Importance of potassium in patients with antihypertensive medication – a Danish register-based approach

Krogager, Maria Lukacs

Publication date:
2020

Document Version
Publisher's PDF, also known as Version of record

IMPORTANCE OF POTASSIUM IN PATIENTS WITH ANTIHYPERTENSIVE MEDICATION – A DANISH REGISTER-BASED APPROACH

BY
MARIA LUKÁCS KROGAGER

DISSERTATION SUBMITTED 2020

AALBORG UNIVERSITY
DENMARK

Importance of potassium in patients with antihypertensive medication – a Danish register-based approach

by

Maria Lukács Krogager

Dissertation submitted: September 2020

PhD supervisor: Professor Christian Torp-Pedersen, MD, DMSc
Department of Cardiology and Clinical Research
Nordsjællands Hospital, Hillerød, Denmark.

Co-PhD supervisor: Professor Peter Søgaard, MD, DMSc
Department of Cardiology,
Aalborg University Hospital, Denmark.

Assistant PhD supervisor: Kristian Kragholm, MD, PhD
Department of Cardiology,
Aalborg University Hospital, Denmark.

PhD committee: Clinical Professor Torben Bjerregaard Larsen (chair)
Department of Clinical Medicine
Aalborg University

Professor Patrick Rossignol
Centre d'Investigation Clinique Plurithématique Pierre Drouin-INSERM CHU de Nancy,
Université de Lorraine, FCRIN INI-CRCT, Nancy

Clinical Associate Professor Kristina Procida
Department of Clinical Medicine
Zealand University Hospital

PhD Series: Faculty of Medicine, Aalborg University

Institut: Department of Clinical Medicine

ISSN (online): 2246-1302
ISBN (online): 978-87-7210-804-9

Published by:
Aalborg University Press
Kroghstræde 3
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Rosendahls, 2021

Papers

This PhD thesis is based on the following studies:

I. Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data

Maria Lukács Krogager, Christian Torp-Pedersen, Rikke Nørmark Mortensen, Lars Køber, Gunnar Gislason, Peter Søgaard, Kristian Aasbjerg.

European Heart Journal, 7 January 2017
https://doi.org/10.1093/eurheartj/ehw129

II. Impact of plasma potassium normalization on short-term mortality in patients with hypertension and hypokalemia or low normal potassium

Maria Lukács Krogager, Peter Søgaard, Christian Torp-Pedersen, Henrik Bøggild, Christina Ji-Young Lee, Anders Bonde, Jesper Q. Thomassen, Gunnar Gislason, Manan Parek, Kristian Kragholm

BMC Cardiovascular disorders, 24 August 2020
https://bmccardiovascdisord.biomedcentral.com/articles/10.1186/s12872-020-01654-3

III. Impact of plasma potassium normalization on short-term mortality in patients with hypertension and hyperkalemia

Maria Lukács Krogager, Peter Søgaard, Christian Torp-Pedersen, Henrik Bøggild, Gunnar Gislason, Kristian Kragholm

IV. Risk of developing hypokalemia in patients with hypertension treated with combination antihypertensive therapy

Maria Lukács Krogager, Rikke Nørmark Mortensen, Peter Enemark Lund, Henrik Bøggild, Steen Møller Hansen, Kristian Kragholm, Kristian Aasbjerg, Peter Søgaard, Christian Torp-Pedersen

Hypertension, 2 March 2020
https://www.ahajournals.org/doi/abs/10.1161/HYPERTENSIONAHA.119.14223

English summary

Potassium has a pivotal role in cardiovascular disease and maintenance of potassium homeostasis is essential to prevent adverse events. Individuals with hypertension are one large subgroup of patients with heart disease that are usually prescribed drugs with effect on blood potassium concentrations. Often, targeted blood pressure is achieved with combination therapy only, which can lead to potassium disarrays. The normal potassium interval (serum potassium: 3.5-5.0 mmol/L, plasma potassium 3.5-4.6 mmol/L) is defined based on apparently healthy individuals, and levels outside this range are associated with increased morbidity and mortality.

This thesis examines optimal potassium concentrations and impact of potassium normalization after the first episode with hypo- or hyperkalemia on short-term mortality in patients with hypertension treated with at least two classes of antihypertensive drugs. We also investigated short-term hypokalemia risk in relation to different combinations of antihypertensive therapies.

Study I. From 1995-2012, 44,799 patients with hypertension were treated with minimum two antihypertensive drug classes and had at least one potassium measurement within 90-days from treatment initiation. The relationship between potassium and mortality was U-shaped. We observed that patients with potassium concentrations outside the interval 4.1-4.7 mmol/L including low and high normal potassium range had increased short-term mortality risk (90-days follow-up) compared to the reference (K: 4.1-4.4 mmol/L).

Study II. A total of 8,976 patients with hypertension and potassium concentrations ≤ 3.7 mmol/L at the first measurement within 100 days from hypertension diagnosis were identified. We retained the results of a second potassium draw within 6-100 days after the episode with hypokalemia. Of the patients with potassium levels between 3.5-3.7 mmol/L at the first draw, 13% had measurements below 3.5 mmol/L and 5.7% had concentrations above 4.6 mmol/L at the second draw. Persistent hypokalemia (<3.5 mmol/L) was frequent (28.5%) and associated with increased short-term all-cause

and cardiovascular death. Increased all-cause and cardiovascular mortality risk was also observed when low potassium concentrations were overcorrected to levels above 4.6 mmol/L.

Study III. We included 7,620 patients with hypertension and potassium concentrations ≥4.7 mmol/L (hyperkalemia) at the first measurement within 100-days from diagnosis. A subsequent measurement within 6-100 days following the first draw was required. The results showed that potassium concentrations outside the interval 4.1-5.5 mmol/L after an episode with hyperkalemia were associated with increased all-cause and cardiovascular mortality risk.

Study IV. By matching 463 patients with hypokalemia to 926 patients with normal potassium concentrations, we observed that combinations of thiazides with calcium channel blockers, beta-blockers or renin-angiotensin system inhibitors were associated with increased odds of developing hypokalemia within 90-days of treatment initiation, regardless of potassium supplementation.

In conclusion, our studies suggested that a more strict normal potassium interval (4.1-4.7 mmol/L) was beneficial in patients with hypertension. Persistent hypokalemia was associated with poor outcomes. Patients with initial plasma potassium concentrations between 3.5-3.7 mmol/L were at high risk of mortality, partly because of further decrease in potassium and partly due to overcorrection. Increase in potassium concentrations >4.6 mmol/L after an episode with potassium ≤3.7 mmol/L was associated with increased risk of all-cause and cardiovascular mortality. Decrease in plasma potassium to levels <4.1 mmol/L and potassium concentrations >5.5 mmol/L after an episode with hyperkalemia were associated with increased risk of all-cause and cardiovascular mortality. Combination of any antihypertensive drugs with thiazide diuretics was associated with high odds of hypokalemia within 90-days from treatment initiation.

Dansk resume

Kalium har en central rolle i udviklingen af hjertekarsygdomme. For at forhindre komplikationer hos patienter der er kendt med hjertesygdomme er opretholdelse af kalium homeostasen essentiel. Patienter behandlet for hypertension er en stor subgruppe af patienter med hjertesygdom, der ofte er ordineret medicin med virkning på kalium koncentrationen i blodet. Kombinationsterapi er tit nødvendig for at opnå den anbefalede blodtryk, hvilket kan føre til kaliumforstyrrelser. Det normale kaliuminterval (serum kalium:3.5-5.0 mmol / L, plasma kalium:3.5-4.6 mmol / L) er defineret baseret på tilsyneladende sunde individer, og niveauer uden for dette område er forbundet med øget sygelighed og dødelighed.

Denne afhandling undersøger de optimale kaliumkoncentrationer hos patienter med hypertension behandlet med mindst to klasser af antihypertensiva. Derudover, kigger vi på virkningen af kaliumnormalisering efter den første episode med hypo- eller hyperkaliæmi på overlevelsen hos samme patientgruppe. Sidst, undersøgte vi sandsynligheden for hurtig indsættende hypokaliæmi i relation til forskellige kombinationer af antihypertensiv behandling.

Studie I. Fra 1995 til 2012 identificerede vi 44,799 patienter med hypertension behandlet med mindst to klasser af antihypertensiva som havde mindst en kaliummåling inden for 90-dage efter behandlingsstart. Vi observerede i U-formet sammenhæng mellem kalium og 90-dages dødeligheden. Patienter med kaliumkoncentrationer uden for intervallet 4.1-4.7 mmol/L havde øget risiko for 90-dages dødelighed sammenlignet med referencen (K: 4.1-4.4 mmol / L).

Studie II. Vi identificerede 8,976 patienter med hypertension med kaliumkoncentrationer ≤3.7 mmol/L, ved den første måling, inden for 100 dage fra behandlingsstart. Vi gemte resultaterne af en anden måling fortaget inden for 6-100 dage efter episoden med hypokalæmi eller borderline hypokaliæmi. Af patienterne med kaliumniveauer mellem 3.5-3.7 mmol/L ved den første måling havde 13% målinger under 3.5 mmol/L ved den anden måling og 5.7% havde koncentrationer over

4.6 mmol/L ved den anden måling. Vedvarende hypokaliæmi (<3.5 mmol/L) var hyppig (28.5%) og forbundet med øget kardiovaskulær død og død af alle årsager. Forøget dødelighed (kardiovaskulær og af alle årsager) blev også observeret, når lave kaliumkoncentrationer blev overkorrigeret til niveauer over 4.6 mmol/L.

Studie III. Vi inkluderede 7,620 patienter med hypertension og kaliumkoncentrationer ≥4,7 mmol/L (hyperkaliæmi) ved den første måling inden for 100 dage efter start kombinationsbehandling. En efterfølgende måling inden for 6-100 dage efter den første mål var påkrævet. Resultaterne viste, at kalium koncentrationer udenfor intervallet 4.1-5.5 mmol/L, efter episode med hyperkaliæmi, var associerede med forøget risiko for kardiovaskulær død og død af alle årsager.

Studie IV. Ved at matche 463 patienter med hypokaliæmi med 926 patienter med normale kaliumkoncentrationer, observerede vi, at kombinationer af thiazider med calciumkanalblokkere, beta-blokkere eller renin-angiotensin system inhibitorer var forbundet med høj sandsynlighed for hypokaliæmi inden for 90 dage efter start kombinationsbehandling, på trods af kaliumtilskud hos mange patienter.

Afslutningsvis, viste vores studier, at et mere snævert normalt kaliuminterval (4.1-4.7 mmol/L) var forbundet med større sandsynlighed for overlevelse hos patienter med hypertension behandlet med mindst to klasser af antihypertensiva. Vedvarende hypokaliæmi var forbundet med dårlig korttids prognose. Patienter med initiel plasma kalium niveau mellem 3.5-3.7 mmol/L havde øget risiko for kortids dødelighed, dels pga. yderligere fald i kalium og dels pga. overkorrektion. Fald i kaliumkoncentrationer til niveauer <4.1 mmol/L og >5.5 mmol/L var forbundet med øget risiko for kardiovaskulær død og død af alle årsager. Kombination af antihypertensiva med thiazid diuretika var forbundet med høj sandsynlighed for hypokaliæmi inden for 90 dage fra start kombinationsterapi.

Preface

This thesis is based on four studies carried out during medical school and as a PhD student at the Department of Cardiology, Aalborg University Hospital and affiliated to the Unit of Epidemiology and Biostatistics, Aalborg University Hospital.

A number of persons made this work possible. However, Christian Torp-Pedersen and Peter Søgaard have been by my side during the whole process. Thank you for giving me the opportunity to work and learn from you. I have always appreciated your availability at any time, regardless of working hours, weekends or holidays. I have enjoyed your advice both personally and professionally. Thank you for always having my best interest in mind.

I would also like to express my gratitude to Kristian Kragholm for his supervision, friendship and for building bridges between me and other researchers.

Finally, I would like to thank my husband, Kristian, for accepting and supporting my priorities.

Maria Lukács Krogager, February 2020

Table of contents

Papers 3
English summary 4
Dansk resume 6
Preface 8
1. Introduction 12
1.1 Hypertension 12
1.2 Potassium homeostasis 13
1.3 Potassium biochemistry (blood potassium measurement) 14
1.4 Potassium and cardiovascular disease 16
1.4.1 Hypokalemia 16
1.4.2 Hyperkalemia 17
2. Aims 19
3. Methods 20
3.1 Data sources 20
3.2 Study I 21
3.2.1 Study population 21
3.2.2 Comorbidities and drugs 22
3.2.3 Exposure variable 23
3.2.4 Outcome definition 23
3.2.5 Statistical analysis 23
3.3 Study II 24
3.3.1 Study population 24
3.3.2 Comorbidities and drugs 25
3.3.3 Exposure variable 25
3.3.4 Outcome definition 26
3.3.5 Statistical analysis 26
3.4 Study III 27
3.4.1 Study population 27
3.4.2 Comorbidities and drugs 27
3.4.3 Exposure variable 28
3.4.4 Outcome definition 28
3.4.5 Statistical analysis 28
3.5 Study IV 30

3.5.1 Study population 30
3.5.2 Comorbidities and drugs 30
3.5.3 Exposure variable 31
3.5.4 Outcome definition 32
3.5.5 Statistical analysis 32
4. Results 33
4.1 Study I 33
4.1.1 Demographics 33
4.1.2 Survival analysis 36
4.1.3 Sensitivity analyses 38
4.2 Study II 39
4.2.1 Demographics 39
4.2.2 Survival analysis 42
4.2.3 Subgroup and sensitivity analyses 44
4.3 Study III 45
4.3.1 Demographics 45
4.3.2 Survival analysis 49
4.3.3 Sensitivity analyses 50
4.4 Study IV 52
4.4.1 Demographics 52
4.4.2 Antihypertensive combination therapies and risk of hypokalemia 54
4.4.3 Sensitivity analyses 55
5. Discussion 56
5.1 Study I 56
5.2 Study II 58
5.3 Study III 61
5.4 Study IV 63
6. Strengths and limitations 65
6.1 Study I 66
6.2 Study II-III 67
6.3 Study IV 67
7. Conclusions 68
7.1 Study I 68
7.2 Study II 68

7.3 Study III 68
7.4 Study IV 68
8. Clinical implications and perspectives 69
8.1 Study I 69
8.2 Study II 69
8.3 Study III 70
8.4 Study IV 70
9. References 72
10. Appendices 79

1. Introduction

1.1 Hypertension

Worldwide, approximately 26% of the population is diagnosed with hypertension and the prevalence is anticipated to increase to 29% by 2025.[1] Hypertension increases the risk of cardiovascular disease and is considered the most important modifiable risk factor for disability and adjusted life-years[2,3].

Hypertension is defined as systolic blood pressure (SBP) values ≥140 mmHg and/or diastolic blood pressure (DBP) values ≥90 mmHg.[4] Hypertension can be classified according to its etiology as primary or as secondary to other diseases such as hyperaldosteronism, diabetic nephropathy or coarctation of the aorta.[5] Based on office blood pressure measurements, hypertension can be subdivided into four categories: grade 1 hypertension (SBP 140-159 mmHg and/or DBP 90-99 mmHg), grade 2 hypertension (SBP 160-179 mmHg and/or DBP 100-109 mmHg), grade 3 hypertension (SBP ≥180 mmHg and/or DBP ≥110 mmHg) and isolated systolic hypertension (SBP ≥140 mmHg and DBP <90 mmHg).[4]

Management of arterial hypertension implies non-pharmacological and pharmacological strategies. To achieve optimal blood pressure control, most of the patients require drug therapy in addition to lifestyle changes. Guidelines recommend five major drug classes for treatment of hypertension: diuretics (especially thiazides and thiazide-like diuretics), calcium channel blockers (CCBs), beta-blockers (BB), angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).[4] Despite the effectiveness of antihypertensive medication, only approximately 30% of the patients with high blood pressure achieve the therapeutic goal of <140/90 mmHg with monotherapy.[6] As a result, a large proportion of the patients require combination antihypertensive therapy, which can lead to adverse events. One of the most common side effects of antihypertensive medication is disruption of potassium homeostasis, despite use of agents with opposite effects on potassium metabolism.[7]

1.2 Potassium homeostasis

Potassium is the most abundant cation in the intracellular fluid and normal cell function is highly dependent on maintaining a proper distribution of potassium across the cell membrane.[8] Regulation of potassium homeostasis is a complex process with many participating actors. In the following paragraphs, a brief summary of the most important mechanism are listed.

The sodium and potassium pump (Na^+-K^+ ATPase) controls the potassium gradient between the extracellular and intracellular fluid, a process also known as internal potassium balance. Insulin and catecholamines are among the most important factors in regulating this process.[9]

The kidney is the main actor of external potassium homeostasis, eliminating approximately 90% of the ingested potassium.[10] Unbound potassium is filtered in the glomerulus and less than 10% of the filtered load reaches the distal nephron. The rate of potassium excretion is highly dependent on potassium reabsorption and secretion.[11] The highest proportion of potassium is reabsorbed in the proximal convoluted tubule and thick ascending Loop of Henle, while potassium secretion occurs mainly in the distal tubule and collecting duct. Reabsorption in the proximal tubule is primarily a passive process proportional to the amount of water and sodium. Potassium absorption along the thick ascending Loop of Henle occurs through both transcellular and paracellular pathways.[9,12] Aldosterone has a major role in stimulating potassium secretion. First, aldosterone stimulates the activity of the Na^+-K^+ ATPase in the basolateral membrane, process that results with increased intracellular potassium concentration. Second, aldosterone stimulates sodium reabsorption across the luminal membrane with potassium secretion into the lumen in consequence. Lastly, aldosterone increases luminal membrane permeability to potassium.[13] The rate of distal delivery of sodium and water is also a major determinant affecting potassium secretion. Increased sodium concentration in the distal nephron stimulates its reabsorption, which makes the luminal potential more negative and, hence, increases potassium secretion.[9]

In patients with chronic kidney disease there is an adaptive increase in potassium secretion in the healthy nephrons, such that potassium homeostasis is maintained until a drop in glomerular filtration rate below 15-20 ml/min.[14]

1.3 Potassium biochemistry (blood potassium measurement)

Blood potassium concentrations can be measured both in serum and in plasma.[15] During the clotting process, platelets burst and release potassium, resulting in higher potassium levels in serum as compared to plasma.[16] Studies have shown that the difference between serum and plasma potassium concentrations is minimal in the lower end (<0.1 mmol/L) and substantial in the higher end (>0.5 mmol/L).[17]

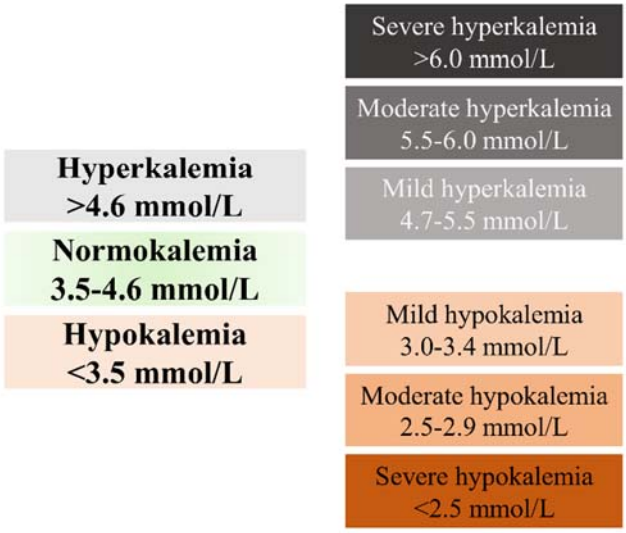
The normal potassium reference interval is based on measurements from healthy individuals and depends on the population and the methods used to assess blood potassium concentrations. Table 1.1 gives an overview on reference intervals for potassium in both serum and plasma for different populations. The normal range for serum potassium is 3.5-5.0 mmol/L, whereas levels between 3.5-4.6 mmol/L are considered normal for plasma potassium.[17–19]

Table 1.1 Reference intervals for potassium in serum and plasma in different populations

Population	**US**[18]	**German**[17]	**Nordic**[19]
Plasma reference interval	3.4-4.8 mmol/L	3.5-4.6 mmol/L	3.5-4.4 mmol/L
Serum reference interval	3.5-5.1 mmol/L	3.7-5.1 mmol/L	3.6-4.6 mmol/L

The severity of hypokalemia and hyperkalemia and be categorized as shown in Figure 1.1.

Figure 1.1 Definitions of normokalemia, hypokalemia and hyperkalemia (potassium concentrations assessed in plasma).



As intracellular potassium concentration is approximately 40 times greater than the extracellular concentration, even small sampling errors that would result in release of a small amount of intracellular potassium will falsely increase potassium levels. Pseudohyperkalemia is defined as a difference of more than 0.4 mmol/L between serum and plasma potassium concentrations, given that the samples remain at room temperature and are tested within an hour from collection.[20] There are different causes of pseudohyperkalemia: mechanical causes (tourniquet, fist clenching, traumatic venipuncture, inappropriate needle diameter), temperature (above room temperature or between 2ºC and 8ºC), chemical factors (ethanol), time, thrombocytosis, alkalosis and contaminants.[15]

Pseudohypokalemia is not just as common as pseudohyperkalemia, but can be encountered in blood draws with very high white cell count kept at room temperature for a long time and blood samples from patients who were administered intravenous insulin kept at room temperature for prolonged period.[21]

1.4 Potassium and cardiovascular disease

Potassium has a pivotal role in the development and exacerbation of cardiovascular diseases.[22] Potassium has vasodilatory effect, thus, a blood pressure lowering property.[23] Clinical studies demonstrated that high-sodium and low-potassium diet causes sodium retention and raises blood pressure. On average, SBP increased by 6 mmHg and DBP by 4 mmHg in normotensive participants, and SBP increased by 7 mmHg and DBP by 6 mmHg in hypertensive participants.[24,25]

Most cases of hypokalemia and hyperkalemia occur in the setting of specific disease states such as cardiovascular and renal disease. In patients with ongoing cardiovascular disease, cardiac medication is the main cause of potassium disarrays.[26,27] Thiazide and loop diuretics decrease blood potassium concentrations, while potassium sparing diuretics, beta-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers commonly cause hyperkalemia.[26,28]

A great focus is set on preventing dyskalemias because of their arrhythmogenic effect, especially in patients with heart disease who already have a high proarrhythmic substrate. The electrophysiology of hypokalemia and hyperkalemia is rather complex, and the electrophysiological effects that typically induce cardiac arrhythmias are not solely based on potassium disarrays, but also on balances of sodium and calcium.[29] In the two following subparagraphs, electrophysiological consequences, symptoms and electrocardiographic manifestations and treatment of hypokalemia and hyperkalemia are presented. However, it is important to note that electrocardiographic changes are not always present in patients with dyskalemias and that electrocardiographic changes depend on the severity of potassium imbalances.

1.4.1 Hypokalemia

The electrophysiological effects of hypokalemia on cardiac conduction system include: resting membrane hyperpolarization, Na^+-K^+ ATPase inhibition, prolongation of action potential duration,

reduced repolarization reserve, automaticity, early afterdepolarization-mediated arrhythmias and delayed afterdepolarization-mediated arrhythmias.[29]

Typically, the earliest electrocardiographic manifestation of hypokalemia is decreased T-wave amplitude or inversion (mild hypokalemia), followed by ST-segment depression, T-wave inversion, PR-interval prolongation and U-wave (moderate hypokalemia).[30–34] Sinus bradycardia, atrial and ventricular tachycardia or ventricular fibrillation and Torsades de Pointes are commonly seen arrhythmias in patients with severe hypokalemia.[31,35,36] Yet, some patients, even with severe hypokalemia, do not have electrocardiographic changes.[32]

Most of the patients with mild hypokalemia do not experience any symptoms. The clinical manifestations of hypokalemia include fatigue, muscle weakness, cardiac arrhythmias or cramping and gastrointestinal hypomotility.[30]

Management of hypokalemia includes three strategies: (1) identification of the underlying cause, (2) decrease potassium losses (commonly through renal or gastrointestinal system) and (3) replenishing of potassium stores (e.g. according to the severity p.o. or i.v. of potassium chloride, potassium phosphate, potassium bicarbonate).

1.4.2 Hyperkalemia

The cardiac electrophysiological effects of systemic hyperkalemia are: action potential duration shortening, increased repolarization reserve and decreased conduction velocity.[29] The earliest electrocardiographic sign of hyperkalemia is tall T-waves. In patients with hyperkalemia, the electrocardiogram can also show P-wave flattening, PR-interval prolongation, widening of the QRS complex and sine waves. Arrhythmias associated with hyperkalemia include sinus bradycardia, sinus arrest, ventricular tachycardia, ventricular fibrillation and asystole. Some of the symptoms related to hyperkalemia are tiredness, numbness or tingling, nausea, chest pain or palpitations.[30]

Acute, life-threatening hyperkalemia, should be treated immediately to prevent adverse outcomes and treatment strategies can divided into three main categories: (1) Shift of potassium from the extracellular into the intracellular space (β2-adrenergic agonists, insulin ± glucose, sodium bicarbonate in case of metabolic acidosis), (2) Heart membrane stabilization (calcium chloride or gluconate, hypertonic saline (3-5%)), (3) Increase potassium elimination (loop diuretics, hemodialysis, cation-exchange resins (sodium polystyrene sulfonate), sodium bicarbonate or potassium binders (patiromer, sodium zirconium cyclosilicate)).[37]

2. Aims

The general aim of this thesis is to contribute to the current knowledge on goals for potassium levels in patients with hypertension using data from the Danish national registers.

The specific aims of the four studies were to investigate:

I. Short-term mortality risk associated with different potassium concentrations in patients treated with combination antihypertensive therapy.

II. The impact of plasma potassium normalization on short-term mortality in patients with hypertension and hypokalemia or low normal potassium levels

III. The impact of plasma potassium normalization on short-term mortality in patients with hypertension and hyperkalemia or high normal potassium levels

IV. The risk of hypokalemia shortly after combination antihypertensive therapy initiation in relation to different combinations of blood pressure agents

3. Methods

3.1 Data sources

All four studies in this thesis are register based cohort studies, where following nationwide registers were used: The Civil Registration System,[38] The Danish Register of Causes of Death,[39] The Danish National Patient Register,[40,41] The Danish Prescription Register[42] and The Electronic Registers of Laboratory Data.

In Denmark, all citizens are given at birth or migration a personal, unique and permanent civil registration number, which enables cross-linkage between the administrative registers and ensures a high degree of follow-up.

Information from The Civil Registration System was used in all four studies and covers data on date of birth, sex and vital status since 1968.[38]

The Danish Register of Causes of Death supplements with information on both underlying and contributing causes of death, coded with an International Classification of Diseases (ICD) code. Before 2007, non-physicians coded the causes of death supervised by the National Board of Health. However, after 2007, death certificates are filled and submitted electronically by a physician without central validation.[39]

The Danish National Patient Register contains information on all hospital admissions since April 1977. Hospitalizations are coded with one primary and one or more secondary diagnoses using ICD-8 codes until 1994, and ICD-10 thereafter. The register also covers data on all outpatient visits, emergency room and psychiatric ward contacts since 1995. Since 2003, it has been mandatory for private hospitals to register all contacts, yet the registration is incomplete.[40,41] The Danish National Patient Register holds data on surgeries and clinical procedures since 1996, coded according to The Nordic Medical Statistics Committees Classification of Surgical Procedures.

The Danish Prescription Registry, also known as The Register of Medicinal Product Statistics, contains information about all dispensed prescriptions from outpatient pharmacies since 1994. Data completeness is though available from 1995. Redeemed drugs are registered according to the Anatomical Therapeutic Chemical Classification system (ATC).[43]

The electronic registers of laboratory data do not contain nationwide data and registration is available since 1995. Currently, the database contains information on blood test results from The Region of Northern Jutland, Region of Southern Denmark, Region Zealand and Capital Region of Denmark.

3.2 Study I

3.2.1 Study population

Hypertension was defined as redemption of at least two antihypertensive drug classes in two concomitant quarters. Patients entered the study in the second quarter. This time was referred to as hypertension date. ATC codes of the drugs used to identify patients with hypertension were included in Appendix 1.

We used this definition of hypertension for different reasons. First, most of the patients with hypertension do not require hospitalization or ambulatory contact, and the Danish National Patient Register only registers patients with hypertension based on hospital or outpatient contacts. Had we identified patients with hypertension based on ICD code only, we would have excluded a considerable sample of patients with high blood pressure who are highly representative for the aim of this work. Second, many antihypertensive agents can be used for management of other cardiovascular diseases such as heart failure, myocardial infarction or atrial fibrillation. By using the dual- or polytherapy approach, we tried to ensure that high blood pressure was at least one of the causes for dispensing antihypertensive drugs. A similar definition was used by Olesen et al.[44] where the authors defined hypertension as combination treatment with at least two antihypertensive drugs. The authors also

reported a positive predictive value of hypertension for treatment with two classes of antihypertensive agents of 80.0% and a specificity of 94.7%.[44]

With "combination therapy/treatment" we refer to prescription of antihypertensive drugs either as single pill combination or as a combination of two or more individual blood pressure drugs.

After identifying individuals with hypertension based on combination therapy, we retained the first available potassium measurement within 90 days from the hypertension date. Patients younger than 30 years were excluded. The population was censored after 90-day follow-up or December 31, 2012, whichever came first.

3.2.2 Comorbidities and drugs

Besides age and sex we identified following relevant comorbidities dated before hypertension date: chronic obstructive pulmonary disease, stroke, atrial fibrillation, acute myocardial infarction, heart failure, renal insufficiency and diabetes. Most of the patients with diabetes are treated in the primary sector and are not registered with an ICD code for diabetes in the Danish National Patient Register. Therefore, we defined diabetes as dispensed prescriptions of glucose lowering drugs (see Appendix 2 for ICD and ATC codes used). Serum sodium measurements available the same day as serum potassium were retained. Renal insufficiency was defined based on creatinine measurement obtained the same day as serum potassium or within a week from serum potassium measurement. Patients were regarded as having renal insufficiency if serum creatinine level was:

>105 μmol/L for men ≤70 years

>125 μmol/L for men >70 years

>90 μmol/L for women ≤70 years

>105 μmol/L for women >70 years[19,45]

Patients with past history of acute kidney disease, chronic kidney disease (including proteinuria) and primary hyperaldosteronism were excluded from the study. Besides antihypertensive medication we also identified potassium supplements due to their influence on potassium homeostasis.

3.2.3 Exposure variable

In this study both serum and plasma potassium measurements were used to perform the analyses, as we could not differentiate between the two methods of measuring blood potassium concentrations. We referred to all measurements as serum potassium. Potassium levels outside 1.5 times the interquartile range above the upper quartile (>5.8 mmol/L) and bellow the lower quartile (<2.9 mmol/L) were regarded as outliers and were excluded.

Seven potassium intervals were constructed: <3.5, 3.5-3.7, 3.8-4.0, 4.1-4.4, 4.5-4.7, 4.8-5.0 and >5.0 mmol/L. Hypokalemia was defined as potassium <3.5 mmol/L and hyperkalemia as concentrations >5.0 mmol/L. Serum potassium interval 4.1-4.4 mmol/L was used as reference for statistical analyses. It was chosen based on restricted cubic splines results and based on lowest number of events observed.

3.2.4 Outcome definition

The outcome of the study was 90-day all-cause mortality.

3.2.5 Statistical analysis

Baseline characteristics were presented as frequencies and percentages or means with standard deviation. To estimate the differences of continuous variables, we used the Kruskal-Wallis test and Persons' Chi-squared test was used for categorical variables. The probability of 90-day survival for the seven potassium intervals was illustrated using Kaplan-Meier survival curve. Cox proportional hazard model was used to investigate the association between the different potassium intervals and short-term mortality in patients with hypertension. The assumptions of linearity, interaction with relevant variables and proportionality of the hazards were assessed. We used "age" as a categorical variable in the adjusted model as no linearity with short-term mortality was observed. We predefined

four age intervals: 30-50 years, 51-70 years (reference), 71-80 years, and >80 years. The following variables were tested for interaction with potassium on mortality: age, sex, diabetes and renal insufficiency. The multivariable model was adjusted for age, gender, chronic obstructive pulmonary disease, stroke, atrial fibrillation, acute myocardial infarction, heart failure, renal insufficiency and diabetes. As for antihypertensive medication, we included in the adjusted model the five most prescribed antihypertensive combination therapies observed in our population: ACEIs/ARBs+BB, ACEIs/ARBs+CCB, ACEIs/ARBs+Thiazides+Potassium supplement (reference in the statistical analyses), BB+Thiazides+Potassium supplement. Combinations outside top five were named "Other combinations of antihypertensive medication". Besides potassium supplements as single pill therapy with thiazides, we also accounted for potassium supplements as an individual pill in the multivariable analysis.

We also assessed the association between potassium as a continuous variable and short-term mortality using restricted cubic splines with knots at the 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} percentiles of potassium. The 90-day mortality risk was presented as hazard ratios (HR) with 95% confidence intervals (95%CI). P-values below 0.05 were considered statistically significant. Analyses were performed with SAS (version 9.4, SAS institute, Cary, NC, USA) and R statistical software (version 3.0.1, R development core team).[46]

3.3 Study II

3.3.1 Study population

We identified patients with hypertension treated with at least two classes of antihypertensive drugs. Rationale for using this definition of hypertension is presented in section 3.2.1. Thereafter, we retained the first plasma potassium measurement within 100 days from hypertension date and patients with concentrations ≤3.7 mmol/L were included in the study. This potassium measurement was referred to as K_1. We identified a second potassium measurement (K_2) in the interval 6-100 days from

K_1, and the first draw within this timeframe was retained. Blood tests performed within 1-5 days from K_1 were not included in the analyses as potassium imbalances are usually corrected within a few days, regardless of the strategies applied. Patients younger than 18 years were excluded from the study. Appendix 3 (flowchart) illustrates the patient selection for Study II.

3.3.2 Comorbidities and drugs

Comorbidities associated with dyskalemias were dated up to five years before the index date (K_2 date) were identified: heart failure, ischemic heart disease, stroke, chronic obstructive pulmonary disease, chronic liver disease, diabetes mellitus, inflammatory bowel disease and malignancy. Furthermore, patients with a past history of primary adrenal insufficiency, primary hyperaldosteronism, and diabetes insipidus were excluded (see Appendix 2 for ICD codes). Based on creatinine measurements, we calculated the estimated glomerular filtration rate (eGFR) using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[47]. Significant renal insufficiency was defined as an eGFR < 30 mL/min/1.73 m^2. Patients with unavailable creatinine measurements the same day as or within a week from the index date were excluded.

The following hypo- and hyperkalemia associated drug prescriptions redeemed up to 90-days before the index date were identified: potassium supplements, non-steroidal anti-inflammatory drugs, corticosteroids, laxatives, xanthines and antimicrobials (Appendix 2 includes relevant ATC codes).

3.3.3 Exposure variable

For K_2 we constructed seven plasma potassium intervals: 1.5-2.9 mmol/L, 3.0-3.4 mmol/L, 3.5-3.7 mmol/L, 3.8-4.0 mmol/L and K: 4.1-4.6 mmol/L, 4.7-5.0 mmol/L, and 5.1-7.1 mmol/L. Plasma potassium interval K: 3.8-4.0 mmol/L was used as reference for statistical analyses. We chose this interval as the reference group because it had the largest number of patients and lowest mortality rate. Hypokalemia was defined as plasma potassium concentrations below 3.5 mmol/L and borderline

hypokalemia as potassium levels within the interval 3.5-3.7 mmol/L. Hyperkalemia was defined as potassium levels above 4.6 mmol/L.[17]

3.3.4 Outcome definition

The primary outcome was 60-day all-cause mortality. The secondary outcome was presumed cardiovascular death within 60 days of follow-up.

3.3.5 Statistical analysis

Continuous variables were presented as median with corresponding 25^{th} and 75^{th} percentiles and categorical variables as counts and percentages. Differences between variables were compared using Kruskal-Wallis and Chi^2 tests, as appropriate.

Survival probability for the seven plasma potassium intervals was illustrated using Kaplan-Meier curves. To investigate the relationship between plasma potassium as a continuous variable and 60-day mortality, we constructed a restricted cubic splines curve illustrating absolute mortality risk in an age, sex, comorbidity and drug standardized population.

To assess the risk of 60-day all-cause and presumed cardiovascular mortality in relation to the seven potassium intervals we used Cox proportional hazard model. The multivariable model was adjusted for: age, sex, serum sodium, renal insufficiency, malignancy, heart failure, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, atrial flutter/fibrillation, stroke and ischemic heart disease, antihypertensive therapy, corticosteroids, antimicrobials, non-steroidal anti-inflammatory drugs, potassium supplement, xanthines and laxatives.

Based on the Cox regression principle, we also modelled an average effect to estimate the 60-day absolute risk of all-cause mortality.

The proportional hazard assumption was tested by plotting Schoenfeld residuals and was not violated. Interactions on mortality were tested by comparing the likelihood ratio of the Cox regression model

with and without the interaction term. The following variables were tested for interaction with plasma potassium on mortality: age, sex, diabetes mellitus and renal insufficiency. A two-sided p-value < 0.01 was considered statistically significant for interactions. We found no statistically significant interactions. For other analyses, the level of statistical significance was set at <0.05. Linearity of age on mortality was also assessed through a likelihood ratio test comparing a linear description with a categorical one. Age was found to violate linearity and was included as a categorical variable with five levels, using cut-off values from every 20th percentiles (55, 64, 72, 79 and 101 years). Hazard ratios (HR) were estimated with 95% confidence intervals (95% CI). All data management and analyses were performed using SAS, version 9.4 and R, version 3.5.0.[46]

3.4 Study III

3.4.1 Study population

We identified patients with hypertension treated with at least two classes of antihypertensive drugs. Rationale for using this definition of hypertension is presented in section 3.2.1. First plasma potassium measurement within 100 days from hypertension date was retained and patients with concentrations ≥4.7 mmol/L (hyperkalemia) were included in the study. This potassium measurement was referred to as K_1. We identified a second potassium measurement (K_2) in the interval 6-100 days from K_1 and the first draw within this timeframe was retained. Like in study II, we did not analyze on potassium drawn within 1-5 days from K_1, as in most circumstances dyskalemias are balanced within a few days. Patients below 18 years were excluded from the study (Appendix 4 for population flowchart).

3.4.2 Comorbidities and drugs

We identified comorbidities and medication that either clinically or theoretically can be regarded as confounders in examining the relation between plasma potassium and mortality. The following comorbidities were identified: heart failure, chronic obstructive pulmonary disease, ischemic heart disease, chronic liver disease, stroke, diabetes, inflammatory bowel disease and malignancy.

Moreover, we excluded patients with prior history of primary adrenal insufficiency, primary hyperaldosteronism, or diabetes insipidus. The ICD codes used to identify these comorbidities can be seen in Appendix 2. Like in Study II, renal dysfunction was defined as an eGFR < 30 mL/min/1.73 m^2 and eGFR was calculated using CKD-EPI formula.[47] We retained creatinine measurements available the same day as K_2 or within a week from K_2 in case of missing values the same day. Patients were excluded if no creatinine concentrations were available in this time limit. Additionally, patients with missing sodium measurements the same day as K_2 were also excluded.

3.4.3 Exposure variable

As Study I demonstrated a non-linear relationship between potassium and short-term mortality, K_2 was divided into eight intervals: 2.2-2.9 mmol/L, 3.0-3.4 mmol/L, 3.5-3.7 mmol/L, 3.8-4.0 mmol/L, 4.1-4.6 mmol/L, 4.7-5.0 mmol/L, 5.1-5.5 mmol/L and 5.6-7.8 mmol/L. Plasma potassium interval 4.1-4.6 mmol/L was used as reference for statistical analyses. Hypokalemia was defined as plasma potassium concentrations below 3.5 mmol/L and hyperkalemia and potassium levels above 4.6 mmol/L.[48]

3.4.4 Outcome definition

The primary outcome of the study was 90-day all-cause mortality. The secondary outcome was cardiovascular death within 90 days of follow-up.

3.4.5 Statistical analysis

Categorical variables were presented as counts and percentages, and continuous variables as median and 25th and 75th percentiles. Differences between variables were compared using Kruskal-Wallis and Chi^2 tests, as appropriate.

Survival probability in the eight predefined plasma potassium strata was illustrated using Kaplan-Meier curves. To investigate the relationship between plasma potassium as a continuous variable and

90-day mortality, we constructed a restricted cubic splines curve with knots at the 25th, 50th and 75th percentiles of plasma potassium.

Cox proportional regression model was used to investigate the association between the eight potassium groups and mortality. Proportionality of the hazards assumption was tested using log-rank test and Schoenfeld residuals. Age, gender, diabetes and renal dysfunction were tested for interaction with potassium on mortality. A likelihood ratio test comparing the model with and without the interaction term was performed. A p-value under 0.01 was considered as a statistically significant interaction. We observed no interaction between potassium and age, gender, diabetes or renal dysfunction on mortality. The same approach was used to assess whether age had a linear relationship on mortality. As the linearity assumption was not fulfilled for age as a continuous variable, age was included in the regression models as a categorical variable with five levels, using cut-off values from 20th percentiles: 18-58, 59-67, 68-73, 74-81, 82-102. The multivariable model was adjusted for: age, sex, plasma sodium, renal insufficiency, malignancy, heart failure, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, stroke, atrial flutter/fibrillation, ischemic heart disease, inflammatory bowel disease, antihypertensive therapy, corticosteroids, antimicrobials, non-steroidal anti-inflammatory drugs, xanthines, laxatives, digoxin and potassium supplements. Hazard rate ratios (HR) were estimated with 95% confidence intervals (95% CI).

Nine sensitivity analyses were conducted to test the robustness of the main results: (1) subgroup of patients with normal kidney function; (2) patients without past history of any malignancy; (3) patients without past history of heart failure or loop diuretic prescriptions; (4) patients without past history of ischemic heart disease; (5) patients with available ICD-10 hypertension diagnosis; (6) analyses investigating risk of cardiovascular death in relation to the eight potassium intervals; (7) analyses using last instead of first available potassium concentrations within 6-100 days from first

measurement; (8) multivariable model adjusted for the first potassium measurement as well, and (9) multivariable model adjusted for time between first and second potassium measurement as well.

In the survival analyses p-values <0.05 were considered statistically significant. All data management and analyses were performed using SAS, version 9.4 and R, version 3.5.0.[46]

3.5 Study IV

3.5.1 Study population

We identified patients with hypertension treated with at least two classes of antihypertensive drugs. Rationale for using this definition of hypertension is presented in section 3.2.1. The first potassium measurement within 90 days from hypertension date was kept. The following exclusion criteria were applied: age <18 years, no available potassium measurements up to 30 days before index date, hypokalemia or hyperkalemia up to 30 days before index date, hyperkalemia at the first potassium measurement within 90 days from hypertension date. The population flowchart with inclusion and exclusion criteria is illustrated in Appendix 5.

We used a case-control design and incidence density matching to match two patients without hypokalemia (K^+, ≥3.5 mmol/L) to a patients with hypokalemia (K^+, <3.5 mmol/L) on age, sex, renal function and time between hypertension date and date of potassium draw.

3.5.2 Comorbidities and drugs

To characterize the population, we identified following discharge diagnoses or outpatient contacts with ICD-10 diagnoses present before hypertension date: ischemic heart disease, heart failure, acute myocardial infarction, atrial fibrillation, atrial flutter, second- or third-degree atrioventricular block, ventricular tachycardia or fibrillation, stroke, chronic obstructive pulmonary disease, chronic liver disease, inflammatory bowel disease, diabetes mellitus, hypothyroidism, cancer, and stroke. Exclusion criteria were past history of diabetes insipidus, syndrome of inappropriate antidiuretic, hormone secretion, primary hyperaldosteronism, or Addison disease. Estimated glomerular filtration

rate (eGFR) was calculated based on creatinine measurements using the formula developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[47] Renal insufficiency was defined as an eGFR<30 mL/min per 1.73 m^2. Creatinine measurement was obtained the same day as potassium or within 7 days before potassium measurement. Patients with missing creatinine values within this time frame were excluded.

From the Danish National Prescription Registry, drugs associated with dyskalemias were identified: potassium supplements, antimicrobials, β 2-agonists, mineralo- and glucocorticoids, laxatives, xanthines, and macrolides. We identified both potassium supplements as single pill therapy with a diuretic or as an individual pill. Only potassium supplementation, antimicrobials, and β2-agonists were present in the nested case-control population. Both ICD and ATC codes of the above mentioned conditions and drugs are illustrated in Appendix 2.

3.5.3 Exposure variable

The exposure variable defining the combinations of antihypertensive drugs in the population was divided into ten groups according to the frequency:

1. BB+CCB
2. BB+RASi
3. BB+RASi+mineral receptor antagonist
4. BB+RASi+thiazides
5. BB+thiazides
6. CCB+RASi (reference)
7. CCB+RASi+thiazides
8. CCB+thiazides
9. RASi+thiazides
10. Other combinations

When mentioning CCBs, we refer to dihydropyridine derivatives, such as amlodipine. We used CCB+RASi as reference in the multivariable analysis as this combination was one of the most commonly prescribed in our population and theoretically not associated with hypokalemia.

3.5.4 Outcome definition

Outcome was onset of hypokalemia within 90 days of follow-up.

3.5.5 Statistical analysis

Conditional logistic regression analysis was used to estimate the odds of hypokalemia within 90 days from hypertension date in relation to different combinations of blood pressure drugs. The multivariable model was adjusted for: sodium, malignancy, inflammatory bowel disease, diabetes mellitus and chronic liver disease.

Some antihypertensive drugs can be used in the management of ischemic heart disease or heart failure. Therefore, we performed a sensitivity analysis where we also matched the controls on past history with ischemic heart disease/acute myocardial infarction and heart failure. Apart from this, we also assessed the prevalence of different diseases in patients treated with combination antihypertensive therapy who did not have a potassium measurement available within 90 days from the hypertension date.

Categorical variables were reported as counts and percentages and continuous variables as medians with 25th to 75th percentiles. Differences between variables were compared using Chi^2 and Kruskal-Wallis tests, as appropriate. Odds ratios (OR) with p-values below 0.05 were considered statistically significant.

Data management and analyses were performed using SAS, version 9.4 (SAS Institute, Inc, Cary, NC) and R, version 3.5.1 (R Core Team [2018]). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; https:// www.R-project.org/.[46]

4. Results

4.1 Study I

4.1.1 Demographics

In the period 1995-2012, Study I included 44,799 patients with hypertension, treated with at least two antihypertensive drug classes, who had a potassium measurement available within 90 days from the hypertension date. The cohort had an average age of 67.1 (±12.6) years and males accounted for 52.8% of the population. Both mean and median serum potassium was 4.2 mmol/L. Of the total population, 3.8% had hypokalemia and 2.3% hyperkalemia. Women were more prone to hypokalemia, while men were more susceptible to hyperkalemia. Between 10-20% of the population had prevalent cardiovascular disease, and a similar prevalence of diabetes was found. As for antihypertensive therapy, about a quarter of the population was treated with the combination of ACEIs/ARBs+Thiazides with or without potassium supplementation (Table 4.1.1.1). The great majority of the population had their first potassium draw in the first 45 days (65.1%). As for mortality, 72.9% deceased in the first 45 days of the total follow-up time of 90 days (Appendix 6).

Table 4.1.1.1 Demographics stratified according to the seven potassium intervals

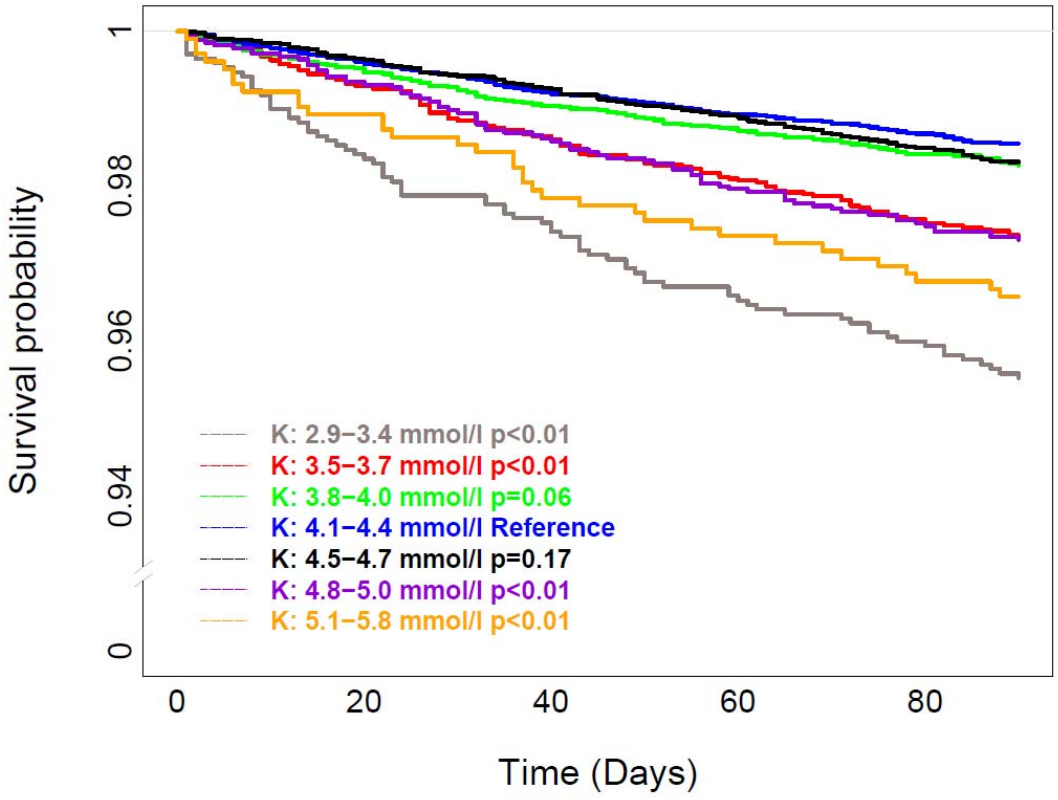
	K: 2.9-3.4 mmol/L	K: 3.5-3.7 mmol/L	K: 3.8-4.0 mmol/L	K: 4.1-4.4 mmol/L	K: 4.5-4.7 mmol/L	K: 4.8-5.0 mmol/L	K: 5.1-5.8 mmol/L	Total
Gender, female	1095 (64.4%)	2401 (60.1%)	5176 (55.0%)	8908 (49.1%)	3521 (45.3%)	1203 (43.7%)	484 (47.2%)	22 788 (50.9%)
Age, mean/SD	67 (±13.8)	66.7 (±13.2)	66.4 (±12.8)	66.9 (±12.4)	67.7 (±12.3)	68.9 (±12.2)	70.7 (±12.3)	67.1 (±12.6)
No. of antihypertensive drug prescriptions, mean/SD	2.2 (±0.5)	2.2 (±0.5)	2.2 (±0.5)	2.2 (±0.5)	2.2 (±0.5)	2.2 (±0.5)	2.3 (±0.5)	2.2 (±0.5)
Day of potassium measurement, mean/SD	34.8 (±25.7)	36.2 (±25.8)	36.9 (±25.7)	37.1 (±25.6)	36.4 (±25.4)	33.7 (±24.5)	33.7 (±24.5)	36.6 (±25.6)
Serum creatinine, mean/SD	77 (±16)	79.1 (±15.8)	80.1 (±15.8)	82.2 (±15.6)	83.9 (±15.8)	85.8 (±16.2)	87.5 (±16.8)	81.9 (±15.9)
Serum natrium, mean/SD	138.8 (±5.2)	139.5 (±4.2)	139.8 (±3.8)	139.9 (±3.6)	139.6 (±3.9)	139.2 (±4.3)	138.2 (±4.9)	139.7 (±3.9)
missing	47	142	412	759	318	109	29	1816
Antihypertensive medication								
Thiazide diuretics	1168 (68.7%)	2633 (65.9%)	5866 (62.3%)	9474 (52.2%)	3359 (43.2%)	1027 (37.3%)	389 (38.0%)	23 916 (53.4%)
Loop diuretics	422 (24.8%)	875 (21.9%)	1857 (19.7%)	3484 (19.2%)	1696 (21.8%)	738 (26.8%)	334 (32.6%)	9406 (21.0%)
Potassium-sparing diuretics	71 (4.2%)	130 (3.3%)	265 (2.8%)	738 (4.1%)	467 (6.0%)	249 (9.1%)	142 (13.9%)	2062 (4.6%)
Aldosteron antagonist	71 (4.2%)	127 (3.2%)	260 (2.8%)	736 (4.1%)	463 (6.0%)	248 (9.0%)	141 (13.8%)	2046 (4.6%)
ACEIs/ARBs	878 (51.7%)	2343 (58.7%)	6215 (66.0%)	12 986 (71.5%)	5994 (77.2%)	2121 (77.1%)	816 (79.6%)	31 353 (70.0%)
β-blockers (BB)	618 (36.4%)	1505 (37.7%)	3810 (40.5%)	8209 (45.2%)	3822 (49.2%)	1445 (52.5%)	505 (49.3%)	19 914 (44.5%)
Calcium channel blockers (CCB)	763 (44.9%)	1553 (38.9%)	3100 (32.9%)	5768 (31.8%)	2219 (28.6%)	729 (26.5%)	272 (26.5%)	14 404 (32.2%)
Antihypertensive drugs that contain potassium supplement	893 (52.6%)	1907 (47.7%)	3998 (42.5%)	6322 (34.8%)	2242 (28.9%)	706 (25.7%)	260 (25.4%)	16 328 (36.4%)
Potassium supplement	792 (46.6%)	1901 (47.6%)	4518 (48.0%)	8687 (47.9%)	3766 (48.5%)	1354 (49.2%)	476 (46.4%)	21 494 (48%)
Antiadrenergic drugs	32 (1.9%)	45 (1.1%)	113 (1.2%)	220 (1.2%)	83 (1.1%)	33 (1.2%)	8 (0.8%)	534 (1.2%)
-antihypertensive drug combinations								
ACEIs/ARBs + BB	50 (2.9%)	188 (4.7%)	695 (7.4%)	2393 (13.2%)	1371 (17.6%)	532 (19.3%)	148 (14.4%)	5377 (12.0%)
ACEIs/ARBs + CCB	57 (3.4%)	167 (4.2%)	500 (5.3%)	1398 (7.7%)	679 (8.7%)	245 (8.9%)	84 (8.2%)	3130 (7.0%)
ACEIs/ARBs + thiazides	138 (8.1%)	437 (10.9%)	1259 (13.4%)	2179 (12.0%)	784 (10.1%)	213 (7.7%)	77 (7.5%)	5087 (11.4%)

ACEIs/ARBs + thiazides + potassium supplement	190 (11.2%)	558 (14.0%)	1442 (15.3%)	2492 (13.7%)	972 (12.5%)	303 (11.0%)	111 (10.8%)	6068 (13.5%)
BB + thiazides + potassium supplement	162 (9.5%)	397 (9.9%)	854 (9.1%)	1315 (7.2%)	430 (5.5%)	135 (4.9%)	38 (3.7%)	3331 (7.4%)
Other combinations	1102 (64.9%)	2247 (56.3%)	4662 (49.5%)	8373 (46.1%)	3532 (45.5%)	1323 (48.1%)	567 (55.3%)	21 806 (48.7%)
Comorbidities								
Atrial fibrillation	189 (11.1%)	525 (13.1%)	1193 (12.7%)	2505 (13.8%)	1187 (15.3%)	465 (16.9%)	183 (17.9%)	6247 (13.9%)
Acute myocardial infarction	103 (6.1%)	300 (7.5%)	838 (8.9%)	2165 (11.9%)	1089 (14.0%)	443 (16.1%)	133 (13.0%)	5071 (11.3%)
Heart failure	148 (8.7%)	350 (8.8%)	876 (9.3%)	1943 (10.7%)	1115 (14.4%)	464 (16.9%)	207 (20.2%)	5103 (11.4%)
Stroke	247 (14.5%)	515 (12.9%)	1130 (12.0%)	2124 (11.7%)	920 (11.8%)	363 (13.2%)	143 (14.0%)	5442 (12.1%)
Chronic obstructive pulmonary disease	181 (10.7%)	381 (9.5%)	788 (8.4%)	1492 (8.2%)	707 (9.1%)	316 (11.5%)	146 (14.2%)	4011 (9.0%)
Antidiabetic drugs	121 (7.1%)	330 (8.3%)	941 (10.0%)	2158 (11.9%)	1213 (15.6%)	509 (18.5%)	214 (20.9%)	5486 (12.2%)
Insulin	20 (1.2%)	35 (0.9%)	112 (1.2%)	208 (1.1%)	126 (1.6)	65 (2.4%)	27 (2.6%)	593 (1.3%)
Deceased within 90 days	77 (4.5%)	108 (2.7%)	168 (1.8%)	269 (1.5%)	133 (1.7%)	74 (2.7%)	37 (3.6%)	866 (1.9%)

4.1.2 Survival analysis

Of the patients 866 (1.9%) had the event. Mortality within 90-days in the seven strata was: 4.5, 2.7, 1.8, 1.5, 1.7, 2.7, and 3.6%, respectively (Table 4.1.1.1). Kaplan-Meier survival curves are illustrated in Figure 4.1.2.1.

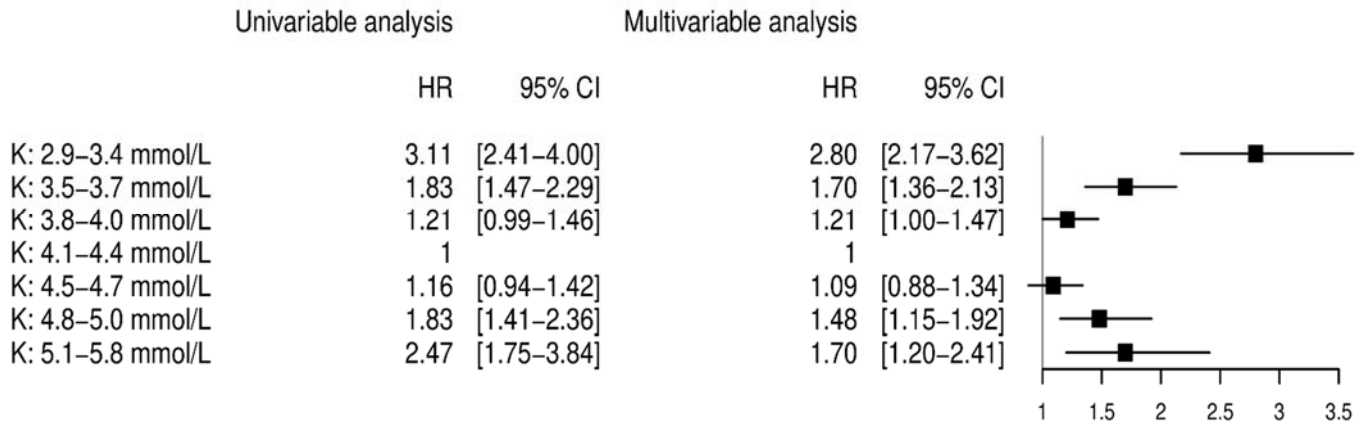
Figure 4.1.2.1 Kaplan-Meier curves displaying the estimated 90-day survival probability for seven different potassium intervals (n=44,799).



Univariable analysis (Figure 4.1.2.2) showed that hypokalemia and hyperkalemia were associated with increased 90-day mortality risk (HR 3.11, 95% CI 2.41-4.00 and HR 2.47, 95% CI 1.75-3.84, respectively). In addition, low normal (3.5-3.7 mmol/L, HR 1.83, 95% CI 1.47-2.29) and high normal potassium (4.8-5.0 mmol/L, HR 1.83, 95% CI 1.41-2.36) concentrations were also associated with

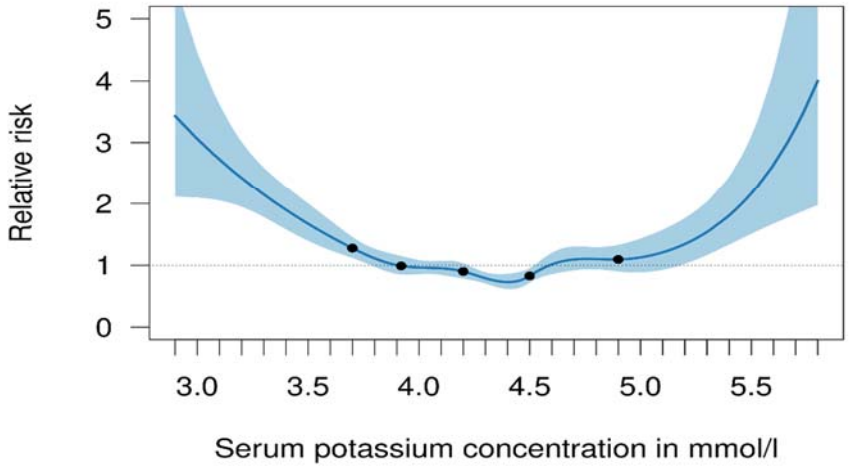
increased risk of death within 90-days. The results of the multivariable analysis showed similar results (Figure 4.1.2.2).

Figure 4.1.2.2 All-cause mortality in patients with hypertension according to seven potassium intervals (90-days follow-up, n=44,799). Reference interval represented by K: 4.1-4.4 mmol/L. Multivariable analysis adjusted for: age, gender, atrial fibrillation, acute myocardial infarction, heart failure, stroke, chronic obstructive pulmonary disease, diabetes, potassium supplements and antihypertensive drugs.



Analysis with potassium as a continuous variable showed a U-shaped relationship with short-term mortality, with an optimal potassium value of 4.4 mmol/L (Figure 4.1.2.3).

Figure 4.1.2.3 Restricted cubic splines showing the adjusted hazard ratios for all-cause mortality as a function of potassium concentration. Knots at the 10th, 25th, 50th, 75th, and 90th percentiles of potassium. Model adjusted for age, sex, chronic obstructive pulmonary disease, stroke, acute myocardial infarction, atrial fibrillation, heart failure, diabetes mellitus, potassium supplement, antihypertensive medication (n=44,799).



4.1.3 Sensitivity analyses

To reduce possible uncertainty related to the main results, we conducted three sensitivity analyses and the results are illustrated in Table 4.1.2.1.

First, we performed an analysis on patients treated with combination antihypertensive therapy who also had a registered hypertension ICD diagnosis code in the hospital sector (n=26,126). The results were similar to the ones obtained in the main analysis, though with slightly lower HRs.

Second, patients who redeemed loop diuretics were excluded as they are primarily used in heart failure management and not hypertension, which was our target population. Overall, we observed the same significant associations and trends as in our initial findings.

Third, we excluded patients with past history of myocardial infarction and/or heart failure as both diseases are associated with increased mortality risk and in both cases patients can be prescribed antihypertensive medication, without necessarily having high blood pressure. The analysis suggested

that potassium concentrations outside the interval 4.1-4.7 mmol/L were associated with poor prognosis.

Table 4.1.2.1 Sensitivity analyses

Potassium (mmol/L)	Hypertension definition based on ICD codes (*n* = 26,126)				Patients with loop diuretic prescription were excluded (*n* = 35,393)				Patients with an acute myocardial infarction or heart failure diagnosis before hypertension were excluded (*n* = 35,827)			
	HR	**Low 95%**	**High 95%**	***P***	**HR**	**Low 95%**	**High 95%**	***P***	**HR**	**Low 95%**	**High 95%**	***P***
2.9–3.4	1.91	1.63	2.24	<0.01	3.49	2.43	5.00	<0.01	2.99	2.21	4.06	<0.01
3.5–3.7	1.49	1.28	1.74	<0.01	2.03	1.48	2.79	<0.01	1.89	1.44	2.48	<0.01
3.8–4.0	1.14	0.98	1.32	0.10	1.24	0.94	1.64	0.12	1.31	1.04	1.66	0.02
4.1–4.4	1	Reference			1	Reference			1	Reference		
4.5–4.7	1.18	0.98	1.43	0.07	0.95	0.69	1.30	0.74	1.18	0.91	1.53	0.22
4.8–5.0	1.38	1.07	1.78	0.01	1.50	1.01	2.22	0.04	1.85	1.34	2.55	<0.01
5.1–5.8	2.20	1.66	2.91	<0.01	1.89	1.11	3.24	0.02	2.13	1.37	3.29	<0.01

4.2 Study II

4.2.1 Demographics

We identified 8,976 patients treated with multiple antihypertensive agents, who had potassium concentrations ≤3.7 mmol/L within the first 100 days from hypertension date. Approximately 50% of the population was hospitalized at K_1 and 80% at K_2. Median time from K_1 to K_2 was 22 days (25^{th} and 75^{th} percentiles: [6,100]). Of the patients with potassium levels within 3.5-3.7 mmol/L K_1, 13% developed hypokalemia and 5.7% hyperkalemia at K_2. As for patients with hypokalemia at K_1, we observed that 28.5% remained hypokalemic at the second blood draw and 4.8% developed hyperkalemia. Related to K_2, thiazides were more common in patients with potassium levels ≤3.7 mmol/L, whereas loop diuretics were more common among patients with hyperkalemia. Of the total thiazides prescriptions, thiazide-like diuretics accounted for 4.4% (Table 4.2.1.1).

Table 4.2.1.1 Demographics stratified according to the seven predefined plasma potassium intervals in a cohort of 8,976 patients treated with combination antihypertensive therapy and initial potassium concentrations ≤3.7 mmol/L

		1.5-2.9 mmol/L (n=271)	3.0-3.4 mmol/L (n=1341)	3.5-3.7 mmol/L (n=1982)	3.8-4.0 mmol/L (n=2398)	4.1-4.6 mmol/L (n=2498)	4.7-5.0 mmol/L (n=352)	5.1-7.1 mmol/L (n=134)	p-value
Age	median(range)	70.6(21.4, 94.9)	67(19.2, 100.8)	67(22.1, 97.7)	67.7(19.2, 97.5)	69.7(18.2, 99.9)	69.9(20.2, 98.6)	71.9(27.7, 97.8)	<0.01
Sex	Female	157 (57.9)	757 (56.5)	1,087 (54.8)	1,276 (53.2)	1,250 (50.0)	172 (48.9)	57 (42.5)	
Renal insufficiency (second measuremt)		26 (9.6)	78 (5.8)	118 (6.0)	127 (5.3)	142 (5.7)	43 (12.2)	38 (28.4)	<0.01
Serum sodium (second measurement)	median(range)	138(111, 157)	139(117, 179)	140(105, 155)	140(101, 161)	139(107, 159)	138(114, 166)	136(112, 149)	<0.01
Plasma potassium (first measurement)	3.5-3.7 mmol/L	97 (35.8)	700 (52.2)	1,322 (66.7)	1,768 (73.7)	1,877 (75.1)	258 (73.3)	89 (66.4)	
	<3.5 mmol/L	174 (64.2)	641 (47.8)	660 (33.3)	630 (26.3)	621 (24.9)	94 (26.7)	45 (33.6)	<0.01
Renal insufficiency (first measuremt)		25 (9.8)	87 (6.9)	117 (6.2)	127 (5.5)	166 (6.9)	47 (13.7)	32 (24.8)	<0.01
	missing creatinine	17	77	92	82	77	8	5	
Hospitalization at the time of second potassium measurement		232 (85.6)	1050 (78.4)	1538 (77.7)	1860 (77.6)	2050 (82.1)	303 (86.1)	118 (88.1)	<0.01
Time from first to second potassium measurement (days)	median(range)	14(6, 97)	21(6, 100)	25(6, 100)	26(6, 100)	21(6, 100)	13.5(6, 100)	14(6, 97)	<0.01
Death-60 days		39 (14.4)	94 (7.0)	125 (6.3)	124 (5.2)	168 (6.7)	48 (13.6)	29 (21.6)	<0.01
60-day cardiovascular mortality		21 (7.7)	50 (3.7)	68 (3.4)	59 (2.5)	91 (3.6)	28 (8.0)	14 (10.4)	<0.01
Comorbidities									
Any malignancy		58 (21.4)	252 (18.8)	389 (19.6)	429 (17.9)	478 (19.1)	71 (20.2)	28 (20.9)	0.66
Chronic obstructive pulmonary disease		41 (15.1)	180 (13.4)	238 (12.0)	290 (12.1)	395 (15.8)	63 (17.9)	28 (20.9)	<0.01
Diabetes		43 (15.9)	221 (16.5)	324 (16.3)	432 (18.0)	453 (18.1)	77 (21.9)	36 (26.9)	0.01
Chronic kidney disease		16 (5.9)	116 (8.7)	176 (8.9)	170 (7.1)	194 (7.8)	38 (10.8)	26 (19.4)	<0.01
Chronic liver disease		23 (8.5)	55 (4.1)	90 (4.5)	109 (4.5)	124 (5.0)	21 (6.0)	12 (9.0)	0.01
Atrial fibrillation/Atrial flutter		37 (13.7)	209 (15.6)	337 (17.0)	446 (18.6)	535 (21.4)	85 (24.1)	43 (32.1)	<0.01
Hypertension (ICD-10)		112 (41.3)	475 (35.4)	755 (38.1)	895 (37.3)	941 (37.7)	121 (34.4)	35 (26.1)	0.04

Heart failure		47 (17.3)	212 (15.8)	348 (17.6)	453 (18.9)	624 (25.0)	102 (29.0)	59 (44.0)	<0.01
Ischemic heart disease		54 (19.9)	257 (19.2)	420 (21.2)	594 (24.8)	729 (29.2)	126 (35.8)	53 (39.6)	<0.01
Stroke		36 (13.3)	147 (11.0)	241 (12.2)	292 (12.2)	320 (12.8)	40 (11.4)	13 (9.7)	0.67
Inflammatory bowel disease		4 (1.5)	19 (1.4)	43 (2.2)	39 (1.6)	38 (1.5)	5 (1.4)	6 (4.5)	0.12
Pharmacotherapy									
Potassium supplement	ATC: A12B	163 (60.1)	699 (52.1)	895 (45.2)	1083 (45.2)	1219 (48.8)	192 (54.5)	80 (59.7)	<0.01
	ATC: C03	67 (24.7)	415 (30.9)	557 (28.1)	674 (28.1)	577 (23.1)	67 (19.0)	13 (9.7)	<0.01
Antimicrobials		152 (56.1)	742 (55.3)	1082 (54.6)	1347 (56.2)	1434 (57.4)	204 (58.0)	78 (58.2)	0.59
Beta-2 agonists		58 (21.4)	337 (25.1)	451 (22.8)	576 (24.0)	625 (25.0)	93 (26.4)	38 (28.4)	0.30
Corticoids		54 (19.9)	284 (21.2)	417 (21.0)	499 (20.8)	534 (21.4)	81 (23.0)	33 (24.6)	0.90
Laxatives		7 (2.6)	41 (3.1)	51 (2.6)	58 (2.4)	74 (3.0)	23 (6.5)	4 (3.0)	<0.01
Xantines		11 (4.1)	43 (3.2)	57 (2.9)	56 (2.3)	81 (3.2)	15 (4.3)	5 (3.7)	0.26
NSAIDs		153 (56.5)	739 (55.1)	1090 (55.0)	1362 (56.8)	1438 (57.6)	197 (56.0)	76 (56.7)	0.67
Antiadrenergic drugs		4 (1.5)	21 (1.6)	18 (0.9)	26 (1.1)	26 (1.0)	≤3	4 (3.0)	0.24
Vasodilators		0 (0.0)	0 (0.0)	≤3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.74
Beta blockers		97 (35.8)	497 (37.1)	775 (39.1)	972 (40.5)	1213 (48.6)	174 (49.4)	71 (53.0)	<0.01
Calcium channel blockers		117 (43.2)	514 (38.3)	687 (34.7)	843 (35.2)	780 (31.2)	93 (26.4)	38 (28.4)	<0.01
Renin angiotensin system inhibitors		134 (49.4)	716 (53.4)	1158 (58.4)	1487 (62.0)	1506 (60.3)	209 (59.4)	81 (60.4)	<0.01
Loop diuretics		115 (42.4)	533 (39.7)	720 (36.3)	841 (35.1)	1112 (44.5)	179 (50.9)	87 (64.9)	<0.01
Thiazide diuretics		127 (46.9)	682 (50.9)	934 (47.1)	1110 (46.3)	909 (36.4)	95 (27.0)	20 (14.9)	<0.01
Thiazilde-like diuretics		7 (2.6)	28 (2.1)	46 (2.3)	47 (2.0)	37 (1.5)	4 (1.1)	≤3	0.38
Potassium sparing diuretics		15 (5.5)	40 (3.0)	50 (2.5)	54 (2.3)	48 (1.9)	7 (2.0)	≤3	<0.01
Mineral receptor antagonists		51 (18.8)	181 (13.5)	250 (12.6)	281 (11.7)	372 (14.9)	83 (23.6)	35 (26.1)	<0.01

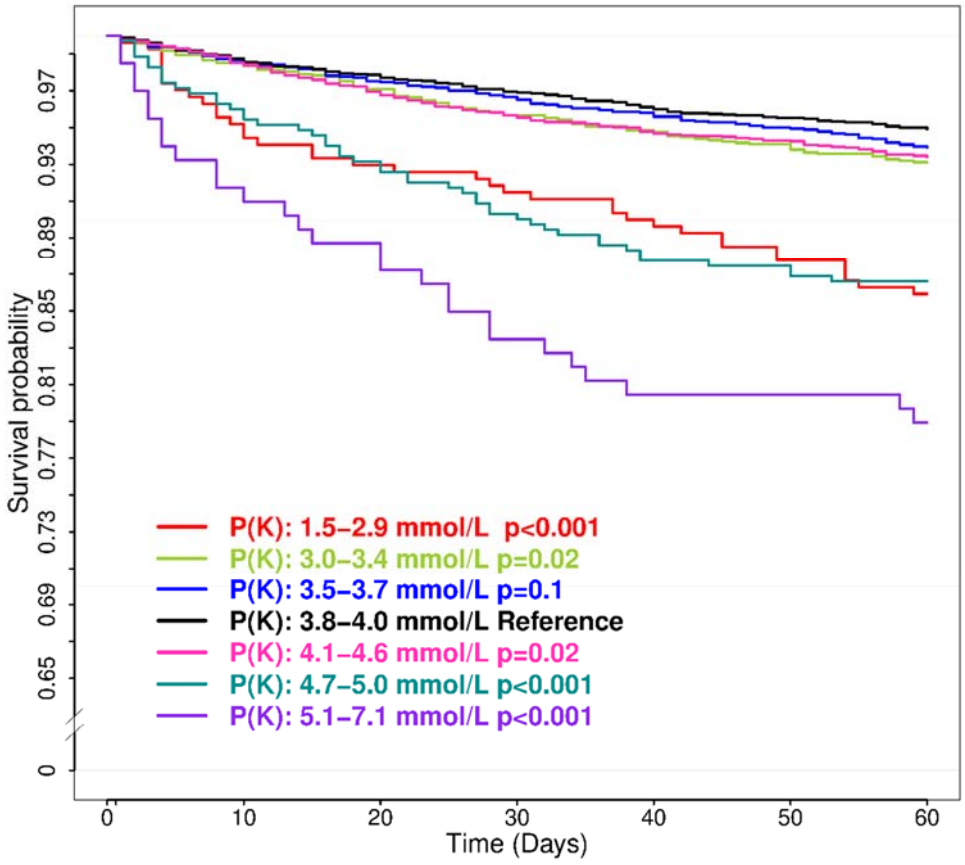
ICD-10 International Classification of Disease 10th version, *ATC* Anatomical Therapeutic Chemical Classification System, *NSAIDs* Non-steroidal anti-inflammatory drugs

≤3- Is ascertained cells where the frequency is 1, 2 or 3 in order to ensure anonymization of the data

4.2.2 Survival analysis

Totally, 7% (n=627) of the population died within 60-days from K_2. Mortality in the seven strata was: 14.4%, 7.0%, 6.3%, 5.2%, 6.7%, 13.6% and 21.6%, respectively (Table 4.2.1.1, Figure 4.2.2.1).

Figure 4.2.2.1 Kaplan-Meier curves displaying the estimated 60-day survival probability for seven different potassium intervals (n=8,976).

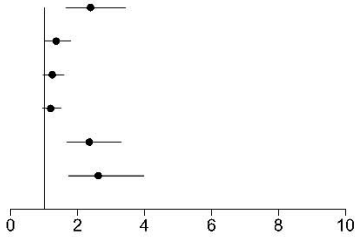


A significant association with all-cause mortality was observed in patients with hypokalemia (1.5-2.9 mmol/L HR 2.39, 95% CI 1.66-3.43 and 3.0-3.4 mmol/L HR 1.36, 95% CI 1.04-1.78) and hyperkalemia (4.7-5.0 mmol/L HR 2.36, 95% CI 1.68-3.30 and 5.1-5.7 mmol/L HR 2.62, 95% CI 1.73-3.98) (Figure 4.2.2.2). The univariable analysis showed similar results (Figure 4.2.2.2). There was no interaction between K_1 and K_2 on 60-day mortality.

Figure 4.2.2.2 All-cause and cardiovascular mortality after hypokalemia or borderline hypokalemia according to subsequent potassium measurements in patients treated with combination antihypertensive therapy (60-days follow-up, n=8,976). Potassium interval K: 3.8-4.0 mmol/L represented the reference range. Adjusted for age, gender, serum sodium, renal insufficiency, malignancy, heart failure, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, atrial flutter/fibrillation, stroke and ischemic heart disease, antihypertensive therapy, corticosteroids, antimicrobials, non-steroidal anti-inflammatory drugs, potassium supplement, xanthines, laxatives.

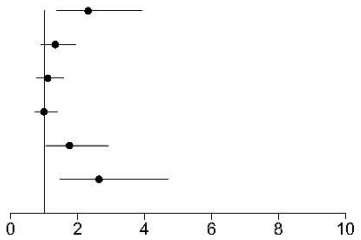
All-cause mortality

Variable		Univariable HR [95% CI]	Multivariable HR [95% CI]
Plasma potassium intervals	P(K): 1.5-2.9 mmol/L	2.93 [2.05;4.20]	2.39 [1.66,3.43]
	P(K): 3.0-3.4 mmol/L	1.37 [1.05;1.79]	1.36 [1.04,1.78]
	P(K): 3.5-3.7 mmol/L	1.23 [0.96;1.57]	1.24 [0.97,1.59]
	P(K): 4.1-4.6 mmol/L	1.31 [1.04;1.65]	1.20 [0.95,1.51]
	P(K): 4.7-5.0 mmol/L	2.79 [2.00;3.89]	2.36 [1.68,3.30]
	P(K): 5.1-7.1 mmol/L	4.71 [3.14;7.06]	2.62 [1.73,3.98]



Cardiovascular mortality

Variable		Univariable HR [95% CI]	Multivariable HR [95% CI]
Plasma potassium intervals	P(K): 1.5-2.9 mmol/L	2.57 [1.53;4.34]	2.32 [1.36,3.93]
	P(K): 3.0-3.4 mmol/L	1.22 [0.83;1.79]	1.33 [0.90,1.95]
	P(K): 3.5-3.7 mmol/L	1.07 [0.75;1.52]	1.11 [0.77,1.58]
	P(K): 4.1-4.6 mmol/L	1.15 [0.82;1.59]	1.00 [0.72,1.39]
	P(K): 4.7-5.0 mmol/L	2.21 [1.34;3.65]	1.76 [1.06,2.92]
	P(K): 5.1-7.1 mmol/L	4.63 [2.64;8.11]	2.64 [1.48,4.71]



As for cardiovascular mortality, we observed that about 53% of all deaths were recorded as having a cardiovascular cause. Significant associations with cardiovascular death were observed in patients with potassium concentrations <3.0 mmol/L and above 4.6 mmol/L after an episode with plasma potassium ≤3.7 mmol/L (Figure 4.2.2.2). The standardized 60-day absolute risk of all-cause mortality in relation to potassium was lowest in patients with potassium levels between 3.8–4.0 mmol/L (AR 5.4, 95% CI 4.5–6.3%, Table 4.2.2.1).

Table 4.2.2.1 60-day standardized absolute risk for all-cause death after hypokalemia or borderline hypokalemia according to subsequent potassium measurements in patients treated with combination antihypertensive therapy ($n = 8976$). Potassium interval K: 3.8–4.0 mmol/L represented the reference range. Adjusted for age, gender, serum sodium, renal insufficiency, malignancy, heart failure, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, atrial flutter/fibrillation, stroke and ischemic heart disease, antihypertensive therapy, corticosteroids, antimicrobials, non-steroidal anti-inflammatory drugs, potassium supplement, xanthines, laxatives

	Absolute risk %, (95% CI)	**60-d Risk difference %, (95%CI)**	***p*-value**	**Average risk ratio %, (95%CI)**	***p*-value**
P(K) 1.5–2.9 mmol/L	11.7% (8.3–15.0)	6.3 (2.9–9.7)	< 0.001	2.17 (1.46–2.88)	0.001
P(K) 3.0–3.4 mmol/L	7.1% (5.8–8.5)	1.7 (0.1–3.4)	0.03	1.32 (0.99–1.66)	0.06
P(K) 3.5–3.7 mmol/L	6.4% (5.3–7.5)	1.0 (− 0.3–2.4)	0.14	1.19 (0.91–1.47)	0.17
P(K) 3.8–4.0 mmol/L	5.4% (4.5–6.3)	REF.		REF.	
P(K) 4.1–4.6 mmol/L	6.3% (5.4–7.2)	0.9 (−0.3–2.2)	0.13	1.18 (0.92–1.44)	0.17
P(K) 4.7–5.0 mmol/L	11.6% (8.7–14.6)	6.2 (3.2–9.3)	< 0.001	2.17 (1.51–2.82)	< 0.001
P(K) 5.1–7.1 mmol/L	12.6% (8.2–16.9)	7.2 (2.8–11.6)	0.001	2.34 (1.45–3.22)	0.003

4.2.3 Subgroup and sensitivity analyses

We performed eleven additional analyses to test the accuracy and robustness of the main results and the findings are enclosed in Appendix 7. Most important results are highlighted.

Patients with borderline hypokalemia who developed hypokalemia or hyperkalemia had in increased 60-day mortality compared to those corrected to a level within 3.8-4.0 mmol/L.

Overall, subgroup analyses on patients without significant renal insufficiency, or without past history of ischemic heart disease, any malignancy or heart failure or loop diuretic prescription, showed similar results to the main analysis.

4.3 Study III

4.3.1 Demographics

Totally, 7,620 patients fulfilled the inclusion criteria and demographic characteristics according to the eight potassium groups are shown in Tabel 4.3.1.1. Of the total population with hyperkalemia at K_1 about 39 % had dyskalemia at K_2. We observed that 36.1% of the patients with hyperkalemia at K_1 had elevated potassium concentrations at K_2. Of the total patients, 2.9% were overbalanced to hypokalemia. Among patients with potassium between 4.7 and 5.5 mmol/L at K_1, 3.4 % had higher (>5.5 mmol/L) levels at K_2. The great majority of the patients had their K_1 and K_2 measured during hospitalization. Median time from K_1 to K_2 was 24 days (range [6,100]).

Table 4.3.1.1 Demographics stratified according to the eight predefined plasma potassium intervals.

		2.2-2.9 mmol/L (n=37)	**3.0-3.4 mmol/L (n=184)**	**3.5-3.7 mmol/L (n=325)**	**3.8-4.0 mmol/L (n=791)**	**4.1-4.6 mmol/L (n=3533)**	**4.7-5.0 mmol/L (n=1786)**	**5.1-5.5 mmol/L (n=720)**	**5.6-7.8 mmol/L (n=244)**	**Total (n=7620)**	**p-value**
Age	median(range)	73.8(28.4, 94.5)	70.9(26.2, 95.9)	70.4(20.1, 98.7)	70.2(18.6, 97.9)	69.7(18.2, 102.3)	71(18.3, 98.7)	70.5(19.2, 99.0)	71(21.3, 101.8)	70.3(18.2, 102.3)	0.01
Gender	Male	19 (51.4)	79 (42.9)	166 (51.1)	428 (54.1)	2120 (60.0)	1150 (64.4)	453 (62.9)	144 (59.0)	4,559 (59.8)	< 0.001
Renal insufficiency (second measuremt)		10 (27.0)	41 (22.3)	47 (14.5)	102 (12.9)	344 (9.7)	279 (15.6)	189 (26.2)	103 (42.2)	1,115 (14.6)	< 0.001
Plasma sodium (second measurement)	median(range)	138(123, 169)	138(108, 151)	138(112, 159)	139(110, 164)	139(112, 160)	139(112, 166)	138(112, 151)	137(114, 147)	139(108, 169)	< 0.001
Plasma potassium (first measurement)	4.7-5.5 mmol/L	30 (81.1)	163 (88.6)	310 (95.4)	755 (95.4)	3,422 (96.9)	1,690 (94.6)	661 (91.8)	196 (80.3)	7,227 (94.8)	
	>5.5 mmol/L	7 (18.9)	21 (11.4)	15 (4.6)	36 (4.6)	111 (3.1)	96 (5.4)	59 (8.2)	48 (19.7)	393 (5.2)	< 0.001
Renal insufficiency (first measuremt)		12 (35.3)	40 (22.2)	49 (16.4)	92 (12.9)	357 (10.8)	251 (14.7)	163 (23.6)	83 (35.0)	1,047 (14.6)	< 0.001
	missing									446	
Time from first to second potassium measurement	median(range)	9(6, 81)	7(6, 99)	11(6, 99)	19(6, 100)	27(6, 100)	27(6, 100)	26(6, 100)	21(6, 98)	24(6, 100)	<0.001
Hospitalization at the time of second potassium measurement		36 (97.3)	171 (92.9)	313 (96.3)	712 (90.0)	2977 (84.3)	1457 (81.6)	581 (80.7)	205 (84.0)	6,452 (84.7)	< 0.001
Time from the second potassium measurement to death	mean(sd)	68.5 (32.5)	78.1 (25.2)	80.7 (24)	84.3 (18.9)	86.4 (15.1)	86.5 (15)	84.7 (18.1)	79.4 (25.6)	85.3 (17.3)	<0.001
Death 90-days		14 (37.8)	39 (21.2)	47 (14.5)	76 (9.6)	224 (6.3)	110 (6.2)	72 (10.0)	40 (16.4)	622 (8.2)	< 0.001

	Cardiovascular death	5 (13.5)	14 (7.6)	26 (8.0)	38 (4.8)	125 (3.5)	59 (3.3)	29 (4.0)	22 (9.0)	318 (4.2)	<0.001
Comorbidities											
Malignancy		10 (27.0)	42 (22.8)	59 (18.2)	125 (15.8)	580 (16.4)	253 (14.2)	130 (18.1)	38 (15.6)	1,237 (16.2)	0.01
Chronic obstructive pulmonary disease		7 (18.9)	44 (23.9)	72 (22.2)	136 (17.2)	467 (13.2)	237 (13.3)	89 (12.4)	30 (12.3)	1,082 (14.2)	< 0.001
Chronic kidney disease		≤3	38 (20.7)	38 (11.7)	81 (10.2)	344 (9.7)	244 (13.7)	139 (19.3)	66 (27.0)	≤953	< 0.001
Chronic liver disease		4 (10.8)	14 (7.6)	15 (4.6)	55 (7.0)	152 (4.3)	65 (3.6)	36 (5.0)	13 (5.3)	354 (4.6)	0.003
Stroke		≤3	24 (13.0)	33 (10.2)	79 (10.0)	354 (10.0)	155 (8.7)	72 (10.0)	21 (8.6)	≤741	0.59
Hypertension (ICD-10)		13 (35.1)	75 (40.8)	122 (37.5)	270 (34.1)	1084 (30.7)	544 (30.5)	233 (32.4)	69 (28.3)	2,410 (31.6)	0.01
Atrial fibrillation/Atrial flutter		9 (24.3)	45 (24.5)	82 (25.2)	179 (22.6)	849 (24.0)	385 (21.6)	136 (18.9)	49 (20.1)	1,734 (22.8)	0.06
Ischemic heart disease		13 (35.1)	49 (26.6)	112 (34.5)	253 (32.0)	1216 (34.4)	585 (32.8)	200 (27.8)	71 (29.1)	2,499 (32.8)	0.01
Heart failure		12 (32.4)	57 (31.0)	91 (28.0)	233 (29.5)	1189 (33.7)	644 (36.1)	219 (30.4)	84 (34.4)	2,529 (33.2)	0.01
Diabetes		6 (16.2)	38 (20.7)	71 (21.8)	156 (19.7)	865 (24.5)	478 (26.8)	222 (30.8)	79 (32.4)	1,915 (25.1)	< 0.001
Pharmacotherapy											
Digoxin		7 (18.9)	32 (17.4)	64 (19.7)	140 (17.7)	655 (18.5)	325 (18.2)	113 (15.7)	53 (21.7)	1,389 (18.2)	0.53
Potassium supplement	ATC: A12B	26 (70.3)	112 (60.9)	194 (59.7)	378 (47.8)	1629 (46.1)	773 (43.3)	306 (42.5)	124 (50.8)	3,542 (46.5)	< 0.001
	ATC: C03	≤3	34 (18.5)	57 (17.5)	135 (17.1)	499 (14.1)	235 (13.2)	100 (13.9)	27 (11.1)	≤1,090	0.03
Beta-blockers		22 (59.5)	90 (48.9)	155 (47.7)	398 (50.3)	1983 (56.1)	1012 (56.7)	372 (51.7)	124 (50.8)	4,156 (54.5)	0.001
Calcium channel blockers		12 (32.4)	50 (27.2)	76 (23.4)	207 (26.2)	914 (25.9)	432 (24.2)	204 (28.3)	59 (24.2)	1,954 (25.6)	0.41
Renin angiotensin system inhibitors		20 (54.1)	90 (48.9)	175 (53.8)	486 (61.4)	2496 (70.6)	1315 (73.6)	485 (67.4)	176 (72.1)	5,243 (68.8)	< 0.001
Loop diuretics		20 (54.1)	114 (62.0)	186 (57.2)	384 (48.5)	1570 (44.4)	827 (46.3)	355 (49.3)	139 (57.0)	3,595 (47.2)	< 0.001

Thiazides	7 (18.9)	52 (28.3)	97 (29.8)	226 (28.6)	819 (23.2)	376 (21.1)	179 (24.9)	43 (17.6)	1,799 (23.6)	< 0.001
Thiazide-like diuretics									73 (1.0)	0.27
Potassium sparing diuretics	≤3	7 (3.8)	11 (3.4)	10 (1.3)	45 (1.3)	27 (1.5)	10 (1.4)	6 (2.5)	≤119	0.004
Mineral receptor antagonists	12 (32.4)	46 (25.0)	74 (22.8)	161 (20.4)	730 (20.7)	421 (23.6)	181 (25.1)	66 (27.0)	1,691 (22.2)	0.01
Vaso	0 (0.0)	0 (0.0)	0 (0.0)	≤3	≤3	0 (0.0)	0 (0.0)	0 (0.0)	≤6	0.79
AntiAdrenerg	0 (0.0)	4 (2.2)	7 (2.2)	9 (1.1)	35 (1.0)	23 (1.3)	13 (1.8)	≤3	≤94	0.31
Antimicrobials	21 (56.8)	111 (60.3)	220 (67.7)	446 (56.4)	2044 (57.9)	1009 (56.5)	391 (54.3)	137 (56.1)	4,379 (57.5)	0.01
Beta-2 agonists	6 (16.2)	61 (33.2)	100 (30.8)	225 (28.4)	858 (24.3)	418 (23.4)	162 (22.5)	54 (22.1)	1,884 (24.7)	0.001
Corticoids	6 (16.2)	35 (19.0)	76 (23.4)	166 (21.0)	717 (20.3)	385 (21.6)	138 (19.2)	41 (16.8)	1,564 (20.5)	0.47
Laxatives	≤3	8 (4.3)	12 (3.7)	32 (4.0)	105 (3.0)	61 (3.4)	26 (3.6)	13 (5.3)	≤260	0.48
Xantines	≤3	8 (4.3)	17 (5.2)	25 (3.2)	93 (2.6)	46 (2.6)	26 (3.6)	5 (2.0)	≤223	0.12
NSAIDs	23 (62.2)	103 (56.0)	210 (64.6)	430 (54.4)	1995 (56.5)	1032 (57.8)	403 (56.0)	142 (58.2)	4,338 (56.9)	0.11

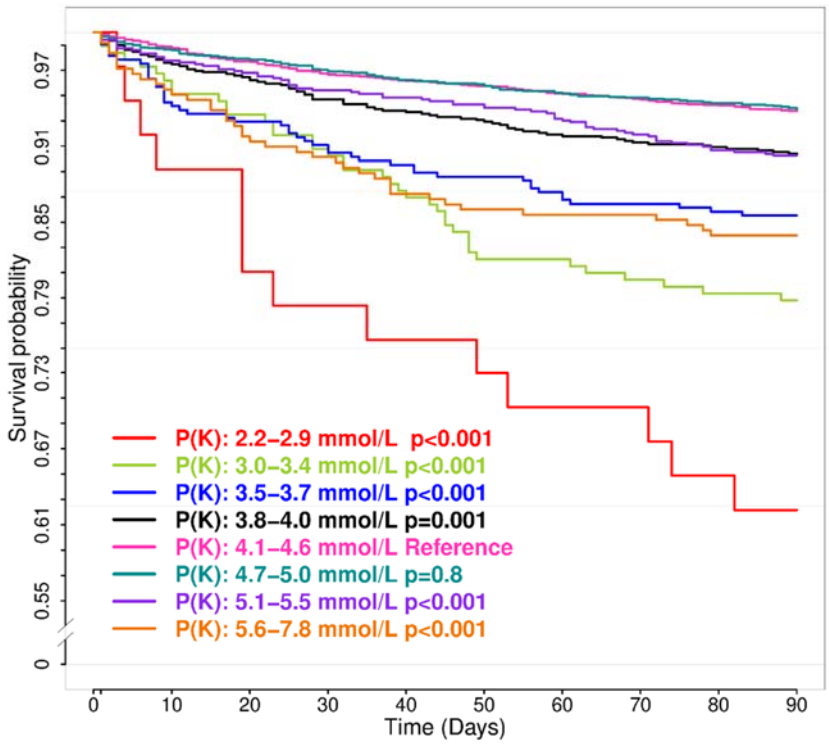
NSAIDs- Nonsteroidal anti-inflammatory drugs

≤3 was attributed to variables with values between 1 and 3 to secure anonymity and protection of personal data

4.3.2 Survival analysis

Totally, 622 (8.2%) patients died within 90-days follow-up. Mortality reported according to the eight plasma potassium strata was: 37.8%, 21.2%, 14.5%, 9.6%, 6.3%, 6.2%, 10.0%, and 16.4%, respectively (Table 4.3.1.1). Kaplan-Meier survival curves are illustrated in Figure 4.3.2.1. Patients who died were older, with higher kidney insufficiency burden at K_2, higher hospitalization rate at K_2, and more likely with a previous history of malignancy, stroke, chronic obstructive pulmonary disease, atrial fibrillation and chronic liver disease within the past five years (Appendix 8).

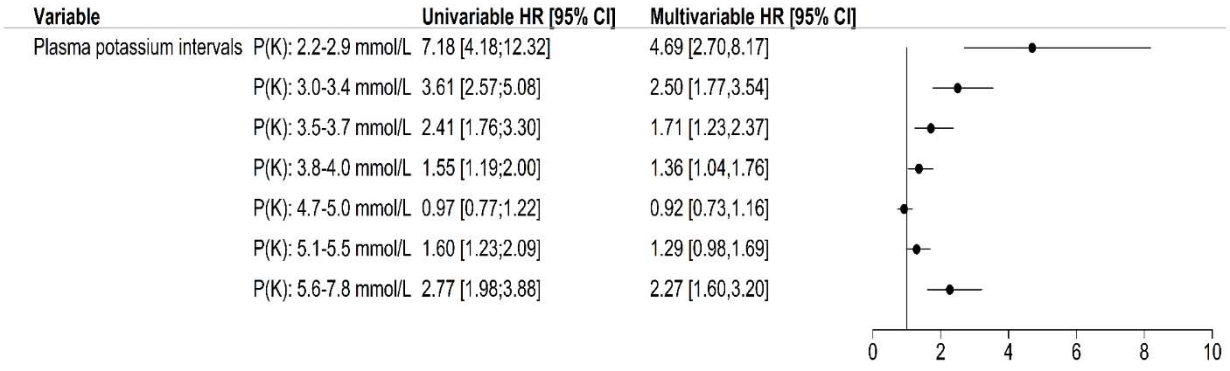
Figure 4.3.2.1 – Kaplan Meier survival curves across the eight plasma potassium intervals. The p-values indicate the difference among plasma potassium groups compared to the reference group based on an unadjusted Cox regression model.



The results of the univariable and multivariable Cox proportional regression, with plasma potassium 4.1-4.6 mmol/L as the reference group, are shown in Figure 4.3.2.2. The multivariable analysis showed that patients with hypokalemia following an episode with hyperkalemia have an increased

90-day mortality risk (2.2-2.9 mmol/L: HR 4.69, 95% CI 2.70-8.17; 3.0-3.4 mmol/L: HR 2.50, 95% CI 1.77-3.54). Patients with potassium concentrations between 3.5-4.0 mmol/L also had an increased risk of death within 90-days (3.5-3.7 mmol/L: HR 1.71, 95% CI 1.23-2.37; 3.8-4.0 mmol/L: HR 1.36, 95% CI 1.04-1.76). As for patients with persisting hyperkalemia, we observed that potassium concentrations within the interval 5.6-7.8 mmol/L was associated with increased 90-day mortality risk (HR 2.27, 95% CI 1.60-3.20).

Figure 4.3.2.2 All-cause mortality after hyperkalemia according to subsequent potassium measurements in patients treated with combination antihypertensive therapy (90-days follow-up, n=7,620). Potassium interval K: 4.1-4.6 mmol/L represented the reference range.



4.3.3 Sensitivity analyses

To test the robustness of our main results we performed nine sensitivity analyses (Appendix 9).

First, we performed analysis on a subpopulation with eGFR ≥30 mL/min/1.73 m^2 (n=6,505). The results were similar to the main analysis.

Second, analyses using patients without past history of any malignancy (n= 6,383) showed similar results to the main analysis, although potassium interval 3.8-4.0 mmol/L was no longer statistically significant (HR 1.33, 95% CI 0.95-1.84).

Third, 3,149 patients had no history of heart failure and/or loop diuretic prescriptions. Analysis using this subgroup of patients showed that only hypokalemia was significantly associated with increased 90-day mortality risk following an episode with hyperkalemia (2.2-2.9 mmol/L: HR 7.79, 95% CI 2.54-23.90 and 3.0-3.4 mmol/L: HR 2.79, 95% CI 1.35-5.78).

Fourth, analysis using patients without past history of ischemic heart disease (n= 5,121) showed similar results to the main analysis. Although, potassium interval 3.8-4.0 mmol/L was no longer statistically significant (HR 1.30, 95% CI 0.95-1.77). Conversely, potassium levels within the interval 5.1-5.5 mmol/L were associated with increased risk of short-term mortality after an episode with hyperkalemia.

Fifth, including patients with hypertension defined by relevant ICD diagnosis codes (n= 2,410), we observed that patients who developed hypokalemia after an episode with hyperkalemia had increased 90-day mortality risk (2.2-2.9 mmol/L: HR 5.15, 95% CI 2.09-12.69 and 3.0-3.4 mmol/L: HR 2.84, 95% CI 1.52-5.29). Patients with potassium concentrations above 5.0 mmol/L after an episode with hyperkalemia had also increased risk of death within 90-days (5.1-5.5 mmol/L: HR 2.31, 95% CI 1.43-3.75 and 5.6-7.8 mmol/L: HR 2.54, 95% CI 1.22-5.29).

Sixth, potassium concentrations outside the interval 4.1-5.0 mmol/L were associated with increased cardiovascular mortality risk (2.2-2.9 mmol/L: HR 6.86, 95% CI 3.40-13.85; 3.0-3.4 mmol/L: HR 3.21, 95% CI 2.05-5.04; 3.5-3.7 mmol/L: HR 1.85. 95% CI 1.15-2.96; 3.8-4.0 mmol/L: HR 1.56, 95% CI 1.09-2.25; 5.1-5.5 mmol/L: HR 1.80, 95% CI 1.26-2.57; 5.6-7.8 mmol/L: HR 2.61, 95% CI 1.56-4.35).

Seventh, by performing the analyses on the last available potassium draw within 6-100 days from K_1, the results were similar to the main analysis.

Eighth, we performed multivariable analyses where we adjusted for potassium concentrations obtained at K_1. The results were similar to the main analysis: potassium levels outside the interval 4.6-5.5 mmol/L after a recent episode with hyperkalemia were associated with increased short-term mortality risk.

Ninth, analyses including time between first and second potassium draw as a covariate in the multivariable model showed similar results to the main analysis.

4.4 Study IV

4.4.1 Demographics

During 1995 to 2017, 11,896 patients fulfilled the inclusion criteria. Nearly half of the population was prescribed thiazide diuretics, of which 1.6 % were thiazide-like diuretics. Roughly one third of the population redeemed potassium supplements, mostly as single pill combined with an antihypertensive (86.7%). Hypokalemia represented 3.9% of the total population. Predominant comorbidities were ischemic heart disease, heart failure, diabetes and 2% had renal dysfunction (Appendix 10).

After matching on age, sex, eGFR, renal insufficiency, and time from index date to potassium measurement, 463 cases and 926 controls were identified. Median time from index date to potassium measurement was 30 days (IQR 0, 90). Patients treated with RASi+Thiazides and CCB+Thiazides had the highest prevalence of hypokalemia (30.7% and 12.1%, respectively) compared to patients treated with the other combinations. Almost half of the cases redeemed potassium supplement (Table 4.4.1.1).

Table 4.4.1.1. Demographics of the matched population. Variables written in *Italic* represent the variables we matched on.

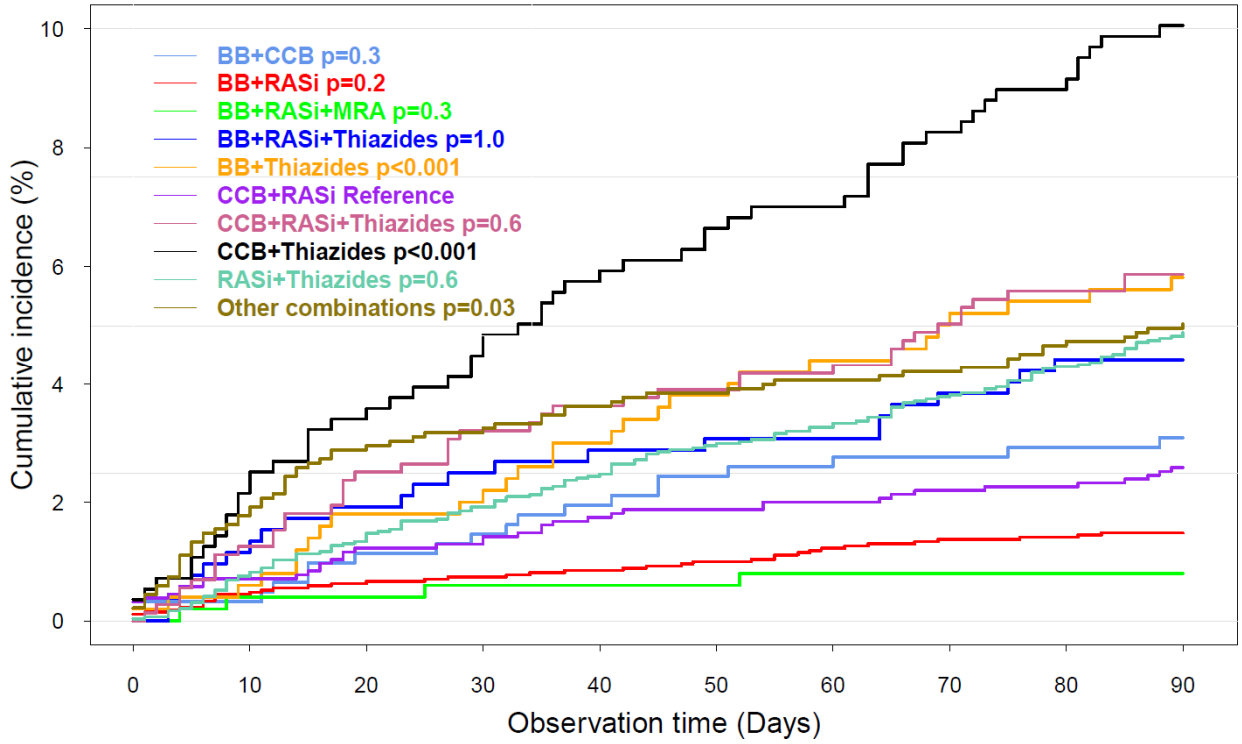
		Controls (n=926)	**Cases (n=463)**	**Total (n=1389)**	**p-value**
Gender	*Female*	*484 (52.3)*	*242 (52.3)*	*726 (52.3)*	*1.0*
Age	*median(range)*	*65.0(21.0, 95.0)*	*66.0(23.0, 95.0)*	*65.0(21.0, 95.0)*	*0.55*
Days from hypertension to potassium measurement	*median(range)*	*30.0(0.0, 90.0)*	*31.0(0.0, 90.0)*	*30.0(0.0, 90.0)*	*0.68*
Serum sodium	*median(range)*	*140.0(113.0, 146.0)*	*140.0(118.0, 148.0)*	*140.0(113.0, 148.0)*	*0.15*
Renal insufficiency		*10 (1.1)*	*5 (1.1)*	*15 (1.1)*	*1.0*
eGFR	median(range)	77.0(10.0, 214.0)	79.0(7.0, 222.0)	78.0(7.0, 222.0)	0.32
Treatment combinations	BB+CCB	41 (4.4)	19 (4.1)	60 (4.3)	
	BB+RASi	195 (21.1)	40 (8.6)	235 (16.9)	
	BB+RASi+MRA	40 (4.3)	4 (0.9)	44 (3.2)	
	BB+RASi+Thiazides	33 (3.6)	23 (5.0)	56 (4.0)	
	BB+Thiazides	32 (3.5)	29 (6.3)	61 (4.4)	
	CCB+RASi	134 (14.5)	40 (8.6)	174 (12.5)	
	CCB+RASi+Thiazides	49 (5.3)	42 (9.1)	91 (6.6)	
	CCB+Thiazides	37 (4.0)	56 (12.1)	93 (6.7)	
	RASi+Thiazides	264 (28.5)	142 (30.7)	406 (29.2)	
	Other combinations	101 (10.9)	68 (14.7)	169 (12.2)	< 0.0001
Heart failure		153 (16.5)	30 (6.5)	183 (13.2)	< 0.0001
IHD/MI		224 (24.2)	68 (14.7)	292 (21.0)	< 0.0001
COPD		56 (6.0)	30 (6.5)	86 (6.2)	0.84
Diabetes		121 (13.1)	41 (8.9)	162 (11.7)	0.03
Chronic liver disease		24 (2.6)	9 (1.9)	33 (2.4)	0.57
Hemodialysis		≤3	≤3	≤6	-
Malignancy		115 (12.4)	73 (15.8)	188 (13.5)	0.10
Stroke		83 (9.0)	55 (11.9)	138 (9.9)	0.11
Atrial flutter/fibrillation		120 (13.0)	41 (8.9)	161 (11.6)	0.03
Atrioventricular block		13 (1.4)	≤3	≤16	-
VT/VF		36 (3.9)	13 (2.8)	49 (3.5)	0.38
Inflammatory bowel disease		16 (1.7)	11 (2.4)	27 (1.9)	0.54
Hypothyroidism		18 (1.9)	9 (1.9)	27 (1.9)	1.0
Potassium supplement		312 (33.7)	212 (45.8)	524 (37.7)	< 0.0001
Antimicrobials		≤3	≤3	≤6	-
Beta-2 agonists		≤3	≤3	≤6	-

≤3 was attributed to variables with values between 1 and 3 to secure anonymity and protection of personal data

4.4.2 Antihypertensive combination therapies and risk of hypokalemia

Cumulative incidence curve drawn on the original population (n=11,898) and stratified on the ten combination therapies showed that CCB+Thiazides had a significantly higher incidence of hypokalemia (10%) compared with the other antihypertensive combination therapies (Figure 4.4.2.1).

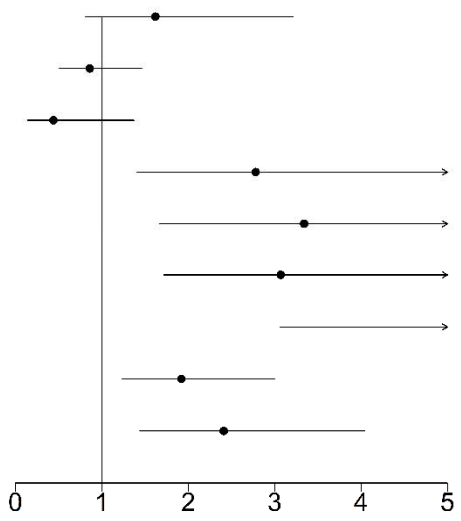
Figure 4.4.2.1 Cumulative incidence curve of hypokalemia risk stratified on the ten combination therapies



The multivariable conditional logistic regression analysis with CCB+RASi as reference showed 5.82 times increased hypokalemia odds within 90 days if administered CCB+Thiazides (95% CI 3.06-11.08). Following blood pressure drug combinations were also associated with increased odds of hypokalemia: BB+Thiazides (OR 3.34, 95% CI 1.67-6.66), CCB+RASi+Thiazides (OR 3.07, 95% CI 1.72-5.46) and BB+RASi+Thiazides (OR 2.78, 95% CI 1.41-5.47, Figure 4.4.2.2). The univariable analysis showed similar results (Appendix 11).

Figure 4.4.2.2. Forestplot of multivariable conditional logistic regression analysis for the development of hypokalemia. Population matched on age, gender, renal insufficiency and time index date initiation to serum potassium measurement. The model was adjusted for serum sodium, renal insufficiency, malignancy, IBD, diabetes, alcoholism and chronic liver disease. The combination of calcium channel blockers with renin-angiotensin system inhibitors was used as reference. BB- Beta Blockers, CCB- Calcium Channel Blockers, RASi- Renin-Angiotensin System Inhibitors, MRA- Mineral Receptor Antagonist.

Combination therapies	Odds ratio	Lower CI	Upper CI
BB+CCB	1.62	0.81	3.21
BB+RASi	0.86	0.51	1.46
BB+RASi+MRA	0.44	0.14	1.37
BB+RASi+Thiazides	2.78	1.41	5.47
BB+Thiazides	3.34	1.67	6.66
CCB+RASi+Thiazides	3.07	1.72	5.46
CCB+Thiazides	5.82	3.06	11.08
RASi+Thiazides	1.92	1.23	3.00
Other combinations	2.41	1.44	4.04



4.4.3 Sensitivity analyses

We performed an additional analysis on a population matched on age, sex, eGFR, renal insufficiency, time from index date to potassium measurement, heart failure, and ischemic heart disease/myocardial infarction. The results were similar to the main analyses (Appendix 12 and 13).

We observed that in the general population, treated with combination antihypertensive therapy who did not have available serum potassium measurements within 90 days from index date, the prevalence of most comorbidities of interest had lower proportions than in the nested case-control population (Appendix 14).

Appendices 15,16 and 17 include the published papers for Study I, Study II and Study IV.

5. Discussion

To summarize, the four studies demonstrated not only the importance of maintaining potassium homeostasis in patients treated with at least two classes of antihypertensive drugs, but also the importance of aiming potassium concentrations in the middle of the currently used reference interval. We observed that patients with initial potassium ≤3.7 mmol/L had increased short-term mortality risk (all-cause and cardiovascular) if they persisted hypokalemic or if they developed hyperkalemia. As for patients with initial hyperkalemia, potassium concentrations above 5.5 mmol/L and below 4.1 mmol/L were associated with increased all-cause and cardiovascular mortality. For patients on ≥2 antihypertensive drugs, we found that use of thiazide diuretics was associated with increased odds of hypokalemia, regardless of concomitant administration of a blood pressure drug with opposite effect on blood potassium concentrations, such as RASi or potassium supplement.

5.1 Study I

In study I, we investigated 90-day all-cause mortality risk in relation to seven predefined potassium intervals. Expectedly, hypokalemia and hyperkalemia were associated with increased risk of death within 90 days, compared with the reference 4.1-4.4 mmol/L. However, three potassium intervals within normal range (3.5-3.7, 3.8-4.0 and 4.8-5.0 mmol/L) were also associated with poor short-term prognosis. These results were not biased by great cardiovascular disease burden as subgroup analyses performed on populations without loop diuretic prescriptions, past history with myocardial infarction and heart failure showed similar results as in the main analyses. In addition, patients with acute and chronic kidney disease were excluded from all analyses. This suggests that potassium levels below 4.1 mmol/L and above 4.7 mmol/L are a risk factor of mortality in patients treated with minimum two classes of antihypertensive drugs.

Consistency in results was also observed both when defining hypertension based on combination antihypertensive therapy and by using ICD codes. This adds to the validity of hypertension definition used in this study.

The window period of 90 days for retaining the first potassium measurement was considered appropriate as a review showed that, in patients with hypertension, dyskalemias as a results of adverse drug reaction peaked at 3 months.[49]

To our knowledge, few, if any studies[50] have investigated which is the optimal potassium interval in patients with hypertension. Most studies explored the risk of potassium disturbances related to different antihypertensive drugs or risk of arrhythmias in hypokalemia and hyperkalemia. Macdonald et al.[50] recommended a potassium range between 3.5 and 5.0 mmol/L in patients with hypertension. This recommendation was based on studies analyzing the effect of potassium rich diet/potassium supplementation on lowering blood pressure or based on studies examining the risk arrhythmia in relation to different potassium concentrations.

An older study by Hulting, showed that out of 1,315 patients, 3.5% had in-hospital episodes of ventricular fibrillation and that they typically occurred in the presence of hypokalemia. The author also observed relatively high incidence of ventricular fibrillation in patients with low normal serum potassium concentrations: 4% in those with serum potassium between 3.5-3.8 mmol/L, 2% when serum potassium was between 3.9-4.2 mmol/L and 1% in patients with serum potassium between 4.3-4.6 mmol/L. No episodes with ventricular fibrillation was observed in patients with admission potassium levels above 4.6 mmol/L. The author also concluded that serum potassium concentrations below 3.9 mmol/L were associated with fivefold increase in the risk of ventricular tachycardia.[51] Hultings observations are quite similar with our results, though different but relatable outcomes. In patients with hyperkalemia arrhythmias and sudden cardiac death may occur at different thresholds.

In patients with chronic diseases such as heart failure, diabetes and chronic kidney disease slow rise in potassium over time often occurs without consequences, whereas rapid-onset hyperkalemia can be fatal.[37]

In other populations with cardiovascular disease, we observed similar optimal potassium interval as in the current study. For example, in patients with acute and chronic heart failure potassium concentrations 3.9-4.5 mmol/L[52] and 4.2-4.7 mmol/L,[53] respectively, were associated with increased survival. Cooper et al. suggested that an optimal potassium value of 4.2 mmol/L in patients with heart failure.[54] In patients with atrial fibrillation or flutter co-treated with diuretics and rate-or rhythm-controlling drugs, we found that potassium levels outside the interval 3.8-4.4 mmol/L were associated with increased short-term mortality risk.[55] As hypertension is a great risk factor for atrial fibrillation and flutter, we believe that this population resembles our hypertensive population. As we can see, there is a minimal variation in the optimal intervals recommended in different categories of heart disease. However, the most outstanding similarities/overlaps are that low normal (≤3.7 mmol/L) and high normal (≥4.8 mmol/L) potassium concentrations are associated with poor prognosis. Yet, this study cannot answer whether low normal and high normal potassium concentrations should be regarded as risk factors or risk markers. It is possible for patients with borderline potassium levels to develop more extreme concentrations and that low normal and high normal potassium should be regarded as a proxy for dyskalemias.

5.2 Study II

In study II, we investigated 60-day mortality among 8,976 patients with hypertension and hypokalemia or low normal potassium concentrations in relation to a subsequent measurement. Five major findings characterize the results in this study: (1) Persistent hypokalemia following plasma potassium concentrations ≤3.7 mmol/L was more than twice as frequent as development of hyperkalemia. (2) Persistent hypokalemia associated with increased all-cause and presumed

cardiovascular mortality; (3) Elevation of potassium to levels >4.6 mmol/L in patients with initial potassium concentrations ≤3.7 mmol/L was associated with increased all-cause mortality; (4) Among patients with potassium levels between 3.5-3.7 mmol/L at K_1, development of hypokalemia or hyperkalemia was associated with increased mortality risk; (5) Correcting hypokalemia was associated with increased survival.

It was not a surprise that we observed significantly higher 60-day mortality risk in patients with potassium concentrations <3.5 or >4.6 mmol/L after an episode with potassium ≤3.7 mmol/L. In Study I, we noted an apparent optimal potassium range within 4.1-4.7 mmol/L in a similar population.[56]

Our study suggested that potassium deficit is frequently underestimated than overestimated by health care providers as 18% of the patients still had potassium concentrations ≤3.7 mmol/L at K_2 (vs. 5.4% >4.6 mmol/L). Hypokalemia (at K_2) was present in 13% of the patients with borderline hypokalemia at K_1. Possibly, the association of low normal potassium concentrations with mortality we noted in Study I, can partly be explained by further declines in potassium levels, and that low normal potassium concentrations might be a marker for an ongoing decrease in potassium.

Several studies demonstrated an association between hypokalemia and high risk of mortality among patients with cardiovascular disease.[55,57–59] Yet, only one previous study performed on heart failure patients demonstrated improved 90-day survival in patients who had their hypokalemia corrected within 8-30 days.[60] In addition, Harkness et al.[63] found that patients with hypokalemia whose potassium level was not corrected to ≥3.5 mmol/L within 24 h were at increased odds of developing arrhythmias. Although, the study did not describe or account for the cause of admission, comorbidities or pharmacotherapy. The authors excluded patients with history of ischemic heart disease and arrhythmia, but included patients with heart failure who have a high arrhythmia risk.

A study using 5,916 participants from the general population found no significant associations between borderline hypokalemia (3.4-3.6 mmol/L) and risk of all-cause mortality.[61] The results of this study and ours are very difficult to compare due to major differences in methodology, aim and population characteristics. First, in our population all patients are users of antihypertensive medication. In the study by Mattsson et al.[61] 49.6% of the total population had high blood pressure at baseline, 13.9% were prescribed heart medication and 10.9% were treated with diuretics. Second, our aim was to investigate the impact of correcting plasma potassium concentrations ≤3.7 mmol/L on short-term all-cause and cardiovascular mortality. In the study by Mattsson et al.[61], mortality was assessed from participants' fourth examination (between 2001-2003) until November 2014 or death, having a median follow-up of 11.9 years (Q1-Q3: 11.4-12.5 years). Potassium concentrations may not be constant over time, especially in patients with cardiovascular disease or patients treated with heart medication. Therefore, we believe that use of a single potassium measurement to assess association with long-term mortality can make interpretation of the results difficult. Shorter follow-up time or time varying analysis where serial potassium measurements were modelled would have improved the methodology and results. Although, it is important to acknowledge that borderline hypokalemia might have different impact/effect in general population compared to our population, where the burden of cardiac disease is high.

Among intensive care unit (ICU) patients, Bouadma et. al [62] investigated the effect of dyskalemia at admission and early dyskalemia correcting on short-term survival and cardiac events. The authors concluded that persisting hypokalemia or hyperkalemia within the first two days in ICU was associated with increased risk of death. We cannot compare the two populations, however both studies emphasize the importance of correcting hypokalemia to improve short-term mortality.

As we can see, the impact of correcting hypokalemia is highly dependent on the study population and burden of disease, especially cardiovascular. Guidelines in the US recommend a higher threshold for

potassium replacement therapy (<4.0 mmol/L), especially in patients with cardiovascular disease, who have a high risk of developing ventricular arrhythmias.[64]

5.3 Study III

In this register-based cohort study we investigated the 90-day mortality among 7,620 patients with hypertension and hyperkalemia in relation to a subsequent plasma potassium measurement.

The major findings were: (1) One third of the patients with initial hyperkalemia persisted having hyperkalemia at a subsequent measurement, (2) Potassium levels above 5.5 mmol/L were associated with increased all-cause and cardiovascular death, (3) Decrease in potassium to levels below 4.1 mmol/L in patients with initial hyperkalemia was associated with increased all-cause and cardiovascular mortality compared with the reference (4.1-4.6 mmol/L), (4) Potassium concentrations between 4.1-5.5 mmol/L after an episode with hyperkalemia were associated with increased survival.

Numerous studies have previously demonstrated the importance of maintaining potassium homeostasis in patients with cardiovascular disease. Study I, but also other studies, have also emphasized, that aiming potassium concentrations in the middle of the normal reference interval is beneficial in patients with heart disease.[52,53,55,56,65,66] However, no prior studies examined the impact of potassium normalization during a short period of time, after an episode with hyperkalemia, in patients with hypertension. In this study, we observed that downregulation of potassium to levels <4.1 mmol/L within 6-100 days after an episode with potassium >4.6 mmol/L was associated with increased all-cause and cardiovascular mortality. This finding confirmed the results from Study I where we observed an apparent optimal potassium range within 4.1-4.7 mmol/L in a similar population. In the same time, this study also indicated that in many cases initial hyperkalemia was followed by a steep downregulation of potassium, which was associated with bad prognosis.

A large scale study, using electronical records of 114,977 emergency department patients, demonstrated that in patients with hyperkalemia (≥5.5 mmol/L) at admission (n=1033), potassium normalization within the first eight hours was associated with 50% mortality reduction.[67] The authors did not present the distribution of comorbidities, however, their results are a wake-up call. In our study, we also observed that persisting moderate to severe hyperkalemia (plasma potassium >5.5 mmol/L) over a period of 6-100 days was associated with higher mortality compared to concentrations between 4.1-4.6 mmol/L. Yet, the study populations are not comparable.

Another study by McMahon et al.[68] investigated the association between the highest potassium concentration on the admission day and 30-, 90- and 365-day mortality in >39,000 intensive care unit treated patients. The authors observed increased mortality risk in patients with potassium levels >4.5 mmol/L. The authors also observed better prognosis in patients who had a decline in potassium concentration >1 mmol/L within 48 h following critical care initiation. Our study population is not described by intensive care unit patients, however the results of the two studies are rather comparable. Our study showed a clear benefit in lowering potassium levels in patients who originally had concentrations above 4.6 mmol/L. However, the survival benefit was lost when potassium was corrected to levels below 4.1 mmol/L.

We noted that kidney insufficiency, age, history of malignancy, stroke, chronic obstructive pulmonary disease, atrial fibrillation and chronic liver disease, hospitalization at the time of K_2 potassium measurement and fast down correction of high potassium levels were significant predictors of mortality. An et al. found similar predictors of mortality in patients with severe hyperkalemia requiring hospitalization.[69]

5.4 Study IV

In study IV, we estimated the odds of hypokalemia within 90 days from hypertension date in relation to different antihypertensive combination therapies. We observed that hypokalemia was common (4%) despite the short follow-up time. Thiazides were present in each of the combinations significantly associated with hypokalemia, regardless of supplementation with potassium in approximately 50% of the cases. This leads to the question whether supplementation with potassium was sufficient or not and whether use of thiazide-like diuretics instead of thiazide-type diuretics would reduce the risk of hypokalemia. In our population, only 1.6% of the patients were prescribed thiazide-like diuretics. A meta-analysis from 2017, concluded that thiazide-like diuretics have better blood pressure lowering effect without increasing the incidence of hypokalemia and hyponatremia.[70]

It is also intriguing that the combination therapies significantly associated with increased hypokalemia risk, have opposite effects on potassium homeostasis. In a meta-analysis based on the results of four randomized trials, the most frequent adverse event related to CCB+diuretic was hypokalemia.[71] Although, there is poor evidence about the risk and mechanisms of hypokalemia associated with the combination CCB+Thiazides. Looking at the two drugs independently, several studies demonstrated thiazide related hypokalemia.[72–74] As for CCBs, evidence is more uncertain. On one hand, in vitro, in vivo and case report studies reported hyperkalemia following initiation of CCB.[75–78] On the other hand, case studies and animal studies observed an association between administration of CCB and hypokalemia.[79–84] It seems that CCBs augment extra-renal loss of potassium, while thiazides enhance renal potassium disposal.[80,85–87] Despite the differences in mechanisms of action between the two major classes of CCBs (dihydropyridines and non-dihydropyridines) there is no pattern that one class is more susceptible to hypokalemia or hyperkalemia.

There are no available studies comparing the risk of hypokalemia in relation to the combinations of Thiazides with BB or RASi. Most studies compare the risk of hypokalemia in patients treated with thiazides versus other classes of antihypertensives.

Unquestionably, we should not forget that besides drugs, also advanced chronic disease states, diet and genetics can be responsible for potassium homeostasis disruption, especially hypokalemia. Unfortunately, we were unable to account for these factors in the analyses.

6. Strengths and limitations

All four studies included in this PhD thesis are based on Danish national registers, and the limitations mainly relate to the observational nature. This means that our findings cannot implicate causal inference. Data registered in the national registers is primarily collected for administrative purposes and secondarily for research. Therefore, the validity of the data is highly dependent on the ICD codes used to define different diseases. The ICD codes allocated each patient after hospitalization or out-patients visit are besides national surveillance also used for reimbursement, which can lead to a diagnostic drift towards diagnoses with the highest reimbursement.[88] Moreover, clinically relevant data such as alcohol consumption, ejection fraction, symptoms related to dyskalemias (vomiting, diarrhea, arrhythmias), and treatment indication were not available, which may lead to residual confounding. Though, there are also many advantages and strengths linked with register based studies such as: low costs, large sample size, limited selection bias, and (nearly) no loss to follow-up.[89]

Applicable to all four studies was the definition of hypertension based on redemption of minimum two antihypertensive drug classes in two concomitant quarters. Despite validation of a similar definition[44], there still are some limitations attached to it. First, in order to capture patients who have not been ascertained ICD-code of hypertension, we used blood pressure lowering drugs as a proxy. This can lead to identification of patients with other cardiovascular diseases (heart failure, atrial fibrillation and ischemic heart disease) where same medication can be used to treat or ease symptoms. In other words, misclassification bias can be present. Second, by using this definition of hypertension, we miss those patients with high blood pressure treated with monotherapy only. Still, by identifying patients based solely on monotherapy, we would have increased the misclassification bias as no treatment indication was available. Third, patients with high blood pressure who did not receive medication or was registered an ICD code from the secondary sector could have been misclassified as healthy. Fourth, the results cannot be generalized to the entire population treated for high blood

pressure, as we did not included patients on monotherapy or patients where lifestyle changes were preferred in order to lower blood pressure.

Another limitation that applies all four studies is missing information about blood draw indication. Some patients might have been tested due to hypokalemia or hyperkalemia symptoms, while others were tested during hospitalization or regular check-up at the general practitioner. In addition, we did not have information about the quality of the blood draws. Yet, in case of significant deviations from the norms, no values were reported to the registries.

In the following paragraphs I will present the major strengths and limitations that apply each study individually.

6.1 Study I

To obtain a normal distribution of potassium measurements and account for possible bias in potassium measurement, we excluded outliers, which resulted with few extreme concentrations. We do not believe that this represents a great limitation for the study as the main aim was to investigate whether potassium concentrations even within the normal reference interval were associated with increased mortality.

At the time this study was performed we could not differentiate between serum and plasma potassium measurement, which represents a limitation of the study. We referred to all measurements as serum potassium. The lower reference range does not really differ in the two methods of measuring potassium. However, the higher reference range can vary with more than 0.5 mmol/L.[17] We recently performed a validation study, where we only used plasma potassium measurements. The results resembled the original study.[90] In addition, the validation study also assessed the risk of cardiovascular mortality within 90 days from potassium measurement. We observed that potassium concentrations outside the interval 4.1-5.0 mmol/L were associated with high risk of cardiovascular mortality.

6.2 Study II-III

A major limitation of the two studies was the inability to investigate which initiatives physicians undertook to correct the initial low/high plasma potassium concentrations. The Danish National Prescription Registry records filled prescriptions and changes in dosage of a prescribed drug or treatment given during hospitalization is not registered.

Likewise, we were unable to compare electrocardiographic findings in patients whose plasma potassium was normalized or remained decreased/elevated. Although, our results should be considered hypothesis generating associations.

Last, in both studies we assessed the risk of presumed cardiovascular death in relation to potassium. Autopsies are not common in Denmark, therefore we cannot be certain that patients were attributed correctly cardiac vs. non-cardiac cause of death.

6.3 Study IV

A major strength of this study is that we ensured that all participants were normokalemic up to 30 days before inclusion in the study. This strengthens the hypothesis that hypokalemia was induced by antihypertensive medication. Although, a great limitation of this study was missing information about the dosage of redeemed antihypertensive drugs. Due to the short follow-up time it was impossible to calculate the dosage. In as such, we cannot rule out the possibility that the associations observed could be dose dependent. Moreover, problems with compliance and overdose could not be identified, which can lead to non-differential misclassification.

Patients could also have been misclassified due to the mix of potassium measurements in serum and plasma. However, a study has shown that the difference in serum and plasma potassium measurements do not exceed 0.1 mmol/L when referring to the lower reference range.[17] Therefore, we believe that the great majority of the cases were correctly classified.

7. Conclusions

7.1 Study I

Potassium concentrations outside the interval 4.1-4.7 mmol/L were associated with increased 90-day all-cause mortality risk in patients with hypertension treated with minimum two classes of antihypertensive drugs.

7.2 Study II

Persistent hypokalemia (<3.5 mmol/L) was frequent and associated with increased all-cause and cardiovascular death after an episode with potassium ≤3.7 mmol/L. Increase in potassium to levels >4.6 mmol/L in patients with initial hypokalemia or low normal potassium (≤3.7 mmol/L) was associated with increased all-cause mortality. Among patients with initial borderline hypokalemia, development of hypokalemia or hyperkalemia was associated with poor outcomes.

7.3 Study III

Overcorrection of hyperkalemia to levels <4.1 mmol/L was frequent and associated with increased all-cause mortality. Persistent hyperkalemia >5.0 mmol/L seemed to be associated with an increased risk of death as well.

7.4 Study IV

Combinations of thiazide diuretics with CCB, RASi, or BB were strongly associated with increased odds of hypokalemia within 90 days of treatment initiation, regardless of potassium supplementation in nearly half of the population.

8. Clinical implications and perspectives

8.1 Study I

Not only hypokalemia and hyperkalemia, but also low- and high- normal potassium concentrations were associated with increased short-term mortality risk. This suggests that a narrower potassium reference range should be aimed in patients with hypertension treated with combination antihypertensive therapy. Our study also suggested that potassium monitoring closely after combination therapy initiation might be relevant as many patients experienced dyskalemias. Future studies examining frequency of potassium measurement, potassium fluctuations over time, and effect of stringent potassium regulation on mortality and arrhythmia onset would supply, explain and put into perspective the observations made based on this study. These studies are important pieces in understanding the complexity of potassium homeostasis and its effects and their results can potentially save lives.

8.2 Study II

We were not able to report the initiatives medical doctors undertook after observing potassium levels ≤3.7 mmol/L at the first measurement. However, our results emphasize the importance of aiming at potassium concentrations in the middle of the currently used RI and that overcorrection is associated with an increased risk of death (after an episode with potassium concentrations ≤3.7 mmol/L). Potassium concentrations in the middle of the normal reference interval are associated with good prognosis. Future research, investigating the effect of elevating potassium on mortality and other relevant clinical outcomes (hospitalization rate, arrhythmias) in patients with potassium concentrations between 3.5-3.7 mmol/L are warranted.

Possibly, potassium supplementation, use of mineral receptor antagonists or thiazide-like diuretics instead of thiazide-type in patients with potassium concentrations ≤3.7 mmol/L could be of clinical importance, but requires further study, preferably through a randomized controlled trial.

8.3 Study III

Even though we were not able to report the initiatives physicians undertook when evaluating the results of first potassium measurement >4.6 mmol/L, our results emphasized the importance of potassium normalization after an episode with hyperkalemia and non-radical correction of hyperkalemia in patients with hypertension treated with combination antihypertensive therapy. Future studies should determine whether rapid reduction of potassium and stringent potassium control has a causal relation with (reduced) mortality and arrhythmic events. Generally, studies investigating the rate of correction and importance of immediately increasing/decreasing potassium in symptomatic and asymptomatic patients with dyskalemias are missing.

8.4 Study IV

Optimal management of hypertension is very important as numerous studies showed benefits both related to the risk of death but also to development of other cardiovascular conditions and health-related quality of life. Most of the drugs used for management of high blood pressure can cause hypokalemia and hyperkalemia. In these days, where guidelines recommend polytherapy rather than monotherapy to lower blood pressure, awareness of the risk factors associated with potassium disturbances is also important. Our study strongly suggested that any combination with thiazide diuretics was associated with high odds of hypokalemia within 90 days from combination therapy initiation, despite supplementation with potassium in a considerable proportion of the population. Therefore, we recommend close potassium monitoring in patients treated with thiazide diuretics. How close? It is difficult to define as evidence regarding the frequency of potassium monitoring when patients are administered diuretics is missing. A couple of small scale studies suggested that hypokalemia typically develops within 2-19 weeks from start diuretic treatment.[91,92] Studies investigating the time frame where patients treated with diuretics are most vulnerable to develop hypokalemia are important both for the patient itself (to prevent adverse events) and for the healthcare

system (guidelines that specify the frequency of potassium monitoring). Another important aspect that should be focused on in future studies, is the risk of potassium disarrays associated to thiazide-like and thiazide-type diuretics. In Denmark, thiazide-type diuretics are the most commonly used thiazide diuretics. Comparing our study with others, we believe that use of thiazide-like diuretics might be associated with fewer hypokalemia events. For example, in SPRINT trial (Systolic Blood Pressure Intervention Trial), hypokalemia occurred in 1.7% of the total patients regardless of treatment with indapamide. Yet, it occurred more frequently among patients treated with thiazides (3.0%) than in patients not taking thiazides (0.4%).[93] Although, the lower frequency of hypokalemia in SPRINT can also be explained by strict follow-up of trial patients, healthier and younger population.

9. References

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet (London, England)* England; 2005;**365**:217–223.

2. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet (London, England)* England; 2016;**388**:1659–1724.

3. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet (London, England)* England; 2015;**385**:117–171.

4. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, Simone G de, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* England; 2018;**39**:3021–3104.

5. Carretero OA, Oparil S. Essential hypertension. Part I: definition and etiology. *Circulation* United States; 2000;**101**:329–335.

6. Whelton PK, Carey RM, Aronow WS, Casey DEJ, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SCJ, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KAS, Williamson JD, Wright JTJ. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task F. *Circulation* United States; 2018;**138**:e426–e483.

7. Sica DA. Antihypertensive therapy and its effects on potassium homeostasis. J. Clin. Hypertens. (Greenwich). 2006. p. 67–73.

8. Udensi UK, Tchounwou PB. Potassium Homeostasis, Oxidative Stress, and Human Disease. *Int J Clin Exp Physiol* India; 2017;**4**:111–122.

9. Palmer BF. Regulation of Potassium Homeostasis. *Clin J Am Soc Nephrol* United States; 2015;**10**:1050–1060.

10. Zacchia M, Abategiovanni ML, Stratigis S, Capasso G. Potassium: From Physiology to Clinical Implications. *Kidney Dis (Basel, Switzerland)* Switzerland; 2016;**2**:72–79.

11. Gumz ML, Rabinowitz L, Wingo CS. An Integrated View of Potassium Homeostasis. N. Engl. J. Med. United States; 2015. p. 1787–1788.

12. Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis. *Adv Physiol Educ* United States; 2016;**40**:480–490.

13. Stokes JB, Lee I. Mineralocorticoid effect on K+ permeability of the rabbit cortical collecting tubule. *Kidney Int* 1985;**28**:640–645.

14. Ypersele de Strihou C Van. Potassium homeostasis in renal failure. *Kidney Int* 1977;**11**:491–504.

15. Asirvatham JR, Moses V, Bjornson L. Errors in potassium measurement: a laboratory

perspective for the clinician. *N Am J Med Sci* India; 2013;**5**:255–259.

16. Nijsten MWN, Smet B j. g. l. de, Dofferhoff ASM. Pseudohyperkalemia and Platelet Counts. N. Engl. J. Med. 1991. p. 1107.

17. Drogies T, Ittermann T, Lüdemann J, Klinke D, Kohlmann T, Lubenow N, Greinacher A, Völzke H, Nauck M. Potassium - Reference intervals for lithium-heparin plasma and serum from a population-based cohort. *LaboratoriumsMedizin* 2010;**34**:39–44.

18. Burtis CA, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 5th ed. St. Louis, Missouri, USA: Elsevier Saunders; 2012.

19. Rustad P, Felding P, Franzson L, Kairisto V, Lahti A, Martensson A, Hyltoft Petersen P, Simonsson P, Steensland H, Uldall A. The Nordic Reference Interval Project 2000: recommended reference intervals for 25 common biochemical properties. *Scand J Clin Lab Invest* Furst Medical Laboratory, Soren Bulls vei 25, NO-1051 Oslo, Norway. prustad@furst.no; 2004;**64**:271–284.

20. Sevastos N, Theodossiades G, Archimandritis AJ. Pseudohyperkalemia in serum: A new insight into an old phenomenon. Clin. Med. Res. 2008. p. 30–32.

21. Liamis G, Liberopoulos E, Barkas F, Elisaf M. Spurious electrolyte disorders: A diagnostic challenge for clinicians. Am. J. Nephrol. 2013. p. 50–57.

22. Sica DA, Struthers AD, Cushman WC, Wood M, Banas JS, Epstein M. Importance of potassium in cardiovascular disease. *J Clin Hypertens* 2002;**4**:198–206.

23. Adrogué HJ, Madias NE. Sodium and potassium in the pathogenesis of hypertension. N. Engl. J. Med. 2007. p. 1966.

24. Krishna GG, Miller E, Kapoor S. Increased Blood Pressure during Potassium Depletion in Normotensive Men. *N Engl J Med* 1989;**320**:1177–1182.

25. Krishna GG, Kapoor SC. Potassium depletion exacerbates essential hypertension. *Ann Intern Med* United States; 1991;**115**:77–83.

26. Veltri KT, Mason C. Medication-induced hypokalemia. *P T* United States; 2015;**40**:185–190.

27. Mandava P, Raja Kiranmai TKNV, Mounika PS, Babu AM. S. Combinational Drug Therapy and Electrolyte Disorder in a Hypertensive Patient–A Case Report. *Indian J Pharm Pract* 2016;**9**:269–271.

28. Perazella MA. Drug-induced hyperkalemia: Old culprits and new offenders. Am. J. Med. 2000. p. 307–314.

29. Weiss JN, Qu Z, Shivkumar K. Electrophysiology of hypokalemia and hyperkalemia. *Circ Arrhythmia Electrophysiol* 2017;**10**.

30. Viera AJ, Wouk N. Potassium disorders: Hypokalemia and hyperkalemia. *Am Fam Physician* 2015;**92**:487–495.

31. Diercks DB, Shumaik GM, Harrigan RA, Brady WJ, Chan TC. Electrocardiographic manifestations: electrolyte abnormalities. *J Emerg Med* United States; 2004;**27**:153–160.

32. WEAVER WF, BURCHELL HB. Serum potassium and the electrocardiogram in hypokalemia. *Circulation* United States; 1960;**21**:505–521.

33. Drew BJ, Califf RM, Funk M, Kaufman ES, Krucoff MW, Laks MM, Macfarlane PW, Sommargren C, Swiryn S, Hare GF Van. Practice standards for electrocardiographic monitoring in hospital settings: An American Heart Association scientific statement from the councils on cardiovascular nursing, clinical cardiology, and cardiovascular disease in the young. Circulation. 2004.

34. Krogager ML, Kragholm K, Skals RK, Mortensen RN, Polcwiartek C, Graff C, Nielsen JB, Kanters JK, Holst AG, Sogaard P, Pietersen A, Torp-Pedersen C, Hansen SM. The relationship between serum potassium concentrations and electrocardiographic characteristics in 163,547 individuals from primary care. *J Electrocardiol* United States; 2019;**57**:104–111.

35. Levis JT. ECG diagnosis: hypokalemia. *Perm J* Santa Clara Medical Center, CA, USA. joel.levis@kp.org; 2012;**16**:57.

36. Chua CE, Choi E, Khoo EYH. ECG changes of severe hypokalemia. *QJM* 2018;

37. Rosano GMC, Tamargo J, Kjeldsen KP, Lainscak M, Agewall S, Anker SD, Ceconi C, Coats AJS, Drexel H, Filippatos G, Kaski JC, Lund L, Niessner A, Ponikowski P, Savarese G, Schmidt TA, Seferovic P, Wassmann S, Walther T, Lewis BS. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society o. *Eur Hear journal Cardiovasc Pharmacother* England; 2018;**4**:180–188.

38. Pedersen CB. The Danish civil registration system. *Scand J Public Health* 2011;**39**:22–25.

39. Helweg-Larsen K. The Danish Register of Causes of Death. *Scand J Public Health* Sweden; 2011;**39**:26–29.

40. Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. *Scand J Public Health* 2011;**39**:30–33.

41. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* New Zealand; 2015;**7**:449–490.

42. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;**39**:38–41.

43. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* Center for Healthy Ageing, Department of Public Health, University of Copenhagen, Denmark. hewk@sund.ku.dk; 2011;**39**:38–41.

44. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* Department of Cardiology, Copenhagen University Hospital Gentofte, 2900 Hellerup, Denmark. jo@heart.dk; 2011;**342**:d124.

45. Carlsson L, Lind L, Larsson A. Reference values for 27 clinical chemistry tests in 70-year-old males and females. *Gerontology* Department of Medical Sciences, Uppsala University, Sweden.: S. Karger AG, Basel; 2010;**56**:259–265.

46. R Core Team. R: A language and environment for statistical computing. R Foundation for

Statistical Computing, Vienna, Austria. 2018.

47. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, Kusek JW, Eggers P, Lente F Van, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–612.

48. Rustad P, Felding P, Franzson L, Kairisto V, Lahti A, Martensson A, Hyltoft Petersen P, Simonsson P, Steensland H, Uldall A. The Nordic Reference Interval Project 2000: recommended reference intervals for 25 common biochemical properties. *Scand J Clin Lab Invest* Furst Medical Laboratory, Soren Bulls vei 25, NO-1051 Oslo, Norway. prustad@furst.no; 2004;**64**:271–284.

49. McDowell SE, Ferner RE. Biochemical monitoring of patients treated with antihypertensive therapy for adverse drug reactions: a systematic review. *Drug Saf* West Midlands Centre for Adverse Drug Reactions, Birmingham, UK.; 2011;**34**:1049–1059.

50. Macdonald JE, Struthers AD. What is the optimal serum potassium level in cardiovascular patients? *J Am Coll Cardiol* Department of Clinical Pharmacology, Ninewells Hospital, Dundee, United Kingdom. macdonald_je@hotmail.com; 2004;**43**:155–161.

51. Hulting J. In-hospital ventricular fibrillation and its relation to serum potassium. *Acta Med Scand Suppl* Sweden; 1981;**647**:109–116.

52. Krogager ML, Eggers-Kaas L, Aasbjerg K, Mortensen RN, Køber L, Gislason G, Torp-Pedersen C, Søgaard P. Short-term mortality risk of serum potassium levels in acute heart failure following myocardial infarction. *Eur Hear journal Cardiovasc Pharmacother* 2015;**1**:245–251.

53. Aldahl M, Jensen A-SC, Davidsen L, Eriksen MA, Moller Hansen S, Nielsen BJ, Krogager ML, Kober L, Torp-Pedersen C, Sogaard P. Associations of serum potassium levels with mortality in chronic heart failure patients. *Eur Heart J* England; 2017;**38**:2890–2896.

54. Cooper LB, Benson L, Mentz R, Savarese G, DeVore A, Carrero JJ, Dahlstrom U, Anker S, Lainscak M, Hernandez A, Pitt B, Lund L. ASSOCIATION BETWEEN SERUM POTASSIUM LEVEL AND OUTCOMES IN HEART FAILURE WITH REDUCED EJECTION FRACTION: A COHORT STUDY FROM THE SWEDISH HEART FAILURE REGISTRY. *J Am Coll Cardiol* 2017;

55. Hagengaard L, Sogaard P, Espersen M, Sessa M, Lund PE, Krogager ML, Torp-Pedersen C, Kragholm KH, Polcwiartek C. Association Between Serum Potassium Levels and Short-Term Mortality in Patients With Atrial Fibrillation or Flutter Co-treated With Diuretics and Rate- or Rhythm-Controlling Drugs. *Eur Hear journal Cardiovasc Pharmacother* England; 2019;

56. Krogager ML, Torp-Pedersen C, Mortensen RN, Køber L, Gislason G, Søgaard P, Aasbjerg K. Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. *Eur Heart J* 2017;**38**:104–112.

57. Alderman MH, Piller LB, Ford CE, Probstfield JL, Oparil S, Cushman WC, Einhorn PT, Franklin SS, Papademetriou V, Ong ST, Eckfeldt JH, Furberg CD, Calhoun DA, Davis BR, Group A and L-LT to PHATCR. Clinical significance of incident hypokalemia and hyperkalemia in treated hypertensive patients in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension* Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Bronx, NY, USA.; 2012;**59**:926–933.

58. Aldahl M, Caroline Jensen A-S, Davidsen L, Eriksen MA, Hansen SM, Nielsen BJ, Krogager

ML, Køber L, Torp-Pedersen C, Søgaard P. Associations of serumpotassiumlevels with mortality in chronic heart failure patients. *Eur Heart J* 2017;**38**.

59. Krogager ML, Eggers-Kaas L, Aasbjerg K, Mortensen RN, Køber L, Gislason G, Torp-Pedersen C, Søgaard P. Short-Term mortality risk of serum potassium levels in acute heart failure following myocardial infarction. *Eur Hear J - Cardiovasc Pharmacother* 2015;**1**.

60. Aldahl M, Polcwiartek C, Davidsen L, Kragholm K, Søgaard P, Torp-Pedersen C, Krogager ML. Short-term prognosis of normalising serum potassium following an episode of hypokalaemia in patients with chronic heart failure. *Eur J Prev Cardiol* 2020;

61. Mattsson N, Nielsen OW, Johnson L, Prescott E, Schnohr P, Jensen GB, Kober L, Sajadieh A. Prognostic Impact of Mild Hypokalemia in Terms of Death and Stroke in the General Population-A Prospective Population Study. *Am J Med* United States; 2018;**131**:318.e9-318.e19.

62. Bouadma L, Mankikian S, Darmon M, Argaud L, Vinclair C, Siami S, Garrouste-Orgeas M, Papazian L, Cohen Y, Marcotte G, Styfalova L, Reignier J, Lautrette A, Schwebel C, Timsit JF, Timsit JF, Azoulay E, Garrouste-Orgeas M, Zahar JR, Adrie C, Darmon M, Clec'h C, Alberti C, Francąis A, Vesin A, Ruckly S, Bailly S, Lecorre F, Nakache D, Vannieuwenhuyze A, et al. Influence of dyskalemia at admission and early dyskalemia correction on survival and cardiac events of critically ill patients. *Crit Care* 2019;

63. Harkness W, Watts P, Kopstein M, Dziadkowiec O, Hicks G, Scherbak D. Correcting Hypokalemia in Hospitalized Patients Does Not Decrease Risk of Cardiac Arrhythmias. *Adv Med* 2019;**2019**:1–4.

64. Cohn JN, Kowey PR, Whelton PK, Prisant LM. New guidelines for potassium replacement in clinical practice: a contemporary review by the National Council on Potassium in Clinical Practice. *Arch Intern Med* 2000;**160**:2429–2436.

65. Collins AJ, Pitt B, Reaven N, Funk S, McGaughey K, Wilson D, Bushinsky DA. Association of Serum Potassium with All-Cause Mortality in Patients with and without Heart Failure, Chronic Kidney Disease, and/or Diabetes. *Am J Nephrol* Switzerland; 2017;**46**:213–221.

66. Brueske B, Sidhu MS, Schulman-Marcus J, Kashani KB, Barsness GW, Jentzer JC. Hyperkalemia Is Associated With Increased Mortality Among Unselected Cardiac Intensive Care Unit Patients. *J Am Heart Assoc* England; 2019;**8**:e011814.

67. Singer AJ, Thode HCJ, Peacock WF. Rapid correction of hyperkalemia is associated with reduced mortality in ED patients. *Am J Emerg Med* United States; 2019;

68. McMahon GM, Mendu ML, Gibbons FK, Christopher KB. Association between hyperkalemia at critical care initiation and mortality. *Intensive Care Med* United States; 2012;**38**:1834–1842.

69. An JN, Lee JP, Jeon HJ, Kim DH, Oh YK, Kim YS, Lim CS. Severe hyperkalemia requiring hospitalization: predictors of mortality. *Crit Care* England; 2012;**16**:R225.

70. Liang W, Ma H, Cao L, Yan W, Yang J. Comparison of thiazide-like diuretics versus thiazide-type diuretics: a meta-analysis. J. Cell. Mol. Med. 2017.

71. Rimoldi SF, Messerli FH, Chavez P, Stefanini GG, Scherrer U. Efficacy and safety of calcium channel blocker/diuretics combination therapy in hypertensive patients: a meta-analysis. *J Clin Hypertens (Greenwich)* United States; 2015;**17**:193–199.

72. Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL. Thiazide diuretics, potassium, and the development of diabetes: A quantitative review. *Hypertension* 2006;**48**:219–224.

73. Rodenburg EM, Visser LE, Hoorn EJ, Ruiter R, Lous JJ, Hofman A, Uitterlinden AG, Stricker BH. Thiazides and the risk of hypokalemia in the general population. *J Hypertens* 2014;**32**:2092–2097.

74. Sica DA, Carter B, Cushman W, Hamm L. Thiazide and loop diuretics. *J Clin Hypertens (Greenwich)* United States; 2011;**13**:639–643.

75. Fakunding JL, Catt KJ. Dependence of aldosterone stimulation in adrenal glomerulosa cells on calcium uptake: Effects of lanthanum and verapamil. *Endocrinology* 1980;**107**:1345–1353.

76. Blanchouin-Emeric N, Zenatti M, Defaye G, Aupetit B. Verapamil directly inhibits aldosterone synthesis by adrenal mitochondria in vitro. *J Steroid Biochem* 1988;**30**:453–456.

77. Imamura T, Matsuura Y, Nagoshi T, Ishikawa T, Date H, Kita T, Matsuyama A, Matsuo T, Eto T. Hyperkalemia induced by the calcium channel blocker, benidipine. *Intern Med* Japan; 2003;**42**:503–506.

78. Salem C Ben, Badreddine A, Fathallah N, Slim R, Hmouda H. Drug-Induced Hyperkalemia. Drug Saf. 2014. p. 677–692.

79. Sugarman A, Kahn T. Calcium channel blockers enhance extrarenal potassium disposal in the rat. *Am J Physiol* 1986;**250**:F695-701.

80. Minella RA, Schulman DS. Fatal verapamil toxicity and hypokalemia. *Am Heart J* 1991;**121**:1810–1812.

81. Freed MI, Rastegar A, Bia MJ. Effects of calcium channel blockers on potassium homeostasis. *Yale J Biol Med* United States; 1991;**64**:177–186.

82. Popiliev I, Angelova I, Kundurdzhiev A. [Hypokalemia caused by nifedipine]. *Vutr Boles* Bulgaria; 1990;**29**:126–129.

83. Tishler M, Armon S. Nifedipine-induced hypokalemia. *Drug Intell Clin Pharm* United States; 1986;**20**:370–371.

84. Soliman AR, Akmal M, Massry SG. Parathyroid hormone interferes with extrarenal disposition of potassium in chronic renal failure. *Nephron* Switzerland; 1989;**52**:262–267.

85. Bettinelli A, Bianchetti MG, Girardin E, Caringella A, Cecconi M, Appiani AC, Pavanello L, Gastaldi R, Isimbaldi C, Lama G, Marchesoni C, Matteucci C, Patriarca P, Natale B Di, Setzu C, Vitucci P. Use of calcium excretion values to distinguish two forms of primary renal tubular hypokalemic alkalosis: Bartter and Gitelman syndromes. *J Pediatr* 1992;**120**:38–43.

86. Okusa MD, Velázquez H, Ellison DH, Wright FS. Luminal calcium regulates potassium transport by the renal distal tubule. *Am J Physiol* 1990;**258**:F423-8.

87. Sands JM, Naruse M, Baum M, Jo I, Hebert SC, Brown EM, Harris HW. Apical extracellular calcium/polyvalent cation-sensing receptor regulates vasopressin-elicited water permeability in rat kidney inner medullary collecting duct. *J Clin Invest* United States; 1997;**99**:1399–1405.

88. Hsia DC, Krushat WM, Fagan AB, Tebbutt JA, Kusserow RP. Accuracy of diagnostic coding for Medicare patients under the prospective-payment system. *N Engl J Med* United States;

1988;**318**:352–355.

89. Thygesen LC, Ersboll AK. When the entire population is the sample: strengths and limitations in register-based epidemiology. *Eur J Epidemiol* Netherlands; 2014;**29**:551–558.

90. Krogager ML, Torp-Pedersen C. Short-term mortality risk of different plasma potassium levels in patients treated with combination antihypertensive therapy. *Eur J Prev Cardiol* 2020;

91. Penhall RK, Frewin DB. Plasma potassium levels in hypertensive patients receiving fixed-combination diuretic therapy. *Med J Aust* Australia; 1980;**1**:376–378.

92. Lumme JAJ, Jounela AJ. Left ventricular mass, serum electrolyte levels and cardiac arrhythmias in patients with mild hypertension treated with cilazapril or hydrochlorothiazide. *Int J Cardiol* 1993;

93. Tsujimoto T, Kajio H. Thiazide Use and Decreased Risk of Heart Failure in Nondiabetic Patients Receiving Intensive Blood Pressure Treatment. *Hypertens (Dallas, Tex 1979)* 2020;**76**:432–441.

10. Appendices

Appendix 1. List of antihypertensive drugs and corresponding ATC codes used to define hypertension

ATC codes	Name of drug
C02A	Antiadrenergic agents, centrally acting
C02B	Antiadrenergic agents, ganglion blocking
C02C	Antiadrenergic agents, peripherally acting
C02DA	Thiazide-derivatives
C02DB	Hydrazynophthalazin-derivatives
C02DD	Nitroferricyanide-derivatives
C02DG	Guanidin-derivatives
C02L	Antihypertensives and diuretics in combination
C03AA	Thiazides
C03AB	Thiazides and potassium in combination
C03BA	Sulfonamides
C03BB	Sulfonamides and potassium in combination
C03C	Loop diuretics
C03DA	Aldosteron antagonists
C03DB	Other potassium sparing agents
C03EA	Low-ceiling diuretics and potassium sparing agents
C03EB	High-ceiling diuretics and potassium sparing agents
C03X	Other diuretics
C07A	Beta-blockers
C07B	Beta-blockers and thiazides
C07C	Beta-blockers and other diuretics
C07D	Beta-blockers, thiazides and other diuretics
C07FB	Beta-blockers and calcium antagonists
C07FX	Beta-blockers and other combinations

C08C	Selective calcium antagonists primarily with vascular effect
C08D	Selective calcium antagonists with direct cardiac effect
C08E	Non-selective calcium antagonists
C08G	Calcium antagonists and diuretics
C09AA	Angiotensin converting enzyme inhibitors
C09BA	Angiotensin converting enzyme inhibitors and diuretics
C09BB	Angiotensin converting enzyme inhibitors and calcium antagonists
C09CA	Angiotensin II antagonists
C09DA	Angiotensin II antagonists and diuretics
C09DB	Angiotensin II antagonists and calcium antagonists
C09XA	Renin-inhibitors

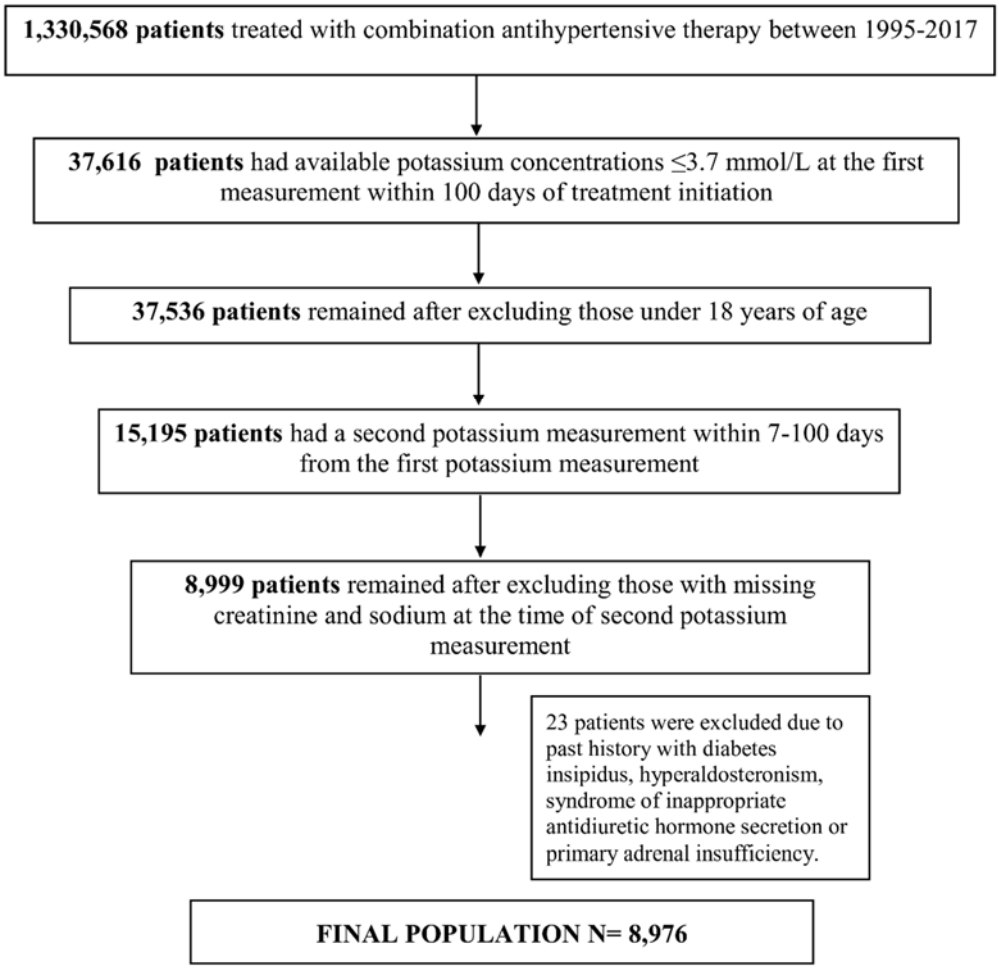
Appendix 2. Definitions of comorbidities, procedures and concomitant medications based on different ICD-10, Nordic Classification of Surgical Procedures (NCSP), and ATC codes identified prior to index date.

Comorbidities and procedures	ICD-10 codes	ICD-8 codes	Time prior to index date	NCSP codes	Time prior to index date	ATC codes	Time prior to index date
Ischemic heart disease including myocardial infarction[1]	I20-25	–	5 years	KFNG, KFNA-E	5 years	–	–
Hemodialysis	–	–	–	BJFD20	5 years	–	–
Atrial flutter or fibrillation	I48	–	5 years	–	–	–	–
Second- or third-degree atrioventricular block	I44.1-.3	–	5 years	–	–	–	–
Ventricular tachycardia or fibrillation	I47.2, I49	–	5 years	–	–	–	–
Chronic obstructive pulmonary disease	J40-44	491, 492	5 years	–	–	–	–
Chronic liver disease	B18, C22, K71-77	–	5 years	–	–	–	–
Syndrome of inappropriate antidiuretic hormone secretion	E22.2	–	5 years	–	–	–	–
Diabetes insipidus	E23.2, N25.1	–	5 years	–	–	–	–
Hypothyroidism	E00.1, E02-03, E89.0	–	5 years	–	–	–	–
Hyperthyroidism	DE050-59	–	5 years	–	–	–	–
Addison disease	E27.1	–	5 years	–	–	–	–
Primary hyperaldosteronism	E26.0	–	5 years	–	–	–	–
Diabetes	E10-14	–	5 years	–	–	–	–
Any malignancy	C00-99	–	5 years	–	–	–	–
Hypertension	DI11-15	–	5 years	–	–	–	–
Heart failure	I110, I130, I132, I42, I50, J81	–	5 years	–	–	–	–
Stroke	DI61, DI62, DI63, DI64, DG458-459, DG433-438	433-438	5 years	–	–	–	–

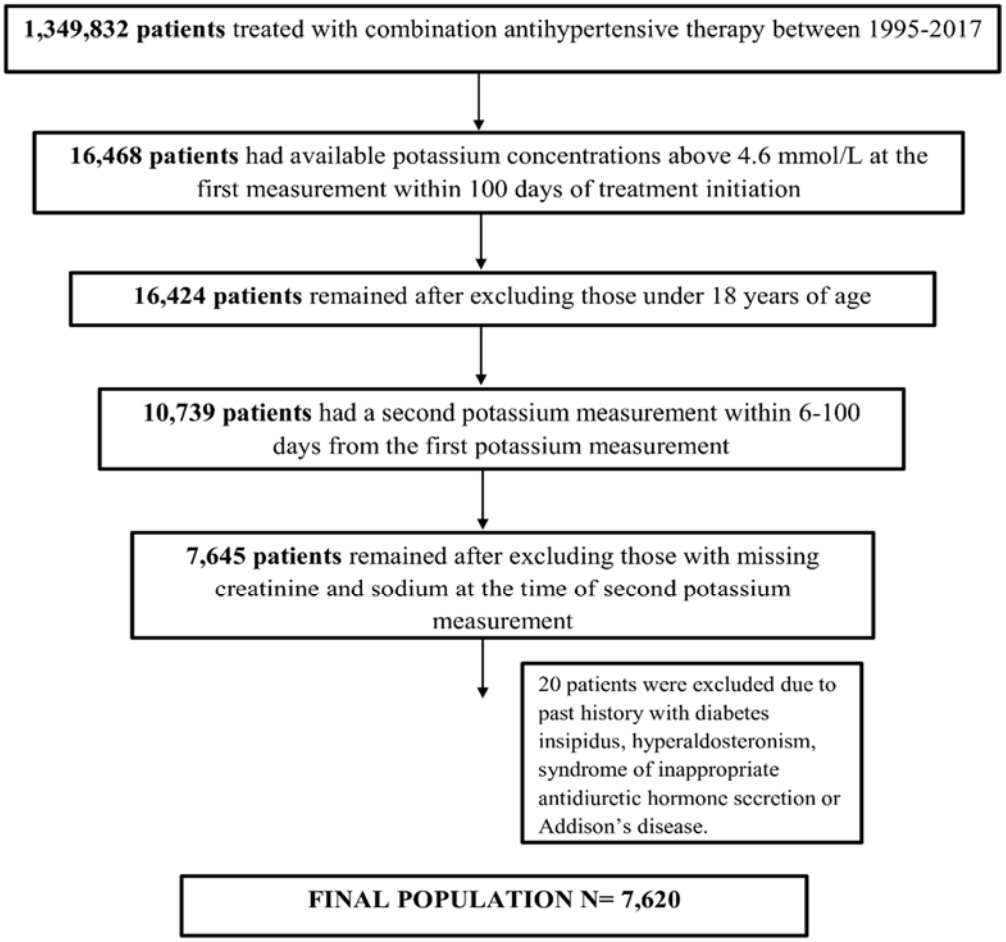
Acute kidney disease	DN17, DN19, DR34	–	–	–	–	–	–
Chronic kidney disease (incl. proteinuria)	DN02–08, DN11–12, DN14, DN18–19, DN26, DN158–160, DN162–164, DN168, DN313, DQ612–613, DQ615, DQ619, DE102, DE112, DI120, DM300, DM319, DM321B	–	–	–	–	–	–
Inflammatory bowel disease (IBD)	DK50-51	–	5 years	–	–	–	–
Concomitant medications	**ICD-10 codes**	–	**Time prior to index date**	**NCSP codes**	**Time prior to index date**	**ATC codes**	**Time prior to index date**
Potassium supplements	–	–	–	–	–	A12B C03AB C03BB C03CB	90 days
Loop diuretics	–	–	–	–	–	C03C	90 days
Non-steroidal anti-inflammatory drugs	–	–	–	–	–	M01A	180 days
Antimicrobials	–	–	–	–	–	J01CF06, J01CA01, J01CE, J01G, J02AA01, J05AD01, J01CF05	30 days
β2-agonists	–	–	–	–	–	R03AC02, C01CA2, C01CA24, R03AC13 C01CA02, R03AB02 R03CB01, R01BA02, R03AC03, R03AC12	90 days

Mineralo- and glucocorticoids	–	–	–	–	–	A01AC03, A07EA02, C05AA01, D07AA02, H02AB09, S01BA02, S02BA01, H02AA02, A07EA03, H02AB07	90 days
Laxatives	–	–	–	–	–	V03AE01, A06AB04, A06AG10	30 days
Xantines	–	–	–	–	–	R03DA04, N06BC01	30 days
Macrolides	–	–	–	–	–	J01FA	30 days
Trimethoprim	–	–	–	–	–	J01EA, J01EE	30 days

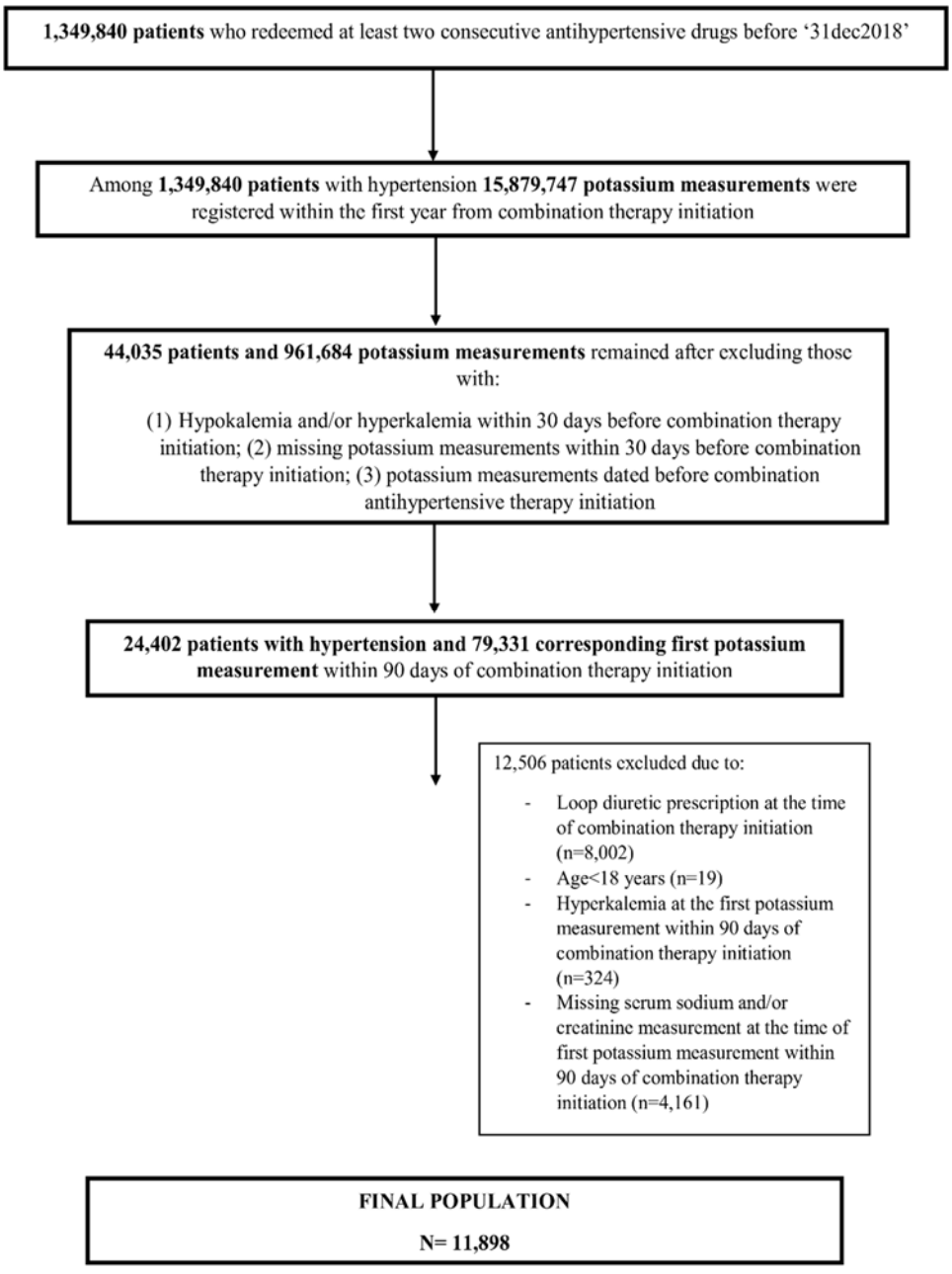
Appendix 3. Population flowchart study II



Appendix 4. Population flowchart Study III



Appendix 5. Population flowchart Study IV



Appendix 6. Time to potassium measurement and mortality within 90-days

Days from index date/hypertension date to potassium measurement	**01–10**	**11–20**	**21–30**	**31–40**	**41–50**	**51–60**	**61–70**	**71–80**	**81 –90**
No. of patients with serum potassium measurement	8480	6733	6194	5426	4233	3870	3571	3264	3028
Days from potassium measurement to death	**01–10**	**11–20**	**21–30**	**31–40**	**41–50**	**51–60**	**61–70**	**71–80**	**81 –90**
No. of patients deceased	252	119	107	104	78	60	52	58	36

Appendix 7. Sensitivity analyses. Potassium interval K: 3.8-4.0 mmol/L represented the reference range. Adjusted for age, gender, serum sodium, renal insufficiency, malignancy, heart failure, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, atrial flutter/fibrillation, stroke and ischemic heart disease, antihypertensive therapy, corticosteroids, antimicrobials, non-steroidal anti-inflammatory drugs, potassium supplement, xanthines, laxatives.

		Unadjusted		**Adjusted**		
1. Patients with normal kidney function (N= 8404)	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
P(K) 1.5-2.9 mmol/L	2.83	[1.91;4.20]	<0.001	2.33	[1.56;3.46]	< 0.001
P(K) 3.0-3.4 mmol/L	1.40	[1.06;1.86]	0.02	1.35	[1.02;1.79]	0.04
P(K) 3.5-3.7 mmol/L	1.21	[0.93;1.58]	0.16	1.18	[0.90;1.54]	0.23
P(K) 3.8-4.0 mmol/L	REF.					
P(K) 4.1-4.6 mmol/L	1.37	[1.07;1.75]	0.01	1.21	[0.95;1.55]	0.12
P(K) 4.7-5.0 mmol/L	2.68	[1.85;3.87]	<0.001	2.29	[1.58;3.32]	< 0.001
P(K) 5.1-7.1 mmol/L	5.68	[3.62;8.90]	<0.001	2.81	[1.76;4.47]	< 0.001
2. Patients without past history with malignancy (N= 7271)						
P(K) 1.5-2.9 mmol/L	3.10	[1.97;4.87]	<0.001	2.39	[1.51;3.77]	< 0.001
P(K) 3.0-3.4 mmol/L	1.27	[0.90;1.80]	0.17	1.21	[0.86;1.72]	0.28
P(K) 3.5-3.7 mmol/L	1.17	[0.85;1.62]	0.32	1.16	[0.84;1.60]	0.36
P(K) 3.8-4.0 mmol/L	REF.					
P(K) 4.1-4.6 mmol/L	1.23	[0.91;1.66]	0.17	1.05	[0.78;1.42]	0.74
P(K) 4.7-5.0 mmol/L	2.95	[1.94;4.47]	<0.001	2.34	[1.53;3.57]	< 0.001
P(K) 5.1-7.1 mmol/L	5.69	[3.51;9.22]	<0.001	3.59	[2.17;5.93]	< 0.001
3. Patients without past history with heart failure or loop diuretic prescription (N= 4882)						
P(K) 1.5-2.9 mmol/L	3.79	[2.06;7.00]	< 0.001	3.26	[1.73;6.14]	<0.001
P(K) 3.0-3.4 mmol/L	1.68	[1.05;2.66]	0.03	1.64	[1.02;2.63]	0.04
P(K) 3.5-3.7 mmol/L	1.17	[0.74;1.84]	0.50	1.07	[0.67;1.70]	0.77

P(K) 3.8-4.0 mmol/L	REF.					
P(K) 4.1-4.6 mmol/L	1.63	[1.07;2.47]	0.02	1.37	[0.90;2.09]	0.14
P(K) 4.7-5.0 mmol/L	2.98	[1.52;5.83]	0.001	2.12	[1.07;4.18]	0.03
P(K) 5.1-7.1 mmol/L	5.59	[2.00;15.67]	0.001	1.73	[0.58;5.13]	0.32
4. Patients without past history with ischemic heart disease (N= 6743)						
P(K) 1.5-2.9 mmol/L	2.70	[1.78;4.10]	<0.001	2.16	[1.41;3.29]	< 0.001
P(K) 3.0-3.4 mmol/L	1.32	[0.97;1.79]	0.07	1.33	[0.98;1.80]	0.07
P(K) 3.5-3.7 mmol/L	1.27	[0.96;1.68]	0.09	1.30	[0.98;1.72]	0.07
P(K) 3.8-4.0 mmol/L	REF.					
P(K) 4.1-4.6 mmol/L	1.37	[1.05;1.79]	0.02	1.23	[0.94;1.61]	0.13
P(K) 4.7-5.0 mmol/L	3.17	[2.15;4.67]	<0.001	2.43	[1.64;3.60]	< 0.001
P(K) 5.1-7.1 mmol/L	5.80	[3.62;9.31]	<0.001	2.66	[1.62;4.38]	< 0.001
5. Patients with P(K) 3.5-3.7 mmol/L at the first potassium measurement (N= 6111)						
P(K) 1.5-2.9 mmol/L	3.82	[2.24;6.53]	<0.001	2.16	[1.25;3.73]	0.006
P(K) 3.0-3.4 mmol/L	1.95	[1.40;2.72]	<0.001	1.70	[1.22;2.37]	0.001
P(K) 3.5-3.7 mmol/L	1.16	[0.84;1.59]	0.36	1.09	[0.79;1.49]	0.61
P(K) 3.8-4.0 mmol/L	REF.					
P(K) 4.1-4.6 mmol/L	1.26	[0.95;1.68]	0.11	1.06	[0.80;1.42]	0.68
P(K) 4.7-5.0 mmol/L	2.35	[1.52;3.64]	<0.001	1.84	[1.18;2.86]	0.007
P(K) 5.1-7.1 mmol/L	5.54	[3.40;9.03]	<0.001	2.81	[1.68;4.71]	< 0.001
6. Patients with P(K)<3.5 mmol/L at the first potassium measurement (N= 2865)						
P(K) 1.5-2.9 mmol/L	2.07	[1.23;3.48]	0.006	2.44	[1.43;4.14]	0.001
P(K) 3.0-3.4 mmol/L	0.73	[0.46;1.18]	0.20	0.89	[0.55;1.44]	0.65
P(K) 3.5-3.7 mmol/L	1.18	[0.78;1.80]	0.43	1.36	[0.89;2.09]	0.15
P(K) 3.8-4.0 mmol/L	REF.					
P(K) 4.1-4.6 mmol/L	1.44	[0.96;2.17]	0.08	1.55	[1.03;2.33]	0.04
P(K) 4.7-5.0 mmol/L	3.70	[2.16;6.32]	< 0.001	3.71	[2.15;6.39]	< 0.001
P(K) 5.1-7.1 mmol/L	3.08	[1.44;6.59]	0.004	1.88	[0.86;4.11]	0.12

7. Last potassium measurement available within 6-100 days from the first potassium measurement (N= 8976)*						
P(K) 1.5-2.9 mmol/L	1.74	[1.31;2.29]	<0.001	1.41	[1.06;1.86]	0.02
P(K) 3.0-3.4 mmol/L	0.79	[0.62;1.01]	0.06	0.74	[0.58;0.95]	0.02
P(K) 3.5-3.7 mmol/L	0.74	[0.58;0.95]	0.02	0.68	[0.53;0.87]	0.002
P(K) 3.8-4.0 mmol/L	REF.					
P(K) 4.1-4.6 mmol/L	0.88	[0.64;1.21]	0.44	0.88	[0.64;1.21]	0.43
P(K) 4.7-5.0 mmol/L	1.21	[0.64;2.69]	0.47	1.26	[0.63;2.50]	0.51
P(K) 5.1-7.1 mmol/L	2.36	[0.75;7.46]	0.14	2.11	[0.77;5.77]	0.15
8. Analyses perfomed on patients with time from first to second potassium measurement <=45 days (N= 8976)						
P(K) 1.5-2.9 mmol/L	2.52	[1.75;3.64]	<0.001	2.15	[1.49;3.12]	< 0.001
P(K) 3.0-3.4 mmol/L	1.20	[0.90;1.60]	0.20	1.22	[0.92;1.63]	0.17
P(K) 3.5-3.7 mmol/L	1.20	[0.93;1.56]	0.15	1.20	[0.93;1.55]	0.16
P(K) 3.8-4.0 mmol/L	REF.					
P(K) 4.1-4.6 mmol/L	1.16	[0.91;1.47]	0.24	1.10	[0.87;1.41]	0.43
P(K) 4.7-5.0 mmol/L	2.43	[1.73;3.42]	<0.001	2.22	[1.57;3.14]	< 0.001
P(K) 5.1-7.1 mmol/L	3.76	[2.47;5.71]	<0.001	2.51	[1.64;3.87]	< 0.001
9. Analyses perfomed on patients with time from first to second potassium measurement >45 days (N= 8976)						
P(K) 1.5-2.9 mmol/L	2.21	[0.28;17.67]	0.45	2.20	[0.26;18.87]	0.47
P(K) 3.0-3.4 mmol/L	3.30	[1.37;7.97]	0.01	3.03	[1.21;7.62]	0.02
P(K) 3.5-3.7 mmol/L	1.13	[0.41;3.12]	0.81	1.23	[0.44;3.44]	0.69
P(K) 3.8-4.0 mmol/L	REF.					
P(K) 4.1-4.6 mmol/L	2.88	[1.27;6.53]	0.01	2.22	[0.96;5.10]	0.06
P(K) 4.7-5.0 mmol/L	2.97	[0.63;13.99]	0.17	2.00	[0.40;9.86]	0.39
P(K) 5.1-7.1 mmol/L	11.43	[2.43;53.82]	0.002	2.46	[0.39;15.61]	0.34
10. Analyses performed on 3 predefined potassium intervals with 3.5-4.6 mmol/L as reference (8976)						
P(K) 1.5-3.4 mmol/L	1.38	[1.13;1.67]	0.001	1.36	[1.12;1.66]	0.002
P(K) 4.7-7.1 mmol/L	2.80	[2.19;3.57]	< 0.001	2.13	[1.66;2.74]	< 0.001

11. Analyses performed on patients with available magnesium measurements at the time of plasma potassium draw (N=839)**						
P(K) 1.5-2.9 mmol/L	2.53	[1.11;5.74]	0.03	2.46	[1.05;5.74]	0.04
P(K) 3.0-3.4 mmol/L	1.49	[0.79;2.78]	0.22	1.81	[0.95;3.46]	0.07
P(K) 3.5-3.7 mmol/L	1.20	[0.66;2.19]	0.54	1.05	[0.57;1.94]	0.87
P(K) 3.8-4.0 mmol/L	REF.					
P(K) 4.1-4.6 mmol/L	1.54	[0.88;2.71]	0.13	1.39	[0.78;2.48]	0.26
P(K) 4.7-5.0 mmol/L	2.92	[1.40;6.10]	0.004	2.52	[1.18;5.39]	0.02
P(K) 5.1-7.1 mmol/L	2.69	[1.08;6.69]	0.04	1.98	[0.75;5.22]	0.17

*At the last available potassium measurement within 6-100 days the number of patients in each of the seven predefine potassium intervals was:

P(K) 1.5-2.9 mmol/L	781
P(K) 3.0-3.4 mmol/L	2986
P(K) 3.5-3.7 mmol/L	2855
P(K) 3.8-4.0 mmol/L	1314
P(K) 4.1-4.6 mmol/L	936
P(K) 4.7-5.0 mmol/L	84
P(K) 5.1-7.1 mmol/L	20

**At the time of first potassium measurement, 116 patients had hypomagnesemia (<0.7 mmol/L). Among patients with potassium concentrations below 3.5 mmol/L, 47 had hypomagnesemia at the time of first potassium measurement.

At the time of second potassium measurement, 109 patients had hypomagesemia, of which 42 had hypokalemia or borderline hypokalemia.

Appendix 8. Demographics by survival status (Study III)

		Alive (n=6998)	Deceased (n=622)	Total (n=7620)	p-value
Second potassium measurement	median(range)	4.5(2.3, 7.8)	4.4(2.2, 7.6)	4.5(2.2, 7.8)	0.001
First potassium measurement	median(range)	4.8(4.7, 9.1)	4.9(4.7, 7.4)	4.8(4.7, 9.1)	< 0.0001
Age	median(range)	69.8(18.2, 102.3)	75.1(19.5, 101.8)	70.3(18.2, 102.3)	< 0.0001
Gender	Female	2,769 (39.6)	292 (46.9)	3,061 (40.2)	
	Male	4229 (60.4)	330 (53.1)	4,559 (59.8)	0.0004
Renal insufficiency (second measuremt)		973 (13.9)	142 (22.8)	1,115 (14.6)	< 0.0001
Serum sodium (second measurement)	median(range)	139(108, 166)	135(112, 169)	139(108, 169)	< 0.0001
Renal insufficiency (first measuremt)		924 (14.1)	123 (20.5)	1,047 (14.6)	< 0.0001
	missing			446	
Hospitalization at the time of first potassium measurement		1992 (28.6)	400 (64.3)	2,392 (31.5)	< 0.0001
Hospitalization at the time of second potassium measurement		5876 (84.0)	576 (92.6)	6,452 (84.7)	< 0.0001
Malignancy		1012 (14.5)	225 (36.2)	1,237 (16.2)	< 0.0001
Chronic obstructive pulmonary disease		938 (13.4)	144 (23.2)	1,082 (14.2)	< 0.0001
Atrial fibrillation/Atrial flutter		1569 (22.4)	165 (26.5)	1,734 (22.8)	0.02
Chronic kidney disease		881 (12.6)	72 (11.6)	953 (12.5)	0.50
Chronic liver disease		276 (3.9)	78 (12.5)	354 (4.6)	< 0.0001
Hypertension (ICD-10)		2243 (32.1)	167 (26.8)	2,410 (31.6)	0.01
Ischemic heart disease		2342 (33.5)	157 (25.2)	2,499 (32.8)	< 0.0001
Diabetes		1798 (25.7)	117 (18.8)	1,915 (25.1)	0.0002
Heart failure		2315 (33.1)	214 (34.4)	2,529 (33.2)	0.53
Stroke		653 (9.3)	88 (14.1)	741 (9.7)	0.0001

Appendix 9. Sensitivity analyses (Study III). Multivariable model adjusted for age, sex, plasma sodium, renal insufficiency, malignancy, heart failure, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, stroke, atrial flutter/fibrillation, ischemic heart disease, inflammatory bowel disease, antihypertensive therapy, corticosteroids, antimicrobials, non-steroidal anti-inflammatory drugs, xanthines, laxatives, digoxin and potassium supplement.

		Univariable analysis			**Multivariable analysis**	
1. Patients with normal kidney function (N= 6505)	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
2.2-2.9 mmol/L	6.55	[3.35;12.78]	< 0.001	5.36	[2.71;10.62]	< 0.001
3.0-3.4 mmol/L	4.17	[2.87;6.08]	< 0.001	2.90	[1.98;4.25]	< 0.001
3.5-3.7 mmol/L	2.63	[1.87;3.70]	< 0.001	1.81	[1.27;2.59]	0.001
3.8-4.0 mmol/L	1.52	[1.14;2.03]	0.005	1.39	[1.04;1.87]	0.03
4.1-4.6 mmol/L	REF.					
4.7-5.0 mmol/L	0.90	[0.69;1.17]	0.42	0.87	[0.66;1.13]	0.29
5.1-5.5 mmol/L	1.58	[1.15;2.17]	0.005	1.28	[0.93;1.76]	0.13
5.6-7.8 mmmol/L	3.43	[2.28;5.17]	< 0.001	2.73	[1.80;4.14]	< 0.001
2. Patients without past history of malignancy (N= 6383)						
2.2-2.9 mmol/L	7.15	[3.51;14.57]	< 0.001	4.21	[2.00;8.86]	< 0.001
3.0-3.4 mmol/L	4.15	[2.73;6.30]	< 0.001	2.91	[1.90;4.44]	< 0.001
3.5-3.7 mmol/L	2.47	[1.67;3.67]	< 0.001	1.89	[1.27;2.82]	0.002
3.8-4.0 mmol/L	1.57	[1.13;2.17]	0.007	1.33	[0.95;1.84]	0.09
4.1-4.6 mmol/L	REF.					
4.7-5.0 mmol/L	1.00	[0.75;1.32]	0.99	0.92	[0.69;1.23]	0.57
5.1-5.5 mmol/L	1.51	[1.07;2.13]	0.02	1.16	[0.81;1.64]	0.42
5.6-7.8 mmmol/L	3.01	[2.01;4.52]	< 0.001	2.35	[1.54;3.57]	< 0.001

3. Patients without past history of heart failure or loop diuretic prescriptions (N= 3149)						
2.2-2.9 mmol/L	11.31	[4.55;28.13]	< 0.001	7.79	[2.54;23.90]	< 0.001
3.0-3.4 mmol/L	3.80	[1.89;7.64]	< 0.001	2.79	[1.35;5.78]	0.006
3.5-3.7 mmol/L	1.75	[0.84;3.66]	0.13	1.54	[0.72;3.28]	0.27
3.8-4.0 mmol/L	1.33	[0.79;2.25]	0.28	1.28	[0.75;2.18]	0.37
4.1-4.6 mmol/L	REF.					
4.7-5.0 mmol/L	0.85	[0.54;1.36]	0.50	0.82	[0.51;1.31]	0.40
5.1-5.5 mmol/L	1.39	[0.82;2.39]	0.22	1.26	[0.73;2.19]	0.41
5.6-7.8 mmmol/L	2.58	[1.28;5.18]	0.008	1.88	[0.90;3.91]	0.09
4. Patients without past history of ischemic heart disease (N= 5121)						
2.2-2.9 mmol/L	8.30	[4.51;15.29]	< 0.001	6.35	[3.39;11.89]	< 0.001
3.0-3.4 mmol/L	3.64	[2.49;5.31]	< 0.001	2.66	[1.80;3.92]	< 0.001
3.5-3.7 mmol/L	2.87	[2.03;4.06]	< 0.001	2.53	[1.78;3.60]	< 0.001
3.8-4.0 mmol/L	1.41	[1.03;1.92]	0.03	1.30	[0.95;1.77]	0.10
4.1-4.6 mmol/L	REF.					
4.7-5.0 mmol/L	0.91	[0.70;1.19]	0.49	0.87	[0.66;1.14]	0.31
5.1-5.5 mmol/L	1.63	[1.21;2.20]	0.001	1.51	[1.11;2.04]	0.008
5.6-7.8 mmmol/L	2.35	[1.56;3.52]	< 0.001	2.34	[1.55;3.55]	< 0.001
5. Patients with an ICD-10 hypertension diagnosis (N= 2410)						
2.2-2.9 mmol/L	10.89	[4.68;25.32]	< 0.001	5.15	[2.09;12.69]	< 0.001
3.0-3.4 mmol/L	3.66	[2.00;6.71]	< 0.001	2.84	[1.52;5.29]	0.001
3.5-3.7 mmol/L	1.53	[0.75;3.09]	0.24	1.04	[0.49;2.18]	0.92
3.8-4.0 mmol/L	1.67	[1.02;2.75]	0.04	1.75	[1.05;2.89]	0.03
4.1-4.6 mmol/L	REF.					
4.7-5.0 mmol/L	1.08	[0.69;1.69]	0.75	1.07	[0.68;1.69]	0.77
5.1-5.5 mmol/L	2.22	[1.38;3.57]	< 0.001	2.31	[1.43;3.75]	< 0.001
5.6-7.8 mmmol/L	2.82	[1.39;5.71]	0.004	2.54	[1.22;5.29]	0.01

6. Cardiovascular death (all-cause mortality as competing risk, N= 7620)						
2.2-2.9 mmol/L	10.02	[5.07;19.80]	< 0.001	6.86	[3.40;13.85]	< 0.001
3.0-3.4 mmol/L	5.01	[3.24;7.75]	< 0.001	3.21	[2.05;5.04]	< 0.001
3.5-3.7 mmol/L	2.44	[1.54;3.86]	< 0.001	1.85	[1.15;2.96]	0.01
3.8-4.0 mmol/L	1.80	[1.25;2.58]	0.001	1.56	[1.09;2.25]	0.02
4.1-4.6 mmol/L	REF.					
4.7-5.0 mmol/L	0.99	[0.71;1.38]	0.95	0.97	[0.70;1.37]	0.88
5.1-5.5 mmol/L	2.11	[1.48;3.00]	< 0.001	1.80	[1.26;2.57]	0.001
5.6-7.8 mmmol/L	2.70	[1.63;4.45]	< 0.001	2.61	[1.56;4.35]	<0.001
7. Last potassium measurement available within 6-100 days from the first potassium measurement (N= 7620)						
2.2-2.9 mmol/L	10.54	[6.02;18.47]	<0.001	8.00	[4.53;14.13]	< 0.001
3.0-3.4 mmol/L	4.44	[3.17;6.23]	<0.001	3.29	[2.33;4.64]	< 0.001
3.5-3.7 mmol/L	3.17	[2.40;4.18]	<0.001	2.55	[1.92;3.38]	< 0.001
3.8-4.0 mmol/L	1.43	[1.09;1.87]	0.01	1.28	[0.97;1.68]	0.08
4.1-4.6 mmol/L	REF.					
4.7-5.0 mmol/L	1.18	[0.94;1.49]	0.16	1.16	[0.92;1.47]	0.21
5.1-5.5 mmol/L	1.93	[1.45;2.55]	<0.001	1.59	[1.19;2.13]	0.002
5.6-7.8 mmmol/L	7.04	[5.22;9.51]	<0.001	3.73	[2.70;5.15]	<0.001
8. Multivariable analyses adjusted for potassium concentrations obtained at the first measurement as well						
2.2-2.9 mmol/L				4.63	[2.66;8.06]	<0.001
3.0-3.4 mmol/L				2.39	[1.69;3.40]	<0.001
3.5-3.7 mmol/L				1.74	[1.26;2.39]	<0.001
3.8-4.0 mmol/L				1.38	[1.06;1.78]	0.01
4.1-4.6 mmol/L	REF.					
4.7-5.0 mmol/L				0.90	[0.72;1.14]	0.39
5.1-5.5 mmol/L				1.27	[0.97;1.66]	0.08
5.6-7.8 mmmol/L				2.17	[1.53;3.07]	<0.001

9. Multivariable analysis adjusted for time between first and second potassium measurement as well				
2.2-2.9 mmol/L		3.74	[2.15;6.51]	<0.001
3.0-3.4 mmol/L		1.95	[1.38;2.76]	<0.001
3.5-3.7 mmol/L		1.55	[1.13;2.14]	0.007
3.8-4.0 mmol/L		1.24	[0.96;1.61]	0.10
4.1-4.6 mmol/L	REF.			
4.7-5.0 mmol/L		0.92	[0.73;1.16]	0.50
5.1-5.5 mmol/L		1.32	[1.01;1.73]	0.04
5.6-7.8 mmmol/L		2.25	[1.60;3.18]	<0.001

Appendix 10. Demographics of patients treated with combination antihypertensive therapy who had available potassium measurements within 90-days from index date and no potassium imbalances up to 30 days before index date.

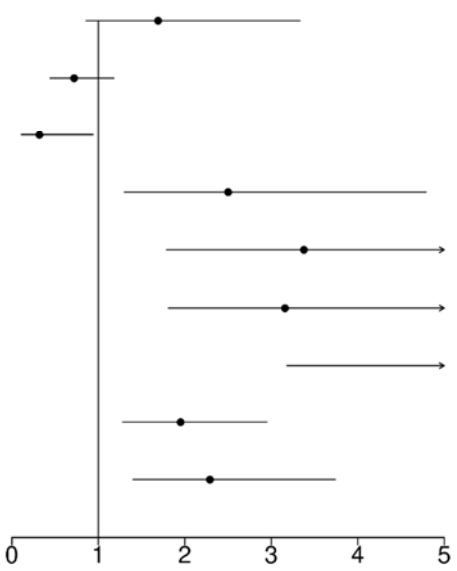
		3.5-5.0 mmol/L (n=11433)	K: 1.7-3.4 mmol/L (n=463)	Total (n=11896)	p-value
Age	median(range)	66.0(18.0, 101.0)	66.0(23.0, 95.0)	66.0(18.0, 101.0)	0.58
Gender	Male	6440 (56.3)	221 (47.7)	6661 (56.0)	0.0003
Days from hypertension to potassium measurement	median(range)	29.0(0.0, 90.0)	31.0(0.0, 90.0)	29.0(0.0, 90.0)	0.42
Serum sodium	median(range)	140.0(110.0, 161.0)	140.0(118.0, 148.0)	140.0(110.0, 161.0)	0.02
Renal insufficiency		228 (2.0)	5 (1.1)	233 (2.0)	0.22
Treatment combinations	BB+CCB	595 (5.2)	19 (4.1)	614 (5.2)	
	BB+RASi	2649 (23.2)	40 (8.6)	2689 (22.6)	
	BB+RASi+MRA	497 (4.3)	4 (0.9)	501 (4.2)	
	BB+RASi+Thiazides	497 (4.3)	23 (5.0)	520 (4.4)	
	BB+Thiazides	470 (4.1)	29 (6.3)	499 (4.2)	
	CCB+RASi	1504 (13.2)	40 (8.6)	1544 (13.0)	
	CCB+RASi+Thiazides	674 (5.9)	42 (9.1)	716 (6.0)	
	CCB+Thiazides	501 (4.4)	56 (12.1)	557 (4.7)	
	RASi+Thiazides	2763 (24.2)	142 (30.7)	2905 (24.4)	
	Other combinations	1283 (11.2)	68 (14.7)	1351 (11.4)	< 0.0001
Thiazides		5431 (47.5)	333 (71.9)	5764 (48.5)	< 0.0001
	Hydrochlorothiazide	2442 (21.4)	151 (32.6)	2593 (21.8)	< 0.0001
	Thiazide-like diuretics	87	≤3	≤90	-
Potassium supplement		3566 (31.2)	212 (45.8)	3778 (31.8)	< 0.0001
	ATC: 'C03'	3093 (27.1)	183 (39.5)	3276 (27.5)	<0.0001
	ATC: 'A12B'	631 (5.5)	45 (9.7)	676 (5.7)	0.0002
Heart failure		2157 (18.9)	30 (6.5)	2187 (18.4)	< 0.0001
IHD/MI		2948 (25.8)	68 (14.7)	3016 (25.4)	< 0.0001

Atrial flutter/fibrillation	1628 (14.2)	41 (8.9)	1669 (14.0)	0.001
Atrioventricular block	112	≤3	≤115	-
VT/VF	466 (4.1)	13 (2.8)	479 (4.0)	0.21
Stroke	1050 (9.2)	55 (11.9)	1105 (9.3)	0.06
COPD	736 (6.4)	30 (6.5)	766 (6.4)	1.0
Hemodialysis	26	≤3	≤29	-
Diabetes	1207 (10.6)	41 (8.9)	1248 (10.5)	0.27
Inflammatory bowel disease	150 (1.3)	11 (2.4)	161 (1.4)	0.08
Hypothyroidism	226 (2.0)	9 (1.9)	235 (2.0)	1.0
Malignancy	1562 (13.7)	73 (15.8)	1635 (13.7)	0.22
Antimicrobials	35	≤3	≤38	-
Beta 2 agonists	29	≤3	≤32	-
Corticoids	≤3	0	≤3	-
NSAIDs	183 (1.6)	5 (1.1)	188 (1.6)	0.49

BB- Beta blockers
CCB- Calcium channel blockers
RASi- Renin-angiotensin system inhibitors
IHD/MI- Ischemic heart disease/Myocardial infarction
VT/VF- Ventricular tachycardia/ventricular fibrillation
NSAIDs- Non-steroidal anti-inflammatory drugs
"Potassium supplement" addressed supplementation as a single pill therapy with an antihypertensive and as an individual pill.

Appendix 11. Forestplot of univariable conditional logistic regression analysis for development of hypokalemia. Population matched on age, gender, renal insufficiency and time from combination therapy initiation to serum potassium measurement. The combination of calcium channel blockers with thiazide diuretics was used as reference.

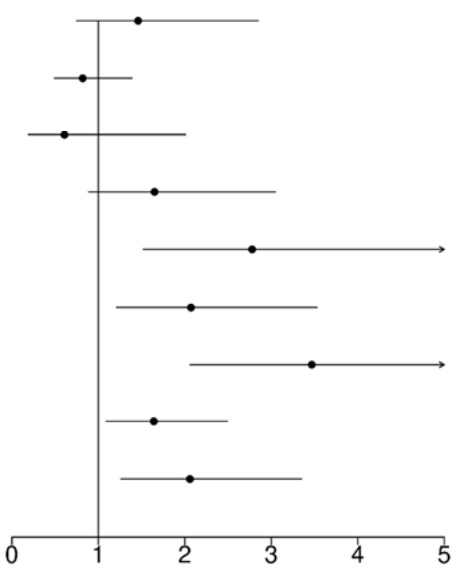
Combination therapies	Odds ratio	Lower CI	Upper CI
BB+CCB	1.69	0.86	3.33
BB+RASi	0.72	0.44	1.18
BB+RASi+MRA	0.32	0.11	0.94
BB+RASi+Thiazides	2.50	1.30	4.79
BB+Thiazides	3.38	1.79	6.37
CCB+RASi+Thiazides	3.16	1.81	5.54
CCB+Thiazides	5.62	3.18	9.95
RASi+Thiazides	1.95	1.28	2.95
Other combinations	2.29	1.40	3.74



BB- Beta blockers
CCB- Calcium channel blockers
RASi- Renin-angiotensin system inhibitors
"Potassium supplement" addressed supplementation as a single pill therapy with an antihypertensive and as an individual pill.

Appendix 12. Forestplot of univariable conditional logistic regression analysis for development of hypokalemia. Population matched on age, gender, time from combination therapy initiation to serum potassium measurement, renal insufficiency, history with heart failure and history with ischemic heart disease/myocardial infarction. The combination of calcium channel blockers with thiazide diuretics was used as reference.

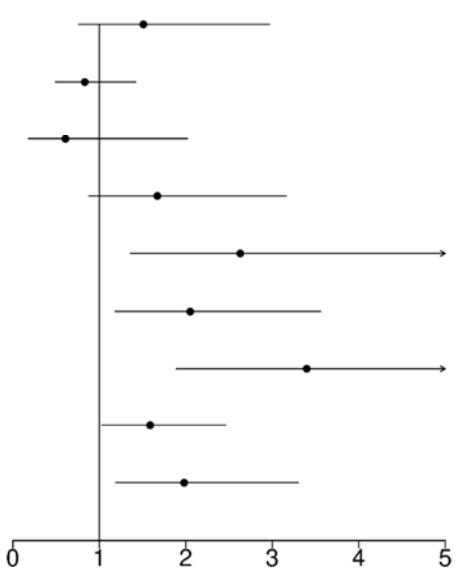
Combination therapies	Odds ratio	Lower CI	Upper CI
BB+CCB	1.46	0.75	2.85
BB+RASi	0.82	0.49	1.39
BB+RASi+MRA	0.61	0.19	2.01
BB+RASi+Thiazides	1.65	0.89	3.05
BB+Thiazides	2.78	1.52	5.08
CCB+RASi+Thiazides	2.07	1.21	3.53
CCB+Thiazides	3.47	2.06	5.83
RASi+Thiazides	1.64	1.09	2.49
Other combinations	2.06	1.26	3.35



BB- Beta blockers
CCB- Calcium channel blockers
RASi- Renin-angiotensin system inhibitors
"Potassium supplement" addressed supplementation as a single pill therapy with an antihypertensive and as an individual pill.

Appendix 13. Forestplot of multivariable conditional logistic regression analysis for development of hypokalemia. Population matched on age, renal insufficiency, gender, and time from combination therapy initiation to serum potassium measurement, history with heart failure and history with ischemic heart disease/myocardial infarction. The model was adjusted for serum sodium, renal insufficiency, malignancy, IBD, diabetes and chronic liver disease. The combination of calcium channel blockers with thiazide diuretics was used as reference.

Combination therapies	Odds ratio	Lower CI	Upper CI
BB+CCB	1.51	0.76	2.97
BB+RASi	0.83	0.49	1.42
BB+RASi+MRA	0.61	0.18	2.02
BB+RASi+Thiazides	1.67	0.88	3.16
BB+Thiazides	2.63	1.36	5.09
CCB+RASi+Thiazides	2.05	1.18	3.56
CCB+Thiazides	3.40	1.89	6.14
RASi+Thiazides	1.59	1.03	2.46
Other combinations	1.98	1.19	3.30



BB- Beta blockers
CCB- Calcium channel blockers
RASi- Renin-angiotensin system inhibitors
"Potassium supplement" addressed supplementation as a single pill therapy with an antihypertensive and as an individual pill.

Appendix 14. Demographics of patients treated with combination antihypertensive therapy who did not have available potassium measurements within 90 days from combination therapy initiation (N=1,336,750).

		Total
Age	median(range)	65.0(19.0, 110.0)
Sex	Female	693325 (51.9)
	Male	643425 (48.1)
Treatment combinations	BB	44067 (3.3)
	BB+CCB	67329 (5.0)
	BB+RASi	117647 (8.8)
	BB+Thiazides+Potassium supplement	97645 (7.3)
	CCB+RASi	131292 (9.8)
	CCB+Thiazides+Potassium supplement	103378 (7.7)
	Other combination	412901 (30.9)
	RASi+Thiazides	200313 (15.0)
	RASi+Thiazides+Potassium supplement	162178 (12.1)
Heart failure		100262 (7.5)
IHD/MI		187983 (14.1)
Atrial flutter/fibrillation		98578 (7.4)
Stroke		83037 (6.2)
COPD		62605 (4.7)
Chronic kidney disease		24353 (1.8)
Hemodialysis		1831 (0.1)
Chronic liver disease		12745 (1.0)
Diabetes		91554 (6.8)
Inflammatory bowel disease		7691 (0.6)
Hypothyroidism		11863 (0.9)
Malignancy		79230 (5.9)
ICD		2613 (0.2)

IHD/MI- ischemic heart disease/myocardial infarction
COPD- chronic obstructive pulmonary disease
ICD- implantable cardioverter defibrillator
BB- Beta blockers
CCB- Calcium channel blockers
RASi- Renin-angiotensin system inhibitors
“Potassium supplement” addressed supplementation as a single pill therapy with an antihypertensive and not as an individual pill

European Heart Journal (2017) **38**, 104–112
doi:10.1093/eurheartj/ehw129

Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data

Maria Lukács Krogager[1]*, Christian Torp-Pedersen[2,3], Rikke Nørmark Mortensen[3], Lars Køber[4], Gunnar Gislason[5,6], Peter Søgaard[7,8], and Kristian Aasbjerg[8]

[1]Faculty of Health Science, Aalborg University, Fredrik Bajers Vej 5, 9100 Aalborg, Denmark; [2]Department of Health Science and Technology, Aalborg University Hospital, Søndre Skovvej 15, 9000 Aalborg, Denmark; [3]Department of Clinical Epidemiology, Aalborg University Hospital, Søndre Skovvej 15, 9000 Aalborg, Denmark; [4]Department of Cardiology, The Heart Center, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark; [5]Department of Cardiology, Copenhagen University Hospital Gentofte, Kildegårdsvej 28, 2900 Hellerup, Denmark; [6]Denmark and National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark; [7]Heart Centre and Clinical Institute, Aalborg University Hospital, Aalborg, Denmark; and [8]Department of Cardiology, Aalborg University Hospital, Hobrovej 18-22, 9000 Aalborg, Denmark

Received 14 September 2015; revised 10 January 2016; accepted 7 March 2016; online publish-ahead-of-print 20 April 2016

See page 113 for the editorial comment on this article (doi:10.1093/eurheartj/ehw209)

Aims Diuretics and renin–angiotensin–aldosterone system inhibitors are central in the treatment of hypertension, but may cause serum potassium abnormalities. We examined mortality in relation to serum potassium in hypertensive patients.

Methods and results From Danish National Registries, we identified 44 799 hypertensive patients, aged 30 years or older, who had a serum potassium measurement within 90 days from diagnosis between 1995 and 2012. All-cause mortality was analysed according to seven predefined potassium levels: <3.5 (hypokalaemia), 3.5–3.7, 3.8–4.0, 4.1–4.4, 4.5–4.7, 4.8–5.0, and >5.0 mmol/L (hyperkalaemia). Outcome was 90-day mortality, estimated with multivariable Cox proportional hazard model, with the potassium interval of 4.1–4.4 mmol/L as reference. During 90-day follow-up, mortalities in the seven strata were 4.5, 2.7, 1.8, 1.5, 1.7, 2.7, and 3.6%, respectively. Adjusted risk for death was statistically significant for patients with hypokalaemia [hazard ratio (HR): 2.80, 95% confidence interval (95% CI): 2.17–3.62], and hyperkalaemia (HR: 1.70, 95% CI: 1.36–2.13). Notably, normal potassium levels were also associated with increased mortality: K: 3.5–3.7 mmol/L (HR: 1.70, 95% CI: 1.36–2.13), K: 3.8–4.0 mmol/L (HR: 1.21, 95% CI: 1.00–1.47), and K: 4.8–5.0 mmol/L (HR: 1.48, 95% CI: 1.15–1.92). Thus, mortality in relation to the seven potassium ranges was U-shaped, with the lowest mortality in the interval of 4.1–4.4 mmol/L.

Conclusion Potassium levels outside the interval of 4.1–4.7 mmol/L were associated with increased mortality risk in patients with hypertension.

Keywords Serum potassium • Hypertension • Mortality

Introduction

The overall prevalence of hypertension in Europe is about 30–45% of the total population[1] with a treatment range from 11 to 66%.[2] Many antihypertensive agents including diuretics, β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) can cause potassium disturbances[3,4] and influence survival.[5] Whereas the mechanisms that influence patient survival due to potassium disturbances are well known, little is known about the optimal range of serum potassium in disease and the levels associated with increased risk.[6,7] The normal potassium interval is defined based on apparently healthy individuals. The current guidelines provide normal lower potassium limit from 3.5 to 3.8 mmol/L, while the upper limit is between 5.0 and 5.5 mmol/L.[4,8,9]

Well-defined hyperkalaemia and hypokalaemia in patients with hypertension is known to increase the risk of death.[5] In patients with acute heart failure, potassium levels within the normal range are associated with increased risk of death, highlighting that the optimal level of potassium may differ from current definitions of the normal range.[10] Despite the widespread use of diuretics and other drugs that influence potassium levels in patients with hypertension, a search for optimal values of serum potassium has not

* Corresponding author. Tel: +45 53 14 88 24, Fax: +45 97 66 44 80, Email: lkcsmaria@yahoo.com; maria.krogager@rn.dk

been performed.[3,5,9] To address this issue, we used data from >40 000 individuals with hypertension to examine the relation between serum potassium and all-cause mortality.

Methods

Databases

All residents in Denmark have a personal, unique, and permanent civil registration number that enables individual linkage of administrative registries. The Danish National Patient Registry consists of information about all hospital admissions since 1978. At discharge, each hospitalization is registered with one primary and, if applicable, one or more secondary diagnoses according to the International Classification of Disease (ICD). Until 1994, the 8th revision (ICD-8) was in use and from 1994 onwards the 10th revision (ICD-10). The National Register for Medicinal Statistics includes all dispensed prescriptions from Danish pharmacies since 1995 based on the Anatomical Therapeutic Chemical System (ATC). As the healthcare system is state financed and partly reimburses drug costs, all Danish pharmacies are legally required to register all dispensed drug prescriptions, providing a valid and accurate register. Date of death, date of birth, and vital status were obtained from the Danish Register of Causes of Death and the Central Personal Registry. Blood test results were obtained from electronic registries of laboratory data, and we had access to data covering ~1.5 million individuals.

Study population

Hypertension was primarily defined by the use of at least two concomitant antihypertensive drugs in two concomitant quarters. Patients entered the study in the second quarter. This definition has previously been validated: positive predictive value 80% and specificity 94.7%.[1,11] We performed two sensitivity analyses where we selected the population based on ICD codes and where we excluded patients receiving loop diuretics. The first serum potassium measurement within 90 days of antihypertensive treatment was selected. To avoid extreme outliers, patients with potassium levels <2.9 mmol/L and >5.8 mmol/L were excluded. Patients under the age of 30 years were excluded because it is unlikely that this group would have essential hypertension. The patients were censored on 31 December 2012 or after 90-day follow-up. Patients with serum potassium measurements up to 90 days after dual single-pill antihypertensive drug treatment were included in the study. The outcome of the study was 90-day mortality from the date of serum potassium measurement.

Co-morbidities and drugs

The statistical analyses were performed on patients stratified in groups by the following potassium levels: <3.5, 3.5–3.7, 3.8–4.0, 4.1–4.4, 4.5–4.7, 4.8–5.0, and >5.0 mmol/L. Hypokalaemia was defined as potassium <3.5 mmol/L and hyperkalaemia as >5.0 mmol/L. Serum potassium interval of 4.1–4.4 mmol/L was used as reference for statistical analysis. The reference interval was chosen based on the restricted cubic splines results, and also other analysis, which confirmed that the lowest mortality risk was found in this range.

Besides age and gender, the following conditions present before the date of hypertension were assessed and used as covariates in the analysis: chronic obstructive pulmonary disease (ICD-8: 491, 492; ICD-10: J42–44), stroke (ICD-8: 433–438; ICD-10: I61, I62, I63, I64, DG458, DG459), acute myocardial infarction (ICD-10: I21), atrial fibrillation (ICD-10: I48), heart failure (ICD-10: I50), and diabetes.[12,13] Diabetes was defined as more than two dispensed prescriptions of glucose-lowering drugs (ATC code A10; insulin or oral hypoglycaemic agents), because patients with diabetes were not necessarily admitted to hospital with this specific diagnosis.[10,14–16] Serum creatinine was obtained within a week of serum potassium measurement. Patients with renal insufficiency and missing creatinine levels were excluded. Renal insufficiency was defined by a serum creatinine level: (i) >105 μmol/L for men <70 years, (ii) >125 μmol/L for men >70 years, (iii) >90 μmol/L for women <70 years, and (iv) >105 μmol/L for women >70 years.[17,18] A total of 1857 patients did not have a serum creatinine measurement. Serum sodium measured same day as serum potassium was also identified.

Patients who prior to the administration of two concomitant antihypertensives were diagnosed with acute (ICD-10: DN17, DN19, DR34) chronic kidney disease, including proteinuria (ICD-10: DN02–08, DN11–12, DN14, DN18–19, DN26, DN158–160, DN162–164, DN168, DN313, DQ612–613, DQ615, DQ619, DE102, DE112, DI120, DM300, DM319, DM321B) or primary hyperaldosteronism (ICD-10: DE260), were also excluded.

We included the five most prescribed antihypertensive single-pill drug combinations in the multivariable analysis: ACEIs/ARBs and thiazide diuretics; ACEIs/ARBs and β-blockers; ACEIs/ARBs and calcium channel blockers; ACEIs/ARBs, thiazide diuretics, and potassium supplements; and β-blockers, thiazide diuretics, and potassium supplements. The remaining possible combinations were categorized as other combinations of antihypertensive medication. The combination of ACEIs/ARBs with thiazide diuretics and potassium supplements was used as reference for statistical analysis. The following medications (ATC codes) were identified: renin–angiotensin system inhibitors C09; calcium channel blockers C08; β-blockers C07; diuretics C03; antiadrenergic drugs C02A, C02B, and C02C; and other antihypertensives C02DA, C02DB, C02DD, C02DG, and C02L. Apart from medication for hypertension, we have also included potassium supplements (ATC: A12B) in the multivariable statistical analysis.

Statistical analysis

Kaplan–Meier cumulative mortality curves were plotted for the seven preselected potassium intervals to illustrate trends in mortality. Cox proportional hazard regression models were used to determine the risk of death in hypertensive patients with different potassium intervals, adjusted for all covariates. To validate this statistical model, the three Cox proportional hazard model assumptions were assessed: proportionality, linearity, and interaction. As linearity assumption had not been fulfilled regarding the continuous variable age, we predefined four age intervals: 30–50 years, 51–70 years, 71–80 years, and >80 years. Age interval of 50–70 years was used as reference.

The association of potassium with mortality was also assessed using restricted cubic splines with knots at the 10th, 25th, 50th, 75th, and 90th percentiles of potassium.

Relative risks are presented as hazard ratios (HR) with 95% confidence intervals (95% CI). *P*-values of <0.05 were considered significant. Analyses were performed with SAS (version 9·4, SAS Institute, Cary, NC, USA) and R statistical software (version 3.0.1, R development core team).

Results

Demographics

In the period 1995–2012, we identified 44 799 hypertensive patients that had a potassium measurement within 90 days from diagnosis. The average age in the population was 67.1 (±12.6)

Table 1 **Demographics stratification according to potassium levels**

	K: 2.9–3.4 mmol/L	K: 3.5–3.7 mmol/L	K: 3.8–4.0 mmol/L	K: 4.1–4.4 mmol/L	K: 4.5–4.7 mmol/L	K: 4.8–5.0 mmol/L	K: 5.1–5.8 mmol/L	Total
Gender								
Female	1095 (64.4%)	2401 (60.1%)	5176 (55.0%)	8908 (49.1%)	3521 (45.3%)	1203 (43.7%)	484 (47.2%)	22 788 (50.9%)
Male	604 (35.6%)	1593 (39.9%)	4236 (45.0%)	9242 (50.9%)	4247 (54.7%)	1548 (56.3%)	541 (52.8%)	22 011 (49.1%)
Age, mean/SD	67 (±13.8)	66.7 (±13.2)	66.4 (±12.8)	66.9 (±12.4)	67.7 (±12.3)	68.9 (±12.2)	70.7 (±12.3)	67.1 (±12.6)
No. of antihypertensive drug prescription, mean/SD	2.2 (±0.5)	2.2 (±0.5)	2.2 (±0.5)	2.2 (±0.5)	2.2 (±0.5)	2.2 (±0.5)	2.3 (±0.5)	2.2 (±0.5)
Thiazide diuretics	1168 (68.7%)	2633 (65.9%)	5866 (62.3%)	9474 (52.2%)	3359 (43.2%)	1027 (37.3%)	389 (38.0%)	23 916 (53.4%)
Loop diuretics	422 (24.8%)	875 (21.9%)	1857 (19.7%)	3484 (19.2%)	1696 (21.8%)	738 (26.8%)	334 (32.6%)	9406 (21.0%)
Potassium-sparing diuretics	71 (4.2%)	130 (3.3%)	265 (2.8%)	738 (4.1%)	467 (6.0%)	249 (9.1%)	142 (13.9%)	2062 (4.6%)
Aldosteron antagonist	71 (4.2%)	127 (3.2%)	260 (2.8%)	736 (4.1%)	463 (6.0%)	248 (9.0%)	141 (13.8%)	2046 (4.6%)
ACEIs/ARBs	878 (51.7%)	2343 (58.7%)	6215 (66.0%)	12 986 (71.5%)	5994 (77.2%)	2121 (77.1%)	816 (79.6%)	31 353 (70.0%)
β-blockers (BB)	618 (36.4%)	1505 (37.7%)	3810 (40.5%)	8209 (45.2%)	3822 (49.2%)	1445 (52.5%)	505 (49.3%)	19 914 (44.5%)
Calcium channel blockers (CCB)	763 (44.9%)	1553 (38.9%)	3100 (32.9%)	5768 (31.8%)	2219 (28.6%)	729 (26.5%)	272 (26.5%)	14 404 (32.2%)
Antihypertensive drugs that contain potassium	893 (52.6%)	1907 (47.7%)	3998 (42.5%)	6322 (34.8%)	2242 (28.9%)	706 (25.7%)	260 (25.4%)	16 328 (36.4%)
Potassium supplement	792 (46.6%)	1901 (47.6%)	4518 (48.0%)	8687 (47.9%)	3766 (48.5%)	1354 (49.2%)	476 (46.4%)	21 494 (48%)
Antiadrenergic drugs	32 (1.9%)	45 (1.1%)	113 (1.2%)	220 (1.2%)	83 (1.1%)	33 (1.2%)	8 (0.8%)	534 (1.2%)
Antihypertensive drug combinations								
ACEIs/ARBs + BB	50 (2.9%)	188 (4.7%)	695 (7.4%)	2393 (13.2%)	1371 (17.6%)	532 (19.3%)	148 (14.4%)	5377 (12.0%)
ACEIs/ARBs + CCB	57 (3.4%)	167 (4.2%)	500 (5.3%)	1398 (7.7%)	679 (8.7%)	245 (8.9%)	84 (8.2%)	3130 (7.0%)
ACEIs/ARBs + thiazides	138 (8.1%)	437 (10.9%)	1259 (13.4%)	2179 (12.0%)	784 (10.1%)	213 (7.7%)	77 (7.5%)	5087 (11.4%)
ACEIs/ARBs + thiazides + potassium supplement	190 (11.2%)	558 (14.0%)	1442 (15.3%)	2492 (13.7%)	972 (12.5%)	303 (11.0%)	111 (10.8%)	6068 (13.5%)
BB + thiazides + potassium supplement	162 (9.5%)	397 (9.9%)	854 (9.1%)	1315 (7.2%)	430 (5.5%)	135 (4.9%)	38 (3.7%)	3331 (7.4%)
Other combinations	1102 (64.9%)	2247 (56.3%)	4662 (49.5%)	8373 (46.1%)	3532 (45.5%)	1323 (48.1%)	567 (55.3%)	21 806 (48.7%)
Atrial fibrillation	189 (11.1%)	525 (13.1%)	1193 (12.7%)	2505 (13.8%)	1187 (15.3%)	465 (16.9%)	183 (17.9%)	6247 (13.9%)
Acute myocardial infarction	103 (6.1%)	300 (7.5%)	838 (8.9%)	2165 (11.9%)	1089 (14.0%)	443 (16.1%)	133 (13.0%)	5071 (11.3%)
Heart failure	148 (8.7%)	350 (8.8%)	876 (9.3%)	1943 (10.7%)	1115 (14.4%)	464 (16.9%)	207 (20.2%)	5103 (11.4%)
Stroke	247 (14.5%)	515 (12.9%)	1130 (12.0%)	2124 (11.7%)	920 (11.8%)	363 (13.2%)	143 (14.0%)	5442 (12.1%)
Chronic obstructive pulmonary disease	181 (10.7%)	381 (9.5%)	788 (8.4%)	1492 (8.2%)	707 (9.1%)	316 (11.5%)	146 (14.2%)	4011 (9.0%)

Continued

Table 1 *Continued*

	K: 2.9–3.4 mmol/L	K: 3.5–3.7 mmol/L	K: 3.8–4.0 mmol/L	K: 4.1–4.4 mmol/L	K: 4.5–4.7 mmol/L	K: 4.8–5.0 mmol/L	K: 5.1–5.8 mmol/L	Total
Antidiabetic drugs	121 (7.1%)	330 (8.3%)	941 (10.0%)	2158 (11.9%)	1213 (15.6%)	509 (18.5%)	214 (20.9%)	5486 (12.2%)
Insulin	20 (1.2%)	35 (0.9%)	112 (1.2%)	208 (1.1%)	126 (1.6%)	65 (2.4%)	27 (2.6%)	593 (1.3%)
Serum natrium, mean/SD	138.8 (±5.2)	139.5 (±4.2)	139.8 (±3.8)	139.9 (±3.6)	139.6 (±3.9)	139.2 (±4.3)	138.2 (±4.9)	139.7 (±3.9)
Missing	47	142	412	759	318	109	29	1816
Serum creatinine, mean/SD	77 (±16)	79.1 (±15.8)	80.1 (±15.8)	82.2 (±15.6)	83.9 (±15.8)	85.8 (±16.2)	87.5 (±16.8)	81.9 (±15.9)
Day at potassium measurement, mean/SD	34.8 (±25.7)	36.2 (±25.8)	36.9 (±25.7)	37.1 (±25.6)	36.4 (±25.4)	33.7 (±24.5)	33.7 (±24.5)	36.6 (±25.6)
Status: 90 days								
Alive	1622 (95.5%)	3886 (97.3%)	9244 (98.2%)	17 881 (98.5%)	7635 (98.3%)	2677 (97.3%)	988 (96.4%)	43 933 (98.1%)
Deceased	77 (4.5%)	108 (2.7%)	168 (1.8%)	269 (1.5%)	133 (1.7%)	74 (2.7%)	37 (3.6%)	866 (1.9%)

Data are presented as mean ± SD (age) or number of patients and percentage (all others).
ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.
$n = 44\,799$.

years. The characteristics of the population, reported according to the seven potassium levels, are presented in *Table 1*. No significant difference in gender distribution was observed within the total population. Women were overall more susceptible to hypokalaemia, whereas men more often had hyperkalaemia. The overall potassium distribution was mean 4.20 mmol/L and median 4.2 mmol/L. The 25th and 75th percentiles for potassium were 3.92 and 4.5 mmol/L, respectively. Mean serum sodium was 139.7 (± 3.9). Of the patients, 5486 were prescribed antidiabetic drugs and ∼1% were treated with insulin. The other co-morbid conditions such as atrial fibrillation, heart failure, and acute myocardial infarction were present in a rate of ∼10% each.

The major antihypertensive drug combinations were ACEIs/ARBs combined with thiazides and potassium supplement 13.5%; ACEIs/ARBs with β-blockers 12%; ACEIs/ARBs with thiazide diuretics 11.4%; β-blockers combined with thiazides and potassium supplement 7.4%; and ACEIs/ARBs with calcium channel blockers 7%. In total, 21 494 patients were prescribed potassium supplements. Serum potassium level was measured 36.6 (± 25.6) days, on average, after administration of minimum two concomitant antihypertensive drugs. Supplementary material online, *S1* illustrates that in the first 45 days from dual antihypertensive therapy initiation, most potassium measurements are effectuated (65.1%) and most events (death) registered (72.9%). As there can be seen in Supplementary material online, *S2*, 74.8% of the total population was administered diuretics and 70% ACEIs/ARBs. There can also be observed that the administration of diuretics in the low normal potassium level was slightly higher than the administration of ACEIs/ARBs. Likewise, ACEIs/ARBs prescription was marginally higher than diuretic prescription in the upper potassium interval.

Survival analysis

Survival curves are illustrated in *Figure 1*. Of the patients, 866 (1.9%) died during the 90-day follow-up. Mortality in the seven strata was low: 4.5, 2.7, 1.8, 1.5, 1.7, 2.7, and 3.6%, respectively. The highest 90-day mortality rates were observed in 2005 and 2010 with 80 and 83 observations, respectively. Univariate HRs of each potassium level are shown in *Figure 2*. The lowest mortality risk was observed in the interval of 4.1–4.4 mmol/L, while hypo- and hyperkalaemia were associated with increased mortality. Risk of all-cause mortality was also increased in potassium intervals: 3.5–3.7 and 4.8–5.0 mmol/L. Likewise, we observed a trend towards excess mortality in the intervals of 3.8–4.0 and 4.5–4.7 mmol/L.

The results of the multivariable analysis with potassium 4.1–4.4 mmol/L as reference are shown in *Figure 3*. After adjusting the model for age, sex, biologically relevant co-morbidities, and concomitant medication, the mortality remained significantly increased for all potassium ranges outside the interval of 3.8–4.7 mmol/L.

Being a female or over the age of 70 years were overall associated with increased mortality. Patients with co-morbid conditions such as chronic obstructive pulmonary disease, atrial fibrillation, heart failure, and stroke also had an increased risk of death. Considering the different antihypertensive drug combinations, we observed a trend that ACEIs/ARBs in combination with thiazide diuretics were a safe treatment (HR: 0.65, 95% CI: 0.42–1.01, $P = 0.05$). However, the combination of β-blockers with thiazide diuretics and potassium supplements was associated with an increased

mortality risk (HR: 1.46, 95% CI: 1.03–2.08, $P = 0.03$). Moreover, other single-pill antihypertensive drug combinations than the top five included in the adjusted model were significantly associated with increased risk of death, with HR 1.85.

The U-shaped restricted cubic splines curve shown in *Figure 4* indicated that the lower and the higher the serum potassium level, the greater the mortality risk. Additionally, the splines curve indicated differences in risk within the normal potassium ranges, where potassium interval of 4.1–4.4 mmol/L was associated with the lowest risk of death.

Other analyses

Three additional sensitivity analyses were applied to verify the initial findings. The results of these analyses are illustrated in *Table 2*. First, we selected our hypertensive population based on ICD codes from the National Patient Registry, and we included in the analysis the patients who received minimum two concomitant antihypertensive drugs in the interval of 90 days before the diagnosis or 30 days after the diagnosis. Potassium interval of 3.8–4.0 mmol/L was no longer significantly associated with increased risk, although with a clear tendency towards our initial findings (HR: 1.14, 95% CI: 0.98–1.32, $P = 0.10$).

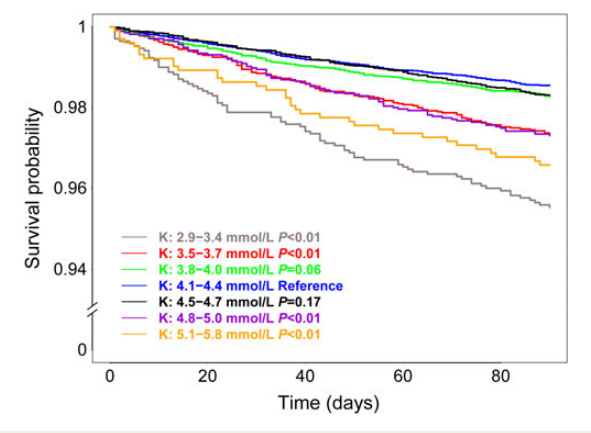


Figure 1 Kaplan–Meier analysis of the survival probability among the different potassium intervals. $n = 44\,799$.

Second, we excluded patients who were administered loop diuretics according to the Prescription Registry as loop diuretics could indicate heart failure. This analysis also showed that potassium level of 3.8–4.0 mmol/L was not significantly associated with the increased risk of death, although evidently with the same overall trends as in our initial findings (HR: 1.24, 95% CI: 0.94–1.64, $P = 0.12$).

Third, we excluded patients who, prior hypertension date, were diagnosed with myocardial infarction or heart failure as both could be treated with medication used for hypertension. This analysis showed that potassium levels outside the interval of 4.1–4.7 mmol/L were associated with increased mortality risk.

Discussion

This study analysed the short-time mortality risk in relation to different potassium intervals in hypertensive patients administered various classes of blood-pressure-lowering drugs. The major finding was that even mild deviations within the normal potassium range (3.5–5.0 mmol/L) were associated with increased mortality. Although it was expected that hypo- and hyperkalaemia would be associated with increased risk of death, it was unexpected that three normal potassium levels (K: 3.5–3.7, 3.8–4.0, and 4.8–5.0 mmol/L) were also associated with a significantly increased mortality in hypertensive patients.

We considered the time frame of potassium measurement within 90 days from start of antihypertensive treatment optimal for analysing the acute mortality risk in patients with hypertension for two reasons. First, Mcdowell and Ferner[19] showed in a review about monitoring of hypertensive patients for adverse drugs reactions that the peak follow-up time of potassium and creatinine was 3 months and 1 year after treatment initiation, respectively. Second, Podrid[7] illustrated in a review that potassium concentrations were directly related to the dosage of the administered diuretic. Low potassium can be observed from 4 to 40 weeks after treatment with diuretics in patients with hypertension. Moreover, Supplementary material online, *S1* reveal that the majority of the population had a potassium measurement in the first 45 days (65.1%) and that most of the patients deceased (72.9%) in the same timeframe. However, methodologically, it would not have been appropriate to reduce the follow-up time as a considerable number of patients did not have their potassium measured and we would have missed

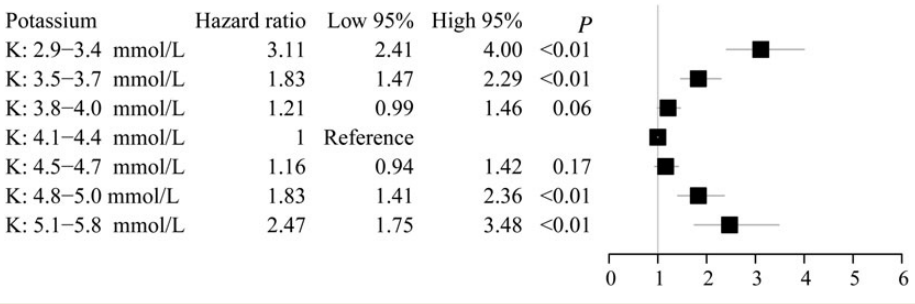


Figure 2 All-cause mortality in hypertensive patients stratified by potassium intervals (90-day follow-up). $n = 44\,799$. Reference interval represented by the interval K: 4.1–4.4 mmol/L.

Potassium:	Hazard ratio	Low 95%	High 95%	P
K: 2.9–3.4 mmol/L	2.80	2.17	3.62	<0.01
K: 3.5–3.7 mmol/L	1.70	1.36	2.13	<0.01
K: 3.8–4.0 mmol/L	1.21	1.00	1.47	0.05
K: 4.1–4.4 mmol/L	1	Reference		
K: 4.5–4.7 mmol/L	1.09	0.88	1.34	0.44
K: 4.8–5.0 mmol/L	1.48	1.15	1.92	<0.01
K: 5.1–5.8 mmol/L	1.70	1.20	2.41	<0.01
Age: 30–50 years	0.62	0.41	0.96	0.03
Age: 51–70 years	1	Reference		
Age: 71–80 years	1.89	1.57	2.28	<0.01
Age: >80 years	4.49	3.75	5.38	<0.01
Gender, Female	1.50	1.31	1.72	<0.01
Atrial fibrillation	1.34	1.14	1.57	<0.01
Acute myocardial infarction	1.12	0.91	1.36	0.28
COPD	2.02	1.71	2.38	<0.01
Stroke	1.44	1.21	1.70	<0.01
Heart failure	1.46	1.23	1.72	<0.01
Diabetes	1.05	0.85	1.31	0.64
Potassium supplements	0.92	0.81	1.06	0.25
ACEIs/ARBs & Beta blockers	0.84	0.58	1.22	0.36
Beta blockers & Thiazide diuretics & Potassium supplements	1.46	1.03	2.08	0.03
ACEIs/ARBs & Calcium channel blockers	1.03	0.68	1.57	0.87
Other single pill antihypertensive drug combinations	1.85	1.43	2.40	<0.01
ACEIs/ARBs & Thiazide diuretics	0.65	0.42	1.01	0.05
ACEIs/ARBs & Thiazide diuretics & Potassium supplements	1	Reference		

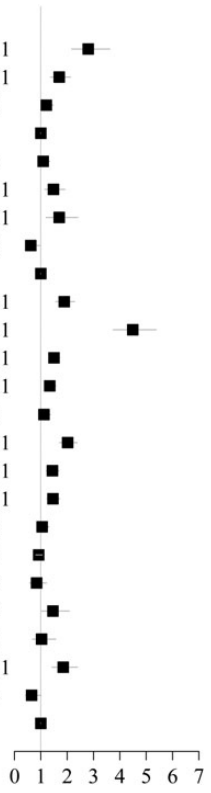


Figure 3 All-cause mortality in hypertensive patients stratified by potassium intervals (90-day follow-up). $n = 44\,799$. Model adjusted for covariates. Reference interval represented by the interval K: 4.1–4.4 mmol/L; and single-pill combination of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, thiazide diuretics, and potassium supplements. ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

27.1% of the events. Furthermore, a longer follow-up time would have been a great bias, as data showed a trend in less potassium measurement and less events over time. In as such, within a window period of 90 days from hypertension treatment, we intended to register both the immediate and the slow onset potassium disarrays. It is important to acknowledge that all patients have been treated with two antihypertensive drugs for two concomitant quarters (180 days) before the first potassium measurement.

As for the definition of hypertension, Olesen *et al.*[11] have validated the model of identifying hypertensive patients according to blood-pressure-lowering drug prescriptions. Nevertheless, we performed a sensitivity analysis where we attempted to identify major difference in identification of hypertensive population based on ICD codes vs. pharmacological treatment. We did not observe any major difference in the association of the defined potassium intervals and mortality risk. Moreover, the combination of ACEIs/ARBs with loop diuretics can indicate heart failure and not hypertension.[1] For this reason, we completed a second sensitivity analysis where patients with loop diuretic prescription were excluded. This analysis did not show any considerable difference in results when compared with the initial analysis. Additionally, we performed a third analysis where patients with history of myocardial infarction and heart failure were excluded. This was because combination of ACEIs with β-blockers could indicate one of the above mentioned conditions and not hypertension.[20,21] This analysis did not show major difference when compared with the other two sensitivity analysis, or main analysis. Overall, these analyses showed almost identical results to our primary analysis, with small variations in statistical significance probably related to fewer individuals in each potassium interval group. All these analyses indicated that serum potassium >4.0 and <4.7 mmol/L is optimal in hypertensive patients.

To our knowledge, few, if any, studies[3,9] have investigated which potassium interval is the safest in hypertensive patients; most studies have analysed the effect of different classes of antihypertensive drugs on potassium homeostasis, mortality, and cardiovascular and non-cardiovascular events. Alderman *et al.* demonstrated that patients are more prone to hypokalaemia if treated with chlorthalidone compared with amlodipine or lisinopril, and that hypokalaemic patients have a higher mortality risk than do those with normokalaemia.[12] Moreover, Ikram mentioned in his article 'a crossover study design in hypertensive patients with coronary disease' that mild degrees of hypokalaemia induced by thiazide diuretics increased the tendency to arrhythmia when compared with normokalaemia on a potassium-sparing diuretic.[22–24] These findings are in agreement with our study. We observed increased all-cause mortality in hypokalaemic patients, and that thiazides in combination with ACEIs/ARBs seemed to be particularly safe for hypertensive patients when compared with the reference (ACEIs/ARBs combined with

thiazide diuretics and potassium supplements). Alderman *et al.* also demonstrated that ACEIs increase the risk of elevated potassium and that this patient group had 'a significantly increased risk of combined cardiovascular disease compared with normokalaemics'. Similarly, our study demonstrated that hyperkalaemic patients are associated with increased mortality risk compared with normokalaemic patients, and that patients in this group are characterized by a higher administration rate of ACEIs/ARBs than are hypokalaemic and normokalaemic patients. Nevertheless, several studies and guidelines recommend dual therapy of ACEIs/ARBs with calcium channel blockers, diuretics, or β-blockers.[1,25,26] This statement is strongly supported by our study that showed that single-pill combination of ACEIs/ARBs with β-blockers and thiazide diuretics was associated with decreased mortality risk, in spite of insignificant *P*-values.

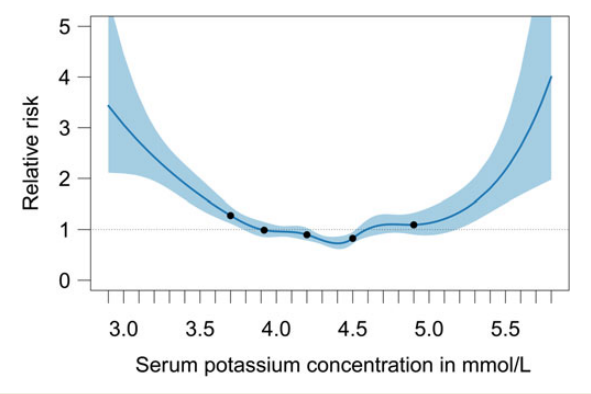


Figure 4 Restricted cubic splines showing the adjusted hazard ratios for all-cause mortality as a function of potassium concentration. Knots at the 10th, 25th, 50th, 75th, and 90th percentiles of potassium. Model adjusted for age, sex, chronic obstructive pulmonary disease, stroke, acute myocardial infarction, atrial fibrillation, heart failure, diabetes mellitus, potassium supplement, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers in combination with thiazides, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers in combination with calcium channel blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers in combination with β-blockers, β-blockers in combination with thiazides and potassium supplements, and other single-pill antihypertensive drug combinations. $n = 44\,799$. This figure shows an approximation of the function relating serum potassium to the hazard rate of death, and should not be interpreted with respect to some reference.

The study by Macdonald and Struthers was the only study/review we identified that contained exact recommendations for a potassium interval in patients with hypertension.[9] The authors indicated that it is favourable for hypertensive patients to maintain potassium between 3.5 and 5.0 mmol/L. This was based on studies that evaluate the link between hypokalaemia and development of ventricular arrhythmias and sudden cardiac death. However, most of the cited studies did not directly examine the relationship between serum potassium and mortality in hypertensive patients.

Overall, we were unable to identify any studies that provide direct evidence to select optimum levels of serum potassium in disease or health. Here, we demonstrate a significantly increased risk of death among hypertensive patients with serum potassium <4.1 or >4.7 mmol/L.

Study limitations

The limitations largely relate to the observational nature of the study. However, the Danish National Health registries contain uniquely detailed information, and we were able to extract reliable data on co-morbid illnesses and concomitant medication, as well as potassium measurements and date of death, overall strengthening the reliability of our findings. All factors that were considered possible confounders were included in the Cox multivariable analysis.

Limitations of this study are represented by the lack of information regarding the cause of death. In certain circumstances, it might

Table 2 Sensitivity analysis 1 (hypertensive patients found according to International Classification of Disease codes) and sensitivity analysis 2 (patients with loop diuretic prescription excluded from main analysis) and sensitivity analysis 3 (Patients with acute myocardial infarction or heart failure diagnosis before hypertension diagnosis were excluded from the main analysis)

Potassium (mmol/L)	Hypertension definition based on ICD codes (n = 26 126)				Patients with loop diuretic prescription were excluded (n = 35 393)				Patients with an acute myocardial infarction or heart failure diagnosis before hypertension were excluded (n = 35 827)			
	HR	Low 95%	High 95%	*P*	HR	Low 95%	High 95%	*P*	HR	Low 95%	High 95%	*P*
2.9–3.4	1.91	1.63	2.24	<0.01	3.49	2.43	5.00	<0.01	2.99	2.21	4.06	<0.01
3.5–3.7	1.49	1.28	1.74	<0.01	2.03	1.48	2.79	<0.01	1.89	1.44	2.48	<0.01
3.8–4.0	1.14	0.98	1.32	0.10	1.24	0.94	1.64	0.12	1.31	1.04	1.66	0.02
4.1–4.4	1		Reference		1		Reference		1		Reference	
4.5–4.7	1.18	0.98	1.43	0.07	0.95	0.69	1.30	0.74	1.18	0.91	1.53	0.22
4.8–5.0	1.38	1.07	1.78	0.01	1.50	1.01	2.22	0.04	1.85	1.34	2.55	<0.01
5.1–5.8	2.20	1.66	2.91	<0.01	1.89	1.11	3.24	0.02	2.13	1.37	3.29	<0.01

Model adjusted for covariates. Reference interval represented by the interval K: 4.1–4.4 mmol/L.
All-cause mortality in hypertensive patients stratified by potassium intervals (90-day follow-up).
ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

be difficult to determine the primary cause of death when a patient can be attributed one or more codes in situations where autopsy is missing.

As the Danish National Health registries do not contain reliable diagnostic codes for differentiating whether hypertension was diagnosed in hospital vs. general practitioner, we used an alternative modality based on a validated algorithm for identifying patients with hypertension. Despite the high predictive value and specificity of this method, misclassification of some patients as hypertensive could occur. With regard to the definition of diabetes, we could encounter similar problems as with hypertension. Patients with diabetes who were treated by their general practitioner and never hospitalized do not have diabetes diagnostic codes available. Therefore, we considered that more than two prescriptions of glucose-lowering drugs may increase the predictive value in our cohort. However, misclassification cannot be excluded.

Furthermore, our population may not extend to other populations, which can lead to difficulty in reproducing these results worldwide. Despite the fact that we performed three sensitivity analyses to adjust for major confounders, we cannot exclude a possible effect of unmeasured confounders. Additionally, the characteristics of the patients with hypertension, who had a serum potassium measurement within 90 days from dual single-pill therapy, may be different from the hypertensive patients who did not have a potassium measurement in this time interval. Moreover, it is discussable whether the use of the first serum potassium measurement within the 90 days of antihypertensive treatment was optimal for the analysis of 90-day mortality. However, we observed decrease in both potassium measurements and death rate in time. Last but not least, we cannot affirm whether mortality is increased due to the influence of potassium influence on myocardial membrane potential or it is a marker of other processes.

Conclusion

In conclusion, our results strongly indicate that serum potassium levels <4.1 or >4.7 mmol/L are associated with a significantly increased mortality in hypertensive individuals.

Clinical implications

This study indicates that low- and high-normal potassium levels may be associated with increased risk of death, which suggests that a narrower normal interval might improve outcome in patients with hypertension. Most drugs against hypertension influence in some way potassium homeostasis. Therefore, monitoring soon after the onset of medication would probably be relevant to achieve stable potassium levels and improve survival. Future studies that focus on frequency of potassium measurement, potassium fluctuations over time, and effect of potassium regulation on mortality can surely complement this study's findings.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

R.N.M., K.A., and M.L.K. performed statistical analysis. P.S. and C.T.-P. handled funding and supervision. C.T.-P., K.A., M.L.K., and R.N.M. acquired the data. C.T.-P., K.A., P.S., M.L.K., L.K., and G.G. conceived and designed the research. M.L.K., K.A., and P.S. drafted the manuscript. C.T.-P., P.S., L.K., G.G., K.A., and R.N.M. made critical revision of the manuscript for key intellectual content.

Funding

Research grant from Aalborg University Hospital, Aalborg, Denmark..

Conflict of interest: none declared.

References

1. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. 2013 ESH/ESC practice guidelines for the management of arterial hypertension. *Blood Press* 2014;**23**:3–16.
2. Pereira M, Lunet N, Azevedo A, Barros H. Differences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. *J Hypertens* 2009;**27**:963–975.
3. Liamis G, Milionis H, Elisaf M. Blood pressure drug therapy and electrolyte disturbances. *Int J Clin Pract* 2008;**62**:1572–1580.
4. Sica DA. Antihypertensive therapy and its effects on potassium homeostasis. *J Clin Hypertens (Greenwich)* 2006;**8**:67–73.
5. Kotchen TA. Antihypertensive therapy-associated hypokalemia and hyperkalemia: clinical implications. *Hypertension* 2012;**59**:906–907.
6. Montoye CK, Eagle KA, Michigan ACC-GAP Investigators, ACC-GAP Steering Committee, American College of Cardiology. An organizational framework for the AMI ACC-GAP Project. *J Am Coll Cardiol* 2005;**46**:1–29.
7. Podrid PJ. Potassium and ventricular arrhytmias. *Am J Cardiol* 1990;**65**:12–33E.
8. Kjeldsen K. Hypokalemia and sudden cardiac death. *Exp Clin Cardiol* 2010;**15**:e96–e99.
9. Macdonald JE, Struthers AD. What is the optimal serum potassium level in cardiovascular patients? *J Am Coll Cardiol* 2004;**43**:155–161.
10. Krogager ML, Eggers-Kaas L, Aasbjerg K, Mortensen RN, Køber L, Gislason G, Torp-Pedersen C, Søgaard P. Short-term mortality risk of serum potassium levels in acute heart failure following myocardial infarction. *Eur Heart J Cardiovasc Pharmacother* 2015;**1**:245–251.
11. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2011;**342**:d124.
12. Alderman MH, Piller LB, Ford CE, Probstfield JL, Oparil S, Cushman WC, Einhorn PT, Franklin SS, Papademetriou V, Ong ST, Eckfeldt JH, Furberg CD, Calhoun DA, Davis BR, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Clinical significance of incident hypokalemia and hyperkalemia in treated hypertensive patients in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension* 2012;**59**:926–933.
13. Sakkijha H, Idrees MM. Saudi guidelines on the diagnosis and treatment of pulmonary hypertension: pulmonary hypertension due to lung diseases and/or hypoxia. *Ann Thorac Med* 2014;**9**:S56–S61.
14. Andersson C, Lyngbaek S, Nguyen CD, Nielsen M, Gislason GH, Kober L, Torp-Pedersen C. Association of clopidogrel treatment with risk of mortality and cardiovascular events following myocardial infarction in patients with and without diabetes. *JAMA* 2012;**308**:882–889.
15. Gjesing A, Gislason GH, Kober L, Gustav Smith J, Christensen SB, Gustafsson F, Olsen AM, Torp-Pedersen C, Andersson C. Nationwide trends in development of heart failure and mortality after first-time myocardial infarction 1997–2010: a Danish cohort study. *Eur J Intern Med* 2014;**25**:731–738.
16. Schramm TK, Gislason GH, Kober L, Rasmussen S, Rasmussen JN, Abildstrom SZ, Hansen ML, Folke F, Buch P, Madsen M, Vaag A, Torp-Pedersen C. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. *Circulation* 2008;**117**:1945–1954.
17. Carlsson L, Lind L, Larsson A. Reference values for 27 clinical chemistry tests in 70-year-old males and females. *Gerontology* 2010;**56**:259–265.

18. Rustad P, Felding P, Franzson L, Kairisto V, Lahti A, Martensson A, Hyltoft Petersen P, Simonsson P, Steensland H, Uldall A. The Nordic Reference Interval Project 2000: recommended reference intervals for 25 common biochemical properties. *Scand J Clin Lab Invest* 2004;**64**:271–284.
19. McDowell SE, Ferner RE. Biochemical monitoring of patients treated with antihypertensive therapy for adverse drug reactions: a systematic review. *Drug Saf* 2011; **34**:1049–1059.
20. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, American College of Cardiology, American Heart Association, Canadian Cardiovascular Society. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol* 2004;**44**: 671–719.
21. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;**62**:e147–e239.
22. Ikram H. Arrhythmias, electrolytes, and ACE inhibitor therapy in the elderly. *Gerontology* 1987;**33**(Suppl. 1):42–47.
23. Morgan TO, Adams WR, Hodgson M, Gibberd RW. Failure of therapy to improve prognosis in elderly males with hypertension. *Med J Aust* 1980;**2**:27–31.
24. Multiple Risk Factor Intervention Trial Research Group. Baseline rest electrocardiographic abnormalities, antihypertensive treatment, and mortality in the Multiple Risk Factor Intervention Trial. *Am J Cardiol* 1985;**55**:1–15.
25. Yutaka M, Mifune M, Kubota E, Itoh H, Saito I. Comparison of effects of low dose of spironolactone and a thiazide diuretic in patients with hypertension treated with an angiotensin-converting enzyme inhibitor or an angiotensin type 1 receptor blocker. *Clin Exp Hypertens* 2009;**31**:648–656.
26. Chrysant SG. Single-pill triple-combination therapy: an alternative to multiple-drug treatment of hypertension. *Postgrad Med* 2011;**123**:21–31.

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Impact of plasma potassium normalization on short-term mortality in patients with hypertension and hypokalemia or low normal potassium

Maria Lukács Krogager[1*], Peter Søgaard[1], Christian Torp-Pedersen[2], Henrik Bøggild[3,4], Christina Ji-Young Lee[2,5], Anders Bonde[5], Jesper Q. Thomassen[6], Gunnar Gislason[7,8,9], Manan Pareek[2,10,11] and Kristian Kragholm[1,4,12]

Abstract

Background: Hypokalemia is common in patients treated with antihypertensive drugs, but the impact of correcting hypokalemia is insufficiently studied. We examined the consequences of hypokalemia and borderline hypokalemia correction in patients with hypertension.

Methods: We identified 8976 patients with hypertension and plasma potassium concentrations ≤3.7 mmol/L within 100 days from combination antihypertensive therapy initiation. The first measurement between 6 and 100 days after the episode with potassium ≤3.7 mmol/L was retained. We investigated all-cause and cardiovascular mortality within 60-days from the second potassium measurement using Cox regression. Mortality was examined for seven predefined potassium intervals derived from the second measurement: 1.5–2.9 mmol/L ($n = 271$), 3.0–3.4 mmol/L ($n = 1341$), 3.5–3.7 ($n = 1982$) mmol/L, 3.8–4.0 mmol/L ($n = 2398$, reference), 4.1–4.6 mmol/L ($n = 2498$), 4.7–5.0 mmol/L ($n = 352$) and 5.1–7.1 mmol/L ($n = 134$).

Results: Multivariable analysis showed that potassium concentrations 1.5–2.9 mmol/L, 3.0–3.4 mmol/L, 4.7–5.0 mmol/L and 5.1–7.1 mmol/L were associated with increased all-cause mortality (HR 2.39, 95% CI 1.66–3.43; HR 1.36, 95% CI 1.04–1.78; HR 2.36, 95% CI 1.68–3.30 and HR 2.62, 95% CI 1.73–3.98, respectively). Potassium levels <3.0 and > 4.6 mmol/L were associated with increased cardiovascular mortality. The adjusted standardized 60-day mortality risks in the seven strata were: 11.7% (95% CI 8.3–15.0%), 7.1% (95% CI 5.8–8.5%), 6.4% (95% CI 5.3–7.5%), 5.4% (4.5–6.3%), 6.3% (5.4–7.2%), 11.6% (95% CI 8.7–14.6%) and 12.6% (95% CI 8.2–16.9%), respectively.

Conclusions: Persistent hypokalemia was frequent and associated with increased all-cause and cardiovascular mortality. Increase in potassium to levels > 4.6 mmol/L in patients with initial hypokalemia or low normal potassium was associated with increased all-cause and cardiovascular mortality.

Keywords: Hypokalemia, Borderline hypokalemia, Hypokalemia correction, Mortality, Low potassium.

* Correspondence: lkcsmaria@yahoo.com; maria.krogager@rn.dk
[1]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark
Full list of author information is available at the end of the article

Novelty and Significance

What is new?

- Correcting plasma potassium concentrations ≤3.7 mmol/L to levels between 3.5–4.6 mmol/L was associated with improved short-term prognosis

What is relevant?

- Increased mortality risk was observed in patients who initially had borderline hypokalemia, partly because they developed hypokalemia. This emphasizes that potassium supplementation might be relevant in patients with low normal potassium concentrations
- Correcting hypokalemia and borderline hypokalemia shortly was associated with good prognosis
- Low potassium concentrations have previously been associated with arrhythmogenesis and increased mortality risk in patients with hypertension.

Summary

In this register based study we investigated the impact of correcting hypokalemia and borderline hypokalemia on 60-day mortality among 8976 patients treated with combination antihypertensive therapy. We observed that: (1) persistent hypokalemia was common and associated with increased all-cause and cardiovascular mortality; (2) Increase in potassium to levels > 4.6 mmol/L in patients with initial hypokalemia or low normal potassium was associated with increased all-cause and cardiovascular mortality; (3) Among patients with borderline hypokalemia initially, development of hypokalemia or hyperkalemia was associated with increased mortality risk; (4) Correcting hypokalemia associated with increased survival.

Background

Several common clinical conditions and drugs are known to cause or precipitate hypokalemia [1]. Among patients with hypertension, thiazides are the antihypertensive drugs most frequently associated with hypokalemia [2–4].

We recently demonstrated a U-shaped relationship between potassium levels and mortality among patients with hypertension. We observed an increased mortality risk even in patients with low and high normal serum potassium concentrations, suggesting a narrower than previously thought normal interval for potassium of 4.1–4.7 mmol/L. [5] However, at present there is no evidence regarding the consequences of potassium normalization in patients with hypertension and hypokalemia. Therefore, it is essential to examine how correction and even overcorrection of hypokalemia affect prognosis in patients with hypertension.

Using Danish national registers, we investigated the 60-day mortality among patients with hypertension and hypokalemia or low normal potassium concentrations, according to their subsequent plasma potassium concentrations measured within 6–100 days following the initial episode with low potassium levels.

Methods

Data sources

In Denmark, a unique and personal identification number is allocated to all individuals at the time of birth or immigration. This unique identifier allows linkage of health and administrative data at the individual level [6] and ensures nearly complete follow-up. We used anonymized data from five different registers made available by Statistics Denmark after central encryption of the unique identifiers [7]. An overview of the registers used in this study is available in Supplementary Table S1. In Denmark, register-based studies using anonymized data provided by Statistics Denmark are not warranted approval from the ethics committee.

Study population

We defined hypertension as redemption of minimum two antihypertensive agents in two consecutive quarters. This definition has previously been validated [8]. Patients entered the present study in the second quarter, referred to as the date of hypertension. An overview of the Anatomical Therapeutic Chemical Classification System (ATC) codes used to identify patients with hypertension is available in Supplementary Table S2. We required a plasma potassium measurement ≤3.7 mmol/L within 100 days from the date of hypertension for inclusion. The first measurement within this time interval was retained and referred to as the first potassium measurement (K_1). The second potassium measurement (K_2) was identified in the interval 6–100 days from K_1 and the first draw within this timeframe was retained. We did not include potassium concentrations within 1–5 days from K_1 as, potassium disarrays are usually corrected within a few days, regardless of the strategies applied. Patients below 18 years of age were excluded from the study. Supplementary Figure S1 illustrates the population flowchart.

Comorbidities and medication

We identified comorbidities and medications regarded as confounders when studying the association between changes in potassium levels and short-term mortality. The following comorbidities dated up to 5 years before the index date (K_2 date) were identified: hospitalization for heart failure, ischemic heart disease, stroke, chronic

obstructive pulmonary disease, chronic liver disease, diabetes mellitus, inflammatory bowel disease and malignancy. Furthermore, patients with a past history of primary adrenal insufficiency, primary hyperaldosteronism, and diabetes insipidus were excluded. The International Classification of Disease (ICD) codes used to identify above-mentioned comorbidities are shown in Supplementary Table S3. We used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [9] to calculate renal function, and an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 described significant renal insufficiency. Patients were excluded if no creatinine concentrations were available the same day as or within a week from the index date. Patients with missing serum sodium measurements on the index date were also excluded.

Prescriptions redeemed up to 90-days before the index date were identified for the following drugs: potassium supplements, non-steroidal anti-inflammatory drugs, corticosteroids, laxatives, xanthines, and antimicrobials. See Supplementary Table S3 for relevant ATC codes.

Exposure variable

Serum and plasma measurements yield similar results, but for serum samples there is a risk of contamination with potassium from burst platelets during coagulation in the range of 0.1–0.5 mmol/L due to non-standard sample handling [10]. Therefore, we only used plasma potassium measurements.

There is not a consensus on the normal plasma potassium interval, as it can vary from population to population. Supplementary Table S4 gives an overview on the three most used reference intervals in serum and plasma originating from different populations. We defined hypokalemia as plasma potassium concentrations below 3.5 mmol/L and borderline hypokalemia as potassium levels within the interval 3.5–3.7 mmol/L. Hyperkalemia was defined as potassium levels above 4.6 mmol/L. [11] For K_2, seven predefined potassium intervals were constructed: 1.5–2.9 mmol/L, 3.0–3.4 mmol/L, 3.5–3.7 mmol/L, 3.8–4.0 mmol/L, 4.1–4.6 mmol/L, 4.7–5.0 mmol/L and 5.1–7.1 mmol/L. Plasma potassium interval K: 3.8–4.0 mmol/L was used as the reference for statistical analyses. We chose this interval as the reference group because it had one of the largest number of patients and lowest mortality rate.

Outcome

The primary outcome was all-cause mortality within 60 days from K_2. The secondary outcome was presumed cardiovascular death within 60 days from K_2.

Statistical analyses

Categorical variables were presented as counts and percentages, and continuous variables as median with corresponding 25th and 75th percentiles. Differences between variables were compared using chi-squared and Kruskal-Wallis tests, as appropriate.

To illustrate survival probability, Kaplan Meier curves were plotted for the seven potassium intervals. A restricted cubic spline curve was constructed to investigate the relationship between potassium as a continuous variable and absolute mortality risk in an age, sex, comorbidity and drug standardized population.

Cox proportional hazard modeling was used to analyze the association between the seven predefined potassium intervals and 60-day all-cause and presumed cardiovascular mortality. Based on the Cox regression principle, we modelled an average effect to estimate the 60-day absolute risk of all-cause mortality, with potassium interval 3.8–4.0 mmol/L as reference.

The multivariable model was adjusted for: age, sex, serum sodium, renal insufficiency, malignancy, heart failure, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, stroke, atrial flutter/fibrillation, ischemic heart disease, inflammatory bowel disease, antihypertensive therapy, corticosteroids, antimicrobials, non-steroidal anti-inflammatory drugs, xanthines, laxatives, and potassium supplements. The proportional hazard assumption was tested by plotting Schoenfeld residuals and was not violated. Interactions on mortality were tested by comparing the likelihood ratio of the Cox regression model with and without the interaction term. The following variables were tested for interaction with plasma potassium on mortality: age, sex, and renal insufficiency. A two-sided p-value < 0.01 was considered statistically significant for interactions. We found no statistically significant interactions. For other analyses, a two-sided p-value < 0.05 was considered statistically significant. Linearity of age on mortality was also assessed through a likelihood ratio test comparing a linear description with a categorical one. Age was found to violate linearity and was included as a categorical variable with five levels, using cut-off values from every 20th percentiles (55, 64, 72, 79 and 101 years). Hazard ratios (HR) and absolute risks (AR) were estimated with 95% confidence intervals (95% CI). All data management and analyses were performed using SAS, version 9.4 and R, version 3.5.0 [12].

Results

Demographics

We identified 8976 patients treated with combination antihypertensive therapy who had potassium concentrations ≤3.7 mmol/L within the first 100 days from combination therapy initiation. Baseline characteristics for

the cohort stratified on the seven predefined K_2 intervals are presented in Table 1. Females accounted for 53% of the total population and median age was 68.3 years (range 18.2–100.8 years). Of the patients with borderline hypokalemia at K_1, 13% developed hypokalemia and 5.7% hyperkalemia at K_2. As for patients with hypokalemia at K_1, we observed that 28.5% remained hypokalemic at the second blood draw and 4.8% developed hyperkalemia. Approximately half of the population was hospitalized at K_1 and four fifths at K_2. See supplementary Figure S2 displaying the distribution of K_1, average of potassium measurements drawn within 1–5 days from K_1, and K_2. A low number of patients (n = 572) had renal insufficiency at the time of second potassium draw. Median time from K_1 to K_2 was 22 days (range: 6–100 days). As for diuretic treatment, thiazides were common in patients with potassium concentrations ≤3.7 mmol/L, whereas loop diuretics were more common among patients with high potassium levels. Thiazide-like diuretics accounted for 4.4% of the total prescriptions of thiazides.

Demographics stratified on survival status showed that age, renal insufficiency, lower sodium concentrations, hospitalization at the time K_1, prior history of malignancy, chronic liver disease, chronic obstructive pulmonary disease, atrial fibrillation/atrial flutter, heart failure, and stroke were predominant among the deceased (Supplementary Table S5).

60-day survival after the second potassium measurement

During 60-day follow-up after K_2, 627 (7.0%) patients died, 331 from a cardiovascular cause. Mortality in the seven strata was: 14.4, 7.0, 6.3, 5.2, 6.7, 13.6 and 21.6%, respectively. The restricted cubic spline curve revealed a U-shaped relationship between potassium and mortality (Fig. 1).

The results of the multivariable Cox regression, with plasma potassium 3.8–4.0 mmol/L as the reference group are shown in Fig. 2. All-cause mortality was significantly increased in patients with hypokalemia (1.5–2.9 mmol/L HR 2.39, 95% CI 1.66–3.43 and 3.0–3.4 mmol/L HR 1.36, 95% CI 1.04–1.78) when compared with the reference. We observed a trend towards increased mortality in patients with borderline hypokalemia and with potassium levels within the interval 4.1–4.6 mmol/L (HR 1.24, 95% CI 0.97–1.59 and HR 1.20, 95% CI 0.95–1.51, respectively). All-cause mortality was also elevated in patients with hyperkalemia (4.7–5.0 mmol/L HR 2.36, 95% CI 1.68–3.30; 5.1–5.7 mmol/L HR 2.62, 95% CI 1.73–3.98). The univariable analysis showed similar results. We observed no interaction between K_1 and K_2 on 60-day mortality.

Cardiovascular mortality accounted for nearly 53% of all deaths. We observed increased risk of cardiovascular death in patients with initial hypokalemia or low normal potassium levels who had potassium concentrations < 3.0 mmol/L and > 4.6 mmol/L at the second measurement.

The standardized 60-day absolute risk of all-cause mortality was lowest in patients with potassium concentrations between 3.8–4.0 mmol/L (AR 5.4, 95% CI 4.5–6.3%, Table 2). Significant differences in risks (reported against the reference) were observed for the following potassium intervals: 1.5–2.9 mmol/L risk difference 6.3% (95% CI 2.9–9.7%); 4.7–5.0 mmol/L risk difference 6.2% (95% CI 3.2–9.3%); 5.1–7.1 mmol/L risk difference 7.2% (95% CI 2.8–11.6%).

Subgroup and sensitivity analyses

We performed eleven additional analyses to test the accuracy and robustness of the main results (Table S6).

First, multivariable analysis performed on a subgroup of patients without kidney insufficiency showed that potassium levels within the intervals 1.5–2.9 mmol/L and 3.0–3.4 mmol/L were associated with increased mortality risk compared with the reference (3.8–4.0 mmol/L) (HR 2.33, 95% CI 1.56–3.46 and HR 1.35, 95% CI 1.02–1.79, respectively).

Second, in a subpopulation without history of malignancy, adjusted analyses showed that potassium concentrations outside the interval 3.0–4.6 mmol/L were associated with increased risk of death compared with the reference.

Third, subgroup analysis on patients without history of heart failure and no loop diuretic prescription showed that patients with hypokalemia and hyperkalemia had an increased mortality risk compared with patients with potassium levels in the interval 3.8–4.0 mmol/L.

Fourth, analysis performed on a subgroup of patients without ischemic heart disease showed that patients with severe hypokalemia, and hyperkalemia had increased risk short-term mortality risk when compared with the reference.

Fifth, looking at patients with borderline hypokalemia at the first potassium measurement, we observed that patients who developed hypokalemia (1.5–2.9 mmol/L: HR 2.16, 95% CI 1.25–3.73; 3.0–3.4 mmol/L: HR 1.70, 95% CI 1.22–2.37), or hyperkalemia (4.7–5.0 mmol/L: HR 1.84, 95% CI 1.18–2.86; 5.1–7.1 mmol/L: HR 2.81, 95% CI 1.68–4.71) had an increased risk of death within 60-days when compared with the reference.

Sixth, among patients with hypokalemia at K_1, analyses showed that potassium concentrations within the intervals 1.5–2.9 mmol/L, 4.1–4.6 mmol/L and 4.7–5.0 mmol/L were associated with increased short-term mortality risk.

Seventh, by performing the analyses on the last available potassium measurement within 6–100 days from K_1

Table 1 Demographics stratified according to the eight predefined plasma potassium intervals in a cohort of 8976 patients treated with combination antihypertensive therapy

		1.5–2.9 mmol/L (***n*** = 271)	3.0–3.4 mmol/L (***n*** = 1341)	3.5–3.7 mmol/L (***n*** = 1982)	3.8–4.0 mmol/L (***n*** = 2398)	4.1–4.6 mmol/L (***n*** = 2498)	4.7–5.0 mmol/L (***n*** = 352)	5.1–7.1 mmol/L (***n*** = 134)	***p***-value
Age	median (range)	70.6(21.4, 94.9)	67(19.2, 100.8)	67(22.1, 97.7)	67.7(19.2, 97.5)	69.7(18.2, 99.9)	69.9(20.2, 98.6)	71.9(27.7, 97.8)	< 0.01
Sex	Female	157 (57.9)	757 (56.5)	1087 (54.8)	1276 (53.2)	1250 (50.0)	172 (48.9)	57 (42.5)	
Renal insufficiency (second measuremt)		26 (9.6)	78 (5.8)	118 (6.0)	127 (5.3)	142 (5.7)	43 (12.2)	38 (28.4)	< 0.01
Serum sodium (second measurement)	median (range)	138(111, 157)	139(117, 179)	140(105, 155)	140(101, 161)	139(107, 159)	138(114, 166)	136(112, 149)	< 0.01
Plasma potassium (first measurement)	3.5–3.7 mmol/L	97 (35.8)	700 (52.2)	1322 (66.7)	1768 (73.7)	1877 (75.1)	258 (73.3)	89 (66.4)	
	< 3.5 mmol/L	174 (64.2)	641 (47.8)	660 (33.3)	630 (26.3)	621 (24.9)	94 (26.7)	45 (33.6)	< 0.01
Renal insufficiency (first measuremt)		25 (9.8)	87 (6.9)	117 (6.2)	127 (5.5)	166 (6.9)	47 (13.7)	32 (24.8)	< 0.01
	missing creatinine	17	77	92	82	77	8	5	
Hospitalization at the time of second potassium measurement		232 (85.6)	1050 (78.4)	1538 (77.7)	1860 (77.6)	2050 (82.1)	303 (86.1)	118 (88.1)	< 0.01
Time from first to second potassium measurement (days)	median (range)	14(6, 97)	21(6, 100)	25(6, 100)	26(6, 100)	21(6, 100)	13.5(6, 100)	14(6, 97)	< 0.01
Death-60 days		39 (14.4)	94 (7.0)	125 (6.3)	124 (5.2)	168 (6.7)	48 (13.6)	29 (21.6)	< 0.01
60-day cardiovascular mortality		21 (7.7)	50 (3.7)	68 (3.4)	59 (2.5)	91 (3.6)	28 (8.0)	14 (10.4)	< 0.01
Comorbidities									
Any malignancy		58 (21.4)	252 (18.8)	389 (19.6)	429 (17.9)	478 (19.1)	71 (20.2)	28 (20.9)	0.66
Chronic obstructive pulmonary disease		41 (15.1)	180 (13.4)	238 (12.0)	290 (12.1)	395 (15.8)	63 (17.9)	28 (20.9)	< 0.01
Diabetes		43 (15.9)	221 (16.5)	324 (16.3)	432 (18.0)	453 (18.1)	77 (21.9)	36 (26.9)	0.01
Chronic kidney disease		16 (5.9)	116 (8.7)	176 (8.9)	170 (7.1)	194 (7.8)	38 (10.8)	26 (19.4)	< 0.01
Chronic liver disease		23 (8.5)	55 (4.1)	90 (4.5)	109 (4.5)	124 (5.0)	21 (6.0)	12 (9.0)	0.01
Atrial fibrillation/Atrial flutter		37 (13.7)	209 (15.6)	337 (17.0)	446 (18.6)	535 (21.4)	85 (24.1)	43 (32.1)	< 0.01
Hypertension (ICD-10)		112 (41.3)	475 (35.4)	755 (38.1)	895 (37.3)	941 (37.7)	121 (34.4)	35 (26.1)	0.04
Heart failure		47 (17.3)	212 (15.8)	348 (17.6)	453 (18.9)	624 (25.0)	102 (29.0)	59 (44.0)	< 0.01
Ischemic heart disease		54 (19.9)	257 (19.2)	420 (21.2)	594 (24.8)	729 (29.2)	126 (35.8)	53 (39.6)	< 0.01
Stroke		36 (13.3)	147 (11.0)	241 (12.2)	292 (12.2)	320 (12.8)	40 (11.4)	13 (9.7)	0.67
Inflammatory bowel disease		4 (1.5)	19 (1.4)	43 (2.2)	39 (1.6)	38 (1.5)	5 (1.4)	6 (4.5)	0.12

Table 1 Demographics stratified according to the eight predefined plasma potassium intervals in a cohort of 8976 patients treated with combination antihypertensive therapy *(Continued)*

		1.5–2.9 mmol/L (***n*** = 271)	3.0–3.4 mmol/L (***n*** = 1341)	3.5–3.7 mmol/L (***n*** = 1982)	3.8–4.0 mmol/L (***n*** = 2398)	4.1–4.6 mmol/L (***n*** = 2498)	4.7–5.0 mmol/L (***n*** = 352)	5.1–7.1 mmol/L (***n*** = 134)	***p***-value
Pharmacotherapy									
Potassium supplement	ATC: A12B	163 (60.1)	699 (52.1)	895 (45.2)	1083 (45.2)	1219 (48.8)	192 (54.5)	80 (59.7)	< 0.01
	ATC: C03	67 (24.7)	415 (30.9)	557 (28.1)	674 (28.1)	577 (23.1)	67 (19.0)	13 (9.7)	< 0.01
Antimicrobials		152 (56.1)	742 (55.3)	1082 (54.6)	1347 (56.2)	1434 (57.4)	204 (58.0)	78 (58.2)	0.59
Beta-2 agonists		58 (21.4)	337 (25.1)	451 (22.8)	576 (24.0)	625 (25.0)	93 (26.4)	38 (28.4)	0.30
Corticoids		54 (19.9)	284 (21.2)	417 (21.0)	499 (20.8)	534 (21.4)	81 (23.0)	33 (24.6)	0.90
Laxatives		7 (2.6)	41 (3.1)	51 (2.6)	58 (2.4)	74 (3.0)	23 (6.5)	4 (3.0)	< 0.01
Xantines		11 (4.1)	43 (3.2)	57 (2.9)	56 (2.3)	81 (3.2)	15 (4.3)	5 (3.7)	0.26
NSAIDs		153 (56.5)	739 (55.1)	1090 (55.0)	1362 (56.8)	1438 (57.6)	197 (56.0)	76 (56.7)	0.67
Antiadrenergic drugs		4 (1.5)	21 (1.6)	18 (0.9)	26 (1.1)	26 (1.0)	≤3	4 (3.0)	0.24
Vasodilators		0 (0.0)	0 (0.0)	≤3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.74
Beta blockers		97 (35.8)	497 (37.1)	775 (39.1)	972 (40.5)	1213 (48.6)	174 (49.4)	71 (53.0)	< 0.01
Calcium channel blockers		117 (43.2)	514 (38.3)	687 (34.7)	843 (35.2)	780 (31.2)	93 (26.4)	38 (28.4)	< 0.01
Renin angiotensin system inhibitors		134 (49.4)	716 (53.4)	1158 (58.4)	1487 (62.0)	1506 (60.3)	209 (59.4)	81 (60.4)	< 0.01
Loop diuretics		115 (42.4)	533 (39.7)	720 (36.3)	841 (35.1)	1112 (44.5)	179 (50.9)	87 (64.9)	< 0.01
Thiazide diuretics		127 (46.9)	682 (50.9)	934 (47.1)	1110 (46.3)	909 (36.4)	95 (27.0)	20 (14.9)	< 0.01
Thiazilde-like diuretics		7 (2.6)	28 (2.1)	46 (2.3)	47 (2.0)	37 (1.5)	4 (1.1)	≤3	0.38
Potassium sparing diuretics		15 (5.5)	40 (3.0)	50 (2.5)	54 (2.3)	48 (1.9)	7 (2.0)	≤3	< 0.01
Mineral receptor antagonists		51 (18.8)	181 (13.5)	250 (12.6)	281 (11.7)	372 (14.9)	83 (23.6)	35 (26.1)	< 0.01

ICD-10 International Classification of Disease 10th version, *ATC* Anatomical Therapeutic Chemical Classification System, *NSAIDs* Non-steroidal anti-inflammatory drugs
≤3- Is ascertained cells where the frequency is 1, 2 or 3 in order to ensure anonymization of the data

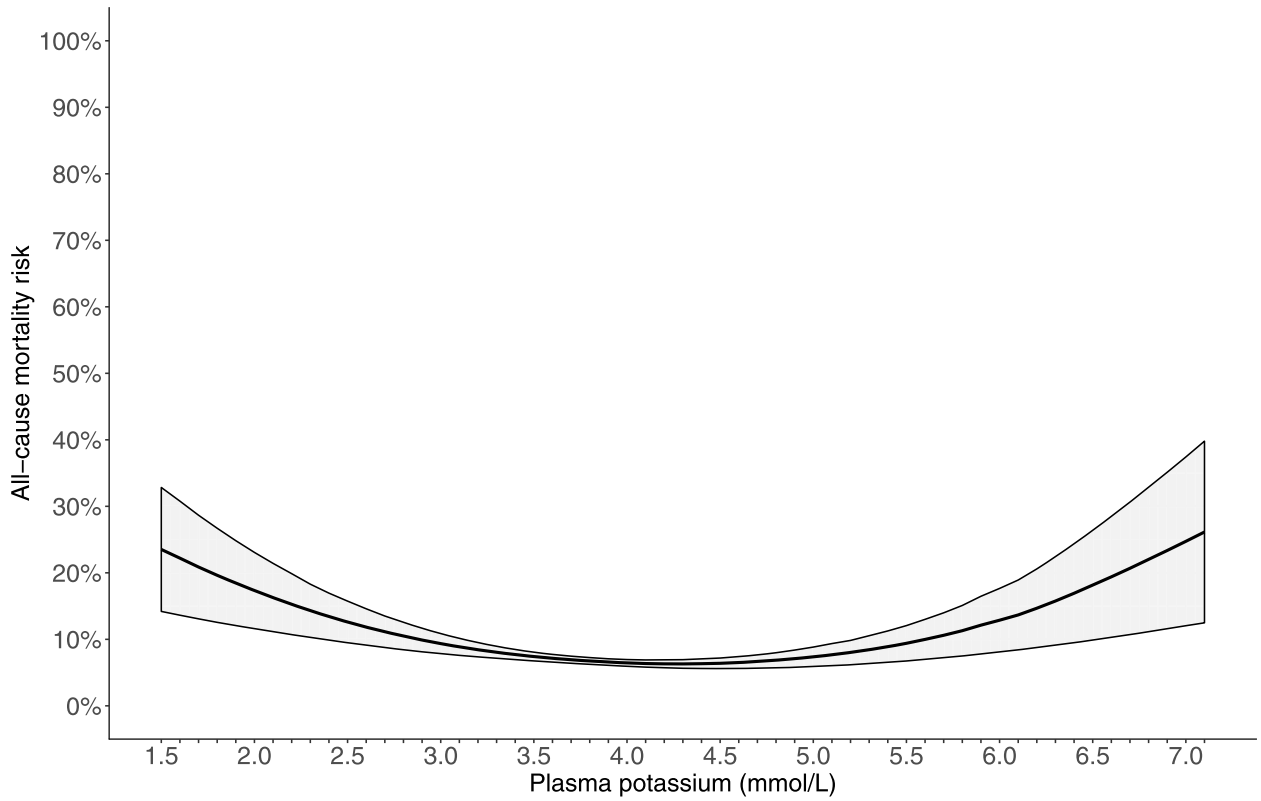


Fig. 1 Age, sex, comorbidity and drug standardized 60-day risk of all-cause death in relation to plasma potassium as a continuous variable. Model adjusted for age, gender, plasma sodium, renal insufficiency, malignancy, heart failure, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, atrial flutter/fibrillation, stroke and ischemic heart disease, antihypertensive therapy, corticosteroids, antimicrobials, non-steroidal anti-inflammatory drugs, potassium supplement, xanthines, laxatives

instead of the first measurement, we noted that potassium levels below 3.8 mmol/L were associated with increased short-term mortality.

Eighth, analyses on patients with available K_2 measurements within 6–45 days from K_1, showed that severe hypokalemia and hyperkalemia were associated with 60-day all-cause mortality.

Ninth, analyses on patients with available K_2 measurements above 45 days from K_1, showed that potassium interval 3.0–3.4 mmol/L was associated with 60-day all-cause mortality.

Tenth, we stratified K_2 in three intervals: 1.5–3.4 mmol/L (hypokalemia), 3.5–4.6 mmol/L (normokalemia) and 4.7–7.1 mmol/L (hyperkalemia). Mortality within 60-days was increased both in patients with hypokalemia (HR 1.36, 95% CI 1.12–1.66) and in patients with hyperkalemia (HR 2.13, 95% CI 1.66–2.74) at K_2 measurement compared with patients with normal potassium concentrations.

Eleventh, multivariable analysis on patients with available magnesium measurements at the time of plasma potassium draws, showed significant association of potassium levels below 3.0 mmol/L and mortality (HR 2.46, 95% CI 1.05–5.74). In addition, we also observed a trend towards increased risk of death in patients with potassium between 3.0–3.4 mmol/L.

Discussion

This Danish register-based cohort study investigated 60-day mortality among 8976 patients with hypertension and hypokalemia or low normal potassium in relation to a subsequent potassium measurement. The major findings were: (1) Persistent hypokalemia following low potassium was more than twice as frequent as development of hyperkalemia. (2) Persistent hypokalemia was common and associated with increased all-cause and presumed cardiovascular mortality; (3) Increase in potassium to levels > 4.6 mmol/L in patients with initial hypokalemia or low normal potassium was associated with increased all-cause and cardiovascular mortality; (4) Among patients with borderline hypokalemia initially, development of hypokalemia or hyperkalemia was associated with increased mortality risk; (5) Correcting hypokalemia associated with increased survival.

In the current study, we observed significantly higher 60-day mortality risk in patients with potassium

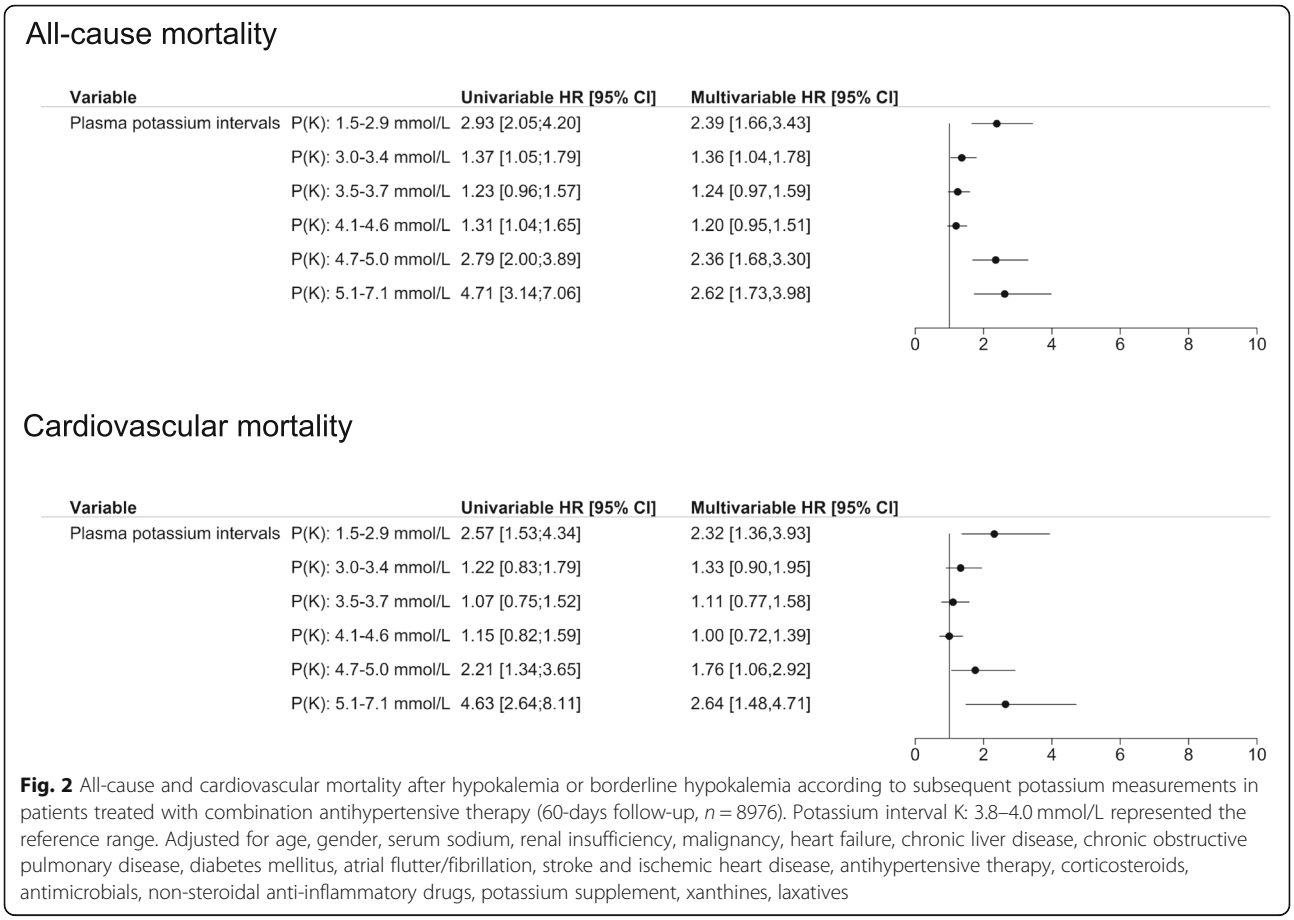


Fig. 2 All-cause and cardiovascular mortality after hypokalemia or borderline hypokalemia according to subsequent potassium measurements in patients treated with combination antihypertensive therapy (60-days follow-up, $n = 8976$). Potassium interval K: 3.8–4.0 mmol/L represented the reference range. Adjusted for age, gender, serum sodium, renal insufficiency, malignancy, heart failure, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, atrial flutter/fibrillation, stroke and ischemic heart disease, antihypertensive therapy, corticosteroids, antimicrobials, non-steroidal anti-inflammatory drugs, potassium supplement, xanthines, laxatives

concentrations < 3.5 or > 4.6 mmol/L after an episode with hypokalemia or low normal potassium. This finding was not surprising as we previously observed an apparent optimal potassium range within 4.1–4.7 mmol/L in a similar population [5]. Of 8976 patients with initial plasma potassium ≤3.7 mmol/L, 18% had potassium concentrations ≤3.7 mmol/L at the second measurement and 5.4% > 4.6 mmol/L, suggesting that potassium deficit is frequently underestimated than overestimated by physicians. Notably, 13% of the patients with borderline hypokalemia (K: 3.5 and 3.7 mmol/L) at the first measurement experienced a further decrease in potassium (< 3.5 mmol/L) at the second measurement. This suggests that the association of low normal potassium

Table 2 60-day standardized absolute risk for all-cause death after hypokalemia or borderline hypokalemia according to subsequent potassium measurements in patients treated with combination antihypertensive therapy ($n = 8976$). Potassium interval K: 3.8–4.0 mmol/L represented the reference range. Adjusted for age, gender, serum sodium, renal insufficiency, malignancy, heart failure, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, atrial flutter/fibrillation, stroke and ischemic heart disease, antihypertensive therapy, corticosteroids, antimicrobials, non-steroidal anti-inflammatory drugs, potassium supplement, xanthines, laxatives

	Absolute risk %, (95% CI)	60-d Risk difference %, (95%CI)	*p*-value	Average risk ratio %, (95%CI)	*p*-value
P(K) 1.5–2.9 mmol/L	11.7% (8.3–15.0)	6.3 (2.9–9.7)	< 0.001	2.17 (1.46–2.88)	0.001
P(K) 3.0–3.4 mmol/L	7.1% (5.8–8.5)	1.7 (0.1–3.4)	0.03	1.32 (0.99–1.66)	0.06
P(K) 3.5–3.7 mmol/L	6.4% (5.3–7.5)	1.0 (− 0.3–2.4)	0.14	1.19 (0.91–1.47)	0.17
P(K) 3.8–4.0 mmol/L	5.4% (4.5–6.3)	REF.		REF.	
P(K) 4.1–4.6 mmol/L	6.3% (5.4–7.2)	0.9 (−0.3–2.2)	0.13	1.18 (0.92–1.44)	0.17
P(K) 4.7–5.0 mmol/L	11.6% (8.7–14.6)	6.2 (3.2–9.3)	< 0.001	2.17 (1.51–2.82)	< 0.001
P(K) 5.1–7.1 mmol/L	12.6% (8.2–16.9)	7.2 (2.8–11.6)	0.001	2.34 (1.45–3.22)	0.003

concentrations with mortality that we previously observed [5] can partly be explained by further declines in potassium levels, and that low normal potassium concentrations might be a marker for an ongoing decrease in potassium.

Our results also suggest that correction of hypokalemia is important in relation to short-term mortality, as patients in the middle of the normal reference interval had good prognosis. Guidelines recommend supplementation with potassium when plasma potassium levels are below 3.5 mmol/L. [13] However, in this study we cannot elucidate because of the low follow-up time the mechanism through which patients increased or decreased in potassium concentrations. It is also difficult to state whether potassium is a risk factor or a risk marker regarding mortality. Our population is relatively old, patients are treated with at least two antihypertensive drugs, and about 20% of the patients have history of heart failure, ischemic heart disease, atrial fibrillation/flutter, chronic obstructive pulmonary disease and diabetes. Possibly, potassium concentrations at non-cardiotoxic levels more likely are a risk marker of great disease burden, which is very important to recognize and identify.

Potassium supplementation of asymptomatic patients with low normal concentrations is controversial. Guidelines in the US recommend a stricter standard for potassium replacement therapy (< 4.0 mmol/L) especially in patients with cardiovascular disease who are at high risk of ventricular tachyarrhythmias [13]. Our study suggests that potassium concentrations in the middle of the reference interval are beneficial even in patients with potassium levels ≤3.7 mmol/L.

Various studies have previously demonstrated that hypokalemia among patients with cardiovascular disease is associated with an increased mortality risk [14–18]. However, no prior studies have investigated the impact of potassium normalization on short-term survival. Though, one study examined the impact of correcting hypokalemia within 24 h on the risk of cardiac arrhythmias in hospitalized patients without coronary syndromes or history of arrhythmias [19]. The authors did not find increased odds of arrhythmia in patients with hypokalemia whose potassium levels were not corrected ≥3.5 mmol/L. Although, the study does not describe or account for the cause of admission, comorbidities or pharmacotherapy. The investigators excluded patients with history of ischemic heart disease and arrhythmia, but included patients with heart failure who have a high arrhythmia risk. Overall, both the study population and the outcome measure differed in this paper compared with our study.

Another study performed on 5916 individuals from the general population found no significant associations between borderline hypokalemia (3.4–3.6 mmol/L) and risk of all-cause mortality, risk of stroke or risk of acute myocardial infarction [20]. Comparing the results of our study with this study is difficult due to major differences in study population, methodology and aim. First, our population was characterized by redemption of at least two antihypertensive drugs. Mattsson et al. [20] enrolled participants from the general population, where 49.6% had high blood pressure at baseline, 13.9% were prescribed heart medication and 10.9% were treated with diuretics. In our population, we observed higher burden of cardiovascular disease and use of diuretics. Second, our aim was to investigate the impact of correcting hypokalemia or borderline hypokalemia on short-term all-cause and cardiovascular mortality. In terms of mortality, Mattsson et al. [20] followed participants from their fourth examination in 2001–2003 until November 2014 or death, having a median follow-up of 11.9 years (Q1-Q3: 11.4–12.5 years). As potassium is varying over time especially in patients with cardiovascular disease or treated with antihypertensive drugs, use of one potassium measurement to assess mortality over more than 10 years can provide results that are difficult to interpret. Shorter follow-up time or time varying analysis where the authors accounted for both multiple measurements over time and change in relevant medication would have provided better methodology. Although, it is important to acknowledge that correcting hypokalemia and low normal potassium might not have the same impact in general population compared to a population with heart disease.

Another study investigated the influence of dyskalemia at admission and early dyskalemia correcting on short-term survival and cardiac events among intensive care unit (ICU) patients [21]. The authors concluded that patients with persisting hypokalemia or hyperkalemia within the first 2 days in ICU had increased risk of death. The two populations are not comparable, however both studies emphasize the importance of rapid correction of hypokalemia to improve short-term mortality.

Limitations

The limitations are related to the observational nature of register-based studies, which imply non-causal interpretation of the results.

We did not have information about comorbidities and risk factors from the primary sector. Therefore, patients who did not redeem any medication of interest or were not registered an ICD-code from the secondary sector could have been misclassified as “healthy”. Patients with complications related to hypertension have a larger likelihood for being referred to the secondary sector and therefore also a higher probability for being diagnosed with other conditions (compared with patients with

uncomplicated hypertension), leading to an ascertainment/surveillance bias and non-differential misclassification bias. To reduce this bias, we defined hypertension as use of at least two antihypertensive drugs in two concomitant quarters. Whether hypertension was resistant, controlled or uncontrolled was unkown, and data about ejection fraction and type of heart failure was not available.

We cannot exclude that the blood draws may contain hemolysis. However, in case of significant hemolysis the samples submitted are rejected and no potassium value is available.

We could not investigate the effect of any potential treatment or drug dosage adjustment in the time between the first and second potassium measurement. The Danish National Prescription Registry records filled prescriptions; thus, changes in dosage cannot be identified, unless a new drug is prescribed. In addition, the majority of the patients were hospitalized at the time of potassium measurement and any treatment during hospitalization is not registered in the Danish National Prescription Registry. Moreover, it was also difficult to identify the cause of hypokalemia using the registers. Hypokalemia might have occurred due to administration of diuretics, alkalosis, derangements in the renin angiotensin aldosterone system, gastroenteritis or other pathologies. However, the purpose of this study was neither to investigate the cause of hypokalemia, nor to assess the strategies used to correct low potassium concentrations. The purpose of this study was to find a clue, whether normalization of potassium had an effect on short-term mortality, whether we should increase potassium concentrations in patients with borderline hypokalemia and whether potassium actually increased.

It is also important to acknowledge that plasma potassium is not always a good predictor of the whole body potassium. Yet, it is the most commonly used method to assess potassium and only in patients with persistent hypokalemia over a longer period of time total body potassium is calculated.

Conclusion

Persistent hypokalemia was frequent and associated with increased all-cause and cardiovascular mortality. Increase in potassium to levels > 4.6 mmol/L in patients with initial hypokalemia or low normal potassium was associated with increased all-cause and cardiovascular mortality.

Perspectives

We were not able to report the initiatives medical doctors undertook after observing potassium levels below 3.8 mmol/L at the first measurement. However, our results emphasize the importance of potassium normalization after an episode with hypokalemia and low normal potassium and that overcorrection is associated with an increased risk of death. Potassium concentrations in the middle of the normal reference interval are associated with good prognosis. Possibly, potassium supplementation, use of mineral receptor antagonists or thiazide-like diuretics instead of thiazide-type in patients with potassium concentrations ≤3.7 mmol/L could be of clinical importance, but requires further study, preferably through a randomized controlled trial.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12872-020-01654-3.

Additional file 1.

Abbreviations

ATC: Anatomical therapeutic chemical classification system; K_1: First potassium measurement within 100 days from combination antihypertensive therapy initiation; K_2: First potassium measurement within 6–100 days from K_1; ICD: International classification of disease; CKD-EPI: Chronic kidney disease epidemiology collaboration; eGFR: Estimated glomerular filtration rate; HR: Hazard ratio; AR: Absolute risk; 95% CI: 95% confidence interval; NSAIDs: Non-steroidal anti-inflammatory drugs

Acknowledgements

None.

Authors' contributions

Conception or design of the work: MLK, PS, CTP, KK, JQT, AB, HB. Acquisition of data: MLK, PS, CTP, KK, AB, CJYL. Analysis and interpretation of data: MLK, PS, CTP, AB, KK, CJYL, HB, JQT. Draftet the manuscript: MLK. Critically revised the manuscript: Peter Søgaard, Christian Torp-Pedersen, Henrik Bøggild, Christina Ji-Young Lee, Anders Bonde, Jesper Q. Thomassen, Gunnar Gislason, Manan Pareek, Kristian Kragholm, All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Funding

This study was funded using departmental funding sources only. The funding covered labor costs.

Availability of data and materials

Due to restrictions related to Danish law and protecting patient privacy, the combined set of data used in this study can only be made available through a trusted third party, Statistics Denmark. This state organisation holds the data used for this study. University-based Danish scientific organisations can be authorized to work with data within Statistics Denmark and such organisation can provide access to individual scientists inside and outside of Denmark. Data are available upon request to authorized scientists by contacting Statistics Denmark: http://www.dst.dk/en/OmDS/organisation/TelefonbogOrg.aspx?kontor=13&tlfbogsort=sektion or the Danish Data Protection Agency: https://www.datatilsynet.dk/english/the-danish-data-protection-agency/contact/. More information regarding data access is available at https://www.dst.dk/en/TilSalg/Forskningsservice.

Ethics approval and consent to participate

Retrospective studies do not require ethics approval in Denmark and all data were deidentified and only available through Statistics Denmark. Approval from the Danish Data Protection Agency was secured, and the need for patient informed consent was not needed.

Consent for publication

Not applicable.

Competing interests
None to declare.

Author details
[1]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark. [2]Department of Cardiology and Clinical Research, Nordsjællands Hospital, Hillerød, Denmark. [3]Public Health and Epidemiology Group, Department of Health Science and Technology, Aalborg University, Aalborg, Denmark. [4]Unit of Epidemiology and Biostatistics, Aalborg University Hospital, Aalborg, Denmark. [5]Department of Cardiology, Copenhagen University Hospital, Herlev and Gentofte, Hellerup, Denmark. [6]Department of Clinical Biochemistry, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark. [7]Department of Cardiology, Herlev and Gentofte University Hospital, Hellerup, Denmark. [8]The Danish Heart Foundation, Copenhagen, Denmark. [9]The National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark. [10]Department of Internal Medicine, Yale New Haven Hospital, Yale University School of Medicine, New Haven, USA. [11]Brigham and Women's Hospital, Heart & Vascular Center, Harvard Medical School, Boston, USA. [12]Department of Cardiology, Regionshospital Nordjylland, Hjørring, Denmark.

Received: 16 April 2020 Accepted: 4 August 2020
Published online: 24 August 2020

References

1. Veltri KT, Mason C. Medication-induced hypokalemia. P T United States. 2015;40:185–90.
2. Sica DA, Carter B, Cushman W, Hamm L. Thiazide and loop diuretics. J Clin Hypertens (Greenwich) United States. 2011;13:639–43.
3. Tamargo J, Segura J, Ruilope LM. Diuretics in the treatment of hypertension. Part 2: loop diuretics and potassium-sparing agents. Expert Opin Pharmacother. 2014;15(5):605–21.
4. Rodenburg EM, Visser LE, Hoorn EJ, Ruiter R, Lous JJ, Hofman A, Uitterlinden AG, Stricker BH. Thiazides and the risk of hypokalemia in the general population. J Hypertens. 2014;32:2092–7.
5. Krogager ML, Torp-Pedersen C, Mortensen RN, Køber L, Gislason G, Søgaard P, Aasbjerg K. Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. Eur Heart J. 2017;38:104–12.
6. Thygesen LC, Daasnes C, Thaulow I, Bronnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. Scand J Public Health Sweden. 2011;39:12–6.
7. Pedersen CB. The Danish civil registration system. Scand J Public Health. 2011;39:22–5.
8. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ. 2011;342:d124 Department of Cardiology, Copenhagen University Hospital Gentofte, 2900 Hellerup, Denmark. jo@heart.dk.
9. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–12.
10. Burtis CA, Ashwood ER, Bruns DE. Tietz textbook of clinical chemistry and molecular diagnostics. 5th ed. St. Louis, Missouri, USA: Elsevier Saunders; 2012.
11. Drogies T, Ittermann T, Lüdemann J, Klinke D, Kohlmann T, Lubenow N, Greinacher A, Völzke H, Nauck M. Potassium - reference intervals for lithium-heparin plasma and serum from a population-based cohort. LaboratoriumsMedizin. 2010;34:39–44.
12. Article citationsMore>> R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2018. https://www.R-project.org.
13. Cohn JN, Kowey PR, Whelton PK, Prisant LM. New guidelines for potassium replacement in clinical practice: a contemporary review by the National Council on potassium in clinical practice. Arch Intern Med United States. 2000;160:2429–36.
14. Alderman MH, Piller LB, Ford CE, Probstfield JL, Oparil S, Cushman WC, Einhorn PT, Franklin SS, Papademetriou V, Ong ST, Eckfeldt JH, Furberg CD, Calhoun DA, Davis BR, Group A and L-LT to PHATCR. Clinical significance of incident hypokalemia and hyperkalemia in treated hypertensive patients in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Hypertension. 2012;59:926–33 Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Bronx, NY, USA.
15. Aldahl M, Jensen A-SC, Davidsen L, Eriksen MA, Moller Hansen S, Nielsen BJ, Krogager ML, Kober L, Torp-Pedersen C, Sogaard P. Associations of serum potassium levels with mortality in chronic heart failure patients. Eur Heart J England. 2017;38:2890–6.
16. Krogager ML, Eggers-Kaas L, Aasbjerg K, Mortensen RN, Køber L, Gislason G, Torp-Pedersen C, Søgaard P. Short-term mortality risk of serum potassium levels in acute heart failure following myocardial infarction. Eur Hear J - Cardiovasc Pharmacother. 2015;1:245–51.
17. Hagengaard L, Søgaard P, Espersen M, et al. Association between serum potassium levels and short-term mortality in patients with atrial fibrillationor flutter co-treated with diuretics and rate- or rhythm-controlling drugs. Eur Heart J Cardiovasc Pharmacother. 2020;6(3):137-44.
18. Tishler M, Armon S. Nifedipine-induced hypokalemia. Drug Intell Clin Pharm United States. 1986;20:370–1.
19. Harkness W, Watts P, Kopstein M, Dziadkowiec O, Hicks G, Scherbak D. Correcting hypokalemia in hospitalized patients does not decrease risk of cardiac arrhythmias. Adv Med. 2019;2019:1–4.
20. Mattsson N, Nielsen OW, Johnson L, Prescott E, Schnohr P, Jensen GB, Kober L, Sajadieh A. Prognostic impact of mild hypokalemia in terms of death and stroke in the general population-a prospective population study. Am J Med United States. 2018;131:318.e9–318.e19.
21. Bouadma L, Mankikian S, Darmon M, Argaud L, Vinclair C, Siami S, Garrouste-Orgeas M, Papazian L, Cohen Y, Marcotte G, Styfalova L, Reignier J, Lautrette A, Schwebel C, Timsit JF, Timsit JF, Azoulay E, Garrouste-Orgeas M, Zahar JR, Adrie C, Darmon M, Clec'h C, Alberti C, Francąis A, Vesin A, Ruckly S, Bailly S, Lecorre F, Nakache D, Vannieuwenhuyze A, et al. Influence of dyskalemia at admission and early dyskalemia correction on survival and cardiac events of critically ill patients. Crit Care. 2019.

Publisher's Note

Risk of Developing Hypokalemia in Patients With Hypertension Treated With Combination Antihypertensive Therapy

Maria Lukács Krogager, Rikke Nørmark Mortensen, Peter Enemark Lund, Henrik Bøggild, Steen Møller Hansen, Kristian Kragholm, Kristian Aasbjerg, Peter Søgaard, Christian Torp-Pedersen

Abstract—Little is known about the occurrence of hypokalemia due to combination therapy for hypertension. Using data from Danish administrative registries, we investigated the association between different combinations of antihypertensive therapy and risk of developing hypokalemia. Using incidence density matching, 2 patients without hypokalemia were matched to a patient with hypokalemia (K, <3.5 mmol/L) on age, sex, renal function, and time between index date and date of potassium measurement. Combination therapies were subdivided into 10 groups including β-blockers (BB)+thiazides (BB+thiazides), calcium channel blockers (CCB)+renin angiotensin system inhibitors (RASi)+thiazides (CCB+RASi+Thiazides), calcium channel blockers+thiazides (CCB+thiazides), and β-blockers+renin angiotensin system inhibitors+thiazides (BB+RASi+thiazides). We used conditional logistic regression to estimate the odds of developing hypokalemia for different combinations of antihypertensive drugs within 90 days of combination therapy initiation. We matched 463 patients with hypokalemia to 926 patients with normal potassium concentrations. The multivariable analysis showed 5.82× increased odds of developing hypokalemia if administered CCB+thiazides (95% CI, 3.06–11.08) compared with CCB+RASi. Other combinations significantly associated with increased hypokalemia odds were BB+thiazides (odds ratio, 3.34 [95% CI, 1.67–6.66]), CCB+RASi+thiazides (odds ratio, 3.07 [95% CI, 1.72–5.46]), and BB+RASi+thiazides (odds ratio, 2.78 [95% CI, 1.41–5.47]). Combinations of thiazides with CCB, RASi, or BB were strongly associated with increased hypokalemia risk within 90 days of treatment initiation. **(*Hypertension*. 2020;75:966-972. DOI: 10.1161/HYPERTENSIONAHA.119.14223.)** ● **Online Data Supplement**

Key Words: calcium channel blockers ■ hypertension ■ hypokalemia ■ potassium ■ thiazides

Current guidelines for the management of hypertension recommend 5 major drug classes, namely calcium channel blockers (CCB), ACE (angiotensin-converting enzyme) inhibitors, ARBs (angiotensin receptor blockers), β-blockers, and thiazides/thiazide-like diuretics. In patients who do not have an optimal response on monotherapy, guidelines recommend sequentially adding other antihypertensive drugs until blood pressure target is achieved.[1]

Most of the drugs used for the treatment of hypertension, especially thiazide diuretics, ACE inhibitors, and ARBs, are known to influence potassium homeostasis through different mechanisms.[2] In combination therapy, avoidance of potassium imbalances can be a challenge and prevention of potassium imbalances is important as they can elicit arrhythmias and sudden cardiac death.[2–5] Moreover, a previous study showed that potassium levels outside the interval 4.1 to 4.7 mmol/L were associated with increased mortality risk in patients with hypertension.[6] However, there is little knowledge on the occurrence of potassium imbalances in relation to different combination therapies.

Using the Danish nationwide administrative registries, we investigated the risk of developing hypokalemia within 90 days depending on different antihypertensive combination therapies.

Method

Data Availability

Due to restrictions related to Danish law and protecting patient privacy, the combined set of data used in this study can only be made available through a trusted third party, Statistics Denmark. This state organization holds the data used for this study. University-based Danish scientific organizations can be authorized to work with data within Statistics Denmark and such organization can provide access to individual scientists inside and outside of Denmark. Data are available on request to authorized scientists by contacting Statistics

Received October 17, 2019; first decision October 29, 2019; revision accepted January 17, 2020.

From the Unit of Epidemiology and Biostatistics (M.L.K., R.N.M., P.E.L., H.B., S.M.H., K.K., K.A., P.S., C.T.-P.), Department of Cardiology (M.L.K., S.M.H., K.K., C.T.-P.), Department of Ophthalmology (K.A.), and Heart Centre and Clinical Institute (P.S.), Aalborg University Hospital, Aalborg, Denmark; Public Health and Epidemiology Group, Department of Health Science and Technology, Aalborg University, Aalborg Øst, Denmark (H.B.); and Department of Cardiology and Clinical Research, Nordsjællands Hospital, Hillerød, Denmark (C.T.-P.).

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.119.14223.

Correspondence to Maria Lukács Krogager, Department of Cardiology, Hobrovej 18-22, 9000, Aalborg, Denmark. Email lkcsmaria@yahoo.com

Denmark: http://www.dst.dk/en/OmDS/organisation/TelefonbogOrg.aspx?kontor=13&tlfbogsort=sektion or the Danish Data Protection Agency: https://www.datatilsynet.dk/english/the-danish-data-protection-agency/contact/. More information regarding data access is available at https://www.dst.dk/en/TilSalg/Forskningsservice.

Databases

All residents in Denmark have a personal, unique, and permanent civil registration number that enables linkage of data between all nationwide administrative registries.

We used The Danish Civil Registration System[7] to collect data regarding age and gender. From The Danish National Patient Registry,[8] we obtained information about hospital admission dates, hospital discharge dates, discharge diagnoses, dates of operation, and procedure codes. Diagnoses are classified as primary and secondary according to World Health Organization *International Classification of Disease*. From 1994 and onwards the *International Classification of Disease, Tenth Revision* was in use. The Danish National Patient Registry covers information from 1978 until present time.

From The Danish National Prescription Registry,[9] information on each individual's drug redemption was collected. This register includes all dispensed prescriptions from all Danish pharmacies since 1995 based on the Anatomic Therapeutic Chemical system. The Danish healthcare system is state-financed and partly reimburses drug costs. For this reason, all Danish pharmacies are required by law to register all dispensed drug prescriptions, providing a complete overview of all prescriptions. From 1995, registries of laboratory data contain blood test results from 3 of the 5 regions in Denmark, covering ≈ 4 058 000 inhabitants.

Study Population and Design

Hypertension was defined as the redemption of at least 2 antihypertensive drugs in 2 consecutive quarters. Patients entered the study after the first occurrence of redeeming prescriptions for combination antihypertensive therapy in 2 subsequent quarters.[10] This time was referred to as the index date. Anatomic Therapeutic Chemical codes of the drugs used to define patients as having hypertension were included in Table S1 in the online-only Data Supplement. We defined hypertension as redemption of at least 2 antihypertensive drugs in at least 2 consecutive quarters for different reasons. First, by using Danish registries, it was difficult to ascertain whether patients were treated for hypertension with monotherapy only. The majority of the drugs used to treat high blood pressure can be used for other cardiovascular diseases, such as atrial fibrillation, heart failure, or myocardial infarction. Second, by using diagnosis code approach to identify patients with hypertension, we would have lost a considerable sample of patients as in many cases treatment and monitoring takes place in a primary care setting. In a study by Olesen et al,[10] this definition of hypertension was validated and the authors found that the positive predictive value of treatment with 2 classes of antihypertensive drugs was 80% and the specificity 94.7%.

The first potassium measurement within 90 days from index date was kept methods for blood potassium analysis have not been similar in all laboratories over the entire study period, having measured both serum and plasma potassium concentrations. As the normal ranges for the 2 methods of measuring blood potassium concentrations do not differ substantially, we referred to all measurements as serum potassium.

Exclusion criterias were age below 18 years, no potassium measurement up to 30 days before index date, hypokalemia, or hyperkalemia up to 30 days before index date, hyperkalemia at the first potassium measurement after combination therapy initiation and prescription of loop diuretics. The population flow chart with inclusion and exclusion criteria was shown in Figure S1.

This study used a nested case-control design. Using incidence density matching, 2 patients without hypokalemia (K, >3.5 mmol/L; n=926) were matched to each patient with hypokalemia (K, <3.5 mmol/L; n=463) on age, sex, renal function, and time between index date and date of potassium measurement.

Comorbidities, Procedures, and Concomitant Medication

The following discharge diagnoses present before index date were assessed to characterize the population: heart failure, ischemic heart disease, acute myocardial infarction, atrial fibrillation, atrial flutter, second- or third-degree atrioventricular block, ventricular tachycardia or fibrillation, stroke, chronic obstructive pulmonary disease, chronic liver disease, inflammatory bowel disease, diabetes mellitus, hypothyroidism, cancer, and stroke. None of the patients had a history of diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion, primary hyperaldosteronism, or Addison disease.

The kidney function of each patient was assessed by calculating the estimated glomerular filtration rate (eGFR),[11] and an eGFR <30 mL/(min·1.73 m^2) suggested renal insufficiency. This cutoff level was chosen, as we did not have information on whether patients had evidence of kidney damage (ie, albuminuria, hematuria, structural changes, or biopsy verification). Serum creatinine used to calculate eGFR was obtained within 7 days before potassium measurement, and patients with missing creatinine values were excluded.

From the Danish National Prescription Registry, we identified the following redeemed medication known to be associated with potassium disturbances: potassium supplements, antimicrobials, β2-agonists, mineralo- and glucocorticoids, laxatives, xanthines, and macrolides. Only potassium supplementation, antimicrobials, and β2-agonists were present in the nested case-control population. Potassium supplements were supplements as a single pill therapy combined with an antihypertensive (Anatomic Therapeutic Chemical C03) or as an individual pill (ATC A12B). Definitions of comorbidities and concomitant medication before index date were illustrated in Table S2.

Statistical Analyses

Categorical variables were reported as counts and percentages and continuous variables as medians with 25th to 75th percentiles. Differences between variables were compared using χ^2 and Kruskal-Wallis tests, as appropriate.

An incident episode of hypokalemia was defined as a blood potassium level <3.5 mmol/L within 90 days from index date.

Cumulative incidence proportion curves for developing hypokalemia in patients treated with combination antihypertensive therapy, who had available potassium measurements within 90 days from index date and no potassium imbalances up to 30 days before index date, were estimated.

The independent variable defining the different possible combinations of antihypertensive treatment was coded as a dummy variable with the 10 most frequent possibilities identified in the population:

1. BB (β-blockers)+CCB
2. BB+RASi (renin-angiotensin system inhibitors)
3. BB+RASi+mineral receptor antagonist
4. BB+RASi+thiazides
5. BB+thiazides
6. CCB+RASi (reference)
7. CCB+RASi+thiazides
8. CCB+thiazides
9. RASi+thiazides
10. Other combinations.

Antihypertensive drug groups 1, 6, 7, and 8 referred to combinations of CCBs with other blood pressure drugs. However, these groups only contain one type of CCBs, namely dihydropyridine derivatives, such as amlodipine. Conditional logistic regression analysis was used to estimate the odds ratio and 95% CI between different combination therapies and developing hypokalemia with CCB+RASi as reference.

When investigating the association between hypokalemia and the 10 antihypertensive drug groups the model was adjusted for initial serum sodium, malignancy, inflammatory bowel disease, diabetes mellitus, and chronic liver disease.

As some of the antihypertensive drug combinations can also indicate cardiovascular diagnoses other than hypertension, we performed a sensitivity analysis where we also matched the controls on history with ischemic heart disease/myocardial infarction and heart failure.

A 2-Sided *P* Value <0.05 was considered statistically significant since not every patient with hypertension, treated with combination therapy, had a potassium measurement available within 90 days from treatment initiation, we also looked at the prevalence of different comorbidities between our population and the general population with no potassium concentrations within the predefined timeline.

Data management and analyses were performed using SAS, version 9.4 (SAS Institute, Inc, Cary, NC) and R, version 3.5.1 (R Core Team [2018]). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/.

Ethics

The Danish Data Protection Agency approved the use of data (reference: 2007-58-0015, internal reference: GEH-2014-015, I-Suite number: 02733). By Danish law, ethical approval is not required for retrospective registry-based studies.

Results

Demographics

Population characteristics of the cohort, from which cases and controls were identified and matched on different variables, were illustrated in Table S3. During 1995 to 2018, 11 896 patients treated for hypertension with combination therapies had a potassium measurement within 90 days of index date. Among the patients, 3.9% had potassium concentrations below 3.5 mmol/L. Furthermore, we observed that 48.5% of the patients redeemed thiazides, of which 1.6% were thiazide-like diuretics and 45% hydrochlorothiazides. Additionally, 31.8% of the population was prescribed potassium supplements, of which 86.7% represented potassium chloride as single pill combined with an antihypertensive.

After matching on age, sex, eGFR, renal insufficiency, and time from index date to potassium measurement, we ended up with 463 cases and 926 controls. Median time from index date to potassium measurement was 30 days (0, 90). Following proportions were observed in each of the 10 combination antihypertensive therapies: BB+CCB 4.3%, BB+RASi 16.9%, BB+RASi+mineral receptor antagonist 3.2%, BB+RASi+thiazides 4.0%, BB+thiazides 4.4%, CCB+RASi 12.5%, CCB+RASi+thiazides 6.5%, CCB+thiazides 6.7%, RASi+thiazides 12.2%, and Other combinations 12.2% (Table).

We also observed higher prevalence of hypokalemia in patients redeeming CCB+thiazides (12.1%) and RASi+thiazides (30.7%) than in patients treated with any of the other drug groups. Among the cases (with hypokalemia), 45.8% redeemed potassium supplement.

Antihypertensive Combination Therapies and Risk of Hypokalemia

Figure S2 illustrated the cumulative incidence proportion of hypokalemia in patients treated with combination antihypertensive therapy who had available potassium measurements within 90 days of the index date and no potassium imbalances up to 30 days before index date (n=11 896). After stratifying on the 10 combination therapies the cumulative incidence curves showed that the combination of CCB+thiazides had a significantly higher incidence of hypokalemia than the other groups (about 10%; Figure S3).

In the nested case-control population the adjusted conditional logistic regression analysis with CCB+RASi as reference showed 5.82× increased odds for development of hypokalemia if administered CCB+thiazides (95% CI, 3.06–11.08). Moreover, patients on BB+thiazides had an odds ratio of 3.34 for developing hypokalemia (95% CI, 1.67–6.66). Other drug combinations significantly associated with increased hypokalemia risk were CCB+RASi+thiazides (odds ratio, 3.07 [95% CI, 1.72–5.46]) and BB+RASi+thiazides (odds ratio, 2.78 [95% CI, 1.41–5.47]; Figure). The univariable analysis showed similar results (Figure S4).

Sensitivity Analyses

We performed an additional conditional logistic regression analysis on a population matched on age, sex, eGFR, renal insufficiency, time from index date to potassium measurement, heart failure, and ischemic heart disease/myocardial infarction. The results were similar to the main analyses, though with slightly lower effect sizes (Figure S5 and Figure S6).

We also looked at differences in comorbidity proportions in our nested case-control population versus general population treated with combination antihypertensive therapy who did not have available serum potassium measurements within 90 days from index date. We observed that nearly all comorbidities had higher rates in the nested case-control population than in the general population. See Table S4 and the Table for general population demographics.

Discussion

The main findings in this article were (1) hypokalemia among patients treated with combination antihypertensive therapies was common, (2) the 3 antihypertensive drug combinations with the highest odds of developing hypokalemia were CCB+thiazides, BB+thiazides, CCB+RASi+thiazides.

Current guidelines recommend combination antihypertensive drug treatment strategies in patients not achieving targeted blood pressure.[1] Pharmacologically, the great majority of the patients in this study were treated with combination therapies with opposite effects on potassium homeostasis. Despite this approach, the occurrence of hypokalemia remained high considering the short study period. A large scale Swedish study investigating determinants of hyperkalemia and hypokalemia showed that patients with hypertension had 1.80 and 1.05× higher odds of developing hypokalemia and hyperkalemia within 3 years, respectively.[12] This is in line with our findings where we observed increased odds of hypokalemia related to some specific antihypertensive combination therapies. Yet, the 2 studies are not utterly comparable as we both had different approaches for defining hypertension (*International Classification of Disease* codes versus 2 concomitant antihypertensive drugs) and different aims.

Comparison of our findings with other studies was difficult, as the great majority of previous articles focused on outcomes like stroke and cardiovascular events[1] instead of dyskalemias. We found that CCB+thiazides, CCB+RASi+thiazides, and BB+thiazides were highly associated with increased risk of hypokalemia when compared with CCB+RASi. In the following paragraphs, each of the drug combinations and their association to hypokalemia will be discussed.

Table. Demographics of the Matched Population

	Controls (n=926)	Cases (n=463)	Total (n=1389)	*P* Value
Sex				
Female	484 (52.3)*	242 (52.3)*	726 (52.3)*	1.0*
Age, median (range)	65.0 (21.0–95.0)*	66.0 (23.0–95.0)*	65.0 (21.0–95.0)*	0.55*
Days from hypertension to potassium measurement, median (range)	30.0 (0.0–90.0)*	31.0 (0.0–90.0)*	30.0 (0.0–90.0)*	0.68*
Serum sodium, median (range)	140.0 (113.0–146.0)*	140.0 (118.0–148.0)*	140.0 (113.0–148.0)*	0.15*
Renal insufficiency	10 (1.1)*	5 (1.1)*	15 (1.1)*	1.0*
eGFR, median (range)	77.0 (10.0–214.0)	79.0 (7.0–222.0)	78.0 (7.0–222.0)	0.32
Treatment combinations				
BB+CCB	41 (4.4)	19 (4.1)	60 (4.3)	
BB+RASi	195 (21.1)	40 (8.6)	235 (16.9)	
BB+RASi+MRA	40 (4.3)	4 (0.9)	44 (3.2)	
BB+RASi+thiazides	33 (3.6)	23 (5.0)	56 (4.0)	
BB+thiazides	32 (3.5)	29 (6.3)	61 (4.4)	
CCB+RASi	134 (14.5)	40 (8.6)	174 (12.5)	
CCB+RASi+thiazides	49 (5.3)	42 (9.1)	91 (6.6)	
CCB+thiazides	37 (4.0)	56 (12.1)	93 (6.7)	
RASi+thiazides	264 (28.5)	142 (30.7)	406 (29.2)	
Other combinations	101 (10.9)	68 (14.7)	169 (12.2)	< 0.0001
Heart failure	153 (16.5)	30 (6.5)	183 (13.2)	< 0.0001
IHD/MI	224 (24.2)	68 (14.7)	292 (21.0)	< 0.0001
COPD	56 (6.0)	30 (6.5)	86 (6.2)	0.84
Diabetes mellitus	121 (13.1)	41 (8.9)	162 (11.7)	0.03
Chronic liver disease	24 (2.6)	9 (1.9)	33 (2.4)	0.57
Hemodialysis	≤3	≤3	≤6	…
Malignancy	115 (12.4)	73 (15.8)	188 (13.5)	0.10
Stroke	83 (9.0)	55 (11.9)	138 (9.9)	0.11
Atrial flutter/fibrillation	120 (13.0)	41 (8.9)	161 (11.6)	0.03
Atrioventricular block	13 (1.4)	≤3	≤16	…
VT/VF	36 (3.9)	13 (2.8)	49 (3.5)	0.38
Inflammatory bowel disease	16 (1.7)	11 (2.4)	27 (1.9)	0.54
Hypothyroidism	18 (1.9)	9 (1.9)	27 (1.9)	1.0
Potassium supplement	312 (33.7)	212 (45.8)	524 (37.7)	< 0.0001
Antimicrobials	≤3	≤3	≤6	…
β-2 agonists	≤3	≤3	≤6	…

Potassium supplement addressed supplementation as a single pill therapy with an antihypertensive and as an individual pill. We attribute <=3 to variables with values between 1 and 3 to secure anonymity and protection of personal data. BB indicates β-blockers; CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; IHD/MI, ischemic heart disease/myocardial infarction; MRA, mineral receptor antagonist; RASi, renin-angiotensin system inhibitors; and VT/VF, ventricular tachycardia/ventricular fibrillation.

*Variables represent the variables we matched on.

CCB+Thiazides

A meta-analysis based on the results of 4 randomized trials investigated the efficacy and safety of CCBs and thiazide (-like) diuretics. The authors observed that the most frequent adverse event related to CCB+diuretic combination was hypokalemia.[13] Because of the insufficient knowledge about dyskalemias caused by CCB+thiazides, we searched literature treating the 2 drugs individually. There is little recent knowledge on the effect of CCB on potassium homeostasis either in large or small-scale studies. On one hand, numerous

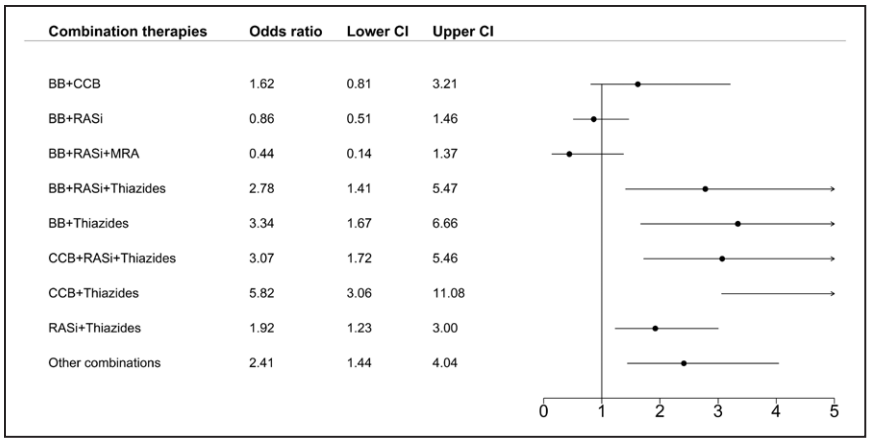


Figure. Forestplot of multivariable conditional logistic regression analysis for the development of hypokalemia. Population matched on age, sex, renal insufficiency, and time index date initiation to serum potassium measurement. The model was adjusted for serum sodium, renal insufficiency, malignancy, inflammatory bowel disease, diabetes mellitus, alcoholism, and chronic liver disease. The combination of calcium channel blockers with renin-angiotensin system inhibitors was used as reference. BB indicates β-blockers; CCB, calcium channel blockers; MRA, mineral receptor antagonist; and RASi, renin-angiotensin system inhibitors.

in vitro, in vivo and case report publications reported hyperkalemia following initiation of CCB.[14–19] On the contrary, case studies and studies on rats showed hypokalemia in relation to administration of CCB.[20–25] As for thiazide diuretics, numerous studies showed that monotherapy is associated with development of hypokalemia.[26–28] The mechanisms through which the 2 drug types lead to hypokalemia seemed to be very different: thiazides enhance renal potassium disposal, while CCBs augment extrarenal loss of potassium.[21,29–31] However, the mechanisms through which CCB can cause both hypo- and hyperkalemia are poorly elucidated.

CCB+RASi+Thiazides

No study directly compared the risk of hypokalemia related to this combination therapy in relation to other combination therapies. Most studies compare the risk of hypokalemia in patients treated with thiazides alone versus different combinations of antihypertensive drugs with complementary effect on potassium homeostasis.[32]

BB+Thiazides

The combination of BB and thiazides is no longer first-line treatment of arterial hypertension but certainly an effective combination in prevention of adverse cardiovascular events.[1] To our knowledge, no study reported increased hypokalemia risk in patients prescribed BB+thiazides. Although we do know that use of thiazides diuretics can lead to hypokalemia,[33] while use of some BB is associated with increased hyperkalemia risk especially in patients with renal dysfunction and insulin insufficiency.[33]

Our results suggested that high odds of hypokalemia were strongly related to the use of thiazides as they were present in each of the combination therapy groups with significant increased odds of low potassium concentrations. This adverse effect was also observed in patients administered potassium supplements.

Should we be concerned about hypokalemia? Both hypokalemia and hyperkalemia have previously been shown to be associated with increased risk of all-cause mortality[6,34,35] and cardiovascular disease[36] in different populations with heart disease. Regarding patients with hypertension, current studies have discrepant results. In a previous study, we found that potassium concentrations outside the interval 4.1 to 4.7 mmol/L were associated with increased mortality risk.[6] Contrarily, Franse et al[37] found no significant difference in the relative risk of all-cause mortality for participants who received low-dose chlorthalidone and who experienced hypokalemia compared with placebo group. Additionally, Alderman et al[38] observed a higher all-cause mortality (hazard ratio, 1.21) in patients with hypokalemia than in normokalemics. However, the authors also found heterogeneity in hazard ratios across the 3 treatment arms (chlorthalidone, amlodipine, and lisinopril). Comparison of the 3 studies is difficult as the only common features were that patients were treated for hypertension and had their blood potassium measured. Yet, there are 2 very essential differences in these studies that could explain the discrepancy in results, namely the burden of disease. First, in our large epidemiological study, we included patients who redeemed at least 2 concomitant antihypertensive drugs,[6] while the randomized trials either compare monotherapy with placebo or monotherpies within themselves. Undoubtely, patients included in the epidemiological study had more advanced hypertension that the patients in the randomized trials.

Second, the time when mortality was assessed could be a strong influencer of the results. The randomized trials used year-1 potassium measurement to investigate long-term mortality (y), while we examined the effect of different potassium concentrations measured within 90 days from combination antihypertensive therapy on 90 days all-cause mortality.[6,37,38] Ultimately, we believe that hypokalemia is an important risk factor or risk marker of cardiovascular disease and mortality. Yet, further studies are needed to explain which patients are at high risk of adverse effects after an episode of hypokalemia.

Limitations

Most of the limitation were related to the observational nature of the study design meaning that unmeasured confounding such as vomiting, diarrhea, and diet may affect our findings. Information on the clinical indication for blood tests or symptoms of dyskalemias and electrocardiographic changes were not available. However, according to guidelines patients with hypertension need to have their blood pressure monitored and standard blood test performed within 3 to 6 months of treatment initiation. Therefore, we believe that cases where clinicians specifically test for potassium imbalances in our population are negligible.

Furthermore, due to the short follow-up time, it was difficult to calculate dosage of redeemed antihypertensive drugs.

Therefore, compliance issues or overdose could not be identified for any of the drug groups, which can lead to nondifferential misclassification.

Finally, the fact that potassium concentrations were measured in both serum and plasma within the different laboratories over the years is an inevitable limitation, due to cases with misclassification of the patients. Reference ranges for normal serum potassium and plasma potassium concentrations do not differ substantially. The Nordic Reference Interval Project recommends that an interval of 3.6 to 4.6 mmol/L is considered to be normal for serum potassium, whereas an interval of 3.5 to 4.4 mmol/L is suggested to be normal for plasma potassium.[39] False-positive hyperkalemia was presumably uncommon as all laboratories left out reporting of potassium values in presence of hemolysis.

Conclusions

Combinations of thiazide diuretics with CCB, RASi, or BB were strongly associated with increased hypokalemia risk within 90 days of treatment initiation, regardless of potassium supplementation.

Perspectives

Focus on optimal management of hypertension in clinical practice is emphasized in the current practice due to the numerous studies showing benefits both related to the risk of death but also to cardiovascular comorbidity and health-related quality of life.[40,41] Hypo- and hyperkalemia are common side effects of the drugs used to treat hypertension. Awareness of the risk factors associated with potassium disturbances is important to identify patients at risk. For example, our study strongly suggested that patients treated with CCB+thiazides had an increased probability of developing hypokalemia within 90 days from index date, despite potassium supplementation. Therefore, it would be prudent to recommend identifying and closely monitoring patients at high risk of potassium imbalances as important goals in everyday clinical settings.

Sources of Funding

This study was funded using departmental funding sources only.

Disclosures

None.

References

1. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, et al; ESC Scientific Document Group. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39:3021–3104. doi: 10.1093/eurheartj/ehy339
2. Sica DA. Antihypertensive therapy and its effects on potassium homeostasis. *J Clin Hypertens (Greenwich)*. 2006;8:67–73. doi: 10.1111/j.1524-6175.2006.05139.x
3. Kjeldsen K. Hypokalemia and sudden cardiac death. *Exp Clin Cardiol*. 2010;15:e96–e99.
4. Ravens U, Cerbai E. Role of potassium currents in cardiac arrhythmias. *Europace*. 2008;10:1133–1137. doi: 10.1093/europace/eun193
5. Bowling CB, Pitt B, Ahmed MI, Aban IB, Sanders PW, Mujib M, Campbell RC, Love TE, Aronow WS, Allman RM, et al. Hypokalemia and outcomes in patients with chronic heart failure and chronic kidney disease: findings from propensity-matched studies. *Circ Heart Fail*. 2010;3:253–260. doi: 10.1161/CIRCHEARTFAILURE.109.899526
6. Krogager ML, Torp-Pedersen C, Mortensen RN, Køber L, Gislason G, Søgaard P, Aasbjerg K. Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. *Eur Heart J*. 2017;38:104–112. doi: 10.1093/eurheartj/ehw129
7. Pedersen CB. The danish civil registration system. *Scand J Public Health*. 2011;39(7 suppl):22–25. doi: 10.1177/1403494810387965
8. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The danish national patient registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449–490. doi: 10.2147/CLEP.S91125
9. Kildemoes HW, Sørensen HT, Hallas J. The danish national prescription registry. *Scand J Public Health*. 2011;39(7 suppl):38–41. doi: 10.1177/1403494810394717
10. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2011;342:d124. doi: 10.1136/bmj.d124
11. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612. doi: 10.7326/0003-4819-150-9-200905050-00006
12. Nilsson E, Gasparini A, Ärnlöv J, Xu H, Henriksson KM, Coresh J, Grams ME, Carrero JJ. Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system. *Int J Cardiol*. 2017;245:277–284. doi: 10.1016/j.ijcard.2017.07.035
13. Rimoldi SF, Messerli FH, Chavez P, Stefanini GG, Scherrer U. Efficacy and safety of calcium channel blocker/diuretics combination therapy in hypertensive patients: a meta-analysis. *J Clin Hypertens (Greenwich)*. 2015;17:193–199. doi: 10.1111/jch.12462
14. Fakunding JL, Catt KJ. Dependence of aldosterone stimulation in adrenal glomerulosa cells on calcium uptake: effects of lanthanum nd verapamil. *Endocrinology*. 1980;107:1345–1353. doi: 10.1210/endo-107-5-1345
15. Foster R, Lobo MV, Rasmussen H, Marusic ET. Calcium: its role in the mechanism of action of angiotensin II and potassium in aldosterone production. *Endocrinology*. 1981;109:2196–2201. doi: 10.1210/endo-109-6-2196
16. Schiffrin EL, Lis M, Gutkowska J, Genest J. Role of Ca2+ in response of adrenal glomerulosa cells to angiotensin II, ACTH, K+, and ouabain. *Am J Physiol*. 1981;241:e42-e46. doi: 10.1152/ajpendo.1981.241.1.E42
17. Blanchouin-Emeric N, Zenatti M, Defaye G, Aupetit B. Verapamil directly inhibits aldosterone synthesis by adrenal mitochondria in vitro. *J Steroid Biochem*. 1988;30:453–456. doi: 10.1016/0022-4731(88)90141-0
18. Imamura T, Matsuura Y, Nagoshi T, Ishikawa T, Date H, Kita T, Matsuyama A, Matsuo T, Eto T. Hyperkalemia induced by the calcium channel blocker, benidipine. *Intern Med*. 2003;42:503–506. doi: 10.2169/internalmedicine.42.503
19. BenSalem C, Badreddine A, Fathallah N, Slim R, Hmouda H. Drug-induced hyperkalemia. *Drug Saf*. 2014;37:677–692. doi: 10.1007/s40264-014-0196-1
20. Sugarman A, Kahn T. Calcium channel blockers enhance extrarenal potassium disposal in the rat. *Am J Physiol*. 1986;250(4 pt 2):F695–F701. doi: 10.1152/ajprenal.1986.250.4.F695
21. Minella RA, Schulman DS. Fatal verapamil toxicity and hypokalemia. *Am Heart J*. 1991;121(6 pt 1):1810–1812. doi: 10.1016/0002-8703(91)90033-e
22. Freed MI, Rastegar A, Bia MJ. Effects of calcium channel blockers on potassium homeostasis. *Yale J Biol Med*. 1991;64:177–186.
23. Popiliev I, Angelova I, Kundurdzhiev A. [Hypokalemia caused by nifedipine]. *Vutr Boles*. 1990;29:126–129.
24. Tishler M, Armon S. Nifedipine-induced hypokalemia. *Drug Intell Clin Pharm*. 1986;20:370–371. doi: 10.1177/106002808602000507
25. Soliman AR, Akmal M, Massry SG. Parathyroid hormone interferes with extrarenal disposition of potassium in chronic renal failure. *Nephron*. 1989;52:262–267. doi: 10.1159/000185654
26. Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension*. 2006;48:219–224. doi: 10.1161/01.HYP.0000231552.10054.aa
27. Rodenburg EM, Visser LE, Hoorn EJ, Ruiter R, Lous JJ, Hofman A, Uitterlinden AG, Stricker BH. Thiazides and the risk of hypokalemia in the general population. *J Hypertens*. 2014;32:2092–2097; discussion 2097. doi: 10.1097/HJH.0000000000000299
28. Sica DA, Carter B, Cushman W, Hamm L. Thiazide and loop diuretics. *J Clin Hypertens (Greenwich)*. 2011;13:639–643. doi: 10.1111/j.1751-7176.2011.00512.x

29. Bettinelli A, Bianchetti MG, Girardin E, Caringella A, Cecconi M, Appiani AC, Pavanello L, Gastaldi R, Isimbaldi C, Lama G. Use of calcium excretion values to distinguish two forms of primary renal tubular hypokalemic alkalosis: bartter and gitelman syndromes. *J Pediatr*. 1992;120:38–43. doi: 10.1016/s0022-3476(05)80594-3
30. Okusa MD, Velázquez H, Ellison DH, Wright FS. Luminal calcium regulates potassium transport by the renal distal tubule. *Am J Physiol*. 1990;258(2 pt 2):F423–F428. doi: 10.1152/ajprenal.1990.258.2.F423
31. Sands JM, Naruse M, Baum M, Jo I, Hebert SC, Brown EM, Harris HW. Apical extracellular calcium/polyvalent cation-sensing receptor regulates vasopressin-elicited water permeability in rat kidney inner medullary collecting duct. *J Clin Invest*. 1997;99:1399–1405. doi: 10.1172/JCI119299
32. Calhoun DA, Lacourcière Y, Chiang YT, Glazer RD. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: a randomized clinical trial. *Hypertension*. 2009;54:32–39. doi: 10.1161/HYPERTENSIONAHA.109.131300
33. Kotchen TA. Antihypertensive therapy-associated hypokalemia and hyperkalemia: clinical implications. *Hypertension*. 2012;59:906–907. doi: 10.1161/HYPERTENSIONAHA.112.192526
34. Krogager ML, Eggers-Kaas L, Aasbjerg K, Mortensen RN, Køber L, Gislason G, Torp-Pedersen C, Søgaard P. Short-term mortality risk of serum potassium levels in acute heart failure following myocardial infarction. *Eur Heart J Cardiovasc Pharmacother*. 2015;1:245–251. doi: 10.1093/ehjcvp/pvv026
35. Aldahl M, Jensen AC, Davidsen L, Eriksen MA, Møller Hansen S, Nielsen BJ, Krogager ML, Køber L, Torp-Pedersen C, Søgaard P. Associations of serum potassium levels with mortality in chronic heart failure patients. *Eur Heart J*. 2017;38:2890–2896. doi: 10.1093/eurheartj/ehx460
36. Toto RD. Serum potassium and cardiovascular outcomes: the highs and the lows. *Clin J Am Soc Nephrol*. 2017;12:220–221. doi: 10.2215/CJN.00030117
37. Franse LV, Pahor M, Di Bari M, Somes GW, Cushman WC, Applegate WB. Hypokalemia associated with diuretic use and cardiovascular events in the systolic hypertension in the elderly program. *Hypertension*. 2000;35:1025–1030. doi: 10.1161/01.hyp.35.5.1025
38. Alderman MH, Piller LB, Ford CE, Probstfield JL, Oparil S, Cushman WC, Einhorn PT, Franklin SS, Papademetriou V, Ong ST, et al; Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Clinical significance of incident hypokalemia and hyperkalemia in treated hypertensive patients in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension*. 2012;59:926–933. doi: 10.1161/HYPERTENSIONAHA.111.180554
39. Rustad P, Felding P, Franzson L, Kairisto V, Lahti A, Mårtensson A, Hyltoft Petersen P, Simonsson P, Steensland H, Uldall A. The nordic reference interval project 2000: recommended reference intervals for 25 common biochemical properties. *Scand J Clin Lab Invest*. 2004;64:271–284. doi: 10.1080/00365510410006324
40. Arima H, Barzi F, Chalmers J. Mortality patterns in hypertension. *J Hypertens*. 2011;29(suppl 1):S3–S7. doi: 10.1097/01.hjh.0000410246.59221.b1
41. Soni RK, Porter AC, Lash JP, Unruh ML. Health-related quality of life in hypertension, chronic kidney disease, and coexistent chronic health conditions. *Adv Chronic Kidney Dis*. 2010;17:e17–e26. doi: 10.1053/j.ackd.2010.04.002

Novelty and significance

What Is New?

- Patients treated with thiazide diuretics in combination with calcium antagonists, β-blockers, or renin-angiotensin system inhibitors had an increased hypokalemia risk within 90 days from combination therapy initiation.
- Increased hypokalemia risk was observed also in patients administered potassium supplements.

What Is Relevant?

- Increased hypokalemia risk was present despite all patients being treated with combination of antihypertensive drugs with opposite effect on potassium homeostasis and despite supplementation with potassium in some of the cases.
- Low potassium concentrations have previously been associated with arrhythmogenesis and increased mortality risk in patients with hypertension.

Summary

In this register study comprising 463 patients with hypokalemia and 926 patients with normal potassium concentrations, we observed that combination of thiazides with β-blockers, calcium channel blockers, and renin-angiotensin system inhibitors had increased hypokalemia risk compared with the combination of calcium antagonists with renin-angiotensin system inhibitors.

ISSN (online): 2246-1302
ISBN (online): 978-87-7210-804-9

AALBORG UNIVERSITY PRESS