ARTICLE

Dyskalemia risk associated with fixed-dose anti-hypertensive medication combinations

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A model-based meta-analysis quantified comparative dyskalemia risk (hyper- or hypo-kalemia) in hypertensive patients treated with angiotensin receptor blockers (ARBs), a calcium channel blocker (CCB) and/or a thiazide diuretic (hydrochlorothiazide; HCTZ) as monotherapy or as fixed-dose combinations. Among 15 randomized controlled trials in a US Food and Drug Administration regulatory review database, dyskalemia events were reported by five trials (24 treatment arms, 11,030 subjects, 8-week median follow up time). The five trials evaluated monotherapy (ARB or HCTZ) alongside dual (ARB + HCTZ, ARB + CCB, or HCTZ + CCB) or triple fixed-dose combinations (ARB + CCB + HCTZ). Hypo- and hyper-kalemia rates were analyzed jointly to account for correlation. Significant drug class, drug, or dose effects were included in the final model. Effect on various drug- and dose combinations on dyskalemia risk were simulated and compared with model-estimated placebo arm dyskalemia risk. After a typical follow-up of 8 weeks, fixed-dose combinations of ARB with a high dose (25 mg) of HCTZ were associated with a higher hypokalemia risk difference (RD) from placebo (e.g.,Valsartan + HCTZ: 2.52%[95%CIs:1.17, 4.38%]). However, when ARB was combined with a lower, 12.5 mg dose of HCTZ, hypokalemia RD from placebo was not significant (Valsartan + HCTZ: −0.03%[−0.80, 0.71%]). ARB monotherapy raised hyperkalemia RD from placebo (1.3%[0.3, 3.6%]). Hyperkalemia risk was not appreciably higher than placebo for any FDC that combined ARB with HCTZ (Valsartan + HCTZ: 0.06%[−1.48, 1.64%]). In uncomplicated hypertensive patients, ARB + 12.5 mg HCTZ fixed-dose combinations are safer with respect to dyskalemia than either ARB or HCTZ monotherapy for initial antihypertensive treatment.

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INTRODUCTION

Guidelines for the management of hypertension recommend using initial monotherapy for most treatment-naive patients, include any one of either thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACE-I), or angiotensin receptor blocker (ARB), with addition of a second drug from one of the classes if monotherapy is ineffective [1]. In practice, about 75% of patients require at least two anti-hypertensive medications to reach their guideline-recommended blood pressure goal [2]. Initial fixed-dose combination (FDC) anti-hypertensive medication therapy is superior to initial monotherapy in terms of greater blood pressure-lowering effect and shorter time to blood pressure control [3].

Recommended anti-hypertensive medications are widely prescribed and very safe, but are occasionally associated with adverse events, including dyskalemia. Thiazide or thiazide-like diuretics increase risk of *hypo*kalemia [4]. Thiazides can induce hypokalemia via increased aldosterone triggered by hypovolemia and increased delivery of sodium to the distal tubule of the nephron, which together drive increased renal potassium secretion and loss [5]. ACEI's and ARBs can induce hyperkalemia by blocking aldosterone release and decreasing delivery of sodium delivery and increasing potassium resorption at the distal tubule [6, 7]. Combining anti-hypertensive medication classes may minimize these risks: e.g., raised potassium from an ARB may be offset by thiazide-induced potassium lowering. Effects of anti-hypertensive drugs on potassium regulation may be dose dependent. Quantification of dyskalemia risk across major anti-hypertensive drug class and dose combinations may identify an optimal combination that minimizes dyskalemia risk, making blood-pressure lowering treatment safer for patients.

Even major antihypertensive medication clinical trials are powered to detect only composite adverse event outcome differences, and little is known about the specific risks of dyskalemia due to different doses and dose-combinations of anti-hypertensive medications. As a result, optimal class and dose combinations of FDCs remain poorly understood. Model-based meta-analyses (MBMA) is a robust regression-based technique based on network meta-analysis concepts that estimates dose-dependent drug treatment effects, possible drug interactions, and patient risk characteristics across different clinical trials, and has been applied to inform decision making at various stages of drug development [8–11].

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The objective of this MBMA of anti-hypertensive medication regulatory trials is to yield an independent estimate of the comparative dyskalemia (hyper- and hypokalemia) risk associated with widely used anti-hypertensive monotherapies and FDCs.

MATERIALS AND METHODS

Review and trials inclusion

An initial systematic review searched for randomized controlled trials published in PubMed up until March 2020, using keywords "hypertension OR hypertensive" indication, intervention on "ARBs AND amlodipine AND (fixed or combination or add-on) AND (chlorthalidone or hydrochlorothiazide)" and restricted to articles published in English. A review of eligible 64 references with at least one arm using a combination therapy containing ARBs, amlodipine, chlorthalidone, or hydrochlorothiazide revealed sparse or inconsistent reporting on dyskalemia outcomes. We therefore turned to evaluating randomized controlled trials (RCTs) of various anti-hypertension treatment combinations identified from regulatory reviews [U.S. Food and Drug Administration or European Medicines Authority]. We then reviewed these trials of anti-hypertensive therapies for reporting on dyskalemia endpoints (hyperkalemia or hypokalemia event rate, as detected by the trials' scheduled laboratory measurements of serum potassium levels). The primary treatment combinations were limited to drug classes of CCB (amlodipine), ARBs, diuretic (hydrochlorothiazide, HCTZ) and ACE-Is. Summary level clinical safety information on dyskalemia from 15 RCTs were identified. No trials reported on dyskalemia related to combination medicines including ACE-Is. Dyskalemia events were defined by laboratory-measured serum potassium changes from baseline (increase or decrease) of >20% or >0.5 mmol/L, or absolute values <3.5 mmol/L (hypokalemia) or >5.0 mmol/L (hyperkalemia) [12] in the five RCTs.

Meta-analysis of dyskalemia response rates

A joint response model describing the proportion of patients with hypo- or hyperkalemia response rates were analyzed jointly to appreciate the correlation between these event rates within each treatment arm. The probability of dyskalemia endpoint *k* was described as the inverse logit (log-odds) sum of an unstructured placebo response in trial *i* (eo_i) and an event in active treatment arm *j* of trial *i* (Eq. 1):

$$P(event)_{ijk} = inverse\ logit\left(eo_{ik} + f\left(drug_{ijk}, dose_{ijk}, \theta_{ik}\right)\right) \quad (1)$$

Treatment response f() represented the log odds-ratio (log OR) of endpoint k between treatment arm *j* in the trial *i*, and its corresponding placebo arm, and it consisted of drug effect of $drug_{ijk}$, and, if detected, dose response ($dose_{ijk}$) of related drug. We also tested separate parameters for low and high therapeutic doses for each drug to capture dose effects [e.g., $f(HCTZ)_{dose,12.5}$ for low HCTZ dose; $f(HCTZ)_{dose25}$ for high HCTZ dose]. These relationships were characterized as fixed effects (θ_{ik}).

A general interaction model between drug class and monotherapy versus FDC accounted for non-additivity of drug classes in the combination product (Eq. 2):

$$f(combi) = f(ARB) + f(HCTZ) + f(CCB) + int_{ARB+HCTZ} \cdot f(ARB_{class}) \cdot f(HCTZ_{class}) + int_{ARB+CCB} \cdot f(ARB_{class}) \cdot f(CCB_{class}) \quad (2)$$

In this equation, *f*(*combi*) is the effect of the combination treatment; *f*(*ARB*) could be a drug class or drug-within-class specific effect. The magnitude of the interactions for dual or triple FDCs was characterized by the additional interaction coefficient *int*, and further accounts for non-additivity of drug class effect. An *int* of zero indicates completely independent class effects, that is, that the combined effect was the sum of the two or more drug classes. A positive *int* indicates that the dyskalemia effect was more than the sum of the two individual drug class effects, while a negative *int* indicates a less than additive effect.

The number of patients with dyskalemia event k in treatment arm *j* of trial *i* $N_{event,ijk}$ was assumed to follow a binomial distribution with probability of event $P(event)_{ijk}$ and sample size N_{ijk} (Eq. 3):

$$N_{event.ijk} \sim binomial\left(N_{ijk}, P(event)_{ijk}\right) \quad (3)$$

Each observation was weighted based on variance function for a binary endpoint k in treatment arm *j* of study *i* with probability of event $P(event)_{ijk}$ and sample size N_{ijk}(Eq. 4):

$$\sigma^2_{ik} = P(event)_{ijk}(1 - P(event)_{ijk})/N_{ijk}\Big) \quad (4)$$

Since the true probability of event $P(event)_{ijk}$ is unknown, the best estimate from the fitting algorithm was used in the model. The maximum likelihood estimates of the model parameters were obtained assuming a large sample size normal approximation to the binomial likelihood.

The correlation between of hyper- and hypokalemia event rates within each trial arm was accounted for by assuming a compound symmetry correlation structure. Although the addition of an interaction terms—between ARB + HCTZ on both hyperkalemia and hypokalemia, and ARB +CCB on hyperkalemia—did not statistically improve model fit, the interaction term was included in the model to address the possibility of combination effect among drug classes.

The absolute and drug treatment effect vs. placebo were presented as risk difference (RD) and log OR of drug for endpoint k response as shown by Eqs. 5 and 6.

$$RD_k = inverse\ logit(eo_k + f(drug_k)) - inverse\ logit(eo_k) \quad (5)$$

$$Log\ OR = f(drug_k) \quad (6)$$

eo_k was a typical placebo reponse for endpoint k, and $f(drug_k)$ was log OR of drug vs. placebo.

Candidate models were evaluated with maximum likelihood criteria [Akaike Information Criterion (AIC); p value of <0.05 used to define statistical significance] and graphical diagnostics, with observed response plotted against population and trial-specific predictions in order to evaluate the overall goodness-of-fit plots (precision, absence of bias). In forest plots, model predictions for each study arm (vertical bars in the forest plots presented in this report) are compared to observed values (including confidence intervals). In order to construct confidence intervals for expected dyskalemia event rates for the relevant drug combination treatments, a total of 1,000 sets of model parameter estimates were resampled from the variance-covariance matrix of the final model for dyskalemia event rate. These analyses were conducted using generalized least squares regression function (gnls) provided in the nlme package in R (version 3.5.3 or later, 64 bit).

RESULTS

Trial and patient characteristics

Five randomized controlled trials of anti-hypertensive medication FDCs with dyskalemia events reported according to our pre-defined definitions were included in the meta-analysis (Table 1). Two of the five trials included a placebo arm and only one included ARB and HCTZ monotherapy arms. The dataset included dyskalemia data from a total of 11,029 subjects treated with HCTZ or ARB monotherapy or combination treatment (ARB+CCB, ARB +HCTZ, HCZ+CCB, or ARB+CCB+HCTZ), with a median follow-up time of 8 weeks. Dyskalemia events typically occurred at either week 8 (three trials) or week 12 (two trials) after medication initiation. Criteria for observed dyskalemia events matched with our a priori definition for 24 treatment combinations studied in all five trials. All five reported both hypo- and hyperkalemia rates.

Meta-regression analysis of hyper/hypokalemia incidence rates

A moderate (negative) correlation was observed between hypokalemia and hyperkalemia risks ($R^2 = 0.31$, weighted by treatment group size, Fig. 1). Therefore, these two endpoints were analyzed jointly. Treatment effects for both mono-, dual, and (triple) combination therapy could be estimated for all treatments. The final parameter estimates for hyperkalemia and hypokalemia from the joint meta-analysis are listed in Table 2. Observed and model-estimated drug class-specific hyperkalemia and hypokalemia event rates are shown in Fig. 2. Higher dose HCTZ (25 mg) was associated with higher odds of hypokalemia compared with placebo (log odds = 2.36, 95% confidence interval [1.91–2.81], P value < 0.05). The model was able to differentiate hypokalemia

Table 1. Summary of baseline patients' characteristics and dyskalemia incidence in five included regulatory trials, according to trial arm.

Study	Phase	Time (weeks)	Dyskalemia definition	Treatment (mg/day)	N	K+ (%)	K- (%)	Age (mean years)	Male (%)	Black race (%)	Diabetes (%)	CVD (%)	CKD (%)	Potassium (mean mmol/l)
CS8635-A-U301 [13]	2	12	>5 mmol/L (K+) <3.5 mmol/L (K-)	amlodipine 10 hydrochlorothiazide 25	600	1.7	9.8	54.6	55.7	32.0	15.3	9.2	4.8	–
				olmesartan 40 amlodipine 10	628	7.6	0.6	55.1	51.8	28.8	15.9	8.9	4.6	–
				olmesartan 40 amlodipine 10 hydrochlorothiazide 25	626	5.9	2.2	54.7	51.0	29.3	15.3	8.8	3.2	–
				olmesartan 40 hydrochlorothiazide 25	637	4.9	2.4	55.9	53.2	31.4	15.5	9.6	3.9	–
CS8663-A-U301 | E303 [14–16]	3	12	>5 mmol/L (K+) <3.5 mmol/L (K-)	olmesartan 40 amlodipine 10	1367	4.5	0.6	55.0	57.0	–	–	–	–	–
				olmesartan 40 amlodipine 10 hydrochlorothiazide 12.5	829	2.4	0.8	55.0	57.0	–	–	–	–	–
				olmesartan 40 amlodipine 10 hydrochlorothiazide 25	468	2.8	7.5	55.0	57.0	–	–	–	–	–
				olmesartan 40 amlodipine 5	2370	5.3	0.6	55.0	57.0	–	–	–	–	–
VEA-A2302 [17]	3	8	>20% increase (K+) >20% decrease (K-)	amlodipine 10 hydrochlorothiazide 25	550	2.2	19.3	53.6	56.5	19.1	8.2	–	–	4.3
				valsartan 320 amlodipine 10	552	6.2	0.4	52.8	56.2	16.0	8.5	–	–	4.3
				valsartan 320 amlodipine 10 hydrochlorothiazide 25	567	3.5	6.5	53.3	54.2	16.8	10.6	–	–	4.3
				valsartan 320 hydrochlorothiazide 25	549	2.4	3.3	53.1	54.2	16.6	10.6	–	–	4.2
Protocol 301 [18]	2	8	>20% increase (K+) >20% decrease (K-)	hydrochlorothiazide 12.5	97	1.0	6.2	52.0	58.0	22.0	–	–	–	–
				hydrochlorothiazide 25	99	3.0	11.1	52.0	55.0	11.0	–	–	–	–
				placebo	91	4.4	3.3	52.0	58.0	14.0	–	–	–	–
				valsartan 160	96	6.3	0.0	52.0	61.0	13.0	–	–	–	–
				valsartan 160 hydrochlorothiazide 12.5	95	6.4	2.1	53.0	58.0	11.0	–	–	–	–
				valsartan 160 hydrochlorothiazide 25	92	3.3	4.4	53.0	51.0	15.0	–	–	–	–
				valsartan 80	98	10.2	1.0	52.0	63.0	15.0	–	–	–	–
				valsartan 80 hydrochlorothiazide 12.5	96	3.1	1.0	52.0	58.0	12.0	–	–	–	–
				valsartan 80 hydrochlorothiazide 25	90	5.6	8.9	51.0	47.0	9.0	–	–	–	–
Protocol 228 [19]	2	8	>0.5 mmol/L increase (K+) >0.5 mmol/L decrease (K-)	LOS 100 hydrochlorothiazide 25	170	4.1	12.4	52.3	–	25.4	4.6	–	–	3.5–5.5
				LOS 50 hydrochlorothiazide 12.5	180	5.0	7.2	53.2	–	22.3	3.3	–	–	3.5–5.5
				placebo	83	1.2	3.6	52.8	–	21.3	5.6	–	–	3.5–5.5

– no information reported, *CVD* cardiovascular disease, *CKD* chronic kidney disease, *K+* hyperkalemia, *K-* hypokalemia.

risk between higher (25 mg) and lower daily dose (12.5 mg) HCTZ (P value < 0.05). However, the analysis did not detect any differential effect of different ARB doses on dyskalemia risk (losartan 50 vs. 100 mg daily; valsartan 80 vs. 160 vs. 320 mg daily). The network meta-analysis framework also estimated indirect treatment effects of losartan, olmesartan and amlodipine, although no directly observed monotherapy treatment data were available for these drugs.

Model-based simulations of comparative dyskalemia response rates for FDC anti-hypertension drug treatments

Comparisons of probabilities of dyskalemia events for FDCs including higher (25 mg) and lower (12.5 mg) daily HCTZ doses, are presented in Fig. 3 and Table 3 based on the simulation results from final joint model. As expected, hyperkalemia risk for ARB alone was higher than placebo (VAL 1.31% [0.26, 3.56%], with simulated absolute risk 2.95%:1.27–6.8%); hyperkalemia risk with the ARB+CCB combination was also significantly higher than placebo (for example LOS/OLM+CCB 5.16%[3.27–12.58%] higher than placebo). Simulated hyperkalemia risk was not appreciably higher than placebo (95% confidence overlapped zero difference) for any FDC that combined HCTZ with an ARB in a dual FDC (e.g., VAL+HCTZ 0.06%[−1.48, 1.64%], with simulated absolute risk 1.7%[0.81, 3.67%]). This advantage regarding lower hyperkalemia risk appeared to be attenuated in the arms where CCB was added to ARB + HCTZ in a triple FDC.

Compared with placebo, absolute hypokalemia risk difference was higher for HCTZ 25 mg monotherapy (8.73% higher than placebo [4.12–17.08%], with simulated absolute risk 9.74%[4.69, 18.97%]) than for HCTZ 12.5 mg monotherapy (2.10% higher than placebo [0.85–4.80%]. With simulated absolute risk 3.11%[1.46, 6.53%]); this pattern also held for CCB+HCTZ combinations. Even when combined with an ARB, hypokalemia risk difference was at least 2% higher than placebo for FDCs that included an HCTZ dose of 25 mg daily (e.g., VAL+HCTZ 25 mg 2.52%[1.17, 4.38%] higher than placebo, with simulated absolute risk 3.53% [2.17, 5.68%]). However, hypokalemia risk was not appreciably greater than placebo for combination therapies including ARB plus the lower 12.5 mg HCTZ dose (e.g., VAL+HCTZ 12.5 mg −0.03% [−0.8, 0.71%] compare to placebo, with simulated absolute risk 0.98% [0.50, 1.86%]).

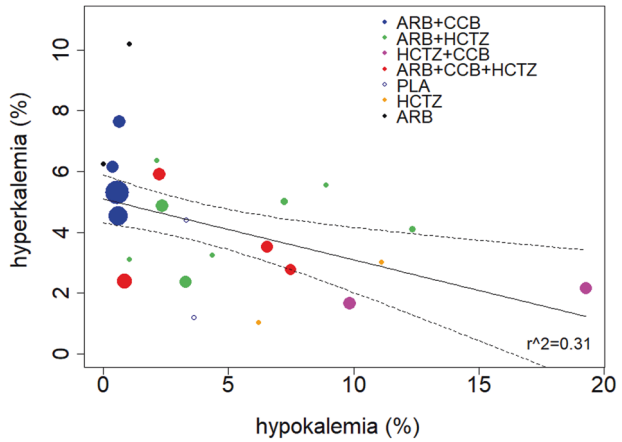

Fig. 1 The correlation of observed hypokalemia and hyperkalemia event in 24 antihypertensive medication treatment arms from five randomized regulatory trials. Symbol size is proportional to sample size of each arm, colored by the different combination of treatment class; Line is fitted regression line ($R^2 = 0.31$, weighted by sample size in treatment arm) AML - Amlodipine, HCTZ – hydrochlorothiazide; LOS - losartan; OLM – olmesartan; VAL-valsartan; PLA- placebo.

DISCUSSION

The results of this joint meta-analysis and model-based simulation suggest that risk of dyskalemia is not appreciably higher than placebo when ARBs are combined with HCTZ at the lower daily dose of 12.5 mg. About 75% hypertensive patients will require dual anti-hypertensive drug therapy [2]. For uncomplicated hypertension patients requiring two or more drugs to control their blood pressure, ARB+12.5 mg HCTZ dual therapy fixed-dose combinations are safer with respect to dyskalemia compared with either ARB or HCTZ monotherapy.

Thiazide diuretics induce hypokalemia more frequently than other antihypertensive classes [4], and low serum potassium may provoke cardiac arrhythmia and sudden death [20]. However, hypokalemia risk related to HCTZ is dose-dependent. A earlier meta-analysis of clinical studies indicated that low-dose (12.5 to 25 mg/d HCTZ) and high-dose (≥50 mg/d) diuretic therapy lowered BP to a similar degree and exerted a similar benefit in reducing stroke, congestive HF, CV and total mortality, but only lower dose diuretic therapy significantly reduced CHD incidence [21]. In the RCTs analyzed in this study, HCTZ was given as. 12.5 or 25 mg daily as monotherapy, combination with one of either ARB or CCB, or combined with both ARB and CCB. We found that the

Table 2. Parameter estimates from the final dyskalemia model [joint model of hyperkalemia (K+) or hypokalemia (K-) event].

Parameter	Parameter description	Estimate [95% CI]	RSE%
$E_{los.K+}$	Drug effect of Losartan or Olmesartan on K+	1.24 [0.55 to 1.92]	27%
$E_{val.K+}$	Drug effect of Valsartan on K+	0.60 [0.13 to 1.07]	38%
$E_{aml.K+}$	Drug effect of Amlodipine on K+	0.56 [−0.31 to 1.44]	76%
$E_{hctz.K+}$	Drug effect of HCTZ on K+	−0.77 [−1.34 to −0.19]	37%
$Int_{arb+hctz.K+}$	Additional interaction between ARB and HCTZ class on K+	−0.44 [−1.48 to 0.59]	115%
$Int_{arb+ccb.K+}$	Interaction between ARB and CCB class on K+	−0.47 [−1.41 to 0.48]	98%
$E_{los.K-}$	Drug effect of Losartan or Olmesartan on K-	−1.27 [−1.75 to −0.79]	18%
$E_{val.K-}$	Drug effect of Valsartan on K-	−1.26 [−1.63 to −0.89]	14%
$E_{aml.K-}$	Drug effect of Amlodipine on K-	0.66 [−0.10 to 1.43]	56%
$E_{hctz.h.K-}$	Drug effect of HCTZ (dose = 25 mg/day) on K-	2.36 [1.91 to 2.81]	9%
$E_{hctz.l.K-}$	Drug effect of HCTZ (dose = 12.5 mg/day) on K-	−1.21 [−1.64 to −0.79]	17%
$Int_{arb+hctz.K-}$	Interaction between ARB and HCTZ class on K-	−0.06 [−0.3 to 0.18]	198%
ρ	Correlation coefficient between K+ and K-	0.40	

Parameter estimates are reported in mean [95% CI] on the logit scale; *RSE* relative SE, *K+* hyperkalemia, *K-* hypokalemia.

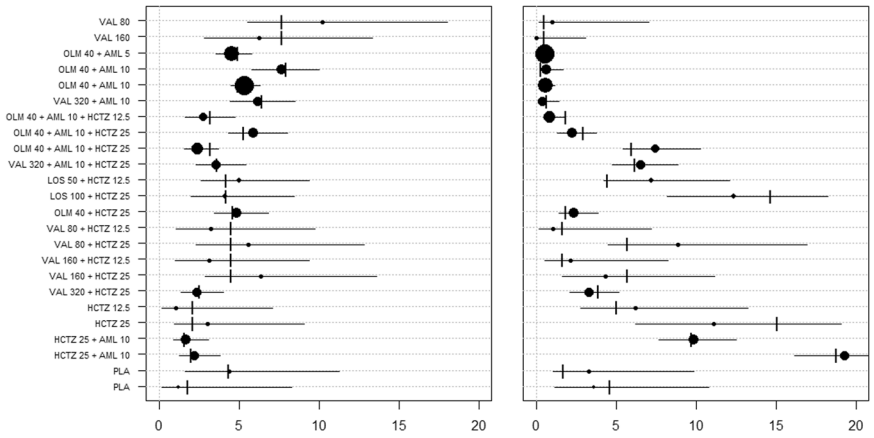

Fig. 2 Observed (circle) and model-estimated (vertical bar) hyper- and hypokalemia rates in 24 treatment arms. The horizontal error bars represent the 95% confidence intervals of an observed event rate. Circle size is proportional to sample size of each arm. AML - Amlodipine, HCTZ – hydrochlorothiazide; LOS - losartan; OLM – olmesartan; VAL- valsartan; PLA- placebo.

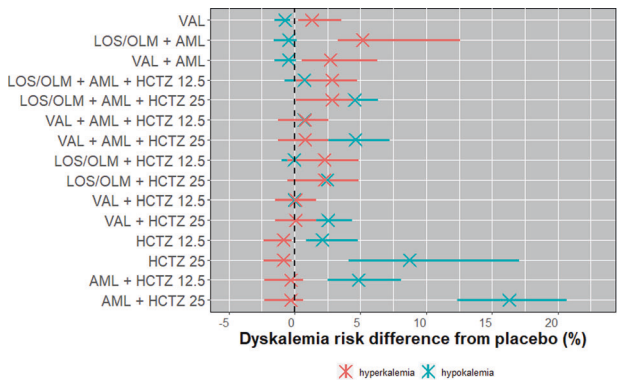

Fig. 3 Simulated absolute risk of hypokalemia and hyperkalemia for the different FDCs observed in five randomized controlled trials. Simulations assume a typical placebo response. Symbols indicate maximum likelihood model predictions and error bars present 95% confidence interval of resampling parameter estimates from the final model variance-covariance matrix 1000 times.

25 mg dose of HCTZ led to an increased hypokalemia risk that was only partially attenuated by, but not eliminated by combination with ARB. However, combining ARB with the lower 12.5 mg dose of HCTZ appears to be relatively safe, with a hypokalemia risk not appreciably higher than placebo. A previous meta-analysis reported a similar dose-dependent effect of HCTZ monotherapy on serum potassium levels [22]. ARBs alone raise hyperkalemia risk. In our analysis of five FDC trials, hyperkalemia risk was not appreciably higher than placebo when ARB was combined with HCTZ.

Risks of hyper- and hypokalemia associated with FDC anti-hypertensive medications remain poorly understood. Lack of certainty about dyskalemia risk may explain why dual drug FDCs have not been taken up more quickly by the clinical community, despite that they are recommended by multiple national or international guidelines [1]. The existing literature mostly quantifies incidence of dyskalemia after initiating anti-hypertensive medication monotherapy. In the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, incidence of dyskalemia at one year was 14.1% (12.9% with hypokalemia and 1.2% with hyperkalemia) for chlorthalidone, 4.1% (2.1% with hypokalemia and 2.0% with hyperkalemia) for amlodipine, and 4.6% (1.0% with hypokalemia and 3.6% with hyperkalemia) for lisinopiril [6]. Observational studies suggest that risk of hyperkalemia after initiating ACE-I or ARB monotherapy ranges between 0.7% and 5.6% [12, 23]. Our monotherapy findings are consistent with these reports, but extend this evidence by quantifying the comparative risks of dyskalemia across the combinations of two or more classes of anti-hypertensive medications relative to placebo or monotherapy. Our results are supported by one published trial with multiple combination arms that also reported no risk of hypokalemia when HCTZ was combined with ARB [18].

This study fills an evidence gap by using a model-based meta-analysis approach to quantify rigorously-defined dyskalemia risk differences for multiple anti-hypertensive drug combinations in reference to the placebo rate while preserving the advantages unbiased RCT design. However, this study is limited by analyzing only five total trials, with only two of the trials including placebo arms, and only one trial studying monotherapies. While we were able to quantify dyskalemia risk at higher and lower doses of HCTZ, our model did not detect expected dyskalemia risk differences by ARB dose. Dyskalemia risk is higher in those with chronic kidney disease (CKD) and proportional to the severity of CKD. Very limited information of baseline renal function inclusion of patients with CKD were reported by the included RCTs, such that we were not able to adjust model estimates for, or stratify by a continuous measure of kidney function or CKD status. Without adjustment for baseline renal function, the clinical application of our current findings is limited, and should only be considered when selecting anti-hypertensive therapy for patients with hypertension uncomplicated by CKD, which is associated with hyperkalemia risk [24].

This model-based meta-analysis found that initial FDC treatments combining ARB with 12.5 mg HCTZ results in a better safety profile and is associated with lower dyskalemia rate than either initial ARB or HCTZ monotherapy. ARB combinations with HCTZ 12.5 mg should be considered a preferred and safe choice of initial FDC dual drug anti-hypertensive therapy in uncomplicated hypertension patients when dyskalemia risk is considered.

Summary table

What is known about this topic

- Most hypertensive patients require two or more antihypertensive medications to achieve blood pressure control.
- An increasing number of clinical guidelines recommend fixed dose combination antihypertensive medications as initial hypertension therapy.
- Standard antihypertensive medication trials report on composite adverse event outcomes, so very little is known

Table 3. Drug effect on hyperkalemia and hypokalemia rate at 8–12 weeks of follow-up after anthihypertensive mediacations treatment initiation.

	Hyperkalemia (%)		Hypokalemia (%)	
Treatment	**Model predicted risk (95% CI)**	**Model predicted risk difference from placebo (95%CI)**	**Model predicted risk (95% CI)**	**Model predicted risk difference from placebo (95%CI)**
VAL	2.95(1.27,6.8)	1.31(0.26,3.56)	0.29(0.13,0.63)	−0.72(−1.55,−0.34)
LOS/OLM + AML	6.8(5.25,14.09)	5.16(3.27,12.58)	0.56(0.37,0.84)	−0.46(−1.58,0.14)
VAL + AML	4.37(2.32,8.17)	2.73(0.53,6.30)	0.56(0.33,0.91)	−0.45(−1.55,0.12)
LOS/OLM + AML + HCTZ 12.5	4.48(3.46,5.83)	2.84(0.08,4.77)	1.72(1.15,2.63)	0.71(−0.76,1.93)
LOS/OLM + AML + HCTZ 25	4.48(3.46,5.83)	2.84(0.08,4.77)	5.57(4.37,7.13)	4.56(2.69,6.32)
VAL + AML + HCTZ 12.5	2.43(1.42,4.01)	0.78(−1.24,2.56)	1.74(1.02,2.96)	0.73(−0.57,2.06)
VAL + AML + HCTZ 25	2.43(1.42,4.01)	0.78(−1.24,2.56)	5.61(3.71,8.39)	4.6(2.4,7.23)
LOS/OLM + HCTZ 12.5	3.89(2.42,6.19)	2.24(−0.54,4.89)	0.98(0.55,1.73)	−0.04(−0.98,0.69)
LOS/OLM + HCTZ 25	3.89(2.42,6.19)	2.24(−0.54,4.89)	3.50(2.37,5.16)	2.49(1.16,4.01)
VAL + HCTZ 12.5	1.70(0.82,3.67)	0.06(−1.48,1.64)	0.98(0.50,1.86)	−0.03(−0.8,0.71)
VAL + HCTZ 25	1.70(0.82,3.67)	0.06(−1.48,1.64)	3.53(2.17,5.68)	2.52(1.17,4.38)
HCTZ 12.5	0.77(0.33,1.74)	−0.87(−2.33,−0.21)	3.11(1.46,6.53)	2.10(0.85,4.8)
HCTZ 25	0.77(0.33,1.74)	−0.87(−2.33,−0.21)	9.74(4.69,18.97)	8.73(4.12,17.08)
AML + HCTZ 12.5	1.35(0.81,2.14)	−0.30(−2.30,0.67)	5.86(3.87,9.12)	4.85(2.49,8.09)
AML + HCTZ 25	1.35(0.81,2.14)	−0.30(−2.3,0.67)	17.31(13.43,22.07)	16.29(12.36,20.69)
PLA	1.64(0.7,3.92)	na	1.01(0.48,2.09)	na

Values are mean parameter estimates based on maximum likelihood model predictions, with 95% confidence interval of resampling parameter estimates from the final model variance-covariance matrix 1000 times.

regarding the rate of dyskalemia (hypo- or hyper-kalemia) with different medication combinations.
- Lack of evidence for dyskalemia risk may impede the uptake of combination therapy by practicing clinicians.

What does this study add

- This model-based meta-analysis of randomized regulatory trials quantified dyskalemia risk for combinations of the most widely used antihypertensive medications [calcium channel blockers (CCBs), angiotensin II receptor blockers ARBs, and thiazide diuretic (HCTZ)].
- Hypokalemia risk was not appreciably greater than placebo when ARB was combined with a lower, 12.5 mg dose of HCTZ.
- Hyperkalemia risk was not appreciably higher than placebo for any FDC that combined ARB with HCTZ.
- In patients with uncomplicated hypertension, risk for dyskalemia with combination antihypertensive therapy combining ARB with 12.5 mg HCTZ is no higher than, and may be less than that of monotherapy with either component drug.

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AUTHOR CONTRIBUTIONS

L.Q., N.Z., J.I., E.R.M., M.P., A.E.M., and E.C. wrote the manuscript; L.Q., N.Z., A.E.M., and E.C. designed the research; L.Q., N.Z., and E.C. performed the research; L.Q., and E.C. analyzed the data.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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