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

Royal College of Physicians of Edinburgh
Educating doctors, improving care.

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THE HULL YORK MEDICAL SCHOOL

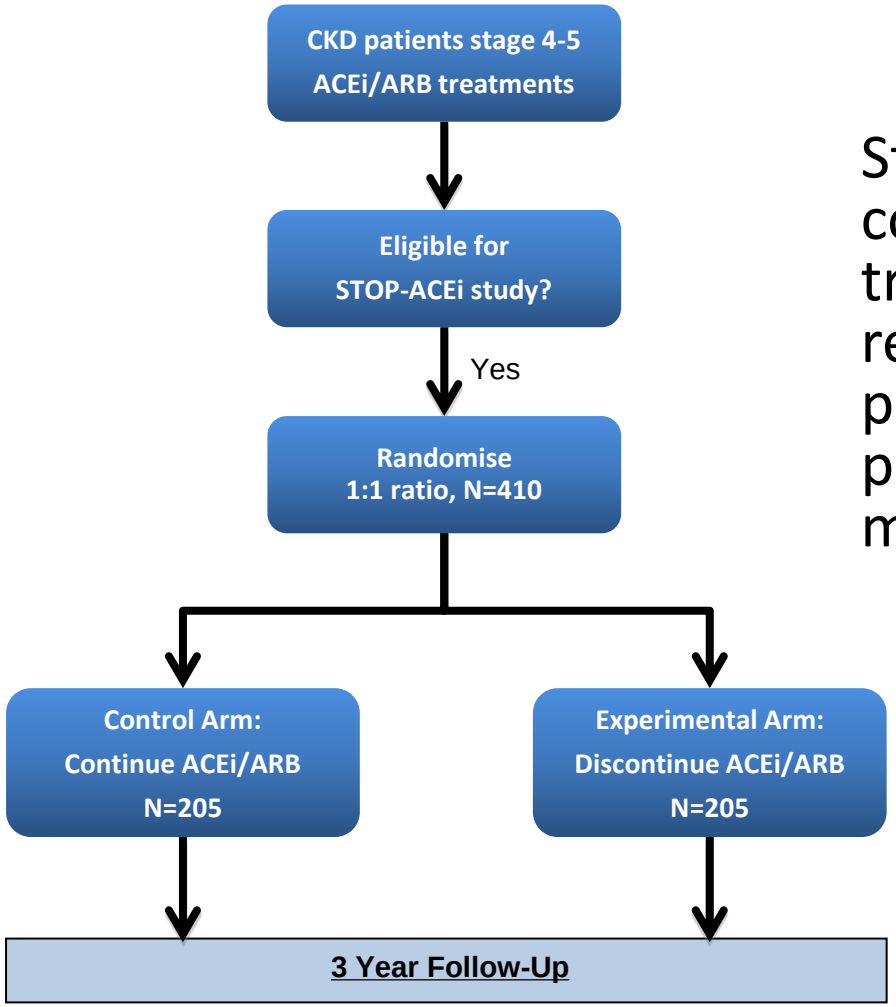
Investigator Meetings

1st and 2nd September 2016 - London and Leeds

Prof Sunil Bhandari
Consultant Nephrologist
Honorary Clinical Professor
International Director RCPE

UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit | Hull and East Yorkshire Hospitals NHS Trust | NHS

Multi-centre Randomised Controlled Trial of Angiotensin Converting Enzyme inhibitor/Angiotensin Receptor Blocker withdrawal in advanced renal disease



Stopping ACEi or ARB treatment, compared with continuing on these treatments, improves or stabilises renal function in patients with progressive stages G4 or G5 CKD provided good BP control is maintained

MRC Medical Research Council

NHS National Institute for Health Research

Efficacy and Mechanism Evaluation Programme

Eligibility

Key Inclusion Criteria	Key exclusion criteria
• Aged ≥18 years (male or female) • CKD stage G4 or G5 (MDRD eGFR <30ml/min) & not on dialysis • Progressive deterioration in renal function (fall in eGFR of >2ml/min/year) • Treatment with an ACEi or ARB or a combination of both for >6 months with at least 25% of the maximum recommended daily dose • Resting BP ≤160/90 mmHg • At least 3 months 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 MI or stroke in preceding 3 months • Pregnancy or breastfeeding • Immune mediated renal disease requiring disease specific therapy

Pre- specified Minimisation Variables

- **Diabetes Mellitus**: Type 1; Type 2; none
- **Blood pressure**: MAP <100; ≥ 100(diastolic x2 + systolic/3)
- **Age**: <65; ≥ 65 years
- **Proteinuria**: PCR <100 ; ≥100 mg/mmol
- **eGFR**: <15 ≥ 15 ml/min

End-points

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 ESA use
Cystatin C	Survival	
	KD QOL	

EQUIPOISE for a Study

- As GFR falls below 30 ml/min (stages G4 to G5), 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
  - Hypotension

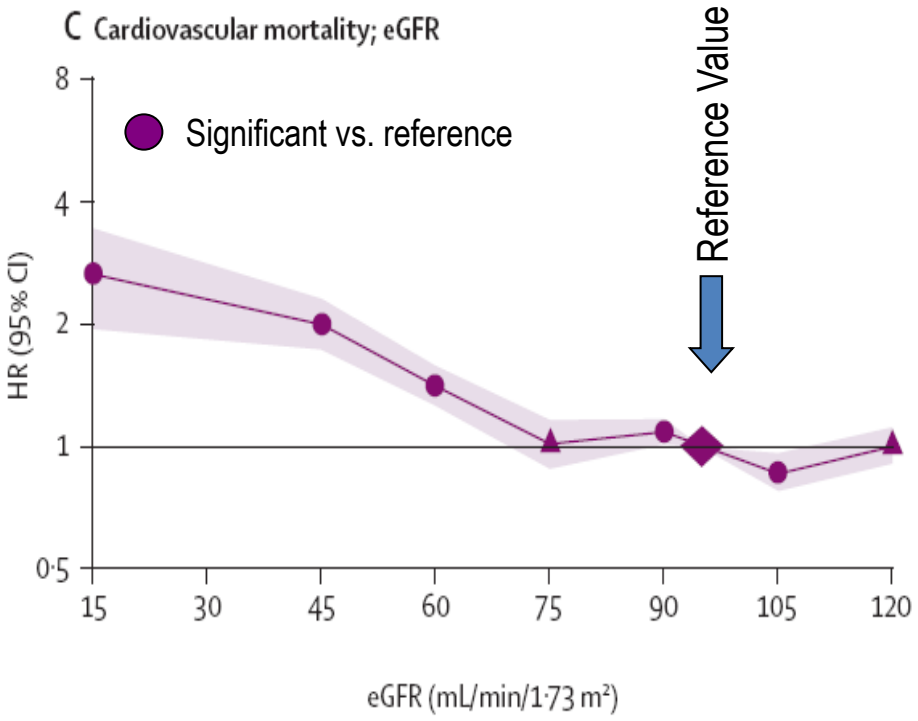
Retardation of CKD progression may be a strategy for CVD Protection

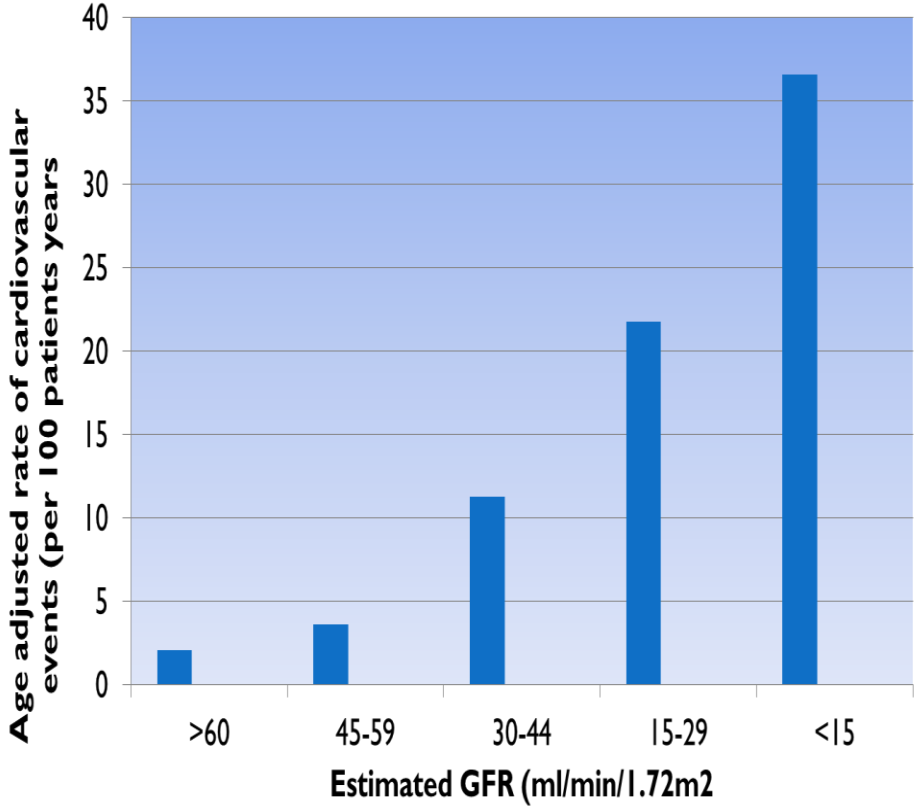
Outline

- Latest research
  - Renal
  - Cardiology
- Recruitment issues
- Trial update and possible changes
- Future
  - Follow-up
  - Retention of patients to end of study and beyond

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

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

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

Reducing Cardiac Outcomes

Does the potential gain of eGFR with ACEi/ARB cessation lead to improved morbidity & mortality or an increase in adverse cardiovascular outcomes?

Cardiovascular guidelines have recommended caution with the use of ACEi/ARBs for patients with HF and advanced CKD

McMurray JJ et al; ESC Committee for Practice Guidelines: ESC guidelines for the diagnosis and treatment of acute and chronic heart failure : European society of Cardiology. Developed in collaboration with the heart failure association (HFA) of the ESC. Eur Heart J 2012; 14: 1787–1847

HF studies provide little information to direct care in advanced CKD - patients with significant renal dysfunction were excluded

Table 1. Heart failure trials with baseline renal function

Trial (reference)	Intervention	Cohort	Sample	Follow-up	Creatinine/ eGFR	Outcome
CONSENSUS [46]	Enalapril vs. placebo	NYHA IV HF	253	188 days	124–132 µm/l	Improved symptoms and life expectancy vs. placebo, no impact on sudden cardiac death
Val-HeFT [43]	Valsartan vs. placebo	NYHA I–II HF	5,010	27 months	58 ml/min	Reduced composite mortality and morbidity and improved symptoms
V-HeFT-II [45]	Enalapril vs. hydralazine/ isosorbide dinitrate	Men; NYHA class II–III HF	804	2.5 years	Not measured	Sudden death 14%; mortality from progressive HF 12 vs. 23%
SOLVD-treatment [44]	Enalapril vs. placebo	NYHA class II/III HF and EF <35%	2,569	41 months	1.2 mg/dl (106 µmol/l)	Sixteen percent fewer deaths in enalapril group ($p = 0.0036$), 26% less hospitalizations ($p < 0.0001$)
SOLVD-prevention [42]	Enalapril vs. placebo	Asymptomatic patients with EF ≤35%	4,228	37 months	1.2 mg/dl (106 µmol/l)	Eight percent lower mortality (NS); fewer deaths and hospitalizations due to HF ($p < 0.001$)
CHARM-added trial [38]	Candesartan vs. placebo	LV dysfunction already taking ACEi	2,548	42 months	Not measured excluded >3.0 mg/dl (265 µmol/l)	Candesartan significantly improved all-cause mortality
CHARM alternative [37]	Candesartan vs. placebo	LV dysfunction intolerant to ACEi	2,028	42 months	Nil Excluded >3.0 mg/dl (265 µmol/l)	Candesartan significantly improved all-cause mortality
ELITE I [39]	Losartan vs. captopril	>65 years with HF NYHA II–IV; EF <40%	722	48 weeks	106 µmol/l	No difference in outcomes of worsening renal function
ELITE II [40]	Losartan vs. captopril	>60 years with HF NYHA II–IV; EF <40%	3,152	555 days	Nil	No difference in all-cause mortality 1.13 (0.95–1.35)
ATLAS [41]	Lisinopril vs. losartan	LV dysfunction	3,163	~4 years	1.3 mg/dl (117 µmol/l)	Reduced mortality 8% NS Combined death and hospitalisation 15%

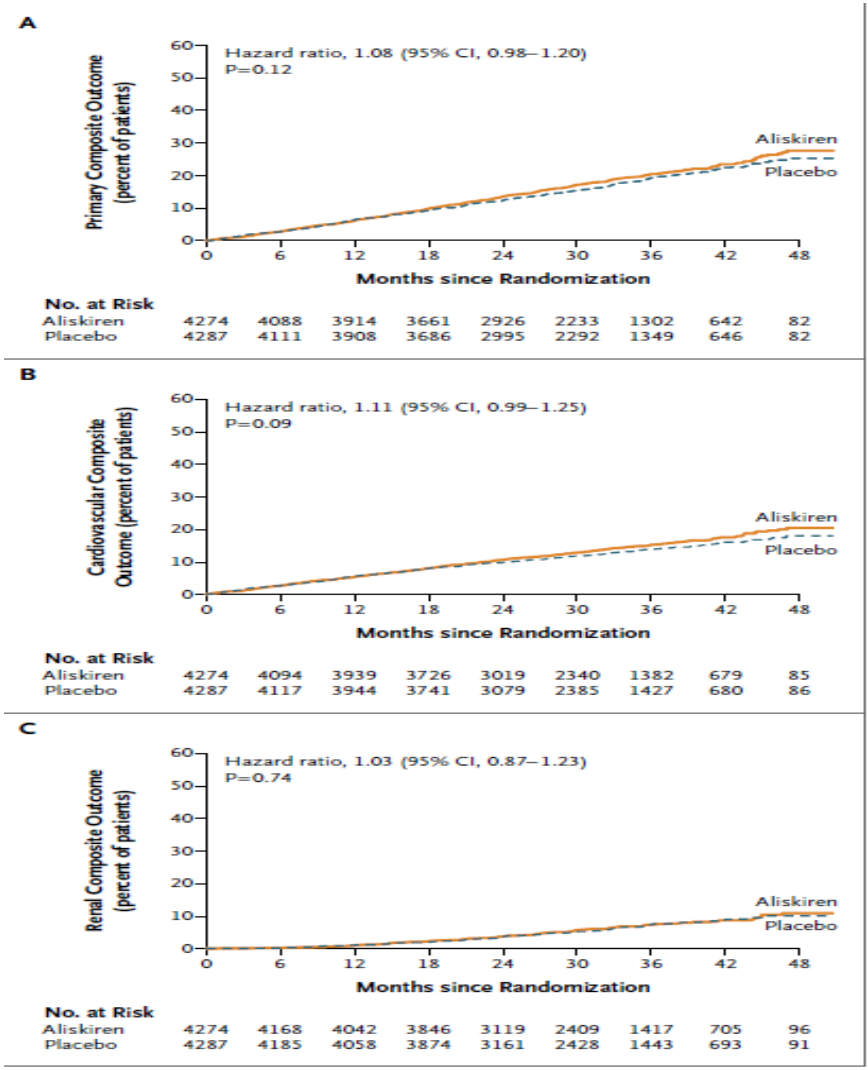
Ahmed/Jorna/Bhandari DOI: Nephron 10.1159/000447068

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

The ALTITUDE Trial

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



Renin Inhibition ? Reduces CV events

- ASTRONAUT – acute heart failure outcomes
- N=16150
  - Heart failure and reduced EF%
  - 4% diabetics (n=662)

Primary endpoint – CV death or rehospitalisation <6/12 with heart failure

Results –No difference in outcomes but with combination

- Increased risk hyperkalaemia - HR 2.39
- Increased risk of hypotension
- Increased mortality with diabetics at 12 months from CV death/rehospitalisation and all cause mortality

Maggtoni AP et al Eur H J 2013

Renin Inhibition ? Reduces CV events

- ATMOSPHERE – minimising outcomes in HF patients; n=7016 with 37 months follow-up

	Primar CV death or hospitalisation for HF	
Alkiskirin	33.8%	NS
Enalipril	34.6%	NS
Both	32.9%	NS Increased adverse outcomes

McMurray J NEJM 2016, 374, 1521

LCZ696 (nephrilysin inhibitor secubitril and valsartan)

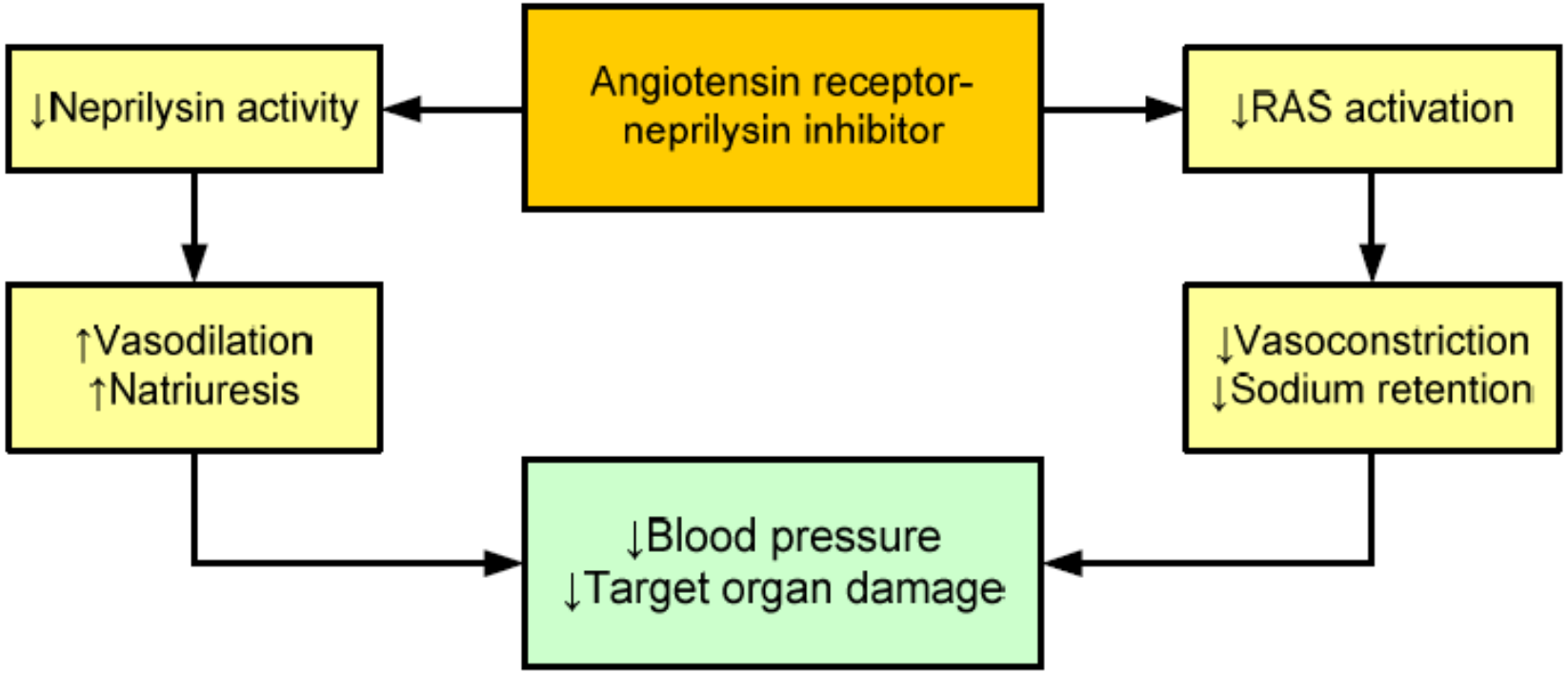
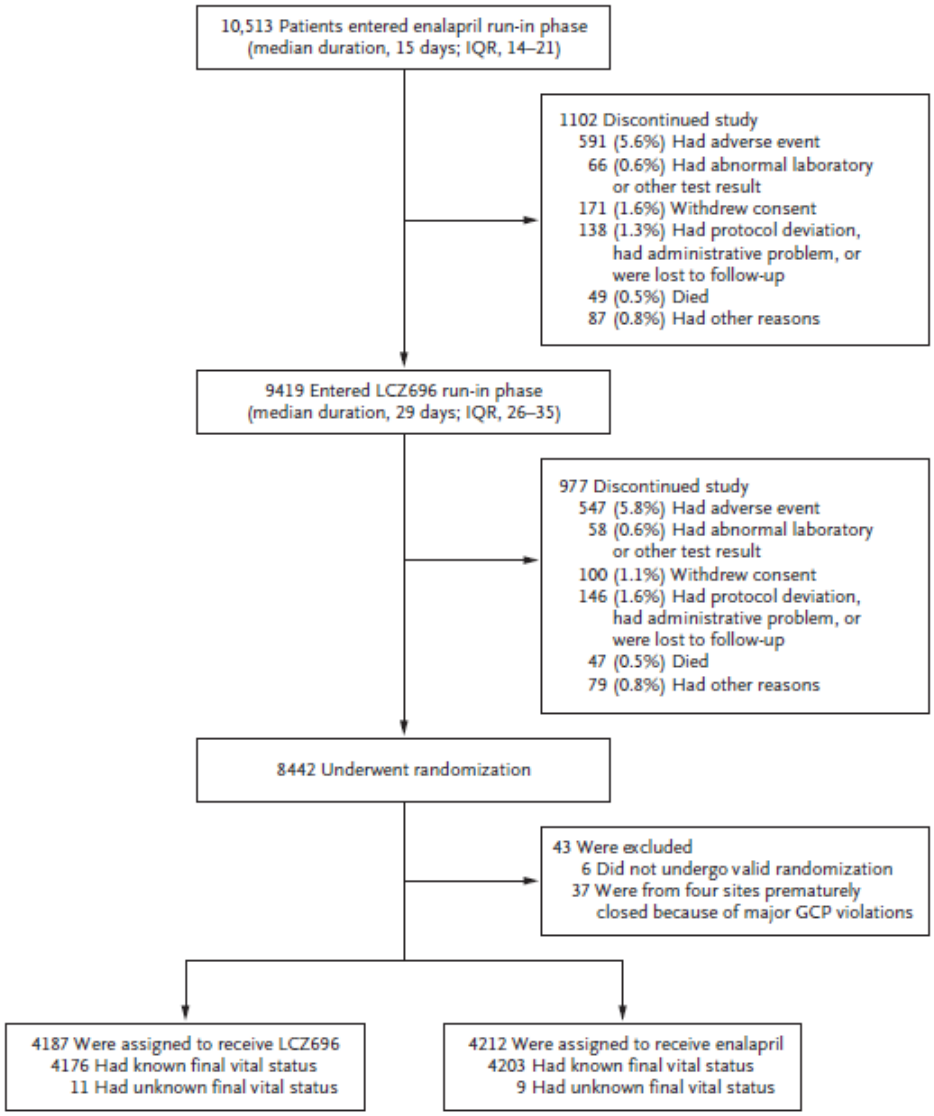


Figure 2: Putative synergy between neprilysin inhibition and angiotensin 2 receptor blockade

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 secubitril and valsartan 400mg BD

Enalapril 10mg BD

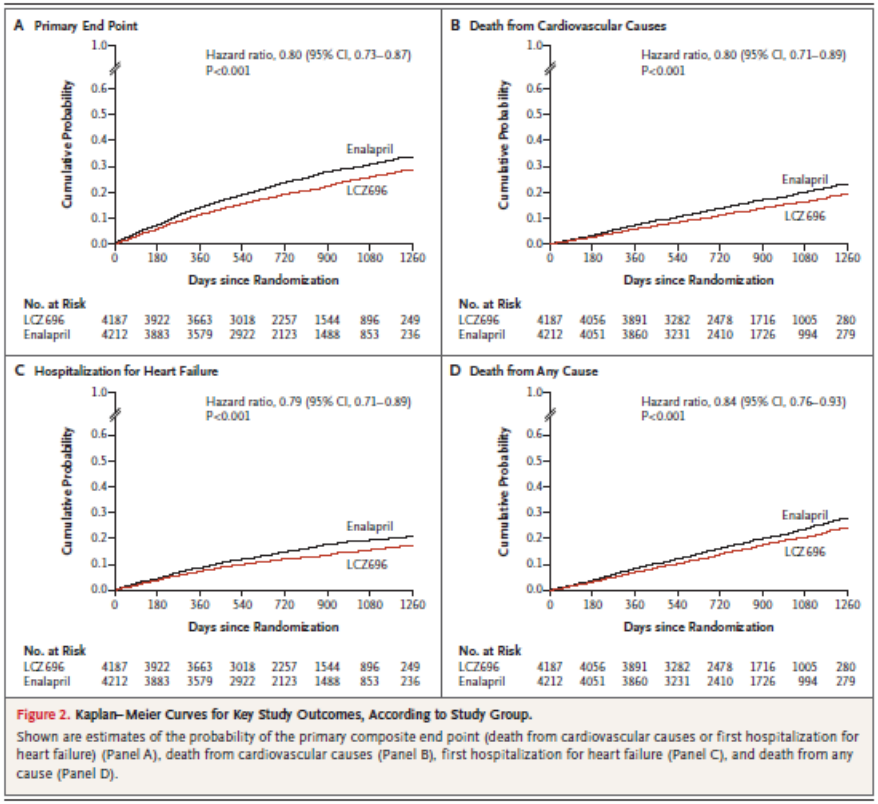


Figure 2. Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.
Shown are estimates of the probability of the primary composite end point (death from cardiovascular causes or first hospitalization for heart failure) (Panel A), death from cardiovascular causes (Panel B), first hospitalization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

PARADIGM-HF

"Miracle Drug"

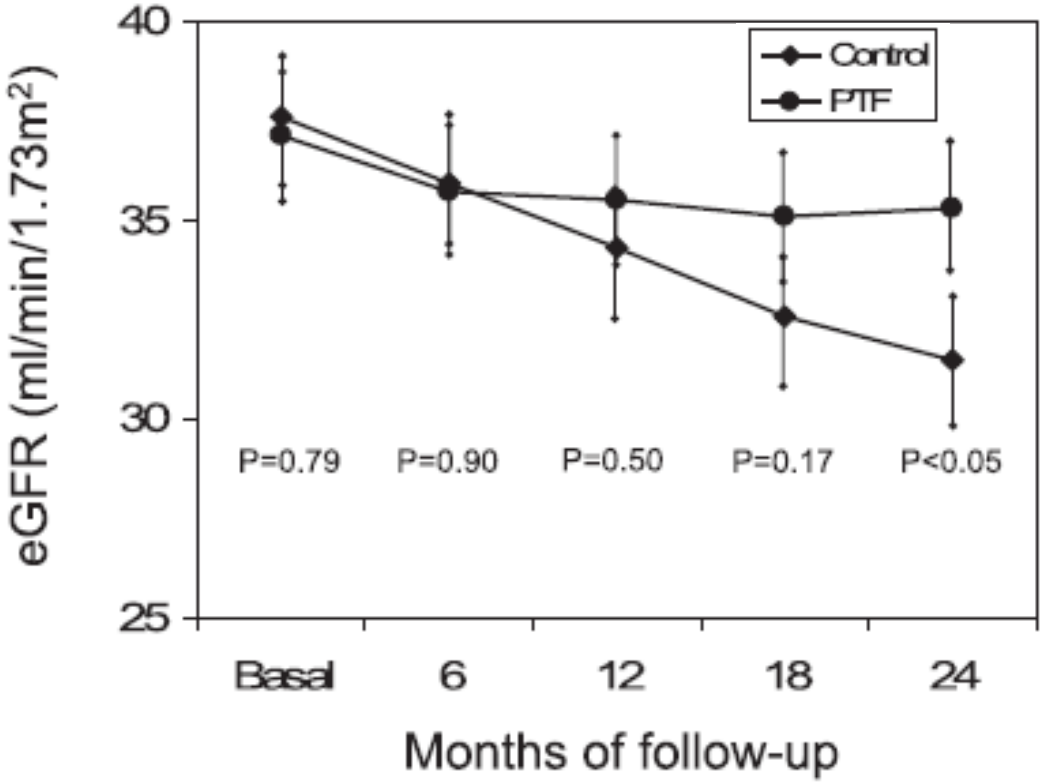
Table 2. Primary and Secondary Outcomes.*

Outcome	LCZ696 (N=4187)	Enalapril (N=4212)	Hazard Ratio or Difference (95% CI)	P Value
Primary composite outcome — no. (%)				
Death from cardiovascular causes or first hospitalization for worsening heart failure	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from cardiovascular causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalization for worsening heart failure	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001
Secondary outcomes — no. (%)				
Death from any cause	711 (17.0)	835 (19.8)	0.84 (0.76–0.93)	<0.001
Change in KCCQ clinical summary score at 8 mo†	−2.99±0.36	−4.63±0.36	1.64 (0.63–2.65)	0.001
New-onset atrial fibrillation‡	84 (3.1)	83 (3.1)	0.97 (0.72–1.31)	0.83
Decline in renal function§	94 (2.2)	108 (2.6)	0.86 (0.65–1.13)	0.28

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

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*



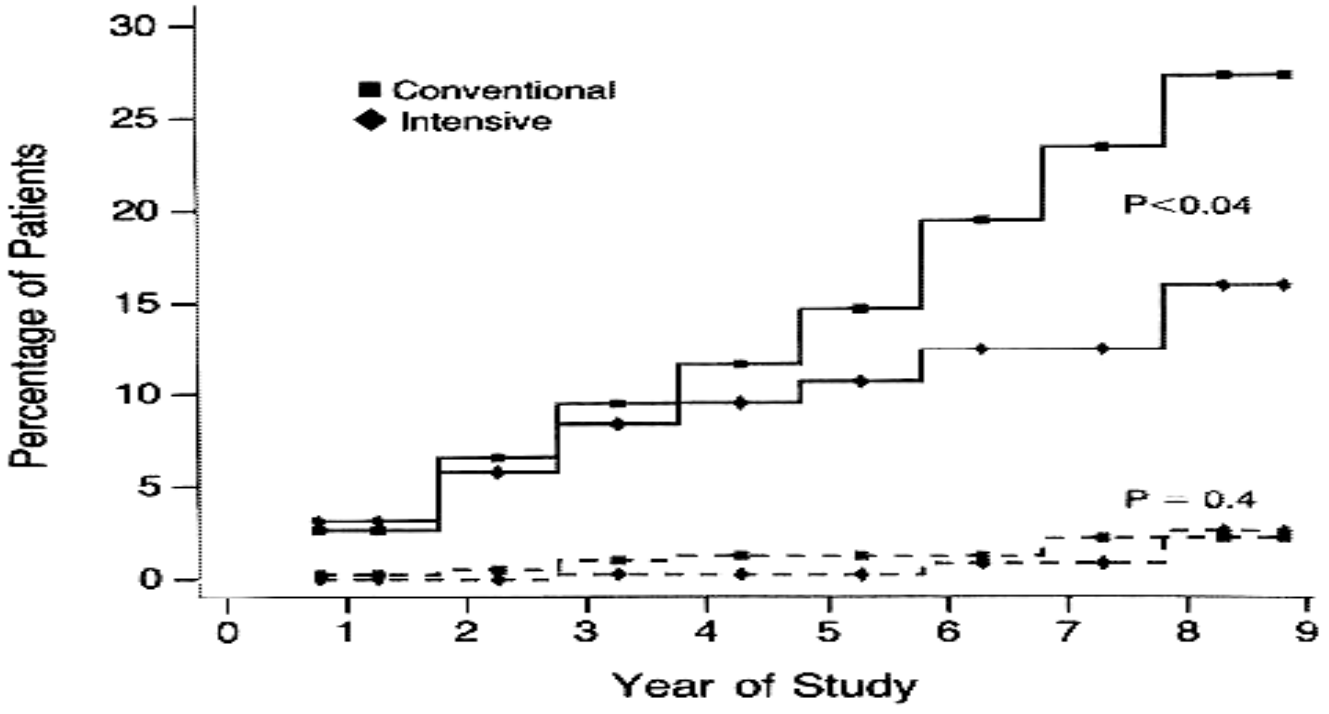
	PTF	Placebo
GFR 1 y ml/min	-1.2	-3.4
GFR 2 y ml/min	-2.1	-6.5
Monthly rate	0.08±0.14	0.27±0.8
ACR mg/dL	-13	+4.9
BP mmHg	140.8 85	139.8 83.8

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

Is it worth optimising the diabetes control?

DCCT STUDY

- Tight Diabetic control (type 1 DM)
  - **Nephropathy reduced by 35-75%**
  - Risk of progression of retinopathy reduced by 50%
  - 3x more severe hypos than the control group



The Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment of Diabetes on the Development and Progression of long term complications in IDDM N Engl J Med 1993: 329: 977-86

ACCORD Glycaemic Trial

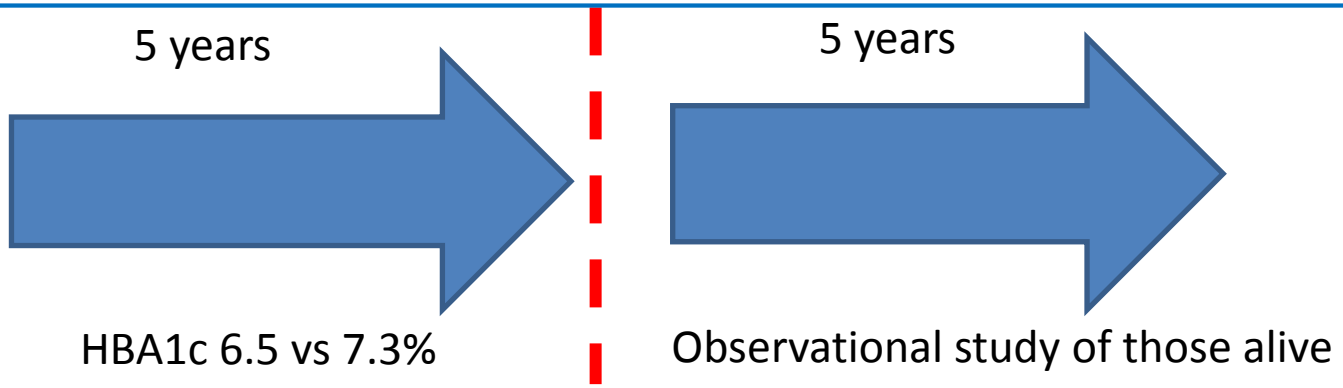
Deaths	Standard Glycemic Control	Intensive Glycemic Control
n	203 (11/1000/y)	257 (14/1000/y)

Despite 10% lowering of primary outcome (MI rates) there was a 20% higher death rate

http://www.nhlbi.nih.gov/health/prof/heart/other/accord/q_a.htm

ADVANCE to ADVANCE ON STUDY

DM II >55y Standard therapy to control HbA1
vs
intensive therapy
n=8494

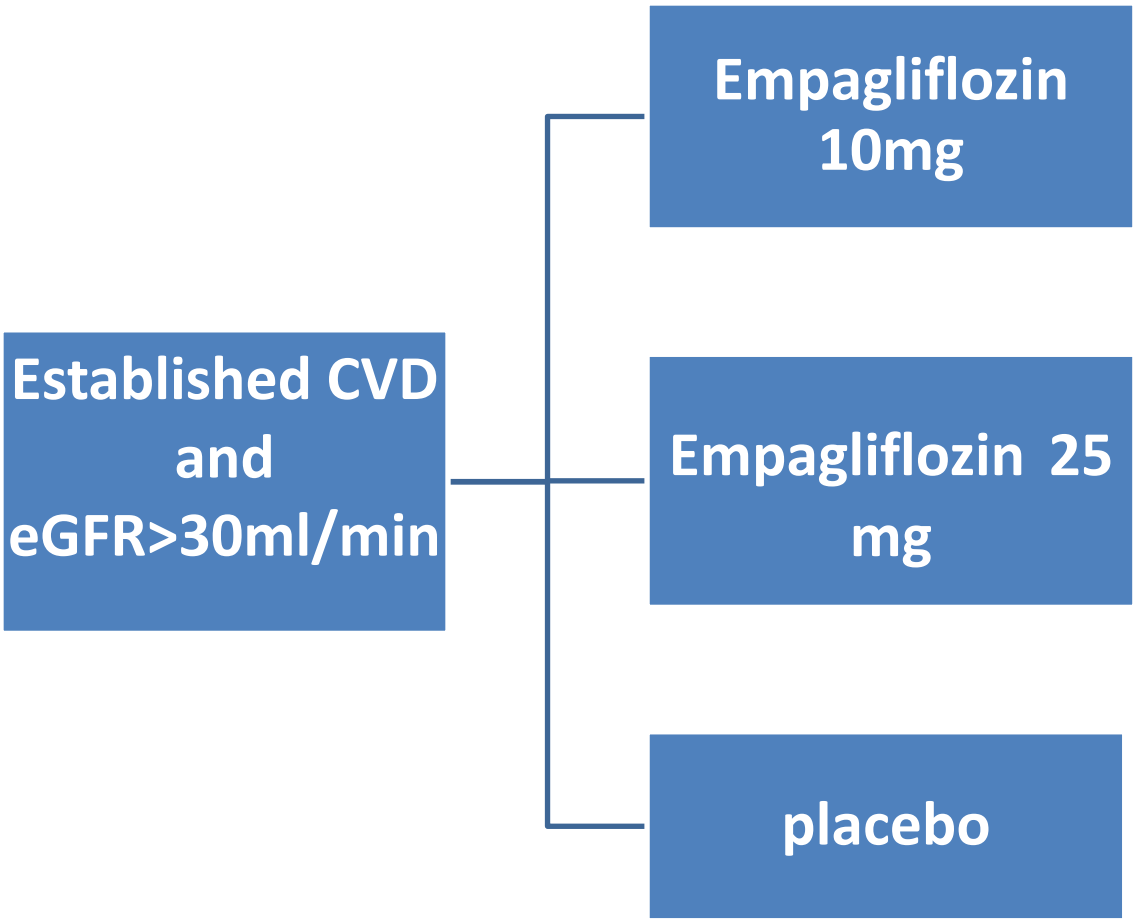


after 10 years median 5.9 years	Outcome/ HR	CI	
HBA1c	Similar		
Death	1.00	0.92 - 1.08	No difference
macro vascular outcomes	1.00	0.92 – 1.08	No difference
ESRD	**HR 0.54**	**0.34 - 0.85**	**46% reduction**

Only those with NO CKD benefited HR 0.16. There was no benefit in CKD stage 3 or worse (HR 0.89) – Early intense glycaemic control beneficial if no CKD

Sophia Zoungas et al Follow-up of Blood-Pressure Lowering and Glucose Control in Type 2 Diabetes for the ADVANCE-ON Collaborative Group N Engl J Med 2014; 371:1392-1406, 2014
Wing MG et al Diabetes Care 2016; 39; 694

SGLT-2 –inhibitors
EMPA-REG OUTCOME STUDY



Outcomes
CV Death - REDUCED
Microvascular Outcomes
Progression of ACR to Proteinuria Doubling SC eGFR <45 ml/min RRT Renal death
Rate of renal progression

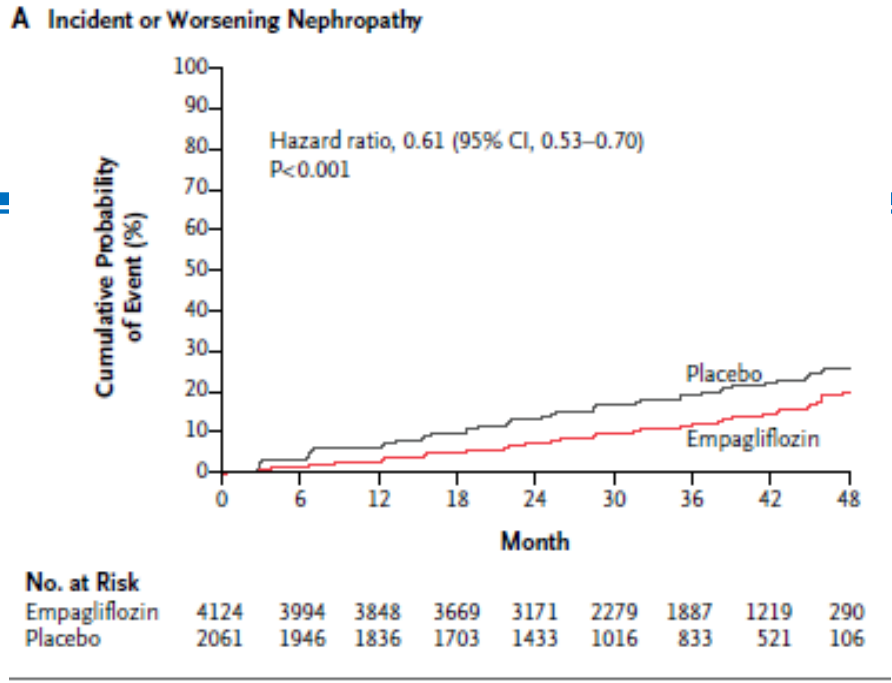
Zinman B et al N Engl J Med 2015
Wanner C et al N Engl J Med 2016 DOI: 10.1056/NEJMoa15159

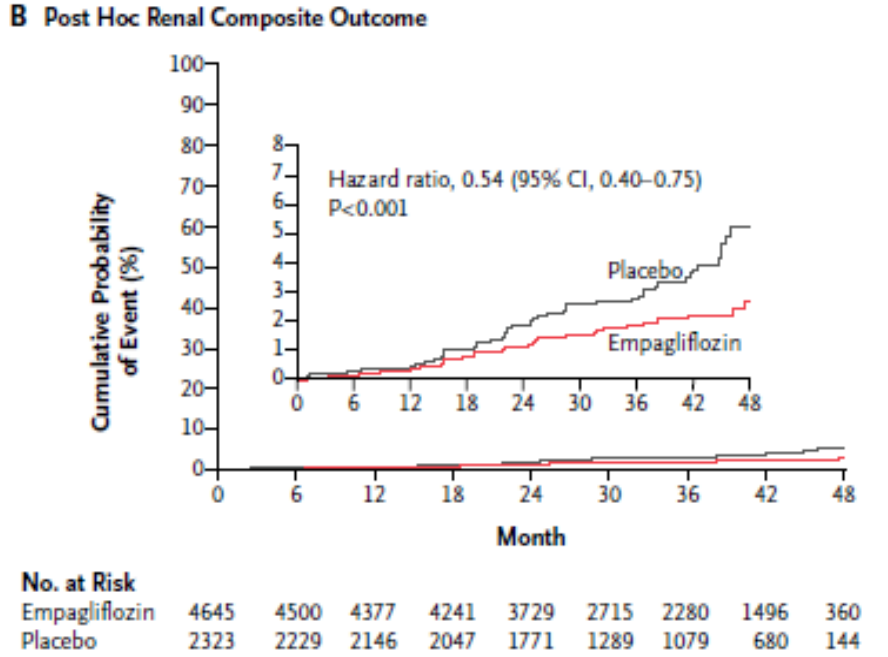
Kaplan–Meier Analysis
Renal Outcomes to 48 mon

A. Probability of a first occurrence of a pre-specified renal composite outcome of incident or worsening nephropathy

B. Post hoc renal composite outcome
- doubling of the serum creatinine
- initiation of RRT
- death from renal disease

among patients who received at least one dose of either empagliflozin or placebo.

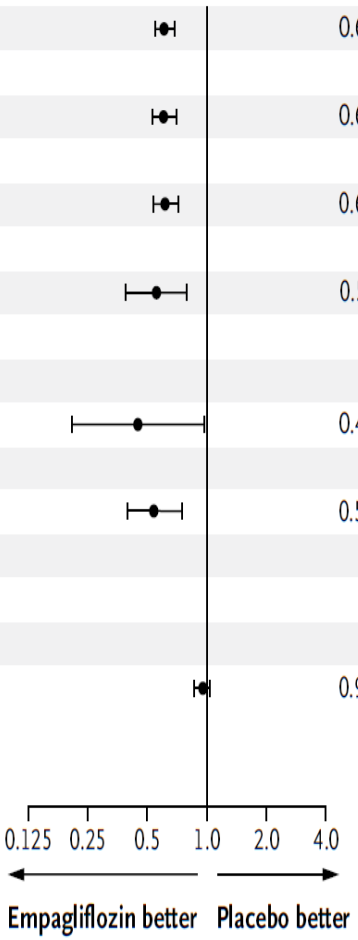




Wanner C et al N Engl J Med 2016 DOI: 10.1056/NEJMoa15159

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Renal Outcome Measure	Empagliflozin no. with event/ no. analyzed (%)	Empagliflozin rate/1000 patient-yr	Placebo no. with event/ no. analyzed (%)	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25



Wanner C et al N Engl J Med 2016 DOI: 10.1056/NEJMoa15159

Proton Pump Inhibitors

10,482 – ARIC data base
- Follow-up >10y
- initial eGFR >60ml/min

Incidence of
eGFR <60 ml/min

248, 757 Geisinger Health System in Pennsylvania

	ARIC		GHS	
	Hazard R.	CI	HR	CI
Unadjusted PPI vs no PPI	1.45	1.11-1.90		
Adjusted PPI vs placebo	1.50	1.14-1.96	1.24	1.2-1.28
PPI vs H2 block	1.39	1.01-1.91		
PPI BD			1.46	1.28-1.67

Lazarus B et al JAMA 2016; 176 (2)

AKI and ACEi in Elderly

Issues

- ACEi – renal cleared while ARB liver cleared
- Increased overdosing with ACEi and hence risk of AKI in community

- Retrospective cross-sectional study
  - 324 patients
  - mean age 77 years
  - baseline mean eGFR 34.5 ml/min (70.4% stage G3b or worse)

Martin Chaumont et al from Belgium J of Clinical Hypertension 2016:18,6

TABLE I. Dosing of Most Prescribed ACE Inhibitors and ARBs

Drug Name	Renal/Hepatic Excretion	Maximal Dosage in Renal Dysfunction, mL/min[a]	Maximal Dosage Across All Indications	American Manufacturer's Recommendations[b]
ACE inhibitors				
Captopril	100%/0%	≥50: 100 mg/d 20–49: 50 mg/d <20 or HD or DP: contraindicated except for specialist	150 mg/d	10–50: 75% normal dosage <10: 50% normal dosage Maximal dosage: 450 mg/d
Lisinopril	100%/0%	Adaptation of the starting dose then titrate to a maximum dosage of 40 mg/d	40 mg/d HTN: 80 mg/d	Idem
Perindopril arginine	100%/0%	≥60: 5 mg/d 30<Clr<60: 2.5 mg/d 15<Clr<30: 2.5 mg 1 d/2 HD: 2.5 mg dialysis day	10 mg/d	Not found
Ramipril	100%/0%	≥60: 10 mg/d 30<Clr<60: 5 mg/d 15<Clr<30: 5 mg/d HD: 5 mg dialysis day	10 mg/d	<40: 5 mg/d <10: 25% to 50% of the normal dosage Maximal dosage: 20 mg/d
ARBS				
Candesartan	33%/67%	Adaptation of the starting dosage then titrate <15: limited experience	32 mg/d	Idem
Losartan	10%/90%	Dosage adjustment not required unless patient is volume depleted	150 mg/d	Maximal dosage: 100 mg/d
Olmesartan		20–60: 20 mg/d <20: contraindicated to limited experience	40 mg/d	Dosage adjustment not required
Telmisartan	0%/100%	Mild to moderate CKD: dosage adjustment not required Severe CKD: adaptation of the starting dosage	80 mg/d	Idem
Valsartan	30%/70%	>10: dosage adjustment not required <10: caution	320 mg/d	<30: caution

Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARBs, angiotensin receptor blockers; CKD, chronic kidney disease; Clr, clearance; DP, peritoneal dialysis; HD, hemodialysis; HTN, hypertension; Idem, same as European manufacturer's recommendations.

[a]Adapted from official European manufacturer's recommendations (May 21, 2015).

[b]Adapted from official American manufacturer's recommendations (May 21, 2015).

AKI and ACEi in Elderly

Results

40% had AKI (91% stage 1 – 68.6% pre-renal)

Variable increasing risk of AKI:

- Younger age
- Male
- Chronic use of >/= 3 antihypertensive meds
- PVD
- Low BP at admission to hospital
- Dehydration

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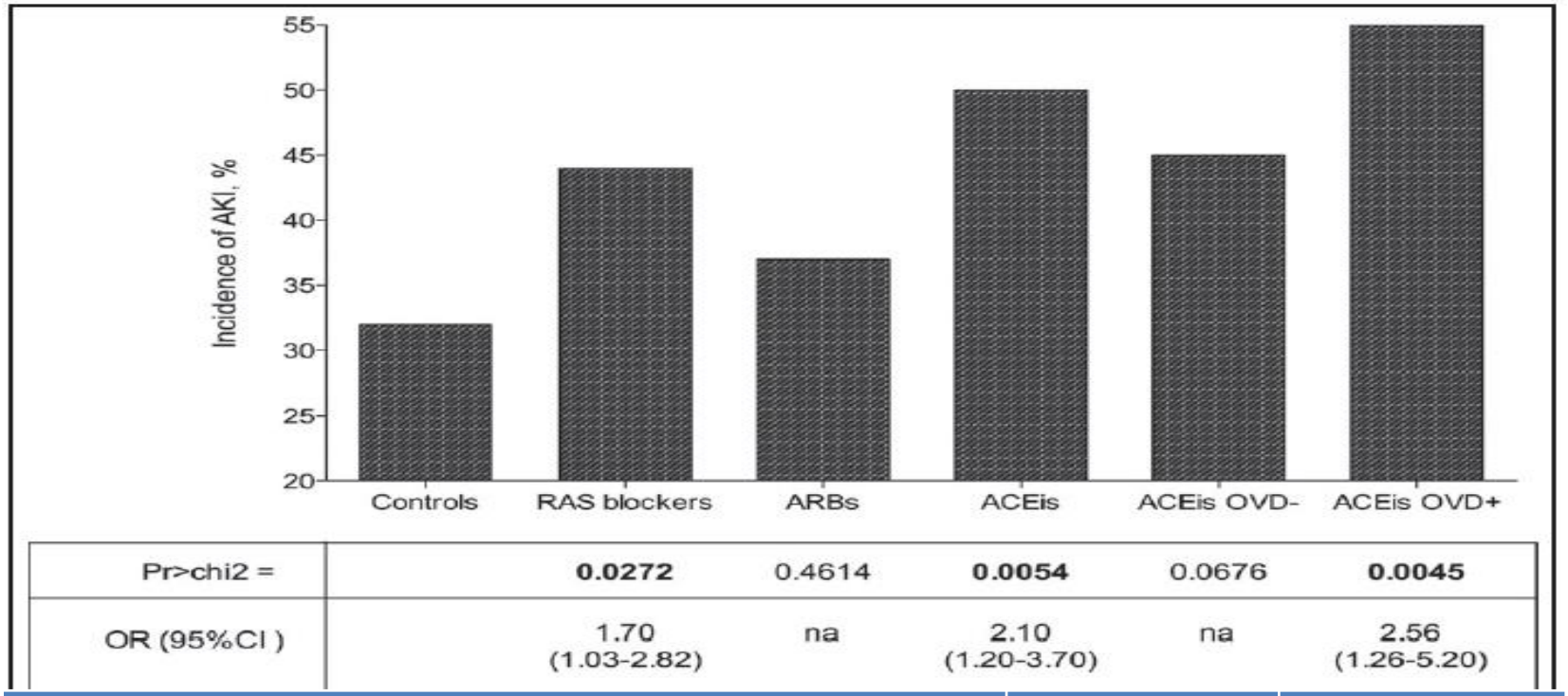
Incidence of AKI compared with controls depending on the class and dose of RAS blockers. OR indicates odds ratio



Pr>chi2 =	**0.0272**	0.4614	**0.0054**	0.0676	**0.0045**
OR (95%CI)	1.70 (1.03-2.82)	na	2.10 (1.20-3.70)	na	2.56 (1.26-5.20)

Stepwise regression analysis of variables variable independently associated with AKI	OR	CI
ACEi	1.9	1.1 - 3.10
Dehydration	30.8	3.9 - 2.39
increased length of AKI duration	3.5 days	5.4 days

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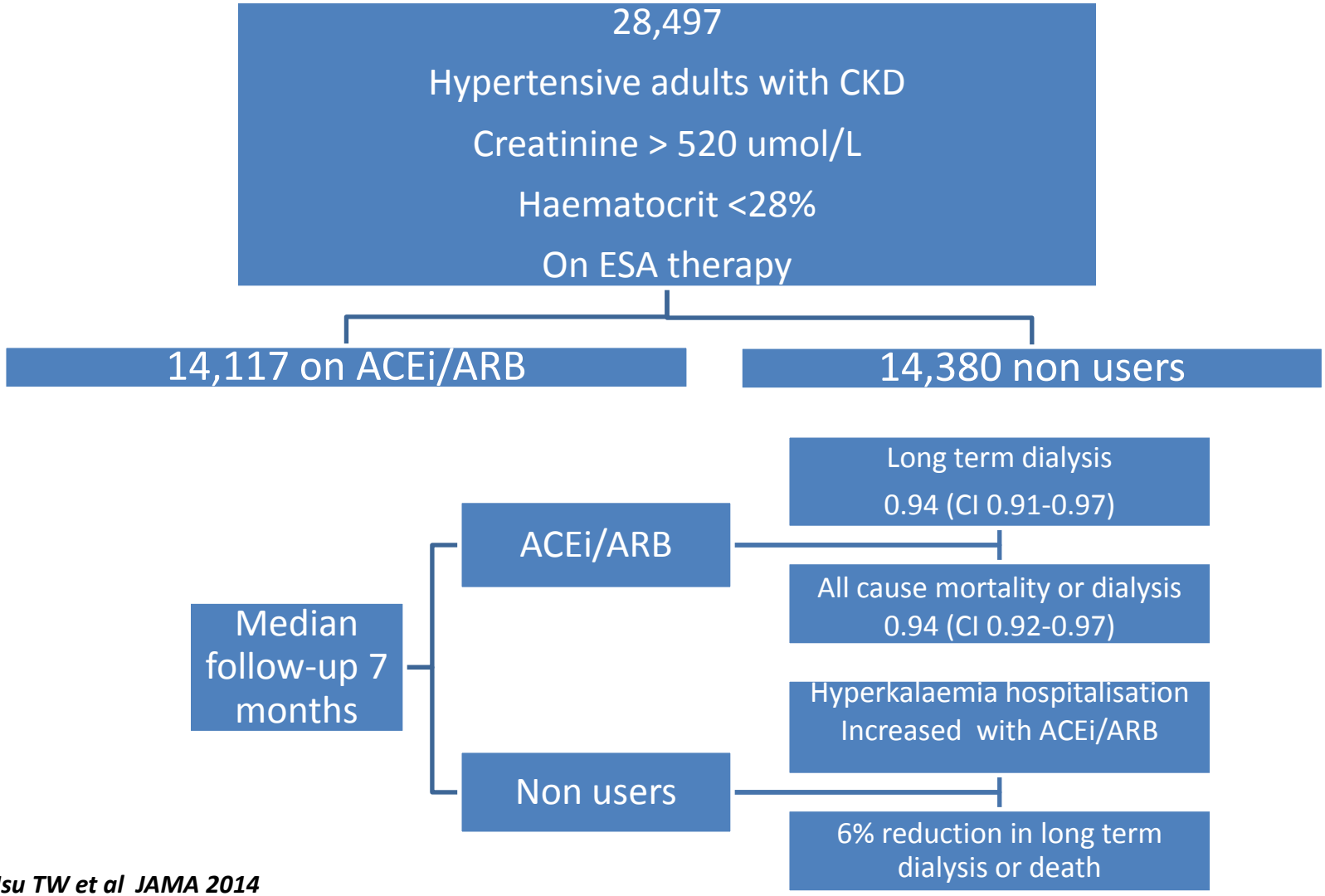
Prospective Cohort Study

Effectiveness and safety of ACEi/ARB use in advanced CKD



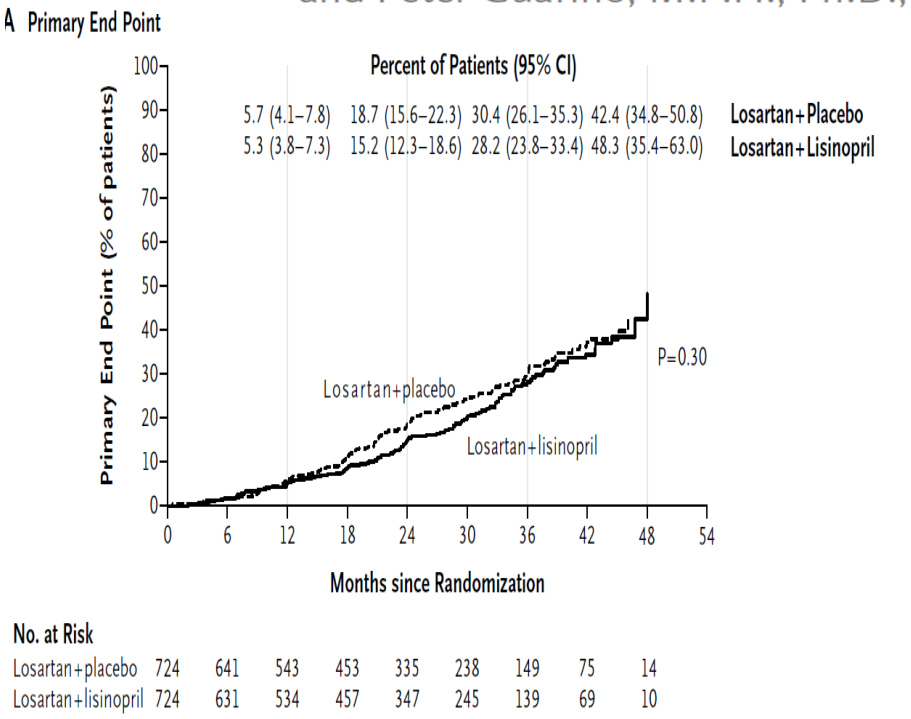
Hsu TW et al JAMA 2014

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*



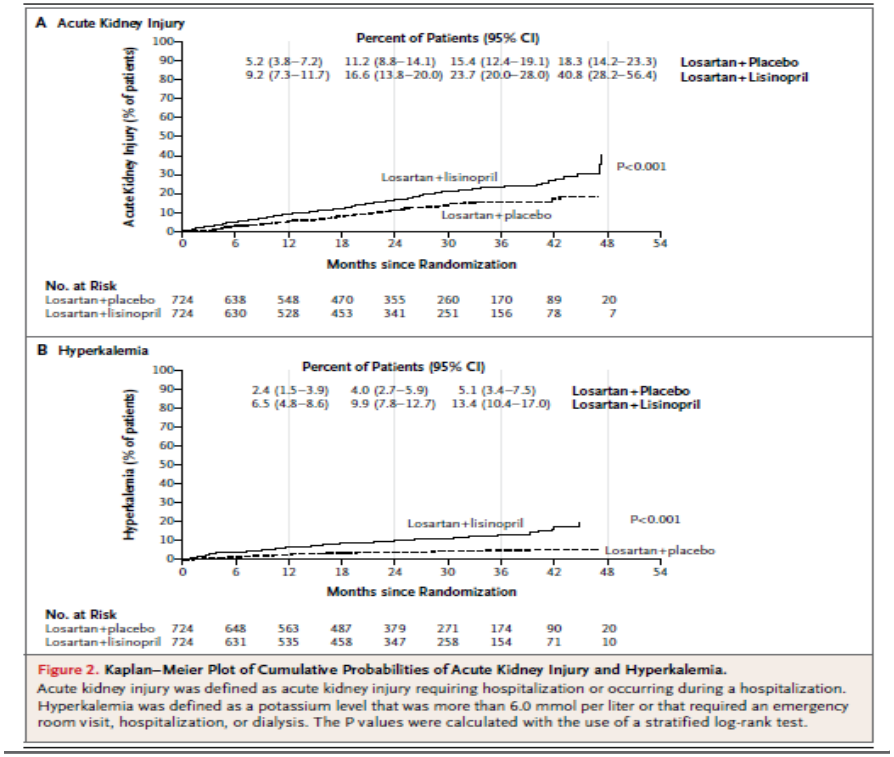


Figure 2. Kaplan–Meier Plot of Cumulative Probabilities of Acute Kidney Injury and Hyperkalemia.
Acute kidney injury was defined as acute kidney injury requiring hospitalization or occurring during a hospitalization. Hyperkalemia was defined as a potassium level that was more than 6.0 mmol per liter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

VA NEPHRON D – “not a total loss”

- **What the Literature says and we believe**

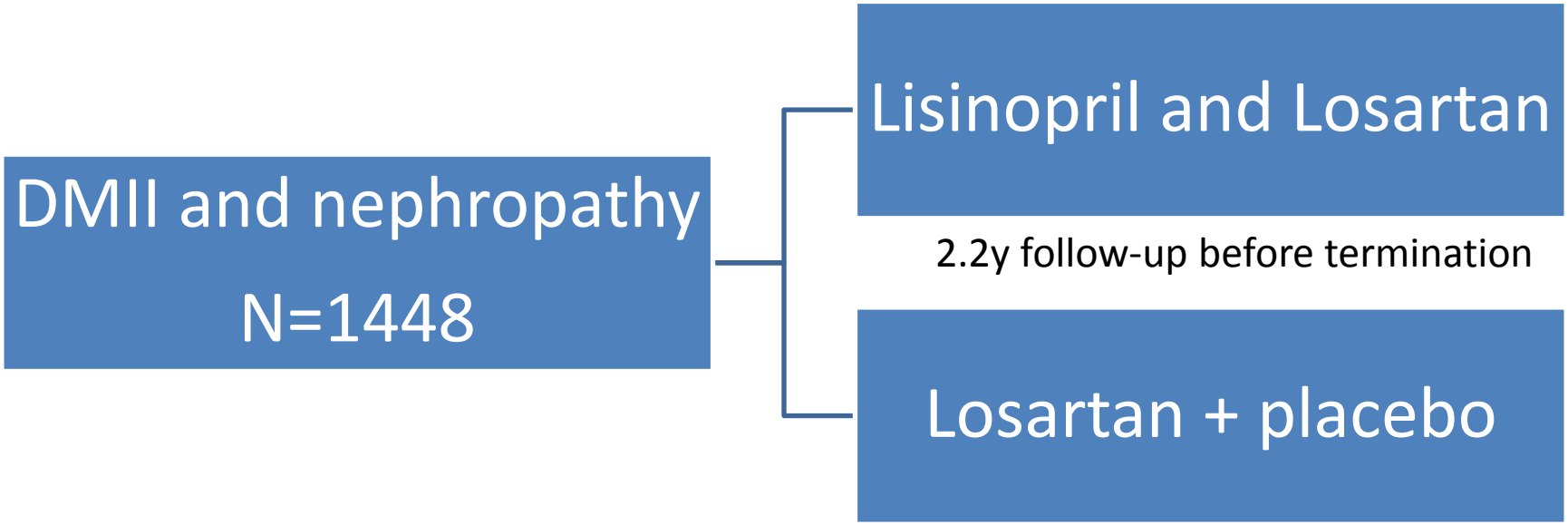
- Early GFR reduction with dual blockade or ACEi is associated with RAS inhibition

  – predicts slower GFR decline

  – **ONLY** if GFR>30ml/min at start.

VA- NEPHRON D post Hoc

At study closure – increased AKI. Hyperkalaemia and hypotension



34% reduction in ERSD
Losartan had a higher proteinuria reduction

"complete" RAS inhibition may blunt kidney vascular adaptation (autoregulation) to the decrease in perfusion pressure

VALID Trial – does larger proteinuria reduction by half doses of ACEi and ARB vs full dose of each alone delay ESRD in DM11 (n=102)

DM as a compelling indication for use of RAAS blockers: systematic review & meta-analysis of randomized trials

Table 1 | Baseline characteristics and risk of bias assessment of included trials

Trials	Year	Sample size	Follow-up (years)	Cohort	Age (years)	Black people (%)	Risk of bias*
RAS blockers versus calcium channel blockers:							
ABCD (hypertensive)[13, 14]	1998	470	5.6	Diabetes mellitus and hypertension	58	14	+ + +
ABCD (normotensive)[15]	2002	354	5.3	Diabetes mellitus and normotensive	59	7	+ + +
ALLHAT[16, 17] (diabetes mellitus)	2002	7107	4.9	Diabetes mellitus and hypertension	67	39	+ + +
ALLHAT[16, 17, 18] (impaired fasting glucose)	2002	771	4.9	Impaired fasting glucose and hypertension	67	30	+ + +
BENEDICT[19]	2004	604	3.6	Diabetes mellitus and hypertension	62	NR	± ± +
CAMELOT[20] (diabetes mellitus)	2004	233	2	Diabetes mellitus and coronary artery disease	58	NR	+ + +
CAMELOT[20] (impaired fasting glucose)	2004	233	2	Impaired fasting glucose and coronary artery disease	58	NR	+ + +
CASE-J[21, 22, 23] (diabetes mellitus)	2008	1195	3.2	Diabetes mellitus and hypertension	67	NR	+ + +
FACET[24]	1998	380	2.9	Diabetes mellitus and hypertension	63	NR	+ ± +
Fogari et al[25]	2002	205	4	Diabetes mellitus with proteinuria and hypertension	63	NR	+ ± ±
IDNT[26, 27, 28]	2001	1146	2.6	Diabetes mellitus with nephropathy and hypertension	60	13	± + +
JMIC-B[29, 30] (diabetes mellitus)	2004	372	3	Diabetes mellitus, hypertension, and coronary artery disease	64	NR	+ + +
J-MIND[31]	2001	436	2	Diabetes mellitus and hypertension	60	NR	+ + ±
MITEC[32]	2009	209	2	Diabetes mellitus and hypertension	60	NR	+ ± +
MOSES[33, 34] (diabetes mellitus)	2005	498	2.5	Diabetes mellitus, hypertension, and cerebrovascular accident	70	NR	+ + +
NAGOYA HEART[35]	2012	1150	3.2	Diabetes mellitus and hypertension	63	NR	+ ± +
STOP-Hypertension-2[36] (diabetes mellitus)	1999	466	5	Diabetes mellitus and elderly hypertension	76	NR	± + +
RAS blockers versus diuretic:							
ALLHAT[16, 17] (diabetes mellitus)	2002	9504	4.9	Diabetes mellitus and hypertension	67	39	+ + +
ALLHAT[16, 17, 18] (impaired fasting glucose)	2002	1035	4.9	Impaired fasting glucose and hypertension	67	30	+ + +
ANBP2[37, 38] (diabetes mellitus)	2003	441	4.1	Diabetes mellitus and elderly hypertension	72	NR	± + +
NESTOR[39]	2003	569	1	Diabetes mellitus with microalbuminuria and hypertension	60	5	+ ± +
RAS blockers versus β blockers:							
UKPDS 39[40]	1998	758	8.4	Diabetes mellitus and hypertension	56	8	+ + +
LIFE[41, 42, 43, 44] (diabetes mellitus)	2002	1195	4.8	Diabetes mellitus and hypertension with left ventricular hypertrophy	67	12	+ + +

ABCD=Appropriate Blood Pressure Control in Diabetes; ALLHAT=Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP2=Second Australian National Blood Pressure Study; BENEDICT=Bergamo Nephrologic Diabetes Complications Trial; CAMELOT=Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis; CASE-J=Candesartan Antihypertensive Survival Evaluation in Japan; FACET=Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial; IDNT=Irbesartan Type II Diabetic Nephropathy Trial; JMIC-B=Japan Multicenter Investigation for Cardiovascular Diseases-B; J-MIND=Japan Multicenter Investigation of Antihypertensive Treatment for Nephropathy in Diabetics; LIFE=Losartan Intervention For Endpoint reduction; MITEC=Media Intima Thickness Evaluation with Candesartan cilexetil; MOSES=Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention; NAGOYA HEART=Comparison between valsartan and amlodipine regarding morbidity and mortality in patients with hypertension and glucose intolerance; NESTOR=Natrilix SR versus Enalapril Study in Type 2 diabetic hypertensives with micrOalbuminuRia; NR=not reported; RAS-inh=Renin-Angiotensin System inhibitor; STOP-Hypertension=Swedish Trial in Old Patients with Hypertension; UKPDS=UK Prospective Diabetes Study Group.
*Represents risk of bias based on: sequence generation of allocation; allocation concealment and blinding. + represents low bias risk and ± unclear bias risk.

Bangalore S et al Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. BMJ 2016; 352:i438.

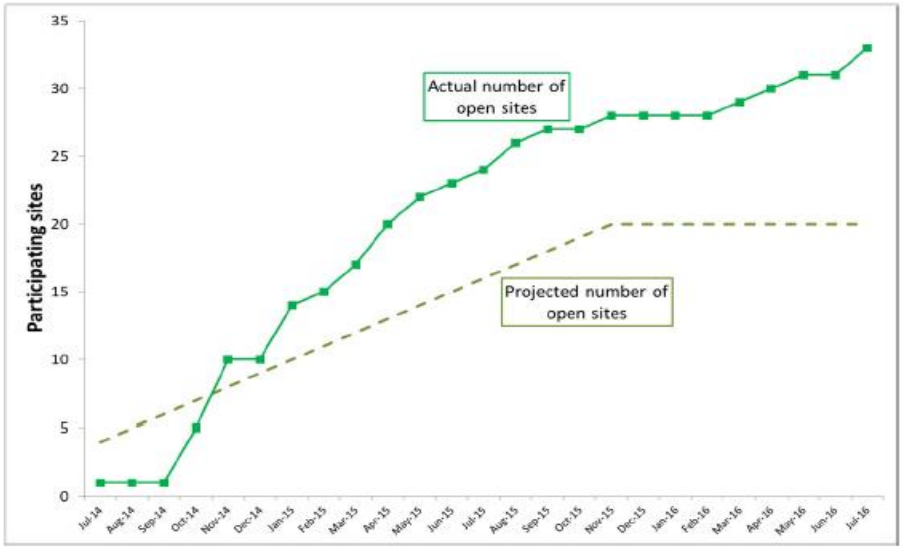
Renal Disease Outcomes

		Intensive		Standard			
		Events	%/yr	Events	%/yr	HR (95% CI)	P
Participants with CKD at Baseline							
	Primary CKD outcome	***14***	***0.33***	***15***	***0.36***	***0.89 (0.42, 1.87)***	***0.76***
	*≥50% reduction in eGFR**	*10*	*0.23*	*11*	*0.26*	*0.87 (0.36, 2.07)*	*0.75*
	Dialysis	*6*	*0.14*	*10*	*0.24*	*0.57 (0.19, 1.54)*	*0.27*
	Kidney transplant	*0*	*-*	*0*	*-*	*-*	*.*
	Secondary CKD Outcome						
	*Incident albuminuria***	*49*	*3.02*	*59*	*3.90*	*0.72 (0.48, 1.07)*	*0.11*
Participants without CKD at Baseline							
	Secondary CKD outcomes						
	*≥30% reduction in eGFR**	*127*	*1.21*	*37*	*0.35*	*3.48 (2.44, 5.10)*	*<.0001*
	*Incident albuminuria***	*110*	*2.00*	*135*	*2.41*	*0.81 (0.63, 1.04)*	*0.10*

SPRINT
Systolic Blood Pressure Intervention Trial

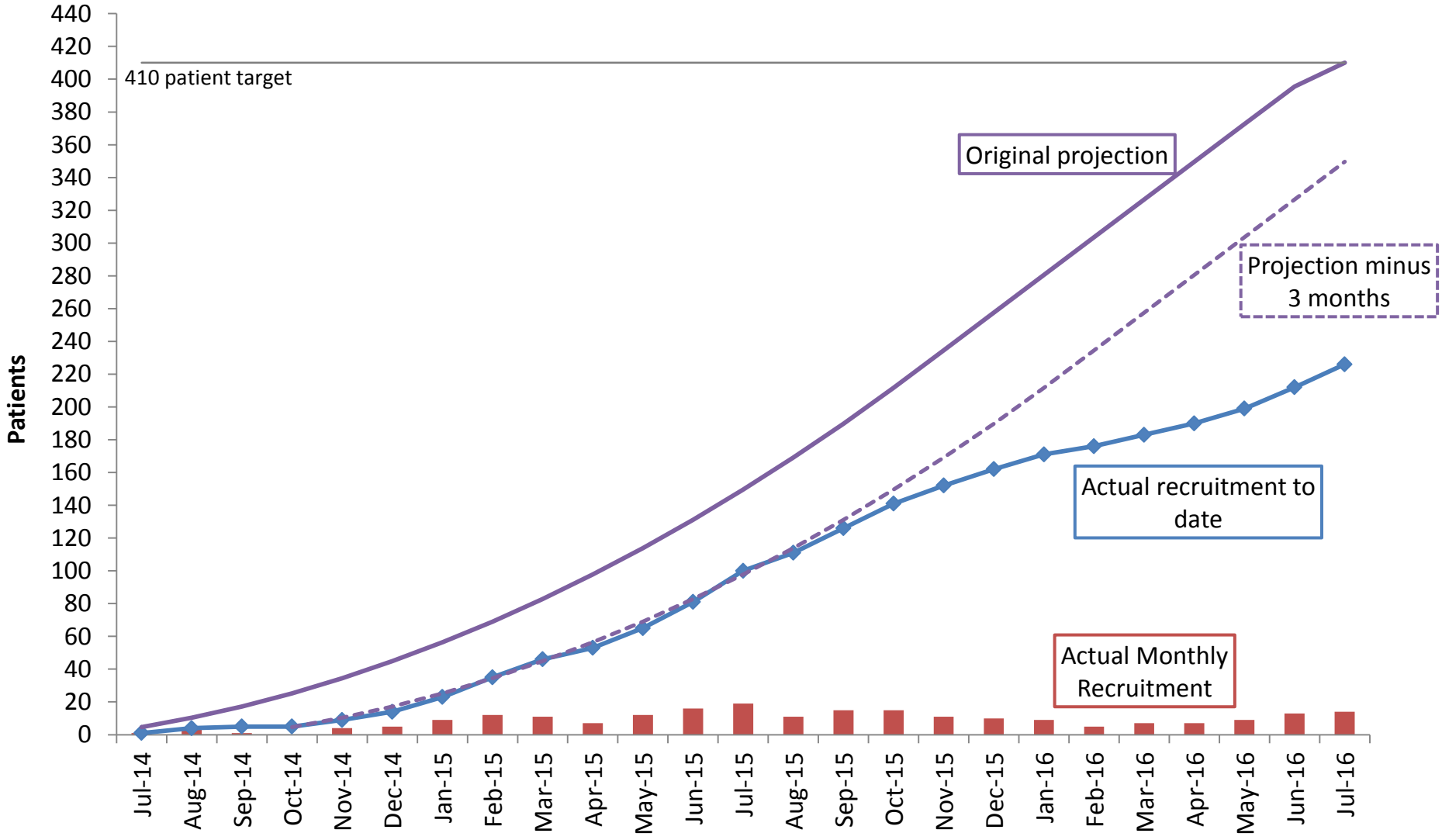
Participating sites

Graph and map of participating STOP-ACEi sites

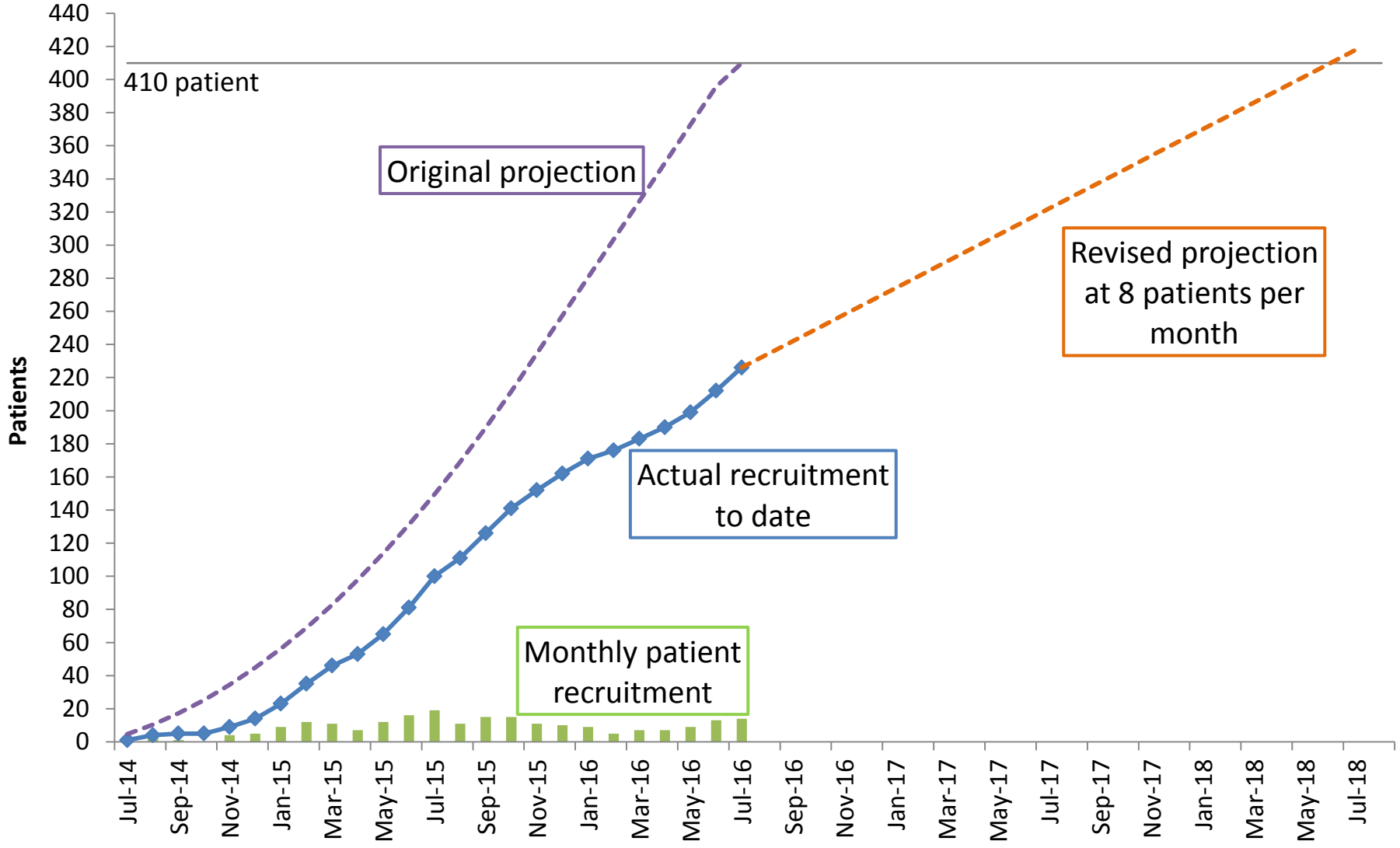


- 33 UK renal units are open to patient recruitment
- There is still time for new sites to join

Patient Recruitment



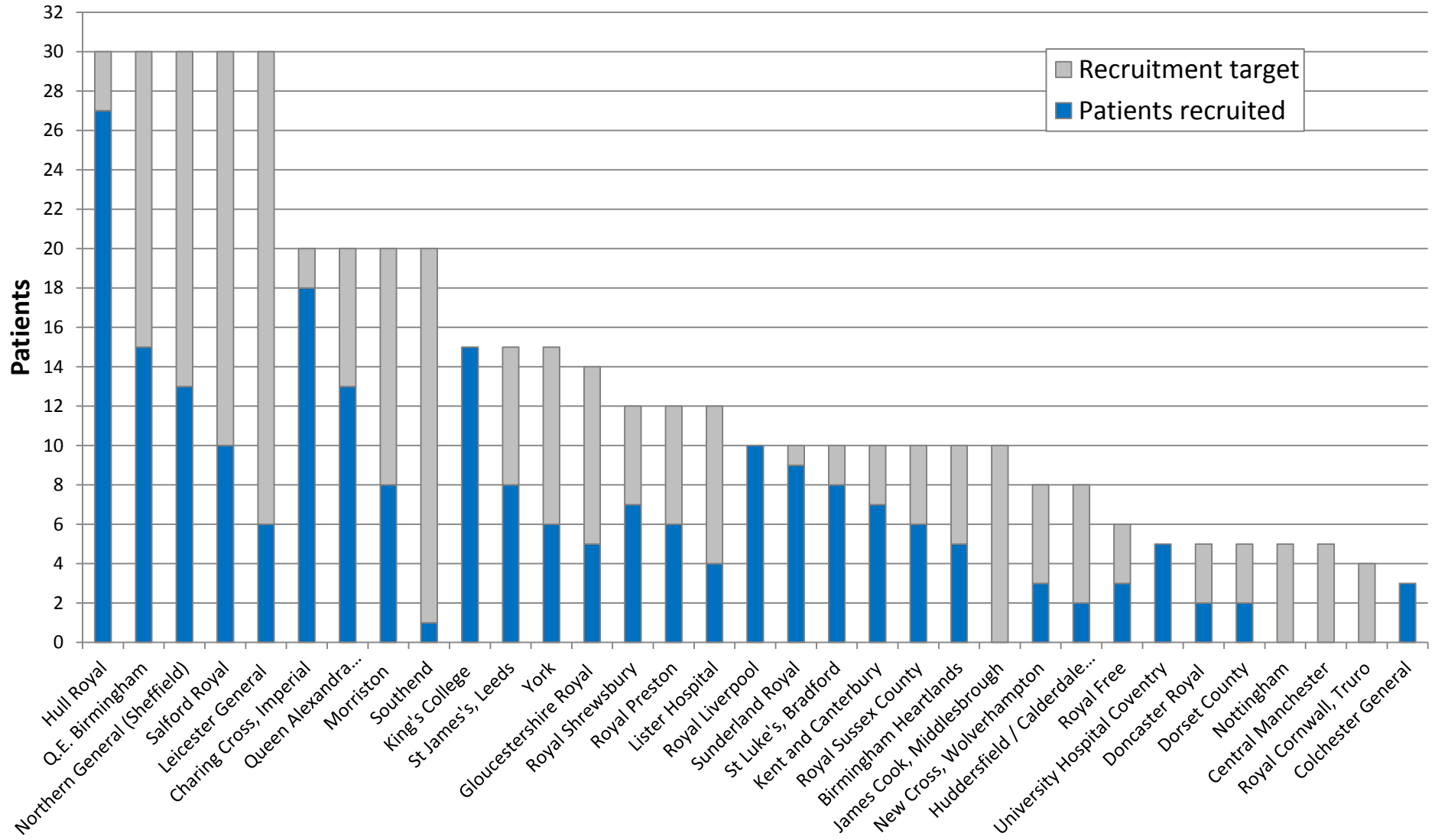
Actual Patient Recruitment with Original and Revised Projections



Key recruitment figures

Total recruitment target	410
Recruitment to date	227 (55%)
Sum of site recruitment targets	439 (107%)
Average recruitment rate	9.0 patients per month
Average rate of recruitment per site	0.5 patients per month
Range of site recruitment rates	0.1 - 1.2 patients per month
Sites open to recruitment	33
Sites that have recruited ≥1 patient	29 (88%)
Sites that have recruited in 2016	25 (76%)

Recruitment per site against target



Recruitment issues

- **Patient related**
  - "feel too old"
  - Anxious to stop medication
  - Much effort required
- **Trial related**
  - Inclusion criteria
  - Progression and proteinuria
  - Follow-up
- **Clinical Practice related**
  - "Think Kidneys program" – stopping ACEi
  - Drug Holiday program
- **Researcher related**
  - Movement of patients to peripheral units – follow-up challenging
  - Change in care pathway – eg move to PD or HD or Tx