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Hyponatraemia on admission to hospital is associated with increased long-term risk of mortality in survivors of myocardial infarction

Katrin Burkhardt[1], Inge Kirchberger[2,3], Margit Heier[2,3], Angelika Zirngibl[3], Elisabeth Kling[1], Wolfgang von Scheidt[4], Bernhard Kuch[4,5] and Christa Meisinger[2,3]

Abstract

Background: Hyponatremia is associated with an increased risk of mortality in patients with heart failure and in acute ST-segment elevation myocardial infarction (STEMI). The aim was to assess the impact of hyponatremia on admission on long-term mortality of patients with first ever STEMI or non-STEMI (NSTEMI).

Design: This was a longitudinal observation study

Methods: The study population consisted of 3558 patients, aged 25–74 years, with an incident acute myocardial infarction (AMI) in the years 2000–2008 who survived for at least 28 days. All consecutive patients were registered through the Cooperative Health Research in the Region of Augsburg (KORA) Myocardial Infarction Registry. Serum sodium levels were obtained on admission. The association with long-term-mortality was examined using Cox regression models.

Results: Hyponatraemia, defined as a sodium level less than 136 mmol/l, was present in 658 (18.5%) patients on admission. During a median follow-up period of six years (interquartile range (IQR) 4.0–8.2 years), 526 patients (14.8%) died. Hyponatraemia was significantly associated with long-term mortality by an 83% higher risk in the age- and sex-adjusted analysis. After further adjustment for reduced left ventricular ejection fraction (LVEF), glomerular filtration rate, haemoglobin, hypertension, hyperlipidaemia, any recanalization therapy, diabetes, medication with diuretics and angiotensin-converting enzyme (ACE) inhibitor/angiotensin-receptor blocker before admission and other parameters hyponatraemia remained a strong predictor for higher long-term mortality (hazard ratio 1.61; 95% confidence interval 1.32–1.97).

Conclusions: Patients with incident AMI and hyponatraemia on admission showed a significantly higher risk of long-term mortality than patients without. This strong predictive value was independent of a number of prognostic factors, including diabetes, glomerular filtration rate or reduced LVEF.

Keywords

Hyponatraemia, myocardial infarction, mortality, Cooperative Health Research in the Region of Augsburg

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[1]Department of Laboratory Medicine and Microbiology, Central Hospital of Augsburg, Germany
[2]MONICA/KORA Myocardial Infarction Registry, Central Hospital of Augsburg, Germany
[3]Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Envirionmental Health (GmbH), Germany
[4]Department of Internal Medicine 1- Cardiology, Central Hospital of Augsburg, Germany
[5]Department for Internal Medicine/Cardiology, Donau-Ries-Kliniken, Germany

Corresponding author:
Inge Kirchberger, MONICA/KORA Myocardial Infarction Registry, Central Hospital of Augsburg, Stenglinstr. 2, D-86156 Augsburg, Germany.
Email: inge.kirchberger@Helmholtz-muenchen.de

Introduction

Hyponatraemia is the most common electrolyte disorder in hospitalised patients.[1] Its prevalence in patients with myocardial infarction ranges from 12.5%–23.2%.[2,3] Hyponatraemia has been identified as a predictor of short-term mortality in ST-segment elevation myocardial infarction (STEMI) patients as well as of long-term mortality, and rehospitalisation due to heart failure.[4,5] It is related to the release of vasopressin, activation of the renin-angiotensin system and catecholamine production.[6,7]

Previously conducted studies investigating an association between hyponatraemia on admission and short- and long-term prognosis were mostly smaller and conducted in selected groups of acute myocardial infarction (AMI) patients,[8] were based on diabetic or non-diabetic subjects[9] and included incident as well as recurrent myocardial infarctions.[3] Other studies included only STEMIs in the analysis.[2–4,10–13] Data regarding admission serum sodium levels and long-term prognosis after an incident AMI in men and women from the general population treated with modern therapy are scarce.[2] Therefore, the aim of this study was to assess the impact of hyponatraemia on long-term mortality of patients with STEMI, non-STEMI (NSTEMI) or bundle branch block (BBB) based on the data of the population-based Cooperative Health Research in the Region of Augsburg (KORA) Myocardial Infarction Registry, including all consecutive incident AMI cases in men and women, aged 25–74 years, hospitalised in 2000–2008.

Methods

Patients

The population-based KORA Myocardial Infarction Registry was implemented in October 1984 as part of the World Health Organisation (WHO) Monitoring Trends and Determinants on Cardiovascular Diseases (MONICA) project.[14–16] Since 1996, the registry is carried on within the framework of KORA. All cases of coronary death and non-fatal myocardial infarction of the 25–74 years-old study population in the city of Augsburg and the counties Augsburg and Aichach-Friedberg (about 600,000 inhabitants) are continuously registered.[14,16] Data sources for hospitalised patients include eight hospitals within the study region and two hospitals in the adjacent areas. Approximately 80% of all AMI cases of the study region are treated in the major hospital, Klinikum Augsburg, a tertiary care centre offering invasive and interventional cardiovascular procedures, as well as heart surgery facilities. All patients with AMI diagnosed according to the European Society of Cardiology and the American College of Cardiology criteria have been included.[15] Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1964 Declaration of Helsinki. The study was approved by the ethics committee of the Bavarian Medical Association.

In the present analysis, all registered patients with an incident myocardial infarction from 1 January 2000–31 December 2008 surviving at least 28 days were included ($n = 4424$). Of those, admission sodium concentrations were available for 4259 persons (96.3%), who constituted the study group. From those, all subjects with incomplete data on any of the covariables ($n = 701$) were excluded. Finally, the present analysis comprised 3558 persons aged 25–74 years with an incident AMI.

Laboratory measurements

Venous blood samples were taken on admission, usually within 15 min, and sodium level, lipids, glucose, creatinine kinases and creatinine values were measured on autoanalysers (Dimension RXL, Siemens, Eschborn, Germany) in the laboratory of the Central Hospital of Augsburg in 80% of all cases. Hyponatraemia was defined as a sodium level less than 136mmol/l according to Siemens' manufacturer instructions. The remaining 20% of laboratory tests in the study region were performed in the respective hospitals on Hitachi, Integra (Roche, Penzberg, Germany), Vitros (Ortho-Clinical Diagnostics, Neckargemünd, Germany), Olympus AU (ABS, Dallas, USA) and Opera (Beyer GmbH, Düsseldorf, Germany) autoanalysers. The analysing systems for the measurement of serum sodium did not change within the laboratories during the course of the study. Each external quality control for serum sodium was passed successfully during the course of time, four times a year.

Further, haemoglobin was measured on Beckman Coulter analysers (Krefeld, Germany) in 80% of all cases, and on Sysmex (Norderstedt, Germany) and Cell-Dyn (Abbott, Wiesbaden, Germany) in the other 20% of all cases.

Assessment of clinical characteristics

Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula

$$\begin{aligned}\text{eGFR (ml/min/1.73 m}^2\text{)} &= 186.3 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \\ &\quad \times 0.742(\text{if female}) \times 1.212\ (\text{if black})\end{aligned}$$

where serum creatinine is measured in mg/dl, and age in years. Detailed information from each patient was gathered by a personal interview and abstracted from the charts by specially trained nurses. Demographic data, data on cardiovascular risk factors, disease history, comorbidities, including diabetes, drug treatment before and during hospital stay as well as at discharge were collected. Furthermore, electrocardiogram (ECG) data, and the process of care in hospital were also determined. The application of reperfusion therapy (thrombolysis, percutaneous coronary intervention, and coronary artery bypass grafting) was documented. Left ventricular ejection fraction (LVEF) was assessed by intracardiac catheter examination or by echocardiography during hospital stay. A strongly reduced LVEF was defined as LVEF<30%.

Assessment of the study end point

The end point of this study was all-cause mortality. Mortality was assessed by checking the vital status of all registered persons of the KORA MI registry through the population registries inside and outside the study area in 2010; this procedure guaranteed that the vital status of cohort members who had moved out of the study area could also be assessed. Death certificates were obtained from local health departments and all diagnoses on the death certificates were coded by a single trained person using the 9th revision of the International Classification of Diseases (ICD-9). However, underlying causes of deaths were not determined.

Statistical analysis

The chi^2-test was used to test the differences in prevalences. The general linear model was used to compare means (F-test). The study population was stratified into two groups of sodium concentrations of less or equal/higher than 136 mmol/l. A sodium value of <136 mmol/l was defined as hyponatraemia. Relative risks of all-cause mortality were computed for persons with hyponatraemia in comparison to persons with normal sodium values in Cox proportional hazards models. The first model included hyponatraemia and in addition age (continuous) and sex. The second model included all previous factors plus glucose on admission (continuous), body mass index (BMI) (continuous), smoking status (current smoker yes/no), hypertension (yes/no), hyperlipidaemia (yes/no), any recanalisation therapy (yes/no), diabetes (yes/no), medication with diuretics before admission (yes/no), medication with angiotensin-converting enzyme (ACE) inhibitor/angiotensin-receptor blocker (ARB) before admission (yes/no), maximum creatine kinase (CK) value during hospital stay (continuous). Because GFR values and LVEF were not available for the whole study group, several subgroup analyses were performed using the same modelling strategy as described above. Formal tests of interactions between sodium and sex, diabetes, type of infarction, and recanalisation therapy were performed using likelihood ratio test which compared the –2 log (likelihood) between the model which contained only the main effects and the model which contained both the main effects and the interaction term. Kaplan–Meier survival plots of sodium groups in relation to all-cause mortality were examined. Significance tests were two-tailed and p-values less than 0.05 are stated as statistically significant. All analyses were performed using the Statistical Analysis System (Version 9.2, SAS Institute Inc., Cary, North Carolina, USA).

Results

From a total of 3558 included patients (881 females) hyponatraemia (<136 mmol/l) was assessed in 658 patients (182 female) on admission (18.5%). The median follow-up time was 6.0 years (IQR 4.0–8.2 years) and altogether 526 patients died during follow-up; 21.3% with hyponatraemia and 13.3% without hyponatraemia. Twenty-four percent of all patients taking diuretics before admission had low sodium levels versus 17% of those patients without diuretics intake. There was no statistically significant difference regarding the frequency of hyponatraemia between men and women.

Characteristics of the patients by sodium level are shown in Table 1. Patients with hyponatraemia in comparison to persons with normal sodium values were older (60.3 years versus 59.8 years) and had a lower BMI (27.2 versus 27.7 kg/m^2). The mean glucose level of patients with hyponatraemia was higher on admission (171.5 mg/dl versus 142.8 mg/dl) but their maximum CK value during hospital stay did not differ significantly (1071 U/l versus 1041 U/l). Patients with hyponatraemia were more likely to have diabetes mellitus ($p < 0.0001$), and took diuretics ($p = 0.0001$), ACE-inhibitors or ARBs ($p = 0.0034$), and antiplatelets ($p = 0.0012$) more frequently before hospital admission.

Figure 1 presents Kaplan-Meier curves for long-term mortality by the presence of hyponatraemia. Patients with hyponatraemia had a significantly lower survival rate in comparison to persons with normal sodium values (log-rank test $p \leq 0.0001$). In Cox proportional hazards analyses the age- and sex-adjusted hazard ratios (HRs) were significantly increased for all-cause mortality in AMI-patients with hyponatraemia (HR 1.83; 95% confidence interval (CI) 1.50–2.22). After adjustment for a number of confounding variables, the relative risk was attenuated but remained

Table 1. Clinical characteristics according to sodium level.

Characteristics	Sodium ≥136 mmol/l ($n=2900$)	Sodium < 136 mmol/l ($n=658$)	p-value
Men	2201 (75.9%)	476 (72.3%)	0.056
Women	699 (24.1%)	182 (27.7%)	
STEMI	1155 (39.8%)	259 (39.4%)	0.42
NSTEMI	1609 (55.5%)	360 (54.7%)	
Bundle branch block	136 (4.7%)	39 (5.9%)	
Mean age (years)	59.8	60.3	0.25
Body mass index	768 (26.5%)	215 (32.7%)	0.0043
<25 kg/m^2	1395 (48.1%)	282 (42.9%)	
25–29.9 kg/m^2	737 (25.4%)	162 (24.6%)	
≥30 kg/m^2			
Current smoker	1134 (39.1%)	262 (39.8%)	0.73
Hypertension	2184 (75.3%)	498 (75.7%)	0.84
Hyperlipidaemia	2052 (70.8%)	454 (69.0%)	0.37
Diabetes	749 (25.8%)	257 (39.0%)	<0.0001
Medications before admission			
Diuretics	503 (17.3%)	157 (23.9%)	0.0001
ACE-inhibitor/ARB	692 (23.9%)	193 (29.3%)	0.0034
Beta blocker	753 (26.0%)	193 (29.3%)	0.078
Antiplatelets	583 (20.1%)	170 (25.8%)	0.001
Medications at discharge			
ACE-inhibitor/ARB	2383 (82.2%)	555 (84.4%)	0.18
Beta blocker	2781 (95.9%)	624 (94.8%)	0.22
Antiplatelets	2797 (96.5%)	638 (97.0%)	0.52
Any recanalisation therapy	2501 (86.2%)	541 (82.2%)	0.008
LVEF<30%[1]	398 of 2242 (17.8%)	55 of 279 (19.7%)	0.42
eGFR[2]	79.4	79.8	0.78
CK max.	1041.7	1071.2	0.63
Laboratory at admission			
Haemoglobin value[3]	144.2	141.4	0.006
Women	135.4	132.9	0.16
Men	147.0	144.9	0.07
Glucose level	142.8 mg/dl	171.5 mg/dl	<0.0001

ACE: angiotensin converting enzyme; ARB: angiotensin-receptor blocker; eGFR: estimated glomerular filtration rate; CK: creatine kinase; LVEF: left ventricular ejection fraction; NSTEMI: Non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction. [1]LVEF data available for $n=2521$. [2]eGFR data available for $n=1670$ [3]Data available for $n=1665$ (1245 men, 420 women)

statistically significantly elevated for persons with hyponatraemia in comparison to patients with normal sodium values (HR 1.61; 95% CI 1.32–1.97) (Table 2).

Restricting the analysis to patients with available eGFR ($n=1670$; 155 deaths during follow-up) similar results were found. In these analyses low serum sodium levels were also significantly associated with all-cause mortality after multivariable adjustment including eGFR (HR 1.51; 95% CI 1.07–2.15; data not shown). In addition, the analyses were repeated for the subgroup with available LVEF fraction ($n=2521$; 345 deaths during follow-up). In these analyses after multivariable adjustment including the confounding variable LVEF, the relative risk was also significantly elevated for persons with hyponatraemia in comparison to patients with normal sodium values (HR 1.50; 95% CI 1.16–1.93; data not shown).

Subgroup analysis

A significantly elevated risk for all-cause mortality was consistently found for patients with hyponatraemia in

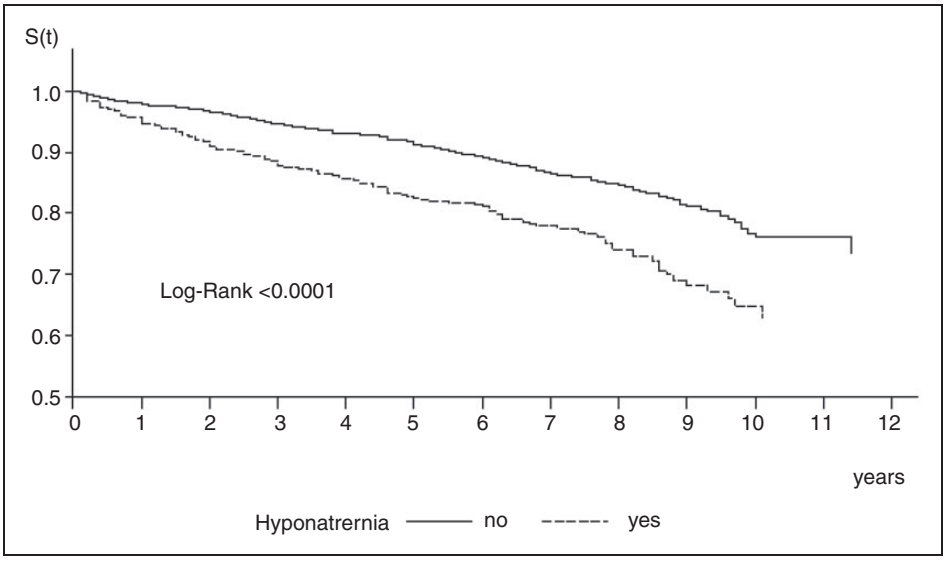

Figure 1. Kaplan-Meier curves for long-term mortality by hyponatraemia for persons with an incident acute myocardial infarction (AMI).

Table 2. Hazard ratio (HR) and 95% confidence interval (CI) for mortality according to hyponatraemia on admission.

	Hyponatraemia on admission ($n = 3558$; 526 events) HR (95% CI)
Model 1[a]	1.83 (1.50–2.22)
Model 2[b]	1.61 (1.30–1.97)

[a]Model 1: adjusted for age and sex. [b]Model 2: adjusted for age, sex, glucose on admission, body mass index, smoking status, hypertension, hyperlipidaemia, any recanalisation therapy, diabetes, medication with diuretics before admission, medication with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker before admission, maximum creatine kinase value.

Table 3. Hazard ratios and 95% confidence interval for mortality according to hyponatraemia in different subgroup analysis.

	Females	Males
Model 1[a]	1.80 (1.24–2.61)	1.83 (1.46–2.30)
Model 2[b]	1.69 (1.14–2.50)	1.72 (1.36–2.17)
	Recanalisation yes	Recanalisation no
Model 1[a]	1.65 (1.30–2.10)	2.10 (1.50–2.94)
Model 2[b]	1.48 (1.16–1.89)	1.97 (1.38–2.82)
	STEMI	NSTEMI
Model 1[a]	1.67 (1.20–2.33)	1.87 (1.44–2.42)
Model 2[b]	1.48 (1.05–2.09)	1.68 (1.28–2.20)
	Persons with diabetes	Persons without diabetes
Model 1[a]	1.68 (1.27–2.23)	1.77 (1.35–2.33)
Model 2[b]	1.65 (1.23–2.22)	1.61 (1.22–2.12)

NSTEMI: non-ST-segment elevation myocardial infarction STEMI: ST-segment elevation myocardial infarction. [a]Model 1: adjusted for age and sex. [b]Model 2: adjusted for age, sex, glucose at admission, body mass index, smoking status, hypertension, hyperlipidaemia, any recanalisation therapy, diabetes, medication with diuretics before admission, medication with angiotensin converting enzyme inhibitor/angiotensin receptor blocker before admission, maximum creatine kinase value.

subgroup analyses. A higher mortality risk could be observed for this group among both: males and females, diabetic and non-diabetic persons, persons with STEMI or NSTEMI, and persons with or without any reperfusion therapy after age- and sex as well as after multivariable adjustment (see Table 3). There was no major difference in outcome between the single subgroups. Due to the low number of patients with BBB, no subgroup analysis was conducted for this group. However, there were no significant interactions between sodium and sex, diabetes, type of infarction, or reperfusion therapy.

Discussion

The present study including a large number of consecutive patients with an incident AMI surviving the first 28 days after admission showed a strong and independent association between hyponatraemia on admission and increased risk of long-term mortality. The risk associated with hyponatraemia was apparent in STEMI and NSTEMI patients, in males and females, in diabetic and non-diabetic persons, and in persons with or without any reperfusion therapy.

The frequency of hyponatraemia (18.5%) among patients with AMI in the present study was comparable

with the proportion described in previous studies.[2,3,8] As shown by previous studies, patients with hyponatraemia were only slightly older (60.3 versus 59.8 years) than patients with normal sodium values.[2–4] Hyponatraemia occurred more frequently in patients with diabetes, in patients taking diuretics, ACE-inhibitors/angiotensin-receptor blockers and antiplatelets before hospital admission. Thus, it may be assumed, that patients with low serum sodium concentrations more often had some sort of previously diagnosed and treated cardiac or vascular disease or cardiac risk factors although patients with recurrent MIs were excluded from this study.

After adjusting for a variety of confounding factors, including renal function, diabetes, type of infarction and strongly reduced LVEF, the independent prognostic impact of hyponatraemia on long-term mortality remained almost unchanged in our study. This result is in accordance with other publications which, however, differed from our study regarding sample characteristics and follow-up interval.[2–4,9–13,17] In the 1980s studies showed that patients with heart failure and low serum sodium concentrations had higher circulating levels of catecholamines, renin, angiotensin II, aldosterone and vasopressin than patients without hyponatraemia.[18–21] Thus, hyponatraemia could be a marker for stress on the heart independent of the AMI patients' volume status or comorbidities. Probably, hyponatraemia which is a marker of excessive neurohormonal activation may be associated with poor long-term outcome due to the development of heart failure subsequently after discharge.[4,18,20]

Prior studies have shown that low serum sodium levels on hospital admission are not only a predictor of short-term[2,10,12] and long-term mortality in patients with acute STEMI[4,11,13] but also of short-term mortality in patients with NSTEMI.[22] Studies on the association between hyponatraemia and long-term mortality in NSTEMI patients, however, are scare so far. In a recent study, Qureshi et al. found hyponatraemia (persisting from the first 24 h of admission to the last 24 h prior to discharge) to be a strong predictor (HR 5.45; 95% CI 3.69–8.06) of long-term mortality (mean follow-up duration 5.5 years) in 11,562 patients with AMI (93.5% NSTEMI).[17] Our study confirmed prior findings on the association between hyponatraemia and long-term mortality in STEMI patients and adds evidence that this association also exists in patients with NSTEMI. Interestingly, in our study NSTEMI patients with low serum sodium levels showed an even higher risk of dying compared with STEMI patients. Further studies are necessary to confirm or refute our findings on the association between hyponatraemia and long-term mortality in survivors of NSTEMI.

Lazzeri et al. included 1231 Italian patients with primary percutaneus coronary intervention (PCI) who were admitted to intensive coronary care unit, not excluding those who died within the first 28 days.[3] In their study, mortality increased to 21.9% in hyponatraemic patients versus 13.5% in patients without hyponatraemia during a maximum follow-up time of 6.75 years. The authors suggested that hyponatraemia is a marker of disease severity, because patients with hyponatraemia had greater use of ventilatory support, intra-aortic balloon pump implantation, inotropic agents, nitrates and diuretics during their hospital stay. This assumption was corroborated by the fact that after adjustment for propensity score and baseline covariates in their study the significant effect of hyponatraemia on long-term mortality disappeared.

Recently, a meta-analysis including 850,222 patients with different clinical conditions showed that hyponatraemia is a common disorder with 17.4% affected subjects and is significantly related to an increased risk of all-cause mortality conditions.[23] Hyponatraemia is associated with a poor prognosis in patients with cardiac conditions such as chronic heart failure[23–25] and myocardial infarction.[23] In addition, the meta-analysis including eight studies on patients with cirrhosis and five studies on patients with pulmonary infections showed a significantly increased risk of all-cause mortality for individuals with hyponatraemia. A negative effect of hyponatraemia on mortality was also found in studies with mixed diseases or studies including hospitalised patients.[23]

Sahin et al. found an increased impact of hyponatraemia on mortality in patients with haemodialysis if there was diabetes additionally present[9] and another study including older patients from an internal medicine department, showed that mortality was higher in hyponatremic patients.[26]

Whether hyponatraemia is causative for increased mortality or is only a marker of the underlying disease severity is not yet entirely clear.[27] Currently, a case-control study investigated whether hyponatremic patients had significantly greater inpatient mortality compared with controls despite no difference with regard to gender, age, comorbidities and type of primary pathology. The study found that hyponatraemia was an independent predictor of mortality, and thus suggested that hyponatraemia per se is likely to contribute to excess mortality.[28]

Thus, it might be important to correct a hyponatremic state either by slow sodium loading, which is a well-known clinical approach to treat hyponatraemia[29] or vasopressin receptor antagonists in patients with such conditions. Qureshi et al. demonstrated that the achievement of normonatraemia at discharge had no effect on the short-term mortality of patients with AMI but had a

beneficial effect on long-term-mortality.[17] Vaptan use was the most effective method to correct sodium level resulting in a decrease of short-term mortality. However, other studies showed that adding vasopressin receptor antagonists to diuretic therapy in patients with heart failure in order to increase serum sodium, did not affect patients long-term mortality.[30,31] While vaptans are expensive and are not approved for treatment of hyponatraemia in post-MI patients randomised controlled trials would be an appropriate option to investigate whether slow sodium loading is beneficial in such patients.

The present study has some limitations that need to be considered. Patients older than 74 years are not represented in this study. We cannot exclude the possibility that unknown risk factors may have biased or confounded the present analysis. The measurements of sodium levels were performed on different laboratory analysers. There have been no comparative studies between the most frequently used Siemens systems (80%) and the Hitachi systems (used in most of the other 20% of centres). However, serum sodium is a stable analyte, which can be proved in the external quality controls that are documented for the Klinikum Augsburg measurements. Finally, cardiovascular mortality in addition to all-cause mortality as a study end-point was not available in the present study. The strengths of the present study are its population-based design, including unselected patients of a general population presenting with an incident AMI registered according to a standardised protocol and the long-term mortality follow-up.

In conclusion, in patients with incident AMI there is a strong and independent association between admission serum sodium values and long-term mortality. Therefore, the consideration of sodium, a routinely measured, relatively inexpensive laboratory marker might turn out to be a valuable tool to identify high-risk AMI patients and to stratify risk for optimal management even after discharge from hospital.

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Conflict of interest

None declared.

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