GCC Organ Transplant and Nephrology Congress 2017 Kuwait

Measures to delay progression of CKD
Perspectives and Precautions

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International Society of Nephrology

a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA

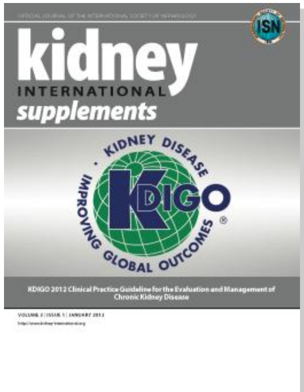
BCRenal agency of the Provincial Health Services Authority

The Kidney Foundation of Canada
The foundation of kidney care.

Providence Health Care
How you want to be treated.

Outline

- Progression of CKD
- What we know and don't know
  - Treatment
  - Predictions
- New horizons

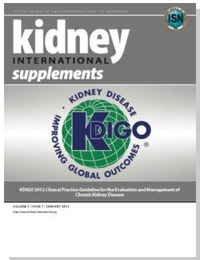


Defining Progression

2.1.2 Recognize that small fluctuations in GFR are common and are not necessarily indicative of progression (ungraded)

Longitudinal Studies of Progression

Patient group	Annual rate of progression (mL/min/yr)
Healthy adults	0.36–0.90
Adults with comorbidity	0.05 (no proteinuria); 1.71 (ACR >300)
Older adults (>65 yrs)	0.8–1.4 (no DM); 2.1–2.7 (DM)
Adults with CKD (MDRD study)	2.3–4.9
Adults with CKD (Stage 3–5 referrals)	0.35–2.65



Defining Progression

2.1.3 CKD progression based on one of more of the following *(*Not Graded*)*:

- Decline in GFR category (≥90, 60–89, 45–59, 30–44, 15–29, <15 mL/min/1.73m^2). A drop in eGFR is defined as a drop in GFR category accompanied by a 25% or greater drop in eGFR from baseline
- Rapid progression is defined as a sustained decline in eGFR of more than 5 mL/1.73m^2/year

The confidence in assessing progression is increased with increasing number of serum creatinine measurements and duration of follow-up

Progression to what?

- Kidney failure
  - Dialysis
  - Transplantation
- Cardiovascular events
  - MI, CVA, PVD
  - CHF
- Death

Key points about Progression

- Patient outcomes are variable
- Predicting patient and kidney outcomes remains problematic due to
  - Biological variability of disease process(es)
  - Need for multiple measurements
  - Interaction of environment, exposures and biology
- Prevention of progression is possible & variable

So many factors impact our understanding of variability of progression:

- Populations studied
  - General populations
  - Referred populations

- Specific disease(s)
  - General conditions (DM, CHF etc)
  - Kidney specific (GN, PCKD)

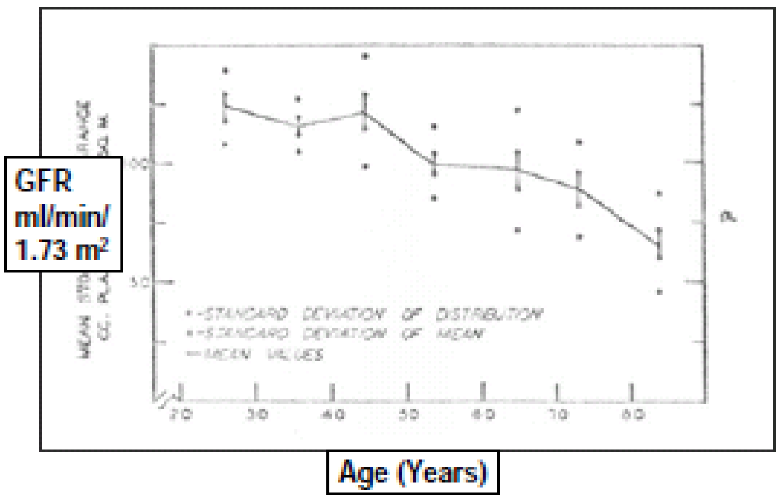
- Other factors (difficult to capture)
  - Inter-current events
  - Inherited/ environmental

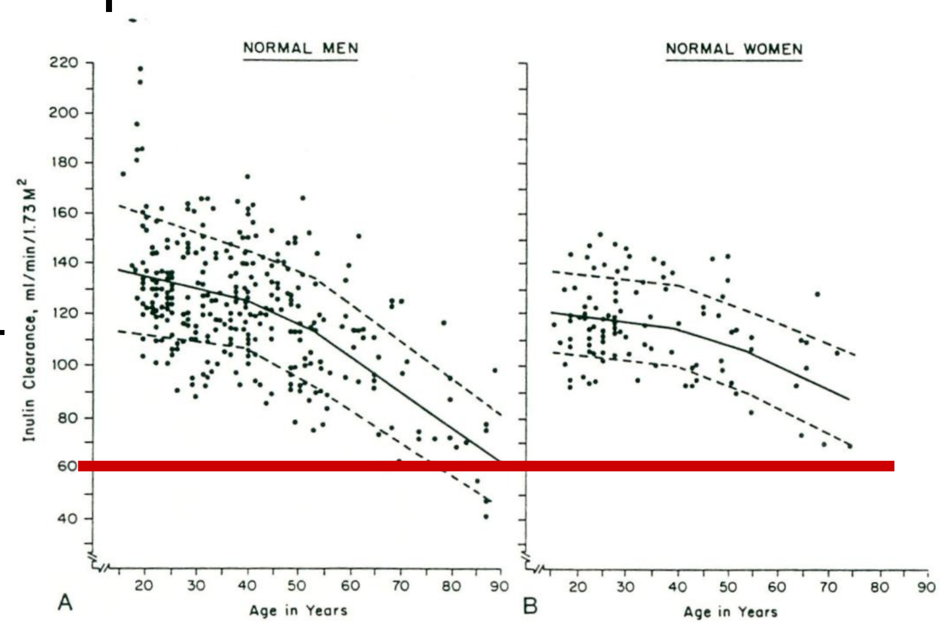
What we know….

There is wide variability in GFR decline with age

Decline in GFR with Aging

Davies DF, Shock NW. JCI 29:496, 1950





Progression of CKD in the Elderly: varies according to other conditions (DM)

10,184 aged 66 and older: 24,525 person yrs FU in Alberta
7,912 baseline eGFR <90 ml/min/1.73m2

Age Adjusted Rate of GFR Decline mL/min/1.73m^2/yr

GFR Level	60-89	30-59	<30
♀No DM	0.6 (0.3–0.9)	1.1 (0.8–1.4)	1.8 (1.2–2.4)
♂No DM	1.1 (0.8–1.4)	1.9 (1.5–2.3)	2.0 (1.3–2.7)
♀DM	1.6 (1.0–2.1)	2.8 (2.3–3.3)	2.9 (2.2–3.7)
♂DM	2.1 (1.6–2.6)	3.6 (3.1–4.2)	3.2 (2.3–4.0)

Hemmelgarn et al. Kidney Int 2006;69:2155-2161

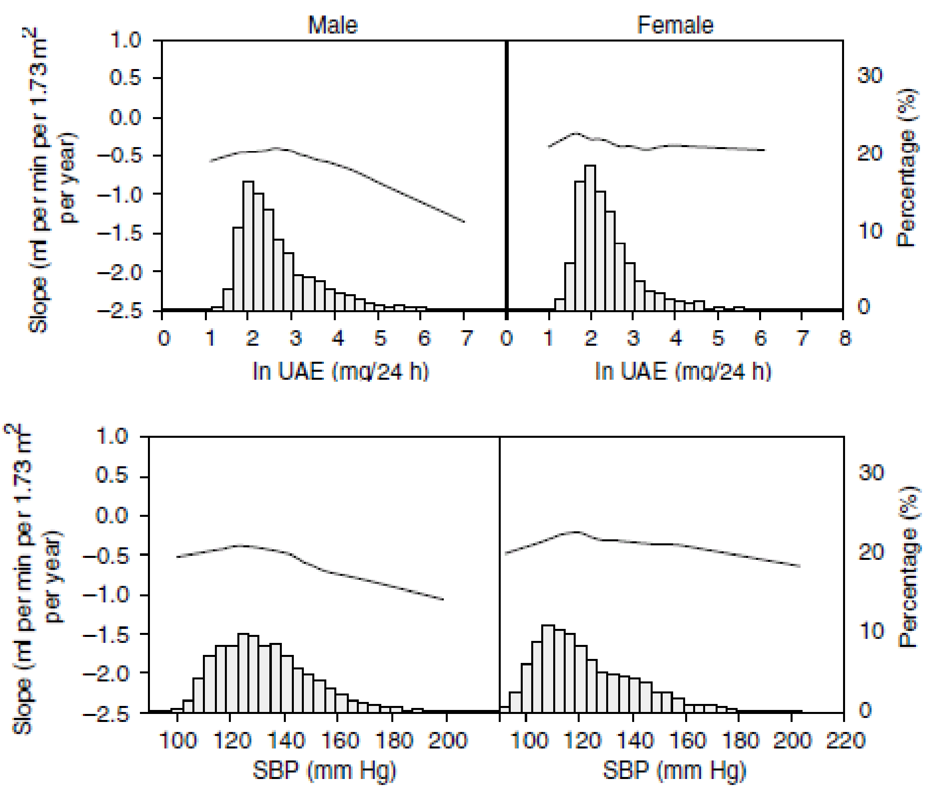
Men have faster decline than women

http://www.kidney-international.org original article

see commentary on page 415

Gender differences in predictors of the decline of renal function in the general population

Nynke Halbesma[1], Auke H. Brantsma[1], Stephan J.L. Bakker[1], Desiree F. Jansen[2], Ronald P. Stolk[2], Dick D[illegible] group



Gender differences in chronic kidney disease

Kunitoshi Iseki[1]

Women live longer than men. Can this phenomenon be explained by chr[illegible] inci[illegible] Kidne[illegible]

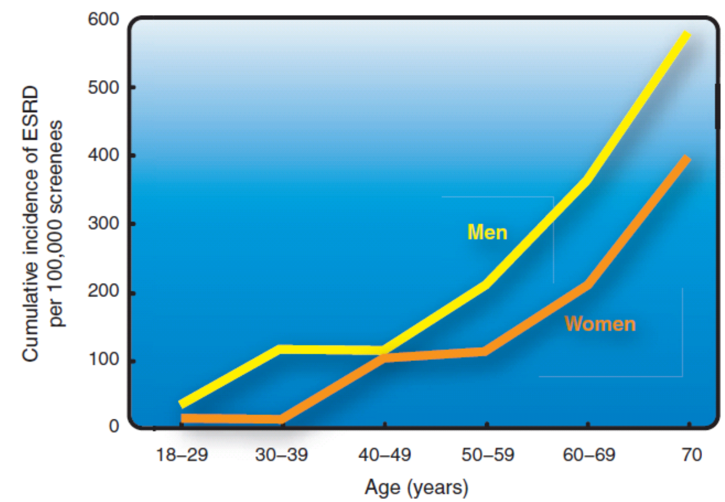


Figure 1 | The cumulative incidence of ESRD per 100,000 screenees, shown by age at screening in both men and women. Figure was created from database of ref. 2.

Different etiologies of CKD and co-morbidities CKD predict different rates of decline

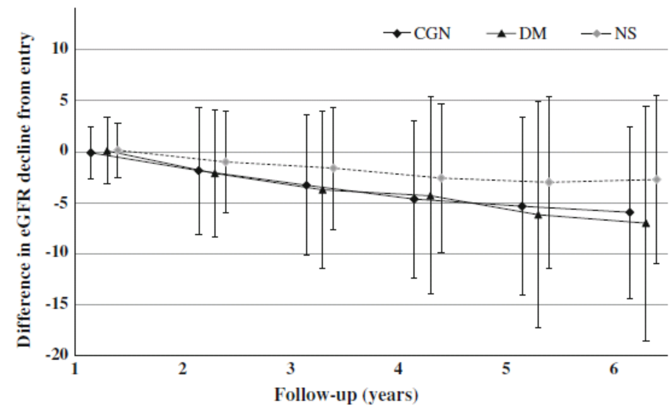
Clin Exp Nephrol
DOI 10.1007/s10157-011-0501-6

ORIGINAL ARTICLE

Clinical outcomes in patients with chronic kidney disease: a 5-yea retrospective cohort study at a University Hospital in Japan

Tetsuri Yamashita · Takumi Yoshida · Tetsuya Ogawa · Ken Tsuchiya · Kosaku Nitta

Fig. 3 Annual changes in estimated glomerular filtration rate (eGFR) in three groups divided by causes of CKD patients. *CGN* chronic glomerulonephritis, *DN* CKD with diabetes mellitus, *NS* nephrosclerosis



GN, DM, Nephrotic syndrome

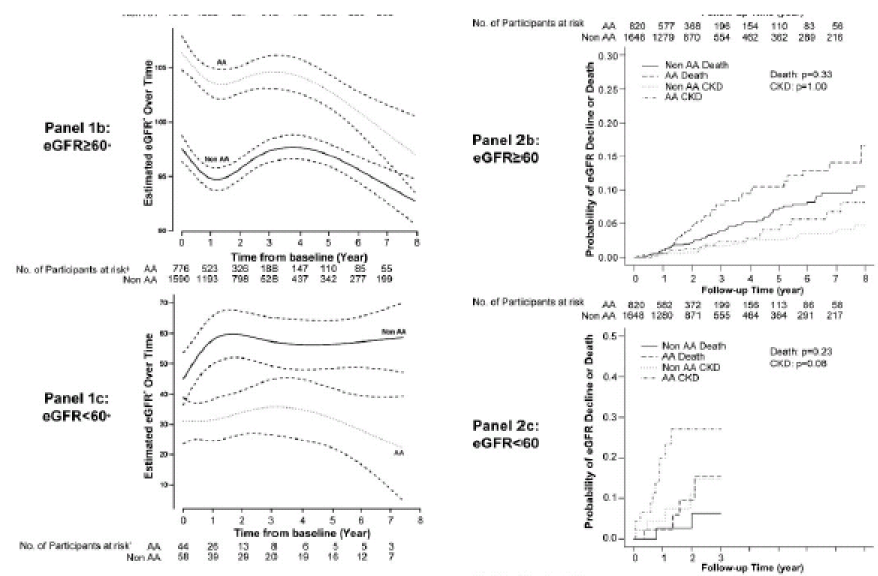
Race, Kidney Disease Progression, and Mortality Risk in HIV-Infected Persons

Tahira P. Alves,* Todd Hulgan,† Pingsheng Wu,‡ Timothy R. Sterling,† Samuel E. Stinnette,† Peter F. Rebeiro,† Andrew J. Vincz,* Marino Bruce,§ and T. Alp Ikizler*

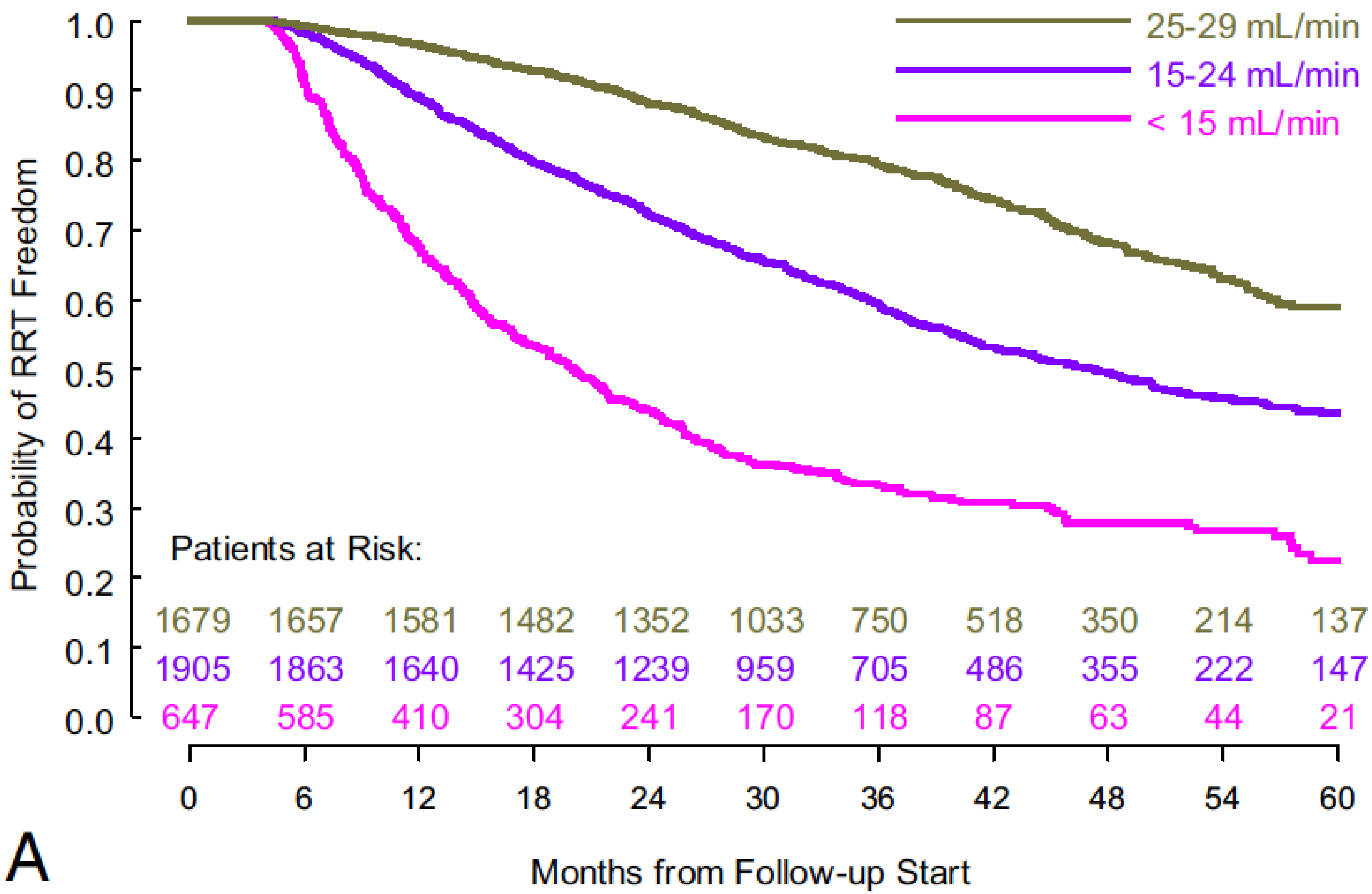
*Division of Nephrology, Department of Medicine, †Division of Infectious Diseases, Department of Medicine, and ‡Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee; and §Department of Family and Community Medicine, Meharry Medical College, Nashville, Tennessee

Clin J Am Soc Nephrol 5: 2269–2275, 2010. c

Race and HIV status



Even at low eGFR levels, there is variability in time to RRT



Levin A et al. Am J Kidney Dis 52;4:661-671, 2008

Non linearity of trajectory over time......

AJKD

Original Investigation

Longitudinal Progression Trajectory of GFR Among Patients With CKD

Liang Li, PhD,[1] Brad C. Astor, PhD,[2] Julia Lewis, MD,[3] Bo Hu, PhD,[1]
Lawrence J. Appel, MD, MPH,[4] Michael S. Lipkowitz, MD,[5] Robert D. Toto, MD,[6]
Xuelei Wang, MS,[7] Jackson T. Wright Jr, MD, PhD,[7] and Tom H. Greene, PhD[8]

12 year follow up AASK Study
Longitudinal observational cohort

Non linearity of progression over time has implications for clinical care and design of research studies

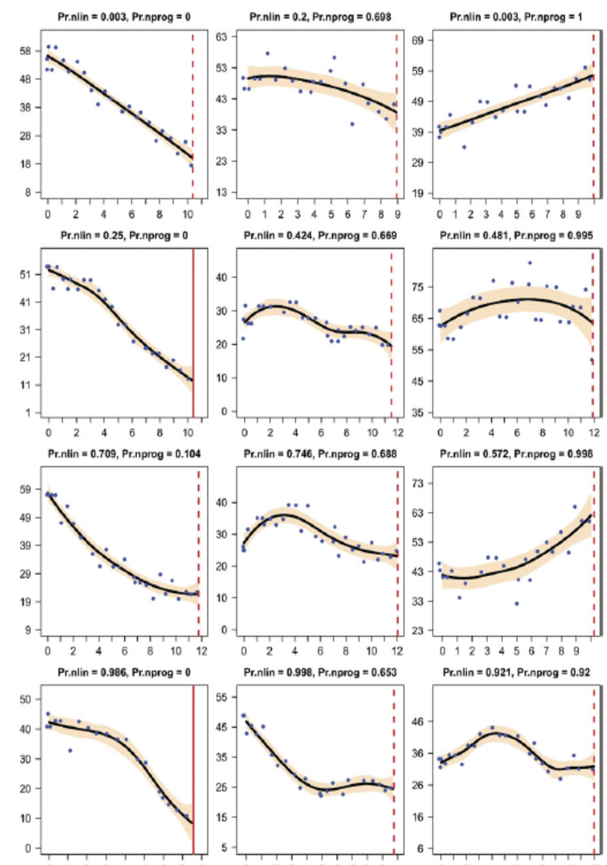


Figure 4. Glomerular filtration rate trajectories of 12 patients and their probabilities of nonlinearity (Pr.nlin) and nonprogression (Pr.nprog). The setup of each trajectory plot is similar to those in Fig 1.

But irrespective…decline of kidney function leads to adverse outcomes

- GFR decline adversely affects prognosis
  - any decline
  - rates of decline
  - impact on morbidity and mortality

GFR Decline and Mortality Risk among Patients with Chronic Kidney Disease

Robert M. Perkins,[‡] Ion D. Bucaloiu,[†] H. Lester Kirchner,[*] Nasrin Ashouian,[†] James E. Hartle,[†] and Taher Yahya[†]*

CLINICAL EPIDEMIOLOGY www.jasn.org

Change in Estimated GFR Associates with Coronary Heart Disease and Mortality

Kunihiro Matsushita,[*] Elizabeth Selvin,[*] Lori D. Bash,[*] Nora Franceschini,[†] Brad C. Astor,[*] and Josef Coresh[*]

CLINICAL EPIDEMIOLOGY www.jasn.org

Rate of Kidney Function Decline Associates with Mortality

Ziyad Al-Aly,[*†] Angelique Zeringue,[†] John Fu,[†‡] Michael I. Rauchman,[*] Jay R. McDonald,[†§] Tarek M. El-Achkar,[*] Sumitra Balasubramanian,[†] Diana Nurutdinova,[†§] Hong Xian,[†] Kevin C. Abbott,[¶] and Seth Eisen[†**]

CLINICAL EPIDEMIOLOGY www.jasn.org

Rapid Decline of Kidney Function Increases Cardiovascular Risk in the Elderly

Michael G. Shlipak,[*] Ronit Katz,[†] Bryan Kestenbaum,[‡] David Siscovick,[§] Linda Fried,[||] Anne Newman,[¶] Dena Rifkin,[**] and Mark J. Sarnak[**]

Rapid Kidney Function Decline and Mortality Risk in Older Adults

Dena E. Rifkin, MD; Michael G. Shlipak, MD, MPH; Ronit Katz, DPhil; Linda F. Fried, MD, MPH; David Siscovick, MD, MPH; Michel Chonchol, MD; Anne B. Newman, MD; Mark J. Sarnak, MD, MS

What we know about preventing progression

- Risk Factors

- Interventions

Listing of Risk factors for CKD progression

- GFR
- Proteinuria
- Hypertension
- Anemia
- Uric acid
- Metabolic acidosis
- Disorders of bone and mineral metabolism, eg hyperphosphatemia
- Ethnicity
- Diabetes

Mechanisms:
Simplistic view Progression of CKD

Initial insult

↓

Pathophysiological phenotype

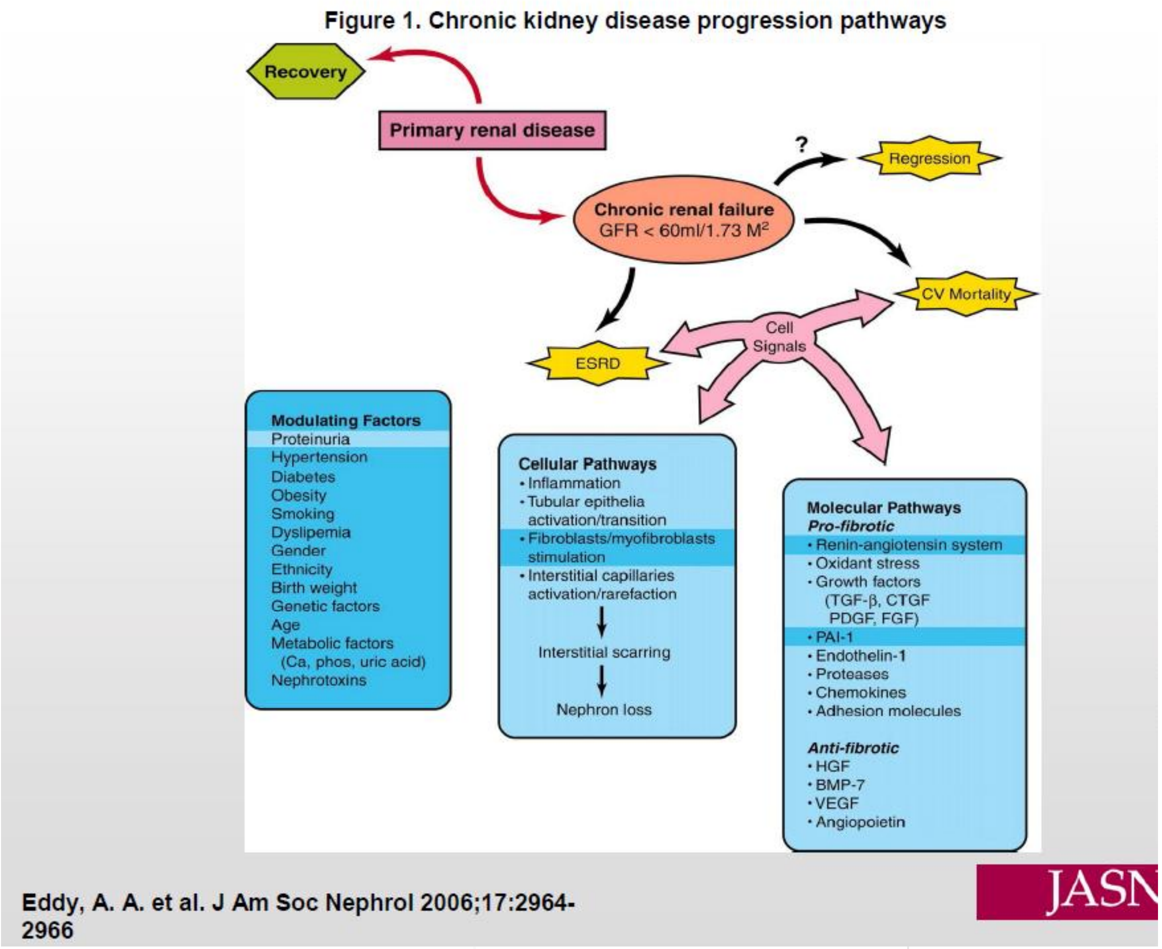
↓

Reduction # nephrons

↓

Increase fibrosis / interstitial scarring

But …complexity of processes and pathways



- Cell injury
- Cell repair
- Modulating processes
- Cellular pathways
- Molecular pathways

Multiplicity of factors important in progression...

Metabolic factors:

proteinuria, hyperglycaemia, dyslipidaemia, oxidative stress, hypoxia

Paracrine factors:

angiotensin 2, endothelin, growth factors.

Genetic factors

Haemodynamic factors:

arterial hypertension, glomerular hypertension, *shear stress.*

Cellular factors:

epithelial mesenchymal transition (EMT), myofibroblasts.

Inflammatory factors:

cytokines, chemokines, *Toll like receptors.*

We can aim treatment at processes

Table 1. Treatments used to retard progression of chronic renal failure

Interventions that affect multiple systems involved in development of fibrosis

- Anti-angiotensin treatments (ACE inhibitors, ARB, combined ACE+ARB, suppression of intrarenal angiotensinogen)
- Statins
- Nitric oxide donors
- Mycophenolate mofetil
- COX II inhibitors
- Rapamycin
- Pirfenidone
- Relaxin
- MCP-1 inhibitors
- IκBα
- Endothelin receptor blockade
- Aldosterone antagonists
- Retinoids
- Erythropoietin
- Vitamin D
- VEGF

Interventions in specific pathways leading to tubulointerstitial fibrosis

- HGF
- BMP-7
- ROCK inhibitors (Y-27632)
- Anti-TGF-β neutralizing antibodies
- Antisense CTGF
- Imatinib mesylate

Overall benefit but variable success; ind responses

?

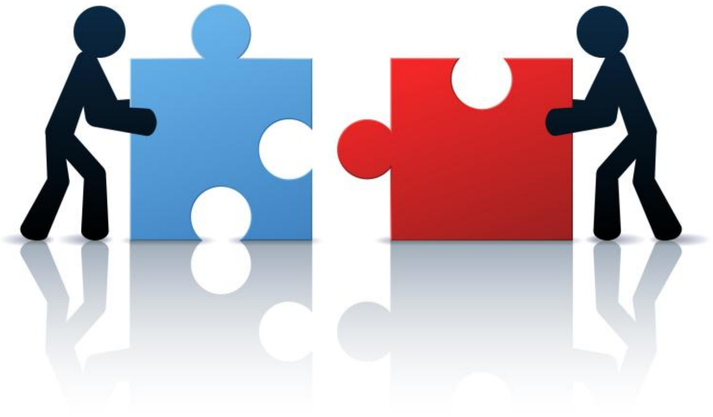
++ side effects

animal vs human data

++ side effects

Interventions: what we know

- Progression of CKD
- Progression of CVD



Key measures to delay progression

- Blood pressure and RAAS inhibition
- AKI risk and management:
  - Increasing recognition of impact on trajectory and variability
- Protein intake
- Glycemic control
- Salt intake
- Hyperuricemia
- Life style
- Other dietary advice
- CV Risk reduction: Lipid lowering

Specific recommendations: Delay progression of CKD

- Treatment of the underlying condition if possible
- Aggressive BP control to target values per current guidelines
- Treatment of hyperlipidemia to target levels per current guidelines
- Aggressive glycemic control per the Diabetes guideline recommendations (target hemoglobin A1c [HbA1C] < 7%)
- Avoidance of nephrotoxins,
  - intravenous (IV) radiocontrast media,
  - nonsteroidal anti-inflammatory agents (NSAIDs), and
  - aminoglycosides
- Use of renin-angiotensin system (RAS) blockers
  - Among patients with diabetic kidney disease (DKD) and proteinuria
  - Use of (ACEIs) or angiotensin-receptor blockers (ARBs) in patients with proteinuria

Clinical trials to delay progression of CKD

- ACEI, ARB(Renin inhibitors)
- Blood pressure control
- Aldosterone blockers

- Vitamin D supplementation
- Bicarbonate therapy
- Allopurinol
- SGLT2 inhibitors

- Directed Antifibrotic therapies
- Immuno-modulatory

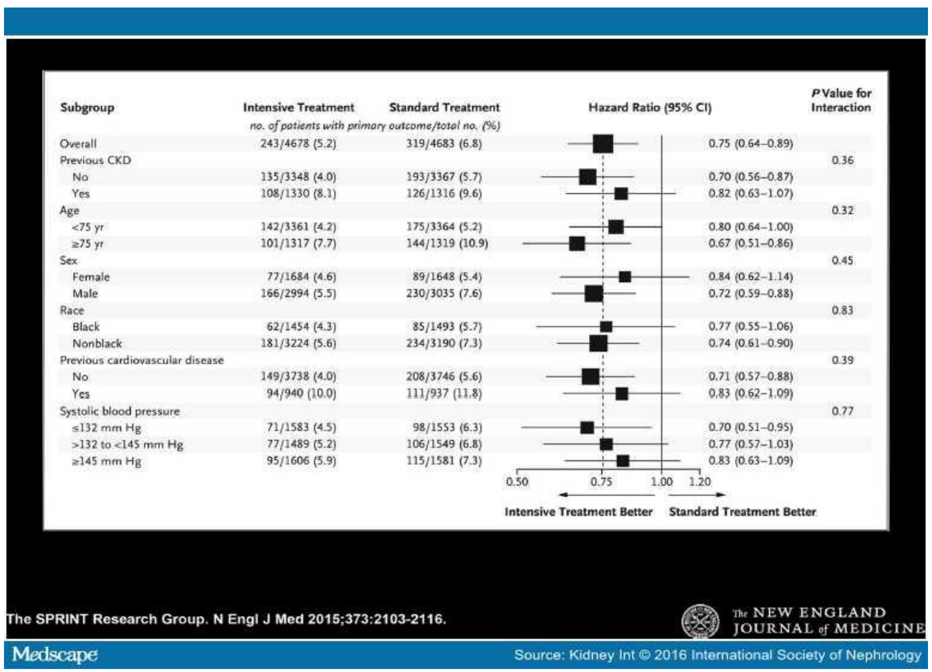
Limited studies
Variable results
Situation / disease specific
Side effect profiles ?

Interruption of RAAS benefits CKD and CVD outcomes

- HOPE; Micro-HOPE (ACEi)
- REIN (ACEi)
- RENNAL (ARB)
- IDNT (ARB)
- BENEDICT (Benazapril)
- ALTITUDE (Aliskarin)
- ………..

BP Control: Newer thoughts

- Lower is better (130/80)
- Systolic Blood Pressure Intervention Trial (SPRINT) *NEJM 2015*



- Timing of medications CKD
  - Nocturnal dosing of benefit
  - Median follow-up of 5.4 years, If 1 BP med at bedtime: 1/3 lower adjusted risk for total cardiovascular events vs those who took all meds in am *Hermida et al, JASN 2011*

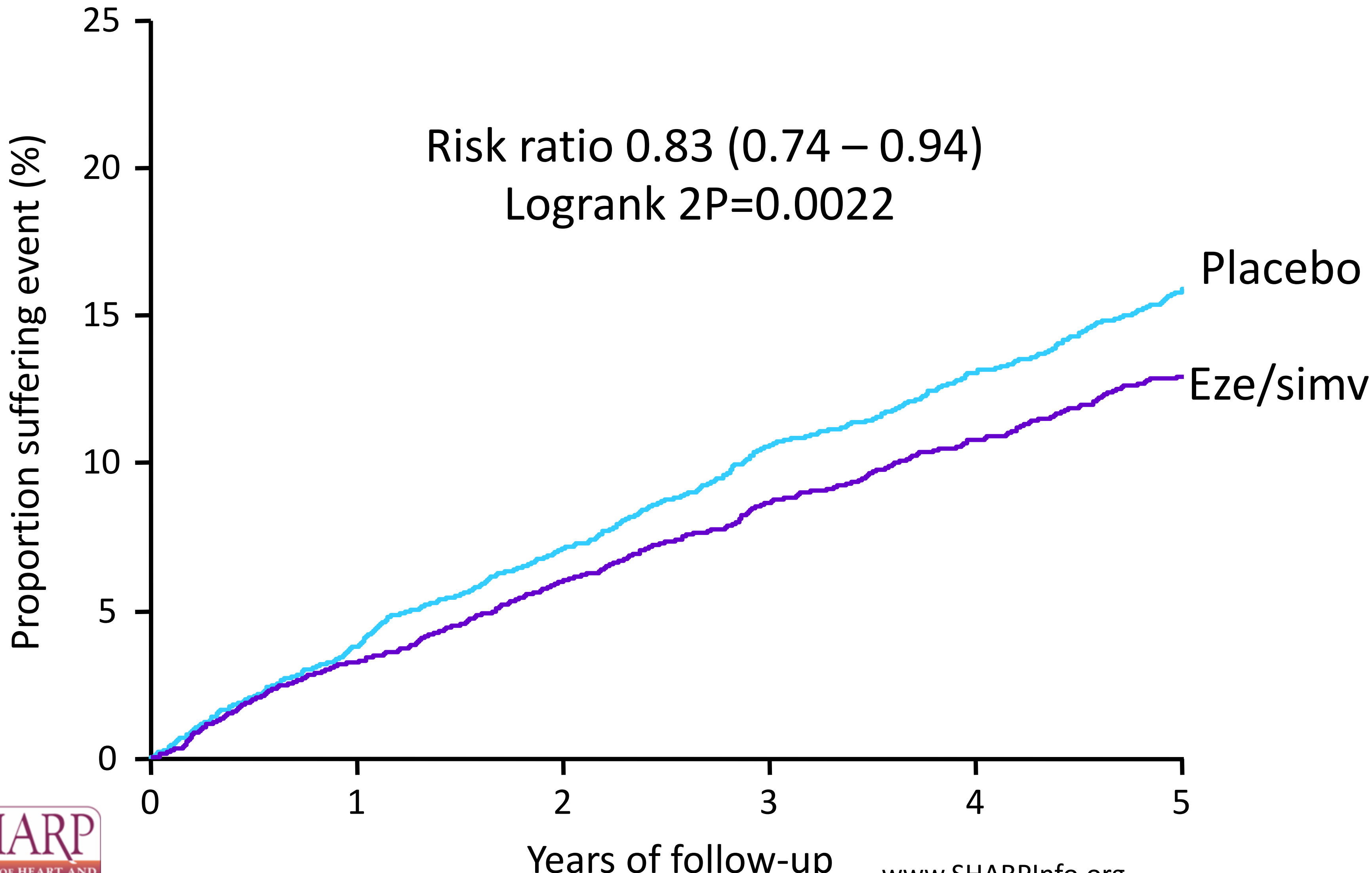
Lipid lowering strategies to improve CVD outcomes

SHARP
STUDY OF HEART AND RENAL PROTECTION

- Fixed dose lipid lowering strategy in CKD patients
  - Simvastatin and ezetrol
  - No entry criteria lipid level
  - No target
- Positive impact on outcomes directly related to intervention: atherosclerotic events
- No impact on mortality
  - not powered
  - Recognized complexity of processes leading to moratlity in CKD patients.

Baigent et al Lancet, 2011

SHARP: Major Atherosclerotic Events



SHARP
STUDY OF HEART AND RENAL PROTECTION

www.SHARPInfo.org

Exploring old and new information progression of CKD (& CVD)

- Focus on some more novel risk factors
  - Vitamin D
  - Uric Acid
  - Bicarbonate

Animal models: Vitamin D Impacts on inflammatory cytokines and transforming growth factors

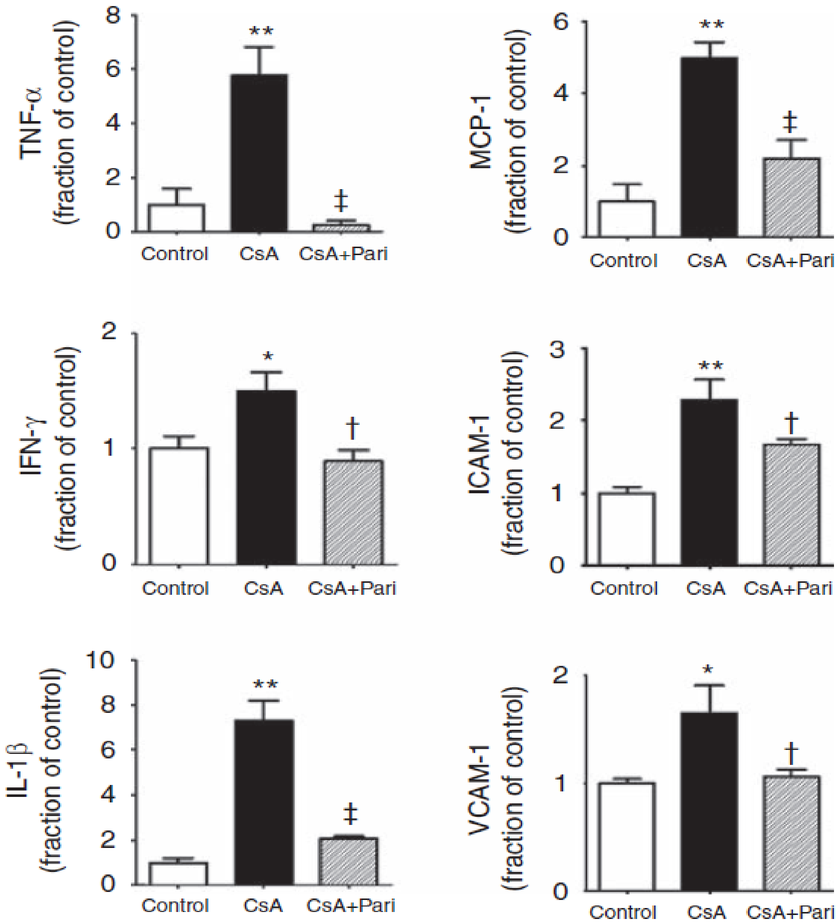


Figure 3 | Effects of paricalcitol on inflammatory cytokines and adhesion molecules. Real-time polymerase chain reaction

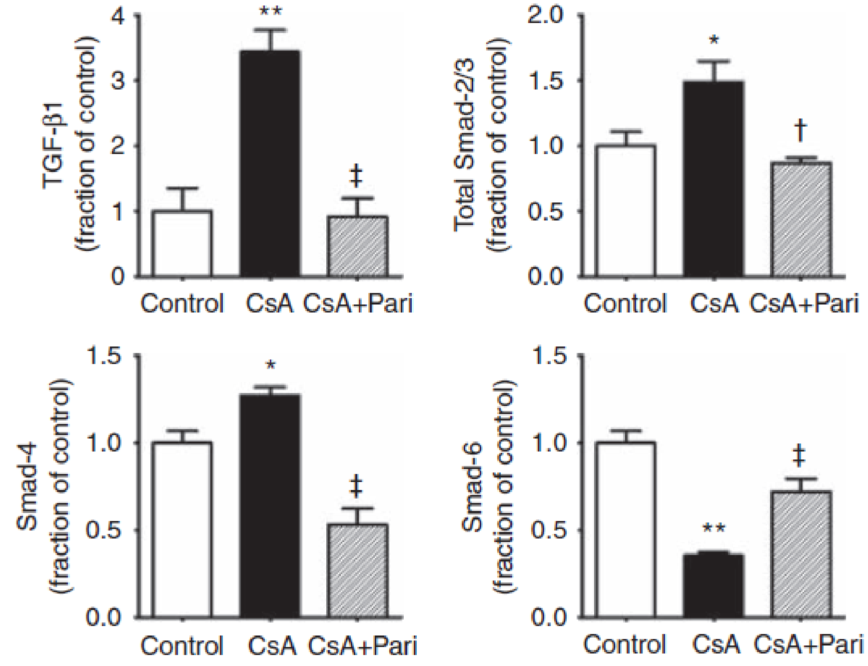


Figure 5 | Effects of paricalcitol on transforming growth factor (TGF)-β1 expression and Smad proteins in CsA-induced renal

And assessing Vitamin D in Clinical trials

Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial

Dick de Zeeuw, Rajiv Agarwal, Michael Amdahl, Paul Audhya, Daniel Coyne, Tushar Garimella, Hans-Henrik Parving, Yili Pritchett, Giuseppe Remuzzi, Eberhard Ritz, Dennis Andress

- N=280
- RCT placebo vs paricalcitol (VD)trial to demonstrate reduction of proteinuira ~15%
  - pts with DM II on ACEi or ARB, optimally controlled

  - Data support reduction of proteinuria with addition of VD
  - No longer term outcomes/ progression available.

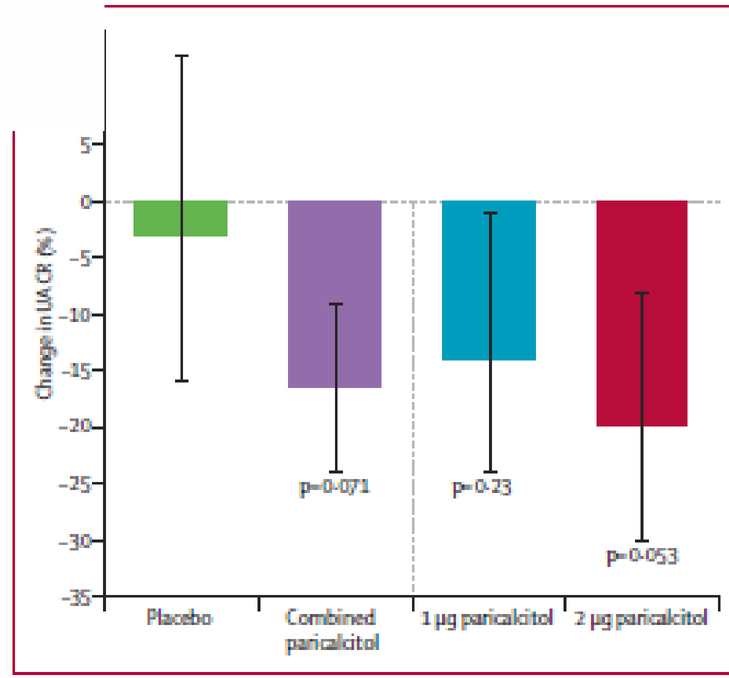


Figure 2: Change in urinary albumin-to-creatinine ratio from baseline to the last measurement during treatment

Error bars represent 95% CIs. p values are for the comparison of paricalcitol

Lancet 2010; 376: 1543–51

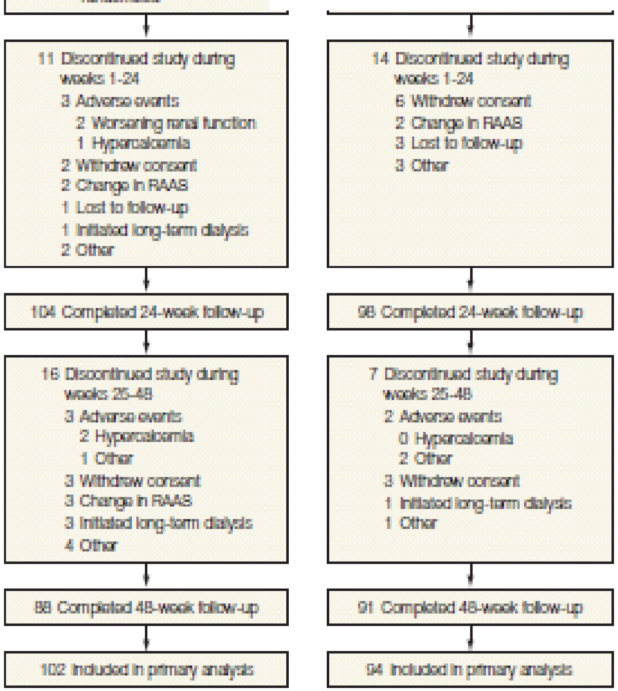
Vitamin D Therapy and Cardiac Structure and Function in Patients With Chronic Kidney Disease

The PRIMO Randomized Controlled Trial

JAMA. 2012;307(7):674-684

Corresponding Author: Ravi Thadhani, MD, MPH, Massachusetts General Hospital, 55 Fruit St, Bulfinch 127,

Design, Setting, and Participants Multinational, double-blind, randomized placebo-controlled trial among 227 patients with chronic kidney disease, mild to moderate left ventricular hypertrophy, and preserved left ventricular ejection fraction, conducted in 11 countries from July 2008 through September 2010.



Vitamin D therapy lowers PTH in CKD 3-4

Figure 2. Blood Levels of Intact Parathyroid Hormone During the Study by Treatment Group

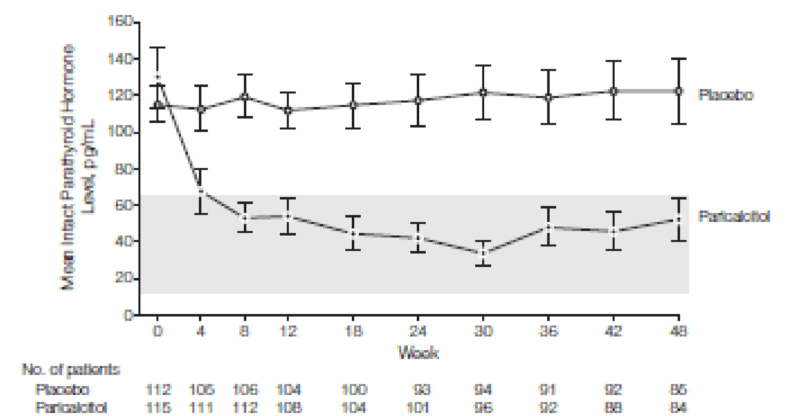


Table 5. Cardiovascular Hospitalizations by Treatment Group

Reason for Hospitalization	No. of Participants/ Cardiovascular Events	Follow-up, No. of Person-Years	Event Rate per 100 Person-Years	Study Day at Hospitalization
Placebo group	7/8	91.0	8.8	
Congestive heart failure[a]				16
Congestive heart failure				104
Chest pain				135
Chest pain				163
Aortic dissection				179
Congestive heart failure[a]				241
Congestive heart failure				289
Congestive heart failure				361
Paricalcitol group	1/1	94.3	1.1	
Chest pain				22
P value	.03		.04	

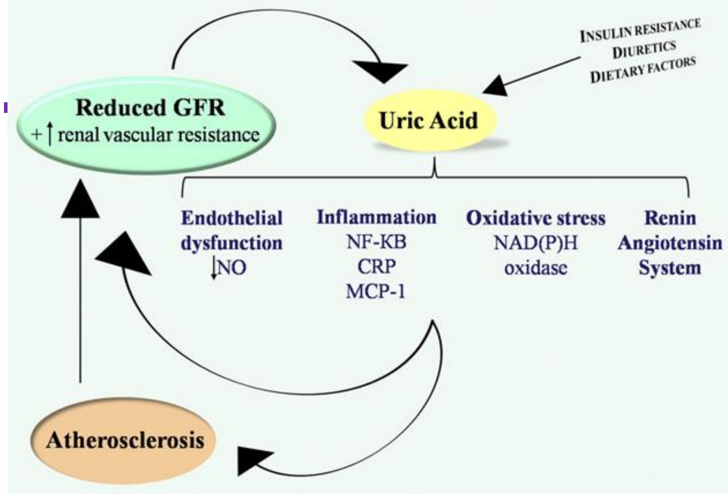
[a] These 2 hospitalizations were for the same participant.

No impact on LVMI

BUT…associated with reduced CV hosptializations

In conclusion, in this 48-week study of patients with CKD and mild to moderate LVH, the active vitamin D compound paricalcitol did not regress left ventricular mass or improve certain Doppler measures of diastolic function. Paricalcitol appeared to be associated with fewer cardiovascular-related hospitalizations, an attenuated increase in blood levels of BNP, but a greater incidence of hypercalcemia; however, these results warrant further confirmation.

Uric Acid and CVD in CKD …



- Accumulating data
  - Animal data
  - UA associated with CVD outcomes in large databases
  - Reanalysis of RENALL and FOCUS
    - Higher uric acid associated with CVD events
  - Biological mechanisms
    - Direct and indirect vascular effects: Oxidative stress, activiation of RAAS…
  - Small interventional studies

Allopurinol studies: changes in eGFR, uACR, vascular health

- CJASN: M. Goicoechea et al June 2010
  - RCT N=113 ; 24 m
  - Allopurinol 100 mg vs P
  - Reduce UA, CRP
  - Delta eGFR

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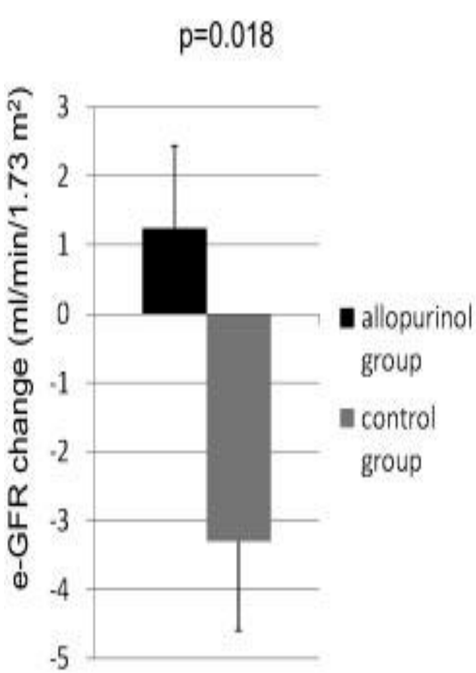
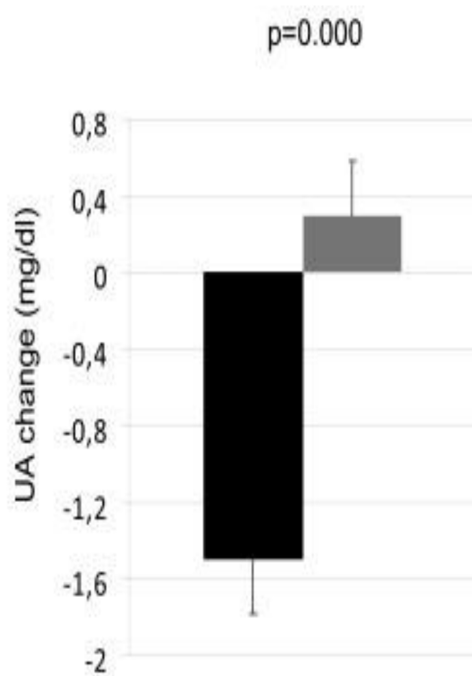
Allopurinol Benefits Left Ventricular Mass and Endothelial Dysfunction in Chronic Kidney Disease

Michelle P. Kao,* Donald S. Ang,* Stephen J. Gandy,† M. Adnan Nadir,* J. Graeme Houston,† Chim C. Lang,* and Allan D. Struthers*

*Division of Medical Sciences and †Department of Radiology, University of Dundee, Ninewells Hospital and Medical School, Dundee, United Kingdom





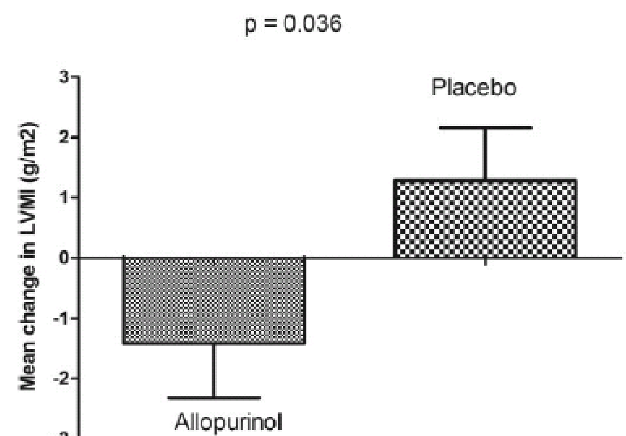


Figure 2. Significant regression of LVMI in the allopurinol group compared to the placebo group after 9 months, as measured by cardiac MRI.

Reduction in AIX, PwV , LVMI, diastolic dysfunction,
N= 67 (9 mo)

5 interventional studies…

Table 2. Main Interventional Studies to Decrease Serum Uric Acid Levels in CKD

Study	Study Design and Population	Treatment	Study End Points	Main Findings
Siu et al[69]	RCT of 54 hyperuricemic patients with mild to moderate CKD	12 mo of either allopurinol, 100-300 mg/d, or no treatment	Decreased kidney function with SCr ≥40% of baseline, initiation of dialysis, or death	Nonsignificant trend toward lower SCr in the treatment group ($P = 0.08$); overall, 16% (4/25) of allopurinol group reached the combined end points vs 46.1% (12/26) in control group ($P = 0.015$)
Goicoechea et al[70]	RCT of 113 hyperuricemic patients with mild to moderate CKD	24 mo of either allopurinol, 100 mg/d, or no treatment	Progression of CKD (defined as eGFR decrease >0.2/mo), CV events, hospitalizations for any cause, or death	ΔeGFRs of -3.3 ± 1.2 (control) and $+1.3 \pm 1.3$ (allopurinol group), $P = 0.018$; compared with controls, allopurinol treatment slowed CKD progression in a Cox regression model (adjusted for age, sex, diabetes, uric acid) and reduced risk of CV events and number of hospitalizations (aHR, 0.29; 95% CI, 0.09-0.86; $P = 0.026$)
Kanbay et al[73]	Case-control study of 59 hyperuricemic patients with eGFR >60 and 21 normouricemic controls; only hyperuricemic patients received allopurinol*	3 mo of allopurinol, 300 mg/d	eGFR <60	eGFR significantly increased (from 79.2 ± 32 to 92.9 ± 37; $P = 0.008$) and BP and plasma CRP decreased in allopurinol group; no significant change in control group
Talaat & el-Sheikh[33]	Intervention trial of allopurinol withdrawal in 50 hyperuricemic patients with CKD3-4 treated with allopurinol	12 mo after allopurinol withdrawal	Changes in eGFR and urinary TGFβ1	Significant acceleration of rate of eGFR loss and significant increases in BP and urinary TGFβ1 only in those who were not receiving ACEI
Miao et al[74]	Placebo-controlled RCT of patients treated with losartan in a post hoc analysis of the RENAAL trial; N=1,342 patients with type 2 diabetes and nephropathy	Post hoc analysis of first 6 mo of treatment	Progression of CKD (defined as doubling of SCr or ESRD)	Losartan decreased serum uric acid by 0.16 (95% CI, 0.30-0.01) mg/dL ($P = 0.031$) vs placebo; risk of renal events was decreased by 6% (95% CI, 10%-3%) per 0.5-mg/dL decrement in serum uric acid during the first 6 mo of treatment after adjustment for age, sex, treatment assignment (losartan or placebo), eGFR, SBP, albuminuria, serum albumin, ACEI or ARB use at baseline, changes in albuminuria and eGFR

N range = 50 – 113

- RCT
- Case Control
- Post hoc analysis (1342)
- Limited duration; Small N, different outcomes

New larger study: CKD FIX

- PI: David Johnston: 2016……?2019+
- Australian Kidney Trials Network

- 600+ pts RCT : Allopurinol vs Placebo
- eGFR 25- 45 ml/min
- Safety and efficacy
- Powered to address progression of CKD
  Secondary outcomes = CVD

And there is alkanalization…

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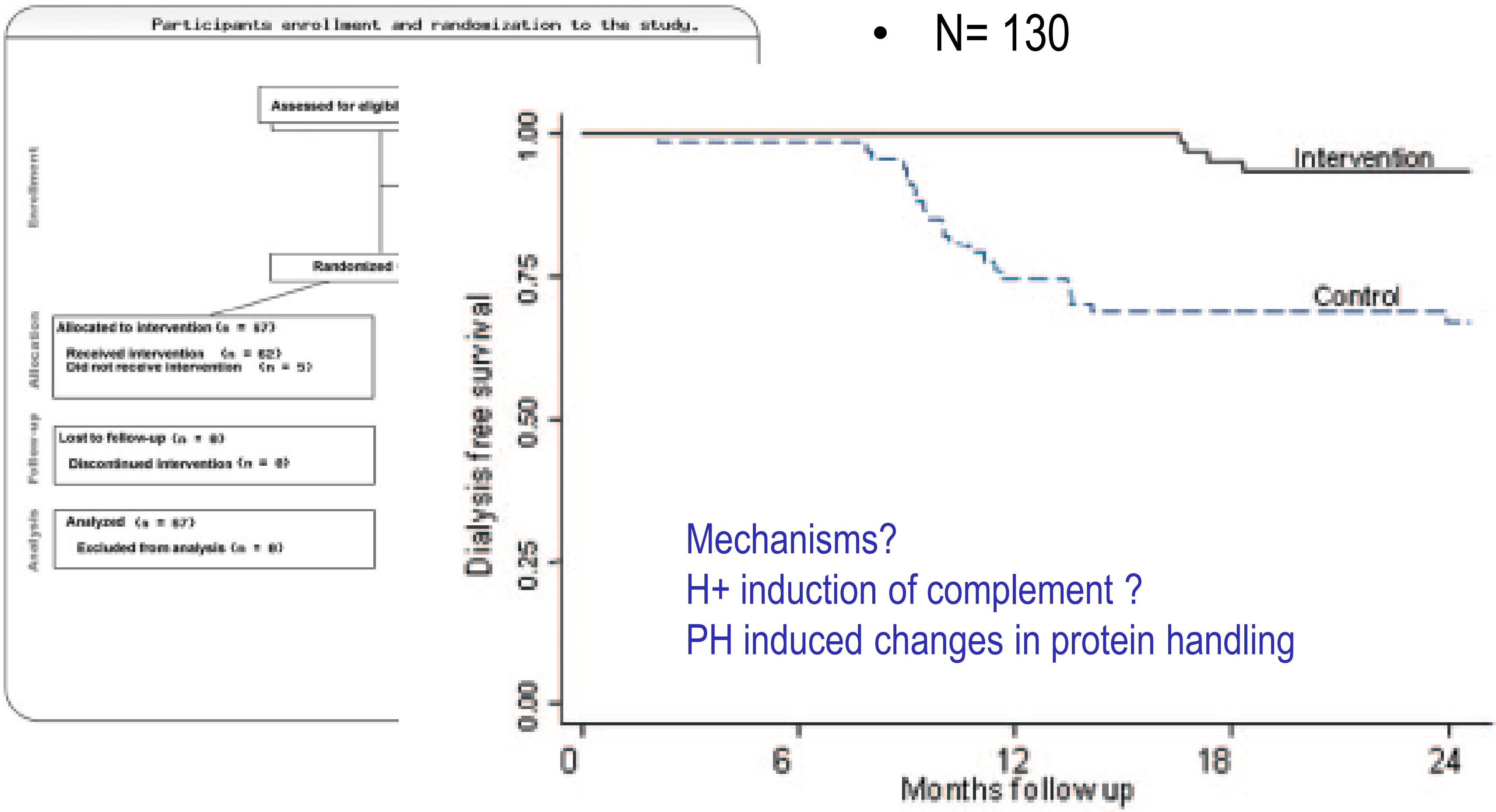
Bicarbonate Supplementation Slows Progression of CKD and Improves Nutritional Status

Ione de Brito-Ashurst, Mira Varagunam, Martin J. Raftery, and Muhammad M. Yaqoob

- N= 130



Mechanisms?
H+ induction of complement ?
PH induced changes in protein handling

http://www.kidney-international.org

original article

Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy

Ashutosh Mahajan[1,2], Jan Simoni[3], Simon J. Sheather[4], Kristine R. Broglio[4,5], M.H. Rajab[5] and Donald E. Wesson[1,2]

- Small RCT demonstrating benefit of HCO3 over 5 year period

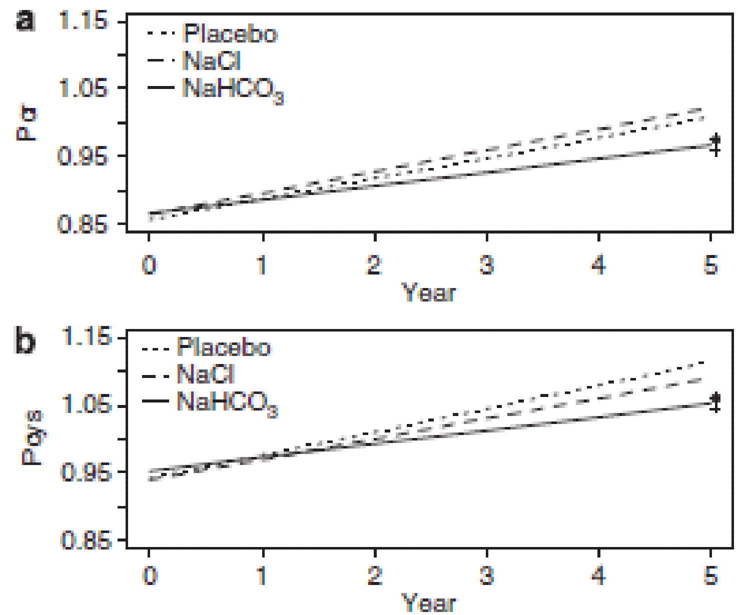
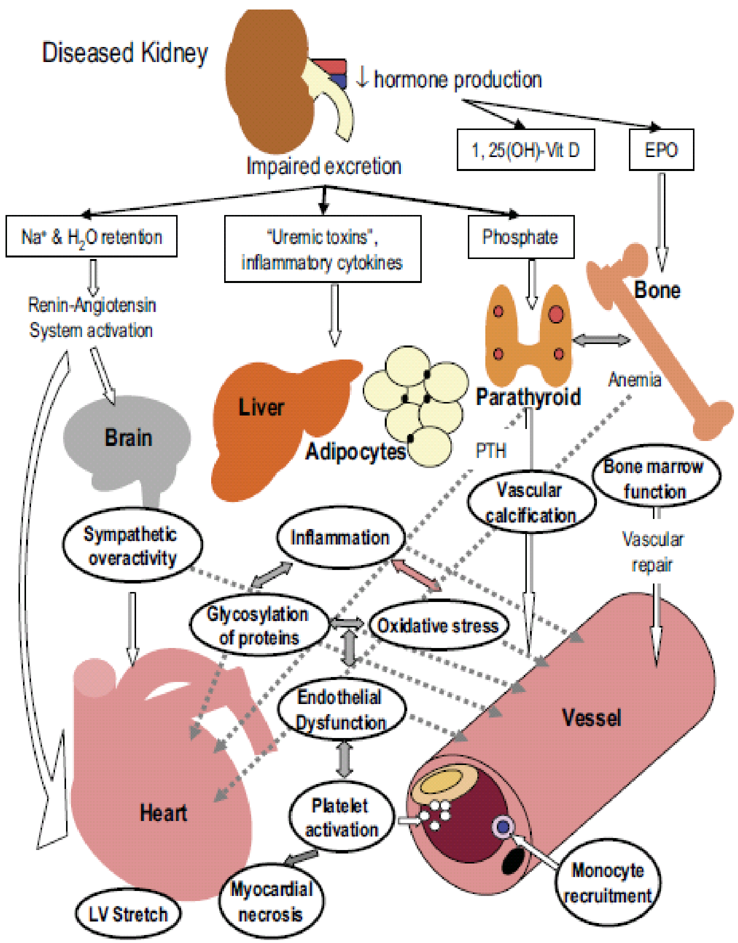


Figure 1 | Course of plasma values for creatinine and cystatin C. Trajectories of plasma creatinine (**a**) and plasma cystatin C (**b**) in subjects taking placebo, NaCl, or $NaHCO_3$ for 5 years estimated using linear mixed models (Methods). *$P < 0.05$ vs placebo; $^{+}P < 0.05$ vs NaCl.

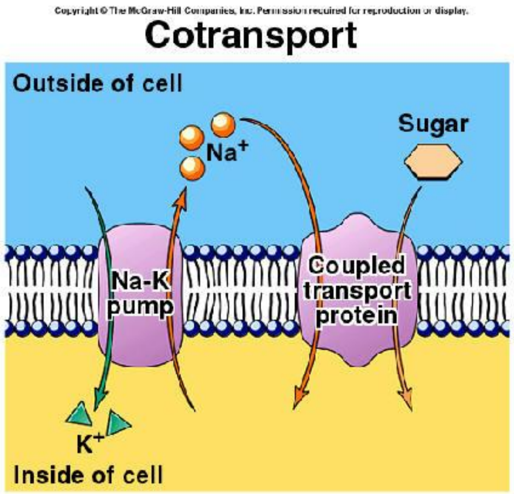
Kidney (& other) Outcomes are related to complex processes

- Inflammation
- Fibrosis
- Oxidative stress
- ……………



Newer Agents…CVD and CKD impact

- Anti-fibrotic (Bardoxalone,……)
- Endothelin 1 Antagonists
- Protein-kinase C inihibitors
- Sodium Glucose Co-transporter inhibitors (SGLT-I)



The new engl and jour nal *of* medicine

Original Article

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D.,
David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D.,
Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H.,
Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

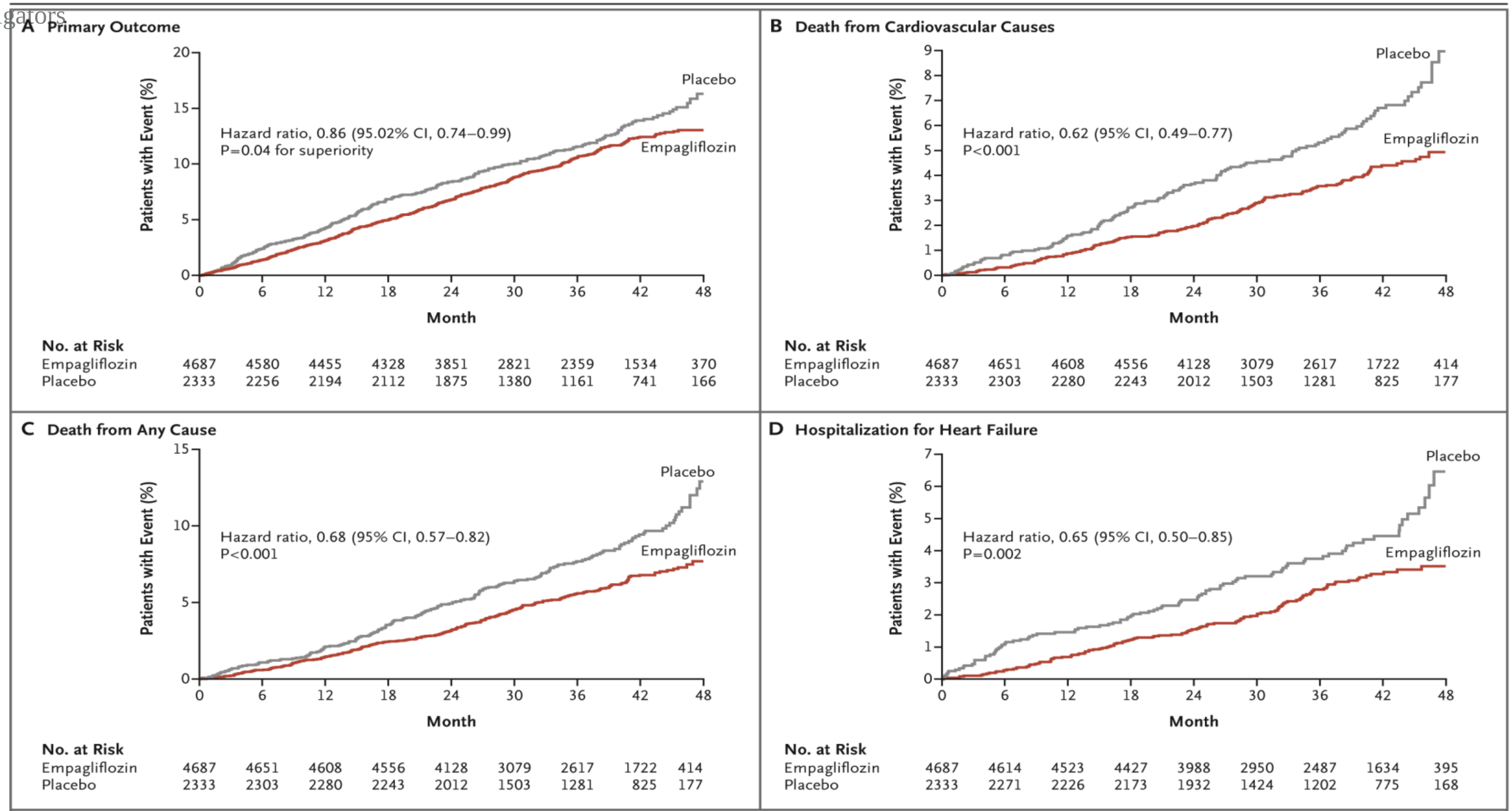
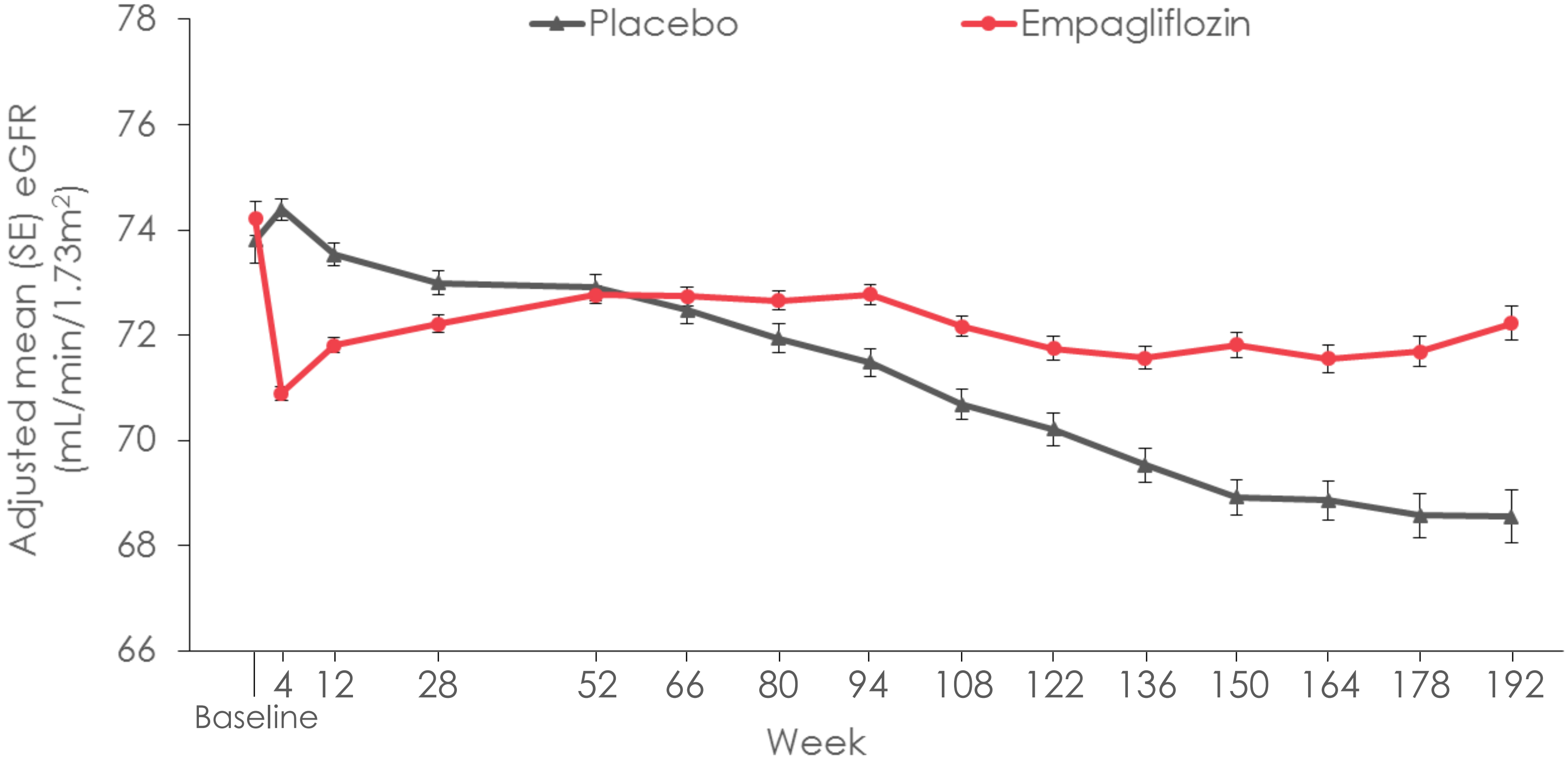


Figure 1. Cardiovascular Outcomes and Death from Any Cause.

Shown are the cumulative incidence of the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), cumulative incidence of death from cardiovascular causes (Panel B), the Kaplan–Meier estimate for death from any cause (Panel C), and the cumulative incidence of hospitalization for heart failure (Panel D) in the pooled empagliflozin group and the placebo group among patients who received at least one dose of a study drug. Hazard ratios are based on Cox regression analyses.

Impact on renal endpoints over time of SGLT2 inhibitors in Diabetics

eGFR over 192 weeks



Patients analyzed	Baseline	4	28	52	66	80	94	108	122	136	150	164	178	192
Placebo	2323	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin	4644	4533	4451	4318	4225	4018	4131	3710	3103	2654	2387	2087	1623	1037

eGFR according to MDRD formula. Pre-specified mixed model repeated measures analysis in patients treated with ≥1 dose of study drug who had a baseline and post-baseline measurement.
MDRD, Modification of Diet in Renal Disease.

Wanner C et al. N Engl J Med 2016;375:323–34

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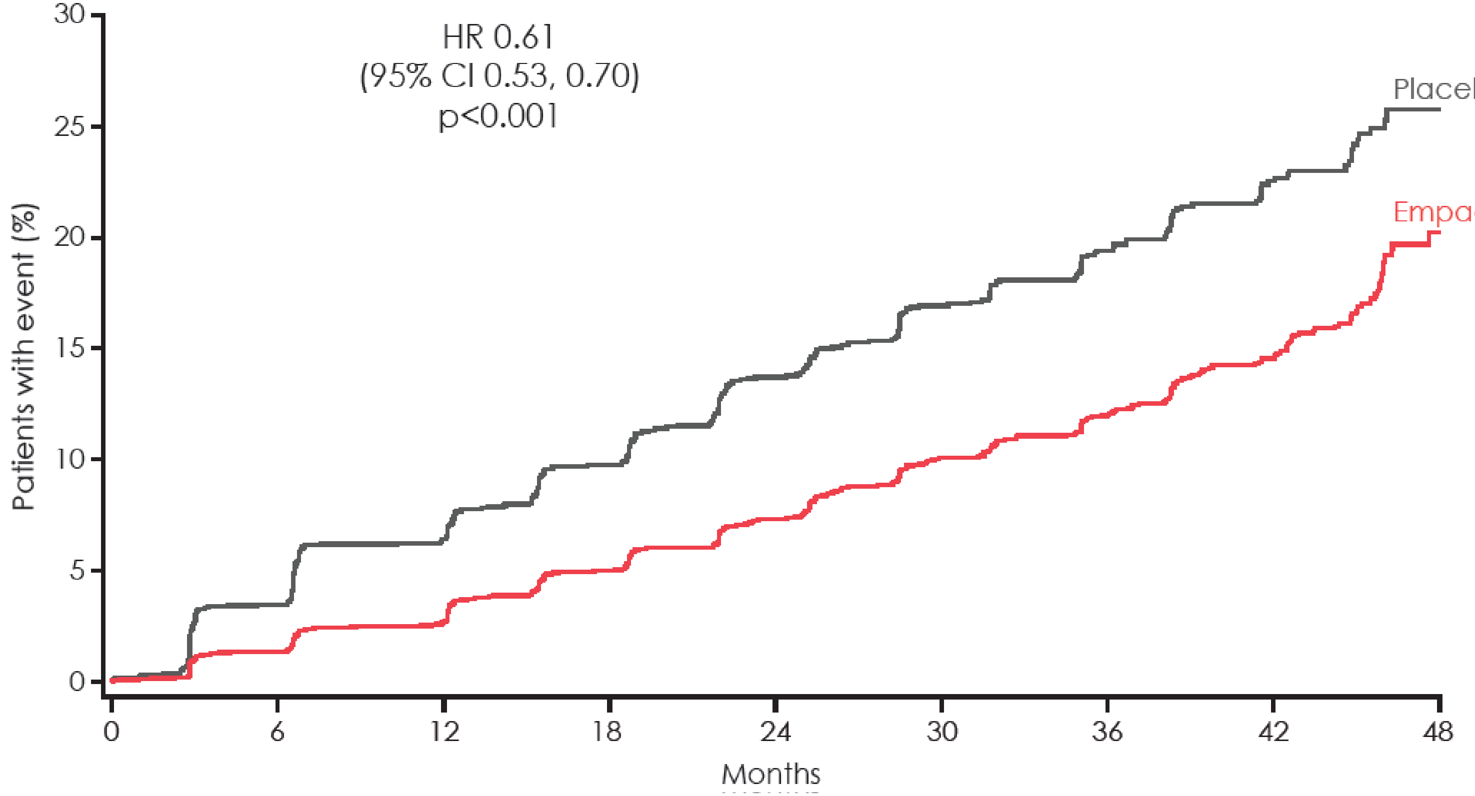
Impact on renal endpoints over time of SGLT2 inhibitors in Diabetics

Incident or worsening nephropathy



No. of patients									
Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

Kaplan-Meier estimate. Hazard ratio based on Cox regression analyses.
Wanner C et al. N Engl J Med 2016;375:323–34

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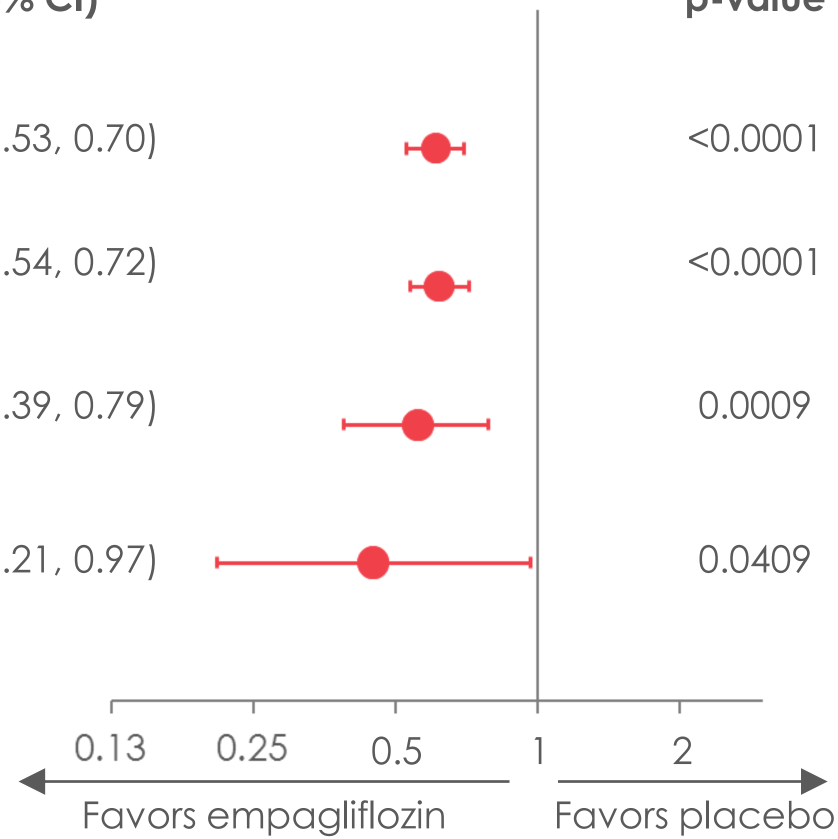
Incident or worsening nephropathy and its components

	Empagliflozin	Placebo	Hazard ratio (95% CI)	p-value
	n with event/ N analyzed			
Incident or worsening nephropathy	525/4124	388/2061	0.61 (0.53, 0.70)	<0.0001
New onset macroalbuminuria	459/4091	330/2033	0.62 (0.54, 0.72)	<0.0001
Doubling of serum-creatinine*	70/4645	60/2323	0.56 (0.39, 0.79)	0.0009
Initiation of renal replacement therapy	13/4687	14/2333	0.45 (0.21, 0.97)	0.0409



*Accompanied by eGFR (MDRD) ≤45 mL/min/1.73m[2].
Cox regression analyses.
Wanner C et al. N Engl J Med 2016;375:323–34

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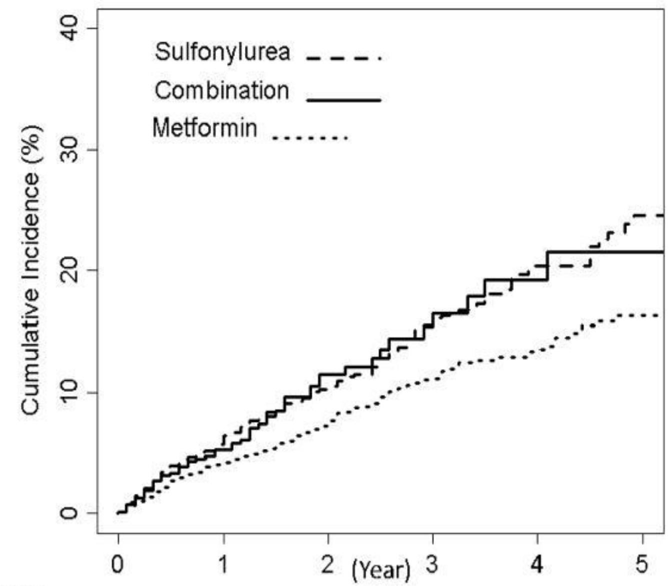
……and then there is METFORMIN ?

Kidney function decline in metformin versus sulfonylurea initiators: assessment of time-dependent contribution of weight, blood pressure and glycemic control;

Hung et al, Pharmacology and Drug Safety 2013

- 13,238 incident patients
- included metformin (58%), sulfonylureas (33%),
- combination of both (8%) and
- thiazolidinediones (1%)
- Median age 59
- Cohort from 1999-2008
  - With drug exposure at least 90 days



Total at risk (%)	13238 (100)	5589 (42)	2714 (21)	1353 (10)	642 (5)	256 (2)
Metformin	7728 (100)	3426 (44)	1683 (22)	844 (11)	392 (5)	139 (2)
Sulfonylurea	4425 (100)	1777 (40)	847 (19)	427 (10)	210 (5)	102 (2)
Combination	1000 (100)	353 (35)	171 (17)	79 (8)	39 (4)	14 (1)

Lower probability of progression for those on Metformin……

Metformin ? mechanism

- Metformin Therapeutic effects
  - mainly via activation of AMP-activated kinase (AMPK) pathway.
- Renal cells under hyperglycemic or proteinuric conditions exhibit

  -inactivation of cell defense mechanisms eg AMPK and autophagy, and

  -activation of pathologic pathways (mTOR), endoplasmic reticulum (ER) stress, epithelial-to-mesenchymal transition (EMT), oxidative stress, and hypoxia.
- The pathologic pathways are intertwined with AMPK signaling, so
- ? ? potential benefits of metformin therapy in patients may extend beyond its anti-hyperglycemic effects.

Progression of CKD : unanswered questions

- The relative role of different mediators of progression
  - At different points in time
  - In different conditions
  - In different populations
  - Together or alone
- What to target in clinical studies
  - Single vs multiple markers of processes
    - Urine vs blood markers
  - ? Change in eGFR slope
  - Biopsy changes or Imaging (kidney volume/ other measures of function/ activity)
  - Patient reported outcomes : QOL , symptoms

Unanswered questions

- When:
  - Timing of interventions
- What :
  - What drug or other therapies ?
  - What outcomes: CKD, CVD both
- Who?
  - Which populations (level of eGFR/ uACR, DM vs ?)
- How?
  - Robust study design(s)

Overview

- What we know
- What we do not know
- What we need to do now….

Explore and commit to better understanding

- Descriptive studies:
  - Large cohort studies with bio-banking
  - Long term follow up to understand variability and risk
- Well designed physiological studies
  - Understand mechanisms of disease and interactions
  - Human physiology and complex interactions
- Large clinical trials
  - With representative populations

Towards an Integrated Understanding

Clinical observations ↔ Clinical Trials

Physiology

Cell biology

Molecular mechanisms

New hypotheses/ validation

Interpretations / understanding

Patient Outcomes

The real question:

Can we identify patients at risk for rapid progression and other important outcomes …and then test targeted interventions or strategies ?

Summary:

Challenges in delaying progression of CKD: perspectives and precautions

- Variability and multiplicity of processes
- Variability of outcomes
- Challenges of clinical trials to test therapies
  - Isolation of single processes
  - Predicting high risk populations

- It is possible to delay progression in some….
  - Beware the single intervention ☺ for a complex processes

Thank you for your attention

- And to my colleagues and collaborators

Thank you to colleagues and collaborators

- UBC Division of Nephrology
- Pacific Nephrology Group
- BC Provincial Renal Agency
- Patients and their families… for their patience while we work this out

BCRenal
an agency of the Provincial Health Services Authority

a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA

THE KIDNEY FOUNDATION OF CANADA
The foundation of kidney care.

Providence HEALTH CARE
How you want to be treated.

Newer biomarkers: ?adding to current prediction models

- Reflective of additional biologic or discriminatory processes
  - Cystatin C
  - Troponin, NT proBNP
  - FGF 23
  - ADMA
  - TGF beta
  - CRP
  - ……. What value could be added?

Potential value add for newer biomarkers

- Identify with greater accuracy those with and without events
- Identify therapeutic targets for intervention
- Identify new pathways for diseases
- ……
- But, need to demonstrate
  - Reliable risk thresholds
  - Stability over time/ reliability of assays
  - Reponsiveness to interventions

Newer biomarkers in Progression for CKD cohorts : what we do not know

- The relative role of different mediators of progression
  - At different points in time
  - In different conditions
  - In different populations

- The role of change in these mediators in predicting outcomes

- (Genomics, proteomics, metabolomics)

Summary: Progression of CKD

- Progression in CKD is variable

- Risk prediction models offer an opportunity to systematically quantify ‘clinical intuition’ and more uniformly predict outcomes for improved perceptions by patients and caregivers

- Ongoing studies are needed
  - To better understand variability in biological processes and outcomes
  - How to use prediction models in clinical practice
  - Existing large cohort studies offer one method of integrating knowledge
- Delaying progression of CKD Is possible: