

Achieving hypertension control in elderly with the right approach : The stand point of Angiotensin II Receptor Blocker

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Prevalence of hypertension

Global prevalence was estimated 1.13 billion in 2015

Consistent across the world

Overall prevalence in adults around 30-45%

Progressively more common with advancing age
(>60% in people age > 60 years & ~ 75% over the age 75)

Estimated increase by 15-20% in 2025

HYPERTENSION



LVH, atherosclerosis, myocardial ischemia, myocardial infarction



Systolic or diastolic dysfunction, renal impairment, stroke

Classification of office BP and definition of hypertension grade

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension ^b	≥140	and	<90

CONVENTIONAL OFFICE BP MEASUREMENT

Initially be measured in both upper arms at the first visit

Using an appropriate cuff size

Should be seated comfortably in a quiet environment for 5 min

Should be 2 times recorded, 1-2 min apart, 3rd measurement only if the 1st two readings differ > 10 mmHg and for patient with arrhythmia

The cuff should be positioned at the level of the heart with the back and arm supported

CONFIRMING THE DIAGNOSIS OF HYPERTENSION

Should not be based on a single set at a single office visit

Unless grade 3 hypertension or clear evidence of HMOD

Definitions of hypertension according to office, ambulatory, and home blood pressure levels

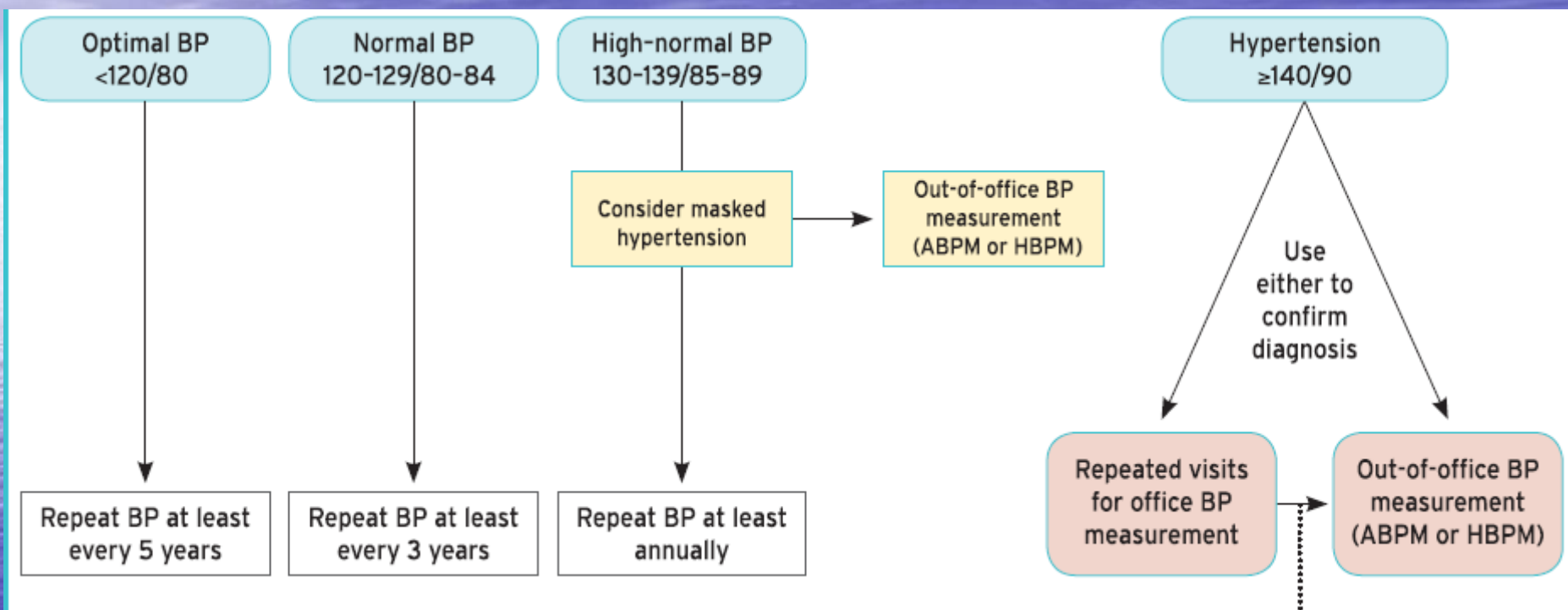
Category	SBP (mmHg)		DBP (mmHg)
Office BP ^a	≥140	and/or	≥90
Ambulatory BP			
Daytime (or awake) mean	≥135	and/or	≥85
Night-time (or asleep) mean	≥120	and/or	≥70
24 h mean	≥130	and/or	≥80
Home BP mean	≥135	and/or	≥85

BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Factors affecting accuracy of BP measure

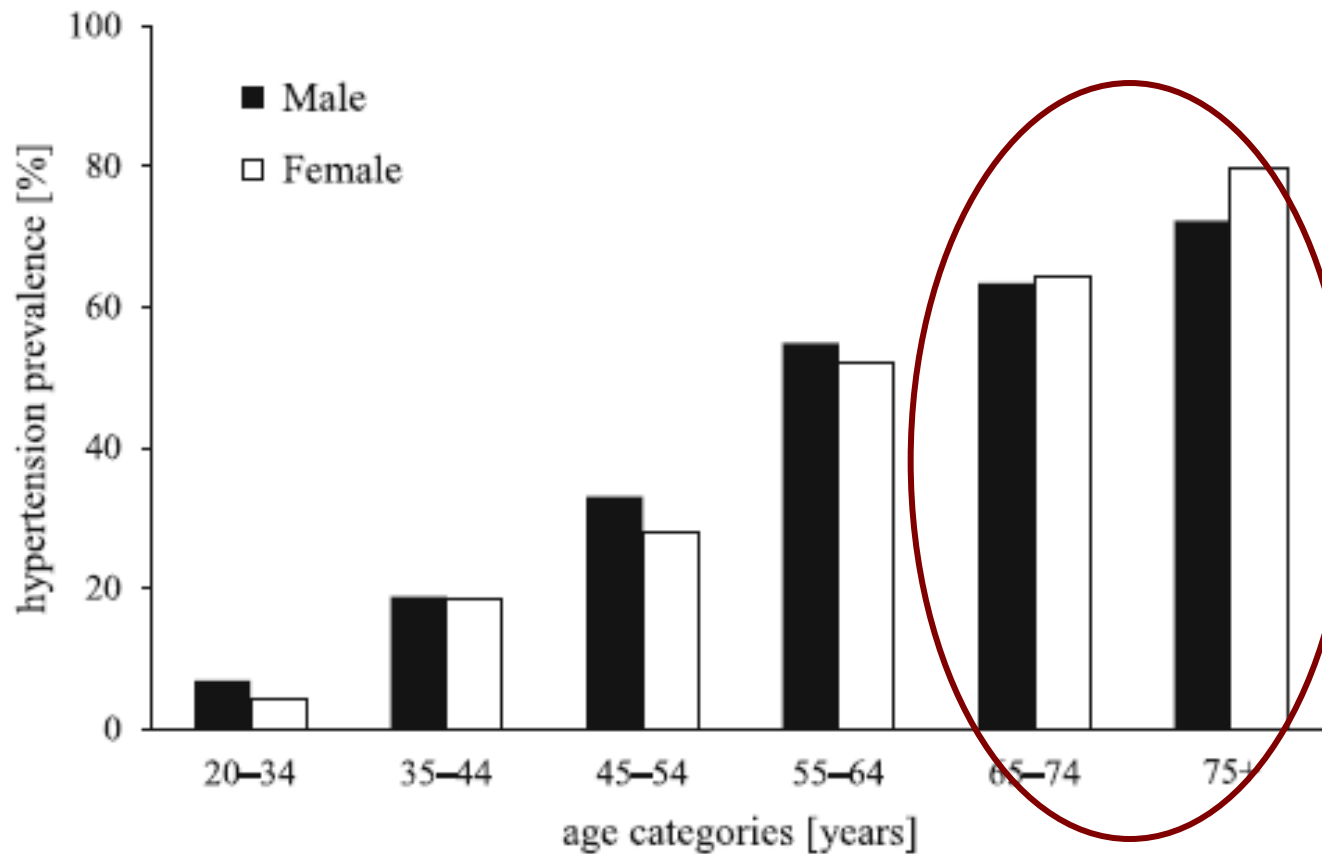
Factor	Magnitude of systolic/diastolic blood pressure discrepancy (mm Hg)
Talking or active listening	10 / 10
Distended bladder	15 / 10
Cuff over clothing	5-50 / Not applicable (NA)
Cuff too small	10 / 2-8
Smoking within 30 minutes of measurement	6-20 / NA
Paralyzed arm	2-5 / NA
Back unsupported	6-10 / NA
Arm unsupported, sitting	1-7 / 5-11
Arm unsupported, standing	6-8 / NA

Handler J. The important of accurate blood pressure measurement. Perm J 2009; 13 (3)



Williams B., et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Euro H Journal 2018, 39 (33)

Hypertension in the elderly



Anker D., et al. Screening and treatment of hypertension in older adults: less is more?.
Public Health Reviews 2018, 39 (33)

Hypertension in the elderly

Older is defined ≥ 65 years, very old as ≥ 80 years

For many years advanced age has been a barrier to tx

Target organ damage has likely already occurred

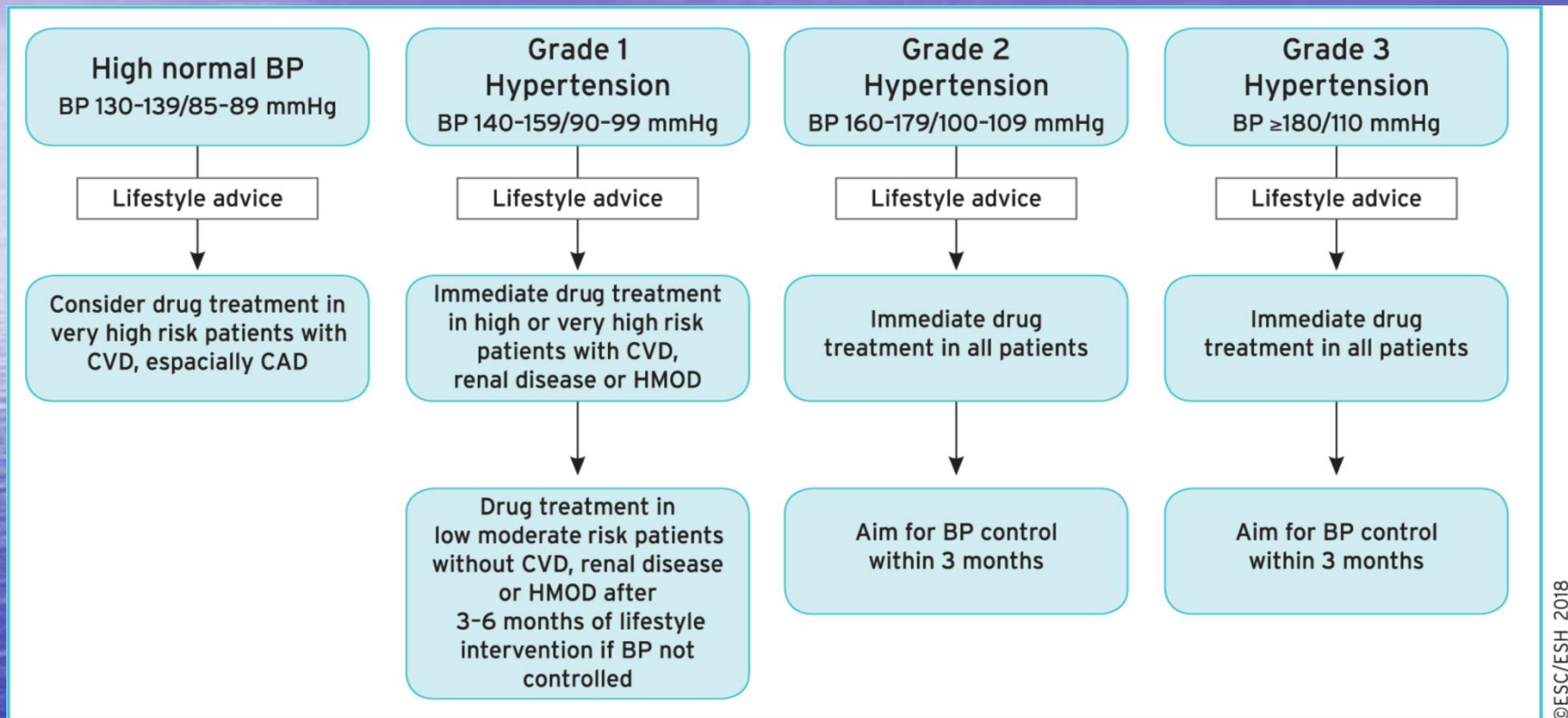
Often have multiple pathologies requiring multiple medications

Weber MA. Angiotensin receptor blockers in older patients. Am J Geriatr Cardiol 2004. 13 (4)

Williams B., et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Euro H Journal 2018, 39 (33)

Study acronym or first author, country, publication year	Population	Intervention or exposure BP category	Comparison or reference BP category	Outcomes (mortality and CVD)	Conclusion
Randomized controlled trials					
SPRINT, USA, 2016 [39]	≥ 75 years; N = 2636 Condition: hypertension but no diabetes	Intensive treatment: SBP targets < 120 mmHg	Standard treatment: SBP targets < 140 mmHg	HR (95% CI) for all-cause mortality: 0.67 (0.49–0.91) HR (95% CI) for composite CVD events (primary endpoint): 0.66 (0.51–0.85)	More intensive treatment among adults aged 75 years or older significantly reduced the rates of fatal and nonfatal major cardiovascular events and death from any cause, irrespective of frailty status
HYVET, Europe, China, Australasia, and Tunisia, 2008 [38]	80 years or older; N = 3845 Condition: sustained SBP of ≥ 160 mmHg	Active treatment	Placebo	HR (95% CI) for all-cause mortality: 0.79 (0.65–0.95) HR (95% CI) for fatal and nonfatal stroke (primary endpoint): 0.70 (0.49–1.01)	Active treatment in persons 80 years of age or older reduced the rate of death from any cause and cardiovascular events, irrespective of frailty status

Initiation of BP lowering treatment



Ten year cardiovascular risk categories

<p>Very high risk</p>	<p>People with any of the following:</p> <p>Documented CVD, either clinical or unequivocal on imaging.</p> <ul style="list-style-type: none"> ● Clinical CVD includes acute myocardial infarction, acute coronary syndrome, coronary or other arterial revascularization, stroke, TIA, aortic aneurysm, and PAD ● Unequivocal documented CVD on imaging includes significant plaque (i.e. $\geq 50\%$ stenosis) on angiography or ultrasound; it does not include increase in carotid intima-media thickness ● Diabetes mellitus with target organ damage, e.g. proteinuria or a with a major risk factor such as grade 3 hypertension or hypercholesterolaemia ● Severe CKD (eGFR < 30 mL/min/1.73 m²) ● A calculated 10 year SCORE of $\geq 10\%$
<p>High risk</p>	<p>People with any of the following:</p> <ul style="list-style-type: none"> ● Marked elevation of a single risk factor, particularly cholesterol > 8 mmol/L (> 310 mg/dL), e.g. familial hypercholesterolaemia or grade 3 hypertension (BP $\geq 180/110$ mmHg) ● Most other people with diabetes mellitus (except some young people with type 1 diabetes mellitus and without major risk factors, who may be at moderate-risk) <p>Hypertensive LVH</p> <p>Moderate CKD eGFR 30-59 mL/min/1.73 m²)</p> <p>A calculated 10 year SCORE of 5-10%</p>
<p>Moderate risk</p>	<p>People with:</p> <ul style="list-style-type: none"> ● A calculated 10 year SCORE of ≥ 1 to $< 5\%$ ● Grade 2 hypertension ● Many middle-aged people belong to this category
<p>Low risk</p>	<p>People with:</p> <ul style="list-style-type: none"> ● A calculated 10 year SCORE of $< 1\%$

Lifestyle interventions for patients with hypertension

Recommendations	Class ^a	Level ^b
Salt restriction to <5 g per day is recommended. ^{248,250,255,258}	I	A
It is recommended to restrict alcohol consumption to: <ul style="list-style-type: none"> ● Less than 14 units per week for men. ● Less than 8 units per week for women.³⁵ 	I	A
It is recommended to avoid binge drinking.	III	C
Increased consumption of vegetables, fresh fruits, fish, nuts, and unsaturated fatty acids (olive oil); low consumption of red meat; and consumption of low-fat dairy products are recommended. ^{262,265}	I	A

Lifestyle interventions for patients with hypertension

Body-weight control is indicated to avoid obesity (BMI >30 kg/m ² or waist circumference >102 cm in men and >88 cm in women), as is aiming at healthy BMI (about 20–25 kg/m ²) and waist circumference values (<94 cm in men and <80 cm in women) to reduce BP and CV risk. ^{262,271,273,290}	I	A
Regular aerobic exercise (e.g. at least 30 min of moderate dynamic exercise on 5–7 days per week) is recommended. ^{262,278,279}	I	A
Smoking cessation, supportive care, and referral to smoking cessation programs are recommended. ^{286,288,291}	I	B

Summary of office BP thresholds for treatment

Age group	Office SBP treatment threshold (mmHg)					Office DBP treatment threshold (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke/TIA	
18 - 65 years	≥140	≥140	≥140	≥140 ^a	≥140 ^a	≥90
65 - 79 years	≥140	≥140	≥140	≥140 ^a	≥140 ^a	≥90
≥80 years	≥160	≥160	≥160	≥160	≥160	≥90
Office DBP treatment threshold (mmHg)	≥90	≥90	≥90	≥90	≥90	

BP = blood pressure; CAD = coronary artery disease; CKD = chronic kidney disease; DBP = diastolic blood pressure; SBP = systolic blood pressure; TIA = transient ischaemic attack.

^aTreatment may be considered in these very high-risk patients with high-normal SBP (i.e. SBP 130–140 mmHg).

Hypertension treatment guidelines

Guideline	Target Goals	Example
American College of Cardiology/American Heart Association	<140/90 for ages 60 and older	A 65-year-old patient with a blood pressure (BP) of 145/90 would be started on drug therapy with a goal target BP of <140/90.
Eighth Joint National Committee	<150/90 for ages 60 and older	A 65-year-old patient would not need to be treated until BP reaches 150/90 with a goal BP of <150/90 (not 140/90).
American Society of Hypertension	<150/90 for ages 80 and older	A 65-year-old patient with a BP of 145/90 would be started on drug therapy with a goal target BP of <140/90. If the patient is aged 80 or older, BP treatment would be started if BP is >150/90 with a goal BP of <150/90.

Office BP treatment target range

Age group	Office SBP treatment target ranges (mmHg)					Office DBP treatment target range (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke ² /TIA	
18 - 65 years	Target to 130 <i>or lower if tolerated</i> Not <120	Target to 130 <i>or lower if tolerated</i> Not <120	Target to <140 to 130 <i>if tolerated</i>	Target to 130 <i>or lower if tolerated</i> Not <120	Target to 130 <i>or lower if tolerated</i> Not <120	70-79
65 - 79 years ^b	Target to 130-139 <i>if tolerated</i>	Target to 130-139 <i>if tolerated</i>	Target to 130-139 <i>if tolerated</i>	Target to 130-139 <i>if tolerated</i>	Target to 130-139 <i>if tolerated</i>	70-79
≥80 years ^b	Target to 130-139 <i>if tolerated</i>	Target to 130-139 <i>if tolerated</i>	Target to 130-139 <i>if tolerated</i>	Target to 130-139 <i>if tolerated</i>	Target to 130-139 <i>if tolerated</i>	70-79
Office DBP treatment target range (mmHg)	70-79	70-79	70-79	70-79	70-79	

Williams B., et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Euro H Journal 2018, 39 (33) : 46

Recomendations for pharmacological treatment

Initiation treatment with single pill combination of two drugs
→ Improve the speed, efficiency and predictability

Preferred two drugs are RAS blockers + CCB or diuretic

Use monotherapy for low risk patients with stage 1 hypertension whose SBP < 150 mmHg, very high risk patients with high normal and for frail older patients

Use three drugs comprising RAS blockers + CCB + diuretic if BP is not controlled with two combinations

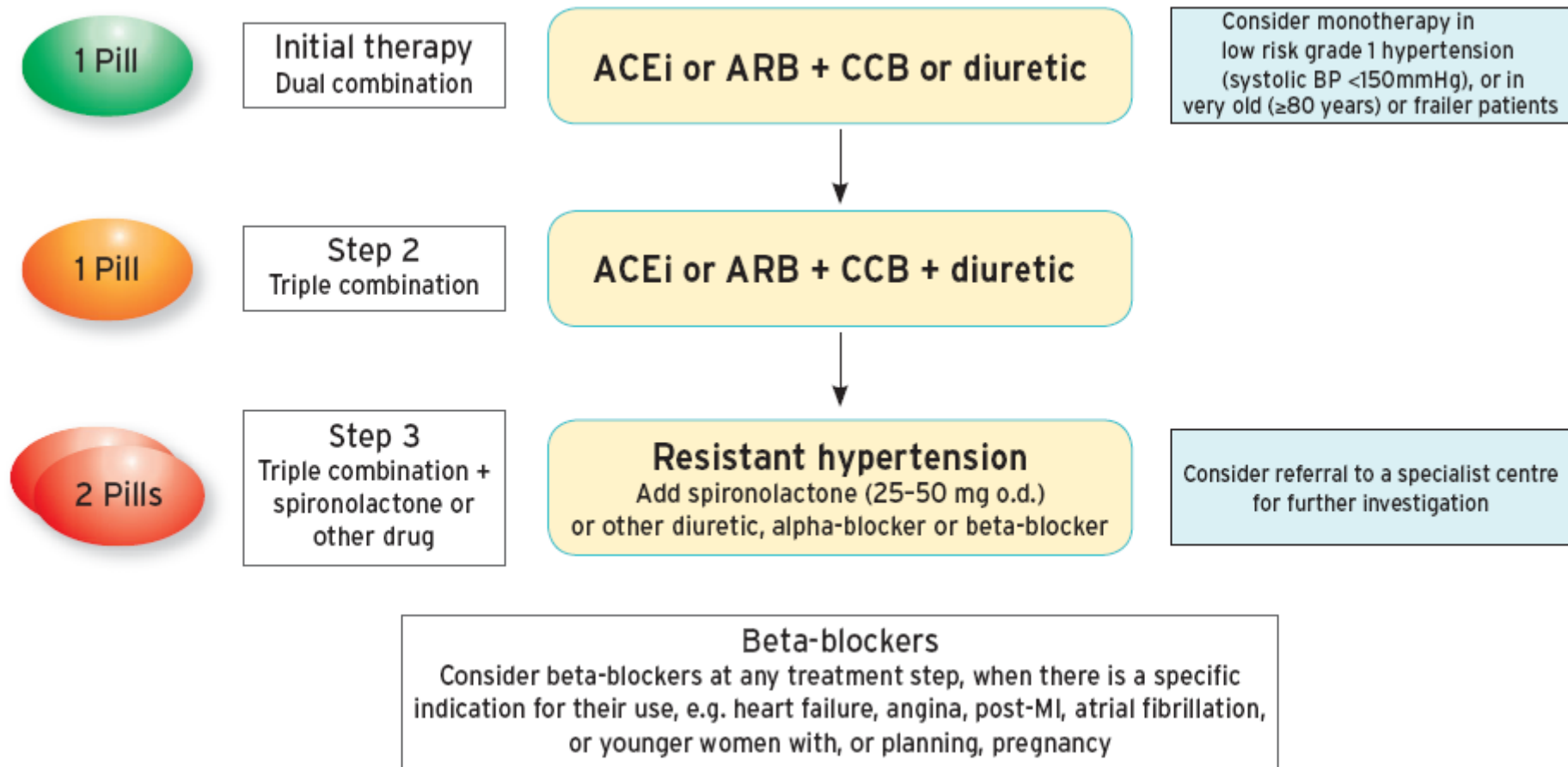
Drug treatment strategy for hypertension

Recommendations	Class ^a	Level ^b
Among all antihypertensive drugs, ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies. ²	I	A
Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used. ^{233,318,327,329,341–345}	I	A
It is recommended that beta-blockers are combined with any of the other major drug classes when there are specific clinical situations, e.g. angina, post-myocardial infarction, heart failure, or heart rate control. ^{300,341}	I	A

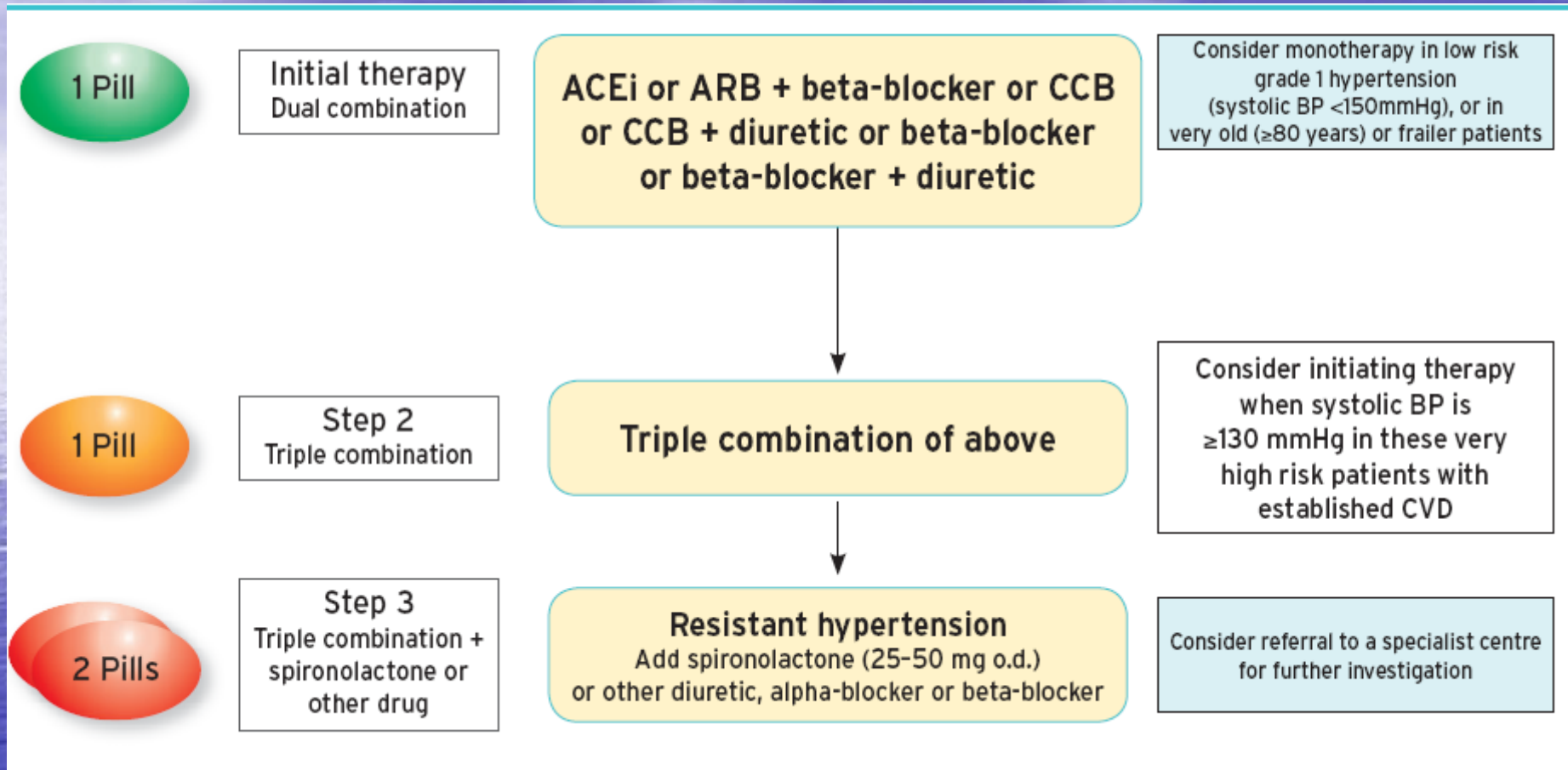
Drug treatment strategy for hypertension

It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in an SPC. Exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is <150 mmHg). ^{342,346,351}	I	B
It is recommended that if BP is not controlled ^c with a two-drug combination, treatment should be increased to a three-drug combination, usually a RAS blocker with a CCB and a thiazide/thiazide-like diuretic, preferably as an SPC. ^{349,350}	I	A
It is recommended that if BP is not controlled ^c with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, a beta-blocker, or an alpha-blocker. ³¹⁰	I	B
The combination of two RAS blockers is not recommended. ^{291,298,299}	III	A

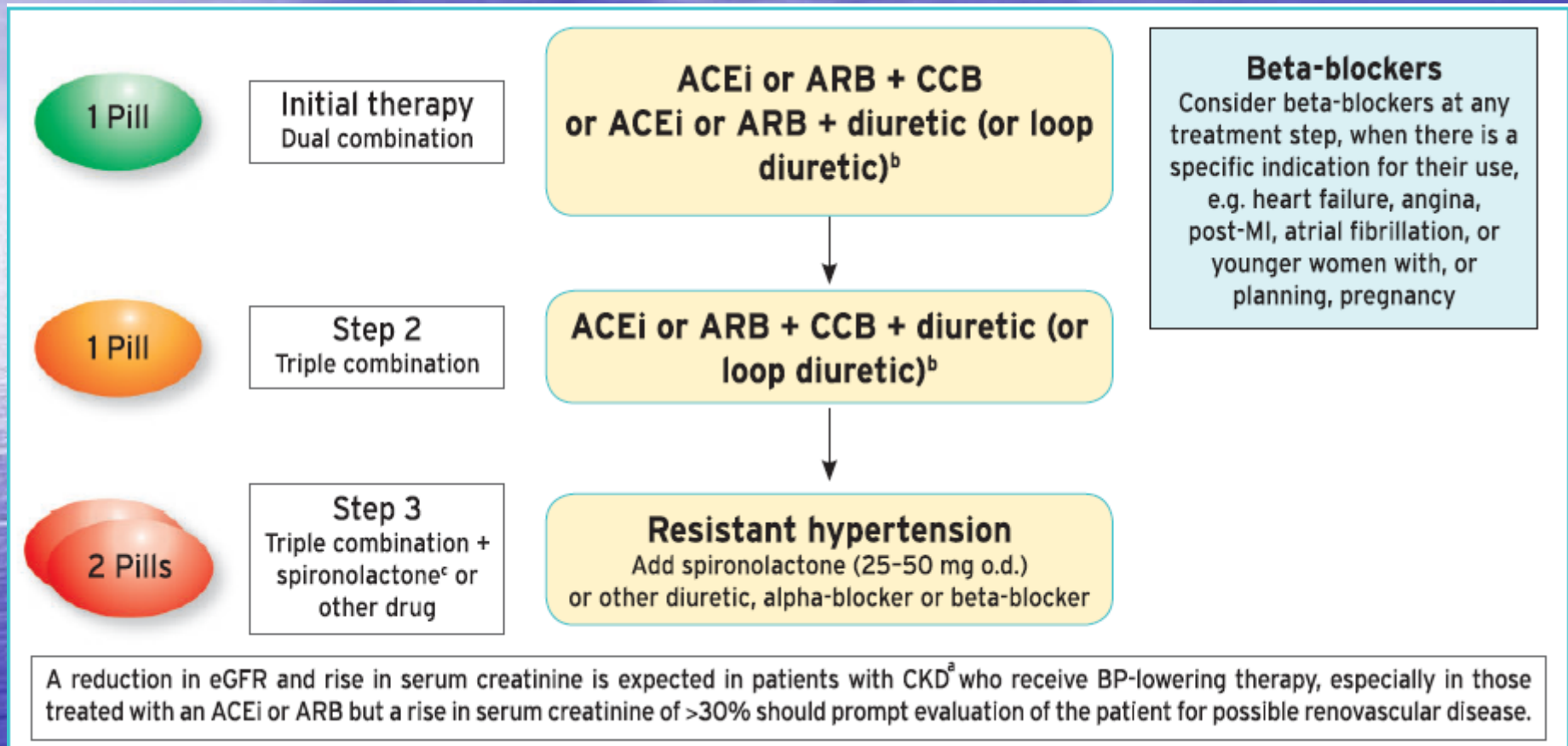
Strategy for uncomplicated hypertension



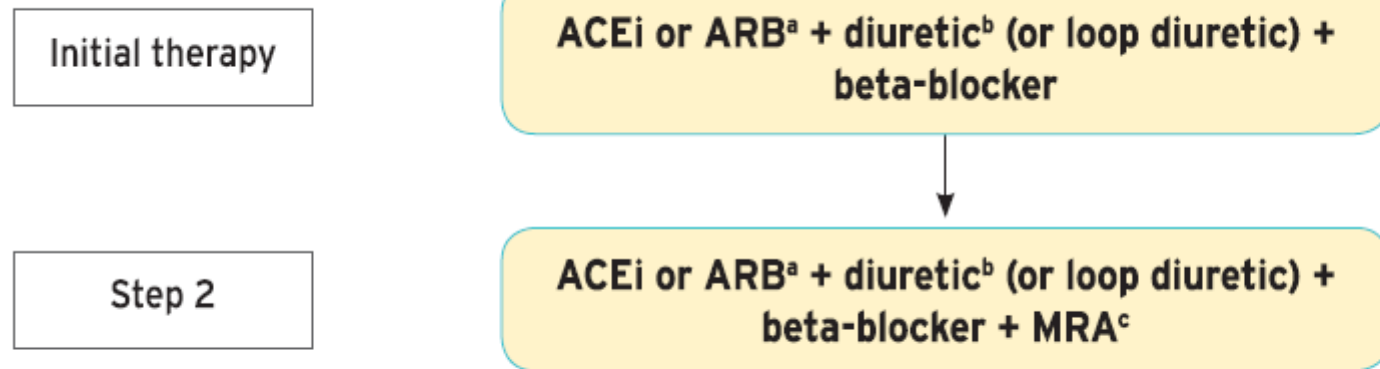
Strategy for hypertension and coronary artery disease



Strategy for hypertension and chronic kidney disease



Strategy for hypertension and heart failure with Reduced ejection fraction



When antihypertensive therapy is not required in HFrEF, treatment should be prescribed according to the ESC Heart Failure Guidelines.¹³⁶

Strategy for hypertension and atrial fibrillation

Initial therapy
Dual combination

**ACEi or ARB + beta-blocker
or non-DHP CCB^a,
or beta-blocker + CCB**

Step 2
Triple combination

**ACEi or ARB + beta-blocker
+ DHP CCB or diuretic
or beta-blocker + DHP CCB + diuretic**

Add oral anticoagulation when indicated according to the CHA₂DS₂-VASc score, unless contraindicated.

^a Routine combination of beta-blockers with non-dihydropyridine CCBs (e.g. verapamil or diltiazem) is not recommended due to a potential marked reduction in heart rate.

Possible contraindications

Drug	Contraindications	
	Compelling	Possible
Diuretics (thiazides/thiazide-like, e.g. chlorthalidone and indapamide)	<ul style="list-style-type: none"> ● Gout 	<ul style="list-style-type: none"> ● Metabolic syndrome ● Glucose intolerance ● Pregnancy ● Hypercalcaemia ● Hypokalaemia
Beta-blockers	<ul style="list-style-type: none"> ● Asthma ● Any high-grade sinoatrial or atrioventricular block ● Bradycardia (heart rate <60 beats per min) 	<ul style="list-style-type: none"> ● Metabolic syndrome ● Glucose intolerance ● Athletes and physically active patients
Calcium antagonists (dihydropyridines)		<ul style="list-style-type: none"> ● Tachyarrhythmia ● Heart failure (HFrEF, class III or IV) ● Pre-existing severe leg oedema
Calcium antagonists (verapamil, diltiazem)	<ul style="list-style-type: none"> ● Any high-grade sinoatrial or atrioventricular block ● Severe LV dysfunction (LV ejection fraction <40%) ● Bradycardia (heart rate <60 beats per min) 	<ul style="list-style-type: none"> ● Constipation
ACE inhibitors	<ul style="list-style-type: none"> ● Pregnancy ● Previous angioneurotic oedema ● Hyperkalaemia (potassium >5.5 mmol/L) ● Bilateral renal artery stenosis 	<ul style="list-style-type: none"> ● Women of child-bearing potential without reliable contraception
ARBs	<ul style="list-style-type: none"> ● Pregnancy ● Hyperkalaemia (potassium >5.5 mmol/L) ● Bilateral renal artery stenosis 	<ul style="list-style-type: none"> ● Women of child-bearing potential without reliable contraception

Individualizing Blood Pressure treatment

Patients should be monitored closely for orthostatic symptoms

And other non specific symptoms such as weakness, failure to thrive, cognitive complaints that may be related to low BP levels

Should be individualized regardless of treatment guidelines

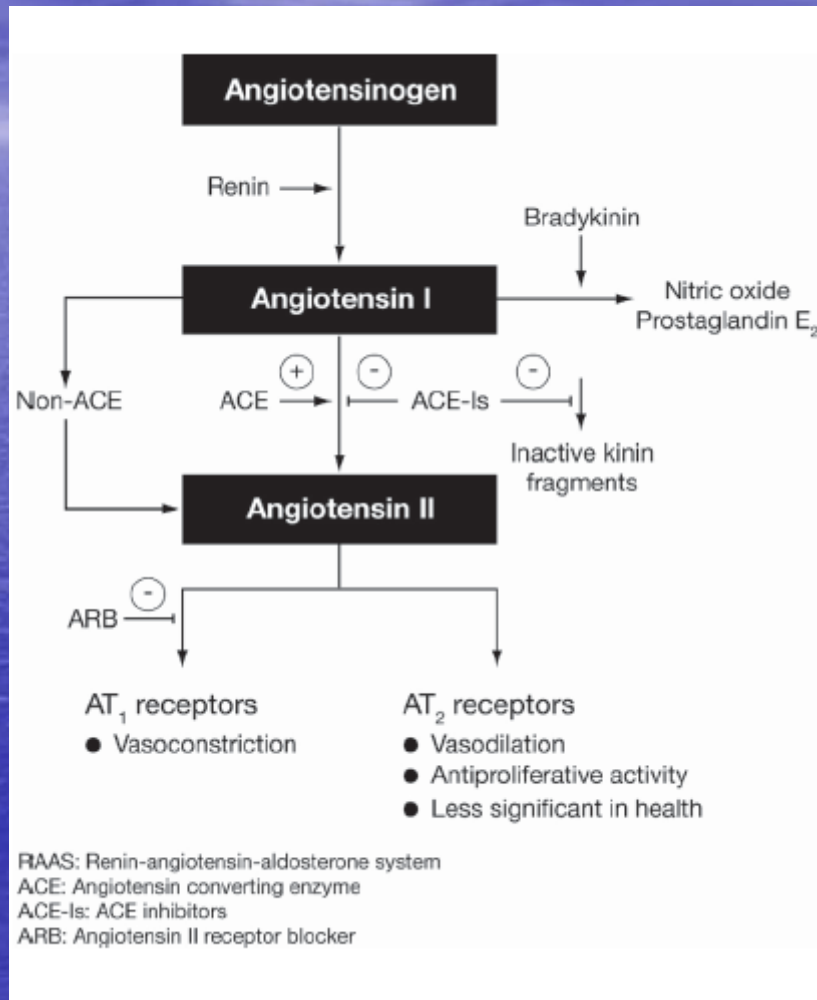
> 80 years : SBP < 130 and DBP < 65 should be avoided

> 65 years : SBP target 130-140, SBP should not < 120 and DBP < 80

Coggins MD. Treating hypertension. Today's Ger Med 2015; 8 (2)

Currie G. Blood pressure targets in the elderly. J of Hypertension 2018; 36

The stand point of Angiotensin II Receptor Blocker



Angiotensin receptor blockers in older patients

With LVH : LIFE

With heart failure : ELITE, ELITE II, Val-HeFT, CHARM

Post MI : OPTIMAAL, VALIANT

With renal disease : MARVAL, IRMA-2, RENAAL & IDNT

Maintained cognitive function : Syst-Eur, SCOPE

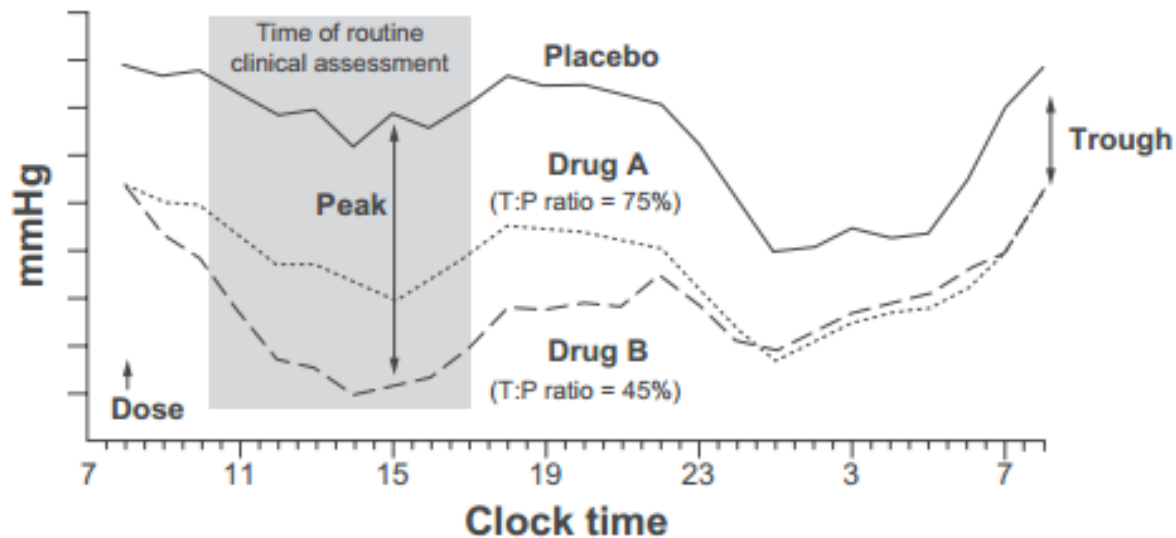
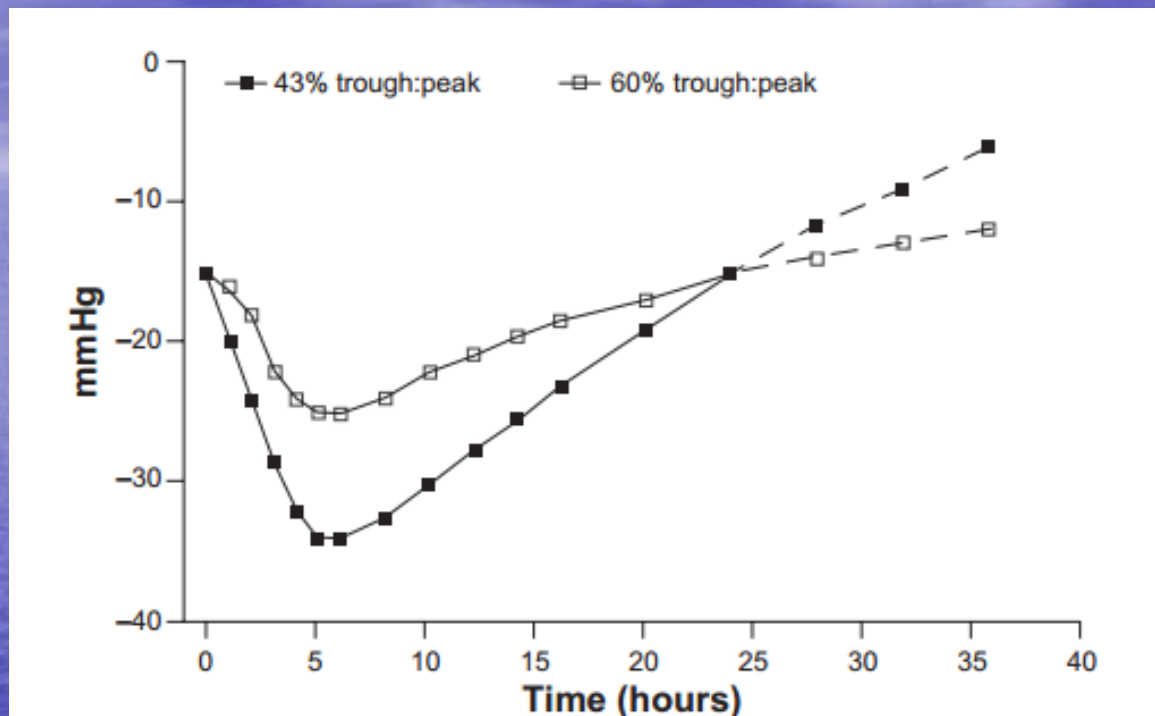


Figure 1 Blood pressure responses during a steady-state 24-hour dose interval for an agent with an acceptable (75%) trough-to-peak ratio (**A**) and an agent with an unacceptable (45%) trough-to-peak ratio (**B**).

BP response for an agent with acceptable (75%) trough to peak ratio (A)
 And an agent with an unacceptable (45%) trough to peak ratio (B)

BP response for an agent with 60% trough to peak ratio and an agent with 43% trough to peak ratio



Drugs with low trough to peak ratio = insufficient 24 hour coverage + Possible peak effect intolerance

Flack JM. Benefits of once-daily therapies in the treatment of hypertension. Vasc Risk and Health Management 2011 : 7.

Zannad F. \through-to-peak ratio, smoothness index and morning-to-evening ratio:why, which and when? J of Hypertension 2003 : 21.

Comparison of the trough:peak ratio of the ACEi and CCB

Agent (dose)	Average trough-to-peak ratio, %		
	More than 50%	50%	Less than 50%
Angiotensin-converting enzyme inhibitors			
Perindopril ^a (2–16 mg)	–75–100		
Fosinopril (20 mg)	64		
Ramipril (5 and 10 mg)	50–63		
Trandolapril (1 and 2 mg)	50–100		
Enalapril (5, 10, and 20 mg)	40–64		
Benazepril ^a (20–80 mg)		–50	
Quinapril ^a (10–80 mg)		–50	
Lisinopril (10–80 mg)		30–70	
Captopril ^b (25–100 mg)			25
Cilazapril (2.5 and 5.0 mg)			10–80
Calcium channel blockers			
Amlodipine (5–10 mg)	50–100		
Lacidipine (2–6 mg)	40–100		
Nifedipine Coat-Core (30 and 60 mg)	50–69		
Nifedipine GITS (30 and 60 mg)	60–94		
Verapamil slow-release formulations (240 mg)	45–100		
Isradipine slow-release formulations ^a (5, 10, 15, and 20 mg)	76–100		
Diltiazem slow-release formulations (120, 240, 300, 360, and 480 mg)		20–80	
Felodipine ER ^a (2.5, 5, 10, and 20 mg)			–40–50
Nitrendipine (10–20 mg)			10–80

Comparison of the trough:peak ratio of the β -blockers

Agent (dose)	Trough-to-peak ratio, %
Acebutolol DBP (400–800 mg)	71
Atenolol DBP and MAP ^a (50–200 mg)	46 and 104 ^a
Bisoprolol MAP (5 mg)	58
Betaxolol SBP/DBP (10 and 20 mg)	73/72
Carvedilol 12-hour MAP (25 mg)	85
Carvedilol CR DBP	
20 mg/day	73
40 mg/day	64
80 mg/day	65
Metoprolol MAP (200, 300, and 400 mg)	44 ^b
Metoprolol tartrate extended-release SBP/DBP (100 and 200 mg)	71/67
Nebivolol	
Overall, 5 mg	91
SBP/DBP, 5 mg	72/88
Pindolol MAP (15, 30, and 45 mg)	70
Propranolol, slow-release formulation MAP (160, 320, 480, and 640 mg)	107

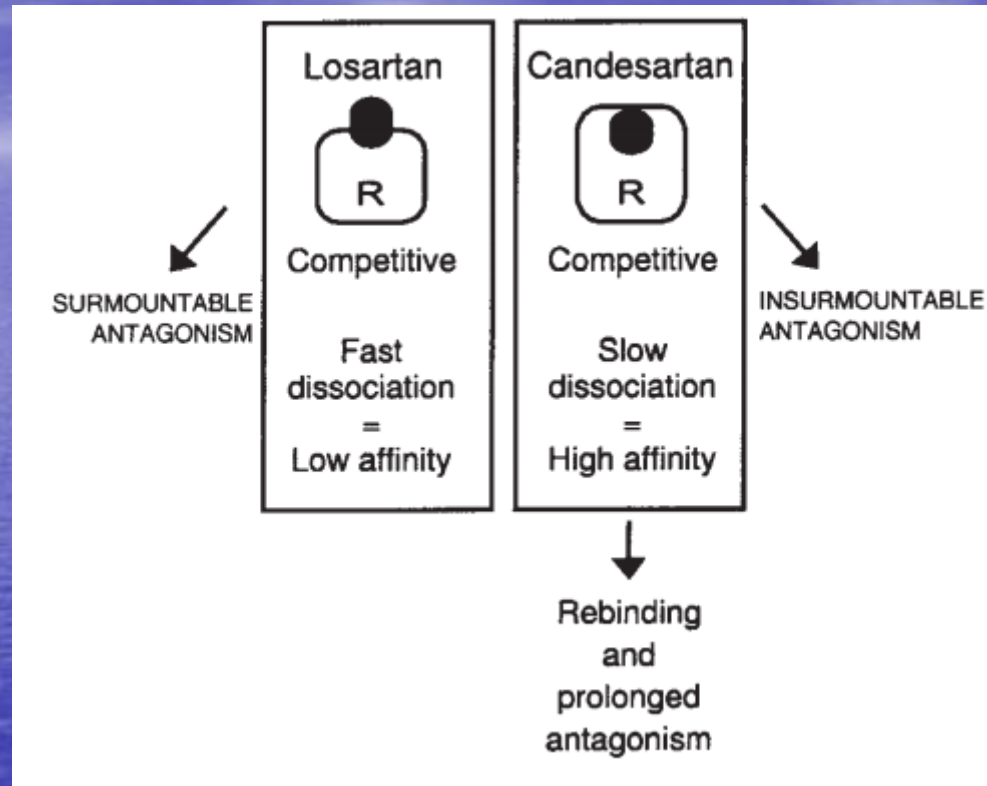
Comparison of the trough:peak ratio of the ARBs

ARB	Trough: peak ratio*	Recommended doses**
Candesartan	0.9–1.1 (DBP)	Starting dose: 8 mg od Maximum: 32 mg od
Eprosartan	0.65–0.8 (DBP)	Starting dose: 300 mg od Maximum: 800 mg od
Irbesartan	0.6–0.7 (SBP & DBP)	Starting dose: 75 mg od Maximum: 300 mg od
Losartan	0.7 (DBP)	Starting dose: 25 mg od Maximum: 100 mg od
Olmесartan	0.6–0.8 (SBP & DBP)	Starting dose: 10 mg od Maximum: 20 mg od***
Telmisartan	0.85 (SBP)- 0.61 (DBP)	Starting dose: 40 mg od Maximum: 80 mg od
Valsartan	0.66 (SBP & DBP)	Starting dose: 40 mg od Maximum: 160 mg od

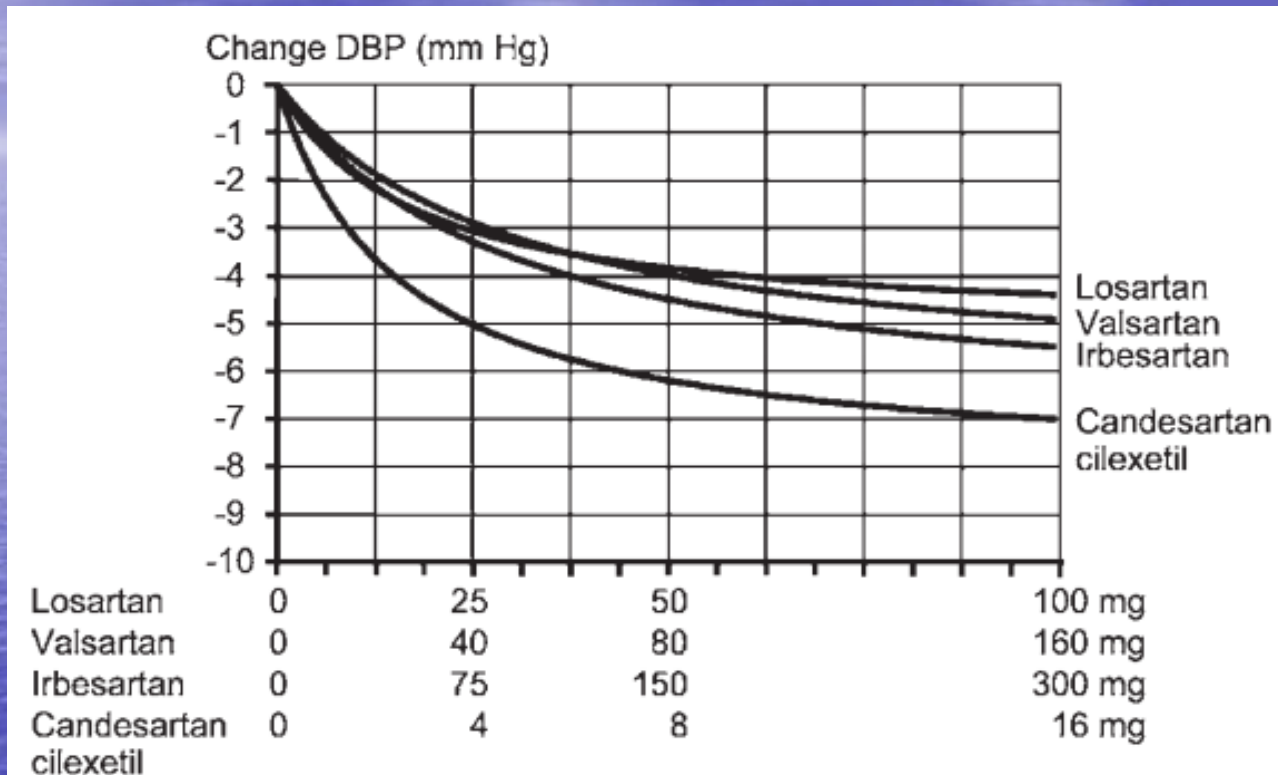
Croxson S. Using ARBs in elderly patients. Geriatr Med 2007.

Candesartan trough peak ratio 0.89 – 1.08 for SBP

Gradman AH. AT1 receptor blockers: differences that matter. J of Human Hypertension 2002 : 16.



Gradman AH. AT1 receptor blockers: differences that matter. J of Human Hypertension 2002 : 16.



Gradman AH. AT1 receptor blockers: differences that matter. J of Human Hypertension 2002 : 16.

TAKE HOME MESSAGE

Optimal treatment of hypertension can reduce the morbidity and mortality of cardiovascular

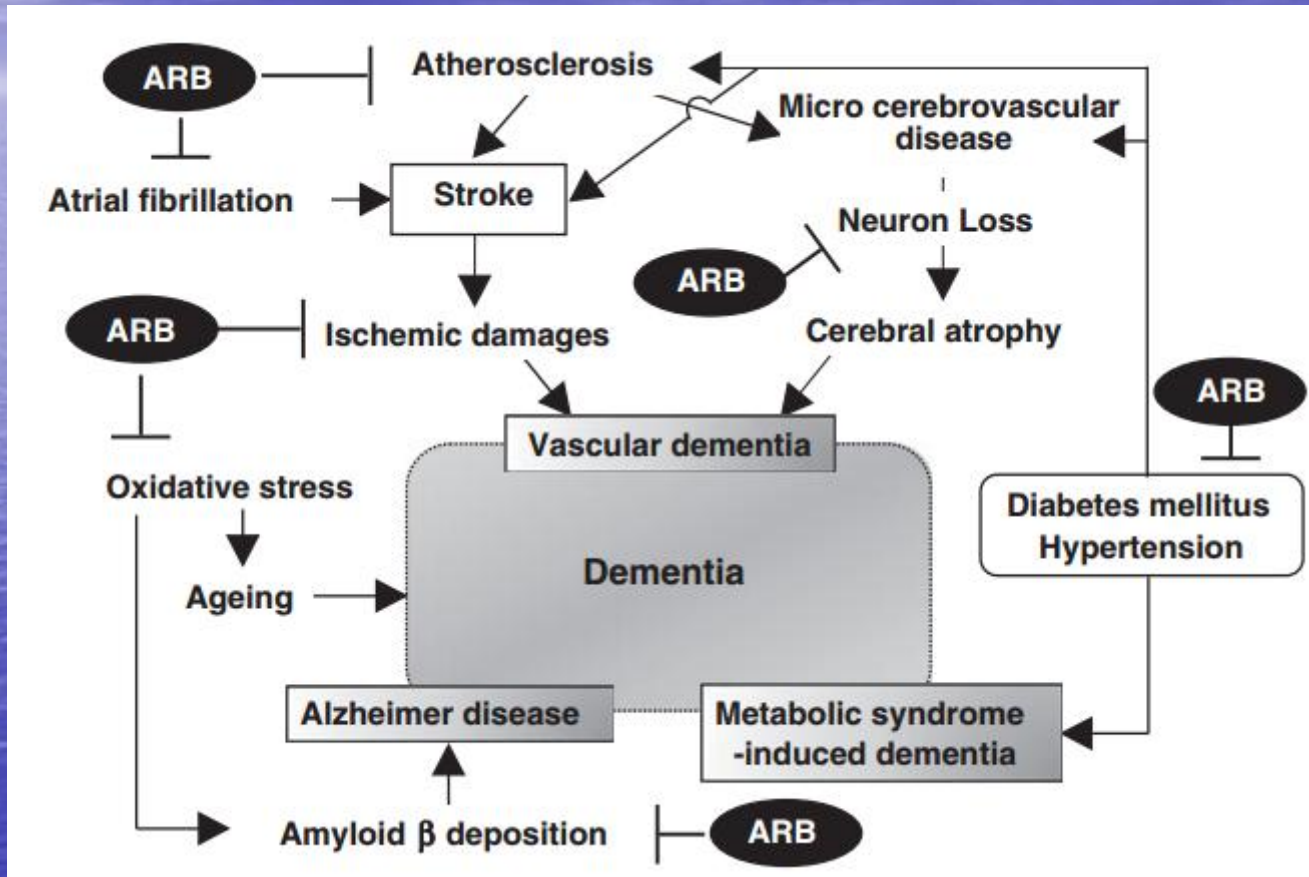
Do not hesitate to treat the elderly hypertension patients (>65 years)

ARBs can be used in many co-morbidities with few side effects

Always do the individualizing treatment

End Game

Terima kasih



Clinical indications of ABPM or HBPM

Conditions in which white-coat hypertension is more common, e.g.:

- Grade I hypertension on office BP measurement
- Marked office BP elevation without HMOD

Conditions in which masked hypertension is more common, e.g.:

- High-normal office BP
- Normal office BP in individuals with HMOD or at high total CV risk

Postural and post-prandial hypotension in untreated and treated patients

Evaluation of resistant hypertension

Evaluation of BP control, especially in treated higher-risk patients

Exaggerated BP response to exercise

When there is considerable variability in the office BP

Evaluating symptoms consistent with hypotension during treatment

Specific indications for ABPM rather than HBPM:

- Assessment of nocturnal BP values and dipping status (e.g. suspicion of nocturnal hypertension, such as in sleep apnoea, CKD, diabetes, endocrine hypertension, or autonomic dysfunction)

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; HBPM = home blood pressure monitoring; HMOD = hypertension-mediated organ damage.