Hellenic Journal of Cardiology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Hellenic Journal of Cardiology

journal homepage: http://www.journals.elsevier.com/hellenic-journal-of-cardiology/

Opinion Paper

Exercise and cardiac rehabilitation in hypertensive patients with heart failure with preserved ejection fraction: A position statement on behalf of the Working Group of Arterial Hypertension of the Hellenic Society of Cardiology

Keywords:
Hypertension
Heart failure with preserved ejection fraction
Exercise
Rehabilitation

A B S T R A C T

Arterial hypertension is a major cause of cardiovascular morbidity and mortality and the most common cause of comorbidity in heart failure (HF) with preserved ejection fraction (HFpEF). As an adjunct to medication, healthy lifestyle modifications with emphasis on regular exercise are strongly recommended by both the hypertension and the HF guidelines of the European Society of Cardiology. Several long-term studies have shown that exercise is associated with a reduction in all-cause mortality, a favorable cardiac and metabolic risk profile, mental health, and other non-cardiovascular benefits, as well as an improvement in overall quality of life. However, the instructions for the prescriptive or recommended exercise in hypertensive patients and, more specifically, in those with HFpEF are not well defined. Moreover, the evidence is based on observational or small randomized studies, while well-designed clinical trials are lacking. Despite the proven benefit and the guidelines' recommendations, exercise programs and cardiac rehabilitation in patients with hypertensive heart disease and HFpEF are grossly underutilized. This position statement provides a general framework for exercise and exercise-based rehabilitation in patients with hypertension and HFpEF, guides clinicians' rehabilitation strategies, and facilitates clinical practice. It has been endorsed by the Working Group of Arterial Hypertension of the Hellenic Society of Cardiology and is focused on the Health Care System in Greece.
© 2023 Hellenic Society of Cardiology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Hypertension affects close to one billion adults in the worldwide population, and this number is forecast to increase to over 1.5 billion by 2025.[1,2] Although various conditions and diseases may lead to the development of heart failure (HF), arterial hypertension represents a major risk factor because of its high prevalence.[1,2] Untreated high blood pressure (BP) may progress, leading to endothelial dysfunction and a range of subclinical or clinical organ damage, such as left ventricular hypertrophy (LVH), microalbuminuria, coronary heart disease, chronic kidney disease, stroke, and HF with preserved (HFpEF) or reduced ejection fraction (HFrEF).[3,4] A patient with hypertension may proceed to develop HF, with devastating effects in terms of cardiovascular morbidity and mortality,[2,3] through several mechanisms, including endothelial dysfunction, accelerating atheromatosis, and LVH.

On top of medication, healthy lifestyle modifications with emphasis on regular exercise are strongly recommended by both the hypertension and the HF guidelines of the European Society of Cardiology (ESC).[2,3] Several long-term studies have shown that exercise is associated with a reduction in all-cause mortality and may modestly increase life expectancy. Exercise may also improve the patient's cardiac and metabolic risk profile, benefit mental health, and bring other non-cardiovascular benefits, including improvement of the overall quality of life.[5-7] However, the instructions for prescriptive or recommended exercise are not well defined, since the evidence is based on either observational or small randomized studies, while well-designed clinical trials are lacking. In Greece in particular, the infrastructure for exercise rehabilitation in patients with cardiovascular disease is practically nonexistent. Apart from barriers in the health care system, one of the most important obstacles is the physician's inertia toward this approach, while the training of health professionals in rehabilitation in this field is grossly underdeveloped. At the same time, the country has high obesity rates, and the population's culture tends to lean away from healthy lifestyles and exercise. Consequently, we believe that interventions by scientific societies in this matter for the sensitization and education of doctors are necessary.

This comprehensive document summarizes and critically evaluates available evidence on the recommended exercise and rehabilitation programs for patients with hypertension or hypertension-associated HFpEF. It also presents the principles supported by existing published evidence in cardiovascular medicine, examines them in the light of practical experience, and provides recommendations

Peer review under responsibility of Hellenic Society of Cardiology.

https://doi.org/10.1016/j.hjc.2023.08.008
1109-9666/© 2023 Hellenic Society of Cardiology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Please cite this article as: M. Kallistratos, D. Konstantinidis, K. Dimitriadis *et al.*, Exercise and cardiac rehabilitation in hypertensive patients with heart failure with preserved ejection fraction: A position statement on behalf of the Working Group of Arterial Hypertension of the Hellenic Society of Cardiology, Hellenic Journal of Cardiology, https://doi.org/10.1016/j.hjc.2023.08.008

that can easily be implemented within the healthcare system. This position statement is endorsed by the Working Group of Arterial Hypertension of the Hellenic Society of Cardiology and is focused on the sociosanitary setting of Greece.

2. Characteristics of different types of exercise

Physical fitness includes five major components: a) a morphological component, which refers to the different physical characteristics of the person undertaking exercise; b) a metabolic component, related to glucose, lipid metabolism, etc.; c) a motor component; d) a muscular component (e.g., isometric strength, muscular endurance); and lastly, e) a cardiorespiratory component, which mainly refers to endurance or exercise capacity, maximal aerobic power, and heart function (Fig. 1).[8,9] The basic principles of exercise prescription have traditionally been described using the "FITT" concept (frequency, intensity, time, type). At the same time, the mode of exercise is also an important characteristic, as discussed below. The types of exercise have previously been presented in a binary fashion, such as endurance or resistance, aerobic versus anaerobic exercise, or those related to the type of muscle contraction, such as isotonic (concentric or eccentric) versus isometric; however, the reality is that exercise training frequently involves a range of different types, as opposed to a distinct pattern.[10]

In brief, aerobic exercise generally refers to training that is performed at an intensity that allows metabolism mainly through aerobic glycolysis and fat metabolism (b-oxidation).[11] Large muscle groups performing dynamic activities are engaged, resulting in substantial increases in heart rate: examples of this type of training include cycling, running, and swimming.[12] Aerobic training can either be continuous or interval based. Interval training programs include higher intensities, such as high-intensity interval training (HIIT) (4×4 min at 85-90% peak heart rate, with 3 min active recovery). Growing evidence has suggested comparable and even superior cardiovascular benefits, as well as fitness and performance improvements, in certain populations.[13,14] However, more data are required for more solid conclusions.

Finally, resistance exercise is typically prescribed in terms of one repetition maximum (1 RM), which is the maximum amount of weight a person can lift throughout a range of motion with one repetition. It should be noted that resistance training using less than 20% of 1 RM is generally considered aerobic endurance training, while more than 20% of 1 RM renders muscular capillaries susceptible to compression during muscle contraction, resulting in a hypoxic stimulus. Resistance exercise, which can either be isometric (unchanged muscle length) or dynamic (contraction with change in length), focuses on particular muscle groups using own bodyweight exercises or weight machines.[10,15] Resistance in combination with endurance programs may specifically be considered for low-risk patients, providing certain benefits such as increased muscle strength and aerobic capacity and a better quality of life.[16,17]

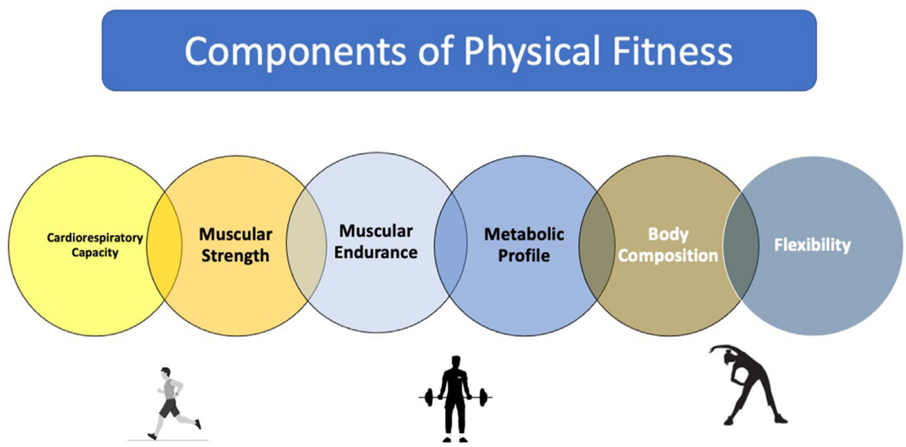

Figure 1. Components of physical fitness that present a target for intervention.

3. Factors affecting exercise tolerance in hypertensive patients with HFpEF

Exercise challenges many organ systems of the body to maintain homeostasis and to respond to the increased demand for oxygen and nutrients. Exercise capacity largely depends on the greatest amount of oxygen an individual can use during exercise. This is expressed by VO2 max, which represents the highest amount of oxygen received, transported, and used by cellular metabolism. Oxygen delivery to the skeletal muscles by the circulation and removal of carbon dioxide are essential for sustained exercise and have been considered the most important limiting factors. Glycolysis is a major factor that regulates the balance between fatty acids and glycogen as substrates for exercise; it determines energy production and is controlled by the activity of intramuscular glycogen phosphorylase.

In cardiovascular patients, clinical status, cardiac stress tolerance, and comorbidities delineate the exercise capacity, while an adequate increase in cardiac output is one of the most critical criteria of exercise performance in those patients. This is accomplished by an appropriate increase in heart rate and stroke volume—mainly modulated by sympathetic nervous system overdrive—which results in a vigorous increase in cardiac output. Heart rate response is influenced by several factors, including age, since it is known that the mean maximum heart rate declines with age.[18] This plays a partial role in the impaired exercise performance in HFpEF. In addition, local vasodilators, such as nitric oxide from endothelial cells, ensure adequate blood flow in skeletal muscles and the pulmonary system. Ventilation rate and lung perfusion should increase sufficiently, in parallel with the increase of the surface area for gas exchange. Another important factor is the condition of the neuromuscular system and the type of muscle mass involved in the exercise. For example, older HFpEF patients have lower lean skeletal muscle mass and abnormal O2 utilization that

Please cite this article as: M. Kallistratos, D. Konstantinidis, K. Dimitriadis *et al.*, Exercise and cardiac rehabilitation in hypertensive patients with heart failure with preserved ejection fraction: A position statement on behalf of the Working Group of Arterial Hypertension of the Hellenic Society of Cardiology, Hellenic Journal of Cardiology, https://doi.org/10.1016/j.hjc.2023.08.008

is independent of and in addition to the reduced muscle mass, fewer type I (oxidative-fatigue resistant) muscle fibers, and impaired blood flow to the active skeletal muscles.[19,20] Other common factors that may limit exercise capacity in elderly hypertensive individuals are neurological conditions—for example, spasticity of the lower extremities or poor motor coordination.[21]

Apart from the function of human physiological systems, another important factor is the type of exercise *per se*. The type of exercise plays a significant role in exercise performance since it relates to different levels of physiological response from the body. For example, dynamic training with high resistance produces a vigorous increase in peripheral vascular resistance, which may not be tolerated or even harmful in some cardiovascular pathological conditions. In addition, environmental factors such as temperature, humidity, and altitude play a large role in guiding patients to exercise and should be taken seriously into consideration in exercise prescription.

Exercise performance also depends on the individual's intrinsic motivation, psychosocial commitments, and resources. People with stronger motivation are more likely to pursue it, dedicate effort to it, and adhere to a program of physical activity. Consequently, psychological support of these individuals, who in most cases are reluctant to engage in physical activity, is an influential parameter.

Individuals with hypertension and HFpEF present with autonomic system dysfunction and often develop skeletal myopathy, which results in abnormal responses to this central and ergoreflex processing and has a significant impact on exercise capacity. The cardiovascular response to exercise in hypertensives is hyperdynamic because of the over-activation of neural and humoral factors. The exercise reflex activation is enhanced in hypertension, and this makes a major contribution to the excessive sympathetic tone and the over-activation of neural and humoral factors.[22]

In dynamic exercise of a high intensity, there is a marked increase in systolic blood pressure (SBP) and a small increase or a decrease in diastolic blood pressure (DBP). Heart rate and stroke volume are also markedly increased. In static exercise, such as powerlifting, there is a higher increase in sympathetic efferent activity compared to dynamic exercise, with a marked increase in both SBP and DBP and a moderate increase in heart rate. Hypertensive individuals may reach higher BP at a given rate of work, and VO2 max is lower in sedentary hypertensives compared to sedentary normotensives, a phenomenon that is reversed in trained individuals.[23,24] In addition, post-exercise hypotension following endurance training seems to be greater in people with higher pre-exercise BP values.[25,26]

Total cardiovascular reserve in HFpEF is compromised by a blunted heart rate response and peripheral vascular vasodilator reserve, a drop in peak exercise cardiac output, and reduced O2 extraction at the muscle level.[27,28] Apart from the diminished capacity of the cardiovascular system to supply oxygen, the skeletal muscles are unable to utilize the delivered oxygen efficiently.[29] Exercise performance is also compromised by a variety of factors related to low cardiac output, pulmonary abnormalities, autonomic imbalance, impaired peripheral perfusion, and altered muscle function and structure.[20,30] In addition, these patients develop increased ergoreflex sensitivity, which is believed to contribute to dyspnea on effort and fatigue.[31]

4. Role of exercise in hypertensive patients with HFpEF

Previous studies have emphasized the beneficial role of exercise in hypertension and hypertensive heart disease (see Supplementary material). Although there are no studies focusing on patients with hypertension and HFpEF, the vast majority of patients included had hypertension, at a rate of up to 90%. Patients with HFpEF are very often obese and usually adopt a sedentary lifestyle because of severe exercise intolerance, with further deterioration in the signs and symptoms of HF. In addition, patients with HFpEF are older and have a higher prevalence of sarcopenia. It is well known that aerobic and resistance exercise promotes skeletal muscle anabolism and enhances physical capacity. Resistance exercise improves the muscle protein synthetic rates, promotes type II muscle fiber anabolism, and is the most valuable defense against age-related muscle loss.[32] Exercise (aerobic and mainly resistance) has been shown to effectively improve many indexes of the upper and lower extremity muscle function in people with HFpEF.[32,33]

A supervised, exercise-based, cardiac rehabilitation program should be considered in patients with HFpEF. However, well-designed, large, long-term randomized studies are lacking, mainly because of difficulties in the management of this fragile population. Supplementary Table summarizes the most important randomized studies in this field. Gary et al,[34] in the first randomized controlled trials, showed that home-based, low-to-moderate-intensity exercise, in addition to education, is an effective strategy for improving the functional capacity and quality of life in women with HFpEF. A few years later, Kitzman et al, evaluating exercise training in patients with HFpEF, showed a substantial improvement in cardiorespiratory fitness.[35,36] Since that time, several other studies have substantiated this benefit and demonstrated favorable effects on a variety of parameters.[37-39] The Ex-DHF pilot study, which enrolled 64 patients with HFpEF, showed that a supervised combined endurance and resistance training program was associated with improvements in peak VO2, markers of diastolic function, and reported physical functioning over 3 months.[40] There is some evidence that high-intensity interval training is more effective than moderate continuous training in improving peak VO2, without any difference in other CPET parameters or quality of life score,[41,42] but a more recent multicenter trial with 180 patients did not confirm any clinically significant difference between these two training programs.[43] A post-hoc analysis of the TOPCAT trial showed that patients who reported the ideal physical activity had lower rates of HF hospitalization, as well as cardiovascular and all-cause mortality, compared with those with a poor or intermediate level of physical activity.[44] Furthermore, aerobic exercise training improves quality of life and exercise capacity measured by peak VO2 and 6-min walk distance, and there is evidence indicating a beneficial action on cardiac hemodynamics and myocardial systolic and diastolic function.[45-49] Moreover, cardiac rehabilitation programs in patients with HFpEF promote physical activity. Regular physical activity can further decrease BP levels beyond those achieved with the commonly used antihypertensive agents.[2]

In order to design a training protocol, the appropriate intensity should be selected based on parameters such as peak oxygen uptake, peak heart rate, and ventilatory threshold, assessed during incremental cardiopulmonary exercise testing. Guidelines published by the European Society of Cardiology recommend an exercise program that combines moderate endurance and dynamic resistance training in patients with HFpEF.[10] High-intensity physical activity is considered an effective method that improves cardiorespiratory and metabolic function. However, the data are not definitive in the context of HFpEF (see Fig. 1).

5. Recommendations for exercise initiation in hypertension with HFpEF

A comprehensive clinical evaluation and risk stratification of patients are mandatory before the initiation of an exercise program. On the other hand, exercise training in HFpEF might be an adjuvant treatment option for ameliorating breathlessness, fatigue, and impaired exercise capacity, which are the main symptoms associated with this disease and pose a problem that is difficult to solve. Moreover, physical activity and exercise added to the usual care may have a further beneficial effect on BP control.[2] However, exercise training should be initiated in a clinically and hemodynamically stable patient who is receiving the optimal medical therapy.[50] A detailed clinical evaluation and cardiovascular risk stratification should be carried out initially before exercise counseling. BP monitoring should preferably be performed using out-of-office measurements. Basic laboratory tests, an echocardiogram, and an exercise test may also be advised before the initiation of an exercise program, particularly in sedentary patients (Fig. 2, Table 1). In high- or very high-risk patients, coronary computed tomographic angiography (CCTA) could be considered before the initiation of a moderate or intensive exercise program (Fig. 2, Table 1). Our clinical practice recommendation was based on studies in preventive cardiology, where cardiac CT has been studied in large populations of asymptomatic individuals for its potential benefit to guide treatment decisions and improve clinical outcomes. These studies in high-risk populations indicated that findings in the cardiac CT arm may change treatment management and beneficially affect their outcomes.[51-54] Recently, the American Society for Preventive Cardiology has proposed that a judicious approach to the use of CCTA in asymptomatic populations may be to target high-risk individuals.[55] Based on this, and given that exercise may trigger adverse cardiac events, we consider that in this group, a thorough noninvasive evaluation is even more imperative.

Pre-participation cardiovascular screening (natriuretic peptides, echocardiography, cardiopulmonary exercise testing) prior to the initiation of an exercise program is mandatory in patients with HF. Physical activity is contraindicated in those with deteriorating signs or symptoms of HF or hypotension.[10] Patients with uncontrolled hypertension should delay training until BP is controlled. Resting systolic BP > 200 mmHg and/or diastolic BP > 110 mmHg represent relative contraindications to exercise. Moreover, an exaggerated BP response to exercise (systolic BP > 250 mmHg or diastolic BP > 115 mmHg) has been associated with a higher risk of incident hypertension and is a relative indication to reduce training intensity.[56]

Patients with HFpEF usually have a cluster of comorbidities, and exercise-based cardiac rehabilitation programs are a cornerstone in the holistic prevention and management of hypertension and HFpEF.[57-66] Evaluation of functional capacity, chronotropic reserve, and BP response to exercise, as well as screening for ischemia or exercise-induced arrhythmia, are recommended before prescribing an exercise program. Peak VO2, measured during a cardiopulmonary exercise test, has been identified as the primary outcome for assessing the ventilatory, hemodynamic, and metabolic effect of exercise as a therapeutic intervention in HFpEF and as a fundamental component of exercise training and assessment of exercise intolerance in patients with HFpEF. Baseline evaluation should include an

Table 1
Clinical and laboratory tests recommended before the initiation of a regular exercise program in hypertensive patients with HFpEF

Clinical/laboratory test	
Detailed clinical history for symptoms during physical activity	In all patients
Detailed physical examination	In all patients
Orthostatic hypotension test	In patients ≥65 years old or those with neurological diseases
Out-of-office blood pressure measurements to ensure the control of hypertension	In all patients
Home blood pressure measurement at least once per week during the exercise program	In all patients
12-lead electrocardiogram	In all patients
Hemoglobin and/or hematocrit, fasting blood sugar, serum creatinine and eGFR, serum sodium, and potassium	In all patients
Echocardiogram to evaluate left ventricular mass, ascending aorta dimension, ejection fraction	In all patients
Exercise test	In patients engaging in moderate or high-intensity programs
Cardiopulmonary exercise test (once it is available)	In patients engaging in moderate or high-intensity programs
Coronary computed tomographic angiography	May be considered in patients with high or very high 10-year cardiovascular death risk who will engage in high-intensity programs

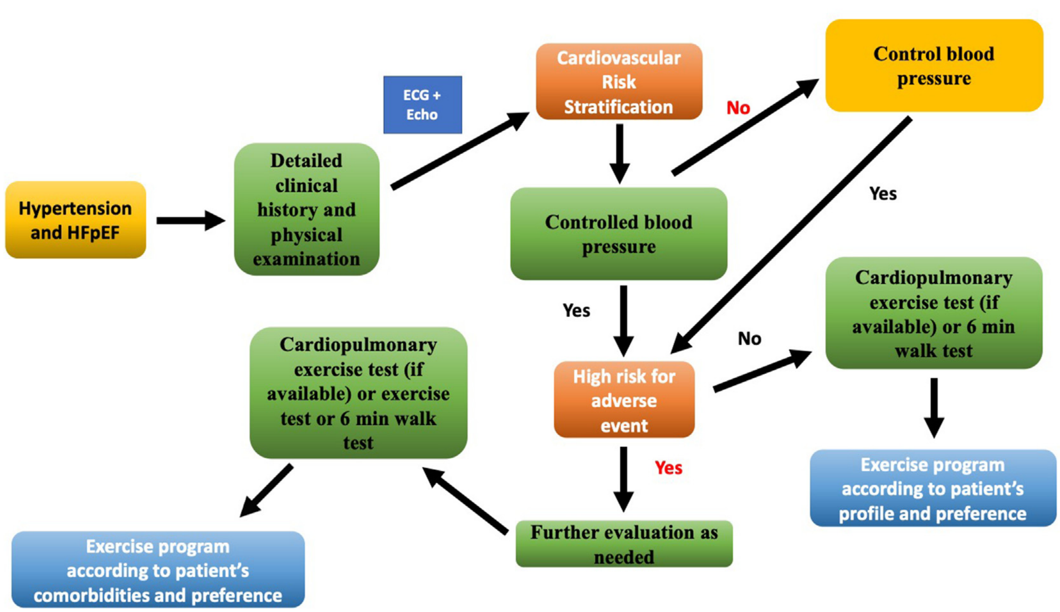

Figure 2. Evaluation guide before the initiation of an exercise-based rehabilitation program in hypertensive patients with heart failure with preserved ejection fraction.

Please cite this article as: M. Kallistratos, D. Konstantinidis, K. Dimitriadis *et al.*, Exercise and cardiac rehabilitation in hypertensive patients with heart failure with preserved ejection fraction: A position statement on behalf of the Working Group of Arterial Hypertension of the Hellenic Society of Cardiology, Hellenic Journal of Cardiology, https://doi.org/10.1016/j.hjc.2023.08.008

exercise test (preferably cardiopulmonary exercise testing) in order to prescribe the optimal exercise intensity. Exercise sessions should preferably start gradually, with short phases of 10 min of endurance and 10 min of resistance exercises; in time, over a period of 4 weeks, these should be extended to the final aim of at least 30-45 min for ≥3 days per week (Fig. 3).[10] Regarding the exercise regimen, it should be tailored to each patient's capacity, with a combination of moderate-intensity endurance (3-5.9 metabolic equivalents) and dynamic exercise (30-50% of one repetition maximum).[10] Moderate intensity for endurance exercise is defined as that which produces 40-69% of peak VO2, 55-74% of the maximum heart rate, or 40-69% of the heart rate reserve.[10] For additional benefit in fitter adults, a gradual increase in aerobic physical activity is recommended. Additional resistance training is effective in further reducing BP and is recommended at a moderate intensity for 2-3 days per week.[2] Moderate-intensity resistance training is defined as 30-50% of the maximum amount of weight the person can lift throughout a range of motion with one repetition (RM), and it is advised to schedule a gradual increase up to sets of 15 repetitions.[10] Exercise that promotes balance and flexibility is also strongly recommended at least 2-3 times per week. In addition, Borg's rating of perceived exertion (RPE) 6-20 scale should be used to monitor the patient's subjective assessment of exercise intensity.[67] Aquatic therapy is the preferred exercise for patients who suffer from arthritis or any other orthopedic issue.

The majority of patients with HFpEF are treated for hypertension in community-based medical offices. The development of interprofessional care, including the internist, general practitioner, cardiologist, dietician, physical therapist, and psychologist, should form the basis of this approach. Apart from the lack of rehabilitation centers oriented toward cardiovascular patients, frailty, cognitive dysfunction, depression, and other psychosocial problems are major barriers to be overcome.

6. Choice of drugs

Given that the basic prerequisite for participation in exercise programs is a well-controlled BP, all drug categories, especially first-line, can be used accordingly. The choice of medication should be based on the patient's clinical profile and comorbidities. Angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers may be preferable to drugs that have a negative inotropic or chronotropic effect, which may have a negative impact on functional performance. B-blockers, unless clearly indicated, must be avoided since patients with HFpEF have a low exercise chronotropic reserve. In addition, diuretics should be used in minimally effective doses because of the increased risk of dehydration, electrolytic imbalance, and post-exercise hypotension.

Apart from the mainstream antihypertensive agents, sodium-glucose cotransporter 2 (SGLT2) inhibitors seem to confer a mild to moderate reduction in SBP and DBP.[68,69] In addition, SGLT2 inhibitors can decrease cardiovascular mortality and the risk of hospitalization while improving the health status of HFpEF patients.[69-80] Dapagliflozin improved the health status of patients with HFpEF, mainly via improvements in symptoms and physical limitations, irrespective of diabetes mellitus status, and is recommended as a therapeutic option in those patients.[77-80]

7. Challenges in implementation of CR programs

Cardiac rehabilitation in Greece, despite its proven benefit to the patient's outcome, so far remains at a low level, without there being

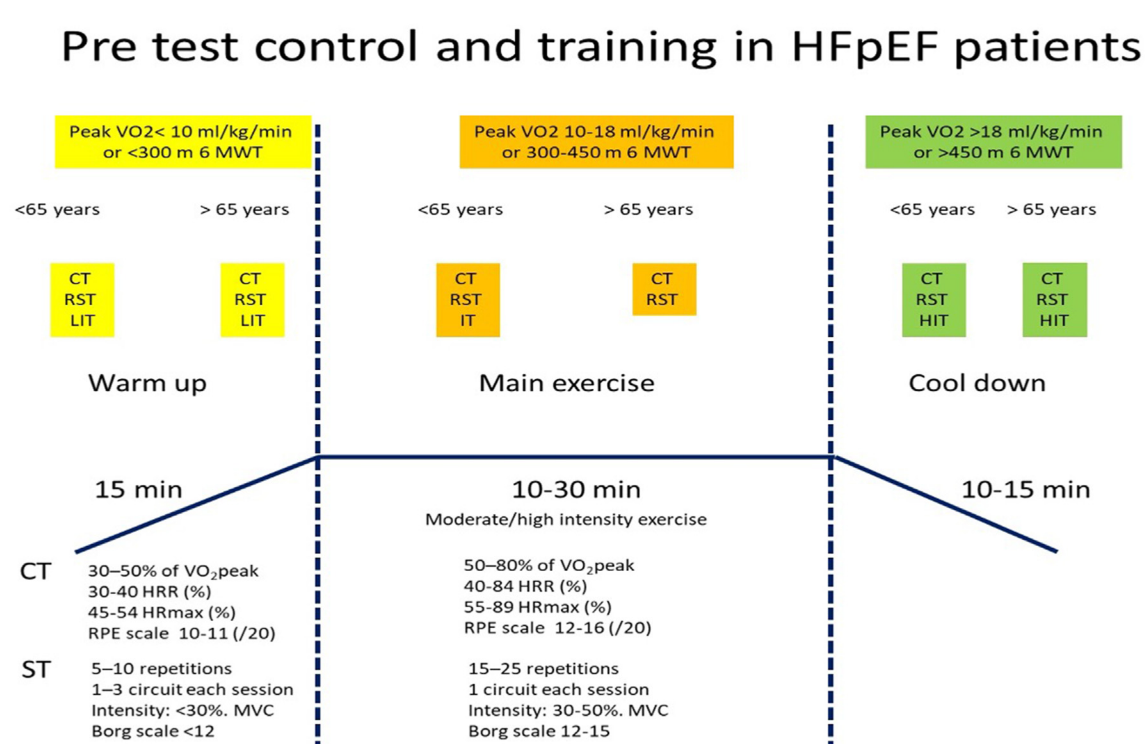

Figure 3. Proposed exercise training in HFpEF patients. Exercise training must take into consideration the patients' functional capacity, clinical status, and comorbidities. Moderate exercise training is highly recommended. A higher intensity of exercise must be individualized according to patients' characteristics and comorbidities. Exercise frequency, intensity, and duration must be tailored to each patient's capacity. HFpEF: heart failure with preserved ejection fraction, HRR: heart rate reserve, HRmax (%): heart rate max, RPE scale: ratings of perceived exertion, CT: continuous training, ST: strength training, MVC: maximal voluntary contraction, HIT, high-intensity interval training, IT: interval training, LIT: low-intensity interval training, RST: resistance strength training).

Please cite this article as: M. Kallistratos, D. Konstantinidis, K. Dimitriadis *et al.*, Exercise and cardiac rehabilitation in hypertensive patients with heart failure with preserved ejection fraction: A position statement on behalf of the Working Group of Arterial Hypertension of the Hellenic Society of Cardiology, Hellenic Journal of Cardiology, https://doi.org/10.1016/j.hjc.2023.08.008

any organized structures or a specific strategy for such a thing. The outlook is even worse for patients with HFpEF, who are older, with a worse functional status and many comorbidities, and who are often dependent on family caregivers. There is a great need for the formulation of a national health policy in Greece that will endorse the provision of cardiac rehabilitation in those patients. Major obstacles related to structure, availability, integration into the healthcare system, and reimbursement remain to be overcome. Scientific societies may exert a powerful influence on this issue by proposing realistic strategic plans to the state and enhancing the training of physicians, health care practitioners, and patients in this direction. Clinicians should listen carefully to the patient's concerns and assess their level of commitment to the CR program while providing guidance and support at the patient's current level.

The implementation strategy for CR programs should include stakeholder encouragement and meetings, the creation of educational materials, training of the supervising teams, and program assessment. In addition, the incorporation of hybrid programs with digital applications supplementary and complementary to the in-person meetings would be of help since many of these patients are dependent and have difficulties with mobility.

8. Gaps in the evidence

Although exercise is strongly recommended and rehabilitation is enthusiastically encouraged in HFpEF patients, adequate evidence resulting from randomized large trials with “hard” primary endpoints is lacking for this specific population. In addition, the published literature has not addressed patients’ clinical complexity and the intersection of health, psychological impact, and social dimensions. Interventional research studies have excluded patients with multiple comorbidities or more fragile individuals. Finally, high-quality evidence and adequate comparative data evaluating the most beneficial modes of exercise among patient populations are lacking.

9. Conclusions

Participation in exercise programs and/or cardiac rehabilitation is associated with a significant benefit in hypertensive patients and patients with HFpEF. Exercise training should be initiated in clinically and hemodynamically stable patients in whom a detailed clinical evaluation and cardiovascular risk stratification should be performed before exercise counseling. BP control and monitoring are essential requirements for these patients. Exercise programs and cardiac rehabilitation in patients with hypertensive heart disease and HFpEF offer a proven benefit, and for this reason, they are strongly indicated in the guidelines. However, they are significantly underutilized, and national implementation practices are needed for this purpose. Apart from the practical difficulties involved in implementing CR through the healthcare system, one of the most important barriers is physicians' lack of awareness. This consensus document provides a general framework for exercise and planned rehabilitation in those patients, aiming to guide clinicians’ decisions and facilitate clinical practice.

Funding

None.

Conflicts of interest

There is nothing to declare in relation to this manuscript.

Acknowledgment

The authors thank Mr. Philip Lees for writing assistance and language editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hjc.2023.08.008.

Supplementary materials

Role of exercise in hypertension and hypertensive heart disease.

Appendix

Collaborating Experts.

- Haralambos Grassos, Cardiology Department, KAT General Hospital, Athens, Greece
- Athanasios Manolis, Cardiology Department, Metropolitan Hospital, Piraeus, Greece
- Thomas Makris, Elena Venizelou General Hospital, Athens, Greece
- Spyros Maragkoudakis, Cardiology Department, Chania ‘St. George’, General Hospital, Crete, Greece
- Dimitris Papadopoulos, Cardiology Department, Laiko General Hospital, Athens, Greece
- Ourania Papazaxou, Elena Venizelou General Hospital, Athens, Greece
- Maria Papavasileiou
- Andreas Pittaras
- Leonidas Poulimenos, Cardiology Departement, Asklipieio Voula Hospital, Athens, Greece
- Kostas Thomopoulos, Cardiology Department, Elena Venizelou General Hospital, Athens, Greece
- Helen Triantafillidi, Cardiology Department, Attikon University General Hospital, Athens, Greece
- John Zarifis, Cardiology Department, General Hospital of Thessaloniki “George Papanikolaou”, Thessaloniki, Greece

References

1. Keamey PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005;365:217−223.
2. Williams B, Mancia G, Spiering W, et al. ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39(33):3021−3104, 2018.
3. Ponikowski P, Voors AA, Anker SD, et al. 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(27):2129−2200, 2016.
4. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA*. 1996;275:1557−1562.
5. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol*. 2012;2:1143−1211.
6. Blair SN, Kampert JB, Kohl 3rd HW, et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA*. 1996;276:205−210.
7. Nystoriak MA, Bhatnagar A. Cardiovascular effects and benefits of exercise. *Front Cardiovasc Med*. 2018;5:135.
8. Vanhees L, Geladas N, Hansen D, et al. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular risk factors: recommendations from the EACPR. Part II. *Eur J Prev Cardiol*. 2012;19:1005−1033.
9. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Publ Health Rep*. 1985;100:126−131.

10. Pelliccia A, Sharma S, Gati S, et al. ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J*. 2020;42:17–96, 2021.
11. Mul JD, Stanford KI, Hirshman MF, Goodyear LJ. Exercise and Regulation of Carbohydrate Metabolism. *Prog Mol Biol Transl Sci*. 2015;135:17–37.
12. Patel H, Alkhawam H, Madanieh R, et al. Aerobic vs anaerobic exercise training effects on the cardiovascular system. *World J Cardiol*. 2017;9:134–138.
13. MacDonald MJ, Currie KD. Interval exercise is a path to good health, but how much, how often and for whom? *Clin Sci (Lond)*. 2009;116:315–316.
14. Tjonna AE, Lee SJ, Rognmo O, et al. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation*. 2008;118:346–354.
15. Gordon NF, Kohl 3rd HW, Pollock ML, et al. Cardiovascular safety of maximal strength testing in healthy adults. *Am J Cardiol*. 1995;76:851–853.
16. Cosentino F, Grant PJ, Aboyans V, et al. ESC Guidelines on diabetes, prediabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2019;41:255–323, 2020.
17. Magalhaes JP, Judice PB, Ribeiro R, et al. Effectiveness of high-intensity interval training combined with resistance training versus continuous moderate-intensity training combined with resistance training in patients with type 2 diabetes: A one-year randomized controlled trial. *Diabetes Obes Metabol*. 2019;21:550–559.
18. Londeree BR, Moeschberger ML. Influence of age and other factors on maximal heart rate. *J Cardiac Rehabil*. 1984;4:44–49.
19. Haykowsky MJ, Brubaker PH, Morgan TM, Kritchevsky S, Eggebeen J, Kitzman DW. Impaired aerobic capacity and physical functional performance in older heart failure patients with preserved ejection fraction: Role of lean body mass. *J Gerontol A Biol Sci Med Sci*. 2013;68:968–975.
20. Haykowsky M, Brubaker P, Kitzman D. Role of physical training in heart failure with preserved ejection fraction. *Curr Heart Fail Rep*. 2012;9:101–106.
21. Gordon NF, Gulanick M, Costa F, et al. Physical activity and exercise recommendations for stroke survivors. *Circulation*. 2004;109:2031–2041.
22. Mitchell JH. Abnormal cardiovascular response to exercise in hypertension: contribution of neural factors. *Am J Physiol Regul Integr Comp Physiol*. 2017;312(6):R851–R863.
23. Fagard R, Staessen J, Amery A. Maximal aerobic power in essential hypertension. *J Hypertens*. 1988;6:859–865.
24. Lim PO, MacFadyen RJ, Clarkson PB, MacDonald TM. Impaired exercise tolerance in hypertensive patients. *Ann Intern Med*. 1996;124:41–55.
25. Alpsoy Ş. Exercise and Hypertension. *Adv Exp Med Biol*. 2020;1228:153–167.
26. Perrier-Melo RJ, Costa EC, Farah BQ, Costa MDC. Acute effect of interval vs. continuous exercise on BP: Systematic review and meta-analysis. *Arq Bras Cardiol*. 2020;115(1):5–14.
27. Mortensen SP, Nyberg M, Gliemann L, Thaning P, Saltin B, Hellsten Y. Exercise training modulates functional sympatholysis and α-adrenergic vasoconstrictor responsiveness in hypertensive and normotensive individuals. *J Physiol*. 2014;592:3063–3073.
28. Borlaug BA, Olson TP, Lam CS, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2010;56:845–854.
29. Haykowsky MJ, Brubaker PH, John JM, Stewart KP, Morgan TM, Kitzman DW. Determinants of exercise intolerance in elderly heart failure patients with preserved ejection fraction. *J Am Coll Cardiol*. 2011;58:265–274.
30. Wasserman K, Zhang YY, Gitt A, et al. Lung function and exercise gas exchange in chronic heart failure. *Circulation*. 1997;96(7):2221–2227.
31. Snijders T, Nederveen JP, Joanisse S, et al. Muscle fibre capillarization is a critical factor in muscle fibre hypertrophy during resistance exercise training in older men. *J Cachexia Sarcopenia Muscle*. 2017;8:267–276.
32. Prokopidis K, Isanejad M, Akpan A, et al. Exercise and nutritional interventions on sarcopenia and frailty in heart failure: a narrative review of systematic reviews and meta-analyses. *ESC Heart Fail*. 2022;9(5):2787–2799.
33. Palevičiūtė E, Šimbelytė T, Eichstaedt CA, et al. The effect of exercise training and physiotherapy on left and right heart function in heart failure with preserved ejection fraction: a systematic literature review. *Heart Fail Rev*. 2022;28(1):193–206.
34. Gary RA, Sueta CA, Dougherty M, et al. Home-based exercise improves functional performance and quality of life in women with diastolic heart failure. *Heart Lung*. 2004;33:210–218.
35. Kitzman D, Brubaker P, Morgan T, Stewart K, Little W. Exercise training in older patients with heart failure and preserved ejection fraction. *Circ Heart Fail*. 2010;3:659–667.
36. Kitzman DW, Brubaker PH, Herrington DM, et al. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *J Am Coll Cardiol*. 2013;62:584–592.
37. Pandey A, Kitzman DW, Brubaker P, et al. Response to endurance exercise training in older adults with heart failure with preserved or reduced ejection fraction. *J Am Geriatr Soc*. 2017;65(8):1698–1704.
38. Palau P, Domínguez E, López L, et al. Inspiratory muscle training and functional electrical stimulation for treatment of heart failure with preserved ejection fraction: The TRAINING-HF Trial. *Rev Esp Cardiol*. 2019;72(4):288–297.
39. Smart NA, Haluska B, Jeffriess L, Leung D. Exercise training in heart failure with preserved systolic function: a randomized controlled trial of the effects on cardiac function and functional capacity. *Congest Heart Fail*. 2012;18:295–301.
40. Edelmann F, Gelbrich G, Düngen HD, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. *J Am Coll Cardiol*. 2011 Oct 18;58(17):1780–1791.
41. Haykowsky MJ, Brubaker PH, Stewart KP, Morgan TM, Eggebeen J, Kitzman DW. Effect of endurance training on the determinants of peak exercise oxygen consumption in elderly patients with stable compensated heart failure and preserved ejection fraction. *J Am Coll Cardiol*. 2012;60:120–128.
42. Donelli da Silveira A, Beust de Lima J, da Silva Piardi D, et al. High-intensity interval training is effective and superior to moderate continuous training in patients with heart failure with preserved ejection fraction: A randomized clinical trial. *Eur J Prev Cardiol*. 2020;27(16):1733–1743.
43. Mueller S, Winzer EB, Duvinage A, et al, OptimEx-Clin Study Group. Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction: A randomized clinical trial. *JAMA*. 2021;325(6):542–551.
44. Hegde SM, Claggett B, Shah AM, et al. Physical activity and prognosis in the TOPCAT Trial (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist). *Circulation*. 2017;136(11):982–999.
45. Fukuta H, Goto T, Wakami K, Kamiya T, Ohte N. Effects of exercise training on cardiac function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. *Heart Fail Rev*. 2019;24:535–547.
46. Kaltsatou AC, Kouidi EI, Anifanti MA, Douka SI, Deligiannis AP. Functional and psychosocial effects of either a traditional dancing or a formal exercising training program in patients with chronic heart failure:a comparative randomized controlled study. *Clin Rehabil*. 2014;28(2):128–138.
47. Fu TC, Yang NI, Wang CH, et al. Aerobic interval training elicits different hemodynamic adaptations between heart failure patients with preserved and reduced ejection fraction. *Am J Phys Med Rehabil*. 2016;95(1):15–27.
48. Angadi SS, Mookadam F, Lee CD, Tucker WJ, Haykowsky MJ, Gaesser GA. High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study. *J Appl Physiol*. 1985;119(6):753–758, 2015.
49. Lang CC, Smith K, Wingham J, investigatorsREACH-HF, et al. Arandomised controlled trial of a facilitated home-based rehabilitationintervention in patients with heart failure with preserved ejection fractionand their caregivers: the REACH-HFpEF PilotStudy. *BMJOpen*. 2018;8(4):e019649.
50. McDonagh TA, Metra M, Adamo M, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599–3726, 2021.
51. Muhlestein JB, Lappe DL, Lima JA, et al. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. *JAMA*. 2014;312(21):2234–2243.
52. Cho I, Al'Aref SJ, Berger A, et al. Prognostic value of coronary computed tomographic angiography findings in asymptomatic individuals: a 6-year follow-up from the prospective multicentre international CONFIRM study. *Eur Heart J*. 2018;39:934–941.
53. van Rosendael AR, Narula J, Lin FY, et al. Association of high-density calcified 1K plaque with risk of acute coronary syndrome. *JAMA Cardiol*. 2020;5(3):282–290.
54. Bergstrom G, Persson M, Adiels M, et al. Prevalence of subclinical coronary artery atherosclerosis in the general population. *Circulation*. 2021;144(12):916–929.
55. Budoff MJ, Lakshmanan S, Toth PP, et al. Cardiac CT angiography in current practice: An American society for preventive cardiology clinical practice statement. *Am J Prev Cardiol*. 2022;20(9):100318.
56. Sharman JE, La Gerche A, Coombes JS. Exercise and cardiovascular risk in patients with hypertension. *Am J Hypertens*. 2015;28(2):147–158.
57. Dassanayake S, Sole G, Wilkins G, Gray E, Skinner M. Effectiveness of physical activity and exercise on ambulatory BP in adults with resistant hypertension: A Systematic review and meta-analysis. *High Blood Pres Cardiovasc Prev*. 2022;29:275–286.
58. Tucker WJ, Lijauco CC, Hearon Jr CM, et al. Mechanisms of the improvement in peak VO2 with exercise training in heart failure with reduced or preserved ejection fraction. *Heart Lung Circ*. 2018;27:9–21.
59. Crisci G, De Luca M, D'Assante R, et al. Effects of exercise on heart failure with preserved ejection fraction: An updated review of literature. *J Cardiovasc Dev Dis*. 2022;9:241.
60. Sarullo FM, Fazio G, Brusca I, et al. Cardiopulmonary exercise testing in patients with chronic heart failure: Prognostic comparison from peak VO2 and VE/VCO2 Slope. *Open Cardiovasc Med J*. 2010;4:127–134.
61. Fiuza-Luces C, Santos-Lozano A, Joyner M, et al. Exercise benefits in cardiovascular disease: beyond attenuation of traditional risk factors. *Nat Rev Cardiol*. 2018;15:731–743.
62. Hanssen H, Boardman H, Deiseroth A, et al. Personalized exercise prescription in the prevention and treatment of arterial hypertension: a Consensus Document from the European Association of Preventive Cardiology (EAPC) and the ESC Council on Hypertension. *Eur J Prev Cardiol*. 2022;29:205–215.
63. Bobenko A, Bartels I, Münch M, et al. Amount or intensity? Potential targets of exercise interventions in patients with heart failure with preserved ejection fraction. *ESC Heart Fail*. 2018;5:53–62.
64. Piepoli MF, Abreu A, Albus C, et al. Update on cardiovascular prevention in clinical practice: A position paper of the European Association of Preventive Cardiology of the European Society of Cardiology. *Eur J Prev Cardiol*. 2020;27:181–185.

Please cite this article as: M. Kallistratos, D. Konstantinidis, K. Dimitriadis *et al.*, Exercise and cardiac rehabilitation in hypertensive patients with heart failure with preserved ejection fraction: A position statement on behalf of the Working Group of Arterial Hypertension of the Hellenic Society of Cardiology, Hellenic Journal of Cardiology, https://doi.org/10.1016/j.hjc.2023.08.008

65. Boeno FP, Ramis TR, Munhoz SV, et al. Effect of aerobic and resistance exercise training on inflammation, endothelial function and ambulatory BP in middle-aged hypertensive patients. *J Hypertens*. 2020;38:2501–2509.
66. Corso LM, Macdonald HV, Johnson BT, et al. Is Concurrent Training Efficacious Antihypertensive Therapy? A Meta-analysis. *Med Sci Sports Exerc*. 2016;48(12): 2398, 2306.
67. Borg GA. Psychophysical bases of perceived exertion. *Inside MS*. 1982;14: 377–381.
68. Kasiakogias A, Rosei EA, Camafort M, et al. Hypertension and heart failure with preserved ejection fraction: position paper by the European Society of Hypertension. *J Hypertens*. 2021 Aug 1;39(8):1522–1545.
69. Sanidas EA, Papadopoulos DP, Hatziagelaki E, Grassos C, Velliou M, Barbetseas J. Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors Across the Spectrum of Hypertension. *Am J Hypertens*. 2020;33(3):207–213.
70. Liakos CI, Papadopoulos DP, Sanidas EA, et al. BP-Lowering Effect of Newer Antihyperglycemic Agents (SGLT-2 Inhibitors, GLP-1 Receptor Agonists, and DPP-4 Inhibitors). *Am J Cardiovasc Drugs*. 2021;21(2):123–137.
71. Tikkanen I, Narko K, Zeller C, et al. Empagliflozin reduces BP in patients with type 2 diabetes and hypertension. *Diabetes Care*. 2015;38(3):420–428.
72. Sjostrom CD, Johansson P, Ptaszynska A, List J, Johnsson E. Dapagliflozin lowers BP in hypertensive and non-hypertensive patients with type 2 diabetes. *Diabetes Vasc Dis Res*. 2015;12(5):352–358.
73. Townsend RR, Machin I, Ren J, et al. Reductions in Mean 24-Hour Ambulatory BP After 6-week treatment with canagliflozin in patients with type 2 diabetes mellitus and hypertension. *J Clin Hypertens*. 2016;18(1):43–52.
74. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373(22):2117–2128.
75. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2019;380(4):347–357.
76. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med*. 2021;385(16):1451–1461.
77. Nassif ME, Windsor SL, Borlaug BA, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. *Nat Med*. 2021;27(11):1954–1960.
78. Solomon SD, de Boer RA, DeMets D, et al. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. *Eur J Heart Fail*. 2021;23(7):1217–1225.
79. Voorrips SN, Saucedo-Orozco H, Sánchez-Aguilera PI, De Boer RA, Van der Meer P, Westenbrink BD. Could SGLT2 Inhibitors Improve Exercise Intolerance in Chronic Heart Failure? *Int J Mol Sci*. 2022;23(15):8631.
80. Heidenreich PA, Bozkurt B, Aguilar D, et al. AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(17):1757–1780, 2022.

Manolis Kallistratos[†]
Cardiology Department, Metropolitan Hospital, Piraeus, Greece

Dimitrios Konstantinidis[†], Kyriakos Dimitriadis
First Department of Cardiology, Medical School, National and Kapodistrian University of Athens, Hippokration Hospital, Athens, Greece

Elias Sanidas
Cardiology Department, LAIKO General Hospital, Athens, Greece

Vasiliki Katsi
First Department of Cardiology, Medical School, National and Kapodistrian University of Athens, Hippokration Hospital, Athens, Greece

Emmanouil Androulakis
Cardiology Department, St. George's, University of London, London, UK

Charalambos Vlachopoulos, Konstantinos Toutouzas
First Department of Cardiology, Medical School, National and Kapodistrian University of Athens, Hippokration Hospital, Athens, Greece

John Kanakakis
Department of Clinical Therapeutics, University of Athens Medical School, 11528 Athens, Greece

Skevos Sideris
First Department of Cardiology, Medical School, National and Kapodistrian University of Athens, Hippokration Hospital, Athens, Greece

Nikolaos Kafkas
Cardiology Department, KAT General Hospital, Athens, Greece

Angeliki Despoina Mavrogianni
Cardiology Department, George Papanikolaou General Hospital, Thessaloniki, Greece

Constantinos H. Papadopoulos
Second Cardiology Department, Korgialenio-Benakio Red Cross Hospital, Athens, Greece

Alexandros Stefanidis
Cardiology Department, General Hospital of Nikea, Athens, Greece

Nikolaos Patsourakos
Department of Cardiology, "Tzaneio" General Hospital of Piraeus, Piraeus, Greece

Ioannis Kachrimanidis
First Department of Cardiology, Medical School, National and Kapodistrian University of Athens, Hippokration Hospital, Athens, Greece

Nikolaos Papaioannou
Department of Cardiology, Asklepeion General Hospital Cardiology, Athens, Greece

Costas Tsioufis
First Department of Cardiology, Medical School, National and Kapodistrian University of Athens, Hippokration Hospital, Athens, Greece

George Kochiadakis, Maria Marketou*
Cardiology Department, Heraklion University General Hospital, Crete, Greece

* *Corresponding author.* FESC Cardiology Department, Heraklion University Hospital, P.O. Box 1352, Stavrakia, Heraklion, Greece. Tel.: +30 2810 392877, 392632; Fax: +30 2810 542055.
E-mail address: maryemarke@yahoo.gr (M. Marketou).

24 April 2023
Available online xxx

† Equal contribution.