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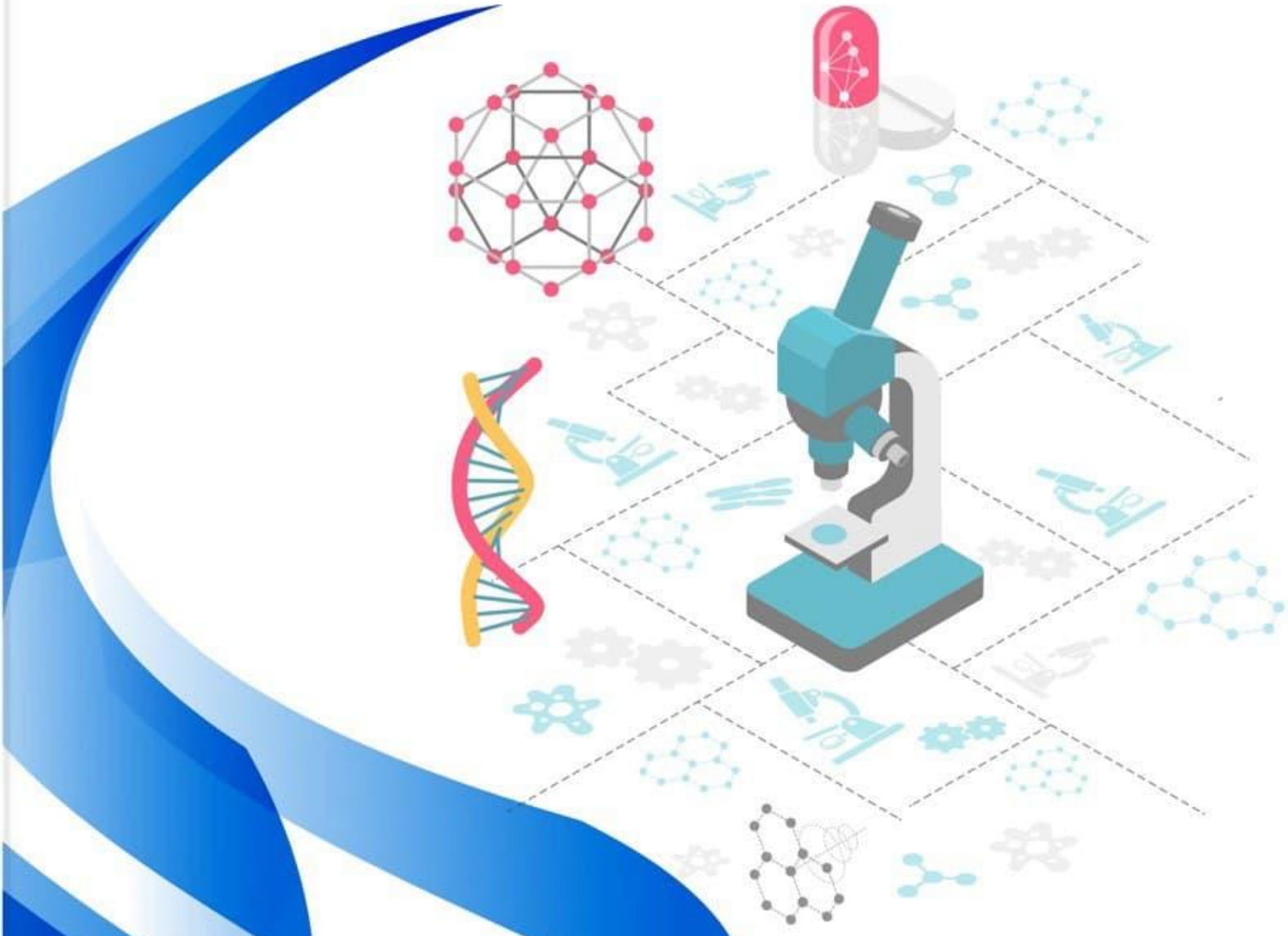

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CONTRAST-INDUCED NEPHROPATHY IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE AND ONE YEAR PROGNOSIS

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Abstract: The purpose of the study was to determine the incidence of contrast-induced nephropathy (CIN) in patients with chronic ischemic heart disease (CHD) and the prognostic significance of CIN within 1 year. 462 patients suffering from stable CAD and having indications for studies with intra-arterial administration of iodine-containing contrast agent were examined. The study was a prospective open cohort study and was registered in the ClinicalTrials system. gov under ID number NCT04014153. The primary endpoint was the development of CIN. Secondary end points were overall mortality, cardiovascular mortality, development of myocardial infarction, stroke, gastrointestinal bleeding (GIB), acute decompensation of chronic heart failure (CHF), coronary artery bypass grafting (CABG), repeat percutaneous coronary intervention (PCI).

Keywords: contrast-induced nephropathy, contrast-associated acute kidney injury, coronary heart disease, percutaneous coronary intervention, contrast agent, prognosis.

INTRODUCTION. The relationship between kidney damage and the cardiovascular system has been studied for a long time. It is now becoming obvious that it is more complex than scientists previously thought [1]. In turn, kidney damage that develops as a result of the administration of contrast agents (CM) has many components, not all of which have been well studied.

Currently, more and more studies are being published demonstrating a decrease in the incidence of contrast-induced nephropathy (CIN) [2,3]. This may be due to both the increased awareness of practicing physicians about this complication of angiographic interventions, as well as the improvement of the CVs themselves [4,5] and the lower frequency of CV administration to patients suffering from chronic kidney disease (CKD) or those with high creatinine levels for other reasons.

The development of CIN is associated with higher mortality in different patient groups [6] and progression of existing CKD [7]. However, according to a meta-analysis by Coca et al., preventive interventions that reduced the frequency of episodes of increased creatinine levels by almost 50% did not demonstrate the same in relation to the risk of death or development of CKD [8]. These observations prove that there is still no clear information about the effect of CIN on long-term prognosis in different groups of patients. In addition, it is still debated how accurate the definition of this syndrome is based solely on creatinine fluctuations without the use of new biomarkers. There are still no randomized studies demonstrating the beneficial effects of measures to prevent CIN on survival. In our study, we examined both the

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frequency of CIN among patients with CIHD and the impact of this complication on long-term prognosis.

Materials and methods. The observational open cohort prospective study included 462 patients with CIHD who were on optimal drug therapy and had indications for studies with intra-arterial administration of iodine-containing CVs, who were hospitalized in 2017, met the inclusion criteria for the study and signed informed consent.

The term "CIN", in accordance with the KDIGO recommendations for acute kidney injury [9], was defined as an increase in creatinine levels by more than 44 μmol/L (0.5 mg/dL) or 25% of baseline within 48 hours after administration of CV. . Hypertension was defined in accordance with the recommendations of the European Society of Cardiology 2018 [10] as an increase in systolic blood pressure of 140 mm Hg. Art. and/or diastolic blood pressure 90 mm Hg. Art. for office measurements.

CHF was generally considered within the framework of the European Society of Cardiology definition [11] as a clinical syndrome characterized by the presence of typical symptoms (for example, shortness of breath, edema of the lower extremities and weakness), which may be accompanied by signs of structural and functional cardiovascular disorders (for example, increased central venous pressure, moist rales in the lungs, peripheral edema), leading to a decrease in cardiac output and/or an increase in pressure inside the chambers of the heart at rest or during exercise.

The diagnosis of diabetes mellitus was established after consultation with an endocrinologist, if it had not been identified earlier. Hyperuricemia was defined as a condition accompanied by an increase in uric acid levels above 7 mg/dL (416 μmol/L) [12].

Anemia, in accordance with WHO recommendations, is a condition in which the hemoglobin level in men is below 13 g/dL and 12 g/dL in women [13]. The clinical characteristics of the patients included in the study are presented in Table 1.

Table 1.

Clinical characteristics of patients included in the study

Characteristic	Number of patients	Number of patients (%)
Age, years	64.5±9.7	
Male	322	69.7
Weight, kg	86.4±17.2	
BMI, kg/m2	29.7±6.3	
History of reaction to iodine	3	0.6
History of allergies	75	16.2
Bronchial asthma	17	3.7
Kidney diseases	85	18.4
Kidney surgeries	5	1
Anemia	56	12.1

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Heart failure	49	10.6
Arterial hypertension	428	92.6
Diabetes	120	26
Hyperuricemia	25	5.4
Total patients	462	100

Patients underwent a general clinical examination, chest X-ray, ECG, ECHO-CG before the intervention, general and biochemical blood test parameters were determined (in particular, initial levels of creatinine, potassium), coagulograms, and a general urinalysis.

After PCI in the absence of complications, ECHO-CG was not performed again. All patients had their creatinine levels determined the next day and 48 hours after CV administration.

Table 2 shows potentially nephrotoxic drugs that patients received, which could also affect the incidence of CIN in the study group of patients with CIHD. Considering the combination of hypertension and HIHD present in the majority of patients, the vast majority received beta blockers. About half of the patients with diabetes received metformin.

The primary endpoint was the development of CIN. Secondary end points were overall mortality, cardiovascular mortality, development of myocardial infarction, stroke, gastrointestinal bleeding (GIB), acute decompensation of chronic heart failure (CHF), repeat coronary artery bypass surgery (CABG), percutaneous coronary intervention (PCI) , as well as combined endpoints - major adverse cardiovascular events (cardiovascular mortality, MI, stroke), repeat revascularization (CABG and PCI). Statistical processing of the material and plotting of graphs were performed using Prism 8 for macOS (version 8.4.2) (California, USA). Odds ratios in contingency tables were determined using the Baptista-Pike method, and statistical significance was assessed using Fisher's exact test.

Table 2.

Frequency of use of potentially nephrotoxic drugs in the study group of patients

A drug	Number of patients	Number of patients (%)
Metformin	66	14.3
Beta blockers	407	88
NSAIDs	1	0.2

Note:*NSAIDs – non-steroidal anti-inflammatory drugs*

Results.CIN developed in 28 patients (6%), which corresponds to literature data. At the same time, when using the definition of CIN only by the absolute

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increase in creatinine level from the initial one (by more than 44 μmol/l), there was only 1 case (0.2%). In women, CIN developed 2 times more often than in men (9.29% and 4.66%, respectively, p = 0.0871, OR 2.095.95% CI 0.9965-4.623), but the differences were not statistically significant. Detailed data are presented in the contingency table (Table 3).

Table 3.

Distribution of patients with and without CIN depending on gender

Floor	Number of patients with CIN (%)	Number of patients without CIN (%)
Female	13 (9.3)	127 (90.7)
Male	15 (4.7)	307 (95.3)

Note:*CIN – contrast-induced nephropathy;*

The number of patients with and without obesity in our study was comparable (221 people and 241, respectively). The presence of a BMI of 30 kg/m2 as a risk factor for the development of CIN did not reach statistical significance (p>0.9999, OR 0.94.95% CI 0.4524-2.061). However, there was a tendency towards a slightly more frequent development of CIN in patients without obesity (5.88% and 6.22%, respectively). Detailed data are presented in Table 4.

Table 4.

Distribution of patients with and without CIN depending on the presence of obesity

Characteristic	Number of patients with CIN (%)	Number of patients without CIN (%)
Obesity	13 (5.9)	208 (94.1)
No obesity	15 (6.2)	226 (93.8)

Note:*CIN – contrast-induced nephropathy*

The vast majority of patients included in the study suffered from hypertension (92.6%). However, the p value determined using Fisher's exact test did not reach statistical significance (p = 0.7109, OR 2.22.95% CI 0.3886-23.55). However, it is important to note that of the 34 patients who did not suffer from hypertension, only one developed CIN (Table 5).

Table 5.

Distribution of patients with and without CIN depending on the presence of hypertension

Characteristic	Number of patients with CIN (%)	Number of patients without CIN (%)
AG	27 (6.3)	401 (93.7)
No AG	1 (2.9)	33 (97.1)

Note:*CIN – contrast-induced nephropathy, AH – arterial hypertension*

Only 10.6% of patients suffered from CHF. When analyzing using a contingency table (Table 6), the results did not reach statistical significance (p=0.7555, OR 0.6334.95% CI 0.1443-2.439). At the same time, the number of patients without CHF with CIN was slightly higher than in the case of heart failure (6.3% and 4.08%).

Table 6.

Distribution of patients with and without CIN depending on the presence of CHF

Characteristic	Number of patients with CIN (%)	Number of patients without CIN (%)
CHF	2 (4.1)	47 (95.9)
No CHF	26 (6.3)	387 (93.7)

Note:*CIN – contrast-induced nephropathy, CHF – chronic heart failure*

Anemia remains an understudied risk factor for CIN. Among the examined sample of patients, noteworthy is the tendency to increase the risk of CIN in patients with anemia (8.9% and 5.7%, respectively, p = 0.3649, OR 1.633.95% CI 0.6507-4.239) (Table 7).

Table 7.

Distribution of patients with and without CIN depending on the presence of anemia

Characteristic	Number of patients with CIN (%)	Number of patients without CIN (%)
Anemia	5 (8.9)	51 (91.1)
No anemia	23 (5.7)	383 (94.3)

Note:*CIN – contrast-induced nephropathy*

Metabolic disorders in patients with coronary artery disease and hypertension contribute to earlier development of CKD and worsening prognosis. Many scientists are currently interested in the role of hyperuricemia as a risk factor for various diseases. In our study, hyperuricemia was detected in only 25 patients (5.4%) (Table 8). At the same time, there was a tendency to a more frequent development of CIN in patients with elevated uric acid levels (8% and 5.95%, p = 0.6575, OR 1.375.95% CI 0.3055-5.808).

Table 8.

Distribution of patients with and without CIN depending on availabilityhyperuricemia

Characteristic	Number of patients with CIN (%)	Number of patients without CIN (%)
Hyperuricemia	2 (8)	23 (92)

No hyperuricemia	26 (6)	411 (94)

Note:*CIN – contrast-induced nephropathy*

Diabetes mellitus is also an important risk factor, the role of which in the development of CIN has been studied for a long time. However, in our study this risk factor did not reach the level of statistical significance. Moreover, in patients with diabetes, the frequency of CIN was 2% higher (p = 0.5045, OR 1.378, 95% CI 0.5861-3.086) (Table 9).

Table 9.

Distribution of patients with and without CIN depending on the presence of diabetes

Characteristic	Number of patients with CIN (%)	Number of patients without CIN (%)
SD	9 (7.5)	111 (92.5)
No SD	19 (5.6)	323 (94.4)

CIN – contrast-induced nephropathy, DM – diabetes mellitus

In 27 patients (5.8%), it was not possible to track the one-year prognosis. Thus, the outcomes are known for 435 patients. During the entire observation period, only 1 case of death from all causes (not related to cardiovascular diseases) was recorded. Therefore, it would be statistically incorrect to reliably interpret these data. Data on other secondary endpoints are presented in Table 10.

Analyzing the one-year prognosis data for patients, it can be noted that the incidence of CIN was highest in the group of patients who developed MI (26.7%) and other major adverse cardiovascular events (18.1%). At the same time, among patients with stroke, no cases of CIN were recorded. Repeat revascularizations were common (9.5%) and episodes of decompensated heart failure were observed (7%).

Discussion. In a prospective open cohort study of 462 patients, the incidence of CIN was 6%, which is consistent with other studies. Our work is distinguished by its prospective nature, since many works devoted to CIN are a retrospective analysis of data from electronic medical records, which indirectly affects the accuracy of the interpreted data.

It is important to note that in our work, contrast was administered to all patients only intra-arterially, in contrast to other studies, where sometimes both patient data after computed tomography (intravenous contrast administration) and data after angiography are analyzed. It has long been known that the intra-arterial route of contrast administration is more dangerous and more often leads to the development of CIN [14].

It should also be noted that we separately analyzed the frequency of CIN depending on the relative increase in creatinine levels and in the case of an increase in serum creatinine by 44 μmol/l (0.5 mg/dl). The fact that CIN, when using a definition with the absolute value of creatinine, was detected in only 1 patient (0.2%),

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in contrast to a relative increase of 25% from the original - in 28 people (6%).

It is also worth noting that all data on serum creatinine levels after contrast administration were obtained 48 hours after contrast administration in accordance with KDIGO recommendations [15]. Although a number of authors still provide information on the level of serum creatinine after contrast administration after 24 hours, which in some cases leads to the omission of up to 50% of CIN cases.

The patients included in the study suffered from CIHD and, in the vast majority of cases, hypertension. This disease itself is known to negatively affect kidney function, especially against the background of long-term coronary artery disease. Therefore, it is advisable to conduct comparative studies and assess the risk in patients with CIHD both with and without hypertension. Such a design, however, will be associated with a number of difficulties in recruiting patients, since, as is known, hypertension is one of the risk factors for the progression of atherosclerosis and the development of coronary artery disease.

Table 10.

Secondary endpoints

Secondary endpoint	Number of patients	Number of patients (%)	SIN frequency
THEM	15	3.4	4 (26.7%)
Stroke	7	1.6	0
Housing and communal services	5	1.1	0
ODSN	57	13.1	4 (7%)
KS	3	0.7	0
Repeat PCI	126	29	12 (9.5%)
CCV+MI+stroke	22	5	4 (18.1%)
MI+stroke	22	5	4 (18.1%)
CABG+PCI	129	29.7	12 (9.3%)

CIN – contrast-induced nephropathy, MI – myocardial infarction, GI – gastrointestinal bleeding, ADHF – acute decompensation of heart failure, CABG – coronary artery bypass grafting, PCI – percutaneous coronary intervention, CVD – cardiovascular mortality

The KDIGO guidelines for AKI will be reviewed in the near future. And contrast is likely to take its place along with other nephrotoxic drugs and substances. This is why it is important to conduct further research in collaboration with clinical pharmacologists, studying the effect of contrast in patients with comorbidities and taking a specific class of drugs. Studying the effect of statins and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers is especially promising. The effect of beta blockers (which the vast majority of our patients received) on the risk of developing CIN also needs to be clarified.

Our data illustrate the negative impact of CIN developing in patients with CIHD on prognosis. Our study is not large enough to evaluate the effect on

cardiovascular mortality, and the 1-year follow-up period probably needs to be extended to 3 or 5 years.

CONCLUSION

A prospective open cohort observational study found that the incidence of CIN in patients with CIHD was 6%. After 1 year of observation, it was found that the development of CIN in this category of patients leads to a more frequent development of myocardial infarction, repeated PCI and acute decompensation of heart failure within a year.

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