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ЧАСТОТА И ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ ОСТРОГО ПЕРИПРОЦЕДУРНОГО ПОВРЕЖДЕНИЯ МИОКАРДА ПРИ ПЛАНОВЫХ ЧРЕСКОЖНЫХ КОРОНАРНЫХ ВМЕШАТЕЛЬСТВАХ

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Frequency and Prognostic Value of Acute Periprocedural Myocardial Injury in Elective Percutaneous Coronary Interventions

Резюме

Обоснование. Острое повреждение миокарда (ОПМ) является перипроцедурным осложнением чрескожных коронарных вмешательств (ЧКВ) у пациентов со стабильной ишемической болезнью сердца. Его частота и связь с прогнозом заболевания особенно важны в связи с низким риском ишемических событий в этой когорте пациентов. Тем не менее, по данным литературы существуют значительные различия в критериях ОПМ и инфарктом миокарда (ИМ) 4а типа, и, соответственно, их частоте и их прогностическом значении. **Цель.** Изучить частоту и величину ОПМ при плановых ЧКВ по уровню перипроцедурного повышения кардиоспецифических ферментов (КСФ), а также определить связь ОПМ с отдаленными неблагоприятными событиями у пациентов с хронической коронарной болезнью сердца. **Материалы и методы.** Проведено одноцентровое открытое ретроспективное когортное исследование, включившее 435 пациентов (367/84,4 % мужчин, средний возраст 58,3±8,6 лет) из регистра плановых ЧКВ, у которых была отслежена динамика КСФ в перипроцедурный период. ОПМ диагностировалось при повышении уровня МВ фракции креатинфосфокиназы (СК-МВ) или или сердечного тропонина I (сTn I) >1×99 перцентиль URL (Upper Reference Limit — верхний референтный предел), при этом регистрировался уровень повышения КСФ >1, 2, 3, 4 или >5×99 перцентиль URL. Повышение КСФ >5×99 перцентиль URL оценивалось как значительное ОПМ, а при наличии клинических и визуализирующих доказательств новой потери жизнеспособного миокарда — как перипроцедурный ИМ. Далее был рассчитан относительный риск (RR) отдаленных неблагоприятных сердечно-сосудистых осложнений, смерти, а также клинически значимых кровотечений и вновь диагностированных злокачественных онкологических заболеваний в течение 5 лет после индексных ЧКВ в зависимости от уровня перипроцедурного повышения КСФ. Корреляция между ОПМ и вышеперечисленными конечными точками была обобщена с помощью анализа Каплана-Мейера. **Результаты.** Частота перипроцедурного ОПМ, диагностированного по повышению КСФ >1×99 перцентиль URL составила 40,2 %, >2×99 перцентиль URL — 9,7 %, >3×99 перцентиль URL — 6,7 %, >4×99 перцентиль URL — 4,8 %, >5×99 перцентиль URL — 3,5 %, ИМ 4а типа — у 2 пациентов (0,46 %). Выявлена ассоциация «большого» ОПМ (>5×99 перцентиль URL) с сердечно-сосудистыми осложнениями, в том числе и смертельными, в течение 3-х лет после планового ЧКВ: для острого инфаркта миокарда (ОИМ) RR составил 6,516, доверительный интервал (CI) [2.375-17.881]; для смерти от сердечно-сосудистых причин RR — 6,538, CI [1.695-25.227]. Показана ассоциация «умеренного» ОПМ (>3, но <5×99 перцентиль URL) с острыми ишемическими собы-

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тиями в течение 3-х лет после планового ЧКВ: для ОИМ RR составил 4,073, CI [1.598-10.378]. Выявлена ассоциация «незначительного» ОПМ (>1, но <3 ×99 перцентиль URL) с вновь диагностированными злокачественными онкологическими заболеваниями в течение 5 лет после индексного ЧКВ: RR 2,319; CI [1.248-4.310]. Выявлена ассоциация отдаленных тромботических событий, таких как тромбоз стентов (индексных и установленных при повторных вмешательствах), окклюзии стентов (индексных и неиндексных) как причины повторного вмешательства в течение 5 лет после индексного ЧКВ — с большинством подгрупп ОПМ. Анализ Каплана-Мейера выявил зависимость клинически значимых кровотечений в течение 5 лет после индексного ЧКВ от развития «умеренного» ОПМ (p=0,003), а также ассоциацию не сердечно-сосудистой смерти в течение 5 лет после индексного ЧКВ с «незначительным» ОПМ (p=0,007). **Заключение.** Регистрация уровня перипроцедурного повышения КСФ должна проводиться при плановых ЧКВ не только с целью диагностики и прогнозирования острых и отдаленных ишемических событий, но и для оценки риска развития окклюзии стентов, клинически значимых кровотечений, прогностически важной сопутствующей патологии и смерти в отдаленный (5-летний) период с целью выделения групп пациентов, требующих активного наблюдения, дополнительного обследования и подбора схемы оптимального лечения на амбулаторном этапе реабилитации.

Ключевые слова: ишемическая болезнь сердца, чрескожное коронарное вмешательство, перипроцедурное повреждение миокарда, МВ фракция креатинфосфокиназы, сердечный тропонин

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Background. Periprocedural myocardial injury (PMI) is an acute complication of percutaneous coronary interventions (PCI) in patients with stable coronary artery disease. Its frequency and relationship with the prognosis of the disease are especially important in elective interventions due to the low risk of ischemic events in this cohort of patients. However, according to the literature, there are significant differences in the criteria for PMI and type 4a myocardial infarction (MI), and, accordingly, their frequency and their prognostic value. **Aim.** To study the frequency and magnitude of PMI during elective PCI in terms of the level of periprocedural increase in cardiospecific biomarkers, as well as to determine the relationship of PMI with long-term adverse events in patients with chronic coronary artery disease. **Materials and methods.** A single-center open retrospective cohort study was conducted, which included 435 patients (367/84.4 % men, mean age 58.3±8.6 years) from the elective PCI registry. PMI was diagnosed with an increase in the level of creatine phosphokinase MB fraction (CK-MB) or or cardiac troponin I (cTn I) >1×99 percentile URL (Upper Reference Limit), while the level of increase in biomarkers >1, 2, 3, 4 or >5×99 percentile URL was recorded. An increase in biomarkers >5×99 URL percentile was assessed as a large PMI, and in the presence of clinical and imaging evidence of new loss of viable myocardium, as periprocedural MI type 4a. Depending on the level of periprocedural increase in biomarkers, the relative risk (RR) of developing long-term (within 5 years after index PCI) adverse cardiovascular events, death, as well as clinically significant bleeding and newly diagnosed malignant oncological diseases was calculated. In addition, the correlation between PMI and the above endpoints was summarized using Kaplan-Meier analysis. **Results.** The frequency of periprocedural PMI diagnosed by increased biomarkers >1×99 percentile URL was 40.2 %, >2×99 percentile URL — 9.7 %, >3×99 percentile URL — 6.7 %, >4×99 percentile URL — 4.8 %, >5×99 percentile URL — 3.5 %, type 4a MI — in 2 patients (0.46 %). An association of "major" PMI (>5×99 percentile URL) with cardiovascular complications within 3 years after elective PCI, including fatal ones, was revealed: for acute myocardial infarction (AMI), RR — 6.516, confidence interval (CI) [2.375-17.881]; for death from cardiovascular causes RR — 6.538, CI [1.695-25.227]. An association of "moderate" PMI (>3, but <5 ×99 URL percentile) with acute ischemic events within 3 years after elective PCI was shown: for AMI, RR was 4.073, CI [1.598 — 10.378]. An association of "minor" AKI (>1, but <3 ×99 URL percentile) with newly diagnosed malignant oncological diseases within 5 years after index PCI was revealed: RR 2.319; CI [1.248-4.310]. An association of late thrombotic events, such as stent thrombosis (index and re-interventions), stent occlusion (index and non-index) as a reason for re-intervention within 5 years after index PCI, was found with most PMI subgroups. Kaplan-Meier analysis of the dependence of clinically significant bleeding within 5 years after index PCI on the development of "moderate" PMI (p=0.003), as well as the association of non-cardiovascular death within 5 years after index PCI with "minor" PMI (p= 0.007). **Conclusion.** Registration of periprocedural increase in cardiac biomarkers should be carried out during planned PCI not only for the purpose of diagnosing and predicting acute and late ischemic events, but also for assessing the risk of developing stent occlusion, clinically significant bleeding and prognostically important comorbidities in the long-term (5-year) period in order to identification of groups of patients requiring active monitoring, additional examination and selection of an optimal treatment regimen at the outpatient stage of rehabilitation.

Key words: ischemic heart disease, percutaneous coronary intervention, periprocedural myocardial injury, creatine kinase-MB, cardiac troponin

Conflict of interests

The authors declare no conflict of interests

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sAMI — significant acute myocardial injury, IHD — ischemic heart disease, MI — myocardial infarction, CI-AKI — contrast-induced acute kidney injury, CSF — cardio-specific ferments, HB — heart bypass, mAMI — minor acute myocardial injury, LBO — lateral branch occlusion, AMI — acute myocardial infarction, ACS — acute coronary syndrome, ACVA — acute cerebrovascular accident, AMIn — acute myocardial injury, AKI — acute kidney injury, CVD — cardiovascular death, modAMI — moderate acute myocardial injury, CCS — chronic coronary syndrome, PCI — percutaneous coronary intervention, ecoCG — echocardiography, Adj OR — adjusted odds ratio, CABG — Coronary Artery Bypass Graft Surgery, CI — confidence interval, CPK-MB — MB fraction of creatine phosphokinase, cTn I — cardiac troponin I, cTnT — cardiac troponin T, KDIGO (Kidney Disease: Improving Global Outcomes) — a global non-profit organisation which develops and implements evidence-based clinical guidelines in kidney diseases, MACCE — major adverse cardiac or cerebrovascular event, PACE — patient centred endpoint, PMI — periprocedural myocardial injury, UDMI — universal definition of myocardial infarction, URL — upper reference limit, RR — relative risk

Introduction

Percutaneous coronary intervention (PCI) is gradually becoming the primary method of coronary artery revascularisation and is believed to be a safe procedure with a low level of serious procedural complications [1], which can be performed even in outpatient settings. PCI complications, for instance, acute stent thrombosis, coronary perforation, stroke and death, are critical, but rare. On the contrary, periprocedural acute myocardial injury (AMIn) is a common complication caused by distal embolisation, lateral occlusion, dissection, blood clot and no-reflow [2–4]. Although major AMIn are caused by technical procedural complications in PCI, a majority of patients with higher biomarker levels do not present with any signs of procedural complications [5]. According to heart magnetic-resonance tomography, there are two various locations of procedural myonecrosis, where the average area of infarction is approximately 5 % of the left ventricle weight; their incidence is similar: the first location is adjacent to the intervention site and is caused by lateral epicardial occlusion, whereas the second one is below the intervention site and is likely to be associated with impaired microcirculation [6].

Several academic groups presented their consensus-based expert definitions of periprocedural myocardial injury and infarction, including various biomarkers, such as MB fraction of creatine phosphokinase (CPK-MB) or cardiac troponin T (cTn), their thresholds and need/no need to perform heart imaging assessment, causing significant differences in terms of sensitivity and specificity of proposed diagnostic methods [7–10]. According to the selected definition, recent studies reported high variability in the incidence of periprocedural AMIn or periprocedural myocardial infarction (MI), which is also called type 4a MI [11, 12], which were [3, 9, 11] or were not associated [13, 14] with unfavourable ischemic events and long-term mortality.

Classification of threshold rise in biomarkers with or without additional criteria as a major AMIn or periprocedural MI has potential consequences for patients and healthcare providers, when it is used as a measure of the quality of care, and also for the development and adequate evaluation of new therapies in clinical trials.

However, predictive power of an increase in cardio-specific ferments (CSF) in terms of recurrent cardiovascular events and long-term mortality is still discussed. Several studies demonstrated a close association between high CPK-MB after PCI with subsequent cardiovascular events [8]. Unfortunately, CPK-MB is no longer used in a majority of medical institutions. The fourth Universal Definition of the myocardial infarction working group [9] included cTn as a biomarker of choice, since it is a more specific and sensitive CSF for early detection of myocardial necrosis and, therefore, facilitates early diagnosis and triage of patients with acute chest pain. Thus, it has become the only biomarker which is routinely used in periprocedural settings. Higher sensitivity can help in identifying the tiniest differences in devices in clinical trials. However, attempts to understand the prognostic value of higher troponin levels associated with coronary surgery, either individually or together with other criteria, give contradicting results. Moreover, although a majority of researchers agree that the definition of periprocedural MI should be related to early and late mortality, it is still a matter of argument whether this relation is causal or just reflects predictive power of more severe atherosclerosis.

Patients with stable ischemic heart disease (IHD) referred to elective endovascular myocardial revascularisation make up the largest population undergoing this procedure. They have a relatively low risk of ischemic events as compared to other patients who need PCI, therefore, it is essential to assess the risk of periprocedural AMIn in this group of patients [15].

The objective of this study was to evaluate the incidence and extent of AMIn in elective PCI using periprocedural increase in CSF, such as MB fraction of creatine phosphokinase (CPK-MB) or cardiac troponin T (cTn), and also to determine the association between AMIn and late unfavourable events in patients with chronic ischaemic heart disease.

Materials and Methods

A single-centre open-label retrospective cohort study was conducted in 435 patients from the register of elective PCIs, performed in the Rehabilitation Department

of the Scientific Research Institute of Cardiology of the Tomsk National Research Medical Centre at the Russian Academy of Sciences. 367 subjects (84.4 %) were males; the patient mean age was 58.3 ± 8.6 years. The primary inclusion criterion was the availability of in-patient examination and therapy results, including changes in cardio-specific ferments. The exclusion criterion was urgent interventions related to the confirmed diagnosis of acute coronary syndrome (ACS). This study was approved by the Local Ethics Committee at the Scientific Research Institute of Cardiology of the Tomsk Scientific Centre at the Siberian Branch of the Russian Academy of Sciences (No. 126 dated December 14, 2008). The study was conducted in accordance with the Declaration of Helsinki. All patients included in the register provided their consent for long-term follow-up.

PCI was performed under the standard method. A drug-eluting stent, technique and the use of additional devices and drugs were selected by the operator. Before PCI, all patients received aspirin and P2Y₁₂ inhibitor (clopidogrel or ticagrelor). During the procedure, unfractionated heparin or bivalirudin were used as anticoagulants.

The baseline characteristics of patients and performed index endovascular interventions are presented in Table 1.

Involvement of index areas of coronary arteries in the study group was in the form of atherosclerosis de novo — 360 (82.7 %) patients, stent restenosis and occlusion — 31 (7.1 %) patients, restenosis and occlusion of previously installed stents — 24 (5.5 %) patients. For 38 (8.7 %) patients, the index PCI was a second step in myocardial revascularisation.

Blood for CSF (CPK-MB and cTn I) was drawn at baseline, 12, 24, 48 hours after the intervention. CPK-MB was quantified photometrically using analyser Konelab 60i, cTnI — using ELISA system (Biomerica, USA). The 99th percentile of the upper reference level (URL) for CPK-MB was 25 U/L, for cTnI — 1.0 ng/mL. AMIn was diagnosed at CPK-MB or Tn I > 1 x 99th percentile of URL; an increase in CSF of >1, 2, 3, 4 or > 5 x 99th percentile of URL was observed. An increase in CSF of > 5 x 99th percentile of URL was suggestive of a major AMIn, and in the presence of clinical and imaging evidence of a new loss of a healthy myocardium — as periprocedural IM [7, 9]. The number of acute periprocedural complications classified as technical (close to the target coronary artery), local (at the site of peripheral arterial access) and clinical (chest pain, blood pressure response, cardiac rhythm disturbances, allergies, acute kidney injury (AKI) etc.) was recorded. Periprocedural AKI was diagnosed in accordance with KDIGO 2012 criteria [16].

Five years after the index PCI, disease outcomes were evaluated: a phone interview was conducted, and medical records were analysed. Primary endpoints were 5-year survival rate, incidence of cardiovascular deaths (CVD)

and all-cause mortality. Secondary endpoints were acute periprocedural complications; diagnosed thrombosis and stent restenosis, including stents deployed during the follow-up period; incidence of adverse cardiovascular complications, such as acute myocardial infarction (AMI), acute coronary syndrome (ACS), acute cerebrovascular accident (ACVA); and the incidence of clinically significant bleeding and newly diagnosed malignancies. Combined endpoints were MACCE (major adverse cardiac or cerebrovascular events), including CVD, ACS and ACVA, as well as PACE (patient centred endpoint), including all-cause mortality, AMI and ACVA. Also, the number of repeated interventions in patients from the study groups one and five years after the index PCI was evaluated; and primary causes of the damage to areas of coronary arteries, which required repeated interventions, were analysed.

Continuous data were presented as mean \pm standard deviation ($M \pm SD$), or as a median value with interquartile range ($Me (Q1-Q3)$) (depending on the normality of distribution). Categorical data were given in percent. Differences in continuous data were verified using t-test for independent samples (normal data) or Mann–Whitney U test (asymmetric data). Similarly, paired variables were verified using t-test for paired samples (normal data) or Wilcoxon criterion (asymmetric data). Proportional differences in categorical data were compared using chi-square or Fisher's exact test (Fisher's exact test was used when the frequency of one or several cells was less than five). Relative risk (RR) was calculated using cross tables, with the calculation of 95 % confidence interval (CI). Correlation between AMIn and endpoints was summarised using Kaplan–Meier analysis. All probability values were two-sided; $p < 0.05$ was significant.

Results

The incidence of periprocedural AMIn diagnosed on the basis of increased CSF of > 1 x 99th percentile of URL was 40.2 %, > 2 x 99th percentile of URL — 9.7 %, > 3 x 99th percentile of URL — 6.7 %, > 4 x 99th percentile of URL — 4.8 %, > 5 x 99th percentile of URL — 3.5 %. Type 4a periprocedural MI (as per the 4-th universal definition of MI) [9] was diagnosed in 2 patients (0.46 %).

The incidence of major acute complications from the index PCI is presented in Figure 1.

According to angiography results performed within 5 years after the index PCI, obliterating atherosclerosis of coronary arteries de novo was diagnosed in 123 (29.4 %) patients. Subacute thrombosis (up to 30 days after PCI) of stents (index or deployed during repeated interventions) was observed in 5 (1.15 %) patients; late thrombosis (30 days to 1 year after PCI) — in 18 (4.1 %) patients; very late thrombosis (over one year after PCI) — in 22 (5.1 %) patients.

One year after the index PCI, haemodynamically relevant restenosis of index stents were recorded in 15 (3.5 %) patients, and index stent occlusions — in 5 (1.2 %) patients. Five years after the index PCI, their number was 30 (7.1 %) and 14 (3.3 %) patients, respectively.

Repeated interventions within a year after the index PCI were performed in 85 (19.9 %) patients, within five years — in 154 (36.5 %) patients. 18 (4.3 %) patients underwent heart bypass (HB) procedure and 139 (32.9 %) patients had endovascular interventions. Causes of repeated revascularisation procedures are presented in Figure 3.

Then, we evaluated the risk of late adverse events each year during 5 years after the index PCI, depending on the rate of periprocedural AMIn. The most relevant associations are given in Table 2.

Hence, we can see that AMIn > 1 , but $\leq 3 \times 99$ th percentile of URL is not associated with late ischemic complications of elective PCI, i.e. it is a minor event of increased CSF and is negligible for prognosis. Moderate AMIn (> 3 , but $\leq 5 \times 99$ th percentile of URL) is associated with ACS and AMI during 3 years after the index PCI. Major AMIn ($> 5 \times 99$ th percentile of URL) is associated not only with late adverse ischemic events, but also with cardiovascular death during midterm follow-up. Therefore, we were able to single out three main groups of AMIn: minor (miAMIn), moderate (moAMIn) and major (maAMIn).

Then we compared survival curves using Kaplan–Meier method for primary and secondary endpoints (AMI, ACS, CVD, all-cause mortality, non-CDV, MACCE, PACE, clinically significant bleeding) which were plotted during the 5-year follow-up after the index PCI, depending on the AMIn group. The zero (baseline) group was a group of patients without periprocedural AMIn. The most important results of this analysis are presented in Figures 4 to 8.

Analysis results demonstrate that miAMIn is associated with non-cardiovascular death, modAMIn — with clinically significant bleeding, and maAMIn — with major adverse ischemic events during the late (5 years) period after the index PCI.

Discussion of Results

In this study, the incidence of periprocedural AMIn was 40.2 %, with an increase in CSF of $> 1 \times 99$ th percentile of URL, and 3.5 % with an increase of $> 5 \times 99$ th percentile of URL. Type 4a periprocedural MI (as per the 4-th universal definition of MI) [9] was diagnosed in 2 patients (0.46 %).

Despite the absence of any clear evidence, in accordance with the 2007 universal definition of myocardial infarction (UDMI), type 4a MI is diagnosed, when CSF values (cTn or CPK-MB) are 3 times higher than the respective URL [17]. This rigorous position was softened in the recent versions (UDMI versions 3 and 4) [7, 9]:

type 4a MI is diagnosed, if cTn values are at least 5 times higher than 99th percentile of URL in patients with normal baseline cTn levels, or if there is a 20 % increase in patients with a high, but stable pre-PCI cTn level, associated with additional criteria, such as signs of a new myocardial infarction, or changes on ECG, imaging, or the presence of procedural complications, which cause reduction in coronary blood flow (coronary dissection, occlusion of a large epicardial artery or lateral occlusion/blood clot, impaired collateral blood flow, slow flow or no-reflow, distal embolisation). A post-procedure increase in CSF values without any additional criteria is required in order to diagnose procedural myocardial injury.

In 2013, the Society for Cardiovascular Angiography and Interventions (SCAI) released an expert consensus paper to argue the definition of periprocedural MI proposed by the UDMI working group [8]. Since there were no post-PCI threshold cTn values, the exceeding of which impacts the long-term prognosis, the paper favoured CPK-MB for the assessment of clinically significant post-PCI events. According to the document, clinically significant MI during post-PCI period was MI with an increase in CPK-MB values of $> 10 \times 99$ th percentile of URL, or a lower threshold ($> 5 \times 99$ th percentile of URL) in patients with new pathologic Q-waves in more than two adjacent leads (or a new stable post-PCI left bundle branch block).

In 2018, the Academic Research Consortium-2 (ARC-2) [18] published a consensus document, noting that over the past several years, cTn has been gradually replacing CPK-MB as a preferable biomarker of myocardial damage in clinical practice; and the authors proposed the cTn value of $\geq 35 \times 99$ th percentile of URL as a reasonable value for PCI-associated periprocedural MI. Also, one more auxiliary criterion was required in addition to an absolute increase in cTn of ≥ 35 in order to confirm periprocedural MI (flow-limiting angiographic complications in a large epicardial vessel or a branch of > 1.5 mm in diameter, new procedure-associated significant Q-waves (or equivalent), or a significant new abnormal procedure-associated wall movement seen on echoCG).

Therefore, the incidence of periprocedural MI in endovascular myocardium revascularisation in patients with chronic coronary syndrome (CCS) varies depending on the definition and the cardiac biomarker used. According to UDMI version 3, the incidence of type 4a MI was 7 % when using highly sensitive cTnT [3] and 10 % when using cTnT [12], whereas when the SCAI guidelines were used to define periprocedural MI, the incidence was just 1.5–2.9 % [3, 11]. Recent literature demonstrates that among 4,404 patients with CCS who underwent PCI [19], periprocedural MI defined as per UDMI versions 3 and 4, ARC-2 и SCAI was recorded in 18.0 %, 14.9 %, 2.0 % and 2.0 % of patients, respectively.

Table 1. Baseline Patient Characteristics, Coronary Lesions, and Index PCI

Parameters	Group n=435
Age, years, M±SD (min-max)	58,3±8,6 (32-81)
Body mass index, Me (Q1-Q3)	28,6 (25,8-31,7)
Family history of cardiovascular diseases, n/%	198 / 46,2
Smoking, n/%	141 / 32,4
Diabetes mellitus, n/%	101 / 23,3
History of acute cerebrovascular accident, n/%	32 / 7,4
Arterial hypertension, n/%	391 / 89,9
Atrial fibrillation, n/%	72 / 16,6
Glomerular filtration rate (CKD-EPI) ≤ 60 ml/min/1.73 m ² , n/%	33 / 7,7
Chronic obstructive pulmonary disease, n/%	54 / 12,4
Multifocal atherosclerosis, n/%	92 / 21,2
Charlson Comorbidity Index, Me (Q1-Q3)	3 (2-4)
Previous myocardial infarction, n/%	309 / 71
Previous myocardial revascularization, n/%	
– PCI	134 / 30,8
– CABG	94 / 21,6
– PCI + CABG	31 / 7,1
9 / 2,1	
Chronic heart failure, NYHA functional class, n/%	
– 1	279 / 64,1
– 2	140 / 32,2
– 3	16 / 3,7
Number of affected areas of the coronary arteries, n/%	
– 1	116 / 26,7
– 2	155 / 35,6
– 3	164 / 37,7
Anatomy of a coronary lesion: n/%	
– Main left coronary artery	22 / 5,06
– Anterior descending artery	336 / 77,2
– Circumflex artery	269 / 61,8
– Right coronary artery	300 / 68,9
Index SYNTAX, Me (Q1-Q3)	11 (7-16,5)
Left ventricular ejection fraction according to ECHO-CG, %, Me (Q1-Q3)	62 (56-66)
n/% ≥ 50 %	386 / 89,15
40-49 %	35 / 8,08
< 40 %	12 / 2,8
Target vessel, n/% – Main left coronary artery	11 / 2,5
– Anterior descending artery	211 / 48,5
– Circumflex artery	145 / 33,3
– Right coronary artery	197 / 45,3
Intervention on chronic occlusion, n/%	110 / 25,3
Drug-eluting stents, n/%	565 / 86
Index stent length, мм, M±SD (min-max), Me (Q1-Q3)	33±16,1(12-107) 28 (23-38)
Index stent diameter, мм, M±SD (min-max), Me (Q1-Q3)	3,15±0,3 (2,5-5) 3 (3-3,5)
Complete revascularization, n/%	252 / 58,1
Volume of injected contrast, мл, Me (Q1-Q3)	250 (200-300)

Note: M±SD — mean ± standard deviation; min-max — minimum and maximum value of the parameters; Me (Q1-Q3) — median with interquartile range; CKD-EPI — Chronic Kidney Disease Epidemiology Collaboration is a research group with interests in measurement and estimation of GFR (Glomerular Filtration Rate); PCI — percutaneous coronary interventions; CABG — Coronary Artery Bypass Graft Surgery; NYHA — stage of chronic heart failure according to the functional classification of the New York Heart Association; Index SYNTAX — scale developed based on the results of the SYNTAX study (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery); ECHO-CG — echocardiography

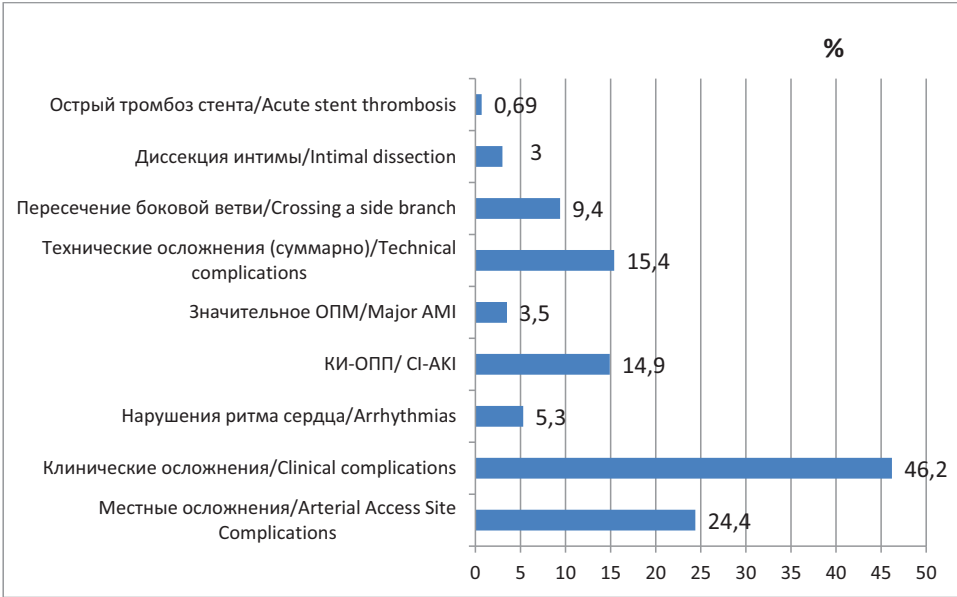


Figure 1. Acute complications of index percutaneous coronary interventions

Note: AMI — acute myocardial injury; CI-AKI — contrast-induced acute kidney injury

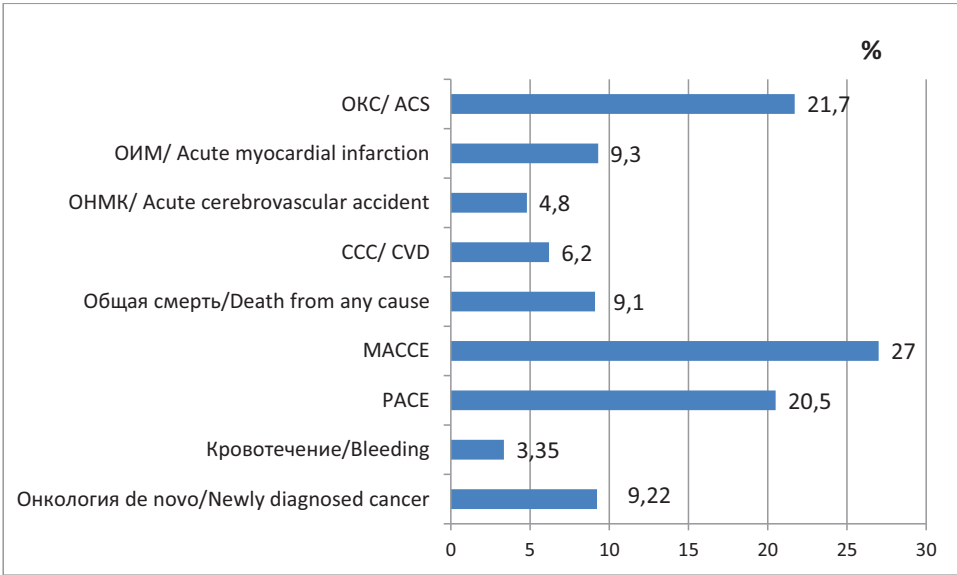


Figure 2. Long-term adverse events within 5 years after index percutaneous coronary interventions

Note: ACS — acute coronary syndrome; CVD — death from cardiovascular causes; MACCE — Major Adverse Cardiac or Cerebrovascular Events; PACE — patient centered endpoint.

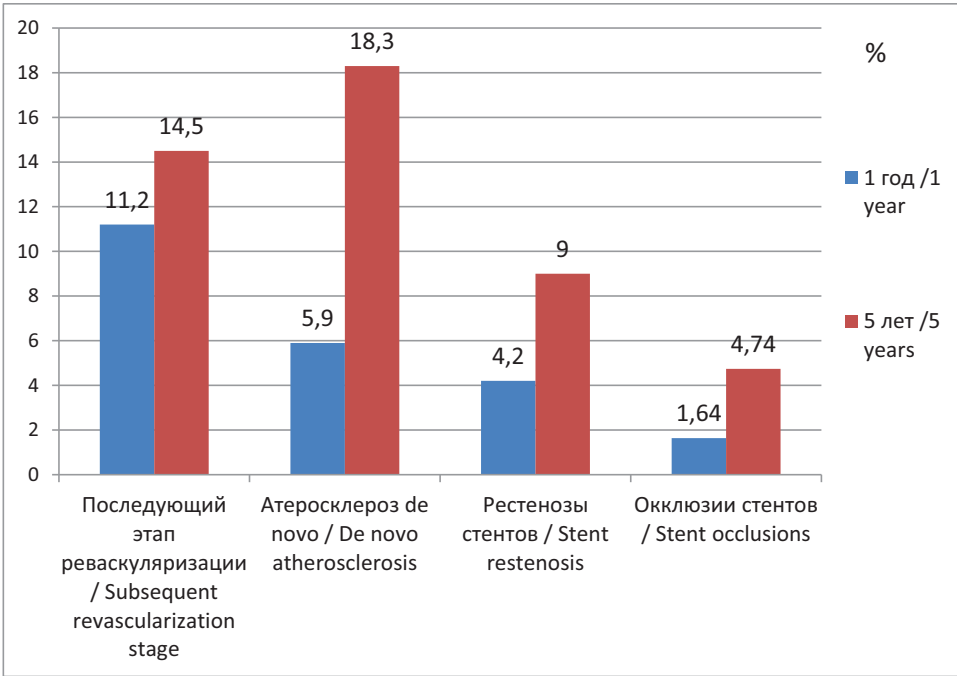


Figure 3. Causes of repeat revascularizations 1 year and 5 years after index PCI

Table 2. The risk of development of long-term adverse events depending on the magnitude of acute periprocedural myocardial injury during elective PCI

	RR	CI	S	P
PMI >5x99 percentile URL				
MACCE within 3 years after index PCI	4,486	[1.680-11.977]	0,501	0,006
CVD within 3 years after index PCI	6,538	[1.695-25.227]	0,689	0,046
AMI within 3 years after index PCI	6,516	[2.375-17.881]	0,515	0,003
PACE within 3 years after index PCI	3,850	[1.371-10.809]	0,527	0,024
Thrombosis of stents (index and non-index) during 5 years of follow-up	3,158	[1.307-7.629]	0,450	0,037
Occlusion of stents (index and non-index) as a reason for re-intervention during 5 years of follow-up	5,143	[1.702-15.539]	0,564	0,024
PMI >4x99 percentile URL				
MACCE within 4 years after index PCI	2,359	[1.009-5.517]	0,433	0,045
AMI within 3 years after index PCI	4,073	[1.598-10.378]	0,477	0,011
PACE during 5 years of follow-up	2,046	[1.154-3.627]	0,292	0,042
Thrombosis of stents (index and non-index) during 5 years of follow-up	2,658	[1.165-6.062]	0,421	0,042
Occlusion of stents (index and non-index) as a reason for re-intervention during 5 years of follow-up	5,482	[1.659-18.110]	0,610	0,024
Second-stage revascularization as a reason for re-intervention within 1 year after index PCI	2,907	[1.404-6.021]	0,372	0,017
PMI >3x99 percentile URL				
AMI within 3 years after index PCI	2,715	[1.113-6.622]	0,455	0,040
Occlusion of stents (index and non-index) as a reason for re-intervention during 5 years of follow-up	3,657	[1.314-10.183]	0,522	0,032
Second-stage revascularization as a reason for re-intervention within 1 year after index PCI	2,433	[1.203-4.919]	0,359	0,038
PMI >2x99 percentile URL				
Occlusion of stents (index and non-index) as a reason for re-intervention during 5 years of follow-up	4,042	[1.331-12.273]	0,567	0,029
PMI >1x99 percentile URL				
Newly diagnosed malignant oncological diseases during 5 years of follow-up	2,319	[1.248-4.310]	0,316	0,0062
Second-stage revascularization as a reason for re-intervention within 1 year after index PCI	1,933	[1.137-3.323]	0,274	0,0059

Note: RR — relative risk; CI — confidence interval; S — standard error of relative risk; p — significance level; PMI — periprocedural myocardial injury; URL — upper reference limit; MACCE — Major Adverse Cardiac or Cerebrovascular Events including cardiovascular death, acute coronary syndrome and acute cerebrovascular accident; CVD — death from cardiovascular causes; AMI — acute myocardial infarction; PCI — percutaneous coronary interventions; PACE — patient centered endpoint, including death from any cause, acute myocardial infarction and acute cerebrovascular accident.

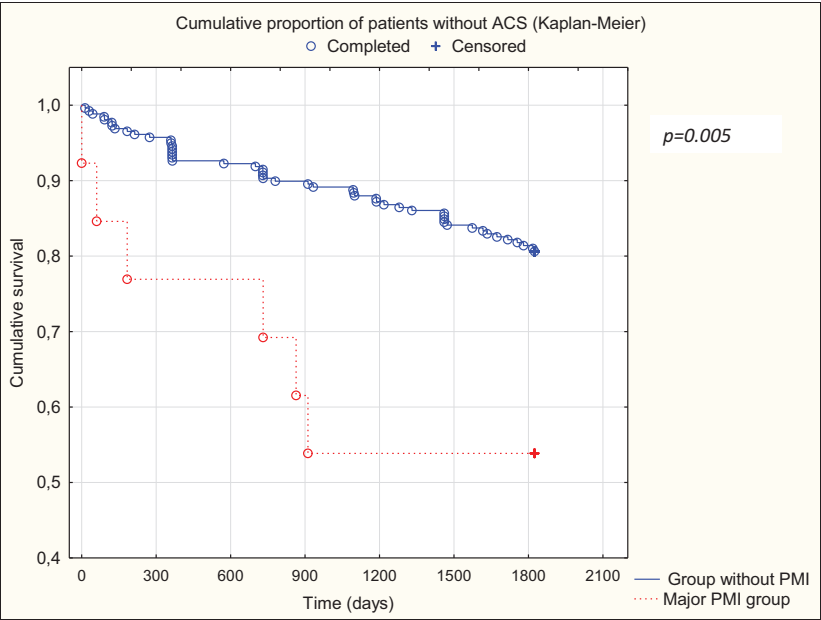


Figure 4. Kaplan-Meier curves for new cases of ACS up to 5 years after index PCI in 2 groups: comparison of no cardiac biomarkers elevation group (group 0) with the «major» PMI group (>5×99 percentile URL), $p=0.005$

Note: ACS — acute coronary syndrome; PCI — percutaneous coronary intervention; PMI — periprocedural myocardial injury; URL — upper reference limit

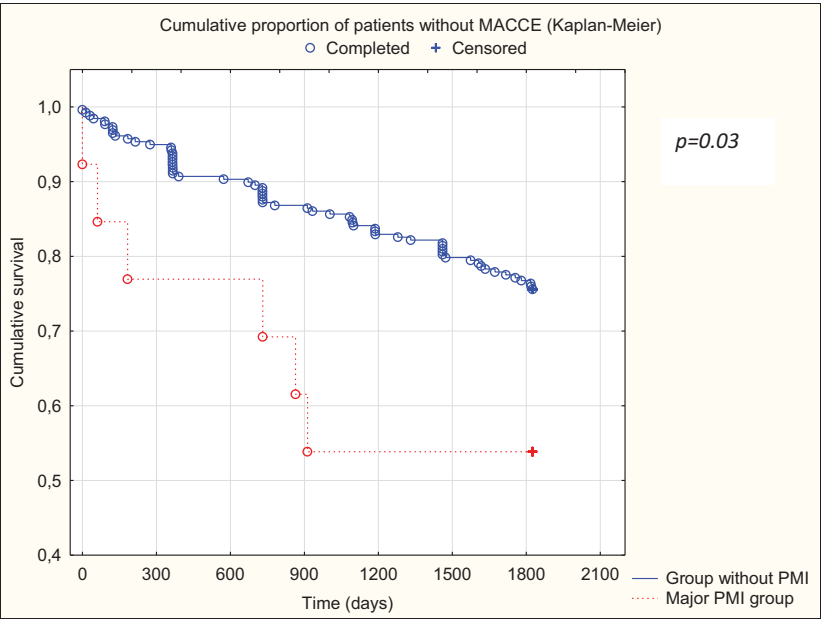


Figure 5. Kaplan-Meier curves for new cases of MACCE up to 5 years after index PCI in 2 groups: comparison of no cardiac biomarkers elevation group (group 0) with the «major» PMI group (>5×99 percentile URL), $p=0.03$.

Note: MACCE — Major Adverse Cardiac or Cerebrovascular Events including cardiovascular death, acute coronary syndrome and acute cerebrovascular accident; PCI — percutaneous coronary intervention; PMI — periprocedural myocardial injury; URL — upper reference limit

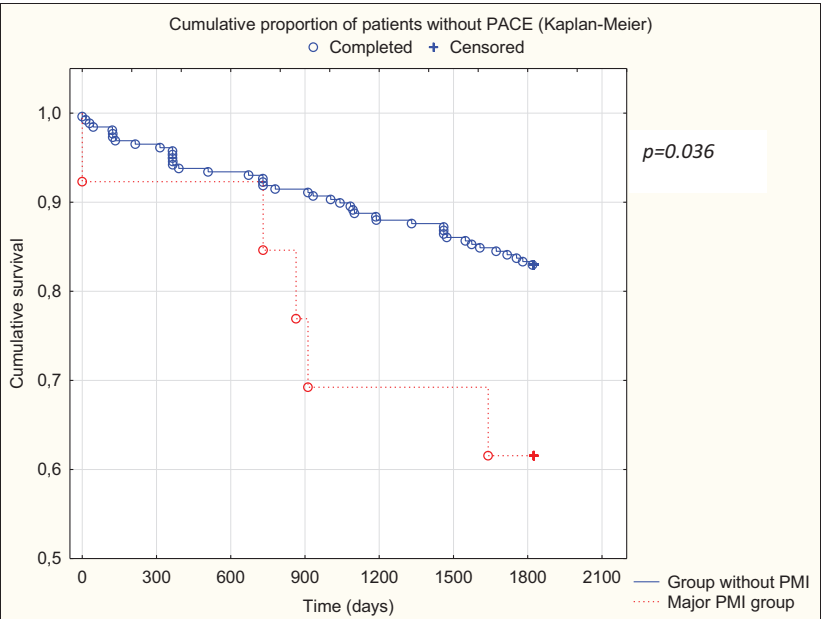


Figure 6. Kaplan-Meier curves for new cases of PACE up to 5 years after index PCI in 2 groups: comparison of no cardiac biomarkers elevation group (group 0) with the «major» PMI group (>5×99 percentile URL), $p=0.036$.

Note: PACE — patient centered endpoint, including death from any cause, acute myocardial infarction and acute cerebrovascular accident; PCI — percutaneous coronary intervention; PMI — periprocedural myocardial injury; URL — upper reference limit

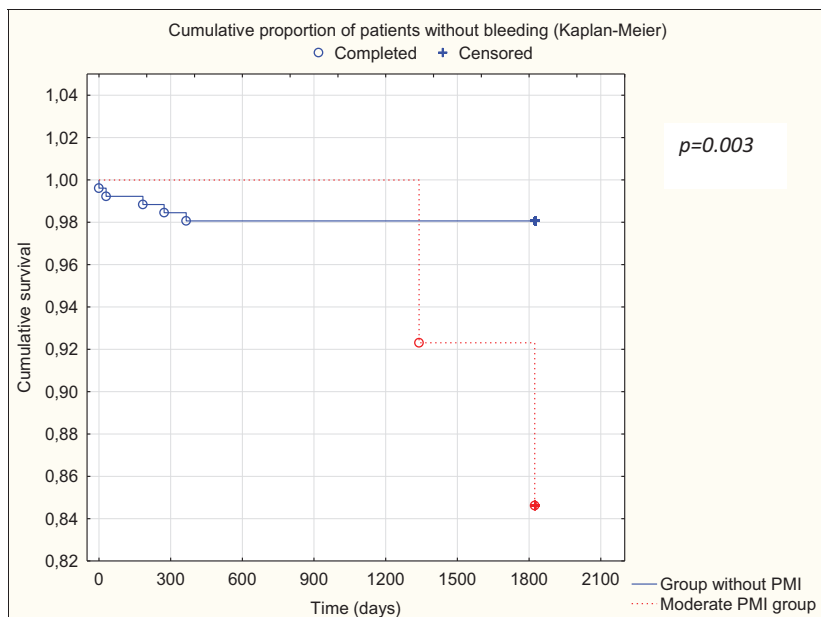


Figure 7. Kaplan-Meier curves for clinically significant bleeding up to 5 years after index PCI in 2 groups: comparison of no cardiac biomarkers elevation group (group 0) with the «moderate» PMI group (>3, but ≤5 ×99 percentile URL), $p=0.003$.

Note: PCI — percutaneous coronary intervention; PMI — periprocedural myocardial injury; URL — upper reference limit

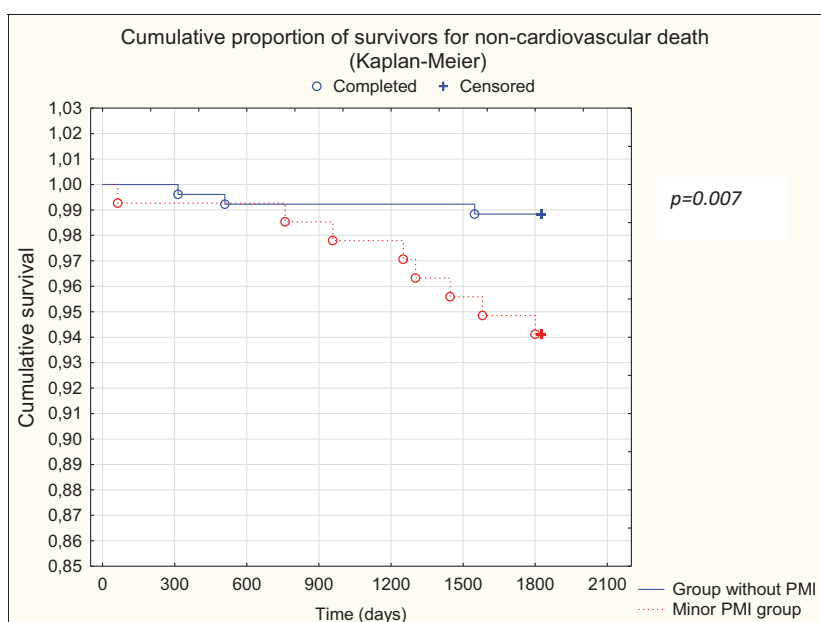


Figure 8. Survival curves for non-cardiovascular death at 5 years after index PCI in 2 groups: comparison of no cardiac biomarkers elevation group (group 0) with «minor» PMI group (>1 but ≤3 ×99 percentile URL), $p=0.007$.

Note: PCI — percutaneous coronary intervention; PMI — periprocedural myocardial injury; URL — upper reference limit

Similar to type 4a MI, there are various definitions of periprocedural myocardial injury in patients with CCS who underwent PCI. UDMI version 4 [9] defines periprocedural AMIn as any post-PCI increase in cTn of $> 1 \times 99$ th percentile of URL in patients with normal baseline values (before PCI). According to ARC-2, a major periprocedural myocardial injury is diagnosed at significantly higher increase in post-PCI cTn ($\geq 70 \times 99$ th percentile of URL) [18]. Predictably, the incidence of periprocedural myocardial injury is also dependent on the definition and the cardiac biomarker used: 2.9 % as per ARC-2 criteria [11] — 20 to 43 % for cardiac troponin T (cTnT) [20], 14 to 52 % for cTnI [21] and 78 to 85 % for highly sensitive cTnT [22].

Thus, currently there is no consensus on the definition of periprocedural myocardial infarction and injury;

the definitions by SCAI and ARC-2 set forth significantly higher thresholds for post-PCI CSF increases as compared to UDMI version 4.

According to UDMI version 4 [7], one of the key criteria for diagnosing type 4a MI in patients with CCS after PCI is new myocardial ischemia seen on coronary angiography scans, suggestive of periprocedural flow-limiting complications, such as coronary dissection, occlusion of a large epicardial artery or lateral occlusion/blood clot, impaired collateral blood flow, slow flow or no-reflow, distal embolisation. ARC-2 [18] presented detailed criteria for the definition of flow-limiting coronary angiographic complications in patients undergoing PCI and suspected periprocedural MI.

According to study results, the key causes of periprocedural AMIn and type 4a MI are lateral branch

occlusion (LBO) and distal embolisation. LBO is the most common cause of type 4a MI in patients with CCS undergoing PCI [23, 24], and its effects on the intervention outcome depend on the size of occluded lateral branches. The incidence of LBO can be associated with the stent type selected, type of procedure (e.g. chronic total occlusion, rotational atherectomy, etc.) and target segment — mid-LAD with the highest density of lateral branches [25]. Distal coronary embolisation with an intracoronary clot and atheromatous material can result in no-reflow/slow-flow during PCI in patients with CCS. It has been shown that, as of now, embolisation cannot be completely prevented, despite the use of anticoagulant and antiplatelet adjunctive therapy and the use of aspirating or protective devices [26].

However, according to the modern idea, PCI complications seen during angiography are not always associated with higher cardiac biomarker levels, and increased CSF can be caused by plaque degradation and local vascular damage without any apparent coronary angiographic complications [10]. Intravascular imaging methods can be used as an addition to coronary angiography in order to better understand the pathophysiology of PCI complications [27].

In our study, technical complications confirmed by angiography results, including acute stent thrombosis (0.7 %), intima dissection (3 %), lateral branch transfixion (9.4 %), etc., were observed in 15.4 % of patients. Significant AMIn of $> 5 \times 99$ th percentile of URL was recorded just in 3.5 % of patients.

Besides, chronically elevated highly sensitive cTnT/I can be seen in 30 % of patients due to comorbidities and risk factors, such as chronic kidney disease, diabetes mellitus, structural heart diseases, skeletal muscle diseases, malignancies and elderly age [28, 29].

A recently published meta-analysis demonstrated that higher post-PCI CPK-MB and cTn levels were independently associated with all-cause mortality within one year; and the following combinations of an increase in CSF were significant for the outcome: CPK-MB ≥ 5 and cTn ≥ 35 , CPK-MB ≥ 10 and cTn < 70 , and CPK-MB ≥ 5 and cTn $\geq 70 \times 99$ th percentile of URL [11].

Silvain J. et al. (2021) [30] also conducted a pooled analysis to assess increased post-PCI cTn levels (they analysed a pool of studies other than a study by Garcia-Garcia HM et al. (2019) [11]) in 9,081 patients with CCS who underwent PCI. The incidence of type 4a MI in a group of 2,316 patients with CCS who underwent PCI and had normal baseline cTn values, was 12.7 %, and its presence was a strong independent predictor of all-cause death in a year (adjusted odds ratio (Adj OR) 3.21, 95 % CI [1.42–7.27], $p = 0.005$). These results confirm predictive power of the cutoff threshold of $> 5 \times 99$ th percentile of URL in elevated post-PCI cTn, selected by UDMI version 4 for the definition of type 4a MI. The incidence of periprocedural myocardial injury (seen as

elevated post-PCI cTn of $> 1 \times 99$ th percentile of URL as per UDMI version 4) in patients with CCS and normal baseline cTn values was 52.8 % (79.8 %, if highly sensitive cTn was used); however, periprocedural myocardial injury was not associated with all-cause death during one year [30]. Besides, a study by Silvain J. et al. demonstrated that elevated post-PCI cTn of $> 3 \times 99$ th percentile of URL was also an independent predictor of all-cause death within a year in patients with ACS who underwent PCI, suggesting that even a slight increase in post-PCI cTn has predictive power.

On the contrary, in a consensus document published in 2021 by the working group of the European Society of Cardiology, patients with elevated post-PCI cTn levels of > 1 , but $\leq 5 \times 99$ th percentile of URL were found to have a minor periprocedural myocardial injury. A significant prognostic or major periprocedural myocardial injury (in the consensus paper, it is elevated post-PCI cTn of $> 5 \times 99$ th percentile of URL) was recorded in 18.2 % of patients with normal baseline cTn values and was an independent predictor of all-cause damage one year later (Adj OR 2.29, 95 % CI [1.32–3.97], $p = 0.004$) [10].

A recent study by Ueki Y. et al. (2022) [19] evaluated AMIn in accordance with the criteria set forth in UDMI version 3 and 4, ARC-2 and SCAI using highly sensitive cTn in patients with stable coronary disease who underwent PCI and were included in the Bern PCI Register. This analysis is the first detailed evaluation of up-to-date definitions of AMIn in patients undergoing elective PCI, which is based on routine measurements of highly sensitive cTn and routine assessment of additional criteria in a large real-life population of PCI patients. The primary endpoint was cardiac death after one year. In patients with AMIn, one year mortality in accordance with UDMI version 3, UDMI version 4, ARC-2 and SCAI was 2.9 %, 3.0 %, 5.8 % and 10.0 %, respectively. ARC-2 (hazard ratio (HR): 3.90; 95 % CI: 1.54–9.93) and SCAI (HR: 7.66; 95 % CI: 3.64–16.11) criteria were more relevant in comparison with UDMI version 3 (HR: 1.76; 95 % CI: 1.04–3.00) and UDMI version 4 (HR: 1.93; 95 % CI: 1.11–3.37) for cardiovascular death within one year after the index PCI.

Therefore, a majority of published studies evaluated the association between AMIn and 1-year disease outcome after elective PCI procedures; and there is no general expert consensus on this matter. Nevertheless, the clinical significance of diagnosing maAMIn is stated in the current guidelines on endovascular myocardial revascularisation.

We have evaluated the incidence and association between AMIn and midterm and late adverse events 1–5 years after index endovascular intervention for chronic coronary syndrome and found out an association between a major AMIn and late post-PCI cardiovascular complications, including fatal ones. At the same time, we have demonstrated the predicative power of moderate

Table 3. Association of periprocedural myocardial injury with complications and patient survival within 5 years after elective PCI

Name	Level of increase in cardiac biomarkers	Association with outcomes
1. Minor periprocedural myocardial injury	>1, but ≤3 ×99 percentile URL	<ul style="list-style-type: none">– no association with long-term ischemic complications and cardiovascular death after elective PCI;– there is an association with non-cardiovascular death in the long-term (5-year) period;– there is an association with newly diagnosed malignant cancers within 5 years after the index PCI;– there is an association with index stent occlusions as a cause of re-interventions during 5 years of follow-up;
2. Moderate periprocedural myocardial injury	>3, but ≤5 ×99 percentile URL	<ul style="list-style-type: none">– there is an association with acute ischemic events (ACS, AMI, MACCE) 3 years after the index elective PCI;– there is an association with clinically significant bleeding within 5 years after elective PCI;– there is an association with stent thrombosis (index and non-index) and index stent occlusions as a cause of re-interventions during 5 years of follow-up;
3. Major periprocedural myocardial injury	>5 ×99 percentile URL	<ul style="list-style-type: none">– there is an association with long-term ischemic events, as well as cardiovascular death within 3 years after the index PCI.

Note: PCI — percutaneous coronary intervention; URL — upper reference limit; ACS — acute coronary syndrome; AMI — acute myocardial infarction; MACCE (Major Adverse Cardiac or Cerebrovascular Events) — a composite endpoint including cardiovascular death, acute coronary syndrome and acute cerebrovascular accident.

and minor AMIn in relation not only to cardiovascular events, but also to clinically significant bleeding, as well as non-cardiovascular death and newly diagnosed malignancies during 5 years after elected PCI (Table 3).

Conclusions

Periprocedural increase in CSF values should be recorded during elective PCI not only for diagnosis and prediction of acute and late ischemic events, but also for evaluation of the risk of stent occlusion, clinically significant bleeding, significant predicative comorbidity and death during the late (5-year) period in order to identify groups of patients requiring active follow-up, additional observation and selection of an optimal outpatient rehabilitation regimen.

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Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией
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Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication
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Repin A.N. (ORCID ID: <https://orcid.org/0000-0001-7123-0645>): scientific consultation, manuscript text editing

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