

# Vai trò thuốc ức chế calci trong điều trị bệnh Tăng huyết áp: Cập nhật các khuyến cáo mới

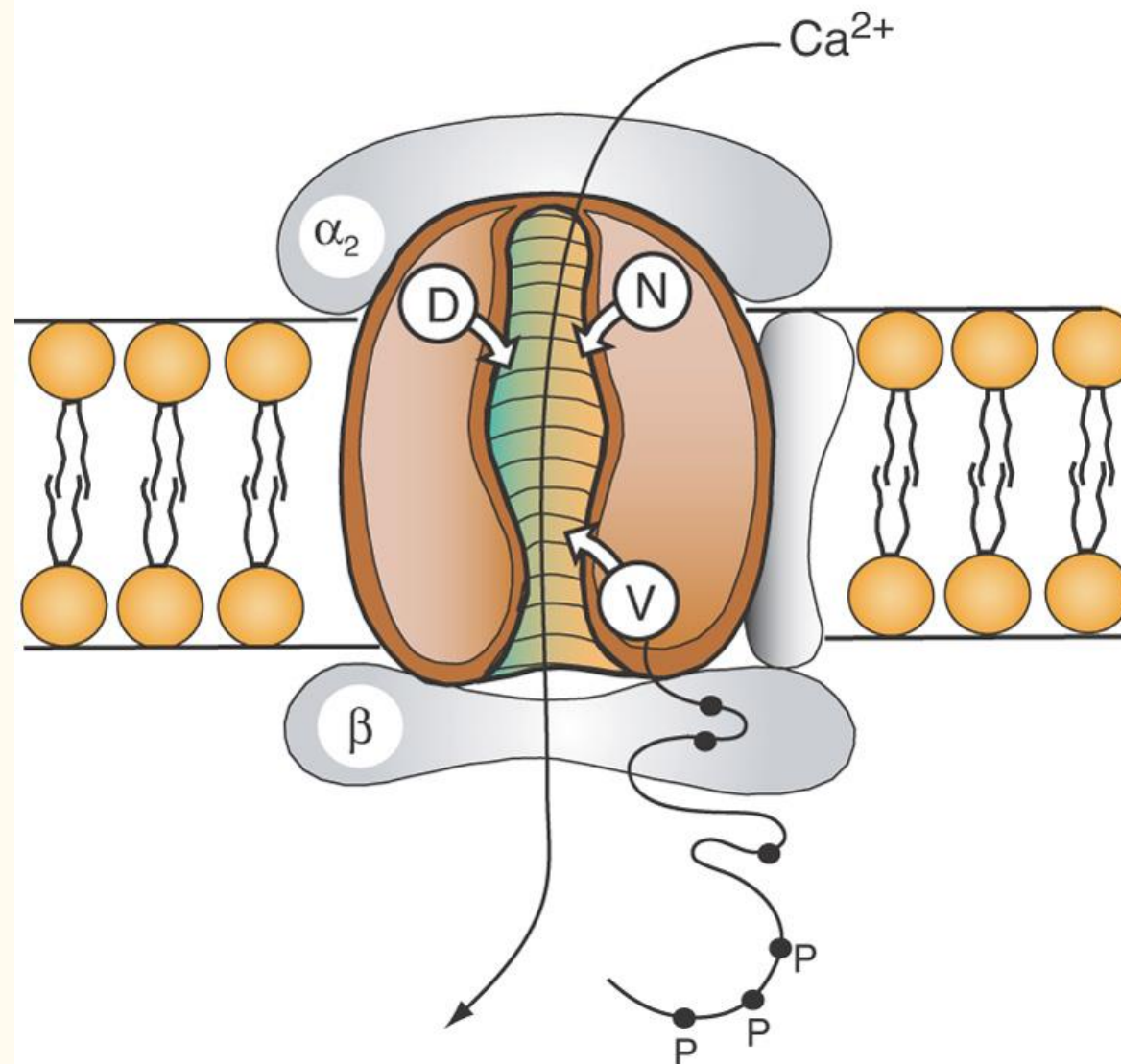
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# Mô hình kênh Calci

- N: Nifedipine
- D: Diltiazem
- V: Verapamil
- P: Phosphorylation
- Tất cả các DHPs gắn kết cùng vị trí Nifedipime

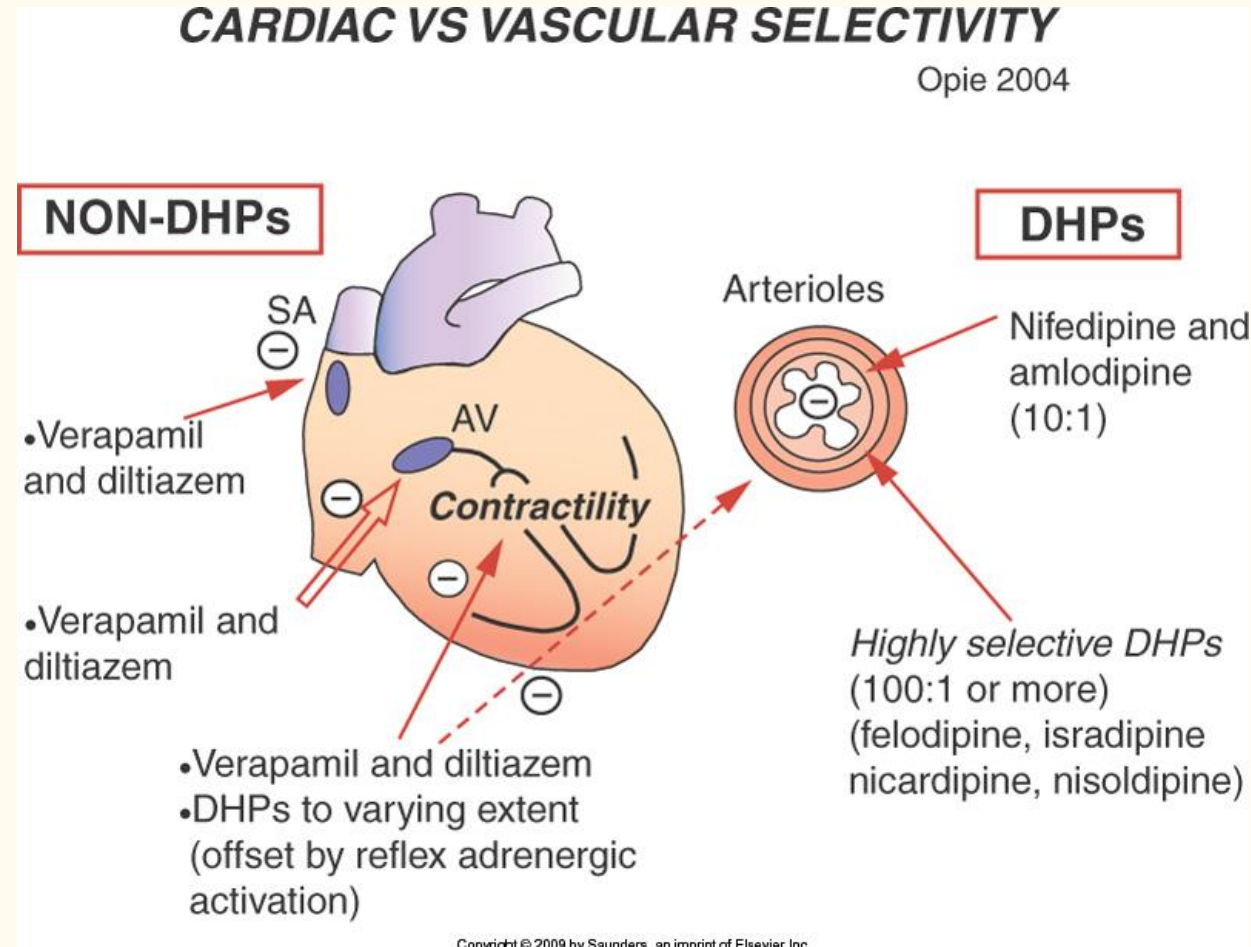
## CALCIUM CHANNEL MODEL

Opie 2004



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# Hiệu quả tim mạch của các ức chế calci nhóm dihydropyridine (DHP) và nhóm không dihydropyridine (non-DHP)



## Hiệu quả của thuốc ức chế calci đối với chức năng thất trái, tần số xoang, điện tâm đồ bề mặt và điện tâm đồ trong tim

Ức chế calci	Hiệu quả lâm sàng							
	Co tâm thất	Dẫn mạch	Tần số xoang	ECG			ECG trong tim	
				PR	QRS	QT	AH	HV
Verapamil	↓↓↓	↑	↓↓	↑↑	<->	<->	↑↑	<->
Diltiazem	↓↓	↑	↓	↑	<->	<->	↑	<->
Dihydropyridine	<->↓	↑↑	↑↑	<->	<->	<->	<->	<->
Bepridil	<->↓	↑	↓↑		↑	↑		

# Các thuốc ức chế Calci sử dụng ở Việt Nam

- Diltiazem
- Verapamil
- Dihydropyridines :
  - \* Nifedipine (Adalat ®)
  - \* Nicardipine (Loxen ®)
  - \* Amlodipine (Amlor ®)
  - \* Felodipine (Plendil ®)
  - \* Nimodipine
  - \* Lacidipine (Lacipil ®)
  - \* Lercanidipine (Zanedit ®)

# Hiệu quả của ức chế calci trong điều trị bệnh THA

- Hữu hiệu trong điều trị bệnh THA và cơn cao HA
- Giảm áp lực tâm thu và tâm trương
- Rất ít tác dụng phụ ; không tác động lên biến dưỡng
- Hiệu quả kháng giao cảm và lợi niệu
- Hữu hiệu cả người già và người trẻ
- Không làm giảm áp lực ở người có HA bình thường
- Giảm xơ vữa động mạch (lacidipine...)

*TL : Frishman WH, Sonnenblick EH : The Heart 8th ed. 1994, p. 1291-1304*

# Systematic Review Questions on High BP in Adults

Question Number	Question
1	Is there evidence that <u>self-directed monitoring of BP</u> and/or ambulatory BP monitoring are superior to office-based measurement of BP by a healthcare worker for 1) preventing adverse outcomes for which high BP is a risk factor and 2) achieving better BP control?
2	What is the <u>optimal target for BP</u> lowering during antihypertensive therapy in adults?
3	In adults with hypertension, do various antihypertensive drug classes differ in their comparative benefits and harms?
4	In adults with hypertension, does initiating treatment with antihypertensive pharmacological <u>monotherapy versus</u> initiating treatment with <u>2 drugs</u> (including fixed-dose combination therapy), either of which may be followed by the addition of sequential drugs, differ in comparative benefits and/or harms on specific health outcomes?

BP indicates blood pressure.

# Categories of BP in Adults\*

BP Category	SBP		DBP
<b>Normal</b>	<120 mm Hg	and	<80 mm Hg
<b>Elevated</b>	120–129 mm Hg	and	<80 mm Hg
<b>Hypertension</b>			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

\*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.

BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure.



# Prevalence of Hypertension Based on 2 SBP/DBP Thresholds\*†

	SBP/DBP ≥130/80 mm Hg or Self-Reported Antihypertensive Medication†		SBP/DBP ≥140/90 mm Hg or Self-Reported Antihypertensive Medication‡	
<b>Overall, crude</b>	46%		32%	
	Men (n=4717)	Women (n=4906)	Men (n=4717)	Women (n=4906)
<b>Overall, age-sex adjusted</b>	48%	43%	31%	32%
<b>Age group, y</b>				
<b>20–44</b>	30%	19%	11%	10%
<b>45–54</b>	50%	44%	33%	27%
<b>55–64</b>	70%	63%	53%	52%
<b>65–74</b>	77%	75%	64%	63%
<b>75+</b>	79%	85%	71%	78%
<b>Race-ethnicity §</b>				
<b>Non-Hispanic White</b>	47%	41%	31%	30%
<b>Non-Hispanic Black</b>	59%	56%	42%	46%
<b>Non-Hispanic Asian</b>	45%	36%	29%	27%
<b>Hispanic</b>	44%	42%	27%	32%

The prevalence estimates have been rounded to the nearest full percentage.

\*130/80 and 140/90 mm Hg in 9623 participants (≥20 years of age) in NHANES 2011–2014.

†BP cutpoints for definition of hypertension in the present guideline.

‡BP cutpoints for definition of hypertension in JNC 7.

§ Adjusted to the 2010 age-sex distribution of the U.S. adult population.

BP indicates blood pressure; DBP, diastolic blood pressure; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

# Choice of Initial Medication

COR	LOE	Recommendation for Choice of Initial Medication
I	A <sup>SR</sup>	For initiation of antihypertensive drug therapy, first-line agents include <u>thiazide diuretics, CCBs, and ACE inhibitors or ARBs.</u>

SR indicates systematic review.

# Choice of Initial Monotherapy Versus Initial Combination Drug Therapy

COR	LOE	Recommendations for Choice of Initial Monotherapy Versus Initial Combination Drug Therapy*
<b>I</b>	<b>C-EO</b>	Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target.
<b>Ila</b>	<b>C-EO</b>	Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mm Hg with dosage titration and sequential addition of other agents to achieve the BP target.

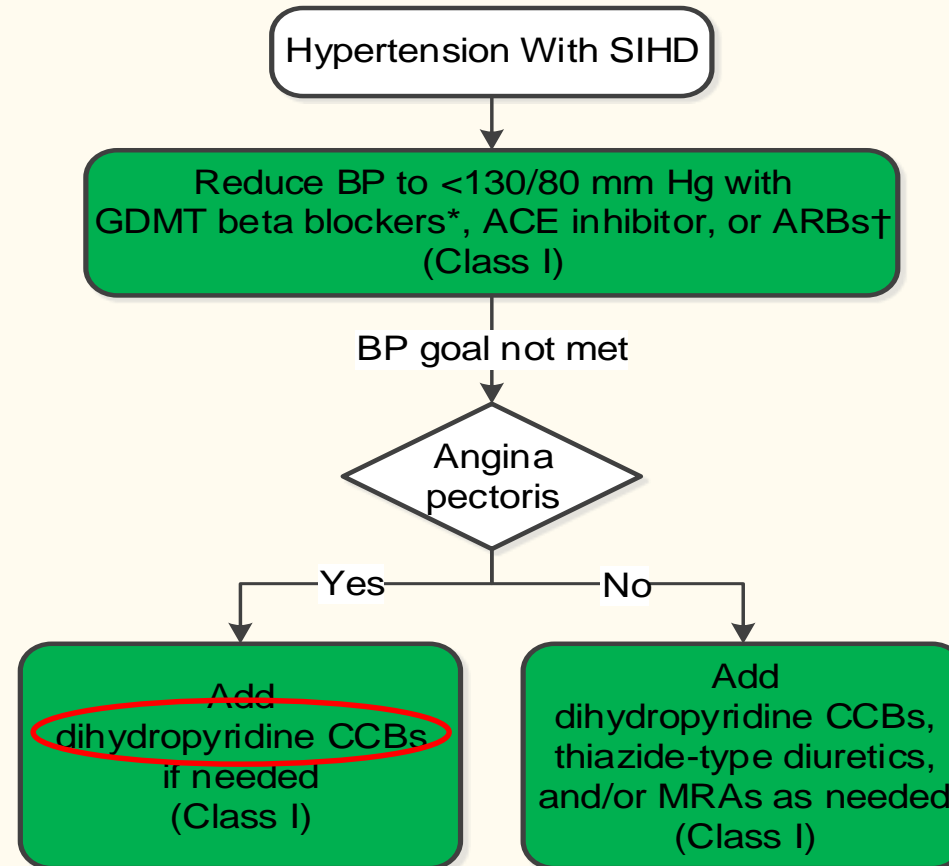
# Stable Ischemic Heart Disease

COR	LOE	Recommendations for Treatment of Hypertension in Patients With Stable Ischemic Heart Disease (SIHD)
I	SBP: B-R	In adults with SIHD and hypertension, a BP target of less than <u>130/80 mm Hg</u> is recommended.
	DBP: C-EO	
I	SBP: B-R	Adults with SIHD and hypertension (BP $\geq$ 130/80 mm Hg) should be treated with medications (e.g., GDMT beta blockers, ACE inhibitors, or ARBs) for <u>compelling indications</u> (e.g., previous MI, stable angina) as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension.
	DBP: C-EO	

# Stable Ischemic Heart Disease (cont.)

COR	LOE	Recommendations for Treatment of Hypertension in Patients With Stable Ischemic Heart Disease (SIHD)
<b>I</b>	<b>B-NR</b>	In adults with SIHD with angina and persistent uncontrolled hypertension, the <u>addition of dihydropyridine CCBs to GDMT beta blockers</u> is recommended.
<b>IIa</b>	<b>B-NR</b>	In adults who have had a MI or acute coronary syndrome, it is reasonable to continue GDMT beta blockers <u>beyond 3 years as long-term therapy</u> for hypertension.
<b>IIb</b>	<b>C-EO</b>	<u>Beta blockers and/or CCBs</u> might be considered to control hypertension in patients with CAD (without HFrEF) who had an MI <u>more than 3 years ago and have angina.</u>

# Management of Hypertension in Patients With SIHD



Colors correspond to Class of Recommendation in Table 1.

\*GDMT beta blockers for BP control or relief of angina include carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol. Avoid beta blockers with intrinsic sympathomimetic activity. The beta blocker atenolol should not be used because it is less effective than placebo in reducing cardiovascular events.

†If needed for BP control.

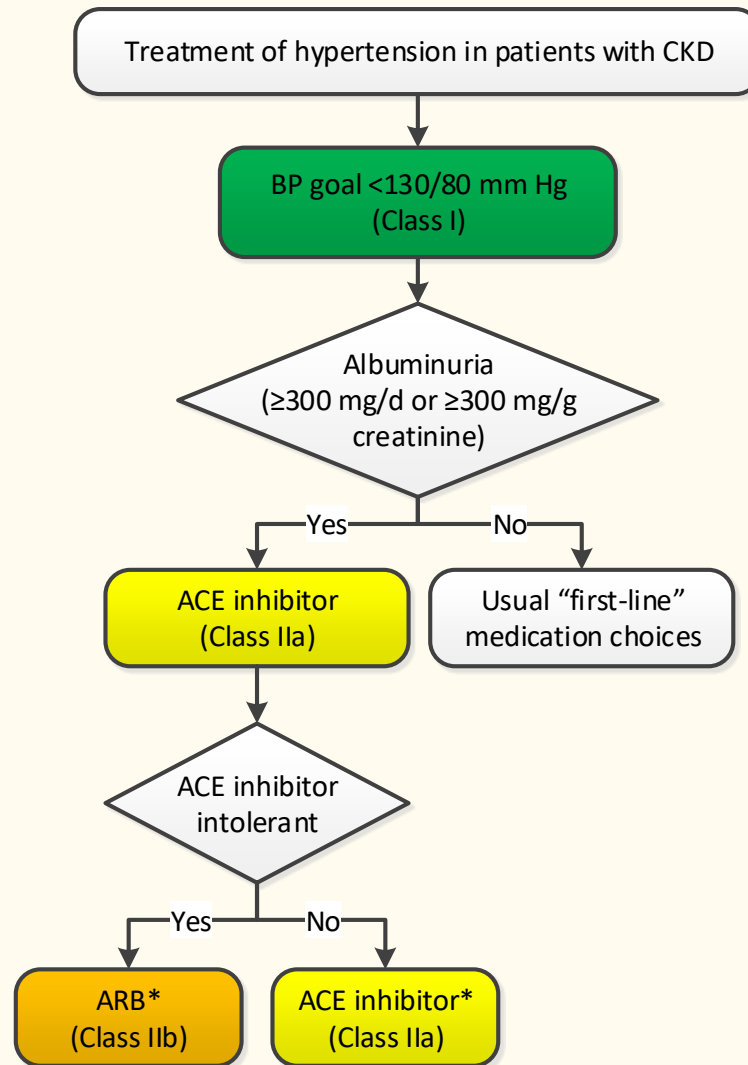
•ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; GDMT, guideline-directed management and therapy; and SIHD, stable ischemic heart disease.

# Chronic Kidney Disease

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

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.

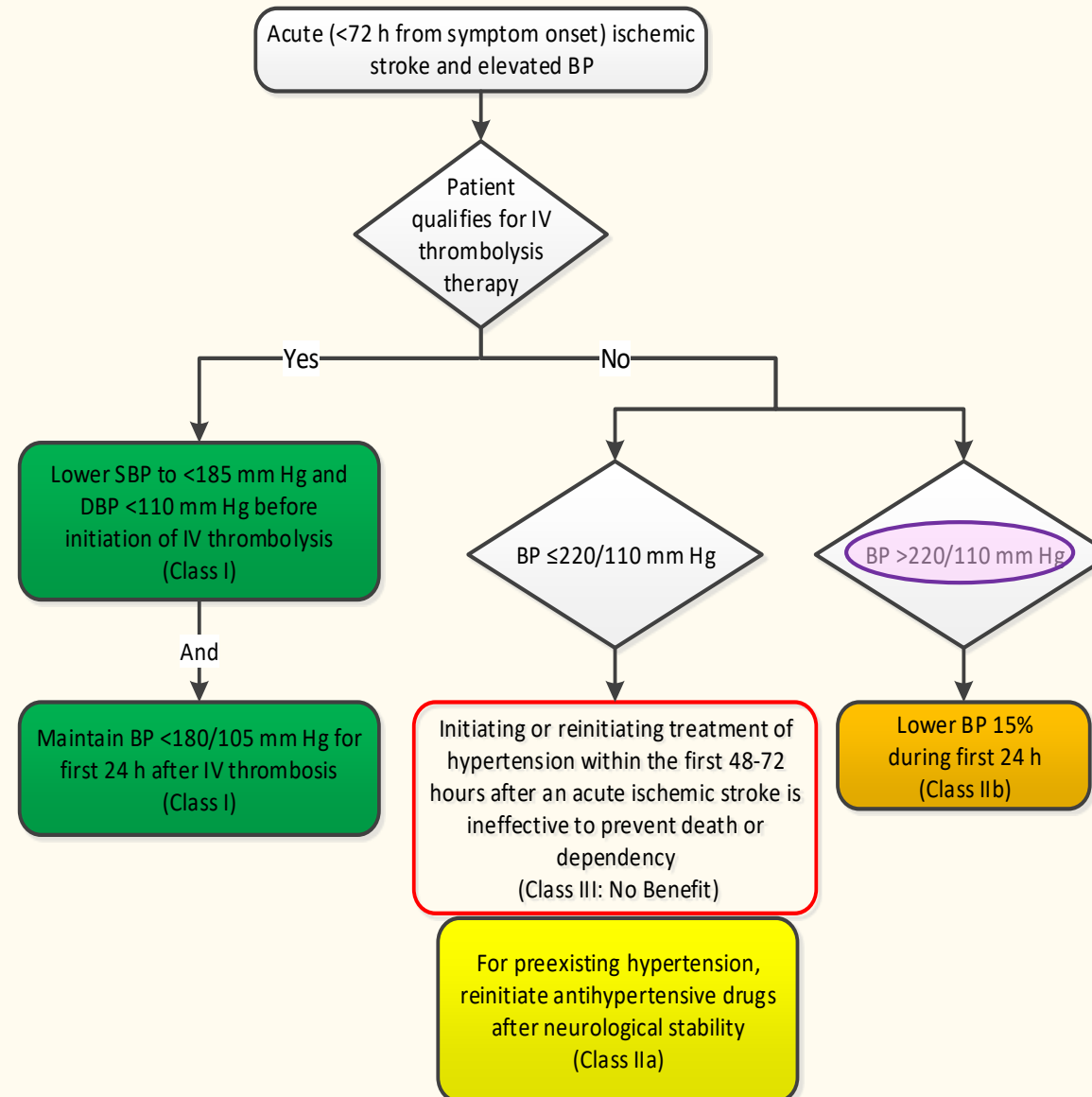
•ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP blood pressure; and CKD, chronic kidney disease.



# Hypertension After Renal Transplantation

COR	LOE	Recommendations for Treatment of Hypertension After Renal Transplantation
IIa	SBP: B-NR	After kidney transplantation, it is reasonable to treat patients with hypertension to a BP goal of <u>less than 130/80 mm Hg</u> .
	DBP: C-EO	
IIa	B-R	After kidney transplantation, it is reasonable to treat patients with hypertension with <u>a calcium antagonist</u> on the basis of <u>improved GFR and kidney survival</u> .

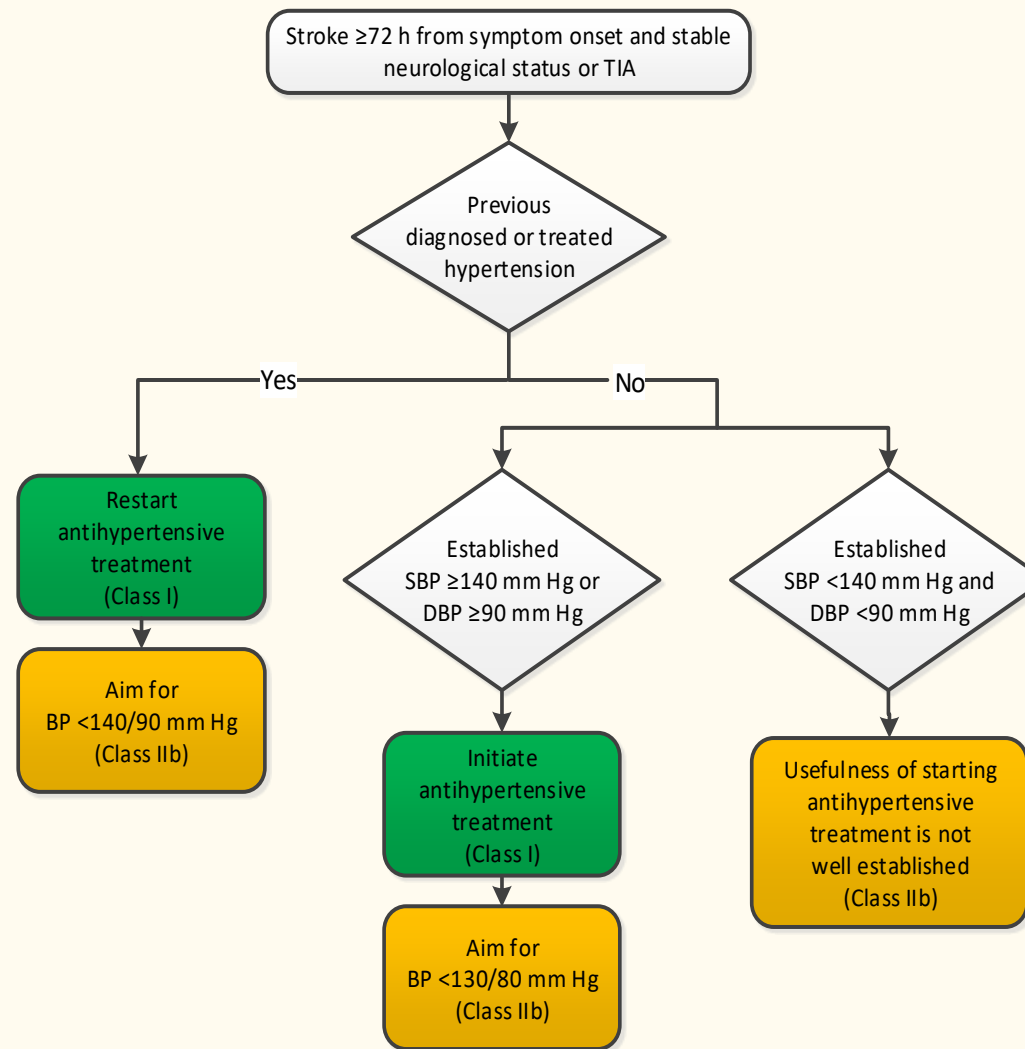
# Management of Hypertension in Patients With Acute Ischemic Stroke



Colors correspond to Class of Recommendation in Table 1.

BP indicates blood pressure; DBP, diastolic blood pressure; IV, intravenous; and SBP, systolic blood pressure.

# Management of Hypertension in Patients With a Previous History of Stroke (Secondary Stroke Prevention)



Colors correspond to Class of Recommendation in Table 1.  
DBP indicates diastolic blood pressure; SBP, systolic blood pressure; and TIA, transient ischemic attack.

# Diabetes Mellitus

COR	LOE	Recommendations for Treatment of Hypertension in Patients With DM
I	SBP: B-R <sup>SR</sup>	In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher with a treatment goal of <u>less than 130/80 mm Hg</u> .
	DBP: C-EO	
I	A <sup>SR</sup>	In adults with DM and hypertension, <u>all first-line classes</u> of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective.
IIb	B-NR	In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria.

SR indicates systematic review.

# Pregnancy

COR	LOE	Recommendations for Treatment of Hypertension in Pregnancy
I	C-LD	Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to <u>methyldopa, nifedipine, and/or labetalol</u> during pregnancy.
III: Harm	C-LD	Women with hypertension who become pregnant <u>should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors.</u>

## BP Thresholds for and Goals of Pharmacological Therapy in Patients With Hypertension According to Clinical Conditions

Clinical Condition(s)	BP Threshold, mm Hg	BP Goal, mm Hg
<b>General</b>		
Clinical CVD or 10-year ASCVD risk $\geq 10\%$	$\geq 130/80$	$< 130/80$
No clinical CVD and 10-year ASCVD risk $< 10\%$	$\geq 140/90$	$< 130/80$
Older persons ( $\geq 65$ years of age; noninstitutionalized, ambulatory, community-living adults)	$\geq 130$ (SBP)	$< 130$ (SBP)
<b>Specific comorbidities</b>		
Diabetes mellitus	$\geq 130/80$	$< 130/80$
Chronic kidney disease	$\geq 130/80$	$< 130/80$
Chronic kidney disease after renal transplantation	$\geq 130/80$	$< 130/80$
Heart failure	$\geq 130/80$	$< 130/80$
Stable ischemic heart disease	$\geq 130/80$	$< 130/80$
Secondary stroke prevention	$\geq 140/90$	$< 130/80$
Secondary stroke prevention (lacunar)	$\geq 130/80$	$< 130/80$
Peripheral arterial disease	$\geq 130/80$	$< 130/80$

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; and SBP, systolic blood pressure.



# Worldwide burden of HBP

- **HTN** affects about **40%** of the industrialized populations and its prevalence is increasing in particular for high risk pts<sup>1</sup>
- **HTN** is associated with **additional RF's** in **over 80%** of patients<sup>2</sup>
- **HNT** is a **co-morbid** condition in **over 85%** of cardiac patients<sup>3</sup>
- On a worldwide base, **NTH** is responsible for 4:
  - **7.6 million deaths** each year (**13.5% of total**)
  - **6.3 millions of years of disability** (4.4% of total)
  - **54% of Stroke** and **47% of CHD**, **≈30% ESRD**<sup>5</sup>

1. Lawes, Hoorn, Rodgers: Lancet 2008; 371: 1513-18

2. Banegas JR, Borghi C et al, Eur Heart J 2011

3. Arnett KD et al, Circulation 2014

4. Lim SS et al, The Lancet 2013;380: 2224 – 2260

5. US Renal Data System, 2015





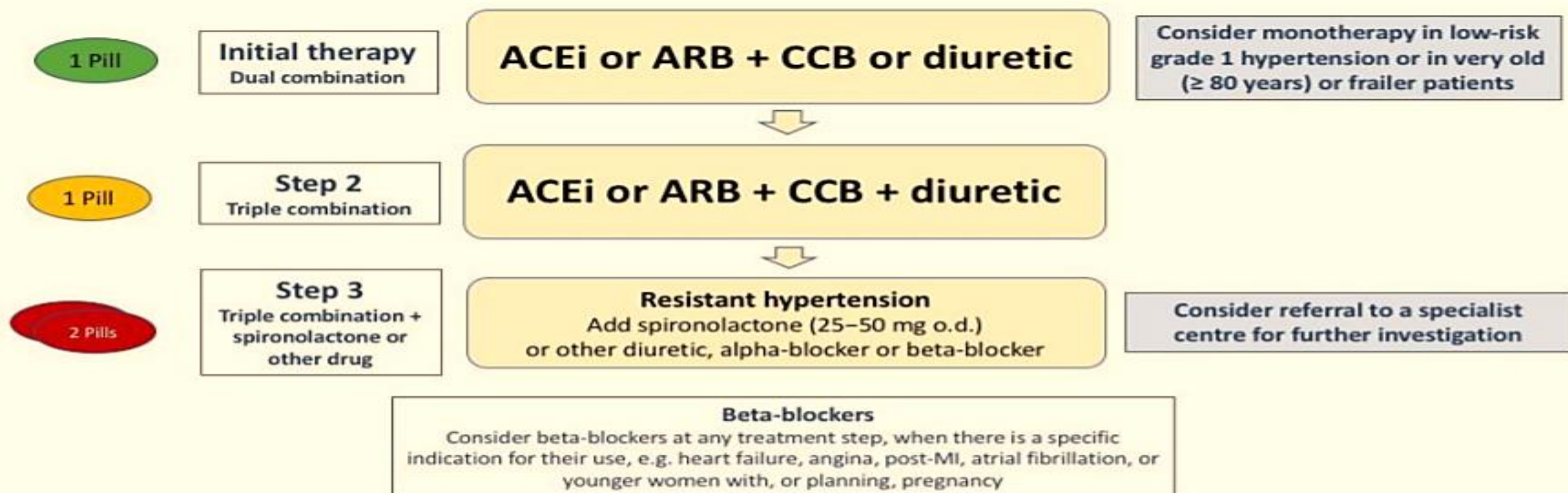


## HTN, antihypertensive drugs and CVD: consolidated evidence

1. BP lowering is associated with a reduced morbidity and mortality and is highly cost/saving.
2. Antihypertensive treatment reduces blood pressure and the incidence of HTN-associated events.
3. Prevention of CV morbidity is mainly related to BP lowering per se, although other effects of the antihypertensive drugs contribute to benefit.

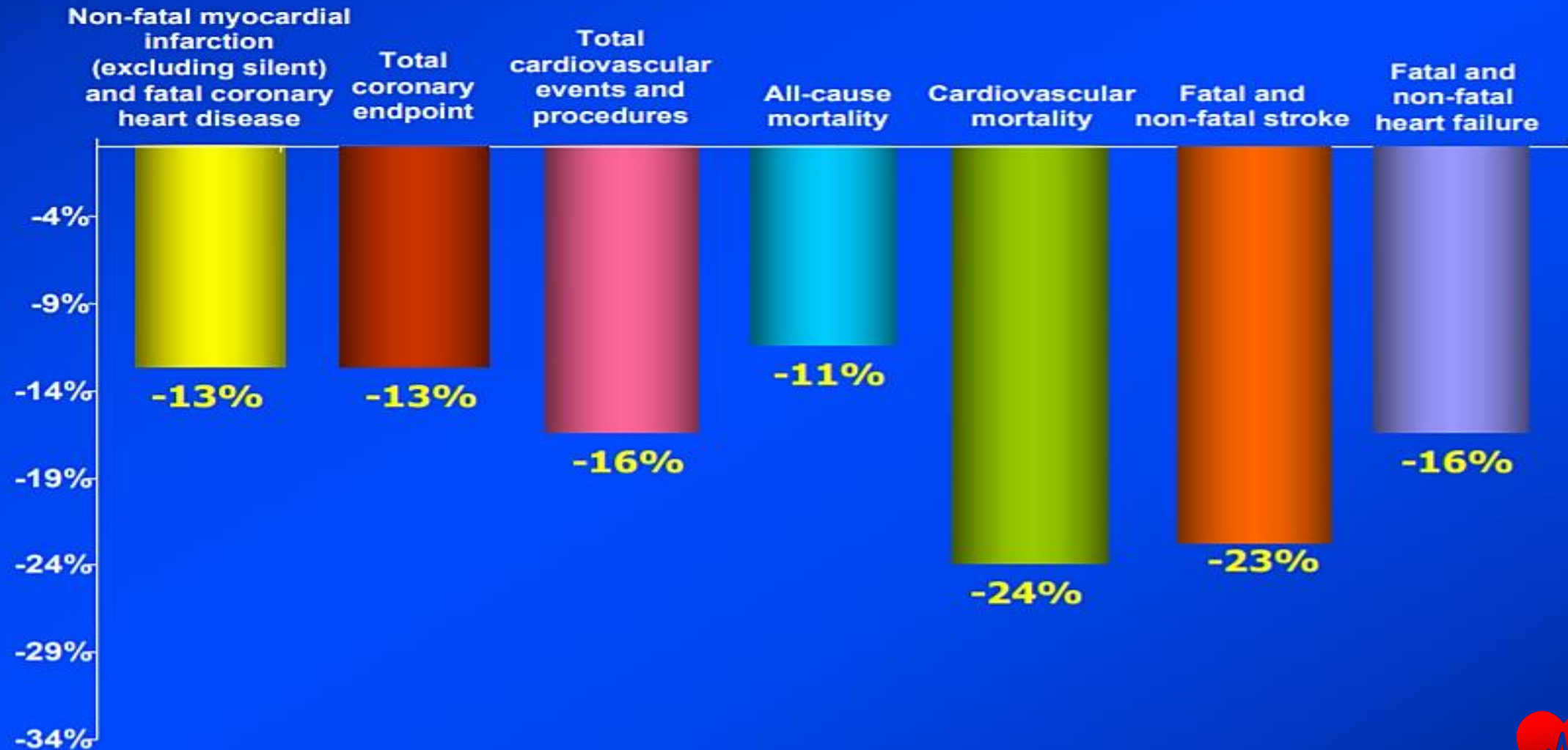


## Core drug-treatment strategy for uncomplicated hypertension



*The core algorithm is also appropriate for most patients with HMOD, cerebrovascular disease, diabetes, or PAD*

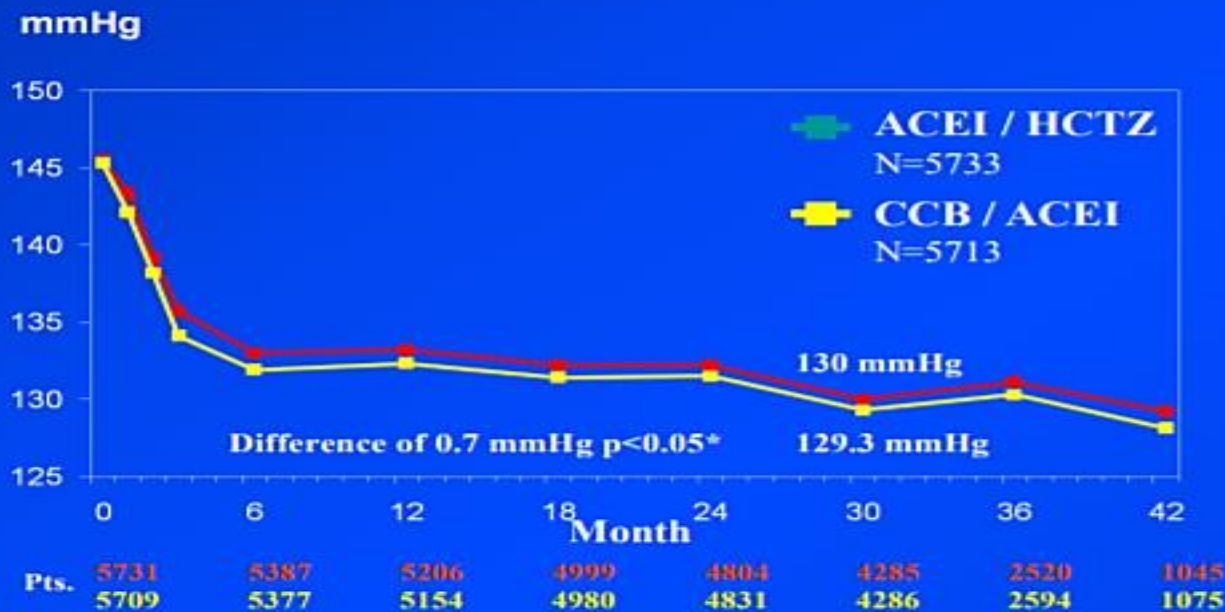
# ASCOT Trial: Endpoints for amlodipine and perindopril versus atenolol and thiazide





# ACCOMPLISH

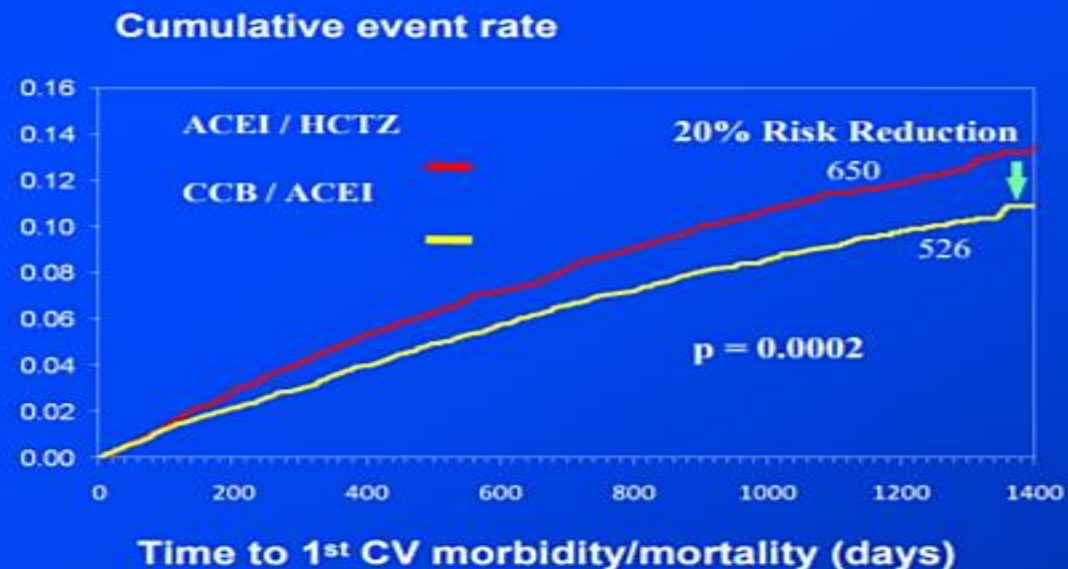
## SBP over time



\*Mean values are taken at 30 months F/U visit

DBP: 71.1 (CCB/ACEI) DBP: 72.8 (ACEI/HCTZ)

## Kaplan-Meier for primary endpoint



HR (95% CI): 0.80 (0.72, 0.90)

# **Effect on Office and Home BP of Lercanidipine/Enalapril Combination: The FELT Study**

- **Double Blind, Placebo controlled trial**
- **100 centres, 7 countries**
- **1039 patients**
- **DBP 100-109 mm Hg, Home: >85 mm Hg**
- **Treatment: Placebo**

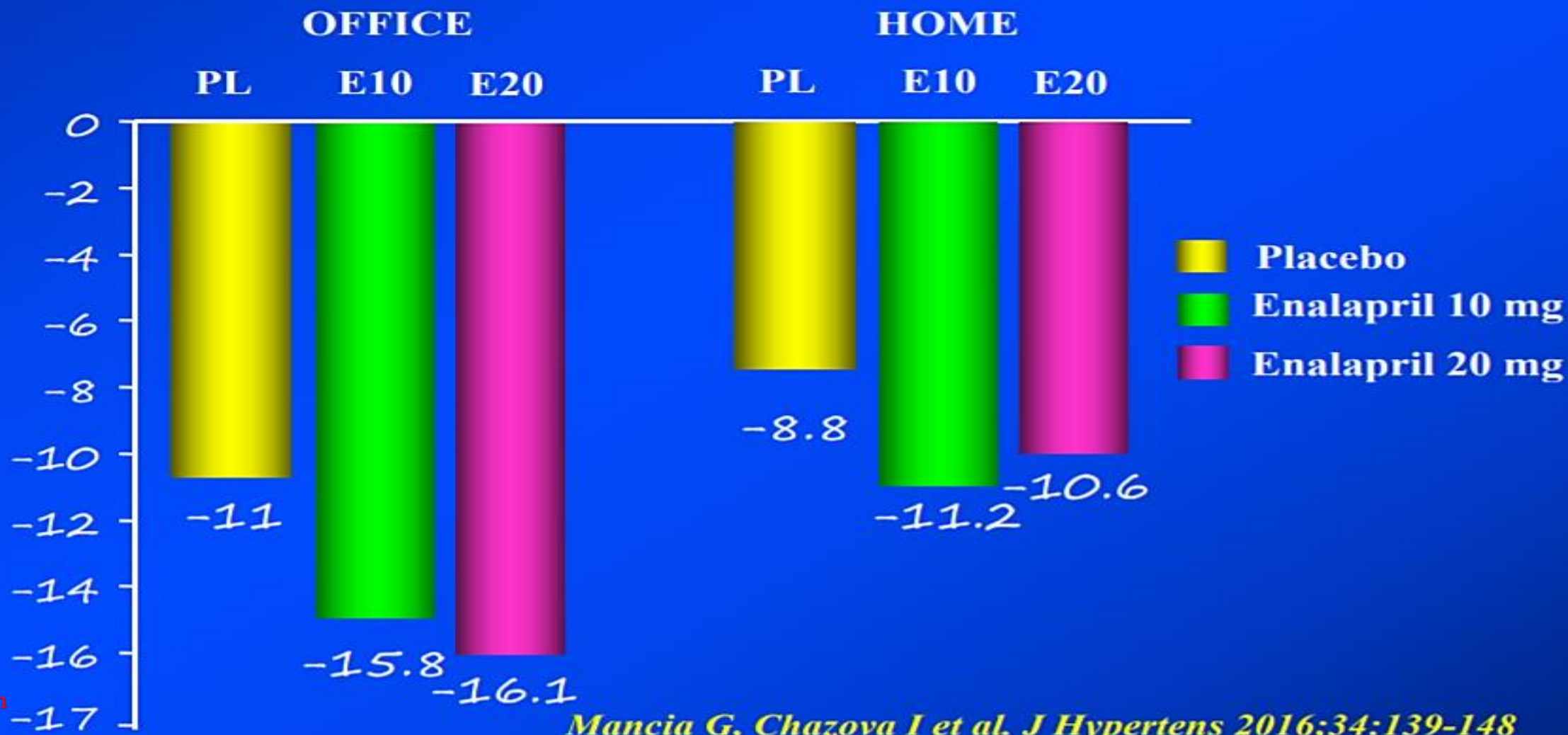
**Lercanidipine 10-20 mg**

**Enalapril 10-20 mg**

**or 4 combinations**

# The FELT Study: Lercanidipine or Enalapril Combination Therapy is Effective on Both Office and out-of-office BP in Patients with Stage 2 Hypertension

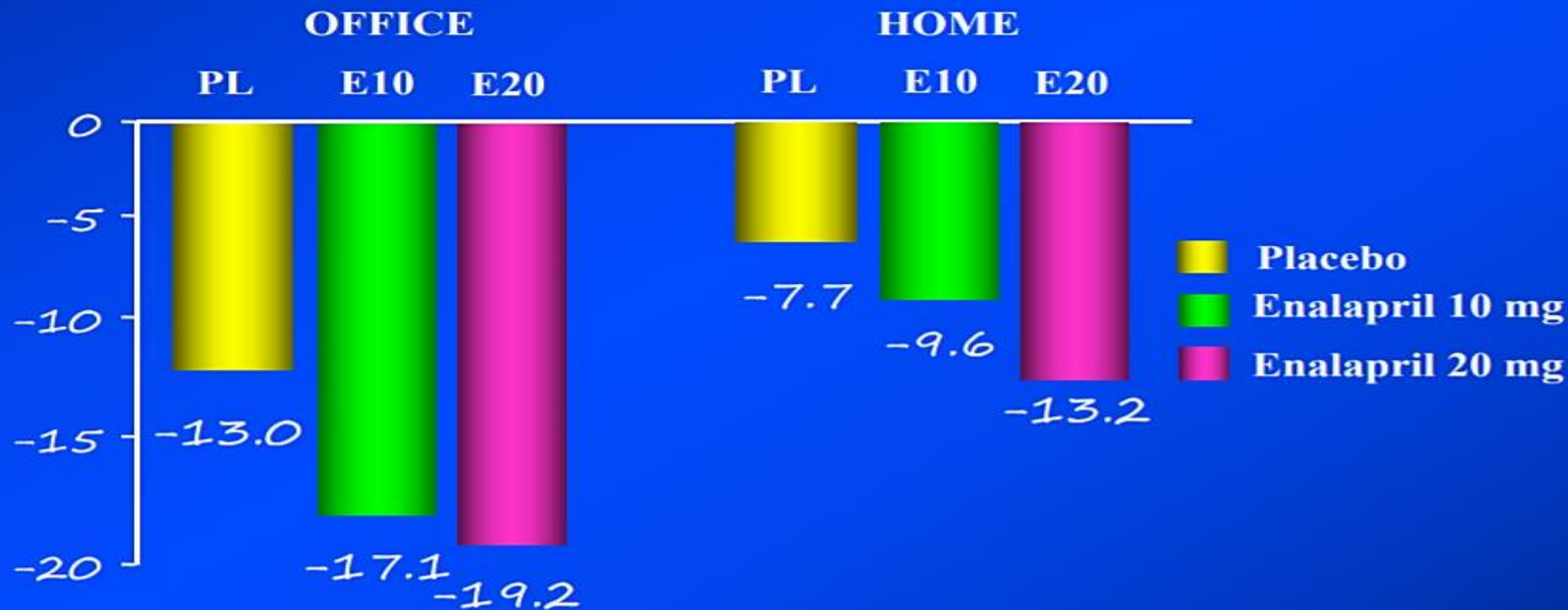
LERCANIDIPINE 10mg plus PLACEBO or ENALAPRIL 10-20 mg





# The FELT Study: Lercanidipine or Enalapril Combination Therapy is Effective on Both Office and out-of-office BP in Patients with Stage 2 Hypertension

LERCANIDIPINE 20mg plus PLACEBO or ENALAPRIL 10-20 mg



# INVEST Study: Metabolic Effects of Various Antihypertensive Agents

## CAS

Calcium antagonist

Calcium antagonist+ACEi (low dose)

Calcium antagonist+ACEi (high dose)

Calcium antagonist+ACEi+HCTZ 12.5 mg

Calcium antagonist+ACEi+HCTZ 25 mg

## NCAS

$\beta$ -blocker

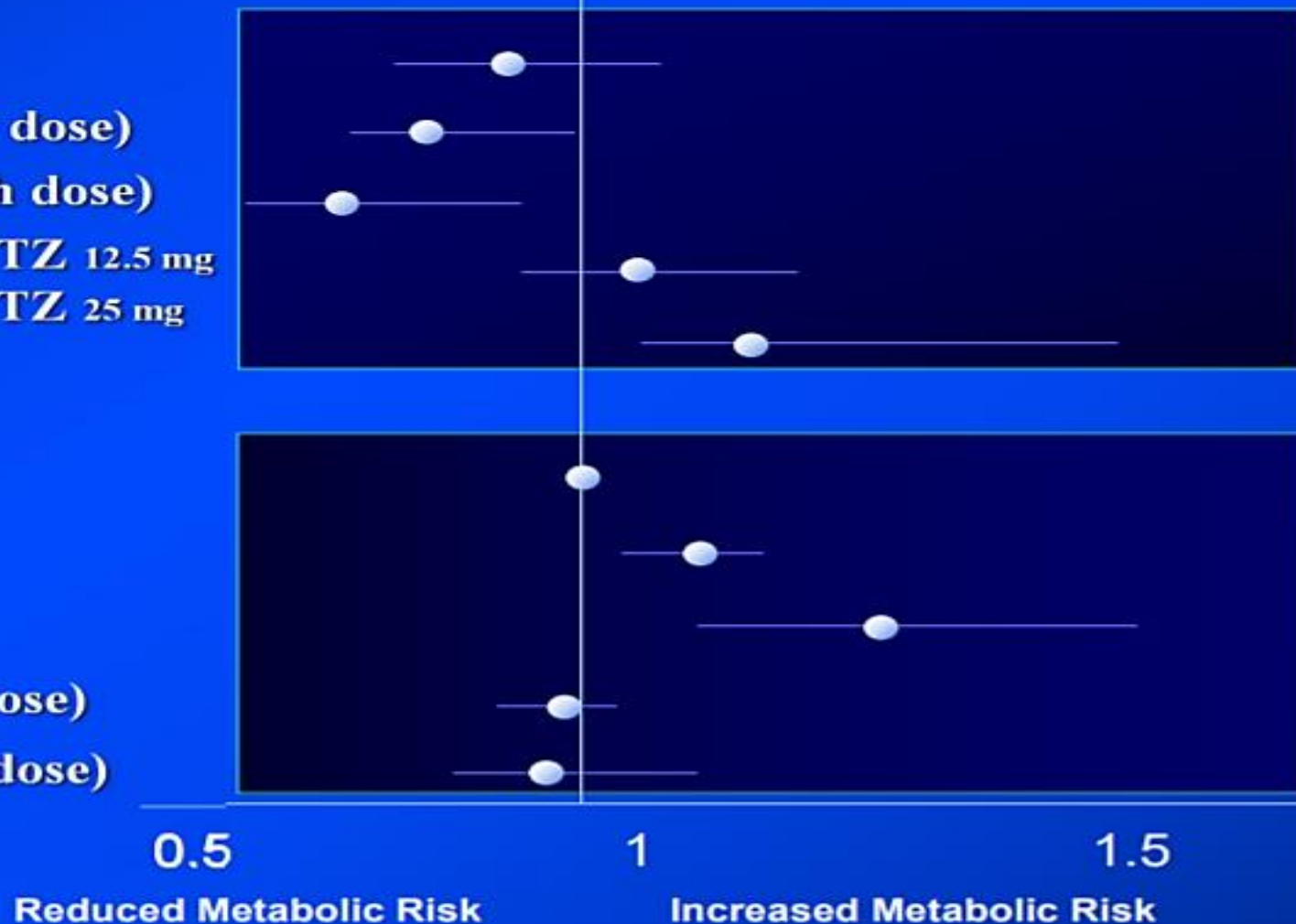
$\beta$ -blocker+HCTZ (12.5mg)

$\beta$ -blocker+HCTZ (25mg)

$\beta$ -blocker+HCTZ+ACEi (low dose)

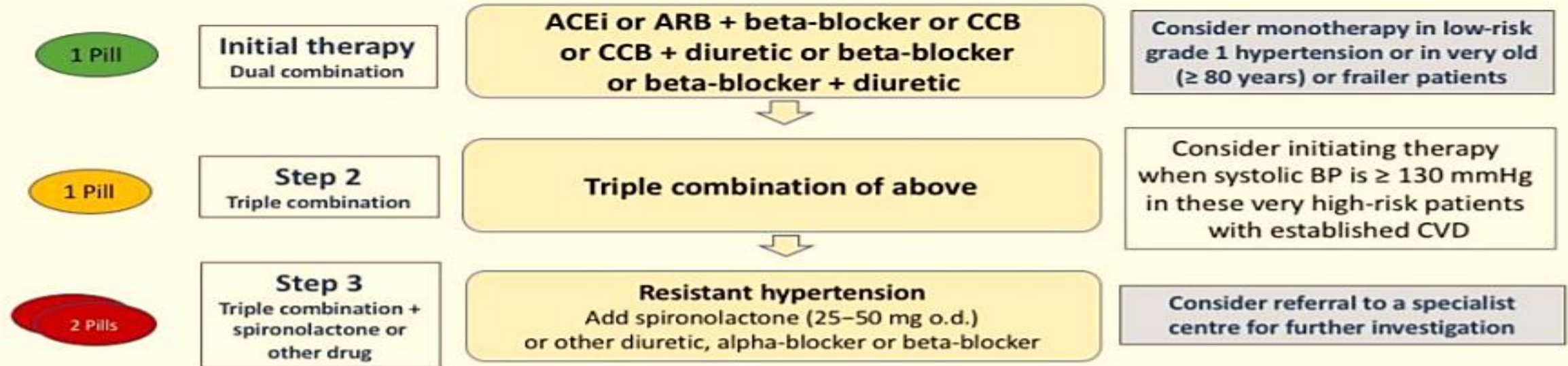
$\beta$ -blocker+HCTZ+ACEi (high dose)

### New Onset Diabetes





## Drug-treatment strategy for hypertension and CAD





## Therapeutic strategies in hypertensive patients with CAD

Recommendations	Class	Level
In patients with CAD receiving BP-lowering drugs, it is recommended:		
• To target SBP to 130 mmHg and lower, if tolerated, but not lower than 120 mmHg.	<b>I</b>	<b>A</b>
• In older patients (aged $\geq 65$ years), to target to a SBP range of 130–140 mmHg.	<b>I</b>	<b>A</b>
• To target DBP to $< 80$ mmHg, but not lower than 70 mmHg.	<b>I</b>	<b>C</b>
In hypertensive patients with a history of myocardial infarction, beta-blockers and RAS blockers are recommended as part of treatment.	<b>I</b>	<b>A</b>
In patients with symptomatic angina, beta-blockers and/or CCBs are recommended.	<b>I</b>	<b>A</b>

# Kết luận

- Chẩn đoán THA: nên dựa vào huyết áp đo tại nhà và ABPM
- Huyết áp kế điện tử; băng quấn cánh tay
- Nên ngưng thuốc lá
- THA do hẹp ĐM thận: điều trị nội là chính
- Thuốc đầu tiên không chỉ định bắt buộc: UCMC, chẹn thụ thể AG II, ức chế calci, lợi tiểu, chẹn beta
- Phối hợp thuốc là cần thiết
- Ức chế calci DHP: vai trò quan trọng trong điều trị THA