THE COSTS AND BENEFITS OF DEPRESCRIBING PROTON PUMP INHIBITORS.

In collaboration with the Twentse apothekers organisatie (TAO-UA).

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Abstract

Background and objective: The use of Proton pump inhibitors (PPIs) has been at an all-time high in the Netherland for many years now. This resulted in an steady increase in concern about the long term safety of PPIs. Especially since many of the PPI users often lack a clear indication for it. Both the increased concern and the lack of a clear indication makes the deprescribing of PPIs an interesting possibility. This was also true for the Twentse Apothekers Organisatie (TAO-UA) who started a deprescribing pilot for PPIs. The aim of this project was to estimate the economic impacts that deprescribing PPIs has for the population of the TAO-UA, including a long term side effect. Furthermore the project aims to determine which patient group inside the population of the TAO-UA gains the most benefit from deprescribing.

Methods: Initially, a literature review was performed using both Pubmed and Embase. The aim of this review was investigate which long term side effect would be the most influential one. After this a cohort level Markov model was made in R-studio based on potential kidney damage. This was done to perform a cost-utility analysis. The model was used to run a simulation for the pilot itself, a diabetic scenario, a loop diuretic using scenario and an age-based scenario. For these runs the uncertainty around the model inputs were also taken into account. Finally several runs were performed for 8 individual TAO-UA pharmacies. During these runs different patient characteristics were introduced and the economic impact for an average TAO-UA pharmacy could be estimated.

Results and discussion: The literature review showed that Chronic Kidney Disease (CKD) was one of the most promising long-term side effect from a cost-effectiveness point of view. The review also showed that both diabetics and diuretic users had an extra risk of CKD associated to it when using PPIs. Therefore different ages, diabetics and loop diuretic users were expected to be the most promising groups for deprescribing. The run for the pilot showed that deprescribing PPIs was likely to dominate nodeprescribing with on average a cost reduction of €6414 while also gaining 0.122 QALYs per person, even when taking into account the uncertainty around the inputs. In a scenario where the population of the pilot was either 100% diabetic or 100% using diuretics the impact of deprescribing increased to a cost reduction of €7537 while also gaining 0.138 QALYs per person and a cost reduction of €7797 while also gaining 0.147 QALYs per person respectively. When looking at different age-groups inside the pilot the younger population (<60 years) was the most cost-effective with a cost reduction of €17262 while also gaining 0.960 QALYs per person. The older population (>60 years) was the least cost-effective with a cost reduction of €3996 while also gaining 0.061 QALYs per person. Finally an average TAO-UA pharmacy was expected to have a cost reduction of €11363 while also gaining 0.366 QALYs per person. This required an initial investment of around €17.47 per person (of the population who remained after the first deprescribing selection step) excluding annual follow-up.

Conclusion: Deprescribing was expected to the dominant strategy for an average TAO-UA pharmacy with on average a cost reduction of €11363 while also gaining 0.366 QALYs per person. This required an initial investment of around €17.47 per person with annual follow-up excluded. If not everyone in the population can be deprescribed the younger population should be prioritized.

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Introduction

Proton pump inhibitors (PPIs) have, since their introduction more than 25 years ago (1), become the medication of choice for many patients to treat acid-related disorders. When compared to earlier agents like histamine$_2$ receptor antagonists the new drug was more potent, while still providing an excellent safety profile (2). Therefore it was not unlikely that PPIs would end up replacing other medication. The rise of PPIs did however not stop with only the substitution of older agents as its increase in popularity vastly exceeds the use of earlier agents. This resulted in PPIs, like omeprazol and pantoprazole, being the most popular medication for many years now in the Netherlands with combined more than 2.5 million users in 2020 (3). In many cases however the use of PPIs did not come with a clear indication as PPIs are one of the medications with the highest probability to be wrongfully prescribed (4). Also the rise of PPIs did not go unnoticed and a growth in literature followed soon after. With the concern about the long term safety of PPI use being a subject in the literature for more than a decade (5) and Dutch media still writing about it today (6).

The lack of a clear indication in the majority of users and the continued concern about the long term side effects fostered interest in the deprescribing of PPIs. Deprescribing is the practice of stopping, withdrawing or reducing medications which are unsafe, inappropriate or ineffective (7). The deprescribing of PPIs is however still in its infancy and the expected benefits or costs related to it are still unknown. Therefore no compensation is currently given for the deprescribing of PPIs, which hinders the implementation in daily practice. To raise interest for deprescribing PPIs the Twentse Apothekers Organisatie (TAO-UA) started a pilot consisting of a small group of patients. The aim of this pilot and of this project was to estimate the economic impacts of deprescribing PPIs for the population of the TAO-UA. Furthermore the project aims to determine which patient group gains the most benefit from deprescribing and should be targeted.

PPIs are available in a lot of different delivery systems like gelatin capsules, enteric-coated tablets, supplied as a powder for suspension or coated granules. These delivery systems are used to protect the medication from degradation by gastric acid. (8) After the medication passes the stomach it is quickly absorbed in the small bowel. Once PPIs have reached the circulation they transit to the parietal cells, where they get activated by acid-catalyzed cleavage. Once activated it binds covalently to the H+/K+ ATPase, which is also known as a proton pump. The binding of PPIs to the proton pump results in the inhibition of acid secretion. This effect can last for around 15 to 21 hours, as new proton pumps have to be synthesized for it to subside. (1) If the use of chronic PPI is halted it can be accompanied by a rebound effect that will subside over time (9). This rebound effect is caused by the sudden increase of acid secretion, because PPIs are no longer inhibiting the proton pumps. This might however confuse the patient as into thinking there previous symptoms have returned and they will restart the use of PPIs. To prevent this from happening careful instruction and coaching from a health care provider is important in the deprescribing process.

To determine whether a long-term prescription of PPIs is justified the correct indications has to be known. According to Dutch guidelines the chronic use of PPIs is only justified for Barrett's esophagitis, Zollinger Ellison syndrome and Reflux esophagitis grade C or D (10). Furthermore PPIs are used in situations where the stomach has to be protected. This is true for medication which can irritate the lining of the stomach like Non-steroidal anti-inflammatory drug (NSAIDs) or low-dose salicylates. The use of these type of medications itself is however not enough to justify the chronic use, as several extra risk factors have to be met. These risk factors mainly consist of age and co-medication. (11)

Background

Introduction and material & methods

A scoping review was performed to find the most promising adverse event related to long term use of PPIs, which could be used in the creation of the model. To start, a search was performed in PubMed on “PPIs” and “adverse events”. During this initial search multiple summaries were found about the potential long term adverse events. After this all the adverse events were indexed: fracture, hypomagnesemia, micronutrient deficiency (vitamin B12 and iron), pneumonia, clostridium difficile infection, microbiome, enteric infections, cardiac events, cancer, dementia, fundic gland polyps and renal disease. Many preliminary individual searches were performed for each of the adverse events. All the searches can be found in **background appendix 1**. The goal of the preliminary searches was to measure the amount of studies available in the literature. This was often measured with the help of a meta-analysis or a systematic review. If no such article was found the search was repeated in Embase.

After the preliminary search a couple of adverse events were excluded as they had less data available in the literature compared to the others. Furthermore during the preliminary searches an expert review by Freedberg et al (Background reference list: 13) was found. This review provided absolute excess risks and ranked the strength of the current evidence. The main focus from here on out consisted of adverse events found in this review. These adverse events were acute kidney injury, acute interstitial nephritis, chronic kidney disease, end stage renal disease, kidney dysfunction, osteoporosis related fractures, dementia, Salmonella & Campylobacter, Community acquired pneumonia, clostridium difficile and digestive tract cancers.

With the adverse events now locked in another search was performed, but now with the goal to find the most recent meta-analysis or systematic review. An example of this search can be seen in **Figure 1**. The key search used in this example was ("PPI" or "Proton pump inhibitors" or "Omeprazol" or "Pantoprazol") and (“CDI” or “Clostridium difficile infection”). Initially the key search was entered into PubMed and afterwards the NCBI filter of “systematic reviews & metaanalyses” was enabled. The remaining articles were screened by looking at the title. If the title did not contain both a variation of the keyword C. difficile and PPIs the articles were excluded. Afterwards the remaining articles were screened to look if a full-text was available in English. If this was not true the article was also discarded. In the end the most recent article was selected. The search was repeated for each adverse event.

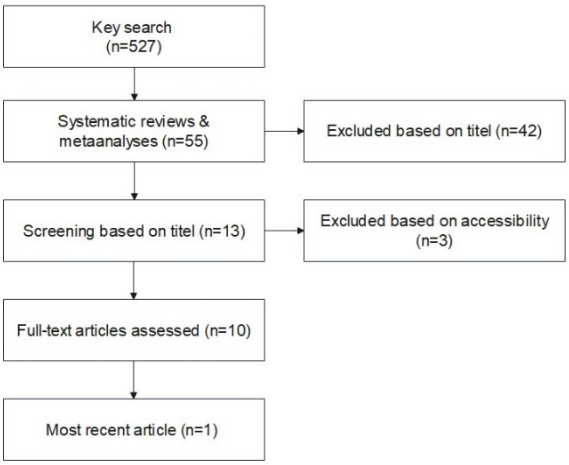

Figure 1 *Flow diagram used to find the most recent meta-analysis or systematic review. Key search: ("PPI" or "Proton pump inhibitors" or ("PPI" or "Proton pump inhibitors" or "Omeprazol" or "Pantoprazol") and (“CDI” or “Clostridium difficile infection”). The search was performed in PubMed.*

Afterwards the prevalence and costs were researched. This was primarily done with the data obtained from volksgezondheidenzorg.info. If no results were available the search was also performed in PubMed and If still no data was available a more generalized search in google was performed. Furthermore an effort was made to find if an economic model had already been made in the past. This was done in PubMed and the key searches can be found in the **background appendix 1**.

Finally newer studies for each of the adverse events were determined. This was done with the searches found in **background appendix 1**. For each search a cutoff date was set depending on the final search date of the meta-analysis.

Results and Discussion

The long term adverse events caused by PPI use are quite popular in recent literature. Therefore a plethora of different adverse events could be found. These adverse events could be categorized into 7 groups: kidney, bone, neurologic, gastro-intestinal, cardiovascular, infections and cancers. In this scoping review 5 out of the 7 different groups are featured. Only gastro-intestinal and cardiovascular were not implemented.

The choice to not implement the gastro-intestinal and cardiovascular groups were based on the available evidence, the impact of the adverse event and the ability to compare the outcome to a generalized audience. For example cardiovascular literature was often performed in a very specific patient group. Also major cardiovascular event (MACE) was often used in the literature. This is an overarching term with a definition that often differs between studies. Finally gastro-intestinal adverse event were not included, because the impact of the disease was considered to be very minor. An example of this would be fundic gland polyps or changes in the microbiome. In both cases the clinical relevance of these disease are still unknown.

One of the adverse events related to the kidney was acute kidney injury (AKI). AKI occurs in a situation in which the kidney does not receive enough blood or when significant damage to the kidney has taken place. This results in a rapid decline of kidney function. Another potential cause of AKI is acute interstitial nephritis (AIN). In which an allergic reaction, potentially caused by PPIs, leads to inflammation of the tubulus located on the kidney. Other adverse events are chronic kidney disease (CKD) and end stage renal disease (ESRD) where the kidney function expressed in estimated glomerular filtration rate (eGFR) is respectively lower than 60 and 15 ml/min/1,73 m^2. The final adverse event of the kidney was the progression of the kidney dysfunction. This was stated by the studies as a decrease in kidney function of 30 ml/min/1,73 m^2 in a period of 5 years.

Other adverse events found in the literature were osteoporosis and fractures, often combined as osteoporosis related fractures. Furthermore the onset of dementia (neurologic) was possibly caused by the use of PPIs and PPI use was associated with many different infections like Clostridium difficile infection (CDI), community acquired pneumonia (CAP) and gastro-enteritis by Salmonella or Campylobacter. Finally PPI use was associated with pancreatic-, stomach-, liver- and colorectal cancer.

Table 1 shows different potential adverse event related to PPIs. For each adverse event the most recent meta-analysis was discovered. Afterwards the strength of the found association, as stated by the meta-analysis, was measured as either significant or not significant. Also the absolute extra risk (per patient / per year) to get the adverse event from the continues use of PPIs can be seen. This was obtained from de meta-analysis itself, the individual studies included in the meta-analysis or from a review of Freedberg et al (Background reference list: 13). Finally the total amount of patients for each meta-analysis was revealed.

Table 1 *The potential adverse events of PPIs with the corresponding meta-analysis. The references can be found in the background reference list.*

Adverse event	Latest meta-analysis	Association	Absolute excess risk (per patient/year)	Patients (n)
Acute kidney injury (AKI)	Wu et al (2018); (1)	Significant	0.151% (12) tot 0.83% (43)	2,396,640
Acute interstitial nephritis (AIN)	Wu et al (2018); (1)	Significant	0.008% (2) tot 0.021% (43)	585,39
Chronic kidney disease (CKD)	Hussain et al (2019); (2)	Significant	0.1 tot 0.3% (13)	804,836
End stage Renal disease (ESRD)	Hussain et al (2019); (2)	Significant	0.015% (45) tot 0.034% (44)	469,141
progression kidney disfunction	Hussain et al (2019); (2)	Significant	1.499% (44) tot 1.637% (45)	461,525
Osteoporosis-related fractures	Liu et al (2019); (3)	Significant	0.1 tot 0.5% (13)	1,478,667
Dementia	Kyu-Tae et al (2021); (4)	Non-significant	Non-significant	394,582
Salmonella and Campylobacter	Hafiz et al (2018); (5)	Significant	0.03 tot 0.2% (13)	…
Community aquired pneumonia (CAP)	Xun et al (2021); (6)	Significant	1.850% (47)	2,098,804
Clostridium difficile Infectie (CDI)	Oshima et al (2018); (7)	Significant	0 tot 0.09% (13)	297,649
Digestive tract cancers	Zeng et al (2021); (8)	Significant	…*	4,355,254

** For stomach cancer an absolute extra risk of 0.147% was found.*

For each adverse event a corresponding meta-analysis was found. In almost all of the cases a statistically significant association between PPI use and the adverse event was found. Only for dementia this was not the case. Furthermore the meta-analysis of Hussain et al (Background reference list: 2) found an association between the use of PPIs and the onset of CKD, ESRD and progression of kidney dysfunction. This association was even more noticeable in a diabetic or diuretic using population. While liu et al (Background reference list: 3) mainly focused on osteoporosis-related fractures also an association was found for non-osteoporosis-related fractures. Additionally the meta-analysis by Xun et al (Background reference list: 6) found an increased risk of getting CAP for patients who survived a stroke, but also for patients only using PPIs. Finally an association was visible for pancreatic-, stomach- and colorectal cancer. The association was however questioned by the author, because these types of cancers are often accompanied by stomach acid related problems in the early onset of the disease. Therefore PPIs could be used to counter the stomach acid related problems of the cancer instead of causing it. This evidence is further strengthened by the fact that the study also looked at esophageal- and liver cancer, for which stomach acid related problems are not common symptoms. In this case no significant association was found.

The biggest absolute extra risk associated with the use of PPIs was the chance of a patient to get CAP, with an absolute extra risk of 1.85% per patient/year. Also the worsening of the kidney function had a high absolute extra risk. This was estimated to be around 1.5% to 1.6% per patient/year. Furthermore AKI and CKD had a relatively high absolute extra risk of 0.151% to 0.83% per patient/year and 0.1% to 0.3% per patient/year respectively. The other side effects related to the kidney, namely AIN and ESRD, were associated with a lower absolute extra risk of 0.008% to 0.021% per patient/year and 0,015% to 0,034% respectively. Osteoporosis related fractures were comparable to the effect seen for AKI and CKD with 0.1% to 0.5% per patient/year. Additionally PPI use was associated with an absolute extra risk of 0 to 0.09% to get CDI and an absolute extra risk of 0.03% to 0.2% for Salmonella and Campylobacter infections. Finally it was impossible to determine an absolute extra risk for all the individual types of digestive tract cancers, because the individual studies from the meta-analysis did not include patient years. For stomach cancer however an absolute extra risk of 0.147% was found.

Table 2 shows newer literature for each adverse event which was too recent to be implemented in the meta-analysis. The evidence obtained from these studies either strengthened or weakened the association found in the meta-analysis and the individual studies can be found in **Background appendix 3**. Furthermore the average amount of new studies each year was determined. This was done to measure the interest about the subject in the literature. Finally existing economic models were gathered, as they could help with the making of the model.

Table 2 *New literature compared to the meta-analysis. The references can be found in the background reference list.*

Adverse event	New (observational) studies	Average amount of new studies per jaar	Inspiration for the model
Acute kidney injury	5 (+)	1.0	kerr et al (2014); (33)
Acute interstitial nephritis	0	0.0	…
Chronic kidney disease	10 (+)	2.4	Sugrue et al (2019); (34)
End stage Renal disease	3 (+) and 1 (-)	1.0	Sugrue et al (2019); (34)
progression kidney disfunction	5 (+) and 3 (-)	1.9	Sugrue et al (2019); (34)
Osteoporosis-related fractures	8 (+) and 1 (-)	2.6	Si et al (2014); (35). Moriarty et al (2019); (36)
Dementia	1 (+) and 5 (-)	1.7	li et al (2018); (37). Hernandez et al (2016); (38)
Salmonella and Campylobacter	1 (+)	0.3	Herrick et al (2012); (39)
Community aquired pneumonia	Recent	Recent	…
C. difficile	6 (+)	1.2	Moriarty et al (2019); (36)
Digestive tract cancers	Recent	Recent	…

The adverse event with the most studies per year were the osteoporosis related fracture, with on average 2.6 new studies per year. Almost all of these newer studies found results corresponding to the meta-analysis. The same could be said for CKD, but in this case no studies were found which contradicts the findings of the meta-analysis. For the progression of the kidney dysfunction 5 new studies were found which strengthened the findings of the meta-analysis, however there were also 3 studies which contradicted it. Furthermore for dementia only newer studies were found where no association could be seen that dementia is caused by PPI use. This correlates with the finding of the meta-analysis. Additionally AKI, ESRD and C. Difficile had about the same amount of new studies per year. For AKI and C. difficile the new found studies strengthened the finding of the meta-analysis. For ESRD 3 studies strengthened the evidence, but also 1 weakened it. The adverse events with the least new literature written about them where gastro-enteritis caused by Salmonella or Campylobacter and AIN. Finally no new studies were found for the different digestive tract cancers and CAP. This was most likely caused by the fact that the meta-analyses in question where very recent (2021) at the time of the search.

Also literature which could be useful for the model building process can be found in **Table 2**. One study contained a model in which the deprescribing of PPIs stood central. This study was done by Moriarty et al (Background reference list: 36) in 2019. Their model focused on C. Difficile and an osteoporosis related fracture (hip fracture) in the Irish healthcare system. They also focused on other potentially significant medication to deprescribe, like benzodiazepines and NSAIDs. For CKD and ESRD a lot of models could be found in the literature, which were summarized in a systematic review. Therefore a good foundation for the economic model was possible. The same was true for dementia. Finally for AKI, Salmonella an Campylobacter only one model each was discovered.

In **Table 3** the quality of the literature was measured for each of the adverse events. To start an average Newcastle-Ottowa Scale (NOS) was given for the individual studies used in the meta-analysis. This was obtained from the meta-analysis itself and gives an indication of the quality of the individual non-randomized studies. A NOS score can be categorized into 3 groups: low risk of bias (NOS > 7), medium risk of bias (4 ≤ NOS ≤ 7) and a high risk of bias (NOS < 4). Secondly a "A Measurment Tool to Assess systematic Reviews 2" (AMSTAR2) score can be seen. This gives an indication of the quality of the meta-analysis itself. These scores were obtained from two Umbrella reviews by Salvo et al (Background reference list: 10) and Veettil et al (Background reference list: 11). The ARMSTAR2 score can be categorized into 4 groups: high (the systematic review provides an accurate and comprehensive summary of the results), moderate (… may provide …), low (… may not provide …) and very low (… should not provide …). Finally a Grading of Recommendations Assessment, Development and Evaluation (GRADE) score is present in the table. The GRADE score gives an assumptions on how much the expected effect corresponds to the true effect. The GRADE scores were obtained from a review by Freedberg et al (Background reference list: 13) and can be categorized into 4 groups: high, mediocre, low and very low.

Table 3 *Quality of the found literature. The references can be found in the background reference list.*

Adverse event	Latest meta-analysis	Average NOS	Amstar2 (10) / (11)	GRADE (13)
Acute kidney injury (AKI)	Wu et al (2018); (1)	7.9	low / …	very low
Acute interstitial nephritis (AIN)	Wu et al (2018); (1)	7.9	Low / …	very low
Chronic kidney disease (CKD)	Hussain et al (2019); (2)	8.8	Moderate / Low	very low
End stage Renal disease (ESRD)	Hussain et al (2019); (2)	8.8	Moderate / Low	very low
progression kidney disfunction	Hussain et al (2019); (2)	8.8	Moderate / Low	very low
Osteoporosis-related fractures	Liu et al (2019); (3)	7	Low / Moderate	(very) low
Dementia	Kyu-Tae et al (2021); (4)	…	… / …	very low
Salmonella and Campylobacter	Hafiz et al (2018); (5)	6.4	Moderate / Moderate	…
Community aquired pneumonia (CAP)	Xun et al (2021); (6)	7.1	… / …	very low
Clostridium difficile	Oshima et al (2018); (7)	…	Low / …	low
Digestive tract cancers	Zeng et al (2021); (8)	7.2	… / …	very low

The found quality of the individual studies (NOS score) had on average a medium to a high risk of bias. Also no real distinction could be made based on the quality of the meta-analysis (AMSTAR2 score), because no meta-analysis was considered to be of a high quality. Finally the quality of evidence for each of the adverse events was either low or very low. This was due the fact that mainly observational studies were included in the meta-analysis. Therefore the benefits of the therapy, if there is a clear indication**,** outweigh the potential risks.

A large randomized control trial (RCT) of 53,152 patients years was performed by Maoyyedi et al (Background reference list: 14) in 2019. This RCT showed no significant difference between the control group and the PPI users for many of the adverse events named in this literature review. Only for the enteric infections a significant difference was found. The usability of the RCT was question by many of the authors, because the RCT would not be able to detect long term adverse events with only a follow-up time of 3 years.

In **Table 4** the prevalence and healthcare costs for each of the adverse events can be found. The prevalence and total healthcare costs are based on a Dutch situation. With both the prevalence and healthcare costs an estimation was made for the cost per patient by dividing the (total healthcare) costs with the prevalence. This was done to more easily compare the different adverse events. If the total healthcare costs or prevalence were not available the cost per patients was obtained from literature.

Table 4 *Costs and prevalence for each of the different adverse events. The references can be found in the background reference list.*

Adverse event	Prevalence	Costs (mln €)	Cost per patient (€)
Acute kidney injury	…	…	…
Acute interstitial nephritis	…	…	…
Chronic kidney disease	20,183 (a)	…	7,526 (b)
End stage Renal disease	17,902 (17)	763 (18)	42,620 (c)
progression kidney disfunction	…	…	…
Osteoporosis-related fractures	38,966 (20)	190 (20)	4876.000
Dementia	290,000 (21)	9052,9 (3)	31,216
Salmonella and Campylobacter	44,000 (22)	36 (22)	818
Community aquired pneumonia	253,800 (24)	412.8* (24)	1,626
C. difficile	4,671 (d)	…	16,978 (e)
Digestive tract cancers	94,320 (f)	827.6 (f)	8,774 (f)

*37% of the total healthcare costs are from patients younger than 1 year.
(a) It is expected that around 10% of the Dutch population has asymptomatic CKD. The prevalence seen here is only for patients who are registered by the nephrologist and do not have an indication for dialysis or kidney transplant (15).
(b) The costs are estimated on several co-morbidities closely related to CKD (15).
(c) For dialysis patients the costs are higher: €77,566 to €105,833. A kidney transplant has in the first year around the same cost as a dialysis, but this decrease in the following years (19).
(d) 15 contaminations per 10,000 hospital admissions (25); 3,114,065 hospital admission in the Netherlands in 2019 (46).
(e) In the age categories 65–74, 75–84 and ≥85 the average hospital costs were €8674, €8770 and €619 respectively (26).
(f) Combination of all the found digestive tract cancers without liver cancer (see **background appendix 2**).

The highest cost per patient was seen in ESRD with €42,630. This value contains both dialysis and kidney transplant. If only dialysis was taken into account the cost per patients would be even higher (€77,556 to €105,833). Dementia was also quite costly with €31,216 per patient and had the highest total healthcare costs between all of the different adverse events. Also C. difficile was relatively high with on average €16,978 per patient. This can be explained by the fact that C. difficile often occurs in a hospital setting and therefore safety measures have to be taken to prevent an outbreak, which are costly. The remaining adverse events were relatively cheap (<€10,000 per patient). Only by isolating hip fractures costs were found of €11,000 to €13,000 per patient. This was high compared to the average cost of €4,876 for all the osteoporosis-related fractures. Furthermore digestive tract cancers cost on average €8,774 per patient. There is however quite a disparity in costs between the individuals cancers, which can be seen in **background appendix 2**. An example of this would be pancreatic cancer with an average cost of €45,817 per patient. Furthermore CAP and gastro-enteritis from Salmonella and Campylobacter had the lowest cost per patient with €1,626 and €818 respectively. Finally no costs or prevalence for AKI, AIN and progressing kidney dysfunction were available.

In **Table 5** the pros and cons for each adverse event was summarized. The adverse events related to the kidney had the most benefits for this project. They had the highest cost per person, were very prominent in the literature and clear potential risk groups were given. Also the model could be based on kidney function. This would make the model more complex, but also more representative to a target population. Another promising adverse event were osteoporosis related fractures, which consists out of multiple individual fractures. This opens up the possibility to combine a lot of different indications into the model. The downside of this adverse event was that a similar deprescribing cost-analysis had recently been performed. This was also true for C. difficile. Another option would be to focus on the adverse event with the strongest evidence, namely gastro-enteritis caused by Salmonella or Campylobacter. For these infections a statistically significant correlation was determined in a RCT. The downside of this adverse event was the low cost per patient corresponding to it. Furthermore CAP had an overall high cost, but the majority of the costs were derived from patients younger than one year, where deprescribing is not that common. Also the cost per patient was relatively low, but the absolute excess risk was among the highest. Another possible adverse event were the digestive tract cancers which, depending on the cancer, have a high cost and disease burden. The association between PPIs and the cancers could be accounted to the fact that in the early onset of the disease stomach related symptoms often occur. Therefore the PPIs are prescribed to treat a symptom caused by the cancer and do not cause the cancer itself. Finally the association between dementia and PPIs was not backed up by the recent findings from literature.

Table 5 *Pros and Cons of the adverse events.*

Adverse infect	Pros	Cons
Kidney	Many different individual adverse events, high cost/disease burden, often talked about in literature, clear guidelines for the model, higher risk diabetic patients and diuretic users	Lowest absolute excess risk for ESRD which has the highest costs
Osteoporosis-related fractures	often talked about in literature , relatively high cost/disease burden, relatively high absolute excess risk	Recent cost-effectiveness analysis performed for deprescribing PPIs
Dementia	Highest overall healthcare costs, often talked about in literature, clear guidelines for the model	The literature is divided about the correlation, Not statistically significant in the meta-analysis
Salmonella and Campylobacter	Randomized Control Trial shows association	Lowest cost/disease burden, interest died down in the literature, low absolute excess risk.
Community acquired pneumonia (CAP)	High total healthcare costs	Costs mainly prevalent in patients younger than 1 year. No absolute excess risk found.
Clostridium difficile Infection (CDI)	Relatively high cost per patient	Cost are bound to the lengthening of the hospital admissions, recent cost-effectiveness analysis performed for deprescribing PPIs
Digestive tract cancers	High cost/disease burden, pancreatic cancer has the highest cost per patient.	Possibly a “False alarm”

Conclusion

In the end no clear winner was found, but after communicating with the TAO-UA it was decided that the adverse events related to the kidney were used to make the model. This choice was made because of the high costs, high disease burden and clear guidelines for the model. Furthermore it was decided to mainly focus on CKD and ESRD as they could be measured with eGFR. This was not the case for AIN and AKI as they were more acute.

Background Reference list

1. Wu B, Shang W, Li Y, et al. Association between proton pump inhibitors use and kidney diseases: a meta-analysis. Int J Clin Exp Med. 2018;11:6465-6473.
2. Salman S. S Hussain. Proton pump inhibitors use and risk of chronic kidney disease: evidence-based meta-analysis of observational studies. Clinical Epidemiology and Global Health 7(1):46-52. Elsevier 2019 22133984. 10.1016/j.cegh.2017.12.008
3. Liu J, Li X, Fan L, Yang J, Wang J, Sun J, Wang Z. Proton pump inhibitors therapy and risk of bone diseases: An update meta-analysis. Life Sci. 2019 Feb 1;218:213-223. doi: 10.1016/j.lfs.2018.12.058. Epub 2018 Dec 31. PMID: 30605646.
4. Kyu-Tae -T K.-T. K Yoon. Proton-pump inhibitors and the risk of dementia: A systematic review and meta-analysis. Korean Journal of Helicobacter and Upper Gastrointestinal Research, The 21(2):135-143.Yong Chan Lee 2021 1738-3331. 10.7704/KJHUGR.2020.0057
5. Hafiz RA, Wong C, Paynter S, David M, Peeters G. The Risk of Community-Acquired Enteric Infection in Proton Pump Inhibitor Therapy: Systematic Review and Meta-analysis. Ann Pharmacother. 2018 Jul;52(7):613-622. doi: 10.1177/1060028018760569. Epub 2018 Feb 18. PMID: 29457492.
6. Xun X, Yin Q, Fu Y, He X, Dong Z. Proton Pump Inhibitors and the Risk of Community-Acquired Pneumonia: An Updated Meta-analysis. Ann Pharmacother. 2021 Aug 23:10600280211039240. doi: 10.1177/10600280211039240. Epub ahead of print. PMID: 34425689.
7. Oshima T, Wu L, Li M, Fukui H, Watari J, Miwa H. Magnitude and direction of the association between Clostridium difficile infection and proton pump inhibitors in adults and pediatric patients: a systematic review and meta-analysis. J Gastroenterol. 2018 Jan;53(1):84-94. doi: 10.1007/s00535-017-1369-3. Epub 2017 Jul 25. Erratum in: J Gastroenterol. 2020 Apr;55(4):475-480. PMID: 28744822.
8. Zeng R, Cheng Y, Luo D, Wang J, Yang J, Jiang L, Zhuo Z, Guo K, Wu H, Leung FW, Sha W, Chen H. Comprehensive analysis of proton pump inhibitors and risk of digestive tract cancers. Eur J Cancer. 2021 Oct;156:190-201. doi: 10.1016/j.ejca.2021.07.030. Epub 2021 Sep 1. PMID: 34481369. (tot 15th January 2021)
9. Martin FC, Chenevix-Trench G, Yeomans ND. Systematic review with meta-analysis: fundic gland polyps and proton pump inhibitors. Aliment Pharmacol Ther. 2016 Nov;44(9):915-925. doi: 10.1111/apt.13800. Epub 2016 Sep 15. PMID: 27634363.
10. Salvo EM, Ferko NC, Cash SB, Gonzalez A, Kahrilas PJ. Umbrella review of 42 systematic reviews with meta-analyses: the safety of proton pump inhibitors. Aliment Pharmacol Ther. 2021 Jul;54(2):129-143. doi: 10.1111/apt.16407. Epub 2021 Jun 11. PMID: 34114655.
11. Veettil SK, Sadoyu S, Bald EM, Chandran VP, Khuu SAT, Pitak P, Lee YY, Nair AB, Antony PT, Ford AC, Chaiyakunapruk N. Association of proton-pump inhibitor use with adverse health outcomes: A systematic umbrella review of meta-analyses of cohort studies and randomised controlled trials. Br J Clin Pharmacol. 2021 Oct 7. doi: 10.1111/bcp.15103. Epub ahead of print. PMID: 34622475.
12. Keiko K. K Ikuta. Association of proton pump inhibitors and concomitant drugs with risk of acute kidney injury: A nested case-control study. BMJ Open 11(2), BMJ Group 2021, 20446055. 10.1136/bmjopen-2020-041543
13. Freedberg DE, Kim LS, Yang YX. The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association. Gastroenterology. 2017 Mar;152(4):706-715. doi: 10.1053/j.gastro.2017.01.031. PMID: 28257716

14. Moayyedi P, Eikelboom JW, Bosch J, et al. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. Gastroenterology. 2019;157:682–91
15. Nieratlas. Chronische nierschade (aantal patiënten) “Chronic kidney disease (amount of patients)”. Nieratlas.nl. Accessed on 22-11-2021, from https://www.nieratlas.nl/thema/aantalpatienten/prevalentie/chronischenierschade
16. Nieratlas. Chronische nierschade (zorgkosten) “Chronic kidney disease (health care costs)”. Nieratlas.nl. Accessed on 22-11-2021, from https://www.nieratlas.nl/kosten/zorgkosten/totalezorgkosten/chronischenierschade
17. Nierstichting. Factsheets: Nierfunctievervangde behandeling “Factsheet: Kidney replacing therapy”. Accessed on 22-11-2021, from https://nierstichting.nl/media/filer_public/c6/48/c64881d4-f0b4-492d-bf78-b72d913c2a4f/fs4-nierfunctievervangende_behandeling_keuzeweb.pdf
18. RIVM: Bilthoven (2021). Kosten van ziekten 2017 “Cost of disease 2017”. Statline.rivm.nl. Accessed on 22 November 2021 from https://statline.rivm.nl/#/RIVM/nl/dataset/50050NED/table?ts=1637569148189
19. Mohnen SM, van Oosten MJM, Los J, Leegte MJH, Jager KJ, Hemmelder MH, Logtenberg SJJ, Stel VS, Hakkaart-van Roijen L, de Wit GA. Healthcare costs of patients on different renal replacement modalities - Analysis of Dutch health insurance claims data. PLoS One. 2019 Aug 15;14(8):e0220800. doi: 10.1371/journal.pone.0220800. PMID: 31415578; PMCID: PMC6695145.
20. Lötters FJ, van den Bergh JP, de Vries F, Rutten-van Mölken MP. Current and Future Incidence and Costs of Osteoporosis-Related Fractures in The Netherlands: Combining Claims Data with BMD Measurements. Calcif Tissue Int. 2016 Mar;98(3):235-43. doi: 10.1007/s00223-015-0089-z. Epub 2016 Jan 9. PMID: 26746477; PMCID: PMC4746227.
21. RIVM: Bilthoven (2021). Dementie huidige situatie “Dementia current situation”. Volksgezondheidenzorg.info. Accessed on 21 November 2021, from https://www.volksgezondheidenzorg.info/onderwerp/dementie/cijfers-context/huidige-situatie#node-aantal-personen-met-dementie-de-bevolking
22. Pijnacker, R., Friesema, I. H. M., Mughini Gras, L., Lagerweij, G. R., Van Pelt, W., & Franz, E. (2019). Disease burden of food-related pathogens in the Netherlands, 2018.
23. Vissink, C.E., Huijts, S.M., de Wit, G.A. et al. Hospitalization costs for community-acquired pneumonia in Dutch elderly: an observational study. BMC Infect Dis 16, 466 (2016). https://doi.org/10.1186/s12879-016-1783-9
24. RIVM: Bilthoven (2021). Infecties van de onderste luchtwegen huidige situatie “lower respiratory tract infections current situation”. Volksgezondheidenzorg.info. Accessed on 21 November 2021, from https://www.volksgezondheidenzorg.info/onderwerp/infecties-van-de-onderste-luchtwegen/cijfers-context/huidige-situatie#node-nieuwe-gevallen-longontsteking-huisartsenpraktijk
25. RIVM: Bilthoven (2021). Clostridium difficile. Lci.RIVM.nl. Accessed on 22 November 2021, from https://lci.rivm.nl/richtlijnen/clostridium-difficile#epidemiologie
26. van Beurden YH, Bomers MK, van der Werff SD, Pompe EAPM, Spiering S, Vandenbroucke-Grauls CMJE, Mulder CJJ. Cost analysis of an outbreak of Clostridium difficile infection ribotype 027 in a Dutch tertiary care centre. J Hosp Infect. 2017 Apr;95(4):421-425. doi: 10.1016/j.jhin.2016.12.019. Epub 2016 Dec 30. PMID: 28169013.
27. Integraal kankercentrum Nederland. 10 jaar prevalentie slokdarm- en maagkanker “10 year prevalence stomach- and esophagus cancer”. Iknl.nl. Accessed on 22 November 2021, from https://iknl.nl/kankersoorten/slokdarm-en-maagkanker/registratie/prevalentie

28. Integraal kankercentrum Nederland. 10 jaar prevalentie Alvleesklierkanker “10 year prevalence pancreatic cancer”. Iknl.nl. Accessed on 22 November 2021, from https://iknl.nl/nkr-cijfers?fs%7Cepidemiologie_id=508&fs%7Ctumor_id=164&fs%7Cprevalentie_id=533&fs%7Cperiode_id=555%2C556%2C557%2C558%2C559%2C560%2C561%2C562%2C563%2C564%2C565%2C566%2C567%2C568%2C569%2C570%2C571%2C572%2C544%2C543%2C542%2C541&fs%7Cgeslacht_id=622&fs%7Cleeftijdsgroep_id=655&fs%7Cjaren_na_diagnose_id=665&cs%7Ctype=line&cs%7CxAxis=periode_id&cs%7Cseries=epidemiologie_id&ts%7CrowDimensions=periode_id&ts%7CcolumnDimensions=&lang%7Clanguage=nl
29. Integraal kankercentrum Nederland. 10 jaar prevalentie leverkanker “10 year prevalence liver cancer”. Iknl.nl. Accessed on 22 November 2021, from https://iknl.nl/nkr-cijfers?fs%7Cepidemiologie_id=508&fs%7Ctumor_id=148&fs%7Cprevalentie_id=533&fs%7Cperiode_id=555%2C556%2C557%2C558%2C559%2C560%2C561%2C562%2C563%2C564%2C565%2C566%2C567%2C568%2C569%2C570%2C571%2C572%2C544%2C543%2C542%2C541&fs%7Cgeslacht_id=622&fs%7Cleeftijdsgroep_id=655&fs%7Cjaren_na_diagnose_id=665&cs%7Ctype=line&cs%7CxAxis=periode_id&cs%7Cseries=epidemiologie_id&ts%7CrowDimensions=periode_id&ts%7CcolumnDimensions=&lang%7Clanguage=nl
30. RIVM: Bilthoven (2021). Kosten van ziekten 2017 “cost of diseases 2017”. Statline.rivm.nl. Geraadpleegd op 22 November 2021 from https://statline.rivm.nl/#/RIVM/nl/dataset/50050NED/table?ts=1637056828058
31. Integraal kankercentrum Nederland. 10 jaar prevalentie dikkedarm- en endeldarmkanker “10 year prevalence colorectal cancer”. Iknl.nl. Accessed on 22 november 2021, from https://iknl.nl/nkr-cijfers?fs%7Cepidemiologie_id=508&fs%7Ctumor_id=122&fs%7Cprevalentie_id=533&fs%7Cperiode_id=555%2C556%2C557%2C558%2C559%2C560%2C561%2C562%2C563%2C564%2C565%2C566%2C567%2C568%2C569%2C570%2C571%2C572%2C544%2C543%2C542%2C541&fs%7Cgeslacht_id=622&fs%7Cleeftijdsgroep_id=655&fs%7Cjaren_na_diagnose_id=665&cs%7Ctype=line&cs%7CxAxis=periode_id&cs%7Cseries=epidemiologie_id&ts%7CrowDimensions=periode_id&ts%7CcolumnDimensions=&lang%7Clanguage=nl
32. Integraal kankercentrum Nederland. 10 jaar prevalentie slokdarmkanker “10 year prevalence esophagus cancer”. Iknl.nl. Accessed on 22 november 2021, from https://iknl.nl/nkr-cijfers?fs%7Cepidemiologie_id=508&fs%7Ctumor_id=137&fs%7Cprevalentie_id=533&fs%7Cperiode_id=555%2C556%2C557%2C558%2C559%2C560%2C561%2C562%2C563%2C564%2C565%2C566%2C567%2C568%2C569%2C570%2C571%2C572%2C544%2C543%2C542%2C541&fs%7Cgeslacht_id=622&fs%7Cleeftijdsgroep_id=655&fs%7Cjaren_na_diagnose_id=665&cs%7Ctype=line&cs%7CxAxis=periode_id&cs%7Cseries=epidemiologie_id&ts%7CrowDimensions=periode_id&ts%7CcolumnDimensions=&lang%7Clanguage=nl
33. Kerr M, Bedford M, Matthews B, O'Donoghue D. The economic impact of acute kidney injury in England. Nephrol Dial Transplant. 2014 Jul;29(7):1362-8. doi: 10.1093/ndt/gfu016. Epub 2014 Apr 21. PMID: 24753459.
34. Sugrue DM, Ward T, Rai S, McEwan P, van Haalen HGM. Economic Modelling of Chronic Kidney Disease: A Systematic Literature Review to Inform Conceptual Model Design. Pharmacoeconomics. 2019 Dec;37(12):1451-1468. doi: 10.1007/s40273-019-00835-z. PMID: 31571136; PMCID: PMC6892339.
35. Si L, Winzenberg TM, Palmer AJ. A systematic review of models used in cost-effectiveness analyses of preventing osteoporotic fractures. Osteoporos Int. 2014 Jan;25(1):51-60. doi: 10.1007/s00198-013-2551-y. Epub 2013 Oct 24. PMID: 24154803.

36. Moriarty F, Cahir C, Bennett K, Fahey T. Economic impact of potentially inappropriate prescribing and related adverse events in older people: a cost-utility analysis using Markov models. BMJ Open. 2019 Jan 30;9(1):e021832. doi: 10.1136/bmjopen-2018-021832. PMID: 30705233; PMCID: PMC6359741.
37. Li L, Nguyen KH, Comans T, Scuffham P. Utility-Based Instruments for People with Dementia: A Systematic Review and Meta-Regression Analysis. Value Health. 2018 Apr;21(4):471-481. doi: 10.1016/j.jval.2017.09.005. Epub 2017 Nov 7. PMID: 29680105.
38. Hernandez L, Ozen A, DosSantos R, Getsios D. Systematic Review of Model-Based Economic Evaluations of Treatments for Alzheimer's Disease. Pharmacoeconomics. 2016 Jul;34(7):681-707. doi: 10.1007/s40273-016-0392-1. PMID: 26899832.
39. Herrick RL, Buchberger SG, Clark RM, Kupferle M, Murray R, Succop P. A Markov model to estimate Salmonella morbidity, mortality, illness duration, and cost. Health Econ. 2012 Oct;21(10):1169-82. doi: 10.1002/hec.1779. Epub 2011 Sep 2. PMID: 21887809.
40. Smith H, Varshoei P, Boushey R, Kuziemsky C. Simulation modeling validity and utility in colorectal cancer screening delivery: A systematic review. J Am Med Inform Assoc. 2020 Jun 1;27(6):908-916. doi: 10.1093/jamia/ocaa022. PMID: 32417894; PMCID: PMC7309251.
41. Matsuda A, Saika K, Tanaka R, Ito Y, Fukui K, Kamo KI. Simulation Models in Gastric Cancer Screening: A Systematic Review. Asian Pac J Cancer Prev. 2018 Dec 25;19(12):3321-3334. doi: 10.31557/APJCP.2018.19.12.3321. PMID: 30583337; PMCID: PMC6428531.
42. "Draus T, Ansari D, Wikström F, Persson U, Andersson R. Projected economic burden of pancreatic cancer in Sweden in 2030. Acta Oncol. 2021 Jul;60(7):866-871. doi: 10.1080/0284186X.2021.1892821. Epub 2021 Mar 17. PMID: 33729903."
43. Antoniou T, Macdonald EM, Hollands S, Gomes T, Mamdani MM, Garg AX, Paterson JM, Juurlink DN. Proton pump inhibitors and the risk of acute kidney injury in older patients: a population-based cohort study. CMAJ Open. 2015 Apr 2;3(2):E166-71. doi: 10.9778/cmajo.20140074. PMID: 26389094; PMCID: PMC4571830.
44. Klatte DCF, Gasparini A, Xu H, de Deco P, Trevisan M, Johansson ALV, Wettermark B, Ärnlöv J, Janmaat CJ, Lindholm B, Dekker FW, Coresh J, Grams ME, Carrero JJ. Association Between Proton Pump Inhibitor Use and Risk of Progression of Chronic Kidney Disease. Gastroenterology. 2017 Sep;153(3):702-710. doi: 10.1053/j.gastro.2017.05.046. Epub 2017 Jun 2. PMID: 28583827.
45. Xie Y, Bowe B, Li T, Xian H, Balasubramanian S, Al-Aly Z. Proton Pump Inhibitors and Risk of Incident CKD and Progression to ESRD. J Am Soc Nephrol. 2016 Oct;27(10):3153-3163. doi: 10.1681/ASN.2015121377. Epub 2016 Apr 14. PMID: 27080976; PMCID: PMC5042677.
46. RIVM: Bilthoven (2021). Ziekenhuiszorg. Volksgezondheidenzorg.info. Geraadpleegd op 23 november 2021, van https://www.volksgezondheidenzorg.info/onderwerp/ziekenhuiszorg/cijfers-context/gebruik#node-ziekenhuisopnamen-naar-leeftijd-en-geslacht
47. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA. 2004 Oct 27;292(16):1955-60. doi: 10.1001/jama.292.16.1955. PMID: 15507580.
48. Seung In I S.I. S Seo. Association between proton pump inhibitor use and gastric cancer: A population-based cohort study using two different types of nationwide databases in Korea. Gut 70(11):2066-2075. BMJ Group 2021, 0017-5749, 10.1136/gutjnl-2020-323845.

Background appendix 1: Key words used in the search.

Preliminary:

-key search: ("PPI" or "Proton Pump inhibitor" or "Omeprazol" or "Pantoprazol" or "Esomeprazol" or "Lansoprazol" or Rabeprazol") + "fracture"

-key search: (…) + "bone mineral density" or "BMD" or "BMC" or "bone mineral content"

-key search: (…) + "hypomagnesemia"

-key search: (…) + "vitamin B12" or "B12" or "cobalamin"

- key search: (…) + "iron deficiency"

-key search: (…) + "micronutrient deficiency"

-key search: (…) + "Community acquired pneumonia" or "CAP" or "pneumonia"

-key search: (…) + "Clostridium difficile infection" or "CDI"

-key search: (…) + "microbiome"

-key search: (…) + "enteric infections"

-key search: (…) + "cardiac event"

-key search: (…) + "cancer"

-key search: (…) + "dementia"

-key search: (…) + "renal disease" or "chronic kidney disease" or "CKD"

-key search: (…) + "mortality"

Adverse events:

-"Acute kidney injury" or "AKI"

-"Acute interstitial nephritis" or "AIN"

-"chronic kidney disease" or "CKD"

-"end stage renal disease" or "ESRD"

-"osteoporosis related fractures" or "fracture"

-"dementia"

-"Salmonella" or "Campylobacter" or "enteric infections"

-"Community acquired pneumonia" or "CAP"

-"clostridium difficile infection" or "CDI"

-"digestive tract cancers" or "stomach cancer" or "liver cancer" or "colorectal cancer" or "esophagus cancer"

Model search:

- key search: “adverse events” and (“cost-effective” or “Markov” or “economic” or “model”)

Newer studies:

-key search: “adverse events” and (“PPI” or “Proton Pump inhibitor” or “Omeprazol” or “Pantoprazol”)

Background appendix 2: Table with individual cancers of the digestive tract.

Digestive tract cancers	Association	Prevalence	Costs (mln €)	Costs per patient (€)
Gastric cancer	significant	2,687 (27)	42.7 (30)	15,891
Pancreatic cancer	significant	2,331 (28)	106.8 (30)	45,817
Liver cancer	significant	1,827 (29)	…	…
Oesophagal cancer	non-significant	6,425 (31)	81.6 (30)	12,7
Colorectal cancer	non-significant	82,877 (32)	596.5 (30)	7,197

Background appendix 3: New studies.

New literature "+" strengthens the evidence that PPI use correlates with the found adverse event, while "-" weakens the evidence.

AKI

+ Hart E, Dunn TE, Feuerstein S, Jacobs DM. Proton Pump Inhibitors and Risk of Acute and Chronic Kidney Disease: A Retrospective Cohort Study. Pharmacotherapy. 2019 Apr;39(4):443-453. doi: 10.1002/phar.2235. Epub 2019 Mar 21. PMID: 30779194; PMCID: PMC6453745. (+)
+ Liabeuf S, Lambert O, Metzger M, Hamroun A, Laville M, Laville SM, Frimat L, Pecoits-Filho R, Fouque D, Massy ZA, Jacquelinet C, Stengel B; Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD REIN) Study Group. Adverse outcomes of proton pump inhibitors in patients with chronic kidney disease: The CKD-REIN cohort study. Br J Clin Pharmacol. 2021 Jul;87(7):2967-2976. doi: 10.1111/bcp.14713. Epub 2021 Jan 19. PMID: 33368448. (+)
+ Keiko K. K Ikuta. Association of proton pump inhibitors and concomitant drugs with risk of acute kidney injury: A nested case-control study. BMJ Open 11(2), BMJ Group 2021, 20446055. 10.1136/bmjopen-2020-041543 (+)
+ Gang G. G Chen. Acute kidney injury following the use of different proton pump inhibitor regimens: A real-world analysis of post-marketing surveillance data. Journal of Gastroenterology and Hepatology 36(1):156-162, Wiley 2021 0815-9319, 10.1111/jgh.15151
+ Wu B, Li D, Xu T, Luo M, He Z, Li Y. Proton pump inhibitors associated acute kidney injury and chronic kidney disease: data mining of US FDA adverse event reporting system. Sci Rep. 2021 Feb 11;11(1):3690. doi: 10.1038/s41598-021-83099-y. PMID: 33574396; PMCID: PMC7878877.

AIN

No full text found, but only supplements.

CKD

+ Guedes JVM, Aquino JA, Castro TLB, Augusto de Morais F, Baldoni AO, Belo VS, Otoni A. Omeprazole use and risk of chronic kidney disease evolution. PLoS One. 2020 Mar 4;15(3):e0229344. doi: 10.1371/journal.pone.0229344. PMID: 32130255; PMCID: PMC7055824.
+ Devraj R, Deshpande M. Demographic and health-related predictors of proton pump inhibitor (PPI) use and association with chronic kidney disease (CKD) stage in NHANES population. Res Social Adm Pharm. 2020 Jun;16(6):776-782. doi: 10.1016/j.sapharm.2019.08.032. Epub 2019 Aug 19. PMID: 31445985.
+ Lee HJ, Lee H, Oh SH, Park J, Park S, Jeon JS, Noh H, Han DC, Kwon SH. Chronic kidney disease (CKD) patients are exposed to more proton pump inhibitor (PPI)s compared to non-CKD patients. PLoS One. 2018 Sep 13;13(9):e0203878. doi: 10.1371/journal.pone.0203878. Erratum in: PLoS One. 2018 Nov 12;13(11):e0207561. PMID: 30212538; PMCID: PMC6136773.
+ Hart E, Dunn TE, Feuerstein S, Jacobs DM. Proton Pump Inhibitors and Risk of Acute and Chronic Kidney Disease: A Retrospective Cohort Study. Pharmacotherapy. 2019 Apr;39(4):443-453. doi: 10.1002/phar.2235. Epub 2019 Mar 21. PMID: 30779194; PMCID: PMC6453745.

+ Liabeuf S, Lambert O, Metzger M, Hamroun A, Laville M, Laville SM, Frimat L, Pecoits-Filho R, Fouque D, Massy ZA, Jacquelinet C, Stengel B; Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD REIN) Study Group. Adverse outcomes of proton pump inhibitors in patients with chronic kidney disease: The CKD-REIN cohort study. Br J Clin Pharmacol. 2021 Jul;87(7):2967-2976. doi: 10.1111/bcp.14713. Epub 2021 Jan 19. PMID: 33368448.
+ Xie Y, Bowe B, Yan Y, Xian H, Li T, Al-Aly Z. Estimates of all cause mortality and cause specific mortality associated with proton pump inhibitors among US veterans: cohort study. BMJ. 2019 May 29;365:l1580. doi: 10.1136/bmj.l1580. PMID: 31147311; PMCID: PMC6538974.
+ Hung SC, Liao KF, Hung HC, Lin CL, Lai SW, Lee PC, Hung SR. Using proton pump inhibitors correlates with an increased risk of chronic kidney disease: a nationwide database-derived case-controlled study. Fam Pract. 2018 Mar 27;35(2):166-171. doi: 10.1093/fampra/cmx102. PMID: 29045621.
+ Wu B, Li D, Xu T, Luo M, He Z, Li Y. Proton pump inhibitors associated acute kidney injury and chronic kidney disease: data mining of US FDA adverse event reporting system. Sci Rep. 2021 Feb 11;11(1):3690. doi: 10.1038/s41598-021-83099-y. PMID: 33574396; PMCID: PMC7878877.
+ Antonio A. A Rodroguez-Poncelas. Duration and dosing of Proton Pump Inhibitors associated with high incidence of chronic kidney disease in population-based cohort. PLoS ONE 13(10), Public Library of Science 2018. 19326203, 10.1371/journal.pone.0204231
+ Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. Kidney Int. 2017 Jun;91(6):1482-1494. doi: 10.1016/j.kint.2016.12.021. Epub 2017 Feb 22. PMID: 28237709.

CKD progression

+ Grant CH, Gillis KA, Lees JS, Traynor JP, Mark PB, Stevens KI. Proton pump inhibitor use and progression to major adverse renal events: a competing risk analysis. QJM. 2019 Nov 1;112(11):835-840. doi: 10.1093/qjmed/hcz166. PMID: 31251364.
- Wakabayashi T, Hosohata K, Oyama S, Inada A, Niinomi I, Kambara H, Iida T, Hasebe K, Matsuoka H, Uchida M, Kumagai E. Association between a low dose of proton pump inhibitors and kidney function decline in elderly hypertensive patients: a retrospective observational study. J Int Med Res. 2021 Apr;49(4):3000605211006653. doi: 10.1177/03000605211006653. PMID: 33845606; PMCID: PMC8047853.
- Austin GL, Weiskopf JR, Czwornog JL. Association of Proton Pump Inhibitor Use With Serum Biomarkers of Inflammation, Insulin Resistance, Cardiovascular Risk, and Renal Function. J Clin Gastroenterol. 2018 Sep;52(8):691-695. doi: 10.1097/MCG.0000000000000921. PMID: 29099466.
+ Hatakeyama Y, Horino T, Matsumoto T, Terada Y, Okuhara Y. Long-term continuous use of proton-pump inhibitors is associated with renal function decline in patients without acute kidney injury. Clin Exp Nephrol. 2021 Oct;25(10):1087-1092. doi: 10.1007/s10157-021-02066-z. Epub 2021 Jun 5. PMID: 34089392.
- Liza L. L Cholin. Proton-pump inhibitor vs. H2-receptor blocker use and overall risk of CKD progression. BMC Nephrology 22(1), BioMed Central 2021, 14712369, 10.1186/s12882-021-02449-0
+ Sixto G. G S.G. S Giusti. The effect of proton pump inhibitor use on the development of metabolic acidosis and decline in kidney function in patients with CKD stages G3A to G4. Journal of the American Society of Nephrology 30:235, 2019, 1533-3450.

+ Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. Kidney Int. 2017 Jun;91(6):1482-1494. doi: 10.1016/j.kint.2016.12.021. Epub 2017 Feb 22. PMID: 28237709.
+ Guedes JVM, Aquino JA, Castro TLB, Augusto de Morais F, Baldoni AO, Belo VS, Otoni A. Omeprazole use and risk of chronic kidney disease evolution. PLoS One. 2020 Mar 4;15(3):e0229344. doi: 10.1371/journal.pone.0229344. PMID: 32130255; PMCID: PMC7055824.

ESRD

+ Liabeuf S, Lambert O, Metzger M, Hamroun A, Laville M, Laville SM, Frimat L, Pecoits-Filho R, Fouque D, Massy ZA, Jacquelinet C, Stengel B; Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD REIN) Study Group. Adverse outcomes of proton pump inhibitors in patients with chronic kidney disease: The CKD-REIN cohort study. Br J Clin Pharmacol. 2021 Jul;87(7):2967-2976. doi: 10.1111/bcp.14713. Epub 2021 Jan 19. PMID: 33368448.
+ Hart E, Dunn TE, Feuerstein S, Jacobs DM. Proton Pump Inhibitors and Risk of Acute and Chronic Kidney Disease: A Retrospective Cohort Study. Pharmacotherapy. 2019 Apr;39(4):443-453. doi: 10.1002/phar.2235. Epub 2019 Mar 21. PMID: 30779194; PMCID: PMC6453745.
+ Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. Kidney Int. 2017 Jun;91(6):1482-1494. doi: 10.1016/j.kint.2016.12.021. Epub 2017 Feb 22. PMID: 28237709.
- Wakabayashi T, Hosohata K, Oyama S, Inada A, Niinomi I, Kambara H, Iida T, Hasebe K, Matsuoka H, Uchida M, Kumagai E. Association between a low dose of proton pump inhibitors and kidney function decline in elderly hypertensive patients: a retrospective observational study. J Int Med Res. 2021 Apr;49(4):3000605211006653. doi: 10.1177/03000605211006653. PMID: 33845606; PMCID: PMC8047853.

Fracture

+ Wei J, Chan AT, Zeng C, Bai X, Lu N, Lei G, Zhang Y. Association between proton pump inhibitors use and risk of hip fracture: A general population-based cohort study. Bone. 2020 Oct;139:115502. doi: 10.1016/j.bone.2020.115502. Epub 2020 Jun 25. PMID: 32593677.
+ Park JH, Lee J, Yu SY, Jung JH, Han K, Kim DH, Rhee J. Comparing proton pump inhibitors with histamin-2 receptor blockers regarding the risk of osteoporotic fractures: a nested case-control study of more than 350,000 Korean patients with GERD and peptic ulcer disease. BMC Geriatr. 2020 Oct 15;20(1):407. doi: 10.1186/s12877-020-01794-3. PMID: 33059626; PMCID: PMC7565339.
+ Park JH, Song YM, Jung JH, Han K. Comparative analysis of the risk of osteoporotic fractures with proton pump inhibitor use and histamine-2 receptor antagonist therapy in elderly women: A nationwide population-based nested case-control study. Bone. 2020 Jun;135:115306. doi: 10.1016/j.bone.2020.115306. Epub 2020 Feb 29. PMID: 32126312.
+ Brozek W, Reichardt B, Zwerina J, Dimai HP, Klaushofer K, Zwettler E. Higher dose but not low dose proton pump inhibitors are associated with increased risk of subsequent hip fractures after first hip fracture: A nationwide observational cohort study. Bone Rep. 2019 Apr 1;10:100204. doi: 10.1016/j.bonr.2019.100204. PMID: 30993153; PMCID: PMC6451165.
+ Paik JM, Rosen HN, Gordon CM, Curhan GC. Proton Pump Inhibitor Use, H2-Receptor Antagonist Use, and Risk of Incident Clinical Vertebral Fracture in Women. Calcif Tissue Int.

2018 Oct;103(4):380-387. doi: 10.1007/s00223-018-0432-2. Epub 2018 May 12. PMID: 29754277; PMCID: PMC6231994.
- Harding BN, Weiss NS, Walker RL, Larson EB, Dublin S. Proton pump inhibitor use and the risk of fractures among an older adult cohort. Pharmacoepidemiol Drug Saf. 2018 Jun;27(6):596-603. doi: 10.1002/pds.4406. Epub 2018 Feb 28. PMID: 29493043; PMCID: PMC5984154.
+ Naiara N. N Fernandez-Arroyabe. Non-union and use of proton pump inhibitors in the treatment of femoral and tibial shaft fractures: a nested case–control study. European Journal of Orthopaedic Surgery and Traumatology. Springer Paris 2021, 1633-8065, 10.1007/s00590-021-03122-w
+ Nathan N. N Fleishman. The Clinical Characteristics of Fractures in Pediatric Patients Exposed to Proton Pump Inhibitors. Journal of Pediatric Gastroenterology and Nutrition 70(6):815-819. Wolters Kluwer Health _ Lippincott Williams and Wilkins 2020, 0277-2116, 10.1097/MPG.0000000000002690.
+ Yang Won W Y.W. Y Min. Proton pump inhibitor use is associated with hip fracture development: A nationwide population-based cohort study. Korean Journal of Internal Medicine, The 35(5):1084-1093. The Korean Association of Internal Medicine 2020, 1226-3303, 10.3904/kjim.2018.331.

Dementia

- Cooksey R, Kennedy J, Dennis MS, Escott-Price V, Lyons RA, Seaborne M, Brophy S. Proton pump inhibitors and dementia risk: Evidence from a cohort study using linked routinely collected national health data in Wales, UK. PLoS One. 2020 Sep 18;15(9):e0237676. doi: 10.1371/journal.pone.0237676. PMID: 32946449; PMCID: PMC7500586.
+ Chen LY, Lin HJ, Wu WT, Chen YC, Chen CL, Kao J, You SL, Chou YC, Sun CA. Clinical Use of Acid Suppressants and Risk of Dementia in the Elderly: A Pharmaco-Epidemiological Cohort Study. Int J Environ Res Public Health. 2020 Nov 9;17(21):8271. doi: 10.3390/ijerph17218271. PMID: 33182362; PMCID: PMC7664895.
- Wu CL, Lei WY, Wang JS, Lin CE, Chen CL, Wen SH. Acid suppressants use and the risk of dementia: A population-based propensity score-matched cohort study. PLoS One. 2020 Nov 30;15(11):e0242975. doi: 10.1371/journal.pone.0242975. Erratum in: PLoS One. 2021 Apr 15;16(4):e0250535. PMID: 33253311; PMCID: PMC7703973.
- Ahn N, Frenzel S, Wittfeld K, Bülow R, Völzke H, Lerch MM, Chenot JF, Schminke U, Nolde M, Amann U, Meisinger C, Linseisen J, Baumeister SE, Grabe HJ, Rückert-Eheberg IM. Lack of association between proton pump inhibitor use and brain aging: a cross-sectional study. Eur J Clin Pharmacol. 2021 Jul;77(7):1039-1048. doi: 10.1007/s00228-020-03068-8. Epub 2021 Jan 13. PMID: 33442768; PMCID: PMC8184524.
- Huang ST, Tseng LY, Chen LK, Peng LN, Hsiao FY. Does Long-Term Proton Pump Inhibitor Use Increase Risk of Dementia? Not Really! Results of the Group-Based Trajectory Analysis. Clin Pharmacol Ther. 2019 Sep;106(3):616-622. doi: 10.1002/cpt.1430. Epub 2019 May 10. PMID: 30861103.
- In Cheol C I.C. I Hwang. A Nationwide Population-Based Cohort Study of Dementia Risk Among Acid Suppressant Users. American Journal of Geriatric Psychiatry 26(11):1175-1183. American Association for Geriatric Psychiatry 2018, 1064-7481, 10.1016/j.jagp.2018.06.002.

Enteric infections

+ Ana-Maria -M A.-M. A Vilcu. Association between Acute Gastroenteritis and Continuous Use of Proton Pump Inhibitors during Winter Periods of Highest Circulation of Enteric Viruses.JAMA Network Open 2(11) 2019, 25743805, 10.1001/jamanetworkopen.2019.16205.

CAP

No more recent observational studies found.

CDI

+ Seo SI, You SC, Park CH, Kim TJ, Ko YS, Kim Y, Yoo JJ, Kim J, Shin WG. Comparative risk of Clostridium difficile infection between proton pump inhibitors and histamine-2 receptor antagonists: A 15-year hospital cohort study using a common data model. J Gastroenterol Hepatol. 2020 Aug;35(8):1325-1330. doi: 10.1111/jgh.14983. Epub 2020 Jan 29. PMID: 31970824.
+ Hong SH, Lee EK, Shin JY. Proton-pump inhibitors and the risk of Clostridium difficile-associated diarrhea in high-risk antibiotics users: A population-based case-crossover study. Pharmacoepidemiol Drug Saf. 2019 Apr;28(4):479-488. doi: 10.1002/pds.4745. Epub 2019 Mar 8. PMID: 30848536.
+ Park YH, Seong JM, Cho S, Han HW, Kim JY, An SH, Gwak HS. Effects of proton pump inhibitor use on risk of Clostridium difficile infection: a hospital cohort study. J Gastroenterol. 2019 Dec;54(12):1052-1060. doi: 10.1007/s00535-019-01598-2. Epub 2019 Jun 11. PMID: 31187275.
+ Lee P, Fike D, Yang H, Hall RG 2nd, Pass S, Alvarez CA. Do the types and routes of proton pump inhibitor treatments affect clostridium difficile in ICU patients? A retrospective cohort study. Expert Rev Clin Pharmacol. 2021 Mar;14(3):399-404. doi: 10.1080/17512433.2021.1890582. Epub 2021 Feb 28. PMID: 33576287.
+ Elbeddini A, Gerochi R. Treatment of Clostridium difficile infection in community teaching hospital: a retrospective study. J Pharm Policy Pract. 2021 Feb 11;14(1):19. doi: 10.1186/s40545-020-00289-1. PMID: 33568232; PMCID: PMC7877108.
+ Inghammar M, Svanström H, Voldstedlund M, Melbye M, Hviid A, Mølbak K, Pasternak B. Proton-Pump Inhibitor Use and the Risk of Community-Associated Clostridium difficile Infection. Clin Infect Dis. 2021 Jun 15;72(12):e1084-e1089. doi: 10.1093/cid/ciaa1857. PMID: 33629099; PMCID: PMC8204777.

Research objective

The primary objective of this project was to determine the economic impact deprescribing has on the patient population of the TAO-UA, including the side effect related to the kidney. The secondary objective of this project was to determine which patient group should be prioritized.

Material and methods

The general research plan can be found in **appendix 12**. To determine the impact of deprescribing a cost-utility analysis was performed. With this type of analysis the costs and effects of different interventions can be compared. One method to perform a cost-utility analysis is with the help of a cohort level Markov model. A Markov model contains a finite set of health states in which an individual can be found. The individual can only be found in one state at a time, but transitions can take place between the states. Transition between the states is only possible during a short time intervals called cycles. The Markov model is run for either a set amount of cycles or until all the individual end up in an absorbing state. This is a state in which the individual can enter but never leave, for example death. Each health state has corresponding rewards, such as quality adjusted life-years (QALYs) and costs, which can be measured during each cycle. Therefore at the end of a Markov model run all the rewards for each cycle can be added together to show the total impact a therapy has over a long period of time. Finally the model was run for 2 situations simultaneously. In the first situation no deprescribing took place, while in the second situation deprescribing did take place. The difference in rewards between the two situations was later calculated to give an estimation of the impact deprescribing has on a population.

To answer the research questions the data from a TAO-UA deprescribing pilot was used. The small scope of this pilot opened up the option to gain a lot of extra information about the population, like kidney function or co-morbidities. This population, which is essential for the project, consists of patients who use Proton Pump Inhibitors (PPIs) chronically without a clear indication. At first the model was used to calculate the cost-effectiveness of the pilot. After this was achieved a closer look was given to different subgroups in the population to figure out which type of patient should be prioritized in the deprescribing process. The focus of the subgroup analysis were diabetics, diuretic users and different ages. Finally with the help of data from individual TAO-UA pharmacies the impact of deprescribing could be estimated for the TAO-UA as a whole.

Software and packages

To showcase the impact of PPI deprescribing on the kidney function a Markov model was developed and programmed in R studio (12). While the model was programmed in R studio both the creation of the model and the presentation of the data was heavily guided by the r-package: HEEMOD and its corresponding tutorial by Filipović et al (13). The presentation of the data was later on personalized with the help of the r-package: ggplot2 (14).

Model and strategy

A schematic drawing of the Chronic kidney disease (CKD) model can be found in **Figure 2**. The framework of the model was based on previously CKD models summarized in a meta-analysis of Sugrue et al (15). In this meta-analysis an example was given which contained the core structure used in most of the individual CKD models. This structure contained different health states for CKD according to the National Kidney Foundation K/DOQI guidelines(16) in which the CKD stadia are stratified by estimated glomerular filtration rate (eGFR). These CKD health states are defined as followed: ckd1 (eGFR ≥ 90 ml/min/1.73 m^2), ckd2 (eGFR 60-89 ml/min/1.73 m^2), ckd3a (eGFR 45-59 ml/min/1.73 m^2), ckd3b (eGFR 30-44 ml/min/1.73 m^2), ckd4 (eGFR 15-29 ml/min/1.73 m^2) and ckd5 (eGFR < 15 ml/min/1.73 m^2). Furthermore the core structure contained 3 separate health states for dialysis (dia), kidney transplant (kt) and death. Finally additional health states were implemented to better suit the situation of a deprescribing process.

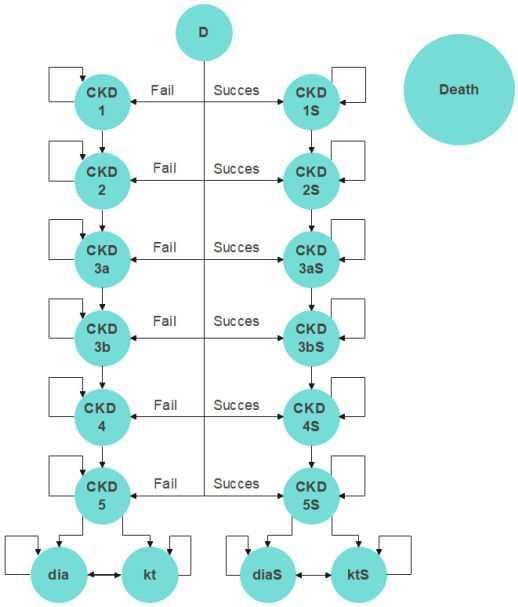

Figure 2 *Schematic drawing of the CKD model.*

Initially the chance of successful deprescribing was either 0% or 100%, while in practice it would be somewhere in-between. Therefore deviation of the example given by Sugrue et al (15) was needed. To start, a duplication of the core structure was done. This resulted in the addition of 7 extra health states identical to the core structure called: ckd1s, ckd2s, ckd3as, ckd3bs, ckd4s, ckd5, dias and kts. Additionally an extra health state was introduced to the model to distribute the patient between the original core structure (failed attempt) and the newly introduced one (successful attempt). Altogether the model contains 18 health states with patients being able to transfer to death from any of them.

To show the effect of deprescribing two strategies were constructed. The first strategy called "nodeprescribing" mimicked a situation in which no deprescribing took place. This results in the patient continuously taking PPI and therefore having a higher risk to get CKD or end stage renal disease (ESRD) as shown by Hussain et al(17). Therefore a higher chance to transition between ckd1-ckd2, ckd2-ckd3a, ckd3b-ckd4 and ckd4-ckd5 was assumed. Furthermore the success rate of deprescribing was set to 0% and only the cost of medication is taken into account. The second strategy called "deprescribing" mimicked a situation in which deprescribing took place. If the deprescribing was successful, the patient stops the use of PPI and therefore no increased risk to get CKD or ESRD was assumed. In this case the initial and the annual costs of the deprescribing process was taken into account. Finally if the deprescribing was unsuccessful, the patient will have a higher chance to transition between ckd1-ckd2, ckd2-ckd3a, ckd3b-ckd4 and ckd4-ckd5. Also both the initial costs of the deprescribing process and the medication cost were taken into account. The distribution of successful and unsuccessful deprescribing was based on the chance of successful deprescribing obtained from the deprescribing pilot of the TAO-UA.

Patient population

Deprescribing pilot

Information needed to make the model was partially obtained from the deprescribing pilot done by the TAO-UA. In this pilot a population was selected with chronic PPI use without an indication. To identify which individuals qualify for the pilot a search was performed in Pharmacon (pharmacy information system) by a pharmacist of the TAO-UA, which can be found in **appendix 4**. The first step

of the selection process was selecting the individuals using PPI chronically. Chronic PPI use was defined as 3 or more dispenses of PPIs in the past year. Secondly individuals who use PPI for stomach protections were excluded based on their age and co-medication. This exclusion was based on Dutch guidelines(18). Finally the individuals who remained after the initial selection process had their medical records from the general practitioner manually checked by a pharmacist. This was necessary to register indications for PPI use which cannot be derived from co-medication. These indications include Barrett's esophagitis, Zollinger Ellison syndrome, Reflux esophagitis grade C or D and patients under guidance of a gastroenterologist.

TAO-UA population

To figure out the impact of deprescribing on the TAO-UA population searches were performed by individual pharmacies inside the TAO-UA. The searches were executed inside the database of "Stichting Farmaceutische Kengetallen" (SFK). This database allows the search of a specific ATC-codes on a pharmacy wide level. Therefore individuals who use medication corresponding with the ATC-code can be found. This enables a similar search to the deprescribing pilot where initially patients are selected who have 3 or more dispenses of PPIs. Afterwards a search was performed on these patients to find potential co-medication which would justify their PPI use. This search was based on stomach protection. The ATC-codes used for the search can be found in **appendix 5**. It was not possible to exclude patients on indications like Barrett's esophagitis, Zollinger Ellison syndrome, Reflux esophagitis grade C or D and patients under guidance of a gastroenterologist. Finally an extrapolation could be made for the whole TAO-UA population with the help of the individual pharmacies.

Model Inputs

Transitions

The state transitions probabilities were derived from a CKD model used in a study of Elbasha et al(19). Furthermore Elbasha et al(19) provided distribution for its transitions. By using these distributions a minimum and maximum value was estimated. This was done by randomly sampling 10,000,000 values from the distribution with the help of R-studio. Out of this sample a minimum and maximum was determined which could be used in the Deterministic Sensitivity Analysis (DSA).

The impact of PPI use was mimicked with the help of risk ratios obtained from a meta-analysis of observational studies by Hussain et al(17). This meta-analysis showed an increase risk of CKD and ESRD among PPI users. Therefore the transition probabilities of PPI users was assumed to be higher. To showcase the increased risk of CKD among PPI users trans_ckd1_ckd2 and trans_ckd2_ckd3a were recalculated with rr_ckd. The increased risk of ESRD among PPI users was shown by recalculating trans_ckd3a_ckd3b, trans_ckd3b_ckd4 and trans_ckd4_ckd5 with rr_esrd. The recalculation was done with a convenient function called rr_to_prob() which HEEMOD provides.

The impact of diabetes was introduced in a similar manner by yet again recalculating certain transition probabilities, also the use of diuretic was introduced this way. The meta-analysis from Hussain et al(17) found that a diabetic population and a population which uses diuretics both had an increase risk to develop CKD. Therefore trans_ckd1_ckd2 and trans_ckd2_ckd3a were recalculated with rr_diabetic and rr_diuretic respectively. If the person also uses PPI then the transitions were first recalculated with rr_ckd and afterwards the new probability was recalculated with rr_diabetic or rr_diuretic.

Both the mean and 95% confidence interval for the risk ratios were provided. The minimum and maximum was assumed to be equal to the bounds of the 95% confidence interval. Furthermore a lognormal distribution was made to fit the current data. This type of distribution has to be in-

between 0 and infinity which is also true for a risk ratio. The distribution was created as described in Gray(2017) (20). First the mean and 95% confidence interval were transformed into the natural log. Followed by the calculation of the standard error on the log scale:

(upper bound 95% Confidence interval to lower bound 95% confidence interval)/(1.96*2).

Finally with both the natural log of the mean and the natural log of the standard error a lognormal distribution could be made which is compatible with HEEMOD.

Mortality

The transition to death depends on the age of the population and because age increases with time spent in the model every cycle will result in a different probability. To counter this problem HEEMOD offers a built in function called get_who_mr(). This function fetches a death probability, as a function of sex and age, from the World Health Organization database for a set country. The only downside to this solution is the fact that a necessary package to actively extracts the probabilities of the current year is missing. Therefore only cached probabilities from 2015 can be accessed. The choice was made to still use this function, because no significant changes in mortality was expected when more recent data was used instead (COVID-19 pandemic excluded).

Later stadia of CKD like ckd5, dialysis (dia) and kidney transplant (kt) are expected to have a higher probability of death. Something that is also visible in the model of Elbasha et al (19). Their model however used additional health states, all with their corresponding transition probabilities, to account for these deaths. However instead of using this method the age-related death probability and CKD related one were combined by using the HEEMOD function called combine_probs(). This function combines independent probabilities with the formula:

$P(A \cup B) = 1 - (1-P(A)) \times (1-P(B))$.

Cost per CKD stadia

The cost per CKD stadia were obtained from an analysis of Dutch healthcare claims by van Oosten et al (in 2016 euro) (21). Therefore not only the direct cost related to CKD are taken into account, but also the comorbidities closely related to the disease can be measured. This is especially critical for stadia which have no direct cost, but still contribute to the total cost because of comorbidities like cardiovascular complications. In the study the population was stratified by age groups: 19-44, 45-64, 65-74 and ≥75. In these age groups a differentiation was made for patients with CKD stadia 4/5 without dialysis, patient undergoing dialysis and patient who underwent a kidney transplant. Also a control group was introduced for each patient group matched by age, sex and SES score with no healthcare claim for CKD. It was assumed that the control group was representative for the earlier CKD stages.

In the article of van Oosten et al (21) the costs were presented with a mean, 25^{th} and 75^{th} percentile. The use of percentiles instead of a standard deviation was preferred to give a better representation of the distribution by the authors. However HEEMOD does not provide an option to use 25^{th} and 75^{th} percentiles to fit a distribution. Therefore it had to be made from scratch. First the choice was made to use a gamma distribution. This was decided because the 75^{th} percentile was less than the mean, which indicates a right skewed distribution. Also costs have to be in-between 0 and infinity which is also true for the gamma distribution. Secondly with a maximum likelihood estimated (MLE) a rough estimation was made for alpha and lambda. This was done with the use of a r-script(22), from now on called MLE script, which can be found in **appendix 9**. The found distributions had a mean which was very close to the true value, however the found percentiles did differ. Therefore the distribution

was optimized with the help of a r-script, from now on called optimize script, which can be found in **appendix 10**.

In the MLE script the given percentiles and the mean was used. This enabled the log-likelihood function (**Equation 1**) to solve which value x will be the estimated value of alpha. This is true if the derivative is equal to 0. The function would be plotted with a range of x from 0 to 10 and a straight line was drawn for f(x)=0. The range of x would then be minimized to get a clear image of the intersection between the log-likelihood function and f(x)=0. Afterwards the lower and upper bound of the x range were used in the uniroot function to find for which x the derivative is equal to 0. This value would be the estimation of alpha. With alpha solved the lambda could be calculated by dividing alpha with the mean.

Equation 1 *log-likelihood function.*

$$f(x) = \log(x) - digamma(x) - \ln(true\ mean) + \ln(mean(dataset))$$

The optimizing script used a range around the found alpha of ± 0.1 with intervals of 5E-6 to find an alpha where the percentiles are closer to the true value. Each interval the lambda was recalculated by dividing alpha with the mean. With both the alpha and the lambda the 25th and 75th percentiles can be calculated with the qgamma() function available in R-studio. Afterwards the difference between the found value corresponding to the percentiles and the true value of the percentiles was calculated. The alpha with the smallest difference was selected.

With the found distribution a minimum and maximum could be calculated. This was yet again done with the qgamma() function, but now for the probabilities of 0.025 and 0.975. These probabilities were subsequently assumed to be the minimum and maximum. Finally a discount rate of 4% was used.

Cost medication

The cost of medication was determined using a cost overview of all the PPIs used in the Netherlands (23). Out of the possible medication omeprazole, esomeprazole and pantoprazole were selected, as they are considered first and second line treatment (24). To fully show the effect of deprescribing a worst case scenario was assumed and the cheapest medication was selected: generic omeprazole capsules 20 mg, generic omeprazole capsules 40 mg, generic esomeprazole tablets 20 mg, generic esomeprazole tablets 40 mg and generic pantoprazole tablets 40mg. The cost of medication was initially given per day, but this was transformed into an annual cost. Also dispensing fees were taken into account. It was assumed that an individual has 3 refills a year which corresponds to the criteria of 3 or more PPI dispenses in a year. The tariff of each dispense was assumed to be €9.28. This value was based on the costs and fees set by the BENU franchise(25). For the distribution only the standard deviation and a mean was needed to calculate a gamma distribution. No uncertainty was assumed on the dispensing tariff. Also the minimum cost was set to generic omeprazole capsules 40 mg and the maximum was set to generic pantoprazole tablets 40mg. Finally a discount rate of 4% was used.

Cost deprescribing

The cost of the deprescribing process was determined by contacting the pharmacist who performed the initial pilot. Each individual step in the deprescribing process was determined and the time needed to perform this step was estimated by the pharmacist. During the estimation process a minimum and maximum time spent on each step was also asked. Therefore a very rough estimation of the standard deviation could be made by assuming that the minimum and maximum were the bounds of a 95% confidence interval. This made it possible to create a gamma distribution to show the uncertainty around the deprescribing process.

With the time needed to perform the deprescribing a hourly wage was needed to transform it into a cost. The hourly wage was obtained from a corresponding wage scale of a pharmacy manager. The monthly wage was multiplied by 3 and afterwards divided by 13 to get a weekly wage. The weekly wage was afterwards divided by the working hours in a week, which was assumed to be 38 hours, to get the hourly wage. The true cost of the pharmacists was assumed to be 150% of the hourly wage. This estimation is also used by the BENU to estimate the total cost per hour of an employee. Furthermore the lowest level of the wage scale was set as the minimum and the highest level as the maximum. Also a gamma distribution was created to determine the uncertainty around the wage.

Effect

Utilities, better known as QALYs, were used to measure the effect of deprescribing. Each health state was valued with a quality of life, which was available in a study by Elbasha et al(19). In this study the distributions corresponding to the quality of life were also given, therefore only a minimum and maximum needed to be calculated. This was done by randomly sampling 10,000,000 values from the distribution by using R-studio. The minimum and maximum was determined from these samples. Finally the QALYs were discounted at a rate of 1.5%.

Population

Population characteristics used in the model consist of age, gender, diabetic, diuretic use and kidney function depending on the type of analysis. The data was obtained from either the pilot or individual TAO-UA pharmacies in collaboration with the TAO-UA.

Data analysis

Pilot

Base case

The model was run with patient characteristics of the deprescribing pilot. Therefore the mean age of the population was set as the starting age and the initial CKD distributions were determined by stratifying the kidney function. Also the gender specific mortality rates were pooled. The results were summarized as a difference in cost and effect between the nodeprescribing and deprescribing strategy. Finally the R-script which was used for the base case analysis can be seen in **appendix 1**. The model was run with a starting age of 76.23 and the following transition matrices: mat_deprescribing_base and mat_nodeprescribing_base.

Population analysis

In the population analysis the model was run with patient characteristics of the deprescribing pilot, but now on an individual basis. Therefore the model ran once for each patient his specific characteristics and the results were weighted and combined afterwards. The patient specific characteristics used were gender, diabetes and diuretic use. The results were summarized as a difference in cost and effect between the nodeprescribing and deprescribing strategy. Finally the R-script used for this analysis can be seen in **appendix 1 & appendix 11**.

Deterministic sensitivity analysis (DSA)

A one-way sensitivity analysis was done for the majority of the parameters used in the model. The analysis was done by introducing the minimum or maximum value of a specific parameters. The success rate of deprescribing, hourly wage pharmacist, time spent deprescribing, cost medication, age, cost per stadia, QALYs, transition probabilities and risk ratios were all varied. Afterwards the results of the DSA was summarized as a tornado diagram, for both the cost and the effects. The decision was made to only show the top 15 most influential parameters to prevent clutter. Finally The R-script used to run the DSA can be seen in **appendix 1 & appendix 2**.

Probabilistic sensitivity analysis (PSA)

The uncertainty around the parameters was measured with a probability sensitivity analysis (PSA). This analysis resamples the parameters with a random value from the predefined distribution resulting in a different result each time. In total one thousand reruns were performed for the PSA. The parameters which were varied include: the success rate of deprescribing, hourly wage pharmacist, time spent deprescribing, cost medication, age, cost per stadia, QALYs, transition probabilities and risk ratios. The results of the PSA were plotted as a uncertainty cloud on the cost-effectiveness plane, where the incremental cost was plotted against the incremental effect. Furthermore a cost effectiveness acceptability curve was made that shows the cost-effectiveness of the therapy as a function of willingness to pay for a QALY gain. Finally the R-script used to run the PSA can be found in **appendix 1 & appendix 3**.

Subgroups

Diabetic and diuretic using population analysis

The model was re-run with the same characteristics as the deprescribing pilot except the whole population was assumed to either be diabetic or use diuretics. Therefore the model was toggled to diabetic or diuretic, which altered certain transition probabilities in the model. No changes in starting CKD distributions or age were implemented. In the end a PSA was run for both the diabetic and diuretic scenario. The results of the PSA were plotted as uncertainty clouds. Finally the R-scripts used to run this analysis can be seen in **appendix 1 & appendix 3**. The model was run with a starting age of 76.23 and the following transition matrices: mat_deprescribing_base and mat_nodeprescribing_base. Also either diabetic or diuretic was set to 1 in the script for the corresponding run.

Age analysis

The model was re-run with patient characteristics of the deprescribing pilot, but the pilot was separated into 2 groups. The first group consists of patients younger than or equal to 60 years and the second group was older than 60 years. Both the starting age and the starting CKD distributions were altered accordingly for each group. In the end a PSA was run for both the younger and the older group. The results of the PSA were plotted as uncertainty clouds.

The R-script used to run the model can be found in **appendix 1 & appendix 3**. For the run of the younger population a starting age of 47.30 years was used with the following transition matrices: mat_deprescribing_younger and mat_nodeprescribing_younger. For the older population a starting age of 81.31 was used with the following transition matrices: mat_deprescribing_older and mat_nodeprescribing_older. In both cases the transition matrices contained the found initial CKD distribution.

TAO-UA

The model was re-run with patient characteristics of an individual pharmacy connected to the TAO-UA and a population analysis was performed. This was repeated for multiple pharmacies. The patient characteristics in question were age, gender, diabetic and diuretic use. For the population analysis not each individual patient was re-run into the model, but the model was re-run for each individual patient characteristics instead (for example 21% of the population was diabetic). Afterwards the results for each characteristic were weighted according to their percentage. This was done to reduce the running time of the model. No kidney function was available for the individuals this population. Therefore the initial CKD distribution could not be established and the CKD distribution stated in Elbasha et al(19) was used instead. The results were summarized as a difference in cost and effect between the nodeprescribing and deprescribing strategy for each of the pharmacies. Also the cost of

deprescribing was estimated for the population. This was done by multiplying the individuals who remained after the first selection process with the estimate cost needed to deprescribe one person. Furthermore an estimation of the amount of individuals who underwent a successful deprescription was made. This was done by multiplying the individuals who remained after the first selection process with the found success rate of the pilot. In the end a run was done for all the pharmacies combined. It was assumed that this run was representative for the TAO-UA as a whole. The script for this run can be found in **appendix 1 & appendix 11** and the following transition matrices were used: mat_nodeprescribing_TAO_UA and mat_deprescribing_TAO_UA.

Results

Model inputs

Inputs obtained from literature

The inputs obtained from literature can be found in **Table 6**. These inputs include transition probabilities, health state utilities, cost per CKD stadia and the cost of medication. For the transition probabilities between ckd1-ckd2, ckd2-ckd3a and ckd3a-ckd3b no distributions were available. Therefore no maximum and minimum were determined as well. Furthermore the natural mortality is not shown in the table as this value differs in age and the transitions of ckd5-death, dia-death and kt-death are not yet combined with it. The combining of the probabilities was done in the model itself. For the health state utilities all the inputs were available in the literature, except for the death state which was set to 0. Therefore no distribution, minimum or maximum was needed. For the cost per CKD stadia a couple of assumptions were made. The cost of health state ckd1, cdk2, ckd3a and ckd3b were assumed to equal to the control group. Therefore the same minimum, maximum and distributions were used. Also ckd4 and ckd5 were assumed to be equal, because the literature study pooled the two together. Finally the cost of medication was calculated from data which can be found in **appendix 6**.

Table 6 *Model inputs from literature.*

Transition probability	Mean	Minimum	Maximum	Distributions	Reference
trans_ckd1_ckd2	0.083	0.083	0.083		(19)
trans_ckd2_ckd3a	0.096	0.096	0.096		(19)
trans_ckd3a_ckd3b	0.096	0.096	0.096		(19)
trans_ckd3b_ckd4	0.137	0.095	0.184	beta(shape1=228.42, shape2=1438.88)	(19)
trans_ckd4_ckd5	0.081	0.048	0.123	beta(shape1=110.09, shape2=1249.03)	(19)
trans_ckd5_dia	0.626	0.433	0.788	beta(shape1=126.69, shape2=75.69)	(19)
trans_ckd5_kt	0.009	0.005	0.016	beta(shape1=77.08, shape2=8487.72)	(19)
trans_dia_kt	0.019	0.009	0.033	beta(shape1=67.16, shape2=3467.81)	(19)
trans_kt_dia	0.046	0.011	0.118	beta(shape1=19.34, shape2=401.12)	(19)
trans_ckd5_death	0.108	0.064	0.166	beta(shape1=105, shape2=867.26)	(19)
trans_dia_death	0.167	0.126	0.210	beta(shape1=348.45, shape2=1738.08)	(19)
trans_kt_death	0.028	0.005	0.078	beta(shape1=16.04, shape2=556.64)	(19)
rr_ckd	1.32	1.190	1.460	lognormal(meanlog=0.277632, sdlog=0.052164)	(17)
rr_esrd	1.88	1.710	2.070	lognormal(meanlog=0.631272, sdlog=0.048739)	(17)
rr_diabetes	1.82	1.220	1.720	lognormal(meanlog=0.598837, sdlog=0.087621)	(17)
rr_diuretica	2.29	2.090	2.500	lognormal(meanlog=0.828552, sdlog=0.045696)	(17)

Health state Quality of life (QOL)	Mean (QOL)	Minimum (QOL)	Maximum (QOL)	Distributions	Reference
qaly_ckd1	0.9	0.728	0.982	beta(shape1=152.76, shape2=16.97)	(19)
qaly_ckd2	0.9	0.728	0.982	beta(shape1=152.76, shape2=16.97)	(19)
qaly_ckd3a	0.87	0.732	0.958	beta(shape1=198.89, shape2=29.72)	(19)
qaly_ckd3b	0.87	0.732	0.958	beta(shape1=198.89, shape2=29.72)	(19)
qaly_ckd4	0.85	0.709	0.939	beta(shape1=229.65, shape2=40.53)	(19)
qaly_ckd5	0.7	0.663	0.871	beta(shape1=344.97, shape2=100.15)	(19)
qaly_dia	0.525	0.454	0.594	beta(shape1=729.38, shape2=659.91)	(19)
qaly_kt	0.84	0.702	0.933	beta(shape1=245.02, shape2=46.67)	(19)
qaly_death	0	0	0		
Cost per stadia (€)	**Mean (€)**	**Minimum (€)**	**Maximum (€)**	**Distributions**	**Reference**
cost_20_ckd1	1,229	0	7,276	gamma(mean=1228, sd=2082)	(21)
cost_20_ckd2	1,229	0	7,276	gamma(mean=1228, sd=2082)	(21)
cost_20_ckd3a	1,229	0	7,276	gamma(mean=1228, sd=2082)	(21)
cost_20_ckd3b	1,229	0	7,276	gamma(mean=1228, sd=2082)	(21)
cost_20_ckd4	8,630	71	36,315	gamma(mean=8633,sd=10029)	(21)
cost_20_ckd5	8,630	71	36,315	gamma(mean=8633, sd=10029)	(21)
cost_20_kt	15,518	569	54,250	gamma(mean=15515, sd=14570)	(21)
cost_20_dia	89,999	36,887	166,353	gamma(mean=89987, sd=33420)	(21)
cost_45_ckd1	2,240	0	13,675	gamma(mean=2237, sd=3926)	(21)
cost_45_ckd2	2,240	0	13,675	gamma(mean=2237, sd=3926)	(21)
cost_45_ckd3a	2,240	0	13,675	gamma(mean=2237, sd=3926)	(21)
cost_45_ckd3b	2,240	0	13,675	gamma(mean=2237, sd=3926)	(21)
cost_45_ckd4	11,571	110	48,005	gamma(mean=11575, sd=13234)	(21)
cost_45_ckd5	11,571	110	48,005	gamma(mean=11575, sd=13234)	(21)
cost_45_kt	15,571	697	52,765	gamma(mean=15570, sd=14086)	(21)
cost_45_dia	94,118	37,963	175,298	gamma(mean=94109, sd=35464)	(21)
cost_65_ckd1	3,614	1	19,622	gamma(mean=3611, sd=5566)	(21)
cost_65_ckd2	3,614	1	19,622	gamma(mean=3611, sd=5566)	(21)
cost_65_ckd3a	3,614	1	19,622	gamma(mean=3611, sd=5566)	(21)
cost_65_ckd3b	3,614	1	19,622	gamma(mean=3611, sd=5566)	(21)
cost_65_ckd4	12,967	207	50,748	gamma(mean=12970,sd=13882)	(21)
cost_65_ckd5	12,967	207	50,748	gamma(mean=12970, sd=13882)	(21)
cost_65_kt	17,497	876	58,165	gamma(mean=17486, sd=15468)	(21)
cost_65_dia	91,828	38,478	167,954	gamma(mean=91818, sd=33407)	(21)
cost_75_ckd1	5,208	9	25,080	gamma(mean=5204, sd=7031)	(21)
cost_75_ckd2	5,208	9	25,080	gamma(mean=5204, sd=7031)	(21)
cost_75_ckd3a	5,208	9	25,080	gamma(mean=5204, sd=7031)	(21)
cost_75_ckd3b	5,208	9	25,080	gamma(mean=5204, sd=7031)	(21)
cost_75_ckd4	11,929	298	44,088	gamma(mean=11926, sd=11956)	(21)
cost_75_ckd5	11,929	298	44,088	gamma(mean=11926, sd=11956)	(21)
cost_75_kt	16,569	893	54,393	gamma(mean=16561, sd=14426)	(21)
cost_75_dia	85,650	40,268	148,520	gamma(mean=85642, sd=27784)	(21)

Cost medication with dispensing fee (€)	Mean (€)	Minimum (€)	Maximum (€)	Distributions	Reference
cost_medication	46.83	38.80	57.06	gamma(mean=46.83, sd=6.28)	(23), (24)

Cost deprescribing

The deprescribing process contained the following steps: first selection, second selection, invitation, consult, evaluation, first follow-up, second follow-up and annual follow-up. The total time spent on each step was calculated first and afterwards divided over the total group size of 48 patients. The time spent on each step of the deprescribing process can be found in **appendix 7**.

The first selection corresponds to the search in Pharmacon which was performed on the whole population of the pharmacy. The search itself took around 1 hour and resulted in 289 potential candidates who qualify for the second selection step. Therefore not 48, but 289 patients were used as a total group size. The total amount of time spent on the first selection, second selection and invitation was given. This was not the case for the consultation, evaluation and follow-up where the time spent per session was estimated. Therefore the time spent per session was multiplied by the amount of sessions done. Furthermore the consult was split into two categories: no reply and reply. In the no reply categories the pharmacist had to contact the patient while in the reply category the patient contacted the pharmacy. The second option resulted in less time spent. Also the hourly wage of a managing pharmacists and a corresponding distribution was estimated with the help of wage scale that can be found in **appendix 8**. On average it took 0.39 hours (23 minutes) to deprescribe one person independent of the outcome and excluding the annual follow-up. The time needed to successfully deprescribe one person was 0.89 hours (53 minutes). Finally the input related to the cost of deprescribing can be seen in **Table 7**.

Table 7 *Input cost deprescribing.*

Deprescribing step	mean (hours)	min (hours)	max (hours)	Distribution
time_first_selection	0.00346	0.003114	0.003806	lognormal(meanlog=-5.667, sdlog=0.050)
time_second_selection	0.167	0.15	0.183	lognormal(meanlog=-1.790, sdlog=0.050)
time_invitation	0.01	0.009	0.011	lognormal(meanlog=-4.605, sdlog=0.050)
time_noreply_consult	0.052	0.042	0.063	lognormal(meanlog=-2.957, sdlog=0.101)
time_reply_consult	0.031	0.021	0.042	lognormal(meanlog=-3.474, sdlog=0.173)
time_evaluation	0.052	0.047	0.057	lognormal(meanlog=-2.957, sdlog=0.048)
time_followup	0.039	0.026	0.052	lognormal(meanlog=-3.244, sdlog=0.173)
time_annual_followup	0.039	0.026	0.052	lognormal(meanlog=-3.244, sdlog=0.173)
Hourly wage	**mean (€)**	**min (€)**	**max (€)**	**Distribution**
hourly_wage_pharmacist	44.39	34.78	56.65	gamma(mean=44.91, sd=6.91)

Pilot

Population characteristics

The pilot contained data of 83 patients and a summary of it can be found in **Table 8**. The data corresponding to each individual pharmacy is stored on Unishare. Full data containing age, gender, diabetic status and loop diuretic use was available for 70 of the patients. The average age of this population was 76.23 (95% CI: 72.93-79.53). Furthermore the majority of this population was female with only 37% (95% CI: 31%–43%) being male. The population also had a high percentage of people with diabetes. This percentage was 33% (95% CI: 27%-38%). Also loop diuretics were prevalent in this population with 14% (95% CI: 10%-19%). Additionally a success rate of deprescribing was estimated. In total 48 patients underwent the full deprescribing process and out of this 15 were successfully deprescribed. This resulted in a success rate of 31% (95% CI: 26%-37%). In the pilot the eGFR values were also available for 70 of the patients. The patients could therefore be stratified into CKD stadia and an initial distribution was made.

Table 8 *Population pilot characteristics.*

Characteristic	Value
Participants	83
Average age (years)	76.23 (95% CI: 72.93-79.53)
Gender male (%)	37 (95% CI: 31–43)
Diabetics (%)	33 (95% CI: 27-38)
Loop diuretic use (%)	14 (95% CI: 10-19)
Success rate deprescribing (%)	31 (95% CI: 26-37)
Stadia CKD	**amount**
Ckd1	6
Ckd2	43
Ckd3a	13
Ckd3b	8
Ckd4	2
Ckd5	0

Base case analysis

The found average age of the pilot population was implemented in the model and transition matrices were made with the corresponding CKD distribution. With these inputs the model predicted that deprescribing of the pilot population would be more effective and cheaper when compared to nodeprescribing, with a cost reduction of €6,359 per person and an increase in effect of 0.124 QALYs per person. Therefore deprescribing is expected to be the dominating strategy.

Population analysis

The model predicted that deprescribing of the pilot population was more effective and cheaper when compared to nodeprescribing, with a cost reduction of €6,733 per person and an increase in effect of 0.234 QALYs per person. Therefore deprescribing is expected to be the dominating strategy.

Deterministic sensitivity analysis (DSA)

In **Figure 3** the top 15 most influential inputs can be seen related to the costs. The tornado diagram shows the difference in cost between the base run and a run in which the parameters were set to minimum or maximum value.

The most influential inputs are cost a person older>75 years has undergoing dialysis, the success rate of deprescribing, cost a person older>75 years has in stadia ckd4, cost a person older>75 years has in stadia ckd3a, cost a person older>75 years has in stadia ckd2, risk ratio related to end stage renal disease, transition ckd4-ckd5, cost a person older>75 years has in stadia ckd5, transition ckd3b-ckd4, transition dia-death, trans ckd5-dia, transition ckd5-death, risk ratio related to chronic kidney disease, cost a person older>75 years has in stadia ckd1 and cost a person older>75 years has in stadia ckd3b.

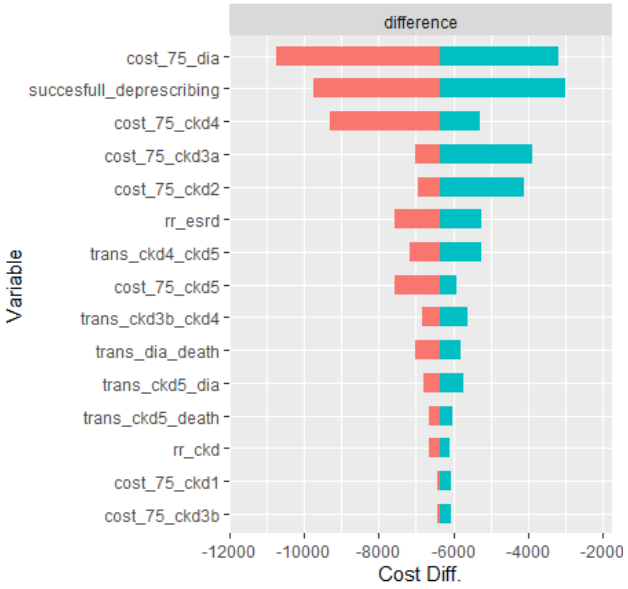

Figure 3 *Tornado diagram of the cost as a result of the DSA..*

In **Figure 4** the top 15 most influential inputs can be seen, but now related to the effect size instead of the cost. The inputs with the most impact are the success rate of deprescribing, transition ckd4-ckd5, risk ratio related to end stage renal disease, the utilities of ckd3a, the utilities of ckd2, transition ckd3b-ckd4, the utilities of ckd4, the utilities related to dialysis, risk ratio related to chronic kidney disease, transition dia-death, the utilities of ckd5, transition ckd5-death , the utilities of ckd3b, the utilities of ckd1 and the transition of ckd5-dia.

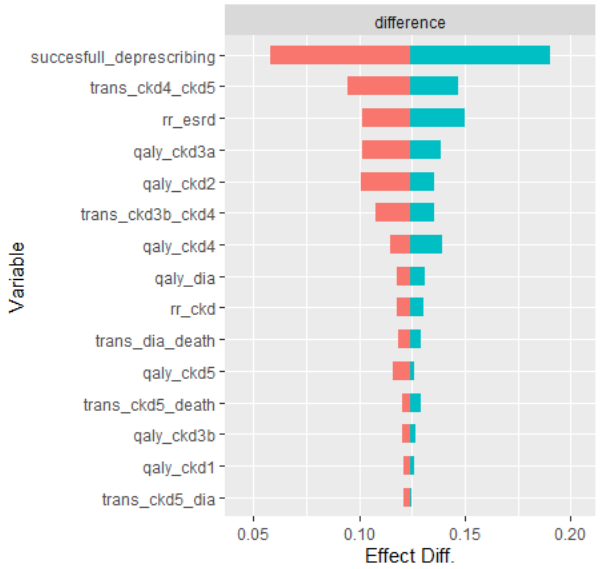

Figure 4 *Tornado diagram of the effect as a result of the DSA.*

Probabilistic sensitivity analysis (PSA)

The cost-effectiveness plane obtained from the PSA can be seen in **Figure 5**. It shows the cost and effects that nodeprescribing has compared to deprescribing. All of the individual re-runs show that nodeprescribing is both the more expensive and less effective strategy. On average the PSA showed that nodeprescribing, when compared to deprescribing, results in an extra cost of €6,414 person and a loss of 0.122 QALYs per person. Also a cost-effectiveness acceptability curve was made which can be seen in **Figure 6**. This showed that even at a willingness to pay of €100 deprescribing still has a probability of being cost-effective of almost 100%. While the chance of nodeprescribing being cost-effective is almost 0% for the same willingness to pay.

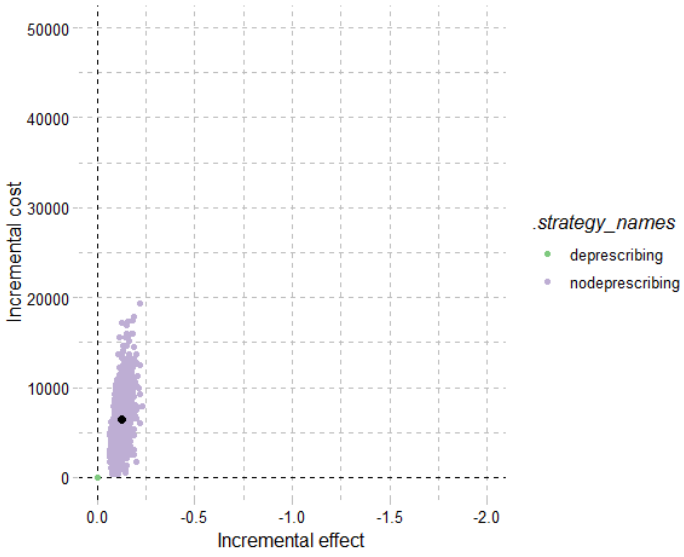

Figure 5 *Cost-effectiveness plane of the base case.*

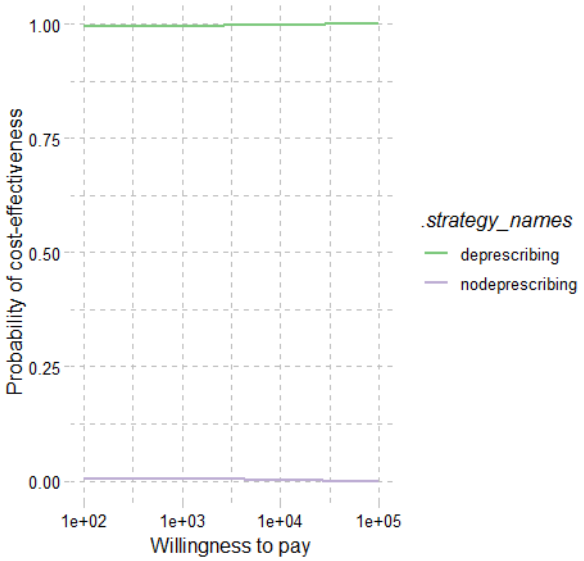

Figure 6 *Cost-effectiveness acceptability curve of the base case.*

Subgroup analysis

The cost-effectiveness plane for the diabetic population can be seen in **Figure 7**. It shows that in the vast majority of the re-runs nodeprescribing is both more expensive and less effective. There are however a couple of re-runs visible where nodeprescribing is less expensive and less effective when compared to deprescribing. On average however the PSA showed that nodeprescribing, when compared to the deprescribing, costs €7,537 more while also a loss of 0.138 QALYs per person was expected. The cost-effectiveness plane for the diuretic using population can be seen in **Figure 8**. The plot shows that in the majority of the resampled runs nodeprescribing is both more expensive and less effective. There are however a couple of runs visible where nodeprescribing is around the same cost or more expensive when compared to deprescribing, but it was always accompanied by a reduction in effect. On average the PSA showed that nodeprescribing, when compared to deprescribing, costs €7,797 while also a loss of 0.147 QALYs was expected. No cost-effectiveness acceptability curve was plotted for both the diabetic and diuretic using population, because these plots were almost identical to the one found in **Figure 6**.

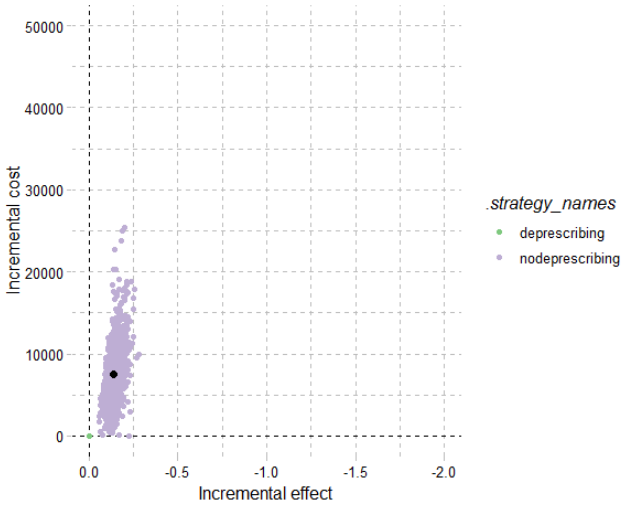

Figure 7 *Cost-effectiveness plane of a fully diabetic population.*

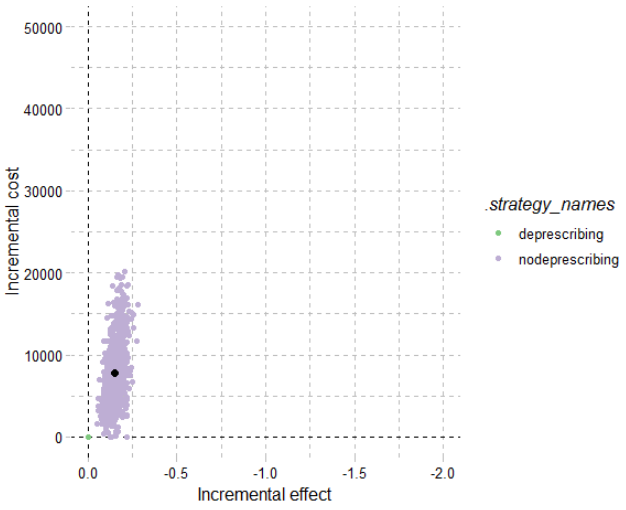

Figure 8 *Cost-effectiveness plane of a fully diuretic using population.*

The second subgroup analysis was based on age. The pilot population was divided into two groups with one group consisting of individuals younger than or equal to 60 years of age, while the other group consisted of individuals older than 60. The characteristics of these populations can be seen in **Table 9**. The younger group consisted of 11 individuals of which only 6 of them had information about the eGFR. This group had an average age of 47.30 years and an initial distribution was made accordingly. The older group consisted of 72 individual of which 66 of them had complete information. This group had an average age of 81.31 years and an initial distribution was made accordingly.

Table 9 *Patient characteristics of the pilot stratified by age .*

Characteristic	Complete pilot	<60 years	>60 years
Participants (complete)	83 (72)	11 (6)	72 (66)
Average age (years)	76.23	47.30	81.31
Ckd1	6	2	4
Ckd2	43	4	39
Ckd3a	13	0	13
Ckd3b	8	0	8
Ckd4	2	0	2
Ckd5	0	0	0

The cost-effectiveness plane for the younger population can be seen in **Figure 9**. The plot shows that in all of the individual re-runs nodeprescribing is both more expensive and less effective. On average the PSA showed that nodeprescribing, when compared to deprescribing, costs €17,262 more while also a loss of 0.960 QALYs per person was expected. Furthermore the cost-effectiveness plane for the older population can be seen in **Figure 10**. On average the PSA showed that nodeprescribing, when compared to deprescribing, costs €3,996 more while also a loss of 0.061 QALYs per person was expected.

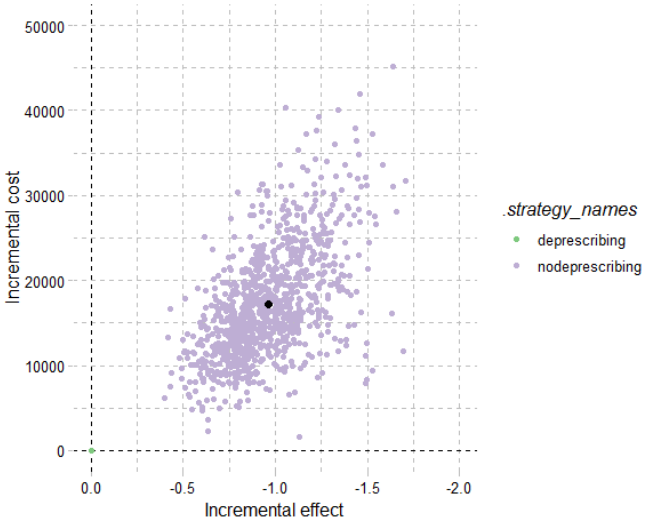

Figure 9 *Cost-effectiveness plane for the pilot population younger than or equal to an age of 60 years.*

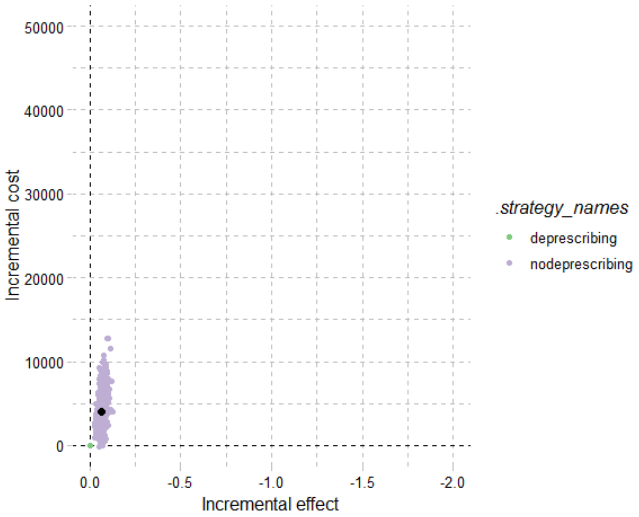

Figure 10 *Cost-effectiveness plane for the pilot population older than 60 years.*

TAO-UA

In total the population of 8 different pharmacies were used to measure the impact of deprescribing on an average TAO-UA pharmacy. The results for each individual pharmacy can be found in **Table 10**. The data corresponding to each individual pharmacy is stored on Unishare. On average a TAO-UA pharmacy had a population of around 11,747 (95% CI: 9,998 to 13,496) patients of which 1,107 (95% CI: 907 to 1,308) used PPI chronically. After the first selection it was estimated that around 797 (95% CI: 661 to 934) would continue the rest of the deprescribing process. This population was predominantly expected to be female with only 46% (95% CI: 45% to 48%) of the population being male. Furthermore the amount of individuals with diabetes was expected to be around 18% (95% CI: 16% to 20%) and around 10% (95% CI: 9% to 12%) of the population was expected to use loop diuretics. In the end it was expected that on average 249 (95% CI: 206 to 291) would be successfully deprescribed. The total cost needed to deprescribe the whole population would cost around €13,928 (95% CI: €11,538 to €16,317) excluding the annual evaluation. Finally deprescribing was expected to be dominant strategy for each of the individual pharmacies. On average nodeprescribing, when compared to deprescribing, would cost €11,363 more while also a loss of 0.366 QALY per person was expected.

Table 10 *Population analysis of several individual TAO-UA pharmacies.*

	Pharmacy 1	Pharmacy 2	Pharmacy 3	Pharmacy 4	Pharmacy 5	Pharmacy 6	Pharmacy 7	Pharmacy 8	Average TAO-UA pharmacy
Population	7637	13181	9865	15177	11733	11895	15089	9400	11747 (95% CI: 9998 to 13496)*
patients with >3 PPIs dispenses per year	825	1551	959	1620	852	909	1085	1057	1107 (95% CI: 907 to 1308)*
Population remaining after the first selection	601	1024	677	1168	615	616	852	826	797 (95% CI: 661 to 934)*
average age (years)	63.70	69.90	65.07	64.01	62.51	64.85	65.44	60.85	65.54 (95% CI: 62.83 to 66.25)*
gender male	44%	42%	47%	45%	49%	47%	48%	47%	46% (95% CI: 45% to 48%)*
diabetics	21%	18%	18%	19%	20%	18%	12%	18%	18% (95% CI: 16% to 20%)*
diuretics	12%	14%	12%	10%	10%	11%	6%	8%	10% (95% CI: 9% to 12%)*
Successfully deprescribed Patients	188	320	212	365	192	193	266	258	249 (95% CI: 206 to 291)*
Cost deprescribing (€)	10497	17886	11825	20402	10742	10759	14882	14428	13928 (95% CI: 11538 to 16317)*
Costs nodeprescribing compared to deprescribing (€)	12060	8666	10867	11407	12461	11384	10633	13433	11363
QALYs nodeprescribing compared to deprescribing	-0.399	-0.226	-0.332	-0.363	-0.423	-0.361	-0.324	-0.497	-0.366

**The confidence interval relates to the mean of the individual pharmacies and is therefore not obtained with the model itself.*

Discussion

For this project a cohort level Markov model was used. This was preferred over simpler methods, because of its ability to analyze processes over a long period of time. Which is an essential factor in chronic kidney disease (CKD) where progression of the disease can take multiple years even decades to manifest. While the meta-analysis of Sugrue et al(15) also provided a summary of state transitions the choice was made to only use the probabilities of an individual study. This was preferable because many of the individual studies in Sugrue et al(15) only used the higher stadia of CKD and did not describe the earlier stages. This led to discrepancies in the earlier stadia.

At first glance the deprescribing pilot done by the TAO-UA was expected to be cost effective according to the model, with the PSA of the base case analysis showing that on average nodeprescribing results in €6,414 extra cost per person while also a loss of 0.122 QALYs was expected when compared to deprescribing. This means that deprescribing dominates nodeprescribing and therefore deprescribing should be prioritized. This was true even for a situation in which no differentiation was made for diabetic and diuretic users inside the population. That deprescribing was the dominating strategy could also be seen in the cost-effectiveness acceptability curve. In which deprescribing had a chance to be cost-effective close to 100% even when the willingness to pay for it was low. In the case of nodeprescribing the chance of this strategy to be cost-effective was close to 0%.

In the population analysis of the pilot different patient characteristics were implemented into the model. These characteristics were gender, diabetes and diuretic use. The updated inputs showed that nodeprescribing resulted in €6,733 extra cost per person and 0.234 QALYs lost person, which is an increase in cost-effectiveness when compared to the base case. This increase in cost-effectiveness could be explained by the introduction of the diabetic and diuretic using population into the model, which was shown in the subgroup analysis to result in an increase from (€6,414 extra cost and 0.122 QALYs lost per person) to (€7,537 extra cost and 0.138 QALYs lost per person) and (€7,797 extra cost and 0.147 QALYs lost per person) respectively. In the subgroup analysis 100% of the population was either diabetic or used loop diuretics. Therefore the increase was expected to be lower in a normal population. Finally gender also impacted the cost-effectiveness of the therapy. In the base case the majority of the population was female. Therefore the individuals would spent more time in the model as women's mortality rate was lower compared to men's mortality rate. This allows the individuals inside the model to reach the later health states more often and there is also more time to get a return of investment from the deprescribing itself.

Diabetic and loop diuretic use were implemented in the model as they were considered risk factors by the meta-analysis from Hussain et al (17). In this analysis diuretics were named in general, but no mechanism of action could be found in the literature. Therefore after communicating with members of the TAO-UA it was restricted to only loop diuretics. Loop diuretics can be used in the case of chronic heart failure to counter a patients water retention, which is a signal that the heart failure is not fully under control (26). Heart failure itself leads to the progression CKD and CKD can lead to chronic heart failure (27). Loop diuretics are also used for hypertension in the case a patient already has an eGFR lower than 45 ml/min/1.73 m^2. Therefore it could be possible that loop diuretic use does not directly decline the kidney function in combination PPIs, but the morbidities it is used for do. This could still make prioritizing loop diuretic users a possibility. Finally diabetes is a known risk factor for CKD (28).

An analysis was done for different age groups inside of the pilot population. The difference in age between these groups was relatively large. With the younger group having an average age of around 47 years while the older population was around 81 years. Furthermore a difference in eGFR was visible between the two groups. With the younger population consisting mostly of individuals with a kidney function correlating to CKD1 and CKD2 while the older population, still with the majority in CKD2, also had individuals who entered stadia ckd3a, ckd3b and ckd4. In the end the younger population was by far the most cost-effective out of all the different analysis, with the PSA showing that on average nodeprescribing costs €17,262 more per person while also a loss of 0.960 QALYs per person was expected. The older population was by far the least cost-effective with the PSA showing that on average nodeprescribing, when compared to deprescribing, costs €3,996 more per person while also a loss of 0.061 QALYs per person was expected.

The difference in cost-effectiveness between the age groups could be explained by the model itself. When the older population entered into the model with a starting age of 81 years the difference between nodeprescribing and deprescribing was relatively small, because the majority of the population had already died before an impactful difference in health states distribution could be established. Therefore the same amount of people would enter the later stadia for both of the strategies. In the younger population however the difference in health states distributions was more clearly visible when the run progressed. To some extent discounting was expected to help the older population as the impact of deprescribing would be reached earlier when compared to the younger population. In reality however the cost of the later stadia were just too high to be discarded by discounting.

The impact the later stadia had on the model was visible in the DSA, with the cost a person older>75 years has undergoing dialysis being the most impactful. The same was true for the cost related to CKD stadium 4 which has also shown to be quite impactful. This could be explained by CKD stadium 4 being the first health state where an increase in cost was established as the previous health states all had the same value. Furthermore CKD stadium 3a and CKD stadium 2 both had a similar impact. The impact of CKD stadium 5 was relatively low compared to the other stadia even though it had the same cost as CKD stadium 4. This can be explained by the fact that the transition probability from CKD stadium 5 to dialysis is very large. Therefore individuals do not spent a lot of time inside of it. The same is true for CKD stadium 3b where the transition between CKD stadium 3b to CKD stadium 4 is larger than the previous one. Also many of the transition probabilities and risk ratios had impact on the overall cost. Both of these types of parameters determine the speed in which individuals enter and exit the later stadia. This can be explained by the fact that the time spent in the later stadia is the predominant force in this model. Finally the success rate of deprescribing was one of the most influential parameters.

The parameters which impact the effectiveness were different compared to the costs. With the Quality of life (QOL) related to the lower stadia being more impactful than the higher ones. In these stadia the QOL rewards are the highest. Furthermore the majority of the population will spent most its time inside these stadia. Therefore a reduction or increase of the rewards will be quite impactful. The same principle is true for several transition probabilities and risk ratios that can be seen in the DSA. These parameters determine the speed in which patients exit the lower stadia and therefore altered the overall QALYs. Also several transitions to death were visible in the DSA, while this was not the case for the costs. This can be explained by the huge difference in QOL between the CKD transition states and death. Finally the success rate of deprescribing was the most influential parameter.

The results from the individual pharmacies of the TAO-UA corresponds with the finding of the subgroup analysis where the starting age was the most impactful. This is also visible in the **Table 10**, where if the pharmacies are sorted by average age from lowest to highest the cost-effectiveness will follow accordingly. The impact of the diabetic and diuretic using population was relatively small. This can be explained by the fact that on average only 18% (95% CI: 16% to 20%) of the population was diabetic and 10% (95% CI: 9% to 12%) of the population used loop diuretics. This was quite a difference from the 100% used in the subgroup analysis. For all the individual pharmacies deprescribing was expected to be the dominant strategy.

The result from the individual pharmacies of the TAO-UA were not fully accurate, because Clopidogrel was forgotten to be included in the search for the first selection step by accident. This results in more patients who can undergo the deprescribing process. Furthermore no second selection step could be done for the individual pharmacies, because the time needed to perform the manual search was not realistic for this research. Therefore no invitation, consults and follow-up could be done as well. This required extrapolation of the results from the pilot to the individual pharmacies, which was done with the found success rate from the pilot. The success rate was determined by dividing the remaining population after the first selection step by the population which was successfully deprescribed. It contained therefore all the unknown individual steps.

All the findings indicate that deprescribing is the dominating strategy for the TAO-UA with on average nodeprescribing, when compared to deprescribing, costing €11,363 more per person while a loss of 0.366 QALY per person was expected. To perform the deprescribing an initial investment has to be made of €13,928 (95% CI: €11,538 to €16,317). This was without the lost revenue of the pharmacy from dispensing PPIs when deprescribing is successful. It is recommended to deprescribe the whole patient population. If this is not possible younger patients should be prioritized first. The diuretic using or diabetic population can also be prioritized and would result in an increase of cost-effectiveness, but a less influential one.

The indication that deprescribing dominated nodeprescribing was expected due to the nature of deprescribing PPIs. In which the patient has no benefit from the medication, but the potential side effects are still there. Therefore even if the deprescribing would be too costly it would still be accompanied by an increase of quality of life. Furthermore a onetime cost related to the deprescribing removes both the constant cost related to the medication and the potential future cost of the side effects if deprescribing was successful. This allowed the deprescribing to pay for itself quite fast. Especially since the time needed to deprescribe a single person was around 0.39 hours (23 minutes) independent of the outcome. This was unexpectedly low when considering the time it takes to successfully deprescribe one person was around 0.89 hours (53 minutes). This difference could be explained by the fact that most individuals quit the process during the second selection step or declined the invitation. In this case no consult, evaluation and follow-up was needed. This cuts the overall time down quite significantly as these steps were among the most time consuming.

The deprescribing process was initially performed by a managing pharmacists, but could in the future be optimized to reduce costs. Firstly a pharmacy assistant could schedule an appointment with the patient. This would be especially useful when a participant does not reply to the initial invitation. Secondly a pharmacy assistant could take over some of the data gathering from the second selection step. Finally the annual follow-up took place in person, but could in the future be done by email or letter.

The strengths of this project came from the close interaction with the TAO-UA, which resulted in the use of different patient populations from multiple pharmacies. Furthermore the model uses costs related to CKD obtained from a recent study done in 2020. This study does not only take into account the direct costs of CKD, but also potential co-morbidities. The model also had a couple of disadvantages. For example, the premise that PPIs induce CKD was based on observational studies. Therefore no strong correlation can be established. Also no extra validation steps for the model were performed. On top of that the uncertainty around age was not implemented in the model, because age was tied to the initial CKD distribution and not enough information was available to establish a distribution for every age. This could be a possible improvement for the future. Finally more research could be done for other potential indications related to PPIs as CKD is only one of many.
The use of HEEMOD to make the model had its up- and downsides. The package made the model building itself very simplistic. This made it possible to build a model very quickly without a lot of experience, especially with the available tutorial. The downside however is that deviation from the template would result in problems. For example, the implementation of a success rate took several tries and even required the addition of extra health states to the existing model. Also using functions was not always possible in the parameter section of the model, as it resulted in problems with the PSA. Therefore functions had to be put into the transition matrix which made them difficult to alter. Finally relatively simple tasks like altering a graph resulted in problems as the data frame used to store the values was considered to be unique.

Conclusion

Deprescribing was expected to the dominant strategy for an average TAO-UA pharmacy with on average cost reduction of €11,363 while also gaining 0.366 QALYs per person. This required an initial investment of around €17.47 per person with the annual follow-up excluded. If not everyone in the population can be deprescribed the younger population should be prioritized.

Reference list

1. Strand DS, Kim D, Peura DA. 25 Years of Proton Pump Inhibitors: A Comprehensive Review. Gut Liver. 2017 Jan 15; 11(1):27–37. Available from: https://www.gutnliver.org/journal/view.html?doi=10.5009/gnl15502

2. Farley A, Wruble LD, Humphries TJ. Rabeprazole versus ranitidine for the treatment of erosive gastroesophageal reflux disease: a double-blind, randomized clinical trial. Raberprazole Study Group. Am J Gastroenterol. 2000; 95(8):1894–9. Available from: https://pubmed.ncbi.nlm.nih.gov/10950032/

3. Stichting Farmaceutische Kengetallen, augustus 2021.

4. Moriarty F, Hardy C, Bennett K, Smith SM, Fahey T. Trends and interaction of polypharmacy and potentially inappropriate prescribing in primary care over 15 years in Ireland: a repeated cross-sectional study. BMJ Open. 2015 Sep 1; 5(9):e008656. Available from: https://bmjopen.bmj.com/content/5/9/e008656

5. Thomson ABR, Sauve MD, Kassam N, Kamitakahara H. Safety of the long-term use of proton pump inhibitors. World J Gastroenterol. 2010 May 21; 16(19):2323–30. Available from: https://www.wjgnet.com/1007-9327/full/v16/i19/2323.htm

6. Veel Nederlanders slikken onnodig maagzuurremmers “Many Dutchmen use unecessary Antacids” . De Volkskrant [Internet]. [cited 2022 Mar 23]. Available from: https://www.volkskrant.nl/wetenschap/veel-nederlanders-slikken-onnodig-maagzuurremmers~bae9bdd6/?utm_source=link&utm_medium=app&utm_campaign=shared%20content&utm_content=free

7. Reeve E, Gnjidic D, Long J, Hilmer S. A systematic review of the emerging definition of ‘deprescribing’ with network analysis: implications for future research and clinical practice. Br J Clin Pharmacol. 2015 Dec 1; 80(6):1254. Available from: /pmc/articles/PMC4693477/

8. Dharmarajan TS. The Use and Misuse of Proton Pump Inhibitors: An Opportunity for Deprescribing. J Am Med Dir Assoc. 2021 Jan 1;22(1):15–22.

9. Waldum HL, Qvigstad G, Fossmark R, Kleveland PM, Sandvik AK. Rebound acid hypersecretion from a physiological, pathophysiological and clinical viewpoint. Scand J Gastroenterol. 2010; 45(4):389–94. Available from: https://www.tandfonline.com/action/journalInformation?journalCode=igas20

10. Kennisdocument Protonpompremmers “Information Protonpumpinhibitors”. NHG.org [Internet]. [cited 2022 Mar 8]. Available from: https://www.nhg.org/actueel/nieuws/nieuwe-module-bij-mdr-polyfarmacie-bij-ouderen-minderen-en-stoppen-van-medicatie

11. Preventie van maagcomplicaties door geneesmiddelgebruik “Prevention of stomachcomplication caused by the use of medication". NHG-Richtlijnen [Internet]. [cited 2022 Mar 25]. Available from: https://richtlijnen.nhg.org/behandelrichtlijnen/preventie-van-maagcomplicaties-door-geneesmiddelgebruik

12. RStudio Team. RStudio: Integrated Development Environment for R [Internet]. Boston, MA: RStudio, PBC; 2021. Available from: http://www.rstudio.com/

13. Filipović-Pierucci A, Zarca K, Durand-Zaleski I. Markov Models for Health Economic Evaluations: The R Package heemod. 2017; Available from: http://arxiv.org/abs/1702.03252

14. Wickham H. ggplot2: Elegant Graphics for Data Analysis [Internet]. Springer-Verlag New York; 2016. Available from: https://ggplot2.tidyverse.org

15. Sugrue DM, Ward T, Rai S, McEwan P, van Haalen HGM. Economic Modelling of Chronic Kidney Disease: A Systematic Literature Review to Inform Conceptual Model Design. Pharmacoeconomics. 2019 Dec 1; 37(12):1451. Available from: /pmc/articles/PMC6892339/

16. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD. Am J Kidney Dis. 2014 May 1; 63(5):713–35. Available from: http://www.ajkd.org/article/S0272638614004910/fulltext

17. Hussain S, Singh A, Habib A, Najmi AK. Proton pump inhibitors use and risk of chronic kidney disease: Evidence-based meta-analysis of observational studies. Clin Epidemiol Glob Heal. 2019 Mar 1;7(1):46–52.

18. Preventie van maagcomplicaties door geneesmiddelgebruik “Prevention of stomachcomplication caused by the use of medication". NHG-Richtlijnen [Internet]. [cited 2022 Mar 13]. Available from: https://richtlijnen.nhg.org/behandelrichtlijnen/preventie-van-maagcomplicaties-door-geneesmiddelgebruik

19. Elbasha E, Greaves W, Roth D, Nwankwo C. Cost-effectiveness of elbasvir/grazoprevir use in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and chronic kidney disease in the United States. J Viral Hepat. 2017 Apr 1; 24(4):268–79. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/jvh.12639

20. Gray A, Clarke PM, Wolstenholme JL, Wordsworth S. Applied methods of cost-effectiveness analysis in health care. 2011; pp.262.

21. van Oosten MJM, Logtenberg SJJ, Leegte MJH, Bilo HJG, Mohnen SM, Hakkaart-Van Roijen L, et al. Age-related difference in health care use and costs of patients with chronic kidney disease and matched controls: analysis of Dutch health care claims data. Nephrol Dial Transplant. 2020 Dec 4; 35(12):2138–46. Available from: https://academic.oup.com/ndt/article/35/12/2138/5584281

22. Alexandernel14. Gamma MLE R [Internet]. github. 2020. Available from: https://github.com/alexandernel14/Gamma-Distribution-MLE/blob/main/Gamma MLE R.R

23. Kostenoverzicht protonpompremmers bij maagbescherming “Cost overview of protonpumpinhibitors indicated for stomachprotection” [Internet]. [cited 2022 Mar 8]. Available from: https://www.farmacotherapeutischkompas.nl/bladeren/indicatieteksten/kostenoverzicht/modal/maagbescherming/maagbescherming/protonpompremmers

24. Maagklachten “Stomach disorders”. NHG-Richtlijnen [Internet]. [cited 2022 Mar 8]. Available from: https://richtlijnen.nhg.org/standaarden/maagklachten

25. Kosten en vergoeding “Costs and compensation”. BENU apotheek [Internet]. [cited 2022 Mar 14]. Available from: https://www.benuapotheek.nl/medische-zorg/medicijnen/kosten-en-vergoeding

26. furosemide [Internet]. [cited 2022 Mar 25]. Available from: https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/f/furosemide

27. Schefold JC, Filippatos G, Hasenfuss G, Anker SD, Von Haehling S. Heart failure and kidney dysfunction: epidemiology, mechanisms and management. Nat Rev Nephrol 2016 1210. 2016 Aug 30; 12(10):610–23. Available from: https://www.nature.com/articles/nrneph.2016.113

28. Thomas MC, Cooper ME, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat Rev Nephrol 2015 122. 2015 Nov 10; 12(2):73–81. Available from: https://www.nature.com/articles/nrneph.2015.173

Appendix 1: R-script base run.

```
library(heemod)
```

#The starting age of the population was implemented into the model by altering age_base. Furthermore age_cycle allows the patients to age with each cycle.

```
par_mod=define_parameters(age_base=76.23, age_cycle=(model_time)+age_base-1)
```

#Get_who_mr() gets a specific mortality probability as a function of age and sex for a specific country. In this run sex=sex_indiv is removed to pool both female and male mortality rates. For the population analysis sex=sex_indiv was enabled by removing the "#".

```
par_mod=modify(par_mod, sex_indiv="MLE",p_death_all=get_who_mr(age=age_cycle, #sex
=sex_indiv, country="NLD", local=TRUE))
```

#Initial determines the amount of people who participant into a run. Also the success rate corresponding to the pilot can be altered here.

```
par_mod=modify(par_mod, initial=289)
par_mod=modify(par_mod, succesfull_deprescribing=15)
par_mod=modify(par_mod, total_deprescribing=48)
par_mod=modify(par_mod, succes=succesfull_deprescribing/total_deprescribing)
```

#Diabetes and diuretic alter the transitions used in the transition matrix. This is done with the help of a workaround in the following transition: rr_to_prob((rr_diabetes^diabetes*rr_diuretica^diuretica),rr_to_prob(rr_nothing,trans_ckd1_ckd2)).

#If, for example, diabetes is set to 0 (rr_diabetes^0) will be 1. Therefore the probability will not be altered in rr_to_prob(). However when diabetes is set to 1 (rr_diabetes^1)=rr_diabetes and the risk ratio will be introduced to the probability. Finally if both diabetes and diuretic are set to 1 rr_diabetes will be multiplied by rr_diuretics. This results in an unrealistic risk ratio and should therefore be prevented.

```
par_mod=modify(par_mod, diabetes=0)
par_mod=modify(par_mod, diuretica=0)
```

#The parameter below set the cost of the medication.

```
par_mod=modify(par_mod, cost_medication=46.83)
```

#The parameters below have to do with the deprescribing costs.

```
par_mod=modify(par_mod, hourly_wage_pharmacist=44.39)
par_mod=modify(par_mod, time_first_selection=0.0035, cost_first_selection=time_fir
st_selection*hourly_wage_pharmacist)
par_mod=modify(par_mod, time_second_selection=0.167, cost_second_selection=time_se
cond_selection*hourly_wage_pharmacist)
par_mod=modify(par_mod, time_invitation=0.010, cost_invitation=time_invitation*hou
rly_wage_pharmacist)
par_mod=modify(par_mod, time_noreply_consult=0.052)
par_mod=modify(par_mod, time_reply_consult=0.031)
par_mod=modify(par_mod, time_total_consult=time_reply_consult+time_noreply_consult
, cost_total_consult=time_total_consult*hourly_wage_pharmacist)
par_mod=modify(par_mod, time_evaluation=0.052, cost_evaluation=time_evaluation*hou
rly_wage_pharmacist)
```

```
par_mod=modify(par_mod, time_followup=0.039*2, cost_followup=time_followup*hourly_
wage_pharmacist)
par_mod=modify(par_mod, cost_init=cost_first_selection+cost_second_selection+cost_
invitation+cost_total_consult+cost_evaluation+cost_followup)
par_mod=modify(par_mod, time_annual_followup=0.039, cost_annual_followup=time_annu
al_followup*hourly_wage_pharmacist)
par_mod=modify(par_mod, cost_annual=cost_annual_followup)
```

#The parameters below all have to do with the costs and qaly per CKD stadia.

```
par_mod=modify(par_mod, cost_20_ckd1=1229, cost_20_ckd2=1229, cost_20_ckd3a=1229,
cost_20_ckd3b=1229, cost_20_ckd4=8630, cost_20_ckd5=8630, cost_20_dia=89990, cost_
20_kt=15518, cost_20_death=0)


par_mod=modify(par_mod, cost_45_ckd1=2240, cost_45_ckd2=2240, cost_45_ckd3a=2240,
cost_45_ckd3b=2240, cost_45_ckd4=11571, cost_45_ckd5=11571, cost_45_dia=94118, cos
t_45_kt=15571, cost_45_death=0)


par_mod=modify(par_mod, cost_65_ckd1=3614, cost_65_ckd2=3614, cost_65_ckd3a=3614,
cost_65_ckd3b=3614, cost_65_ckd4=12967, cost_65_ckd5=12967, cost_65_dia=91828, cos
t_65_kt=17497, cost_65_death=0)


par_mod=modify(par_mod, cost_75_ckd1=5208, cost_75_ckd2=5208, cost_75_ckd3a=5208,
cost_75_ckd3b=5208, cost_75_ckd4=11929, cost_75_ckd5=11929, cost_75_dia=85650, cos
t_75_kt=16569, cost_75_death=0)


par_mod=modify(par_mod, qaly_ckd1=0.9, qaly_ckd2=0.9, qaly_ckd3a=0.87, qaly_ckd3b=
0.87, qaly_ckd4=0.85, qaly_ckd5=0.7, qaly_dia=0.525, qaly_kt=0.84, qaly_death=0)
```

#The parameters below are the discount ratio's used in the model.

```
par_mod=modify(par_mod, dr_cost=0.04)
par_mod=modify(par_mod, dr_effect=0.015)
```

#The parameters below are the transition probabilities which will be used inside of the transition matrix.

```
par_mod=modify(par_mod, trans_ckd5_death=0.108, trans_dia_death=0.167, trans_kt_de
ath=0.028)
par_mod=modify(par_mod, p_death_ckd5=combine_probs(p_death_all, trans_ckd5_death))
par_mod=modify(par_mod, p_death_dia=combine_probs(p_death_all, trans_dia_death))
par_mod=modify(par_mod, p_death_kt=combine_probs(p_death_all, trans_kt_death))
par_mod=modify(par_mod, trans_ckd1_ckd2=0.083, trans_ckd2_ckd3a=0.096, trans_ckd3a
_ckd3b=0.096, trans_ckd3b_ckd4=0.137, trans_ckd4_ckd5=0.081, trans_ckd5_dia=0.626,
trans_ckd5_kt=0.009, trans_dia_kt=0.019, trans_kt_dia=0.046)
```

#The parameters below are the risk ratios used to alter the transition probabilities. If deprescribing is successful then the patient does not use PPIs anymore. Therefore the patient has no excess risk to get CKD. This correlates with rr_nothing. If the patients does use PPIs then an extra risk was assumed with rr_ckd for transition ckd1-ckd2 and ckd2-ckd3a. rr_esrd was used for transition ckd3a-ckd3b, ckd3b-ckd4 and ckd4-ckd5. The transition is altered inside of the transition matrix.

```
par_mod=modify(par_mod, rr_nothing=1)
par_mod=modify(par_mod, rr_ckd=1.32)
par_mod=modify(par_mod, rr_esrd=1.88)
par_mod=modify(par_mod, rr_diabetes=1.82)
par_mod=modify(par_mod, rr_diuretica=2.29)
```

#The transition matrixes can be seen below. The transition matrix shows the transition probabilities for each health state to the next one. The transition takes place from [collumn1, row1] to [column…, row1]. Different transitions matrixes were made for each situation in which the initial CKD distribution was altered. This was done by altering the row of health state "d". Finally for some transitions a maximum was set, for example p_death_ckd5 (ifelse((p_death_ckd5+trans_ckd5_dia+trans_ckd5_kt>1), (1-trans_ckd5_dia-trans_ckd5_kt), p_death_ckd5)). Without the maximum the sum of all the probabilities exceeded 1, which results in an error message. The error occurred when patients started to exceed the age of 100 and therefore the amount of cycles had to be changed for each individual starting age.

```
mat_nodeprescribing_base=define_transition(state_names=c("d","ckd1_s","ck2_s","ckd
3a_s","ckd3b_s","ckd4_s","ckd5_s","dia_s","kt_s","ckd1", "ckd2", "ckd3a", "ckd3b",
"ckd4", "ckd5", "dia", "kt", "death"),0,0,0,0,0,0,0,0,0,0.083,0.597,0.181,0.111,0.
028,0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to_prob(
rr_nothing,trans_ckd1_ckd2)),0,0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,C,rr_to_p
rob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to_prob(rr_nothing,trans_ckd2_c
kd3a)),0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,C,rr_to_prob(rr_nothing, trans_
ckd3a_ckd3b),0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,0,C,rr_to_prob(rr_nothing,
trans_ckd3b_ckd4),0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,0,0,C,ifelse(rr_to_prob(
rr_nothing, trans_ckd4_ckd5)>1, 1, rr_to_prob(rr_nothing, trans_ckd4_ckd5)),0,0,0,
0,0,0,0,0,0,0,ifelse( rr_to_prob(rr_nothing, trans_ckd4_ckd5)+p_death_all>1, 1-rr_
to_prob(rr_nothing, trans_ckd4_ckd5)/rr_to_prob(rr_nothing, trans_ckd4_ckd5), p_de
ath_all),0,0,0,0,0,0,C,trans_ckd5_dia,trans_ckd5_kt,0,0,0,0,0,0,0,0,(ifelse(p_deat
h_ckd5+trans_ckd5_dia+trans_ckd5_kt>1,1-trans_ckd5_dia-trans_ckd5_kt, p_death_ckd5
)),0,0,0,0,0,0,0,0,C,trans_dia_kt,0,0,0,0,0,0,0,0,ifelse(p_death_dia+trans_dia_kt>1,
1-trans_dia_kt, p_death_dia),0,0,0,0,0,0,0,trans_kt_dia,C,0,0,0,0,0,0,0,0,0,p_death_
kt,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_t
o_prob(rr_ckd,trans_ckd1_ckd2)),0,0,0,0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,C,rr_t
o_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to_prob(rr_ckd,trans_ckd2_ck
d3a)),0,0,0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_esrd, trans_ckd3
a_ckd3b),0,0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_esrd, trans_c
kd3b_ckd4),0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,0,0,C,ifelse(rr_to_prob(rr_esrd
, trans_ckd4_ckd5)>1, 1, rr_to_prob(rr_esrd, trans_ckd4_ckd5)),0,0,ifelse( rr_to_p
rob(rr_esrd, trans_ckd4_ckd5)+p_death_all>1, 1-rr_to_prob(rr_esrd, trans_ckd4_ckd5
)/rr_to_prob(rr_esrd, trans_ckd4_ckd5), p_death_all),0,0,0,0,0,0,0,0,0,0,0,0,0,0,C
,trans_ckd5_dia,trans_ckd5_kt,(ifelse(p_death_ckd5+trans_ckd5_dia+trans_ckd5_kt>1,
1-trans_ckd5_dia-trans_ckd5_kt, p_death_ckd5)),0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,C,tra
ns_dia_kt,ifelse(p_death_dia+trans_dia_kt>1, 1-trans_dia_kt, p_death_dia),0,0,0,0,
0,0,0,0,0,0,0,0,0,0,0,trans_kt_dia,C,p_death_kt,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
C)


mat_deprescribing_base=define_transition(state_names=c("d","ckd1_s","ck2_s","ckd3a
_s","ckd3b_s","ckd4_s","ckd5_s","dia_s","kt_s","ckd1", "ckd2", "ckd3a", "ckd3b", "
ckd4", "ckd5", "dia", "kt", "death"),0,0.083*succes,0.597*succes,0.181*succes,0.11
1*succes,0.028*succes,0,0,0,0.083*(1-succes),0.597*(1-succes),0.181*(1-succes),0.1
11*(1-succes),0.028*(1-succes),0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diur
etica^diuretica,rr_to_prob(rr_nothing,trans_ckd1_ckd2)),0,0,0,0,0,0,0,0,0,0,0,0,0,
0,p_death_all,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to_p
rob(rr_nothing,trans_ckd2_ckd3a)),0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,C,rr
_to_prob(rr_nothing, trans_ckd3a_ckd3b),0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,
```

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0,C,rr_to_prob(rr_nothing, trans_ckd3b_ckd4),0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0
,0,0,0,C,ifelse(rr_to_prob(rr_nothing, trans_ckd4_ckd5)>1, 1, rr_to_prob(rr_nothin
g, trans_ckd4_ckd5)),0,0,0,0,0,0,0,0,0,0,ifelse( rr_to_prob(rr_nothing, trans_ckd4
_ckd5)+p_death_all>1, 1-rr_to_prob(rr_nothing, trans_ckd4_ckd5)/rr_to_prob(rr_noth
ing, trans_ckd4_ckd5), p_death_all),0,0,0,0,0,0,C,trans_ckd5_dia,trans_ckd5_kt,0,0
,0,0,0,0,0,0,(ifelse(p_death_ckd5+trans_ckd5_dia+trans_ckd5_kt>1,1-trans_ckd5_dia-
trans_ckd5_kt, p_death_ckd5)),0,0,0,0,0,0,0,C,trans_dia_kt,0,0,0,0,0,0,0,0,ifelse(
p_death_dia+trans_dia_kt>1, 1-trans_dia_kt, p_death_dia),0,0,0,0,0,0,0,trans_kt_di
a,C,0,0,0,0,0,0,0,0,p_death_kt,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes
*rr_diuretica^diuretica,rr_to_prob(rr_ckd,trans_ckd1_ckd2)),0,0,0,0,0,0,p_death_al
l,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_
to_prob(rr_ckd,trans_ckd2_ckd3a)),0,0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,C,rr
_to_prob(rr_esrd, trans_ckd3a_ckd3b),0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,C
,rr_to_prob(rr_esrd, trans_ckd3b_ckd4),0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,0
,C,ifelse(rr_to_prob(rr_esrd, trans_ckd4_ckd5)>1, 1, rr_to_prob(rr_esrd, trans_ckd
4_ckd5)),0,0,ifelse( rr_to_prob(rr_esrd, trans_ckd4_ckd5)+p_death_all>1, 1-rr_to_p
rob(rr_esrd, trans_ckd4_ckd5)/rr_to_prob(rr_esrd, trans_ckd4_ckd5), p_death_all),0
,0,0,0,0,0,0,0,0,0,0,0,0,0,C,trans_ckd5_dia,trans_ckd5_kt,(ifelse(p_death_ckd5+tra
ns_ckd5_dia+trans_ckd5_kt>1,1-trans_ckd5_dia-trans_ckd5_kt, p_death_ckd5)),0,0,0,0
,0,0,0,0,0,0,0,0,0,0,C,trans_dia_kt,ifelse(p_death_dia+trans_dia_kt>1, 1-trans_d
ia_kt, p_death_dia),0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,trans_kt_dia,C,p_death_kt,0,0,0,
0,0,0,0,0,0,0,0,0,0,0,0,0,0,C)


mat_nodeprescribing_kleiner=define_transition(state_names=c("d","ckd1_s","ck2_s","
ckd3a_s","ckd3b_s","ckd4_s","ckd5_s","dia_s","kt_s","ckd1", "ckd2", "ckd3a", "ckd3
b", "ckd4", "ckd5", "dia", "kt", "death"),0,0,0,0,0,0,0,0,0,0.3333,0.6667,0,0,0,0,
0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to_prob(rr_not
hing,trans_ckd1_ckd2)),0,0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,C,rr_to_prob(rr
_diabetes^diabetes*rr_diuretica^diuretica,rr_to_prob(rr_nothing,trans_ckd2_ckd3a))
,0,0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,C,rr_to_prob(rr_nothing, trans_ckd3a_
ckd3b),0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,0,C,rr_to_prob(rr_nothing, trans_
ckd3b_ckd4),0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,0,0,C,ifelse(rr_to_prob(rr_not
hing, trans_ckd4_ckd5)>1, 1, rr_to_prob(rr_nothing, trans_ckd4_ckd5)),0,0,0,0,0,0,
0,0,0,0,ifelse( rr_to_prob(rr_nothing, trans_ckd4_ckd5)+p_death_all>1, 1-rr_to_pro
b(rr_nothing, trans_ckd4_ckd5)/rr_to_prob(rr_nothing, trans_ckd4_ckd5), p_death_al
l),0,0,0,0,0,0,0,C,trans_ckd5_dia,trans_ckd5_kt,0,0,0,0,0,0,0,0,(ifelse(p_death_ckd5
+trans_ckd5_dia+trans_ckd5_kt>1,1-trans_ckd5_dia-trans_ckd5_kt, p_death_ckd5)),0,0
,0,0,0,0,0,0,C,trans_dia_kt,0,0,0,0,0,0,0,0,ifelse(p_death_dia+trans_dia_kt>1, 1-tra
ns_dia_kt, p_death_dia),0,0,0,0,0,0,0,trans_kt_dia,C,0,0,0,0,0,0,0,0,0,p_death_kt,0,
0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to_pro
b(rr_ckd,trans_ckd1_ckd2)),0,0,0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,C,rr_to_pro
b(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to_prob(rr_ckd,trans_ckd2_ckd3a))
,0,0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_esrd, trans_ckd3a_ckd
3b),0,0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_esrd, trans_ckd3b_
ckd4),0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,0,0,C,ifelse(rr_to_prob(rr_esrd, tra
ns_ckd4_ckd5)>1, 1, rr_to_prob(rr_esrd, trans_ckd4_ckd5)),0,0,ifelse( rr_to_prob(r
r_esrd, trans_ckd4_ckd5)+p_death_all>1, 1-rr_to_prob(rr_esrd, trans_ckd4_ckd5)/rr_
to_prob(rr_esrd, trans_ckd4_ckd5), p_death_all),0,0,0,0,0,0,0,0,0,0,0,0,0,0,C,tran
s_ckd5_dia,trans_ckd5_kt,(ifelse(p_death_ckd5+trans_ckd5_dia+trans_ckd5_kt>1,1-tra
ns_ckd5_dia-trans_ckd5_kt, p_death_ckd5)),0,0,0,0,0,0,0,0,0,0,0,0,0,0,C,trans_dia
_kt,ifelse(p_death_dia+trans_dia_kt>1, 1-trans_dia_kt, p_death_dia),0,0,0,0,0,0,0
,0,0,0,0,0,0,0,0,trans_kt_dia,C,p_death_kt,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,C)


mat_deprescribing_kleiner=define_transition(state_names=c("d","ckd1_s","ck2_s","ck
d3a_s","ckd3b_s","ckd4_s","ckd5_s","dia_s","kt_s","ckd1", "ckd2", "ckd3a", "ckd3b"
, "ckd4", "ckd5", "dia", "kt", "death"),0,0.333*succes,0.667*succes,0*succes,0*suc
ces,0*succes,0,0,0,0.333*(1-succes),0.667*(1-succes),0*(1-succes),0*(1-succes),0*(
1-succes),0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to
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_prob(rr_nothing,trans_ckd1_ckd2)),0,0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,C,r
r_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to_prob(rr_nothing,trans_
ckd2_ckd3a)),0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,C,rr_to_prob(rr_nothing,
trans_ckd3a_ckd3b),0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,0,C,rr_to_prob(rr_not
hing, trans_ckd3b_ckd4),0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,0,0,C,ifelse(rr_to
_prob(rr_nothing, trans_ckd4_ckd5)>1, 1, rr_to_prob(rr_nothing, trans_ckd4_ckd5)),
0,0,0,0,0,0,0,0,0,0,ifelse( rr_to_prob(rr_nothing, trans_ckd4_ckd5)+p_death_all>1,
1-rr_to_prob(rr_nothing, trans_ckd4_ckd5)/rr_to_prob(rr_nothing, trans_ckd4_ckd5),
p_death_all),0,0,0,0,0,0,C,trans_ckd5_dia,trans_ckd5_kt,0,0,0,0,0,0,0,0,(ifelse(p_
death_ckd5+trans_ckd5_dia+trans_ckd5_kt>1,1-trans_ckd5_dia-trans_ckd5_kt, p_death_
ckd5)),0,0,0,0,0,0,0,0,C,trans_dia_kt,0,0,0,0,0,0,0,0,0,ifelse(p_death_dia+trans_dia_k
t>1, 1-trans_dia_kt, p_death_dia),0,0,0,0,0,0,0,trans_kt_dia,C,0,0,0,0,0,0,0,0,0,p_d
eath_kt,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica
,rr_to_prob(rr_ckd,trans_ckd1_ckd2)),0,0,0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,C
,rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to_prob(rr_ckd,trans_ck
d2_ckd3a)),0,0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_esrd, trans
_ckd3a_ckd3b),0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_esrd, tr
ans_ckd3b_ckd4),0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,0,0,C,ifelse(rr_to_prob(rr
_esrd, trans_ckd4_ckd5)>1, 1, rr_to_prob(rr_esrd, trans_ckd4_ckd5)),0,0,ifelse( rr
_to_prob(rr_esrd, trans_ckd4_ckd5)+p_death_all>1, 1-rr_to_prob(rr_esrd, trans_ckd4
_ckd5)/rr_to_prob(rr_esrd, trans_ckd4_ckd5), p_death_all),0,0,0,0,0,0,0,0,0,0,0,0,
0,0,C,trans_ckd5_dia,trans_ckd5_kt,(ifelse(p_death_ckd5+trans_ckd5_dia+trans_ckd5_
kt>1,1-trans_ckd5_dia-trans_ckd5_kt, p_death_ckd5)),0,0,0,0,0,0,0,0,0,0,0,0,0,0,
C,trans_dia_kt,ifelse(p_death_dia+trans_dia_kt>1, 1-trans_dia_kt, p_death_dia),0,0
,0,0,0,0,0,0,0,0,0,0,0,0,0,0,trans_kt_dia,C,p_death_kt,0,0,0,0,0,0,0,0,0,0,0,0,0,0
,0,0,C)


mat_nodeprescribing_groter=define_transition(state_names=c("d","ckd1_s","ck2_s","c
kd3a_s","ckd3b_s","ckd4_s","ckd5_s","dia_s","kt_s","ckd1", "ckd2", "ckd3a", "ckd3b
", "ckd4", "ckd5", "dia", "kt", "death"),0,0,0,0,0,0,0,0,0,0.061,0.591,0.197,0.121
,0.03,0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to_pro
b(rr_nothing,trans_ckd1_ckd2)),0,0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,C,rr_to
_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to_prob(rr_nothing,trans_ckd2
_ckd3a)),0,0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,C,rr_to_prob(rr_nothing, tran
s_ckd3a_ckd3b),0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,0,C,rr_to_prob(rr_nothing
, trans_ckd3b_ckd4),0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,0,0,C,ifelse(rr_to_pro
b(rr_nothing, trans_ckd4_ckd5)>1, 1, rr_to_prob(rr_nothing, trans_ckd4_ckd5)),0,0,
0,0,0,0,0,0,0,0,ifelse( rr_to_prob(rr_nothing, trans_ckd4_ckd5)+p_death_all>1, 1-r
r_to_prob(rr_nothing, trans_ckd4_ckd5)/rr_to_prob(rr_nothing, trans_ckd4_ckd5), p_
death_all),0,0,0,0,0,0,0,C,trans_ckd5_dia,trans_ckd5_kt,0,0,0,0,0,0,0,0,(ifelse(p_de
ath_ckd5+trans_ckd5_dia+trans_ckd5_kt>1,1-trans_ckd5_dia-trans_ckd5_kt, p_death_ck
d5)),0,0,0,0,0,0,0,0,C,trans_dia_kt,0,0,0,0,0,0,0,0,0,ifelse(p_death_dia+trans_dia_kt>
1, 1-trans_dia_kt, p_death_dia),0,0,0,0,0,0,0,trans_kt_dia,C,0,0,0,0,0,0,0,0,0,p_dea
th_kt,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,r
r_to_prob(rr_ckd,trans_ckd1_ckd2)),0,0,0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,C,r
r_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to_prob(rr_ckd,trans_ckd2
_ckd3a)),0,0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_esrd, trans_c
kd3a_ckd3b),0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_esrd, tran
s_ckd3b_ckd4),0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,0,0,C,ifelse(rr_to_prob(rr_e
srd, trans_ckd4_ckd5)>1, 1, rr_to_prob(rr_esrd, trans_ckd4_ckd5)),0,0,ifelse( rr_t
o_prob(rr_esrd, trans_ckd4_ckd5)+p_death_all>1, 1-rr_to_prob(rr_esrd, trans_ckd4_c
kd5)/rr_to_prob(rr_esrd, trans_ckd4_ckd5), p_death_all),0,0,0,0,0,0,0,0,0,0,0,0,
0,C,trans_ckd5_dia,trans_ckd5_kt,(ifelse(p_death_ckd5+trans_ckd5_dia+trans_ckd5_kt
>1,1-trans_ckd5_dia-trans_ckd5_kt, p_death_ckd5)),0,0,0,0,0,0,0,0,0,0,0,0,0,0,C,
trans_dia_kt,ifelse(p_death_dia+trans_dia_kt>1, 1-trans_dia_kt, p_death_dia),0,0,0
,0,0,0,0,0,0,0,0,0,0,0,trans_kt_dia,C,p_death_kt,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0
,0,C)
```

```
mat_deprescribing_groter=define_transition(state_names=c("d","ckd1_s","ck2_s","ckd
3a_s","ckd3b_s","ckd4_s","ckd5_s","dia_s","kt_s","ckd1", "ckd2", "ckd3a", "ckd3b",
"ckd4", "ckd5", "dia", "kt", "death"),0,0.061*succes,0.591*succes,0.197*succes,0.1
21*succes,0.03*succes,0,0,0,0.061*(1-succes),0.591*(1-succes),0.197*(1-succes),0.1
21*(1-succes),0.03*(1-succes),0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diure
tica^diuretica,rr_to_prob(rr_nothing,trans_ckd1_ckd2)),0,0,0,0,0,0,0,0,0,0,0,0,0,0
,p_death_all,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to_pr
ob(rr_nothing,trans_ckd2_ckd3a)),0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,C,rr_
to_prob(rr_nothing, trans_ckd3a_ckd3b),0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,0
,C,rr_to_prob(rr_nothing, trans_ckd3b_ckd4),0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,
0,0,0,C,ifelse(rr_to_prob(rr_nothing, trans_ckd4_ckd5)>1, 1, rr_to_prob(rr_nothing
, trans_ckd4_ckd5)),0,0,0,0,0,0,0,0,0,0,ifelse( rr_to_prob(rr_nothing, trans_ckd4_
ckd5)+p_death_all>1, 1-rr_to_prob(rr_nothing, trans_ckd4_ckd5)/rr_to_prob(rr_nothi
ng, trans_ckd4_ckd5), p_death_all),0,0,0,0,0,0,C,trans_ckd5_dia,trans_ckd5_kt,0,0,
0,0,0,0,0,0,0,(ifelse(p_death_ckd5+trans_ckd5_dia+trans_ckd5_kt>1,1-trans_ckd5_dia-t
rans_ckd5_kt, p_death_ckd5)),0,0,0,0,0,0,0,C,trans_dia_kt,0,0,0,0,0,0,0,0,ifelse(p
_death_dia+trans_dia_kt>1, 1-trans_dia_kt, p_death_dia),0,0,0,0,0,0,0,trans_kt_dia
,C,0,0,0,0,0,0,0,0,0,p_death_kt,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes*
rr_diuretica^diuretica,rr_to_prob(rr_ckd,trans_ckd1_ckd2)),0,0,0,0,0,0,0,p_death_all
,0,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_t
o_prob(rr_ckd,trans_ckd2_ckd3a)),0,0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,C,rr_
to_prob(rr_esrd, trans_ckd3a_ckd3b),0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,0,C,
rr_to_prob(rr_esrd, trans_ckd3b_ckd4),0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,0,0,
C,ifelse(rr_to_prob(rr_esrd, trans_ckd4_ckd5)>1, 1, rr_to_prob(rr_esrd, trans_ckd4
_ckd5)),0,0,ifelse( rr_to_prob(rr_esrd, trans_ckd4_ckd5)+p_death_all>1, 1-rr_to_pr
ob(rr_esrd, trans_ckd4_ckd5)/rr_to_prob(rr_esrd, trans_ckd4_ckd5), p_death_all),0,
0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,C,trans_ckd5_dia,trans_ckd5_kt,(ifelse(p_death_ckd5+tran
s_ckd5_dia+trans_ckd5_kt>1,1-trans_ckd5_dia-trans_ckd5_kt, p_death_ckd5)),0,0,0,0,
0,0,0,0,0,0,0,0,0,0,0,0,C,trans_dia_kt,ifelse(p_death_dia+trans_dia_kt>1, 1-trans_di
a_kt, p_death_dia),0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,trans_kt_dia,C,p_death_kt,0,0,0,0
,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,C)


mat_nodeprescribing_TAO_UA=define_transition(state_names=c("d","ckd1_s","ck2_s","c
kd3a_s","ckd3b_s","ckd4_s","ckd5_s","dia_s","kt_s","ckd1", "ckd2", "ckd3a", "ckd3b
", "ckd4", "ckd5", "dia", "kt", "death"),0,0,0,0,0,0,0,0,0,0.393,0.423,0.089,0.089
,0.006,0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to_pr
ob(rr_nothing,trans_ckd1_ckd2)),0,0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,C,rr_t
o_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to_prob(rr_nothing,trans_ckd
2_ckd3a)),0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,C,rr_to_prob(rr_nothing, tra
ns_ckd3a_ckd3b),0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,0,C,rr_to_prob(rr_nothin
g, trans_ckd3b_ckd4),0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,0,0,C,ifelse(rr_to_pr
ob(rr_nothing, trans_ckd4_ckd5)>1, 1, rr_to_prob(rr_nothing, trans_ckd4_ckd5)),0,0
,0,0,0,0,0,0,0,0,ifelse( rr_to_prob(rr_nothing, trans_ckd4_ckd5)+p_death_all>1, 1-
rr_to_prob(rr_nothing, trans_ckd4_ckd5)/rr_to_prob(rr_nothing, trans_ckd4_ckd5), p
_death_all),0,0,0,0,0,0,0,C,trans_ckd5_dia,trans_ckd5_kt,0,0,0,0,0,0,0,0,(ifelse(p_d
eath_ckd5+trans_ckd5_dia+trans_ckd5_kt>1,1-trans_ckd5_dia-trans_ckd5_kt, p_death_c
kd5)),0,0,0,0,0,0,0,C,trans_dia_kt,0,0,0,0,0,0,0,0,ifelse(p_death_dia+trans_dia_kt
>1, 1-trans_dia_kt, p_death_dia),0,0,0,0,0,0,0,trans_kt_dia,C,0,0,0,0,0,0,0,0,0,p_de
ath_kt,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,
rr_to_prob(rr_ckd,trans_ckd1_ckd2)),0,0,0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,C,
rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to_prob(rr_ckd,trans_ckd
2_ckd3a)),0,0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_esrd, trans_
ckd3a_ckd3b),0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_esrd, tra
ns_ckd3b_ckd4),0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,0,0,C,ifelse(rr_to_prob(rr_
esrd, trans_ckd4_ckd5)>1, 1, rr_to_prob(rr_esrd, trans_ckd4_ckd5)),0,0,ifelse( rr_
to_prob(rr_esrd, trans_ckd4_ckd5)+p_death_all>1, 1-rr_to_prob(rr_esrd, trans_ckd4_
ckd5)/rr_to_prob(rr_esrd, trans_ckd4_ckd5), p_death_all),0,0,0,0,0,0,0,0,0,0,0,0,0,0
,0,C,trans_ckd5_dia,trans_ckd5_kt,(ifelse(p_death_ckd5+trans_ckd5_dia+trans_ckd5_k
```

```
t>1,1-trans_ckd5_dia-trans_ckd5_kt, p_death_ckd5)),0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,C
,trans_dia_kt,ifelse(p_death_dia+trans_dia_kt>1, 1-trans_dia_kt, p_death_dia),0,0,
0,0,0,0,0,0,0,0,0,0,0,0,0,trans_kt_dia,C,p_death_kt,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
0,0,C)


mat_deprescribing_TAO_UA=define_transition(state_names=c("d","ckd1_s","ck2_s","ckd
3a_s","ckd3b_s","ckd4_s","ckd5_s","dia_s","kt_s","ckd1", "ckd2", "ckd3a", "ckd3b",
"ckd4", "ckd5", "dia", "kt", "death"),0,0.393*succes,0.423*succes,0.089*succes,0.0
89*succes,0.006*succes,0,0,0,0.393*(1-succes),0.423*(1-succes),0.089*(1-succes),0.
089*(1-succes),0.006*(1-succes),0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diu
retica^diuretica,rr_to_prob(rr_nothing,trans_ckd1_ckd2)),0,0,0,0,0,0,0,0,0,0,0,0,0
,0,p_death_all,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr_to_
prob(rr_nothing,trans_ckd2_ckd3a)),0,0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0,C,r
r_to_prob(rr_nothing, trans_ckd3a_ckd3b),0,0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,0,0
,0,C,rr_to_prob(rr_nothing, trans_ckd3b_ckd4),0,0,0,0,0,0,0,0,0,0,0,p_death_all,0,
0,0,0,0,C,ifelse(rr_to_prob(rr_nothing, trans_ckd4_ckd5)>1, 1, rr_to_prob(rr_nothi
ng, trans_ckd4_ckd5)),0,0,0,0,0,0,0,0,0,0,ifelse( rr_to_prob(rr_nothing, trans_ckd
4_ckd5)+p_death_all>1, 1-rr_to_prob(rr_nothing, trans_ckd4_ckd5)/rr_to_prob(rr_not
hing, trans_ckd4_ckd5), p_death_all),0,0,0,0,0,0,C,trans_ckd5_dia,trans_ckd5_kt,0,
0,0,0,0,0,0,0,0,(ifelse(p_death_ckd5+trans_ckd5_dia+trans_ckd5_kt>1,1-trans_ckd5_dia
-trans_ckd5_kt, p_death_ckd5)),0,0,0,0,0,0,0,C,trans_dia_kt,0,0,0,0,0,0,0,0,ifelse
(p_death_dia+trans_dia_kt>1, 1-trans_dia_kt, p_death_dia),0,0,0,0,0,0,0,trans_kt_d
ia,C,0,0,0,0,0,0,0,0,0,p_death_kt,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabete
s*rr_diuretica^diuretica,rr_to_prob(rr_ckd,trans_ckd1_ckd2)),0,0,0,0,0,0,p_death_a
ll,0,0,0,0,0,0,0,0,0,0,0,C,rr_to_prob(rr_diabetes^diabetes*rr_diuretica^diuretica,rr
_to_prob(rr_ckd,trans_ckd2_ckd3a)),0,0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,C,r
r_to_prob(rr_esrd, trans_ckd3a_ckd3b),0,0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,0,
C,rr_to_prob(rr_esrd, trans_ckd3b_ckd4),0,0,0,p_death_all,0,0,0,0,0,0,0,0,0,0,0,0,
0,C,ifelse(rr_to_prob(rr_esrd, trans_ckd4_ckd5)>1, 1, rr_to_prob(rr_esrd, trans_ck
d4_ckd5)),0,0,ifelse( rr_to_prob(rr_esrd, trans_ckd4_ckd5)+p_death_all>1, 1-rr_to_
prob(rr_esrd, trans_ckd4_ckd5)/rr_to_prob(rr_esrd, trans_ckd4_ckd5), p_death_all),
0,0,0,0,0,0,0,0,0,0,0,0,0,0,C,trans_ckd5_dia,trans_ckd5_kt,(ifelse(p_death_ckd5+tr
ans_ckd5_dia+trans_ckd5_kt>1,1-trans_ckd5_dia-trans_ckd5_kt, p_death_ckd5)),0,0,0,
0,0,0,0,0,0,0,0,0,0,0,C,trans_dia_kt,ifelse(p_death_dia+trans_dia_kt>1, 1-trans_
dia_kt, p_death_dia),0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,trans_kt_dia,C,p_death_kt,0,0,0
,0,0,0,0,0,0,0,0,0,0,0,0,0,0,C)
```

#The rewards corresponding to each health state can be seen below. With dispatch_strategy a different value can be pulled for each strategy. In the case of nodeprescribing only cost_medication was used for both *"state_..."* and *"state_...s.* For deprescribing *"state*..." indicate a failed attempt and cost_medication was in this case combined with the initial costs related to deprescribing. The *"state_..._s"* indicate a successful attempt and cost_annual (annual follow-up) is now combined with the initial costs related to deprescribing. The initial costs related to deprescribing was a onetime cost introduced at the start of the model only. Furthermore the costs corresponding to each CKD stadia was implemented with cost_state and stratified by age. Afterwards cost_total combined the cost per CKD stadium and the cost related to medication/deprescribing. Also for each CKD stadium corresponding QALYs were set as a reward. Finally both cost_total and the QALYs were discounted accordingly.

```
state_d=define_state(cost_treatment=dispatch_strategy(nodeprescribing=0,deprescrib
ing=0+ifelse((model_time == 0), cost_init, 0)),cost_state=(ifelse(age_cycle>=20&ag
e_cycle<45,cost_20_ckd1,0)+ifelse(age_cycle>=45&age_cycle<65,cost_45_ckd1,0)+ifels
e(age_cycle>=65&age_cycle<75,cost_65_ckd1,0)+ifelse(age_cycle>=75,cost_75_ckd1,0))
```

```
,cost_total=discount(cost_treatment+cost_state,r=dr_cost),qaly=discount(qaly_ckd1,
r=dr_effect))


state_ckd1=define_state(cost_treatment=dispatch_strategy(nodeprescribing=cost_medi
cation,deprescribing=cost_medication+ifelse((model_time == 0), cost_init, 0)),cost
_state=(ifelse(age_cycle>=20&age_cycle<45,cost_20_ckd1,0)+ifelse(age_cycle>=45&age
_cycle<65,cost_45_ckd1,0)+ifelse(age_cycle>=65&age_cycle<75,cost_65_ckd1,0)+ifelse
(age_cycle>=75,cost_75_ckd1,0)),cost_total=discount(cost_treatment+cost_state,r=dr
_cost),qaly=discount(qaly_ckd1, r=dr_effect))


state_ckd2=define_state(cost_treatment=dispatch_strategy(nodeprescribing=cost_medi
cation,deprescribing=cost_medication+ifelse((model_time == 0), cost_init, 0)),cost
_state=(ifelse(age_cycle>=20&age_cycle<45,cost_20_ckd2,0)+ifelse(age_cycle>=45&age
_cycle<65,cost_45_ckd2,0)+ifelse(age_cycle>=65&age_cycle<75,cost_65_ckd2,0)+ifelse
(age_cycle>=75,cost_75_ckd2,0)),cost_total=discount(cost_treatment+cost_state,r=dr
_cost),qaly=discount(qaly_ckd2, r=dr_effect))


state_ckd3a=define_state(cost_treatment=dispatch_strategy(nodeprescribing=cost_med
ication,deprescribing=cost_medication+ifelse((model_time == 0), cost_init, 0)),cos
t_state=(ifelse(age_cycle>=20&age_cycle<45,cost_20_ckd3a,0)+ifelse(age_cycle>=45&a
ge_cycle<65,cost_45_ckd3a,0)+ifelse(age_cycle>=65&age_cycle<75,cost_65_ckd3a,0)+if
else(age_cycle>=75,cost_75_ckd3a,0)),cost_total=discount(cost_treatment+cost_state
,r=dr_cost),qaly=discount(qaly_ckd3a, r=dr_effect))


state_ckd3b=define_state(cost_treatment=dispatch_strategy(nodeprescribing=cost_med
ication,deprescribing=cost_medication+ifelse((model_time == 0), cost_init, 0)),cos
t_state=(ifelse(age_cycle>=20&age_cycle<45,cost_20_ckd3b,0)+ifelse(age_cycle>=45&a
ge_cycle<65,cost_45_ckd3b,0)+ifelse(age_cycle>=65&age_cycle<75,cost_65_ckd3b,0)+if
else(age_cycle>=75,cost_75_ckd3b,0)),cost_total=discount(cost_treatment+cost_state
,r=dr_cost),qaly=discount(qaly_ckd3b, r=dr_effect))


state_ckd4=define_state(cost_treatment=dispatch_strategy(nodeprescribing=cost_medi
cation,deprescribing=cost_medication+ifelse((model_time == 0), cost_init, 0)),cost
_state=(ifelse(age_cycle>=20&age_cycle<45,cost_20_ckd4,0)+ifelse(age_cycle>=45&age
_cycle<65,cost_45_ckd4,0)+ifelse(age_cycle>=65&age_cycle<75,cost_65_ckd4,0)+ifelse
(age_cycle>=75,cost_75_ckd4,0)),cost_total=discount(cost_treatment+cost_state,r=dr
_cost),qaly=discount(qaly_ckd4, r=dr_effect))


state_ckd5=define_state(cost_treatment=dispatch_strategy(nodeprescribing=cost_medi
cation,deprescribing=cost_medication+ifelse((model_time == 0), cost_init, 0)),cost
_state=(ifelse(age_cycle>=20&age_cycle<45,cost_20_ckd5,0)+ifelse(age_cycle>=45&age
_cycle<65,cost_45_ckd5,0)+ifelse(age_cycle>=65&age_cycle<75,cost_65_ckd5,0)+ifelse
(age_cycle>=75,cost_75_ckd5,0)),cost_total=discount(cost_treatment+cost_state,r=dr
_cost),qaly=discount(qaly_ckd5, r=dr_effect))


state_dia=define_state(cost_treatment=dispatch_strategy(nodeprescribing=cost_medic
ation,deprescribing=cost_medication+ifelse((model_time == 0), cost_init, 0)),cost_
state=(ifelse(age_cycle>=20&age_cycle<45,cost_20_dia,0)+ifelse(age_cycle>=45&age_c
ycle<65,cost_45_dia,0)+ifelse(age_cycle>=65&age_cycle<75,cost_65_dia,0)+ifelse(age
_cycle>=75,cost_75_dia,0)),cost_total=discount(cost_treatment+cost_state,r=dr_cost
),qaly=discount(qaly_dia, r=dr_effect))
```

```
state_kt=define_state(cost_treatment=dispatch_strategy(nodeprescribing=cost_medica
tion,deprescribing=cost_medication+ifelse((model_time == 0), cost_init, 0)),cost_s
tate=(ifelse(age_cycle>=20&age_cycle<45,cost_20_kt,0)+ifelse(age_cycle>=45&age_cyc
le<65,cost_45_kt,0)+ifelse(age_cycle>=65&age_cycle<75,cost_65_kt,0)+ifelse(age_cyc
le>=75,cost_75_kt,0)),cost_total=discount(cost_treatment+cost_state,r=dr_cost),qal
y=discount(qaly_kt, r=dr_effect))


state_death=define_state(cost_treatment=0, cost_state=0 ,cost_total=discount(cost_
treatment+cost_state,r=dr_cost),qaly=discount(qaly_death, r=dr_effect))


state_ckd1_s=define_state(cost_treatment=dispatch_strategy(nodeprescribing=cost_me
dication,deprescribing=cost_annual+ifelse((model_time == 0), cost_init, 0)),cost_s
tate=(ifelse(age_cycle>=20&age_cycle<45,cost_20_ckd1,0)+ifelse(age_cycle>=45&age_c
ycle<65,cost_45_ckd1,0)+ifelse(age_cycle>=65&age_cycle<75,cost_65_ckd1,0)+ifelse(a
ge_cycle>=75,cost_75_ckd1,0)),cost_total=discount(cost_treatment+cost_state,r=dr_c
ost),qaly=discount(qaly_ckd1, r=dr_effect))


state_ckd2_s=define_state(cost_treatment=dispatch_strategy(nodeprescribing=cost_me
dication,deprescribing=cost_annual+ifelse((model_time == 0), cost_init, 0)),cost_s
tate=(ifelse(age_cycle>=20&age_cycle<45,cost_20_ckd2,0)+ifelse(age_cycle>=45&age_c
ycle<65,cost_45_ckd2,0)+ifelse(age_cycle>=65&age_cycle<75,cost_65_ckd2,0)+ifelse(a
ge_cycle>=75,cost_75_ckd2,0)),cost_total=discount(cost_treatment+cost_state,r=dr_c
ost),qaly=discount(qaly_ckd2, r=dr_effect))


state_ckd3a_s=define_state(cost_treatment=dispatch_strategy(nodeprescribing=cost_m
edication,deprescribing=cost_annual+ifelse((model_time == 0), cost_init, 0)),cost_
state=(ifelse(age_cycle>=20&age_cycle<45,cost_20_ckd3a,0)+ifelse(age_cycle>=45&age
_cycle<65,cost_45_ckd3a,0)+ifelse(age_cycle>=65&age_cycle<75,cost_65_ckd3a,0)+ifel
se(age_cycle>=75,cost_75_ckd3a,0)),cost_total=discount(cost_treatment+cost_state,r
=dr_cost),qaly=discount(qaly_ckd3a, r=dr_effect))


state_ckd3b_s=define_state(cost_treatment=dispatch_strategy(nodeprescribing=cost_m
edication,deprescribing=cost_annual+ifelse((model_time == 0), cost_init, 0)),cost_
state=(ifelse(age_cycle>=20&age_cycle<45,cost_20_ckd3b,0)+ifelse(age_cycle>=45&age
_cycle<65,cost_45_ckd3b,0)+ifelse(age_cycle>=65&age_cycle<75,cost_65_ckd3b,0)+ifel
se(age_cycle>=75,cost_75_ckd3b,0)),cost_total=discount(cost_treatment+cost_state,r
=dr_cost),qaly=discount(qaly_ckd3b, r=dr_effect))


state_ckd4_s=define_state(cost_treatment=dispatch_strategy(nodeprescribing=cost_me
dication,deprescribing=cost_annual+ifelse((model_time == 0), cost_init, 0)),cost_s
tate=(ifelse(age_cycle>=20&age_cycle<45,cost_20_ckd4,0)+ifelse(age_cycle>=45&age_c
ycle<65,cost_45_ckd4,0)+ifelse(age_cycle>=65&age_cycle<75,cost_65_ckd4,0)+ifelse(a
ge_cycle>=75,cost_75_ckd4,0)),cost_total=discount(cost_treatment+cost_state,r=dr_c
ost),qaly=discount(qaly_ckd4, r=dr_effect))


state_ckd5_s=define_state(cost_treatment=dispatch_strategy(nodeprescribing=cost_me
dication,deprescribing=cost_annual+ifelse((model_time == 0), cost_init, 0)),cost_s
tate=(ifelse(age_cycle>=20&age_cycle<45,cost_20_ckd5,0)+ifelse(age_cycle>=45&age_c
ycle<65,cost_45_ckd5,0)+ifelse(age_cycle>=65&age_cycle<75,cost_65_ckd5,0)+ifelse(a
ge_cycle>=75,cost_75_ckd5,0)),cost_total=discount(cost_treatment+cost_state,r=dr_c
ost),qaly=discount(qaly_ckd5, r=dr_effect))
```

```
state_dia_s=define_state(cost_treatment=dispatch_strategy(nodeprescribing=cost_med
ication,deprescribing=cost_annual+ifelse((model_time == 0), cost_init, 0)),cost_st
ate=(ifelse(age_cycle>=20&age_cycle<45,cost_20_dia,0)+ifelse(age_cycle>=45&age_cyc
le<65,cost_45_dia,0)+ifelse(age_cycle>=65&age_cycle<75,cost_65_dia,0)+ifelse(age_c
ycle>=75,cost_75_dia,0)),cost_total=discount(cost_treatment+cost_state,r=dr_cost),
qaly=discount(qaly_dia, r=dr_effect))


state_kt_s=define_state(cost_treatment=dispatch_strategy(nodeprescribing=cost_medi
cation,deprescribing=cost_annual+ifelse((model_time == 0), cost_init, 0)),cost_sta
te=(ifelse(age_cycle>=20&age_cycle<45,cost_20_kt,0)+ifelse(age_cycle>=45&age_cycle
<65,cost_45_kt,0)+ifelse(age_cycle>=65&age_cycle<75,cost_65_kt,0)+ifelse(age_cycle
>=75,cost_75_kt,0)),cost_total=discount(cost_treatment+cost_state,r=dr_cost),qaly=
discount(qaly_kt, r=dr_effect))
```

#Strat_deprescribing combines the rewards corresponding to each health states with the transition matrix.

```
strat_nodeprescribing= define_strategy(transition=mat_nodeprescribing_TAO_UA,"d"=s
tate_d, "ckd1_s" =state_ckd1_s,"ck2_s"=state_ckd2_s,"ckd3a_s"=state_ckd3a_s,"ckd3b
_s"=state_ckd3b_s,"ckd4_s"=state_ckd4_s,"ckd5_s"=state_ckd5_s,"dia_s"=state_dia_s,
"kt_s"=state_kt_s,"ckd1"=state_ckd1, "ckd2"=state_ckd2, "ckd3a"=state_ckd3a, "ckd3
b"=state_ckd3b, "ckd4"=state_ckd4, "ckd5"=state_ckd5, "dia"=state_dia, "kt"=state_
kt, "death"=state_death)


strat_deprescribing= define_strategy(transition=mat_deprescribing_TAO_UA,"d"=state
_d, "ckd1_s" =state_ckd1_s,"ck2_s"=state_ckd2_s,"ckd3a_s"=state_ckd3a_s,"ckd3b_s"=
state_ckd3b_s,"ckd4_s"=state_ckd4_s,"ckd5_s"=state_ckd5_s,"dia_s"=state_dia_s,"kt_
s"=state_kt_s,"ckd1"=state_ckd1, "ckd2"=state_ckd2, "ckd3a"=state_ckd3a, "ckd3b"=s
tate_ckd3b, "ckd4"=state_ckd4, "ckd5"=state_ckd5, "dia"=state_dia, "kt"=state_kt,
"death"=state_death)
```

#Finally the model was run for a certain amount of cycles and half cycle corrections were made.

```
res_mod=run_model(parameters = par_mod, deprescribing=strat_deprescribing, nodepre
scribing=strat_nodeprescribing,cycles=100, init=c(par_mod[["initial"]][["expr"]],
rep(0L, 17)), cost=cost_total, effect=qaly, method ="life-table")
plot(res_mod, type = "ce")
plot(res_mod, type = "counts", panel = "by_state", free_y=TRUE)
plot(res_mod, type = "values", panel = "by_value", free_y=TRUE)
res_mod
```

Appendix 2: R script DSA run

```
library(heemod)
```

#To run the DSA a run of the basis had to be completed. This results in a res_mod which summarizes the finding of the base run and is used in run_dsa(). The DSA was defined below. Each individual parameter was coupled to a minimum and maximum value.

```
def_dsa=define_dsa(
  succesfull_deprescribing, 7, 23,
  hourly_wage_pharmacist,34.78,56.65,
  cost_medication,38.80,57.06,
  #age_base,14,96,
  cost_20_ckd1,0.063,7276,
  cost_20_ckd2,0.063,7276,
  cost_20_ckd3a,0.063,7276,
  cost_20_ckd3b,0.063,7276,
  cost_20_ckd4,71.000,36315,
  cost_20_ckd5,71.000,36315,
  cost_20_kt,569.000,54250,
  cost_20_dia,36887.000,166353,
  cost_45_ckd1,0.057,13675,
  cost_45_ckd2,0.057,13675,
  cost_45_ckd3a,0.057,13675,
  cost_45_ckd3b,0.057,13675,
  cost_45_ckd4,110.000,48005,
  cost_45_ckd5,110.000,48005,
  cost_45_kt,697.000,52765,
  cost_45_dia,37963.000,175298,
  cost_65_ckd1,1.000,19622,
  cost_65_ckd2,1.000,19622,
  cost_65_ckd3a,1.000,19622,
  cost_65_ckd3b,1.000,19622,
  cost_65_ckd4,207.000,50748,
  cost_65_ckd5,207.000,50748,
  cost_65_kt,876.000,58165,
  cost_65_dia,38478.000,167954,
  cost_75_ckd1,9.000,25080,
  cost_75_ckd2,9.000,25080,
  cost_75_ckd3a,9.000,25080,
  cost_75_ckd3b,9.000,25080,
  cost_75_ckd4,298.000,44088,
  cost_75_ckd5,298.000,44088,
  cost_75_kt,893.000,54393,
  cost_75_dia,40268.000,148520,
  qaly_ckd1,0.728,0.982,
  qaly_ckd2,0.728,0.982,
  qaly_ckd3a,0.732,0.958,
  qaly_ckd3b,0.732,0.958,
  qaly_ckd4,0.709,0.939,
  qaly_ckd5,0.663,0.871,
  qaly_dia,0.454,0.594,
  qaly_kt,0.702,0.933,
  trans_ckd5_death,0.064,0.166,
  trans_dia_death,0.126,0.210,
  trans_kt_death,0.005,0.078,
  trans_ckd3b_ckd4,0.095,0.184,
  trans_ckd4_ckd5,0.048,0.123,
  trans_ckd5_dia,0.433,0.788,
```

```
  trans_ckd5_kt,0.005,0.016,
  trans_dia_kt,0.009,0.033,
  trans_kt_dia,0.011,0.118,
  rr_ckd, 1.19, 1.46,
  rr_esrd, 1.71, 2.07,
  rr_diabetes, 1.22, 1.72,
  rr_diuretica, 2.09, 2.50,
  time_first_selection,0.003114187,0.003806228,
  time_second_selection,0.15,0.183,
  time_invitation,0.009,0.011,
  time_noreply_consult,0.042,0.063,
  time_reply_consult,0.021,0.042,
  time_evaluation,0.047,0.057,
  time_followup,0.026,0.052,
  time_annual_followup,0.026,0.052
  )
```

#The DSA was run with this line.

```
res_dsa=run_dsa(res_mod, dsa=def_dsa)
```

#After the DSA was completed a tornado diagram was made for both the costs and the effects.

```
plot(res_dsa, type="difference", result="cost", limits_by_bars = FALSE, shorten_la
bels = TRUE)
plot(res_dsa, type="difference", result="effect", limits_by_bars = FALSE, shorten_
labels = TRUE)
```

Appendix 3: R script PSA run

```
library(heemod)
```

#To run the PSA a run of the basis had to be completed. This results in a res_mod which summarizes the finding of the base run and is used in run_psa(). The psa was defined below. Each individual parameter was coupled to a distribution.

```
def_psa=define_psa (hourly_wage_pharmacist~gamma(44.91,6.91),
                    cost_medication~gamma(46.83,6.28),
                    #age_base~gamma(76.23,15.33),
                    succes~beta(15,48-15),
                    trans_ckd5_death~beta(105,867.26),
                    trans_dia_death~beta(348.45,1738.08),
                    trans_kt_death~ beta(16.04,556.64),
                    trans_ckd3b_ckd4~beta(228.42,1438.88),
                    trans_ckd4_ckd5~beta(110.09,1249.03),
                    trans_ckd5_dia~beta(126.69,75.69),
                    trans_ckd5_kt~beta(77.08,8487.72),
                    trans_dia_kt~ beta(67.16,3467.81),
                    trans_kt_dia~ beta(19.34,401.12),
                    qaly_ckd1~beta(152.76,16.97),
                    qaly_ckd2~beta(152.76,16.97),
                    qaly_ckd3a~beta(198.89,29.72),
                    qaly_ckd3b~beta(198.89,29.72),
                    qaly_ckd4~beta(229.65,40.53),
                    qaly_ckd5~beta(344.97,100.15),
                    qaly_dia~beta(729.38,659.91),
                    qaly_kt~beta(245.02,46.67),
                    rr_ckd~lognormal(meanlog=0.277632, sdlog=0.052164),
                    rr_esrd~lognormal(meanlog=0.631272, sdlog=0.048739),
                    rr_diabetes~lognormal(meanlog=0.598837, sdlog=0.087621),
                    rr_diuretica~lognormal(meanlog=0.828552, sdlog=0.045696),
                    cost_20_ckd1~gamma(mean=1228.092,sd=2082),
                    cost_20_ckd2~gamma(mean=1228.092,sd=2082),
                    cost_20_ckd3a~gamma(mean=1228.092,sd=2082),
                    cost_20_ckd3b~gamma(mean=1228.092,sd=2082),
                    cost_20_ckd4~gamma(mean=8633.391,sd=10029),
                    cost_20_ckd5~gamma(mean=8633.391,sd=10029),
                    cost_20_kt~gamma(mean=15515.388,sd=14570),
                    cost_20_dia~gamma(mean=89987,sd=33420),
                    cost_45_ckd1~gamma(mean=2237.95,sd=3926),
                    cost_45_ckd2~gamma(mean=2237.95,sd=3926),
                    cost_45_ckd3a~gamma(mean=2237.95,sd=3926),
                    cost_45_ckd3b~gamma(mean=2237.95,sd=3926),
                    cost_45_ckd4~gamma(mean=11575.215,sd=13234),
                    cost_45_ckd5~gamma(mean=11575.215,sd=13234),
                    cost_45_kt~gamma(mean=15570.6717,sd=14086),
                    cost_45_dia~gamma(mean=94109.288,sd=35464),
                    cost_65_ckd1~gamma(mean=3611.338,sd=5566),
                    cost_65_ckd2~gamma(mean=3611.338,sd=5566),
                    cost_65_ckd3a~gamma(mean=3611.338,sd=5566),
                    cost_65_ckd3b~gamma(mean=3611.338,sd=5566),
                    cost_65_ckd4~gamma(mean=12970.161,sd=13882),
                    cost_65_ckd5~gamma(mean=12970.161,sd=13882),
                    cost_65_kt~gamma(mean=17486.874,sd=15468),
                    cost_65_dia~gamma(mean=91818.87,sd=33407),
                    cost_75_ckd1~gamma(mean=5204.904,sd=7031),
                    cost_75_ckd2~gamma(mean=5204.904,sd=7031),
```

```
                    cost_75_ckd3a~gamma(mean=5204.904,sd=7031),
                    cost_75_ckd3b~gamma(mean=5204.904,sd=7031),
                    cost_75_ckd4~gamma(mean=11926.07,sd=11956),
                    cost_75_ckd5~gamma(mean=11926.07,sd=11956),
                    cost_75_kt~gamma(mean=16561.988,sd=14426),
                    cost_75_dia~gamma(mean=85642.014,sd=27784),
                    time_first_selection~lognormal(meanlog=-5.666,sdlog=0.0502),
                    time_second_selection~lognormal(meanlog=-1.790,sdlog=0.0497),
                    time_invitation~lognormal(meanlog=-4.605,sdlog=0.0502),
                    time_noreply_consult~lognormal(meanlog=-2.957,sdlog=0.101),
                    time_reply_consult~lognormal(meanlog=-3.474,sdlog=0.173),
                    time_evaluation~lognormal(meanlog=-2.957,sdlog=0.0482),
                    time_followup~lognormal(meanlog=-3.244,sdlog=0.173),
                    time_annual_followup~lognormal(meanlog=-3.244,sdlog=0.173)
)
```

#The PSA was set to run with the previously inserted distributions and the amount of re-runs would be set.

```
res_psa=run_psa(res_mod, psa=def_psa, N=1000)
```

#After the psa was done plots could be made. The first plot showed the cost-effectiveness plane. The second plot showed the cost-effectiveness acceptability curve.

```
library(ggthemes)
library(ggplot2)
plot(res_psa, type= "ce")+xlim(0,-2)+ylim(-100,50000)+geom_hline(yintercept = 0, l
inetype="dashed", size=0.1)+geom_vline(xintercept = 0, linetype="dashed", size=0.1
)+theme_pander()+scale_color_brewer(palette = "Accent")+geom_point()+geom_point(ae
s(x=-0.122, y=6414),col="black", shape=16, size=2))
plot(res_psa, type="ac", size=1)+scale_color_brewer(palette = "Accent")+theme_pand
er()+geom_line(size=1)
```

#Res_psa can be used to summarize the findings of res_psa.

```
res_psa
```

Appendix 4: Search Pharmacon

A. Patient with set amount of PPI (A02BC)
B. Selection on medication: NSAID (M01A)
    a. Selection patient characteristic > 70 years
    b. Selection patient characteristic 60-70 years
        i. Intersection Bb and D
        ii. Intersection Bb and F
        iii. Intersection Bb and G
C. Selection on medication: Platelet aggregation inhibitors (B01AC)
    a. Selection patient characteristic > 80 years
    b. Selection patient characteristic 70-80 years
        i. Intersection Cb and D
D. Selection on medication (vitamin K antagonist B01AA, direct factor Xa inhibitors B01AF + B01AE, Platelet aggregation inhibitors B01AC, Corticosteroids for systematic use H02, Selective serotonin reuptake inhibitors N06AB, Venlafaxine N06AX16, Duloxetine N06AX21, Trazodon N06AX05, Spironolacton C03Da01)
E. Selection contra indication: CI 016 = Ulcus
F. Selection contra indication: CI 006, CI 009, Ci 014 = Heart failure and Diabetes mellitus
G. Selection on medication: methotrexate (L04AX03)
H. Selection on vitamin K antagonist (B01AA)
    a. Intersection H and E
I. Selection on medication: Clopidogrel

PPI users without an indication

- Search A ex search Ba
    - Ex search Bbi
        - Ex search Bbii
            - Ex search Bbiii
                - Ex search Ca
                    - Ex search Cbi
                        - Ex search E
                            - Ex search Ha

Appendix 5: Search SFK ATC-codes

A. A10 (antidiabetics)
B. C03C (loop diuretics)
C. B01AC (ASA)
D. H02 (oral corticosteroid)
E. M01A (NSAID)
F. N06AB + N06AX16 + N06AX21 + N06AX05 (SSRI +) (psycho analeptics)
G. C03DA01 (spironolactone)
H. B01AA + B01AF + B01AE (coumarin and DOAC)
I. A02BC (PPI)

The results of the search performed by the TAO-UA were delivered in an excel format. To start the results of the search were combined, as they were delivered in 2 separate files. Afterwards several functions were made in excel to mimic the first selection step.

Function 1: =IF(AND(B6>=70; K6>0);1;0)
Function 1: =IF(AND(age>=70; NSAID>0);1;0)

Function 2: =IF(AND(B6>=60; K6>0; OR(J6>0;L6>0;N6>0;O6>0));1;0)
Function 2: =IF(AND(age>=60; NSAID>0; OR(oral corticosteroid>0; psycho analeptics>0; Coumarin and DOAC>0; spironolactone>0));1;0)

Function 3: =IF(AND(B6>=80; H6>0);1;0)
Function 3: =IF(AND(age>=80; ASA>0);1;0)

Function 4: =IF(AND(B6>=60; H6>0; OR(J6>0;L6>0;N6>0;O6>0));1;0)
Function 4: =IF(AND(age>=60; ASA >0; OR(oral corticosteroid>0; psycho analeptics>0; Coumarin and DOAC>0; spironolactone>0));1;0)

Function 5: =IF(G6>0;1;0)
Function 5: =IF(antidiabetic>0;1;0)

Function 6: =IF(I6>0;1;0)
Function 6: =IF(loop diuretics>0;1;0)

The sum of the result of all the function was calculated. If the sum would be 0 the patient did not have a clear indication for the PPI. If the sum would be >1 the patient did have a clear indication. Afterwards the sum of all the patients was filtered(row) from low to high. Finally the diabetic status was determined with function 5 and function 6 and further calculation were made accordingly.

Appendix 6: Cost medication

Medication	daily cost (€)	annual cost (€)	annual cost combined with dispensing fee (€)	Reference
Generiek. maagsapresistente tablet 20 mg	0.06	(0.06 *365.25=) 21.91	(21.91+3*9.28=) 49.75	(23)
Generiek. maagsapresistente tablet 40 mg	0.04	(0.04 *365.25=) 14.61	(14.61+3*9.28=) 42.45	(23)
Generiek. maagsapresistente capsule 20 mg	0.05	(0.05 *365.25=) 18.26	(18.26+3*9.28=) 46.10	(23)
Generiek. maagsapresistente capsule 40 mg	0.03	(0.03 *365.25=) 10.96	(10.96+3*9.28=) 38.80	(23)
Generiek. maagsapresistente tablet 40 mg	0.08	(0.08 *365.25=) 29.22	(29.22+3*9.28=) 57.06	(23)

Appendix 7: Time spent per deprescribing step.

Deprescribing step	Total time spent			Time spent per person		
	Mean (hours)	Min (hours)	Max (hours)	Mean (hours)	Min (hours)	Max (hours)
First selection	1.00	0.90	1.10	0.0035	0.0031	0.0038
Second selection	8.00	7.20	8.80	0.167	0.15	0.183
Invitation	0.50	0.45	0.55	0.010	0.009	0.011
Consult no reply	(0.42*6=) 2.50	(0.33*6=) 2.00	(0.50*6=) 3.00	0.052	0.042	0.063
Consult with reply	(0.125*12=) 1.50	(0.083*12=) 1.00	(0.167*12=) 2.00	0.031	0.021	0.042
Evaluation	(0.167*12=) 2.50	(0.150*12=) 2.25	(0.183*12=) 2.75	0.052	0.047	0.057
Follow-up	(0.125*12=) 1.88	(0.083*12=) 1.25	(0.167*12=) 2.50	0.039	0.026	0.052

Time spent per person= first selection + second selection + invitation + consult no reply + consult with reply + evaluation + follow-up*2 = 0.0035 hours + 0.167 hours + 0.010 hours + 0.052 hours + 0.031 hours + 0.052 hours + 0.039 hours *2 = 0.3935 hours (23.61 minutes)

Time spent per successful deprescribing= first selection + second selection + invitation + ((consult no reply + consult with reply) / 2) + evaluation + follow-up*2 = 0.0035 hours + 0.167 hours + 0.010 hours + ((0.167 hours + 0.42 hours) / 2) + 0.167 hours + 0.125 hours *2 = 0.891 hours (53.46 minutes)

Appendix 8: Costs pharmacist

Scale	Wage scale (€)	Weekly wage (€)	Hourly wage (€)	x150%
0	3818.1	881	23.18684	34.78026
1	4009	925	24.34615	36.51923
2	4209.46	971	25.56352	38.34528
3	4419.91	1020	26.84156	40.26234
4	4640.92	1071	28.18372	42.27559
5	4872.96	1125	29.59287	44.38931
6	5116.62	1181	31.07259	46.60889
7	5372.45	1240	32.62621	48.93932
8	5641.06	1302	34.25745	51.38617
9	5923.12	1367	35.97036	53.95555
10	6219.27	1435	37.76885	56.65327

Appendix 9: MLE script

#The given mean was set as x_bar. Sample was set as the values corresponding to the 25th and 75th percentiles.

```
sample=c(638,4646)
xbar=5208
lnsample=log(sample)
head(lnsample)
meanlnsample=mean(lnsample)
```

#The log-likelihood function is used to solve which value x will be the estimated value of alpha which is true if the derivative is equal to 0.

```
f=function(x){
log(x)-digamma(x)-log(xbar) + meanlnsample
}
```

#The function was plotted with a range of x from 0 to 10 and a straight line was drawn for f(x)=0. After this manually the range of x would be shortened to get a clear image of the intersection.

```
curve(f, from=0, to=10)
abline(h=0)

curve(f, from=0.2, to=0.8)
abline(h=0)

curve(f, from=0.560, to=0.568)
abline(h=0)
```

#The uniroot function with the found range of x was used to find for which x the derivative is equal to 0.

```
a=uniroot(f,lower=0.560, upper=0.568)
alpha_hat=a$root
alpha_hat
abline(v=alpha_hat)
```

#With alpha solved the lambda could be calculated by dividing alpha with the mean.

```
lambda_hat=alpha_hat/xbar
lambda_hat
```

#At the end a check was done to see how close the found mean was to the true value. The same was done for the 25th and 75th percentile.

```
25thpercentile=qgamma(.25, alpha_hat, rate=lambda_hat)
75thpercentile=qgamma(.75, alpha_hat, rate=lambda_hat)
estimated_mean=mean(rgamma(n=10000000, alpha_hat, rate=lambda_hat))
print(estimated_mean)
```

Appendix 10: Optimizing script

#The optimizing script was run directly after the MLE script and uses multiple parameters from it. This is the case for x_bar, sample[1], sample[2] and alpha_hat. Furthermore a data.frame with all of the necessary outputs.

```
mean=xbar
goal_25thpercentile=sample[1]
goal_75thpercentile=sample[2]
alfa=alpha_hat-0.1
lambda=mean/alfa
25thpercentile=qgamma(.25, shape=alfa, 1/lambda)
75thpercentile=qgamma(.75, shape=alfa, 1/lambda)
difference=(abs(25thpercentile-goal_25thpercentile))+(abs(75thpercentile-goal_75th
percentile))
data=data.frame(alfa,lambda,25thpercentile,75thpercentile,difference)
```

#alfa was increased in very small increments until alpha increased 0.1 compared to its start. Each time the lambda, 25th percentile, 75th percentile and the difference was refreshed.

```
repeat{
  alfa=alfa+5E-6
  lambda=mean/alfa
  25thpercentile=qgamma(.25, shape=alfa, 1/lambda)
  75thpercentile=qgamma(.75, shape=alfa, 1/lambda)
  difference=(abs(25thpercentile-goal_25thpercentile))+(abs(75thpercentile-goal_75
thpercentile))
  for(i in seq_along(alfa)){
      print(paste(alfa,lambda, 25thpercentile, 75thpercentile, difference))
    }
  test=c(alfa,lambda,25thpercentile,75thpercentile,difference)
  75thpercentile=rbind(75thpercentile,test)
  if ((25thpercentile>goal_25thpercentile*0.9 && 25thpercentile<goal_25thpercentil
e*1.1) && (75thpercentile<(goal_75thpercentile*1.1) && 75thpercentile>(goal_75thpe
rcentile*0.9))){
    print("Ja!")
    difference=(abs(25thpercentile-goal_25thpercentile))+(abs(75thpercentile-goal_
75thpercentile))
    test=c(alfa,lambda,25thpercentile,75thpercentile,difference,mean_aprox)
    75thpercentile=rbind(75thpercentile,test)
  }
  if(alfa>alpha_hat+0.1){
    break
  }
}
```

#After the run was completed the alfa and lambda corresponding to the lowest difference was pulled out of the data.frame. To check if the mean was still correct an extra measurment of the mean was done.

```
alfa=data$alfa[which.min(data$difference)]
lambda=data$lambda[which.min(data$difference)]
mean_aprox=round(mean(rgamma(n=1000000, shape=alfa, 1/lambda)))
data[which.min(data$difference),]

print(paste(mean,goal_25thpercentile,goal_75thpercentile))
mean_aprox=round(mean(rgamma(n=1000000, shape=alfa, 1/lambda)))
print(paste(mean_aprox))
```

Appendix 11: Population analysis

```
library(readxl)
```

#To run the population analysis a run of the basis had to be completed. This results in a res_mod which summarizes the finding of the base run and is used in the population analysis. Furthermore for the population analysis sex=sex_indiv was enabled and the starting age was altered. It did not matter if the starting run was done for only male or only female as it would be changed during the run. The population analysis reads in an excel document containing different parameters: sex_indiv, diabetes, diuretica and weights. The first three are inputs for the base run who are weighted with the final parameter. In the pilot individuals were used. This resulted in 87 unique lines. This is more than the population, because individuals who had both diuretica and diabetes were run twice. Once for diuretica and once for diabetes. For the TAO-UA population also an excel document was made. Only in this case percentages were used as weights instead of individual people with a weight of 1. An example can be found in **table x**.

```
tab_pop <- read_excel("input populatie example.xlsx")
```

#The model was re-run for each line in the excel document and afterwards combined according to the weights.

```
pop_mod=update(res_mod, newdata=tab_pop)
pop_mod
```

Table x: Example of an excel document used in the population analysis for TAO-UA.

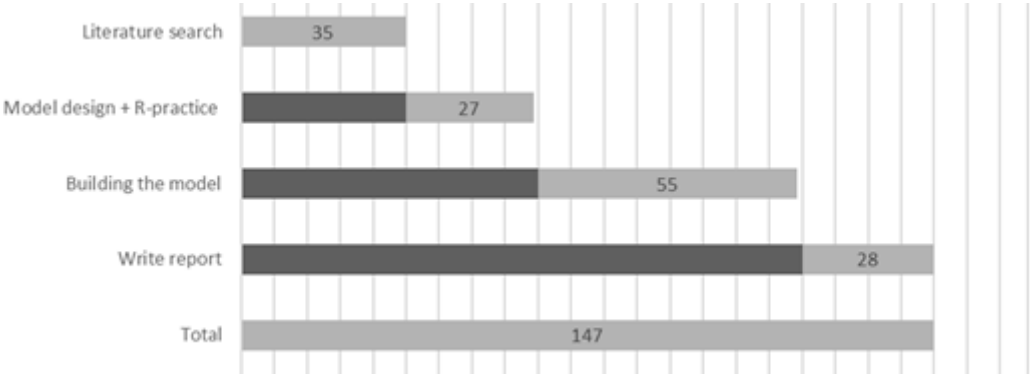
sex_indiv	diabetes	diuretica	.weights
MLE	1		Percentage male * Percentage diabetes
FMLE	1		Percentage female * Percentage diabetes
MLE	0		Percentage male * (1-Percentage diabetes)
FMLE	0		Percentage female * (1- Percentage diabetes)
MLE		1	Percentage male * Percentage diuretic users
FMLE		1	Percentage female * Percentage diuretic users
MLE		0	Percentage male * (1-Percentage diuretic users)
FMLE		0	Percentage female * (1-Percentage diuretic users)

Appendix 12: Research plan

Timeline project:

			DURATION (Days)
START DATE	END DATE	DESCRIPTION	
1-Nov-21	6-Dec-21	Literature search	35
6-Dec-21	3-Jan-22	Model design + R-practice	27
3-Jan-22	28-Feb-22	Building the model	55
28-Feb-22	28-Mar-22	Write report	28

Gantt Chart related to the timeline (in days):



Data management plan:

During the project data from patients of different pharmacies were accessed to make the model. The data was transferred between different parties by using Unishare. The data was already anonymized by the TAO-UA as only a number was given instead of patient information. Furthermore the patient data was only altered and downloaded in the Windows University Workplace (UWP). For the report no data of the individual patients were included, but only a reference to the Unishare folder. After the project was complete the altered data was yet again stored on the Unishare folder. Finally individual pharmacies used for the project were made anonymous (for example, pharmacy 1).