European Journal of Preventive Cardiology

ESC European Society of Cardiology

Review

European Journal of Preventive Cardiology
2018, Vol. 25(6) 576–595

DOI: 10.1177/2047487318759694
journals.sagepub.com/home/ejpc

SAGE

Association of serum potassium concentration with mortality and ventricular arrhythmias in patients with acute myocardial infarction: A systematic review and meta-analysis

Miriam Giovanna Colombo[1,2,*], Inge Kirchberger[1,2,3,4,*], Ute Amann[1,2,3], Lisa Dinser[1,2] and Christa Meisinger[1,2,3]

Abstract

Background: Challenging clinical practice guidelines that recommend serum potassium concentration between 4.0–5.0 mEq/L or ≥4.5 mEq/L in patients with acute myocardial infarction, recent studies found increased mortality risks in patients with a serum potassium concentration of ≥4.5 mEq/L. Studies investigating consequences of hypokalemia after acute myocardial infarction revealed conflicting results. Therefore, the aim of this systematic review and meta-analysis was to combine evidence from previous studies on the association of serum potassium concentration with both short and long-term mortality as well as the occurrence of ventricular arrhythmias.

Design: Systematic review and meta-analysis.

Methods: A structured search of MEDLINE and EMBASE databases yielded 23 articles published between 1990 and January 2017 that met the inclusion criteria. Study selection, data extraction and quality assessment were carried out by three reviewers. Random effects models were used to pool estimates across the included studies and sensitivity analyses were performed when possible.

Results: Twelve studies were included in the meta-analysis. Both pooled results from six studies investigating short-term mortality and from five studies examining long-term mortality revealed significantly increased risks in patients with serum potassium concentrations of <3.5 mEq/L, 4.5–<5.0 mEq/L and ≥5.0 mEq/L after acute myocardial infarction. In addition, a serum potassium concentration of <3.5 mEq/L was significantly associated with the occurrence of ventricular arrhythmias.

Conclusions: Mortality, both short and long term, and the occurrence of ventricular arrhythmias in patients with acute myocardial infarction seem to be negatively associated with hypokalemic serum potassium concentration. There is evidence for adverse consequences of serum potassium concentrations of ≥4.5 mEq/L. Due to the heterogeneity among existing studies, further research is necessary to confirm the need to change clinical practice guidelines.

Keywords

Myocardial infarction, hypokalemia, hyperkalemia, mortality, arrhythmia, meta-analysis

Received 22 November 2017; accepted 26 January 2018

[1]MONICA/KORA Myocardial Infarction Registry, Central Hospital of Augsburg, Germany
[2]Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Germany
[3]Chair of Epidemiology, UNIKA-T, Ludwig-Maximilians-Universität München, Germany
[4]Centro de Investigación Biomédica en Red, Enfermedades Cardiovasculares (CIBERcv), Spain
[*]The first two authors contributed equally

Corresponding author:
Inge Kirchberger, Chair of Epidemiology, UNIKA-T, Neusässer Str. 47, 86156 Augsburg, Germany.
Email: i.kirchberger@unika-t.de

Introduction

Hypokalemia (serum potassium concentration (SPC) < 3.5 mEq/L) and hyperkalemia (SPC ≥ 5.0 mEq/L) can have a variety of adverse consequences in patients hospitalised after a cardiovascular event, for instance higher mortality risks or ventricular arrhythmia (VA).[1–4] For patients with acute myocardial infarction (AMI), clinical practice guidelines recommend SPCs of at least 4.0 mEq/L,[4] between 4.0 and 5.0 mEq/L[6,7] or above 4.5 mEq/L.[8] However, recent studies in patients with AMI indicated that a SPC of 4.5 mEq/L or greater was associated with increased inhospital and 3-year mortality, respectively.[9–11] Moreover, results from available studies investigating the consequences of hypokalemia were conflicting. Hypokalemia was found to be associated with VA[9,12–16] and higher mortality[9,10,15] in some studies, whereas others did not find increased risks for VA[10,17–19] or mortality[11,16,19] in patients with AMI.

So far, although a number of studies are available, it is difficult to reach an evidence-based conclusion to suggest SPC might have adverse consequences in AMI patients. Thus the objective of this study was to provide a systematic review and meta-analysis of studies assessing the association of SPC with both short and long-term mortality as well as VA in patients with AMI.

Methods

The meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[20]

Eligibility criteria

The study's inclusion criteria were as follows: (a) subjects with AMI; (b) assessment of SPC; (c) assessment of mortality and/or VA; (d) humans.

Definition of endpoints

Short-term mortality includes assessments of all-cause mortality within 6 months after AMI whereas long-term mortality was defined as all-cause mortality later than 6 months. VA was defined as abnormal rapid heart rhythms that originate in the lower chambers of the heart, such as ventricular tachycardia (VT) or ventricular fibrillation (VF).

Data sources and search strategy

The MEDLINE and EMBASE databases (1990 to 25 January 2017) were searched for studies that examined the association of SPC with mortality and/or VA in patients with AMI using the following MeSH headings/text words: potassium/blood; hypokalemia; hyperkalemia; mortality; arrhythmia, cardiac; tachycardia, ventricular; fibrillation, ventricular. The detailed strategy is shown in Supplementary Tables 1 and 2. No language restrictions were applied. Electronic searches were supplemented with a review of the reference lists of retrieved articles.

Study selection

The screening of titles and abstracts for eligibility was carried out by two authors independently (MGC and LD, MGC and IK, MGC and UA). Disagreements were solved by discussion or by reading the full text article. The full texts were also read independently by two authors (MGC and IK, MGC and UA). Disagreements were solved by discussion. The decision as to which studies to include in the meta-analysis was based on the quality assessment and on the SPC category used as reference to ensure comparability of effect sizes across studies. Studies scoring higher than five in the quality assessment were included.

Data extraction

Two authors each (MGC and IK, MGC and UA) extracted and collected data independently. Disagreements were resolved by discussion. The following data were abstracted: publication information (authors, title, journal, publication year); study characteristics (design, objectives, data source, data collection period, inclusion/exclusion criteria); patient characteristics (sample size, age, sex, event rates (short and long-term mortality and VA); methods (AMI definition, SPC measurement and classification, statistical methods, confounders); and reported outcomes (definition, assessment, effect sizes). Studies reported SPC in milliequvalents per litre (mEq/L) or millimoles per liter (mmol/L). Both units can be used interchangeably in this case, but for the sake of simplicity mEq/L will be used throughout this article.

Quality assessment

Quality assessment was performed using a selection of 12 items from the checklist for measuring study quality,[21] which are appropriate to assess the quality of observational studies. This checklist was complemented by two items from the Cochrane Collaboration's tool for assessing risk of bias[22] ('Were incomplete outcome data adequately assessed?' and 'Was the study apparently free of other problems that could put it at risk of bias?') as well as three self-developed criteria ('Were withdrawals/drop-outs reported?', 'Were data

collection methods clearly described?' and 'Were appropriate categories chosen to classify SPC?'). Each of the 17 items was scored '1' (yes) or '0' (no or unable to determine) and a summary score was built ranging from 0 (lowest quality) to 17 (highest quality).

Quality assessments were each performed by two authors (MGC and IK, MGC and UA) independently. Disagreements were resolved by discussion.

Meta-analysis

Meta-analysis was performed using the comprehensive meta-analysis software version 3.0.[23] In a conservative approach, the random effects model which allows for variation of true effects across studies was chosen. Heterogeneity was assessed by the I^2 statistics. As the number of included studies was less than 10 for each of the three endpoints, we refrained from any tests on publication bias, which may have too low a power to distinguish chance from reality.[24]

Results

The literature search revealed 2285 publications (see Figure 1). We identified 23 articles fulfilling our inclusion criteria (see Table 1). Apart from one study,[15] all of them were observational studies. Five papers investigated the association between SPC and all three outcomes (short, long-term mortality and VA). The summary quality scores assessed for each paper are provided in Table 1. Overall, only three studies did not reach a quality score higher than five.[25–27] Adjustment for relevant confounders was a crucial determinant during quality assessment. Supplementary Table 3 provides an overview of the confounders considered in each of the included studies.

Short-term mortality

The literature search yielded 12 studies which investigated the association between SPC and short-term mortality (see Table 2). In three out of six studies that

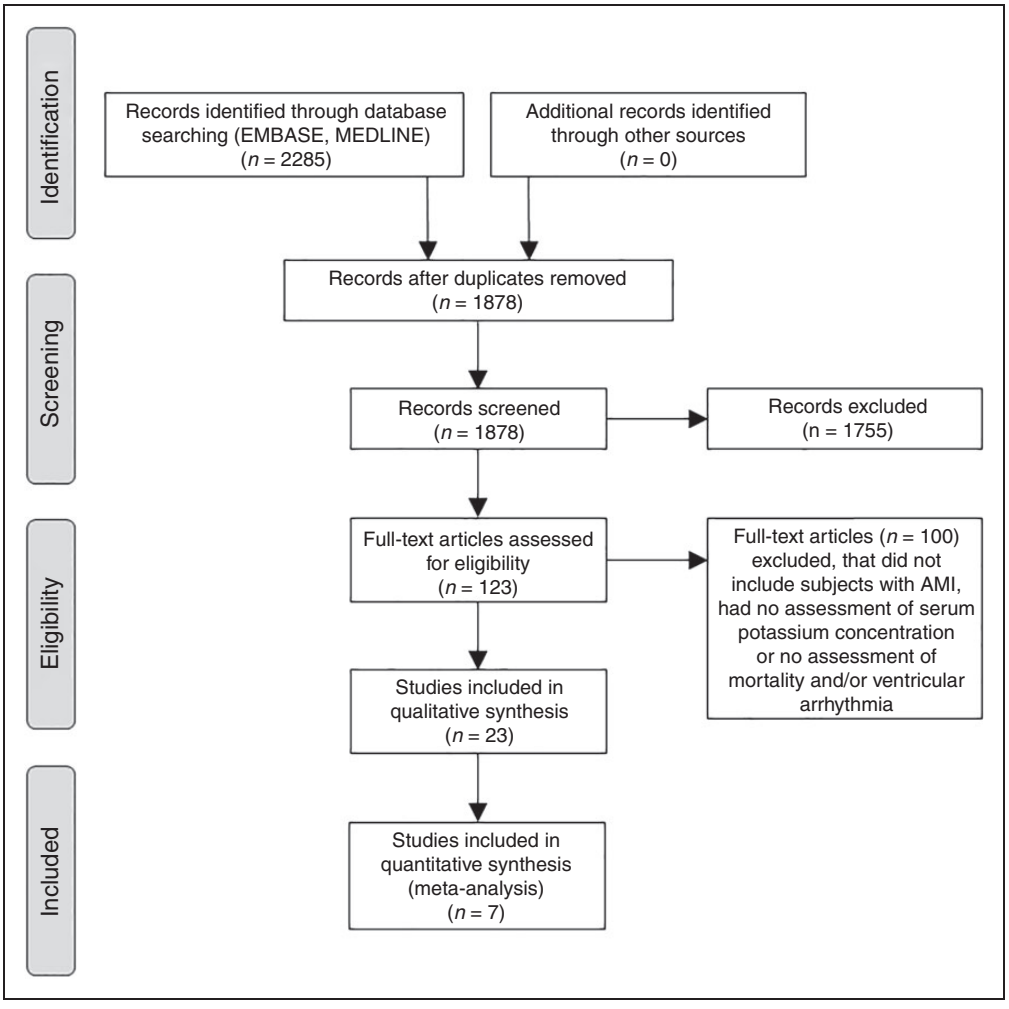

Figure 1. Flow diagram.

Table 1. Summary of 23 studies investigating potassium level with mortality and/or ventricular arrhythmia in patients with acute myocardial infarction.

[Ref.]	Year of publication	Country of data collection	SPC measurement		Sample size	Age Mean ± SD (years)	Sex (% male)	Outcomes and study estimates (e.g. OR, HR)			Quality score 0–17
			Single or mean SPC	Unit				Short-term mortality	Long-term mortality	Ventricular arrhythmia	
[28]	2016	Turkey	Mean SPC	mEq/L	3760	58.0 ± 11.6	81	OR	HR	OR	17
[29]	2016	USA	Single SPC	mmol/L	38,689	NM	55–60.4[a]	OR	N/A	N/A	16
[30]	2016	Israel	Presumably single SPC	mEq/L	1277	64 ± 13	78	HR	HR	% Occurrence	11
[31]	2016	USA	Single SPC	mmol/L	3304	71 ± 23/77 ± 12[b]	62/52[b]	OR	HR	N/A	10
[16]	2016	Turkey	Single SPC on hospital admission	mmol/L	612	59 ± 13.6	86	OR	OR	OR	11
[15]	2015	USA	Single SPC on hospital admission	mEq/L	6515	NM	60.0	HR (related to short-term CV death)	HR	% Event rate	16
[19]	2015	China	Mean post-admission SPC	mEq/L	6613	NM	71.6[c]	HR	N/A	HR	17
[25]	2015	India	Unclear	mEq/L	75 cases (AMI patients) and 25 controls	55	72 (cases)[c]	% Mortality	N/A	N/A	3
[10]	2014	South Korea	Mean of all SPC measure-ments during hospitali-sation	mEq/L	1924	64 ± 12.8	69	% Mortality	HR	% Event rate, OR	16
[11]	2014	Israel	Mean SPC	mEq/L	2434	NM	68.5[c]	N/A	OR	N/A	15
[26]	2013	India	Unclear	mEq/L	75	54.1 ± 11.2	60	N/A	N/A	% Event rate	2
[9]	2012	USA	Admission and mean post-admission SPC	mEq/L	38,689	NM	58.7	OR	N/A	OR (combined with cardiac arrest)	16
[32]	2012	China	Single SPC	mmol/L	468	Median (IQR): 60 (52–69)	77.1	N/A	N/A	OR	7
[33]	2008	Greece	SPC on admission and 2, 4, 6, 12, 36, 48 hours after admission	mg/dL	162	65 ± 12 (survived), 70 ± 12 (deceased)	74.0	% Mortality	N/A	N/A	7
[34]	2003	Poland	Single SPC	mmol/L	204	65	62	N/A	N/A	% Event rate	7
[14]	2011/2001[d]	Iran	Unclear	mEq/L	162	59 ± 6	80.2	N/A	N/A	% Event rate of ventricular tachycardia and OR	4

(continued)

Table 1. Continued

[Ref.]	Year of publication	Country of data collection	SPC measurement: Single or mean SPC	SPC measurement: Unit	Sample size	Age: Mean ± SD (years)	Sex (% male)	Outcomes and study estimates (e.g. OR, HR): Short-term mortality	Outcomes and study estimates (e.g. OR, HR): Long-term mortality	Outcomes and study estimates (e.g. OR, HR): Ventricular arrhythmia	Quality score 0–17
[13]	2000 (data from 1986 to 1989)	USA	SPC on admission	mEq/L	517	63.5 ± 12.3 (LK, $n = 47$)/ 63.1 ± 13.1 (NK, $n = 476$)	68.5[c]	% Mortality	N/A	% Event rate	9
[17]	1994	USA	Single SPC	mg/dL	325 (111 with AMI)	65.0 (all)	63.0 (all)	N/A	N/A	% Event rate	7
[12]	1993	Spain	Single SPC	mEq/L	272	57 ± 11 (with VF), 57 ± 10 (controls)	89	N/A	N/A	OR	8
[35]	1993	Germany	Single SPC	mmol/L	176	67.4	60.2	N/A	N/A	% Event rate	6
[27]	1991	Italy	Unclear	mEq/L	30	60.2 ± 9.7	73	N/A	N/A	OR	3
[36]	1991	Israel	Single SPC	mmol/L	1011	61.1 ± 11	79	N/A	N/A	% Event rate	7
[37]	1993 (data from 1982 to 1983)	Great Britain	Mean SPC	mmol/L	1412 (all) 527 (with MI)	NM	67.5[c]	% Mortality	N/A	% Event rate	8

SPC: serum potassium concentration; IQR: interquartile range; LK: hypokalemia (serum potassium concentration <3.5 mEq/L [13]); NK: normokalemia (not further defined in the article [13]); MI: myocardial infarction; AMI: acute myocardial infarction; N/A: not available; NM: not mentioned; CV: cardiovascular; VA: ventricular arrhythmia; VF: ventricular fibrillation; OR: odds ratio HR: hazard ratio.
[a]Depending on potassium classification group.
[b]Hospital survivors/hospital non-survivors.
[c]Calculated OR by authors of this review.
[d]First published Persian version.

Table 2. Included studies investigating the outcome short-term mortality.

[Ref.]	Included AMI cases	Definition of short-term mortality	SPC measurement: Single or mean SPC	SPC measurement: Unit	SPC categories	*N* per SPC category	Reference category	Mortality %	Effect size: OR or HR or % deaths	Effect size: Estimates	Included in meta-analysis (comment)
[28]	STEMI	Inhospital mortality	Mean SPC	mEq/L	<3.0	22	4.0–<4.5	13.6	OR (95% CI)	2.42 [0.90–10.25]	Included with unadjusted estimates (unfit reference category)
					3.0–<3.5	169		5.3		2.28 [0.78–6.63]	
					3.5–<4.0	819		3.7		1.10 [0.52–2.33]	
					4.0–<4.5	1769		3.1		1 (ref.)	
					4.5–<5.0	693		3.9		1.02 [0.99–2.12]	
					5.0–<5.5	216		8.8		2.28 [1.82–4.13]	
					≥5.5	72		15.3		2.73 [0.96–6.40]	
[29]	STEMI, NSTEMI	Inhospital mortality (stratified by dialysis status)	Single SPC	mmol/L	<5.0	29,560	<5	4.2	OR (95% CI)	1 (ref.) 1.62 [1.41–1.87]	Not included (unfit SPC classification)
					5.0–<5.5	5324		11.1		2.02 [1.68–2.43]	
					5.5–<6.0	2082		16.6		3.18 [2.51–4.03]	
					6.0–<6.5	930		26.6		3.37 [2.60–4.36]	
					≥6.5	793		31.7			
[30]	ACS patients	30-Day mortality	Presumably single SPC	mEq/L	3.5–3.9	330	3.5–3.9	1.5	HR (95% CI)	1 (ref.)	Not included (unfit SPC classification)
					>3.9–4.18	309		2.6		2.43 [0.80–7.36]	
					>4.18–4.45	294		3.1		1.46 [0.47–4.52]	
					4.45–5.2	293		6.1		2.88 [1.05–7.87]	
[31]	AMI (ICD-9 code 410)	Inhospital mortality	Single SPC	mmol/L	<3.3	3304	continuous	10.5	OR (95% CI)	1.17 [1.01–1.35]	Not included (unfit SPC classification)
					3.4–3.7			9.0			
					3.8–4.0			9.6			
					4.1–4.2			11.6			
					≥4.3			15.9			
[16]	STEMI	Inhospital	Single SPC on hospital admission	mmol/L	<3.5	41	3.5–<4.0	2.4	OR (95% CI)	1.08 [0.08–14.50]	Included
					3.5–<4.0	196		1.5		1 (ref.)	
					4.0–<4.5	241		3.3		1.24 [0.27–5.70]	
					4.5–<5.0	108		1.9		0.37 [0.50–2.70]	
					≥5.0	25		16.0		1.77 [0.25–12.40]	
[15]	NSTEMI, unstable angina	14-Day cardio-vascular mortality	Single SPC on hospital admission	mEq/L	<3.5	257	3.5–<4	2.4	HR (95% CI)	3.1 [1.2–8.1]	Included with unadjusted estimates[a] (unfit effect estimate)
					3.5–<4	1696		0.8		1 (ref.)	
					4–<4.5	2684		1.3		1.5 [0.8–2.8]	
					4.5–<5	1378		1.3		1.2 [0.6–2.5]	
					≥5	500		1.8		1.2 [0.5–3.0]	
[19]	STEMI	7-Day all-cause mortality, 30-day all-cause mortality	Mean post-admission SPC	mEq/L	<3.5	272	4.0–<4.5	7-Day: 3.7	HR (95% CI)	7-Day: 0.9 [0.47–1.74]	Included with unadjusted estimates (unfit reference category and effect estimate)
					3.5–<4.0	2146		3.8		1.0 [0.75–1.35]	
					4.0–<4.5	2890		3.7		1 (ref.)	
					4.5–<5.0	1038		5.9		1.43 [1.04–1.97]	
					≥5.0	267		7.1		1.53 [0.93–2.52]	
								30-Day: 6.3		30-Day: 1.03 [0.62–1.71]	
								5.9		1.06 [0.83–1.34]	
								5.3		1 (ref.)	
								8.8		1.52 [1.17–1.98]	
								12.0		1.80 [1.22–2.66]	

(continued)

Table 2. Continued

[Ref.]	Included AMI cases	Definition of short-term mortality	SPC measurement						Effect size		Included in meta-analysis (comment)
			Single or mean SPC	Unit	SPC categories	*N* per SPC category	Reference category	Mortality %	OR or HR or % deaths	Estimates	
[25]	AMI (unclear)	Presumably short-term	Unclear	mEq/L	<3.8, 3.8–5.2, >5.2	75 Cases	N/A	27.2 vs. 10.4[a]	N/A	N/A	Not included (low quality score)
[10]	STEMI, NSTEMI	Inhospital	Mean of all SPC measurements during hospitalisation	mEq/L	<3.5 3.5–<4 4–<4.5 4.5–<5 ≥5	96 907 784 113 24	3.5–<4	6 3 3 9 58	% Deaths	$P < 0.001$	Included
[9]	STEMI, NSTEMI	All-cause in-hospital mortality	Admission and mean post-admission SPC	mEq/L	<3.0 3.0–<3.5 3.5–<4.0 4.0–<4.5 4.5–<5.0 5.0–<5.5 ≥5.5	Admission SPC: 477 3015 11,524 14,261 5949 2094 1369 Mean SPC: 26 778 11,153 16,536 4442 840 251	3.5–<4.0	Admission SPC: 17.2 6.6 4.5 5.0 9.0 15.0 23.1 Mean SPC: 46.2 11.4 4.8 5.0 10.0 24.8 61.4	OR (95% CI)	Admission SPC: 1.93 [1.34–2.78] 1.10 [0.88–1.36] 1 (ref.) 0.93 [0.81–1.08] 1.07 [0.91–1.26] 1.28 [1.04–1.57] 1.31 [1.04–1.64] Mean SPC: 8.11 [2.69–24.4.] 1.45 [1.06–1.99] 1 (ref.) 1.25 [1.09–1.44] 1.96 [1.64–2.34] 3.27 [2.52–4.24] 6.44 [4.27–9.70]	Included
[33]	Patients with discharge diagnosis ACS, AMI or UA who exhibited at least one episode of severe ventricular arrhythmia	Inhospital mortality	SPC on admission and 2, 4, 6, 12, 36, 48 hours after admission	mg/dL	continuous	162	N/A	14.2	Differences in mean SPC according to survival status	0 h, 2 h, 4 h, 6 h, 12 h, 24 h, 36 h: $P > 0.05$ 48 h: $P = 0.06$	Not included (only patients with VA included, no SPC classification)

(continued)

Table 2. Continued

[Ref.]	Included AMI cases	Definition of short-term mortality	SPC measurement						Effect size		Included in meta-analysis (comment)
			Single or mean SPC	Unit	SPC categories	*N* per SPC category	Reference category	Mortality %	OR or HR or % deaths	Estimates	
[13]	STEMI, NSTEMI	All-cause inhospital mortality, cardiac inhospital mortality	SPC on admission	mEq/L	<3.5 ≥3.5	41 476	N/A	All-cause mortality 24.4 18.3 cardiac mortality 17.1 15.3	% Deaths	$P = 0.35$ (all-cause mortality), $P = 0.52$ (cardiac mortality)	Not included (unfit SPC classification)

AMI: acute myocardial infarction; SPC: serum potassium concentration; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; ACS: acute coronary syndrome; N/A: not applicable; NM: not mentioned; HR: hazard ratio; OR: odds ratio; CI: confidence interval.
[a]Hypokalemic patients compared to normokalemic patients.

provided a detailed classification of SPCs, patients with SPC between 3.5 and less than 4.0 mEq/L showed the lowest, unadjusted short-term mortality risk.[9,15,16] In the study by Choi et al.[10] and Ma et al.[19] patients with a SPC of 3.5 to less than 4.0 mEq/L and patients with a SPC of 4.0 to less than 4.5 mEq/L had a similar risk of dying. In contrast, Keskin et al.[28] found a slightly higher inhospital mortality (3.7%) in patients with a SPC of 3.5 to less than 4.0 mEq/L than in patients with a SPC of 4.0 to less than 4.5 mEq/L (3.1%).

Six studies were included in the meta-analysis. The SPC category of 3.5 to less than 4.0 mEq/L served as the reference category. Goyal et al.[9] and Keskin et al.[28] provided more than five SPC categories. In order to fit the required number of categories, both the highest and lowest categories were combined with the next lower or next higher category, respectively. In two studies, adjusted odds ratios (ORs) were used as effect sizes,[9,16] whereas Ma et al.[19] and Patel et al.[15] provided hazard ratios (HRs). Choi et al.[10] reported an unadjusted number of events and Keskin et al.[28] used a different reference category than required. In order to include all studies in the meta-analysis, the unadjusted number of deaths from the studies of Keskin et al.,[28] Ma et al.[19] and Patel et al.[15] was used in the analysis. Four of the included studies investigated inhospital mortality. From Ma et al.[19] the data on 7-day mortality were included, and from Patel et al.[15] data on 14-day mortality were included.

The meta-analysis showed pooled ORs for all SPC categories in a U-shaped manner (see Figure 2). Except for the SPC category of 4.0 to less than 4.5 mEq/L, all estimates were significant. There was no indication for heterogeneity in the analyses of the SPC categories of less than 3.5 mEq/L ($I^2 = 0$), but substantial heterogeneity in the analyses of the SPC categories of 4.0 to less than 4.5 mEq/L ($I^2 = 55.6$), 4.5 to less than 5.0 mEq/L ($I^2 = 74.3$) and 5.0 mEq/L or greater ($I^2 = 89.7$).

As a sensitivity analysis, the studies which were responsible for most of the heterogeneity were excluded and the pooled effect sizes were re-estimated. In the SPC category of 4.0 to less than <4.5 mEq/L, the exclusion of Keskin et al.[28] led to an increase of the pooled OR from 1.06 to 1.17 (95% confidence interval (CI) 1.03–1.33), which was significant in contrast to the previous analysis with all six studies. Exclusion of Uluganyan et al.[16] in the SPC category of 4.5 to less than 5.0 mEq/L resulted in an increase of the pooled effect size from OR 1.53 to 1.60 (95% CI 1.12–2.27). In the SPC category of 5.0 mEq/L or greater the exclusion of Choi et al.[10] led to a reduction of the pooled effect size from OR 3.85 to 2.54 (95% CI 1.64–3.95), which still remained significant.

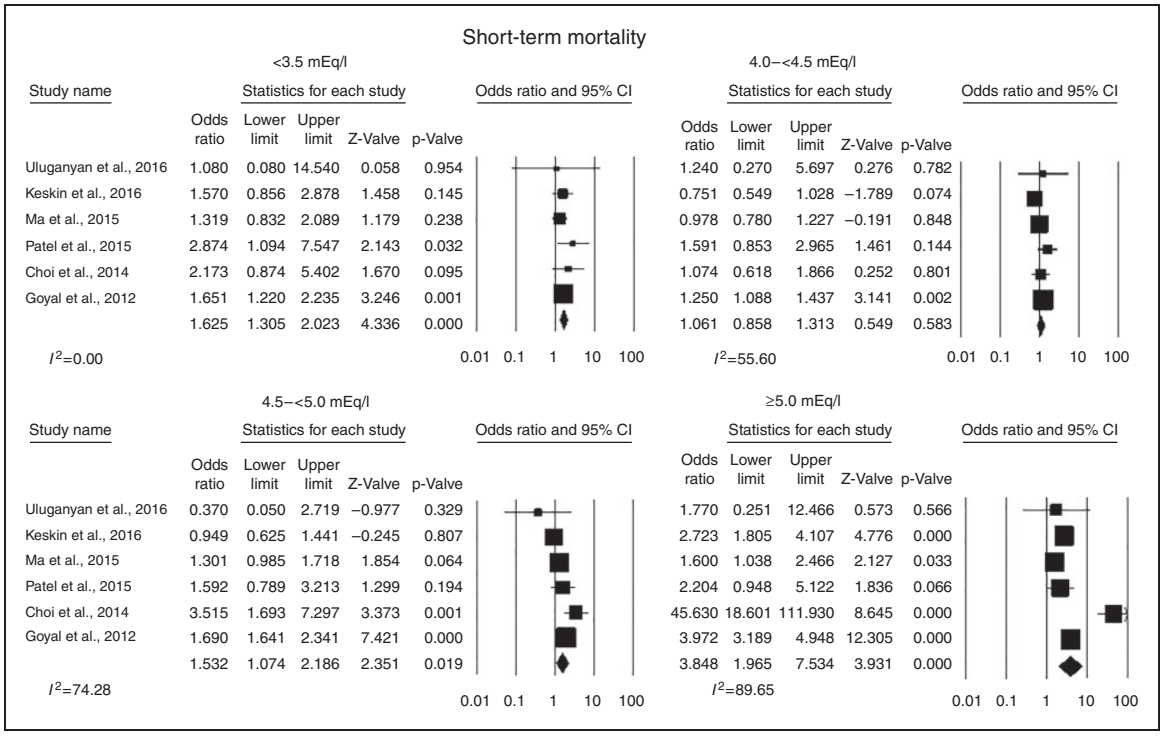

Figure 2. Pooled odds ratios (random effects) of admission serum potassium concentration associated with short-term mortality in patients with acute myocardial infarction.

Long-term mortality

Seven studies were identified investigating the association of SPC and long-term mortality (see Table 3).

In three out of six studies reporting crude mortality rates per SPC category, patients with SPC between 3.5 and less than 4.0 mEq/L showed the lowest, unadjusted long-term mortality risk.[15,16,30] Studies which used a five-level SPC classification with values of 3.5 to less than 4.0 mEq/L as the reference category found a U-shaped association with higher mortality risks for SPC below 3.5 mEq/L, and equal to or above 4.0 mEq/L with a trend for increased risk estimates with increasing SPC[10,15,16] (see Table 3). Shiyovich et al.[11] and Keskin et al.[28] classified SPC into seven categories with values of 4.0 to 4.5 or less as the reference category. Shiyovich et al.[11] showed that a SPC above 4.5 mEq/L was significantly associated with higher mortality at 6 months, 1 year and 5 years. Keskin et al.[28] found that SPCs less than 3.5 mEq/L as well as SPCs greater than 5.0 mEq/L were associated with a higher 4-year mortality risk compared with the reference concentration.

As the seven studies used different effect estimates (OR and HR) and different reference categories it was not possible to perform a meta-analysis on the results from the adjusted regression models. Nonetheless, it was possible to include unadjusted ORs with values of 3.5 to less than 4.0 mEq/L as the reference category from four studies[10,11,15,28] and adjusted ORs from Uluganyan et al.[16] in the meta-analysis. From the study of Shiyovich et al.,[11] the data on 1-year mortality were used. Significantly higher pooled ORs (1.75, 95% CI 1.28–2.40) were found for SPCs of less than 3.5 mEq/L, for 4.5 to less than 5.0 mEq/L (OR 1.60, 95% CI 1.16–2.19) and for greater than 5.0 mEq/L (OR 3.29, 95% CI 2.10–5.15) (see Figure 3).

Moderate heterogeneity was found in the models for SPC of less than 3.5 mEq/L ($I^2 = 46\%$) and for concentrations of 4.0 to less than <4.5 mEq/L ($I^2 = 48\%$). The pooled models on SPC of 4.5 to less than 5.0 mEq/L and greater than 5.0 mEq/L indicated substantial heterogeneity ($I^2 = 68\%$ and 75%, respectively).

Sensitivity analyses showed that replacing data on 1-year mortality from Shiyovich et al.[11] with data on 6-month mortality from the same study yielded comparable results. The inclusion of unadjusted data instead of adjusted data from Uluganyan et al.[16] resulted in slightly higher effect estimates.

Ventricular arrhythmia

The literature search yielded 18 studies which investigated the association between SPC and VA (see Table 4).

A number of studies dichotomised SPC and compared VA rates in SPC groups of less than 3.5,[13,32,37] less than 3.6[12] or less than 4.0 mEq/L[34] with higher

Table 3. Included studies investigating the outcome long-term mortality.

[Ref.]	Included AMI cases	Definition of long-term mortality	SPC measurement		SPC categories	*N* per SPC category	Reference category	Mortality %	Effect size		Included in meta-analysis (comment)
			Single or mean SPC	Unit					OR or HR	Estimates	
[28]	STEMI	4-Year mortality	Mean SPC	mEq/L	<3.0	22	4.0–<4.5	22.7	HR (95% CI)	4.05 [1.23–15.34]	Included with unadjusted estimates (unfit reference category)
					3.0–<3.5	169		8.3		2.28 [1.18–7.51]	
					3.5 –<4.0	819		4.3		1.22 [0.74.2.74]	
					4.0–<4.5	1769		3.4		1 (ref.)	
					4.5–<5.0	693		5.8		1.30 [0.93–3.09]	
					5.0–<5.5	216		10.6		2.11 [1.23–4.74]	
					≥5.5	72		19.4		4.20 [1.08–8.23]	
[30]	ACS	Out-of-hospital 1-year mortality	Presumably single SPC	mEq/L	3.5–3.9	318	3.5–3.9	4.4	HR (95% CI)	1 (ref.)	Not included (unfit SPC classification)
					>3.9–4.18	286		4.9		1.27 [0.06–2.90]	
					>4.18–4.45	298		6.4		1.25 [0.62–2.50]	
					>4.45–5.2	275		12.0		1.98 [1.05–3.75]	
[31]	AMI (ICD-9 code 410)	1-Year mortality	Single SPC	mmol/L	<3.3	NM	Continuous SPC	NM	HR (95% CI)	1.15 [1.06–1.25]	Not included (unfit SPC classification)
					3.4–3.7						
					3.8–4.0						
					4.1–4.2						
					≥4.3						
[16]	STEMI	6-Month mortality	Single SPC at hospital admission	mmol/L	<3.5	41	3.5–<4	4.9	OR (95% CI)	1.62 [0.24–10.8]	Included
					3.5–<4	196		2.6		1 (ref.)	
					4–<4.5	241		5.4		1.53 [0.47–4.90]	
					4.5–<5	108		6.5		1.58 [0.42–5.90]	
					≥5	25		20.0		2.27 [0.54–11.5]	
[15]	NSTEMI, unstable angina	1-Year mortality	Single SPC at hospital admission	mEq/L	<3.5	257	3.5–<4	6.4	HR (95% CI)	2.2 [1.2–4.1]	Included
					3.5–<4	1696		3.0		1 (ref.)	
					4–<4.5	2684		3.8		1.3 [0.9–1.8]	
					4.5–<5	1378		6.2		1.7 [1.1–2.4]	
					≥5	500		7.4		1.6 [0.99–2.5]	
[10]	STEMI, NSTEMI	3-Year mortality	Mean of all SPC measurements during hospitalisation	mEq/L	<3.5	96,907	3.5–<4	20	HR (95% CI)	1.55 [0.94–2.56]	Included
					3.5–<4	784,113		12		1 (ref.)	
					4–<4.5	24		12		1.09 [0.80–1.48]	
					4.5–<5			22		1.71 [1.04–2.81]	
					≥5			62		4.78 [2.14–10.69]	

(continued)

Table 3. Continued

[Ref.]	Included AMI cases	Definition of long-term mortality	SPC measurement						Effect size		Included in meta-analysis (comment)
			Single or mean SPC	Unit	SPC categories	*N* per SPC category	Reference category	Mortality %	OR or HR	Estimates	
[11]	STEMI, NSTEMI	6-Month, 1, 5, 10-year mortality	Mean SPC	mEq/L	<3.0	141	4.0–≤4.5	6-Month	OR (95% CI)	6-Month	Included with unadjusted estimates (unfit reference category)
					3.0–≤3.5	982		12.1		0.62 [0.29–1.32]	
					3.5–≤4.0	4237		11.0		1.06 [0.80–1.42]	
					4.0–≤4.5	6298		8.5		1.08 [0.88–1.31]	
					4.5–≤5.0	3385		7.1		1 (ref.)	
					5.0–≤5.5	849		10.1		1.25 [1.03–1.52]	
					>5.5	291		15.5		1.53 [1.03–2.27]	
								22.0		2.26 [1.14–4.48]	
								1-Year		1-Year	
								19.1		0.76 [0.40–1.44]	
								14.9		1.03 [0.79–1.34]	
								12.2		1.07 [0.91–1.26]	
								10.2		1 (ref.)	
								14.3		1.26 [1.08–1.48]	
								22.0		1.51 [1.09–2.10]	
								29.9		2.26 [1.26–4.07]	
								5-Year		5-Year	
								44.7		0.83 [0.54–1.27]	
								41.0		1.06 [0.87–1.30]	
								32.4		1.12 [1.00–1.24]	
								27.6		1 (ref.)	
								35.4		1.17 [1.05–1.31]	
								46.2		1.27 [1.03–1.57]	
								52.6;		1.40 [0.90–2.20]	
								10-Year		10-Year	
								73.8		1.14 [0.75–1.73]	
								62.2		1.19 [0.98–1.43]	
								47.7		1.04 [0.95–1.14]	
								44.3		1 (ref.)	
								53.6		1.10 [1.00–1.21]	
								63.7		1.12 [0.93–1.36]	
								72.2		1.30 [0.91–1.86]	

AMI: acute myocardial infarction; SPC: serum potassium concentration; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; ACS: acute coronary syndrome; NM: not mentioned, HR: hazard ratio; OR: odds ratio; CI: confidence interval.

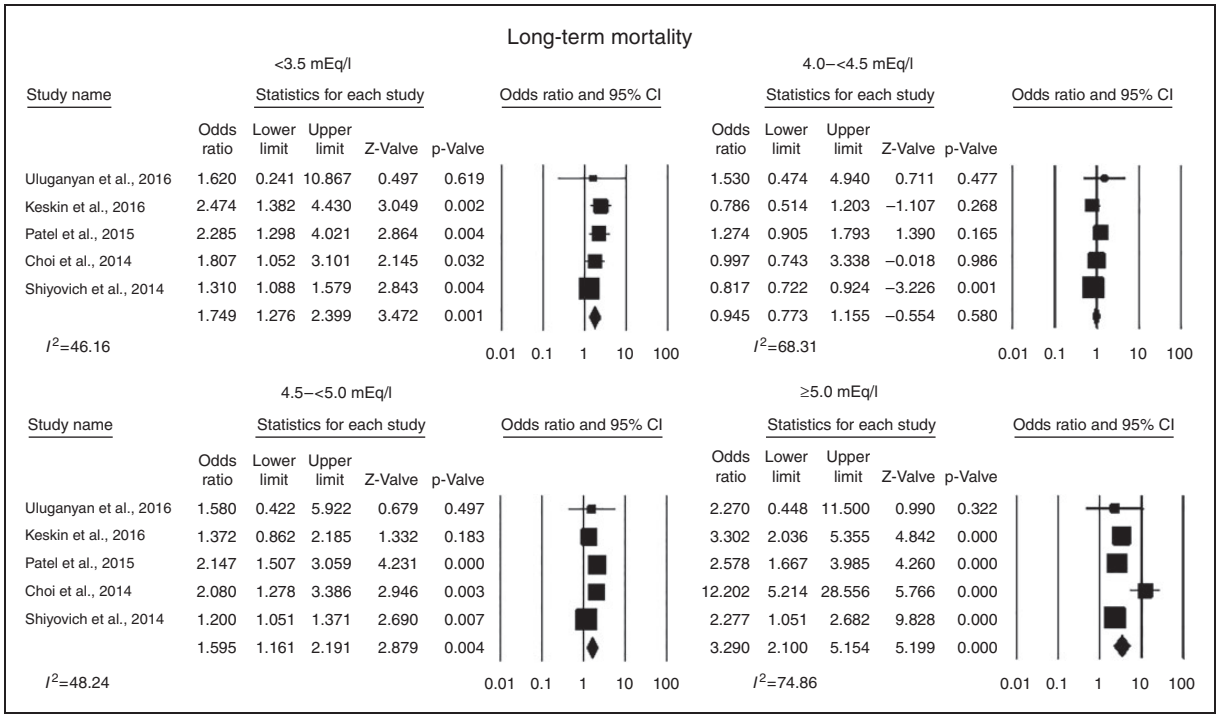

Figure 3. Pooled odds ratios (random effects) of long-term mortality associated with serum potassium concentration relative to category of 3.5–<4.0 mEq/l.

concentrations. Madias et al.[13] found a significantly higher number of VFs in the group of less than 3.5 mEq/L but not a significantly higher occurrence of VT compared with higher SPC. Su et al.[32] and Higham et al.[37] both found a higher number of malignant arrhythmia and VF in patients with SPCs of less than 3.5 mEq/L, and Fiol Sala et al.[12] and Maciejewski et al.[34] confirmed these findings for VF and for VF, VT and atrial fibrillation, with slightly different SPC categories of less than 3.6 and less than 4.0 mEq/L, respectively. Except for Higham et al.,[37] all studies used single admission SPC. Some other studies used a SPC classification that did not match the common categorisation.[17,30,36]

Among the six studies that used a classification of SPC in five or seven categories, four studies reported the highest rates of VA in patients with SPCs less than 3.0 mEq/L[9,28] or less than 3.5 mEq/L.[15,16] In contrast, in the studies from Choi et al.[10] and Ma et al.,[19] patients with SPCs of 5.0 mEq/L or greater had the highest rates of VA occurrence. Multivariable regression analyses revealed a significantly increased VA risk for patients with SPCs less than 3.5 mEq/L in the study by Keskin et al.,[28] whereas Ma et al.,[19] Uluganyan et al.[16] and Choi et al.[10] found no significantly increased risk. Goyal et al.[9] showed a higher odds for SPC of less than 3.5 mEq/L only when single admission SPC was used for the analysis, but not when mean SPC was analysed.

Six studies were included in the meta-analysis.[9,10,15,16,19,28] The SPC category of 3.5 to 4.0 mEq/L or less was used as the reference category. Goyal et al.[9] and Keskin et al.[28] provided more than five SPC categories. In order to fit the required number of categories, both the highest and lowest categories were combined with the next lower or next higher category, respectively. In two studies,[9,16] adjusted ORs were used as effect sizes, whereas Ma et al.[19] provided adjusted HRs and Patel et al.[15] and Choi et al.[10] reported unadjusted numbers of events. Keskin et al.[28] used a different reference category. In order to include all studies in the meta-analysis, the unadjusted number of deaths from the studies of Ma et al.[19] and Keskin et al.[28] was used in the analysis.

For SPCs of less than 3.5 mEq/L a significantly higher pooled OR (1.61, 95% CI 1.31–1.97) was found compared with SPCs of 3.5 to less than 4.0 mEq/L and significantly lower ORs were detected for SPCs of 4.0 to less than 4.5 mEq/L and greater than 5.0 mEq/L (see Figure 4).

No heterogeneity ($I^2 = 0\%$) was found in two of the models. The pooled models on SPCs of 4.5 to less than 5.0 mEq/L and greater than 5.0 mEq/L indicated substantial heterogeneity ($I^2 = 55\%$ and $I^2 = 70\%$, respectively). As the observed heterogeneity may be associated with the differences regarding SPC measurement, separate analyses were run for studies using admission SPCs[9,15,16] or mean SPCs.[9,10,19,28] Within SPCs of less

Table 4. Included studies investigating the outcome ventricular arrhythmia.

[Ref.]	Included AMI cases	Definition of ventricular arrhythmia	SPC measurement: Single or mean SPC	SPC measurement: Unit	SPC categories	*N* per SPC category	Reference category	Ventricular arrhythmia %	Effect size: OR or HR or % events	Effect size: Estimates	Included in meta-analysis (comment)
[28]	STEMI	Inhospital VA	Mean SPC	mEq/L	<3.0 3.0–<3.5 3.5–<4.0 4.0–<4.5 4.5–<5.0 5.0–<5.5 ≥5.5	22 169 819 1769 693 216 72	4.0–<4.5	27.3 10.1 6.6 5.1 5.8 7.4 9.7	OR (%95 CI)	8.23 [2.17–15.89] 2.52 [1.08–5.28] 1.40 [0.99–2.04] 1 (ref.] 1.36 [0.83–1.42] 1.27 [0.96–2.33] 1.82 [0.96–4.18]	Included with unadjusted estimates (unfit reference category)
[30]	ACS	In–hospital VF, VF and VT, VT	Single SPC	mEq/L	3.5–3.9 >3.9–4.18 >4.18–4.45 >4.45–5.2	330 309 294 293	3.5– 3.9	Only shown in Figure 1 in Ref. [29]	% Events	p = 0.26	Not included (unfit SPC classification)
[16]	STEMI	VT, VF	Single SPC on hospital admission	mmol/L	<3.5 3.5–<4 4–<4.5 4.5–<5 ≥5	41 196 241 108 25	3.5–<4	17.1 7.7 10.8 9.3 7.0	OR (95% CI)	2.70 [0.93–7.80] 1 [ref.] 0.93 [0.43–1.90] 0.84 [0.32–2.10] 1.38 [0.34–5.50]	Included
[15]	NSTEMI unstable angina	Non sustained VT ≥8 beats, ventricular pauses ≥3 s	Single SPC on hospital admission	mEq/L	<3.5 3.5–<4 4–<4.5 4.5–<5 ≥5	257 1696 2684 1378 500	3.5–<4	Non-sustained VT: 10.1 7.0 6.9 6.7 4.5 Ventricular pauses: 2.0 3.9 4.7 4.5 5.9	% Events	Non-sustained VT: $P = 0.03$ Ventricular pauses: $P = 0.03$	Included
[10]	STEMI NSTEMI	Inhospital VA occurring before or after coronary angiography	Mean of all SPC measurements during hospitalisation	mEq/L	<3.5 3.5–<4 4–<4.5 4.5–<5 ≥5	96 907 784 113 24	3.5–<4	9 7 5 8 12	% Events	$P = 0.447$	Included

(continued)

Table 4. Continued

[Ref.]	Included AMI cases	Definition of ventricular arrhythmia	SPC measurement: Single or mean SPC	SPC measurement: Unit	SPC categories	*N* per SPC category	Reference category	Ventricular arrhythmia %	Effect size: OR or HR or % events	Effect size: Estimates	Included in meta-analysis (comment)
[9]	STEMI NSTEMI	VF, ventricular flutter or cardiac arrest	Admission and mean post-admission SPC	mEq/L	<3.0 3.0–<3.5 3.5–<4.0 4.0–<4.5 4.5–<5.0 5.0–<5.5 ≥5.5	Admission SPC: 477 3015 11524 14261 5949 2094 1369 Mean SPC: 26 778 11153 16536 4442 840 251	3.5–<4.0	Admission SPC: 15.5 8.2 4.4 3.4 3.8 4.4 5.8 Mean SPC: 19.2 6.3 4.9 4.1 4.1 6.8 14.7	OR (95% CI)	Admission SPC: 2.19 [1.61–2.96] 1.53 [1.28–1.82] 1 (ref.) 0.81 [0.71–0.93] 0.75 [0.63–0.89] 0.75 [0.58–0.96] 0.70 [0.53–0.93] Mean SPC: 2.31 [0.74–7.24] 1.06 [0.761.48] 1 (ref.) 1.03 [0.90–1.17] 1.15 [0.94–1.39] 1.62 [1.16–2.26] 2.65 [1.70–4.13]	Included
[19]	STEMI	7-Day malignant arrhythmia	Mean post-admission SPC	mEq/L	<3.5 3.5–<4.0 4.0–<4.5 4.5–<5.0 ≥5.0	272 2146 2890 1038 267	4.0–<4.5	8.5 6.6 6.4 8.4 10.1	HR (95% CI)	1.24 [0.79–1.92] 1.01 [0.81–1.26] 1 (ref.) 1.20 [0.93–1.55] 1.44 [0.96–2.17]	Included with unadjusted estimates (unfit reference category)
[13]	STEMI NSTEMI	VT, VF	Single SPC on admission	mEq/L	<3.5 ≥3.5	132 378	NM	VT: 22.0, 16.0, VF: 24.4, 13.0	% Event rates	VT: $P = 0.32$, VF: $P = 0.04$	Not included (unfit SPC classification)
[17]	AMI	VT	Single SPC	mg/dL	<3.5 >5.0	21 4	NM	52.4 0	% Event rates	<3.5: $P = 0.88$, >5.0: $P = 0.21$	Not included (unfit SPC classification)
[14]	AMI	VT	Unclear	mEq/L	<3.8 3.8–<4.5 ≥4.5	54 54 54	Unclear	19 10 10	% Event rate of ventricular tachycardia and OR	Risk of tachycardia in SPC category <3.8 sign. ($P < 0.05$) greater than in the two other SPC groups. Sign. ($P = 0.028$) difference between SPC category <3.8 and 3.8 to <4.5.	Not included (low quality score)

(continued)

Table 4. Continued

[Ref.]	Included AMI cases	Definition of ventricular arrhythmia	SPC measurement					Ventricular arrhythmia %	Effect size		Included in meta-analysis (comment)
			Single or mean SPC	Unit	SPC categories	*N* per SPC category	Reference category		OR or HR or % events	Estimates	
[32]	AMI	Malignant VA occurred within 24 hours of symptom onset	Single SPC	mmol/L	<3.5 3.5–5.5	44 424	NM	27.3 7.5	% Event rates	$P < 0.001$	Not included (unfit SPC classification)
[34]	STEMI	VF, VT, atrial fibrillation	Single SPC	mmol/L	<4.0 ≥4.0	69 135	NM	26.0 11.9	% Event rates	$P = 0.001$	Not included (unfit SPC classification)
[12]	AMI	VF	Single SPC	mEq/L	<3.6 ≥3.6	56, 216	≥3.6	NM	OR (95% CI)	1.85 [1.23–2.78]	Not included (unfit SPC classification)
[26]	AMI	Arrhythmia	Unclear	mEq/L	Hypokale-mic/ normoka-lemic[a]	NM	NM	51.1 6.7	% Event rates	'Significant'	Not included (low quality score)
[27]	AMI	VT, premature ventricular contractions	Unclear	mEq/L	Unclear	NM	NM	NM	OR	OR 0.10–0.22 for potassium values >4 mEq/l; under this value a conatant increase of probability with maximum proability at 2.5 mEq/l	Not included (low quality score)
[35]	AMI with Q-waves	VA: <Lown IVb ≥Lown IVb VF	Single SPC	mmol/L	<3.5 3.5–5.1 >5.1	26 141 9	NM	<Lown IVb 42.3 61.0 22.2 ≥Lown IVb 53.8 24.8 55.6 VF 3.8 14.2 22.2	% Event rates	$P > 0.05$	Not included (unfit SPC classification)
[36]	AMI	Malignant arrhythmias	Single SPC	mmol/L	<3.6 3.6–4.2 4.3–5.1 <5.1	NM	NM	68.5 60.7 56.2 50.2	% Event rates	NM	Not included (unfit SPC classification)

(continued)

Table 4. Continued

[Ref.]	Included AMI cases	Definition of ventricular arrhythmia	SPC measurement		SPC categories	*N* per SPC category	Reference category	Ventricular arrhythmia %	Effect size		Included in meta-analysis (comment)
			Single or mean SPC	Unit					OR or HR or % events	Estimates	
[37]	AMI	VF	Mean SPC	mmol/L	<3.5 3.5–5.0	94 340	NM	8.5 2.7	% Event rates	$P < 0.005$	Not included (unfit SPC classification)

AMI: acute myocardial infarction; SPC: serum potassium concentration; STEMI: ST-elevation segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; ACS: acute coronary syndrome; NM: not mentioned; HR: hazard ratio; OR: odds ratio; CI: confidence interval; VA: ventricular arrhythmia; VF: ventricular fibrillation; VT: ventricular tachycardia.

than 3.5 mEq/L in both subgroups a significantly increased pooled risk was found compared with the reference SPC. In contrast, the pooled OR among SPCs of less than 4.0 to less than 4.5 mEq/L was lower and significant in the studies with an admission SPC measurement (OR 0.84, 95% CI 0.75–0.95) compared with the pooled OR in the studies with a mean SPC measurement (OR 0.93, 95% CI 0.81–1.08). In the SPC group 4.5 to 5.0 mEq/L the results were completely different, with a lower pooled OR of 0.80 (95% CI 0.69–0.92) among studies with an admission SPC measurement and a higher pooled OR of 1.15 (95% CI 0.99–1.33) found among studies with a mean SPC measurement. A significant difference between the subgroups was found for SPCs of 5.0 mEq/L or greater with a significantly decreased pooled OR of 0.72 (95% CI 0.60–0.85) in studies with an admission SPC measurement in contrast to a significantly increased pooled OR of 1.61 (95% CI 1.23–2.09) in studies with a mean SPC measurement. No indication of heterogeneity ($I^2 < 34\%$) was found in the analyses above.

Discussion

This systematic review and meta-analysis showed that SPCs less than 3.5 mEq/L and 4.5 mEq/L or greater in patients with AMI were associated with a higher risk of short-term mortality compared with SPCs of 3.5 to less than 4.0 mEq/L. Likewise, a U-shaped association of SPC and long mortality was found, with the exception that patients with SPCs of 4.0 to less than 4.5 mEq/L had a similar risk to patients with SPCs of 3.5 to less than 4.0 mEq/L. In addition, SPCs less than 3.5 mEq/L were associated with an increased risk of VA.

A most interesting result is the finding that the association between SPC and outcomes seems to be U-shaped and that recommendations simply to increase SPC in AMI patients may therefore be misleading. Our meta-analysis indicates that SPCs of 4.5 mEq/L and beyond negatively affect post-AMI survival. This finding may be at least partly explained by the association of hyperkalemia with reduced ventricular excitability that can result in complete heart block and sinus arrest.[38,39] Higher SPCs may also indicate renal failure, which constitutes a major risk factor for post-AMI survival.[40] However, most of the studies included in the meta-analysis have considered renal function as a confounder and SPCs of 5 mEq/L or greater remained significantly associated with higher mortality rates after adjustment.[9,10,15,28]

Overall, the present systematic review and meta-analysis confirmed that SPC of less than 3.5 mEq/L was negatively associated with survival and VA after AMI. This is well known among the medical community and part of all AMI treatment guidelines.[5–8]

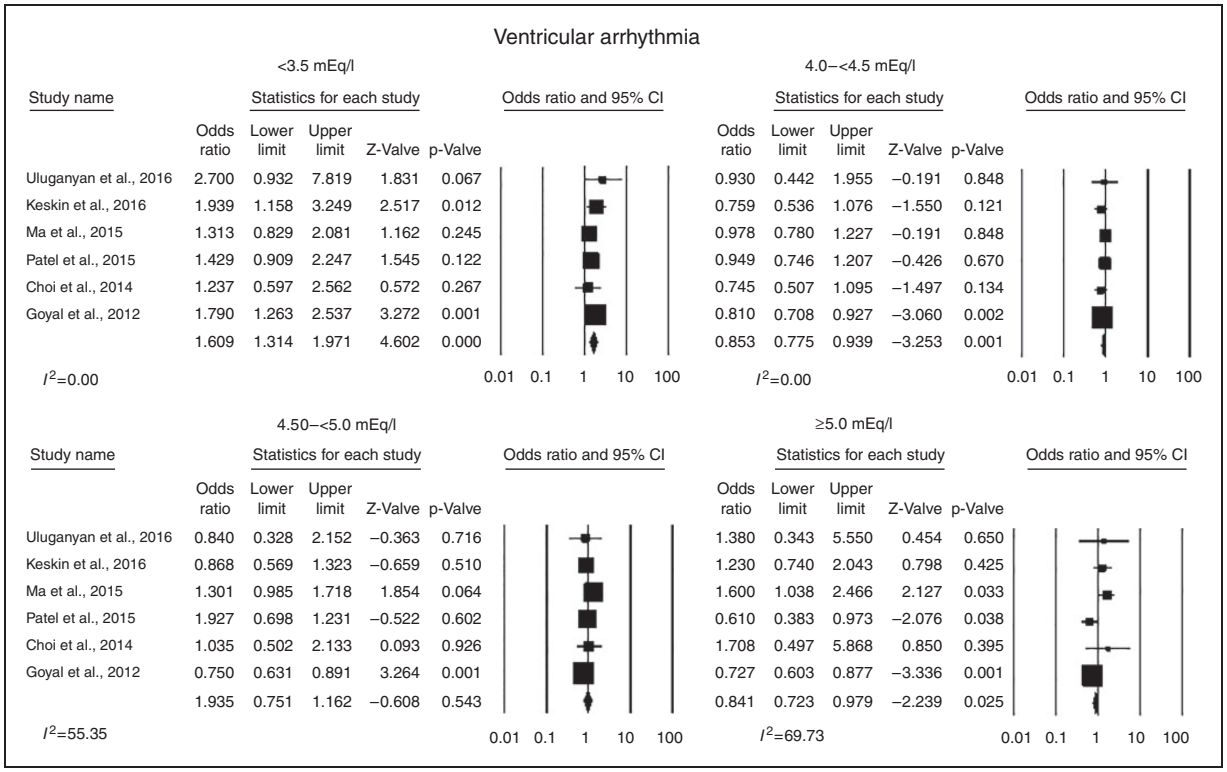

Figure 4. Pooled odds ratios (random effects) of ventricular arrhythmia associated with serum potassium concentration relative to category of 3.5–<4.0 mEq/l.

However, the present analysis also confirmed this finding in more recent studies conducted in the 'reperfusion era', in which standard AMI treatment includes early invasive treatment and routine use of beta-blockers. Beta-blockers raise SPC by blocking epinephrine-induced depression of SPC through beta-receptor stimulation.[41,42] A considerable number of studies on the association between SPC and VA were performed before the reperfusion era[12,17,27,35–37] or analysed data were collected before the year 1990.[13] However, the management of both ST-segment elevation myocardial infarction (STEMI) and non-STEMI has advanced substantially over the past 20 years. The application of beta-blockers in acute coronary syndrome (ACS), reperfusion and antiplatelet treatment has decreased the risk of VF in ACS by at least one third.[43,44] Practice guidelines, including recommendations on SPC in the management of AMI, are based on these older studies that might not apply to contemporarily-treated AMI patients. Almost all of these early studies have investigated the association of hypo and hyperkalemia and VA using a dichotomous classification of SPC. In our meta-analysis we aimed to investigate the effects of a more finely graduated SPC classification, and therefore we excluded earlier studies. The analysis of this more detailed SPC classification yielded interesting results. Our meta-analysis confirmed the well-described association of SPC of less than 3.5 mEq/L and the occurrence of VA, but also yielded conflicting results in terms of higher SPC depending on the type of SPC collection. While the pooled risk of VA in patients with SPC of 4.5 to less than 5.0 mEq/L and 5.0 mEq/L or greater was decreased in studies using single admission SPC,[9,15,16] it was significantly increased in studies using a mean value of several SPC measurements during hospitalisation.[9,10,19,28] Goyal et al.[9] have already observed a similar effect in their study in which they reported results for admission SPC as well as mean SPC. According to American College of Cardiology/American Heart Association STEMI guidelines, aggressively normalising SPC to greater than 4.0 mEq/L in post-AMI patients with VA is recommended.[7] When extracellular SPC falls below 3.5 mEq/L, the risk of VT and VF is increased in patients with AMI due to a number of electrophysiological changes.[45] Efforts to normalise SPC in hypokalemic patients combined with medical and drug treatment affecting potassium homeostasis might cause the SPC subsequently to exceed 4.5 mEq/l.[46,47] Thus hyperkalemia following hypokalemia could explain why studies using the mean SPC found significantly increased risks of VA in patients with SPC of 4.5

to less than 5.0 mEq/l and 5.0 mEq/L or greater, while those using the admission SPC did not. In addition, apart from the information that VA occurred during hospital stay, studies did not report the exact time of VA onset. The mean SPC might contain SPC measurements that were taken before as well as after the onset of VA. Thus this would not allow reliable conclusions to be drawn on the relationship of mean SPC and VA. To conclude, using the mean SPC might overestimate the risk of VA in patients with SPC of 4.5 to less than 5.0 mEq/L and 5.0 mEq/L or greater.

The present systematic review and meta-analysis provided an overview on available scientific evidence regarding SPC and AMI outcomes. A strength of this paper is the inclusion of results of recent and high-quality studies from the reperfusion era, which were not considered in the available practice guidelines for AMI treatment so far. The meta-analysis enabled an increase of statistical power in the extremes of SPC that were often characterised by small numbers of events in the single studies.

However, several limitations should be considered. The studies combined in the meta-analyses on the different outcomes have slightly different study characteristics e.g. in terms of AMI type, follow-up period, time and frequency of SPC assessment. Due to the small number of retrieved studies it was not always possible to perform sensitivity analyses to estimate the effects of these heterogeneous characteristics on the pooled effect sizes. Moreover, it was not possible to include the confounder-adjusted estimates from all studies in the meta-analyses, because studies used HRs as effect sizes instead of ORs or different reference categories. The inclusion of the unadjusted results may have led to an overestimation of the pooled effects. Thus the pooled effects should be interpreted with caution. We have assessed the quality of the studies using a summary score with unweighted items, which may be difficult to interpret and the definition of the threshold for exclusion may be arbitrary.

The results of this systematic review and meta-analysis support the guideline recommendation that SPC should not be lower than 3.5 mEq/L in patients with AMI in order to improve short and long-term survival and to avoid VA. However, guideline recommendations that SPC should be at least 4.5 mEq/L or higher in AMI patients are challenged by the scientific evidence from the studies included in this systematic review and meta-analysis. The results indicate that higher SPC concentrations may be adversely associated with short and long-term survival. The reservation must be made, however, that due to the high heterogeneity among existing studies and the limitations mentioned above, further research is necessary to confirm the need to change clinical practice guidelines.

Author contribution

MGC, IK, UA and CM conceived the study. MGC conducted the literature search. Titles, abstracts and articles were screened by MGC, IK, UA and LD. Data extraction was performed by MGC, IK and UA. IK performed the statistical analysis. MGC, IK and UA drafted the manuscript. CM and LD critically revised the manuscript. All authors approved the final manuscript and agree to be accountable for all aspects of the work ensuring integrity and accuracy. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Schaefer TJ and Wolford RW. Disorders of potassium. *Emerg Med Clin North Am* 2005; 23: 723–747, viii–ix.
2. Clausen T. Hormonal and pharmacological modification of plasma potassium homeostasis. *Fundam Clin Pharmacol* 2010; 24: 595–605.
3. Alfonzo AV, Isles C, Geddes C, et al. Potassium disorders – clinical spectrum and emergency management. *Resuscitation* 2006; 70: 10–25.
4. Heerspink HJ, Gao P, de Zeeuw D, et al. The effect of ramipril and telmisartan on serum potassium and its association with cardiovascular and renal events: results from the ONTARGET trial. *Eur J Prev Cardiol* 2014; 21: 299–309.
5. Cohn JN, Kowey PR, Whelton PK, et al. New guidelines for potassium replacement in clinical practice: a contemporary review by the National Council on Potassium in Clinical Practice. *Arch Intern Med* 2000; 160: 2429–2436.
6. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace* 2006; 8: 746–837.
7. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA Guidelines for the management of patients with ST-elevation myocardial infarction – executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1999

guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol* 2004; 44: 671–719.
8. Macdonald JE and Struthers AD. What is the optimal serum potassium level in cardiovascular patients? *J Am Coll Cardiol* 2004; 43: 155–161.
9. Goyal A, Spertus JA, Gosch K, et al. Serum potassium levels and mortality in acute myocardial infarction. *JAMA* 2012; 307: 157–164.
10. Choi JS, Kim YA, Kim HY, et al. Relation of serum potassium level to long-term outcomes in patients with acute myocardial infarction. *Am J Cardiol* 2014; 113: 1285–1290.
11. Shiyovich A, Gilutz H and Plakht Y. Serum potassium levels and long-term post-discharge mortality in acute myocardial infarction. *Int J Cardiol* 2014; 172: e368–e370.
12. Fiol Sala M IJJ, Benito Vales S, Gutierrez Marti R, et al. Hipocaliemia y fibrilacion ventricualar primaria en pacientes con infarcto agudo de miocardio. *Med Intentiva* 1993; 17: 276–279.
13. Madias JE, Shah B, Chintalapally G, et al. Admission serum potassium in patients with acute myocardial infarction: its correlates and value as a determinant of in-hospital outcome. *Chest* 2000; 118: 904–913.
14. Pourmoghaddas A, Shemirani H and Garakyaraghi M. Association of serum potassium level with ventricular tachycardia after acute myocardial infarction. *ARYA Atheroscler* 2012; 8: 79–81.
15. Patel RB, Tannenbaum S, Viana-Tejedor A, et al. Serum potassium levels, cardiac arrhythmias, and mortality following non-ST-elevation myocardial infarction or unstable angina: insights from MERLIN-TIMI 36. *Eur Heart J Acute Cardiovasc Care* 2015; 6: 18–25.
16. Uluganyan M, Ekmekci A, Murat A, et al. Admission serum potassium level is associated with in-hospital and long-term mortality in ST-elevation myocardial infarction. *Anatol J Cardiol* 2016; 16: 10–15.
17. Ognibene A, Ciniglio R, Greifenstein A, et al. Ventricular tachycardia in acute myocardial infarction: the role of hypophosphatemia. *South Med J* 1994; 87: 65–69.
18. Krijthe BP, Heeringa J, Kors JA, et al. Serum potassium levels and the risk of atrial fibrillation: the Rotterdam Study. *Int J Cardiol* 2013; 168: 5411–5415.
19. Ma W, Liang Y, Zhu J, et al. Serum potassium levels and short-term outcomes in patients with ST-segment elevation myocardial infarction. *Angiology* 2016; 67: 729–736.
20. Moher D, Liberati A, Tetzlaff J, et al.; The PRISMA Group. *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: the PRISMA Statement. *PLoS Med* 2009; 6: e1000097.
21. Downs SH and Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Commun Health* 1998; 52: 377–384.
22. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.
23. Borenstein M, Hedges LV, Higgins JPT, et al. *Software, in Introduction to Meta-Analysis*. Chichester, UK: John Wiley & Sons Ltd., 2009.
24. Higgins JPT and Green S. *Cochrane Handbook for Systematic Reviews of Interventions*, version 5.1.0 (updated March 2011) The Cochrane Collaboration, 2011. www.handbook.cochrane.org (accessed 1 June 2017).
25. Verma S, Agarwal YB, Sharma SK, et al. Dyselectrolytaemia in acute myocardial infarction. *JIACM* 2015; 16: 201–203.
26. Kiranmai P. Serial estimation of serum magnesium, calcium, sodium and potassium levels in myocardial infarction. *Int J Pharm Bio Sci* 2013; 4: 1190–1195.
27. Lettieri B, Chiefari M, Nespoli M, et al. [Hypomagnesemia and hypokalemia as risk factors of arrhythmia in acute phase myocardial infarction]. *Minerva Anestesiol* 1991; 57: 335–339.
28. Keskin M, Kaya A, Tatlisu MA, et al. The effect of serum potassium level on in-hospital and long-term mortality in ST elevation myocardial infarction. *Int J Cardiol* 2016; 221: 505–510.
29. Grodzinsky A, Goyal A, Gosch K, et al. Prevalence and prognosis of hyperkalemia in patients with acute myocardial infarction. *Am J Med* 2016; 129: 858–865.
30. Shlomai G, Berkovitch A, Pinchevski-Kadir S, et al. The association between normal-range admission potassium levels in Israeli patients with acute coronary syndrome and early and late outcomes. *Medicine (Baltimore)* 2016; 95: e3778.
31. Huang YL and Hu ZD. Lower mean corpuscular hemoglobin concentration is associated with poorer outcomes in intensive care unit admitted patients with acute myocardial infarction. *Ann Transl Med* 2016; 4: 190.
32. Su J, Fu X, Tian Y, et al. Additional predictive value of serum potassium to thrombolysis in myocardial infarction risk score for early malignant ventricular arrhythmias in patients with acute myocardial infarction. *Am J Emerg Med* 2012; 30: 1089–1094.
33. Nicolaou VN, Papadakis JE, Chrysohoou C, et al. The prognostic significance of serum glucose levels after the onset of ventricular arrhythmia on in-hospital mortality of patients with acute coronary syndrome. *Rev Diabet Stud* 2008; 5: 47–51.
34. Maciejewski P, Bednarz B, Chamiec T, et al. Acute coronary syndrome: potassium, magnesium and cardiac arrhythmia. *Kardiol Pol* 2003; 59: 402–407.
35. Pohl W, Mory P, Nurnberg M, et al. [Serum magnesium, serum potassium and arrhythmia profile in patients with acute myocardial infarct]. *Wien Klin Wochenschr* 1993; 105: 163–166.
36. Friedensohn A, Faibel HE, Bairey O, et al. Malignant arrhythmias in relation to values of serum potassium in patients with acute myocardial infarction. *Int J Cardiol* 1991; 32: 331–338.
37. Higham PD, Adams PC, Murray A, et al. Plasma potassium, serum magnesium and ventricular fibrillation: a prospective study. *Q J Med* 1993; 86: 609–617.

38. Gettes LS. Electrolyte abnormalities underlying lethal and ventricular arrhythmias. *Circulation* 1992; 85: I70–I76.
39. Podrid PJ. Potassium and ventricular arrhythmias. *Am J Cardiol* 1990; 65: 33E–44E; discussion 52E.
40. Bae EH, Lim SY, Cho KH, et al. GFR and cardiovascular outcomes after acute myocardial infarction: results from the Korea Acute Myocardial Infarction Registry. *Am J Kidney Dis* 2012; 59: 795–802.
41. Traub YM, Rabinov M, Rosenfeld JB, et al. Elevation of serum potassium during beta blockade: absence of relationship to the renin-aldosterone system. *Clin Pharmacol Ther* 1980; 28: 765–768.
42. Johansson BW and Dziamski R. Malignant arrhythmias in acute myocardial infarction. Relationship to serum potassium and effect of selective and non-selective beta-blockade. *Drugs* 1984; 28(Suppl 1): 77–85.
43. Goldberg RJ, Yarzebski J, Spencer FA, et al. Thirty-year trends (1975–2005) in the magnitude, patient characteristics, and hospital outcomes of patients with acute myocardial infarction complicated by ventricular fibrillation. *Am J Cardiol* 2008; 102: 1595–1601.
44. Avezum A, Piegas LS, Goldberg RJ, et al. Magnitude and prognosis associated with ventricular arrhythmias in patients hospitalized with acute coronary syndromes (from the GRACE Registry). *Am J Cardiol* 2008; 102: 1577–1582.
45. Osadchii OE. Mechanisms of hypokalemia-induced ventricular arrhythmogenicity. *Fundam Clin Pharmacol* 2010; 24: 547–559.
46. Gennari FJ. Hypokalemia. *N Engl J Med* 1998; 339: 451–458.
47. Crop MJ, Hoorn EJ, Lindemans J, et al. Hypokalaemia and subsequent hyperkalaemia in hospitalized patients. *Nephrol Dial Transplant* 2007; 22: 3471–3477.