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

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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

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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

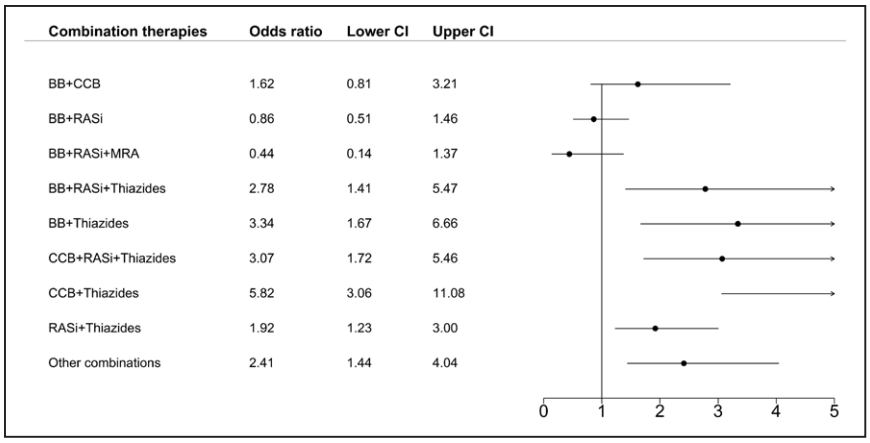

Figure. Forestplot of multivariable conditional logistic regression analysis for the development of hypokalemia. Population matched on age, sex, renal insufficiency, and time index date initiation to serum potassium measurement. The model was adjusted for serum sodium, renal insufficiency, malignancy, 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.

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Disclosures

None.

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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.