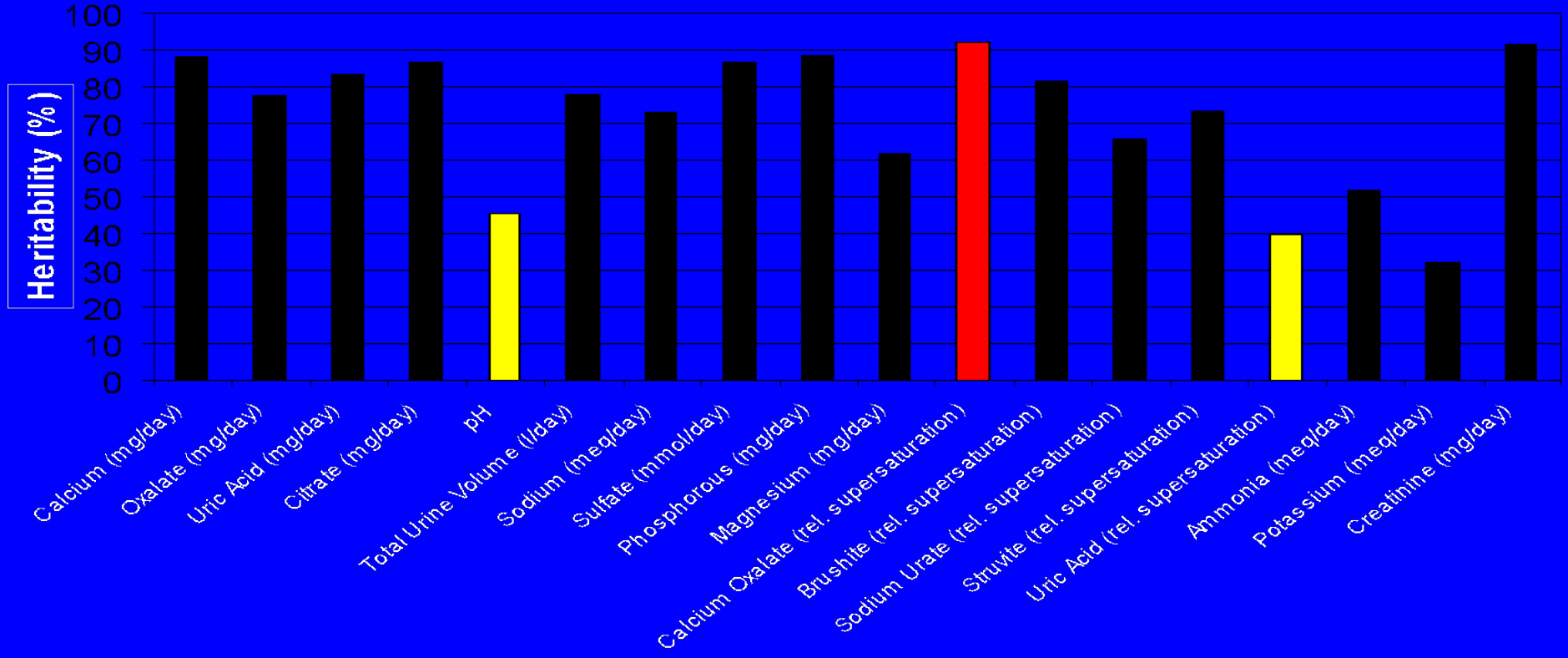

STONES
Dietary and Medical Therapy
Prevention
Adjuvant
Manoj Monga, MD
The Cleveland Clinic

Incidence and Prevalence

- Worldwide, 1 in 10 people experience a kidney stone in their lifetime
- Recurrence rates are high
  - 30% to 50% chance of developing another stone within 5 years
  - Average rate of new stone formation: 1 stone every 2 to 3 years
- Prevalence has increased
  - Faster rate of increase in women

Heritability for Stone Risk



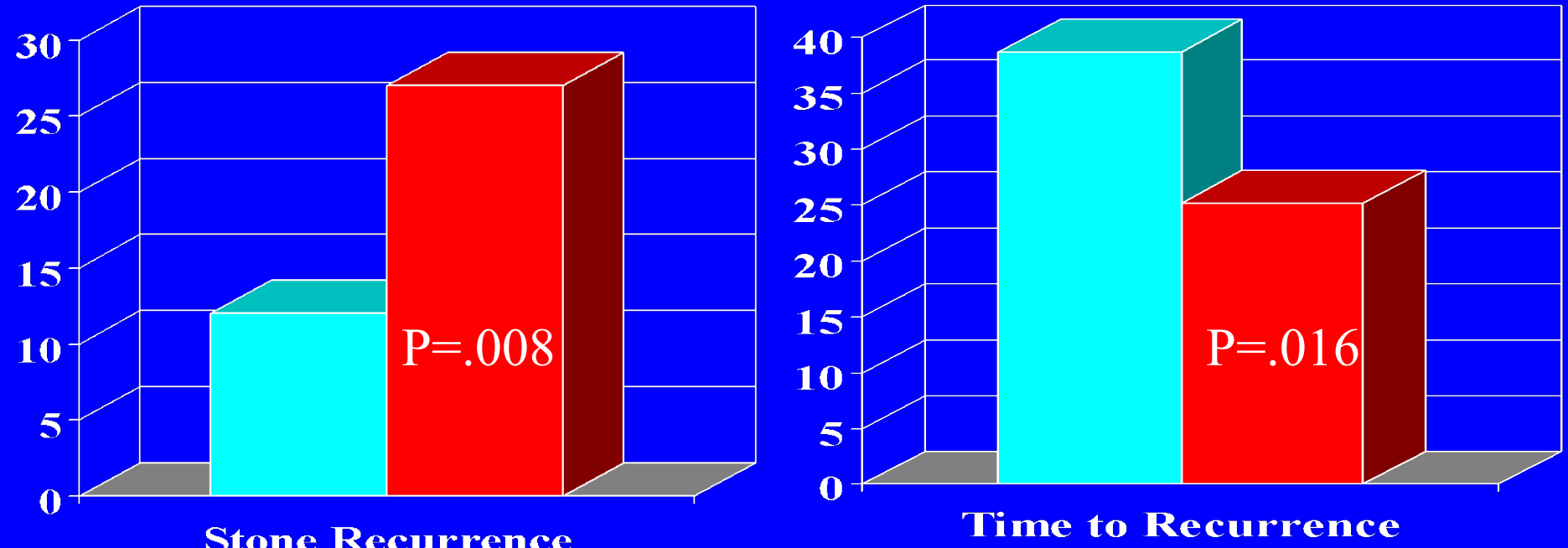
J Urol, June 2006

EMPIRIC DIETARY TX

Conservative treatment plan

- High fluid intake (Ten 10-oz glasses)
- Dietary sodium restriction (1500 mg/day)
- Dietary citrate (4oz concentrated lemon/lime)
- Adequate calcium intake
  - 2 to 3 dairy servings per day
  - 1200 mg daily

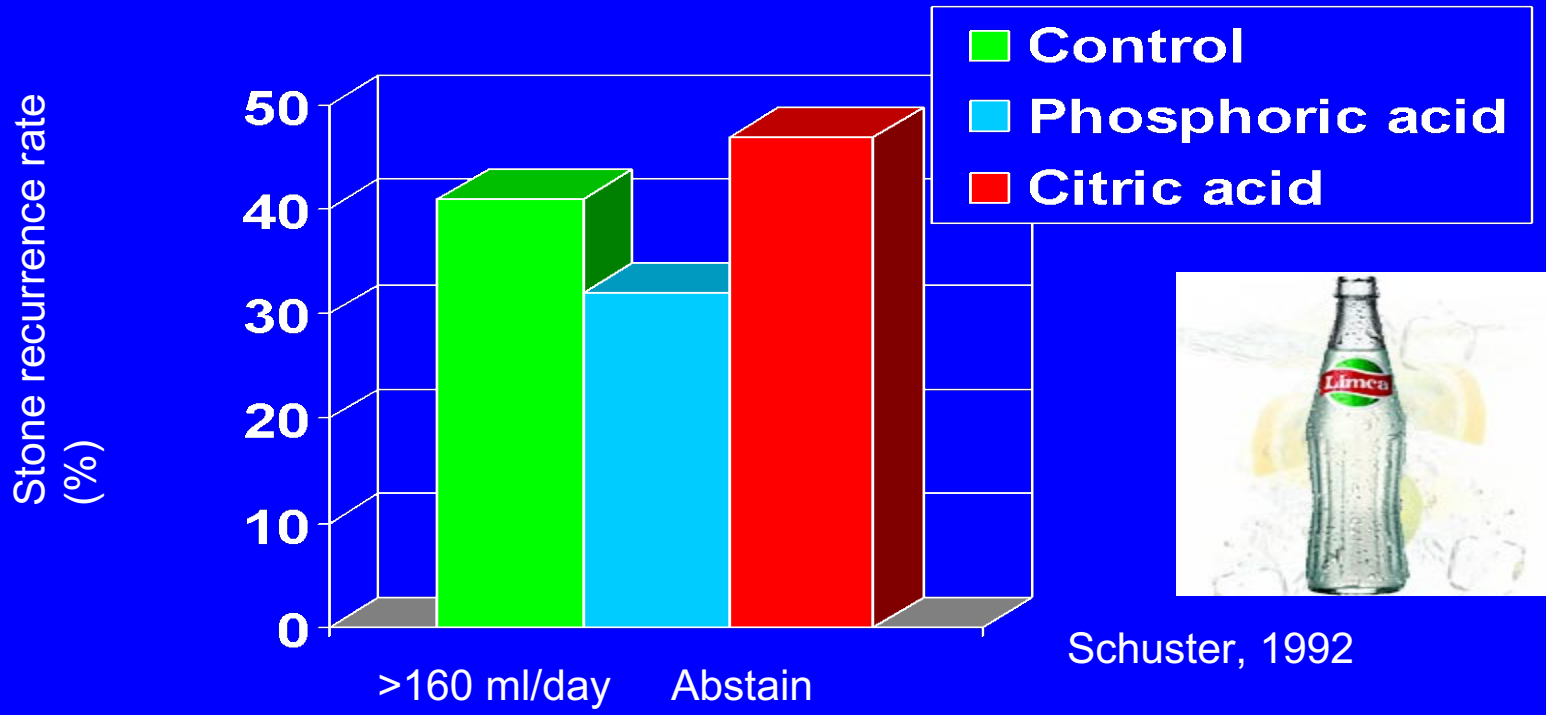
Fluids
Target – 2L of urine
5-year follow-up



J Urol 155: 839, 1996

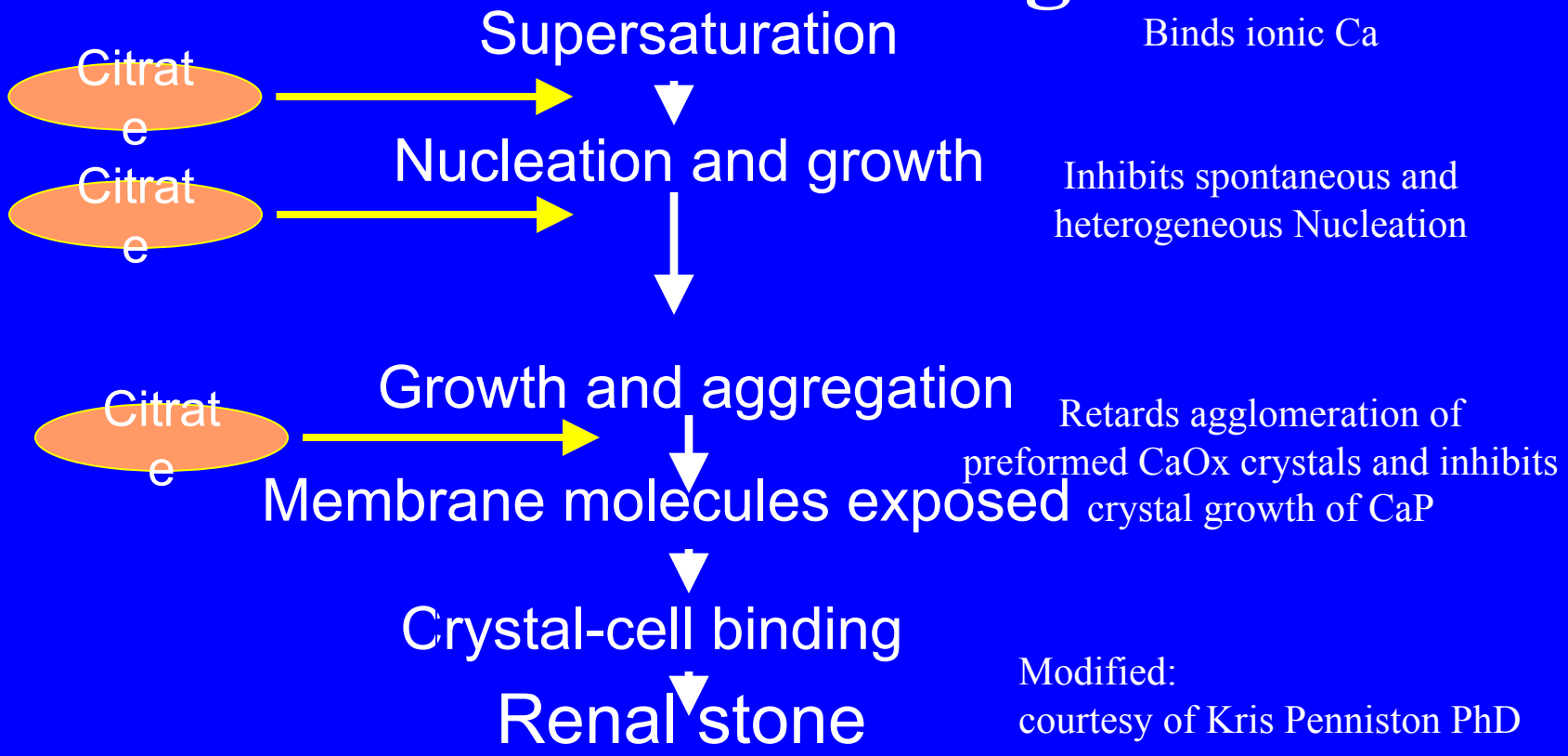

Hormel
Chicken Flavor
Bouillon
With Other Natural Flavors
Sodium Free
Instant Broth & Seasoning
Herb-Ox
Made With Real Chicken
#36087
NET WT. 7.05 OZ. (200g)
50 Packets

Type of Soda – what happens when you stop?



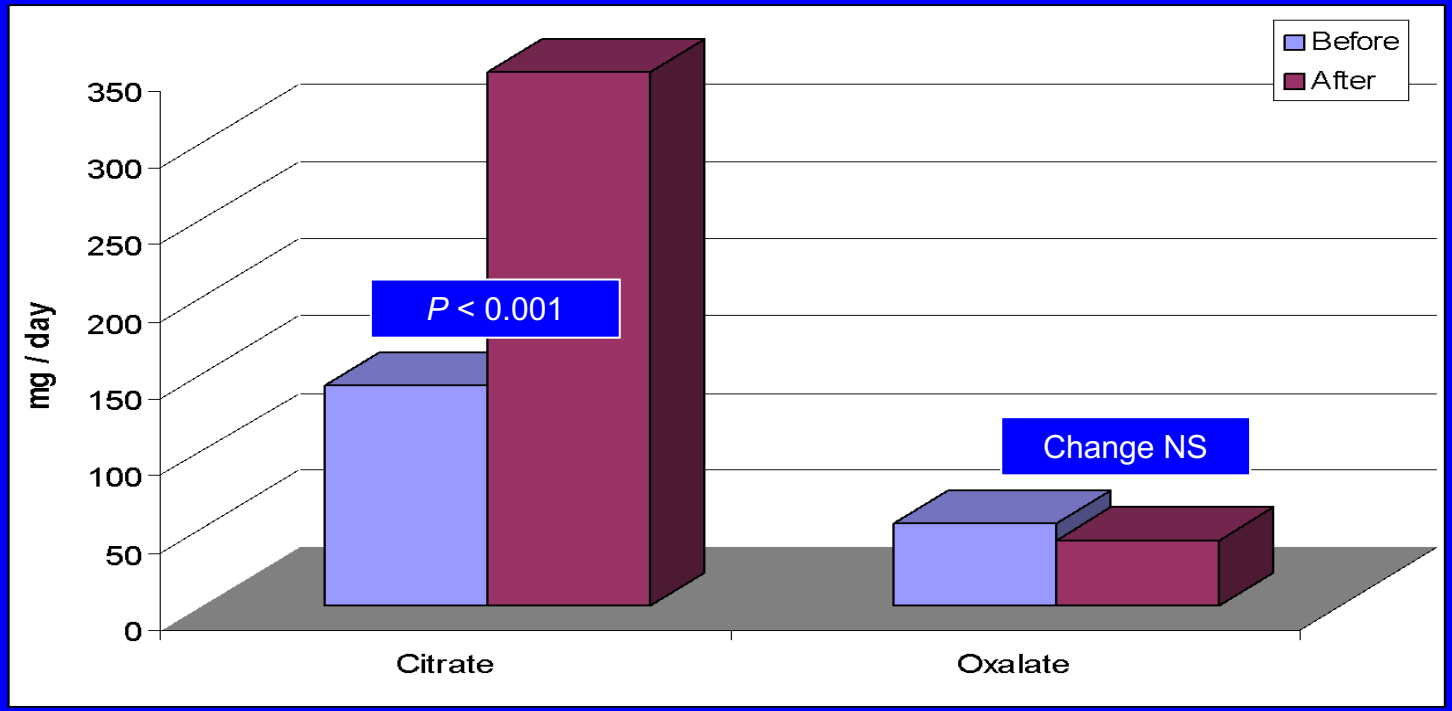
Schuster, 1992

Citrate Effect on Lithogenesis

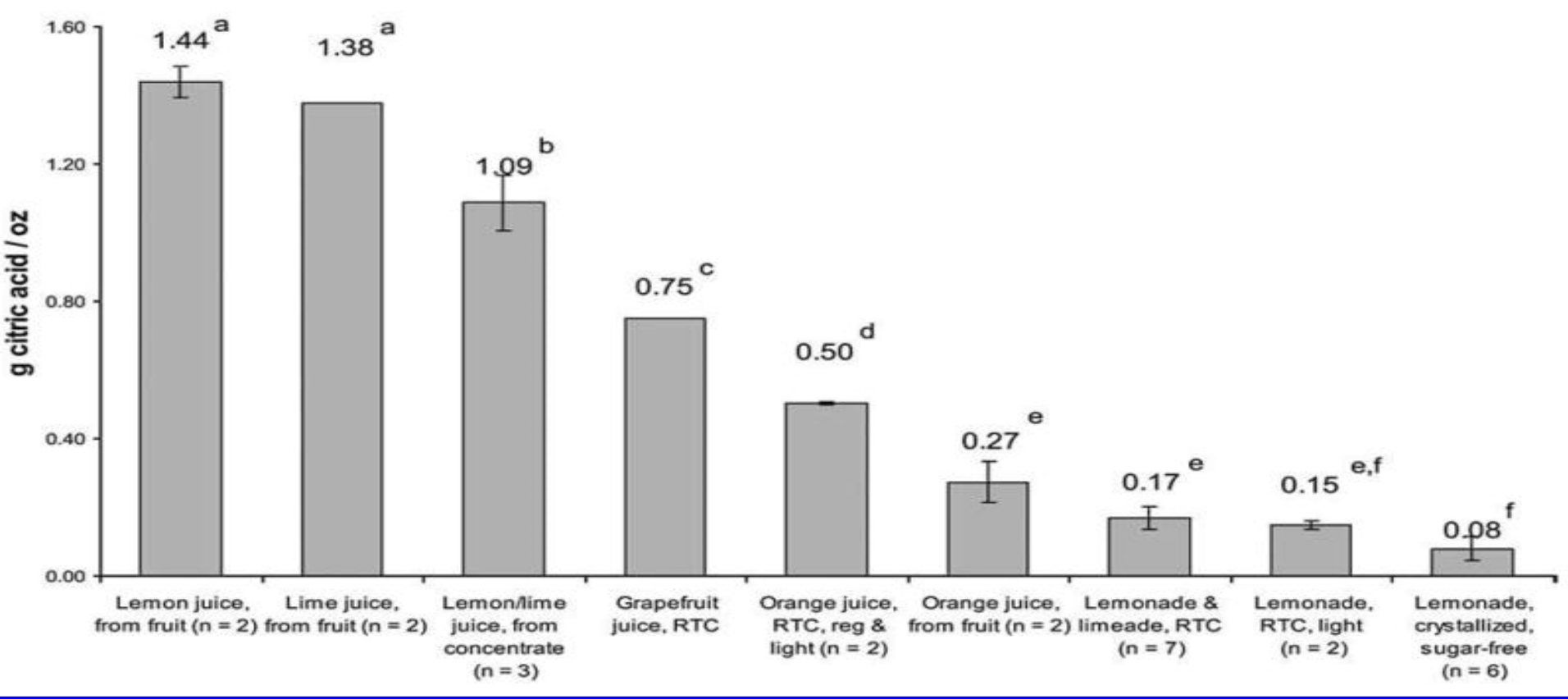


Modified:
courtesy of Kris Penniston PhD

Lemon Juice 4 oz / day



J Urol 156: 907, 1996



J Endourol. 2008 March; 22(3): 567–570.

IMPACT OF FRUITS & VEGGIES

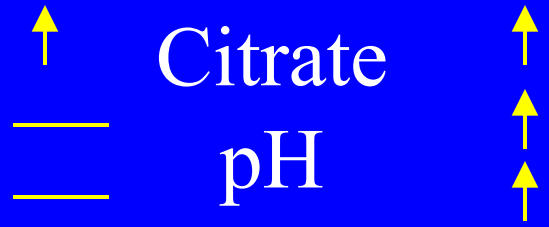
	Elimination of F&V Normal Subjects	Addition of F&V Stone Formers
Urinary K	-62%	+68%
Urinary Mg	-26%	+23%
Urinary Cit	-44%	+68%
Urinary Ca	+49%	+10%
Saturation CaOx	+30%	-52%

Courtesy Dr Glenn Preminger, AUA Review Course Content, 2015 Borghi, et al, 2005

Dietary Citrate

- CITRIC ACID
  - Lemon
  - Lime
- POTASSIUM CITRATE
  - Melon
  - Tomato

Orange



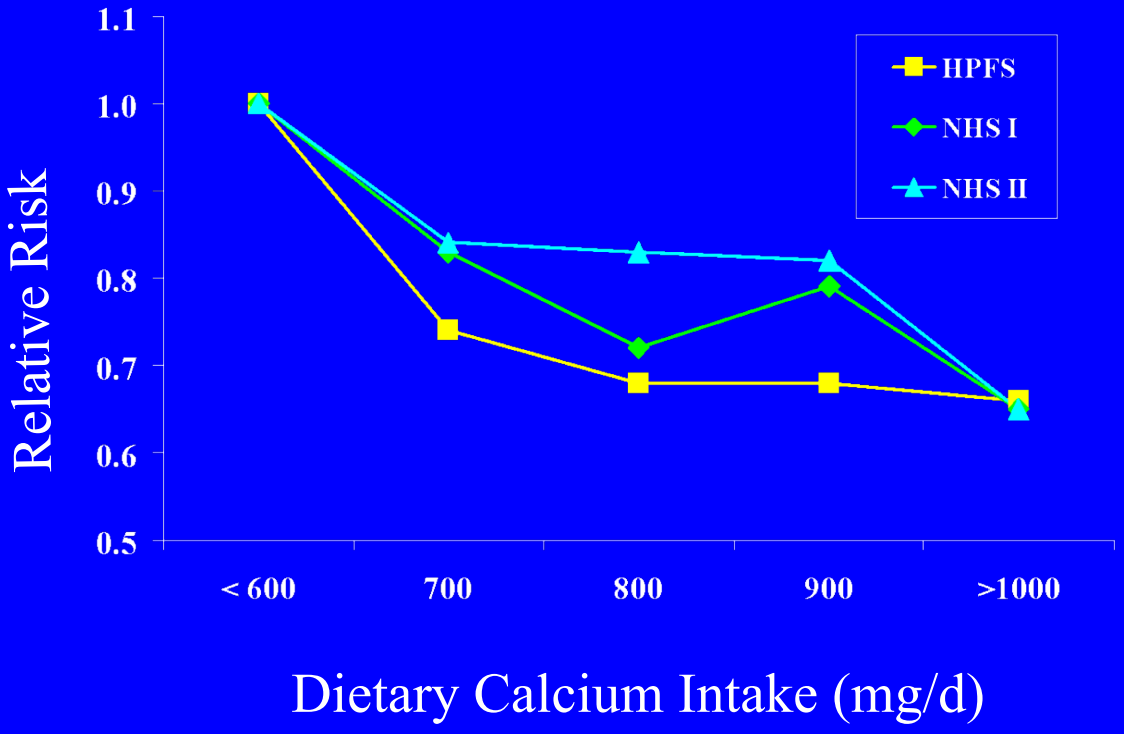
J Endourol 26: 1221-6, 2012

~~Limit Calcium~~

- Low dietary calcium increases risk of symptomatic kidney stones

NEJM 328: 833-8, 1993
Ann Int Med 126: 553-5, 1997
NEJM 346: 77-84, 2002

Stone Formers Have Lower Ca^{++} Intake



Calcium supplement users: RR 1.20

Curhan GC, NEJM 1993; Annals Int Med 1997; Archives Int Med 2004

Calcium Content

1200 mg / day

- Milk 8 oz 300 mg
- Yogurt 8 oz 350 mg
- Cheese 1 oz 200 mg
- Salmon ½ cup 250 mg

Salt

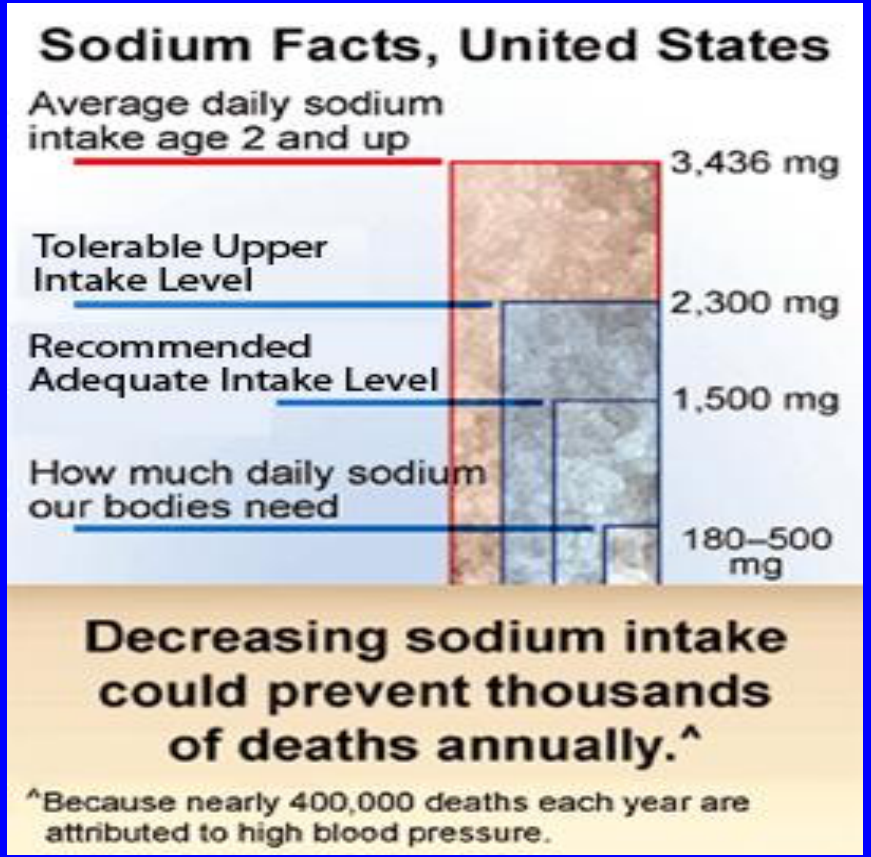
- Every 2300 mg of Salt (one teaspoon)

- 23 mg increase in urinary calcium

•higher rates of bone resorption
•effect greater if low dietary calcium
•decreases urinary citrate 20%

J Am Coll Nutr 19: 83S-99S, 2000
J Urol 150: 310, 1993

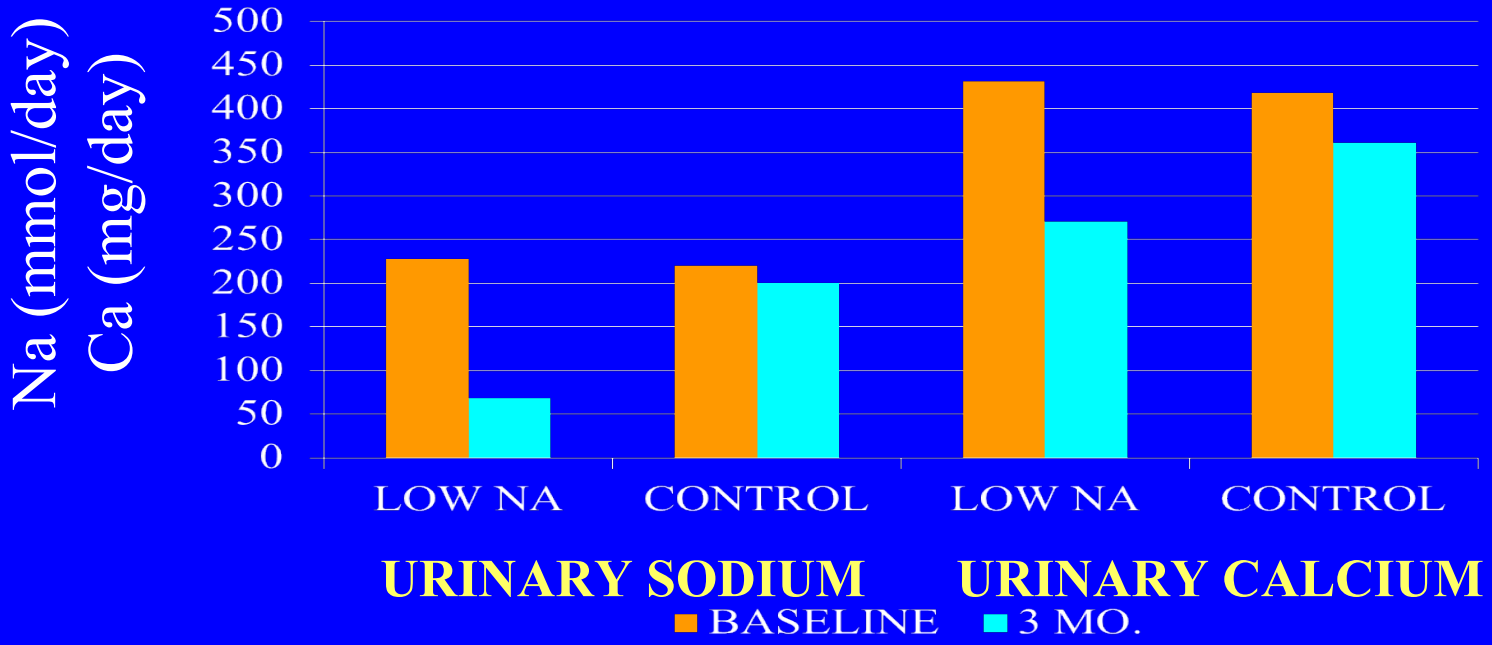
- 77% OF SALT COMES FROM EATING OUT OR EATING PROCESSED FOOD



CDC http://www.google.com/imgres?imgurl

EFFECT OF LOW SALT DIET ON IDIOPATHIC HYPERCALCIURIA

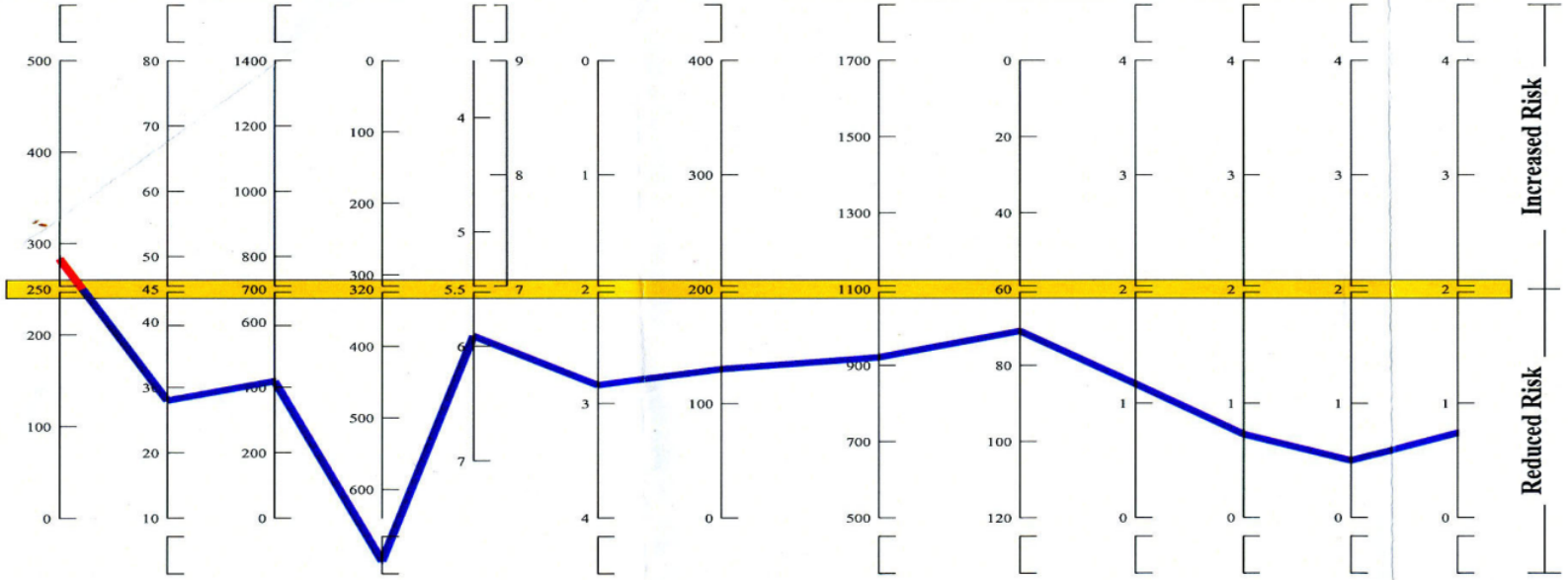
Nouvenne, Borghi et al, Am J Clin Nutr, 91: 565, 2010



62% normalized urinary calcium with sodium restriction

UroRisk®
Diagnostic Profile

Metabolic					Environmental				Relative Supersaturation			
Ca	Ox	UA	Cit	pH	TV	Na	P	Mg	CaOx	Br	NaU	UA
283 mg/day	28 mg/day	419 mg/day	845 mg/day	5.91	2.84 l/day	130 meq/day	921 mg/day	71 mg/day	1.17	0.73	0.50	0.74

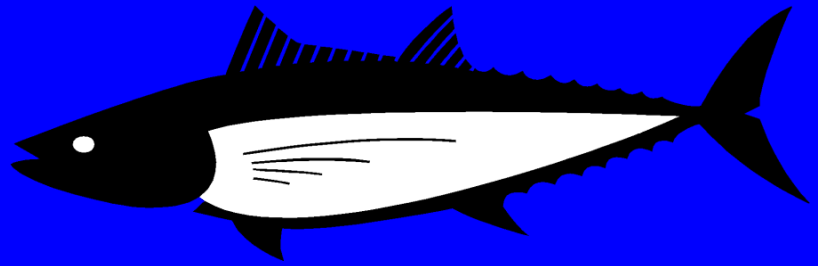


Other Values	
K	57 meq/day
Creatinine	1104 mg/day

Fish Oil

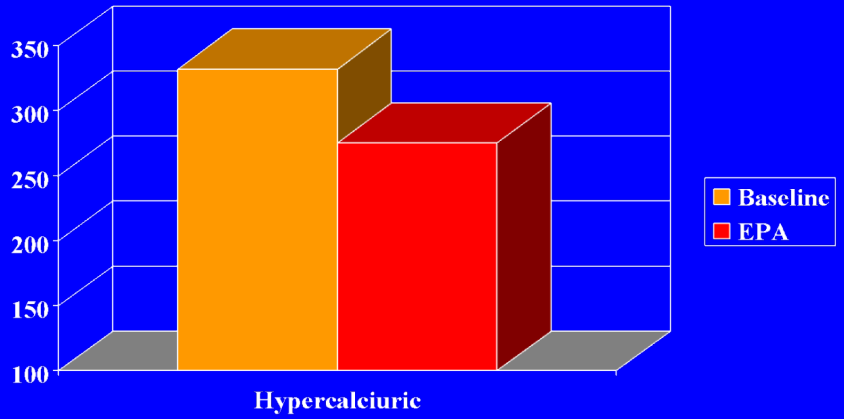
- Cold water fish
- Eicosapentanoic acid (n-3 fatty acid)
- Competes with arachidonic acid (n-6)
- LESS PGE2
  - Less renal CA excretion
  - Activation of Na/K/Ca – more CA reabsorption
  - Decreased 1,25 Vitamin D levels
  - Decreased bone resorption
  - ? Impact on ureteral contractility in obstruction

Hypercalciuria: Omega 3 Fatty Acids



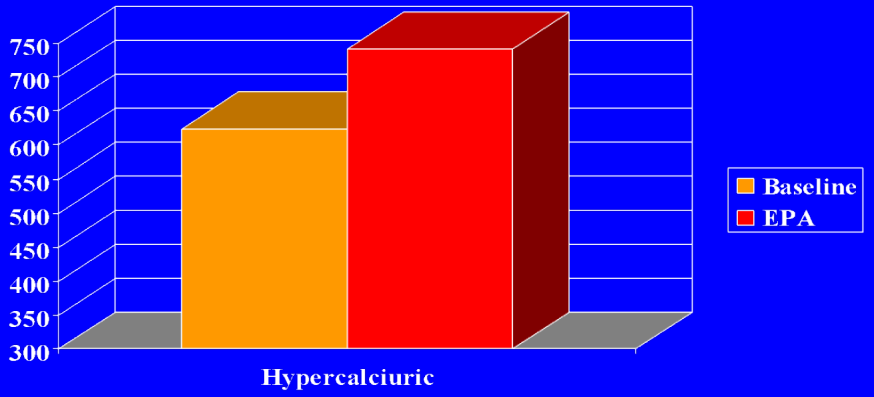
salmon, tuna, mackerel, sardines, walnuts, flax seeds, canola oil

EPA 1800 mg for 18 months



Urinary CA

Yasui et al



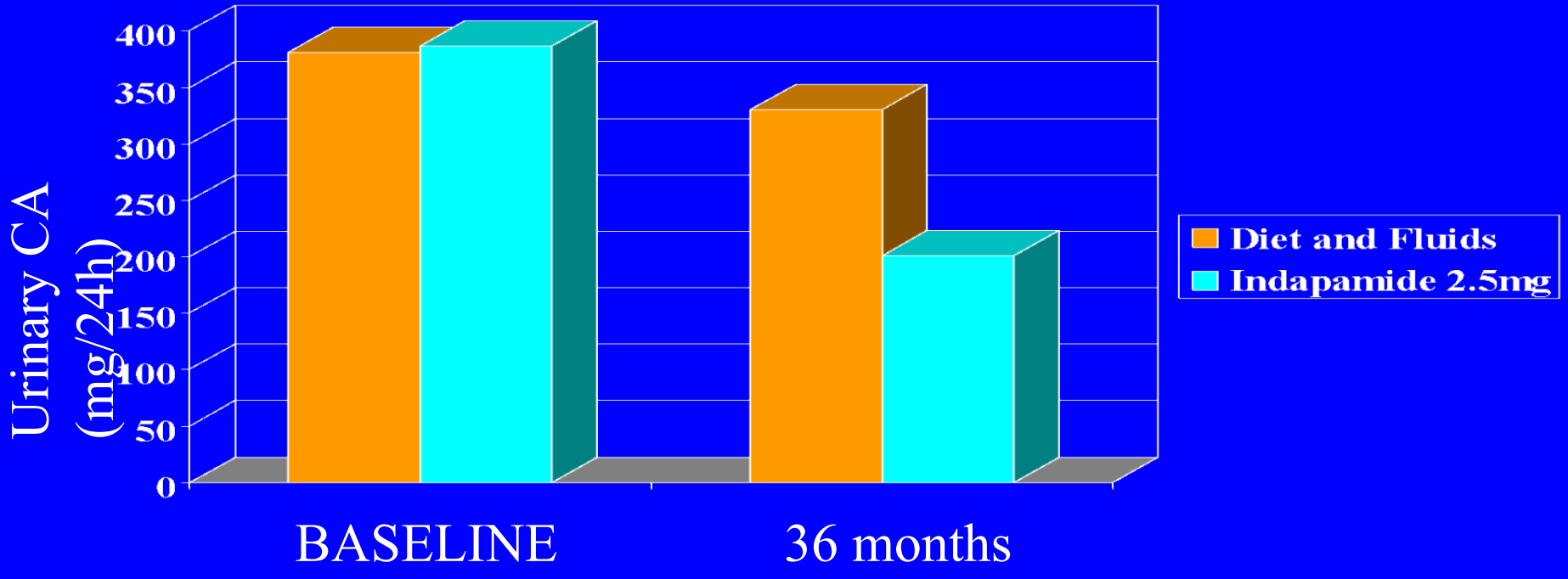
Urinary Citrate

Ito et al

Thiazides

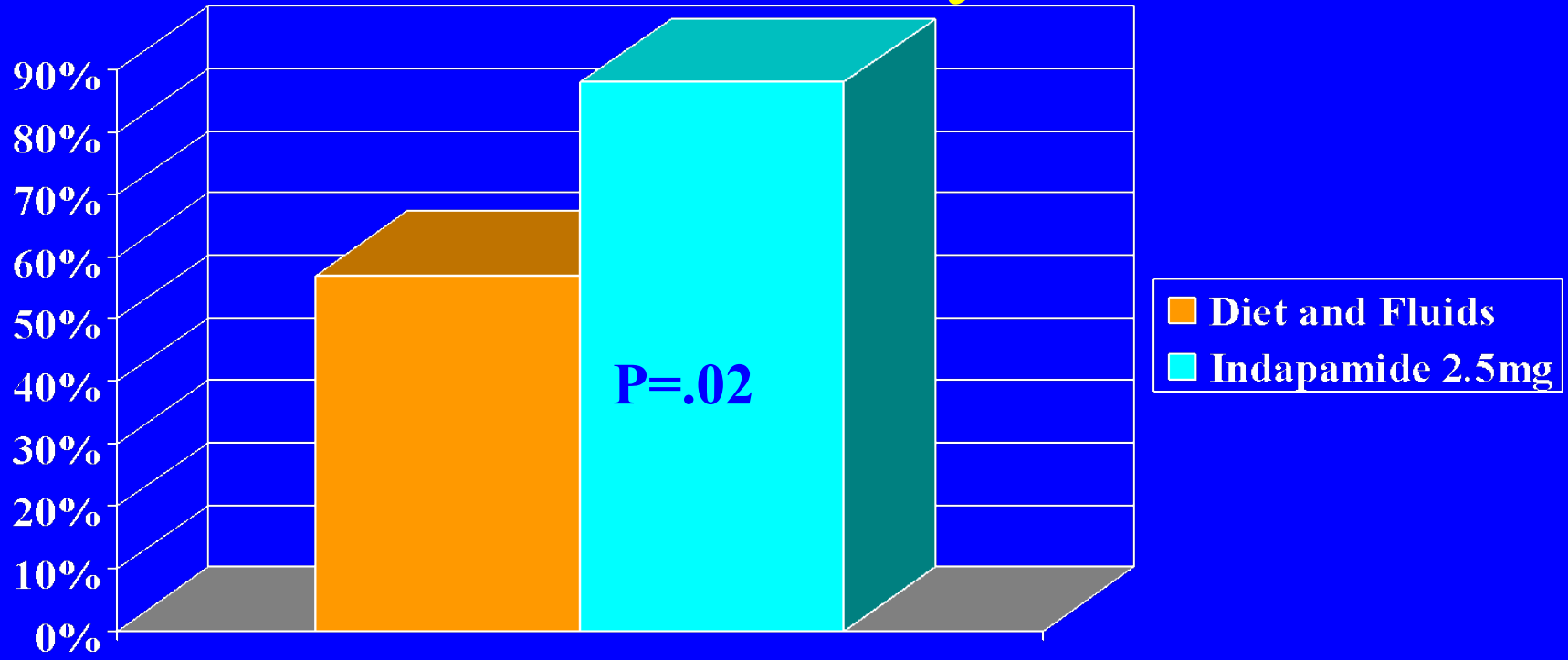
- Decrease urinary CA 20-30%
  - Distal Renal Tubule
  - Inhibit NA reabsorption, Increase CA reabsorption
- Increase Bone Mineral Density
- Ten randomized controlled studies
- *** monitor CA, K, UA, GLU***
- *** limit dietary sodium***

Indapamide
Urinary CA



J Cardiovasc Pharm 22 (Suppl 6: S78-S86, 1993

Indapamide
Stone-free at 3 years



J Cardiovasc Pharm 22 (Suppl 6: S78-S86, 1993

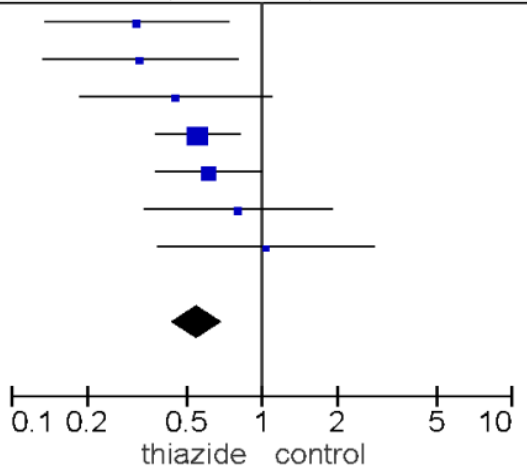
AHRQ project

Thiazides and stone recurrence

Study or Subgroup	Thiazide Events	Thiazide Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Ettinger 1988	6	42	14	31	8.1%	0.32 [0.14, 0.73]
Borghi 1993	6	43	9	21	7.1%	0.33 [0.13, 0.79]
Laerum 1984	5	23	12	25	7.4%	0.45 [0.19, 1.09]
Fernández-Rodriguez 2006	31	100	28	50	38.9%	0.55 [0.38, 0.81]
Ahlstrand 1996	9	17	19	22	24.9%	0.61 [0.38, 0.99]
Ala-Opas 1987	6	28	12	45	7.7%	0.80 [0.34, 1.90]
Scholz 1982	6	25	6	26	5.8%	1.04 [0.39, 2.80]
Total (95% CI)		**278**		**220**	**100.0%**	**0.55 [0.43, 0.70]**
Total events	69		100			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.76$, df = 6 (P = 0.45); $I^2 = 0\%$

Test for overall effect: Z = 4.93 (P < 0.00001)

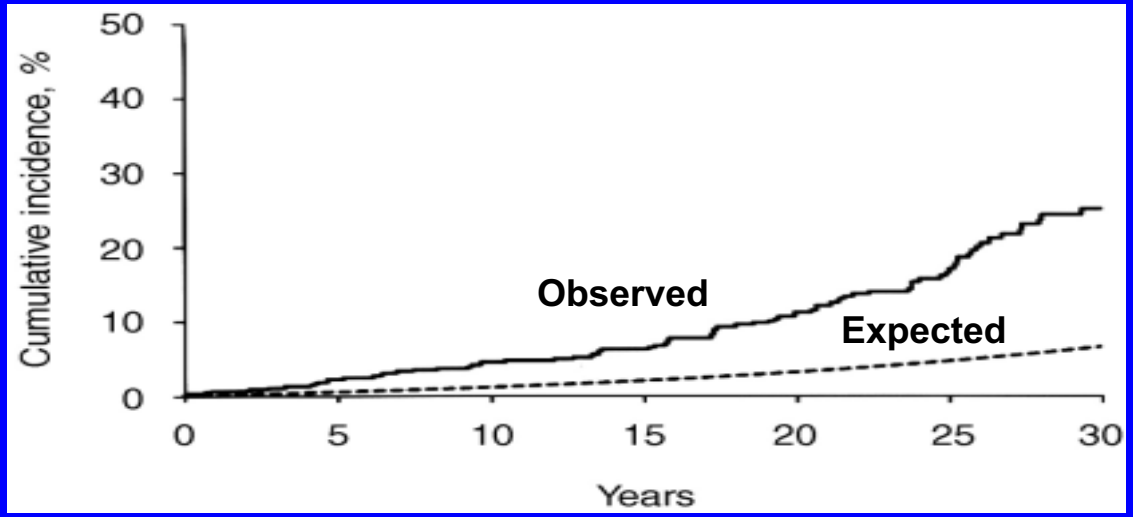


N=565

Mean duration 34 months

Annals of Internal Medicine 158: 535-543, 2013

Cumulative incidence of vertebral fractures among Rochester, Minnesota, residents following the initial episode of symptomatic urolithiasis, 1950 to 1974.



Observed (solid line) and expected (dashed line)

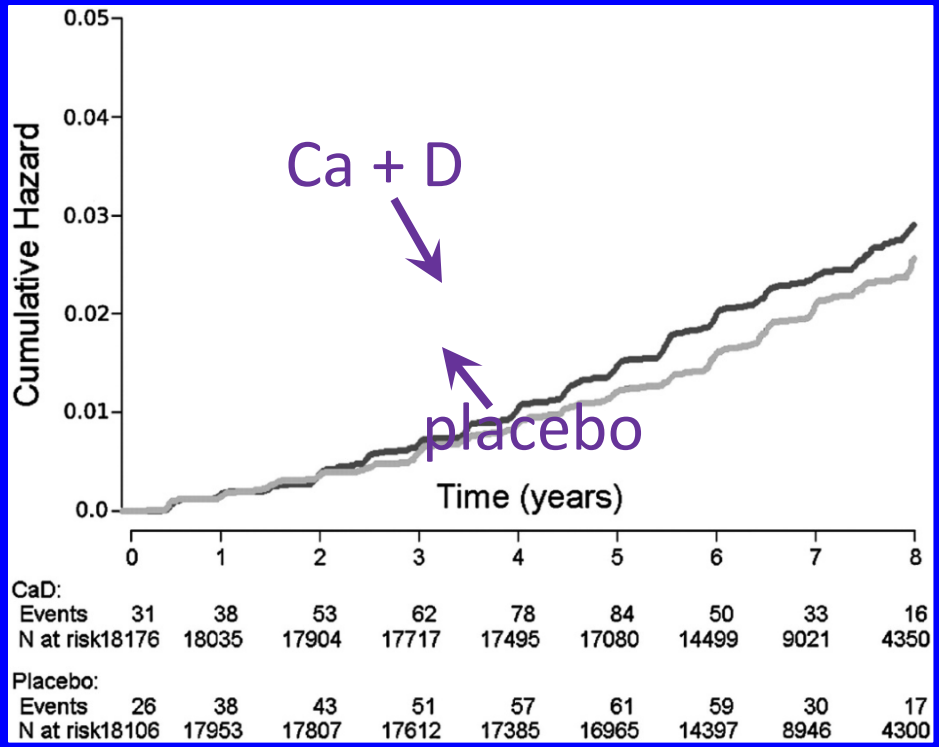
Melton III, et all, Kidney International 1998;53:459

Women's Health Initiative
Risk of Stones in Ca/Vit D vs placebo

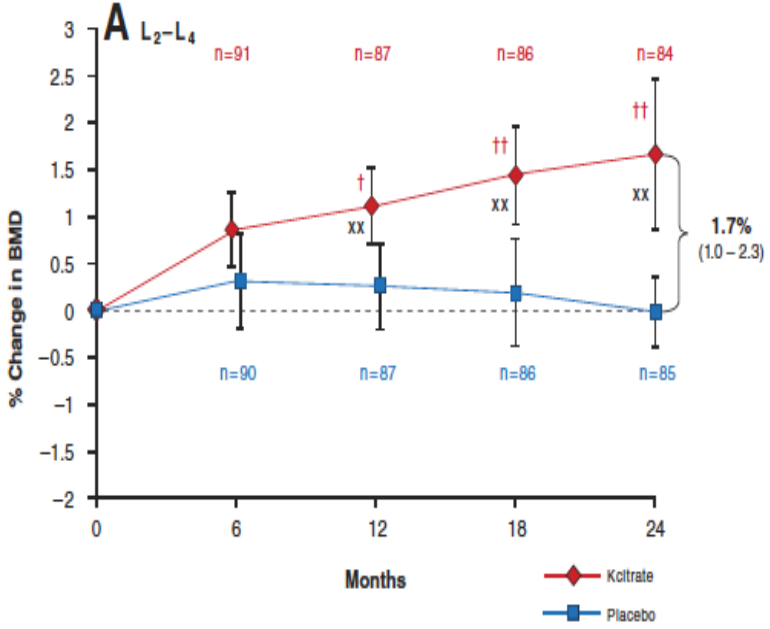
Wallace et al, AM J Clin Nutr 94:270, 2011

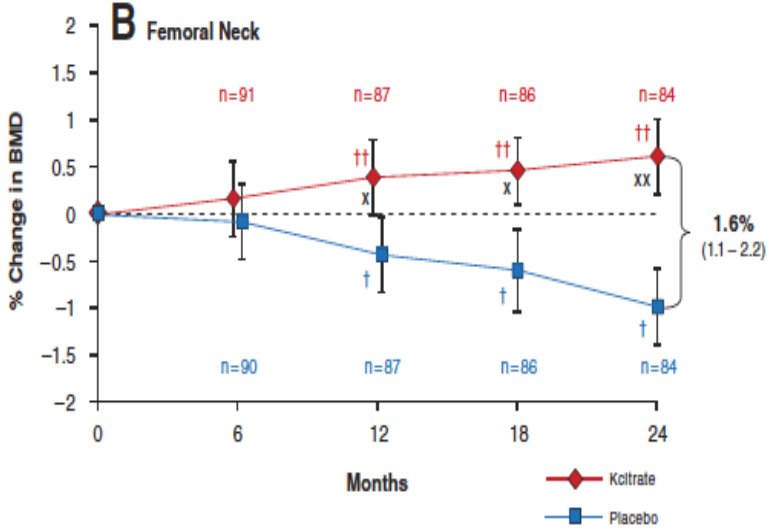
Risk of kidney stones 17% higher in Ca + D group
(HR 1.17, 95% CI 1.02 to 1.34)

Although rate of hip fx was 12% lower with Ca + D, the difference was not significant
(95% CI 0.72-1.08)



Effect of Potassium Citrate on Bone Density, Microarchitecture, and Fracture Risk in Healthy Older Adults without Osteoporosis: A Randomized Controlled Trial





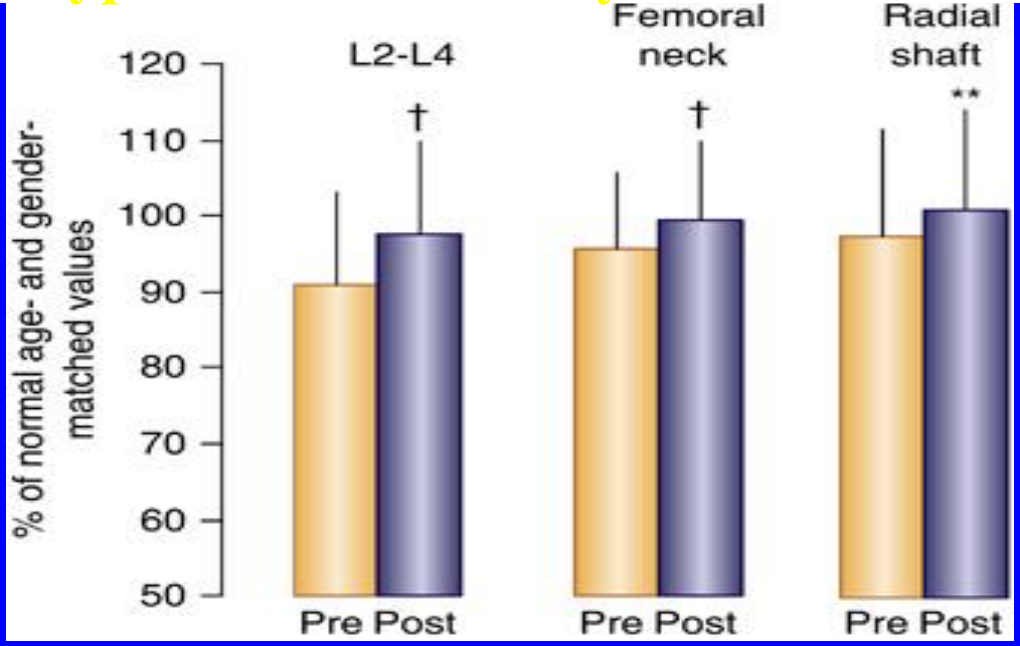
K citrate 60 meq qd with calcium and vitamin D

Jehle S et al, JCEM epub 11/15/2012

Effect of thiazide/indapamide and K-Cit on BMD of the L2–L4 spine, femoral neck, and radial shaft of hypercalciuric kidney stone formers.

Average dose
Kcitrate 35 meq/d

Mean f/u =3.7 yr



Urine Ca (mg/d):
Pre Rx - 346 ± 85
On Rx - 248 ±79

Stone formation rate/year:
Pre Rx – 2.9 ± 9.3
On Rx – 0.05 ± 0.3

Data are expressed as percentage of normal, matched for age and gender (*Z*-score). **Indicates *P*=0.001, †indicates *P*<0.001. Bars above the blocks represent mean±s.d.

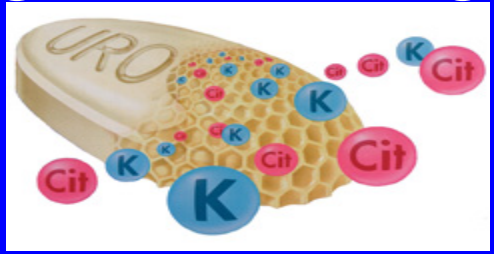
Pak, et al: Journal of Urology 2003;169:465

Hypercalciuria

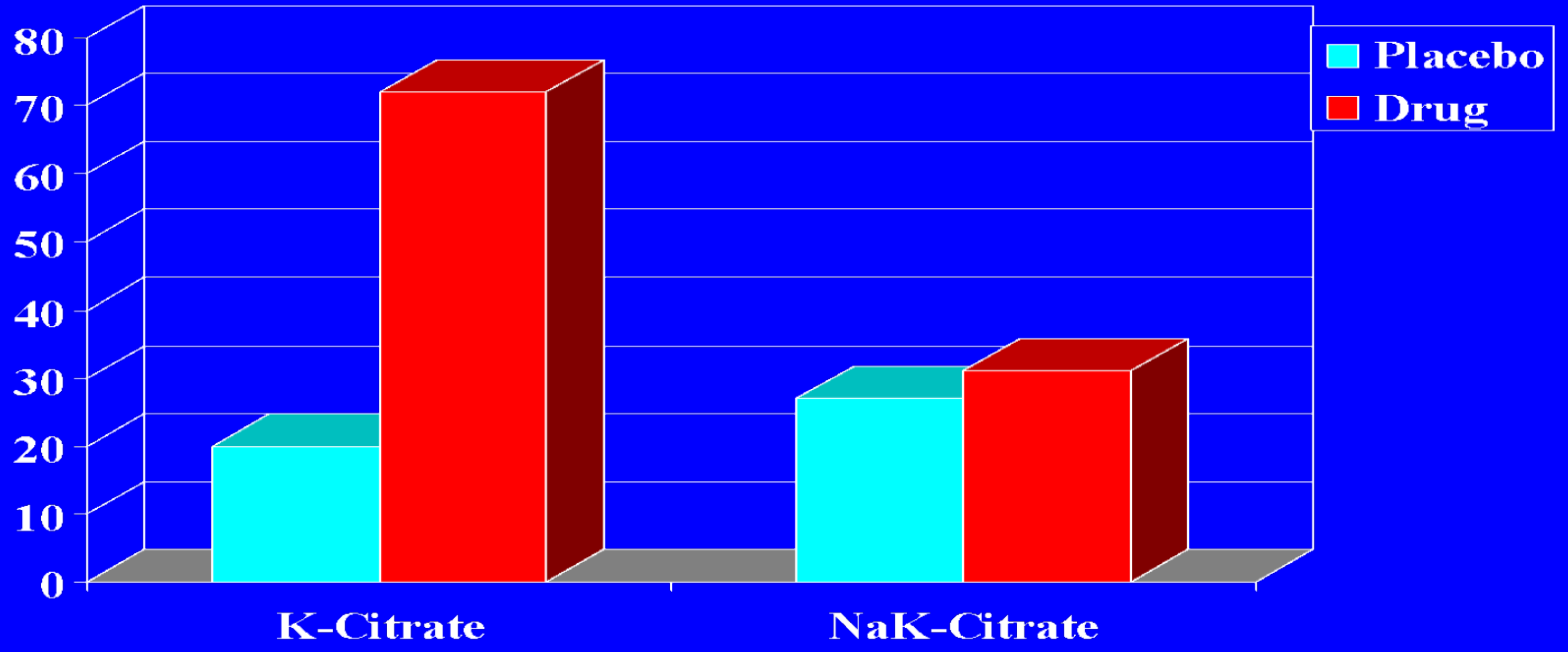
- Indapamide 1.25 to 2.5 mg/day
- Chlorthalidone 25 mg/day
- HCTZ 25mg BID
- + K_3Cit (eg, Urocit®-K)
  - 15 mEq daily

Alkaline therapy

- INCREASE PH
  - Decrease supersaturation of CAOX and CAPH
  - Decrease stone growth and aggregation



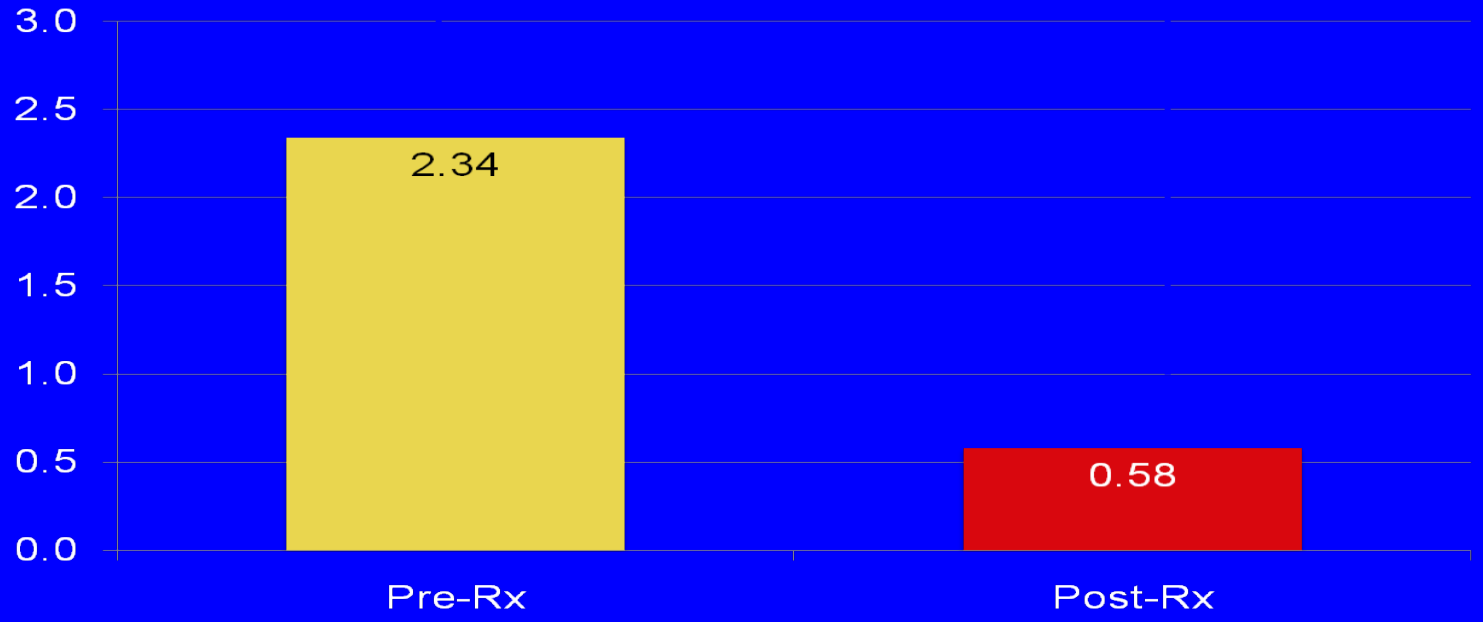
Stone-Free Rate at 3 years



J Urol 150: 1761, 1993
Br J Urol 73: 362, 1994
J Urol 158: 2069, 1997

Stone Formation Rate
Preminger 3year followup

***P*<0.0001**



Robinson MR, et al. Impact of long-term potassium citrate therapy on urinary profiles and recurrent stone formation. J Urol. 2009;181:1145-1150.

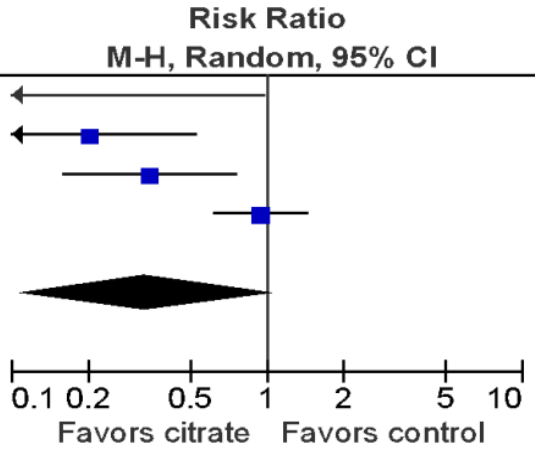
AHRQ PROJECT

Citrates and stone recurrence

Study or Subgroup	Citrate Events	Citrate Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Soygur 2002	0	28	8	28	11.4%	0.06 [0.00, 0.97]
Ettinger 1997	4	31	21	33	27.4%	0.20 [0.08, 0.52]
Barcelo 1993	5	18	16	20	29.1%	0.35 [0.16, 0.75]
Hofbauer 1994	11	16	16	22	32.1%	0.95 [0.62, 1.44]
Total (95% CI)		**93**		**103**	**100.0%**	**0.34 [0.11, 1.08]**
Total events	20		61			

Heterogeneity: $Tau^2 = 1.05$; $Chi^2 = 20.62$, df = 3 (P = 0.0001); $I^2 = 85\%$

Test for overall effect: Z = 1.83 (P = 0.07)



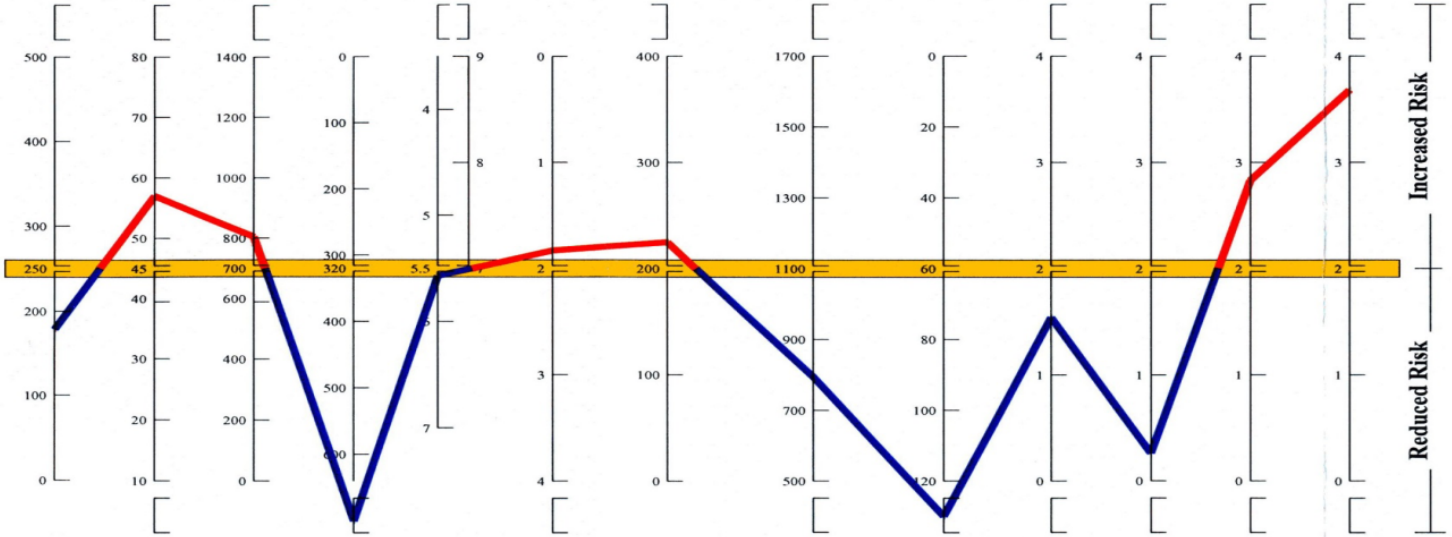
N=479

Mean Duration 29 months

Annals of Internal Medicine 158: 535-543, 2013

UroRisk®
Diagnostic Profile

Metabolic					Environmental				Relative Supersaturation			
Ca	Ox	UA	Cit	pH	TV	Na	P	Mg	CaOx	Br	NaU	UA
179 mg/day	**57** mg/day	**805** mg/day	**1859** mg/day	**5.57**	**1.83** l/day	**225** meq/day	**794** mg/day	**176** mg/day	**1.54**	**0.26**	**2.83**	**3.68**



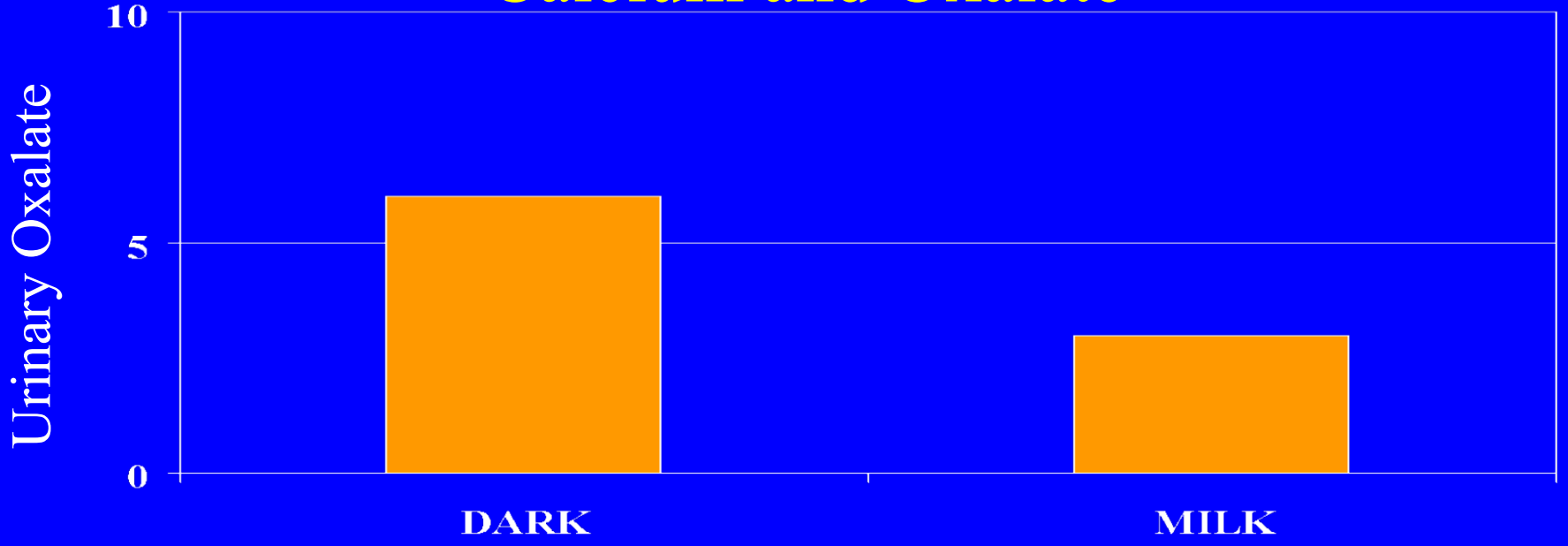
Other Values	
K	75 meq/day
Creatinine	2311 mg/day

	Food item	1 serving	Oxalate content (mg)
Oxalate-rich foods	Spinach, cooked	½ cup	755
	Rhubarb	½ cup	541
	Almonds	1 oz	122
	Beets	½ cup	76

Simplified oxalate diet

- University of Wisconsin
  - focus on spinach, nuts & seeds, and potatoes;
    - 44% of oxalate intake
    - lowest calcium:oxalate ratios….high bioavailability
    - teas, fruits and leafy green vegetables other than spinach accounted for <10% of total oxalate consumed
      - (Abstract 2060)

CHOCOLATE
Calcium and Oxalate



Oxalate (mg)	94	94
Calcium (mg)	26	430

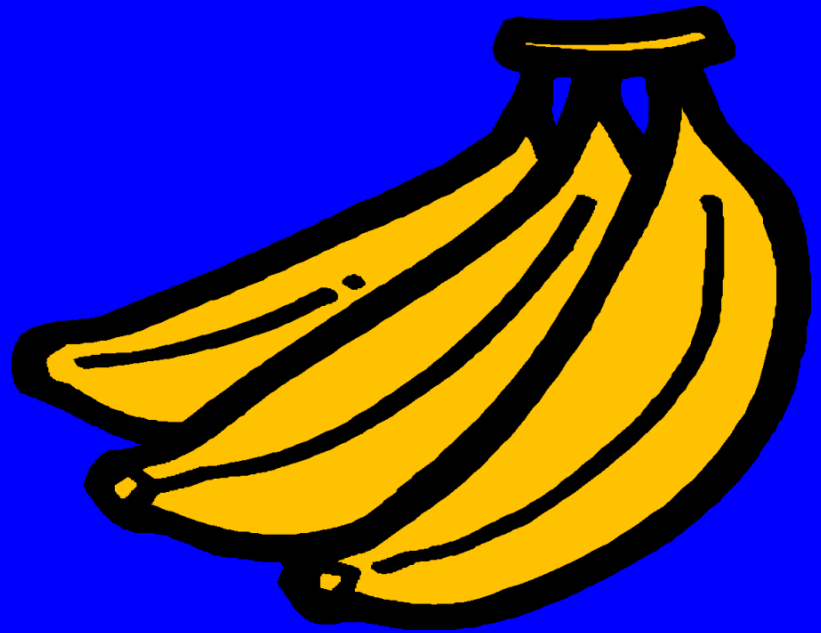
Vitamin B-6

- ↑ oxalate excretion with B-6 deficient diet
- ↓ stone risk with ↑ B-6 intake
- Co-factor in AGT conversion of glyoxylate to glycine

Hyperoxaluria: Vitamin B6

- bananas, avocadoes, soybeans, halibut, mangos, oatmeal

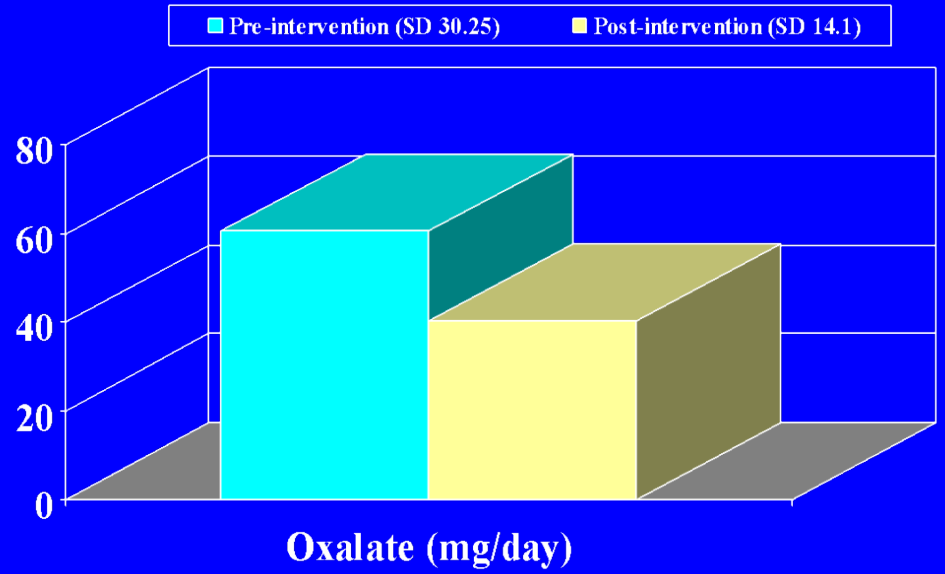
- fortified ready-to-eat cereals, select breads



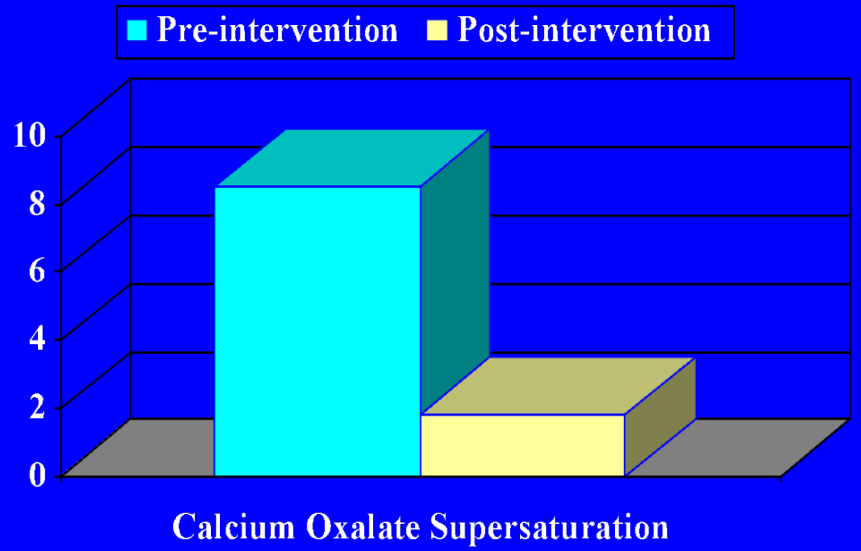
Supplements:

50mg ….100mg…..200mg

Vit B6 and Hyperoxaluria



P<0.0001



P<0.001

57 pts
15 month follow-up
72% of pts responded

URIC ACID STONES

- Radiolucent on KUB
- Hounsfield units <320
- Urine pH <5.5
- Gout
- DISSOLVE – Alkalinize
- PREVENT – Alkalinize and Allopurinol

Sources of Uric Acid

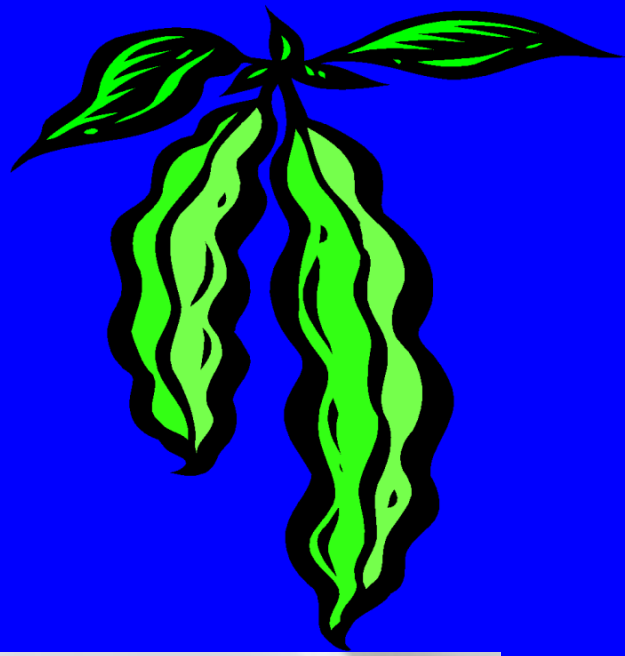
- End product of purine metabolism
  - Endogenous
    - de novo synthesis / catabolism of nucleic acid
    - 300-400 mg/day
  - Exogenous
    - dependent on dietary intake
    - Average 200-300 mg/day

High animal protein diet

- Increases urinary calcium, uric acid
- Decrease citrate and urinary pH
- Increase bone resorption due to increased acid-ash content

Br J Urol 56: 263, 1984
Am J Kid Dis 40: 265, 2002

PROTEIN



- Not a low protein recommendation but rather adequate protein
- 0.8-1.0grams/kilogram
- Plant protein less likely to make urine acidic

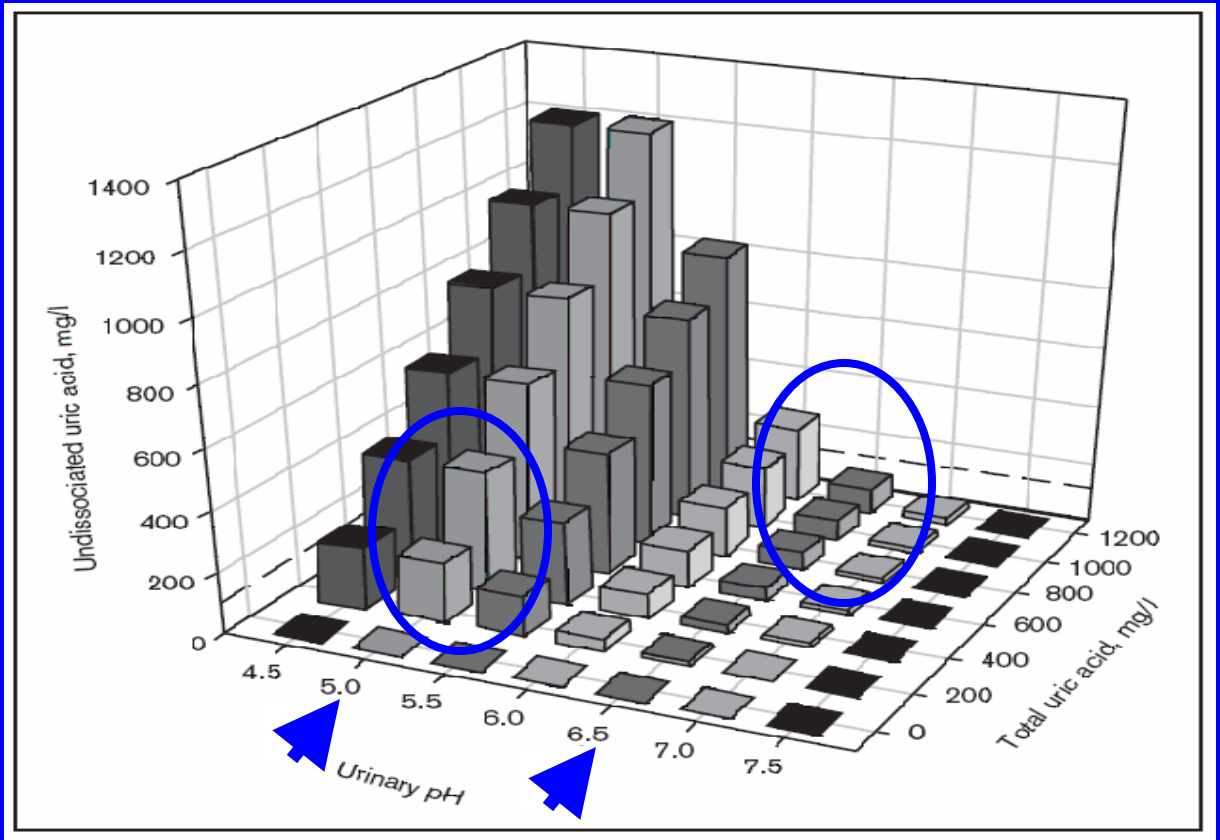
pH Dependence of Uric Acid Solubility

- Solubility of Uric Acid (pKa = 5.57)
  - pH 5.0 60 mg per L
  - pH 6.0 200 mg per L
  - pH 7.0 1600 mg per L

K-Cit 15 mEq qD and titrate up if needed

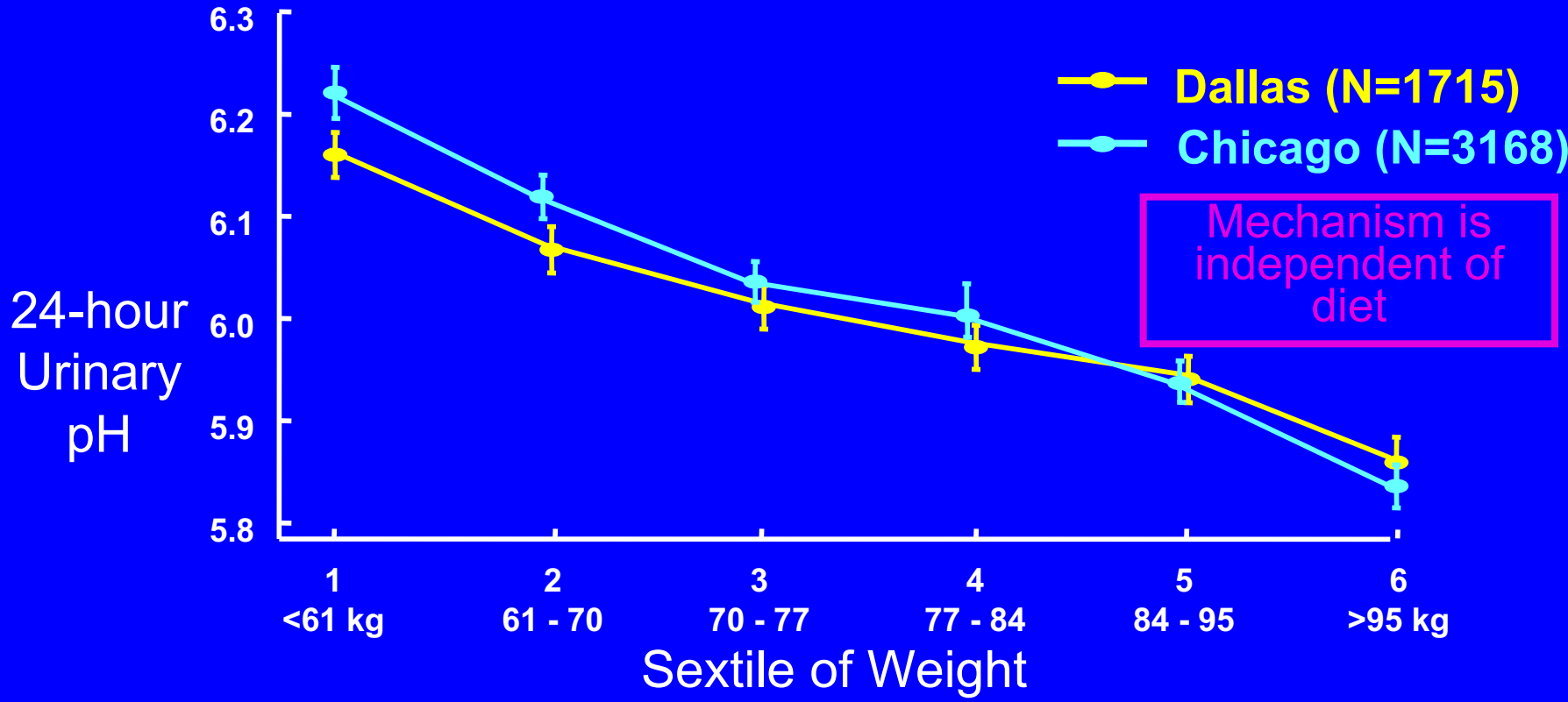
pH 6.5

CHEMISTRY OF URIC ACID



From Maalouf et al Curr Opin Nephrol Hypertens, 2004

BODY WEIGHT AND URINARY PH

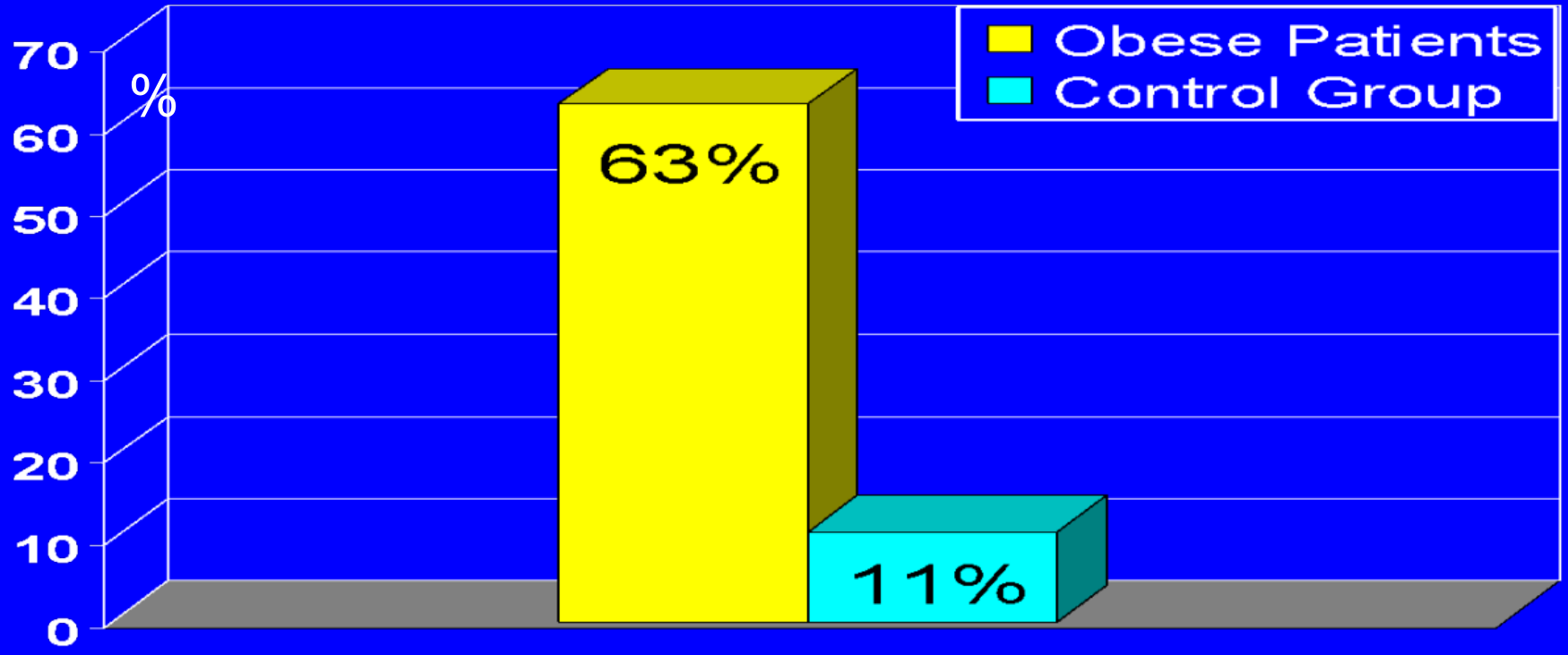


Courtesy Dr Glenn Preminger, AUA Review Course Content, 2015

Sakhaee, Coe, Pak 2004

IMPACT OF OBESITY

% PREVALENCE OF URIC ACID STONES



Courtesy Dr Glenn Preminger, AUA Review Course Content, 2015

Ekeruo, et al, 2004

What's changing in the 24 hour urine?

MP19-10
UCI, UTSW, DUKE

Risk Factors		(1988-1994) (n=309)	(2007-2010) (n = 229)	P Value
Gender	Male Female	175 (57) 134 (43)	101 (44) **128 (56)**	**.004**
Age	<50 ≥50	220 (71) 89 (29)	122 (53) **107 (46)**	**< .001**
BMI	N <25 Overweight Obese (≥30)	129 (41) 112 (36) 68 (22)	83 (36) 65 (28) **81 (35)**	**.003**

What's changing in the 24 hour urine?

Condition	Risk Factors	Group 1	Group 2	P Value
Hypocitraturia	All Patients	142 (46)	137 (60)	**0.001**
	Obese (BMI ≥ 30)	27 (40)	51 (63)	**0.005**
	N (BMI <25)	68 (53)	48 (58)	.465
Hyperoxaluria	All Patients	72 (23)	69 (30)	**0.07**
	Males	56 (32)	53 (53)	**0.001**
	Females	16 (12)	16 (13)	.89

MP01-16: Metabolic syndrome increases the risk for calcium oxalate stone formation: results from a Nationwide Survey on Urolithiasis in Japan

Akinori Iba et al, Wakayama, Japan

- 4,440 pts
- # MetS traits correlated with severity of CaOx stone disease
  - 3 -4 MetS traits, 1.8x risk for recurrent/multiple stones
- MetS traits associated with ⬆odds hypercalciuria

MP01-12: THE ASSOCIATION OF HEMOGLOBIN A1C AND URINARY OXALATE IN STONE FORMERS

Kyle Wood, Birmingham, AL, Marc Colaco, Winston-Salem, NC, John Knight, Ross Holmes, Dean Assimos, Birmingham, AL

- 1,428 Patients
- ⬆ BMI correlated with ⬆ Uox
- ⬆ A1C correlated with ⬆ Uox

Allopurinol

- End product of purine metabolism
  - Endogenous
    - xanthine → uric acid (xanthine oxidase)

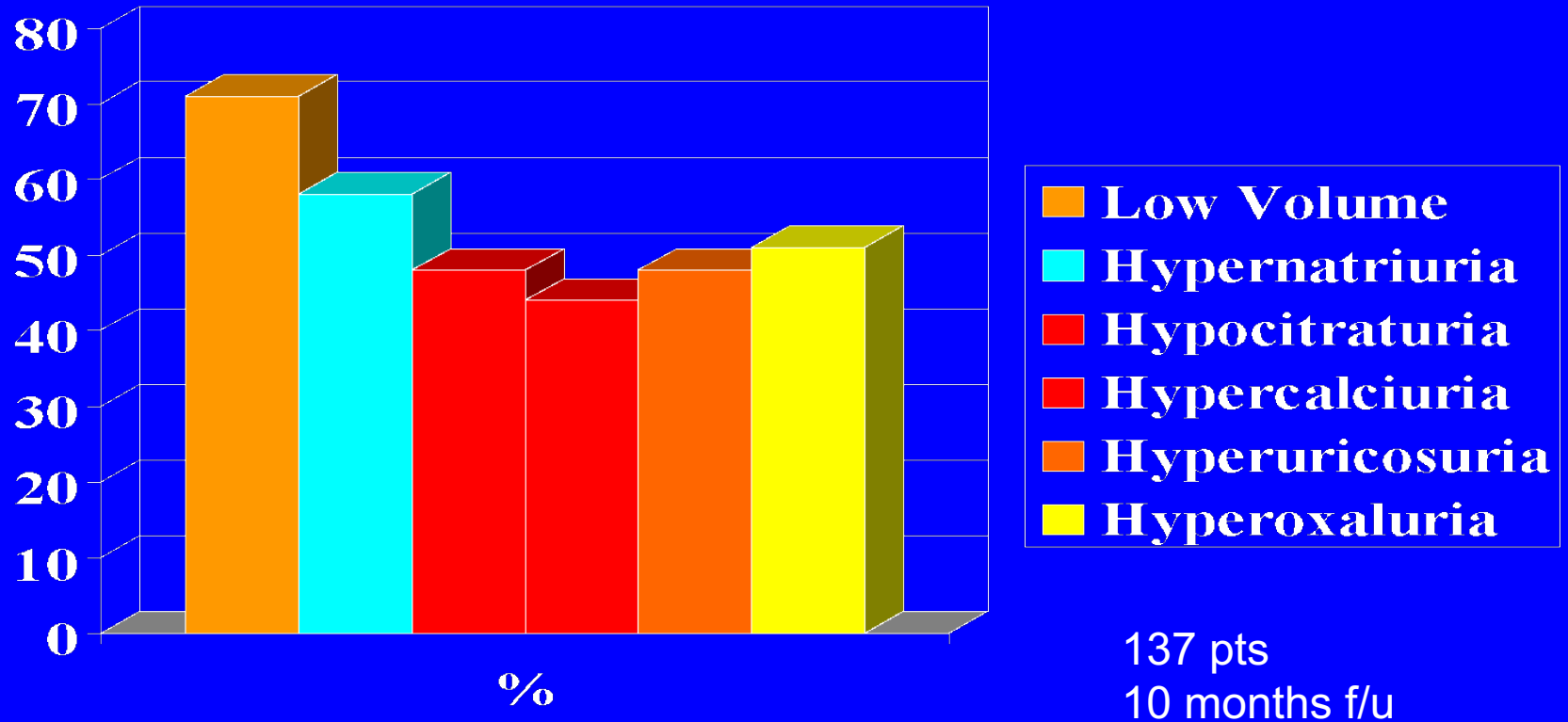
Allopurinol if:

- fails to correct with dietary measures
- Urinary uric acid >900 mg/day
- Start at 100mg and titrate to 300mg if needed

NO RCTs evaluating impact on stone recurrence

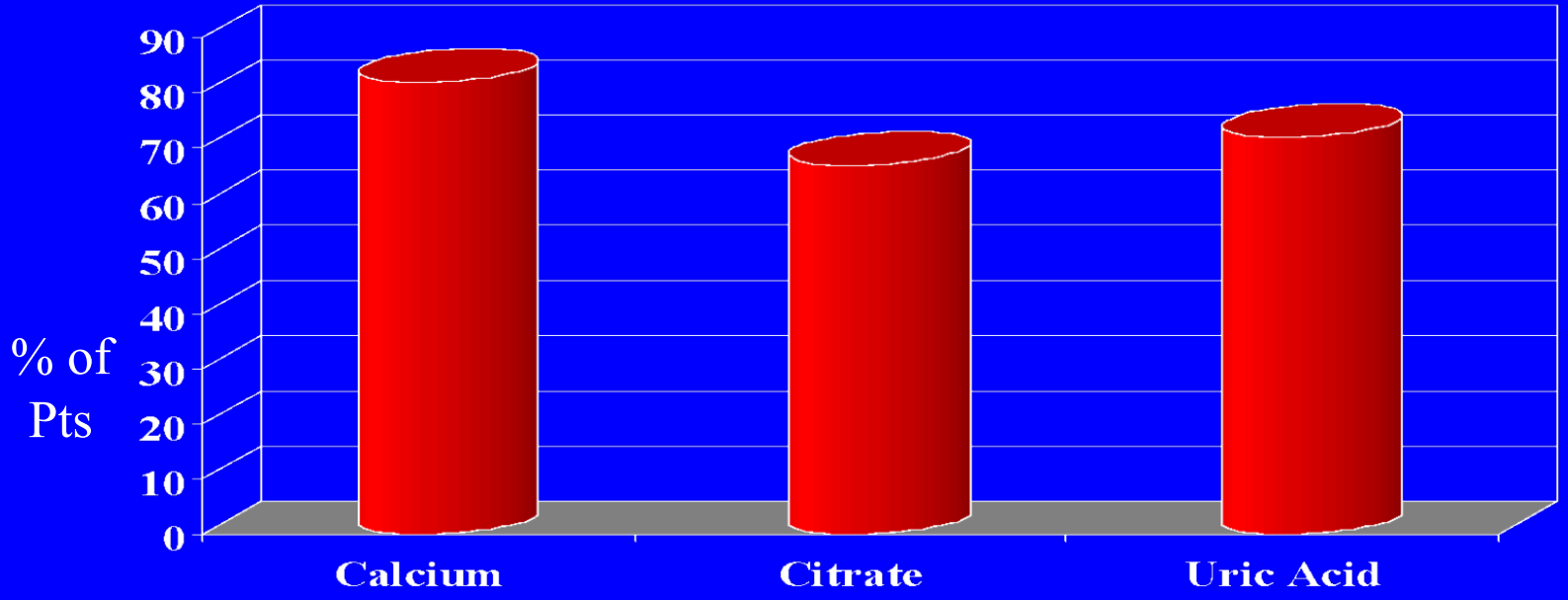
- Uric acid stones
  - Allopurinol
  - Alkalinization

Responders to Diet



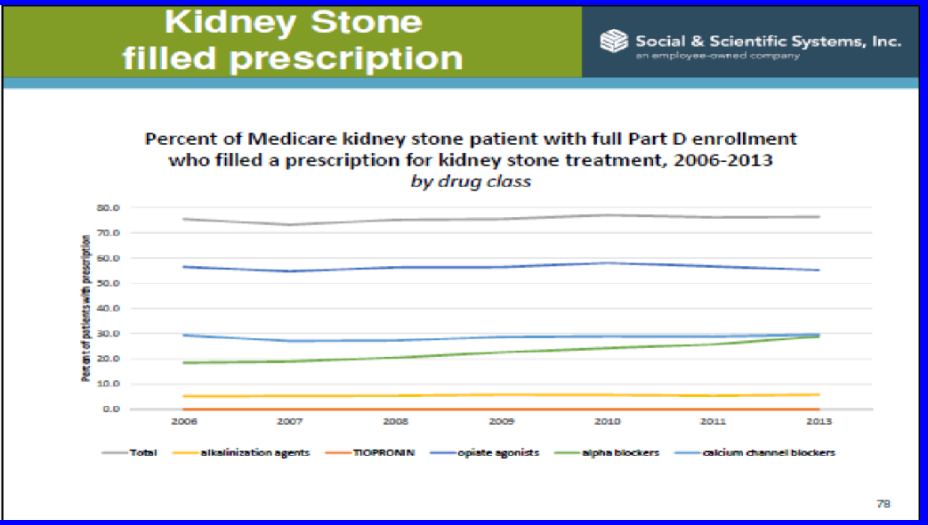
137 pts
10 months f/u

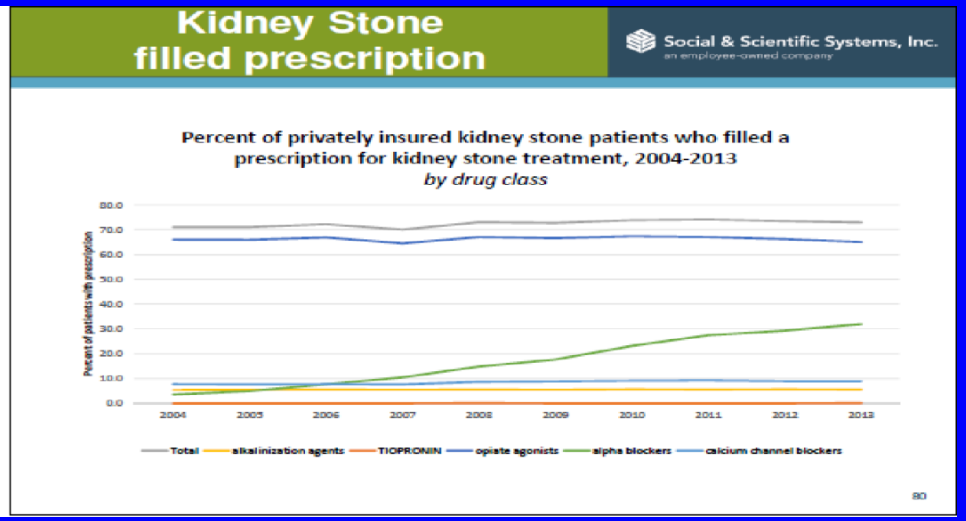
Percentage of patients responding to Medical Therapy



127 pts

Average follow up 14.39±17.36 months





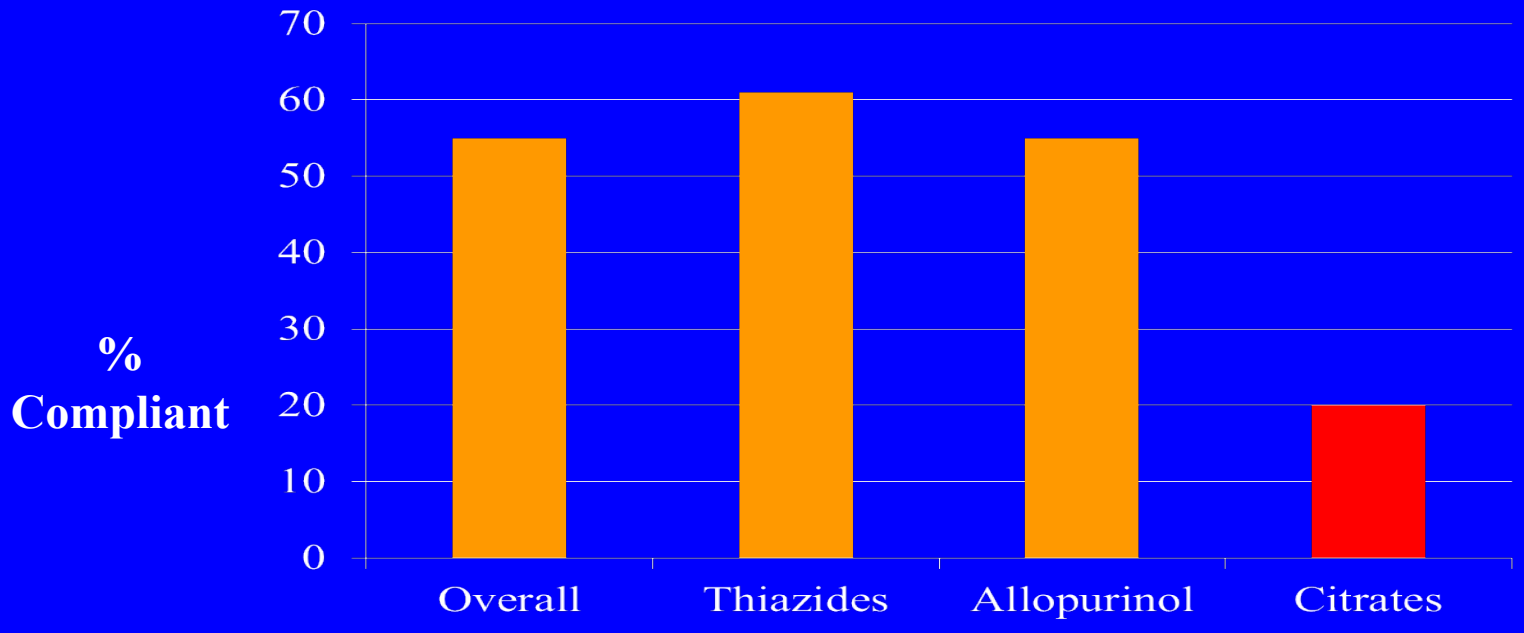
MEDICARE
65 YEARS OR OLDER

PRIVATE
18-64 YEARS OLD

UROLOGIC DISEASES IN AMERICA (NIH-JOHNS HOPKINS)

(COURTESY BRIAN MATLAGA)

MP16-19 Adherence rates for selective medical kidney stone prevention



Claims data – 22102 patients

MORE COMPLIANT:

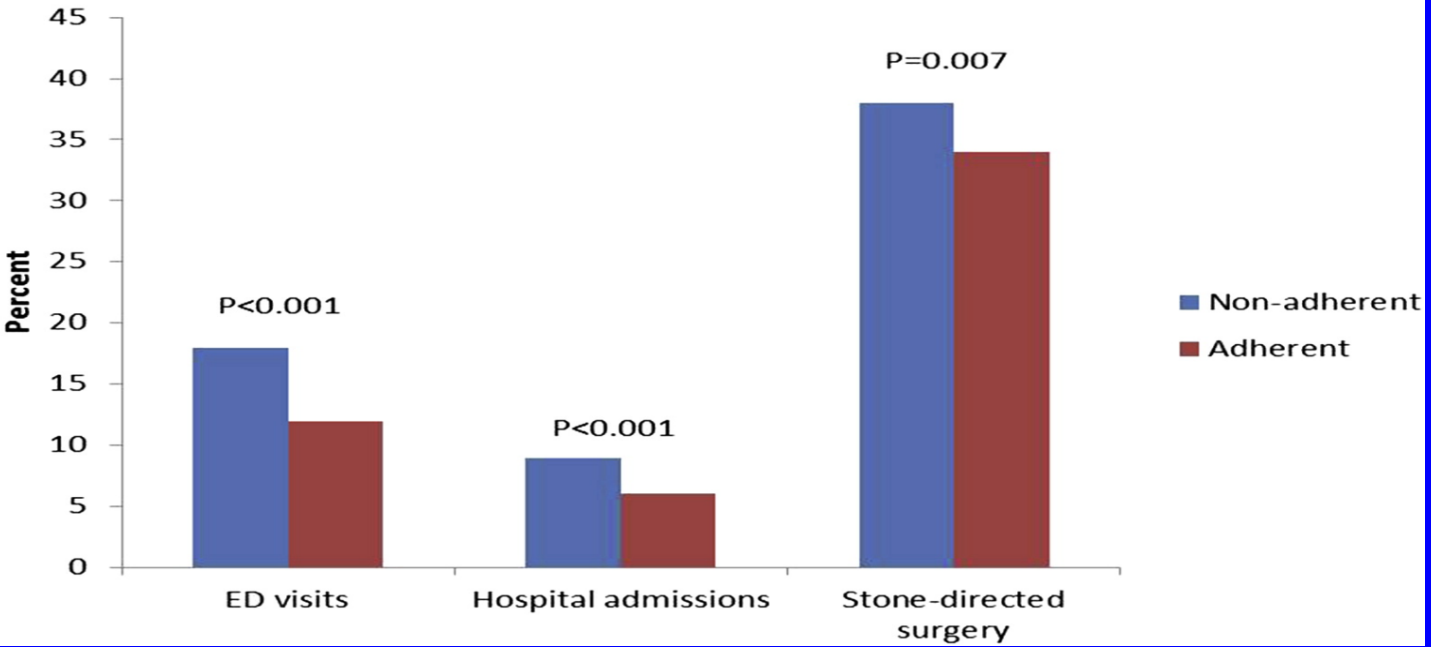
Men, Midwest, Salaried, Multiple drugs

The Journal of Urology 2015 193, DOI: (10.1016/j.juro.2015.02.1632)

MP41-04 CONSEQUENCES OF NON-ADHERENCE TO SELECTIVE MEDICAL THERAPY AMONG PATIENTS WITH KIDNEY STONES

COMPLIANT PATIENTS HAVE LESS ADMISSIONS 30% ED VISITS 25% ED SURGERY 13%

Figure – comparison of rates of intervention based on adherence to selective medical therapy.



Claims data – 8590 patients
57% adherent to preventive medications

The Journal of Urology 2015 193, DOI: (10.1016/j.juro.2015.02.1632)

EXERCISE AND STONES

- National Health and Nutrition Examination Survey database from 2010-2011
  'Have you ever had a kidney stone.' 8.3% YES

Q1: ***moderate intensity sports*** *for at least 10 minutes continuously?*
RR 0.739

Q2: ***vigorous intensity sports*** for at least 10 minutes continuously
RR 0.842

Q3: ***For the usual way you travel*** *do you walk / bicycle for at least 10 minutes*
RR 0.854

Q4: ***Does your work involve vigorous-intensity activity*** *for at least 10 minutes continuously.*
RR 1.334

Can a simplified 12-hour nighttime urine collection predict urinary stone risk?

Bryan D. Hinck, Vishnu Ganesan, Sarah Tarplin, John Asplin, Ignacio Granja, Juan Calle, Sri Sivalingam, Manoj Monga

- Can we do better?....Hypothesis
  - A 12-hour, nighttime urine collection will be as sensitive as a 24-hour urine collection
- May be a BETTER predictor of stone risk:
  - more concentrated: may reveal more abnormalities[4,5]
- Potential Significance:
    - Increased compliance
    - Decreased patient burden
    - Decreased dependence on weekend collections

4. Robert M, et al. B J Urol 1994; 74: 294-297.
5. Ogawa Y, et al. Int J Urol 1996; 3: 356-360.

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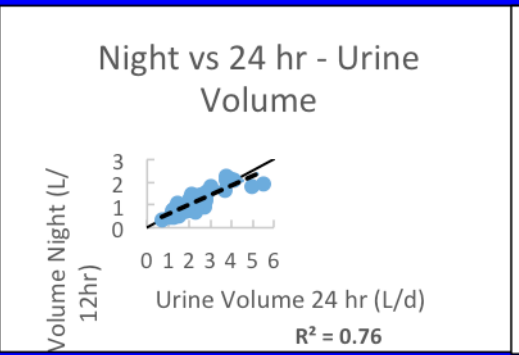
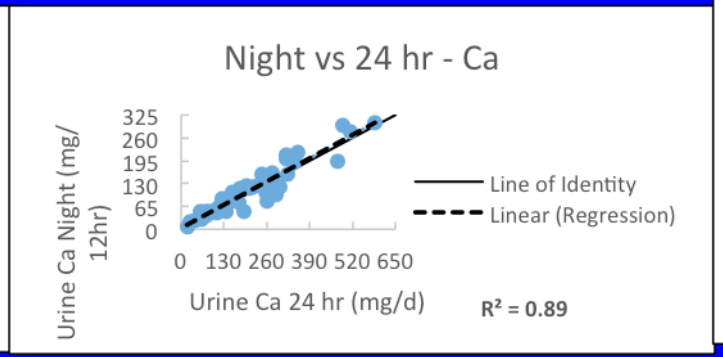
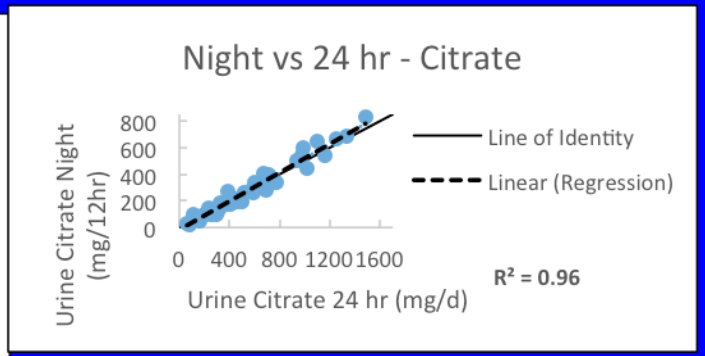
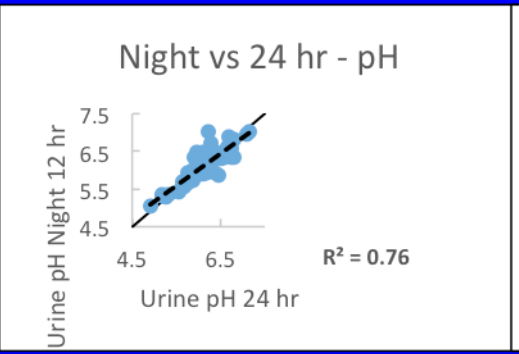
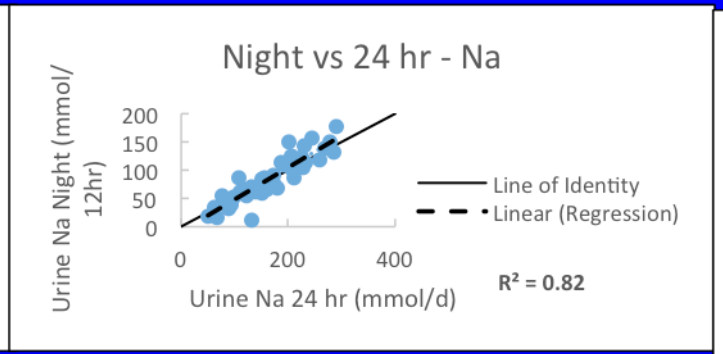
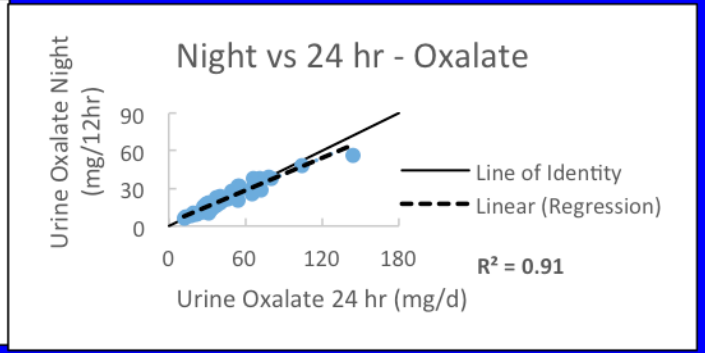


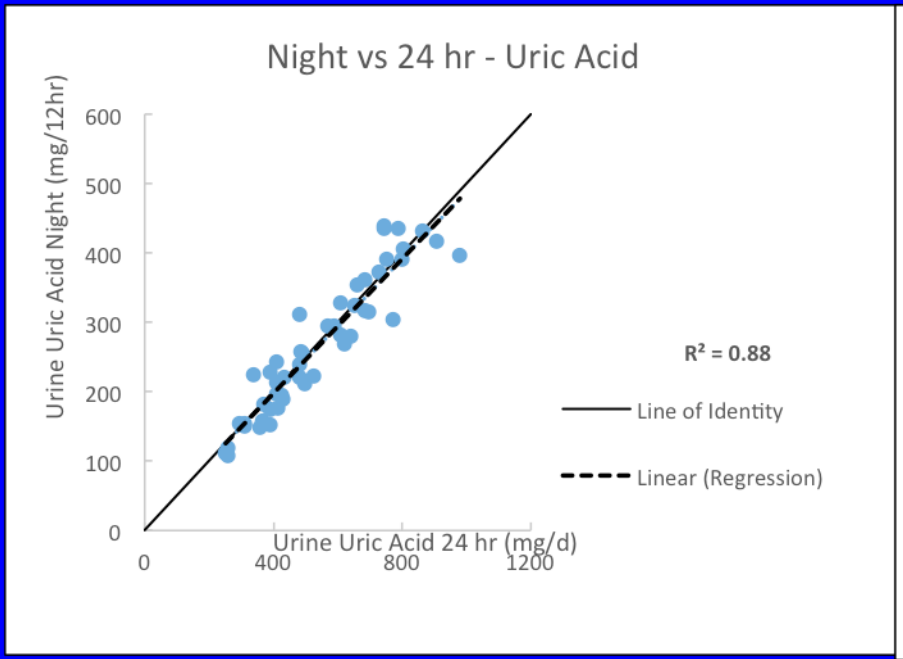


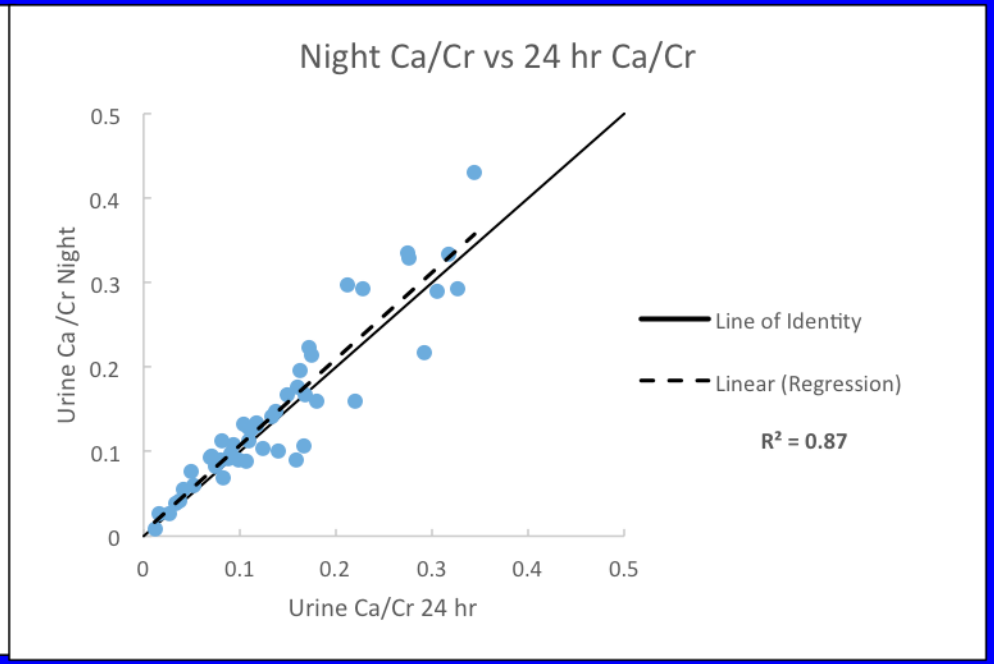




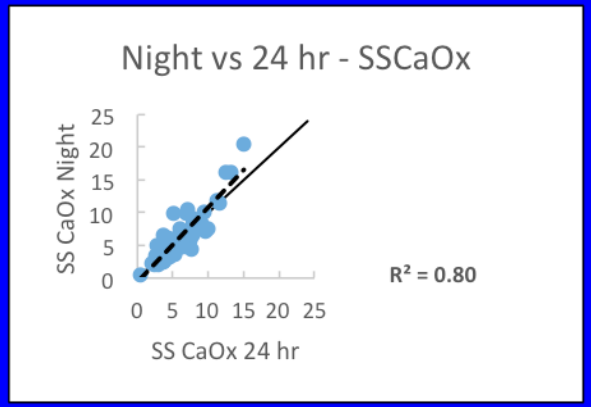


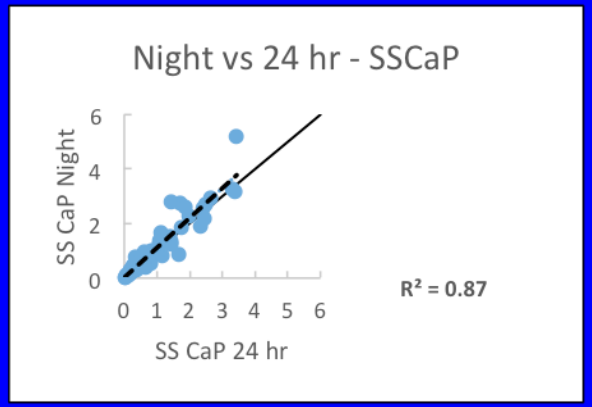


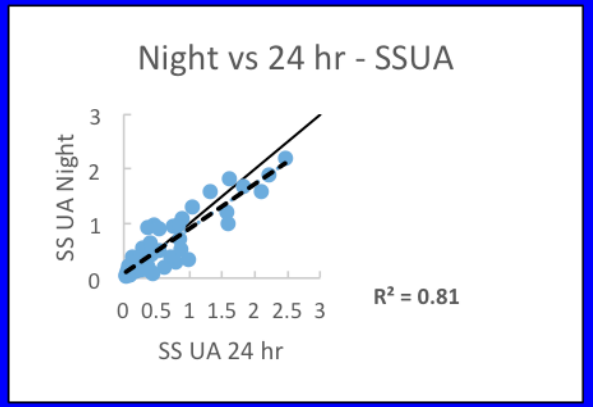

Night vs 24 hr - Uric Acid
Urine Uric Acid Night (mg/12hr)
600
500
400
300
200
100
0
0
400
800
1200
Urine Uric Acid 24 hr (mg/d)
R² = 0.88
Line of Identity
Linear (Regression)


Night Ca/Cr vs 24 hr Ca/Cr
Urine Ca /Cr Night
0.5
0.4
0.3
0.2
0.1
0
0
0.1
0.2
0.3
0.4
0.5
Urine Ca/Cr 24 hr
Line of Identity
Linear (Regression)
R² = 0.87

Night vs. 24 hr urine Supersaturations







-detected 5 of 5
- 2 additional cases

-detected 7 of 8
- 4 additional cases

-detected 8 of 9
- 1 additional case

Is Night-time collection adequate for clinical decision making?

- Night-time values identified:
  - > Ox = 14/14 pts
  - < Cit = 21/21 pts
    - Also an additional pt (F with 266 mg/12hr)
  - > UA = 6/6 pts
    - Also an additional pt (M with 436.2 mg/12hr)
  - > Na = 29/30 pts

Is Night-time collection adequate for clinical decision making?

- Night-time values identified:
  - > Ca = 14/16 pts
    - Pts "missed"
      - 258.81 mg/d (F) vs 81.05 mg/12hr (F)
      - 255.58 mg/d (M) vs 105.48 mg/12hr (M)
      - NOTE: These two pts had elevated night-time NA so would have received appropriate dietary counseling
    - Additional pt identified
      - 177.58 mg/d (F) vs 115.07 mg/12hr (F)

Conclusions

- Strong correlation between 12-hr night collection and 24-hr collection
- BETTER detection of stone risk factors
- Potential benefits:
  - Improved compliance
  - Decrease patient burden
  - Allow for increased weekday collection