KAPITEL 5 / *CHAPTER 5* [5]
EFFECT OF ALLOPURINOL AND QUERCETIN ON MYOCARDIAL FUNCTION AND CORONARY RESERUE IN STABLE ANGINA

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Currently, according to statistical data, approximately 8 million individuals in Ukraine suffer from ischemic heart disease (IHD). Improving the prognosis and reducing mortality in these patients remain the primary objectives of pharmacological therapy for IHD. Uric acid has emerged as a novel marker of cardiovascular risk, having demonstrated associations with adverse cardiovascular events, particularly among patients with high cardiovascular risk profiles. According to the European Society of Cardiology guidelines, pharmacological treatment of stable IHD, in addition to conventional first- and second-line agents, may include the use of allopurinol. However, the role of allopurinol in managing asymptomatic hyperuricemia in patients with IHD and arterial hypertension remains uncertain.

Object of the study: stable exertional angina of functional classes II and III, including cases combined with asymptomatic hyperuricemia, in 120 patients undergoing inpatient treatment in the departments of chronic ischemic heart disease and rehabilitation at the Chernivtsi Regional Clinical Cardiology Dispensary.

Subject of the study: the influence of changes in serum uric acid levels on myocardial functional state, coronary reserve, and a range of biomarkers and hemostatic parameters—including N-terminal pro–B-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP), and total testosterone—in patients with stable angina. The study also investigated the interrelation between changes in uric acid and biomarkers, aiming to enhance prognostication of stable angina progression.

Methods: the study included general clinical examination, biochemical blood testing (lipid profile, creatinine, urea, uric acid), enzyme-linked immunosorbent assay (ELISA) of serum samples to determine NT-proBNP, CRP, and total testosterone levels, as well as non-invasive (electrocardiography, echocardiography, bicycle

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ergometry) and invasive (coronary angiography) assessments of the cardiovascular system. These evaluations were performed both at the beginning of inpatient treatment and after a six-month outpatient follow-up phase. All patients received comprehensive treatment according to current protocols and recommendations for the management of stable coronary artery disease. The therapeutic regimen included β-blockers (bisoprolol [Concor, Merck KGaA, Germany]), statins (atorvastatin [Atorvacor, PJSC "Farmak," Ukraine]), angiotensin-converting enzyme inhibitors (ramipril [Ramizes, PJSC "Farmak," Ukraine]), antiplatelet agents (acetylsalicylic acid [Cardiomagnyl, Takeda GmbH, Germany]), nitrates (isosorbide dinitrate [Cardiket-retard, Aesica Pharmaceuticals, Germany]), and, in cases of fluid retention and decompensated heart failure, diuretics (torasemide [Torsid, PJSC "Farmak," Ukraine]).

In addition to the standard treatment, some patients were prescribed quercetin (Quertin, PJSC "BHFZ," Ukraine), or, in the presence of specific clinical indications (asymptomatic hyperuricemia >773 μmol/L in men and >595 μmol/L in women), the xanthine oxidase inhibitor allopurinol (Allopurinol, PJSC "BHFZ," Ukraine).

Accordingly, patients were divided into three groups:

- Group 1: Standard therapy only (n = 70; 58.33%)
- Group 2: Standard therapy with added allopurinol (n = 23; 19.17%)
- Group 3: Standard therapy with added quercetin (n = 27; 22.50%)

Clinical, laboratory, and instrumental assessments were performed for all patients at the beginning of inpatient treatment and after 6 months of outpatient follow-up.The groups were comparable in terms of age, sex distribution, and presence of arterial hypertension, as shown in Table 1.

Among patients who received additional allopurinol, there was a statistically significant predominance of those with class III stable angina ($p < 0.05$)—both in comparisons between the standard therapy group and the standard therapy + allopurinol group, and between the standard therapy + allopurinol and the standard therapy + quercetin groups. A history of Q-wave myocardial infarction was also significantly more common in the allopurinol group ($p < 0.01$ when comparing standard therapy + quercetin vs. standard therapy + allopurinol). In contrast, non–Q-wave myocardial

Table 1 – Baseline Clinical Characteristics of Patients with Stable Angina Receiving Different Treatment Regimens

Parameter	Standard Therapy	Standard Therapy + Allopurinol	Standard Therapy + Quercetin
Age, years	51.11 ± 0.74	53.13 ± 0.74	51.44 ± 0.99
Female, %	17.14 ± 4.50	21.74 ± 8.60	22.22 ± 8.00
Male, %	82.86 ± 4.50	78.26 ± 8.60	77.78 ± 8.00
Stable angina, functional class II, %	27.14 ± 5.32	8.70 ± 5.88	37.04 ± 9.29
Stable angina, functional class III, %	72.86 ± 5.32	91.30 ± 5.88 ●*	62.96 ± 9.29
Q-wave myocardial infarction (history), %	44.29 ± 5.94	65.22 ± 9.93 *	25.93 ± 8.43
Non–Q-wave myocardial infarction (history), %	14.29 ± 4.18	8.70 ± 5.88 *	33.33 ± 9.07
Arterial hypertension, %	74.29 ± 5.22	82.61 ± 7.90	81.48 ± 7.48

Note: ● – statistically significant difference between the standard therapy group and the standard therapy + allopurinol group ($p < 0.05$);

*– statistically significant difference between the standard therapy + allopurinol group and the standard therapy + quercetin group ($p < 0.05$).

infarction was significantly more frequent in patients receiving quercetin ($p < 0.05$ in comparison between standard therapy + allopurinol and standard therapy + quercetin). Our results indicate that blood pressure normalization was observed in all treatment groups ($p < 0.001$ for all). However, the reduction in systolic blood pressure was significantly more pronounced with the addition of either allopurinol or quercetin (Δ% −13.03 ± 2.49 vs. −25.58 ± 5.82%, $p < 0.05$ for standard therapy vs. allopurinol; Δ% −13.03 ± 2.49 vs. −23.20 ± 4.29%, $p < 0.05$ for standard therapy vs. quercetin).

Echocardiographic analysis showed a significant increase in left ventricular ejection fraction (LVEF) with the addition of allopurinol ($p < 0.001$) and quercetin (p

< 0.05). However, the increase in systolic function was significantly greater in the allopurinol group (Δ% +3.88 ± 1.31 vs. +14.19 ± 4.28%, p < 0.05 compared to standard therapy), while quercetin showed only a non-significant trend toward improvement (Δ% +3.88 ± 1.31 vs. +6.23 ± 2.65%, p > 0.2).

Regression of left ventricular hypertrophy was significant in the allopurinol group (p < 0.05), with a greater reduction in left ventricular myocardial mass (Δ% −4.77 ± 1.67 vs. −14.18 ± 4.39%, p < 0.05 for standard therapy vs. allopurinol). Quercetin also contributed to a more pronounced decrease in myocardial mass (Δ% −4.77 ± 1.67 vs. −19.22 ± 6.21%, p < 0.05 for standard therapy vs. quercetin), though full regression of LV hypertrophy was not achieved (p > 0.1).

Subsequent evaluation of bicycle ergometry data clearly demonstrated that improvement in coronary reserve was most pronounced with allopurinol. Increases in threshold workload were significantly higher in the allopurinol group compared to quercetin (Δ% +97.15 ± 3.47 vs. +41.21 ± 9.47%, p < 0.001), and also when compared to standard therapy (Δ% +2.15 ± 1.73 vs. +97.15 ± 3.47%, p < 0.001). Likewise, quercetin significantly outperformed standard therapy alone (Δ% +2.15 ± 1.73 vs. +41.21 ± 9.47%, p < 0.001).

Physical exercise tolerance improved more substantially with allopurinol compared to quercetin (Δ% +68.33 ± 9.70 vs. +46.21 ± 5.59%, p < 0.05), and compared to standard therapy (Δ% +9.65 ± 3.53 vs. +68.33 ± 9.70%, p < 0.001). Quercetin also significantly improved tolerance compared to standard therapy (Δ% +9.65 ± 3.53 vs. +46.21 ± 5.59%, p < 0.001).

Exercise-induced ischemia was reduced significantly more in both the allopurinol and quercetin groups than in the standard therapy group (Δ% −11.54 ± 4.29 vs. −39.58 ± 12.50%, p < 0.05 for standard therapy vs. allopurinol; Δ% −11.54 ± 4.29 vs. −38.89 ± 13.14%, p < 0.05 for standard therapy vs. quercetin).

The next stage involved analyzing the dynamics of blood biochemical parameters. A statistically significant reduction in total cholesterol levels was observed across all treatment groups (p < 0.05 for the standard therapy group; p < 0.001 for both the allopurinol and quercetin groups). However, the improvement in dyslipidemia was

significantly more pronounced with the addition of allopurinol (Δ% −8.41 ± 2.61 vs. −25.47 ± 7.79%, $p < 0.05$ when comparing standard therapy vs. allopurinol), whereas the addition of quercetin resulted in a non-significant trend toward greater cholesterol reduction (Δ% −8.41 ± 2.61 vs. −20.27 ± 5.51%, $p > 0.1$ for standard therapy vs. quercetin). Triglyceride levels also decreased significantly in all treatment groups ($p < 0.001$ in all cases). Once again, the addition of allopurinol led to a more marked and statistically significant reduction (Δ% −20.10 ± 5.87 vs. −51.72 ± 14.47%, $p < 0.05$ for standard therapy vs. allopurinol), while the quercetin group showed a similar but statistically non-significant trend (Δ% −20.10 ± 5.87 vs. −39.66 ± 14.32%, $p > 0.1$ for standard therapy vs. quercetin).

Significant reductions in serum uric acid and creatinine levels were also recorded in both the allopurinol and quercetin groups ($p < 0.001$ in all cases). In contrast, patients in the standard therapy group exhibited significant increases in both uric acid and creatinine levels ($p < 0.001$ for both). Notably, the reduction in uric acid was significantly more substantial with allopurinol (Δ% −57.09 ± 19.75 vs. −14.56 ± 7.86%, $p < 0.05$), although the reduction in creatinine levels was not significantly different between the allopurinol and quercetin groups (Δ% −30.98 ± 13.28 vs. −14.07 ± 7.71%, $p > 0.1$).

The administration of quercetin and allopurinol significantly reduces the levels of amino-terminal propeptide of natriuretic peptide in patients ($p<0.001$ in the standard therapy + allopurinol group, $p<0.05$ in the standard therapy + quercetin group). Allopurinol demonstrated the greatest efficacy in reducing this biomarker, with a relative decrease of Δ% -12.54±4.49%, compared to -62.79±21.08% ($p<0.05$) when comparing the standard therapy group versus the standard therapy + allopurinol group, and Δ% -12.54±4.49% versus -54.75±17.71% ($p<0.05$) when comparing the standard therapy group versus the standard therapy + quercetin group.

Based on the obtained data, a significant reduction in C-reactive protein (CRP) levels was observed only with the addition of allopurinol to standard therapy ($p<0.001$). This reduction was notably more pronounced in the standard therapy + allopurinol group (Δ% -16.70±5.28) compared to the standard therapy group (Δ% -62.41±16.99,

p<0.05) and significantly greater than in the standard therapy + quercetin group (Δ% -62.41±16.99 vs. -31.61±12.41%, p>0.1).

Furthermore, the addition of allopurinol or quercetin to standard therapy resulted in a more pronounced reduction in systolic blood pressure (Δ%, p<0.05 in the comparison between standard therapy vs. standard therapy + allopurinol, and p<0.05 in the comparison between standard therapy vs. standard therapy + quercetin).

Echocardiographic data (EchoCG) revealed that the addition of allopurinol (p<0.001) and quercetin (p<0.05) to standard therapy significantly increased left ventricular ejection fraction, with a notably greater enhancement in systolic function in the allopurinol group (Δ%, p<0.05 in the comparison between standard therapy vs. standard therapy + allopurinol) and a trend towards improvement in the quercetin group (Δ%, p>0.2 in the comparison between standard therapy vs. standard therapy + quercetin). Additionally, the inclusion of allopurinol in the therapeutic regimen significantly reduced left ventricular hypertrophy (p<0.05), with a more substantial decrease in left ventricular myocardial mass (Δ%, p<0.05 in the comparison between standard therapy vs. standard therapy + allopurinol).

Moreover, the addition of allopurinol resulted in the most pronounced increase in coronary reserve during paired bicycle ergometry, demonstrated by a significant rise in peak exercise tolerance (Δ%, p<0.001 in the comparison between standard therapy + allopurinol vs. standard therapy + quercetin, and Δ%, p<0.001 in the comparison between standard therapy vs. standard therapy + allopurinol), as well as increased exercise capacity (Δ%, p<0.05 in the comparison between standard therapy + allopurinol vs. standard therapy + quercetin, and Δ%, p<0.001 in the comparison between standard therapy vs. standard therapy + allopurinol). Additionally, both allopurinol and quercetin demonstrated a significant reduction in exercise-induced ischemia (Δ%, p<0.05 in the comparison between standard therapy vs. standard therapy + allopurinol, and Δ%, p<0.05 in the comparison between standard therapy vs. standard therapy + quercetin).

The addition of allopurinol to the treatment regimen significantly reduced total cholesterol levels (Δ%, p<0.05 in the comparison between the standard therapy group

vs. the standard therapy + allopurinol group) and triglyceride levels (Δ%, $p<0.05$ in the comparison between the standard therapy group vs. the standard therapy + allopurinol group), with a non-significant trend towards further reductions when quercetin was included (Δ%, $p>0.1$ in both comparisons: standard therapy vs. standard therapy + quercetin).

Adding allopurinol and quercetin to the treatment regimen also significantly reduced serum uric acid and creatinine levels ($p<0.001$ in both cases), with a more pronounced reduction in uric acid observed in the allopurinol group (Δ%, $p<0.05$).

The administration of quercetin and allopurinol resulted in a significant decrease in amino-terminal propeptide of natriuretic peptide levels ($p<0.001$ in the standard therapy + allopurinol group, $p<0.05$ in the standard therapy + quercetin group), with allopurinol demonstrating the greatest effect in reducing this biomarker (Δ%, $p<0.05$ in both comparisons: standard therapy vs. standard therapy + allopurinol, and standard therapy vs. standard therapy + quercetin). A significant reduction in C-reactive protein (CRP) levels was also observed with the addition of allopurinol to standard therapy ($p<0.001$).

Thus, the inclusion of allopurinol in the standard therapy for stable angina in patients with asymptomatic hyperuricemia enhances systolic function and promotes regression of left ventricular hypertrophy, while also positively influencing inflammatory activity, as reflected by reduced baseline CRP levels. The addition of allopurinol or quercetin to standard therapy for stable angina also improves coronary reserve, increases peak exercise capacity, enhances physical activity tolerance, and reduces exercise-induced ischemia during bicycle ergometry. It further normalizes dyslipidemia by reducing total cholesterol and triglyceride levels and improves renal function through decreased creatinine levels, with a more pronounced effect observed for allopurinol.

Additionally, the use of allopurinol or quercetin as part of standard therapy for stable angina can lead to more substantial reductions in baseline blood pressure and amino-terminal propeptide of natriuretic peptide levels, with no significant difference in the magnitude of these effects between the two agents.

Criteria for the addition of allopurinol in patients with stable angina and asymptomatic hyperuricemia should include the presence of left ventricular hypertrophy, reduced coronary reserve, increased inflammatory activity, and dyslipidemia with elevated total cholesterol and triglycerides.