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

ROYAL COLLEGE of PHYSICIANS of EDINBURGH

Investigator Meeting

12th September 2017 - Sheffield

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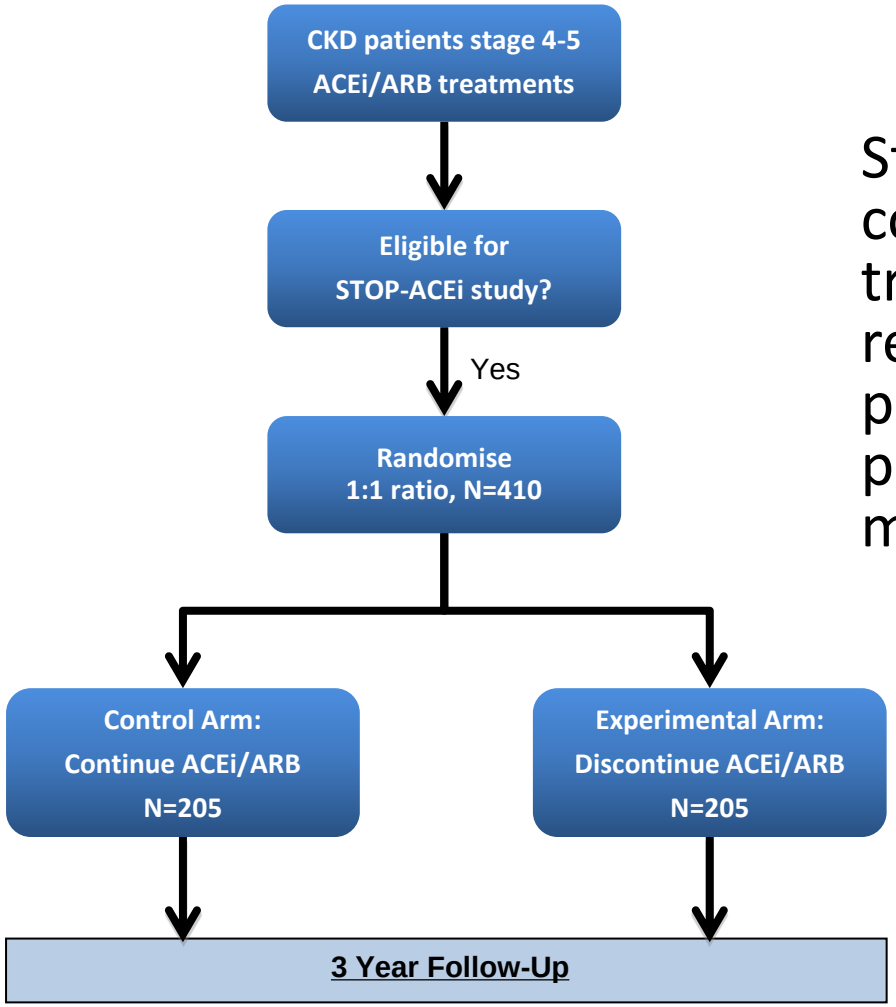
Multi-centre Randomised Controlled Trial of Angiotensin Converting Enzyme inhibitor/Angiotensin Receptor Blocker withdrawal in advanced renal disease



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 –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	

Outline

- Latest research
- Recruitment issues
- Trial update and NIHR
- Future
  - Follow-up
  - Retention of patients to end of study & beyond

Guidelines recommend use of RAAS inhibitors for Heart Failure

Class I recommendation

- ACE inhibitors are recommended for patients with asymptomatic LV systolic dysfunction with or without a history of MI in order to prevent or delay the onset of HF and prolong life

Class II recommendation

- ACE inhibitors should be considered in patients with stable coronary artery disease even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF

EUROPEAN SOCIETY OF CARDIOLOGY®

ACE=angiotensin-converting enzyme; HF=heart failure; LV=left ventricular; MI=myocardial infarction; RAAS=renin–angiotensin–aldosterone system

Ponikowski P, et al. *Eur J Heart Fail.* 2016;18:891–975

"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

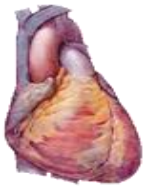
HF studies provide little information to direct care in advanced CKD - patients with significant renal dysfunction were excluded

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

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

Guidelines recommend use of RAAS inhibitors for CKD

NICE

Offer a low-cost RAAS antagonist to people with CKD and:[1]

- Diabetes and ACR of ≥3mg/mmol
- Hypertension and ACR of ≥30mg/mmol
- ACR of ≥70mg/mmol (irrespective of hypertension or CVD)

Level 1 recommendation[2]

- We recommend ARB or ACE inhibitor use in both diabetic & non-diabetic adults with CKD & urine albumin excretion >300mg/24 hours (or equivalent)

Level 2 recommendation[2]

- We suggest ARB or ACE inhibitor use in diabetic adults with CKD and urine albumin excretion 30–300mg/24 hours (or equivalent)

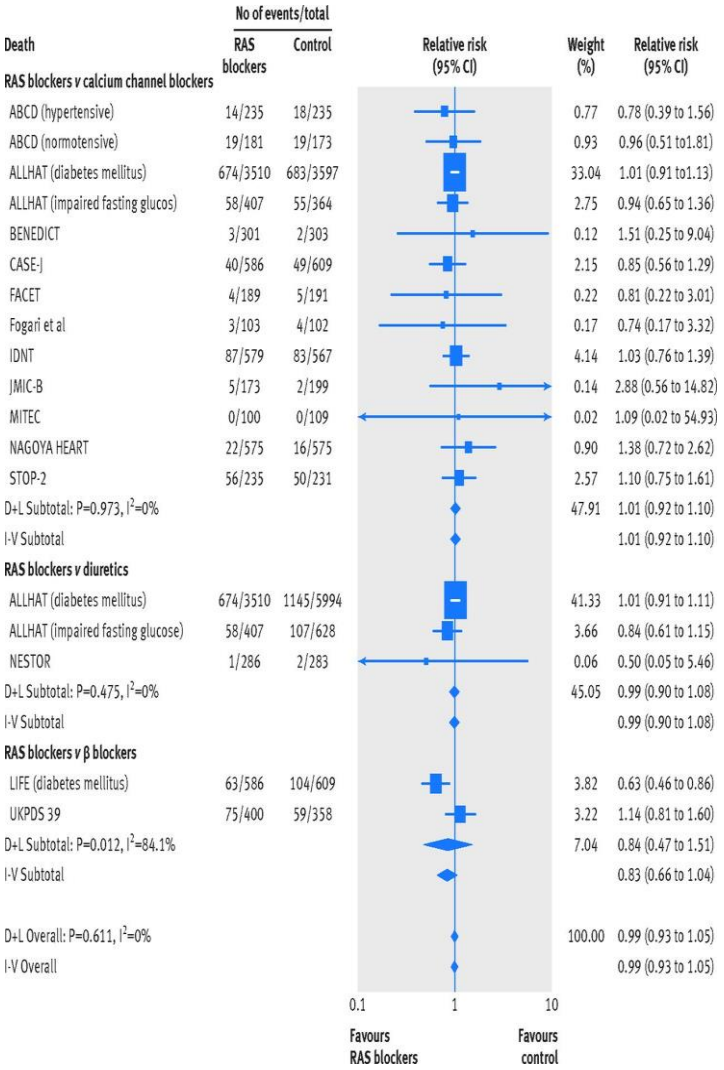
ACE=angiotensin-converting enzyme; ACR=albumin:creatinine ratio; ARB=angiotensin II receptor blocker; CKD=chronic kidney disease; NICE=National Institute for Health and Care Excellence; RAAS=renin–angiotensin–aldosterone system

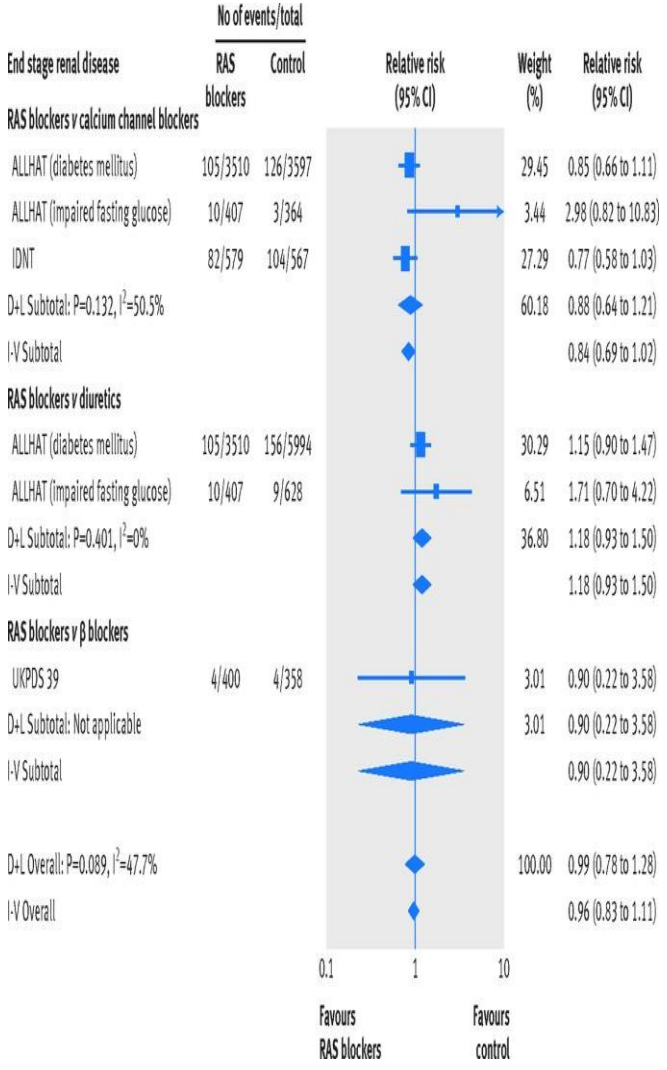
1. NICE. *Chronic kidney disease in adults: assessment and management* [online] 2014. Available at: https://www.nice.org.uk/guidance/cg182 [Last accessed: January 2017]; 2. KDIGO. *Kidney Int Suppl.* 2013;3:5–14

Controversies Meeting 2017
Use of RAAS inhibitors for BP and CKD

- Twitter talk on what to do and really what do we know
  - " We don't yet know whether stopping RAAS blockade in CKD 4/5 improves outcomes but STOP ACEi trial may guide us"
- STOP ACEi trial mentioned

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





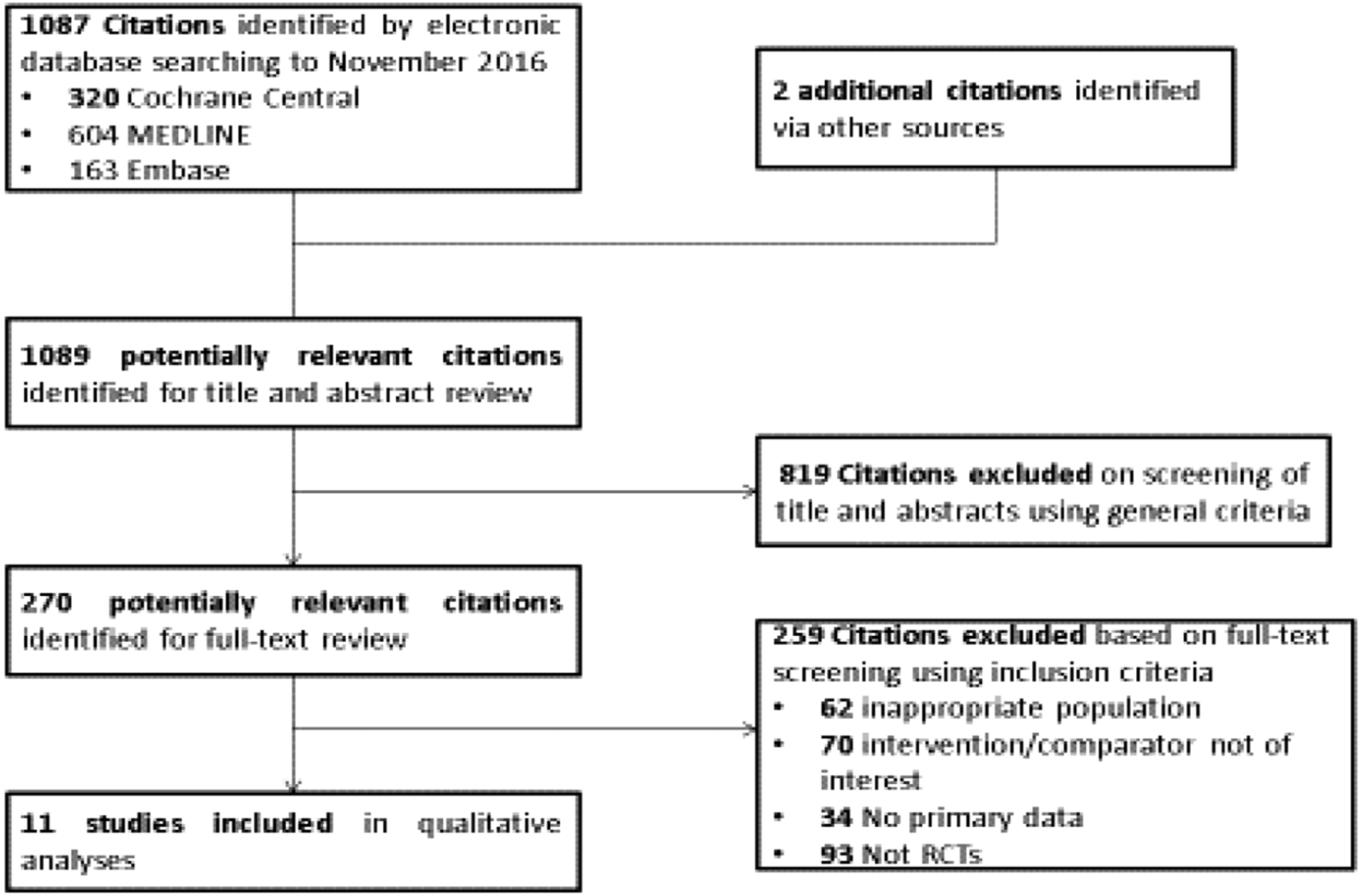
19 RCTs
25414 participants

No difference in

- Death
- CV death
- MI
- Angina
- Stroke
- HF
- Renal Outcomes

Bangalore S et al. BMJ 2016; 352:i438.

Effect of RAAS blockade in adults with diabetes mellitus and advanced CKD not on dialysis: a systematic review and meta-analysis



Nephrol Dial Transplant. Published online July 02, 2017. doi:10.1093/ndt/gfx072

Effect of RAAS blockade in adults with diabetes mellitus and advanced CKD not on dialysis: a systematic review and meta-analysis

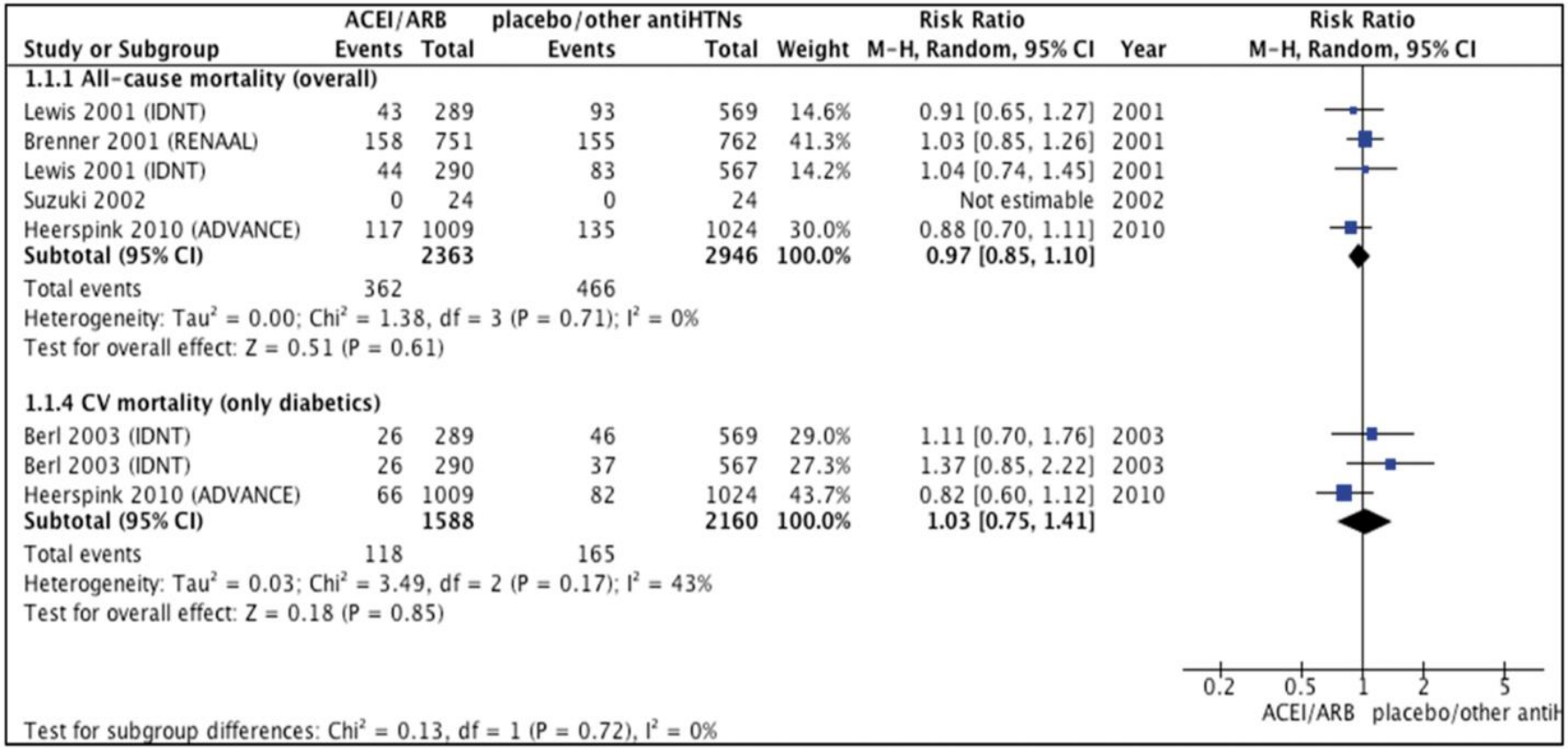


FIGURE 2 All-cause mortality and CV mortality: ACEIs/ARBs versus placebo/other antihypertensive treatment.

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Effect of RAAS blockade in adults with diabetes mellitus and advanced CKD not on dialysis: a systematic review and meta-analysis

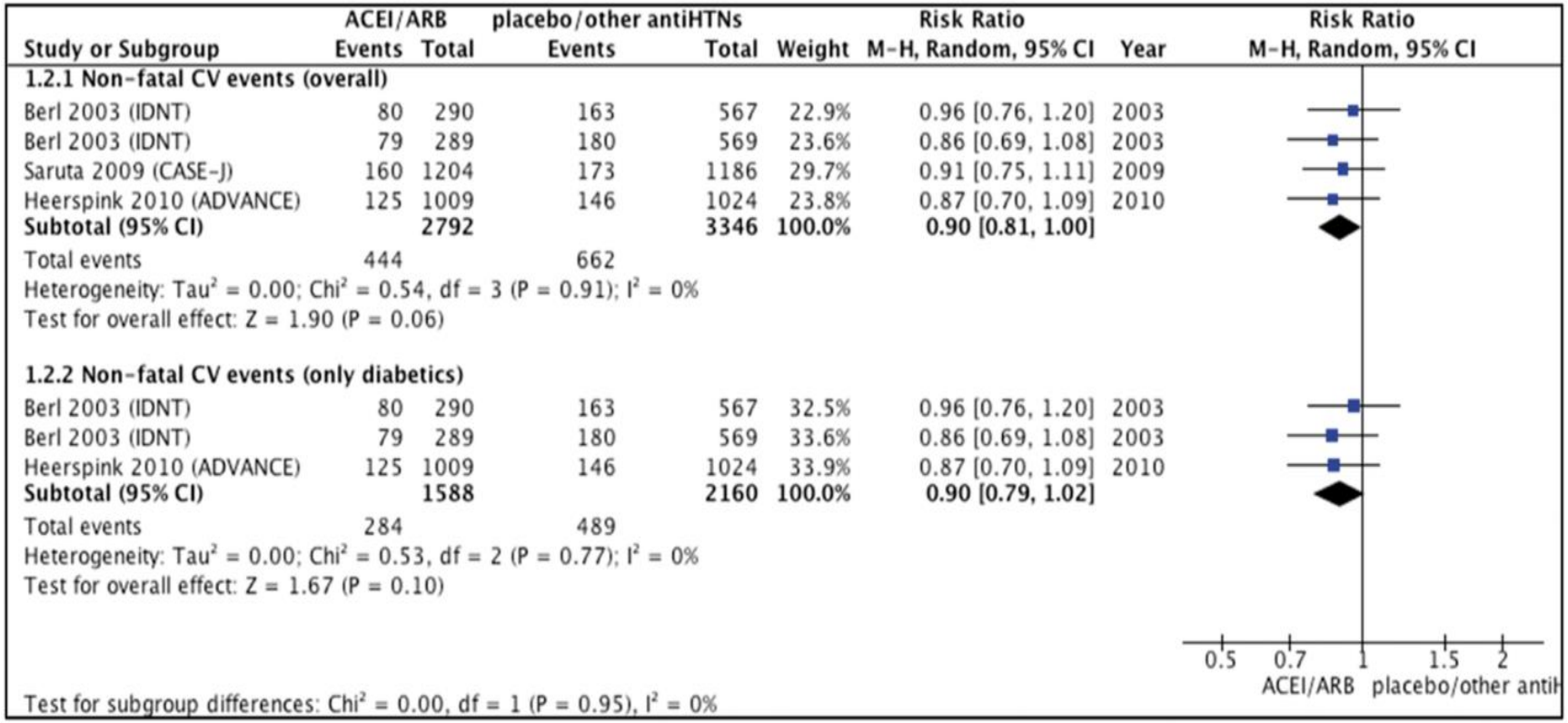

FIGURE 3 Non-fatal CV events: ACEIs/ARBs versus placebo/other antihypertensive treatment.

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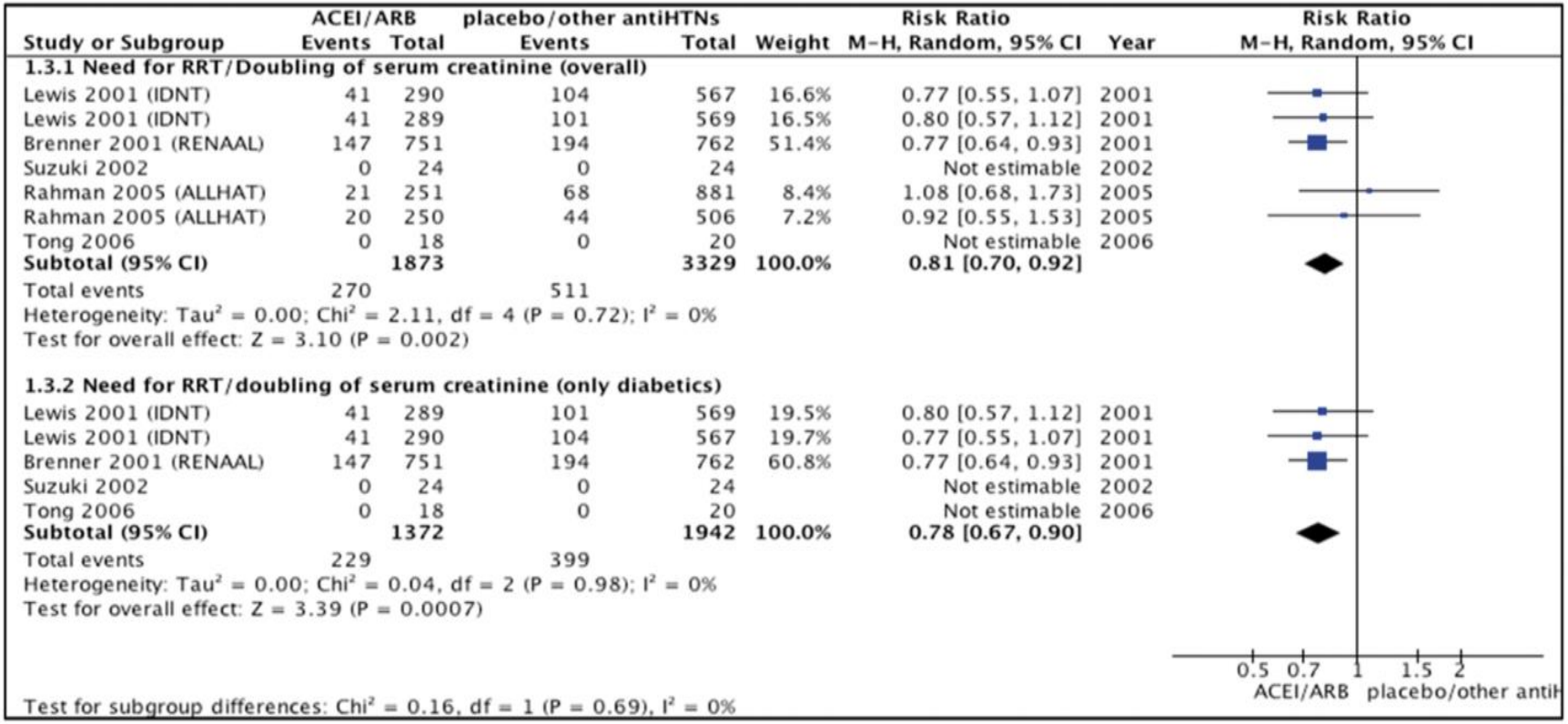

Figure 4: Need for RRT/doubling of serum creatinine: ACEIs/ARBs versus placebo/other antihypertensive treatment

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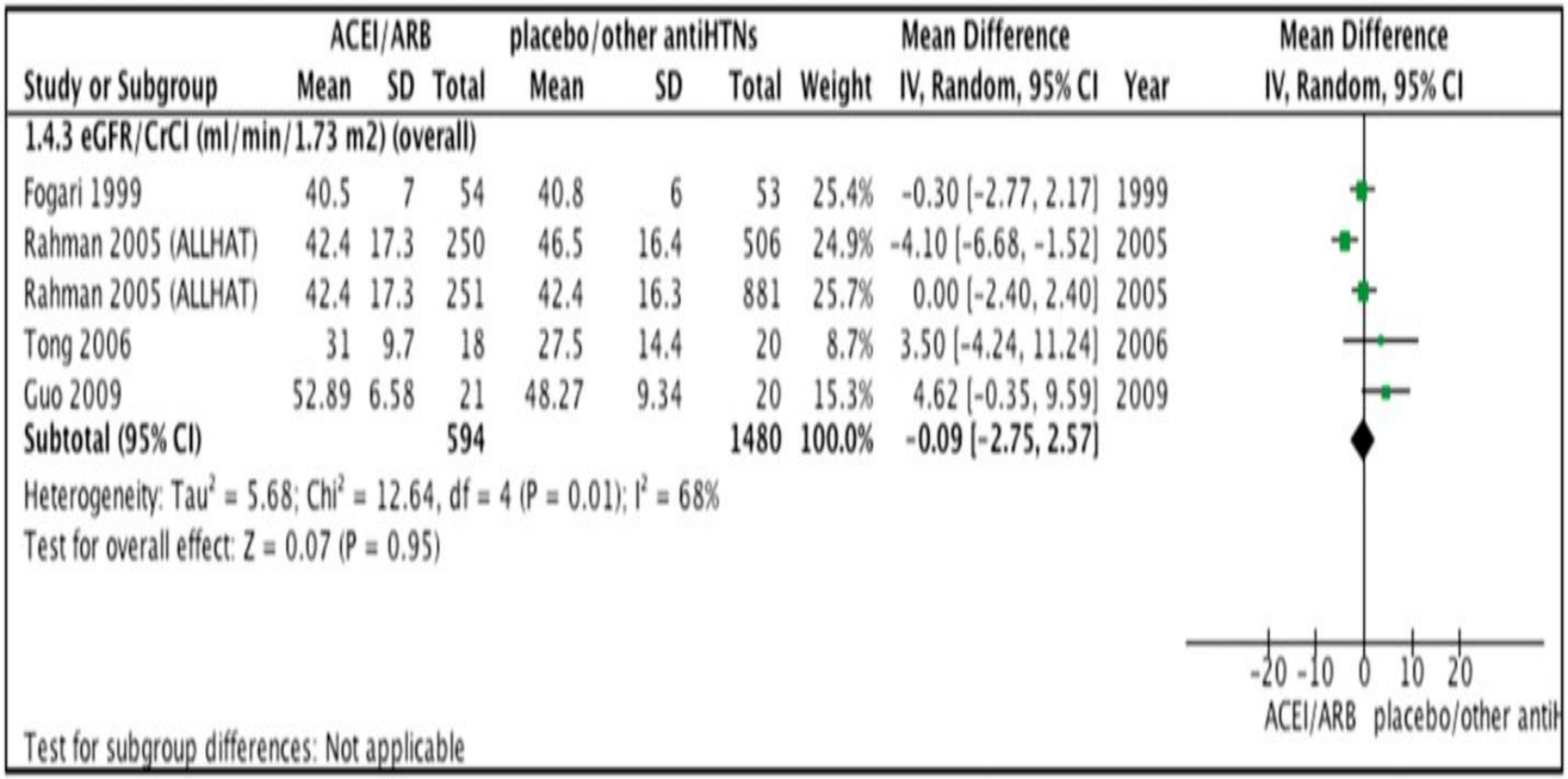


FIGURE 5 eGFR/CrCl (ml/min/1.73 m²), end-of-treatment values: ACEIs/ARBs versus placebo/other antihypertensive treatment.

Nephrol Dial Transplant. Published online July 02, 2017. doi:10.1093/ndt/gfx072

What are the risks and benefits of temporarily discontinuing medications to prevent acute kidney injury? A systematic review and meta-analysis

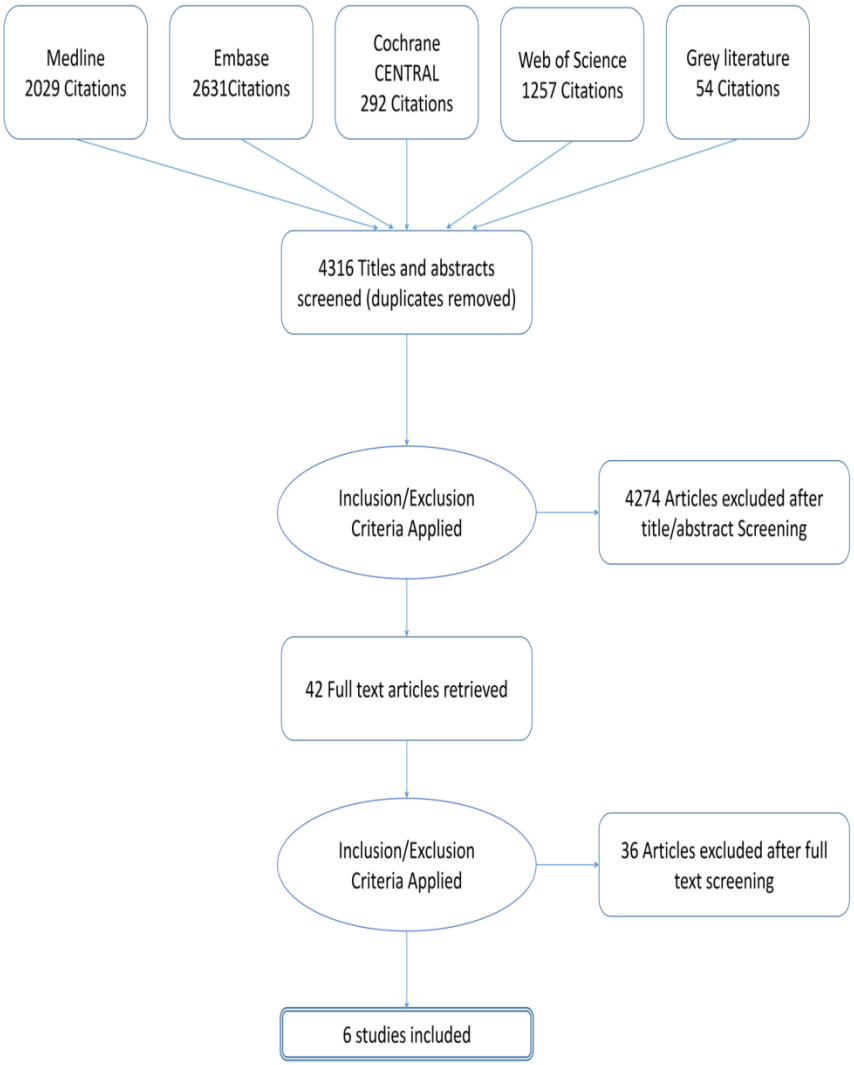


Table 1 Details of studies included in the review

	Bainey *et al*[18]	Rosenstock *et al*[17]	Wolak *et al*[16]	Coca *et al*[19]	Goksuluk *et al*[21*]	Weisbord *et al*[20]
Study design	RCT	RCT	RCT	Prospective cohort	Prospective cohort	Prospective cohort
Sample size	208	220	94	1017	80	44
Country	Canada	USA	Israel	North America	Turkey	USA
Population	Coronary angiography	Coronary angiography	Coronary angiography	Cardiac surgery	Coronary angiography	Coronary angiography
Risk group	CKD	CKD	None	High risk of AKI	Diabetes	CKD
Mean age (SD)	Intervention: 73 (9) Control: 72 (8)	Intervention: 72 (10) Control: 72 (10)	65 (12)	Intervention: 71 (11) Control: 70 (12)	NR	NR
Female (%)	26	52	33	31	NR	NR
AKI definition	Increase in SCr ≥25% or ≥0.5 mg from baseline	Increase in SCr >25% or 0.5 mg from baseline	Increase in SCr ≥25% from baseline	Increase in SCr ≥50% or ≥0.3 mg from baseline	Increase in SCr ≥25% or ≥0.5 mg from baseline	Increase in SCr ≥25% from baseline or ≥0.5 mg from baseline
Comorbidities	Diabetes (54%), hypertension (47%), congestive heart failure (14%), liver cirrhosis (1%)	Hypotension (97%), diabetes (55%)	Diabetes (50%), unstable angina (62%)	Diabetes (47%), Hypertension (88%), congestive heart failure (23%)	Diabetes (100%)	NR
Study drug	ACE/ARB	ACE/ARB	ACE/ARB	ACE/ARB	ACE/ARB	NSAIDs
Intervention: timing of hold	24 hours prior to procedure	Day of procedure	24 hours prior to procedure	Morning of surgery	24 hours before procedure	No details
Intervention: timing of restart	Up to 96 hours postprocedure	24 hours postprocedure	(1) Immediately afterwards; (2) 24 hours after	No details	No details	No details
Control	Continued throughout study	Continued throughout study	Continued throughout study	Continued throughout study	Continued throughout study	Continued throughout study
Risk of bias	Low	Some: randomised by coin toss, no information on allocation concealment. Baseline difference compatible with chance	Some; no information on treatment allocation, baseline difference compatible with chance	Moderate; controlled for confounding but possibility of residual confounding	Critical; no control for confounding	Not assessed

Whiting P, et al. BMJ Open 2017;7:e012674. doi:10.1136/bmjopen-2016-012674

BMJ Open

What are the risks and benefits of temporarily discontinuing medications to prevent acute kidney injury? A systematic review and meta-analysis

Summary Headline

Low-quality evidence that withdrawal of ACEI/ARBs prior to coronary angiography & cardiac surgery may reduce the incidence of AKI.

No evidence of the impact of drug cessation interventions on AKI incidence during intercurrent illness in primary or secondary care.

Impact of AKI in terms of the development of CKD or reductions in baseline GFR was not reported.

UK NICE guidance 2013 recommends consideration of temporarily stopping ACEI and ARBs in adults having iodinated contrast agents if they have CKD, eGFR <40 mL/min, and in adults, children and young people with diarrhoea, vomiting or sepsis.

Sick-Day Rules cards, advising to stop taking ACEIs/ARBs, NSAIDS, diuretics and metformin when they become unwell with vomiting or diarrhoea, and/or fevers sweats and shaking.

Whiting P, et al. BMJ Open 2017;7:e012674. doi:10.1136/bmjopen-2016-012674

BMJ Open

Angiotensin Converting Enzyme Inhibitor, Angiotensin Receptor Blocker Use, and Mortality in Patients With Chronic Kidney Disease

RCTs of ACEI and/or ARB in CKD do not offer a clear answer regarding their effect on mortality.

Large, nationally representative cohort of U.S. veterans with non-dialysis dependent CKD: n = 141,413

Table 1. Baseline Characteristics of Individuals Stratified by ACEI/ARB Exposure

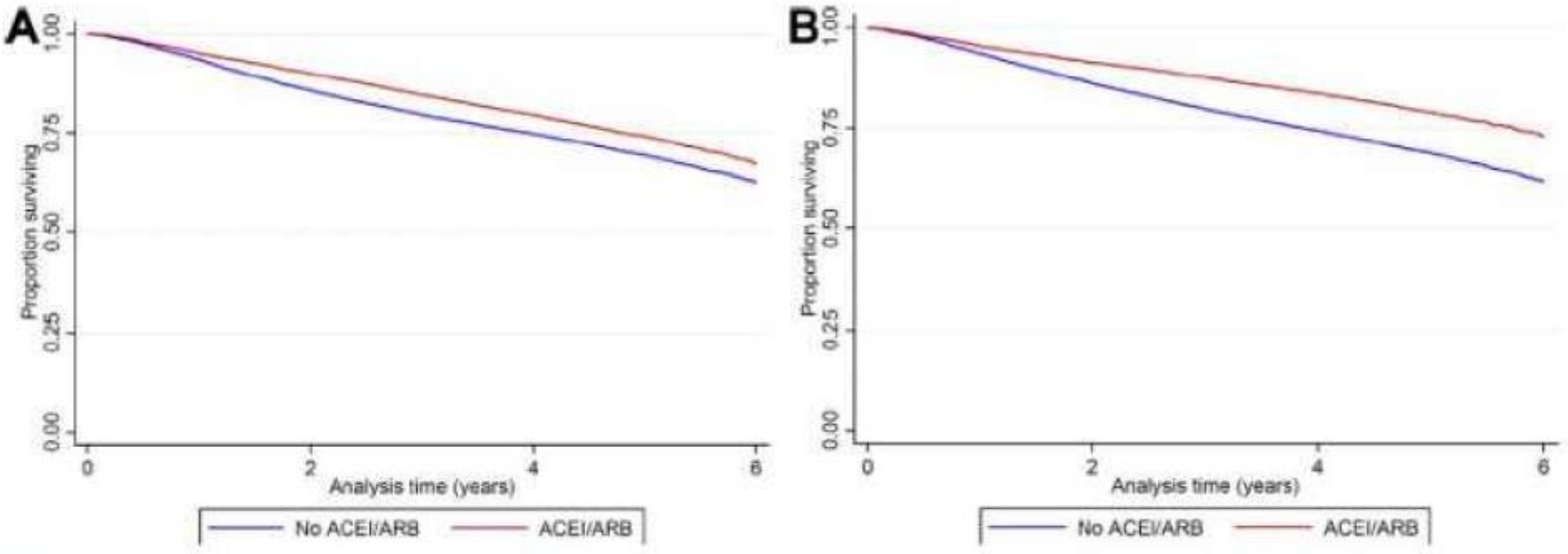
	Total Cohort (N = 141,413)	ACEI/ARB Treated (n = 26,051)	Untreated (n = 115,362)	p Value*
Male	97%	97%	96%	<0.001
Age (yrs)	74.8 ± 9.8	73.1 ± 10.3	75.2 ± 9.7	<0.001
Deaths	39,556 (28%)	6,484 (25%)	33,072 (29%)	<0.001
Race				<0.001
White	89%	85%	90%	
African American	8%	10%	7%	
Hispanic	1%	1%	1%	
Other	2%	4%	2%	
Diabetes mellitus	22%	41%	17%	<0.001
eGFR (ml/min/1.73 m^2)	50 ± 13	52 ± 16	50 ± 12	<0.001

Miklos Z. Molnar; Kamyar KalantarZadeh et al J Am Coll Cardiol. 2014;63(7):650658.

JACC

Angiotensin Converting Enzyme Inhibitor, Angiotensin Receptor Blocker Use, and Mortality in Patients With Chronic Kidney Disease

Figure 1: survival probability of treated and untreated patients in the propensity score matched cohort, with ACEI/ARB treatment -association with lower mortality in both intention to treat and as treated models.



Miklos Z. Molnar; Kamyar KalantarZadeh et al J Am Coll Cardiol. 2014;63(7):650658.

SUMMARY OF FINDINGS

Angiotensin Converting Enzyme Inhibitor, Angiotensin Receptor Blocker Use, and Mortality in Patients With Chronic Kidney Disease

- Administration of ACEI/ARB was associated with lower all cause mortality and a substantial survival benefit in non dialysis dependent patients with CKD even with adjustment for confounders and propensity matching

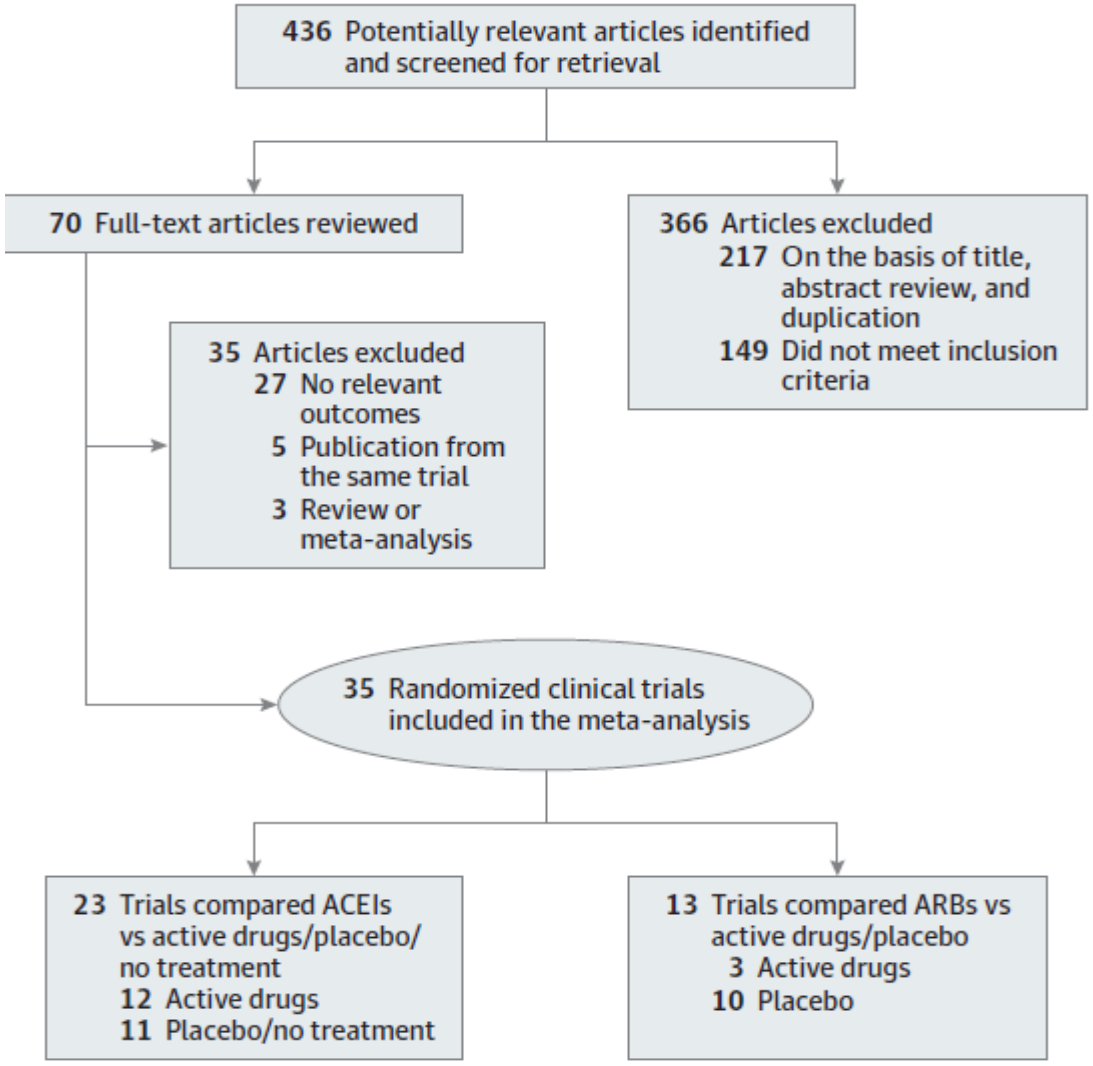
- Non dialysis dependent patients with CKD, discontinuation rates of ACEI/ARB were high:
  - only 66% of treated patients received renewed prescriptions on >50% of their follow up visits
  - only <10% of patients remained on ACEI/ARB therapy throughout all follow up visits

- Patients treated with ACEI/ARB were more likely to be black, have diabetes, hypertension, congestive heart failure, CVD, and higher systolic and diastolic blood pressures

Miklos Z. Molnar; Kamyar KalantarZadeh et al J Am Coll Cardiol. 2014;63(7):650658.

JACC

Effect of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on All-Cause Mortality, Cardiovascular Deaths, and Cardiovascular Events in Patients With Diabetes Mellitus A Meta-analysis



Cardioprotective effects of RAAS blockade were recently called into question.

The NIDDM, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril (DIABHYCAR) study found ACEIs had no effect on CV events in patients with type 2 DM and albuminuria.

There was a higher rate of fatal CV events with olmesartan therapy in ROADMAP (Randomized Olmesartan & Diabetes II Microalbuminuria Prevention)

Cheng et al JAMA Internal Medicine May 2014 Volume 174, Number 5

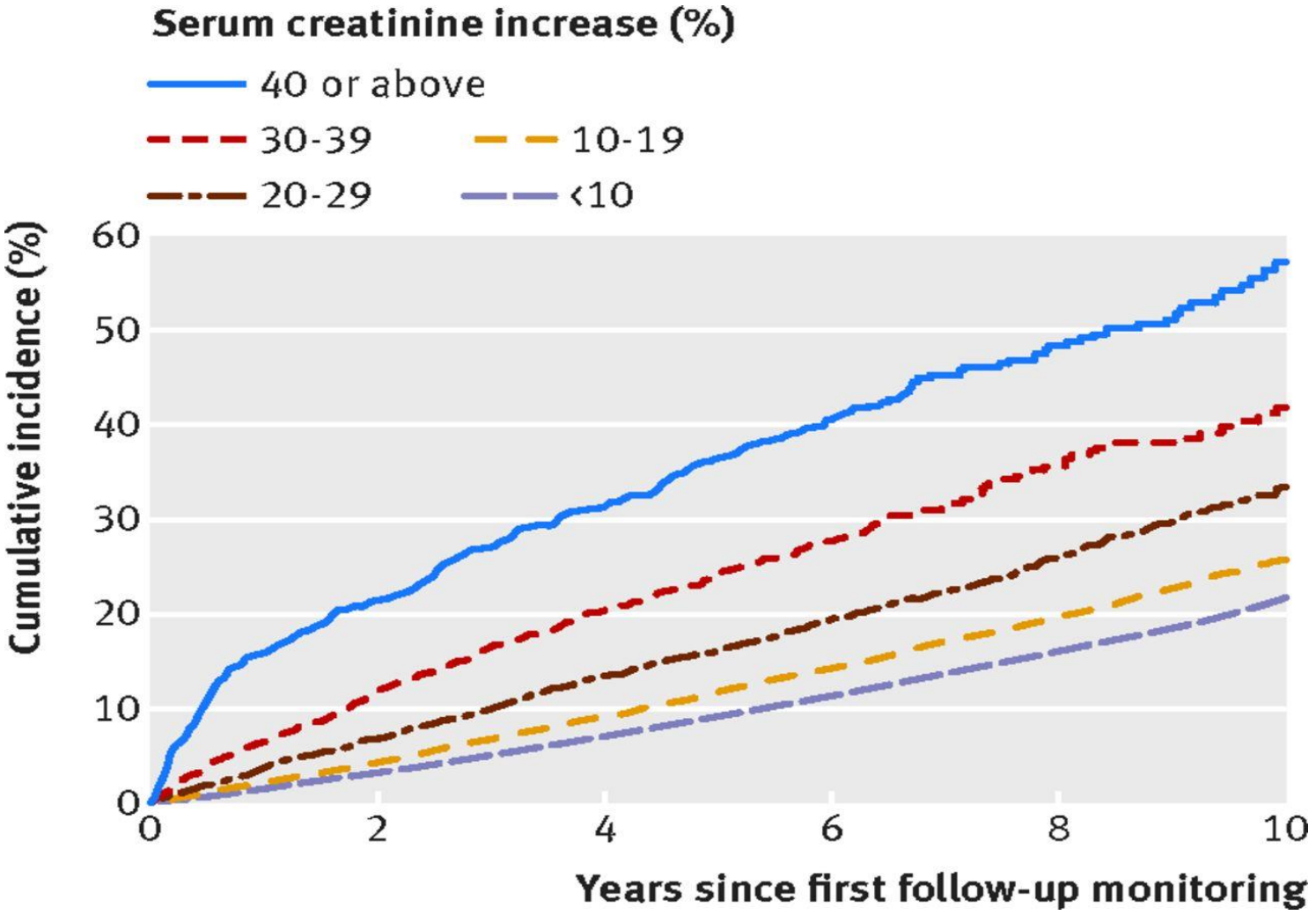
Summary of effects of ACEi and ARBs on All-Cause Mortality, Cardiovascular Deaths, and Cardiovascular Events in Patients With DM

- ACEIs significantly reduced the risk of:
  - all-cause mortality by ~ 13%
  - CV deaths by ~ 17%.
  - major CV events by 14%
    - myocardial infarction by 21%
    - heart failure by 19%

- ARB treatment did not significantly affect
  - all-cause mortality
  - CV death.
- ARB treatment reduced the risk of
  - heart failure by 30%

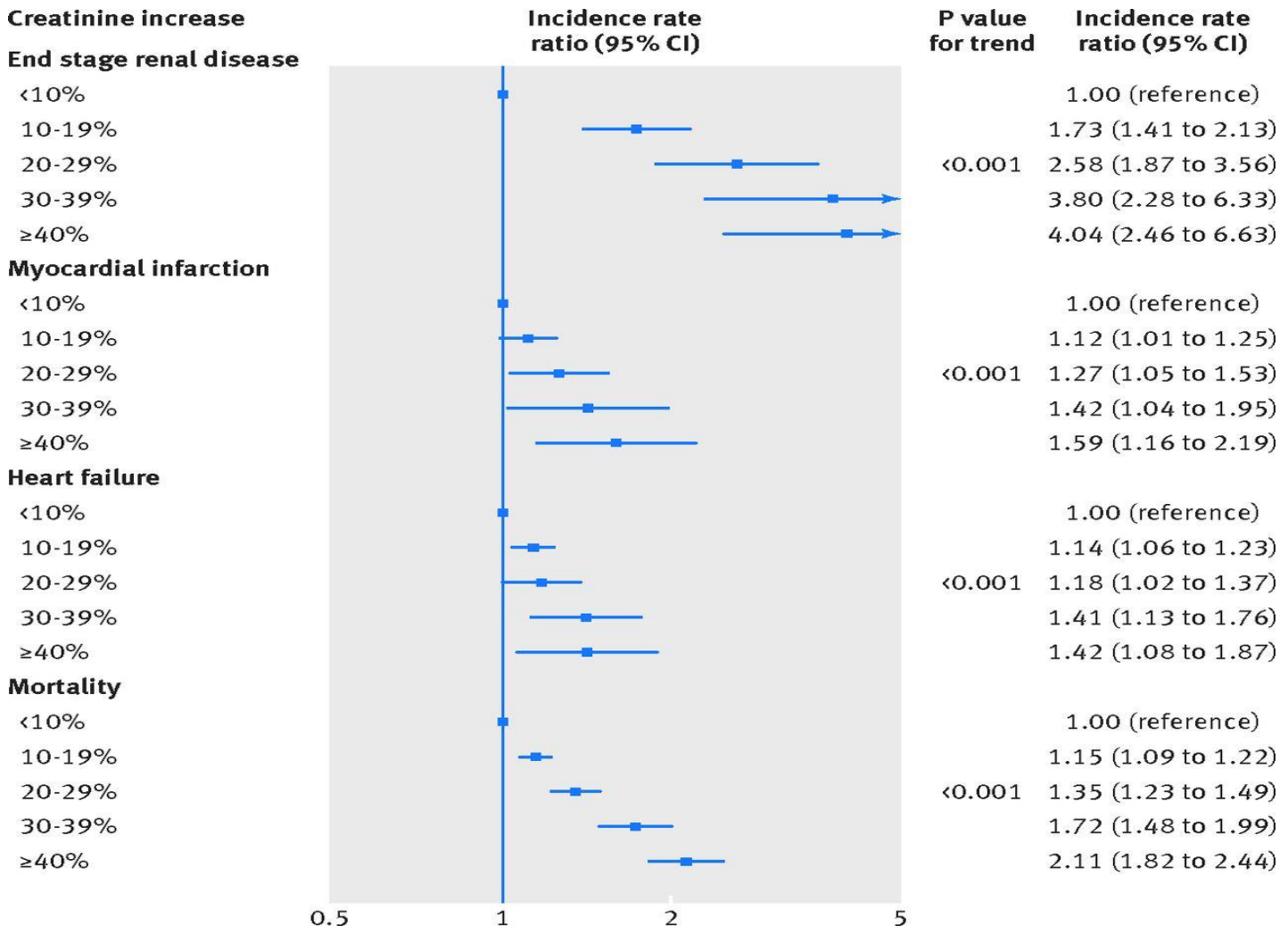
Cheng et al JAMA Internal Medicine May 2014 Volume 174, Number 5

Cumulative mortality according to levels of creatinine increase after renin-angiotensin system blockade.



Morten Schmidt et al. BMJ 2017;356:bmj.j791

Cardiorenal risks associated with levels of creatinine increase after RAAS blockade



Morten Schmidt et al. BMJ 2017;356:bmj.j791

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

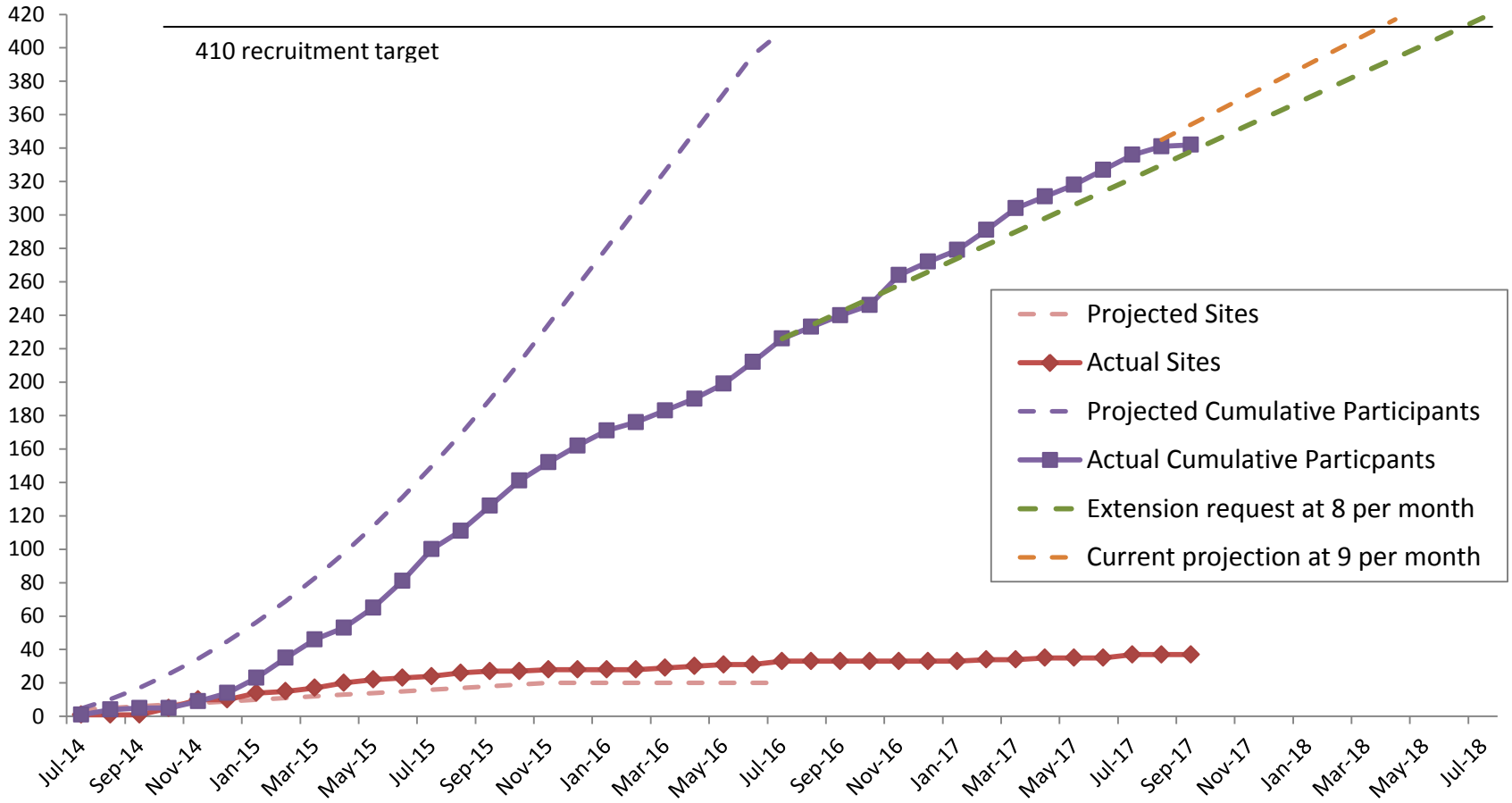
Outline

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

Participating sites

- **37 UK renal units are open to patient recruitment: ~20 active**

Future recruitment projections



	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18
Projected Sites	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	20	20	20	20	20	20	20	20																							
Actual Sites	1	1	1	5	10	10	14	15	17	20	22	23	24	26	27	27	28	28	28	28	29	30	31	31	33	33	33	33	33	33	33	34	34	35	35	35	37	37	37									
Projected Cumulative Participants	5	10	17	25	35	45	56	69	83	98	114	131	150	169	190	212	235	258	281	304	327	350	373	396	410																							
Actual Cumulative Particpants	1	4	5	5	9	14	23	35	46	53	65	81	100	111	126	141	152	162	171	176	183	190	199	212	226	233	240	246	264	272	279	291	304	311	318	327	336	341	342									
Extension request at 8 per month																									226	234	242	250	258	266	274	282	290	298	306	314	322	330	338	346	354	362	370	378	386	394	402	410	418
Current projection at 9 per month																																						345	354	363	372	381	390	399	408	417			

Key recruitment figures

Total recruitment target	410
Recruitment to date	342 (83%)
Sum of site recruitment targets	471 (115%)
Average recruitment rate	~9 patients per month
Average rate of recruitment per site	0.4 patients per month
Range of site recruitment rates	0.1 - 1.0 patients per month
Sites open to recruitment	37
Sites that have recruited ≥1 patient	32 (86%)
Sites that have recruited <6 months	21 (57%)

Recruitment per site against target