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An innovative approach to assessing residual risk using advanced glycation end product autofluorescence in patients with coronary heart disease based on various lipid-lowering therapy regimens

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The aim of the study is to determine the relationship between the autofluorescence index and residual risk as part of a comprehensive assessment based on different cholesterol-lowering regimens in patients with CHD.

Methods. In this prospective study, 120 male patients with CHD underwent stepwise cholesterol-lowering therapy (monotherapy, dual, and triple therapy). Upon achieving the target level of low-density lipoprotein cholesterol (LDL-C), patients were divided into three cohorts. Each cohort underwent a comprehensive clinical and instrumental evaluation, including the determination of advanced glycation end products using the AGE Reader device (Diagnoptics Technologies B.V., Netherlands), which automatically calculated the autofluorescence index.

Results. LDL-C target levels were achieved by 27.5% of patients (n = 33) on monotherapy, 60% (n = 72) on dual therapy, and 12.5% (n = 15) on intensified triple therapy. AFI showed a decreasing trend at 6, 12, and 18 weeks, with final values as follows: cohort 1 (monotherapy) — 1.75 (95% CI: 1.70–1.95), cohort 2 (dual therapy) — 2.85 (95% CI: 2.30–3.80), cohort 3 (triple therapy) — 4.90 (95% CI: 4.15–4.90) To assess the relationship between achieved LDL-C levels and AFI after 18 weeks of treatment, a correlation analysis was performed. The resulting correlation coefficient (ρ = 0.388) indicated a moderate but statistically significant association ($p < 0.05$) according to the Chaddock scale. The relationship was strongest in cohort 3 (triple therapy) and weakest in cohort 1 (statin monotherapy), supporting the potential of AFI as a surrogate marker for residual cardiovascular risk.

Conclusion. The determination of AFI in routine clinical practice may serve as a convenient, non-invasive meth-

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od for the indirect assessment of residual cardiovascular risk in patients with CHD. This approach could enhance the implementation of secondary prevention strategies, including the intensification of lipid-lowering therapy for more stringent control of the lipid component of residual risk.

Keywords: coronary heart disease, residual risk, lipid-lowering therapy, PCSK9 inibitors, autofluorescence, AGE-reader, advanced glycation end products.

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Introduction

Increasing life expectancy, promoting health, and reducing mortality—particularly from cardiovascular diseases — are among the most critical objectives of healthcare systems in all countries [1]. Unfortunately, coronary heart disease (CHD) continues to rank among the leading causes of death worldwide, affecting predominantly males. Antianginal, lipid-lowering, and antiplatelet therapies are the cornerstones of CHD treatment, capable of improving quality of life and long-term outcomes. However, a residual risk remains — often unaccounted for in routine clinical practice. This residual risk refers to the ongoing possibility of adverse cardiovascular events in patients with CHD despite achieving target low-density lipoprotein cholesterol (LDL-C) levels. This type of risk has been recognized as an interdisciplinary issue and has been discussed globally since 2008, when the Residual Risk Reduction Initiative was launched [2–4]. A number of factors directly influence residual risk. These include atherogenic lipoprotein fractions that are rarely considered in routine practice — very-low and intermediate-density lipoproteins; hypertriglyceridemia; elevated lipoprotein(a) [Lp(a)] levels; and genetic polymorphisms related to familial hypercholesterolemia (both homozygous and heterozygous forms). There are also additional or "additive" factors, such as persistent hyperglycemia and glucotoxicity in diabetes mellitus, failure to achieve target glycated hemoglobin (HbA1C) levels, excessive variability in blood pressure with poor control within the target range, decompensated chronic heart failure (CHF) and other comorbid conditions, systemic inflammation, physical inactivity, etc. These conditions influence three critical pathophysiological components of residual risk: lipid, thrombotic, and inflammatory pathways. Their interplay forms the morphological substrate for cardiovascular events [5, 6].

Recently, the role of advanced glycation end-products (AGEs) as biomarkers reflecting a person's "biochemical passport" has been actively studied in the international scientific community. During non-enzymatic biochemical cascade reactions—where the substrate may be protein, lipid, or nucleic acid in nature — Schiff bases are formed. These are metabolically active intermediates that undergo irreversible reactions to form stable Amadori products. Through a series of oxidation processes, these ultimately generate fluorescent compounds, including pentosidine. There is a portable AGE analyzer that has proven convenient in clinical settings: the AGE Reader (Diagnoptics Technologies B.V., Netherlands). This device determines the autofluorescence index and automatically categorizes patients according to their total cardiovascular risk. It has found applications in diverse medical fields — from predicting the onset of diabetes mellitus (DM) to surgical practice [7–10].

However, in patients with CHD, the absolute cardiovascular risk is inherently very high. Therefore, it was hypothesized that this device could be used to assess residual risk in CHD patients, taking into account the influence of additive factors that can significantly modify residual risk. The AGE analysis procedure is non-invasive, quick, and easily applicable in a clinical setting.

The aim of the study is to determine the relationship between the autofluorescence index and residual risk as part of a comprehensive assessment based on different cholesterol-lowering regimens in patients with CHD.

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Methods

In the course of a prospective clinical study conducted in accordance with the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki, 120 male patients aged 55–75 years with CHD and comorbid conditions (arterial hypertension (AH), type 2 DM, metabolic syndrome) were observed. Each patient provided written informed consent to participate (REC protocol No. 3 dated 15.03.2023). Exclusion criteria included: female sex, age over 75 years, class III obesity, coexisting severe chronic kidney disease, CHF with a reduced ejection fraction below 40%, and DM with multiple complications.

At the start of the study, residual risk was comprehensively assessed in all participants based on medical and life history, physical examination, and results from laboratory and instrumental investigations. These included the following laboratory tests: complete blood count, urinalysis, blood biochemistry with lipid profile, Lp(a), glucose levels, HbA1c, creatinine, bilirubin, total protein, potassium, and sodium. The following instrumental tests were also performed: electrocardiography, echocardiography, duplex ultrasound of the brachiocephalic arteries, and autofluorescence analysis using the AGE Reader system (Diagnoptics Technologies B.V., Netherlands). This device measures AGEs in human skin; the autofluorescence index was determined three times on clean forearm skin, with the average value calculated. This method was applied for the first time to assess residual risk in CHD patients based on AGE analysis (invention application No. 2025101284 dated 22.01.2025).

Lipid-lowering therapy was adjusted stepwise:

- **Step 1:** All patients began with monotherapy using rosuvastatin 20 mg.
- **Step 2:** If the target low-density lipoprotein cholesterol (LDL-C) level <1.4 mmol/L was not achieved after 6 weeks, patients were prescribed a fixed combination of rosuvastatin 20 mg and ezetimibe 10 mg.
- **Step 3:** If target LDL-C was still not achieved after another 6 weeks, patients were switched to triple lipid-lowering therapy with the addition of a PCSK9 inhibitor — alirocumab 150 mg subcutaneously once every two weeks.

After 6 weeks, LDL-C target achievement was reassessed. Patients were divided into cohorts:

- **Cohort 1 (n=33):** reached the target LDL-C level on monotherapy
- **Cohort 2 (n=72):** on fixed combination therapy
- **Cohort 3 (n=15):** on triple therapy

All patients received adequate antihypertensive and antiplatelet therapy, as well as treatment for comorbid conditions. Patients who reached the target LDL-C level with any lipid-lowering regimen underwent a repeated comprehensive residual risk assessment, including using the AGE Reader device. The median follow-up period was 18 weeks.

Statistical analysis

Statistical analysis was performed using StatTech v. 4.7.3 (developed by Stattech LLC, Russia). Differences were considered statistically significant at $p < 0.05$. The distribution of quantitative variables was assessed for normality using the Shapiro–Wilk test. If the data did not follow a normal distribution, quantitative variables were described using the median (Me) and interquartile range (Q1–Q3). Categorical data were presented as absolute numbers and percentages. 95% confidence intervals (CIs) for percentages were calculated using the Clopper–Pearson method.

Results

The study design involving 120 patients is illustrated in Figure 1, which shows the selected multicomponent cholesterol inhibition regimen with sequential therapy intensification every 6 weeks.

LDL-C target achievement dynamics: at the beginning of the study (Visit 1), none of the patients had reached the target low-density lipoprotein cholesterol (LDL-C) level of <1.4 mmol/L. All patients were prescribed monotherapy with rosuvastatin 20 mg orally once daily. Additionally, they were educated on key principles of a healthy lifestyle, including a balanced diet with limited animal fats and simple carbohydrates, the importance of daily physical activity, and strict adherence to prescribed treatment. After 6 weeks of rosuvastatin monotherapy (Visit 2), 27% of patients (n=32) had achieved the target LDL-C level. For those who did not reach the target, a fixed-dose combination of rosuvastatin 20 mg + ezetimibe 10 mg was prescribed, with follow-up lipid profiling after another 6 weeks. By Visit 3, 60% of patients (n=72) had achieved LDL-C <1.4 mmol/L. The remaining 13% (n=15) were switched to triple therapy, with the addition of the PCSK9 inhibitor alirocumab 150 mg subcutaneously every two weeks to the statin-ezetimibe combination. By Visit 4, 12% (n=14) of patients had achieved the target LDL-C lev-

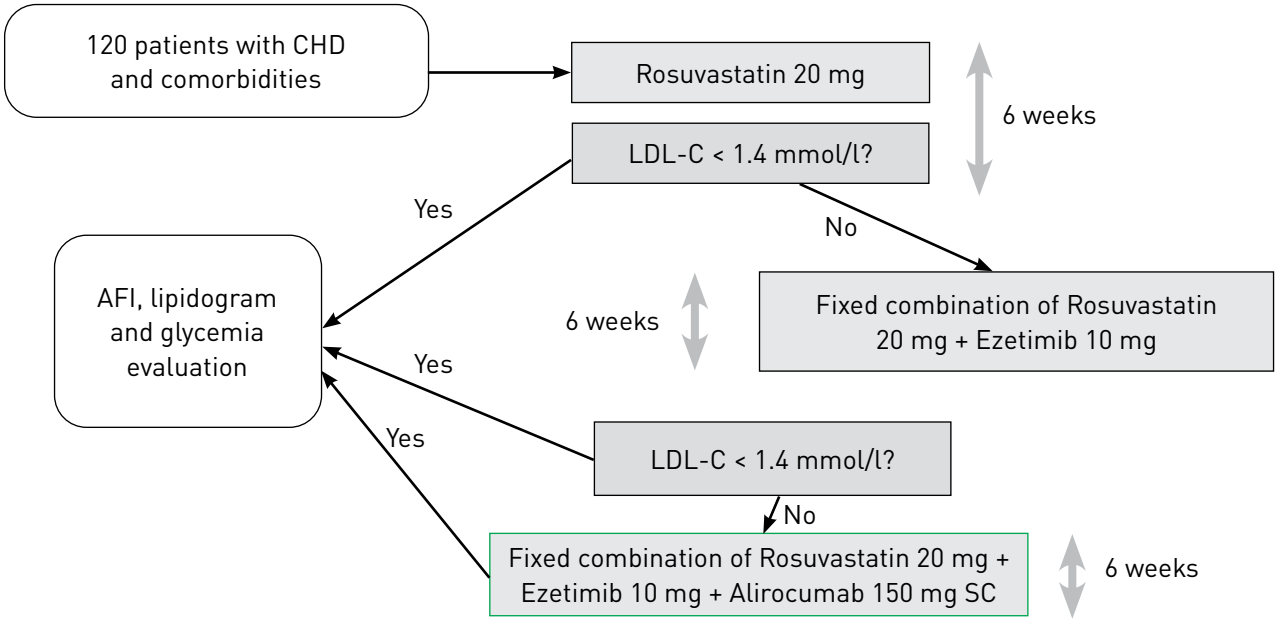

Fig. 1. Study design

el; 1 patient was referred to a regional lipid center for further differential diagnosis of suspected familial hypercholesterolemia. The dynamics of LDL-C target achievement are presented in Figure 2.

Table 1. **Characteristics of study participants by cohort**

Parameter	Cohort 1 n=33	Cohort 2 n=72	Cohort 3 n=15	p
Mean age (M±m)	64±3	63±4	69±2	0.04
History of CVD, n (%)	25 (75.7 %)	54 (75 %)	13 (87 %)	0.03
Smoking, n (%)	19 (58 %)	40 (56 %)	10 (67 %)	0.04
BMI 25-30 kg/m2, n (%)	15 (45 %)	29 (40 %)	6 (40 %)	0.03
BMI 30-39 kg/m2, n (%)	7 (21 %)	15 (20 %)	4 (27 %)	0.02
AH, targeted BP not achieved, n (%)	10 (30 %)	38 (53 %)	7 (47 %)	0.04
CHF, Stage 1, n (%)	14 (42 %)	47 (65 %)	7 (47 %)	0.04
Metabolic syndrome, n (%)	6 (18 %)	11 (15 %)	2 (13 %)	0.04
Type 2 DM, n (%)	8 (32 %)	27 (38 %)	4 (27 %)	0.03

Note. p<0.05.

Based on the achieved LDL-C level and the regimen required to reach it, patients were divided into three cohorts (Cohorts 1–3). Clinical and anamnestic characteristics of the cohorts are shown in Table 1.

An analysis of LDL-C target achievement dynamics in relation to additive factors was conducted using linear regression. Statistically significant associations were observed for parameters such as blood pressure control, body mass index, and Lp(a) level. These results are presented in Table 2.

During the analysis of AGEs using autofluorescence at baseline and at the 4th visit, median values of the autofluorescence index (AFI) were obtained for patients in all three cohorts (Table 3).

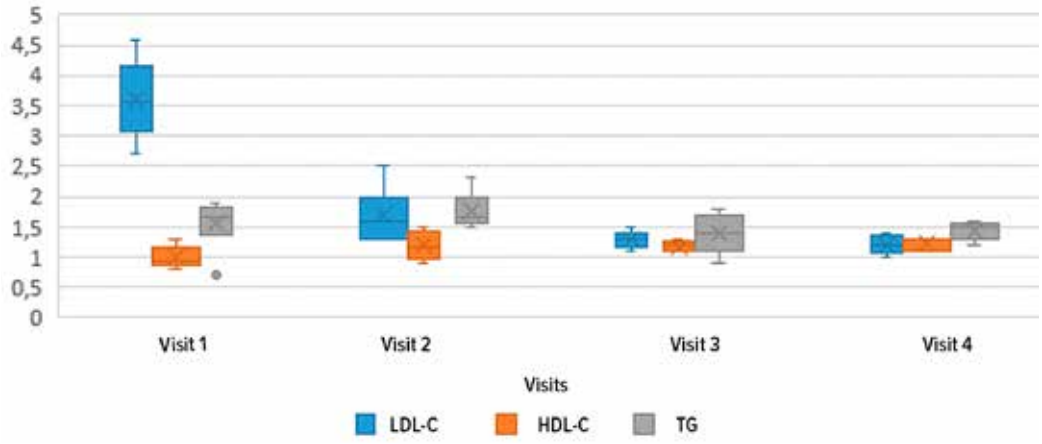

Fig. 2. Dynamics of achieving the target level of LDL-C by visits

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Table 2. **Analysis of the dynamics of LDL-C depending on the control of hypertension, Lp (a)**

	B	Std. error	t	p
Intercept	1.080	0.064	17.014	< 0.001*
Contolled AH	0.092	0.042	2.165	0.039*
Lp(a)	0.269	0.081	3.334	0.002*

Note. * the differences in the parameters are statistically significant (p < 0,05).

Table 3. **Summary of AFI characteristics by cohort**

Parameters	Cohort			p
	Cohort 1	Cohort 2	Cohort 3	
AFI before treatment, Me [IQR]	1.80 [1.80; 2.05]	3.05 [2.55; 4.03]	5.00 [4.90; 5.00]	p<0.05
AFI at 6 weeks, Me [IQR]	1.80 [1.80; 2.05]	3.00 [2.55; 4.00]	4.90 [4.70; 4.95]	p<0.05
AFI at 12 weeks, Me [IQR]	1.80 [1.80; 1.95]	2.90 [2.48; 3.98]	4.90 [4.30; 4.95]	p<0.05
AFI at 18 weeks, Me [IQR]	1.75 [1.70; 1.95]	2.85 [2.30; 3.80]	4.90 [4.15; 4.90]	p<0.05

Note. p<0.05.

The AFI demonstrated a decreasing trend at weeks 6, 12, and 18, respectively. At the final stage of the study, the median values were 1.75 in cohort 1 on monotherapy (CI: 1.70; 1.95), 2.85 in cohort 2 (CI: 2.30; 3.80), 4.9 in cohort 3 on triple therapy (CI: 4.15; 4.90).

To assess the relationship between the achieved LDL-C level and the AFI value after 18 weeks of treatment, a correlation analysis was performed, with the strength of association interpreted using Chaddock's scale (Figure 3). The resulting value of ρ = 0.388 indicates a statistically significant moderate correlation at p < 0.05.

Discussion

In the course of this prospective study, cascade-based multicomponent cholesterol inhibition in male patients with CHD was performed. The key parameter for cohort distribution was the method by which the target LDL-C level of less than 1.4 mmol/L was achieved — this being a strict requirement for patients at very high cardiovascular risk [11,12].

According to the lipid transport system dynamics illustrated in Figure 2, it is evident that at the first visit (baseline), all measured LDL-C values clearly exceeded the target threshold — not a single patient had reached an LDL-C level below 1.4 mmol/L.m. However, by the second visit, 27.5% of patients (n = 33) had achieved the target level. By the third visit on dual lipid-lowering therapy, 60% (n = 72) reached the goal, and on triple intensified therapy, 12.5% (n = 15) achieved it — a trend consistent with global study findings [13–15].

The patients were characterized by the following parameters: mean age — 65 ± 3 years, history of cardiovascular disease — 75%, smoking — 57.5%, uncontrolled arterial hypertension — 46%, type 2 DM — 32.5%. Detailed cohort characteristics are shown in Table 1. Among the factors directly influencing LDL-C target achievement, a statistically significant correlation was found with elevated Lp(a) levels and poor blood pressure control.

During the evaluation of AGEs using autofluorescence and calculation of the AFI, the following patterns were identified: although the baseline AFI level in each cohort was independent, the index tended to

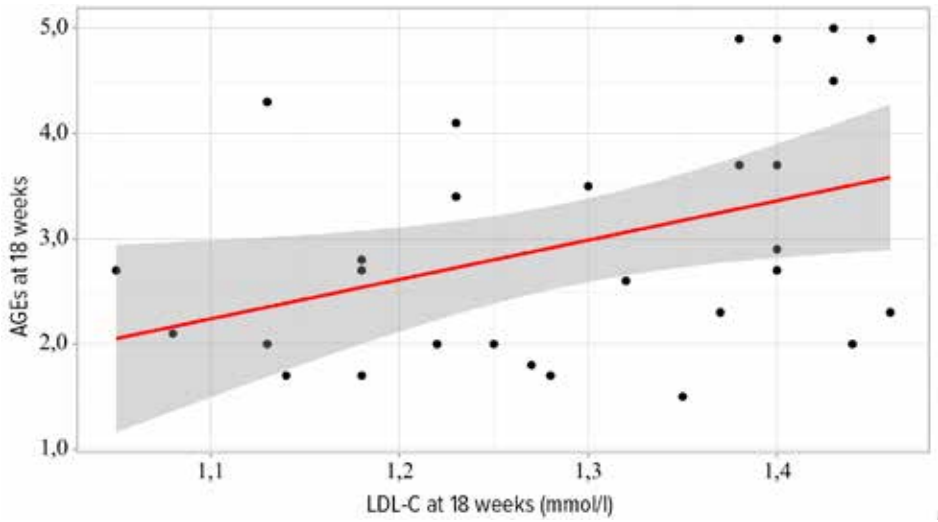

Fig. 3. Regression function graph characterizing the dependence of AGEs on LDL-C at 18 weeks from the start of the study

decline in parallel with achievement of LDL-C goals. The reduction of cholesterol remnants undoubtedly occurred alongside total cholesterol and LDL-C decreases, which ultimately may have led to weakened glycation end-product formation on lipid substrates, reduced AGE synthesis, and a corresponding AFI reduction by 3% in cohort 1, by 3.3% in cohort 2, and by 2% in cohort 3, respectively [16, 17].

To test the hypothesis of a relationship between achieving LDL-C targets and reducing the AFI, a correlation analysis was performed to assess the strength of association, if present (see Figure 3). Upon constructing the regression model, a moderate-strength relationship ($p < 0.05$) was identified, confirming a significant link between these parameters. This relationship was most pronounced in cohort 3 (triple-combination therapy) and least in cohort 1 (statin monotherapy). This suggests that determiningAGEs via the autofluorescence index could serve as a modeling parameter for residual cardiovascular risk. Provided there is adequate control of additive factors — such as glycemia, blood pressure regulation, smoking cessation, and increased physical activity — a further prospective reduction in newly formed AGEs may be possible. This, in turn, may attenuate the intensity of irreversible glycation reactions and lower AFI levels, although this requires further investigation [18–20].

Conclusion

Thus, AFI is influenced by multiple factors. In the process of achieving target LDL-C levels through various lipid-lowering regimens, a reduction in glycation end-product formation intensity occurs, reflecting a decrease in residual cardiovascular risk in patients with CHD — a finding supported by the moderate correlation strength according to the Chaddock scale ($p<0.05$). Multicomponent cholesterol inhibition more reliably reduces residual risk compared to statin monotherapy, and AFI measurement in daily practice may serve as a convenient, non-invasive method for assessing residual risk in patients with CHD.

Conflict of interests: none declared.

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