HEARTS IN THE AMERICAS

Regional Workshop

Punta Cana, Dominican Republic

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Pan American Health Organization
World Health Organization
Americas

PAHO

CDC
Centers for Disease Control and Prevention

World Health Organization

RESOLVE TO SAVE LIVES
An initiative of Vital Strategies

Sociedad Interamericana de Cardiología
SIAC

HEARTS IN THE AMERICAS
Regional Workshop

HEARTS Module E (Evidence-Based Medicine): Incorporating Fixed-Dose Combination Medications

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Learning Objectives

- To understand the barriers that contribute to poor hypertension control, especially “clinical/therapeutic Inertia”.
- To review the Evidence-Based Protocols (E) module of the HEARTS Technical Package in the management of hypertension (diabetes).
- To develop and implement a standardized and simple drug formulary and treatment algorithm in the treatment of hypertension.
- To delineate the advantages and develop, chose, and implement a plan for incorporating FDC drug treatment in the initial management of hypertension.

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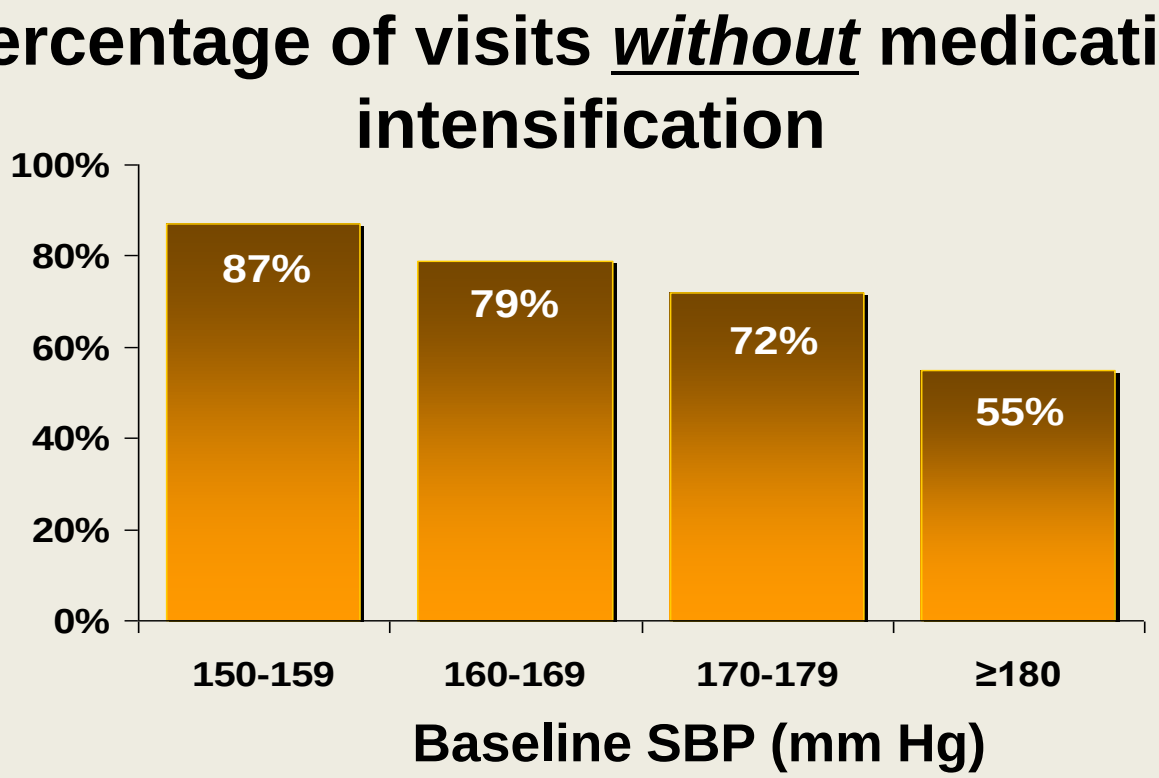
Barriers to Blood Pressure Control

- Patient
  - Limited access to treatment
  - POOR ADHERENCE TO TREATMENT
- Health Care Provider
  - Raised blood pressure attributed to “white coat” hypertension
  - Reluctance to treat an asymptomatic condition
  - Lack of adequate time with patient
  - THERAPEUTIC INERTIA
  - LACK OF ADHERENCE TO TREATMENT GUIDELINES
- Health Systems
  - Failure to delegate responsibility to non-physicians
  - Inappropriate follow-up
  - Absence of feedback to clinicians
  - Issues related to supply, distribution, and cost of medications
  - COMPLEX MEDICATION REGIMENS

Clinical Inertia

*The failure of health care professionals to **initiate** or **intensify** treatment when indicated*

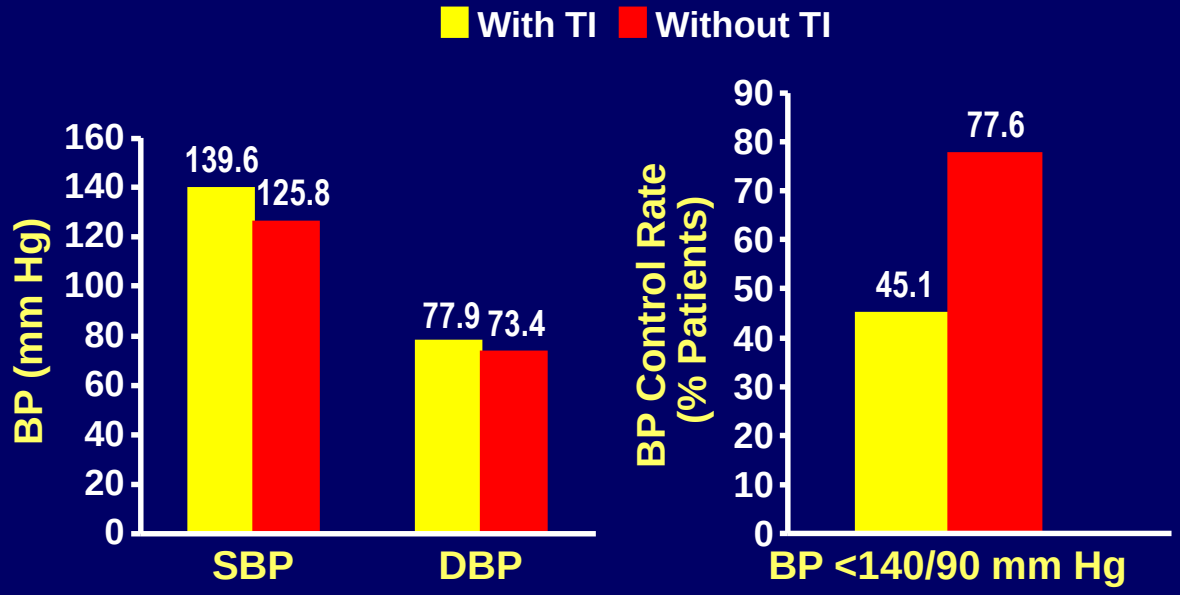
The Closer to Goal the Less Providers Initiate or Change Treatment



Adapted from Andrade et al. Am J Manag Care. 2004;10:481-486

The Effect of Therapeutic Inertia: South Carolina

- 62 practices in N.C., S.C., Ga. Part of the Hypertension Initiative
- N=7,253 hypertensive patients that had ≥4 visits and ≥1 elevated BP
- Therapeutic inertia = SBP ≥140 mm Hg and/or DBP ≥90 mm Hg with no change in antihypertensive therapy
- Occurred in 86.9% of visits



Okonofua EC et al. Hypertension **2006;47:1-7**

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Combination treatment, as two single pills (SPC) or fixed-doses in one pill (FDC), in hypertension

- FDC in the initial treatment of hypertension is **NOT NEW!**
- U.S. Veterans Administration Cooperative Studies
- Used: Hydrochlorothiazide + Reserpine + Hydralazine
- All three agents were in a single pill (FDC)-Ser-Ap-Es

Materson et al. Hypertension 1990: 15; 348-360

Most Guidelines Recommend the Initiation of Two Drugs at Some Point in Hypertension Management

- *Consider initiating therapy with two drugs in patients whose BP is >20/10 mmHg above goal*

"thereby increasing the likelihood of achieving goal BP in a timely manner….Multi-drug combinations often produce greater BP reduction at lower doses of the component agents resulting in fewer side effects. The use of fixed dose combinations may be more convenient and simplify the treatment regimen…."

- ***More than 2/3 of patients will require two or more agents***

Chobanian et al. JAMA 2003 JNC-7

European Society of Cardiology (ESC) and European Society of Hypertension (ESH)-Hypertension Guidelines (2018)

- The guidelines strongly proposed to concentrate on **improving** the current blood pressure treatment control rates.

- Proposed the use of combination pharmacologic therapy and where possible **fixed-dose combination** therapy (FDC) even as **initial treatment**.

Initial Classes of Medications for the Management of Hypertension

b-blockers should be included in the regimen if there is a compelling indication for a b-blocker

Diuretics

ACE inhibitors or ARBs

Calcium antagonists

JAMA 2014; 311(5): 507-520. 2014

Advantages of Combination Pharmacologic Therapy

- Most eventually need multiple drugs
- Greater efficacy (additive or synergistic)-improves blood pressure control rates
- Allows lower dosages of each of the 2 drugs
  - More effective than a higher dose of either single drug
  - Reduced side effects
- Simplified treatment regimen: better adherence
- Reduces clinical inertia
- When complementary drug classers are chosen, lowers BP equally across diverse demographic groups
- Economic benefits
  - Lower health care costs and fewer office visits

Mitigation of Side Effects

Renin angiotensin aldosterone system inhibition blunts many side effects of dihydropyridine calcium channel blockers

- Activation of the SNS leading to increased heart rate
- Pedal edema

Mitigation of Side Effects

Renin angiotensin aldosterone system (RAAS) inhibition blunts many of the side effects of diuretics and visa versa

- Activation of the sympathetic nervous system and RAAS system
- Hypokalemia
- Hyperglycemia
- Hyperuricemia

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Fixed-Dose Combination Pharmacologic Therapy to Improve Hypertension Control Worldwide: Clinical perspective and policy implications

Journal of Clinical Hypertension Volume 21, Issue 1: 2019

Donald J DiPette MD, Jamario Skeete, MD, Emily Ridley Pharm D, Norm RC Campbell MD, Patricio Lopez-Jaramillo MD, PhD, Sandeep P. Kishore MD, PhD, Marc G Jaffe, MD, Antonio Coca, MD, PhD, Raymond R Townsend MD, Pedro Ordunez, MD, PhD

Ideal Characteristics of Fixed Dose Combination (FDC) Medications in the Treatment of Hypertension

Characteristics
High Efficacy (blood pressure reduction)
Additive/synergistic blood pressure reduction
Supported by clinical trials
Mitigation of side-effects of either or both individual agents
Potential for wide availability and affordability
Safe and efficacious in diverse demographic settings (i.e. race, ethnicity, sex, geography, salt-sensitivity)
Daily dosing formulation
Scored tablet with multiple doses which permit split tablet dosing and easy titration

Adapted from: Patel P, Ordunez P, DiPette D, et al. Journal Clinical Hypertension 2016

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Steps in Selecting the Ideal Fixed Dose Combination Drug (DiPette et al. JCH, 2018)

Select the preferred and acceptable pharmacologic drug classes

Select the preferred and acceptable pharmacologic agents within each drug class

Select which preferred and acceptable combinations are available and affordable.

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Which Classes of Two-Drug Combinations?
(DiPette et al. JCH 2018)

- Renin angiotensin aldosterone system (RAAS) inhibitor-Calcium channel blocker (CCB): **Preferred** in the following order:

1. Angiotensin-Receptor Blocker (ARB)-CCB
2. Angiotensin-Converting Enzyme inhibitor (ACEI)-CCB
3. ARB-Thiazide or Thiazide-like diuretic (DIU)
4. ACEI-DIU

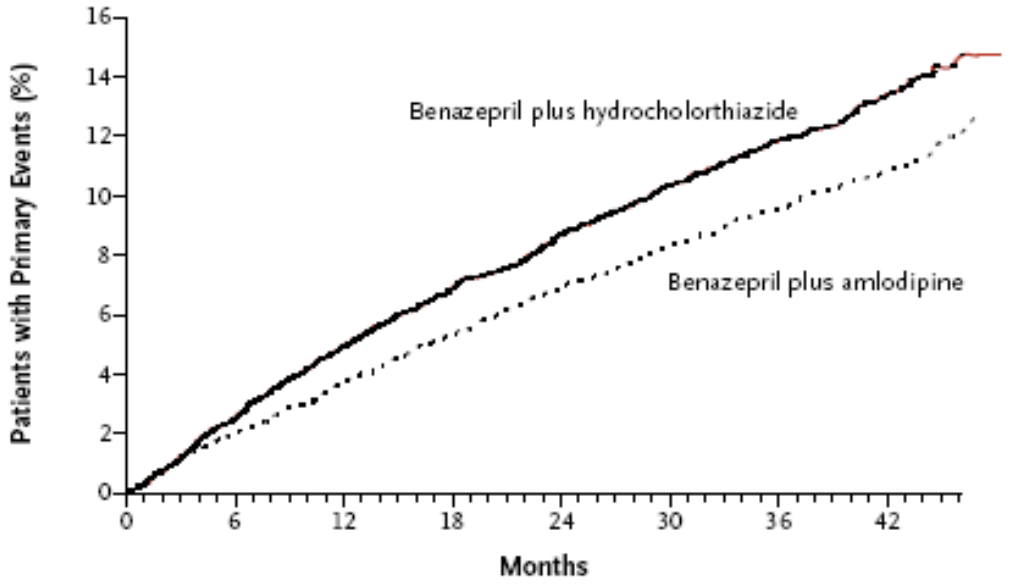
- CCB-DIU and all others **Not-Preferred** unless other indications

ACCOMPLISH Trial

- Benazepril and Amlodipine versus Benazepril plus Hydrochlorothiazide
- 11,506 high-risk patients
- Follow-up: 36 months (stopped early)

Jamerson et al. NEJM. 2008; 359:2417-28

ACCOMPLISH STUDY: Benazepril plus Amlodipine or Hctz for HTN in High-Risk Patients



No. at Risk							
Benazepril plus amlodipine	5512	5317	5141	4959	4739	2826	1447
Benazepril plus hydrochlorothiazide	5483	5274	5082	4892	4655	2749	1390

Figure 2. Kaplan–Meier Curves for Time to First Primary Composite End Point.

There were 552 patients with events (9.6%) in the benazepril–amlodipine group, as compared with 679 patients with events (11.8%) in the benazepril–hydrochlorothiazide group. The relative risk reduction was 20% (hazard ratio, 0.80; 95% CI, 0.72 to 0.90; P<0.001).

NEJM 2008: 359(23); 2417

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CREOLE STUDY: Protocol

(Ojji et al. NEJM 2019)

Black Africans with hypertension (140/90 mmHg or greater)

- Amlodipine (5 mg) + Perindopril (4 mg)
- Amlodipine (5 mg) + Hydrochlorothiazide (12.5 mg)
- Perindopril (4 mg) + Hydrochlorothiazide (12.5 mg)

- Doses doubled at 2 months
- Office BP: baseline, 2, 4, and 6 months
- 24 hr. ABPM: baseline and 6 months
- Primary outcome: change in mean systolic blood pressure on ABPM at 6 months

CREOLE STUDY: Results
(Ojji et al. NEJM 2019)

Change in ABPM mean systolic blood pressure at 6 months

- Amlodipine + Perindopril: decreased 18.1 mmHg
- Amlodipine + Hydrochlorothiazide: decreased 17.1 mmHg
- Perindopril + Hydrochlorothiazide: decreased 14.2 mmHg

- Blood pressure decrease with Amlodipine/Perindopril or Amlodipine/Hydrochlorothiazide significantly greater than Perindopril/Hydrochlorothiazide

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Building the Ideal Fixed Dose Combinations

(DiPette et al. J Clinical Hypertension 2018)

ARB + CCB	
Azilsartan OR Telmisartan OR Irbesartan	Amlodipine
ACE-I + CCB	
Lisinopril OR Ramipril OR Benazepril	Amlodipine
ARB + Thiazide/Thiazide Like Diuretic	
Azilsartan OR Telmisartan OR Irbesartan	Chlorthalidone OR Hydrochlorothiazide
ACE- I + Thiazide/Thiazide Like Diuretic	
Lisinopril OR Benazepril	Chlorthalidone OR Hydrochlorothiazide

Adult Hypertension

care management | institute

NNT CVA[2] = 63
NNT MI[2] = 86
NNT CVA or MI[2] = 36

BLOOD PRESSURE (BP) GOAL

≤ 139 / 89 mm Hg – All Adult Hypertension

ACE-INHIBITOR[1] / THIAZIDE DIURETIC
Lisinopril / HCTZ
(Advance as needed)
20 / 25 mg X ½ daily
20 / 25 mg X 1 daily
20 / 25 mg X 2 daily
Pregnancy Potential: Avoid ACE-Inhibitors[1]

If pregnancy potential →

THIAZIDE DIURETIC
HCTZ 25 mg → 50 mg
OR
Chlorthalidone 12.5 mg → 25 mg

If not in control

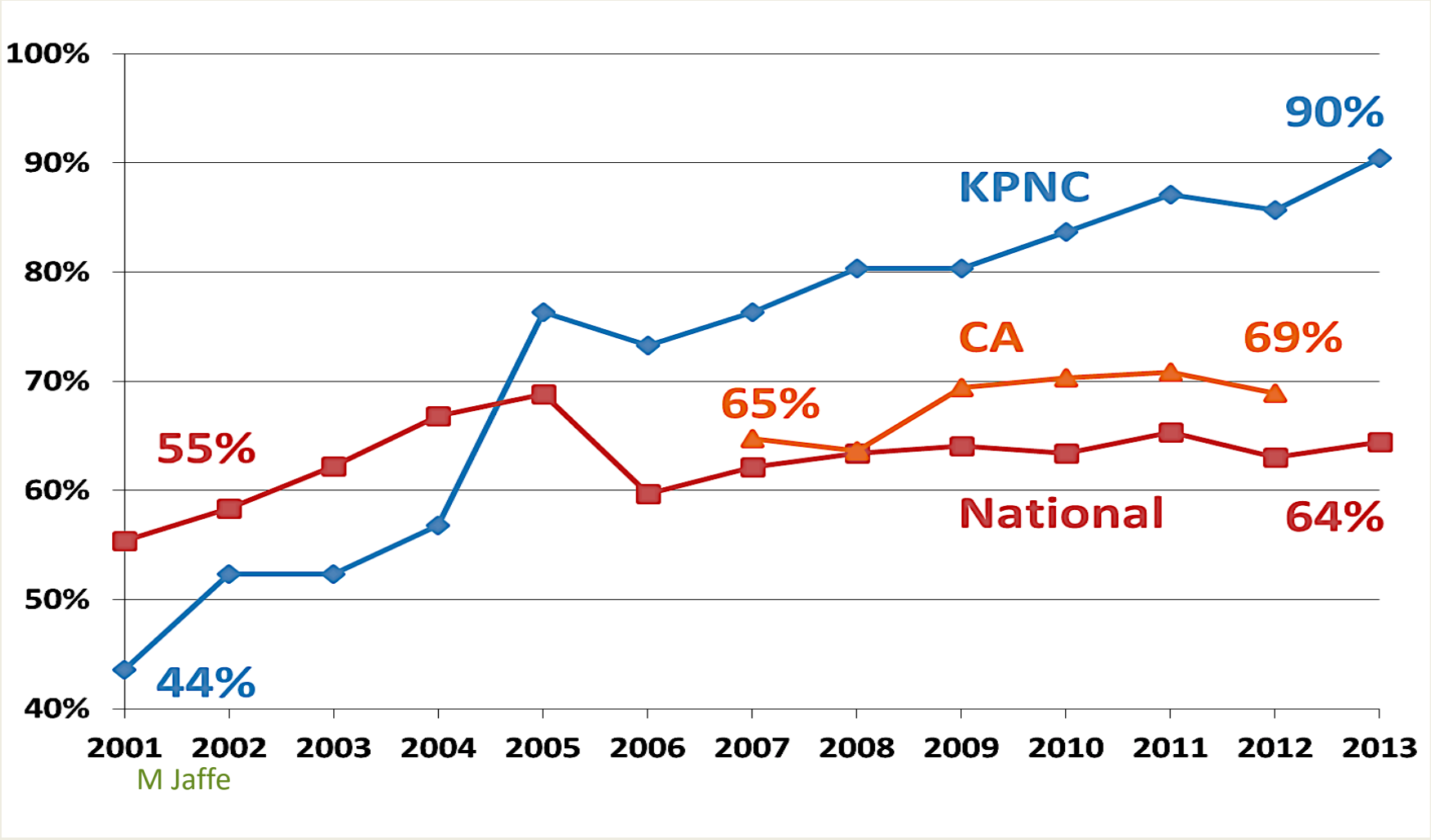
CALCIUM CHANNEL BLOCKER
Add amlodipine 5 mg X ½ daily → 5 mg X 1 daily → 10 mg daily

If not in control

SPIRONOLACTONE OR BETA-BLOCKER
IF on thiazide **AND** eGFR ≥ 60 mL/min/1.73m² **AND** K < 4.5
Add spironolactone 12.5 mg daily → 25 mg daily
OR
Add atenolol 25 mg daily → 50 mg daily (Keep heart rate > 55)

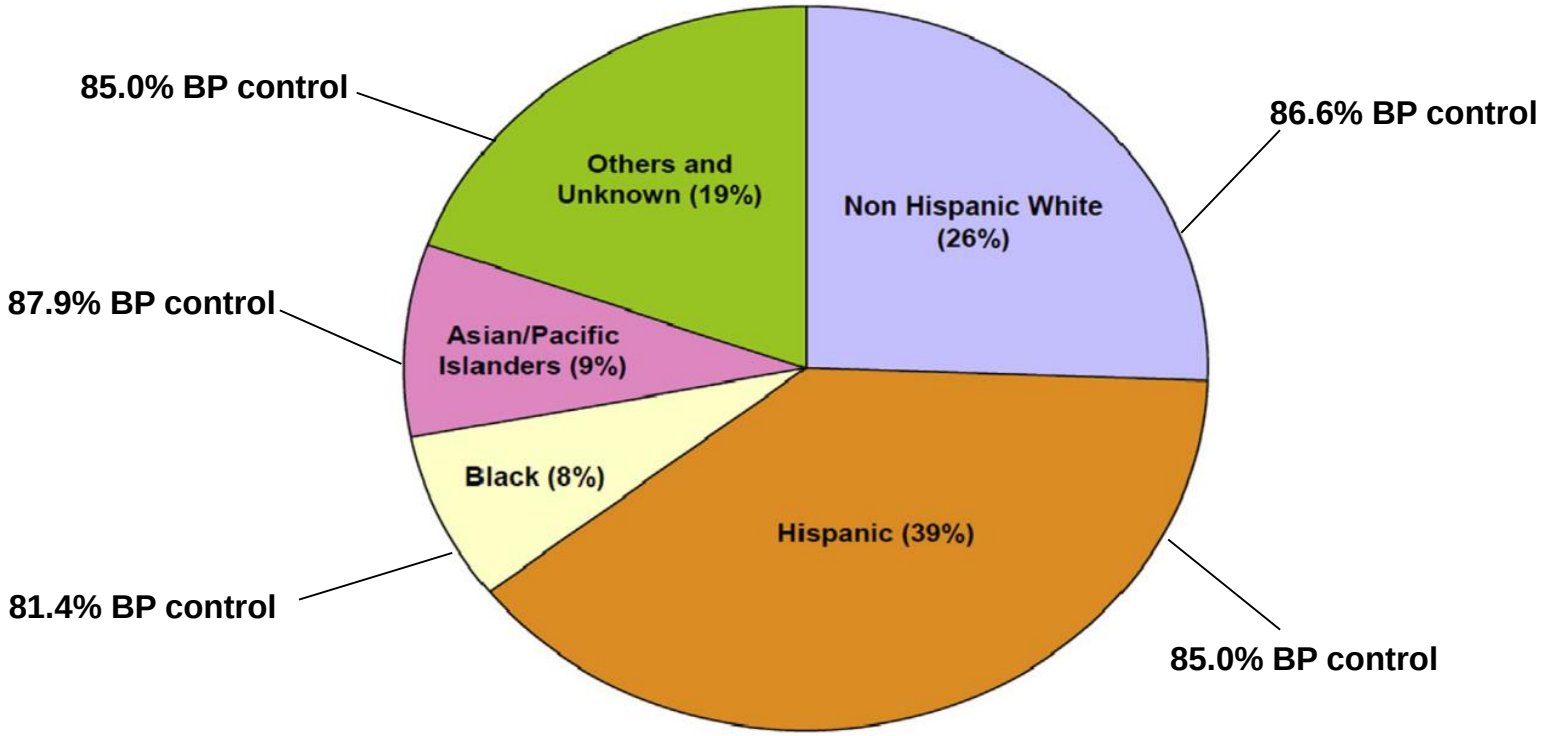
Go,AS et al J Am Coll Cardiol. 2013

Kaiser Permanente Northern California vs. National and California HTN Control



Standardized Treatment Protocols Can Help Reduce Disparate Outcomes Kaiser Permanente Southern California

"Across all ages, races, and sexes, hypertension control exceeded



Shaw KM, Handler J, Wall HK, Kanter MH. Improving Blood Pressure Control in a Large Multiethnic California Population Through Changes in Health Care Delivery, 2004–2012. Prev Chronic Dis 2014;11:140173.
DOI: http://dx.doi.org/10.5888/pcd11.140173

HEARTS in the Americas: Early Results

	BARBADOS	CHILE	COLOMBIA	CUBA
Secured political commitment	✓	✓	✓	✓
Demonstration site in place	✓ (2)	✓ (2)	✓ (2)	✓ (1)
Target (adult) population size	21,000	50,000	75,000	26,000
Staff, trained and certified in HT measuring & PAHO virtual course	✓	✓	✓	✓
Algorithm defined	✓	✓	✓	✓
Core set of medications	✓	✓	✓	✓
• **Fixed dose combination**	**(LIS + HTZ)**	**(VAL-AMP)**	**(LOS-HTZ)**	**(ENA-HTZ)**
Registry	✓ (electronic)	✓ (electronic)	✓ (manual)	✓ (manual)
• Registry completeness (%)	45% & 49%	87%	73%	89%
Metrics M & E defined	✓	✓	✓	✓
Redistribution of Task well defined	✓	✓	✓	✓

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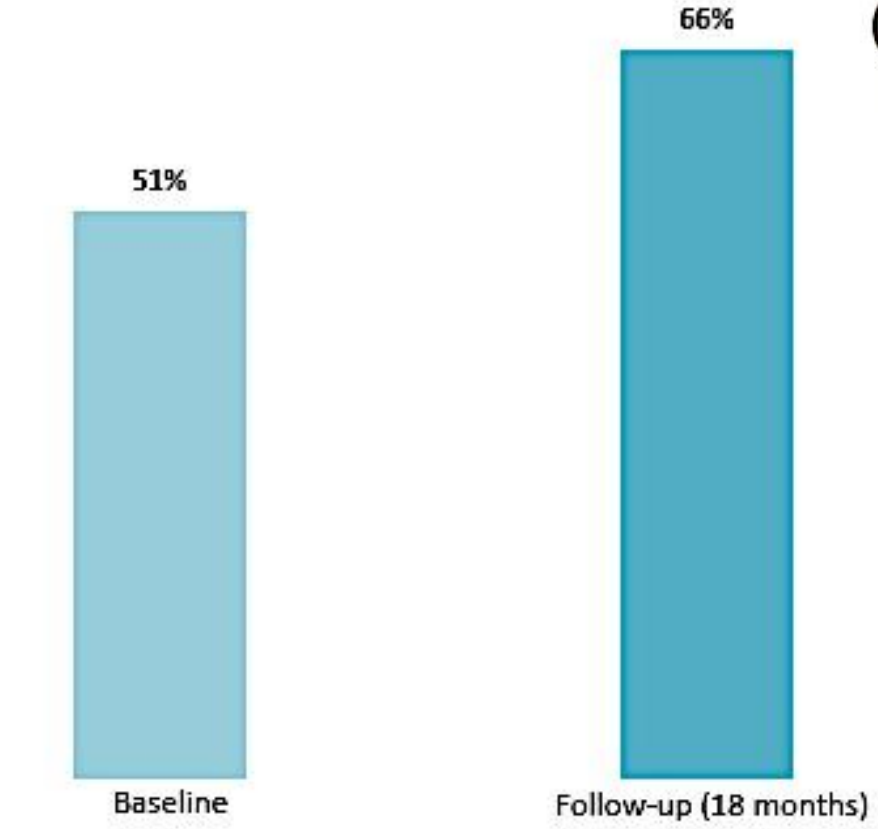
Hypertension control rate at two pilot clinics in Barbados



Global Standardized Hypertension Treatment Project

Sources: GSHTP Barbados Pilot Analysis Report, 2014-2016; Transforming Hypertension Treatment in Barbados, https://blogs.cdc.gov/global/2016/09/29/transforming-hypertension-treatment-in-barbados/

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Single-pill or fixed-dose combination therapy for the treatment of hypertension: **Conclusions**

- **Strongly consider combination therapy especially fixed-dose combinations (FDC) in the drug treatment strategy for hypertension.**
- **Most current guidelines recommend FDC therapy if the baseline blood pressure is 160/100 mmHg or greater or 20/10 mmHg above goal.**
- **Rationale is partially based on the Kaiser Permanente, the HEARTS in the Americas (Barbados, Cuba, Chile, Colombia), and Global HEARTS Program (HEARTS Technical Package) experience.**
- **ESC and ESH (2018) guidelines recommend strong consideration be given to the initial use of combination therapy.**

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MODULES OF THE HEARTS TECHNICAL PACKAGE

Module	What does it include?	Who are the target users?		
		National	Subnational	Primary care
Healthy-lifestyle counselling	Information on the four behavioural risk factors for CVD is provided. Brief interventions are described as an approach to providing counselling on risk factors and encouraging people to have healthy lifestyles.		✓	✓
Evidence-based protocols	**A collection of protocols to standardize a clinical approach to the management of hypertension and diabetes.**	✓	✓	✓
Access to essential medicines and technology	Information on CVD medicine and technology procurement, quantification, distribution, management and handling of supplies at facility level.	✓	✓	✓
Risk-based CVD management	Information on a total risk approach to the assessment and management of CVD, including country-specific risk charts.		✓	✓
Team-based care	Guidance and examples on team-based care and task shifting related to the care of CVD. Some training materials are also provided.		✓	✓
Systems for monitoring	Information on how to monitor and report on the prevention and management of CVD. Contains standardized indicators and data-collection tools.	✓	✓	✓

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E Module Contents

1) Hypertension detection and treatment

- When to measure blood pressure
- How to measure blood pressure
- Diagnosing hypertension
- Hypertension treatment

2) Diabetes detection and treatment

- Diabetes risk factors and symptoms
- Diagnostic testing for diabetes
- Drug therapy
- Screening for chronic complications

3) Identifying emergencies and need for referral

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Hypertension Detection and Treatment

When to measure blood pressure

- Measuring blood pressure is the only way to diagnose hypertension, as most people with raised blood pressure have no symptoms.

Blood pressure measurement and control is particularly important in adults who:

- Have had a prior heart attack or stroke
- Have diabetes
- Have chronic kidney disease (CKD)
- Are obese
- Use tobacco
- Have a family history of heart attack or stroke.

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Hypertension Detection and Treatment

How to measure blood pressure (go to link): General patient preparation recommendations

- No caffeine, exercise, or smoking for 30-60 minutes prior
- Bladder/Bowel comfortable
- Quiet/temperate, relaxed environment, no talking
- Seated position, arm supported and feet resting on floor
- Bare arm with no constrictive clothing
- Patient should stay silent prior and during the procedure
- No acute anxiety, stress or pain

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Diagnosing Hypertension

- The diagnosis of hypertension should be confirmed at an additional patient visit, usually 1 to 4 weeks after the first measurement. In general, hypertension is diagnosed if, on two visits on different days:

  - **systolic blood pressure on both days is ≥ 140 mmHg and/or**
  - **diastolic blood pressure on both days is ≥ 90 mmHg**

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What medications should be used to treat hypertension?

There are four main classes of antihypertensive medications:

- **Angiotensin converting enzyme (ACE) inhibitors,**
- **Angiotensin receptor blockers (ARB)**
- **Calcium channel blockers (CCB)**
- **Thiazide and thiazide-like diuretics.**

Any of these four classes of antihypertensive medication may be used as initial treatment, unless there are specific contraindications. However, to achieve blood pressure control (<140 and <90 mmHg), the treatment of hypertension usually requires at least two hypertension medications from different complementary classes.

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Treatment Targets

- For most patients, blood pressure is considered controlled when **SBP <140 mmHg** and **DBP <90 mmHg.**
- Patients with diabetes or a high risk of CVD, some guidelines recommend lower targets: **SBP <130 mmHg and DBP <80 mmHg.**

Other treatment considerations

- Prior heart attack or stroke, or the person is otherwise at high risk of CVD, start a **statin**. If there is a prior heart attack or ischemic stroke, start **low-dose aspirin**.
- If there are serious adverse events, lack of control of BP, or if a major medical event occurs, **then refer to a specialist.**
- If the patient is already on another BP medication or regimen and the BP is controlled and the medications are accessible and affordable, there is **no reason to change the regimen.**

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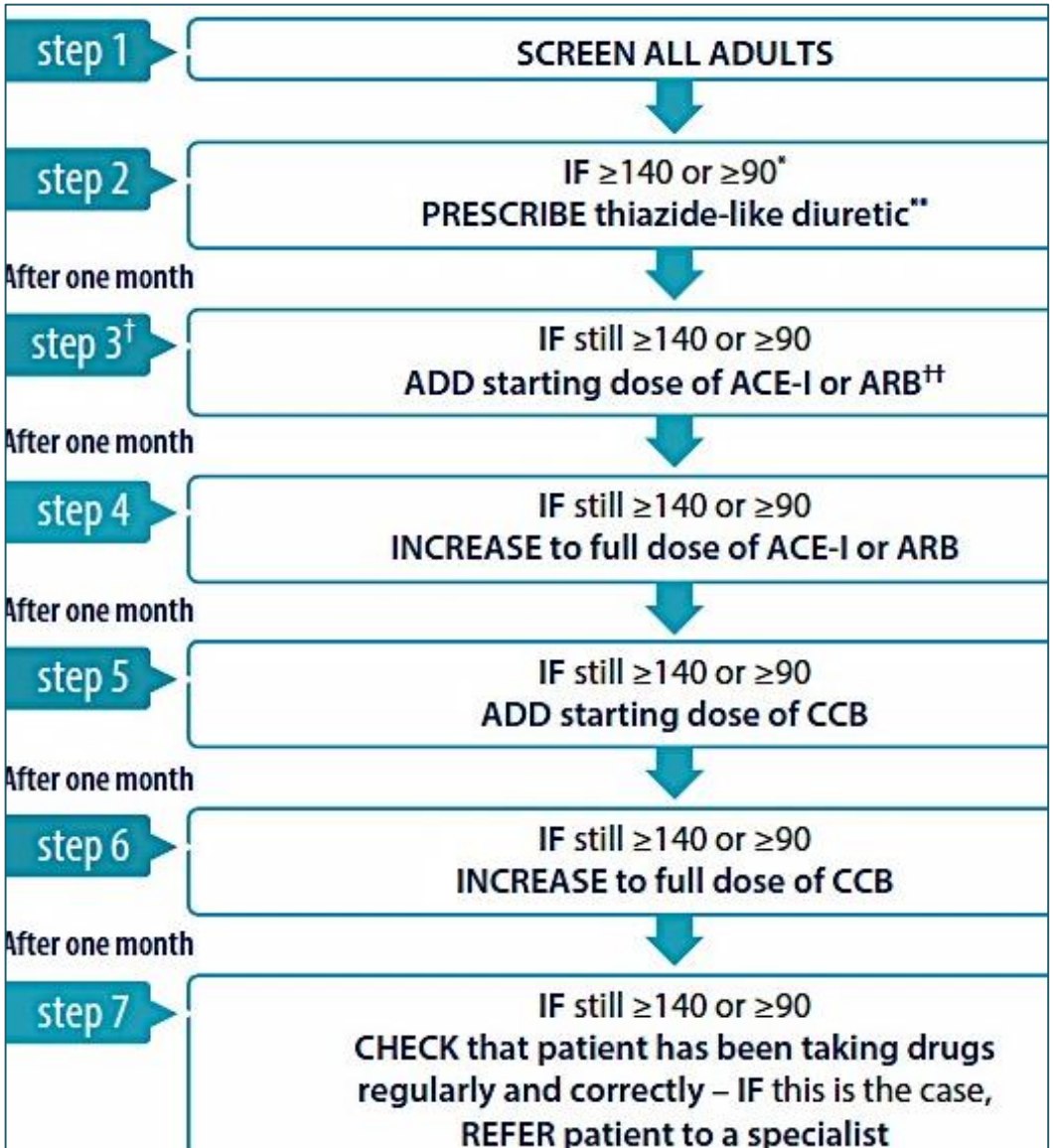
HYPERTENSION PROTOCOL: **DIURETIC as First-line Treatment**



PROVISION FOR SPECIFIC PATIENTS

- **THIS PROTOCOL IS CONTRAINDICATED FOR WOMEN WHO ARE OR COULD BECOME PREGNANT.**
  - Manage diabetes as indicated by national protocol.
  - Aim for BP <130/80 for people at high risk, such as individuals with diabetes, CAD, stroke, or CKD.

- *Neither ACE-I nor ARBs should be given to pregnant women.*

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HYPERTENSION PROTOCOL

Diuretic as First-line treatment

DRUGS AND DOSES¥

Class	Medication	Starti dose
diuretic‡ thiazide-like	chlorthalidone§ or indapamide SR§	12.5 m 1.5 mg
ACE inhibitor‡ (angiotensin-converting-enzyme inhibitor)	lisinopril	20 mg
	ramipril	5 mg
	perindopril	4–5 mg
ARB‡	losartan	50 mg
	telmisartan	40 mg
CCB (calcium channel blocker)	amlodipine	5 mg

LIFESTYLE MANAGEMENT ADVICE FOR ALL PATIENTS

- Stop all tobacco use, avoid secondhand tobacco smoke.
- Drink no more than two units of alcohol per day and do not drink on at least two days of the week.
- Increase physical activity to equivalent of brisk walk 150 minutes per week.
- If overweight, lose weight.
- Eat heart-healthy diet:
  - Eat a low-salt diet.
  - Eat ≥5 servings of vegetables/fruit per day.
  - Use healthy oils (e.g. olive, safflower).
  - Eat nuts, legumes, whole grains and foods rich in potassium.
  - Limit red meat to once or twice a week at most.
  - Eat fish or other food rich in omega 3 fatty acids (e.g., flax seeds) at least twice a week.
  - Avoid added sugar from cakes, cookies, sweets, fizzy drinks and juice.

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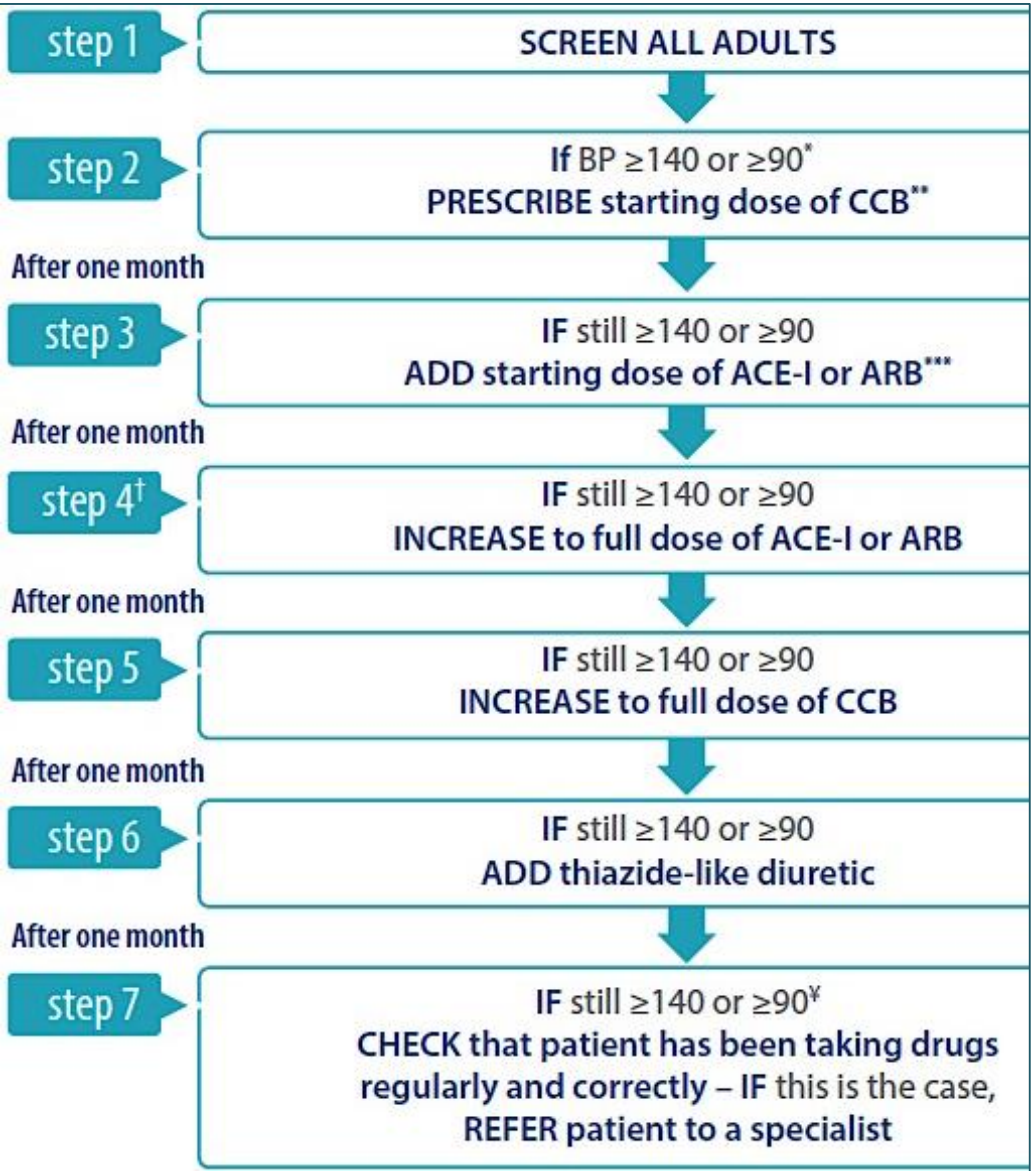
HYPERTENSION PROTOCOL: **CCB as First-line treatment**



PROVISION FOR SPECIFIC PATIENTS

- **THIS PROTOCOL IS CONTRAINDICATED FOR WOMEN WHO ARE OR COULD BECOME PREGNANT.**
  - Manage diabetes as indicated by national protocol.
  - Aim for BP <130/80 for people at high risk, such as individuals with diabetes, CAD, stroke, or CKD.

- *Neither ACE-I nor ARBs should be given to pregnant women.*

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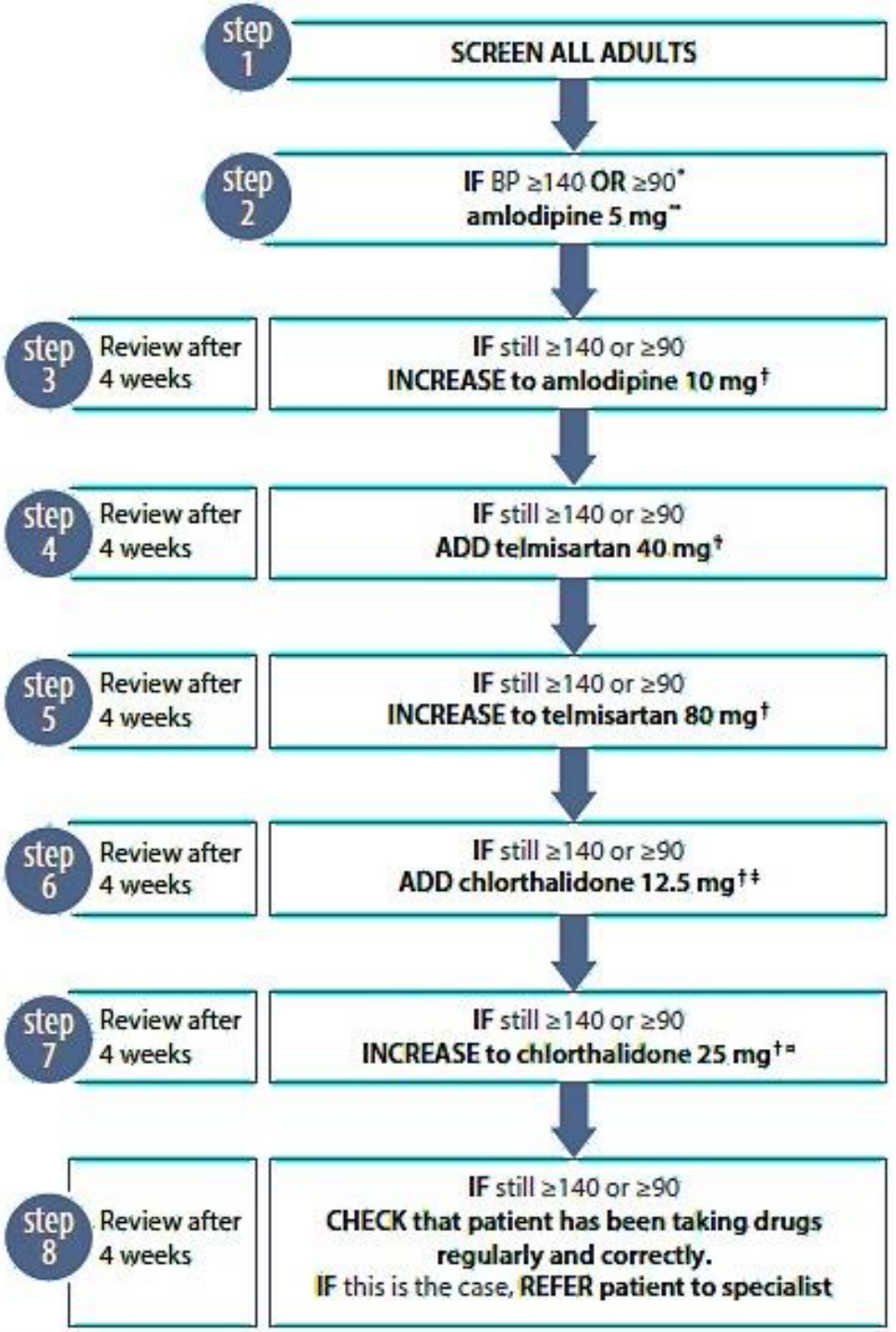
HYPERTENSION PROTOCOL: Adapted example: CCB as First-line treatment



PROVISION FOR SPECIFIC PATIENTS

- Manage diabetes as indicated by national protocol
- Aim for BP <130/80 for people with diabetes or otherwise at high risk
- Start statin and aspirin in people with prior heart attack or ischemic stroke
- Start beta blocker in people with heart attack in past 3 years
- Consider statin in people at high risk

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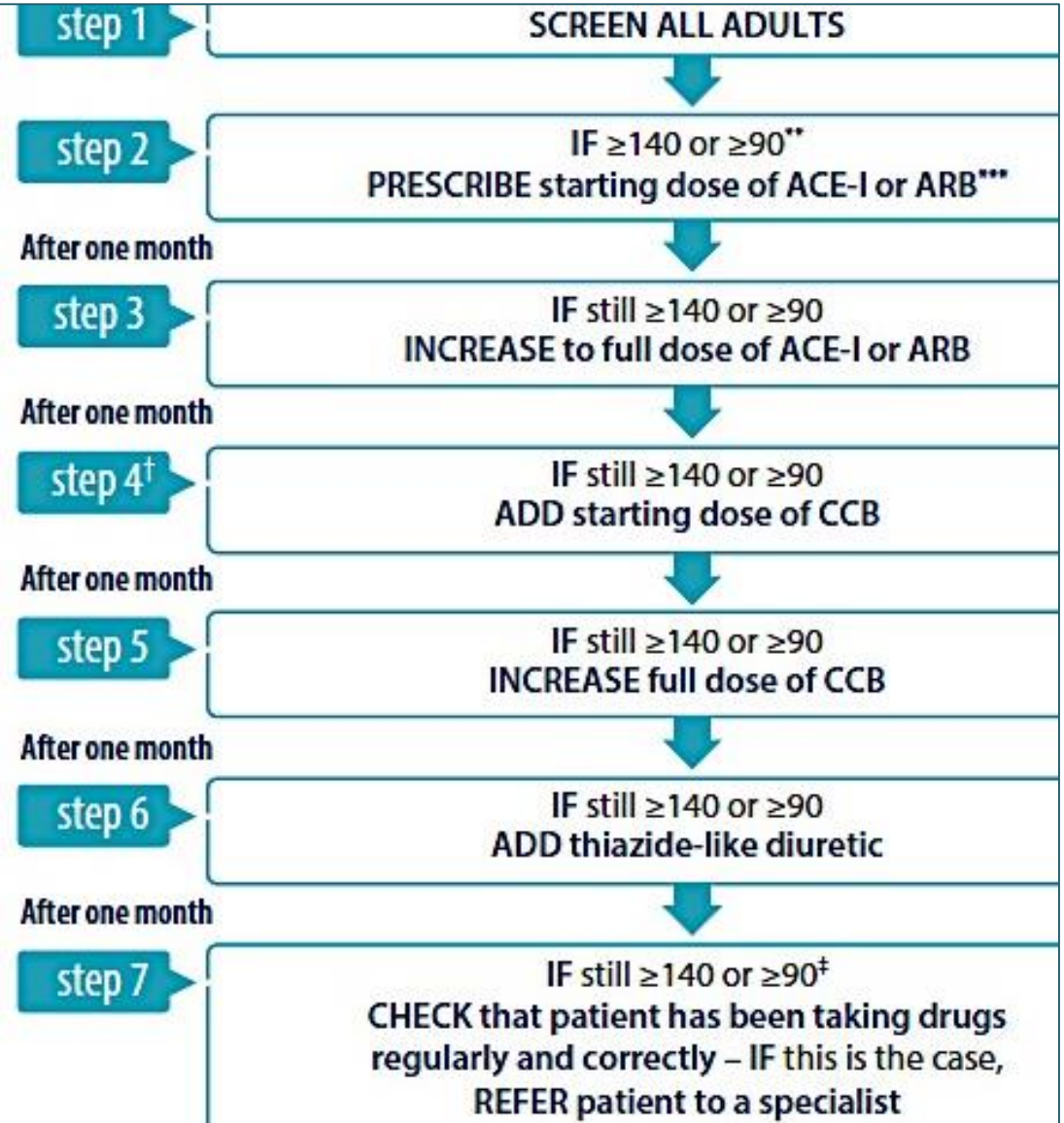
HYPERTENSION PROTOCOL: **ACE-I or ARB* as First-line treatment**



PROVISION FOR SPECIFIC PATIENTS

- **THIS PROTOCOL IS CONTRAINDICATED FOR WOMEN WHO ARE OR COULD BECOME PREGNANT.**
  - Manage diabetes as indicated by national protocol.
  - Aim for BP <130/80 for people at high risk, such as individuals with diabetes, CAD, stroke, or CKD.

- *Neither ACE-I nor ARBs should be given to pregnant women.*

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HYPERTENSION PROTOCOL:
ACE-I or ARB* as First-line treatment

DRUGS AND DOSES¥

Class	Medication	Starting dose	Intensification dose
ACE inhibitor§ (angiotensin-converting-enzyme inhibitor)	lisinopril	20 mg	40 mg
	ramipril	5 mg	10 mg
	perindopril	4–5 mg	8–10 mg
ARB§	losartan	50 mg	100 mg
	telmisartan	40 mg	80 mg
diuretic§ thiazide-like	chlorthalidone¤ or indapamide SR¤	12.5 mg	25 mg
		1.5 mg	stay at 1.5 mg
CCB (calcium channel blocker)	amlodipine	5 mg	10 mg

* ACE-I or ARB according to local guidelines/costs/intolerance to ACE-I. ACE-Inhibitors cause chronic cough in approximately 10% of patients. Neither ACE-I nor ARBs should be given to pregnant women.

** Or other BP target, as determined by clinical factors. If BP ≥160 or ≥100, start same day. If 140–159 or 90–100, check on a different day and if still elevated, start.

*** Consider statin use.

† Consider optional switch of steps 4 and 5 (CCB) with step 6 (thiazide-like diuretic).

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HYPERTENSION PROTOCOL: **ACE-I or ARB + CCB**

step 1 SCREEN ALL ADULTS

step 2 If BP ≥140 or ≥90** PRESCRIBE starting dose of ACE-I or ARB*** + CCB¥

Class	Medication	Starting dose	Intensification dose
ACE inhibitor § (angiotensin-converting-enzyme inhibitor)	lisinopril	20 mg	40 mg
	ramipril	5 mg	10 mg
	perindopril	4–5 mg	8–10 mg
ARB §	losartan	50 mg	100 mg
	telmisartan	40 mg	80 mg
diuretic § thiazide-like	chlorthalidone ¤ or indapamide SR ¤	12.5 mg	25 mg
		1.5 mg	stay at 1.5 mg
CCB (calcium channel blocker)	amlodipine	5 mg	10 mg

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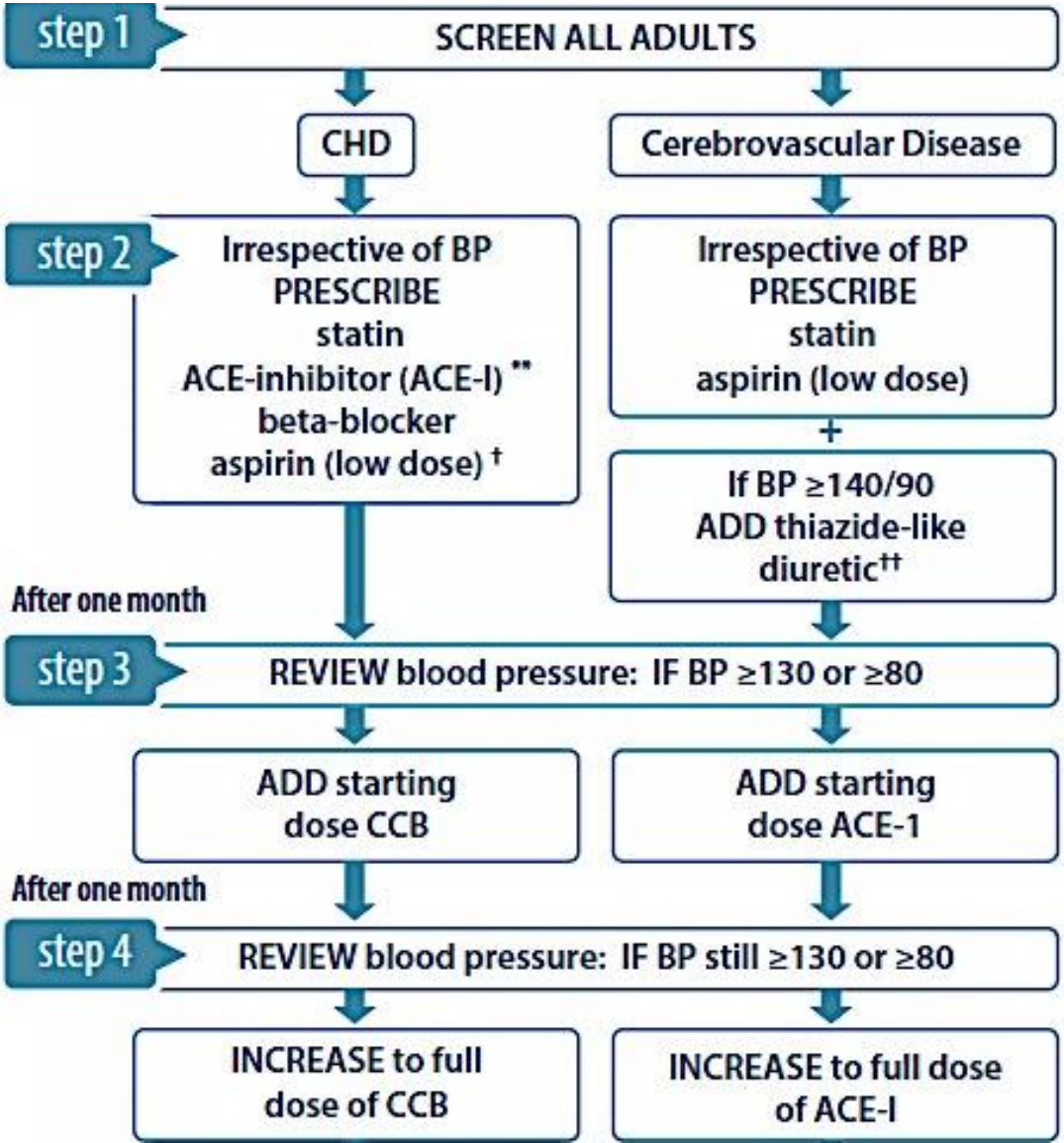
Use of BP-lowering drugs in patients with ischaemic CVD*



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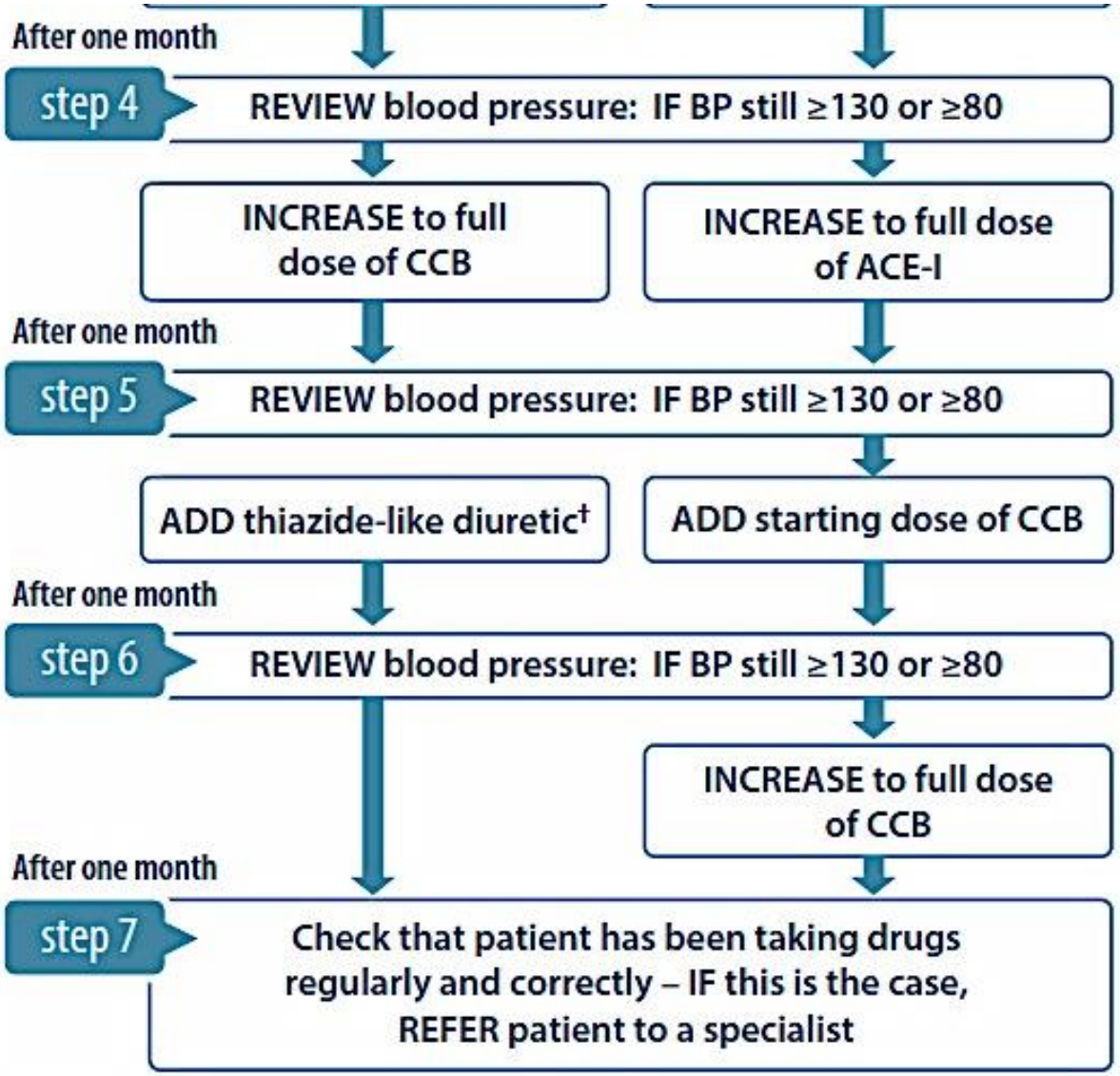
Use of BP-lowering drugs in patients with ischemic CVD*



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Conclusions

- Use a standardized and simplified approach to CVD and CVD risk assessment and reduction, through hypertension and diabetes detection, treatment and control.
- Determine blood pressures with validated equipment and technique in a controlled clinical environment.
- Develop a specific formulary and treatment algorithm for the treatment of hypertension.
- Strongly consider combination therapy (fixed-dose combinations) in the initial treatment of hypertension.
- Rationale is partially based on Kaiser Permanente, HEARTS in the Americas, Global HEARTS Program (Technical Package), and newer hypertension treatment guidelines.

HEARTS

Recommended Reading

1. Shaw KM, Handler J, Wall HK, et al. Improving Blood Pressure Control in a Large Multiethnic California Population Through Changes in Health Care Delivery, 2004–2012. Prev Chronic Dis 2014. DOI: http://dx.doi.org/10.5888/pcd11.140173

2. Williams, Mancia, Spiering et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. 2018. J Hypertens; 36(10), 1953

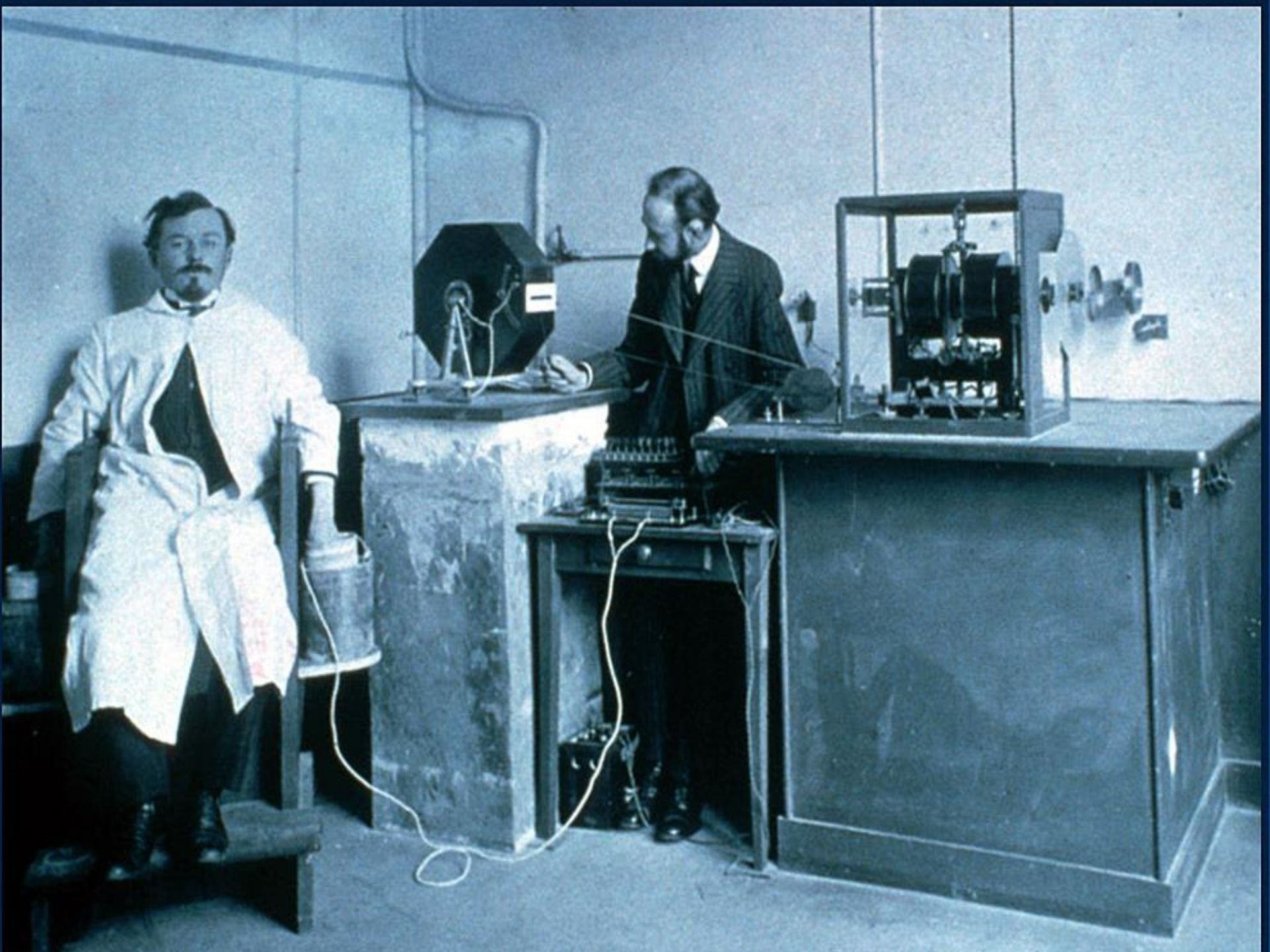
3. DiPette, Skeete, Ridley et al. Fixed-Dose Combination Pharmacologic Therapy to Improve Hypertension Control Worldwide: Clinical perspective and policy implications. 2019. J Clin Hypertens; 21(1): 4-15.

Recommended reading (con't)

1. Patel, P., Ordunez, P., DiPette, D.J., Escobar, M.C., Hassell, T., Wyss, F., Hennis, A., Asma, S., Angell, S. Improved blood pressure control to reduce cardiovascular disease morbidity and mortality: The standardized hypertension treatment and prevention project. 2016. J Clin Hypertens, 18(12), 1284.

2. Colgrove, P.C., Connell, K.L, Lackland, D.T., Ordunez, P. DiPette, D.J. Controlling hypertension and reducing its morbidity and mortality in the Caribbean: Implications of race and ethnicity. 2017, J Clin Hypertens. 19(10), 1010-1014.

3. Skeete, J., Connell, K., Ordunez, P., DiPette, D.J. The American College of Cardiology/American Heart Association 2017 hypertension guideline: Implications for incorporation in Latin America and the Caribbean, and other resource-limited resource limited settings. 2018. J Clin Hypertens, Sep; 20(9): 1342-1349.



Thank You