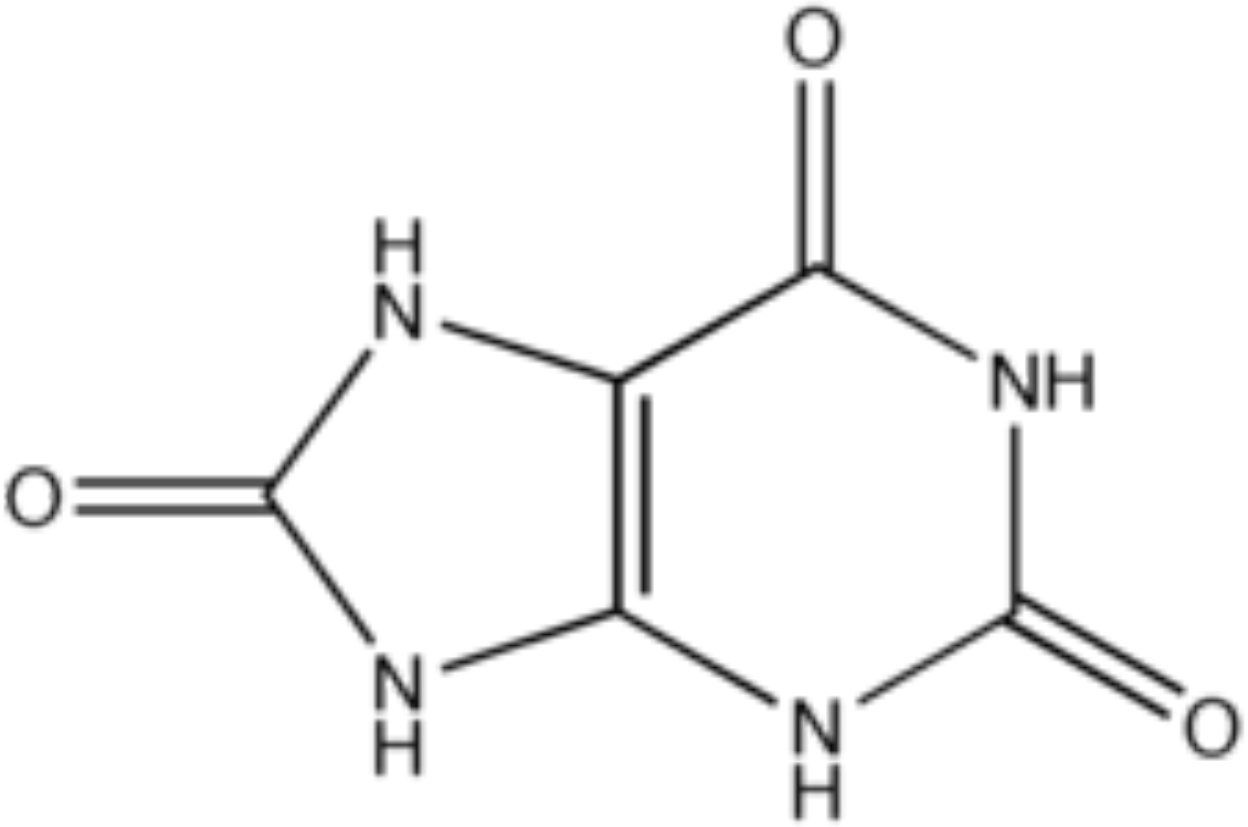
L'ecografia cardiovascolare come link tra cardiologia e medicina interna

L'iperuricemia

Francesco Antonini-Canterin (Pordenone)

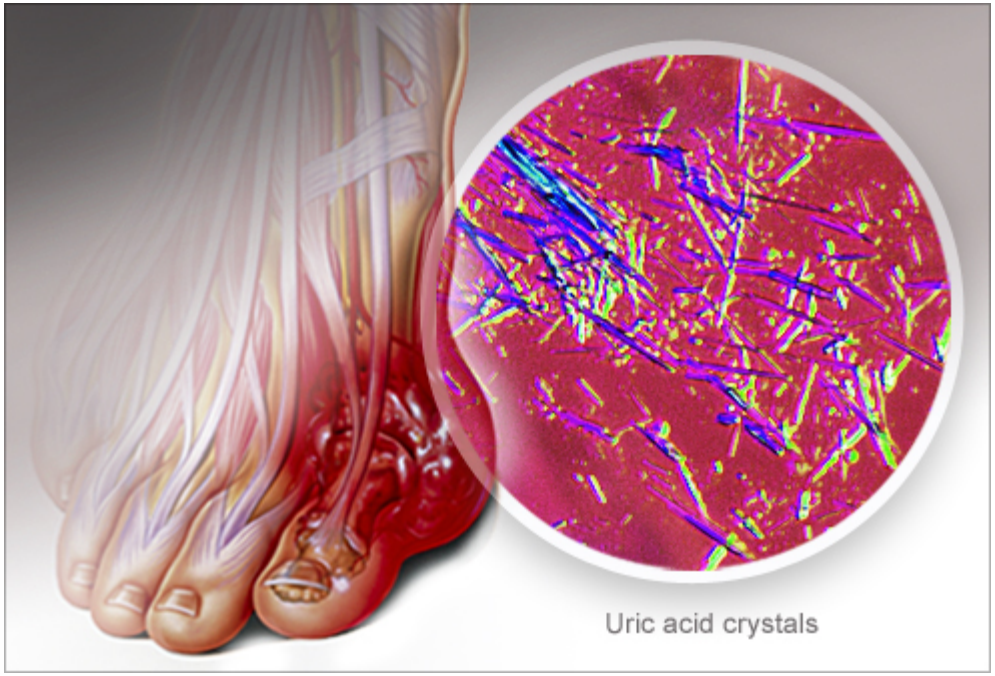
URIC ACID



URIC ACID: an exciting talk!

From the Italian Parlament…

GOUT



Uric Acid and Cardiovascular Risk

Daniel I. Feig, M.D., Ph.D., Duk-Hee Kang, M.D., and Richard J. Johnson, M.D.

N ENGL J MED 359;17 WWW.NEJM.ORG OCTOBER 23, 2008

Table 1. Cardiovascular Conditions and Risk Factors Associated with Elevated Uric Acid.

Hypertension and prehypertension
Renal disease (including reduced glomerular filtration rate and microalbuminuria)
Metabolic syndrome (including abdominal obesity, hypertriglyceridemia, low level of high-density lipoprotein cholesterol, insulin resistance, impaired glucose tolerance, elevated leptin level)
Obstructive sleep apnea
Vascular disease (carotid, peripheral, coronary artery)
Stroke and vascular dementia
Preeclampsia
Inflammation markers (C-reactive protein, plasminogen activator inhibitor type 1, soluble intercellular adhesion molecule type 1)
Endothelial dysfunction
Oxidative stress
Sex and race (postmenopausal women, blacks)
Demographic (movement from rural to urban communities, Westernization, immigration to Western cultures)

GOUT

ACR 2010: Hyperuricemia Linked to Increased Risk for Hypertension

Uric Acid and Cardiovascular Risk

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Table 2. Evidence Linking Uric Acid and Hypertension.

An elevated uric acid level consistently predicts the development of hypertension.

An elevated uric acid level is observed in 25–60% of patients with untreated essential hypertension and in nearly 90% of adolescents with essential hypertension of recent onset.

Raising the uric acid level in rodents results in hypertension with the clinical, hemodynamic, and histologic characteristics of hypertension.

Reducing the uric acid level with xanthine oxidase inhibitors lowers blood pressure in adolescents with hypertension of recent onset.

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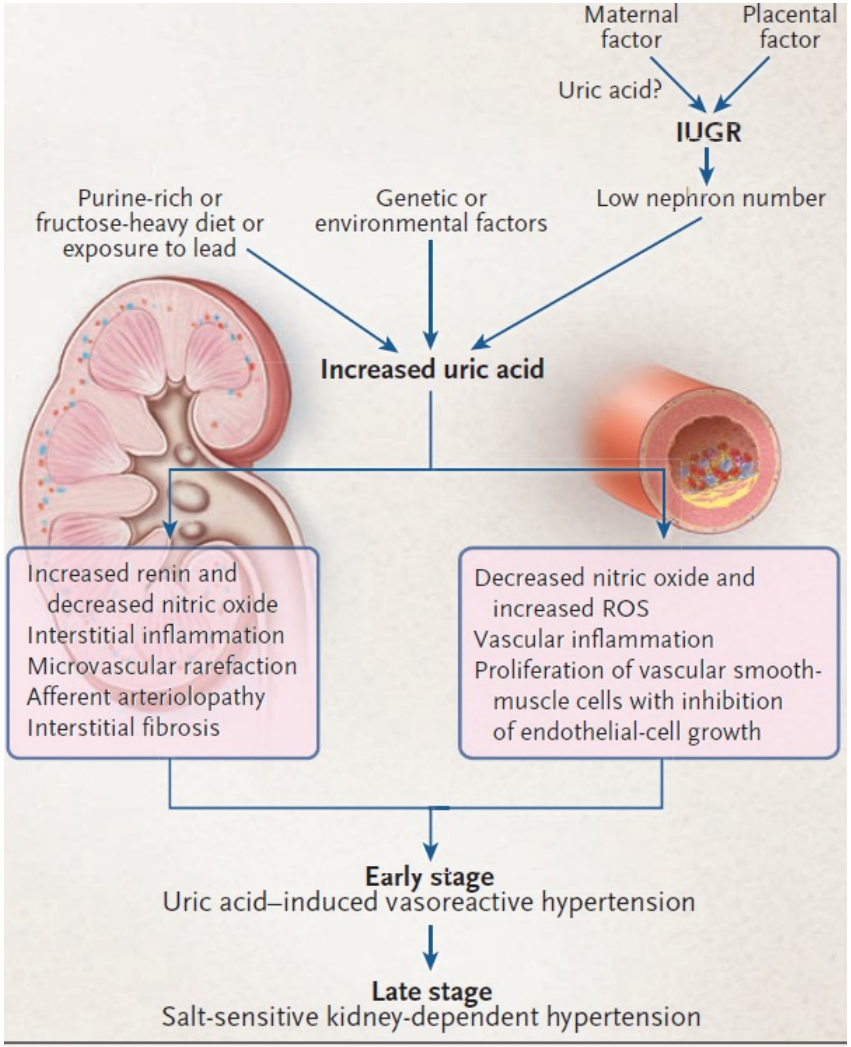

Figure 1. Proposed Mechanism for Uric Acid–Mediated Hypertension.

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Table 3. Hyperuricemia and the Development of Hypertension.*

Study	No. of Patients	Relative Risk of Hypertension	95% CI
Kaiser Permanente, 1990[53]	2062 adults	2.1 times greater at 6 yr (high vs. low quintile)	1.20–3.98
University of Utah, 1991[44]	1482 adults	1.44 times greater per SD increment at 7 yr	1.03–2.01
Olivetti Heart, 1994[46]	619 men	1.23 times greater per 1 mg/dl increase at 12 yr	1.07–1.39
CARDIA, 1999[42]	5115 men	1.21 times greater per SD increment at 10 yr	1.03–1.41
Osaka Health Survey, 2001[56]	6356 men	2 times greater at 10 yr (high vs. low quintile)	1.56–2.60
Hawaii–Los Angeles–Hiroshima, 2001[45]	140 men	2.0 times greater at 15 yr (high vs. low quartile)	1.02–3.9
Osaka Factory, 2003[48]	433 men	1.0 mg/dl, increased 27 mm Hg SBP at 5 yr	Not calculated
Osaka Health Survey, 2003[51]	2310 men	1.13 times greater per SD increment at 6 yr	1.06–1.21
Okinawa, 2004[50]	4489 adults	1.46 times greater for men (uric acid ≥7 mg/dl) and 1.94 for women (uric acid ≥6 mg/dl) at 13yr	1.09–2.03 1.05–3.57
Bogalusa Heart, 2005[41]	679 children	Increased risk for diastolic hypertension at 11 yr	Not calculated
Framingham Heart, 2005[55]	3329 adults	1.17 times greater per SD increment at 4 yr	1.02–1.33
Normative Aging, 2006[52]	2062 men	125 times greater at 21 yr (uric acid >6.5 mg/dl)	1.08–1.34
ARIC, 2006[49]	9104 adults	1.1 times greater per SD increment at 9 yr	1.02–1.14
Beaver Dam Health Survey, 2006[54]	2520 adults	1.65 times greater at 10 yr (high vs. low quintile)	1.41–1.93
Health Professionals' Follow-up, 2006[43]	750 men	1.02 times greater per SD increment at 8 yr	0.92–1.13
MRFIT, 2007[47]	3073 men	1.1 times greater per SD increment at 6 yr	1.02–1.19

Brisighella Heart Study

TABLE 1. Anthropometric and clinical characteristics, hemodynamic parameters, IMT and PWV in the considered population sample

	All	Males	Females	
Patients	619	248	371	
Age (years)	53.3 ± 11.6	53.3 ± 11.8	53.4 ± 11.1	
Smoking (%)	42.6	45.5	40.6	
Hypertension (%)	34.4	38.6	31.4	
Diabetes (%)	13.5	18.4	9.9	**
Metabolic syndrome (%)	34.4	41.8	29.3	**
Height (cm)	165.1 ± 9.2	173.1 ± 7.1	159.9 ± 6.2	***
Weight (kg)	71.7 ± 15.3	81.3 ± 14.6	65.2 ± 12.0	***
BMI (kg/m^2)	26.2 ± 4.8	27.1 ± 4.4	25.6 ± 4.9	***
Waist circumference (cm)	91.3 ± 14.1	97.3 ± 12.5	87.1 ± 13.7	***
Hip circumference (cm)	98.2 ± 11.8	100.3 ± 10.7	96.7 ± 12.3	***
Waist/hip	0.91 ± 0.09	0.96 ± 0.07	0.88 ± 0.09	***
Glucose (mg/d)	96.1 ± 14.1	99.4 ± 14.8	93.9 ± 13.1	***
Triglycerides (mg/dl)	103.4 ± 62.2	116.2 ± 73.8	94.9 ± 51.4	***
Total cholesterol (mg/dl)	207.0 ± 36.1	202.6 ± 34.6	210.0 ± 36.8	*
HDL cholesterol (mg/dl)	48.7 ± 12.6	43.6 ± 10.5	52.0 ± 12.7	***
LDL cholesterol (mg/dl)	137.8 ± 32.0	135.9 ± 32.8	139.0 ± 31.6	
Serum creatinine (mg/dl)	1.00 ± 0.18	1.11 ± 0.16	0.93 ± 0.17	***
eGFR (mg/min per 1.73m^2)	68.1 ± 6.2	65.3 ± 7.5	70.2 ± 8.9	*
Uric acid (mg/dl)	4.8 ± 1.5	5.7 ± 1.4	4.2 ± 1.2	***
Brachial SBP (mmHg)	131.4 ± 18.4	133.2 ± 16.5	130.1 ± 19.5	*
Carotid SBP (mmHg)	119.0 ± 16.8	121.0 ± 14.7	117.5 ± 17.8	*
Brachial PP (mmHg)	53.3 ± 13.8	53.6 ± 11.3	53.0 ± 15.2	
Carotid PP (mmHg)	40.9 ± 12.2	41.5 ± 9.6	40.4 ± 13.6	
DBP (mmHg)	78.1 ± 9.6	79.5 ± 9.6	77.1 ± 9.5	*
MAP (mmHg)	95.9 ± 11.5	97.4 ± 11.1	94.8 ± 11.6	**
Augmentation index (%)	21.6 ± 15.9	15.7 ± 16.5	25.4 ± 14.3	***
PP amplification (%)	32.2 ± 10.1	30.3 ± 9.8	33.5 ± 10.1	***
Heart rate (bpm)	66.7 ± 12.1	63.6 ± 11.9	68.8 ± 11.8	***
IMT (mm)	0.92 ± 0.22	0.93 ± 0.22	0.91 ± 0.22	
cf-PWV (m/s)	7.70 ± 1.81	7.83 ± 1.73	7.61 ± 1.86	
cr-PWV (m/s)	8.56 ± 1.43	8.99 ± 1.49	8.28 ± 1.31	***

Association between serum uric acid, hypertension, vascular stiffness and subclinical atherosclerosis: data from the Brisighella Heart Study

Arrigo F.G. Cicero[a], Paolo Salvi[b], Sergio D'Addato[a], Martina Rosticci[a], Claudio Borghi[a], for the Brisighella Heart Study group

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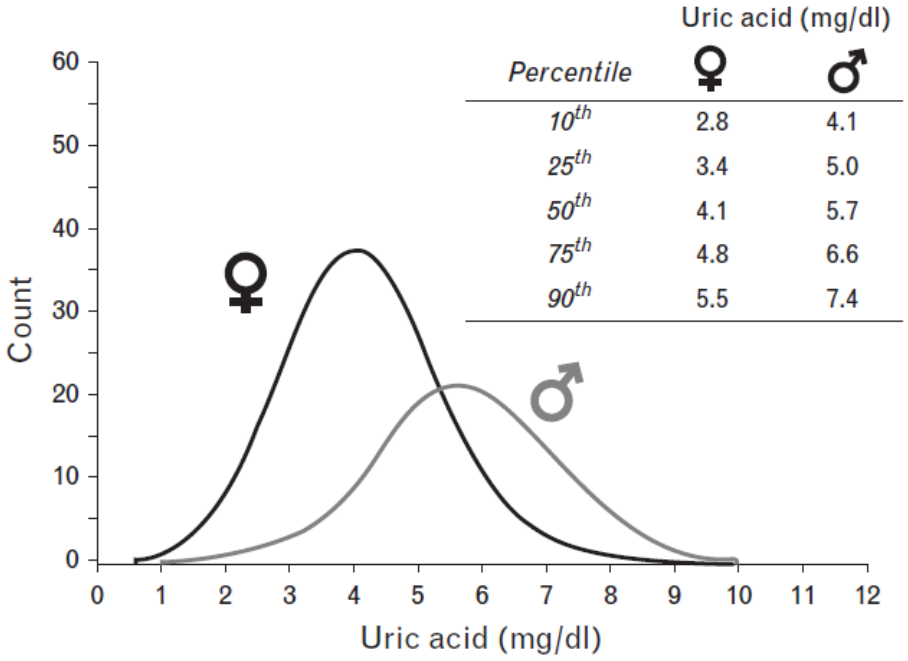

FIGURE 1 Sex-related serum uric acid distribution in the studied population sample.

Association between serum uric acid, hypertension, vascular stiffness and subclinical atherosclerosis: data from the Brisighella Heart Study

Arrigo F.G. Cicero[a], Paolo Salvi[b], Sergio D'Addato[a], Martina Rosticci[a], Claudio Borghi[a], for the Brisighella Heart Study group

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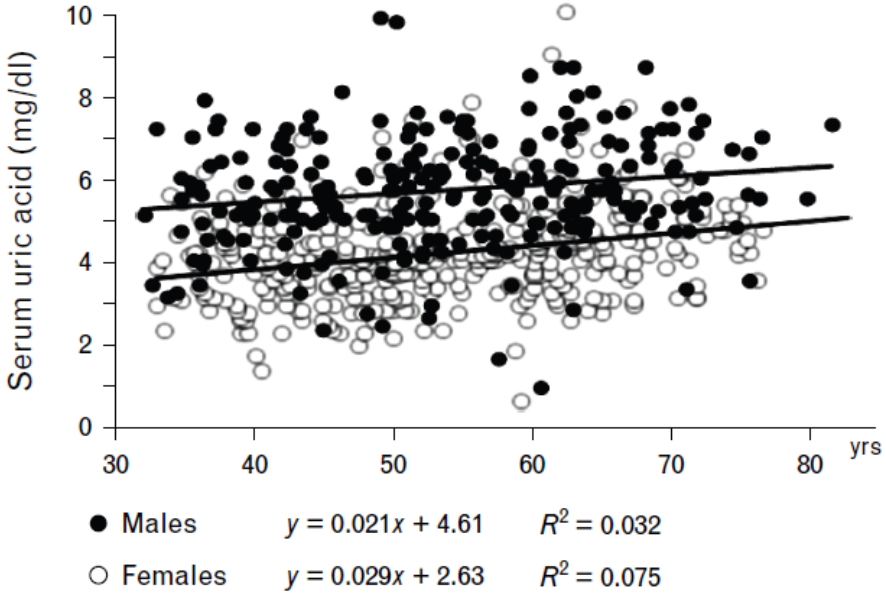

FIGURE 2 Age-related distribution of serum uric acid in the studied population sample.

Association between serum uric acid, hypertension, vascular stiffness and subclinical atherosclerosis: data from the Brisighella Heart Study

Arrigo F.G. Cicero[a], Paolo Salvi[b], Sergio D'Addato[a], Martina Rosticci[a], Claudio Borghi[a], for the Brisighella Heart Study group

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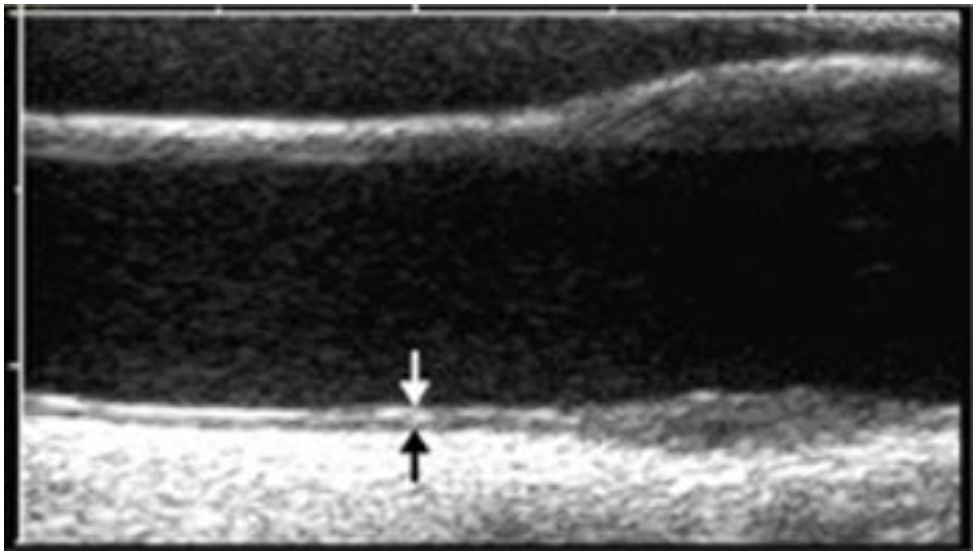
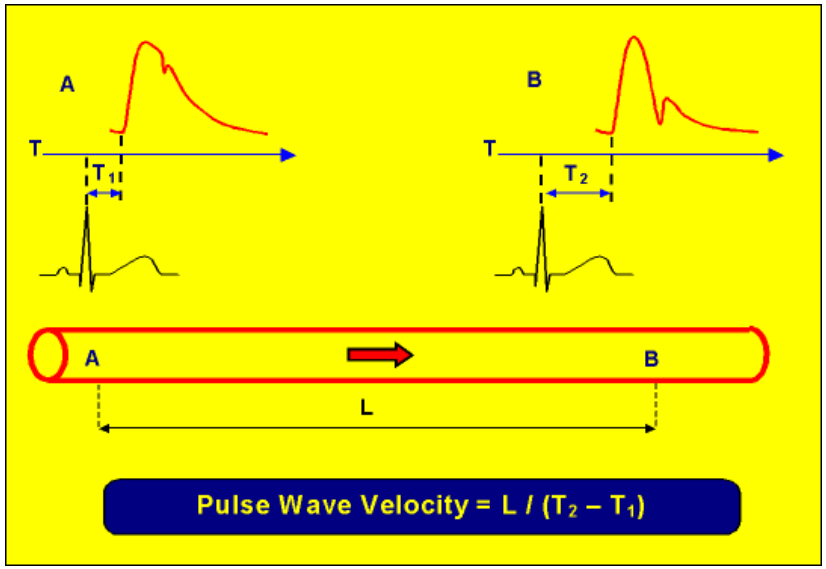
INTIMA MEDIA THICKNESS



CAROTID-FEMORAL PWV



Association between serum uric acid, hypertension, vascular stiffness and subclinical atherosclerosis: data from the Brisighella Heart Study

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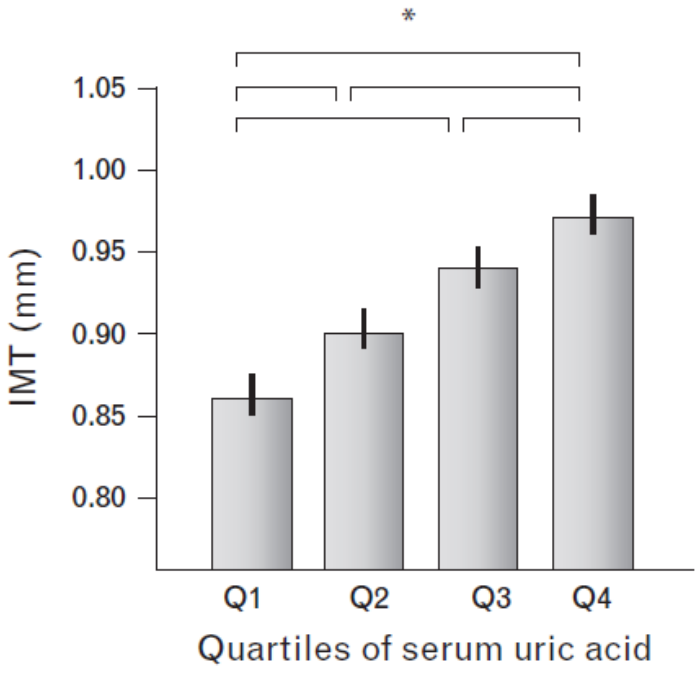

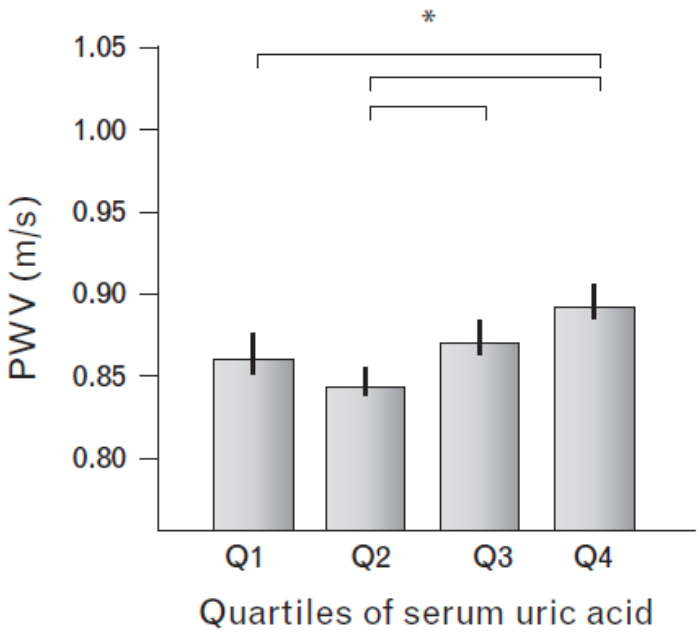

Conclusion: In the studied population sample, after adjustment for a large number of parameters, SUA appears to be significantly correlated to hypertension and IMT, but not to aortic stiffness.

The impact of serum uric acid level on arterial stiffness and carotid atherosclerosis: The Korean Multi-Rural Communities Cohort study

Ji Suk Bae [a], Dong Hoon Shin [b], Pil Sook Park [c], Bo Youl Choi [d], Mi Kyung Kim [d], Min-Ho Shin [e], Young-Hoon Lee [f], Byung-Yeol Chun [g,*,1], Seong-Kyu Kim [h,**,1]

Atherosclerosis 231 (2013) 145–151

Table 1
Baseline characteristics of the study participants: the Korean Multi-Rural Communities Cohort study in rural communities.

Characteristic	Males ($n = 2167$)	Females ($n = 3401$)	p value[a]
Age (year)	61.5 ± 9.9	59.5 ± 10.0	<0.0001
BMI (kg/m^2)	23.6 ± 2.9	24.1 ± 3.2	<0.0001
Waist circumference (cm)	84.4 ± 8.2	82.2 ± 8.9	<0.0001
SBP (mmHg)	124.0 ± 16.1	120.6 ± 17.3	<0.0001
DBP (mmHg)	79.5 ± 10.0	77.2 ± 10.0	<0.0001
Uric acid (mg/dL)	5.7 ± 1.4	4.2 ± 1.0	<0.0001
Triglyceride (mg/dL)	156.8 ± 116.1	136.1 ± 80.6	<0.0001
HDL cholesterol (mg/dL)	44.4 ± 11.8	45.9 ± 10.4	<0.0001
Fasting serum glucose (mg/dL)	99.0 ± 19.6	94.6 ± 13.8	<0.0001

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Linear regression coefficients[a] between serum uric acid level (mg/dL) and carotid IMT and brachial-ankle PWV.

		Male		Female	
		Carotid IMT (mm), $n = 2167$	Brachial-ankle PWV (cm/s)[b] $n = 1932$	Carotid IMT (mm) $n = 3401$	Brachial-ankle PWV (cm/s)[b] $n = 3124$
Age-adjusted	β	0.37	0.0008	0.25	0.0002
	p value	0.10	<0.0001	0.08	0.0002
Multivariate-adjusted	β	0.16	0.0006	0.09	0.0001
	p value	0.45	<0.0001	0.54	0.04

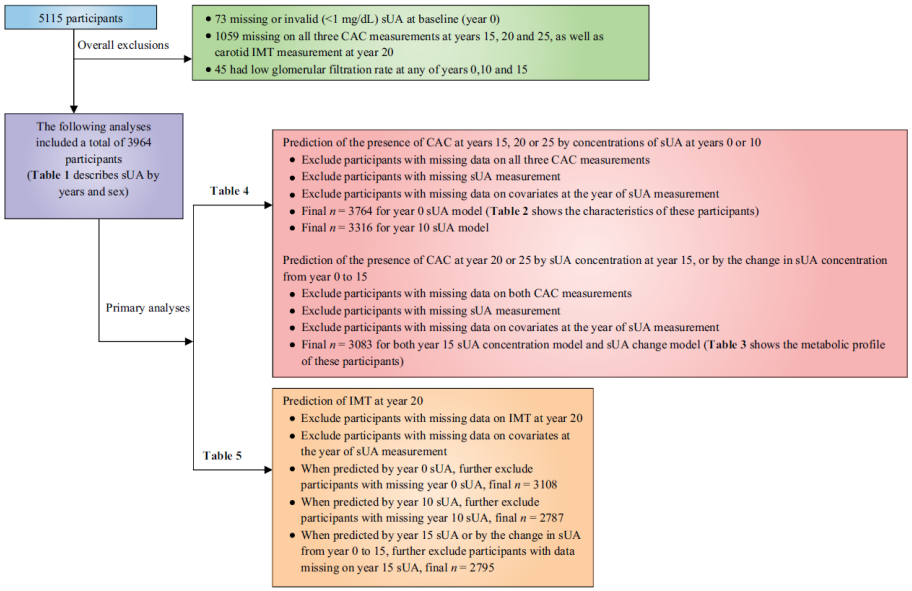
Conclusion: Serum uric acid level could be considered an important risk factor for arterial stiffness in Korean population, whereas carotid IMT is not associated with serum uric acid in either gender when using data from the Korean Multi-Rural Communities Cohort study.

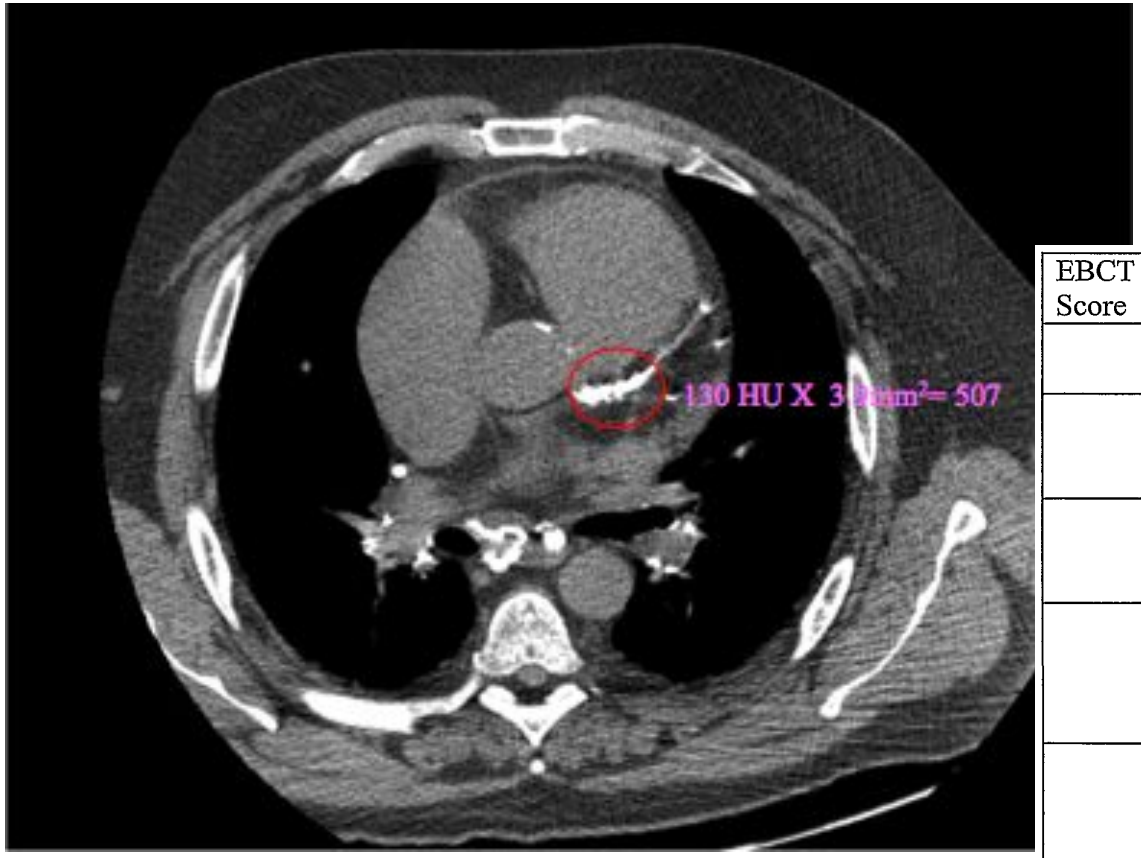
Longitudinal association between serum urate and subclinical atherosclerosis: the Coronary Artery Risk Development in Young Adults (CARDIA) study

H. Wang[1,2], D. R. Jacobs Jr[1], A. L. Gaffo[3], M. D. Gross[4], D. C. Goff Jr[5,6] & J. J. Carr[7,8]

274: 594–609

Design and setting. The CARDIA study followed 5115 Black and White individuals aged 18–30 years in 1985–1986 (year 0). Subclinical atherosclerosis comprised coronary artery calcified plaque (CAC; years 15, 20 and 25), and maximum common carotid intima–media thickness (IMT; year 20). sUA (years 0, 10, 15 and 20) was modelled as gender-specific quartiles that were pooled. Discrete-time





EBCT Calcium Score	Plaque Burden	Probability of Significant CAD
0	No identifiable plaque burden	Very low (generally <5% likelihood)
0-10	Minimal identifiable plaque burden	Very unlikely (generally <10% likelihood)
11-100	Definite (at least mild)	Mild or minimal coronary stenoses likely
101-400	Definite (at least moderate atherosclerotic plaque burden)	Nonobstructive CAD highly likely, although obstructive disease possible
>400	Extensive	High likelihood (>90%) of at least one "significant" coronary stenosis

The figure depicts extensive coronary artery calcification involving the left main and the left anterior descending arteries. Agatston score is calculated by multiplying the area of the calcification (mm^2) by its density in Hounsefeld units (HU). The total calcium score is much higher than that for the lesion depicted.

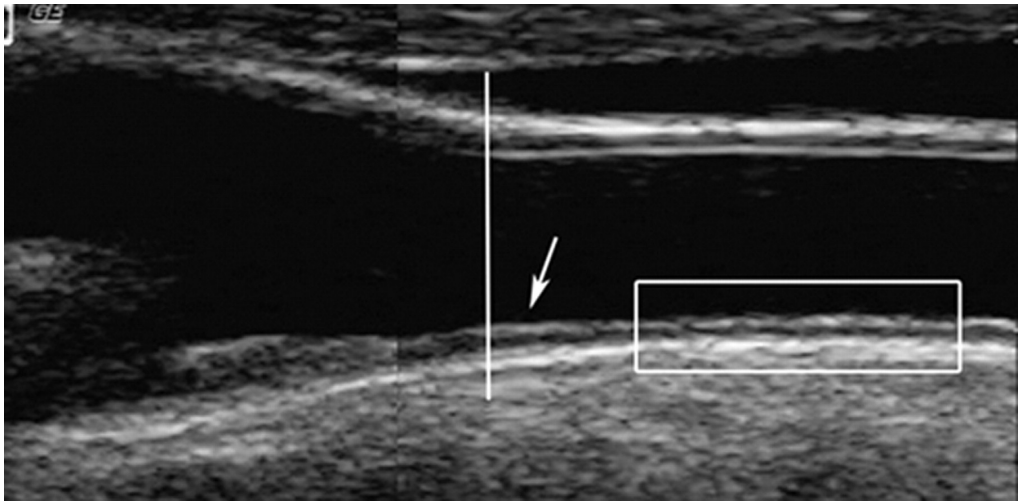


TABLE 2. **Mean Values and Upper Limit (75 Percentile) of Normal Distribution of Average Intima-Media Thickness, by Segment and Age Group in Men and Women**

Carotid Segment	Age Group, y (n)	Men		Women	
		Mean, mm	Upper Limit, mm	Mean, mm	Upper Limit, mm
Average common carotid IMT	<25 (22)	0.5637	0.6124	0.5174	0.5593
	25-34 (22)	0.6083	0.6678	0.5732	0.634
	35-44 (25)	0.6179	0.6943	0.5801	0.6294
	45-54 (25)	0.6716	0.6879	0.6508	0.713
	55-64 (22)	0.7474	0.7941	0.7269	0.7696
	>64 (22)	0.8343	0.9126	0.8673	0.9781
Average carotid sinus IMT	<25 (22)	0.6056	0.6618	0.5358	0.5918
	25-34 (22)	0.619	0.7243	0.6222	0.684
	35-44 (25)	0.6593	0.7142	0.6474	0.7161
	45-54 (25)	0.7811	0.8143	0.6998	0.7668
	55-64 (22)	0.8379	0.9214	0.7604	0.8611
	>64 (22)	0.9429	1.0542	0.9296	1.0436
Average internal carotid IMT	<25 (22)	0.4702	0.5638	0.4398	0.4758
	25-34 (22)	0.5686	0.6632	0.4732	0.5359
	35-44 (25)	0.5981	0.6556	0.5259	0.6006
	45-54 (25)	0.6055	0.7043	0.5876	0.6241
	55-64 (22)	0.7372	0.8066	0.6274	0.7103
	>64 (22)	0.8842	1.008	0.7905	0.9435
3-segment average IMT	<25 (22)	0.5465	0.5891	0.4977	0.5184
	25-34 (22)	0.5986	0.6665	0.5562	0.5831
	35-44 (25)	0.6251	0.663	0.5844	0.6483
	45-54 (25)	0.6861	0.7185	0.6461	0.7037
	55-64 (22)	0.7742	0.811	0.7049	0.7961
	>64 (22)	0.8906	0.9521	0.8625	0.9342

Longitudinal association between serum urate and subclinical atherosclerosis: the Coronary Artery Risk Development in Young Adults (CARDIA) study

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274: 594–609

Table 4 *Hazard ratio (95% CI) of the presence of CAC across quartiles of sUA concentrations* [a]

	Quartiles of sUA concentration						
	Q1	Q2	Q3	Q4	P_{trend}	β [b] ±SE	P [c]
Y0 sUA in relation to the presence of CAC during Y15 to Y25 (n = 3764)							
Y0 sUA concentration (median and range)	3.70 (1.00, 5.40)	4.30 (3.90, 6.10)	4.90 (4.40, 6.70)	6.60 (5.10, 11.20)			

Conclusion. sUA may be an early biomarker for subclinical atherosclerosis in young adults; starting in early middle age, sUA predicts subclinical atherosclerosis independently of BMI.

Y15 sUA in relation to the presence of CAC during Y20 to Y25 (n = 3083)							
Y15 sUA concentration (median and range)	3.91 (2.10, 5.53)	4.48 (4.01, 6.20)	5.24 (4.67, 7.15)	7.05 (5.44, 11.91)			
No. of CAC cases	169	217	251	281			
CAC rates/1000 person-years	25.07	31.91	37.41	43.70			
Model 3 [h]	1.00	1.47 (1.17, 1.84) [i]	1.68 (1.35, 2.09)	2.07 (1.66, 2.58)	<0.001	0.22 ± 0.03	<0.001
Model 3 + Y15 BMI	1.00	1.35 (1.08, 1.70)	1.41 (1.12, 1.77)	1.51 (1.19, 1.91)	0.01	0.13 ± 0.03	<0.001
Change of sUA from Y0 to Y15 in relation to the presence of CAC at Y20 to Y25 (n = 3083)							

Serum Uric Acid and Cardiovascular Risk Among Portuguese Adolescents

Jean-Pierre Gonçalves, M.D. [a,b,c], Elisabete Ramos, Ph.D. [a,b,c], Milton Severo, Ph.D. [a,b,c], Max C. Y. Wong, Ph.D. [d], Ken K. Ong, Ph.D. [e], David B. Dunger, Ph.D. [d], and Carla Lopes,

Journal of Adolescent Health 56 (2015) 376–381

Table 2
Characterization of classes with low, medium, and high cardiovascular (CV) risk identified in the EPITeen cohort adolescents aged 17 years, by sex (Porto, Portugal 2007–2008)

	CV risk classes (N = 1,286)			*p* value
	Low (n = 769)	Medium (n = 445)	High (n = 72)	
Female	383	270	29	
Male	386	175	43	
Waist circumference (cm); mean (SD)				
♀	72.86 (6.12)	76.8 (9.47)	84.7 (10.30)	.001
♂	75.78 (5.57)	82.00 (9.99)	90.33 (11.18)	.001
Triglycerides (g/L); mean (SD)				
♀	.57 (.13)	.89 (.31)	1.38 (.67)	.001
♂	.54 (1.34)	.85 (.28)	1.09 (.57)	.001
Total cholesterol (g/L); mean (SD)				
♀	1.63 (.26)	1.77 (.33)	2.07 (.50)	.001
♂	1.45 (.22)	1.55 (.30)	1.77 (.34)	.001
HDLc (g/L); mean (SD)				
♀	.59 (.11)	.59 (.13)	.59 (.13)	.479
♂	.52 (.10)	.47 (.11)	.49 (.10)	.001
SBP (mm Hg); mean (SD)				
♀	111.62 (10.94)	112.99 (9.90)	118.45 (18.83)	.003
♂	118.79 (11.94)	118.46 (10.79)	130.44 (17.65)	.001
DBP (mm Hg); mean (SD)				
♀	66.60 (8.13)	67.02 (8.35)	72.69 (13.10)	.001
♂	60.30 (8.77)	69.93 (8.26)	76.56 (16.89)	.001
Glucose (g/L); mean (SD)				
♀	.83 (.08)	.83 (.07)	.82 (.08)	.454
♂	.86 (.08)	.88 (.07)	.93 (.26)	.001
Insulin (μIU/mL); mean (SD)				
♀	4.16 (2.14)	7.26 (3.49)	15.00 (8.27)	.001
♂	4.25 (2.09)	7.26 (3.50)	12.13 (9.44)	.001

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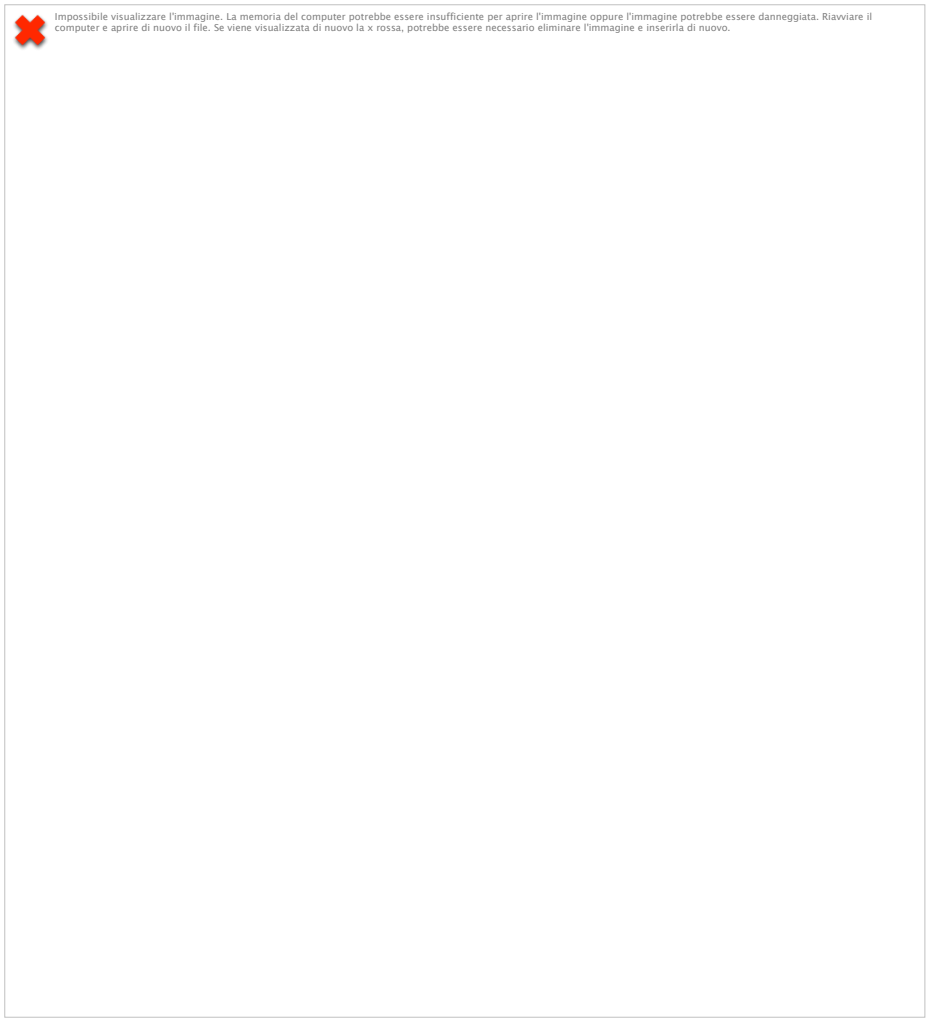

Role of Serum Uric Acid Levels on local carotid arterial stiffness and intima-media thickness: a high resolution echo-tracking study.

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	Total Population N=698	Non-hyperuricemic N=562	Hyperuricemic N=136	P
Age (years)	57.3 ± 13.7	57.1± 14.0	58.0±12.4	0.509
Male sex (%)	45.1	44.7	47.1	0.341
Uric Acid (mg/dL)	5.3±1.3	4.9±1.0	7.2±0.8	<0.001
Index of stiffness Beta	7.7±2.8	7.5±2.7	8.3±3.2	0.005
average IMT (mm)	0.92±0.19	0.91±0.18	0.97±0.22	<0.001
SBP (mmHg)	146±18	146±18	148±19	0.203
DBP (mmHg)	87±10	87±10	89±11	0.014

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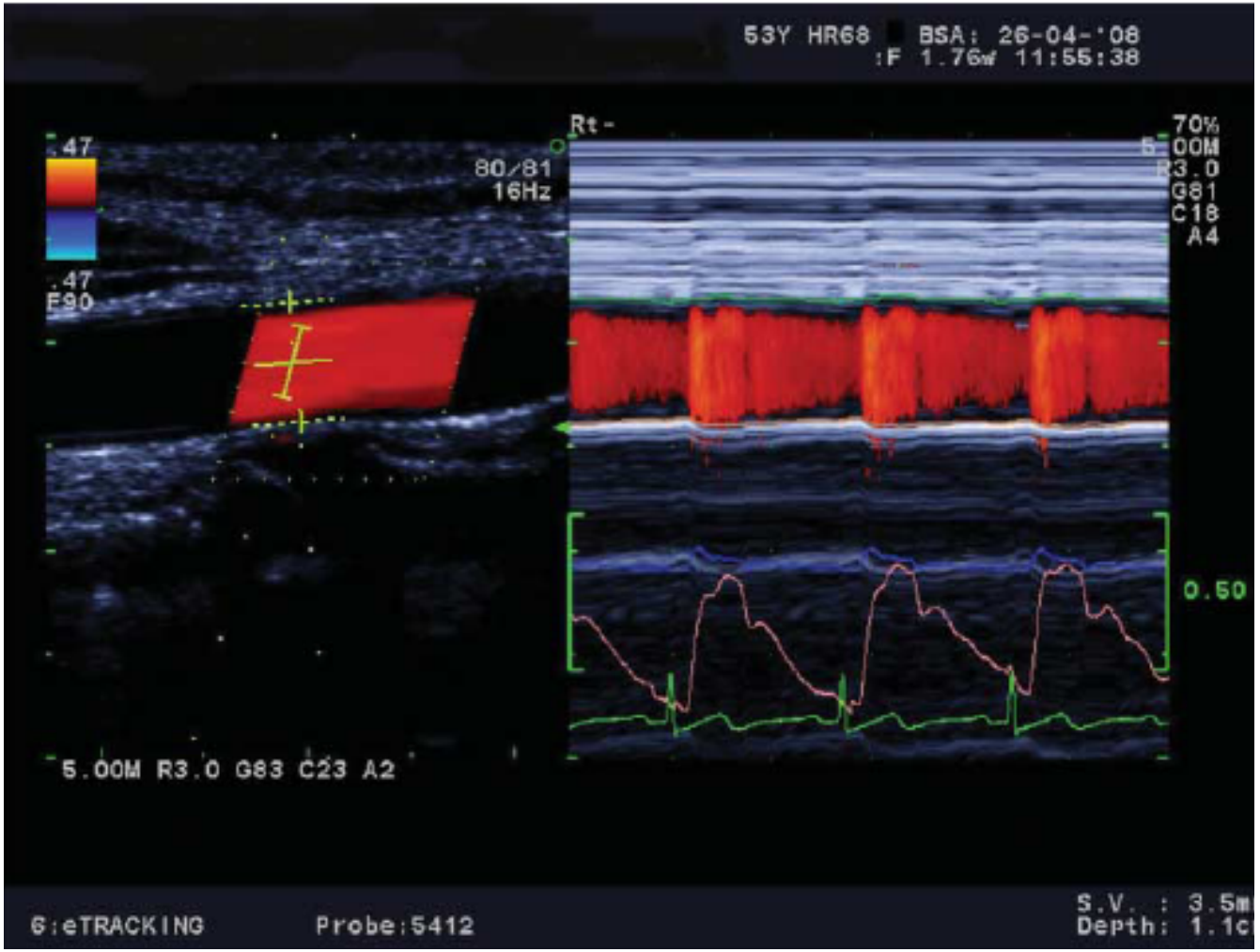

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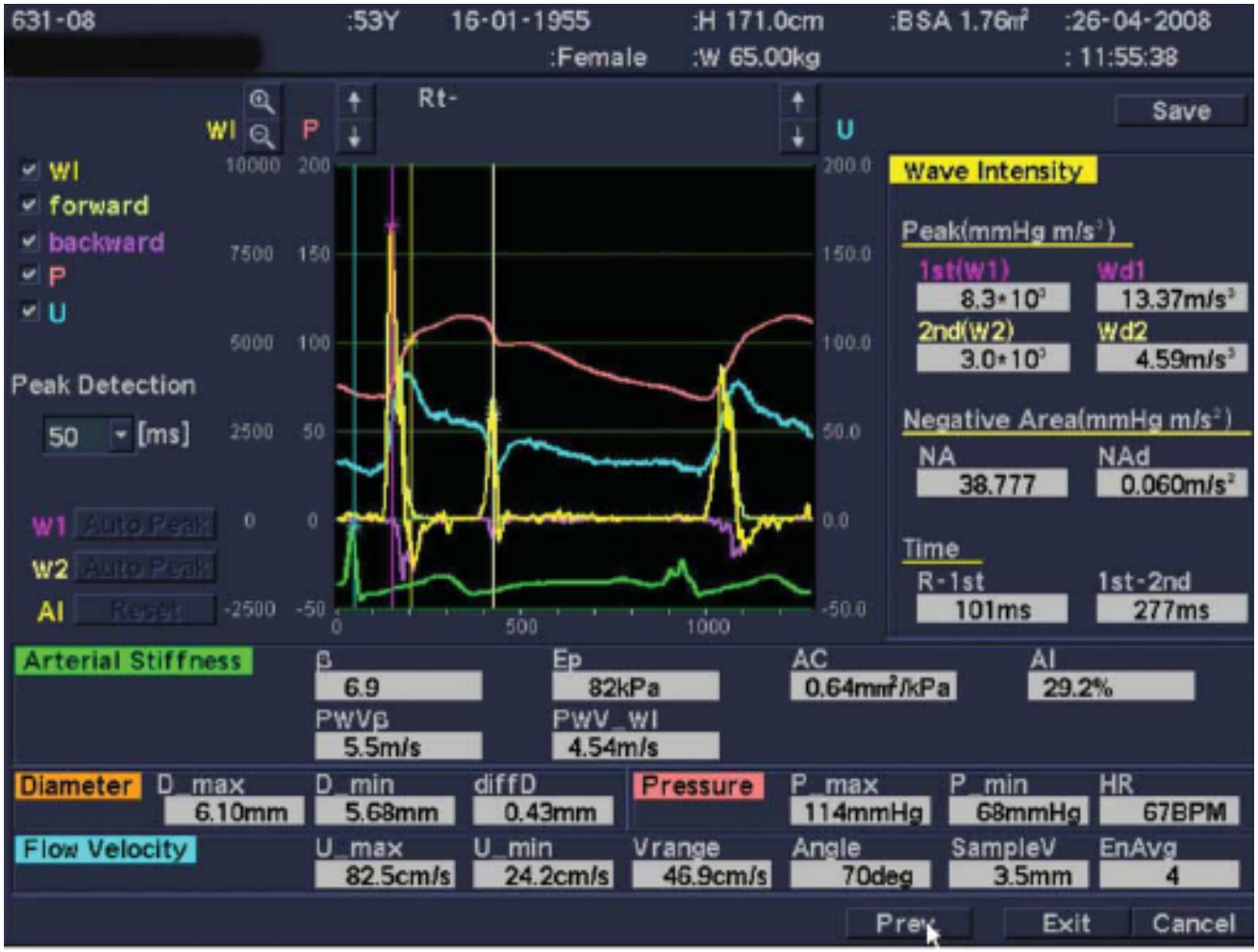

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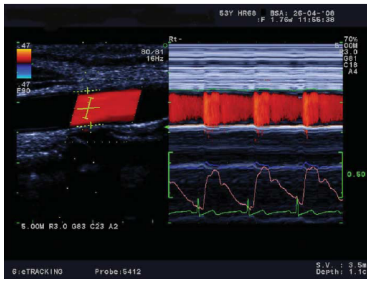

Table 2 Regression analysis assessing the capacity of uric acid serum level to predict index of stiffness Beta.

	Males (N=315)		Females (N=383)	
	Standardized Regression Coefficient	P	Standardized Regression Coefficient	P
Uric Acid	*0.171*	*0.001*	*0.120*	*0.002*
Age	0.407	<0.001	0.361	<0.001
Glucose	0.018	0.727	0.028	0.469
PAS	0.112	0.085	0.494	<0.001
PAD	-0.151	0.020	-0.301	<0.001
LDL	0.010	0.848	0.188	0.851

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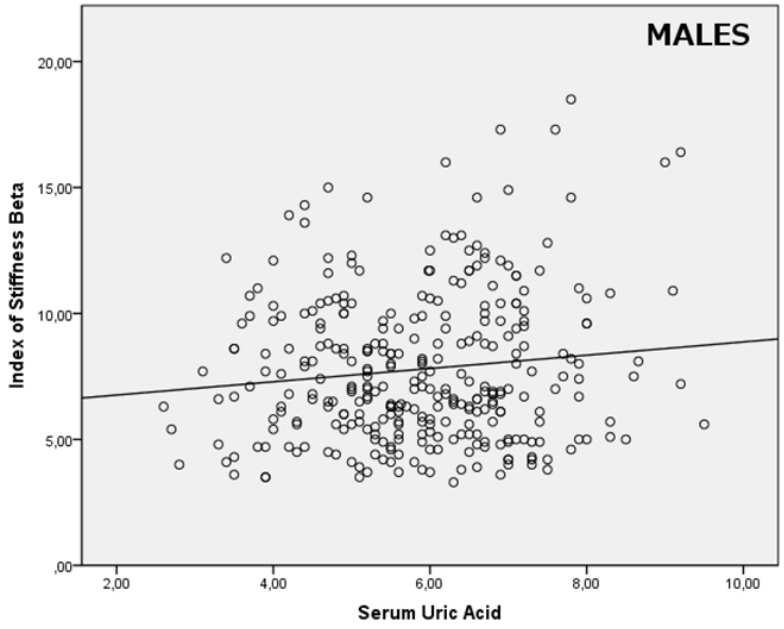
Figure 1 Relationship between Serum Uric Acid (mg/dL) and Index of Arterial Stiffness Beta in males (r=0.116; p=0.039) and females (r=0.190; p=<0,001).



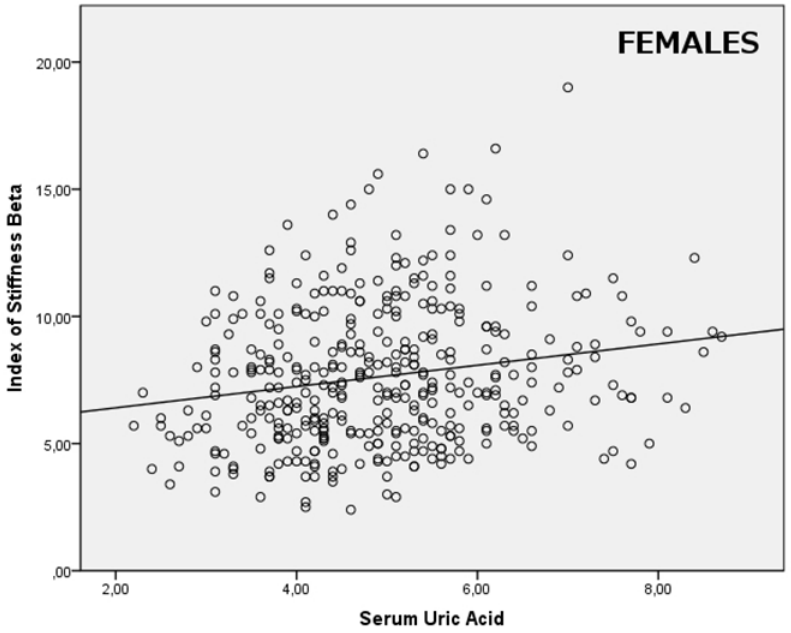


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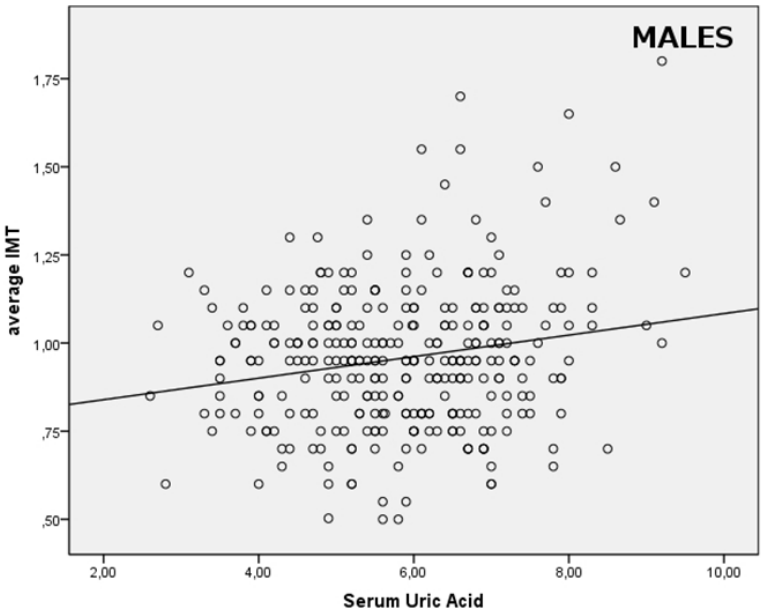
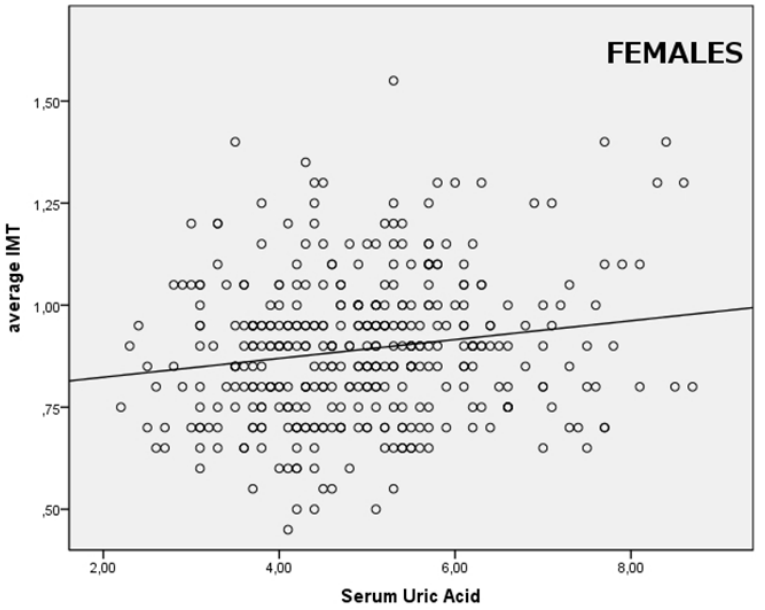
Figure 2 Relationship between Serum Uric Acid (mg/dL) and average intimal-medial thickness (IMT) in millimetres, in males (r=0.196; p=<0.001) and females (r=0.163; p=0.001).





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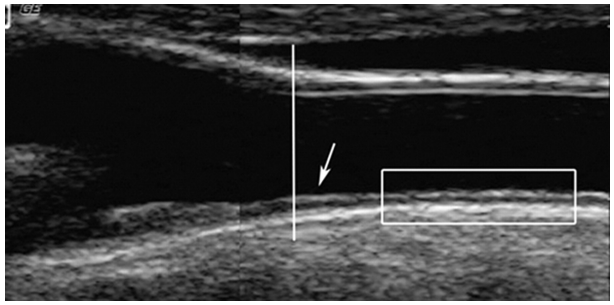

Table 3 Regression analysis assessing the capacity of uric acid serum level to predict IMT.

	Males (N=315)		Females (N=383)	
	Standardized Regression Coefficient	P	Standardized Regression Coefficient	P
Uric Acid	*0.243*	*<0.001*	*0.090*	*0.030*
Age	0.525	<0.001	0.577	<0.001
Glucose	0.006	0.899	0.046	0.272
PAS	0.128	0.029	0.027	0.633
PAD	-0.003	0.959	-0.003	0.959
LDL	0.074	0.121	0.044	0.295

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Conclusions: Our data show that carotid IMT and local stiffness index Beta are related to UA independently of established CV risk factors and therefore may play a role in the atherosclerosis development of atherosclerosis.

The Impact of Uric Acid on Long-term Mortality in Patients with Asymptomatic Carotid Atherosclerotic Disease

Florian J. Mayer, MD,*†‡ Christine Mannhalter, PhD,* Erich Minar, MD,§ Martin Schillinger, MD,§ Triantafyllos Chavakis, MD,†‡ Gabriele Siegert, MD,‡ Borros M. Arneth, MD,‡ Renate Koppensteiner, MD,§ and Matthias Hoke, MD§

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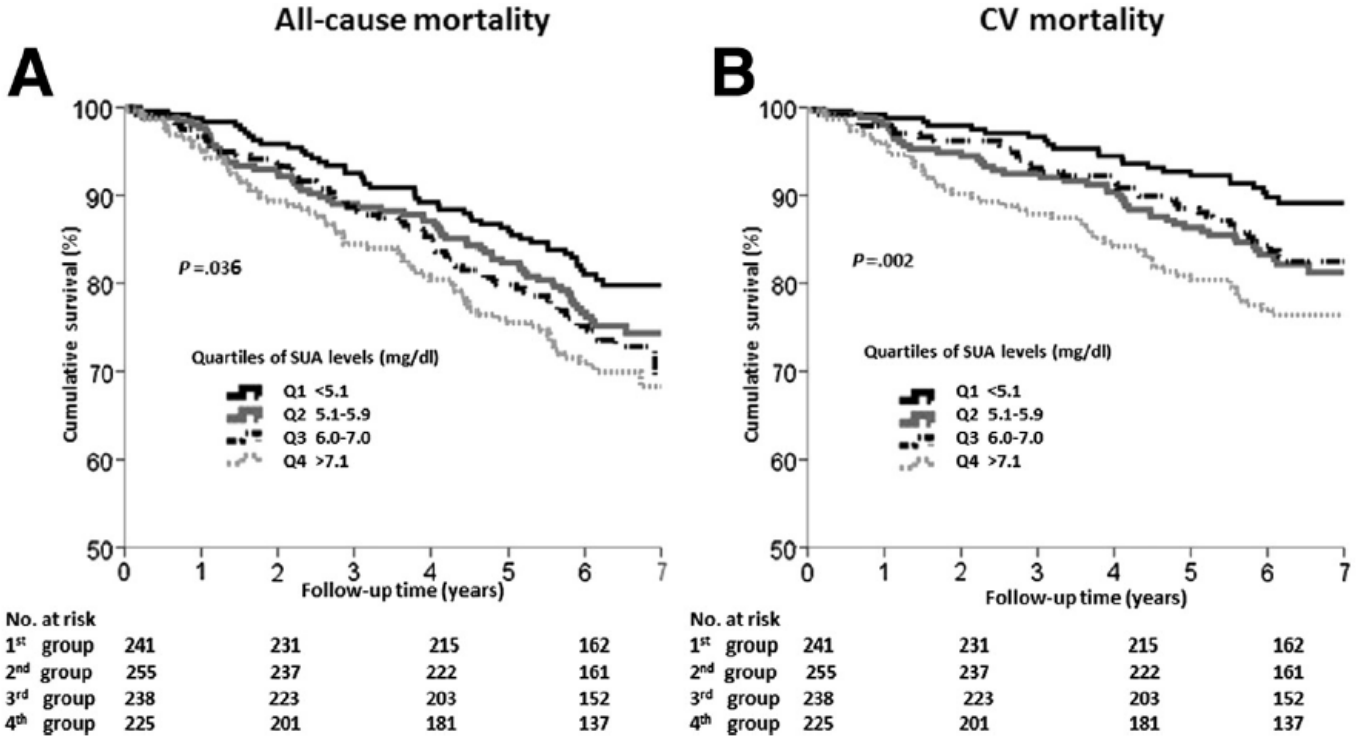

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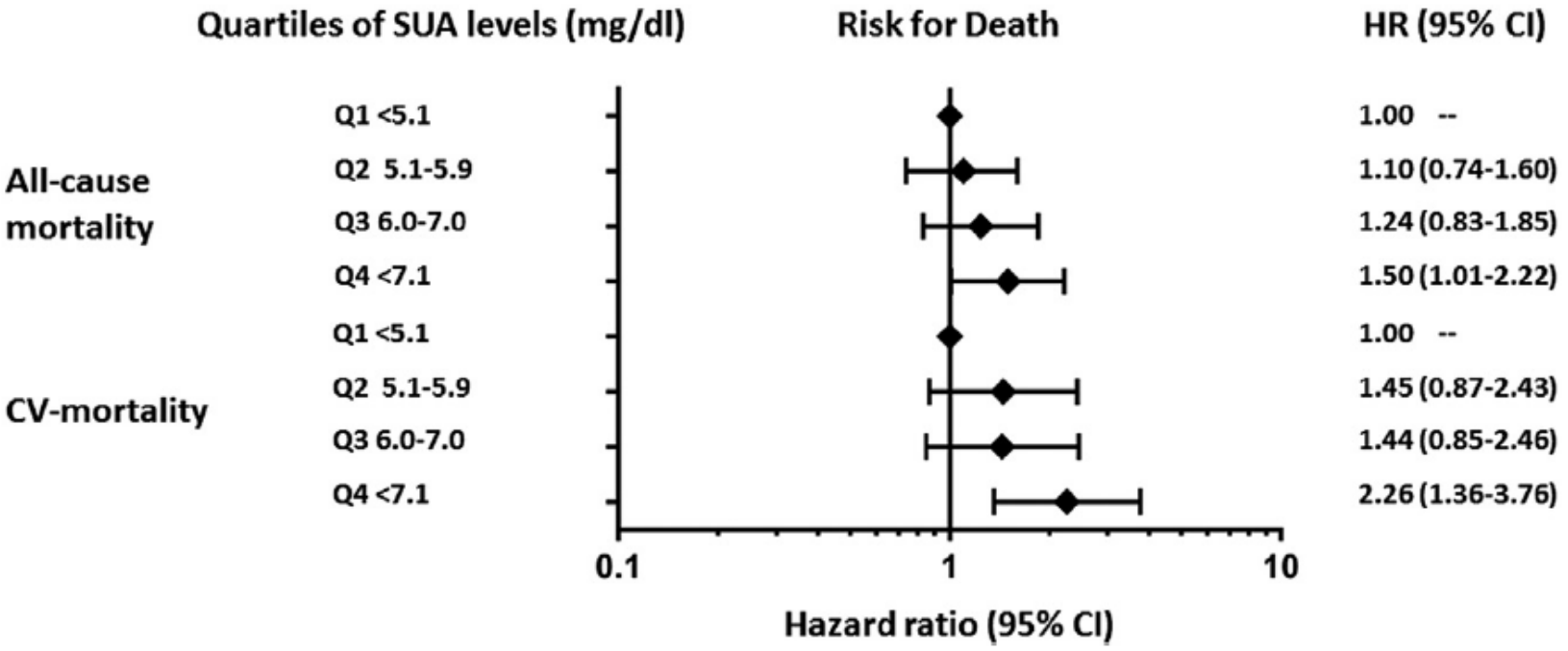


JAMES MONTGOMERY FLAGG

1. Acido urico non è solo sinonimo di gotta e patologie del metabolismo ma si configura anche come un marcatore precoce di aterosclerosi, fin dall'adolescenza
2. Non è del tutto chiara la correlazione tra iperuricemia ed aterosclerosi in termini di IMT o stiffness aortica/carotidea, forse in parte condizionata da possibili fattori genetici e/o razziali
3. Possibile ruolo prognostico dell'iperuricemia nei pazienti con accertata vasculopatia carotidea

Editorial

Serum Uric Acid and Cardiovascular Risk: An Early Wake-up Call

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