Relationship Between Hypertension and Heart Failure

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Mechanisms involved in BP regulation and the pathophysiology of hypertension

2023 ESH Guidelines for the Management of Arterial 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>
<thead>
<tr>
<th>Type of HF</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptoms ± Signs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Symptoms ± Signs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Symptoms ± Signs&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>LVEF ≤40%</td>
<td>LVEF 41–49%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>LVEF ≥50%</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
<td>–</td>
<td>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&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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.

<sup>a</sup>Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.

<sup>b</sup>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.

<sup>c</sup>For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.
Heart failure is a clinical diagnosis!

### Recommended diagnostic tests in all patients with suspected chronic heart failure

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP/NT-proBNP&lt;sup&gt;c&lt;/sup&gt;</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>12-lead ECG</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Transthoracic echocardiography</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Chest radiography (X-ray)</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Routine blood tests for comorbidities, including full blood count, urea and electrolytes, thyroid function, fasting glucose and HbA1c, lipids, iron status (TSAT and ferritin)</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>
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)

Degree I
- LV diastolic dysfunction
- No LV hypertrophy

Degree II
- LV diastolic dysfunction and LV hypertrophy

Degree III
- Clinical heart failure with Preserved LV ejection fraction

Degree IV
- Eccentric LV hypertrophy
- Reduced LV ejection fraction

LV = left ventricular.
Pathophysiological alterations present in hypertensive heart disease (Macroscopic changes).

- Aortic dilation
- Arterial stiffness
- Arterial wall thickness
- LA myopathy
- LA dysfunction
- RA enlargement
- RA dysfunction
- LV hypertrophy (concentric or eccentric)
- LV systolic and diastolic dysfunction
- LV dyssynchrony
- LV torsion
- RV hypertrophy
- RV systolic and diastolic dysfunction
- Accumulation of extracellular matrix proteins in the myocardium and surrounding microvasculature
- Cardiac fibrosis
Pathophysiological alterations present in hypertensive heart disease (Microscopic changes).

**Molecular factors**
- Neurohormonal activation
- Growth factors
- Cytokines
- Mitochondrial dysfunction/ROS
- Endothelial dysfunction
- Aberrant Ca2+ handling

**Cellular factors**
- Activation of myofibroblasts and ECM remodeling
- Cardiomyocyte hypertrophy remodeling
- T helper type 2 cell
- Differentiation

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

Pathophysiology of hypertension and HFpEF, and contributors to symptomatic HFpEF

A. Pathophysiology of Hypertension
- Activation of the RAS
- Autonomic dysfunction
- Increased LV afterload
  - LV hypertrophy
  - LV interstitial fibrosis
  - Microvascular dysfunction
- Systemic inflammation
  - Endothelial dysfunction
    - Reactive Oxygen Species
    - JAK-STAT bioavailability
- Increased arterial stiffness
  - Pulse wave velocity
  - Central aortic pressure
  - Arterial wave reflections

B. Pathophysiology of HFpEF
- Increased LV diastolic stiffness
  - ECM degradation
  - Collagen deposition
  - Alterations in Titin phosphorylation
  - Cardiomyocyte hypertrophy
- Impaired LV diastolic relaxation
  - NO signalling
  - cGMP
  - Impaired Ca²⁺ handling
  - Microvascular ischemia
- Subclinical systolic LV dysfunction
  - Preserved or supranormal EF
  - Impaired longitudinal/radial function
  - ↑End systolic elastance
- Abnormal ventriculo-arterial coupling

C. Symptomatic HFpEF
- Left ventricle
  - ↑LVEDP
  - Exercise reserve
  - ↓Chronotropic reserve
  - Volume expansion
- Left atrium
  - Left atrial hypertension
  - Left atrial enlargement
  - Left atrial systolic reserve
  - Atrial fibrillation
- Right heart
  - Pulmonary hypertension
  - Right heart failure
  - Right ventricular-arterial uncoupling
  - Right atrial dysfunction
- Skeletal muscle
  - ↑Inflammation
  - ↓Peripheral O₂ extraction
  - Loss of lean mass

Contributing risk factors/comorbidities among several others mechanisms are: coronary artery disease, atrial fibrillation, valvular disease (cardiac), aging, sedentary lifestyle, obesity, diabetes, non-alcoholic fatty liver disease, chronic kidney disease, volume loading, anemia, chronic lung disease, obstructive sleep apnea (extra-cardiac).

Kasiakogias, Kreuzt, J of Hypertension 2021.
Progressive nature of CVD

Risk Factors
- CHD
- Hypertension
- Obesity
- Diabetes
- Insulin resistance

Cardiomyocyte injury → Pathologic remodeling (hypertrophy, fibrosis, myocyte loss) → LV remodeling and dysfunction → Neurohormonal activation → Arrhythmia → Death → Pump failure

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

Asymptomatic Left Ventricular Dysfunction

- Post-MI Remodeling
- Cardiotoxic Drugs
- Coronary Artery Disease Other CVD Risk Factors
- Diabetes
- Metabolic Syndrome

Left Ventricular Hypertrophy
- Hypertension
- Obesity
- Familial/Idiopathic Cardiomyopathy
Heart Failure and Cardiac Hypertrophy

(ECG)

Age-Adjusted Annual Rate/1000

35-64 yr | 65-94 yr | 35-64 yr | 65-94 yr

Men     | Women

None    | Voltage only | Voltage +ST +T wave changes

LV Hypertrophy is a predictor of CVD and:

1925 Patients with arterial Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.06 (1.04–1.08)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diabetes, yes vs no</td>
<td>1.50 (1.01–2.23)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Cigarette smoking, yes vs no</td>
<td>1.62 (1.66–2.25)</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Gender, men vs women</td>
<td>1.77 (1.29–2.42)</td>
<td>&lt; 0.0004</td>
</tr>
<tr>
<td>24-h systolic BP, mm Hg</td>
<td>1.02 (1.01–1.03)</td>
<td>&lt; 0.006</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L</td>
<td>1.16 (1.01–1.33)</td>
<td>&lt; 0.03</td>
</tr>
<tr>
<td>LV mass index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintile 2 vs quintile 1</td>
<td>1.55 (0.78–3.08)</td>
<td>0.18</td>
</tr>
<tr>
<td>Quintile 3 vs quintile 1</td>
<td>1.92 (1.01–3.98)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Quintile 4 vs quintile 1</td>
<td>2.97 (1.51–5.84)</td>
<td>&lt; 0.002</td>
</tr>
<tr>
<td>Quintile 5 vs quintile 1</td>
<td>3.51 (1.82–6.78)</td>
<td>&lt; 0.0002</td>
</tr>
</tbody>
</table>

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.

Cardiac Hypertrophy and Myocardial Norepinephrine Release

Control  HTN + LVH  all patients
HTN  HCM

* p<0.05 vs Control, HTN and HTN + LVH

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. Devereaux, 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

Regression from baseline Cornell product LVH

- ----- < 236 mm · msec
- ----- ≥ 236 mm · msec

<table>
<thead>
<tr>
<th>Follow-up, mo</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>New-Onset Heart Failure, %</td>
<td>0</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
<td>3.5</td>
</tr>
</tbody>
</table>

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)

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


<table>
<thead>
<tr>
<th>Studies</th>
<th>Intervention</th>
<th>Control</th>
<th>RR (95% CI) per 10 mm Hg reduction in systolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Participants</td>
<td>Events</td>
</tr>
<tr>
<td>Major cardiovascular events</td>
<td>55</td>
<td>13209</td>
<td>137319</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>56</td>
<td>4862</td>
<td>136986</td>
</tr>
<tr>
<td>Stroke</td>
<td>54</td>
<td>4635</td>
<td>136682</td>
</tr>
<tr>
<td>Heart failure</td>
<td>43</td>
<td>3284</td>
<td>115411</td>
</tr>
<tr>
<td>Renal failure</td>
<td>16</td>
<td>890</td>
<td>39888</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>57</td>
<td>9775</td>
<td>138298</td>
</tr>
</tbody>
</table>

RR per 10 mm Hg reduction in systolic blood pressure

- Favours intervention
- Favours control
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

<table>
<thead>
<tr>
<th>Recommendations and statements</th>
<th>CoR</th>
<th>LoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of hypertension is recommended to effectively prevent heart failure.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>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.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>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 retention and tachycardia.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>SGLT2is should be used for the prevention of heart failure in patients with type-2 diabetes.</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>
2023 ESH guidelines for the management 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

<table>
<thead>
<tr>
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<th>LoE</th>
</tr>
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<tbody>
<tr>
<td>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.</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

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 \( \gamma \text{ Diuretic if eGFR } \geq 45 \text{ ml/min}/1.73 \text{ m}^2 \). 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/edema.
<table>
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<td>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.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>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.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Use of non-DHP-CCB is not recommended in HFrEF due to their pronounced negative-inotrop effect</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
2023 ESH Guidelines for the management of arterial hypertension

**FIGURE 17** BP-lowering therapy in hypertension and HFrEF. (a) Use of Diuretics: Use \( \text{\textit{\textsc{R}}} \) Diuretic if eGFR \( >45 \text{ ml/min/1.73 m}^2 \). Consider transition to Loop Diuretic if eGFR is between 30 to 45 ml/min/1.73 m\(^2\). Use loop Diuretic if eGFR \( <30 \text{ ml/min/1.73 m}^2 \) 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)

<table>
<thead>
<tr>
<th>Recommendations and statements</th>
<th>CoR</th>
<th>LoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>SGLT2is are recommended independently from the presence of type 2 diabetes.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Substitution of a RAS-inhibitor by an ARNI (sacubitril/valsartan) can be considered, particularly in the lower HFpEF spectrum.</td>
<td>II</td>
<td>B</td>
</tr>
<tr>
<td>Treatment with a MRA (spironolactone) regardless of diagnosed resistant hypertension can be considered, particularly in the lower HFpEF spectrum.</td>
<td>II</td>
<td>B</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of hypertension is recommended to prevent or delay the onset of HF, and to prevent HF hospitalizations.</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>