”Hypertensive Care Beyond BP Control: Evidence for treatment with co-morbid conditions”

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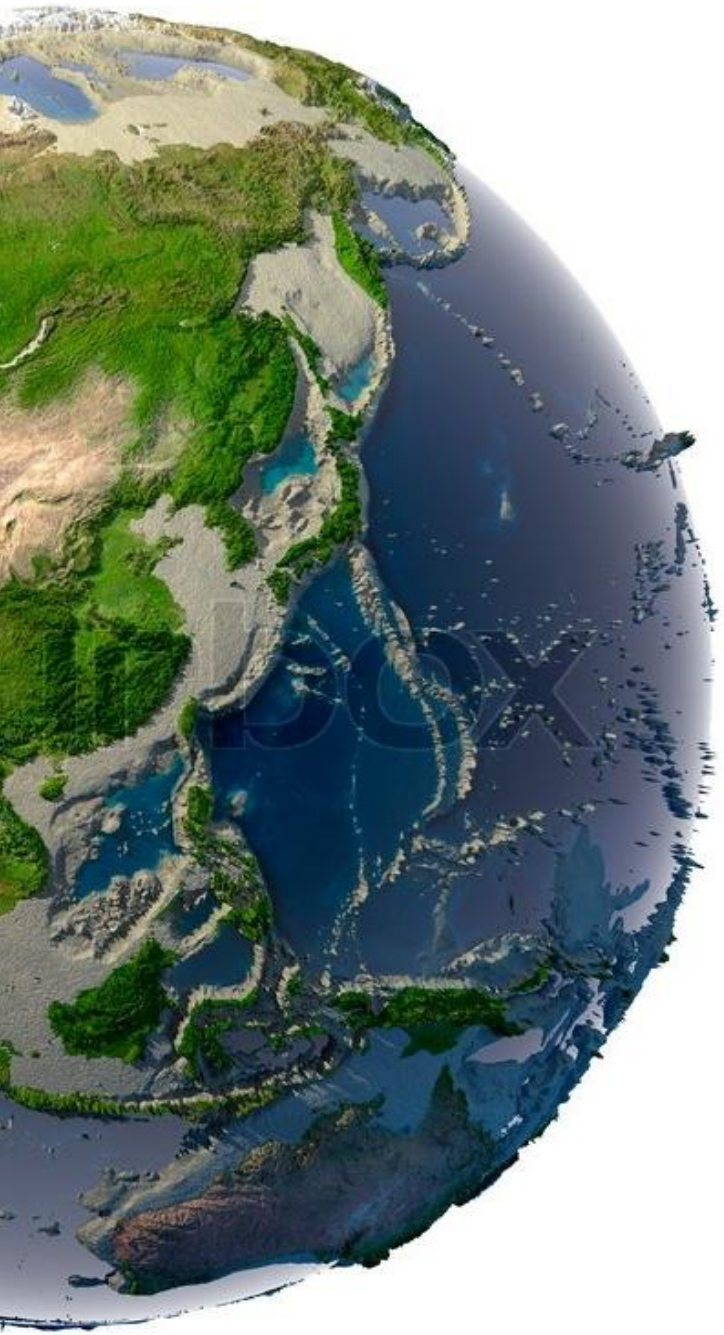
HIGHLITE

- Hypertension and Heart Failure
- Hypertension: What the guideline says
- How to improved outcome?

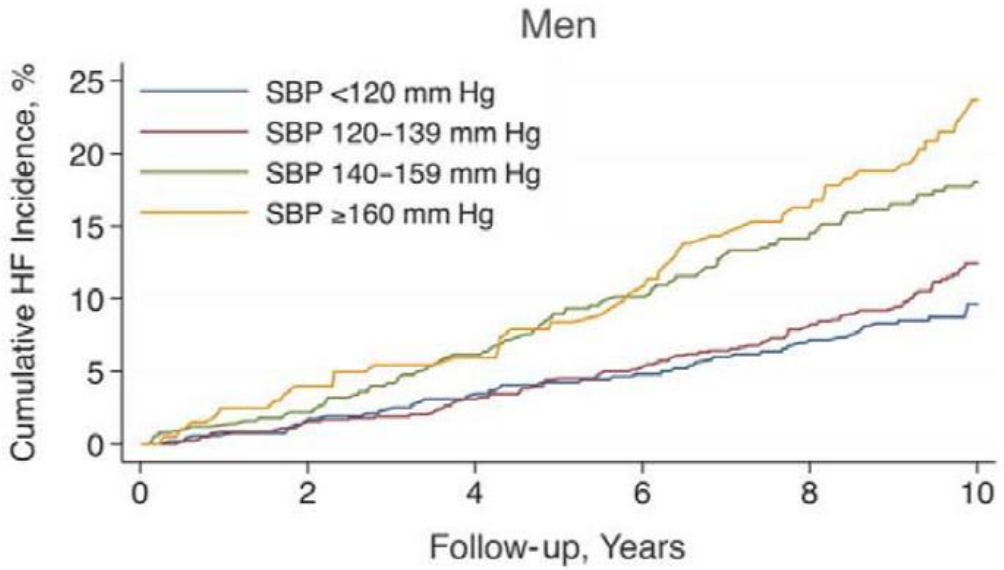


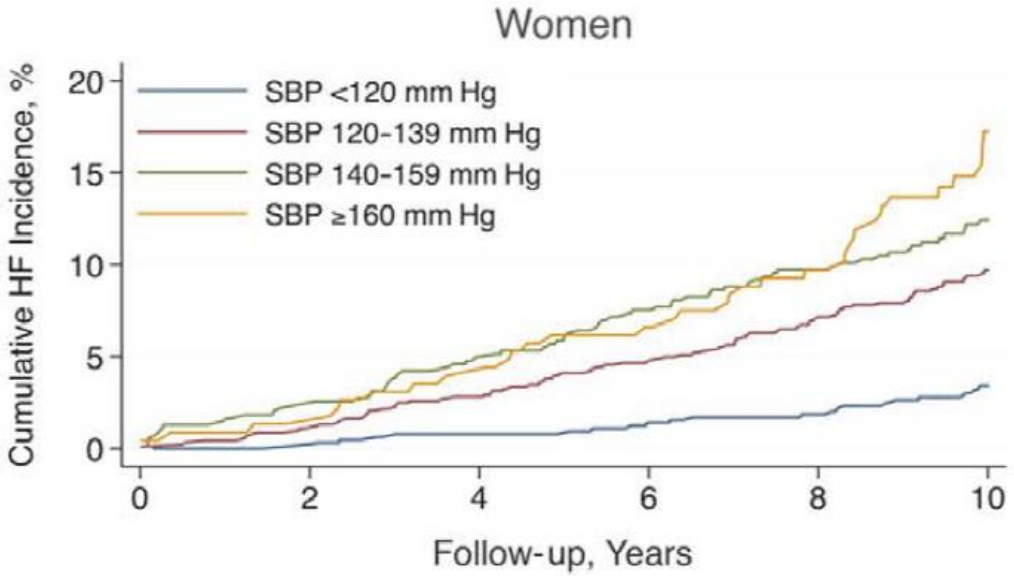
1 in 3 adults suffer from hypertension

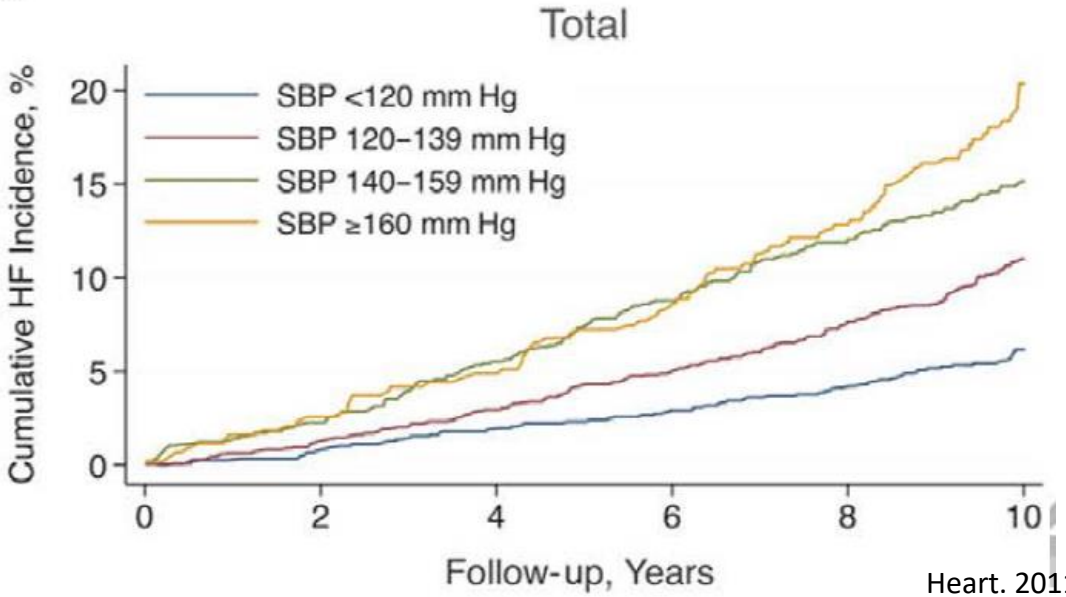
1 in 3 adults with hypertension do not know they have this disease

1 in 3 adults treating their hypertension cannot keep it under 140/90

Hypertension & Heart Failure

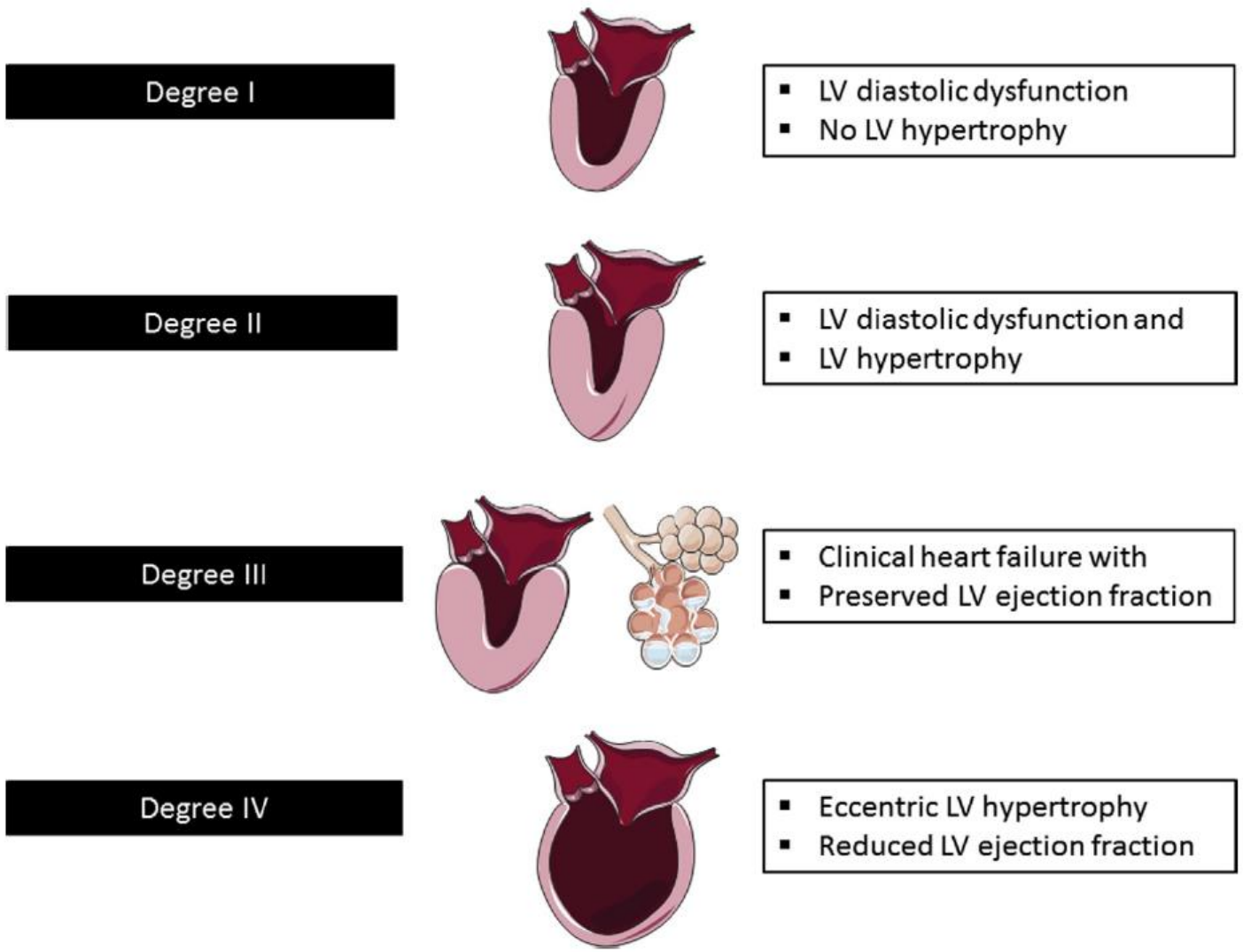






Heart. 2011;97:1304–1311. doi: 10.1136/hrt.2011.225482.

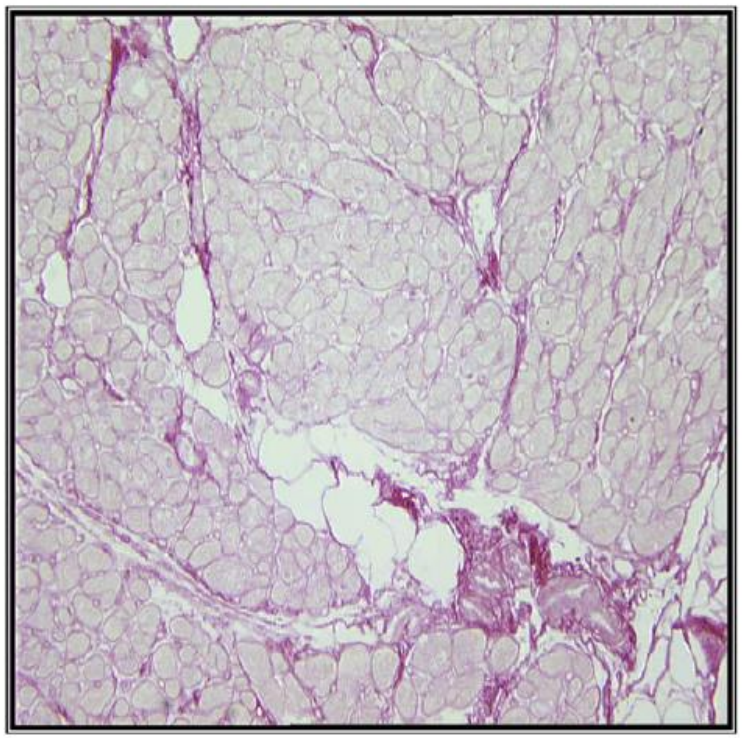
FIGURE 1 Staging of Hypertensive Heart Disease



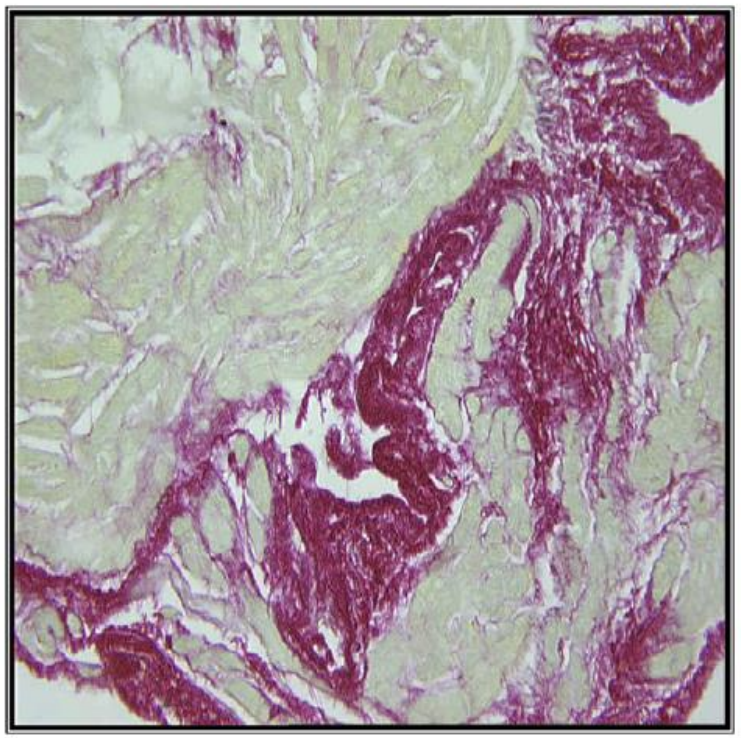
LV = left ventricular.

Iriarte M, Murga N, Sagastagoitia D, et al. Classification of hypertensive cardiomyopathy. Eur Heart J 1993;14 Suppl J:95–101.

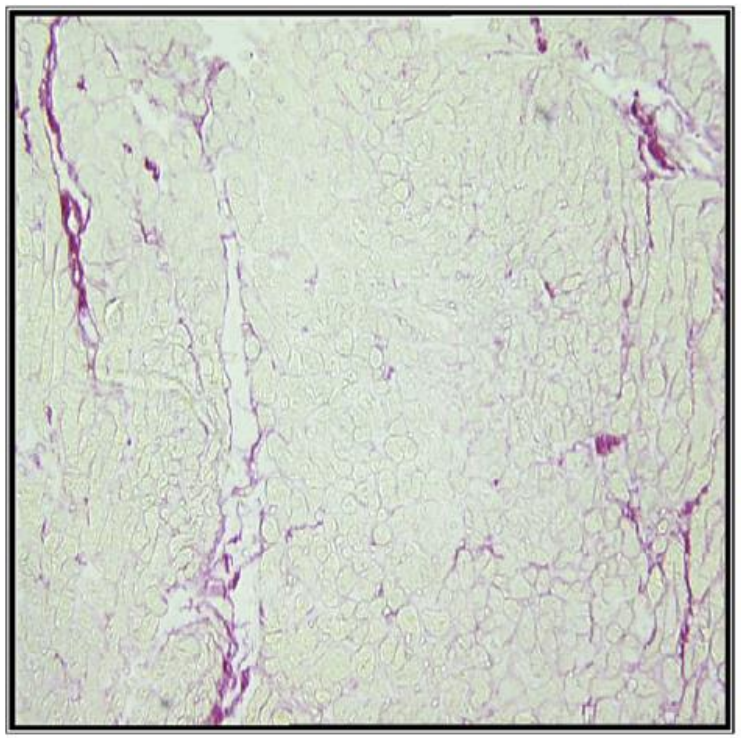
Hypertensive patients



Patient with asymptomatic LVH



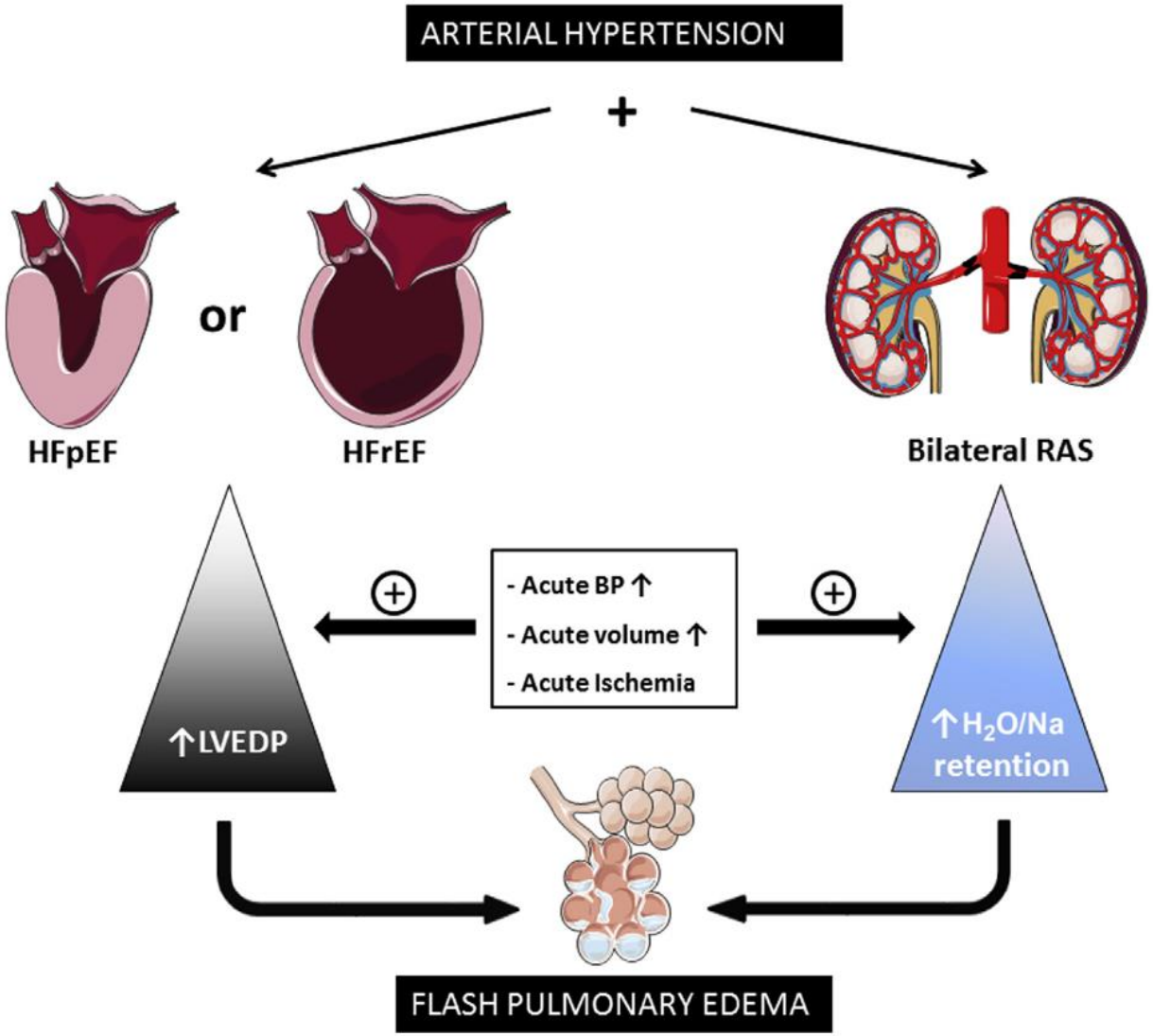
Patient with HFPEF



Patient with HFREF

Heart Failure Clin 10 (2014) 233–242. doi:10.1016/j.hfc.2013.12.004

FIGURE 2 Pickering Syndrome



Three main pathophysiological mechanisms contribute to the development of flash pulmonary edema: 1) defective pressure natriuresis with sodium and fluid retention; 2) increased left ventricular end-diastolic pressure (LVEDP) associated with left ventricular hypertrophy and stiffening; and 3) failure of the pulmonary capillary blood-gas barrier. BP = blood pressure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; RAS = renal artery stenosis.

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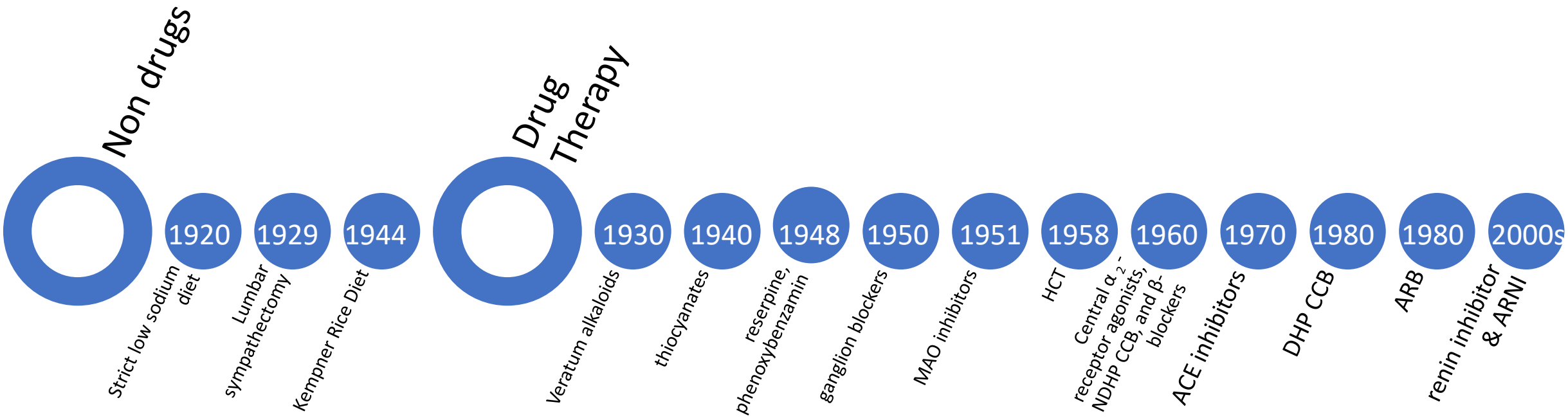
Millestones of Antihypertension Drugs



John J.V. McMurray and Marc A. Pfeffer. 2020; Goldman-Cecil Medicine, 53, 281-297.e1

Trials

Therapy	Stage A	Stage B	Stage C	Stage D
Antihypertensive agents	✓	✓	✓	
Statins	✓	✓	(✓)	(✓)
β-blockers		✓	✓	✓
ACE inhibitors	✓	✓	✓	✓
Angiotensin II receptor blockers (ARBs)		✓	✓	✓
Hydralazine/ nitrates			✓	✓
ARNI			✓	✓
Digoxin			✓	✓
Ivabradine			✓	✓
Mineralocorticoid antagonists			✓	✓
Implantable cardioverter-defibrillator (ICD)		✓	✓	(✓)
Cardiac resynchronization therapy (CRT)			✓	✓
Left ventricle assist device (LVAD)				✓
	Stage A High risk for HF without structural heart disease or symptoms of HF	**Stage B** Structural heart disease but without signs or symptoms of HF	**Stage C** Structural heart disease with prior or current symptoms of HF	**Stage D** Refractory HF requiring specialized interventions
	Patients with • Hypertension	Patients with • Previous MI	Patients with • Known structural heart	Patients with marked symptoms at rest despite

Contributory Risk and Management of Comorbidities of Hypertension, Obesity, Diabetes Mellitus, Hyperlipidemia, and Metabolic Syndrome in Chronic Heart Failure

A Scientific Statement From the American Heart Association

Table 2. Recommendation for the Treatment of Hypertension in Stage A HF: Asymptomatic Patients at Risk for HF

Recommendation	COR	LOE	Referenced Guideline	References
Hypertension should be controlled in accordance with contemporary guidelines to lower the risk of development of HF.	I	A	7–9	14, 21–28, 30, 31

Circulation. 2016;134:00–00. DOI: 10.1161/CIR.0000000000000450

Contributory Risk and Management of Comorbidities of Hypertension, Obesity, Diabetes Mellitus, Hyperlipidemia, and Metabolic Syndrome in Chronic Heart Failure

A Scientific Statement From the American Heart Association

Table 3. Recommendations for the Treatment of Hypertension in Stage B HF: Patients With Cardiac Structural Abnormalities or Remodeling Who Have Not Developed HF Symptoms

Recommendations	COR	LOE	Referenced Guideline	References
In patients with structural cardiac abnormalities, including LV hypertrophy, BP should be controlled in accordance with clinical practice guidelines for hypertension to prevent symptomatic HF.	I	A	7–9, 29	14, 22, 31, 35, 47
Nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low LVEF. α-Adrenergic blockers such as doxazosin should be avoided and might be used only if other drugs for the management of hypertension and HF are inadequate to achieve BP control at maximum tolerated doses.	III: Harm	C	8, 29, 48	46

Circulation. 2016;134:00–00. DOI: 10.1161/CIR.0000000000000450

Table 4. Recommendations for the Treatment of Hypertension in Stage C HF: Patients With Cardiac Structural Abnormalities or Remodeling With Prior or Current Symptoms of HF

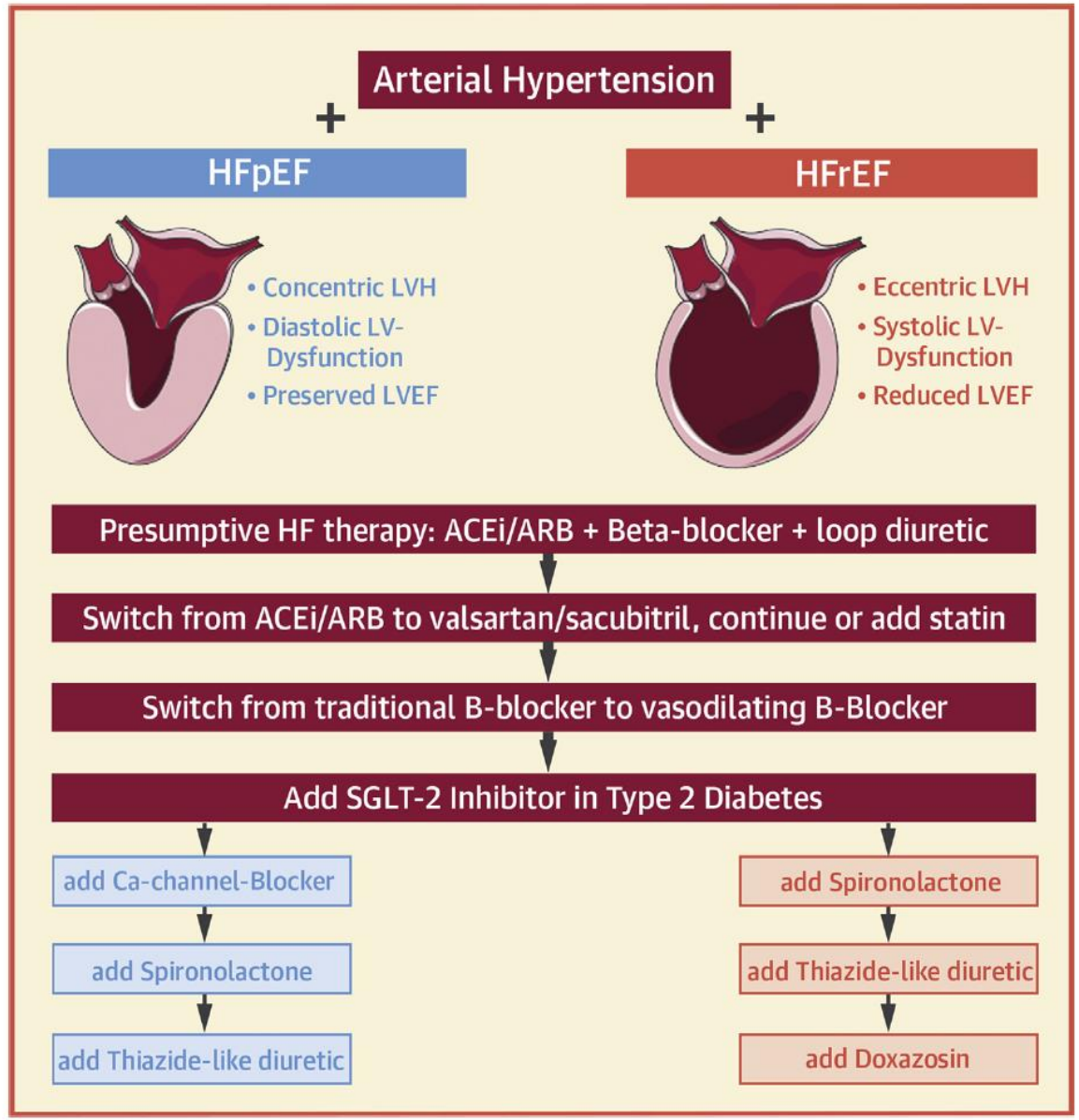
Recommendations	COR	LOE	Referenced Guideline	References
Patients with previous or current symptoms of HFrEF should be treated with GDMT, including diuretics, ACE inhibitors (or ARBs if ACE inhibitor intolerant), β-blockers, and aldosterone receptor antagonists, which have been proven to improve outcomes for patients with HF and can lower BP in hypertensive patients with HFrEF.	I	A for clinical outcomes, B for BP control	8, 29	50, 63–68
Addition of hydralazine/isosorbide dinitrate to the background treatment with ACE inhibitor or ARB and β-blocker in self-described black patients with HFrEF and persistent NYHA class III or IV HF symptoms is beneficial to reduce morbidity and mortality and can lower BP in hypertensive patients with HFrEF.	I	A for reduction in morbidity and mortality in HF, B for BP control	8, 29	69, 70
The treatment of hypertension in patients with HF should include behavioral modification such as sodium restriction and a closely monitored exercise program. Weight reduction in overweight or obese, an appropriate diet, and moderation of alcohol intake are recommended in patients with hypertension.	I	C	7, 9, 14, 48	
Thiazide or thiazide-like diuretics can be useful for BP control and to reverse mild volume overload and associated symptoms in symptomatic patients with HF with volume overload. Loop diuretics, which are the preferred agents for treatment of congestion in symptomatic patients with HF, are less effective than thiazide or thiazide-like diuretics in lowering BP.	IIa	C	7, 8, 48	
Addition of hydralazine isosorbide to the background therapy with ACE inhibitor or ARB and β-blocker may be beneficial for BP control in nonblack patients with HFrEF and hypertension.	IIa	C	8	71
Drugs to avoid in patients with HF and hypertension include nondihydropyridine calcium channel blockers (eg, verapamil and diltiazem) and moxonidine. An attempt should be made to avoid α-adrenergic blockers such as doxazosin; they might be used only if other drugs for the management of hypertension and HF are inadequate to achieve BP control at maximum tolerated doses.	III: Harm	C	8, 14, 29, 48	

Relative Risk and Benefit of Antihypertensive Drug Classes

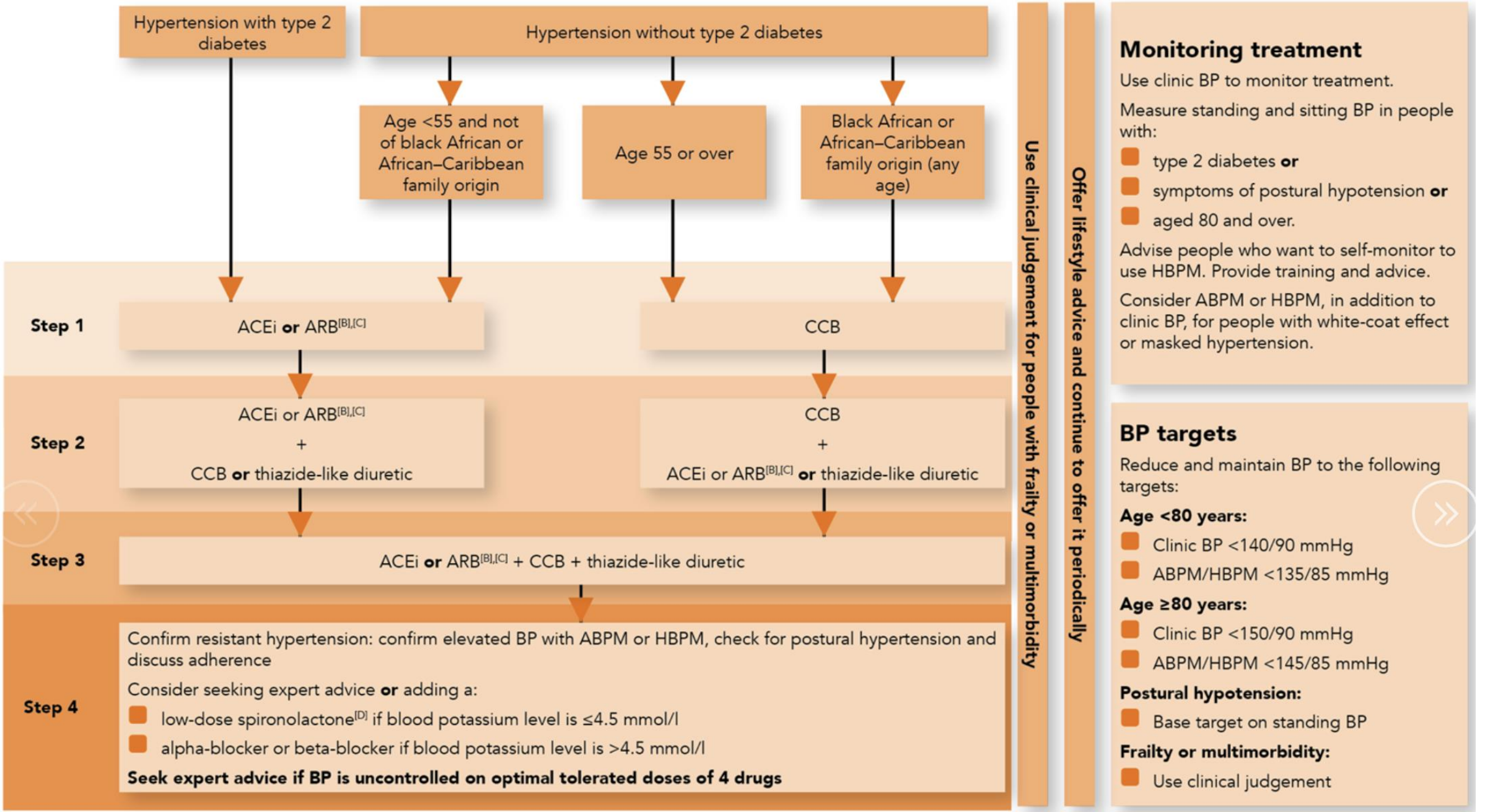
Outcome	Thiazide Diuretics (D)	Calcium Channel Blockers (C)	β-Blockers (B)	ACE/ARBs* (A)
Unstable angina	0.89	0.88	0.98	0.97
Myocardial infarction	0.78	0.79	0.85	0.81
Diabetes	0.98	0.80	1.13	0.72
Stroke	0.69	0.65	0.85	0.73
Heart failure	0.53	0.73	0.76	0.64
Death	0.91	0.88	0.93	0.90

Modified from data at www.nice.org.uk/CG034guidance.

CENTRAL ILLUSTRATION **Suggested Empirical Antihypertensive Strategy in HF Patients With Persisting Hypertension**



Messerli, F.H. et al. J Am Coll Cardiol HF. 2017;5(8):543-51.

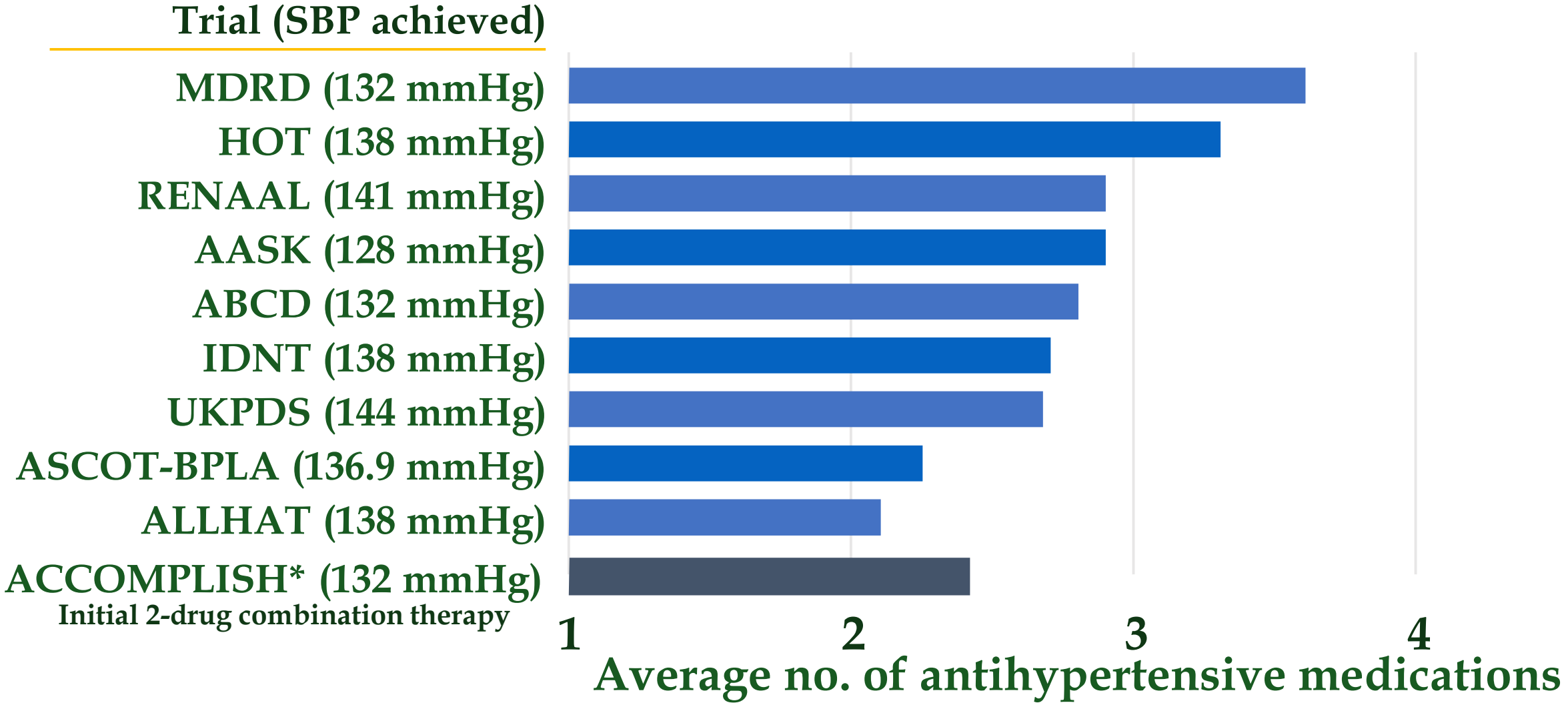


NICE Guidelines on Hypertension, 2019

•Multiple antihypertensive agents are needed to reach BP goal

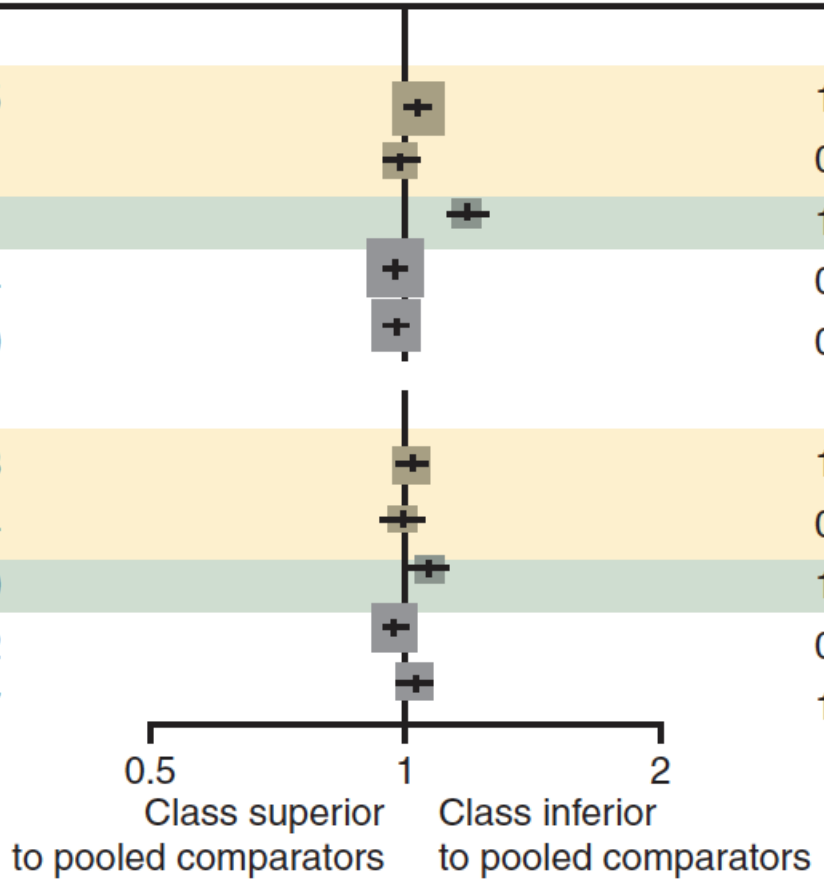
Lancet 2005;366:895-906, Am J Med 2004;116(5A):30S-8.

Monotherapy fails in many patients to reach the goal of BP.
Majority of patients in general and diabetes, in particular, require combination therapy.



Effects of Reduction in Systolic BP Stratified by Class of Antihypertensive

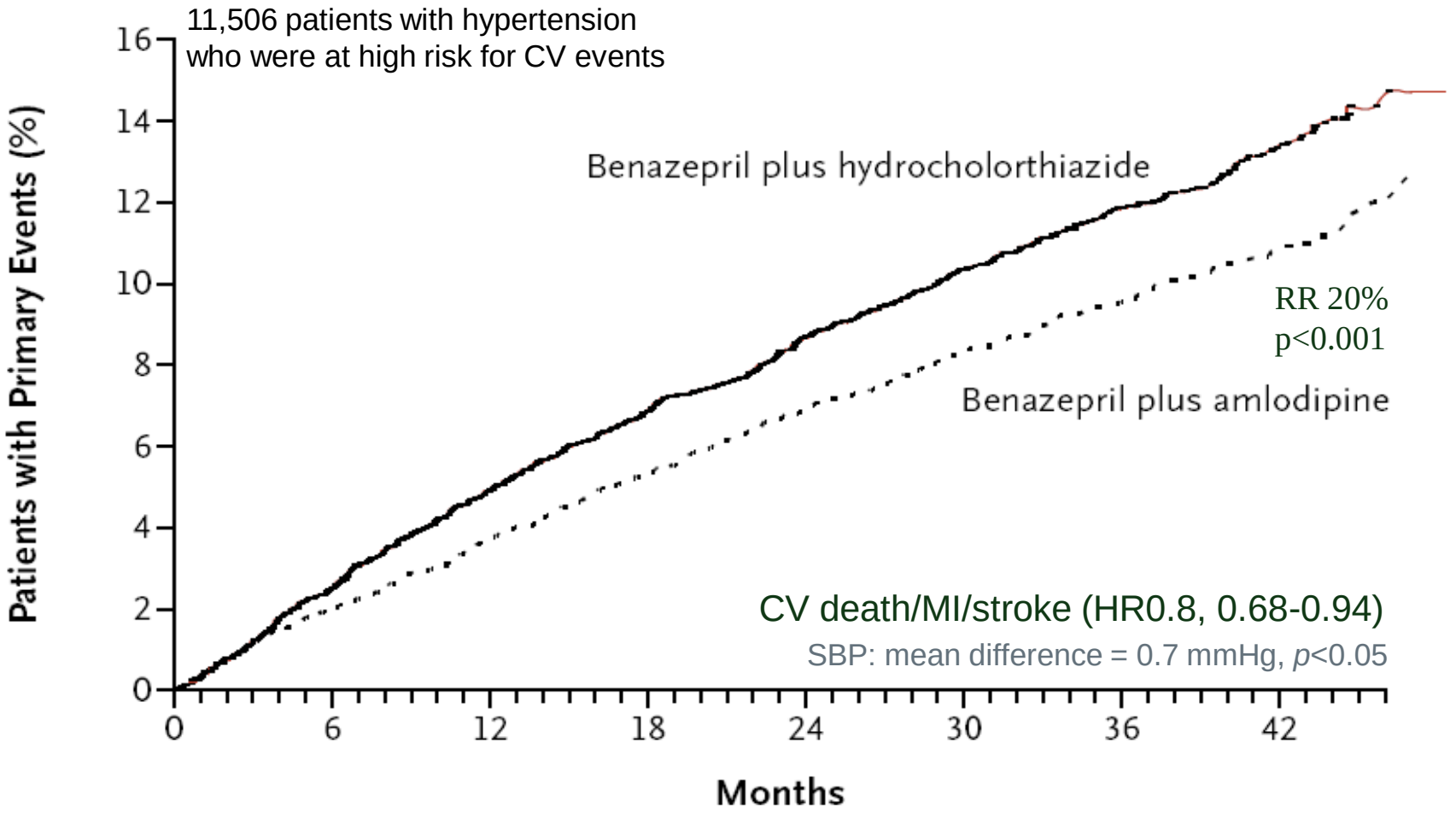
	Studies	Intervention		Control		RR (95% CI)
		Events	Participants	Events	Participants	
Major cardiovascular events						
ACE inhibitor	10	5379	31652	9766	50805	1.03 (1.00–1.06)
ARB	8	3647	27140	3779	29331	0.98 (0.93–1.02)
β blocker	9	2863	25989	2520	27231	1.17 (1.11–1.24)
CCB	21	7857	63693	12808	82904	0.97 (0.94–0.99)
Diuretic	11	5830	38353	6782	42410	0.97 (0.94–1.00)
All-cause mortality						
ACE inhibitor	14	3321	33104	5865	52263	1.01 (0.97–1.05)
ARB	11	2546	29282	2638	31404	0.99 (0.94–1.04)
β blocker	12	2805	40953	2688	42170	1.06 (1.01–1.12)
CCB	26	5602	76672	8428	95932	0.97 (0.94–1.00)
Diuretic	12	3425	41625	3806	45707	1.02 (0.97–1.06)



Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387(10022):957–967.

ACCOMPLISH: Primary Endpoint

CV death/MI/stroke/UA/revascularization

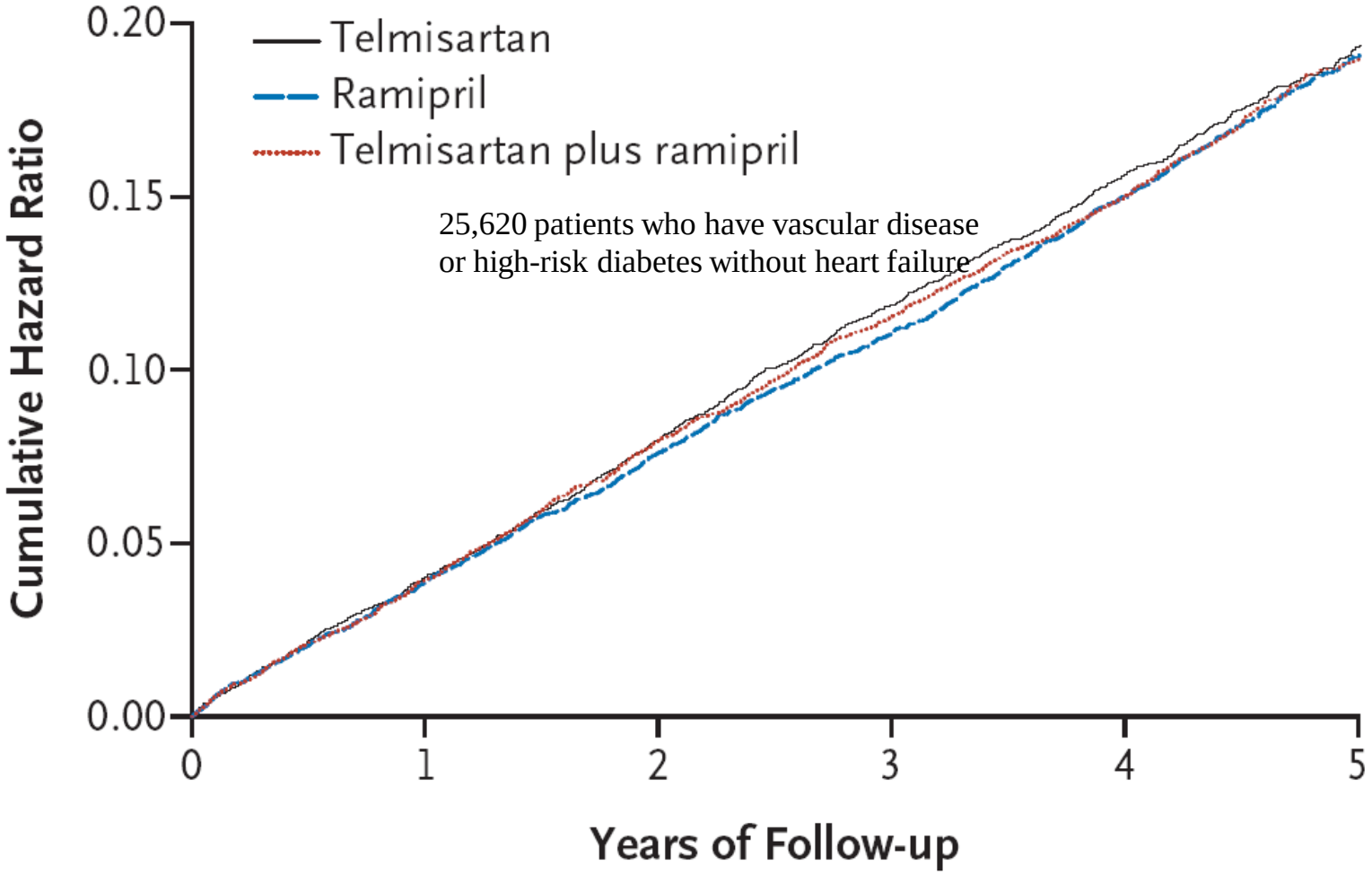


The results of ACCOMPLISH provide compelling evidence for initial combination therapy with ACEI / CCB and challenge diuretic-based regimens.

NEJM 2008;359:2417-28

Which to Choose, ACEi/ARB?? ONTARGET Study

CV death/MI/stroke/admission d/t heart failure



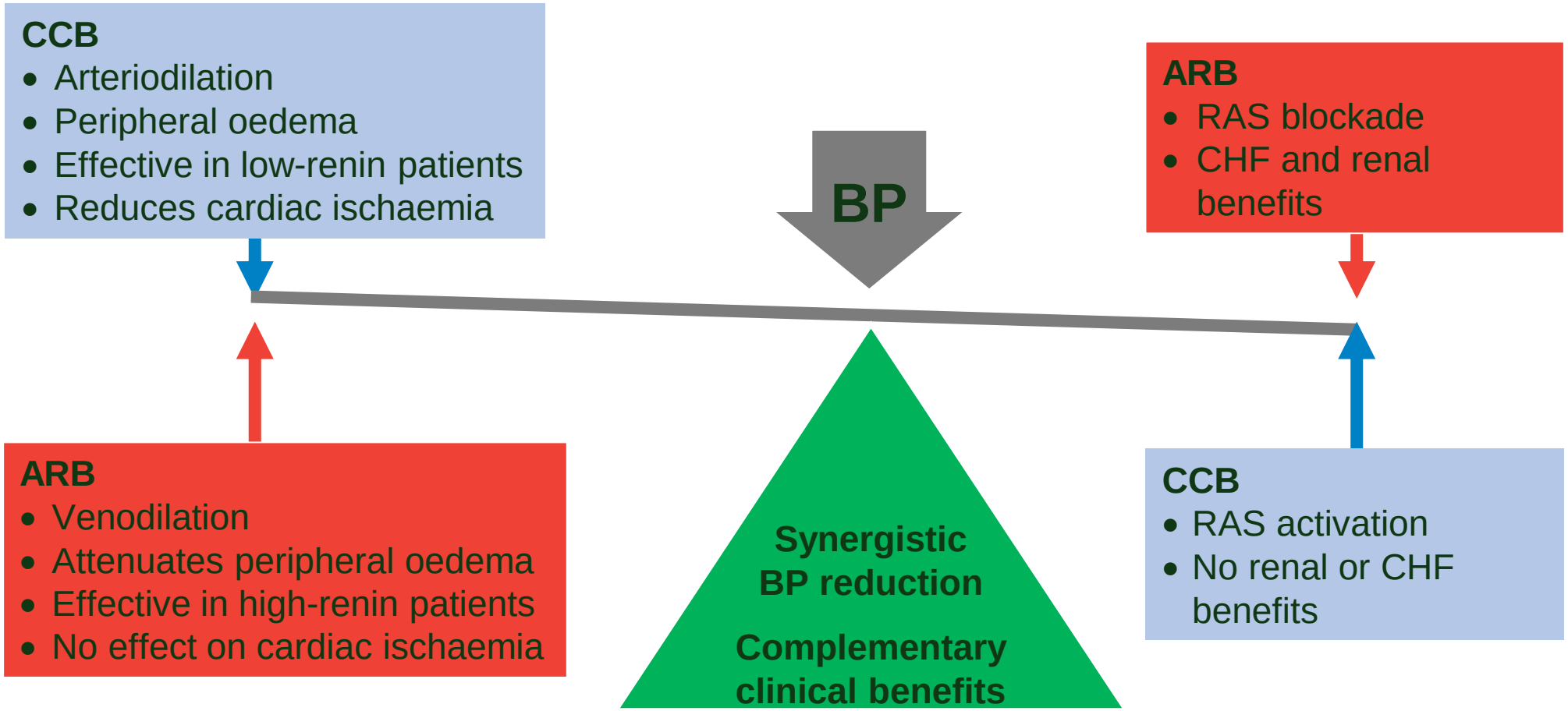
Telmisartan was equivalent to ramipril in patients with vascular disease or high risk diabetes, and was associated with less angioedema & cough.

N Engl J Med 2008;358:1547-59.

•ARB plus CCB Efficacy ⇑, Side Effects ⇓

Optimal combination therapy for hypertension

J Hum Hypertens. 2007;21:770–779



Combination therapy may be theoretically favored by the fact that multiple factors contribute to HT, and achieving control of BP with single agent acting through one particular mechanism may not be possible. Combinations may be individualized according to the presence of comorbidities. Fixed-dose combination in a single pill is useful for the elderly and for patients who are less compliant.

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Clinical Inertia in Heart Failure – PATIENTS MAJOR THREATS

"Ngapain diganti obat?
Pasiennya sudah nyaman kok!!"

"Pake dosis segitu aja, pasien udah enak kok.."

"No need laaah, periksa macam-macam lagi"

"Ga boleh ngapa-ngapain ya..
Wajib istirahat terus!!"

"Gagal jantungnya "ringan" kok"

"Malesnya, nambahi kerjaan aja!"

"……."
(tiba-tiba resep udah jadi, ga ngomong apa-apa)

"Pasien sudah "stabil" kenapa diutak atik??"

Clinical Inertia in Heart Failure – Main Problems

Inertia (*n*)

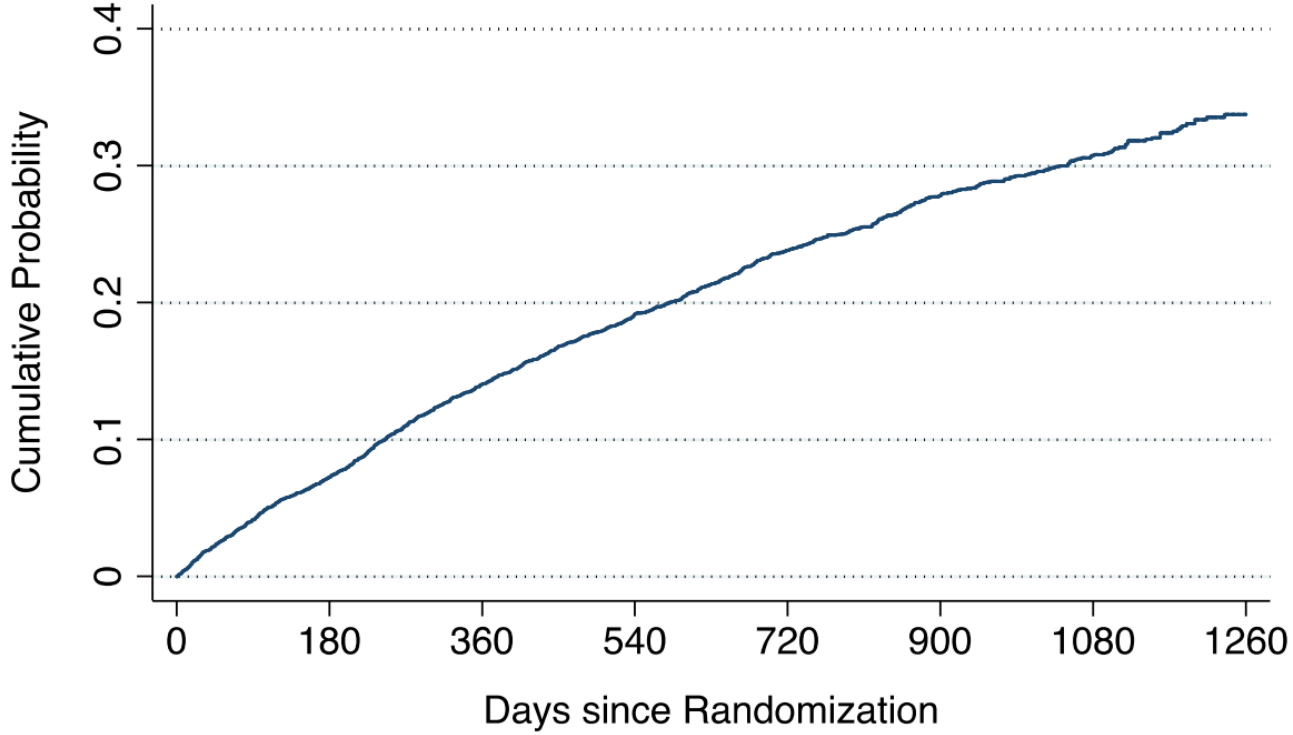
a tendency to do nothing or to remain unchanged

synonyms: inactivity, inaction, inactiveness, inertness, passivity

Cumulative risk of adverse outcome

Enalapril group in PARADIGM-HF
ACE inhibitor 100%, beta-blocker 93%, MRA 57%, digitalis 31%

Primary composite endpoint: CV death or HF hospitalization



Number at risk

Enalapril	4212	3883	3579	2922	2123	1488	853	236

McMurray et al. N Eng J Med 2014;371:993-1004

How to Improved Adherence?

- Adherence to treatment should be at the forefront of clinicians' minds because it is a determinant in achieving and maintaining BP targets and improving CV outcomes
- Unfortunately, adherence is generally low; studies show that up to 50% of patients stop taking their medications after 1 year, with a further 35% of patients stopping after 2 years
- Metaanalysis →single-pill combinations can increase adherence by 23%, respectively, when compared to monotherapy.

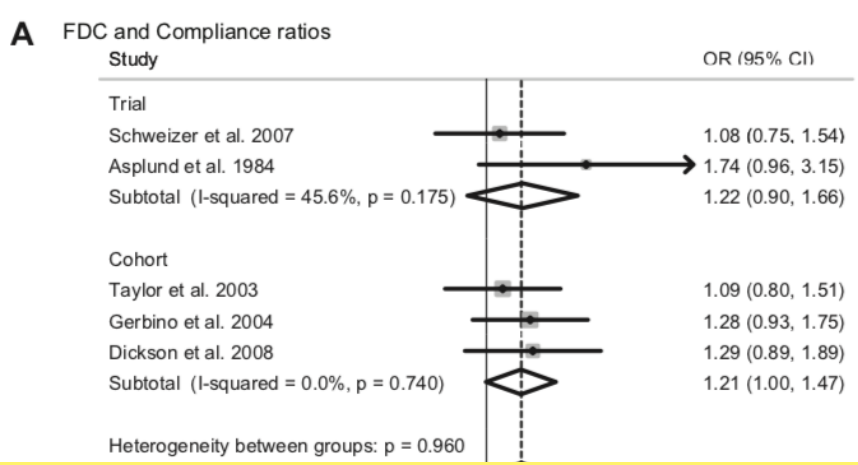
Compliance, Safety, and Effectiveness of Fixed-Dose Combinations of Antihypertensive Agents

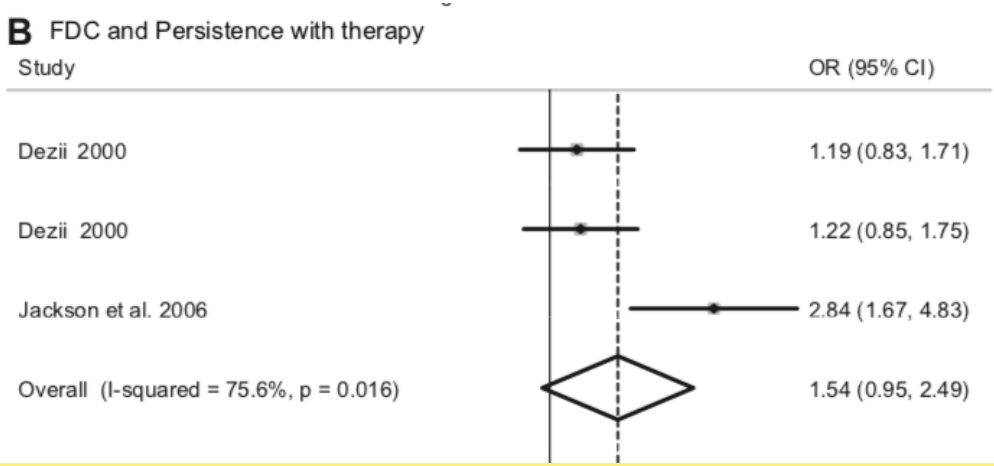
A Meta-Analysis

Ajay K. Gupta, Shazia Arshad, Neil R. Poulter

Abstract—Two or more antihypertensive agents are increasingly used to control blood pressure (BP) in hypertensive patients. However, it is unclear whether fixed-dose combinations (FDCs) of 2 antihypertensive agents in a single tablet provide greater benefits than the corresponding free-drug components given separately. A meta-analysis was performed to assess compliance, persistence, BP control, and safety associated with FDCs in comparison with their free-drug components. Fifteen included studies (n=32331) reported on ≥1 of the evaluated outcomes. In 3 cohort studies and 2 trials reporting on drug compliance (n=17 999), the use of FDCs was associated with significantly better compliance (odds ratio: 1.21 [95% CI: 1.03 to 1.43]; P=0.02) compared with its corresponding free-drug combinations. In 3 cohort studies (n=12 653), there was a nonsignificant improvement in persistence with therapy (odds ratio: 1.54 [95% CI: 0.95 to 2.49]; P=0.08), and in 5 trials (n=1775) the odds ratio for adverse effects for FDC use compared with free-drug combination use was 0.80 (95% CI: 0.58 to 1.11; P=0.19). In 9 trials (n=1671) with BP data, use of an FDC was associated with nonsignificant changes in systolic and diastolic BPs of 4.1 mm Hg (95% CI: −9.8 to 1.5; P=0.15) and 3.1 mm Hg (95% CI: −7.1 to 0.9; P=0.13), respectively. In these BP-lowering comparisons, there was heterogeneity associated with differences in study design but no publication bias. In conclusion, compared with free-drug combinations, FDCs of antihypertensive agents are associated with a significant improvement in compliance and with nonsignificant beneficial trends in BP and adverse effects. **(*Hypertension*. 2010;55:399-407.)**

Key Words: hypertension ■ antihypertensive agents ■ fixed-dose combination ■ treatment ■ drug combination ■ compliance ■ blood pressure





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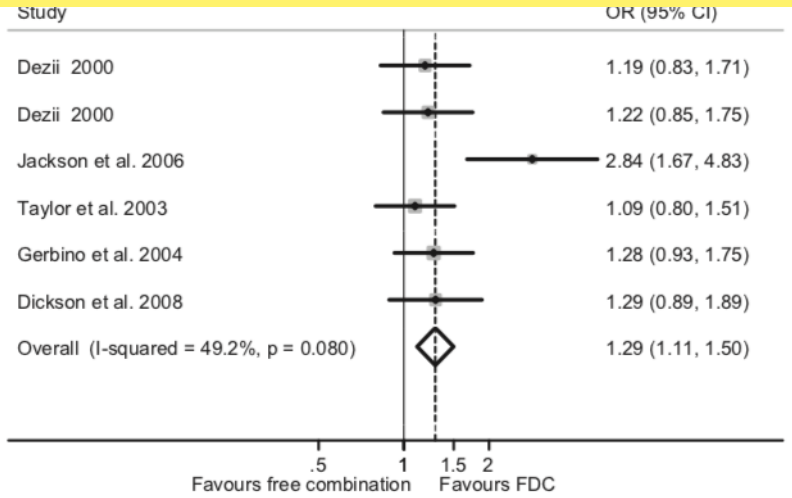

Summary

- Hypertension has become global pandemic, and main contributors to heart failure pathophysiology
- Controlling hypertension in early stages is a must to reduce HF incidence
- According to guidelines, RAAS blockers + CCB DHP is recommended to controlled hypertension in HF population
- Clinical inertia in controlling hypertension can be harm to patients
- Adherence to treatment should be at the forefront of clinicians' minds
- Fixed dose combination can beneficial to patient adherence → decreasing numbers of drop out from medication

Thank You

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