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# Diagnostic value of N-terminal pro-B-type natriuretic peptide in hemodialysis patients

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**Aim.** To assess the diagnostic value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in hemodialysis (HD) patients.

**Material and methods.** A total of 80 patients over the age of 18 with an end-stage renal disease (ESRD) on HD were included in this study. NT-proBNP serum levels were measured for all patients in addition to traditional clinical and biochemical studies. Transthoracic echocardiography and bioimpedance spectroscopy using the Body Composition Monitor (BCM) device (Fresenius, Germany) were performed for all patients on HD. Patients were divided into two groups depending on the hydration status determined by BCM. Patients were also divided into three groups depending on the ejection fraction (EF) of the left ventricle: HF with reduced EF (less than 40%) (HFrEF), mid-range EF (from 40% to 49%) (HFmrEF), and HF with preserved EF (50% or more) (HFpEF). Three groups of patients were identified according to quartile level of NT-proBNP (<1095 pg/ml (n=20); 1095-4016 pg/ml (n=40); >4016 pg/ml (n=20).

**Results.** The median of the NT-proBNP serum level was 2114,6 [1095; 4016] pg/ml. A significant increase in the NT-proBNP levels was found in HD patients with hyperhydration (p<0,05). Statistically significant differences were generally found between the concentration of NT-proBNP depending on the LVEF (n=80). However, in pairwise comparisons, significant differences were found only between the groups of patients with HFpEF and HFmrEF (p=0,02); a tendency to differences was revealed when comparing the groups of HFpEF and HFrEF (p=0,07). A proportional increase in the concentration of prohormone to the increase in systolic dysfunction was found while analyzing the median NT-proBNP, both among all patients and after separation into groups depending on the hydration status. A tendency to increase the frequency of new cardiovascular events, systolic and diastolic myocardial dysfunction in group of patients with prohormone increase was revealed.

**Conclusion.** NT-proBNP serum levels in HD patients are significantly higher than the average population levels. A significant increase in the NT-proBNP levels was found in hemodialysis patients with hyperhydration. NT-proBNP should be used as an additional method for the diagnosis of heart failure on HD, including clarifying of the phenotype of heart failure depending on left ventricle EF. NT-proBNP high levels in patients on HD may be associated with a risk of developing cardiovascular events, systolic and diastolic myocardial dysfunction. It is necessary to use an examination algorithm for the differential diagnosis of heart failure and hyperhydration syndrome during dialysis: clinical examination, bioimpedansometry, transthoracic echocardiography, determination of serum NT-proBNP level.

**Key words:** chronic kidney disease, hemodialysis, NT-proBNP, heart failure, cardiovascular diseases.

**Relationships and Activities:** not.

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Despite advances in dialysis technology, cardiovascular mortality in the population of patients receiving extracorporeal therapy remains high [1-4]. Hemodialysis (HD) patients have both structural and functional cardiovascular changes. Factors such as volume (fluid) overload, hypertension [5], vascular access features [6, 7], anemia, hypoalbuminemia, neurohumoral disorders, the effects of systemic inflammation and drugs [1, 8], and cardiovascular calcification [9] increase the risk of left ventricular (LV) dysfunction. These factors can lead to the development and/or progression of irreversible cardiac dysfunction and severe heart failure (HF), increasing the probability of adverse outcomes in HD patients [10, 11]. The prevalence of HF in HD patients is still the matter of debate [10, 12]. The difference in data on the true HF prevalence in patients on HD is due to many factors and depends on the characteristics of the studied patient population and the difficulties of its diagnosis.

In the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, HF is defined as a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress [13]. However, these "typical" symptoms in HD lose their value, because they can be observed even in patients without HF. The similarity of the clinical symptoms of HF and hyperhydration in the HD patients demonstrates the need for additional diagnostic methods to differentiate these conditions. Such methods, in addition to traditional clinical assessment, include transthoracic echocardiography (TTE), hydration status evaluation by bioelectrical impedance analysis (BIA). It is relevant to use for HF diagnosis and monitoring the N-terminal pro-B-type natriuretic peptide (NT-proBNP) released from ventricular myocytes in response to excessive stretching associated with elevated filling pressure [14, 15].

## Material and methods

The study included 80 patients (52 men — 65%) with end-stage renal disease (ESRD) who received HD during hospitalization at the Saratov Regional Clinical Hospital and have been under observation since the start of extracorporeal therapy. The follow-up period ranged from 1 to 135 months. Patients received hemodiafiltration 3 days a week for at least 4 hours of session time on Fresenius 5008 machine (Germany) using a bicarbonate dialysis solution and high-flux dialyzers. All patients received adequate dialysis (actual dialysis dose per hemodiafiltration session (spKt/V) >1,4; substitution solution volume >63 L/weak).

There were following inclusion criteria: age 18 years or more; signed informed consent. The exclusion criteria were: poor heart visualization by TTE; valvular heart disease (congenital and/or acquired before starting renal replacement therapy); acute infectious diseases (HIV, hepatitis B, C, sepsis, infective endocarditis, tuberculosis, etc.) or chronic disease exacerbations (peptic ulcer, cholecystitis, etc.); cancers and lymphoproliferative disorders, including their history.

Two groups of patients were divided depending on the hydration status. Depending on left ventricular ejection fraction (LVEF), three groups of patients were distinguished: patients with reduced EF (<40%) (HFrEF), with mid-range EF (40% to 49%) (HFmrEF), and with preserved EF (50% or more) (HFpEF).

According to the NT-proBNP level, 3 groups of patients were distinguished based on quartiles to assess the clinical characteristics of each group as the quartile level of prohormone increased: <1095 pg/ml (n=20); 1095-4016 pg/ml (n=40); >4016 pg/ml (n=20).

All 80 patients underwent conventional clinical examination and biochemical tests. We determined the serum level of NT-proBNP by enzyme-linked immunosorbent assay (ELISA) using the NTproBNP-IFA-BEST reagent kit manufactured by AO Vector-Best, Novosibirsk. The reaction results were recorded using the iMark photometer (BioRad, USA). The NTproBNP concentration in the analyzed serum and control samples was determined according to the calibration curves using the Zemfira photometer control program and stated in pg/ml. The reference value is the concentration of NT-proBNP <200 pg/ml, determined in the blood serum of 165 healthy individuals aged 20-50 years. In the inter-dialytic period, all patients underwent TTE on the Acuson 128 XP/10 ultrasound system and BIA on the BCM machine.

The statistical processing was carried out using the IBM SPSS Statistics 23 software package. For the description of quantitative parameters with normal distribution, mean value and standard deviation (M±SD) were used; to describe the parameters with non-normal distribution the median, lower and upper quartiles were used (Med; 25-75%). To assess the differences in quantitative parameters in two independent groups, the Mann-Whitney test was used. When comparing variables in more than two independent groups, Kruskal-Wallis test was used. To assess the differences in the frequency of occurrence

**Table 1**

**Initial clinical and laboratory characteristics of the studied patients receiving hemodialysis**

| Parameter | All patients(n=80); M±SD; Med;25-75% | Patients without hyperhydration (n=62); M±SD; Med;25-75% | Patients with hyperhydration (n=18); M±SD; Med;25-75% | Comparison of groups of patients with normal hydration status and hyperhydration; p value |
|---|---|---|---|---|
| Gender (men/women) | 52/28 | 41/21 | 11/7 | |
| Age, years | 58 [42,5;64,5]<br>53,9±13,8 | 58 [46;66]<br>55±13,3 | 58 [37;62]<br>50,3±15,2 | 0,29 |
| Total time of dialysis, months | 44 [16;94] | 42 [18;86] | 47,5 [9;117] | 0,87 |
| BMI, kg/m$^2$ | 25,6 [22;29,6] | 28,4 [24,5;31,2] | 21,6 [21;22] | 0,002* |
| Ultrafiltration rate, ml/kg/h | 8,2 [6,5;10,1] | 8,1 [6,5;9,9] | 9,6 [6,8;13,2] | 0,13 |
| Effective dialysis time, min/week. | 732 [728;739] | 732 [728;739] | 734 [728;740,5] | 0,91 |
| spKt/V | 1,6 [1,49;1,74] | 1,6 [1,49;1,71] | 1,6 [1,5;1,9] | 0,46 |
| Substitution solution volume, l/weak. | 73 [68,6;78,3] | 72,9 [69,4;78,1] | 75,9 [68,1;78,5] | 0,9 |
| Albumin, g/L | 40 [39;43] | 41 [39;43] | 39,5 [37;42] | 0,27 |
| Bicarbonate, mmol/L | 20 [18,2;21,4] | 20,1 [18,6;21,7] | 19,6 [17,3;20,8] | 0,2 |
| Hemoglobin, g/L | 112 [102;127] | 116 [103;127] | 109 [98;119] | 0,24 |
| CRP, mg/L | 4,5 [1,9;10,7] | 4,2 [1,4;7,35] | 7,2 [3;13,6] | 0,06 |
| PTH, ng/L | 388,5 [277;610] | 379 [276;592] | 480 [300;721] | 0,4 |
| Ca, mmol/L | 2,1 [2;2,3] | 2,1 [2;2,3] | 2,1 [2;2,3] | 0,97 |
| P, mmol/L | 1,6 [1,3;1,8] | 1,6 [1,3;1,8] | 1,7 [1,4;1,8] | 0,8 |
| NT-proBNP, pg/ml | 2114,6 [1095;4016] | 1856 [986;2721] | 2379 [2040;26865] | 0,042* |

**Note:** * — p<0,05.

**Abbreviations:** BMI — body mass index, spKt/V — dialysis dose per hemodiafiltration session, CRP — C-reactive protein, PTH — parathyroid hormone.

of the observed parameters in three independent groups, the Pearson's chi-squared test was used. Differences were considered significant at p<0,05.; p<0,1 was considered as a tendency towards difference.

The study was approved by the ethics committee of the V. I. Razumovsky Saratov State Medical University (Russia). All participants gave written informed consent.

## Results

The age of men was 57,5 [41,5; 63,5] years; total dialysis time — 44 [15; 113] months; the median age of women — 59,5 [49; 66] years, the median total dialysis time — 44,5 [18; 79,5] months. The median serum NT-proBNP level was 2114,6 [1095; 4016] pg/ml, in men — 2143,5 [1087,6; 13750,7] pg/ml, in women — 2044,3 [1095; 2572] pg/ml

The clinical and laboratory characteristics of the studied population and the results of comparing the groups of patients with normal level of hydration and hyperhydration are presented in Table 1. When comparing the NT-proBNP level in patients depending on their hydration status, a statistically significant increase of the prohormone level in hyperhydration patients was revealed.

The concentrations of NT-proBNP in patients (n=80) were compared depending on LVEF (Figure 1) and statistically significant differences were found in patients of three groups. Pairwise comparison revealed the statistically significant differences of NT-proBNP levels between HFpEF and HFmrEF (p=0,02) groups and tendency to differences in HFpEF and HFrEF groups (p=0,07).

NT-proBNP levels were different in patients with normal hydration status and hyperhydration depending on LVEF (Figures 2 and 3). However, the differences identified were not statistically significant, probably due to insufficient sample size.

When analyzing the median NT-proBNP level in all patients as a whole and depending on the hydration status, we observed that the prohormone gradually increased with a decrease in EF.

Significant differences in the age of patients in groups depending on the prohormone quartile were

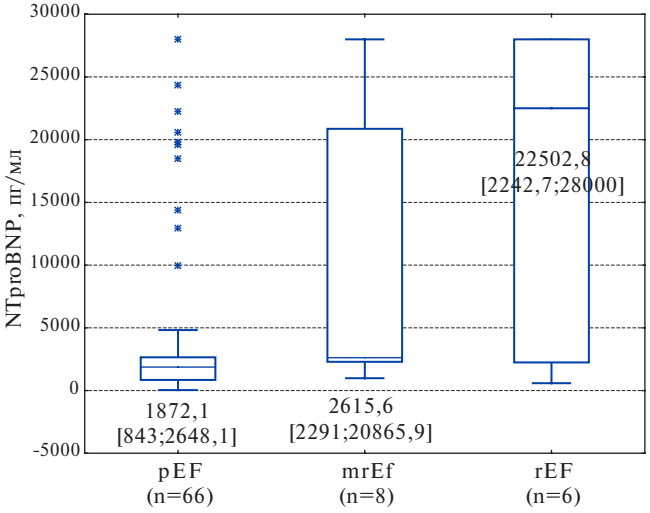


**Figure 1.** NT-proBNP level depending on LVEF (n=80, H=6,07, df=2, p=0,048).
**Abbreviations:** pEF — preserved ejection fraction, mrEF — mid-range ejection fraction, rEF — reduced ejection fraction.

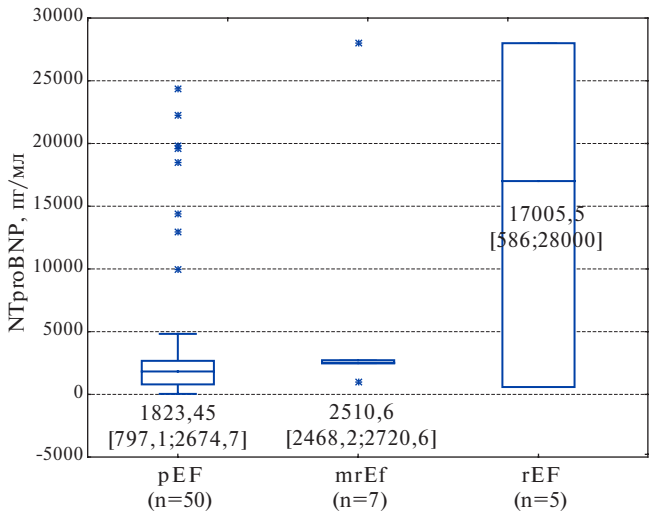


**Figure 2.** NT-proBNP level depending on LVEF in normal hydration patients (n=62, H=2,466, df=2, p=0,29).
**Abbreviations:** pEF — preserved ejection fraction, mrEF — mid-range ejection fraction, rEF — reduced ejection fraction.

established. Pairwise comparisons demonstrated statistically significant differences in age between groups with levels of NT-proBNP <1095 pg/ml and 1095-4016 pg/ml (p=0,01); a tendency to difference was detected in groups with NT-proBNP <1095 pg/ml and >4016 pg/ml (p=0,057). Thus, patients with a higher NT-proBNP quartile were older (Table 2).

Significant differences in the incidence of new cardiovascular events (CVE) were detected in patients of all three groups. Pairwise comparisons revealed differences between groups with NT-proBNP levels <1095 pg/ml and 1095-4016 pg/ml (p=0,01), and between groups with NT-proBNP levels <1095 pg/ml and >4016 pg/ml (p=0,0024) (Table 2).

The incidence of atrial fibrillation also differs in all three groups. In a pairwise comparison, significant differences were found between groups of patients with NT-proBNP 1095-4016 pg/ml and >4016 pg/ml (p=0,013); a tendency to difference was detected in patients with NT-proBNP <1095 pg/ml and >4016 pg/ml (p=0,051).

A tendency to increase the incidence of new cardiovascular events, systolic and diastolic dysfunction in patients with a prohormone increase was established (Table 2).

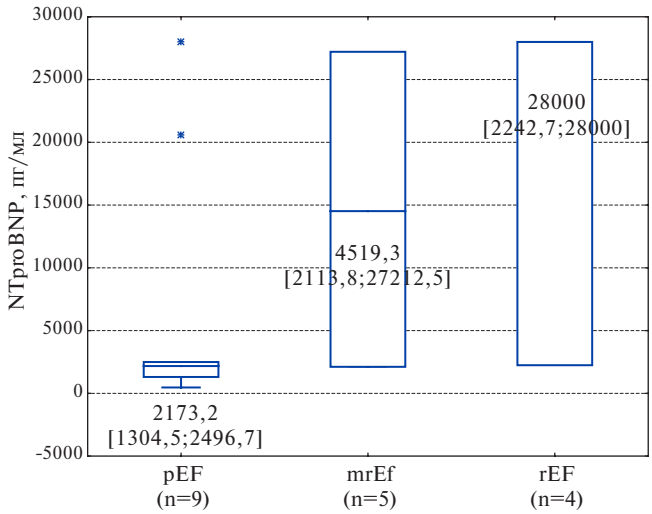


**Figure 3.** NT-proBNP level depending on LVEF in hyperhydration patients (n=18, H=1,6, df=2, p=0,44).
**Abbreviations:** pEF — preserved ejection fraction, mrEF — mid-range ejection fraction, rEF — reduced ejection fraction.

## Discussion

The significant value of NT-proBNP for HF diagnosis is >125 pg/ml [13]. Serum levels of NT-proBNP in HD patients significantly exceeded the average population values. It is noteworthy that the scatter in the prohormone concentration was significant: from values several times larger than normal ones to extreme concentrations that are many times higher than the upper boundary of the reference interval. Such an increase in the NT-proBNP level is probably due to the severity of structural and functional cardiac changes in patients undergoing extracorporeal therapy. A significant NT-proBNP increase was noted in patients with hyperhydration, which, most likely, is a reaction of excessive prohormone production in response to an increase in filling pressure with volume overload. All this complicates the interpretation of the NT-proBNP level and use of prohormone

**Table 2**

**Clinical characteristics of patients in groups depending on serum NT-proBNP level**

| Parameter | NT-proBNP <1095 пг/мл (n=20); M±SD; Med;25-75% | NT-proBNP [1095-4016] пг/мл (n=40); M±SD; Med;25-75% | NT-proBNP >4016 пг/мл (n=20); M±SD; Med;25-75% | p value |
|---|---|---|---|---|
| Gender (men/women) | 13/7 | 23/17 | 16/4 | |
| Age, years | 48,5 [39,5;57,5]<br>48±12,7 | 59,5 [48;66]<br>56±13 | 59,5 [42,3;66,8]<br>55,5±15,4 | 0,043* |
| New cardiovascular events on HD | 2 (10%) | 17 (42,5%) | 11 (55%) | 0,008* |
| Fatal cardiovascular events on HD | - | 5 (12,5%) | 3 (15%) | 0,21 |
| Number of patients with hyperhydration | 2 (10%) | 9 (22,5%) | 7 (35%) | 0,16 |
| Systolic dysfunction | 2 (10%) | 8 (20%) | 7 (35%) | 0,14 |
| Diastolic dysfunction | 17 (85%) | 37 (92,5%) | 20 (100%) | 0,18 |
| HFpEF | 16 (80%) | 30 (75%) | 11 (55%) | 0,058 |
| HFmrEF | 1 (5%) | 4 (10%) | 3 (15%) | 0,65 |
| HFrEF | 1 (5%) | 1 (2,5%) | 4 (20%) | 0,23 |
| AF | 2 (10%) | 5 (12,5%) | 8 (40%) | 0,026* |
| Obesity (BMI >30 kg/m$^2$) | 6 (30%) | 7 (17,5%) | 2 (10%) | 0,25 |
| ACE/ARB therapy | 1 (5%) | 8 (20%) | 4 (20%) | 0,38 |

**Note:** * — p<0,05.

**Abbreviations**: HD — hemodialysis, HFpEF — heart failure with preserved ejection fraction, HFmrEF — heart failure with mid-range ejection fraction, HFrEF — heart failure with reduced ejection fraction, AF — atrial fibrillation, BMI — body mass index, ACE inhibitors — angiotensin-converting-enzyme inhibitors, ARB — angiotensin II receptor blockers.

for the diagnosis and monitoring of HF in HD patients [10].

It is important to determine the NT-proBNP level in patients with different phenotypes of HF depending on LVEF. Of particular interest is the study of the NT-proBNP role in the diagnosis of HFpEF. Despite the relevance, in recent years there have been only few studies devoted to this issue.

In the study by Antlanger M, et al. (2017), patients were divided into three groups: without HF, with HFpEF, and with HFrEF. In these groups, there was a significant increase in prohormone levels above reference values, which is consistent with our data. The level of NT-proBNP was significantly higher in HFrEF patients than in patients without HF, while there were no significant differences between patients with HFpEF and without HF. From the study it follows that determination of NT-proBNP levels can be used only to exclude HFrEF, but not to differentiate patients with HFpEF and without HF [10].

In our study, when assessing the NT-proBNP level both in all patients as a whole and depending on the hydration status, the prohormone concentration was higher than the normal level, not allowing to exclude the HF, and increased with EF decreasing. The revealed significant differences between the NT-proBNP levels in patients with HFpEF and HFmrEF and a tendency to differences in patients with HFpED and HFrEF demonstrate the potential of NT-proBNP use in the differential diagnosis of HF phenotypes depending on LVEF.

NT-proBNP is considered as a CVE risk factor and unfavorable prognosis both in the general population and in patients with cardiovascular disease and chronic kidney disease [14]. According to our results, NT-proBNP increase in HD patients can also be associated with a risk of CVE, systolic and diastolic dysfunction. The preliminary data obtained indicate the need for further research of this marker as a predictor of CVE and an adverse outcome in patients on HD.

**Study limitations.** The obtained results are preliminary due to small sample size. The research of revealed tendencies in a larger patient population, prospective observation, and further study of NT-proBNP as a CVE predictor in patients receiving extracorporeal therapy are required.

## Conclusion

The serum NT-proBNP level in HD patients is significantly higher than the average population val-

ues. A significant NT-proBNP increase in hyperhydration patients was found. Determination of NT-proBNP should be used as an additional method for the HF diagnosis in HD patients, including for clarifying its phenotype depending on LVEF. An increase of NT-proBNP concentration in HD patients is associated with a risk of CVE, systolic and diastolic dysfunction. The similarity of HF and hyperhydration manifestations during dialysis requires the use of additional differential diagnosis methods using a sequential algorithm: clinical assessment, BIA, TTE, and NT-proBNP determination.

**Relationships and Activities**: not.

## References


1. McCullough PA, Chan CT, Weinhandl ED, et al. Intensive Hemodialysis, Left Ventricular Hypertrophy, and Cardiovascular Disease. Am J Kidney Dis. 2016;68(5S1):5-14. doi:10.1053/j.ajkd.2016.05.025.
2. Kim H, Kim KH, Ahn SV, et al. Risk of major cardiovascular events among incident dialysis patients: A Korean national population-based study. Int J Cardiol. 2015;198:95-101. doi:10.1016/j.ijcard.2015.06.120.
3. Sedov DS, Rebrov AP. Cardiac remodeling in patients with chronic kidney disease (review). Saratov Journal of Medical Scientific Research. 2019;15(2):217-21. (in Russ.).
4. Saran R, Li Y, Robinson B, et al. US Renal Data System 2014 Annual Data Report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2015;66(1) (suppl 1):1-305. doi:10.1053/j.ajkd.2015.05.001.
5. Yano Y, Bakris GL, Matsushita K, et al. Both chronic kidney disease and nocturnal blood pressure associate with strokes in the elderly. Am J Nephrol. 2013;38(3):195-203. doi:10.1159/000354232.
6. Wohlfahrt P, Rokosny S, Melenovsky V, et al. Cardiac remodeling after reduction of high-flow arteriovenous fistulas in end-stage renal disease. Hypertens Res. 2016;39:654-9. doi:10.1038/hr.2016.50.
7. Liao R, Wang L, Li J, et al. Hemodialysis access type is associated with blood pressure variability and echocardiographic changes in end-stage renal disease patients. J Nephrol. 2019;32(4):627-34. doi:10.1007/s40620-018-00574-y.
8. Nowak KL, Chonchol M. Does inflammation affect outcomes in dialysis patients? Seminars in dialysis. 2018;31(4):388-97. doi:10.1111/sdi.12686.
9. Efremova OA, Golovin AI, Hodykina JuE. Peculiarities of calcium and phosphorus metabolism of the patients undergoing maintenance haemodialysis. Research result. 2016;2(4):24-9. (In Russ.) doi:10.18413/2313-8955-2016-2-4-24-29.
10. Antlanger M, Aschauer S, Kopecky C, et al. Heart Failure with Preserved and Reduced Ejection Fraction in Hemodialysis Patients: Prevalence, Disease Prediction and Prognosis. Kidney Blood Press Res. 2017;42:165-76. doi:10.1159/000473868.
11. Segall L, Nistor I, Covic A. Heart failure in patients with chronic kidney disease: a systematic integrative review. Biomed Res Int. 2014;2014:937398. doi:10.1155/2014/937398.
12. Sipahi I, Fang JC. Treating heart failure on dialysis. Finally getting some evidence. J Am Coll Cardiol. 2010;56(21):1709-11. doi:10.1016/j.jacc.2010.03.106.
13. Ponikowski P, Voors AA, Anker SD, et al. Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18(8):891-975. doi:10.1002/ejhf.592.
14. Zhu Q, Xiao W, Bai Y, et al. The prognostic value of the plasma N-terminal pro-brain natriuretic peptide level on all-cause death and major cardiovascular events in a community-based population. Clin Interv Aging. 2016;11:245-53. doi:10.2147/CIA.S98151.
15. Ndumele CE, Matsushita K, Sang Y, et al. N-Terminal Pro-Brain Natriuretic Peptide and Heart Failure Risk Among Individuals With and Without Obesity: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2016;133(7):631-8. doi:10.1161/CIRCULATIONAHA.115.017298.