Influence of Drugs and Comorbidity on Serum Potassium in 15’000 Consecutive Hospital Admissions

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Abstract

Context: Drug studies often exclude subjects with relevant comorbidity or comedication. Nevertheless, after approval, these drugs will be prescribed to a much broader collective.

Objective: Our goal was to quantify the impact of drugs and comorbidity on serum potassium in unselected patients admitted to the hospital.

Design: Retrospective pharmacoepidemiologic study in 15'000 consecutive patients admitted between January 2002 and July 2004.

Setting: Medical department of the Kantonsspital St. Gallen, a 700-bed tertiary public hospital in eastern Switzerland.

Patients: Patients with "hemolytic" plasma and patients on dialysis or with an estimated creatinine-clearance <10 ml/min were excluded. For the remaining 14'146 patients drug history on admission, age, sex, body weight, physical findings, and ICD-10 diagnoses (comorbidities: e.g. liver cirrhosis, congestive heart failure, diabetes) were extracted from the electronic medical record. Laboratory information (potassium and creatinine) was added from electronic laboratory sources.

Main Outcome measure: Influence of comorbidity and comedication on the dose-effect relationship of drugs on serum potassium.

Results: Serum potassium at hospital admission was 3.96 ± 0.54 mmol/l. Creatinine clearance was the strongest predictor of serum potassium (p<0.0001). Angiotensin-converting enzyme inhibitors, cyclosporine, loop diuretics, and potassium sparing diuretics all showed a significant effect-modification with decreasing creatinine clearance (p<0.001). Similarly, in patients with liver cirrhosis a significantly stronger effect on potassium was found for angiotensin receptor blockers, betablockers, and loop diuretics (p<0.01). Several significant drug-drug interactions were identified. Diabetes, male sex, younger age, lower
blood pressure, and higher body weight were all independently associated with higher serum potassium levels (p<0.001).

Conclusions: The effects of various drugs on serum potassium are highly influenced by comorbidity and co-medication. Although effect modifications by acute diseases leading to hospitalization have to be kept in mind, clinical databases can be used to analyze issues of postmarketing drug safety.

Key words: potassium, hypokalemia, hyperkalemia, creatinine clearance, interaction, adverse drug effects, pharmacoepidemiology, DDD
Introduction

Potassium is the most abundant cation in the body. The vast majority (98%) of total body potassium (4000 mmol) is stored in the intracellular fluid compartment, whereas only about 60 mmol are in the extracellular fluid.\(^1,2\) Total body potassium contents are balanced by food-intake and urinary and fecal losses. The two main regulators of renal potassium excretion are mineralocorticoid activity and the availability of sodium in the distal nephron.\(^3\) In healthy people, serum potassium is further maintained in a narrow range by key hormones (insulin, \(\beta\)-adrenergic agonists) promoting its entry into the cells via Na\(^+\)/K\(^+\)-ATPase.\(^2\) Imbalances of serum potassium can result in deleterious effects on the cardiovascular system. Both hypokalemia and hyperkalemia are associated with increased mortality, mainly due to a higher risk of potentially fatal arrhythmia.\(^2,4,5\)

Several clinical conditions are known to be associated with either increased (e.g. renal dysfunction, hypoaldosteronism) or decreased (e.g. diarrhea, hyperaldosteronism) serum potassium concentration.\(^5,6\) Many frequently prescribed drugs influence the serum potassium concentration by either modulating renal potassium excretion (e.g. diuretics) or by transcellular shifting (e.g. insulin and \(\beta\)-mimetics).\(^1,6\) The prevalence of disorders of potassium balance in outpatients is not exactly known, but potassium at hospital admission is an excellent surrogate for the chronic effect of drugs in outpatients if the effects of acute derangements leading to hospital admission are kept in mind and if the analysis is done in a sufficiently large cohort. We therefore aimed to determine the relative contributions of different drugs and comorbidities on serum potassium in an unselected cohort of patients admitted to a representative tertiary referral center.
Methods

Patients

The Kantonsspital St. Gallen is the main tertiary referral center in eastern Switzerland. 15000 consecutive patients admitted to the Department of Internal Medicine between January 2002 and July 2004 were included in this study. Patients on dialysis and those with a creatinine clearance (Cr-Cl) < 10 mL/min were excluded. If the first blood sample was “hemolytic” the patient was also excluded unless a nonhemolytic sample was available within 24 hours of admission. Complete drug history on admission, age, sex, body weight, blood pressure, and comorbidities (ICD-10-diagnoses: congestive heart failure, liver cirrhosis, diabetes, diarrhea, vomiting, and malabsorption) were derived from the electronic patient record (Phoenix©, Parametrix, Lachen, Switzerland).

Drug history and defined daily doses

Sixteen drugs or groups of drugs with either a potassium-lowering or a potassium-increasing potential were recorded: angiotensin-converting enzyme inhibitors (ACEIs; 12 different generic substances), angiotensin receptor blockers (ARBs; 4), betablockers (14), β2-mimetics (5), carboanhydrase inhibitors (1), corticosteroids (5), calcineurin inhibitors (2), digitalis (1), L-Dopa or dopamine agonists (4), high- and low molecular heparin (4), laxatives (>10), loop diuretics (2), nonsteroidal antiinflammatory drugs (NSAID; 18), K-sparing diuretics (3), theophylline (1), as well as thiazides (6). Insulin and other antidiabetics were not included in the analysis because they were considered substitutes for an endogenous hormone deficiency and at the same time highly collinear with the variable diabetes, which was included in the analysis. Potassium supplements were also excluded from multivariate analysis because they are biased by indication: Since they are prescribed to correct hypokalemia, they would incorrectly be attributed a potassium-lowering effect. To standardize doses of different drugs within a class the daily dose of a given substance was expressed as multiples of a Defined Daily Dose (DDD) as defined by the world health
Drugs containing several substances, e.g. an ACEI and a thiazide diuretic, contributed to each class according to the dose of the respective component.

Laboratory analysis
Creatinine and potassium values were extracted from the laboratory database. The creatinine clearance (Cr-Cl) was estimated according the formula of Cockcroft and Gault.

Statistical analysis
Statistical analysis was performed using the statistical packages SAS release 8.2 (SAS institute Inc., Cary, NC, USA) and MATLAB release 7.0.4.365 (Natick, MA, USA). Continuous variables are presented as means ± standard deviations, or as medians and interquartile range (IQR), and categorical variables as percentage and rates. Missing values for body weight were imputed using a regression model with the variables gender and age. If the strength of the drug or the exact dosing schedule was not reported or ambiguous, the daily intake of 1 DDD was assumed. If the drug was taken “on demand” the daily intake of ½ DDD was assumed.

All variables were included in a multivariate regression model irrespective of their statistical significance. Predefined interactions were only included in the final model if their p-level was <0.05. Predictors of low (<3.0 mmol/l) and high (>5.0 mmol/l) potassium were also identified using logistic regression. A second analysis was performed using a neural network. For the graphical display of the results the patients were stratified according to the National Kidney Foundation (NKF) classification: I) Cr-Cl > 90 mL/min, II) Cr-Cl 60-89 mL/min, III) Cr-Cl 30-59 mL/min, IV Cr-Cl 15-29 mL/min, and V) Cr-Cl <15 mL/min.
Results

From the original cohort of 15000 patients 283 were excluded due to dialysis or (Cr-Cl) <10 ml/min and 571 were excluded due to “hemolytic” plasma. The present analysis is based on the data of 14146 patients, 5918 (42 %) were females and 8228 (58%) males. The mean (± standard deviation) age was 63.1 ± 16.1 years, and the weight was 70.0 ± 15.6 kg. Cr-Cl was overall 74 ± 34 ml/min, and serum potassium (K) 3.96 ± 0.53 mmol/l. Potassium increased from an average of 3.9 ± 0.4 mmol/l in class I (normal) kidney function to 4.6 ± 1.0 mmol/l in patients with class V kidney dysfunction.

The prevalence of comorbidities and the intake of the various drug-classes are summarized in table 1. If kidney dysfunction is omitted, overall 2829 (20%) had at least one comorbidity with alleged influence on serum potassium. The most prevalent condition was diabetes (13.4%), followed by congestive heart failure (CHF; 10.7%). 8909 (63%) took at least one drug with the potential to modify potassium. Betablockers were taken by almost 30%, the second largest group were inhibitors of the renin-angiotensin-aldosterone- (RAA-)system, followed by various diuretics.

Predictors of excessively low or high potassium levels

In a multivariate logistic regression analysis diarrhea was the strongest predictor of K< 3.0 mmol/l, followed by anorexia/malabsorption. The potential of thiazide diuretics to induce hypokalemia {Odds ratio (OR) 2.1, p<0.0001} was much higher than that of loop diuretics (OR 1.05, p=0.2). But also liver cirrhosis, lower weight, and surprisingly, female gender were independent predictors of hypokalemia (table 2).

The strongest predictor of K>5.0 mmol/l was the combination of ACE-inhibitors with K-sparing diuretics (OR 4.0; p<0.0001). K-sparing diuretics alone, cyclosporine, ACE-inhibitors, and ARBs were also associated with hyperkalemia. ARBs had an identical OR of 1.2 per DDD as ACE-inhibitors, but due to a smaller sample size (only 974 patients took ARBs as
opposed to 2538 patients taking ACE-inhibitors) the former association was only a statistical trend. Among non-pharmaceutical influences, impaired kidney function, diabetes, and higher body weight were all significantly associated with hyperkalemia (table 2).

Linear regression model

In multivariate linear regression, renal function expressed as log Cr-Cl evolved as the strongest predictor of serum potassium (p<0.0001). Interestingly this association seems to be age-dependent: older persons with similar Cr-Cl had significantly lower potassium values than younger persons (p<0.0001). This may reflect an adaptive effect to the invariable decrease of Cr-Cl with age. Indeed Cr-Cl decreased by 13 μmol/l per decade (p<0.0001) and as a result the unadjusted serum-potassium value even slightly increased by 0.04 mmol/l per decade. Moreover male sex was independently associated with higher serum potassium (p<0.0001). A strong positive relationship between serum-potassium and higher weight (p<0.0001) and a negative association between blood pressure and potassium were further evident (p<0.001) figure 1.

For ACE inhibitors (p<0.0001), cyclosporine (p<0.001), K-sparing diuretics (p<0.0001), and surprisingly also inhalative beta stimulants (p<0.01) and laxatives (p<0.0001) a significant association with higher serum potassium was found, whereas the intake of loop diuretics (p<0.01) and thiazides (p<0.0001) was associated with lower values. For several drugs no significant association between dose and serum potassium could be proven in this multivariate analysis (ARBs, betablockers, carboanhydrase inhibitors, digitalis, NSAIDs, corticosteroids, theophylline) or there was only a statistical trend (dopaminergic drugs and heparin). We believe, that – despite the relatively large sample size - this is mainly due to limited power. Nevertheless the model undoubtedly has to be adjusted for the well-known effects of these variables. Moreover, many of the latter drugs had significant interactions with other drugs or comorbidity figures 2A and 2B.
Diabetes was associated with significantly higher potassium even after adjustment for body weight (p<0.0001). A mild elevation of potassium in the presence of CHF or liver cirrhosis in the univariate analysis was no longer present after multivariate adjustment, however a strong potassium-lowering effect could be attributed to vomiting and diarrhea (p<0.0001). The effect of ACE inhibitors, cyclosporine, and K-sparing diuretics on serum potassium was amplified with decreasing renal function (p<0.001), whereas the potassium-lowering effect of loop-diuretics decreased with lower Cr-Cl (p<0.0001). Similarly, liver cirrhosis significantly enhanced the effect of ARBs, betablockers, and loop diuretics on serum potassium (p<0.01). Likewise, the potassium-lowering effect of thiazide diuretics was diminished in CHF figure 3.

Significant additive drug-drug interactions were found for ACE inhibitors with K-sparing diuretics and for betablockers with NSAIDs, whereas the potassium-lowering effect of thiazide diuretics was significantly reduced by ACE-inhibitors, NSAIDs, and K-sparing diuretics. Similarly ARBs attenuated the potassium-lowering effect of loop diuretics. In figure 4 some common drug-drug interactions are displayed three-dimensionally. The R^2, i.e. the explained variance of serum potassium by the linear regression model, amounted to 0.14.

Non-linear model

The neural network also yielded an R^2 of 0.14. Given an almost identical R^2 of both modeling techniques and also very similar overall results, we chose only to present the linear regression model.
Discussion

We have shown that in an unselected population admitted to a representative tertiary referral center, several drugs as well as comorbidities and demographic factors have a significant impact on serum potassium. In addition, the present analysis has revealed that the potassium-modifying effects of several classes of drugs are altered by renal or hepatic dysfunction. The majority of the identified relationships are in line with the knowledge about pharmakokinetics and pharmakodynamics of the tested drugs, whereas some of them are unexpected, warrant further explanation, or highlight some limitations of our study.

Renal function

As anticipated we identified a strong inverse relation between Cr-Cl and serum potassium. Several mechanisms impair the excretion of potassium with decreasing renal function: i) decreased delivery of sodium to the distal nephron, ii) aldosterone deficiency, and iii) abnormal function of the cortical collecting ducts. Metabolic acidosis may contribute to hyperkalemia. Renal dysfunction additionally enhanced the potassium-retaining effect of cyclosporine and of some inhibitors of the RAA system (see below).

Liver cirrhosis

Liver cirrhosis is commonly associated with secondary hyperaldosteronism. Nevertheless cirrhosis did not translate into a significant reduction of serum potassium in our model. This may be attributed to renal sodium sparing in cirrhosis: Effective kaliuresis in hyperaldosteronism is only possible if sufficient sodium reaches the distal renal tubule. Intravascular volume depletion with consecutive hyponatremia due to nonosmotic vasopressin secretion are commonly associated with cirrhosis and may limit natriuresis and thereby kaliuresis. Indeed, serum sodium concentration was on average 4 mmol/l lower (p<0.0001) in patients with liver cirrhosis than in other patients. Cirrhosis also resulted in a significant amplification of the potassium-modifying effects of ARBs, betablockers, and loop diuretics. This may be explained by the potent natriuresis in the case of loop-diuretics, an
antagonism of hyperaldosteronism (ARBs), or increased bioavailability due to portosystemic
shunts and reduced hepatic drug metabolism (ARBs, betablockers).\textsuperscript{11}

\textit{Congestive heart failure and blood pressure}

The presence of CHF alone was not associated with a significant effect on serum potassium,
although the RAA system is also typically activated in CHF patients. Nonetheless the
potassium-lowering effect of thiazide diuretics was mitigated in patients with CHF. This may
be attributed to the fact that hypotension reduces the glomerular filtration of sodium and thus
kaliuresis.\textsuperscript{12} This concept of pressure natriuresis is nicely illustrated by a significant inverse
relationship between blood pressure and serum potassium in our data.

\textit{Demographic factors, weight, and diabetes}

A striking finding of the present analysis is the highly significant association of younger age,
male sex, and higher body weight with higher serum potassium. This result may be attributed
to a generally higher food and thus potassium intake in younger persons, in men and in
subjects with higher body weight. Indeed, young individuals have a higher caloric intake in
comparison with elderly persons. Nevertheless a tendency for lower serum potassium in
older individuals is neither evident in clinical practice nor in our unadjusted data, because this
effect is offset by a gradual decline of kidney function, which in turn increases serum
potassium. Higher potassium levels in males as opposed to females may similarly be
attributable to the higher caloric intake, and higher resting energy expenditure of males.\textsuperscript{13} It is
further trivial to assume, that obese persons eat more. Higher body weight is also associated
with diabetes, and a strong independent association between diabetes and higher potassium
concentrations was also evident. This is best explained by hyporeninemic
hypoaldosteronism, which often accompanies diabetic nephropathy.\textsuperscript{3}

\textit{Inhibitors of the renin-angiotensin-aldosterone system}
In patients with CHF clinical trials have shown a survival benefit for ACE-inhibitors and ARBs either alone\textsuperscript{14, 15} or in combination\textsuperscript{16, 17}. Interestingly, the rate of hyperkalemia was very low in these major trials, whereas in unselected outpatients 10% develop hyperkalemia during one year of therapy\textsuperscript{18}. This discrepancy can be explained by the fact that patients with renal failure were excluded from most of these studies. We found a strong dose-effect relationship between therapy with ACEIs and serum potassium. A milder, albeit insignificant, relationship was observed for ARBs. Due to an interaction with kidney function, this effect was most pronounced in patients with lower Cr-Cl taking ACE inhibitors. No similar effect-amplification was found for ARBs, which is consistent with prospective clinical trials\textsuperscript{19-21}. One plausible explanation for this difference may be that many ACE inhibitors (mostly lisinopril and enalapril in the present study) accumulate in renal failure, whereas ARBs are usually eliminated by the liver.

Potassium-sparing diuretics

The intake of K-sparing diuretics was strongly predictive of higher serum potassium and the magnitude of this effect increased with declining renal function. Drugs affecting the RAA system at various sites are increasingly combined. Spironolactone has been shown to provide additional cardiovascular protection in patients with CHF, maximal therapy and NYHA class III-IV\textsuperscript{22}. The rate of hyperkalemia in the key study\textsuperscript{22} was extremely low (1%), probably due to careful selection (average serum creatinine level was 1.2 mg/dL \{106 μmol/L\}) and rigorous monitoring of the participating patients. However there is substantial evidence that the incidence of hyperkalemia is much higher, if patients with more advanced renal failure, comorbidities, and less intense monitoring undergo the same treatment\textsuperscript{23, 24}. This holds especially true if several drugs with an influence on the RAA-system are combined\textsuperscript{25}. Indeed we found an OR of four for the development of hyperkalemia if ACEIs were combined with K-sparing diuretics.

Non-potassium sparing diuretics

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We found a much stronger potassium-lowering effect for thiazides than for loop diuretics. This is well in accordance with previous studies. Only 35 persons took the carboanhydrase inhibitor acetazolamide at admission. Regardless of a lack of significance in our limited sample, this drug has a strong potential to induce severe hypokalemia and metabolic acidosis.

**Beta-blockers and β2-mimetics**

According to our data the potassium-retaining potential of beta-blocker therapy is substantially enhanced by a concomitant treatment with NSAIDs, whereas co-medication with inhibitors of the RAA system only showed additive effects.

In contrast to our expectations we could not demonstrate a potassium-lowering effect in patients with a drug history of inhalative β2-mimetics. Intriguingly we even found significantly higher potassium concentrations in this collective. These drugs induce a short term potassium shift into the cell, which has also been documented in several studies for their inhalative forms. One explanation for our seemingly paradox findings may be a partial β2-antagonistic effect of salbutamol. In a state of increased adrenergic tone this effect has been shown to lead to an increase of serum potassium similarly to the effect of beta blocking agents. Patients with obstructive pulmonary disease will often have increased adrenergic tone at hospital admission, especially during asthma attacks.

**Heparin**

Heparin impairs the biosynthesis of aldosterone in the adrenal gland, with consecutive hyperkalemia. In a recent study, which only included patients, who had been treated with low-molecular heparin for at least five days, the mean increase in serum potassium was 0.3 mmol/l. We only found a mild tendency towards higher serum potassium in patients receiving heparin at hospital admission. However the exposure to heparin may have been
too short, since most persons with heparin therapy at admission were transferred from regional hospitals due to acute coronary syndromes.

**Calcineurin inhibitors**

Immunosuppressive therapy with calcineurin inhibitors was strongly predictive of elevated potassium levels even after adjustment for hyperkalemia due to impaired kidney function. Our results are in accordance with previous studies, which found hyperkalemia in up to 73% of transplant recipients treated with cyclosporine or tacrolimus. The mechanisms of cyclosporine-induced hyperkalemia seem to include renal tubular dysfunction and secondary hypoaldosteronism.

**Non-steroidal anti-inflammatory drugs**

NSAIDs reduce prostaglandin-dependent renin-release and vasodilation of the renal afferent arteriole. This predisposes to impaired kidney function and hyperkalemia. In our data a strong tendency towards higher serum potassium levels in patients taking NSAIDs was no longer significant after adjustment for renal dysfunction. Therefore the potential of NSAIDs to increase potassium *beyond* a drug-mediated worsening of kidney function may be rather small. Our analysis however suggests a significant potassium-retaining interaction between NSAIDs and beta-blockers as well as thiazide diuretics. The decreased potassium-lowering effect of thiazide diuretics in the presence of NSAIDs might be due to reduced glomerular sodium filtration with a consecutively diminished diuretic and probably also kaliuretic effect.

**Laxatives**

The most unexpected finding in our study was a significantly higher serum-potassium in patients taking laxatives. Although hypokalemia can be observed in laxative abuse, no changes of serum electrolytes is usually found if newer laxatives are taken at the recommended doses. However the use of laxatives indicates the presence of constipation and patients usually do not overcorrect constipation to the point of inducing diarrhea. Stool
volumes and the consecutive electrolyte losses may thus be smaller in constipated persons even if they report the intake of laxatives. Furthermore constipated persons are often recommended to eat fiber-rich foods. These foods typically contain abundant potassium, which could also explain our seemingly paradox findings.

Hospital databases as sources of pharmacoepidemiologic data

Our study demonstrates, that hospital databases can be used to study the effect of drugs in severely ill patients. Many of the patients in this analysis would have been excluded from drug studies due to comorbidity. In recent years several drugs had to be withdrawn from the market (e.g. cerivastatin\textsuperscript{37} or rofecoxib\textsuperscript{38}) or their indication had to be restricted (e.g. spironolactone\textsuperscript{23} or aprotinin\textsuperscript{39}) only after thousands of patients had been exposed to them. Many tragic deaths could have been prevented if the information of hospital databases would systematically be analyzed. Unfortunately this information is often little structured. We therefore propose to define standards for the electronic documentation of medical diagnoses, laboratory data, and drug exposure, and that the regulatory authorities should have access to the safety signals derived from the analysis of aggregated data in a timely manner.\textsuperscript{40, 41}
Limitations of the study

Our study is retrospective and the whole analysis is based on the assumption, that a steady state is present for all of the included drugs and conditions at hospital admission. This assumption has to be challenged because acute derangements leading to admission, as dehydration or fever, may influence serum electrolytes. Patients might further report to take a prescribed drug although they were incompliant. This leads to an underestimation of the true effect of this drug. On the other hand some drugs may not have been reported, because patients did not consider them to be drugs. Many drugs not only influence the excretion of potassium but they can also impair kidney function (e.g. cyclosporine). If the effect of the drug is statistically adjusted for the degree of kidney dysfunction, which was also caused by this drug, the true effect of the drug on potassium is again underestimated. Finally our model only explains 14% of the variation of serum potassium. The residual variation may primarily be caused by large interindividual variations of potassium intake with food. However it could also be the consequence of genetic differences in the handling of potassium, drug metabolism, and differences at the molecular site of drug action, which have yet to be elucidated.

Conclusions

Despite these limitations several conclusion can be drawn from the present analysis: Renal function is the strongest single predictor of serum potassium at hospital admission. The effects of various drugs are significantly influenced by comedication and comorbidity. As the studied drugs and diseases are common, our analysis adds to the understanding of disturbances of serum potassium in patients with several comorbidities and who are treated with a large number of different drugs. Finally our analysis demonstrates, that hospital databases could provide cheap and reliant information for the analysis of post-marketing drug-safety.
Conflict of interests

All authors declare, that they have no potential conflicts of interests in respect to the content of this paper.
References

8. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine.


## Table 1  Co-morbidity and drug-use at admission

<table>
<thead>
<tr>
<th>Co-morbidities</th>
<th>N</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Creatinine-clearance &lt; 15 mL/min</td>
<td>185</td>
<td>1.3</td>
</tr>
<tr>
<td>Creatinine-clearance 15 – 29 mL/min</td>
<td>952</td>
<td>6.7</td>
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<tr>
<td>Creatinine-clearance 30 – 59 mL/min</td>
<td>4355</td>
<td>30.8</td>
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<tr>
<td>Creatinine-clearance 60 – 90 mL/min</td>
<td>4490</td>
<td>31.7</td>
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<td>Creatinine-clearance &gt; 90 mL/min</td>
<td>4163</td>
<td>29.4</td>
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<tr>
<td>Diabetes</td>
<td>1891</td>
<td>13.4</td>
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<tr>
<td>Congestive heart failure</td>
<td>1511</td>
<td>10.7</td>
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<tr>
<td>Diarrhea</td>
<td>544</td>
<td>3.9</td>
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<td>Liver cirrhosis</td>
<td>269</td>
<td>1.9</td>
</tr>
<tr>
<td>Anorexia or Malabsorption</td>
<td>60</td>
<td>0.4</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Drugs</th>
<th>N</th>
<th>%</th>
<th>Daily Dose (median; IQR)</th>
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</thead>
<tbody>
<tr>
<td>ACE-Inhibitors</td>
<td>2538</td>
<td>17.9</td>
<td>1.0 (1.0 – 2.0)</td>
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<tr>
<td>Angiotensin Receptor blockers</td>
<td>974</td>
<td>6.9</td>
<td>1.0 (1.0 – 2.0)</td>
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<td>Potassium-sparing diuretics</td>
<td>1000</td>
<td>7.1</td>
<td>0.5 (0.3 – 0.7)</td>
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<td>Loop diuretics</td>
<td>2291</td>
<td>16.2</td>
<td>1.0 (0.5 – 1.3)</td>
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<td>Thiazide diuretics</td>
<td>1168</td>
<td>8.3</td>
<td>0.5 (0.5 – 1.0)</td>
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<td>Carboanhydrase inhibitors</td>
<td>35</td>
<td>0.3</td>
<td>0.3 (0.3 – 0.7)</td>
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<td>Betablockers</td>
<td>4210</td>
<td>29.8</td>
<td>0.5 (0.3 – 0.7)</td>
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<td>Betaadrenergic stimulants</td>
<td>852</td>
<td>6.0</td>
<td>0.8 (0.8 – 1.1)</td>
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<tr>
<td>Dopaminergic drugs</td>
<td>160</td>
<td>1.1</td>
<td>0.6 (0.3 – 1.0)</td>
</tr>
<tr>
<td>Theophyllin</td>
<td>62</td>
<td>0.4</td>
<td>1.0 (0.8 – 1.0)</td>
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<tr>
<td>Corticosteroids</td>
<td>922</td>
<td>6.5</td>
<td>1.0 (0.5 – 2.5)</td>
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<tr>
<td>Heparinoids</td>
<td>925</td>
<td>6.5</td>
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<td>Cyclosporin</td>
<td>167</td>
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<td>Nonsteroidal anti-inflammatory drugs</td>
<td>796</td>
<td>5.6</td>
<td>0.5 (0.3 – 1.3)</td>
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<td>Digitalis</td>
<td>445</td>
<td>3.2</td>
<td>0.5 (0.5 – 1.0)</td>
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<td>Laxatives</td>
<td>944</td>
<td>6.7</td>
<td>2.0 (1.0 – 4.0)</td>
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<tr>
<td>Potassium supplements</td>
<td>134</td>
<td>1.0</td>
<td>1.0 (0.7 – 2.0)</td>
</tr>
</tbody>
</table>

**Legend to Table 1:** N: number of persons affected. Daily dose: cumulative daily dose expressed as multiples of defined daily dose (DDD) according to WHO. IQR: interquartile range
Table 2     Predictors of extreme potassium-values

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p=</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potassium &lt; 3.0 mmol/l</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.0</td>
<td>2.9 - 5.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Malabsorption or anorexia</td>
<td>3.6</td>
<td>1.6 - 8.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>3.5</td>
<td>2.6 - 4.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>2.7</td>
<td>1.5 - 5.0</td>
<td>0.0008</td>
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<tr>
<td>Female gender</td>
<td>1.6</td>
<td>1.3 - 2.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight (per 10 kg lower)</td>
<td>1.2</td>
<td>0.7 - 0.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>1.1</td>
<td>1.0 - 1.2</td>
<td>0.06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p=</th>
</tr>
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<tbody>
<tr>
<td><strong>Potassium &gt; 5.0 mmol/l</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ACE-inhibitors in combination with potassium-sparing diuretics</td>
<td>4.0</td>
<td>2.7 - 5.9</td>
<td>&lt;0.01</td>
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<tr>
<td>Creatinine clearance (per 10 ml/min lower)</td>
<td>2.0</td>
<td>1.9 - 2.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Potassium sparing diuretics</td>
<td>1.9</td>
<td>1.4 - 2.7</td>
<td>&lt;0.0001</td>
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<tr>
<td>Diabetes</td>
<td>1.7</td>
<td>1.3 - 2.2</td>
<td>&lt;0.0001</td>
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<tr>
<td>Cyclosporine</td>
<td>1.4</td>
<td>1.1 - 1.7</td>
<td>&lt;0.001</td>
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<tr>
<td>Weight (per 10 kg higher)</td>
<td>1.3</td>
<td>1.2 - 1.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>1.2</td>
<td>1.02 - 1.4</td>
<td>0.02</td>
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<tr>
<td>AT2-receptor blockers</td>
<td>1.2</td>
<td>0.9 - 1.5</td>
<td>0.1</td>
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</tbody>
</table>

Legend to Table 2: Adjusted for risk factors and drugs with alleged influence on potassium. OR: odds ratio per 1 defined daily dose (DDD), 95% CI: lower and upper 95% confidence intervals.
Figure Legends

Figure 1  Influence of patient characteristics on serum potassium
Vertical axis: serum potassium concentration in mmol/liter. Mean blood pressure is diastolic blood pressure + (systolic blood-pressure – diastolic blood pressure /3).

Figures 2A & 2B  Effect of drugs on serum potassium
Vertical axis: serum potassium concentration in mmol/liter. Horizontal axis: DDD (defined daily dose of a drug-class according to WHO definitions). All drug-effects are normalized for a 50-jeary old male patient with a creatinine clearance of 50 ml/min, and a body weight of 75 kg. * Denotes a significant interaction between drug and creatinine clearance.

Figure 3  Influence of comorbidity on serum potassium and on drug effects
Vertical axis: serum potassium concentration in mmol/liter. Horizontal axis: DDD (defined daily dose of a drug-class according to WHO definitions). CHF denotes congestive heart failure. All drug-effects are normalized for a 50-jeary old male patient with a creatinine clearance of 50 ml/min, and a body weight of 75 kg. * Denotes a significant interaction between the marked co-morbidity and the drug.

Figure 4  Effect of drug-drug interactions on serum potassium
Vertical axis: serum potassium concentration in mmol/liter. The horizontal axes show the daily intake of the respective drug classes expressed as multiples of DDD (defined daily doses according to WHO-definitions). All drug-effects are normalized for a 50-jeary old male patient with a creatinine clearance of 50 ml/min, and a body weight of 75 kg. * Denotes a significant drug-drug interaction.