DOES ALLOPURINOL IMPROVE CARDIOVASCULAR AND KIDNEY RISK IN NON-DIALYSIS CHRONIC KIDNEY DISEASE PATIENTS?

A-M. Mehedinți[1], O. Popa[2], M. Lipan[1], D. Dumitru[1], G. Mircescu[1,2], C Căpuşă[1,2]

[1] "Dr. Carol Davila" Teaching Hospital of Nephrology, Bucharest, Romania

[1] Nephrology Dept. - "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

BACKGROUND AND AIMS

Recent data on small sample size suggested the beneficial effect of lowering uric acid levels with allopurinol therapy on long-term cardiovascular (CV) risk[1,2], as well as chronic kidney disease (CKD) progression[3]. However, the contribution of hyperuricemia to the decline of glomerular filtration rate (eGFR) and mortality is still an active debate, since divergent results were also reported[4,5].

Consequently, the study aimed to assess the CV and renal outcomes in stage 2 to 5 non-dialysis CKD patients, constantly treated with allopurinol or not.

METHODS

STUDY DESIGN: Single centre, retrospective cohort study.

PRIMARY OUTCOMES:

- Time to renal replacement therapy (RRT) initiation;
- Time to major CV events defined as: death or non-fatal stroke / myocardial infarction, or coronary / peripheral revascularization (CV).

STATISTICAL ANALYSIS: Data were expressed as percentages, median or means, and compared by Chi^2, ANOVA or Mann-Whitney, according to their type and distribution. Multiple logistic regression and Kaplan-Meier analyses were used to assess predictors of outcomes. $p<0.05$ was considered significant.

SUBJECTS

Two hundred eighteen non-dialysis CKD subjects with asymptomatic increased serum uric acid selected from the patients admitted in 2010-2011 [56% males, 48% >60 years-old, eGFR 41 (95%CI 38-44) mL/min, 26% low, 18% moderate, 34% high and 22% very high risk according to KDIGO classification] were enrolled. Exclusion criteria were:

- Known gout, uric acid lithiasis,
- Kidney graft, nephrotic syndrome,
- Systemic immune-inflammatory diseases (lupus erythematosus, vasculitis etc)
- Immunosuppressive therapy.

Two study groups were defined according to the presence (n=108) or absence (n=110) of allopurinol treatment. Eight subjects in allopurinol-treated group and seventeen in the control group were lost of follow-up.

The allopurinol administration and dose (100mg/day) remained unchanged in the studied patients.

Patients' outcome was assessed in October - December 2015, by both methods:

- Active (phone contact + medical visit);
- Passive (data retrieved from the Romanian Renal Registry database).

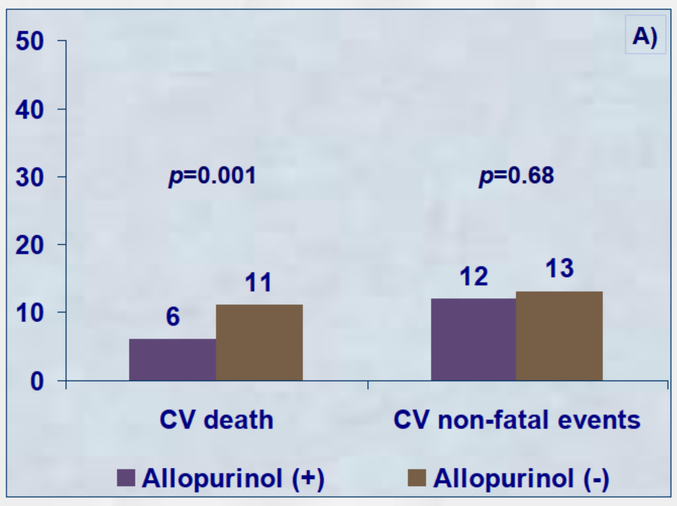
RESULTS

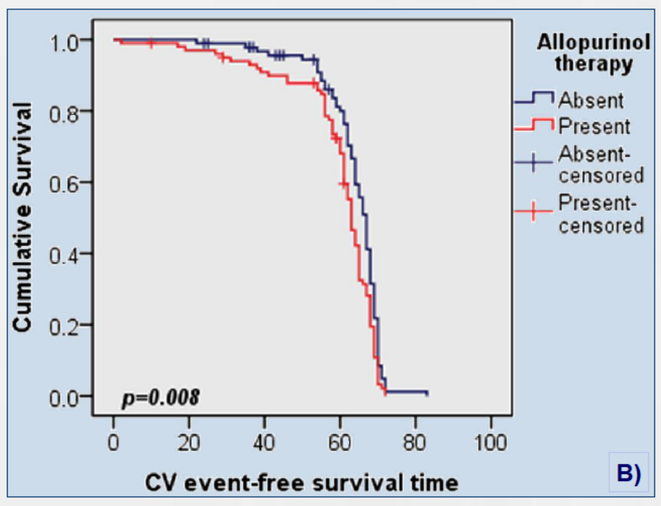
The median follow-up period was 62 (53;58) months.

INFLUENCE OF ALLOPURINOL ON THE CARDIOVASCULAR RISK

During the follow-up the relative risk for (RR) CV death and non-fatal events in treated subjects was 0.56 (95%CI 0.2-1.47) and 0.79 (95%CI 0.38-1.63), respectively.

Less CV deaths occurred in allopurinol-treated group (6% vs. 11%, $p=0.001$), while a similar incidence of non-fatal CV events was recorded in both groups (*Figure A*).





However, Kaplan Meier analysis showed worse CV event-free survival in patients on hypouricemiant therapy (*Figure B*). Also, in multivariate logistic regression analysis [adjusted for demographics, comorbidities, eGFR, urinary albumin-to-creatinine ratio (uACR), chronic treatment with statins and anti-angiotensin drugs], allopurinol was not retained as an independent protective factor. The only predictors of poor CV outcome were the absence of statin therapy, higher albuminuria, and older age:

Variable	*B*	*SE*	*Exp(B)*	*95% CI for Exp(B)*	*p*
Statins use	1.69	0.60	5.42	1.6 to 17.7	0.005
Log(Age)	13.2	4.24	524768.046	130.2 to 2.115E9	0.002
Log(uACR)	1.01	0.36	2.78	1.4 to 5.6	0.005
Adjusted R^2 = 0.14. $p<0.001$					
Dependent variable: Cardiovascular death					
Variables entered in step 1: Gender, KDIGO risk categories, Arterial hypertension, Diabetes mellitus, Coronary artery disease, ACE inhibitors, Angiotensin-receptor blockers, Statins, Serum hemoglobin, Serum uric acid, Log(Age), Log(eGFR), Log(Cholesterol), Log(Tryglicerides), Log(C-reactive protein), Log(uACR).					

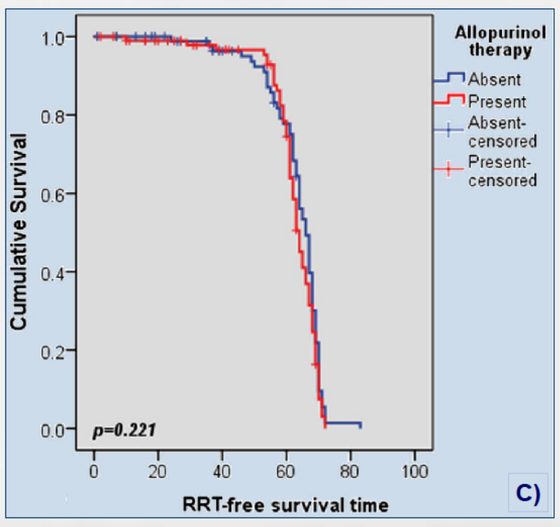
INFLUENCE OF ALLOPURINOL ON THE KIDNEY OUTCOME

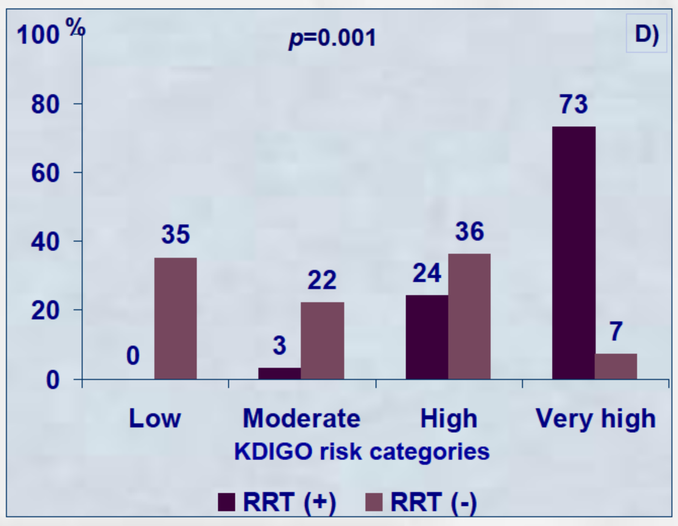
Allopurinol-treated subjects had a not significant 27% higher risk for initiation of RRT (RR 1.27, 95%CI 0.7-2.1) (Figure C), at least partially explained by the lower eGFR which probably triggered the more severe KDIGO risk category (Figure D) and was expressed by the higher serum uric acid.

SUBJECTS' GENERAL CHARACTERISTICS

Parameter \ CKD-Group	A (+) (n=100)	A (–) (n=93)	*p*
Age (years)*	60 (51;72)	60 (52;71)	0.81
Males (%)	70	41	0.001
Diabetes mellitus (%)	19	22	0.67
Arterial Hypertension (%)	87	83	0.54
Cerebro-vascular disease (%)	14	13	0.61
Coronary artery diseases (%)	51	50	0.83
Peripheral artery disease (%)	17	12	0.31
ACE inhibitors use (%)	50	53	0.71
ARB use (%)	42	34	0.28
Statins use (%)	70	62	0.26
Calcium salts use (%)	18	11	0.15
Vitamin D derivatives use (%)	34	26	0.20
eGFR (mL/min)*	35 (22;47)	54 (27;58)	0.003
Urinary albumin-to-creatinine (mg/g)*	87 (20;744)	57 (13;522)	0.35
KDIGO risk categories			0.01
- Low (%)	19	34	
- Moderate (%)	16	19	
- High (%)	41	26	
- Very high (%)	24	20	
Serum hemoglobin (g/dL)#	13.1 1.8	12.9 1.7	0.41
Serum C-reactive protein (mg/L)*	3 (2;6)	3 (2;5)	0.35
Serum cholesterol (mg/dL)*	200 (166;224)	206 (175;227)	0.31
Serum tryglicerides (mg/dL)*	152 (113;152)	125 (89;189)	0.008
Serum uric acid (mg/dL)#	6.9 ± 1.7	5.8 ± 1.6	0.001

* Median (quartiles 1; 3); # Mean standard deviation; ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blockers; eGFR: Estimated glomerular filtration rate.





CONCLUSIONS

Even the crude incidence of cardiovascular deaths was lower in our allopurinol-treated group, the current results did not sustain an independent effect of hypo-uricemiant therapy on reducing either cardiovascular risk or chronic kidney disease progression in older non-dialysis CKD patients.

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Ana-Maria Mehedinti

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