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The prognostic value of high-sensitivity C-reactive protein blood level after coronary stenting for the development of stent restenosis

Aim	To analyze the relationship between serum concentrations of high-sensitivity C-reactive protein (hsCRP) in dynamics and development of restenosis at 12 months following elective coronary stent placement (CSP).
Material and methods	The key role in atherogenesis, neointimal proliferation and restenosis belongs to inflammation. This study included 91 patients (median age, 60 [56; 66] years) with stable exertional angina after an elective CSP using second-generation stents. Follow-up coronarography was performed for 60 patients at 12 months. Concentration of hsCRP was measured immediately prior to CSP and at 1, 3, 6, and 12 months after CSP. Restenosis of the stented segment (50% or more narrowing of the stented segment or a 5-mm vessel segment proximally or distally adjacent to the stented segment) was observed in 8 patients.
Results	According to results of the ROC analysis, the increase in hsCRP concentration >0.9 mg/l (>25%) at one month after CSP had the highest predictive significance with respect of restenosis (area under the ROC curve, 0.89 at 95% confidence interval (CI) from 0.79 to 0.99; sensitivity, 87.5%; specificity, 82.8%; p=0.0005), which was superior to the absolute value of hsCRP concentration >3.0 mg/l (area under the ROC curve, 0.82 at 95% CI from 0.68 to 0.96; p=0.0007).
Conclusion	Increased concentration of hsCRP ≥0.9 mg/l (≥25%) at a month after CSP was associated with restenosis of the coronary artery stented segment.

Keywords	Atherosclerosis; inflammation; coronary stent placement; high-sensitivity C-reactive protein
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Coronary artery disease (CAD) is currently the most prevalent form of cardiovascular disease [1]. The morphological basis of CAD is atherosclerosis, which is currently regarded as chronic non-specific inflammation of the vascular wall, stimulated by traditional risk factors (RFs), mainly disorders of lipid metabolism [2, 3]. The inflammatory theory of atherogenesis has dominated for three decades due to the extensive evidence base for the crucial role of inflammatory and autoimmune components in the initiation and progression of atherosclerosis [4, 5].

Coronary stenting (CS) is a common technique used to treat patients with stable exertional angina. However, short- and long-term postoperative outcomes remain a relevant issue despite improved stent designs. In-stent restenosis remains a relevant clinical problem as it leads to recurrent angina symptoms and the need for repeat intervention and revascularization [6]. Various predictors of recurrent stenosis are actively studied [7, 8]. Inflammation has also been shown to have a role in the development of adverse clinical outcomes after coronary stenting [9–14]. For example, according to control coronary angiogram (CAG) 12 months after CS, patients with registered restenosis had a higher incidence of arterial hypertension (AH), and diabetes mellitus (DM); higher serum levels of uric acid, low-density lipoprotein cholesterol (LDL–C), and high-sensitivity C-reactive protein (hs-CRP); and more extended target lesion and implanted stent compared to patients without restenosis. The presence of DM, higher serum levels of uric acid, LDL–C, and hs-CRP were independent predictors of restenosis [15].

CRP, an acute-phase protein, is one of the most versatile markers of inflammation in CAD. CRP can be present both in the areas of initial vessel damage and in the formed atherosclerotic plaque (ASP) [16].

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The opsonizing properties of CRP promote enhanced monocyte accumulation in ASP and induce endothelial dysfunction by inhibiting the release of nitric oxide [17]. Moreover, CRP interacts with many proteins, including oxidized LDL and lectin-like oxidized LDL receptor-1 [18] and scavenger receptors A [19]; increases the expression of the inhibitor of plasminogen activator and other adhesion molecules [17], and stimulates the macrophages to produce monocytic chemotactic protein-1 and matrix metalloproteinases, which are involved in the destabilization of ASP [20]. The proatherogenic effect of CRP was demonstrated in atherosclerosis-prone apolipoprotein E-deficient ($Apoe^{-/-}$) mice, resulting from the accelerated development of the atherosclerotic process in the aorta [21]. The correlation between the elevated serum hs-CRP levels and the risk of coronary atherosclerosis and cardiovascular complications has been shown in several clinical studies [22–25]. For example, a meta-analysis of six prospective studies of predictors of in-stent coronary restenosis in patients with CAD showed that preoperative hs-CRP levels were associated with an increased risk of restenosis [26].

To provide the most effective treatment, it is of great importance to study the changes in inflammatory biomarkers in CS and assess their predictive value. We suggest that the prolongation of the inflammatory response after CS may be associated with subsequent restenosis of the stented artery.

Study objective: Analyze the correlation between the changes in serum hs-CRP levels and in-stent coronary restenosis 12 months after the scheduled CS.

Material and methods

The study included 91 patients (median age 60 [56; 66] years, 69 [76%] male) with stable exertional angina pectoris of functional class (FC) II–III according to the classification of the Canadian Cardiovascular Society, who underwent a scheduled CS with implantation of the second-generation everolimus- and zotarolimus-eluting stents.

The following patients were excluded: those with a history of the acute coronary syndrome, stroke, or surgery in the previous 6 months; patients with concomitant severe somatic pathology that affects the prognosis; patients with a history of acute inflammatory or infectious diseases in the previous 2 months; patients with decompensated DM or requiring insulin therapy; patients with neoplasms, autoimmune diseases, or taking immunomodulating drugs.

The exclusion criteria also included left CA stenting, bifurcation stenting, stent implantation overlapping a previously implanted stent, implantation of more than two stents in one coronary artery, and recanalization of chronic coronary occlusion.

The study was performed under the principles of the Declaration of Helsinki. The ethics committee of the Russian National Cardiology Research Center approved the study protocol.

All patients underwent standard clinical examination, which included the collection of anamnesis, physical examination, complete blood count and biochemical profile, electrocardiography, echocardiography, 24-hour electrocardiographic monitoring, treadmill stress testing, and selective CAG.

Acetylsalicylic acid 75–100 mg/day, clopidogrel 75 mg/day, statins depending on the levels of total cholesterol (TC), LDL according to current recommendations, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors or sartans, and nitrates, if indicated, were administered to each patient at inclusion.

Blood samples for hs-CRP levels, as well as a complete blood count and biochemical profile, were obtained from each patient before and 1, 3, 6, 12 months after CS. Peripheral blood samples were taken from the ulnar vein 12 hours after a meal between 8 and 10 am. Blood samples were taken using citrate as an anticoagulant and stored for not more than 2 hours before the hs-CRP assay.

The serum hs-CRP assay was performed by latex-enhanced immunonephelometry on an automatic BN ProSpect analyzer using the CardioPhase hs-CRP reagent.

CAG was performed using the AlluraXper FD 10/10 or Coroscop system with radial or femoral access. The condition of the main arteries and their lateral branches with a diameter of at least 2 mm was evaluated in the visualizable areas. Each part of the vessel to be visualized was evaluated in at least two views. The state of the coronary bed was assessed before and after the intra-coronary administration of 125 μg of nitroglycerin. Vessel lumen and the severity of coronary stenosis were measured using XceleraR2.2L 1 SP2 software. Two independent operators analyzed angiograms.

The control CAG was performed 1 year after CS when angina resumed, or its FC increased, or in the case of a positive/uninformative stress test. Contrast-enhanced vessel imaging was performed in the same views as the initial CAG. Restenosis of the stented portion of the vessel was defined as the appearance of 50% or more severe narrowing of the stented segment or the part of the vessel adjacent proximally or distally to the stented segment for 5 mm.

Statistical analysis was carried out using the Statistica 9.0 and SPSS Statistics 20.0 software suites. The variables of interest are expressed as the median and the inter-quartile range [25th percentile; 75th percentile] as they do not comply with the normal distribution. The number of cases per group was given using the letter n. The Wilcoxon W-test was used to analyze the changes of parameters from the baseline levels, and the Mann-Whitney U-test was used for pairwise intergroup comparisons. Fisher's exact test was used to compare groups by categorical characteristics. An ROC (receiver operating characteristic curve analysis using SPSS Statistics 20.0 was used to analyze the diagnostic value of various parameters. The highest area under the ROC corresponded to the highest diagnostic value. Differences were significant at $p<0.05$.

Results

All patients who underwent CS and were included in the study (n=91) were followed up for 12 months after the intervention. During this time, no cases of myocardial infarction (MI) or death were reported.

The baseline angiographic characteristics of patients included in the study are detailed in Table 1.

Control CAG 12 months after CS was performed in 60 patients (66% of all patients included in the study). In-stent restenosis was detected in 8 patients (13% of control CAGs), and no restenosis in 52 patients (87% of control CAGs). Subgroups of patients were comparable in the diameter and length of the implanted stents: 2.7 (2.5; 3.0) and 22.0 (20.0; 28.0) mm in patients with restenosis and 2.7 (2.5; 3.0) and 20.0 (16.0; 26.0) mm in patients without restenosis (p=0.83 and p=0.26, respectively).

The subgroups did not differ statistically significantly by the main RFs for CAD (smoking, hypertension and DM, history of MI) and serum levels of total cholesterol, LDL-C, and hs-CRP before the scheduled CS (Table 2).

The correlation of changes in the serum levels of hs-CRP and restenosis 12 months after the scheduled CS was analyzed (Table 3).

Serum levels of hs-CRP increased significantly in patients with restenosis 1 month after CS versus the pre-CS levels, and were significantly higher than in patients without restenosis. Serum levels of hs-CRP decreased significantly in patients with developing restenosis 3 months after CS. Serum hs-CRP did not change statistically significantly in patients with restenosis and did not differ from that in patients without restenosis from the 3rd month and later. According to the ROC-analysis, the greatest predictive value for the development of restenosis within 1 year after the intervention is shown by the difference (delta) between serum hs-CRP 1 month after CS and immediately before the intervention (area under the ROC 0.93 with 95% confidence interval [CI] 0.85–1.0, sensitivity 88%, specificity 91%; p=0.00009), which is higher than the absolute value of serum hs-CRP 1 month after CS

Table 1. Angiographic characteristics of patients included in the study (n = 91)

Parameter	Value
Number of main coronary arteries involved, n (%)	
1	55 (60)
2	26 (28)
3	10 (11)
Number of stents implanted per patient, n (% of all stents implanted)	
1	64 (70)
2	24 (27)
3	3 (3)
Mean diameter of implanted stents per patient, mm	2.7 [2.5; 3.0]
Mean length of implanted stents per patient, mm	20.0 [18.0; 27.0]

* Data are presented as the absolute and relative numbers: n (%) or the median and the interquartile range [25th percentile; 75th percentile].

Table 2. Clinical profiles of patients according to the control CAG 12 months after CS

Parameter	No restenosis (n=52)*	Restenosis (n=8)*	p
Sex, male, n (%)	42 (81)	5 (63)	0.353
Male >55 years and female > 65 years, n (%)	34 (65)	5 (63)	1.000
Smoking, n (%)	36 (69)	5 (63)	0.699
Hypertension, n (%)	43 (82)	6 (75)	0.631
History of MI, n (%)	35 (67)	3 (38)	0.129
Type 2 DM, n (%)	6 (11)	2 (25)	0.287
BMI >30 kg/m^2, n (%)	18 (35)	2 (25)	0.707
LDL-C before CS, mmol/L*	2.4 [2.0; 3.0]	2.4 [2.2; 3.4]	0.692
Total cholesterol before CS, mmol/L*	4.1 [3.6; 4.7]	4.2 [3.8; 4.5]	0.391
hs-CRP before CS, mg/L*	1.7 [0.9; 2.9]	1.2 [0.8; 1.7]	0.143

*, Data are presented as the median and the interquartile range [25th percentile; 75th percentile]. CAG, coronary angiography; CS, coronary stenting; MI, myocardial infarction; DM, diabetes mellitus; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; hs-CRP, highly sensitive C-reactive protein.

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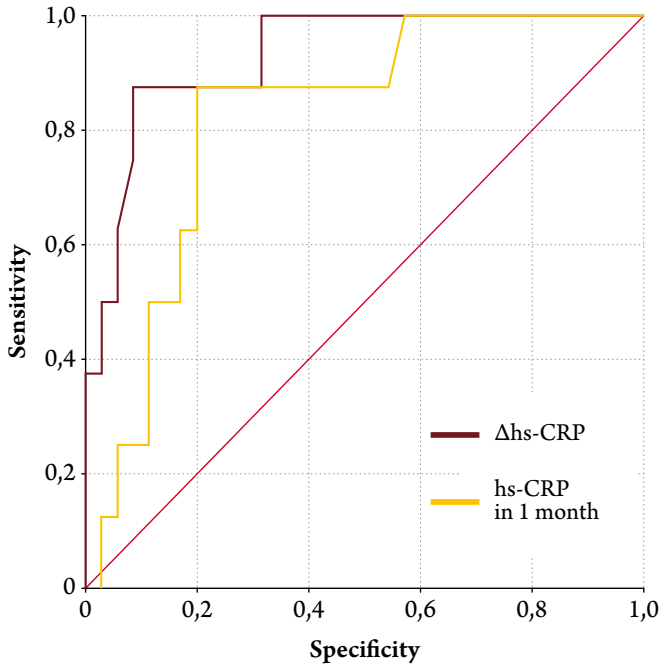
Figure 1. ROC analysis of the absolute values of hs-CRP 1 month after CS and delta (Δ) hf-CRP associated with the development of post-CS restenosis



hs-CRP, highly sensitive C-reactive protein; CS, coronary stenting.

Table 3. Changes in the levels of hs-CRP and LDL-C in patients with/without post-CS restenosis as shown by the control CAG

Parameter	No restenosis (n=52)	Restenosis (n=8)
Before CS		
LDL-C, mmol/L	2.4 [2.0; 3.0]	2.4 [2.2; 3.4]
hs-CRP, mg/L	1.7 [0.9; 2.9]	1.2 [0.8; 1.7]
1 month after CS		
LDL-C, mmol/L	2.3 [1.9; 2.7]	2.0 [1.8; 2.2]
hs-CRP, mg/L	1.0 [0.6; 2.0]	2.9 [1.6; 4.2]*,**
3 month after CS		
LDL-C, mmol/L	2.3 [1.9; 2.6]	2.0 [1.8; 2.3]
hs-CRP, mg/L	1.3 [0.7; 2.0]	1.5 [1.1; 2.0]*
6 month after CS		
LDL-C, mmol/L	2.4 [2.0; 2.8]	2.3 [2.2; 2.4]
hs-CRP, mg/L	1.1 [0.4; 1.9]	1.4 [1.0; 1.7]
12 month after CS		
LDL-C, mmol/L	2.5 [2.1; 2.8]	2.1 [1.8; 2.5]
hs-CRP, mg/L	1.1 [0.5; 1.5]	1.3 [1.1; 1.6]

*, p<0.05 versus the previous value in this subgroup;
**, p<0.05 versus the subgroup of patients without significant changes in the coronary artery at this point. hs-CRP, highly sensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; CS, coronary stenting; CAG, coronary angiography.

>3.0 mg/L (area under the ROC 0.82 with 95 % CI 0.68–0.96; p=0.0007). Δhs-CRP ≥0.9 mg/L (Figure 1) or a 25% increase in the hs-CRP levels (area under the ROC-curve 0.89 with 95% CI 0.79–0.99, sensitivity 87.5%, specificity 82.8%; p=0.0005) had the best ratio of sensitivity (87.5%) and specificity (91.4%).

We did not establish the predictive value of traditional RFs for CAD regarding the development of restenosis according to CAG data 12 months after CS, which can possibly be explained by the small number of patient subgroups.

Discussion

According to modern concepts, atherosclerosis is a chronic indolent inflammatory and autoimmune condition of the arterial wall, activated by various factors, mainly lipid metabolism disorders [2, 3]. This fact reflects the close correlation between blood inflammation markers and traditional RFs for atherosclerosis.

Several studies have shown that inflammation is a predictor of early and late adverse outcomes of CS [27-32]. hs-CRP is the most studied soluble marker of the inflammatory response in atherosclerosis and is considered an independent predictive RF for the development of cardiovascular complications [31]. Oemrawsingh et al. [25] showed that elevated levels of hs-CRP at the time of intervention were associated with the development of MI and death within 10 years. According to Dan et al. [32], patients with chronic kidney disease and elevated hs-CRP (≥3 mg/L) had the worst post-CS prognosis. We have detected a correlation between increased levels of hs-CRP ≥2.6 mg/L before CS and the progression of coronary atherosclerosis within 1 year [33].

The involvement of inflammation in the development of restenosis has also been proven in several studies. According to a recently published study [34], the levels of pro-inflammatory cytokines of tumor necrosis factor, interleukin (IL)-6, -7A, and -23 before the procedure were higher in patients with restenosis developed 12 months after CS as shown by CAG in comparison to the control group, and the level of anti-inflammatory IL-4 was lower than in patients without restenosis. Increased levels of IL-6/IL-8 and hs-CRP before the procedure, the presence of hypercholesterolemia, and DM were independent predictors of restenosis. In another study [35], the levels of hs-CRP and homocysteine in the early post-procedure period, DM, bifurcation involvement, and long stents were considered independent predictors of restenosis within the first year after CS. The size of the necrotic

core of ASP in patients with restenosis (according to 9-month CAG) after intravascular ultrasound-guided CS was larger before stent implantation than in patients without restenosis. However, only hs-CRP before the procedure and age were independent RFs for restenosis according to multivariate analysis [36]. In this study, a statistically significant increase in hs-CRP levels 1 month after CS versus the baseline values was shown in patients with restenosis. Increased levels of serum hs-CRP ≥0.9 mg/L (≥25%) 1 month after CS had the most significant predictive value for restenosis within the first year after CS compared to the absolute values of this measurement after 1 month. Prolongation of the inflammatory response comparable to the duration of elution of an antiproliferative agent from the stent surface may be associated with a greater probability of in-stent restenosis.

The involvement of CRP in the opsonization of modified LDL particles with subsequent capture by macrophages is considered a critical link in the relationship between CRP, lipids, and the atherosclerotic process [16]. CRP is also a marker of chronic inflammation and is associated with a greater likelihood of CAD destabilization [37]. According to the IMPROVE-IT study, the most significant reduction in the risk of cardiovascular complications in patients who remained stable after acute coronary syndrome was observed when the dual target of treatment was achieved: LDL-C levels below 1.8 mmol/L and hs-CRP level below 2 mg/L [38]. However, according to the results of the recently published ARIC study [39], hs-CRP levels ≥2.4 mg/L were associated with the risk of atherosclerosis-associated cardiovascular diseases regardless of the serum levels of atherogenic lipoprotein fractions. In our study, hs-CRP was the most sensitive marker of restenosis, and the patient groups were comparable in serum levels of LDL-C.

Conclusion

The study of post-stenting changes in the levels of inflammatory markers, such as highly sensitive C-reactive protein, can make an additional contribution to the identification of patients prone to developing in-stent restenosis. According to our data, an increase in the levels of highly sensitive C-reactive protein ≥0.9 mg/L (≥25 %) within 1 month after coronary stenting is associated with a greater likelihood of restenosis. The study was limited by the small number of patients examined and control angiographic examination of only a part of the included patients. Further research is required to determine the prognostic significance of biochemical markers of stent restenosis.

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No conflict of interest is reported.

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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.

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