Relationship Between Hypertension and Heart Failure

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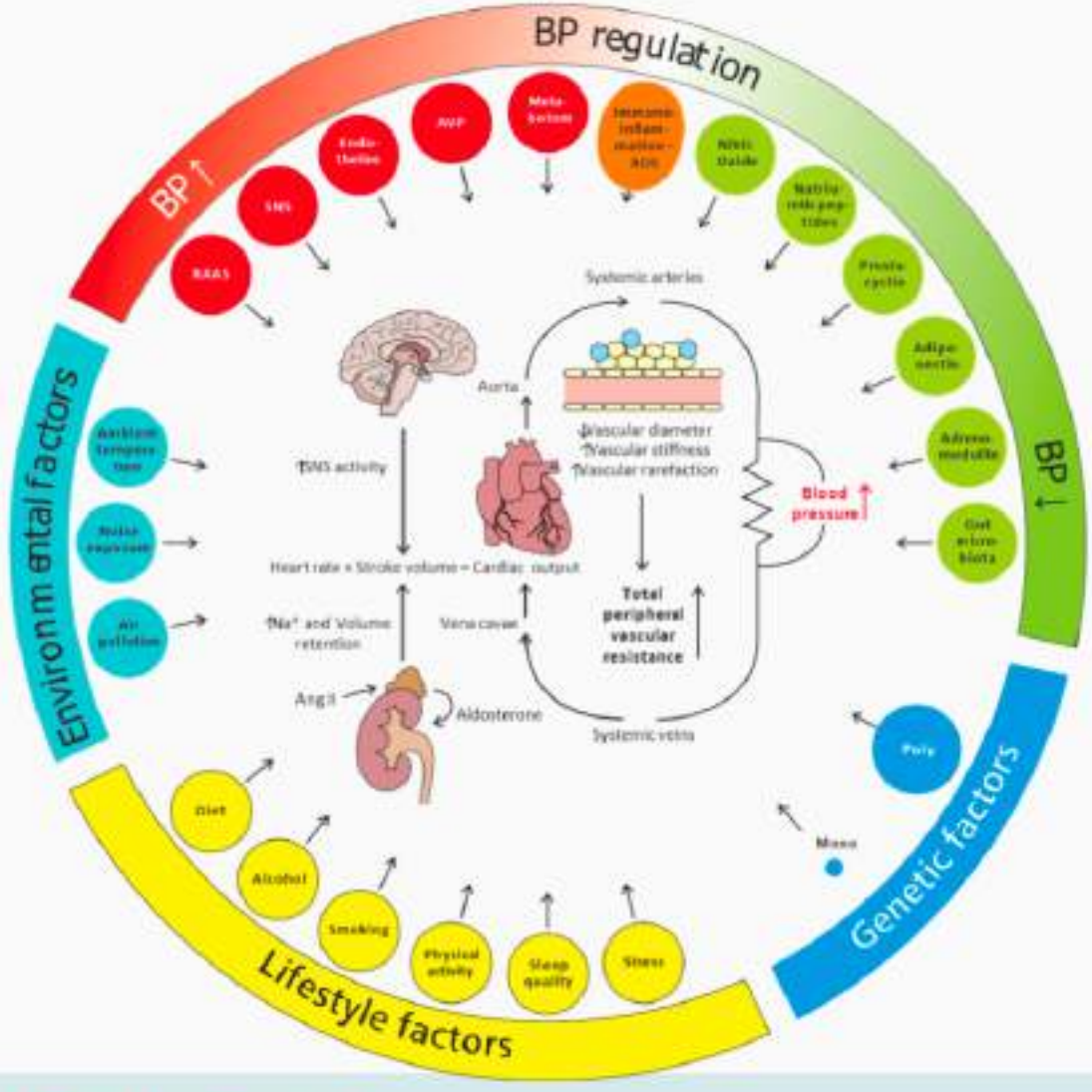
Mechanisms involved in BP regulation and the pathophysiology of hypertension



How does this relationship works?

- HT causes HF with direct effects (pressure and volume overload, neurohumoral activation)

- HT causes HF with indirect effects (via increased risk for coronary artery disease, increased risk for arrhythmias such as atrial fibrillation)

Definition of Heart Failure (HF)

Table 3 **Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction and preserved ejection fraction**

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.

[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.

[b]For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy or echocardiographic measures of impaired LV filling) makes the diagnosis more likely.

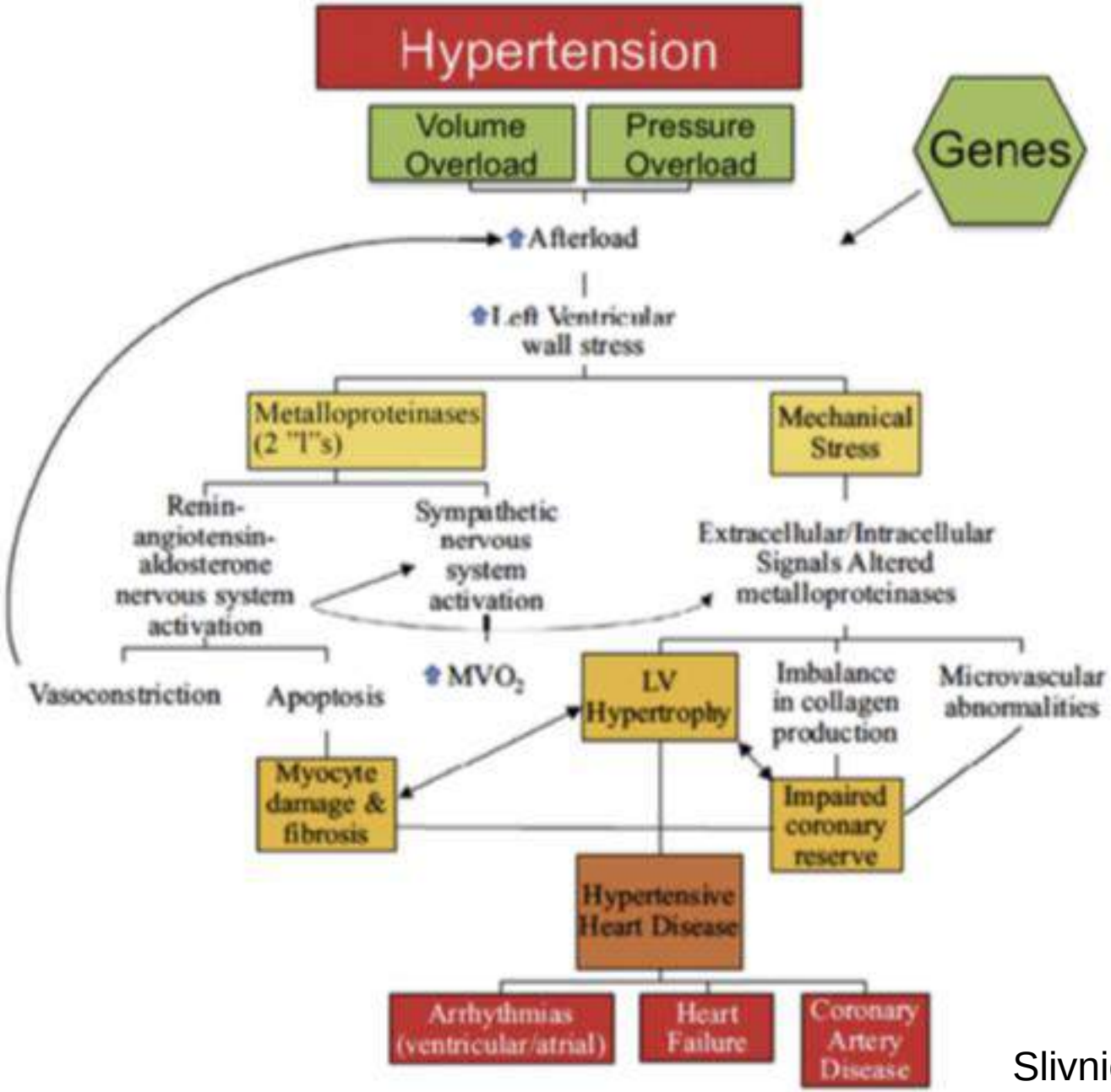
[c]For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

European Heart Journal (2021) 42, 3599□ 3726

Heart failure is a clinical diagnosis!

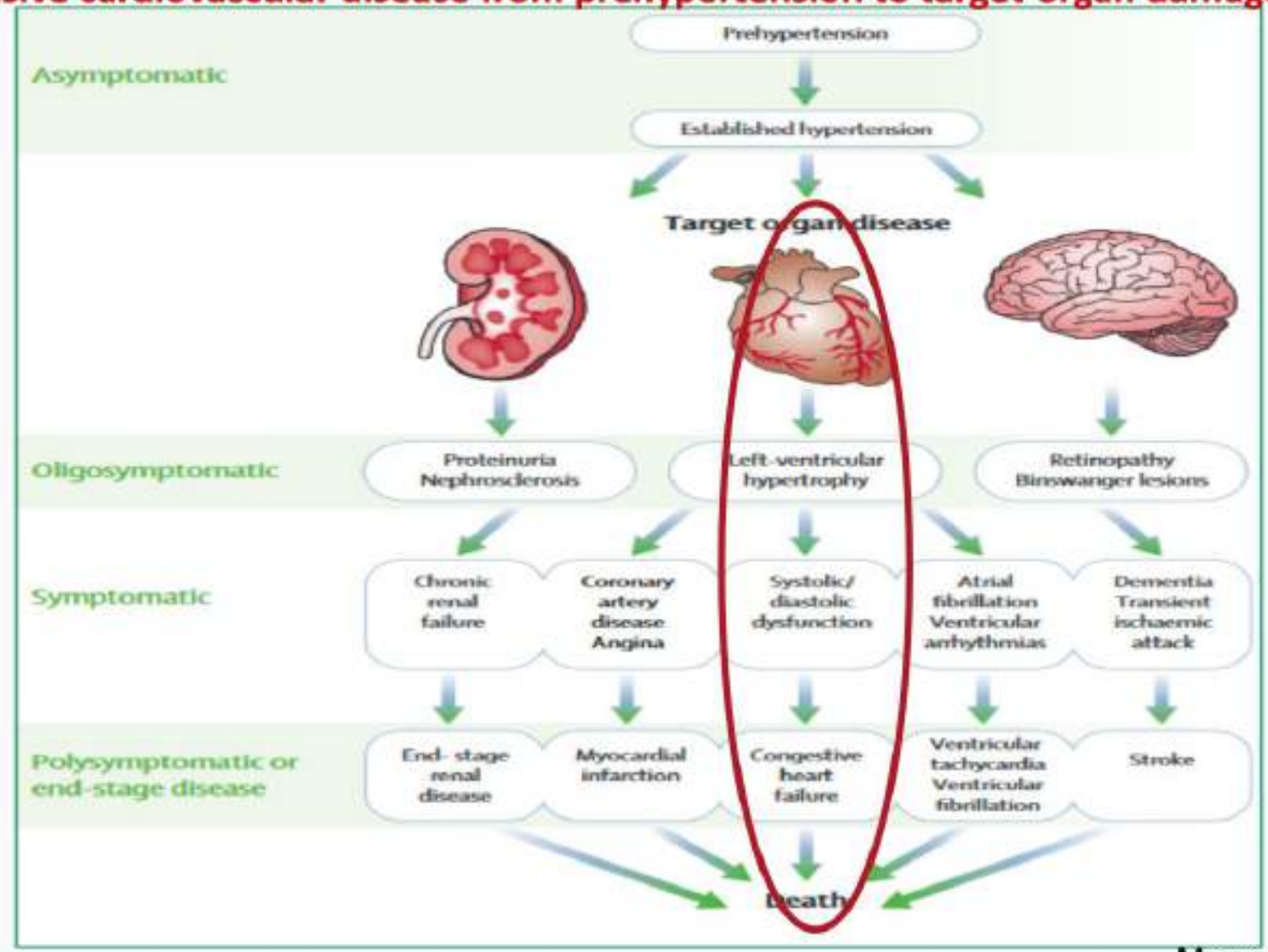
Recommended diagnostic tests in all patients with suspected chronic heart failure

Recommendations	Class[a]	Level[b]
BNP/NT-proBNP[c]	I	B
12-lead ECG	I	C
Transthoracic echocardiography	I	C
Chest radiography (X-ray)	I	C
Routine blood tests for comorbidities, including full blood count, urea and electrolytes, thyroid function, fasting glucose and HbA1c, lipids, iron status (TSAT and ferritin)	I	C



Slivnick and Lampert, doi.org/10.1016/j.hfc.2019.06.007

Range of hypertensive cardiovascular disease from prehypertension to target-organ damage and end-stage disease

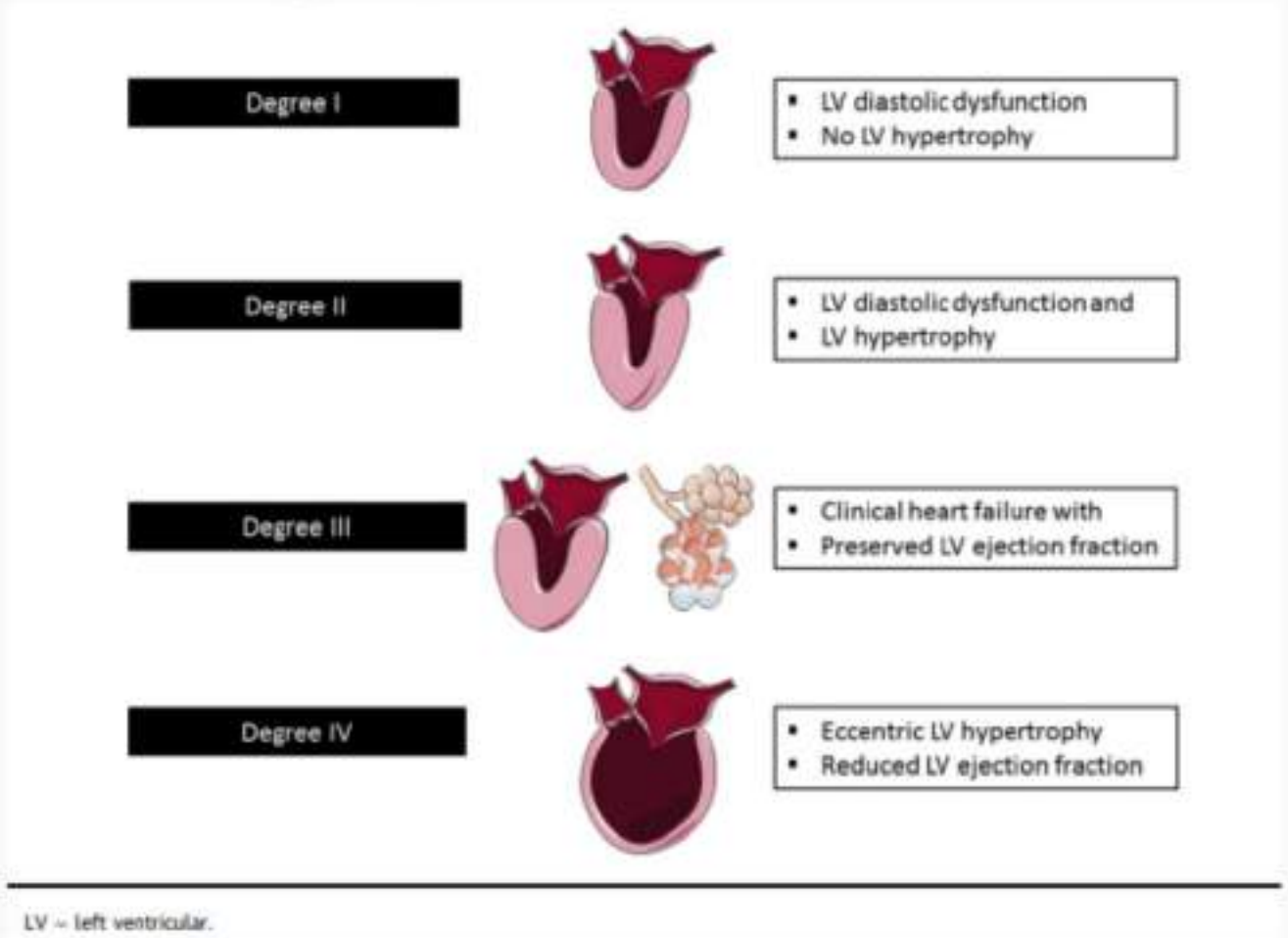


Messerli et al, Lancet 2007

Hypertensive heart disease and heart failure

- Changes in the left ventricle, left atrium, and coronary arteries as a result of chronic blood pressure elevation, which increases the workload on the heart inducing structural and functional changes
- Hypertrophy of the left ventricle, conduction arrhythmias, especially atrial fibrillation, and increased risk of coronary artery disease which can progress to heart failure

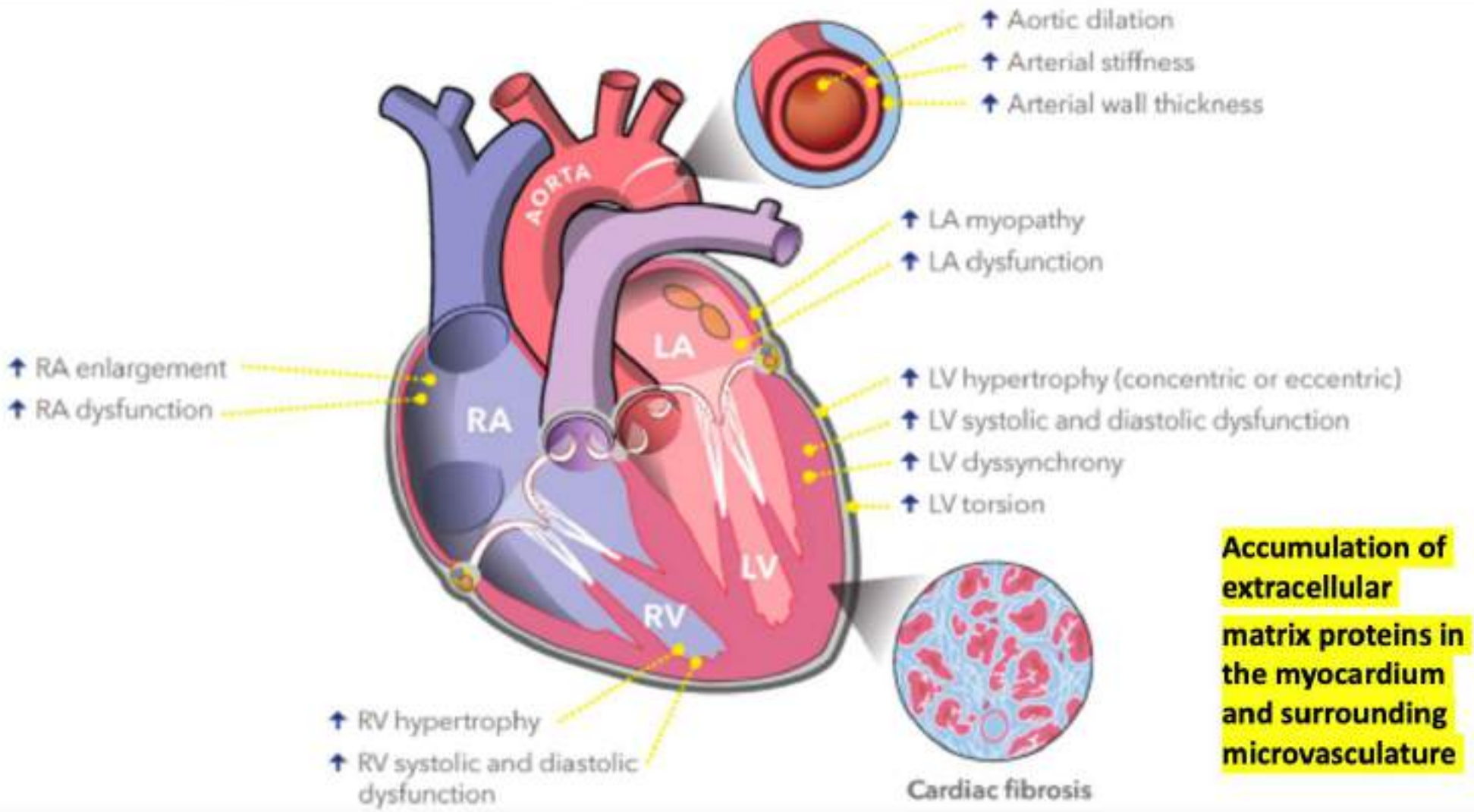
Staging of Hypertensive Heart Disease (Macroscopic changes)



LV = left ventricular.

Messerli et al., JACC 2017

Pathophysiological alterations present in hypertensive heart disease (Macroscopic changes).



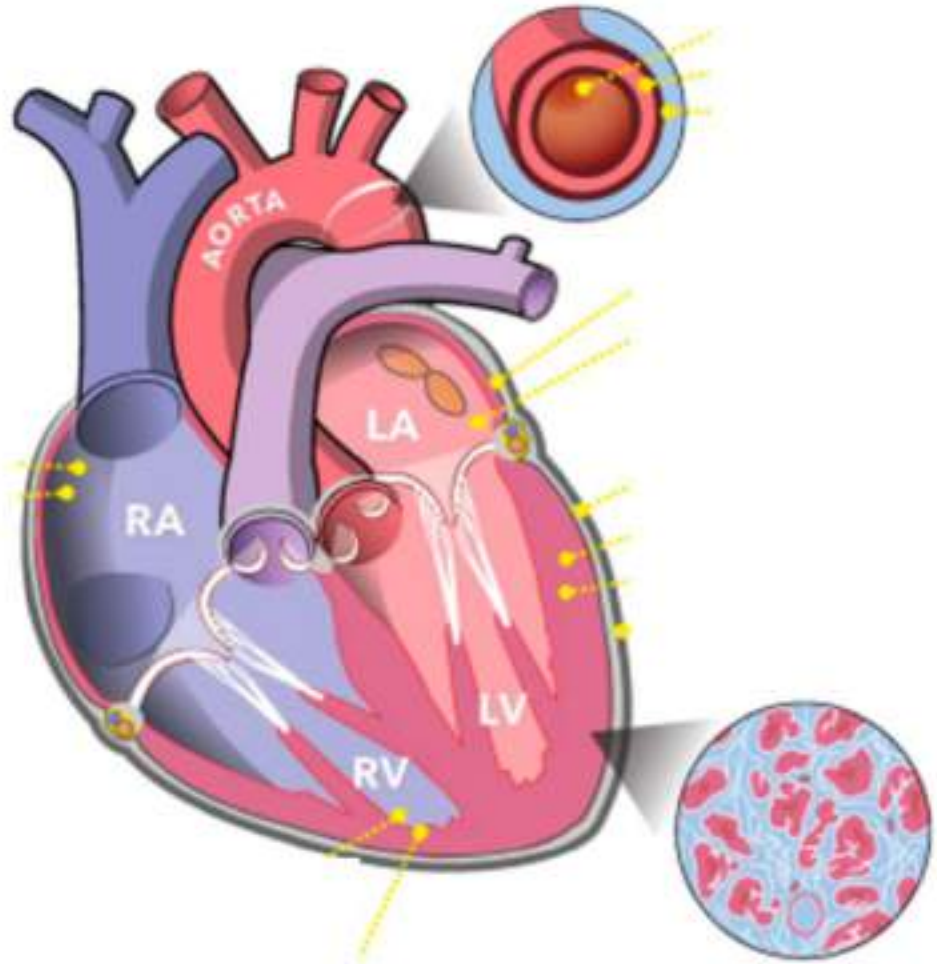
Accumulation of extracellular matrix proteins in the myocardium and surrounding microvasculature

Nwabuo, Vasan; Current Hypertension Reports (2020) 22: 11

Pathophysiological alterations present in hypertensive heart disease (Microscopic changes).

Molecular factors

- Neurohormonal activation
- Growth factors
- Cytokines
- Mitochondrial dysfunction/ROS
- Endothelial dysfunction
- Abberant Ca2+ handling



Cellular factors

- Activation of myofibroblasts and ECM remodeling
- Cardiomyocyte hypertrophy remodeling
- T helper type 2 cell
- differentiation

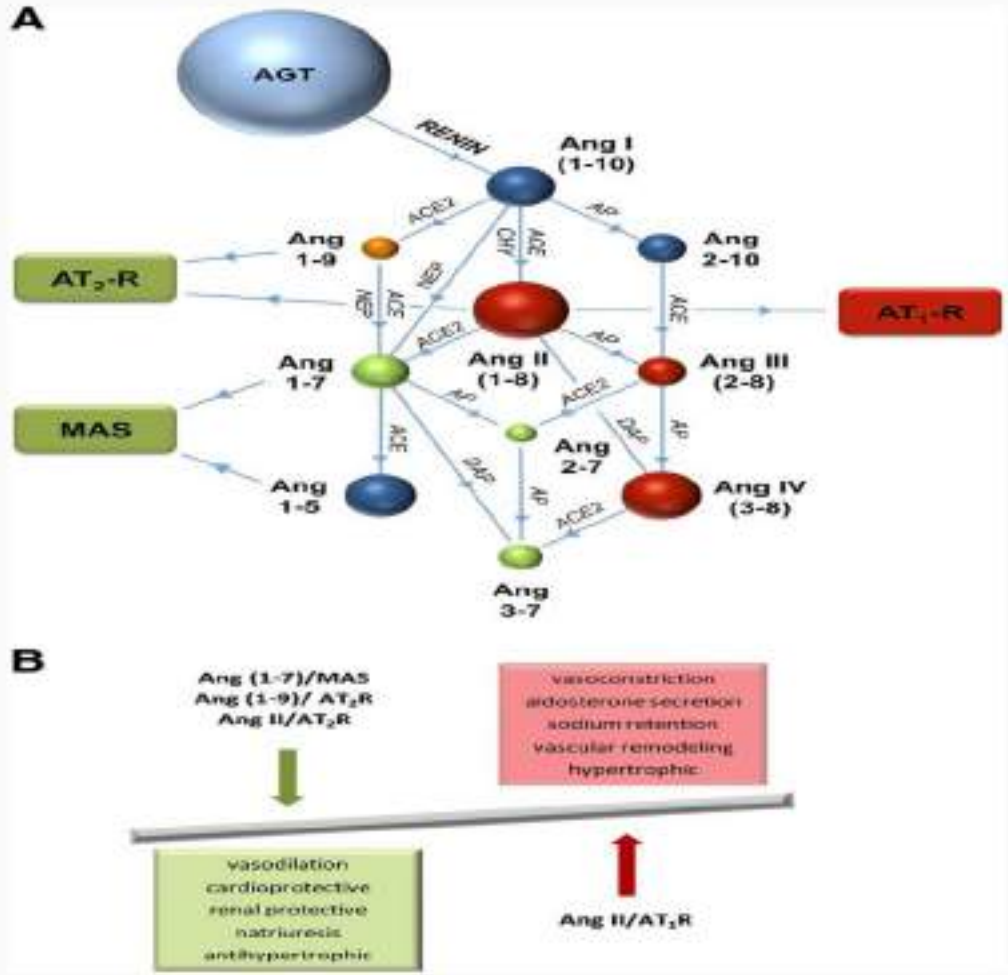
Nwabuo, Vasan; Current Hypertension Reports (2020) 22: 11

- Cardiac fibrosis involves the activation of RAAS system.
- Three types of myocardial fibrosis:

Diffuse interstitial, perivascular, replacement fibrosis

- Change in cardiomyocytes
- Changes in density and structural organization of the sarcomere
- Concentric hypertrophy, eccentric remodelling, reduction in maximum generated tension by the cardiomyocytes

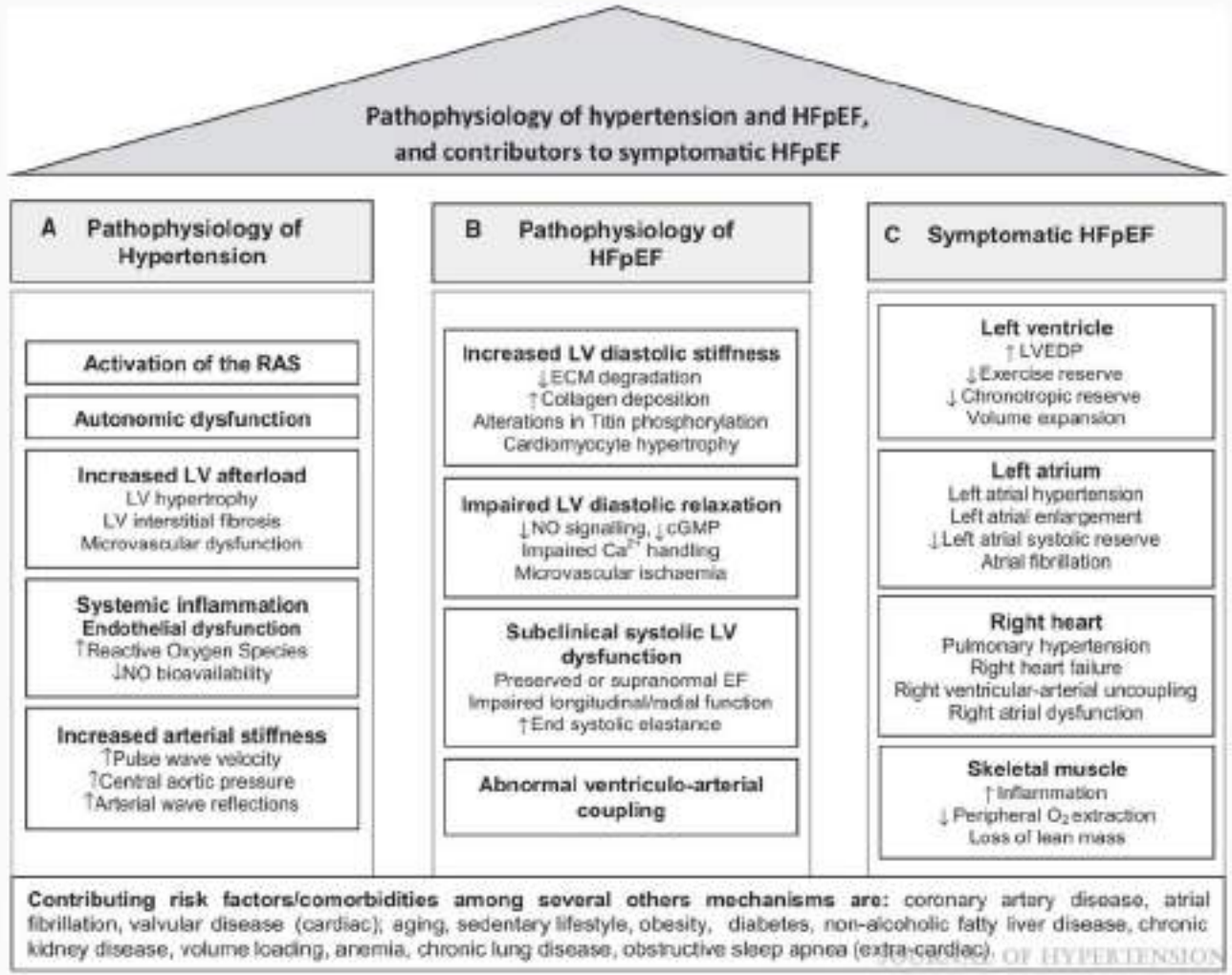
Angiotensin metabolism.



Nwabuo, Vasan; Current Hypertension Reports (2020) 22: 11

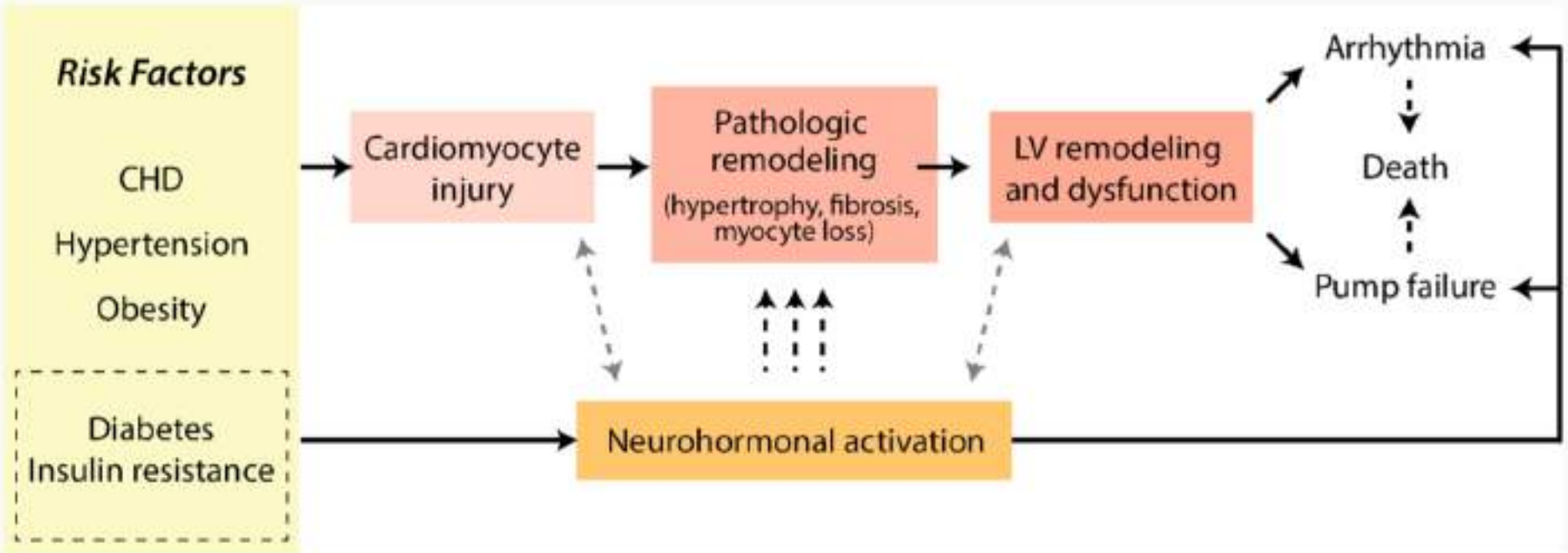
Lauren B. Arendse et al. Pharmacol Rev 2019;71:539-570

Hypertension and heart failure with preserved ejection fraction: position paper by the ESH



Kasiakogias,..Kreutz, J of Hypertension 2021.

Progressive nature of CVD



➔ Need for early identification and better risk stratification strategies of patients at risk to counteract progression

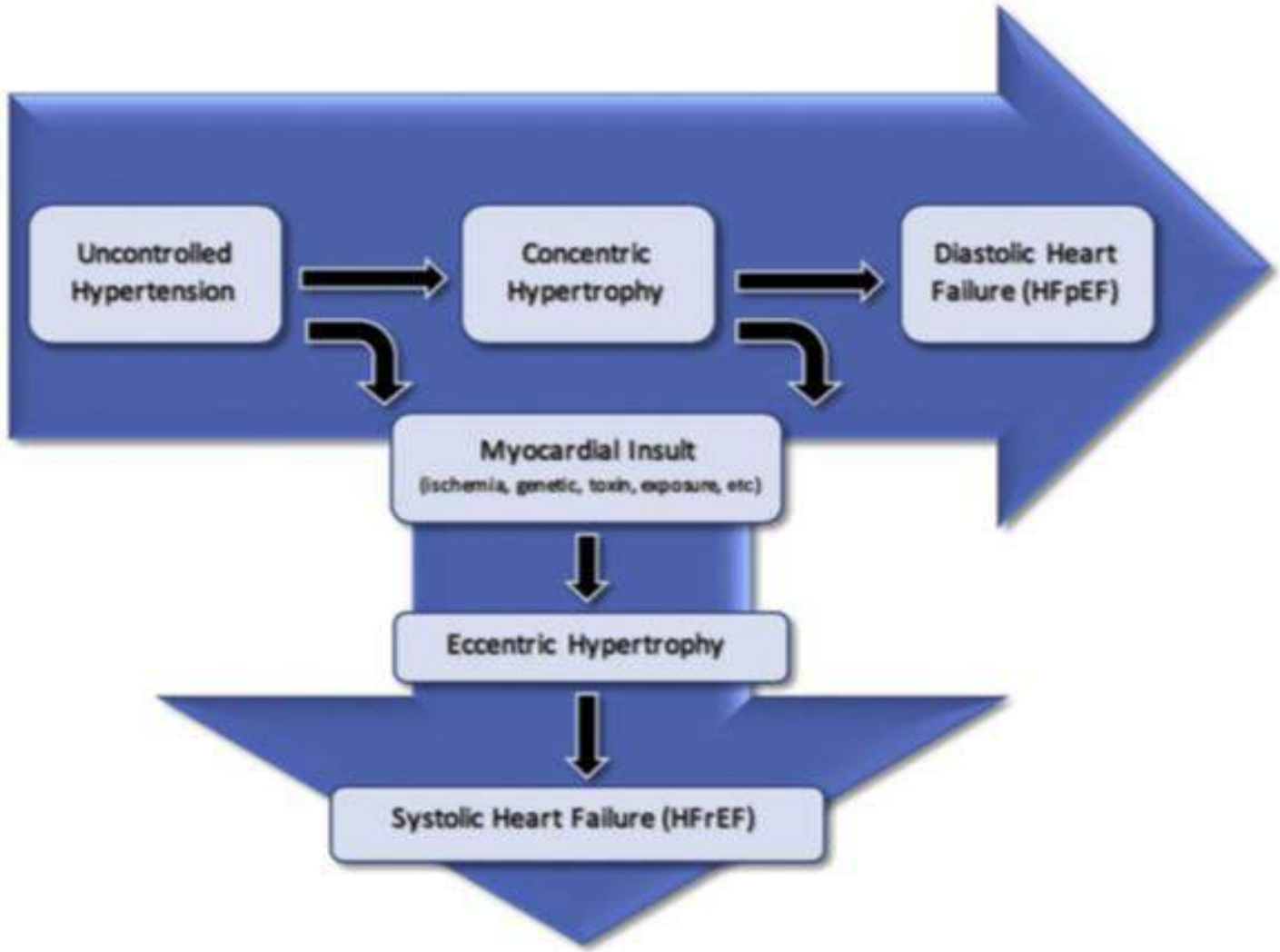


Fig. 4. Proposed mechanism for the development of hypertensive heart failure. The natural progression of heart failure owing to hypertension is concentric hypertrophy leading to diastolic heart failure. A subset of patients will develop systolic heart failure, generally through a second insult leading to myocyte loss. *(Modified from* Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation 2011;123(18).)

'**Second hit**' idea proposed by Borlaug and Redfield, hence in epidemiologic studies HT does not appear to be a common sole cause of HFrEF.

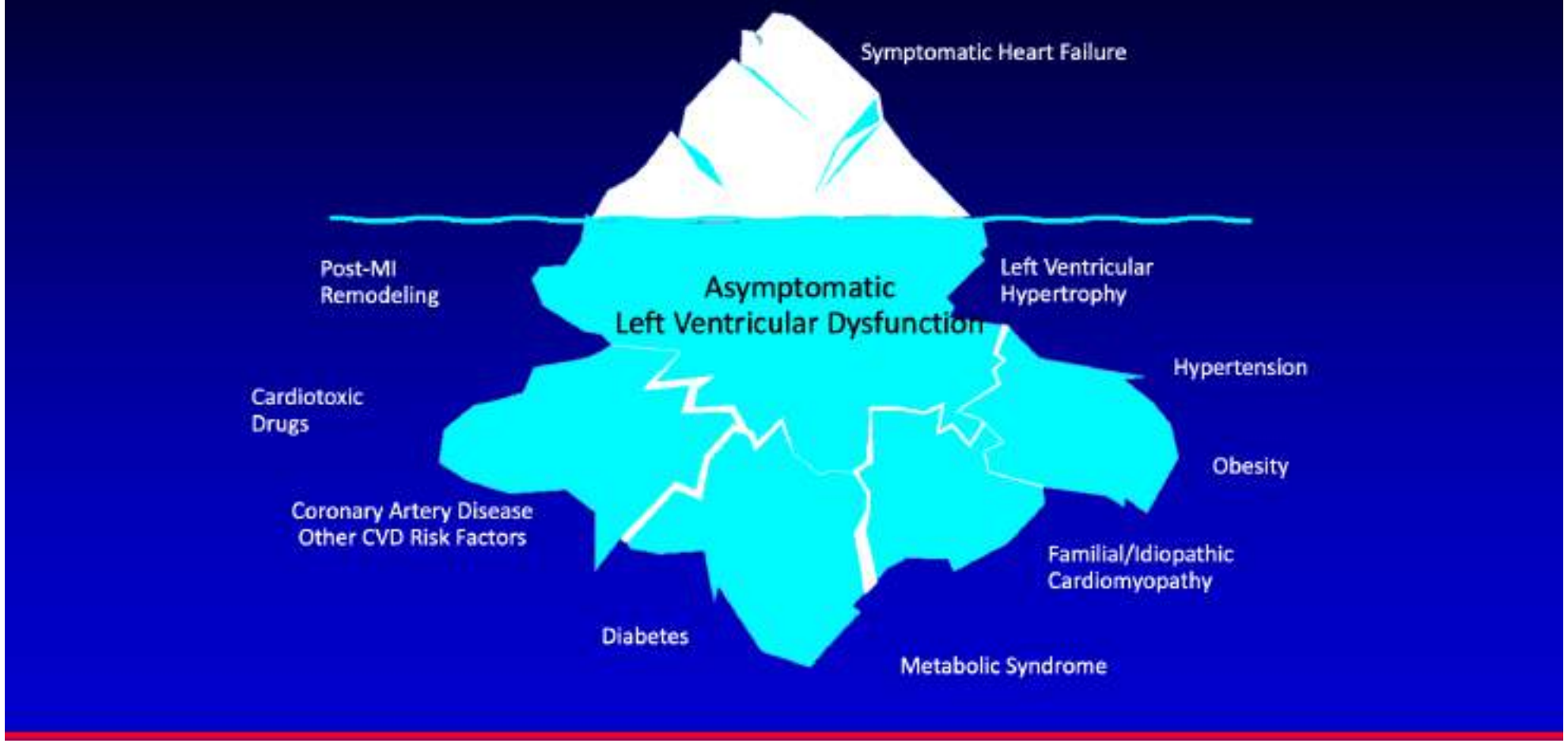
Hypertensive heart disease that progresses for a long time before second hit may closely resemble HFpEF.

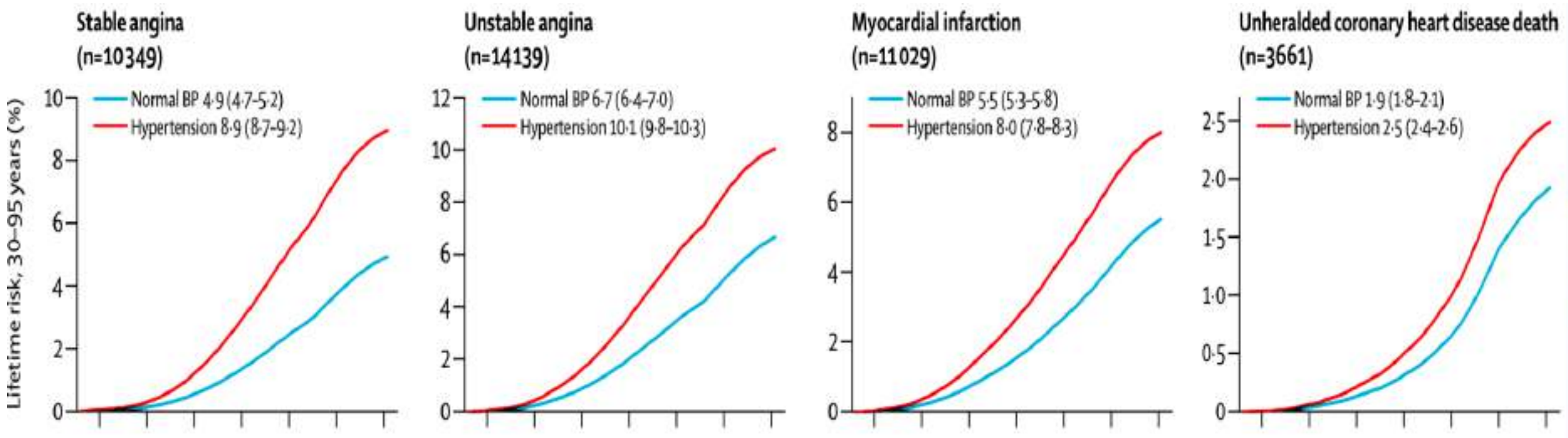
Such a second hit may occur from myocardial infarction, medications, toxins, or genetic polymorphism.

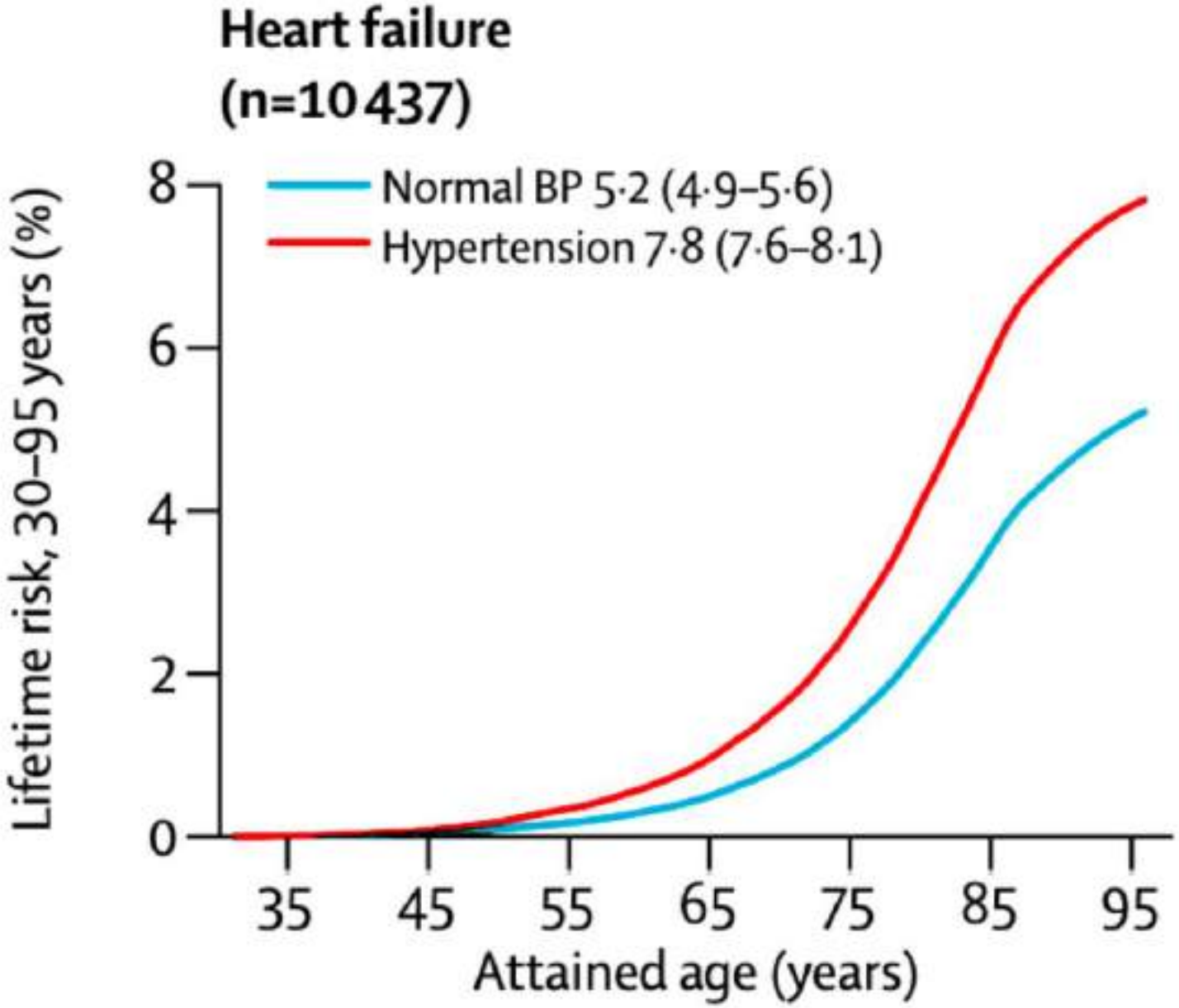
(%42 of hypertensive HF patients from Framingham cohort had preceding MI)

doi.org/10.1016/j.hfc.2019.06.007

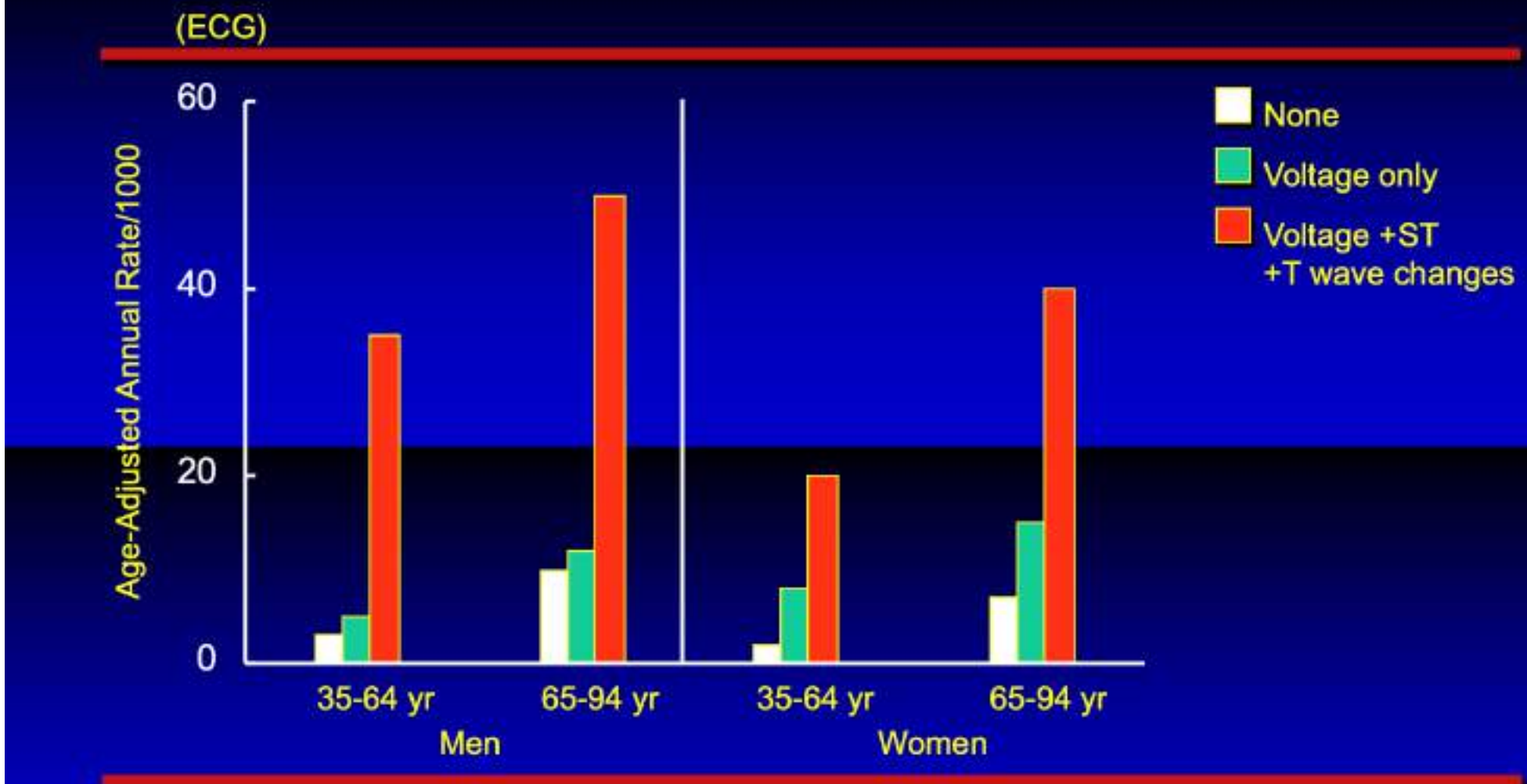
Symptomatic Heart Failure: Just the Tip of the Iceberg




Stable angina
(n=10349)
Normal BP 4·9 (4·7–5·2)
Hypertension 8·9 (8·7–9·2)
Unstable angina
(n=14139)
Normal BP 6·7 (6·4–7·0)
Hypertension 10·1 (9·8–10·3)
Myocardial infarction
(n=11029)
Normal BP 5·5 (5·3–5·8)
Hypertension 8·0 (7·8–8·3)
Unheralded coronary heart disease death
(n=3661)
Normal BP 1·9 (1·8–2·1)
Hypertension 2·5 (2·4–2·6)
Lifetime risk, 30–95 years (%)
0
2
4
6
8
10
12
0·5
1·0
1·5
2·0
2·5


Heart failure
(n=10 437)
Normal BP 5·2 (4·9–5·6)
Hypertension 7·8 (7·6–8·1)
Lifetime risk, 30–95 years (%)
0
2
4
6
8
35
45
55
65
75
85
95
Attained age (years)

Heart Failure and Cardiac Hypertrophy



Kannel et al, J Cardiovasc Pharmacol 10 (Suppl 6):135-140, 1987

LV Hypertrophy is predictor of CVD and

1925 Patients with arterial Hypertension

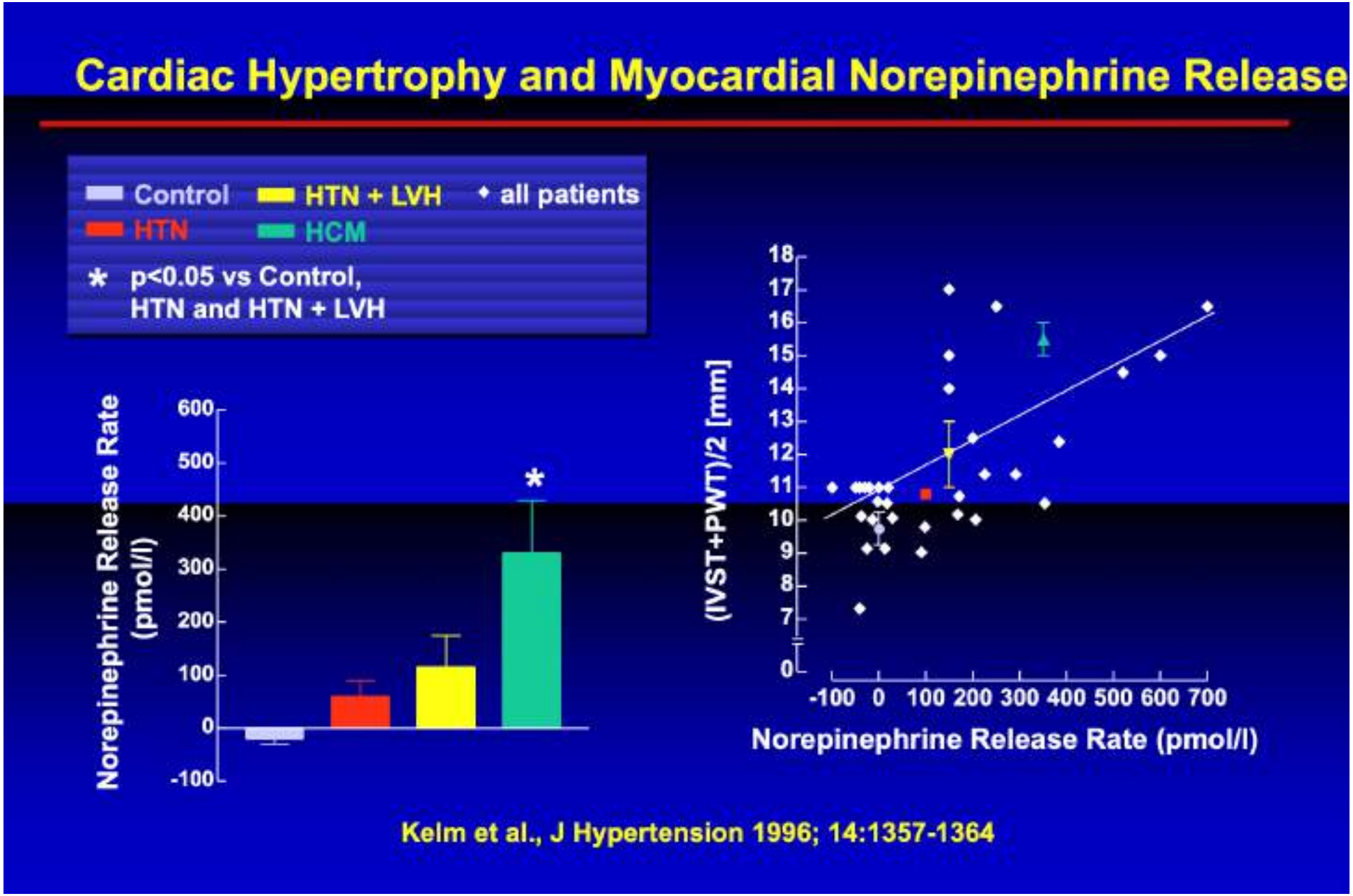
TABLE 3. Independent Predictors of Total Cardiovascular Morbid Events (Cox Model)

Variable	Adjusted Hazard Ratio (95% CI)	*P*
Age, y	1.06 (1.04–1.08)	<0.0001
Diabetes, yes vs no	1.50 (1.01–2.23)	<0.05
Cigarette smoking, yes vs no	1.62 (1.16–2.25)	<0.005
Gender, men vs women	1.77 (1.29–2.42)	<0.0004
24-h systolic BP, mm Hg	1.02 (1.01–1.03)	<0.006
Serum cholesterol, mmol/L	1.16 (1.01–1.33)	<0.03
LV mass index		
Quintile 2 vs quintile 1	1.55 (0.78–3.08)	0.18
Quintile 3 vs quintile 1	1.92 (1.01–3.98)	<0.05
Quintile 4 vs quintile 1	2.97 (1.51–5.84)	<0.002
Quintile 5 vs quintile 1	3.51 (1.82–6.78)	<0.0002

Family history for premature cardiovascular disease, clinic systolic and diastolic BP, 24-hour diastolic BP, body mass index, treatment status, and relative wall thickness failed to enter the equation. See Table 2 for details.

Schillaci et al., *Hypertension* 2000;35:580-586.

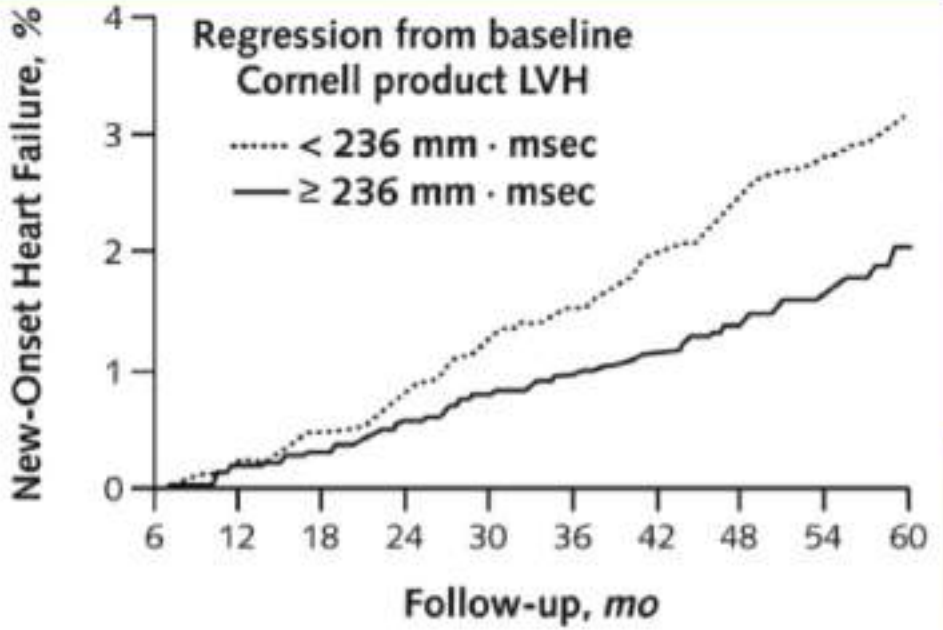
Cardiac Hypertrophy and Myocardial Norepinephrine Release



Kelm et al., J Hypertension 1996; 14:1357-1364

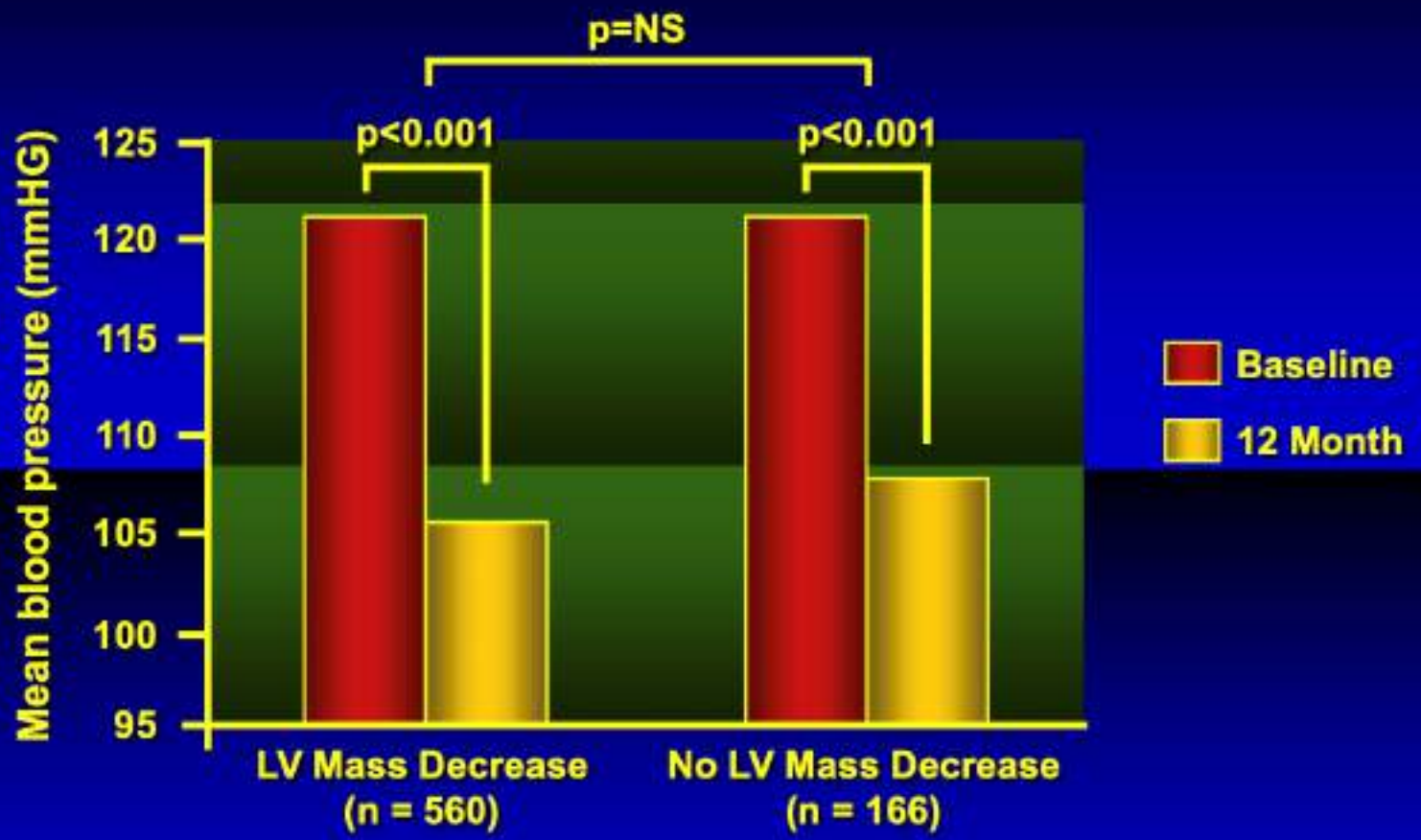
Regression of Electrocardiographic Left Ventricular Hypertrophy Is Associated with Less Hospitalization for Heart Failure in Hypertensive Patients

Peter M. Okin, MD; Richard B. Devereux, MD; Katherine E. Harris, DrPH; Sverker Jern, MD; Sverre E. Kjeldsen, MD, PhD; Stevo Julius, MD, ScD; Jonathan M. Edelman, MD; and Björn Dahlöf, MD, PhD, for the LIFE Study Investigators



Cornell product LVH regression < 236 mm · msec						
Cumulative events, *n*	0	12	39	68	106	128
Patients at risk, *n*	5331	4632	4094	3905	3868	1439
Cornell product LVH regression ≥ 236 mm · msec						
Cumulative events, *n*	0	6	20	37	53	73
Patients at risk, *n*	3012	3671	4033	4025	3887	1649

Hypertrophy Regression and Blood Pressure Reduction (LIFE)

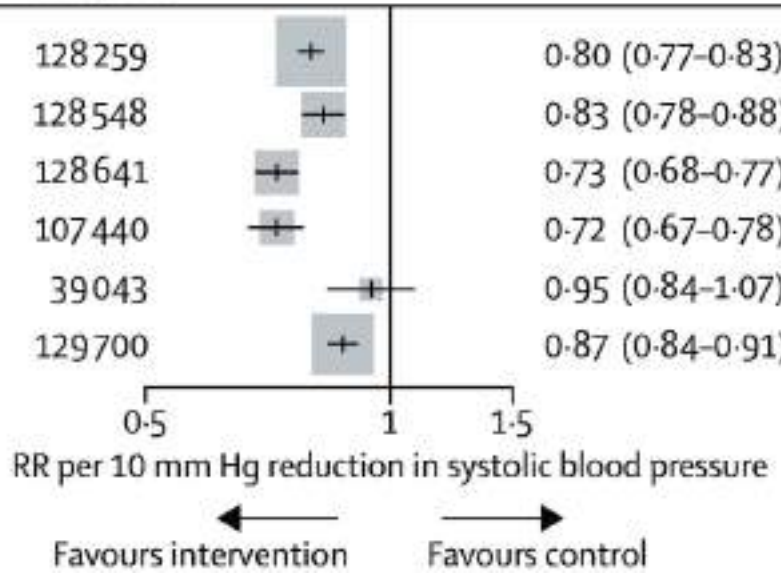


Wachtell et al, Circulation 105 (2002): 1071-1076

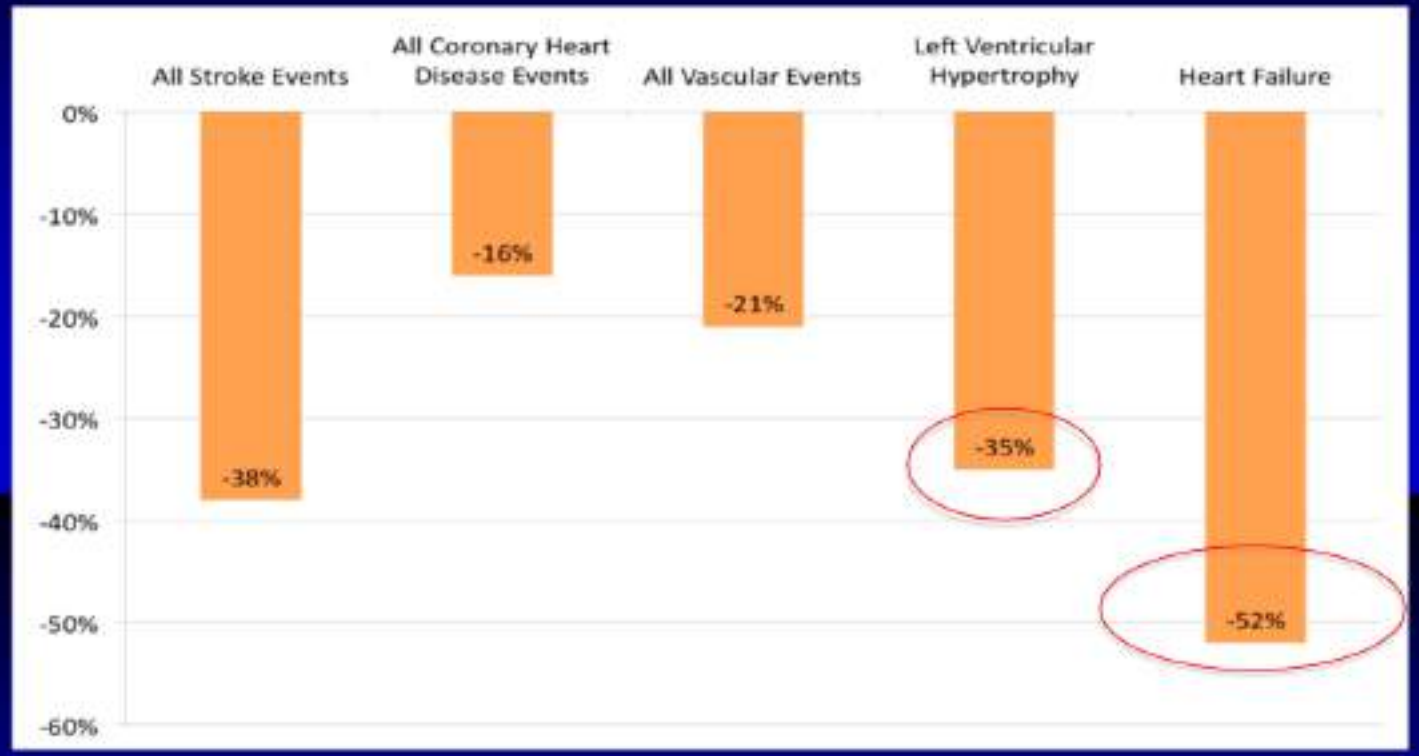
Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis

Dena Ettehad, Connor A Emdin, Amit Kiran, Simon G Anderson, Thomas Callender, Jonathan Emberson, John Chalmers, Anthony Rodgers, Kazem Rahimi

	Studies	Intervention		Control		RR (95% CI) per 10 mm Hg reduction in systolic blood pressure
		Events	Participants	Events	Participants	
Major cardiovascular events	55	13209	137319	14068	128259	0·80 (0·77–0·83)
Coronary heart disease	56	4862	136986	5301	128548	0·83 (0·78–0·88)
Stroke	54	4635	136682	5378	128641	0·73 (0·68–0·77)
Heart failure	43	3284	115411	3760	107440	0·72 (0·67–0·78)
Renal failure	16	890	39888	834	39043	0·95 (0·84–1·07)
All-cause mortality	57	9775	138298	9998	129700	0·87 (0·84–0·91)



Beneficial Effect of HTN Treatment



Meta-analyses of 12 randomized trials of antihypertensive medication therapy on the impact of BP reduction

Blood pressure and HF treatment

- Reducing BP itself is probably the most important factor in HF prevention (for every 10 mmHg reduction in BP, the HF rate declines by 12%).
- Thiazid like diuretics, which are widely used to treat HT (but not so frequent in HF), reduces new-onset HF rate compared with placebo.
- HT related HF treatment relies on many classes of drugs (ACEİ, ARB, BB, CCB, diuretics).
- BP targets are uncertain in both of HFpEF and HFrEF. Comorbidities and patient’s age can be helpful to personalize the BP target.

Prevention of heart failure in hypertension

Recommendations and statements	CoR	LoE
Treatment of hypertension is recommended to effectively prevent heart failure.	I	A
Hypertension treatment with all major antihypertensive drug classes, including ACEis, ARBs, BBs, CCBs and Thiazide/Thiazide-like diuretics, can be used for the prevention of heart failure.	I	A
Alpha-1 blockers (e.g. doxazosin) can be used for the prevention of heart failure in hypertension, preferably in combination with Thiazide/Thiazide-like diuretics and BBs to avoid fluid retension and tachycardia.	I	B
SGLT2is should be used for the prevention of heart failure in patients with type-2 diabetes.	I	A

2023 ESH guidelines for the management of hypertension

European Society of Hypertension

Treatment of hypertension in heart failure with reduced ejection fraction (HFrEF)

In patients with clinically manifest HFrEF, an elevated BP is not a common problem

Recommendations and statements	CoR	LoE
In patients with hypertension and heart failure with reduced ejection fraction (HFrEF) it is recommended to combine drugs with documented outcome benefits including ACEis (ARBs if not tolerated), which could be substituted by ARNI (sacubitril/valsartan), BBs, MRAs, and SGLT2is, if not contraindicated and well tolerated.	I	A

The fantastic 4

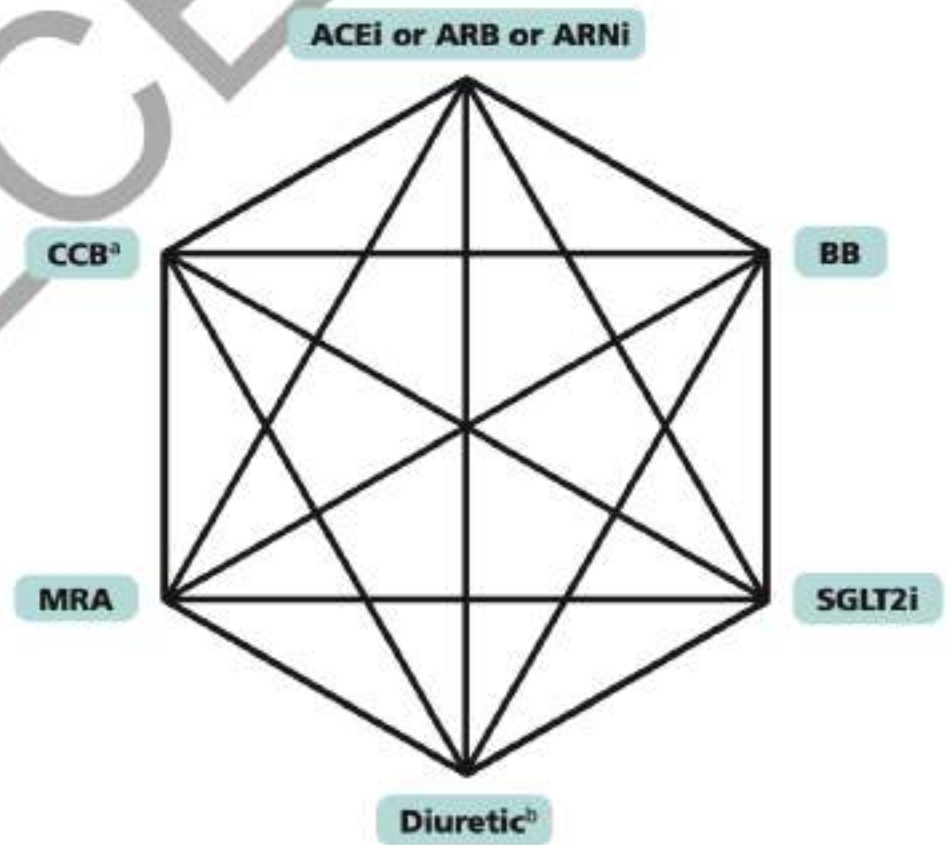


FIGURE 16 BP-lowering drugs in hypertension and heart failure. (a) Non-DHP CCB are not recommended in HFrEF and should not be combined with BB. (b) Use of Diuretics: Use $_{T/TL}$Diuretic if eGFR >45 ml/min/1.73 m^2. Consider transition to Loop Diuretic if eGFR is between 30 to 45 ml/min/1.73 m^2. Use loop Diuretic if eGFR <30 ml/min/1.73 m2 or in patients with fluid retention/oedema.

Treatment of hypertension in heart failure with reduced ejection fraction (HFrEF)

Recommendations and statements	CoR	LoE
In patients with hypertension and heart failure with reduced ejection fraction (HFrEF) it is recommended to combine drugs with documented outcome benefits including ACEis (ARBs if not tolerated),which could be substituted by ARNI (sacubitril/valsartan), BBs, MRAs, and SGLT2is, if not contraindicated and well tolerated.	I	A
If patients remain with uncontrolled hypertension despite up-titration of drugs from the four major drug classes (RAS-inhibitors, BBs, MRAs, and SGLT2is) and use of additional treatment with a diuretic to manage fluid balance, a DHP-CCB can be added for BP control.	I	B
Use of non-DHP-CCB is not recommended in HFrEF due to their pronounced negative-inotropic effect	III	C

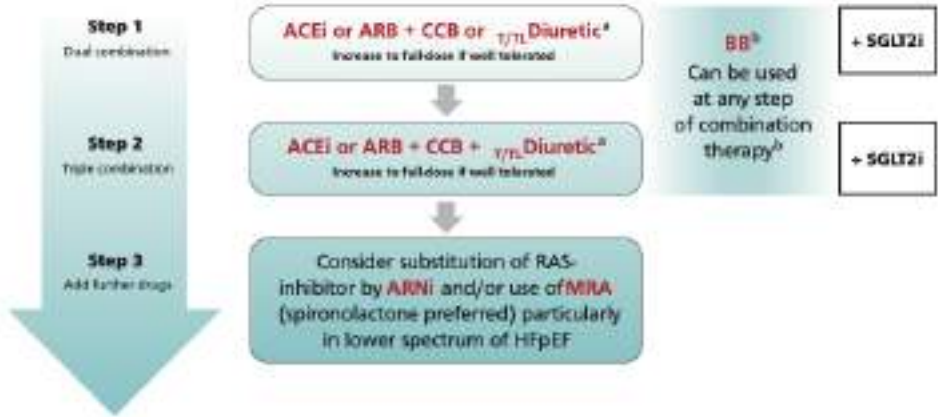


FIGURE 17 BP-lowering therapy in hypertension and HFpEF. (a) Use of Diuretics: Use $_{T/TL}$Diuretic if eGFR >45 ml/min/1.73 m^2. Consider transition to Loop Diuretic if eGFR is between 30 to 45 ml/min/1.73 m^2. Use loop Diuretic if eGFR <30 ml/min/1.73 m^2 or in patients with fluid retention/oedema. (b) BB should be used as guideline directed medical therapy in respective indications or considered in several other conditions (Table 16).

Treatment of hypertension in heart failure with preserved ejection fraction (HFpEF)

Recommendations and statements	CoR	LoE
Treatment of hypertension with all major antihypertensive drug classes (ACEis or ARBs, BBs, CCBs, and Thiazide/Thiazide-like diuretics) is recommended in patients with HFpEF.	I	A
SGLT2is are recommended independently from the presence of type 2 diabetes.	I	A
Substitution of a RAS-inhibitor by an ARNI (sacubitril/valsartan) can be considered, particularly in the lower HFpEF spectrum.	II	B
Treatment with a MRA (spironolactone) regardless of diagnosed resistant hypertension can be considered, particularly in the lower HFpEF spectrum.	II	B

Conclusion:

- There is a strong relationship between HT and HF.
- Regardless of how it occurs, once LVH develops, the risk for HF increases. Once HF develops prognosis become markedly worse.
- HFpEF represents the natural trajectory of uncontrolled hypertensive heart disease, via pressure overload and neurohumoral influences. A second insult (such as ischemia) is mainly required to develop HFrEF.

Recommendations for the primary prevention of heart failure in patients with risk factors for its development

Recommendations	Class[a]	Level[b]
Treatment of hypertension is recommended to prevent or delay the onset of HF, and to prevent HF hospitalizations.[287–290]	I	A