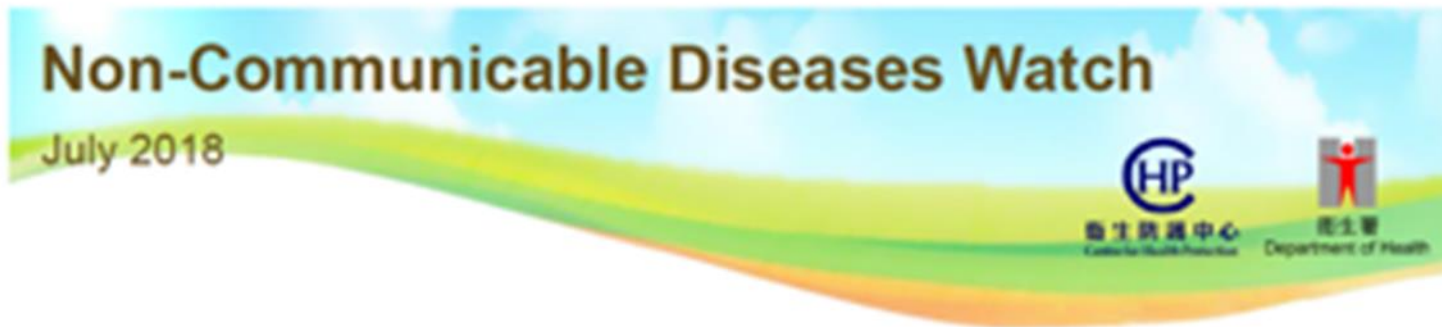




Strategies for better BP control and outcomes in hypertensive patients

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Department of Medicine
University of Hong Kong

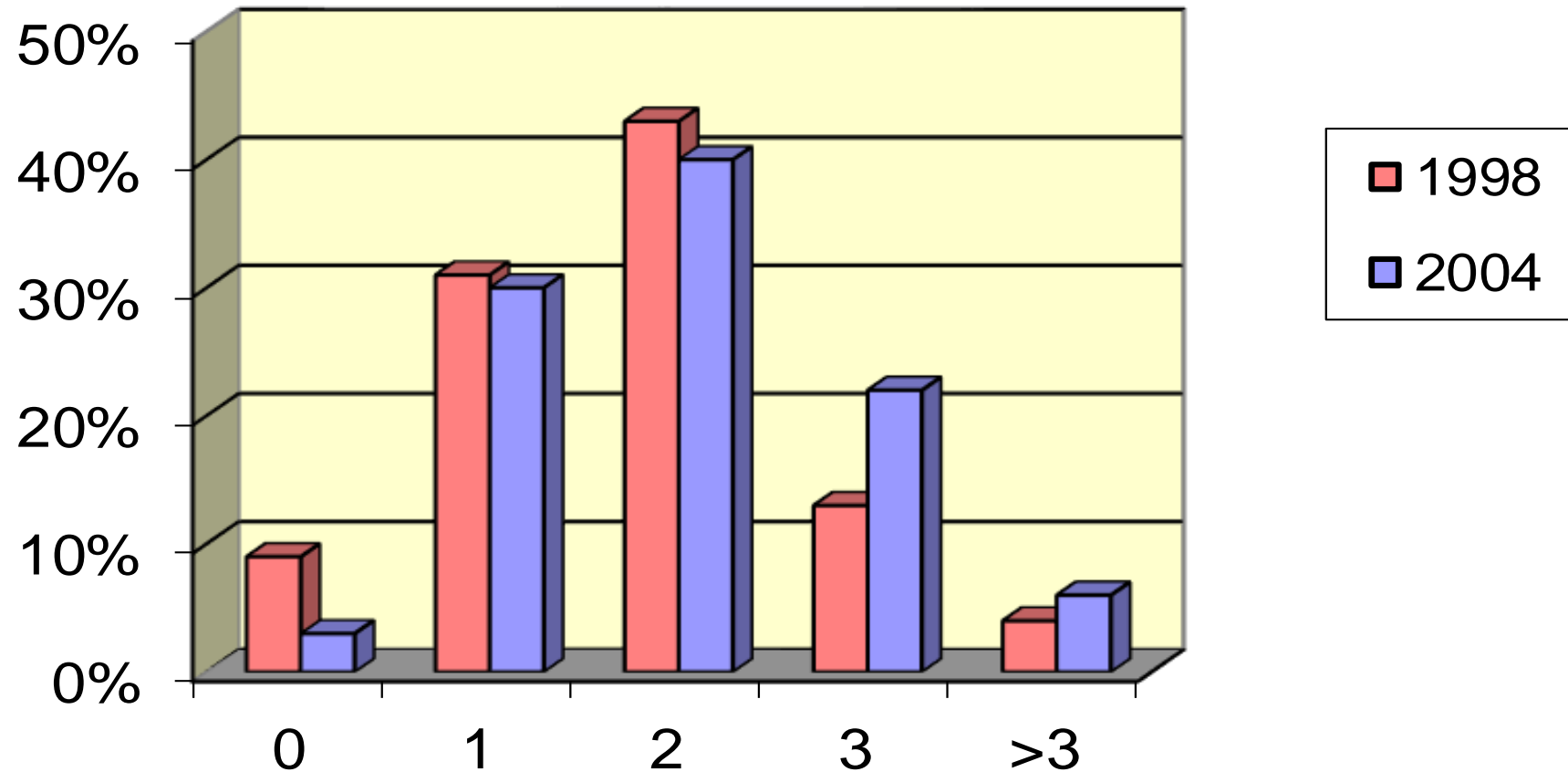


Hypertension: A Burning Health Problem

Hong Kong Centre for Health Protection Population Health Survey 2014/5

	Prevalence
Diagnosed hypertension	14.6%
Undiagnosed hypertension	13.2%
General obesity (BMI \geq 25)	30%
Hypercholesterolaemia (TC \geq 5.2)	50%

Number of antihypertensive drugs taken by patients in the Hypertension Clinic



No. of drugs

Cheung et al. BJCP 2005

Combination therapy for hypertension

Introduction

Hypertension affects more than one tenth of the adult population in Hong Kong.¹ In fact, using the latest recommended cut-off points for systolic blood pressure of 140 mm Hg and diastolic blood pressure of 90 mm Hg,² the prevalence of hypertension in Hong Kong adults is close to 20%. The apparent increase in the prevalence of hypertension in recent years is largely due to increased recognition of isolated systolic hypertension and its associated risks.

Ideal blood pressure

The Hypertension Optimal Treatment (HOT) study failed to show any significant differences in outcomes for target diastolic blood pressures of less than 80, 85, or 90 mm Hg, but did at least show that a target of 80 mm Hg is safe.³ More than one drug is frequently needed to decrease the blood pressure to this level, however. For high-risk groups such as patients with diabetes or nephropathy, the target blood pressure has been reduced to a lower level. In the UK Prospective Diabetes Study (UKPDS), tight blood pressure control, rather than glycaemic control, was responsible for reducing the incidence of macrovascular complications.⁴ Patients with diabetes in the HOT study also benefited from lower target blood pressures despite small differences in the achieved blood pressure values among the randomised groups.³

In the Heart Outcomes Prevention Evaluation (HOPE) study, patients treated with an angiotensin converting enzyme inhibitor (ACEI) had a lower cardiovascular event rate even if they were normotensive.⁵ It is generally believed that ACEIs have a protective effect beyond blood pressure reduction. An alternative possibility is that lowering the blood pressure by a small amount for people at high cardiovascular risk is beneficial, even for normotensive people. This leads to the new hypothesis that instead of treating patients whose blood pressure exceeds a certain level, blood pressure should be lowered for all people who are at risk from strokes and heart attacks.⁶

Blood pressure control in reality

While the prevalence of hypertension in the community is alarming, more disturbing is how badly blood pressure is controlled in patients who are known to be hypertensive. Given the relationship between raised blood pressure and stroke risk, good control of blood pressure is crucial for stroke prevention.⁷ In Hong Kong, as in the US, blood pressure is effectively controlled in no more than 50% of patients.^{2,8}

Why is blood pressure so poorly controlled? The reasons include disease severity, patient factors, doctor factors, and drug-related factors. As hypertension is usually

asymptomatic and complications such as stroke, heart attack, and heart and kidney failures usually appear only after time, patients are unlikely to present with characteristic symptoms. Treatment does not bring immediately obvious benefits to patients and involves inconvenience, medication side-effects, and expense, all of which influence compliance. Treatment failure may also be due to suboptimal drug therapy, with low doses, inappropriate or wrong dose schedules, or suboptimal use of therapeutic options (monotherapy or combination therapy).

Synergism

Currently available antihypertensive drugs are similar in their overall effectiveness in lowering blood pressure. The response to different agents varies from person to person, however.^{9,10} To effectively control blood pressure, the clinician may increase the drug dose or change to another drug.

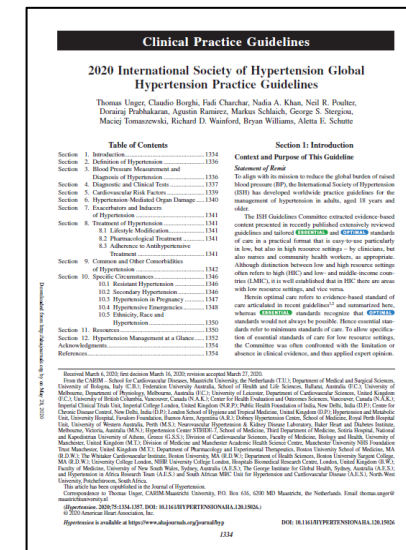
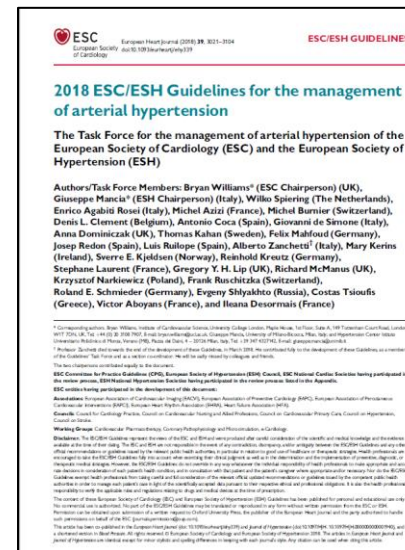
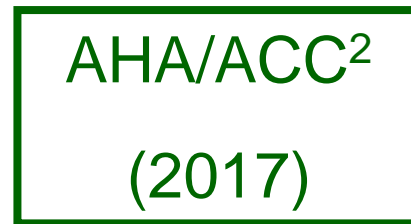
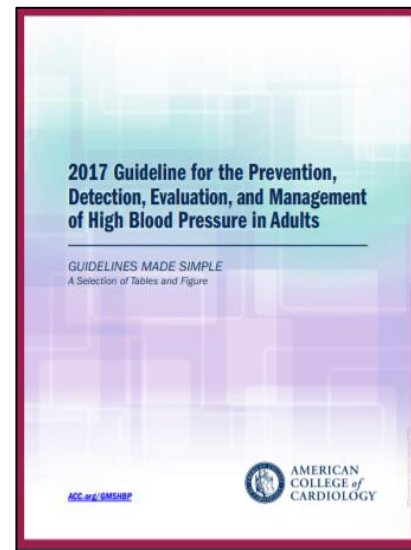
There are non-empirical ways of predicting response, such as using renin measurements¹¹ or the 'Cambridge ABCD rule'.⁹ Plasma renin can be measured,¹¹ usually in a research clinic setting—as a simple rule of thumb, younger and older patients can be assumed to have high or low renin levels, respectively.⁹ The high renin form of hypertension is more responsive to drugs that block the renin-angiotensin system, whereas the low renin form is more responsive to diuretics and calcium channel blockers. Nevertheless, these strategies only serve to select the best monotherapy for a patient. A survey of the utilisation of antihypertensive drugs in the Hypertension Clinic at Queen Mary Hospital showed that 60% of patients were taking more than one antihypertensive agent.¹² Rather than combining drugs on an empirical basis, there are rational combinations of drugs with different and complementary modes of action that should be considered. Examples of recognised combinations include diuretics and β -blockers,¹³ diuretics and ACEIs,¹⁴ diuretics and angiotensin receptor blockers (ARBs),¹⁵ and ACEIs and calcium channel blockers.¹⁶

The combination of a diuretic and a blocker of the renin-angiotensin system such as an ACEI or an ARB is synergistic in terms of efficacy. In terms of side-effects, combination therapy is also better. For example, diuretics stimulate the renin-angiotensin system and can cause hypokalaemia in up to 50% of patients.¹⁷ This is reduced by the addition of an ACEI or ARB.^{14,17} In general, the enhanced antihypertensive efficacy of synergistic combinations allows lower doses of ingredient drugs with fewer dose-dependent adverse effects.

Evidence-based therapy

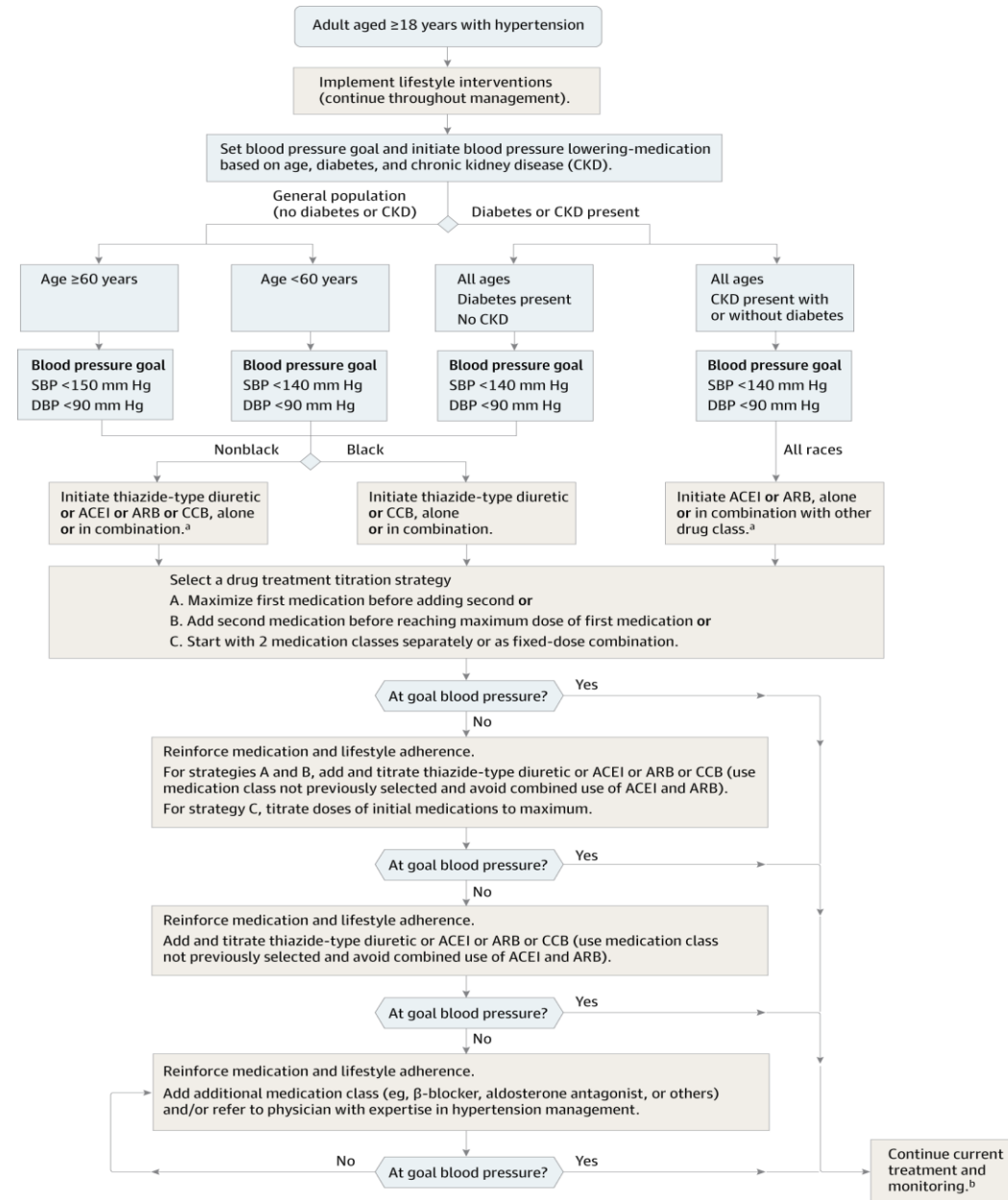
Most of the early hypertension trials employed diuretics in combination with another agent, usually a potassium-

International hypertension guidelines



1. James PA et al. *JAMA*. 2014;311(5):507-520.
2. Whelton PK et al. *Circulation*. 2018;138(17):e484-e594.
3. Williams B et al. *Eur Heart J*. 2018;39(33):3021-3104.
4. Unger T et al. *Hypertension*. 2020;75(6):1334-1357.

JNC VIII Guideline: Treatment algorithm



ACC/AHA guideline: Treatment algorithm

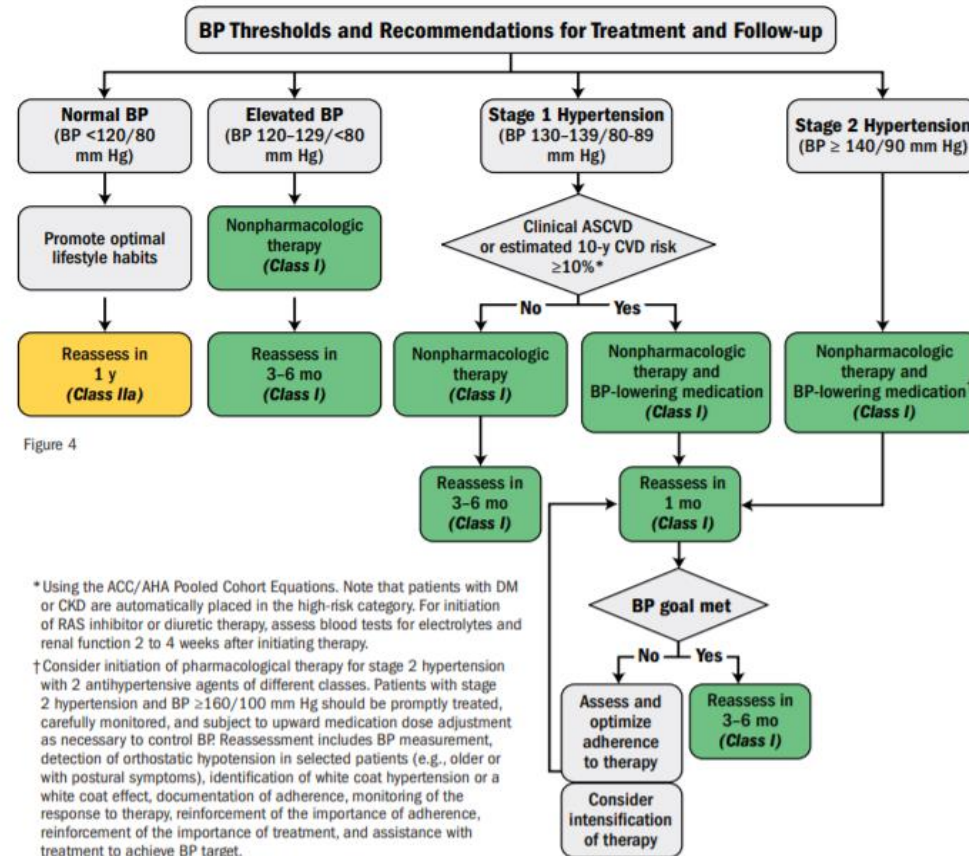
BP

GUIDELINES MADE SIMPLE

[Back to Table of Contents](#)

2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

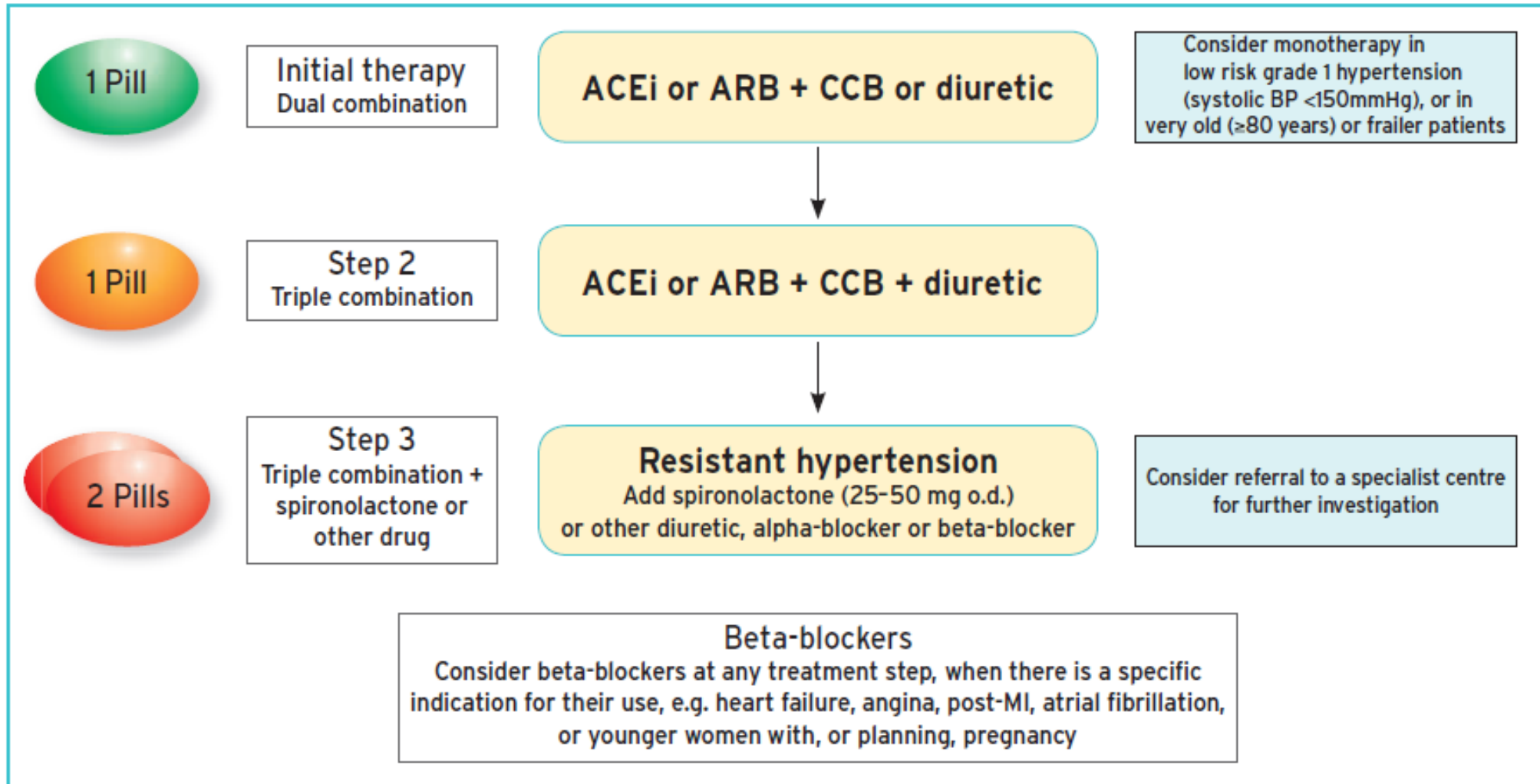
Blood Pressure (BP) Thresholds and Recommendations for Treatment and Follow-Up



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ESC/ESH guideline: Treatment algorithm



NEW

ISH guideline

- Published in May 2020
- Last update in 2013
- Written by global experts
- Applicable globally
- Developed based on evidence and fit for use in both high and low socio-economic countries (Optimal and Essential goals)

Guidelines

2020 International Society of Hypertension global hypertension practice guidelines

Thomas Unger^a, Claudio Borghi^b, Fadi Charchar^{c,d,e}, Nadia A. Khan^{f,g}, Neil R. Poulter^h, Dorairaj Prabhakaran^{i,j,k}, Agustin Ramirez^l, Markus Schlaich^{m,n}, George S. Stergiou^o, Maciej Tomaszewski^{p,q}, Richard D. Wainford^{r,s,t}, Bryan Williams^u, and Aletta E. Schutte^{v,w}

ISH guideline: Classification of hypertension

ISH Category ¹	Systolic (mmHg)		Diastolic (mmHg)
Normal BP	<130	and	<85
High-normal BP	130-139	and/or	85-89
Grade 1 Hypertension	140-159	and/or	90-99
Grade 2 Hypertension	≥ 160	and/or	≥100

ISH guideline: Blood pressure target



Aim for BP Control within 3 month

Essential

- Target BP reduction at least 20/10mmHg, ideally to <140/90mmHg

Optimal

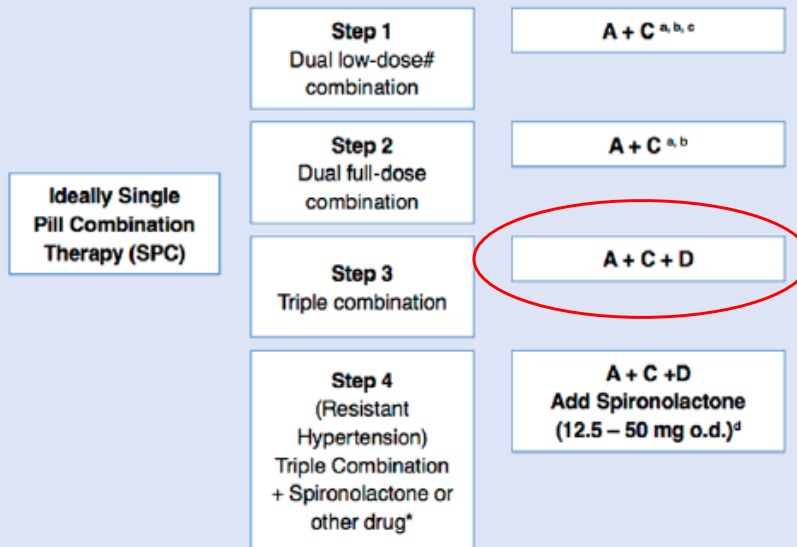
- <65 years old, BP target <130/80mmHg if tolerated (but >120/70mmHg)
- ≥ 65 years old, BP target <140/90mmHg but consider an individualized BP target in the context of frailty, independence and likely tolerability of treatment

ISH Guideline: Treatment algorithm

ESSENTIAL

- Use whatever drugs are available with as many of the ideal characteristics (see **Table 9**) as possible.
- Use free combinations if SPCs are not available or unaffordable
- Use thiazide diuretics if thiazide-like diuretics are not available
- Use alternative to DHP-CCBs if these are not available or not tolerated (i.e. Non-DHP-CCBs: diltiazem or verapamil).

OPTIMAL



- Consider monotherapy in low risk grade 1 hypertension or in very old (≥ 80 yrs) or frailer patients.
- Consider A + D in post-stroke, very elderly, incipient HF or CCB intolerance.
- Consider A + C or C + D in black patients.
- Caution with spironolactone or other potassium sparing diuretics when estimated GFR < 45 ml/min/1.73m² or K⁺ > 4.5 mmol/L.

A = ACE-Inhibitor or ARB (Angiotensin Receptor Blocker)
 C = DHP-CCB (Dihydropyridine -Calcium Channel Blocker)
 D = Thiazide-like diuretic

Supportive references: A + C,^{69,70} Spironolactone,⁷¹ Alpha-blocker,⁷² C + D⁷³.

* Alternatives include: Amiloride, doxazosin, eplerenone, clonidine or beta-blocker.

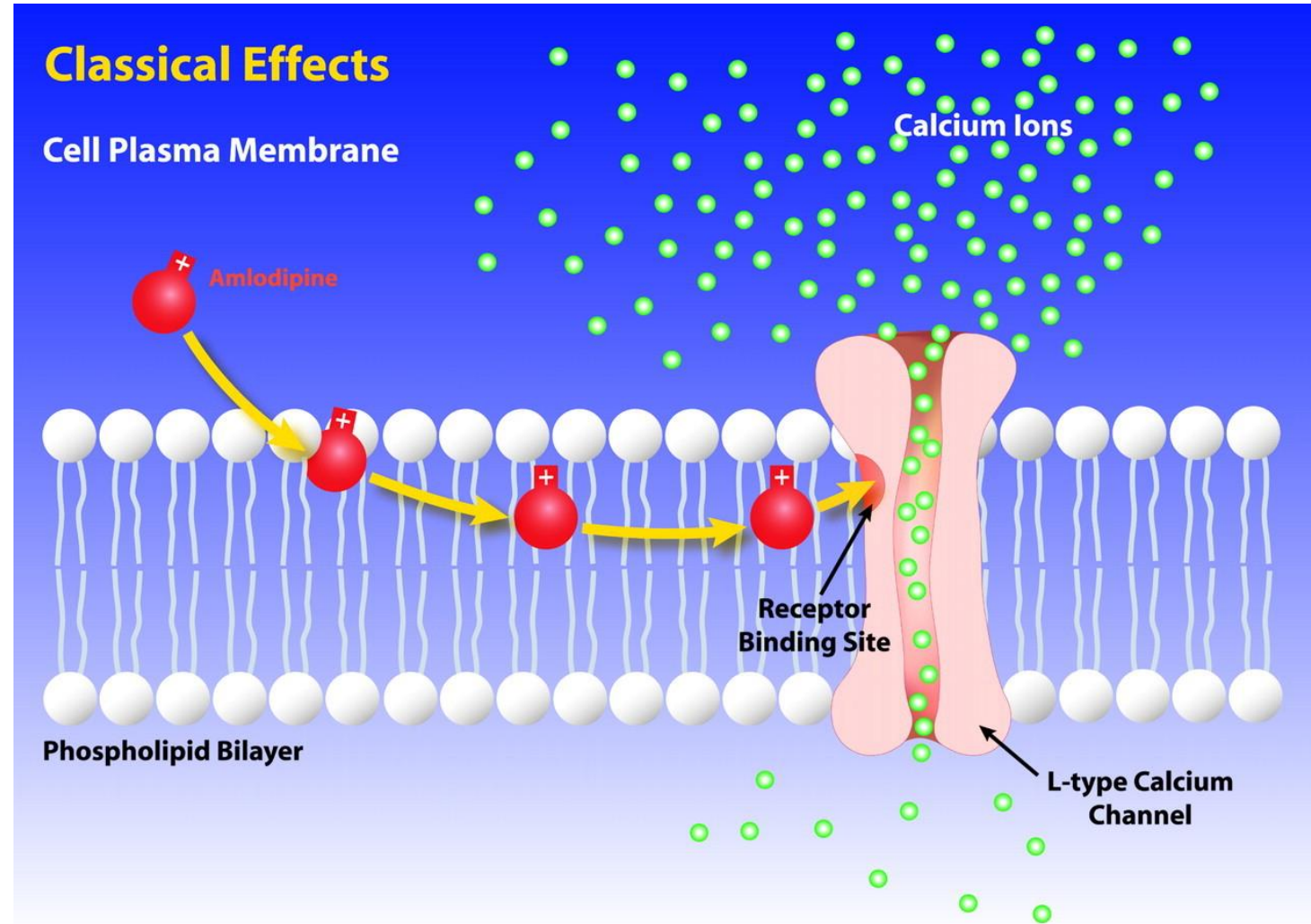
low-dose generally refers to half of the maximum recommended dose

RCT-based benefits between ACE-I's and ARB's were not always identical in different patient populations. Choice between the two classes of RAS-Blockers will depend on patient characteristics, availability, costs and tolerability.

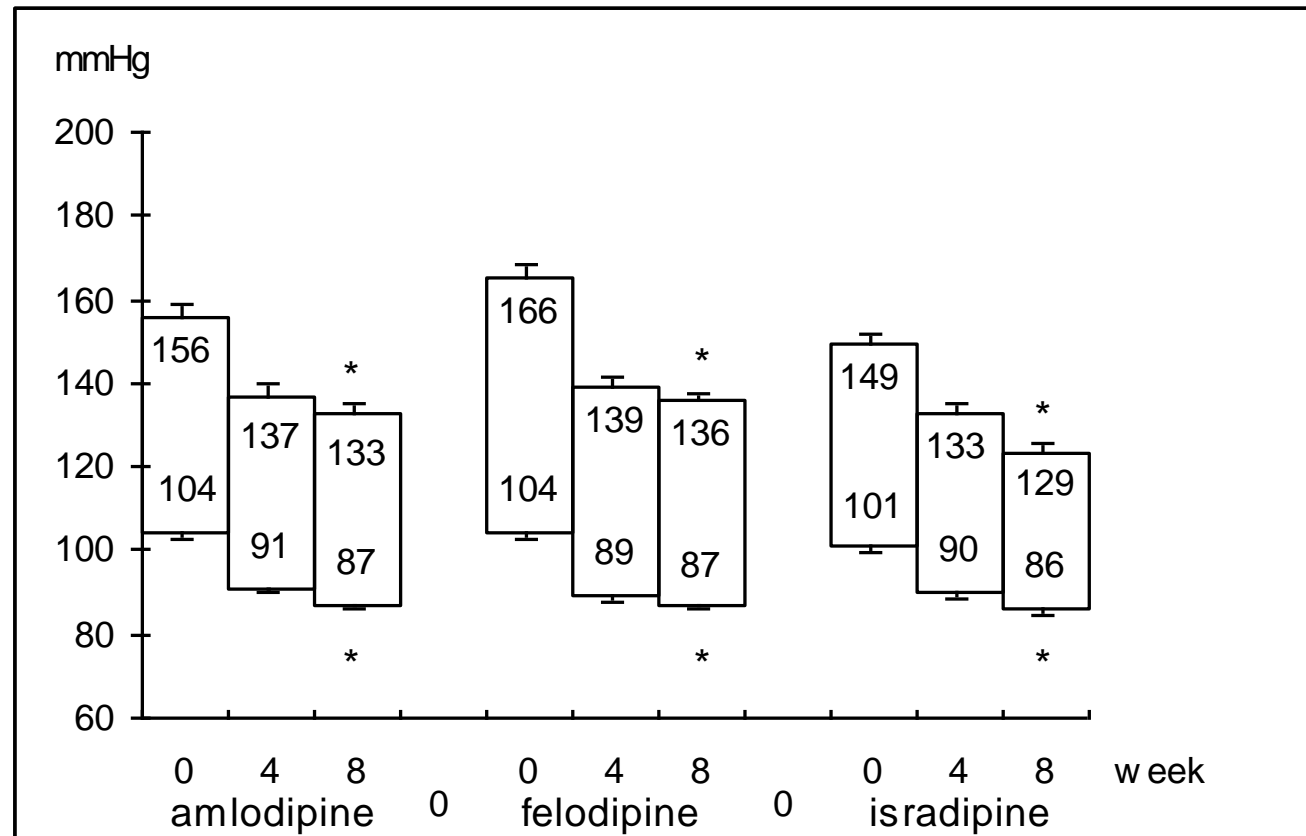


Treatment options

Calcium channel blocker: Mechanism of action

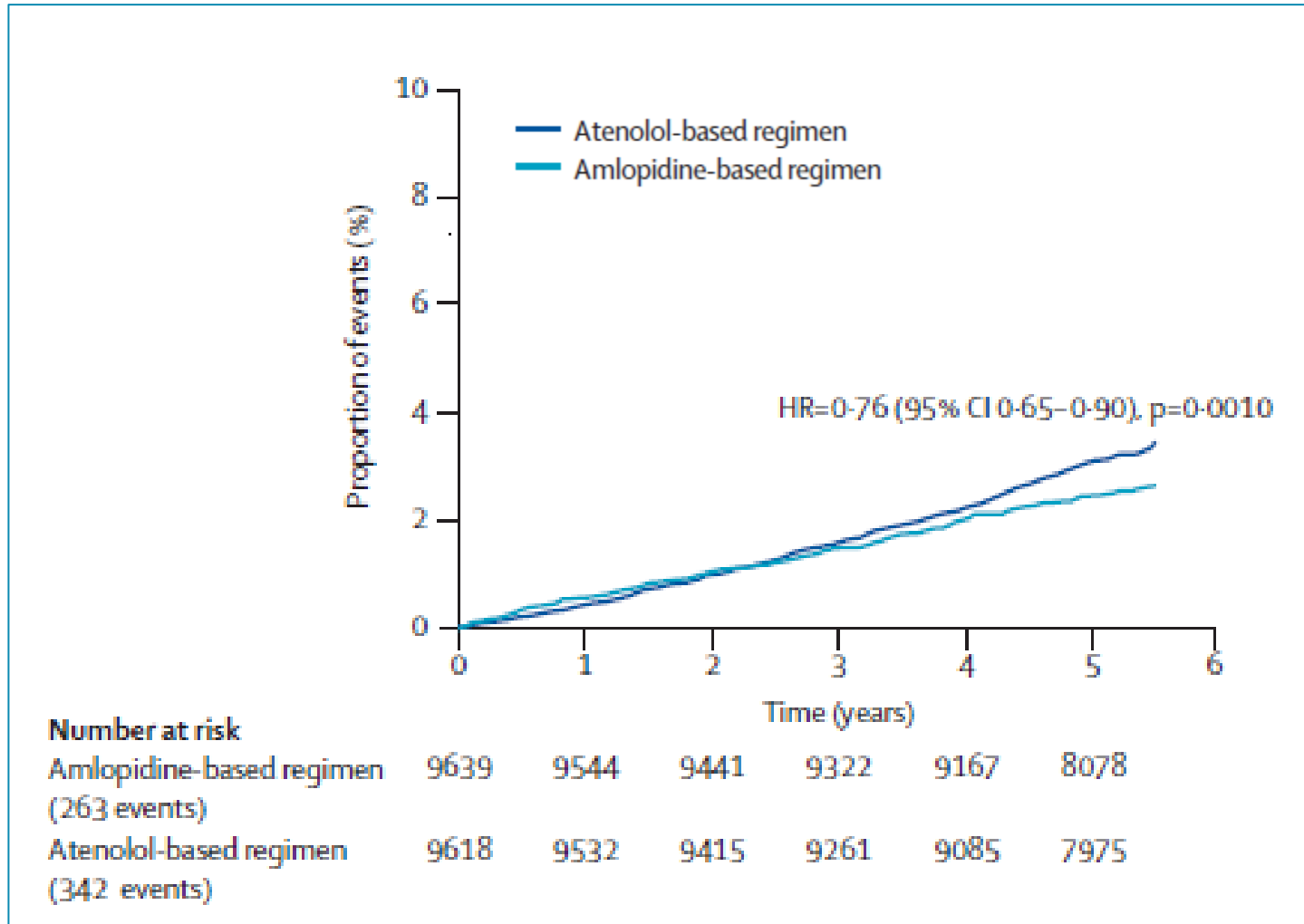


Calcium channel blocker: Efficacy



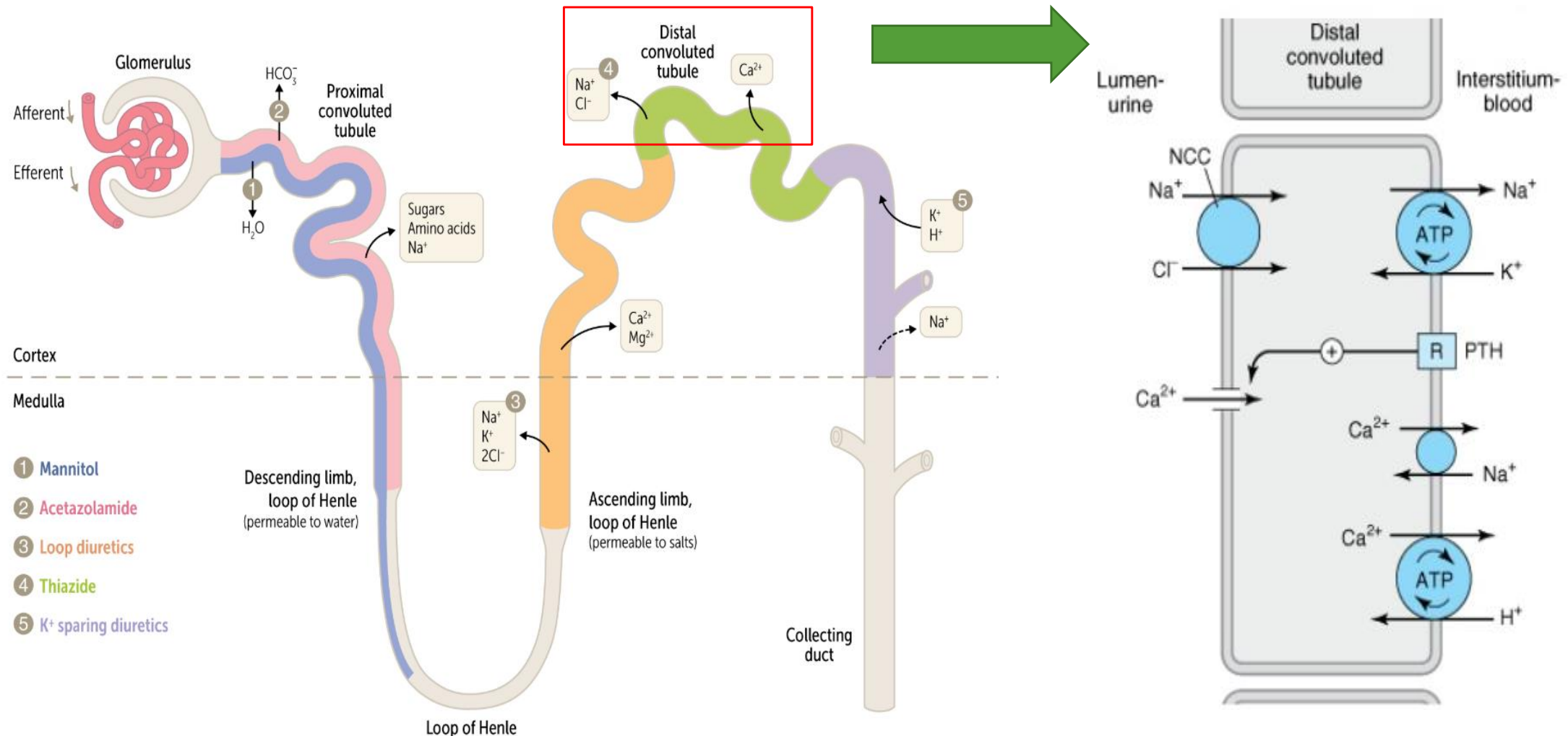
Cheung et al. 1998

Calcium channel blocker: Cardiovascular mortality



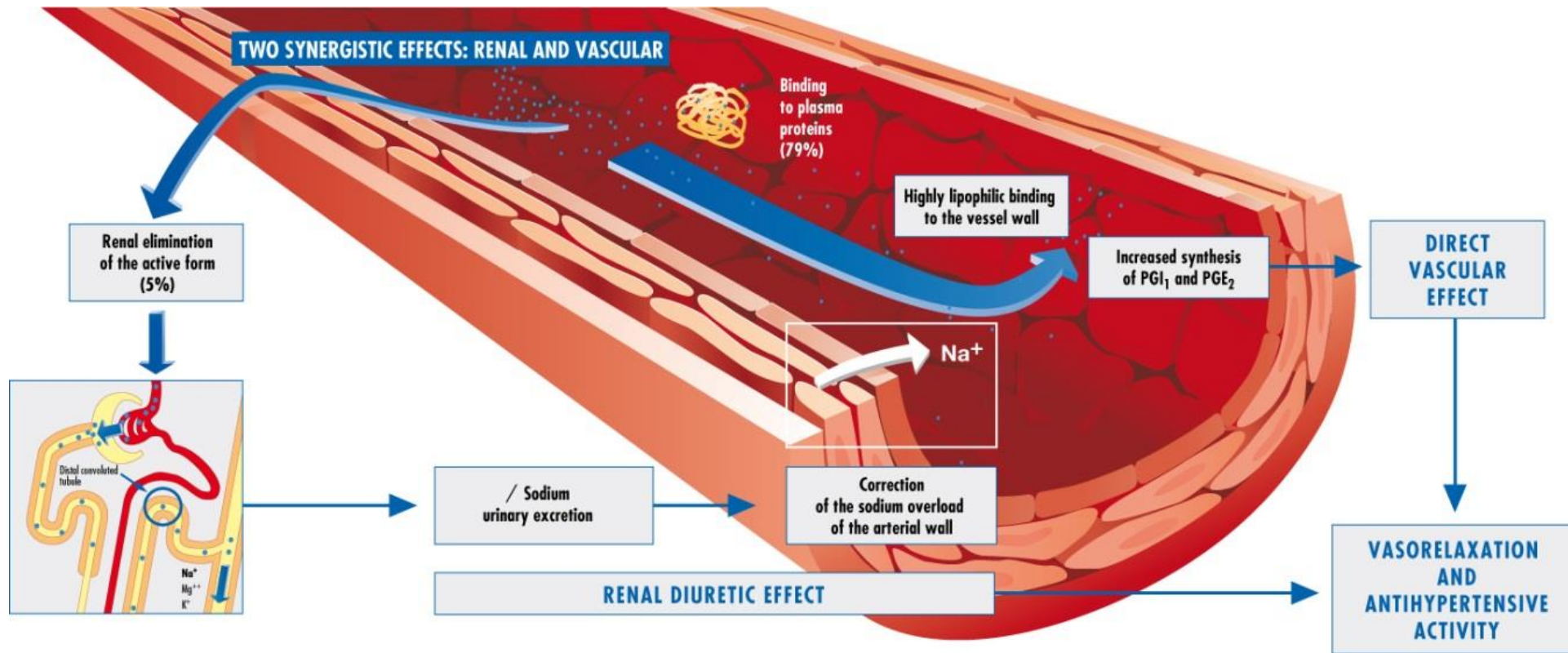
Thiazide: Thiazide-type and thiazide-like diuretics

– Sites of action

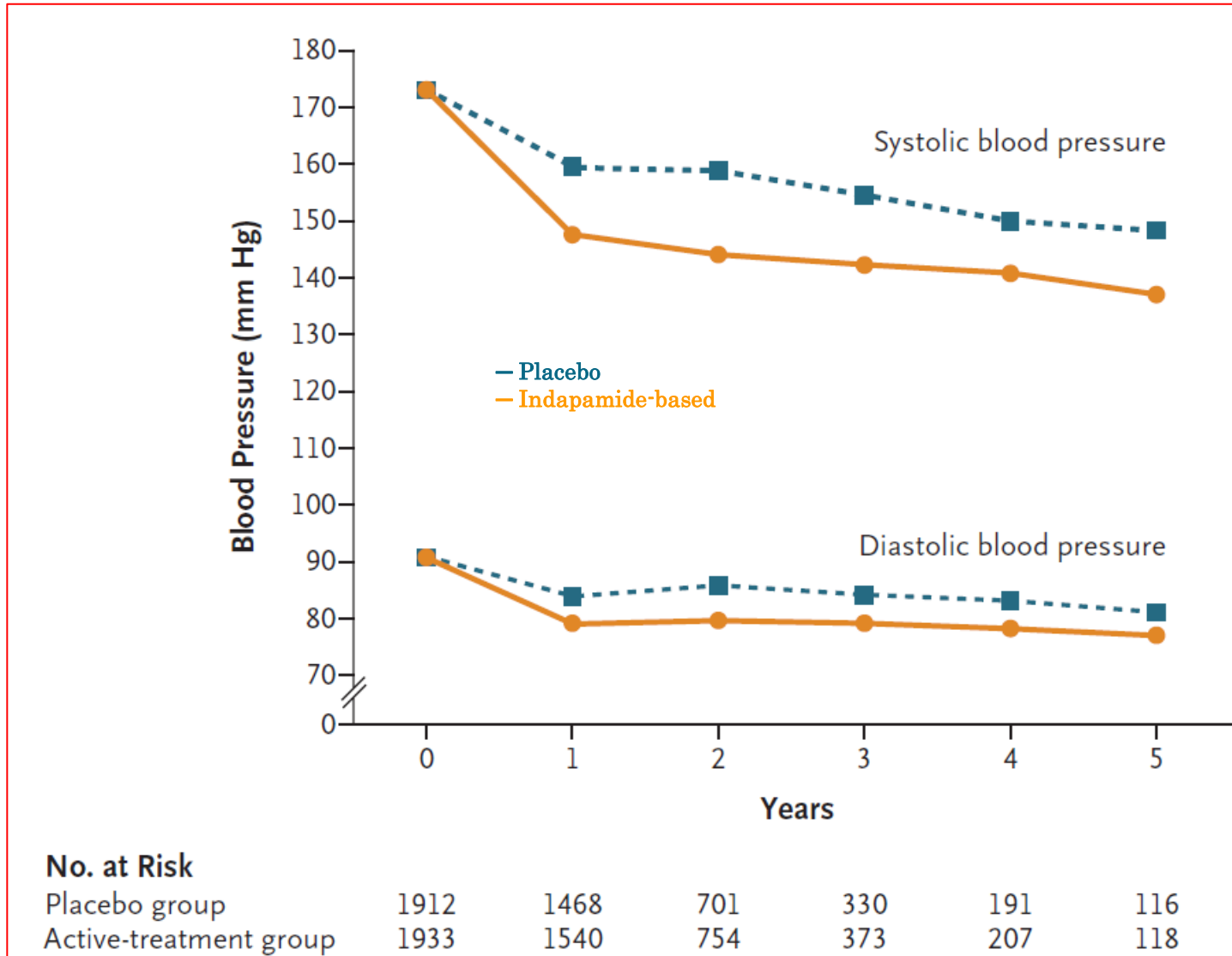


Thiazide-like diuretic:

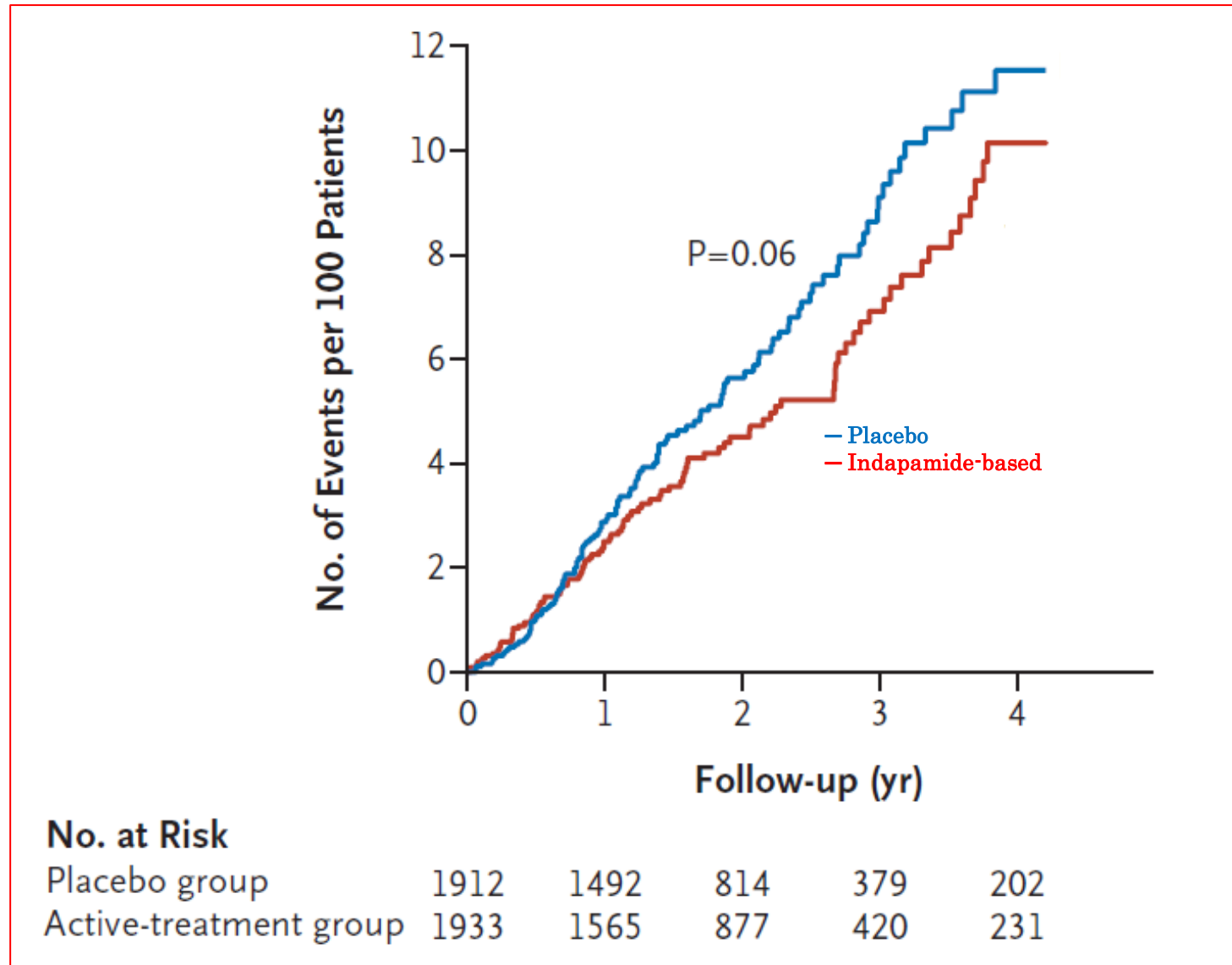
Mild diuretic effect plus direct vascular effect



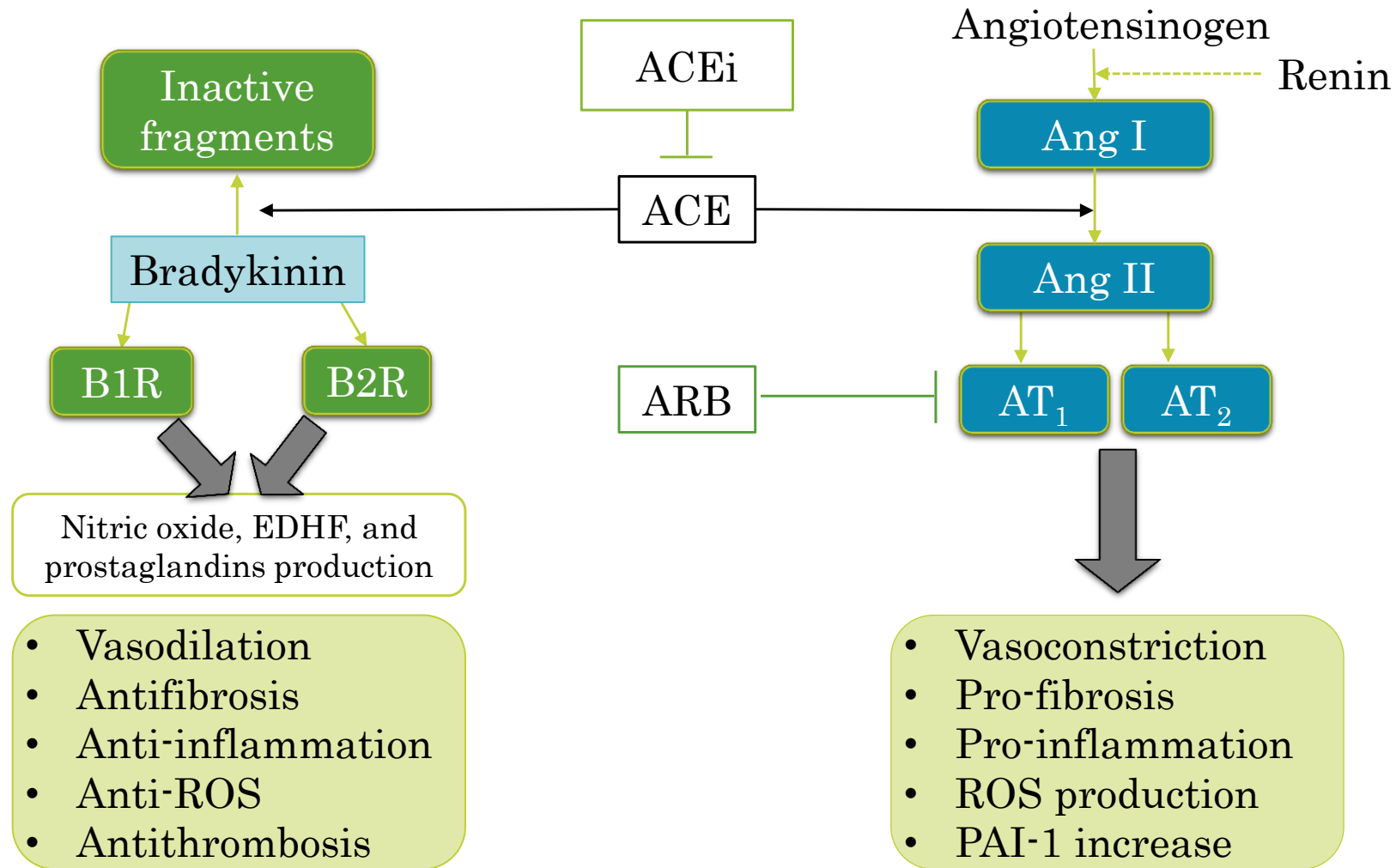
Thiazide-like diuretic: Efficacy



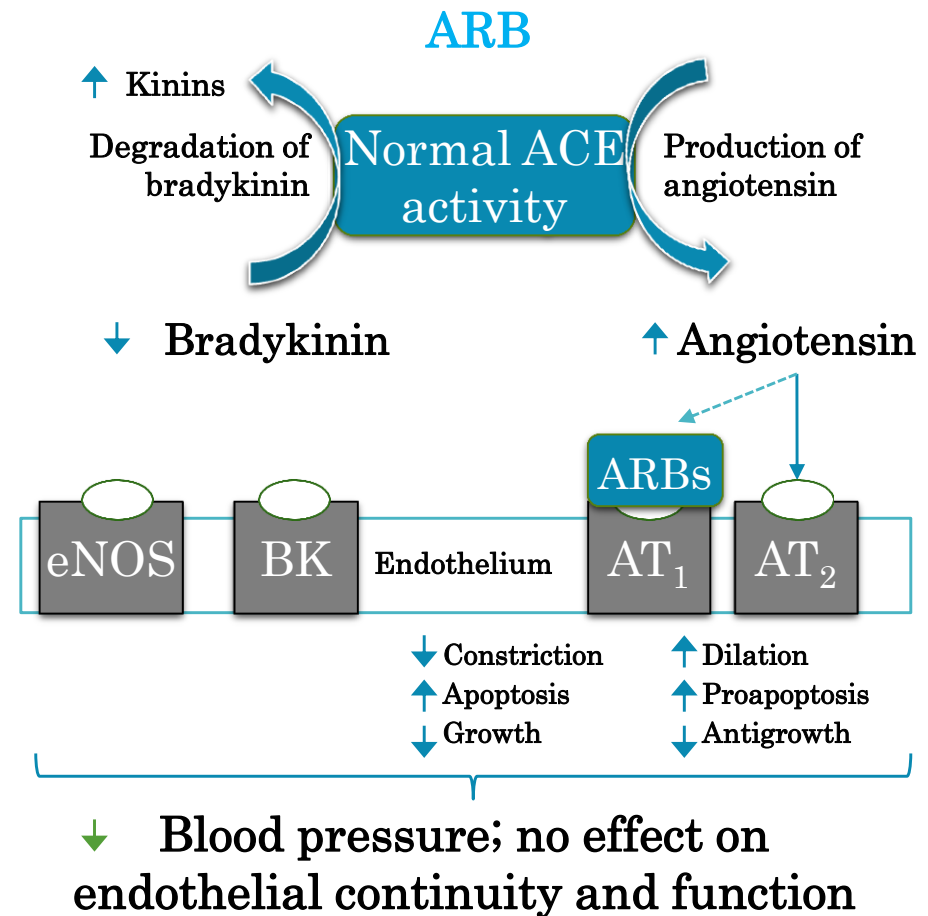
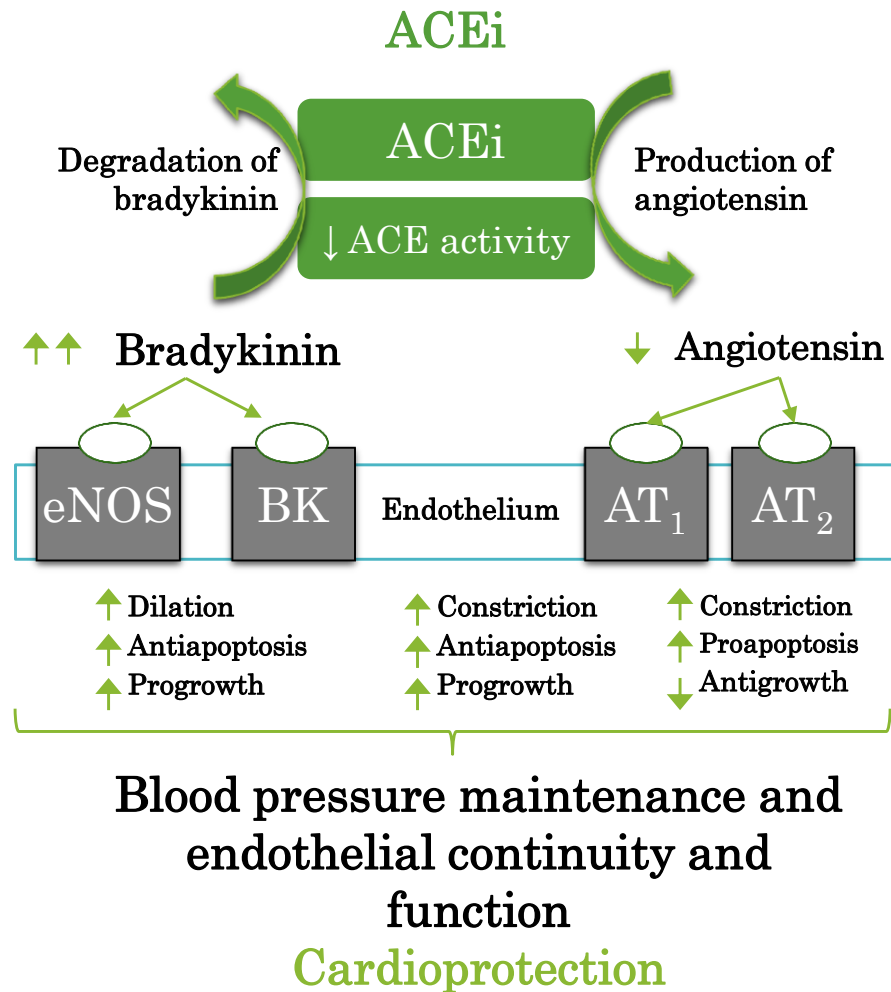
Thiazide-like diuretic: Cardiovascular mortality



ACEi and ARBs: Different Mechanisms, Different Effects



Difference in outcomes between ACEi and ARBs



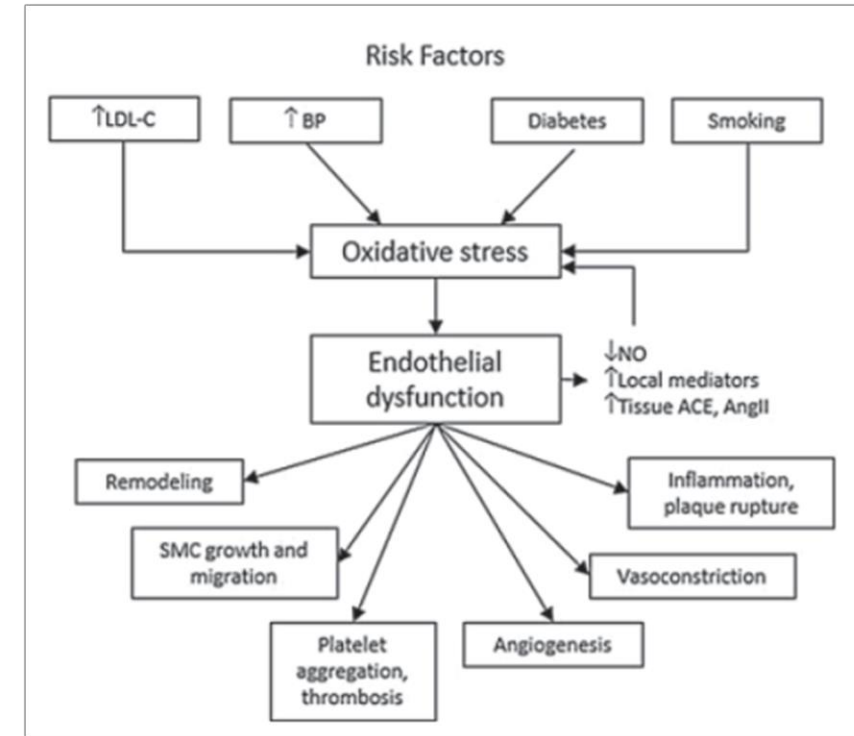
Perindopril improves the endothelial function

Bradykinin¹

- Contributes to net CV benefits
- Potentiates the fibrinolytic balance
- Enhances ischemic preconditioning
- Improves endothelial function

Perindopril has greatest effect on bradykinin²

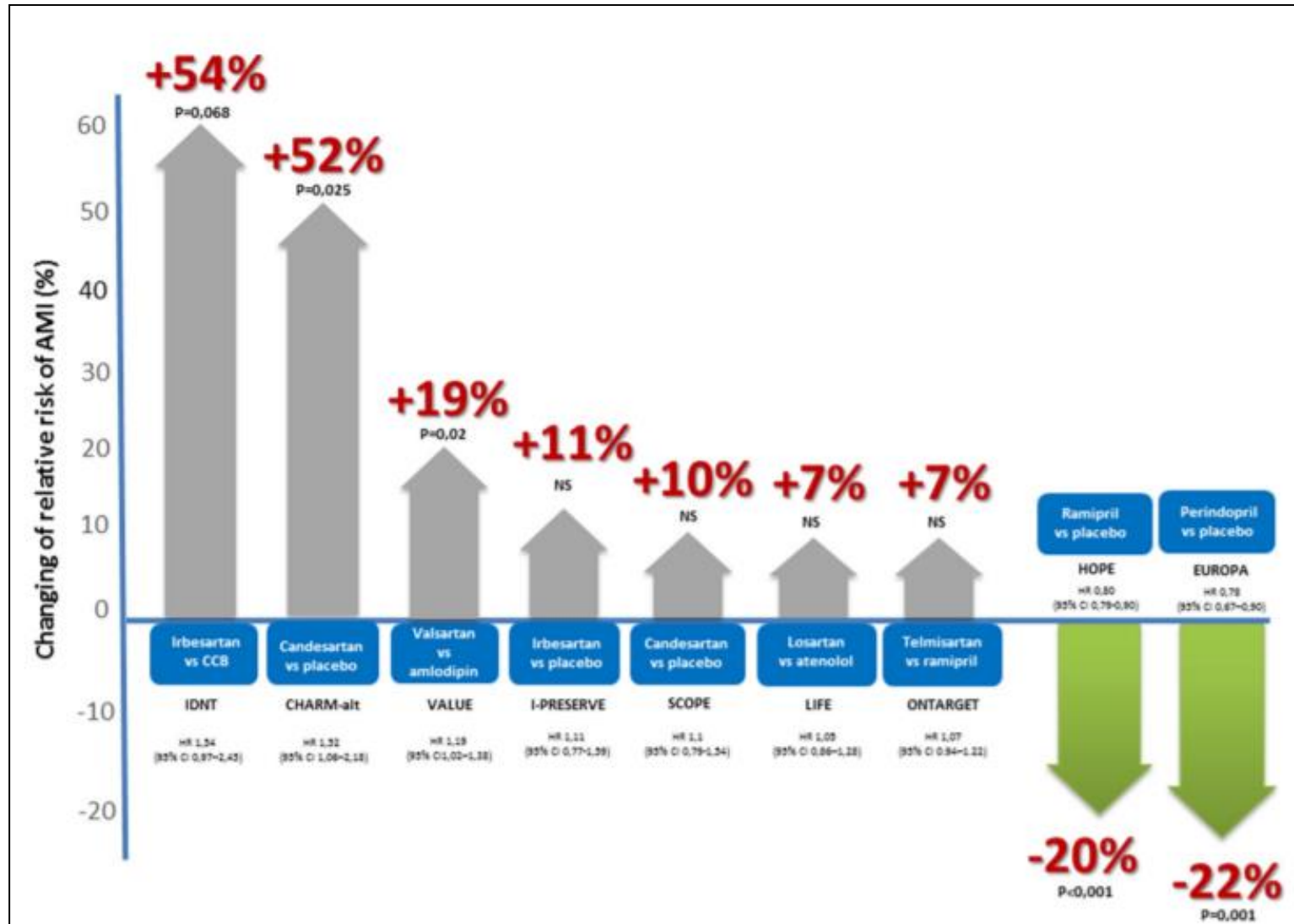
- Effective on a number of markers of endothelial dysfunction
- Provide benefits on endothelial protection



1. Ann SH, et al. *Int J Cardiol.* 2020;306:35-41.

2. Ancion A, et al. *Cardiol Ther.* 2019;8(2):179-191.

ACEi decreased the risk of acute myocardial infarction





Single-pill combination

Single-pill combinations are recommended by latest guidelines

ISH 2020

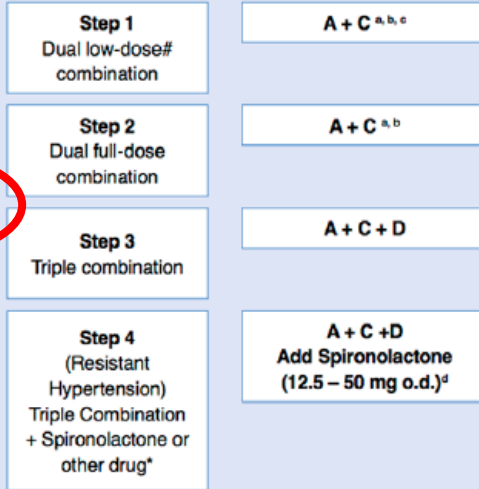
ESC/ESH 2018

ESSENTIAL

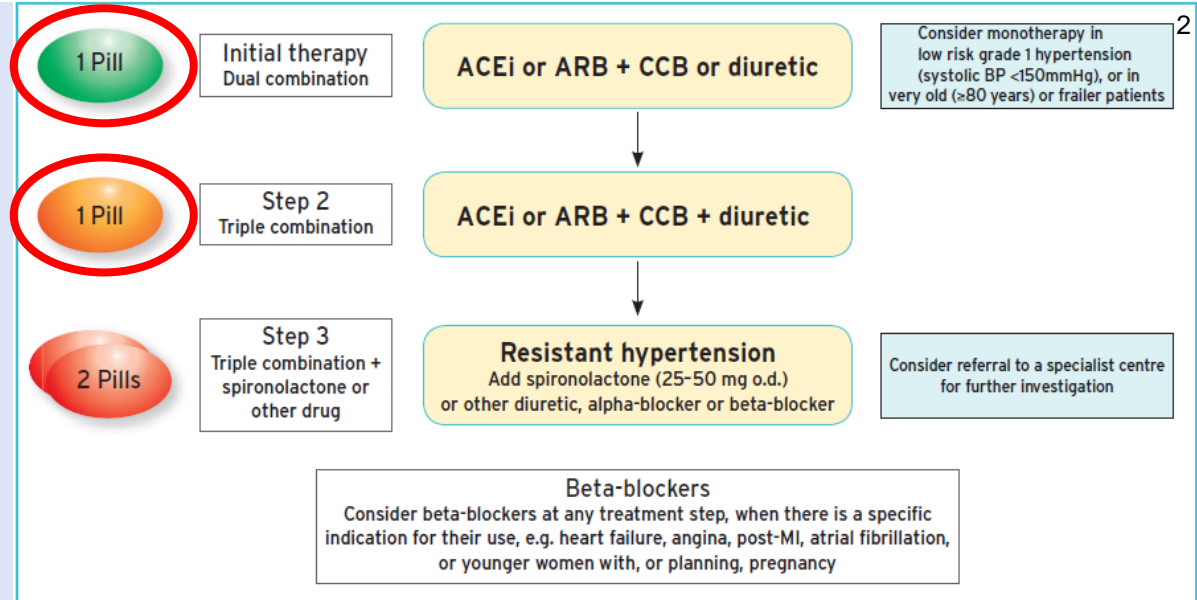
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OPTIMAL

Ideally Single Pill Combination Therapy (SPC)



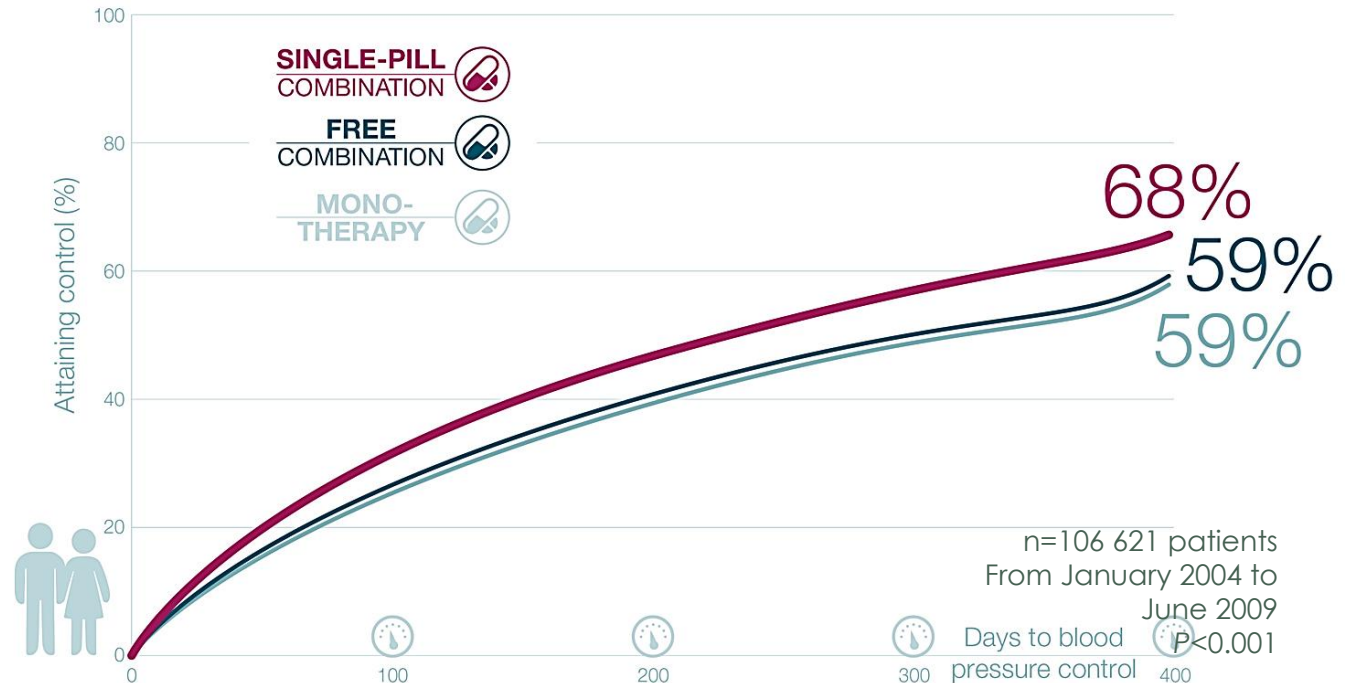
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2

Single-pill combinations are more effective and higher compliance than free combinations

- Use of single-pill combinations as initial therapy improves hypertension control and cardiovascular outcomes in the first year of treatment¹
- The use of single-pill combinations vs free combinations reduces the risk of discontinuing treatment by **73%**² ($P<0,001$)
- Single-pill combinations reduce the risk of noncompliance by **24%** vs free combinations³ ($P<0,001$)



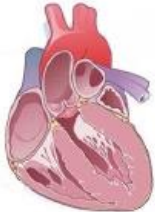
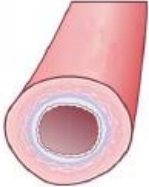




1. Egan BM et al. *Hypertension*. 2012;59:1124-1131.

2. Corrao G et al. *J Hypertens*. 2010;28:1584-1590.

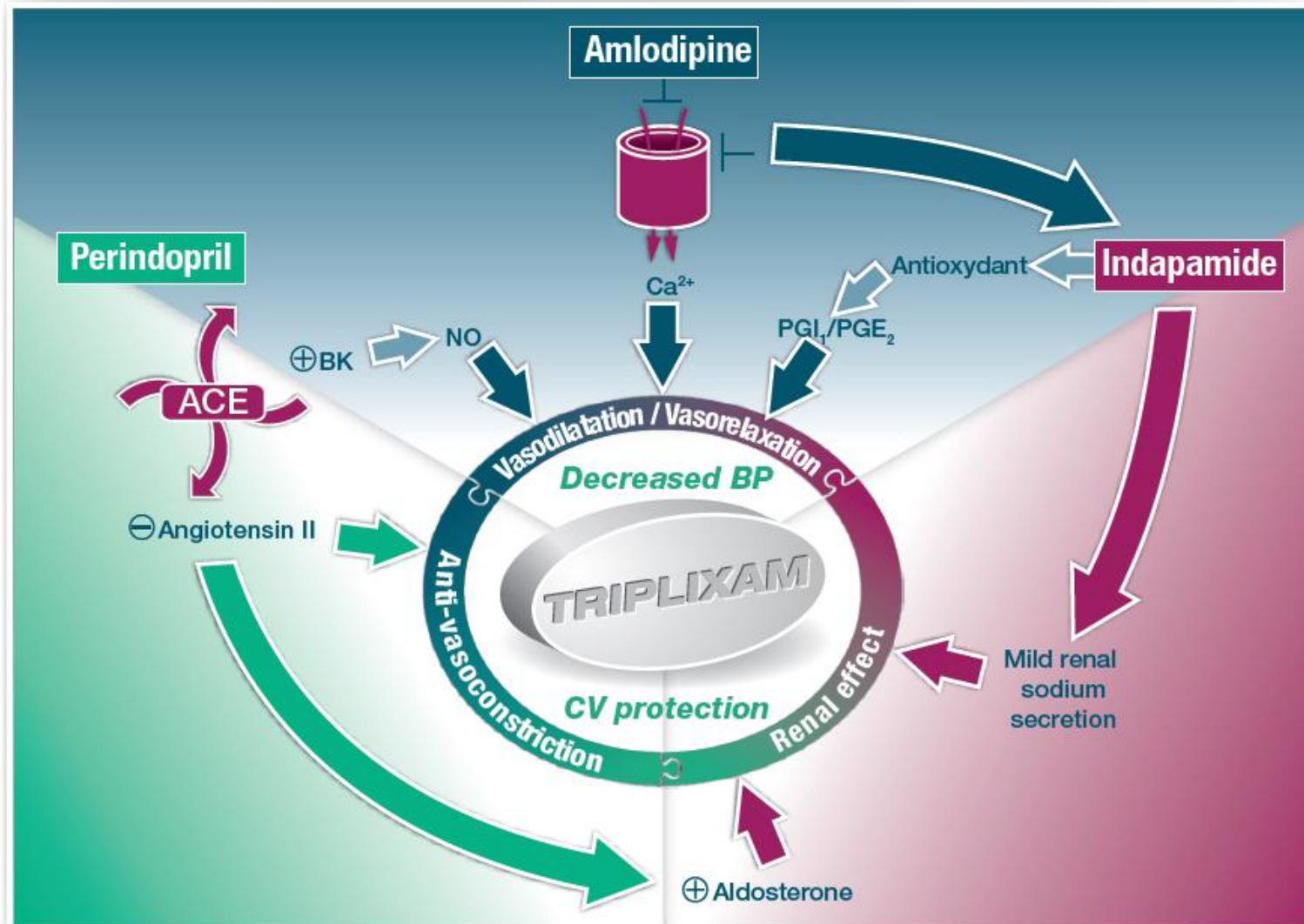
3. Bangalore S et al. *Am J Med*. 2007;120:713-719.

Perindopril /Indapamide / Amlodipine: 3 agents with 3 different protections

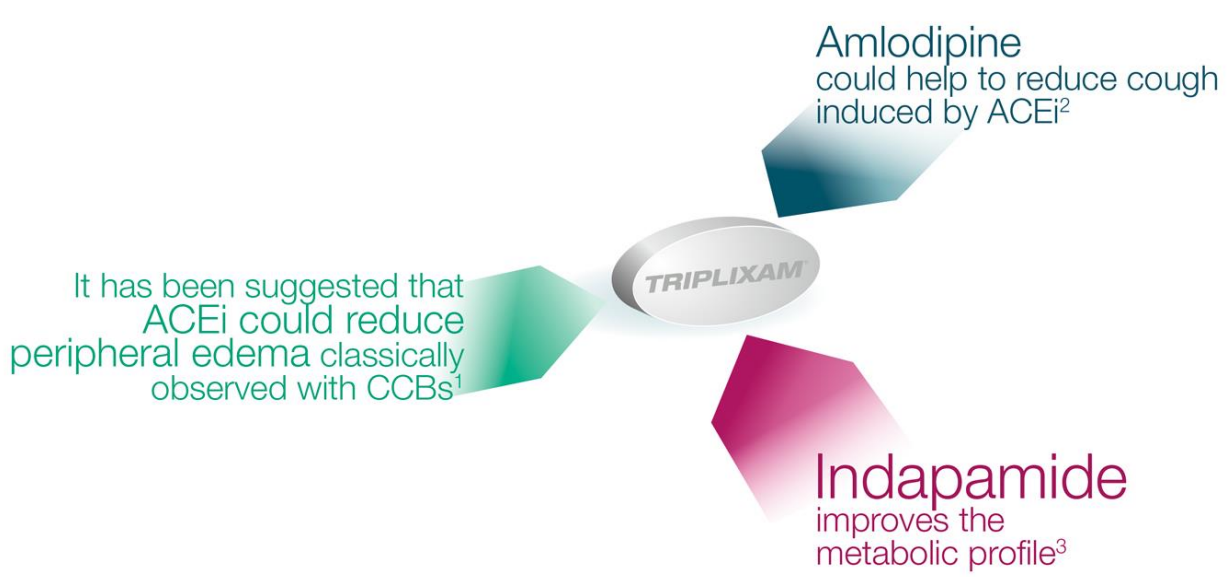
Evidence in favor of perindopril/amlodipine/indapamide

Cardioprotection	Vasculoprotection	SNCprotection
		
<p>LIVE </p> <p>PREAMI Perindopril and Remodeling in Elderly with Acute Myocardial Infarction</p> <p>EUROPA EUROPEAN TRIAL ON TREATMENT OF SYSTEMIC HYPERTENSION IN OVER 80 YEAR OLD PATIENTS</p> <p>Anglo-Scandinavian ascot Cardiac Outcomes Trial</p> <p>PICXEL</p> <p> chf</p>	<p>REASON #Effectiveness in regression of Arterial Calcification in a Large Obstructive Lung</p> <p>CAMELOT</p> <p>DAPHNET</p> <p>PREVENT</p> <p>ascot cafe </p>	<p>PATS</p> <p>PROGRESS PROGRESS: PROGRESS OF PROGRESSIVE RETINOPATHY IN HYPERTENSION</p> <p>HYVET HYPERTENSION IN VERY OLD PEOPLE TRIAL</p> <p>ALLHAT</p> <p>VALUE</p>

Perindopril / Indapamide / Amlodipine SPC Triplixam: 3 complementary modes of action



Three complementary compounds for an optimized tolerability

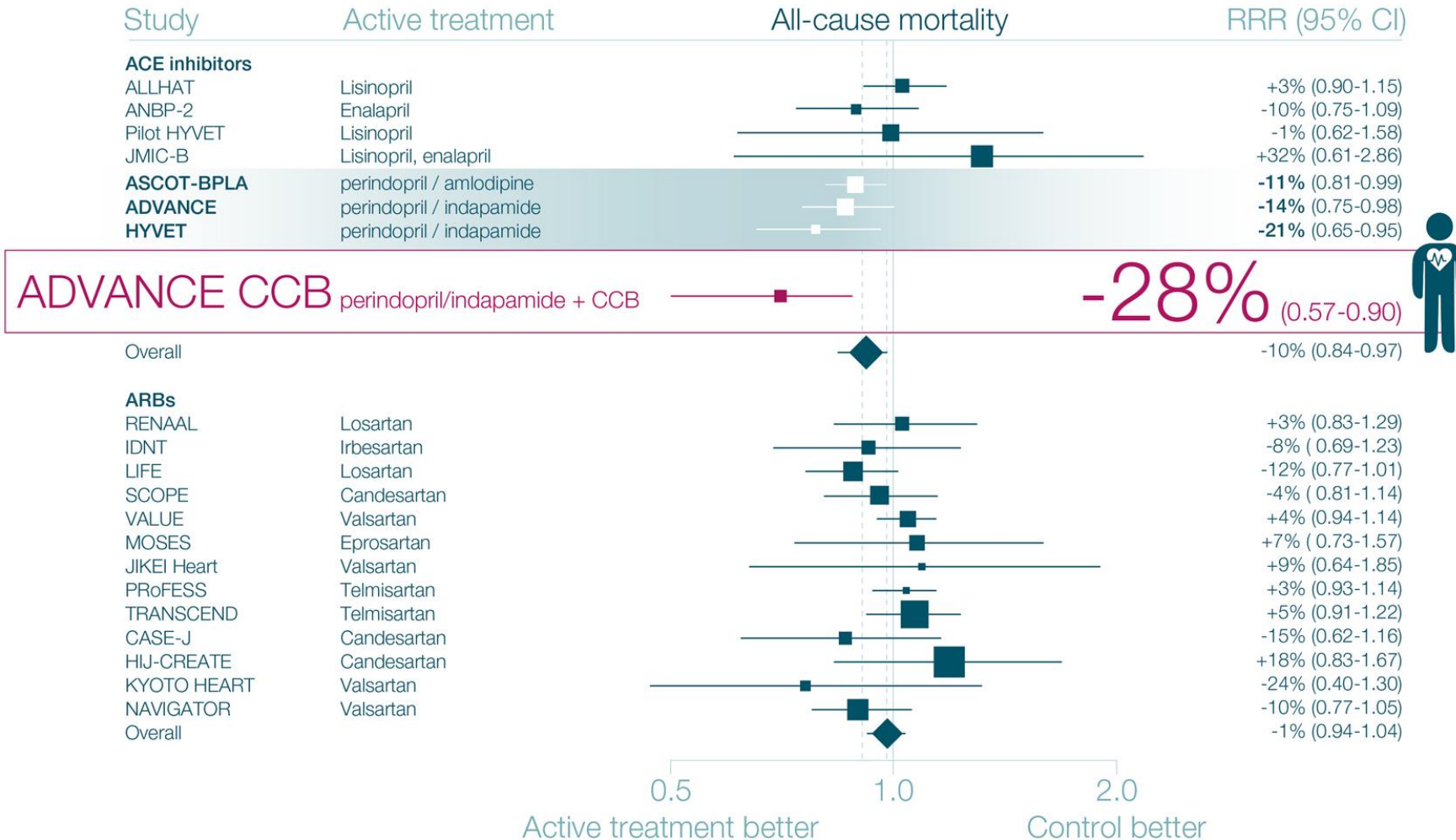


PIANIST

HIGHEST DOSAGE*

Parameter	Patients with an event after 4 months (%)
Cough 	0.08%
Edema 	0.2%
Hypotension 	0.1%

The rational choice for mortality reduction¹⁻²

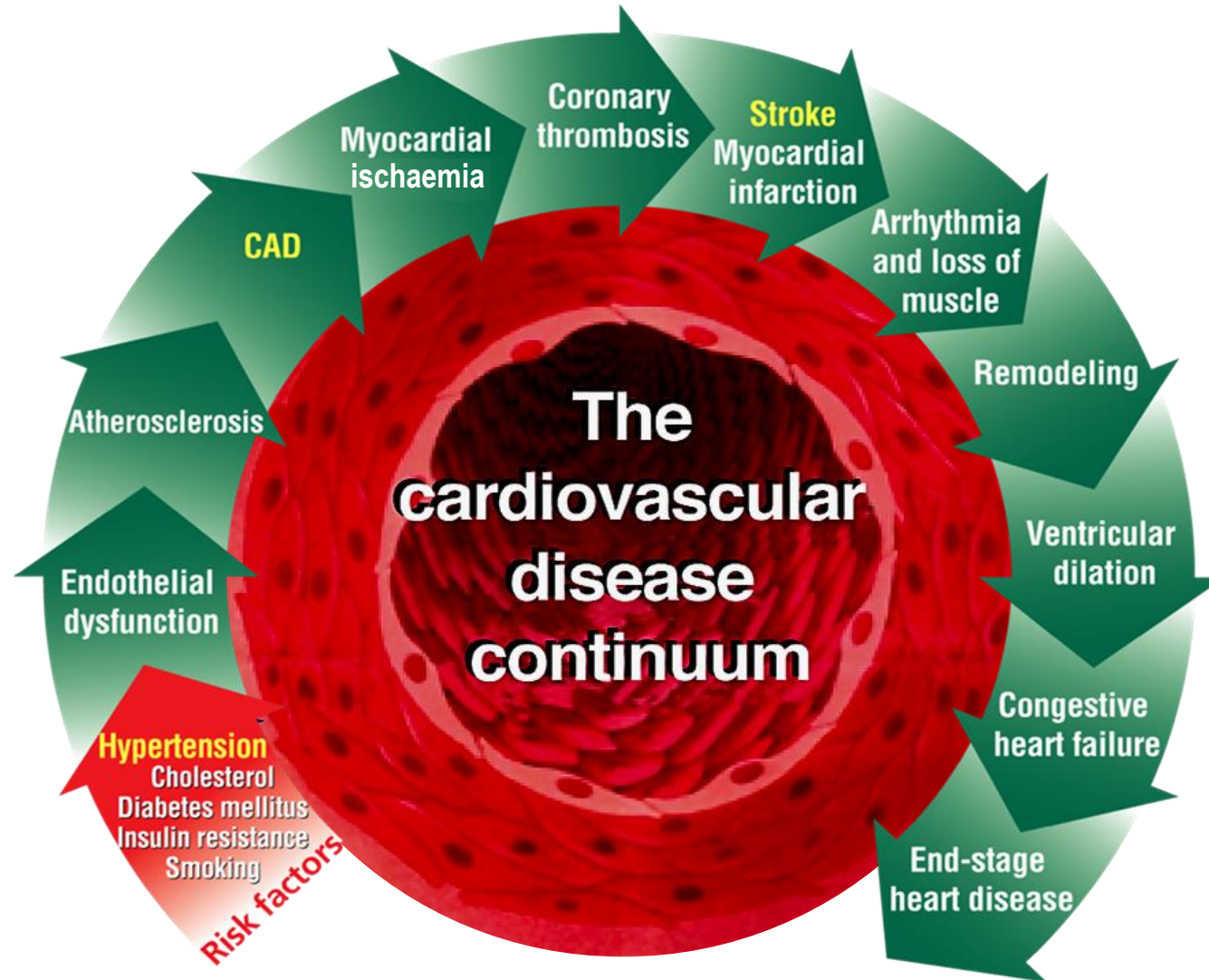


1. Chalmers J et al. *Hypertension*. 2014;63:259-264
 2. van Vark LC et al. *Eur Heart J*. 2012;33:2088-2097.

Take-home messages

- Hypertension is a significant health problem in Hong Kong and globally
- Latest guidelines (ISH & ESC/ESH) endorsed single-pill combination (SPC) therapy
- ACEi and ARB have different mechanisms and thus different effects such as outcome data and endothelial function
- A new SPC: Perindopril/Indapamide/Amlodipine has proven CV outcome and strong efficacy in lowering blood pressure over 24H
- The 3 different mechanisms of action allow balance and/or counteract some pharmacological effects with improved tolerability

Hypertension in the Cardiovascular Continuum – Risk Factor of Development of CAD and HF





Q & A