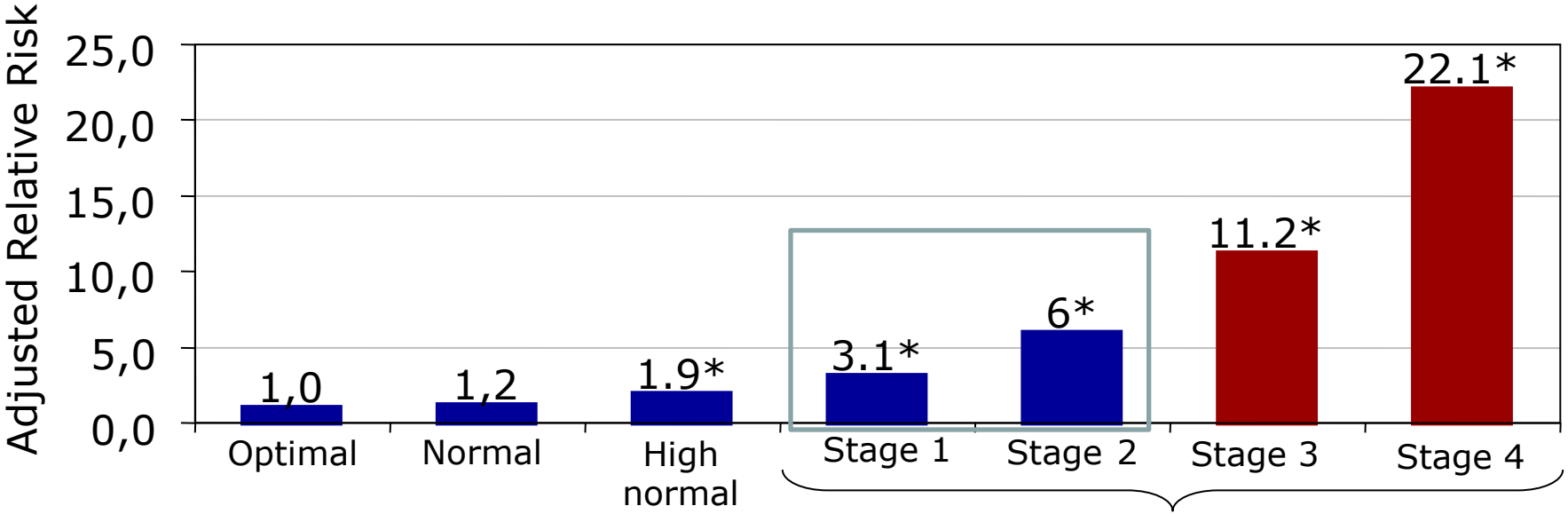
Tác dụng bảo vệ cơ quan đích (thận) của chẹn kênh canxi thế hệ mới Lercanidipine

Target Organ Protection of the new generation of Calcium channel blockers

GS. Huỳnh văn Minh, FACC, FAsCC, MISH, MAPSH

Introduction

The risk of End Stage Renal Disease (ESRD) increases with hypertension



*** p<0.001**

§ Men with optimal blood pressure was the reference category.

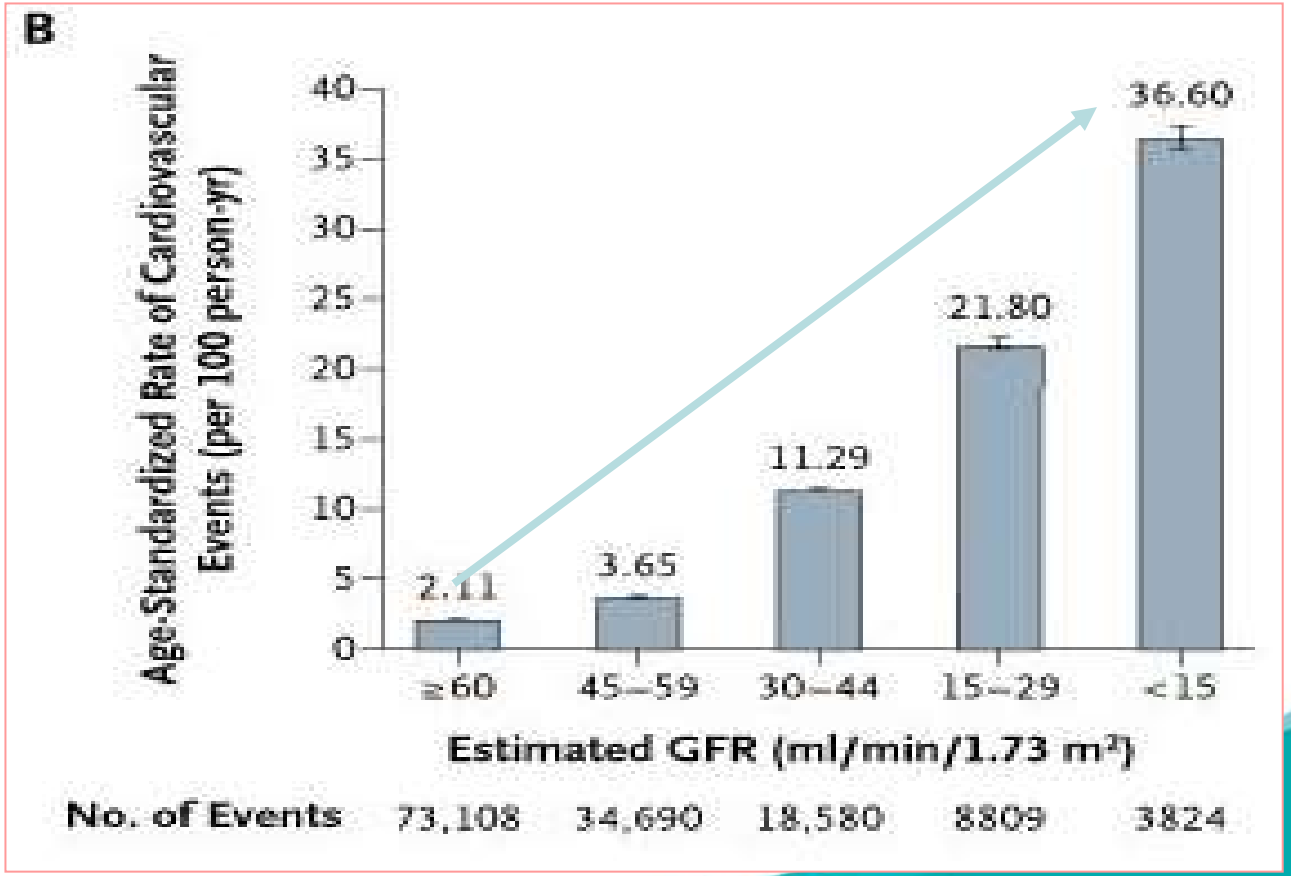
BP category

Hypertension	Systol	Diastol
Stage 4	>210	>120
Stage 3	180–209	110–119
Stage 2	160–179	100–109
Stage 1	140–159	90–99
High normal	130–139	85–89
Normal	<130	<85
Optimal	<120	<80

Klag MJ, et al. N Engl J Med. 1996;334(1):13-18

Chronic Kidney Disease is an important cardiovascular risk factor

Age-Standardized Rates of Death from Cardiovascular Events According to the Estimated GFR among 1,120,295 Ambulatory Adults



Go, A. S. et al. N Engl J Med 2004;351:1296-1305

Circulation changes in hypertension

Macro-ciculation	Micro-circulation
↑ Arterial Stiffness	↑ Wall/lumen ratio of small arteries
↑ Central Systolic Blood Pressure	↓ Capillaries and arterioles
↑ Pulse Wave Velocity	↑ Microvascular permeability
↑ Pulse Pressure	

Vascular structure

Microcirculation:

- ❑ Increase of the wall/lumen ratio of small arteries
- ❑ Rarefaction of arterioles and capillaries

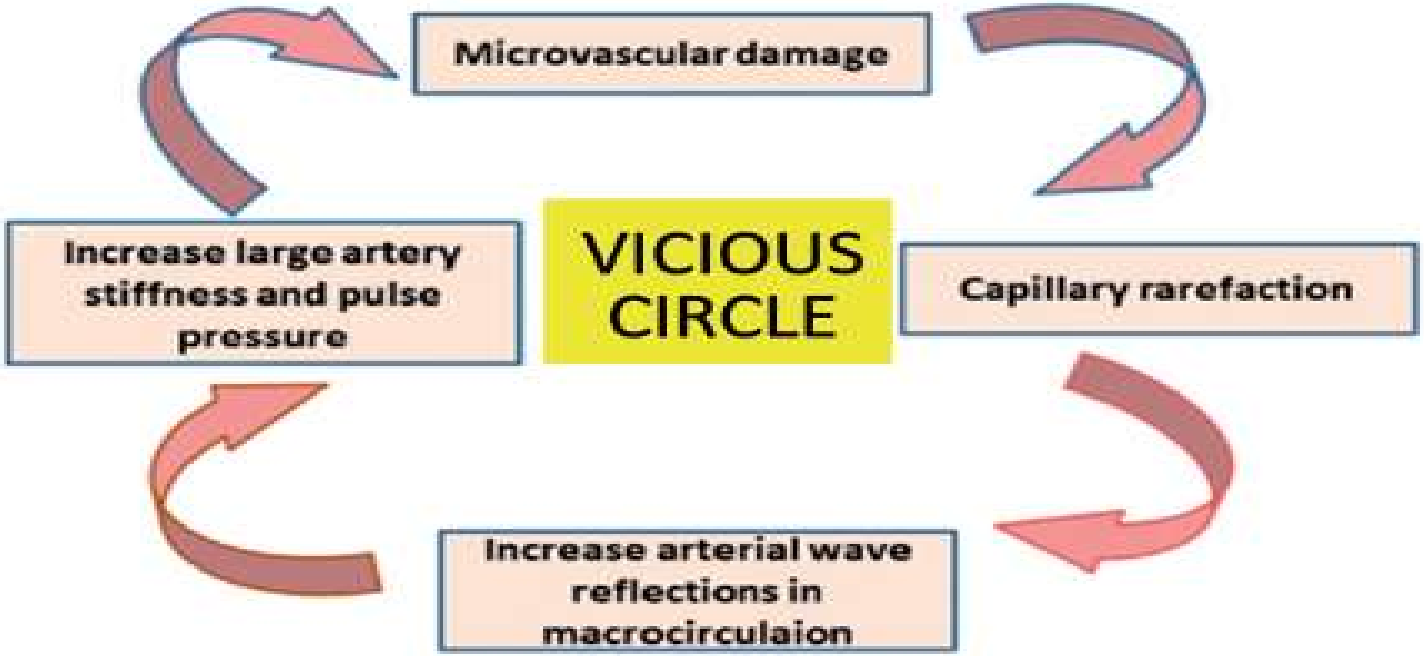
Structural remodeling

Functional changes

- ❑ Enhancement of microvascular permeability

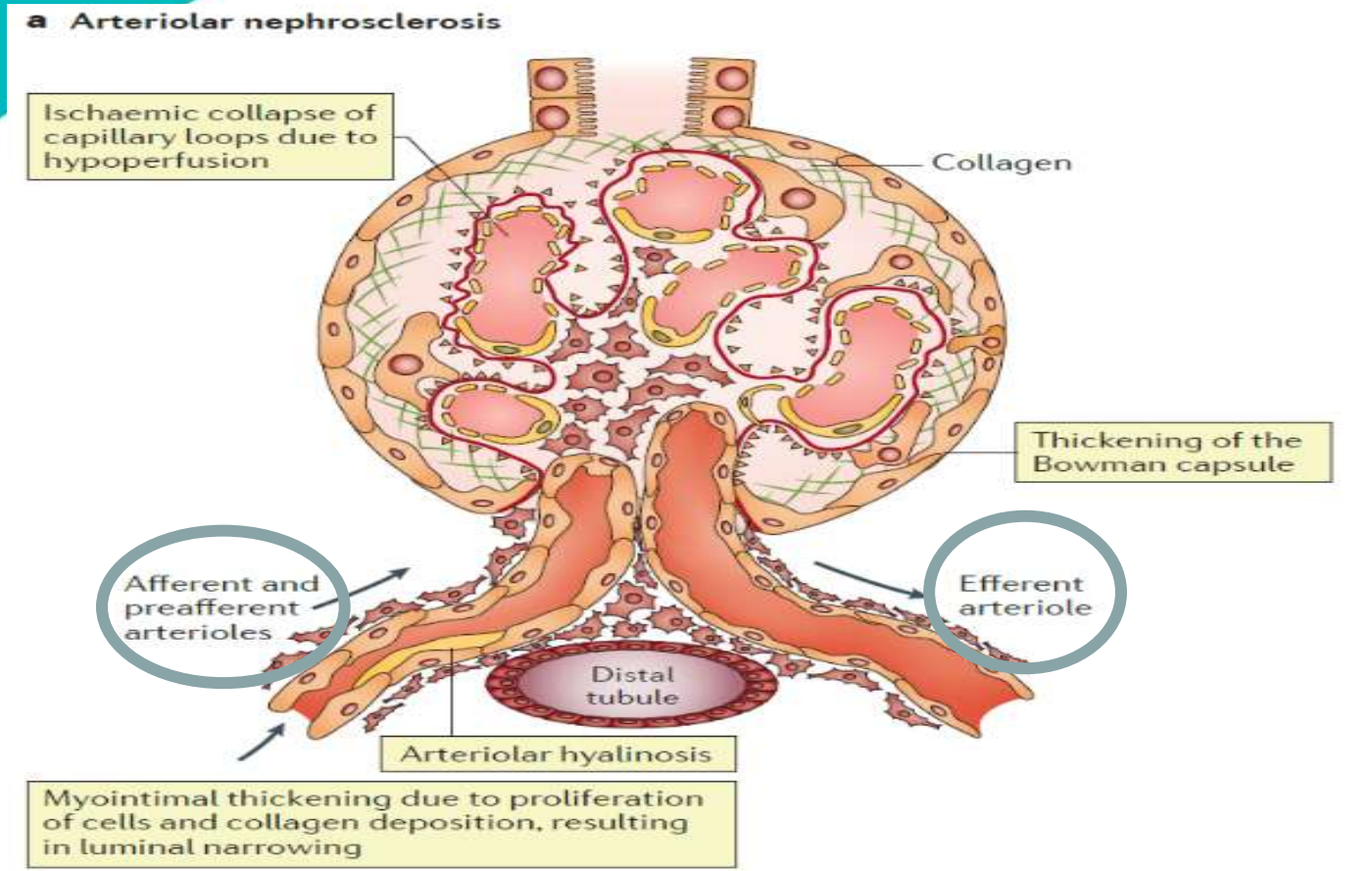
Organ Damage

Feihl F et al; The macrocirculation and microcirculation of hypertension Curr Hypertens Rep 2009 Jun;11(3):182-9



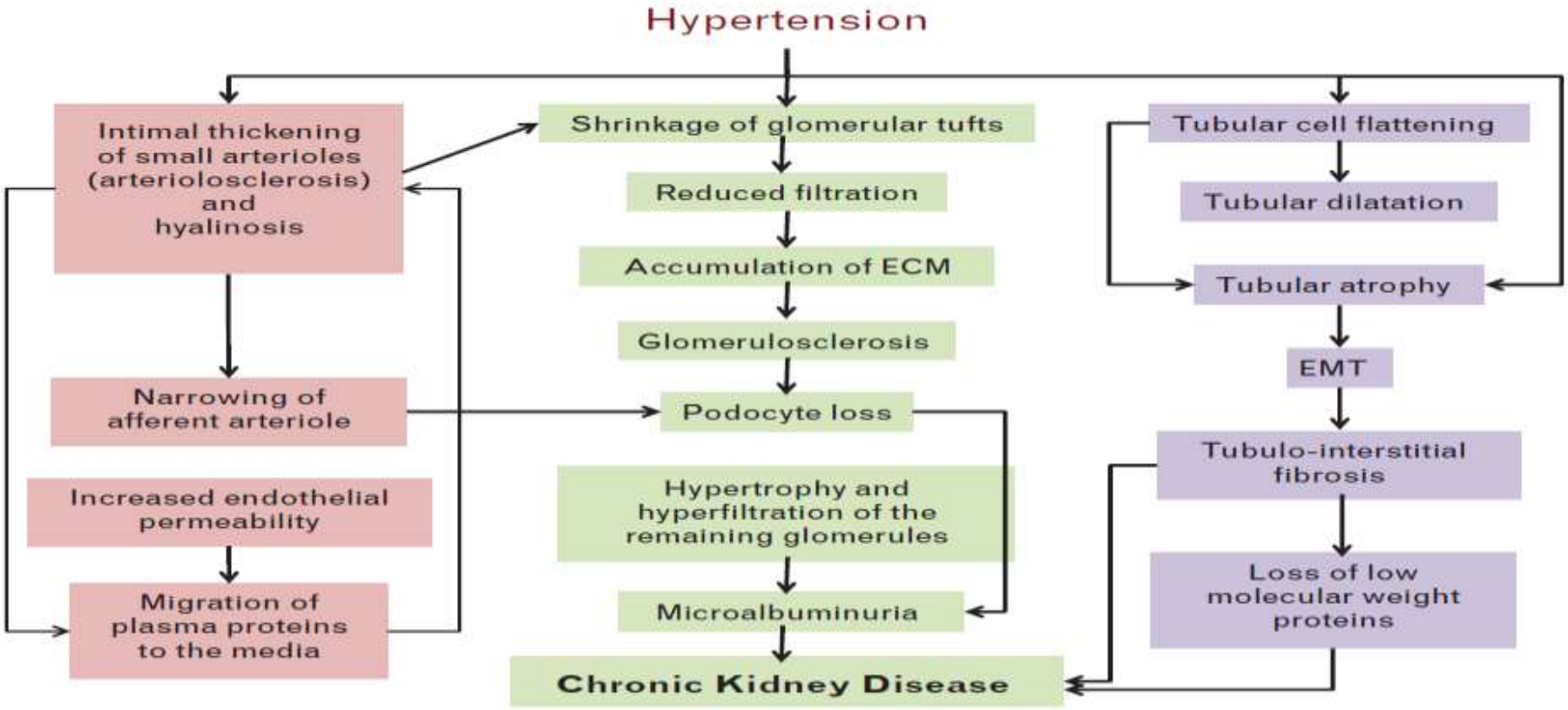
PARATI G. CURRENT MEDICAL RESEARCH AND OPINION, 2016, 32, S2, 25-28

Glomerural Consequences of Hypertension



Freedman B & Cohen AH, Nat Rev Nephrol 2016;12:27

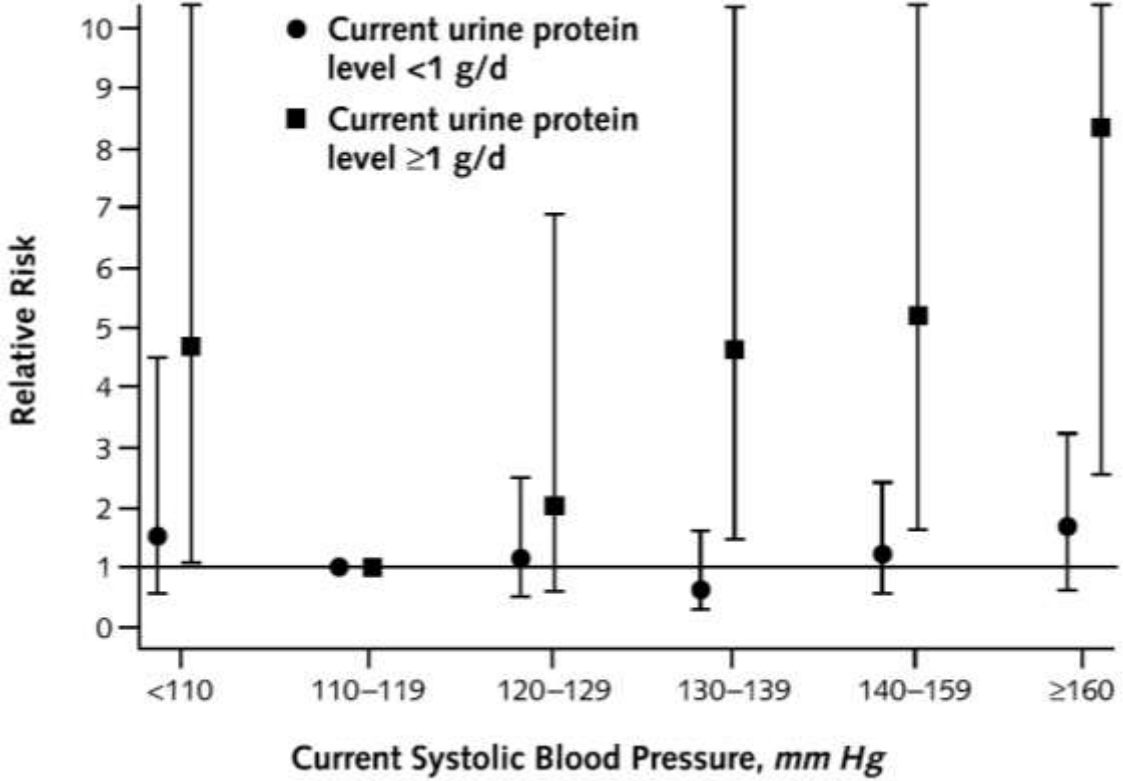
Renal Consequences of Hypertension



Seccia T et al., Journal of Hypertension 2017, 35:205–212

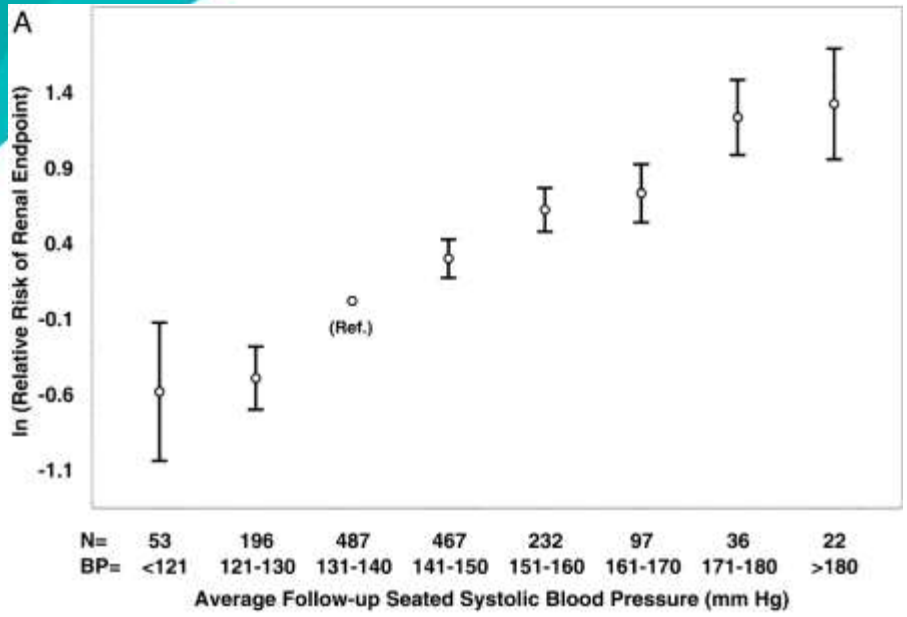
Clinical Trials
Calcium Channel blockers and Renal protection effect

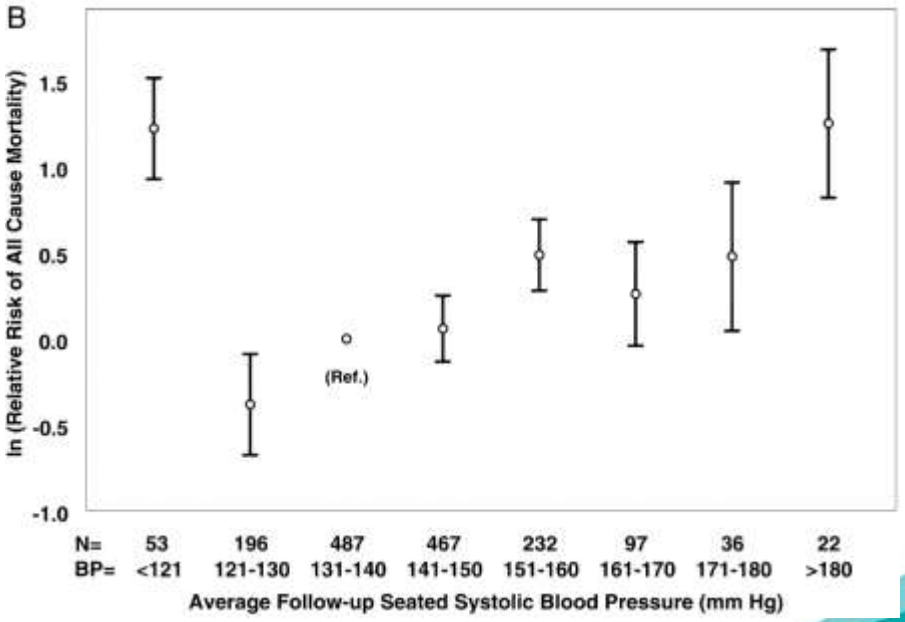
Current Blood Pressure and CKD Progression



Jafar TH et al. Ann Intern Med 2003

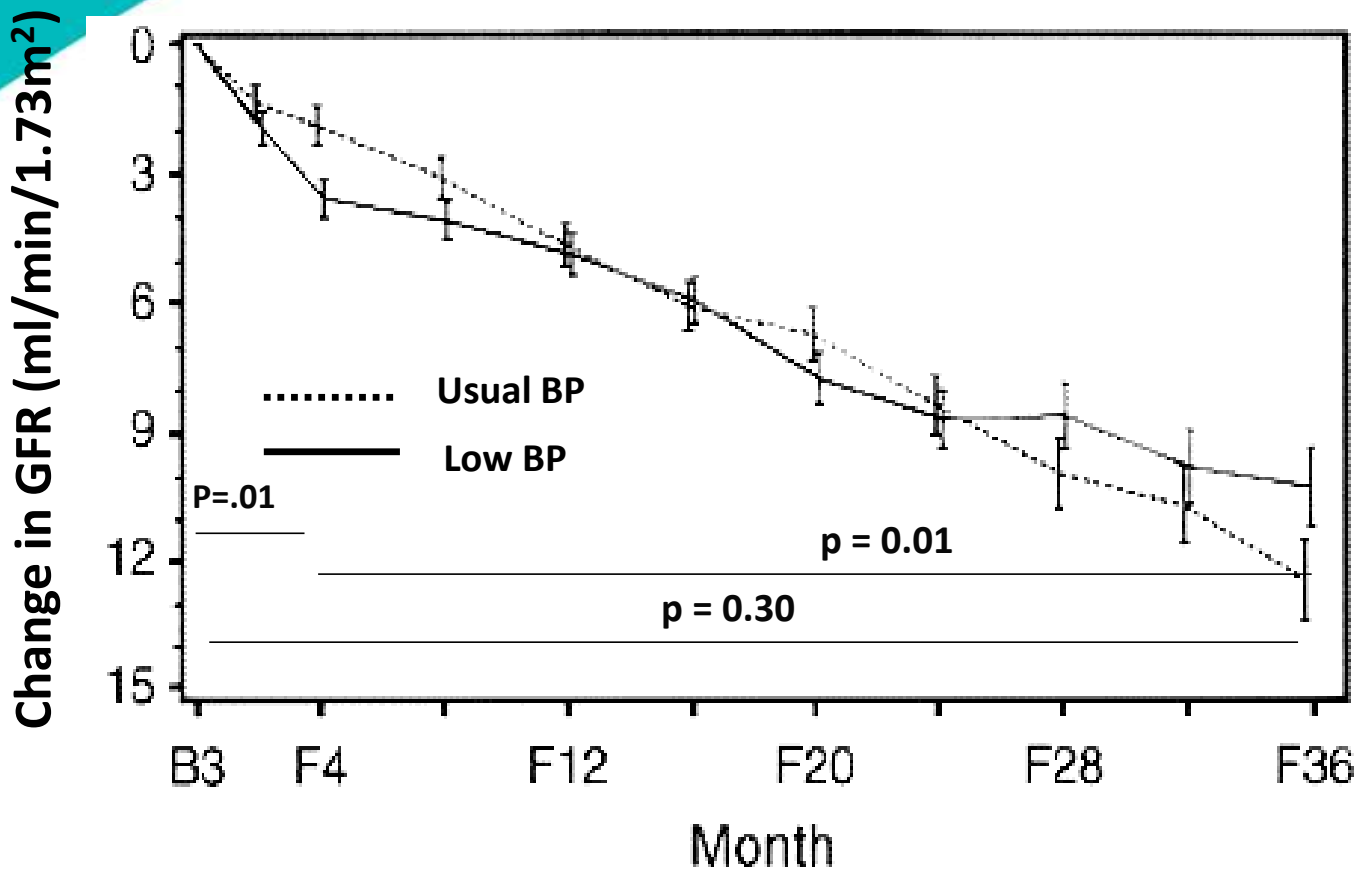
Achieved Blood Pressure and CKD Progression: IDNT





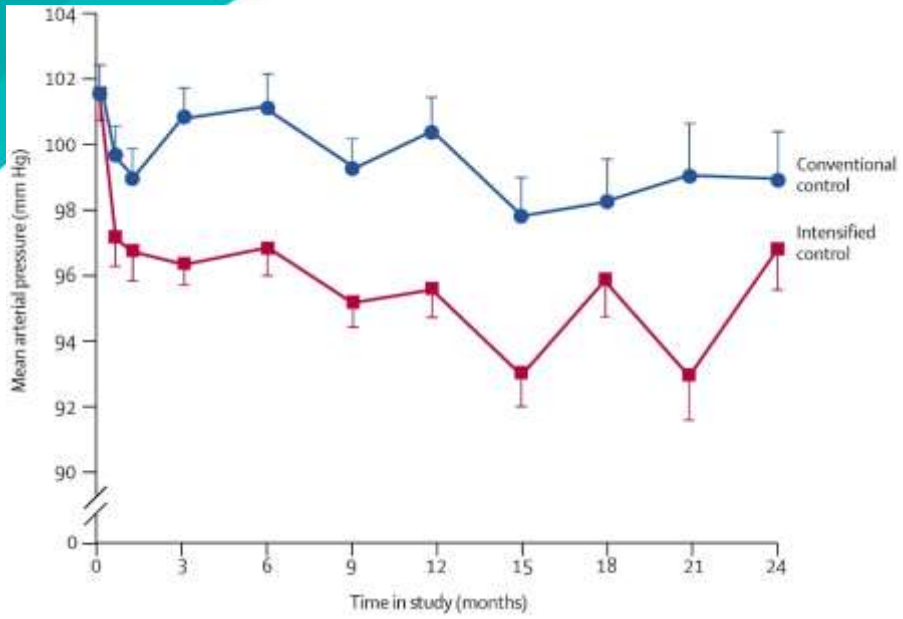
Pohl MA et al. JASN 2005

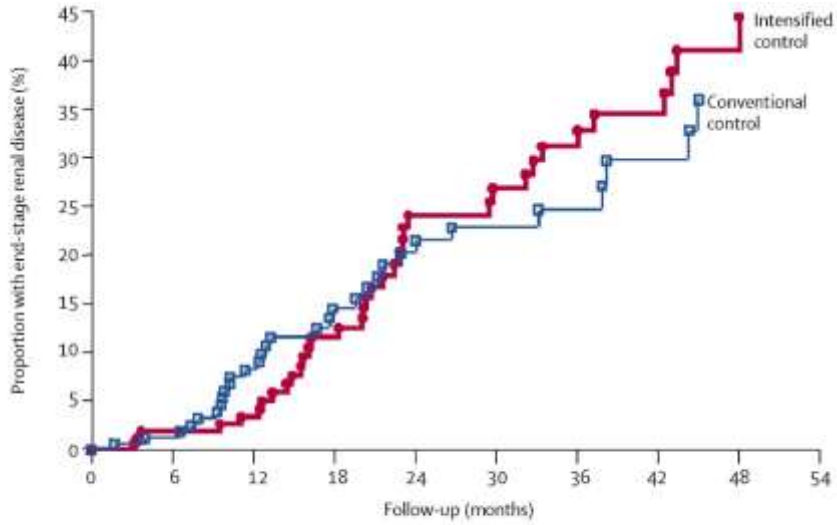
Target Blood Pressure: MDRD



Klahr S et a. NEJM 1994

Target Blood Pressure: REIN-2



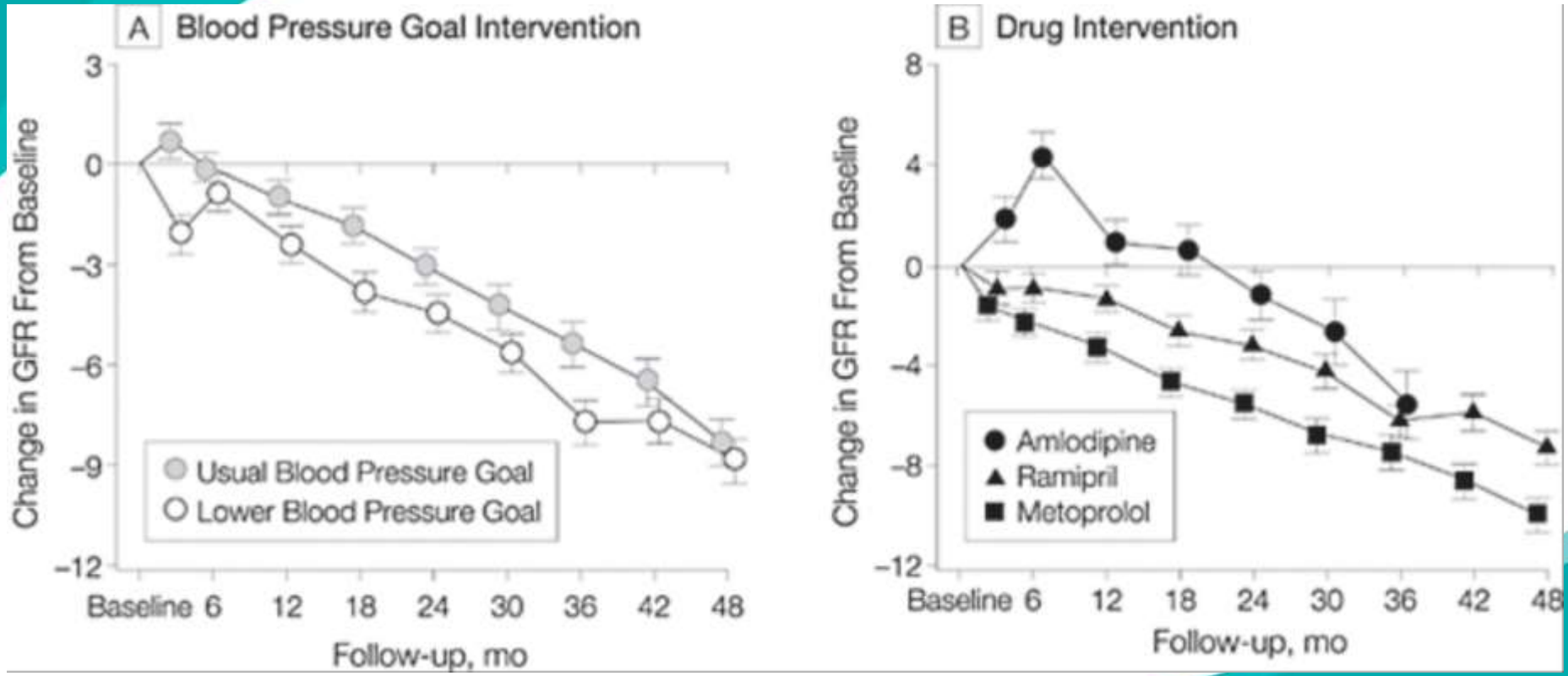


Number at risk

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

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

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

Side Effects

Hyperkalaemia

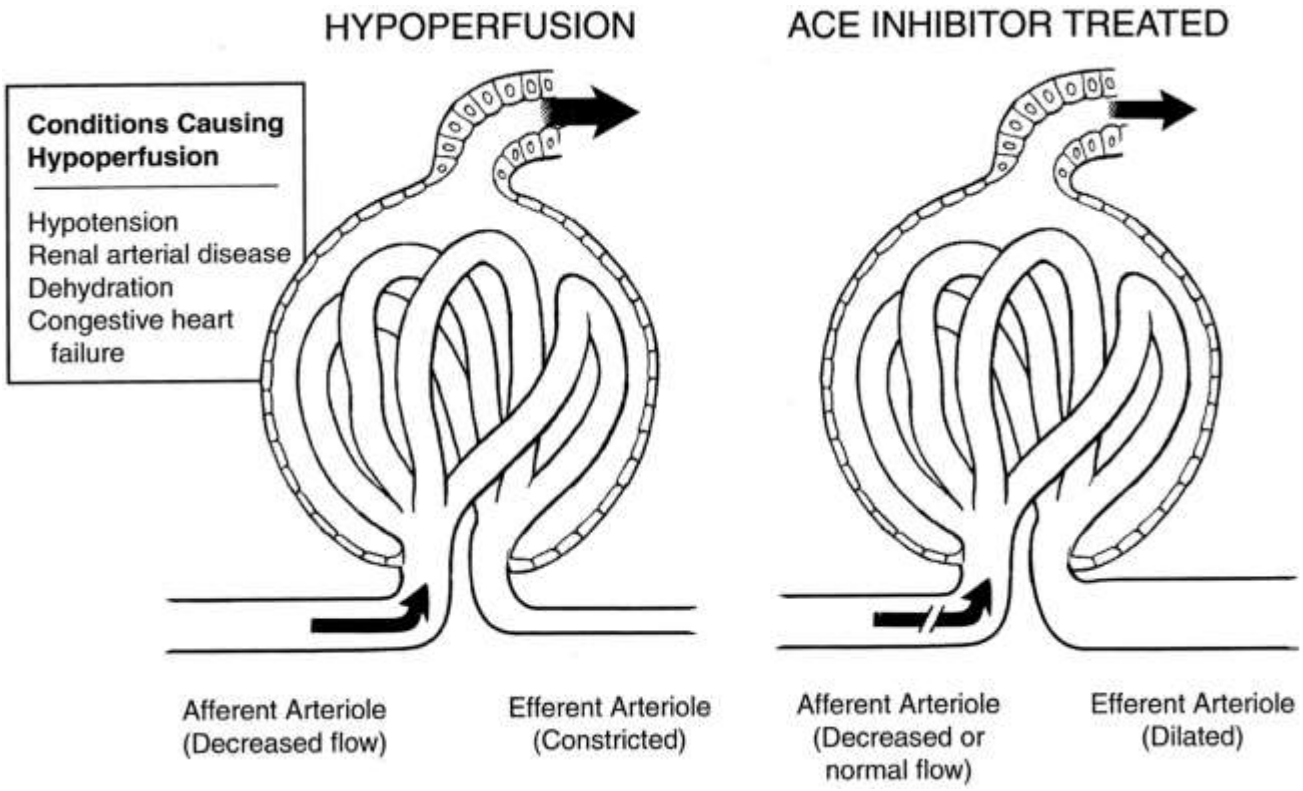
Higher risk of hyperkalaemia in combination with potassium-sparing diuretics

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

Pharmacological Treatment

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Beta-blockers	Antihypertensive + statins + + antiplatelet treatment
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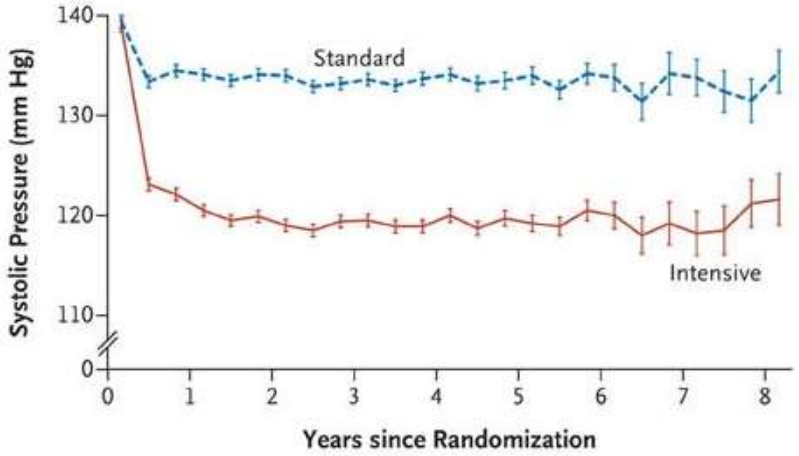
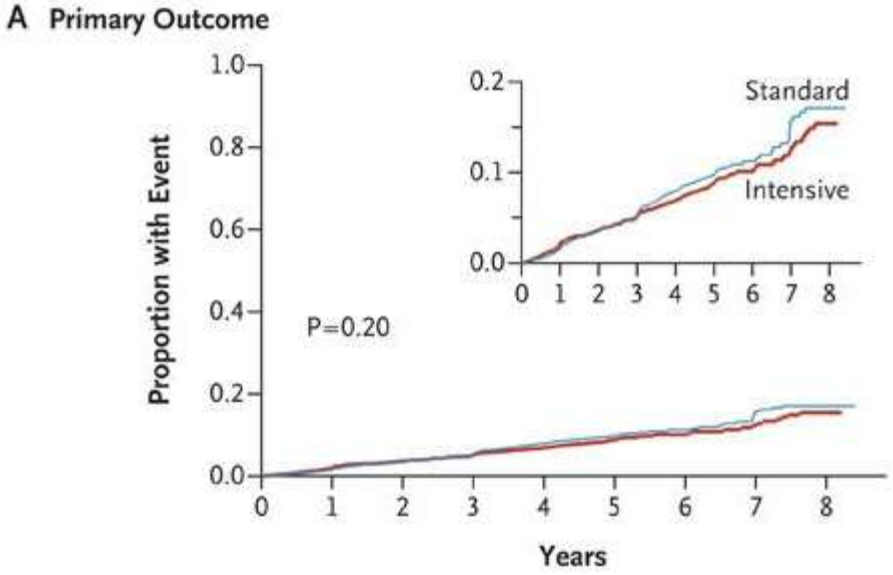
Rodicio JL & Alcazar JM. ESH Newsletter 2011, No. 4

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

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

Table 1. Summary of the antihypertensive actions, pharmacokinetics and side effects of four generations of DHP CCBs.

DHP CCBs	First generation	Second generation	Third generation	Fourth generation
Antihypertensive actions:				
L-type Ca channel block	+++	+++	++	++
N-type Ca channel block	–	–	–	+
Onset	Rapid	Gradual	Slow	Slow
Strength	Strong	Strong	Strong	Strong
Duration	Short-acting	Moderate	Long-lasting	Long-lasting
Renoprotection	–	–	+	++
Vasodilation	+++	+++	+++	+++
Sympathoexcitation	+++	++	+	–
Blood norepinephrine	↑	↑	–	–
Tolerated	Badly	Badly	Well	Well
Pharmacokinetics				
Half-life, h	2	7	10–36	7.5–10
Lipophilic	+	+	++	+++
Side-effects				
Hypotension	+	+	+	+
Tachycardia	+++	++		–
Headache	+++	++	+	
Flushing	+++	++	+	+
Edema	++	++	+	–

CCB: calcium channel blocker; DHP: dihydropyridine. +: strong; ++: very strong; +++: strongest.

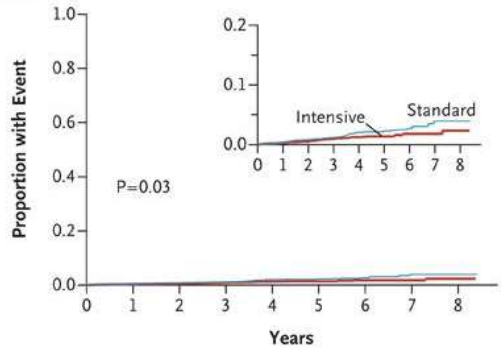
Evidence from clinical trial

Preserving kidney function in HTA pts with proteinuria

Albumin Excretion Rate (AER)			amlo	ACE-I/ARB	Results
Viberti, 2002	**Losartan vs amlodipine**	AER	-8%	-44%	Losartan>> amlo (p>0.001)
Agodoa, 2001	**Ramipril vs Amlodpine**	AER	+58%	-20%	Ramipril>>amlo (p>0.001)
Lewis, 2001	**Ibesartan vs Amlodipine**	AER	-6%	-33%	Ibersartan>>amlo (placebo -10%)
			lerca		Results
Dalla Vestra, 2004	**Ramipril vs Lercanidipine**	AER Pts with AER>50%	-20% -34%	-29% -22%	Ramipril=Lerca
Robles, 2005	**Lercanidipine (add on ACE/ARB)**	AER	-80%		
Robles, 2010	**Lercanidipine (add on ACE/ARB)**	AER	-33%		

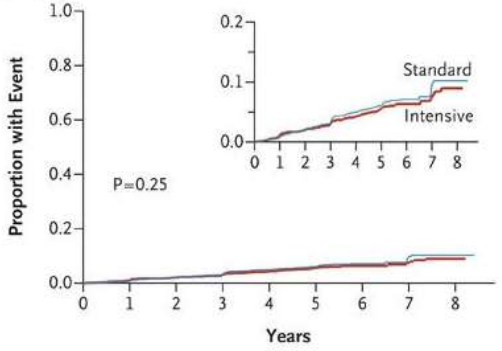
Diabetes: ACCORD

B Nonfatal Stroke



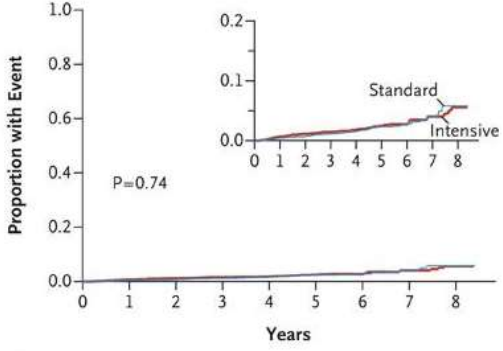
No. at Risk									
Intensive	2362	2291	2223	2174	1841	1128	313	186	88
Standard	2371	2287	2235	2186	1879	1196	382	215	114

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

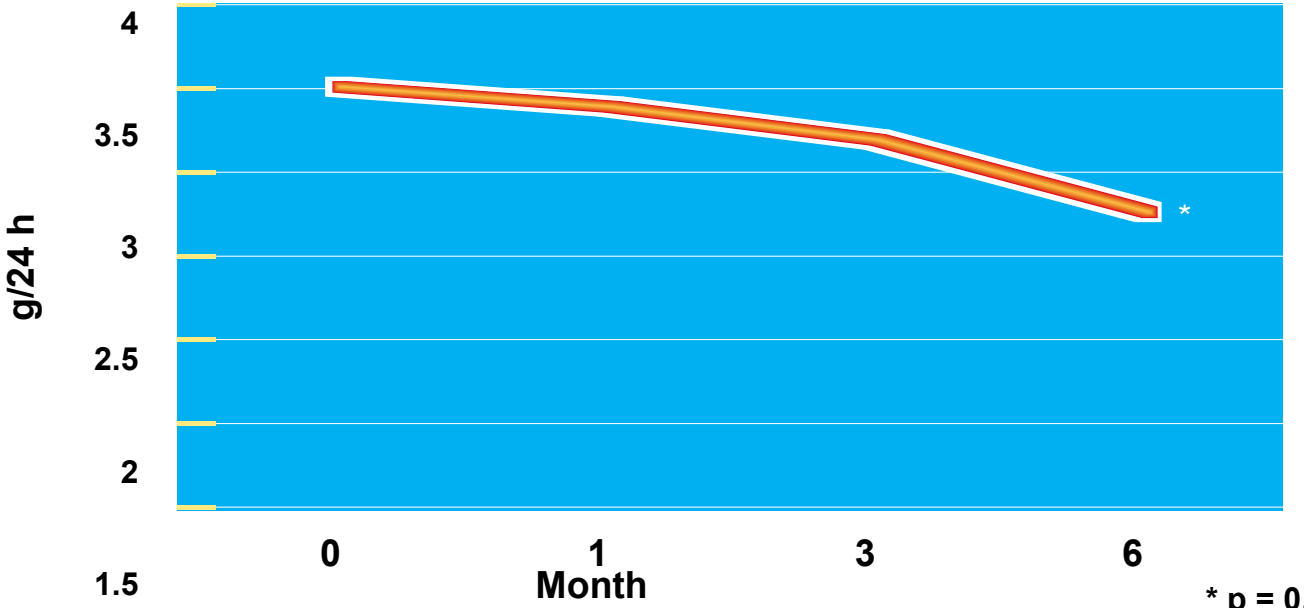


No. at Risk									
Intensive	2362	2304	2252	2201	1870	1143	317	188	91
Standard	2371	2313	2268	2218	1922	1220	393	221	118

ACCORD Study Group. NEJM 2010

Target-organ protection (ZAFRA study)

Proteinuria decreased after adding lercanidipine to ACE inhibitors/ARB therapy in patients with chronic renal failure



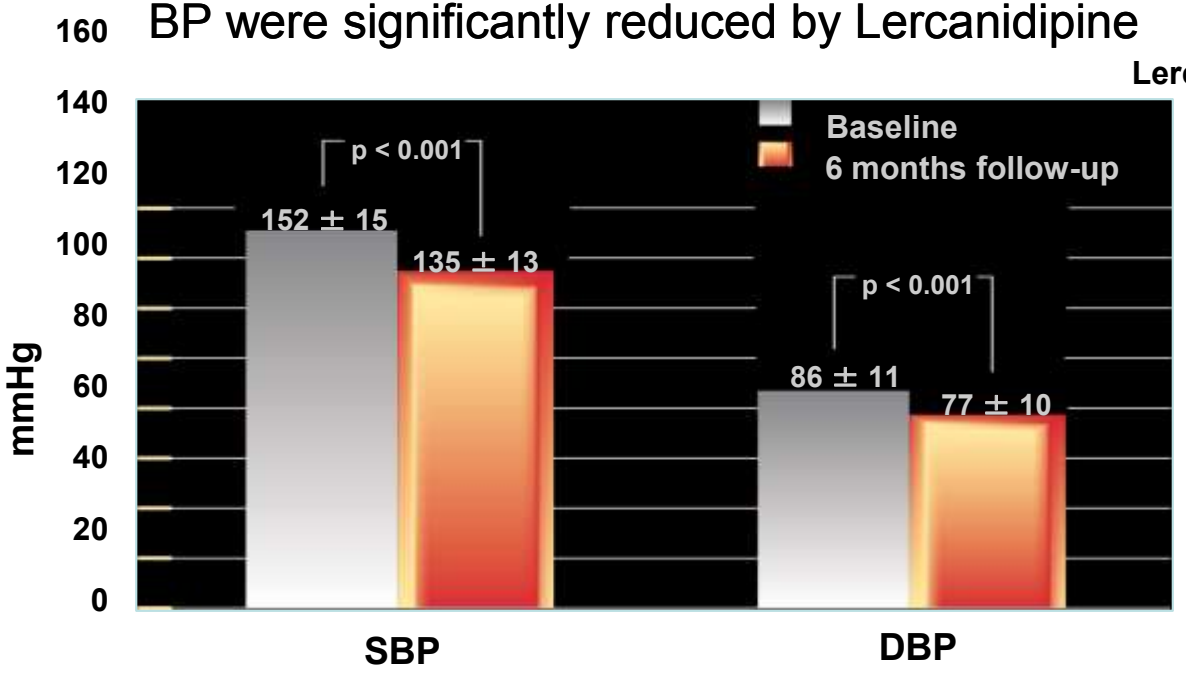
*** p = 0.015 vs pretreatment with lercanidipine**

Robles et al., Ren Fail. 2005;27(1):73-80

Hypertensive proteinuric patients

BP were significantly reduced by Lercanidipine

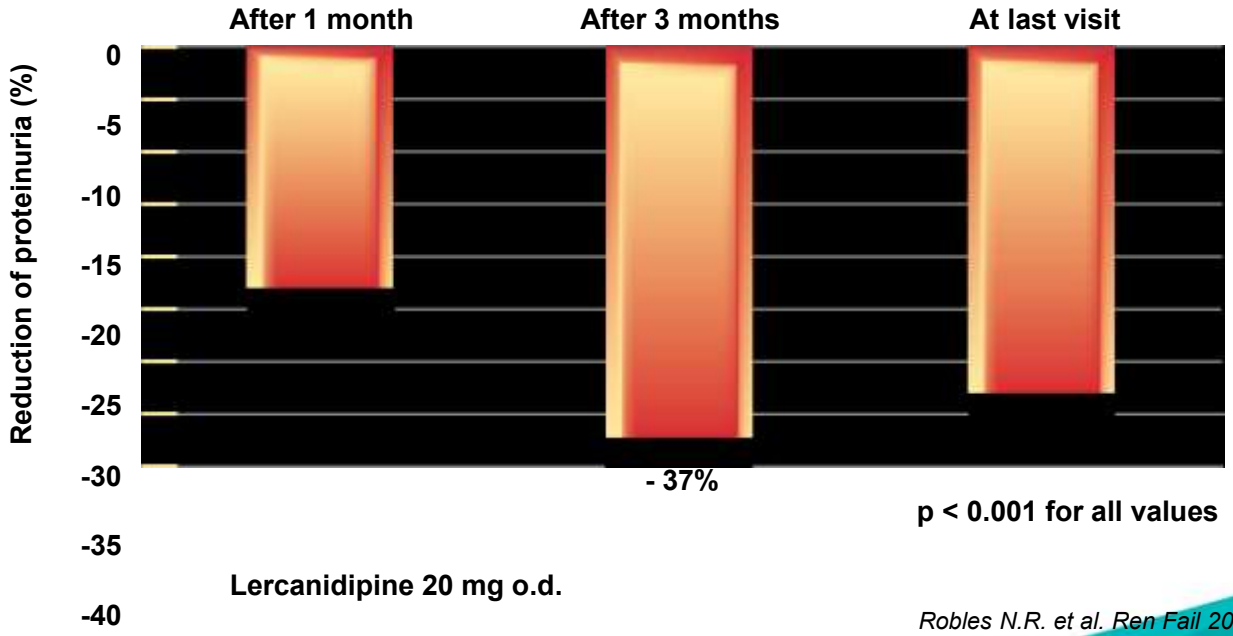
Lercanidipine, 20 mg o.d



Robles et al., Ren Fail 2010; 32 (2): 192-197

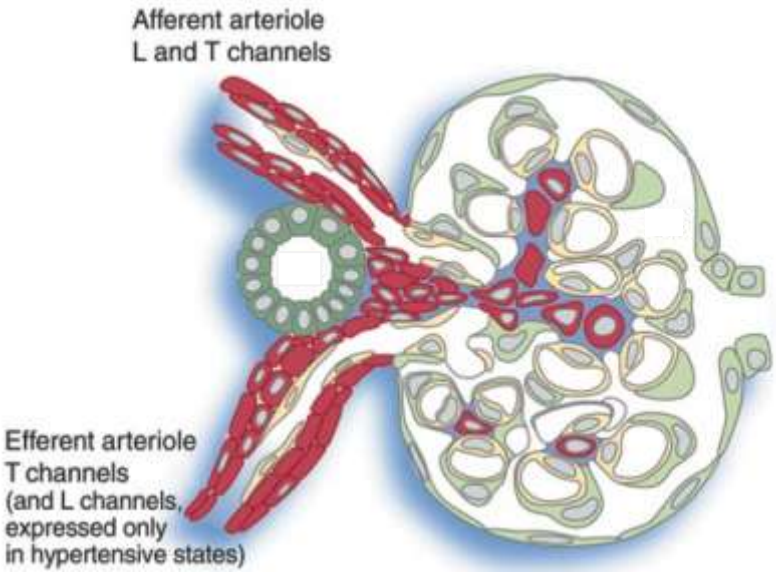
Reducing proteinuria in hypertensive pts

68 proteinuric patients with hypertension received ACE inhibitors (51.4%) or angiotensin II receptor blocker (78.6%) and lercanidipine (20 mg/day).



Robles N.R. et al. Ren Fail 2010; 32 (2): 192-197

L and T channels in the glomerulus



The distribution of the calcium channels varies throughout the kidney vasculature:

L-type channels are located primarily on the afferent (**preglomerular**) arteriole and hence, when antagonized, results in impairment of renal autoregulation

IN CONTRAST

T-type calcium channels are expressed in both the afferent (preglomerular) and the efferent (**postglomerular**) arterioles, and hence, their inhibition may overcome the effect of increased glomerular pressure transmission, as both arterioles would be dilated

L- and T-type Ca^{2+} channels

Traditional Ca channels blockers (CCBs) act predominantly on L-type Ca channels, whereas novel CCBs inhibit both L-type and T-type Ca channels

L-type CCBs preferentially dilate afferent arterioles, whereas L-/T-type CCBs dilate afferent and efferent arterioles

L-type CCBs favour an increase in glomerular capillary pressure, whereas L-/T-type CCBs alleviate glomerular hypertension

Cơ chế bảo vệ thận của Lercanidipine

1. Tác dụng lên tiểu ĐM thận đến và đi tương đương.

2. Làm giảm nồng độ Ca++ nội bào, ức chế sự hoạt hóa angiotensin-induced protein kinase C(PKC) α và δ, giảm viêm và xơ hóa → tăng tác dụng sinh học của NO.

3. Cải thiện tính đàn hồi mạch máu, giảm stress oxi hóa, ức chế sự tăng sinh tế bào -→ giảm khả năng tổn thương của tế bào nội mạc cầu thận và xơ hóa ống thận.

4. Cân bằng các yếu tố ức chế tăng sinh tiểu cầu và yếu tố hoạt hóa tiểu cầu.

Lercanidipine and renal function in renal artery stenosis. Peng et al. Curent Medical Research & opinion. Volume 31, No 1, January 2015.

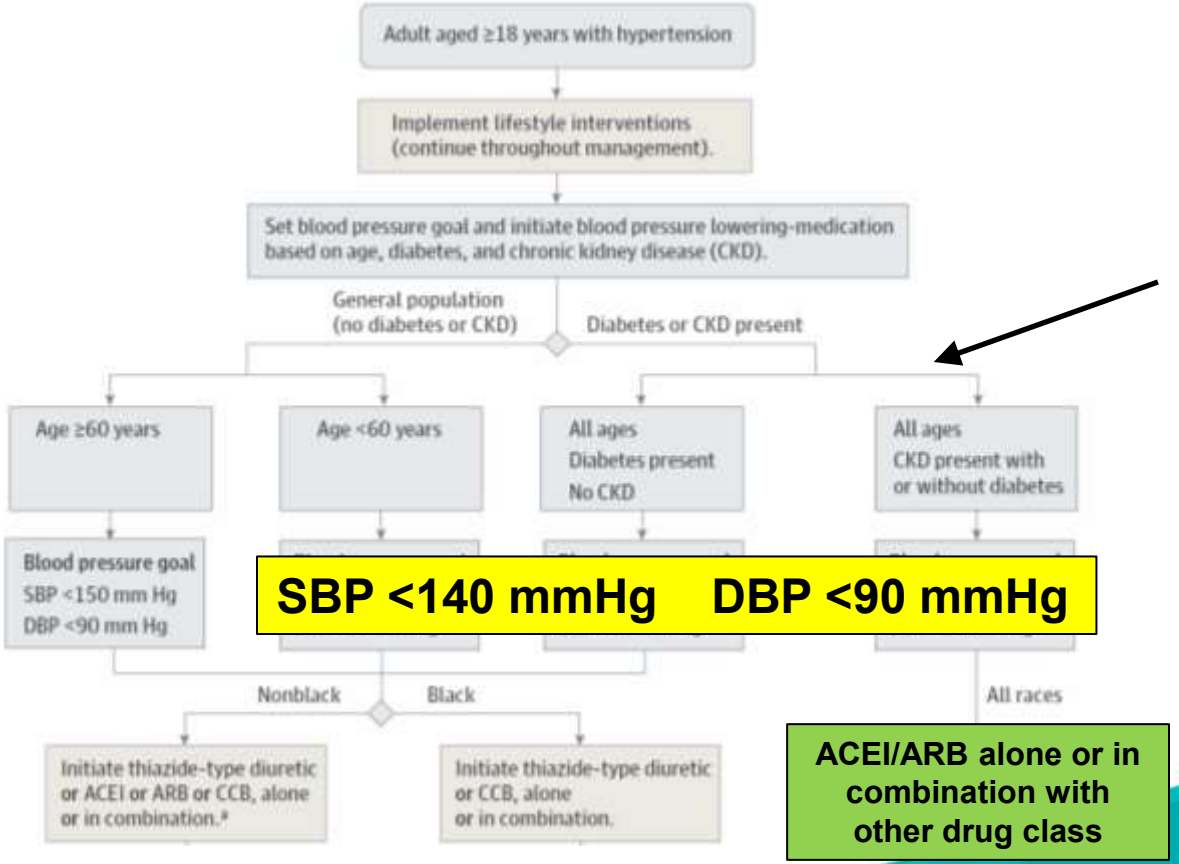
Tác dụng phụ của Lercanidipine & Amlodipine

Adverse Event	Lercanidipine		Amlodipine		p value
	N	%	n	%	
Patients with AE	3	5.7	10	19.2	0.03
Flushing	3	5.7	8	15.4	0.11
Ankle oedema	2	3.8	4	7.7	0.66
Headache	0	0.0	2	3.8	(-)
Dizziness	0	0.0	1	1.9	(-)
Total Side Effects(F+ Ao+ H + D)	5	9.6	15	28.8	0.02
Flushing and Ankle oedema/Patient	2	3.8	5	9.6	0.42
Flushing + A oedema + Headache/Patient	0	0.0	2	3.8	(-)
≥2 Adverse events	2	3.8	7	13.6	0.14

Current Medical Research & Opinion Vol. 31, No. 1, 2015, 163–170

How about guidelines say?

JNC 8



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
1–2 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • 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
≥3 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
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 normoalbuminuric
  ≤130 mmHg systolic and ≤80 mmHg diastolic if micro or macroalbuminuric

- **Diabetic adults with non dialysis-dependent CKD:**
  ≤140 mmHg systolic and ≤90 mmHg diastolic if normoalbuminuric
  ≤130 mmHg systolic and ≤80 mmHg diastolic if micro or macroalbuminuric

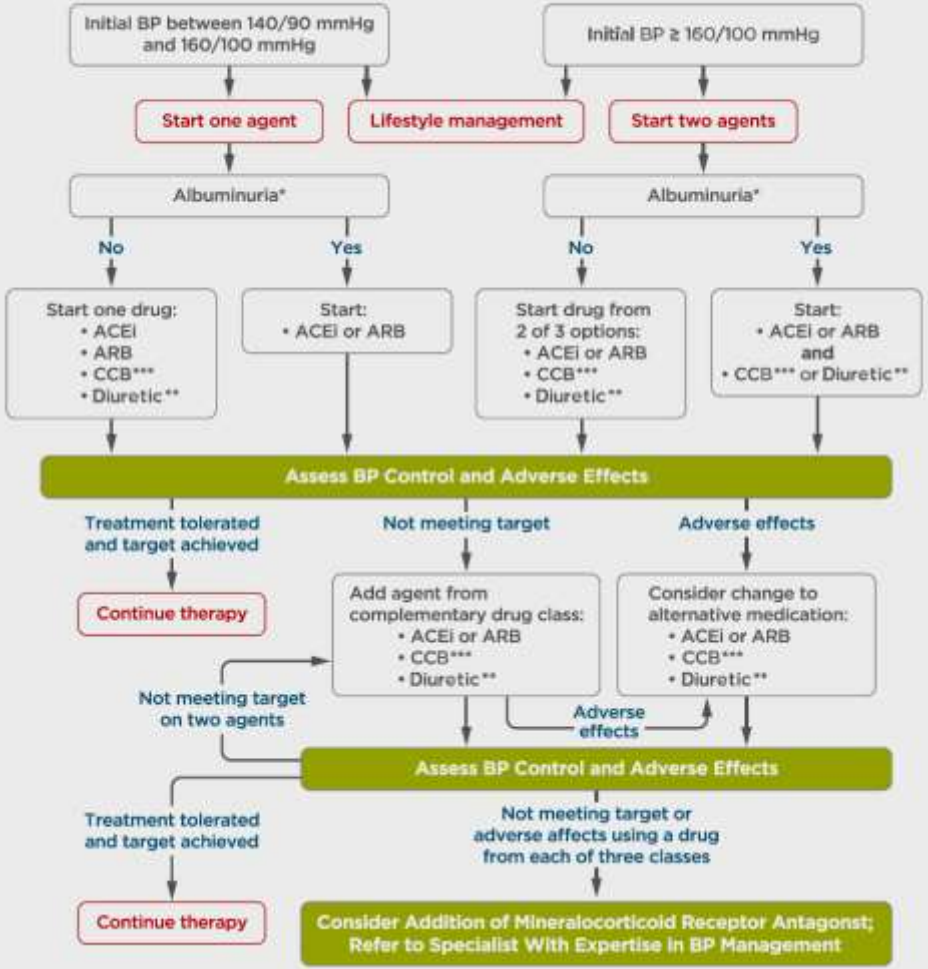
- **Kidney transplant recipients:**
  ≤130 mmHg systolic and ≤90 mmHg diastolic

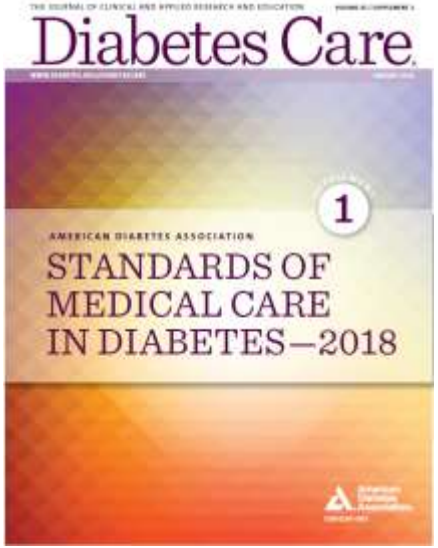
- **Elderly people with CKD:**
  probably ≤140 mmHg systolic and ≤90 mmHg diastolic, but set targets after consideration of co-morbidities

Aim for <130/80 mmHg if albuminuria is present

KDIGO Blood Pressure Work Group. Kidney Int Suppl 2012

Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes



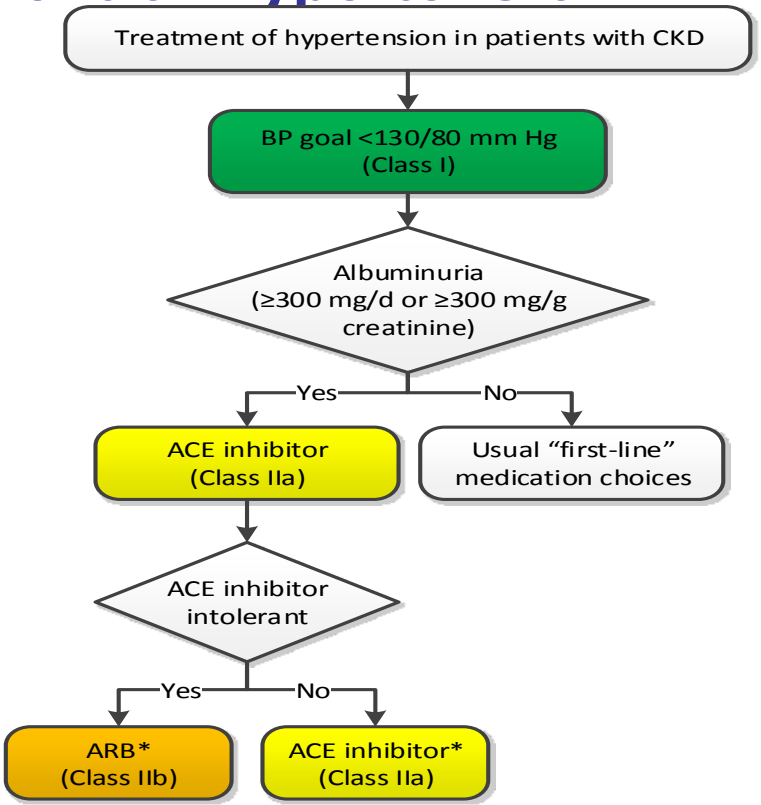


Chronic Kidney Disease/ ACCF/AHA 2017

COR	LOE	Recommendations for Treatment of Hypertension in Patients With CKD
I	SBP: B-R^{SR} DBP: C-EO	Adults with hypertension and CKD should be treated to a BP goal of less than 130/80 mm Hg.
IIa	B-R	In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void]), treatment with an ACE inhibitor is reasonable to slow kidney disease progression.
IIb	C-EO	In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio in the first morning void]), treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated.

SR indicates systematic review.

Management of Hypertension in Patients With CKD



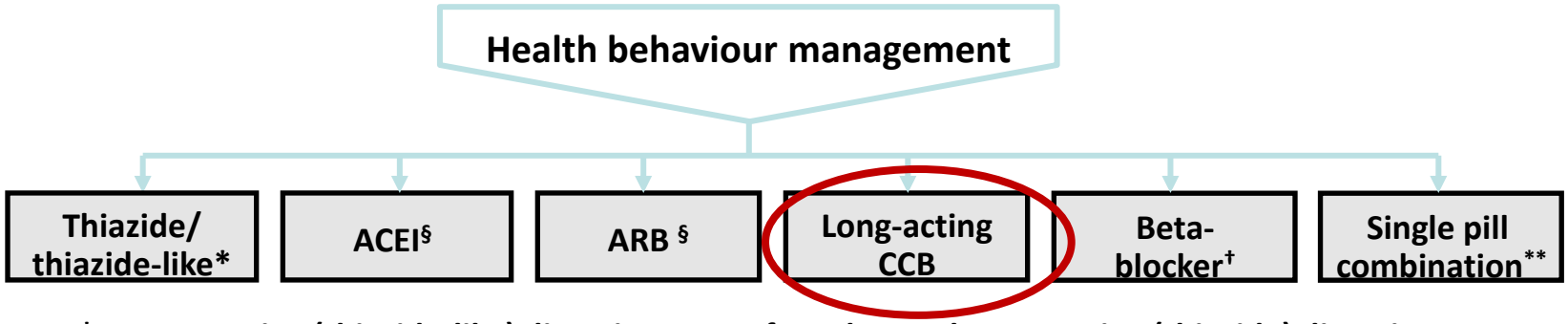
•Colors correspond to Class of Recommendation in Table 1.*CKD stage 3 or higher or stage 1 or 2 with albuminuria ≥300 mg/d or ≥300 mg/g creatinine. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP blood pressure; and CKD, chronic kidney disease.

First Line Treatment of Adults with Systolic/Diastolic Hypertension Without Other Compelling Indications

New 2017

TARGET <135/85 mmHg (automated measurement method)

INITIAL TREATMENT



*** Longer-acting (thiazide-like) diuretics are preferred over shorter-acting (thiazide) diuretics**

† BBs are not indicated as first line therapy for age 60 and above

§Renin angiotensin system (RAS) inhibitors are contraindicated in pregnancy and caution is required in prescribing to women of child bearing potential

****Recommended SPC choices are those in which an ACE-I is combined with a CCB, an ARB with a CCB, or an ACE-I or ARB with a diuretic**

CONCLUSION

Có mối liên quan chặc chẽ giữa THA và tổn thương thận, trị số HA càng cao suy thận càng nặng và ngược lại.

Các thuốc chẹn Canxi đặc biệt thế hệ mới như Lercanidipine (Zanedip) có tác dụng bảo vệ tốt cơ quan đích quan trọng là thận.

Các khuyến cáo gần đây đều thống nhất việc xử dụng chẹn canxi như là những thuốc đầu tiên trong điều trị THA nhằm bảo vệ cơ quan đích./.


Chân thành cám ơn quí Đại biểu.
Hẹn gặp lại Hội nghị Tim mạch Miền Trung
lần thứ X năm 2019 tại Huế
Thank you for your attention
And see you in 10th Central Congress of Cardiology in Huecity 2018
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