COMBINATION THERAPY IN HYPERTENSION

Hypertension global burden

- Globally prevalence in adults aged > 25 years : 40%.
- It is estimated to cause 7.5 million deaths;12.8% of the total deaths.
- Hypertension accounts for 57 million disability adjusted life years (DALYS) or 3.7% of total DALYS
- 62% of cerebrovascular diseases and 49% of ischemic heart diseases are attributable to suboptimal BP.
- One in three adults worldwide has high blood pressure.

Tanu Midha etal, World J Meta-Anal 2013 August 26; 1(2): 83-8

BP Control Rates are Suboptimal

- Despite the clear benefits of reducing BP to target levels, rates of BP control are suboptimal in most countries
- BP control rates are particularly poor in low-income countries
- BP control rates are <30% in several Asia-Pacific countries

1. http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_part2.pdf
2. Peter L, *Int. J. Epidemiol. (2014), 1- 13*
3. C-E Chiang,„*Journal of Human Hypertension* (2008) **22,** 441–443

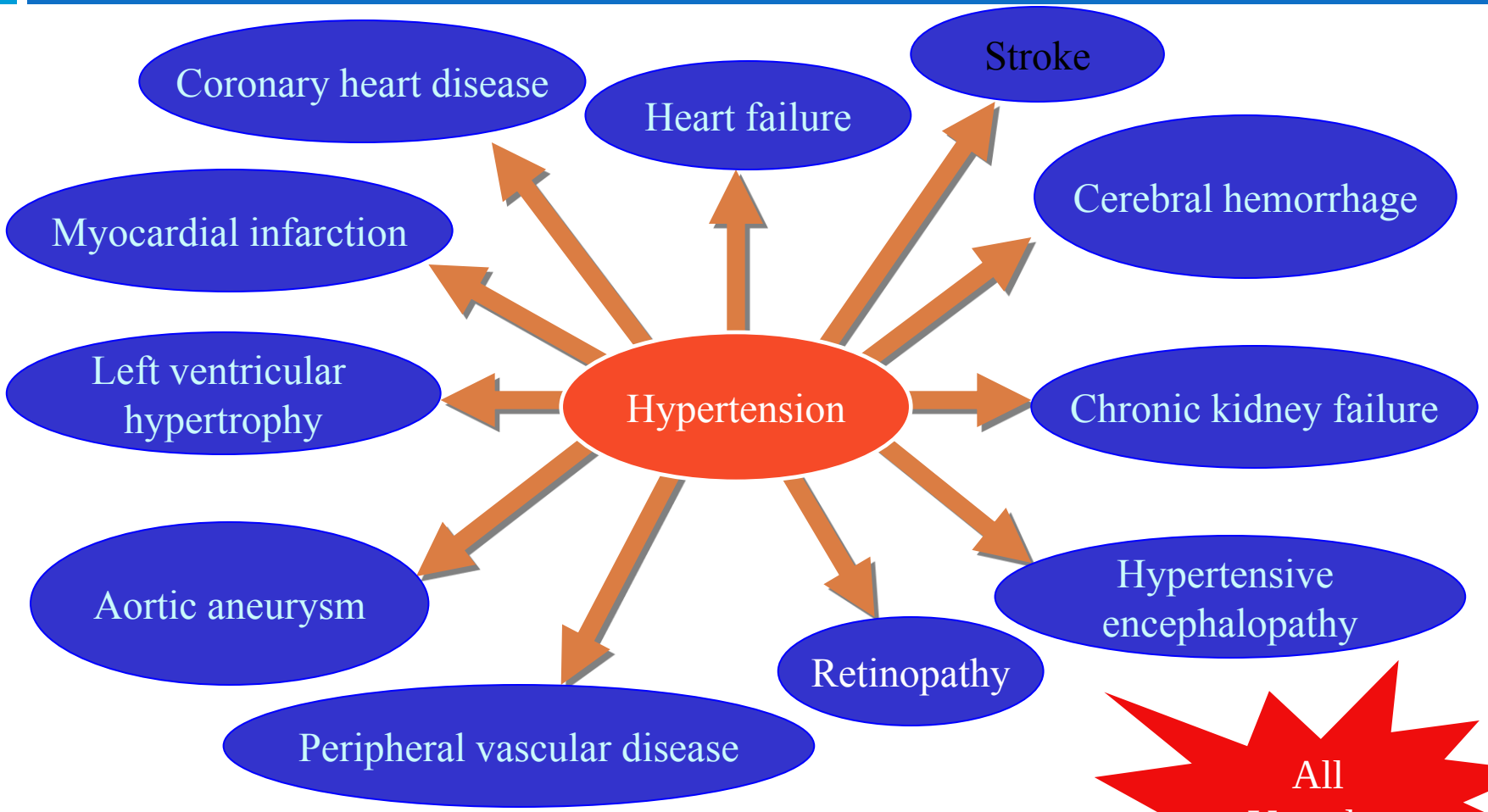
Get The Pressure Down!!

51%	Of Deaths from Stroke
45%	Of Deaths from Coronary Heart Disease
7.5 million	Deaths due to HT
13%	Total global deaths

Awareness, Diagnosis & Best antihypertensive which prevent complications will save lives !

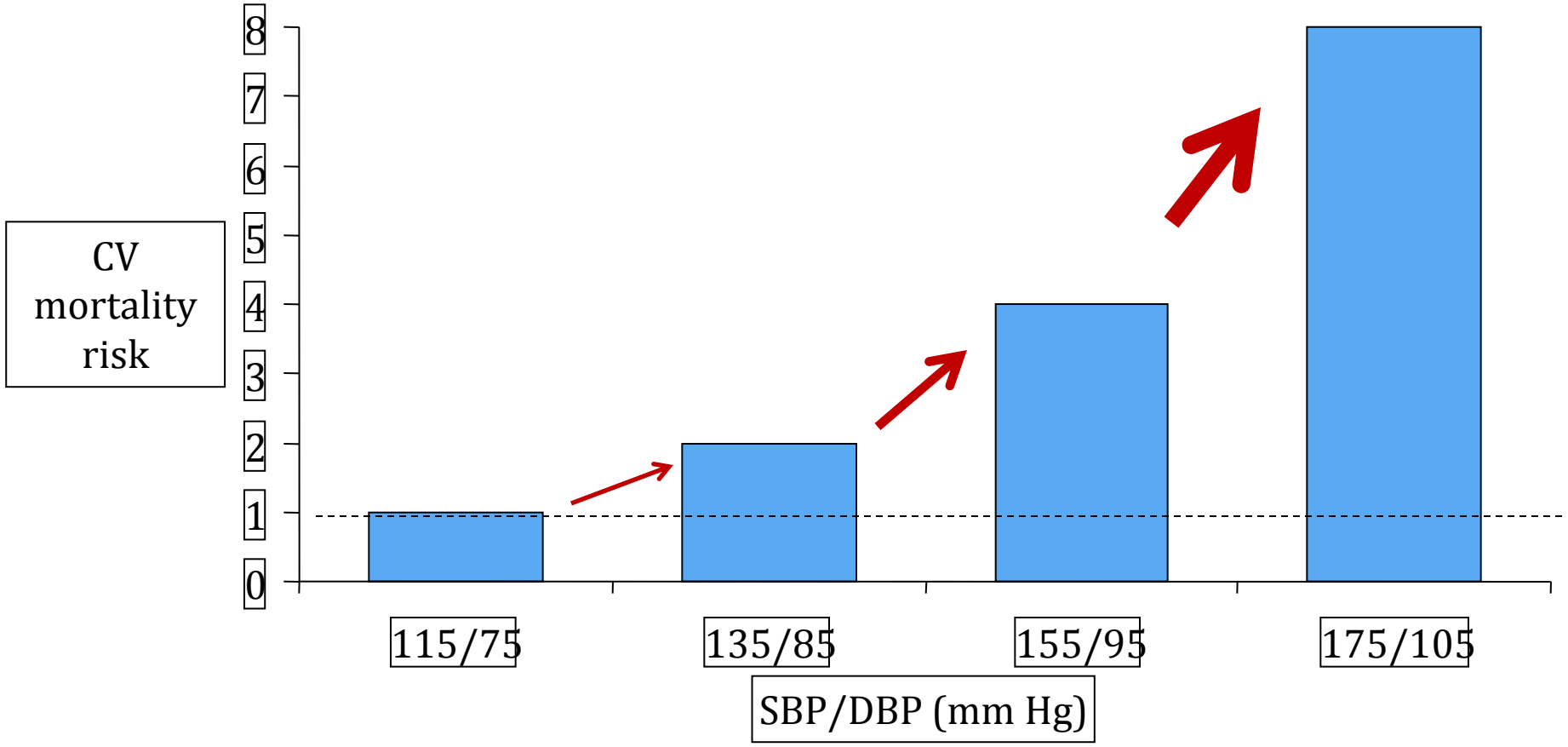
http://www.who.int/gho/ncd/risk_factors/blood_pressure_prevalence_text/en/

Diseases Attributable to Hypertension



http://www.mayoclinic.org/diseases-conditions/high-blood-pressure/in-depth/high-blood-pressure/art-20045868.

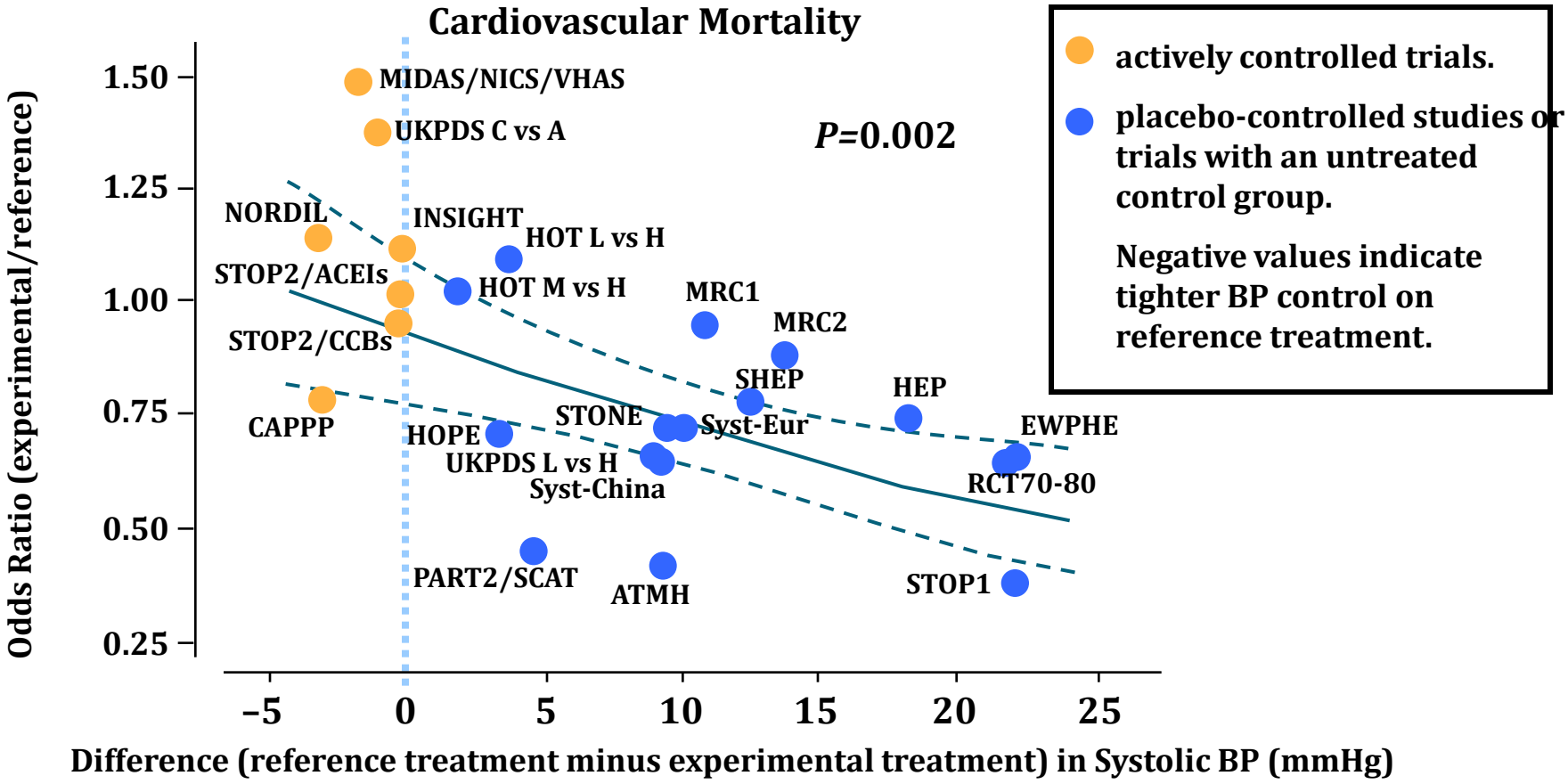
CV Mortality Risk Doubles With Each 20/10 mm Hg BP Increment*



Assadi F. Prehypertension: Int J Prev Med. 2014 Mar;5(Suppl 1):S4-9.

Importance of Lowering BP

(Data from Multiple Clinical Trials Measuring the Impact of Hypertensive Therapy on Cardiovascular Mortality)



Greater differences in BP reduction mean greater reductions in the risk of cardiovascular mortality.

BP, blood pressure

Staessen JA et al. *Hypertension Research.* 2005;28:385-407.

Reasons for Not Achieving BP Control

- Poor adherence and persistence with therapy.
- Physicians' reluctance to switch to an alternative treatment and/or increase doses if BP remains uncontrolled.
- Selected antihypertensive drug does not target the mechanism causing the patient's hypertension.

http://www.mayoclinic.org/diseases-conditions/high-blood-pressure/basics/treatment/con-20019580 accessed on 9-oct-2015

Need for Combination Therapy

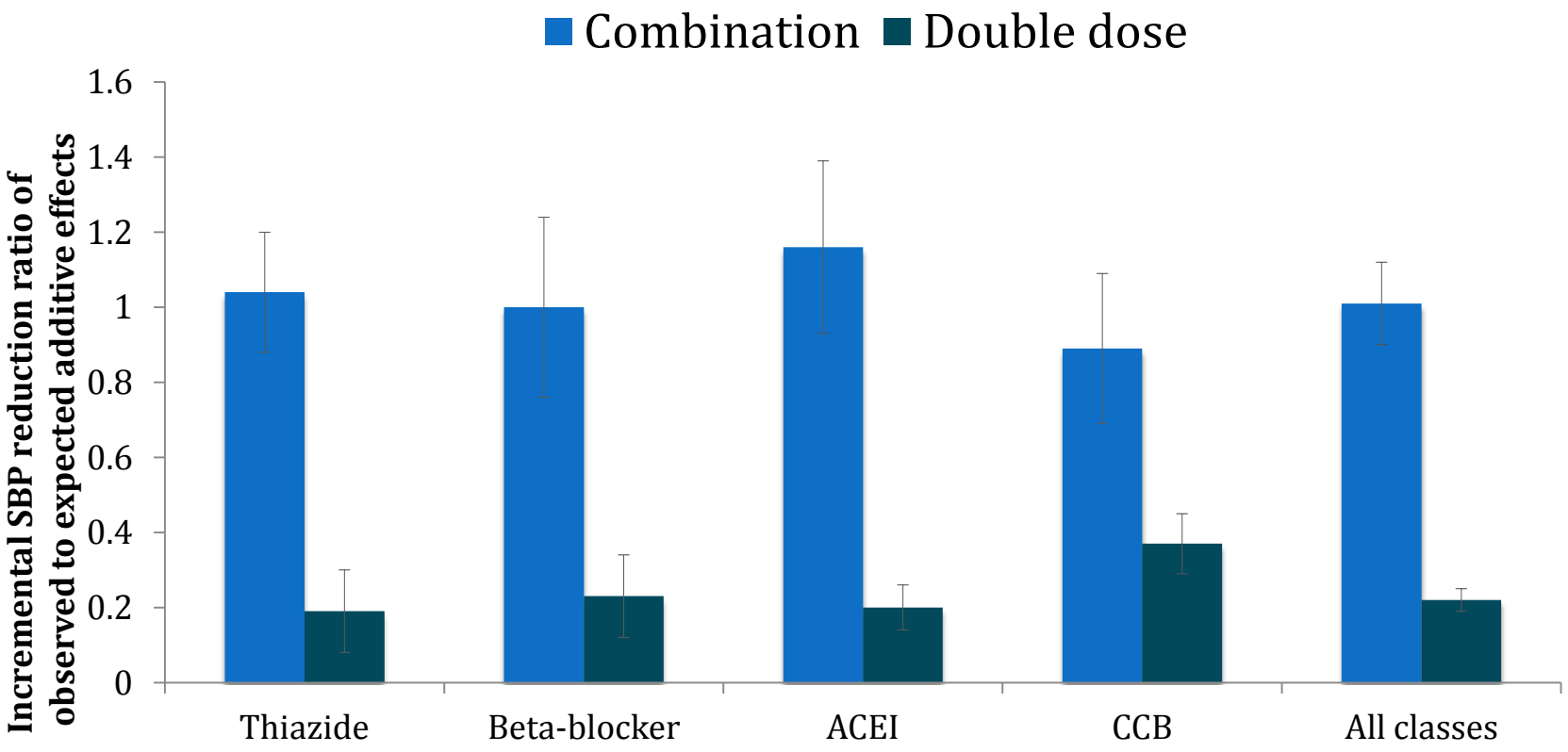
Clinical Evidences

Combination Therapy: *A Practical Necessity*

- Required in ~ 75% of hypertensives to achieve target BP
- Greater efficacy
- Faster achievement of target BP
- Higher response rates
- May make therapy effective in broader population
- Additive antihypertensive effects through complimentary pharmacologic mechanisms
- In some cases, improved side effect profile

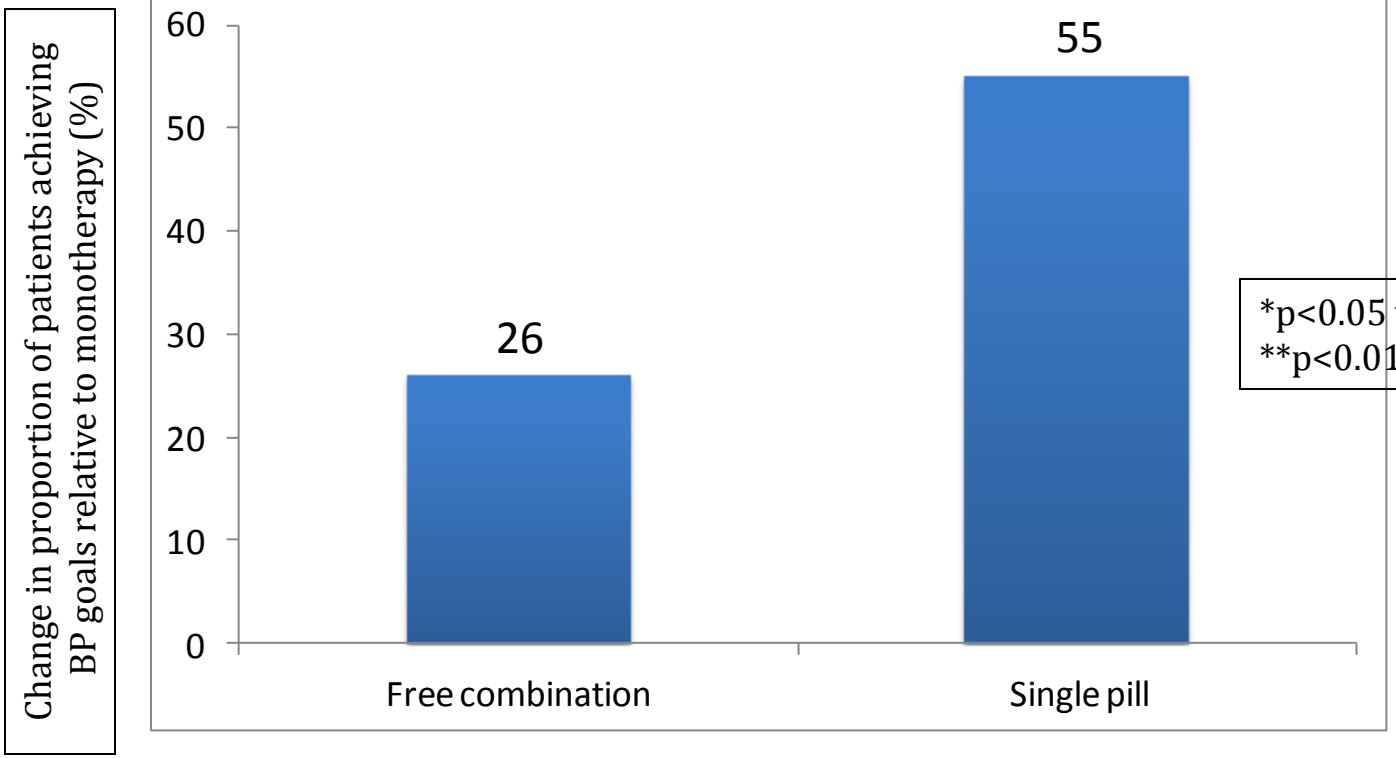
•Gradman AH, Basile JN, Carter BL, et al. J Clin Hypertens (Greenwich). 2011;13:146–154.

Combination Therapy is More Effective Than High Dose Monotherapy



Wald DS, et al. Am J Med 2009;122:290-300

Higher BP Control Rates Are Achieved With Single Pill Combinations



Patients receiving a single pill combination are more likely to achieve BP goals than those receiving free combinations or monotherapy

Gu Q, et al. Circulation 2012;126:2105-14

Single Pill Combinations are Recommended by Guidelines

- Single pill combinations (SPCs) or fixed-dose combinations have numerous advantages over multiple drug combination therapy

- Current hypertension guidelines generally recommend SPCs over multiple drug treatment with their individual components

1. Gupta AK, et al. Hypertension 2010;55:399-407
2. Bangalore S, et al. Am J Med 2007;120:713-9
3. Dusig R. VHRM 2010;6:321-5
4. Mancia G, et al. J Hypertens 2009;27:2121-58

Comparison of Monotherapy and Free and Single Pill Combinations

	Monotherapy	Free combination	Single pill combination
Convenience	✔	✗	✔✔[a]
Adherence	–	–	✔
Efficacy	✗	✔	✔
Tolerability	✗	✔	✔[b]
Flexibility	✔✔	✔✔	✔[c]

a Switching and dose titration less likely to be required than for monotherapy
b Single pill may be better tolerated as doses tend to be lower than in free combinations
c Flexibility with single pill combinations is increasing as the range of doses increases

Xinhuan Wana et al., Asian Journal of Pharmaceutical Sciences Volume 9, Issue 1, February 2014, 1–7

European Heart Journal
doi:10.1093/eurheartj/eht151

2013 ESH/ESC Guidelines for the management of arterial hypertension

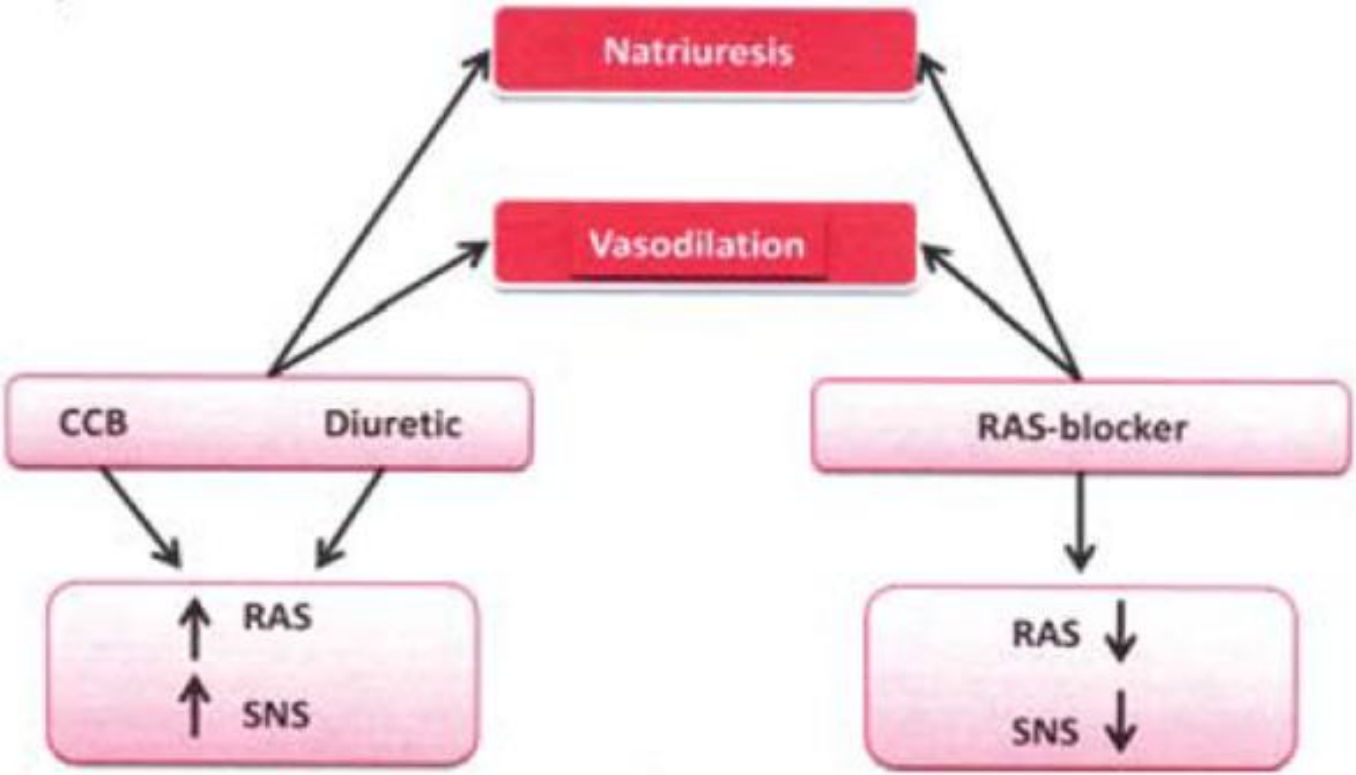
The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

- *" Whenever possible , use of fixed dose combinations should be preferred because simplification of treatment carries advantages for compliance with treatment"*

Combination Therapy

Right Combination for the Right Condition

Renin- angiotensin system and Sympathetic nervous system activation and deactivation.



Compensatory mechanisms of action of CCBs, diuretics and RAS-blockers on vascular and renal function, SNS* activity and RAS - activity

Peter S. Sever, European Heart Journal (2011) 32, 2499–2506

Combination 1

BETA.BLOCKERS	CALCIUM CHANNEL BLOCKER (DHP)
Decreased Cardiac Output, suppression of renin release.	Decreased PR

PREFERRED IN:

1. High coronary risk disease
2. Diabetes
3. Heart failure

DON'T COMBINE B BLOCKERS & NON DHP CA BLOCKERS

Jennifer F ,*Am Fam Physician.* 2008 May 1;77(9):1279-1286.

Combination 2

BETA. BLOCKERS	ANGIOTENSIN RECEPTOR INHIBITORS
Decreased Cardiac Output	Decreased Peripheral Resistance

PREFERRED IN:

1. Chronic kidney disease
2. Diabetes
3. Heart failure

Jennifer F ,*Am Fam Physician.* 2008 May 1;77(9):1279-1286.

Combination 3

DIURETIC	CAlCIUM CHANNEL BLOCKER (DHP)
Decreased Cardiac Output	Decreased Peripheral Resistance

PREFERRED IN:

1.Diabetes

2.High coronary artery disease

Jennifer F ,*Am Fam Physician.* 2008 May 1;77(9):1279-1286.

Combination 4

DIURETIC (Thiazide type)	ACE I /ARBs
Decreased Cardiac Output	Decreased Peripheral Resistance

PREFERRED IN:

1. Diabetes
2. Heart failure
3. High coronary disease risk
4. Recurrent stroke prevention

Diuretic
Aldasterone Antagonists
ACEI/ARBs
IN HEART FAILURE

Jennifer F ,*Am Fam Physician.* 2008 May 1;77(9):1279-1286.

Combination 5

CALCIUM CHANNEL. BLOCKER	**ACE Inhibitors**
Decreased peripheral resistance	Decreased Peripheral Resistance

PREFERRED IN:

1. Diabetes
2. High coronary disease risk

Jennifer F ,*Am Fam Physician.* 2008 May 1;77(9):1279-1286.

Combinations to be avoided

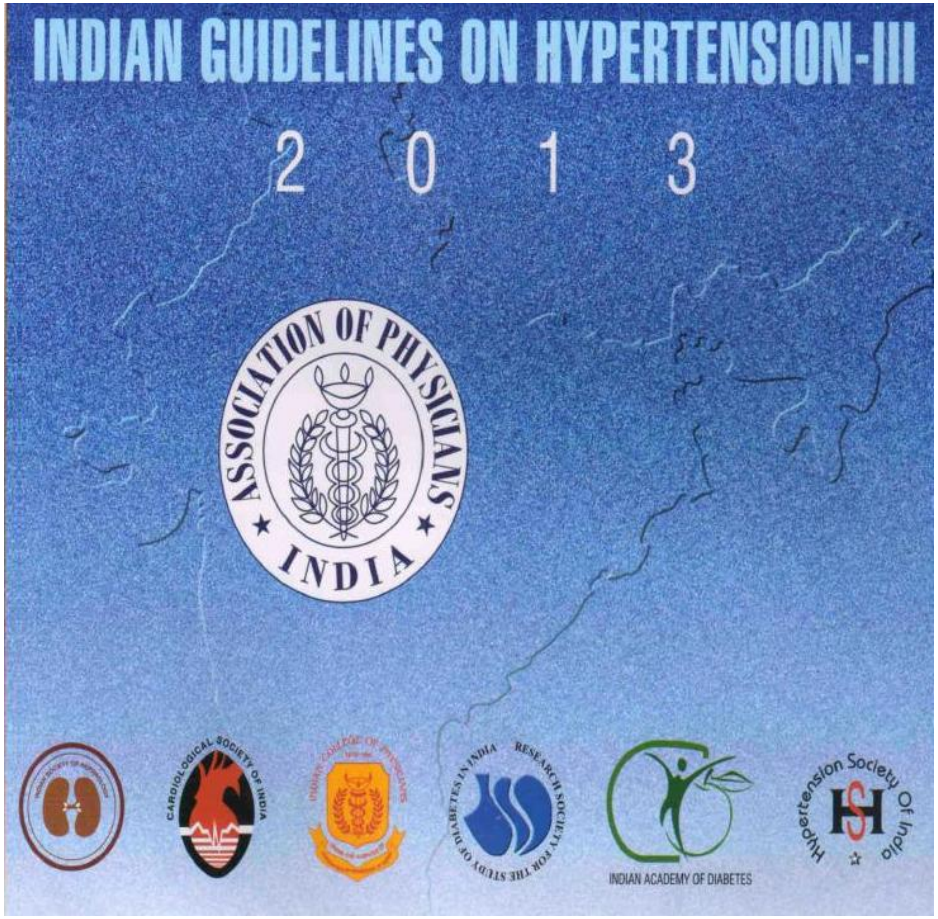
- ACEI and ARB –Contraindicated
- B blockers and diuretics – Diabetes
- B blockers and clonidine - bradycardia
- B blockers and non DHP CCB – bradycardia
- B blockers and ACEI or ARB –uncomplicated hypertension

Peter S. Sever, European Heart Journal (2011) 32, 2499–2506

Hypertension Management

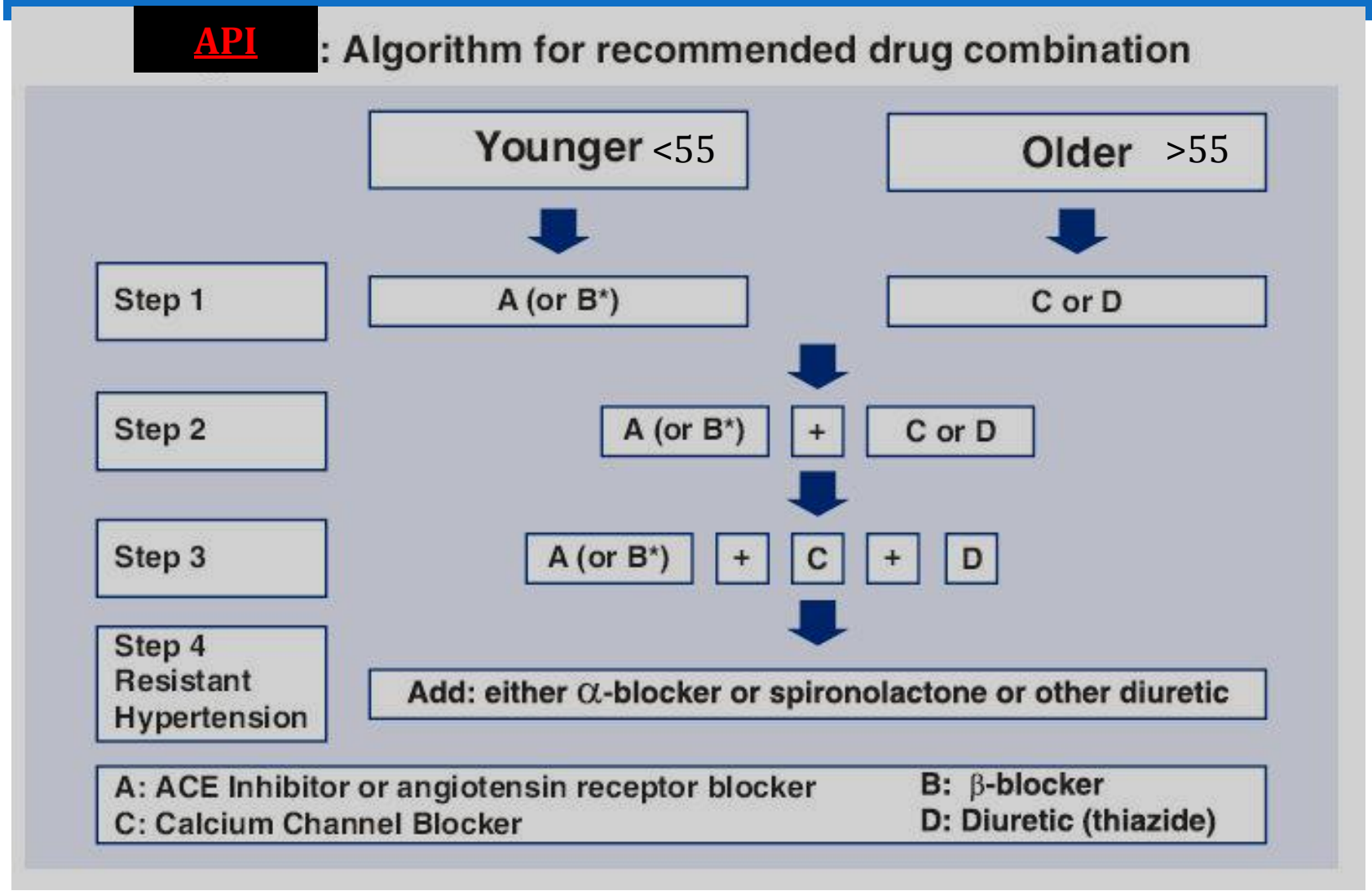
Guidelines

India



1. National Rural Health Mission guidelines 2. Association of Physicians of India guidelines 3. Williams B, et al. BMJ 2004;328:634-40

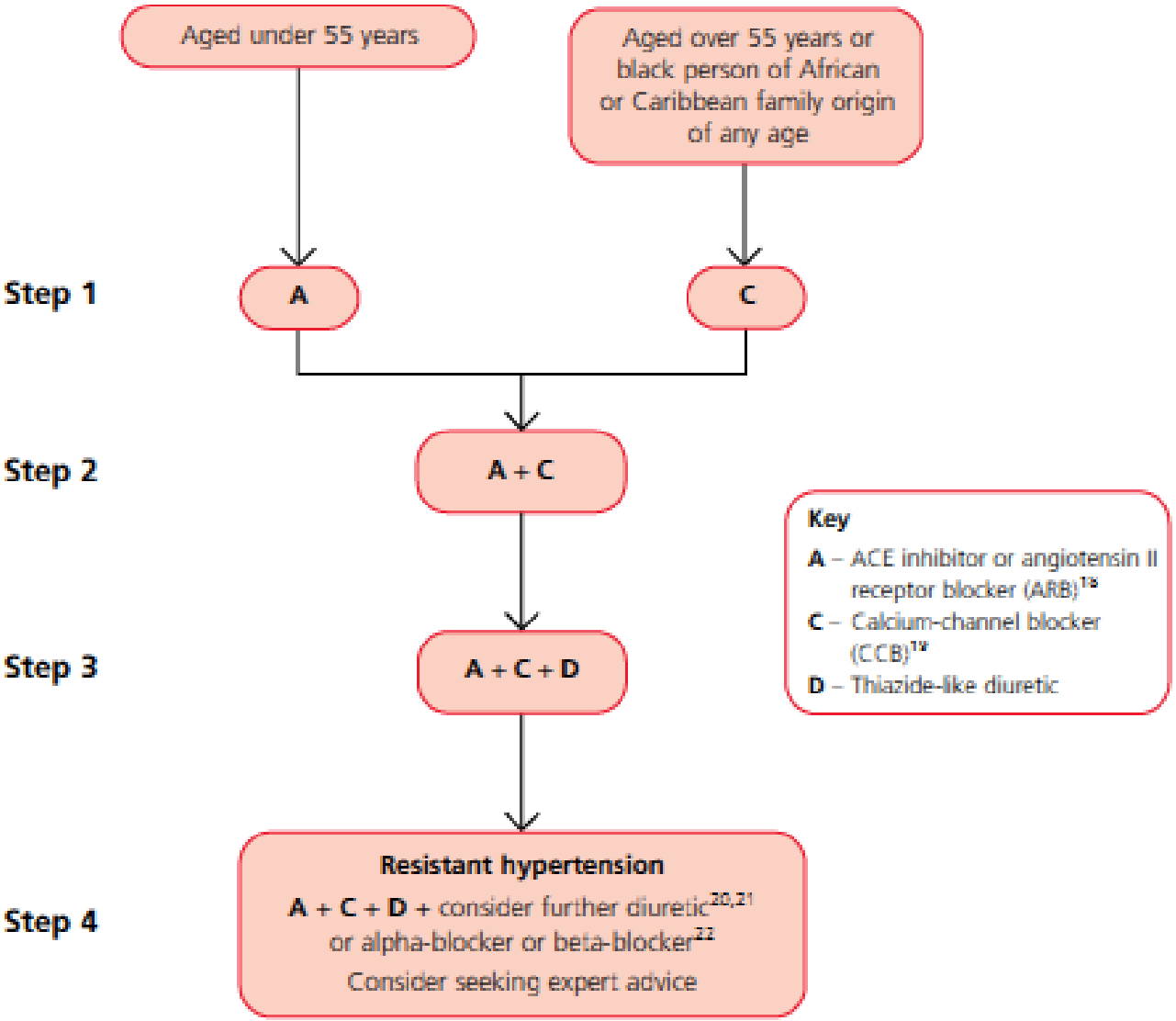
GUIDELINES - API



BHS
British Hypertension Society

NHS
National Institute for
Health and Clinical Excellence

NICE Clinical Guideline 2011



HYPERTENSION COMBINATION THERAPY PROTOCOL DURING ASSOCIATED CO-MORBIDITIES

Treatment of Hypertension in Patients with Ischemic Heart Disease

Stable angina → 1. Beta-blocker
2. Long-acting CCB

ACEI are recommended for most patients with established CAD*

ARBs are not inferior to ACEI in IHD

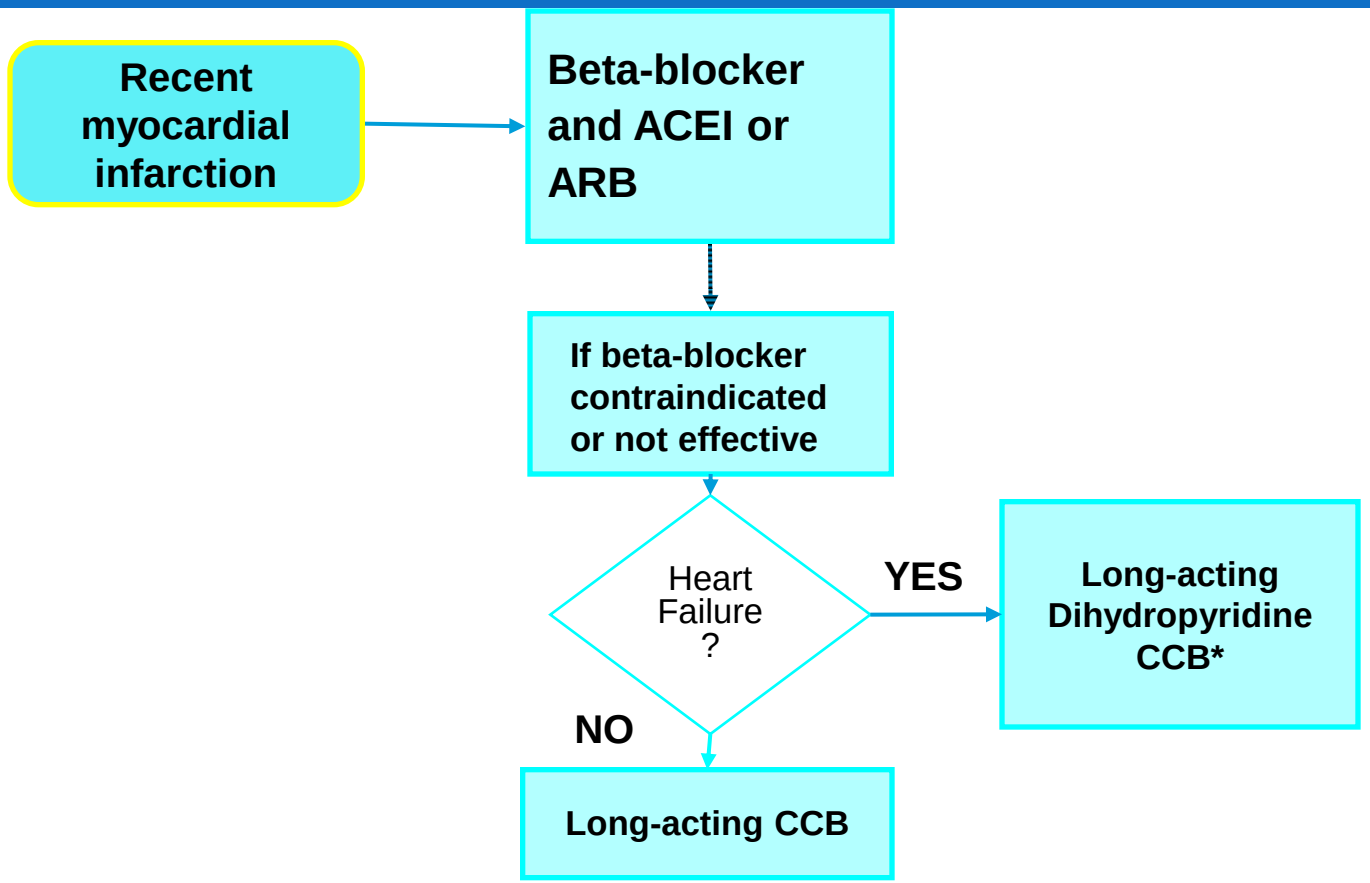
- Caution should be exercised when combining a non DHP-CCB and a beta-blocker
- If abnormal systolic left ventricular function: avoid non DHP-CCB (Verapamil or Diltiazem)
- Dual therapy with an ACEI and an ARB are not recommended in the absence of refractory heart failure
- The combination of an ACEi and CCB is preferred

***Those at low risk with well controlled risk factors may not benefit from ACEI therapy**

~~Short-acting nifedipine~~

CHEP guidelines 2014

Treatment of Hypertension in Patients *with* Recent ST Segment Elevation-MI or non-ST Segment Elevation-MI



***Avoid non dihydropyridine CCBs (diltiazem, verapamil)**

CHEP guidelines 2014

Treatment of Hypertension with Left Ventricular Systolic Dysfunction

Systolic cardiac dysfunction

- **ACEI and Beta blocker**
- **if ACEI intolerant: ARB**

Titrate doses of ACEI or ARB to those used in clinical trials

If additional therapy is needed:

- Diuretic (Thiazide for hypertension; Loop for volume control)
- **for CHF class II-IV or post MI and selected patients with LV dysfunction (see notes): Aldosterone Antagonist**

If ACEI and ARB are contraindicated: Hydralazine and Isosorbide dinitrate in combination

If additional antihypertensive therapy is needed:

- ACEI / ARB Combination
- Long-acting DHP-CCB (Amlodipine)

~~Non dihydropyridine CCB~~

Beta-blockers used in clinical trials were bisoprolol, carvedilol and metoprolol.

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Treatment of Hypertension in Patients with Non Diabetic Chronic Kidney Disease

Target BP: < 140/90 mmHg

Chronic kidney disease and proteinuria *

→ **ACEI or ARB (if ACEI intolerant)**

Additive therapy: Thiazide diuretic.
Alternate: If volume overload: loop diuretic

Combination with other agents

*** albumin:creatinine ratio [ACR] > 30 mg/mmol**
or **urinary protein > 500 mg/24hr**

~~ACEI/ARB:~~
~~Bilateral renal artery stenosis~~

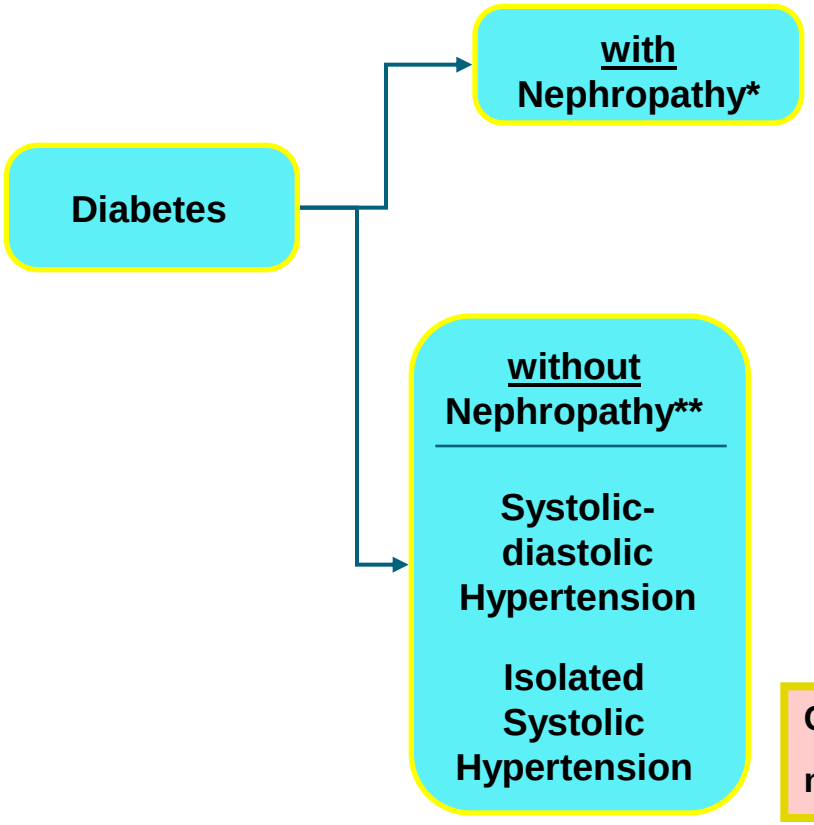
Monitor serum potassium and creatinine carefully in patients with CKD prescribed an ACEI or ARB

Combinations of a ACEI and a ARB are specifically not recommended in the absence of proteinuria

CHEP guidelines 2014

Treatment of Hypertension in association with Diabetes Mellitus

Threshold equal or over 130/80 mmHg and Target below 130/80 mmHg



Urinary albumin to creatinine ratio ≥ 2.0 mg/mmol in men or ≥ 2.8mg/mmol in women

A combination of 2 first line drugs may be considered as initial therapy if the blood pressure is ≥20 mmHg systolic or ≥10 mmHg diastolic above target

Combinations of an ACEI with an ARB are specifically not recommended in the absence of proteinuria

*** based on at least 2 of 3 measurements**

CHEP guidelines 2014

Treatment of Hypertension in association with Diabetic Nephropathy

THRESHOLD equal or over 130/80 mmHg and TARGET below 130/80 mmHg

DIABETES with Nephropathy

→ **ACE Inhibitor or ARB**

→ **Addition of one or more of** Long-acting CCB or Thiazide diuretic

IF ACEI and ARB are contraindicated or not tolerated, SUBSTITUTE
- **Long-acting CCB or**
- **Thiazide diuretic**

3 - 4 drugs combination may be needed

If Creatinine over 150 µmol/L or creatinine clearance below 30 ml/min (0.5 ml/sec), a loop diuretic should be substituted for a thiazide diuretic if control of volume is desired

Monitor serum potassium and creatinine carefully in patients with CKD prescribed an ACEI or ARB

CHEP guidelines 2014

Treatment of Systolic-Diastolic Hypertension without Diabetic Nephropathy

Threshold equal or over 130/80 mmHg and TARGET below 130/80 mmHg

Diabetes <u>without</u> Nephropathy

1. ACE Inhibitor or ARB or

2. Dihydropyridine CCB or Thiazide diuretic

Combination of first line agents

Addition of one or more of: Cardioselective BB or Long-acting CCB

DHP: dihydropyridine

IF ACE Inhibitor and ARB and DHP-CCB and Thiazide are contraindicated or not tolerated,
SUBSTITUTE
- **Cardioselective BB* or**
- **Long-acting NON DHP-CCB**

Combinations of an ACE Inhibitor with an ARB are specifically not recommended in the absence of proteinuria

*** Cardioselective BB: Acebutolol, Atenolol, Bisoprolol , Metoprolol**

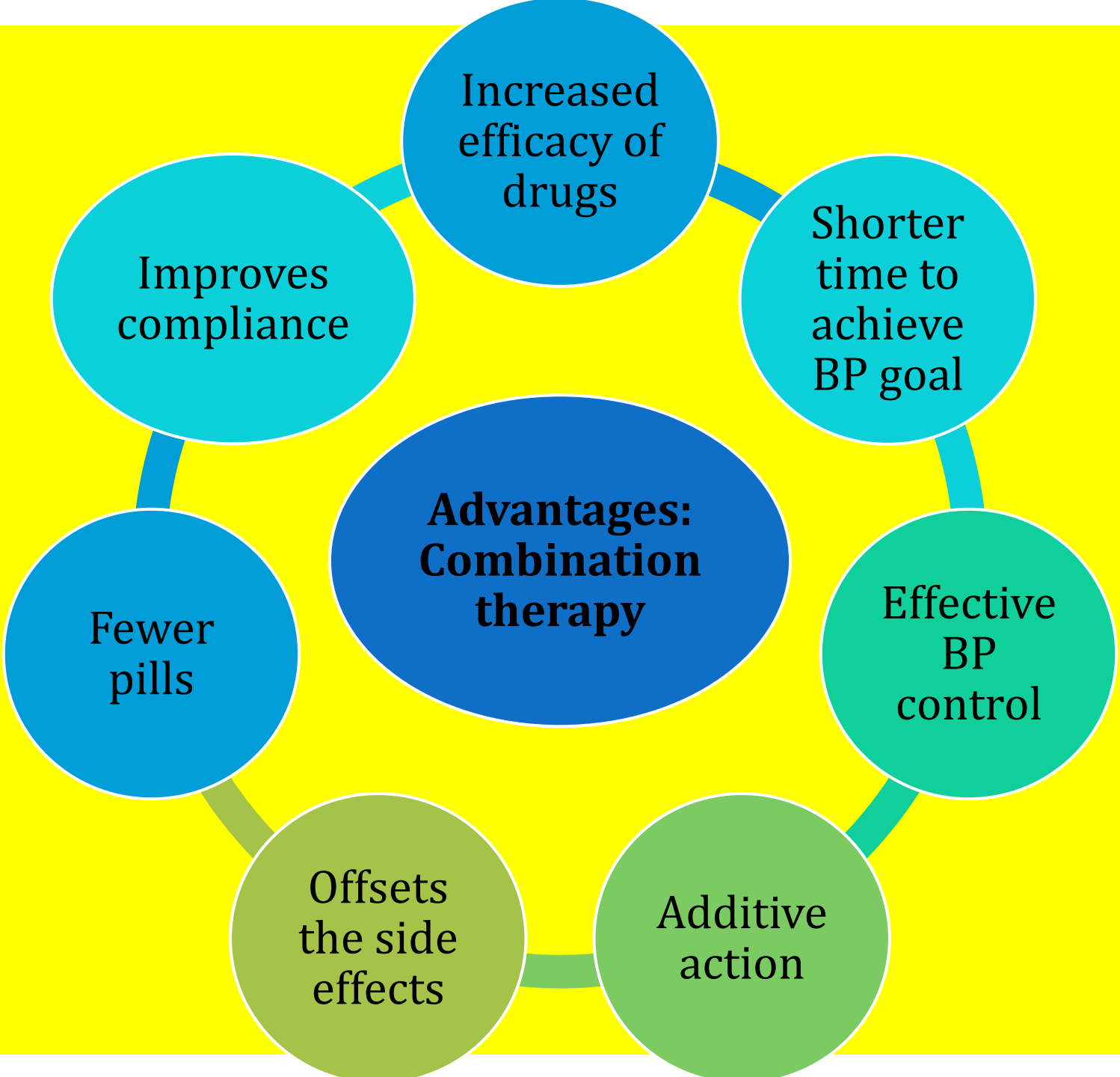
More than 3 drugs may be needed to reach target values for diabetic patients

CHEP guidelines 2014

Summary & Conclusion

Summary 1

- Controlling hypertension reduces CV outcomes
- Doubling of CV risk with BP increases of 20/10mmHg
- Majority of patients require >2 drugs to achieve BP goal
- The use of single pill combinations can further improve BP control and reduce cardiovascular morbidity and mortality
- Combination therapy is recommended in treatment guidelines


Increased efficacy of drugs
Shorter time to achieve BP goal
Effective BP control
Additive action
Offsets the side effects
Fewer pills
Improves compliance
Advantages: Combination therapy


thank you
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рахмат
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Баярлалаа
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