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

## Investigator Meeting

1st May 2015, University of Birmingham Medical School


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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
- New Research

# The Renin-Angiotensin-Aldosterone System


Angiotensinogen

Renin

Angiotensin I

Angiotensin escape
- Chymase
- Cathespsin G

ACE

ACEi

Angiotensin II

ARB

Adrenal glomerulosa

spironolactone

Aldosterone

CKD

Biological Integrity and function

Haemodynamic Changes

NA/K exchanger

TGF-b and cytokine cascade

Sodium Retention Via ENac

Glomerular capillary Pressure

K loss
Mg loss
NA

Cell proliferation & angiogenesis

Type IV collagen production

IL-6 and superoxide

proteinuria

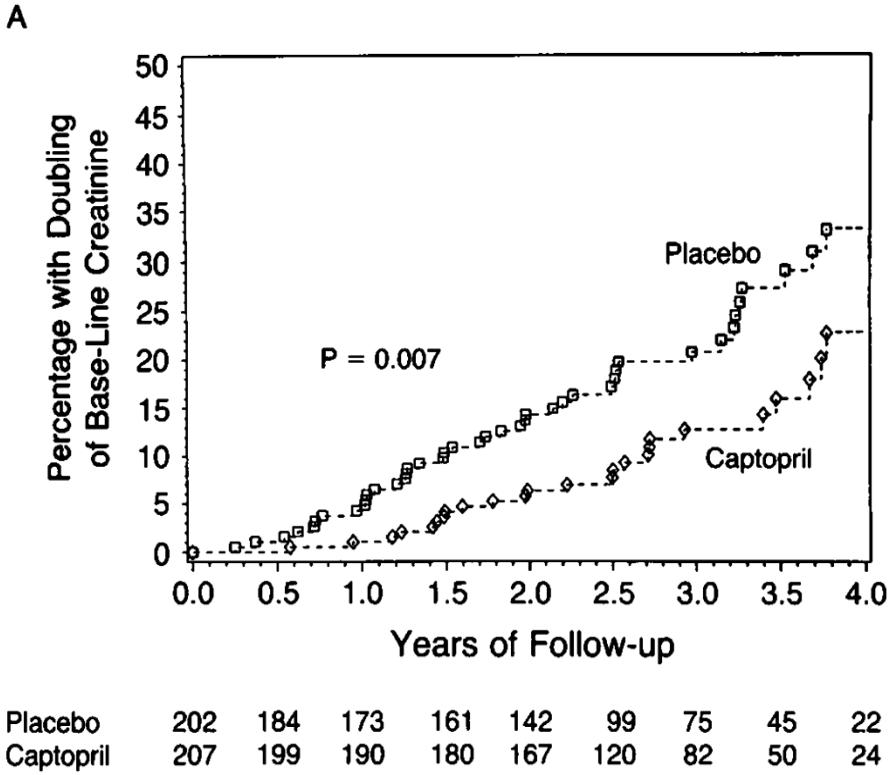
Increase BP

renal growth

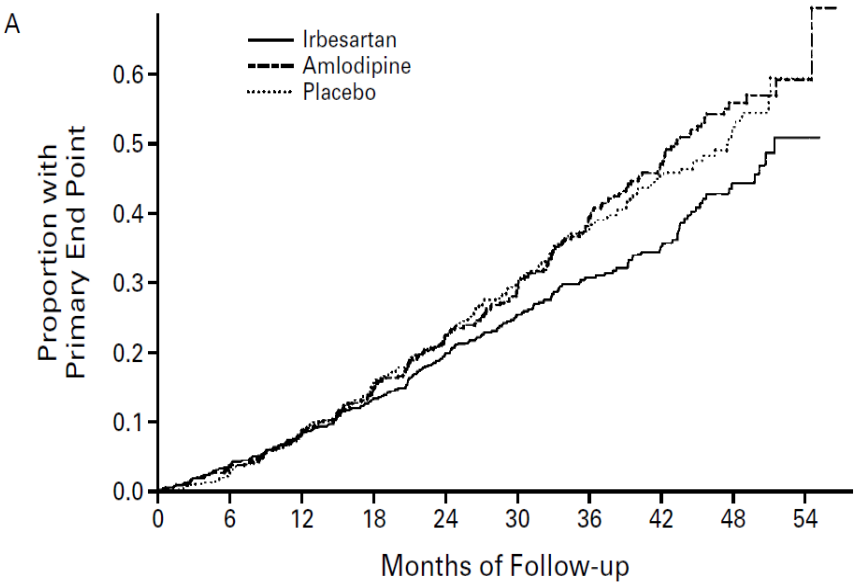
ECM Accumulation

Tubulointerstitial fibrosis and glomerulosclerosis

# Seminal - Lewis Studies




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



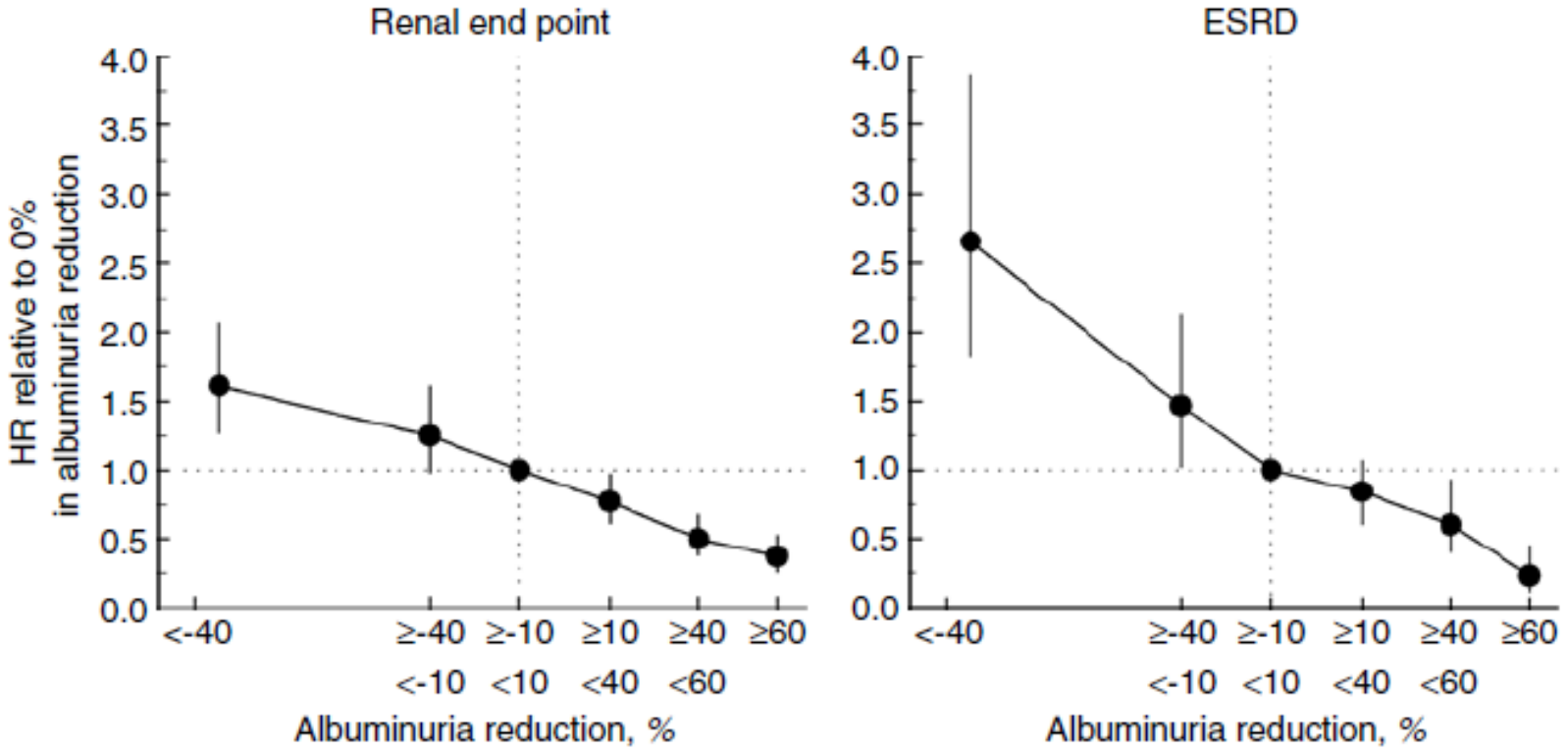

| No. at Risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Irbesartan | 579 | 555 | 528 | 496 | 400 | 304 | 216 | 146 | 65 |
| Amlodipine | 565 | 542 | 508 | 474 | 385 | 287 | 187 | 128 | 46 |
| Placebo | 568 | 551 | 512 | 471 | 401 | 280 | 190 | 122 | 53 |

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 |

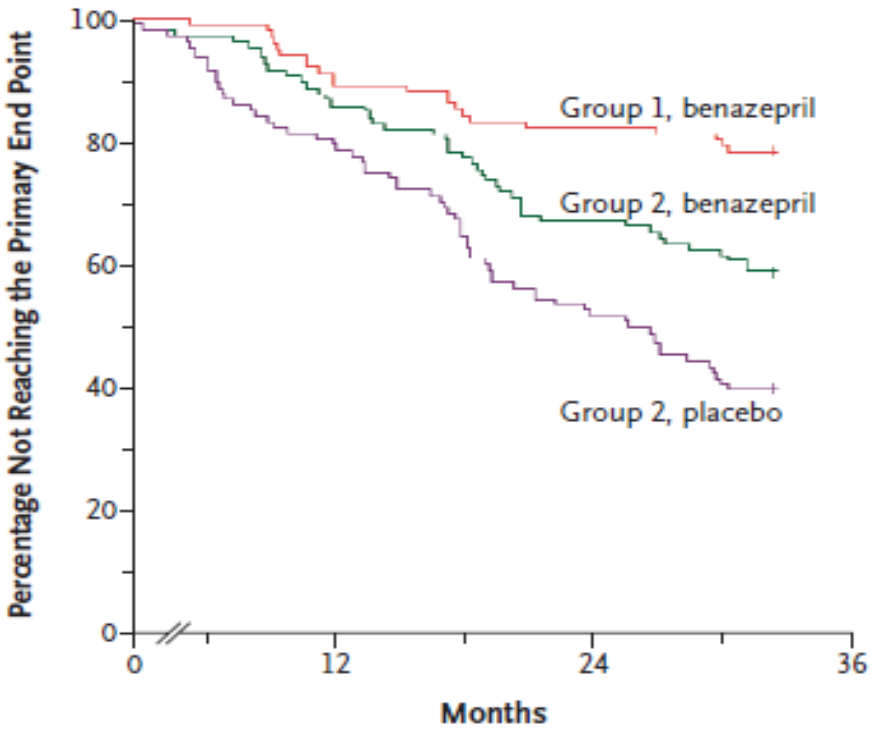
# ACEi in advanced CKD, creatinine > 273umol/L

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

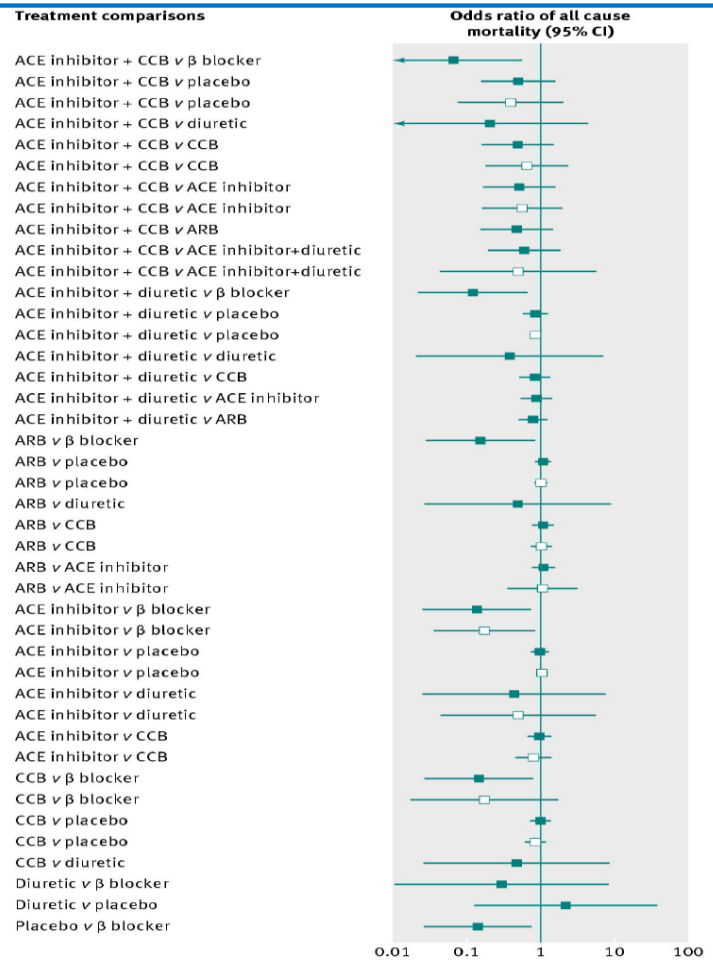
Suissa et al KI 2006:69. 913-919

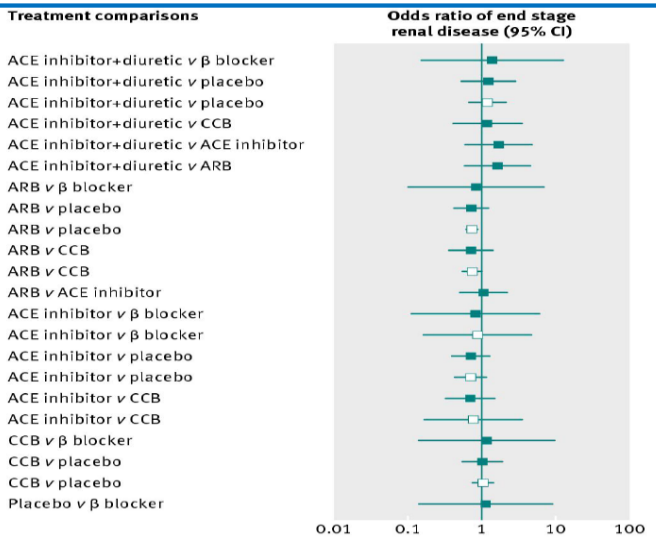
# Is it all Blood Pressure?

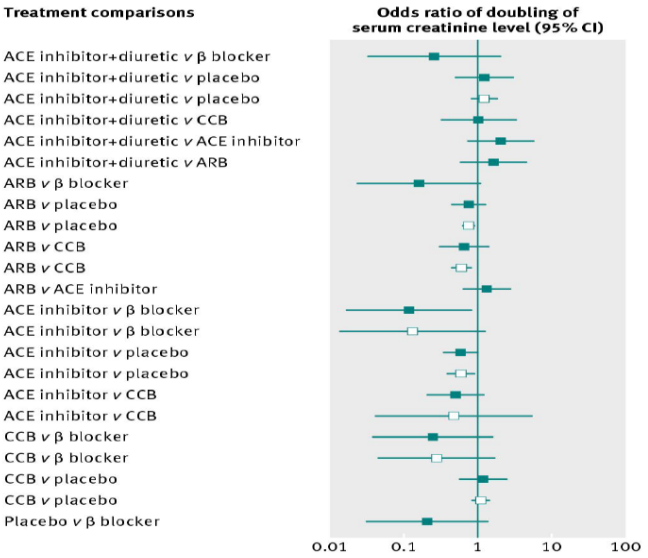
Or a specific ACEi effect for CVD and CKD protection?

The data from AASK and REIN-2 with a 14 mmHg and 4.8 mmHg difference in systolic BP suggest that patients with substantially 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 independent of drug class




***BMJ October 2013***

# On Target Study

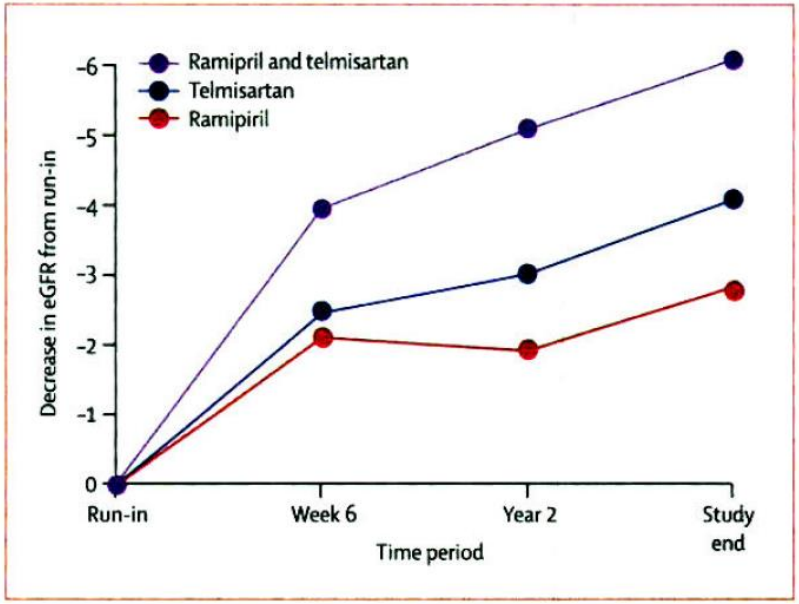
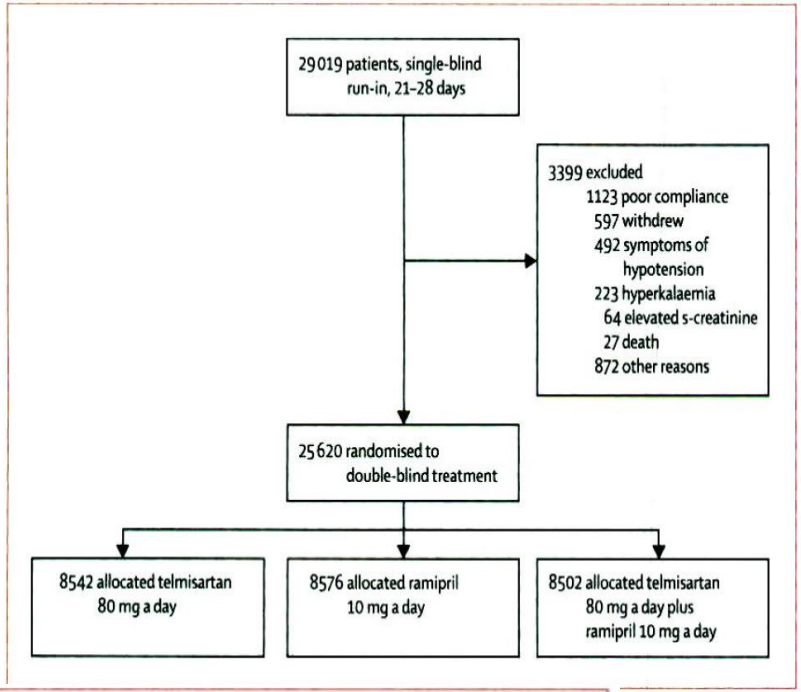



***Figure 2:*** **Decrease in estimated glomerular filtration rate (eGFR) during the trial, from baseline to study end**




| | 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.

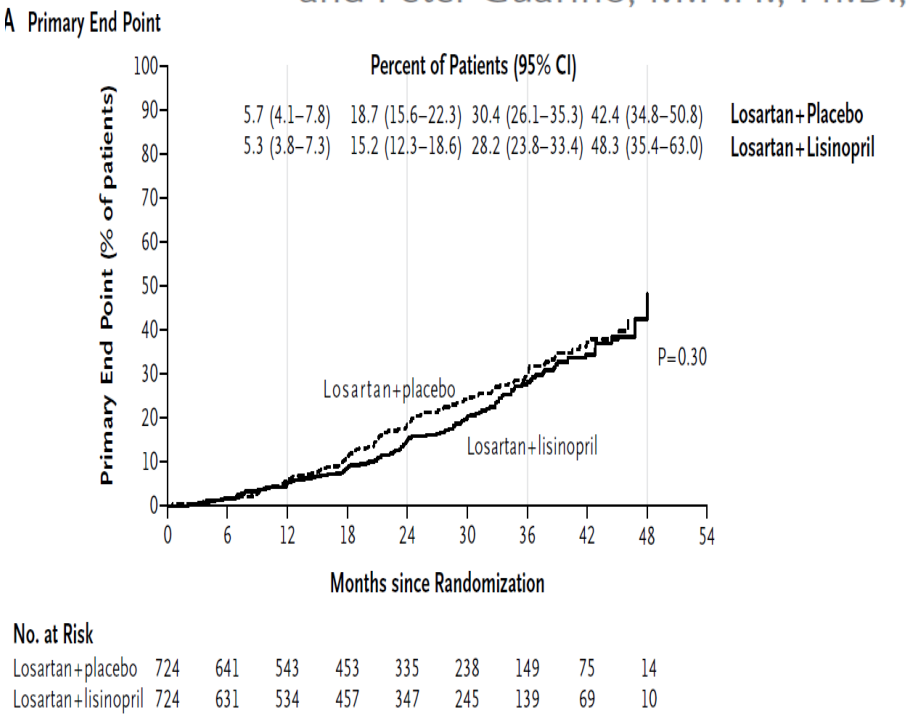
***Table 1:*** **Estimated glomerular filtration rate at baseline and changes of eGFR**

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*



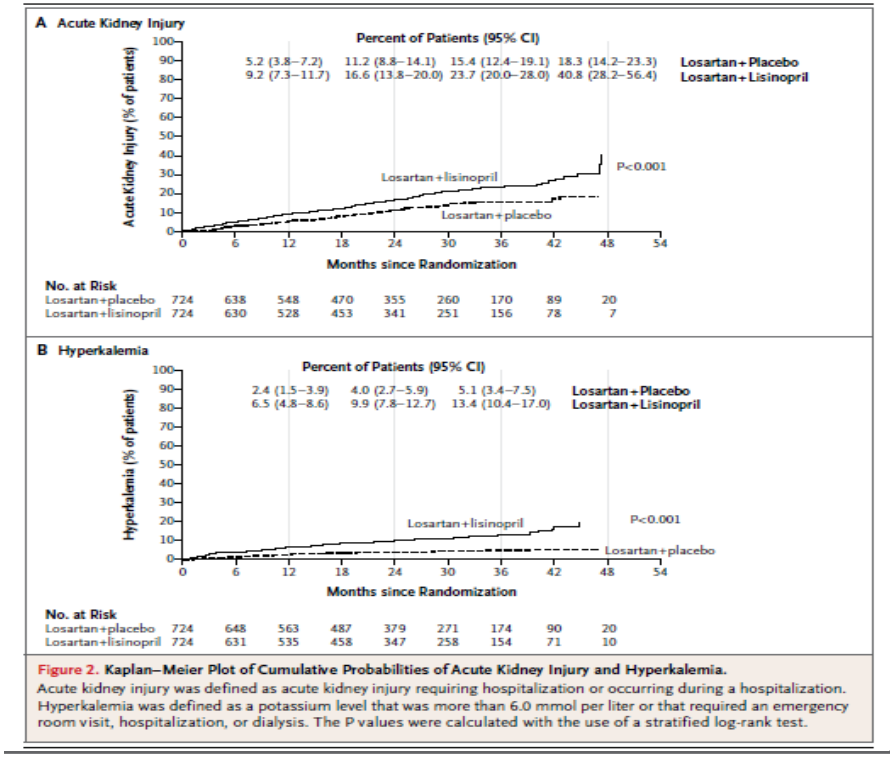
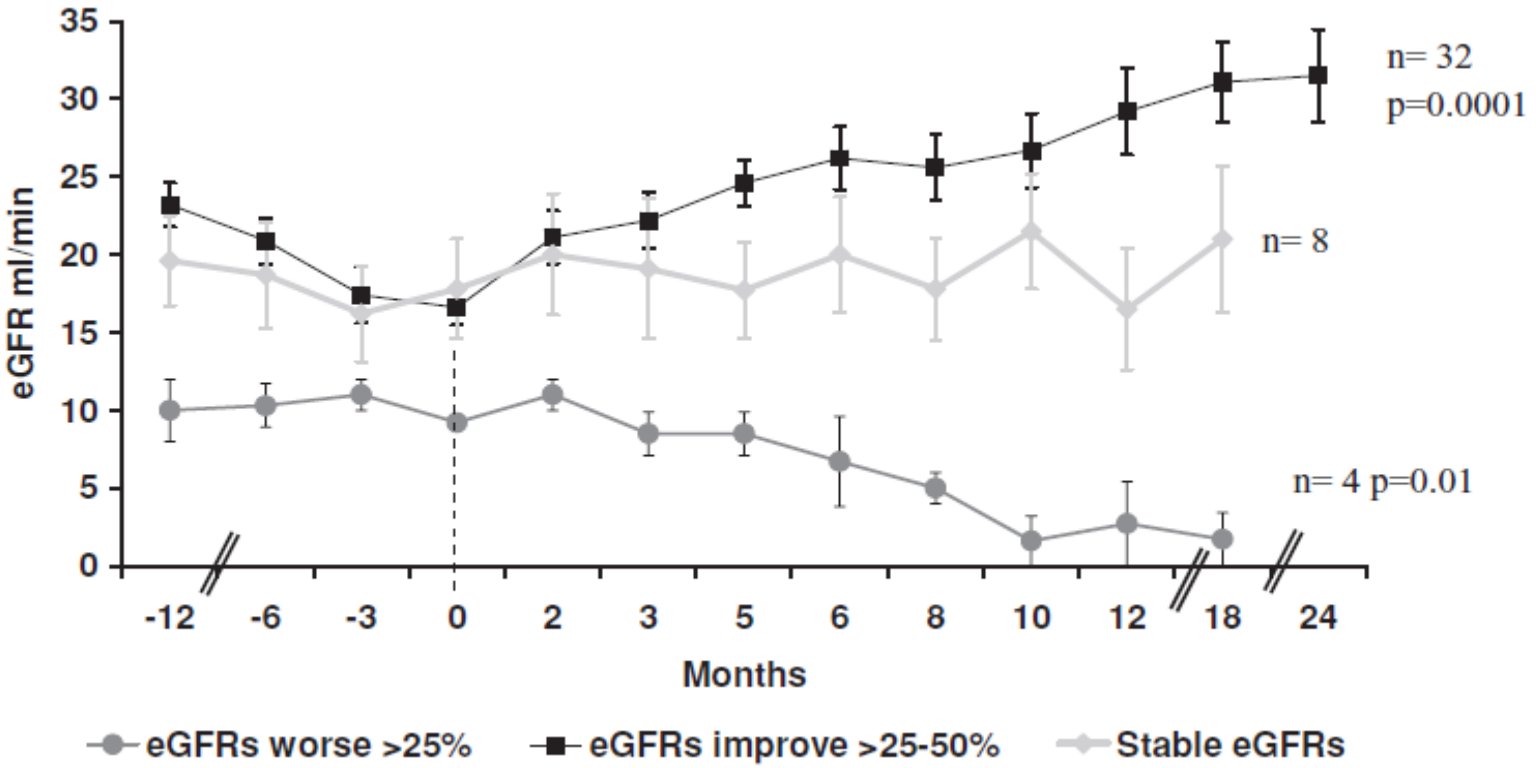




**Figure 2. Kaplan–Meier Plot of Cumulative Probabilities of Acute Kidney Injury and Hyperkalemia.**
Acute kidney injury was defined as acute kidney injury requiring hospitalization or occurring during a hospitalization. Hyperkalemia was defined as a potassium level that was more than 6.0 mmol per liter 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

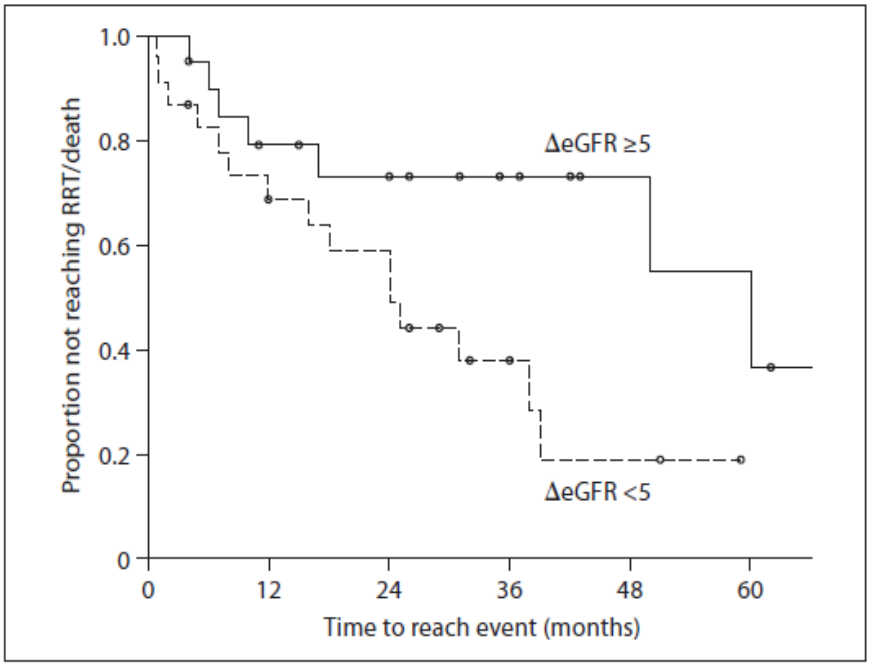
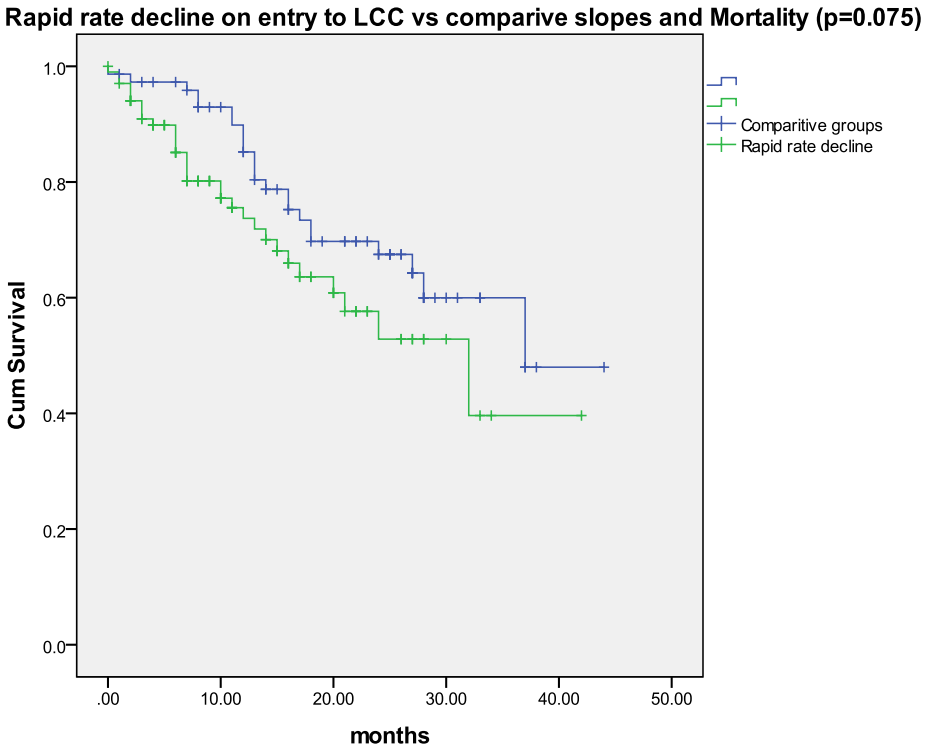



**Fig. 2.** Kaplan-Meier estimates of patients surviving without RRT. Time zero is when RAS inhibitors were stopped. Events were RRT or death. Solid line: patients with *baseline* to *after* eGFR increment ≥5 ml/min/1.73 $m^2$ (ΔeGFR ≥5); dashed line: those with eGFR increment <5 ml/min/1.73 $m^2$ (ΔeGFR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

# EQUIPOISE for a Study

- As GFR falls below 30 ml/min (stages 4 to 5), the situation changes: the vessels stiffen and calcify, statins lose their effectiveness, the heart often fails and the evidence base for clinical decision making becomes scanty.
- **Cardio-protective effect**
  - No clear evidence of reduced or increased CV morbidity/mortality
  - In non CKD – many studies – YES
  - Heart failure some post hoc evidence
  - No studies in advanced non dialysis CKD
- **Anti-proteinuric effect** – is it important in advanced CKD?
  - ?less relevant due to severe glomerulosclerosis
- **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**

# Decline in Estimated Glomerular Filtration Rate and Subsequent Risk of End-Stage Renal Disease and Mortality

JAMA June 25, 2014 Volume 311, Number 24

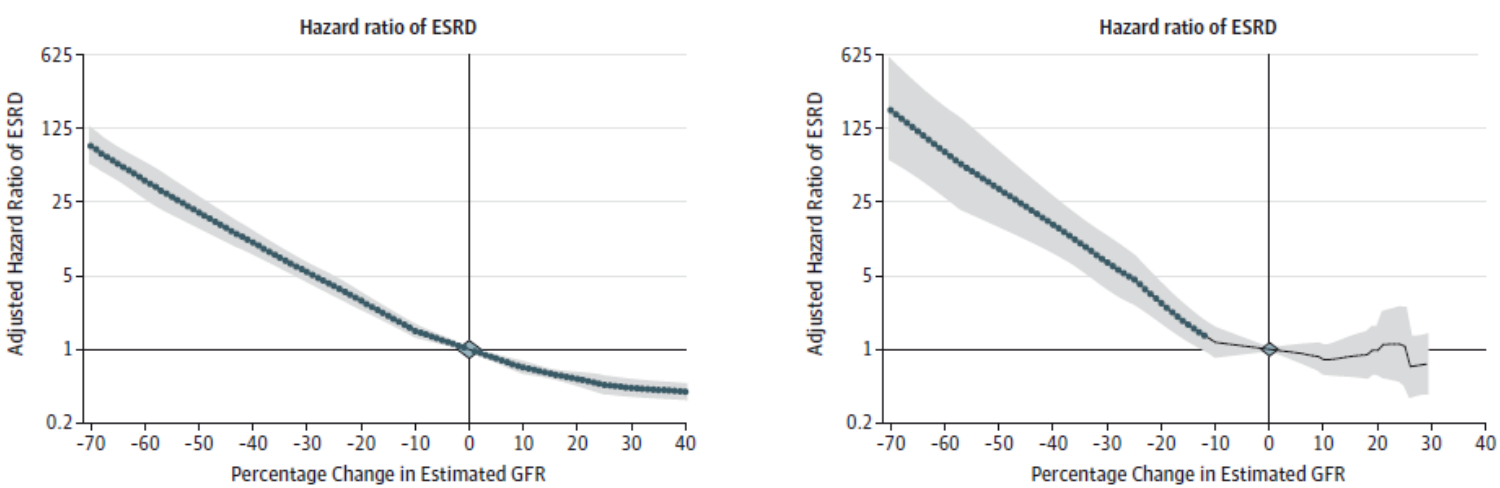
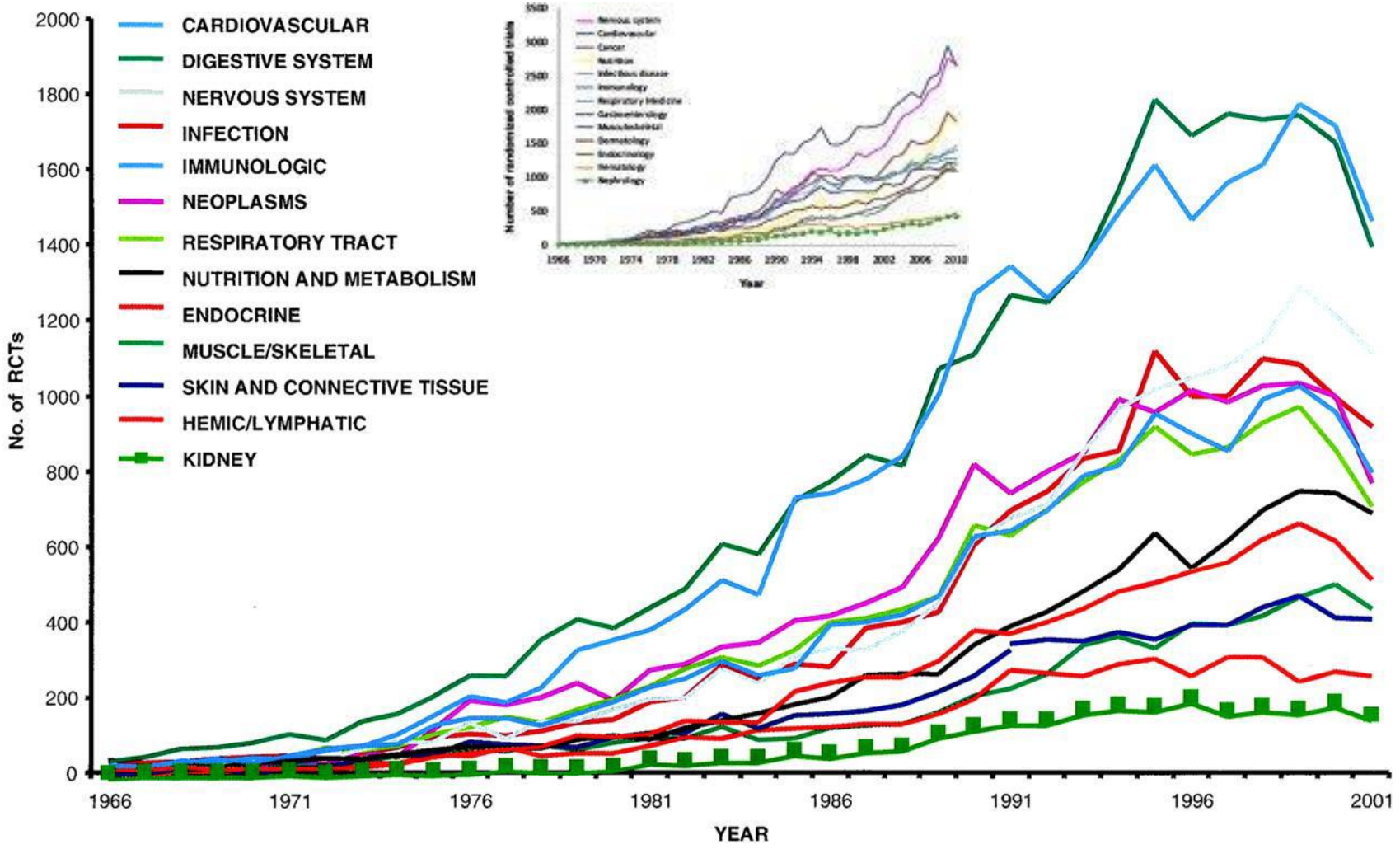



**Figure 2. Risk of End-Stage Renal Disease by Change in Estimated Glomerular Filtration Rate (GFR) During a 2-Year Baseline Period, First Estimated GFR, and Subsequent Follow-up**

| First Estimated GFR During a 2-Year Baseline Period | Follow-up After Last Estimated GFR, y | Change in Estimated GFR During 2-Year Baseline Period, % | | | | | |
|---|---|---|---|---|---|---|---|
| | | -57 | -40 | -30 | -25 | -20 | 0 (Stable) |
| 20 | 1 | 63 | 31 | 19 | 15 | 11 | 3.9 |
| | 3 | 97 | 72 | 52 | 43 | 34 | 13 |
| | 5 | 100 | 94 | 80 | 71 | 60 | 26 |
| | 10 | 100 | 100 | 99 | 97 | 92 | 57 |
| 35 | 1 | 20 | 8.1 | 4.8 | 3.7 | 2.7 | 0.95 |
| | 3 | 54 | 25 | 16 | 12 | 9.2 | 3.3 |
| | 5 | 82 | 47 | 31 | 25 | 19 | 7.0 |
| | 10 | 99 | 83 | 64 | 55 | 44 | 18 |

# RCTs for intervention in Kidney Disease




*Strippoli GFM et al JASN 2004; 15, 411-419*

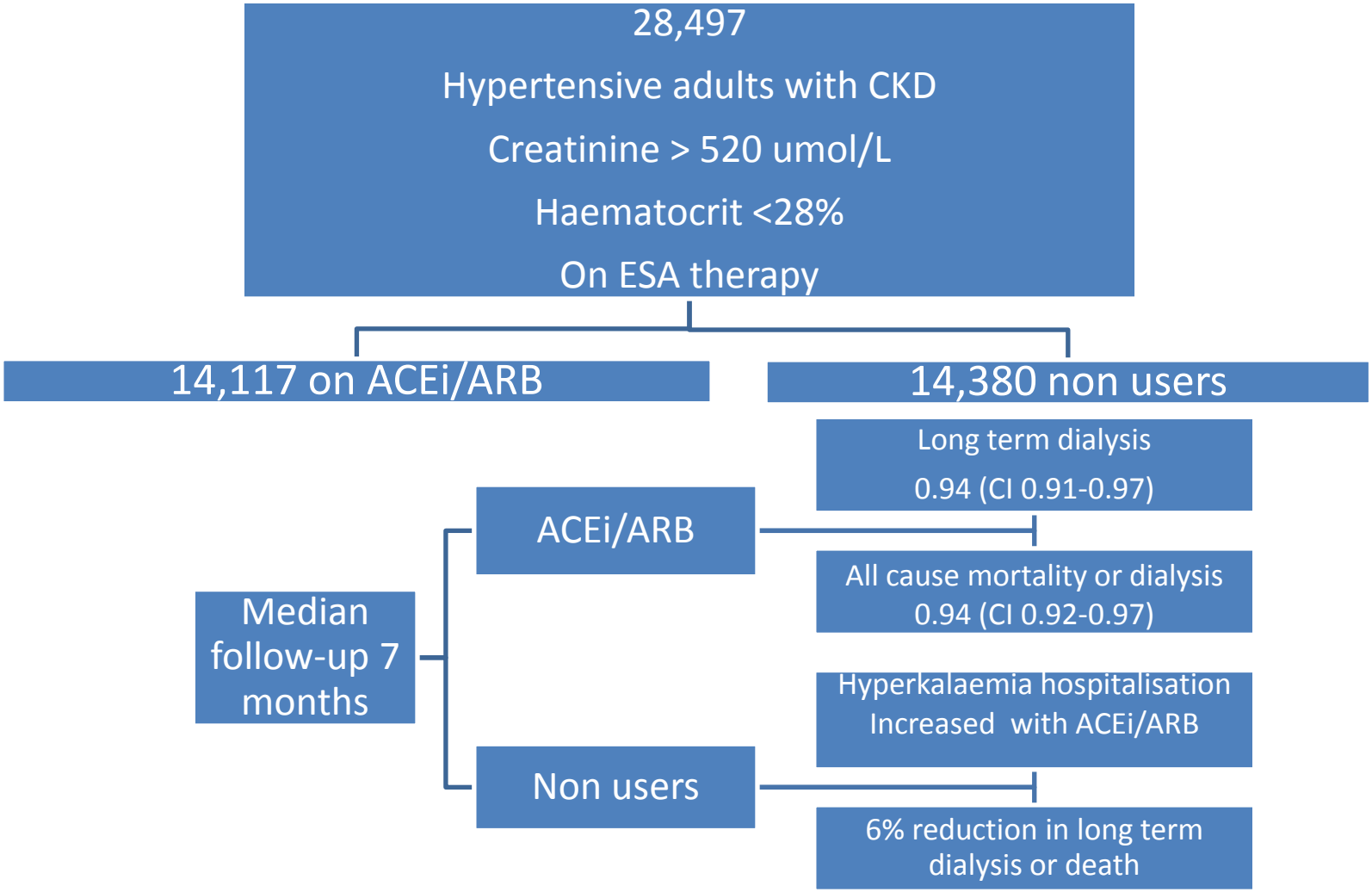
# View of Clinicians on ACEi/ARBs

- 141,413 US veterans with CKD
- GFR >60 mls/min + proteinuria v GFR <60 ml/min
- ACEi/ARB use declined in patients as their eGFR declined
- Patients taking ACEi/ARB had lower risk for mortality (HR 0.81: CI 0.78-0.84)

Molnar MZ, Kalanter-Zadeh K et al J Am Coll Cardiol 2014; 63:650-658

# Prospective Cohort Study

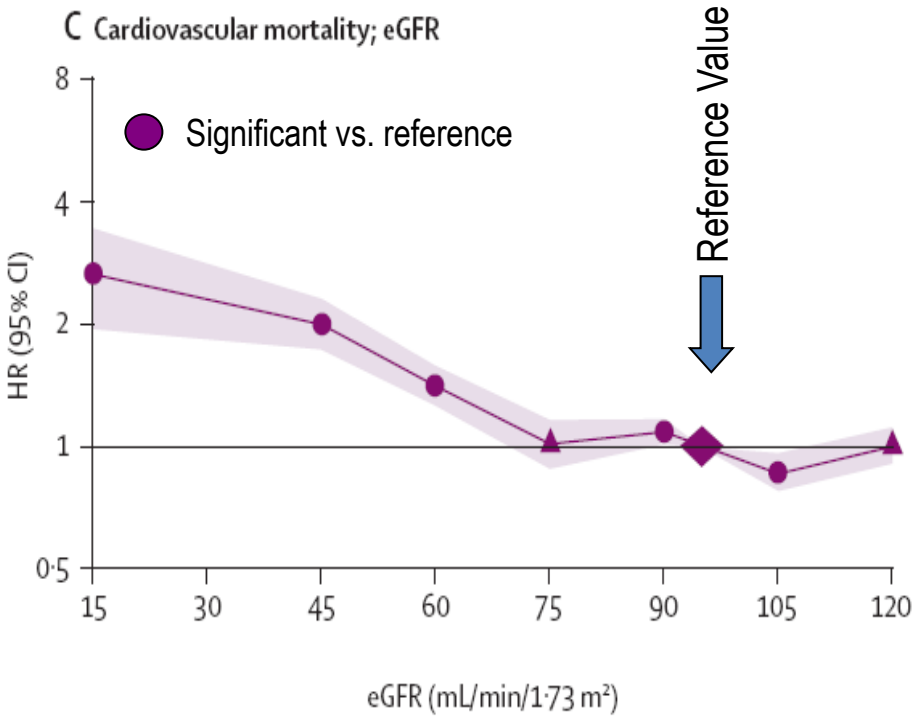
## Effectiveness and safety of ACEi/ARB use in advanced CKD

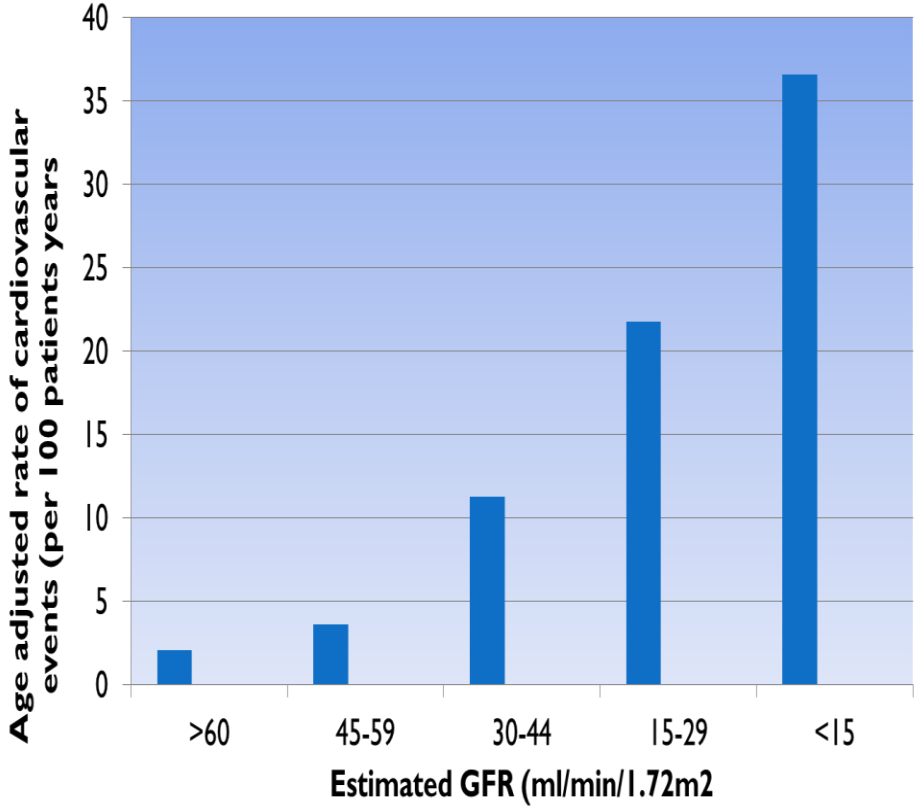



Hsu TW et al JAMA 2014

# 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*

# "Heat Maps" of risk in CKD patients

***Levey AS et al, Kidney Intern 2011;80-17-28***

Summary of relative risks from categorical meta-analysis (dipstick included) (−, ±, +, ⩾++)

### All-cause mortality

| | ACR <10 | ACR 10–29 | ACR 30–299 | ACR ⩾300 |
|---|---|---|---|---|
| eGFR >105 | 1.1 | 1.5 | 2.2 | 5.0 |
| eGFR 90–105 | Ref | 1.4 | 1.5 | 3.1 |
| eGFR 75–90 | 1.0 | 1.3 | 1.7 | 2.3 |
| eGFR 60–75 | 1.0 | 1.4 | 1.8 | 2.7 |
| eGFR 45–60 | 1.3 | 1.7 | 2.2 | 3.6 |
| eGFR 30–45 | 1.9 | 2.3 | 3.3 | 4.9 |
| eGFR 15–30 | 5.3 | 3.6 | 4.7 | 6.6 |

### Cardiovascular mortality

| | ACR <10 | ACR 10–29 | ACR 30–299 | ACR ⩾300 |
|---|---|---|---|---|
| eGFR >105 | 0.9 | 1.3 | 2.3 | 2.1 |
| eGFR 90–105 | Ref | 1.5 | 1.7 | 3.7 |
| eGFR 75–90 | 1.0 | 1.3 | 1.6 | 3.7 |
| eGFR 60–75 | 1.1 | 1.4 | 2.0 | 4.1 |
| eGFR 45–60 | 1.5 | 2.2 | 2.8 | 4.3 |
| eGFR 30–45 | 2.2 | 2.7 | 3.4 | 5.2 |
| eGFR 15–30 | 14 | 7.9 | 4.8 | 8.1 |

### Kidney failure (ESRD)

| | ACR <10 | ACR 10–29 | ACR 30–299 | ACR ⩾300 |
|---|---|---|---|---|
| eGFR >105 | Ref | Ref | 7.8 | 18 |
| eGFR 90–105 | Ref | Ref | 11 | 20 |
| eGFR 75–90 | Ref | Ref | 3.8 | 48 |
| eGFR 60–75 | Ref | Ref | 7.4 | 67 |
| eGFR 45–60 | 5.2 | 22 | 40 | 147 |
| eGFR 30–45 | 56 | 74 | 294 | 763 |
| eGFR 15–30 | 433 | 1044 | 1056 | 2286 |

### Acute kidney injury (AKI)

| | ACR <10 | ACR 10–29 | ACR 30–299 | ACR ⩾300 |
|---|---|---|---|---|
| eGFR >105 | Ref | Ref | 2.7 | 8.4 |
| eGFR 90–105 | Ref | Ref | 2.4 | 5.8 |
| eGFR 75–90 | Ref | Ref | 2.5 | 4.1 |
| eGFR 60–75 | Ref | Ref | 3.3 | 6.4 |
| eGFR 45–60 | 2.2 | 4.9 | 6.4 | 5.9 |
| eGFR 30–45 | 7.3 | 10 | 12 | 20 |
| eGFR 15–30 | 17 | 17 | 21 | 29 |

### Progressive CKD

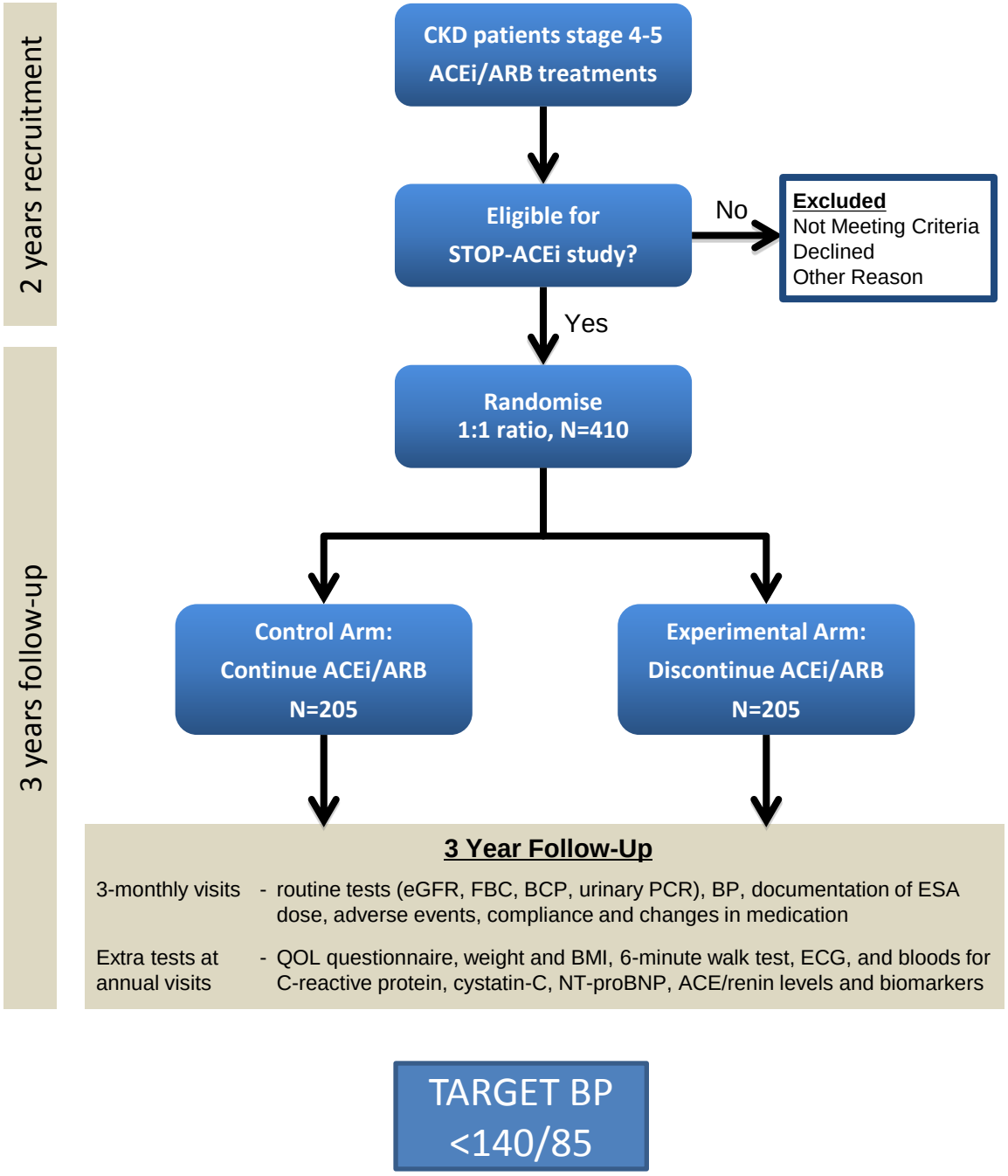
| | ACR <10 | ACR 10–29 | ACR 30–299 | ACR ⩾300 |
|---|---|---|---|---|
| eGFR >105 | Ref | Ref | 0.4 | 3.0 |
| eGFR 90–105 | Ref | Ref | 0.9 | 3.3 |
| eGFR 75–90 | Ref | Ref | 1.9 | 5.0 |
| eGFR 60–75 | Ref | Ref | 3.2 | 8.1 |
| eGFR 45–60 | 3.1 | 4.0 | 9.4 | 57 |
| eGFR 30–45 | 3.0 | 19 | 15 | 22 |
| eGFR 15–30 | 4.0 | 12 | 21 | 7.7 |

# 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)<br>• CKD stage 4 or 5 (eGFR <30mls/minute using the MDRD equation) and not on dialysis therapy<br>• Progressive deterioration in renal function (fall in eGFR of >2ml/min/year)<br>• 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<br>• Resting blood pressure (BP) ≤160/90 mmHg<br>• At least 3 months of specialist renal follow-up at the time of entry into the trial | • Aged <18 years<br>• Undergoing dialysis therapy<br>• Previous kidney transplant<br>• Uncontrolled hypertension (>160/90mmHg) or requirement for 5 or more agents to control BP<br>• History of myocardial infarction or stroke in preceding 3 months<br>• Immune mediated renal disease requiring disease specific therapy |

# Pre- specified Minimisation Variables

**Pre- specified**

- Diabetes Mellitus
- Blood pressure - MAP <100 or ≥ 100 (diastolic x2=systolic/3)
- Age - <65 or ≥ 65 years
- Proteinuria - PCR <100 or ≥ 100 mg/mmol
- eGFR - <15 or ≥ 15 ml/min

# Objectives - End-point

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

| ACEi/ARB | STOP- ACEi |
|---|---|

Primary Endpoint = eGFR based on MDRD at 3 years
(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 | ESA use |
| Cystatin C | Survival | |
| | KD QOL | |

# Recent and Future Potential Targets to Slow Progression of CKD

- Inflammatory and fibrotic targets
  - Aliskerin
  - Bardoxylone (BEACON and BEAM)
  - TGF- beta
  - Cytokine retention products
  - Complement fragment products

- Aldosterone Antagonist

- SONAR

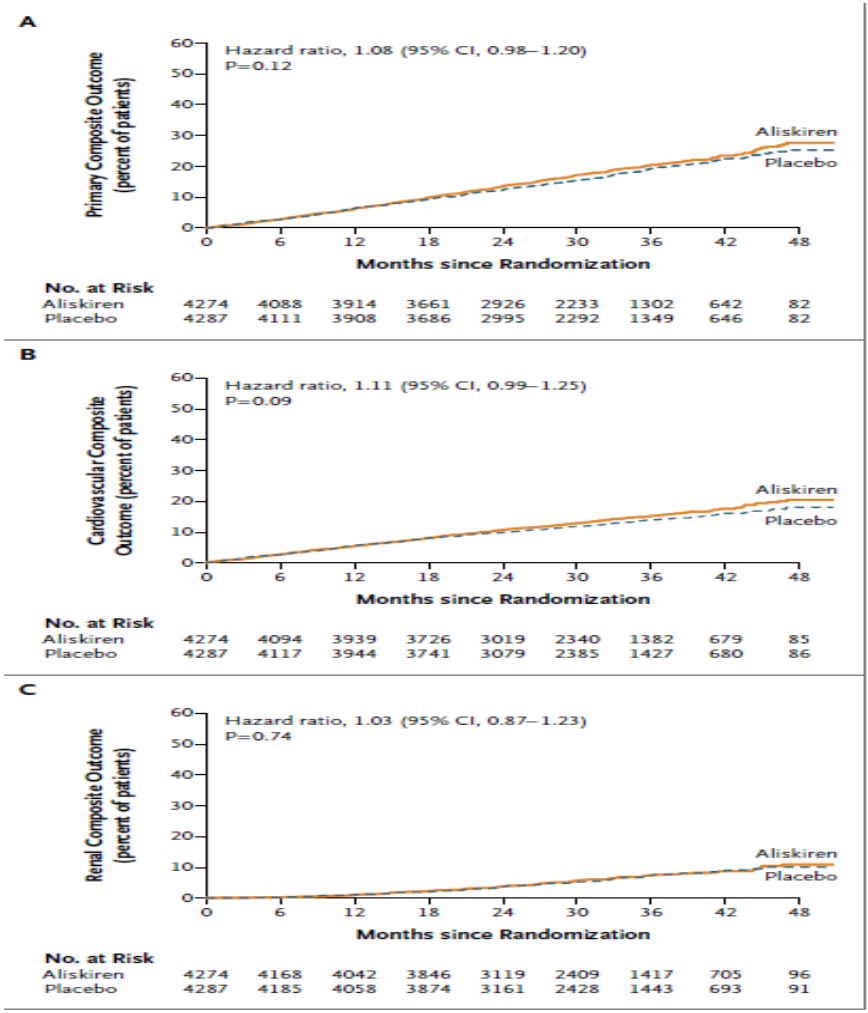
- Allopurinol

- Tolvaptan
- Oxidative stress
  - Reactive oxygen species
- Notch pathway
- APOL1

# Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes

**Table 3. Most Commonly Reported Adverse Events and Study-Drug Discontinuation.***

| Event | Any Event Reported | | P Value | Event Leading to Permanent Study-Drug Discontinuation | | P Value |
|---|---|---|---|---|---|---|
| | Aliskiren (N=4272) | Placebo (N=4285) | | Aliskiren (N=4272) | Placebo (N=4285) | |
| | *no. of patients (%)* | | | *no. of patients (%)* | | |
| Hyperkalemia | 1670 (39.1) | 1244 (29.0) | <0.001 | 205 (4.8) | 111 (2.6) | <0.001 |
| Peripheral edema | 686 (16.1) | 706 (16.5) | 0.60 | 11 (0.3) | 7 (0.2) | 0.34 |
| Hypotension | 519 (12.1) | 357 (8.3) | <0.001 | 28 (0.7) | 13 (0.3) | 0.02 |
| Diarrhea | 417 (9.8) | 312 (7.3) | <0.001 | 11 (0.3) | 7 (0.2) | 0.34 |
| Hypertension | 429 (10.0) | 469 (10.9) | 0.17 | 3 (0.1) | 9 (0.2) | 0.15 |
| Renal impairment | 418 (9.8) | 371 (8.7) | 0.07 | 65 (1.5) | 54 (1.3) | 0.30 |
| Nasopharyngitis | 405 (9.5) | 383 (8.9) | 0.39 | 1 (<0.1) | 0 | NA |
| Hypoglycemia | 393 (9.2) | 341 (8.0) | 0.04 | 1 (<0.1) | 3 (0.1) | NA |
| Back pain | 363 (8.5) | 353 (8.2) | 0.67 | 1 (<0.1) | 2 (<0.1) | NA |
| Dizziness | 327 (7.7) | 314 (7.3) | 0.57 | 4 (0.1) | 4 (0.1) | NA |
| Urinary tract infection | 326 (7.6) | 288 (6.7) | 0.10 | 4 (0.1) | 2 (<0.1) | NA |
| Anemia | 316 (7.4) | 307 (7.2) | 0.68 | 0 | 0 | — |
| Pain in extremity | 302 (7.1) | 317 (7.4) | 0.56 | 1 (<0.1) | 2 (<0.1) | NA |
| Arthralgia | 302 (7.1) | 313 (7.3) | 0.67 | 0 | 1 (<0.1) | NA |
| Cough | 265 (6.2) | 283 (6.6) | 0.45 | 1 (<0.1) | 1 (<0.1) | NA |
| Bronchitis | 242 (5.7) | 239 (5.6) | 0.86 | 0 | 0 | — |
| Dyspnea | 223 (5.2) | 213 (5.0) | 0.60 | 6 (0.1) | 5 (0.1) | 0.76 |
| Upper respiratory tract infection | 223 (5.2) | 229 (5.3) | 0.80 | 1 (<0.1) | 0 | NA |
| Cataract | 229 (5.4) | 223 (5.2) | 0.75 | 0 | 0 | — |
| Constipation | 203 (4.8) | 241 (5.6) | 0.07 | 0 | 1 (<0.1) | NA |
| Headache | 200 (4.7) | 220 (5.1) | 0.33 | 2 (<0.1) | 4 (0.1) | NA |



# Bardoxolone Methyl in Type 2 Diabetes and Stage 4 Chronic Kidney Disease

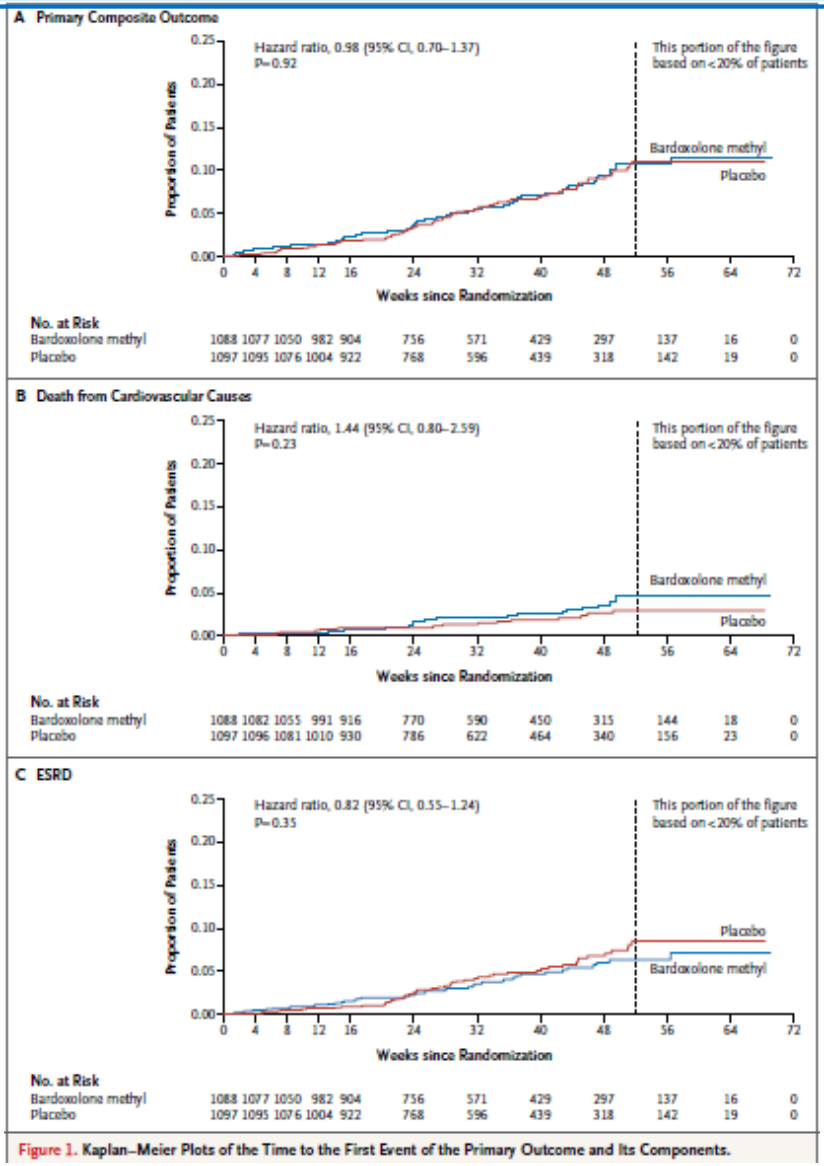



Figure 1. Kaplan–Meier Plots of the Time to the First Event of the Primary Outcome and Its Components.

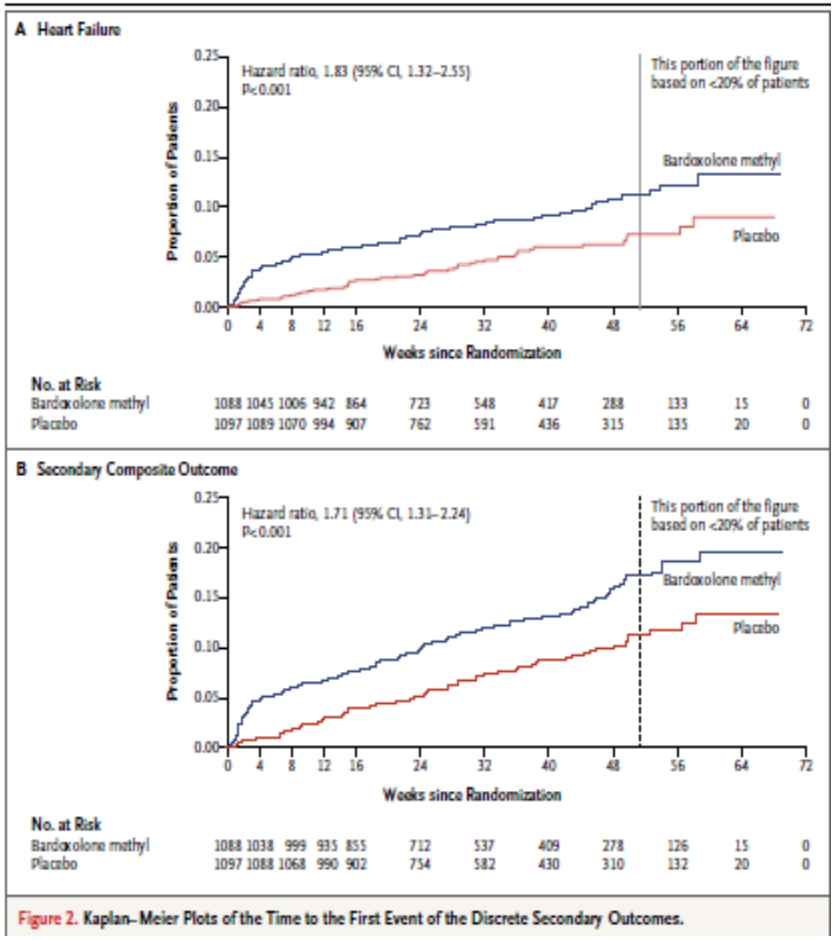



Figure 2. Kaplan–Meier Plots of the Time to the First Event of the Discrete Secondary Outcomes.

# Meta-analysis of Endothelin Antagonists

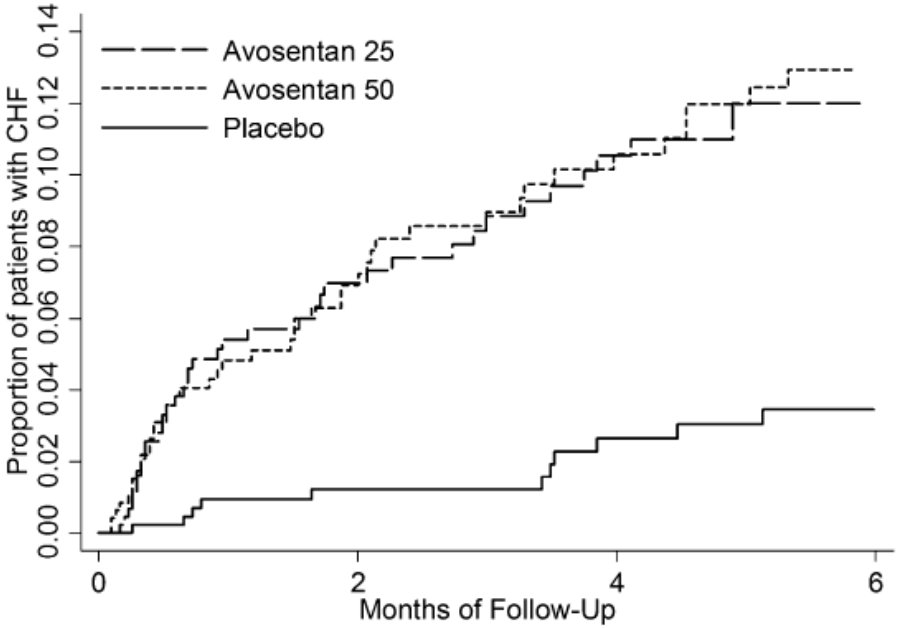
## 5 RCTs including the ASCEND Study
## Endothelin Antagonist vs Placebo
## n = 2034 participants

| | % benefit/harm | RR | CI |
|---|---|---|---|
| Albuminuria | 31% reduction | 0.69 | 0.56-0.77 |
| Death | NS | 1.49 | 0.31-2.73 |
| Cardiovascular Events | 45% increase | 1.45 | 1.07-1.97 |
| Other serious Adverse Events | 32% increase | 1.32 | 1.1-1.51 |

Yuan W et al Nephrology 2015

# Predictors of Congestive Heart Failure after Treatment with an Endothelin Receptor Antagonist

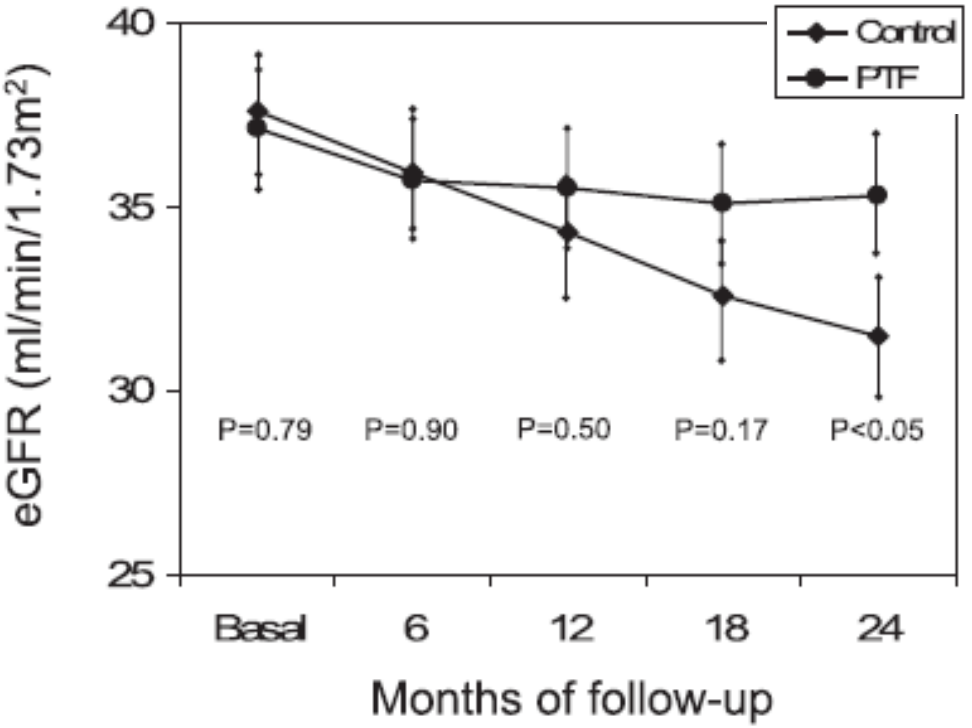
*Jamo Hoekman,* Hiddo J. Lambers Heerspink,* Giancarlo Viberti,† Damien Green,‡ Johannes F.E. Mann,§‖¶ and Dick de Zeeuw**




| Number at risk | | | | |
|---|---|---|---|---|
| Avosentan 25 | 455 | 274 | 201 | 162 |
| Avosentan 50 | 478 | 289 | 207 | 159 |
| Placebo | 459 | 347 | 263 | 207 |

# Effect of Pentoxifylline on Renal Function and Urinary Albumin Excretion in Patients with Diabetic Kidney Disease: The PREDIAN Trial

Juan F. Navarro-González,*†‡ Carmen Mora-Fernández,†‡ Mercedes Muros de Fuentes,‡§ Jesús Chahin,* María L. Méndez,* Eduardo Gallego,* Manuel Macía,* Nieves del Castillo,* Antonio Rivero,* María A. Getino,* Patricia García,* Ana Jarque,* and Javier García*




| | PTF | Placebo |
|---|---|---|
| GFR 1 y ml/min | -1.2 | -3.4 |
| GFR 2 y ml/min | -2.1 | -6.5 |
| Monthly rate | 0.08±0.14 | 0.27±0.8 |
| ACR mg/dL | -13 | +4.9 |
| BP mmHg | 140.8<br>85 | 139.8<br>83.8 |
| | | |

J Am Soc Nephrol **26:** 220–229, 2015

# LCZ696 (nephrilysin inhibitor) sacubitril and valsartan

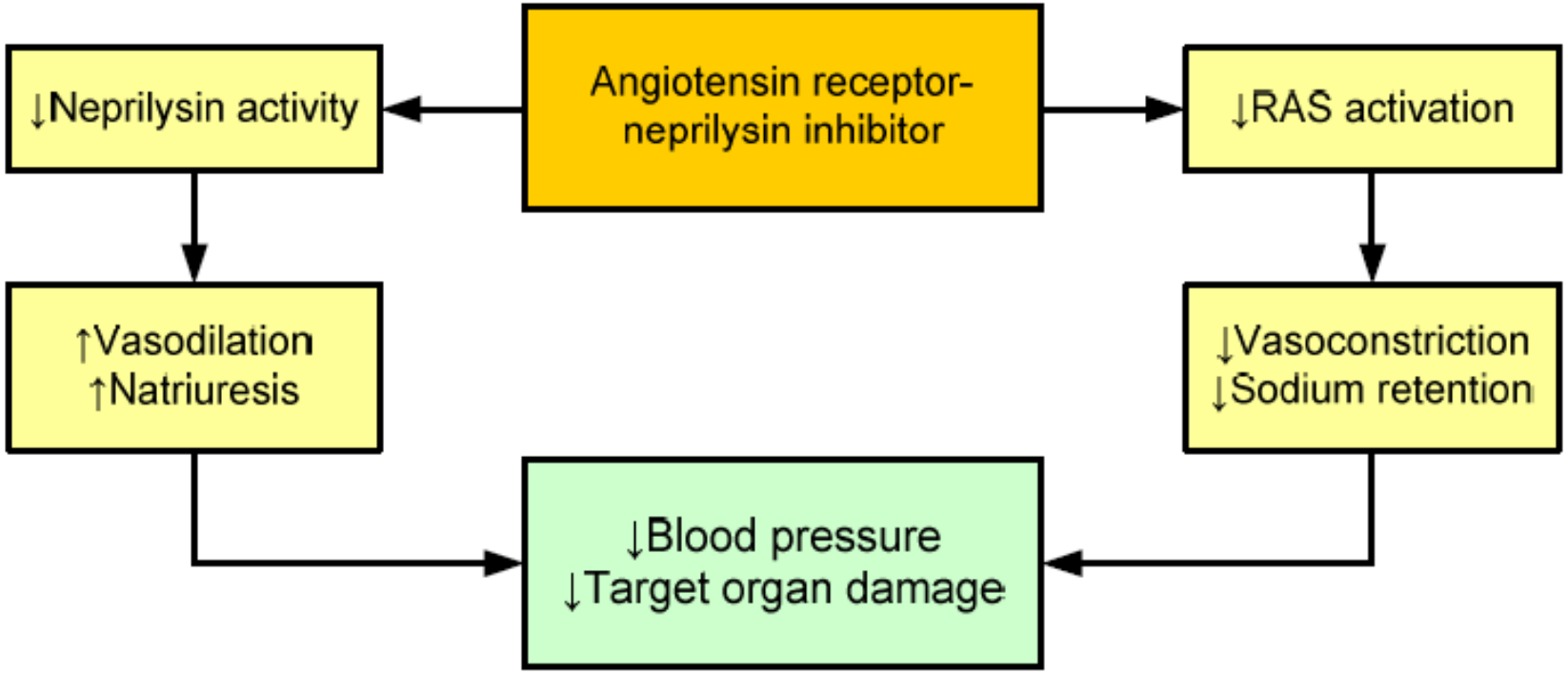
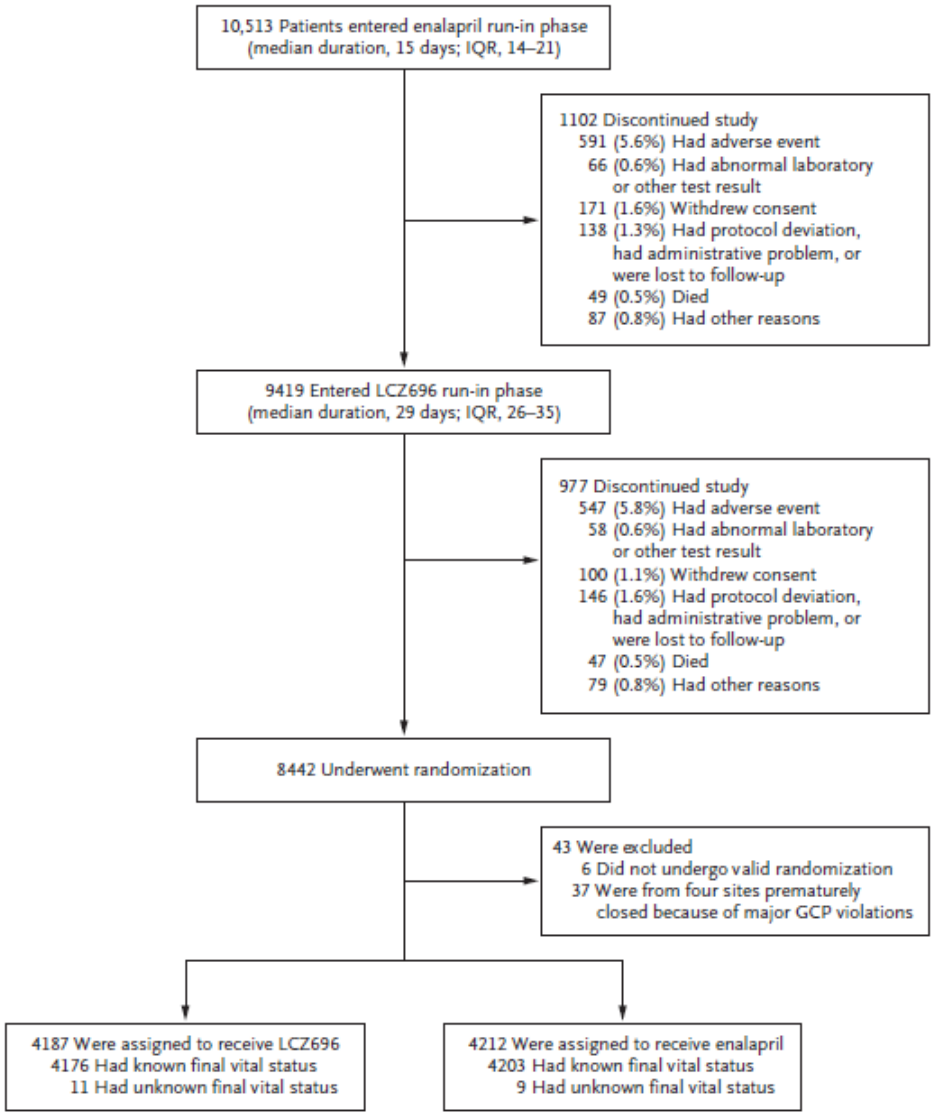



**Figure 2:** Putative synergy between neprilysin inhibition and angiotensin 2 receptor blockade

**HARPIII Study in CKD**

# PARADIGM-HF

***McMurray JJ et al N Eng Journal of Med 2014, 371: 993-1004***
***Paker M et al Circulation 2014***




LCZ696 (nephrilysin inhibitor) sacubitril and valsartan 400mg BD

Enalapril 10mg BD

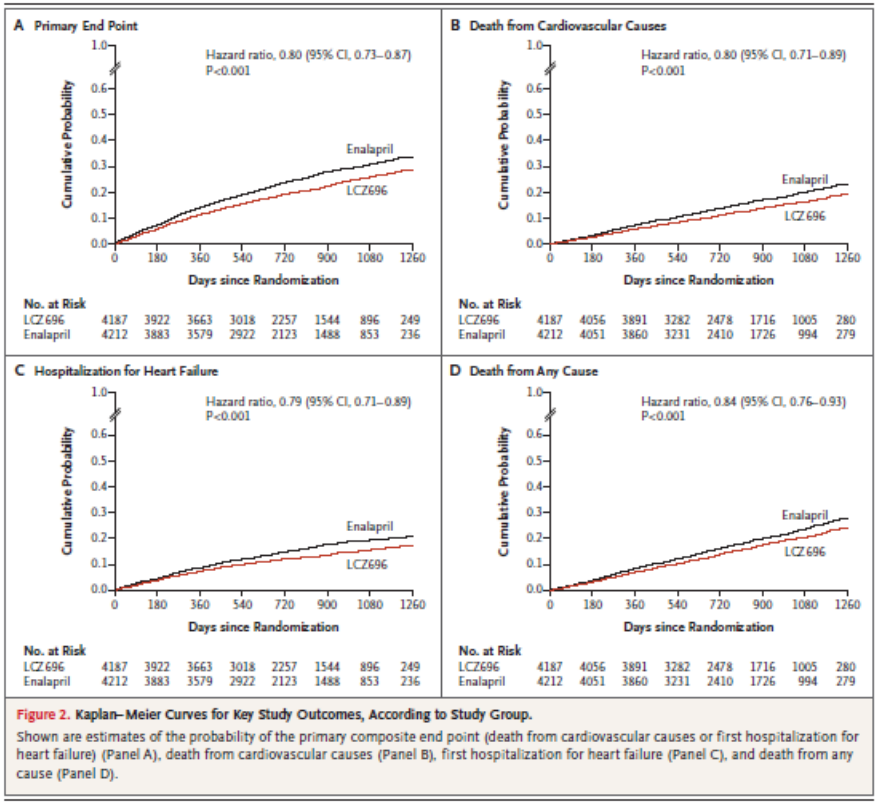
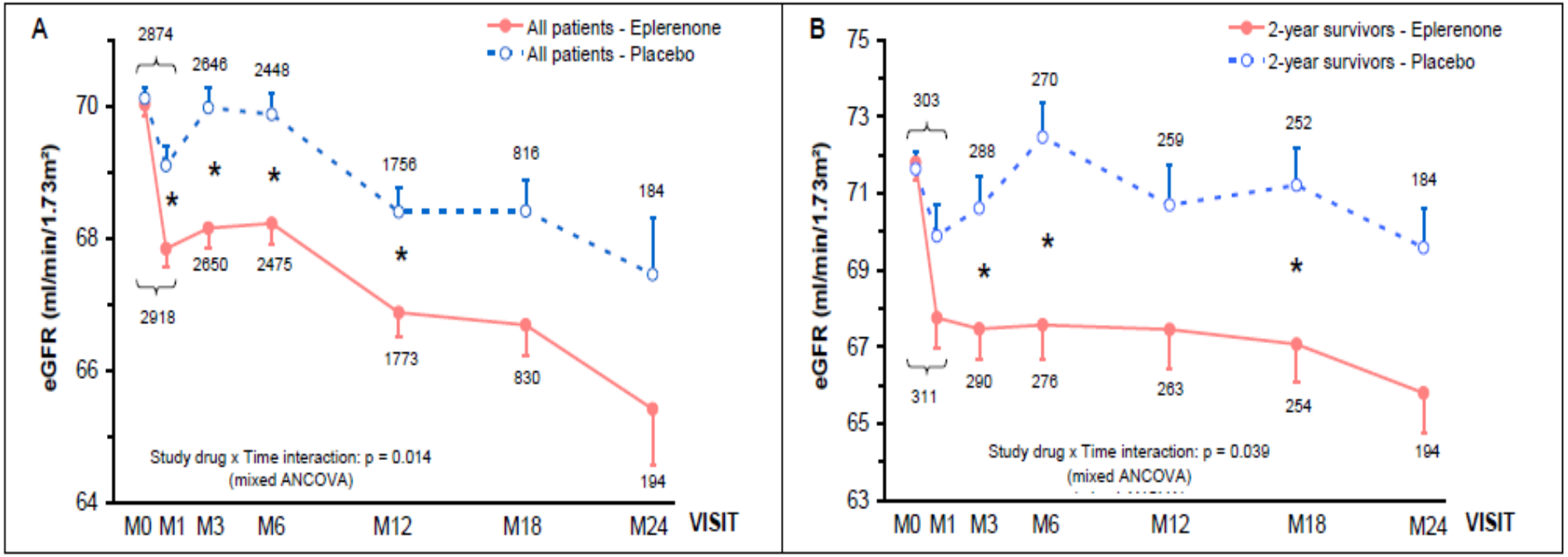



**Figure 2. Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.**
Shown are estimates of the probability of the primary composite end point (death from cardiovascular causes or first hospitalization for heart failure) (Panel A), death from cardiovascular causes (Panel B), first hospitalization for heart failure (Panel C), and death from any cause (Panel D).

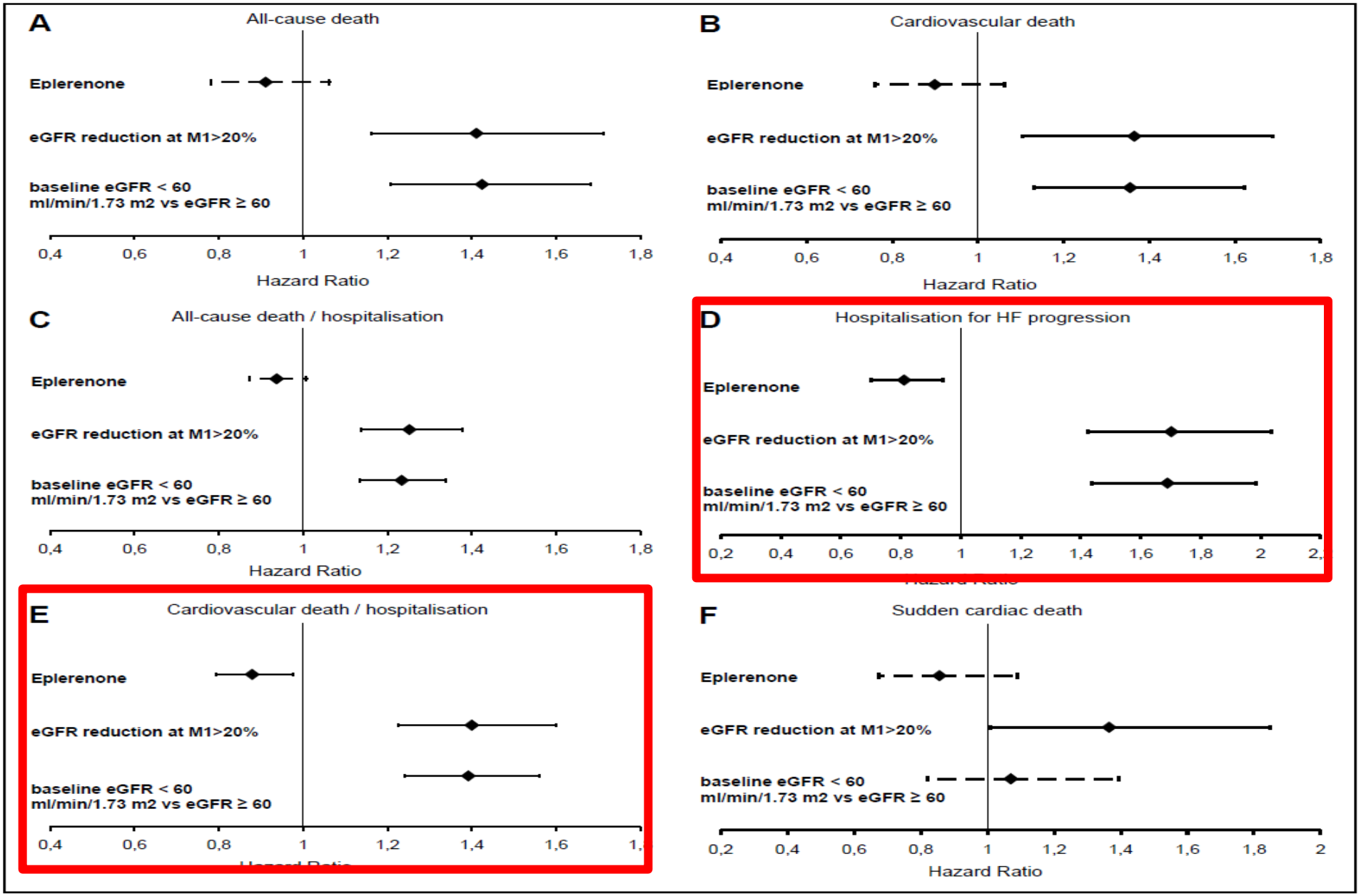
# Aldosterone Antagonists Effects on Renal Function



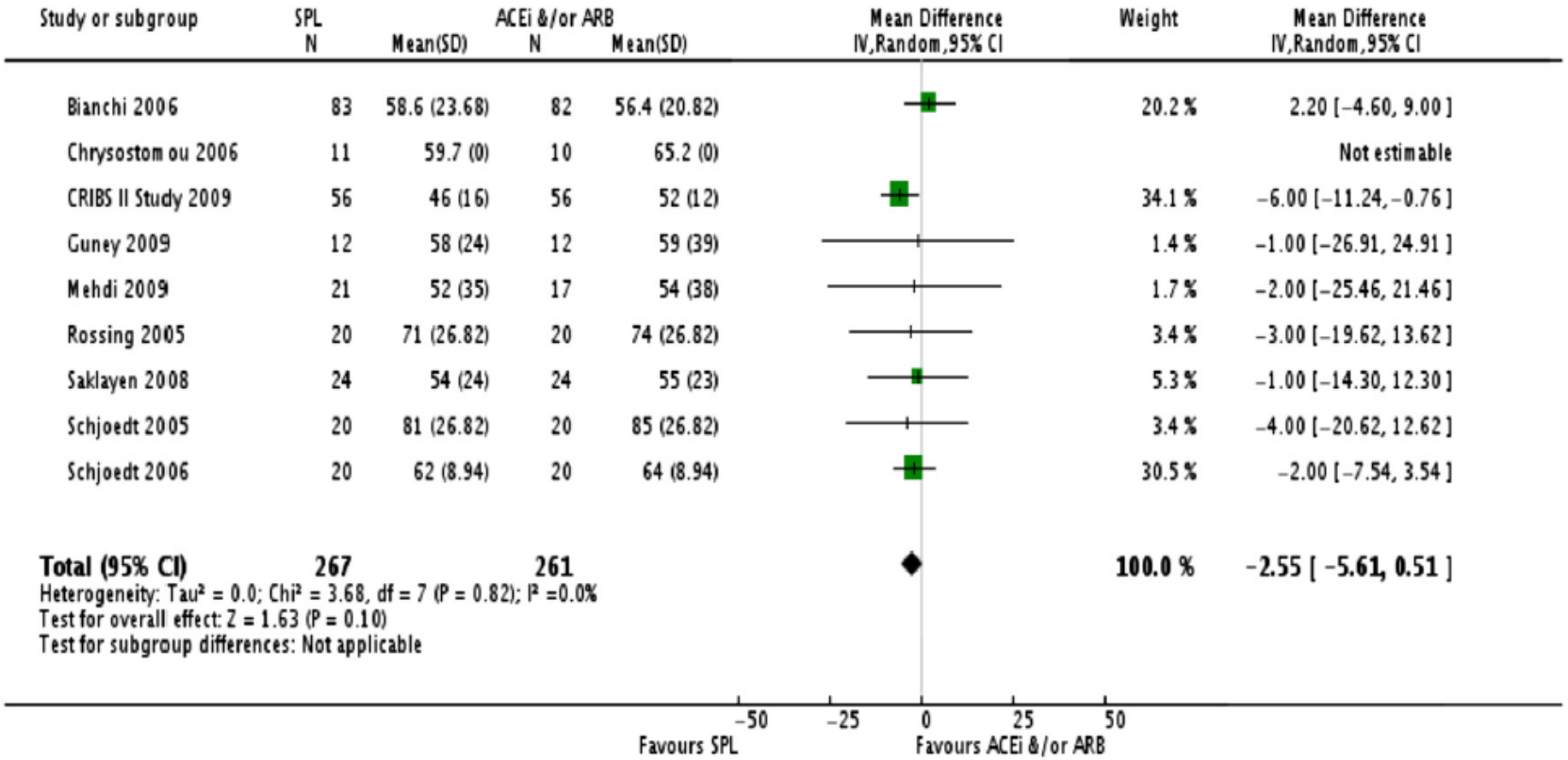

**Early decline in renal function compared to placebo 1.4ml/min which persisted after 2years and after sensitivity analysis**

*Rossignol P, Cleland J, Bhandari S et al. Circulation 2012, 125, 271-279*

**Figure 2: Influence of early worsening renal function on cardiovascular outcomes**



# Meta-analysis of treatment studies, mineralocorticoid receptor blocker therapy added to ACEi or ARBs




**No significant affect on eGFR compared to ACEi or ARB alone**

Bolignano D et al Cochrane Database Syst Rev 2014; CD007004

# Spironolactone Studies

**MiREnDa Study**
Mineralocorticoid Receptor Antagonists in End Stage Renal Disease
Primarily looking at intermediate cardiovascular outcomes - LV mass index, LV geometry, LV function, and so forth

**ALCHEMIST**
Conducted in Belgium, using spironolactone 25 mg daily and looking at harder cardiovascular outcomes

# SONAR (Study Of Diabetic Nephropathy with Atrasentan) to assess the effects of atrasentan - when added to standard care - on renal progression in patients with CKD 2-4 & DMII

Randomized, double-blind, parallel, placebo-controlled, multicenter study

**Inclusion criteria**
eGFR 25 to 75 mL/min/1.73 $m^2$
UACR ≥300 and <5,000 mg/g
systolic blood pressure within 110 and 160 mgHg

**Primary endpoint** : Effect of atrasentan on time to doubling of serum creatinine or the onset of ESRD, as defined by need for chronic dialysis, transplant or death due to renal failure.

**Secondary endpoints**; Effects of atrasentan on UAE, eGFR and cardiovascular events including cardiovascular death, heart attack and stroke. Quality of life evaluations .

Receive atrasentan 0.75 mg/day for 6 weeks to determine their UACR response and to assess tolerability of atrasentan.
3,150 responders (UACR reduction ≥ 30 percent from baseline) and approximately 1,000 non-responders (UACR < 30 percent reduction from baseline) will be randomized 1:1 into a double-blind treatment period, which will continue for approximately 48 months

# Advice about using ACEi & ARBs in CKD

- **Does the patient really need to be on an ACEi or ARB?**
  - Care should always be taken with the frail elderly.
  - ACEi and ARBs have no renoprotective effects over other anti-hypertensives unless the patient has type 1 diabetes or hypertension and significant proteinuria (PCR >100mg/mmol or ACR >70mg/mmol).
  - ACEi or ARBs are only specifically indicated in patients with CKD if they have hypertension and significant proteinuria.

- **Measure serum creatinine and potassium**
  - A rise in sCr of up to 25% above baseline is acceptable.
  - A rise in potassium up to 6mmol/L is safe.
  - If the potassium is >6mmol/L: review all drugs; reduce or stop the ACEi or ARB; give appropriate dietary advice.

- **Avoid excessive hypotension**
  - For most elderly patients (>80 years old) a systolic blood pressure of around 160mmHg is probably acceptable.

# Advice about using ACEi & ARBs in CKD

- **Suspected renal artery stenosis (RAS)**
  - Patients at risk of RAS are those with widespread vascular disease, are usually severely hypertensive and may have had episodes of flash pulmonary oedema. A very large rise in sCr (more than 50% of baseline) in high risk patients may signify RAS. If this occurs stop the ACEi or ARB and discuss with a nephrologist.

- **Avoid other nephrotoxic drugs**
  - Specifically NSAIDs, trimethoprim and potassium sparing diuretics. A small number of patients do benefit from combinations of all of the above with ACEi or ARBs. Patients should be warned about NSAIDs bought over the counter.

- **"Sick day rules"**
  - Patients should be advised to seek medical or nursing advice early if they develop a severe dehydrating illness or symptoms of hypotension. Interrupting the ACEi or ARB for a few days may prevent avoidable AKI.

- **Re-introduction of ACEi/ARBs**
  - Where ACEi or ARBs are essential (e.g. in cardiac failure) and need to be re-introduced after being stopped, it is advisable to recommence with a low dose and titrate up as clinically indicated.

# QUESTIONS