KAPITEL 13 / *CHAPTER 13* [13]
BIOMARKERS OF MYOCARDIAL REMODELING AND CORONARY RESERVE IN PATIENTS WITH STABLE ANGINA: THE PROGNOSTIC ROLE OF URIC ACID, NT-PROBNP AND CRP

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In recent years, there has been growing interest in cardiovascular biomarkers due to the need for simple, non-invasive screening methods and early diagnosis of cardiovascular diseases.C-reactive protein (CRP), uric acid, along with triglycerides and fibrinogen, are among the biomarkers identified as predictors of 10-year risk for atherosclerotic cardiovascular disease (ASCVD). Uric acid has been recognized as a marker of coronary artery disease (CAD) severity and, according to certain studies—including the EVINCI study—correlates with both the presence and severity of anatomical coronary occlusion and myocardial ischemia when assessed alongside N-terminal pro-B-type natriuretic peptide (NT-proBNP). According to findings from the DETECT study, measuring NT-proBNP, in addition to CRP, significantly enhances the prediction of cardiovascular events, and NT-proBNP levels exceeding 250 pg/mL serve as an independent predictor of angiographically confirmed coronary atherosclerosis. However, the overall contribution of biomarkers to improved prediction of the development and progression of cardiovascular diseases remains insufficiently defined.

To investigate the pathogenetic role of biomarker alterations in stable angina, particularly in relation to changes in uric acid levels and their association with myocardial functional status and coronary reserve for improved disease course prediction, a cohort of 120 patients diagnosed with stable angina was examined.A change (Δ%) of more than 5% in the studied parameters was considered clinically significant. Based on the dynamics of these indicators, patients were stratified into the following groups:

with an increase in left ventricular ejection fraction and those with a decline in

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left ventricular contractile function—31 individuals (70.45%) and 13 individuals (29.55%), respectively;

with an increase and a decrease in the threshold load (33 individuals (66.00% of cases) and 17 individuals (34.00% of cases), respectively);

with an increase and a decrease in uric acid levels (both groups comprising 60 individuals (50% of cases), respectively);

with an increase and a decrease in the concentration of N-terminal propeptide of natriuretic peptide (16 individuals (34.78% of cases) and 30 individuals (65.22% of cases), respectively);

with an increase and a decrease in C-reactive protein levels (14 individuals (31.11% of cases) and 30 individuals (68.89% of cases), respectively);

with an increase and a decrease in total testosterone levels (31 individuals (67.39% of cases) and 15 individuals (32.61% of cases), respectively).

At the beginning of inpatient treatment and again after 6 months in the outpatient phase, all patients underwent clinical, laboratory, and instrumental examinations. A positive trend in left ventricular myocardial contractile function was associated with a significantly greater reduction in systolic blood pressure (Δ% -22.64±1.60 vs. -14.31±1.80%, $p<0.001$). At the same time, there was no significant difference in the degree of heart rate reduction depending on the dynamics of the left ventricular ejection fraction (Δ% -7.50±2.45 vs. -6.94±3.64%, $p>0.5$).

A positive dynamic of the left ventricular ejection fraction was associated with a significant decrease in total cholesterol levels (Δ% -17.76±3.89 vs. +12.51±6.01%, $p<0.001$), creatinine (Δ% -11.20±8.75 vs. +64.73±31.25%, $p<0.01$), uric acid (Δ% -30.89±8.60 vs. +53.35±12.20%, $p<0.001$), C-reactive protein (Δ% -34.42±1.46 vs. +148.38±38.88%, $p<0.001$), and N-terminal propeptide of natriuretic peptide (Δ% -65.81±9.06 vs. +175.31±10.58%, $p<0.001$), as well as a significantly greater reduction in triglyceride levels (Δ% -46.91±2.45 vs. -18.61±3.64%, $p<0.001$).

Analysis of echocardiographic (EchoCG) parameter dynamics revealed that an improvement in left ventricular (LV) systolic function was associated with a significant reduction in LV dimensions (based on end-systolic dimension: Δ% -11.77±2.21 vs.

+19.16±3.33%, $p<0.001$; and end-diastolic dimension: Δ% -6.42±2.04 vs. +9.77±2.81%, $p<0.001$) as well as in LV myocardial mass (Δ% -15.13±3.73 vs. +18.74±5.71%, $p<0.001$). Over the observation period, no association was found between changes in left atrial size and left ventricular ejection fraction (LVEF).

A positive dynamic in LVEF was associated with an improvement in coronary reserve, as evidenced by a significant increase in threshold load (Δ% +59.19±7.31 vs. -14.46±2.96%, $p<0.001$), exercise tolerance (Δ% +57.82±10.70 vs. -11.61±1.20%, $p<0.001$), and a significantly greater reduction in exercise-induced ischemia (measured by cumulative ST-segment depression: Δ% -46.00±11.50 vs. -19.34±1.20%, $p<0.05$).

An increase in threshold load was accompanied by a non-significantly greater reduction in systolic blood pressure (Δ% -18.31±1.90 vs. -13.61±1.75%, $p>0.1$), with no significant difference in heart rate reduction (Δ% -7.95±2.27 vs. -9.27±2.40%, $p>0.5$).

Positive dynamics in threshold load were associated with significant decreases in serum creatinine (Δ% -9.52±3.80 vs. +11.81±6.35%, $p<0.01$), uric acid (Δ% -14.98±5.91 vs. +10.99±4.57%, $p<0.01$), N-terminal propeptide of natriuretic peptide (Δ% -61.65±26.95 vs. +88.99±34.95%, $p<0.001$), and C-reactive protein (Δ% -26.10±3.37 vs. +101.37±45.85%, $p<0.01$).

Improvement in threshold load was also associated with a significant reduction in left ventricular dimensions (end-systolic dimension: Δ% -9.36±3.30 vs. +9.12±4.18%, $p<0.001$; end-diastolic dimension: Δ% -6.84±1.11 vs. +4.59±0.89%, $p<0.001$) and LV myocardial mass (Δ% -18.86±3.30 vs. +14.21±4.18%, $p<0.001$), as well as a significant increase in LVEF (Δ% +7.51±2.42 vs. -9.46±3.24%, $p<0.001$).

An increase in threshold load was accompanied by a statistically significant improvement in exercise tolerance (Δ% +46.26±6.91 vs. +1.55±0.49%, $p<0.001$) and a significant reduction in exercise-induced ischemia (based on cumulative ST-segment depression: Δ% -30.36±7.47 vs. +3.71±0.49%, $p<0.05$).

When comparing groups according to the increase or decrease in uric acid levels, it was found that a favorable reduction in serum uric acid levels after 6 months was associated with a significantly greater decrease in systolic blood pressure (Δ% -

20.33±1.30 vs. -12.12±1.30%, $p<0.001$), as well as total cholesterol (Δ% -19.66±1.50 vs. -4.71±3.01%, $p<0.001$) and triglycerides (Δ% -45.78±10.50 vs. -19.83±6.01%, $p<0.05$).

Only in the group with decreased uric acid levels was a significant reduction observed in creatinine levels (Δ% -17.24±2.26 vs. +21.57±6.88%, $p<0.001$), N-terminal propeptide of natriuretic peptide (Δ% -64.43±15.89 vs. +63.28±13.88%, $p<0.001$), and C-reactive protein (Δ% -50.21±5.46 vs. +153.49±56.04%, $p<0.001$). No significant difference in heart rate reduction was observed depending on the dynamics of serum uric acid levels (Δ% -7.32±1.66 vs. -8.17±1.39%, $p>0.5$).

A favorable trend toward reduced serum uric acid levels was also associated with a statistically significant decrease in left ventricular size (end-systolic dimension: Δ% -7.25±2.09 vs. +4.71±0.09%, $p<0.001$; end-diastolic dimension: Δ% -4.15±2.10 vs. +2.34±0.10%, $p<0.01$), left ventricular myocardial mass (Δ% -13.54±6.39 vs. +4.33±0.44%, $p<0.01$), and a significant increase in left ventricular ejection fraction (Δ% +8.11±2.75 vs. -13.54±0.99%, $p<0.001$).

In a comparison of patients with increased versus decreased serum uric acid levels, it was found that a reduction in uric acid was associated with improved coronary reserve, as evidenced by a significantly greater increase in threshold exercise load (Δ% +50.45±5.00 vs. +4.42±2.38%, $p<0.001$) and exercise tolerance (Δ% +47.14±5.14 vs. +12.68±3.29%, $p<0.01$), along with a reduction in exercise-induced ischemia assessed by cumulative ST-segment depression (Δ% -37.58±9.81 vs. -13.35±3.15%, $p<0.05$).

A favorable decrease in N-terminal propeptide of natriuretic peptide (NT-proBNP), compared to an increase in this marker, was associated with a significantly greater reduction in systolic blood pressure (Δ% -22.81±1.49 vs. -12.05±1.69%, $p<0.001$), a non-significant trend toward greater heart rate reduction (Δ% -8.30±2.35 vs. -3.86±1.02%, $p>0.1$), and a significantly greater decrease in triglyceride levels (Δ% -45.68±5.14 vs. -14.65±3.35%, $p<0.001$). Only in this group was a reduction observed in total cholesterol (Δ% -16.75±4.00 vs. +6.12±8.44%, $p<0.05$), creatinine (Δ% -8.91±4.18 vs. +60.33±19.53%, $p<0.001$), uric acid (Δ% -28.72±8.89 vs. +45.49±11.13%, $p<0.001$), and C-reactive protein (Δ% -35.07±10.98 vs.

+145.02±55.59%, $p<0.01$).

As in the previous comparison, a favorable reduction in NT-proBNP levels was associated with a significant decrease in left ventricular size, assessed by end-systolic dimension (Δ% -10.09±2.22 vs. +13.15±3.61%, $p<0.001$), end-diastolic dimension (Δ% -5.81±2.03 vs. +6.52±2.52%, $p<0.001$), and left ventricular myocardial mass (Δ% -15.59±3.58 vs. +12.96±4.72%, $p<0.001$), as well as a significantly greater improvement in left ventricular ejection fraction (Δ% +12.75±5.05 vs. -11.34±4.78%, $p<0.001$).

Additionally, a decrease in NT-proBNP levels was associated with an increase in coronary reserve, with a significant rise in threshold load (Δ% +54.68±14.26 vs. -3.60±1.43%, $p<0.001$) and exercise tolerance (Δ% +53.08±13.50 vs. +1.66±0.02%, $p<0.001$), as well as a reduction in exercise-induced ischemia as measured by cumulative ST-segment depression (Δ% -42.14±15.77 vs. -8.95±0.92%, $p<0.05$).

In the comparison of patients with increased versus decreased levels of C-reactive protein (CRP), it was established that a reduction in CRP was associated with a significantly greater decrease in systolic blood pressure (Δ% -21.83±1.51 vs. -12.72±2.20%, $p<0.001$), as well as triglyceride levels (Δ% -42.76±3.56 vs. -16.26±3.69%, $p<0.001$). Only patients in this group demonstrated reductions in total cholesterol (Δ% -19.59±2.12 vs. +17.17±10.05%, $p<0.001$), creatinine (Δ% -20.96±4.03 vs. +96.26±19.20%, $p<0.001$), uric acid (Δ% -36.72±4.32 vs. +72.49±11.36%, $p<0.001$), and N-terminal propeptide of natriuretic peptide (NT-proBNP) (Δ% -34.43±17.68 vs. +132.46±49.26%, $p<0.01$).

However, patients with increased inflammatory activity (CRP elevation) were characterized by a significantly greater increase in total testosterone levels (Δ% +28.57±4.16 vs. +8.09±2.31%, $p<0.001$). No significant difference was found in the extent of heart rate reduction depending on the CRP dynamics (Δ% -5.64±2.37 vs. -8.26±3.09%, $p>0.5$).

In this comparison, a favorable reduction in CRP was also associated with a significant decrease in left ventricular size based on the end-systolic dimension (Δ% -7.11±2.22 vs. +11.05±5.08%, $p<0.01$), end-diastolic dimension (Δ% -4.59±1.91 vs.

+6.24±3.26%, $p<0.01$), and left ventricular myocardial mass (Δ% -13.08±3.56 vs. +12.33±5.97%, $p<0.001$), as well as a significant increase in left ventricular ejection fraction (Δ% +9.79±2.27 vs. -8.65±4.07%, $p<0.001$).

A decrease in CRP levels was also associated with an improvement in coronary reserve, shown by a significant increase in threshold exercise load (Δ% +56.64±6.47 vs. -11.90±3.15%, $p<0.001$) and exercise tolerance (Δ% +51.22±23.50 vs. -10.22±2.65%, $p<0.05$), along with a reduction in exercise-induced ischemia based on cumulative ST-segment depression (Δ% -43.38±13.96 vs. -7.41±1.97%, $p<0.05$).

When analyzing the interplay between changes in total testosterone levels and the dynamics of myocardial functional parameters, coronary reserve, and other vasoactive and homeostatic indicators, it is important to consider the gender composition of the groups, which influenced both the testosterone dynamics and the course of the disease. In the group with an increase in total testosterone, men predominated over women (64.52±8.59% vs. 35.48±8.59%, $p<0.05$), while the opposite distribution was observed in the group with a decrease in testosterone levels (33.01±12.17% vs. 66.99±12.17%, $p<0.05$).

A significant slowing of heart rate was observed only in men with an increase in total testosterone (73.39±1.99 vs. 68.06±1.09 bpm, $p<0.05$). In contrast, in women, an increase in total testosterone was not associated with a statistically significant change in heart rate (73.60±2.90 vs. 68.40±1.75 bpm, $p>0.5$). Therefore, no significant difference in the extent of heart rate reduction was noted depending on the dynamics of total testosterone levels (Δ% -5.92±2.09 vs. -5.74±3.25%, $p>0.5$).

A reduction in systolic blood pressure was statistically significant both in men with increasing testosterone levels and in women with decreasing levels, but this effect was significantly more pronounced in women (Δ% -16.82±1.75 vs. -22.65±2.00%, $p<0.05$). A similar trend was observed for triglycerides, with a significantly more intensive reduction in women (Δ% -31.09±2.03 vs. -41.36±4.31%, $p<0.05$). A significant reduction in total cholesterol was observed only in women with a decrease in total testosterone (Δ% -18.22±3.31 vs. -4.02±1.88%, $p<0.01$).

No statistically significant differences were found in changes in creatinine, uric

acid, or N-terminal propeptide of natriuretic peptide (NT-proBNP) levels. Notably, in the female subgroup with decreased testosterone levels, a significant reduction in C-reactive protein was observed (Δ% -18.64±3.54 vs. +31.06±17.50%, $p<0.05$).

A decrease in total testosterone levels in women was associated with a significant reduction in left ventricular dimensions, whereas, based on our data during the selected observation period, left ventricular size and geometry did not change significantly. Specifically, the end-systolic dimension showed a significant decrease (Δ% -9.54±3.60 vs. +1.76±0.11%, $p<0.01$), as did the end-diastolic dimension (Δ% -6.96±2.63 vs. +1.10±0.21%, $p<0.01$) and left ventricular myocardial mass (Δ% -14.88±5.56 vs. -0.80±0.21%, $p<0.05$).

An increase in coronary reserve was observed both in men with rising total testosterone levels and in women with decreasing testosterone, although the improvement was significantly more pronounced in the female group. In women, there was a significantly greater increase in exercise threshold (Δ% +61.03±4.85 vs. +25.98±4.73%, $p<0.001$), exercise tolerance (Δ% +60.85±4.95 vs. +20.96±4.20%, $p<0.05$), and a greater reduction in exercise-induced ischemia assessed via total ST-segment depression (Δ% -36.44±2.66 vs. -23.83±4.40%, $p<0.05$).

Thus, an increase in left ventricular ejection fraction was accompanied by reductions in total cholesterol ($p<0.001$), creatinine ($p<0.01$), uric acid ($p<0.001$), C-reactive protein ($p<0.001$), and N-terminal propeptide of natriuretic peptide (NT-proBNP, $p<0.001$). The improvement in ejection fraction was associated with a reduction in left ventricular size (based on both end-systolic and end-diastolic dimensions, $p<0.001$), regression of left ventricular hypertrophy (based on myocardial mass, $p<0.001$), enhanced coronary reserve (based on exercise threshold and physical exercise tolerance, $p<0.001$), and decreased test-induced ischemia (based on total ST-segment depression, $p<0.05$).

A decrease in total testosterone levels in women was associated with a significant reduction in left ventricular dimensions, whereas, based on our data during the selected observation period, left ventricular size and geometry did not change significantly. Specifically, the end-systolic dimension showed a significant decrease (Δ% -9.54±3.60

vs. +1.76±0.11%, $p<0.01$), as did the end-diastolic dimension (Δ% -6.96±2.63 vs. +1.10±0.21%, $p<0.01$) and left ventricular myocardial mass (Δ% -14.88±5.56 vs. -0.80±0.21%, $p<0.05$).

An increase in coronary reserve was observed both in men with rising total testosterone levels and in women with decreasing testosterone, although the improvement was significantly more pronounced in the female group. In women, there was a significantly greater increase in exercise threshold (Δ% +61.03±4.85 vs. +25.98±4.73%, $p<0.001$), exercise tolerance (Δ% +60.85±4.95 vs. +20.96±4.20%, $p<0.05$), and a greater reduction in exercise-induced ischemia assessed via total ST-segment depression (Δ% -36.44±2.66 vs. -23.83±4.40%, $p<0.05$).

Thus, an increase in left ventricular ejection fraction was accompanied by reductions in total cholesterol ($p<0.001$), creatinine ($p<0.01$), uric acid ($p<0.001$), C-reactive protein ($p<0.001$), and N-terminal propeptide of natriuretic peptide (NT-proBNP, $p<0.001$). The improvement in ejection fraction was associated with a reduction in left ventricular size (based on both end-systolic and end-diastolic dimensions, $p<0.001$), regression of left ventricular hypertrophy (based on myocardial mass, $p<0.001$), enhanced coronary reserve (based on exercise threshold and physical exercise tolerance, $p<0.001$), and decreased test-induced ischemia (based on total ST-segment depression, $p<0.05$).

A reduction in C-reactive protein levels was associated with predominant decreases in total cholesterol ($p<0.001$), creatinine ($p<0.001$), uric acid ($p<0.001$), and N-terminal propeptide of natriuretic peptide ($p<0.01$), as well as with a more pronounced reduction in systolic blood pressure ($p<0.001$) and triglyceride levels ($p<0.001$). This dynamic of C-reactive protein was accompanied by a reduction in left ventricular dimensions (end-systolic and end-diastolic diameters, $p<0.01$), a decrease in left ventricular myocardial mass ($p<0.001$), and an increase in left ventricular ejection fraction ($p<0.001$). Additionally, there was a significant improvement in coronary reserve, with increased exercise threshold ($p<0.001$), enhanced exercise tolerance ($p<0.05$), and reduced exercise-induced ischemia as assessed by total ST-segment depression ($p<0.05$).

An increase in total testosterone in men and a decrease in this parameter in women were both associated with a reduction in systolic blood pressure ($p<0.05$ in both cases), with a significantly greater effect observed in women ($p<0.05$). Similarly, both changes were linked to reduced triglyceride levels ($p<0.05$ in both groups), again with a more pronounced decrease in women ($p<0.05$). Improvements in coronary reserve were observed in both groups, though significantly more marked in women, as indicated by increased exercise threshold ($p<0.001$), improved physical exercise tolerance ($p<0.05$), and reduced test-induced ischemia (based on total ST-segment depression, $p<0.05$). In women, a decrease in total testosterone was also associated with a significant reduction in total cholesterol ($p<0.01$) and C-reactive protein levels ($p<0.05$).

Thus, uric acid may serve as a biomarker of limitations in both functional and coronary reserves, as its dynamic changes demonstrate prognostic value for the reduction in left ventricular size, regression of left ventricular hypertrophy, improvement in systolic function, and enhancement of coronary reserve. Even in the presence of preserved left ventricular systolic function with normal ejection fraction values—and regardless of the clinical severity of heart failure symptoms—N-terminal propeptide of natriuretic peptide (NT-proBNP) holds predictive significance for the reduction in left ventricular dimensions, regression of hypertrophy, and improvement in coronary reserve. C-reactive protein has been identified as a biomarker for predicting cardiac remodeling, enhanced systolic function of the left ventricle, and improved coronary reserve.

Considering their prognostic value in the progression of dyslipidemia, alterations in coronary reserve, and functional status in patients with stable angina, uric acid, NT-proBNP levels, and C-reactive protein may be utilized as biomarkers of individual responsiveness to therapy. These markers may aid in identifying patients who would benefit from intensified pharmacological treatment in order to preserve work capacity, as well as those suitable for interventional procedures. Given the growing interest in circulating cardiovascular biomarkers and the current lack of consensus regarding their clinical utility, further studies in patients with stable coronary artery disease are warranted.