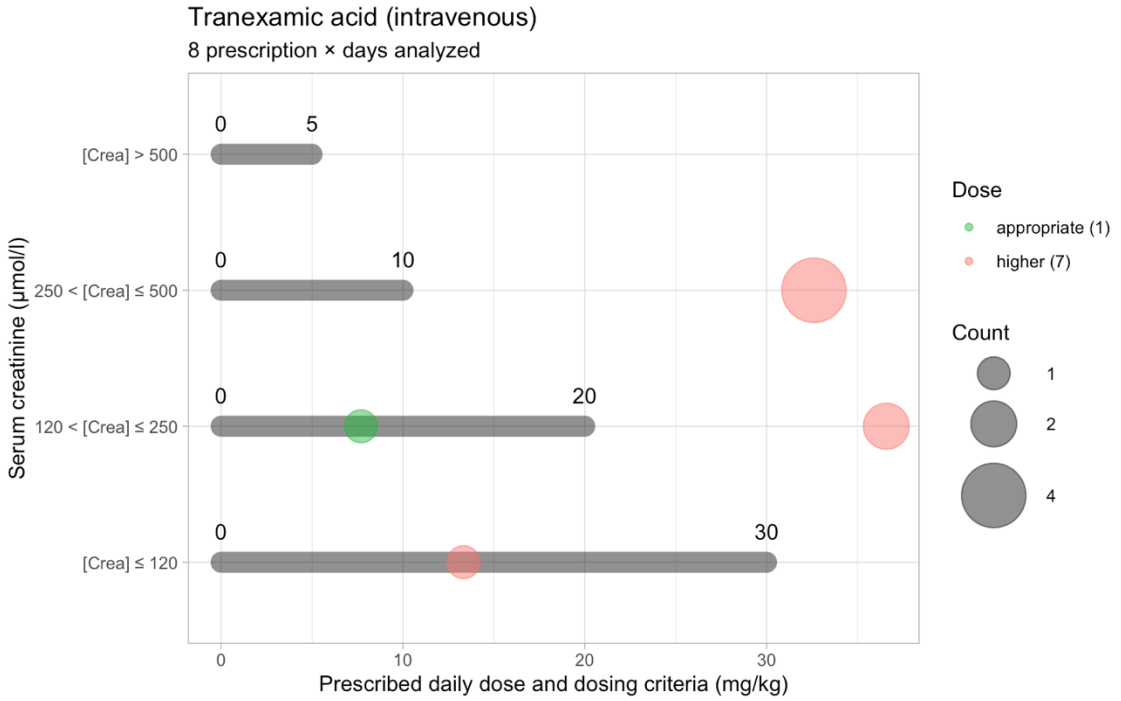

Rivaroxaban (oral) for vte
3 prescription × days analyzed
eGFR ≤ 15
15 < eGFR ≤ 50
eGFR > 50
eGFR (ml/min/1.73 m²)
0
15
15
40
0
10
20
30
40
Prescribed daily dose and dosing criteria (mg)
Count
1
2
Dose
appropriate (3)

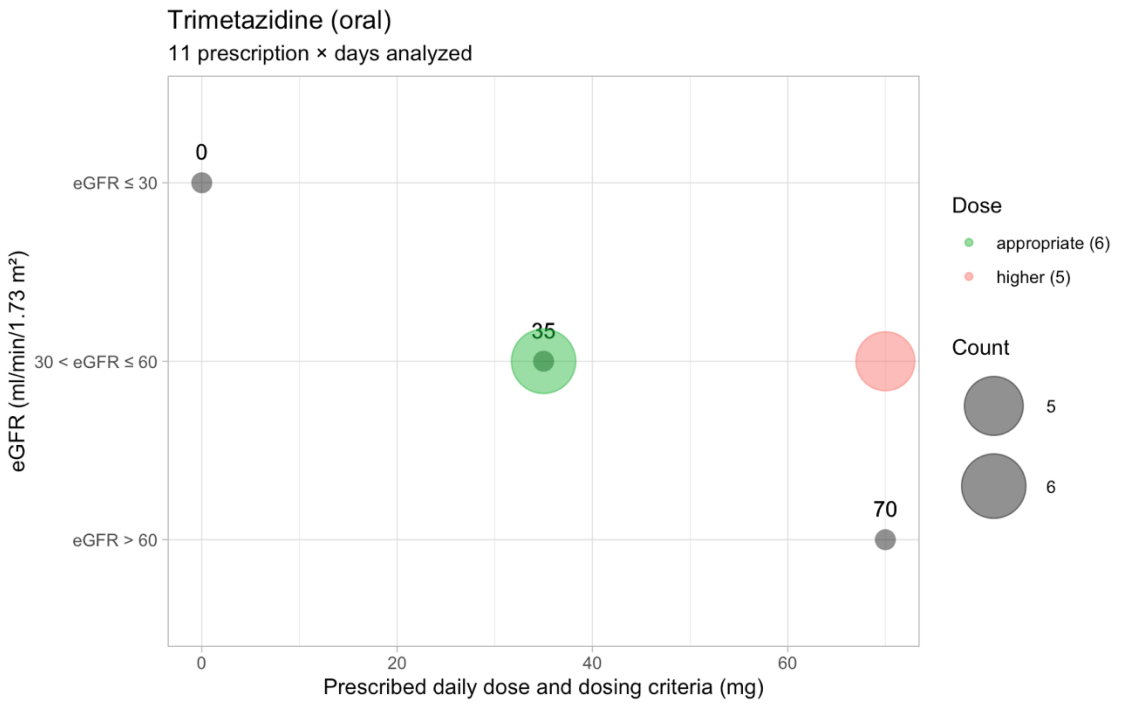

Rivaroxaban (oral) for prophylaxis
15 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 15
15 < eGFR ≤ 50
eGFR > 50
0
2.5
15
2.5
20
0
5
10
15
20
Prescribed daily dose and dosing criteria (mg)
Count
2
4
7
Dose
appropriate (15)

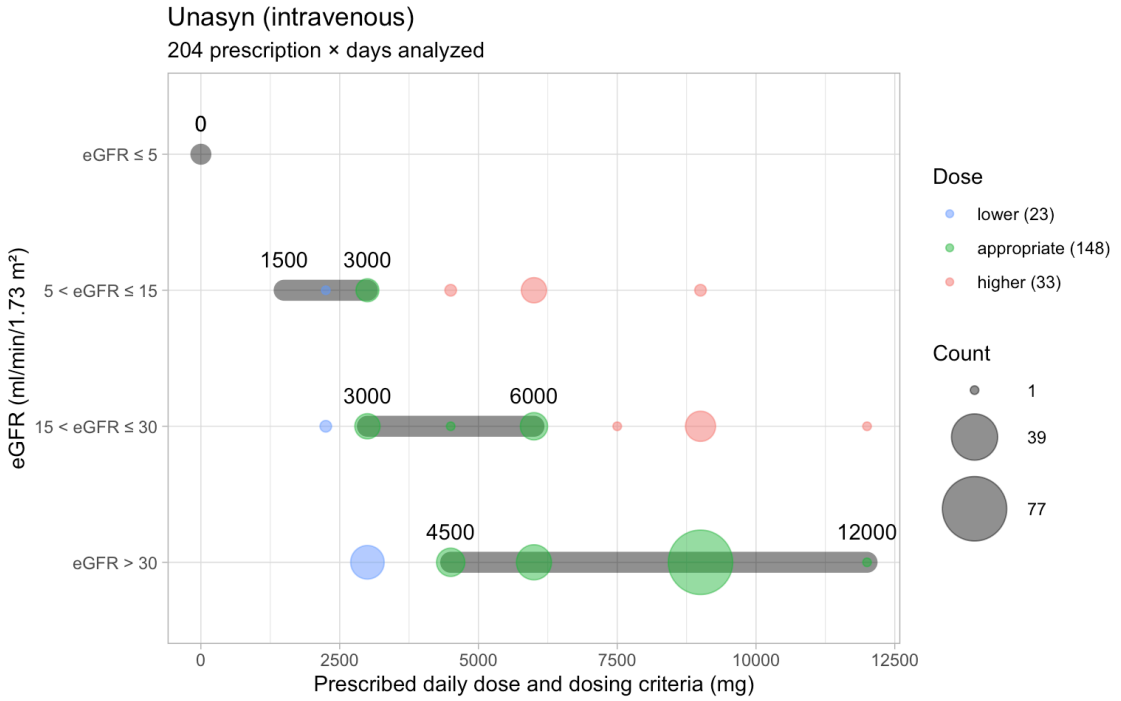

Rosuvastatin (oral)
197 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 30
30 < eGFR ≤ 60
eGFR > 60
5
10
5
20
5
40
10
20
30
40
Prescribed daily dose and dosing criteria (mg)
Dose
appropriate (159)
higher (38)
Count
3
64
126


Sitagliptin (oral)
13 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 30
30 < eGFR ≤ 45
eGFR > 45
25
25
50
25
100
40
60
80
100
Prescribed daily dose and dosing criteria (mg)
Dose
appropriate (7)
higher (6)
Count
1
2
4


Sultamicillin (oral)
13 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 10
10 < eGFR ≤ 30
eGFR > 30
375
750
750
1125
600
900
1200
1500
Prescribed daily dose and dosing criteria (mg)
Dose
lower (3)
appropriate (5)
higher (5)
Count
1
2
3


Tranexamic acid (intravenous)
8 prescription × days analyzed
Serum creatinine (µmol/l)
[Crea] > 500
250 < [Crea] ≤ 500
120 < [Crea] ≤ 250
[Crea] ≤ 120
0
5
0
10
0
20
0
30
0
10
20
30
Prescribed daily dose and dosing criteria (mg/kg)
Dose
appropriate (1)
higher (7)
Count
1
2
4


Trimetazidine (oral)
11 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 30
30 < eGFR ≤ 60
eGFR > 60
0
35
70
0
20
40
60
Prescribed daily dose and dosing criteria (mg)
Dose
appropriate (6)
higher (5)
Count
5
6


Unasyn (intravenous)
204 prescription × days analyzed
eGFR (ml/min/1.73 m²)
eGFR ≤ 5
5 < eGFR ≤ 15
15 < eGFR ≤ 30
eGFR > 30
0
1500
3000
3000
6000
4500
12000
0
2500
5000
7500
10000
12500
Prescribed daily dose and dosing criteria (mg)
Dose
lower (23)
appropriate (148)
higher (33)
Count
1
39
77

# Appendix 10

# Changes in dosing recommendations when using absolute glomerular filtration rate instead of relative glomerular filtration rate

| Medication | Prescriptions§, n | Lower dose, n (%) | Equal dose, n (%) | Higher dose, n (%) |
|---|---|---|---|---|
| Enoxaparin | 453 (330) | 2 (0.6% [0.0 … 1.4]) | 312 (94.5% [92.1 … 97.0]) | 16 (4.8% [2.5 … 7.2]) |
| Ampicillin/Sulbactam | 213 (154) | 3 (1.9% [0.0 … 4.1]) | 137 (89.0% [84.0 … 93.9]) | 14 (9.1% [4.6 … 13.6]) |
| Rosuvastatin | 197 (188) | 1 (0.5% [0.0 … 1.6]) | 134 (71.3% [64.8 … 77.7]) | 53 (28.2% [21.8 … 34.6]) |
| Spironolactone | 149 (111) | 2 (1.8% [0.0 … 4.3]) | 86 (77.5% [69.7 … 85.2]) | 23 (20.7% [13.2 … 28.3]) |
| Ramipril | 145 (103) | 0 (0.0%) | 83 (80.6% [72.9 … 88.2]) | 20 (19.4% [11.8 … 27.1]) |
| Metformin | 102 (85) | 3 (3.5% [0.0 … 7.5]) | 67 (78.8% [70.1 … 87.5]) | 15 (17.6% [9.5 … 25.8]) |
| Amoxicillin/Clavulanic acid | 101 (63) | 0 (0.0%) | 54 (85.7% [77.1 … 94.4]) | 9 (14.3% [5.6 … 22.9]) |
| Cefuroxime | 76 (52) | 0 (0.0%) | 52 (100.0%) | 0 (0.0%) |
| Rivaroxaban | 74 (65) | 2 (3.1% [0.0 … 7.3]) | 49 (75.4% [64.9 … 85.9]) | 14 (21.5% [11.5 … 31.5]) |
| Allopurinol | 61 (56) | 0 (0.0%) | 55 (98.2% [94.7 … 100.0]) | 1 (1.8% [0.0 … 5.3]) |
| Tramadol | 61 (55) | 1 (1.8% [0.0 … 5.3]) | 49 (89.1% [80.9 … 97.3]) | 5 (9.1% [1.5 … 16.7]) |
| Metoclopramide | 60 (53) | 0 (0.0%) | 48 (90.6% [82.7 … 98.4]) | 5 (9.4% [1.6 … 17.3]) |
| Apixaban | 59 (55) | 0 (0.0%) | 55 (100.0%) | 0 (0.0%) |
| Ciprofloxacin | 58 (46) | 1 (2.2% [0.0 … 6.4]) | 38 (82.6% [71.7 … 93.6]) | 7 (15.2% [4.8 … 25.6]) |
| Hydrochlorothiazide | 56 (55) | 2 (3.6% [0.0 … 8.6]) | 52 (94.5% [88.5 … 100.0]) | 1 (1.8% [0.0 … 5.3]) |
| Dexketoprofen | 53 (47) | 0 (0.0%) | 39 (83.0% [72.2 … 93.7]) | 8 (17.0% [6.3 … 27.8]) |
| Digoxin | 46 (32) | 1 (3.1% [0.0 … 9.2]) | 29 (90.6% [80.5 … 100.0]) | 2 (6.2% [0.0 … 14.6]) |
| Cefotaxime | 45 (32) | 0 (0.0%) | 32 (100.0%) | 0 (0.0%) |
| Indapamide | 44 (43) | 0 (0.0%) | 41 (95.3% [89.1 … 100.0]) | 2 (4.7% [0.0 … 10.9]) |
| Codeine | 38 (32) | 0 (0.0%) | 26 (81.2% [67.7 … 94.8]) | 6 (18.8% [5.2 … 32.3]) |
| Oseltamivir | 36 (28) | 0 (0.0%) | 27 (96.4% [89.6 … 100.0]) | 1 (3.6% [0.0 … 10.4]) |

| Medication | Prescriptions§, n | Lower dose, n (%) | Equal dose, n (%) | Higher dose, n (%) |
|---|---|---|---|---|
| Etoricoxib | 32 (30) | 0 (0.0%) | 30 (100.0%) | 0 (0.0%) |
| Pethidine | 27 (24) | 0 (0.0%) | 16 (66.7% [47.8 … 85.5]) | 8 (33.3% [14.5 … 52.2]) |
| Clarithromycin | 26 (14) | 0 (0.0%) | 14 (100.0%) | 0 (0.0%) |
| Simvastatin | 25 (15) | 0 (0.0%) | 15 (100.0%) | 0 (0.0%) |
| Cefazolin | 23 (20) | 1 (5.0% [0.0 … 14.6]) | 15 (75.0% [56.0 … 94.0]) | 4 (20.0% [2.5 … 37.5]) |
| Bisoprolol | 20 (4) | 0 (0.0%) | 3 (75.0% [32.6 … 100.0]) | 1 (25.0% [0.0 … 67.4]) |
| Piperacillin/Tazobactam | 19 (18) | 0 (0.0%) | 17 (94.4% [83.9 … 100.0]) | 1 (5.6% [0.0 … 16.1]) |
| Glimepiride | 18 (14) | 0 (0.0%) | 13 (92.9% [79.4 … 100.0]) | 1 (7.1% [0.0 … 20.6]) |
| Pentoxifylline | 13 | 0 (0.0%) | 13 (100.0%) | 0 (0.0%) |
| Sitagliptin | 13 (9) | 0 (0.0%) | 6 (66.7% [35.9 … 97.5]) | 3 (33.3% [2.5 … 64.1]) |
| Sultamicillin | 13 (9) | 0 (0.0%) | 9 (100.0%) | 0 (0.0%) |
| Dabigatran | 12 (11) | 0 (0.0%) | 9 (81.8% [59.0 … 100.0]) | 2 (18.2% [0.0 … 41.0]) |
| Gabapentin | 11 | 0 (0.0%) | 10 (90.9% [73.9 … 100.0]) | 1 (9.1% [0.0 … 26.1]) |
| Morphine | 11 (9) | 0 (0.0%) | 9 (100.0%) | 0 (0.0%) |
| Trimetazidine | 11 (10) | 0 (0.0%) | 7 (70.0% [41.6 … 98.4]) | 3 (30.0% [1.6 … 58.4]) |
| Ibuprofen | 8 | 0 (0.0%) | 6 (75.0% [45.0 … 100.0]) | 2 (25.0% [0.0 … 55.0]) |
| Tranexamic acid | 8 | 0 (0.0%) | 8 (100.0%) | 0 (0.0%) |
| Trimethoprim/Sulfamethoxazole | 7 (5) | 0 (0.0%) | 5 (100.0%) | 0 (0.0%) |
| Ertapenem | 7 (4) | 0 (0.0%) | 4 (100.0%) | 0 (0.0%) |
| Fluconazole | 7 (5) | 0 (0.0%) | 5 (100.0%) | 0 (0.0%) |
| Gliclazide | 6 (3) | 0 (0.0%) | 3 (100.0%) | 0 (0.0%) |

| Medication | Prescriptions§, n | Lower dose, n (%) | Equal dose, n (%) | Higher dose, n (%) |
|---|---|---|---|---|
| Pregabalin | 6 | 0 (0.0%) | 4 (66.7% [28.9 … 100.0]) | 2 (33.3% [0.0 … 71.1]) |
| Risperidone | 4 (2) | 0 (0.0%) | 2 (100.0%) | 0 (0.0%) |
| Diclofenac | 3 (1) | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |
| Cefoxitin | 2 | 0 (0.0%) | 2 (100.0%) | 0 (0.0%) |
| Ceftazidime | 1 (0) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Memantine | 1 | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |
| Naproxen | 1 | 0 (0.0%) | 0 (0.0%) | 1 (100.0%) |
| Nitrofurantoin | 1 | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |
| Pramipexole | 1 | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |
| Ranolazine | 1 | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |
| Topiramate | 1 | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |
| Venlafaxine | 1 | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |

§number in the brackets refers to the number of prescriptions available for absGFR and eCrCl

# Appendix 11

# Changes in dosing recommendations when using estimated creatinine clearance instead of relative glomerular filtration rate

| Medication | Prescriptions§, n | Lower dose, n (%) | Equal dose, n (%) | Higher dose, n (%) |
|---|---|---|---|---|
| Enoxaparin | 453 (330) | 15 (4.5% [2.3 … 6.8]) | 288 (87.3% [83.7 … 90.9]) | 27 (8.2% [5.2 … 11.1]) |
| Ampicillin/Sulbactam | 213 (154) | 9 (5.8% [2.1 … 9.5]) | 125 (81.2% [75.0 … 87.3]) | 20 (13.0% [7.7 … 18.3]) |
| Rosuvastatin | 197 (188) | 7 (3.7% [1.0 … 6.4]) | 158 (84.0% [78.8 … 89.3]) | 23 (12.2% [7.6 … 16.9]) |
| Spironolactone | 149 (111) | 13 (11.7% [5.7 … 17.7]) | 87 (78.4% [70.7 … 86.0]) | 11 (9.9% [4.4 … 15.5]) |
| Ramipril | 145 (103) | 0 (0.0%) | 96 (93.2% [88.3 … 98.1]) | 7 (6.8% [1.9 … 11.7]) |
| Metformin | 102 (85) | 21 (24.7% [15.5 … 33.9]) | 56 (65.9% [55.8 … 76.0]) | 8 (9.4% [3.2 … 15.6]) |
| Amoxicillin/Clavulanic acid | 101 (63) | 8 (12.7% [4.5 … 20.9]) | 48 (76.2% [65.7 … 86.7]) | 7 (11.1% [3.4 … 18.9]) |
| Cefuroxime | 76 (52) | 0 (0.0%) | 46 (88.5% [79.8 … 97.1]) | 6 (11.5% [2.9 … 20.2]) |
| Rivaroxaban | 74 (65) | 15 (23.1% [12.8 … 33.3]) | 41 (63.1% [51.3 … 74.8]) | 9 (13.8% [5.4 … 22.2]) |
| Allopurinol | 61 (56) | 0 (0.0%) | 49 (87.5% [78.8 … 96.2]) | 7 (12.5% [3.8 … 21.2]) |
| Tramadol | 61 (55) | 5 (9.1% [1.5 … 16.7]) | 43 (78.2% [67.3 … 89.1]) | 7 (12.7% [3.9 … 21.5]) |
| Metoclopramide | 60 (53) | 0 (0.0%) | 42 (79.2% [68.3 … 90.2]) | 11 (20.8% [9.8 … 31.7]) |
| Apixaban | 59 (55) | 0 (0.0%) | 55 (100.0%) | 0 (0.0%) |
| Ciprofloxacin | 58 (46) | 2 (4.3% [0.0 … 10.2]) | 42 (91.3% [83.2 … 99.4]) | 2 (4.3% [0.0 … 10.2]) |
| Hydrochlorothiazide | 56 (55) | 3 (5.5% [0.0 … 11.5]) | 51 (92.7% [85.9 … 99.6]) | 1 (1.8% [0.0 … 5.3]) |
| Dexketoprofen | 53 (47) | 2 (4.3% [0.0 … 10.0]) | 40 (85.1% [74.9 … 95.3]) | 5 (10.6% [1.8 … 19.5]) |
| Digoxin | 46 (32) | 8 (25.0% [10.0 … 40.0]) | 21 (65.6% [49.2 … 82.1]) | 3 (9.4% [0.0 … 19.5]) |
| Cefotaxime | 45 (32) | 0 (0.0%) | 32 (100.0%) | 0 (0.0%) |
| Indapamide | 44 (43) | 0 (0.0%) | 41 (95.3% [89.1 … 100.0]) | 2 (4.7% [0.0 … 10.9]) |
| Codeine | 38 (32) | 0 (0.0%) | 31 (96.9% [90.8 … 100.0]) | 1 (3.1% [0.0 … 9.2]) |
| Oseltamivir | 36 (28) | 1 (3.6% [0.0 … 10.4]) | 27 (96.4% [89.6 … 100.0]) | 0 (0.0%) |

| Medication | Prescriptions§, n | Lower dose, n (%) | Equal dose, n (%) | Higher dose, n (%) |
|---|---|---|---|---|
| Etoricoxib | 32 (30) | 2 (6.7% [0.0 … 15.6]) | 28 (93.3% [84.4 … 100.0]) | 0 (0.0%) |
| Pethidine | 27 (24) | 0 (0.0%) | 17 (70.8% [52.6 … 89.0]) | 7 (29.2% [11.0 … 47.4]) |
| Clarithromycin | 26 (14) | 0 (0.0%) | 14 (100.0%) | 0 (0.0%) |
| Simvastatin | 25 (15) | 2 (13.3% [0.0 … 30.5]) | 13 (86.7% [69.5 … 100.0]) | 0 (0.0%) |
| Cefazolin | 23 (20) | 5 (25.0% [6.0 … 44.0]) | 11 (55.0% [33.2 … 76.8]) | 4 (20.0% [2.5 … 37.5]) |
| Bisoprolol | 20 (4) | 0 (0.0%) | 3 (75.0% [32.6 … 100.0]) | 1 (25.0% [0.0 … 67.4]) |
| Piperacillin/Tazobactam | 19 (18) | 0 (0.0%) | 17 (94.4% [83.9 … 100.0]) | 1 (5.6% [0.0 … 16.1]) |
| Glimepiride | 18 (14) | 0 (0.0%) | 13 (92.9% [79.4 … 100.0]) | 1 (7.1% [0.0 … 20.6]) |
| Pentoxifylline | 13 | 0 (0.0%) | 13 (100.0%) | 0 (0.0%) |
| Sitagliptin | 13 (9) | 0 (0.0%) | 6 (66.7% [35.9 … 97.5]) | 3 (33.3% [2.5 … 64.1]) |
| Sultamicillin | 13 (9) | 0 (0.0%) | 9 (100.0%) | 0 (0.0%) |
| Dabigatran | 12 (11) | 0 (0.0%) | 9 (81.8% [59.0 … 100.0]) | 2 (18.2% [0.0 … 41.0]) |
| Gabapentin | 11 | 2 (18.2% [0.0 … 41.0]) | 9 (81.8% [59.0 … 100.0]) | 0 (0.0%) |
| Morphine | 11 (9) | 1 (11.1% [0.0 … 31.6]) | 8 (88.9% [68.4 … 100.0]) | 0 (0.0%) |
| Trimetazidine | 11 (10) | 0 (0.0%) | 10 (100.0%) | 0 (0.0%) |
| Ibuprofen | 8 | 1 (12.5% [0.0 … 35.4]) | 5 (62.5% [29.0 … 96.0]) | 2 (25.0% [0.0 … 55.0]) |
| Tranexamic acid | 8 | 0 (0.0%) | 8 (100.0%) | 0 (0.0%) |
| Trimethoprim/Sulfamethoxazole | 7 (5) | 2 (40.0% [0.0 … 82.9]) | 3 (60.0% [17.1 … 100.0]) | 0 (0.0%) |
| Ertapenem | 7 (4) | 0 (0.0%) | 4 (100.0%) | 0 (0.0%) |
| Fluconazole | 7 (5) | 0 (0.0%) | 5 (100.0%) | 0 (0.0%) |
| Gliclazide | 6 (3) | 0 (0.0%) | 3 (100.0%) | 0 (0.0%) |

| Medication | Prescriptions§, n | Lower dose, n (%) | Equal dose, n (%) | Higher dose, n (%) |
|---|---|---|---|---|
| Pregabalin | 6 | 0 (0.0%) | 5 (83.3% [53.5 … 100.0]) | 1 (16.7% [0.0 … 46.5]) |
| Risperidone | 4 (2) | 0 (0.0%) | 2 (100.0%) | 0 (0.0%) |
| Diclofenac | 3 (1) | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |
| Cefoxitin | 2 | 0 (0.0%) | 2 (100.0%) | 0 (0.0%) |
| Ceftazidime | 1 (0) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Memantine | 1 | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |
| Naproxen | 1 | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |
| Nitrofurantoin | 1 | 1 (100.0%) | 0 (0.0%) | 0 (0.0%) |
| Pramipexole | 1 | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |
| Ranolazine | 1 | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |
| Topiramate | 1 | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |
| Venlafaxine | 1 | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |

§number in the brackets refers to the number of prescriptions available for absGFR and eCrCl

# Appendix 12

# Predictors of inappropriate prescribing at patient level

| Characteristic | Value | IP absent (% or SD) | IP present (% or SD) | Univariable OR (95% CI) | Multivariable OR (95% CI) |
|---|---|---|---|---|---|
| Age | Mean (SD) | 77.3 (10.1) | 77.5 (10.1) | 1.00 (0.98 … 1.02, p=0.884) | |
| Gender | male | 52 (34.9) | 97 (65.1) | | |
| | female | 111 (44.4) | 139 (55.6) | 0.67 (0.44 … 1.02, p=0.062) | 0.59 (0.37 … 0.94, p=0.029) |
| Body mass index | Mean (SD) | 29.3 (6.4) | 29.1 (6.5) | 1.00 (0.96 … 1.03, p=0.793) | |
| Length of stay | Mean (SD) | 5.3 (3.7) | 7.7 (6.0) | 1.11 (1.06 … 1.16, p<0.001) | 1.06 (1.01 … 1.12, p=0.021) |
| Surgery | no | 140 (42.0) | 193 (58.0) | | |
| | yes | 23 (34.8) | 43 (65.2) | 1.36 (0.79 … 2.38, p=0.279) | 1.83 (1.02 … 3.33, p=0.045) |
| Contrast | no | 125 (39.7) | 190 (60.3) | | |
| | yes | 38 (45.2) | 46 (54.8) | 0.80 (0.49 … 1.30, p=0.358) | 0.65 (0.37 … 1.14, p=0.138) |
| Charlson index | Mean (SD) | 5.2 (2.0) | 5.9 (2.2) | 1.17 (1.06 … 1.30, p=0.002) | |
| Acute kidney injury | absent | 156 (47.7) | 171 (52.3) | | |
| | present | 7 (9.7) | 65 (90.3) | 8.47 (4.03 … 20.80, p<0.001) | 7.08 (3.21 … 17.97, p<0.001) |
| Atrial fibrillation | absent | 116 (44.8) | 143 (55.2) | | |
| | present | 47 (33.6) | 93 (66.4) | 1.61 (1.05 … 2.47, p=0.030) | |
| Diabetes | absent | 137 (46.6) | 157 (53.4) | | |
| | present | 26 (24.8) | 79 (75.2) | 2.65 (1.63 … 4.43, p<0.001) | 2.94 (1.74 … 5.10, p<0.001) |
| Heart failure | absent | 116 (46.2) | 135 (53.8) | | |
| | present | 47 (31.8) | 101 (68.2) | 1.85 (1.21 … 2.84, p=0.005) | |
| Hypertension | absent | 50 (50.5) | 49 (49.5) | | |
| | present | 113 (37.7) | 187 (62.3) | 1.69 (1.07 … 2.67, p=0.025) | |
| Myocardial infarction | absent | 151 (41.7) | 211 (58.3) | | |
| | present | 12 (32.4) | 25 (67.6) | 1.49 (0.74 … 3.16, p=0.276) | |
| Venous thromboembolism | absent | 160 (42.2) | 219 (57.8) | | |
| | present | 3 (15.0) | 17 (85.0) | 4.14 (1.36 … 17.95, p=0.025) | 4.05 (1.21 … 18.53, p=0.038) |