Revista Colombiana de
Cardiología

Volume 31 Supplement 3
ISSN:0120-5633

November 2024
www.rccardiologia.com
www.revcolcard.org

EXPERT CONSENSUS: DIAGNOSIS AND TREATMENT OF HEART FAILURE WITH PRESERVED AND SLIGHTLY REDUCED EJECTION FRACTION

CONSENSO DE EXPERTOS: DIAGNÓSTICO Y TRATAMIENTO DE LA INSUFICIENCIA CARDIACA CON FRACCIÓN DE EYECCIÓN PRESERVADA Y LIGERAMENTE REDUCIDA

Órgano oficial de la Asociación
SOCIEDAD COLOMBIANA
DE CARDIOLOGÍA & CIRUGÍA
CARDIOVASCULAR

Revista Colombiana de
Cardiología

Órgano oficial de la Asociación
SOCIEDAD COLOMBIANA
DE CARDIOLOGÍA & CIRUGÍA CARDIOVASCULAR

La *Revista Colombiana de Cardiología (RCC)* es la publicación científica oficial de la Sociedad Colombiana de Cardiología y Cirugía Cardiovascular.
Es una publicación bimestral, *open access* (abierta sin costo para autores y lectores), de revisión por pares, que se publica en versión electrónica y acepta manuscritos para evaluación en español o inglés sobre aspectos básicos, epidemiológicos, quirúrgicos y clínicos en el área de la cardiología. Cuenta con un Comité Editorial compuesto de expertos nacionales e internacionales. La revista se encarga de divulgar artículos originales clínicos y experimentales sobre enfermedades cardiovasculares, reportes sobre terapéutica médica y quirúrgica, cardiología pediátrica, estudios cooperativos, epidemiología, estudios de medicamentos, métodos diagnósticos, reportes de casos clínicos, cartas al editor y editoriales.

Revista Colombiana de Cardiología (RCC) *is the official scientific publication of the Sociedad Colombiana de Cardiología y Cirugía Cardiovascular.*
It is a peer reviewed, bimonthly journal, that publishes online open access (free of charge for authors and readers) articles in Spanish or English about basic, epidemiological, surgical or clinical aspects in the field of Cardiology. It has an Editorial Committee composed of national and international experts. The journal's objective is to spread original articles, clinical and experimental, about cardiovascular diseases, reports about medical and surgery therapy, pediatric cardiology, cooperative studies, epidemiology, drug studies, diagnostic methods, case reports, letters to the editor and editorials.

Los trabajos originales deberán ser depositados en su versión electrónica en el siguiente URL:

http://publisher.rccar.permanyer.com

Revista Colombiana de Cardiología
Órgano oficial de la Asociación SOCIEDAD COLOMBIANA DE CARDIOLOGÍA & CIRUGÍA CARDIOVASCULAR
PERMANYER

Presentation

Presentación

Darío Echeverri[1*]

[1]*Editor in Chief, Revista Colombiana de Cardiología.*

On behalf of Sociedad Colombiana de Cardiología y Cirugía Cardiovascular and its official organ, Revista Colombiana de Cardiología, we would like to recognize Dr. María Juliana Rodríguez, guest editor, and all the members of the Heart Failure Chapter of Sociedad Colombiana de Cardiología y Cirugía Cardiovascular who participated in creating and drafting the current Supplement: Expert consensus: Diagnosis and treatment of heart failure with preserved and mildly reduced ejection fraction, for all their effort in achieving this special issue with the different topics treated with such professionalism and scientific quality.

Heart failure is a growing global problem with a rising prevalence that causes high mortality and hospitalization rates as well as high healthcare system costs. Slightly more than 64 million people around the world had heart failure a decade ago, and the prevalence is expected to gradually increase over the next few years due to population aging and the growing burden of comorbidities. Today, more than half of the patients have a preserved ejection fraction, which makes them harder to diagnose in clinical settings, while still constituting a risky condition. Due to its growing prevalence and limited treatment options, it is considered to be a significant and escalating problem with a special and diverse pathophysiology. Furthermore, it is associated with multiple cardiac and non-cardiac abnormalities, has a significant impact on the cardiac chambers and pulmonary circulation, and causes peripheral organ abnormalities.

This special issue is devoted to an even better understanding of the pathophysiology, phenotyping, diagnosis and treatment of heart failure with preserved and mildly reduced ejection fraction based on the criteria of a group of experts from Sociedad Colombiana de Cardiología.

We would like to express our sincere gratitude to the authors who kindly contributed to this issue, for all their effort and time invested.

Correspondence:
*Darío Echeverri
E-mail: decheverri@lacardio.org

Date of reception: 05-11-2024
Date of acceptance: 05-11-2024
Available online: 04-12-2024
Rev Colomb Cardiol. 2024;31(Suppl3):1
www.rccardiologia.com

Revista Colombiana de Cardiología
Órgano oficial de la Asociación SOCIEDAD COLOMBIANA DE CARDIOLOGÍA & CIRUGÍA CARDIOVASCULAR
PERMANYER

Prologue

Prólogo

*María J. Rodríguez-González[1]**

[1]Departament of Heart Failure and Transplantation, La Cardio, Fundación Cardioinfantil, Bogotá.

Heart failure (HF) continues to be a significant global health problem, affecting millions of people and placing a substantial burden on healthcare systems. Within the spectrum of heart failure diseases, heart failure with preserved ejection fraction (HFpEF) and heart failure with mildly reduced ejection fraction (HFmrEF) have garnered the most attention in recent years. These disorders challenge traditional perceptions of heart failure, especially regarding the diagnosis, treatment and outcomes of these patients. The goal of this consensus is to elucidate the different diagnostic approaches to, and treatment of, these conditions.

The diagnosis of HFpEF and HFmrEF requires a comprehensive approach that includes clinical assessment, echocardiography and biomarker analysis. Physicians should evaluate the patients' symptoms, comorbidities and functional status to make an accurate diagnosis. Echocardiography plays an essential role in confirming the ejection fraction and evaluating diastolic function. In addition, biomarkers like natriuretic peptides can provide valuable diagnostic information.

The treatment strategies for HFpEF and HFmrEF are different from those for HFrEF, mainly because the evidence-based treatments for the latter often do not translate effectively to the former. The current treatment for HFpEF focuses on controlling comorbidities, optimizing the fluid status and improving physical activity, with evidence for only one type of therapy.

In HFmrEF, treatment strategies may incorporate elements from both HFpEF and HFrEF guidelines, emphasizing the need for personalized care.

Heart failure with preserved and mildly reduced ejection fraction represents an important and developing field in cardiovascular medicine. As our understanding of these diseases deepens, it is increasingly clear that they require a nuanced approach to diagnosis and treatment. Both HFpEF and HFmrEF challenge the traditional heart failure paradigms, forcing healthcare providers to reconsider their treatment and patient care strategies. With studies and clinical trials in progress, there is hope for improving the outcomes and quality of life of patients affected by these complex heart failure phenotypes.

The road toward effective treatment of HFpEF and HFmrEF is far from over but is an essential effort in the fight against heart failure.

Correspondence:
*María J. Rodríguez-González
E-mail: mjrodriguez@lacardio.org

Date of reception: 04-10-2024
Date of acceptance: 04-10-2024
Available online: 04-12-2024
Rev Colomb Cardiol. 2024;31(Suppl3):2
www.rccardiologia.com

Revista Colombiana de Cardiología
Órgano oficial de la Asociación Sociedad Colombiana de Cardiología & Cirugía Cardiovascular
Permanyer

SPECIAL ARTICLE

Expert consensus: diagnosis and treatment of heart failure with preserved and slightly reduced ejection fraction

Consenso de expertos: diagnóstico y tratamiento de la insuficiencia cardiaca con fracción de eyección preservada y ligeramente reducida

María J. Rodríguez-González[1]*, Ángel A. García-Peña[2], Alex Rivera-Toquica[3,4], Carlos A. Arias-Barrera[5], Erick F. Castaño-Contreras[6-8], Juan M. Cárdenas-Castellanos[9,3], Jeffrey Castellanos-Parada[10], Luis E. Echeverría[11], Luis A. Fajardo-Andrade[12-14], Catalina Gallego-Muñoz[12], Efraín A. Gómez-López[15], Juan E. Gómez-Mesa[16,17], Gina González-Robledo[18,19], Juan D. López-Ponce de Leon[20], Alejandro Mariño-Correa[21], Erika M. Martínez-Carreño[22], Fernán D. Mendoza-Beltrán[23,24], Solón Navarrete-Hurtado[25,26], John A. Ramírez-Martínez[1], Nubia L. Roa-Buitrago[27], Jaime A. Rodríguez-Plazas[28,29], Nohra Romero-Vanegas[27], Clara I. Saldarriaga-Giraldo[30-32], Alejando Sánchez-Velásquez[33], Adriana Torres-Navas[34,35], Julián E. Vanegas-Eljach[36,37] y Andrés F. Buitrago-Sandoval[27]

[1]Departament of Heart Failure and Transplantation, La Cardio, Fundación Cardioinfantil, Bogotá; [2]Departament of Internal Medicine, Cardiology Unit, Pontificia Universidad Javeriana, Hospital Universitario San Ignacio, Bogotá; [3]Centro Médico para el Corazón, Pereira; [4]Internal Medicine Graduate Program, Universidad Tecnológica de Pereira, Pereira; [5]Heart Failure and Transplantation Service, Fundación Clínica Shaio, Clínica Colsanitas, Bogotá; [6]Heart Failure Group, Instituto del Corazón de Bucaramanga, Bucaramanga; [7]Internal Medicine, Universidad Industrial de Santander (UIS). [8]Internal Medicine, Universidad Autónoma de Bucaramanga (UNAB), Bucaramanga; [9]Universidad Tecnológica de Pereira. [10]Heart Failure and Cardiac Transplantation Unit, Clínica Colsanitas, Bogotá; [11]Heart Failure and Cardiac Transplantation Program, Fundación Cardiovascular de Colombia, Floridablanca; [12]Clínica CardioVID, Medellín; [13]Cardiology Service, Centro Clínico y de Investigación SICOR, Medellín; [14]Cardiology Service, Centro de Biociencias SURA, Medellín; [15]Departament of Internal Medicine, Cardiovascular ICU, Fundación Clínica Shaio, Bogotá; [16]Departament of Internal Medicine, Cardiology Service, Fundación Valle del Lili, Cali; [17]Faculty of Health Sciences. Universidad Icesi, Cali; [18]Heart Failure Clinic, Hospital Universitario Fundación Santa Fe de Bogotá, Bogotá; [19]Universidad de Los Andes, Bogotá; [20]Cardiology Service, Fundación Valle del Lili, Cali; [21]Heart Failure and Cardiac Transplantation Program, Hospital Universitario San Ignacio, Pontificia Universidad Javeriana; Bogotá; [22]Heart Failure Program, Clínica Iberoamericana, Barranquilla; [23]Heart Failure and Transplantation Service, Fundación Clínica Shaio, Bogotá; [24]Graduate Program in Cardiology, Universidad El Bosque, Bogotá; [25]CARDIOLAB, Bogotá; [26]Cardiology Service, Hospital Central de la Policía Nacional, Bogotá; [27]Cardiology Service, Hospital Universitario Fundación Santa Fe, Bogotá; [28]Unit of Non-Invasive Diagnostic Techniques and Heart Failure and Transplantation Clinic, Fundación Cardiovascular de Colombia, Floridablanca; [29]Sociedad Colombiana de Cardiología y Cirugía Cardiovascular, Bogotá; [30]Cardiology Program, Clínica Cardio VID, Medellín; [31]Faculty of Medicine, Universidad de Antioquia, Medellín; [32]Cardiology Program, Universidad Pontificia Bolivariana, Medellín; [33]Instituto del Corazón, Bucaramanga; [34]Cardiovascular Service, Los Cobos Medical Center, Bogotá; [35]Faculty of Medicine, Universidad El Bosque, Bogotá; [36]Cardiology Service, Hospital Alma Máter de Antioquia, Universidad de Antioquia, Medellín; [37]Cardiology Service, Hospital General de Medellín, Medellín.

Abstract

Introduction: the prevalence of heart failure with preserved and mildly reduced ejection fraction is high and is associated with increased hospitalizations, cardiovascular mortality, and all-cause mortality. Evidence regarding the optimal treatment for these patients can be controversial; thus, a high level of clinical suspicion and education is required to establish early and accurate treatment. **Objective:** to conduct an expert consensus on the treatment of patients with heart failure with preserved and mildly reduced ejection fraction, in charge of the Chapter of Heart Failure, Heart Transplantation and Pulmonary Hypertension of the Colombian Society of Cardiology and Cardiovascular Surgery (SCC). **Materials and method:** 27 cardiologists from the Chapter of Heart Failure, Cardiac Transplantation, and Pulmonary Hypertension of the SCC were selected. Twelve

Correspondence:
*María J. Rodríguez-González
E-mail: mjrodriguez@lacardio.org

Date of reception: 04-06-2024
Date of acceptance: 18-09-2024
DOI: 10.24875/RCCARE.M24000115
Available online: 04-12-2024
Rev Colomb Cardiol. 2024;31(Suppl3):3-50
www.rccardiologia.com

questions were defined to be addressed during the consensus. A literature review related to each of the questions was conducted. The consensus was developed in nine phases, and the Nominal Group Technique was used. **Results:** Twelve recommendations were proposed regarding the management of patients with heart failure with preserved and mildly reduced ejection fraction, along with a precise diagnostic algorithm for the evaluation of patients suspected of having this condition. **Conclusions:** This consensus addresses the need for clear guidelines to improve the diagnosis and treatment of patients with heart failure with preserved and mildly reduced ejection fraction.

Keywords: *Heart failure. Consensus. Pharmacological treatment. Disease management. Heart failure with preserved and mildly reduced ejection fraction.*

Resumen

Introducción: la prevalencia de la insuficiencia cardiaca con fracción de eyección preservada y ligeramente reducida es alta y está asociada a un aumento de las hospitalizaciones, de la mortalidad cardiovascular y de la muerte por todas las causas. La evidencia sobre el tratamiento óptimo de estos pacientes puede ser controversial, pues se requiere un alto nivel de sospecha clínica y de educación para instaurar un tratamiento temprano y acertado. **Objetivo:** realizar un consenso de expertos sobre el tratamiento de pacientes con insuficiencia cardiaca con fracción de eyección preservada y ligeramente reducida, a cargo del Capítulo de Falla Cardiaca, Trasplante Cardiaco e Hipertensión Pulmonar de la Sociedad Colombiana de Cardiología y Cirugía Cardiovascular (SCC). **Materiales y método:** se seleccionaron 27 médicos cardiólogos pertenecientes al Capítulo de Falla Cardíaca, Trasplante Cardiaco e Hipertensión Pulmonar de la SCC. Se definieron doce preguntas para ser resueltas durante el consenso. Se realizó una revisión de la literatura relacionada con cada una de las preguntas planteadas. El consenso se desarrolló en nueve fases, y se usó la Técnica de Grupo Nominal. **Resultados:** se propusieron doce recomendaciones sobre el manejo de pacientes con insuficiencia cardiaca con fracción de eyección preservada y ligeramente reducida y un algoritmo diagnóstico preciso para la evaluación del paciente con sospecha de esta enfermedad. **Conclusiones:** Este consenso responde a la necesidad de disponer de guías claras, para mejorar el diagnóstico y tratamiento de los pacientes con insuficiencia cardíaca con fracción de eyección preservada y ligeramente reducida.

Palabras clave: *Insuficiencia cardíaca. Consenso. Tratamiento farmacológico. Manejo de la enfermedad. Insuficiencia cardíaca con fracción de eyección preservada y ligeramente reducida.*

Introduction

A better understanding of the pathophysiological processes related to heart failure, and especially to preserved ejection fraction (HFpEF) or mildly reduced ejection fraction (HFmrEF), along with a better identification of this group of patients has helped determine that its prevalence is growing and is associated with higher hospitalization rates. It is a disease that occurs frequently in the general population, mainly in female adults with cardiovascular risk factors like hypertension, dyslipidemia, obesity, chronic kidney disease, sleep apnea, diabetes mellitus and atrial fibrillation[1].

Knowledge regarding HFpEF and HFmrEF has helped improve diagnostic precision and offer patients more information on disease progression and prognosis and the possibility of receiving treatment with proven benefits in quality of life, reduced hospitalization and even, in some cases, decreased mortality.

Given the high burden of morbidity and mortality in this population, simple, practical and updated guidelines are needed, based on the best available scientific evidence, to guide users in the proper diagnostic and therapeutic approach in low and high complexity settings in our country.

Therefore, the Heart Failure, Cardiac Transplantation and Pulmonary Hypertension Chapter of the SCC has carried out an expert consensus to synthesize the available evidence and provide flowcharts and guidelines to impact on the health outcomes of patients with HFmrHF and HFpEF in Colombia.

Materials and method

Technique

The nominal group technique (NGT) was used, which was developed as a consensus strategy by Delbecq and Van de Ven in the 60s and has been widely used in the healthcare field as a formal consensus mechanism for decision making related to clinical interventions, the development of new practices and the identification of health outcomes, among other topics. It is a highly structured technique

that allows interaction within a panel of experts, in which participants are empowered to express their opinions and are asked to systematically evaluate those of their peers[2-4].

The technique has four essential steps:

- Individual (silent) generation of ideas, opinions or responses
- Review of peers' responses with the opportunity to adjust, modify or alter their own responses
- Clarification of opinions or concepts
- Voting

Traditionally, the NGT was conducted in person, which sometimes limited its use due to logistical or financial constraints. This consensus was done using an Information and Communications Technology (ICT) supported version, which allowed it to be conducted remotely and asynchronously. Thus, the individual generation and response review phases were done through a web application, while the clarification and voting phases were done synchronously, using teleconferences and online voting applications.

The NGT used to conduct this consensus met the key characteristics of a consensus method proposed by Jones and Hunter[5]: anonymity, which avoids dominance; interaction, which allows participants to change their own opinions or responses; controlled feedback, which gives participants access to the information provided by the group; and a statistical summary of the responses, which provides quantitative support to the consensus solution. The NGT version used in this consensus helps complement the benefits of the review and the agreement of individualized responses (a fundamental characteristic of the technique) with some advantages of other consensus strategies, like the Delphi method (anonymity during the two initial phases and the use of larger groups of experts)[6].

However, unlike the Delphi method, the consensus reached occurred within the individual and is not mediated by the judgements made by the coordinating group, as there is no third-party structuring of the agreement among participants. Likewise, the voting process was repeated until the rules of agreement explicitly articulated from the beginning of the process were reached[2,7].

Participants

Twenty-seven cardiologists, who were members of the chapter and appear in the list of participants and article authors, were selected according to their interest in, knowledge of and experience with the topic. Four of the clinical and methodological experts in the group of participants acted as coordinators and were responsible for drafting the initial questionnaire to be answered and serving as the first recourse for solving all problems emerging during the consensus process.

An inception meeting was held, attended by all the physicians who had been invited to be part of the consensus group, to inform them of the methodology, timeline and deliverables and answer their questions regarding participation in the project. At the end of the meeting, all the attendees agreed to participate in the consensus according to the established guidelines.

Phases

This project was carried out in nine phases, using the nominal group technique (NGT):

Phase 1 – Question standardization

The questions were standardized in the Patient, Intervention, Comparison, Outcome (PICO) format[8]. The final list of questions is found in Annex A.

Phase 2 – Literature search

This phase was made up of two stages: defining the search strategy and selecting the articles.

Search strategy

The questions drafted by the heart failure consensus group were evaluated, and systematic search strategies were created accordingly, partially based on the PICO structure. The comparator was omitted in the searches in order to favor their sensitivity. The searches were created for the PubMed and Embase search engines, using both free and standardized terms for the search engine employed (MeSH, Emtree). The searches were limited to publications between 2014 and August 2023. Articles after this date were added for some of the proposed questions.

The search for Question 11 was constructed only for the Embase search engine, based on the low rate of recovery of references using the previously described strategy. Proximity searching was used, a strategy which is not available for PubMed.

All searches were developed in a paired fashion by two independent individuals and subsequently integrated into a single strategy for each search engine.

The search structures are described in Annex B.

Article selection

The articles were selected by title and abstract, in a paired fashion and considering the proposed questions. Articles with full text available in English or Spanish were included. As per the methodology, clinical trials and systematic reviews of clinical trials, with or without meta-analyses, were included.

Meta-analyses of individual studies and conference summaries that were not published as full text were excluded.

For Question 11, the inclusion criteria were expanded to include any type of methodological design or review, since no clinical trials were found that could potentially answer the question.

Selection discrepancies between the reviewers were resolved by consensus, in the presence of a third reviewer.

Table 1 shows the number of articles selected for each of the questions.

Phase 3 – Defining the maximum number of options

It was determined that the experts would be requested to provide a single recommendation for all questions, except number 11. For Question 11, the experts were given the option of a maximum of three recommendations.

Phase 4 – Producing solutions or individual responses

During this phase, each of the experts received the questions and instructions for recording their responses or solutions using the licensed Survey Monkey web application. They also received the full text of the articles selected during Phase 2.

The experts were asked to annex any reference they considered relevant, and which was not included in the application.

Annex C presents the individual responses to each question which were generated during this phase. Table 2 shows the final number of articles (between those selected in the search and those submitted by the experts) which constituted the body of evidence for each of the questions.

El traductor, escribe acerca del llamado a tabla 2:

Esta tabla da recomendaciones en lugar del número de referencias. Creo que aquí debe ir “Table 1”

Phase 5 – Evaluating and grading the evidence

This consensus employed the strength of recommendations grading scheme used by the

Table 1. Final number of articles that constituted the body of evidence for each of the questions.

Question	References
1. In patients with heart failure with mildly reduced ejection fraction, is the administration of an angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) effective in reducing hospitalizations for and mortality from heart failure?	8
2. In patients with heart failure with preserved ejection fraction, is the administration of an ACE inhibitor/ARB effective in reducing hospitalizations for and mortality from heart failure?	23
3. In patients with heart failure with mildly reduced ejection fraction, is the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) effective in reducing hospitalizations for and mortality from heart failure?	8
4. In patients with heart failure with preserved ejection fraction, is the administration of an ARNI effective in reducing hospitalizations for and mortality from heart failure?	21
5. In patients with heart failure with mildly reduced ejection fraction, is the administration of a mineralocorticoid receptor antagonist (MRA) effective in reducing hospitalizations for and mortality from heart failure?	5
6. In patients with heart failure with preserved ejection fraction, is the administration of an MRA effective in reducing hospitalizations for and mortality from heart failure?	16
7. In patients with heart failure with mildly reduced ejection fraction, is the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor effective in reducing hospitalizations for and mortality from heart failure?	5
8. In patients with heart failure with preserved ejection fraction, is the administration of an SGLT2 inhibitor effective in reducing hospitalizations for and mortality from heart failure?	16
9. In patients with heart failure with mildly reduced ejection fraction, is the administration of a beta blocker effective in reducing hospitalizations for or mortality from heart failure?	9
10. In patients with heart failure with preserved ejection fraction, is the administration of a beta blocker effective in reducing hospitalizations for and mortality from heart failure?	14
11. In patients with heart failure, both with preserved ejection fraction as well as mildly reduced ejection fraction, is the administration of IV iron effective in reducing hospitalizations for and mortality from heart failure?	1
12. In patients with heart failure, both with preserved as well as mildly reduced ejection fraction, is cardiac rehabilitation added to the instated medical treatment effective in reducing hospitalizations for and mortality from heart failure?	1

Table 2. Recommendations.

Questions	Recommendations
Question 1	**Recommendation 1**
In patients with heart failure with mildly reduced ejection fraction, is the administration of an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) effective in reducing hospitalizations for heart failure and cardiovascular and all-cause mortality?	In patients with heart failure with mildly reduced ejection fraction, the use of an ACE inhibitor, or an ARB in case of ACE inhibitor intolerance, can be considered effective in reducing the number of hospitalizations for heart failure. No benefit has been proven in decreasing cardiovascular or all-cause mortality, except in the context of ischemic heart failure[12,18]. • *Class IIb (57%)* • *Level of recommendation A (69%)*
Question 2	**Recommendation 2**
In patients with heart failure with preserved ejection fraction, is the administration of an ACE inhibitor or ARB effective in reducing hospitalizations for heart failure and cardiovascular and all-cause mortality?	In patients with heart failure with preserved ejection fraction, the administration of an ARB or an ACE inhibitor is effective in reducing hospitalizations for heart failure, but not for reducing cardiovascular or all-cause mortality [14,16,18-34]. • *Class IIb (92%)* • *Level of recommendation A (86%)*
Question 3	**Recommendation 3**
In patients with heart failure with mildly reduced ejection fraction, is the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) effective in reducing hospitalizations for heart failure and cardiovascular and all-cause mortality?	In patients with heart failure with mildly reduced ejection fraction, the administration of an ARNI can be considered for reducing hospitalizations for heart failure, but has no effect in reducing cardiovascular and all-cause mortality [12,13,15,16,27,35]. • *Class IIb (85%)* • *Level of recommendation A (92%)*
Question 4	**Recommendation 4**
In patients with heart failure with preserved ejection fraction, is the administration of an ARNI effective in reducing hospitalizations for heart failure and cardiovascular and all-cause mortality?	In patients with heart failure with preserved ejection fraction, the administration of ARNIs reduces hospitalizations for heart failure, but has no benefit in cardiovascular or all-cause mortality [16,19-21,23-26,28-33,35-39]. • *Class IIb (100%)* • *Level of recommendation B (100%)*
Question 5	**Recommendation 5**
In patients with heart failure with mildly reduced ejection fraction, is the administration of a mineralocorticoid receptor antagonist (MRA) effective in reducing hospitalizations for heart failure and cardiovascular and all-cause mortality?	In patients with heart failure with mildly reduced ejection fraction, the administration of an MRA could reduce hospitalizations for heart failure, but shows no benefit in reducing cardiovascular or all-cause mortality [40-42]. Explanatory note: the consensus leaders recognize that some studies with mineralocorticoid receptor antagonists were being conducted during the course of this consensus. Due to the growing evidence obtained in Phase III studies with this class of drugs in high-risk populations (CKD and diabetes mellitus) with both mildly reduced and preserved LVEF, the grade of recommendation could be modified in the future. • *Class IIb (100%)* • *Level of recommendation B (92%)*
Question 6	**Recommendation 6**
In patients with heart failure with preserved ejection fraction, is the administration of an MRA effective in reducing hospitalizations for heart failure and cardiovascular and all-cause mortality?	In patients with heart failure with preserved ejection fraction, the administration of an MRA could reduce hospitalizations for heart failure, but shows no benefit in reducing cardiovascular or all-cause mortality [40-53]. • *Class IIb (100%)* • *Level of recommendation B (100%)*

Question 7	**Recommendation 7**
In patients with heart failure with mildly reduced ejection fraction, is the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor effective in reducing hospitalizations for heart failure and cardiovascular and all-cause mortality?	In patients with heart failure with mildly reduced ejection fraction, the administration of an SGLT2 inhibitor is recommended to reduce the risk of hospitalization for heart failure and cardiovascular and all-cause mortality[16,54-56]. • *Class I (92%)* • *Level of recommendation A (100%)*
Question 8	**Recommendation 8**
In patients with heart failure with preserved ejection fraction, is the administration of an SGLT2 inhibitor effective in reducing hospitalizations for heart failure and cardiovascular and all-cause mortality?	In patients with symptomatic heart failure with preserved ejection fraction, the administration of an SGLT2 inhibitor is recommended to reduce the risk of hospitalization for heart failure and cardiovascular and all-cause mortality[16,54-67]. • *Class I (93%)* • *Level of recommendation A (100%)*
Question 9	**Recommendation 9**
In patients with heart failure with mildly reduced ejection fraction, is the administration of a beta blocker effective in reducing hospitalizations for heart failure and cardiovascular and all-cause mortality?	In patients with heart failure with mildly reduced ejection fraction, the administration of a beta blocker may be useful in reducing hospitalizations for heart failure and cardiovascular and all-cause mortality[16,54]. • *Class I (84%)* • *Level of recommendation B (92%)*
Question 10	**Recommendation 10**
In patients with heart failure with preserved ejection fraction, is the administration of a beta blocker effective in reducing hospitalizations for heart failure and cardiovascular and all-cause mortality?	In patients with heart failure with preserved ejection fraction, beta blockers could have a marginal benefit in reducing cardiovascular mortality and hospitalizations for heart failure, when associated with comorbidities like coronary disease and hypertension, in patients with sinus rhythm. In other subpopulations, it is not routinely recommended[16,25,29,36,68,69]. • *Class IIb (82%)* • *Level of recommendation B (91%)*
Question 11	**Recommendation 11**
In patients with heart failure, both with preserved as well as mildly reduced ejection fraction, is the administration of intravenous (IV) iron effective in reducing hospitalizations for heart failure and cardiovascular and all-cause mortality?	In patients with heart failure with an ejection fraction < 50% and iron deficiency (defined as serum ferritin < 100 g/l or serum ferritin between 100 and 299 g/l and transferrin saturation < 20%), the administration of IV iron with ferric carboxymaltose or ferric derisomaltose reduces hospitalizations for heart failure, with no impact on cardiovascular or all-cause mortality. In patients with heart failure with preserved ejection fraction, the administration of intravenous iron has not proven to reduce hospitalizations for heart failure, cardiovascular mortality or all-cause mortality. • *Class IIa (100%)* • *Level of recommendation A (90%)*
Question 12	**Recommendation 12**
In patients with heart failure, both with preserved as well as mildly reduced ejection fraction, is cardiac rehabilitation in addition to the instated medical treatment effective in reducing hospitalizations for heart failure and cardiovascular and all-cause mortality?	In patients with heart failure with preserved and mildly reduced ejection fraction, cardiac rehabilitation in addition to pharmacological treatment reduces the risk of hospitalization for heart failure and reduces cardiovascular mortality. In addition, there are benefits in improved quality of life, functional capacity, and empowerment in disease self-management. • *Class IIa (90%)* • *Level of recommendation B (82%)*

American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines[9]. This involved conducting a quality assessment of the articles that made up the body of evidence for each question in the consensus.

For this activity, it was determined that only systematic reviews of the literature with meta-analyses and randomized clinical trials would undergo validity assessment.

Randomized clinical trials were evaluated for risk of bias using the RoB2 tool[10]. For systematic reviews and meta-analyses of clinical trials, the RoBis[11] tool was used to evaluate the quality of the evidence. The assessment was paired and discrepancies were resolved by consensus, in the presence of a third reviewer.

Annex D presents the references that constituted the body of evidence for each of the questions and the risk of bias of each of the studies evaluated.

Phase 6 – Individual review of the responses

Using the application, each participant reviewed the individual responses of the other experts to each of the questions and was able to modify his/her previous responses based on this review.

Annex E provides the experts' final individual responses.

Phase 7 – Analysis and synthesis of the information

The final responses of each of the experts were verified and synthesized through affinity matrixes. Responses that were not structured as a recommendation were eliminated. In turn, responses with related topics and organization were synthesized into individual recommendations. The results of this process were presented to the experts in Phase 8.

Annex F presents the options that were offered to the group of experts during the voting and clarification meetings.

Phase 8 – Asynchronous voting

The experts were asked to carry out asynchronous voting on the options synthesized for each question, through the web application.

Phase 9 – Synchronous meeting for clarification and voting

The experts were invited to two video conference meetings. In these meetings, the text of the recommendations, as well as their level and class, were clarified and voted on.

The rules of the consensus process entailed a maximum of three voting cycles. The options were accepted if they reached a minimum of 80% agreement. The options that did not achieve a more than 30% agreement were eliminated in the next voting cycle. If the minimum level of agreement was not reached after the third voting cycle, the option with the highest number of votes was accepted as the final option.

When agreement was not reached in the first round of voting or when there were two or more options with very similar votes, the process of argument clarification was opened. The experts could present the arguments for or against each option. Once the clarification process was completed, the next voting cycle was conducted.

For each of the questions, the baseline format of the recommendation was initially voted on.

Once the minimum level of agreement (80%) for the class was reached, the baseline recommendation was then reviewed and adjusted.

Annex G summarizes the iterative voting process and the versions of the recommendations that were discussed in the meetings.

Finally, with the final version of the adjusted recommendation, the class of the recommendation (for example, expected benefit, harm, considered risk) and level of evidence (for example, quality of the individual studies, including design and execution) was then voted on for each recommendation (Annex G). This voting was based on the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines format[9].

Results

As a result of the consensus, 12 updated recommendations were proposed for the management of patients with heart failure with preserved and mildly reduced ejection fraction, along with a diagnostic algorithm (Fig.1) to evaluate patients suspected to have this disease.

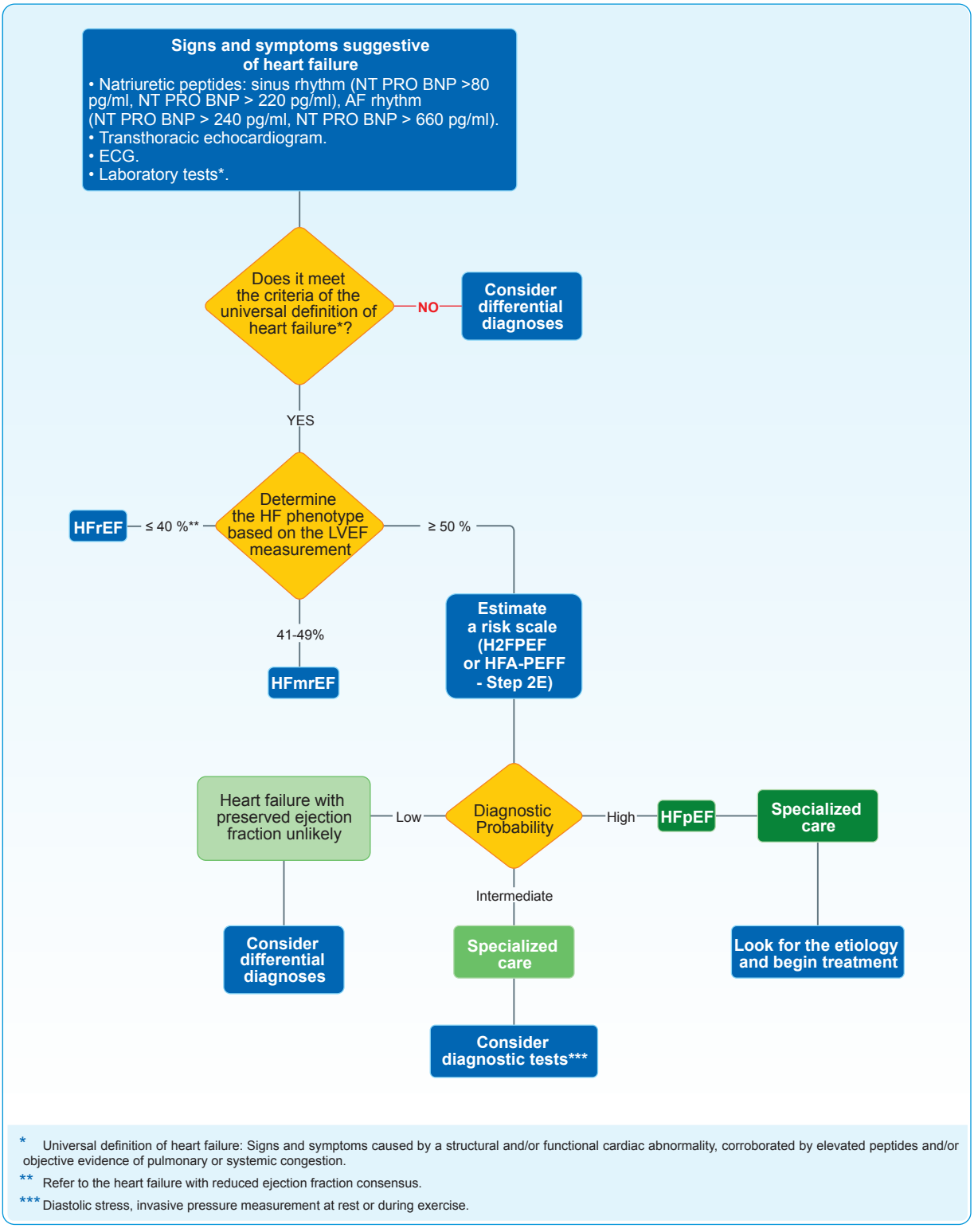
Good practice points

Diagnosis of heart failure with preserved ejection fraction

In general, patients with heart failure are a clinical challenge due to their complexity and the multiplicity of signs and symptoms that raise the index of suspicion.

Therefore, the universal definition of heart failure[71] was recently accepted, with three specific components: signs and symptoms, structural abnormalities and elevated natriuretic peptide levels.

Fgure 1. Diagnostic algorithm of heart failure with preserved ejection fraction[2,3,70].



* Universal definition of heart failure: Signs and symptoms caused by a structural and/or functional cardiac abnormality, corroborated by elevated peptides and/or objective evidence of pulmonary or systemic congestion.

** Refer to the heart failure with reduced ejection fraction consensus.

*** Diastolic stress, invasive pressure measurement at rest or during exercise.

- Initial tests recommended for patients with heart failure: chest x-ray, electrocardiogram, natriuretic peptide, echocardiogram, BUN, creatinine, potassium, sodium, chloride, complete blood count, thyroid function, glucose, glycosylated hemoglobin, iron kinetics and lipid profile.
- The main associated etiologies and comorbidities are: coronary disease, hypertension, diabetes mellitus, atrial fibrillation, obesity, obstructive sleep apnea-hypopnea syndrome, and chronic kidney disease

It is accepted that the presence of signs or symptoms, such as functional class deterioration (NYHA II, III, IV)[72], orthopnea, paroxysmal nocturnal dyspnea, bendopnea, lower extremity edema, palpitations, and asthenia or adynamia, associated with clearly identified structural or functional abnormalities (or both), along with objective evidence of pulmonary or systemic congestion with increased natriuretic peptides, confirm the diagnosis of heart failure.

However, in patients with heart failure that does not affect systolic function or without serious abnormalities (commonly known as HFpEF), some tools may need to be used to increase the index of diagnostic certainty and lead to early treatment.

Clinical scoring systems may be useful in the diagnostic process of patients with heart failure with preserved systolic function. The H2FPEF and HFA-PEFF[73,74] clinical scoring scales help determine the probability of heart failure. By considering the likelihood (with either of these scales), the diagnosis can be ruled out with a low pretest probability, additional specialized tests may be required with an intermediate probability (for example, a diastolic stress echocardiogram, invasive pressure measurement at rest or invasive pressure measurement during exercise), or the diagnosis can be confirmed with an elevated pretest probability, with no additional studies.

Scales for the diagnostic approach to heart failure with preserved ejection fraction

Interpretation (Fig. 2)

The interpretation of the HFA-PEFF and H2FPEF scores is essential for diagnosing HFpEF.

HFA-PEFF Score*

Designed to guide the diagnosis of HFpEF through a structured, stepwise assessment, with each step assigning points based on different tests and clinical findings.

- *Score of 0 to 1: low probability of HFpEF. If the score is very low, an HFpEF diagnosis is unlikely. Other causes of the patient's symptoms should be considered.

- *Score of 2 to 4: intermediate probability of HFpEF. In these cases, the diagnosis is inconclusive. Additional functional tests are recommended to confirm or rule out HFpEF.

- *Score of 5 or more: high probability of HFpEF, which is generally considered a definitive diagnosis. Based on this score, the patient can be diagnosed with HFpEF and the etiology and specific treatment can begin to be identified.

H2FPEF Score*

This scoring system uses six clinical and echocardiographic variables, each with a weighted score, to determine the probability of HFpEF. The score components are:

- *H (heavy - obesity): 2 points if the patient is obese.

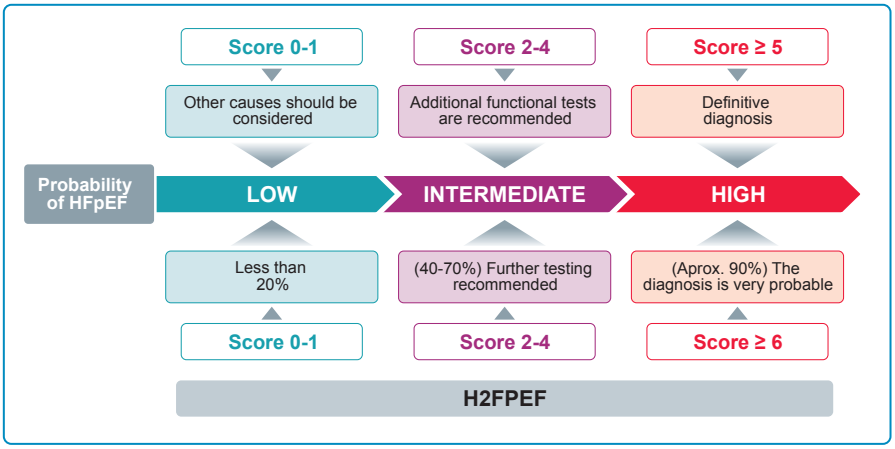
- *H (hypertension): 1 point if the patient has hypertension.

- *F (atrial fibrillation):1 point if the patient has atrial fibrillation.

- *P (pulmonary hypertension): 1 point if pulmonary hypertension is detected.

- *E (age): 1 point if the patient is more than 60 years old.

Fgure 2. Flowchart for interpreting HFA-PEFF and H2FPEF scores.



- *F (filling pressure): 1 point if there are elevated left ventricular filling pressures.

H2FPEF Score Interpretation

- *Score of 0-1: low probability of HFpEF (less than 20%).

- *Score of 2-4: intermediate probability of HFpEF (40-70%). More tests are recommended to confirm the diagnosis.

- *Score of 6 or more: high probability of HFpEF (approximately 90%). The diagnosis of HFpEF is very likely.

Conclusion

Both scores complement each other to guide the physician in diagnosing HFpEF. A high score in either system indicates a high probability of the disease, while low scores suggest that HFpEF is less likely and other causes of the patient's symptoms should be considered. In intermediate cases, more tests should be done to clarify the diagnosis.

It should be recalled that diseases similar to HFpEF may be encountered, but they are different from an etiological perspective and would not benefit from HFpEF treatment. These include some with a non-cardiovascular profile (kidney failure, nephrotic syndrome, liver failure, anemia, severe obesity, pulmonary disease, pulmonary hypertension, and chronic hypoventilation syndrome) and others with a cardiovascular profile (restrictive and hypertrophic cardiomyopathy, valve disease, and pericardial disease, among others).

Once the diagnosis is made, it is important to focus on the main treatment goals, which are[75]:

- Risk stratification and treatment of comorbidities (hypertension, diabetes mellitus, obesity, atrial fibrillation, coronary disease, chronic kidney disease, and obstructive sleep apnea-hypopnea syndrome, among others).
- Non-pharmacological treatment aimed at guided physical activity and weight loss.
- Use of disease-modifying therapy (with a favorable recommendation and level of evidence reported) and treatment of congestive symptoms with loop diuretics.

The main thing is to achieve improved quality of life and decreased hospitalizations with some neutral impact on cardiovascular and all-cause mortality[75].

Clearly, with a diagnosis of heart failure with a preserved or mildly reduced phenotype, the physician should focus on managing symptoms with the appropriate use of diuretics (using the ideal dose according to whether the patient has taken diuretics previously). It is recommended that treatment be started with SGLT2 inhibitors and, depending on the patient's condition, ACE inhibitors/ARBs/ARNIs, BBs and MRAs.

Follow up by a multidisciplinary group should be considered in the overall approach and additional control of cardiovascular risk factors.

Acknowledgements

The authors would like to thank the Heart Failure Chapter and all its members for their tireless and constant work which supports the group's scientific development and has a positive impact on the Colombian medical community and patients.

Funding

Asociación Sociedad Colombiana de Cardiología y Cirugía Cardiovascular.

Conflicts of Interest Statment

MJ.R-G has written papers and given educational lectures for Pfizer , AstraZeneca and Novartis. Grant paid to the institution by Pfizer. AA. G-P has provided consulting services, acted as an expert witness, and received compensation for drafting manuscripts and conducting educational presentations. This person has also received stocks or stock options as well as reimbursements for travel, lodging and attendance at meetings not directly related to the stated activities. These activities have been carried out for various entities and advisory committees in areas related to the topic discussed in the present document. A.R-T has provided consulting services for Astra Zeneca, Boehringer Ingelheim and Novartis, as well as compensation from Astra Zeneca, Boehringer Ingelheim, Merck and Novartis for conducting educational presentations. JM.C-C has received compensation from Boehringer Ingelheim, AstraZeneca, Servier and Abbott for giving lectures. C.G-M has received compensation from Novartis de Colombia, Pfizer Colombia, Boehringer Colombia, Merck Colombia, Farma de Colombia and AstraZeneca Centroamérica for giving lectures; has received compensation from Novartis Colombia for conducting educational presentations; and has received travel, lodging and/or attendance expenses for meetings from Pfizer Colombia, Boehringer Colombia, Abbott Colombia and AstraZeneca Colombia. JE.GM has received compensation from Astra Zeneca and Pfizer for giving lectures and educational presentations; as well as reimbursement of travel, lodging and/or meeting attendance expenses from Pfizer and Boehringer Ingelheim. G.G-R has received compensation from Pfizer, PTC Therapeutics, CSL Vifor, Vifor Farma, AstraZeneca,

and Boehringer Ingelheim for giving lectures that have no effect on the production of this paper. JD.L-P has been a member of the board as coordinator of the SCC familial heart disease group; has provided consulting services for Astra Zeneca, Boehringer Ingelheim, Novartis, Sanofi, Amgen, Bristol, Pfizer, Merck and MSN; has acted as an expert witness for Astra Zeneca, Boehringer Ingelheim, Merck, Menarini and PTC; received a grant in 2021 as an expert in familial heart disease; has received compensation from Astra Zeneca, Boehringer Ingelheim, Novartis, Sanofi, Amgen, Bristol, Pfizer, Merck, Menarini and PTC for giving lectures; and has received reimbursement for travel, lodging and attendance expenses for Amyloidosis PT consensus meetings. Also, this person's institution has received patents from Grand Pfizer for the cardiac amyloidosis registry and for studies sponsored by Pfizer and MSD. EM.M-C has provided consulting services, acted as an expert witness, and received compensation for giving lectures, preparing manuscripts and conducting educational presentations. Likewise, this person has received travel, lodging and attendance expenses for meetings not directly related to the stated activities. JA. R-P has received compensation from Novartis and Amgen for giving lectures. CI.S-G has provided consulting services for Bayer, Merck, and Novo Nordisk; and has received compensation from Bayer, Merck Novo Nordisk, AstraZeneca, Boehringer Ingelheim, Servier, Sanofi and Pfizer for giving lectures. A.T-N, JA.R-M, J.C-P, NL.R-B, N.R-V, S.N-H, LA.F-A, JE.V-E, EF.C-C, EA.G-L, LE.E, CA.A-B, A.S-V, A.M-C, NL.R-B, FD.M-B, and AF.B-S have no conflicts of interest to declare related to this article.

However, none of the previously mentioned activities has a direct effect on the study results or causes a conflict of interest with them.

Editorial coordination

Integralis HGS (Daniel Rodríguez, MD and María Stella Salazar, MD).

Ethical considerations

Human and animal protection. The authors declare that no experiments were conducted on humans or animals in the course of this study.

Data confidentiality. The authors declare that no patient data appear in this article. In addition, the authors have acknowledged and followed the SAGER guidelines according to the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence to generate text. The authors declare that they have not used any type of generative artificial intelligence in writing this manuscript nor in creating figures, graphs, tables or their respective captions or legends.

References

1. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017;14(10):591-602.
2. McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. Int J Clin Pharm. 2016;38(3):655-62.
3. Potter M, Gordon S, Hammer P. The Nominal Group Technique: a useful consensus methodology in physiotherapy research. New Zeal J Physiother. 2008;32(3):126-30.
4. Lloyd, S. Applying the nominal group technique to specify the domain of a construct. Qual Market Res Int J. 2011;14:105-21.
5. Jones J, Hunter D. Consensus methods for medical and health services research. BMJ. 1995;311(7001):376-80.
6. Dunham BR. Nominal group technique: A users' guide. Organ Behav; 2006.
7. Nasa P, Jain R, Juneja D. Delphi methodology in healthcare research: How to decide its appropriateness. World J Methodol. 2021;11(4):116-29.
8. Elsevier. Formulando preguntas para la práctica clínica (formato PICO). https://www.elsevier.com/es-es/connect/tipos-de-pregunta-para-la-practica-clinica-pico. [Cited: 3 Mar 2024].
9. Halperin JL, Levine GN, Al-Khatib SM, Birtcher KK, Bozkurt B, Brindis RG, et al. Further Evolution of the ACC/AHA Clinical Practice Guideline Recommendation Classification System: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016;67(13):1572-4.
10. [Minozzi S, Cinquini M, Gianola S, Gonzalez-Lorenzo M, Banzi R. The revised Cochrane risk of bias tool for randomized trials (RoB 2) showed low interrater reliability and challenges in its application. J Clin Epidemiol. 2020;126:37-44.
11. Whiting P, Savović J, Higgins JP, Caldwell DM, Reeves BC, Shea B, et al; ROBIS group. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016;69:225-34.
12. Qin J, Wang W, Wei P, Huang P, Lin R, Yue J. Effects of sacubitril-valsartan on heart failure patients with mid-range ejection fractions: A systematic review and meta-analysis. Front Pharmacol. 2022; 13:982372.
13. Leite M, Sampaio F, Saraiva FA, Diaz SO, Barros AS, Fontes-Carvalho R. The impact of heart failure therapy in patients with mildly reduced ejection fraction: a network meta-analysis. ESC Heart Fail. 2023;10(3):1822-34.
14. Zhang H, Huetteman AT, Reyes EA, Appelbaum JS. Effects of sacubitril-valsartan in patients with various types of heart failure: a meta-analysis. J Cardiovasc Pharmacol. 2023;81(6):434-44.
15. Nie D, Xiong B, Qian J, Rong S, Yao Y, Huang J. The effect of sacubitril-valsartan in heart failure patients with mid-range and preserved ejection fraction: a meta-analysis. Heart Lung Circ. 2021;30(5):683-91.
16. Xiang B, Zhang R, Wu X, Zhou X. Optimal pharmacologic treatment of heart failure with preserved and mildly reduced ejection fraction: a meta-analysis. JAMA Netw Open. 2022;5(9):e2231963.

17. Alzahrani T, Tiu J, Panjrath G, Solomon A. The effect of angiotensin-converting enzyme inhibitors on clinical outcomes in patients with ischemic cardiomyopathy and midrange ejection fraction: a post hoc subgroup analysis from the PEACE trial. Ther Adv Cardiovasc Dis. 2018;12(12):351-9.
18. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail. 2018;20(8):1230-9.
19. Yang L, Ye N, Bian W, Cheng H. Efficacy of medication therapy for patients with chronic kidney disease and heart failure with preserved ejection fraction: a systematic review and meta-analysis. Int Urol Nephrol. 2022;54(6):1435-44.
20. Lin Y, Cai Z, Yuan J, Liu H, Pang X, Chen Q. Effect of pharmacological treatment on outcomes of heart failure with preserved ejection fraction: an updated systematic review and network meta-analysis of randomized controlled trials. Cardiovasc Diabetol 2022;21(1):237.
21. Faisal S, Ahmad Ganaie Z, Batool S. The efficacy of various pharmacological agents on long-term outcomes in patients with heart failure with preserved ejection fraction: a meta-analysis of randomized control trials. Cureus. 2022;14(8):e28145.
22. Khan MS, Fonarow GC, Khan H, Greene SJ, Anker SD, Gheorghiade M, Butler J. Renin-angiotensin blockade in heart failure with preserved ejection fraction: a systematic review and meta-analysis. ESC Heart Fail. 2017;4(4):402-8.
23. Yu W, Zhang H, Shen W, Luo F, Yang S, Gan L, Zhao Y, Yang P, Wu Q. Efficacy and safety of sacubitril/valsartan on heart failure with preserved ejection fraction: A meta-analysis of randomized controlled trials. Front Cardiovasc Med. 2022;9:897423.
24. Lin Y, Wu M, Liao B, Pang X, Chen Q, Yuan J, Dong S. Comparison of pharmacological treatment effects on long-time outcomes in heart failure with preserved ejection fraction: a network meta-analysis of randomized controlled trials. Front Pharmacol. 2021;12:707777.
25. Zheng SL, Chan FT, Nabeebaccus AA, Shah AM, McDonagh T, Okonko DO, et al. Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Heart. 2018;104(5):407-15.
26. Basile C, Paolillo S, Gargiulo P, Marzano F, Asile G, Parlati ALM, et al. Sacubitril/valsartan reduces cardiac decompensation in heart failure with preserved ejection fraction: a meta-analysis. J Cardiovasc Med (Hagerstown). 2023;24(1):44-51.
27. Mentz RJ, Ward JH, Hernandez AF, Lepage S, Morrow DA, Sarwat S, et al; PARAGLIDE-HF Investigators. Angiotensin-neprilysin inhibition in patients with mildly reduced or preserved ejection fraction and worsening heart failure. J Am Coll Cardiol. 2023;82(1):1-12.
28. Zhang Q, Chen Y, Liu Q, Shan Q. Effects of renin-angiotensin-aldosterone system inhibitors on mortality, hospitalization, and diastolic function in patients with HFpEF. A meta-analysis of 13 randomized controlled trials. Herz. 2016;41(1):76-86.
29. Bonsu KO, Arunmanakul P, Chaiyakunapruk N. Pharmacological treatments for heart failure with preserved ejection fraction-a systematic review and indirect comparison. Heart Fail Rev. 2018;23(2):147-56.
30. Butt JH, Dewan P, Jhund PS, Anand IS, Atar D, Ge J, et al. Sacubitril/valsartan and frailty in patients with heart failure and preserved ejection fraction. J Am Coll Cardiol. 2022;80(12):1130-43.
31. McMurray JJV, Jackson AM, Lam CSP, Redfield MM, Anand IS, Ge J, et al. Effects of sacubitril-valsartan versus valsartan in women compared with men with heart failure and preserved ejection fraction: insights from PARAGON-HF. Circulation. 2020;141(5):338-51.
32. Suzuki K, Claggett B, Minamisawa M, Nochioka K, Mitchell GF, Anand IS, et al. Pulse pressure, prognosis, and influence of sacubitril/valsartan in heart failure with preserved ejection fraction. Hypertension. 2021;77(2):546-56.
33. Selvaraj S, Claggett BL, Böhm M, Anker SD, Vaduganathan M, Zannad F, et al. Systolic blood pressure in heart failure with preserved ejection fraction treated with sacubitril/valsartan. J Am Coll Cardiol. 2020;75(14):1644-56.
34. Martin N, Manoharan K, Davies C, Lumbers RT. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. Cochrane Database Syst Rev. 2021;5(5):CD012721.
35. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med. 2019;381(17):1609-20.
36. Ostrominski JW, Claggett BL, Packer M, Pfeffer MA, Lam CSP, Zile MR, et al. Duration of heart failure with preserved ejection fraction and outcomes with sacubitril/valsartan: insights from the PARAGON-HF Trial. J Card Fail. 2023;29(11):1494-503.
37. Vaduganathan M, Claggett BL, Desai AS, Anker SD, Perrone SV, Janssens S, et al. Prior heart failure hospitalization, clinical outcomes, and response to sacubitril/valsartan compared with valsartan in HFpEF. J Am Coll Cardiol. 2020;75(3):245-54.
38. Berbenetz NM, Mrkobrada M. Mineralocorticoid receptor antagonists for heart failure: systematic review and meta-analysis. BMC Cardiovasc Disord. 2016;16(1):246.
39. Japp D, Shah A, Fisken S, Denvir M, Shenkin S, Japp A. Mineralocorticoid receptor antagonists in elderly patients with heart failure: a systematic review and meta-analysis. Age Ageing. 2017;46(1):18-25.
40. Xiang Y, Shi W, Li Z, Yang Y, Wang SY, Xiang R, et al. Efficacy and safety of spironolactone in the heart failure with mid-range ejection fraction and heart failure with preserved ejection fraction: A meta-analysis of randomized clinical trials. Medicine (Baltimore). 2019;98(13):e14967.
41. Chen Y, Wang H, Lu Y, Huang X, Liao Y, Bin J. Effects of mineralocorticoid receptor antagonists in patients with preserved ejection fraction: a meta-analysis of randomized clinical trials. BMC Med. 2015;13:10.
42. Li S, Zhang X, Dong M, Gong S, Shang Z, Jia X, et al. Effects of spironolactone in heart failure with preserved ejection fraction: A meta-analysis of randomized controlled trials. Medicine (Baltimore). 2018;97(35):e11942.
43. Beldhuis IE, Myhre PL, Bristow M, Claggett B, Damman K, Fang JC, et al. Spironolactone in patients with heart failure, preserved ejection fraction, and worsening renal function. J Am Coll Cardiol. 2021;77(9):1211-21.
44. Merrill M, Sweitzer NK, Lindenfeld J, Kao DP. Sex differences in outcomes and responses to spironolactone in heart failure with preserved ejection fraction: a secondary analysis of TOPCAT trial. JACC Heart Fail. 2019;7(3):228-38.
45. Sperry BW, Hanna M, Shah SJ, Jaber WA, Spertus JA. Spironolactone in patients with an echocardiographic hfpef phenotype suggestive of cardiac amyloidosis: results from TOPCAT. JACC Heart Fail. 2021;9(11):795-802.
46. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, et al; TOPCAT Investigators. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J. 2016;37(5):455-62.

47. Sun J, Tai S, Guo Y, Tang L, Yang H, Li X, et al. Sex differences in characteristics and outcomes in elderly heart failure patients with preserved ejection fraction: a post-hoc analysis from TOPCAT. Front Cardiovasc Med. 2021;8:721850.
48. Tsujimoto T, Kajio H. Spironolactone use and improved outcomes in patients with heart failure with preserved ejection fraction with resistant hypertension. J Am Heart Assoc. 2020;9(23):e018827.
49. Cohen JB, Schrauben SJ, Zhao L, Basso MD, Cvijic ME, Li Z, et al. Clinical phenogroups in heart failure with preserved ejection fraction: detailed phenotypes, prognosis, and response to spironolactone. JACC Heart Fail. 2020;8(3):172-84.
50. Elkholey K, Papadimitriou L, Butler J, Thadani U, Stavrakis S. Effect of obesity on response to spironolactone in patients with heart failure with preserved ejection fraction. Am J Cardiol. 2021;146:36-47.
51. Lin Y, Zhong X, Liu M, Zhang S, Xiong Z, Huang Y, et al. Risk stratification and efficacy of spironolactone in patients with heart failure with preserved ejection fraction: secondary analysis of the TOPCAT randomized clinical trial. Cardiovasc Drugs Ther. 2022;36(2):323-31.
52. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, , et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2022;387(12):1089-98.
53. 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(16):1451-61. doi: 10.1056/NEJMoa2107038.
54. Zhao L, Guo W, Huang W, Wang L, Huang S. Benefit of sodium-glucose cotransporter-2 inhibitors on survival outcome is related to the type of heart failure: A meta-analysis. Diabetes Res Clin Pract. 2022;187:109871.
55. Adamson C, Kondo T, Jhund PS, de Boer RA, Cabrera Honorio JW, Claggett B, et al. Dapagliflozin for heart failure according to body mass index: the DELIVER trial. Eur Heart J. 2022;43(41):4406-17. doi: 10.1093/eurheartj/ehac481.
56. Butler J, Filippatos G, Siddiqi TJ, Ferreira JP, Brueckmann M, Bocchi E, et al. Effects of empagliflozin in women and men with heart failure and preserved ejection fraction. Circulation. 2022;146(14):1046-55. doi: 10.1161/CIRCULATIONAHA.122.059755.
57. De Marzo V, Savarese G, Porto I, Metra M, Ameri P. Efficacy of SGLT2-inhibitors across different definitions of heart failure with preserved ejection fraction. J Cardiovasc Med (Hagerstown). 2023;24(8):537-43. doi: 10.2459/JCM.0000000000001504.
58. Filippatos G, Butler J, Farmakis D, Zannad F, Ofstad AP, Ferreira JP, et al. Empagliflozin for heart failure with preserved left ventricular ejection fraction with and without diabetes. Circulation. 2022;146(9):676-86. doi: 10.1161/CIRCULATIONAHA.122.059785.
59. Böhm M, Butler J, Filippatos G, Ferreira JP, Pocock SJ, Abdin A, Mahfoud F, et al. Empagliflozin improves outcomes in patients with heart failure and preserved ejection fraction irrespective of age. J Am Coll Cardiol. 2022;80(1):1-18.
60. Savarese G, Uijl A, Lund LH, Anker SD, Asselbergs F, Fitchett D, et al. Empagliflozin in heart failure with predicted preserved versus reduced ejection fraction: data from the EMPA-REG OUTCOME trial. J Card Fail. 2021;27(8):888-95.
61. Wagdy K, Nagy S. EMPEROR-Preserved: SGLT2 inhibitors breakthrough in the management of heart failure with preserved ejection fraction. Glob Cardiol Sci Pract. 2021;2021(3):e202117. doi: 10.21542/gcsp.2021.17.
62. Ferreira JP, Butler J, Zannad F, Filippatos G, Schueler E, Steubl D, et al. Mineralocorticoid receptor antagonists and empagliflozin in patients with heart failure and preserved ejection fraction. J Am Coll Cardiol. 2022;79(12):1129-37. doi: 10.1016/j.jacc.2022.01.029.
63. Tsampasian V, Elghazaly H, Chattopadhyay R, Ali O, Corballis N, Chousou PA, et al. Sodium glucose co-transporter 2 inhibitors in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Eur J Prev Cardiol. 2022;29(6):e227-9. doi: 10.1093/eurjpc/zwab189.
64. Ji PJ, Zhang ZY, Yan Q, Cao HL, Zhao YJ, Yang B, Li J. The cardiovascular effects of SGLT2 inhibitors, RAS inhibitors, and ARN inhibitors in heart failure. ESC Heart Fail. 2023;10(2):1314-25. doi: 10.1002/ehf2.14298.
65. Alegría J, Rada G. Are beta-blockers effective in heart failure with preserved ejection fraction? Medwave. 2016;16(Suppl5):e6593. doi: 10.5867/medwave.2016.6593.
66. Bavishi C, Chatterjee S, Ather S, Patel D, Messerli FH. Beta-blockers in heart failure with preserved ejection fraction: a meta-analysis. Heart Fail Rev. 2015;20(2):193-201. https://doi.org/10.1007/s10741-014-9453-8
67. Jones J, Hunter D. Qualitative research: consensus methods for medical and health services research. BMJ. 1995;311:(7001):376-80. https://doi.org/10.1136/bmj.311.7001.376
68. Leśniak W. Definición universal y clasificación de la insuficiencia cardiaca (HFSA/HFA/JHFS 2021). Empendium Guías. 2022. https://empendium.com/manualmibe/noticias/310021,guias-hfsahfajhfs-2021-clasificaciones-seleccionadas-de-la-insuficiencia-cardiaca,1. [Cited 3 Mar 2024].
69. Gómez-Mesa E J, Saldarriaga C, Jurado AM, Mariño A, Rivera A, Herrera A, et al. Consenso colombiano de falla cardíaca avanzada: Capítulo de Falla Cardiaca, Trasplante Cardiaco e Hipertensión Pulmonar de la Sociedad Colombiana de Cardiología y Cirugía Cardiovascular. Rev Colomb Cardiol. 2019;26:3-24. https://doi.org/10.1016/j.rccar.2019.06.001
70. Rodríguez J. Nueva herramienta diagnóstica en IC con FEVI conservada: H2FPEF score. Sociedad Española de Cardiología. 2019. https://www.secardiologia.es/blog/10224-nueva-herramienta-diagnostica-en-ic-con-fevi-conservada-h2fpef-score. [Cited 10 Mar 2024].
71. Casado J, Pérez Silvestre J, Fernández JM, Chivite D, Lorenzo A, Soler L, Casado PP, Cubo P, García R, Alonso B. Insuficiencia cardiaca con fracción de eyección preservada [Internet]. Madrid: Sociedad Española de Medicina Interna (SEMI); [citado 15 de marzo de 2024]. Disponible en: https://www.fesemi.org/sites/default/files/documentos/publicaciones/cuadriptico_insuficiencia_cardiaca.pdf
72. Kittleson MM, Panjrath GS, Amancherla K, Davis LL, Deswal A, Dixon DL, et al. 2023 ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2023;81(18):1835-78. https://doi.org/10.1016/j.jacc.2023.03.393

Annexes

Annex A. Questions standardized in PICO format.

Question
1. In patients with heart failure with mildly reduced ejection fraction, is the administration of an angiotensin converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB) effective in reducing hospitalizations for and mortality from heart failure?
2. In patients with heart failure with preserved ejection fraction, is the administration of an angiotensin converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB) effective in reducing hospitalizations for and mortality from heart failure?
3. In patients with heart failure with mildly reduced ejection fraction, is the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) effective in reducing hospitalizations for and mortality from heart failure?
4. In patients with heart failure with preserved ejection fraction, is the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) effective in reducing hospitalizations for and mortality from heart failure?
5. In patients with heart failure with mildly reduced ejection fraction, is the administration of a mineralocorticoid receptor antagonist (MRA) effective in reducing hospitalizations for and mortality from heart failure?
6. In patients with heart failure with preserved ejection fraction, is the administration of a mineralocorticoid receptor antagonist (MRA) effective in reducing hospitalizations for and mortality from heart failure?
7. In patients with heart failure with mildly reduced ejection fraction, is the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor effective in reducing hospitalizations for and mortality from heart failure?
8. In patients with heart failure with preserved ejection fraction, is the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor effective in reducing hospitalizations for and mortality from heart failure?
9. In patients with heart failure with mildly reduced ejection fraction, is the administration of a beta blocker effective in reducing hospitalizations for and mortality from heart failure?
10. In patients with heart failure with preserved ejection fraction, is the administration of a beta blocker effective in reducing hospitalizations for and mortality from heart failure?
11. In patients with heart failure, both with preserved as well as mildly reduced ejection fraction, is the administration of IV iron effective in reducing hospitalizations for and mortality from heart failure?
12. In patients with heart failure, both with preserved as well as mildly reduced ejection fraction, is cardiac rehabilitation added to the instated medical treatment effective in reducing hospitalizations for and mortality from heart failure?

Annex B. Search strategies by question. Consensus on Heart Failure with Reduced Ejection Fraction.

Question
Questions 1 and 2 **1. In patients with heart failure with mildly reduced ejection fraction, is the administration of an angiotensin converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB) effective in reducing hospitalizations for and mortality from heart failure?** **2. In patients with heart failure with preserved ejection fraction, is the administration of an angiotensin converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB) effective in reducing hospitalizations for and mortality from heart failure?** ((“preserved”[Title/Abstract] OR “mildly-reduced”[Title/Abstract] OR “mid-range”[Title/Abstract]) AND (“Ejection fraction”[Title/Abstract] OR “Heart Failure”[MeSH Terms] OR “ventricular function, left”[MeSH Terms] OR “Stroke Volume”[MeSH Terms])) AND (“Angiotensin-Converting Enzyme Inhibitors/administration and dosage”[Mesh] OR “Angiotensin-Converting Enzyme Inhibitors/pharmacology”[Mesh] OR “Angiotensin-Converting Enzyme Inhibitors/therapeutic use”[Mesh] OR “Angiotensin-Converting Enzyme Inhibitors” [Pharmacological Action] OR “Lisinopril/administration and dosage”[Mesh] OR “Lisinopril/pharmacology”[Mesh] OR “Lisinopril/therapeutic use”[Mesh] OR “Cilazapril/administration and dosage”[Mesh] OR “Cilazapril/pharmacology”[Mesh] OR “Cilazapril/therapeutic use”[Mesh] OR “Enalapril/administration and dosage”[Mesh] OR “Enalapril/pharmacology”[Mesh] OR “Enalapril/therapeutic use”[-Mesh] OR “Angiotensin Receptor Antagonists/administration and dosage”[Mesh] OR “Angiotensin Receptor Antagonists/pharmacology”[Mesh] OR “Angiotensin Receptor Antagonists/therapeutic use”[Mesh] OR “Angiotensin Receptor Antagonists”[Pharmacological Action] OR “Angiotensin-Converting Enzyme Inhibitors”[Title/Abstract] OR “Angiotensin Receptor Antagonists”[Title/Abstract] OR “ACE-inhibitors”[Title/Abstract] OR “ARA-II”[Title/Abstract] OR “Captopril”[Title/Abstract] OR “Ramipril” [Title/Abstract] OR “Enalapril” [Title/Abstract] OR “Lisinopril”[Title/Abstract] OR “Losartan”[Title/Abstract] OR “Valsartan”[Title/Abstract] OR “Telmisartan”[Title/Abstract] OR “ACEi”[Title/Abstract] OR “ARB”[Title/Abstract] OR “ACEi/ARB”[Title/Abstract] OR “ACEi/ARB”[All Fields] OR “Angiotensin Receptor–Neprilysin Inhibitor” [All Fields] OR “sacubitril and valsartan sodium hydrate drug combination” [Supplementary Concept] OR “LCZ696”[Title/Abstract] OR “sacubitril valsartan sodium hydrate” [All Fields] OR “ARNI”[Title/Abstract] OR “Sacubitril/Valsartan”[Title/Abstract] OR “Sacubitril-Valsartan”[All Fields] OR “neprilysin inhibition”[Title/Abstract] OR “Sacubitril”[Title/Abstract]) AND (“Hospitalization”[MeSH Terms] OR “Efficacy”[Title/Abstract] OR “heart-failure-hospitalizations”[Title/Abstract] OR “hospitalizations”

[Title/Abstract] OR "Mortality"[Title/Abstract] OR "outcome"[Title/Abstract] OR "cardiovascular death"[Title/Abstract] OR "Treatment Outcome"[MeSH Major Topic] OR "Patient Readmission"[MeSH Terms] OR "Vital Statistics"[MeSH Terms]) AND ("Randomized Controlled Trial" [Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "controlled clinical trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "random allocation"[MeSH Terms] OR "double blind method"[MeSH Terms] OR "single blind method"[MeSH Terms] OR "mask*"[Text Word] OR "blind*"[Text Word] OR "latin square"[Text Word] OR "placebos"[MeSH Terms] OR "placebo*"[Text Word] OR "random*"[Text Word] OR "cross over studies"[MeSH Terms] OR "meta analysis"[Publication Type] OR "meta analysis"[Title] OR "metaanalysis"[Title] OR "Meta-Analysis as Topic"[MeSH Terms] OR "Systematic Reviews as Topic"[MeSH Terms] OR "Systematic Review"[Filter] OR "Systematic Review"[Title:~3] OR "Systematic Review"[Title] OR "Systematic Review"[Publication Type] OR "cochrane database syst rev"[Journal])

Questions 3 and 4

3. In patients with heart failure with mildly reduced ejection fraction, is the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) effective in reducing hospitalizations for and mortality from heart failure?

4. In patients with heart failure with preserved ejection fraction, is the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) effective in reducing hospitalizations for and mortality from heart failure?

(("preserved"[Title/Abstract] OR "mildly-reduced"[Title/Abstract] OR "mid-range"[Title/Abstract]) AND ("Ejection fraction"[Title/Abstract] OR "Heart Failure"[MeSH Terms] OR "heart failure/drug therapy"[MeSH Terms] OR "ventricular function, left"[MeSH Terms] OR "Stroke Volume"[MeSH Terms])) AND ("Angiotensin Receptor–Neprilysin Inhibitor" [All Fields] OR "sacubitril and valsartan sodium hydrate drug combination" [Supplementary Concept] OR "sacubitril and valsartan sodium hydrate drug combination" [All Fields] OR "LCZ696" [All Fields] OR "sacubitril valsartan sodium hydrate" [All Fields] OR "ARNI" [All Fields] OR "Sacubitril/Valsartan"[Title/Abstract] OR "Sacubitril-Valsartan"[All Fields] OR "neprilysin inhibition"[Title/Abstract] OR "Sacubitril"[Title/Abstract]) AND ("Hospitalization"[MeSH Terms] OR "Efficacy"[Title/Abstract] OR "heart-failure-hospitalizations"[Title/Abstract] OR "hospitalizations"[Title/Abstract] OR "Mortality"[Title/Abstract] OR "outcome"[Title/Abstract] OR "cardiovascular death"[Title/Abstract] OR "Treatment Outcome"[MeSH Major Topic] OR "Patient Readmission"[MeSH Terms] OR "Vital Statistics"[MeSH Terms]) AND ("Randomized controlled trials" [Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "random allocation"[MeSH Terms] OR "double blind method"[MeSH Terms] OR "single blind method"[MeSH Terms] OR "clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[Text Word] OR "mask*"[Text Word] OR "blind*"[Text Word] OR "latin square"[Text Word] OR "placebos"[MeSH Terms] OR "placebo*"[Text Word] OR "random*"[Text Word] OR "Comparative Study" [Publication Type] OR "Evaluation Study" [Publication Type] OR "follow up studies"[MeSH Terms] OR "prospective studies"[MeSH Terms] OR "cross over studies"[MeSH Terms] OR "control*"[Text Word] OR "prospectiv*"[Text Word] OR "volunteer*"[Text Word] OR "meta analysis"[Publication Type] OR "meta analysis"[Title] OR "metaanalysis"[Title] OR "Meta-Analysis as Topic"[MeSH Terms] OR "Systematic Reviews as Topic"[MeSH Terms] OR "Systematic Review"[Filter] OR "Systematic Review"[Title:~3] OR "Systematic Review"[Title] OR "Systematic Review"[Publication Type] OR "cochrane database syst rev"[Journal]) "sacubitril and valsartan sodium hydrate drug combination"[All Fields] "sacubitril/valsartan"[All Fields]

Questions 5 and 6

5. In patients with heart failure with mildly reduced ejection fraction, is the administration of a mineralocorticoid receptor antagonist (MRA) effective in reducing hospitalizations for and mortality from heart failure?

6. In patients with heart failure with preserved ejection fraction, is the administration of a mineralocorticoid receptor antagonist (MRA) effective in reducing hospitalizations for and mortality from heart failure?

(("preserved"[Title/Abstract] OR "mildly-reduced"[Title/Abstract] OR "mid-range"[Title/Abstract]) AND ("Ejection fraction"[Title/Abstract] OR "Heart Failure"[MeSH Terms] OR "heart failure/drug therapy"[MeSH Terms] OR "ventricular function, left"[MeSH Terms] OR "Stroke Volume"[MeSH Terms])) AND ("Mineralocorticoid Receptor Antagonists/administration and dosage"[Mesh] OR "Mineralocorticoid Receptor Antagonists/therapeutic use"[Mesh] OR "Mineralocorticoid Receptor Antagonists" [Pharmacological Action] OR "Spironolactone/administration and dosage"[Mesh] OR "Spironolactone/pharmacology"[Mesh] OR "Spironolactone/therapeutic use"[Mesh] OR "Spironolactone"[Title/Abstract] OR "Eplerenone/administration and dosage"[Mesh] OR "Eplerenone/pharmacology"[Mesh] OR "Eplerenone/therapeutic use"[Mesh] OR "Eplerenone"[Title/Abstract] OR "drospirenone" [Supplementary Concept] OR "drospirenone" [Title/Abstract] OR "MRA"[Title/Abstract] OR "MRAs"[Title/Abstract]) AND ("Hospitalization"[MeSH Terms] OR "Efficacy"[Title/Abstract] OR "heart-failure-hospitalizations"[Title/Abstract] OR "hospitalizations"[Title/Abstract] OR "Mortality"[Title/Abstract] OR "outcome"[Title/Abstract] OR "cardiovascular death"[Title/Abstract] OR "Treatment Outcome"[MeSH Major Topic] OR "Patient Readmission"[MeSH Terms] OR "Vital Statistics"[MeSH Terms]) AND ("Hospitalization"[MeSH Terms] OR "Efficacy"[Title/Abstract] OR "heart-failure-hospitalizations"[Title/Abstract] OR "hospitalizations"[Title/Abstract] OR "Mortality"[Title/Abstract] OR "outcome"[Title/Abstract] OR "cardiovascular death"[Title/Abstract] OR "Treatment Outcome"[MeSH Major Topic] OR "Patient Readmission"[MeSH Terms] OR "Vital Statistics"[MeSH Terms]) AND ("Randomized Controlled Trial" [Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "controlled clinical trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "random allocation"[MeSH Terms] OR "double blind method"[MeSH Terms] OR "single blind method"[MeSH Terms] OR "mask*"[Text Word] OR "blind*"[Text Word] OR "latin square"[Text Word] OR "placebos"[MeSH Terms] OR "placebo*"[Text Word] OR "random*"[Text Word] OR "cross over studies"[MeSH Terms] OR "meta analysis"[Publication Type] OR "meta analysis"[Title] OR "metaanalysis"[Title] OR "Meta-Analysis as Topic"[MeSH Terms] OR "Systematic Reviews as Topic"[MeSH Terms] OR "Systematic Review"[Filter] OR "Systematic Review"[Title:~3] OR "Systematic Review"[Title] OR "Systematic Review"[Publication Type] OR "cochrane database syst rev"[Journal])

Question 7

7. In patients with heart failure with mildly reduced ejection fraction, is the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor effective in reducing hospitalizations for and mortality from heart failure?

(("preserved"[Title/Abstract] OR "mildly-reduced"[Title/Abstract] OR "mid-range"[Title/Abstract]) AND ("Ejection fraction"[Title/Abstract] OR "Heart Failure"[MeSH Terms] OR "heart failure/drug therapy"[MeSH Terms] OR "ventricular function, left"[MeSH Terms] OR "Stroke Volume"[MeSH Terms])) AND ("benzhydryl compounds/pharmacology"[MeSH Terms:noexp] OR "benzhydryl compounds/therapeutic use"[MeSH Terms:noexp] OR "glucosides/therapeutic use"[MeSH Terms] OR "sodium glucose transporter 2 inhibitors"[MeSH Terms] OR "sodium-glucose- cotransporter-2-inhibitors"[Title/Abstract] OR "sodium glucose transporter 2 inhibitors/therapeutic use"[MeSH Terms] OR "sodium glucose transporter 2/therapeutic use"[MeSH Terms] OR "Dapagliflozin"[Title/Abstract] OR

"Empagliflozin"[Title/Abstract] OR "ertugliflozin"[Title/Abstract]OR "sotagliflozin"[Title/Abstract]) AND ("Randomized Controlled Trial" [Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "controlled clinical trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "random allocation"[MeSH Terms] OR "double blind method"[MeSH Terms] OR "single blind method"[MeSH Terms] OR "mask*"[Text Word] OR "blind*"[Text Word] OR "latin square"[Text Word] OR "placebos"[MeSH Terms] OR "placebo*"[Text Word] OR "random*"[Text Word] OR "cross over studies"[MeSH Terms] OR "meta analysis"[Publication Type] OR "meta analysis"[Title] OR "metaanalysis"[Title] OR "Meta-Analysis as Topic"[MeSH Terms] OR "Systematic Reviews as Topic"[MeSH Terms] OR "Systematic Review"[Filter] OR "Systematic Review"[Title:~3] OR "Systematic Review"[Title] OR "Systematic Review"[Publication Type] OR "cochrane database syst rev"[Journal])

Question 8

8. In patients with heart failure with preserved ejection fraction, is the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor effective in reducing hospitalizations for and mortality from heart failure?

(("preserved"[Title/Abstract] OR "mildly-reduced"[Title/Abstract] OR "mid-range"[Title/Abstract]) AND ("Ejection fraction"[Title/Abstract] OR "Heart Failure"[MeSH Terms] OR "heart failure/drug therapy"[MeSH Terms] OR "ventricular function, left"[MeSH Terms] OR "Stroke Volume"[MeSH Terms])) AND ("benzhydryl compounds/pharmacology"[MeSH Terms:noexp] OR "benzhydryl compounds/therapeutic use"[MeSH Terms:noexp] OR "glucosides/therapeutic use"[MeSH Terms] OR "sodium glucose transporter 2 inhibitors"[MeSH Terms] OR "sodium-glucose- cotransporter-2-inhibitors"[Title/Abstract] OR "sodium glucose transporter 2 inhibitors/therapeutic use"[MeSH Terms] OR "sodium glucose transporter 2/therapeutic use"[MeSH Terms] OR "Dapagliflozin"[Title/Abstract] OR "Empagliflozin"[Title/Abstract] OR "ertugliflozin"[Title/Abstract]OR "sotagliflozin"[Title/Abstract]) AND ("Randomized Controlled Trial" [Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "controlled clinical trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "random allocation"[MeSH Terms] OR "double blind method"[MeSH Terms] OR "single blind method"[MeSH Terms] OR "mask*"[Text Word] OR "blind*"[Text Word] OR "latin square"[Text Word] OR "placebos"[MeSH Terms] OR "placebo*"[Text Word] OR "random*"[Text Word] OR "cross over studies"[MeSH Terms] OR "meta analysis"[Publication Type] OR "meta analysis"[Title] OR "metaanalysis"[Title] OR "Meta-Analysis as Topic"[MeSH Terms] OR "Systematic Reviews as Topic"[MeSH Terms] OR "Systematic Review"[Filter] OR "Systematic Review"[Title:~3] OR "Systematic Review"[Title] OR "Systematic Review"[Publication Type] OR "cochrane database syst rev"[Journal])

Question 9

9. In patients with heart failure with mildly reduced ejection fraction, is the administration of a beta blocker effective in reducing hospitalizations for and mortality from heart failure?

(("preserved"[Title/Abstract] OR "mildly-reduced"[Title/Abstract] OR "mid-range"[Title/Abstract]) AND ("Ejection fraction"[Title/Abstract] OR "Heart Failure"[MeSH Terms] OR "heart failure/drug therapy"[MeSH Terms] OR "ventricular function, left"[MeSH Terms] OR "Stroke Volume"[MeSH Terms])) AND ("beta-blocker"[Title/Abstract] OR "Adrenergic beta-Antagonists/pharmacology"[Mesh] OR "Adrenergic beta-Antagonists/therapeutic use"[Mesh] OR "Carvedilol"[Mesh] OR "Carbazoles/therapeutic use"[Mesh] OR "Nebivolol"[Mesh] OR "Propanolamines"[Mesh]) AND ("Hospitalization"[MeSH Terms] OR "Efficacy"[Title/Abstract] OR "heart-failure-hospitalizations"[Title/Abstract] OR "hospitalizations"[Title/Abstract] OR "Mortality"[Title/Abstract] OR "outcome"[Title/Abstract] OR "cardiovascular death"[Title/Abstract] OR "Treatment Outcome"[MeSH Major Topic] OR "Patient Readmission"[MeSH Terms] OR "Vital Statistics"[MeSH Terms]) AND ("Randomized Controlled Trial" [Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "controlled clinical trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "random allocation"[MeSH Terms] OR "double blind method"[MeSH Terms] OR "single blind method"[MeSH Terms] OR "mask*"[Text Word] OR "blind*"[Text Word] OR "latin square"[Text Word] OR "placebos"[MeSH Terms] OR "placebo*"[Text Word] OR "random*"[Text Word] OR "prospective studies"[MeSH Terms] OR "propensity-score-adjusted-cohort"[Title/Abstract] OR "cross over studies"[MeSH Terms] OR "meta analysis"[Publication Type] OR "meta analysis"[Title] OR "metaanalysis"[Title] OR "Meta-Analysis as Topic"[MeSH Terms] OR "Systematic Reviews as Topic"[MeSH Terms] OR "Systematic Review"[Filter] OR "Systematic Review"[Title:~3] OR "Systematic Review"[Title] OR "Systematic Review"[Publication Type] OR "cochrane database syst rev"[Journal])

Question 10

10. In patients with heart failure with preserved ejection fraction, is the administration of a beta blocker effective in reducing hospitalizations for and mortality from heart failure?

(("preserved"[Title/Abstract] OR "mildly-reduced"[Title/Abstract] OR "mid-range"[Title/Abstract]) AND ("Ejection fraction"[Title/Abstract] OR "Heart Failure"[MeSH Terms] OR "heart failure/drug therapy"[MeSH Terms] OR "ventricular function, left"[MeSH Terms] OR "Stroke Volume"[MeSH Terms])) AND ("beta-blocker"[Title/Abstract] OR "Adrenergic beta-Antagonists/pharmacology"[Mesh] OR "Adrenergic beta-Antagonists/therapeutic use"[Mesh] OR "Carvedilol"[Mesh] OR "Carbazoles/therapeutic use"[Mesh] OR "Nebivolol"[Mesh] OR "Propanolamines"[Mesh]) AND ("Hospitalization"[MeSH Terms] OR "Efficacy"[Title/Abstract] OR "heart-failure-hospitalizations"[Title/Abstract] OR "hospitalizations"[Title/Abstract] OR "Mortality"[Title/Abstract] OR "outcome"[Title/Abstract] OR "cardiovascular death"[Title/Abstract] OR "Treatment Outcome"[MeSH Major Topic] OR "Patient Readmission"[MeSH Terms] OR "Vital Statistics"[MeSH Terms]) AND ("Randomized Controlled Trial" [Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "controlled clinical trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "random allocation"[MeSH Terms] OR "double blind method"[MeSH Terms] OR "single blind method"[MeSH Terms] OR "mask*"[Text Word] OR "blind*"[Text Word] OR "latin square"[Text Word] OR "placebos"[MeSH Terms] OR "placebo*"[Text Word] OR "random*"[Text Word] OR "prospective studies"[MeSH Terms] OR "propensity-score-adjusted-cohort"[Title/Abstract] OR "cross over studies"[MeSH Terms] OR "meta analysis"[Publication Type] OR "meta analysis"[Title] OR "metaanalysis"[Title] OR "Meta-Analysis as Topic"[MeSH Terms] OR "Systematic Reviews as Topic"[MeSH Terms] OR "Systematic Review"[Filter] OR "Systematic Review"[Title:~3] OR "Systematic Review"[Title] OR "Systematic Review"[Publication Type] OR "cochrane database syst rev"[Journal])

Question 11

11. In patients with heart failure, both with preserved as well as mildly reduced ejection fraction, is the administration of IV iron effective in reducing hospitalizations for and mortality from heart failure?

(("preserved"[Title/Abstract] OR "mildly-reduced"[Title/Abstract] OR "mid-range"[Title/Abstract]) AND ("Ejection fraction"[Title/Abstract] OR "Heart Failure"[MeSH Terms] OR "heart failure/drug therapy"[MeSH Terms] OR "ventricular function, left"[MeSH Terms] OR "Stroke Volume"[MeSH Terms])) AND ("Infusions, Intravenous"[Mesh] OR "Iron infusion"[All Fields] OR "Ferric Compounds"[Mesh]

OR “Maltose/therapeutic use”[Mesh] OR “ferric derisomaltose”[All Fields] OR “ferric carboxymaltose”[All Fields] OR “Iron sucrose”[All Fields] OR “ferric gluconate” [All Fields]) AND (“Randomized Controlled Trial” [Publication Type] OR “Randomized Controlled Trials as Topic”[Mesh] OR “controlled clinical trial”[Publication Type] OR “randomized controlled trials as topic”[MeSH Terms] OR “random allocation”[MeSH Terms] OR “double blind method”[MeSH Terms] OR “single blind method”[MeSH Terms] OR “mask*”[Text Word] OR “blind*”[Text Word] OR “latin square”[Text Word] OR “placebos”[MeSH Terms] OR “placebo*”[Text Word] OR “random*”[Text Word] OR “cross over studies”[MeSH Terms] OR “meta analysis”[Publication Type] OR “meta analysis”[Title] OR “metaanalysis”[Title] OR “Meta-Analysis as Topic”[MeSH Terms] OR “Systematic Reviews as Topic”[MeSH Terms] OR “Systematic Review”[Filter] OR “Systematic Review”[Title:~3] OR “Systematic Review”[Title] OR “Systematic Review”[Publication Type] OR “cochrane database syst rev”[Journal])

Question 12

12. In patients with heart failure, both with preserved as well as mildly reduced ejection fraction, is cardiac rehabilitation, compared to usual care, effective in reducing hospitalizations for heart failure and mortality?

((“preserved”[Title/Abstract] OR “mildly-reduced”[Title/Abstract] OR “mid-range”[Title/Abstract]) AND (“Ejection fraction”[Title/Abstract] OR “Heart Failure”[MeSH Terms] OR “heart failure/drug therapy”[MeSH Terms] OR “ventricular function, left”[MeSH Terms] OR “Stroke Volume”[MeSH Terms])) AND (“Cardiac Rehabilitation”[Mesh] OR “Exercise Therapy”[Mesh] OR “Exercise training”[Title/Abstract] OR “cardiorespiratory fitness”[Title/Abstract] OR “endurance training”[Title/Abstract] OR “outpatient cardiac rehabilitation”[Title/Abstract]) AND (“Hospitalization”[MeSH Terms] OR “Efficacy”[Title/Abstract] OR “heart-failure-hospitalizations”[Title/Abstract] OR “hospitalizations”[Title/Abstract] OR “Mortality”[Title/Abstract] OR “outcome”[Title/Abstract] OR “cardiovascular death”[Title/Abstract] OR “Treatment Outcome”[MeSH Major Topic] OR “Patient Readmission”[MeSH Terms] OR “Vital Statistics”[MeSH Terms] OR “Prognosis”[Mesh]) AND (“Randomized Controlled Trial” [Publication Type] OR “Randomized Controlled Trials as Topic”[Mesh] OR “controlled clinical trial”[Publication Type] OR “randomized controlled trials as topic”[MeSH Terms] OR “random allocation”[MeSH Terms] OR “double blind method”[MeSH Terms] OR “single blind method”[MeSH Terms] OR “mask*”[Text Word] OR “blind*”[Text Word] OR “latin square”[Text Word] OR “placebos”[MeSH Terms] OR “placebo*”[Text Word] OR “random*”[Text Word] OR “cross over studies”[MeSH Terms] OR “meta analysis”[Publication Type] OR “meta analysis”[Title] OR “metaanalysis”[Title] OR “Meta-Analysis as Topic”[MeSH Terms] OR “Systematic Reviews as Topic”[MeSH Terms] OR “Systematic Review”[Filter] OR “Systematic Review”[Title:~3] OR “Systematic Review”[Title] OR “Systematic Review”[Publication Type] OR “cochrane database syst rev”[Journal] OR “Observational Study” [Publication Type] OR “post-hoc-analysis”[Title/Abstract])

Annex C. Individual responses to each of the questions generated in Phase 4.

Question	Phase IV Responses
1	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) is effective in reducing hospitalizations for heart failure, not mortality.
1	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB) is effective in reducing cardiovascular deaths and hospitalizations for heart failure, with greater benefit in patients with VEFs closer to the lowest value in this range.
1	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB) is NOT effective in reducing hospitalizations for and mortality from heart failure.
1	In patients with heart failure with mildly reduced ejection fraction, the use of an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) can be considered in order to reduce hospitalizations for and death from heart failure.
1	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor, or angiotensin receptor blocker (ARB) in the event of ACE inhibitor intolerance, is recommended, to reduce hospitalizations for heart failure. In patients with ischemic heart failure with mildly reduced ejection fraction, the use of an angiotensin converting enzyme (ACE) inhibitor could reduce cardiovascular mortality.
1	Agree
1	In patients with heart failure with mildly reduced ejection fraction, the use of ACE inhibitors and ARBs can be considered effective for decreasing the number of hospitalizations for heart failure, with no proven categorical benefit in decreased mortality to date.
1	The use of an ACE inhibitor or ARB is recommended in patients with heart failure with mildly reduced function to reduce hospitalizations for and mortality from heart failure.
1	In these patients, the use of an angiotensin converting enzyme inhibitor / angiotensin receptor blocker is effective in reducing hospitalizations by up to 28%, with better results if used with other drugs like SGLT2 inhibitors and beta blockers.
1	Yes
1	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin receptor blocker (ARB) or angiotensin converting enzyme (ACE) inhibitor may be considered when an angiotensin receptor/neprilysin inhibitor (ARNI) is contraindicated due to intolerance or inaccessibility, in order to reduce hospitalizations for heart failure.

1	In patients with heart failure with mildly reduced ejection fraction, the administration of an ACE inhibitor/ARB is effective in reducing hospitalizations for HF, but not in cardiovascular mortality and all-cause mortality.
1	In patients with heart failure with mildly reduced ejection fraction, the studies do not have the power to show clear effectiveness (ACE inhibitor, ARB) in reducing hospitalizations for and mortality from heart failure. Therefore, the recommendation continues to be IIb for this scenario, where usefulness efficacy is less established than evidence opinion.
1	1. For patients with HFmrEF, an ACE inhibitor may be considered in order to reduce the risk of hospitalization for HF and mortality. Class IIB-C. 2. For patients with HFmrEF, an ARB may be considered in order to reduce the risk of hospitalization for HF and mortality. Class IIB-C.
2	1. ACE inhibitors and ARBs have no reduction in hospitalizations for and mortality from HF in this group. 2. Depending on comorbidities like HTN, AF, they can be used post-AMI. 3. Screening and treatment for cardiovascular and other etiologies and comorbidities are recommended for patients with HFpEF. Class IC
2	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB) is NOT effective in reducing hospitalizations for and mortality from heart failure.
2	In patients with heart failure with preserved ejection fraction, the administration of an ACE inhibitor is effective in reducing hospitalizations. The ARBs showed no benefit in reducing hospitalization in meta-analyses.
2	In patients with HF with preserved ejection fraction, angiotensin converting enzyme inhibitors and angiotensin receptor blockers are effective in significantly reducing hospitalizations for HF; but not for significantly reducing mortality from HF.
2	In patients with heart failure with preserved ejection fraction, administration of an angiotensin converting enzyme (ACE) inhibitor can be considered in order to reduce hospitalizations for heart failure.
2	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin receptor blocker (ARB) or angiotensin converting enzyme (ACE) inhibitor can be considered when an angiotensin receptor/neprilysin inhibitor (ARNI) is contraindicated due to intolerance or inaccessibility, in order to reduce hospitalizations for heart failure.
2	In patients with heart failure with preserved ejection fraction, the administration of ACE inhibitors and ARBs can be considered effective in reducing hospitalizations for heart failure.
2	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin receptor blocker (ARB) is effective in reducing hospitalizations for heart failure, mainly in those with ejection fractions close to 50%.
2	The use of an ACE inhibitor or ARB is suggested in patients with heart failure with preserved ejection fraction, to reduce hospitalizations.
2	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB) is effective in reducing hospitalizations for heart failure, with greater benefit in patients with LVEFs closer to the lowest value in this range.
2	In patients with heart failure with preserved ejection fraction, the studies do not have the power to show clear effectiveness (ACE inhibitors, ARBs) in reducing hospitalizations for and mortality from heart failure. Therefore, the recommendation continues to be IIb for this scenario, where usefulness efficacy is less established than evidence opinion.
2	Agree
2	Yes
2	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB) can be considered for reducing hospitalizations for and mortality from heart failure.
3	In patients with HF with mildly reduced ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is effective in significantly reducing hospitalizations for HF; but not significantly reducing mortality from HF.
3	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is effective in reducing hospitalizations for heart failure, not in mortality.
3	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is effective in reducing hospitalizations for heart failure.
3	In patients with heart failure with mildly reduced ejection fraction, the administration of an ARNI can be considered effective in reducing hospitalizations for heart failure. It cannot be concluded that the current evidence supports its use for decreasing mortality.
3	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is NOT effective in reducing hospitalizations for and mortality from heart failure.
3	Yes

3	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is effective in reducing hospitalizations for worsening heart failure.
3	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is recommended, to reduce hospitalizations for heart failure.
3	In patients with heart failure with mildly reduced ejection fraction, the use of an angiotensin receptor/neprilysin inhibitor (ARNI) can be considered for reducing hospitalizations for and mortality from heart failure.
3	The use of an angiotensin receptor/neprilysin inhibitor (ARNI) can be considered in patients with heart failure with mildly reduced ejection fraction, to reduce the risk of hospitalization for heart failure and cardiovascular mortality.
3	In patients with heart failure with mildly reduced function, the administration of an ARNI is recommended, to reduce hospitalizations for heart failure.
3	1. For patients with HFmrEF, sacubitril-valsartan can be considered, in order to reduce the risk of hospitalization for HF and death. Class IIB-C 2. Evidence based on Paragon HF and Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure.
3	Agree
3	In patients with heart failure with mildly reduced ejection fraction, the studies do not have the power to show a clear effectiveness of an angiotensin receptor/neprilysin inhibitor (ARNI) in reducing hospitalizations for and mortality from heart failure. Therefore, the recommendation continues to be IIb for this scenario, where usefulness efficacy is less established than evidence opinion.
4	In patients with heart failure with preserved ejection fraction, the administration of an ARNI can be considered effective for reducing hospitalizations for heart failure but has not been proven to have an impact on heart failure mortality.
4	In selected patients with HFpEF, ARNIs can be considered to reduce hospitalizations, especially in patients with LVEFs at the lower end of this spectrum. Class IIB-BR
4	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is recommended, to reduce hospitalizations for heart failure.
4	Agree
4	In patients with heart failure with preserved ejection fraction, the administration of an ARNI is suggested to reduce hospitalizations in women.
4	In patients with HF with preserved ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is not effective in significantly reducing hospitalizations for HF, nor for significantly reducing mortality from HF.
4	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is effective in reducing hospitalizations, mainly in patients with ejection fractions close to 50%. They have no effect on mortality.
4	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is effective in reducing hospitalizations for heart failure, with greater benefit in patients with LVEFs closer to the lowest value in this range.
4	Hospitalizations YES Mortality NO
4	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is NOT effective in reducing hospitalizations for and mortality from heart failure.
4	In patients with heart failure with preserved ejection fraction, the studies do not have the power to show clear effectiveness of an angiotensin receptor/neprilysin inhibitor (ARNI) in reducing hospitalizations for and mortality from heart failure. Therefore, the recommendation continues to be IIb for this scenario, where usefulness efficacy is less established than evidence opinion.
4	In patients with heart failure with preserved ejection fraction, the use of an angiotensin receptor/neprilysin inhibitor (ARNI) can be considered for reducing hospitalizations for and mortality from heart failure.
4	The use of an angiotensin receptor/neprilysin inhibitor (ARNI) can be considered in patients with heart failure with preserved ejection fraction, to reduce the risk of hospitalization for heart failure.
4	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is effective in reducing hospitalizations. In a meta-analysis (Basile) the composite point of heart failure decompensation and all-cause mortality decreased significantly with ARNIs. With controversial results in other meta-analyses. The effect of sacubitril valsartan improved as the time elapsed with heart failure increased; it would also seem to be more useful with a higher frailty index.
5	In patients with heart failure with mildly reduced ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is effective in reducing hospitalizations for heart failure, not mortality.

5	In patients with heart failure with mildly reduced ejection fraction, the use of a mineralocorticoid receptor antagonist (MRA) can be considered in order to reduce hospitalizations for and mortality from heart failure.
5	The use of MRAs is recommended in patients with heart failure with mildly reduced function, to decrease hospitalizations.
5	In patients with heart failure with mildly reduced ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is effective in reducing hospitalizations for and mortality from heart failure, with greater benefit in patients with LVEFs closer to the lowest value in this range.
5	The use of a mineralocorticoid receptor antagonist (MRA) can be considered in patients with heart failure with mildly reduced ejection fraction, to reduce the risk of hospitalization for heart failure, ensuring adequate monitoring of potassium and kidney function to reduce the risk of hyperkalemia and worsening kidney function.
5	For patients with HFmrEF, an MRA can be considered in order to reduce the risk of hospitalization for HF and death. Class IIB-C In selected patients with HFpEF, the MRAs can be considered to reduce hospitalizations, especially in patients with LVEFs on the lower end of this spectrum. IIB-BR Depending on comorbidities like HTN, AF, they can be used post-AMI. 2. Screening and treatment for cardiovascular and other etiologies and comorbidities are recommended for patients with HFpEF. Class IC
5	In patients with heart failure with mildly reduced ejection fraction, the studies do not have the power to show clear effectiveness of mineralocorticoid receptor antagonists (MRAs) in reducing hospitalizations for and mortality from heart failure. Therefore, the recommendation continues to be IIb for this scenario, where usefulness efficacy is less established than evidence opinion.
5	No
5	In patients with heart failure with mildly reduced ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is effective in reducing hospitalizations.
5	In patients with heart failure with mildly reduced ejection fraction, the administration of an MRA can be considered, in order to reduce hospitalizations for heart failure, with special consideration for the risk of developing side effects like gynecomastia and hyperkalemia.
5	In patients with heart failure with mildly reduced ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is effective in significantly reducing hospitalizations for, but not mortality from, heart failure.
5	Agree
5	In patients with heart failure with mildly reduced ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) can be considered, in order to reduce hospitalizations for heart failure.
5	In patients with heart failure with mildly reduced ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is NOT effective in reducing hospitalizations for and mortality from heart failure.
6	In patients with heart failure with preserved ejection fraction, the studies do not have the power to show clear effectiveness of a mineralocorticoid receptor antagonist (MRA) in reducing hospitalizations for and mortality from heart failure. Therefore, the recommendation for this scenario continues to be IIb, where usefulness efficacy is less established than evidence opinion.
6	In patients with heart failure with preserved ejection fraction, spironolactone is not recommended to reduce hospitalizations for and mortality from heart failure.
6	The administration of either selective or nonselective MRAs is not recommended for patients with heart failure with preserved ejection fraction, as a reduction in hospitalizations for and mortality from heart failure has not been proven and, on the contrary, an increase in adverse events associated with the medication has been seen.
6	No
6	In patients with heart failure with preserved ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is effective in reducing hospitalizations for heart failure, mainly in those with ejection fractions close to 50%. They have no effect on mortality.
6	In patients with heart failure with preserved ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is not effective in significantly reducing hospitalizations for and mortality from heart failure.
6	In patients with heart failure with preserved ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is effective in reducing hospitalizations for heart failure, with greater benefit in patients with LVEFs closer to the lowest value in this range.
6	In patients with heart failure with preserved ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) can be considered, in order to reduce hospitalizations for heart failure.
6	Agree
6	In patients with heart failure with preserved ejection fraction, the use of a mineralocorticoid receptor antagonist (MRA) can be considered for reducing hospitalizations for and mortality from heart failure.

6	In patients with heart failure with preserved ejection fraction, there has been significant controversy over whether the use of mineralocorticoid receptor antagonists is effective in reducing hospitalizations for heart failure; women have been found to respond better to spironolactone. In a study of the TOPCAT population, using frozen samples, three phenogroups were described, with phenogroup 3 having the best response to spironolactone. (Middle aged, with diabetes mellitus, obesity, more functional problems, chronic kidney failure, depression, more African American participants.)
6	In selected patients with HFpEF, MRAs can be considered to reduce hospitalizations and death, Class IIB-BR
6	The use of a mineralocorticoid receptor antagonist (MRA) can be considered in patients with heart failure with preserved ejection fraction to reduce the risk of hospitalization for heart failure, ensuring adequate monitoring of potassium and kidney function to reduce the risk of hyperkalemia and worsening kidney function.
6	In patients with heart failure and preserved ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is NOT effective in reducing hospitalizations for and mortality from heart failure.
7	The use of SGLT2 inhibitors is recommended in patients with chronic heart failure with mildly reduced LVEF and residual congestion, added to conventional treatment, with or without diabetes mellitus, to impact the composite outcomes of worsening heart failure or cardiovascular death or emergency room visits, in addition to medical therapy (ACE inhibitors/ARBs/ARNIs beta blockers and aldosterone antagonists), with results that depend on the drug classes added to the treatment.
7	In patients with heart failure with mildly reduced ejection fraction, the sodium-glucose cotransporter-2 (SGLT2) inhibitors have proven to reduce the risk of the composite of hospitalization for heart failure decompensation and cardiovascular death. However, in the individual analysis of each outcome, only empagliflozin showed a significant reduction in cardiovascular death.
7	It is effective, with solid IA evidence based on EMPEROR-Preserved and the DELIVER trial, coupled with the meta-analysis. An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death. I submit for consideration whether the question is:…effective in reducing hospitalizations for and mortality from heart failure? Or, is it effective in reducing hospitalizations for or mortality from heart failure? The same applies for the following question.
7	In patients with symptomatic heart failure with mildly reduced ejection fraction, the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor is recommended to reduce the risk of hospitalization for heart failure or cardiovascular death.
7	In patients with heart failure with mildly reduced ejection fraction, the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor is effective in reducing hospitalizations for and mortality from heart failure.
7	Yes. They are effective and even superior to the other three standard medical treatment drug groups, considering the findings of different studies of dapagliflozin and empagliflozin that were carried out in patients with preserved or mildly reduced LVEF. Evaluating combined outcomes of cardiovascular death and hospitalizations for HF.
7	Yes, I completely agree, high positive evidence supporting this statement.
7	An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of hospitalization for HF or CV death.
7	YES: SGLT2 inhibitors have proven their usefulness over the entire spectrum of the current definition of heart failure, in reducing morbidity (hospitalizations) and mortality.
7	An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with intermediate ejection fractions, reduces the risk of hospitalizations or cardiovascular deaths. Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and mildly reduced or preserved ejection fraction.
7	Agree. The 2023 European Heart Failure Guidelines update is pending.
7	Yes, I agree.
7	Yes. They are superior to other standard medical therapy drugs, based on the different studies of dapagliflozin and empagliflozin that were carried out in patients with preserved or mildly reduced LVEF. Evaluating combined outcomes of cardiovascular death and hospitalizations for HF.
8	Yes, it is effective, with solid IA evidence based on EMPEROR-Preserved and the DELIVER trial. An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death.
8	Yes. New studies have been showing that they are effective regardless of comorbidities or the concomitant use of other disease-modifying drugs.

8	An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of hospitalization for HF or CV death.
8	An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with preserved ejection fraction, reduces the risk of cardiovascular hospitalizations or deaths. Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and preserved ejection fraction, regardless of the presence or absence of diabetes. Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death in patients with heart failure and mildly reduced or preserved ejection fraction, Solomon et al., 2022.
8	Agree. However, this study will be released next week: “STEP HFpEF, a trial comparing the effects of once-weekly semaglutide in people with heart failure with preserved ejection fraction (HFpEF) and obesity,” which is positive. I suggest adding it to the questions. The 2023 European Heart Failure Guidelines update is pending.
8	Yes, although we only have two large studies in this field using the two drugs.
8	Yes. The results of preserved LVEF studies showed effectiveness regardless of comorbidities or the use of other standard medical therapy drugs. Tsampasian, 2022.
8	In patients with symptomatic heart failure with preserved ejection fraction, the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor is recommended to reduce the risk of hospitalization for heart failure or cardiovascular death.
8	In patients with heart failure with preserved ejection fraction, the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor is effective in reducing the combined outcome of hospitalizations for and mortality from heart failure.
8	YES: It is clearly the only drug class that has proven its benefit in this group of patients, in whom comorbidities are more important than structural heart damage.
8	Yes, I agree.
8	In heart failure with preserved LVEF (>50%), the SGLT2 inhibitors reduce the risk of hospitalization for heart failure or the combined outcome of cardiovascular death/cardiovascular hospitalization vs. placebo. The SGLT2 inhibitors have no impact on overall mortality or cardiovascular mortality alone in preserved LVEF, regardless of sex.
8	In patients with heart failure with preserved ejection fraction, sodium-glucose cotransporter-2 (SGLT2) inhibitors have proven to reduce the risk of the composite of cardiovascular death and hospitalization for heart failure decompensation. In the individual analysis of each outcome, they did not show a significant reduction in cardiovascular death, but did show a significant reduction in the risk of hospitalization for heart failure decompensation.
9	In patients with heart failure with mildly reduced ejection fraction, the administration of a beta blocker could be effective in reducing hospitalizations for and mortality from heart failure, when added to an SGLT2 inhibitor.
9	Agree. The 2023 European Heart Failure Guidelines update is pending.
9	No. In the studies, the use of BBs in heart failure with mildly reduced ejection fraction showed a reduction in all-cause mortality, but no statistically significant differences were found in reducing hospitalizations.
9	It is effective, but currently with a IIB level of evidence.
9	In patients with symptomatic heart failure with mildly reduced ejection fraction, the administration of a beta blocker can be considered, in order to reduce the risk of hospitalization for heart failure and death.
9	A beta blocker can be considered for patients with HFmrEF to reduce the risk of hospitalization for and death from HF.
9	In patients with mildly reduced LVEFs, the use of beta blockers in patients taking them for any indication decreases the composite point of cardiovascular death due to heart failure. It does not reduce the hospitalization rate.
9	The use of BBs showed a significant reduction in CV deaths in patients with HF and LVEFs between 40% and 49%, in sinus rhythm (HR 0.48; 95% CI 0.24-0.97; P = 0.04). No significant results were found for CV hospitalization (HR 0.95, 95% CI 0.68–1.32; P = 0.76) or the composite evaluation criterion of CV death or hospitalization (HR 0.83, 95% CI 0.60–1.13; P = 0.23).
9	For patients with heart failure, in sinus rhythm and with mildly reduced LVEF, beta blockers improve left ventricular systolic function and reduce cardiovascular morbidity and mortality.
9	No. In studies of heart failure with mildly reduced ejection fraction, BBs showed reduced all-cause mortality, but no statistically significant differences were found in reducing hospitalizations.
9	It is not very effective. It is a IIb recommendation. The meta-analysis did not show a significant outcome for CV hospitalization (HR 0.95, 95% CI 0.68–1.32; P = 0.76) nor for the composite outcome of cardiovascular death or hospitalization (HR 0.83, 95% CI 0.60–1.13; P = 0.23).

9	In patients with heart failure with mildly reduced ejection fraction, the addition of a beta blocker to optimal medical treatment could reduce hospitalizations for and mortality from heart failure.
9	It is feasible to find a benefit, if recovering from HF, but the associated clinical conditions should be evaluated, where the effect on ventricular function is a consequence of the comorbidity and not itself the cause of heart failure symptoms.
10	With the use of beta blockers in patients with heart failure with pLVEF >50%, there is a tendency to decrease cardiovascular mortality, with no effect on total all-cause mortality. There is no evidence in hospitalizations for heart failure.
10	No. The use of BBs in HF with preserved LVEF showed no reduction in hospitalizations for or death from HF.
10	The use of beta blockers probably causes little or no difference in the risk of death of patients with heart failure with preserved ejection fraction. The certainty of the evidence is moderate.
10	Agree. The 2023 European Heart Failure Guidelines update is pending.
10	In patients with heart failure with preserved ejection fraction, the administration of a beta blocker could be effective in reducing cardiovascular mortality but has no effect on the rate of hospitalization for heart failure.
10	No. In studies, the use of BBs in heart failure with preserved ejection fraction showed no reduction in hospitalization for or death from HF.
10	In patients with heart failure with preserved ejection fraction, the administration of a beta blocker is not effective in reducing hospitalizations for and mortality from heart failure.
10	NOT NECESSARILY: the patients and associated comorbidities should be chosen carefully. As mentioned previously, this is a consequence, NOT A CAUSE. Therefore, patients with HTN, DM with heart failure with preserved EF do not benefit, but patients with coronary disease, atrial fibrillation may benefit.
10	The current evidence in patients with HFpEF and ischemic heart disease only recommends prescribing BBs in the early phase after an acute coronary syndrome, for tachyarrhythmias, and to manage angina.
10	The review of the evidence in Cochrane shows that there may be a reduction in mortality, but the quality of the evidence is low, and although a sensitivity analysis has been done, no conclusions can be drawn, either.
10	For patients with heart failure and preserved LVEFs, beta blockers are safe; however, their benefit in reducing mortality and hospitalizations is not clear.
10	Few studies support their use, they have no impact on mortality and there is a slight reduction in hospitalizations.
10	In patients with heart failure with preserved ejection fraction, the administration of a beta blocker has not proven to be effective in reducing hospitalizations for and mortality from heart failure?
11	In patients with heart failure with ejection fractions >50% and iron deficiency (defined as serum ferritin < 100 µg/L or serum ferritin between 100 and 299 µg/L and transferrin saturation < 20%), the administration of IV iron has not proven to reduce hospitalizations for or mortality from heart failure. In patients with heart failure with mildly reduced ejection fraction (40-49%) and iron deficiency, the administration of IV iron could be considered, in order to reduce hospitalizations for and mortality from heart failure.
11	The administration of intravenous carboxymaltose or derisomaltose iron in chronic and acute stabilized heart failure with iron deficiency in patients with mrLVEF and pLVEF improves fatigability and dyspnea symptoms and quality of life. It also reduces the risk of cardiovascular hospitalizations. The effects are seen from week 4 until week 24 after treatment.
11	In patients with heart failure with both preserved and mildly reduced ejection fractions, there is insufficient evidence to recommend the administration of IV iron to reduce hospitalizations for and mortality from heart failure.
11	Among patients with acute heart failure with iron deficiency and mildly reduced ejection fraction, intravenous ferric carboxymaltose showed no effectiveness in this subgroup of patients in reducing recurrent hospitalizations for heart failure and cardiovascular mortality. We must await the developing evidence.
11	Improved symptoms and reduced hospitalizations, no impact on mortality, recommendation II A
11	NO: insufficient data
11	The studies are in LVEF less than 50%. AFFIRM-HF and IRONMAN trials. The 2023 European Heart Failure Guidelines update is pending.
11	The administration of intravenous iron in mildly reduced and reduced has its best evidence in improving quality of life, but is IIa in reducing hospitalizations, especially with LVEFs < 45%. I do not see recommended references in this question.

11	The administration of IV iron is effective in reducing hospitalizations for and mortality from heart failure, in symptomatic patients with heart failure with reduced and mildly reduced LVEF.
11	In patients with symptomatic heart failure with mildly reduced ejection fraction and iron deficiency (defined as serum ferritin < 100 µg/L or serum ferritin between 100 and 299 µg/L and transferrin saturation < 20%), the administration of intravenous iron supplements with ferric carboxymaltose or ferric derisomaltose is recommended to alleviate heart failure symptoms, improve the quality of life and reduce the risk of hospitalization for heart failure.
11	No. The administration of IV iron in the different studies showed improvement in HF patients' functional capacity, regardless of LVEF. Reference AFFIRM-AHF. Life 2022, 12(11), 1828; https://doi.org/10.3390/life12111828
11	No. The use of IV iron in HF in any LVEF range only showed improvement in functional capacity.
11	Intravenous iron supplementation is recommended in symptomatic patients with HFrEF and HFrEF and iron deficiency, to alleviate the HF symptoms and improve the quality of life.
12	The effect of structured cardiac rehabilitation* in patients with heart failure with mrLVEF has an impact on ventricular diastole, decreasing the size of the left atrium. There are no consistent results regarding cardiac output, right ventricular function and pulmonary pressure. In patients with heart failure with pLVEF >50%, a structured cardiac rehabilitation program* improved exercise capacity, the six-minute walk test and the quality of life questionnaire vs. the control. The results with diastolic function derivatives are conflicting. *The protocols should be structured over 12-16 weeks, with a frequency of 2-3 sessions per week lasting 20-60 minutes per session, with aerobic, resistance, walking, treadmill and cycling exercises.
12	The enrollment in cardiac rehabilitation or structured exercise therapy programs could improve the quality of life and functional capacity of people with HFpEF, especially those with prior hospitalizations.
12	Improves the functional capacity of our patients with HF, regardless of their left ventricular ejection fraction (LVEF), which leads to the clinical outcomes of improved quality of life and reduced readmissions. It also summarizes the available evidence, both in HF with reduced as well as preserved LVEF, and even in advanced HF (Stage D).
12	In patients with heart failure with both preserved and mildly reduced ejection fraction, there is no evidence to date that cardiac rehabilitation added to the instated medical therapy is effective in reducing hospitalizations for or mortality from heart failure.
12	In patients with HF and preserved and mildly reduced ejection fractions, guided cardiac rehabilitation could improve quality of life and functional capacity, but has no significant effect on readmissions or death.
12	In patients with heart failure with both preserved and mildly reduced ejection fraction, cardiac rehabilitation or physical training (regular physical activity) added to the instated medical treatment is effective in reducing the risk of hospitalization for and death from heart failure, and improving functional capacity, exercise tolerance and quality of life.
12	In patients with heart failure with both preserved and mildly reduced ejection fraction, cardiac rehabilitation should be an adjunct to medical therapy to improve the quality of life.
12	No. Improved functional capacity has been shown in all patients with HF, regardless of LVEF and HF stage. References Hosseini Mohammadi NS, Shaki Katouli MH, Masoudkabir F, Meysamie A, Tavakoli K, Vasheghani-Farahani A. Cardiac rehabilitation in heart failure with severely reduced ejection fraction: effects on mortality. Heart Fail Rev. 2022 May 21. Sawan MA, Calhoun AE, Fatade YA, Wenger NK. Cardiac rehabilitation in women, challenges and opportunities. Prog Cardiovasc Dis. 2022 Jan-Feb;70:111-118.
12	No. The studies have shown functional class improvement in all patients with HF and cardiovascular risk.
12	Cardiac rehabilitation improves the quality of life and functional class in patients with heart failure and preserved LVEF.
12	There are no references; however, multiple meta-analyses confirm its benefit. The important point in the discussion is the type (protocol, duration) of cardiac rehabilitation.
12	NO: insufficient data. It would be useful to improve the peak O2, aerobic endurance and quality of life of patients with HFpEF.
12	As outlined above, most of the evidence for cardiac rehabilitation has been reported in HFrEF. However, there is a growing randomized trial literature demonstrating the potential benefits in heart failure with preserved ejection fraction (HFpEF) in terms of improvement in health-related quality of life, exercise capacity, and mechanistic echocardiographic measures. However, whilst exercise capacity and health-related quality of life are strong prognostic predictors in HFpEF, given the small number of recruited patients and relatively short follow-up of trials of exercise training interventions, there are insufficient data at this time to fully determine the impact of cardiac rehabilitation on clinical events, including mortality and hospital admission in HFpEF.

Annex D. References that made up the body of evidence for each of the questions and the risk of bias of each of the studies evaluated.

Question
Question 1 [1] Qin J, Wang W, Wei P, Huang P, Lin R, Yue J. Effects of sacubitril-valsartan on heart failure patients with mid-range ejection fractions: A systematic review and meta-analysis. Front Pharmacol 2022;13:982372. https://doi.org/10.3389/fphar.2022.982372. [2] Zhang H, Huetteman AT, Reyes EA, Appelbaum JS. Effects of Sacubitril–Valsartan in Patients With Various Types of Heart Failure: A Meta-analysis 2023. [3] Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. European J of Heart Fail 2018;20:1230–9. https://doi.org/10.1002/ejhf.1149. [4] Xiang B, Zhang R, Wu X, Zhou X. Optimal Pharmacologic Treatment of Heart Failure With Preserved and Mildly Reduced Ejection Fraction: A Meta-analysis. JAMA Netw Open 2022;5:e2231963. https://doi.org/10.1001/jamanetworkopen.2022.31963. [5] Alzahrani T, Tiu J, Panjrath G, Solomon A. The effect of angiotensin-converting enzyme inhibitors on clinical outcomes in patients with ischemic cardiomyopathy and midrange ejection fraction: a post hoc subgroup analysis from the PEACE trial. Therapeutic Advances in Cardiovascular Disease 2018;12:351–9. https://doi.org/10.1177/1753944718809266. [6] Nie D, Xiong B, Qian J, Rong S, Yao Y, Huang J. The Effect of Sacubitril-Valsartan in Heart Failure Patients With Mid-Range and Preserved Ejection Fraction: A Meta-Analysis. Heart, Lung and Circulation 2021;30:683–91. https://doi.org/10.1016/j.hlc.2020.10.012. [7] Leite M, Sampaio F, Saraiva FA, Diaz SO, Barros AS, Fontes-Carvalho R. The impact of heart failure therapy in patients with mildly reduced ejection fraction: a network meta-analysis. ESC Heart Failure 2023;10:1822–34. https://doi.org/10.1002/ehf2.14284.
Question 2 [1] 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. https://doi.org/10.1056/NEJMoa1908655. [2] Lin Y, Wu M, Liao B, Pang X, Chen Q, Yuan J, et al. Comparison of Pharmacological Treatment Effects on Long-Time Outcomes in Heart Failure With Preserved Ejection Fraction: A Network Meta-analysis of Randomized Controlled Trials. Front Pharmacol 2021;12:707777. https://doi.org/10.3389/fphar.2021.707777. [3] Zheng SL, Chan FT, Nabeebaccus AA, Shah AM, McDonagh T, Okonko DO, et al. Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Heart 2018;104:407–15. https://doi.org/10.1136/heartjnl-2017-311652. [4] Ostrominski JW, Claggett BL, Packer M, Pfeffer MA, Lam CSP, Zile MR, et al. Duration of Heart Failure With Preserved Ejection Fraction and Outcomes With Sacubitril/Valsartan: Insights From the PARAGON-HF Trial. Journal of Cardiac Failure 2023;29:1494–503. https://doi.org/10.1016/j.cardfail.2023.05.003. [5] Lin Y, Cai Z, Yuan J, Liu H, Pang X, Chen Q, et al. Effect of pharmacological treatment on outcomes of heart failure with preserved ejection fraction: an updated systematic review and network meta-analysis of randomized controlled trials. Cardiovasc Diabetol 2022;21:237. https://doi.org/10.1186/s12933-022-01679-2. [6] Zhang Q, Chen Y, Liu Q, Shan Q. Effects of renin–angiotensin–aldosterone system inhibitors on mortality, hospitalization, and diastolic function in patients with HFpEF: A meta-analysis of 13 randomized controlled trials. Herz 2016;41:76–86. https://doi.org/10.1007/s00059-015-4346-8. [7] McMurray JJV, Jackson AM, Lam CSP, Redfield MM, Anand IS, Ge J, et al. Effects of Sacubitril-Valsartan Versus Valsartan in Women Compared With Men With Heart Failure and Preserved Ejection Fraction: Insights From PARAGON-HF. Circulation 2020;141:338–51. https://doi.org/10.1161/CIRCULATIONAHA.119.044491. [8] Zhang H, Huetteman AT, Reyes EA, Appelbaum JS. Effects of Sacubitril–Valsartan in Patients With Various Types of Heart Failure: A Meta-analysis 2023. [9] Yu W, Zhang H, Shen W, Luo F, Yang S, Gan L, et al. Efficacy and safety of sacubitril/valsartan on heart failure with preserved ejection fraction: A meta-analysis of randomized controlled trials. Front Cardiovasc Med 2022;9:897423. https://doi.org/10.3389/fcvm.2022.897423. [10] Yang L, Ye N, Bian W, Cheng H. Efficacy of medication therapy for patients with chronic kidney disease and heart failure with preserved ejection fraction: a systematic review and meta-analysis. Int Urol Nephrol 2022;54:1435–44. https://doi.org/10.1007/s11255-021-03025-z. [11] Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. European J of Heart Fail 2018;20:1230–9. https://doi.org/10.1002/ejhf.1149. [12] Kuno T, Ueyama H, Fujisaki T, Briasouli A, Takagi H, Briasoulis A. Meta-Analysis Evaluating the Effects of Renin-Angiotensin-Aldosterone System Blockade on Outcomes of Heart Failure With Preserved Ejection Fraction. The American Journal of Cardiology 2020;125:1187–93. https://doi.org/10.1016/j.amjcard.2020.01.009. [13] Xiang B, Zhang R, Wu X, Zhou X. Optimal Pharmacologic Treatment of Heart Failure With Preserved and Mildly Reduced Ejection Fraction: A Meta-analysis. JAMA Netw Open 2022;5:e2231963. https://doi.org/10.1001/jamanetworkopen.2022.31963. [14] Bonsu KO, Arunmanakul P, Chaiyakunapruk N. Pharmacological treatments for heart failure with preserved ejection fraction—a systematic review and indirect comparison. Heart Fail Rev 2018;23:147–56. https://doi.org/10.1007/s10741-018-9679-y.

[15] Vaduganathan M, Claggett BL, Desai AS, Anker SD, Perrone SV, Janssens S, et al. Prior Heart Failure Hospitalization, Clinical Outcomes, and Response to Sacubitril/Valsartan Compared With Valsartan in HFpEF. Journal of the American College of Cardiology 2020;75:245–54. https://doi.org/10.1016/j.jacc.2019.11.003.

[16] Suzuki K, Claggett B, Minamisawa M, Nochioka K, Mitchell GF, Anand IS, et al. Pulse Pressure, Prognosis, and Influence of Sacubitril/Valsartan in Heart Failure With Preserved Ejection Fraction. Hypertension 2021;77:546–56. https://doi.org/10.1161/HYPERTENSIONAHA.120.16277.

[17] Khan MS, Fonarow GC, Khan H, Greene SJ, Anker SD, Gheorghiade M, et al. Renin–angiotensin blockade in heart failure with preserved ejection fraction: a systematic review and meta-analysis. ESC Heart Failure 2017;4:402–8. https://doi.org/10.1002/ehf2.12204.

[18] Butt JH, Dewan P, Jhund PS, Anand IS, Atar D, Ge J, et al. Sacubitril/Valsartan and Frailty in Patients With Heart Failure and Preserved Ejection Fraction. Journal of the American College of Cardiology 2022;80:1130–43. https://doi.org/10.1016/j.jacc.2022.06.037.

[19] Basile C, Paolillo S, Gargiulo P, Marzano F, Asile G, Parlati ALM, et al. Sacubitril/valsartan reduces cardiac decompensation in heart failure with preserved ejection fraction: a meta-analysis. Journal of Cardiovascular Medicine 2023;24:44–51. https://doi.org/10.2459/JCM.0000000000001411.

[20] Selvaraj S, Claggett BL, Böhm M, Anker SD, Vaduganathan M, Zannad F, et al. Systolic Blood Pressure in Heart Failure With Preserved Ejection Fraction Treated With Sacubitril/Valsartan. Journal of the American College of Cardiology 2020;75:1644–56. https://doi.org/10.1016/j.jacc.2020.02.009.

[21] Faisal S, Ahmad Ganaie Z, Batool S, Lokhandwala DHI, Hankins J, Chaudhari SS, et al. The Efficacy of Various Pharmacological Agents on Long-Term Outcomes in Patients With Heart Failure With Preserved Ejection Fraction: A Meta-Analysis of Randomized Control Trials. Cureus 2022. https://doi.org/10.7759/cureus.28145.

Question 3

[1] Mentz RJ, Ward JH, Hernandez AF, Lepage S, Morrow DA, Sarwat S, et al. Angiotensin-Neprilysin Inhibition in Patients With Mildly Reduced or Preserved Ejection Fraction and Worsening Heart Failure. Journal of the American College of Cardiology 2023;82:1–12. https://doi.org/10.1016/j.jacc.2023.04.019.

[2] Qin J, Wang W, Wei P, Huang P, Lin R, Yue J. Effects of sacubitril-valsartan on heart failure patients with mid-range ejection fractions: A systematic review and meta-analysis. Front Pharmacol 2022;13:982372. https://doi.org/10.3389/fphar.2022.982372.

[3] Zhang H, Huetteman AT, Reyes EA, Appelbaum JS. Effects of Sacubitril–Valsartan in Patients With Various Types of Heart Failure: A Meta-analysis 2023.

[4] Xiang B, Zhang R, Wu X, Zhou X. Optimal Pharmacologic Treatment of Heart Failure With Preserved and Mildly Reduced Ejection Fraction: A Meta-analysis. JAMA Netw Open 2022;5:e2231963. https://doi.org/10.1001/jamanetworkopen.2022.31963.

[5] Nie D, Xiong B, Qian J, Rong S, Yao Y, Huang J. The Effect of Sacubitril-Valsartan in Heart Failure Patients With Mid-Range and Preserved Ejection Fraction: A Meta-Analysis. Heart, Lung and Circulation 2021;30:683–91. https://doi.org/10.1016/j.hlc.2020.10.012.

[6] Leite M, Sampaio F, Saraiva FA, Diaz SO, Barros AS, Fontes-Carvalho R. The impact of heart failure therapy in patients with mildly reduced ejection fraction: a network meta-analysis. ESC Heart Failure 2023;10:1822–34. https://doi.org/10.1002/ehf2.14284.

Question 4

[1] 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. https://doi.org/10.1056/NEJMoa1908655.

[2] Martin N, Manoharan K, Davies C, Lumbers RT. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. Cochrane Database of Systematic Reviews 2021;2021. https://doi.org/10.1002/14651858.CD012721.pub3.

[3] Lin Y, Wu M, Liao B, Pang X, Chen Q, Yuan J, et al. Comparison of Pharmacological Treatment Effects on Long-Time Outcomes in Heart Failure With Preserved Ejection Fraction: A Network Meta-analysis of Randomized Controlled Trials. Front Pharmacol 2021;12:707777. https://doi.org/10.3389/fphar.2021.707777.

[4] Zheng SL, Chan FT, Nabeebaccus AA, Shah AM, McDonagh T, Okonko DO, et al. Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Heart 2018;104:407–15. https://doi.org/10.1136/heartjnl-2017-311652.

[5] Ostrominski JW, Claggett BL, Packer M, Pfeffer MA, Lam CSP, Zile MR, et al. Duration of Heart Failure With Preserved Ejection Fraction and Outcomes With Sacubitril/Valsartan: Insights From the PARAGON-HF Trial. Journal of Cardiac Failure 2023;29:1494–503. https://doi.org/10.1016/j.cardfail.2023.05.003.

[6] Lin Y, Cai Z, Yuan J, Liu H, Pang X, Chen Q, et al. Effect of pharmacological treatment on outcomes of heart failure with preserved ejection fraction: an updated systematic review and network meta-analysis of randomized controlled trials. Cardiovasc Diabetol 2022;21:237. https://doi.org/10.1186/s12933-022-01679-2.

[7] Zhang Q, Chen Y, Liu Q, Shan Q. Effects of renin–angiotensin–aldosterone system inhibitors on mortality, hospitalization, and diastolic function in patients with HFpEF: A meta-analysis of 13 randomized controlled trials. Herz 2016;41:76–86. https://doi.org/10.1007/s00059-015-4346-8.

[8] McMurray JJV, Jackson AM, Lam CSP, Redfield MM, Anand IS, Ge J, et al. Effects of Sacubitril-Valsartan Versus Valsartan in Women Compared With Men With Heart Failure and Preserved Ejection Fraction: Insights From PARAGON-HF. Circulation 2020;141:338–51. https://doi.org/10.1161/CIRCULATIONAHA.119.044491.

[9] Zhang H, Huetteman AT, Reyes EA, Appelbaum JS. Effects of Sacubitril–Valsartan in Patients With Various Types of Heart Failure: A Meta-analysis 2023.

[11] Yang L, Ye N, Bian W, Cheng H. Efficacy of medication therapy for patients with chronic kidney disease and heart failure with preserved ejection fraction: a systematic review and meta-analysis. Int Urol Nephrol 2022;54:1435–44. https://doi.org/10.1007/s11255-021-03025-z.

[12] Xiang B, Zhang R, Wu X, Zhou X. Optimal Pharmacologic Treatment of Heart Failure With Preserved and Mildly Reduced Ejection Fraction: A Meta-analysis. JAMA Netw Open 2022;5:e2231963. https://doi.org/10.1001/jamanetworkopen.2022.31963.

[13] Bonsu KO, Arunmanakul P, Chaiyakunapruk N. Pharmacological treatments for heart failure with preserved ejection fraction—a systematic review and indirect comparison. Heart Fail Rev 2018;23:147–56. https://doi.org/10.1007/s10741-018-9679-y.

[14] Vaduganathan M, Claggett BL, Desai AS, Anker SD, Perrone SV, Janssens S, et al. Prior Heart Failure Hospitalization, Clinical Outcomes, and Response to Sacubitril/Valsartan Compared With Valsartan in HFpEF. Journal of the American College of Cardiology 2020;75:245–54. https://doi.org/10.1016/j.jacc.2019.11.003.

[15] Suzuki K, Claggett B, Minamisawa M, Nochioka K, Mitchell GF, Anand IS, et al. Pulse Pressure, Prognosis, and Influence of Sacubitril/Valsartan in Heart Failure With Preserved Ejection Fraction. Hypertension 2021;77:546–56. https://doi.org/10.1161/HYPERTENSIONAHA.120.16277.

[16] Butt JH, Dewan P, Jhund PS, Anand IS, Atar D, Ge J, et al. Sacubitril/Valsartan and Frailty in Patients With Heart Failure and Preserved Ejection Fraction. Journal of the American College of Cardiology 2022;80:1130–43. https://doi.org/10.1016/j.jacc.2022.06.037.

[17] Basile C, Paolillo S, Gargiulo P, Marzano F, Asile G, Parlati ALM, et al. Sacubitril/valsartan reduces cardiac decompensation in heart failure with preserved ejection fraction: a meta-analysis. Journal of Cardiovascular Medicine 2023;24:44–51. https://doi.org/10.2459/JCM.0000000000001411.

[18] Selvaraj S, Claggett BL, Böhm M, Anker SD, Vaduganathan M, Zannad F, et al. Systolic Blood Pressure in Heart Failure With Preserved Ejection Fraction Treated With Sacubitril/Valsartan. Journal of the American College of Cardiology 2020;75:1644–56. https://doi.org/10.1016/j.jacc.2020.02.009.

[19] Faisal S, Ahmad Ganaie Z, Batool S, Lokhandwala DHI, Hankins J, Chaudhari SS, et al. The Efficacy of Various Pharmacological Agents on Long-Term Outcomes in Patients With Heart Failure With Preserved Ejection Fraction: A Meta-Analysis of Randomized Control Trials. Cureus 2022. https://doi.org/10.7759/cureus.28145.

Question 5

[1] Xiang Y, Shi W, Li Z, Yang Y, Wang SY, Xiang R, et al. Efficacy and safety of spironolactone in the heart failure with mid-range ejection fraction and heart failure with preserved ejection fraction: A meta-analysis of randomized clinical trials. Medicine 2019;98:e14967. https://doi.org/10.1097/MD.0000000000014967.

[2] Berbenetz NM, Mrkobrada M. Mineralocorticoid receptor antagonists for heart failure: systematic review and meta-analysis. BMC Cardiovasc Disord 2016;16:246. https://doi.org/10.1186/s12872-016-0425-x.

[3] Japp D, Shah A, Fisken S, Denvir M, Shenkin S, Japp A. Mineralocorticoid receptor antagonists in elderly patients with heart failure: a systematic review and meta-analysis. Age Ageing 2016:ageing;afw138v1. https://doi.org/10.1093/ageing/afw138.

Question 6

[1] Cohen JB, Schrauben SJ, Zhao L, Basso MD, Cvijic ME, Li Z, et al. Clinical Phenogroups in Heart Failure With Preserved Ejection Fraction. JACC: Heart Failure 2020;8:172–84. https://doi.org/10.1016/j.jchf.2019.09.009.

[2] Elkholey K, Papadimitriou L, Butler J, Thadani U, Stavrakis S. Effect of Obesity on Response to Spironolactone in Patients With Heart Failure With Preserved Ejection Fraction. The American Journal of Cardiology 2021;146:36–47. https://doi.org/10.1016/j.amjcard.2021.01.018.

[3] Chen Y, Wang H, Lu Y, Huang X, Liao Y, Bin J. Effects of mineralocorticoid receptor antagonists in patients with preserved ejection fraction: a meta-analysis of randomized clinical trials. BMC Med 2015;13:10. https://doi.org/10.1186/s12916-014-0261-8.

[4] Li S, Zhang X, Dong M, Gong S, Shang Z, Jia X, et al. Effects of spironolactone in heart failure with preserved ejection fraction: A meta-analysis of randomized controlled trials. Medicine 2018;97:e11942. https://doi.org/10.1097/MD.0000000000011942.

[5] Xiang Y, Shi W, Li Z, Yang Y, Wang SY, Xiang R, et al. Efficacy and safety of spironolactone in the heart failure with mid-range ejection fraction and heart failure with preserved ejection fraction: A meta-analysis of randomized clinical trials. Medicine 2019;98:e14967. https://doi.org/10.1097/MD.0000000000014967.

[6] 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. https://doi.org/10.1093/eurheartj/ehv464.

[7] Berbenetz NM, Mrkobrada M. Mineralocorticoid receptor antagonists for heart failure: systematic review and meta-analysis. BMC Cardiovasc Disord 2016;16:246. https://doi.org/10.1186/s12872-016-0425-x.

[8] Japp D, Shah A, Fisken S, Denvir M, Shenkin S, Japp A. Mineralocorticoid receptor antagonists in elderly patients with heart failure: a systematic review and meta-analysis. Age Ageing 2016:ageing;afw138v1. https://doi.org/10.1093/ageing/afw138.

[9] Lin Y, Zhong X, Liu M, Zhang S, Xiong Z, Huang Y, et al. Risk Stratification and Efficacy of Spironolactone in Patients with Heart Failure with Preserved Ejection Fraction: Secondary Analysis of the TOPCAT Randomized Clinical Trial. Cardiovasc Drugs Ther 2022;36:323–31. https://doi.org/10.1007/s10557-021-07178-y.

[10] Sun J, Tai S, Guo Y, Tang L, Yang H, Li X, et al. Sex Differences in Characteristics and Outcomes in Elderly Heart Failure Patients With Preserved Ejection Fraction: A Post-hoc Analysis From TOPCAT. Front Cardiovasc Med 2021;8:721850. https://doi.org/10.3389/fcvm.2021.721850.

[11] Merrill M, Sweitzer NK, Lindenfeld J, Kao DP. Sex Differences in Outcomes and Responses to Spironolactone in Heart Failure With Preserved Ejection Fraction. JACC: Heart Failure 2019;7:228–38. https://doi.org/10.1016/j.jchf.2019.01.003.

[12] Sperry BW, Hanna M, Shah SJ, Jaber WA, Spertus JA. Spironolactone in Patients With an Echocardiographic HFpEF Phenotype Suggestive of Cardiac Amyloidosis. JACC: Heart Failure 2021;9:795–802. https://doi.org/10.1016/j.jchf.2021.06.007.

[13] Beldhuis IE, Myhre PL, Bristow M, Claggett B, Damman K, Fang JC, et al. Spironolactone in Patients With Heart Failure, Preserved Ejection Fraction, and Worsening Renal Function. Journal of the American College of Cardiology 2021;77:1211–21. https://doi.org/10.1016/j.jacc.2020.12.057.

[14] Tsujimoto T, Kajio H. Spironolactone Use and Improved Outcomes in Patients With Heart Failure With Preserved Ejection Fraction With Resistant Hypertension. JAHA 2020;9:e018827. https://doi.org/10.1161/JAHA.120.018827.

[4] Li S, Zhang X, Dong M, Gong S, Shang Z, Jia X, et al. Effects of spironolactone in heart failure with preserved ejection fraction: A meta-analysis of randomized controlled trials. Medicine 2018;97:e11942. https://doi.org/10.1097/MD.0000000000011942.

[5] Xiang Y, Shi W, Li Z, Yang Y, Wang SY, Xiang R, et al. Efficacy and safety of spironolactone in the heart failure with mid-range ejection fraction and heart failure with preserved ejection fraction: A meta-analysis of randomized clinical trials. Medicine 2019;98:e14967. https://doi.org/10.1097/MD.0000000000014967.

[6] 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. https://doi.org/10.1093/eurheartj/ehv464.

[7] Berbenetz NM, Mrkobrada M. Mineralocorticoid receptor antagonists for heart failure: systematic review and meta-analysis. BMC Cardiovasc Disord 2016;16:246. https://doi.org/10.1186/s12872-016-0425-x.

[8] Japp D, Shah A, Fisken S, Denvir M, Shenkin S, Japp A. Mineralocorticoid receptor antagonists in elderly patients with heart failure: a systematic review and meta-analysis. Age Ageing 2016:ageing;afw138v1. https://doi.org/10.1093/ageing/afw138.

[9] Lin Y, Zhong X, Liu M, Zhang S, Xiong Z, Huang Y, et al. Risk Stratification and Efficacy of Spironolactone in Patients with Heart Failure with Preserved Ejection Fraction: Secondary Analysis of the TOPCAT Randomized Clinical Trial. Cardiovasc Drugs Ther 2022;36:323–31. https://doi.org/10.1007/s10557-021-07178-y.

[10] Sun J, Tai S, Guo Y, Tang L, Yang H, Li X, et al. Sex Differences in Characteristics and Outcomes in Elderly Heart Failure Patients With Preserved Ejection Fraction: A Post-hoc Analysis From TOPCAT. Front Cardiovasc Med 2021;8:721850. https://doi.org/10.3389/fcvm.2021.721850.

Question 7

[1] Solomon SD, McMurray JJV, Claggett B, De Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med 2022;387:1089–98. https://doi.org/10.1056/NEJMoa2206286.

[2] 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. https://doi.org/10.1056/NEJMoa2107038.

[3] Xiang B, Zhang R, Wu X, Zhou X. Optimal Pharmacologic Treatment of Heart Failure With Preserved and Mildly Reduced Ejection Fraction: A Meta-analysis. JAMA Netw Open 2022;5:e2231963. https://doi.org/10.1001/jamanetworkopen.2022.31963.

[4] Leite M, Sampaio F, Saraiva FA, Diaz SO, Barros AS, Fontes-Carvalho R. The impact of heart failure therapy in patients with mildly reduced ejection fraction: a network meta-analysis. ESC Heart Failure 2023;10:1822–34. https://doi.org/10.1002/ehf2.14284.

Question 8

[1] Zhao L, Guo W, Huang W, Wang L, Huang S. Benefit of sodium-glucose cotransporter-2 inhibitors on survival outcome is related to the type of heart failure: A meta-analysis. Diabetes Research and Clinical Practice 2022;187:109871. https://doi.org/10.1016/j.diabres.2022.109871.

[2] Adamson C, Kondo T, Jhund PS, De Boer RA, Cabrera Honorio JW, Claggett B, et al. Dapagliflozin for heart failure according to body mass index: the DELIVER trial. European Heart Journal 2022;43:4406–17. https://doi.org/10.1093/eurheartj/ehac481.

[3] Solomon SD, McMurray JJV, Claggett B, De Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med 2022;387:1089–98. https://doi.org/10.1056/NEJMoa2206286.

[4] Butler J, Filippatos G, Siddiqi TJ, Ferreira JP, Brueckmann M, Bocchi E, et al. Effects of Empagliflozin in Women and Men With Heart Failure and Preserved Ejection Fraction. Circulation 2022;146:1046–55. https://doi.org/10.1161/CIRCULATIONAHA.122.059755.

[5] De Marzo V, Savarese G, Porto I, Metra M, Ameri P. Efficacy of SGLT2-inhibitors across different definitions of heart failure with preserved ejection fraction. Journal of Cardiovascular Medicine 2023;24:537–43. https://doi.org/10.2459/JCM.0000000000001504.

[6] Filippatos G, Butler J, Farmakis D, Zannad F, Ofstad AP, Ferreira JP, et al. Empagliflozin for Heart Failure With Preserved Left Ventricular Ejection Fraction With and Without Diabetes. Circulation 2022;146:676–86. https://doi.org/10.1161/CIRCULATIONAHA.122.059785.

[7] Böhm M, Butler J, Filippatos G, Ferreira JP, Pocock SJ, Abdin A, et al. Empagliflozin Improves Outcomes in Patients With Heart Failure and Preserved Ejection Fraction Irrespective of Age. Journal of the American College of Cardiology 2022;80:1–18. https://doi.org/10.1016/j.jacc.2022.04.040.

[8] 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. https://doi.org/10.1056/NEJMoa2107038.

[9] Savarese G, Uijl A, Lund LH, Anker SD, Asselbergs FW, Fitchett D, et al. Empagliflozin in Heart Failure With Predicted Preserved Versus Reduced Ejection Fraction: Data From the EMPA-REG OUTCOME Trial. Journal of Cardiac Failure 2021;27:888–95. https://doi.org/10.1016/j.cardfail.2021.05.012.

[10] Wagdy K, Nagy S. EMPEROR-Preserved: SGLT2 inhibitors breakthrough in the management of heart failure with preserved ejection fraction. Gcsp 2021;2021. https://doi.org/10.21542/gcsp.2021.17.

[11] Ferreira JP, Butler J, Zannad F, Filippatos G, Schueler E, Steubl D, et al. Mineralocorticoid Receptor Antagonists and Empagliflozin in Patients With Heart Failure and Preserved Ejection Fraction. Journal of the American College of Cardiology 2022;79:1129–37. https://doi.org/10.1016/j.jacc.2022.01.029.

[12] Xiang B, Zhang R, Wu X, Zhou X. Optimal Pharmacologic Treatment of Heart Failure With Preserved and Mildly Reduced Ejection Fraction: A Meta-analysis. JAMA Netw Open 2022;5:e2231963. https://doi.org/10.1001/jamanetworkopen.2022.31963.

[13] Tsampasian V, Elghazaly H, Chattopadhyay R, Ali O, Corballis N, Chousou PA, et al. Sodium glucose co-transporter 2 inhibitors in heart failure with preserved ejection fraction: a systematic review and meta-analysis. European Journal of Preventive Cardiology 2022;29:e227–9. https://doi.org/10.1093/eurjpc/zwab189.

[14] Ji P, Zhang Z, Yan Q, Cao H, Zhao Y, Yang B, et al. The cardiovascular effects of SGLT2 inhibitors, RAS inhibitors, and ARN inhibitors in heart failure. ESC Heart Failure 2023;10:1314–25. https://doi.org/10.1002/ehf2.14298.

[15] Leite M, Sampaio F, Saraiva FA, Diaz SO, Barros AS, Fontes-Carvalho R. The impact of heart failure therapy in patients with mildly reduced ejection fraction: a network meta-analysis. ESC Heart Failure 2023;10:1822–34. https://doi.org/10.1002/ehf2.14284.

Question 9

[1] Xiang B, Zhang R, Wu X, Zhou X. Optimal Pharmacologic Treatment of Heart Failure With Preserved and Mildly Reduced Ejection Fraction: A Meta-analysis. JAMA Netw Open 2022;5:e2231963. https://doi.org/10.1001/jamanetworkopen.2022.31963.

[2] Leite M, Sampaio F, Saraiva FA, Diaz SO, Barros AS, Fontes-Carvalho R. The impact of heart failure therapy in patients with mildly reduced ejection fraction: a network meta-analysis. ESC Heart Failure 2023;10:1822–34. https://doi.org/10.1002/ehf2.14284.

Question 10

[1] Alegría J, Rada G. Are beta-blockers effective in heart failure with preserved ejection fraction? Medwave 2016;16:e6593–e6593. https://doi.org/10.5867/medwave.2016.6593.

[2] Martin N, Manoharan K, Thomas J, Davies C, Lumbers RT. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. Cochrane Database of Systematic Reviews 2018. https://doi.org/10.1002/14651858.CD012721.pub2.

[3] Bavishi C, Chatterjee S, Ather S, Patel D, Messerli FH. Beta-blockers in heart failure with preserved ejection fraction: a meta-analysis. Heart Fail Rev 2015;20:193–201. https://doi.org/10.1007/s10741-014-9453-8.

[4] Zheng SL, Chan FT, Nabeebaccus AA, Shah AM, McDonagh T, Okonko DO, et al. Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Heart 2018;104:407–15. https://doi.org/10.1136/heartjnl-2017-311652.

[5] Xiang B, Zhang R, Wu X, Zhou X. Optimal Pharmacologic Treatment of Heart Failure With Preserved and Mildly Reduced Ejection Fraction: A Meta-analysis. JAMA Netw Open 2022;5:e2231963. https://doi.org/10.1001/jamanetworkopen.2022.31963.

[6] Bonsu KO, Arunmanakul P, Chaiyakunapruk N. Pharmacological treatments for heart failure with preserved ejection fraction—a systematic review and indirect comparison. Heart Fail Rev 2018;23:147–56. https://doi.org/10.1007/s10741-018-9679-y.

Annex E. The experts' final individual responses (Phase 6).

Question	Phase 6 Responses
1	1. For patients with HFmrEF, an ACE inhibitor can be considered in order to reduce the risk of hospitalization for HF and mortality. Class IIB-C. Clase IIB-C. 2. For patients with HFmrEF, an ARB can be considered in order to reduce the risk of hospitalization for HF and mortality. Class IIB-C. Clase IIB-C.
1	Agree
1	In these patients, the use of an angiotensin converting enzyme inhibitor / angiotensin receptor blocker is effective in reducing hospitalizations by up to 28%, with better results if used with other drugs like SGLT2 inhibitors and B blockers. In heart failure with mildly reduced ejection fraction due to ischemic heart disease, angiotensin converting enzyme inhibitors could reduce the risk of death.
1	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin receptor blocker (ARB) or an angiotensin converting enzyme (ACE) inhibitor could be considered when an angiotensin receptor/neprilysin inhibitor (ARNI) is contraindicated due to intolerance or inaccessibility, in order to reduce hospitalizations for heart failure.
1	In patients with heart failure with mildly reduced ejection fraction, the administration of an ACE inhibitor/ARB is effective in reducing hospitalizations for HF, without showing a significant reduction in cardiovascular mortality or all-cause mortality.

1	In patients with heart failure with mildly reduced ejection fraction, the studies do not have the power to show clear effectiveness (ACE inhibitors, ARBs) in reducing hospitalizations for and mortality from heart failure. Therefore, the recommendation continues to be IIb for this scenario, where usefulness efficacy is less established than evidence opinion.
1	In patients with heart failure with mildly reduced ejection fraction, the use of ACE inhibitors, or angiotensin receptor blockers (ARBs) in the event of ACE inhibitor intolerance, can be considered effective in reducing the number of hospitalizations for heart failure, without showing a categorical benefit thus far in reducing mortality, except in the context of ischemic heart failure, in which patients with mildly reduced ejection fraction on ACE inhibitors could lower cardiovascular mortality.
1	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor, or angiotensin receptor blocker (ARB) in the event of ACE inhibitor intolerance, is recommended to reduce hospitalizations for heart failure. In patients with ischemic heart failure with mildly reduced ejection fraction, the use of an angiotensin converting enzyme (ACE) inhibitor could reduce cardiovascular mortality.
1	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor, or angiotensin receptor blocker (ARB) in the event of ACE inhibitor intolerance, is recommended to reduce hospitalizations for heart failure.
1	In patients with heart failure with mildly reduced ejection fraction, the use of an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) can be considered in order to reduce hospitalizations for and death from heart failure.
1	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB) is effective in reducing cardiovascular deaths and hospitalizations for heart failure, with greater benefit in patients with VEFs closer to the lowest value in this range.
1	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) is effective in reducing hospitalizations for heart failure, not mortality.
1	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) is effective in reducing hospitalizations for heart failure, but not for reducing mortality.
1	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB) is **NOT** effective in reducing hospitalizations for **and** mortality from heart failure.
2	1. ACE inhibitors and ARBs have no reduction in hospitalizations for and mortality from HF in this group. 2. Depending on comorbidities like HTN and AF, they can be used post-AMI. 3. Screening and treatment for cardiovascular and other etiologies and comorbidities are recommended for patients with HFpEF. Class IC
2	Agree
2	In patients with HF with preserved ejection fraction, angiotensin converting enzyme inhibitors and angiotensin receptor blockers are effective in significantly reducing hospitalizations for HF, but do not significantly reduce HF mortality.
2	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin receptor blocker (ARB) or angiotensin converting enzyme (ACE) inhibitor can be considered when an angiotensin receptor/neprilysin inhibitor (ARNI) is contraindicated due to intolerance or inaccessibility, in order to reduce hospitalizations for heart failure.
2	In patients with preserved ejection fractions, ACE inhibitors/ARNIs are effective in reducing hospitalizations for HF, but not for reducing mortality.
2	In patients with heart failure with preserved ejection fraction, the administration of ACE inhibitors is effective in reducing hospitalizations. The ARBs showed no benefit in reducing hospitalizations on meta-analysis.
2	In patients with heart failure with preserved ejection fraction, the administration of ACE inhibitors can be considered effective in reducing hospitalizations for heart failure. The evidence is not categorical regarding the use of ARBs in this group of patients to reduce hospitalizations nor has it proven to decrease mortality.
2	In patients with heart failure with preserved ejection fraction, the studies do not have the power to show clear effectiveness (ACE inhibitors, ARBs) in reducing hospitalizations for and mortality from heart failure. Therefore, the recommendation continues to be IIb for this scenario, where usefulness efficacy is less established than evidence opinion.
2	In patients with heart failure with preserved ejection fraction, the studies do not have the power to show clear effectiveness of an angiotensin receptor/neprilysin inhibitor (ARNI) in reducing hospitalizations for and mortality from heart failure.
2	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor can be considered in order to reduce hospitalizations for heart failure.
2	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin receptor blocker (ARB) is effective in reducing hospitalizations for heart failure, mainly in those with ejection fractions close to 50%.

2	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB) is effective in reducing hospitalizations for heart failure, with greater benefit in patients with LVEFs closer to the lowest value in this range.
2	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB) can be considered in order to reduce hospitalizations for and mortality from heart failure.
2	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB) is NOT effective in reducing hospitalizations for and mortality from heart failure.
3	1. For patients with HFmrEF, sacubitril-valsartan can be considered in order to reduce the risk of hospitalization for HF and death. Class IIB-C 2. Evidence based on the PARAGON HF and Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure studies.
3	Agree
3	In patients with HF with mildly reduced ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is effective in significantly reducing hospitalizations for HF, but no significant reduction in HF mortality.
3	In patients with heart failure with mildly reduced ejection fraction, the studies do not have the power to show clear effectiveness of an angiotensin receptor/neprilysin inhibitor (ARNI) in reducing hospitalizations for and mortality from heart failure. Therefore, the recommendation for this scenario continues to be IIb, where usefulness efficacy is less established than evidence opinion.
3	In patients with heart failure with mildly reduced ejection fraction, the administration of an ARNI can be considered effective in reducing hospitalizations for heart failure. It cannot be concluded that the current evidence supports its use for decreasing mortality.
3	In patients with heart failure with mildly reduced ejection fraction, the administration of an ARNI is recommended to reduce hospitalizations for heart failure.
3	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is effective in reducing hospitalizations for worsening heart failure.
3	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is recommended to reduce hospitalizations for heart failure.
3	In patients with heart failure with mildly reduced ejection fraction, the use of an angiotensin receptor/neprilysin inhibitor (ARNI) can be considered in order to reduce hospitalizations for and mortality from heart failure.
3	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is effective in reducing hospitalizations but not for decreasing mortality.
3	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is effective in reducing hospitalizations for heart failure, not mortality.
3	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is effective in reducing hospitalizations for heart failure. No clear evidence of a proven benefit in mortality reduction.
3	In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is NOT effective in reducing hospitalizations for and mortality from heart failure.
3	The use of an angiotensin receptor/neprilysin inhibitor (ARNI) can be considered in patients with heart failure with mildly reduced ejection fraction, to reduce the risk of hospitalization for heart failure and cardiovascular mortality.
4	Agree
4	In patients with HF with preserved ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is not effective in significantly reducing hospitalizations for HF, nor in significantly reducing HF mortality.
4	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is effective in reducing hospitalizations. In a meta-analysis (Basile), the composite point of heart failure decompensation and all-cause mortality decreased significantly with ARNIs. With controversial results in other meta-analyses. The effect of sacubitril valsartan improved as the time elapsed with heart failure increased; it also would seem to be more useful with a higher frailty index.
4	In patients with heart failure with preserved ejection fraction, the studies do not have the power to show clear effectiveness of an angiotensin receptor/neprilysin inhibitor (ARNI) in reducing hospitalizations for and mortality from heart failure. Therefore, the recommendation in this scenario continues to be IIb, where usefulness efficacy is less established than evidence opinion.
4	In patients with heart failure with preserved function, the administration of an ARNI is suggested to reduce hospitalizations in women.

4	In patients with heart failure with mildly preserved ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) can be considered in order to reduce hospitalizations for heart failure but has no impact on mortality.
4	In patients with heart failure with preserved ejection fraction, the administration of an ARNI can be considered effective for reducing hospitalizations for heart failure but has no proven impact on heart failure mortality.
4	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is recommended to reduce hospitalizations for heart failure.
4	In patients with heart failure with preserved ejection fraction, the use of an angiotensin receptor/neprilysin inhibitor (ARNI) can be considered for reducing cardiovascular hospitalizations and mortality. Although there are no categorical results in heart failure mortality, the benefit of reduced readmissions may reduce mortality, therefore its use can also be considered in these patients.
4	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is effective in reducing hospitalizations for heart failure, with greater benefit in patients with LVEFs closer to the lowest value in this range.
4	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is effective in reducing hospitalizations, mainly in patients with ejection fractions close to 50%. They have no effect on mortality.
4	In patients with heart failure with preserved ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is NOT effective in reducing hospitalizations for and mortality from heart failure.
4	In selected patients with HFpEF, ARNIs can be considered to decrease hospitalizations, especially among patients with LVEFs on the lower end of this spectrum. Class IIB -BR
4	The use of an angiotensin receptor/neprilysin inhibitor (ARNI) can be considered in patients with heart failure with preserved ejection fraction to reduce the risk of hospitalization for heart failure.
5	Agree
5	In patients with heart failure with mildly reduced ejection fraction, the administration of an MRA can be considered in order to reduce hospitalizations for heart failure, with greater benefit in patients with LVEFs closer to the lowest level in this range. The risk of developing side effects like gynecomastia and hyperkalemia should be very particularly considered.
5	In patients with heart failure with mildly reduced ejection fraction, the administration of mineralocorticoid receptor antagonists (MRAs) is effective in reducing hospitalizations.
5	In patients with heart failure with mildly reduced ejection fraction, the studies do not have the power to show clear effectiveness of a mineralocorticoid receptor antagonist (MRA) in reducing hospitalizations for and mortality from heart failure. Therefore, the recommendation for this scenario continues to be IIb, where usefulness efficacy is less established than evidence opinion.
5	In patients with heart failure with mildly reduced ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) can be considered in order to reduce hospitalizations for heart failure.
5	In patients with heart failure with mildly reduced ejection fraction, the use of a mineralocorticoid receptor antagonist (MRA) can be considered in order to reduce hospitalizations for and mortality from heart failure.
5	In patients with heart failure with mildly reduced ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is effective in reducing hospitalizations for heart failure, not mortality.
5	In patients with heart failure with mildly reduced ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is effective in reducing hospitalizations for and mortality from heart failure, with greater benefit in patients with LVEFs closer to the lowest value in this range.
5	In patients with heart failure with mildly reduced ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is effective in significantly reducing hospitalizations for, but not mortality from, heart failure.
5	In patients with heart failure with mildly reduced ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is not effective in reducing hospitalizations for or mortality from heart failure.
5	In patients with heart failure with mildly reduced ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is NOT effective in reducing hospitalizations for and mortality from heart failure.
5	For patients with HFmrEF, an MRA can be considered in order to reduce the risk of hospitalization for HF and death. Class IIB-C In selected patients with HFpEF, the MRAs can be considered to reduce hospitalizations, especially among patients with LVEFs on the lower end of this spectrum. IIB-BRE Depending on comorbidities like HTN and AF, they can be used post-AMI. Screening and treatment for cardiovascular and other etiologies and comorbidities are recommended for patients with HFpEF. Class IC

5	The use of a mineralocorticoid receptor antagonist (MRA) can be considered in patients with heart failure with mildly reduced ejection fraction, to reduce the risk of hospitalization for heart failure, ensuring adequate monitoring of potassium and kidney function to reduce the risk of hyperkalemia and worsening kidney function.
5	The use of MRAs is recommended in patients with heart failure with mildly reduced function to decrease hospitalizations.
6	Agree
6	In patients with heart failure with preserved ejection fraction, there has been significant controversy regarding whether the use of mineralocorticoid receptor antagonists is effective in reducing hospitalizations for heart failure; women have been found to respond better to spironolactone. In a study conducted on the TOPCAT population, using frozen samples, three phenogroups are described, with Group 3 having the best response to spironolactone (middle aged, with diabetes mellitus, obesity, more functional abnormalities, chronic kidney disease, depression, more African American participants); with these types of characteristics, it may reduce hospitalizations.
6	In patients with heart failure with preserved ejection fraction, the studies do not have the power to show clear effectiveness of a mineralocorticoid receptor antagonist (MRA) in reducing hospitalizations for and mortality from heart failure. Therefore, the recommendation for this scenario continues to be IIb, where usefulness efficacy is less established than evidence opinion.
6	In patients with heart failure with preserved ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) can be considered in order to reduce hospitalizations for heart failure.
6	In patients with heart failure with preserved ejection fraction, the use of a mineralocorticoid receptor antagonist (MRA) can be considered for reducing hospitalizations for and mortality from heart failure.
6	In patients with heart failure with preserved ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is effective in reducing hospitalizations for heart failure, with greater benefit in patients with LVEFs closer to the lowest level in this range. There is insufficient evidence of a benefit in reducing mortality.
6	In patients with heart failure with preserved ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is effective in reducing hospitalizations for heart failure, mainly in those with ejection fractions close to 50%. They have no effect on mortality.
6	In patients with heart failure with preserved ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is not effective in significantly reducing hospitalizations for and mortality from heart failure.
6	In patients with heart failure with preserved ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is not effective in reducing hospitalizations for or mortality from heart failure.
6	In patients with heart failure with preserved ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is NOT effective in reducing hospitalizations for and mortality from heart failure.
6	In patients with heart failure with preserved ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is NOT effective in reducing hospitalizations for and mortality from heart failure.
6	In selected patients with HFpEF, MRAs can be considered to reduce hospitalizations and death, Class IIB-BR
6	The administration of either selective or nonselective MRAs is not recommended in patients with heart failure with preserved ejection fraction, as a reduction in hospitalizations for and mortality from heart failure has not been proven and, on the contrary, increased drug-related adverse events have been found.
6	The use of a mineralocorticoid receptor antagonist (MRA) in patients with heart failure with preserved ejection fraction can be considered in order to reduce the risk of hospitalization for heart failure, ensuring adequate monitoring of potassium and kidney function to reduce the risk of hyperkalemia and worsening kidney function.
7	Agree… The 2023 European Heart Failure Guidelines update is pending.
7	In patients with heart failure with mildly reduced ejection fraction, the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor (empagliflozin or dapagliflozin) is effective in reducing hospitalizations for heart failure and cardiovascular mortality.
7	In patients with heart failure with mildly reduced ejection fraction, the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor is effective in reducing hospitalizations for and mortality from heart failure.
7	In patients with heart failure with mildly reduced ejection fraction, sodium-glucose cotransporter-2 (SGLT2) inhibitors have proven to decrease the risk of the composite of hospitalization for heart failure decompensation and cardiovascular death. However, the individual analysis of each outcome only showed a significant reduction in hospitalization for heart failure decompensation.

7	In patients with symptomatic heart failure with mildly reduced ejection fraction, the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor is recommended to reduce the risk of hospitalization for heart failure or cardiovascular death. NOTE: I suggest modifying the last part of the question to read as follows: 1. In patients with heart failure with mildly reduced ejection fraction, is the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor effective in reducing hospitalizations for heart failure and cardiovascular mortality?
7	YES: SGLT2 inhibitors have proven their usefulness across the entire spectrum of the current definition of heart failure in reducing morbidity (hospitalizations) and mortality.
7	The use of SGLT2 inhibitors is recommended in patients with chronic heart failure with mrLVEF and residual congestion, in addition to conventional treatment and with or without diabetes mellitus, to impact on the composite outcomes of worsening heart failure or cardiovascular death or emergency room visits, in addition to medical treatment (ACE inhibitors/ARBs/ARNIs, beta blockers and aldosterone antagonists), with results depending on the drug groups added to the treatment.
7	It is effective and has solid A1 evidence based on the EMPEROR-Preserved and DELIVER trials, coupled with the meta-analysis. An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death. I propose the following for consideration: should the question read …effective in reducing hospitalizations for and mortality from heart failure? Or …effective in reducing hospitalizations for or mortality from heart failure?
7	Yes, I completely agree, there is high positive evidence supporting this statement.
7	Yes. They are effective and even superior to the other three standard medical treatment drug groups, considering the findings of different studies of dapagliflozin and empagliflozin that were done on patients with preserved or mildly reduced LVEF. Evaluating the combined outcomes of cardiovascular death and hospitalizations for HF.
7	Yes. They are superior to other drugs in standard medical treatment, based on the studies of dapagliflozin and empagliflozin that were done on patients with preserved or mildly reduced LVEF. Evaluating the combined outcomes of cardiovascular death and hospitalizations for HF.
7	An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended for patients with heart failure with mildly reduced ejection fraction to reduce the risk of hospitalization for HF or CV death.
7	An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with intermediate ejection fractions, reduces the risk of cardiovascular hospitalizations or deaths.
8	Agree. However, the following study will be released next week: “STEP HFpEF, a trial comparing the effects of once-weekly semaglutide in people with heart failure with preserved ejection fraction (HFpEF) and obesity,” which is positive. I would suggest adding it to the questions. The 2023 European Heart Failure Guidelines update is pending.
8	In heart failure with preserved LVEF (>50%), SGLT2 inhibitors reduce the risk of hospitalization for heart failure or the combined outcome of cardiovascular death/hospitalization vs. placebo. The SGLT2 inhibitors have no effect on total mortality or cardiovascular mortality alone in preserved LVEF, regardless of sex.
8	In patients with heart failure with mildly reduced ejection fraction, the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor (empagliflozin or dapagliflozin) is effective in reducing hospitalizations for heart failure and cardiovascular mortality.
8	In patients with heart failure with preserved ejection fraction, the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor is effective in reducing the combined outcome of hospitalizations for and mortality from heart failure.
8	In patients with heart failure with preserved ejection fraction, sodium-glucose cotransporter-2 (SGLT2) inhibitors have proven to reduce the risk of the composite of cardiovascular death and hospitalization for heart failure decompensation. However, the individual analysis of each outcome only showed a significant reduction in hospitalization for heart failure decompensation.
8	In patients with symptomatic heart failure with preserved ejection fraction, the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor is recommended to reduce the risk of hospitalization for heart failure or cardiovascular death. NOTE: I suggest modifying the last part of the question to read as follows: 1. In patients with heart failure with preserved ejection fraction, is the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor effective in reducing hospitalizations for heart failure and cardiovascular mortality?
8	YES: It is clearly the only therapeutic class that has a proven benefit in this group of patients, in whom comorbidities prevail over structural heart damage.

8	Yes, it is effective, with solid IA evidence based on the EMPEROR-Preserved and DELIVER trials. An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death, regardless of the presence of diabetes.
8	Yes, although we only have two large studies in this field with the use of the two molecules.
8	Yes. The results of studies on preserved LVEF showed effectiveness regardless of comorbidities or the use of other standard medical therapy drugs.
8	Yes. New studies have been proving that they are effective regardless of comorbidities or the concomitant use of other disease-modifying drugs.
8	An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommend in patients with heart failure with preserved ejection fraction to reduce the risk of hospitalization for HF or CV death.
8	An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with preserved ejection fraction, reduces the risk of cardiovascular hospitalizations or deaths. Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and preserved ejection fraction, regardless of the presence or absence of diabetes. Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and mildly reduced or preserved ejection fraction, Solomon et al., 2022.
9	Agree. The 2023 European Heart Failure Guidelines update is pending.
9	Studies of the use of BBs in heart failure with mildly reduced ejection fraction have shown a reduction in deaths from all causes but have not found statistically significant differences in the reduction of hospitalizations.
9	In patients with mrLVEF, the use of beta blockers in patients taking them for any reason decreases the composite point of cardiovascular death due to heart failure. It does not reduce the hospitalization rate.
9	In patients with heart failure with mildly reduced ejection fraction, the administration of a beta blocker could be effective in reducing hospitalizations for and mortality from heart failure, when added to an SGLT2 inhibitor.
9	In patients with heart failure with mildly reduced ejection fraction, the addition of a beta blocker to optimal medical treatment could reduce hospitalizations for and mortality from heart failure.
9	In patients with heart failure with mildly reduced ejection fraction, the addition of a beta blocker to optimal medical treatment could reduce hospitalizations for and mortality from heart failure.
9	In patients with symptomatic heart failure with mildly reduced ejection fraction, the administration of a beta blocker can be considered in order to reduce the risk of hospitalization for heart failure and death.
9	No. Studies of beta blockers in heart failure with mildly reduced ejection fraction have shown a reduction in deaths from all causes, but no statistically significant differences were found in reducing hospitalizations.
9	For patients with heart failure in sinus rhythm and with mildly reduced LVEF, beta blockers improve left ventricular systolic function and reduce cardiovascular morbidity and mortality.
9	Could be considered a IIb recommendation. The meta-analysis did not show a significant result for CV hospitalization (HR 0.95, 95% CI 0.68–1.32; P = 0.76) or the composite outcome of cardiovascular death or hospitalization (HR 0.83, 95% CI 0.60–1.13; P = 0.23).
9	A beta blocker can be considered for patients with mildly reduced ejection fractions, to reduce the risk of hospitalization for and death from HF.
9	Yes, a benefit is feasible if the patient's EF is recovering, but the associated clinical conditions should be evaluated when the ventricular function is affected by the comorbidity rather than being itself the cause of heart failure symptoms.
9	It is effective, but currently with a IIB level of evidence.
10	With the use of beta blockers in patients with heart failure with pLVEF >50%, there is a tendency to decrease cardiovascular mortality, with no effect on all-cause mortality. There is no evidence regarding hospitalizations for heart failure. Therefore, they could be used if indicated for the respective comorbidities, only to affect the cardiovascular outcome.
10	Agree. The 2023 European Heart Failure Guidelines update is pending.

10	The use of beta blockers probably produces little or no difference in the risk of death of patients with heart failure with preserved ejection fraction. The certainty of the evidence is moderate. The use of beta blockers probably produces little or no difference in the risk of hospitalization of patients with heart failure with preserved ejection fraction. The certainty of the evidence is moderate.
10	In patients with heart failure with preserved ejection fraction, the use of a beta blocker has not proven to be effective in reducing hospitalizations for and mortality from heart failure?
10	In patients with heart failure with preserved ejection fraction, the administration of a beta blocker is not effective in reducing hospitalizations for and mortality from heart failure.
10	In patients with heart failure with preserved ejection fraction, the administration of a beta blocker could be effective in reducing cardiovascular mortality but has no effect on the rates of hospitalization for heart failure.
10	The current evidence in patients with heart failure with preserved ejection fraction and ischemic heart disease only recommends the prescription of BBs in the early phase after an acute coronary syndrome, for tachyarrhythmias and for managing angina.
10	The review of the evidence in Cochrane shows that there may be a reduction in mortality, but the quality of the evidence is low, and although a sensitivity analysis has been done, no conclusions can be drawn, either.
10	NOT NECESSARILY: the patients and associated comorbidities must be selected carefully. As I have previously stated, this is a consequence NOT A CAUSE. Therefore, patients with HTN, DM with heart failure with preserved EF are not benefited, but patients with coronary disease, atrial fibrillation may benefit.
10	No. The use of beta blockers in HF with preserved LVEF showed no reduction in hospitalizations for and death from HF.
10	No. Studies of the use of BBs in heart failure with preserved ejection fraction showed no reduction in hospitalizations for and death from HF.
10	For patients with heart failure and preserved LVEF, beta blockers are safe; however, their benefit in reducing mortality and hospitalizations is not clear. They may be used in people with specific indications, such as an ischemic etiology; however, they should be used with caution in patients with other etiologies or atrial fibrillation.
10	Few studies support their use, they have no effect on mortality and there is a slight reduction in hospitalizations.
11	In patients with symptomatic heart failure (HF) with mildly reduced ejection fraction (mrEF) and iron deficiency (defined as serum ferritin < 100 µg/L or serum ferritin between 100 and 299 µg/L and transferrin saturation < 20%), the administration of intravenous iron supplements with ferric carboxymaltose or ferric derisomaltose is recommended to alleviate the symptoms of HF and improve the quality of life. In patients with symptomatic HF with mrEF and iron deficiency, the administration of intravenous iron supplements with ferric carboxymaltose or ferric derisomaltose should be considered to reduce the risk of hospitalizations for HF. There is insufficient evidence to recommend the administration of IV iron in patients with HF with mrEF and iron deficiency to reduce mortality. There are no solid studies on the administration of IV iron in patients with HF with preserved EF and iron deficiency to reduce hospitalizations for and mortality from HF.
11	In patients with heart failure with ejection fractions >50% and iron deficiency (defined as serum ferritin < 100 µg/L or serum ferritin between 100 and 299 µg/L and transferrin saturation < 20%), the administration of IV iron has not proven to reduce hospitalizations for or mortality from heart failure. In patients with heart failure with mildly reduced ejection fraction (40-49%) and iron deficiency, the administration of IV iron could be considered in order to reduce hospitalizations for heart failure.
11	In patients with heart failure with both preserved and mildly reduced ejection fractions, there is insufficient evidence to recommend the administration of IV iron to reduce hospitalizations for and mortality from heart failure.
11	Among patients with exacerbated heart failure with mildly reduced ejection fraction or with a recent exacerbation, and iron deficiency, intravenous ferric carboxymaltose showed effectiveness in this subgroup of patients in reducing recurrent hospitalizations for heart failure and improving the quality of life, with no clear effects on mortality. In patients with preserved LVEF, we still do not have enough evidence to be able to make a recommendation.
11	The administration of intravenous iron in mildly reduced and reduced shows its best evidence in improving quality of life, but is IIa in reducing hospitalizations, especially when the LVEF is < 45%. I do not see recommended references in this question.
11	The administration of IV iron is effective in reducing hospitalizations for and mortality from heart failure in symptomatic patients with heart failure with reduced and mildly reduced LVEF.
11	The administration of intravenous carboxymaltose or derisomaltose iron in chronic and stabilized acute heart failure with iron deficiency and in patients with mrLVEF and pLVEF improves fatigability and dyspnea symptoms and quality of life. It also reduces the risk of cardiovascular hospitalizations. The effects are seen from week 4 to week 24 after treatment.

11	The studies are on LVEF less than 50%. AFFIRM-HF and IRONMAN trials. The 2023 European Heart Failure Guidelines update is pending.
11	NO: there is insufficient data.
11	No. The use of IV iron in HF with any range of LVEF only showed improvement in functional capacity.
11	No. In the various studies, the administration of IV iron showed improvement in the functional capacity of patients with HF regardless of LVEF. Reference AFFIRM-AHF. Life 2022, 12(11), 1828; https://doi.org/10.3390/life12111828
11	Intravenous iron supplementation is recommended in symptomatic patients with preserved ejection fraction as well as those with mildly reduced ejection fraction and iron deficiency to alleviate HF symptoms and improve quality of life.
11	Improved symptoms and reduced hospitalizations, no impact on mortality, II A recommendation.
12	The effect of structured cardiac rehabilitation* on patients with heart failure with mrLVEF has an impact on cardiac structure: ventricular diastole and reduced left atrial size. There are no consistent results regarding cardiac output, right ventricular function and pulmonary pressure. In patients with heart failure with pLVEF >50%, a structured cardiac rehabilitation program* improved exercise capacity, the six-minute walk and the quality-of-life questionnaire vs. the control. The results with diastolic function derivatives are contradictory. It could also improve peak O2, aerobic endurance and quality of life, but the sample sizes are small. *The protocols should be structured over 12-16 weeks with 2-3 weekly sessions lasting 20-60 min. each, including aerobic, resistance, walking, treadmill and bicycling exercises
12	In patients with HF with preserved and mildly reduced ejection fraction, directed cardiac rehabilitation could improve quality of life and functional capacity, but has no significant effect on readmissions or death.
12	In patients with heart failure with both preserved and mildly reduced ejection fraction, cardiac rehabilitation should be an adjunct to medical therapy to improve quality of life.
12	In patients with heart failure with both preserved and mildly reduced ejection fraction, cardiac rehabilitation or physical training (regular physical activity), added to the instated medical treatment, is effective in reducing the risk of hospitalization for and death from heart failure, and in improving functional capacity, exercise tolerance and quality of life.
12	In patients with heart failure with both preserved as well as mildly reduced ejection fraction, there is no evidence to date that cardiac rehabilitation added to the instated medical treatment is effective in reducing hospitalizations for or mortality from heart failure.
12	Enrollment in cardiac rehabilitation or structured exercise programs could improve the quality of life and functional capacity of people with preserved as well as mildly reduced ejection fractions, especially those with previous hospitalizations.
12	Most of the evidence has been reported for HFrEF. However, there are recent studies on preserved, showing potential benefits in improved quality of life, exercise capacity and echocardiographic parameters. Since the studies on preserved have a small number of patients and short follow up, the data to date are insufficient to determine the real impact in terms of clinical events, including mortality and hospitalizations.
12	Cardiac rehabilitation improves the quality of life and functional class of patients with heart failure with preserved LVEF.
12	NO: there is insufficient data. It would be useful for improving peak O2, aerobic endurance and quality of life in patients with HFpEF.
12	There are no references; however, multiple meta-analyses confirm its benefit. The important point in the discussion is the type (protocol, duration) of cardiac rehabilitation.
12	No. The studies have only shown functional class improvement in all patients with HF and cardiovascular risk.
12	No. Functional class improvement has been shown in all patients with HF regardless of LVEF and HF stage. References Hosseini Mohammadi NS, Shaki Katouli MH, Masoudkabir F, Meysamie A, Tavakoli K, Vasheghani-Farahani A. Cardiac rehabilitation in heart failure with severely reduced ejection fraction: effects on mortality. Heart Fail Rev. 2022 May 21. Sawan MA, Calhoun AE, Fatade YA, Wenger NK. Cardiac rehabilitation in women, challenges and opportunities. Prog Cardiovasc Dis. 2022 Jan-Feb;70:111-118
12	Improves the functional capacity of our patients with HF, regardless of their left ventricular ejection fraction (LVEF), which leads to the clinical outcomes of improved quality of life and reduced readmissions. It also summarizes the existent evidence in HF with both reduced as well as preserved LVEF, and even in advanced HF (Stage D).

Annex F. Options offered to the group of experts during voting and clarification meetings (Phase 7).

Question
Question 1 Recommendation In patients with heart failure with mildly reduced ejection fraction, the use of an ACE inhibitor or an angiotensin receptor blocker (ARB), in the event of ACE inhibitor intolerance, may be considered effective for decreasing the number of hospitalizations for heart failure, without a categorical benefit proven to date in decreasing cardiovascular and all-cause mortality, except in the context of ischemic heart failure, where it could reduce cardiovascular mortality in patients with mildly reduced ejection fraction. In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin converting enzyme (ACE) inhibitor / angiotensin receptor blocker (ARB) is effective for both reducing hospitalizations for heart failure as well as cardiovascular deaths, with greater benefit in patients with VEFs closer to the lowest value in the range and those with an ischemic etiology.
Question 2 Recommendation In patients with heart failure with preserved ejection fraction, the administration of an angiotensin receptor blocker (ARB) or an angiotensin converting enzyme (ACE) inhibitor can be considered effective in reducing hospitalizations for heart failure, mainly in those with ejection fractions close to 50%, but not in significantly reducing HF mortality. In patients with heart failure with preserved ejection fraction, the studies do not have the power to show clear effectiveness (ACE inhibitors, ARBs) in reducing hospitalizations for or mortality from heart failure.
Question 3 Recommendation In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor (ARNI) is effective in reducing hospitalizations for heart failure. However, it cannot be concluded that the current evidence shows a benefit in decreasing mortality. In patients with heart failure with mildly reduced ejection fraction, the use of an angiotensin receptor/neprilysin inhibitor (ARNI) can be considered in order to reduce the risk of hospitalization for heart failure and cardiovascular mortality.
Question 4 Recommendation In patients with heart failure with preserved ejection fraction, the administration of an ARNI can be considered effective for reducing hospitalizations for heart failure, especially in patients with LVEFs at the lower end of this spectrum, that is, with ejection fractions close to 50%. However, the administration of an ARNI has not shown an impact on mortality from heart failure. In patients with heart failure with preserved ejection fraction, the studies do not have the power to show clear effectiveness of angiotensin receptor/neprilysin inhibitors (ARNIs) in reducing hospitalizations or reducing mortality from heart failure.
Question 5 Recommendation In patients with heart failure with mildly reduced ejection fraction, the administration of an MRA can be considered for reducing hospitalizations for heart failure, with greater benefit in patients with LVEFs closer to the lowest value in this range. The risk of developing side effects like gynecomastia and hyperkalemia should be carefully considered, ensuring adequate monitoring of potassium and kidney function to reduce the risk of hyperkalemia and worsening kidney function. In patients with heart failure with mildly reduced ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is effective in reducing hospitalizations for heart failure, not mortality.
Question 6 Recommendation In patients with heart failure with preserved ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) is effective in reducing hospitalizations for heart failure, with greater benefit in patients with LVEFs closer to the lowest value in this range, that is, in patients with ejection fractions close to 50%, ensuring adequate potassium and kidney function monitoring to reduce the risk of hyperkalemia and worsening kidney function. However, there is insufficient evidence of its benefit in reducing mortality. The administration of either selective or non-selective MRAs is not recommended in patients with heart failure with preserved ejection fraction, as a reduction in hospitalizations for and mortality from heart failure has not been proven and, on the contrary, there has been evidence of increased adverse events associated with the medication.
Question 7 Recommendation In patients with symptomatic heart failure with mildly reduced ejection fraction, the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor is recommended to reduce the risk of hospitalization for heart failure or cardiovascular death, as combined/composite outcomes of these two have been shown. In addition to SGLT2s being effective, they are superior to other drugs in standard medical treatment. While SGLT2 inhibitors have proven to reduce the risk of the composite of hospitalization for heart failure decompensation and cardiovascular death, the individual analysis of each outcome only showed significant reduction of hospitalizations for heart failure decompensation.

Question 8

Recommendation

In patients with symptomatic heart failure with preserved ejection fraction, the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor is recommended to reduce the risk of hospitalization for heart failure or cardiovascular death. The results of studies on preserved LVEF have been showing that they are effective regardless of comorbidities or the concomitant use of other standard medical therapy drugs.

In patients with heart failure with preserved ejection fraction, although sodium-glucose cotransporter-2 (SGLT2) inhibitors have been proven to reduce the composite risk of cardiovascular death and hospitalization for heart failure decompensation, the individual analysis of each outcome only showed a significant reduction in hospitalization for heart failure decompensation.

Question 9

Recommendation

In patients with symptomatic heart failure with mildly reduced ejection fraction, the administration of a beta blocker could reduce hospitalizations for and mortality from heart failure.

In patients with heart failure with mildly reduced ejection fraction, studies have shown that the administration of a beta blocker is effective in reducing death from all causes, but no statistically significant differences were found in reducing hospitalizations.

A benefit is feasible, if the patient's EF is recovering, but the associated clinical conditions should be evaluated, where ventricular function abnormalities are a consequence of the comorbidity and not, in themselves, the cause of the heart failure symptoms.

Question 10

Recommendation

For patients with heart failure and preserved LVEF, beta blockers are safe; however, their benefit in reducing mortality and hospitalizations is not clear. They can be used in people with specific indications, like an ischemic etiology; however, they should be used cautiously in patients with other etiologies or atrial fibrillation.

In patients with heart failure with preserved ejection fraction, the administration of a beta blocker showed little or no reduction in hospitalizations for and deaths from heart failure. The certainty of the evidence is low or moderate.

Question 11

Recommendation

In patients with heart failure with both preserved and mildly reduced ejection fraction, there is insufficient evidence to recommend the administration of IV iron to reduce hospitalizations for and mortality from heart failure. However, improved functional capacity, fatigability and dyspnea symptoms, and quality of life have been shown in patients with HF, regardless of LVEF.

In patients with heart failure with an ejection fraction >50% and iron deficiency (defined as serum ferritin < 100 µg/L or serum ferritin between 100 and 299 µg/L and transferrin saturation < 20%), the administration of IV iron has shown no reduction in hospitalizations for or mortality from heart failure. In patients with heart failure with mildly reduced ejection fraction (40-49%) and iron deficiency, the administration of IV iron could be considered in order to reduce hospitalizations for heart failure.

In patients with heart failure with mildly reduced ejection fraction, the administration of intravenous iron supplements with ferric carboxymaltose or ferric derisolmaltose should be considered to reduce the risk of hospitalization for HF. However, there is insufficient evidence to recommend the administration of IV iron to reduce mortality.

Question 12

Recommendation

No. The data is insufficient to date to determine the real impact in terms of clinical events including mortality and hospitalizations. However, it has proven to be useful and improve functional capacity, peak O2, aerobic endurance, functional class and quality of life in all patients with HF, regardless of LVEF and HF stage, especially those with previous hospitalizations.

In patients with heart failure with both preserved and mildly reduced ejection fraction, cardiac rehabilitation added to the instated medical therapy improves functional capacity regardless of the left ventricular ejection fraction (LVEF), which leads to the clinical outcomes of improved quality of life and fewer readmissions.

In patients with heart failure with both preserved and mildly reduced ejection fraction, cardiac rehabilitation or physical training (regular physical activity) coupled with the instated medical treatment is effective in reducing the risk of hospitalization for and death from heart failure, and in improving functional capacity, exercise tolerance and quality of life.

Annex G. Iterative voting process and versions of the recommendations discussed in the meetings. Class of recommendation and level of evidence of each recommendation.

Meeting 1
Question 1. Recommendation: *First vote: 12 experts.* Option 1: 100% - 12 experts Option 2: 0%

Class-reaction results:

First vote: 13 experts

Class Ia: 0%

Class IIa: 69% - 9 experts

Arguments:
- The evidence shows that it does not have to be given, it sounds reasonable to give it with the hospitalization outcomes.

Class IIb: 31% - 4 experts

Arguments:
- Despite having a benefit, the benefit leans more to one side than the other, it is still not reasonable to leave it as an option for patients with mildly reduced, despite having benefits it is not high enough to leave as iia mainly in hospitalizations, it is still lacking in mortality, specifically. Some better-designed studies for the evidence

Class III: 0%

Second vote: 13 experts.

Class Ia: 0%

Class IIa: 62% - 8 experts

Arguments:
- It should be used not to decrease the two outcomes, but rather the evidence favors a reduction in hospitalizations, not so much mortality. The recommendation is being given without grading the evidence

Class IIb: 38% - 5 experts

Arguments:
- The studies are not homogenous and consistent in hospitalization reduction, there is evidence in favor, but it is not categorical, there are gaps.

Class III: 0%

Third vote: 14 experts.

Class Ia: 0%

Class IIa: 43% - 6 experts

Class IIb: 57% - 8 experts

Class III: 0%

Final level: 13 experts.

Level A: 69% - 9 experts

Level B: 31% - 4 experts

Level C: 0%

Final version:

In patients with heart failure with mildly reduced ejection fraction, the use of an ACE inhibitor or an angiotensin receptor blocker (ARB), in the event of ACE inhibitor intolerance, can be considered to be effective according to the reduction in the number of hospitalizations for heart failure. A categorical benefit in reduced cardiovascular and all-cause mortality has not been shown, except in the context of ischemic heart failure.

Question 2.

Recommendation:

First vote: 13 experts.

Option 1: 85% - 11 experts

Option 2: 15% - 2 experts

Class-reaction results

First vote: 13 experts.

Class Ia: 0%

Class IIa: 8% - 1 expert

Clase IIb: 92% - 12 experts

Clase III: 0%

Final level:

First vote: 13 experts.

Level A: 77% - 10 experts

Arguments:
- There are no clinical studies separating patients with preserved or mildly reduced, therefore the evidence is the same as in the previous question, as the studies were done in patients with more than 40%.

Level B: 23% - 3 experts

Level C: 0%

Second vote: 14 experts.

Level A: 86% - 12 experts

Level B: 14% - 2 experts
Level C: 0%

Final version:
In patients with heart failure with preserved ejection fraction, the administration of an angiotensin receptor blocker (ARB) or an angiotensin converting enzyme (ACE) inhibitor can be considered effective in reducing hospitalizations for heart failure, but not for reducing HF mortality.

Question 3.

Recommendation:

First vote: 13 experts.

Option 1: 85% - 11 experts

Option 2: 15% - 2 experts

Class-reaction results:

First vote: 13 experts.

Class Ia: 0%

Class IIa: 15% - 2 experts

Class IIb: 85% - 11 experts

Class III: 0%

Final level:

First vote: 12 experts.

Level A: 50% - 6 experts

Arguments:
- Other types of studies should be considered and move away from the heterogeneity of the studies, because they are clearly heterogenous and there are subrogated outcomes. It is necessary to go to the additional studies because there are differential scenarios in which these populations are present.

Level B: 50% - 6 experts

Arguments:
- There are no strong and multiple meta-analyses.
- The evidence is limited, there is one clinical study, there is not a lot of evidence to support the recommendation.

Level C: 0%

Second vote: 14 experts.

Level A: 29% - 4 experts

Level B: 71% - 10 experts

Arguments:
- There are few trials showing the evidence that is proposed, it needs more evidence to give it more weight

Level C: 0%

Third vote: 13 experts.

Level A: 8% - 1 expert

Level B: 92% - 12 experts

Level C: 0%

Final version:

In patients with heart failure with mildly reduced ejection fraction, the administration of an angiotensin receptor/neprilysin inhibitor can be considered in order to reduce hospitalizations for heart failure, but not to reduce mortality.

Question 4.

Recommendation:

First vote: 13 experts.

Option 1: 85% - 11 experts

Option 2: 15% - 2 experts

Class-reaction results:

First vote: 12 experts.

Class Ia: 0%

Class IIa: 0%

Class IIb: 100% - 12 experts

Class III: 0%

Final level:

First vote: 12 experts.

Level A: 0%

Level B: 100% - 12 experts

Level C: 0%

Total agreement on Level B.

Final version:

In patients with heart failure with preserved ejection fraction, the administration of an ARNI can be considered in order to reduce hospitalizations for heart failure, but not mortality.

Question 5.

Recommendation:
First vote: 14 experts.

Option 1: 29% - 4 experts

Option 2: 71% - 10 experts

Second vote: 14 experts.

Option 1: 7% - 1 expert

Option 2: 93% - 13 experts

Class-reaction results:

First vote: 13 experts.

Class Ia: 0%

Class IIa: 0%

Class IIb: 100% - 13 experts

Class III: 0%

Final level:

First vote: 13 experts.

Level A: 8% - 1 expert

Level B: 92% - 12 experts

Level C: 0%

Final version:
In patients with heart failure with mildly reduced ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) could be considered in order to reduce hospitalizations for heart failure, but not mortality.

Question 6.

Recommendation:

First vote: 14 experts.

Option 1: 79% - 11 experts

Option 2: 21% - 3 experts

Class-reaction results:

First vote: 12 experts.

Class Ia: 0%

Class IIa: 0%

Class IIb: 100% - 12 experts

Class III: 0%

Final level:

First vote: 14 experts.

Level A: 0%

Level B: 100% - 14 experts

Level C: 0%

Total agreement on Level B.

Final version:

In patients with heart failure with mildly preserved ejection fraction, the administration of a mineralocorticoid receptor antagonist (MRA) could be considered in order to reduce hospitalizations for heart failure, but not mortality.

Meeting 2

Question 1.

Recommendation:

First vote: 11 experts.

Option 1: 91% - 10 experts

Option 2: 9% - 1 expert

Class-reaction results:

First vote: 12 experts.

Class Ia: 92% - 11 experts

Class IIa: 8% - 1 expert

Class IIb: 0%

Class III: 0%

Final level: 11 experts.

Level A: 100% - 11 experts

Level B: 0%

Level C: 0%

Complete agreement on Level A.

Final version:

In patients with heart failure with mildly reduced ejection fraction, the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor is recommended to reduce the risk of hospitalization for heart failure or cardiovascular death, as combined/composite outcomes of these two have been shown. Besides SGLT2 inhibitors being effective, they are superior to other drugs in standard medical therapy.

Question 2

Recommendation:

First vote: 10 experts.

Option 1: 100% - 10 experts

Option 2: 0%

Class-reaction results:

First vote: 12 experts.

Class Ia: 92% - 11 experts

Class IIa: 8% - 1 expert

Class IIb: 0%

Class III: 0%

Final level: 12 experts.

Level A: 100% - 12 experts

Level B: 0%

Level C: 0%

Complete agreement on Level A.

Final version:
In patients with symptomatic heart failure with preserved ejection fraction, the administration of a sodium-glucose cotransporter-2 (SGLT2) inhibitor is recommended to reduce the risk of hospitalization for heart failure or cardiovascular death.

Question 3

Recommendation:

First vote: 11 experts.

Option 1: 91% - 10 experts

Option 2: 9% - 1 expert

Option 3: 0%

Class-reaction results:

First vote: 12 experts.

Class Ia: 8% - 1 expert

Class IIa: 84% - 10 experts

Class IIb: 8% - 1 expert

Class III: 0%

Final level: 12 experts.

Level A: 8% - 1 expert

Level B: 92% - 11 experts

Level C: 0%

Final version:
In patients with heart failure with ejection fraction, the administration of a beta blocker could be useful in reducing hospitalizations for heart failure and cardiovascular mortality.

Question 4

Recommendation:

First vote: 11 experts.

Option 1: 73% - 8 experts

Arguments:
- There is no clear benefit in preserved, but in some patients, clinical contexts and comorbidities, it may have a greater benefit.
- More emphasis must be placed on the phenotype.
- It is the most indicative of what must be done

Option 2: 27% - 3 experts

Arguments:
- It has no benefit in heart failure, the benefit is for the other diseases.

Second vote: 12 experts.

Option 1: 100% - 12 experts

Option 2: 0%

Class-reaction results:

First vote: 12 experts.

Class Ia: 0%

Class IIa: 8% - 1 expert

Class IIb: 92% - 11 experts

Class III: 0%

Final level:

First vote: 12 experts.

Level A: 17% - 2 experts

Level B: 83% - 10 experts

Level C: 0%

Final version:

In patients with heart failure with preserved LVEF, beta blockers could have a marginal benefit in reducing cardiovascular mortality and hospitalizations for heart failure, when it is associated with comorbidities like coronary disease and hypertension, in patients with sinus rhythm. In other subpopulations, its use is not routinely recommended.

Question 4 – 2 (after the modification)

Recommendation:

First vote: 10 experts.

Option 1: 100% - 10 experts

Option 2: 0%

Class-reaction results:

First vote: 11 experts.

Class Ia: 9% - 1 expert

Class IIa: 9% - 1 expert

Class IIb: 82% - 9 experts

Class III: 0%

Final level:

First vote: 11 experts.

Level A: 9% - 1 expert

Level B: 91% - 10 experts

Level C: 0%

Second vote: 11 experts.

Level A: 91% - 10 experts

Level B: 9% - 1 expert

Level C: 0%

Question 5

Recommendation:

First vote: 11 experts.

Option 1: 36% - 4 experts

Arguments:
- Only refers to the preserved fraction

Option 2: 64% - 7 experts

Arguments:
- Includes patients with both preserved and reduced fractions

Option 3: 0%

Second vote: 11 experts.

Option 1: 91% - 10 experts

Option 2: 9% - 1 expert

Class-reaction results:

First vote: 10 experts.

Class Ia: 30% - 3 experts

Arguments:
- There are four meta-analyses in favor of reducing hospitalization and definite functional class improvement, and there is only one study under 50%

Class IIa: 70% - 7 experts

Arguments:
- The benefit is not large, the effect size is relatively small

Class IIb: 0%

Class III: 0%

Second vote: 9 experts.

Class Ia: 0%

Class IIa: 100% - 9 experts

Class IIb: 0%

Class III: 0%

Final level: 10 experts.

Level A: 90% - 9 experts

Level B: 10% - 1 expert

Level C: 0%

Final version:

In patients with heart failure with an ejection fraction <50% and iron deficiency (defined as serum ferritin <100 μg/L or serum ferritin between 100 and 299 μg/L and transferrin saturation <20%), the administration of intravenous (IV) carboxymaltose iron reduces hospitalizations for heart failure, with no proven impact on cardiovascular mortality.

In patients with heart failure with preserved LVEF, there is no proven reduction in hospitalizations for heart failure or cardiovascular mortality.

Question 6

Recommendation:

First vote: 9 experts.

Option 1: 22% - 2 experts

Arguments:
- There are no studies on this

Option 2: 45% - 4 experts

Option 3: 33% - 3 experts

Second vote: 11 experts.

Option 1: 100% - 11 experts

Option 2: 0%

Class-reaction results:

First vote: 10 experts.

Class Ia: 0%

Class IIa: 90% - 9 experts

Class IIb: 10% - 1 expert

Class III: 0%

Final level: 11 experts.

Level A: 18% - 2 experts

Level B: 82% - 9 experts

Level C: 0%

Final version:

In patients with HF with preserved and mildly reduced ejection fraction, cardiac rehabilitation added to pharmacological treatment reduces the risk of hospitalization for HF and reduces cardiovascular mortality. There are also benefits in improved quality of life, functional capacity and empowerment for disease self-management.