Trends in the evolution of inappropriate prescribing in CKD between 2018-2022: an explorative analysis

Frauke Leroy, KU Leuven

Promotor: Prof. Dr. Bert Aertgeerts, KU Leuven

Co-promotoren: Dr. Gijs Van Pottelbergh, KU Leuven

Master of Family Medicine

Masterproef Huisartsgeneeskunde
Academiejaar: [2020 – 2023]

Deze masterproef is een examendocument dat niet werd gecorrigeerd voor eventueel vastgestelde fouten. Zonder voorafgaande schriftelijke toestemming van zowel de promotor(en) als de auteur(s) is overnemen, kopiëren, gebruiken of realiseren van deze uitgave of gedeelten ervan verboden. Voor aanvragen tot of informatie i.v.m. het overnemen en/of gebruik en/of realisatie van gedeelten uit deze publicatie, wendt u tot de universiteit waaraan de auteur is ingeschreven.

Voorafgaande schriftelijke toestemming van de promotor(en) is eveneens vereist voor het aanwenden van de in dit afstudeerwerk beschreven (originele) methoden, producten, schakelingen en programma's voor industrieel of commercieel nut en voor de inzending van deze publicatie ter deelname aan wetenschappelijke prijzen of wedstrijden.

Table of contents

Abstract 4

Introduction 6

Methods 8

Results 9

Discussion 14

Conclusion 16

Acknowledgements 16

References 17

Appendix 19

Abstract

Inleiding

Chronische nierinsufficiëntie (CNI) is een wereldwijd probleem waarbij een adequate opvolging kan zorgen voor een vertraagde evolutie van de ziekte. Een belangrijke pijler hierbij is het correct doseren van medicatie, wat mede door de vaak verschillende co-morbiditeiten en de begeleidende polyfarmacie geen sinecure is. Het is dan ook een van de kerntaken van een huisarts om bij deze paiënten hun verschillende behandelingen te coördineren en een veilig medicatiebeleid te voorzien. Deze masterthesis heeft als doel na te gaan of er een evolutie merkbaar is in het adequaat doseren van vaak voorgeschreven geneesmiddelen bij patiënten met CNI in 2018 ten opzichte van 2022.

Methoden

Een literatuurstudie werd uitgevoerd om een beter inzicht te verkrijgen in de definitie en prevalentie van CNI alsook de invloed van co-mobiditeiten en polyfarmacie en welke hulpmiddelen voor een correct voorschrijfgedrag momenteel al aanwezig zijn.
Daarnaast werden op de INTEGO databank analyses uitgevoerd. Alle patiënten met een eGFR<50, met een onderverdeling in 3 groepen volgens graad van CNI, werden geanaliseerd, en dit over een periode van 2018-2022. Tevens werd een lijst van vaak voorgeschreven geneesmiddelen opgesteld. Voor elke medicatie werd het aantal te hoog gedoseerde voorschriften ten opzichte van het total aantal voorschriften bepaald voor elk jaar tussen 2018 en 2022. Nadien werd een exploratieve analyse uitgevoerd.

Resultaten

Deze exploratieve analyse suggereert de aanwezigheid van een aantal trends in het voorschijfgedrag van huisartsen. Bij de onderzochte medicaties waarbij een dosisaanpassing noodzakelijk is, zien we een dalende trend in zowel het aantal voorschriften als in het aandeel inadequate voorschriften. Het aandeel van inadequate voorschriften varieerde tussen 47-69% in 2018 en 34-59% in 2022, wat een gemiddelde daling van ongeveer 13% zou betekenen. Ook bij medicatie waarbij een dosisaanspassing noodzakelijk is werd een gelijkaardige neerwaartse trend opgemerkt, met een relatieve daling tussen 10% en 83%. Opvallend genoeg kon voor Ciprofloxacine geen duidelijke trend worden opgemerkt.

Conclusie

Opvolging van patiënten met CNI is een belangrijke, maar moeilijke taak van de huisarts. Een van de hoekstenen in dit management is het correct voorschrijven van bepaalde klassen van medicaties. Deze analyse suggereert een positieve trend in het voorschrijfgedrag van huisartsen tussen 2018 en 2022. Dit toont dat groter en langduriger onderzoek nuttig kan zijn, aangezien het hier een eerder kleinschalige studie betreft uitgevoerd over een korte tijddspanne. Daarnaast zou ook een beter inzicht in de motieven van huisartsen in hun voorschrijfgedrag zinvol kunnen zijn.

Background

Chronic renal insufficiency (CKD) is a worldwide problem where an adequate management can delay the progression of this disease. An important pillar is the correct dosing of medication, which is no sinecure, due to the often-multiple co-morbidities and the accompanying polypharmacy. It is therefore one of the main challenges of a General Practitioner (GP) to coordinate the various treatments for these patients and to provide them a safe medication policy. This master thesis aims to investigate whether there is a noticeable evolution in the adequate dosing of commonly prescribed drugs in patients with CKD in 2018 compared to 2022.

Methods

A literature study was performed to gain a better understanding of the definition and prevalence of CNI as well as the influence of co-morbidities and polypharmacy and which tools for correct prescribing behavior are currently already available.

In addition, a database analysis was performed using the INTEGO database. In the analysis, all patients with an eGFR<50 were included with a subdivision into 3 groups according to degree of CKD over a period of 2018-2022. In addition, a group of commonly prescribed drugs was established. For each drug, the number of too high dosed prescriptions, relative to the total number of prescriptions, was determined for every year between 2018-2022 in each group. An exploratory analysis of the collected data was performed afterwards.

Results

This exploratory analysis suggests the presence of a variety of trends in GP prescription behavior. We see a decreasing trend in both the number of prescriptions and the proportion of inadequate prescriptions for the medications studied that require a dose adjustment. The rate of inappropriate prescriptions varied between 47-69% in 2018 and 34-59% in 2022, which would mean an average decrease of about 13%. A similar downward trend was also noted for medications with a contraindication, with a relative decrease between 10% and 83%. Surprisingly, no clear trend could be observed for Ciprofloxacin.

Conclusions

Follow-up of patients with CNI is an important but difficult task for the GP. One of the cornerstones of this management is the correct prescription of certain classes of medications. This analysis suggests a positive trend in GP prescribing behavior between 2018 and 2022. This shows that larger and longer-term studies may be helpful, as this is a small-scale study conducted over a short period of time. In addition, a better insight into the motives of GPs in their prescribing behavior could also be useful.

Introduction

(Alle tables can be found in appendix 1)

Chronic Kidney Disease (CKD) is a global health burden. It is highly prevalent as it affects approximately 8-16% of the population worldwide and comes with a high economic cost to health systems. [1] Due to its tendency to remain asymptomatic for a long time, CKD is frequently unrecognized by patients and their physicians. [2] The prevalence of CKD in 2012 was about 13% in Flanders, similar results could be found in the United States with a prevalence of 11%. [3] [4] The global estimated prevalence of CKD stage 1-5 was 10,5-13,1% and stages 3-5 were 10,6%. [5]

CKD is a clinical syndrome secondary to the definitive change in function and/or structure of the kidney Characteristic is its irreversibility and slow and progressive evolution. Adult patients are diagnosed with CKD when they present, for a period equal to or greater than three months, a glomerular filtration rate (GFR) lower than 60 ml/min/1.73m^2 or a GFR greater than 60 ml/min/1.73m^2 but with evidence of injury of the renal structure. [6]

CKD is classified into five stages or three stages, according to GFR and albuminuria respectively. (**Table 1 – 2**). This classification is a useful tool for physicians to determine the method and intensity of monitoring needed for CKD patients. (**Table 3**) Some of the main causes of CKD include diabetes, hypertension, chronic glomerulonephritis, chronic pyelonephritis, and chronic use of anti-inflammatory medication. [6] As most patients with CKD are asymptomatic, screening may be important for early detection. [2]

Early detection ensures an appropriate treatment and management of the disease which can slow progression to end stage renal failure. One important pillar is the adjustment of drug dosing. Common medications that require a dose reduction are antibiotics, NSAID, direct oral anticoagulants, gabapentin and pregabalin, oral hypoglycemic agents, insulin, chemotherapeutic agents, and opiates. [2] [3] [6]

Patients suffering from CKD often deal with several comorbidities including Type 2 Diabetes Mellitus (T2DM), hypertension (HT) and heart failure (HF). CKD, HF and T2DM are major health problems worldwide with a rising prevalence of all three conditions because of the aging of the population and longer survival rates of affected persons. [7] Each of these 3 conditions not only often co-exist, but they also worsen the prognosis of the other 2 resulting in a series of vicious circles. [7]

The co-existence of the conditions and mostly single disease centered guidelines, often lead to the use of multiple medications. A higher number of prescribed drugs evidently leads to a higher risk of drug-drug interactions that may lead to severe drug-related adverse events. [8] Another risk-factor that should be considered is potentially inappropriate medication (PIM). A particular number of drugs are metabolized by the kidney. Therefore, a loss of kidney function can lead to altered drug pharmacokinetics (PK) and drug pharmacodynamics (PD). All mechanisms of excretion by the kidney are altered in patients with CKD, meaning changes in clearance, therapeutic effects, and risk of toxicity of many drugs. [9] [10] A special attention is needed for those drugs routinely used in the management of CKD and its common co-morbidities, e.g., diuretics, RAAS blockers, treatments for anemia, antihyperglycemic agents. [9]

For primary care practitioners it is one of their main challenges in patients with CKD to coordinate the various treatments of CKD and its common co-morbidities and provide a safe medication policy. As stated earlier, CKD is often underrecognized by both physicians and patients, leading to a lost opportunity to minimize medication errors. [9] It is important to note there is still a lack of consensus and an unambiguous international guideline to evaluate and to follow-up medication use in CKD. Moreover, in certain cases it is advisable to choose for an individual approach considering the patients' choice and specific circumstances. [9]

In the first place, primary care practitioners need to pay attention to **appropriate prescribing** of new medication, especially in elderly. They should focus on: **(1)** A correct indication setting for new medication according to appropriate guidelines and provide an evidence-based agent selection. **(2)** Adapt medication doses based on altered kidney function and drug pharmacokinetics (PK) and pharmacodynamics (PD). A good starting point for evaluation of medication appropriateness are the in 2012 published Kidney Disease Improving Global Outcomes Guidelines (KDIGO). **(3)** A strict follow-up of patients with monitoring of drug therapy response and kidney function. [9]

In addition, there is also the phenomenon of **deprescribing** meaning "systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits". [11] Unfortunately, deprescribing guidelines specifically for predialysis CKD patients are lacking, however general principles of deprescribing can be used. (**Table 4**) [9]

Polypharmacy is a common problem in elderly patients. Helpful tools such as "the Screening Tool of Older Persons" (STOPP) and "the Screening Tool Alert doctors to Right Treatment" (START) are well-known and worldwide used to detect PIM, however, there is no validity and clinical relevance of these criteria in patients with CKD documented yet. [12] In Belgium, PCP can utilize guidelines provided by Domus Medica as well Dutch guidelines summarized in "Landelijke transmurale afspraak chronische nierschade". In 2014 a practical instrument was published with an unlimited list of medications that require a dose adjustment. [13] [14]

Thanks to the introduction of such tools, the expanding and refining of guidelines and a constant technical evolution, better medication control can be expected. The aim of this retrospective cohort study is therefore to investigate, via an analysis of the INTEGO database, whether there is an evolution in the inadequate dosing of commonly used drugs in patients with CKD in 2018-2022 by comparing the number of overdoses of medication in the selected drugs.

Methods

Literature

A literature search was performed to better understand the definition and prevalence of CKD as well as the influence of co-morbidities and the resulting polypharmacy. Finally, the current approaches to maintain correct prescribing behavior were also examined.

To include interesting articles in the study a search through PUBMED/Medline and EMBASE was performed, using the following terms: "Renal Insufficiency, Chronic", "Prevalence", "Comorbidity", "Diabetes Mellitus", "Hypertension", "Physicians, Primary Care", "Inappropriate Prescribing".

Furthermore, the Belgian guideline for CKD and the practical guidelines published in 2014 by Mertens et al where used. (**Appendix 3**)

INTEGO Database

To gather information about the prevalence and prescribing behavior, a database called INTEGO with representative data for the Flemish population is used.

INTEGO is a computerized morbidity registration network in Belgium based on general practice data and collects data from over 90 general practitioners spread across Belgium. [15] INTEGO is a large database as the result of continuous recording in a network of general practices since 1994 (440,140 different patients, 4,478,275 diagnoses, 44,747,161 million lab results, 17,516,940 medication prescriptions and 700,000 vaccination data). This is the only operational computerized morbidity registration network in Belgium based on general practice data. [15] [16]

The following data are collected: Year of birth, gender, the years that the patient contacted the practice, diagnoses, drug prescriptions, laboratory result and some biomedical parameters (weight, height, smoking status). [15] All data are recorded by the GP by using keywords in the electronic health record. New diagnoses were classified according to a very detailed thesaurus (Medidoc ® codes) automatically linked to the International Classification of Primary Care (ICPC-2). [15] Drugs were classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system. The database is representative for the Flemish population in terms of lifestyle, gender, and income. [15] [16]

Data collection

To collect data from the database, multiple queries were formulated of which a list can be found in **appendix 3**, coded via ATC- and CNK-codes (**appendix 2**).

Based on these queries a retrospective population study was performed. The data were collected over a period of 5 years, namely from 2018-2022. Patients with an eGFR <50 were included and divided in 3 groups: eGFR 50-30; eGFR 30-10; eGFR <10. Based on the practical guidelines published in 2014 by Mertens et al., a selection of commonly used drugs for which a dose adjustment is necessary was made, which can be found in **appendix 3**. This list was compiled based on the presumably most prescribed drugs and of which the wrong dose is relatively easy to determine and investigated via INTEGO. For each drug, the number of too high dosed prescriptions relative to the total number of prescriptions, was determined for every year between 2018-2022 in each group.

Separately, to get an idea whether a specific trend can be observed in the presence of CKD in the Flemish population, the total number of patients for each group in each year was also determined. Only results until 2021 could be included, since the data of 2022 had not yet been fully processed at the time of finishing this thesis.

An exploratory analysis of the collected data was performed afterwards.

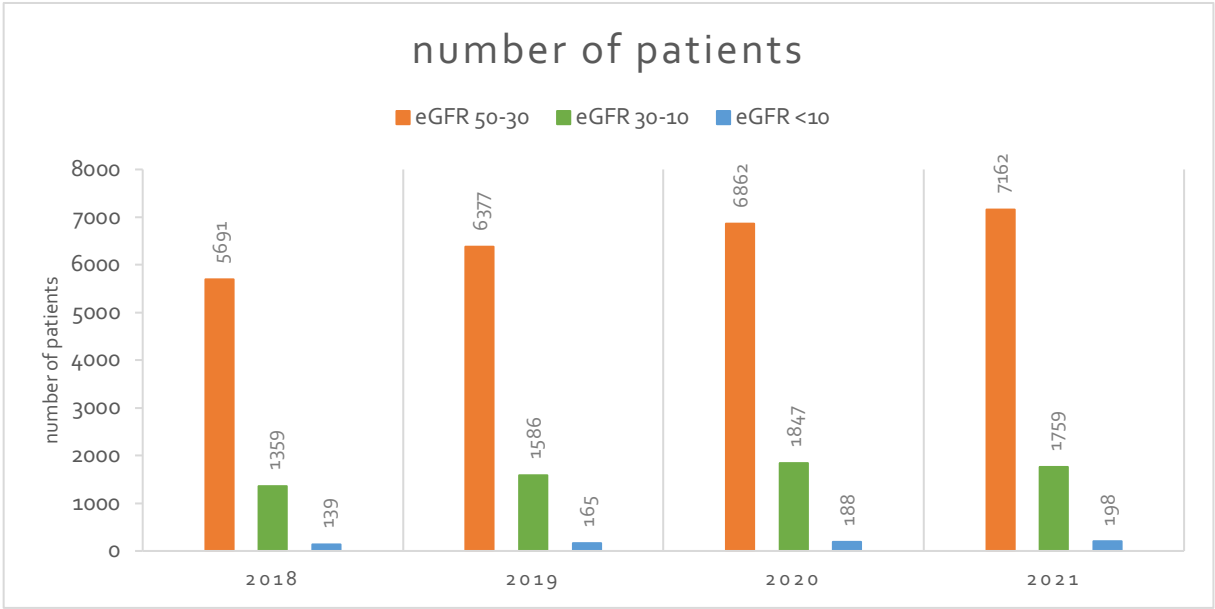
Results

(All graphs can be found in appendix 4)

The study included all patients older than 18 years with an eGFR less than 50 from the INTEGO-database. This group was divided into 3 groups: eGFR 50-30, eGFR 30-10 and eGFR <10. **Table 5 and graph 1** show the breakdown of the number of patients present per group per year. We notice a trend of a slight increase in each eGFR-group.

	Number of patients		
	eGFR 50-30	eGFR 30-10	eGFR <10
2018	5691	1359	139
2019	6377	1586	165
2020	6862	1847	188
2021	7162	1759	198

Table 5: number of patients in each group, for each year

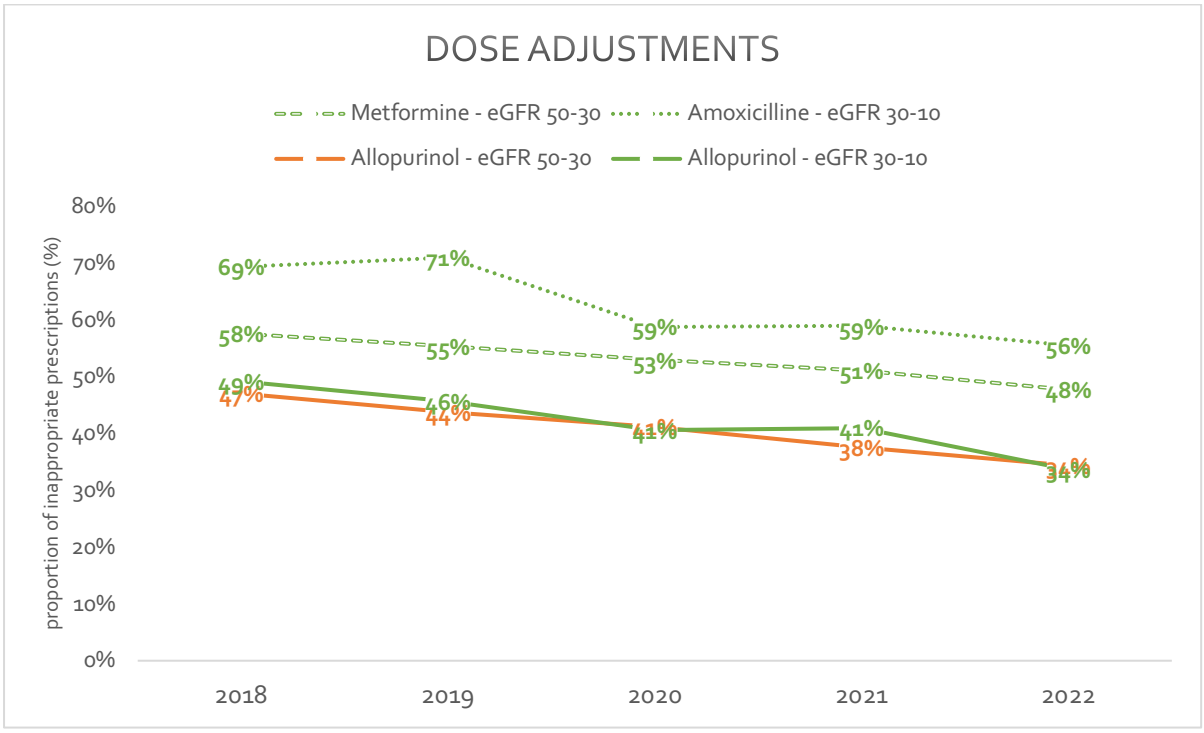


Graph 1: number of patients in each group

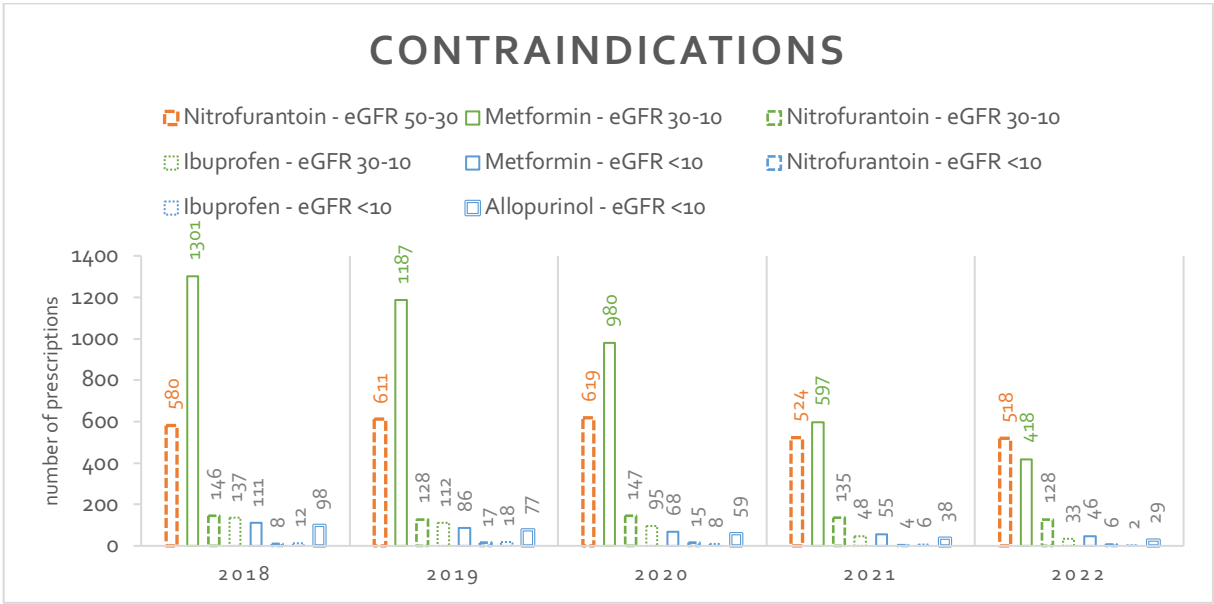
A group of commonly prescribed medications was also included: Metformin (ATC code A10BA02), Amoxicillin (ATC code J01CA04), Ciprofloxacin (ATC code J01MA02), Nitrofurantoin (ATC code J01XE01), Ibuprofen (ATC code M01AE01) and Allopurinol (ATC code M04AA01). For each of these medications, it was examined in each eGFR group how many too highly dosed prescriptions were made compared to the total number of prescriptions for a period from 2018-2022. **Table 6** shows an overview of the investigated medication and the number of inappropriate prescriptions per eGFR category for each year between 2018 and 2022 compared to the total number of prescriptions.

As described later more in detail, 3 trends could be withheld. Overall, we see a decreasing trend for medications requiring **dose adjustment**, both in the number of prescriptions and in the rate of over-dosed

prescriptions. The rate of inappropriate drug prescription for these medications ranged from 47-69% in 2018 and 34-59% in 2022, giving a mean decrease of approximately 13% (**Graph 2**) In medications with a **contraindication** for certain eGFR groups, we could observe a clear downward trend in number of prescriptions as well with a relative decrease ranging between 58,6% and 83,3%. (**Graph 3**) A notable exception is ciprofloxacin, whereby no clear trend could be observed.



Graph 2: Trend in proportion of inappropriate prescriptions in medication with dose-adjustments



Graph 3: Trend in number of prescriptions in medication with contraindications

Metformin

For metformin, the maximum appropriate daily dose is 1000mg for patients with an eGFR between 50 and 30. **Graph 4** shows a clear decrease in both the total number of prescriptions and in the number of inappropriate prescriptions. In 2018 a total number of 4918 prescriptions were made for metformin in this category, of which 2834 were inappropriate, whereas in 2022 a total of 3455 prescriptions were made of which 1650 inappropriate. **Graph 5** shows the evolution of the proportions of inadequate prescriptions. Here as well, a decreasing trend can be observed: in 2018 we see that 58% of the prescriptions were dosed too high, compared to 48% in 2022.

There is a contraindication for the administration of metformin in patients with an eGFR below 30. In 2018 a total of 1412 prescriptions were created, of which 1301 in the eGFR 30-10 group and 111 in the eGFR <10 group, while in 2022 this happened only 464 times in total (418 in eGFR 30-10 and 46 in eGFR <10). Resulting in a total decrease of 67,1% and 67,9% and 58,6% in the eGFR 30-10 and eGFR <10 groups respectively. This decreasing trend is clearly shown in **graph 6**.

Amoxicillin

In case of amoxicillin, doses must be reduced from an eGFR lower than 30. For patients with an eGFR between 30 and 10, the maximum appropriate daily dose is 2000mg. In 2018, a total of 281 prescriptions were created, of which 195 were inappropriate. In 2022 there were only 117 and 69 of them respectively, a decrease that is clearly visible in **graph 7**. The proportion of excessively dosed medication also decreased from 69% to 59%. (**Graph 8**)

In patients with eGFR lower than 10, a maximum daily dose of 1000mg is allowed. In this group, amoxicillin is remarkably less prescribed: in 2018 a total of 45 prescriptions were created, while in 2022 there were only 10 prescriptions. It is remarkable that almost all prescriptions were dosed too high: in 2018 96% of the prescriptions, in 2022 even 100%. (**Graph 9** & **graph 10**).

Ciprofloxacin

For ciprofloxacin, the maximum appropriate daily dose is 1000mg for patients with an eGFR between 50 and 30**. Graph 11 & 12** show that no clear trend can be found in prescribing behavior between 2018 and 2022. However, the amount of incorrectly dosed prescriptions is very low: in 2018 this concerns only 7% of the prescriptions, in 2022 this rose slightly to 10%. Remarkably, this even dropped to just 2% in 2020.

In patients with an eGFR lower than 30, the daily dose must be lowered to 500mg. In the eGFR 30-10 group, we can note a slight decrease, with a total number of prescriptions of 140 in 2018, of which 84 were inappropriate, while in 2022 this dropped to 91 and 58 respectively, shown in **graph 13**. As can be seen in **graph 14**, the proportion of over-dosed prescriptions rises slightly: 64% in 2022 compared to 60% in 2018, with a notable decrease to 55% in 2020. These numbers are notably much higher compared to the eGFR 50-30 group.

In the eGFR <10 group, ciprofloxacin is noticeably less prescribed: a total of 21 prescriptions in 2018 and only 5 in 2022, of which 5 and 1 were inappropriate respectively (**Graph 15**). The proportion of overdosed prescriptions remains stable as seen in **graph 16**. We observe again a clear deviation in 2020, with this time a striking increase to 58% of the prescriptions that is overdosed.

Nitrofurantoin

Nitrofurantoin is contraindicated in patients with an eGFR lower than 50. We found a decrease in number of prescriptions of 10% (eGFR 50-30), 12% (eGFR 30-10) and 25% (eGFR <10) between 2018 and 2022, however an increase of prescriptions was recorded in 2019 and 2022. (**Graph 17**).
The number of prescriptions does decrease sharply with lowering eGFR, for example in 2018 nitrofurantoin is prescribed 580 times for patients with an eGFR of 50-30, while this is only 146 and 8 prescriptions for patients with an eGFR of 30-10 and <10.

Ibuprofen

Ibuprofen is contraindicated in patients with an eGFR lower than 30. As can be seen in **graph 18**, a clear downward trend can be observed in the eGFR 30-10 group: in 2018, 137 prescriptions were still created in this group, while this has fallen to 33 in 2022, giving a decrease of 76%. In patients with eGFR lower than 10, ibuprofen is clearly prescribed less. However, a clear trend can be observed here as well: 12 prescriptions in 2018, in 2022 this were only 2, giving a decrease of 83%.

Allopurinol

For allopurinol, the maximum appropriate daily dose is 200mg for patients with an eGFR between 50 and 30. As showed in **graph 19**, the total number of prescriptions remains stable over the period from 2018 to 2022. However, we note a declining trend in the number of inappropriate prescriptions: in 2018 there were still 1113 too highly dosed prescriptions, while this has dropped to 822 in 2022. This results in a decrease in the proportion of overdosed prescriptions of approximately 10%. This downward trend is clearly visible in **graph 20**.

In the eGFR 30-10 group, daily doses must be lowered to 100mg. Unlike the previous group, we now remark a decreasing trend in both number of prescriptions and in proportions of inappropriate prescriptions. In 2018, allopurinol was 902 times prescribed, 444 times it was too highly dosed, whereas in 2022 this drops to 635 and 214 times respectively. The proportion of inappropriate prescriptions drops again with approximately 10% (**graph 22 & 22**).

For patients with an eGFR lower than 10, allopurinol is contraindicated. Again, we see a clear declining trend in the prescribing of allopurinol in this group as shown in **graph 23**. In 2018, 98 prescriptions were still created, while this has fallen to 29 in 2022, a decrease of 70%.

				2018			2019			2020			2021			2022		
MEDICATION	**ATC code**	**eGFR**	**Max appropriated daily dose based on eGFR, in mg**	***Inappropriate prescriptions****	***Total prescriptions*** **	**%**	***Inappropriate prescriptions****	***Total prescriptions*** **	**%**	***Inappropriate prescriptions****	***Total prescriptions*** **	**%**	***Inappropriate prescriptions****	***Total prescriptions*** **	**%**	***Inappropriate prescriptions****	***Total prescriptions*** **	**%**
Metformin	**A10BA02**	50-30	1000	2834	4918	**58%**	2747	4961	**55%**	2573	4854	**53%**	1952	3816	**51%**	1650	3455	**48%**
		30-10	Contraindication	**1301**	1301	100%	**1187**	1187	100%	**980**	980	100%	**597**	597	100%	**418**	418	100%
		<10	Contraindication	**111**	111	100%	**86**	86	100%	**68**	68	100%	**55**	55	100%	**46**	46	100%
Amoxicillin	**J01CA04**	30-10	2000	195	281	**69%**	211	297	**71%**	87	148	**59%**	60	108	**56%**	69	117	**59%**
		<10	1000	43	45	**96%**	34	38	**89%**	23	24	**96%**	6	6	**100%**	10	10	**100%**
Ciprofloxacin	**J01MA02**	50-30	1000	25	360	**7%**	13	316	**4%**	6	336	**2%**	14	358	**4%**	32	305	**10%**
		30-10	500	84	140	**60%**	73	120	**61%**	56	102	**55%**	70	113	**62%**	58	91	**64%**
		<10	500	5	21	**24%**	5	11	**45%**	7	12	**58%**	4	14	**29%**	1	5	**20%**
Nitrofurantoin	**J01XE01**	50-30	Contraindication	**580**	580	100%	**611**	611	100%	**619**	619	100%	**524**	524	100%	**518**	518	100%
		30-10	Contraindication	**146**	146	100%	**128**	128	100%	**147**	147	100%	**135**	135	100%	**128**	128	100%
		<10	Contraindication	**8**	8	100%	**17**	17	100%	**15**	15	100%	**4**	4	100%	**6**	6	100%
Ibuprofen	M01AE01	30-10	Contraindication	**137**	137	100%	**112**	112	100%	**95**	95	100%	**48**	48	100%	**33**	33	100%
		<10	Contraindication	**12**	12	100%	**18**	18	100%	**8**	8	100%	**6**	6	100%	**2**	2	100%
Allopurinol	**M04AA01**	50-30	200	1113	2364	**47%**	1102	2518	**44%**	994	2412	**41%**	856	2274	**38%**	822	2390	**34%**
		30-10	100	444	902	**49%**	422	922	**46%**	332	818	**41%**	297	725	**41%**	214	635	**34%**
		<10	Contraindication	**98**	98	100%	**77**	77	100%	**59**	59	100%	**38**	38	100%	**29**	29	100%

Table 6: Overview of the investigated medication, the number of inappropriate prescriptions per eGFR category for each year between 2018 and 2022 compared to the total number of prescriptions.

* Total amount of prescriptions dosed higher than appropriate dose, based on last known eGFR, 01/01/20xx-31/12/20xx

** Total amount of prescriptions of drug regardless of dose, in patients below eGFR, based on last known eGFR, 01/01/20xx-31/12/20xx

Discussion

The aim of this study was to note an evolution in the number of overdosed prescriptions for a given number of commonly prescribed medications between 2018 and 2022.

In general, we see a slight increasing trend in number of patients for each eGFR group. Given the increasing aging of the population, this is a trend we would have expected. Although the results of 2022 are not yet known, we suspect that this trend will probably continue. The correct prescription of medication is just one of the measures to try to stabilize or decrease this trend.

This data analysis from the INTEGO database shows a decreasing trend for medications requiring **dose adjustment**, both in the number of prescriptions and in the proportions of over-dosed prescriptions. This is the case for metformin (eGFR 50-30), amoxicillin (eGFR 30-10) and allopurinol (eGFR30-10). The rate of inappropriate drug prescription for these medications ranged from 47-69% in 2018 and 34-59% in 2022.

In the eGFR <10 group of amoxicillin, there is only a downward trend in the number of prescriptions, but not in the rate of over-dosed prescriptions. Whereas in the eGFR 50-30 group of allopurinol there is only a downward trend in the proportion of inappropriate dosed prescriptions.
A notable exception is ciprofloxacin whereby no clear trend could be observed. However, in the eGFR 50-30 group a remarkably low proportion of prescriptions was overdosed, 7% in 2018 towards 10% in 2022. In the eGFR 30-10 group even a slight increase can be found.

In medications with a **contraindication** for certain eGFR groups, we could observe a clear downward trend in number of prescriptions as well. This is the case for metformin (eGFR <30), nitrofurantoin (eGFR <50), ibuprofen (eGFR <30) and allopurinol (eGFR <10). However, these decreases ranged from 10-83%

Previous studies have already shown that PIMs are an important health problem, specifically in elderly and patients with various co-morbidities and therefore important polypharmacy. In 2004, rates of noncompliance ranged from 19-69%, with highest rates occurring in ambulatory care. [17] A follow-up study in 2017 showed a prevalence of inappropriate drug use ranging from 1-37% in outpatient setting. [18] A retrospective case record analysis showed a prevalence of 13%. [19] Our study also points to a still significant presence of inadequate medication prescription in patients with CKD, with results indicating even higher values than in the previously mentioned studies. Important to note, comparing different studies has proven to be a difficult task in the past and present, mainly because of the many differences in methodology: e.g., use of different medications, use of different dose adjustment guidelines and different equations for eGFR calculation. Studies that examine the evolution over a certain period are in our knowledge currently lacking.

However, this study suggests a decreasing trend and thus an improved prescribing behavior due to PCP. This downward trend could possibly be explained by the increasing development of helpful tools and the digitalization of medicine overall. In recent years a new digital era has dawned with the emergence of digital tools, mobile applications and a modernization, constant renewal and refinement of software programs designed for PCP. This included the introduction of following tools: Evidence-based linkers, automatically medication monitoring, quick links to medication leaflets, easy access to digital health networks, providing information from other PCPs, secondary care providers, laboratories, paramedics, … However, clear evidence for this is still lacking, which means that further and specific research is recommended.

This study faces several limitations. The initial goal of this study was to determine the number of too high dosed prescriptions relative to the total number of prescriptions for each group from 2010-2020 and to perform a trend analysis afterwards. Retrieving the prescribed posology from the INTEGO database has been an enormous challenge. Until 2018, a different medical computer program was used in which coding of posology was not done accurately, which makes it impossible to acquire correct data before this change of program was implemented. As a result, the study period had to be shortened to 2018-2022. This period turned out to be too short to carry out a trend analysis or any other statistical analysis due to the limited data. Therefore, only an explorative analysis of the obtained data could be performed. The fact that data could only be collected over such a short period of time, the data-collection of only 6 medications and that no statistical trend analysis could be performed, are strong limitations for this study.
Due to the complexity of data collection from INTEGO in this case and the limited time, the exact number of patients in the data set could unfortunately not be provided.
The INTEGO-database is representative for the Flemish population in terms of lifestyle, gender, and income. However, it is possible that PCPs who commit to sharing data for scientific research are also more inclined to follow guidelines and continue to train extensively. In this way a collection bias is not excluded.

Since this study suggests a favorable evolution in inadequately prescribing medication in patients with CKD, a larger multi-drug study, conducted over a longer period, is necessary to confirm these findings. A better worldwide consensus in guidelines on dosages may be helpful to draw more concrete conclusions. It remains unclear as well whether the development of helpful decision-making tools and the use of prescribing and deprescribing aids leads to better prescribing behavior of PCPs. It might be helpful to get a better idea of the current prescribing behavior of PCPs and what influences, or would influence them, in this.

Although this study can only highlight certain trends, there seems to be a favorable evolution between 2018 and 2022 in the prescribing behavior of PCPs with a suggesting decrease in the rate of inadequate prescriptions.

Conclusion

CKD is an important and complex disease whose management, partly due to the presence of comorbidities and polypharmacy, represents a major challenge for PCPs. A correct prescribing behavior of specific medications in this patient group has an important role in this. This exploratory analysis could indicate 3 important trends in this matter. For medications requiring a **dose adjustment**, we see a decreasing trend both in the number of prescriptions and in the rate of over-dosed prescriptions. In medications with a **contraindication** for certain eGFR groups, we could observe a clear downward trend in number of prescriptions as well. Ciprofloxacin is a notable exception as no clear trend could be observed.
As a result, there seems to be a favorable evolution in the prescribing behavior of PCPs between 2018 and 2022. As this is only a small-scale study, a larger and longer-term study could be helpful as well as more in-depth research into motives of PCPs in their prescribing behavior.

Acknowledgements

I would like to thank my promotor Prof. Dr. Bert Aertgeerts for his guidance and advice during the realization of this thesis. In addition, I would like to thank my co-promoter Dr. Gijs Van Pottelbergh for providing his expertise and guidance during the INTEGO searches.

Special thanks go to the INTEGO team for their constructive collaboration on the data collection.

References

[1] N. R. Hill, S. T. Fatoba, J. L. Oke, J. A. Hirst, C. A. O'Callaghan, D. S. Lsserson and R. F. Hobbs, "Global Prevalence of Chronic Kidney Disease – A Systematic Review and Meta-Analysis," *PloS one*, vol. 11, no. 7, p. e0158765–e0158765, 2016.

[2] T. K. Chen, D. H. Knicely and M. E. Grams, "Chronic Kidney Disease Diagnosis and Management A Review," *JAMA : the journal of the American Medical Association,* vol. 322, no. 13, pp. 1294-1304, 2019.

[3] G. Van Pottelbergh, A. Avonts, H. Cloetens, M. Goossens, S. Maes, L. Van Heden and P. Van Royen , *Chronische Nierinsufficiëntie,* Domus Medica, 2012.

[4] J. Coresh, E. Selvin , L. A. Stevens, J. Manzi, J. W. Kusek, P. Eggers, F. Van Lente and A. S. Levey, "Prevalence of chronic kidney disease in the United States," *JAMA,* vol. 298, no. 17, pp. 2038-2047, 2007.

[5] J.-C. Lv and L.-X. Zhang, "Prevalence and Disease Burden of Chronic Kidney Disease," in *Advances in Experimental Medicine and Biology: Renal Fibrosis: Mechanisms and Therapies*, Singapore, Springer, 2019, pp. 3-15.

[6] A. L. Ammirati, "Chronic Kidney Disease," *Revista da Associação Médica Brasileira,* no. 66, pp. 3-9, 2020.

[7] E. Braunwald, "Diabetes, heart failure, and renal dysfunction: The vicious circles," *Progress in Cardiovascular Diseases,* vol. 62, no. 4, pp. 298-302, 2019.

[8] J. Sommer, A. Seeling and H. Rupprecht, " Adverse Drug Events in Patients with Chronic Kidney Disease Associated with Multiple Drug Interactions and Polypharmacy," *Drugs & aging,* vol. 37, pp. 359-372, 2020.

[9] C. F. Whittaker, M. A. Miklich, R. S. Patel and J. C. Fink, "Medication Safety Principles and Practice in CKD," *Nephropharmacology for the Clinician,* vol. 13, no. 11, pp. 1738-1746, 2018.

[10] A. Secora, C. Alexander, S. Ballew, J. Coresh and M. Grams, "KIDNEY FUNCTION, POLYPHARMACY, AND POTENTIALLY INAPPROPRIATE MEDICATION USE IN A COMMUNITY-BASED COHORT OF OLDER ADULTS," *Drugs Aging,* vol. 35, no. 8, pp. 735-750, 2018.

[11] I. A. Scott, S. N. Hilmer, E. Reeve, K. Potter, D. Le Couteur, D. Rigby, D. Gnjidic, C. B. Del Mar, E. E. Roughead, A. Page, J. Jansen and J. H. Martin, "Reducing Inappropriate Polypharmacy: The Process of Deprescribing," *JAMA internal medicine,* vol. 175, no. 5, pp. 827-834, 2015.

[12] K. Parker, I. Bull-Engelstad, J. Š. Benth, W. Aasebø, N. von der Lippe, M. Reier-Nilsen, I. Os and K. Stavem, "Effectiveness of using STOPP/START criteria to identify potentially inappropriate medication in people aged ≥ 65 years with chronic kidney disease: a randomized clinical trial," *European journal of clinical pharmacology,* vol. 75, no. 11, pp. 1503-1511, 2019.

[13] A. Mertens, G. Van Pottelbergh, L. De Groote , K. Claes, A. Spinewine and J. Degryse, "Noodzakelijke dosisaanpassingen voor vaak gebruikte medicatie bij patiënten met een gedaalde nierfunctie: een poging om door de bomen het bos te zien.," *Tijdschrift voor geneeskunde,* vol. 70, no. 21, pp. 1279-1294, 2014.

[14] W. De Grauw, H. Kaasjager, E. Faber, S. Flikweert, C. Gaillaird, S. Labpts-Vogelesang, M. Verduijn, W. Verstappen, L. Vleming, E. Walma and J. Van Balen, "Landelijke Transmurale Afspraak Chronische nierschade," *Huisarts & wetenschap,* vol. 52, no. 12, pp. 586-597, 2009.

[15] C. Truyers, G. Goderis, H. Dewitte, M. vanden Akker and F. Buntinx, "The Intego database: background, methods and basic results of a Flemish general practice-based continuous morbidity registration project," *BMC Medical Informatics and Decision Making,* vol. 14, no. 48, 2014.

[16] B. Vaes, E. Beke, C. truyers, S. Elli, F. Buntinx, J. Verbakel, G. Goderis and G. Van Pottelbergh , "The correlation between blood pressure and kidney function decline in older people: a registry-based cohort study," *BMJ Journals,* vol. 5, no. 6, 2015.

[17] C. L. Long, M. A. raebel, D. W. Price and D. J. Magid, " Compliance with Dosing Guidelines in Patients with Chronic Kidney Disease," *he Annals of Pharmacotherapy,* vol. 38, no. 5, pp. 853-858, 2004.

[18] M. Dörks, K. Allers, G. Schmiemann, S. Herget-Rosenthal and F. Hoffmann, "Inappropriate Medication in Non-Hospitalized Patients With Renal Insufficiency: A Systematic Review," *ournal of the American Geriatrics Society (JAGS),* vol. 65, no. 4, pp. 853-862, 2017.

[19] S. A. Jones and S. Bhandari, "The prevalence of potentially inappropriate medication prescribing in elderly patients with chronic kidney disease," *Postgraduate Medical Journal,* vol. 89, no. 1051, pp. 247-250, 2013.

[20] M. Cirillo, M. Laurenzi, M. Mancini, A. Zanchetti, C. Lombardi and N. De Santo, "Low glomerular filtration in the population: Prevalence, associated disorders, and awareness," *Kidney international,* vol. 70, no. 4, pp. 800-806, 2006.

[21] S. Murabito and B. F. Hallmark, "Complications of Kidney Disease," *The Nursing clinics of North America,* vol. 53, no. 4, pp. 579-588, 2018.

[22] V. A. Moyer, "Screening for Chronic Kidney Disease: U.S. Preventive Services Task Force Recommendation Statement," *Annals of internal medicine,* vol. 157, no. 8, pp. 567-570, 2012.

Appendix

Appendix (1): **Tables**

STAGE	**GFR (ml/min/1,73m²)**	**Classification**
I	>90	Normal or high
II	60-89	Slightly decreased
III A	45-59	Mild to moderately decreased
III B	30-44	Moderately to severely decreases
IV	15-29	Severely decreased
V	<15	Kidney failure

Table 1: CKD stage. [6]

GFR = Glomerular Filtration Rate

Category	**24-hour albuminuria** ***(mg/24h)***	**A/C ratio** ***(Mg/g)***	**Classification**
A1	<30	<30	Normal to discrete
A2	30-300	30-300	Moderate
A3	>300	>300	Severe

Table 2: Categories of albuminuria [6]

A/C ratio = Albumin/Creatinine ratio in isolated urine samples

			Albuminuria *(mg/ml)*		
			<30	30-300	>300
GFR *(ml/min/1,73m2)*	I	>90	Low	Moderate	High
	II	60-89	Low	Moderate	High
	III A	45-59	Moderate	High	Very High
	III B	30-44	High	Very High	Very High
	IV	15-29	Very High	Very High	Very High
	V	<15	Very High	Very High	Very High

Table 3: Risk classification. [6]

1	Assess kidney function
2	Complete medication list & history - including prescription, over-the-counter, and dietary supplements
3	Medication review - Nephrotoxic? - Contra-indicated in CKD? - Prolonged half-time in CKD? - Risk of adverse effects of drug-drug interactions CKD? - Narrow toxic or therapeutic range?
4	Adjust regime
5	Drug therapy monitoring

Table 4: Deprescribing in CKD [9]

Appendix (2): **List of selected commonly used drugs and their CNK- and ATC codes**

CNKcode	amppnm	atc	atcnm_n
1555689	ADASTER 850 TABL 100 X 850 MG	A10BA02	metformine
1543784	DIABOMET COMP 60X500MG CFR METFORMINE CNK 2071-561	A10BA02	metformine
1543792	DIABOMET COMP100X850MG CFR METFORMINE CNK 2071-579	A10BA02	metformine
1740141	DOCMETFORMI 500 COMP ENROB 60 X 500 MG	A10BA02	metformine
1740133	DOCMETFORMI 850 COMP ENROB 100 X 850 MG	A10BA02	metformine
114066	GLUCOPHAGE COMP 50 X 500 MG	A10BA02	metformine
44842	GLUCOPHAGE COMP 150 X 500 MG	A10BA02	metformine
44057	GLUCOPHAGE 850 COMP 100 X 850MG	A10BA02	metformine
321612	GLUCOPHAGE 500 COMP 60 X 500MG	A10BA02	metformine
2040871	METFORMAX 850 TABL 120 X 850 MG UD	A10BA02	metformine
1517200	METFORMAX 850 TABL 120 X 850 MG	A10BA02	metformine
1517192	METFORMAX 850 TABL 40 X 850 MG	A10BA02	metformine
1645175	METFORMINE SANDOZ 500MG TABL 60X500MG	A10BA02	metformine
1645183	METFORMINE SANDOZ 850MG TABL 100X850MG	A10BA02	metformine
2220754	METFORMINE SANDOZ 1000 MG COMP 120 X 1000 MG	A10BA02	metformine
1539246	METFORMINE MYLAN 850 TABL 100X850MG	A10BA02	metformine
1539238	METFORMINE MYLAN 500 TABL 60X500MG	A10BA02	metformine
2727337	METFORMINE PFIZER 850 MG FILMOMH TABL 100 X 850 MG	A10BA02	metformine
2071579	METFORMINE SANDOZ 850 MG COMP 100 X 850 MG	A10BA02	metformine
2071561	METFORMINE SANDOZ 500 MG COMP 60 X 500 MG	A10BA02	metformine
1609486	METFORMINE TEVA 850MG COMP 100X850MG	A10BA02	metformine
1609478	METFORMINE TEVA 500MG COMP 60X500MG	A10BA02	metformine
1652296	METFORMIPHAR 500MG COMP 120X500MG	A10BA02	metformine
1652304	METFORMIPHAR 850MG COMP 200X850MG	A10BA02	metformine
1782507	METFORTOP 500 TABL 60 X 500 MG	A10BA02	metformine
1784016	METFORTOP 850 TABL 100 X 850 MG	A10BA02	metformine
2734465	VALE METFORMINE MYLAN 500MG MYLAN COMP 100X 500MG	A10BA02	metformine
2734473	VALE METFORMINE MYLAN 850MG MYLAN COMP 60X 850MG	A10BA02	metformine
2734481	VALE METFORMINE MYLAN 1000MG MYLAN COMP 60X1000MG	A10BA02	metformine
2734499	VALE METFORMINE MYLAN 1000MG MYLAN COMP 100X1000MG	A10BA02	metformine
433730	AMOXI-500 PULV OR 16 X 500 MG	J01CA04	amoxicilline
868604	AMOXI-250 FL 1 X 80 ML 250 MG/5 ML	J01CA04	amoxicilline
868612	AMOXI-500 CAPS 16 X 500 MG	J01CA04	amoxicilline
2732717	AMOXICILLINE APOTEX COMP EFF - BRUIS 20 X 1 G	J01CA04	amoxicilline
2729846	AMOXICILLINE APOTEX COMP EFF - BRUIS 8 X 1 G	J01CA04	amoxicilline
2729838	AMOXICILLINE APOTEX CAPS 16 X 500 MG	J01CA04	amoxicilline
2729820	AMOXICILLINE APOTEX PULV ORALE SUSP 250MG 5ML 80ML	J01CA04	amoxicilline
2159697	AMOXICILLINE BEXAL 1000 MG COMP 8 OLD SANDOZ	J01CA04	amoxicilline
1358001	AMOXICILLINE EFEKA CAPS 16 X 500 MG	J01CA04	amoxicilline
2650604	AMOXICILLINE EG 1000 MG PI PHARMA COMP 20 PIP	J01CA04	amoxicilline
2738276	AMOXICILLINE EG COMP EFF 24 X 1000 MG	J01CA04	amoxicilline
2257095	AMOXICILLINE EG COMP EFF 8 X 1000 MG	J01CA04	amoxicilline
2237253	AMOXICILLINE EG COMP 20 X 1 G	J01CA04	amoxicilline
2257103	AMOXICILLINE EG COMP EFF 20 X 1000 MG	J01CA04	amoxicilline
2207512	AMOXICILLINE EG COMP 20 X 1000 MG	J01CA04	amoxicilline

2744761	AMOXICILLINE EG 1000 MG FILMOMH TABL 24 X 1000 MG	J01CA04	amoxicilline
1373158	AMOXICILLINE EG COMP 8 X 1 G	J01CA04	amoxicilline
613364	AMOXICILLINE EG CAPS 16 X 500 MG	J01CA04	amoxicilline
2208783	AMOXICILLINE EG CAPS 30 X 500 MG	J01CA04	amoxicilline
2646933	AMOXICILLINE EG PI PHARMA CAPS 16 X 500 MG PIP	J01CA04	amoxicilline
1722651	AMOXICILLINE EG SIR 100 ML 250MG/5ML	J01CA04	amoxicilline
3491859	AMOXICILLINE EG 500MG/5ML PDR ORALE SUSP 100ML	J01CA04	amoxicilline
2824332	AMOXICILLINE FAR 250 MG SOCOBOM DISP COMP 16	J01CA04	amoxicilline
2824340	AMOXICILLINE FAR 375 MG SOCOBOM DISP COMP 16	J01CA04	amoxicilline
2824357	AMOXICILLINE FAR 500 MG SOCOBOM DISP COMP 16	J01CA04	amoxicilline
2824373	AMOXICILLINE FAR 750 MG SOCOBOM DISP COMP 16	J01CA04	amoxicilline
1480714	AMOXICILLINE MYLAN 500 MG CAPS 16 X 500 MG	J01CA04	amoxicilline
1713098	AMOXICILLINE MYLAN 500 MG CAPS 24 X 500 MG	J01CA04	amoxicilline
1543289	AMOXICILLINE RATIO 500MGCOMP DISP16	J01CA04	amoxicilline
1543297	AMOXICILLINE RATIO 750MGCOMP DISP16	J01CA04	amoxicilline
1525500	AMOXICILLINE SANDOZ 500 MG TABL DISP 16	J01CA04	amoxicilline
2202372	AMOXICILLINE SANDOZ 1000 MG TABL DISP 20	J01CA04	amoxicilline
2697670	AMOXICILLINE SANDOZ 1000 MG TABL DISP 24	J01CA04	amoxicilline
2202364	AMOXICILLINE SANDOZ 500 MG TABL DISP 30	J01CA04	amoxicilline
1525518	AMOXICILLINE SANDOZ 1000 MG TABL DISP 8	J01CA04	amoxicilline
2358810	AMOXICILLINE SANDOZ 500 MG CAPS 16	J01CA04	amoxicilline
2114346	AMOXICILLINE SANDOZ 250MG/5ML PULV SUSP OR 100ML	J01CA04	amoxicilline
2707180	AMOXICILLINE SANDOZ 500MG/5ML PDR ORALE SUSP 100ML	J01CA04	amoxicilline
671297	AMOXICILLINE EG SIR 80 ML 250MG/5ML	J01CA04	amoxicilline
1357995	AMOXICILLINE EFEKA SIR80ML 250MG/ML	J01CA04	amoxicilline
2330843	AMOXICILLINE TEVA COMP EFF BRUISTABL 20 X 1000 MG	J01CA04	amoxicilline
1539089	AMOXICILLINE TEVA DISP COMP 16X500MG	J01CA04	amoxicilline
1539071	AMOXICILLINE TEVA DISP COMP 16X750MG	J01CA04	amoxicilline
1226075	AMOXICILLINE TEVA SIR 80 ML 250MG/5ML	J01CA04	amoxicilline
1662410	AMOXIMED 500 COMP. DISP. 16 X 500 MG	J01CA04	amoxicilline
1662402	AMOXIMED 1000 COMP. DISP. 8 X 1000 MG	J01CA04	amoxicilline
1218726	AMOXICILLINE TEVA 500 CAPS 16X500MG	J01CA04	amoxicilline
1539055	AMOXIPHAR DISP COMP 16X250MG	J01CA04	amoxicilline
1539063	AMOXIPHAR DISP COMP 16X375MG	J01CA04	amoxicilline
1766443	AMOXICILLINE TEVA SOLUBLE TABL 8 X 1000 MG	J01CA04	amoxicilline
607358	AMOXYCAPS CAPS 16 X 500 MG	J01CA04	amoxicilline
1612654	AMOXYPEN 250MG TABL DISP 16 X 250MG	J01CA04	amoxicilline
1612662	AMOXYPEN 375MG TABL DISP 16 X 375MG	J01CA04	amoxicilline
1612670	AMOXYPEN 500MG TABL DISP 16 X 500MG	J01CA04	amoxicilline
2231520	AMOXYPEN COMP EFF SEC 20X1G	J01CA04	amoxicilline
1652106	AMOXYPEN COMP EFF SEC 8X1G	J01CA04	amoxicilline
688176	AMOXYPEN CAPS 16 X 500 MG	J01CA04	amoxicilline
1597160	AMOXYPEN COMP DISP 16 X 750 MG	J01CA04	amoxicilline
290254	AMOXYPEN SACH 16 X 500 MG	J01CA04	amoxicilline
688184	AMOXYPEN SIR PULV 1X100ML 250MG/5ML	J01CA04	amoxicilline
1462514	BACTIMED 500 MG CAPS 16	J01CA04	amoxicilline
2612729	CLAMOXYL 1 G PI PHARMA COMP DISP 24 X 1 G PIP	J01CA04	amoxicilline
2600286	CLAMOXYL 1 G PI PHARMA COMP DISP 8 X 1 G PIP	J01CA04	amoxicilline

1665371	CLAMOXYL PI PHARMA CAPS 16X500MG PIP	J01CA04	amoxicilline
1665389	CLAMOXYL PI PHARMA COMP 8X1000MG PIP	J01CA04	amoxicilline
899724	CLAMOXYL CAPS 100 X 500 MG UD	J01CA04	amoxicilline
2312619	CLAMOXYL 1000 ""TABS"" COMP 24X1000MG	J01CA04	amoxicilline
1100239	CLAMOXYL 1000 ""TABS"" COMP 8X1000MG	J01CA04	amoxicilline
852244	CLAMOXYL FL INJ IM-IV 6X1G	J01CA04	amoxicilline
852251	CLAMOXYL FL INJ IM-IV6X250MG	J01CA04	amoxicilline
852228	CLAMOXYL FL INJ IM-IV6X500MG	J01CA04	amoxicilline
29256	CLAMOXYL FL INJ IM/IV (3X10)500MG	J01CA04	amoxicilline
107235	CLAMOXYL CAPS 16 X 500 MG	J01CA04	amoxicilline
804633	CLAMOXYL INJ IM 3 X 1G+ALC BENZ 3 %	J01CA04	amoxicilline
804641	CLAMOXYL INJ IM 6 X 1G+ALC BENZ 3 %	J01CA04	amoxicilline
30395	CLAMOXYL FL INJ IM/IV (3X10) 1G	J01CA04	amoxicilline
3499415	CLAMOXYL IV/IM 1G PDR OPL INF INJ FL 10	J01CA04	amoxicilline
107219	CLAMOXYL PULV 16 X 500 MG	J01CA04	amoxicilline
107201	CLAMOXYL PULV 16 X 250 MG	J01CA04	amoxicilline
3677820	CLAMOXYL 125MG/5ML PDR VOOR SIROOP 25MG/ML FL100ML	J01CA04	amoxicilline
3677838	CLAMOXYL 250MG/5ML PDR VOOR SIROOP 50MG/ML FL100ML	J01CA04	amoxicilline
107342	CLAMOXYL SIR 1 X 80 ML 125MG/5ML	J01CA04	amoxicilline
107359	CLAMOXYL SIR 1 X 80 ML 250MG/5ML	J01CA04	amoxicilline
2121051	DOCAMOXICI 1000 MG COMP DISP 16 X 1000 MG	J01CA04	amoxicilline
1717354	DOCAMOXICI 1000 MG COMP DISP 8 X 1000 MG	J01CA04	amoxicilline
1717347	DOCAMOXICI 500 MG COMP DISP 16 X 500 MG	J01CA04	amoxicilline
1487156	DOCAMOXICI PULV SUSP 80ML 250MG/5ML	J01CA04	amoxicilline
861765	FIMOXIL PULV OR 16 X 500 MG	J01CA04	amoxicilline
2650638	FLEMOXIN PI PHARMA SOLUTAB 24 X 1 G PIP	J01CA04	amoxicilline
1027614	FLEMOXIN PULV SUSP OR 80 ML 250MG/5ML	J01CA04	amoxicilline
2513901	FLEMOXIN SOLUTAB 24X1G	J01CA04	amoxicilline
2055010	FLEMOXIN SOLUTAB 30X500MG	J01CA04	amoxicilline
2215903	FLEMOXIN PULV SUSP OR 100ML 250MG/5ML	J01CA04	amoxicilline
12054	FLEMOXIN SOLUTAB 16X500MG	J01CA04	amoxicilline
12047	FLEMOXIN SOLUTAB PED 16X250MG	J01CA04	amoxicilline
1752336	FLEMOXIN SOLUTAB 20X1G	J01CA04	amoxicilline
1238161	FLEMOXIN SOLUTAB 8X1G	J01CA04	amoxicilline
115170	HICONCIL CAPS 16 X 500 MG	J01CA04	amoxicilline
47613	HICONCIL SUSP OR 1 X 80ML 250MG/5ML	J01CA04	amoxicilline
490664	LENKOFIM CFR NOVABRITINE 500MG TABS	J01CA04	amoxicilline
1517473	AMOXICILLINE MYLAN CAPS 16X500MG	J01CA04	amoxicilline
119792	MOXALINE CAPS 16X500MG	J01CA04	amoxicilline
57802	MOXALINE PULV SUSP 1X80ML 250MG/5ML	J01CA04	amoxicilline
1399088	MOXITOP APOTEX CAPS 16X500MG	J01CA04	amoxicilline
1075647	NOVABRITINE 500 TABS COMP16X 500MG	J01CA04	amoxicilline
1100247	NOVABRITINE 1000 TABS COMP 8X1000MG	J01CA04	amoxicilline
121665	NOVABRITINE CAPS 16 X 500MG	J01CA04	amoxicilline
139618	NOVABRITINE DISP 500MG CFR CLAMOXYL	J01CA04	amoxicilline
139626	NOVABRITINE IM INJ 3 X 1 G + SOLV	J01CA04	amoxicilline
139873	NOVABRITINE IM INJ 6 X 1 G + SOLV	J01CA04	amoxicilline
139543	NOVABRITINE IM/IV 6 X 1 G + SOLV	J01CA04	amoxicilline

139493	NOVABRITINE IM/IV 6 X 500 MG+SOLV	J01CA04	amoxicilline
121590	NOVABRITINE PULV 16 X 250 MG	J01CA04	amoxicilline
121954	NOVABRITINE SIR 1 X 80ML 125MG/5ML	J01CA04	amoxicilline
122036	NOVABRITINE SIR 1 X 80ML 250MG/5ML	J01CA04	amoxicilline
1612720	CIPROBEL 500MG TABL 20 X 500 MG	J01MA02	ciprofloxacine
2308294	CIPROFLOXACINE RANBAXY 250 MG COMP. 10 X 250 MG	J01MA02	ciprofloxacine
2309797	CIPROFLOXACINE RANBAXY 500 MG COMP. 20 X 500 MG	J01MA02	ciprofloxacine
2309805	CIPROFLOXACINE RANBAXY 750 MG COMP. 20 X 750 MG	J01MA02	ciprofloxacine
3531712	CIPROFLOXACINE AB 250MG FILMOMH TABL 10 X 250MG	J01MA02	ciprofloxacine
3531720	CIPROFLOXACINE AB 500MG FILMOMH TABL 20 X 500MG	J01MA02	ciprofloxacine
3531738	CIPROFLOXACINE AB 750MG FILMOMH TABL 20 X 750MG	J01MA02	ciprofloxacine
1732882	CIPROFLOXACINE BEXAL 250 MG COMP 10 OLD SANDOZ	J01MA02	ciprofloxacine
1732890	CIPROFLOXACINE BEXAL 500 MG COMP 20 OLD SANDOZ	J01MA02	ciprofloxacine
2630788	CIPROFLOXACINE EG PI PHARMA COMP 20X500MG PIP	J01MA02	ciprofloxacine
2049823	CIPROFLOXACINE EG 250 MG COMP 20 X 250 MG	J01MA02	ciprofloxacine
2049815	CIPROFLOXACINE EG 250 MG COMP 10 X 250 MG	J01MA02	ciprofloxacine
2049831	CIPROFLOXACINE EG 500 MG COMP 20 X 500 MG	J01MA02	ciprofloxacine
2049849	CIPROFLOXACINE EG 750 MG COMP 20 X 750 MG	J01MA02	ciprofloxacine
1670371	CIPROFLOXACINE MYLAN 250MG COMP 10 X 250 MG	J01MA02	ciprofloxacine
1670363	CIPROFLOXACINE MYLAN 500MG COMP 20 X 500 MG	J01MA02	ciprofloxacine
2747848	CIPROFLOXACINE PFIZER COMP 10 X 250 MG	J01MA02	ciprofloxacine
2747863	CIPROFLOXACINE PFIZER COMP 20 X 500 MG	J01MA02	ciprofloxacine
2747889	CIPROFLOXACINE PFIZER COMP 20 X 750 MG	J01MA02	ciprofloxacine
1766096	CIPROFLOXACINE RATIOPHARM COMP 20 X 500 MG	J01MA02	ciprofloxacine
1676618	CIPROFLOXACINE SANDOZ 250MG TABL 10 NEW SANDOZ	J01MA02	ciprofloxacine
1676626	CIPROFLOXACINE SANDOZ 500MG TABL 20 NEW SANDOZ	J01MA02	ciprofloxacine
1732908	CIPROFLOXACINE SANDOZ 750 MG COMP 20 X 750 MG	J01MA02	ciprofloxacine
2729804	CIPROFLOXACINE TEVA COMP 10 X 250 MG	J01MA02	ciprofloxacine
2729812	CIPROFLOXACINE TEVA COMP 20 X 500 MG	J01MA02	ciprofloxacine
2732725	CIPROFLOXACINE TEVA COMP 20 X 750 MG	J01MA02	ciprofloxacine
2041523	CIPROFLOXAPHAR TEVA COMP ENROB 10 X 250 MG	J01MA02	ciprofloxacine
2041515	CIPROFLOXAPHAR TEVA COMP ENROB 20 X 500 MG	J01MA02	ciprofloxacine
1467026	CIPROXINE 250 PI PHARMA COMP10X250MG PIP	J01MA02	ciprofloxacine
318733	CIPROXINE 500 COMP 120 X 500 MG UD	J01MA02	ciprofloxacine
430892	CIPROXINE 250 COMP 10 X 250 MG	J01MA02	ciprofloxacine
1359611	CIPROXINE 500 COMP 20 X 500 MG	J01MA02	ciprofloxacine
1705474	CIPROXINE SUSP ORALE 2X100ML 250MG/5ML	J01MA02	ciprofloxacine
1729979	DOCCIPROFLO 250 TABL 10 X 250 MG	J01MA02	ciprofloxacine
1729987	DOCCIPROFLO 500 TABL 20 X 500 MG	J01MA02	ciprofloxacine
1729995	DOCCIPROFLO 750 TABL 20 X 750 MG	J01MA02	ciprofloxacine
1612712	CIPROBEL 250MG TABL 10 X 250 MG	J01MA02	ciprofloxacine
1691229	MERCK CIPROFLOXACINE 250MG COMP 20 X 250 MG	J01MA02	ciprofloxacine
1784990	ADULFEN LYSINE CFR NUROFEN FASTTABS CNK 2652-048	M01AE01	ibuprofen
1414812	ADVIL MONO DRAG 20 X 400 MG	M01AE01	ibuprofen
1660133	ADVIL MONO LIQUID CAPS 200 ZACHTE CAPS 20	M01AE01	ibuprofen
2072247	ADVIL MONO LIQUID CAPS 200 ZACHTE CAPS 50	M01AE01	ibuprofen
2789543	BRUFEN GRAN 600 MG ZAKJES 40 X 600 MG	M01AE01	ibuprofen
2789535	BRUFEN GRAN 600 MG ZAKJES 20 X 600 MG	M01AE01	ibuprofen

27565	BRUFEN COMP ENROB - OMHULDE TABL 100 X 200 MG	M01AE01	ibuprofen
104596	BRUFEN 400 MG FILMOMH TABL 100 X 400 MG	M01AE01	ibuprofen
3491875	BRUFEN 400 MG FILMOMH TABL 20 X 400 MG	M01AE01	ibuprofen
3607462	BRUFEN 400 MG FILMOMH TABL 30 X 400 MG	M01AE01	ibuprofen
867556	BRUFEN FORTE 600 MG FILMOMH TABL 30 X 600 MG	M01AE01	ibuprofen
2639763	BRUFEN FORTE 600 MG FILMOMH TABL 60 X 600 MG	M01AE01	ibuprofen
104554	BRUFEN SUPP 12 X 500 MG	M01AE01	ibuprofen
290247	BRUFEN RETARD COMP 28 X 800 MG	M01AE01	ibuprofen
431452	BRUFEN RETARD COMP 60 X 800 MG	M01AE01	ibuprofen
1456425	BUPROPHAR 400 MG DRAG 30 X 400 MG	M01AE01	ibuprofen
1352491	BUPROPHAR 200 MG DRAG 30 X 200 MG	M01AE01	ibuprofen
1024926	DOLOFIN BLISTERS 10X10DRAGX400MG	M01AE01	ibuprofen
1713841	DOLOFIN DRAG 30X200MG	M01AE01	ibuprofen
1026632	DOLOFIN BLISTERS 3X10DRAGX400MG	M01AE01	ibuprofen
1694918	DOLOFIN DRAG 30X600MG	M01AE01	ibuprofen
2061976	EPSILON 400 MG COMP ENROB OMHULDE 30X400MG	M01AE01	ibuprofen
99036	IBU SLOW CAPS 40 X 300 MG	M01AE01	ibuprofen
669689	IBU SLOW COMP SEC 60 X 600 MG	M01AE01	ibuprofen
3227683	IBUCAPS 400MG APOTEX CAPS ZACHT 10	M01AE01	ibuprofen
3227691	IBUCAPS 400MG APOTEX CAPS ZACHT 20	M01AE01	ibuprofen
3304292	IBUCAPS 200MG APOTEX CAPS ZACHT 30	M01AE01	ibuprofen
3227709	IBUCAPS 400MG APOTEX CAPS ZACHT 30	M01AE01	ibuprofen
449967	IBUMED 200 MG FILMOMH TABL 24 X 200 MG	M01AE01	ibuprofen
1303262	IBUPHAR DRAG 100 X 200 MG	M01AE01	ibuprofen
3044633	IBUPROFEN A 600 MG FILMOMH TABL 30 X 600 MG	M01AE01	ibuprofen
3044625	IBUPROFEN ACTAVIS 600 MG FILMOMH TABL 60 X 600 MG	M01AE01	ibuprofen
1414333	IBUPROFEN EG 600 MG FILMOMH TABL 30 X 600 MG	M01AE01	ibuprofen
1430636	IBUPROFEN EG 600 MG FILMOMH TABL 50 X 600 MG	M01AE01	ibuprofen
92502	IBUPROFEN EG 400 MG FILMOMH TABL 100 X 400 MG	M01AE01	ibuprofen
3021433	IBUPROFEN EG 200 MG OMHULDE TABL 30 X 200 MG	M01AE01	ibuprofen
1132885	IBUPROFEN EG 400 MG FILMOMH TABL 30 X 400 MG	M01AE01	ibuprofen
2883031	IBUPROFEN EG 40 MG/ML SUSP ORAAL GEBRUIK 100 ML	M01AE01	ibuprofen
664227	IBUPROFEN RETARD EG 800 MG TABL VERL.AFG. 30X800MG	M01AE01	ibuprofen
3276904	IBUPROFEN RETARD EG 800 MG VERL.AFG. COMP 60X800MG	M01AE01	ibuprofen
3075249	IBUPROFEN LYSINE MYLAN 400MG FILM TABL 100X400MG	M01AE01	ibuprofen
3075231	IBUPROFEN LYSINE MYLAN 400MG FILM TABL 30X400MG	M01AE01	ibuprofen
3075223	IBUPROFEN LYSINE MYLAN PHARMA FILM TABL 30X200MG	M01AE01	ibuprofen
2568202	IBUPROFEN SANDOZ 200MG COMP PELL 100X200MG	M01AE01	ibuprofen
2568228	IBUPROFEN SANDOZ 400MG COMP PELL 100X400MG	M01AE01	ibuprofen
2568210	IBUPROFEN SANDOZ 400MG COMP PELL 30X400MG	M01AE01	ibuprofen
1541564	IBUPROFEN SANDOZ 600MG COMP PELL 30X600MG	M01AE01	ibuprofen
2674034	IBUPROFEN SANDOZ 600MG OMHULDE TABL 50X600MG	M01AE01	ibuprofen
2568194	IBUPROFEN SANDOZ 200MG COMP PELL 30X200MG	M01AE01	ibuprofen
2990125	IBUPROFEN SANDOZ 100 MG/5 ML X 100 ML OR SUSP 2%	M01AE01	ibuprofen
2999696	IBUPROFEN SANDOZ 200 MG/5 ML X 100 ML OR SUSP 4%	M01AE01	ibuprofen
2990133	IBUPROFEN SANDOZ 100 MG/5 ML X 200 ML OR SUSP 2%	M01AE01	ibuprofen
2410447	IBUPROFEN TEVA 2% SIR 200 ML	M01AE01	ibuprofen
1303288	IBUPROFEN TEVA DRAG 100 X 400 MG	M01AE01	ibuprofen

1309764	IBUPROFEN TEVA DRAG 30 X 200 MG	M01AE01	ibuprofen
1303270	IBUPROFEN TEVA DRAG 30 X 400 MG	M01AE01	ibuprofen
1547330	IBUPROFEN TEVA COMP 30 X 600 MG	M01AE01	ibuprofen
2567428	IBUPROFEN TEVA COMP ENROB. 60 X 600 MG	M01AE01	ibuprofen
3055498	IFENIN 200 MG ACTAVIS FILMOMH TABL 24	M01AE01	ibuprofen
3055506	IFENIN 400 MG ACTAVIS FILMOMH TABL 24	M01AE01	ibuprofen
1180660	INABRIN COMP 20X200MG	M01AE01	ibuprofen
1639624	JUNIFEN 200 DRAG 24 X 200 MG CFR 2475-739	M01AE01	ibuprofen
1639632	JUNIFEN 200 MICROGRAN SACH. 24	M01AE01	ibuprofen
1404888	JUNIFEN ZONDER SUIKER SUSP 100 ML	M01AE01	ibuprofen
1553999	JUNIFEN ZONDER SUIKER SUSP 150 ML CFR 2475-713	M01AE01	ibuprofen
1553981	JUNIFEN SIR 150 ML CFR 2475-721	M01AE01	ibuprofen
841916	JUNIFEN SIR 100 ML	M01AE01	ibuprofen
2355956	JUNIFEN SUPPO 10 X 125 MG CFR 2475-689	M01AE01	ibuprofen
2355949	JUNIFEN SUPPO 10 X 60 MG CFR 2475-705	M01AE01	ibuprofen
1177138	MALAFENE SIR. 100 ML	M01AE01	ibuprofen
1692599	MITHRA IBUPROFEN DRAG 30X400MG	M01AE01	ibuprofen
1692607	MITHRA IBUPROFEN DRAG 100X400MG	M01AE01	ibuprofen
1175439	MOTRIN COMP 50X600MG	M01AE01	ibuprofen
814707	NUROFEN DRAG 24X200MGVOIR-ZIE CNK 2475-671	M01AE01	ibuprofen
2219574	NUROFEBRYL 400 GRAN EFF 12 X 400 MG	M01AE01	ibuprofen
3153400	NUROFEN IMPEXECO 4% SIROP STRAWBERRY ZS KIND 150ML	M01AE01	ibuprofen
3164241	NUROFEN 400 IMPEXECO FILMOMH TABL 30X400MG PIP	M01AE01	ibuprofen
2547925	NUROFEN KIND SINAAS SUSP SUIKERVRIJ 200 ML	M01AE01	ibuprofen
2556264	NUROFEN KIND SUIKERVRIJ AARDBEI 2 % 200ML	M01AE01	ibuprofen
2964062	NUROFEN KIND SINAAS 4% SUSP SUIKERVRIJ 150 ML	M01AE01	ibuprofen
2922607	NUROFEN KIND SUIKERVRIJ 4% AARDBEI ORALE SUSP150ML	M01AE01	ibuprofen
1409556	NUROFEN 400 DRAG 24 X 400 MG	M01AE01	ibuprofen
2459006	NUROFEN 400 LIQUID CAPS 20X400MG CFR 2570-950	M01AE01	ibuprofen
3078789	NUROFEN 200 FASTCAPS CAPS 20	M01AE01	ibuprofen
1173657	NUROFEN COMP SOL/OPLOSTABL 24X200MG	M01AE01	ibuprofen
1433580	NUROFEN BRUISTABL. 12 X 200 MG	M01AE01	ibuprofen
2218238	NUROFEN DRAG 12X200MG	M01AE01	ibuprofen
2652048	NUROFEN 400 FASTTABS 24 X 400 MG	M01AE01	ibuprofen
2475721	NUROFEN KIND SIROOP 150 ML	M01AE01	ibuprofen
2754968	NUROFEN KIND SUIKER/V ROOD 4% 100ML CFR 2922-607	M01AE01	ibuprofen
2475713	NUROFEN KIND SUSPENSIE SUIKERVRIJ 150 ML	M01AE01	ibuprofen
2475671	NUROFEN OMHULDE TABL 30 X 200 MG	M01AE01	ibuprofen
2547958	NUROFEN OMHULDE TABL 30 X 400 MG	M01AE01	ibuprofen
1180645	NUROFEN DRAG 48X200MG	M01AE01	ibuprofen
3181229	NUROFEN KIND 200MG FILMOMH TABL 24 VERV.2475739	M01AE01	ibuprofen
2833028	NUROFEN 400 FASTPOWDER 400 MG SACH 10	M01AE01	ibuprofen
1768886	NUROFEN SMELTTABL-COMP FONDANTS 12 X 200 MG	M01AE01	ibuprofen
2475739	NUROFEN KIND +12 JAAR 200 MG FILMOMH TABL 24	M01AE01	ibuprofen
2570950	NUROFEN 400 FASTCAPS CAPS 20 X 400 MG	M01AE01	ibuprofen
3042082	NUROFEN 400 FASTCAPS CAPS 30 X 400 MG	M01AE01	ibuprofen
3546579	NUROFEN KIND 100MG ZACHTE KAUWCAPS 24	M01AE01	ibuprofen
2475689	NUROFEN KIND 125MG SUPPO 10 X 125 MG	M01AE01	ibuprofen

2475705	NUROFEN KIND 60MG SUPPO 10 X 60 MG	M01AE01	ibuprofen
2195089	OPTALIDON NF TABL 24 X 400 MG	M01AE01	ibuprofen
2718203	PERDOFEMINA TABL 30 X 400 MG	M01AE01	ibuprofen
2335370	PERDOFEMINA TABL 20 X 400 MG	M01AE01	ibuprofen
2335008	PERDOPHEN PEDIATRIE SUSP OR 100 ML 20MG/ML	M01AE01	ibuprofen
3399557	PERDOPHEN FILMOMH TABL 30 X 400MG	M01AE01	ibuprofen
3111994	PERDOTENSIO 200 MG TABL 40	M01AE01	ibuprofen
1437243	PERVIAM TABL 20 X 200 MG	M01AE01	ibuprofen
1431410	SIPROFEN COMP. 20 X 200 MG	M01AE01	ibuprofen
636936	SOLUFEN CAPS. 20 X 200 MG	M01AE01	ibuprofen
636944	SOLUFEN CAPS. 24 X 200 MG	M01AE01	ibuprofen
1784206	SPIDIFEN 400 COMP ENROB 24 X 400 MG	M01AE01	ibuprofen
3690294	SPIDIFEN 400MG FILMOMH TABL 30	M01AE01	ibuprofen
1782499	SPIDIFEN 200 DOS GRAN 24	M01AE01	ibuprofen
1281492	SPIDIFEN 400 DOS GRAN 30	M01AE01	ibuprofen
3081338	SPIDIFEN 200 MG TABL 20 X 200 MG	M01AE01	ibuprofen
2646925	ALLOPURINOL EG PI PHARMA CAPS 90X300MG PIP	M04AA01	allopurinol
16832	ALLOPURINOL EG COMP 90 X 300 MG	M04AA01	allopurinol
1480698	ALLOPURINOL MYLAN 300 MG COMP 90 X 300 MG	M04AA01	allopurinol
2104024	ALLOPURINOL SANDOZ 100MG TABL 100	M04AA01	allopurinol
2104032	ALLOPURINOL SANDOZ 300MG TABL 30	M04AA01	allopurinol
2104016	ALLOPURINOL SANDOZ 300MG TABL 90	M04AA01	allopurinol
1358027	ALLOPURINOL TABS 90 X 300 MG	M04AA01	allopurinol
1358035	ALLOPURINOL TABS 100 X 100 MG	M04AA01	allopurinol
2748150	ALLOPURINOL TEVA 100 MG TABL 100	M04AA01	allopurinol
2748119	ALLOPURINOL TEVA 300 MG TABL 100	M04AA01	allopurinol
1534866	ALLOPURINOL RATIOPHARM COMP 100X100MG	M04AA01	allopurinol
1534882	ALLOPURINOL RATIOPHARM COMP 90X300MG	M04AA01	allopurinol
1226067	ALPURIC CAPS 90X300MG	M04AA01	allopurinol
1226059	ALPURIC CAPS 100X100MG	M04AA01	allopurinol
2195816	ZYLORIC PI PHARMA COMP 100 X 100 MG PIP	M04AA01	allopurinol
137810	ZYLORIC 100 COMP 100 X 100 MG	M04AA01	allopurinol
99457	ZYLORIC 300 COMP 30 X 300 MG	M04AA01	allopurinol
866236	ZYLORIC 300 COMP 90 X 300 MG	M04AA01	allopurinol
113381	FURADANTINE MC 50MG CAPS 50 x 50MG	J01XE01	Nitrofurantoïne
113399	FURADANTINE MC 100MG CAPS 50 x 100MG	J01XE01	Nitrofurantoïne

Appendix (3): **Queries INTEGO:** % prescriptions too high dosed (based on last known eGFR) in INTEGO database during 2018-2022

2018

Medication	**ATC code**	**eGFR**	**max appropriated daily dose based on eGFR, in mg**	***Total # prescriptions of drug dosed higher than appropriate dose in patients below eGFR, based on last known eGFR, 01/01/2018-31/12/2018***	***Total # prescriptions of drug regardless of dose, in patients below eGFR based on last known eGFR, 01/01/2018-31/12/2018***	**Ratio**
Ibuprofen	**M01AE01**	50-30	2400			
Ibuprofen	**M01AE01**	30-10	0			
Ibuprofen	**M01AE01**	<10	0			
Amoxicilline	**J01CA04**	50-30	4000			
Amoxicilline	**J01CA04**	30-10	2000			
Amoxicilline	**J01CA04**	<10	1000			
Ciprofloxacine	**J01MA02**	50-30	1000			
Ciprofloxacine	**J01MA02**	30-10	500			
Ciprofloxacine	**J01MA02**	<10	500			
Nitrofurantoine	**J01XE01**	50-30	0			
Nitrofurantoine	**J01XE01**	30-10	0			
Nitrofurantoine	**J01XE01**	<10	0			
Allopurinol	**M04AA01**	50-30	200			
Allopurinol	**M04AA01**	30-10	100			
Allopurinol	**M04AA01**	<10	0			
Metformine	**A10BA02**	50-30	1000			
Metformine	**A10BA02**	30-10	0			
Metformine	**A10BA02**	<10	0			

2019

Medication	**ATC code**	**eGFR**	**max appropriated daily dose based on eGFR, in mg**	***Total # prescriptions of drug dosed higher than appropriate dose in patients below eGFR, based on last known eGFR, 01/01/2019-31/12/2019***	***Total # prescriptions of drug regardless of dose, in patients below eGFR based on last known eGFR, 01/01/2019-31/12/2019***	**Ratio**
Ibuprofen	**M01AE01**	50-30	2400			
Ibuprofen	**M01AE01**	30-10	0			
Ibuprofen	**M01AE01**	<10	0			
Amoxicilline	**J01CA04**	50-30	4000			
Amoxicilline	**J01CA04**	30-10	2000			
Amoxicilline	**J01CA04**	<10	1000			
Ciprofloxacine	**J01MA02**	50-30	1000			
Ciprofloxacine	**J01MA02**	30-10	500			
Ciprofloxacine	**J01MA02**	<10	500			
Nitrofurantoine	**J01XE01**	50-30	0			
Nitrofurantoine	**J01XE01**	30-10	0			
Nitrofurantoine	**J01XE01**	<10	0			
Allopurinol	**M04AA01**	50-30	200			
Allopurinol	**M04AA01**	30-10	100			
Allopurinol	**M04AA01**	<10	0			
Metformine	**A10BA02**	50-30	1000			
Metformine	**A10BA02**	30-10	0			
Metformine	**A10BA02**	<10	0			

2020

Medication	**ATC code**	**eGFR**	**max appropriated daily dose based on eGFR, in mg**	***Total # prescriptions of drug dosed higher than appropriate dose in patients below eGFR, based on last known eGFR, 01/01/2020-31/12/2020***	***Total # prescriptions of drug regardless of dose, in patients below eGFR based on last known eGFR, 01/01/2020-31/12/2020***	**Ratio**
Ibuprofen	**M01AE01**	50-30	2400			
Ibuprofen	**M01AE01**	30-10	0			
Ibuprofen	**M01AE01**	<10	0			
Amoxicilline	**J01CA04**	50-30	4000			
Amoxicilline	**J01CA04**	30-10	2000			
Amoxicilline	**J01CA04**	<10	1000			
Ciprofloxacine	**J01MA02**	50-30	1000			
Ciprofloxacine	**J01MA02**	30-10	500			
Ciprofloxacine	**J01MA02**	<10	500			
Nitrofurantoine	**J01XE01**	50-30	0			
Nitrofurantoine	**J01XE01**	30-10	0			
Nitrofurantoine	**J01XE01**	<10	0			
Allopurinol	**M04AA01**	50-30	200			
Allopurinol	**M04AA01**	30-10	100			
Allopurinol	**M04AA01**	<10	0			
Metformine	**A10BA02**	50-30	1000			
Metformine	**A10BA02**	30-10	0			
Metformine	**A10BA02**	<10	0			

2021

Medication	**ATC code**	**eGFR**	**max appropriated daily dose based on eGFR, in mg**	***Total # prescriptions of drug dosed higher than appropriate dose in patients below eGFR, based on last known eGFR, 01/01/2021-31/12/2021***	***Total # prescriptions of drug regardless of dose, in patients below eGFR based on last known eGFR, 01/01/2021-31/12/2021***	**Ratio**
Ibuprofen	**M01AE01**	50-30	2400			
Ibuprofen	**M01AE01**	30-10	0			
Ibuprofen	**M01AE01**	<10	0			
Amoxicilline	**J01CA04**	50-30	4000			
Amoxicilline	**J01CA04**	30-10	2000			
Amoxicilline	**J01CA04**	<10	1000			
Ciprofloxacine	**J01MA02**	50-30	1000			
Ciprofloxacine	**J01MA02**	30-10	500			
Ciprofloxacine	**J01MA02**	<10	500			
Nitrofurantoine	**J01XE01**	50-30	0			
Nitrofurantoine	**J01XE01**	30-10	0			
Nitrofurantoine	**J01XE01**	<10	0			
Allopurinol	**M04AA01**	50-30	200			
Allopurinol	**M04AA01**	30-10	100			
Allopurinol	**M04AA01**	<10	0			
Metformine	**A10BA02**	50-30	1000			
Metformine	**A10BA02**	30-10	0			
Metformine	**A10BA02**	<10	0			

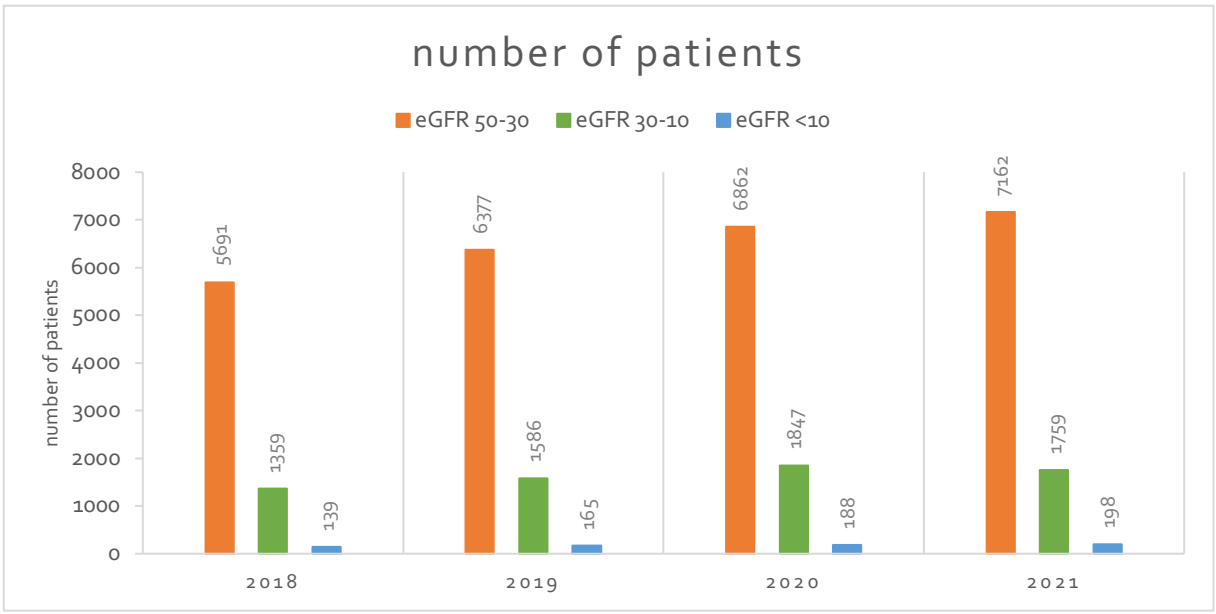
2022

Medication	**ATC code**	**eGFR**	**max appropriated daily dose based on eGFR, in mg**	***Total # prescriptions of drug dosed higher than appropriate dose in patients below eGFR, based on last known eGFR, 01/01/2022-31/12/2022***	***Total # prescriptions of drug regardless of dose, in patients below eGFR based on last known eGFR, 01/01/2022-31/12/2022***	**Ratio**
Ibuprofen	**M01AE01**	50-30	2400			
Ibuprofen	**M01AE01**	30-10	0			
Ibuprofen	**M01AE01**	<10	0			
Amoxicilline	**J01CA04**	50-30	4000			
Amoxicilline	**J01CA04**	30-10	2000			
Amoxicilline	**J01CA04**	<10	1000			
Ciprofloxacine	**J01MA02**	50-30	1000			
Ciprofloxacine	**J01MA02**	30-10	500			
Ciprofloxacine	**J01MA02**	<10	500			
Nitrofurantoine	**J01XE01**	50-30	0			
Nitrofurantoine	**J01XE01**	30-10	0			
Nitrofurantoine	**J01XE01**	<10	0			
Allopurinol	**M04AA01**	50-30	200			
Allopurinol	**M04AA01**	30-10	100			
Allopurinol	**M04AA01**	<10	0			
Metformine	**A10BA02**	50-30	1000			
Metformine	**A10BA02**	30-10	0			
Metformine	**A10BA02**	<10	0			

Appendix (4): **Results INTEGO**

	Number of patients		
	eGFR 50-30	eGFR 30-10	eGFR <10
2018	5691	1359	139
2019	6377	1586	165
2020	6862	1847	188
2021	7162	1759	198

Table 5: number of patients in each group, for each year

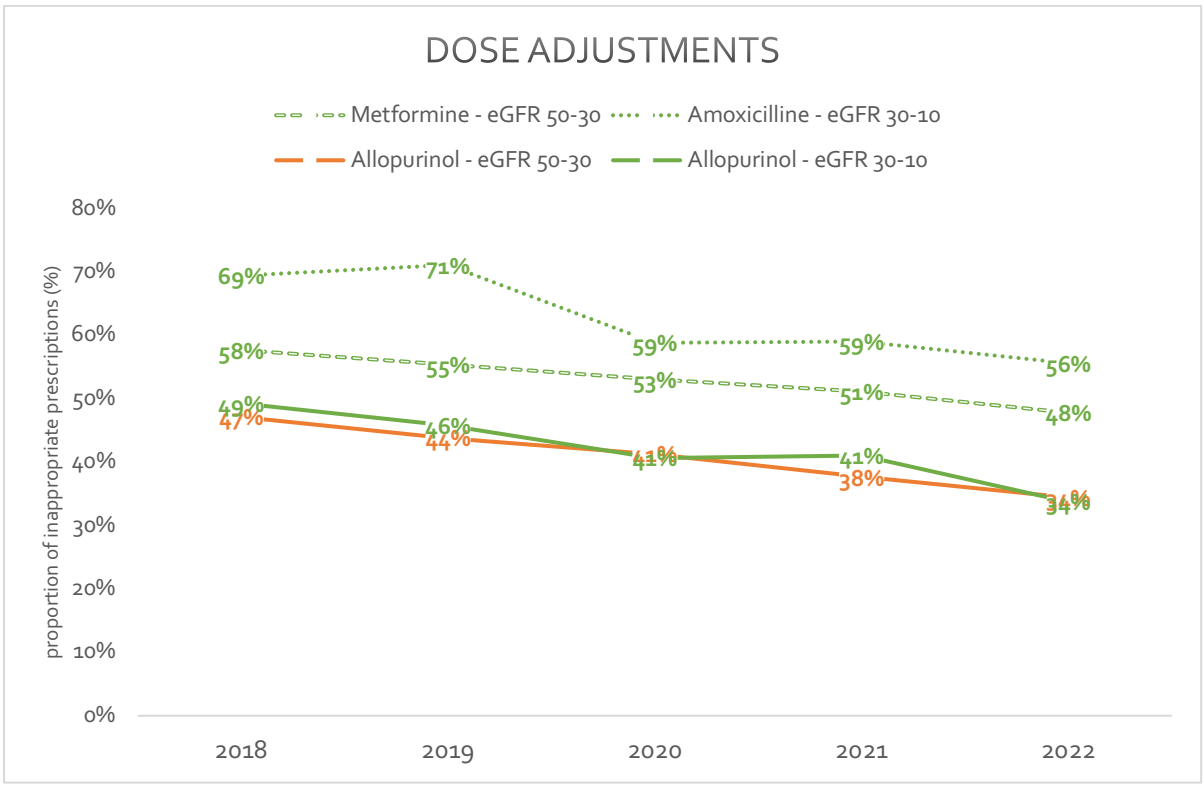


Graph 1: number of patients in each group

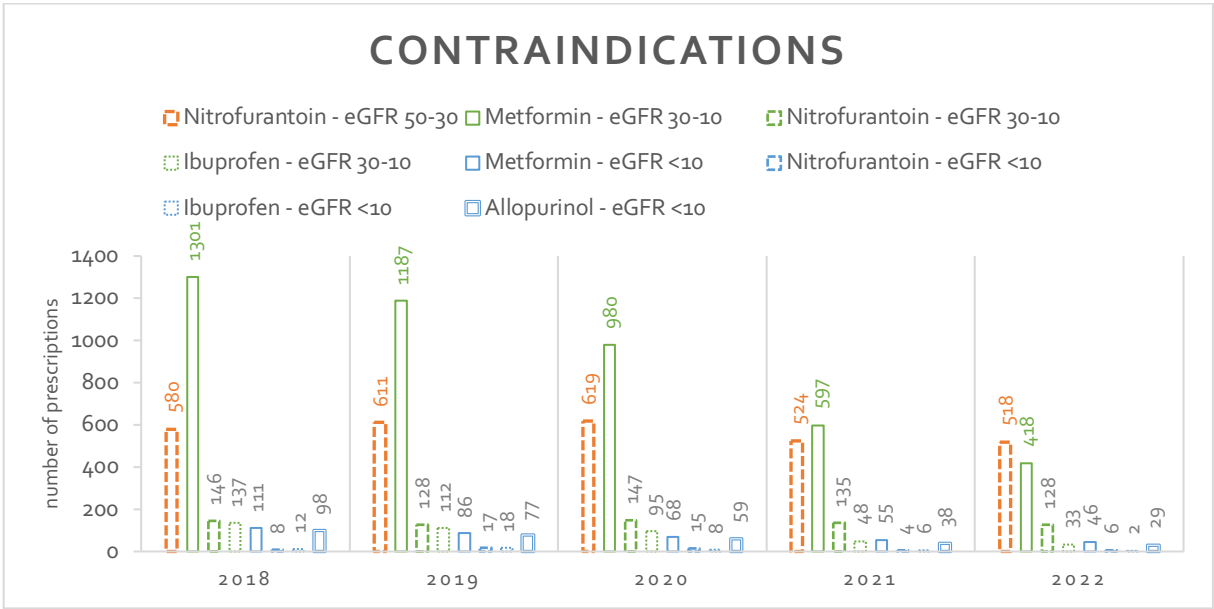
				2018			2019			2020			2021			2022		
MEDICATION	**ATC code**	**eGFR**	**Max appropriated daily dose based on eGFR, in mg**	***Inappropriate prescriptions****	***Total prescriptions*** **	**%**	***Inappropriate prescriptions****	***Total prescriptions*** **	**%**	***Inappropriate prescriptions****	***Total prescriptions*** **	**%**	***Inappropriate prescriptions****	***Total prescriptions*** **	**%**	***Inappropriate prescriptions****	***Total prescriptions*** **	**%**
Metformin	**A10BA02**	50-30	1000	2834	4918	**58%**	2747	4961	**55%**	2573	4854	**53%**	1952	3816	**51%**	1650	3455	**48%**
		30-10	Contraindication	**1301**	1301	100%	**1187**	1187	100%	**980**	980	100%	**597**	597	100%	**418**	418	100%
		<10	Contraindication	**111**	111	100%	**86**	86	100%	**68**	68	100%	**55**	55	100%	**46**	46	100%
Amoxicillin	**J01CA04**	30-10	2000	195	281	**69%**	211	297	**71%**	87	148	**59%**	60	108	**56%**	69	117	**59%**
		<10	1000	43	45	**96%**	34	38	**89%**	23	24	**96%**	6	6	**100%**	10	10	**100%**
Ciprofloxacin	**J01MA02**	50-30	1000	25	360	**7%**	13	316	**4%**	6	336	**2%**	14	358	**4%**	32	305	**10%**
		30-10	500	84	140	**60%**	73	120	**61%**	56	102	**55%**	70	113	**62%**	58	91	**64%**
		<10	500	5	21	**24%**	5	11	**45%**	7	12	**58%**	4	14	**29%**	1	5	**20%**
Nitrofurantoin	**J01XE01**	50-30	Contraindication	**580**	580	100%	**611**	611	100%	**619**	619	100%	**524**	524	100%	**518**	518	100%
		30-10	Contraindication	**146**	146	100%	**128**	128	100%	**147**	147	100%	**135**	135	100%	**128**	128	100%
		<10	Contraindication	**8**	8	100%	**17**	17	100%	**15**	15	100%	**4**	4	100%	**6**	6	100%
Ibuprofen	M01AE01	30-10	Contraindication	**137**	137	100%	**112**	112	100%	**95**	95	100%	**48**	48	100%	**33**	33	100%
		<10	Contraindication	**12**	12	100%	**18**	18	100%	**8**	8	100%	**6**	6	100%	**2**	2	100%
Allopurinol	**M04AA01**	50-30	200	1113	2364	**47%**	1102	2518	**44%**	994	2412	**41%**	856	2274	**38%**	822	2390	**34%**
		30-10	100	444	902	**49%**	422	922	**46%**	332	818	**41%**	297	725	**41%**	214	635	**34%**
		<10	Contraindication	**98**	98	100%	**77**	77	100%	**59**	59	100%	**38**	38	100%	**29**	29	100%

Table 6: Overview of the investigated medication, the number of inappropriate prescriptions per eGFR category for each year between 2018 and 2022 compared to the total number of prescriptions.

* Total amount of prescriptions dosed higher than appropriate dose, based on last known eGFR, 01/01/20xx-31/12/20xx ** Total amount of prescriptions of drug regardless of dose, in patients below eGFR, based on last known eGFR, 01/01/20xx-31/12/20xx



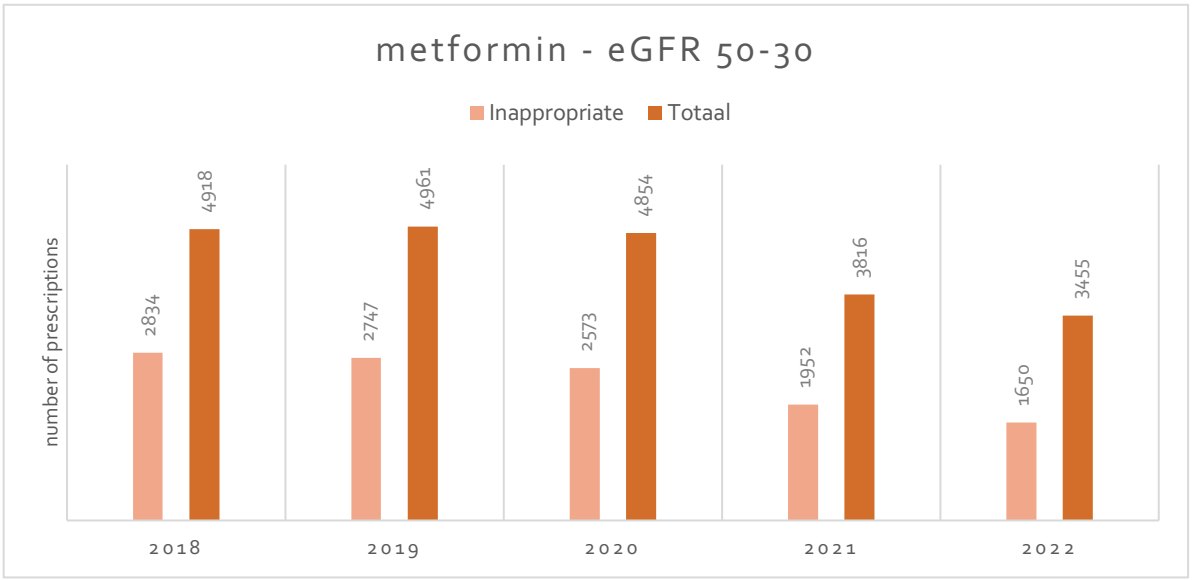
Graph 2: Trend in proportion of inappropriate prescriptions in medication with dose-adjustments



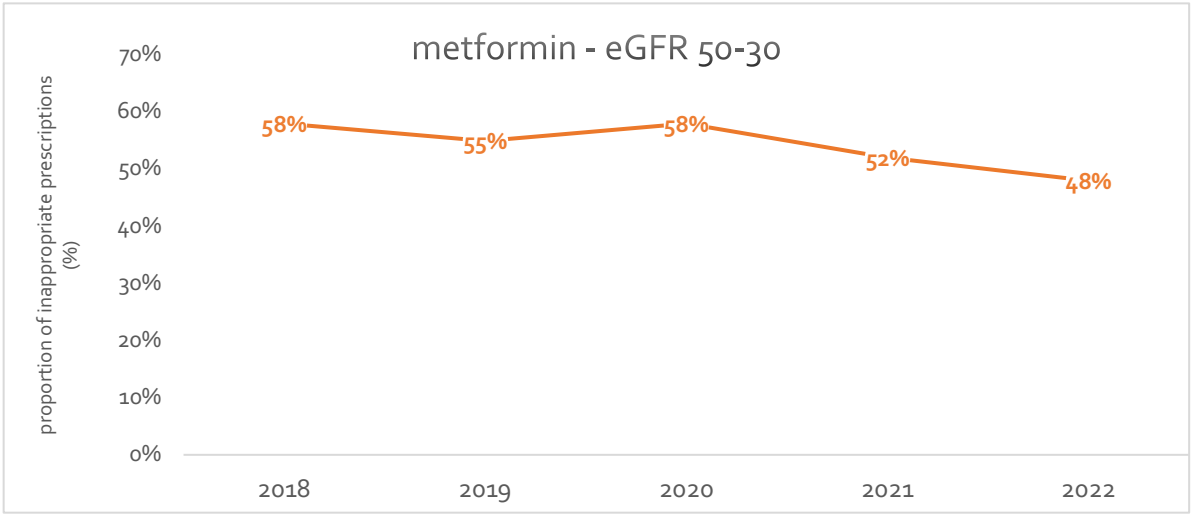
Graph 3: Trend in number of prescriptions in medication with contraindications

Metformin

eGFR 50-30

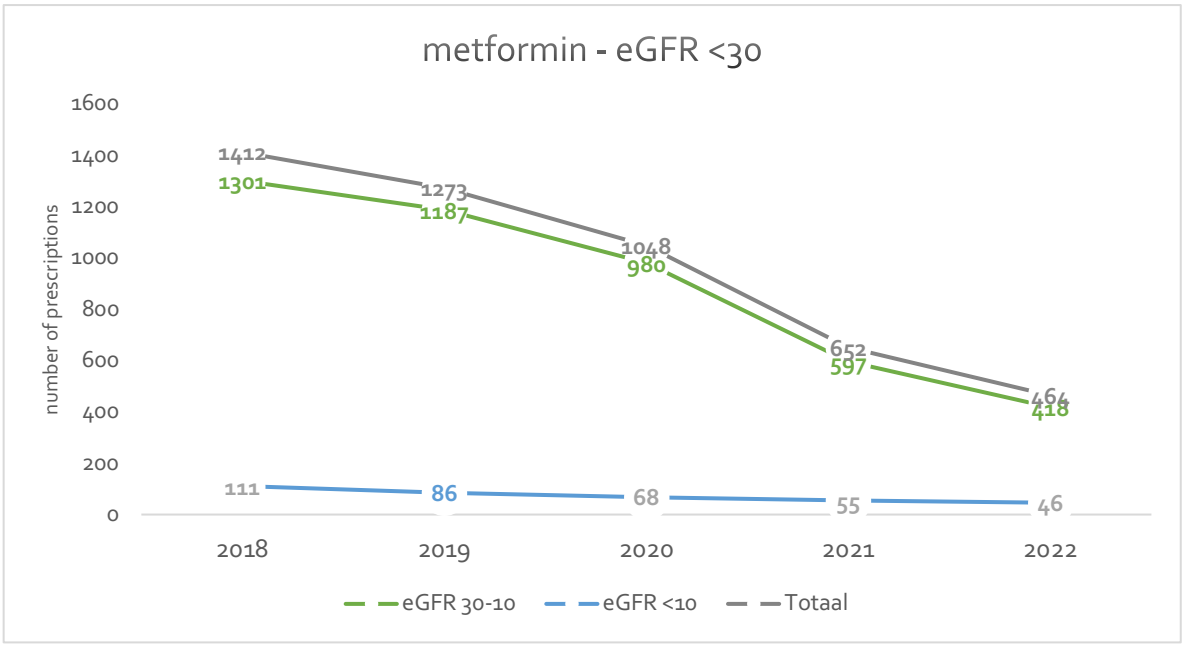


Graph 4: Trend in number of prescriptions in METFORMIN – eGFR 50-30



Graph 5: Trend in proportion of inappropriate prescriptions in METFORMIN – eGFR 50-30

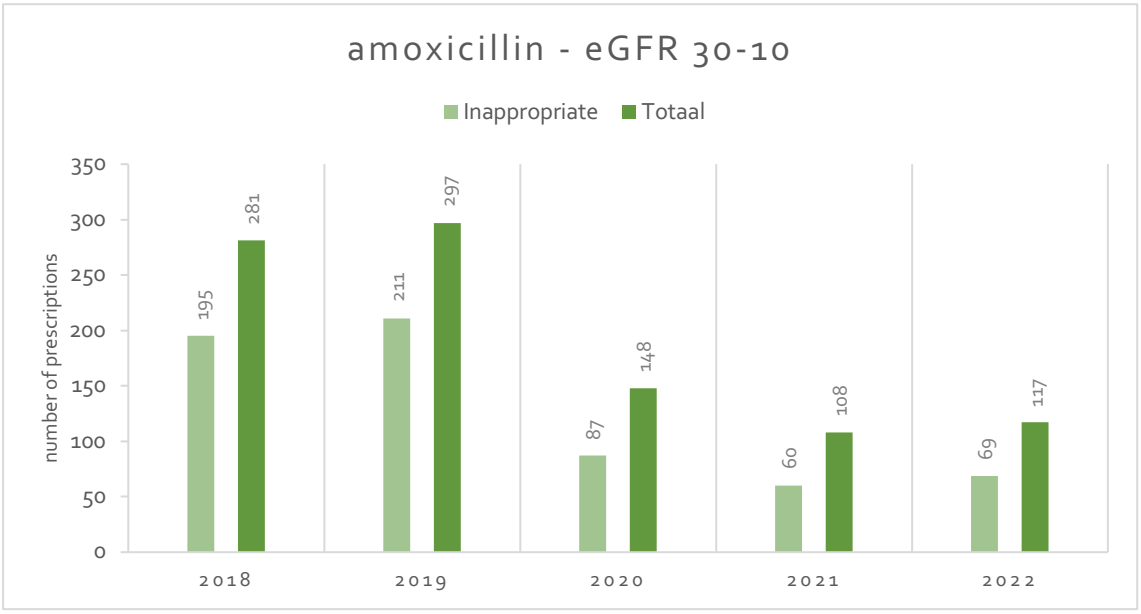
eGFR 30-10 & eGFR <10



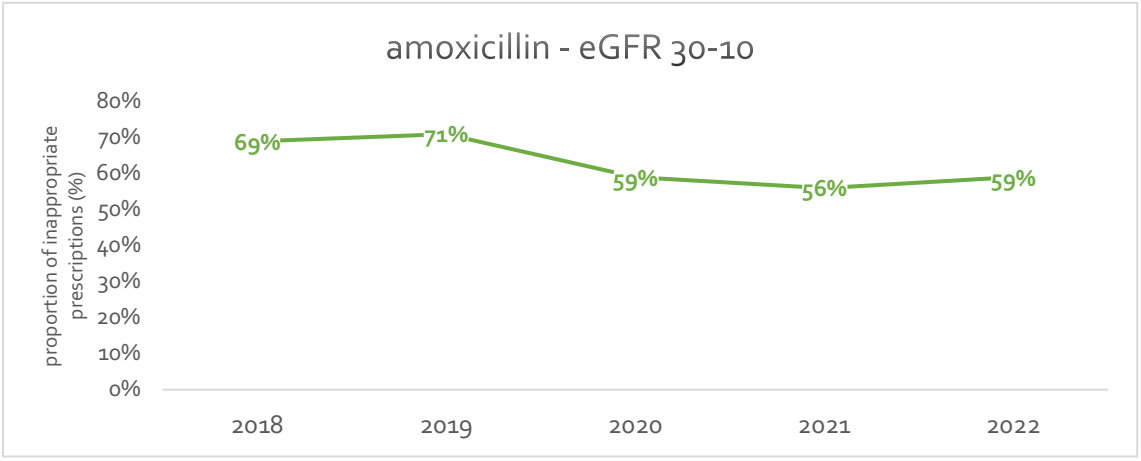
Graph 6: Trend in proportion of inappropriate prescriptions in METFORMIN – eGFR <30

Amoxicilline

eGFR 30-10

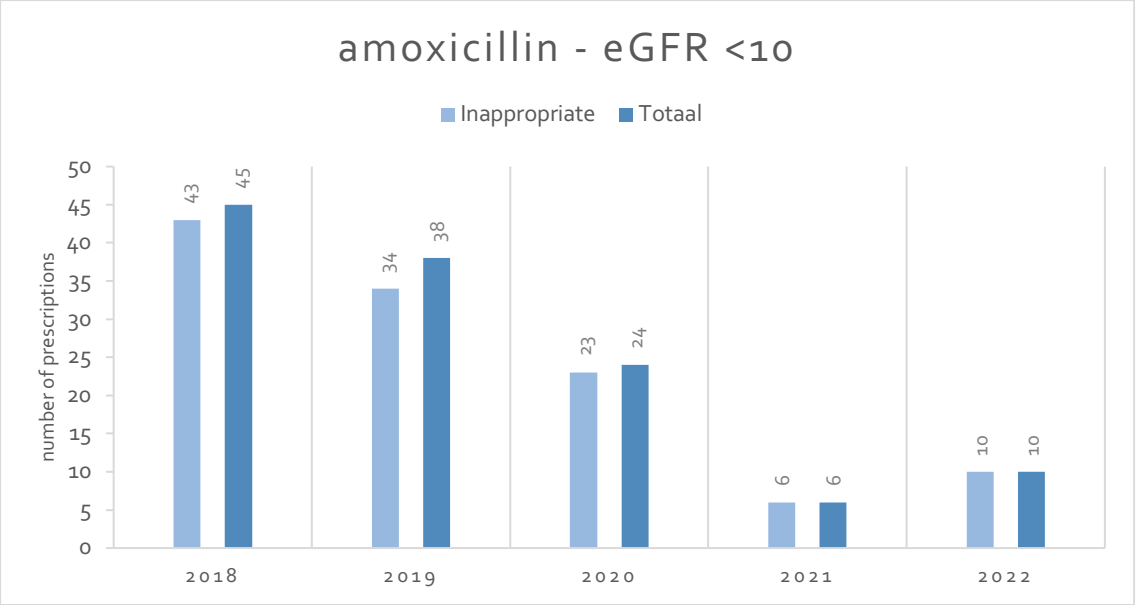


Graph 7: Trend in number of prescriptions in AMOXICILLIN – eGFR 30-10

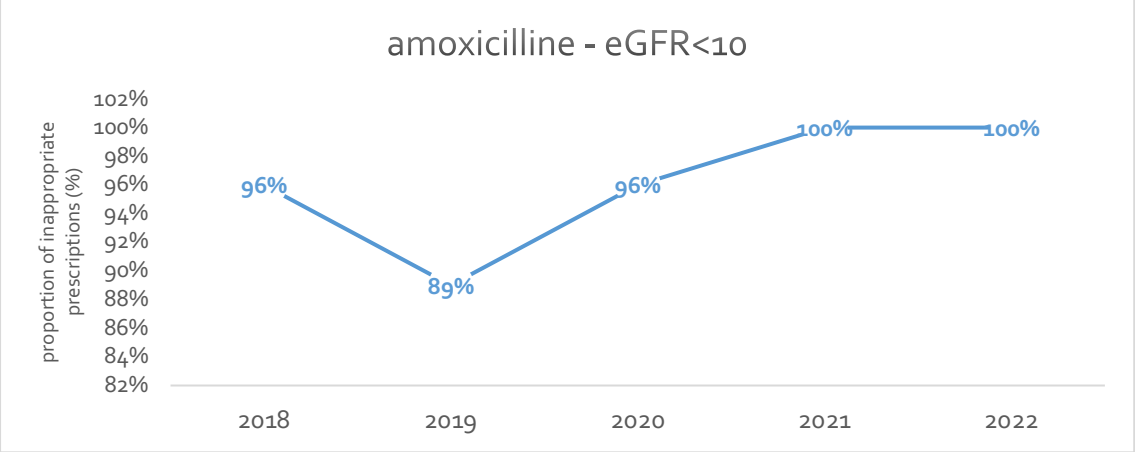


Graph 8: Trend in proportion of inappropriate prescriptions in AMOXICILLIN – eGFR 30-10

eGFR <10



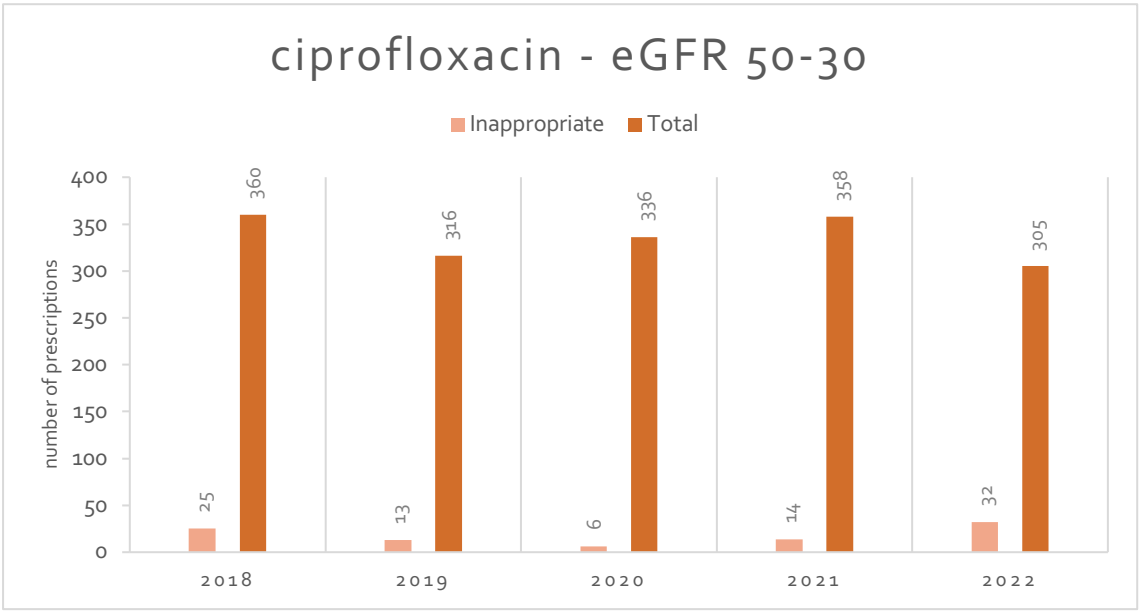
Graph 9: Trend in number of prescriptions in AMOXICILLIN – eGFR <10



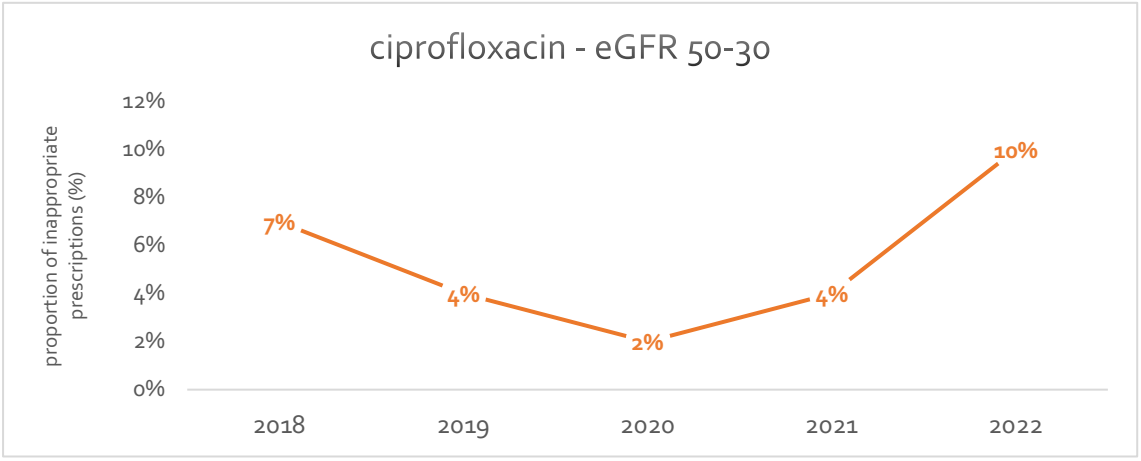
Graph 10: Trend in proportion of inappropriate prescriptions in AMOXICILLIN – eGFR <10

Ciprofloxacine

eGFR 50-30

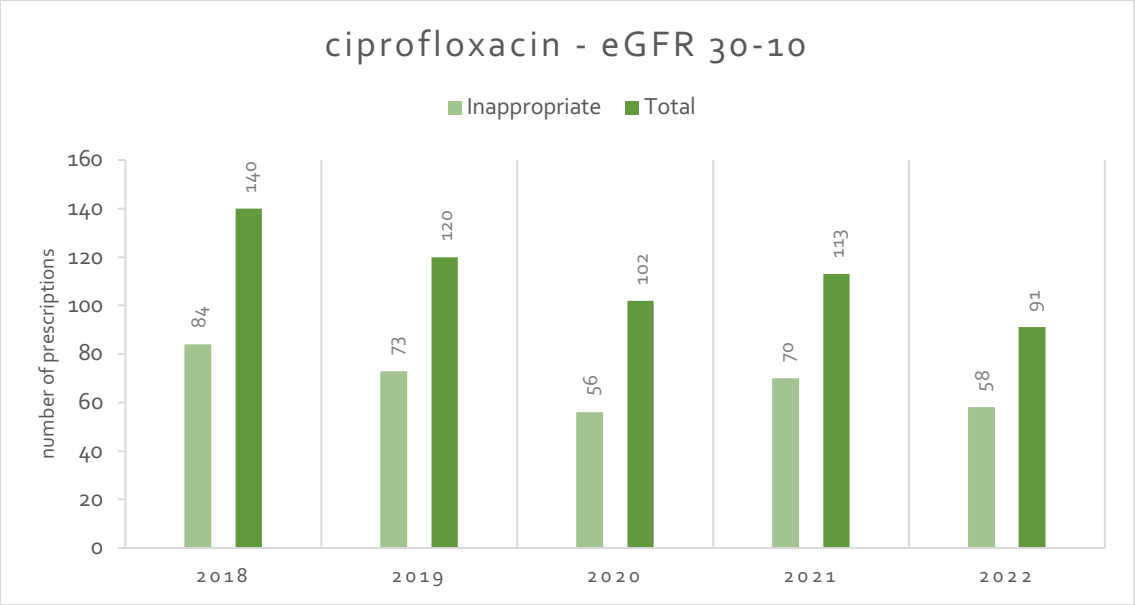


Graph 11: Trend in number of prescriptions in CIPROFLOXACIN – eGFR 50-30

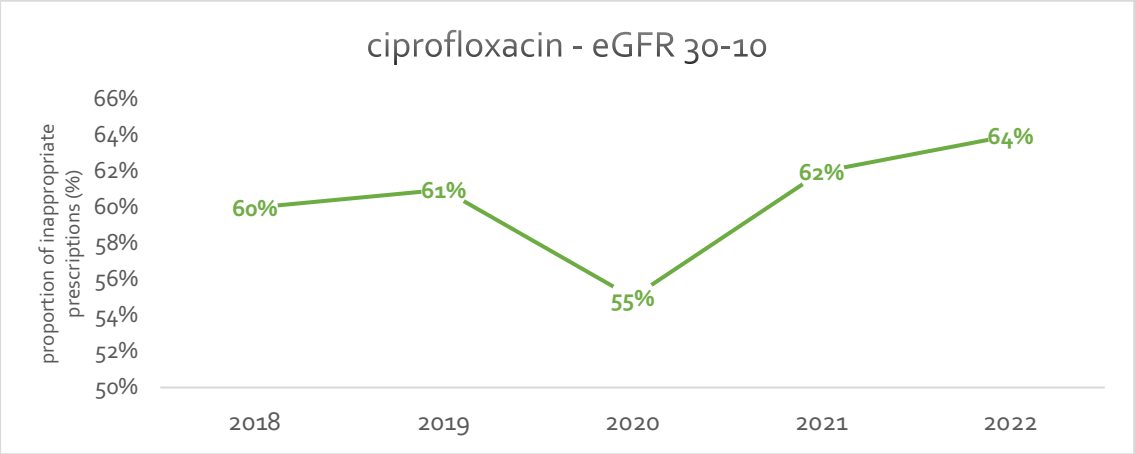


Graph 12: Trend in proportion of inappropriate prescriptions in CIPROFLOXACIN – eGFR 50-30

eGFR 30-10

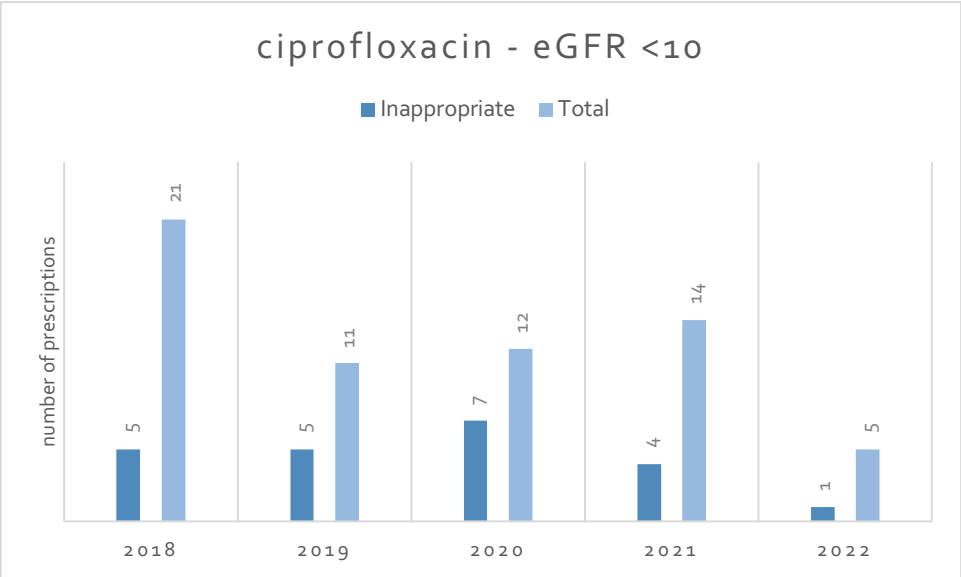


Graph 13: Trend in number of prescriptions in CIPROFLOXACIN – eGFR 30-10

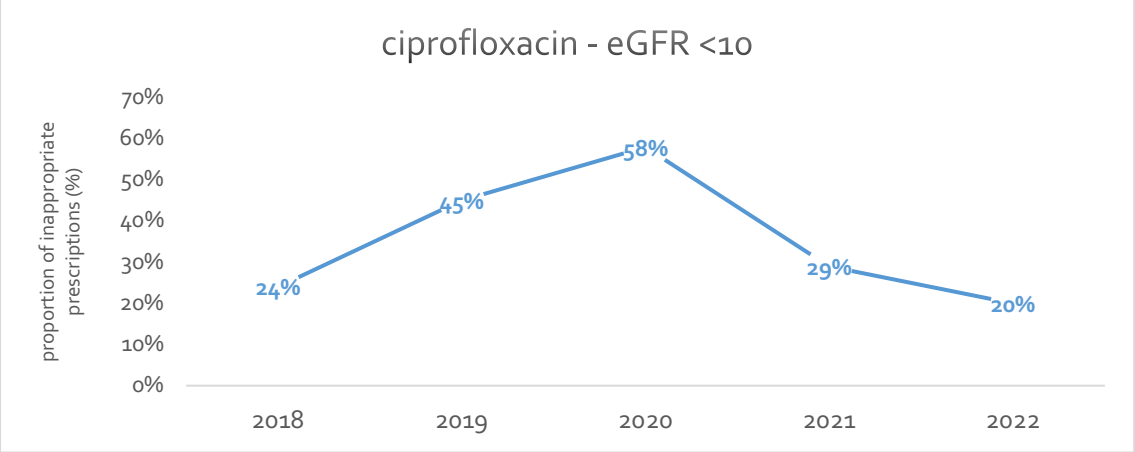


Graph 14: Trend in proportion of inappropriate prescriptions in CIPROFLOXACIN – eGFR 30-10

eGFR <10



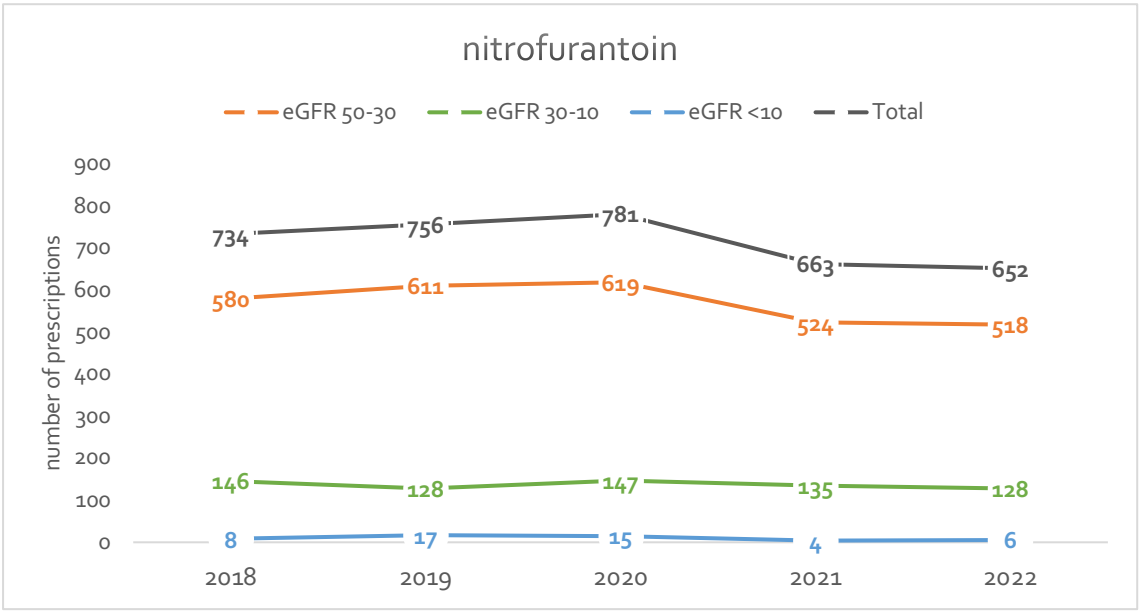
Graph 15: Trend in number of prescriptions in CIPROFLOXACIN – eGFR <10



Graph 16: Trend in proportion of inappropriate prescriptions in CIPROFLOXACIN – eGFR <10

Nitrofurantoin

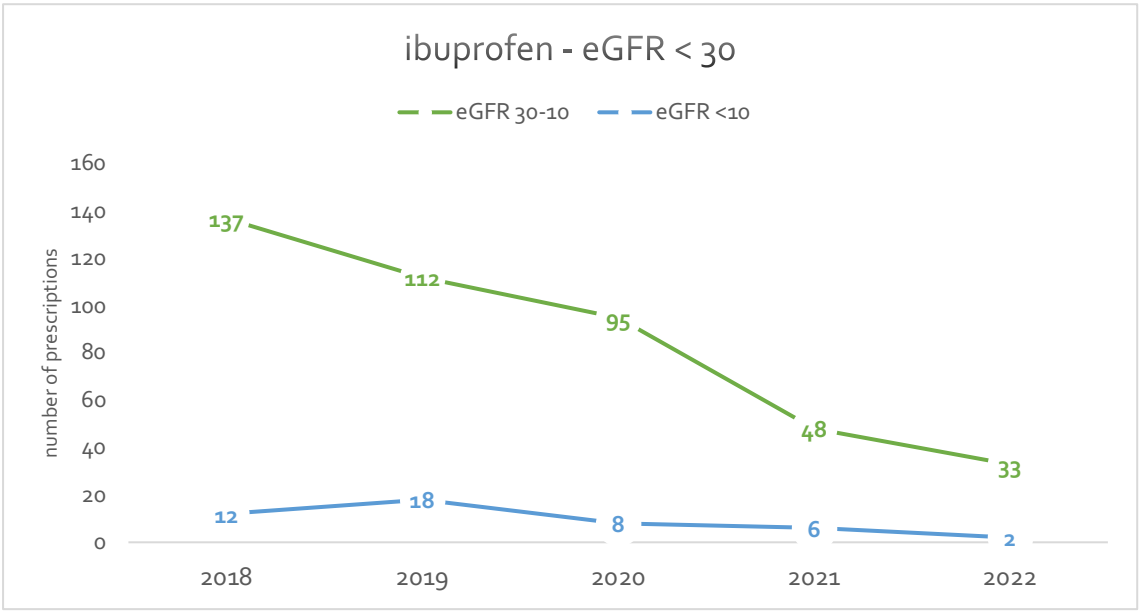
eGFR 50-30 & eGFR 30-10 & eGFR <10



Graph 17: Trend in number of prescriptions in NITROFURANTOIN – eGFR <50

Ibuprofen

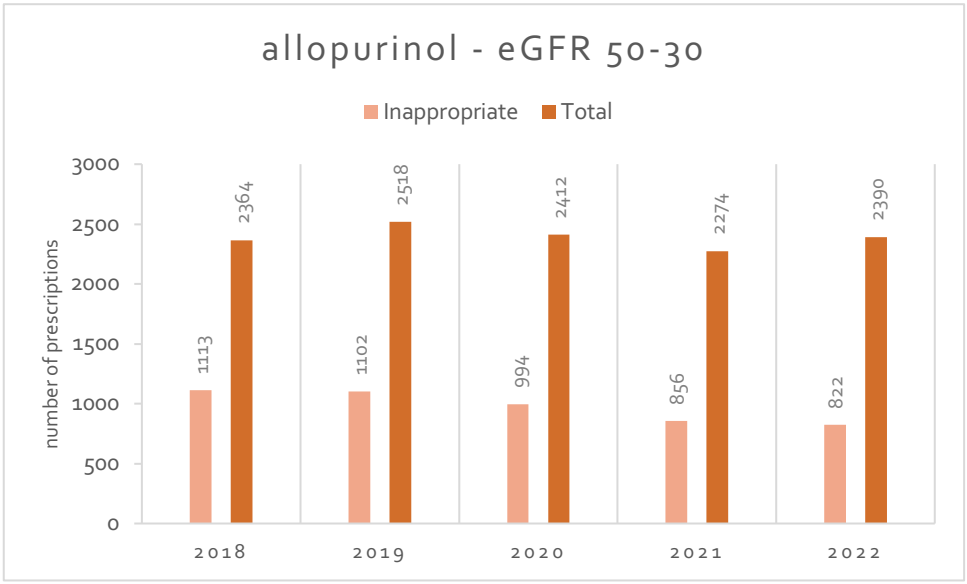
eGFR 30-10 & eGFR <10



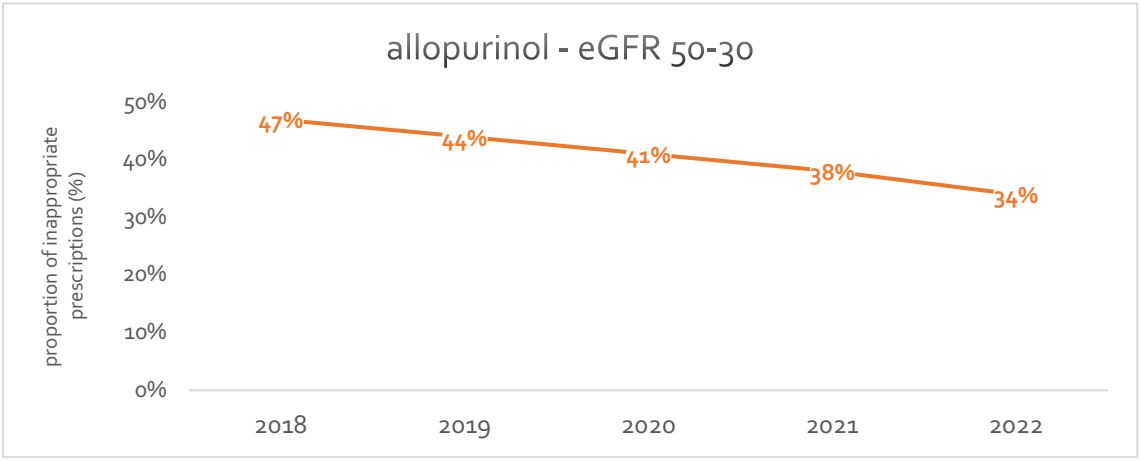
Graph 18: Trend in number of prescriptions in IBUPROFEN – eGFR <30

Allopurinol

eGFR 50-30

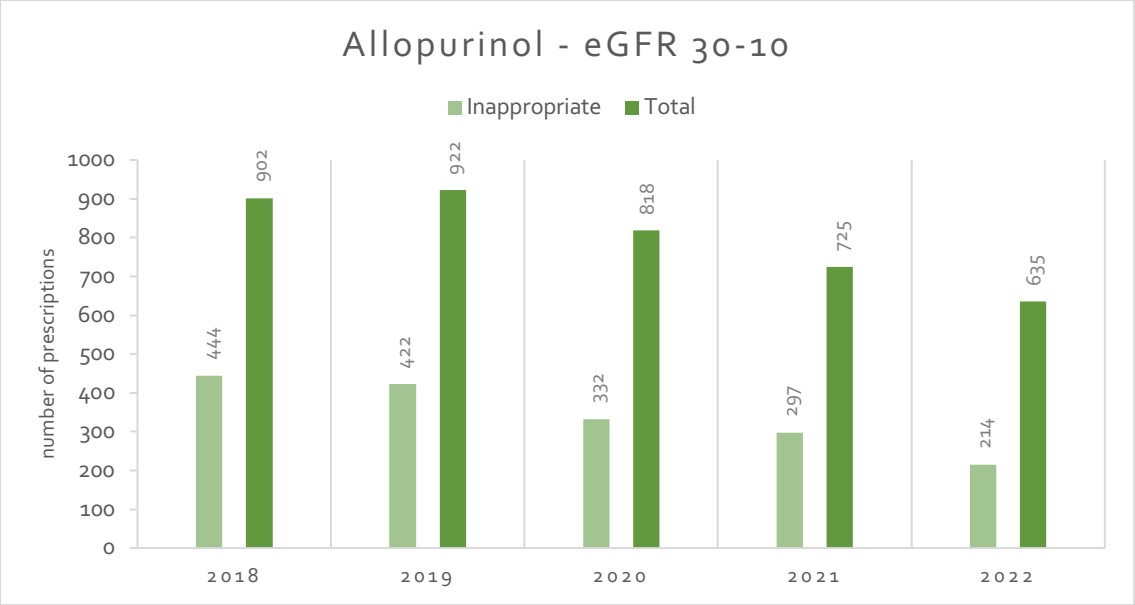


Graph 19: Trend in number of prescriptions in ALLOPURINOL – eGFR <10

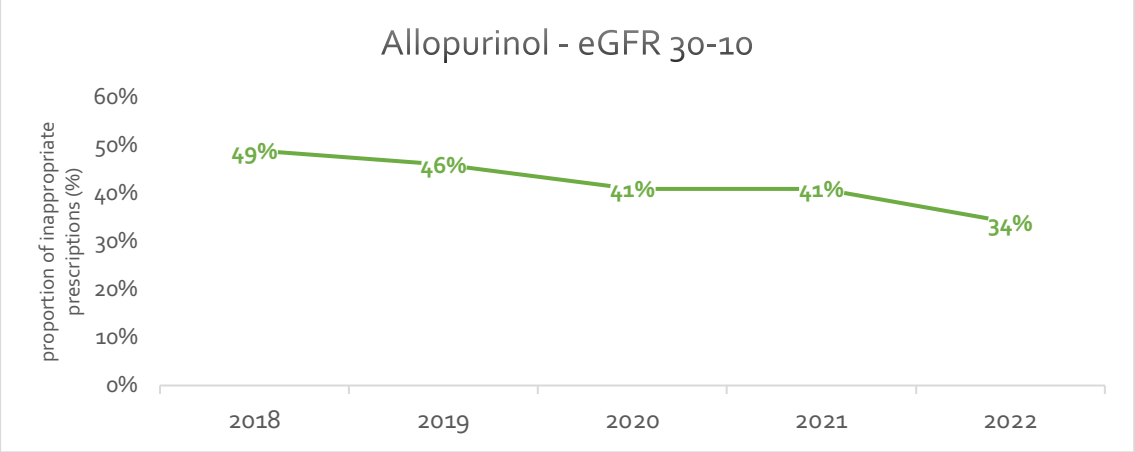


Graph 20: Trend in proportion of inappropriate prescriptions in ALLOPURINOL – eGFR 50-30

eGFR 30-10

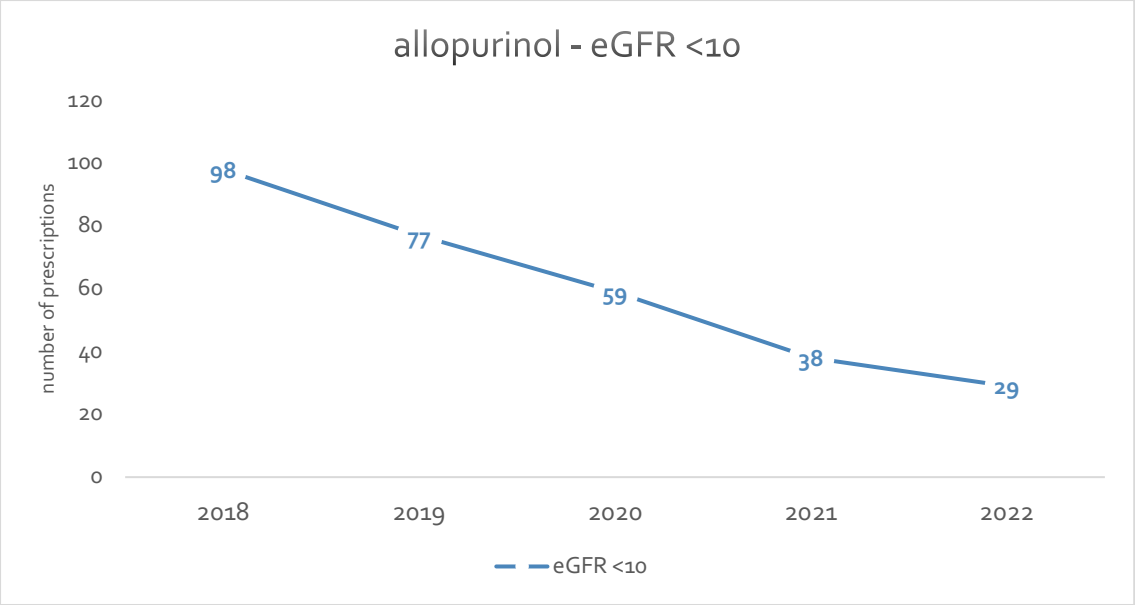


Graph 21: Trend in number of prescriptions in ALLOPURINOL – eGFR 30-10



Graph 22: Trend in proportion of inappropriate prescriptions in ALLOPURINOL – eGFR 30-10

eGFR <10



Graph 23: Trend in number of prescriptions in ALLOPURINOL – eGFR <10

Appendix (5): **Literature study**

* PUBMED/Medline (laatste search op 22/05/2021)

=> Search with **Renal Insufficiency, Chronic"[Mesh]**", combining with following [Mesh]-terms:

- **"Prevalence"[Mesh]**
- **"Comorbidity"[Mesh]**
- **"Diabetes Mellitus"[Mesh] OR "Hypertension"[Mesh]**
- **"Physicians, Primary Care"[Mesh]**
- **("Inappropriate Prescribing"[Mesh]**

=> Results:

("Renal Insufficiency, Chronic"[Mesh] AND "Prevalence"[Mesh])

-> hits: 1394
=> filters: Reviews, publication < 5y -> hits: 144
=> based on title -> Hits: 9
*=> based on abstract -> **Hits: 3***

("Renal Insufficiency, Chronic"[Mesh] AND "Comorbidity"[Mesh])

-> hits: 3784
=> filters: Reviews, publicatiedatum < 5j -> hits: 142
=> based on title -> hits: 6
*=> based on abstract -> **hits: 3***

("Renal Insufficiency, Chronic"[Mesh]) AND ("Diabetes Mellitus"[Mesh] OR "Hypertension"[Mesh])

-> hits: 3489
=> filters: Reviews, publicatiedatum < 5j -> hits: 608
=> based on title itel -> hits: 18
*=> based on abstract -> **hits: 10***

("Renal Insufficiency, Chronic"[Mesh]) AND "Physicians, Primary Care"[Mesh])

-> Hits: 49
=> based on title itel -> hits: 10
*=> based on abstract -> **hits: 7***

("Renal Insufficiency, Chronic"[Mesh] AND ("Inappropriate Prescribing"[Mesh]))

-> Hits: 58
=> based on title -> hits: 17
=> based on abstract -> hits: 12

* EMBASE (laatste search op 22/05/2021)

Search with a combination of same of similar seach terms yielded no additional results

* DOMUS MEDICA richtlijn

* Mertens, Ann, et al. "Noodzakelijke Dosisaanpassingen Voor Vaak Gebruikte Medicatie Bij Patiënten Met Een Gedaalde Nierfunctie: Een Poging Om Door De Bomen Het Bos Te Zien." Tijdschrift Voor Geneeskunde, vol. 70, no. 21, 2014, pp. 1279–1294.

* "snowball effect" -> useful publications in references of found articles

=> total of **37 hits**

Appendix (5): **Onderzoeksprotocol**

ONDERWERP

Medicatiegebruik onaangepast aan nierfunctie bij chronische nierinsufficiëntie

TYPE

Kwalitatief onderzoek of kwantitatieve research

ACHTERGROND

Chronische nierinsufficiëntie is een veelvoorkomend en belangrijk gezondheidsprobleem, zeker in de oudere populatie. De nierfunctie is o.a. onderhevig aan leeftijd en nierziekten. Vaak moet echter ook rekening gehouden worden met de aanwezigheid van co-morbiditeiten als Diabetes Mellitus, hartfalen en hypertensie, die allen eveneens een invloed hebben op de nierfunctie van de patiënt. Ook gebruik van medicatie onaangepast aan de nierfunctie van de patiënt kan een belangrijke impact hebben met niet alleen ontstaan van belangrijke neveneffecten van medicatie, maar ook verdere achteruitgang van nierfunctie. Het correct voorschrijven van medicatie bij patiënten met chronische nierinsufficiëntie is dan ook primordiaal. Als huisarts spelen wij dan ook een belangrijke rol in het correct voorschrijven van deze medicatie en is het tevens onze taak om te waken over een effectief correct gebruik van de medicatie bij deze patiëntenpopulatie. Onderzoek heeft in het verleden echter reeds aangetoond dat dit, ondanks het gebruik van hulpmiddelen, niet evident blijkt te zijn. Daarom rijst de vraag of de afgelopen jaren een evolutie te zien is in het onaangepast aan nierfunctie voorschrijven van medicatie bij patiënten met chronische nierinsufficiëntie.

ONDERZOEKSVRAAG

Wat is de evolutie in het onaangepast medicatiegebruik aan de nierfunctie bij patiënten met chronische nierinsufficiëntie tussen 2018 -2022

GEPLANDE ONDERZOEKSMETHODE

Retrospectief observationeel onderzoek op de INTEGO Databank, exploratieve analyse

STUDIEPROTOCOL INTEGO

C. Truyers, G. Goderis, H. Dewitte, M. vanden Akker and F. Buntinx, "The Intego database: background, methods and basic results of a Flemish general practice-based continuous morbidity registration project," *BMC Medical Informatics and Decision Making*, vol. 14, no. 48, 2014.

Appendix (6):

Goedkeuring Ethische Commissie

Since this study is an integral part of an existing study that has already been approved by a recognized ethics committee, it was not necessary to submit a new file. The study was conducted at "het Academisch centrum voor huisartsgeneeskunde" at KULeuven.

Medicatiegebruik onaangepast aan nierfunctie bij chronische nierinsufficiëntie, evolutie voorbije 10 jaar

Dossiernr.:	MP018583
Masterproef:	Masterproef I HAIO, 2020 – 2023
Faculteit/opleiding:	Faculteit Geneeskunde - Master in de huisartsgeneeskunde
Studiefase:	eerste fase
Academiejaar:	2021-2022
Gewenste taal van communicatie:	nl
Promotor:	Prof Bert Aertgeerts (u0002409)
Copromotor:	Dr. Gijs Van Pottelbergh (u0064216)
Organisatie:	KU Leuven
Dienst:	Academisch Centrum voor Huisartsgeneeskunde
Discipline:	Masterproef
Extra groepsleden:	Frauke Leroy frauke.leroy@student.kuleuven.be r0468261

De verstrekte informatie toont aan dat het onderzoek in het kader van de masterproef integraal deel uitmaakt van een studie die reeds werd goedgekeurd door een erkend ethisch comité.

U hoeft bijgevolg geen nieuw dossier in te dienen in het kader van uw masterproef. Wel dient u het UZ/KU Leuven toe te voegen als nieuw deelnemend centrum aan het huidige dossier indien dit nog niet het geval was. Gelieve u bij het betreffende comité te informeren en u te conformeren aan de daar geldende procedures en hun adviezen te volgen.

Onder voorbehoud van de volledigheid en correctheid van de door u verstrekte gegevens, krijgt u hierbij de goedkeuring om het onderzoek in het kader van de masterproef te starten.

Wij willen u erop attent maken dat u zelf verantwoordelijk blijft voor uw onderzoek. Bovendien doet elke wijziging aan de door u verstrekte gegevens omtrent de onderzoeksopzet elke eerdere goedkeuring vervallen. U dient in dat geval een amendement te maken aan uw huidig dossier bij het comité dat eerder uw dossier goedkeurde.