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Is the N-terminal pro-B-type natriuretic peptide a predictor of cardiovascular events in hemodialysis patients?

Aim	To evaluate the role of N-terminal pro-hormone brain natriuretic peptide (NT-proBNP) as a predictor of cardiovascular events (CVE) in patients receiving programmed hemodialysis (PHD).
Material and methods	This study included 74 patients (men, 64.8%) older than 18 years receiving PHD. Data were processed using mean values of standard biochemical indexes for 16 months. NT-proBNP level was measured and transthoracic echocardiography (EchoCG) and bioimpedancemetry were performed at the time of inclusion into the study. Cumulative incidence of CVE for 16 months was evaluated in patients with different levels of NT-proBNP (quartile 1: <1127 pg/ml; quartile 1–4: 1127–3210 pg/ml; quartile 4: >3210 pg/ml) using the Kaplan-Meier method. For assessment of NT-proBNP as a CVE predictor, receiver operational characteristic curves (ROC curves) were constructed.
Results	The serum concentration of NT-proBNP was 2114.5 [1127; 3210.4] pg/ml. During 16 months, CVE were observed in 25.6% of patients. The risk of CVE increased with increasing NT-proBNP quartile in the analysis of Kaplan-Meier curves (Log-Rank test, p=0.032). In this process, CVE did not develop in patients with NT-proBNP concentrations lower than 1127 pg/ml. The ROC analysis demonstrated a good predictive value of NT-proBNP (p=0.006, AUC 0.71, 95% CI: 0.59–0.83). The optimum cut-off threshold of the NT-proBNP level predictive of CVE was 2093 pg/ml (sensitivity, 84.2%, specificity, 58.2%). CVE developed in patients with greater values of volumetric myocardial parameters, indirect signs of hyperhydration (higher predialysis sodium level and pulmonary artery systolic pressure), smaller volumes of substituate per dialysis procedure, and left ventricular systolic dysfunction (p<0.05).
Conclusion	In patients receiving programmed extracorporeal therapy, the serum concentration of NT-proBNP was considerably higher than mean values in the general population. Apparently, serum NT-proBNP concentrations in the range of 1127–2093 pg/ml can be used as a predictor for a high risk of CVE in the dialysis population. Pronounced structural alterations of the myocardium, left ventricular systolic dysfunction, and hyperhydration are the factors that provide development of CVE on PHD. Large volumes of the PHD substitution solution are associated with a lower incidence of CVE in the dialysis population.

Keywords	Chronic kidney disease; programmed hemodialysis; NT-proBNP; cardiovascular risk; cardiovascular diseases
For citation	Sedov D. S., Fedotov E. A., Rebrov A. P. Is the N-terminal pro-B-type natriuretic peptide a predictor of cardiovascular events in hemodialysis patients? Kardiologiia. 2020;60 (10):55–61. [Russian: Седов Д. С., Федотов Э. А., Ребров А. П. Является ли N-терминальный фрагмент прогормона мозгового натрийуретического пептида предиктором сердечно-сосудистых событий у пациентов на программном гемодиализе? Кардиология. 2020;60(10):55–61]

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Introduction

Cardiovascular diseases (CVDs) are more common than other death causes in patients receiving long-term hemodialysis [1–3]. Diagnosis of CVDs and prognosis of cardiovascular events (CVEs) remain the most important issue in the prospect of identifying risk groups for long-term hemodialysis and developing measures to improve the prognosis. It has recently been shown that such markers as the N-terminal prohormone brain natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP) are associated with the development of CVEs in the general population [4]. At the same time, NT-proBNP has a longer half-life and is more stable in vitro, making its definition more convenient and reliable [5]. The question remains now whether NT-proBNP can be used to predict CVEs during long-term hemodialysis [6]. According to the European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (ESC, 2016), the level of NT-proBNP affecting the prognosis in the general population is more than 125 pg/mL [7]. It has been published earlier that the

serum levels of NT-proBNP in patients on hemodialysis is significantly higher than the population means [8]. This should be taken into account when estimating NT-proBNP in the dialysis population, ыштсу the prohormone levels affecting the prognosis for patients on long-term hemodialysis may differ from those in the general population.

Material and Methods

Seventy-four patients (48 males [64.8%]) with terminal stage chronic kidney disease (CKD) were followed up for 16 months while receiving long-term outpatient therapy with hemodiafiltration in a Fresenius 5008 device (Germany) using bicarbonate dialysis solution and high-flow dialyzers. All patients received the best possible dialysis: 3 days a week, at least 4 hours of effective time per procedure, actual dialysis dose per hemodiafiltration session (spKt/V) >1.4; a weekly volume of the substituent (replacement solution) >63 L/week.

Patients met inclusion criteria (age over 18 years; signed informed consent) and had no exclusion criteria (poor cardiac echocardiography imaging; valvular heart disease (congenital and/or acquired before renal replacement therapy); acute infectious diseases (HIV, hepatitis B and C, sepsis, infectious endocarditis, tuberculosis, etc.) or exacerbated chronic diseases (ulcers, cholecystitis, etc.); chronic obstructive pulmonary disease; cancer, lymphoproliferative diseases, including the history.

All subjects underwent standard monthly clinical biochemical examinations. Given the lability of the long-term hemodialysis indicators, the mean 16-month laboratory values and dialysis doses were used in the statistical processing. At the time of inclusion, serum levels of NT-proBNP were determined in all patients by enzyme-linked immunosorbent assay (Elisa) using a commercial reagent kit NT-proBNP-IFA-BEST (Vector-Best, JSC, Novosibirsk, Russia). Prohormone levels were estimated on day 2 after the hemodialysis procedure.

The reaction results were recorded by an iMark photometer (BioRad, USA). Serum levels of NT-proBNP were determined in the test and control samples according to the calibration graph using the Zemfira photometer control software and expressed in pg/mL. The reference concentration was NT-proBNP <200 pg/mL, which was determined in 165 healthy individuals at the age of 20–50 years. All patients underwent standard echocardiographic measurements in an Acuson 128 XP/10 complex (Siemens-Acuson, USA) and bioelectrical impedance analysis on a Body Composition Monitor (Fresenius, Germany) between the dialysis sessions.

Three groups of patients were defined according to the serum NT-proBNP levels with increasing quartile level of the prohormone: quartile 1: <1127 pg/mL, quartile 1–4: 1127–3210 pg/mL, quartile 4: >3210 pg/mL.

The statistical processing of data was performed using the IBM SPSS Statistics v23 software suite. The median and the lower and upper quartiles (Me; 25–75%) were used to describe signs with non-normal distribution. The correlation between the indicators was evaluated using non-parametric Spearman's rank correlations. The quantitative signs were compared in two independent samples using the Mann-Whitney test. The differences in sign rates in several independent groups were estimated using Pearson's χ^2 test. The cumulative rate of CVEs, depending on the NT-proBNP quartile, was evaluated using the Kaplan-Meyer method. Receiver Operating Characteristic (ROC) curves were constructed to estimate the predictive value of NT-proBNP as a predictor of CVEs. The differences were statistically significant at $p<0.05$; $p<0.1$ were considered a trend toward difference.

The study was carried out following the Good Clinical Practice and the Declaration of Helsinki. The Ethics Committee of Saratov State Medical University n.a. V. I. Razumovskiy approved the study protocol.

Results

The duration of follow-up period was 16 months. Median age of males was 55.5 [41.5; 63] years, median dialysis age was 60 [32.5; 123.5] months; median age of females was 60.5 [51;67] years, and median dialysis age was 60.5 [33;95] months. The median serum level of NT-proBNP was 2114.5 [1127; 3210.4] pg/mL, 2143.5 [1087,6; 11482.1] pg/mL in males, 2044.3 [1127; 2580] pg/mL in females.

Table 1 provides clinical, laboratory, and echocardiographic characteristics of the study dialysis population and the results of patient group comparisons with respect to the development of CVEs during the follow-up period. Patients with CVEs had significantly higher serum levels of NT-proBNP, predialysis serum sodium, pulmonary artery systolic pressure (PASP), and the volumetric echocardiographic parameters than patients without CVEs ($p<0.05$ for all measurements except intraventricular septal thickness ($p=0.058$)). It should be noted that a history of coronary artery disease (CAD, 17% of patients) did not affect the levels of prohormone ($p=0.177$) and PASP ($p=0.8$) during long-term hemodialysis.

ISSN 0022-9040. Kardiologiia. 2020;60(10). DOI: 10.18087/cardio.2020.10.n1109

Cardiovascular events were more likely to occur in patients with left ventricular systolic dysfunction (χ^2=9.8, cc=1, p=0.002) and lower volume of substituent (p=0.02). There was also a trend to different serum phosphorus levels with lower levels in the group with CVEs (p=0.07).

Correlation analysis revealed correlations between NT-proBNP concentration and echocardiographic parameters. The inverse correlation between the prohormone levels and left ventricular ejection fraction (r= –0.35) confirms that the prohormone reflects the severity of systolic dysfunction and is associated with the prognosis of adverse outcomes during long-term hemodialysis. Positive correlations between the prohormone levels and left ventricular mass index (r=0.39), end-diastolic dimension (r=0.3), end-systolic dimension (r=0.37), left atrial dimension (r=0.32), and right atrial dimension (r=0.3) reflect

Table 1. Clinical, laboratory, and echocardiographic indicators depending on the presence of CVEs

Indicator	All patients (n=74)	Patients without CVEs (n=55)	Patients with CVEs (n=19)	Comparison of patient groups depending on the presence of CVEs during the follow-up period, p-value
Sex, n male/female	48/26	35/20	13/6	0.7
Age, years	57.5 [42; 64]	55 [42; 63]	62 [53; 67]	0.13
NT-proBNP, pg/mL	2114.6 [1127; 3210]	1808 [843; 2648]	2563 [2114; 20543]	0.005
Volume of substituent, L/week	79 [69.6; 91.3]	82.8 [71.6; 92.3]	73.3 [66.8; 78.5]	0.02
Sodium before dialysis, mmol/L	138.3 [139.9]	138.3 [137; 139.2]	140 [137.6; 140.7]	0.02
Phosphorus, mmol/L	1.55 [1.37; 1.76]	1.58 [1.38; 1.8]	1.47 [1.27; 1.58]	0.07*
LVM, g	275.5 [230.5; 325]	262 [219; 320]	320 [266; 351]	0.008
LVMI, g/m	141 [124; 165]	133.5 [114; 151]	168 [143; 212]	0.0004
EDD, cm	5.4 [5; 5.7]	5.3 [4.9; 5.6]	5.7 [5.3; 6.13]	0.008
ESD, cm	3.6 [3.3; 4]	3.4 [3.2; 3.74]	3.93 [3.72; 4.6]	0.0004
EDV, cm	146 [121; 170]	141 [115; 154]	172 [130; 195]	0.03
ESV, cm	54.5 [45; 69.5]	48.8 [40; 62]	67 [59; 108]	0.0009
LVPWT, cm	1.2 [1.1; 1.34]	1.2 [1.1; 1.31]	1.25 [1.2; 1.4]	0.04
IVST, cm	1.22 [1.13; 1.4]	1.2 [1.1; 1.37]	1.27 [1.21; 1.45]	0.058*
Left atrium, cm	4.22 [3.9; 4.6]	4.11 [3.9; 4.5]	4.79 [4; 5]	0.004
Right atrium, cm	4.06 [3.9; 4.5]	4 [3.8; 4.34]	4.51 [3.9; 4.9]	0.02
RV diastolic dimension, cm	2.99 [2.81; 3.1]	2.9 [2.8; 3]	3 [2.95; 3.3]	0.03
RVAWT, cm	0.52 [0.5; 0.58]	0.5 [0.5; 0.56]	0.57 [0.52; 0.6]	0.02
T-gradient, mm Hg	30.1 [25.2; 38]	27.5 [24; 33]	40.5 [30.1; 55]	0.0006
Systolic aortic valve opening	1.79 [1.65; 1.9]	1.83 [1.7; 2]	1.7 [1.6; 1.8]	0.009
SPAP, mm Hg	35 [29; 48]	33 [29; 40]	48 [35; 64.5]	0.008
Inferior vena cava, cm	2 [1.8; 2.2]	1.91 [1.74; 2.1]	2.18 [1.95; 2.58]	0.03
LVEF, %	61 [56; 65.3]	62 [60; 66]	55.7 [45; 60]	0.0007
Percentage of patients with systolic dysfunction (LVEF <50%), n (%)	13 (17.6%)	5 (9%)	8 (42.1%)	0.002

Data is expressed as Me (25–75%). The exact significance of the p criterion is given.
*, p < 0.1. CVEs, cardiovascular events; NT-proBNP, N-terminal probrain natriuretic peptide; LVM, left ventricular mass; LVMI, left ventricular mass index; EDD, end diastolic dimension; ESD, end systolic dimension; EDV, end diastolic volume; ESV, end systolic volume; LVPW, left ventricular posterior wall; IVS, interventricular septum; RV, right ventricle; RVAW, right ventricular anterior wall; PASP, pulmonary artery systolic pressure; LVEF, left ventricular ejection fraction.

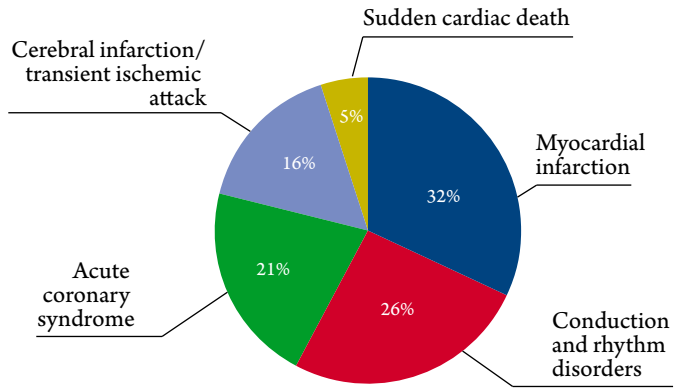
a direct correlation of NT-proBNP with the severity of structural changes in myocardium (r<0.05 for all of the indicators mentioned).

The review of medical records revealed various forms of CAD in 13 (17%) patients with CKD before dialysis therapy: myocardial infarction in 9 (69.2%) patients, stable forms of CAD in 4 (30.8%) patients. During the follow-up period with long-term hemodialysis, CVEs were reported in 19 (25.6%) patients (Figure 1). Within the 12 months of follow-up, 7 (36.8%) patients experienced fatal CVEs: myocardial infarction in 5 (26.3%) patients, sudden cardiac death in 1 (5.2%) patient, and cerebral infarction in 1 (5.2%) patient. CVEs occurred in patients with significantly higher levels of NT-proBNP (p=0.005) (Table 1). Serum NT-proBNP concentrations were not different in patients with fatal and non-fatal CVEs (p > 0.05).

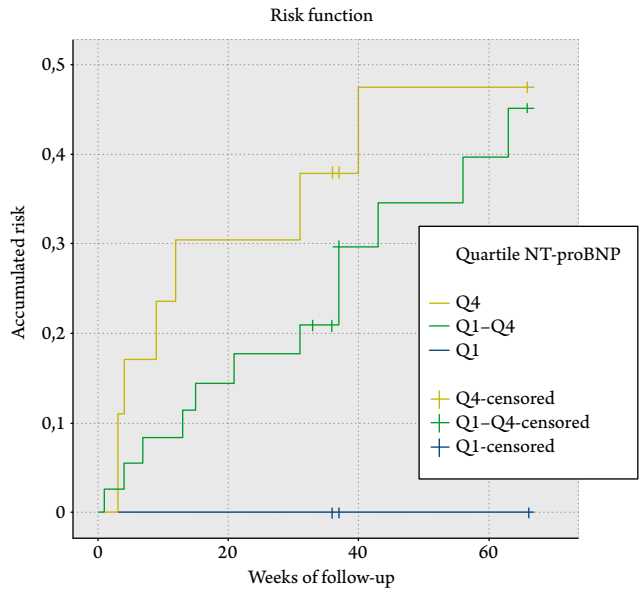
Within 16 months, patients with NT-proBNP <1127 pg/mL did not have CVEs, but the rate of CVEs increased from 32.4% (n=12) in dialysis patients with NT-proBNP 1127–3210 pg/mL (n=37) to 36.8% (n=7) in patients with the highest NT-proBNP concentrations (>3210 pg/mL) (n=19) (Figure 2). The differences were significant when the three patient groups were between each other (χ^2=8.3, cc=2, p=0.02). However, in the pairwise comparison, significant differences were found between patients with NT-proBNP below quartile 1 and quartile 1–4 (χ^2=7.4, cc=1, p=0.006), and patients with the prohormone levels in quartile 1 and quartile 4 (χ^2=8.2, cc=1, p=0.004).

In the ROC analysis, the area under the curve (AUC) was 0.71 (95% confidence interval 0.59–0.83, p=0.006), which is indicative of a good model quality (Figure 3). The optimal NT-proBNP cut-off point predicting the development of CVEs was 2093 pg/mL (sensitivity 84.2%, specificity 58.2%). Thus, NT-proBNP at 2093 pg/mL is suggested to be possibly used as the cut-off point to predict CVEs in the dialysis population.

Figures 1. Structure of cardiovascular events in patients receiving long-term hemodialysis within 16 months of follow-up

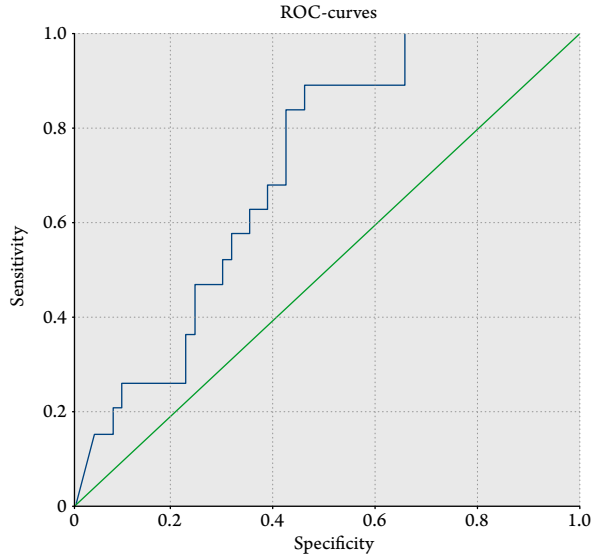


Figures 2. Kaplan–Meyer curves showing the cumulative rate of cardiovascular events within 16 months of follow-up in dialysis patients with varying levels of NT-proBNP



Quartile 1: <1127 pg/mL, quartile 1–4: 1127–3210 pg/mL, quartile 4: >3210 pg/mL (Log-Rank test, p=0.032).
N-terminal pro-brain natriuretic peptide.

Figures 3. ROC-curves reflecting the predictive capability of NT-proBNP for cardiovascular events in patients receiving long-term hemodialysis



Area under the curve AUC AUC 0,71 (95% confidence interval 0.59–0.83, p=0.006). ROC – receiver operating characteristics; NT-proBNP – n-terminal pro-brain natriuretic peptide; AUC – area under the curve.

ISSN 0022-9040. Kardiologiia. 2020;60(10). DOI: 10.18087/cardio.2020.10.n1109

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КРАТКАЯ ИНСТРУКЦИЯ ПО МЕДИЦИНСКОМУ ПРИМЕНЕНИЮ ЛЕКАРСТВЕННОГО ПРЕПАРАТА ФОРСИГА®: РЕГИСТРАЦИОННЫЙ НОМЕР: ЛП-002596 **ТОРГОВОЕ НАЗВАНИЕ:** ФОРСИГА (FORXIGA)®. **МЕЖДУНАРОДНОЕ НЕПАТЕНТОВАННОЕ НАЗВАНИЕ:** ДАПАГЛИФЛОЗИН. **ЛЕКАРСТВЕННАЯ ФОРМА:** таблетки, покрытые плёночной оболочкой. **ПОКАЗАНИЯ К ПРИМЕНЕНИЮ: САХАРНЫЙ ДИАБЕТ 2 ТИПА** у взрослых пациентов в дополнение к диете и физическим упражнениям для улучшения гликемического контроля в качестве: монотерапии, когда применение метформина невозможно ввиду непереносимости; комбинированной терапии с метформином, производными сульфонилмочевины (в том числе, в комбинации с метформином), тиазолидиндионами, ингибиторами дипептидилпептидазы 4 (ДПП-4) (в том числе, в комбинации с метформином); агонистом рецепторов глюкагоноподобного полипептида-1 (ГПП-1) эксенатидом пролонгированного действия в комбинации с метформином; препаратами инсулина (в том числе, в комбинации с одним или двумя гипогликемическими препаратами для перорального применения) при отсутствии адекватного гликемического контроля на данной терапии; стартовой комбинированной терапии с метформином, при целесообразности данной терапии. Сахарный диабет 2 типа у взрослых пациентов с установленным диагнозом сердечно-сосудистого заболевания или двумя и более факторами сердечно-сосудистого риска (возраст у мужчин ≥ 55 лет или ≥ 60 лет у женщин и наличие не менее одного фактора риска: дислипидемия, артериальная гипертензия, курение) для снижения риска госпитализации по поводу сердечной недостаточности. **СЕРДЕЧНАЯ НЕДОСТАТОЧНОСТЬ (II-IV функциональный класс по классификации NYHA) со сниженной фракцией выброса у взрослых пациентов для снижения риска сердечно-сосудистой смерти и госпитализации по поводу сердечной недостаточности. ПРОТИВОПОКАЗАНИЯ:** повышенная индивидуальная чувствительность к любому компоненту препарата; сахарный диабет 1-го типа; диабетический кетоацидоз; нарушение функции почек при расчетной СКФ (рСКФ) стабильно менее 45 мл/мин/1,73 м², включая нарушение функции почек тяжелой степени и терминальную стадию почечной недостаточности, при применении по показанию «сахарный диабет 2 типа»; нарушение функции почек тяжелой степени и терминальная стадия почечной недостаточности (рСКФ < 30 мл/мин/1,73 м²), при применении по показанию «сердечная недостаточность» (в связи с ограниченным опытом применения в клинических исследованиях); наследственная непереносимость лактозы, дефицит лактазы или глюкозо-галактозная мальабсорбция; беременность и период грудного вскармливания; детский возраст до 18 лет (безопасность и эффективность не изучены). **С ОСТОРОЖНОСТЬЮ:** печеночная недостаточность тяжелой степени, инфекции мочевыделительной системы, повышенное значение гематокрита. **ПРИМЕНЕНИЕ В ПЕРИОД БЕРЕМЕННОСТИ И ГРУДНОГО ВСКАРМЛИВАНИЯ** В связи с тем, что применение дапаглифлозина в период беременности не изучено, препарат противопоказан в период беременности. В случае диагностирования беременности терапия дапаглифлозином должна быть прекращена. Неизвестно, проникает ли дапаглифлозин и/или его неактивные метаболиты в грудное молоко. Нельзя исключить риск для новорожденных/младенцев. Дапаглифлозин противопоказан в период грудного вскармливания. **СПОСОБ ПРИМЕНЕНИЯ И ДОЗЫ:** Внутрь, независимо от приёма пищи, не разжевывая. Сахарный диабет 2 типа. Монотерапия: рекомендуемая доза препарата Форсига составляет 10 мг один раз в сутки. Комбинированная терапия: рекомендуемая доза препарата Форсига составляет 10 мг один раз в сутки в комбинации с метформином, производными сульфонилмочевины (в том числе, в комбинации с метформином), тиазолидиндионами, ингибиторами ДПП-4 (в том числе, в комбинации с метформином); агонистом рецепторов ГПП-1 – эксенатидом пролонгированного действия, в комбинации с метформином; препаратами инсулина (в том числе, в комбинации с одним или двумя гипогликемическими препаратами для перорального применения). С целью снижения риска гипогликемии при совместном назначении препарата Форсига с препаратами инсулина или препаратами, повышающими секрецию инсулина (например, с производным сульфонилмочевины), может потребоваться снижение дозы препаратов инсулина или препаратов, повышающих секрецию инсулина. Стартовая комбинированная терапия с метформином: рекомендуемая доза препарата Форсига составляет 10 мг один раз в сутки, доза метформина – 500 мг один раз в сутки. В случае неадекватного гликемического контроля дозу метформина следует увеличить. СД2 у взрослых пациентов с установленным диагнозом сердечно-сосудистого заболевания или двумя и более факторами сердечно-сосудистого риска для снижения риска госпитализации по поводу сердечной недостаточности: рекомендуемая доза препарата Форсига составляет 10 мг один раз в сутки. **Сердечная недостаточность: рекомендуемая доза препарата Форсига составляет 10 мг один раз в сутки. ПОБОЧНОЕ ДЕЙСТВИЕ.** Краткий обзор профиля безопасности. В клинических исследованиях СД2 более 15000 пациентов получали терапию дапаглифлозином. Первичная оценка безопасности и переносимости проводилась в заранее запланированном анализе объединенных данных 13 краткосрочных (до 24 недель) плацебо-контролируемых исследований, в которых 2360 пациентов принимали дапаглифлозин в дозе 10 мг и 2295 пациентов получали плацебо. В исследовании дапаглифлозина в отношении сердечно-сосудистых исходов при СД2 (DECLARE) 8574 пациента получали дапаглифлозин 10 мг и 8569 получали плацебо (медиана воздействия 48 месяцев). В общей сложности экспозиция дапаглифлозина составила 30623 пациенто-лет. В исследовании дапаглифлозина в отношении сердечно-сосудистых исходов у пациентов с сердечной недостаточностью со сниженной фракцией выброса (DAPA-HF) 2368 пациентов получали дапаглифлозин 10 мг и 2368 получали плацебо (медиана воздействия 18 месяцев). Популяция включала пациентов с СД2 и без него, и пациентов с рСКФ ≥ 30 мл/мин/1,73 м². Профиль безопасности дапаглифлозина в исследованиях был в целом схожим по изучаемым показаниям. Тяжелую гипогликемию и диабетический кетоацидоз отмечали только у пациентов с сахарным диабетом. Ниже представлены НР, отмечавшиеся в плацебо-контролируемых клинических исследованиях и при пострегистрационном применении. Ни одна из них не зависела от дозы препарата. НР классифицированы по частоте и классу систем и органов. Частота НР представлена в виде следующей градации: очень часто (≥1/10), часто (≥1/100, <1/10), нечасто (≥1/1000, <1/100), редко (≥1/10000, <1/1000), очень редко (<1/10000) и неуточненной частоты (невозможно оценить по полученным данным). Инфекционные и паразитарные заболевания: часто – вульвовагинит, баланит и связанные с ними генитальные инфекции, инфекция мочевыводящих путей; нечасто – вульвовагинальный зуд, грибковые инфекционные заболевания; очень редко – некротизирующий фасциит промежности (гангрена Фурнье). Нарушения со стороны обмена веществ и питания: очень часто – гипогликемия (при применении в комбинации с производным сульфонилмочевины или инсулином); нечасто – снижение ОЦК, жажда; редко – диабетический кетоацидоз (при применении при СД2). Нарушения со стороны нервной системы: часто – головокружение. Нарушения со стороны желудочно-кишечного тракта: нечасто – запор, сухость во рту. Нарушения со стороны кожи и подкожных тканей: часто – сыпь; очень редко – ангионевротический отек. Нарушения со стороны костно-мышечной системы и соединительной ткани: часто – боль в спине. Нарушения со стороны почек и мочевыводящих путей: часто – дизурия, полиурия; нечасто – никтурия. Лабораторные и инструментальные данные: часто – дислипидемия, повышение значения гематокрита, снижение почечного клиренса креатинина на начальном этапе терапии; нечасто – повышение концентрации мочевины в крови, повышение концентрации креатинина в крови на начальном этапе терапии.

Ссылка на полную инструкцию: Инструкция по медицинскому применению лекарственного препарата Форсига ® (таблетки, покрытые пленочной оболочкой, 5 мг, 10 мг). Регистрационное удостоверение ЛП-002596 от 21.08.2014

ХСНнФВ – хроническая сердечная недостаточность со сниженной фракцией выброса; СС – сердечно-сосудистый; СН – сердечная недостаточность.

* Включая неотложные обращения по причине СН. # Снижение относительного риска сердечно-сосудистой смерти и смерти от всех причин в группе дапаглифлозина по сравнению с плацебо в исследовании DAPA HF.

1. Инструкция по медицинскому применению лекарственного препарата Форсига® (таблетки, покрытые пленочной оболочкой, 5 мг, 10 мг). Регистрационное удостоверение № ЛП 002596 от 21.08.2014.
2. Перечень жизненно необходимых и важнейших лекарственных препаратов для медицинского применения 3. Перечень лекарств для обеспечения отдельных категорий граждан. 4. McMurray JJV et al., N Engl J Med. 2019;381(21):1995–2008.
5. Клинические рекомендации Хроническая сердечная недостаточность 2020. https://scardio.ru/content/Guidelines/2020/Clinic_rekom_HSN.pdf (дата обращения 14.10.2020)

Материал предназначен для специалистов здравоохранения.

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FOR-RU-8650. Дата одобрения: 14.10.2020. Дата истечения: 13.10.2022.

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Discussion

Within the 16-month follow-up period, the rate of CVEs in patients receiving long-term hemodialysis was 25.6%, which is relatively high. Understandably, the higher NT-proBNP quartile is, the higher is the rate of CVEs (both fatal and non-fatal). This can be associated with the fact that the concentration of NT-proBNP increases as the structural (myocardial remodeling) and functional (left ventricular systolic dysfunction) changes in the heart occur during long-term hemodialysis, which naturally increases the risk of CVEs [9].

It should be noted that patients with the prohormone levels less than 1127 pg/mL developed no CVEs, which requires further research, since, according to several authors, NT-proBNP <1200 ng/L is not always an indicant in patients with CKD, unlike in the general population [10].

In our study, NT-proBNP demonstrated good predictive value as a predictor of CVEs. Our findings made it possible to establish that the NT-proBNP level of 2093 pg/mL can be used as the NT-proBNP cut-off point to predict CVEs in the dialysis population with high sensitivity (84.2%) and good specificity (58.2%). Above the specified level, the sensitivity of this CVE predictor increases, but its specificity decreases, causing an increase in the number of negative results.

It is also necessary to discuss an increased predialysis level of serum sodium and higher PASP in patients who had CVEs. Increased predialysis sodium levels are associated with higher gain between the dialysis sessions. And increased PASP develops in response to afterload in hyperhydrated patients. Thus, both indicators provide indirect evidence that patients have hyperhydration, which increases the risk of adverse outcomes during long-term hemodialysis [11].

The lower weekly volume of the substituent in the patients studied who had CVEs corresponds to the available evidence that large volumes of the replacement solution are associated with a lower rate of CVEs and improve the prognosis for long-term hemodialysis [12].

Conclusion

Serum levels of NT-proBNP in patients receiving long-term extracorporeal therapy are significantly higher than the mean values in the general population. NT-proBNP at serum concentrations of 1127–2093 pg/mL may be expected to be used as a predictor of the high risk of CVEs in the dialysis population. Severe structural changes in myocardium, left ventricular systolic dysfunction, and hyperhydration are factors contributing to the development of CVDs during long-term hemodialysis. Large amounts of the substituent in long-term hemodialysis are associated with a lower rate of CVDs in the dialysis population.

Limitations

The study was conducted in a relatively small sample of patients who were monitored at different points of long-term extracorporeal therapy. The prospective follow-up was limited to 16 months in our study, which is why the long-term predictive capability of NT-proBNP was not studied. The prospective follow-up should be continued, and the findings should be studied in a larger sample of patients. The correlation of the prohormone with volumetric echocardiographic parameters and hyperhydration was not described in detail because it was not the study's objective. Care should be taken when extrapolating the study findings to patients from other dialysis populations.

No conflict of interest is reported.

The article was received on 26/03/2020

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