Strategies to halt the progression of CKD G4+: Evidence from Randomized Trials

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Outline

- Evidence gap in CKD G4+

- Available evidence for the following interventions

  - Bicarbonate
  - Uric Acid Reduction
  - ACE/ARB
  - Phosphate Binders

Evidence Gap

- Patients with CKD Stages G4-5 are often excluded from randomized trials in the general population
- Very few positive trials exist in patients with kidney failure
- Difficult to extrapolate findings from CKD Stage G1-G3A and from patients on dialysis

Bicarbonate – Treatment of Met Acidosis

- Metabolic acidosis is common in patients with advanced CKD
- Patients with diabetes may be at additional risk
- Prolonged metabolic acidosis can lead to bone loss and impaired muscle function
- Clinical practice guidelines recommend bicarbonate supplementation at levels < 22 mEq/l

Susantitaphong et al. AJN 2012

Evidence for Alkali Therapy in CKD

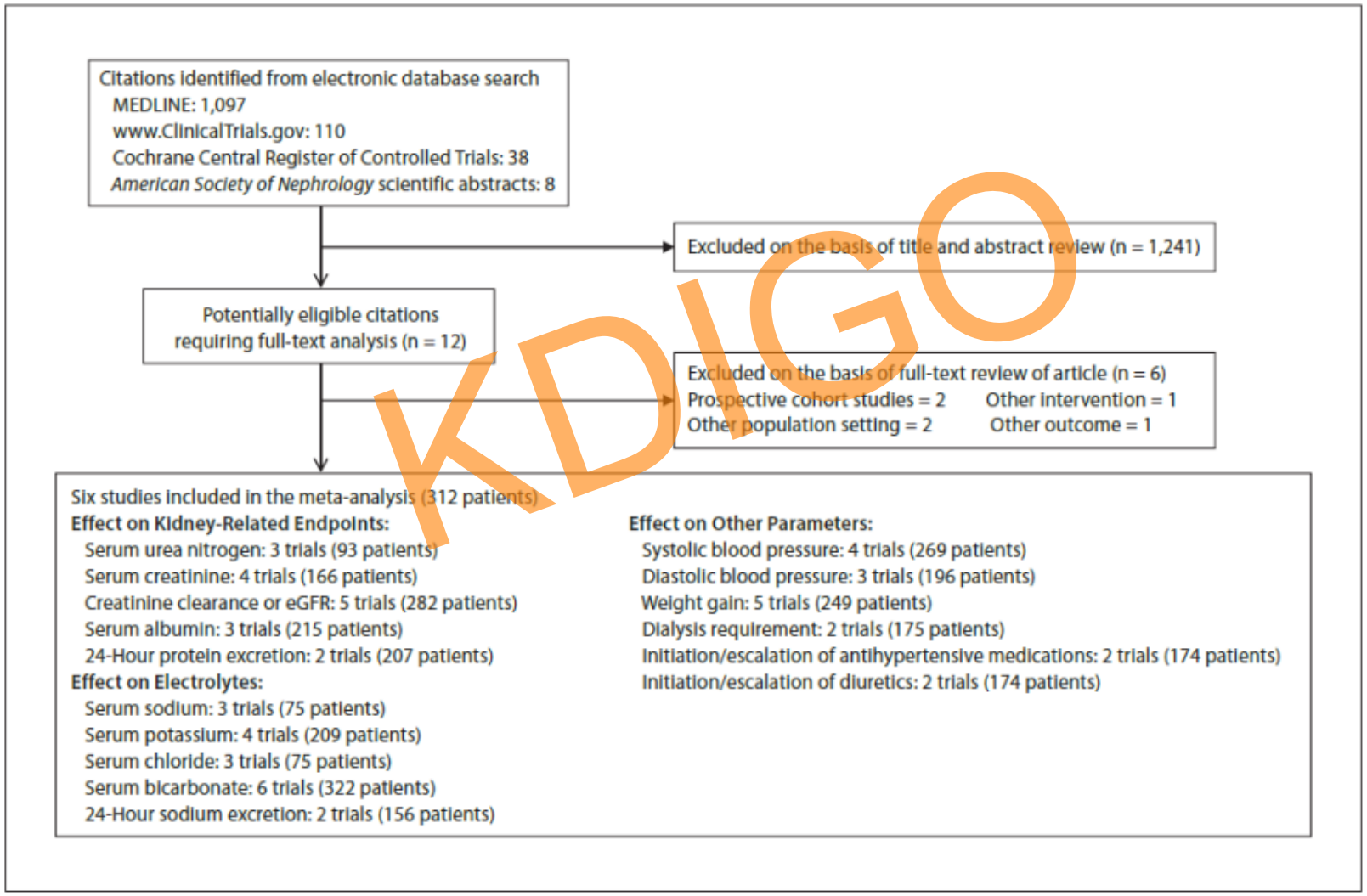


Fig. 1. Study selection flow diagram.

Evidence for Alkali Therapy

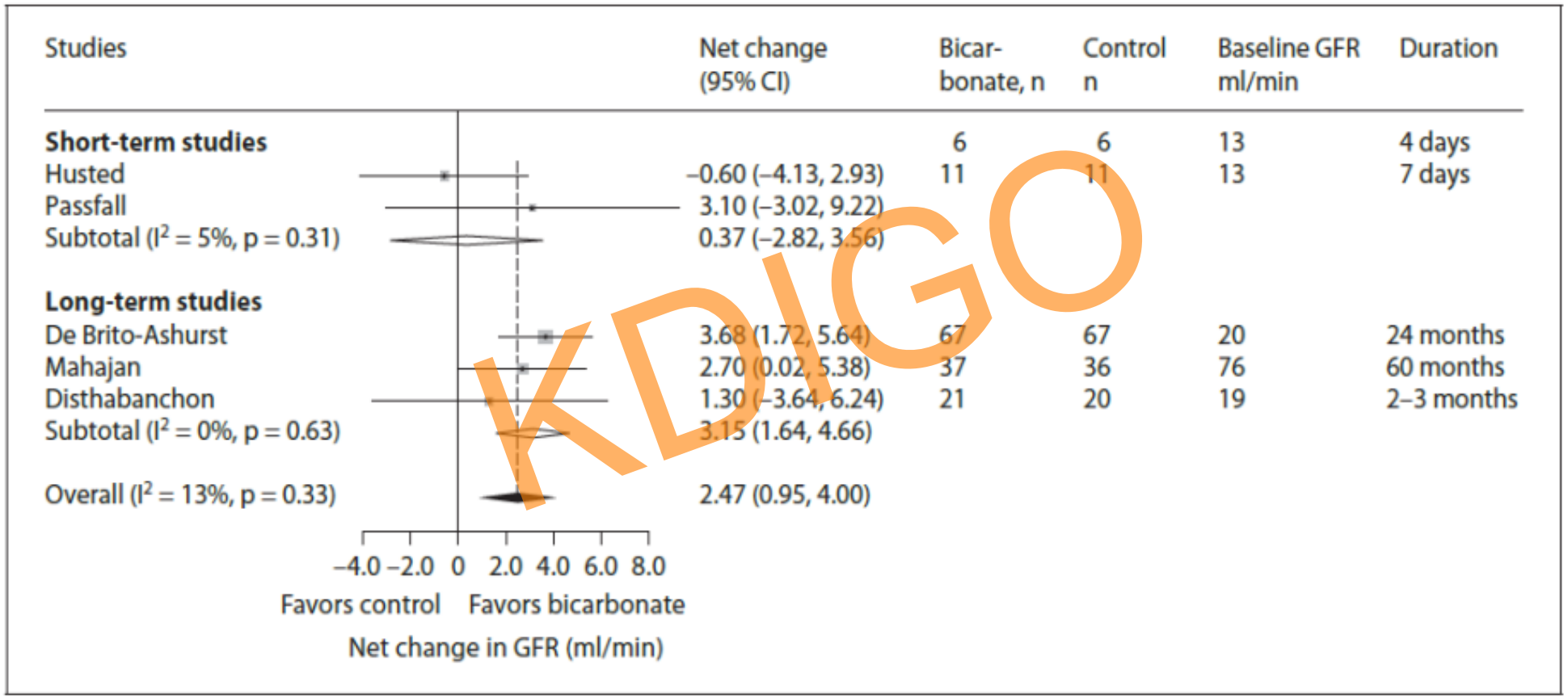


Fig. 2. Forest plot displaying the effect of bicarbonate therapy in patients with CKD on change in GFR (ml/min or ml/min/1.73 m^2).

Evidence for Alkali Therapy

- Largest trial – Debrito-Ashurst et al.
- Mean eGFR 20 ml/min, mean HCO3 – 20 mEq/l
- Bicarbonate dose – 22 +/- 10 mEq/day
- Pooled Estimates
  - Slight increase in DBP 2.8 mm Hg
  - Increase in sodium excretion (24 mEq/day)
  - Decrease in serum potassium (0.7 mEq/L)

Uric Acid Reduction

- Uric acid levels are strongly and consistently associated with CKD and CVD in observational studies
- Uric acid reduction in patients with normal kidney function may lead to improvements in blood pressure control
- Randomized controlled trial evidence in patients with advanced CKD remains scarce

Kanji et al. BMC Nephrology 2015

Evidence for Uric Acid Reduction

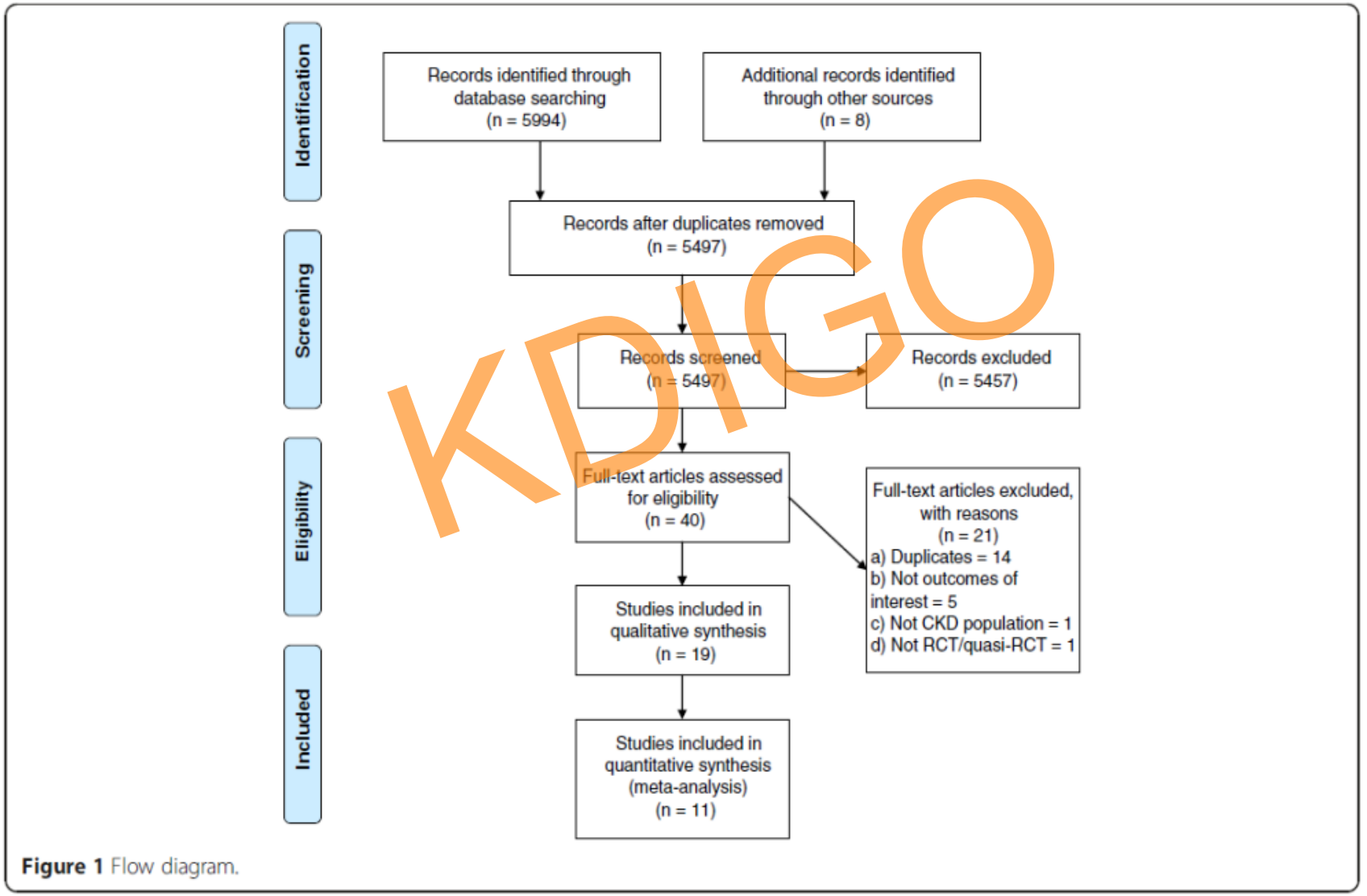


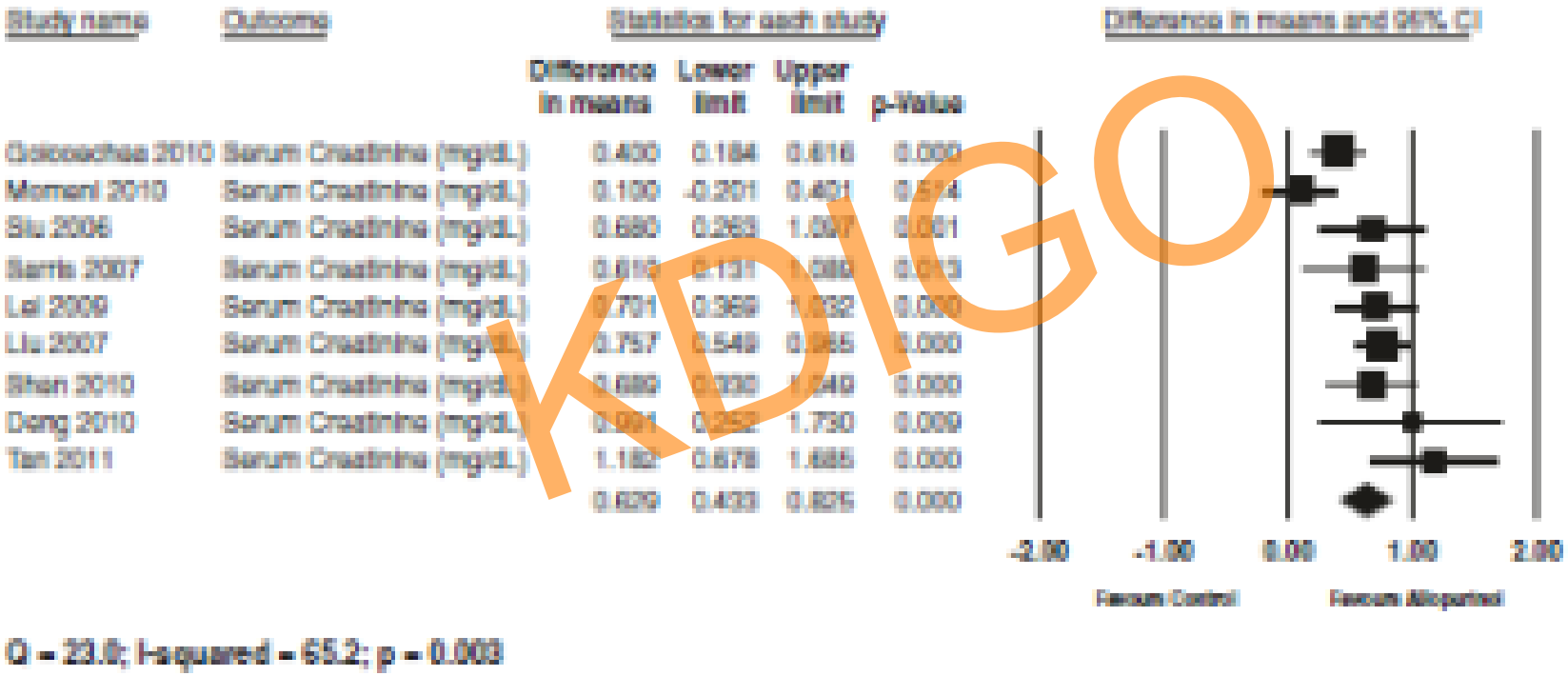
Figure 1 Flow diagram.

Evidence for Uric Acid Reduction

Table 1 Study characteristics

First author (Ref No.)	Year of publication	Journal	Location of trial	Study design	Duration of follow-up	Sample size	Treatment	Control
Katholi [51]	1998	American Journal of Kidney Diseases	Springfield, Illinois	Parallel Group RCT with 2x2 factorial design	2 days	39	Allopurinol	Placebo
Perez-Ruiz [56]	1999	Journal of Clinical Rheumatology	Pais Vasco, Spain	Parallel Group RCT	9-12 months	36	Benzbromarone	Allopurinol
Kamper [50]	2001	Clinical Transplantation	Herlev, Denmark	Cross-over RCT	2 weeks	26	Losartan	No treatment
Schmidt [53]	2001	Nephrology Dialysis Transplantation	Vienna, Austria	Cross-over RCT	3 weeks	13	Losartan	Enalapril
Doehner [35]	2002	Circulation	London, UK	Cross-over RCT	2 weeks	14	Allopurinol	Placebo
Chanard [54]	2003	Nephrology Dialysis Transplantation	Three centres in France	Parallel Group RCT	2 months	48	Amlodipine	Tertatolol
Siu [48]	2006	American Journal of Kidney Diseases	Hong Kong, China	Parallel Group RCT	12 months	54	Allopurinol	No treatment
Liu [36]	2007	China Pharmacy	Guangzhou and Luzhou, China	Parallel Group RCT	12 months	47	Allopurinol	No treatment
Sarris [34]	2007	Nephrology Dialysis Transplantation	Athens, Greece	Parallel Group RCT	12 months	36	Allopurinol	No treatment
Lei [40]	2009	Shaanxi Medical Journal	Xi'an, China	Parallel Group RCT	12 months	57	Allopurinol	No treatment
Malaguarnera [55]	2009	Expert Opinion Pharmacotherapy	Catania, Italy	Parallel Group RCT	2 months	38	Rasburicase	Placebo
Nouri-Majalan [52]	2009	Vascular Health and Risk Management	Yazd, Iran	Parallel Group RCT	5 days	60	Allopurinol and vitamin E	No treatment
Deng [37]	2010	Journal of Practical Medicine	Beijing, China	Parallel Group RCT	12 months	68	Allopurinol	No treatment
Goicoechea [44]	2010	Clinical Journal of American Soc of Neph	Madrid, Spain	Parallel Group RCT	24 months	113	Allopurinol	No treatment
Momeni [46]	2010	Iranian Journal of Kidney Diseases	Isfahan, Iran	Parallel Group RCT	4 months	44	Allopurinol	Placebo
Shen [38]	2010	China Foreign Medical Treatment	Chengdu, China	Parallel Group RCT	12 months	52	Allopurinol	No treatment
Kao [45]	2011	Journal of American Soc of Neph	Dundee, UK	Parallel Group RCT	9 months	67	Allopurinol	Placebo
Tan [39]	2011	Modern Hospital	Guangzhou, China	Parallel Group RCT	24 months	140	Allopurinol	No treatment
Shi [47]	2012	Kidney and Blood Pressure Research	Guangzhou, China	Parallel Group RCT	6 months	40	Allopurinol	No treatment

Evidence for Uric Acid Reduction



For eGFR – A change of 3 ml/min over follow up was detected

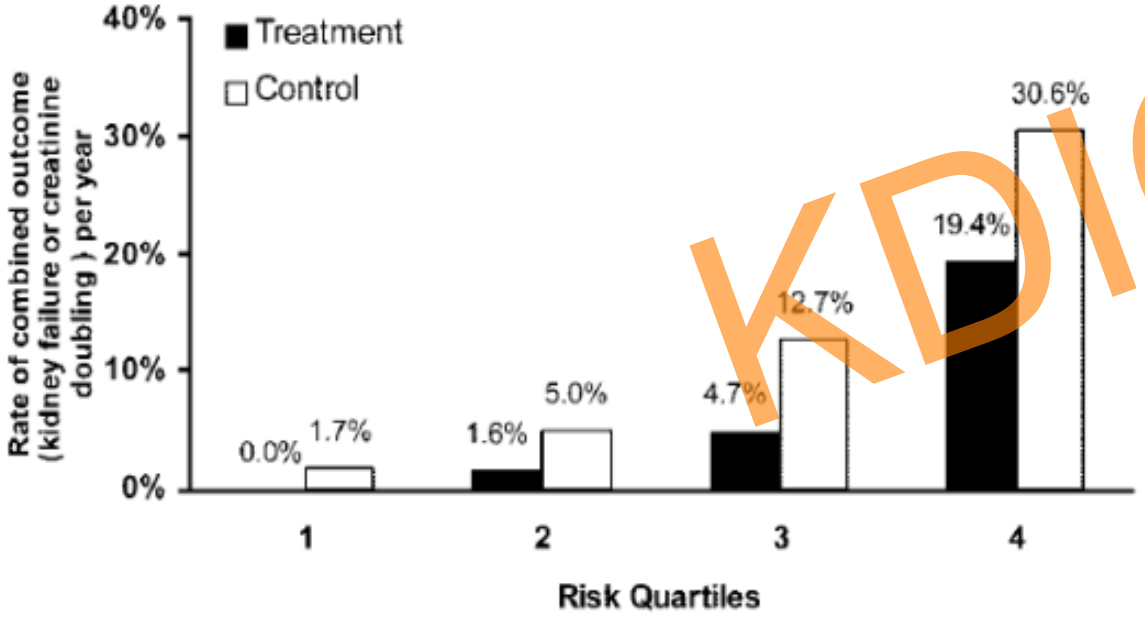
ACE/ARB in advanced CKD

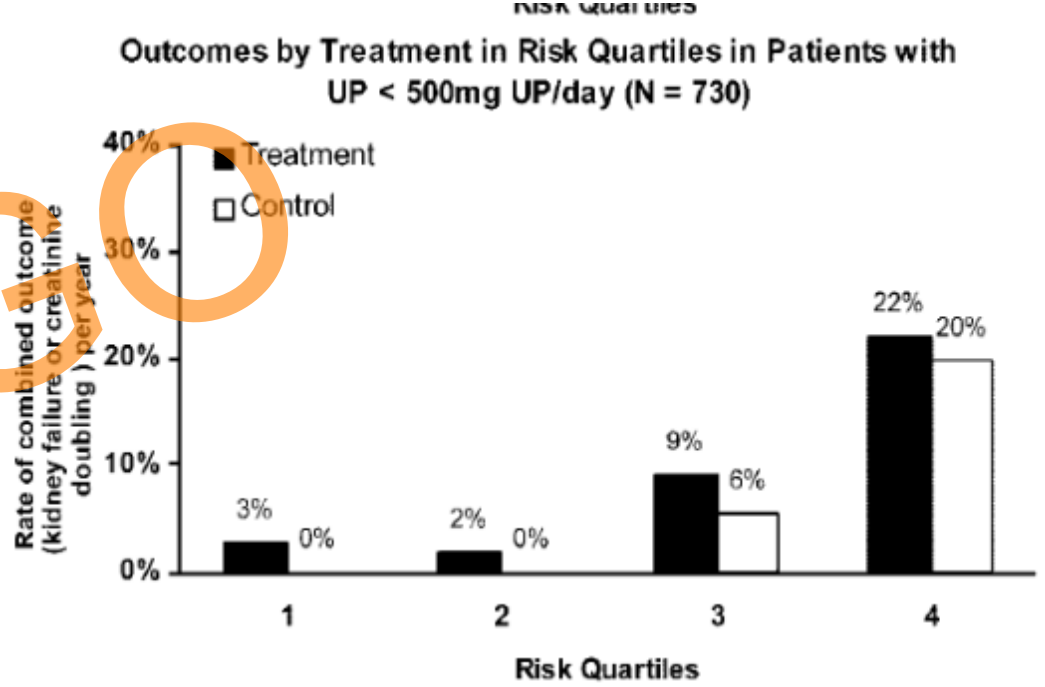
- Mainstay of treatment to prevent CKD progression
- Landmark studies enrolled patients with earlier stages of CKD
- Efficacy may be modified by presence of proteinuria
- Safety may be modified by age

Landmark Trials

- RENAAL
  - Mean eGFR 38 ml/min, Patients with Cr > 3.0 mg/dl excluded
- IDNT
  - Mean eGFR 43 ml/min, Patients with Cr > 3.0 mg/dl excluded
- REIN study
  - Nondiabetic kidney disease, CrCl 20-70, mean eGFR 45 ml/min
  - Baseline proteinuria > 3 g/day

Landmark Trials





Jafar et al. JASN 2007

STOP ACEI Trial

- Motivated by recent findings from ONTARGET and TRANSCEND
- Aims to enroll 410 patients with CKD Stages G4-G5 from 15 UK based Pre Dialysis Clinics
- 3 years of follow up
- Stratified enrollment to ensure balance in proteinuria and CKD Stage
- Measurement of appropriate clinical and surrogate endpoints

Phosphate Binders

- Hyperphosphatemia is associated with early mortality in the general population and in patients on dialysis
- High phosphorous and low calcium levels are associated with progression to kidney failure
- Phosphate loads in the presence of reduced kidney function can lead to FGF23 expression, which may have downstream CV effects

Evidence for phosphate binders

- Two recent meta analyses suggesting non-calcium binders may be associated with improved survival
- Evidence is largely from dialysis trials
- Smaller trials with surrogate outcomes have been performed in the CKD population

Evidence for phosphate binders

- Block et al. – JASN 2012 – Calcium and non-calcium binders vs Placebo
  - N=148
  - No effect on FGF23, slight increase in CAC with binders
- Independent Study – De Iorio et al. CJASN 2013 – Sevelamer vs Calcium Carbonate
  - N=212
  - 50 % Relative risk reduction in death or dialysis
- Two small recent studies on ferric citrate – short follow up (<12 weeks)

Summary

- Limited high quality evidence exists for medical interventions to halt the progression of CKD Stage 4+
- Most randomized trials from the general population do not include these patients
- Dedicated large simple randomized trials should be performed to confirm these preliminary findings