Latest Strategies to Delay Renal Progression:

The next best things to RAAS blockade?

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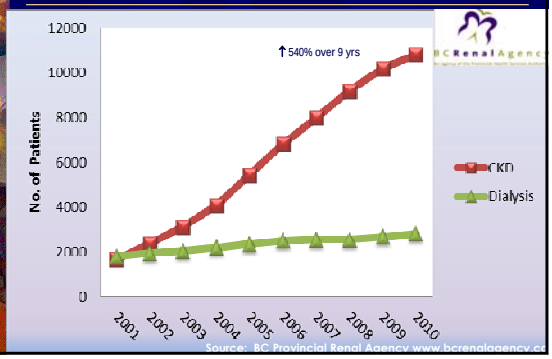
April 8, 2011

No conflict of interest to declare

Learning Objectives

- To briefly review the evidence behind current recommendations in delaying renal progression
- To describe the role of the following strategies in renal progression
  - Treating metabolic acidosis
  - Treating hyperuricemia

No. of Renal Patients in BC (2001-2010)



Risk Factors and Renal Progression

Proven …
- Proteinuria
- Hypertension
- Diabetes

Emerging …
- Metabolic acidosis
- Hyperuricemia

Association….
- Genetics
- Dyslipidemia
- Anemia
- Vitamin D deficiency
- Smoking
- Obesity

Wuhl E at al. Curr Opin Pediatr 2010;22:170-5
Francois H etal. J Nephrol 2011;24:133-41.

Proven Renoprotective Strategies

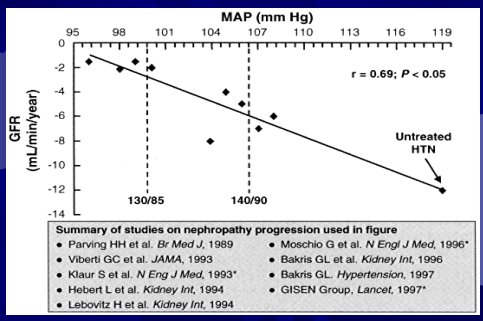
Or Are They?

RAAS blockade

RAAS blockade	Studies	↓ Proteinuria	↓ Rate of GFR decline
ACEIs	REIN*, AASK, Collaborative Study MicroHOPE	✓	✓* ↓ ESRD
ARBs	RENAAL*, IDNT	✓	✓* ↓ ESRD
High dose ARBs	DROP SMART	✓	✗
ACEI + ARB	CALM ONTARGET	✓	✗
+ Aldosterone Antagonist	Meta-analysis	✓	✗
+ Direct Renin Inhibitor	AVOID	✓	✗

Lancet1997;349:1857-63; JAMA2002;288:2421-31; NEJM1993;329:1456-62; Lancet2000;355:253-9; NEJM2001;345:861-9; NEJM2001;345:851-60; J Hypertension2007;25:1921-6; JASN2009;20:883-92; BMJ2000:321:1440-4; Lancet2008;372:547-53; CJASN2009;4:542-51; NEJM2008;358:2433-46

Blood Pressure Control



Summary of studies on nephropathy progression used in figure

- Parving HH et al. *Br Med J*, 1989
- Viberti GC et al. *JAMA*, 1993
- Klaur S et al. *N Eng J Med*, 1993*
- Hebert L et al. *Kidney Int*, 1994
- Lebovitz H et al. *Kidney Int*, 1994
- Moschio G et al. *N Engl J Med*, 1996*
- Bakris GL et al. *Kidney Int*, 1996
- Bakris GL. *Hypertension*, 1997
- GISEN Group, *Lancet*, 1997*

Bakris GL AJKD 2000;36:646-61

Blood Pressure Target

BP	Studies	CV Outcomes	Renal Outcomes
SBP < 160	SHEP	✓	✗
SBP < 150	SYST-EUR	✓	↓ Proteinuria
< 150/85	UKPDS-38	✓	✗
DBP < 80	HOT	✓ (DM)	✗
DBP < 80	ABCD n	✓	↓ Proteinuria
MAP ≤ 92 (125/75)	MDRD	✗	✗ ✓ (UP >3g/day + OL 12-yr f/u)
MAP ≤ 92	Lewis	✗	↓ Proteinuria
MAP ≤ 92	AASK	✗	✗ ✓ (P:Cr ratio > 0.22)
SBP < 120	ACCORD	✗ ✓ (CVA)	↓ Proteinuria ✗ (↑AKI)

Adapted from Dr. P. McFarlane, Can BP Control Prevent Renal Disease? Prevention in Renal Disease Conf 2010

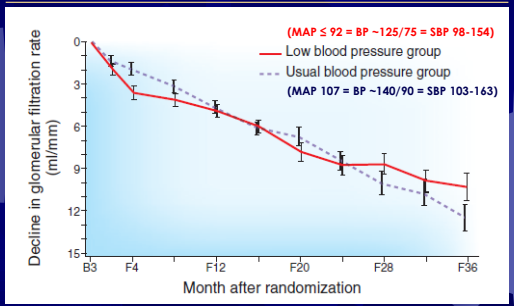
MDRD

Design	RCT
P	n = 840 Mean age 52
I	Intense control (MAP ≤92 age18-60; MAP≤98 age ≥61)
C	Usual control (MAP ≤107 age 18-60; MAP ≤113 age ≥61)
O	1° = Rate of GFR decline 2° = Adverse events (mortality, ESRD, CVD)

	Study 1	Study 2
GFR range (mL/min)	25-55	13-24
Mean GFR (mL/min)	39	19
BP (mmHg)	131/81	133/81
MAP	98	98

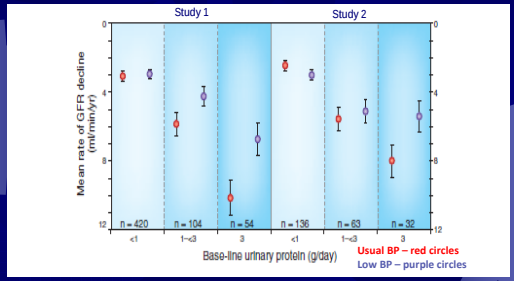
Klahr S et al NEJM 1994;330:877-84
Peterson JC et al Ann Intern Med 1995;123:754-62

MDRD Results



Lewis J JASN 2010;21:1086-92

MDRD Results



ACEI use unequal in usual vs low BP group

- Study 1: 34% vs 54%
- Study 2: 27% vs 43%

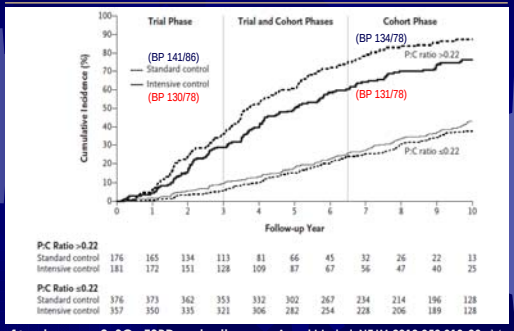
Lewis J JASN 2010;21:1086-92

AASK

Design	RCT, 2x2 factorial design
P	n = 1094 African Americans Hypertensive Nephrosclerosis Mean age 55 GFR 20-65 mL/min, mean 46 mL/min P:Cr Ratio 0.33 Urine protein 0.41- 0.61g/24h ACEI 38%
I	Intense MAP control (MAP ≤92 mmHg)
C	Usual MAP control (MAP 102-107 mmHg)
O	1° = Chronic GFR slope (after 3 months) OR mean total slope from baseline 2° = Composite of ↓GFR by 50% or 25 mL/min, ESRD, and death OR urinary protein excretion

Jackson T et al. JAMA 2002;288:2421-31

AASK Long Term Follow-Up



1° outcome = 2xSCr, ESRD or death

Appel LJ et al. NEJM 2010;353:918-29 14

Negative Studies

Studies	CV Outcomes	Renal Outcomes
REIN-2	✖	✖

Outcomes	BP < 130/80 (n=167)	DBP<90 (n=168)	HR (95% CI)	P value
1° = Progression to ESRD	23%	20%	1.00 (0.61-1.64	0.99
2° = GFR decline(mL/min/month) (regardless of proteinuria)	0.22	0.24		0.62

IDNT	✖	✓

2° Outcomes	BP ≤ 120 (n=53)	BP > 120 (n=1537)	RR (95% CI)	P value
All cause mortality	28%	12%	3.05 (1.80-5.17)	< 0.0001
CV mortality	19%	6%	4.06 (2.11-7.80)	< 0.0001

Ruggenenti P et al. Lancet 2005;365:939-46
Lewis et al. NEJM 2001;345:851-60 15

BP Target Summary

- No conclusive evidence to show BP target < 130/80 improves clinical outcomes
- Lower target may be beneficial in pts with proteinuria > 0.3-1g/day
- Individualize BP target based on risk vs benefit, pt tolerance and preferences
- ↑ vigilance to monitor for hypotension

Upadhyay A et al Ann Int Med 2011/03/11 online release 16

Blood Sugar Control

A1c	Studies	CV Outcomes	↓ Proteinuria	↓ Rate of GFR decline
7.3% vs 9%	DCCT	✖	✓	✖
7.9% vs 8.2%	EDIC 17 yrs f/u	✓	✓	✖
FBG <6 vs <15 (7% vs 7.9%)	UKPDS 33	✖	✓	✓ ↓ESRD
8% vs 8.1%	UKPDS 80 10 yrs f/u	✓	✓	✖
<6% vs 7-7.9% (6.4% vs 7.5%)	ACCORD	✖ (↑ all cause & CV death)	✓	✖
<6.5% (6.5% vs 7.3%)	ADVANCE	✖ (NSS all cause & CV death)	✓	✖

17

Emerging Therapies

All truth passes through 3 stages

1. *It is ridiculed*
2. *It is violently opposed*
3. *It is accepted as being self-evident*

Arthur Schopenhauer (1788-1860)

Metabolic Acidosis and Renal Progression

What is the evidence?

- Pathophysiology
- Experimental evidence
- Epidemiology evidence
- Clinical evidence

21

Case 1: Meet LI

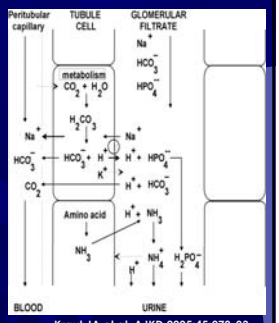
ID	LI, 74 yo Italian male, weight= 88 kg
CC	Weakness, feeling unwell, stomach upset

PMH	Meds
CKD stage V	Ramipril 2.5 mg po daliy
Hypertension	Nifedipine XL 60 mg po daily
Dyslipidemia	Simvastatin 40 mg po HS
Atrial fibrillation	Propranolol 80 mg po BID Warfarin 2.5 mg po HS

	eGFR (mL/min)	ACR (mg/mmol)	BP (mmHg)	HCO_3 (umol/L)	K (mmol/L)
May '10	12	346	125/80	16	5.3
Oct '10	14	389	146/82	16	5.5
Mar '11	11	205	127/86	14	5.2

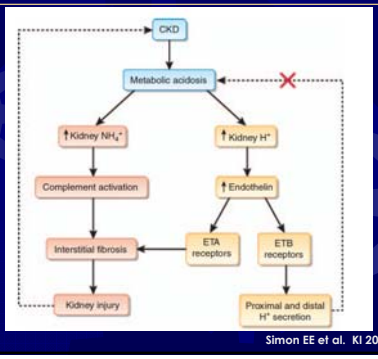
Pathophysiology

- ~ 1 mEq/kg/day H^+ ion generated by food metabolism
- Acid-base balance is achieved by urinary excretion of H^+ ion as titratable acidity (as phosphate) and as $NH4^+$
- AS GFR < 40-50mL/min
  - ↓ $NH4^+$ excretion
  - ↓ Phosphate excretion (2° dietary restriction)



Kraut JA et al. AJKD 2005;45:978-93

Pathophysiology – CKD progression



Simon EE et al. KI 2010;77:567-9

Prevalence

- ~ 80% pts with GFR < 20-30mL/min have mild to moderate acidosis
  - plasma [HCO_3^-] 12-22 mEq/L
  - Blood pH > 7.2
- ~10-20% stage 5 CKD have normal [HCO_3^-]
  - ↓'d protein intake → ↓'d daily acid load
  - ↑'d fruit intake which provides citrate → HCO_3^-
  - DM pts tend to have normal HCO_3^- and anion gaps
  - diuretic use

Kraut JA et al. AJKD 2005;45:978-93 25

Clinical Manifestations

CNS	Headache, fatigue, lethargy, weakness, drowsiness, confusion, obtundation/coma
EENT	Decreased visual acuity
Resp	Hyperventilation, respiratory muscle fatigue
CV	Hypotension, impaired myocardial contractility, arrhythmias
GI	Nausea, vomiting, diarrhea, anorexia
Endo	Insulin resistance
Lytes	Hyperkalemia
MSK	Muscle weakness, bone pain

Kraut JA et al. AJKD 2005;45:978-93

Complications

- ↑'d protein catabolism w/ muscle wasting
- ↓'d albumin synthesis
- Bone disease w/↑'d PTH production
- Stunting of growth in children
- Insulin resistance
- ↑'d corticosteroid production
- Impaired thyroid metabolism
- ↑'d inflammatory mediators
- Exacerbation of renal progression

Kraut JA et al. AJKD 2005;45:978-93 27

Experimental Evidence

Positive Studies

In rat models, metabolic acidosis associated with:

- New or worsening proteinuria
- Worsening tubulointerstitial injury
- Progressive renal failure
- Cystic enlargement, interstitial fibrosis and renal insufficiency in PCKD
- NaHCO3 or citrate ↓'d degree of tubulointerstitial injury and GFR decline

Nath KA et al J Clin Invest 1985;76:667-675; Torres VE et al Exp Nephrol 2001;9:171-80
Gadola L et al Kidney Int 2004;65:1224-30; Phisitkul S et al Kidney Int 2008;73:192-9 29

Conflicting results

- Other rat studies did not confirm results
- In rats with renal failure fed a high phosphate diet, metabolic acidosis lessened rate of decline by reducing extent of Ca-P precipitation in kidney

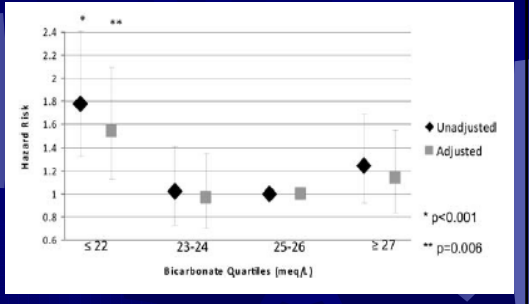
Jara A et al. KI 2000;58:103-32
Jara A et al. NDT 2004;19:1993-8 30

Epidemiology Evidence

Study Design	Retrospective cohort study
Population	N = 5422 Mean age 52 yrs; 69% ♀; 45% African American; 31% Hispanic; 21% DM; 41% HTN
Outcomes	CKD progression defined as ↓ GFR by 50% or eGFR < 15 mL/min
Duration	Median 3.4 yrs
Results	6.2% pts progressed Compared with ref group ([HCO_3^- 25-26mEq/L], •HCO_3^- ≤ 22mEq/L: HR 1.54 (95%CI, 1.13-2.09) •HCO_3^- 23-24mEq/L: HR 0.94 (95%CI, 0.70-1.35) •HCO_3^- ≥ 27mEq/L: HR 1.14 (95%CI, 0.84-1.55) Multivariate adjustment for confounders
Conclusion	• Low serum HCO_3^- level is associated with CKD progression
Limitations	• Observational • No information on other meds or protein intake

Shah SN et al. AJKD 2009;54:270-7 32

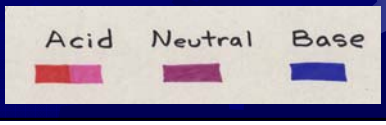
Risk for Progression



Shah SN et al. A 2009;54:270-7 33

Clinical Evidence

A "Basic" Approach to Slow Renal Progression



In Advanced CKD

Design	Single center, open label, R, prospective, 2 yrs	
P	Inclusions: •Age > 18 yrs •CrCl 15-30mL/min •[HCO_3^-] 17-19mmol/L •Stable clinical conditions	Exclusions: •Malignancy •Morbid obesity •Cognitive impairment •Chronic sepsis •BP > 150/90 despite 4 agents •Overt HF
I	$NaHCO_3$ 600mg po TID, adjust to achieve [HCO_3^-] ≥ 23mmol/L (n=67)	
C	Standard care (n=67)	
O	1° = Rate of CrCl decline, % pts w/ rapid CrCl decline (>3mL/min) and ESRD (CrCl <10mL/min) 2° = dietary protein intake, serum albumin, mid-arm muscle circumference	

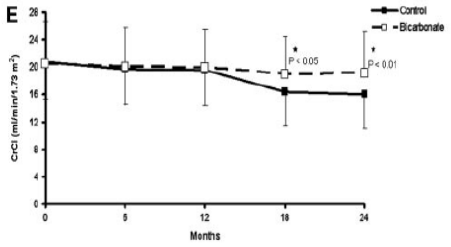
De Brito-Ashurst I et al. JASN 2009;20:2075-84 35

Baseline Characteristics

Variables	$NaHCO_3$	Control
Age, mean ± SD (yr)	54.8 ± 2.6	54.8 ± 2.3
Male (%)	52	51
White (%)	52	52
Weight, mean ± SD (kg)	76.6 ± 21.1	74.9 ± 11.5
DM (%)	37	36
HTN (%)	29	26
Glomerulonephritis (%)	10	13
BP, mean ± SD (mmHg)	124.0/76.1 ± 1.3/1.5	123.7/75.4 ± 1.2/1.9
CrCl, mean ± SD (mL/min)	20.1 ± 6.5	20.7 ± 5.6
[HCO_3^-] , mean ± SD (mmol/L)	19.8 ± 2.2	19.9 ± 1.5
Loop diuretics (%)	70	67
ACEI/ARB (%)	50	48
Allopurinol (%)	0	3

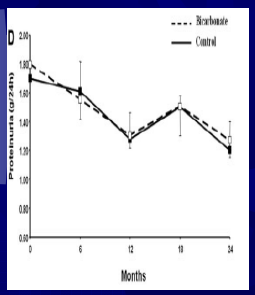
De Brito-Ashurst I et al. JASN 2009;20:2075-84

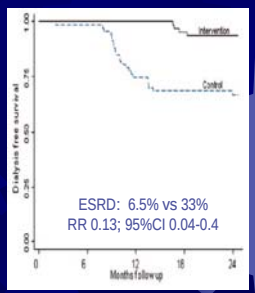
Results



- CrCl decline: 1.88 vs 5.93 mL/min; p<0.0001
- % pts w/ rapid CrCl decline: 9% vs 45%; RR 0.15

Results

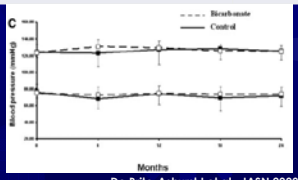




ESRD: 6.5% vs 33%
RR 0.13; 95%CI 0.04-0.4

Adverse Effects

Adverse Effects	$[HCO_3^-]$ % pts	Control % pts
Hospitalization for CHF	0	0
Worsening HTN requiring ↑ in therapy	61	48
Worsening edema requiring ↑ in loop diuretics	39	30
Bad taste	6.5	n/a



Conclusion

Limitations	• Single center • Small sample • Open label • Lack of placebo use • Low RAAS blockade (~60% by end of study) • Underpowered to detect ADRs • ?generalizable
Authors' Conclusion	$NaHCO_3$ in pts with advanced CKD and low plasma $[HCO_3^-]$ slows rate of renal function decline

In Advanced CKD

Design	Single center, prospective, 2 yrs	
P	Inclusions: •≥ 18 yrs •Non-malignant HTN •GFR ≥ 20 to < 60mL/min •Plasma $[CO_2]$ < 22mM •≥ 2 clinic visits showing compliance •ACEI/ARB therapy	Exclusions: •DM •Primary kidney failure, hematuria •Malignancy •Chronic infections •Pregnancy •CVD •Edema (HF, liver failure, nephrotic syndrome) •Taking AI products •RAS +/- hyperaldosteronism
I	Na citrate 1mEq/kg/day (n=30)	
C	Control (unable or unwilling to take Na citrate) (n=29)	
O	1° = Urine endothelin (UET) 2° = UNAG, reduction in rate of GFR decline	

Baseline Characteristics

Variables	Na citrate (n =30)	Control (n =29)
Age, mean ± SD (yr)	54.1 ± 6.4	53.9 ± 5.0
Male (%)	47	48
Black (%)	53	55
Hispanic (%)	23	31
SBP, mean ± SD (mmHg)	161.8 ± 10.8	160.5 ± 8.9
GFR, mean ± SD (mL/min)	33.0 ± 8.5	33.4 ± 8.4
$[CO_2]$, mean ± SD (mM)	20.8 ± 1.2	20.6 ± 0.8

Results

Variables	Na citrate (n =30)	Control (n =29)
GFR, mean ± SD (mL/min)	29.5 ± 8.8	24.9 ± 9.7
SBP, mean ± SD (mmHg)	132.7 ± 5.7	131.9 ± 3.8
$[CO_2]$, mean ± SD (mM)	23.8 ± 1.0	19.6 ± 1.2
Ualb (mg/g Cr)	107.1 ± 48.7	146.9 ± 44.6

- UET and UNAG significantly reduced in Na citrate group
- GFR decline: -1.6 ± 0.13 vs -3.79 ± 0.3 mL/min/yr

Phisitkul S A et al. KI 2010;77:617-23 43

Conclusion

Limitations	• Open label • Single center • Small sample • Non-randomized • Lack of placebo use • Mainly Black & Hispanic • ?generalizability (# exclusions) • ? # antihypertensives to maintain BP • ? diuretic use • 1° endpoint = surrogate marker • Did not adjust for multiple comparisons • ADR not reported
Authors' Conclusion	Na citrate in pts with low $[HCO_3]$ and advanced CKD due to hypertensive nephropathy reduces markers of kidney injury

Phisitkul S A et al. KI 2010;77:617-23

In Early CKD

Design	Single center, Prospective, R, DB, PC, 5 yrs	
P	Inclusions: •≥ 18 yrs •Non-malignant HTN •Ualb ≥ 200 to < 2000 mg/g (macroalbuminuria) •GFR ≥ 60 to < 90mL/min •≥ 2 clinic visits showing compliance •ACEI/ARB therapy	Exclusions: •DM •Primary kidney failure, hematuria •Malignancy •Chronic infections •Pregnancy •CVD •Edema (HF, liver failure, nephrotic syndrome) •Smoking within 1 yr •Plasma $[CO_2]$ < 24.5mM
I	$NaHCO_3$ 0.5mEq/kg/day (n=40)	
C	NaCl 0.5mEq/kg/day (n=40) vs placebo (sucrose) (n=40)	
O	1° = Reduction in rate of GFR decline 2° = UET, Ualb, UNAG	

Mahajan A et al. KI 2010;78:303-9

Baseline Characteristics

Variables	$NaHCO_3$ (n =40)	NaCl (n =40)	Placebo (n =40)
Age, mean ± SD (yr)	51.2 ± 8.2	51.5 ± 8.3	51.3 ± 8.5
Male (%)	48	48	48
Black (%)	63	63	63
Hispanic (%)	20	23	25
SBP, mean ± SD (mmHg)	155.3 ± 12.6	152.6 ± 14.7	155.2 ± 12.9
GFR, mean ± SD (mL/min)	75.3 ± 6.1	75.6 ± 6.5	75.6 ± 6.2
$[CO_2]$, mean ± SD (mM)	26.2 ± 0.7	26.4 ± 0.8	26.0 ± 0.9
Ualb (mg/g Cr)	419.3 ± 150.8	413.6 ± 147.9	422.2 ± 151.6

Mahajan A et al. KI 2010;78:303-9 46

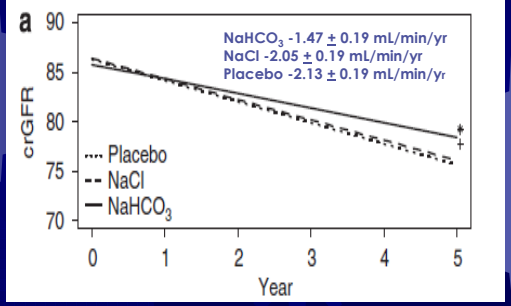
Results

Variables	$NaHCO_3$ (n =37)	NaCl (n =36)	Placebo (n =34)
GFR, mean ± SD (mL/min)	67.6 ± 4.9	65.2 ± 5.5	64.0 ± 6.1
SBP, mean ± SD (mmHg)	135.1 ± 6.2	132.1 ± 6.6	133.3 ± 8.1
$[CO_2]$, mean ± SD (mM)	26.4 ± 0.6	26.3 ± 0.6	26.1 ± 0.8
Ualb (mg/g Cr)	387.5 ± 163.1	466.5 ± 179.4	507.5 ± 228.2

- UET and UNAG significantly reduced in $NaHCO_3$ group

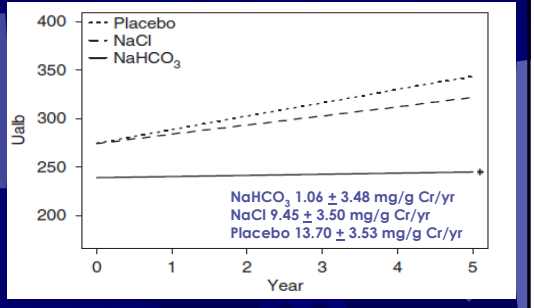
Mahajan A et al. KI 2010;78:303-9 47

Results



Mahajan A et al. KI 2010;78:303-9 48

Results



Mahajan A et al. KI 2010;78:303-9 49

Conclusion

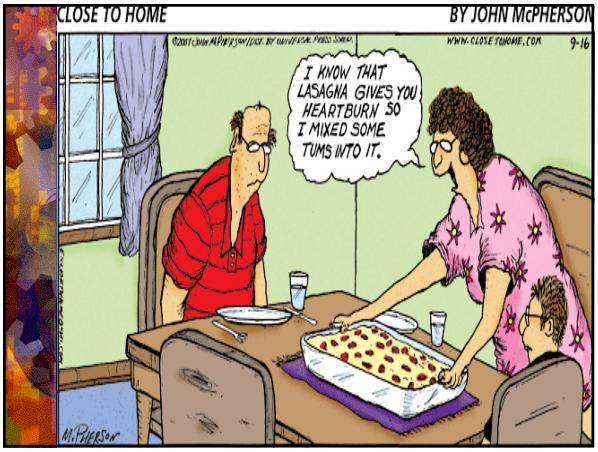
Limitations	• Single center • Small size • Per protocol analysis • Mainly Black & Hispanic • ? generalizability (# of exclusions) • ? # antihypertensives to maintain BP • ? diuretic use • ADR not reported
Conclusion	$NaHCO_3$ in pts with relatively preserved GFR due to hypertensive nephropathy slows rate of renal function decline

Mahajan A et al. KI 2010;78:303-9 50

What is the evidence?

- ☑ Pathophysiology
- ☐ Experimental evidence
- ☑ Epidemiology evidence
- ☑ Clinical evidence

51



Dietary Acid Load

Alkaline & Acid Forming Foods Chart

Most Alkaline	Alkaline	Lowest Alkaline	FOOD CATEGORY	Lowest Acid	Acid	Most Acid
		Raw Honey, Raw Sugar	SWEETENERS	Processed Honey, Molasses	White Sugar, Brown Sugar	Nutrasweet, Equal, Aspartame, Sweet 'N Low
Lemons, Watermelon, Limes, Grapefruit, Mangoes, Papayas	Dates, Figs, Melons, Grapes, Papaya, Kiwi, Pineapple, Apples, Pears, Raisins	Oranges, Bananas, Cherries, Strawberries, Peaches, Avocados	FRUITS	Plums, Processed Fruit Juices	Sour Cherries, Rhubarb	Blueberries, Cranberries, Prunes
Asparagus, Onions, Vegetable Juices, Parsley, Raw Spinach, Broccoli, Garlic	Okra, Squash, Green Beans, Raw Celery, Lettuce, Zucchini, Sweet Potato, Carrots	Carrots, Tomatoes, Fresh Corn, Green Peas, Cabbage, Peas, Potato Skins, Olives, Soybeans, Tofu	BEANS VEGETABLES LEGUMES	Cooked Spinach, Kidney Beans, String Beans	Potatoes (without skins), Pinto Beans, Navy Beans, Lima Beans	Chocolate
	Almonds	Chestnuts	NUTS SEEDS	Pumpkin Seeds, Sunflower Seeds	Pecans, Cashews	Peanuts, Walnuts
	Flax Seed Oil	Canola Oil	OILS	Corn Oil		
		Amaranth, Millet, Wild Rice, Quinoa	GRAINS CEREALS	Sprouted Wheat Bread, Spelt, Brown Rice	White Rice, Corn, Buckwheat, Oats, Rye	Wheat, White Flour, Pastries, Pasta
			MEATS	Venison, Cold Water Fish, Eggs, Butter, Yogurt	Turkey, Chicken, Lamb	Beef, Pork, Shellfish
	Breast Milk	Soy Cheese, Soy Milk, Goat Milk, Goat Cheese, Whey	EGGS DAIRY	Buttermilk, Cottage Cheese	Raw Milk	Cheese, Homogenized Milk, Ice Cream
Herb Teas, Lemon Water	Green Tea	Ginger Tea	BEVERAGES	Tea	Coffee	Beer, Soft Drinks

Metabolic Acidosis Summary

PRO

- May delay renal progression at various CKD stages
- Symptom control

CON

- Consider comorbidities
  - Volume overload/HF
  - Edema
  - Worsening HTN
- ? worseing vascular calcification
- Pill burden
- Cost
- ADRs (GI)

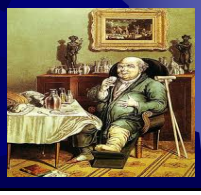
54

Metabolic Acidosis Summary

- When to initiate?
  - Ensure traditional risk factors are addressed
  - Early vs Advanced CKD
- Who to initiate?
  - Hypertensive or rapidly declining GFR
- What to use?
  - $NaHCO_3$ vs Na citrate vs $CaCO_3$
- What is the target?
  - $[HCO_3]$ level ≥ 24mmol/L

55

Hyperuricemia and Renal Progression



Case 2: Meet FM

ID	35 yo Persian Male, wt =72 kg					
CC	Feels well					
PMH	CKD Stage III Alport Syndrome Alopecia					
Meds	Ramipril 10mg po daily HCTZ 25mg po daily Finasteride 1.25mg po daily CaCO3 1250mg po daily					
Labs		eGFR (mL/min)	ACR (mg/mmol)	BP (mmHg)	Uric acid (umol/L)	K (mmol/L)
	May '10	45	276.2	125/88	556	5.1
	Aug '10	42	45.6	112/66		5.8
	Nov '10	41	164.1	123/65	495	5.5
	Feb '11	33	123.9	115/67		5.2

What is the evidence?

- Pathophysiology
- Experimental evidence
- Epidemiology evidence
- Clinical evidence

58

Innocent Bystander vs Vicious Cycle

VS

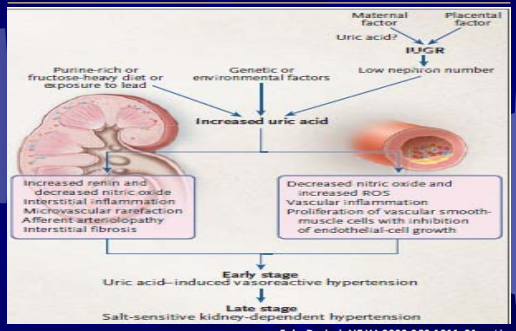
Prevalence

- >70% pts with gout were obese, > 50% HTN
- Almost all had renal disease
- ~90% had some heart disease
- Asymptomatic hyperuricemia – similar association

Heinig M et al. CCJM 2006:73:1059-64

60

Pathophysiology



Feig D et al. NEJM 2008;359:1811-21 61

Experimental Evidence

Experimental Evidence

In rat models , hyperuricemia

- ↑'d SCr
- ↑'d tubulointerstitial fibrosis & glomerulosclerosis
- worsened renal lesions in rats with pre-existing renal disease
- when prevented by xanthine oxidase adm'n, ↑ in BP and renal injury abolished
- Co-administration of thiazide ↓'d BP but no Δ in hyperuricemia or renal injury

Feig D. Curr Opin Nephrol Hypertens 2009;18:526-30
Heinig M et al. CCJM 2006;73:1059-64 63

Epidemiology Evidence

Uric Acid and BP

Serum uric acid and relative risk of hypertension

STUDY	YEAR	POPULATION	RELATIVE RISK
Kahn et al[13]	1972	10,000 males	2-fold risk at 5 years
Selby et al[14]	1990	2,062 subjects	2-fold risk at 6 years
Hunt et al[27]	1991	1,482 adults	2-fold risk at 7 years
Jossa et al[28]	1994	619 males	2-fold risk at 12 years
Taniguchi et al[15]	2001	6,356 males	2-fold risk at 10 years
Masuo et al[16]	2003	433 males	1.0-mg/dL increase in serum uric acid predicts a 27-mm Hg elevation in systolic blood pressure at 5 years
Nakanishi et al[31]	2003	2,310 males	1.6-fold risk at 6 years
Nagahama et al[29]	2004	4,489 adults	1.7-fold risk at 13 years
Alper et al[26]	2005	679 children	Increased risk at 11 years
Sundstrom et al[30]	2005	3,329 adults	1.6-fold risk at 4 years

Heinig M et al. CCJM2006;73:1059-64 65

Uric Acid and CKD

First author	Year	Participants	Major findings
Hsu	2009	177 570, USRDS	Higher uric acid quartile conferred 2.14-fold increased risk of ESRD over 25 years (+)
Obermayr	2008	21 457 Vienna Health Screening Project	Uric acid >7 mg/dl increased risk of CKD 1.74-fold in men and 3.12-fold in women (+)
Weiner	2008	13 338, ARIC	Each 1 mg/dl increase in uric acid increased risk of CKD 7–11%
Iseki	2001	6403, Okinawa General Health	Uric acid >8 mg/dl increased CKD risk three-fold in men and 10-fold in women (+)
Borges	2009	385	Elevated uric acid associated with 2.63-fold increased risk of CKD in hypertensive women (+)
Chen	2009	2596, Ruijin Hospital, China	Linear correlation between uric acid and degree of CKD (+)
Park	2009	134, Yonsei University	Uric acid >7 mg/dl correlates with more rapid decline in residual renal function in peritoneal dialysis patients (+)
Sturm	2008	227, MMKD study	Uric acid predicted progression of CKD only in unadjusted sample (–)
Chonchol	2007	5808, Cardiovascular Health study	Uric acid strongly associated with prevalent but weakly with incident CKD (–)
See	2009	28 745, Chang Gung University	Uric acid >7.7 mg/dl in men and >6.6 mg/dl in women only weakly associated with prevalent renal impairment (–)
Madero	2009	840, Instituto Nacional de Cardiologia, Mexico	CKD 3–4 and uric acid correlate with death but not with ESRD (–)

Feig D. Curr Opin Nephrol Hypertens 2009;18:526-30 66

Clinical Evidence

Does Allopurinol Slow Renal Progression?

In Normal GFR

Design	Single center, prospective, observational, 3 months	
P	Inclusions: •GFR > 60 mL/min •Serum UA > 7 mg/dL (416.4 µmol/L) •Not taking allopurinol	Exclusions: •Gouty arthritis, renal stones •Proteinuria (>500 mg/day) •Uncontrolled hypertension •DM •HF •Atherosclerosis (CVA, CAD, PVD) •Infection •Alcohol abuse •Cancer •Allopurinol hypersensitivity
I	Allopurinol 300 mg po daily (n=48)	
C	Age- & sex-matched control with normal UA (n=21)	
O	Change in GFR, proteinuria, and BP	

UA = uric acid

Kanbay M et al. Int Urol Nephrol 2007;39:1227-33. 68

Baseline Characteristics

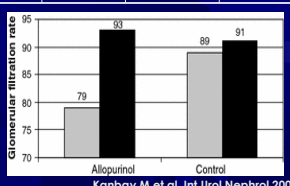
Variable	Allopurinol (n =48)	Control (n =21)
Age, mean ± SD (yr)	66.4 ± 11.3	64.5 ±12.5
Male (%)	71%	62%
BMI (kg/m2)	26.4 ± 2.6	27.3 ± 3.4
Smoking	33.3%	47.6%
HTN	71%	62%
SBP, mean ± SD (mmHg)	135.4/80.2 ± 4.6/6.2	133.2/82.7 ± 6.9/5.6
ACEI ARB	31% 25%	33% 23%
Thiazides	46%	38%

Kanbay M et al. Int Urol Nephrol 2007;39:1227-33 69

Results

	Allopurinol (n=41)		Control (n=18)	
Uric acid (µmol/L)	475.9 ± 45	327.2 ± 71.4*	345 ± 11.9	345 ± 0
eGFR (mL/min)	79.2 ± 31.9	92.9 ± 36.8*	89.4 ± 3	91.0 ± 6.1
Urine protein(mg/day)	134.5 ± 132	131.5 ± 108.1	111 ± 17.5	114.6 ± 12.9
BP (mm Hg)	135.4/80.2 ± 4.6/6.2	131.5/78.3* ± 4.1/3.1	133.2/82.1 ± 6.9/5.6	132.6/80.8 ± 7.9/6.4

*P<0.05



Kanbay M et al. Int Urol Nephrol 2007;39:1227-33 70

Conclusion

Limitations	• Small trial • Not randomized or controlled • Short duration • Significant drop outs • Per protocol analysis • Included normotensive patients (25%) • Significant baseline differences in antihypertensive medications • Endpoint = Surrogate markers • BP reduced, but clinical significance? • ACEI/ARB not optimized • ? External validity
Authors' Conclusion	• Allopurinol improves GFR in patients with normal renal function

Kanbay M et al. Int Urol Nephrol 2007;39:1227-33 71

In Early-Moderate CKD

Design	Single-centre, prospective, RCT, 1 yr	
P	Inclusions: •Renal disease (proteinuria > 0.5 g or SCr > 120 umol/L) •Stable clinical condition •Stable renal function (< 40% change w/n 3 mos of study) •Not taking allopurinol	Exclusions: •Gouty arthritis, renal stones •Advanced CKD (SCr > 400 umol/L) •Taking azathioprine •Allopurinol hypersensitivity •♀ of childbearing age not willing to use contraception •Pregnant/lactating ♀
I	Allopurinol 100 mg or 200 mg daily (per SCr); adjust dose to maintain normal serum UA (max 300 mg daily) (n =25)	
C	Standard treatment (n=26)	
O	Stable SCr (< 40% increase over baseline) Worsening SCr (> 40% increase over baseline, not requiring HD) ESRD Death	

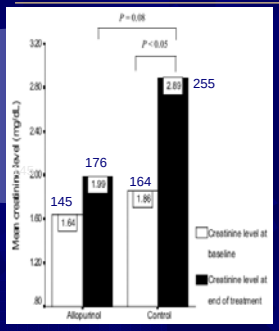
Siu YP et al. AJKD 2005;47:51-9 72

Patient Characteristics

Variables	Allopurinol (n =25)	Control (n =26)
Age, mean ± SD (yr)	47.7 ± 12.9	48.8 ± 16.8
Male (%)	8%	48%
Body weight (kg)	70.5 ± 10.4	65.4 ± 127
DM	24%	27%
HTN	84%	73%
Chronic GN	28%	23%
SBP, mean ± SD (mmHg)	138/79 ± 20/10	135/71 ± 19/14
Cr, mean ± SD (μmol/L)	145 ± 56	164 ± 61
Uric acid, mean (μmol/L) Baseline End of study	 580 ± 70.2 349.8 ± 60	 590 ± 100 600 ± 100
ACEI ARB	57.7% 30.8%	56% 20%

Siu YP et al. AJKD 2005;47:51-9

Results - SCr



Allopurinol group:
- NSS increase in SCr

Control group:
- SS increase in SCr

Allopurinol vs Control:
- NSS difference in SCr between groups at end of treatment

Siu YP et al. AJKD 2005;47:51-9

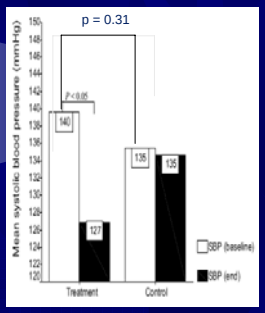
Results

	Allopurinol (n = 25)	Control (n = 26)
Stable SCr (< 40% increase over baseline)	21/25 (84%)	14/26 (53.8%)
Worsening SCr (> 40% increase over baseline, not requiring HD)	3/25 (12%)	11/26* (42.3%)
ESRD (requiring HD)	1/25 (4%)	1/26 (3.8%)
Death	None	None

*p = 0.015

Siu YP et al. AJKD 2005;47:51-9

Results - BP



Allopurinol group:
- SS lower SBP after treatment

Control group:
- No change in SBP

Allopurinol vs. Control:
- NSS difference in SBP between groups at end of treatment

Siu YP et al. AJKD 2005;47:51-9

Conclusion

Limitations	• Small trial • Likely underpowered to detect differences in ESRD and death • Single center • Not placebo controlled • ? Open label • Per protocol analysis • ACE/ARB not optimized • Used SCr as surrogate
Authors' Conclusion	Allopurinol is safe and helps preserve kidney function

Siu YP et al. AJKD 2005;47:51-9

In Moderate CKD

Design	Single-centre, prospective, RCT, 2 yr	
P	Inclusions: •Renal disease (GFR < 60 mL/min) •Stable clinical condition •Stable renal function (< 50% change w/n 3 mos of study) •Not taking allopurinol	Exclusions: •Allopurinol hypersensitivity •Active infections •Inflammatory diseases •HIV infection •Chronic hepatopathy •Taking immunosuppressants
I	Allopurinol 100 mg po daily (n=57)	
C	Control (n=56)	
O	• Hospitalizations • CVE • ESRD • Mortality	

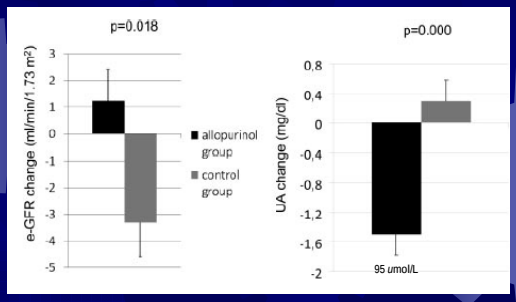
Goicoechea M et al. CJASN 2010; 5:1388-93

Baseline Characteristics

Variables	Allopurinol (n =57)	Control (n =56)
Age, mean ± SD (yr)	71.4 ± 9.5	72.1 ± 7.9
DM (%)	22%	20%
Vascular nephropathy (%)	28%	25%
Chronic GN (%)	1%	5%
Ischemic cardiopathy (%)	16%	10%
SBP, mean ± SD (mmHg)	147/77 ± 20/11	146/76 ± 17/13
eGFR, mean ± SD (*mL/min*)	40.6 ± 11.3	39.5 ± 12.4
Uric acid, mean (μmol/L)	464 ± 125	434 ± 95
RAAS blockade (%)	47%	41%
Diuretics (%)	36%	30%
Statins (%)	27%	24%
Antiplatelet (%)	15%	18%

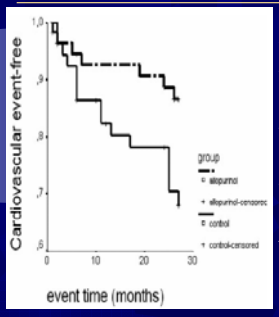
Goicoechea M et al. CJASN 2010; 5:1388-93 79

Results



Goicoechea M et al. CJASN 2010; 5:1388-93 80

Results



Allopurinol vs Control

Hospitalization
- 12 vs 22 pts (p=0.032)

Death
- 0 vs 2 pts (NSS)

ESRD
- 1 vs 1 pt (NSS)

Adverse Events
- 2 pts (GI) vs 0

Goicoechea M et al. CJASN 2010; 5:1388-93 81

Conclusion

Limitations	• Small trial • Single center • Not placebo controlled • Not double blind • ? Adjustment for multiple analysis • Baseline ACE/ARB, statins not optimized • BP not optimized • Dietary advice given but its role not evaluated • ? ACE/ARB, statins use at end of study
Authors' Conclusion	Allopurinol slows renal progression and reduces CV and hospitalization risks in pts with CKD

Goicoechea M et al. CJASN 2010; 5:1388-93 82

Low Purine DIET GUIDE	
Group I: Select from these Foods	
Cheese	Fruits (except those in group III)
Eggs	Gelatine
Cereals/ cereal products	Milk
Bread	Coffee and tea
Butter/ margarine	Vegetables
Beverages	Syrups
Group II: Use in Moderation	
Fish (expect those in group III)	Chicken (poultry products)
Legumes (beans)	Seafoods (crabs, shrimps, oysters)
Meat (meat soup and broth)	Vegetables (spinach, mushrooms, asparagus, cauliflowers)
Oatmeal	
Group III: Avoid these Foods	
Gravies	Nuts-Peanuts, cashew nuts . . .
Mackerel/Sardines	Fruits (avocado)
Mussels	Sweet beans
Meat Extracts	Fish (Tuna)
Internal organs	Fructose (fruit juices and soft drinks)
Yeast	Alcohol (red wine, beer)

83

Hyperuricemia Summary

PRO
- May delay renal progression at various CKD stages
- Symptom control
- Concomittent CV risks

CON
- ADRs
  - Allopurinol Hypersensitivity syndrome
  - Steven-Johnson
- Pill burden
- Cost

84

Hyperuricemia Summary

- When to initiate?
  - Ensure traditional risk factors are addressed
  - Early vs moderate CKD
  - Eliminate hyperuricemic drugs, if feasible
- Who to initiate?
  - Pts. with gouty attacks or metabolic syndrome or rapidly ↓'ing GFR
- What to use?
  - Allopurinol vs febuxostat
- What is the target?
  - Dose vs uric acid level

85

Back to Case 1. LI

ID	LI, 74 yo Italian male, weight= 88 kg
CC	Weakness, feeling unwell, stomach upset

PMH	Meds
CKD stage V	Ramipril 2.5 mg po daliy
Hypertension	Nifedipine XL 60 mg po daily
Dyslipidemia	Simvastatin 40 mg po HS
Atrial fibrillation	Propranolol 80 mg po BID Warfarin 2.5 mg po HS

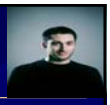
	eGFR (mL/min)	ACR (mg/mmol)	BP (mmHg)	HCO_3 (umol/L)	K (mmol/L)
May '10	12	346	125/80	16	5.3
Oct '10	14	389	146/82	16	5.5
Mar '11	11	205	127/86	14	5.2

Case 1. LI

What would you do?	
What would you use?	
What dose?	
What target?	

87

Back to Case 2. FM



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CC	Feels well
PMH	CKD Stage III Alport Syndrome Alopecia
Meds	Ramipril 10mg po daily HCTZ 25mg po daily Finasteride 1.25mg po daily CaCO3 1250mg po daily

Labs

	eGFR (mL/min)	ACR (mg/mmol)	BP (mmHg)	Uric acid (umol/L)	K (mmol/L)
May '10	45	276.2	125/88	556	5.1
Aug '10	42	45.6	112/66		5.8
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Feb '11	33	123.9	115/67		5.2

Case 2. FM

What would you do?	
What would you use?	
What dose?	
What target?	

89

90