Hipertensión y riesgo vascular 39 (2022) 34–41

Hipertensión y riesgo vascular

www.elsevier.es/hipertension

REVIEW

Hypertension and heart failure with preserved ejection fraction. A past, present, and future relationship

M. Camafort[a,b,*], **O. Valdez-Tiburcio**[c], **F. Wyss**[d]

[a] *Unidad de Hipertensión, Unidad de Insuficiencia Cardiaca, Servicio de Medicina Interna, ICMID, Hospital Clínic IDIBAPS, Universidad de Barcelona, Spain*
[b] *CIBER-OBN, Instituto de Salud Carlos III, Madrid, Spain*
[c] *Unidad de Cardiología, Hospital Central Romana, y Centro Especialidades Médicas Romana (CEMER), Dominican Republic*
[d] *Servicios y Tecnología Cardiovascular de Guatemala – Sociedad Centroamericana y del Caribe de Hipertensión Arterial y Prevención Cardiovascular, Guatemala*

Received 15 November 2021; accepted 31 December 2021
Available online 25 January 2022

KEYWORDS
Heart failure;
Hypertension;
Non-pharmacological treatment;
Pharmacological treatment;
Preserved ejection fraction

Abstract Heart failure with preserved ejection fraction (HFpEF) is an increasingly prevalent syndrome with high cardiovascular and non-cardiovascular morbidity and mortality. Hypertension (HT) is one of its major risk factors and participates in its origin, development, and prognosis. The guidelines do not set out specific treatments, as clinical trials show limitations. Hypertension control is fundamental in the prevention and treatment of HFpEF. The guidelines recommend renin–angiotensin system blockade as the mainstay of hypertension treatment in patients with HFpEF. Spironolactone and angiotensin receptor-neprilysin inhibitors are also recommended in some cases. There are also new treatments that are already indicated, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors, and promising treatments such as finerenone. A phenotypic classification that allows for more targeted treatments and studies that cover pending issues are yet to be undertaken.

PALABRAS CLAVE
Insuficiencia cardiaca;
Hipertensión arterial;
Tratamiento no farmacológico;

Hipertensión e insuficiencia cardiaca con fracción de eyección preservada. Una relación de pasado, presente y futuro

Resumen La insuficiencia cardiaca con fracción de eyección preservada (ICFEp) es un síndrome de prevalencia creciente con una gran morbilidad y mortalidad, tanto cardiovascular como por otras causas. La hipertensión arterial (HTA) es uno de sus principales factores de riesgo e interviene en su origen, desarrollo y pronóstico. Las guías no establecen tratamientos

* Corresponding author.
E-mail addresses: camafort@clinic.cat, miguel.camafort@gmail.com (M. Camafort).

https://doi.org/10.1016/j.hipert.2021.12.003

Tratamiento farmacológico; Fracción de eyección preservada

específicos, ya que los ensayos clínicos muestran limitaciones. El control de la presión arterial es fundamental en la prevención y tratamiento de la ICFEp. Las guías recomiendan el bloqueo del sistema renina-angiotensina como eje del tratamiento de la HTA en pacientes con ICFEp. Asimismo, se recomienda espironolactona y antagonistas del receptor de angiotensina e inhibidor de neprilisina en algunos casos. Existen además novedades ya indicadas, como los inhibidores del cotransportador-2 de sodio-glucosa (SGLT2), y prometedoras como la finerenona. Queda pendiente el desarrollo de una clasificación fenotípica que permita tratamientos más dirigidos y estudios que respondan a aspectos pendientes.

Introduction and objective

Heart failure with preserved left ventricular ejection fraction (HFpEF) has become a pandemic in recent years, accounting for 50% of all hospital admissions for heart failure (HF) in some series.[1] The European Society of Cardiology Heart Failure-Long-Term Registry (ESC-HF-LT) notes that 60% of outpatients from cardiology departments across Europe have HF with reduced left ventricular ejection fraction (HFrEF), 24% with moderately reduced left ventricular ejection fraction (HFmrEF), and 16% with HFpEF.[2] In Spain, however, the RICA registry that includes patients admitted to internal medicine departments with HF shows that 62.2% of these patients have HFpEF.[3]

Patients with HFpEF compared to those with HF and reduced ejection fraction (HFrEF) are older, a higher percentage are women, the aetiology is predominantly hypertensive (89% of patients have hypertension [HT]), and they have a different comorbidity profile and poorer functional capacity[1,3] compared to patients with HFrEF.

Given the close relationship between HT and HFpEF in origin, development and prognosis, the aim of this review is to summarise the main aspects that link HT and HFpEF.

Search strategy and study selection

For this review, we conducted a literature search in PubMed for clinical practice guidelines on arterial hypertension and HF, using MESH terms and position papers published by the main scientific societies in the last 5 years. After careful reading, the authors selected the aspects they considered relevant to daily clinical practice.

Relationship between hypertension and HFpEF

Hypertension (HT) is a major risk factor in the development of HF,[4] either HFrEF or HF with moderately reduced (HFmrEF) or preserved (HFpEF) ejection fraction. According to the recent HF guidelines of the European Society of Cardiology,[2] HF should be classified as follows:

- HFrEF with a significant reduction in left ventricle (LV) systolic function (LVEF < 40%).
- HFmrEF with mildly reduced LV systolic function, i.e., LVEF between 40% and 49%.
- HFpEF that presents in patients with signs and symptoms of HF, with evidence of structural and/or functional cardiac abnormalities and/or elevated natriuretic peptides (NP), and with an LVEF > 50%.

As well as being a major risk factor, HT modulates the progression of HF such that the clinical course is worse and mortality increases in hypertensive patients with HF.[5,6] Therefore, the treatment of HT has a significant impact on reducing the risk of HF and reducing hospitalisation due to HF.[7]

HFpEF is a highly relevant and growing problem and up to half of all patients with HF have the condition. And, although the risk of death and recurrent hospitalisation is like that of patients with HFrEF,[1] HFpEF is increasing in prevalence.

Although the available evidence is limited, adequate blood pressure (BP) control is considered essential in the prevention and treatment of patients with HFpEF. Therefore, guidelines, such as those of the International Society of Hypertension (ISH), recommend reducing BP when levels are $\geq$140/90 mm Hg, to a target <130/80 mm Hg, but >120/70 mm Hg, as this has a major impact on reducing hospitalisation due to HF.[5]

Epidemiological situation

Data from the US GWTG-HF (Get with The Guidelines-HF) registry, which includes patients hospitalised for exacerbation of HF, or who have developed symptoms of HF while hospitalised, and for whom HF is the primary discharge diagnosis,[1] show us that of the 39982 patients included, 46.0% had HFrEF, 45.8% had HFpEF, and the remainder had HFmrEF. As in other registries, patients with HFpEF are older on average, and are more often female than patients with HFrEF. Patients with HFpEF also have more comorbidities than those with HFrEF (prevalence in HFpEF vs. HFrEF in brackets), primarily hypertension (77.9% vs 69.8%), atrial fibrillation/flutter (38.9% vs. 34.5%), and anaemia (20.3% vs. 14.7%), among others.

If we look at registries of internal medicine patients such as the RICA registry, the prevalence of HFpEF in these patients is even higher, accounting for 62% of the total.[3] Furthermore, 89% in this registry had hypertension, and

hypertensive heart disease was considered the cause in 50% of cases, compared to only 15% in those with HFrEF. This same registry shows that patients with HFpEF have significantly higher systolic blood pressure (SBP) than those with HFrEF (140 ± 27 mm Hg vs 131 ± 26 mm Hg, $p < .001$).

From HT to HFpEF

HF is a major and highly relevant clinical consequence of HT-mediated organ damage (HMOD).[8]

Maintained and uncontrolled HT has a detrimental effect on the heart chambers, which is evidenced by deterioration of echocardiographic markers of cardiac structure and function. A persistent increase in the workload of the LV results in increased mass in the form of left ventricular hypertrophy (LVH) and causes alterations to the architecture of the left atrium (both in diameter and area). It also impairs diastolic function, and these alterations are clear precursors of both HFpEF and atrial fibrillation, inter alia.[9]

These alterations in the form of HMOD at the cardiac level coincide in time and form with the approach of the 2005 AHA/ACC guidelines on HF, which emphasised both the development and progression of HF and identified 4 stages in the development of HF syndrome. The first two stages (A and B), which are non-symptomatic phases of HF, help to identify early hypertensive patients at risk of developing symptomatic HF.

For example, patients with hypertension who do not yet show impaired LV function or architecture would be considered stage A, whereas asymptomatic patients with LVH would be considered stage B.[10]

Therefore, effective treatment of HFpEF starts with the early detection of HMOD in hypertensive patients. There are both classical and innovative tools to assess HMOD. The 12-lead electrocardiogram (ECG), although not a sensitive method for detecting LVH because a normal ECG does not rule out LVH, is very specific, as detection of LVH by ECG provides independent prognostic information. Its prevalence increases with the severity of HT.[11,12]

LVH should preferably be diagnosed by echocardiography because it is a non-invasive method of visually measuring all parameters of the heart structure. Furthermore, its high sensitivity and specificity make it a gold standard in detecting LVH, diastolic dysfunction, and left atrial dilatation, all of which precede the onset of HFpEF. LVH diagnosed by electrocardiogram is also a major predictor of mortality in hypertensive patients and in the general population.[13,14] The presence of left atrial (LA) dilatation is associated with diastolic dysfunction and incidental atrial fibrillation (AF).[15] It is assessed by transmitral flow study and tissue Doppler imaging.[16] These disorders are associated with the onset of HFpEF[15] and increased risk of hospitalisation due to HF.[17]

Antihypertensive treatment, which reduces BP, can result in regression of LVH. Therefore, the duration of antihypertensive treatment and the level of SBP reduction are related to the magnitude of LVH regression.[18] This effect has been seen with the use of beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin 2 receptor antagonists (ARA2), whereas the effect was less with the use of calcium channel blockers (CCBs).[19]

Although similar evidence regarding LVH regression in patients with HFpEF has not yet been established, these data may indicate that a reduction in LVH should also be a goal in individuals with HFpEF, using strategies to reduce cardiac afterload, peripheral vascular resistance, and central BP.[20,21]

Blood pressure targets

The ISH guidelines recommend reducing BP to a target <130/80 mm Hg, but >120/70 mm Hg.[5] The ACC/AHA guidelines on HF recommend SBP levels below 130 mm Hg for patients with HFpEF.[9]

However, there is no evidence-based recommendation for the optimal target BP in hypertensive patients with HFpEF, and therefore the current recommendations are based on extrapolations from clinical trials and registries.[22]

If we review the main randomised clinical trials in patients with HFpEF, with renin–angiotensin–aldosterone-system (RAAS) blockers, the first aspect to consider is that these patients' BP is generally well controlled at the baseline visit. However, data suggests that there is a J or U curve in terms of BP levels and the prognosis of HFpEF.[23] In fact, in the TOPCAT trial mean follow-up SBP readings, between 120 and 139 mm Hg, are associated with a lower risk of poor prognosis.[24] Moreover, a post-hoc analysis of the OPTIMIZE-HF registry (which collects data from US patients admitted for HF), shows that a discharge SBP of less than 120 mm Hg in elderly patients with HFpEF is associated with a worse prognosis.[25]

However, there is limited published data on ambulatory BP monitoring (ABPM) in hypertensive patients with HFpEF. Recent small observational cohort studies in Japanese[26,27] and Spanish[28] patients hospitalised due to HFpEF, suggest that a pattern of increased nocturnal BP may be associated with overall mortality and cardiovascular events. The Ambulatory Blood Pressure in HFpEF Outcomes Global Registry (HFPEF Global, NCT04065620) is an ongoing observational cohort study designed to assess the association of 24-h ABPM-derived BP parameters with death and hospitalisation for HF, and covers confounding factors such as comorbidities, frailty, and functional capacity.[29]

According to the 2018 ESH/ESC guidelines, because hypertensive patients with HFpEF are included in the high/very high-risk category, immediate lifestyle changes would be indicated for them along with antihypertensive treatment. The same guidelines, in patients under 65 years of age, recommend a target SBP of 120–129 mm Hg. In those over the age of 65 years, they recommend a target SBP of between 130 and 139 mm Hg, although these targets should be tailored to tolerability, frailty, and comorbidities.[6,30] Therefore, in elderly patients the initiation of combination therapy with different drugs at the lowest available doses is recommended, while for the very elderly (>80 years), monotherapy may be appropriate. A target DBP of between 70 mm Hg and 79 mm Hg is recommended for all patients with hypertension.

In line with the current recommendations, it seems prudent to avoid lowering BP below 120/70 mm Hg, as the disadvantages may outweigh the benefits.[6,31]

Recommendations for lifestyle changes

The evidence is limited on the effect of different lifestyle change measures in patients with HFpEF. However, changes should be encouraged to improve BP control and potentially reduce cardiovascular events.[6]

Although there is no optimal body weight target, and an obesity paradox has been described, there is evidence of a beneficial effect of diet-induced weight loss on exercise capacity in obese patients with HFpEF.[32] Regular exercise has been shown to improve cardiorespiratory fitness in patients with HFpEF and may also improve prognosis.[6]

The role of salt in the pathophysiology of congestion in HFpEF is unclear, and the evidence for restricting salt even in patients with HFrEF is weak.[33] Until there is more data available, the current general recommendation to restrict salt to less than 5 g/day should be followed in all hypertensive patients, including those with HFpEF, particularly those prone to volume overload, to reduce congestive symptoms.[6]

Hypertensive patients with HFpEF should be advised to follow a balanced diet rich in vegetables, legumes, whole grains, fresh fruit, low-fat dairy products, fish, and unsaturated fatty acids, and low in red meat and saturated fatty acids.[6]

Pharmacological treatment

The pharmacological treatment of HFpEF with antihypertensive drugs has 3 fundamental objectives[6]:

- To control BP per se,
- To manage symptoms,
- To improve prognosis.

The position paper on the treatment of hypertensive patients with HFpEF recommends[6] following the pharmacological treatment strategy proposed by the 2018 ESC/ESH guidelines for hypertensive patients with HFpEF including modifications. In sum, the following is recommended with respect to each drug group:

1. RAS blockers: in addition to effectively reducing BP, drugs belonging to this group have been shown to reverse LVH and improve diastolic function.[21,34] Moreover, because patients with HFpEF often have diabetes and chronic kidney disease (CKD) we should bear in mind that these drugs reduce albuminuria and delay the progression of diabetic and non-diabetic CKD. Finally, clinical trials with this group of drugs have shown improved exercise capacity and reduced hospitalisations due to HF in these patients.[35–37] Therefore, they should be prescribed for all patients with HFpEF, provided they are not contraindicated. In addition, as mentioned above, CKD and diabetes mellitus are common comorbidities in patients with HFpEF and it is well documented that RAS blockade improves prognosis.
2. Diuretics: thiazide diuretics are recommended for BP control in hypertension, whereas loop diuretics are recommended in patients with glomerular filtration rates below 30 ml/min/1.73 m^2.[8] It is important to remember that loop diuretics are essential in patients with signs and symptoms of congestion in HFpEF to reduce congestion-related symptoms.
3. Mineralocorticoid receptor antagonists (MRAs): Spironolactone is the drug in this group for which we have the most data in HFpEF. In addition to its use in resistant HT, post-hoc analyses from the TOPCAT clinical trial show that patients who can benefit most from treatment are those with HFpEF, elevated natriuretic peptide levels, those who have required admission to hospital due to HF in the previous 12 months, and those with preserved LVEF, but at the lower end of the spectrum.[38] Results will be available shortly of the FINEARTS-HF study, NCT04435626, designed to assess the efficacy of the non-steroidal MRA finerenone in reducing cardiovascular death and hospitalisation for HF in patients with HF and an ejection fraction of at least 40%.
4. Angiotensin receptor-neprilysin antagonists (ARNIs): Although the results of PARAGON-HF have not provided unequivocal evidence of the superiority of ARNIs over ARA2 in HFpEF, post-hoc studies suggest that certain patient groups, such as women and those with an LVEF at the lower end of the HFpEF spectrum, could benefit. Therefore, ARNIs should be considered as a substitute for conventional RAS blockers in these patient groups to reduce hospitalisation for HF.[39]
5. Calcium channel blockers (CCBs): The data on use of these drugs in HFpEF is very limited. Non-dihydropyridine CCBs are effective for rate control in patients with atrial fibrillation, but with no clear prognostic benefit.[6]
6. Beta-blockers (BBs): According to the 2018 guidelines of the ESC/ESH on HT, beta-blockers are generally

Table 1 Principles of treatment.

Lifestyle changes
• Control of body weight to avoid obesity
• Healthy diet
• Salt restriction
• Moderate intensity aerobic/dynamic exercise
• Alcohol restriction
• Smoking cessation
BP control targets
• SBP target in the clinic
• <65 years: 120–129 mm Hg
• ≥65 years: 130–139 mm Hg
• To be tailored according to tolerance, especially in the frail elderly
• Close monitoring for adverse effects in the elderly is recommended
• DBP target in the clinic
• 70–79 mm Hg
Patient education, counselling, and support
• Adherence to drug treatment
• Healthy lifestyles
• Daily weight, if required
• Self-measurement of BP at home (SBPM)
• Risk factor monitoring

BP: blood pressure; DBP: diastolic blood pressure; SBPM: self-blood pressure monitoring.

Table 2 Pharmacological recommendations.

General recommendations

- Combination therapy is recommended as initial therapy in most patients.
- Preferred combinations should comprise an RAS blocker (either an ACEi or ARA2) with a thiazide diuretic or CCB.
- It is recommended that the combination therapy be given in a single tablet combination.
- Beta-blockers can be combined with the other drug classes for BP control, especially in specific clinical situations, such as angina, post-myocardial infarction, or heart rate control.
- The addition of low-dose spironolactone, if tolerated, to BP control therapy is recommended in patients with HFpEF and resistant hypertension.

Recommendations specific to HFpEF

- Intensive use of diuretics, including loop diuretics, is recommended to relieve congestion and control symptoms.
- Irrespective of the BP target, consideration should be given to:
  - Low-dose spironolactone to reduce hospitalisations for HF.
  - Sacubitril/valsartan as an alternative to ACEis or ARA2 to reduce hospitalisations for HF.
- SGLT2 inhibitors are recommended in hypertensive patients with diabetes mellitus to reduce the risk of hospitalisation for HF. Treat the most important comorbidities
  - AF:
    - Rhythm/rate control strategy and/or
    - Catheter ablation,
    - Anticoagulation
  - Coronary artery disease,
  - Anti-anginal treatment and/or
  - Revascularisation
- Treat other risk factors/comorbidities:
  - Diabetes
  - Thyroid disorders
  - Obesity
  - Frailty, cachexia, sarcopenia
  - Iron deficiency and anaemia
  - Renal dysfunction
  - Electolyte disorders: hipokalaemia, hyperkalaemia, hyponatraemia, hypochloraemia
  - Lung disease, sleep-related breathing disorders
  - Hyperlipidaemia and lipid-monitoring therapy
  - Other

ACEi: angiotensin converting enzyme inhibitor; ARA2: angiotensin 2 receptor antagonists; BP: blood pressure; CCB: calcium channel blocker; HF: heart failure; HFpEF: heart failure with preserved ejection fraction.

recommended when there is a specific indication, such as angina, post-myocardial infarction, or arrhythmia, including atrial fibrillation, which requires heart rate control. However, they should be used with caution in HFpEF, especially in patients with limited chronotropic reserve.[40,41]

SGLT2 inhibitors (SGLT2is): These drugs warrant special mention as they are anti-diabetic drugs. This group (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, and sotagliflozin) have been shown to reduce the risk of HF events in patients with diabetes mellitus and cardiovascular disease.[42–44] However, only empagliflozin has shown a benefit in HFpEF to date. The EMPEROR PRESERVED trial sought to assess its effects in patient with HFpEF with and without diabetes, as it had been shown to reduce the risk of hospitalisation for HF in patients with HFrEF.[45] The results show that empagliflozin reduces the combined risk of cardiovascular death and hospitalisation for HF in patients with HFpEF, regardless of the presence or absence of diabetes.[46] There are currently no data available on other SGLT2is in HFpEF and therefore the current guidelines have not updated this aspect, possible pending future studies with other SGLT2is, as it is known that different mechanisms such as diuretic and haemodynamic improvement could be decisive for a better prognosis for HFpEF. It should also be noted that in combined use of diuretics with SGLT2is, the diuretic and natriuretic effect of SGLT2is can produce benefits in reducing congestion and may require doses of loop diuretics to be reduced.[47] These recommendations are summarised in Tables 1 and 2 and in Fig. 1.

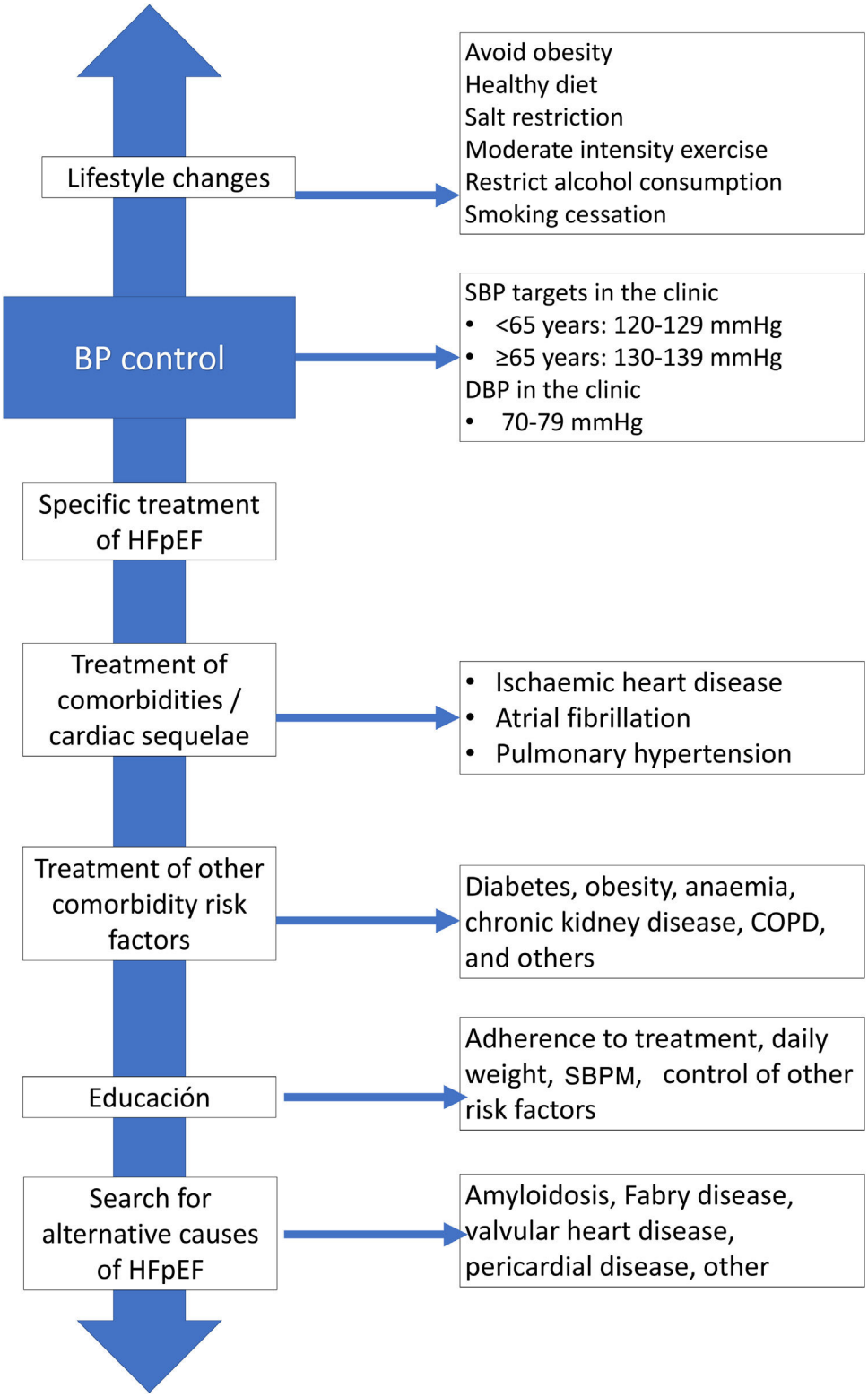

Figure 1 Therapeutic approach to the hypertensive patient with HFpEF.
BP: blood pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure, HFpEF: heart failure with preserved ejection fraction. COPD: chronic obstructive pulmonary disease. SBPM: self-blood pressure monitoring.
Modified from reference 5.

Conclusions

To conclude, HFpEF is an increasingly common syndrome, which to date has been underdiagnosed. Given the increased survival of the population, and risk factors increasingly present in older people, it is predicted to increase in frequency in the coming years.

Due to the relationship between HFpEF and HT, adequate control is required to prevent HFpEF through effective treatment of HT, as this will delay the onset of HFpEF.

Adequate control of HT greatly influences prognosis in patients with symptomatic HFpEF. Therefore, lifestyle changes (weight loss, dietary changes, exercise) are recommended that are effective and should be started as soon as possible. Antihypertensive drugs can be used in HFpEF; as well as adequately controlling BP they can reduce hospital admissions and even mortality. RAS inhibitors are still the mainstay of treatment. ARNIs and MRAs can be used to reduce hospitalisation in a certain group of patients.

Of the ISGLT2is, empagliflozin has been shown to effectively reduce HFpEF hospitalisations and mortality in diabetic and non-diabetic patients, and therefore it seems that this group will be the mainstay of treatment for HFpEF.

References

1. Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. J Am Coll Cardiol. 2017;70:2476–86.
2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. ESC Scientific Document Group 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42:3599–726. Erratum in: Eur Heart J. 2021 Oct 14.
3. Trullàs JC, Pérez-Calvo JI, Conde-Martel A, Llàcer Iborra P, Suárez Pedreira I, et al. Epidemiology of heart failure with preserved ejection fraction: results from the RICA Registry. Med Clin (Barc). 2021;157:1–9.
4. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. Lancet. 2014;383:1899–911.
5. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020;75:1334–57.
6. Kasiakogias A, Rosei EA, Camafort M, Ehret G, Faconti L, Ferreira JP, et al. Hypertension and heart failure with preserved ejection fraction: position paper by the European Society of Hypertension. J Hypertens. 2021;39:1522–45.
7. Beckett N, Peters R, Leonetti G, Duggan J, Fagard R, Thijs L, et al. Subgroup and per-protocol analyses from the Hypertension in the Very Elderly Trial. J Hypertens. 2014;32:1478–87.
8. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hyper-tension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018;36:1953–2041.
9. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71:e13–15.
10. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al., 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009;119:e391–479.
11. Lehtonen AO, Puukka P, Varis J, Porthan K, Tikkanen JT, Nieminen MS, et al. Prevalence and prognosis of ECG abnormalities in normotensive and hypertensive individuals. J Hypertens. 2016;34:959–66.
12. Bacharova L, Schocken D, Estes EH, Strauss D. The role of ECG in the diagnosis of left ventricular hypertrophy. Curr Cardiol Rev. 2014;10:257–61.
13. de Simone G, Izzo R, Chinali M, De Marco M, Casalnuovo G, Rozza F, et al. Does information on systolic and diastolic function improve prediction of a cardiovascular event by left ventricular hypertrophy in arterial hypertension? Hypertension. 2010;56:99–104.
14. Bombelli M, Facchetti R, Cuspidi C, Villa P, Dozio D, Brambilla G, et al. Prognostic significance of left atrial enlargement in a general population: results of the PAMELA study. Hypertension. 2014;64:1205–11.
15. Douglas PS. The left atrium: a biomarker of chronic diastolic dysfunction and cardiovascular disease risk. J Am Coll Cardiol. 2003;42:1206–7.
16. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37:2129–200.
17. Santos AB, Roca GQ, Claggett B, Sweitzer NK, Shah SJ, Anand IS, et al. Prognostic relevance of left atrial dysfunction in heart failure with preserved ejection fraction. Circ Heart Fail. 2016;9:e002763.
18. Soliman EZ, Byington RP, Bigger JT, Evans G, Okin PM, Goff DC Jr, et al. Effect of intensive blood pressure lowering on left ventricular hypertrophy in patients with diabetes mellitus: action to control cardiovascular risk in diabetes blood pressure trial. Hypertension. 2015;66:1123–9.
19. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure-lowering treatment. 6. Prevention of heart failure and new-onset heart failure – metaanalyses of randomized trials. J Hypertens. 2016;34:373–84.
20. Okin PM, Devereux RB, Harris KE, Jern S, Kjeldsen SE, Julius S, et al. Regression of electrocardiographic left ventricular hypertrophy is associated with less hospitalization for heart failure in hypertensive patients. Ann Intern Med. 2007;147:311–9.
21. Fagard Robert H, Celis H, Thijs L, Wouters S. Regression of left ventricular mass by antihypertensive treatment: a meta-analysis of randomized comparative studies. Hypertension. 2009;54:1084–91.
22. Kawano H, Fujiwara A, Kai H, Kumagai E, Okamoto R, Shibata R, et al. Effects of blood pressure lowering in patients with heart failure with preserved ejection fraction: a systematic review and meta-analysis. Hypertens Res. 2019;42:504–13.

23. Itoga NK, Tawfik DS, Montez-Rath ME, Chang TI. Contributions of systolic and diastolic blood pressures to cardiovascular outcomes in the ALLHAT study. J Am Coll Cardiol. 2021;78:1671–8.
24. Huang P, Yu Y, Wei F, Zhu W, Xue R, Dong Y, et al. Association of long-term SBP with clinical outcomes and quality of life in heart failure with preserved ejection fraction: an analysis of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial. J Hypertens. 2021;39:1378–85.
25. Tsimploulis A, Lam PH, Arundel C, Singh SN, Morgan CJ, Faselis C, et al. Systolic blood pressure and outcomes in patients with heart failure with preserved ejection fraction. JAMA Cardiol. 2018;3:288–97.
26. Komori T, Eguchi K, Saito T, Hoshide S, Kario K. Riser pattern is a novel predictor of adverse events in heart failure patients with preserved ejection fraction. Circ J. 2017;81:220–6.
27. Ueda T, Kawakami R, Nakada Y, Nakano T, Nakagawa H, Matsui M, et al. Differences in blood pressure riser pattern in patients with acute heart failure with reduced mid-range and preserved ejection fraction. ESC Heart Fail. 2019;6:1057–67.
28. Camafort M, Jhund PS, Formiga F, Castro-Salomó A, Arévalo-Lorido JC, Sobrino-Martínez J, et al. Prognostic value of ambulatory blood pressure values in elderly patients with heart failure. Results of the DICUMAP study. Rev Clin Esp. 2021;221:433–40.
29. Camafort-Babkowski M, Adeseye A, Coca A, Damasceno A, De Simone G, Dorobantu M. The Global Ambulatory Blood Pressure Monitoring (ABPM) in Heart Failure with Preserved Ejection Fraction (HFpEF) Registry. Rationale, design, and objectives. J Hum Hypertens. 2020;(November), http://dx.doi.org/10.1038/s41371-020-00446-8. Epub ahead of print. PMID: 33239742.
30. Camafort M, Kario K. Hypertension, heart failure, and frailty in older people: a common but unclear situation. J Clin Hypertens (Greenwich). 2020;22:1763–8.
31. Lee SE, Lee H-Y, Cho H-J, Choe W-S, Kim H, Choi J-O, et al. Reverse j–curve relationship between on-treatment blood pressure and mortality in patients with heart failure. JACC Heart Fail. 2017;5:810–9.
32. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA. 2016;315:36–46.
33. García-García A, Alvarez-Sala-Walther LA, Lee HY, Sierra C, Pascual-Figal D, Camafort M. Is there sufficient evidence to justify changes in dietary habits in heart failure patients? A systematic review. Korean J Intern Med. 2021;(September), http://dx.doi.org/10.3904/kjim.2020.623. Epub ahead of print. PMID: 34482681.
34. Wachtell K, Bella Jonathan N, Rokkedal J, Palmieri V, Papademetriou V, Dahlöf B, et al. Change in diastolic left ventricular filling after one year of antihypertensive treatment: the losartan intervention for endpoint reduction in hypertension (LIFE) study. Circulation. 2002;105:1071–6.
35. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;362:777–81.
36. Cleland JGF, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. 2006;27:2338–45.
37. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008;359:2456–67.
38. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J. 2016;37:455–62.
39. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med. 2019;381:1609–20.
40. Borlaug Barry A, Melenovsky V, Russell Stuart D, Kessler K, Pacak K, Becker Lewis C, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation. 2006;114:2138–47.
41. Meyer M, LeWinter Martin M. Heart rate and heart failure with preserved ejection fraction: time to slow β-blocker use? Circ Heart Fail. 2019;12:e006213.
42. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–28.
43. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380:2295–306.
44. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380:347–57.
45. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381:1995–2008.
46. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385:1451–61.
47. Jackson AM, Dewan P, Anand IS, Belohlavek J, Bengtsson O, de Boer RA, et al. Dapagliflozin and diuretic use in patients with heart failure and reduced ejection fraction in DAPA-HF. Circulation. 2020;142:1040–54.