Research Article

Calculated Serum Osmolality, Acute Kidney Injury, and Relationship to Mortality after Percutaneous Coronary Intervention

Serdar Farhan^{a, b} Birgit Vogel^a Usman Baber^a Samantha Sartori^a
Melissa Aquino^a Jaya Chandrasekhar^a Sabato Sorrentino^a
Gennaro Giustino^a Madhav Sharma^a Paul Guedeney^a Miklos Rohla^b
Reyna Bhandari^a Nitin Barman^a Joseph Sweeny^a George Dangas^a
Roxana Mehran^a Annapoorna Kini^a Samin Sharma^a

^aThe Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ^bThird Department of Medicine, Cardiology, and Intensive Care Medicine, Wilhelminen Hospital Vienna, Vienna, Austria

Keywords

Serum osmolality · Acute kidney injury · Coronary artery disease · Percutaneous coronary intervention · Contrast media

Abstract

Background: Data on the associations between serum osmolality (sOsmo) and acute kidney injury (AKI) as well as short- and long-term mortality in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) are limited. **Objectives:** To investigate the association between sOsmo and development of AKI and clinical outcomes in patients undergoing PCI. **Methods:** We investigated 1,927 consecutive patients undergoing PCI from the registry of a single center. Patients were divided into quartiles according to sOsmo at admission (Q1–Q4). sOsmo was calculated using the following equation: $(1.86 \times \text{serum sodium [mmol/L]} + (\text{glucose [mg/dL]} / 18) + (\text{blood urea nitrogen [mg/dL]} / 2.8) + 9$. The primary endpoint was AKI, per Kidney Disease: Improving Global Outcomes (KDIGO) definition. The secondary endpoints were 30-day and 1-year all-cause mortality. **Results:** Patients with the highest sOsmo (Q4) were older and more likely female, with significantly more cardiovascular risk factors and comorbidities compared to those with lower sOsmo (Q1–Q3). Incidence of AKI was highest in Q4 and lowest in Q2. In the multivariate logistic regression model, high sOsmo independently predicted the development of AKI (OR 2.00, 95% CI 1.26–3.19, $p = 0.003$). Patients with Q4 had a higher risk of 1-year mortality compared to patients with Q2 (HR 2.11, 95% CI 1.10–4.15; $p = 0.031$), but not after adding AKI to the multivariate model (HR 1.71, 95% CI 0.87–3.39; $p = 0.12$). **Conclusion:** sOsmo is a valid and easily obtainable predictor of AKI af-

Dr. Samin Sharma
Mount Sinai Medical Center
One Gustave L. Levy Place, Box 1030
New York, NY 10029 (USA)
E-Mail samin.sharma@mountsinai.org

ter PCI. High sOsmo is associated with increased risk of AKI and 1-year mortality in patients undergoing PCI. Further research is warranted to clarify whether the use of an sOsmo-directed hydration protocol might reduce the incidence of AKI in patients undergoing PCI.

© 2019 S. Karger AG, Basel

Introduction

Coronary artery disease (CAD) is the leading cause of mortality worldwide and puts an increasing burden on the healthcare system. Percutaneous coronary intervention (PCI) is a principal treatment option for patients with CAD. However, acute kidney injury (AKI) is a complication not infrequently observed in patients undergoing PCI which is not only associated with prolonged hospitalization and higher costs, but also with increased mortality [1]. Hydration status prior to and after PCI has been shown to be independently associated with development of AKI [2]. Serum osmolality (sOsmo) has been shown to be associated with a higher risk of short-term mortality after PCI in patients with acute coronary syndrome (ACS) and predicts the all-cause mortality in patients hospitalized for heart failure [3, 4].

Currently, no data are available regarding the predictive associations between preprocedural sOsmo and development of AKI after PCI. Therefore, we aimed to investigate the association between sOsmo and the development of AKI after PCI, as well as related clinical outcomes, from the PCI database of a single tertiary center with a high volume of complex procedures.

Methods

Patients

A total of 1,927 consecutive patients undergoing PCI between June 2012 and May 2017 from a prospective database maintained at Mount Sinai Hospital were included in the present analysis. Patient- and procedure-related data were entered into the database within 24 h of the index PCI. An institutional review board approved the registry. Patients' medications and interventional treatments were at the discretion of the treating physician.

Patients were excluded if preprocedural sodium (Na), plasma glucose, or blood urea nitrogen (BUN) were not available and if serial serum creatinine (sCr) was not measured before and/or within 48 h after the procedure. End-stage renal failure requiring chronic hemodialysis was also considered an exclusion criterion for the present analysis.

sOsmo was calculated from laboratory results obtained before PCI using the following equation: $sOsmo = (1.86 \times Na [mmol/L]) + (glucose [mg/dL] / 18) + (BUN [mg/dL] / 2.8) + 9$ [5], as described in an earlier study in patients with CAD [3]. The normal reference range of sOsmo is 275–295 mOsm/kg (mmol/kg). Blood samples for measurement of serum glucose, Na, and BUN were collected before intravenous hydration was initiated.

Patients were stratified by sOsmo quartiles (Q1–Q4), with Q1 representing patients with lowest sOsmo values and Q4 representing patients with highest sOsmo values.

Hydration Protocol

Patients with admission sCr ≥ 1.3 mg/dL received standardized hydration (0.45–0.9% normal saline at 0.5–1.0 mL/kg/h) for 3–12 h before angiography and PCI. Hydration therapy was continued for up to 12 h after PCI based on the treating physician's assessment.

Endpoints

The primary endpoint of the study was the development of AKI after PCI according to the Kidney Disease: Improving Global Outcomes (KDIGO) [6, 7]: increase in serum sCr by ≥ 0.3 mg/dL or at least 1.5 times the baseline level of sCr within 48 h. The secondary endpoints were 30-day and 1-year all-cause mortality.

Table 1. Clinical and angiographic characteristics of the patients divided into sOsmo quartiles (Q1–Q4)

	Q1 (n = 564)	Q2 (n = 513)	Q3 (n = 473)	Q4 (n = 377)	p value
Age, years	62.91±12.8	65.20±12.7	67.9±12.4	71.3±11.7	<0.0001
Female sex	169 (30.0%)	146 (28.5%)	169 (35.7%)	166 (44.0%)	<0.0001
Body mass index	28.6±6.5	28.9±6.1	29.00±6.7	29.6±7.1	0.11
Hyperlipidemia	469 (83.2%)	419 (81.7%)	419 (88.6%)	329 (87.3%)	0.006
Hypertension	490 (86.9%)	428 (83.4%)	430 (90.9%)	349 (92.6%)	<0.0001
Diabetes mellitus	197 (34.9%)	227 (44.2%)	239 (50.5%)	261 (69.2%)	<0.0001
Chronic kidney disease	100 (17.9%)	122 (23.9%)	183 (38.9%)	267 (71.4%)	<0.0001
Anemia	258 (45.8%)	212 (41.4%)	255 (54.1%)	263 (69.9%)	<0.0001
Current smoker	104 (18.4%)	102 (19.9%)	63 (13.3%)	38 (10.1%)	0.0001
Previous myocardial infarction	132 (23.4%)	115 (22.4%)	123 (26.0%)	114 (30.2%)	0.039
Family history of CAD	112 (19.9%)	87 (17.0%)	73 (15.4%)	43 (11.4%)	0.006
Cerebrovascular disease	48 (8.5%)	45 (8.8%)	54 (11.4%)	68 (18.0%)	<0.0001
Presentation non-STEMI	163 (28.9%)	133 (25.9%)	131 (27.7%)	118 (31.3%)	0.35
Presentation STEMI	37 (6.6%)	20 (3.9%)	13 (2.7%)	16 (4.2%)	0.023
sCr, mg/dL	1.04±1.28	1.03±0.38	1.16±0.47	1.66±1.02	<0.0001
eGFR, mL/min	80.52±21.70	76.16±21.86	67.69±22.94	48.19±23.77	<0.0001
Glucose, mg/dL	111.3±37.3	121.1±43.6	140.7±67.6	184.6±98.2	<0.0001
LVEF	50.8±12.9	51.7±12.3	51.2±12.7	48.01±13.6	0.0003
In-stent restenosis	44 (7.8%)	41 (8.0%)	55 (11.6%)	44 (11.7%)	0.051
Chronic total occlusion	41 (7.3%)	38 (7.4%)	29 (6.1%)	10 (2.7%)	0.013
Bifurcation lesion	134 (23.8%)	105 (20.5%)	97 (20.5%)	78 (20.7%)	0.48
ACC/AHA type B2 or C lesion	431 (76.4%)	405 (78.9%)	358 (75.7%)	288 (76.4%)	0.63
Severe calcified lesion	75 (13.3%)	69 (13.5%)	73 (15.4%)	79 (21.0%)	0.012
SYNTAX score	13.1±11.8	12.9±11.5	13.16±11.6	14.3±13.5	0.36
Contrast media, mL	149.4±66.2	146.5±61.5	140.83±58.0	125.4±56.3	<0.0001

Q1: 251–278 mOsm/kg; Q2: 279–282 mOsm/kg; Q3: 283–287 mOsm/kg; Q4: 288–328 mOsm/kg. ACC, American College of Cardiology; AHA, American Heart Association; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; sCr, serum creatinine; sOsmo, serum osmolality; STEMI, ST elevation myocardial infarction.

Statistical Analysis

Continuous variables are presented as means ± SD, categorical variables as percentages. Analysis of variance was used to compare continuous variables with normal distribution, and the Mann-Whitney test was used to compare continuous variables without a normal distribution. The χ^2 test was used to compare the difference between categorical variables. The incidence of 30-day and 1-year all-cause mortality is presented as crude rates. Uni- as well as multivariate logistic regression analysis were used to estimate the relationship between sOsmo and development of AKI as well as 30-day all-cause mortality. A uni- and multivariate Cox regression model was used to estimate the association between sOsmo and 1-year all-cause mortality. Confounders included in the multivariate logistic regression model for AKI were age, sex, mechanical assist device (intra-aortic balloon pump or percutaneous left ventricular assist device [Impella]), anemia, diabetes mellitus (DM), contrast media volume, estimated glomerular filtration rate, and chronic kidney disease (CKD). For this reason we did not include BUN and glucose in our multivariate models, nor did we include serum Na. Confounders included in the Cox regression model were age, sex, smoking status, hypertension, DM, and presentation modality (ACS versus stable CAD). To identify the risk of mortality attributable to AKI, a further Cox regression analysis including AKI as a confounding variable was performed.

Results

The patients' clinical and angiographic characteristics are presented in Table 1. Patients of Q4 were older and more frequently female, with a higher prevalence of cardiovascular risk factors including hypertension, DM, and hyperlipidemia. In addition, history of CAD and CKD

Fig. 1. Bar graph illustrating the incidence of AKI in patients after PCI according to sOsmo quartiles 1–4 (Q1–Q4). AKI, acute kidney injury; PCI, percutaneous coronary intervention; sOsmo, serum osmolality.

Fig. 2. Forrest plot illustrating adjusted ORs (aORs) and 95% CIs for the development of AKI with sOsmo quartiles 1–4 (Q1–Q4). AKI, acute kidney injury; sOsmo, serum osmolality.

was more prevalent in Q4 compared to the other quartiles. Conversely, patients from Q4 were less likely to present with ST elevation myocardial infarction (STEMI) compared to those from the other groups. With respect to target lesion characteristics, Q4 had the highest prevalence of chronic total occlusion and severely calcified lesions ($p = 0.012$), whereas the rates of in-stent restenosis and American College of Cardiology/American Heart Association type B2 or C lesions were similar between groups. In addition, no differences in mean SYNTAX score were found across sOsmo quartiles. Mean contrast media volume was lowest in Q4 patients compared to patients in the other quartiles.

Incidence of AKI and Association with sOsmo

Overall, AKI occurred in 10.1% of patients ($n = 165$), with the highest rates in Q4 (16.2%) and the lowest rates in Q2 (8.3%) ($p < 0.0001$ across groups) (Fig. 1). While Q1 patients had a higher incidence of AKI compared to Q2 patients, their sOsmo values were also entirely below the range that was referenced as normal. Therefore, Q2 was chosen as the reference group when multivariate logistic regression was performed. After adjustment for baseline risk, Q4 patients remained at increased risk of AKI compared with Q2 patients (adjusted OR 2.00, 95% CI 1.26–3.19; $p = 0.003$) (Fig. 2).

Mortality and Association with sOsmo

At 30 days and 1 year, a total of 35 and 77 deaths, respectively, occurred in the overall sample. Similar to the occurrence of AKI, 30-day mortality rates were highest in Q4 and lowest in Q2. However, there was no statistically significant difference across groups (1.4% in Q1, 1.6% in Q2, 1.9% in Q3, and 3.5% in Q4; $p = 0.12$). One-year mortality significantly differed across groups, with highest rates in Q4 and lowest rates in Q2 (Q1: 4.1%; Q2: 3.7%; Q3: 5.7%; Q4: 10.1%; $p = 0.0017$) (Fig. 3). After adjustment for baseline risk, Q4 patients remained at increased risk of 1-year mortality compared with the reference group Q2 (HR 2.11, 95% CI

Fig. 3. Kaplan-Meier curve of 1-year all-cause mortality after PCI according to sOsmo quartiles 1–4 (Q1–Q4). PCI, percutaneous coronary intervention; sOsmo, serum osmolality.

1.10–4.15; $p = 0.031$). When AKI was added to the multivariate model, the increased risk of 1-year mortality of Q4 compared with Q2 was not statistically significant anymore (HR 1.71, 95% CI 0.87–3.39; $p = 0.12$).

Discussion

This is the first study to investigate the association between sOsmo and AKI in patients undergoing PCI. The key findings are the following: (1) High sOsmo correlated with high-risk clinical characteristics. (2) After adjustment for baseline risk, patients in the highest sOsmo quartile remained at increased risk of AKI compared with the reference group (Q2). (3) High sOsmo was a predictor of 1-year mortality, but not after adding AKI to the multivariate model.

The present analysis shows an association between sOsmo calculated at admission and development of AKI in patients undergoing PCI. This finding extends prior work evaluating the links between sOsmo and development of chronic renal impairment. In a large-scale retrospective analysis including 13,201 patients without renal disease, elevated sOsmo independently predicted the development of CKD over a follow-up period of 5 years [8]. In addition, sOsmo has been linked to the development of CKD in the absence of classic risk factors (e.g., DM and hypertension) [9, 10]. In contrast to these earlier reports, we demonstrate similar associations with respect to short-term renal injury after PCI. While dehydration associated with high sOsmo might be one contributor to an increased risk of AKI, the higher prevalence of comorbidities found in our patients with high sOsmo values might also have influenced this association. However, even after adjustment for baseline risk, the association of high sOsmo with increased risk of AKI remained significant. Further aspects of this relationship between sOsmo and AKI after PCI might include the individual components used for the calculation of sOsmo. With respect to glucose, acute hyperglycemia in patients with STEMI undergoing primary PCI has been previously reported to be associated with AKI [11] and mortality. BUN, which is also included in the equation, has not been investigated as a risk

factor for AKI, but has been documented to be associated with mortality in patients with ACS [12]. Furthermore, patients in the highest sOsmo quartile showed higher complexity of CAD, including chronic total occlusion and severely calcified lesions, and more advanced comorbidities (e.g., DM and CKD) as compared to those in the remaining quartiles, which might have had an influence on our findings. Application of contrast dye during PCI with subsequent increase of the osmotic gradient in the kidneys results in oxidative stress, inflammation, and medullary hypoxia [13]. These adverse effects of contrast media application may constitute a particular risk for patients with high sOsmo, as suggested by this analysis. In the present study the highest sOsmo quartile was associated with the highest risk of AKI. However, although not significant, the lowest sOsmo quartile was also associated with higher risk of AKI as compared to Q2. This finding is not surprising since the sOsmo of Q1 was lower than the accepted reference range [4]. Furthermore, an earlier study showed an association of low osmolality with higher risk of all-cause mortality and readmission for heart failure [4].

The relationship between sOsmo and mortality has already been investigated in different patient populations. Bhalla et al. [14] found an association between increased osmolality and short-term mortality in 167 consecutive patients with acute stroke. Recently, two studies showed an association of increased sOsmo and short- as well as long-term mortality in patients after ACS [3, 15]. Rohla et al. [3] analyzed the data of 985 consecutive patients with non-STEMI and STEMI in whom sOsmo was calculated from laboratory results obtained within 8 h of admission. Patients in the highest sOsmo quartile had the highest risk of 30-day mortality compared to patients in the other quartiles combined. An analysis of a larger patient population ($n = 3,748$) with STEMI was reported by Tatlisu et al. [15] and investigated sOsmo measured within 8 h of admission. The authors found a strong independent relationship between sOsmo and in-hospital as well as long-term mortality (mean follow-up period 22 ± 10 months). Furthermore, the crude rates of AKI, acute stent thrombosis, recurrent myocardial infarction, and revascularization were significantly higher in patients in the highest sOsmo quartile compared to those in the other quartiles [15]. It is important to note that our results stem from mostly stable CAD patients, whereas the analyses of Tatlisu et al. [15] and Rohla et al. [3] were done in patients with STEMI and non-STEMI. Although our patients were more stable, the prevalence of cardiovascular risk factors and comorbidities was much higher in our patient population compared to the other two studies. These differences in the characteristics of the patient populations as well as in the timing of sOsmo measurement may have contributed to the differences in short-term mortality. Nevertheless, in all of the studies, high sOsmo was associated with elevated risk of long-term mortality, even after adjustment for baseline risk. However, this association was not independent from AKI, suggesting that the increased mortality associated with high osmolality may be driven by the increased occurrence of AKI in these patients. Several previous investigations have documented an increased risk of mortality in patients with AKI [1].

Early evaluation of the risk of AKI after PCI can help identify patients who may profit from prevention strategies and close follow-up. The calculation of sOsmo may constitute a cost-effective and easy tool to predict the risk of postprocedural AKI. Further research is warranted to clarify whether sOsmo-guided preprocedural hydration therapy reduces the occurrence of AKI after PCI.

The present analysis is subject to several limitations. First, our study represents a single-center experience using data derived from a prospective PCI registry. Therefore, the present findings should be interpreted as hypothesis-generating rather than conclusive in nature. Second, we included only those patients who had at least one post-PCI sCr concentration collected within 48 h. Thereby patients discharged the same day were not considered in the present investigation, limiting the external validity of the findings. Third, we did not collect urine albumin excretion, and information on whether patients were under chronic diuretics

was not available, which might have had an impact on our findings. Fourth, in the present analysis, AKI was defined according to the KDIGO criteria. However, previous studies have shown accordance with other AKI definitions [16, 17]. Finally, we used calculated rather than measured sOsmo. Therefore, a physiological osmolal gap of up to 10 mOsm/kg [18] has to be considered when interpreting the results of our study. Several osmolality equations were introduced in the past [19]. However, we selected a particular equation since it was applied in two previous studies in patients with CAD undergoing angiography and PCI [3, 15].

Conclusion

Our data suggest that calculated sOsmo is a valid and easy-to-obtain measure to predict AKI in patients undergoing PCI. High sOsmo is associated with increased risk of AKI and 1-year mortality. Further research is warranted to clarify whether an sOsmo directed hydration protocol might reduce the incidence of AKI and improve clinical outcomes in patients undergoing PCI.

Acknowledgment

The authors are grateful to Ms. Elena Ramos for her support with the submission of the manuscript.

Statement of Ethics

The study results are derived from a prospective registry maintained at Mount Sinai Heart and was approved by an institutional review board at Mount Sinai Hospital.

Disclosure Statement

S. Farhan, B. Vogel, U. Baber, S. Sartori, M. Aquino, J. Chandrasekhar, S. Sorrentino, G. Giustino, M. Sharma, P. Guedeney, M. Rohla, R. Bhandari, and N. Barman have no conflicts of interest to declare. J. Sweeny: <http://icahn.mssm.edu/about-us/services-and-resources/faculty-resources/handbooks-and-policies/faculty-handbook>. G. Dangas has received consulting fees and honoraria from Johnson & Johnson, Sanofi, Covidien, The Medicines Company, Merck, CSL Behring, AstraZeneca, Medtronic, Abbott Laboratories, Bayer, Boston Scientific, Osprey Medical, and GE Healthcare, and research grant support from Sanofi, Bristol-Myers Squibb, and Eli Lilly/Daiichi-Sankyo. R. Mehran has received institutional research grant support from Eli Lilly, AstraZeneca, The Medicines Company, and BMS/Sanofi-Aventis, and consulting fees from AstraZeneca, Bayer, CSL Behring, Janssen Pharmaceuticals, Merck, Osprey Medical, and Watermark Research Partners. She is a Scientific Advisory Board member for Abbott Laboratories, Boston Scientific, Covidien, Janssen Pharmaceuticals, The Medicines Company, and Sanofi-Aventis. A. Kini: <http://icahn.mssm.edu/about-us/services-and-resources/faculty-resources/handbooks-and-policies/faculty-handbook>. S. Sharma has held industry-sponsored lectures for Abbott Laboratories, AngioScore, Boston Scientific, Cardiovascular Systems, Daiichi-Sankyo/Eli Lilly Partnership, Medtronic, The Medicines Company, and the Scientific Advisory Board for Cardiovascular Systems.

Author Contributions

Conceptualization: S. Farhan, B. Vogel, U. Baber, P. Guedeney, and S. Sorrentino. Data curation: U. Baber, S. Sartori, and M. Sharma. Formal analysis: S. Sartori, M. Aquino, and A. Kini. Investigation: S. Farhan, G. Giustino, M. Sharma, and R. Bhandari. Methodology: S. Farhan and B. Vogel. Supervision: N. Barman. Original draft: S. Farhan, B. Vogel, and S. Sharma. Review and editing: J. Chandrasekhar, M. Rohla, J. Sweeny, G. Dangas, R. Mehran, A. Kini, and S. Sharma.

References

- 1 Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol*. 2005 Nov;16(11):3365–70.
- 2 Maioli M, Toso A, Leoncini M, Musilli N, Bellandi F, Rosner MH, et al. Pre-procedural bioimpedance vectorial analysis of fluid status and prediction of contrast-induced acute kidney injury. *J Am Coll Cardiol*. 2014 Apr;63(14):1387–94.
- 3 Rohla M, Freynhofer MK, Tentzeris I, Farhan S, Wojta J, Huber K, et al. Plasma osmolality predicts clinical outcome in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Eur Heart J Acute Cardiovasc Care*. 2014 Mar;3(1):84–92.
- 4 Vaduganathan M, Marti CN, Mentz RJ, Greene SJ, Ambrosy AP, Subacius HP, et al.; EVEREST trial investigators. Serum Osmolality and Postdischarge Outcomes After Hospitalization for Heart Failure. *Am J Cardiol*. 2016 Apr;117(7):1144–50.
- 5 Dorwart WV, Chalmers L. Comparison of methods for calculating serum osmolality from chemical concentrations, and the prognostic value of such calculations. *Clin Chem*. 1975 Feb;21(2):190–4.
- 6 Summary of Recommendation Statements. *Kidney Int Suppl* (2011). 2013 Nov;3(3):263–65.
- 7 Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120(4):c179–84.
- 8 Kuwabara M, Hisatome I, Roncal-Jimenez CA, Niwa K, Andres-Hernando A, Jensen T, et al. Increased Serum Sodium and Serum Osmolarity Are Independent Risk Factors for Developing Chronic Kidney Disease; 5 Year Cohort Study. *PLoS One*. 2017 Jan;12(1):e0169137.
- 9 Correa-Rotter R, Wesseling C, Johnson RJ. CKD of unknown origin in Central America: the case for a Meso-american nephropathy. *Am J Kidney Dis*. 2014 Mar;63(3):506–20.
- 10 Laws RL, Brooks DR, Amador JJ, Weiner DE, Kaufman JS, Ramirez-Rubio O, et al. Biomarkers of Kidney Injury Among Nicaraguan Sugarcane Workers. *Am J Kidney Dis*. 2016 Feb;67(2):209–17.
- 11 Marenzi G, De Metrio M, Rubino M, Lauri G, Cavallero A, Assanelli E, et al. Acute hyperglycemia and contrast-induced nephropathy in primary percutaneous coronary intervention. *Am Heart J*. 2010 Dec;160(6):1170–7.
- 12 Kirtane AJ, Leder DM, Waikar SS, Chertow GM, Ray KK, Pinto DS, et al.; TIMI Study Group. Serum blood urea nitrogen as an independent marker of subsequent mortality among patients with acute coronary syndromes and normal to mildly reduced glomerular filtration rates. *J Am Coll Cardiol*. 2005 Jun;45(11):1781–6.
- 13 Geenen RW, Kingma HJ, van der Molen AJ. Contrast-induced nephropathy: pharmacology, pathophysiology and prevention. *Insights Imaging*. 2013 Dec;4(6):811–20.
- 14 Bhalla A, Sankaralingam S, Dundas R, Swaminathan R, Wolfe CD, Rudd AG. Influence of raised plasma osmolality on clinical outcome after acute stroke. *Stroke*. 2000 Sep;31(9):2043–8.
- 15 Tatlisu MA, Kaya A, Keskin M, Uzman O, Borklu EB, Cinier G, et al. Can we use plasma hyperosmolality as a predictor of mortality for ST-segment elevation myocardial infarction? *Coron Artery Dis*. 2017 Jan;28(1):70–6.
- 16 Acute Kidney Injury. *Prevention*. London: Detection and Management Up to the Point of Renal Replacement Therapy; 2013.
- 17 Bastin AJ, Ostermann M, Slack AJ, Diller GP, Finney SJ, Evans TW. Acute kidney injury after cardiac surgery according to Risk/Injury/Failure/Loss/End-stage, Acute Kidney Injury Network, and Kidney Disease: Improving Global Outcomes classifications. *J Crit Care*. 2013 Aug;28(4):389–96.
- 18 Hoffman RS, Smilkstein MJ, Howland MA, Goldfrank LR. Osmol gaps revisited: normal values and limitations. *J Toxicol Clin Toxicol*. 1993;31(1):81–93.
- 19 Martín-Calderón JL, Bustos F, Tuesta-Reina LR, Varona JM, Caballero L, Solano F. Choice of the best equation for plasma osmolality calculation: comparison of fourteen formulae. *Clin Biochem*. 2015 May;48(7–8):529–33.