

Effects of Uric Acid Lowering Therapy in Patients With Essential Arterial Hypertension

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Abstract

Background

Asymptomatic hyperuricemia (AHU) is defined as elevated serum uric acid (UA) concentration without symptoms. This study aimed to determine the effects of AHU treatment with allopurinol on selected hypertension mediated organ damage (HMOD) indices in patients with uncomplicated essential arterial hypertension (AH).

Methods

Patients aged 30-70 years with AHU and essential hypertension grade 1-2 with adequate blood pressure (BP) control, without previous urate lowering therapy (ULT) were divided into two groups: a) receiving allopurinol (ULT group) and b) age-and sex matched patients without ULT (control group). Both groups received UA-lowering diet. BP (office, 24 hour and central), echocardiographic parameters, pulse-wave velocity, carotid intima-media thickness (IMT) and lab tests (high-sensitivity C-reactive protein (hs-CRP) were measured at baseline and at 6 months follow-up.

Results

Out of 100 participants 87 completed the study (44 ULT patients and 43 controls). At 6 months follow-up, there was a significantly greater reduction in serum UA concentration in the ULT group than in the control group ($464 \pm 68.8 \mu\text{mol/l}$ vs $314 \pm 55.6 \mu\text{mol/l}$, $p < 0.0001$). Patients receiving allopurinol had significant reductions in office systolic ($137 \pm 11.8 \text{ mmHg}$ vs $134 \pm 9.3 \text{ mmHg}$; $p = 0.025$) and diastolic BP ($83 \pm 9.9 \text{ mmHg}$ vs $79 \pm 8.7 \text{ mmHg}$, $p = 0.017$), central systolic BP ($56 \pm 8.9 \text{ mmHg}$ vs $51 \pm 12.9 \text{ mmHg}$, $p = 0.046$), pulse pressure ($43 \pm 10.4 \text{ mmHg}$ vs $39 \pm 11.2 \text{ mmHg}$, $p = 0.017$), IMT ($0.773 \pm 0.121 \text{ mm}$ vs $0.752 \pm 0.13 \text{ mm}$, $p = 0.044$), left atrium volume index ($40 \pm 13.5 \text{ ml/m}^2$ vs $38 \pm 12.3 \text{ ml/m}^2$, $p = 0.044$), and hs-CRP level ($3.36 \pm 2.73 \text{ mg/l}$ vs $2.74 \pm 1.91 \text{ mg/l}$, $p = 0.028$) compared to controls. The decrease in UA concentration was significantly related to the reduction in IMT ($R = 0.37$, $p < 0.001$), central SBP ($R = 0.26$, $p = 0.015$) and hs-CRP concentration ($R = 0.30$, $p = 0.004$). Multivariate regression analysis revealed the independent relationship between reduction in IMT and UA lowering ($R = 0.3234$, $R^2 = 0.0722$, $p < 0.026$).

Conclusions

In patients with AH and asymptomatic hyperuricemia treatment with allopurinol leads to further improvement in BP control and reduction in HMOD intensity, in particular IMT. The decrease in hs-CRP concentration associated with ULT may have a beneficial effect on patient long-term prognosis.

Background

Asymptomatic hyperuricemia (AHU) is traditionally defined as elevated serum uric acid (UA) concentration but in which neither symptoms of monosodium urate crystal deposition disease, such as gout, nor uric acid renal disease have occurred [1]. The prevalence of AHU has increased over several

decades and nowadays it affects 16.9% of the adult population [2]. AHU is more common in subjects with arterial hypertension (AH) than in the general population [3,4]. High UA concentration is one of the important factors associated with the development of AH and promotes vascular and renal organ damage [5]. Experimental and epidemiological data reveal associations between hyperuricemia and hypertension, cardiovascular risk, chronic kidney disease (CKD), and metabolic syndrome [6-8]. The risk of coronary artery disease mortality increases by 13% for each 1 mg/dl (60 μ mol/L) increase in UA concentration [9]. However, it is still debatable whether hyperuricemia is an independent cardiovascular risk factor. Numerous clinical disorders associated with high UA serum level support the decision to treat AHU to reduce cardiovascular risk. Some results of previous studies showed beneficial effects of AHU pharmacological treatment such as: decreased concentration of inflammation markers (high-sensitivity C-reactive protein, hs-CRP), reduced carotid intima-media thickness (IMT) [10], reduced levels of oxidative stress markers, improved endothelial function [11], reduced serum creatinine and increased estimated glomerular filtration rate (eGFR) [12] as well as reduced blood pressure (BP) [13]. Allopurinol mainly is used to treat AHU, especially in patients at high cardiovascular risk, but there is no evidence for its effect on hard end-points, and this topic still needs further investigations [14-16]. Nevertheless, Borghi et al. [15] in the "Expert consensus for the diagnosis and treatment of patient with hyperuricemia and high cardiovascular risk" recommend considering treatment of AHU as a part of cardiovascular events prevention when serum UA concentration is ≥ 5 mg/dl (300 μ mol/l) in patients with high cardiovascular risk and when serum UA concentration is ≥ 6 mg/dl (360 μ mol/l) in other patients. Generally, treatment of AHU as a component of cardiovascular prevention is not a gold standard due to the lack of sufficient evidence from clinical studies.

The aim of the study was to determine the effects of AHU treatment with allopurinol on selected Hypertension Mediated Organ Damage (HMOD) indices in patients with uncomplicated essential AH.

Methods

The study population consisted of 562 patients aged 30-70 years, both women and men consecutively admitted to the hypertension outpatient department between September 2017 and March 2018 with: diagnosed AHU defined as a serum UA ≥ 6 mg/dl (360 μ mol/l) [15, 17] and with essential hypertension grade 1 or 2 (BP $\geq 140/90$ and $<180/110$ mmHg) in accordance with the 2018 ESH/ESC guidelines [18] with previously confirmed adequate BP control on antihypertensive treatment (below 140/90 mmHg in office measurements). Patients, who received allopurinol (100-300 mg/day) according to Expert consensus [15] comprised urate lowering therapy (ULT) group (n=50). Then, within 5 days from recruitment of the ULT patient, a control patient with AHU and AH who did not receive allopurinol treatment, with age ± 3 years and preferably the same gender was recruited in a ratio of 1:1 (n=50 cases and n =50 controls). All patients were given the same dietary advice recommended for AH and AHU. All examinations were performed prior to treatment initiation and after 6 months of follow-up.

The exclusion criteria included: any symptoms of monosodium urate crystal deposition disease, especially gout; coronary heart disease (previous myocardial infarction, coronary angioplasty procedure

or coronary artery bypass surgery); symptomatic heart failure more than New York Heart Association (NYHA) class I or reduced ejection fraction < 50%; kidney or liver failure; inflammatory diseases; history of allergy to allopurinol or other serious drug reactions (e.g. Lyell's syndrome); or treatment change during follow-up. Study flowchart is presented in Figure 1.

The study was performed in accordance with the 1975 Declaration of Helsinki for Human Research and approved by the Jagiellonian University Bioethical Committee (No. 122.6120.94.2017 of April 27th, 2017). A written informed consent was obtained from all patients.

Measurement of peripheral blood pressure

All participants underwent physical examination and office BP measurements (mean of three measurements at one-minute intervals) in standard conditions, after 10 minutes rest, in sitting position on the non-dominant arm with the use of the validated Omron M5-I oscillometric device (Omron Healthcare Co., Japan).

24-hour ambulatory BP monitoring (ABPM) was performed using a SpaceLabs 90207 recorder (SpaceLabs Inc, Richmond, Washington, USA) to confirm BP control. Measurements were taken every 15 minutes during daily activity (06:00–22:00h) and every 20 minutes at night-time (22:00– 06:00 h). For further analyses the mean values of the 24-hour, daytime, and night-time systolic (SBP) and diastolic blood pressure (DBP), and heart rate were calculated. BP measurements were performed according to the ESH/ESC guidelines for the management of hypertension [18].

Echocardiographic measurements

Echocardiographic examination using the Vivid®E95 (GE-Healthcare Chicago, IL, USA) device and 2,7-3,6 MHz transducer was performed. Left ventricular mass (LVM) was calculated according to the ASE formula [19, 20]. Left ventricular mass index (LVMI) was calculated $LVM/height^{2.7}$ [21]. Left atrium volume (LAV) was assessed using the modified Simpson's method [22]. Left atrium volume index (LAVI) was calculated as LAV/body surface area. Global longitudinal strain (GLS) by speckle tracking echocardiography was measured as the average value of 18 segments, based on three apical imaging planes [23].

Central blood pressure, pulse wave velocity and intima-media thickness measurements

SphygmoCor (AtCor Medical, Sydney, Australia) device was used to examine arterial stiffness. Carotid-femoral pulse wave velocity (PWV) and central BP in the aorta were measured according to the recommendations of ESH experts [24, 25].

Intima-media thickness (IMT) measurement of common carotid artery was carried out in accordance with the Mannheim consensus with the use of the Vivid®E95 (GE-Healthcare Chicago, IL, USA) and a 10 MHz linear transducer. After at least 10 minutes of patient rest in supine position, good-quality B-mode ultrasound images of left and right common carotid arteries were recorded during five consecutive heart

cycles. The intima - media thickness (IMT) of the far wall was measured offline using EchoPAC workstation software. Automatic IMT measurement was based on tracing of 1 cm (starting about 1 cm proximally from bifurcation) of the leading edge of the intima surface and the leading edge of the adventitia surface followed by multiple measurements between pairs of pixels located on both traces. Mean IMT was calculated as the average of the left and right IMT [26].

Other measurements

In all patients medical history was collected including concomitant diseases, smoking and drinking habits and the use of medications. Laboratory tests: serum concentrations of uric acid, creatinine, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and hs-CRP were also obtained at the initial visit.

All performed examinations and laboratory tests were then repeated after 6 months of follow-up.

Statistical analyses

Data are presented as means and standard deviations (SD) and medians and interquartile ranges in cases where nonparametric tests were used. To determine the study sample, we chose as optimal parameter the IMT because of the association with atherosclerosis, BP and potential reversibility during ULT. The analysis showed that to determine a 0.1 mm difference in IMT with mean value of 0.9 and SD of 0.16 mm [27, 28] with a power of 80% and with a significance of $p=0.05$, using the two-tailed test, the population of 42 people in each group is required. Normality of variables distribution was tested and, if confirmed, parametric tests were used. When studied variables did not have normal distribution nonparametric tests were used. Between group differences were evaluated using Student's t-test, Mann-Whitney U test or chi-squared test, as appropriate. To assess the effects of the therapy the repeated-measures t-test, Wilcoxon signed-rank test, ANCOVA and the association between variables using the Spearman rank correlation were used. Univariate and multivariate regression analyses were used to determine the influence of independent factors on IMT. P-values <0.05 were considered statistically significant for all tests. Statistical analyses were performed using STATISTICA software (StatSoft, Poland), version 13.1.

Results

The flow of participants in the study is presented in Figure 1.

The final analysis included 87 patients: 44 in the ULT group (20 females and 24 males) and 43 in the control group (23 females, 20 males). During the study follow-up, 13 patients ($n=6$ in the ULT group, $n=7$ in the control group) were withdrawn from the study due to the need of antihypertensive therapy modification or lack of follow-up appointment. There were no significant differences in studied parameters at baseline visit between patients who dropped out and those who completed the study.

Baseline characteristics

Baseline characteristics of the study patients are presented in Table 1.

There were no significant differences between the ULT group and the control group in age, sex distribution, and baseline serum UA concentration ($p=0.054$). However, they did differ in BMI and total cholesterol (see Tables 1 and 2).

The effects of uric acid lowering therapy

In this study, ULT was safe and no treatment-related adverse effects were observed.

Biochemistry

Changes in laboratory parameters from baseline to 6 months follow-up in both groups are summarized in Table 2. Urate-lowering therapy with the use of allopurinol 100-300 mg daily (mean 184 ± 91.3 mg, median 150 (100; 300) mg) in the ULT group was associated with a significant reduction in serum uric acid concentration level (464 ± 68.8 vs. 314 ± 55.6 $\mu\text{mol/l}$; $p<0.001$). In the control group a small albeit statistically significant reduction in serum UA concentration was observed (437 ± 61.1 vs. 426 ± 56.9 $\mu\text{mol/l}$, $p=0.044$). Compared to controls, there was a significant reduction in hs-CRP levels in the ULT group at 6 months follow-up.

Blood pressure

Baseline office and central BPs were higher in the ULT group than in the control group, however the unadjusted decline in DBP at 6 months follow-up in the ULT group was significantly higher compared to controls (Figure 2).

The ANCOVA analysis corrected for baseline BP values showed no differences between study groups in observed BP decrease after 6 months observation.

HMOD

Among the assessed echocardiographic parameters, significant reductions in LAV and LAVI were noticed in the ULT group at 6 months follow-up (Table 4). There were no comparable changes in the echocardiographic parameters in the control group at follow-up.

Compared to the control group, there was a significant reduction in carotid IMT in the ULT group at 6 months follow-up (Figure 3, Table 4).

In our study, UA lowering therapy had no effect on the change in arterial stiffness determined by PWV (Table 4).

The magnitude of reduction in IMT, CRP, LAVI, and UA was greater in the ULT group than in the control group (Figure 2).

In all patients, the amount of reduction in serum UA concentration was related to the reduction in IMT ($R=0.37$, $p<0.001$) (Figure 4), central SBP ($R=0.26$, $p=0.015$), TG ($R=0.31$, $p=0.003$), hs-CRP concentration ($R=0.30$, $p=0.004$), LAV ($R=0.35$, $p<0.001$), LAVI ($R=0.35$, $p<0.001$), and with an increase in E wave ($R=-0.27$, $p=0.012$), and E wave deceleration time ($R=-0.26$, $p=0.017$).

The multivariate regression analyses showed a significant association between UA lowering and IMT reduction in the entire study group after adjustment for changes in LDL and PP values (the known pathophysiological factors influencing IMT) ($R=0.3234$, $R^2=0.0722$, $p<0.026$).

Discussion

The 2018 ESC/ESH Guidelines for the management of arterial hypertension recommend routine measurement of serum UA as part of the screening in hypertensive patients, because elevated UA level is independently associated with increased cardiovascular risk in both hypertensive patients and general population [18]. Reduction in serum UA concentration with ULT may have an impact on the reduction in parameters related to cardiovascular risk such as IMT, LAVI or serum hs-CRP level. In a three-year randomized parallel-controlled study in patients with type 2 diabetes and AHU, Liu et al. found that effective control of the serum UA level with allopurinol therapy decreases the serum hs-CRP level and carotid IMT [10]. Our study demonstrates that UA lowering therapy is associated with a significant reduction in hs-CRP and IMT in patients with hypertension, however in a substantially shorter duration (i.e. 6 months). Based on these results, the reduction in hs-CRP indicates that ULT has an anti-inflammatory effect likely to explain the accompanying reduction in carotid IMT which is a surrogate marker for atherosclerosis, commonly known as a chronic inflammatory disease.

In a study by Higgins et al. one-year treatment with allopurinol at a dose of 300 mg daily resulted in a decrease in central SBP and augmentation index, and prevented progression in IMT in patients following ischemic stroke or transient ischemic attack (TIA) [27].

Carotid IMT has been shown to predict cardiovascular risk in multiple large studies [29], however its reproducibility and usefulness in daily practice is limited [18]. In our study we used an automatic IMT measuring technique (using multiple measurement points) to increase the accuracy and repeatability of measurements according to the Mannheim consensus [26].

Our study found a significant reduction in office (SBP, DBP, PP) and central (SBP, PP) BP values but not in ambulatory BP values in the ULT group. Our findings suggest that treatment with allopurinol is safe and despite the minor impact on ambulatory BP levels (Table 3), UA lowering therapy significantly improves HMOD even after a relatively short time of treatment. Limited office BP changes following allopurinol therapy in our study may result from adequate BP control at baseline and short study duration in the ULT group (6 months) compared to a longer (3 years) study by Liu et al. [10].

While most available data indicate that allopurinol reduces BP regardless of antihypertensive drugs, the underlying mechanism is not clear [13]. In the meta-analysis of 15 randomized controlled trials performed in patients with hyperuricemia, with length of follow-up from 2 to 23 months, allopurinol decreased BP and creatinine level [30]. A sub-analysis revealed that allopurinol significantly decreased SBP irrespective of antihypertensive drug therapy, however a decrease in DBP was only observed in patients receiving antihypertensive drugs. In patients receiving combination of antihypertensive drugs and allopurinol in a dose ≤ 300 mg/day the reduction in SBP was larger compared to patients receiving allopurinol at higher dose (>300 mg/day) [30].

A further interesting finding derived from our study is a significant reduction in left atrium volume index, likely as a result of the decrease in central BP (afterload) following ULT.

The noticeable decrease in UA concentration in the ULT group is comparable to previous studies [10], confirming the adherence to drug therapy. Interestingly, a slight, but significant decrease in UA concentration was also present in the control group indicating that patients follow a dietary advice which previously has proven its efficacy. In the study by Rai et al. the Dietary Approaches to Stop Hypertension (DASH) diet resulted in up to 32% reduction in the incidence of gout over the 26-year follow-up (HR 0.68, 95% CI 0.57-0.80, p value for trend <0.001) [31].

Previous studies found a strong relationship with systemic inflammation even in the absence of gout [32]. Moreover, serum urate was found to independently predict changes in circulating CRP [33]. Indeed, allopurinol treatment was associated with a decrease in hs-CRP and insulin resistance in patients with AHU [34]. Our findings support this observation documenting a reduction in hs-CRP in the ULT group and a significant association between changes in hs-CRP and serum UA level.

Findings related to BP changes following allopurinol therapy are inconsistent. A study by Jalal et al. conducted in chronic kidney disease (CKD) patients found that a 3-month therapy with allopurinol had no effects on BP levels, inflammation and oxidative stress markers compared to placebo [35]. In contrast, a study by Kanbay et al. has shown that a 4-month treatment with allopurinol led to a decrease in SBP and an increase in flow-mediated dilation and eGFR in patients without CKD [36]. Different results in both studies on BP changes during allopurinol treatment are likely to be explained by advanced and irreversible atherosclerotic changes in the arteries in high risk CKD patients. In line with this observation, our study population was limited to patients with essential hypertension grade 1 or 2 without previous history of coronary heart disease, CKD or symptomatic heart failure. In our opinion patients with potentially reversible cardiovascular changes are most likely to receive the greatest benefits from intensive ULT used in parallel with the modification of other cardiovascular risk factors as part of primary prevention of ischemic heart disease. We have previously shown that a higher UA concentration via higher serum matrix metalloproteinase (MMP) 3 enhances selected HMOD, especially carotid IMT in patients with AH [37]. Extracellular MMPs are part of inflammation leading to the degradation of collagen, vessel remodelling and atherosclerotic plaque rupture [38,39]. It is still the matter of controversy whether

hyperuricemia is only a biomarker of cardiovascular risk or a direct factor attributable to the harmful effects on cardiovascular system [40].

The study limitations

A small sample size could be viewed as a study limitation. However, all patients enrolled in this study were comprehensively phenotyped concerning BP levels and associated HMOD to determine the true effects of allopurinol therapy. Secondly, the short length of follow-up may limit our findings, however the study duration was planned based on available data and allopurinol efficacy.

Conclusions

Allopurinol in patients with arterial hypertension and hyperuricemia decreases blood pressure and, in a relatively short time, seems to favourably influence hypertension-mediated organ damage, in particular intima-media thickness. Our findings indicate that the beneficial effects of urate lowering therapy with allopurinol on blood pressure and organ damage may result from anti-inflammatory and anti-atherosclerotic actions, with a potential impact on long-term patient outcomes Further prospective studies in larger patient groups are required to support our findings.

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the 1975 Declaration of Helsinki for Human Research and approved by the Jagiellonian University Bioethical Committee (No. 122.6120.94.2017 of April 27th, 2017). A written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

Funding

Not applicable.

Authors' contributions

K.G. and M.R. designed the study. K.G., T.D., W.W., P.J., M.T., M.B., D.H., G.B. and MR wrote the main manuscript text. K.G., T.D. and M.R. recruited patients for the study. K.G., T.D., W.W., and M.T. and G.B. performed statistical analyses. M.T., M.B. and D.H. prepared figures 1 and 3. W.W. and P.J. prepared figures 2 and 4. All authors reviewed the manuscript.

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List Of Abbreviations

ABPM: ambulatory blood pressure monitoring; AH: arterial hypertension; AHU: asymptomatic hyperuricemia; ANOVA: analysis of variance; BP: blood pressure; CKD: chronic kidney disease; E: early ventricular filling velocity; E/e': early diastolic mitral annulus velocity ratio; eGFR: estimated glomerular filtration rate; ESC: European Society of Cardiology; ESH: European Society of Hypertension; GLS: left ventricular global longitudinal strain; HDL: high-density lipoprotein cholesterol; HMOD: hypertension mediated organ damage; hs-CRP: high sensitivity C- reactive protein; IMT: carotid intima-media thickness; IVRT: isovolumic relaxation time; LAVI: left atrium volume index; LDL: low-density lipoprotein cholesterol; LVM: left ventricular mass; NHANES: National Health and Nutrition Examination Survey; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NYHA: New York Heart Association; PP: pulse pressure; PWV: carotid-femoral pulse wave velocity; SBP: systolic blood pressure; TG: triglycerides; UA: uric acid; ULT: urate-lowering therapy.

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Tables

Table 1. Baseline clinical data in the i urate-lowering therapy (ULT) and control groups.

Characteristics	Study population N=87	ULT group N=44	Control group N=43	P
Anthropometrics				
Age [years]				
median	62 (50.5; 68)	62 (48,5; 69)	62 (53; 67)	0.699*
mean	57.8 ± 12.3	57.6 ± 12.9	57.9 ± 11.7	0.918
Female [<i>n</i> (%)]	43 (50.59%)	20 (45.45%)	23 (53.49%)	0.454#
Body mass index [kg/m ²]	27.9 ± 4.2	29.1 ± 4	26.7 ± 4.2	0.008
Risk factors [<i>n</i> (%)]				
Current smoking	15 (17.24%)	7 (15.91%)	8 (18.6%)	0.739#
Alcohol intake	20 (23%)	11 (25%)	9 (20.93%)	0.651#
Regular physical activity	31 (35.63%)	12 (27.27%)	19 (44.19%)	0.099#
Hypercholesterolemia	57 (65.52%)	29 (65.91%)	28 (65.12%)	0.938#
Diabetes	16 (18.39%)	9 (20.45%)	7 (16.28%)	0.615#
Hypertension treatment				
Antihypertensive medication use [<i>n</i> (%)]	87 (100%)	44 (100%)	43 (100%)	1.000#
Number of antihypertensive drugs	2 (1;3) 2.5 ± 1.2	3 (1;3) 2.5 ± 1.2	3 (1;3) 2.5 ± 1.2	0.972*
Time of hypertension treatment [years]	13.6 ± 8.4	15 ± 8.2	13 ± 8.1	0.147

Values presented as mean ± standard deviation or median (25th; 75th percentile).

* Mann-Whitney U test

chi-squared test

Table 2. Longitudinal changes in laboratory parameters in the urate-lowering therapy (ULT) and control groups.

	ULT group			Control group		
	N=44			N=43		
	Baseline	Follow-up	P	Baseline	Follow-up	P
Uric acid [$\mu\text{mol/l}$]	464 \pm 68.8	314 \pm 55.6	<0.0001	437 \pm 61.1	426 \pm 56.9	0.044
eGRF [ml/min/1,75m ²]	80 \pm 18.6	80 \pm 18.1	0.935	87 \pm 20.1	89 \pm 20.7	0.125
Lipids						
Total cholesterol [mmol/l]	4.3 \pm 0.77	4.3 \pm 0.97	0.829	4.7 \pm 0.86[#]	4.7 \pm 0.77	0.841
LDL cholesterol [mmol/l]	2.2 \pm 0.62	2.2 \pm 0.79	0.703	2.4 \pm 0.74	2.5 \pm 0.69	0.450
HDL cholesterol [mmol/l]	1.43 (1.18; 1.77) 1.46 \pm 0.4	1.47 (1.2; 1.76) 1.46 \pm 0.38	0.163*	1.38 (1.11; 1.64) 1.43 \pm 0.46	1.36 (1.12; 1.6) 1.42 \pm 0.41	0.888*
Triglycerides [mmol/l]	1.36 \pm 0.54	1.31 \pm 0.56	0.374	1.7 \pm 1.04	1.76 \pm 0.91	0.048
NT-proBNP [pg/ml]	88 (46; 221) 165 \pm 180.1	128 (40; 212) 154 \pm 173	0.548*	67 (38; 131) 95 \pm 67.3	73 (40; 153) 92 \pm 60	0.845*
hs-CRP [mg/l]	2.65 (1.4; 5)	2.16 (1.45; 3.58)	0.028*	1.23 (1; 3.2)	1.31 (0.9; 3.41)	0.682*

3.36 ± 2.73	2.74 ± 1.91	1.92 ± 1.28[#]	2 ± 1.44
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Values presented as mean ± standard deviation or median (25th; 75th percentile).

[#] differences between ULT group and control group at baseline (p<0,05) * Mann-Whitney U test

eGFR – estimated glomerular filtration rate, LDL – low density lipoprotein, HDL – high density lipoprotein, NT-proBNP – N-terminal pro hormone B-type natriuretic peptide, hs-CRP – high-sensitivity C-reactive protein

Table 3. Longitudinal changes in blood pressure in the urate-lowering therapy (ULT) and control groups.

	ULT group N=44			Control group N=43		
mmHg	Baseline	Follow-up	P	Baseline	Follow-up	P
Peripheral haemodynamics						
Office SBP [mmHg]	137 ± 11.8	134 ± 9.3	0.025	133 ± 11.5	131 ± 11.3	0.383
Office DBP [mmHg]	83 ± 9.9	79 ± 8.7	0.017	79 ± 8.6[#]	78 ± 8.9	0.665
Office PP [mmHg]	56 ± 8.9	51 ± 12.9	0.046	55 ± 14.9	54 ± 14.4	0.626
Central haemodynamics						
Central SBP [mmHg]	129 ± 12	123 ± 11.8	0.004	123 ± 10.2 [#]	122 ± 9.6	0.787
Central DBP [mmHg]	87 ± 10	85 ± 9.4	0.217	82 ± 8.3 [#]	82 ± 9.2	0.913
Central PP [mmHg]	43 ± 10.4	39 ± 11.2	0.017	42 ± 11.5	41 ± 10.7	0.723
ABPM 24 hours						
24 h SBP [mmHg]	119 ± 9.6	120 ± 9.7	0.368	115 ± 9.3	116 ± 8.9	0.399
24 h DBP [mmHg]	72 ± 7.4	72 ± 6.6	0.555	71 ± 7	71 ± 7.4	0.766
24 h PP [mmHg]	46 ± 7.2	48 ± 8.0	0.099	44 ± 6.5	45 ± 7.4	0.574
ABPM daytime						
Day SBP [mmHg]	125 ± 8.2	125 ± 8.8	0.984	120 ± 9.7	120 ± 10.1	0.431
Day DBP [mmHg]	76 ± 7.8	76 ± 6.2	0.725	75 ± 6.7	75 ± 7.8	0.868
Day PP [mmHg]	48 ± 7.7	48 ± 7.3	0.925	45 ± 7.2	45 ± 7.9	0.442

ABPM nighttime						
Night SBP [mmHg]	111 ± 10.7	112 ± 10.4	0.410	106 ± 9.1 [#]	106 ± 9.1	0.541
Night DBP [mmHg]	65 ± 8.6	65 ± 7.5	1.000	62 ± 7.1	63 ± 7.1	0.477
Night PP [mmHg]	47 ± 8.8	48 ± 7.8	0.321	43 ± 7.3	43 ± 7.7	0.951

Values presented as mean ± standard deviation.

[#] differences between ULT group and control group at baseline (p<0.05)

ABPM - ambulatory blood pressure monitoring, PP – pulse pressure. 24 h – 24 hour

Table 4. Longitudinal changes in echocardiographic parameters, pulse wave velocity (PWV) and carotid intima-media thickness (IMT) in the urate-lowering therapy (ULT) and control groups.

	ULT group N=44			Control group N=43		
	Baseline	Follow-up	P	Baseline	Follow-up	P
Echocardiography						
LVMI [g/m ²] *	109 (94.9; 121.3) 112 ± 31.5	105 (93.4; 117.5) 108 ± 24.8	0.069	95 (81.5; 117.3) 99 ± 24.7	96 (76.1; 111.4) 98 ± 25.9	0.648
LVMI [g/m ^{2.7}] *	48 (44.2; 57.8) 53 ± 17.0	48 (41.7; 55.5) 51 ± 14.3	0.056	42 (33.6; 57.0) 45 ± 13.7	42 (34.2; 53.4) 45 ± 14.2	0.682
LVM [g] *#	206 (179.1; 234.8) 216 ± 66.2	200 (177.9; 227.1) 209 ± 52.4	0.053	176 (151.8; 213.2) 184 ± 49.9	181.4 (148.1; 206.4) 184 ± 52.2	0.756
LAVI [ml/m ²] #	40 ± 13.5	38 ± 12.3	0.044	34 ± 8.9	36 ± 8.6	0.009
LAV [ml]	77 ± 26.8	74 ± 23.2	0.044	65 ± 19.5	67 ± 19.2	0.009
IVRT [ms] *	91 (82.5; 106.5) 96.6 ± 23.1	103 (87; 122) 103 ± 24	0.016	91 (75; 103) 85 ± 27	98 (86; 111) 97 ± 20.2	0.003

EF [%]	62 ± 5.1	62 ± 5.5	0.311	62 ± 5.9	62 ± 4.9	0.229
GLS [%]*	-19.2 (-18.1; -19.9)	-18.9 (-18.3; -20.5)	0.769	-20 (-18.7; -21)	-20 (-19; -20.2)	0.885
	-19.3 ± 2.2	-19.2 ± 2.2		-20 ± -1.7	-20 ± 1.3	
Arterial stiffness						
PWV [m/s] *	7.8 (7; 10)	7.8 (7.1; 9.6)	0.109	7.6 (6.8; 9.1)	8.1 (7.1; 8.9)	0.691
	8.6 ± 2	8.3 ± 1.7		8 ± 1.5	8.1 ± 1.3	
Carotid ultrasound						
IMT [mm]	0.773 ± 0.121	0.752 ± 0.130	0.044	0.729 ± 0.133	0.734 ± 0.130	0.330

Values presented as mean ± standard deviation or median (25th; 75th percentile).

* Mann-Whitney U test

differences between ULT group and control group at baseline (p<0,05)

LVMI – left ventricular mass index, LVM – left ventricular mass, LAVI – left atrium volume index, LAV – left atrium volume, IVRT – isovolumic relaxation time, EF – left ventricular ejection fraction, GLS – left ventricular global longitudinal strain, PWV – carotid-femoral pulse wave velocity, IMT – intima-media thickness

Figures

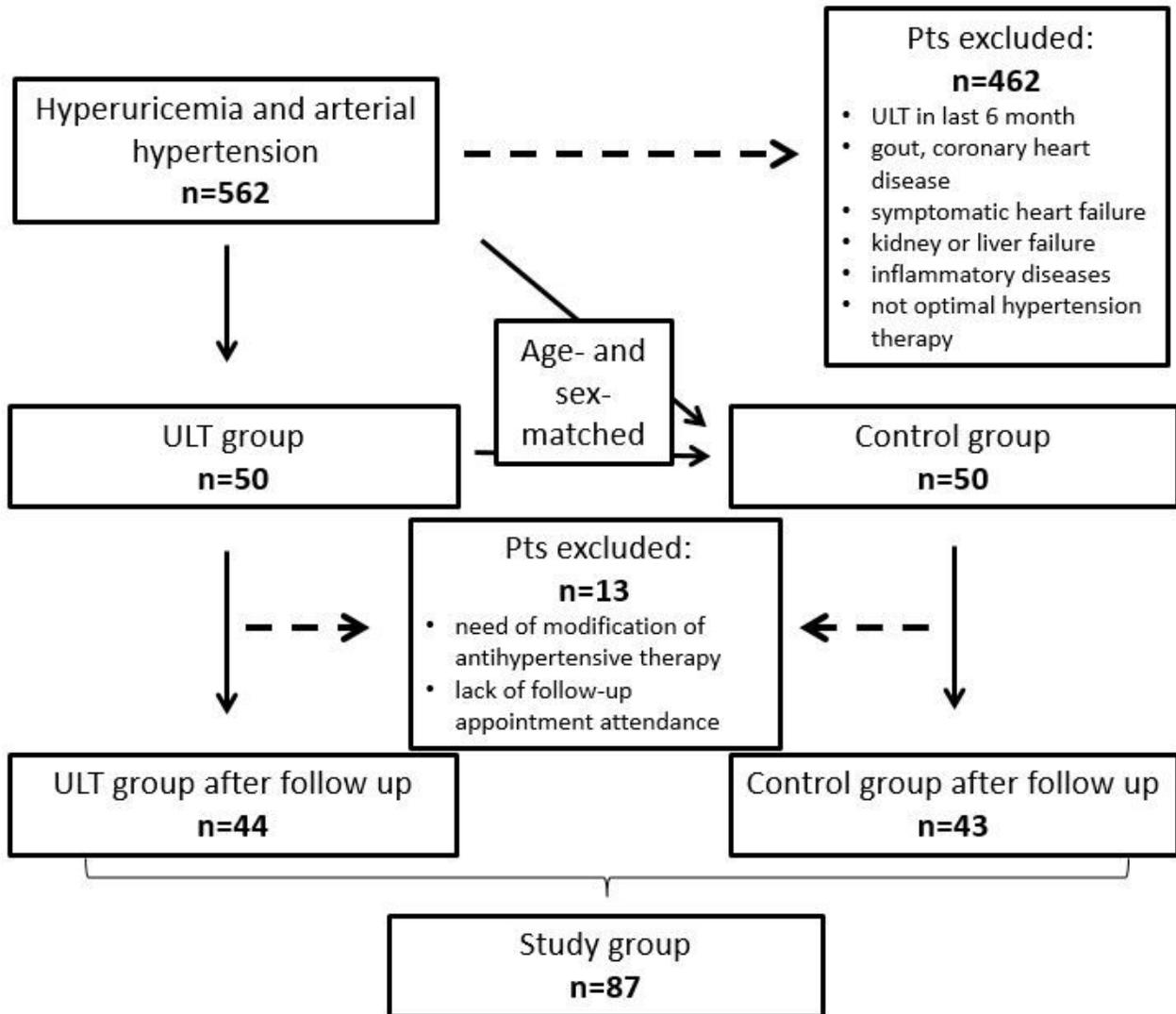


Figure 1

Study flowchart ULT – urate lowering therapy

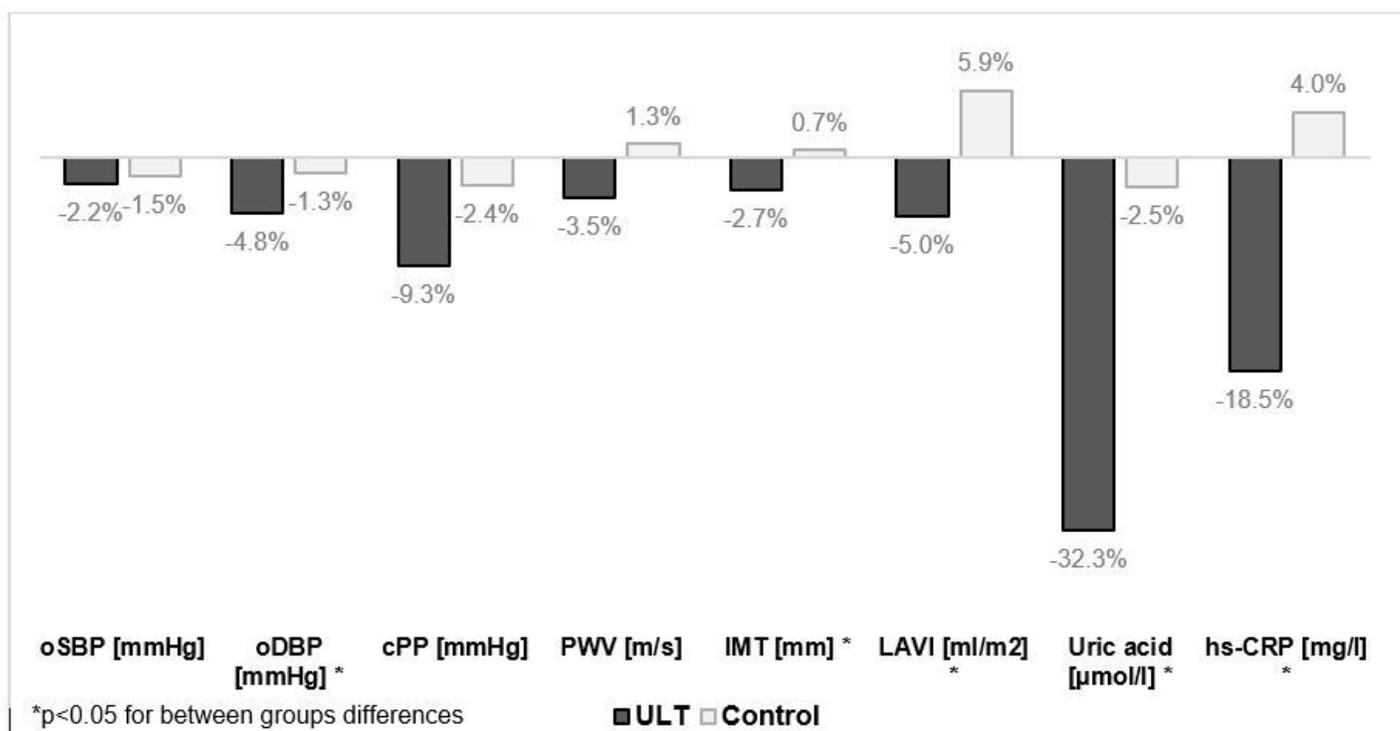


Figure 2

Relative to baseline level changes (presented as percentage) in selected parameters in the urate-lowering therapy (ULT) and control groups. oSBP – office systolic blood pressure, oDBP – office diastolic blood pressure, cPP – central pulse pressure, PWV – carotid-femoral pulse wave velocity, IMT – carotid intima-media thickness, LAVI – left atrium volume index, hs-CRP – high sensitivity C- reactive protein

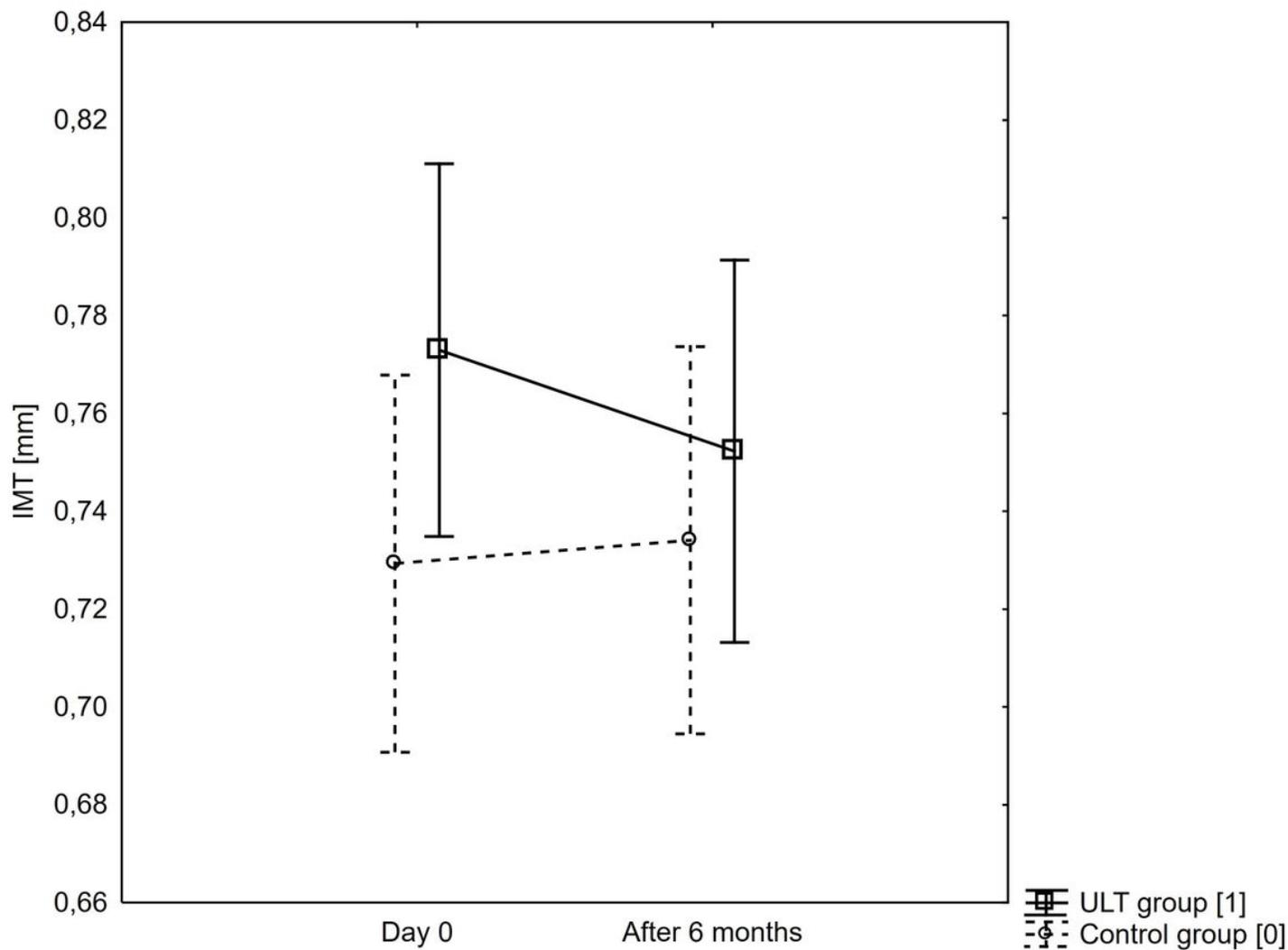


Figure 3

Intima-media thickness (IMT) changes in the urate-lowering therapy (ULT) group [1] and in the control group [0] at 6 months follow-up.

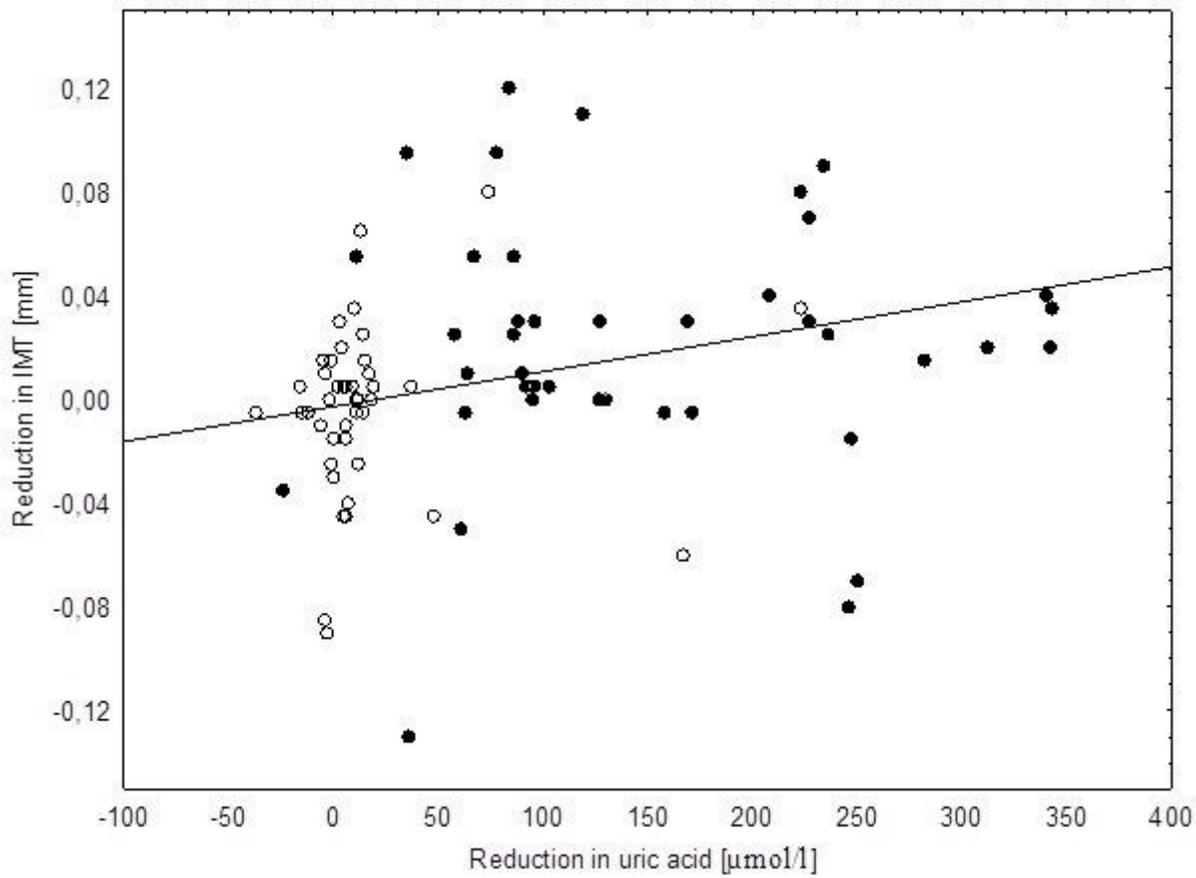


Figure 4

Correlation between reduction in uric acid (UA) concentration and reduction in intima-media thickness (IMT) in the whole study group at follow up. Reduction = day 0 value – after 6 months value