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REVIEW ARTICLE

Association of Abnormal Serum Potassium Levels with Arrhythmias and Cardiovascular Mortality: a Systematic Review and Meta-Analysis of Observational Studies

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Abstract

Purpose To provide the first systematic review and meta-analysis of observational studies on the association of abnormal serum potassium and cardiovascular outcomes.

Methods Medline and ISI Web of Knowledge were systematically searched from inception until November 24, 2017. Data synthesis of relevant studies was performed using random effects model meta-analyses.

Results Meta-analyses included 310,825 participants from 24 studies. In the older general population, low serum potassium was associated with a 1.6-fold increased risk of supraventricular arrhythmias (risk ratio [95% confidence interval] 1.62 [1.02–2.55]). Contrarily, high serum potassium was associated with increased cardiovascular mortality (CVM) (1.38 [1.14–1.66]). In patients with acute myocardial infarction, the risk of ventricular arrhythmias was increased for high serum potassium (2.33 [1.60–3.38]). A U-shaped association was observed with a composite cardiovascular outcome in hypertensive patients (2.6-fold increased risk with hypokalemia and 1.7-fold increased risk with hyperkalemia), with CVM in dialysis patients (1.1-fold increased risk with hypokalemia and 1.4-fold increased risk with hyperkalemia) and with CVM in heart failure patients (albeit not statistically significant). Further, only hyperkalemia was associated with an increased risk of a composite cardiovascular outcome in both dialysis (1.12 [1.03–1.23]) and chronic kidney disease (1.34 [1.06–1.71]) patients.

Conclusions Controlled clinical trials are needed to determine which populations may profit from more frequent potassium-monitoring and subsequent interventions, e.g., change or withdrawal of potassium-influencing drugs, in order to restore normal values and prevent cardiovascular outcomes.

Registration Details Registration in PROSPERO (Centre for Reviews and Dissemination University of York, York, UK): CRD42016048897 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=48897).

Keywords Serum potassium · Arrhythmia · Cardiovascular mortality · Systematic review · Meta-analysis · Observational studies

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Introduction

Cardiovascular disease (CVD) is the number one cause of death worldwide [1]. In 2012, CVD was responsible for 31% of all global deaths, representing 17.5 million people.

Potassium plays a crucial role for sufficient functioning of the heart [2]. Under physiological conditions, extracellular serum potassium (serum K^+) levels are within the range of 3.5 and 5.1 mmol/L [3], which is maintained by renal elimination and by the sodium-potassium ATPase pump activity [2]. Nevertheless, if these mechanisms fail to compensate potassium imbalances, this can result in either hypokalemia (serum $K^+ < 3.5$ mmol/L) or hyperkalemia (serum $K^+ >$ 5.1 mmol/L) [3].

Sensitivity towards abnormal serum K^+ levels seems to be important for the prognosis of CVD and may be different according to the patient's history of morbidity. In patients with acute myocardial infarction (AMI), for instance, excessively released catecholamines stimulate an intracellular shift of potassium. This results in potassium depletion which in turn increases the risk of ventricular fibrillation [4, 5]. Moreover, subjects with chronic kidney disease (CKD) are prone to experience imbalances in serum K^+ concentration due to impaired renal clearance [6].

Many observational studies have assessed the association between serum K^+ levels and cardiovascular (CV) outcomes. However, to the best of our knowledge, no review of this study type has been done so far. Therefore, we conducted a systematic review of observational studies reporting on the association of abnormal serum K^+ levels with supraventricular and ventricular arrhythmias, and cardiovascular mortality (CVM). Meta-analyses were conducted separately for the older general population, and populations with history of hypertension, AMI, heart failure, CKD, or dialysis.

Methods

This systematic review and meta-analysis was performed in accordance to the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines [7]. The MOOSE checklist is provided in Online Resource 1.

Patient Involvement

Patients were not involved in the design of this systematic review.

Data Sources and Search Strategy

We conducted a systematic literature search using the databases *Medline* (Ovid Technologies, New York) and *ISI Web of Knowledge* (Thomson Scientific Technical Support, New York) from inception until November 24, 2017. No language or publication date restrictions were imposed. After consulting a librarian, the search strategy was developed. It combined synonymous and related terms which describe the exposure (potassium), the outcomes (arrhythmias and CVM), and the study type (observational study). A complete version of the full electronic search strategy for Medline is shown in Online Resource 2. The reference manager *Endnote X7* (Thomson Scientific Technical Support, New York) was used throughout the literature search and screening process.

Literature Screening and Selection Criteria

The literature was screened in four steps. First, publication types others than observational studies were deleted by keyword search in Endnote (e.g., reviews, editorials, commentaries). In steps 2 to 4, the title, abstract, and full text of studies were screened for content relevant to this review topic. Two reviewers (LKH and DCM) independently performed the full text screening by using the following exclusion criteria: (a) no observational study design, (b) study not conducted in humans, (c) serum K^+ levels not measured, (d) no association of serum K^+ levels with one of the defined outcomes (arrhythmias, CVM, or composite CV outcomes) assessed, and (e) intervention influencing serum K^+ levels or outcome.

Data Extraction and Risk of Bias Assessment

Two reviewers (LKH and DCM) independently extracted data from the studies included in the review. Consensus was reached through discussion or consultation of the third reviewer (BS). Risk of bias and quality of the included studies were assessed by using a modified version of the Newcastle-Ottawa-Scale [8].

Statistical Analysis

Studies were included in meta-analyses if (1) serum K^+ [mmol/L] was investigated as a categorical variable with a cutoff for low serum K^+ of ≤ 4.0 mmol/L or lower and a cutoff for high serum K^+ of ≥ 4.5 mmol/L or higher, if (2) a reference category for serum K^+ was used that did not include hypokalemic (< 3.5 mmol/L) or hyperkalemic serum K^+ levels ($>$ 5.5 mmol/L), if (3) effect estimates (risk ratio, hazard ratio, or odds ratio) and confidence intervals were reported, could be calculated or were provided by the authors when contacted, and if (4) sufficient information about the study outcome was provided. If a study reported effect estimates for several categories in the hypokalemic range (< 3.5 mmol/L) or the hyperkalemic range (> 5.5 mmol/L), these estimates were pooled by fixed effect meta-analyses and the pooled results were used for the meta-analyses with other studies.

Meta-analyses were conducted separately for study outcome and study population, namely older general population and populations with a history of hypertension, AMI, heart failure, CKD, or dialysis. Random effects meta-analyses with inverse variance weighting were applied to allow for between-study heterogeneity. We tested for statistically significant heterogeneity with Cochrane's Q test. Additionally, I^2 was calculated. Publication bias was assessed with Kendall's tau and Egger's test of the intercept (one-tailed). The software *Comprehensive Meta-Analysis 2.0* (Biostat, Englewood, NJ, USA) was used for all analyses.

Results

Screening Results and Study Selection

A flow diagram of the literature screening and selection process is given in Fig. 1. After removing duplicates, the literature search revealed 1424 articles. Further exclusions during the study type, title, and abstract screening resulted in 103 articles for the full text selection. The references of the studies excluded during full text selection are shown in Online Resource 3. Overall, this review included 54 studies [9–62], 5 of which were identified by cross-referencing [11, 31, 32, 55, 61]. Finally, 24 studies [9–11, 14, 16, 18, 24, 27, 31, 32, 35–40, 43, 50, 55, 57–61] were suitable for meta-analyses.

Study Design of Included Studies

We detected 28, 24, and 4 studies reporting on the association of abnormal serum K^+ levels with arrhythmias [12, 15, 17, 19–23, 25, 27–30, 33, 34, 36, 39, 44, 45, 47–49, 51–54, 56, 57], CVM [9–11, 13, 14, 16, 24, 26, 31, 32, 37, 38, 40–42, 44, 46, 50, 55, 58–62], and composite CV outcomes [18, 35, 37, 43], respectively. Two [37, 44] studies appear twice. Details of included studies sorted by study outcome and study population are shown in Tables S1 to S3 (Online Resource 4). A comprehensive list of outcome definitions of the included studies is provided in Online Resource 5.

Among the studies assessing the outcome arrhythmias (Online Resource 4, Table S1), the study of Krijthe et al. is the only study on arrhythmias with a prospective cohort

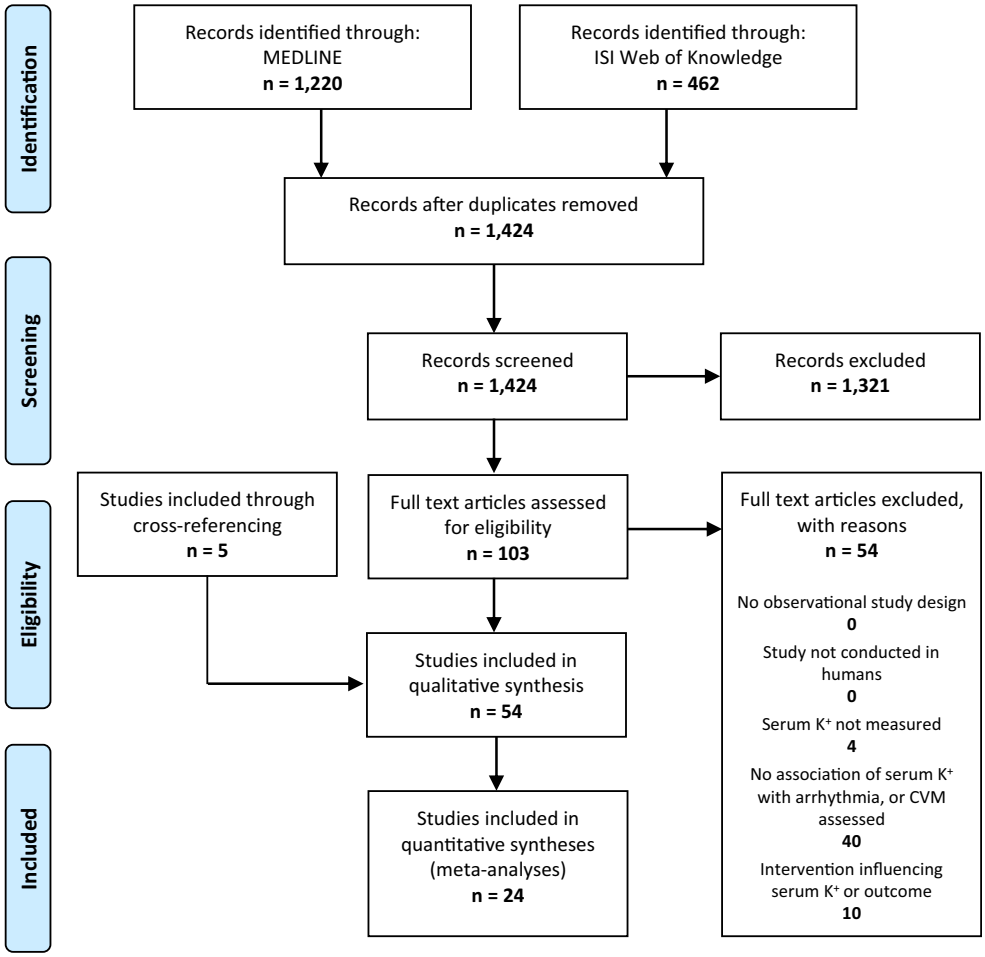


Fig. 1 Flow diagram showing the systematic literature screening with inclusion and exclusion process. *CVM* cardiovascular mortality, K^+ potassium

design [39]. All other studies reporting on the outcome "arrhythmias" were classified as cross-sectional studies because measurement of potassium was at the same hospital stay as the arrhythmia diagnosis, in most cases less than 2 days apart. Studies about "arrhythmias" mainly investigated patients with AMI [12, 15, 23, 25, 27, 29, 30, 34, 36, 44, 45, 47, 49, 51, 53, 54, 57]. The study sizes ranged from 50 [22] to 38,689 participants [27] with an arrhythmia prevalence of 1.5% [48, 51] to 61.0% [17, 19]. With exception of the study of Krijthe et al. [39], which investigated supraventricular arrhythmias, and the study of Madias et al. [44], which analyzed both supra- and ventricular arrhythmias, all other studies investigated ventricular arrhythmias.

Among the studies assessing the outcome CVM (Online Resource 4, Table S2), the study of Chow et al. was the only one with a case-control design [16], while the others were cohort studies. Regarding the study population, most of the studies investigated dialysis [16, 26, 31, 38, 41, 50, 55, 61, 62], older general [14, 24, 32, 40, 59, 60], and heart failure [9–11, 42, 46] subjects. Additionally, there was one study in hypertensive patients [13], one study in AMI patients [44], and another two studies in CKD patients [37, 58]. The largest study [38] comprised 74,219 participants and the smallest study [31, 41] 312 subjects. Subjects were followed up for at least 0.3 years [11] and up to a maximum of 23.5 years [14]. During follow-up, the CVM rate ranged from 1.5% [59] to 28.7% [10].

The four studies with composite CV outcomes (Online Resource 4, Table S3) were prospective cohort studies in patients with hypertension [18], CKD [37, 43], or dialysis [35] and had study sizes of 7653 [18], 820 [37], 55,266 [43], and 45,511 [35] subjects, respectively.

Risk of Bias and Quality Assessment of Included Studies

Results of the risk of bias and quality assessment are shown in Tables S4 to S6 of Online Resource 6.

For the evaluation of cross-sectional studies, we used a modified version of the Newcastle-Ottawa-Scale restricted to five categories and a maximum of six accessible points (Online Resource 6, Table S4). The 27 cross-sectional studies on "arrhythmias" were on average rated with 3.3 points (range 1 to 5 points).

Cohort studies (Online Resource 6, Table S5) and the case-control study (Online Resource 6, Table S6) were evaluated in eight categories and could be awarded a maximum of nine points. While the cohort study on supraventricular arrhythmias [39] was awarded 9 points, the average number of points per study was 6.9 (range 5 to 9 points) and 7.0 (range 6 to 8 points) for studies assessing the outcome CVM and studies assessing composite CV outcomes, respectively.

Outcome Details of Included Studies

Results of 24 studies, which comprised 310,825 participants, were suitable for meta-analyses and are presented in Table 1. The studies are sorted by study outcome and study population. Risk ratios (RRs) and confidence intervals (CIs) are shown separately for the low and high serum K^+ category with preferably levels of < 3.5 and ≥ 5.5 mmol/L, but alternatively cutoffs up to ≤ 4.0 and ≥ 4.5 mmol/L, respectively, were also accepted if no stricter cutoffs were applied in the studies. If a study reported effect estimates for several categories in the hypokalemic (< 3.5 mmol/L) or the hyperkalemic range (≥ 5.5 mmol/L), pooled estimates are shown in Table 1. The risk categories were compared to a reference category that was not allowed to include abnormal serum K^+ values < 3.5 or > 5.5 mmol/L. All studies are adjusted for age and sex. However, only 2 [18, 39] out of 23 studies are adjusted for all eight covariates that we judged to be important to consider in a model for the association of serum K^+ levels and CV outcomes: age, sex, body mass index (BMI) or other weight measure, smoking, diabetes, history of CVD, hypertension, and kidney disease. A comprehensive list of covariates, which the studies are adjusted for, is provided in Online Resource 7.

Results from 30 studies could not be included in the meta-analyses and are summarized in Tables S7 to S12 of Online Resource 8. The studies compared either frequencies of outcomes in serum K^+ categories [12, 15, 20, 21, 23, 25, 28, 29, 33, 34, 44, 45, 49, 51, 54] (Table S7) or mean serum K^+ levels in case and control groups [13, 22, 30] (Table S8) by statistical tests. Other studies either assessed the correlation of serum K^+ with an outcome [17, 19] (Table S9), or modeled serum K^+ as a continuous variable in a regression analysis [34, 46, 47, 56] (Table S10). Additionally, six studies [26, 41, 42, 52, 53, 62] were excluded from meta-analyses, which included either hypo- or hyperkalemic values in the reference group (Table S11). One study [48] could not be included in meta-analyses, as the outcome of "in-hospital arrhythmia" was not further specified (Table S12). The results of these 30 studies are not further regarded in this review.

Results of Meta-Analyses by Study Outcome and Specific Population

Pooled effect estimates and 95% CIs of study results for low and high serum K^+ are shown separately by study outcome and study population in Table 2. Pooled estimates and corresponding heterogeneity statistics are presented if there was more than one study per analysis. Additionally, meta-analyses are presented in forest plots in Fig. 2. No publication bias was detected in any of the meta-analyses (all $p > 0.05$).

Table 1 Details of included studies for meta-analysis about the association of serum potassium levels and cardiovascular outcomes

Outcome	First author, (year)[Ref]	Population	Outcome	Reference serum K^+	Low serum K^+		High serum K^+		Covariates								
			n [%]	Definition [mmol/L]	Definition [mmol/L]	RR (95% CI)	Definition [mmol/L]	RR (95% CI)	Age	Sex	BMI/ weight	Smoking	Diabetes	History of CVD	Hypertension	Kidney disease	Others[a]
SVA	Krijthe, (2013)[b] [39]	Older general	474 [11.7]	3.5 to 5.0	< 3.5	1.62 (1.02; 2.55)	> 5.0	0.96 (0.24; 3.91)	X	X	X	X	X	X	X	X	X
VA	Goyal, (2012)[c] [27]	AMI	1707 [4.4]	3.5 to < 4	< 3.5	1.13 (0.82; 1.55)	≥ 5.5	2.65 (1.70; 4.13)	X	X			X	X	X	X	X
	Keskin, (2016)[d] [36]	AMI	230 [6.1]	4.0 to < 4.5	< 3.5	3.54 (1.79; 7.02)	≥ 5.5	1.82 (0.95; 4.18)	X	X			X	X	X	X	X
	Uluganyan, (2016)[e] [57]	AMI	65 [10.6]	3.5 to < 4	< 3.5	2.70 (0.93; 7.80)	≥ 5.0	1.38 (0.34; 5.50)	X	X		X	X	X	X	X	X
CVM	Chen, (2016) [14]	Older general	534 [3.4]	3.5 to < 5.5	< 3.5	1.38 (0.94; 2.03)	≥ 5.5	1.25 (0.67; 2.32)	X	X			X	X	X	X	X
	Fang, (2000) [24]	Older general	272 [9.6]	3.8 to < 4.5	< 3.8	0.96 (0.61; 1.50)	≥ 4.5	1.54 (1.03; 2.31)	X	X		X		X	X	X	X
	Hughes-Austin, (2017) [32]	Older general	1087 [11.3]	4.0 to < 4.5	< 3.5	0.84 (0.63; 1.12)	≥ 5.0	1.50 (1.00; 2.26)	X	X		X	X		X	X	X
	Lai, (2015) [40]	Older general	219 [10.6]	3.9 to < 4.5	< 3.5	1.60 (0.70; 3.40)	≥ 4.5	1.30 (1.00; 1.80)	X	X	X		X	X	X	X	X
	Walsh, (2002) [59]	Older general	46 [1.5]	> 4.0 to < 5.2	≤ 4.0	1.40 (0.30; 5.90)	≥ 5.2	1.30 (0.70; 2.60)	X	X	X	X	X		X	X	X
	Wannamethee, (1997) [60]	Older general	370 [5.1]	> 4.5 to < 4.9	< 4.0	0.77 (0.52; 1.15)	≥ 5.2	1.15 (0.52; 2.80)	X	X	X	X	X	X	X		X
	Ahmed A., (2007) [9]	Heart failure	653 [27.5]	4.0 to 5.5	< 4.0	1.27 (1.06; 1.51)	N.A.	N.A.	X	X	X		X	X	X		X
	Ahmed, M.I., (2010) [10]	Heart failure	625 [28.7]	4.0 to < 5.0	N.A.	N.A.	≥ 5.0	1.08 (0.89; 1.30)	X	X	X		X	X	X	X	X
	Aldahl, (2017) [11]	Heart failure	N.R.	4.2 to < 4.5	< 3.5	2.86 (2.10; 3.89)	> 5.5	3.24 (2.49; 4.23)	X	X			X	X		X	X
	Korgaonkar, (2010) [37]	CKD	N.R.	> 4.0 to < 5.5	≤ 4.0	0. 97 (0.62; 1.54)	≥ 5.5	1.49 (0.91; 2.45)	X	X			X	X	X	X	X
	Wagner, (2017) [58]	CKD	83 [4.0]	4.0 to 5.0	< 4	1.01 (0.52; 1.95)	> 5	1.47 (0.67; 3.24)	X	X	X	X	X			X	X
	Chow, (2009) [16]	Dialysis	24 [33.3]	N.R.	< 3.5	3.36 (0.59; 19.04)	N.A.	N.A.	X	X		X	X		X	X	X
	Huang, (2015) [31]	Dialysis	31 [9.9]	4.0 to 5.0	< 4.0	2.82 (0.52; 15.40)	> 5.0	4.11 (1.62; 10.41)	X	X	X		X	X		X	X
	Kovesdy, (2007) [38]	Dialysis	8679 [11.7]	4.6 to < 5.0	< 4.0	1.11 (1.01; 1.20)	≥ 5.6	1.25 (1.17; 1.33)	X	X	X	X	X			X	X
	Ribeiro, (2015) [50]	Dialysis	169 [9.3]	4.0 to 4.5	< 3.5	1.49 (1.01; 2.21)	N.A.	N.A.	X	X	X		X			X	X
	Torlén, (2012) [55]	Dialysis	N.R.	4.0 to < 4.5	< 3.5	1.05 (0.88; 1.25)	≥ 5.5	1.27 (1.05; 1.52)	X	X	X	X	X	X		X	X
	Xu, (2014) [61]	Dialysis	69 [7.8]	4.0 to < 4.5	< 3.5	1.10 (0.63; 1,94)	≥ 5.5	2.29 (0.80; 6.53)	X	X	X		X			X	X
Composite CV outcome	Cohen, (2001)[f] [18]	Hypertension[g]	470 [6.1]	> 3.5 to < 5.1	≤ 3.5	2.57 (1.51; 4.36)	≥ 5.1	1.65 (1.02; 2.67)	X	X	X	X	X	X	X	X	X
		CKD	190 [23.2]	> 4.0 to < 5.5	≤ 4.0		≥ 5.5		X	X			X	X	X	X	X

Table 1 (continued)

Outcome	First author, (year)[Ref]	Population	Outcome	Reference serum K^+	Low serum K^+		High serum K^+		Covariates								
			n [%]	Definition [mmol/L]	Definition [mmol/L]	RR (95% CI)	Definition [mmol/L]	RR (95% CI)	Age	Sex	BMI/ weight	Smoking	Diabetes	History of CVD	Hypertension	Kidney disease	Others[a]
	Korgaonkar, (2010)[h] [37]					1.13 (0.76; 1.67)		1.69 (1.09; 2.60)									
	Luo, (2016)[i] [43]	CKD	N.R.	4.5 to < 5.0	< 3.5	1.89 (1.72; 2.09)	≥ 5.5	1.26 (1.19; 1.34)	X	X			X	X		X	X
	Karaboyas, (2017)[j] [35]	Dialysis	3300 [7.3]	4.0 to 5.0	< 4.0	0.94 (0.83; 1.05)	> 5.5	1.12 (1.03; 1.23)	X	X	X		X	X	X	X	X

AMI acute myocardial infarction, *BMI* body mass index, *CI* confidence interval, *CKD* chronic kidney disease, *CV* cardiovascular, *CVD* cardiovascular disease, *CVM* cardiovascular mortality, *ECG* electrocardiography, *ICD* international classification of diseases, K^+ potassium, *No.* number, *N.A.* not applicable, *N.R.* not reported, *Ref* reference, *RR* risk ratio, *SVA* supraventricular arrhythmias, *VA* ventricular arrhythmias

[a] A comprehensive list of covariates, which the studies are adjusted for, is given in Online Resource 7

[b] Krijthe (2013): Definition of arrhythmia: Atrial fibrillation and atrial flutter diagnosed by ECG processing with the modular ECG analysis system (MEANS) and manual verification by two blinded specialists

[c] Goyal (2012): Definition of arrhythmia: In-hospital ventricular fibrillation or ventricular flutter (documented by ICD-9-CM codes 427.4, 427.41, or 427.42), or cardiac arrest (ICD-9-CM code 427.5)

[d] Keskin (2016): Definition of arrhythmia: ventricular arrhythmias were evaluated by a trained study coordinator. However, ventricular arrhythmias were not categorized by the respect of time and long-term ventricular arrhythmias were not included

[e] Uluganyan (2016): Definition of arrhythmia: ventricular arrhythmias

[f] Cohen (2001): Definition of composite CV outcome: admissions to hospital because of myocardial infarction, angioplasty or coronary bypass surgery, cerebrovascular disease, unstable angina, congestive heart failure, and deaths from all causes of CVD

[g] Cohen (2001): Hypertensive study population treated with mainly non-potassium sparing diuretics (thiazides)

[h] Korgaonkar (2010): Definition of composite CV outcome: death or any CV event defined as pre-specified coronary disease-, cerebrovascular disease-, or peripheral vascular disease-related events that required hospitalization or revascularization procedures in any of the named three major arterial beds

[i] Luo (2016): Definition of composite CV outcome: arrhythmia, myocardial infarction, stroke, and heart failure exacerbation

[j] Karaboyas (2017): Definition of composite CV outcome: death due to hyperkalemia, hypokalemia, cardiac arrhythmia, or cardiac arrest; inpatient hospitalization due to atrial fibrillation or other arrhythmia; procedure for cardioversion or automatic implantable cardioverter-defibrillator or pacemaker placement

Table 2 Effect estimates for the association of serum potassium levels and cardiovascular outcomes

Outcome	Population	Low serum K^+					High serum K^+				
		No. of studies	n_{total}	n_{cases}	RR (95% CI)	Heterogeneity Q; *P*; I^2 [%]	No. of studies	n_{total}	n_{cases}	RR (95% CI)	Heterogeneity Q; *P;* I^2 [%]
SVA	Older general	1[a]	4059	474	*1.62 (1.02; 2.55)*	N.A.	1[a]	4059	474	0.96 (0.24; 3.91)	N.A.
VA	AMI	3[b]	43,060	2002	2.08 (0.89; 4.85)	10.23; 0.01; 80.4	3[b]	43,060	2002	*2.33 (1.60; 3.38)*	1.24; 0.54; 0.0
CVM	Older general	6[c]	40,504	2528	1.00 (0.79; 1.26)	7.26; 0.20; 31.1	6[c]	40,504	2528	*1.38 (1.14; 1.66)*	0.89; 0.97; 0.0
	Heart failure	2[d]	21,932	653[e]	1.87 (0.85; 4.18)	20.04; 0.00; 95.0	2[f]	21,726	625[g]	1.86 (0.64; 5.47)	43.70; 0.00; 97.7
	CKD	2[h]	2898	83[i]	0.98 (0.68; 1.43)	0.01; 0.92; 0.0	2[h]	2898	83[i]	1.48 (0.98; 2.26)	0.00; 0.98; 0.0
	Dialysis	6[j]	87,774	8972[k]	*1.11 (1.02; 1.21)*	5.33; 0.38; 6.1	4[l]	85,885	8779[k]	*1.36 (1.10; 1.68)*	7.53; 0.06; 60.2
Composite CV outcome	Hypertension[m]	1[n]	7653	470	*2.57 (1.51; 4.36)*	N.A.	1[n]	7653	470	*1.65 (1.02; 2.67)*	N.A.
	CKD	2[o]	56,086	190[p]	1.52 (0.92; 2.50)	6.18; 0.01; 83.8	2[o]	56,086	190[p]	*1.34 (1.06; 1.71)*	1.72; 0.19; 41.9
	Dialysis	1[q]	45,511	3300	0.94 (0.83; 1.05)	N.A.	1[q]	45,511	3300	*1.12 (1.03; 1.23)*	N.A.

A pooled effect estimate is shown if there is more than one study per population. Italicized printed effect estimates indicate statistically significant results ($P < 0.05$)

AMI acute myocardial infarction, *CI* confidence interval, *CKD* chronic kidney disease, *CV* cardiovascular, *CVM* cardiovascular mortality, K^+ potassium; *N.A.* not applicable, *No.* number, *RR* risk ratio, *SVA* supraventricular arrhythmias, *VA* ventricular arrhythmias

[a] Krijthe (2013)

[b] Goyal (2012); Keskin (2016); Uluganyan (2016)

[c] Chen (2016); Fang (2000); Hughes-Austin (2017); Lai (2015); Walsh (2002); Wannamethee (1997)

[d] Ahmed (2007); Aldahl (2017)

[e] Ahmed (2007): $n_{cases} = 653$; Aldahl (2017): n_{cases} = N.R.

[f] Ahmed (2010); Aldahl (2017)

[g] Ahmed (2010): $n_{cases} = 625$; Aldahl (2017): n_{cases} = N.R.

[h] Korgaonkar (2010); Wagner (2017)

[i] Korgaonkar (2010): n_{cases} = N.R.; Wagner (2017): $n_{cases} = 83$

[j] Chow (2008); Huang (2015); Kovesdy (2007); Ribeiro (2015); Torlén (2012); Xu (2014)

[k] Torlén (2012): n_{cases} = N.R.

[l] Huang (2015); Kovesdy (2007); Torlén (2012); Xu (2014)

[m] Cohen (2001): Hypertensive study population treated with mainly non-potassium sparing diuretics (thiazides)

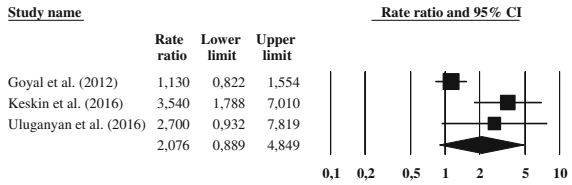
[n] Cohen (2001)

[o] Korgaonkar (2010); Luo (2016)

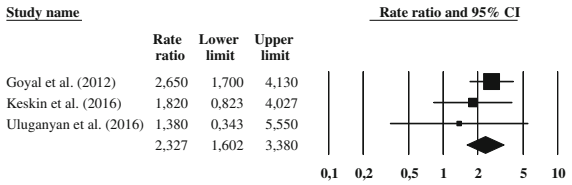
[p] Korgaonkar (2010): $n_{cases} = 190$; Luo (2016): n_{cases} = N.R.

[q] Karaboyas (2017)

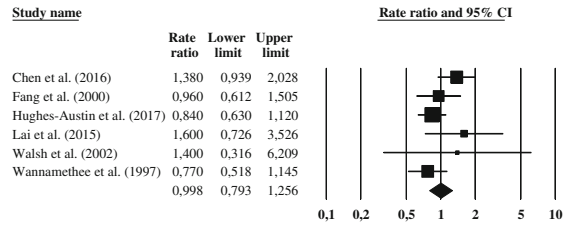
Association of hypokalemia and ventricular arrhythmias in AMI population



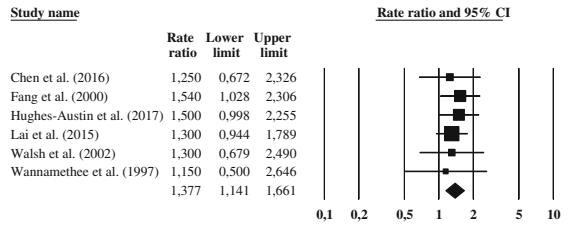
Association of hyperkalemia and ventricular arrhythmias in AMI population



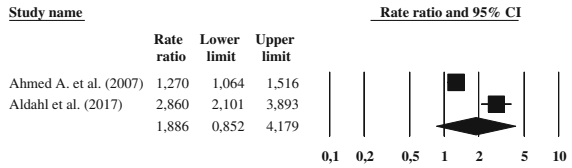
Association of hypokalemia and CVM in the older general population



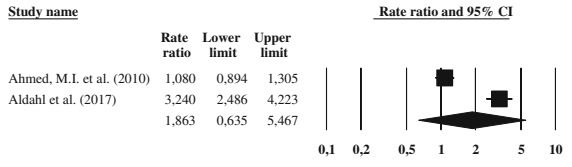
Association of hyperkalemia and CVM in the older general population



Association of hypokalemia and CVM in heart failure population



Association of hyperkalemia and CVM in heart failure population



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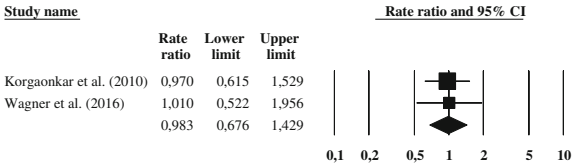
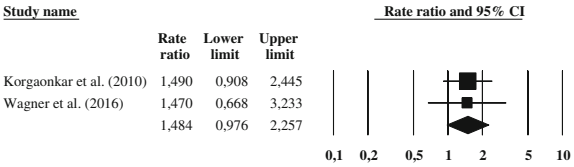


Association of hyperkalemia and CVM in CKD population



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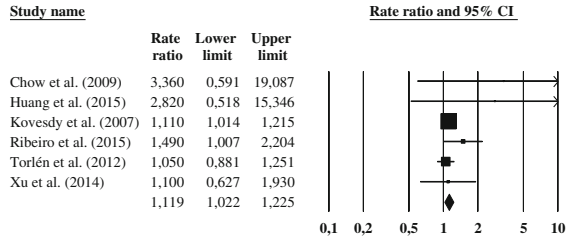

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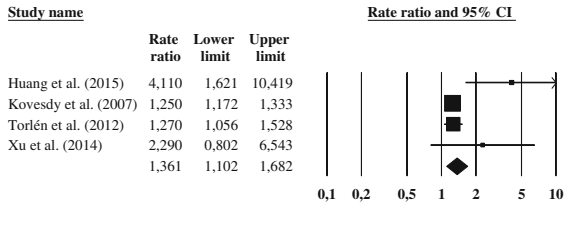
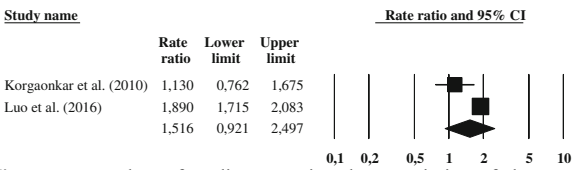


Association of hypokalemia and composite CV outcomes in CKD population



Association of hyperkalemia and composite CV outcomes in CKD population

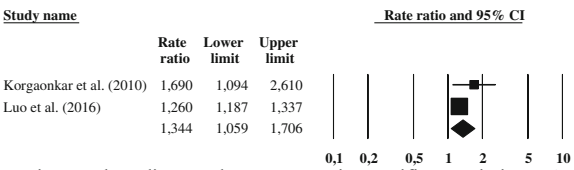


Fig. 2 Forest plots of studies assessing the association of abnormal serum potassium and cardiovascular outcomes in specific populations. *AMI* acute myocardial infarction, *CKD* chronic kidney disease, *CV* cardiovascular, *CVM* cardiovascular mortality, *CI* Confidence interval

Supraventricular and Ventricular Arrhythmias

In the older general population, the low serum K^+ group had an increased risk of supraventricular arrhythmias by 62% (1.62 [1.02; 2.55]). When an AMI was diagnosed, risk of ventricular arrhythmias was increased by even 108% (2.08 [0.89; 4.85]). However, this result was not statistically significant. In addition, there was a 133% increased risk of ventricular arrhythmias in AMI patients with high serum K^+ levels (2.33 [1.60; 3.38]). However, no increased risk of supraventricular arrhythmias was observed for hyperkalemia in the older general population (0.96 [0.24; 3.91]).

Cardiovascular Mortality (CVM)

In contrast to the outcome of supraventricular arrhythmias, high serum K^+ levels in the older general population were associated with a 1.4-fold increased CVM, while no association was detected for low serum K^+ levels and CVM. Furthermore, CVM was significantly increased in dialysis patients for both low (1.11 [1.02; 1.21]) and high (1.36 [1.10; 1.68]) serum K^+ levels. The same pattern of increased CVM in subjects with low or high serum K^+ levels was observed in heart failure patients but effect estimates were not statistically significant.

Composite Cardiovascular (CV) Outcome

In hypertensive patients, the risk of CV outcomes was significantly increased by 157% (2.57 [1.51; 4.36]) and 65% (1.65 [1.02; 2.67]) for the low and the high serum K^+ category, respectively. Moreover, both CKD patients (1.34 [1.06; 1.71]) and dialysis patients (1.12 [1.03; 1.23]) with high serum K^+ had an increased risk of CV outcomes.

Shape of the Relationship of Serum K^+ Levels and Cardiovascular (CV) Outcomes

For a visual assessment of the association of serum K^+ levels and CV outcomes, the RRs and CIs reported in Table 2 have been illustrated in Fig. 3. A U-shaped relationship was found for a composite CV outcome in a population with hypertension (Fig. 3c), for ventricular arrhythmias in patients with AMI (Fig. 3d), for CVM in heart failure patients (Fig. 3e), for a composite CV outcome in a population with CKD (Fig. 3f), and for CVM in patients on dialysis (Fig. 3h). However, it should be noted that some RRs were not statistically significant as their CIs included the value 1.

No U-shaped association was found for the risk of supraventricular arrhythmias in the older general population. Instead, there was an increased risk for subjects in the low serum K^+ category only (Fig. 3a).

In contrast, only the high serum K^+ category was associated with increased CVM in both the older general population (Fig. 3b) and in CKD patients (Fig. 3g). Likewise, high serum K^+ was associated with a composite CV outcome in dialysis patients (Fig. 3i).

Discussion

Summary of the Findings

This systematic review and meta-analysis examined the association of abnormal serum K^+ levels with CV outcomes in the older general population and populations with hypertension, AMI, heart failure, CKD, and dialysis treatment. Results showed partly strong associations of abnormal serum potassium levels with supraventricular and ventricular arrhythmias, CVM, and composite CV outcomes.

Discussion of Results of the Meta-Analyses

Older General Population

While hypokalemia was associated with an increased risk of supraventricular arrhythmias (defined as atrial flutter and atrial fibrillation) [39] in the older general population, it was not associated with CVM. Therefore, we presume that hypokalemia-induced arrhythmias, especially atrial arrhythmias, rarely have a fatal outcome in the older general population.

In contrary, hyperkalemia was not associated with an increased risk of supraventricular arrhythmias defined as atrial flutter and atrial fibrillation in one small study [39]. As no other study assessed the association of hyperkalemia and arrhythmias, we cannot rule out that hyperkalemia possibly is associated with ventricular arrhythmias in the older general population. In fact, it is well known that hyperkalemia can cause fatal cardiac arrhythmias [63–65]. Moreover, ventricular fibrillation represents the main cause of sudden cardiac death [66, 67]. Consistent with this, is the observation that hyperkalemia was associated with increased CVM. Hence, the observed increased CVM could result at least partly from fatal ventricular arrhythmias in the course of hyperkalemia.

Subjects with Acute Myocardial Infarction (AMI)

A different systematic review identified low serum K^+ levels as a risk factor for primary ventricular fibrillation during AMI [68]. Even if only on the border to statistical significance, our review similarly revealed an increased risk of ventricular arrhythmias in hypokalemic patients with AMI [27, 36, 57].

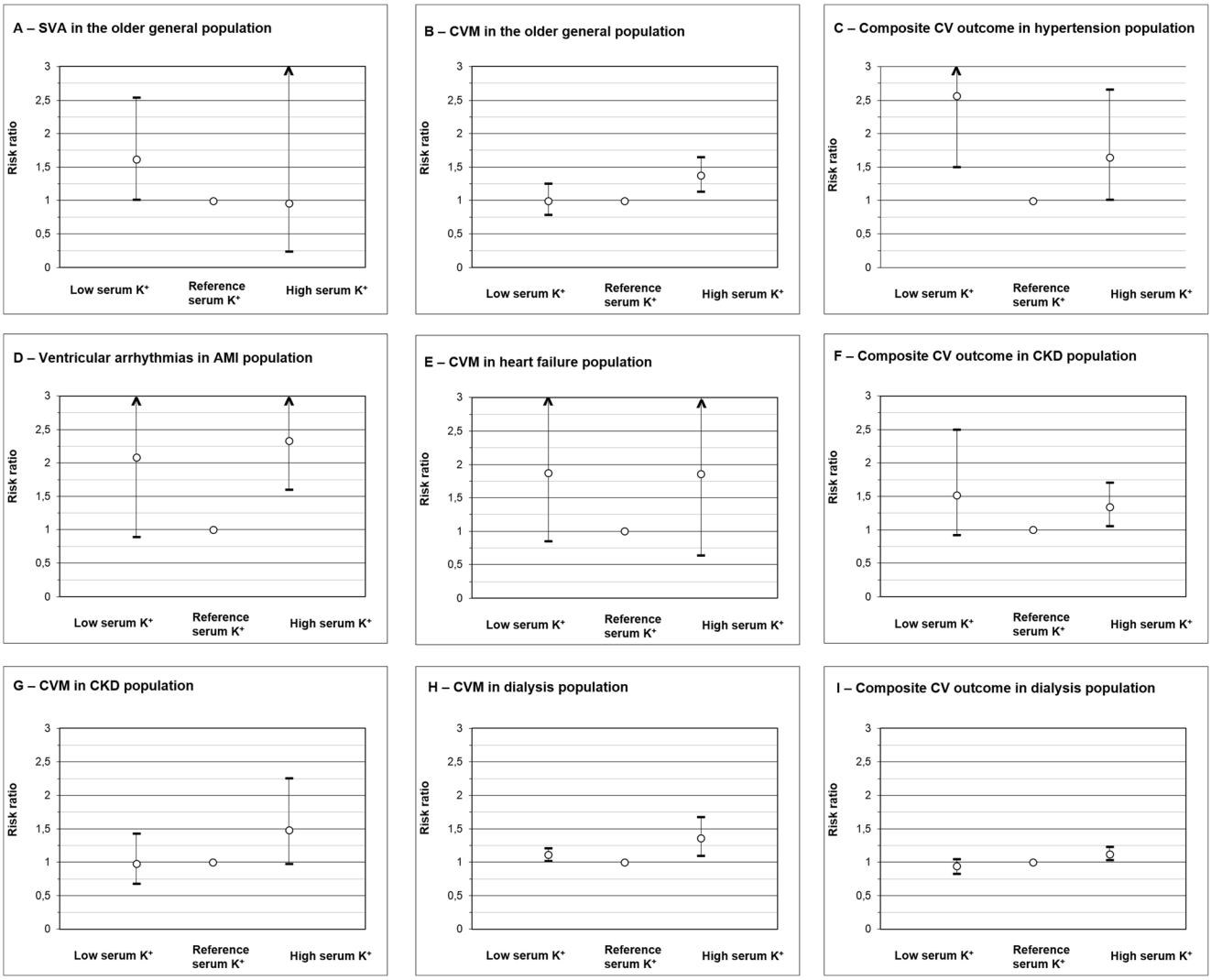


Fig. 3 Risk ratios of cardiovascular outcomes for low and high serum potassium levels within specific populations. Cardiovascular outcomes are shown for the older general population (**a**, **b**) and populations with hypertension (**c**), acute myocardial infarction (**d**), heart failure (**e**), chronic kidney disease (**f**, **g**), and dialysis treatment (**h**, **i**). A pooled estimate is shown if there is more than one study per population. *AMI* acute myocardial infarction, *CKD* chronic kidney disease, *CV* cardiovascular, *CVM* cardiovascular mortality, K^+ potassium, *SVA* supraventricular arrhythmias

During AMI, hypokalemia-induced arrhythmias are known to result from the effects of highly released catecholamines which cause an intracellular shift of potassium [4]. Interestingly, the risk of ventricular arrhythmias during AMI was also increased under hyperkalemic conditions. This result supports our aforementioned hypothesis that the association between hyperkalemia and the risk of arrhythmias might be restricted to specific arrhythmias.

Subjects with Heart Failure

We identified two studies which evaluated the association between hypokalemia and CVM in heart failure patients [9, 11]. Both studies individually reported statistically significantly increased associations of hypokalemia and CVM, while the pooled result was not statistically significant. This was due to high heterogeneity between the two studies ($I = 95.0\%$), which could origin from different serum K^+ categories used. The study of Ahmed A. et al. [9] reported a slightly increased CVM (1.27 [1.06, 1.51]) in patients with chronic heart failure who had serum K^+ levels below 4 mmol/L [9], whereas the study of Aldahl et al. [11] reported a very strongly increased CVM (2.86 [2.10; 3.89]) in heart failure patients with serum K^+ levels below 3.5 mmol/L. Moreover, in the study of Ahmed A. et al., which was published in 2007, the majority of the study population received angiotensin-converting enzyme (ACE) inhibitors and mainly non-potassium-sparing diuretics, such as thiazides and loop diuretics. However, these diuretics, especially if used in higher doses, are able to lower serum K^+ levels, which then may induce fatal

arrhythmias and ultimately increase CVM through this mechanism.

Similarly, the meta-analysis of the two studies on the association of hyperkalemia and CVM [10, 11] also showed high heterogeneity ($I = 97.7\%$) and the pooled result lacked statistical significance (1.86 [0.64; 5.47]). While Ahmed M.I. et al. did not observe an increased CVM in a group with serum K^+ levels above 5 mmol/L (1.08 [0.89; 1.30]), the study of Aldahl et al. showed statistically significant associations with CVM for serum K^+ levels above 4.5 mmol/L, with the strongest association in a group with levels above 5.5 mmol/L (3.24 [2.49; 4.23]. Therefore, further studies are needed for the endpoint CVM in heart failure patients because of the high heterogeneity of the limited number of studies.

According to current guidelines of the European Society of Cardiology (ESC) [69], first-choice drugs in heart failure patients include ACE inhibitors, β-blockers, angiotensin receptor blockers, and aldosterone receptor blockers. Apart from β-blockers, these disease-modifying drugs all retain serum K^+. Low-dose (non-potassium-sparing) diuretics are additionally used for symptomatic relief in patients with signs and/or symptoms of congestion. Thus, theoretically instead of hypokalemia rather hyperkalemia becomes the more serious problem in heart failure patients.

Subjects with Chronic Kidney Disease (CKD)

As renal elimination is crucial to maintain physiological serum K^+ levels, subjects with impaired kidney function are at increased risk of hyperkalemia [6, 70]. Consequently, hyperkalemia can be regarded as a symptom of progressive CKD, which is known to be a risk factor for CVD [71]. Accordingly, non-significant increased CVM (1.48 [0.98, 2.26]) and a significantly increased risk for composite CV outcomes (1.34 [1.06, 1.71]) were detected for hyperkalemic subjects with CKD in this review. In contrast, while no significant association of hypokalemic conditions and CVM was found, the association with an increased risk of composite CV outcomes was on the border to statistical significance (1.52 [0.92, 2.50]).

Subjects Receiving Dialysis

In subjects with end-stage renal disease, dialysis is used to imitate kidney function. During dialytic procedures, waste products and excessive substances from the blood are filtered into an individually mixed dialysate solution. Due to a concentration gradient between the dialysate potassium and the serum K^+, excessive potassium is removed and the serum K^+ level normalizes. Many studies have already assessed the association between dialysate potassium and risk of CV outcomes, such as sudden cardiac death [38, 72–78]. Although low dialysate potassium is needed to normalize predialysis hyperkalemia, excessive filtering of serum K^+ can result in hypokalemia. Therefore, subjects on dialysis are at an increased risk of both hypo- and hyperkalemia, which both may cause arrhythmias leading even to sudden cardiac death. Accordingly, our meta-analyses showed that both low and high serum K^+ levels were statistically significantly associated with increased CVM in patients on dialysis.

Subjects with Hypertension

Among other drugs, (non-potassium-sparing) diuretics are used as a first-line treatment in subjects with hypertension [79]. One study [18] specifically focused on subjects with hypertension receiving diuretic treatment and observed a highly increased risk of a composite CV outcome for both hypo- and hyperkalemia. Moreover, this study detected that diuretic use was more prevalent in hypokalemic subjects and less prevalent in hyperkalemic subjects when compared to subjects with normokalemic levels. This finding supports the assumption that hypertensive subjects who receive diuretic treatment have a particularly high risk of hypokalemia. However, it should be considered, that the aforementioned observational study covered more than 20 years (1973 to 1996) with crucial changes concerning the usage and dosage of (non-potassium sparing) diuretics. Nowadays, treatment of hypertension includes only low-dose hydrochlorothiazides, which have minor potential effects on serum K^+.

In addition, the increased CV risk by hyperkalemia in hypertension might be explained by renal comorbidity, which is frequent in hypertensive patients because high blood pressure can damage renal blood vessels [80]. Therefore, also in patients with hypertension, the association of hyperkalemia and CV endpoints may not be causal because hyperkalemia could be a symptom of progressive CKD, which is known to be a risk factor for CVD [71].

Research Gaps and Implications for Future Studies

Due to various outcomes and populations, we had a maximum of six studies pooled per meta-analysis. Future research should therefore continue to add studies on populations and outcomes where statistically significant results are currently lacking in the meta-analyses or where no study has been conducted so far. In addition, future studies on arrhythmias should have a prospective design by performing regular follow-up investigations with ECG recordings. New studies on abnormal serum K^+ levels and CV outcomes are still needed to close these surprisingly many gaps of evidence in the literature.

Strengths and Limitations

Literature Search

As we only searched two medical databases, we could have missed potentially relevant studies. However, as only five additional studies were identified through a thorough cross-referencing, we do not think that an important study was missed.

Reported Study Results

Many included studies were quite old and lacked adequate statistical analyses and reporting of results. In particular, many studies on arrhythmias originate from the 1980s and had low scores in the risk of bias assessment. Moreover, in former studies among patients receiving diuretics, higher doses of non-potassium sparing diuretics were prescribed until the late 1980s, which may explain the high arrhythmia rate and possibly resulting CV deaths. Furthermore, cutoff values for low, reference, and high serum K^+ levels differed between the included studies. However, by including only studies with appropriate reference categories of serum K^+ levels in the meta-analyses, we managed that the studies were mostly comparable and similar to the limits proposed by the American Heart Association (3.5–5.1 mmol/L [3]). New studies should categorize serum K^+ levels according to recommended clinical cut-off values and thoroughly report risk estimates and CIs.

Control of Confounding

The studies included in the meta-analyses were quite heterogeneous with regard to covariate adjustment. While all of the studies are adjusted for at least age and sex, only few studies had comparable additional adjustments and lacked adjustment for important confounders. Therefore, we suggest a set of key covariates, which future studies on this topic could use, i.e., age, sex, BMI or other weight measure, smoking, diabetes, hypertension, history of CVD, and kidney disease.

Heterogeneity

Despite the described differences in study designs, heterogeneity was low in most of the meta-analyses. However, significant heterogeneity ($p < 0.05$) was detected among the three studies assessing the association of low serum K^+ levels and ventricular arrhythmias in AMI patients ($I^2 = 80.4\%$), the two studies on CVM in hypokalemic heart failure patients ($I = 95.0\%$) and the two studies on CVM and hyperkalemic heart failure patients (97.7%). Furthermore, there was significant heterogeneity among the two studies investigating the association of low serum K^+ levels and a composite CV outcome in CKD patients ($I^2 = 83.8\%$). Of note is that all four meta-analyses revealed non-significant increased associations of abnormal serum K^+ levels and the corresponding outcome. One possible explanation of the heterogeneity in the latter meta-analysis is that definitions of the composite CV outcomes were quite different in the included studies (Online Resource 5).

Composite Outcomes

In addition, atherosclerotic events, namely myocardial infarction and not specified stroke, were part of the composite CV outcomes. Although there is no plausible association for low serum K^+ levels and myocardial infarction, the latter was part of the search strategy in order to identify CV deaths due to myocardial infarction. However, we did not explicitly implement "cerebrovascular diseases" in our search strategy, as except for embolic stroke, which may develop in the course of hypokalemia-induced atrial fibrillation, abnormal serum K^+ levels have not been reported to be risk factors for cerebrovascular disease events. Therefore, we suspect that the included studies with composite CV outcomes might have underestimated the risk of hypo- and hyperkalemia. Thus, we suggest that future studies with composite CV endpoints should consider excluding atherosclerotic events, such as myocardial infarction and ischemic stroke, from their endpoint definitions.

Similarly, the definitions of the outcome "ventricular arrhythmias" were heterogeneous between included studies (Online Resource 5). While some studies investigated ventricular tachycardia, ventricular flutter, or ventricular fibrillation, others measured abnormal ectopic ventricular activity or premature ventricular complexes. Consequently, the percentages of subjects experiencing ventricular arrhythmias ranged widely in the included studies. We intended to do arrhythmia subtype-specific meta-analyses but this was not completely possible because only three studies had sufficient data for meta-analysis and used composite arrhythmia outcomes [27, 36, 57]. These three studies had quite comparable arrhythmia rates (4.4, 6.1, and 10.6%, respectively) and were finally pooled in a meta-analysis. Future studies should be large enough to address clearly defined arrhythmia sub-types instead of composite arrhythmia definitions.

Clinical Implications for Maintaining Serum Potassium Levels in Specific Ranges

As recommended by experts with affiliation to the American Heart association [3], serum K^+ levels should be maintained between 3.5 and 5.1 mmol/L in the older general population in order to prevent supraventricular and ventricular arrhythmias, as well as CVM. For patients with hypertension or heart failure a higher cutoff of

4.0 mmol/L has been suggested for hypokalemia [81, 82]. This recommendation is supported by the observed increased CV risk for low serum K^+ levels in these two aforementioned patient groups sometimes treated with non-potassium-sparing diuretics. As the corresponding studies had been conducted before current guidelines for the management of hypertension [79] and heart failure [69] were published, the study results need to be interpreted with caution. In patients with hypertension, non-potassium-sparing diuretics are nowadays used in low doses and often in combination with potassium-sparing agents. In patients with heart failure, the aforementioned CV risk for hypokalemia should no longer exist since they receive ACE inhibitors, angiotensin receptor blockers, or aldosterone antagonists, all retaining serum K^+. However, we believe that it is important to cautiously monitor serum K^+ levels when thiazide or even loop diuretics, especially in higher doses, are prescribed for patients with hypertension or heart failure.

For patients with AMI, an even higher threshold for hypokalemia has been suggested, namely 4.5 mmol/L during or shortly after AMI [83]. As we detected a borderline significant 2-fold increased risk of arrhythmias in AMI patients with low serum K^+ levels, we agree with this recommendation to target serum K^+ levels in the high-normal range in these patients. However, hyperkalemia could also be a threat because AMI patients showed a strongly increased arrhythmia risk with serum K^+ levels ≥ 5.5 mmol/L [27].

For subjects with CKD or end-stage renal disease requiring dialysis, it is difficult to reach serum K^+ levels $\leq$ 5.1 mmol/L. Therefore, some studies suggested a higher cutoff of > 5.5 mmol/L for hyperkalemia in these patients [76, 84]. However, this systematic review included large cohort studies in patients with impaired kidney function [43] and dialysis treatment [38], which assessed the shape of the association of serum K^+ levels and CV outcomes and did observe an increased risk for serum K^+ levels above 5.0 mmol/L [38, 43]. In addition, it should be noted that another large observational study with almost 100,000 CKD patients [85] showed in a spline analysis that all-cause mortality of CKD patients already started to increase at serum K^+ levels above 5.0 mmol/L.

Conclusions

This systematic review and meta-analysis observed associations of low serum K^+ levels with supraventricular arrhythmias and associations of high serum K^+ levels with CVM in the older general population. Associations of abnormal serum K^+ levels and CV outcomes were even more pronounced in populations with hypertension, AMI, heart failure, CKD, or dialysis. Although the observational studies included in this systematic review cannot ascertain causality of the aforementioned significant associations, their results highlight the clinical relevance of maintaining serum K^+ levels within the reference range. More frequent potassium-monitoring and subsequent interventions, e.g., change or withdrawal of potassium-influencing drugs, might help to restore normal values and prevent cardiovascular events.

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Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflict of interest.

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