Blood Pressure Targets in CKD and Diabetes

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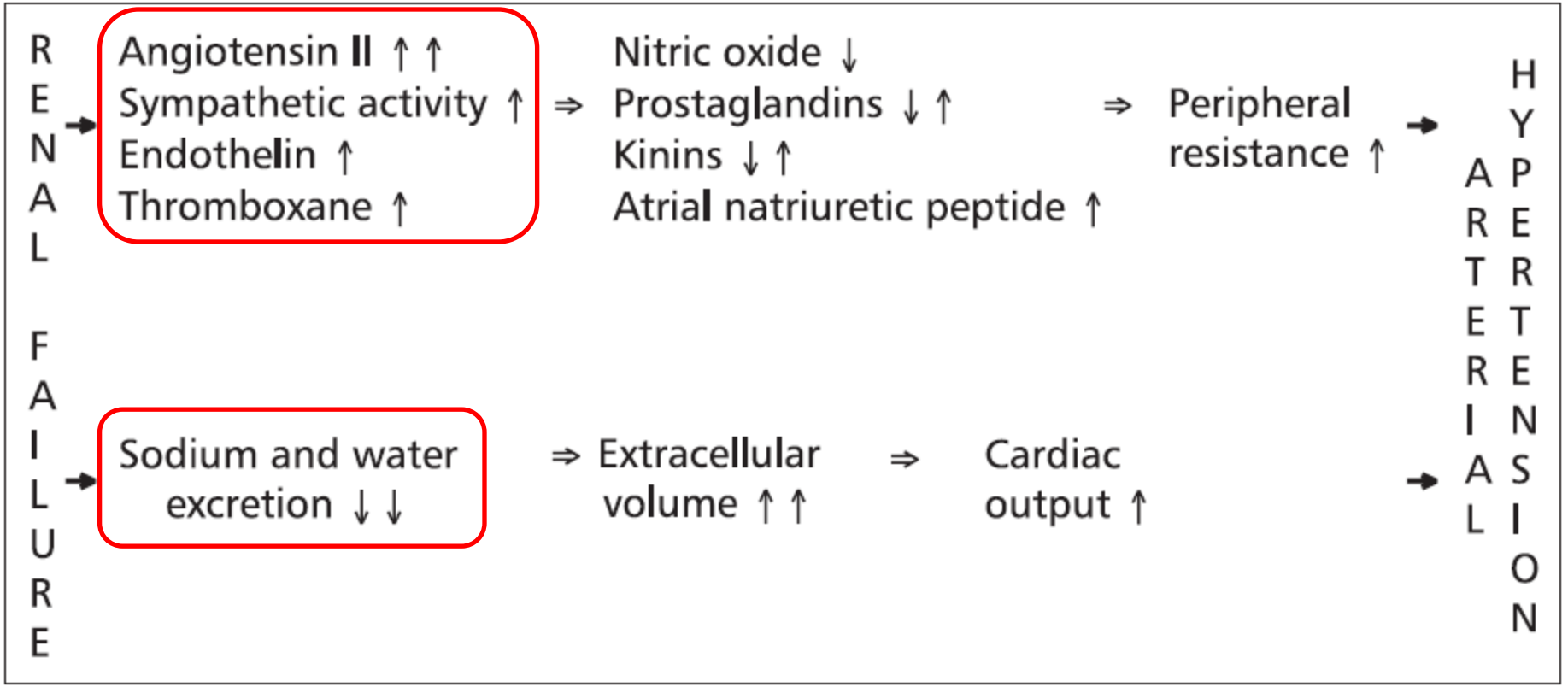
Arterial Hypertension in Chronic Kidney Disease



Rodicio JL & Alcazar JM. ESH Newsletter 2011, No. 4

Prevalence of Hypertension in Renal Parenchymal Disease

Table 1. Prevalence of hypertension in renal parenchymal disease

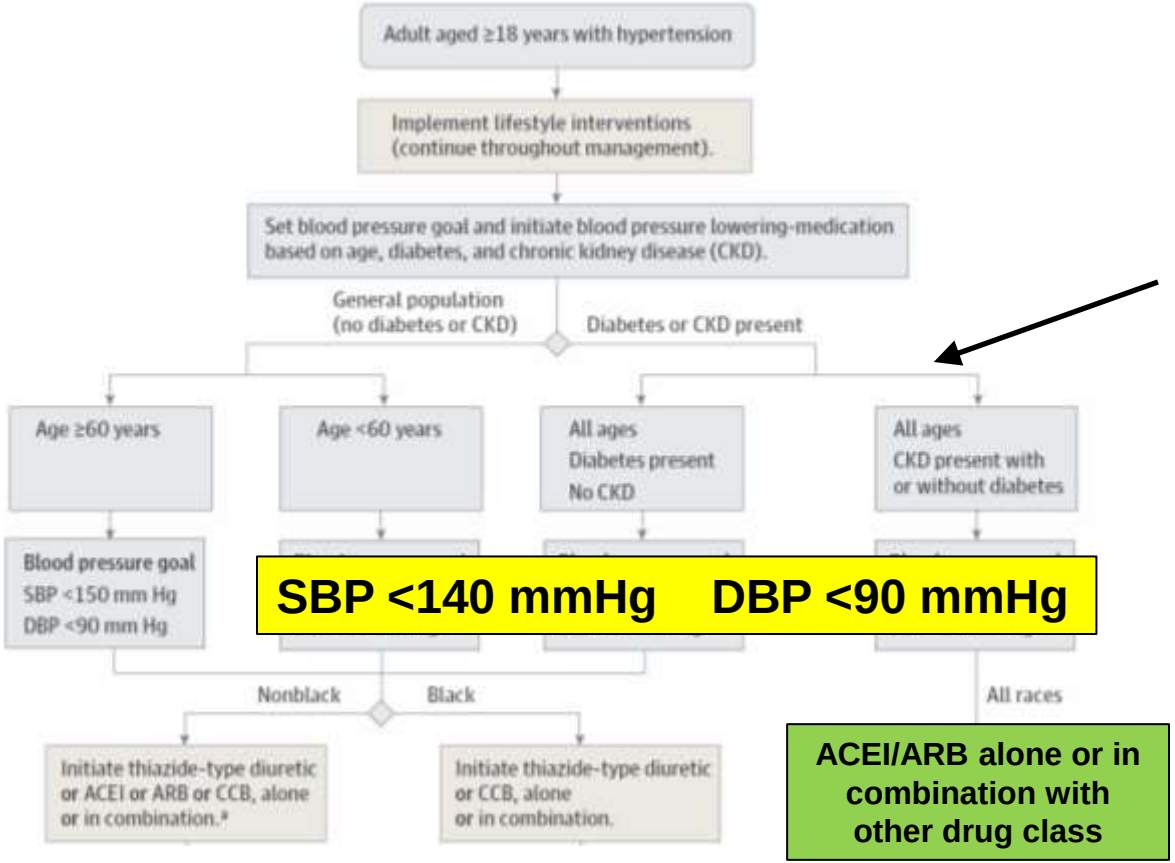
Focal glomerulosclerosis 75–85%	Diabetic nephropathy 65–75%
Membranoproliferative glomerulonephritis 60–70%	Membranous nephropathy 35–45%
Mesangioproliferative glomerulonephritis 30–40%	Ig A nephropathy 20–30%
Minimal change disease 10–15%	Interstitial nephritis 15–25%
Polycystic kidney disease 55–65%	

Rodicio JL & Alcazar JM. ESH Newsletter 2011, No. 4

Management of Hypertension in Chronic Kidney Disease

- Investigations into the nature of the patient's renal disease
- Blood pressure goal
- Non-pharmacological treatment
- Pharmacological treatment

JNC 8



CKD

SBP <140 mmHg DBP <90 mmHg

James PA et al. JAMA 2014

ESH/ESC

Other risk factors, asymptomatic organ damage or disease	Blood Pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF	• No BP intervention	• Lifestyle changes for several months • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
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OD, CKD stage 3 or diabetes	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs	• Lifestyle changes • BP drugs	• Lifestyle changes • Immediate BP drugs
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	• Lifestyle changes • No BP intervention	• BP drugs targeting <140/90	• BP drugs targeting <140/90	• Immediate BP drugs targeting <140/90

CKD

SBP <140 mmHg DBP <90 mmHg

2013 ESH/ESC Guidelines. J Hypertens 2013

ESH/ESC

Type of kidney disease	Protein excretion < 0.3 g/day (normoalbuminuria, microalbuminuria, 30–150 mg/day)	Protein excretion 0.3–1 g/day (microalbuminuria 150–300 mg/day, macroalbuminuria 300–500 mg/day)	Protein excretion > 1 g/day (macroalbuminuria > 500 mg/day)
Non-diabetic kidney disease	< 140/90 mm Hg	< 130/80 mm Hg	<125/75 mm Hg*
Diabetic kidney disease	SBP < 130–140 mm Hg** DBP < 80 mm Hg**	< 130/80 mm Hg***	<130/80 mm Hg*** (<125/75 mm Hg*** for young patients with heavy proteinuria)

*As evident from MDRD study B trial phase and MDRD long-term study (see *text*); **from cardiovascular outcome trials (see *text*); ***through extrapolation from data in non-diabetic CKD and post-hoc or observational analyses in diabetic CKD (see *text*)

Sarafidis PA & Ruilope LM. ESH Newsletter 2013, No. 55

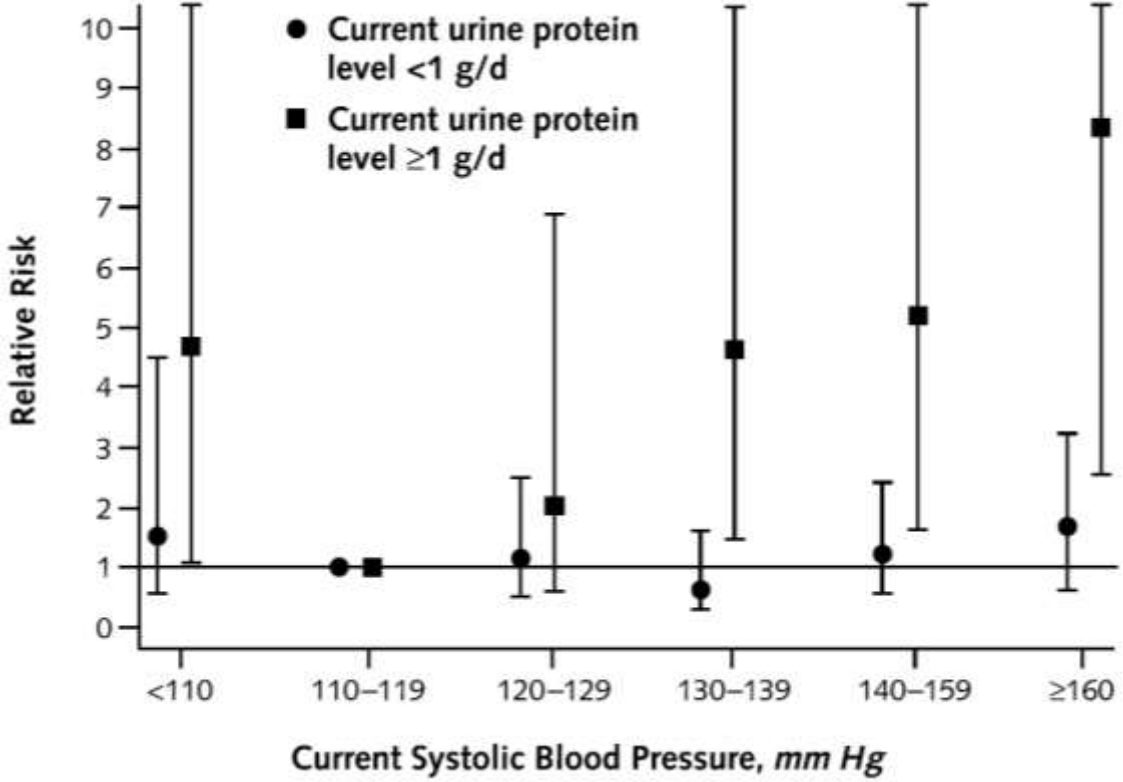
KDIGO

- **Non-diabetic adults with CKD:**
  ≤140 mmHg systolic and ≤90 mmHg diastolic if norm[illegible]minuric
  ≤130 mmHg systolic and ≤80 mmHg diastolic if m[illegible]r macroalbuminuric
- **Diabetic adults with non dialysis-depend[illegible]KD:**
  ≤140 mmHg systolic and ≤90 mmHg [illegible]olic if normoalbuminuric
  ≤130 mmHg systolic and ≤80 m[illegible]iastolic if micro or macroalbuminuric
- **Kidney transplant recipi[illegible]**
  ≤130 mmHg systoli[illegible]≤80 mmHg diastolic
- **Elderly people [illegible]th CKD:**
  probably ≤140 mmHg systolic and ≤90 mmHg diastolic, but set targets after consideration of co-morbidities

Aim for <130/80 mmHg if albuminuria is present

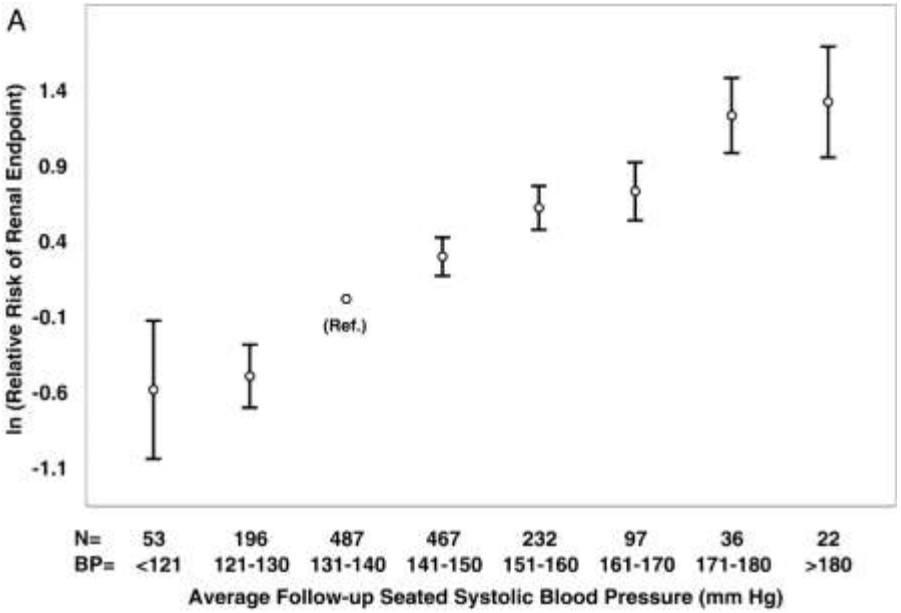
KDIGO Blood Pressure Work Group. Kidney Int Suppl 2012

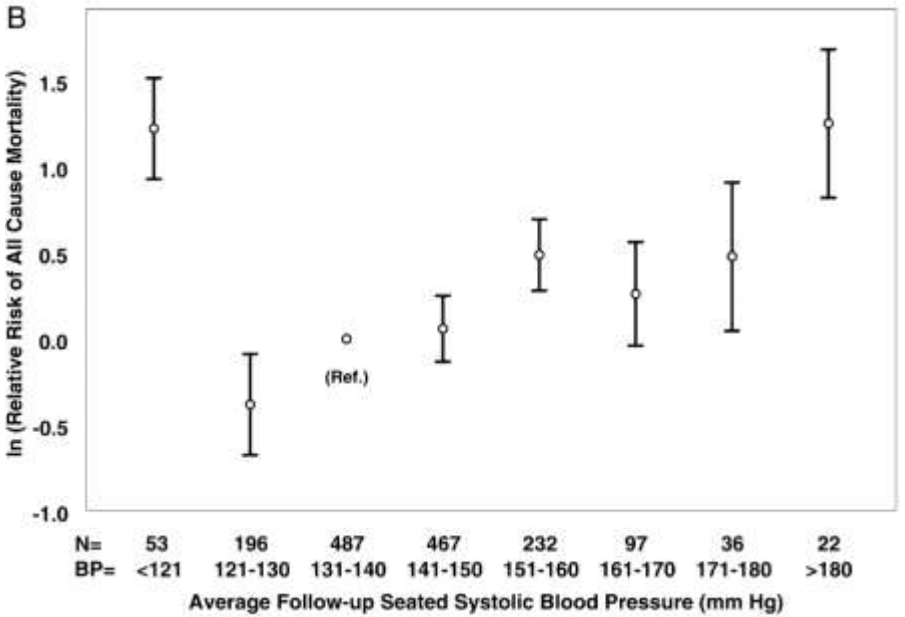
Current Blood Pressure and CKD Progression



Jafar TH et al. Ann Intern Med 2003

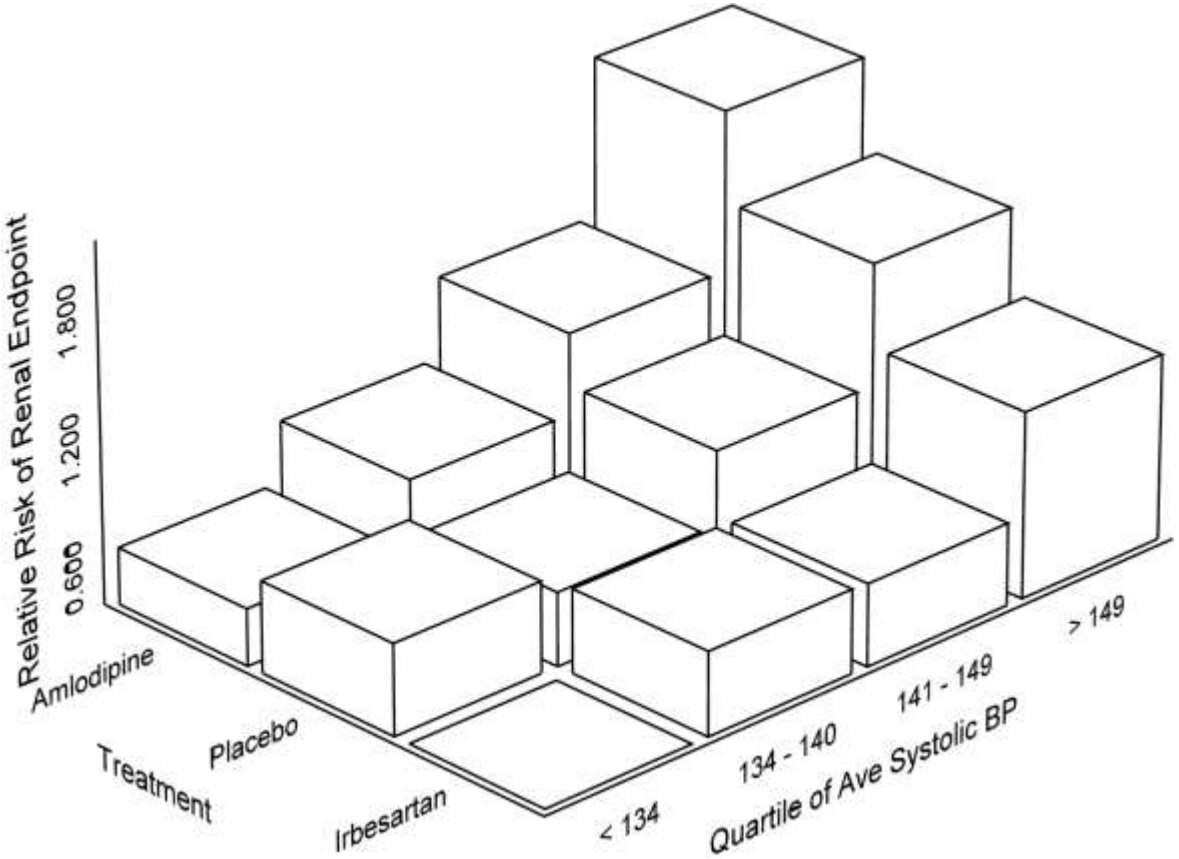
Achieved Blood Pressure and CKD Progression: IDNT





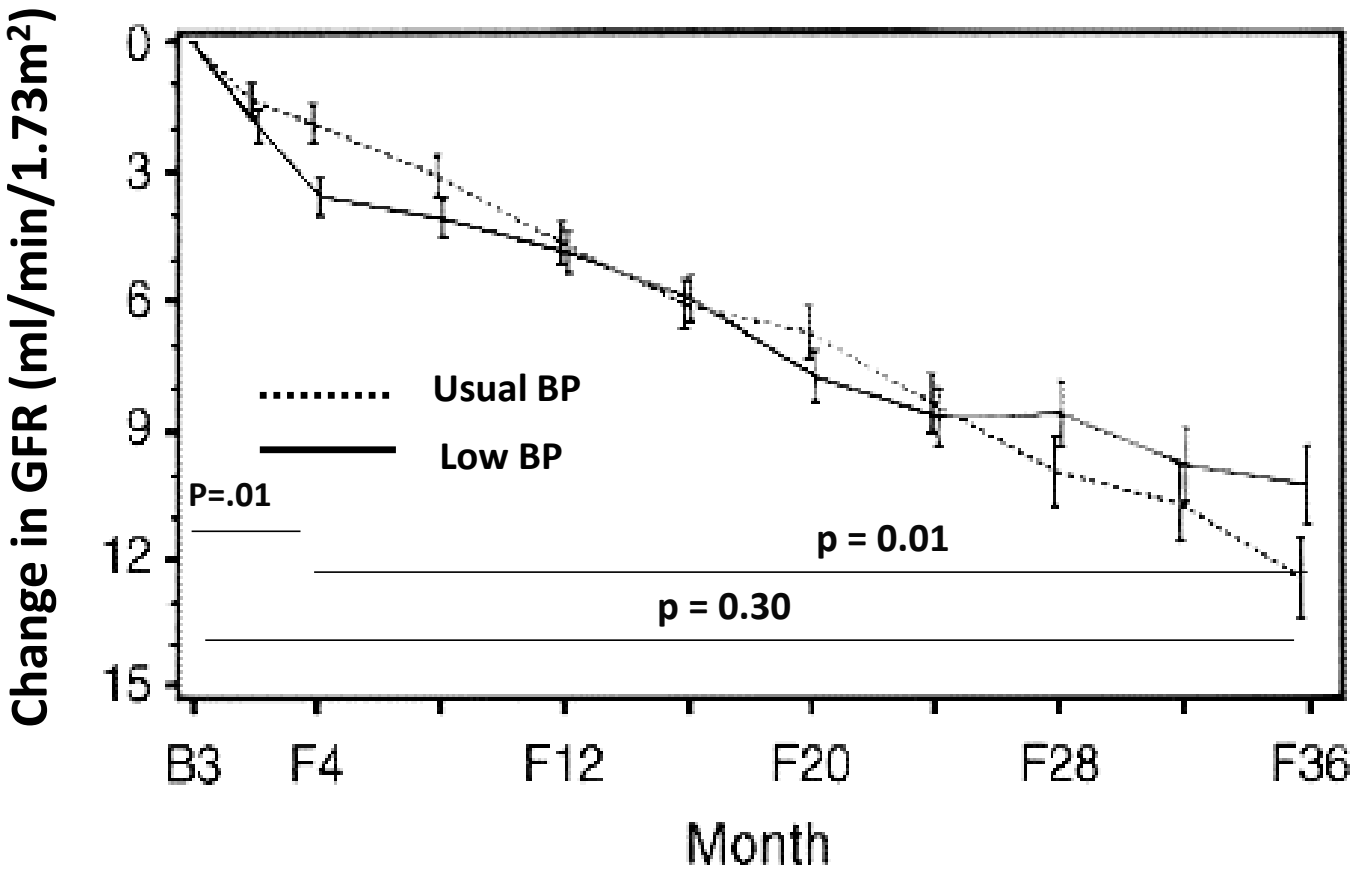
Pohl MA et al. JASN 2005

Achieved Blood Pressure and CKD Progression: IDNT



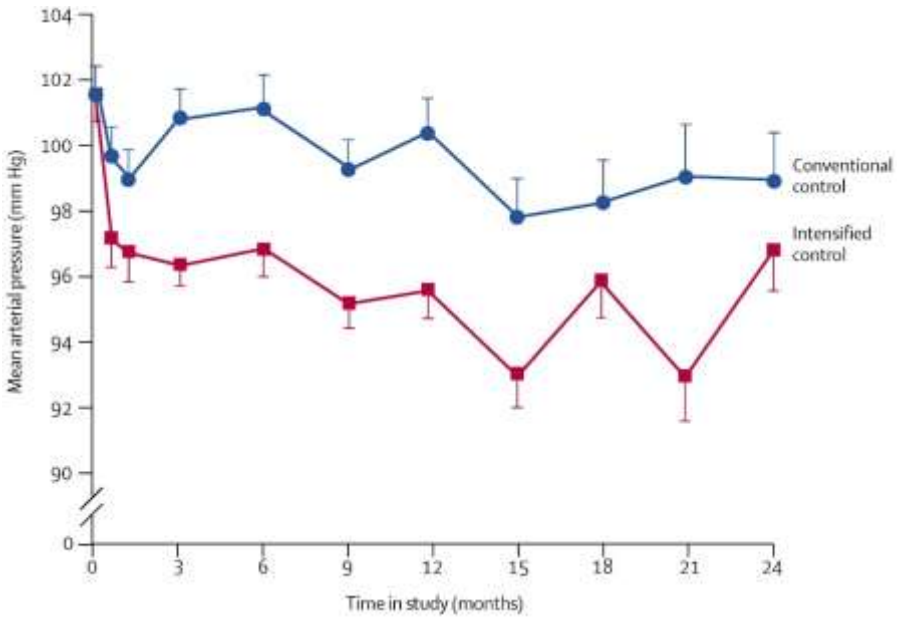
Pohl MA et al. JASN 2005

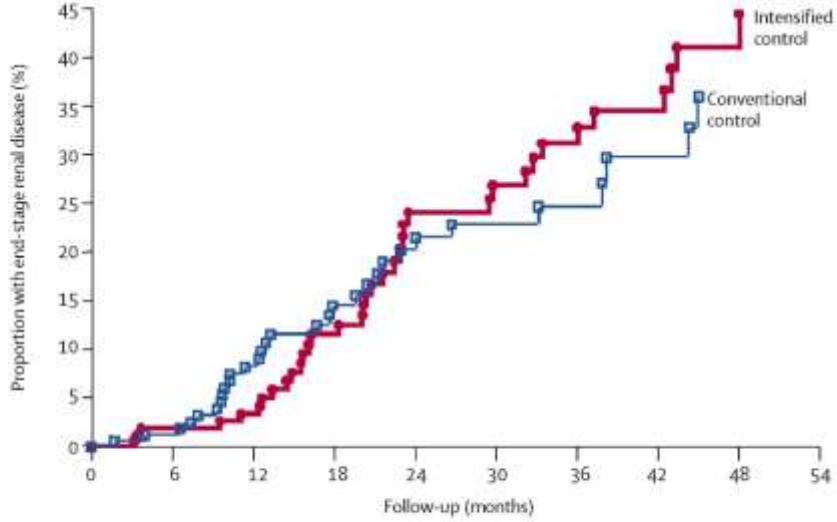
Target Blood Pressure: MDRD



Klahr S et a. NEJM 1994

Target Blood Pressure: REIN-2



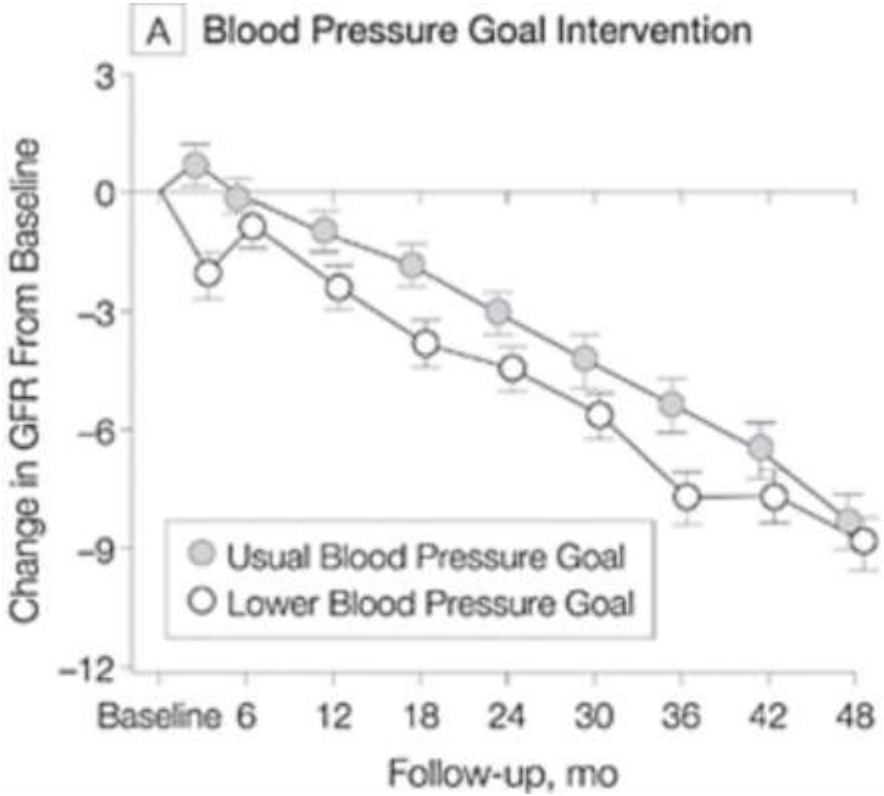


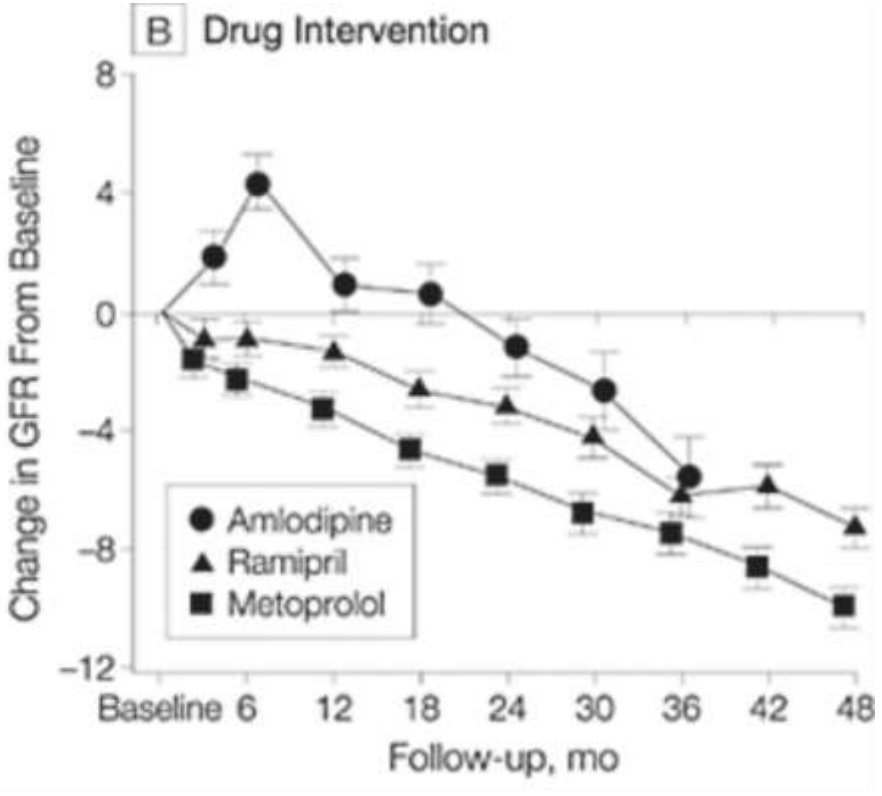
Number at risk

Conventional control	168	158	121	84	64	50	34	24	13	2
Intensified control	167	155	126	88	59	51	43	31	17	0

Ruggenenti P et al. Lancet 2005

Target Blood Pressure: AASK



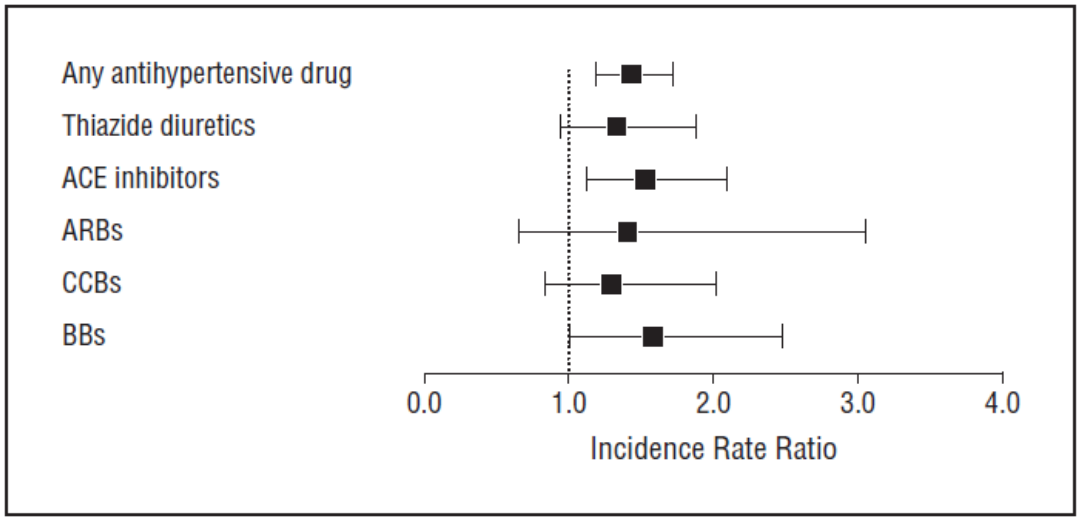


Wright JT et al. JAMA 2002

Postural Hypotension

The Risk of Hip Fracture After Initiating Antihypertensive Drugs in the Elderly

Debra A. Butt, MD, MSc, CCFP, FCFP; Muhammad Mamdani, PharmD, MPH; Peter C. Austin, PhD; Karen Tu, MD, MSc, CCFP, FCFP; Tara Gomes, MHSc; Richard H. Glazier, MD, MPH, CCFP, FCFP



Butt DA et al. Arch Intern Med 2013

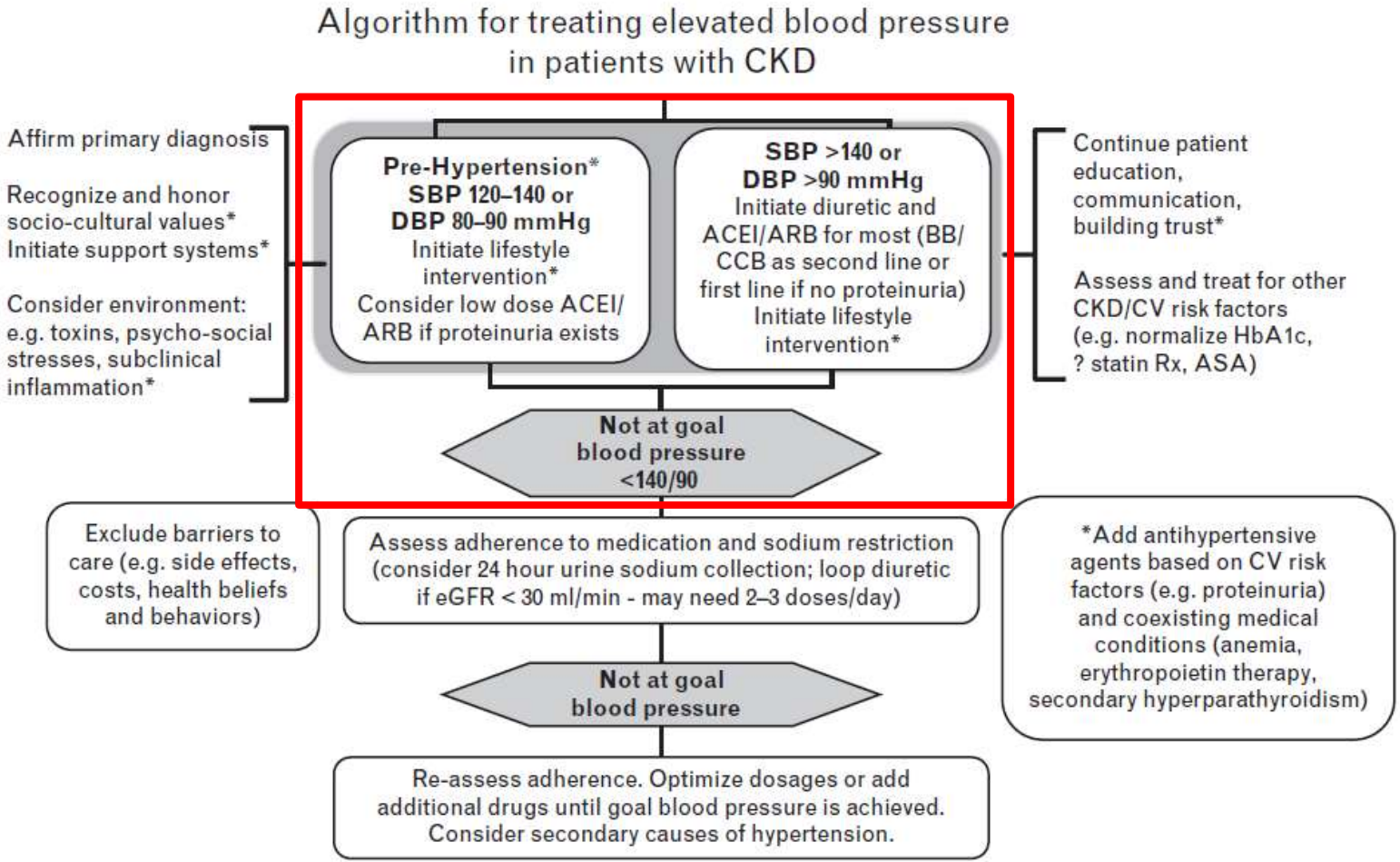
Blood Pressure Goals in CKD

There is little evidence among patients with CKD that a BP goal of less than 130/80mmHg saves lives, saves kidneys or reduces cardiovascular events.

Nonetheless, BP control is important. Therefore, as in the general population, BP should be targeted to less than 140/90mmHg.

Hypertension therapy personalized and individualized using home BP monitoring holds great promise.

Agarwal R. Curr Opin Nephrol Hypertens 2011



Nicholas SB et al. Curr Opin Cardiol 2013

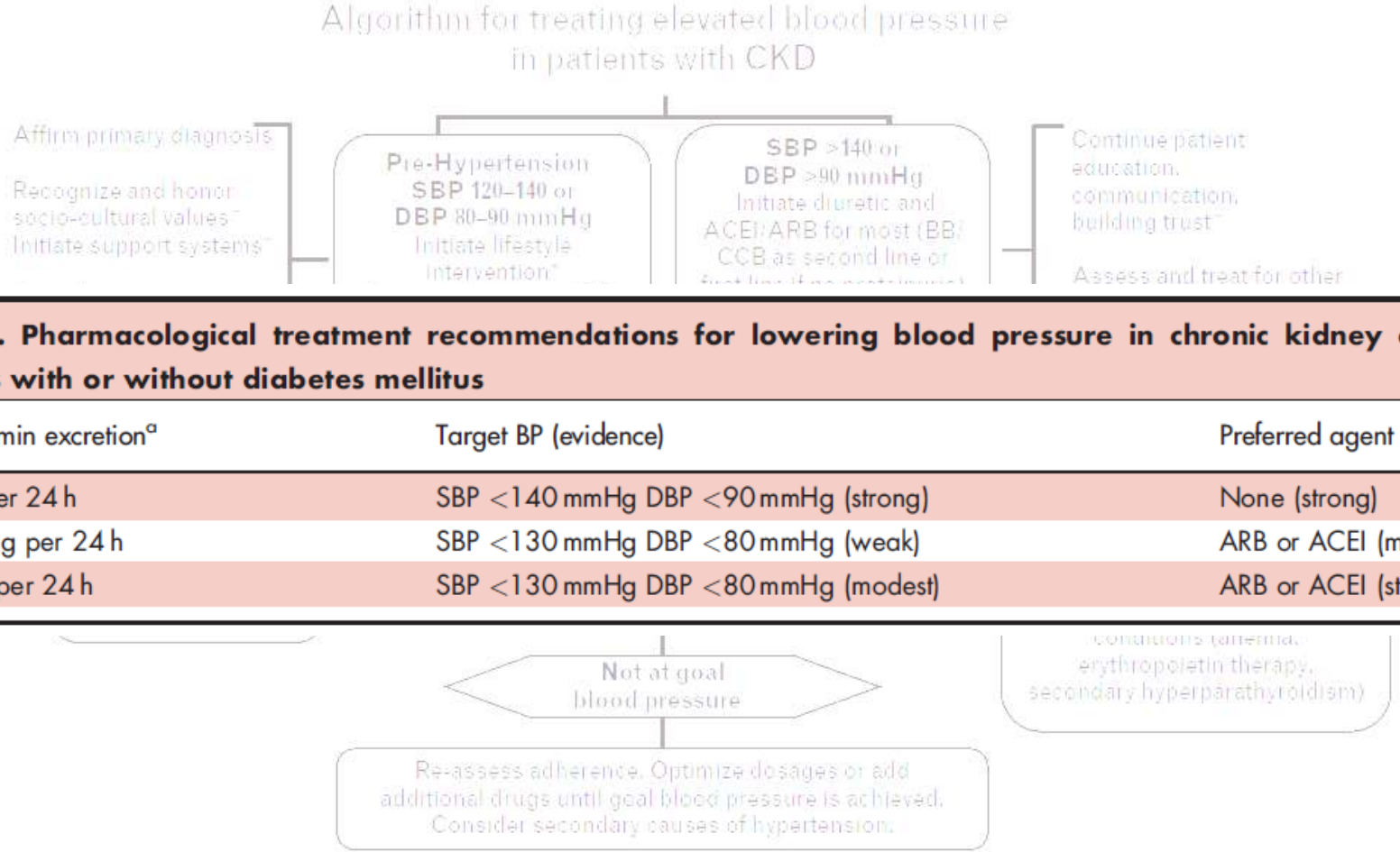


Table 2. Pharmacological treatment recommendations for lowering blood pressure in chronic kidney disease patients with or without diabetes mellitus

Urine albumin excretion[a]	Target BP (evidence)	Preferred agent (evidence)
<30 mg per 24 h	SBP <140 mmHg DBP <90 mmHg (strong)	None (strong)
30–300 mg per 24 h	SBP <130 mmHg DBP <80 mmHg (weak)	ARB or ACEI (modest)
>300 mg per 24 h	SBP <130 mmHg DBP <80 mmHg (modest)	ARB or ACEI (strong)

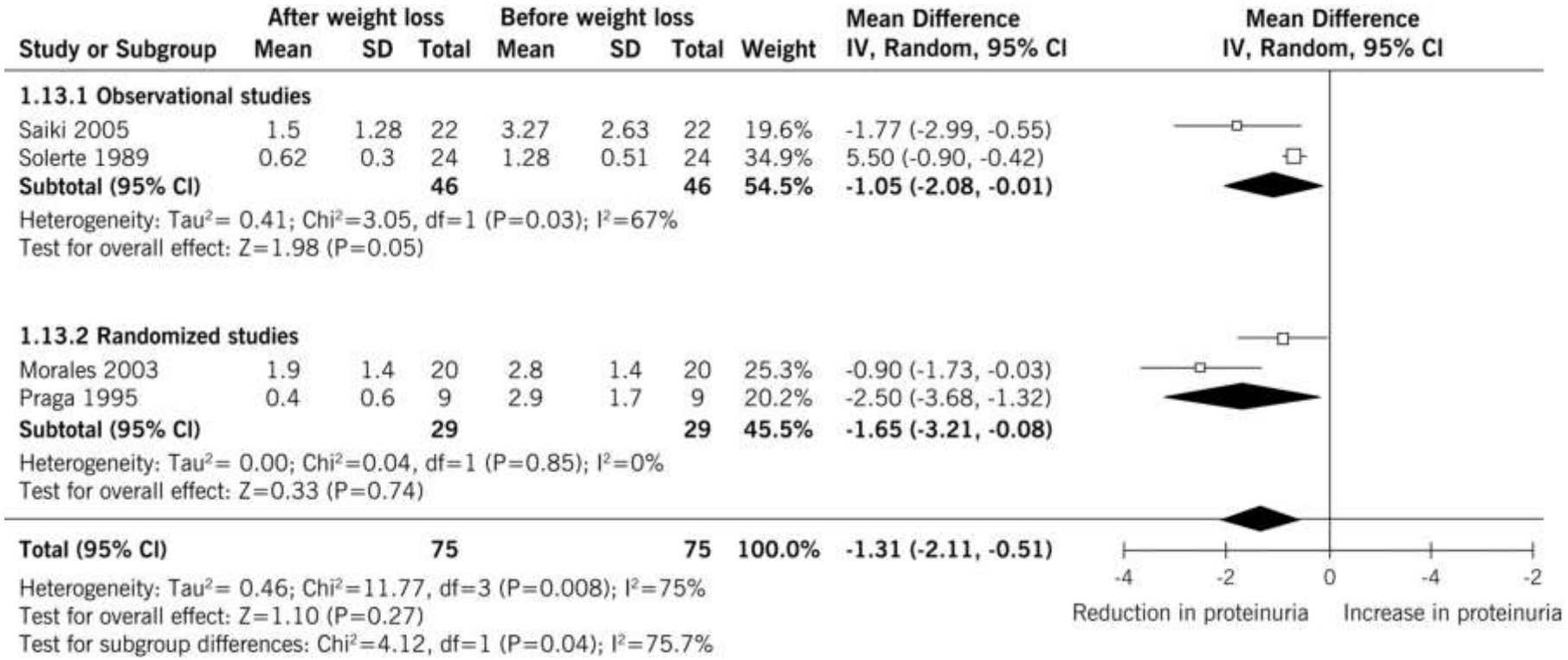
Nicholas SB et al. Curr Opin Cardiol 2013

Lifestyle Measures: KDIGO

- **Weight:**
  Achieve or maintain a normal weight (BMI 20-25 kg/m²)
- **Salt:**
  < 2 g sodium (5 g salt) per day unless contraindicated
- **Exercise:**
  At least 30 minutes 5 times per week
- **Alcohol:**
  Limit to maximum of 2 standard drinks per day
- **Smoking:**
  No direct effect on long-term BP but cessation reduces CV risk.

KDIGO Blood Pressure Work Group. Kidney Int Suppl 2012

Weight Reduction



Navaneethan SD et al. CJASN 2009

Pharmacological Treatment

Table 4. Pharmacological treatment

Angiotensin converting enzyme inhibitors (ACEI)	Combination therapy ACEI, ARB or RI + diuretics
Angiotensin II receptor blockers (ARB)	ACEI, ARB or RI + calcium-antagonist ACEI or ARB + RI
Renin inhibitors (RI)	Beta-blockers + diuretics
Diuretics	Antihypertensive + statins +
Calcium antagonists	+ antiplatelet treatment
Beta-blockers	
Alpha-blockers	

Rodicio JL & Alcazar JM. ESH Newsletter 2011, No. 4

ACEIs and ARBs

- **Generalised arterial vasodilatation:**
  Reduction of blood pressure

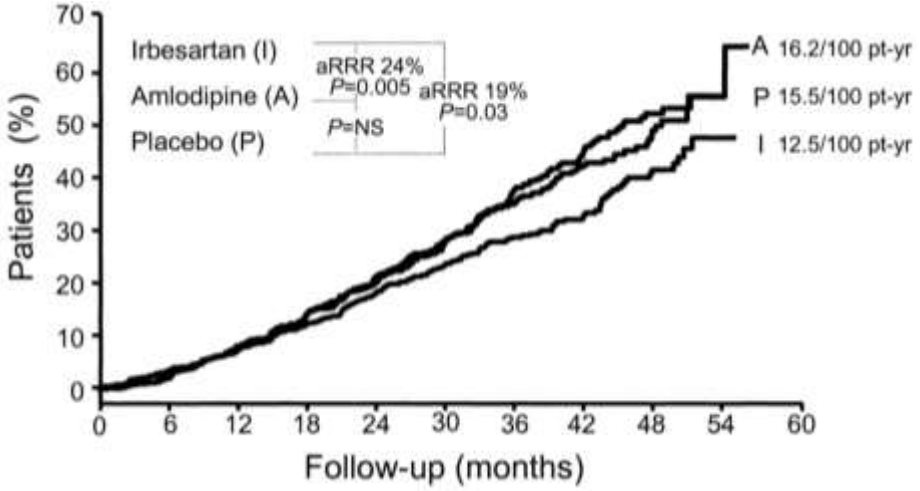
- **Vasodilatation particularly of the efferent glomerular arteriole:**
  Reduction of glomerular pressure
  Reduction of proteinuria
  Long-term renoprotection

- **Reduction of adrenal aldosterone secretion:**
  But note aldosterone breakthrough

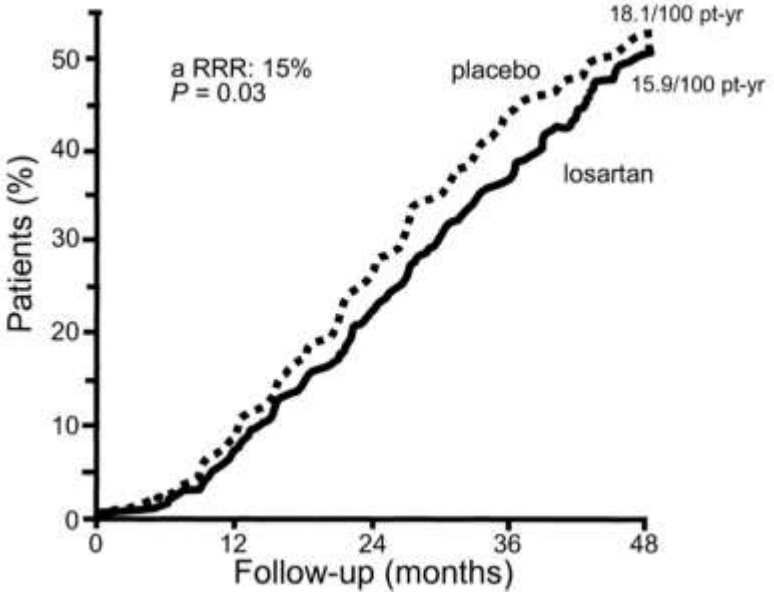
KDIGO Blood Pressure Work Group. Kidney Int Suppl 2012

IDNT and RENAAL Studies

Time to primary composite end point (doubling of serum creatinine, end-stage renal disease, or death)

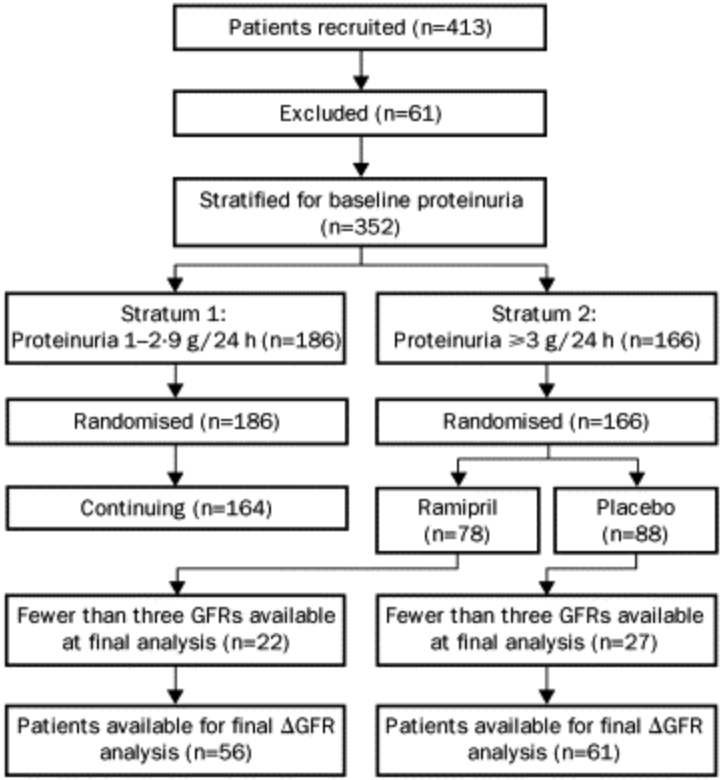


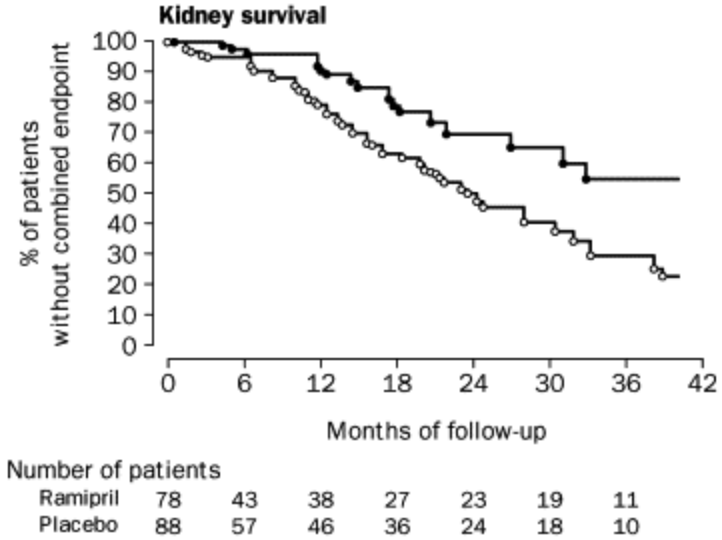
Lewis EJ et al. NEJM 2001



Brenner BM et al. NEJM 2001

Non-diabetic CKD: GISEN





The Gisen Group. Lancet 1997

ACEIs and ARBs: Sequential Marketing

ACEIs first marketed (captopril in 1977), ARBs later (losartan in 1995)

First large scale RCT of RAAS blockade in diabetes involved patients with type 1 disease given captopril.

By the time ARBs were introduced, the benefits of ACE-Is (in CKD patients with type 1 diabetes) were well established.

Thus RCTs involving ARBs generally targeted individuals with type 2 diabetes.

This has led to some bias in the evidence base underpinning recommendations for using ACE-Is or ARBs in the treatment of BP.

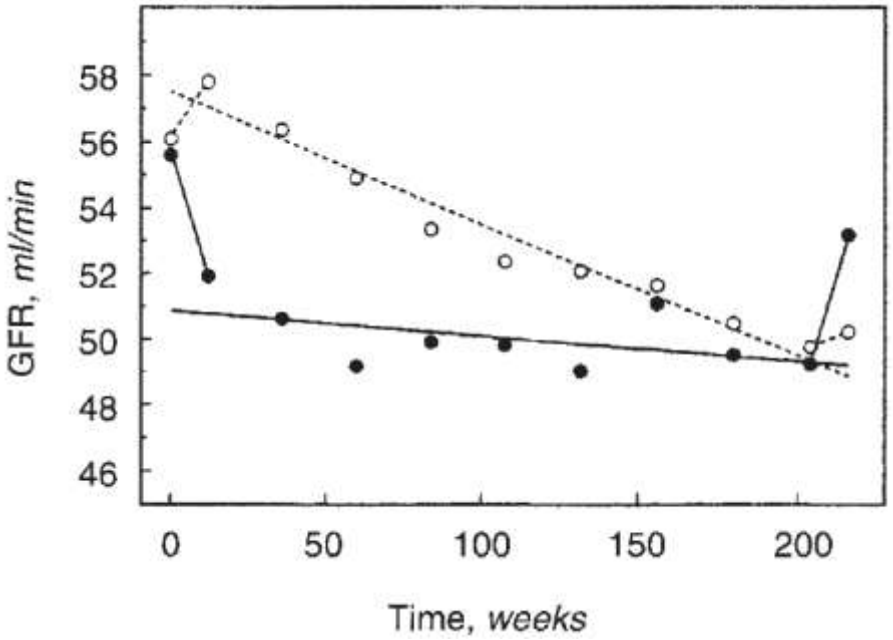
KDIGO Blood Pressure Work Group. Kidney Int Suppl 2012

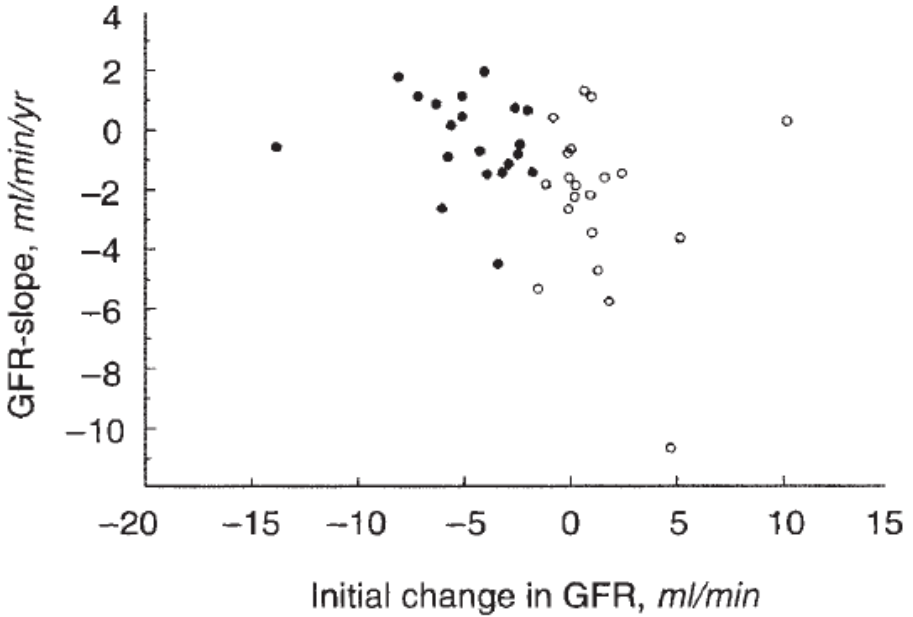
ACEIs and ARBs

Indicated in all hypertensive patients with CKD, especially in proteinuric diabetic and non-diabetic CKD.

Will lead to deterioration of renal function in short term but then to slower progression of renal failure in longer term.

Short-term GFR Reduction vs Long-term Protection



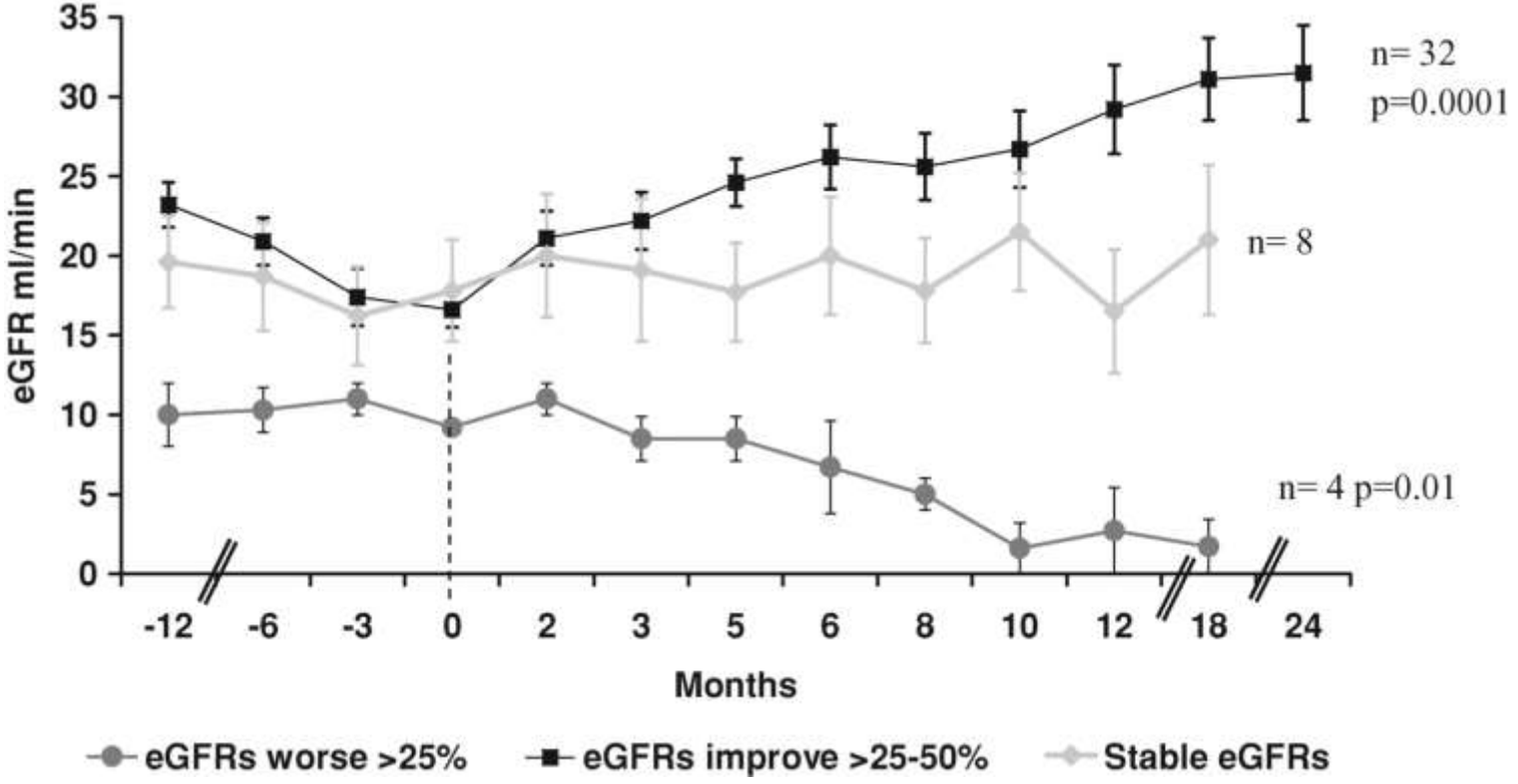


○ Patients in whom GFR did not fall after start of treatment

● Patients who initially showed a distinct fall in GFR

Apperloo AJ et al. Kidney Int 1997

Stopping ACEI/ARB in Advanced CKD?



Ahmed AK et al. NDT 2010

Side Effects

Hyperkalaemia

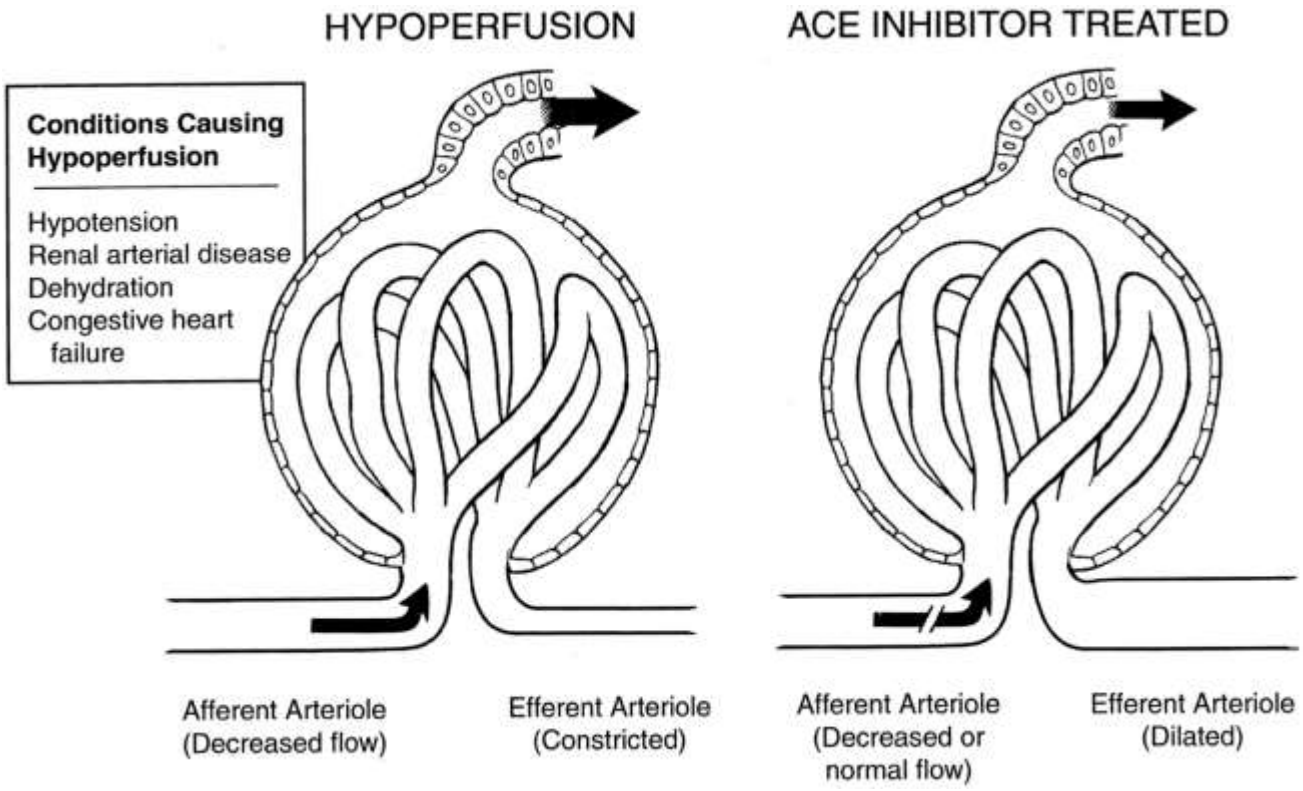
Higher risk of hyperkalaemia in combination with potassium-sparing diuretics

ACEI: mainly renal excretion (except fosinopril, trandolapril), ARB mainly hepatic excretion, therefore reduce dose (stop?) at GFR <15 mL/min

Other treatment strategies in Hyperkalaemia:

- Dietary advice
- Furosemide
- Dose reduction of ACEI/ARB

Side Effects

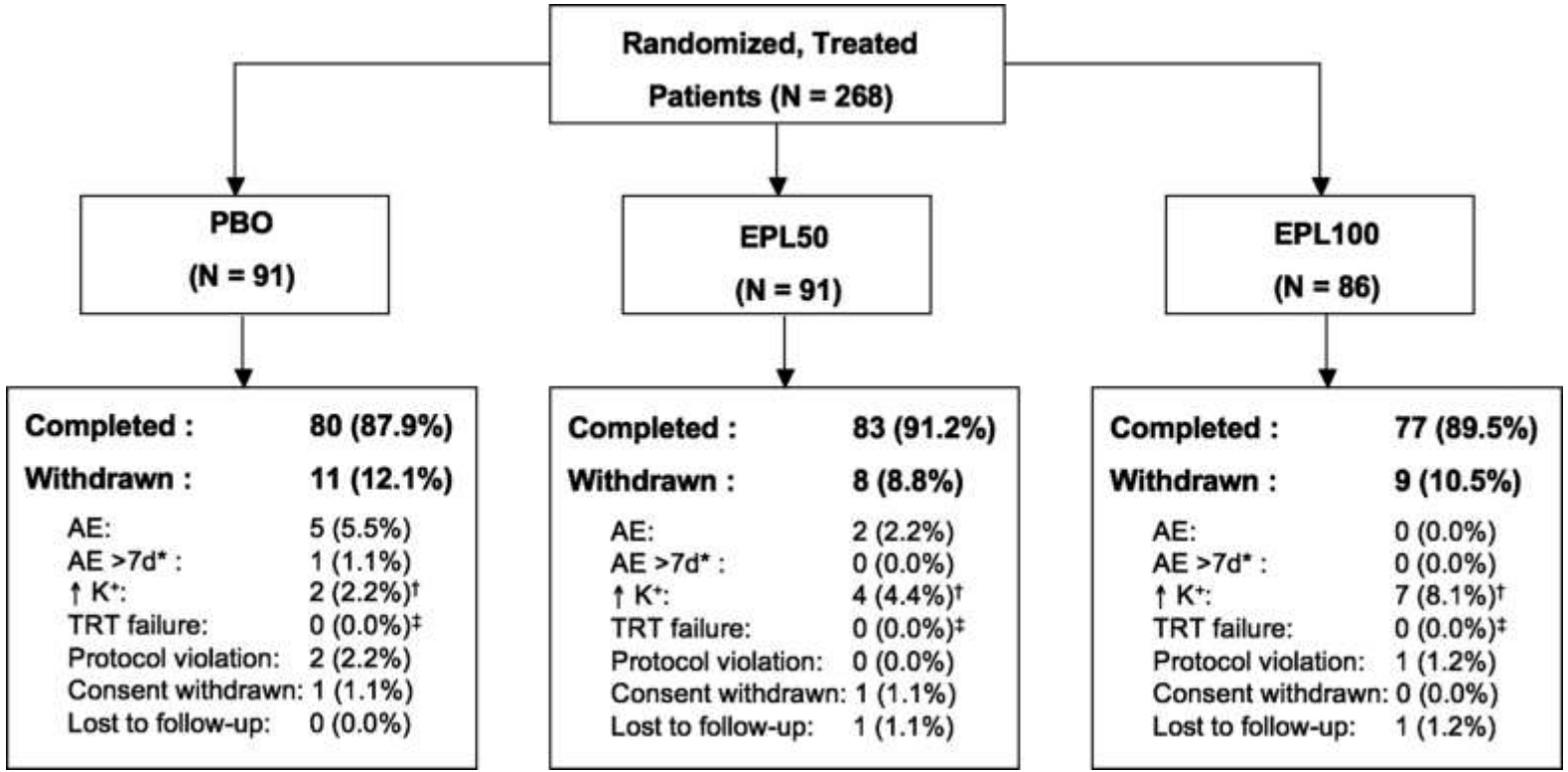


AKI, especially in:

- Bilateral renal stenosis
- Diabetes and sepsis
- Combination with NSAIDs
- State of volume depletion (diarrhoea/ vomiting)

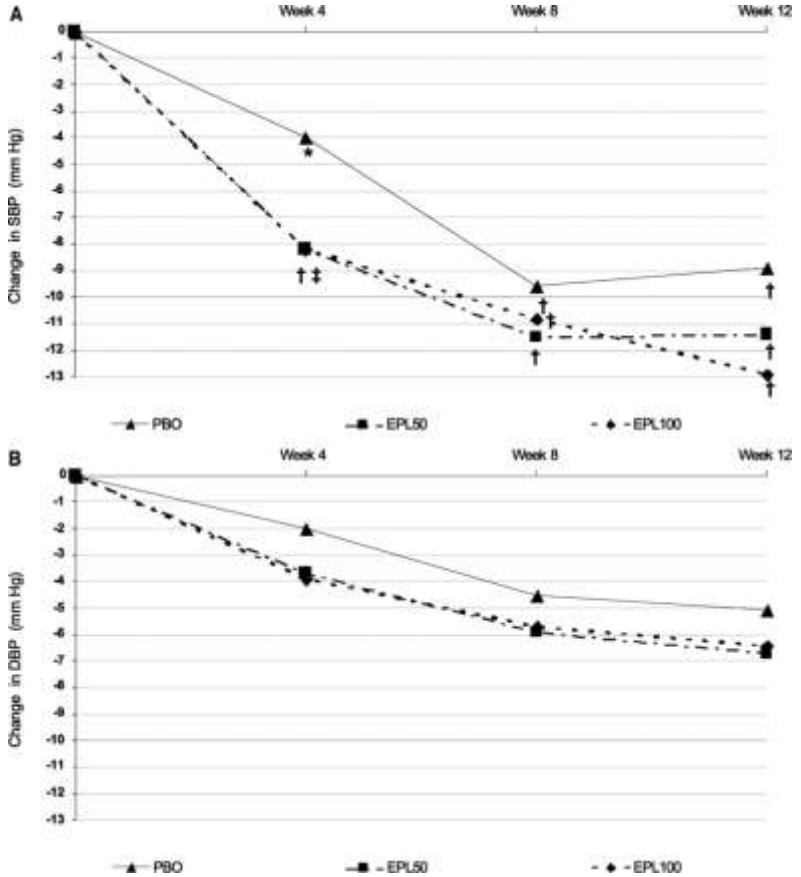
Schoolwert AC et al. Circulation 2001

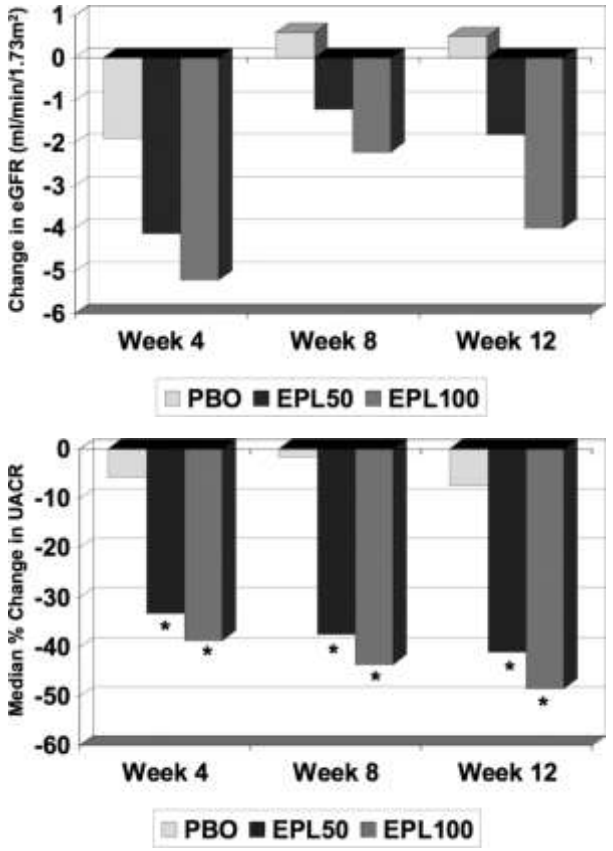
Aldosterone Antagonists



Epstein M et al. CJASN 2006

Aldosterone Antagonists





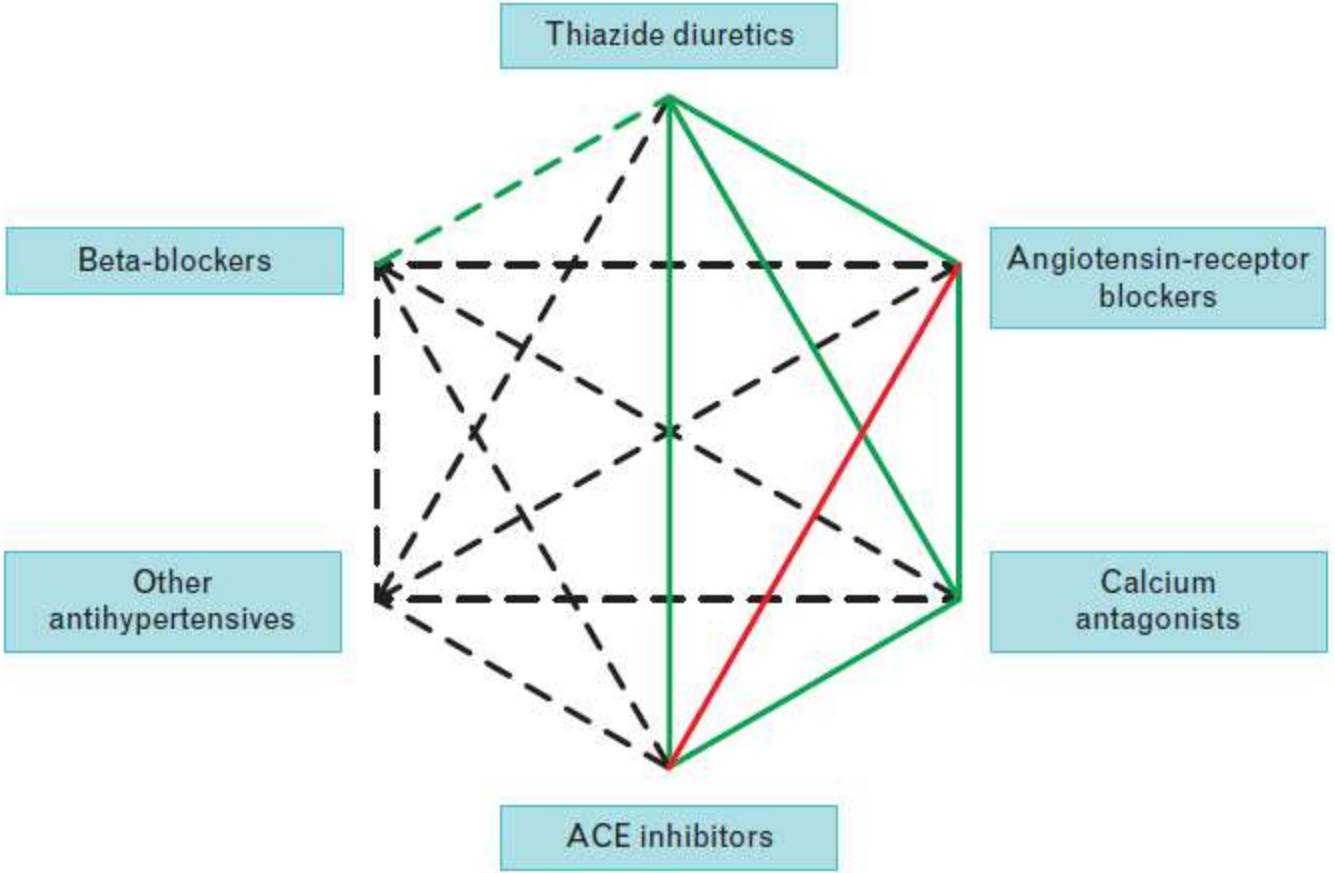
Epstein M et al. CJASN 2006

Aldosterone Antagonists

It is premature to draw a definite conclusion as to whether aldosterone antagonists—through their anti-albuminuric, anti-hypertensive, or anti-fibrotic effects—reduce the rate of decline in kidney function in the long term. This is an area for future research.

KDIGO Blood Pressure Work Group. Kidney Int Suppl 2012

Often Combination Therapy will be Required



2013 ESH/ESC Guidelines. J Hypertens 2013

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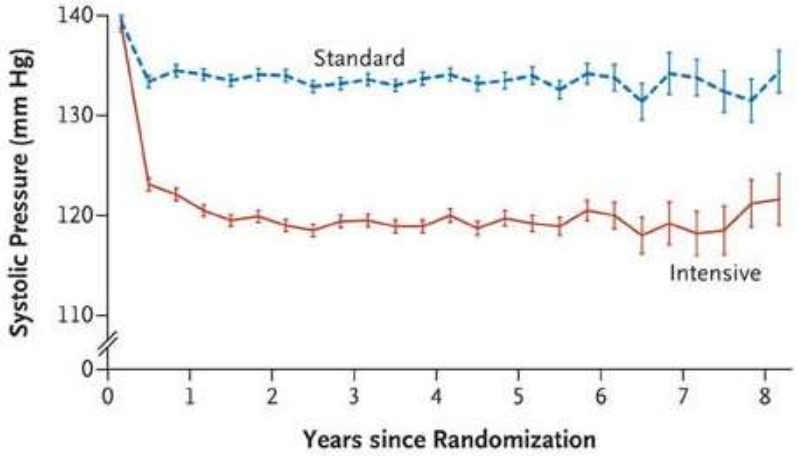
Calcium antagonists	Beta-blockers + diuretics
Beta-blockers	Antihypertensive + statins + + antiplatelet treatment
Alpha-blockers	

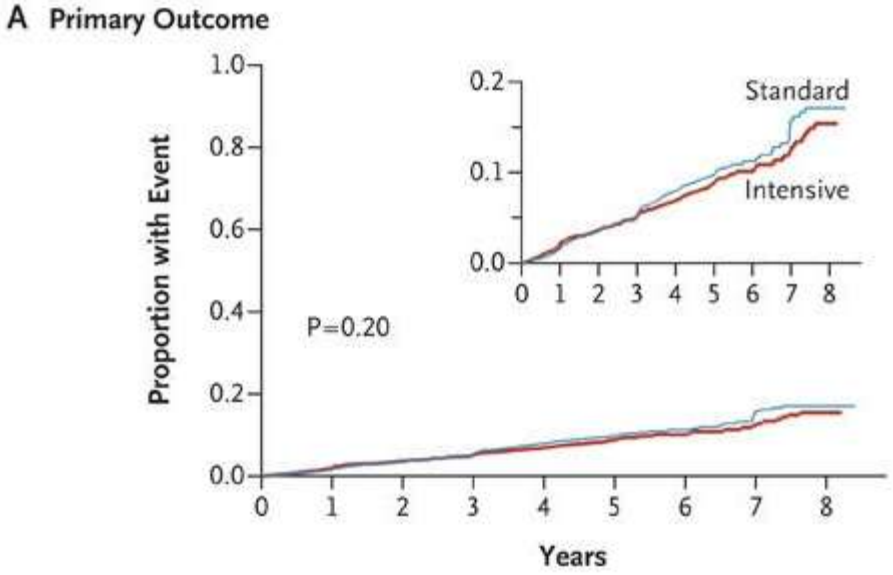
Rodicio JL & Alcazar JM. ESH Newsletter 2011, No. 4

Diabetes: ACCORD – Major CV Events



Mean No. of Medications Prescribed								
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3

No. of Patients								
Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201



No. at Risk									
Intensive	2362	2273	2182	2117	1770	1080	298	175	80
Standard	2371	2274	2196	2120	1793	1127	358	195	108

ACCORD Study Group. NEJM 2010

Summary

	ESH/ESC 2013 Guidelines	AHA/ACC/CDC Scientific Advisory	JNC 8	ASH/ISH Statement
in general	<140/90	<140/90	≥ 60 years: <150/90 < 60 years: < 140/90	>140/90
Exception or special comment	Elderly > 80 years < 150/90 Elderly < 80 years < 150/90 Fit elderly < 140/90 Diabetes < 140/85 CKD+Proteinuria < 130/90	„lower“ targets for • elderly • LVH • systolic or diastolic LV dysfunction • diabetes • kidney disease	Diabetes < 140/90 CKD < 140/90	< 80 years < 150/90 CKD + Proteinuria < 130/80

ESH/ESC

Other risk factors, asymptomatic organ damage or disease	Blood Pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
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OD, CKD stage 3 or diabetes	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs	• Lifestyle changes • BP drugs	• Lifestyle changes • Immediate BP drugs
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	• Lifestyle changes • No BP intervention	• BP drugs targeting <140/90	• BP drugs targeting <140/90	• Immediate BP drugs targeting <140/90

SBP <140 mmHg DBP <90 mmHg

2013 ESH/ESC Guidelines. J Hypertens 2013

KDIGO

- **Non-diabetic adults with CKD:**
  ≤140 mmHg systolic and ≤90 mmHg diastolic if norm[illegible]minuric
  ≤130 mmHg systolic and ≤80 mmHg diastolic if m[illegible]r macroalbuminuric
- **Diabetic adults with non dialysis-depend[illegible]KD:**
  ≤140 mmHg systolic and ≤90 mmHg [illegible]olic if normoalbuminuric
  ≤130 mmHg systolic and ≤80 m[illegible]iastolic if micro or macroalbuminuric
- **Kidney transplant recipi[illegible]**
  ≤130 mmHg systoli[illegible]≤80 mmHg diastolic
- **Elderly people [illegible]th CKD:**
  probably ≤140 mmHg systolic and ≤90 mmHg diastolic, but set targets after consideration of co-morbidities

Aim for <130/80 mmHg if albuminuria is present

KDIGO Blood Pressure Work Group. Kidney Int Suppl 2012

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Welcome to Seoul, Korea!

The 26th International Society of Hypertension
Biennial Scientific Meeting 2016

***September 24**(Sat) – **29**(Thu), **2016**, Coex, Seoul, Korea*

www.ish2016.org

Diuretics

Thiazide diuretics: e.g. Hydrochlorothiazide, Bendroflumethiazide

Thiazide-like diuretics: e.g. Chlorthalidone, Indapamide

Loop diuretics: e.g. Furosemide, Torasemide

Widely used as patients with CKD are characterised by sodium and water retention

For antihypertensive therapy:

GFR >50 mL/min: Thiazides alone or in combination with distal diuretics (e.g. spironolactone)

GFR <30 mL/min: Loop diuretics. Avoid distal (potassium sparing) diuretics.

Calcium Channel Blockers

Antihypertensive action.

Oedema and fluid retention.

Dihydropyridines predominantly dilate the afferent arteriole and thereby increase GFR but also the glomerular pressure.

Non-DHPs seem not to have this effect.

Calcium Channel Blockers

	Class	Accumulate in renal failure	Increase CNI levels	Increase sirolimus levels
Amlodipine	D	N	Y	—
Diltiazem	B	N	Y	Y
Felodipine	D	N	—	—
Isradipine	D	N	—	—
Lercanidipine	D	N	—	—
Nicardipine	D	Y	Y	Y
Nifedipine	D	N	N	—
Nimodipine	—	Y	—	—
Nisoldipine	D	N	—	—
Verapamil	P	N	Y	Y

B, non-dihydropyridine benzothiazepine; CNI, calcineurin inhibitor; D, Dihydropyridine; N, No; P, phenylalkylamine; Y, Yes; —, no data.

KDIGO Blood Pressure Work Group. Kidney Int Suppl 2012

Beta-Blockers

Beta-blockers reduce increased sympathetic activity in CKD.

Indication in heart failure.

Often combined with diuretics in RCTs but no reason why not combine with others.

No robust evidence for superiority of certain beta-blockers.

Alpha-Blockers

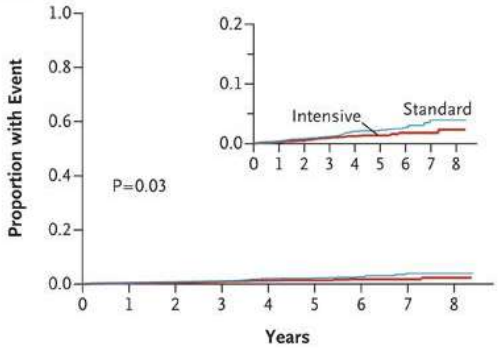
Alpha-blockers have additional antiproliferative properties.

Hepatic excretion.

Beneficial in prostate hypertrophy.

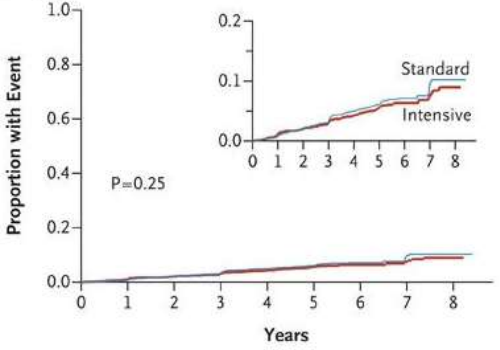
Diabetes: ACCORD

B Nonfatal Stroke



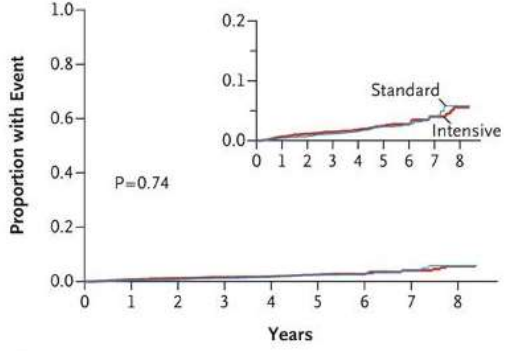
No. at Risk									
Intensive	2362	2291	2223	2174	1841	1128	313	186	88
Standard	2371	2287	2235	2186	1879	1196	382	215	114

C Nonfatal Myocardial Infarction



No. at Risk									
Intensive	2362	2278	2190	2133	1787	1087	299	177	82
Standard	2371	2278	2208	2141	1818	1145	365	201	112

D Death from Cardiovascular Disease



No. at Risk									
Intensive	2362	2304	2252	2201	1870	1143	317	188	91
Standard	2371	2313	2268	2218	1922	1220	393	221	118

ACCORD Study Group. NEJM 2010