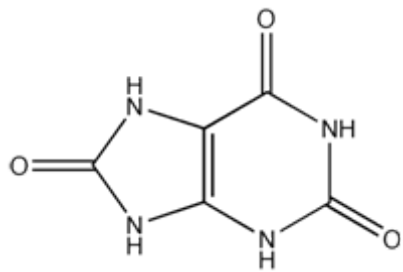
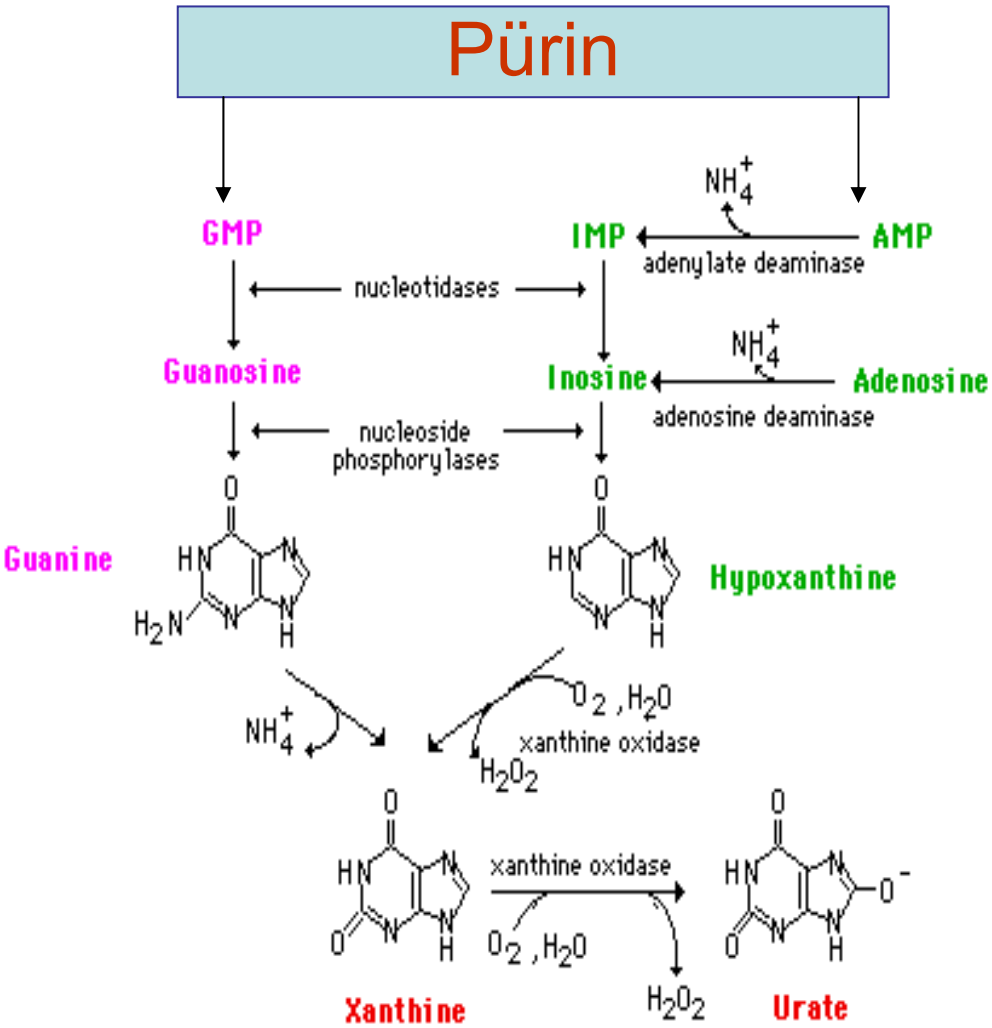
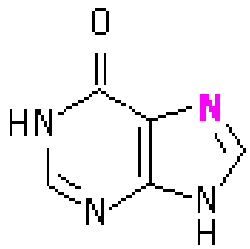
HİPERÜRİSEMİ VE HİPERTANSİYON

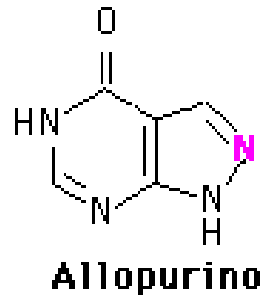
Dr. Savaş Öztürk
Haseki Eğitim ve Araştırma Hastanesi
Nefroloji Kliniği, İstanbul



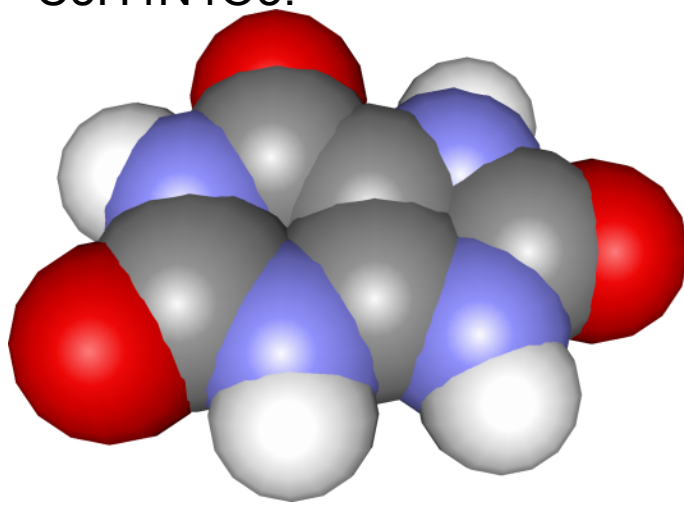
Ürik Asit ve Metabolizması





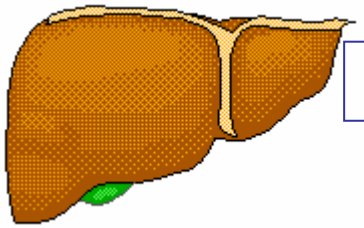


$C_5H_4N_4O_3$.



7,9-dihydro-1H-purine-2,6,8(3H)-trione

Ürik Asit ve Metabolizması



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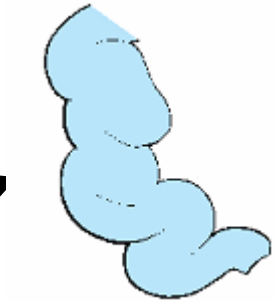

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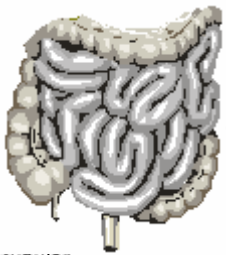
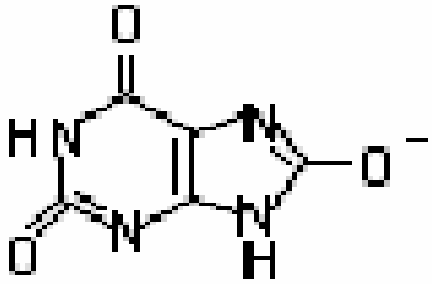
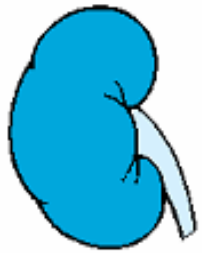
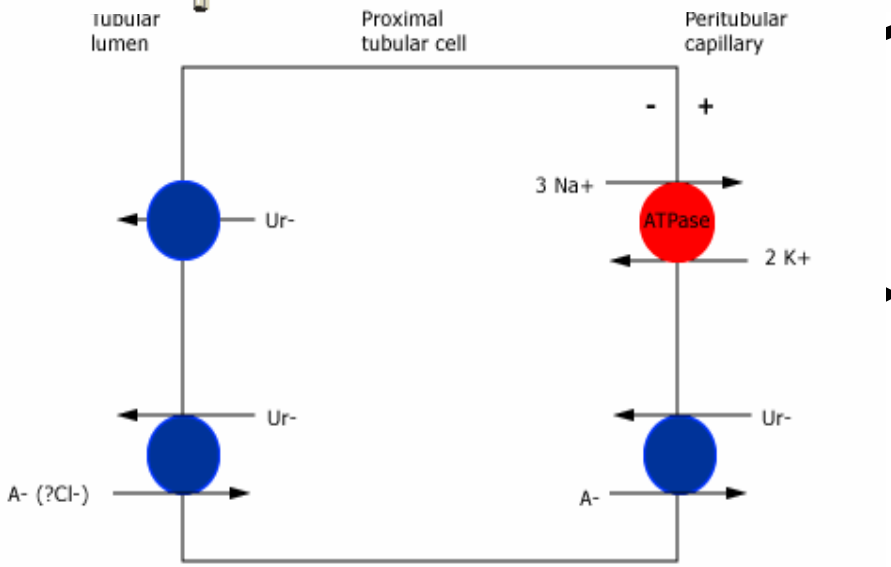


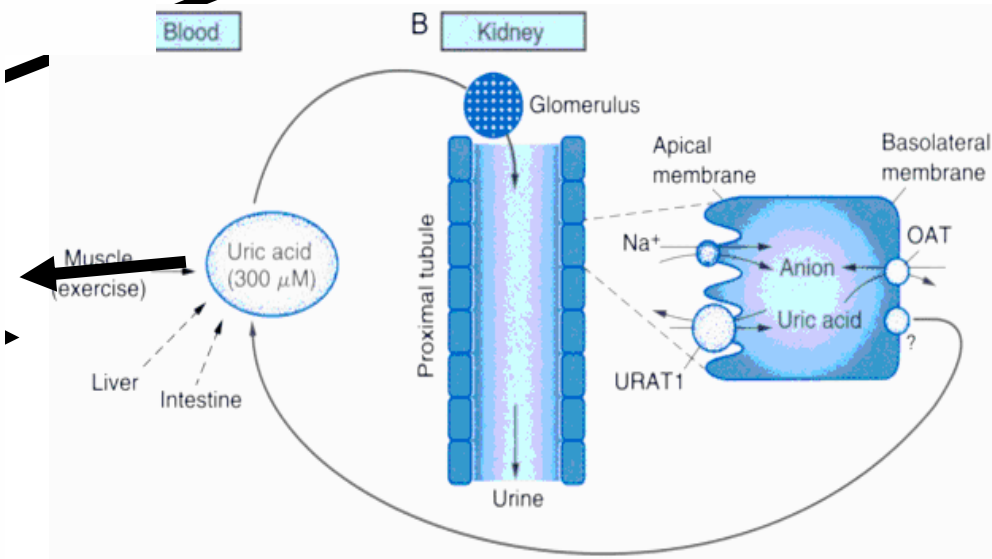


Urate

0





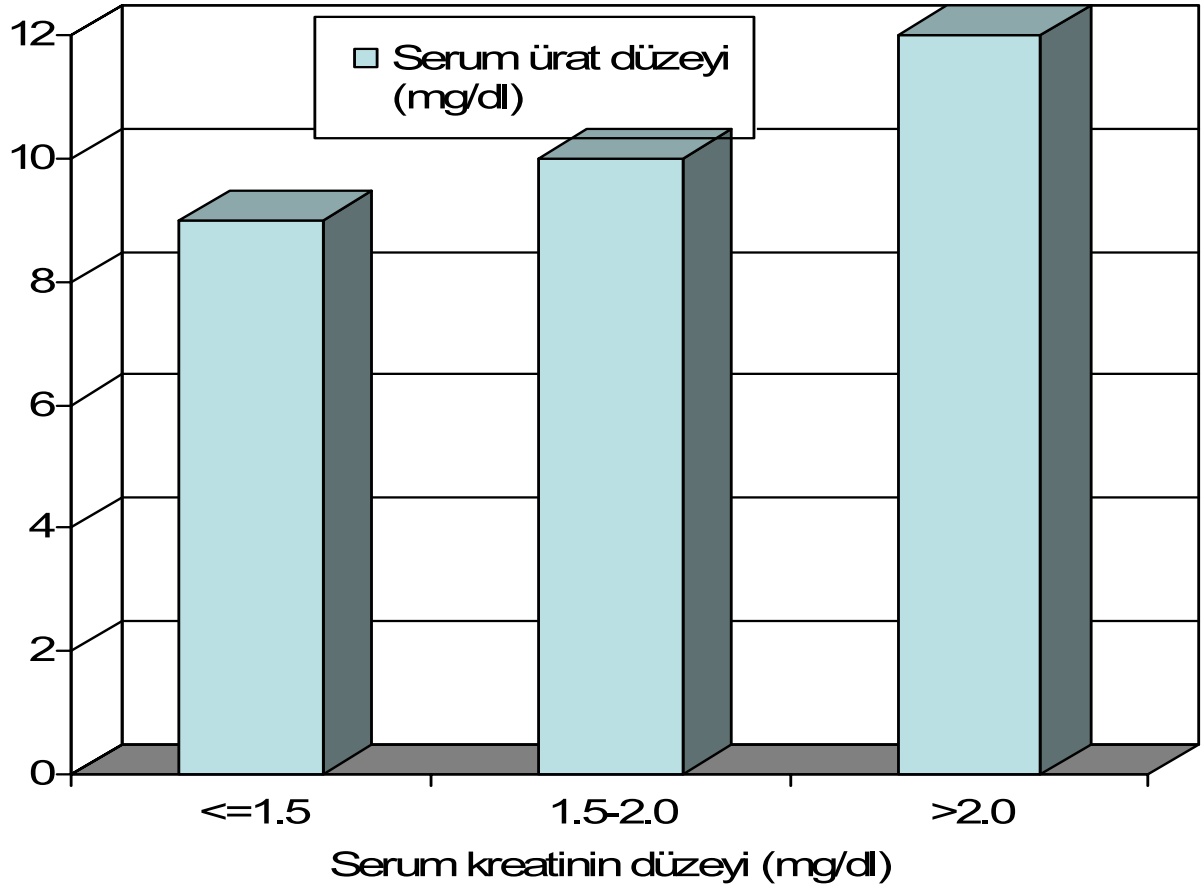


Nature 417:393, 2002

Hiperürisemi

Erkek>7.0-7.5mg/dl

Kadın> 6.0mg/dl

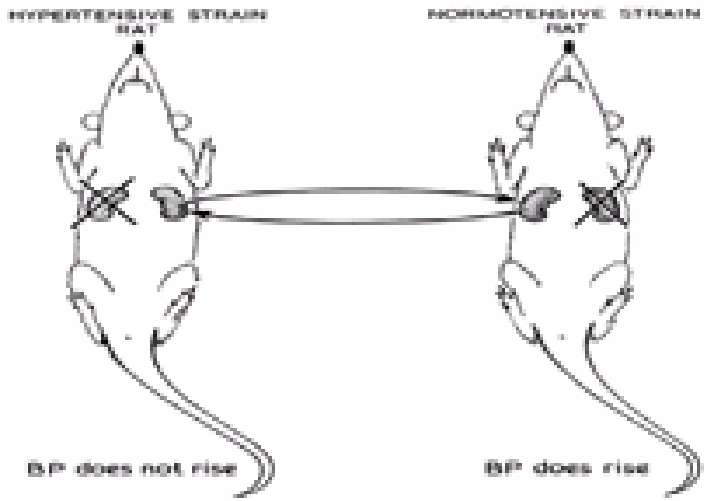


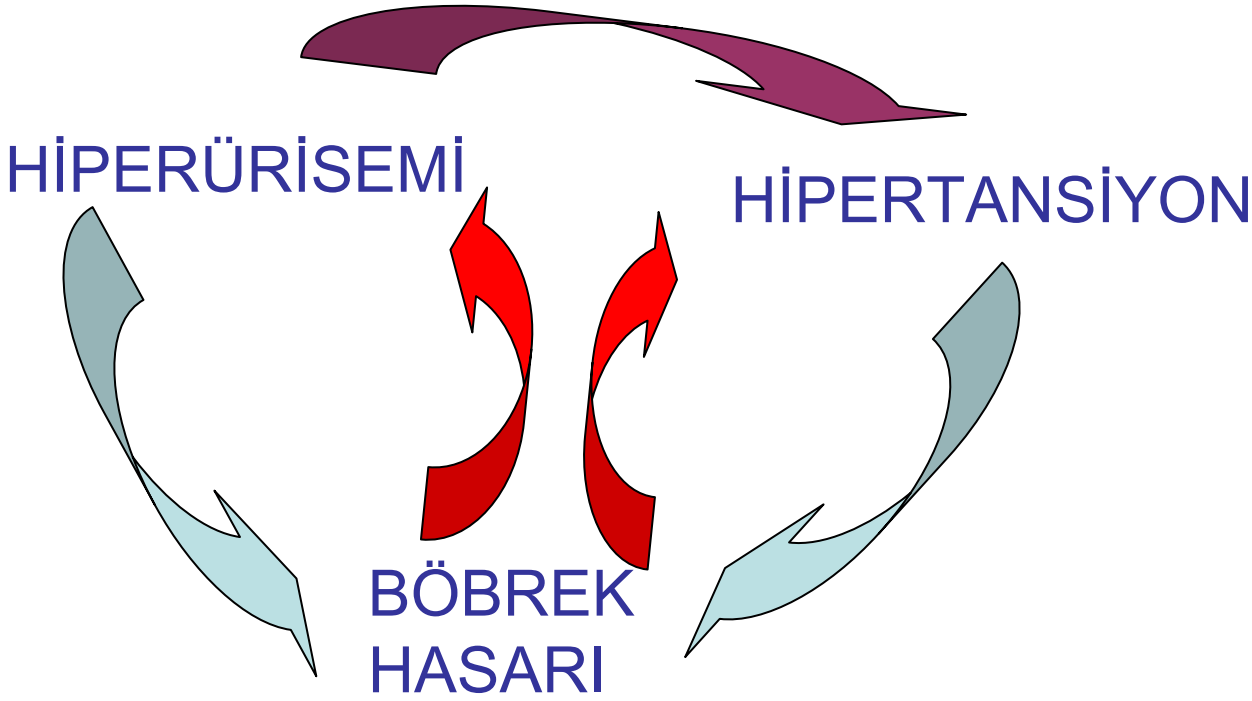
Murray T. Ann Int Med 82:453, 1975

HİPERÜRİSEMİ

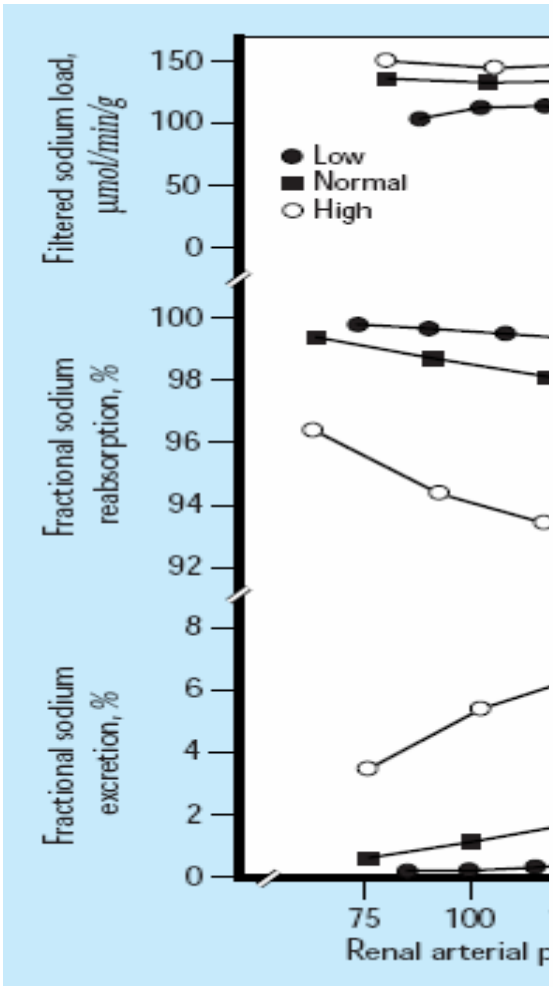
HİPERTANSİYON

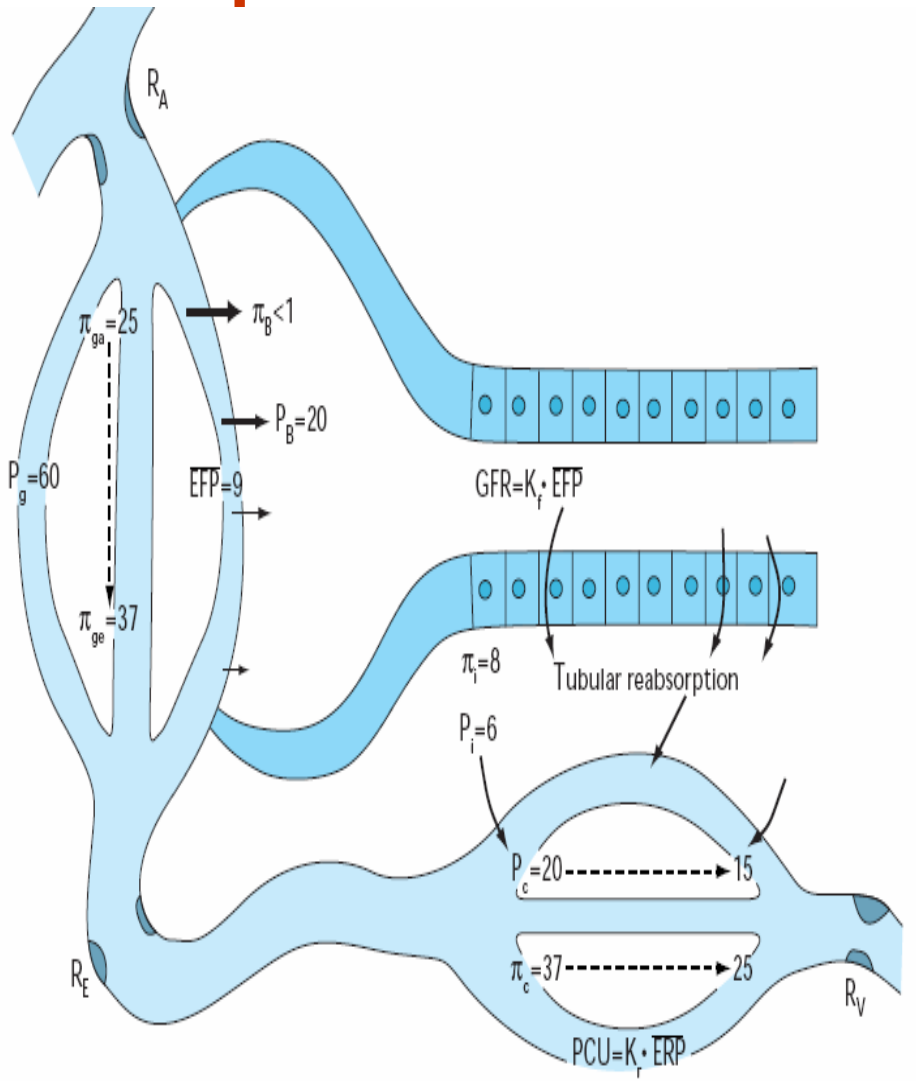
BÖBREK HASARI




HİPERÜRİSEMİ
HİPERTANSİYON
BÖBREK
HASARI

HT ve Hiperürisemi





Ürik Asit

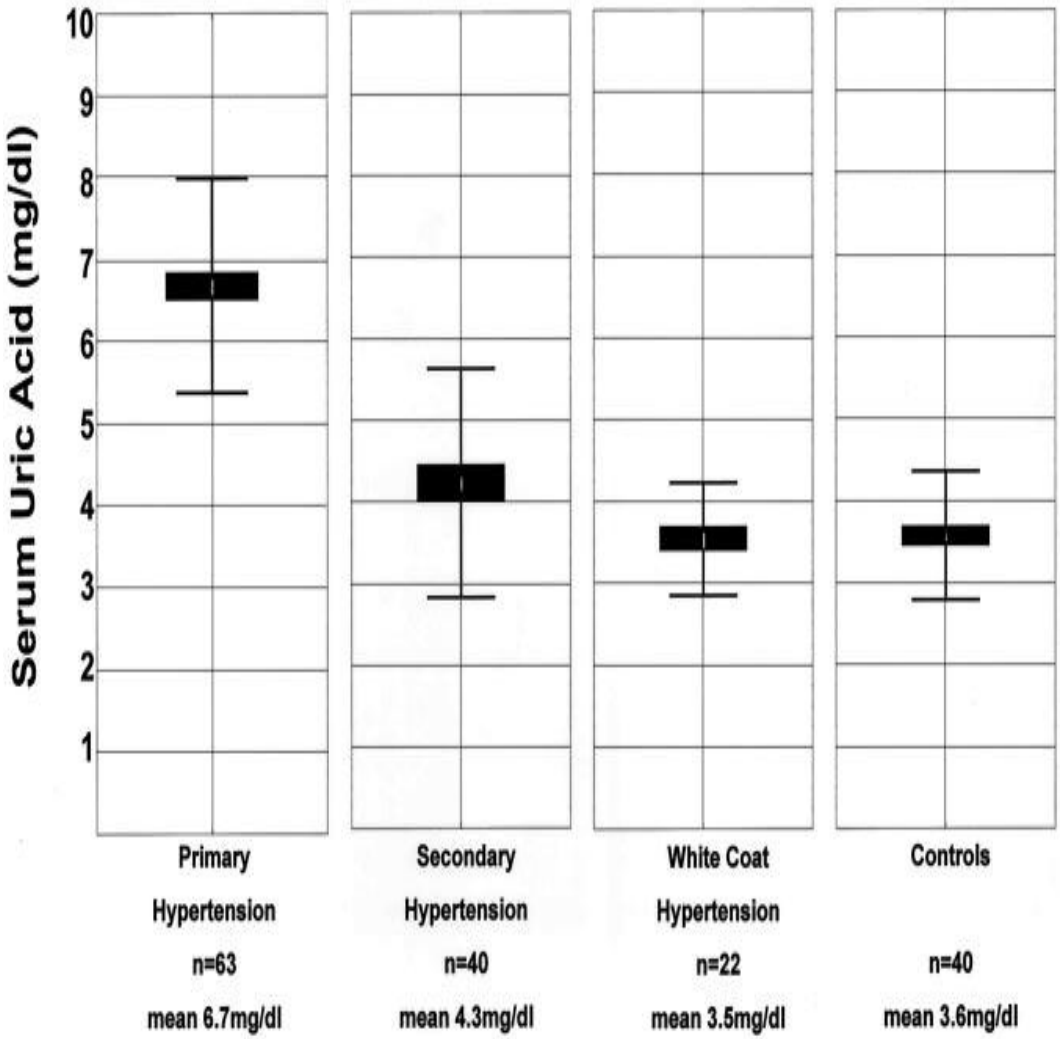
Vazokonstriksiyon

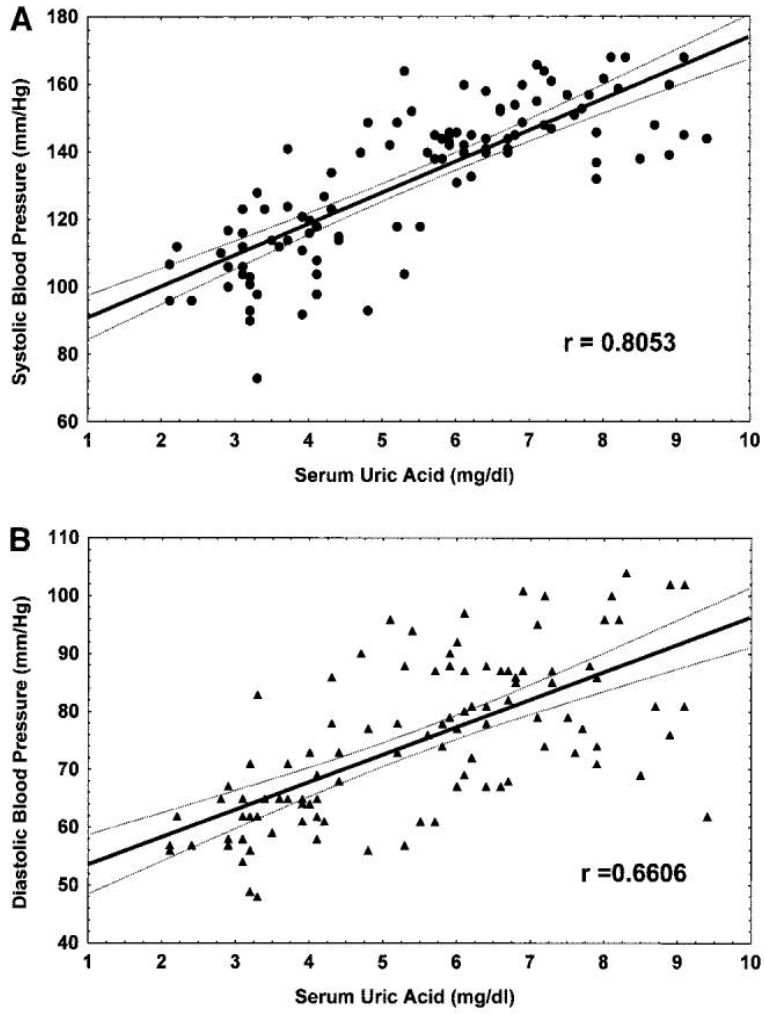
Guyton AC, Am J Med 52:584–594, 1972

Navar LG, Curr Opin Nephrol Hypertens 1996, 5:64–71

Johnson RJ, N Engl J Med 346:913–923, 2002

Hiperürisemi, daha çok esansiyel HT'da görülür





FeigDI, Hypertension 42:247–252, 2003

Ürik Asit ve yeni HT

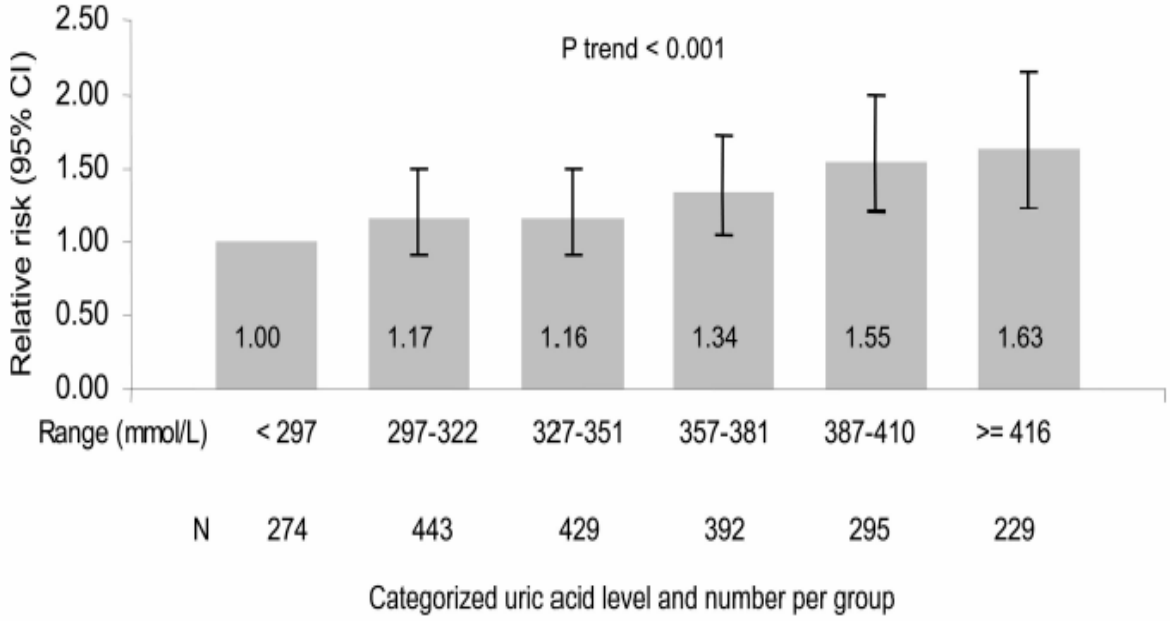


Figure 1. Age-adjusted association of baseline serum uric acid level with incident hypertension in the full cohort of the NAS (N=2062); *P* value for trend over the categories of SUA <0.001.

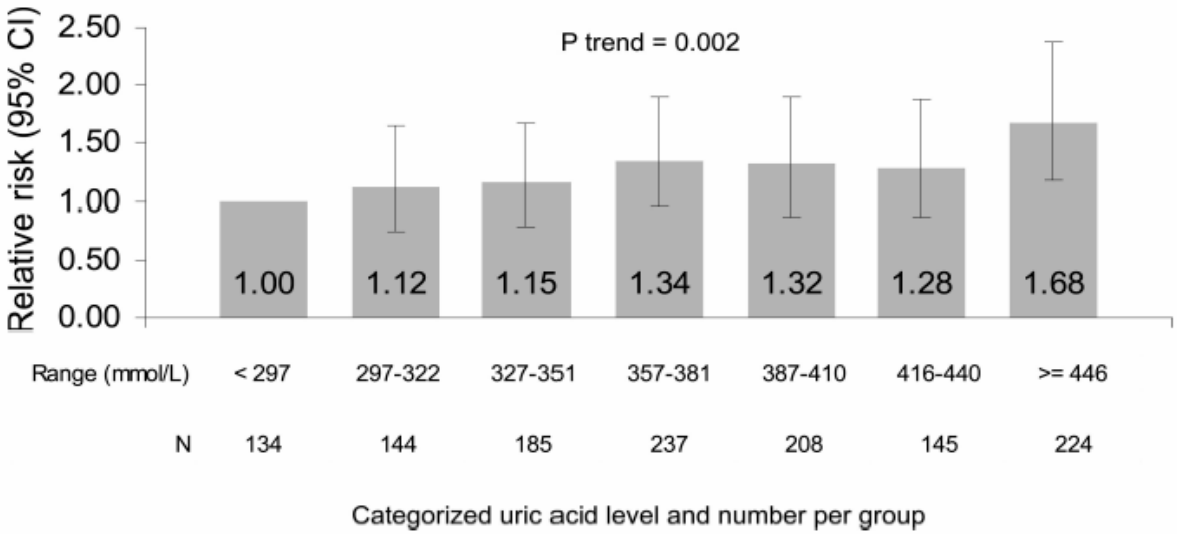
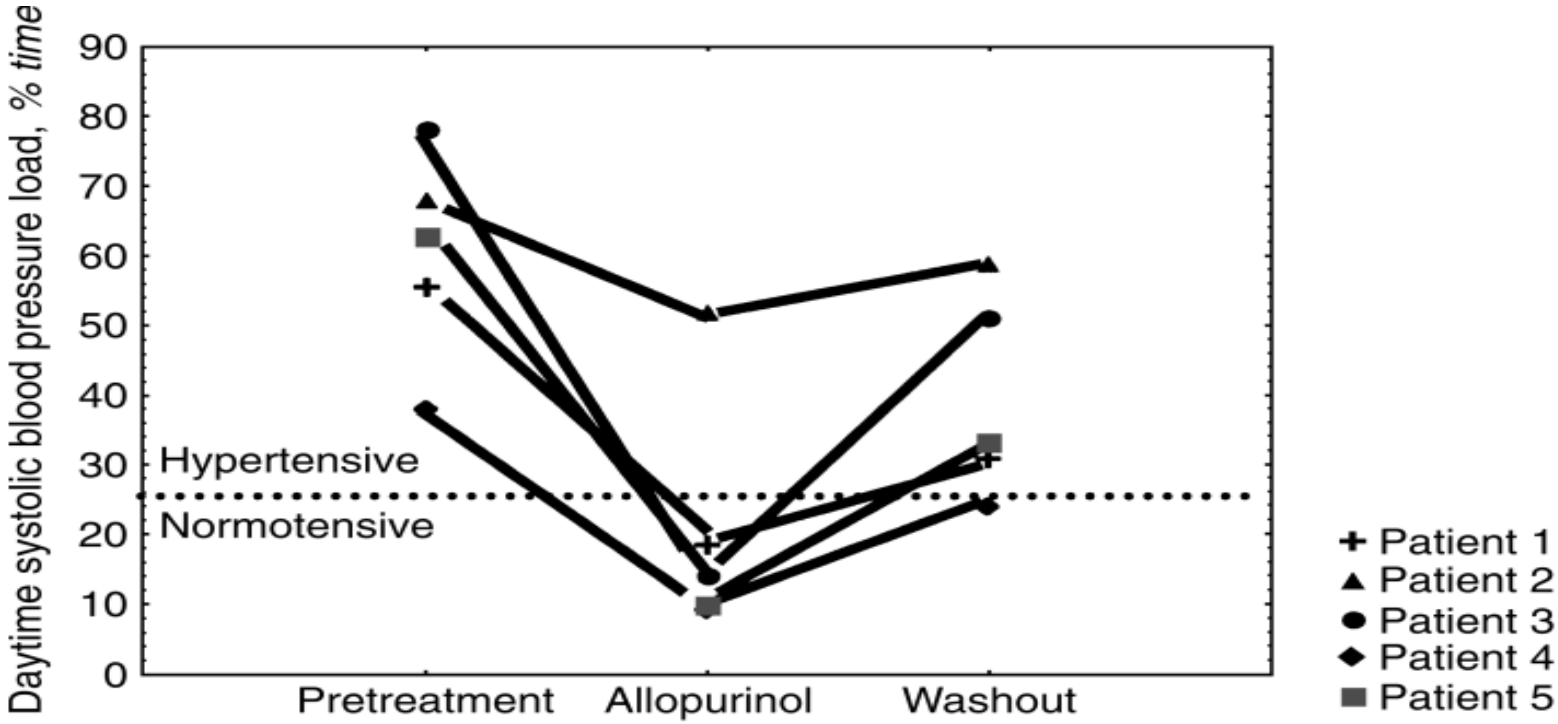


Figure 3. Age- and log-transformed GFR-adjusted association of baseline serum uric acid level with incident hypertension among those men at risk for hypertension at the time of their first creatinine determination (N=1277); *P* value for trend over the categories of SUA=0.002.

Hypertension 2006; 1031-1036

Allopürinol serum ürik asit düzeyini ve kan basıncını düşürür



	Pretreatment	Allopurinol	Washout
Uric acid (mg/dL)	6.9 ± 0.6	3.3 ± 0.4 (0.0005)	5.9 ± 0.2 (0.02)
SBP (mm Hg)	140 ± 3.6	131.2 ± 6.1 (0.017)	137.8 ± 5.5 (NS)
DBP (mm Hg)	77.0 ± 8.3	72.8 ± 7.5 (NS)	76.8 ± 7.2 (NS)
SBP load (%)	60.5 ± 14.9	20.7 ± 17.9 (0.009)	39.7 ± 14.7 (0.02)

Kidney International (2004) 66, 281–287

Hiperürisemi, düşük doğum ağırlığı ile ilişkilidir

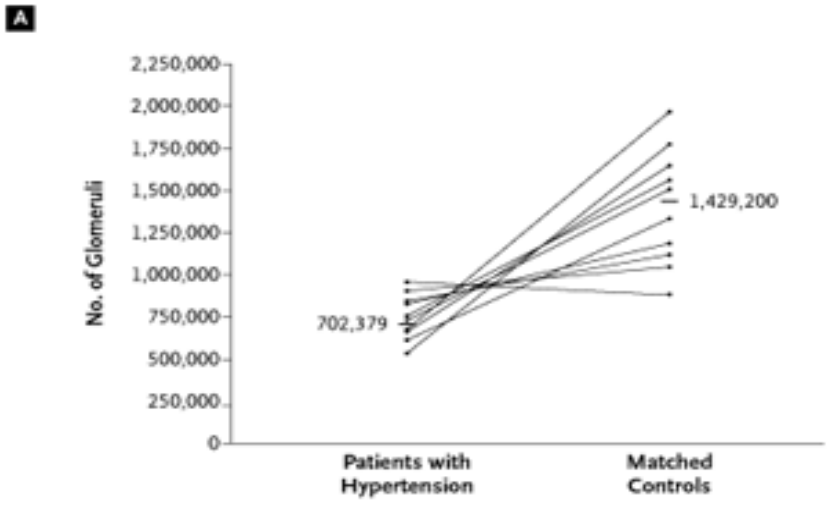


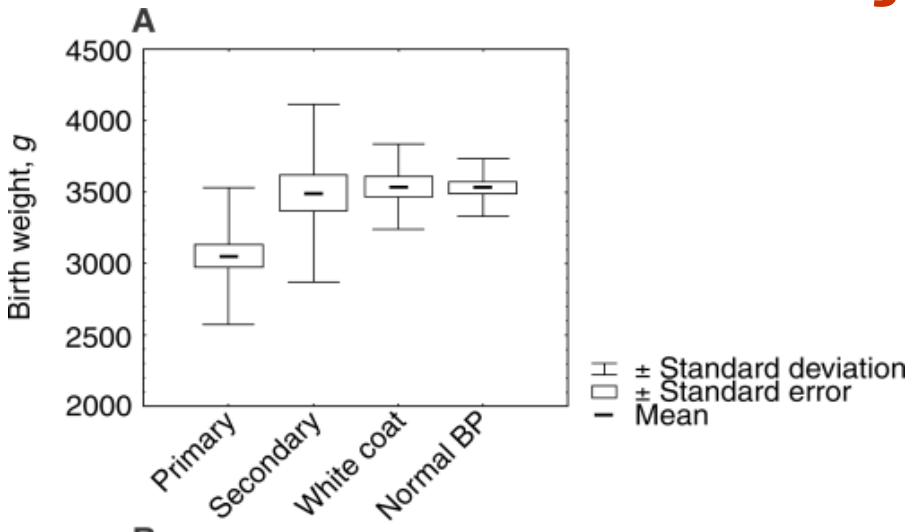
Table 2. Number and Mean Volume of Glomeruli.

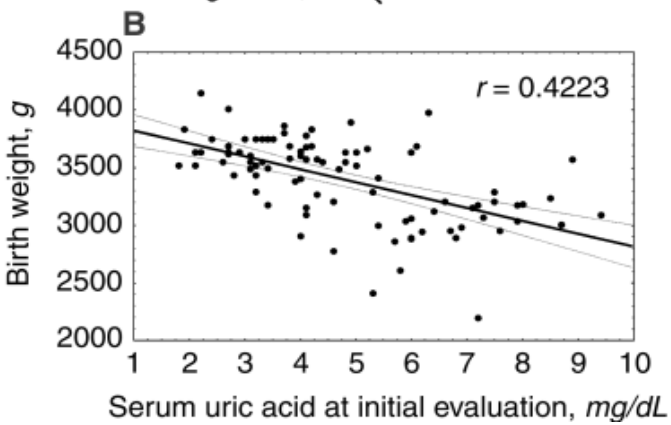
Variable	Patients with Hypertension		Matched Controls	
	No. of Glomeruli	Mean Glomerular Volume ×10⁻³ mm³	No. of Glomeruli	Mean Glomerular Volume ×10⁻³ mm³
Pair no.				
1	680,450	8.49	1,959,914	1.99
2	614,596	5.74	1,339,622	2.79
3	901,995	5.84	1,043,416	3.28
4	827,527	6.79	1,183,679	2.62
5	843,290	7.29	1,112,479	3.96
6	724,307	5.82	1,518,778	1.78
7	662,177	6.92	1,649,525	2.11
8	724,307	6.20	1,559,938	2.78
9	531,140	7.44	1,771,787	2.94
10	954,893	6.09	884,458	4.42
Median	702,379*	6.50*	1,429,200	2.79
25th–75th percentiles	626,491–801,722	5.90–7.20	1,130,279–1,627,128	2.24–3.20

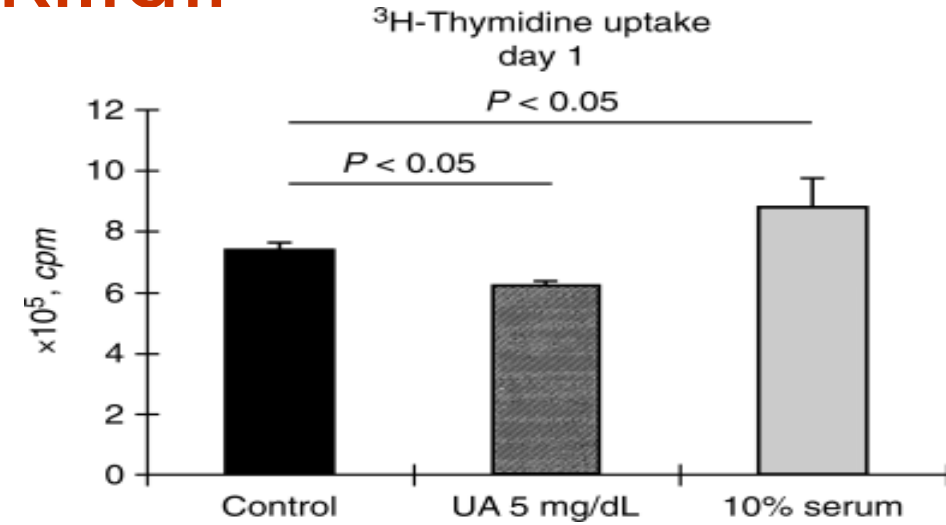
* P<0.001 for the comparison with the controls.

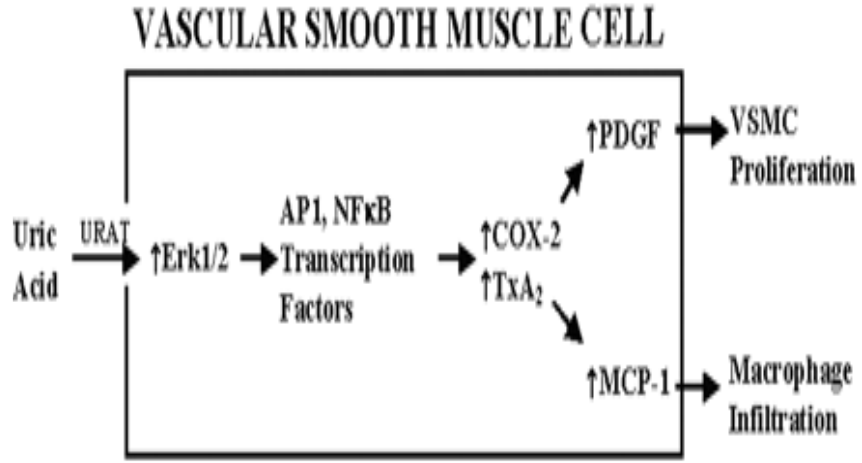
NEJM, 348:1001-1008, 2003

Hiperürisemi, düşük doğum ağırlığı ile ilişkilidir









Kidney International (2004) 66, 281–287

Preeklamsi-ürik asit ilişkisi

- Preeklamptik anneden doğan çocuklarda HT gelişim sıklığı artmıştır

CHANG FM. Biol Res Pregnancy Perinatol 1987; 8: 35−39.

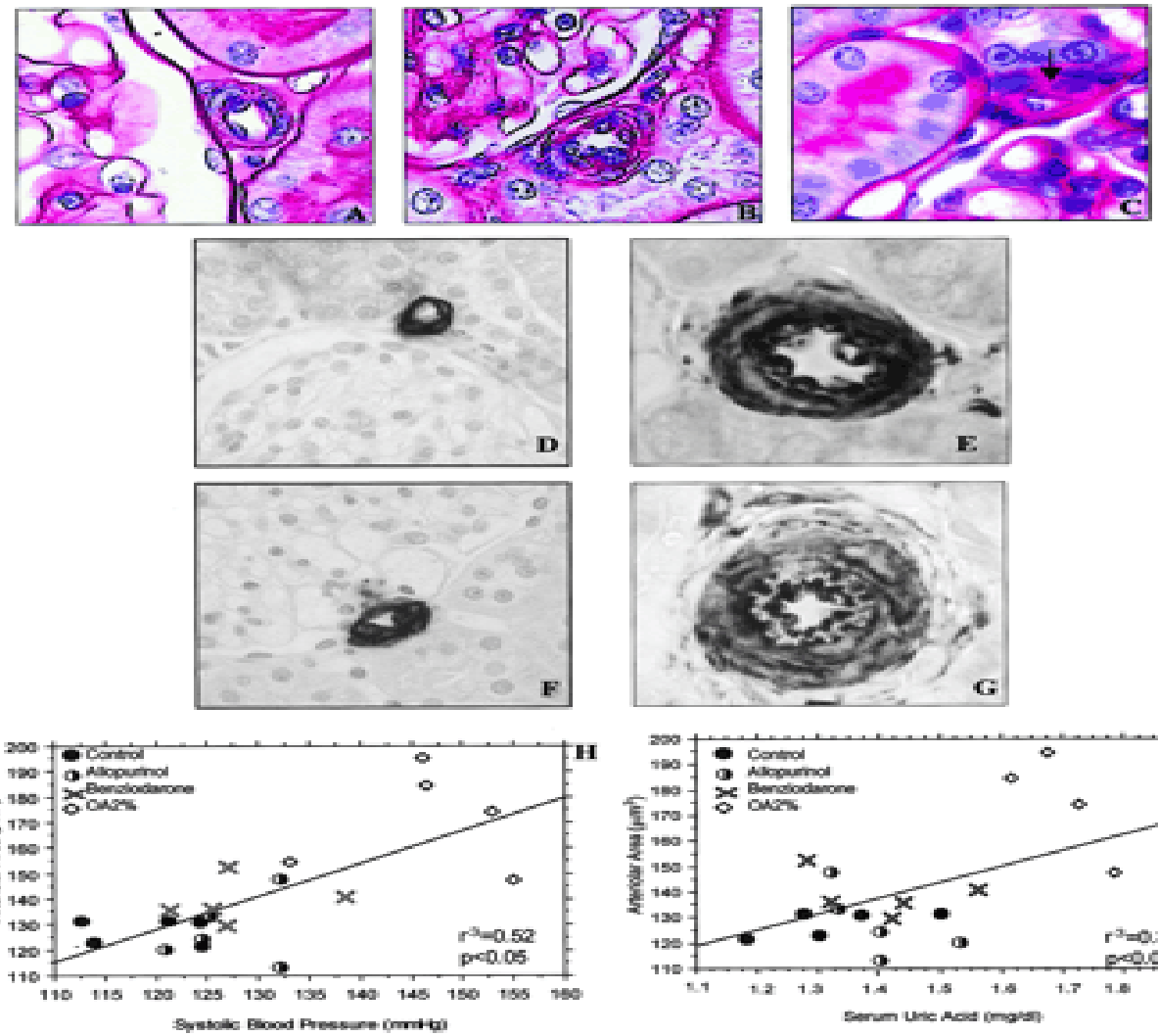
- Preeklampside ürik asit yüksekliği, nefronların oluştuğu 3. trimestırda olur

KONJE JC. Clin Sci (Lond) 1996; 91: 169−175.

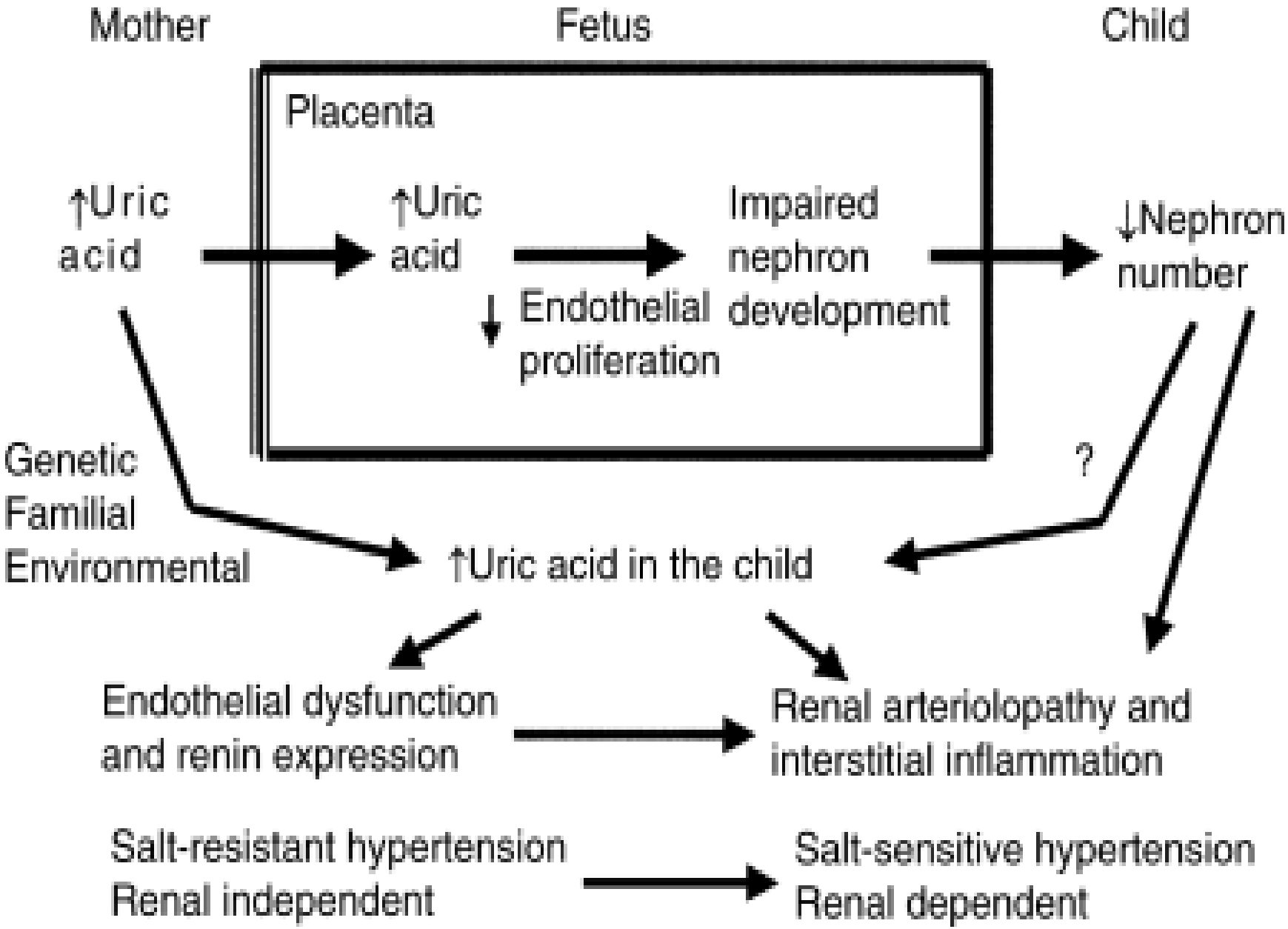
- Preeklamptik anneden doğan çocuklardaki fetal sağkalımda ürik asit düzeyi; anne kan basıncından daha iyi bir göstergedir

REDMAN CW. Lancet 1976; 1: 1370−1373

Hiperürisemi, arteriyopati ve glomerüler hipertrofi ile ilişkilidir



Am J Physiol Renal Physiol 282:991-997, 2002

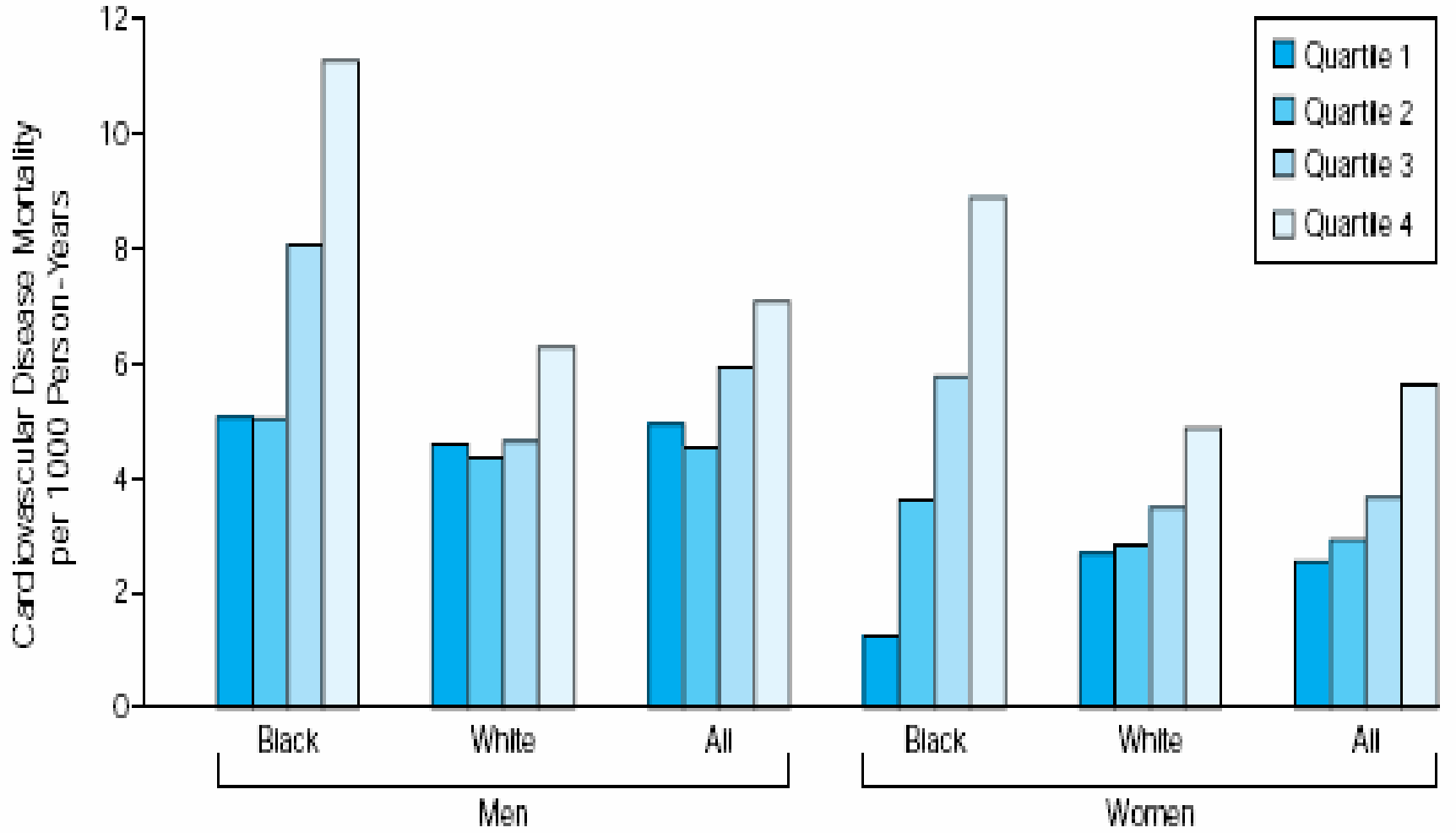


Kidney International (2004) **66**, 281–287

Hiperürisemi, HT gelişimi için bir öngördürücüdür

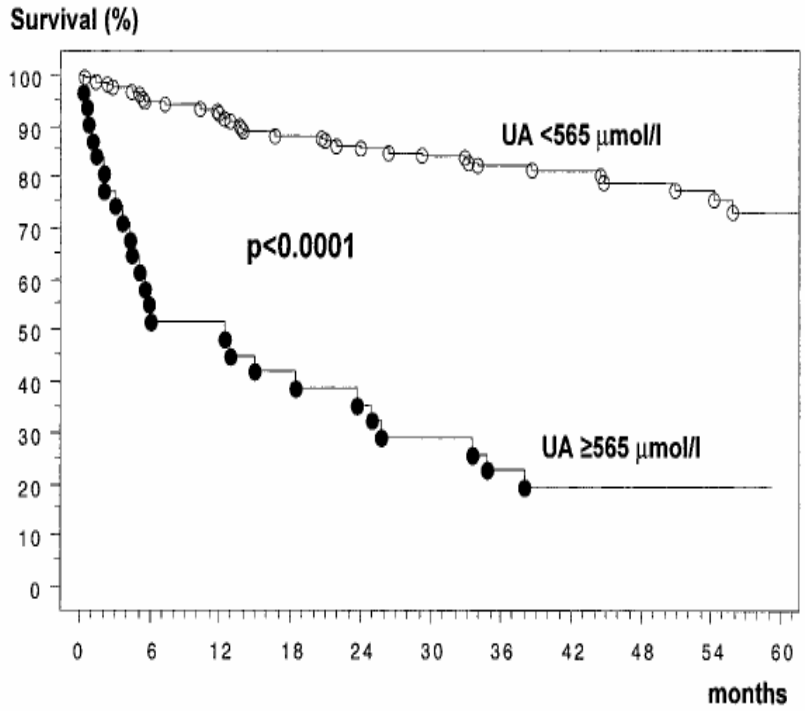
Yazar	Yıl	Sayı	Takip süresi	Risk artışı
Kahn *et al.*	1972	10,000 erkek	5	2-kat
Selby *et al.*	1990	2062 erişkin	6	3-kat
Hunt *et al.*	1991	1482 erişkin	7	2-kat
Jossa *et al.*	1994	619 erkek	12	1.2-kat
Taniguchi *et al.*	2001	6356 erkek	10	2-kat
Masuo *et al.*	2003	433 erkek	5	UA 1mg/dl ↑ +27mmHg sistolik KB
Nakanishi *et al.*	2003	2310 erkek	6	1.6-kat
Nagahama *et al.*	2004	4489 erişkin	23	erkekte1.5-kat kadında 1.9-kat
Alper *et al.*	2005	577 çocuk	11	diyastolik KB ilişkili
Sundstrom *et al.*	2005	3119 erişkin	4	1.5-kat

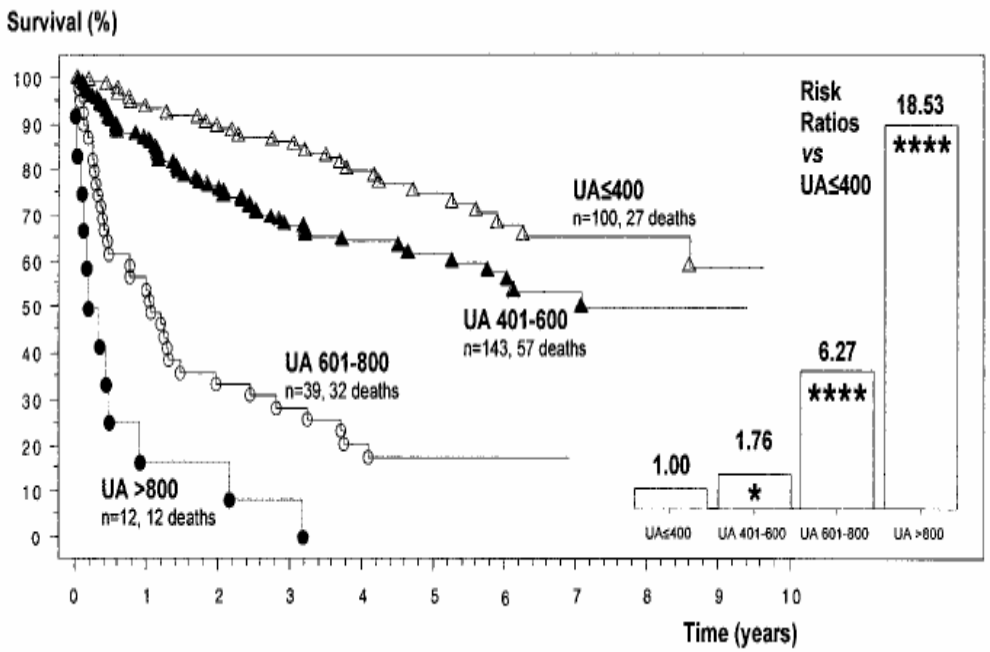
Ürik asit ve KV mortalite



The NHANES I Epidemiologic Follow-up Study, 1971-1992
JAMA. 2000;283:2404-2410.

Ürik asit ve KV mortalite

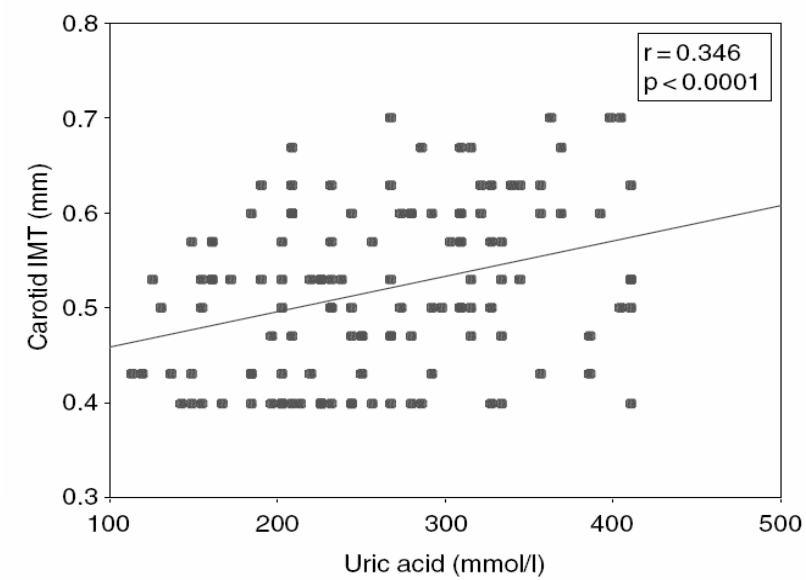


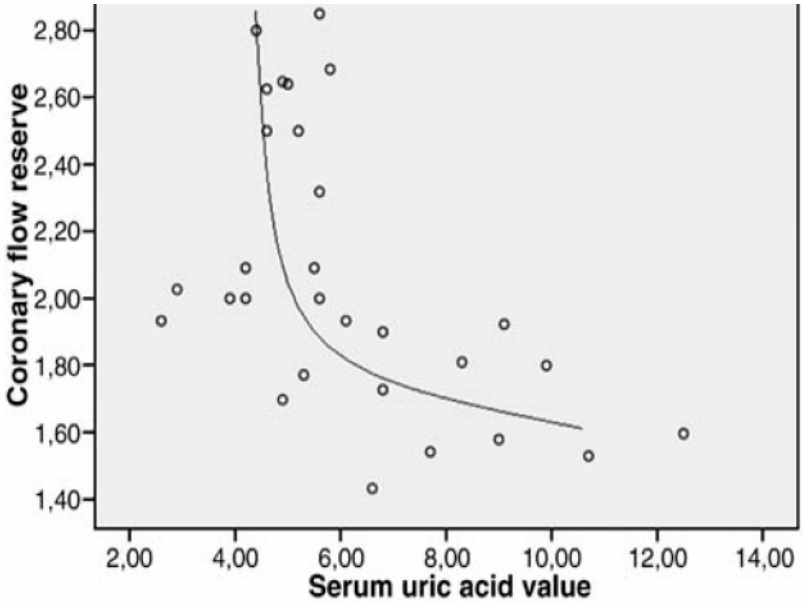


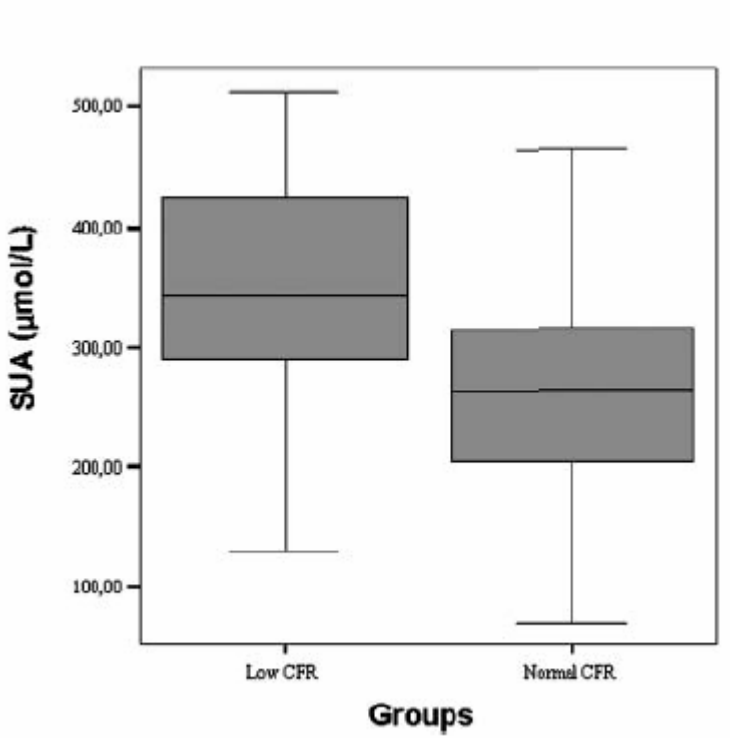
	Univariate Analysis		(Stepwise, Forward)	
	χ^2	*P*	χ^2	*P*
UA, µmol/L	29.53	<0.0001	16.66	<0.0001
Urea, mmol/L	20.15	<0.0001	4.30	0.038
Age, y	14.55	0.0001	7.81	0.0052
Peak Vo_2, mL/kg per minute, n=108*	14.13	0.0002	2.57	0.11
LVEF, %, n=99	8.69	0.003	11.09	0.0009
Creatinine, µmol/L	6.71	0.010	2.95	0.09
Sodium, mmol/L	5.33	0.021	1.52	0.22

Circulation 2003;107;1991-1997;

Ürik asit-ateroskleroz ilişkisi

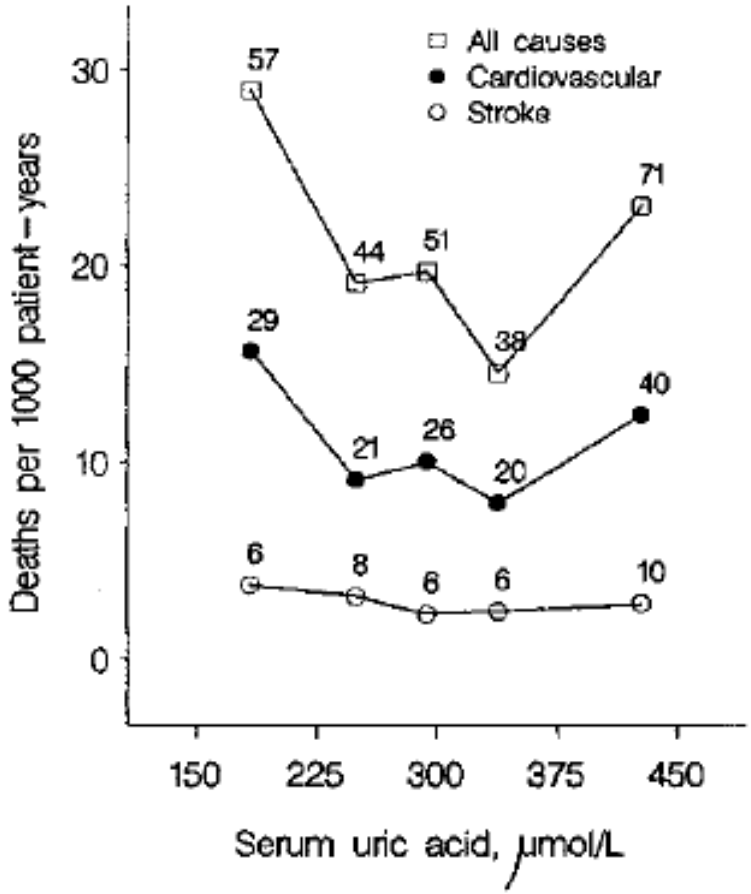


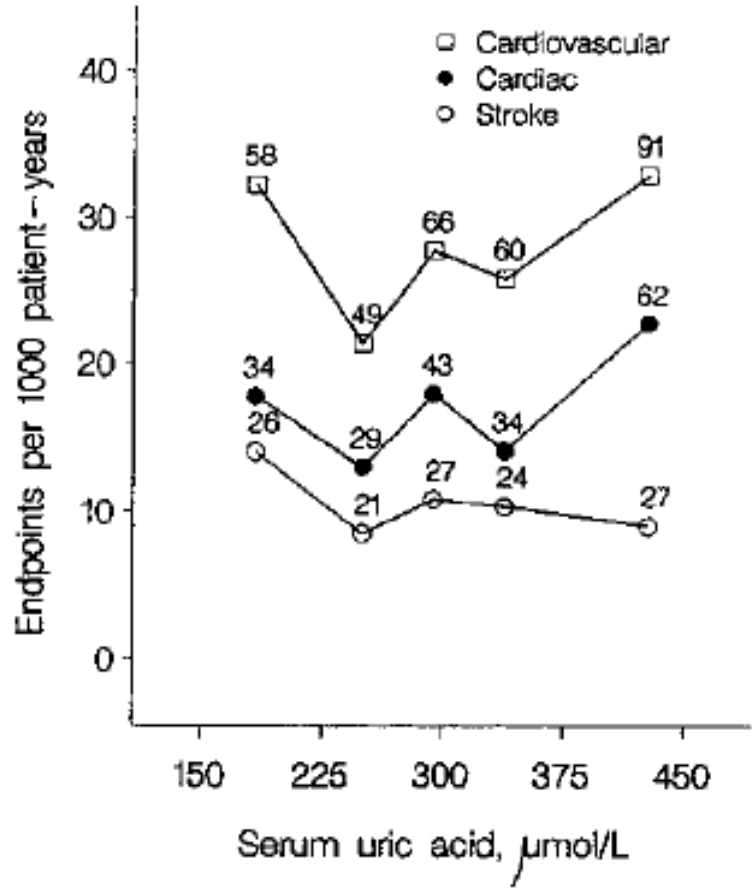




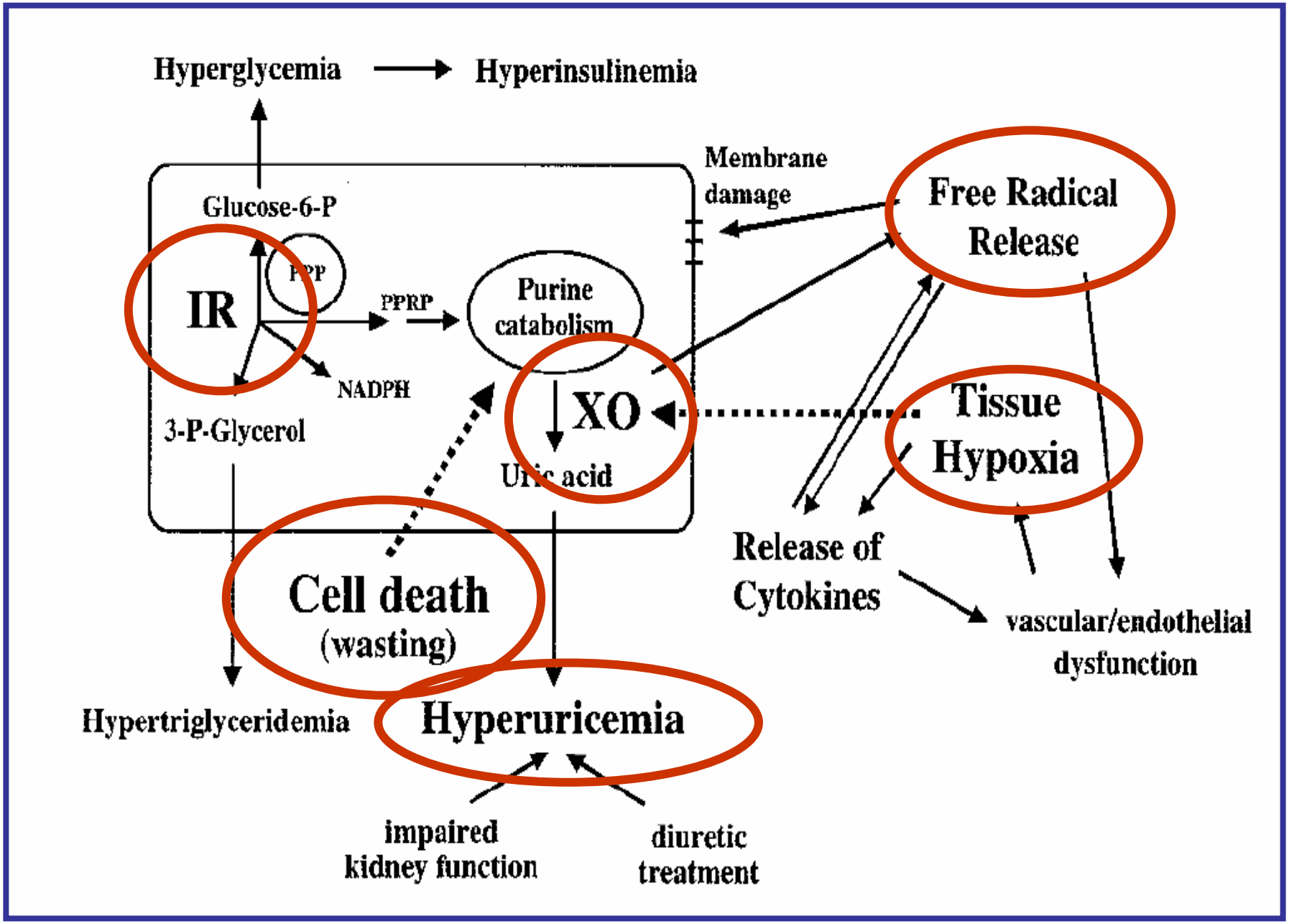
Erdogan D. Int J Clin Pract,2005, 59, 1276–1282
Erdogan D. Circulation. 2007, 115:593-9
Gullu H. Eur J Heart Fail 9: 466–468

İzole sistolik HT'de ürik asit düzeyi prognoz göstergesidir

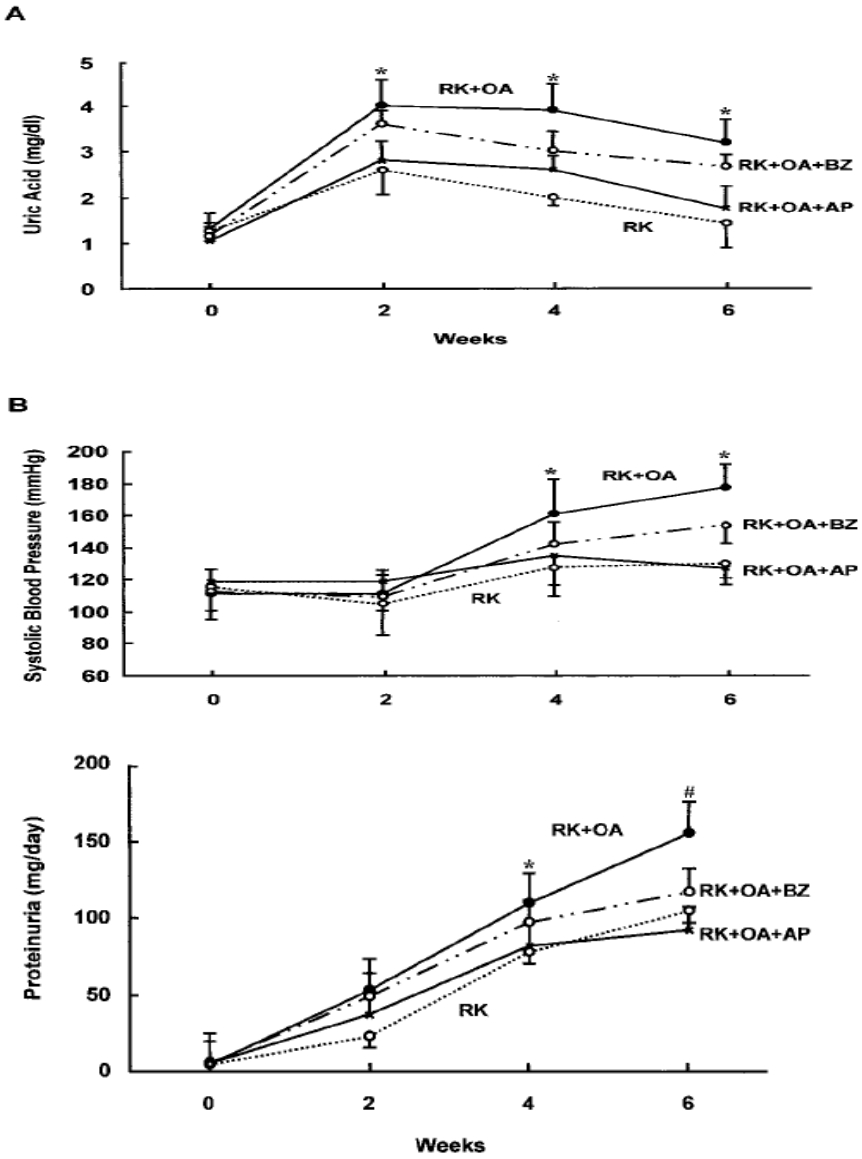


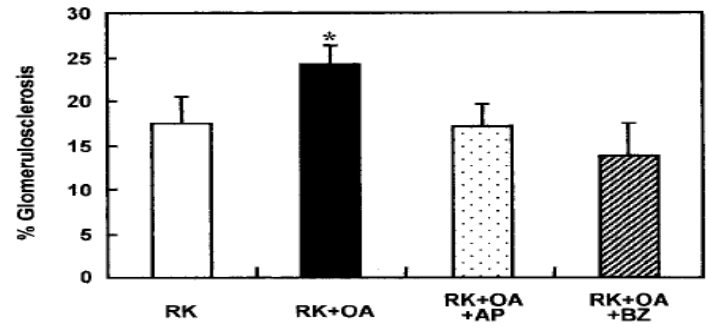


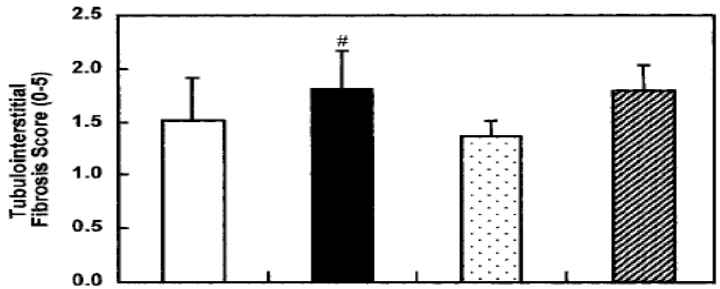
Syst-Eur trial,J Am Soc Nephrol 13: 2213–2222, 2002

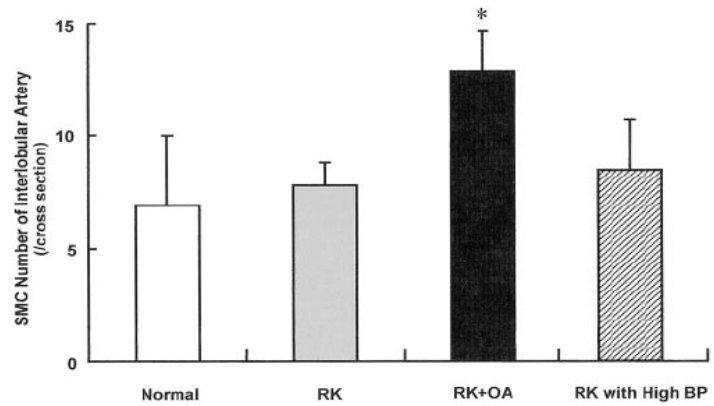

Hyperglycemia
Hyperinsulinemia
Membrane damage
Free Radical Release
Glucose-6-P
IR
PPP
PPRP
Purine catabolism
NADPH
XO
Uric acid
3-P-Glycerol
Tissue Hypoxia
Release of Cytokines
vascular/endothelial dysfunction
Cell death (wasting)
Hypertriglyceridemia
Hyperuricemia
impaired kidney function
diuretic treatment

Ürik asit ve renal hastalık progresyonu



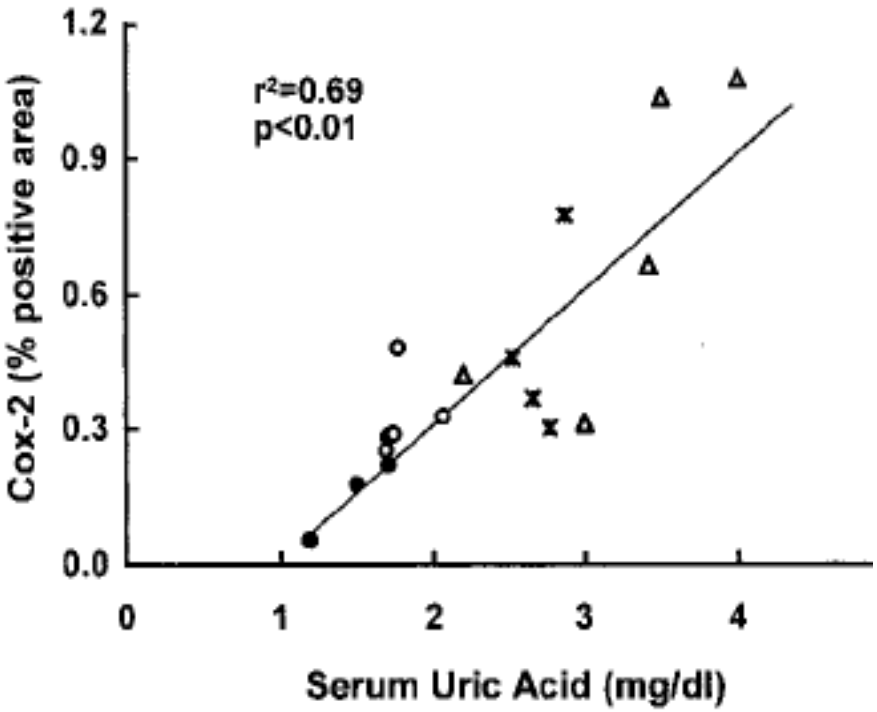


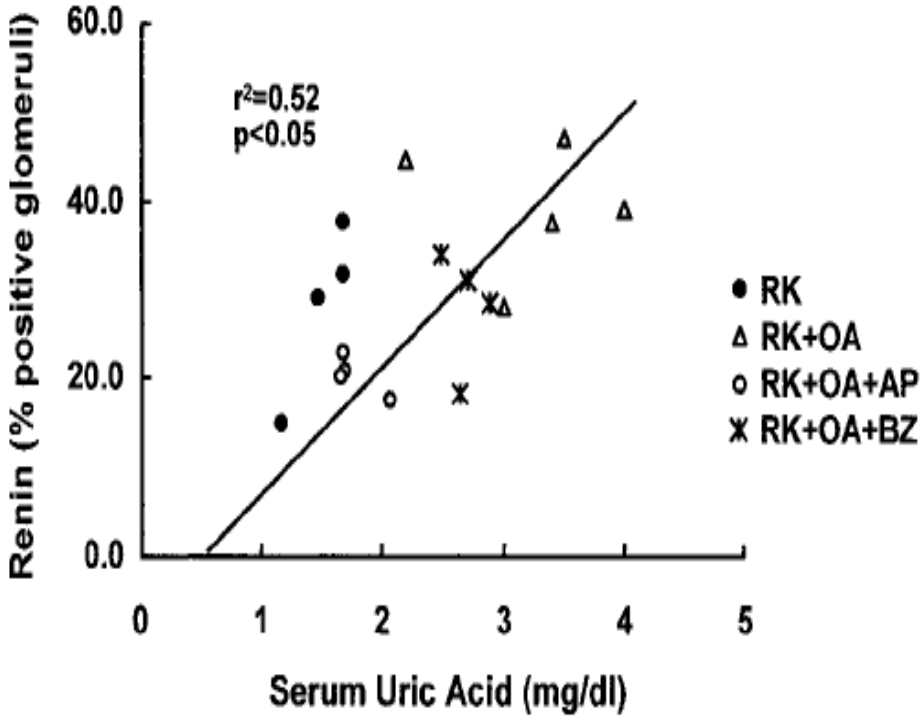




J Am Soc Nephrol 13: 2888–2897, 2002

Ürik asit ve renal hastalık progresyonu





J Am Soc Nephrol 13: 2888–2897, 2002

Hiperürisemik HT'nin tedavisi

- Prospektif, randomize, uzun dönem takipli çalışma yok
- Hiperürisemi tedavisinin fayda/zarar oranı göz önünde bulundurulmalı
- Anamnez, muayene ve tetiklerle hiperürisemiye yol açabilecek hastalıklar dışlanmalı
  - Lenfo-miyeloproliferatif veya hemolitik hastalıklar
  - Enzim bozuklukları
  - Diyetle alım
    - Alkol, bira, et, deniz ürünleri, sakatat, bezelye, fasülye, mercimek
  - Böbrek yetersizliği (atılım bozukluğu)
    - $FE_{\text{ürik asit}} < \%6$
  - İlaçlar
    - Diüretikler, varfarin, kalsinörin inhibitörleri

Hiperürisemik HT'nin tedavisi

- Diyet
  - Alkol, bira, et (sakatat), deniz ürünleri, bezelye, fasülye,mercimek
  - Kilo vermek
- Diüretiklerin kesilmesi?

- Farmakolojik Ajanlar
  - Kanıt yok
  - Otör görüşleri yok
  - Toksisite riski var

→

- Klinik tecrübe önemli
- Bireyselleştirilmiş tedavi?

- Adölesan ve öncesi > 7.0mg/dl
- Erişkin > 9mg/dl

→ **İLAÇ**

Allopürinol

- Ksantin oksidaz inhibitörü
- Kendisi ve metaboliti (oksipürinol) üzerinden etkilidir
- Gut, tümör lizis ve ürik asit taşları için ruhsatlandırılmıştır
- Maksimum doz 800mg/gün
- Böbrek yetersizliğinde doz azaltılmalıdır

Yan etkileri

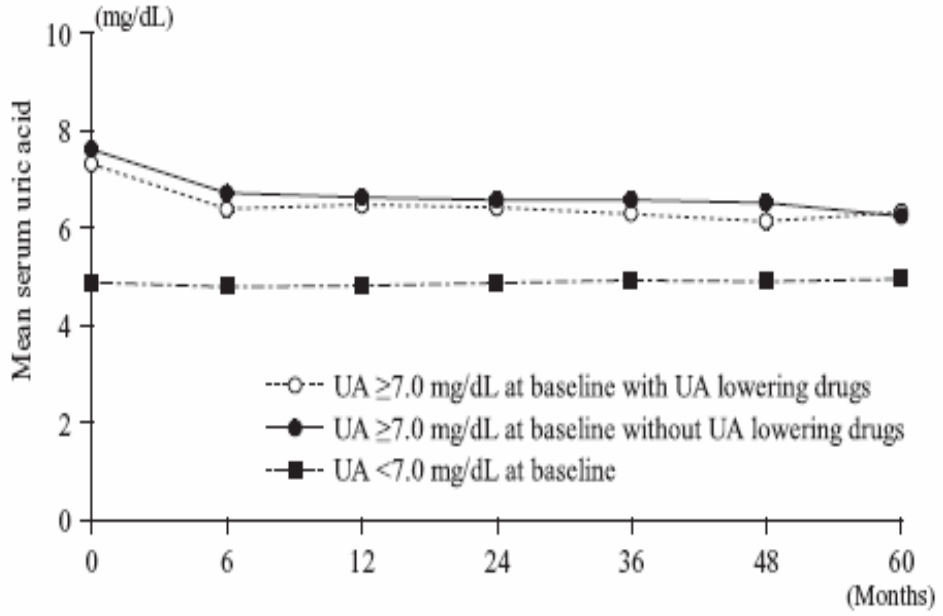
- Döküntü (%10)
  - Böbrek yetersizliğinde artar
- Lökopeni
- Vaskülit
- Hepatit
- İnterstisyel nefrit
- Ateş
- Nörit
- Alopesi

Gebelikte kategori C

- Riskli olabilir, yarar/zarar oranına bakılmalı

Losartan-ürik asit düzeyi

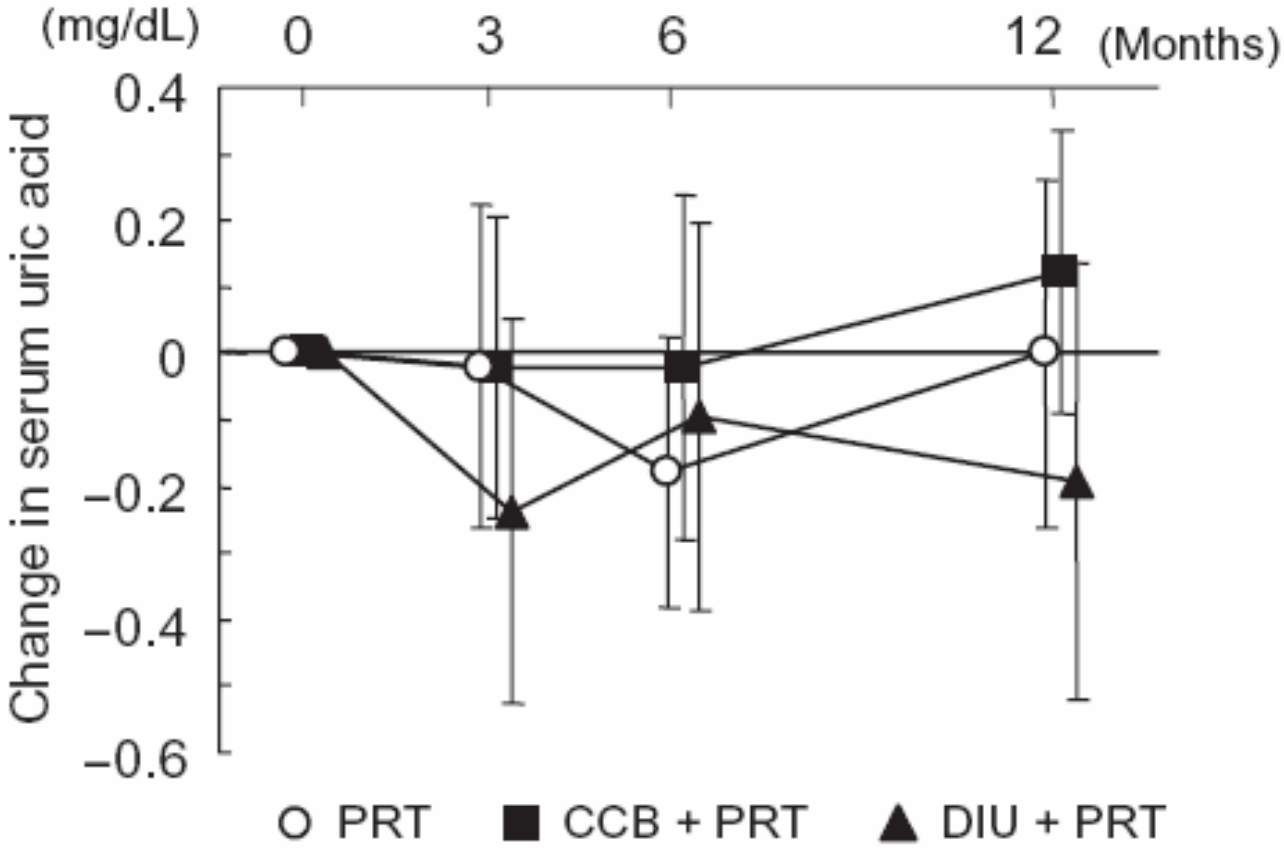
- Losartan: 7.6→6.3mg/dl
- Ürik asit azaltıcı ilaç: 7.3→6.3mg/dl



≥7.0, drugs	854	533	542	465	417	265	62
≥7.0, no drugs	1,310	711	729	581	514	317	95
<7.0	10,524	5,386	6,015	5,107	4,613	2,941	633

Hypertens Res. 31, **2008; 31: 295–304**

Pratosartan, yeni ARB, serum ürik asitini düşürür



Hypertension Research 31 (2008) , 281-287

Rasburicase: Drug information U.S. BRAND NAMES — Elitek™

Enzyme, Urate-Oxidase (Recombinant) U.S. BRAND NAMES — Elitek™

PHARMACOLOGIC CATEGORY Enzyme, Urate-Oxidase (Recombinant)

DOSING: ADULTS — Management of malignancy-associated hyperuricemia (unlabeled use): 0.2 mg/kg/day for 3-7 days, beginning the day before or day of chemotherapy or 0.15-0.2 mg/kg as a single dose, repeated if needed based on uric acid levels or 3-6 mg as a single dose, repeated (1.5-6 mg) if needed based on uric acid levels

DOSING: PEDIATRIC Management of uric acid levels: I.V.: Children: 0.15 mg/kg or 0.2 mg/kg once daily for 5 days (manufacturer-recommended duration); begin chemotherapy 4-24 hours after the first dose

Note: Limited data suggest that a single prechemotherapy dose (versus multiple-day administration) may be sufficiently efficacious. Monitoring electrolytes, hydration status, and uric acid concentrations are necessary to identify the need for additional doses. Other clinical manifestations of tumor lysis syndrome (eg, hyperphosphatemia, hypocalcemia, and hyperkalemia) may occur.

DOSING: ELDERLY — Refer to adult dosing. Insufficient data collected in geriatric patients to determine response to treatment.

DOSAGE FORMS — Excipient information presented when available (limited, particularly for generics); consult specific product labeling.Injection, powder for reconstitution:

Elitek™: 1.5 mg [packaged with three 1 mL ampuls of diluent]; 7.5 mg [packaged with 5 mL of diluent]

DOSAGE FORMS: CONCISE

Injection, powder for reconstitution:

Elitek™: 1.5 mg, 7.5 mg

GENERIC EQUIVALENT AVAILABLE — No

ADMINISTRATION — I.V. infusion over 30 minutes; do not administer as a bolus infusion. Do not filter during infusion. If not possible to administer through a separate line, I.V. line should be flushed with at least 15 mL saline prior to and following rasburicase infusion.

USE — Initial management of uric acid levels in pediatric patients with leukemia, lymphoma, and solid tumor malignancies receiving anticancer therapy expected to result in tumor lysis and elevation of plasma uric acid

USE - UNLABELED / INVESTIGATIONAL — Prevention and treatment of malignancy-associated hyperuricemia in adults

ADVERSE REACTIONS SIGNIFICANT — As reported in patients receiving rasburicase with antitumor therapy versus active-control:

>10%:

Central nervous system: Fever (5% to 46%), headache (26%)
Dermatologic: Rash (13%)
Gastrointestinal: Vomiting (50%), nausea (27%), abdominal pain (20%), constipation (20%), mucositis (2% to 15%), diarrhea (≤1% to 20%)

1% to 10%:

Hematologic: Neutropenia with fever (4%), neutropenia (2%)
Respiratory: Respiratory distress (3%)
Miscellaneous: Sepsis (3%)

<1% (Limited to important or life-threatening): Anaphylaxis, convulsions, hemolysis, methemoglobinemia, pulmonary edema

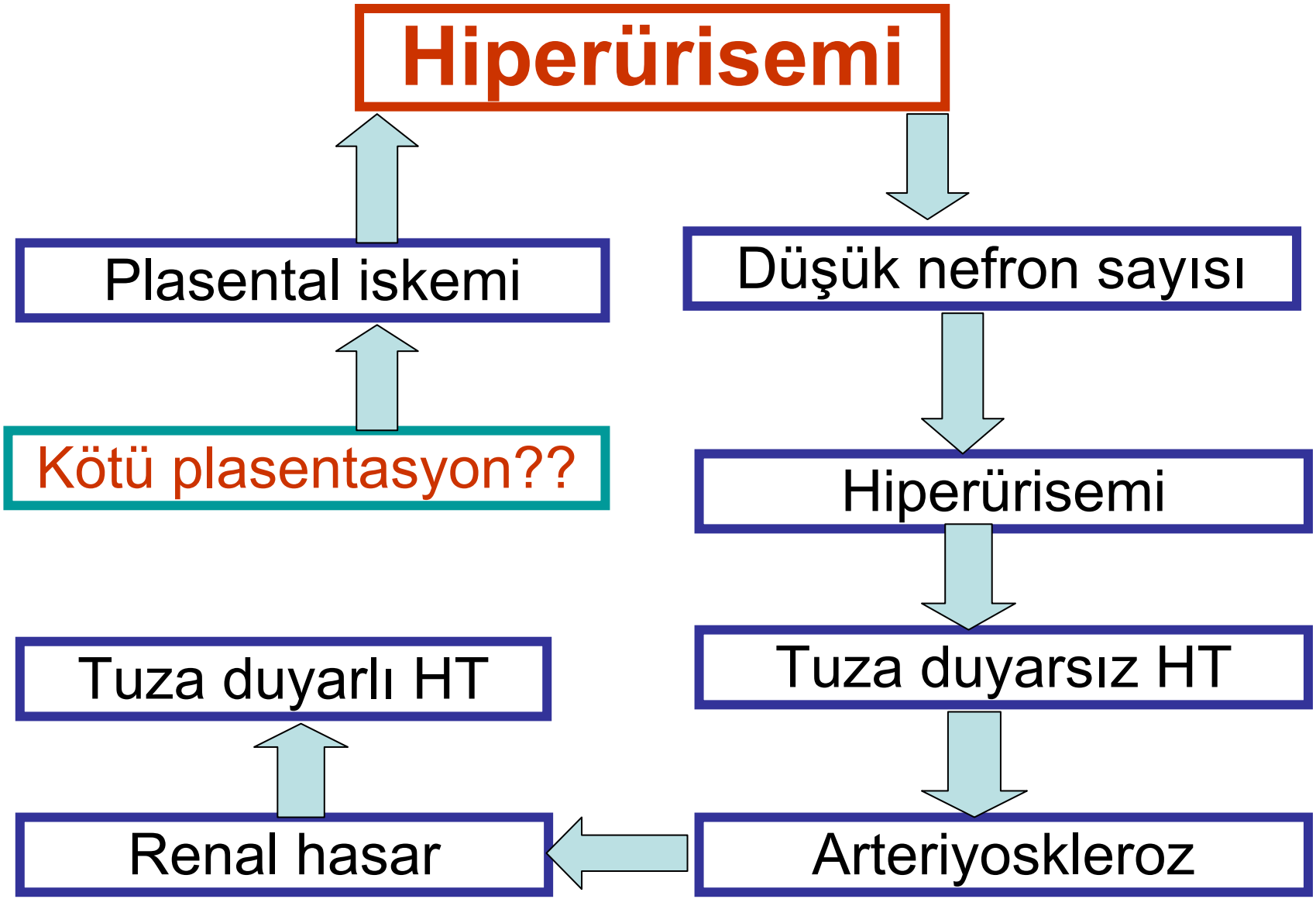
CONTRAINDICATIONS — Hypersensitivity, hemolytic or methemoglobinemia reactions to rasburicase or any component of the formulation; glucose-6-phosphatase dehydrogenase (G6PD) deficiency

PREGNANCY RISK FACTOR — C **PREGNANCY IMPLICATIONS** — Reproduction studies have not been conducted.

LACTATION — Excretion in breast milk unknown/not recommended**ND NAMES** — Fasturtec (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IT, KP, NL, NO, PL, PT, RU, SE, SG, TR, TW); No disponible (MX)

MECHANISM OF ACTION — Rasburicase is a recombinant urate-oxidase enzyme, which converts uric acid to allantoin (an inactive and soluble metabolite of uric acid); it does not inhibit the formation of uric acid.


Tuza duyarlı HT
Düşük Doğum Ağırlığı
Renal Hasar
Preeklampsi
ÜRİK ASİT
Endotel Disfonksiyonu
Vasküler Düz Kas Prolif.
Arteriyoskleroz Ateroskleroz
KV Hastalık


Hiperürisemi
Plasental iskemi
Düşük nefron sayısı
Kötü plasentasyon??
Hiperürisemi
Tuza duyarlı HT
Tuza duyarsız HT
Renal hasar
Arteriyoskleroz