Angiotensin Converting Enzyme inhibitor (ACEi) / Angiotensin Receptor Blocker (ARB) – To STOP OR Not in Advanced Renal Disease

Launch Meeting

3rd April 2014, Lucas House, Birmingham

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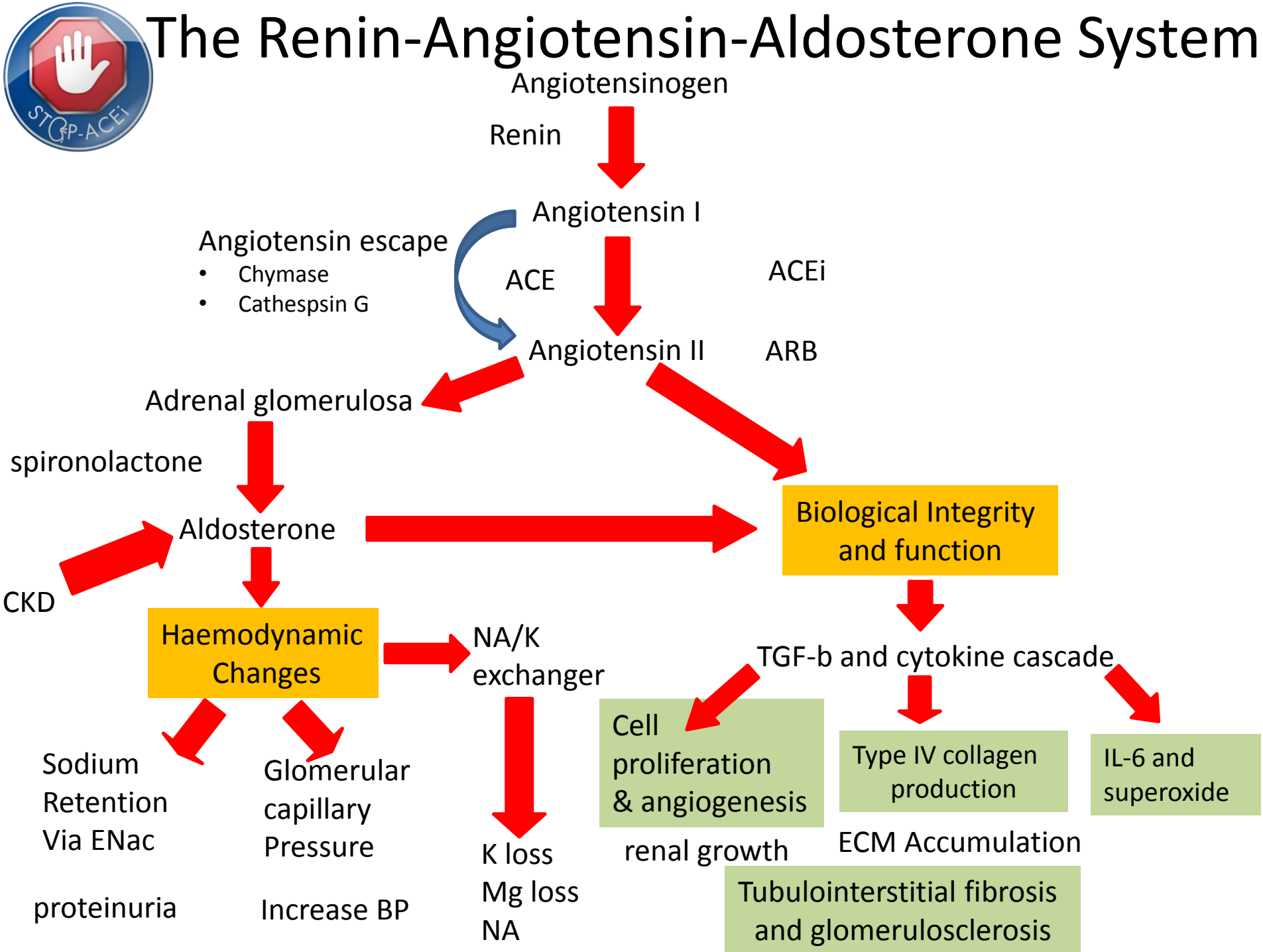
NHS

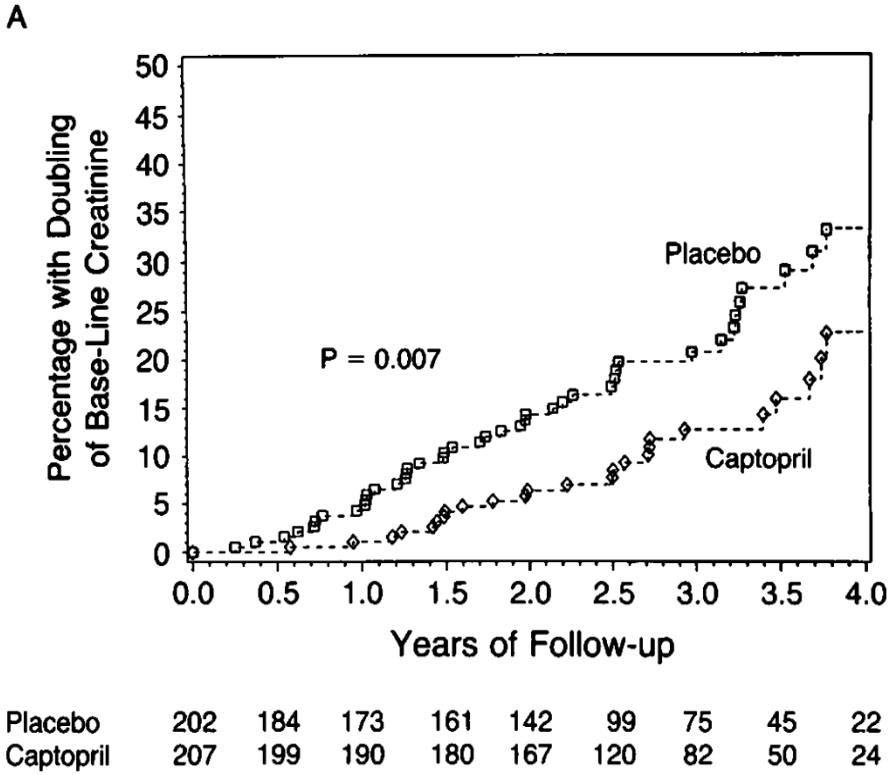
Aims

- Background and Rationale
  - Limiting renal progression
  - Cardiovascular disease and the kidney
  - Equipoise
- Trial Design
- Eligibility Criteria
  - Inclusion
  - Exclusion
- Objectives
  - Primary
  - Secondary
- Screening and Consent
- Trial Procedures/Assessments

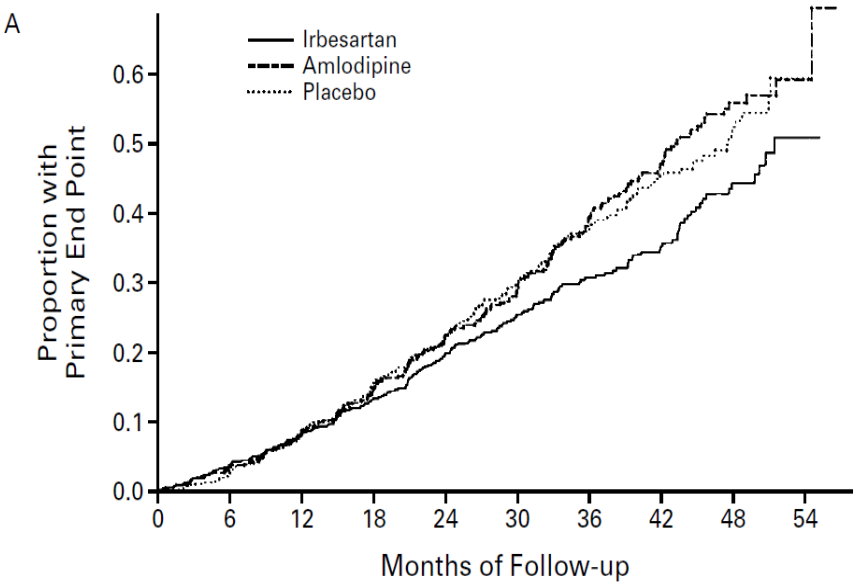
The Renin-Angiotensin-Aldosterone System



Seminal - Lewis Studies



Placebo	202	184	173	161	142	99	75	45	22
Captopril	207	199	190	180	167	120	82	50	24



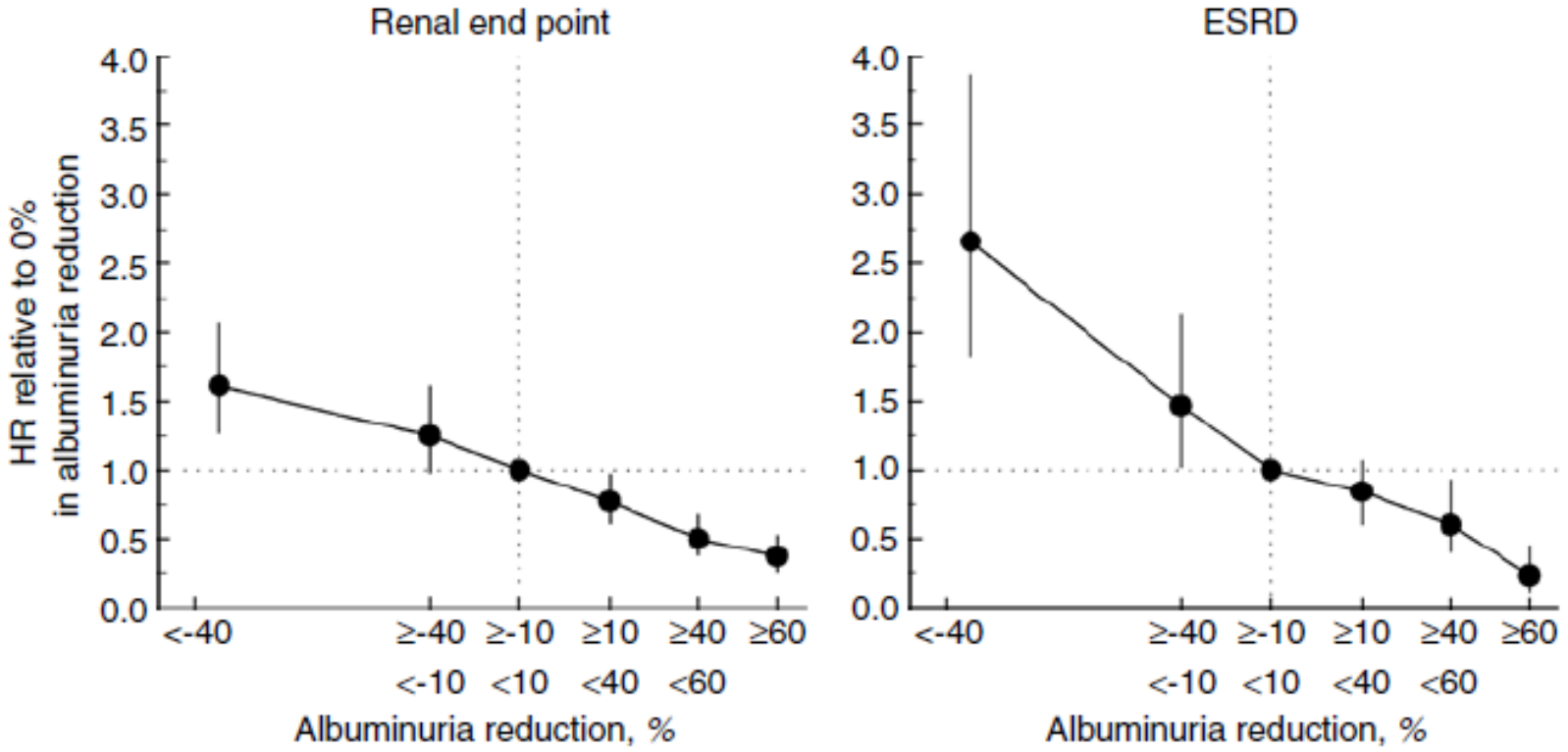
No. at Risk									
Irbesartan	579	555	528	496	400	304	216	146	65
Amlodipine	565	542	508	474	385	287	187	128	46
Placebo	568	551	512	471	401	280	190	122	53

Lewis et al NEJM 1993
Lewis et al NEJM 2001

RCTs Demonstrating Benefit of ACEi and ARB on Kidney Outcomes

Study	N	Study arms	Study population	Proteinuric at baseline %	Proteinuria reduced	Renal outcome
REIN	352	Ramapril Placebo	Non diabetic CKD	100	Yes	Decline in GFR
AIPRI	583	Benazapril Placebo	Non diabetic CKD	100	Yes	Doubling Scr or ESRD
RENAAL	1513	Losartan Placebo	Type II diabetes with Nephropathy	100	Yes	Doubling Scr or ESRD, death
IDNT	1713	Irbesartan Amlodipine placebo	Type II diabetes with Nephropathy	100	Yes	Doubling Scr or ESRD, death
AASK	1089	Ramapril Amlodipione Metoprolol	Hypertensive nephrosclerosis	33	Yes	Decline in GFR
Captopril LEWIS	409	Captopril Placebo	Type I diabetes with Nephropathy	100	Yes	Doubling Scr
Cooperative	240	Trandolaprol Losartan Comination	Non diabetic CKD	100	Yes	Doubling Scr or ESRD
Advanced CKD	328	Benazapril plaebo	Non diabetic CKD	100	yes	Doubling Scr or ESRD, death

RENAAL: Antiproteinuric effect of losartan explains the renal protective effect



	Outcome		Outcome Adjusted for proteinuria	
	RR (97% CI)	P value	RR (97% CI)	P value
Primary Composite	16.1 (2.5-27.8)	0.022	1.7 (-14.5-15.5)	0.829
ESRD	28.6 (11.5-42.4)	0.002	14.1 (-6,6-30.8)	0.168

DE Zeeuw KI 2004

Studies with Renal Endpoints with RAAS blockage ? Generalisation to all levels of CKD

	Studies demonstrating differences in renal endpoints			
Non diabetic	Baseline GFR (ml/min)		diabetic	Baseline GFR (ml/min)
MDRD	40		Captopril	68
AIPRI	52		IDNT	59
REIN	56		RENAAL	58
AASK	46		Bakris et al	59
COOPERATE	51			
	Studies demonstrating no difference in renal endpoints			
diabetic	Baseline GFR		Diabetic & non diabetic	Baseline GFR
ABCD	84		Casas J	74
Barnett A et al	93		ALLHAT	71-78
ACCOMPLISH	45		BENEDICT	79

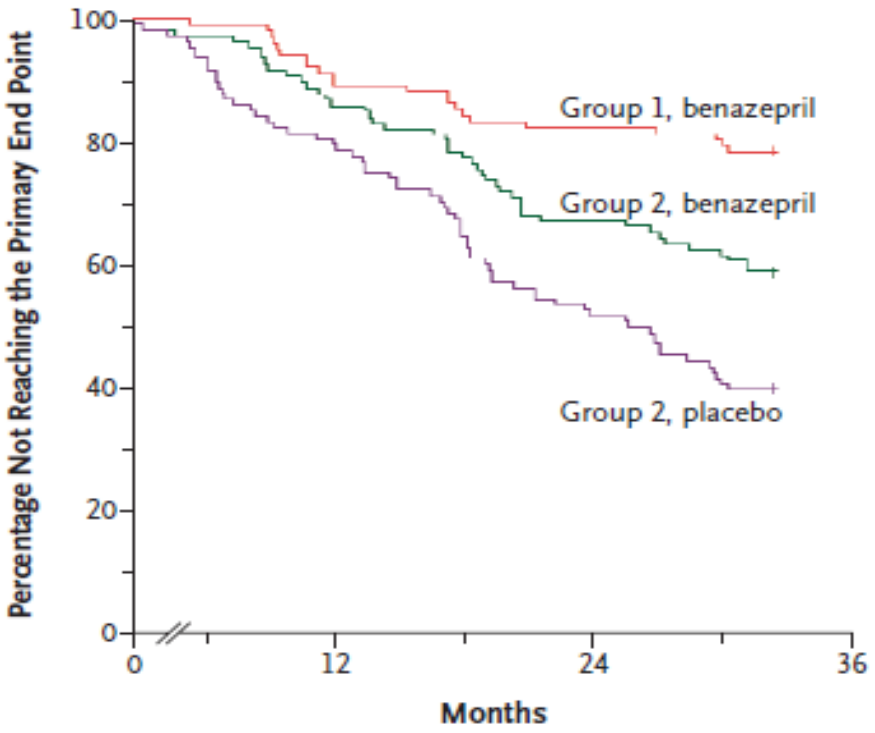
ACEi in advanced CKD creatinine > 273umol/L

422 patients with non-diabetic CKD :
Group 1: (SC 133-265µmol/L) received 20mg of benazepri/day

Group 2: (SC 274-442µmol/L) randomised to 20mg of benazepril/day or placebo and then followed for 3.4 years

43% decrease in the composite end point of doubling of serum creatinine level, ESRD, or death in the benazepril group compared to placebo.

Hou et al N Engl J Med 2006: 354: 131-140



No. at Risk				
Group 1, benazepril	102	96	84	40
Group 2, benazepril	107	96	73	32
Group 2, placebo	108	88	59	22

Figure 2. Kaplan–Meier Estimates of the Percentage of Patients Not Reaching the Primary Composite End Point of a Doubling of the Serum Creatinine Level, End-Stage Renal Disease, or Death.

Group 1 had a serum creatinine level of 1.5 to 3.0 mg per deciliter, and group 2 had a serum creatinine level of 3.1 to 5.0 mg per deciliter at baseline.

ACEi cause Renal Progression?

Antihypertensive	RR	CI
ACEi	2.5	1.3-4.7
B-Blocker	0.8	0.5-1.4
CCB	0.7	0.4-1.3
Thiazide	1.0	reference

Adjusted for age, sex, CVD and CCF: 7.8 y follow-up

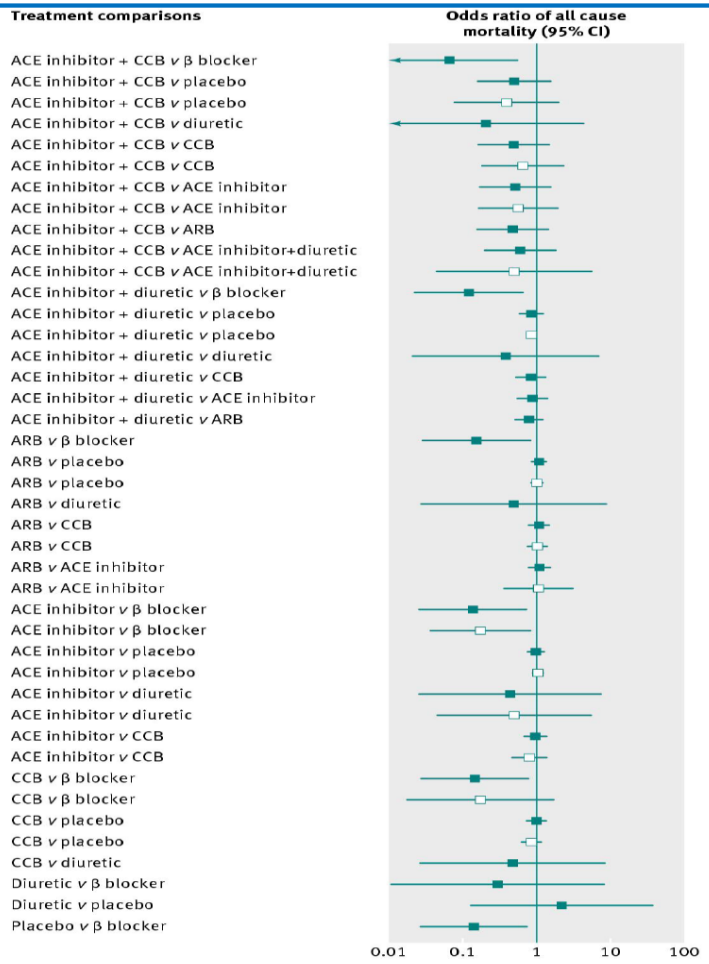
Suissa et al KI 2006:69. 913-919

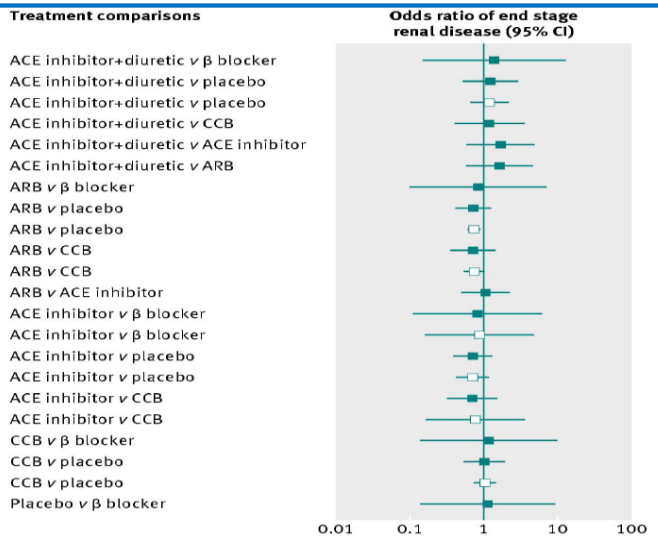
Is it all Blood pressure?

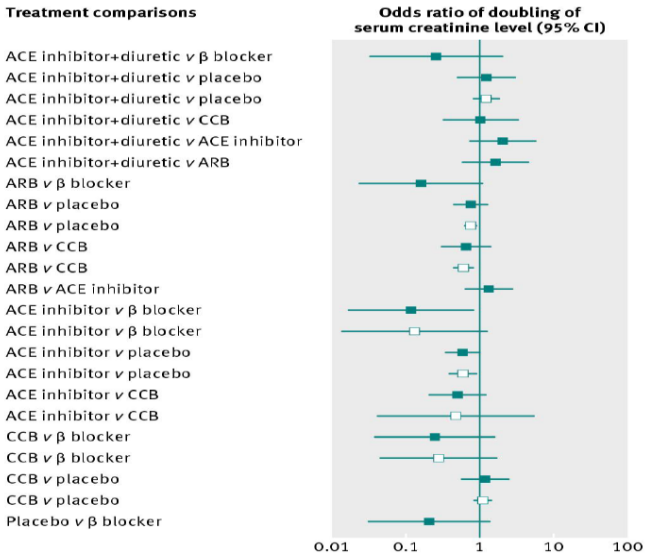
Or a specific ACEi effect for CVD and CKD protection?

The data from AASK and REIN-2 with a 14 mmHg and 4.8 mmHg difference in systolic BP suggest that patients with substantial reduced kidney function would not derive similar benefit to RAAS blockade on CKD progression apart from BP lowering

Beneficial effects of lowering BP for CV protection and mortality is class of drug independent







BMJ October 2013

On Target Study

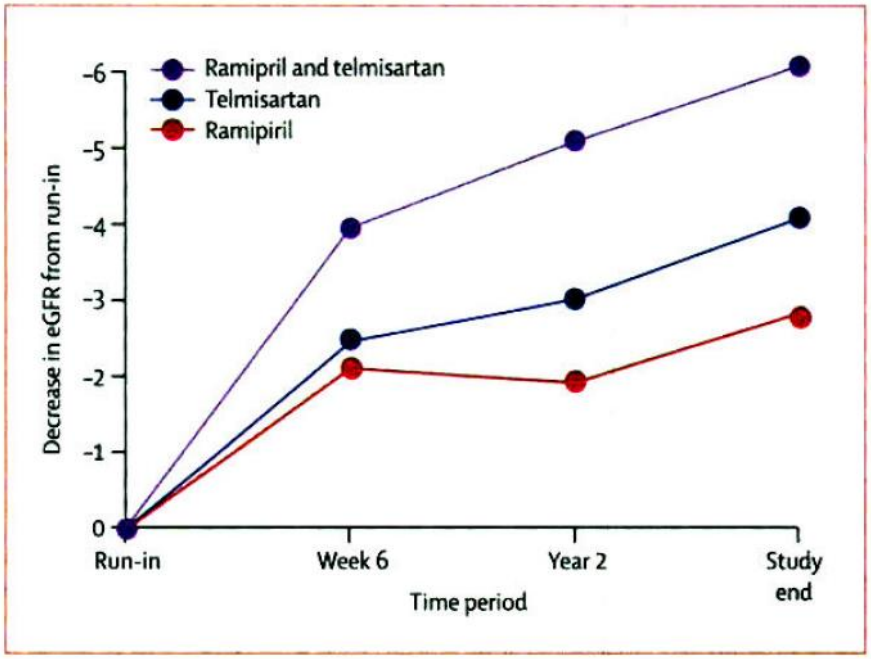
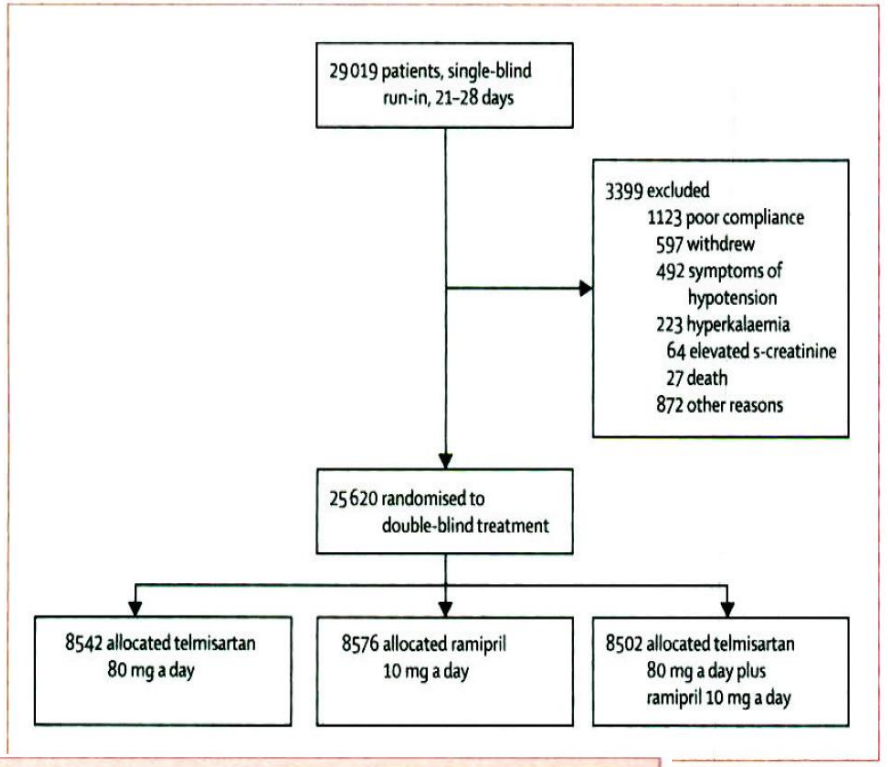


Figure 2: **Decrease in estimated glomerular filtration rate (eGFR) during the trial, from baseline to study end**



	Ramipril	Telmisartan	Ramipril+ telmisartan	Telmisartan vs ramipril p	Ramipril+telmisartan vs ramipril p
eGFR, baseline	73·7 (19·3)	73·6 (19·9)	73·4 (19·5)	0·915	0·388
eGFR change baseline to 6 weeks	−2·14 (12·9)	−2·51 (13·2)	−4·01 (13·3)	0·070	<0·0001
eGFR change baseline to 2 years	−1·96 (15·1)	−3·05 (15·1)	−5·12 (15·7)	<0·0001	<0·0001
eGFR change 6 baseline to final	−2·82 (17·2)	−4·12 (17·4)	−6·11 (17·9)	<0·0001	<0·0001
eGFR change 6 weeks to final	−1·17 (17·1)	−2·06 (17·1)	−2·49 (17·4)	0·0032	<0·0001

eGFR=estimated glomerular filtration rate (mL/min/1·73 m² [SD]). Number of participants with measurements=25 551 at baseline, 24 970 at 6 weeks, 22 573 at 2 years, 19 601 at study end.

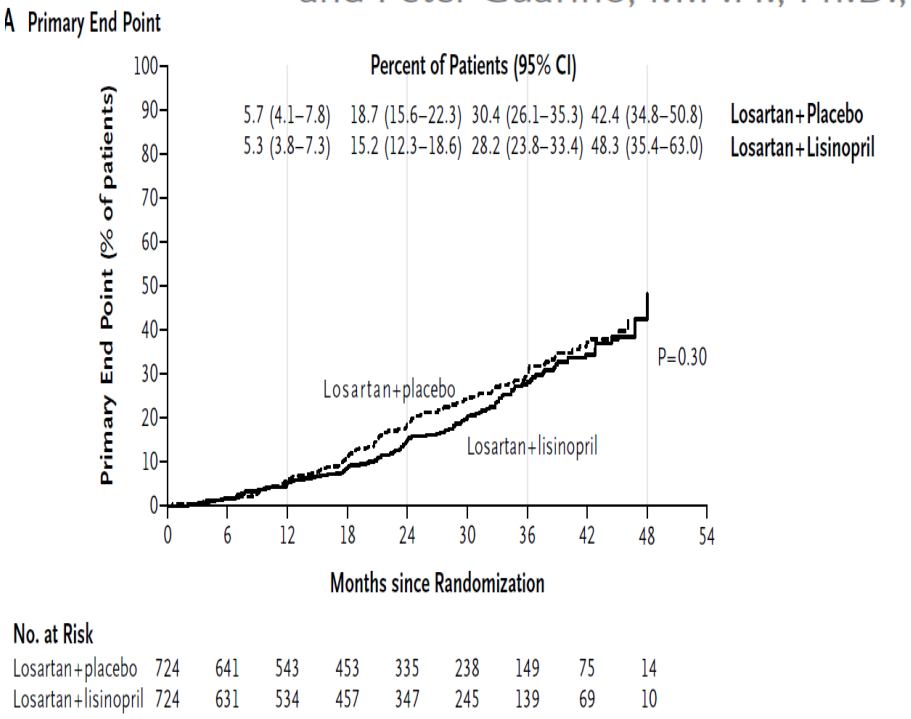
Table 1: **Estimated glomerular filtration rate at baseline and changes of eGFR**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

Linda F. Fried, M.D., M.P.H., Nicholas Emanuele, M.D., Jane H. Zhang, Ph.D., Mary Brophy, M.D., Todd A. Conner, Pharm.D., William Duckworth, M.D., David J. Leehey, M.D., Peter A. McCullough, M.D., M.P.H., Theresa O'Connor, Ph.D., Paul M. Palevsky, M.D., Robert F. Reilly, M.D., Stephen L. Seliger, M.D., Stuart R. Warren, J.D., Pharm.D., Suzanne Watnick, M.D., Peter Peduzzi, Ph.D., and Peter Guarino, M.P.H., Ph.D., for the VA NEPHRON-D Investigators*



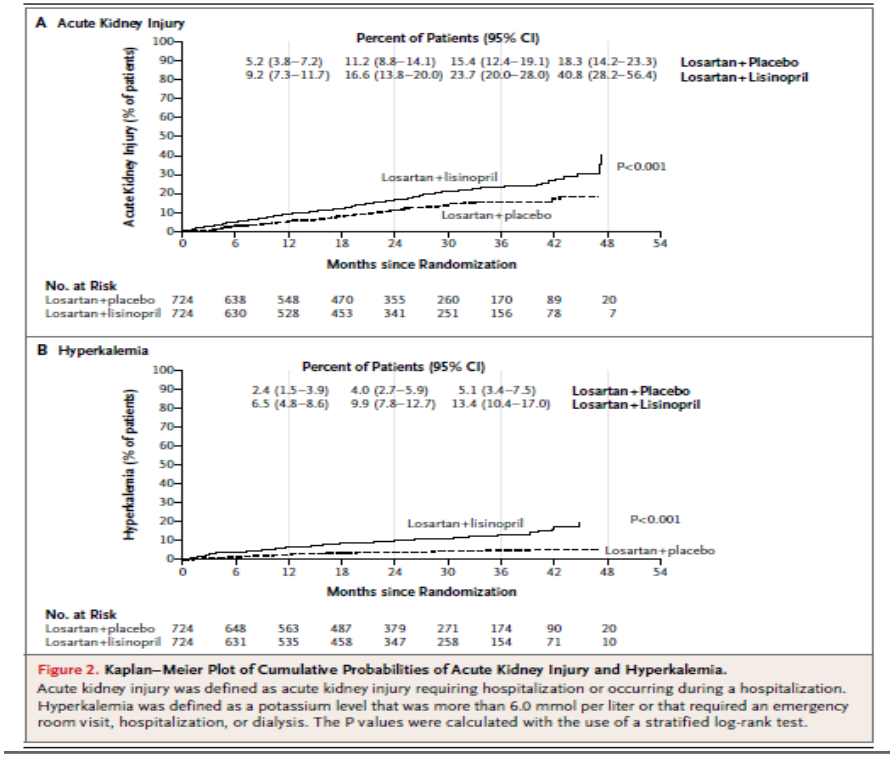
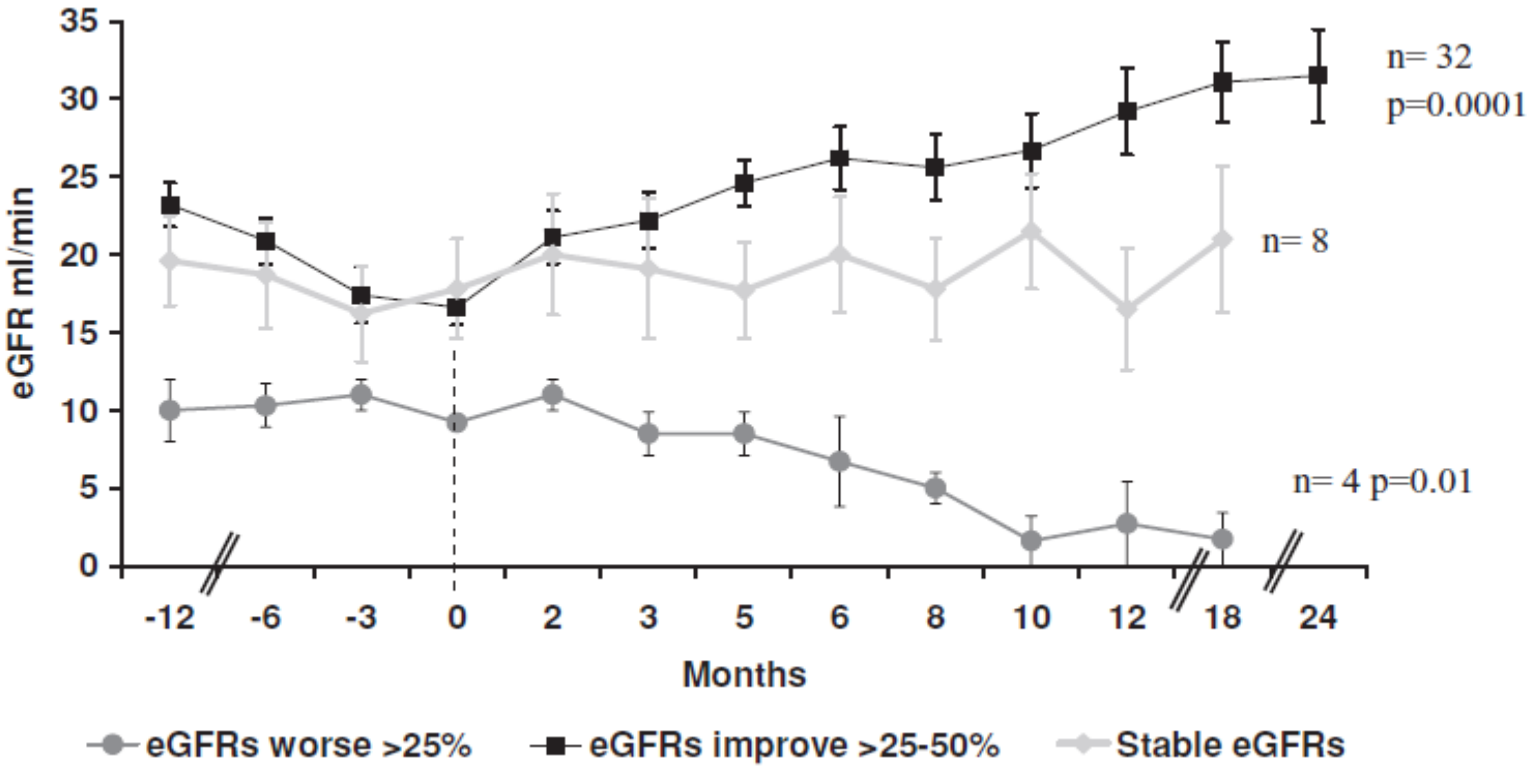


Figure 2. Kaplan–Meier Plot of Cumulative Probabilities of Acute Kidney Injury and Hyperkalemia.
Acute kidney injury was defined as acute kidney injury requiring hospitalization or occurring during a hospitalization. Hyperkalemia was defined as a potassium level that was more than 6.0 mmol per liter or that required an emergency room visit, hospitalization, or dialysis. The P values were calculated with the use of a stratified log-rank test.

Change in GFR after stopping ACEi



Ahmed AK et al NDT 2009: 25; 3977-

A >4ml improvement in GFR was predictive of survival without RRT

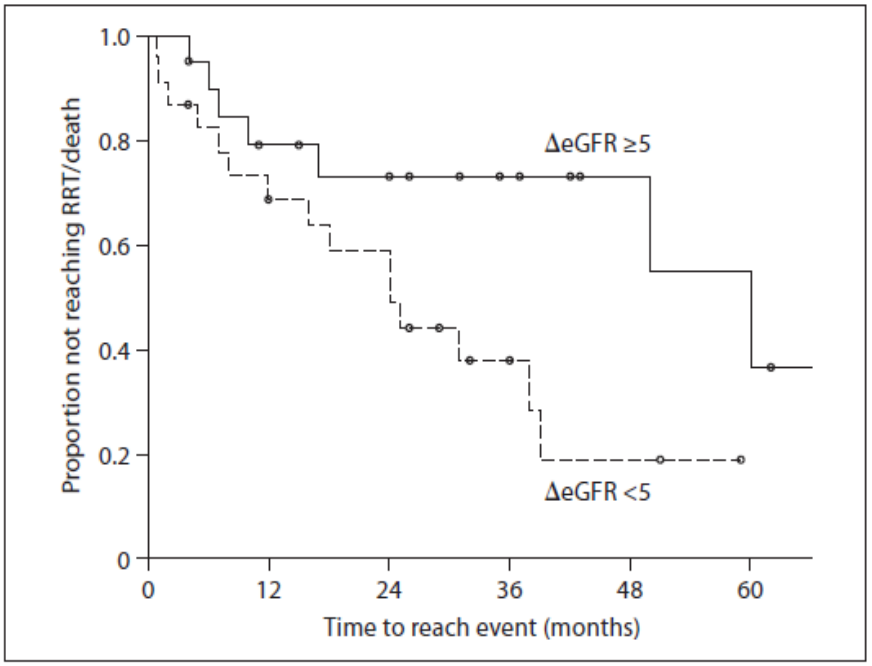
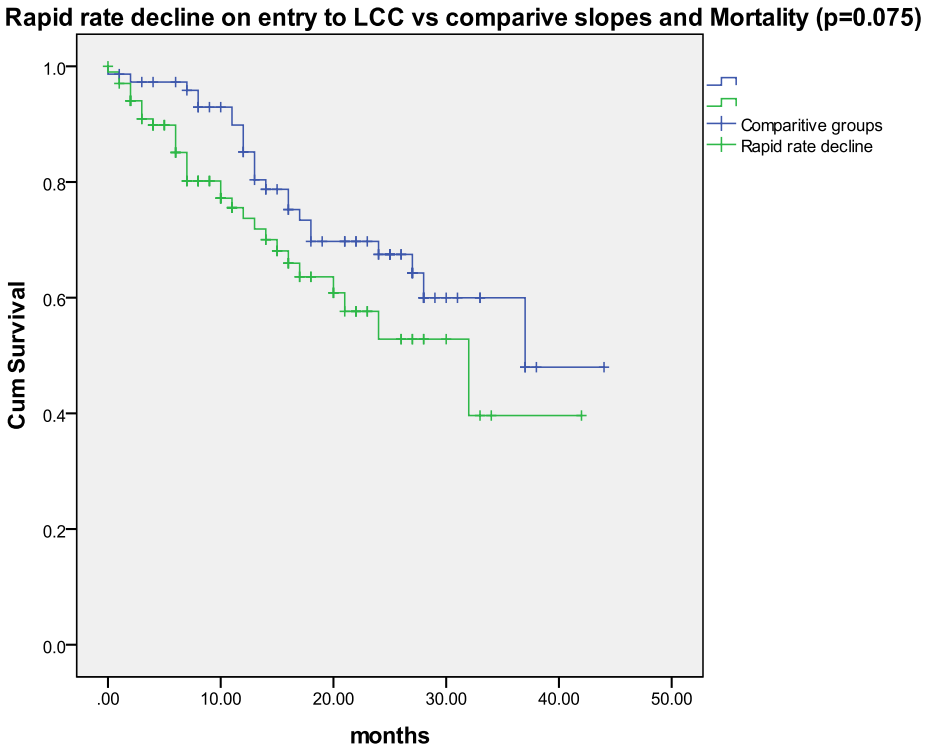


Fig. 2. Kaplan-Meier estimates of patients surviving without RRT. Time zero is when RAS inhibitors were stopped. Events were RRT or death. Solid line: patients with *baseline* to *after* eGFR increment ≥5 ml/min/1.73 m^2 (ΔeGFR ≥5); dashed line: those with eGFR increment <5 ml/min/1.73 m^2 (ΔeGFR<5). log-rank test, p = 0.03.



Comparison of >4ml/min decline versus slow decline on mortality

Goncalves AR, El Nahas M et al Nephron Clinical Practice 2011: 119: 348-354
Brown O, Bhandari S Renal Assocatiaon 2013 (abstract)

Clinical Equipoise in Advanced CKD?

- Studies have failed to dissociated beneficial effect of RAAS versus BP lowering (Hou data from 2006 on benezipril is conflicting)

- Cardio-protective effect
  - No evidence of reduced CV morbidity/mortality

- Anti-proteinuric effect – is it important in advanced CKD?
  - ?less relevant due to severe glomerulosclerosis

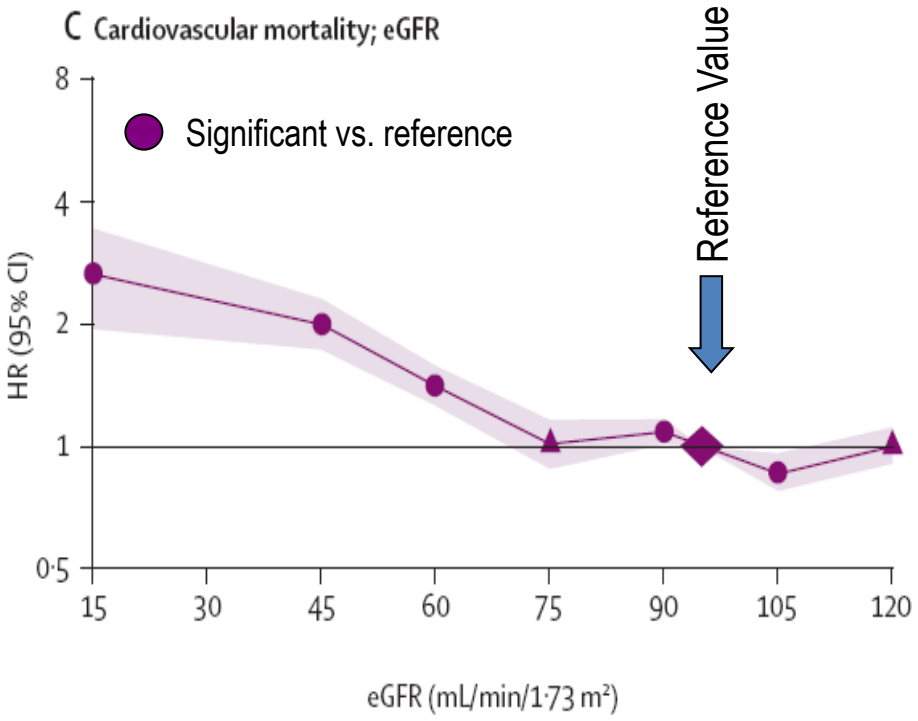
- Reduction in ESRD incidence – data lacking in advanced progressive CKD

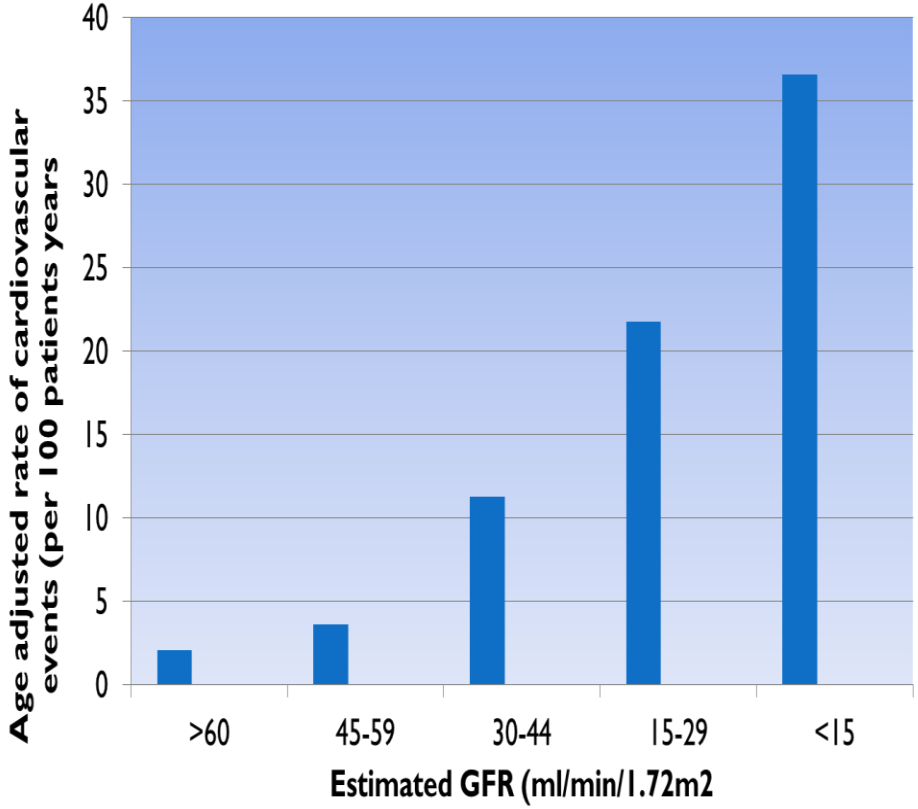
- Causes progressive renal dysfunction
- Increase hyperkalaemia
- ? Sudden cardiac death
- Increase anaemia and potentially ESA use

Retardation of CKD progression may be a strategy for CVD Protection

Kidney function is an independent risk factor for CV mortality in the general population

n=105,872





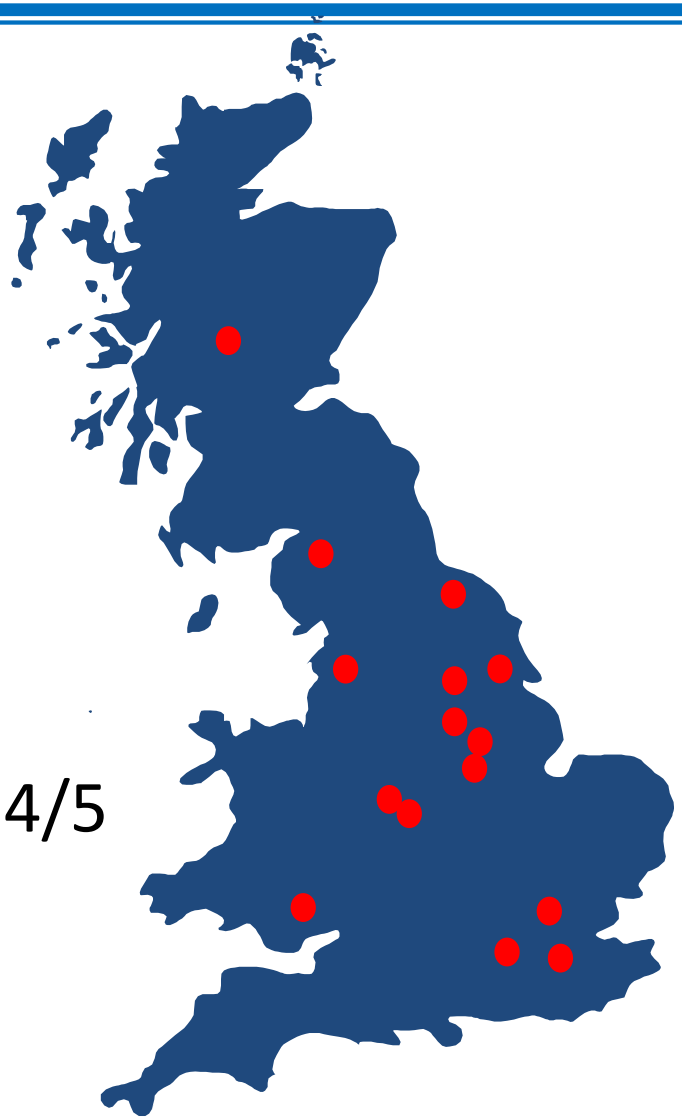
CKD Prognosis Consortium Lancet Matsushsita et al 2010; 375: 2073–2081
Go et al 2004

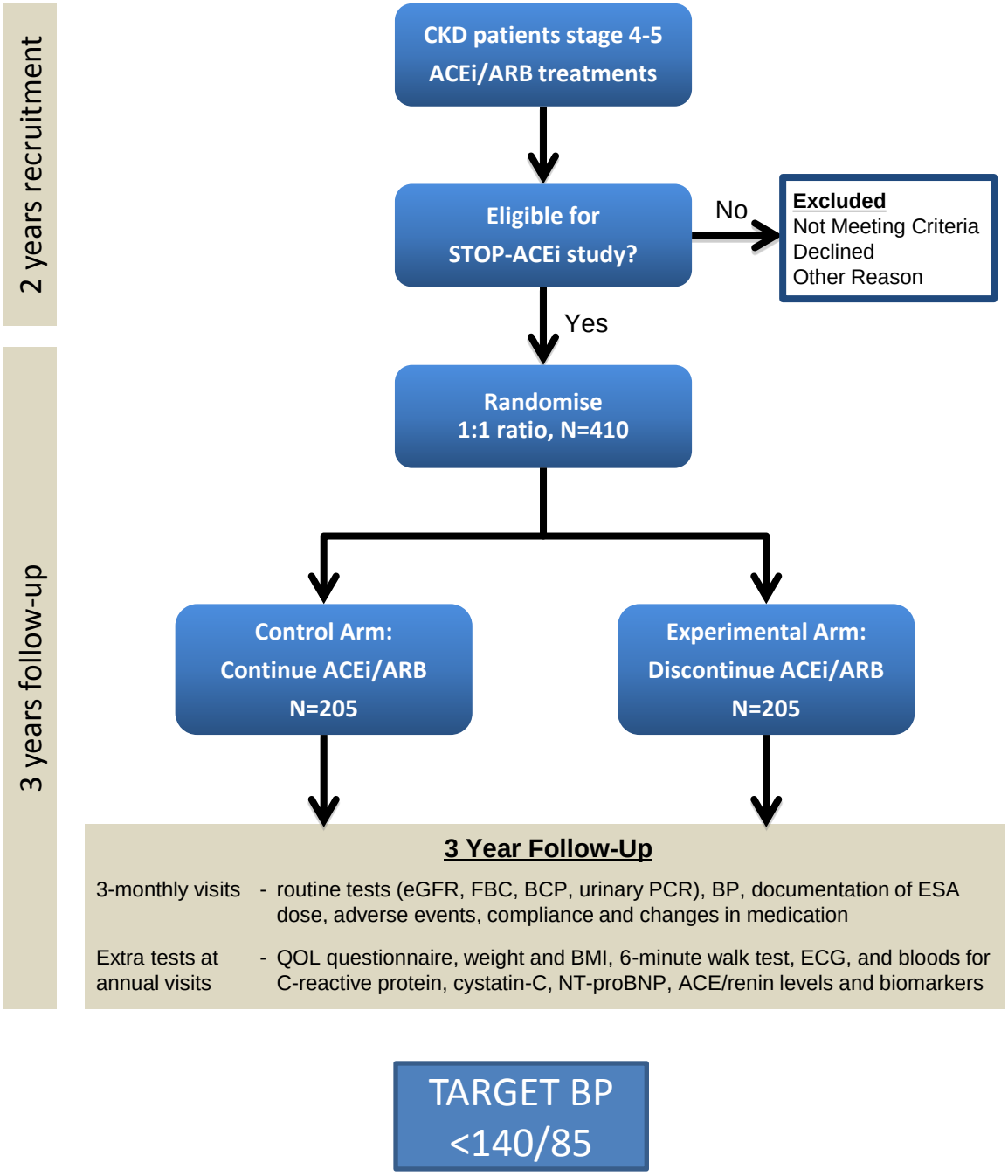
Trial Purpose - Main Research Question - Hypothesis

Stopping ACEi or ARB treatment, compared with continuing on these treatments, improves or stabilises renal function in patients with progressive stages 4 or 5 CKD based on assessment of renal function using the MDRD 4-variable eGFR at 3 years follow-up (provided good blood pressure control is maintained)

TRIAL DESIGN

- An investigator led
  - multi-centre
  - open-label
  - randomized controlled
  - clinical study
  - 410 participants
  - advanced progressive CKD Stage 4/5
  - receiving ACEi and/or ARBs





TARGET BP
<140/85

Eligibility

Key Inclusion Criteria	Key exclusion criteria
• Aged ≥18 years (male or female) • CKD stage 4 or 5 (eGFR <30mls/minute using the MDRD equation) and not on dialysis therapy • Progressive deterioration in renal function (fall in eGFR of >2ml/min/year) • Treatment with either an ACEi or ARB or a combination of both for >6 months with at least 25% of the maximum recommended daily dose • Resting blood pressure (BP) ≤160/90 mmHg • At least 3 months of specialist renal follow-up at the time of entry into the trial	• Aged <18 years • Undergoing dialysis therapy • Uncontrolled hypertension (>160/90mmHg) or requirement for 5 or more agents to control BP • History of myocardial infarction or stroke in preceding 3 months • Pregnancy or breastfeeding • Immune mediated renal disease requiring disease specific therapy

Screening and Randomisation

CKD STAGE 4 or 5

>2ml/min fall eGFR in 12months – 3 values

BP	≤160/90 mmHg
ACEi/ARB	>6/12

Consent

Randomisation -Minimisation Variables

One to one

- Online
- telephone

Computer generated programme at BCTU using a minimisation algorithm

Pre- specified

- Diabetes Mellitus
- Blood pressure MAP <100; ≥ 100(diastolic x2=systolic/3)
- Age <65; ≥ 65 years
- Proteinuria <1g; ≥ 1g
- eGFR <15 ≥ 15 ml/min

Objectives - End-point

410 patients with eGFR <30ml/min and >2ml/min/year loss of eGFR over I year – 3 measures and BP ≤160/90 mmHg and on ACEi/ARB for at least 3 months

ACEi/ARB	STOP- ACEi

Primary Endpoint = 5ml difference at 3 years in eGFR based on MDRD (effect size 0.31 with 80% power and alpha =0.05)

BP	Hospitalisation rates	Urine PCR
RRT/>50% decline	6 minutes walk test	Hb concentration
Time to reach ESRD/RRT	Cardiac events	Change in
Cystatin C	Survival	ESA use
	KD QOL	

Trial visits and procedures (assessments)

- Screening, baseline and randomisation
- Telephone follow-up at 4-6 weeks post-randomisation
- 3-monthly follow-up visits for 3 years

Baseline	Informed consent	Randomisation	Demographics
	Medical history	CKD aetiology	Lifestyle indicators
	Baseline medications		
Telephone follow-up	Compliance	Medication changes	AEs
3-monthly visits	Blood pressure	eGFR	Biochemistry +PCR
	FBC	ESA dose	AEs
	Compliance	Medication changes	
Annual visits	QOL questionnaire	Weight & BMI	6-minute walk test
	ECG	CRP	Cystatin-C
	NT-proBNP	ACE/renin levels	Biomarker samples

Trial visits and procedures

Trial visit number		1	Phone call	2	3	4	5	6	7	8	9	10	11	12	13
Visit/month (± 2 weeks)	Screening	Baseline		3	6	9	12	15	18	21	24	27	30	33	36
Inclusion and exclusion criteria	Y	Y													
Informed consent / randomisation		Y													
Demographics: Date of birth, gender, ethnicity		Y													
Medical history including cardiovascular co-morbidity & CKD aetiology		Y													
Smoking status / alcohol intake		Y													
Height		Y													
Weight / BMI		Y					Y				Y				Y
Blood pressure		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Record ESA dose		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Record data from cardiac echo †		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Changes to anti-hypertensive / con-medication ‡		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Compliance with the trial treatment allocation		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Adverse event documentation		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Routine tests														
eGFR and BCP*		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
FBC**		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Urinary PCR by early morning spot urine		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
CRP		Y					Y				Y				Y
	Additional tests														
Six minute walk test		Y					Y				Y				Y
KDQOL-SF™ v1.3 Questionnaire		Y					Y				Y				Y
12 Lead ECG		Y					Y				Y				Y
Cystatin-C / NT proBNP / ACE / Renin		Y					Y				Y				Y
Serum and urine samples for biomarker analysis ***		Y					Y								Y

Questions?

Ensuring Patient Safety

- **DMEC will monitor relatedness of adverse events**
- **Cardiac events**