Drug-related Kidney Injury
and Safe Pharmacotherapy in the Elderly

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ISBN 978-94-6169-596-3

Layout and printing: Optima Grafische Communicatie, Rotterdam, The Netherlands.

Financial support for printing this thesis was generously provided by the Interdisciplinary Processing of Clinical Information (IPCI) group of the Department of Medical Informatics, Erasmus University Medical Center and the Dutch Evaluation Board

Drug-Induced Kidney Injury
and Safe Pharmacotherapy in the Elderly

Geneesmiddel gerelateerde nierschade
en veilig geneesmiddelgebruik bij ouderen

Proefschrift

Ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
Op gezag van de rector magnificus

Prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties
De openbare verdediging zal plaatsvinden op
dinsdag 9 december 2014 om 15.30 uur

door

Jan Cornelis van Blijderveen
Geboren te Rhenen

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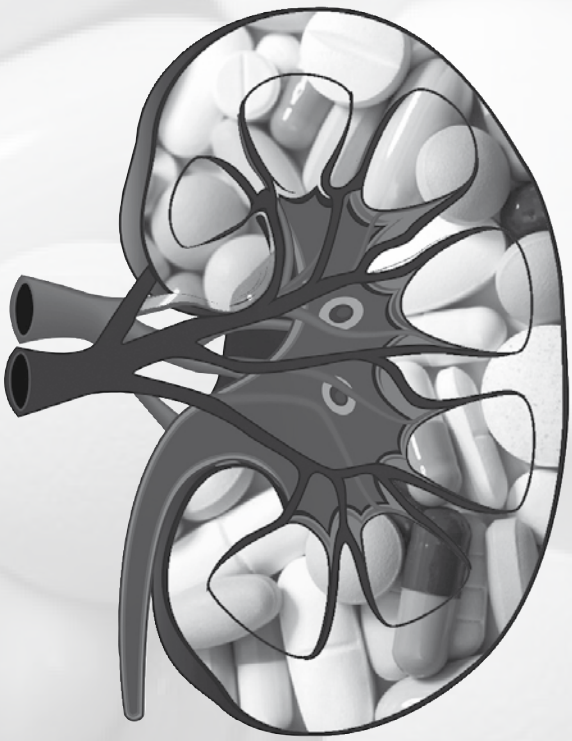
Chapter 1

General Introduction



GENERAL INTRODUCTION

The kidney performs two functions that are essential for life. First, it participates in the homeostasis of the extracellular environment that is required for adequate functioning of the cells. This is achieved by excretion of some of the waste products of metabolism and by specifically adjusting the urinary excretion of water and electrolytes to match net intake and endogenous production. Second, it secretes hormones that participate in the regulation of systemic and renal hemodynamics, red blood cell production, and bone metabolism.

Many medicines have nephrotoxic potential, either by direct damage of tubular cells or by glomerular or interstitial damage following immune-complex formation (1). Well-known examples of nephrotoxicity include cytotoxic chemotherapeutic agents such as cisplatin and aminoglycoside antibiotics such as gentamycin. Despite the risk of nephrotoxicity, use of these drugs is justified in case no safer alternatives are available and if the underlying condition is more serious than the risk of renal damage. However, history provides several examples where these conditions were not met. Examples are the chronic nephropathy caused by non-steroidal anti-inflammatory drugs (NSAIDs) and related analgesics, most notably phenacetin, that was ultimately withdrawn in 1983 (2), and the acute renal failure associated with lactic acidosis from phenformin that was ultimately withdrawn in 1976 (3). A more recent example is the combined use of drugs affecting the renin-angiotensin system. In relation to this, the Pharmacovigilance Risk Assessment Committee (PRAC) issued a negative advice against combined use of these drugs in 2014 (4).

It is estimated that between 18-27% of all cases of acute kidney injury in United States hospitals are drug-induced (5). Although only severe renal function impairment requires dialysis or a renal transplant, also a subtle impairment in renal function has clinical consequences as it is associated with an increase in cardiovascular and all-cause mortality (6). Moreover, renal function can also have consequences for the metabolism of other drugs. Both EU and US legislations on drug authorization recognize the fact that pharmacokinetics studies are important in patient with impaired renal function (7, 8). In addition, to detect potential renal toxicity in an early stage, studies evaluating the pharmacokinetics of a drug have become standard in the pre-authorization phase of medicine authorization (9). Post-marketing, regulatory authorities, such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), continuously evaluate the safety of a drug through spontaneous reporting and post-marketing safety studies to ascertain a positive benefit risk balance.

Despite these measures, undesirable drug effects involving the kidney, either through direct kidney damage or as a result of modified kidney function, still do occur in current clinical practice. First, a substantial number of medicines that are currently

available, were approved years ago, in a period with less stringent requirements with regard to (pre-authorization) clinical studies. Second, it is well known that the population and conditions in clinical trials do not necessarily reflect large-scale drug use in clinical practice. In general, clinical trial patients are younger and healthier than the population which ultimately uses the medicine in real life (10). This is illustrated with the example of acute renal failure after use of dronedarone, an anti-arrhythmic drug, in patients with heart failure. When this adverse drug reaction was further investigated, it was observed that patients with heart failure were underrepresented in the dronedarone trials explaining why acute renal failure was only identified post-registration. If a medicine is metabolized or excreted via the kidney, patients with impaired kidney function might especially be at risk to develop adverse drug reactions. Third, potential nephrotoxic effects of medication might be enhanced when used in combination with other nephrotoxic drugs. Again, as clinical studies are generally conducted in a selected patient population, according to strict protocols, it is difficult to investigate all potential drug interactions. An example of drug-drug interactions resulting in increased nephrotoxicity is the combined use of non-steroidal anti-inflammatory drugs with tenofovir disoproxil fumarate, an antiretroviral drug (11). Fourth, as adverse drug reactions might be rare and idiosyncratic, clinical studies often have insufficient sample size to demonstrate a difference between treatment arms. Because of their infrequent nature, these adverse drug reactions might be less interesting from a population perspective. However for the individual patient, early recognition of such adverse drug reactions remains highly important. Examples include proton-pump inhibitor induced acute interstitial nephritis (12) and benzodiazepine induced hyponatremia (13).

All of the above mentioned arguments underline the importance of post-marketing studies to better characterize the safety profile of drug therapy in the clinical setting. These post-marketing studies complement spontaneous reporting systems, which might identify but not quantify new drug safety issues. [These post-marketing studies might then also be used to evaluate how safety measures laid down in the summary of product characteristics result in the appropriate actions in clinical practice to avoid adverse drug reactions.

Aims and outline of this thesis

The objectives of this thesis are the following:

- to describe the epidemiology of chronic kidney disease in the general population
- to study the association between the use of drugs and renal function decline
- to study the association between the use of drugs and water and electrolyte balance
- To check adherence to guidelines on kidney function monitoring upon initiation of antihypertensive drug treatment

The epidemiology of chronic kidney disease is described in chapter 2. For this research, we used data from the Integrated Primary Care Information (IPCI) project, an electronic primary care information database from the Netherlands including more than 1.1 million individuals. In this paper, we describe the incidence and prevalence of CKD, stratified by gender, age category and calendar year.

The second and main objective of this thesis was to identify and quantify undesirable renal effects of medicines with data from the Rotterdam Study, a large prospective population-based cohort study among elderly, and from the IPCI project.

Effects of medicines which may cause kidney damage are described in chapter 3, including the results of a study on the effects of overanticoagulation and renal function decline (chapter 3.1) and the results of a study that describes the occurrence of simple renal cysts in relation to serum uric acid levels. This association was relevant for the research as outlined in this thesis as uric acid levels may be increased by several drugs such as diuretics (chapter 3.2). Effects of medicines that are possibly mediated through the kidney are described in chapter 4. The important role of the kidney in the body's regulation of the sodium and water might be disrupted by medicines. We investigated whether diuretics with a similar indication of use (chlorthalidone and hydrochlorothiazide) are differently associated with hyponatremia (chapter 4.1). Also, we investigated the association of antidepressants and hyponatremia (chapter 4.2), benzodiazepines and hyponatremia (chapter 4.3), and medicines in relation to hypovolemia (chapter 4.4).

As part of the fourth objective we studied the adherence to renal function monitoring guidelines in patients starting antihypertensive therapy with diuretics and renin-angiotensin system inhibitors (chapter 5).

In Chapter 6, we discuss the main findings of the studies included in this thesis and we provide suggestions for future research.

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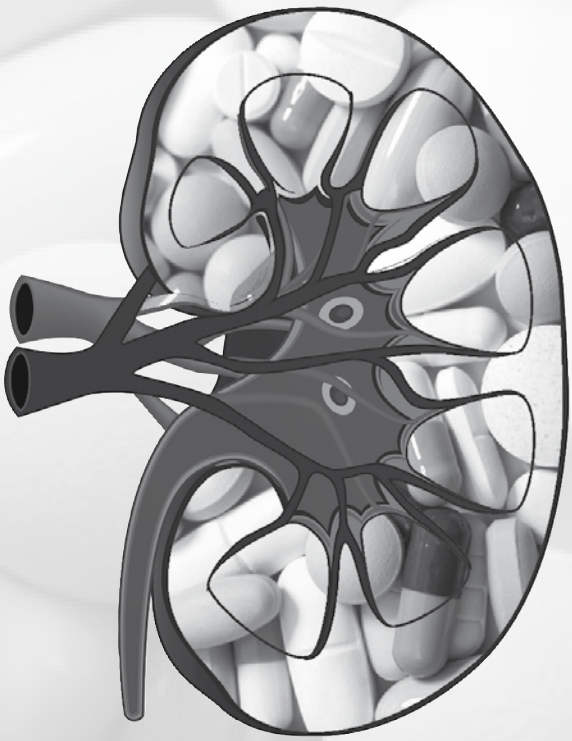
Chapter 2

The epidemiology of chronic kidney disease



Chapter 2.1

The epidemiology of chronic kidney disease in the general population

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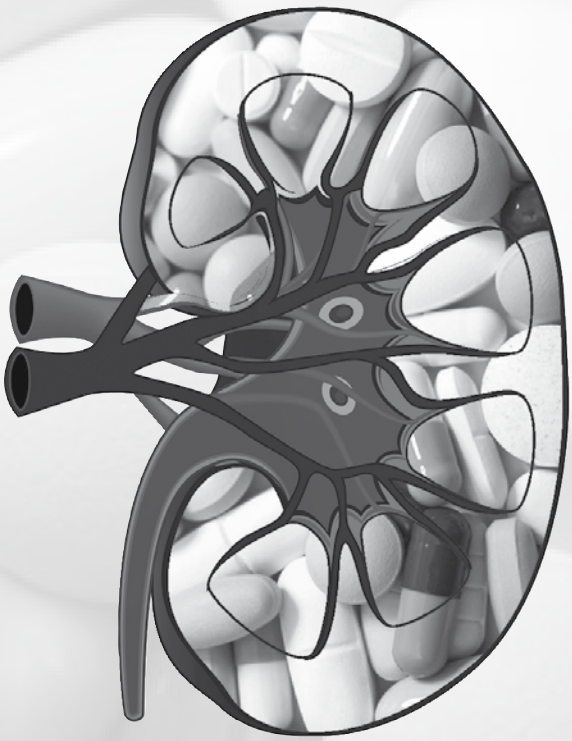
Bruno H. Stricker, Miriam C. Sturkenboom, Katia M. Verhamme

Int Urol Nephrol. 2014 Mar;46(3):583-92.



ABSTRACT

Background

Because most population-based studies on the epidemiology of chronic kidney disease (CKD) are cross-sectional, there is, except for end-stage renal disease, hardly any information on incidence rates.

Methods

We conducted a retrospective cohort study in a dynamic population, using data of 784,563 adult participants retrieved from the Integrated Primary Care Information database, a primary care database containing the complete electronic longitudinal medical records. CKD (both incidence and prevalence) was based on (1) an increased urine albumin-to-creatinine ratio, (2) a decreased estimated glomerular filtration rate, or (3) explicit statement in the medical record. Results were stratified by age according to the WHO standard population, sex, and diabetes mellitus.

Results

Based on a single measurement only, the incidence rate of CKD in adults was 1,213 per 100,000 person-years, and 6.7 percent of the adult population had a prevalent diagnosis of CKD. The incidence rate increased by age and was the highest in participants with diabetes with an incidence of 25,000 per 100,000 person-years, affecting over 75 percent of participants with diabetes.

Conclusions

This is the first study to report the incidence rates of all stages of CKD for the entire adult population, stratified by sex, 5-year age groups, and diabetes. Our data demonstrate that the incidence of CKD increases with age and is the highest in participants with diabetes mellitus.

INTRODUCTION

Background

The prevalence of chronic kidney disease (CKD) has been widely studied in population-based, cross-sectional studies, with marked heterogeneity in prevalence data ranging from 19 to 71 percent for the highest age category [1-3], probably due to selection bias [4]. Limited information is available on (age-specific) incidence rates for CKD [2, 5-13].

CKD is associated with an increased risk of hospitalization, cardiovascular and all-cause mortality and constitutes a major health problem with substantial healthcare costs [14-18]. A recent meta-analysis showed that the relative risk of mortality, stratified by estimated Glomerular Filtration Rate (eGFR), is similar in those with and without diabetes [19]. This suggests that the underlying CKD is an important predictor for mortality. Another meta-analysis reported a similar pattern in patients with hypertension [20] emphasizing the importance of CKD as a predictor of clinical outcomes [19, 21].

Objective

The objective of this study was to investigate the epidemiology, in particular the incidence, of CKD using prospectively gathered electronic health care records from a community-dwelling adult population. We studied the incidence and prevalence of CKD in the adult population stratified by sex, 5 year age categories (WHO standard population) [22], and the presence of diabetes mellitus.

METHODS

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) project, a longitudinal observational, dynamic database which contains the electronic medical records of a group of 150 general practitioners (GPs) in the Netherlands. In the Dutch health care system, the GP plays a pivotal role and acts as a gatekeeper of medical care and information. All persons are registered with a GP, independent of their health status. Details of the IPCI database have been described elsewhere [23, 24]. Briefly, the database contains the complete electronic medical records of approximately 1,000,000 patients. These records contain anonymous longitudinal data on patient demographics, symptoms and diagnoses (coded and in free text), referrals, laboratory findings, hospitalizations, discharge letters, and drug prescriptions (inclusive indication and dosage regimen). To maximize completeness of the data, general practitioners participating in the IPCI project are not allowed to maintain a system of paper-based records besides the electronic medical records. The system complies with European Union guidelines on the

use of data for medical research and has been proven valid for pharmaco-epidemiologic studies [24]. The Scientific and Ethical Advisory Board of the IPCI project approved the study.

Study design

Retrospective cohort study in a dynamic population

Participants

The source population comprised all adults (20 years or older) who were registered with a GP for at least 365 days. The study period started on January 1st, 1996 and ended on March 1st, 2011. Subjects with (a history of) a renal transplant prior to study entry were excluded. Subjects were followed until renal transplant, death, transfer out of practice, last data draw-down, or end of the study period, whichever came first.

Outcome

CKD was based on abnormalities in estimated glomerular filtration rate (eGFR), albuminuria as a marker of kidney damage, or an explicit statement in the medical record, and stratified by stages 1-5 [25]. The eGFR was obtained from the equation published by the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration [26]:
eGFR = 141 * min(Scr/κ,1)α * max(Scr/κ,1)-1.209 * 0.993Age * 1.018 [if female] * 1.159 [if black].
Where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

For the urine Albumin to Creatinine Ratio (ACR) we used a cut-off of 3.5 mg/mmol (~30mg/g) for women and 2.5 mg/mmol (~22mg/g) for men for (micro-) albuminuria as a marker for kidney damage to define stages 1 and 2 of CKD. The last eGFR before the ACR measurement was used to distinguish between stage 1 and 2 of CKD. If no SCR measurement was available, the eGFR was assumed to be >90 ml/min/1.73m2.

In addition the complete electronic medical record was screened using an algorithm including "kidney/renal" in combination with "insufficiency/failure", "renal replacement therapy", "dialysis" and "transplantation".

A definite diagnosis of CKD was made according to KDIGO guidelines if there were two measurements, at least 90 days apart, indicating either (micro-) albuminuria or eGFR<60 ml/min/1.73m2, or two explicit statements in the medical record (at least 90 days apart) indicating CKD. The first date was used as index date. A 'possible diagnosis' was based on a single measurement or at least one explicit statement indicating CKD in the medical record. Subjects with a statement in the medical record indicating CKD before the start of follow-up that could not be confirmed by subsequent measurements

were excluded from the stage specific analysis. Subjects with a statement in the medical record indicating CKD after start of follow-up that could not be confirmed by subsequent measurements were not accounted and follow-up was censored from that date. The following stages were used: stage 1 "eGFR≥90 ml/min/1.73m2 with kidney damage", stage 2 "eGFR 60-89 ml/min/1.73m2 with kidney damage", stage 3 "eGFR 30-59 ml/min/1.73m2", stage 4 "eGFR 15-29 ml/min/1.73m2", stage 5 "eGFR <15 ml/min/1.73m2 or dialysis" [27].

Diabetes mellitus

Because diabetes is a risk factor for the development of End Stage Renal Disease (ESRD) we stratified our analyses by underlying diabetes [14-16]. The diagnosis of diabetes was based on a prescription of a drug within the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system "A10" (Drugs used in diabetes) [28].

Statistical analysis

The incidence rate was determined by dividing the number of cases by the total number of person-years of follow-up. Subjects were censored on the date of first diagnosis for the respective disease stage. Overall incidence rates were calculated for the adult study population. Incidence rates were expressed per 100,000 person-years. Ninety-five percent confidence intervals were calculated based on a Poisson distribution [29].

Prevalence was determined by dividing the number of cases by the number of persons with follow-up in the study population on 1st January of each calendar year. Cases included subjects with a prevalent diagnosis or an incident diagnosis of CKD prior to the 1st of January. As CKD is a progressive disease, subjects were allowed to move between stage specific categories of CKD. Results displayed were weighted for the calendar year specific denominator. Ninety-five percent confidence intervals were calculated based on normal distribution.

The results on the incidence and prevalence of CKD were stratified for age according to the WHO standard population, sex, and presence of diabetes mellitus [30].

RESULTS

Participants

The source population consisted of 784,856 adult subjects with a valid history of at least 365 days in the IPCI database. A total of 293 participants were excluded because of a history of a renal transplant prior to start of follow-up, leaving 784,563 subjects available for analysis.

Descriptives

The median age of the study population was 44.4 years at start of follow-up (Interquartile Range [IQR]: 31.7 – 59.2 years), 48.1% were males and 4.3% of participants had a diagnosis of diabetes. A total of 2.1 million person-years of follow-up was available for the study population, the maximal duration of follow-up being 10.7 years, with a median of 2.3 years (IQR: 1.3-3.4 years). Detailed population characteristics are available (online table 1 and 2).

Outcome data

For the study population, 1,379,097 eGFR measurements and 178,425 ACR measurements were available. A total of 42,870 participants had evidence of CKD prior to start of follow-up; of these, 41,343 subjects had an abnormal measurement and in an additional 1,437 subjects the presence of CKD was explicitly stated in the medical record with no measurement available prior to start of follow-up. There were 23,643 incident cases of CKD; of these, 22,722 were based on abnormal measurements and an additional 921 cases were based on explicit statements in the medical record.

Main Results

Incidence of CKD

The overall incidence of a possible diagnosis of CKD in adults was 1,213 per 100,000 person-years (95% CI 1,198-1,283 per 100,000 person-years). The overall incidence of a definite diagnosis of CKD was 479 per 100,000 person-years (95% CI 470-489 per 100,000 person-years). Confirmation of the first incident abnormal SCR or ACR measurement by a subsequent abnormal measurement (as required for definite diagnosis of CKD), was obtained after a median of 301 days (Interquartile Range 148-444 days).

For a possible diagnosis, the incidence rate was higher in females (1,362 per 100,000 person-years) than in males (1,029 per 100,000 person-years), $p<0.001$. The incidence rates were higher in subjects with diabetes (7,120 per 100,000 person-years) than in those without (973 per 100,000 person-years; $p<0.001$). The highest incidence rate of CKD was reached in women with diabetes, older than 85 years (25,000 per 100,000 person-years). Results stratified by age, sex and diabetes are shown in figure 1 and table 1. There was a marked increase of the incidence rate for stage 3 and 4 CKD as of the age of 50 years and older, both in subjects with and without diabetes, whereas the incidence rate of stage 2 CKD only increased with age in subjects with diabetes. (Figures 2a-e) Comprehensive stage-specific tables are available (online tables 3A-E)

Table 1 Overall incidence of Chronic Kidney Disease

Age (years)	No diabetes						Diabetes					
	males			females			males			females		
	Cases	IR*	95%CI	cases	IR*	95%CI	cases	IR*	95%CI	cases	IR*	95%CI
20-24	20	24	(15 - 37)	24	29	(19 - 43)	0	-	(-)	2	823	(164 - 2,637)
25-29	18	21	(13 - 33)	50	57	(43 - 75)	1	329	(30 - 1,534)	9	2,680	(1,323 - 4,891)
30-34	23	25	(16 - 37)	58	63	(48 - 81)	15	2,542	(1,485 - 4,087)	11	1,749	(928 - 3,026)
35-39	70	67	(53 - 84)	99	93	(76 - 113)	25	2,511	(1,665 - 3,646)	20	1,990	(1,254 - 3,013)
40-44	124	114	(95 - 135)	214	193	(169 - 221)	36	2,096	(1,492 - 2,868)	42	2,822	(2,062 - 3,777)
45-49	200	193	(167 - 221)	344	326	(293 - 361)	84	3,031	(2,433 - 3,732)	66	3,036	(2,368 - 3,837)
50-54	334	359	(322 - 399)	570	608	(560 - 660)	129	3,391	(2,843 - 4,015)	118	3,839	(3,193 - 4,580)
55-59	562	704	(648 - 764)	718	899	(835 - 966)	232	4,209	(3,693 - 4,777)	171	4,250	(3,649 - 4,924)
60-64	846	1,247	(1,165 - 1,334)	1,117	1,636	(1,542 - 1,734)	330	5,134	(4,602 - 5,711)	287	6,006	(5,341 - 6,731)
65-69	1,048	2,235	(2,103 - 2,374)	1,280	2,628	(2,487 - 2,775)	408	7,503	(6,801 - 8,258)	332	7,287	(6,535 - 8,103)
70-74	1,225	3,651	(3,451 - 3,860)	1,649	4,461	(4,249 - 4,680)	466	10,567	(9,640 - 11,559)	439	10,525	(9,574 - 11,544)
75-79	1,319	6,072	(5,751 - 6,406)	1,823	6,640	(6,341 - 6,950)	400	13,912	(12,598 - 15,326)	490	14,758	(13,495 - 16,109)
80-84	973	8,586	(8,059 - 9,138)	1,561	9,263	(8,812 - 9,731)	258	17,989	(15,894 - 20,287)	369	19,073	(17,201 - 21,095)
85+	746	12,764	(11,873 - 13,705)	1,518	12,697	(12,071 - 13,348)	112	22,355	(18,497 - 26,790)	258	24,722	(21,842 - 27,879)

*IR = Overall Incidence rate of a possible diagnosis of Chronic Kidney Disease (all stages), per 100,000 person-years

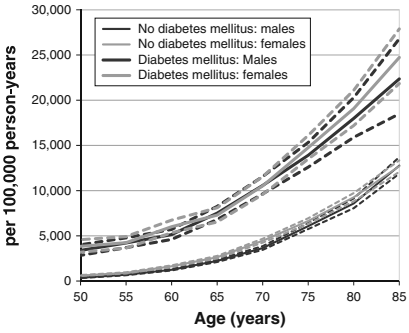


Figure 1 Incidence of Chronic Kidney Disease (possible diagnosis) - all stages

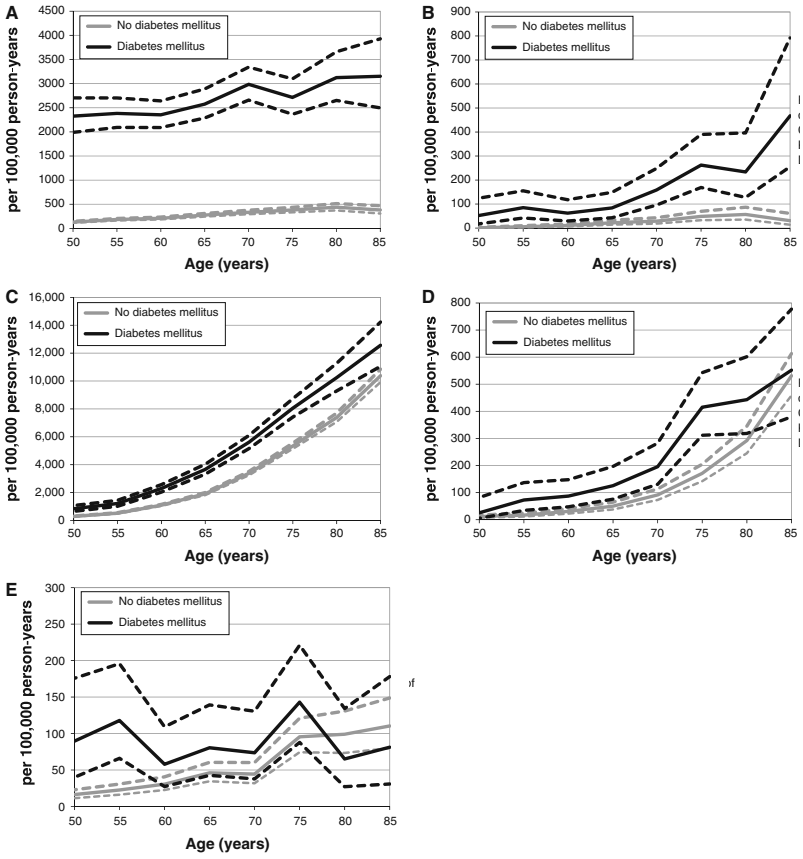


Figure 2 Incidence of chronic kidney disease (possible diagnosis): 2a chronic kidney disease stage 1; 2b chronic kidney disease stage 2; 2c chronic kidney disease stage 3; 2d chronic kidney disease stage 4; 2e chronic kidney disease stage 5

Table 2 Overall prevalence of Chronic Kidney Disease

	No diabetes						Diabetes					
	males			females			males			females		
age (years)	cases	%	95%CI	cases	%	95%CI	cases	%	95%CI	cases	%	95%CI
20-24	112	0.1	(0.1 - 0.1)	113	0.1	(0.1 - 0.1)	3	1.0	(0.0 - 2.1)	4	1.4	(0.0 - 2.7)
25-29	89	0.1	(0.1 - 0.1)	172	0.2	(0.1 - 0.2)	7	2.0	(0.5 - 3.5)	29	7.3	(4.7 - 9.8)
30-34	119	0.1	(0.1 - 0.1)	239	0.2	(0.2 - 0.3)	55	7.9	(5.9 - 9.9)	45	6.1	(4.4 - 7.8)
35-39	261	0.2	(0.2 - 0.3)	430	0.4	(0.3 - 0.4)	108	8.8	(7.2 - 10.4)	100	8.2	(6.6 - 9.7)
40-44	400	0.3	(0.3 - 0.4)	803	0.6	(0.6 - 0.7)	194	9.0	(7.8 - 10.2)	189	10.0	(8.6 - 11.3)
45-49	746	0.6	(0.6 - 0.7)	1,345	1.1	(1.1 - 1.2)	324	9.4	(8.4 - 10.4)	301	11.0	(9.8 - 12.1)
50-54	1,088	1.0	(1.0 - 1.1)	2,346	2.2	(2.1 - 2.3)	565	11.8	(10.9 - 12.7)	583	14.4	(13.3 - 15.5)
55-59	1,925	2.1	(2.0 - 2.2)	3,651	3.9	(3.8 - 4.1)	962	13.4	(12.6 - 14.2)	877	16.4	(15.4 - 17.3)
60-64	3,471	4.3	(4.1 - 4.4)	6,121	7.3	(7.1 - 7.4)	1,723	18.9	(18.0 - 19.7)	1,562	21.9	(21.0 - 22.9)
65-69	4,779	8.4	(8.2 - 8.6)	7,777	12.5	(12.3 - 12.8)	2,189	26.3	(25.4 - 27.3)	2,254	30.7	(29.7 - 31.8)
70-74	6,720	15.2	(14.9 - 15.5)	11,026	21.2	(20.8 - 21.5)	2,815	36.1	(35.1 - 37.2)	3,169	40.5	(39.4 - 41.6)
75-79	8,376	25.7	(25.2 - 26.1)	13,549	30.8	(30.3 - 31.2)	3,161	49.5	(48.3 - 50.7)	4,347	53.9	(52.9 - 55.0)
80-84	7,465	36.8	(36.1 - 37.4)	14,318	42.9	(42.4 - 43.5)	2,574	61.3	(59.8 - 62.7)	4,475	67.1	(66.0 - 68.3)
85+	6,033	48.2	(47.3 - 49.0)	15,818	54.3	(53.8 - 54.9)	1,528	72.9	(71.0 - 74.8)	3,973	77.1	(76.0 - 78.3)

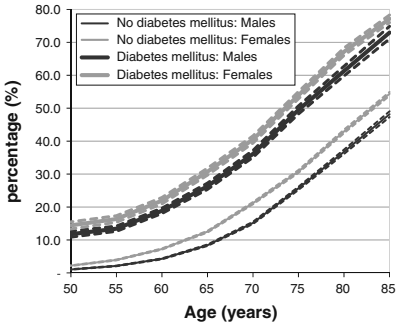


Figure 3 Prevalence of Chronic Kidney Disease (possible diagnosis) - all stages

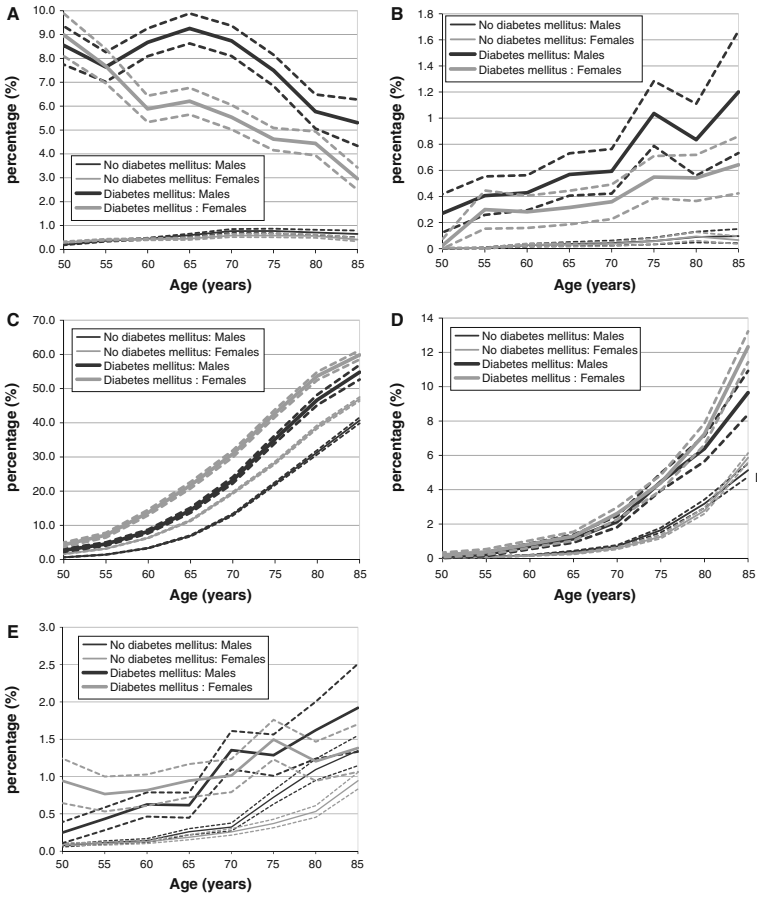


Figure 4 Prevalence of chronic kidney disease (possible diagnosis): 2a chronic kidney disease stage 1; 2b chronic kidney disease stage 2; 2c chronic kidney disease stage 3; 2d chronic kidney disease stage 4; 2e chronic kidney disease stage 5

Prevalence of CKD

The overall prevalence of CKD was 6.7 % (95CI% 6.6 – 6.7 %) for a possible diagnosis of CKD and 5.1% (5.1 – 5.1%) for a definite diagnosis of CKD. In line with the incidence data, the prevalence of CKD, increased with age, female sex, and diabetes to more than 75% in diabetic female subjects aged ≥85 years as shown in table 2 and figure 3. Prevalence of all stages of CKD, except for stage 1, increased with age (figure 4a-e). In patients with diabetes, the prevalence of stage 1 and 2 CKD was higher in males, especially in patients with diabetes. In patients without diabetes, stage 5 CKD was significantly more prevalent in males than in females from the age of 75 onwards (figure 4e). Irrespective of the presence of diabetes, the prevalence of stage 3 CKD was higher in females than in males for all age groups. Comprehensive stage-specific tables are available (online tables 4A-E).

DISCUSSION

Key Results

This is the first study to report incidence rates of CKD for the entire community-dwelling adult population for stage 1-5 of CKD, stratified by sex, 5-year age groups and diabetes. The overall incidence of CKD in adults in our study was 1,213 per 100,000 person-years. The incidence rate increased with age and was the highest in females and in patients with diabetes mellitus. Indeed, in female diabetic patients, the incidence rate was close to 25,000 per 100,000 person-years. For stage 1 of CKD - especially in patients with diabetes – the prevalence decreased with advancing age, despite an increase in incidence rate, possibly due to a more rapid decline in eGFR with reclassification to prevalent stage 3 of CKD or excess mortality. Strengths of our data are the population-based setting, large sample size and the use of laboratory data to define CKD. In addition, risk of selection bias is unlikely as almost all inhabitants in the Netherlands are registered with a GP and data are collected as part of routine patient care, irrespective of any research questions.

Limitations

As for all observational research, our study has potential limitations as well. Diagnostic bias might be a concern as laboratory results were taken in the process of day-to-day patient care – in asymptomatic patients this could imply that the incidence and prevalence of CKD are underestimated as no laboratory results were available. Estimated GFR might not adequately reflected actual GFR, especially in those with diabetes [31-38]. Our data reflect clinical practice because there is no general accepted formula to estimate GFR from serum creatinine with adjustment for diabetes at this point in time. In addition,

potential misclassification is reported to be limited for GFR<90 ml/min/1.73m2 [31]. Finally, patients with stage 5 CKD are detected, however, for those patients referred to the specialist,, there is limited correspondence after initial diagnosis. Therefore, it is not possible to evaluate whether the patient progressed to end-stage renal disease.

Interpretation

Few studies have reported incidence rates for CKD in the general population [5-13]. Of those studies that did, comparison of incidence data is difficult as different case definitions of CKD were used. The overall prevalence of our study is in line with findings from previous cross-sectional studies, although there is substantial heterogeneity among these studies as well, with reported prevalence rates of 19 to 71 percent in the older age categories (table 3) [2]. In prospective studies, where data are progressively collected during the study period, it is possible to confirm a first abnormal measurement (indicating CKD), with a second abnormal measurement ("definite diagnosis") within a reasonable time. In our study population that reflects day-to-day clinical practice, a first abnormal measurement is followed by a second measurement only after a median

TABLE 3 Prevalence of reduced estimated Glomerular Filtration Rate (< 60 ml/min/1.73m^2)

Age (years)	IPCI: (Current Study) subjects	IPCI (Current Study)‡	Viktorsdottir et al. 2005[39]	Coresh et al. 2005 [40] *,**	Nitsch et al. 2006[41]	Cirillo et al. 2006 [42]	Hallan et al. 2006 [3]*	Brown et al. 2005 [43]	McClellan et al. 2006 [1]
20 to 24	98,712	0.0	NA	0.2	†4.6	†0.2	0.2	†2.5	NA
25 to 29	73,241	0.1	NA			0.3			NA
30 to 34	72,520	0.1	NA					5.7	NA
35 to 39	79,139	0.2	1.5			0.4			NA
40 to 44	78,280	0.3	1.9	1.8			1.4	10.3	NA
45 to 49	73,208	0.7	2.9			1.9			19.3
50 to 54	64,338	1.4	4.2		15.2	6.2	6.3	26.7	31.6
55 to 59	58,002	2.8	5.3	7.2					
60 to 64	53,439	5.8	8.8			12.8			51.3
65 to 69	39,505	11.0	26.4		25.3		18.6	43.1	62.7
70 to 74	32,973	19.3	28.5	24.9		32.7			
75 to 79	26,934	30.4	28.6						
80 to 84	19,286	43.0	43.8						
85+	14,986	54.7							71.0

*categories 15-29 and 30-59 ml/min/1.73m^2 combined; **1988-1994 data; †age 18 and above; ‡ Prevalent Chronic Kidney Disease, stage 3,4 and 5 (possible diagnosis)

301 days (IQR: 148-444 days). Therefore, the use of a definite diagnosis of CKD likely underestimates the real values in a population-based study.

In conclusion, this study is the first to report incidence rates for stages 1-5 of CKD stratified by age, sex and diabetes. CKD is a major health problem, which affects the majority of the population at older age, especially in those with diabetes.

Generalizability

Our results are generalizable to a western, predominantly Caucasian population.

Funding

The first author works for the Medicine Evaluation Board, the drug regulatory agency in the Netherlands. The author declares not to have any competing interests. The views expressed in this article are the personal view of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agency.

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ONLINE TABLES

Online table 1 Study population characteristics at start of follow-up

Online table 1 Characteristics of study population

Age at start of follow-up (years)	Males		Females		Overall	
	Number	%	Number	%	Number	%
20-24	47,532	(12.6)	51,180	(12.6)	98,712	(12.6)
25-29	34,876	(9.2)	38,365	(9.4)	73,241	(9.3)
30-34	35,803	(9.5)	36,717	(9.0)	72,520	(9.2)
35-39	39,243	(10.4)	39,896	(9.8)	79,139	(10.1)
40-44	39,119	(10.4)	39,161	(9.6)	78,280	(10.0)
45-49	36,543	(9.7)	36,665	(9.0)	73,208	(9.3)
50-54	31,953	(8.5)	32,385	(8.0)	64,338	(8.2)
55-59	28,970	(7.7)	29,032	(7.1)	58,002	(7.4)
60-64	26,403	(7.0)	27,036	(6.6)	53,439	(6.8)
65-69	19,169	(5.1)	20,336	(5.0)	39,505	(5.0)
70-74	15,124	(4.0)	17,849	(4.4)	32,973	(4.2)
75-79	11,464	(3.0)	15,470	(3.8)	26,934	(3.4)
80-84	7,080	(1.9)	12,206	(3.0)	19,286	(2.5)
85+	4,343	(1.2)	10,643	(2.6)	14,986	(1.9)
Total	377,622	(100.0)	406,941	(100.0)	784,563	(100.0)

Online table 2 Diabetes in study population at start of follow-up

Online table 2 Diabetes in study population

Age at start of follow-up (years)	Males		Females		Overall	
	Number	%*	Number	%*	Number	%*
20-24	123	(0.3)	139	(0.3)	262	(0.3)
25-29	124	(0.4)	140	(0.4)	264	(0.4)
30-34	221	(0.6)	201	(0.5)	422	(0.6)
35-39	398	(1.0)	357	(0.9)	755	(1.0)
40-44	665	(1.7)	576	(1.5)	1,241	(1.6)
45-49	1,013	(2.8)	784	(2.1)	1,797	(2.5)
50-54	1,423	(4.5)	1,159	(3.6)	2,582	(4.0)
55-59	2,088	(7.2)	1,573	(5.4)	3,661	(6.3)
60-64	2,587	(9.8)	2,026	(7.5)	4,613	(8.6)
65-69	2,416	(12.6)	2,149	(10.6)	4,565	(11.6)
70-74	2,154	(14.2)	2,274	(12.7)	4,428	(13.4)
75-79	1,838	(16.0)	2,284	(14.8)	4,122	(15.3)
80-84	1,111	(15.7)	1,962	(16.1)	3,073	(15.9)
85+	593	(13.7)	1,523	(14.3)	2,116	(14.1)
Overall	16,754	(4.4)	17,147	(4.2)	33,901	(4.3)

* Percentage of sex specific age category

Online table 3 stage specific incidence of CKD (possible diagnosis)

Online table 3A Incidence of CKD – stage 1

	No diabetes						Diabetes					
	males			females			males			females		
Age(years)	cases	IR*	95%CI	cases	IR*	95%CI	cases	IR*	95%CI	cases	IR*	95%CI
20-24	5	6	(2-13)	6	7	(3-15)	0	-	(-)	2	823	(164-2,637)
25-29	7	8	(4-16)	20	23	(14-35)	1	328	(30-1,530)	7	2,061	(919-4,047)
30-34	8	9	(4-17)	19	21	(13-31)	11	1,843	(978-3,191)	7	1,091	(487-2,142)
35-39	23	22	(14-33)	36	34	(24-46)	21	2,085	(1,329-3,127)	15	1,459	(853-2,346)
40-44	45	41	(30-55)	64	58	(45-73)	31	1,796	(1,244-2,515)	33	2,189	(1,534-3,035)
45-49	66	63	(50-80)	101	95	(78-115)	64	2,282	(1,773-2,894)	48	2,173	(1,622-2,855)
50-54	108	115	(95-139)	138	146	(123-172)	88	2,280	(1,840-2,795)	75	2,383	(1,888-2,969)
55-59	142	176	(149-207)	156	193	(164-225)	139	2,458	(2,074-2,893)	95	2,282	(1,857-2,776)
60-64	160	232	(198-270)	131	187	(157-221)	184	2,732	(2,359-3,149)	95	1,855	(1,510-2,257)
65-69	149	308	(261-360)	126	247	(207-293)	175	2,989	(2,571-3,457)	106	2,096	(1,725-2,524)
70-74	122	343	(286-408)	130	325	(272-384)	172	3,452	(2,965-3,998)	122	2,508	(2,092-2,983)
75-79	103	429	(352-517)	108	347	(286-417)	115	3,297	(2,735-3,942)	95	2,235	(1,818-2,719)
80-84	57	435	(333-559)	89	442	(357-541)	69	3,558	(2,791-4,474)	79	2,824	(2,252-3,500)
85+	31	426	(295-596)	55	362	(276-468)	24	3,329	(2,188-4,870)	51	3,075	(2,315-4,008)

*IR Incidence rate per 100,000 person-years

Online table 3B Incidence of CKD – stage 2

	No diabetes						Diabetes					
	males			females			males			females		
Age(years)	cases	IR*	95%CI	cases	IR*	95%CI	cases	IR*	95%CI	cases	IR*	95%CI
20-24	0	-	(-)	0	-	(-)	0	-	(-)	0	-	(-)
25-29	0	-	(-)	0	-	(-)	0	-	(-)	0	-	(-)
30-34	0	-	(-)	0	-	(-)	0	-	(-)	0	-	(-)
35-39	0	-	(-)	0	-	(-)	0	-	(-)	0	-	(-)
40-44	0	-	(-)	0	-	(-)	0	-	(-)	0	-	(-)
45-49	1	1	(0 - 4)	3	3	(1 - 8)	1	33	(3 - 155)	0	-	(-)
50-54	0	-	(-)	2	2	(- 7)	3	72	(20 - 191)	1	29	(3 - 135)
55-59	4	5	(2 - 12)	5	6	(2 - 13)	4	66	(22 - 156)	5	112	(42 - 245)
60-64	6	9	(4 - 18)	9	13	(6 - 23)	5	68	(26 - 149)	3	55	(15 - 147)
65-69	11	23	(12 - 39)	11	21	(11 - 37)	6	93	(39 - 191)	4	74	(25 - 176)
70-74	12	34	(18 - 57)	10	25	(13 - 44)	5	91	(34 - 199)	12	231	(126 - 392)
75-79	13	54	(30 - 89)	14	45	(26 - 73)	12	312	(170 - 529)	10	220	(113 - 391)
80-84	6	45	(19 - 94)	13	64	(36 - 107)	2	94	(19 - 302)	10	333	(171 - 590)
85+	3	41	(11 - 109)	4	26	(9 - 62)	4	501	(168 - 1,192)	8	452	(213 - 853)

*IR Incidence rate per 100,000 person-years

Online table 3C Incidence of CKD – stage 3

	No diabetes						Diabetes					
	males			females			males			females		
Age (years)	cases	IR*	95%CI	cases	IR*	95%CI	cases	IR*	95%CI	cases	IR*	95%CI
20-24	5	6	2 - 13)	4	5	2 - 12)	0	-	-)	0	-	-)
25-29	3	4	1 - 9)	18	21	13 - 32)	0	-	-)	1	282	26 - 1,316)
30-34	6	7	3 - 14)	21	23	14 - 34)	1	158	14 - 738)	2	303	60 - 970)
35-39	25	24	16 - 35)	37	35	25 - 47)	2	185	37 - 594)	2	186	37 - 595)
40-44	45	41	30 - 55)	107	96	79 - 116)	3	162	45 - 433)	4	247	82 - 587)
45-49	94	90	74 - 110)	196	185	161 - 212)	12	402	220 - 681)	10	424	217 - 752)
50-54	175	187	161 - 217)	362	385	347 - 426)	29	698	477 - 988)	34	1,003	707 - 1,385)
55-59	350	436	392 - 484)	481	599	548 - 655)	68	1,129	884 - 1,422)	58	1,324	1,015 - 1,698)
60-64	600	880	811 - 952)	893	1,300	1,217 - 1,388)	121	1,695	1,413 - 2,018)	161	3,107	2,655 - 3,616)
65-69	771	1,630	(1,518 - 1,748)	1,066	2,174	2,046 - 2,307)	199	3,233	2,807 - 3,706)	209	4,186	3,647 - 4,783)
70-74	982	2,889	(2,712 - 3,074)	1,429	3,828	3,633 - 4,030)	267	5,280	4,675 - 5,942)	274	5,979	5,303 - 6,719)
75-79	1,098	4,956	(4,669 - 5,256)	1,574	5,648	5,375 - 5,933)	240	7,085	6,231 - 8,025)	336	8,926	8,009 - 9,919)
80-84	791	6,784	(6,323 - 7,269)	1,343	7,782	7,374 - 8,207)	167	9,772	8,373 - 11,341)	244	10,592	9,325 - 11,985)
85+	621	10,142	(9,368 - 10,964)	1,302	10,490	9,932 - 11,072)	70	11,214	8,812 - 14,079)	170	13,217	11,341 - 15,319)

*IR Incidence rate per 100,000 person-years

Online table 3D Incidence of CKD – stage 4

	No diabetes						Diabetes					
	males			females			males			females		
Age(years)	cases	IR*	95%CI	cases	IR*	95%CI	cases	IR*	95%CI	cases	IR*	95%CI
20-24	1	1	- 6)	2	2	- 8)	0	-	-)	0	-	-)
25-29	1	1	- 5)	1	1	- 5)	0	-	-)	0	-	-)
30-34	1	1	- 5)	-	-	-)	0	-	-)	0	-	-)
35-39	4	4	1 - 9)	1	1	- 4)	2	184	37 - 590)	0	-	-)
40-44	4	4	1 - 9)	2	2	- 6)	0	-	-)	0	-	-)
45-49	6	6	2 - 12)	3	3	1 - 8)	1	33	3 - 154)	2	83	17 - 265)
50-54	8	9	4 - 16)	14	15	8 - 24)	0	-	-)	2	56	11 - 181)
55-59	16	20	12 - 31)	12	14	8 - 25)	4	63	21 - 151)	4	85	28 - 202)
60-64	23	33	21 - 48)	21	29	18 - 43)	4	52	17 - 123)	8	133	63 - 252)
65-69	34	67	47 - 93)	19	34	21 - 53)	11	153	81 - 265)	6	94	39 - 195)
70-74	48	123	92 - 162)	30	65	45 - 91)	11	167	88 - 288)	15	225	131 - 361)
75-79	59	208	160 - 266)	56	144	110 - 186)	17	320	194 - 501)	33	490	344 - 680)
80-84	61	360	278 - 459)	71	251	198 - 315)	10	302	155 - 535)	28	532	361 - 758)
85+	63	610	473 - 775)	119	498	414 - 593)	8	504	238 - 952)	22	572	368 - 850)

*IR Incidence rate per 100,000 person-years

Online table 3E Incidence of CKD – stage 5

	No diabetes						Diabetes					
	males			females			males			females		
Age(years)	cases	IR*	95%CI	cases	IR*	95%CI	cases	IR*	95%CI	cases	IR*	95%CI
20-24	2	2	- 8)	1	1	- 6)	0	-	-)	0	-	-)
25-29	1	1	- 5)	2	2	- 7)	0	-	-)	1	282	26 - 1,314)
30-34	1	1	- 5)	3	3	1 - 9)	2	317	63 - 1,017)	2	302	60 - 969)
35-39	8	8	4 - 14)	12	11	6 - 19)	0	-	-)	4	372	124 - 884)
40-44	8	7	3 - 14)	11	10	5 - 17)	1	54	5 - 250)	1	61	6 - 286)
45-49	11	11	6 - 18)	11	10	5 - 18)	1	33	3 - 154)	3	125	34 - 332)
50-54	20	21	13 - 32)	11	12	6 - 20)	3	70	19 - 187)	4	113	38 - 268)
55-59	21	26	16 - 39)	16	19	11 - 31)	9	143	71 - 261)	4	85	28 - 201)
60-64	23	33	21 - 48)	21	29	18 - 43)	2	26	5 - 82)	6	99	41 - 205)
65-69	29	57	39 - 81)	20	36	23 - 55)	6	83	34 - 171)	5	78	30 - 171)
70-74	27	69	46 - 99)	11	24	13 - 41)	6	89	37 - 184)	4	58	20 - 139)
75-79	30	104	72 - 147)	35	89	63 - 123)	8	144	68 - 272)	10	142	73 - 252)
80-84	26	149	100 - 215)	20	69	43 - 104)	5	141	54 - 310)	1	18	2 - 82)
85+	15	138	81 - 222)	25	99	65 - 143)	2	114	23 - 365)	3	68	19 - 182)

*IR Incidence rate per 100,000 person-years

Online tables 4 Stage specific prevalence of CKD (possible diagnosis)

Online table 4A Prevalence of Chronic Kidney Disease – stage 1

	No diabetes						Diabetes					
	males			females			males			females		
age (years)	cases	%	95%CI	cases	%	95%CI	cases	%	95%CI	cases	%	95%CI
20-24	19	0.0	(0.0 - 0.0)	25	0.0	(0.0 - 0.0)	0	0.0	(0.0 - 0.0)	4	1.4	(0.0 - 2.8)
25-29	9	0.0	(0.0 - 0.0)	39	0.0	(0.0 - 0.1)	5	1.5	(0.2 - 2.8)	21	5.5	(3.2 - 7.7)
30-34	24	0.0	(0.0 - 0.0)	70	0.1	(0.1 - 0.1)	41	6.1	(4.3 - 7.9)	29	4.1	(2.6 - 5.6)
35-39	55	0.0	(0.0 - 0.1)	107	0.1	(0.1 - 0.1)	81	6.8	(5.3 - 8.2)	63	5.3	(4.0 - 6.5)
40-44	94	0.1	(0.1 - 0.1)	170	0.1	(0.1 - 0.2)	154	7.4	(6.3 - 8.5)	144	7.8	(6.6 - 9.0)
45-49	169	0.1	(0.1 - 0.2)	240	0.2	(0.2 - 0.2)	237	7.0	(6.2 - 7.9)	194	7.3	(6.3 - 8.3)
50-54	208	0.2	(0.2 - 0.2)	328	0.3	(0.3 - 0.3)	398	8.5	(7.7 - 9.3)	355	9.0	(8.1 - 9.9)
55-59	327	0.4	(0.3 - 0.4)	379	0.4	(0.4 - 0.4)	533	7.6	(7.0 - 8.3)	403	7.7	(7.0 - 8.4)
60-64	360	0.4	(0.4 - 0.5)	360	0.4	(0.4 - 0.5)	778	8.7	(8.1 - 9.3)	410	5.9	(5.3 - 6.4)
65-69	338	0.6	(0.5 - 0.7)	279	0.5	(0.4 - 0.5)	754	9.3	(8.6 - 9.9)	444	6.2	(5.6 - 6.8)
70-74	340	0.8	(0.7 - 0.9)	301	0.6	(0.5 - 0.6)	663	8.7	(8.1 - 9.4)	421	5.5	(5.0 - 6.1)
75-79	251	0.8	(0.7 - 0.9)	255	0.6	(0.5 - 0.7)	469	7.5	(6.8 - 8.2)	361	4.6	(4.2 - 5.1)
80-84	143	0.7	(0.6 - 0.8)	188	0.6	(0.5 - 0.6)	237	5.8	(5.1 - 6.5)	288	4.4	(3.9 - 4.9)
85+	81	0.6	(0.5 - 0.8)	119	0.4	(0.3 - 0.5)	109	5.3	(4.3 - 6.3)	149	3.0	(2.5 - 3.4)

Online table 4B Prevalence of Chronic Kidney Disease – stage 2

	No diabetes						Diabetes					
	males			females			males			females		
age (years)	cases	%	95%CI	cases	%	95%CI	cases	%	95%CI	cases	%	95%CI
20-24	0	0.0	(0.0 - 0.0)	0	0.0	(0.0 - 0.0)	0	0.0	(0.0 - 0.0)	0	0.0	(0.0 - 0.0)
25-29	0	0.0	(0.0 - 0.0)	0	0.0	(0.0 - 0.0)	0	0.0	(0.0 - 0.0)	0	0.0	(0.0 - 0.0)
30-34	0	0.0	(0.0 - 0.0)	0	0.0	(0.0 - 0.0)	1	0.1	(0.0 - 0.4)	0	0.0	(0.0 - 0.0)
35-39	1	0.0	(0.0 - 0.0)	0	0.0	(0.0 - 0.0)	2	0.2	(0.0 - 0.4)	0	0.0	(0.0 - 0.0)
40-44	2	0.0	(0.0 - 0.0)	6	0.0	(0.0 - 0.0)	0	0.0	(0.0 - 0.0)	2	0.1	(0.0 - 0.3)
45-49	3	0.0	(0.0 - 0.0)	6	0.0	(0.0 - 0.0)	10	0.3	(0.1 - 0.5)	2	0.1	(0.0 - 0.2)
50-54	0	0.0	(0.0 - 0.0)	6	0.0	(0.0 - 0.0)	13	0.3	(0.1 - 0.4)	1	0.0	(0.0 - 0.1)
55-59	5	0.0	(0.0 - 0.0)	4	0.0	(0.0 - 0.0)	29	0.4	(0.3 - 0.6)	16	0.3	(0.2 - 0.4)
60-64	21	0.0	(0.0 - 0.0)	24	0.0	(0.0 - 0.0)	39	0.4	(0.3 - 0.6)	20	0.3	(0.2 - 0.4)
65-69	20	0.0	(0.0 - 0.1)	18	0.0	(0.0 - 0.0)	47	0.6	(0.4 - 0.7)	23	0.3	(0.2 - 0.4)
70-74	19	0.0	(0.0 - 0.1)	19	0.0	(0.0 - 0.1)	46	0.6	(0.4 - 0.8)	28	0.4	(0.2 - 0.5)
75-79	19	0.1	(0.0 - 0.1)	25	0.1	(0.0 - 0.1)	66	1.0	(0.8 - 1.3)	44	0.5	(0.4 - 0.7)
80-84	18	0.1	(0.0 - 0.1)	31	0.1	(0.1 - 0.1)	35	0.8	(0.6 - 1.1)	36	0.5	(0.4 - 0.7)
85+	12	0.1	(0.0 - 0.2)	19	0.1	(0.0 - 0.1)	25	1.2	(0.7 - 1.7)	33	0.6	(0.4 - 0.9)

Online table 4C Prevalence of Chronic Kidney Disease – stage 3

	No diabetes						Diabetes					
	males			females			males			females		
age (years)	cases	%	95%CI	cases	%	95%CI	cases	%	95%CI	cases	%	95%CI
20-24	20	0.0	(0.0 - 0.0)	16	0.0	(0.0 - 0.0)	0	0.0	(0.0 - 0.0)	0	0.0	(0.0 - 0.0)
25-29	27	0.0	(0.0 - 0.0)	58	0.1	(0.0 - 0.1)	0	0.0	(0.0 - 0.0)	4	1.0	(0.0 - 2.0)
30-34	39	0.0	(0.0 - 0.1)	86	0.1	(0.1 - 0.1)	3	0.4	(0.0 - 0.9)	7	0.9	(0.2 - 1.6)
35-39	74	0.1	(0.0 - 0.1)	179	0.2	(0.1 - 0.2)	10	0.8	(0.3 - 1.3)	12	1.0	(0.4 - 1.5)
40-44	153	0.1	(0.1 - 0.1)	436	0.3	(0.3 - 0.4)	21	1.0	(0.6 - 1.4)	18	1.0	(0.5 - 1.4)
45-49	401	0.3	(0.3 - 0.4)	872	0.7	(0.7 - 0.8)	53	1.5	(1.1 - 2.0)	65	2.4	(1.8 - 2.9)
50-54	670	0.6	(0.6 - 0.7)	1,726	1.6	(1.5 - 1.7)	129	2.7	(2.2 - 3.1)	175	4.3	(3.7 - 5.0)
55-59	1,317	1.5	(1.4 - 1.5)	2,963	3.2	(3.1 - 3.3)	325	4.6	(4.1 - 5.0)	382	7.1	(6.5 - 7.8)
60-64	2,724	3.4	(3.2 - 3.5)	5,344	6.3	(6.2 - 6.5)	749	8.2	(7.7 - 8.8)	976	13.8	(13.0 - 14.6)
65-69	3,942	6.9	(6.7 - 7.2)	7,071	11.4	(11.2 - 11.7)	1,193	14.4	(13.7 - 15.2)	1,586	21.7	(20.8 - 22.7)
70-74	5,803	13.1	(12.8 - 13.5)	10,121	19.5	(19.2 - 19.8)	1,799	23.2	(22.3 - 24.1)	2,410	30.9	(29.9 - 31.9)
75-79	7,220	22.2	(21.8 - 22.7)	12,419	28.3	(27.9 - 28.7)	2,246	35.2	(34.1 - 36.4)	3,433	42.8	(41.7 - 43.9)
80-84	6,340	31.4	(30.7 - 32.0)	12,910	38.8	(38.3 - 39.3)	1,958	46.7	(45.2 - 48.2)	3,566	53.7	(52.5 - 54.9)
85+	5,072	40.7	(39.8 - 41.5)	13,623	46.9	(46.4 - 47.5)	1,141	54.8	(52.6 - 56.9)	3,075	59.8	(58.5 - 61.2)

Online table 4D Prevalence of Chronic Kidney Disease – stage 4

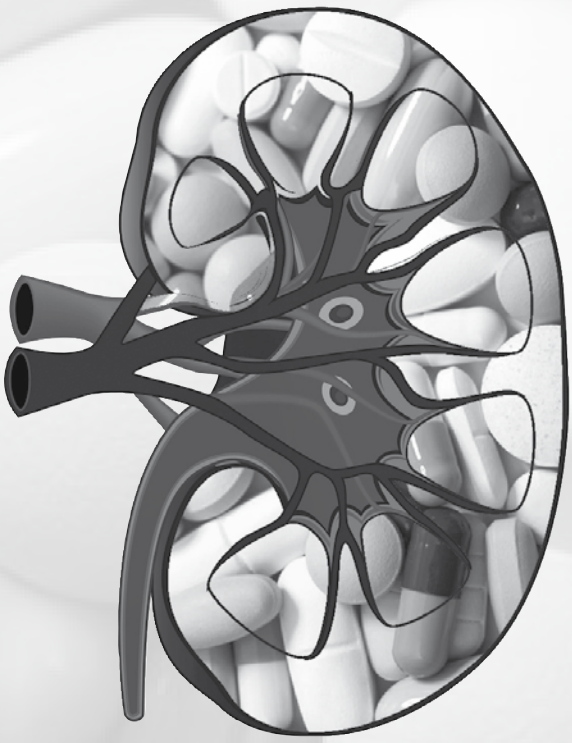
	No diabetes						Diabetes					
	males			females			males			females		
age (years)	cases	%	95%CI	cases	%	95%CI	cases	%	95%CI	cases	%	95%CI
20-24	3	0.0	(0.0 - 0.0)	5	0.0	(0.0 - 0.0)	0	0.0	(0.0 - 0.0)	0	0.0	(0.0 - 0.0)
25-29	9	0.0	(0.0 - 0.0)	8	0.0	(0.0 - 0.0)	0	0.0	(0.0 - 0.0)	1	0.3	(0.0 - 0.7)
30-34	6	0.0	(0.0 - 0.0)	8	0.0	(0.0 - 0.0)	0	0.0	(0.0 - 0.0)	0	0.0	(0.0 - 0.0)
35-39	19	0.0	(0.0 - 0.0)	8	0.0	(0.0 - 0.0)	3	0.2	(0.0 - 0.5)	0	0.0	(0.0 - 0.0)
40-44	36	0.0	(0.0 - 0.0)	14	0.0	(0.0 - 0.0)	1	0.0	(0.0 - 0.1)	4	0.2	(0.0 - 0.4)
45-49	17	0.0	(0.0 - 0.0)	30	0.0	(0.0 - 0.0)	6	0.2	(0.0 - 0.3)	1	0.0	(0.0 - 0.1)
50-54	39	0.0	(0.0 - 0.0)	59	0.1	(0.0 - 0.1)	5	0.1	(0.0 - 0.2)	8	0.2	(0.1 - 0.3)
55-59	80	0.1	(0.1 - 0.1)	59	0.1	(0.0 - 0.1)	18	0.3	(0.1 - 0.4)	20	0.4	(0.2 - 0.5)
60-64	145	0.2	(0.1 - 0.2)	137	0.2	(0.1 - 0.2)	64	0.7	(0.5 - 0.9)	59	0.8	(0.6 - 1.0)
65-69	224	0.4	(0.3 - 0.4)	171	0.3	(0.2 - 0.3)	95	1.1	(0.9 - 1.4)	94	1.3	(1.0 - 1.5)
70-74	308	0.7	(0.6 - 0.8)	306	0.6	(0.5 - 0.7)	166	2.1	(1.8 - 2.5)	204	2.6	(2.3 - 3.0)
75-79	535	1.6	(1.5 - 1.8)	554	1.3	(1.2 - 1.4)	284	4.5	(3.9 - 5.0)	353	4.4	(3.9 - 4.8)
80-84	643	3.2	(2.9 - 3.4)	923	2.8	(2.6 - 3.0)	268	6.4	(5.7 - 7.1)	481	7.2	(6.6 - 7.9)
85+	640	5.1	(4.7 - 5.5)	1,701	5.9	(5.6 - 6.1)	201	9.6	(8.4 - 10.9)	633	12.3	(11.4 - 13.2)

Online table 4E Prevalence of Chronic Kidney Disease – stage 5

	No diabetes						Diabetes					
	males			females			males			females		
age (years)	cases	%	95%CI	cases	%	95%CI	cases	%	95%CI	cases	%	95%CI
20-24	13	0.0	(0.0 - 0.0)	22	0.0	(0.0 - 0.0)	0	0.0	(-)	0	0.0	(0.0 - 0.0)
25-29	8	0.0	(0.0 - 0.0)	16	0.0	(0.0 - 0.0)	1	0.3	(0.0 - 0.9)	3	0.8	(0.0 - 1.6)
30-34	11	0.0	(0.0 - 0.0)	24	0.0	(0.0 - 0.0)	6	0.9	(0.2 - 1.6)	9	1.2	(0.4 - 2.0)
35-39	32	0.0	(0.0 - 0.0)	36	0.0	(0.0 - 0.0)	9	0.7	(0.3 - 1.2)	15	1.2	(0.6 - 1.8)
40-44	42	0.0	(0.0 - 0.0)	64	0.1	(0.0 - 0.1)	5	0.2	(0.0 - 0.4)	19	1.0	(0.6 - 1.5)
45-49	59	0.1	(0.0 - 0.1)	76	0.1	(0.0 - 0.1)	10	0.3	(0.1 - 0.5)	27	1.0	(0.6 - 1.4)
50-54	77	0.1	(0.1 - 0.1)	99	0.1	(0.1 - 0.1)	12	0.3	(0.1 - 0.4)	38	0.9	(0.6 - 1.2)
55-59	105	0.1	(0.1 - 0.1)	94	0.1	(0.1 - 0.1)	31	0.4	(0.3 - 0.6)	41	0.8	(0.5 - 1.0)
60-64	116	0.1	(0.1 - 0.2)	107	0.1	(0.1 - 0.2)	57	0.6	(0.5 - 0.8)	58	0.8	(0.6 - 1.0)
65-69	148	0.3	(0.2 - 0.3)	116	0.2	(0.2 - 0.2)	51	0.6	(0.4 - 0.8)	69	0.9	(0.7 - 1.2)
70-74	143	0.3	(0.3 - 0.4)	134	0.3	(0.2 - 0.3)	105	1.4	(1.1 - 1.6)	79	1.0	(0.8 - 1.2)
75-79	235	0.7	(0.6 - 0.8)	163	0.4	(0.3 - 0.4)	82	1.3	(1.0 - 1.6)	120	1.5	(1.2 - 1.8)
80-84	221	1.1	(1.0 - 1.2)	177	0.5	(0.5 - 0.6)	68	1.6	(1.2 - 2.0)	80	1.2	(0.9 - 1.5)
85+	168	1.3	(1.1 - 1.5)	274	0.9	(0.8 - 1.1)	40	1.9	(1.3 - 2.5)	71	1.4	(1.1 - 1.7)

Chapter 3

Drug use and renal function decline



Chapter 3.1

Overanticoagulation and renal function decline

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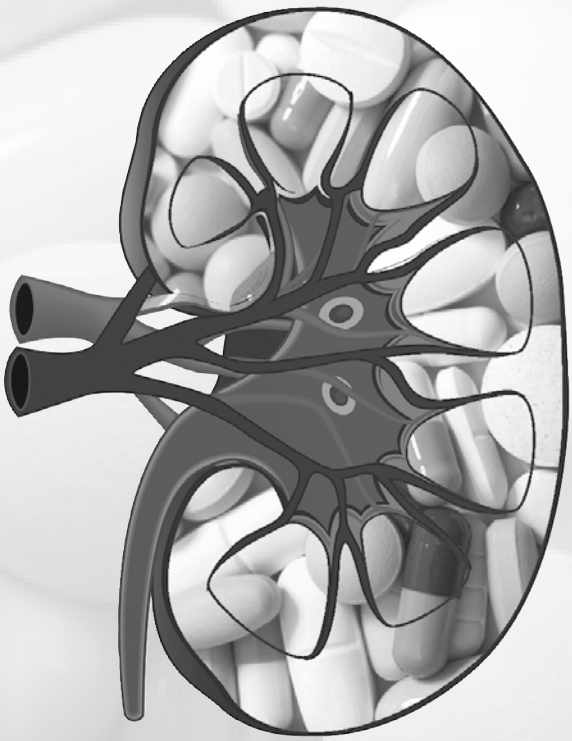
Overanticoagulation is associated with renal function decline.
J Nephrol. 2013 Jul-Aug;26(4):691-8.



ABSTRACT

Background

Recent studies suggest that overanticoagulation impairs renal function in patients on warfarin therapy, due to renal tubular obstruction from glomerular hemorrhage.

Methods

Data from the Rotterdam Study (The Netherlands), a prospective population-based cohort study of patients 55 years and older, were used for this study. Information on vitamin K antagonist (VKA) therapy was obtained from the regional anticoagulation clinic, where prothrombin times were monitored every 1-6 weeks depending on target level and stability of the international normalized ratio (INR). Linear regression was performed to study the association between the cumulative number of instances of overanticoagulation (defined as a measurement of an INR >6.0) and the change in renal function between baseline and third examination round based on estimated glomerular filtration rate (CKD-EPI equation). Age, sex, baseline renal function, baseline and incident heart failure, and indication for VKA therapy were included as potential confounders.

Results

Information was available for analysis on 2,802 study participants in whom overanticoagulation was significantly associated with a decline in renal function, after adjustment for confounding by age, sex, heart failure, baseline glomerular filtration rate and indication for VKA therapy (-0.180 ml/min per 1.73 m(2) per year per event for INR >6.0, p = 0.030).

Conclusions

Overanticoagulation (INR >6.0) is associated with a decline in renal function. Further studies are needed to evaluate the causal role of different degrees of overanticoagulation, including transient effects, in high-risk groups, and the association with the new oral anticoagulants.

INTRODUCTION

Background

Vitamin K antagonists (VKA) comprise several therapeutic agents, including warfarin, acenocoumarol and phenprocoumon. Warfarin is a commonly used anticoagulant, with roughly two million persons initiating warfarin each year in the United States alone [1]. In the Netherlands, the majority of patients are treated with acenocoumarol or phenprocoumon. In 2010, approximately 398,000 patients of the Dutch population of 16.6 million people were treated with VKA[2-3].

An association between warfarin and renal function has been described in two case reports and one case series of 9 patients [4-6]. More recently, two cohort studies reported overanticoagulation, defined as an International Normalized Ratio (INR)>3.0, as a cause of decline of renal function in patients on warfarin therapy [7-10]

Because of the risk of bleeding, anticoagulant treatment is tightly monitored via INR, which has been investigated in multiple studies [11-22]. However these did not address specific effects of overanticoagulation on renal function.

Objective

In this study we investigated whether overanticoagulation, and in particular repeated events of INR>6.0, during VKA therapy is associated with a decline of renal function. Additionally, we investigated whether the association is present at a lower threshold for overanticoagulation, down to an INR>3.0, as previously reported from two cohort studies. [8-9]

SUBJECTS AND METHODS

Study design

We used data from baseline and the third examination round of the Rotterdam Study, a prospective population-based cohort study designed to study chronic diseases in the elderly.

Setting

In the Rotterdam study, 10,275 inhabitants of the Rotterdam district Ommoord, aged 55 years or older, were invited to the baseline examination round of the study. The first cohort included 7,983 participants. Serum Creatinine (SCR) was measured at baseline

(1989-1993) and during the third examination round (1997-1999). The design of the Rotterdam study have been described elsewhere [23].

Participants

For this study, we used data of participants who had a baseline SCR measurement and a SCR measurement during the third examination round.

Variables

The outcome of this study is the difference in estimated Glomerular Filtration Rate (eGFR) between first and third examination round. eGFR was estimated with the equation of the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration, which is a follows [24]:

eGFR = 141 * min(Scr/κ,1)α * max(Scr/κ,1)-1.209 * 0.993Age * 1.018 [if female] * 1.159 [if black] ;Where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

The following variables were included as potential confounders: age, sex, baseline renal function, baseline and incident heart failure, and indication for VKA therapy.

Data sources

Glomerular Filtration Rate was estimated from serum creatinine. Age, sex and baseline renal function were determined at the first (baseline) examination round. Heart failure at the first examination round was assessed using a validated score of the European Society of Cardiology. [25-26]. Cases of incident heart failure were obtained by continuous monitoring of participants and case validation [25, 27].

Overanticoagulation, duration and indication for VKA therapy were obtained from the regional anticoagulation clinic, which monitors all outpatients in the Rotterdam region. This clinic has a near complete coverage of participants from the Rotterdam Study. Data were available from as of January 1984 to September 2009. The physician who treats the patient decides about the type of anticoagulant prescribed and the prothrombin times are monitored every 1–6 weeks, depending on the target level and stability of the INR. [28] The cumulative number of events of overanticoagulation, defined as an INR>6.0 was calculated for the period between baseline and third examination round. We used the most recent indication for VKA therapy prior to the third examination round. The number of individual indications was reduced to four groups, (1) treatment of deep venous thrombosis and pulmonary embolism, (2) perioperative, (3) peripheral arterial

and structural heart disease, and (4) atrial fibrillation and other heart rhythm disorders, based on their expected potential to confound the studied association.

Statistical methods

We included overanticoagulation as a linear variable in the model. Age was included as a linear variable. Sex, baseline and incident heart failure, indication for VKA therapy and baseline renal function were included as a categorical variables. For the latter, stages G1-5 were used according to Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines [29].

We performed sensitivity analyses for different cut-offs of overanticoagulation (INR>3.0, >4.0, and >5.0). Additionally we studied a possible non-linear effect of overanticoagulation categorizing the cumulative number of overanticoagulation using quartiles when possible and tertiles in case of low numbers or skewed distribution.

Statistical analyses were performed using the statistical package SPSS, Version 20 (IBM; Armonk, N.Y., USA).

RESULTS

Participants

At the baseline examination round 7,121 out of 7,983 participants provided a blood sample; SCR was measured in 5,280 of these samples. Of these, 4,336 participants were alive at the start of the third examination round and 2,910 participants provided a blood sample; SCR was measured in 96.2% of these samples, leaving 2,802 participants available for analysis.

Descriptive data

Median age of the study population was 67 years, with 61% female (table 1). During the interval between baseline and third examination round a total of 354 participants used any VKA therapy. Median duration of VKA therapy was 251 days, during which a total of 181 events of INR>6.0 were observed, being 8 events per 10,000 days of VKA therapy. Except for one, all had one single indication for use of VKA therapy during follow-up (figure 1; table 2).

Table 1 Baseline population characteristics of participants with serum creatinine measurement during baseline and third examination round

Number of participants	2 802	
Age at baseline examination round in years (median,IQR)	66.5	(61.1 - 71.4)
Sex - female (n,%)	1 699	(60.6)
Prevalent heart failure (n,%)	37	(1.3)
Baseline estimated Glomerular Filtration Rate ml/min/1.73m^2 (mean, standard deviation)	74	(13.1)
- ≥90+ ml/min/1.73m^2 (n,%)	376	(13.4)
- 60-90 ml/min/1.73m^2 (n,%)	2 023	(72.2)
- 30-60 ml/min/1.73m^2 (n,%)	401	(14.3)
- 15-30 ml/min/1.73m^2 (n,%)	0	(0.0)
- <15 ml/min/1.73m^2 (n,%)	2	(0.1)
Prior use of vitamin K antagonists (n,%)	73	(2.6)
Duration of prior vitamin K antagonist use in days (median, IQR)	89	(55 - 246)

IQR: Interquartile range; n: number; %: percentage

Table 2 Vitamin K Antagonist therapy

Indication for VKA therapy	Number of participants	Duration of VKA therapy (days)			Cumulative number of excess anticoagulation measurements(participants)*							
		Median	IQR	Sum	INR>3.0		INR >4.0		INR >5.0		INR >6.0	
Perioperative	99	78	(62;109)	10,921	288	(78)	74	(31)	20	(10)	6	(4)
DVT/PE	36	218	(156;939)	19,505	602	(33)	153	(25)	48	(18)	17	(10)
AF /oHRD	76	663	(214;1,501)	63,249	2,156	(75)	663	(63)	146	(47)	41	(23)
PAD / SHD	143	768	(171;1,531)	126,434	4,804	(141)	1,687	(128)	378	(9)	117	(61)
All indications	354	251	(250;1,231)	220,109	7,850	(327)	2,577	(247)	592	(174)	181	(98)

*= Participants and measurements are not mutually exclusive for different cut-offs of overanticoagulation; AF = Atrial Fibrillation; DVT = Deep Venous Thrombosis; INR = International Normalized Ratio; IQR = Interquartile range; oHRD = Other Hearth Rhythm Disorder; PAD = Peripheral Artery Disease; PE = Pulmonary Embolism; SHD = Structural Heart Disease; VKA = Vitamin K antagonist

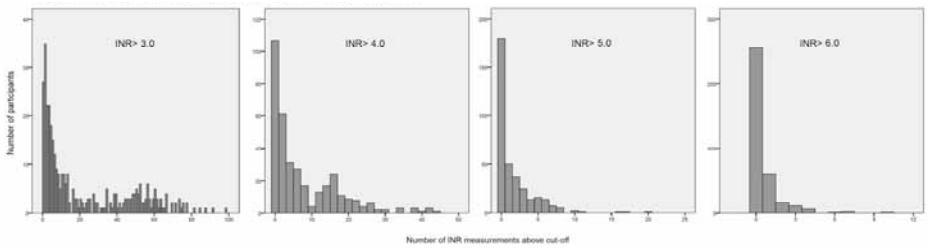


Figure 1 Cumulative number of overanticoagulation instances during vitamin K antagonist therapy – for all indications. INR =international normalized ratio.

Outcome data

The median time interval between baseline and third examination round was 6.5 years, during which the median eGFR in the 2,802 participants changed with a median -.29 ml/min/1.73m2/year.

Main results

In the univariable analysis, there was a significant association between the cumulative number of instances of overanticoagulation (INR>6.0) and the change in eGFR between baseline and third examination round (figure 2). After adjustment for confounding factors the additional change in eGFR associated with the cumulative number of INR>6.0 remained significant [-0.180 ml/min/1.73m2 per year per INR>6.0, p-value=0.030 (table 3)]. Similar trends were observed if indications were analyzed separately (results not shown).

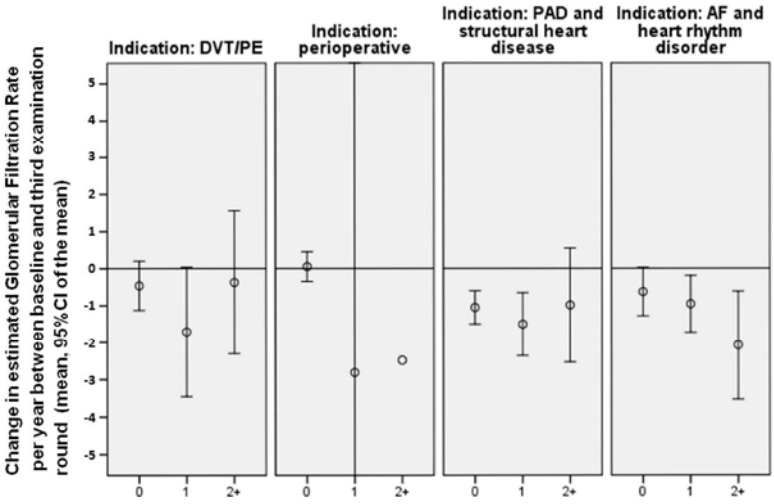


Figure 2 Change in estimated glomerular filtration rate in participants who used vitamin K antagonist therapy – per indication. AF = atrial fibrillation; DVT/PE = deep venous thrombosis/pulmonary embolism; INR = international normalized ratio;PAD = peripheral artery disease.

Table 3 Change in estimated Glomerular Filtration Rate between baseline and third examination round

Variable	estimate*	p-value	95% Confidence interval
(Constant)	-1.213	**.000**	(-1.434 ; -.992)
Baseline age above 50 years (years)	-.033	**.000**	(-.043 ; -.023)
Female sex (male = referent)	.705	**.000**	(.567 ; .843)
Baseline eGFR (ml/min/1.73m^2) (≥90 ml/min/1.73m^2 = referent)			
- 60 to 89	1.143	**.000**	(.945 ; 1.340)
- 30 to 59	2.157	**.000**	(1.885 ; 2.429)
Heart failure (no heart failure during follow-up = referent)			
-At baseline	.505	.125	(-.141 ; 1.151)
-During follow-up	-.678	**.000**	(-1.018 ; -.339)
Indication vitamin K antagonist therapy (no use = referent)			
-DVT/PE	-.453	**.**092	(-.980 ; .074)
-Perioperative	-.149	.361	(-.470 ; .171)
–PAD / structural heart disease	-.425	**.007**	(-.733 ; -.117)
- AF /other heart rhythm disorders	-.220	.284	(-.623 ; .183)
Per event of overanticoagulation (defined as INR>6.0)	-.180	**.030**	(-.342 ; -.017)

* = Change in estimated glomerular filtration rate is calculated from baseline and third examination round serum creatinine, fully adjusted model; AF = Atrial Fib rillation; DVT = Deep Venous Thrombosis; eGFR = estimated Glomerular Filtration Rate (Chronic Kidney Disease Epidemiology Collaboration equation); INR = International Normalized Ratio; PAD = Peripheral Artery Disease; PE = Pulmonary Embolism

Other analysis

In univariable analysis using categories, renal function decline was significantly greater with a higher cumulative number of instances of overanticoagulation compared to the reference with the lowest cumulative number. This also applied to other cut-offs of INR, with exception of the 4th quartile of INR>3.0 as shown in table 4. Trends over the categories of cumulative overanticoagulation, adjusted for age, sex, baseline eGFR, baseline and incident heart failure, and indication for VKA therapy, were not significant at $p<0.05$, except for INR>6.0. If participants were assigned to mutually exclusive categories by maximum overanticoagulation observed during follow-up, the association was significant for INR>6.0 after adjustment for confounding factors (results not shown).

We examined the cause of death in the 944 participants, who died before the start of the third examination round. A total of 12 participants died due to chronic kidney disease (CKD) and two due to acute renal failure. Of these, 3 had used VKA therapy but in

Table 4 Contribution to change in estimated Glomerular Filtration Rate per year between baseline and third examination round for different cut-offs of overanticoagulation

Cumulative number of INR measurements above cut-off	Number of participants *	Estimate **	p-value	95% Confidence Interval	p-value for trend over categories**
INR>3.0					
0	84	Ref.			
3-8	84	-.675	**.006**	(-1.159 ; -.192)	
9-42	94	-1.169	**.000**	(-1.699 ; -.639)	.945
43+	92	-.272	.330	(-.820 ; .275)	
INR>4.0					
0	107	Ref.			
1-7	123	-.668	**.003**	(-1.103 ; -.233)	.253
8+	124	-.618	**.012**	(-1.101 ; -.134)	
INR>5.0					
0	180	Ref.			
1-2	87	-.467	**.046**	(-.925 ; -.009)	.100
3+	87	-.663	**.006**	(-1.139 ; -.188)	
INR>6.0					
0	256	Ref.			
1	60	-.625	**.015**	(-1.128 ; -.122)	**.031**
2+	38	-.749	**.015**	(-1.350 ; -.147)	

* = For each INR cut-off the total number of participants with VKA therapy is 354 ; ** = Change in estimated glomerular filtration rate is calculated from baseline and third examination round serum creatinine, adjusted for age, sex, baseline estimated glomerular filtration rate, baseline and incident heart failure, and indication for VKA therapy; INR = International Normalized Ratio; Ref. = Referent category

2 VKA therapy was discontinued more than 3 years before date of death. One participant died due to CKD while on VKA therapy for 13 months.

DISCUSSION

Key results

In this paper, we found a significant association between the cumulative number of instances of overanticoagulation (INR>6.0) and the change in eGFR after adjustment for confounding factors. We were not able to identify an association between VKA therapy and renal failure, possibly by a relative lack of power. Strengths of our study are its

population-based design, the long-term follow-up, insensitivity to detection bias, and the gathering of data without prior knowledge of the research question.

Limitations

Results are conditional on participation in the third examination round of the Rotterdam Study. The majority of our study population did not have CKD. Therefore the studied association might be stronger and present at INRs ≤ 6.0. Participants might have died with renal failure from other causes, with renal failure not reported as a cause of death.

Interpretation

Our results are consistent with the mechanism proposed by Brodsky et al. who reported renal function decline in individuals who experienced events of overanticoagulation in two cohort studies [7,8]. We did observe an association for INRs >6.0, which is in line with the suggestion that renal tubular obstruction from bleeding might be an important step in the causal pathway, especially as the chance of bleeding increases exponentially for high INR [22]. Selection bias and information bias are unlikely. We were not able to demonstrate an effect of INRs ≤6.0 over the studied period, possibly due to a relatively small sample size, differences in study design as we studied the cumulative effect of repeated events, or because effects are transient and renal function might have recovered before re-evaluation during the third study examination round. Alternatively, previously reported effects at lower INRs might include false positive findings. Therefore, confirmation for our results should come a prospective study which is specifically designed to test these hypotheses [8].

We were not able to demonstrate an association between overanticoagulation and acute renal failure. The previously reported cases of acute renal failure following overanticoagulation support our findings, although it should be mentioned that the majority of these cases had an active glomerular disease, for which acute renal failure has been described without the use of VKA therapy [4-6, 30-33]. Therefore, it remains difficult to distinguish amongst VKA therapy as a cause, innocent bystander, or effect modifier of underlying disease such as IgA nephropathy.

Best evidence thus far comes from two animal studies showing an increase in serum creatinine with increasing INR, reversible on vitamin K administration [34-35] . The generalizability of these findings to other more common glomerulopathies in men, such as diabetic nephropathy warrants further evaluation. A study with random assignment to overanticoagulation is not ethical, however secondary analysis of data on renal function possibly available in studies that randomized between VKA therapy and other modalities

of anticoagulation (e.g. Active W study), might help to better understand the association between overanticoagulation and renal function [36].

Generalizability

In conclusion, our result are the first that support the previously reported association between events of overanticoagulation for INRs>6.0 and a decline of renal function. Our results apply to a healthy elderly Caucasian population without underlying CKD. Further studies are needed to demonstrate effects of INRs≤6.0, to identify high risk groups, and to establish its role in acute kidney injury.

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Chapter 3.2

Serum uric acid and the presence of simple renal cysts

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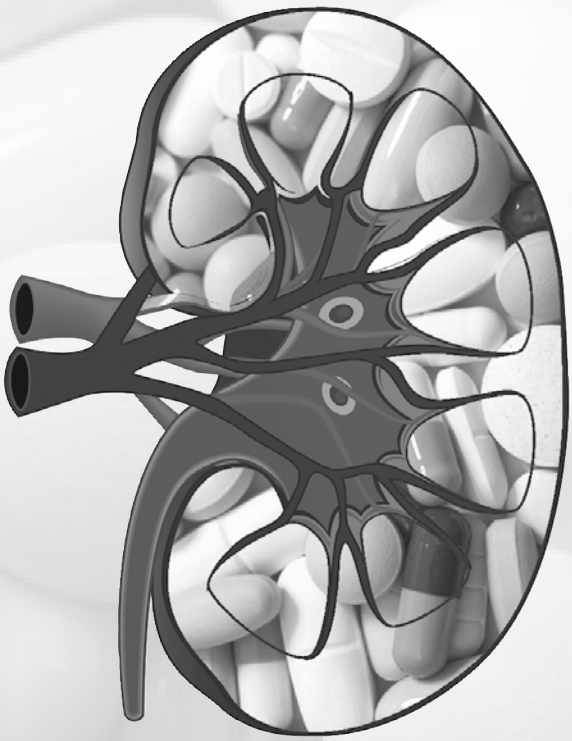


ABSTRACT

Background

A recent study suggested that simple renal cysts are more frequent in patients with gout. An increased serum uric acid is often present in patients with gout. Our objective was to study whether increased serum uric acid is associated with an increased risk of simple renal cysts and to confirm the association with gout.

Methods

We used data on 4,437 participants from the Rotterdam study, a population-based cohort study, including individuals ≥45 years, living in a suburb of Rotterdam, the Netherlands, who had their serum uric acid measured and underwent abdominal ultrasound.

Results

In females the risk of a simple renal cyst increased by 78% from the lowest to the highest serum uric acid measurement with a point estimate of 0.14 (per unit increase serum uric acid in mg/dl), p-value=0.024, 95%CI 0.02 to 0.26. In males a serum uric acid < 4.0 mg/dl was associated with a significantly lower risk of a simple renal cyst when compared to a serum uric acid ≥4.0 mg/dl: odds ratio adjusted for age, estimated glomerular filtration rate and (earlier) presence of renal stones 0.40, p-value=0.037, 95% CI 0.16 to 0.95.

Conclusions

High Serum uric acid level is associated with the presence of a simple renal cyst.

INTRODUCTION

Simple renal cysts are frequently observed in normal kidneys and account for approximately 65 to 70 percent of renal masses [1, 2]. Their prevalence depends on the imaging modality, the population studied and the prevalence is the highest in patients >50 years of age and in men [3-9].

Typically, simple renal cysts are asymptomatic although large cysts may cause renal artery and/or vein compression, massive hematuria or severe loin pain [10] and occasionally a renal cyst might become infected and require specific treatment [11]. A recent large study found cysts ≥5 mm to be associated with higher albumin excretion, hypertension, and hyperfiltration [8]. The association with hypertension has also been reported in other studies [12-16], although not in a series of >1000 patients [4]. Other studies also describe associations with an increased serum creatinine [9] and reduced estimated glomerular filtration rate (eGFR) [12, 17]. Renal abnormalities that are reported in association with simple renal cysts include increased parenchymal echogenicity [18], atrophic kidney(s) [18], renal stones [18, 19], hydronephrosis/dilatation of the pelvicalyceal system [18] and hematuria [18]

Despite the high prevalence of simple renal cysts, only a limited number of risk factors has been reported in addition to age, male gender and hypertension such as smoking [19], renal stones [18-20] and obesity [21, 22]. A recent case-control study reported a higher prevalence of simple renal cysts in patients with gout (26%) in comparison to a control group of age- and sex-matched healthy kidney donors (11%) [20]. However, as the prevalence of gout is relatively low (3 to 41 per 1,000 adults, depending on age), the population impact would be limited [23, 24]. Serum uric acid (SUA) is a well-recognized risk factor for gout [25-27]. The prevalence of asymptomatic hyperuricemia is much higher than the prevalence of gout and ranges between 130 and 210 per 1,000 adults, depending on age [24]. Consequently, any association between increased levels of SUA and renal cysts might be of clinical importance. Therefore, we investigated this association in a large prospective cohort study in a community-dwelling aged population.

SUBJECTS AND METHODS

Setting

Data were obtained from the Rotterdam Study, an ongoing prospective population-based cohort study of chronic diseases in the elderly. All inhabitants of Ommoord, a suburb of the city of Rotterdam in the Netherlands, aged 55 years or older were invited

in 1990 to participate in the study. The medical ethics committee of the Erasmus Medical Center approved the study and informed consent was obtained from all participants. The rationale and design of the study are described elsewhere [28]. The first cohort encompassed 7,983 individuals who were interviewed and examined at baseline in 1989-1993 (Rotterdam Study-1 [RS-I]). In 2000, all inhabitants of Ommoord 55 years and older at that time and not yet participating in RS-I were invited to participate in the second cohort (RS-II). This cohort encompassed 3,011 individuals who entered the study after giving written informed consent. In 2006, a further extension of the cohort (third cohort, RS-III) was initiated, in which 3,932 individuals 45 years and older were included.

Study Population

For the analysis of the association with SUA we included all participants with a SUA measurement in whom both kidneys were visualized during abdominal ultrasound. We excluded patients with gout prior to the date of SUA measurement. Gout was defined by the use of anti-gout medication (ATC code 'M04') from medication dispensing data or medication home interview. Medication dispensing data have been monitored continuously since January 1, 1991, through computerized pharmacy records of the pharmacies in the Ommoord district. The pharmacy data include ATC code, dispensing date, total number of drug units per prescription, prescribed daily number of units, and product name of the drug. During the medication home interview, in the month preceding the study center visit, participants were asked to show containers of all drugs, both prescription and over-the-counter, taken at any time during the 2 weeks preceding the interview. We only used data from participants with complete medication dispensing data, evidenced by at least one medication dispensing after the date of SUA measurement or the denial of the use of prescription medication during the medication home interview. SUA was measured during the third examination visit of first cohort (RS-I-3) between April 1997 and December 1999, the first visit of the second cohort (RS-II-1) between January 2000 and December 2001, and the first visit of the third cohort (RS-III-1) between March 2006 and January 2009. It was also measured during the baseline visit of the first cohort (RS-I-1) between November 1989 and June 1993. This measurement was only used to evaluate within subject change over time for the first cohort. SUA was expressed in milligram per deciliter (mg/dl). Strata of SUA were created according to those used by Kuo et al. [30]. SUA below 4.0 and SUA levels ≥7.0 mg/dl were combined due to a limited number of observations in these strata. Because we also wanted to assess the association with gout we also studied participants with gout newly diagnosed after SUA measurement in whom both kidneys were visualized during abdominal ultrasound.

Study outcome

The outcome of this study was the presence of a unilateral or bilateral simple renal cyst during abdominal ultrasound investigation, which was performed during the fifth examination round between January 2009 and April 2014 encompassing the fifth visit of the first cohort (RS-I-5), the third visit of the second cohort (RS-II-3), and the second visit of the third cohort (RS-III-2). All of the following 4 ultrasound criteria had to be met for the diagnosis of a simple renal cyst: (1) spherical or ovoid shape; (2) absence of internal echoes; (3) presence of a thin, smooth wall that is separate from the surrounding parenchyma; and (4) enhancement of the posterior wall, indicating ultrasound transmission through the water-filled cyst [29].

Co-variables

The following other variables measured at the date of abdominal ultrasound were studied as potential confounders or effect modifiers based on the results of prior studies: age and sex [3-9], renal stones[18-20], hypertension [8, 12-15], estimated glomerular filtration rate (eGFR) [12], smoking [19] and Body Mass Index (BMI) [21, 22]. Variables were stratified to account for possible non-linear effects and included in the final model if there was a significant association with the presence of a simple renal cyst after adjustment for age and sex. Age was included in the analyses within 5-year age strata. Ages ≥85 years were combined due to the low number of observations. The presence of renal stones was determined from self-reported medical history and abdominal ultrasound investigation. Hypertension was assumed to be present if the participants had a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥ 90 mm Hg, or received blood-pressure lowering medication at the fifth examination round. Body mass index (BMI) was included with strata as proposed by the National Institutes of Health's [30]. Underweight (<18.5 kg/m2) and normal weight (18.5–24.9 kg/m2), as well as the obesity class 2 (35–39.9 kg/m2) and extreme obesity class 3 ≥40 kg/m2 were combined due to the limited number of observations. eGFR was used, because it is already adjusted for age and sex, in contrast to serum creatinine. eGFR was estimated from serum creatinine measured during the fifth examination round with the equation of the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration [31]. Strata for eGFR were made according to the Kidney Disease Improving Global Outcomes (KDIGO) foundation 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease[32]. eGFR strata G4 severely decreased (15-29 ml/min/1.73m2) and G5 kidney failure (<15 ml/min/1.73m2) were combined due to the limited number of observations.

Statistics

We performed logistic regression to study the association between SUA and the presence of a simple renal cyst. Age and sex were included in all multivariable models to

account for confounding by age and sex. Other covariables that remained significant after adjustment for age and sex were also included in the final model. Because SUA level as well as the prevalence of a simple renal cysts are different between males and females we also performed a stratified analysis by gender. SUA was included as a continuous and a categorical determinant with strata as detailed above. We converted odds to probabilities by the following formula: probability=odds/(odds+1). For continuous determinants the odds for one unit increase is provided. P-values <0.05 were considered significant. Analyses were performed with SPSS version 20 (IBM Inc., Chicago, IL, USA).

RESULTS

SUA measurement was available for 9,939 participants during examination visits RS-I-3, RS-II-1 and RS-III-1. The medication dispensing history was complete for 9,465 (95.2%) participants at the date of SUA measurement. Of these, 117 (1.2%) participants were excluded because of use of anti-gout medication prior to the date of SUA measurement. Between February 3, 2009 and April 1, 2014, 5,195 of the remaining participants underwent abdominal ultrasound during the fifth examination round (RSI-5,RSII-3,RSIII-2) (figure 1). A total of 29 (0.6%) of participants were excluded because of a missing kidney (congenital, extirpation, donation) and an additional 729 patients were excluded as not both kidneys were visualized resulting in a total of 4,437 participants.

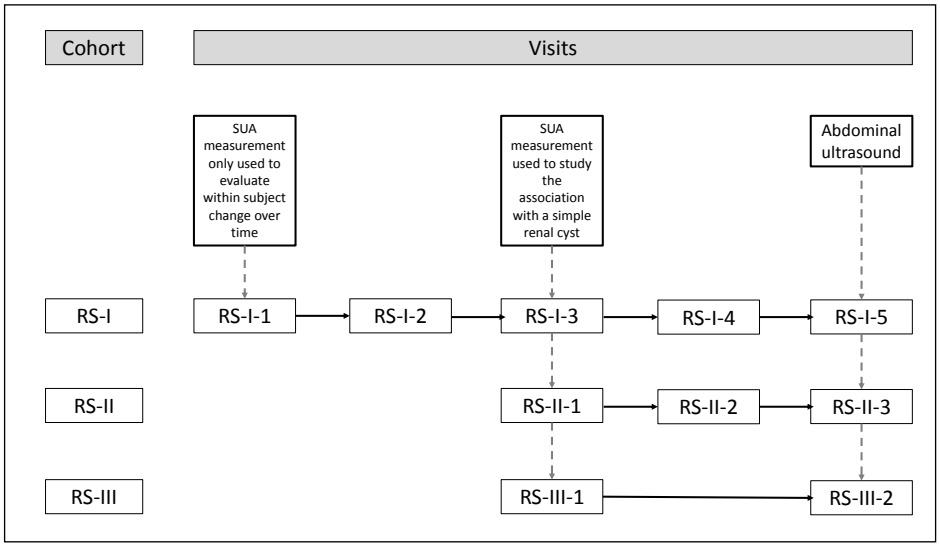


Figure 1 Study scheme

Median age of study population at abdominal ultrasound was 69 years (Interquartile Range (IQR) 63 to 76 years). A total of 1,962 (44.2%) participants were males. Detailed patient characteristics are given in table 1.

Table 1 Partipicant characteristics at the date of abdominal ultrasound

Variable		number	percentage(%)
Serum uric acid (mg/dl)	<4.0	597	(13.5)
	4.0-4.9	1,271	(28.6)
	5.0-5.9	1,347	(30.4)
	6.0-6.9	775	(17.5)
	7.0+	447	(10.1)
Renal stone	No	4,422	(99.7)
	Yes	15	(0.3)
Age at fifth examination round (years)	50-54	237	(5.3)
	55-59	545	(12.3)
	60-64	646	(14.6)
	65-69	1024	(23.1)
	70-74	792	(17.8)
	75-79	658	(14.8)
	80-84	358	(8.1)
	85+	177	(4.0)
Sex	Males	1,962	(44.2)
	Females	2,475	(55.8)
eGFR (ml/min/1.73m2)	90+	736	(16.8)
	60-89	3,045	(69.7)
	45-59	480	(11.0)
	30-44	91	(2.1)
	15-29	14	(0.3)
	0-14	4	(0.1)
	Missing eGFR	67	
Hypertension	no	1,561	(35.3)
	yes	2,857	(64.7)
	Missing hypertension status	19	
BMI (kg/m2)	<18.5	16	(0.4)
	18.5-24.9	1,242	(28.0)
	25.0-29.9	2,153	(48.5)
	30.0-34.9	795	(17.9)
	35.0-39.9	184	(4.1)
	40.0+	45	(1.0)
	Missing BMI	2	
Smoking	Never	1,399	(31.7)
	Former	2,506	(56.7)
	Current	513	(11.6)
	Missing smoking status	19	

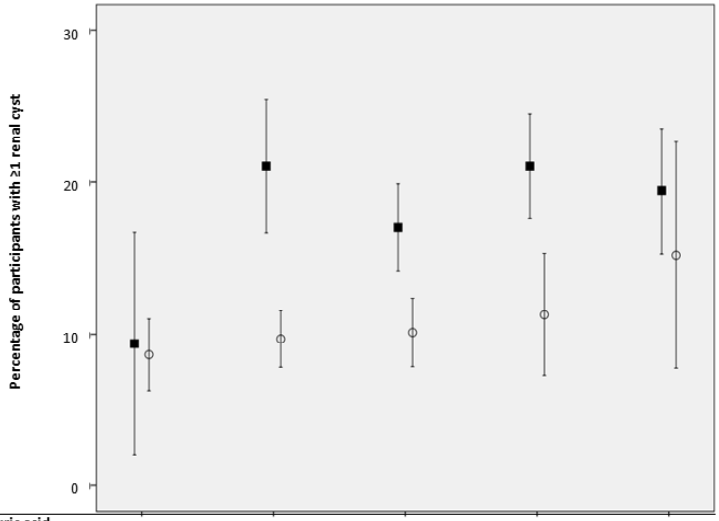
Table 2 Logistic regression analysis for the presence of a simple renal cyst

		model 1[a]			model 2[b]			model 3[c]		
Variable	**Case / Total**	**OR[d]**	**P**	**95%CI**	**OR[d]**	**P**	**95%CI**	**OR[d]**	**p**	**95%CI**
Uric acid (mg/dL)	619 / 4,437	1.20		1.13 - 1.28	1.11		1.03 - 1.20	1.09		1.01 - 1.18
Renal stone, No=ref.[d]	613 4,422									
yes	6 15	4.14		1.47 - 11.68	4.17		1.38 - 12.64	3.94		1.30 - 11.91
Age (years) 50-54=ref.[d]	17 / 237									
55-59	40 / 545	1.03		1.85 - 3.04	1.02		0.56 - 1.84	1.02		0.56 - 1.85
60-64	44 / 646	0.95		1.69 - 2.85	0.94		0.52 - 1.68	0.94		0.52 - 1.70
65-69	133 / 1,024	1.93		3.27 - 5.40	1.93		1.13 - 3.27	1.93		1.12 - 3.31
70-74	130 / 792	2.54		4.31 - 6.60	2.58		1.52 - 4.39	2.70		1.55 - 4.69
75-79	142 / 658	3.56		6.03 - 8.44	3.61		2.12 - 6.13	3.58		2.05 - 6.25
80-84	73 / 358	3.31		5.78 - 8.33	3.43		1.96 - 6.01	3.26		1.80 - 5.88
85+	40 / 177	3.78		6.93 - 8.96	4.17		2.26 - 7.69	3.71		1.93 - 7.12
Sex, male=ref.[d]	373 / 1,962									
female	246 / 2,475	0.47		0.40 - 0.56	0.45		0.38 - 0.54	0.50		0.41 - 0.61
eGFR (ml/min/1.73m^2) 90+=ref.[d]	72 / 736									
60-89	404 / 3,045	1.41		1.08 - 1.84	0.88		0.66 - 1.18	0.86		0.64 - 1.15
45-59	103 / 480	2.52		1.82 - 3.49	1.22		0.84 - 1.76	1.14		0.79 - 1.67
<45	32 / 109	3.83		2.37 - 6.19	1.66		0.98 - 2.79	1.51		0.89 - 2.57
Hypertension, no=ref.[d]	147 / 1,561									
yes	467 / 2,857	1.88		1.54 - 2.29	1.23		0.99 - 1.53			
BMI (kg/m^2), <25=ref.	154 / 1,258									
25-29	321 / 2,153	1.26		1.02 - 1.54	1.13		0.91 - 1.39			
30-34	109 / 795	1.14		0.88 - 1.48	1.12		0.85 - 1.46			
35+	34 / 229	1.25		0.84 - 1.87	1.45		0.96 - 2.19			
Smoking, no=ref.[d]	165 / 1,399									
current	64 / 513	1.37		1.13 - 1.67	1.08		0.88 - 1.33			
past	389 / 2,506	1.07		0.78 - 1.45	1.12		0.81 - 1.54			

BMI Body Mass Index, *eGFR* estimated Glomerular Filtration Rate, *OR* Odds Ratio, Ref. Reference; [a] unadjusted model; [b] model adjusted for age and sex; [c] fully adjusted model ; [d] p-values for type 3 analysis of effects

619(14.0%) participants had a simple renal cyst. In the univariate analysis, SUA as continuous variable was significantly associated with the presence of a simple renal cyst, OR 1.20, 95%CI 1.13 to 1.28, p-value<0.001(table 2 model 1). This association remained in the final model upon adjustment for age, sex, eGFR, and renal stones, OR 1.09, p-value=0.033, 95%CI 1.01 to1.18 (table 2, model 3). The association between SUA and the presence of a simple renal cyst differed between sexes: in females the prevalence of a simple renal cyst increased with SUA across the entire range, whereas in males only SUA <4.0 mg/dl was associated with a lower prevalence of a simple renal cyst (figure 2).

In analyses stratified for sex (data not shown), SUA as a continuous variable was significantly associated with the presence of a simple renal cyst in females, OR adjusted for age 1.15, 95%CI 1.02 to 1.29, p-value=0.024. Adjustment for eGFR and renal stones was not indicated, because these were not significantly associated with a simple renal cyst in females after adjustment for age. In females the range in SUA is 9.2 mg/dl, from 1.9 mg/dl to 11.1 mg/dl. Across this range the risk of a simple renal cyst increased by 78%:



Serum uric acid (mg/dl)	<4.0	4.0-4.9	5.0-5.9	6.0-6.9	7.0+
males: number of participants with ≥1 renal cyst	6	70	115	113	69
males: number of participants	64	332	675	536	355
females: number of participants with ≥1 renal cyst	46	91	68	27	14
females: number of participants	533	939	672	239	92

Figure 2 Association between presence of a renal cyst and serum uric acid

exp(9.2*(ln(1.15))/(1+ exp(9.2*(ln(1.15))). In males SUA as a continuous variable was not significantly associated with the presence of a simple renal cyst (OR adjusted for age, eGFR and renal stones 1.06, 95%CI 0.96-1.18). However, in males a SUA <4.0 mg/dl was associated with a significantly lower risk of a simple renal cyst compared to a SUA ≥ 4.0 mg/dl (OR adjusted for age and eGFR and renal stones 0.40, 95%CI 0.16-0.95).

For 673 participants of RS-I SUA was also measured during the first examination visit (RS-I-1), a median 6.4 years (Interquartile range 6.3 to 6.5 years) before RS-I-3 (figure 3). The median within subject change in SUA per 10 years was -0.11 mg/dl (IQR -0.86 to 0.62 mg/dl).

If participants who used anti-gout medication prior to SUA measurement were not excluded, a total of 4,007 participants who underwent abdominal ultrasound also had a complete medication history until the fifth examination round or used anti-gout medication. In males the prevalence of a simple renal cyst was similar in those who used anti-gout medication [23 out of 93 (24.7%)] to those who did not [326 out of 1,676 (19.5%)]. In females, the prevalence of a simple renal cyst was higher in those who used anti-gout medication [8 out of 37 (21.6%)] compared to those who did not [221 out of 2,219 (10.0%). In females this association remained significant after adjustment for age, OR adjusted for age 2.29, 95%CI 1.02 to 5.15, p-value=0.046 (data not shown).

DISCUSSION

In this study, we found an association between increased SUA and risk of renal cysts in females. In males only a SUA <4.0 mg/dl was associated with a significantly lower risk of a simple renal cyst compared to a SUA ≥ 4.0 mg/dl. A recent study that reported a significant association between gout and simple renal cysts was conducted in a predominantly (>85%) male study population [20]. Although for renal cysts we found only a limited association with SUA in males and no association with gout in males, the results of this study might be consistent with our results in relation to SUA. In the former study, the control group consisted of healthy kidney donors only. Although no information on SUA levels in controls was provided, these are generally low (<4.0 mg/dl) in healthy kidney donors [33].

Various (combinations of) pathophysiological mechanisms might underlie the association between gout or SUA and simple renal cysts. First, the signal transducer and activator of transcription 3 (STAT3) which is important for renal cyst growth is strongly expressed in kidneys of simple renal cyst patients and barely in normal kidneys [34].

STAT3 is activated by phosphorylation by hyperuricemia [35, 36] and monosodium urate (MSU) crystals [37], and also STAT3 binding activity is strongly increased by monosodium urate crystals [38]. Indirectly, SUA is related to STAT3 through Interleukin (IL)-6 [39, 40], Il-18 [41, 42], tumor necrosis factor-α [39, 43], and leptin [44, 45]. It is possible that in males androgen receptor activation of signal transducer and activator of transcription 3 (STAT3) is more important than the actual SUA level with SUA ≥4.0 mg/dl [34] explaining why we did not observe the association between increase of SUA and renal cysts in males. Second, because simple renal cysts are associated with renal stones [18, 19], cyst formation might result from mechanical obstruction by renal stones in the kidney. Nephrolithiasis is common in gout: nephrolithiasis (diagnosed by helical CT) was found in 34% of male patients with gout and 68% of the patients with nephrolithiasis did not suffer from symptoms compatible with nephrolithiasis [46]. This might also play a role in hyperuricemia because patients with hyperuricemia have an increased risk of nephrolithiasis via uric acid precipitation in the urine because of low pH

Strengths of our study are its population-based design, the large study population and the ability to adjust for previously reported risk factors. A limitation to this study is a possible degree of misclassification of gout in participants who were exclusively treated with non-steroidal anti-inflammatory drugs (NSAIDs), but not with anti-gout medication. In our study SUA and the presence of simple renal cysts were determined by a single measurement. We showed that variation in SUA within participants is limited over time. Therefore we consider that the use of one single SUA measurement, determined during a preceding study center visit, is justified, although repeated abdominal ultrasound and measurements of SUA would allow a more precise analysis on causality. Finally, we might have missed small and asymptomatic renal stones during abdominal ultrasound investigation, because ultrasound sensitivity to detect renal stones is low.

In conclusion, our results showed an association between increasing values of SUA and the presence of a simple renal cyst. Consistent with previous studies we also found an association between a reduced eGFR and higher prevalence of a simple renal cyst[12]. Currently one trial including 113 patients with chronic kidney disease shows that treatment with allopurinol slows the decline in eGFR[47]. As many more small cysts may have been below the limit of detection[48], we seems possible that SUA might contribute at least in part to the progression of renal function decline through renal cyst formation.

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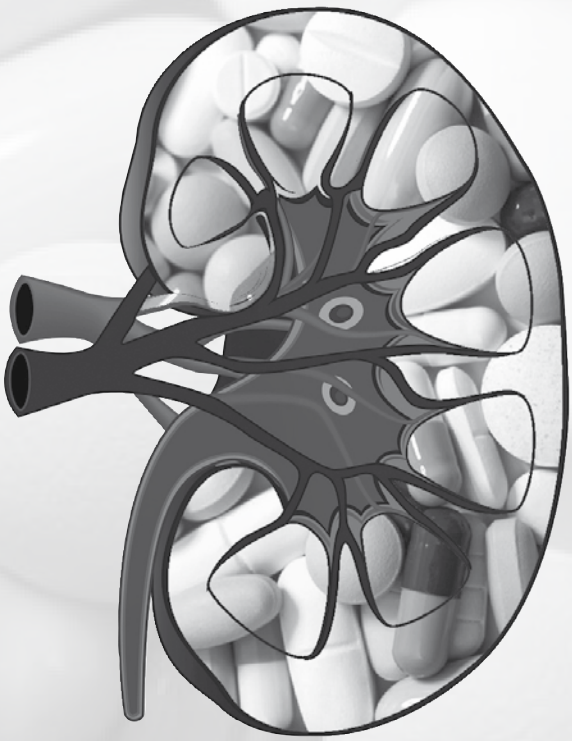
Chapter 4

Drug use and water and electrolyte balance



Chapter 4.1

Risk of hyponatremia with diuretics: chlorthalidone versus hydrochlorothiazide

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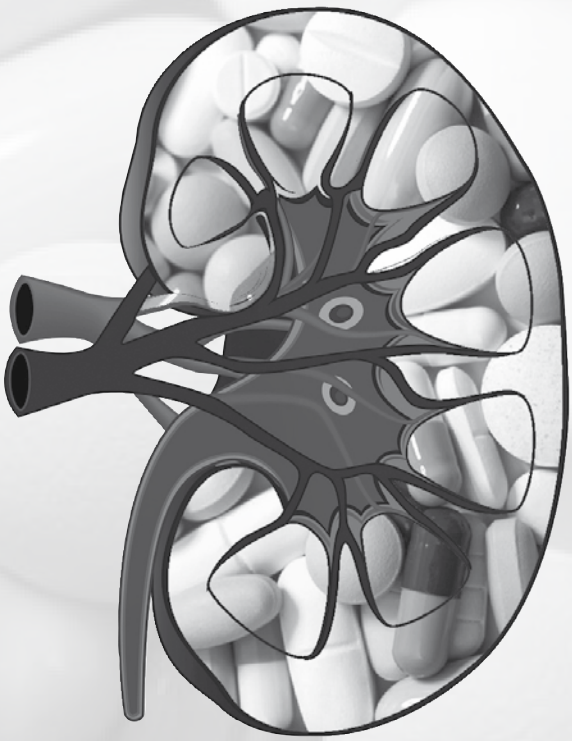
Risk of hyponatremia with diuretics: chlorthalidone versus hydrochlorothiazide.
Am J Med. 2014 Aug;127(8):763-71.



ABSTRACT

Background

Chlorthalidone and hydrochlorothiazide are often considered as interchangeable. However, greater (nighttime) blood pressure reduction, and alleged pleiotropic effects have renewed the interest in chlorthalidone. A recent study showed an increased risk of adverse events with chlorthalidone, including hyponatremia.

Methods

To investigate differences in risk of hyponatremia between chlorthalidone and hydrochlorothiazide, adjusted for daily dose, we conducted a population-based case–control study within the Dutch IPCI (Integrated Primary Care Information) database. The study population included all subjects ≥18 years, without diabetes mellitus, heart failure, liver failure and malignancy, who were registered in the IPCI database from 1996 to 2011. Cases were subjects with a serum sodium <130 millimole per liter or hospitalization due to hyponatremia. Controls were matched on practice, age within 5 years, sex and date of onset.

Results

A total of 1,033 cases of hyponatremia were identified. Hyponatremia was more common with chlorthalidone than with hydrochlorothiazide at equal dose per day: adjusted odds ratio was 2.09 (95%CI 1.13 to 3.88) for 12.5 milligram per day and 1.72 (95%CI 1.15 to 2.57) for 25 milligram per day. Risks were not significantly increased with chlorthalidone compared to twice the dose per day of hydrochlorothiazide.

Conclusions

This is the first study that shows an increased risk of hyponatremia with chlorthalidone relative to hydrochlorothiazide at equal milligram-to-milligram dose per day. The need for a lower dose of chlorthalidone than hydrochlorothiazide to achieve similar blood pressure reduction likely compensates for the increased risk of hyponatremia at equal dose.

INTRODUCTION

Background

A review from 2004 states that the diuretics chlorthalidone (CTDN) and hydrochlorothiazide (HCTZ) are often considered as interchangeable, despite differences in cardiovascular outcomes, pharmacokinetics and pharmacodynamics, as well as in pleiotropic effects [1]. This impression might be strengthened by an identical World Health Organization (WHO) defined daily dose of 25 milligram per day (mg/d). Also in the Netherlands recommended initial dose is identical, being 12.5mg/d, whereas the recently published Joint National Committee 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults suggests to start treatment with CTDN 12.5 mg/d or HCTZ 12.5-25 mg/d[2] . Since the review of 2004, two meta-analyses [3, 4] and two randomized clinical studies [5, 6] showed greater blood pressure reduction with CTDN than HCTZ, in particular for the nighttime mean systolic blood pressure, which contributed to the renewed interest in CTDN [7].

In absence of direct head-to-head studies with clinical endpoints, a debate is ongoing whether CTDN should be preferred over HCTZ, because it appears to be more effective in the prevention of cardiovascular events [8, 9] and whether this is due to a difference in blood pressure reduction and/or pleiotropic effects [10].

Also the relative difference in the incidence of adverse events, in particular hypokalemia and hyponatremia, is a topic of debate [4, 11]. These events are not without consequences, as hypokalemia might result in rhabdomyolysis and cardiac arrhythmia [12-14], whereas acute kidney injury is common in association with hyponatremia [15].

A recent propensity score–matched observational cohort study showed that subjects treated with CTDN were 1.7 times more likely to be hospitalized with hyponatremia than those prescribed HCTZ (all dosing regimens within each treatment combined) [11].

Objective

The objective of this study was to investigate the risk of hyponatremia between CTDN and HCTZ, comparing the risk with both treatments at equal milligram-to-milligram dose per day and CTDN with twice the dose of HCTZ per day, using prospectively gathered electronic health care records from a community-dwelling adult population.

METHODS

Design overview

We performed a population-based case–control study, nested in a cohort of patients who were registered in the Dutch Integrated Primary Care Information (IPCI) general practice

research database, to investigate the risk of hyponatremia with CTDN and HCTZ. The Scientific and Ethical Advisory Board of IPCI project approved the study (study protocol N. 02/13).

Setting

All data were retrieved from the IPCI project, a longitudinal observational, dynamic database which contains the electronic medical records of a group of more than 600 general practitioners in the Netherlands. In the Dutch health care system, the general practitioner plays a pivotal role and acts as a gatekeeper of medical care and information. Almost all inhabitants of the Netherlands are registered with a general practitioner, independently of their health status. Details of the IPCI database have been described elsewhere[16, 17]. Briefly, the database contains the complete electronic medical records of approximately 1,000,000 participants. These records contain anonymous longitudinal data on demographics, symptoms and diagnoses (coded and in free text), referrals, laboratory findings, hospitalizations, discharge letters, and drug prescriptions (inclusive indication and dosage regimen). To maximize completeness of the data, general practitioners participating in the IPCI project are not allowed to maintain a system of paper-based records besides the electronic medical records. The system complies with European Union guidelines on the use of data for medical research and has been proven valid for pharmaco-epidemiologic studies [17].

Study population

The study population comprised all subjects from the IPCI database who were ≥18 years during the study period (January 1st, 1996 to March 1st, 2011) and had ≥1 year of data registered in the database before the study period. Subjects were censored from the first date indicating malignancy, except for squamous and basal cell carcinoma of the skin, because certain malignancies are known to cause hyponatremia and also chemotherapy has been associated with hyponatremia [18]. Subjects with heart failure and/or liver failure might also receive specialist treatment, including diuretics, that is not completely captured in the database. Therefore, they were censored from the first calendar date indicating such conditions. Finally, also subjects with diabetes mellitus were excluded, because hyperglycemia might cause hyponatremia. All remaining subjects were followed until, hyponatremia, death, transfer out of practice, last data draw-down, or end of the study period, whichever came first.

Cases and controls

Cases were all subjects who were first diagnosed with a serum sodium level <130 mmol/l and/or subjects who were hospitalized with a specialist diagnosis of hyponatremia at admission. All cases were validated through manual review of the electronic medical

record while blinded to the exposure. All available controls were selected by incidence density sampling [19] and matched to each case on practice, sex and age within a range of 5 years.

Exposure definition

Exposure to CTDN and HCTZ - and other medications mentioned below that might confound the association of interest - was obtained from the prescription files. Fixed dose combinations were recoded into their individual active pharmaceutical ingredients. The duration of treatment was calculated by dividing the prescribed number of units by the dosing regimen. The dose per day was obtained from the last prescription prior to the index date and calculated from the prescribed strength and the dosing regimen.

Co-variables

We considered the following co-variables: practice, age, sex, and date of onset (matching variables), and medical conditions, based on their ICPC diagnosis code, during the analyses: Addison's disease [20], alcoholism [21], cerebrovascular disease (transient ischemic attack, stroke)[22] , diabetes insipidus [23], hypothyroidism [24], ischemic heart disease (angina pectoris and myocardial infarction) [25], Parkinson's disease [26] and pulmonary obstructive disease (asthma and chronic obstructive pulmonary disease)[27] .

We assessed potential confounding by other medications that have been reported to cause hyponatremia, based on a literature review [18, 28, 29] at 5th level (chemical substance), at 4th level (chemical subgroup), or at 3rd level (pharmacological subgroup) of the anatomical therapeutical chemical (ATC) coding system [30]: proton pump inhibitors (PPI) (plain and in combinations for eradication of Helicobacter Pylori), amiodarone, lorcainide, propafenone, diuretics, agents acting on the renin-angiotensin system, bromocriptine, vasopressin and analogues, thyroid preparations, mineralocorticoids, trimethoprim-sulfamethoxazole, ciprofloxacin, cefoperazone, sulbactam, rifabutin, azithromycin, carboxamide derivatives, valproic acid, lamotrigine, anti-parkinson drugs, opioids, non-steroidal anti-inflammatory drugs (NSAIDS), phenothiazines, butyrophenone derivatives, anxiolytics combined with barbiturates (plain and in combination), anti-depressants, and theophylline. If a chemical or pharmacological subgroup, but none of its chemical substances, indicated possible confounding, we included all medications of the subgroup in the adjusted analysis (but at 3rd level). Also here fixed dose combinations were coded into their individual active pharmaceutical ingredients.

Statistical Analysis

We compared characteristics of cases and controls by using conditional logistic regression analysis. Current exposure to CTDN or HCTZ was included in the first model as a

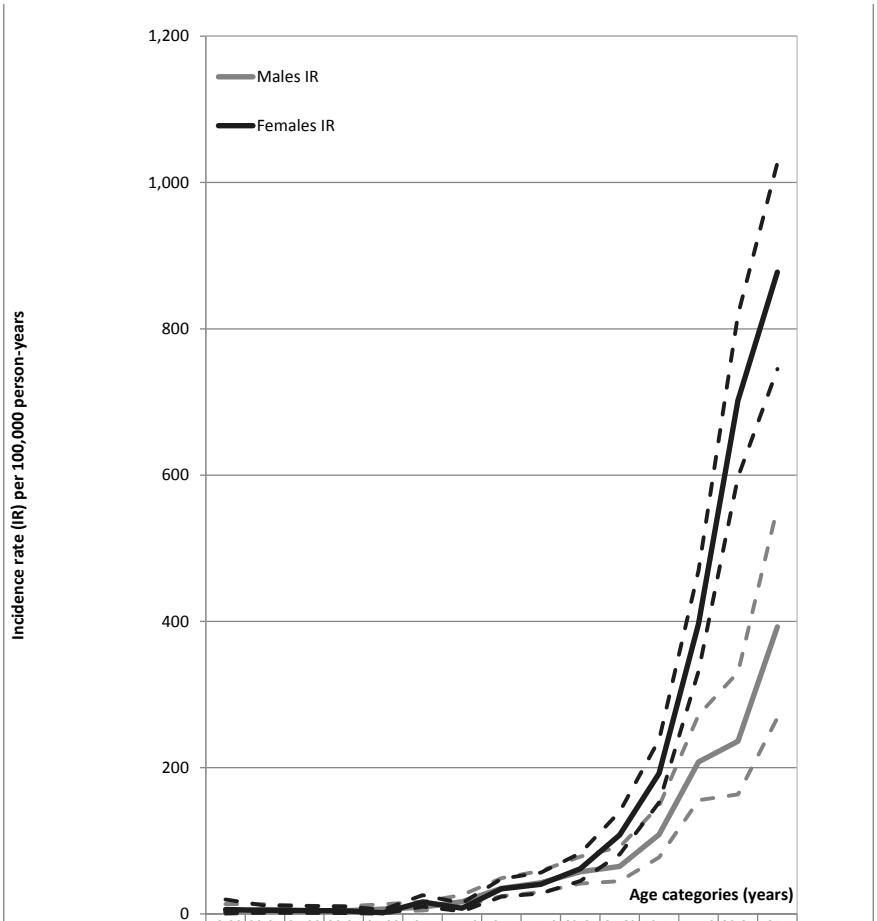
single categorical variable, including: no use, CTDN only, HCTZ only and overlapping prescriptions (most likely indicating a recent switch). In the subsequent models, we replaced use of CTDN only and HCTZ only with their respective dosage per day, being: <12.5mg/d, 12.5mg/d, >12.5mg and <25mg/d, 25mg/d, >25mg/d and <50mg d, 50mg/d and >50mg/d. We compared CTDN to HCTZ in a milligram-to-milligram dose per day, because of their reported interchangeability and with twice the amount dose per day of HCTZ, because these dosages are often compared during clinical studies. As not all conditions and medications known to cause hyponatremia might confound the association between CTDN or HCTZ and hyponatremia to a relevant extent, we included only those co-variables that changed the odds ratio between CTDN and HCTZ by 5% or more, in order to avoid an unnecessary loss of statistical power. We conducted all conditional logistic regression analyses with SAS 9.2, (SAS Institute Inc., Cary, NC, USA). We set the level of significance for all statistical tests at a P-value less than 0.05. We discarded comparisons that included cells with less than 5 subjects. For the incidence figure we used data on all subjects included in the study population. The incidence rate was determined by dividing the number of cases by the total number of person-years of follow-up by the study population. Subjects were censored on the first date of hyponatremia. Incidence rates were calculated per 100,000 person-years. Ninety-five percent confidence (95%CI) intervals were calculated based on a Poisson distribution [31].

RESULTS

The study population comprised 738,016 subjects with a total of 1.96 million person-years of observation. The study population included 17,631 subjects who received one or more prescriptions of CTDN, contributing to a combined exposure of 6,710 person-years and 57,696 subjects who received one or more prescriptions of HCTZ, with a combined exposure of 151,389 person-years. A total of 1,033 subjects developed hyponatremia. The incidence increased from approximately 5 per 100,000 person-years below 40 years of age to 730 per 100,000 person-years in subjects aged 85 and above (figure 1). Females were more likely to develop hyponatremia - 706 (68%) of cases were female subjects, with the highest risk relative to males between 80-84 years of age [incidence rate ratio of 3.0 (95%CI 2.0-4.4)].

The characteristics of cases and controls are provided in table 1. A total of 46 cases were current users of CTDN and 308 cases were current users of HCTZ, details on the dose per day are provided in table 2.

If current use of CTDN or HCTZ (all dose per day of current use combined) was compared to no use of either medication, only current use of an angiotensin receptor blocker (ARB) led to a ≥5% change in estimate and was therefore added as confounder



	18-20	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males IR	3	6	5	4	7	9	17	35	43	58	65	109	208	236	393
Males IR 95%CI LL	0	2	2	1	3	5	10	24	30	42	45	78	155	164	268
Males IR 95%CI UL	14	13	11	11	13	17	26	49	59	78	92	148	272	331	556
Females IR	6	5	5	4	2	17	8	34	41	62	108	192	397	702	877
Females IR 95%CI LL	1	2	2	1	0	10	4	24	28	45	82	153	332	598	745
Females IR 95%CI UL	20	12	11	10	6	26	15	48	57	83	140	239	470	820	1027
IR ratio	2.1	0.8	1.0	1.0	0.3	1.8	0.5	1.0	1.0	1.1	1.7	1.8	1.9	3.0	2.2
IR ratio 95%CI LL	0.2	0.2	0.2	0.2	0.1	0.8	0.2	0.6	0.6	0.7	1.1	1.2	1.4	2.0	1.5
IR ratio 95CI UL	23.1	3.0	3.9	3.9	1.4	3.9	1.1	1.6	1.6	1.7	2.6	2.6	2.7	4.4	3.3
Males cases	1	5	4	4	7	10	17	32	33	38	30	37	49	31	29
Females cases	2	4	4	4	2	18	8	31	31	41	53	77	128	154	149
Males Persontime (x 1000)	34	82	85	90	103	107	102	91	78	66	46	34	24	13	7
Females persontime (x 1000)	32	82	87	91	105	108	102	90	76	66	49	40	32	22	17

Figure 1: Age-specific incidence rate of hyponatremia per 100,000 person-years stratified by sex.
IR = Incidence Rate; 95%CI = 95% Confidence Interval; LL = Lower Limit; UL = Upper Limit

Table 1 Characteristics of cases and controls

Variable	Cases (n=1,033)	Controls (n= 130,814)
Age† (years: median; IQR)	76 (63-83)	62 (51-75)
Age † (years: n(%)		
- 18-40	37 (4)	13,596 (10)
- 40-60	180 (17)	42,859 (33)
- 60-80	453 (44)	57,609 (44)
- 80+	363 (35)	16,750 (13)
Sex† n(%)		
- Male	327 (32)	49,303 (38)
- Female	706 (68)	81,511 (62)
Medical history present n(%)		
- Cerebrovascular disease	141 (14)	5,632 (4)
- Ischemic Heart disease	221 (21)	12,882 (10)
- Obstructive respiratory disease	167 (16)	12,815 (10)
- Hypothyroidism	80 (8)	5,540 (4)
- Parkinson's disease	17 (2)	687 (1)
- Alcohol abuse	51 (5)	1,550 (1)
- Addison's disease	5 (<1)	30 (<1)
- Diabetes insipidus	15 (1)	184 (<1)
Medication use		
- Hydrochlorothiazide	308 (30)	12,179 (9)
- Chlorthalidone	46 (4)	1,254 (1)
Other diuretics		
- Aldosterone antagonists	22 (2)	282 (<1)
- Amiloride	26 (3)	651 (<1)
- Epitizide	19 (2)	577 (<1)
- Loop diuretics	45 (4)	1,709 (1)
- Triamterene	46 (4)	1,784 (1)
- Chlorothiazide	0 (<1)	2 (<1)
- Mefruside	0 (<1)	3 (<1)
- Indapamide	1 (<1)	1 (<1)
Agents acting on the renin-angiotensin system		
- Angiotensin converting enzyme inhibitors	154 (15)	9,020 (7)
- Angiotensin receptor blockers	194 (19)	8,098 (6)
Other medications		
- Proton pump inhibitors	154 (15)	7,862 (6)
- Propafenone	0 (<1)	25 (<1)
- Amiodarone	1 (<1)	116 (<1)

Table 1 Characteristics of cases and controls (continued)

	Cases	Controls
Variable	**(n=1,033)**	**(n= 130,814)**
- Bromocriptine	0 (<1)	7 (<1)
- Vasopressin and analogues	3 (<1)	20 (<1)
- Mineralocorticoids	2 (<1)	8 (<1)
- Thyroid preparations	26 (3)	2,192 (2)
- Trimethoprim-sulfamethoxazole	11 (1)	71 (<1)
- Ciprofloxacin	7 (1)	76 (<1)
- Azithromycin	2 (<1)	68 (<1)
- Non-steroidal anti-inflammatory drugs	61 (6)	4,151 (3)
- Opioids	44 (4)	1,307 (1)
- Carboxamide derivatives	22 (2)	171 (<1)
- Valproic acid	8 (1)	147 (<1)
- Lamotrigine	3 (<1)	26 (<1)
- Anti-parkinson drugs	10 (1)	382 (<1)
- Phenothiazines	1 (<1)	41 (<1)
- Butyrophenone derivatives	13 (1)	187 (<1)
- Anxiolytics and barbiturates	169 (16)	6,524 (5)
- Tricyclic antidepressants	10 (1)	914 (1)
- Selective serotonin re-uptake inhibitors	36 (3)	2,282 (2)
- Monoamine Oxidase Inhibitors (selective and non-selective)	1 (<1)	10 (<1)
- Theophylline	1 (<1)	53 (<1)

†Age and sex differ between cases and controls because of incidence density sampling where all potential controls were selected matched on age and gender. Because of the population demographics, the number of controls per case varies. This difference was accounted for via the conditional logistic regression

Table 2 Use of chlorthalidone and hydrochlorothiazide

	Cases (n=1,033)		Controls (n= 130,814)	
	nr	**%**	**nr**	**%**
No use	681	(66)	117,401	(90)
Use of hydrochlorothiazide:				
- dose unknown	5	(<1)	143	(<1)
- <12.5mg/day	3	(<1)	91	(<1)
- 12.5mg/day	140	(14)	6,535	(5)
- >12.5mg/day and <25mg/day	0	(<1)	18	(<1)
- 25mg/day	130	(13)	4,770	(4)
- >25mg/day and <50mg/day	0	(<1)	2	(<1)
- 50mg/day	28	(3)	594	(<1)

Table 2 Use of chlorthalidone and hydrochlorothiazide (continued)

	Cases (n=1,033)		Controls (n= 130,814)	
	nr	%	nr	%
- >50mg/day	0	(<1)	6	(<1)
Use of chlorthalidone				
- <12.5mg/day	1	(<1)	9	(<1)
- 12.5mg/day	11	(1)	291	(<1)
- 25mg/day	31	(3)	877	(1)
- >25mg/day and <50mg/day	0	(<1)	5	(<1)
- 50mg/day	1	(<1)	52	(<1)
Combined use	2	(<1)	20	(<1)

Table 3 Association between the current use of hydrochlorothiazide or chlorthalidone and hyponatremia

			unadjusted model			adjusted model†		
Current use (mg per day) (Ref. = no use)		**Cases/controls**	**Odds ratio**	**p-value**	**95%CI**	**Odds ratio**	**p-value**	**95%CI**
Hydrochlorothiazide	12.5	140/6,535	3.64	<0.001	3.03 - 4.36	2.61	<0.001	2.13 - 3.20
	25	130/4,770	4.60	<0.001	3.81 - 5.55	3.27	<0.001	2.64 - 4.06
	50	28/594	7.81	<0.001	5.35 - 11.39	6.56	<0.001	4.49 - 9.60
Chlorthalidone	12.5	11/291	6.32	<0.001	3.48 - 11.46	5.46	<0.001	3.01 - 9.92
	25	31/877	5.92	<0.001	4.13 - 8.48	5.62	<0.001	3.92 - 8.06

†model adjusted for current use of angiotensin receptor blockers proton pump inhibitors, carboxamide derivatives and triamterene

Table 4 Risk of hyponatremia compared between current use of hydrochlorothiazide or chlorthalidone

	unadjusted model			adjusted model†		
Current use (mg per day)‡	**Odds ratio**	**p-value**	**95%CI**	**Odds ratio**	**p-value**	**95%CI**
Chlorthalidone 12.5 vs. hydrochlorothiazide 12.5	1.74	0.078	0.94 - 3.21	2.09	0.019	1.13 - 3.88
Chlorthalidone 12.5 vs. hydrochlorothiazide 25.0	1.37	0.313	0.74 - 2.54	1.66	0.110	0.90 - 3.11
Chlorthalidone 25.0 vs. hydrochlorothiazide 25.0	1.29	0.207	0.87 - 1.90	1.72	0.009	1.15 - 2.57
Chlorthalidone 25.0 vs. hydrochlorothiazide 50.0	0.76	0.289	0.45 - 1.26	0.86	0.551	0.51 - 1.43

†model adjusted for current use of angiotensin receptor blockers, proton pump inhibitors, carboxamide derivatives and triamterene; ‡last-referred medication acts as reference

to the final model. Current use of CTDN, adjusted odds ratio (ORadj) 5.62 (95%CI 4.14 to 7.63) or HCTZ, ORadj 5.46 (95%CI 2.97 to 4.04) significantly increased the risk of hyponatremia compared to no use. The risk was 62% higher with current use of CTDN, ORadj 1.62 (95%CI 1.18 to 2.23), compared to current use of HCTZ (data not shown).

With all studied doses per day, current use of CTDN or HCTZ significantly increased the risk of hyponatremia in comparison to no use. The risk was lowest for HCTZ 12.5 mg/d ORadj 2.61 (95%CI 2.13 to 3.20) (table 3).

In the adjusted model, the risk of hyponatremia attributed to CTDN 12.5 mg/day was significantly higher at equivalent milligram dose per day in comparison to HCTZ 12.5 mg/d: ORadj: 2.09 (95%CI 1.13 to 3.88). This also applied to the comparison between CTDN 25 mg/d and HCTZ 25 mg/d, where CTDN was associated with a higher risk of hyponatremia (ORadj 1.72 (95%CI 1.15 to 2.57), (tables 3 and 4). However, there was no significantly increased risk when CTDN and HCTZ were compared at approximately equipotent dose per day (CTDN compared with twice the amount the dose of HCTZ per day), which showed an adjusted OR for CTDN 12.5 mg/d compared to HCTZ 25 mg/d of 1.66 (95%CI 0.89 to 3.11) and adjusted OR for CTDN 25 mg/d compared to HCTZ 50 mg/d of 0.85 (95%CI 0.51 to 1.42).

DISCUSSION

We found an increased risk of hyponatremia compared to no use with CTDN and HCTZ for all studied doses per day, with the lowest risk increase for HCTZ 12.5 mg/d, To our knowledge this is the first study that shows that hyponatremia is more common with CTDN than HCTZ in equal dose. However, we did not find a significantly increased risk of hyponatremia with CTDN compared to twice the dose of HCTZ per day (CTDN 12.5mg/d versus HCTZ 25 mg/d and CTDN 25mg/d versus HCTZ 50mg/d), despite decent exposure to both CTDN and HCTZ. Although dose recommendations for initiation of therapy for hypertension with CTDN or HCTZ in prescribing information and clinical guidelines are identical [32], it is evident that these medications are not equipotent on a milligram-to-milligram basis. The majority of clinical studies report a similar drop in (daytime) blood pressure for CTDN compared to twice the amount of HCTZ [5, 6, 33-35], and during a titrate-to-target blood pressure trial, significantly more patients in the HCTZ arm required up-titration to meet the target goal compared to those treated with CTDN [36]. Therefore, the need for a lower dose of CTDN relative to HCTZ to achieve similar reduction in blood pressure and cardiovascular outcomes might also reduce the risk of hyponatremia that exists at equal milligram-to-milligram dose. We consider that the increased risk of hospitalization with hyponatremia in subjects on CTDN relative

to subjects on HCTZ (all dosing regimens within each treatment combined) observed by Dhalla et al. [11] might result from an imbalance in the equipotent dose per day between CTDN and HCTZ at baseline, as there was little evidence for an increased risk of hyponatremia with CTDN relative to twice the dose of HCTZ per day similar to the results of the current study.

From a physiological perspective, two properties of CTDN might increase the risk of hyponatremia relative to HCTZ. First, in contrast to HCTZ [37-40], CTDN activates the sympathetic nervous system, independently of blood pressure [41], which increases arginine vasopressin (AVP) plasma levels [42, 43]. Second, CTDN' s half-life (35-67 hours) [44] is longer than that of HCTZ (7-11 hours) [45, 46], which might put subjects at increased risk when a medical condition disturbs sodium and water balance.

In our study, the majority of concomitant medications and conditions did not confound the estimate of CTDN relative to HCTZ, which is possible as a similar degree of confounding would not influence the relative effect, whereas exposure to other confounders might be rare and hence not result in a relevant degree of confounding. Unexpectedly, the risk of hyponatremia with CTDN relative to HCTZ was influenced by ARBs, but not by angiotensin-converting-enzyme inhibitors, whereas others found a similar risk of hyponatremia [47]. We consider confounding by indication unlikely as the indication is similar. Although unmeasured confounding [48] cannot be excluded also actual differences might underlie. ARBs suppress aldosterone more effectively[49] and selectively block the angiotensin II subtype 1 receptor that increases sodium reabsorption[50], but not the angiotensin II subtype 2 receptor that promotes sodium excretion[51],[52-55] [56]Also angiotensin II levels are higher with long-term ARB treatment[49] and if HCTZ is used concomitantly, the angiotensin II induced sodium reabsorption via the sodium chloride symporter is abolished [57], which might also apply to CTDN that targets the same renal sodium transporter.

Strengths of our study include its population-based design, representing the population receiving treatment with CTDN and/or HCTZ on a day-to-day basis, the application of strict exclusion criteria, as well as the critical appraisal of, and the adjustment for a large number of important confounders, including medical conditions and concomitant medications. Limitations include the relatively low number of cases that used CTDN and the fact that our data do not allow adjustment for all previously reported risk factors, such as weight [58] and renal function [59], although there is no a-priori reason to believe that these would differ between subjects using CTDN and HCTZ. Finally, medication exposure was based on prescriptions and not on actual intake but as both drugs are chronically used, the mostly timely refills make it likely that the drugs were actually taken.

PERSPECTIVES

Our results indicate that the risk of hyponatremia in users of CTDN is higher than in users of HCTZ when used at the same - but not equipotent - dose of 12.5 or 25 mg/day. We did not find an increased risk of hyponatremia with CTDN compared to twice the dose of HCTZ per day, which is needed to achieve similar reduction in blood pressure. Recent network meta-analyses suggest that CTDN is superior to HCTZ in preventing cardiovascular events, which cannot be attributed entirely to the lesser effect of HCTZ on office systolic blood pressure [8]. Based on our results we conclude that this benefit is not offset by an increased risk of hyponatremia, hence results remain in favor for CTDN. Evaluation of the benefits of CTDN relative to HCTZ should be continued with consideration of the risk of hyponatremia, during future head-to-head clinical studies and antihypertensive treatment selection for the individual patient.

ACKNOWLEDGEMENTS

We thank Marcel de Wilde, Kris Sieradzan and Mees Mosseveld for the collection of data and maintenance of the IPCI database.

SOURCES OF FUNDING

None

CONFLICTS OF INTEREST

None

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Chapter 4.2

Antidepressants and the risk for hyponatremia

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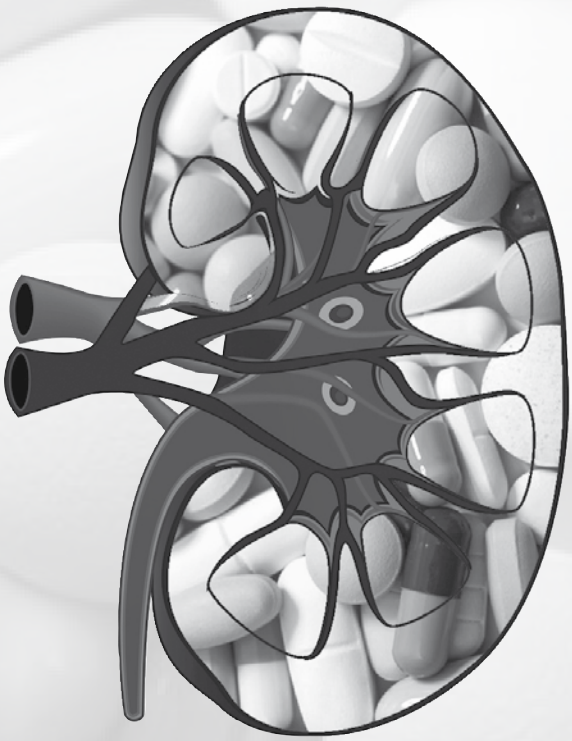
Antidepressants and the risk for hyponatremia: A population-based study in
Dutch electronic healthcare records



ABSTRACT

Background

Drug-induced hyponatremia is a common adverse drug reaction in the elderly. Of the antidepressant drugs, only Selective Serotonin Reuptake Inhibitors (SSRIs) have consistently been associated with hyponatremia. Our objective was to investigate the association between antidepressants and hyponatremia within a large database of community-dwelling adults.

Methods

Design: Matched case-control study. Setting: Data from the Dutch Integrated Primary Care Information database. Participants: We included subjects aged ≥18 years during the period 1996-2011. Cases had a serum sodium level ≤130 mmol/l or were hospitalized due to hyponatremia. Up to 10 controls were matched on practice, year of birth, sex and date of onset. Measurements: Exposure to antidepressants was derived from prescription records and categorized as Tricyclic antidepressants (TCAs), SSRIs or other. Conditional logistic regression was used to estimate odds ratios.

Results

In total, 2,312 cases of hyponatremia were identified and matched to 18,295 controls. Current use of antidepressants increased the risk for hyponatremia relative to non-use: SSRIs (odds ratio (OR) =2.99 (95%CI: 2.11 – 4.22)), TCAs, (OR=1.63 (95%CI: 1.04 – 2.57)) and other antidepressants (OR=1.98 (95% CI: 1.20 – 3.26). The risk was higher during the first month of treatment, for SSRIs (OR=13.37; 95%CI: 6.31 – 28.33) and TCAs (OR=3.70, 95%CI: 1.59 – 8.59) respectively.

Conclusion

Use of all of the antidepressant classes was associated with an increased risk for hyponatremia. Especially within the first month of SSRI and TCA treatment the risk for hyponatremia is higher. Monitoring of sodium levels in daily clinical practice during this period might help to reduce the incidence of hyponatremia.

INTRODUCTION

Hyponatremia is associated with an increased risk of morbidity and mortality, even in mild forms [1, 2]. Clinical symptoms of hyponatremia depend on the severity and acuteness, varying from headache and confusion to convulsions and coma [2, 3]. The use of certain drugs, mainly diuretics and some psychotropic agents, are a risk factor for hyponatremia [4].

Of the psychotropic agents, Selective Serotonin Reuptake Inhibitors (SSRIs) and venlafaxine have consistently been associated with hyponatremia [5-12]. SSRI-induced hyponatremia is an adverse drug reaction with a reported incidence varying from 0.5% to 32%, [8], which develops more frequently in the elderly [12, 13]. Hyponatremia in relation to tricyclic antidepressants (TCAs) and other newer antidepressants has been studied to a lesser extent. The main evidence comes from case reports of hyponatremia related to amitriptyline, imipramine and mirtazapine [14-19]. The number of pharmaco-epidemiological studies on TCAs and hyponatremia is limited and results are conflicting [5, 9, 20-22]. Also the underlying biological mechanism of antidepressant drug-induced hyponatremia is still under debate [6, 10, 21, 23].

All previous studies on SSRI-induced hyponatremia have important limitations, including a limited sample size or missing information on current medical illnesses and drug use. For TCAs and other antidepressants the number of studies is limited and results are inconsistent, but based on the hypothesized biological mechanisms we could also expect an increased risk for some of the TCAs and other antidepressants. Therefore, we investigated the association between all antidepressants and hyponatremia within a large database of prospectively gathered electronic health care records from a community-dwelling adult population.

METHODS

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) project. The IPCI project is a longitudinal observational, dynamic database which contains the electronic medical records of a group of more than 600 general practitioners (GPs) in the Netherlands. The database contains the complete electronic medical records of approximately 1,5 million patients. These medical records are de-identified and contain data on demographics, symptoms and diagnoses (coded and in free text), referrals, laboratory findings, hospitalizations, discharge letters, and drug prescriptions (which includes the ATC code and dosage regimen). In the Dutch health care system, the GP has a crucial role and functions as a gatekeeper of medical care and almost all inhabit-

ants of the Netherlands are registered with a GP. Details of the IPCI database have been described elsewhere [24, 25]. The system complies with European Union guidelines on the use of electronic healthcare data for medical research and has been proven valid for pharmaco-epidemiologic studies [24]. The Scientific and Ethical Advisory Board of IPCI project approved the study (study protocol N. 02/13).

Study population

The source population comprised all subjects from the IPCI database, aged 18 years and above, during the study period from January 1st, 1996 until March 1st, 2011. Subjects should have at least 1 year of data registered in the database, with no occurrence of hyponatremia, before inclusion in our study. All subjects were followed until first occurrence of hyponatremia, death, transfer out of practice, last data draw-down, or end of the study period, whichever came first.

Cases and controls

Subjects who were diagnosed with a serum sodium level below 130 millimole per liter and/or subjects (obtained from laboratory measurement files) or who were hospitalized with a specialist diagnosis of hyponatremia at admission were defined as cases. This serum sodium level was chosen to select the more substantial cases of hyponatremia, representing moderate to severe hyponatremia [26]. All possible cases were validated through manual review of the electronic medical record while blinded to the exposure. Up to 10 controls were selected from the same practice by incidence density sampling [27] and matched to each case on sex, year of birth and index date. The index date was defined as the date of onset of hyponatremia.

Exposure definition

Exposure to antidepressant drugs was obtained from the prescription records. Antidepressants were grouped, based on the anatomical therapeutic coding system (ATC) [28], into SSRI (ATC=N06AB), TCA (ATC=N06AA), and other (ATC=N06AF, N06AG, N06AX) antidepressants. The duration of treatment was calculated by dividing the prescribed amount of pills/suspension by the dosing regimen. The treatment episode was considered to be continuous if the gap between consecutive antidepressant drug prescriptions was less than 30 days. Exposure was classified at the index date and categorized in never, past, current or recurrent antidepressant drug use. Past users were not exposed to an antidepressant at the index date, but were exposed at some time point between start of follow-up and the index date. Subjects were considered to be recurrent users if they were exposed to an antidepressant at the index date and had also used an antidepressant in the past.

Co-variables

We considered medical conditions and other medication use at the index date as potential confounders in our analyses. Medical conditions were based on the International Classification of Primary Care (ICPC) diagnosis code [29], as potential confounders we included: cerebrovascular disease (transient ischemic attack, stroke), diabetes insipidus, hypothyroidism, heart failure, liver failure, alcoholism, ischemic heart disease (angina pectoris and myocardial infarction), malignancies, Parkinson's disease and pulmonary disease (asthma and chronic obstructive pulmonary disease) [2, 22, 30, 31]. In addition, potential confounding drug use was based on previous reports on their association with hyponatremia, and assessed at the 3rd ATC coding system level [32]. We considered the following drugs: drugs for acid related disorders (A02), glucose lowering agents (A10), cardiac therapy (C01), diuretics (C03), beta-blocking agents (C07), calcium channel blockers (C08), agents acting on the renin-angiotensin system (C09), thyroid therapy (H03), anti-bacterial agents (J01), analgesics (N02), anti-epileptics (N03), anti-Parkinson drugs (N04), psycholeptics (N05) and anti-inflammatory and anti-rheumatic drugs (M01) (6, 33, 34).

Statistical analysis

Characteristics of the study population are presented for the cases and controls separately. Differences between cases and controls were tested with chi-square statistics or independent t-test, for dichotomous or continuous variables, respectively. Conditional logistic regression analyses were used to assess the association between antidepressants and hyponatremia. As potential confounders, we included co-variables in the model that changed the association between antidepressants and hyponatremia by minimal 5%. The model included 3 categorical variables for the different antidepressant drug classes (SSRI, TCA or other). Duration of current antidepressant drug treatment was categorized in different groups: 0-30 days, 31-180 days, >180 days. In separate analyses we considered past users as the reference population to control for confounding by indication. First, by including all past users, and secondly by including all past users who ceased antidepressant use at least 1 year before the index date respectively, to minimize the effect of exposure misclassification. Furthermore, we studied the individual antidepressant drugs with a sufficient number of exposed cases (>10). Three additional analyses were performed. First, we analyzed only cases defined by a specialist diagnosis of hyponatremia, to restrict the possibility of diagnostic bias by GP routine measurements. Second, cases were restricted to sodium levels below 125 mmol/L to focus on more severe hyponatremia [26]. Third, subjects with a diagnosis of liver or heart failure were excluded from the analysis and we assessed effect modification by common co-morbidities or thiazide use.

Analyses were performed with SPSS Statistics for Windows (Version 21.0, IBM, Somers, NY, USA). We considered a p-value less than 0.05 as statistically significant.

RESULTS

A total of 2,312 subjects with hyponatremia were identified within the IPCI database between January 1st, 1996 and March 1st, 2011 and matched to 18,295 control subjects. The mean age was 71.5 years and 67.8% was female. Detailed characteristics of the cases and controls are presented in table 1. Despite matching, the mean age of the cases was slightly higher than controls, which is due to variation in the number of available controls per case. The most frequently prescribed antidepressants at the time of hyponatremia onset were amitriptyline (n=96), paroxetine (n=81), citalopram (n=77), and mirtazapine (n=53).

Table 1. Baseline characteristics

	Cases (n=2312)	Controls (n=18295)	P-value
Female gender	1579 (68.3)	12386 (67.7)	0.550
Age years, mean (SD)	74.1 (14.4)	71.1 (13.4)	<0.001
Antidepressant drug use			
Current SSRI use	62 (2.7)	154 (0.8)	<0.001
Current TCA use	32 (1.4)	109 (0.6)	<0.001
Current Other antidepressant use	30 (1.3)	80 (0.4)	<0.001
Concomitant medication			
Drugs for acid related disorders (A02)	630 (27.2)	2479 (13.5)	<0.001
Glucose lowering agents (A10)	353 (15.3)	1715 (9.4)	<0.001
Cardiac therapy (C01)	254 (11.0)	1028 (5.6)	<0.001
Diuretics (C03)	975 (42.2)	3911 (21.4)	<0.001
Beta-blocking agents (C07)	676 (29.2)	3538 (19.3)	<0.001
Calcium channel blockers (C08)	305 (13.2)	1741 (9.5)	<0.001
Agents acting on the renin-angiotensin system (C09)	841 (36.4)	3959 (21.6)	<0.001
Thyroid therapy (H03)	133 (5.8)	764 (4.2)	<0.001
Antibacterials for systemic use (J01)	211 (9.1)	229 (1.3)	<0.001
Analgesics (N02)	270 (11.7)	668 (3.7)	<0.001
Antiepileptic drugs (N03)	132 (5.7)	221 (1.2)	<0.001
Anti-parkinson drugs (N04)	36 (1.6)	99 (0.5)	<0.001
Psycholeptic drugs (N05)	541 (23.4)	1857 (10.1)	<0.001
Antiinflammatory and antirheumatic products (M01)	130 (5.6)	595 (3.3)	<0.001
Co-morbidities			
Heart failure	371 (16.0)	1124 (6.1)	<0.001
Liver failure	40 (1.7)	112 (0.6)	<0.001

Table 1. Baseline characteristics (continued)

	Cases (n=2312)	Controls (n=18295)	P-value
Alcoholism	150 (6.5)	233 (1.3)	<0.001
Asthma/COPD	470 (20.3)	2376 (13.0)	<0.001
Hypothyroidism	139 (6.0)	729 (4.0)	<0.001
Parkinson	25 (1.1)	153 (0.8)	<0.001
Malignancies	402 (17.4)	1498 (8.2)	<0.001
Ischemic stroke	360 (15.5)	1504 (8.2)	<0.001
Heart disease (Myocardial infarction, Angina pectoris)	448 (19.4)	2640 (14.4)	<0.001

The characteristics are presented as numbers (%), unless stated otherwise.

Different antidepressant drugs

Current use of an SSRI was associated with a three times higher risk for hyponatremia compared to non-use (Table 2). Current use of TCAs and other antidepressants showed a more than 1.5 and almost two times higher risk. Also past TCA use was associated with a significantly higher risk (OR=1.25, 95% CI: 1.01 – 1.52), whereas recurrent use of any of the antidepressants was not associated with an increased risk for hyponatremia. In comparison to past use, current SSRI use showed a more than 2.5 times higher risk for hyponatremia, which was not the case for TCAs and other antidepressants. Results did not materially change when past use was restricted to those patients who discontinued more than one year ago (results not shown). The odds ratios of the most commonly used antidepressants, showed point estimates which were in line with the overall SSRI, TCA and other antidepressant point estimates showed in table 2, namely for: amitriptyline (OR=1.56, 95%CI: 0.91 – 2.69), paroxetine (OR=2.85; 1.61 – 5.02), citalopram (OR=2.98; 95%CI: 1.73 – 5.14), and mirtazapine (OR=2.28; 1.15 – 4.50).

Table 2. Association between antidepressant drug use and hyponatremia[1]

	Case / Control	Odds ratio$_{crude}$ (95%CI)	Odds ratio$_{adj}$[2] (95%CI)	Odds ratio$_{adj}$[3] (95%CI)
SSRI				
Non-use	2024 / 16716	1.00 (Reference)	1.00 (Reference)	
Past	169 / 1041	1.16 (0.97 – 1.40)	1.10 (0.90 – 1.33)	1.00 (Reference)
Recurrent	57 / 389	1.16 (0.86 – 1.55)	0.78 (0.56 – 1.08)	0.71 (0.49 – 1.03)
Current	62 / 154	3.36 (2.46 – 4.59)	2.99 (2.11 – 4.22)	2.73 (1.85 – 4.02)
TCA				
Non-use	2085 / 17206	1.00 (Reference)	1.00 (Reference)	
Past	161 / 805	1.53 (1.27 – 1.86)	1.25 (1.01 – 1.52)	1.00 (Reference)
Recurrent	34 / 180	1.43 (0.97 – 2.11)	0.75 (0.49 – 1.15)	0.60 (0.38 – 0.95)

Table 2. Association between antidepressant drug use and hyponatremia[1] (continued)

	Case / Control	Odds ratio$_{crude}$ (95%CI)	Odds ratio$_{adj}$[2] (95%CI)	Odds ratio$_{adj}$[3] (95%CI)
Current	32 / 109	2.45 (1.62 – 3.70)	1.63 (1.04 – 2.57)	1.31 (0.80 – 2.14)
Other				
Non-use	2135 / 17451	1.00 (Reference)	1.00 (Reference)	
Past	121 / 635	1.42 (1.14 – 1.76)	1.19 (0.94 – 1.51)	1.00 (Reference)
Recurrent	26 / 134	1.63 (1.06 – 2.51)	0.94 (0.58 – 1.52)	0.79 (0.47 – 1.33)
Current	30 / 80	2.56 (1.63 – 4.04)	1.98 (1.20 – 3.26)	1.66 (0.97 – 2.86)

Crude odds ratio = matched on sex, age and GP. Adjusted odds ratio[2], adjusted for the following significant covariates (>5%change odds ratio): alcoholism, heart failure, malignancies; and the following comedication: analgesics, antiepileptics, psycholeptics, antibacterials for systemic use, drugs for acid related disorders, diuretics, agents acting on the renin-angiotensin system, drugs used in diabetes, beta blocking agents, anti-inflammatory and antirheumatic products, and the other antidepressant drug groups. Abbreviations: TCAs = tricyclic antidepressants, SSRIs = selective serotonin reuptake inhibitors. [1] = Hyponatremia defined based on a serum sodium level of 130mmol per liter or below and/or hospital admission with a specialist diagnosis of hyponatremia at admission. [2] = Past use as the reference population and adjusted for the same significant covariates as model 2.

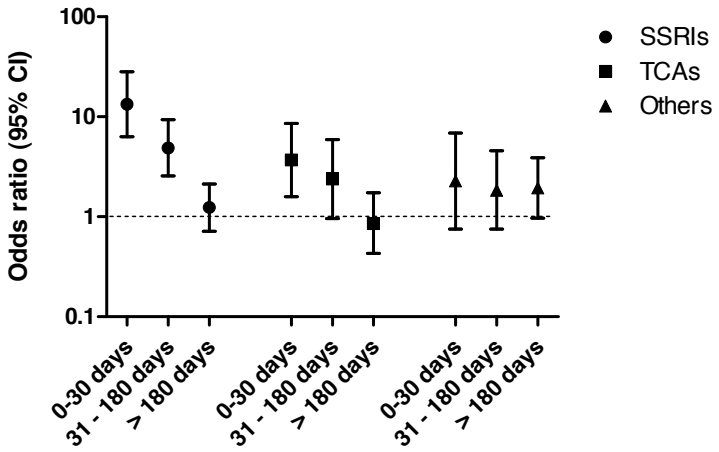


Figure 1. Risk of hyponatremia1 by duration of current antidepressant drug treatment.
Abbreviations: TCAs = tricyclic antidepressants, SSRIs = selective serotonin reuptake inhibitors. Data presented as the odds ratio for the different duration categories of current antidepressant use compared to non-use. Adjusted for the following significant covariates (>5%change odds ratio): alcoholism, heart failure, malignancies; and the following comedication: analgesics, antiepileptics, psycholeptics, antibacterials for systemic use, drugs for acid related disorders, diuretics, agents acting on the renin-angiotensin system, drugs used in diabetes, beta blocking agents, anti-inflammatory and antirheumatic products, and the other antidepressant drug groups. 1 = Hyponatremia defined based on a serum sodium level of 130mmol per liter or below and/or hospital admission with a specialist diagnosis of hyponatremia at admission.

Duration of treatment

For current SSRI use, a higher risk for hyponatremia was observed during the first 6 months of treatment (Figure 1), which was most prominent during the first month of treatment (OR= 13.37, 95%CI: 6.31 – 28.33). For current TCA use, the increased risk for hyponatremia was only present in the first month after initiation of treatment (OR=3.70, 95%CI: 1.59 – 8.59). No effect of duration for other antidepressant drug treatment was observed.

Sensitivity analyses

For the hospitalized cases (i.e. hyponatremia defined at hospital admission with a specialist diagnosis of hyponatremia), we observed an increased risk for hyponatremia for current SSRI and TCAs use, OR=3.25 (95%CI: 2.05 – 5.03) and OR=2.34 (95%CI: 1.27 – 4.33), respectively (Table 3). When the case definition was restricted to <125 mmol/L, the increased risk for hyponatremia showed similar results for SSRIs (OR= 3.74, 95%CI:

Table 3. Association between antidepressant drug use and hyponatremia defined at hospital admission[1]

	Case / Control	Odds ratio$_{crude}$ (95%CI)	Odds ratio$_{adj}$ (95%CI)
Hospitalization[2]			
SSRI			
Non-use	892 / 7676	1.00 (Reference)	1.00 (Reference)
Past	81 / 437	1.34 (1.03 – 1.76)	1.15 (0.86 – 1.54)
Recurrent	26 / 173	1.27 (0.83 – 1.95)	1.10 (0.69 – 1.73)
Current	36 / 86	3.78 (2.51 – 5.70)	3.25 (2.05 – 5.13)
TCA			
Non-use	924 / 7873	1.00 (Reference)	1.00 (Reference)
Past	76 / 373	1.58 (1.20 – 2.09)	1.28 (0.94 – 1.73)
Recurrent	18 / 70	1.81 (1.03 – 3.18)	0.90 (0.48 – 1.70)
Current	17 / 56	2.53 (1.44 – 4.47)	2.34 (1.27 – 4.33)
Other			
Non-use	963 / 8006	1.00 (Reference)	1.00 (Reference)
Past	54 / 277	1.38 (1.00 – 1.90)	1.10 (0.77 – 1.56)
Recurrent	10 / 47	1.70 (0.84 – 3.44)	0.92 (0.42 – 2.01)
Current	8 / 42	1.08 (0.48 – 2.41)	0.78 (0.34 – 1.84)

Crude odds ratio = matched on sex, age and GP. Adjusted odds ratio, adjusted for: alcoholism, heart failure, liver failure, malignancies; and the following comedication: analgesics, antiepileptics, psycholeptics, antibacterials for systemic use, drugs for acid related disorders, diuretics, beta blocking agents, and the other antidepressant drug groups.

[1] Hyponatremia defined at hospital admission with a specialist diagnosis of hyponatremia.

Abbreviations: TCAs = tricyclic antidepressants, SSRIs = selective serotonin reuptake inhibitors.

1.84 – 7.60) and TCAs (OR=3.03, 95%CI: 1.06 – 8.68). Other antidepressant use showed no association with profound hyponatremia (OR=1.30, 95%CI: 0.36 – 4.69).

When we assessed effect modification by common comorbidities, we observed significant effect modification by glucose lowering agents on the association between TCAs and hyponatremia (p=0.018). The risk for hyponatremia was 1.24 (CI: 0.73 – 2.10) for TCA users who did not use glucose lowering agents. While, there was a 5.29 (CI: 1.80 – 15.74) increased risk for hyponatremia in TCAs users who also used glucose lowering agents. Other comorbidities showed no significant effect modification on the association between antidepressant drugs and hyponatremia. Exclusion of subjects with heart and liver failure did not significantly alter our results (results not shown).

DISCUSSION

The results from this matched case-control study show that current use of all antidepressants is associated with an increased risk for hyponatremia compared with non-use, the risk being higher during the first month of TCA and SSRI treatment.

TCA and other antidepressant use was associated with hyponatremia in our matched case-control study. Especially short term TCA use was associated with a high risk for hyponatremia. Prior evidence on the association between TCAs and hyponatremia is inconsistent or based on case-reports [5, 9, 14-18, 20-22]. These studies have important limitations which restrict their implications; including small sample size (≤15 exposed cases) [5, 21, 22], failure to adjust for confounding factors at event date [9, 20], no stratification by treatment duration and no consideration of past users in their analyses [5, 9, 20-22]. The results for other antidepressants in our study are more difficult to interpret because these might be heterogeneous in their mechanism of action and have a low number of cases with the individual drugs. Only venlafaxine has consistently been associated with hyponatremia [7, 10, 33], and some case-reports on mirtazapine-induced hyponatremia have been published [19, 34]. For both TCAs and other antidepressants, the indication of use might explain the association with hyponatremia, as the association disappeared when compared to past antidepressant users. Antidepressant drugs might be prescribed for certain comorbidities which increase the susceptibility to hyponatremia. For example, neuropathic pain, which might be a complication of diabetes mellitus, is a common indication for TCAs and diabetes mellitus has been demonstrated to be a risk factor for hyponatremia [35]. Also, our association between TCA use and hyponatremia was modified by glucose lowering drugs (or presence of diabetes). Stratified by subjects who used glucose lowering drugs, we observed that in both groups the risk for hyponatremia was higher for TCAs, but the association was no longer statistically significant within subjects that did not use glucose lowering drugs.

This might represent power problems, but also implicates an important role of diabetes in the association between TCAs and hyponatremia.

Consistent with previous literature, SSRIs were evidently associated with hyponatremia [5-9, 11, 13, 23, 33, 36]. It is likely a medication class effect, as individual antidepressants with sufficient numbers (e.g. citalopram, paroxetine) demonstrated a similar increase in risk for hyponatremia. The highest risk was observed during the first month of treatment, which shows a strong consistency with earlier studies in which the majority of hyponatremia cases presented within 30 days after initiation of therapy [5, 11, 23, 36, 37]. An increased risk of SSRI-induced hyponatremia was also observed during the first half year, but not for long term use. This confirms the hypothesis that the effect of SSRIs on hyponatremia is transient over time [6, 38]. Besides, patients at high risk for hyponatremia might develop it during the first weeks of treatment, leaving the low risk patients in the long term treatment group. In line with this observation, we observed that recurrent use of any of the antidepressants was not associated with hyponatremia, which might also be due to depletion of susceptibles; patients who reinitiate the antidepressant are those who can tolerate its effects [39]. It could be hypothesized that subjects that did not develop hyponatremia the first time they used an antidepressant, neither developed it later on, unless other risk factors made them possible more susceptible to hyponatremia (e.g. heart failure, diarrhea).

The underlying biological mechanism of SSRI and venlafaxine induced hyponatremia is the non-osmotic inappropriate stimulation of antidiuretic hormone (ADH), possible mediated by the stimulation of the serotonin receptors (5-HT1c and 5-HT2) and α-1-adrenergic receptors [10, 23, 40-43]. This would especially apply for SSRIs and some other antidepressants (e.g. venlafaxine, mirtazapine), but TCAs can also be potent inhibitors of serotonin [44]. Laboratory investigations did not consistently confirm SIADH as the main underlying mechanism of antidepressant-induced hyponatremia [6, 10, 21, 23]. Our results are in line with the anticipated results, based on SIADH as the possible mechanism, however we cannot draw conclusions regarding the mechanism of action as we have no information regarding plasma and urine osmolality. Another proposed alternative mechanism suggests an increased nephrogenic response to ADH leading to inappropriate anti-diuresis [21].

Our study has some strengths which we would like to emphasize. Our study includes a large number of cases with hyponatremia within a population of community dwelling adults. We could study multiple aspects of antidepressant drug exposure, including important confounders as medical conditions and concomitant medications. By using 130mmol/L as a cut-off for hyponatremia we included only the more substantial cases of hyponatremia, and we also performed an additional analysis with a lower cut-off. Misclassification of cases was unlikely in this situation, as only the more serious cases of clinically relevant hyponatremia were included which were confirmed

by sodium measurements. By selecting cases which were diagnosed during hospitalization, we ruled out selection bias, as hyponatremia was not detected during (routine) GP measurements. However, also some limitations should be taken into account. Firstly, our data did not allow for adjustment of bodyweight, which is a significant risk factor for hyponatremia, although bodyweight might not be distinctly related to drug exposure [11, 21]. Secondly, our study might be subject to residual confounding. We had no information regarding the indication of treatment and its severity, although we limited confounding by indication through analyses with past use of antidepressants as the reference population. Finally, medication exposure was based on prescription data and not on actual intake. Episodes of use were calculated based on the prescriptions to determine, as accurate as possible, the drug exposure in our large GP database and misclassification of exposure would be non-differential.

In our study, from a large daily practice adult population, we were able to study the relative risk of antidepressant exposure for hyponatremia. Our results confirm that SSRI treatment is associated with an increased risk for hyponatremia, being higher during the first months of SSRI treatment. Also short term TCA users are at risk to develop hyponatremia. The HARM wrestling treatment criteria (2009) indicate serum sodium measurements during the first 5-9 days after initiation of SSRI treatment, during consecutive use of thiazides in the elderly (>70year) [45]. However, until now, no guidelines exist regarding serum sodium measurements for exclusive use of SSRIs or TCAs in the elderly, while monitoring of sodium levels in daily clinical practice during the first few weeks might help to reduce the incidence of hyponatremia.

ACKNOWLEDGEMENTS

We thank Marcel de Wilde, Kris Sieradzan and Mees Mosseveld for the collection of data and maintenance of the IPCI database.

SOURCES OF FUNDING

None.

CONFLICTS OF INTEREST

None.

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Chapter 4.3

Benzodiazepine-induced hyponatremia and the interaction with thiazide diuretics

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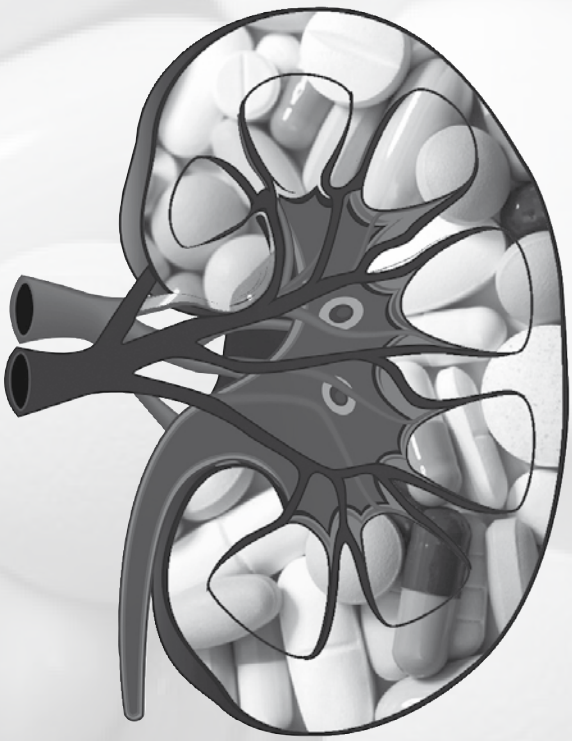
Benzodiazepine-induced hyponatremia and interaction with thiazide diuretics. A population-based study.



ABSTRACT

Background

Hyponatremia is associated with increased morbidity and mortality and is often drug-induced. In a subanalysis of a recent study, we identified a novel association between benzodiazepines and hyponatremia. Here, our objective was to study the potential association between benzodiazepines and hyponatremia in greater detail using an independent cohort.

Methods

A nested case-control study was performed in a general practioner database containing over one million patient records (Integrated Primary Care Information; IPCI). All subjects with a serum sodium level of below 130 mmol/L or a hospital admission diagnosis of hyponatremia were selected and matched with up to 10 controls from similar practice, sex and age. The association with benzodiazepines and their interaction with thiazides was studied using conditional logistic regression analyses.

Results

Of the benzodiazepines, the anxiolytics were associated with a more than 2-fold increased risk of hyponatremia (OR 2.08; 95% CI 1.75-2.48); and 1.5 times increased risk by use of sedatives (OR 1.51; 95% CI 1.26-1.83). The combination of anxiolytics and thiazides increased the risk of hyponatremia > 5-fold (OR 5.02; 95% CI 3.75, 6.72), which was significantly higher than the separate use of these drugs .

Conclusion

Benzodiazepines are associated with an increased risk of hyponatremia. Concomitant use of thiazide diuretics leads to even higher risks. Use of these drugs deserves caution; we recommend serum sodium control measurements and special attention for these drugs in case of symptoms of hyponatremia.

INTRODUCTION

Hyponatremia is the most common electrolyte disorder in the general population. It may cause symptoms such as nausea and headache and in more severe cases seizures and coma.[1, 2] Mild forms are already associated with morbidity, including increased risk of falls and fractures, and higher mortality.[3-5]

Drugs are one of the most frequent causes of hyponatremia, with thiazides being the most common .[1, 6, 7] The mechanism of thiazide-induced hyponatremia is not completely clear, but appears to involve the following: excess renal loss of electrolytes, in combination with impaired renal water excretion (by diminishing NaCl reabsorption and increased ADH secretion), electrolyte shift into the cell, and magnesium depletion .[1, 8-11] Drugs acting on the central nervous system, antidepressants and antiepileptics, have been associated with an increased risk of hyponatremia.[12-14] These drugs seem to affect water homeostasis due to the syndrome of inappropriate secretion

of antidiuretic hormone (SIADH) in three possible ways: they can increase ADH secretion centrally, potentiate the effect of endogenous ADH at the renal medulla, and reset the osmostat, thus lowering the threshold for ADH secretion.

Although many drugs have been associated with hyponatremia,[6] it is important to be aware of unknown associations with other drugs and unknown potential interactions. Recently, we identified an association between benzodiazepines and hyponatremia in a population-based study, and showed an interaction with thiazide diuretics.[15] Two main subclasses of benzodiazepines can be identified, based on their pharmacological mechanism: anxiolytics (e.g. oxazepam) and sedatives. Sedatives cover two main classes based on chemical mechanism (e.g. temazepam versus zopiclone). They are indicated for anxiety disorders (anxiolytics), and sleep disturbances (sedatives). Some case-reports of benzodiazepine-induced hyponatremia have also been reported,[16-18] but this association has not been studied in detail.

Therefore, we conducted this case-control study with patients from general practitioner practices recruited throughout The Netherlands to study the risk of benzodiazepine-induced hyponatremia and to seek confirmation of the interaction between benzodiazepines and thiazides.

METHODS

Setting

A nested case-control study was conducted in the Integrated Primary Care Information (IPCI) database. This longitudinal observational general practitioner (GP) research database contains patient records of 1.5 million patients throughout the Netherlands. In the

Netherlands, all citizens are registered with a GP practice, which forms the central point of healthcare and acts as a gatekeeper for secondary health care. Therefore, the medical record of each patient can be assumed to contain all relevant medical information, including medical findings and diagnoses from specialist health care. To further maximize the completeness of data, GPs contributing data to the IPCI database are not allowed to maintain a system of paper based records next to the electronic medical records. The electronic records contain coded and anonymous data on patient demographics, symptoms (in free text), diagnoses using the International Classification for Primary Care (ICPC) and free text, clinical findings, referrals, laboratory findings and hospitalizations. Furthermore, there are records of all drug prescriptions, their indications and dosage regimen. Further details of the database have been described elsewhere.[19, 20] The system complies with European Union guidelines on the use of electronic healthcare data for medical research and has been proven valid for pharmaco-epidemiologic studies.[19] The Scientific and Ethical Advisory Board of IPCI project approved the study (study protocol N. 02/13).

Selection of cases and controls

Within the IPCI database, all patients who were diagnosed with a clinically relevant serum sodium level of below 130 or patients that were hospitalized for hyponatremia (admission diagnosis in discharge letter) between January 1st, 1996 and March 1st, 2011 were identified as a case. All cases were validated through manual review of the electronic medical record while blinded to the exposure. The date of diagnosis of the hyponatremia was set as the index date.

Up to 10 controls were selected from the same practice by incidence density sampling[21] and matched on practice, year of birth and sex. Both cases and controls required at least 6 months of valid database history prior to the date of prescription in order to allow proper assessment of drug exposure of all study subjects.

Exposure definition

Drug exposure was assessed on the 4th level of the Anatomical Therapeutical Chemical (ATC) coding system.[22] Exposure was defined as exposure to benzodiazepines (anxiolytics covering diazepam, oxazepam, lorazepam (ATC class N05ba); sedatives covering nitrazepam and temazepam (ATC class N05cd); sedatives covering zopiclone and zolpidem (ATC class N05cf)) on the index date and was obtained from the prescription records. The exposure period was calculated by dividing the dispensed number of units by the dosing regimen. Current use was defined as drug exposure at the index date; past use was defined as drug exposure before the index date.

Exposure to thiazides was obtained in the same manner. Exposure to drugs used as covariables was assessed on the 3rd ATC level.

Covariables

Comorbidities were selected on their International Classification of Primary Care (ICPC) diagnosis code: cerebrovascular disease (transient ischemic attack, stroke), diabetes insipidus, hypothyroidism, heart failure, liver failure, alcoholism, ischemic heart disease (angina pectoris and myocardial infarction), malignancies, Parkinson's disease and pulmonary disease (asthma and chronic obstructive pulmonary disease).

Concomitant drug use was assessed based on previous reports on their association with hyponatremia (drugs for acid related disorders (a02), glucose lowering agents (a10, to define the presence of diabetes), cardiac therapy (c01), diuretics (c03), beta-blocking agents (c07), calcium channel blockers (c08), agents acting on the renin-angiotensin system (c09), thyroid therapy (h03), antibacterials (j01), analgesics (n02), antiepileptics (n03), anti-parkinson drugs (n04), psycholeptics (n05) and anti-inflammatory and anti-rheumatic drugs (m01)).[6]

Data analysis

Odds ratios (ORs) of hyponatremia caused by drug exposure, were calculated using conditional logistic regression. We also used past use as a reference to control for confounding by indication. In adjusted models, we included comorbidities and drug groups that were previously associated with hyponatremia if these changed the point estimate more than five percent. For the pharmacological substances that were significantly associated with hyponatremia in the main analysis, we assessed the differences between men and women. All statistical analyses were performed using SPSS software (version 17.0; SPSS Inc., Chicago, Illinois, USA). After correction for multiple testing, p-values below 0.017 (0.05/3) were considered statistically significant.

RESULTS

For this study, 2312 cases of hyponatremia were identified and 18,295 controls were selected (Table 1). The apparent difference in age and comorbidities between cases and controls is due to variation in the number of available controls with age, which we accounted for by conditional logistic regression (see further).

Table 1. Baseline characteristics of the study population

	Cases (n=2312)	Controls (n=18295)	P-value
Female gender	1579 (68.3)	12386 (67.7)	0.550
Age years, mean (SD)	74.1 (14.4)	71.1 (13.4)	<0.001
Benzodiazepine use			
Benzodiazepine derivates (anxiolytics)	271 (11.7)	864 (4.7)	<0.001
Benzodiazepine derivates (sedatives)	288 (12.5)	797 (4.4)	<0.001
Benzodiazepine related drug (zolpidem)	56 (2.4)	223 (1.2)	<0.001
Concomitant medication			
Drugs for acid related disorders	630 (27.2)	2479 (13.5)	<0.001
Glucose lowering agents	353 (15.3)	1715 (9.4)	<0.001
Cardiac therapy	254 (11.0)	1028 (5.6)	<0.001
Diuretics	975 (42.2)	3911 (21.4)	<0.001
Beta-blocking agents	676 (29.2)	3538 (19.3)	<0.001
Calcium channel blockers	305 (13.2)	1741 (9.5)	<0.001
Agents acting on the renin-angiotensin system	841 (36.4)	3959 (21.6)	<0.001
Thyroid therapy	133 (5.8)	764 (4.2)	<0.001
Antibacterials for systemic use	211 (9.1)	229 (1.3)	<0.001
Analgesics	270 (11.7)	668 (3.7)	<0.001
Antiepileptic drugs	132 (5.7)	221 (1.2)	<0.001
Anti-parkinson drugs	36 (1.6)	99 (0.5)	<0.001
Psycholeptic drugs	541 (23.4)	1857 (10.1)	<0.001
Anti-inflammatory and anti-rheumatic products	130 (5.6)	595 (3.3)	<0.001
Co-morbidities			
Heart failure	371 (16.0)	1124 (6.1)	<0.001
Liver cirrhosis	40 (1.7)	112 (0.6)	<0.001
Alcoholism	150 (6.5)	233 (1.3)	<0.001
Asthma/COPD	470 (20.3)	2376 (13.0)	<0.001
Hypothyroidism	139 (6.0)	729 (4.0)	<0.001
Parkinson	25 (1.1)	153 (0.8)	<0.001
Malignancies	402 (17.4)	1498 (8.2)	<0.001
Ischemic stroke	360 (15.5)	1504 (8.2)	<0.001
Heart disease (Myocardial infarction, Angina pectoris)	448 (19.4)	2640 (14.4)	<0.001

The characteristics are presented as numbers (%), unless stated otherwise.

Benzodiazepines and hyponatremia

Exposure to benzodiazepines (anxiolytics or sedatives) was significantly associated with hyponatremia, after adjustment for other drugs and comorbidities (Table 2). Exposure to anxiolytics (ATC class N05ba) was associated with > 2-fold higher risk compared to the non-use (OR 2.08; 95% CI 1.75-2.48); and > 1.5-fold risk compared to past use (OR

Table 2. Benzodiazepines and risk of hyponatremia*

Drug	Control	Case	Crude model	Adjusted model[1]	Adjusted model[2]
	N	N	OR (95% CI)	OR (95% CI)	OR (95% CI)
Benzodiazepine derivatives (anxiolytics)					
Past	4501	717	**1.48 (1.33 – 1.65)**	**1.30 (1.16 – 1.46)**	1.00 (ref)
Current	864	271	**2.81 (2.40 – 3.30)**	**2.08 (1.75 – 2.48)**	**1.60 (1.33 – 1.93)**
Benzodiazepine derivatives (sedatives)					
Past	2913	479	**1.25 (1.11 – 1.41)**	**1.17 (1.03 – 1.33)**	1.00 (ref)
Current	797	288	**2.06 (1.74 – 2.45)**	**1.51 (1.26 – 1.83)**	**1.30 (1.06 – 1.60)**
Zolpidem, Zopiclon					
Past	891	173	**1.23 (1.02 – 1.48)**	1.08 (0.88 – 1.32)	1.00 (ref)
Current	223	56	**1.68 (1.23 – 2.30)**	1.02 (0.72 – 1.45)	0.95 (0.64 – 1.40)

ATC = Anatomical Therapeutic Chemical; Crude model: matched on year of birth, sex, practice, and adjusted for each other; Adjusted model[1]: adjusted for the significant co-morbidities: heart failure, asthma/copd, malignancies, alcoholism and concurrent medications c03 n02 n03 j01 a02; Adjusted model[2]: adjusted for the same covariates as model 1, with past use as the reference population.
* serum sodium level < 130mmol/L

1.60; 95% CI 1.33 – 1.93) Past use increased the risk 1.3 times in comparison to non-use (OR 1.30; 95% CI 1.16, 1.46). Sedatives (ATC class N05cd) were associated with a 1.5-fold higher risk of hyponatremia, compared to non-use (OR 1.51; 95% CI 1.26, 1.83) and a 1.3-fold increased risk compared to past use (OR 1.30; 95% CI 1.06 – 1.60). Past exposure was associated with a slightly increased risk (OR 1.17; 95% CI 1.03, 1.33). No association was found between the benzodiazepines zolpidem and zopiclon (ATC class N05cf) and hyponatremia after adjustment for the effects of other drugs and comorbidities.

Differences between men and women

The number of hyponatremia cases was four times higher in women than in men (anxiolytics: 213 versus 58; sedatives: 184 versus 44). Risk estimates were slightly higher in men (anxiolytics: OR 2.27; 95% CI 1.53, 3.38 and sedatives: OR 1.82; 95% CI 1.15, 2.87) than in women (anxiolytics: OR 1.85; 95% CI 1.54, 2.23 and sedatives: OR 1.43; 95% CI 1.17, 1.74).

Interaction with thiazide diuretics

Exposure to either benzodiazepines or thiazides was associated with an increased risk of hyponatremia compared to exposure to neither of these drugs (Table 3). The combination of anxiolytics and thiazides was associated with a more than five times higher risk of hyponatremia than when none of these drugs were used (OR 5.02; 95% CI 3.75, 6.72). This risk was significantly higher than exposure to either one of these drugs separately

Table 3. Benzodiazepine and thiazide use and the risk of hyponatremia*

Drug	Control	Case	Risk of hyponatremia[1]	
	N	N	OR (95% CI)	P-value
Thiazide	2693	584	**2.17 (1.90 – 2.48)**	< 0.001
Benzodiazepine derivatives (anxiolytics)	691	168	**1.77 (1.44 – 2.18)**	< 0.001
Both	173	103	**5.02 (3.75 – 6.72)**	< 0.001
Thiazide	2705	605	**2.23 (1.96 – 2.55)**	< 0.001
Benzodiazepine derivatives (sedatives)	636	146	**1.50 (1.20 – 1.88)**	< 0.001
Both	161	82	**3.39 (2.47 – 4.67)**	< 0.001
Thiazide	2815	660	**2.19 (1.93 – 2.50)**	< 0.001
Zolpidem, Zopiclon	172	29	0.79 (0.50 – 1.27)	0.53
Both	51	27	**3.91 (2.30 – 6.65)**	< 0.001

ATC = Anatomical Therapeutic Chemical; [1]matched on year of birth, sex and practice; adjusted for the significant co-morbidities: heart failure, asthma/copd, malignancies, alcoholism and concurrent medications: c09 n02 n03 j01 a02 other c03 (except thiazides); * serum sodium level < 130mmol/L

(RERI* 2.08; 95% CI 0.64, 3.54). The combination of sedatives and thiazides also showed an increased risk compared to exposure of either of these drugs, but the confidence intervals overlapped.

* relative excess risk due to interaction (RERI), as the best reflecting value of the joint effects of two factors by an additive pattern. The interaction is considered significant if the value of zero is not enclosed by the 95% confidence interval (CI)).

DISCUSSION

The results from this nested case-control study confirm an increased risk of hyponatremia associated with benzodiazepines. Benzodiazepines from both subgroups, anxiolytics and sedatives, were associated with this increased risk. The risk of hyponatremia with past use is potentially caused by intermittent use of these drugs. Compared with past use, the risk of hyponatremia with current exposure remained. With the current study, we cannot assure that benzodiazepines are the directly causal factor or a surrogate for other(s), but we suggest a plausible explanation based on a few different biological mechanisms, described below.

Benzodiazepines exert their effect by binding to the GABAA receptor in the central nerve system (CNS), with a slight variation in action due to differences in affinity to the specific subunits.[23] Inhibition of this GABAA receptor in rats increased ADH release, which results in water retention and a decrease in serum sodium levels, potentially leading to hyponatremia.[24]

In addition to the GABAA receptors, benzodiazepines also bind to peripheral benzodiazepine receptors (PBR; renamed translocator protein 18kDa (TSPO).[25-28] Peripheral benzodiazepine receptors are localized in various tissues throughout the whole body and are present in the zona glumerulosa of the adrenals and in the distal convoluted tubule of the kidney[29, 30] and are implicated in various mechanisms, such as cell growth and steroid synthesis.[31, 32] Expression of these receptors is influenced by (ischemic) stress and seems to play a role in maintaining kidney function.[33] Because of the presence of these receptors on the site of action of ADH in the renal tubules, a role in water and electrolyte balance was previously suggested.[26, 28, 34]

A rat study showed an increase in PBR density after administration of either hydrochlorothiazide or [3H] Ro 5-4864 (4'-chlorodiazepam; a PBR-inhibitor).[34] Additionally, administration of either of these drugs increased urinary volume and sodium excretion. This may contribute to the interaction between benzodiazepines and thiazides as observed in our study. This interaction was previously observed in a population-based study,[15] in which combined use of benzodiazepines and thiazides was associated with hyponatremia, significantly worse in subjects using both drugs concomitantly (serum sodium 130.3 ± 2.8 mmol/L in subjects exposed to both benzodiazepines and thiazides, versus 133.4 ± 1.8 mmol/L in subjects using benzodiazepines and 132.8 ± 2.3 mmol/L in subjects using thiazides only).

Zolpidem and zopiclon were not significantly associated after adjustment for other factors. This might be due to selectivity in binding to the GABAA receptor, and a lower affinity to the peripheral benzodiazepine receptors. These drugs belong to the imidazopyridine class and have a slightly different receptor-binding pattern than the classical benzodiazepines.[23, 35] They exhibit high-affinity binding at central receptors, but the affinity to peripheral receptor binding sites is lower than classical benzodiazepines.[35, 36]

Indication bias should also be acknowledged as a potential explanation for the association between benzodiazepines and hyponatremia. Sleep disturbances, which are the main indication for sedatives, lead to disturbed cortisol secretion. Cortisol release is suppressed in sleep deprivation,[37] which is related to ADH hypersecretion, leading to water retention and hyponatremia.[38, 39] Psychiatric disorders, potential indications for anxiolytics, are associated with hyponatremia by the medical treatment (antipsychotics) or the disease itself (polydipsia, water intoxication and impaired water excretion).[40]

Although benzodiazepines are frequently used drugs, mainly in the elderly population, and they are consistently associated with falls and a decrease in consciousness, they are usually not taken into account in the association with hyponatremia.[12, 41] We speculate that these drugs could even be causal in hyponatremia-related falls. Some cases have been described in the literature, but these date from earlier days, suggesting that this possible association lost attention.[16-18] All hyponatremic cases presented

with a state of acute confusion after benzodiazepine intake. In only one case the association with the benzodiazepine was confirmed with a water load test and a rechallenge of drug administration, fitting the profile of SIADH.[16]

One of the strengths of this study is the large pool of available data. Data on renal function were missing in a substantial proportion of controls, because they were randomly selected and not on the basis of a laboratory measurement, so unfortunately we could not adjust for that. Drug use was measured on the basis of pharmacy records. Some misclassification could have been present in case of non-compliance, but this is most probably independent of the outcome. The outcome hyponatremia was based on laboratory measurements or a diagnosis of hyponatremia on admission. This is based on the assumption that hyponatremia with a serum sodium level of >130 mmol/L would not directly lead to symptoms requiring hospital admission. Misclassicifation, however, would most probably be random.

Although benzodiazepines are relatively old drugs, the association with hyponatremia has not been well studied. We showed an increased risk of this adverse drug reaction by benzodiazepines used as sedatives and anxiolytics. In addition, we confirmed an interaction with thiazide diuretics, as previously suggested by our former study.[15] Further studies are needed on both experimental and clinical levels. Use of these drugs deserves caution: elderly with unexplained mental changes or symptoms should be tested for hyponatremia and benzodiazepines should be taken into account as potential cause. We recommend serum sodium control measurements in subjects starting benzodiazepines, especially when thiazides are already in use.

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Chapter 4.4

Drug use and hospital admission with dehydration

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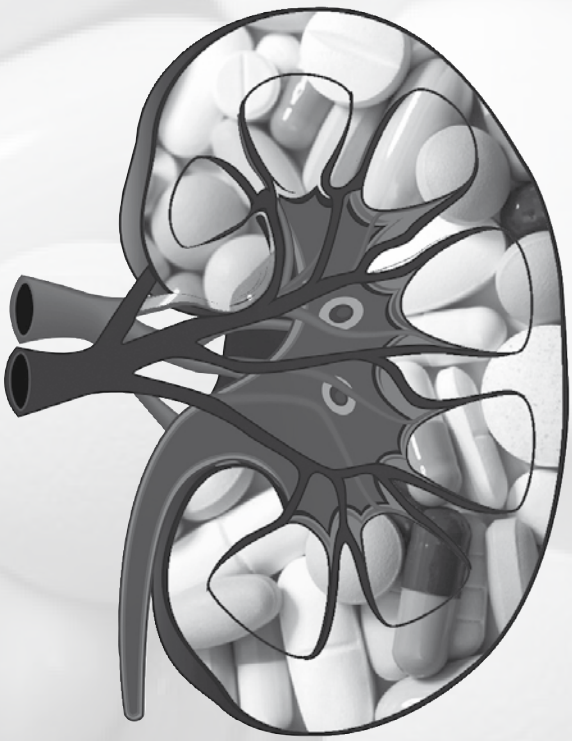
Hospital admission with dehydration and the role of medication: a population-based study.



ABSTRACT

Background

Dehydration, or more appropriately hypovolemia, is the second most frequent precipitating risk factor for acute kidney injury. Medication has been studied in relation to direct acute nephrotoxicity but there are few population-based studies on an indirect cause such as dehydration. Therefore, our objective was to investigate which drugs were associated with hospital admission because of dehydration.

Methods

We conducted a population-based case–control study within the Dutch IPCI (Integrated Primary Care Information) database. The study population included all subjects ≥50 years who were registered in the IPCI database from 1996 to 2011, and who did not have diabetes mellitus, heart failure, severely decreased kidney function, liver failure and/or malignancy. Cases were defined as subjects with a hospital admission with dehydration. Controls were matched on practice, year of birth, sex and date of onset.

Results

A total of 1,246 cases of hospital admission with dehydration were identified. We found a significant association with proton pump inhibitors (OR 1.86; 95CI% 1.54-2.26), non-steroidal anti-inflammatory drugs (OR 1.52; 95%CI 1.15-2.01), opioids (OR 2.06; 95%CI 1.40-3.03) and benzodiazepines (OR 1.57; 95% CI 1.26-1.96) after adjustment for confounding factors.

Conclusions

This study shows a significant association between hospital admission with dehydration and use of proton pump inhibitors, non-steroidal anti-inflammatory drugs, opioids and benzodiazepines. Additional studies are warranted to confirm these results and to elucidate the pathophysiological mechanism.

INTRODUCTION

Background

Acute kidney injury occurs with an incidence of approximately 384 per 100,000 person-years in the general population and is more frequent in elderly aged 80 years and over [1]. After sepsis which causes 47% of cases of acute kidney injury, dehydration - or more appropriately hypovolemia - is with 32% the second most frequent precipitating risk factor for this outcome [2]. Hypovolemia might result from gastrointestinal fluid loss (vomiting, diarrhea, bleeding, external drainage), renal fluid loss (diuretics, osmotic diuresis, salt-wasting nephropathies, hypoaldosteronism), skin fluid loss (sweat, burns), or third-space sequestration. Medication has been studied in relation to direct acute nephrotoxicity but hardly on an indirect cause such as dehydration. Clinically relevant hypovolemia is most likely to occur when water is lost together with sodium. Numerous studies have investigated the role of medicines in relation to hyponatremia [3]. Only few studies [4-6] have investigated drug-induced dehydration/hypovolemia, possibly due to the fact that information from both first and second line care is needed.

Objective

Therefore, the objective of this study was to investigate drug use and the risk of hospital admission with a diagnosis of clinical dehydration , using prospectively gathered electronic health care records from a community-dwelling adult population.

METHODS

Design overview

We performed a population-based case–control study, nested in a cohort of patients who were registered in the Dutch Integrated Primary Care Information (IPCI) general practice research database, to investigate drug use and the risk of dehydration. The Scientific and Ethical Advisory Board of IPCI project approved the study.

Setting

All data were retrieved from the IPCI project, a longitudinal observational, dynamic database, which contains the electronic medical records of a group of more than 600 general practitioners in the Netherlands. In the Dutch health care system, the general practitioner plays a pivotal role and acts as a gatekeeper of all medical care and information. Almost all inhabitants of the Netherlands are registered with a general practitioner, independently of their health status. Details of the IPCI database have been described elsewhere [7, 8]. Briefly, the database contains the complete electronic medical records

of approximately 1,000,000 participants. These records contain anonymous longitudinal data on demographics, symptoms and diagnoses (coded and in free text), referrals, laboratory findings, hospitalizations, discharge letters, and drug prescriptions (inclusive indication and dosage regimen). To maximize completeness of the data, general practitioners participating in the IPCI project are not allowed to maintain a system of paper-based records besides the electronic medical records. The system complies with European Union guidelines on the use of data for medical research and has been proven valid for pharmaco-epidemiologic studies [8].

Study population

The study population comprised all subjects from the IPCI database who were ≥50 years during the study period (January 1st, 1996 to March 1st, 2011) and were at least one year registered in the database before the study period. Subjects with heart failure, liver failure, a severely decreased kidney function (glomerular filtration rate < 30 milliliter per minute), diabetes mellitus and/or malignancy are more likely to receive medication prescriptions from the specialist, which are not necessarily captured in the database. Therefore, these subjects were censored from the first date indicating such conditions. All remaining subjects were followed until hospitalization with dehydration, death, transfer out of practice, last data draw-down, or end of the study period, whichever came first.

Cases and controls

Cases were all subjects who were admitted to the hospital with a clinical diagnosis of dehydration at admission. All cases were validated through manual review of the electronic available discharge letters while being blinded to the exposure. We excluded all hospital admissions with dehydration, secondary to gastrointestinal bleeding, because hypovolemia due to non-steroidal anti-inflammatory drugs induced peptic ulcer disease is already well recognized. For every case, all available controls were selected from the community dwelling population by incidence density sampling, matched on practice, sex and year of birth.

Exposure assessment

We had a number of a priori candidates for dehydration. We investigated exposure from the separate major classes of blood pressure lowering medicines, which might increase the probability of hospitalization with dehydration due to an additional blood pressure lowering effect. These included beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers and diuretics (low-ceiling thiazides diuretics, low-ceiling non-thiazide diuretics, high-ceiling diuretics and potassium-sparing diuretics). Because hypovolemia might be more pronounced

with combined losses of water and salt, we also investigated all first-line medication that might cause hyponatremia based on a literature review [3, 9, 10] at 3rd level (pharmacological subgroup) of the anatomical therapeutic chemical (ATC) coding system [11]: proton pump inhibitors (PPI), amiodarone, lorcainide, propafenone, bromocriptine, vasopressin and analogues, thyroid preparations, mineralocorticoids, trimethoprim-sulfamethoxazole, ciprofloxacin, cefoperazone, sulbactam, rifabutin, azithromycin, carboxamide derivatives, valproic acid, lamotrigine, phenothiazines, butyrophenone derivatives, benzodiazepines and anti-depressants. Medication exposure was obtained from the prescription files. Fixed dose combinations were recoded into their individual active pharmaceutical ingredients. The duration of treatment (prescription length) was calculated by dividing the prescribed number of units by the dosing regimen. The dose per day was obtained from the last prescription prior to the index date and calculated from the prescribed strength and the dosing regimen. Current use was defined as a date of onset within the prescription length of a particular medicine. Past use was defined as prior exposure not covering the date of onset. If a patient did not use a particular medication during the study period this was defined as never use.

Co-variables

We considered the following co-variables: age, sex, and date of onset (matching variables) and medical conditions that might cause dehydration such as Addison's disease [12], alcoholism [13], cerebrovascular disease (transient ischemic attack, stroke) [14] , diabetes insipidus [15], hypothyroidism [16], ischemic heart disease (angina pectoris and myocardial infarction) [17], Parkinson's disease [18] and pulmonary obstructive disease (asthma and chronic obstructive pulmonary disease) [19] .

Statistical Analysis

We compared characteristics of cases and controls by using conditional logistic regression analysis. We only investigated associations with medicines for which we had at least 10 exposed cases. Multivariable modeling in a single model with all exposure categories and co-variables to control for is technically not feasible. In addition it is not necessary to control a single exposure for all other concomitant medications and comorbidities, because many will not confound the exposure-outcome relation for that particular association. Therefore, we investigated one by one which medicines confounded the exposure-outcome association (bivariable model including exposure and possible confounding factor). If there was a relevant degree of confounding, defined as a change in estimate by ≥10% of the exposure-outcome association we included the confounder in the adjusted model. Results of analysis at individual medication level are included as sensitivity analyses. We conducted all conditional logistic regression analyses with SAS 9.2, (SAS Institute Inc., Cary, NC, USA). We set the level of significance for all statisti-

cal tests at a P-value less than 0.05. This level is not yet corrected for multiple testing. We consider that the reader should divide the p-value by the number of tested drug categories (n=16) to account for this.

RESULTS

The source population consisted of 1,016,648 subjects with active follow-up. Of these subjects, 291,745 were included in the study population based on the inclusion and exclusion criteria as described above. A total of 1,246 subjects were hospitalized with dehydration. These could be matched on practice, sex, year of birth and index date to 12,026 controls. The characteristics of cases and controls are provided in table 1. Despite matching on age and sex, there were differences on these variables between cases and controls, due to variation in the number of available controls in higher age-groups but this is accounted for by conditional logistic regression.

Sample size was insufficient (<10 cases exposed) to study amiodarone, lorcainide, propafenone, bromocriptine, vasopressin and analogues, mineralocorticoids, trimethoprim-sulfamethoxazole, ciprofloxacin, cefoperazone, sulbactam, rifabutin, azithromycin, carboxamide derivatives, valproic acid, lamotrigine, phenothiazines. The majority of medications with sufficient exposure were significantly associated with hospital admission with dehydration relative to no current use (including past and never use), including a correction for multiple testing, except for beta blockers, calcium channel blockers, angiotensin receptor blockers, thiazide diuretics and thyroid hormone preparations (table 2, model 1).

After correction for confounding by indication with past use as reference and correction for multiple testing, the use of non-thiazide low-ceiling diuretics, high-ceiling diuretics, potassium-sparing diuretics, angiotensin converting enzyme inhibitors,

Table 1 Characteristics of the study population

	Cases (n=1,246)(%)	Controls (n=12,026)(%)
Female gender	702 (56.3)	7,002 (58,2)
Age years, mean (SD)	75.9 (11.8)	67.5 (11.0)
Comorbidities		
Alcoholism	50 (4.0)	154 (1.3)
Asthma/COPD	236 (18.9)	1,277 (10.6)
Heart disease (Myocardial infarction, Angina pectoris)	253 (20.3)	1,137 (9.5)
Hypothyroidism	38 (3.1)	362 (3.0)
Ischemic stroke	183 (14.7)	635 (5.3)

Table 2 Association between medicines and between hospital admission with dehydration

	exposed cases n=1,246	exposed controls n=12,026	Model 1			Model 2			Model 3			
			OR	p-value	95%CI	OR	p-value	95%CI	OR	p-value	95%CI	
Proton pump inhibitor	**274**	**1,105**	**2.58**	**<0.001**	**(2.18 - 3.05)**	**1.86**	**<0.001**	**(1.54 - 2.26)**	**1.86**	**<0.001**	**(1.54 - 2.26)**	a
Omeprazole	143	610	2.39	<0.001	(1.92 - 2.97)	1.77	<0.001	(1.39 - 2.25)	1.77	<0.001	(1.39 - 2.25)	a
Pantoprazole	93	291	2.64	<0.001	(2 - 3.48)	1.68	0.002	(1.22 - 2.31)	1.68	0.002	(1.22 - 2.31)	a
Esomeprazole	35	132	2.61	<0.001	(1.73 - 3.95)	1.50	0.117	(0.90 - 2.49)	1.50	0.117	(0.90 - 2.49)	a
thiazide diuretics	**143**	**1,189**	**1.00**	**0.971**	**(0.82 - 1.23)**	**0.69**	**0.004**	**(0.54 - 0.89)**	**0.60**	**<0.001**	**(0.47 - 0.78)**	**b**
hydrochlorothiazide	143	1,189	1.00	0.971	(0.82 - 1.23)	0.69	0.004	(0.54 - 0.89)	0.60	<0.001	(0.47 - 0.78)	b
non-thiazide low-ceiling diuretics	**35**	**147**	**1.79**	**0.006**	**(1.18 - 2.71)**	**1.42**	**0.173**	**(0.86 - 2.36)**	**1.42**	**0.173**	**(0.86 - 2.36)**	**a**
chlorthalidone	26	111	1.86	0.010	(1.16 - 2.98)	1.38	0.258	(0.79 - 2.43)	1.38	0.258	(0.79 - 2.43)	a
high-ceiling diuretics	**135**	**249**	**3.19**	**<0.001**	**(2.46 - 4.14)**	**1.49**	**0.011**	**(1.09 - 2.02)**	**1.49**	**0.011**	**(1.09 - 2.02)**	**a**
furosemide	103	205	2.91	<0.001	(2.17 - 3.9)	1.29	0.140	(0.92 - 1.82)	1.29	0.140	(0.92 - 1.82)	a
bumetanide	34	45	4.19	<0.001	(2.51 - 6.99)	1.92	0.046	(1.01 - 3.65)	1.65	0.128	(0.87 - 3.16)	b

Table 2 Association between medicines and between hospital admission with dehydration (continued)

	exposed cases n=1,246	exposed controls n=12,026	Model 1			Model 2			Model 3			
			OR	p-value	95%CI	OR	p-value	95%CI	OR	p-value	95%CI	
potassium-sparing diuretics	**97**	**331**	**2.10**	**<0.001**	**(1.61 - 2.74)**	**1.15**	**0.388**	**(0.83 - 1.60)**	**1.01**	**0.964**	**(0.72 - 1.41)**	**c**
spironolactone	50	66	5.24	<0.001	(3.44 - 7.97)	1.67	0.078	(0.94 - 2.94)	1.16	0.622	(0.65 - 2.08)	d
amiloride	14	72	1.44	0.245	(0.78 - 2.64)	1.32	0.473	(0.62 - 2.81)	1.32	0.473	(0.62 - 2.81)	a
triamterene	33	191	1.12	0.595	(0.73 - 1.72)	0.66	0.093	(0.40 - 1.07)	0.66	0.093	(0.40 - 1.07)	a
Beta blockers	**239**	**1,820**	**1.10**	**0.268**	**(0.93 - 1.3)**	**0.78**	**0.017**	**(0.64 - 0.96)**	**0.78**	**0.017**	**(0.64 - 0.96)**	**a**
Propranolol	15	64	1.87	0.050	(1 - 3.49)	2.17	0.042	(1.03 - 4.59)	2.17	0.042	(1.03 - 4.59)	a
Sotalol	32	157	1.57	0.037	(1.03 - 2.39)	1.14	0.625	(0.67 - 1.94)	1.14	0.625	(0.67 - 1.94)	a
Metoprolol	138	1,067	1.05	0.639	(0.85 - 1.29)	0.78	0.063	(0.60 - 1.01)	0.78	0.063	(0.60 - 1.01)	a
Atenolol	23	262	0.75	0.233	(0.48 - 1.2)	0.63	0.084	(0.38 - 1.06)	0.61	0.068	(0.36 – 1.04	m
Bisoprolol	17	191	0.86	0.581	(0.51 - 1.46)	0.50	0.033	(0.26 - 0.94)	0.44	0.016	(0.23 – 0.86)	c
Carvedilol	10	21	3.02	0.016	(1.23 - 7.39)	1.31	0.654	(0.40 - 4.24)	1.48	0.520	(0.45 – 4.82)	j
Calcium channel blockers	**103**	**717**	**1.10**	**0.449**	**(0.86 - 1.39)**	**0.72**	**0.022**	**(0.54 - 0.95)**	**0.72**	**0.022**	**(0.54 - 0.95)**	**a**
Amlodipine	44	363	0.92	0.627	(0.65 - 1.3)	0.54	0.004	(0.35 - 0.82)	0.54	0.004	(0.35 - 0.82)	a

Table 2 Association between medicines and between hospital admission with dehydration (continued)

	exposed cases n=1,246	exposed controls n=12,026	Model 1			Model 2			Model 3			
			OR	p-value	95%CI	OR	p-value	95%CI	OR	p-value	95%CI	
Nifedipine	22	154	1.12	0.639	(0.69 - 1.82)	0.73	0.270	(0.41 - 1.28)	0.73	0.270	(0.41 - 1.28)	a
Diltiazem	22	78	2.25	0.003	(1.32 - 3.83)	1.11	0.751	(0.59 - 2.10)	1.11	0.751	(0.59 - 2.10)	a
Angiotensin converting enzyme inhibitors	**177**	**1,037**	**1.41**	**<0.001**	**(1.16 - 1.7)**	**0.82**	**0.098**	**(0.64 - 1.04)**	**0.82**	**0.098**	**(0.64 - 1.04)**	**a**
Captopril	12	74	1.14	0.715	(0.57 - 2.27)	0.60	0.217	(0.27 - 1.35)	0.66	0.327	(0.29 – 1.51)	n
Enalapril	55	431	0.99	0.940	(0.72 - 1.35)	0.55	0.002	(0.38 - 0.81)	0.55	0.002	(0.38 - 0.81)	a
Lisinopril	35	163	2.39	<0.001	(1.6 - 3.57)	1.46	0.164	(0.86 - 2.49)	1.46	0.164	(0.86 - 2.49)	a
Perindopril	50	209	1.77	0.001	(1.24 - 2.51)	0.80	0.376	(0.49 - 1.31)	0.59	0.043	(0.35 – 0.64)	d
Angiotensin receptor blockers	**97**	**783**	**1.06**	**0.643**	**(0.83 - 1.34)**	**0.60**	**0.002**	**(0.43 - 0.82)**	**0.60**	**0.002**	**(0.43 - 0.82)**	**a**
Losartan	29	289	0.80	0.296	(0.52 - 1.22)	0.40	0.001	(0.24 - 0.68)	0.40	0.001	(0.24 - 0.68)	a
Valsartan	25	160	1.54	0.058	(0.99 - 2.41)	1.92	0.091	(0.90 - 4.10)	1.92	0.091	(0.90 - 4.10)	a
Irbesartan	16	167	0.83	0.518	(0.48 - 1.45)	0.66	0.278	(0.31 - 1.40)	0.66	0.278	(0.31 - 1.40)	a
Candesartan	15	99	1.10	0.752	(0.6 - 2.02)	0.40	0.029	(0.18 - 0.91)	0.35	0.012	(0.15 – 0.79)	e
Telmisartan	10	44	2.25	0.034	(1.06 - 4.77)	1.55	0.451	(0.49 - 4.87)	1.72	0.356	(0.54 – 5.43)	o

Table 2 Association between medicines and between hospital admission with dehydration (continued)

	exposed cases n=1,246	exposed controls n=12,026	Model 1			Model 2			Model 3			
			OR	p-value	95%CI	OR	p-value	95%CI	OR	p-value	95%CI	
thyroid hormone preparations	**37**	**344**	**1.05**	**0.781**	**(0.73 - 1.53)**	**0.60**	**0.092**	**(0.33 - 1.09)**	**0.60**	**0.092**	**(0.33 - 1.09)**	**a**
Levothyroxine	37	343	1.06	0.770	(0.73 - 1.54)	0.60	0.092	(0.33 - 1.09)	0.60	0.092	(0.33 - 1.09)	a
non-steroidal anti-inflammatory drugs	**82**	**366**	**2.16**	**<0.001**	**(1.65 - 2.82)**	**2.01**	**<0.001**	**(1.53 - 2.63)**	**1.52**	**0.004**	**(1.15 - 2.01)**	**e**
diclofenac	43	172	2.15	<0.001	(1.47 - 3.14)	1.92	0.001	(1.30 - 2.82)	1.45	0.065	(0.98 - 2.15)	e
naproxen	10	28	3.19	0.003	(1.48 - 6.85)	2.76	0.010	(1.27 - 5.99)	2.35	0.032	(1.08 - 5.12)	e
opioids	**51**	**133**	**3.86**	**<0.001**	**(2.68 - 5.54)**	**2.40**	**<0.001**	**(1.64 - 3.5)**	**2.06**	**<0.001**	**(1.40 - 3.03)**	**e**
morphine	11	5	16.91	<0.001	(5.56 - 51.4)	7.62	0.001	(2.3 - 25.23)	6.02	0.004	(1.73 - 20.94)	f
oxycodon	11	12	8.47	<0.001	(3.35 - 21.4)	4.19	0.007	(0.00 - 4.19)	3.80	0.011	(1.37 - 11.60)	g
codeine	10	30	3.45	0.003	(1.52 - 7.86)	2.29	0.054	(0.99 - 5.34)	2.01	0.111	(0.85 - 4.73)	h
tramadol	15	56	2.62	0.002	(1.43 - 4.78)	1.36	0.330	(0.73 - 2.55)	0.53	<0.001	(0.44 - 0.64)	d
anti-parkinson drugs	**20**	**55**	**2.51**	**0.002**	**(1.41 - 4.47)**	**0.81**	**0.555**	**(0 - 0.81)**	**0.74**	**0.424**	**(0.35 -1.56)**	**i**
Butyrophenone derivatives	**21**	**23**	**4.00**	**<0.001**	**(2.03 - 7.88)**	**1.57**	**0.263**	**(0.71 - 3.45)**	**1.74**	**0.175**	**(0.78 - 3.85)**	j

Table 2 Association between medicines and between hospital admission with dehydration (continued)

	exposed cases n=1,246	exposed controls n=12,026	Model 1			Model 2			Model 3			
			OR	p-value	95%CI	OR	p-value	95%CI	OR	p-value	95%CI	
haloperidol	11	12	3.85	0.005	(1.5 - 9.89)	1.21	0.723	(0.43 - 3.42)	0.32	<0.001	(0.20 - 0.50)	j
pipamperone	10	11	4.09	0.004	(1.56 - 10.75)	3.18	0.086	(0.85 - 11.88)	3.14	0.098	(0.81 - 12.19)	k
benzodiazepines	**153**	**695**	**1.99**	**<0.001**	**(1.61 - 2.44)**	**1.57**	**<0.001**	**(1.26 - 1.96)**	**1.57**	**<0.001**	**(1.26 - 1.96)**	**a**
diazepam	10	77	1.07	0.859	(0.52 - 2.21)	0.74	0.418	(0.35 - 1.55)	0.74	0.418	(0.35 - 1.55)	a
oxazepam	52	225	2.13	<0.001	(1.52 - 2.98)	1.65	0.006	(1.16 - 2.36)	1.65	0.006	(1.16 - 2.36)	a
nitrazepam	12	43	2.22	0.023	(1.12 - 4.4)	1.38	0.401	(0.65 - 2.93)	1.38	0.401	(0.65 - 2.93)	a
temazepam	55	191	2.00	<0.001	(1.41 - 2.85)	1.23	0.276	(0.85 - 1.77)	1.23	0.276	(0.85 - 1.77)	a
antidepressants	**87**	**535**	**1.89**	**<0.001**	**(1.46 - 2.44)**	**1.25**	**0.139**	**(0.93 - 1.68)**	**1.25**	**0.139**	**(0.93 - 1.68)**	**a**
amitryptiline	13	83	1.73	0.091	(0.92 - 3.25)	0.92	0.821	(0.47 - 1.82)	0.81	0.551	(0.41 - 1.61)	l
paroxetine	24	143	1.97	0.005	(1.23 - 3.14)	1.28	0.359	(0.75 - 2.19)	1.28	0.359	(0.75 - 2.19)	a
mirtazapine	14	34	3.43	<0.001	(1.72 - 6.85)	2.02	0.097	(0.88 - 4.61)	2.02	0.097	(0.88 - 4.61)	a

Model 1 = Univariable model; Model 2 = Univariable model with past use as reference; Model 3 = Multivariable model with past use as reference and adjustment for confounding, as:

a = not indicated; b = potassium-sparing diuretics; c = high-ceiling diuretics; d = proton pump inhibitors and high ceiling diuretics; e = proton pump inhibitors; f = proton pump inhibitors, high-ceiling diuretics, potassium-sparing diuretics and COPD; g = proton pump inhibitors, COPD; h = high-ceiling diuretics, benzodiazepines, antidepressants; i = COPD, Parkinson (disease code); j = COPD; k = high-ceiling diuretics, opioids, heart disease

l = opioids; m = low-ceiling non-thiazide diuretics; n = cerebrovascular disease; o = benzodiazepines; highlighted in grey: significant findings after correction for multiple testing and confounding by indication

anti-Parkinson drugs, butyrophenone derivatives, and antidepressants was no longer significantly associated with hospital admission due to dehydration (table 2, model 2).

4 categories of medicines: proton pump inhibitors (OR 1.86; 95CI% 1.54-2.26), non-steroidal anti-inflammatory drugs (OR 1.52; 95%CI 1.15-2.01), opioids (OR 2.06; 95%CI 1.40-3.03) and benzodiazepines (OR 1.57; 1.26-1.96), were significantly associated with hospital admission with dehydration in all models, also after adjustment for confounding factors (table 2, model 3).

DISCUSSION

There are four interesting findings in this study. First, we found a significant association between hospital admission with dehydration and the use of proton pump inhibitors (PPIs). This association remained significant after adjustment for confounding by indication and was consistent among individual PPIs for which we had a sufficient number of exposed cases. Until now, few cases detailing PPI induced hyponatremia have been reported [3]. However, the underlying pathophysiological mechanism of PPI induced hyponatremia is not entirely clear. It might be a syndrome of inappropriate anti-diuresis [20], but also excessive loss of urinary sodium has been reported [21]. Also the increased risk of diarrhea due to microscopic colitis or community associated Clostridium difficile infection with PPIs might explain the observed association [22-25]. Second, we found a significant association between hospital admission with dehydration and the use of non-steroidal anti-inflammatory drugs (NSAIDs), which was similar between the individual NSAIDs with a sufficient number of exposed cases. This might be explained by the fact that NSAIDs impair the vasopressin induced upregulation of aquaporin-2 expression in response to dehydration [26, 27]. NSAIDs are also associated with acute diarrhea [28] and microscopic colitis [29, 30]. Third, we found a significantly increased risk of hospital admission with dehydration and the use of benzodiazepines. Because of the localization of peripheral benzodiazepine receptors in the kidney, a role in water and electrolyte balance was suggested earlier [31-34], contributing to an increased sodium excretion [35-42]. Fourth, we found we found a significantly increased risk of hospital admission with dehydration and the use of opioids. Central opiatergic stimulation has been shown to reduce water intake provoked by the activation of central angiotensinergic pathways [43, 44]. Furthermore, dehydration is a known adverse event for opioids [45, 46].

We found no significant association with thiazide diuretics, non-thiazide low-ceiling diuretics, beta blockers, calcium channel blockers, angiotensin receptor blockers and thyroid hormone preparations relative to no use after correction for multiple testing. This might be due to the exclusion of several risk factors for dehydration such as heart failure, diabetes mellitus or a severely decreased kidney function.

If correction for multiple testing is neglected high-ceiling diuretics appear to increase the risk of hospitalization with dehydration which is consistent with the results of another study [6]. The protective effect that is suggested by the comparison of current use of thiazide diuretics and angiotensin receptor blockers relative to their past use is due to a higher risk with past use. However there is no increased risk relative to never use (data not shown). Medication discontinuation for reasons related to hypovolemia, such as hypotension, might underlie the increased risk with past use. High-ceiling and potassium diuretics, anti-parkinson medication, butyrophenone derivatives, and antidepressants showed a significantly increased risk of hospital admission with dehydration relative to no use, but not relative to past use. This might be related to insufficient sample size. An effect of underlying patient comorbidities with a limited drug attributable risk is also possible. In spite of a non-significant association relative to past use, their use should alert physicians of a high risk patient.

During the analysis matching was performed for practice, sex, year of birth and index date. For each group of medication we investigated confounding by concomitant medication and underlying disease including alcoholism, asthma/COPD, heart disease, and ischemic stroke as well as confounding by indication through analysis with past use as a reference. We limited confounding from heart failure, liver failure, a severely decreased kidney function, diabetes mellitus and/or malignancy by means of exclusion. Despite before mentioned strengths, the possibility of residual confounding cannot be fully excluded as with any other observational study. We do not have urine sodium measurements to elaborate on a specific pathophysiological mechanism. We do not have information on over the counter medication, which might include some exposure to NSAIDs (only low dose diclofenac) and PPIs. Finally, while interpreting results with past use acting as a reference it should be noted that characteristics of patients who discontinue medication might differ from those with current use either due to health improvement or health deterioration demanding the use of different medication.

PERSPECTIVES

In conclusion, our results show an increased risk of between hospital admission with dehydration with current use of PPIs, NSAIDs, benzodiazepines and opioids. The increased risk of hospital admission with dehydration with current of high-ceiling and potassium-sparing diuretics, anti-Parkinson drugs, butyrophenone derivatives, and antidepressants might at least partly be explained by comorbidities.

ACKNOWLEDGEMENTS

We thank Marcel de Wilde, Kris Sieradzan and Mees Mosseveld for the collection of data and maintenance of the IPCI database.

SOURCES OF FUNDING

None

CONFLICTS OF INTEREST

None

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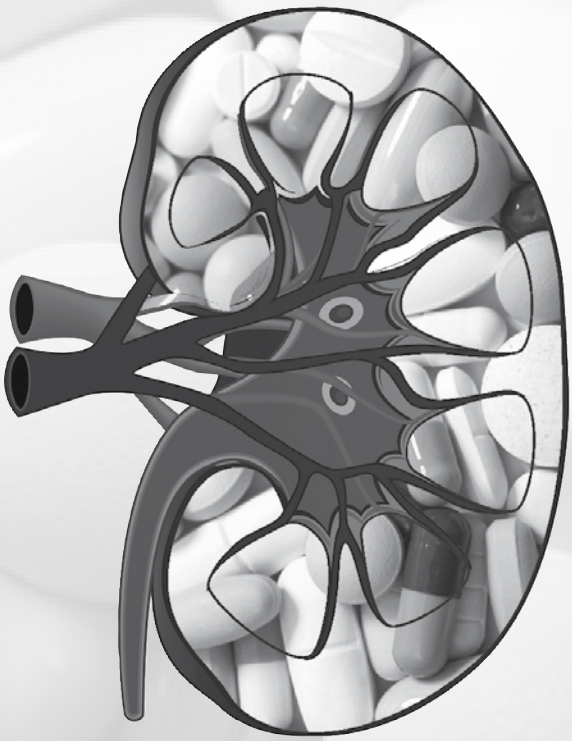
Chapter 5

Adherence to renal function monitoring guidelines



Chapter 5.1

Adherence to renal function monitoring guidelines in patients starting antihypertensive therapy with diuretics and RAAS inhibitors

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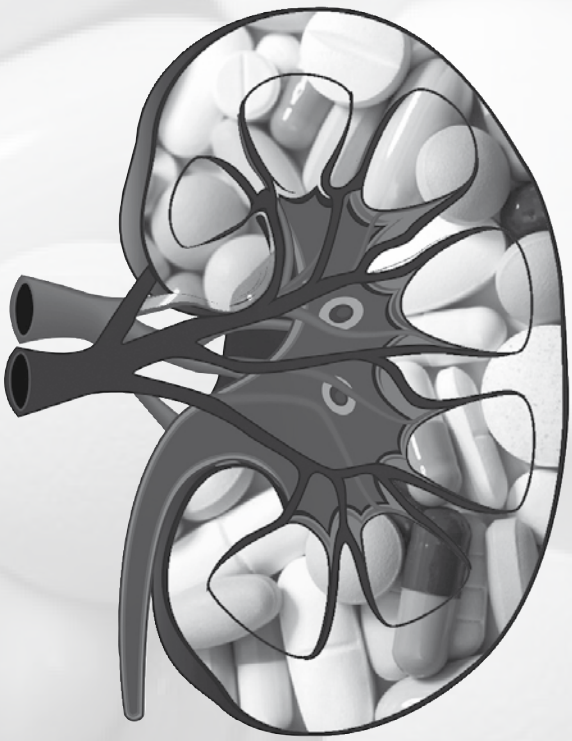
Adherence to Renal Function Monitoring Guidelines in patients starting Antihypertensive Therapy with Diuretics and RAAS Inhibitors: a Retrospective Cohort Study

Drug Saf. 2014 May;37(5):369-77.



ABSTRACT

Background

Acute kidney injury (AKI) might complicate antihypertensive therapy. In The Netherlands, general practitioner clinical practice guidelines provide clear recommendations on monitoring of renal function to minimize this risk. Our objective was to investigate how day-to-day clinical practice corresponds to the guidelines.

Methods

We conducted a retrospective cohort study in a dynamic population, using data on >9,000 adults that was retrieved from the Integrated Primary Care Information database. We investigated whether serum creatinine (SCR) was measured within 30 and 365 days after the start of (combined) use of a diuretic, an angiotensin-converting enzyme inhibitor, and/or angiotensin receptor blocker. We also investigated the association between calendar year, sex, type of therapy, risk factors for AKI and practice and SCR measurement.

Results

Of 6,593 subjects who met the study criteria for single drug therapy, SCR was measured in 1,233 subjects within 30 days and in 3,896 subjects within 365 days. For combined drug therapy recipients (n = 2,497), these were 545 and 1,687, respectively. Associated cumulative probabilities were 19 % and 66 % with single drug therapy, and 22 % and 74 % with combined drug therapy. Significant differences were observed between practices. SCR measurement was associated with other characteristics, except for sex. Within 365 days, SCR increased >30 % of baseline in 103 subjects (1.6 %) after the start of single drug therapy, and in 85 (3.4 %) subjects who initiated combined drug therapy. In the majority (>70 %) of these subjects, this did not result in subsequent monitoring or adjustment of antihypertensive treatment.

Conclusions

Results from this study suggest that, on average, renal function is not monitored as strictly as recommended by relevant clinical practice guidelines.

BACKGROUND

Lowering blood pressure reduces progression of Chronic Kidney Disease (CKD) [1], but may also be associated with an increased risk of acute kidney injury (AKI) resulting from a disturbed auto-regulation of the renin-angiotensin-aldosterone system caused by angiotensin-converting-enzyme inhibitors (ACEIs) [4] or angiotensin receptor blockers (ARBs) [5], or due to volume depletion caused by diuretics [2]. This is illustrated by results from the CHARM trial, where doubling of serum creatinine (SCR) and study medication discontinuation, due to SCR elevation, occurred significantly more often in the ARB treated group than in the placebo group [3]. Certain medication combinations might be more harmful, as illustrated by the ONTARGET trial where combined drug therapy with an ACEI and an ARB increased the risk of renal impairment without an increase in benefit [4]. Another recent study found a 31% higher risk of AKI with a triple medication combination, consisting of non-steroidal anti-inflammatory drugs (NSAIDs) in combination with a diuretic plus an ACEI or ARB. The highest risk was observed in the first 30 days of use, and a trend toward an increased risk was observed for double medication combinations, including a NSAID in combination with a diuretic, ACEI, or ARB [5].

Risk minimization through monitoring of renal function is recommended in clinical guidelines, with subtle differences in timing, duration and frequency of monitoring as well as with regard to changes of renal function that are considered as acceptable. The National Institute for Health and Clinical Excellence (NICE) clinical guideline on CKD recommends monitoring of renal function through serum creatinine (SCR) between 1 to 2 weeks after initiation or dose increase of ACEIs or ARBs. A ≤25% decrease in estimated Glomerular Filtration Rate (eGFR) or ≤30% increase in SCR relative to baseline is accepted [6]. Dutch GP Clinical Guidelines are stricter, and recommendations also relate to diuretics and not only recommend SCR measurements upon treatment initiation but also SCR measurements between 3 and 6 months after introduction or change of therapy and yearly thereafter [7].

Monitoring of renal function in relation to antihypertensive therapy has been investigated in a number of studies [8-17], but data on monitoring during the first 30 days of use - the period with highest risk of AKI - as well as data on the incidence of abnormal renal function during monitoring are limited. Also, possible differences by GP practice have not been evaluated thus far.

The objective of this study was to investigate whether monitoring of renal function, during initiation of diuretics, ACEIs or ARBs by general practitioners (GPs) is in line with the recommendations, as issued by the Dutch College of General Practitioners [7].

METHODS

Study design and Setting

We performed a retrospective cohort study, using data retrieved from the Integrated Primary Care Information (IPCI) project, a longitudinal observational, dynamic database which contains the electronic medical records of a group of more than 600 GPs in the Netherlands. In the Dutch health care system, the GP plays a pivotal role and acts as a gatekeeper of medical care and information. Almost all inhabitants of the Netherlands are registered with a GP, independent of their health status. Details of the IPCI database have been described elsewhere [18, 19]. Briefly, the database contains the complete electronic medical records of approximately 1,000,000 subjects. These records contain anonymous longitudinal data on demographics, symptoms and diagnoses [coded in International Classification of Primary Care (ICPC) codes, and in free text], referrals, laboratory findings, hospitalizations, discharge letters, and medication prescriptions (including indication and dosage regimen). To maximize completeness of the data, GPs participating in the IPCI project are not allowed to maintain a system of paper-based records besides the electronic medical records. The system complies with European Union guidelines on the use of data for medical research and has been proven valid for pharmaco-epidemiologic studies [19]. The scientific and ethical advisory board of the IPCI project approved the study.

Participants

The source population comprised all individuals, who were registered with their GP for at least 365 days. The study period started on January 1st, 2005 and ended on December 31th, 2011. Subjects were followed until death, transfer out of practice, last data drawdown, or end of the study period, whichever came first.

Study population

From the source population two exposure cohorts were defined, i.e. a single therapy cohort and a combined therapy cohort. The single therapy cohort consisted of patients aged ≥40 years who received a new (incident) medication prescription with a chemical substance from one of the Anatomical Therapeutic Chemical (ATC) classes "C03" (diuretics), "C09A" (ACEI) or "C09C" (ARB) as single therapy. Incident use meant that the patient had not used any of these ATC classes in the year before. The combined therapy cohort consisted of subjects aged ≥40 years who were already exposed to one of these ATC classes and started new use of a drug from another ATC class, as mentioned above during follow-up.

The first date of medication prescription that led to inclusion of a subject in the study population of single drug therapy or combined drug therapy is referred to as

"index date". For both exposure cohorts the new medication prescription had to be refilled at least once within 90 days of the first prescription to avoid misclassification of incidental use as chronic therapy. For combined drug therapy the other medication(s) to which a subject was already exposed had to be refilled at least once during the first period of exposure to the new medication to exclude a switch in therapy.

In the Dutch health care system, GP's might continue therapy that is initiated by a specialist. For these patients, if monitoring of renal function is performed by the specialist, SCR measurements might be missing in the database. To include only patients for whom the therapy was initiated by the GP, we excluded patients with heart failure prior to the index date based on disease codes "K77" (heart failure), " K82" (cor pulmonale) and free text "heart failure" and "cardiac decompensation" in the medical record. In addition, subjects were excluded who met the criteria for referral to the nephrologist prior to the index date, being macro-albuminuria in combination with any eGFR, micro-albuminuria with an eGFR <30 ml/min/1.73m2 in subjects <65 years, or eGFR <45 ml/min/1.73m2 in subjects ≥65 years) or without information on eGFR within the year prior to the index date. And finally, patients were excluded in those cases where the indication for antihypertensive therapy at the index date was missing or different from hypertension, based on disease codes."K85" (Elevated blood pressure), "K86" (Hypertension uncomplicated), or "K87" (Hypertension complicated).

Outcome

The outcome of this study was the presence of a SCR measurement performed by the GP within 30 days, and within 365 days following the index date. We also investigated how SCR evolved during the 365 days following index date and whether a SCR increase >30% of baseline resulted in subsequent monitoring or adjustment of antihypertensive treatment.

Co-variables

In this study, we studied the influence of the following variables on renal function monitoring after index date: calendar year; age; sex; concomitant use of NSAIDs and/or high dose (>300mg per day) of acetylsalicylic acid (ASA); diabetes mellitus (DM), based on prescription from the ATC class "A10" (Drugs used in diabetes) [20, 21], and eGFR, which was obtained from the last available SCR measurement within the one year prior to index-date using the equation published by the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration [22]. We used eGFR categories as provided by the Kidney Disease Improving Global Outcomes (KDIGO) foundation: G1 "normal or high" ≥90, G2 "mildly decreased" 60-89, G3a "mildly to moderately decreased" 45-59, G3b "moderately to severely decreased" 30-44 ml/min/1.73m2 [23].

Statistical analysis

For univariable analyses we calculated cumulative survival probabilities. We used Cox proportional hazards regression analysis for multivariable analyses, using GP practice as a stratification variable. We tested for interaction between baseline characteristics and included interaction terms with a P-value of less than 0.05. We constructed survival plots and log(-log(survival)) versus log(time) plots for each baseline co-variable to investigate deviation from proportionality. If indicated by these plots, hazard rates varying with time were modelled. Analyses that were performed to investigate GP practice differences only included GP practice as a multi-level categorical variable. Baseline characteristics of single and combined drug therapy were compared with Student's t-test and Pearson $\chi 2$-tests. All analyses were conducted with SAS 9.2, (SAS Institute Inc., Cary, NC, USA).

RESULTS

The source population consisted of 984,047 subjects with a valid history of at least 365 days in the IPCI database. After application of inclusion and exclusion criteria 6,593 subjects were enclosed in the single drug study population and 2,497 subjects in the combined drug study population. In comparison to single drug therapy, combined drug therapy included older subjects (mean age 64.4 vs. 61.9 years, p-value<0.001), a larger proportion of females (53.7% vs. 51.1%, p-value=0.032), and more subjects with diabetes mellitus (20.4% vs. 17.8%, p-value=0.004), whereas eGFR (78.0 vs. 77.8 ml/min/1.73m2, p-value 0.559) and the proportion of NSAIDs at start of therapy (0.4% vs. 0.5%) were comparable between groups. Detailed baseline characteristics are described in table 1.

Table 1 Study cohort characteristics

Characteristics	Single drug therapy (N=6,593)		Combined drug therapy (N=2,497)	
	n	(%)	n	(%)
Males	3,222	(49)	1,157	(46)
Age category				
• 40-49	1,086	(16)	288	(12)
• 50-59	1,861	(28)	603	(24)
• 60-69	2,032	(31)	788	(32)
• 70-79	1,213	(18)	590	(24)
• 80+	401	(6)	228	(9)
Calendar year at start of treatment				
• 2005	38	(1)	8	(0)
• 2006	168	(3)	34	(1)
• 2007	402	(6)	116	(5)
• 2008	906	(14)	372	(15)

Table 1 Study cohort characteristics (continued)

Characteristics	Single drug therapy (N=6,593)		Combined drug therapy (N=2,497)	
• 2009	1,641	(25)	682	(27)
• 2010	1,997	(30)	758	(30)
• 2011	1,441	(22)	527	(21)
Estimate Glomerular Filtration Rate – ml/min/1.73m^2				
• 90+	2,022	(31)	655	(26)
• 60-89	3,965	(60)	1,471	(59)
• 45-59	525	(8)	318	(13)
• 30-44	81	(1)	53	(2)
Diabetes mellitus	1,173	(18)	509	(20)
NSAIDs[a] and/or high-dose aspirin	34	(1)	9	(0)
Type of therapy				
• Diuretic	3,240	(49)	-	(-)
• ACEI [b]	2,243	(34)	-	(-)
• ARB c	1,110	(17)	-	(-)
• Diuretic and ACEI	-	(-)	1,663	(67)
• Diuretic and ARB	-	(-)	803	(32)
• ACEI and ARB	-	(-)	31	(1)

ACE = Angiotensin Converting Enzyme Inhibitor; ARB = Angiotensin Receptor Blocker; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs

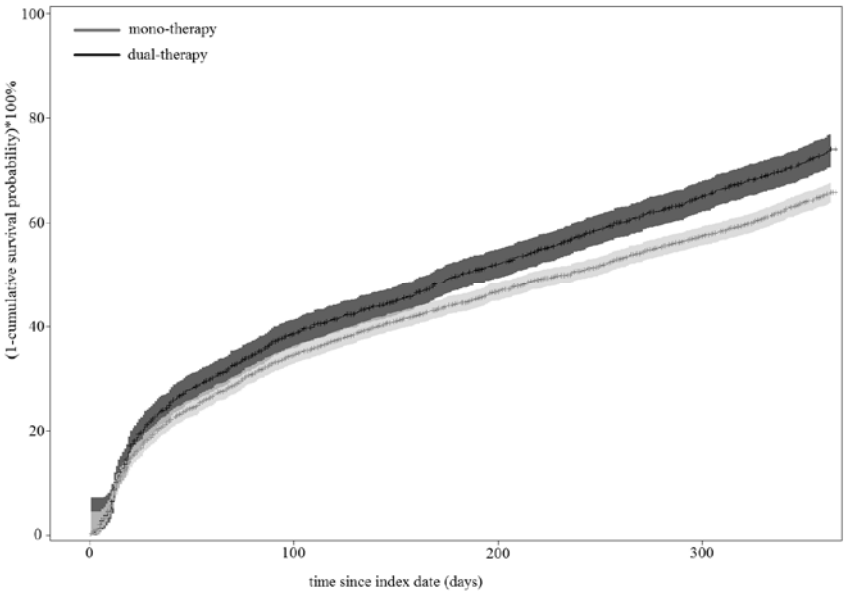


Figure 1 Renal function monitoring with single drug therapy and combined drug therapy

For single medication use, 1,233 subjects had one or more SCR measurement within 30 days after start of treatment and 3,896 subjects had at least one SCR measurement within 365 days after start of therapy. These were 1,687, and 545 for combined therapy, respectively. The associated cumulative probability of a renal function measurement was 18.8% (95% CI 17.9-20.0%) at day 30 and 65.8% (95% CI 64.6-67.0%) at day 365 after start of single drug therapy (figure 1). For combined drug therapy these were significantly higher, being 21.5% (95% CI 19.9-23.2%) and 74.0% (95% CI 72.1-75.9%), respectively. The univariable associations between baseline characteristics and the probability of a renal function measurement within 30 and 365 days after index date are described in table 2.

Table 2 Availability of a serum creatinine measurement within 30 and 365 days after start of antihypertensive therapy

	Single drug therapy				Combined drug therapy			
	Day 30		Day 365		Day 30		Day 365	
	Cum %[a]	95%CI	Cum %[a]	95%CI	Cum %[a]	95%CI	Cum %[a]	95%CI
Calendar year at start of treatment								
• 2005	8	(3 - 23)	50	(35 - 67)	25	(7 - 69)	88	(58 - 99)
• 2006	15	(10 - 21)	51	(44 - 59)	9	(3 - 25)	56	(40 - 73)
• 2007	13	(10 - 17)	59	(55 - 64)	17	(11 - 25)	73	(64 - 81)
• 2008	18	(15 - 20)	66	(63 - 69)	16	(13 - 21)	73	(69 - 78)
• 2009	17	(15 - 19)	65	(63 - 67)	20	(17 - 23)	74	(70 - 77)
• 2010	20	(18 - 22)	68	(65 - 70)	25	(22 - 28)	73	(70 - 77)
• 2011	23	(21 - 25)	71	(65 - 76)	26	(23 - 30)	90	(70 - 99)
Age category – years								
• 40-49	21	(19 - 24)	61	(58 - 64)	25	(20 - 30)	68	(62 - 74)
• 50-59	17	(15 - 19)	60	(57 - 62)	20	(17 - 24)	70	(66 - 74)
• 60-69	18	(17 - 20)	69	(66 - 71)	22	(19 - 25)	76	(73 - 79)
• 70-79	19	(17 - 22)	72	(69 - 75)	23	(20 - 26)	78	(74 - 82)
• 80+	22	(18 - 26)	76	(71 - 81)	20	(15 - 26)	76	(69 - 81)
Sex								
• male	19	(17 - 20)	66	(64 - 68)	23	(21 - 25)	74	(72 - 77)
• female	19	(18 - 20)	66	(64 - 68)	21	(19 - 23)	74	(71 - 76)
Estimate Glomerular Filtration Rate – ml/min/1.73m2								
• 90+	19	(17 - 21)	65	(63 - 68)	22	(19 - 25)	72	(68 - 76)
• 60-89	18	(17 - 20)	65	(64 - 67)	23	(21 - 25)	74	(72 - 77)
• 45-59	20	(17 - 24)	70	(66 - 74)	18	(14 - 22)	75	(70 - 80)
• 30-44	25	(17 - 36)	78	(68 - 87)	23	(14 - 36)	80	(68 - 90)
Diabetes mellitus								
• No	19	(18 - 20)	61	(60 - 62)	23	(21 - 25)	69	(67 - 71)
• Yes	19	(17 - 22)	87	(84 - 89)	18	(15 - 21)	92	(89 - 94)

Table 2 Availability of a serum creatinine measurement within 30 and 365 days after start of antihypertensive therapy (continued)

	Single drug therapy				Combined drug therapy			
	Day 30		Day 365		Day 30		Day 365	
	Cum %[a]	95%CI	Cum %[a]	95%CI	Cum %[a]	95%CI	Cum %[a]	95%CI
Concomitant use of NSAIDs and/or high-dose aspirin								
• No	19	(18 - 20)	66	(64 - 67)	22	(20 - 24)	74	(72 - 76)
• Yes	18	(8 - 35)	83	(69 - 94)	11	(2 - 57)	85	(53 - 99)
Type of therapy								
• Diuretic	17	(16 - 18)	64	(62 - 66)	-	(-)	-	(-)
• ACEI	24	(23 - 26)	73	(71 - 75)	-	(-)	-	(-)
• ARB	14	(12 - 16)	57	(54 - 60)	-	(-)	-	(-)
• Diuretic and ACEI	-	(-)	-	(-)	25	(23 - 28)	75	(73 - 78)
• Diuretic and ARB	-	(-)	-	(-)	15	(12 - 17)	71	(68 - 74)
• ACEI and ARB	-	(-)	-	(-)	19	(9 - 38)	79	(63 - 92)

[a] Cumulative percentage (1-cumulative survival probability)*100% ; ACE = Angiotensin Converting Enzyme Inhibitor; ARB = Angiotensin Receptor Blocker; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs

In the multivariable analyses, the probability of having one or more SCR measurements increased with calendar year both for single drug therapy and combined therapy (table 3). Also baseline use of NSAIDs increased the probability of monitoring with both therapies, whereas age and eGFR was only associated with an increased probability of a SCR measurement following the start of single drug therapy. DM was significantly associated with the probability of a SCR measurement in a time-dependent manner: in the presence of DM the probability of a SCR measurement increased with time from day 41 after start of single therapy and day 40 after start of dual therapy onwards. With single

Table 3 Multivariable analysis: renal function monitoring after start of antihypertensive therapy

	single drug therapy*				combined drug therapy[d]			
Characteristic	**est**	**HR**	**pval**	**95%CI**	**est**	**HR**	**pval**	**95%CI**
Calendar year at start of treatment (2011 = ref.)								
• 2005	-0.88	0.42	**0.001**	(0.25 - 0.69)	0.21	1.23	0.695	(0.43 - 3.53)
• 2006	-0.37	0.69	**0.005**	(0.53 - 0.89)	-0.26	0.77	0.345	(0.45 - 1.32)
• 2007	-0.51	0.60	**<0.001**	(0.51 - 0.72)	-0.25	0.78	0.106	(0.58 - 1.05)
• 2008	-0.34	0.71	**<0.001**	(0.62 - 0.81)	-0.33	0.72	**0.001**	(0.59 - 0.88)
• 2009	-0.29	0.75	**<0.001**	(0.67 - 0.84)	-0.23	0.79	**0.008**	(0.67 - 0.94)
• 2010	-0.15	0.86	**0.006**	(0.78 - 0.96)	-0.07	0.93	0.414	(0.79 - 1.1)

Table 3 Multivariable analysis: renal function monitoring after start of antihypertensive therapy (continued)

	single drug therapy*				combined drug therapy [d]			
Characteristic	**est**	**HR**	**pval**	**95%CI**	**est**	**HR**	**pval**	**95%CI**
Age category –years (40-49 = ref.)								
• 50-59	-0.09	0.92	0.116	(0.83 - 1.02)	-0.08	0.93	0.434	(0.76 - 1.12)
• 60-69	0.08	1.08	0.129	(0.98 - 1.21)	0.08	1.09	0.396	(0.9 - 1.31)
• 70-79	0.08	1.08	0.215	(0.96 - 1.22)	0.11	1.12	0.289	(0.91 - 1.38)
• 80+	0.21	1.24	**0.011**	(1.05 - 1.46)	0.12	1.12	0.383	(0.86 - 1.46)
Sex (male=ref.)								
• Female	0.01	1.01	0.853	(0.94 - 1.08)	0.04	1.04	0.469	(0.94 - 1.16)
Estimated Glomerular Filtration Rate – ml/min/1.73m2 (90+ = ref.)								
• 60-89	0.06	1.06	0.167	(0.98 - 1.15)	-0.04	0.96	0.601	(0.84 - 1.1)
• 45-59	0.17	1.19	**0.018**	(1.03 - 1.37)	-0.01	0.99	0.933	(0.81 - 1.22)
• 30-44	0.19	1.21	0.194	(0.91 - 1.62)	0.32	1.38	0.098	(0.94 - 2.03)
Concomitant use of NSAIDs and/or high-dose aspirin (no use = ref.)								
• Yes	0.45	1.58	**0.027**	(1.05 - 2.36)	0.86	2.35	**0.028**	(1.1 - 5.05)
Type of therapy [a,b] (type 1 = ref.)								
• Type 2	0.28		**<0.001**	(-)	-0.03	0.97	0.626	(0.85 - 1.1)
• Type 3	-0.11		0.082	(-)	0.07	1.08	0.756	(0.67 - 1.72)
Diabetes mellitus (absent = ref.)								
• Present	0.15		0.086	(-)	-0.25		**0.016**	(-)
Diabetes mellitus x Time interaction‡								
•	0.16		**<0.001**	(-)	0.23		**<0.001**	(-)
Diabetes mellitus x Type of therapy interaction [a,c]								
• Diabetes mellitus present and type 2 therapy	-0.25		**0.005**	(-)	-	-	-	(-)
• Diabetes mellitus present and type 3 therapy	0.11		0.378	(-)	-	-	-	(-)

[a] Hazard rates and 95%CI intervals are not provided for characteristics included in an interaction term; [b] Type of therapy: single drug: type1 = diuretic; type2 = ACEI;type3 = ARB combined drug: type1 = diuretic and ACE; type2 = diuretic and ARB; type3 = ACEI and ARB; [c] If diabetes mellitus is present the estimate for the diabetes mellitus time interaction should be multiplied with the natural logarithm of the number of days after day 41 following the start of single drug therapy or the number of days after day 40 following the start of combined drug therapy.; [d] Fully adjusted model

drug therapy, there was a significant interaction between DM and type of therapy: in absence of DM the proportion of subjects with a SCR measurement was larger in the subgroup with ACEI-based single drug therapy as compared to subjects who started single drug therapy with a diuretic or an ARB. In contrast, there were no differences in monitoring within subjects with DM. No differences between types of therapy and monitoring were observed with combined drug therapy.

Between GP practices, there were significant differences in the cumulative probability of renal function monitoring, with a median probability of monitoring of 15.8% (IQR 7.0% – 27.8%) at day 30 and a median of 62.5% (IQR 50.0% – 74.9%) at day 365 for single therapy, and 12.5% (IQR 0.0% – 27.8%) and 66.7% (IQR 47.9%-80.0%) for combined drug therapy (figure 2).

In the cohort with single drug therapy, SCR increased by more than 30% relative to baseline in 103 subjects (1.6% of all subjects who started therapy). Review of the medical record revealed that in 29 subjects this might be caused by another medical condition for example malignancy, cardiovascular events, or infection. Of the remaining

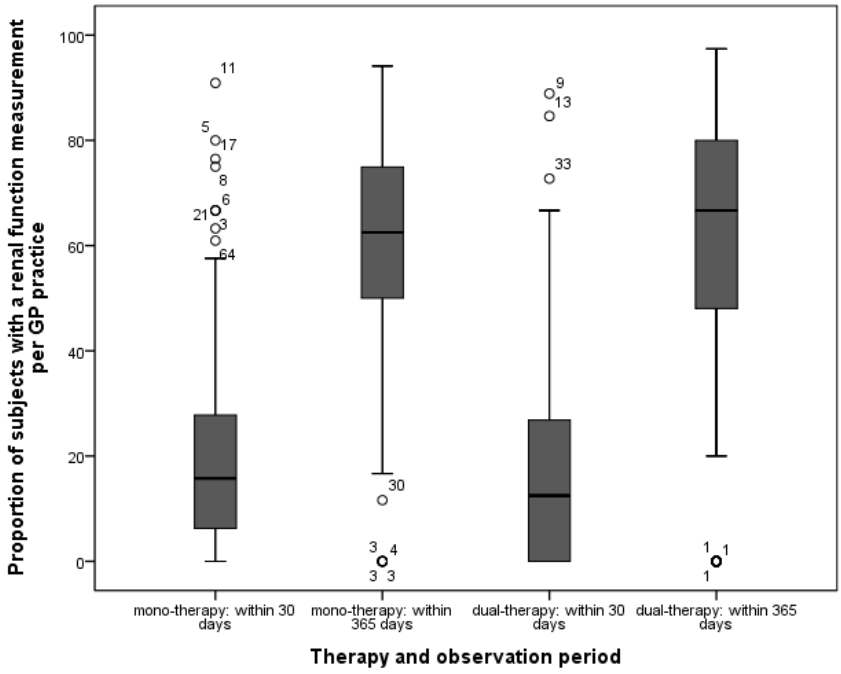


Figure 2 Renal function monitoring with single drug therapy and combined drug therapy across GP practices. Horizontal bar=median; boxes=interquartile range; T-bars=1.5-extension of the 2nd and 3rd quartile; numbers=subjects per practice that started single drug therapy or combined drug therapy respectively for outlying observations; proportion=(1-cumulative survival probability)*100%

74 subjects, 32 received monotherapy, while 42 subjects were switched to combined drug therapy prior to the increase of SCR. In 59 (80%) of the 74 subjects, this did not lead to subsequent SCR measurements within 1 month, a change of therapy or referral to a specialist. In the cohort with combined drug therapy SCR increased by >30% relative to baseline in 85 subjects (3.4% of all subjects who started therapy). In 16 subjects other medical conditions might explain the increase. Of the remaining 69 subjects, 67 still used the same drug at the time of the increased SCR measurement. In 47 (70%) of these 67 subjects, no actions were taken based on the results of the testing.

DISCUSSION

This study shows three important issues. First, that in the majority (>75%) of subjects renal function is not monitored during the first 30 days after start of (combined) antihypertensive therapy with diuretics and/or renin-angiotensin-aldosterone system inhibitors (RASIs) in contrast to recommendations of the guidelines. Second, there is large variability between GP practices with respect to renal function monitoring. Third, the incidence of renal impairment (increase in SCR measurement >30% of baseline) during the first 365 days after treatment initiation is relatively low (2.6-3.4%), and did not lead to subsequent actions in the majority (>70%) of subjects.

Published data on the extent of monitoring during the first 30 days of antihypertensive therapy are limited. Findings in our study are consistent with the results from a previous study that had far lower sample size [13]. No previous study has elaborated on differences between GP practices. Our findings suggest that this is relevant for further studies related to this topic. Our results suggest that monitoring might have improved modestly with calendar year, which was also observed in another study [12]. The extent of monitoring in subjects with DM in our study is much lower than what is reported in a study from Scotland where monitoring is assessed during approximately the same time window after start of therapy [16]. Both in the Netherlands and in the United Kingdom, periodic SCR measurement in subjects with DM is a quality indicator of health care. The discrepancy between both studies might thus be explained by differences in the respective performance management and payment system, which could be subject for further study. Also we found that DM increased the probability of monitoring, although not during the first 30 days. Possibly, renal function monitoring is performed in relation to DM rather than as part of antihypertensive therapy initiation. Unlike another study [16], we found an increased monitoring in subjects using NSAIDs and/or high-dose ASA at the time of index date, both with single drug therapy and when added to combination drug therapy, which has been referred to as 'triple whammy' earlier [24]. However this might also result from other factors associated with the use of NSAIDs and the extent of

monitoring is still low, in particular during the first 30 days (table 2), despite the specific recommendation by the Dutch college of general practitioners to monitor renal function if NSAIDs are used in combination with diuretics or RASIs [25]. This low rate is of concern as renal function might deteriorate within two days of NSAIDs initiation. [26]

Subjects without DM who started single drug therapy with an ARB were monitored to the same extent as those starting therapy with a diuretic, but significantly less frequently than subjects initiating an ACEI, which is in line with results from other studies on monitoring [12, 16]. Still this is surprising as results from the ONTARGET trial do not suggest a difference in renal impairment between ARBs and ACEIs [4]. The observed associations between calendar year and age, as well as the lack of a significant association for gender, are consistent with results of other studies [10, 12, 16].

The incidence of renal impairment (SCR measurement increased by >30% relative to baseline measurement) within 365 days after index date in our study is higher than the rates of discontinuation of study medication due to renal impairment in the ONTARGET trial [4]. However, in the majority of patients in our study the increase in SCR did not result in actions such as treatment discontinuation, specialist referral or subsequent SCR measurements. The controlled setting of a clinical study might explain the difference with monitoring in daily practice as in our study. It is important to note that the rate of AKI might be even higher in subjects with additional risks factors, such as heart failure and moderate-severe CKD, who were not included in our study population. As with monitoring of renal function after start of antihypertensive therapy in general (figure 2), also recognition of accelerated decline of renal function and AKI from antihypertensive therapy might differ between GPs; however, the low numbers precluded further analysis.

Strengths of our study include its population-based design as well as the stringent criteria applied to minimize the risk of underestimation of renal function monitoring. Indeed, we excluded short term therapy or patients who switched therapy as well as patients likely to be monitored by the specialist although this inevitably limits the generalizability of our results to subjects without additional risks factors for AKI. In addition, despite these before mentioned criteria, a small number of subjects might have received specialist care following a referral that was not preceded by a SCR measurement by the GP.

The incidence of non-dialysis requiring community-based AKI has strongly increased between 1996 and 2003 [27], despite renoprotection with ACEI and/or ARBs and it has been argued that the use of these medications might underlie this trend [28]. This applies at least to subjects on dual RAAS blockade [29, 30] which is currently evaluated during an article 31 referral procedure by the European Medicines Agency (EMEA/HA/31/1370). Another study showed that several barriers might impede monitoring [31]. Comparison of our findings with the results of Kalra and colleagues in 1999 [8] suggest that the success of initiatives to bring down these barriers is limited thus far. An

obvious reason for a failure to embrace monitoring enthusiastically is the very low yield on screening, at least in our study population, in which SCR increased by >30% from baseline in just 1.6 to 3.4% of subjects, whereas in a previous large (n=74,096) study hyponatremia, hyperkalemia and hypokalemia were only observed in 0.7%, 0.8% and 1.3% of subjects within 6 months of the initiation of antihypertensive treatment [17].

Studies, including randomized clinical trials, report that quality indicators improve with the use of financial incentives to directly reward performance and 'quality' in healthcare [32, 33]. There are no established indicators for renal function monitoring, due to inter-individual differences in renal function decline with ageing and underlying disease as well as the absence of validated markers of renal renin-angiotensin system activity to identify subjects who are at increased risk of renal impairment or AKI [34, 35].

CONCLUSIONS

Our study shows that the extent of renal function monitoring with antihypertensive therapy might be substantially improved. Renal impairment was found to complicate antihypertensive therapy. In a majority of cases other medical conditions that might explain the renal impairment were lacking. Subsequent actions were not taken in the majority (>70%) of subjects. Future studies should examine to what extent an increase in SCR >30% of baseline is associated with patient harm. Also the implementation of quality indicators to monitor antihypertensive therapy during the first year after start of - or change in - antihypertensive therapy should be investigated, including their impact on the individual practice as our study shows a large variability in the extent of monitoring between practices.

ACKNOWLEDGEMENTS

We thank Marcel de Wilde, Kris Sieradzan and Mees Mosseveld for the collection of data and maintenance of the IPCI database.

FUNDING AND CONFLICTS OF INTEREST

No sources of funding were used to assist in the preparation of this study. Jan C. van Blijderveen, Sabine M. Straus, Maria A. de Ridder, Bruno H. Stricker, Miriam C. Sturkenboom, and Katia M. Verhamme have no other conflicts of interest that are directly relevant to the content of this study.

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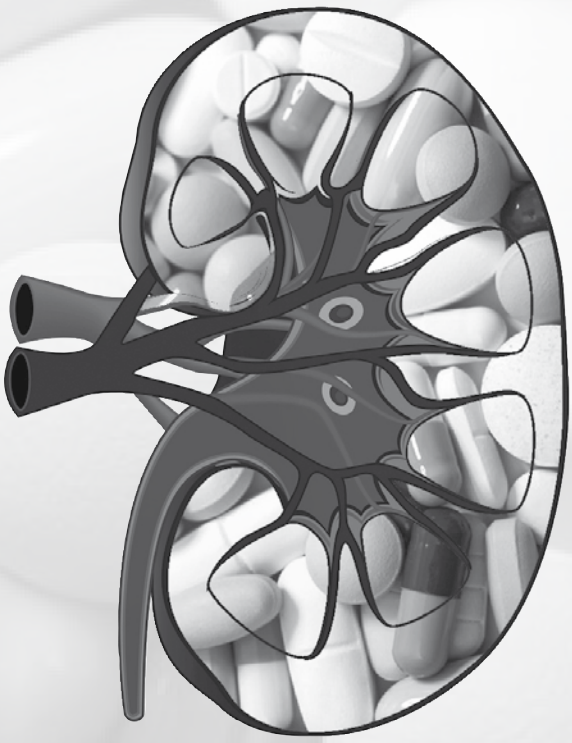
Chapter 6

General discussion



GENERAL DISCUSSION

The kidney has several functions that are essential for life, notably homeostasis of the extracellular environment and regulation of systemic and renal hemodynamics, red blood cell production and bone metabolism. Renal function declines with age but also medical conditions such as diabetes mellitus impair renal function. It is important to identify and minimize risk factors that contribute to renal function decline. Several medicines exhibit direct nephrotoxic potential, while others may indirectly interfere with one of the renal functions. The consequences may be substantial. In general a decreased renal function is associated with an increased risk of hospitalization, cardiovascular events and death [1], while direct drug-induced nephrotoxicity has been shown to be a main determinant of preventable medication-related hospital admission [2]. Consequently, their use is contraindicated in persons with a decreased renal function, e.g. methotrexate [3], gadodiamide [4], and nitrofurantoin [5], while for others dose adjustment is indicated, e.g. enalapril [6], allopurinol [7], and metoclopramide[8]. Failure to take appropriate measures might result in acute kidney injury or chronic kidney disease as well as other complications such as electrolyte disturbances.

This thesis had four objectives. The first objective was to describe the epidemiology of chronic kidney disease in the general population. The second objective was to identify, confirm and quantify new undesirable renal effects of medicines. Hereto, we reported the association between overanticoagulation during therapy with vitamin K antagonists and the risk of renal function decline (chapter 3.1). In addition we studied the association between serum uric acid levels and the occurrence of a simple renal cysts. This is relevant as serum uric acid levels are increased by several medicines, such as diuretics (chapter 3.2). The third objective was to study the role of medicines in relation to water and electrolyte disturbances, because of the prominent role of the kidney in the homeostasis of water and salts. We investigated whether diuretics with a similar indication of use (chlorthalidone and hydrochlorothiazide) are differently associated with hyponatremia (chapter 4.1). Furthermore, we investigated the association between antidepressants and hyponatremia (chapter 4.2), and benzodiazepines and hypovolemia which might result from a combined loss of water and sodium (chapter 4.3). The fourth and last objective was to investigate renal function monitoring in patients at risk of renal function decline. For this research, we studied the adherence to renal function monitoring guidelines in patients initiating antihypertensive therapy with diuretics and renin-angiotensin system inhibitors (chapter 5).

Main findings

1. Prevalence and incidence of chronic kidney disease

Knowledge on the incidence and prevalence of chronic kidney disease in the general population is important because it provides insight into renal function decline as a result of ageing and underlying comorbidities. Incidence rates of chronic kidney disease in the literature are very limited and most lack results stratified for age, sex and underlying diabetes mellitus [9-18]. To study the prevalence and incidence of chronic kidney disease we used data from the Integrated Primary Care Information (IPCI) project, which is a Dutch GP database that holds the complete, anonymized electronic patient records of more than one million subjects. We found a marked increase in the prevalence of chronic kidney disease with age, female sex, and diabetes mellitus. Indeed, the prevalence of chronic kidney disease was higher than 75% in diabetic female participants aged 85 years and over (chapter 2). Especially in the very elderly, we found a substantially higher prevalence of chronic kidney disease than rates reported by cohort studies [19-23]. We found an overall incidence rate of chronic kidney disease in adults of 1,213 per 100,000 person-years. Here as well, the incidence increased with age, female sex and diabetes mellitus. The highest incidence rate of CKD namely 25,000 per 100,000 person-years, was identified in women with diabetes mellitus, aged ≥85 years and over. Our results provide insight into the extent of chronic kidney disease in the Netherlands and might help to increase awareness of chronic kidney disease amongst primary care providers. Given the large number of drugs requiring dose adaptations in case of renal function decrease, it is likely that many elderly with insidious renal function loss may be relatively overdosed. Indeed, recognition of chronic kidney disease remains low among primary care providers [24, 25], while early referral to a nephrologist might help to improve patients outcomes [26].

2. Identification of new undesirable renal effects of medicines

The second objective was to identify, confirm and quantify new undesirable effects of medicines in relation to the kidney. Recently, other studies suggested that overanticoagulation, defined as an International Normalized Ratio (INR)>3.0, in patients on warfarin therapy might be associated with an impaired renal function [27-30]. This might be relevant to many individuals as in 2010 approximately 398,000 patients of the Dutch population of 16.6 million people were treated with oral anticoagulation therapy with vitamin K antagonists, mainly acenocoumarol or phenprocoumon [31, 32]. Already the degree of anticoagulation is strictly regulated because the therapeutic range is narrow and it has been shown that underanticoagulation has been associated with an increased risk of stroke, while overanticoagulation has been associated with an increased risk of bleeding [33-35]. To study the association between overanticoagulation and renal

function decline we used data from the Rotterdam study, which is an ongoing prospective population-based cohort study of chronic diseases in the elderly in the Ommoord district in the city of Rotterdam, the Netherlands. It includes approximately 15,000 subjects aged 45 years or over in three cohorts that were recruited in 1990, 2000 and 2006. All cohorts undergo repeated examinations every 3–4 years in characteristics that change over time contributing to studies on cardiovascular, dermatological, endocrine, liver, neurological, ophthalmic, psychiatric and respiratory disease as well as genetic and biomarker studies and pharmaco-epidemiologic studies. Within the Rotterdam study, we identified a cohort of patients on vitamin K anticoagulation and could not establish an association between an INR between 3 and 6 and risk of renal function decline, possibly due to a relatively small sample size or because of a transient effect. However, we did observe a significant additional decline in renal function for INR>6, after adjustment for age, sex, heart failure, baseline glomerular filtration rate and indication for vitamin K antagonist therapy (chapter 3.1). A previous study suggested that the occurrence of an INR above 6.0 is not infrequent [36]. Hence, apart from the risk of bleeding, the potential of renal function decline with long-term anticoagulant treatment might be an additional argument to prevent INRs above 6.0. Additional prospective studies are needed to further assess the effects of INRs below 6.0 on renal function decline as well as to identify high risk groups.

Several medications, such as diuretics, can raise serum uric acid. Generally, such an increase is asymptomatic, but it might also trigger gout. A recent case-control study in patients with gout reported a higher prevalence of simple renal cysts than in a control group of age- and sex-matched healthy kidney donors [37]. However, because the incidence rate of gout is relatively low [38, 39], the association would concern only a limited number of subjects. Because an increased serum urate level without gout is much more frequent, we investigated the association between serum uric acid and the presence of a simple renal cyst. In females, we found that the risk of a simple renal cyst increased by 78% from the lowest to the highest serum uric acid level, while in males we only found a higher prevalence of a simple renal cyst for serum uric acid 4.0 mg/dl and above compared to a serum uric acid below 4.0 mg/dl (chapter 3.2). As many more small cysts may be present beneath the limit of detection [40], we hypothesize that serum uric acid might contribute to the progression of renal function decline through renal cyst formation [41]. This is an interesting subject for further research.

3. Role of the kidney in electrolyte disturbances

The kidney plays a pivotal role in the homeostasis of water and salts, including sodium. Therefore, the third objective was to study how medicines affect the kidney in its role of water and electrolyte homeostasis. Several medicines cause hyponatremia [42], an adverse effect which has mainly been described for diuretics such as chlorthalidone and

hydrochlorothiazide. These diuretics are often considered as interchangeable, although two meta-analyses [43, 44] and two randomized clinical studies [45, 46] showed greater blood pressure reduction with chlorthalidone than with hydrochlorothiazide. In particular, the reduction of nighttime mean systolic blood pressure contributed to the renewed interest in chlorthalidone [47]. A recent propensity score–matched observational cohort study suggested that subjects treated with chlorthalidone were more likely to be hospitalized with hyponatremia than those prescribed hydrochlorothiazide [48], concluding that this might be a reason to prefer treatment with hydrochlorothiazide over treatment with chlorthalidone. In chapter 4, we used data from the Integrated Primary Care Information (IPCI) project to study these medicines in association to hyponatremia. We found that at equivalent milligram dose per day chlorthalidone was indeed associated with a significantly higher risk of hyponatremia in comparison to hydrochlorothiazide (chapter 4.1). However, the majority of prior clinical studies suggest a similar drop in (daytime) blood pressure for chlorthalidone compared to twice the amount of hydrochlorothiazide [45, 46, 49-51]. At this equipotent dose per day we did not find an increase in the risk of hyponatremia with chlorthalidone 12.5 milligram per day compared to hydrochlorothiazide 25 milligram per day as well as with chlorthalidone 25 milligram per day compared to hydrochlorothiazide 50 milligram per day. In view of studies suggesting better outcomes with chlorthalidone, the findings in this thesis suggest that hyponatremia should not be a reason to refrain from direct head-to-head clinical studies between equipotent doses of chlorthalidone and hydrochlorothiazide.

With anti-depressants we were able to confirm the well-established association of Selective Serotonin Reuptake Inhibitors (SSRIs) with hyponatremia (chapter 4.2) [52-61]. Of specific interest , we found a significantly increased risk of hyponatremia during the first month of use of tricyclic antidepressants (TCAs), while results from previous studies on the association between tricyclic antidepressants and hyponatremia were inconsistent. Some studies suggest a contributory role of tricyclic antidepressants [62-68], while other studies could not confirm an association between hyponatremia and tricyclic antidepressants [53, 59, 69]. These studies have limitations; including small sample size [53, 67], failure to adjust for confounding factors at event date [59, 68, 69], no stratification by treatment duration and no consideration of past use in their analyses [53, 59, 67-69]. Further studies should provide insight into the optimal interval and duration of monitoring for hyponatremia after start of treatment with antidepressants.

We also studied the association between hyponatremia and benzodiazepines. Earlier case-reports of benzodiazepine-induced hyponatremia [70-72], were recently confirmed in a population-based study [73]. In our research we also confirmed this association and in addition we showed a significantly increased relative excess risk for combined use of benzodiazepines and hydrochlorothiazide (chapter 4.3). Further experimental studies should be performed to unravel the pathophysiological mechanism.

Interestingly, benzodiazepines were also associated with an increased risk of hospital admission with clinical hypovolemia – in clinical practice often referred to as dehydration - after adjustment for confounding factors and confounding by indication (chapter 4.4). Possibly this is due to an increased combined loss of water and sodium in accordance with experimental studies suggesting a natriuretic effect of benzodiazepines [74-76]. Other drugs that were also associated with hospital admission with clinical hypovolemia included proton pump inhibitors, non-steroidal anti-inflammatory drugs and opioids. Possible underlying mechanisms are diverse and include an excessive loss of urinary sodium, an increased risk of diarrhea and impairment of the vasopressin induced up regulation of aquaporin-2 expression in response to dehydration. Use of high ceiling diuretics was also associated with hypovolemia but this effect disappeared upon correction for multiple testing. We did not find an association with other medicines, including the other classes of diuretics and agents acting on the renin angiotensin aldosterone system, upon adjustment for confounding by indication using past use as a reference, while these drugs have been associated with acute kidney injury before [77]. This finding underlines the importance of adjustment for confounding by indication in studies investigation the relation between drug exposure and hypovolemia and possibly also acute kidney injury.

4. Monitoring of renal safety

The fourth and final objective of this thesis was to study whether clinical practice guidelines on the monitoring of kidney function are followed. Hereto, we studied the adherence to renal function monitoring guidelines in patients initiating antihypertensive therapy with a combination of diuretics and renin-angiotensin system inhibitors. Consistent with the results from a previous study with a lower sample size [13], we found that in the majority of subjects renal function is not monitored during the first 30 days after start of (combined) antihypertensive therapy with diuretics and/or renin-angiotensin-aldosterone system inhibitors in contrast to recommendations from the guidelines (chapter 5). Also, we found that the extent of monitoring in subjects with diabetes mellitus is much lower than what is reported in a study from Scotland. This might be explained by differences in the respective performance management and payment system [16]. Finally, we found that the incidence of renal impairment during the first 365 days upon treatment initiation is relatively low (2.6-3.4%), and did not lead to subsequent actions in the majority of affected subjects. In summary, clinical practice guidelines for monitoring renal safety are currently insufficiently adhered to. In the first year, consequences of this low adherence seem to be modest but only a longer follow-up can tell whether low adherence results in a higher incidence of renal function impairment. Furthermore, it is important to investigate why there is a rather large discrepancy

between the recommendations from the clinical guidelines and the real-life situation of low adherence by prescribers.

Potential bias and confounding

For this research we used data from either IPCI, a general practitioner database or from the Rotterdam study which is a prospective cohort study. As for all observational research, there is the potential of bias and/or confounding

A limitation of the use of a general practitioner database is that data is collected in the process of day-to-day care. Annual screening for chronic kidney disease is a quality of care indicator within the bundled payment system for diabetes care. Therefore, the incidence and prevalence of chronic kidney disease in individuals who are not subject to annual screening for chronic kidney disease may have been underestimated. Another limitation to the studies with data from a general practitioner database is that, although prescription records are registered for all individuals, prescriptions initiated by specialists or prescriptions given during hospitalization might be missing. Misclassification of exposure will result in an underestimation of the effect size if the drugs of interest are indeed associated with the outcome. Exposure is also misclassified for medicines which are available without a prescription, the so-called over-the-counter (OTC) medicines. Finally, we encountered the potential of exposure misclassification as we used prescription data only and did not have information on dispensing or actual intake, misclassification of exposure. With regard to outcome misclassification, as hyponatremia was based on laboratory measurement or specialist diagnosis, we might have misclassified patients with hyponatremia for whom lab results were not available within the database. This would have resulted in an underestimation of the effect.

Measurements in the Rotterdam Study are performed in all participants without prior knowledge of the research hypothesis. This implies that no major bias or confounding is anticipated. With regard to the study about the association between serum uric acid and a simple renal cyst, in a substantial number of participants, one or both kidneys could not be visualized for technical reasons. However, absence of kidney imaging is not related to serum uric acid measurement and thus would not result in potential bias or confounding.

Future Perspectives

The change from paper based patient records to electronic medical records offer distinct advantages for patient and health care professionals, including improved quality, coordination and patient participation. These electronic medical records capture a wealth of information and can also be used for research purposes allowing, apart from other benefits, to observe changes within patients over time, a feature which is crucial for kidney function monitoring. Recently, the implementation of a limited pay for performance has

resulted in a more structured assessment of risk factors for chronic kidney disease, such as hypertension, weight, smoking and diabetes mellitus. With this information being systematically available on all patients at risk, it will be possible to completely adjust for other risk factors, when investigating the contributory role of medication in the progression of chronic kidney disease. So far, information on weight was not available on all patients within the IPCI database. Information on weight is important in research on medication induced electrolyte disturbances as it has been shown that patient characteristics such as weight modify this association [78]. Initially we intended to study the association between drug use and risk of acute kidney injury but we realized that this research would be difficult when based on primary care data only. Indeed, acute kidney injury is mainly diagnosed in the hospital, but precise information on medication exposure and other risk factors is often only available from primary care data. It would be interesting to investigate whether the association between use of proton pump inhibitors, non-steroidal anti-inflammatory drugs and opioids not only holds for hospital admission with hypovolemia but also for acute kidney injury as an outcome.

The findings in this thesis with regard to overanticoagulation and renal function decline are relatively new, being the first independent observational study to confirm this association. Linkage of primary care data with data from anticoagulation clinics would offer an opportunity for further research. We are the first to report a relation between serum uric acid and simple renal cysts. Already more research on serum uric acid has been done in patients with autosomal-dominant polycystic kidney disease. However as many cysts might lie beneath the level of detection, more research is needed to investigate whether lowering serum uric acid serum uric acid retards the progression of renal function decline.

Electrolyte disturbances are known adverse events of many medicines, although new associations continue to be discovered, also with regard to medicines that were registered a long time ago. Indeed we did find an association for selective serotonin reuptake inhibitors, tricyclic antidepressants and benzodiazepines, all drugs already long on the market. Our studies highlight the importance of safety monitoring even for relatively "old" drugs.

Finally, our observation that clinical guidelines on renal function monitoring are not strictly followed offers a huge potential to improve drug safety through provision of clear, concise and non-contradictory information. Renal function is currently one of the quality indicators in the care for patients with diabetes mellitus, but not in relation to pharmacotherapy. With growing complexity of health care, computer decision support systems and research based on electronic health care records should be further exploited to bring pharmacotherapy with minimal adverse effects one step closer.

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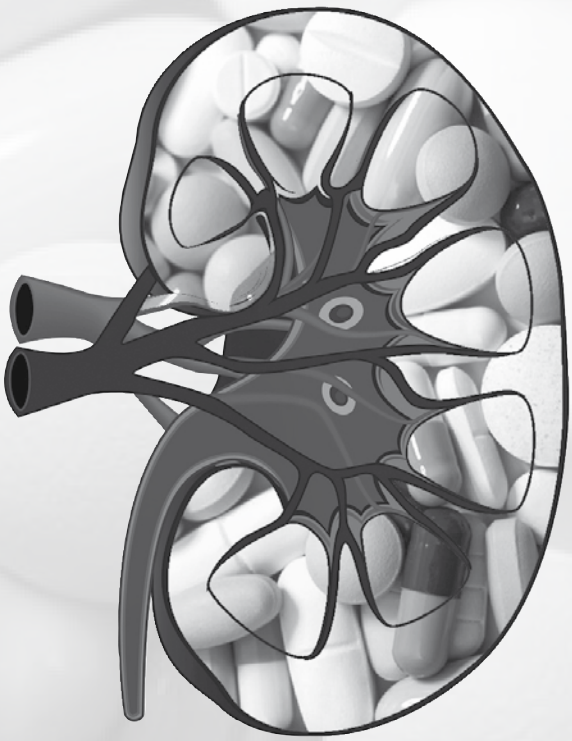
Chapter 7

Summary /samenvatting



SUMMARY

Preservation of kidney function, often represented by the estimated glomerular filtration rate, is important because a decreased renal function is associated with an increased risk of morbidity and mortality. Despite this, drug-induced nephrotoxicity has been shown to be a main determinant of preventable medication-related hospital admission.

Chapter 1 gives a general introduction to the different topics that were studied in this thesis and provides an overview of the data sources used. The chapter concludes with the outline of the thesis.

Chapter 2 describes that the epidemiology of chronic kidney disease in the general population of the Netherlands. It shows that a decreased glomerular filtration rate is present in more than 50 percent of elderly (≥85 years) patients. The fact that with the use of these observational data a higher prevalence of decreased glomerular filtration rate was observed than in selected cohort studies, suggests that it's prevalence might have been underestimated as a result of selection bias.

Chapter 3 describes two associations between drug use and renal function decline. First, it describes the renal function decline in patients who used anticoagulation therapy (chapter 3.1), which appeared to be larger amongst patients with repeated events of overanticoagulation (INR>6.0). Second, it describes that the prevalence of a simple renal cyst increases with serum uric acid (chapter 3.2). As many more small cysts may be present beneath the limit of detection serum uric acid, which is increased by several medications, might contribute to the progression of renal function decline through renal cyst formation.

Chapter 4 describes the role of the kidney in water and electrolyte disturbances. It shows that hydrochlorothiazide and chlorthalidone, two blood pressure lowering medications that are generally considered interchangeable, have a different risk of hyponatremia at equivalent milligram dose per day. However, these agents are not equipotent. With an equipotent dose per day there appeared to be no difference in the risk of hyponatremia in contrast to the results from a previous study (chapter 4.1). With tricyclic antidepressants there was a significantly increased risk of hyponatremia during the first month of use (chapter 4.2). Also benzodiazepines were associated with an increased risk of hyponatremia. There was an increased relative excess risk for the combined use of benzodiazepines and hydrochlorothiazide (chapter 4.3). Interestingly, benzodiazepines were also associated with an increased risk of hospital admission with clinical hypovolemia – in clinical practice often referred to as dehydration. Other drugs that were also associated with hospital admission with clinical hypovolemia included proton pump inhibitors, non-steroidal anti-inflammatory drugs and opioids (chapter 4.4).

Chapter 5 describes studied the adherence to renal function monitoring guidelines in patients initiating anti-hypertensive therapy with diuretics, renin-angiotensin system inhibitors and/or a combination. It appeared that in the majority of subjects renal function was not monitored during the first 30 days after start of therapy, although also a large variability across general practitioners was observed.

Finally in Chapter 6 the main findings of the research presented in this thesis are discussed, appraisals on the methodological consideration of these studies are made together with concluding remarks based on the work in this thesis.

SAMENVATTING

Behoud van nierfunctie, vaak gepresenteerd door de geschatte glomerulaire filtratie snelheid, is belangrijk, omdat een verminderde nierfunctie is gerelateerd aan een verhoogd ziekte- en sterftecijfer. Desniettegenstaande is aangetoond dat geneesmiddel geïnduceerde nierschade de belangrijkste oorzaak is ziekenhuis opname als gen de gebruikte gevolg van geneesmiddel gebruik.

Hoofdstuk 1 geeft een algemene introductie op de verschillende onderwerpen die in dit proefschrift zijn bestudeerd. Tevens wordt een overzicht van de gebruikte gegevensbronnen gepresenteerd. Het hoofdstuk wordt afgesloten met een overzicht van de hoofdstukken opgenomen in dit proefschrift.

Hoofdstuk 2 beschrijft het voorkomen van chronische nierziekten in de algemene bevolking van Nederland. Het laat zien dat een verminderde glomerulaire filtratie snelheid aanwezig is in meer dan de helft van de oudere (≥85 jaar) patiënten. Het feit dat met het gebruik van deze observationele data het voorkomen van een verminderde glomerulaire filtratie snelheid hoger wordt geschat dan in specifieke cohortstudies, suggereert dat het voorkomen eerder kan zijn onderschat ten gevolge van selectie.

Hoofdstuk 3 beschrijft twee associaties tussen het gebruik van geneesmiddelen en de achteruitgang van de nierfunctie. Eerst beschrijft het de achteruitgang van de nierfunctie in patiënten die geneesmiddelen gebruiken welke de bloedstolling vertragen, waarbij de achteruitgang groter is in patiënten met een herhaaldelijk doorgeschoten antistolling (INR>6.0).

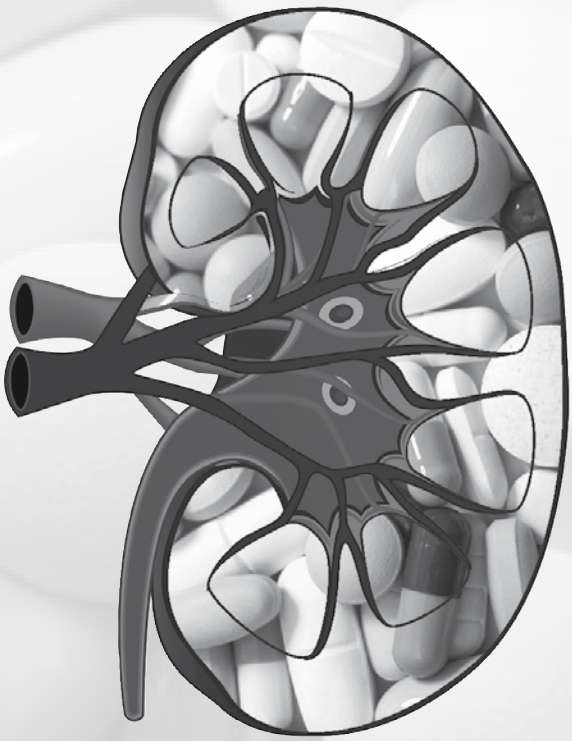
Hoofdstuk 4 beschrijft de rol van de nier in water en elektrolyt stoornissen. Het laat zien dat hydrochloorthiazide en chloortalidon, twee bloeddruk verlagende geneesmiddelen die vaak als uitwisselbaar worden gezien, een verschillend risico geven op verlaagd natrium bij een gelijke dosering in milligrammen. Echter, de sterkte van deze geneesmiddelen verschilt. Bij een dosering die een gelijke daling van de bloeddruk geeft, lijkt er geen verschil te zijn in het risico op een verlaagd natrium, in tegenstelling tot de resultaten van een eerdere studie (hoofdstuk 4.1). Het risico op een verlaagd natrium is significant verhoogd gedurende de eerste maand van het gebruik van tricyclische antidepressiva (hoofdstuk 4.2). Ook benzodiazepines zijn geassocieerd met een significant verhoogd risico op verlaagd natrium. Het risico bij gecombineerd gebruik van benzodiazepines en hydrochloorthiazide is groter dan de som van de losse delen (hoofdstuk 4.3). Belangwekkend genoeg, waren benzodiazepines ook geassocieerd met een verhoogd risico op ziekenhuisopname met een klinische diagnose van hypovolemie – in de praktijk vaak aangeduid als dehydratie. Andere geneesmiddelen die hiermee een verband hadden, waren proton pomp remmers, niet-steroïde anti-inflammatoire geneesmiddelen en opiaten (hoofdstuk 4.4)

Hoofdstuk 5 beschrijft de compliantie aan de richtlijnen die het controleren van de nierfunctie bij mensen die starten met bloeddruk verlagende medicatie middels diuretica, remmers van het renine-angiotensine systeem en/of een combinatie voorschrijven. Het bleek dat in een meerderheid van de gevallen de nierfunctie niet wordt gecontroleerd binnen de eerste 30 dagen na start van therapie, hoewel er een grote variatie werd gezien tussen de verschillende huisartsen.

Tenslotte worden in hoofdstuk 6 de belangrijkste bevindingen van dit proefschrift bediscussieerd en de methodologische aspecten van de studies besproken.

Chapter 8

Dankwoord
List of publications
PhD portfolio
About the author



DANKWOORD

Dit proefschrift kon alleen tot stand komen dankzij de inspiratie en steun van vele mensen.

Mijn dank gaat in het bijzonder uit naar Prof.dr. Bruno Stricker, Prof.dr. Miriam Sturkenboom, Dr. Katia Verhamme, Dr. Sabine Straus, mijn promotores en co-promotores. Bruno, dank voor het gekregen vertrouwen, je creatieve inbreng en je bijzondere betrokkenheid, waarbij je er iedere dinsdagmiddag weer was. Katia, dank voor de intensieve begeleiding, die je niet tussen de soep en de patatten deed, maar met oprechte aandacht. Dank voor het vasthouden van de 'rode draad' en voor het onderscheid maken tussen sisyphusarbeid, de processie van Echternach en gestage progressie. Sabine, dank voor je frisse blik en je begeleiding bij het CBG. Je leiding en efficiënte vergaderstijl hebben mijn tijd daar zeker veraangenaamd. Dankzij jou heb ik de geneesmiddelenregulatie ook buiten de landsgrenzen mogen bekijken. Miriam, dank voor je scherpe geest en de vrijheid die je me hebt gegeven voor het uitwerken van dit onderzoek.

Prof.dr. Bob Zietse, prof.dr. Jan van Saase en prof.dr. Bert Leufkens, dank voor het plaats nemen in de kleine commissie. Beste Bob, dank voor de samenwerking bij het tot stand komen van de artikelen. Ik hoop dat er in de toekomst gelegenheid zal zijn om samen te werken bij verder onderzoek. Beste Jan van Saase, dank het vertrouwen ten aanzien van de opleiding interne geneeskunde. Ik hoop in de nabije toekomst nog veel van u te kunnen leren. Beste Bert Leufkens, dank voor het vertrouwen dat ik dit project vanuit het CBG heb mogen doen. Dank aan prof.dr. Peter de Smet en prof.dr. Dick de Zeeuw voor het plaats nemen in de grote commissie.

Dank aan alle coauteurs. Het was plezierig om met jullie samen te mogen werken.

Mijn collega's en vrienden binnen IPCI, de Medische Informatica wil ik bedanken voor de gezelligheid en het plezier tijdens de uitjes. In het bijzonder mijn dank aan Sandra. Met jou heb ik fun en frustratie vanuit Rotterdam en Den Haag – later Utrecht – mogen delen. Als er iets praktisch geregeld moest worden, dan had jij dit al gedaan. Marjolein en Gwen, dank dat jullie mijn paranimfen willen zijn. Ik ben vereerd dat ik op deze manier met jullie deze periode mag afsluiten. Een goede start voor de klus die hierdoor nog is blijven liggen. Dank aan mijn kamergenoten: Preci, ik heb vaak proefkonijn mogen zijn van jouw keukencreaties op momenten dat het glucoseaanbod aan mijn hersenen sterk verlaagd was; Leonoor, met jou kon ik mijn foxpro frustraties delen, maar gelukkig ook het plezier (aan de kinderen); Ana, Carmen en Osemeke ook jullie dank voor de gezelligheid op Ee-2116 en Na-2715. Vera en Inge, de borrels waren een aangename verrijking van de promotie, ik hoop dat er nog vele volgen. Marcel, dank voor al je uitleg over de IPCI database. Mees en Kris, dank voor alle ondersteuning, wanneer computers niet deden wat ik van ze verwachtte en in het bijzonder toen de harde

schijf het leven gaf. Dank aan Desirée voor al je hulp gedurende de laatste maanden van mijn promotie.

Mijn dank aan alle collega's uit de pharmaco-epi groep voor de gezelligheid en leerzame discussies: Alessandro, Alexandra, Ana, Ann, Annelies, Bouwe, Brenda, Caitlin, Carmen, Charlotte, Daan, Daniël, David, Emine, Fatma, Geert, Gianluca, Gina, Gwen, Inge, Ingrid, Ingrid, Jan, Janna, Jeanne, Kartini, Katia, Kiki, Laura, Leonoor, Lies, Loes, Maarten, Maria, Marieke, Marjolein, Mark, Marlies, Marten, Martijn, Martina, Nikki, Osemeke, Peter, Preci, Raymond, Rikje, Robert-Jan, Roelof Rosa, Sabine, Sandra, Sarah, Seppe, Silvana, Silvia, Sirwan, Toke en Vera.

Mijn dank aan iedereen die betrokken is bij de Rotterdam Study, aan alle deelnemers en huisartsen, aan Prof.dr. Albert Hofman en Dr. Jan Heeringa voor het opzetten en begeleiden van deze studie, aan Jolande, Rene & Rene, Frank en Nano voor de computerondersteuning en aan alle dames van het ERGO-centrum, in het bijzonder Pauline voor het maken van alle echo's.

Dank aan alle collega's van de afdeling farmacovigilantie van het CBG. Ik heb gedurende deze tijd veel geleerd over geneesmiddelenbewaking, wetgeving en vooral het belang van het melden van bijwerkingen. Dank voor jullie belangstelling en het begrip als ik er weer eens niet was. Dank aan Esther en Maarten voor het wegwijs maken in het ambtelijke apparaat. Dank aan Charlotte, Thijs Marjolein, Ineke, Inge, Leonoor, Ruben, Niels, Kartini en Alexandra voor het delen van de ervaringen om onderzoek te combineren met andere werkzaamheden.

Dank aan dr. Paul de Meijer voor de bevlogenheid over het vakgebied interne geneeskunde gedurende de jaren in Leiden. Dank aan de assistenten, internisten, MDL-artsen en longartsen van het Reinier de Graaf Gasthuis voor de gastvrijheid en de prettige samenwerking. Dr. Ward Posthuma en Dr. Henk Boom in het bijzonder dank voor de soepele overgang van promotie onderzoek naar de kliniek. Dr. Dezentjé, beste Vincent, dank voor je begeleiding en inspiratie voorafgaand aan dit promotietraject, alle mooie muziek op vrijdag en het getob met Excel, wat meer dan voldoende prikkel was om uit te vinden dat het inderdaad veel efficiënter kan.

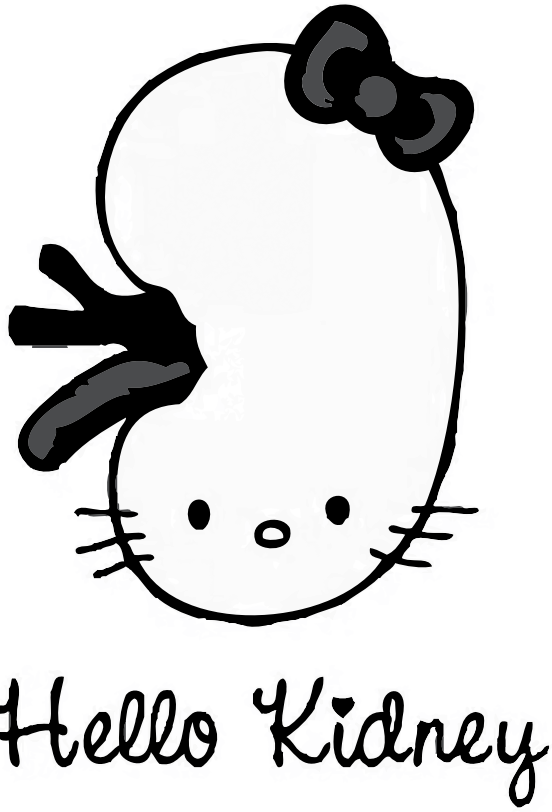
Lieve vrienden, dank voor jullie interesse en steun. Dank aan iedereen die ik niet bij naam genoemd heb, maar de afgelopen tijd toch voor me hebben klaar gestaan.

Dank aan mijn zus(je), zwager en schoonmoeder voor al jullie hulp gedurende de afgelopen 5 jaar.

Dank aan mijn lieve ouders voor jullie onvoorwaardelijke steun, jullie zorg voor onze kinderen en het eindeloze geklus dat ons leven in Delft nu zo aangenaam maakt. Na jaren werken is mijn proefschrift eindelijk klaar, ik hoop dat jullie trots zijn.

Lieve Nina en Lucas. Dank voor alle afleiding gedurende de afgelopen jaren op ieder (on)gewenst moment.

Lieve Emma, je bent prachtig! Zonder jouw inzet was dit alles niet mogelijk geweest. Ik ben vereerd dat ik de partner van deze alleenstaande moeder mag zijn. De promotie is nu af. Het is tijd om samen weer te gaan genieten van andere belangrijke en mooie zaken in het leven!



LIST OF PUBLICATIONS

Manuscripts within this thesis

Chapter 2

van Blijderveen JC, Straus SM, Zietse R, Stricker BH, Sturkenboom MC, Verhamme KM. A population-based study on the prevalence and incidence of chronic kidney disease in the Netherlands. Int Urol Nephrol. 2014 Mar;46(3):583-92.

Chapter 3

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Chapter 4

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Chapter 5

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PHD PORTFOLIO

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Research School	Netherlands Institute for Health Sciences
PhD period	October 2009 – December 2014
Promotores	Prof.dr. B.H.Ch. Stricker; Prof.dr. M.C.J.M. Sturkenboom
Co-promotores	Dr. K.M.C. Verhamme; Dr. S.M.J.M. Straus

PHD TRAINING

Research Skills

2010-2012 Master of Science in Health Science, specialization Clinical Epidemiology, Netherlands Institute for Health Sciences, Rotterdam, the Netherlands - 30 ECTS

Presentations

2013 Monitoring of renal function in patients starting (concurrent) therapy with diuretics and renin-angiotensin-aldosterone system (RAAS)-inhibitors, Netherlands Federation for Innovative Drug Research: Dutch Medicines Days (FIGON), the Netherlands

2013 When follow-up time cannot be assigned: chronic kidney disease and it's diagnosis (poster), 29th International Conference on Pharmaco-epidemiology & Therapeutic Risk Management, Montréal, Canada

2013 Burden of Chronic Kidney Disease (poster), 29th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Montréal, Canada

2012 Renal Function Impairment by Overanticoagulation? (poster), 28th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Barcelona, Spain

(Inter)national conferences and symposia

2013 Netherlands Federation for Innovative Drug Research: Dutch Medicines Days (FIGON), the Netherlands

2012 28th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Barcelona, Spain

Courses, seminars and workshops

2009-2014 Research Seminars, department of Medical Informatics, Erasmus University Medical Center, Rotterdam, the Netherlands

2010 EudraVigilance Data WareHouse Course; European Medicines Agency, London, United Kingdom

OTHER

Teaching activities

2014 Data-analysis in pharmacoepidemiology, NIHES, Rotterdam, the Netherlands

Peer-reviewing of papers

2014 Pharmacoepidemiology and Drug Safety

ABOUT THE AUTHOR

Nico van Blijderveen was born in Rhenen on February 25th, 1983. He started his study Medicine at Leiden University in 2002. In 2009, he obtained his medical degree. He worked for Sanquin Blood Supply Foundation and as an Intensive Care Unit resident in the HAGA hospital in the Hague.

In October 2009 he started the work as described in this thesis. The studies were conducted using data collected within the Integrated Primary Care Information (IPCI) database of the department of Medical Informatics and the Rotterdam Elderly Study of the department of Epidemiology of the Erasmus University Medical Center, Rotterdam, the Netherlands. He was supervised by Prof.dr. Bruno Stricker, prof.dr. Miriam Sturkenboom, dr. Katia Verhamme, and dr. Sabine Straus. In the same period of his PhD research, he also worked as an assessor of pharmacovigilance at the Dutch Medicines Evaluation Board in the Hague and later in Utrecht.

In August 2012 he obtained a Master of Science in Clinical Epidemiology at the Netherlands Institute for Health Sciences (NIHES).

In May 2014 he started working as a resident in Internal Medicine at the Reiner de Graaf hospital in Delft. In January 2015 he will start his specialty training in Internal Medicine under the supervision of dr. Ward Posthuma and prof.dr. Jan van Saase.