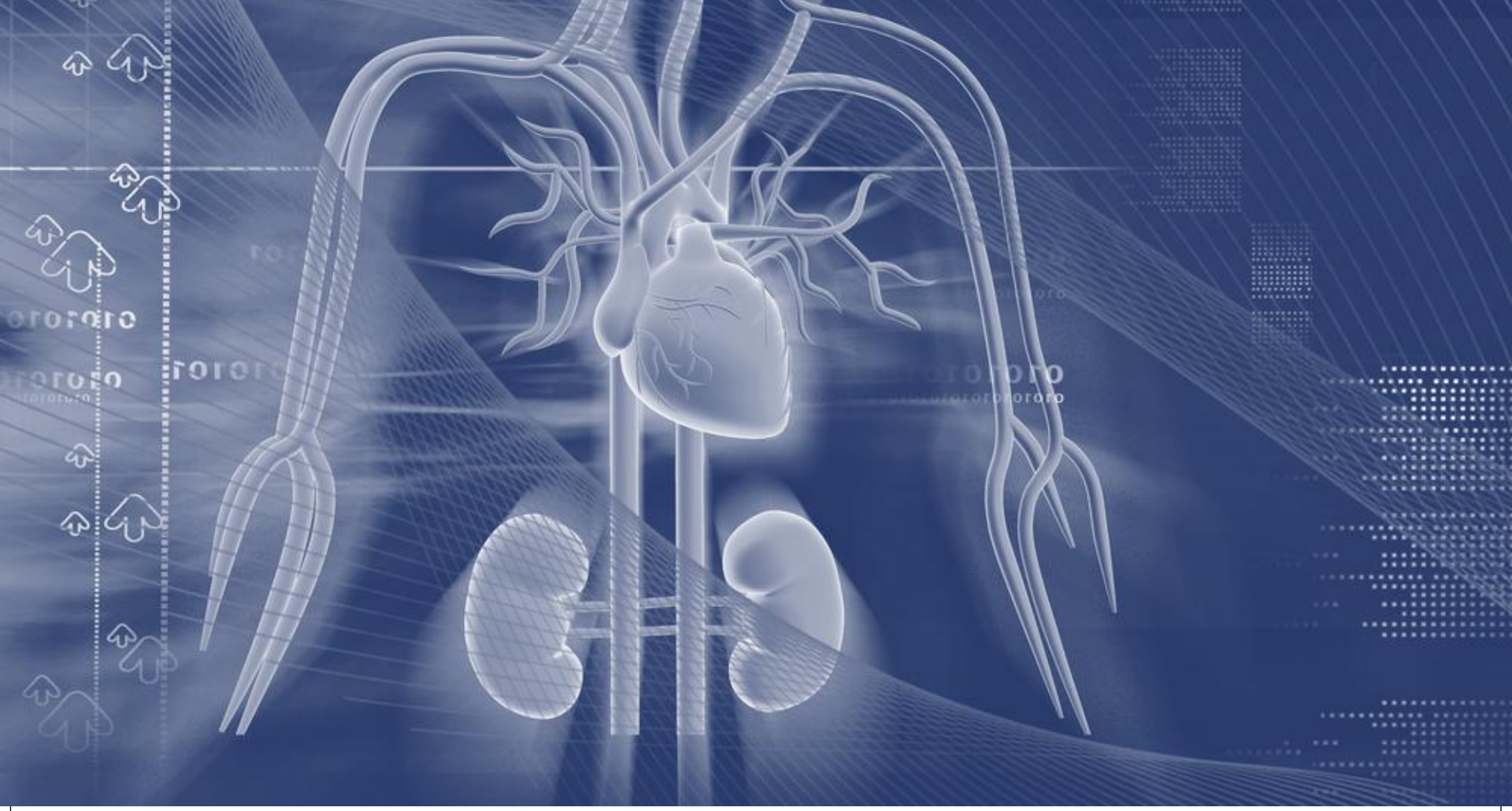


Role of antihypertensives in patients with Hypertension and CKD

Hypertension Burden

970 million — Worldwide prevalence

60% — Increase in the number of adults with HTN globally by 2025

10% — Percent of all global healthcare spending attributable to HTN

$370 billion — Annual worldwide cost of hypertension

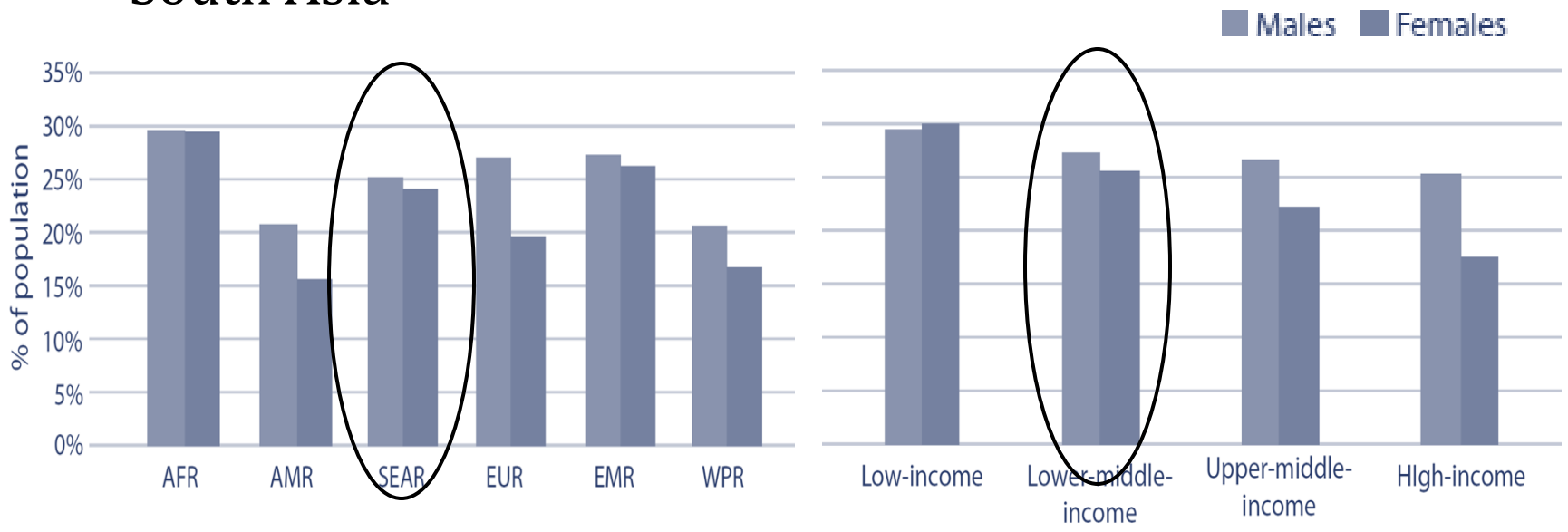
1.6 Billion HTN patients estimated by 2025

Singh PS et al. Int J Res Med Sci. 2017 Apr;5(4):1451-1455
World-heart-federation.org. [Accessed 10 May 2017]

Hypertension: WHO Estimates

•The global prevalence is ≈22%.

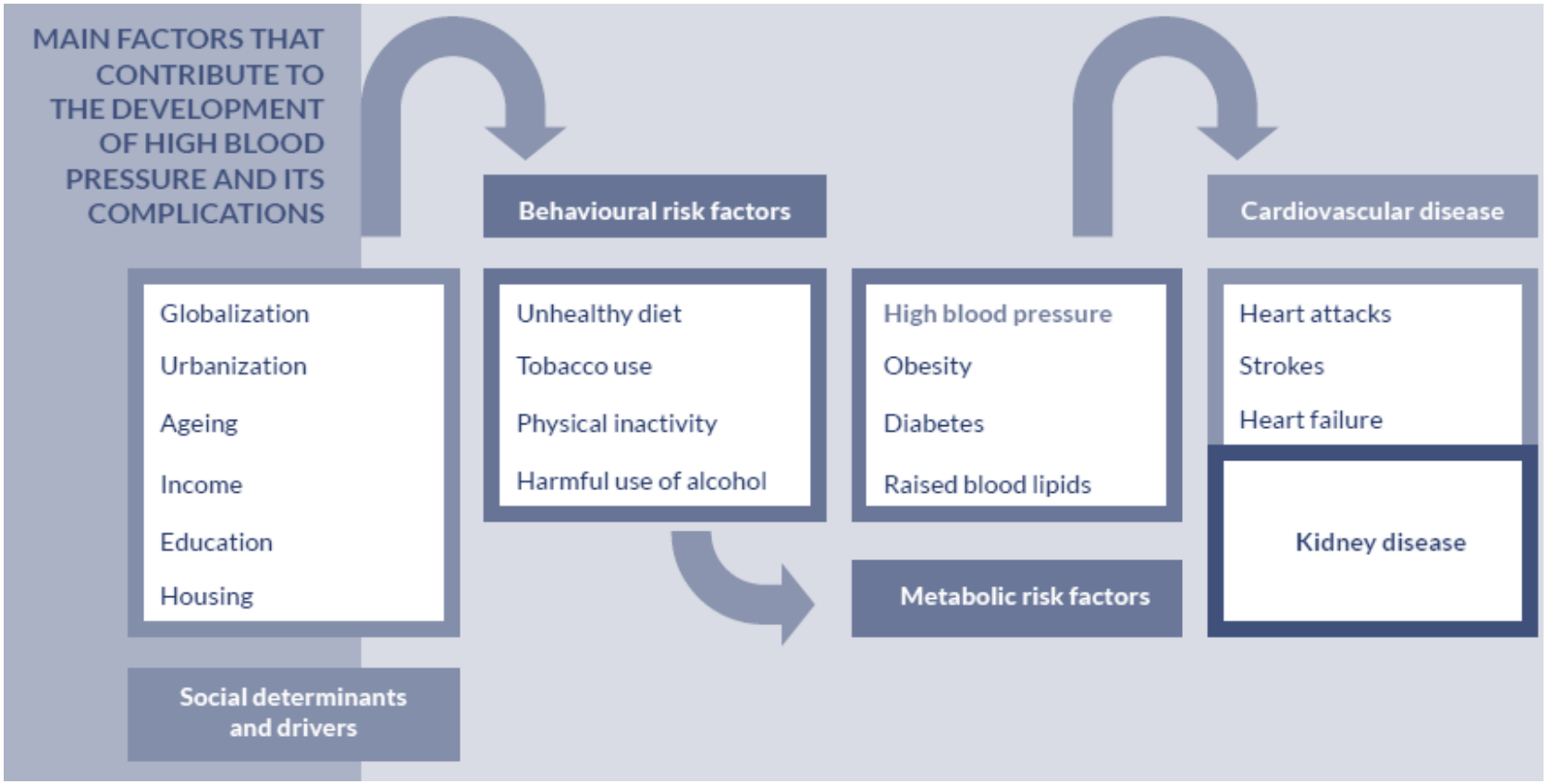
• **Ranked 3rd** most risk factor for hypertension burden in South Asia



AFR=African Region, AMR=Region of the Americas, SEAR =South-East Asia Region, EUR=European Region, EMR=Eastern Mediterranean Region, WPR=Western Pacific Region

Global Status Report, 2014. Apps.WHO.int.

Hypertension Risk Factors



Hypertension is a polygenic disease involving a major contribution of various factors

Who.int. WHO/ A global brief on hypertension

Gupta R et al. *J Hum Hypertens*. 2016 Feb;30(2):79-82.

CKD and Hypertension

- CKD and hypertension are closely associated with an overlapping and intermingled cause and effect relationship.

- Declines in kidney function are typically associated with rises in BP and sustained elevations in BP hasten the progression of kidney function decline

- In the Chronic Renal Insufficiency Cohort (CRIC) study (N= 3612) the prevalence of self-reported HTN was 86% compared with 29% in the general population

Judd A et al. Adv Chronic Kidney Dis. 2015 Mar; 22(2): 116–122.

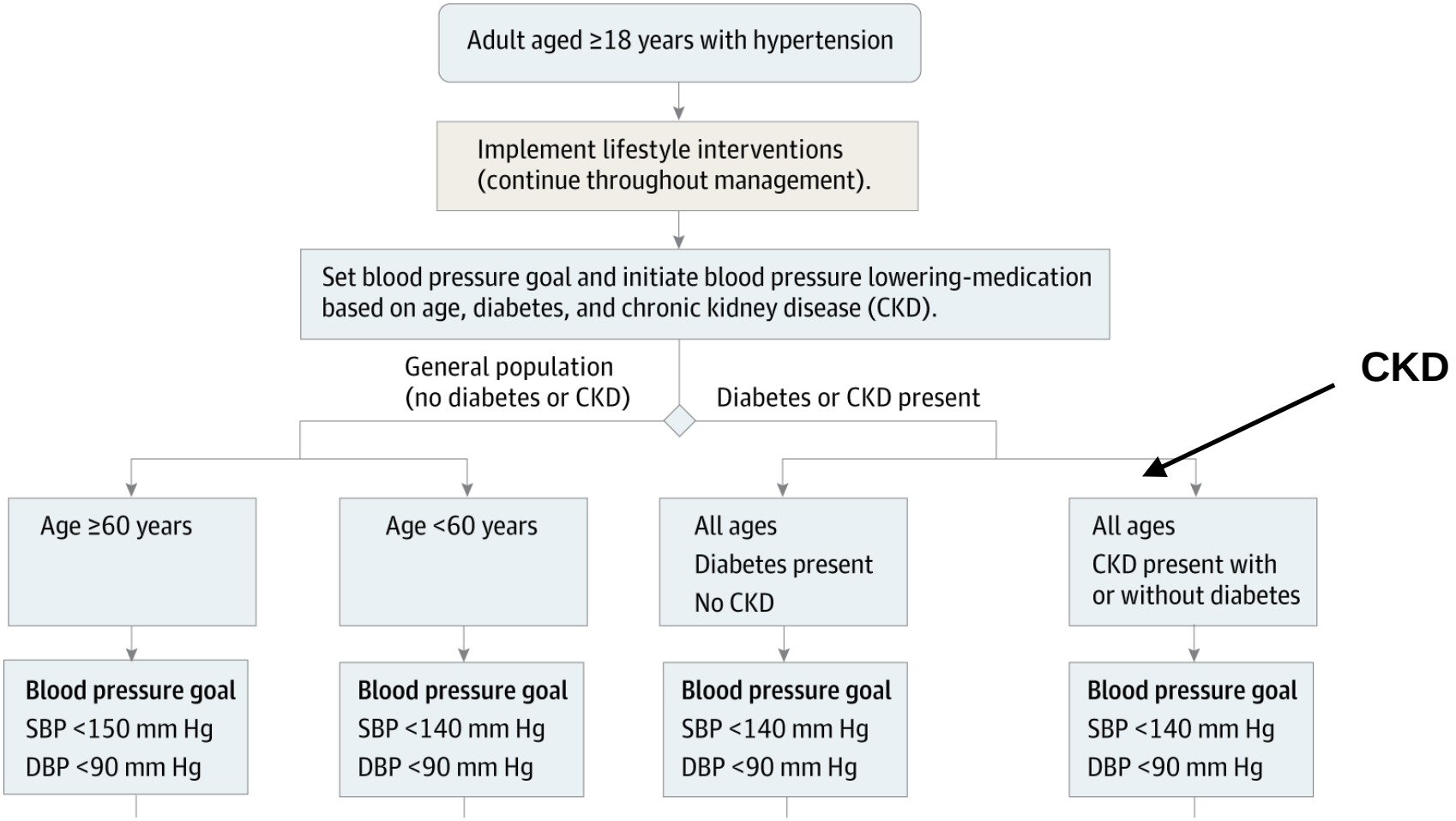
Hypertension and CKD

- Hypertension is a major risk factor for cardiovascular and renal disease.
- Conversely, chronic kidney disease (CKD) is the most common form of secondary hypertension
- Mounting evidence suggests it is an independent risk factor for CV morbidity and mortality
- Evidence from a large number of clinical trials has clearly demonstrated that effective treatment ameliorates the harmful effects of uncontrolled hypertension

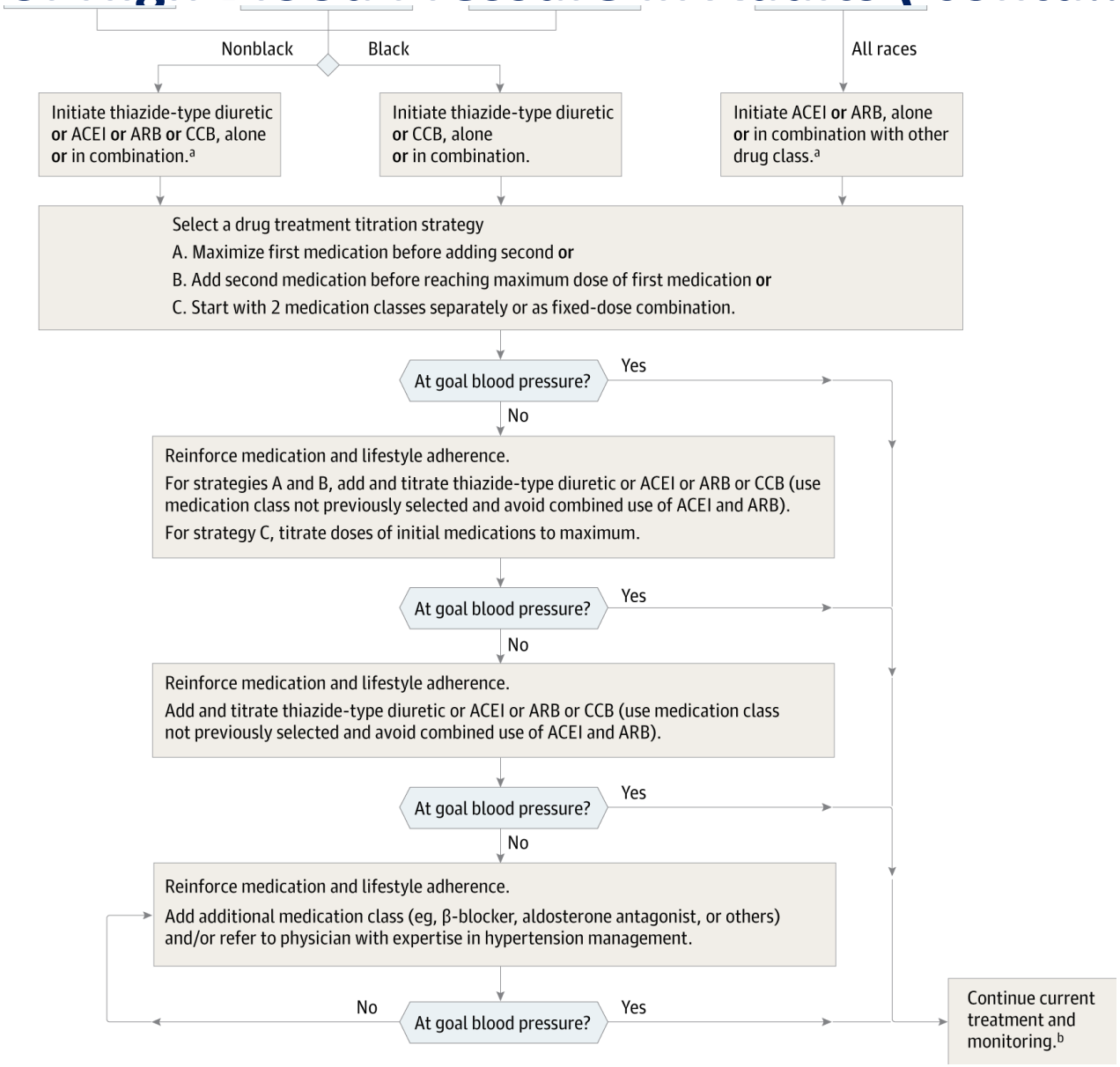
Tedla FM et al. Int J Hypertens. 2011; 2011: 132405.

Hypertension Management Guidelines

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults



2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults (contd..)



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	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90

CKD

SBP <140 mmHg DBP <90 mmHg

2013 ESH/ESC Guidelines

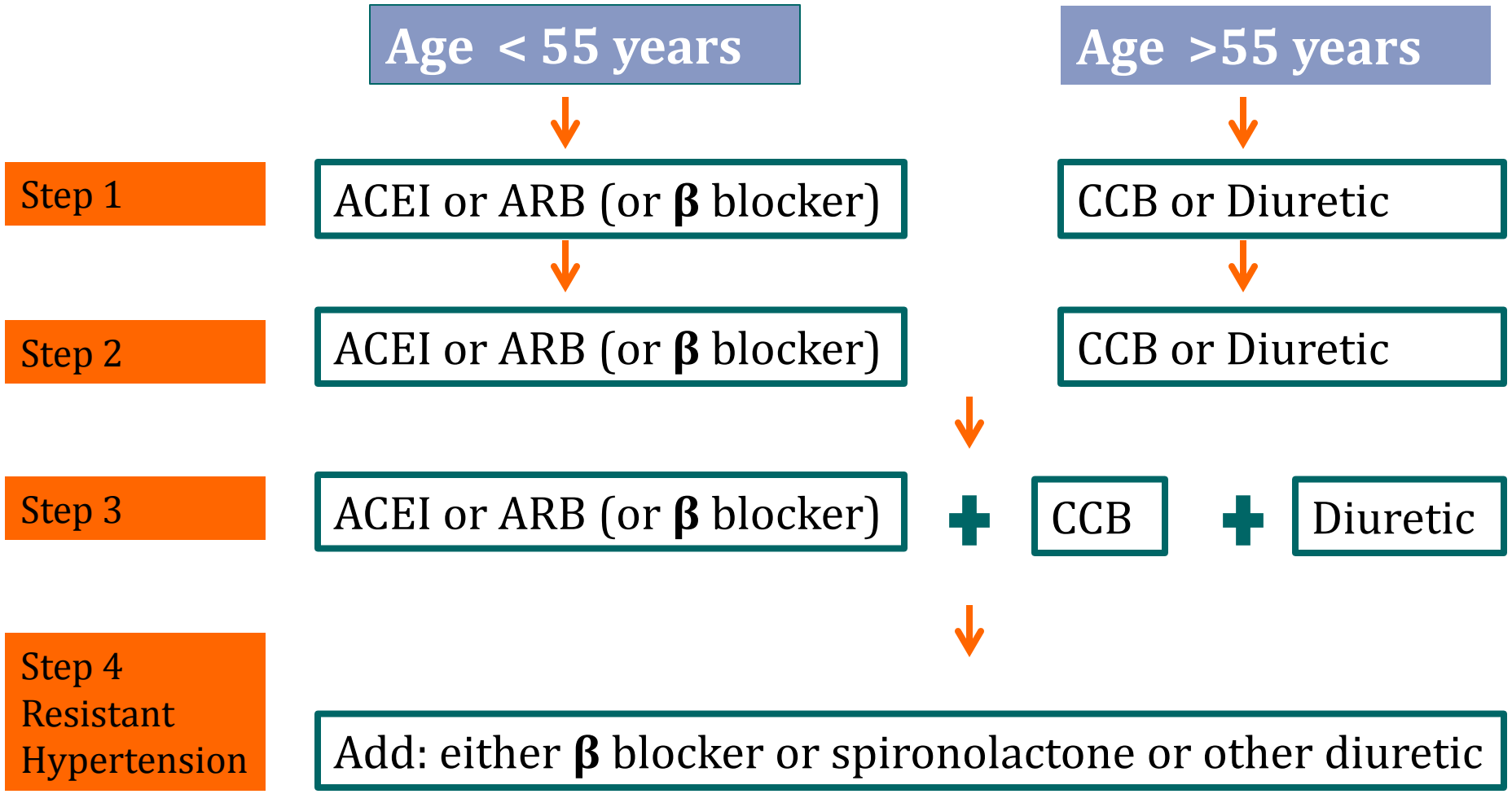
ESH/ESC

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*)

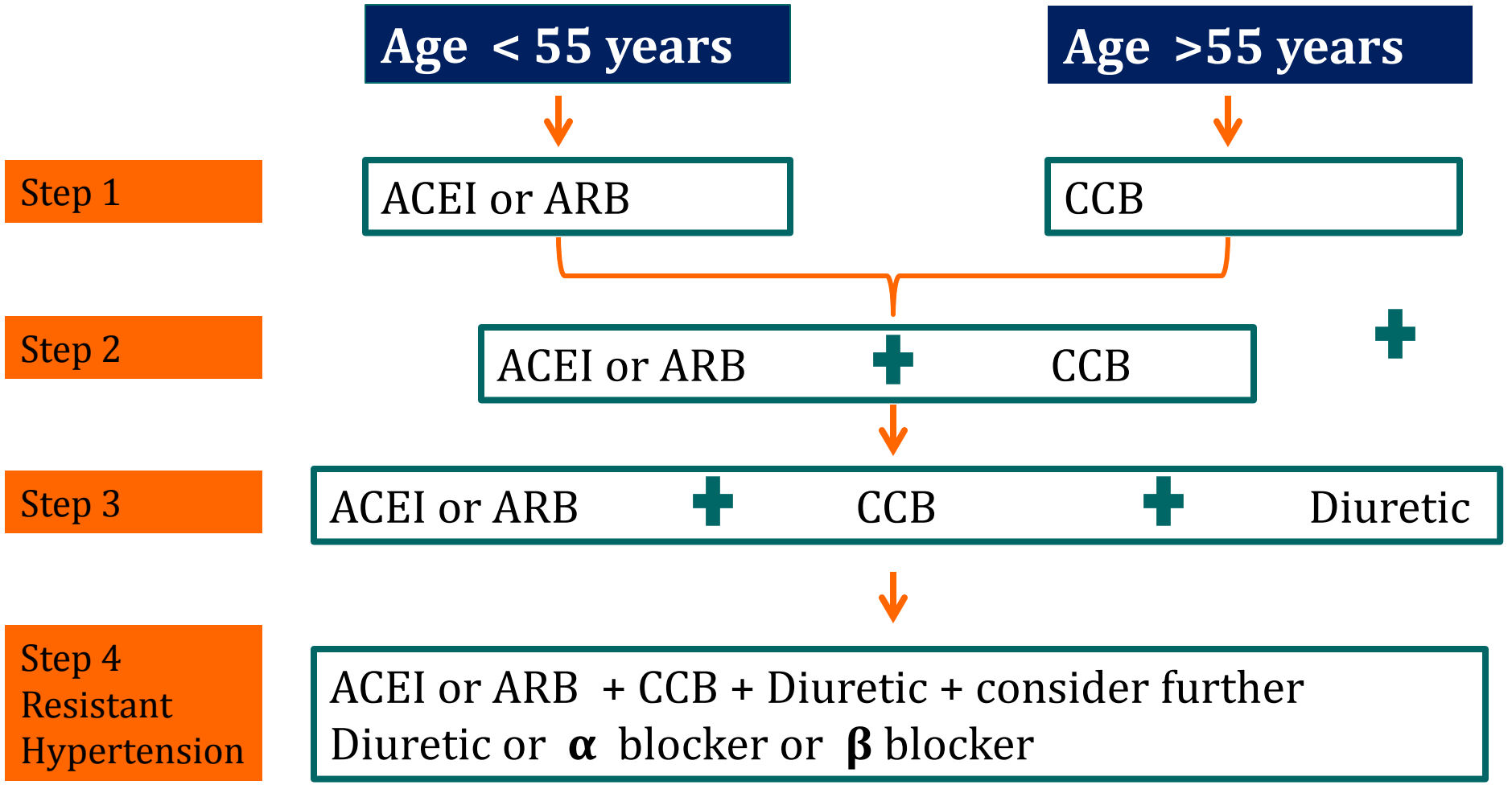
Sarafidis PA & Ruilope LM. ESH Newsletter 2013, No. 55

Association of Physicians of India (API) Guidelines



ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CCB- calcium channel blockers

NICE Clinical Guideline 2011



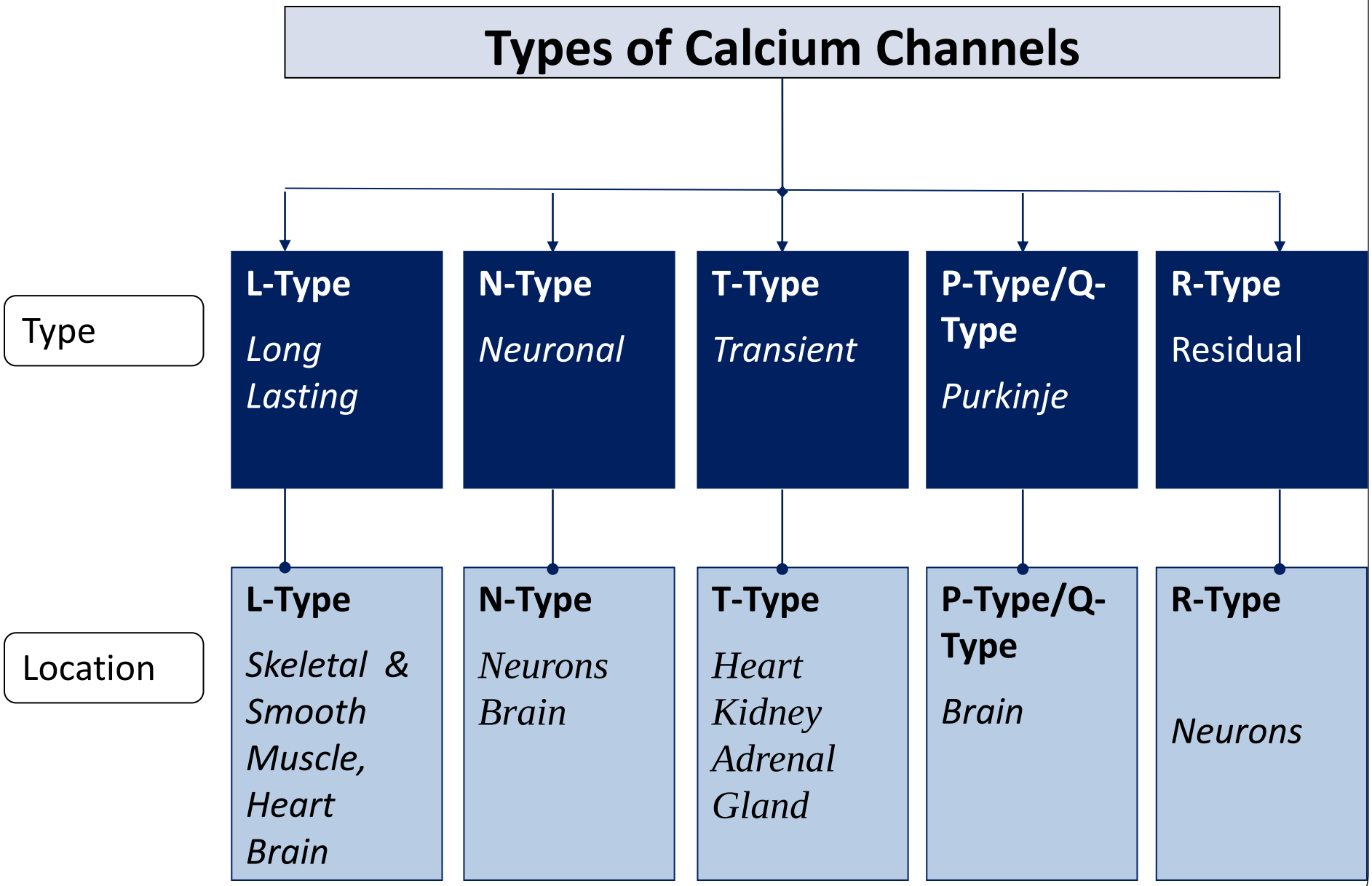
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CCB- calcium channel blockers

Calcium Channel Blockers

Calcium channel blockers

- Calcium channel blocker (CCB) has become one of the most important initial agents for the management of hypertension.
- CCBs have been proved not to increase the risk of coronary events and stroke.
- CCBs appear to be a favorable choice for monotherapy as well as for combination with other agent classes in the treatment of hypertension and may provide specific benefits beyond BP lowering.
- Dihydropyridine CCBs are one group of most frequently prescribed antihypertensive medications

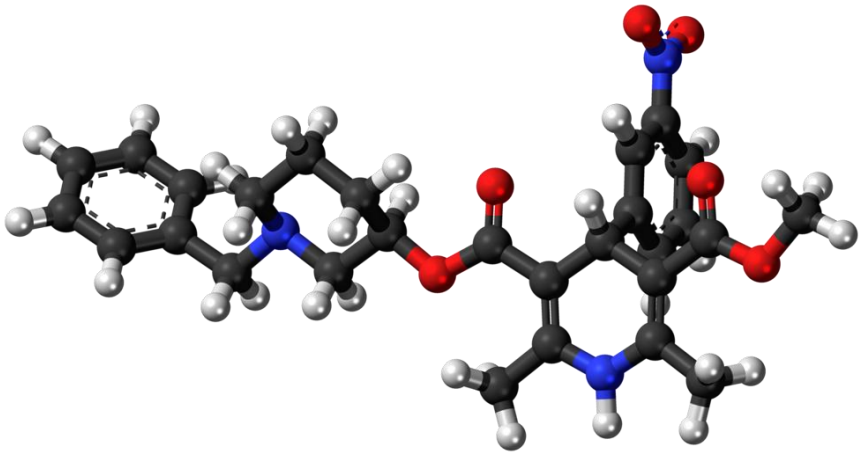
Types of Calcium Channels



Hayashi K, Keio J Med. 2010;59(3):84-95.

Benidipine

- Benidipine is a dihydropyridine derived calcium channel blocker.
- Bendipine is the only CCB with triple Calcium channel blocking action (L, N and T type Ca^{2+} channel).
- Benidipine is an orally active drug for the treatment of hypertension and angina
- Benidipine is effective as a long-lasting antihypertensive and antianginal agent.



Yao K. J Pharmacol Sci. 2006 Apr;100(4):243-61.

Benidipine- The CCB with Unique benefits

- Benidipine inhibits L, N and T type calcium (Ca^{2+}) channels.

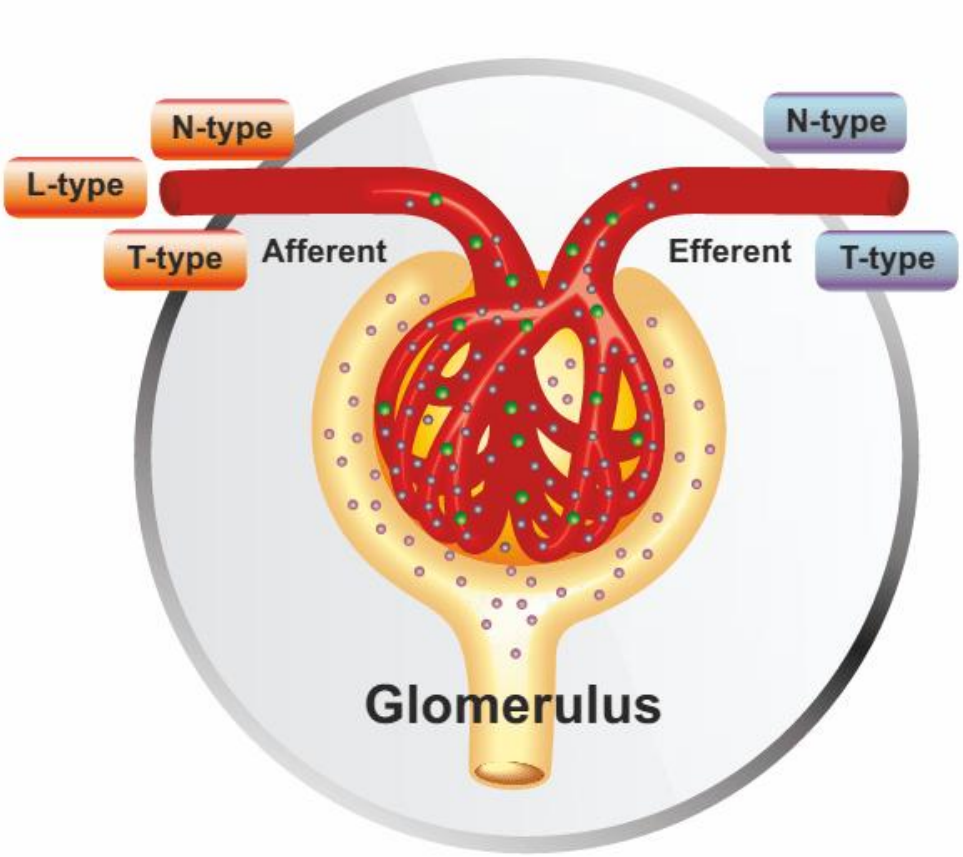
- In addition, it has unique biochemical features not seen in other CCBs

Yao K. J Pharmacol Sci. 2006 Apr;100(4):243-61.
Furukawa T, et al. Eur J Pharmacol 2009; 613: 100–107
Hayashi K et al. Keio J Med. 2010;59(3):84-95.

Dilation of Afferent & Efferent Arterioles

- The L type Ca^{2+} channels predominates at the afferent arteriole. and traditional CCBs like Amlodipine preferentially dilate afferent arterioles rather than efferent arterioles.

- N-.type Ca^{2+} channels are present at sympathetic nerve terminals that are distributed along afferent and efferent arterioles.



Hayashi K et al. Keio J Med. 2010;59(3):84-95

Dilation of Afferent & Efferent Arterioles

- T- type Ca^{2+} channels are prevalent in juxtamedullary efferent arterioles as well as in afferent arterioles of superficial and juxtamedullary nephrons.

- The dilation of only the afferent arterioles and not the efferent arterioles induces elevation in intra glomerularpressure leading to glomerular hypertension.

- Amlodipine being an only L type Ca^{2+} channel blocker dilates only the Afferent. but does not dilate the Efferent Arterioles

Hayashi K et al. Keio J Med. 2010;59(3):84-95

Inhibitory activity against various subtypes of Ca^{2+} channels

- Benidipine inhibits L-type Ca^{2+} channel, N-type Ca^{2+} channel, and T-type Ca^{2+} channels.
- This unique triple Ca^{2+} channel blocking activity of benidipine is not established with other CCBs.

Inhibition of Calcium Channels			
Drugs	**L - type**	**N - type**	**T - type**
Nifedipine	+	X	X
Amlodipine	+	X	X
Efonidipine	+	X	+
Azelnidipine	+	X	+
Benidipine	+	+	+
Cilnidipine	+	+	X

Furukawa T, et al. Eur J Pharmacol 2009; 613: 100–107
Hayashi K et al. Keio J Med. 2010;59(3):84-95.

Clinical Significance of various calcium channel blockade

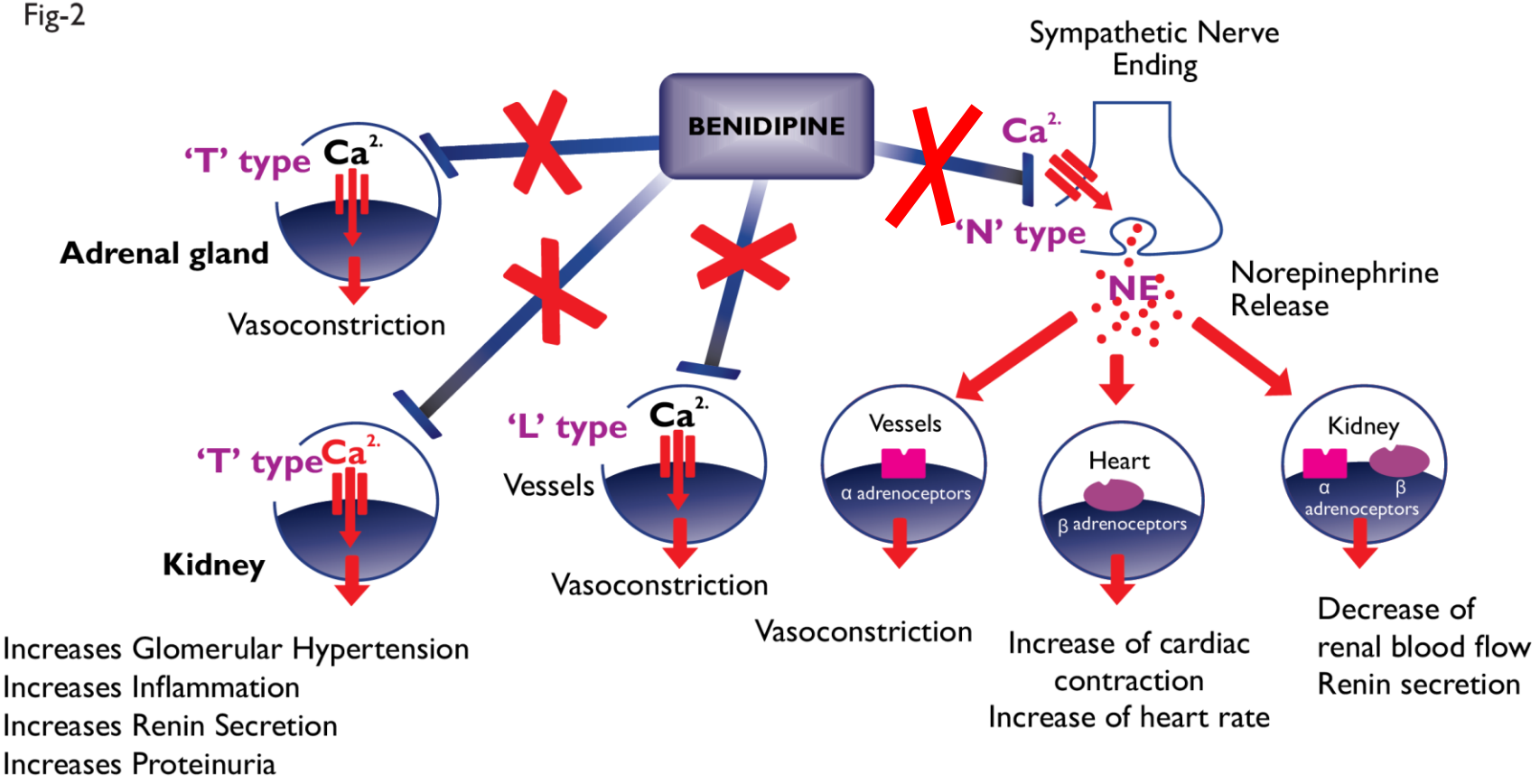
	L - type	**N - type**	**T - type**
Heart	Contractility ↓	Heart rate ↓	Heart rate ↓
Blood vessels	Vasodilatation	Vasodilatation	Vasodilatation
Sympathetic nervous system	Pulse rate ↑	Pulse rate ↓	Pulse rate ↓
Kidney	Glomerular pressure ↑	Glomerular pressure ↓	Glomerular pressure ↓
Adrenal	-	-	Aldosterone secretion ↓

Furukawa T, et al. Eur J Pharmacol 2009; 613: 100–107

Benidpine: Mechanism of action

- Benidipine is a dihydropyridine-derived calcium channel blocker, with triple calcium channels (L, N, and T) blocking action

Fig-2



Yao K. J Pharmacol Sci. 2006 Apr;100(4):243-61.
Furukawa T, et al. Eur J Pharmacol 2009; 613: 100–107
Hayashi K et al. Keio J Med. 2010;59(3):84-95.

High affinity for binding site

- Benidipine has high affinity for the DHP binding site (i.e., the binding site in Ca^{2+} channels) and cell membranes.
- The Ki value of benidipine for the DHP binding site is 0.08 – 0.13 nmol/L, which is higher than nisoldipine, nicardipine, nitrendipine, verapamil, and diltiazem.
- Furthermore, the dissociation of benidipine takes place very slowly.

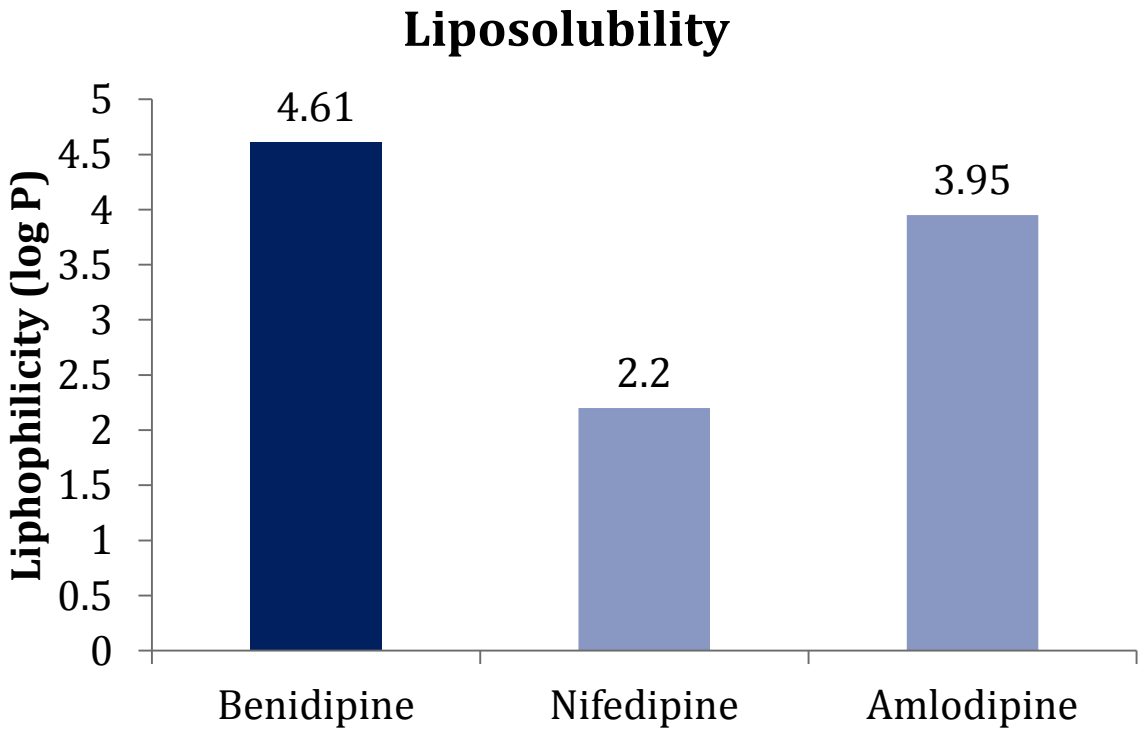
Vascular Selectivity

- The coronary artery selectivity of benidipine was 14.4 times higher than that of nifedipine and 19 times higher than that of amlodipine.
- This enhancement of NO production along with the other pharmacological actions of Benidipine results in cardio-protective and anti-atherosclerotic effects

Yao K. J Pharmacol Sci. 2006 Apr;100(4):243-61. .

High Liposolubility

- Benedipine has the highest liposolubility compared to compared with Nifedipine and Amlodipine



Yao K. J Pharmacol Sci. 2006 Apr;100(4):243-61. .

Pharmacokinetics

Peak Plasma Conc.	<2 hours
Half life	2 hrs
Bioavailability	60%
Protein binding	98%
Metabolism	in the liver by the hepatic enzyme cytochrome P450 (CYP)
Absorption affected by food	No
Excretion/elimination	primarily excreted via bile into feces. Urinary excretion: 36%.
Dose in Hepatic Impairment	Mild - moderate impairment: No dosage adjustment Severe hepatic impairment: Not established.
Dose in Renal Impairment	Mild to severe renal impairment : No dosage adjustment Severe impairment: Not established.

Yao K. J Pharmacol Sci. 2006 Apr;100(4):243-61

Benidipine Dosage & Administration

Recommended Dose

- Hypertension (Adult): 2-4 mg once daily increased to 8 mg once daily, if necessary.
- Angina Pectoris (Adult): 4 mg twice daily

Indication

- Hypertension
- Long-term prophylactic management of angina pectoris

Special Population

- **Pregnancy :** Safety and effectiveness of benidipine in pregnant women have not been established.
- **Lactation:** There is no established safety data.
- **Pediatric use:** Not been established.
- Contraindicated in patients with hypersensitivity to any component in the product.

Yao K. J Pharmacol Sci. 2006 Apr;100(4):243-61. .

CLINICAL STUDIES

Benidipine in elderly hypertensive patients: J-BRAVE study

Objective

To investigate the achievement rate of blood pressure (BP) target and the relationship between on-treatment BP and development of cardiovascular events (i.e., stroke, myocardial infarction, and heart failure)

Study Design

A prospective, 3-year observational study of Benidipine based treatment in hypertensive patients aged ≥65 years as a post-marketing surveillance

Study Population

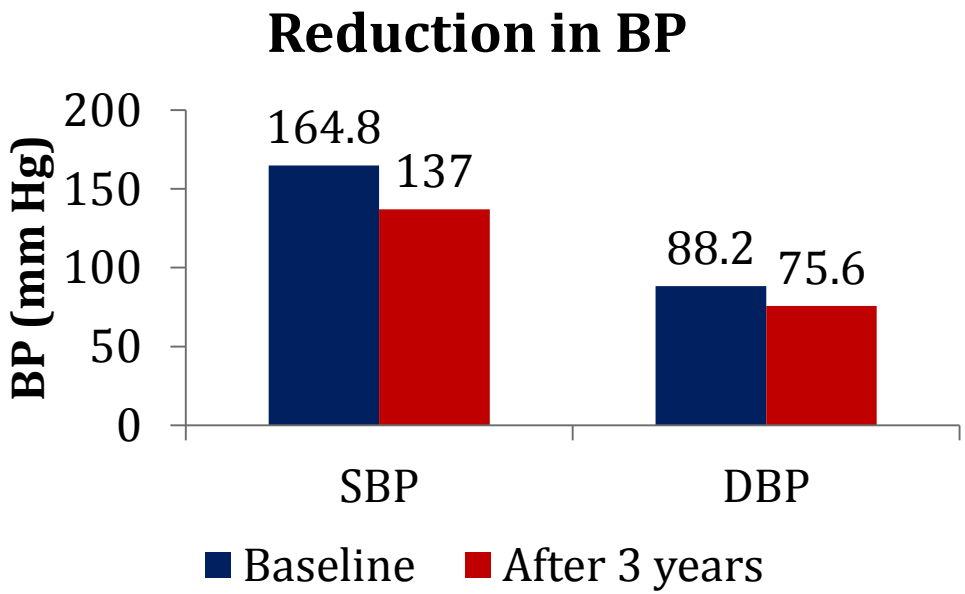
No. of patients: 8,897
Age group: ≥65 years
mean baseline SBP: 164.8 ± 14.1 mmHg
mean baseline DBP: 88.2 ± 10.3 mmHg

J-BRAVE: Japan's Benidipine Research on Antihypertensive Effects in the Elderly

Saito I et al. Clin Exp Hypertens. 2011;33(2):133-40.

Benidipine in elderly hypertensive patients: J-BRAVE study Results…

- Blood pressure decreased significantly from 164.8 ± 14.1/88.2 ± 10.3 mmHg to 137.0 ± 13.5/75.6 ± 9.5 mmHg and the percentage of patients who achieved BP <140/90 mmHg was 57.2% after 3 years.



Benidipine effectively reduces Blood Pressure in elderly.

Saito I et al. Clin Exp Hypertens. 2011;33(2):133-40.

Benidipine in Hypertensive Patients: An Amlodipine-to-Benidipine Changeover (ABC) Study

Objective

To evaluate blood pressure and proteinuria after changeover from amlodipine to benidipine in poorly controlled hypertensive patients

Study Design

Patients administered 5 mg of amlodipine once a day for at least 3 months. Uncontrolled patients were switched to benidipine and BP post-changeover was measured at 1 month and 2 months

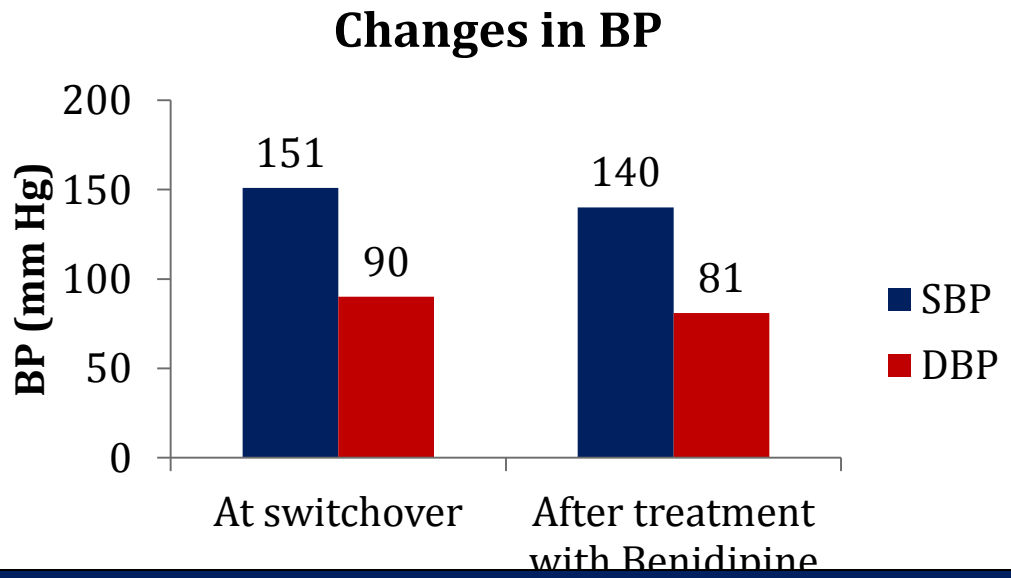
Study Population

No. of patients: 58
Average Age: 64.1±12.8 years
mean switchover SBP/DBP : 151/90 mmHg

Ohishi M et al. Hypertens Res. 2007 Sep;30(9):797-806.

Benidipine in Hypertensive Patients: An Amlodipine-to-Benidipine Changeover (ABC) Study – Results…

- >80% of patients reduced their BP and >40% achieved optimal BP.
- Higher urinary protein excretion (p<0.0001), lower GFR (p=0.0011) and presence of diabetes (p=0.0284) were correlated with reduction of urinary proteins during changeover.



Benidipine has greater efficacy than amlodipine in reducing blood pressure and proteinuria.

Ohishi M et al. Hypertens Res. 2007 Sep;30(9):797-806.

Effect of Benidipine vs Cilnidipine on blood pressure and renal function in hypertensive patients with diabetes mellitus

Objective

To evaluate the effects of benidipine on renal, inflammatory, oxidative, and atherosclerosis markers in hypertensive patients with mild CKD

Study Design

Double blind randomized comparative trial for 12 months

Study Population

No. of patients: 40
Average Age: 62±7.8 years
Mean switchover SBP/DBP : 155.8 ± 13.7 mmHg and 86.5 ± 13.3 mmHg

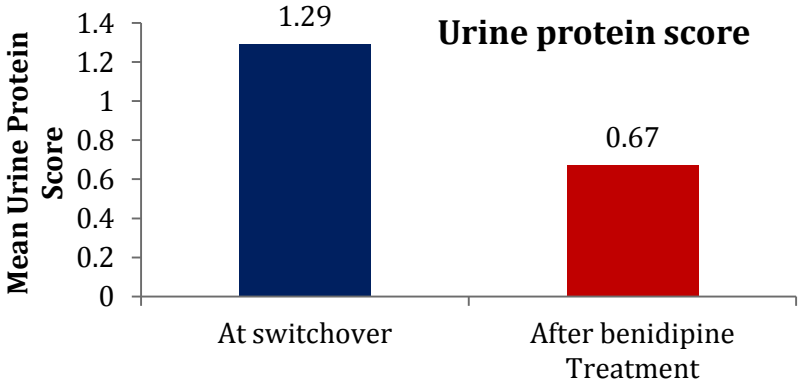
Seino H et al. Arzneimittelforschung. 2007;57(8):526-31.

Effect of Benidipine vs Cilnidipine on blood pressure and renal function in hypertensive patients with diabetes mellitus- Results..

- BP (systolic/diastolic) significantly decreased after treatment with benidipine and this effect was stably maintained for one year (table).

Table: Changes in Blood Pressure		
	Baseline	After Treatment
SBP mm Hg	155.8 ± 13.7	145.9 ± 17.0
DBP mm Hg	76.5 ± 13.3	71.4 ± 13.7

- Urine protein (UP) scores also significantly decreased from 1.29 to 0.67 in the mean score.



Benidipine has a more potent antihypertensive effect than cilnidipine and also has renoprotective effect

Seino H et al. Arzneimittelforschung. 2007;57(8):526-31.

Effect of Benidipine vs Cilnidipine on blood pressure and renal function in hypertensive patients with diabetes mellitus

Objective

To evaluate the effects of switching from cilnidipine to benidipine on blood pressure (BP) lowering and renal function.

Study Design

Patients administered cilnidipine OD for at least 3 months. Uncontrolled patients were switched to benidipine and BP post-changeover was measured at 3 months

Study Population

- No. of patients: 40
- Average Age: 61.1±9.8 years
- Mean switchover SBP/DBP : 155.8 ± 13.7 mmHg and 76.5 ± 13.3 mmHg

Seino H et al. Arzneimittelforschung. 2007;57(8):526-31.

Comparative effects of Benidipine and Amlodipine on renal function in early-stage CKD -- Results

- BP decreased equally in both groups ($P < 0.001$, at 6 and 12 months *vs* baseline).
- Serum creatinine and estimated glomerular filtration rate changed minimally during the experimental period in each group.
- Urinary protein excretion ($P < 0.001$), urinary liver-type fatty acid-binding protein ($P < 0.001$), urinary 8-hydroxy-2'-deoxyguanosine ($P < 0.001$), blood interleukin-6 ($P < 0.001$), blood high mobility group box-1 ($P < 0.05$), and pulse wave velocity ($P < 0.01$) decreased more in Benidipine group than in Amlodipine group with 12 months of treatment.
- The percent reductions in intima-media thickness and blood asymmetric dimethylarginine were significantly greater in Benidipine than Amodipine ($P < 0.001$).

Benidipine is more effective than amlodipine for protecting renal function and potentially for ameliorating atherosclerosis in hypertensive patients with mild CKD.

Nakamura T et al. Am J Med Sci. 2010 Feb;339(2):157-63.

Improvements in Augmentation Index and Urinary Albumin Excretion with Benidipine

Objective

• To compare the augmentation index (AI) effect of benidipine and amlodipine in the treatment of CKD patients as measured through AI and urinary albumin excretion (UAE)

Study Design

Prospective, open-label, randomized, parallel-comparison study

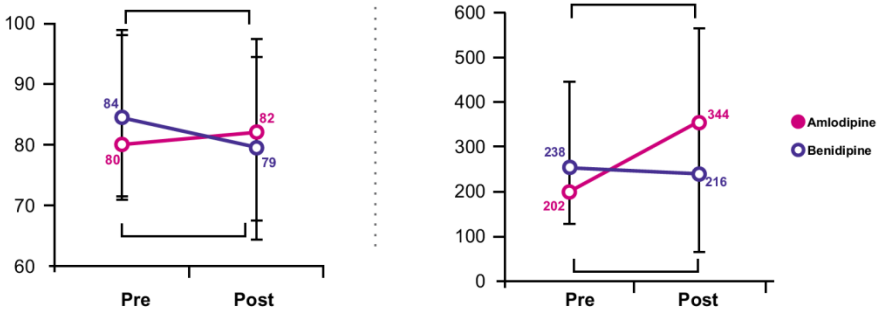
Study Population

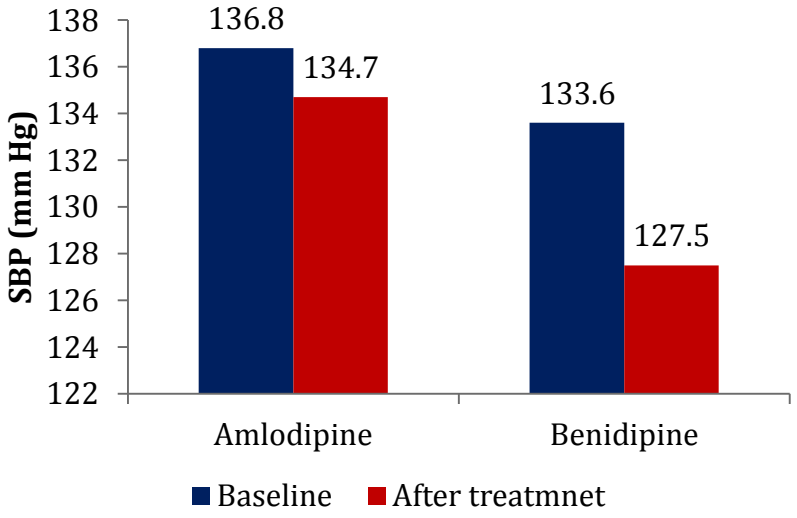
•No. of patients: 108
•Average Age: 8.3 ± 9.8 years
•Mean switchover SBP/DBP: 136.8 ± 15.1 mmHg 71.6 ± 9.0 mmHg

Takayama T et al. Int Heart J. 2016;57(1):53-60.

Improvements in Augmentation Index and Urinary Albumin Excretion with Benidipine

- Significant improvement in AI was noted only in the benidipine group (84.5 ± 13.6% to 79.5 ± 15.2%; P = 0.0138).
- Significant improvement in UAE in the benidipine group was found compared with the amlodipine group (-25 ± 46, 51 ± 60%, P = 0.031, respectively





Benidipine reduce augmentation index and improves urinary albumin excretion than amlodipine

Takayama T et al. Int Heart J. 2016;57(1):53-60.

Benidipine reduces albuminuria and plasma aldosterone in mild-to-moderate stage CKD with albuminuria

Objective

• To compare the effects of benidipine with those of amlodipine on blood pressure, albuminuria and aldosterone concentration in hypertensive patients with mild-to moderate stage chronic kidney disease (CKD)

Study Design

6-month, single-center, prospective, randomized and open label clinical trial.

Study Population

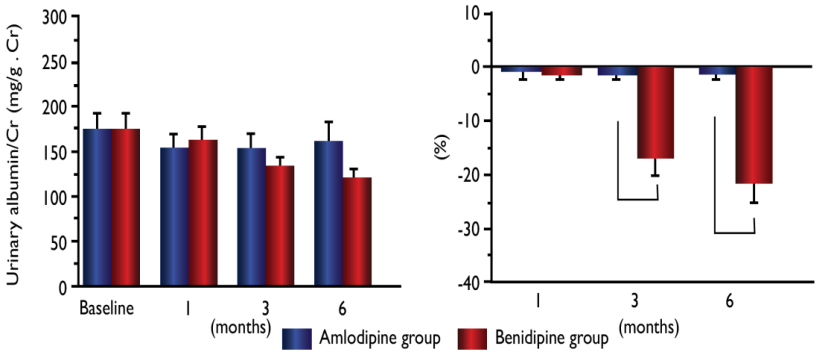
•No. of patients: 104
•Average Age : 67.5±1.5 years
•Mean switchover SBP/DBP: 145± 15.1 mmHg and 81.6 ± 9.0 mmHg

Takayama T et al. Int Heart J. 2016;57(1):53-60.

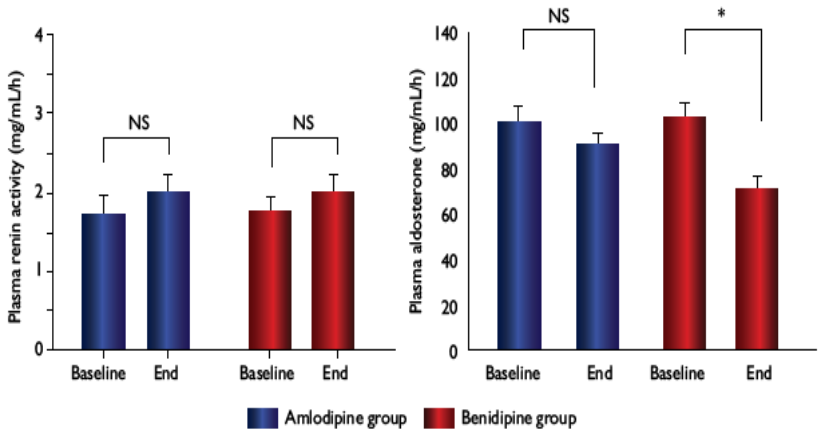
Benidipine reduces albuminuria and plasma aldosterone in mild-to-moderate stage CKD with albuminuria

- The decrease in the urinary albumin to Cr ratio in the benidipine group was significantly lower than that in the amlodipine group.

- Plasma aldosterone levels were significantly decreased in the benidipine group



Changes in the urinary albumin/Cr ratio and the respective percent changes from baseline. Cr, creatinine. *P<0.01, wP<0.0001 vs.



Changes in plasma renin activity and plasma aldosterone levels in the two groups. NS, not significant; *P<0.01 vs. baseline; +P<0.05 vs.

Benidipine results in a greater reduction of plasma aldosterone and albuminuria than amlodipine, and these effects are independent of BP reduction

Abe M et al. Hypertens Res. 2011 Feb;34(2):268-73.

Role of Benidipine vs Amlodipine in patients with hypertension and CKD

Objective

•To investigate the effects of add-on therapy with calcium channel blockers (CCBs) on changes in the composite ranking of relative risk according to KDIGO guidelines.

Study Design

6-month, single-center, prospective, randomized, open-label clinical trial

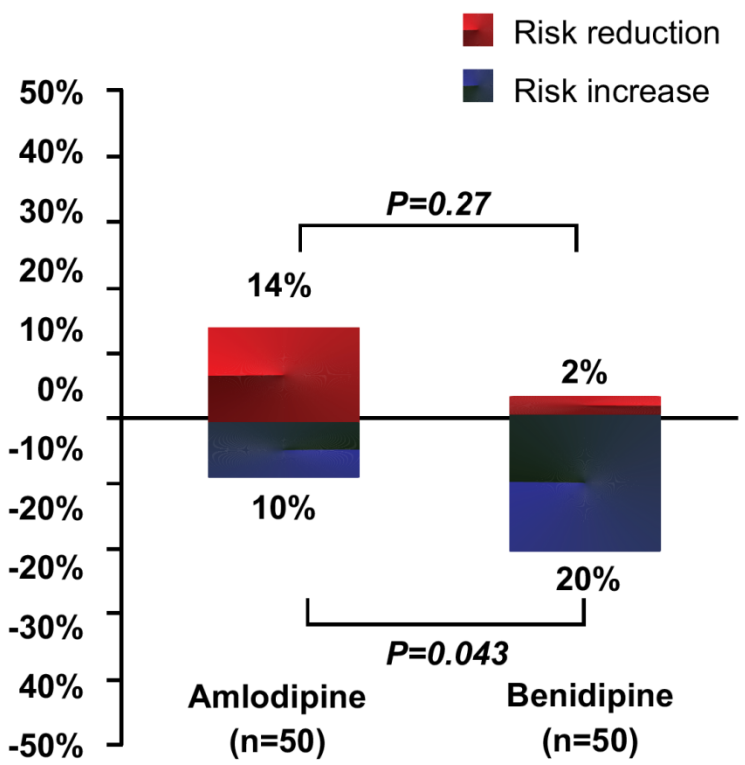
Study Population

•No. of patients : 104
•Average Age: 67.5±1.5 years
•Mean SBP/DBP: 145 ± 1.0mmHg and 82 ± 1.4 mmHg

Takayama T et al. Int Heart J. 2016;57(1):53-60.

Role of Benidipine vs Amlodipine in patients with hypertension and CKD

- The decrease in albuminuria in the benidipine group was significantly lower than in the amlodipine group.
- The composite ranking of relative risk according to the new KDIGO guidelines was significantly improved in the benidipine group;



Compared to amlodipine benidipine results in a greater reduction in albuminuria accompanied by an improved composite ranking of relative risk according to the KDIGO CKD severity classification

Effects of Benidipine on Albuminuria and Plasma Aldosterone levels

Objective

- To examine the effects of benidipine on albuminuria and PAC

Study Design

6-month prospective, single-center, open-label study switching from L-type CCBs to the benidipine

Study Population

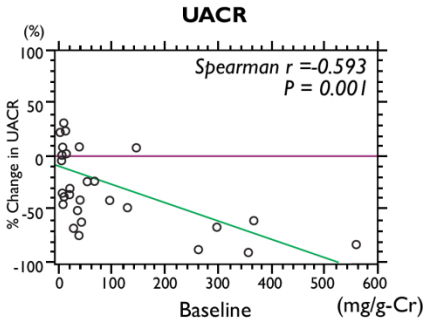
- No. of patients: 31
- Average Age : 67 ± 9.6 years

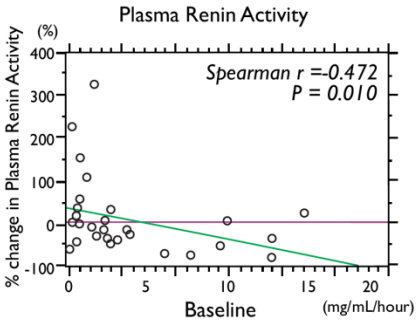
Takayama T et al. Int Heart J. 2016;57(1):53-60.

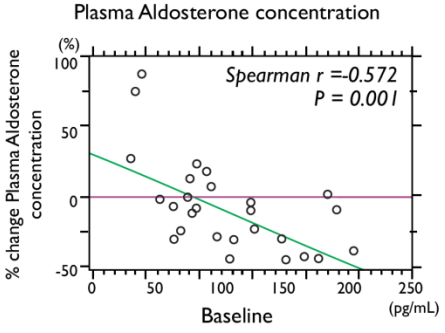
Effects of Benidipine on Albuminuria and Plasma Aldosterone levels

- The urinary-albumin-creatinine ratio (UACR) decreased significantly by 36.9% (P = 0.001). The PAC of all patients decreased significantly by 11.8% (P =0.002).

- In hypertensive patients whose BP is uncontrolled by L-type CCB, switching to the T/L-type CCB benidipine maintained BP control and reduced UACR.







Treatment of hypertension by benidipine with its high selectivity to the T-type Ca2+ channel confers cardio-renal protection.

Tani S et al. Int Heart J. 2014;55(6):519-25.

Conclusion

- In some forms of CKD, HTN may be the earliest sign of kidney dysfunction (eg, polycystic disease).
- Appropriate HTN management reduces both cardiovascular and kidney outcomes.
- Benidipine is the only CCB with triple Blocking action of L, N, T type channels
- Benidipine has Reno protective, Cardio protective and Vaso protective effects
- Benidipine has greater efficacy than amlodipine in reducing blood pressure and proteinuria.
- Benidipine has a more potent antihypertensive effect than cilnidipine and also has renoprotective effect

Thank You